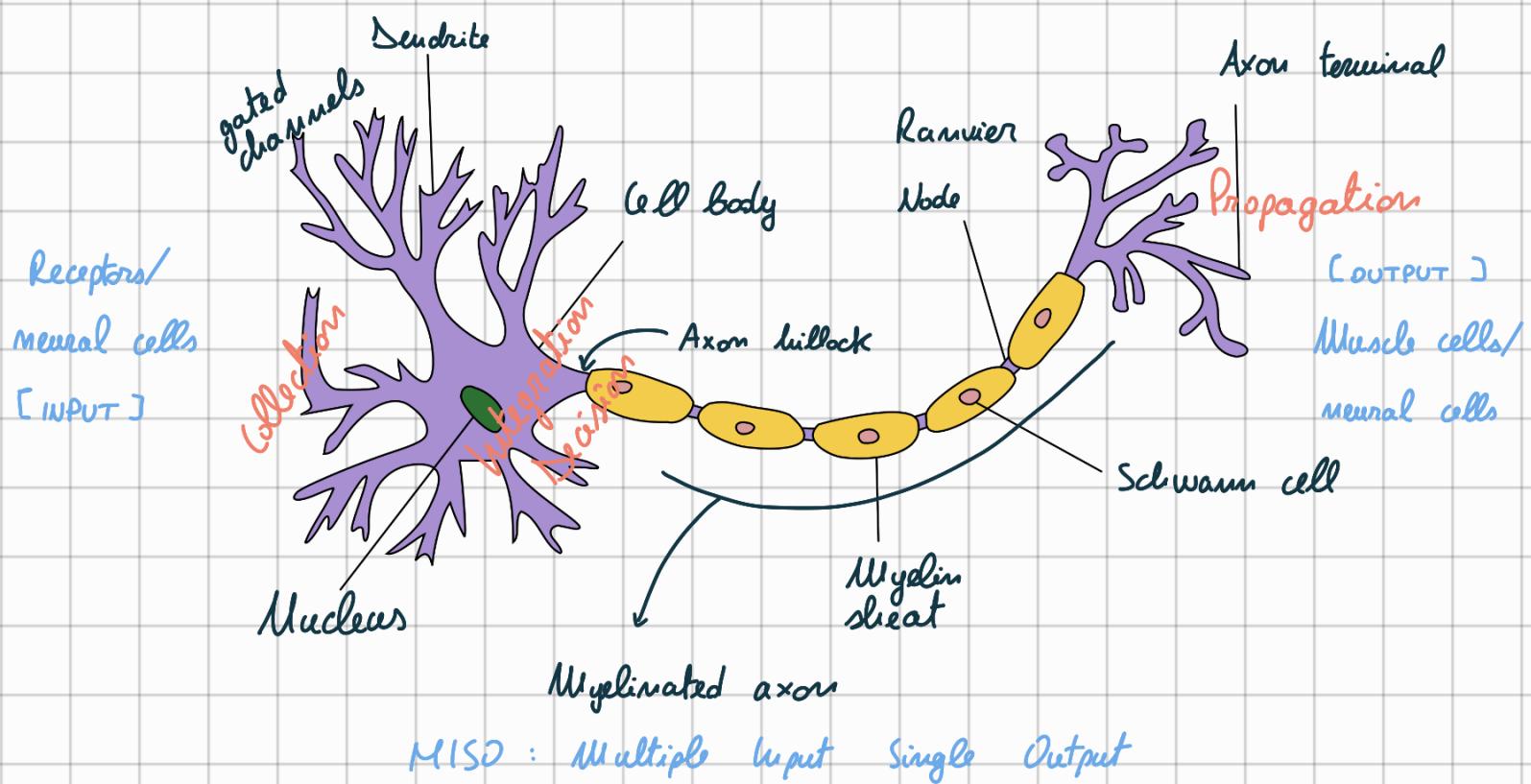


## Neuroni:

i neuroni hanno varie funzioni, ma si limitano a trasmettere segnali.

Possiamo identificare 3 funzioni principali:

1. **collection** of information from multiple sources (other neural cells or receptors)
2. **integration** (in time and space) of incoming information to provide a **binary decision**
3. **generation** and **propagation** of a bit of information up to target cells (other neural cells or muscle cells)



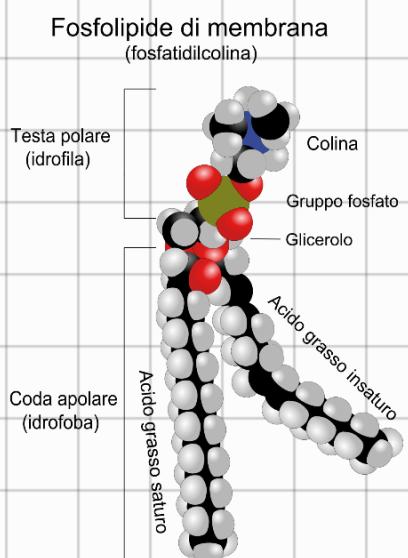
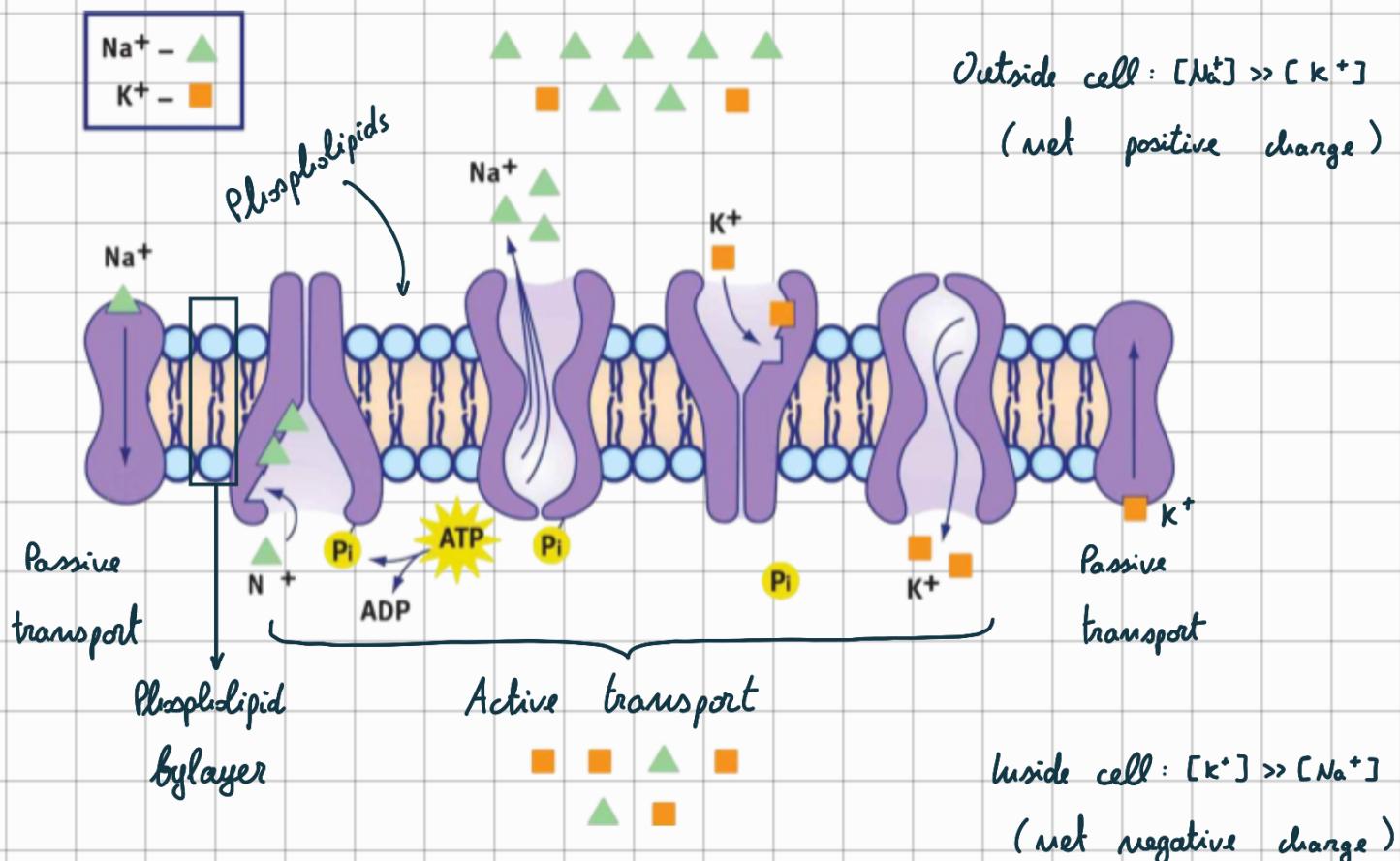
Come risultato dell'integrazione dei segnali in ingresso, la cellula puo' produrre o meno un segnale elettrico che verrà propagato ad altre cellule (neurali o muscolari).

Se le sinapsi sono di tipo chimico, oltre ad una azione eccitatoria possiamo avere un'azione inhibitoria.

## Neuronal Membrane :

The neuronal membrane is the part of the cell responsible for collecting, processing and propagating informations.

La membrana separa il corpo cellulare dall'ambiente esterno, ma non è una separazione netta in quanto permette il passaggio di alcune sostanze: è selettivamente permeabile



$\rightarrow$  *attrae aqua*  
 $\leftarrow$  *hidrophilic (idrofila)*  
 $\leftarrow$  *hidrophobic (idrofoba)*  
 $\curvearrowright$  *respinge aqua*

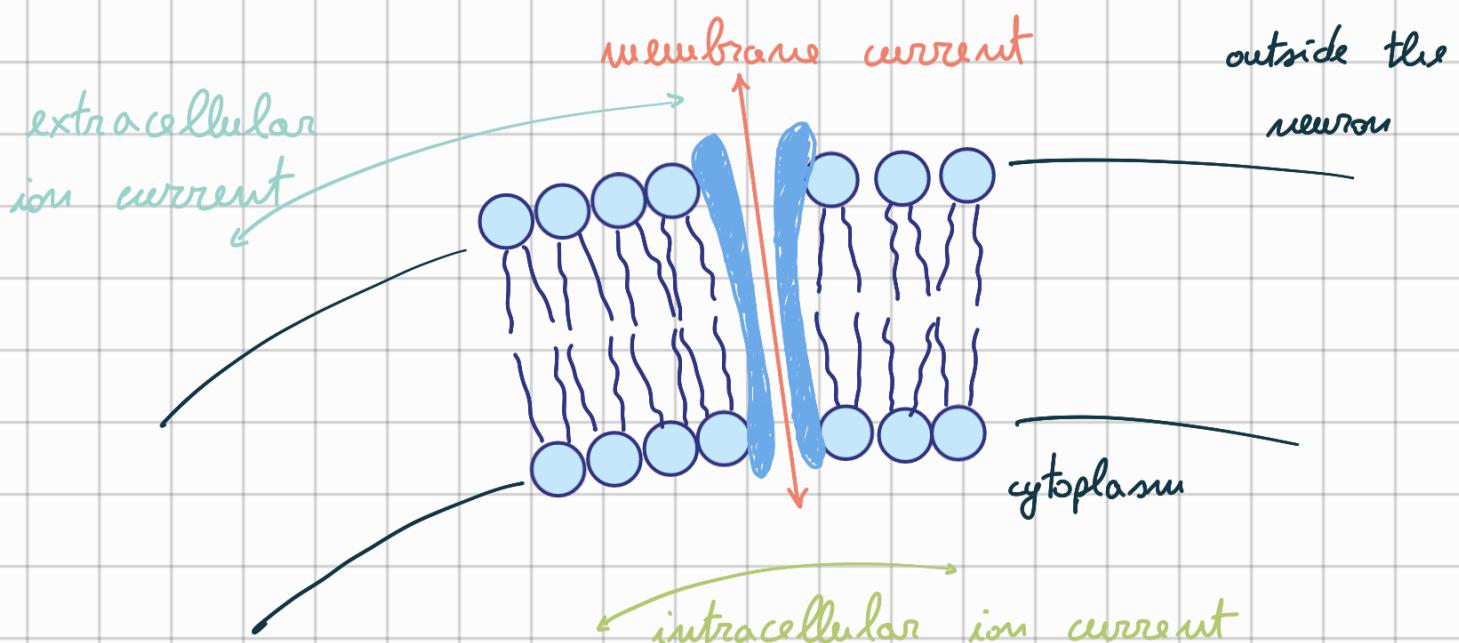
Particelle elettricamente cariche non possono attraversare la membrana (per via delle code dei fosfolipidi). Queste particelle possono passare solo attraverso dei canali.

Il passaggio può essere attivo (impiego di energia per spostare una particella attraverso il canale) o passivo. Il passaggio attivo avviene:

- 1 in risposta a cambiamenti nella differenza di potenziale tra interno ed esterno della cellula
- 2 in risposta a segnali interni o esterni

Segnali →

- membrane potential (different electrical potential at the two sides of the membrane)
- membrane current (movement of ions through the membrane)
- intracellular/extracellular ion currents



These are the signals used by the cell to perform all its functions: collecting, processing information, making a decision and propagating it; everything is due to variations in these electrochemical values.

$\text{Na}^+$	$\longrightarrow$	Sodium	(positively charged)
$\text{K}^+$	$\longrightarrow$	Potassium	(positively charged)
$\text{Cl}^-$	$\longrightarrow$	Chlorine	(negatively charged)
$\text{Ca}^{++}$	$\longrightarrow$	Calcium	(positively charged - double valence)

## Electrochemical equilibrium :

diffusional forces: a molecule is pushed from a region with a higher concentration to a region with a lower concentration. It's driven by the kinetic energy of the molecules themselves (temperature → energy)

**electrical forces** : the particles are charged ; positive ions are attracted towards the region with a negative potential and vice versa  
*due to the electrical gradient*

the sum and balance of diffusional and electrical forces leads to an equilibrium.

The electrochemical equilibrium is given by the Nernst equation

$$\text{electrochemical difference} \xrightarrow{\Delta\mu} RT \ln \frac{[X]_A}{[X]_B} + zF(E_A - E_B)$$

$[X]_A$  = ion concentration on the A side of the membrane

$[X]_B$ : ion concentration on the B side of the membrane

$R$  = universal gas constant =  $N_A K_B$  : Avogadro's number · Boltzmann constant

T : temperature im Kelvin

F = Faraday constant

$Z$  = ion valence

$E_A - E_B$  = membrane potential

At rest, ions are not equally distributed across the membrane. This distribution leads to the inside having a more negative charge compared to the outside.

Sodium ( $\text{Na}^+$ ), calcium ( $\text{Ca}^{2+}$ ) and chloride ( $\text{Cl}^-$ ) are concentrated outside of the cell membrane, in the extracellular solution, whereas Potassium ( $\text{K}^+$ ) and negatively charged molecules like amino acids and proteins are concentrated inside the intracellular solution.

**cations** : has more protons than electrons, consequently giving it a net positive charge.

**anions** : has more electrons than protons, consequently giving it a net negative charge.

These concentration differences lead to varying degrees of electrochemical gradients in different directions.

**Equilibrium potential** : membrane potential at which the electrical and chemical gradients for a given ion balance out.

The movement of an ion across the membrane that is not balanced by the movement of a counter ion leads to charge separation across the membrane; this way one side becomes more positive than the other. We have a **potential difference** across the membrane, called **membrane potential**.

We reach the electrochemical equilibrium when the electrical gradient is equal to the chemical gradient and the forces that move the atoms balance and cancel each other out. The membrane potential that is established at equilibrium is said to be the **equilibrium potential** for the considered ion.

We can derive an equation that will allow us to calculate the value of the equilibrium potential for each ion family.

$$\Delta G_{\text{chemical}} = \frac{RT}{zF} \ln \frac{[X_A]_{\text{outside}}}{[X_B]_{\text{inside}}}$$

↑ absolute temperature      ↑ gas constant

$\Delta G_{\text{electrical}} = zFV$

↑ Faraday constant      ↓ voltage  
↓ valence of the ion

gradient and

At equilibrium,  $\Delta G_c$  and  $\Delta G_e$  are equal

$$RT \ln \frac{[X_A]}{[X_B]} = zFV$$

Solving for V

$$(E_x) V = \frac{RT}{zF} \ln \frac{[X_A]}{[X_B]}$$

Nernst equation

Riammuto da fonte diversa:

Membrane potential (membrane voltage) refers to the difference of electric charges across the cell membrane.

Most cells have a negative membrane potential.

Because membrane potential is defined relative to the exterior of the cell, the negative sign means the cell has more negative charges on the inside. Imagine probing the interior and the exterior of a cell with a voltmeter: you take two electrodes and place them on each side of the membrane; we can measure the electrical difference between those two points; if we keep the outer electrode as a reference ( $\phi$ ), the other one can be equal, more positive or more negative with respect to it. This electrical potential difference is called membrane potential. In most resting neurons the potential difference across the membrane is about -30 to -90 mV (most likely -70 mV).

This is called resting potential (= potential when membrane is undisturbed).

Because of this electrical difference, the membrane is said to be polarized.

If the membrane potential becomes more positive than it is at the resting potential, the membrane is said to be depolarized.

If the membrane potential becomes more negative than it is at the resting potential, the membrane is said to be hyperpolarized.

## Membrane potential

It's the difference in electrical potential between the interior of a neuron and the surrounding extracellular fluid.

It is due to different ion concentrations on the two ends of the membrane.

At rest is usually around  $-70 \text{ mV}$

$$-70 \text{ mV} = E_A - E_B$$

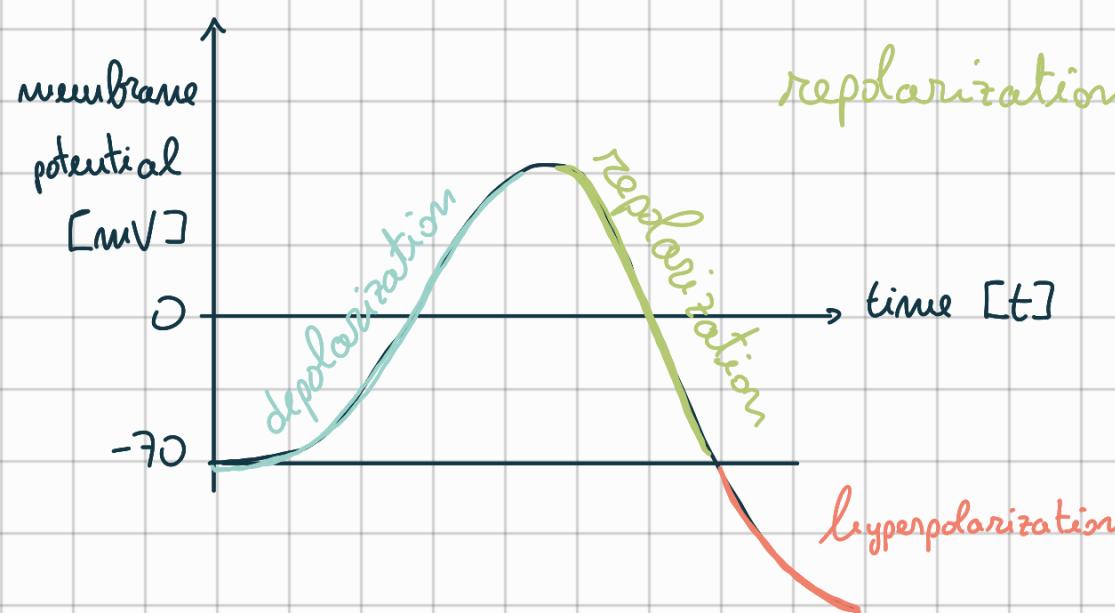
↓ exterior      ↓ interior

after a while (being perturbed) the membrane goes back to this condition.

The cell membrane is said to be **polarized**. The interior of the cell is more negative than the outside.

positively charged ions flowing out  
negatively charged ions flowing in } membrane potential more negative → hyperpolarization

positively charged ions flowing in  
negatively charged ions flowing out } membrane potential more positive → depolarization



repolarization: turning back to normal after depolarization

} the membrane is polarized

depolarization → membrane becomes less negative or even positive

→ positively charged ions flowing in

→ negatively charged ions flowing out

repolarization → going back to the resting potential

→ positively charged ions flowing out

→ negatively charged ions flowing in

hyperpolarization → membrane becomes more negative

→ positively charged ions flowing out

→ negatively charged ions flowing in

The resting membrane potential is determined by the uneven distribution of ions between the inside and the outside of the cell and by the different permeability of the membrane to different type of ions.

The Nernst equation allows us to calculate the potential that will be established across the membrane based on the valence and concentration gradient of the ion. This potential is known as **Nernst potential**

**Nernst potential:** for any given ion family is the membrane potential at which the ionic species is in equilibrium; at equilibrium there is no net movement of the ion across the membrane.

When free to move, ions cross the membrane to reach this state (a specific concentration inside and outside, that leads to a difference in electrical potential between the interior of a neuron and the surrounding extracellular fluid)

$$R \text{ (universal gas constant)} = 8.314 \frac{\text{J}}{\text{K} \cdot \text{mol}}$$

$$T \text{ (temperature in Kelvin)} = \text{usually } 37^\circ \rightarrow K = C^\circ + 273.15$$

$$Z \text{ (valence of the ionic species)} = \begin{array}{l} \text{Na}^+ \longrightarrow +1 \\ \text{K}^+ \longrightarrow +1 \\ \text{Ca}^{2+} \longrightarrow +2 \\ \text{Cl}^- \longrightarrow -1 \end{array}$$

$$F \text{ (Faraday's constant)} = 96.485 \frac{\text{C}}{\text{mol}} \text{ (coulombs per mole)}$$

$X_o/X_A$  = concentration of the ionic species X in the extracellular fluid

$X_i/X_B$  = concentration of the ionic species X in the intracellular fluid

$\Delta\mu = 0$  = electrochemical equilibrium

$$\Delta\mu = RT \ln \frac{[X]_A}{[X]_B} + zF(\bar{E}_A - \bar{E}_B) = 0$$

$$RT \ln \frac{[X]_A}{[X]_B} = -zF(\bar{E}_A - \bar{E}_B)$$

$$\bar{E}_B - \bar{E}_A = E_x = \frac{RT}{zF} \ln \frac{[X]_A}{[X]_B}$$

electrochemical equilibrium potential for ion family X

**Resting potential**: potential at which the membrane is when it's undisturbed

IN CIRCO斯坦ZE NORMALI (temperatura  $\sim 37.5^\circ$ , concentrazione normale degli ioni nei fluidi intra ed extra cellulari, ...) abbiamo:

$$K^+ \rightarrow E_{K^+} = -90 \text{ mV} \quad (\text{milli volt})$$

$$Na^+ \rightarrow E_{Na^+} = 50 \text{ mV} \quad //$$

$$Ca^{++} \rightarrow E_{Ca^{++}} = 150 \text{ mV} \quad //$$

} valori di potenziale elettrico per cui ciascuno ione raggiunge l'equilibrio.

Ions with an equilibrium voltage equal to  $E_x$ , when free to cross the membrane, will flow with net currents that move the membrane potential to that value

If the ion in question is K<sup>+</sup>, the Nernst equilibrium potential for K<sup>+</sup> (V<sub>K</sub>) will be:

$$V_K = \frac{\cancel{RT}}{(+1)\cancel{F}} \ln \frac{[K^+]_o}{[K^+]_i} \quad \text{Eq. 7}$$

8.314      273.15  
?                  ?  
96.485

If the ion in question is Na<sup>+</sup>, the Nernst equilibrium potential for Na<sup>+</sup> (V<sub>Na</sub>) will be:

$$V_{Na} = \frac{RT}{(+1)F} \ln \frac{[Na^+]_o}{[Na^+]_i} \quad \text{Eq. 8}$$

If the ion in question is Ca<sup>2+</sup>, the Nernst equilibrium potential for Ca<sup>2+</sup> (V<sub>Ca</sub>) will be:

$$V_{Ca} = \frac{RT}{(+2)F} \ln \frac{[Ca^{2+}]_o}{[Ca^{2+}]_i} \quad \text{Eq. 9}$$

If the ion in question is H<sup>+</sup> (hydrogen ion or proton), the Nernst equilibrium potential for H<sup>+</sup> (V<sub>H</sub>) will be:

$$V_H = \frac{RT}{(+1)F} \ln \frac{[H^+]_o}{[H^+]_i} \quad \text{Eq. 10}$$

If the ion in question is Cl<sup>-</sup>, the Nernst equilibrium potential for Cl<sup>-</sup> (V<sub>Cl</sub>) will be:

$$V_{Cl} = \frac{RT}{(-1)F} \ln \frac{[Cl^-]_o}{[Cl^-]_i} \quad \text{Eq. 11}$$

If the ion in question is HCO<sub>3</sub><sup>-</sup> (bicarbonate), the Nernst equilibrium potential for HCO<sub>3</sub><sup>-</sup> (V<sub>HCO3-</sub>) will be:

$$V_{HCO_3} = \frac{RT}{(-1)F} \ln \frac{[HCO_3^-]_o}{[HCO_3^-]_i} \quad \text{Eq. 12}$$

If the ion in question is SO<sub>4</sub><sup>2-</sup>, the Nernst equilibrium potential for SO<sub>4</sub><sup>2-</sup> (V<sub>SO4--</sub>) will be:

$$V_{SO_4} = \frac{RT}{(-2)F} \ln \frac{[SO_4^{2-}]_o}{[SO_4^{2-}]_i} \quad \text{Eq. 13}$$

and so on.

Esempio:

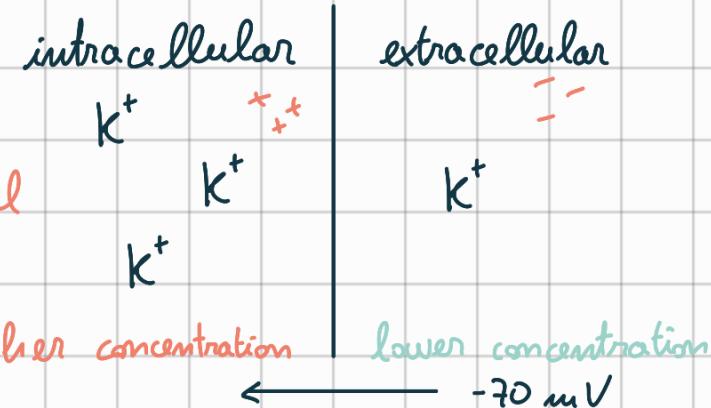
in a point in time, resting potential = -70 mV

1. Potassium ions, when free to move, will try to bring the membrane to -90 mV
2. Sodium ions, when free to move, will try to bring the membrane to 50 mV
3. Calcium ions, when free to move, will try to bring the membrane to 150 mV
4. Chloride ions, when free to move, will try to bring the membrane to -60 mV

1. Potassium:

$$E_{K^+} = -90 \text{ mV} < -70 \text{ mV}$$

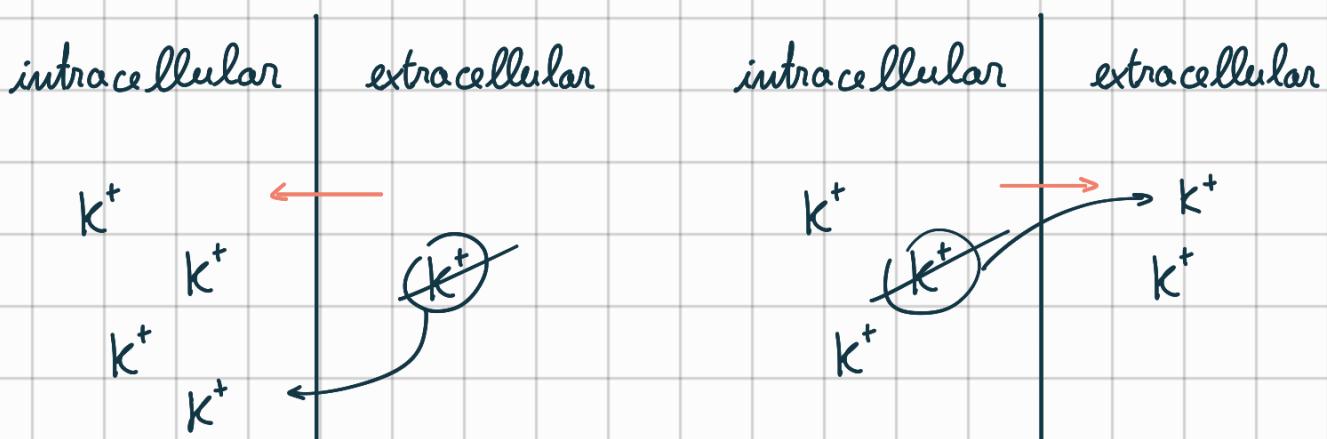
Resting potential



Se gli ioni di potassio si spostano da dentro la cellula a fuori ( $i \rightarrow e$ ) l'interno della cellula sarà più negativo

Se gli ioni di potassio si spostano da fuori la cellula a dentro ( $i \leftarrow e$ ) l'interno della cellula sarà più positivo

Mai dobbiamo ottenere un interno più negativo

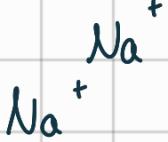


$-90 \text{ mV} < -70 \text{ mV} \rightarrow$  devono raggiungere un potenziale minore all'interno della membrana, quindi gli ioni devono muoversi **dall'interno all'esterno**

## 2. Sodium :

$$E_{Na^+} = 50 \text{ mV} > -70 \text{ mV}$$

intracellular      extracellular



=-

higher concentration



lower concentration

-70 mV

$$E - i < 0 \rightarrow E < i$$

intracellular

extracellular

intracellular

extracellular

interno

esterno

intracellular

esterno

diventa  $\text{Na}^+$

diventa  $\text{Na}^+$

$\text{Na}^+$

diventa  $\text{Na}^+$

più

più

più

positivo  $\text{Na}^+$

negativo

positivo  $\text{Na}^+$

$\text{Na}^+$



←

→

→

→

←



$50 \text{ mV} > -70 \text{ mV} \rightarrow$  devono raggiungere un potenziale maggiore all'interno della membrana, quindi gli ioni devono muoversi **dall'esterno all'interno**

da  $-70$  deve arrivare a  $+50$

## 3. Calcium :

$$E_{Ca^{++}} = 150 \text{ mV}$$



$> -70 \text{ mV}$

da  $-70$  a  $+150$

ione con carica positiva: aumenta il potenziale elettrico della zona in cui si sposta

da  $-70$  dobbiamo salire a  $150$ .

Ioni positivamente carichi devono entrare, ioni negativamente carichi devono uscire

gli ioni si spostano **dall'esterno all'interno**

## L. Chloride

$$E_{Cl^-} = -60 \text{ mV} > -70 \text{ mV}$$

Resting potential = -70 mV

Gli ioni devono spostarsi

per fare in modo che il  
potenziale arrivi a -60 mV

$$-60 \text{ mV} > -70 \text{ mV}$$

Dobbiamo far salire il potenziale

$$\text{Essendo } E = E_i - E_o = -70$$

$$E_i - E_o = T$$

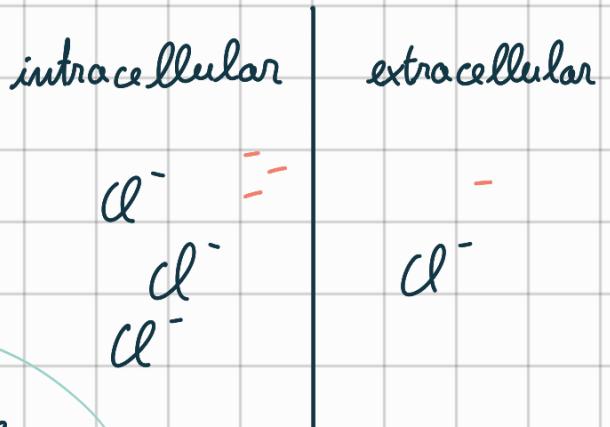
$$E'_i > E_i \rightarrow T' > T \quad \text{increasing potential}$$

$$E'_i < E_i \rightarrow T' < T \quad \text{decreasing potential}$$

$$E'_o > E_o \rightarrow T' < T \quad \text{decreasing potential}$$

$$E'_o < E_o \rightarrow T' > T \quad \text{increasing potential}$$

$$i - e < 0 \\ i < e$$



Per avere un incremento di potenziale :

1. interno più carico
2. esterno meno carico

vuol dire che  
alcune cariche  
negative escono  
o alcune  
cariche positive  
entrono. Abbiamo  
cariche negative  
 $Cl^-$   
 $\hookrightarrow$  escono

Gli ioni hanno valenza negativa ( $Cl^-$ ) quindi devono spostarsi dall'interno della cellula all'esterno, così le cariche negative si spostano fuori (interno meno carico, esterno più carico)  $\rightarrow$  aumento potenziale.

Gli ioni si spostano **dall'interno all'esterno**

$\text{Na}^+$  esterno  $\rightarrow$  interno

$\text{K}^+$  interno  $\rightarrow$  esterno

$\text{Ca}^{++}$  esterno  $\rightarrow$  interno

$\text{Cl}^-$  interno  $\rightarrow$  esterno

*chemical gradient*  
*passive*

diffusional forces : a molecule is pushed from a region with an higher concentration to a region with a lower concentration. It's driven by the kinetic energy of the molecules themselves (temperature  $\rightarrow$  energy)

*electrical gradient*  
*passive*

electrical forces : the particles are charged; positive ions are attracted towards the region with a negative potential and vice versa

*active*

ion pumps : they move ions against their electrochemical gradient by active (energy consuming) transport. The most important one is the sodium-potassium pump  
 $ATP \rightarrow ADP$

Rest potential : diffusional forces + (passive)  
electrical forces + (passive)  
ion pumps (active)

Questo permette al sistema di cambiare attivamente stato e di reagire a stimoli.

## Collecting information

Specific functions are associated to specific structures. Collecting information is performed by the **dendritic tree**. We can have different shapes of this part of the cell, depending to the cell position in the brain and its role. Usually the dendritic tree has a large surface because it needs to collect a lot of informations from many different sources (**1-100 thousands inputs per cell**). The membrane performs an integration on these input signals.

**1000 - 100.000 inputs per cell**

e.g. pyramidal dendritic tree for cortical neurons

# Synapses

There are two kinds of synapses

electrical synapses  
chemical synapses

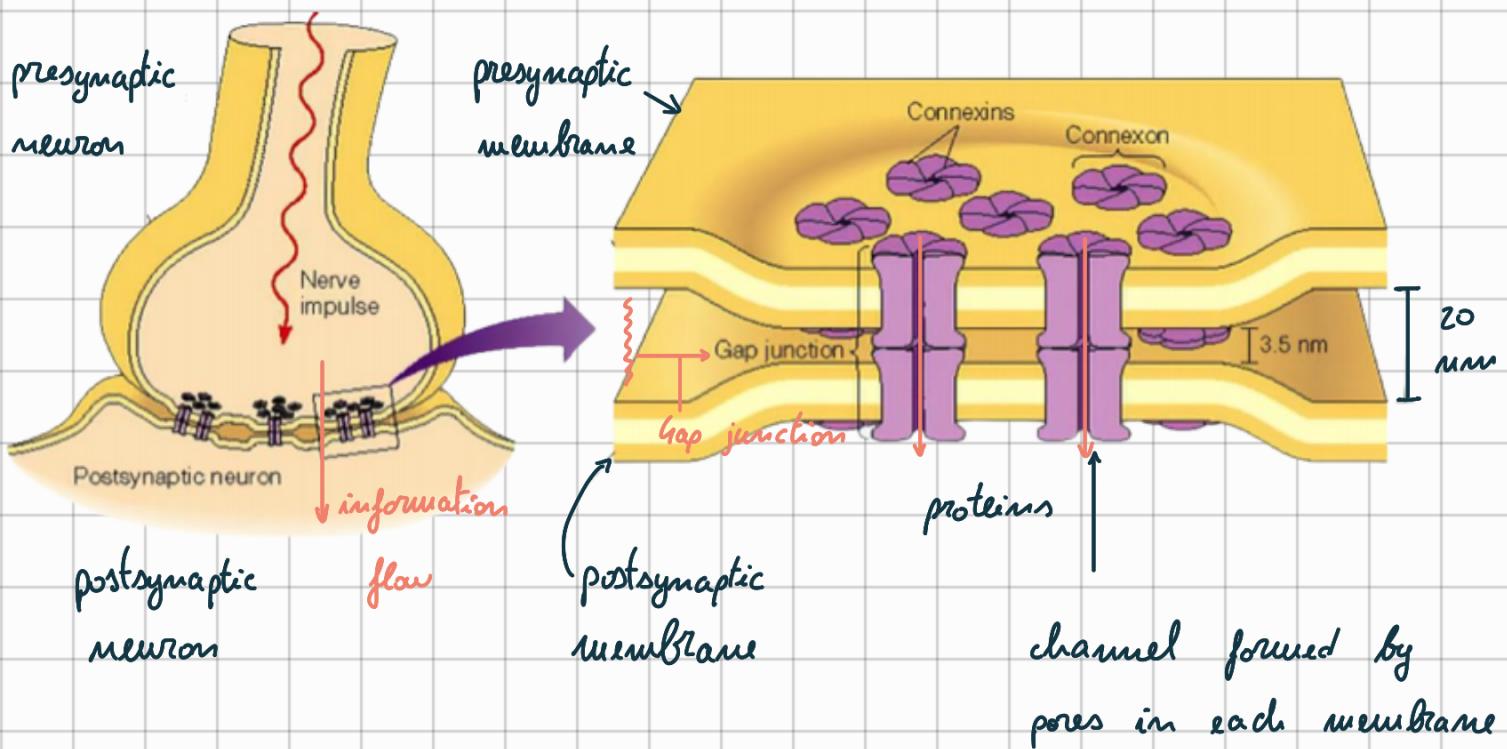
With the electrical synapses we have 3 electrical signals:

membrane potential

membrane current

intracellular/extracellular current

These signals regulate the cell behavior.



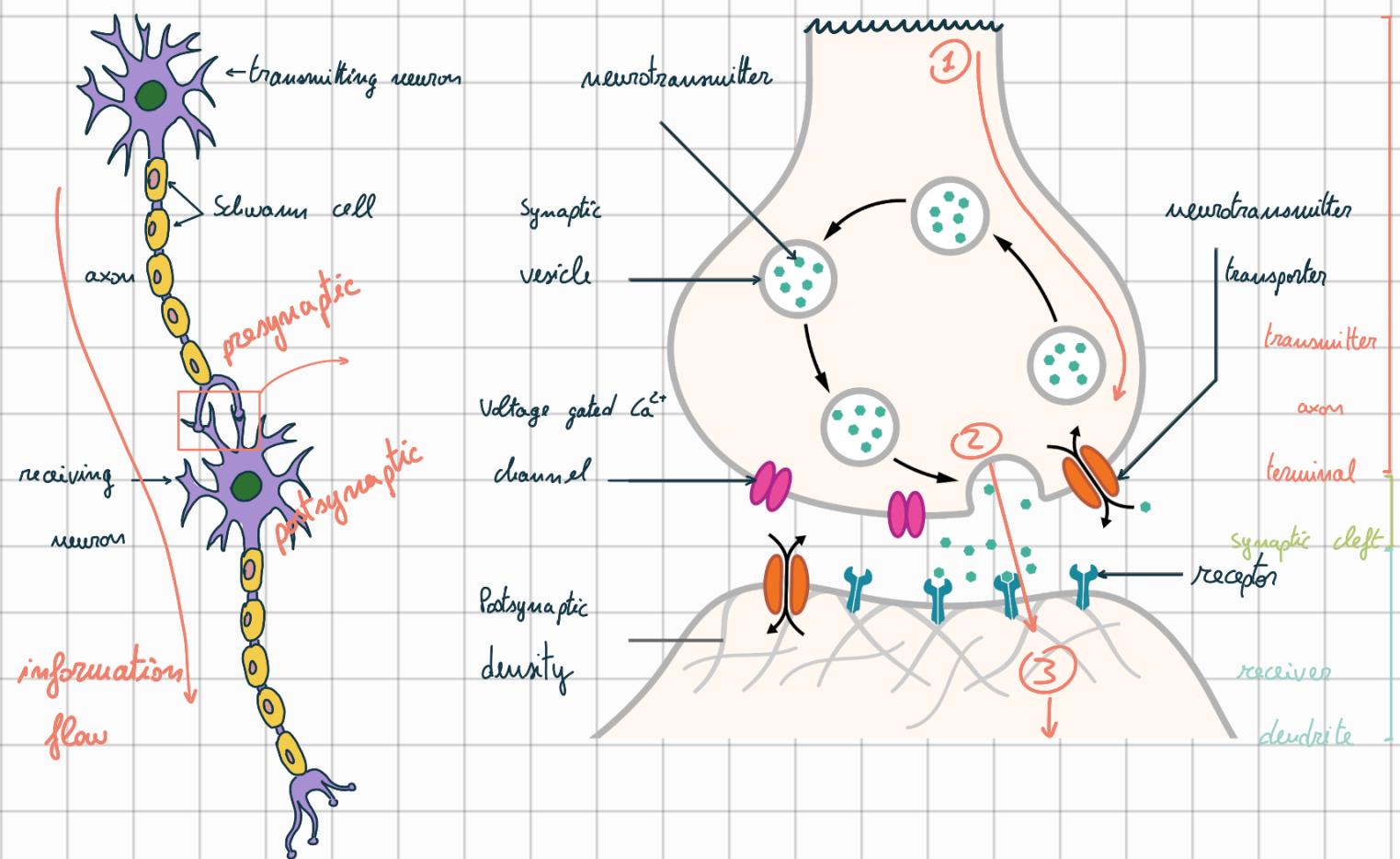
We have a cell **sending information** and a cell **receiving information**

**sending** → presynaptic neuron

**receiving** → postsynaptic neuron

Once a perturbation arrives in a presynaptic cell it's transmitted to the postsynaptic cell in the form of an electrical signal → **ion currents**  
through proteins called **connexons**

most common synapses in our brain are the chemical synapses, much more complex



In a chemical synapses the information is exchanged by means of chemical transmitters (molecules)

- ① electrical signal (information) arriving to the axon terminal in form of a variation in the membrane potential (ion currents)
- ② electrical information transduced into chemical information
- ③ chemical signal received by the other cell and again transduced into an electrical signal

This is slower than the transmission mechanism in electrical synapses but allows for variations in the transmission of the information.

More complicated but also more flexible.

We can have structural changes in big time intervals (e.g. months) but in short periods of time we can only have functional changes (signal dimmed)

in electrical synapses the two cells needs to touch each other, in chemical synapses that's not the case → **synaptic cleft**

gli ioni vengono rilasciati nella synaptic cleft. Dell'altra parte, sulla membrana cellulare dei dendriti riceventi, ci sono delle strutture, i **recessori (receptors)** che sono praticamente delle pompe per gli ioni controllate chimicamente (*chemically controlled ion channels*).

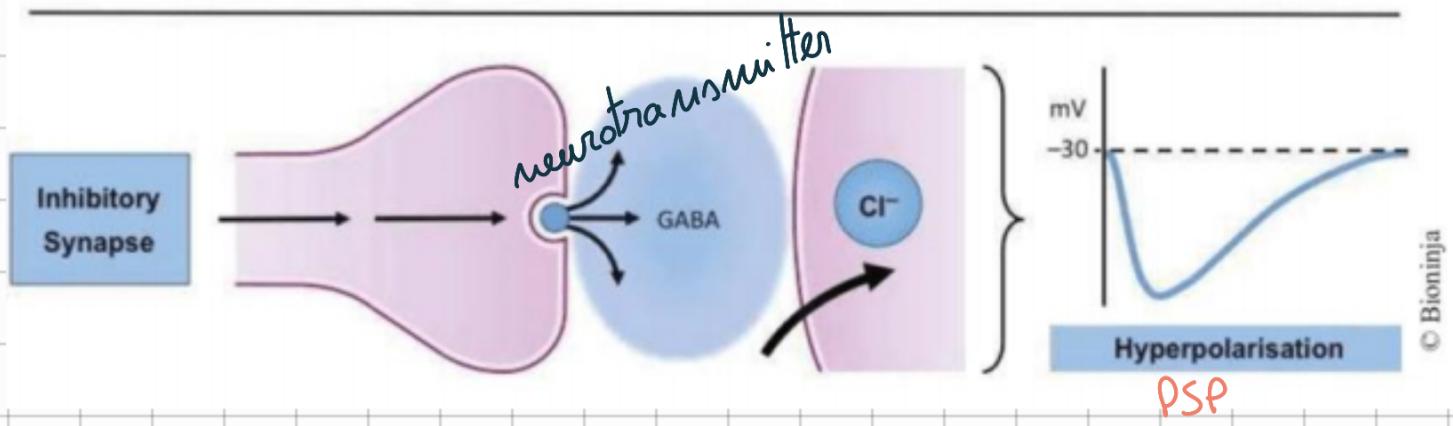
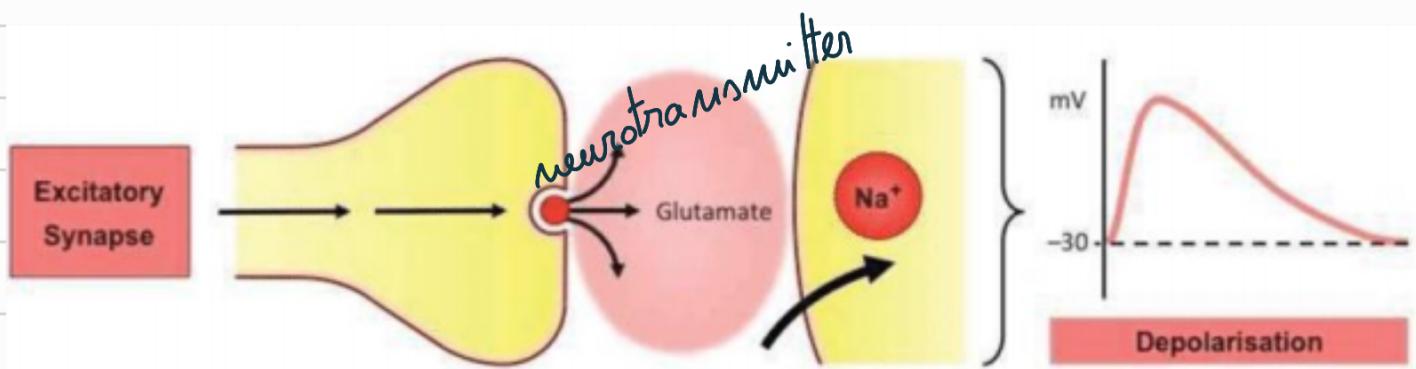
ion channel = protein allowing the passage of ions through it under specific circumstances. They are usually specific for each ion family. They are normally closed, but they can open when a specific molecule binds to them (**neurotransmitter**); this allows for passive ion movement (according to Nernst equation).

Con il flusso di ioni dal neurone presinaptico a quello post-sinaptico, cambia la concentrazione di cariche elettriche



dipende da che ione attraversa il synaptic cleft  
In base a questo le sinapsi possono essere classificate in:

- excitatory
- inhibitory



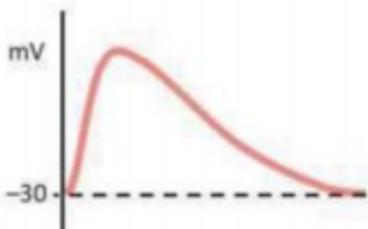
According to the nature of the channels on the receiving side we can have these two reactions (inhibitory or excitatory).

- $\text{Na}$  channel  $\rightarrow$  depolarizing  $\rightarrow$  excitatory synapse
- $\text{Cl}$  channel  $\rightarrow$  hyperpolarizing  $\rightarrow$  inhibitory synapse
- $\text{K}$  channel  $\rightarrow$  depolarizing  $\rightarrow$  excitatory synapse
- $\text{Ca}$  channel  $\rightarrow$  depolarizing  $\rightarrow$  excitatory synapse

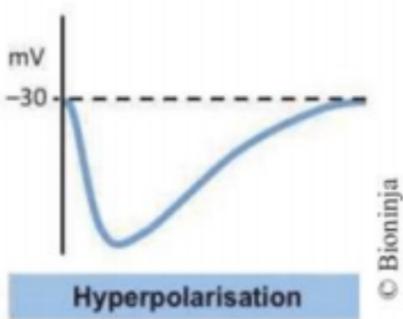
**Post Synaptic Potential** : variation in potential of the post synaptic membrane as a result of the exchange of information between the two cells.

After a while, the neurotransmitter is no longer linked to the ion channels and is absorbed by the presynaptic axon  
 $\rightarrow$  the channels close and ions are no longer free to move between the two cells

When the channels close, the postsynapse potential is at a different level (postsynaptic potential)



Excitatory Post Synaptic Potential (EPSP)



Inhibitory Post Synaptic Potential (IPSP)

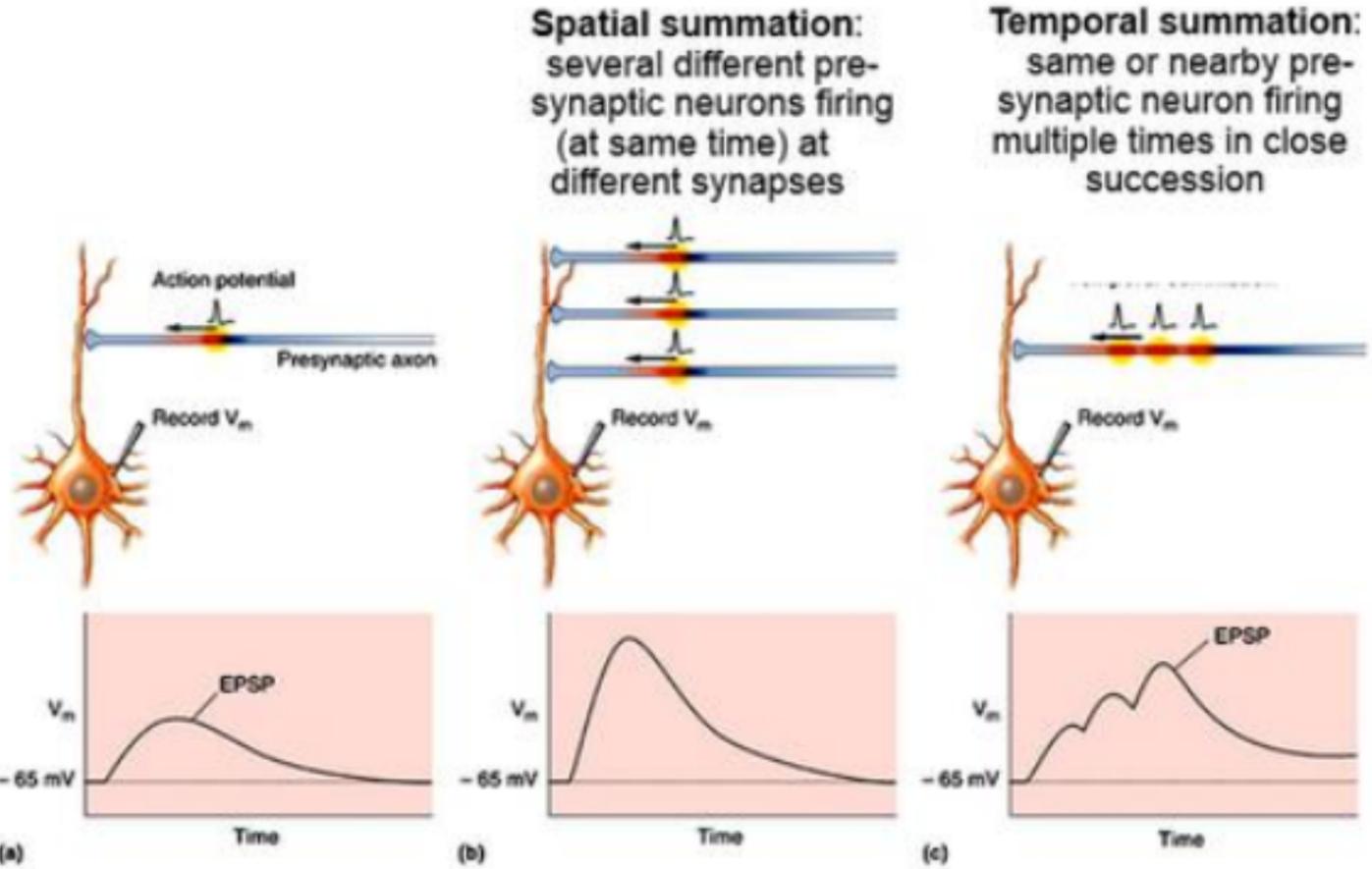
© Bioninja

neuronal response (post) is **excited** or **inhibited**

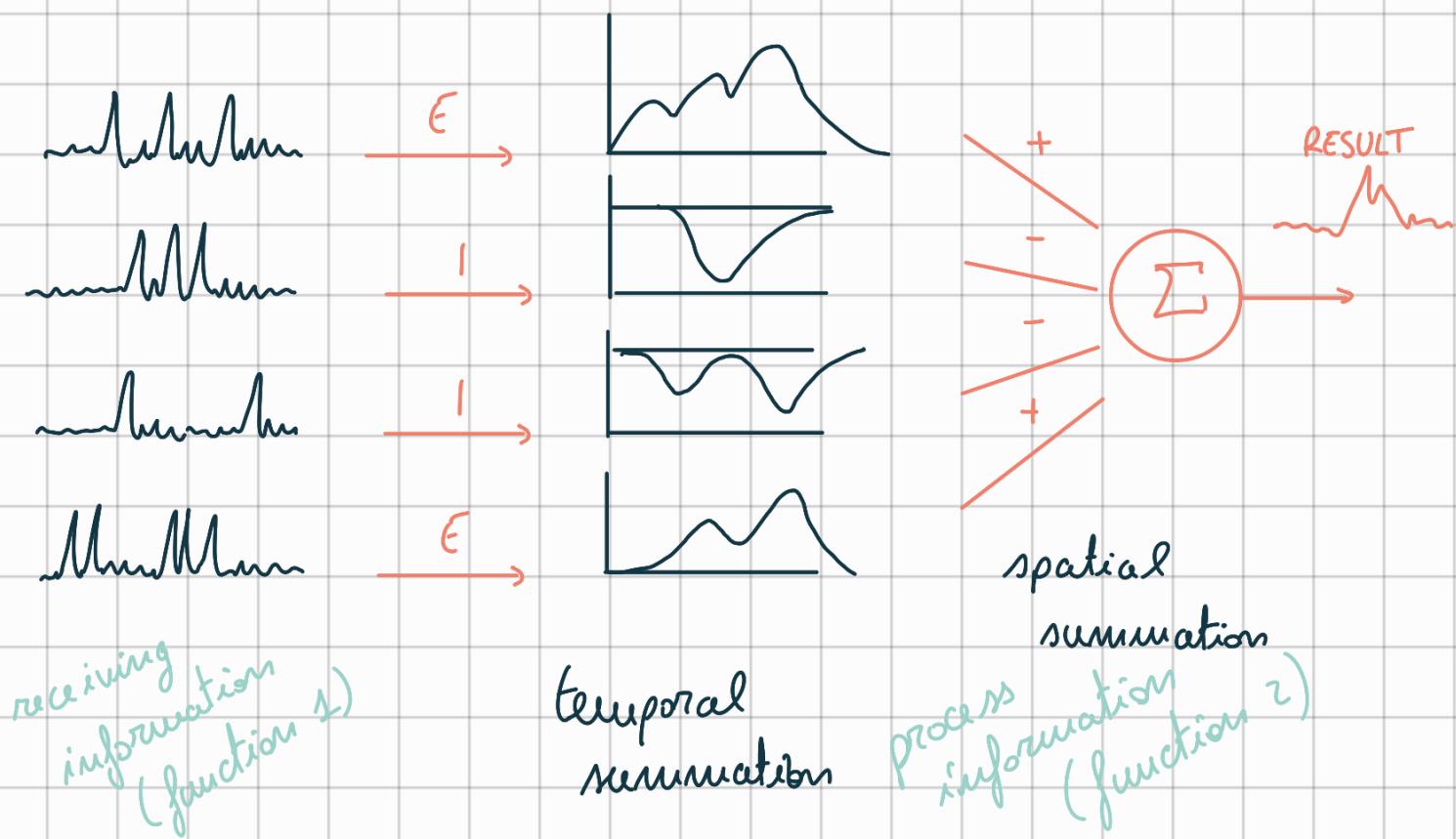
PSP are summed up

different site

same site



They can even cancel each other



Neurotransmitters are the molecules used by the nervous system to transmit messages (information) between neurons, or from neurons to muscles.

Communication between two neurons happens in the synaptic cleft. Here, electrical signals that have traveled along the axon are briefly converted into chemical ones through the release of neurotransmitters, causing a specific response in the receiving neuron.

Whether a neurotransmitter is excitatory or inhibitory depends on the receptor it binds to.

Inhibitory → GABA neurotransmitter

Excitatory → glutamate

Neurotransmitters are synthesized in and released from the axon ending (?) into the synaptic cleft

↓  
axon terminal

The information that the post-synaptic neuron needs to process consists of the summation of EPSPs and IPSPs

How the integration turns into a binary response?

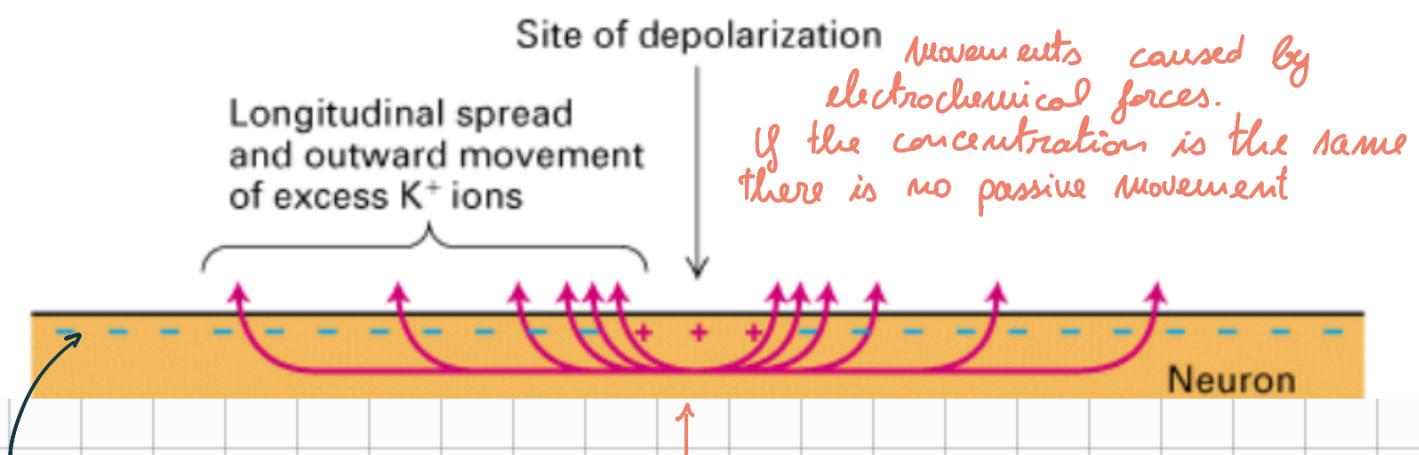
What happens to the dendrites needs to be propagated to the rest of the cell.

Spatial + temporal summation produce the membrane depolarization / hyperpolarization. The result of the integration needs to reach the **axon hillock**, where special structures are located; the signal is propagated along the membrane to the axon hillock.

According to the signal, the cell may or may not fire an **action potential**.

The axon hillock is different with respect to the dendrites.

The propagation to the axon hillock occurs by means of intracellular and extracellular currents. Currents are the result of a perturbation

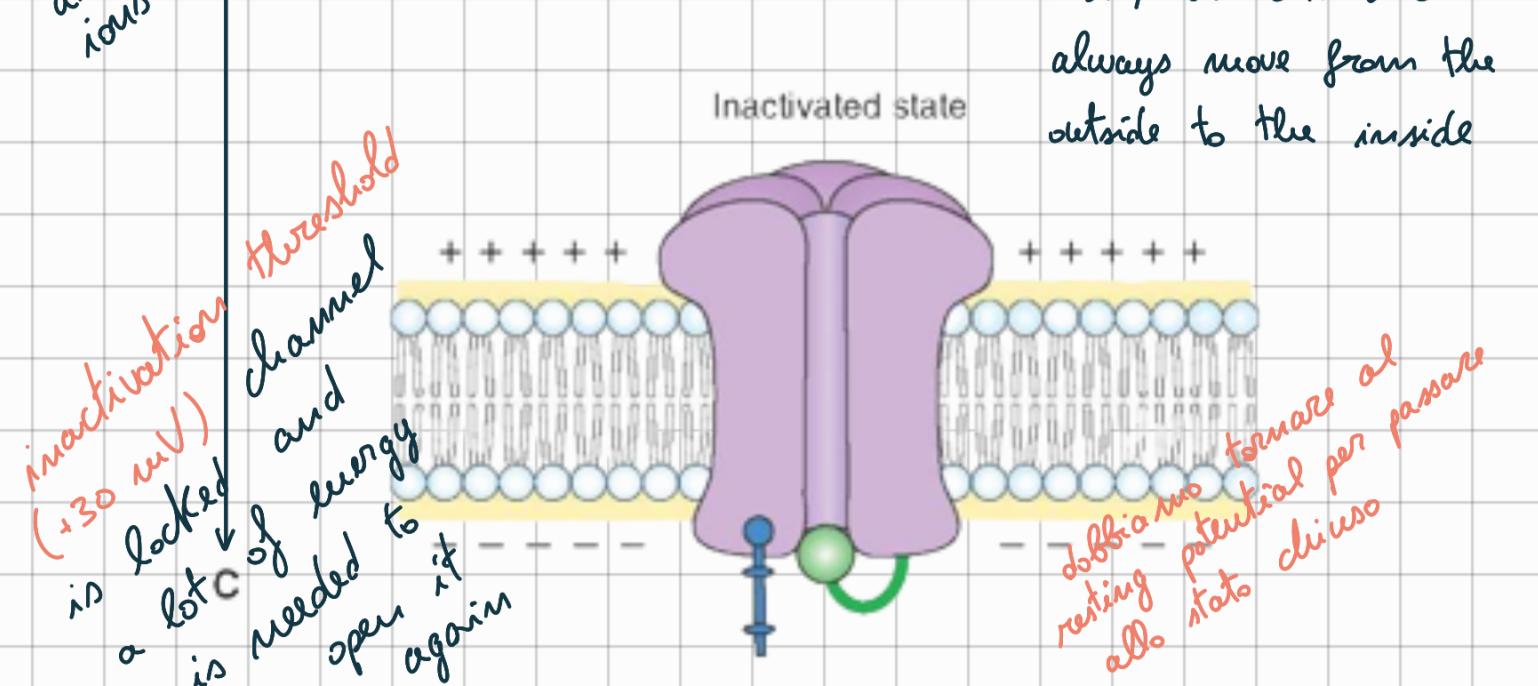
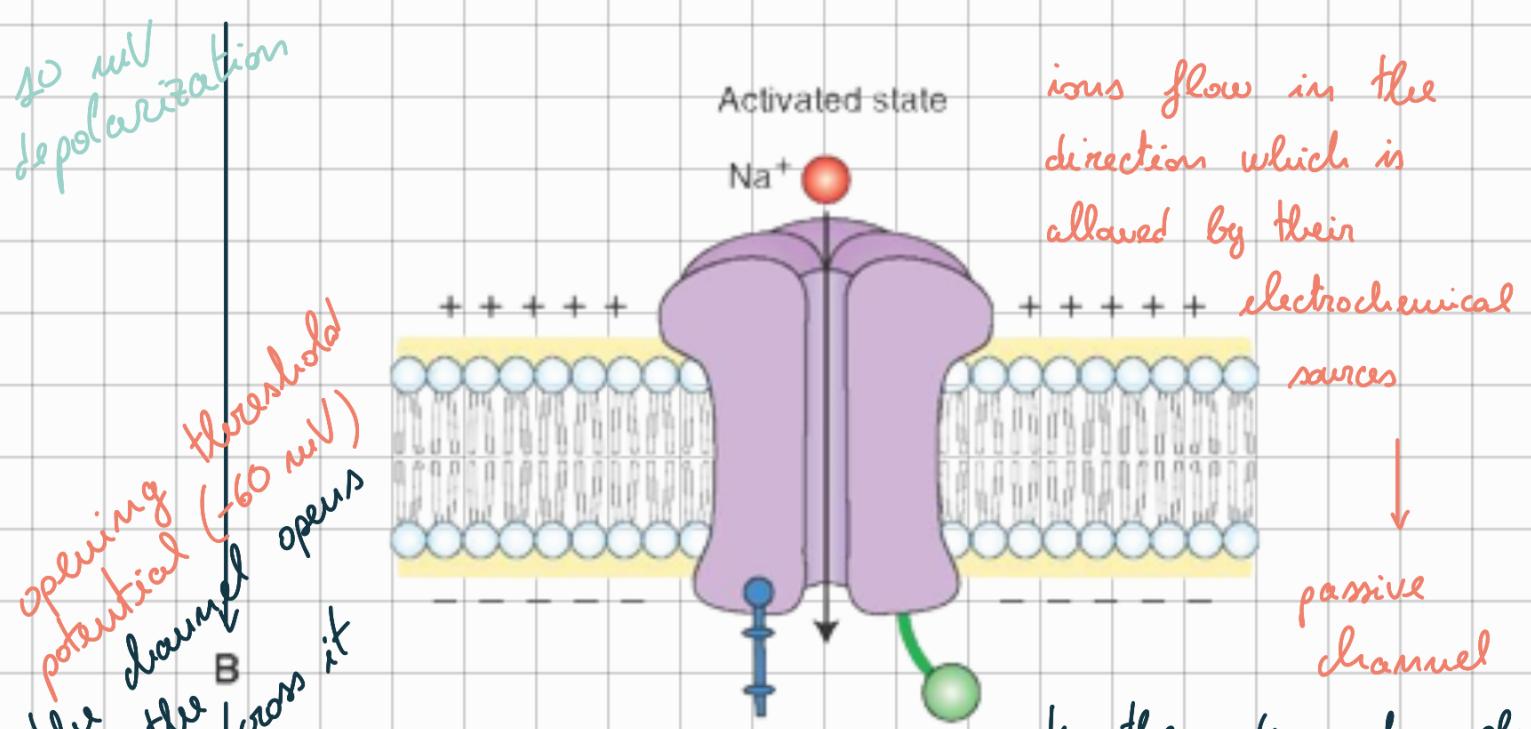
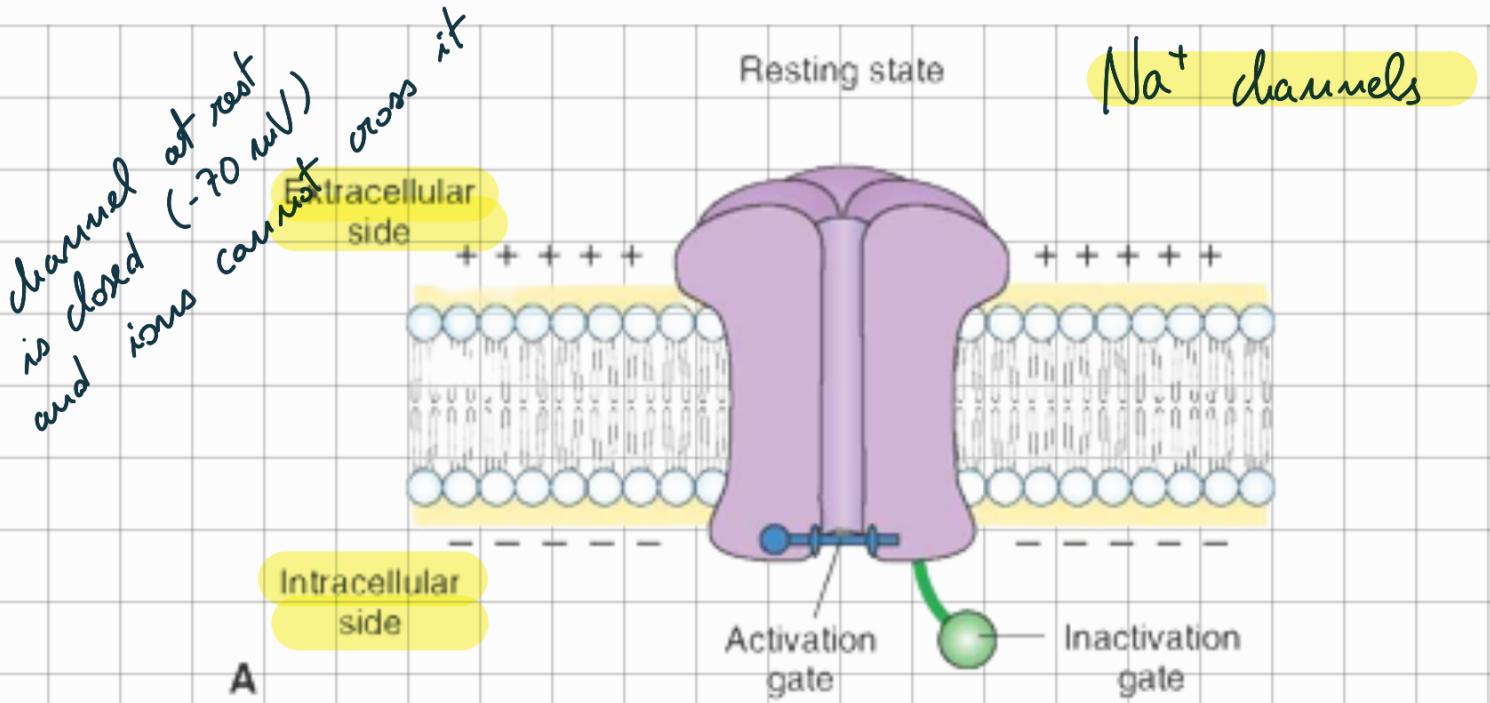


normally the inside of the cell is more negative than the outside  
What happens inside is reciprocal to what happens outside

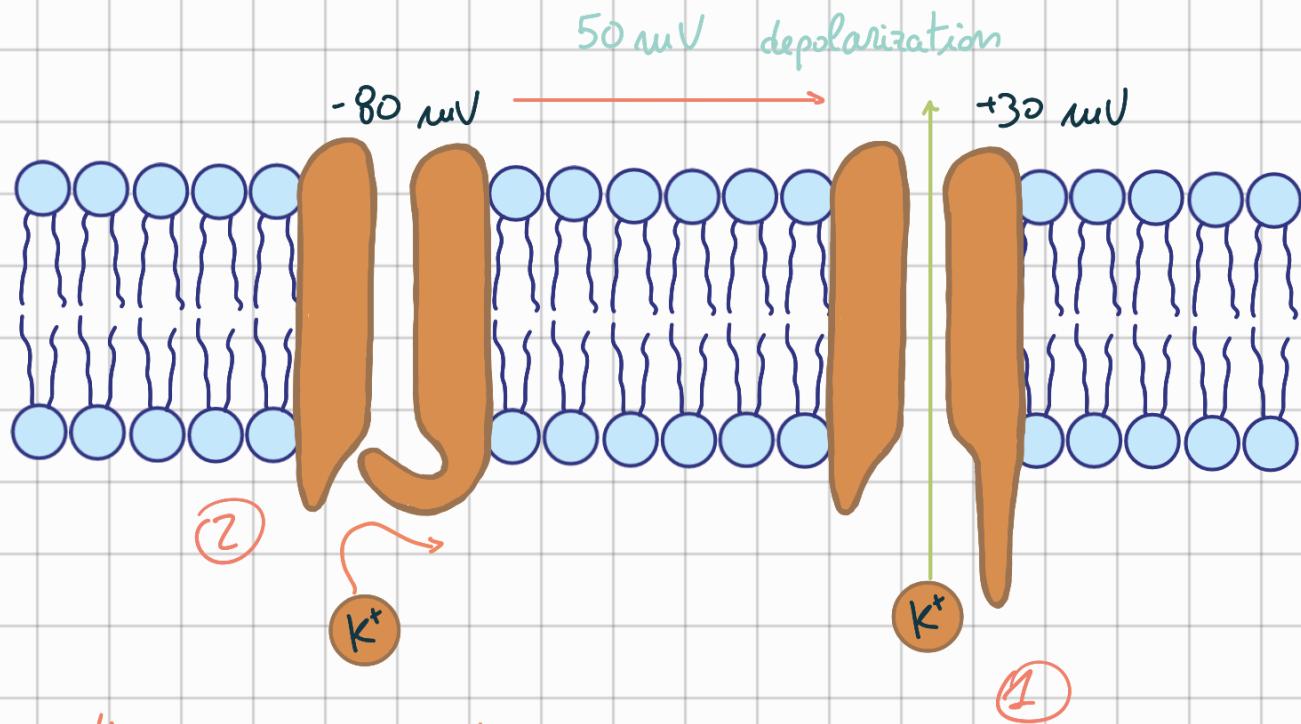
→ inner more negative → outer more positive

after a certain period the perturbation fades out

This kind of propagation can only cover short distances



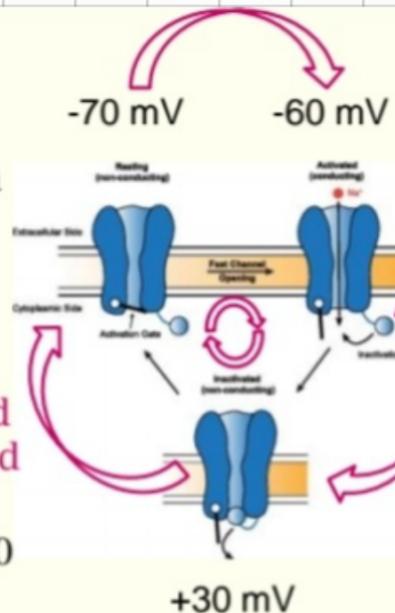
## $K^+$ channels



sotto il resting potential  
è chiuso

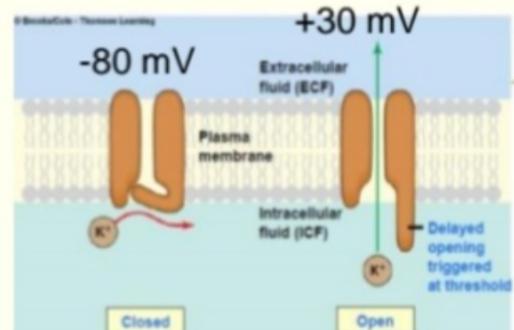
## $Na^+$ channel

- Resting potential ( $-70 \text{ mV}$ ) = **closed** (ions cannot cross it, it can be open)
- Opening threshold potential ( $-60 \text{ mV}$ ) = open**, ions can cross
- Inactivation threshold ( $+30 \text{ mV}$ ) = **inactivated** (it cannot be open)
- Closing threshold ( $-70 \text{ mV}$ ) = closed** (ions cannot cross, it can be open)



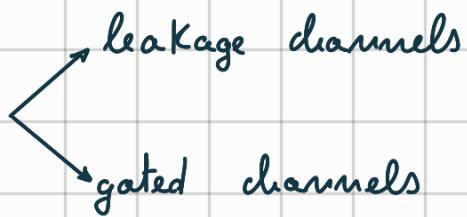
## $K^+$ channel

- Resting potential ( $-70 \text{ mV}$ ) = **closed** (ions cannot cross it, it can be open)
- Opening threshold potential ( $+30 \text{ mV}$ ) = **open**, ions can cross
- Closing threshold ( $-70 \text{ mV}$ ) = **closed** (ions cannot cross, it can be open)



## Ion channels

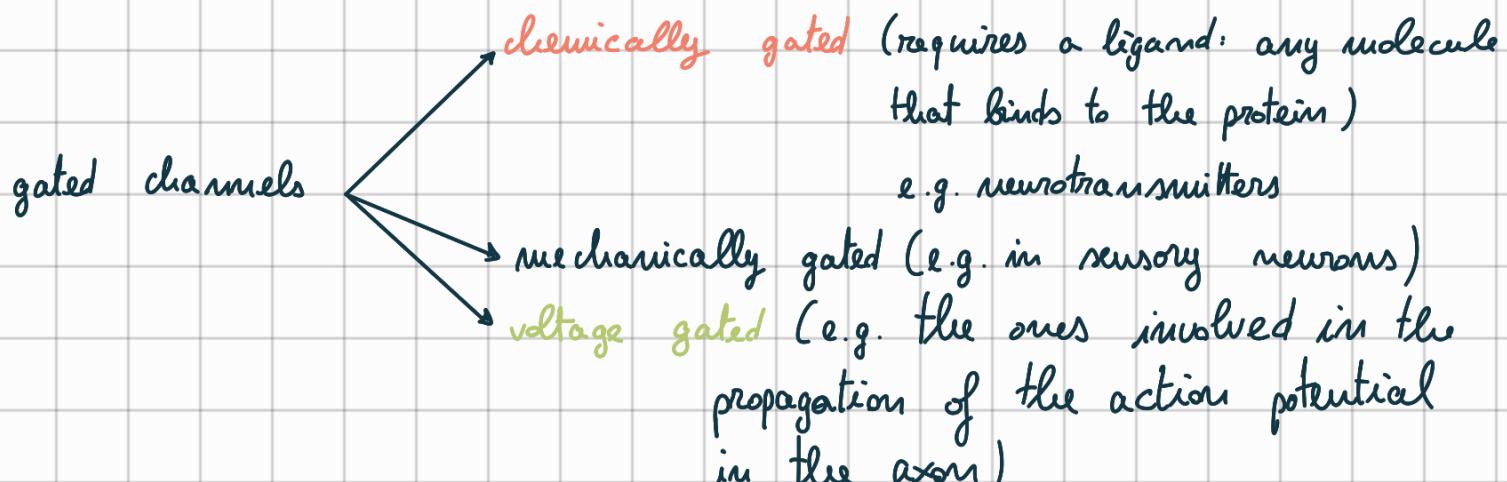
two basic types of ion channels



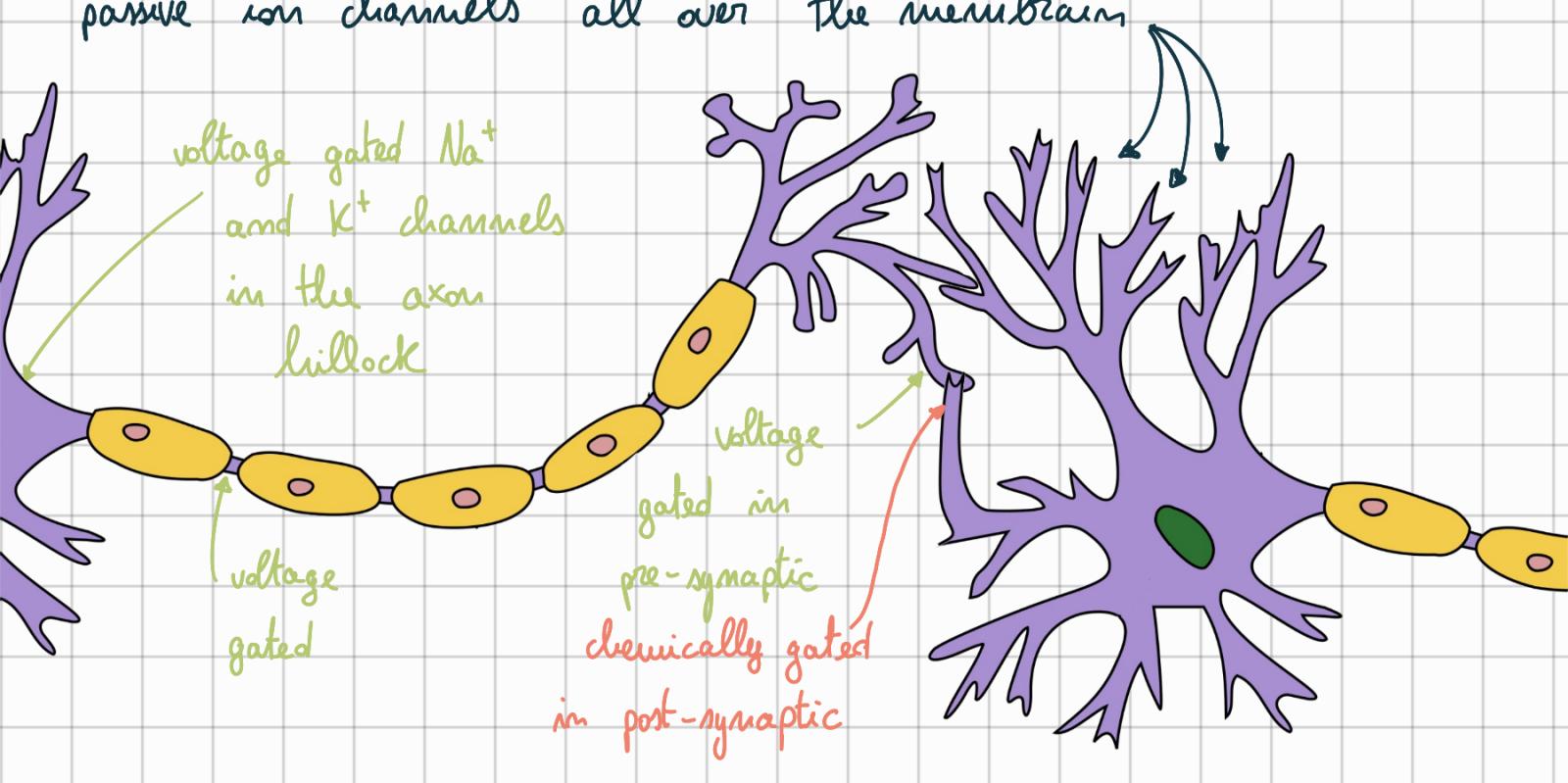
leakage channels are essentially opened all the time and allow ion movement derived by diffusional and electrical forces.

gated channels open and close in response to specific electrical, chemical and/or mechanical signals.

gating : open → close / close → open (transition)



passive ion channels all over the membrane



Second function  
of the cell

{ temporal summation  
spacial summation  
propagation to axon hillock

third function  
of the cell

What happens next?

There are special structures, able to produce the **action potential**.  
action potential = output of a neuron

resting potential → potential at rest

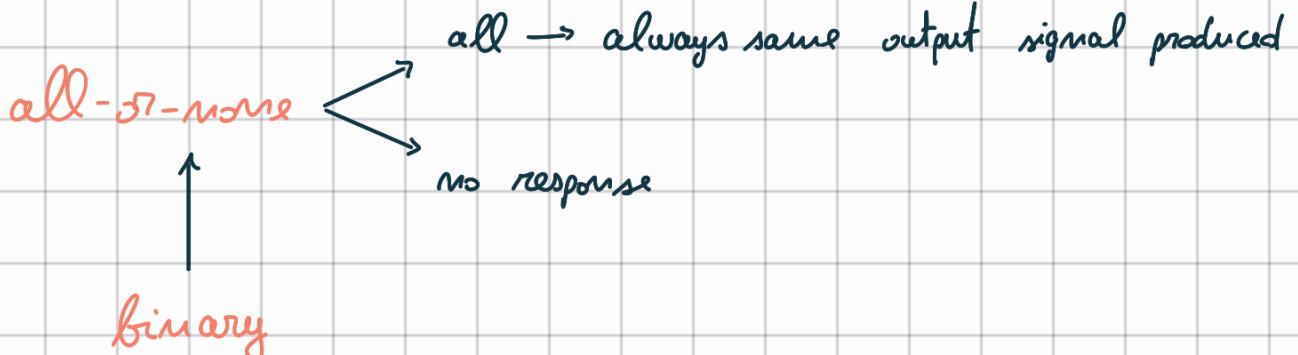
postsynaptic potential → potential after stimulus by input signal

action potential → output of the cell

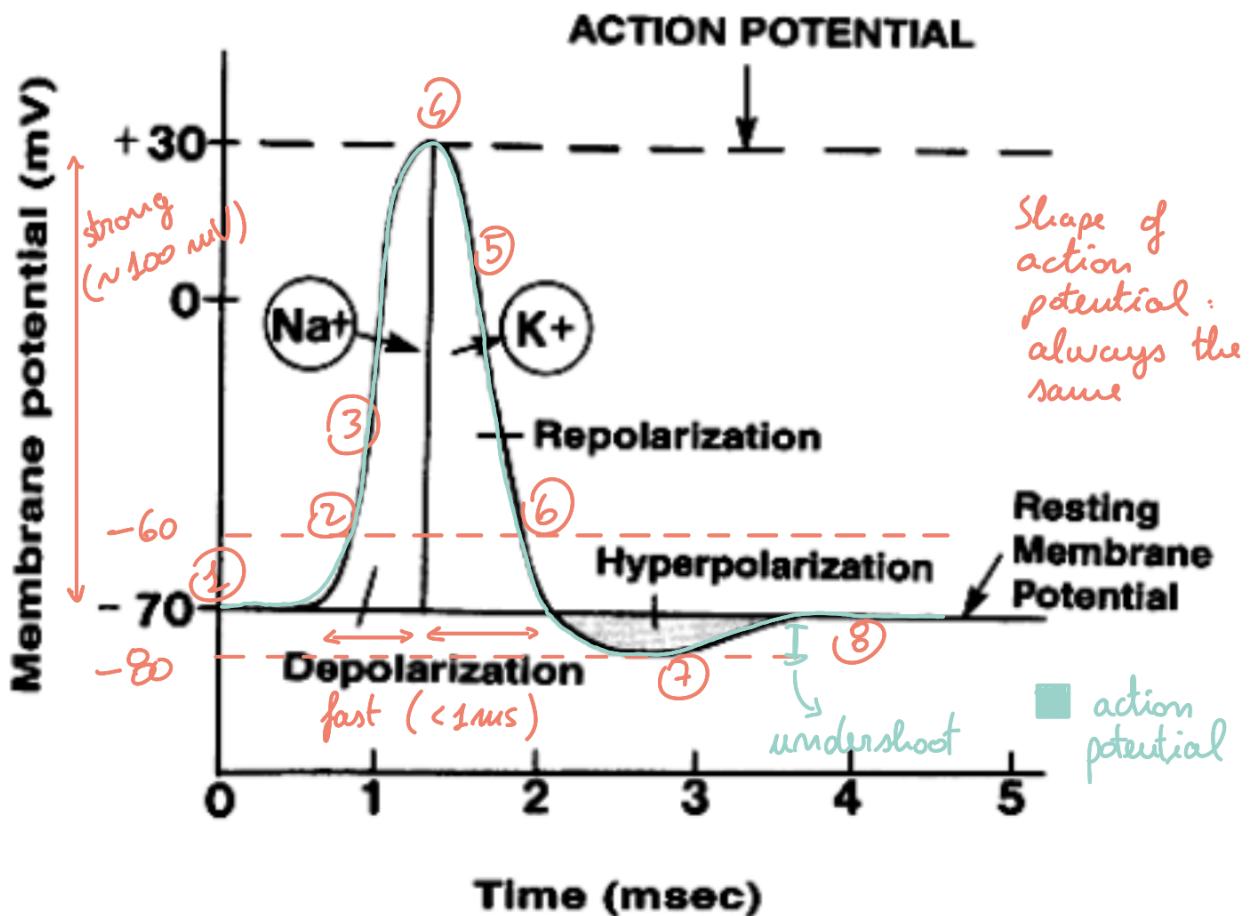
Only in neural, muscular and cardiac cells we have such action potential. Those are called **excitable cells**.

The action potential is different from other kinds of potential because of its **all-or-none** nature:

- if the stimulus does not reach a given **threshold**, it does not happen
- if the **threshold** is reached, the produced signal always have the same shape, duration and intensity.



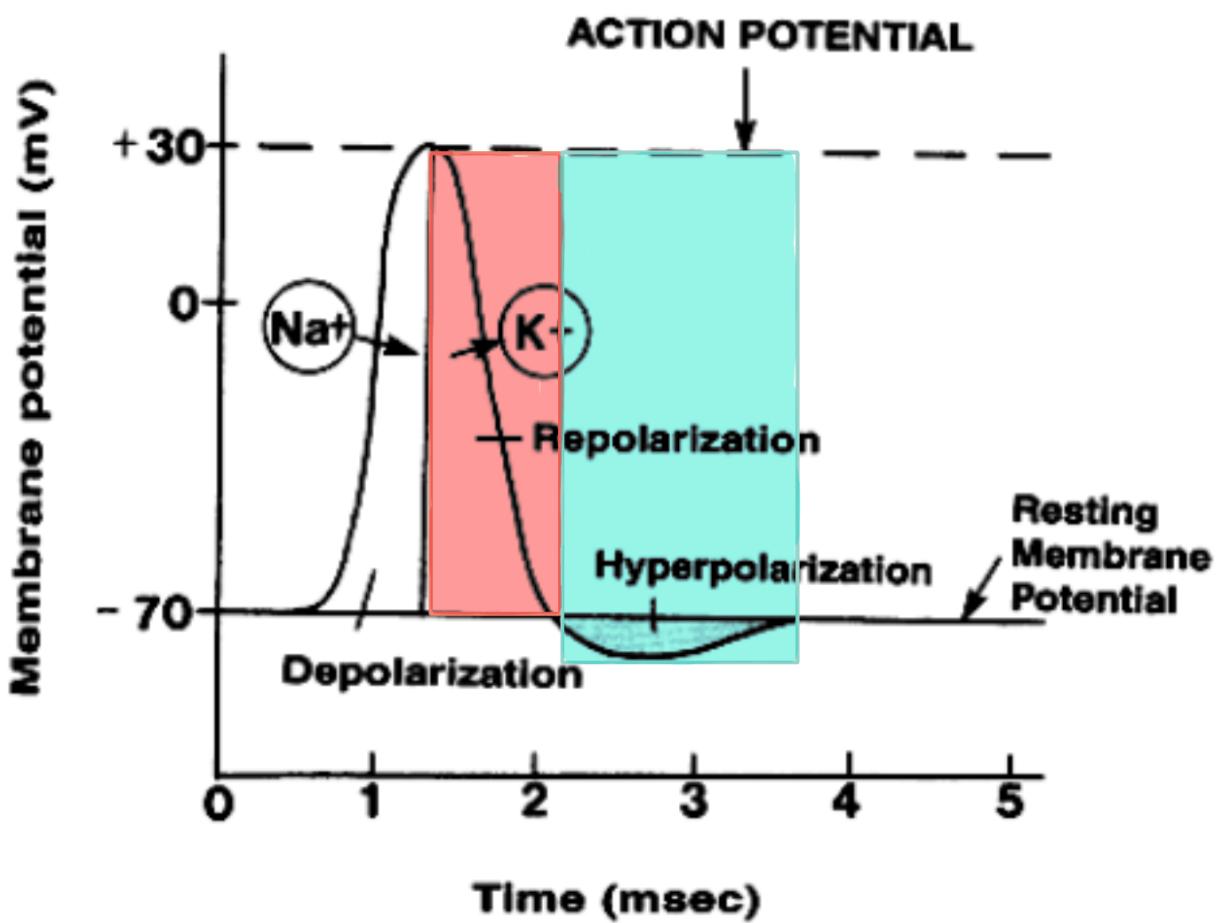
## Generation of action potential



variation of membrane potential over time = action potential

- ① start at resting potential
- ② depolarization leads to surpass the threshold:  $\text{Na}^+$  channels are opened
- ③ fast depolarization due to  $\text{Na}^+$  depolarizing currents ( $\text{Na}^+$  flows into the cell)
- ④ inactivation of  $\text{Na}^+$  channels and opening of  $\text{K}^+$  channels at +30 mV
- ⑤ repolarization ( $\text{K}^+$  flows out the cell)
- ⑥ reached rest potential (-70 mV)  $\text{Na}^+$  channels are closed
- ⑦ hyperpolarization; reaching -80 mV  $\text{K}^+$  channels are closed
- ⑧ back to resting potential;  $\text{Na}^+$  channels are closed but can open again

in attivano le pompe sodio-potassio per tornare a -70



### Absolute refractory period

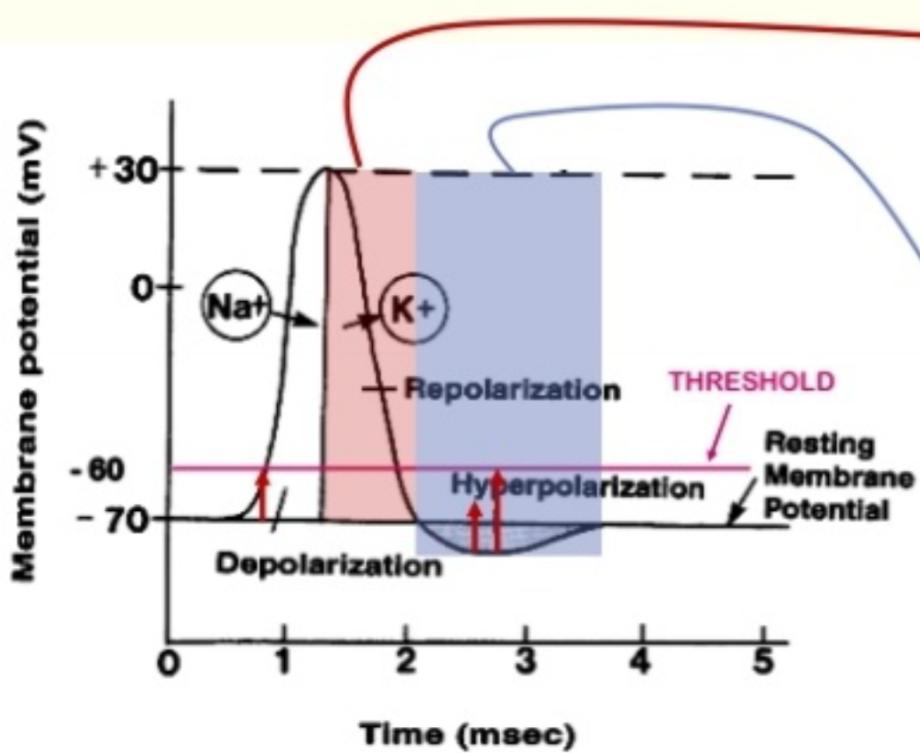
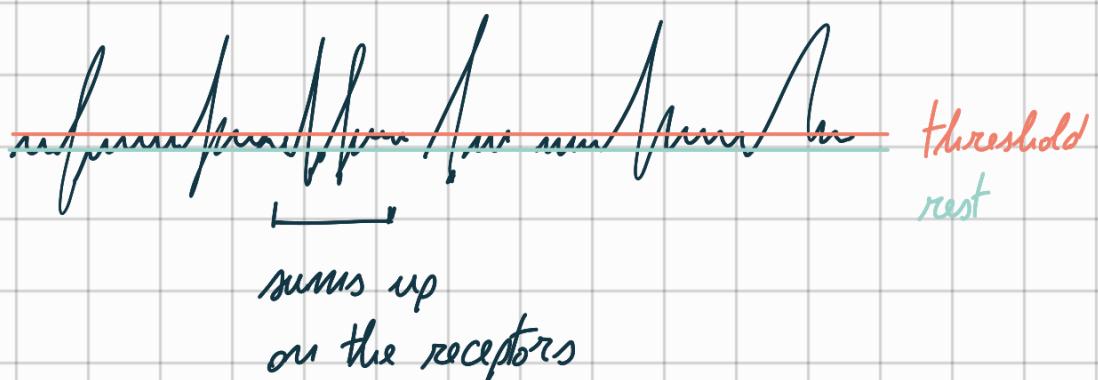
refractory → membrane is less able to produce an action potential  
 period → period of time

In this period, under NO circumstances, we can have another action potential (Na channels are inactivated)  
 If another perturbation reaches the membrane, it will have no effects in this period

### Relative refractory period

During this interval is possible to have another action potential (Na channels closed), but we need a higher depolarization (stronger perturbation) than usual to reach the threshold.

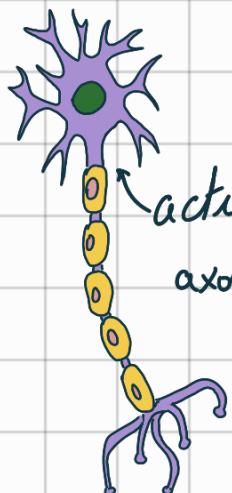
The information is not in the shape of the spikes (that is always the same) but in the temporal distance between them. This is because if the spikes are sufficiently near time wise they can make the receptor fire since their effects sum up



**Absolute refractory period:** due to the  $\text{Na}^+$  voltage-gated channels inactivation. No new action potential can be produced (under any circumstances)

**Relative refractory period:** due to the  $\text{K}^+$  voltage-gated channels. A new action potential can be produced, but it requires a stronger depolarization → it's less likely to occur

## Propagation of the action potential



action potential produced and propagated until the axon hillock

The signal needs to reach other cells

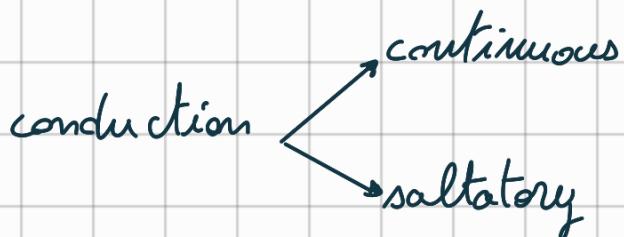
The propagation occurs through the axon thanks to two main mechanisms :

- continuous conduction (unmyelinated fibers)
- saltatory conduction (myelinated fibers)

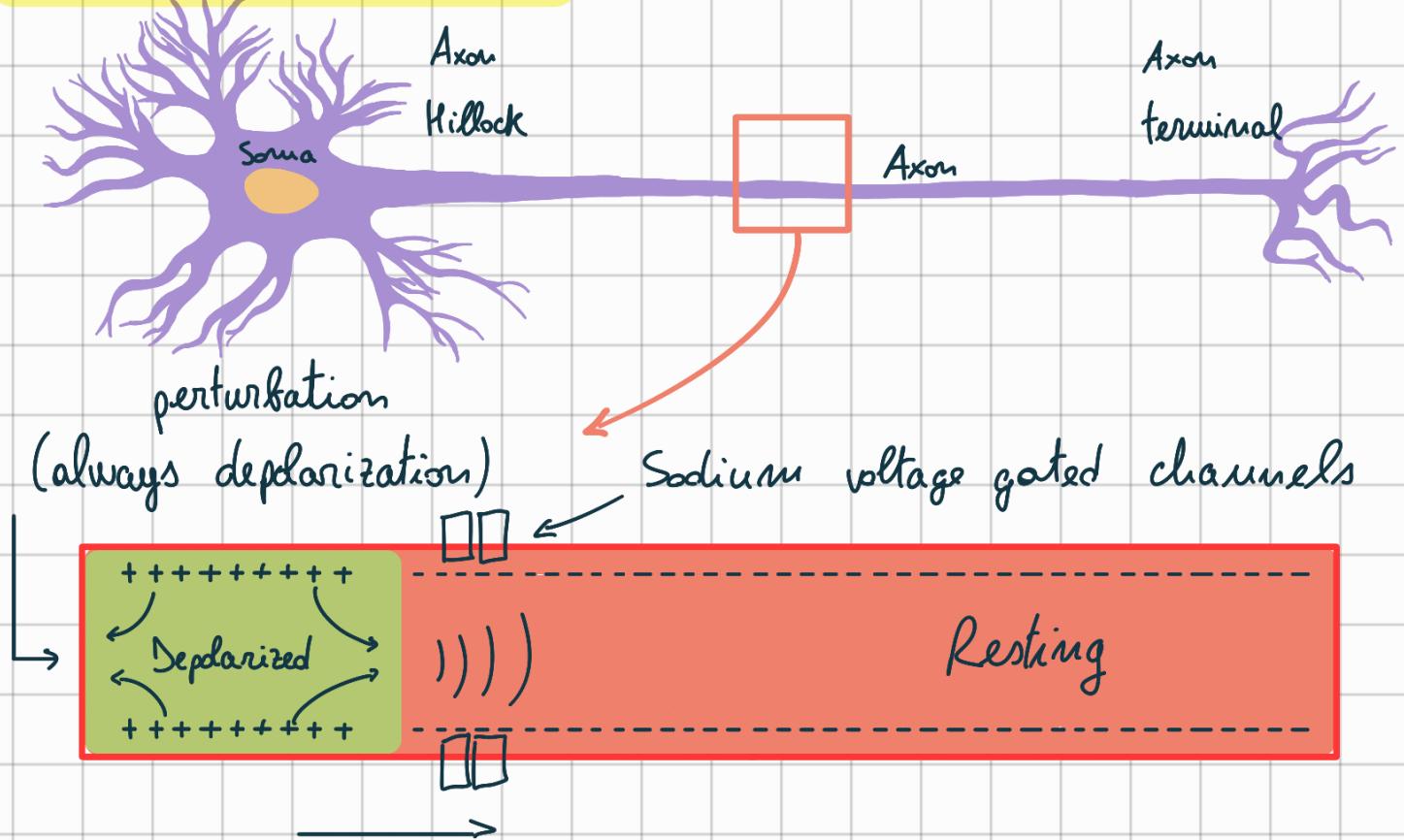
Some cells will have one mechanism, other cells will have the other one; it depends on their structure.

pain → continuous conduction (slower)

muscular cells connection → saltatory conduction (faster)



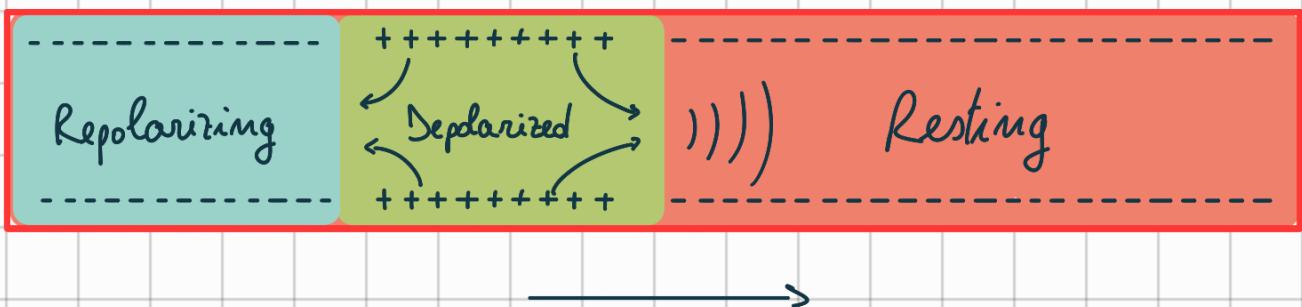
## Continuous conduction



When the perturbation (depolarization) reaches the sodium channels, if they are closed (membrane at rest) they open. A new action potential is produced ( $\text{Na}^+$  ions move inside).

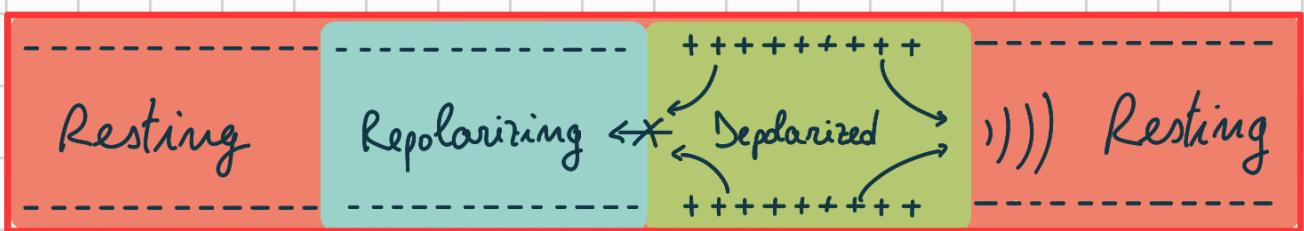
We have :

small passive propagation  
active regeneration.



In the region of the membrane that produced an action potential a few milliseconds ago, the sodium channels will become inactive and will require some time to go back to the closed state (rest potential)

There will be no action potential produced in this zone.



This makes the propagation **unidirectional** thanks to the absolute refractory period



This mechanism is really slow, about 1m/s  
This speed is limited by the time needed by the activation of the voltage gated channels.

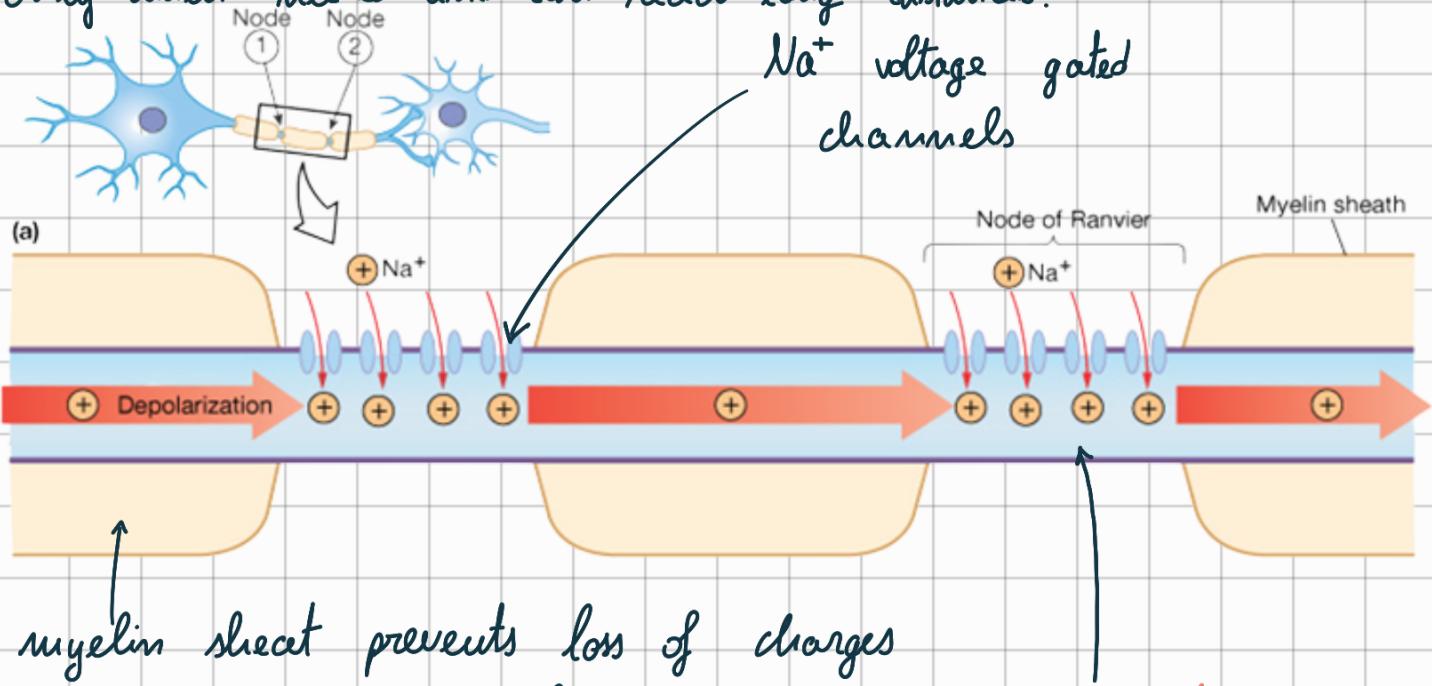
durante l' **absolute refractory period** ( $30\text{mV} \rightarrow -70\text{mV}$ ) non possono assolutamente esserci altri action potential (impossibile)

da  $-70$  a  $-80$  è difficile che ci sia un nuovo action potential ma non è impossibile

Perturbazione molto lenta  $\rightarrow$  tipo il dolore

## Saltatory conduction

The axon needs to be equipped with a different structure. This kind of mechanism is way more common. The action potential is generated only when needed and can reach long distances.



$\text{Na}^+$  voltage gated channels

Node of Ranvier

Myelin sheath

myelin sheath prevents loss of charges

No ion can cross the membrane in  
this area.

Ranvier nodes  
are interruptions on the  
insulation sheet on which  
the axon is exposed to the  
extracellular environment

No channels along the myelinated areas → action potential cannot be generated  
→ only passive conduction in the form of an ion current

Myelin segments cannot be too long, otherwise the signal fades away. Charges can move backwards but will find sodium channels still in inactive state in the previous Ranvier node. Still we can consider the propagation as unidirectional

so times faster

## Brain organization

The brain predicts the future on the basis of the past, helping the individual to survive and perpetuate the species

temporal scale : milliseconds (ms)

spatial scale      soma : micrometers ( $\mu\text{m} = 10^{-6}$ )  
                        membrane thickness : nanometers ( $\text{nm} = 10^{-9}$ )

## Brain evolution

evolution → **individual** : the brain is plastic during the entire lifespan (learning, memorization, spontaneous recovery, neurorehabilitation)  
→ **collective**

## grey and white matter

**Grey matter:** cell bodies and dendrites of the neurons  
(collection and processing)

**White matter:** myelinated axons (fibers)  
(propagation)

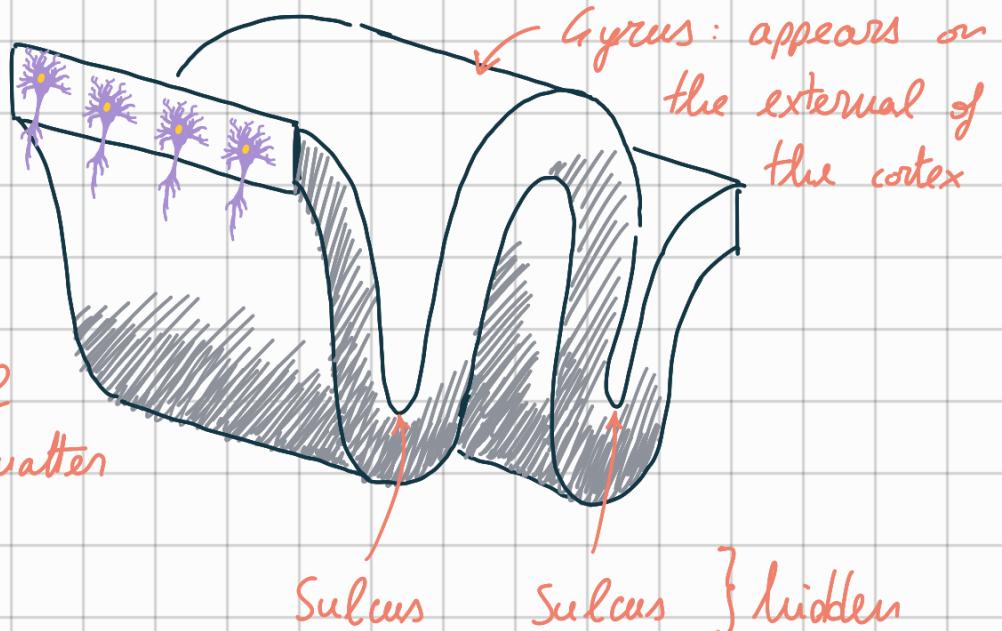
**Corpus callosum:** white matter, highway of information  
between the two hemispheres

The grey matter is where the information is processed while the white matter is what propagates the information (the myelinated sheath is white)

Another distinction can be made between the brain cortex and the subcortical region.

**Brain cortex:** external part of the brain (surface) Made of a significant part of all the neurons that made our brain. It's huge and it's folded to maintain the overall volume approximately the same.

the hidden part  
is approx.  $\frac{2}{3}$  of  
the total grey matter

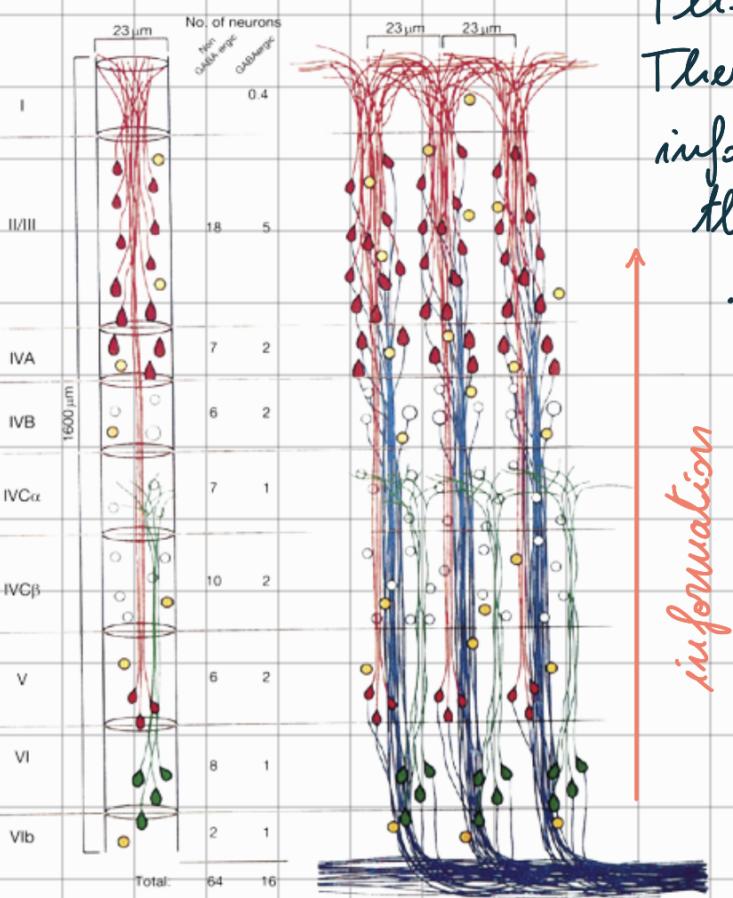


grey matter

the **cortex** is usually organized in columns (0.5 mm in diameter) and each of them is made of 6 vertical layers of neurons strictly interconnected. These columns are perpendicular to the cortical surface.

The layers are intertwined.

There is an order in which the information travels, that is from the internal layers to the external ones.



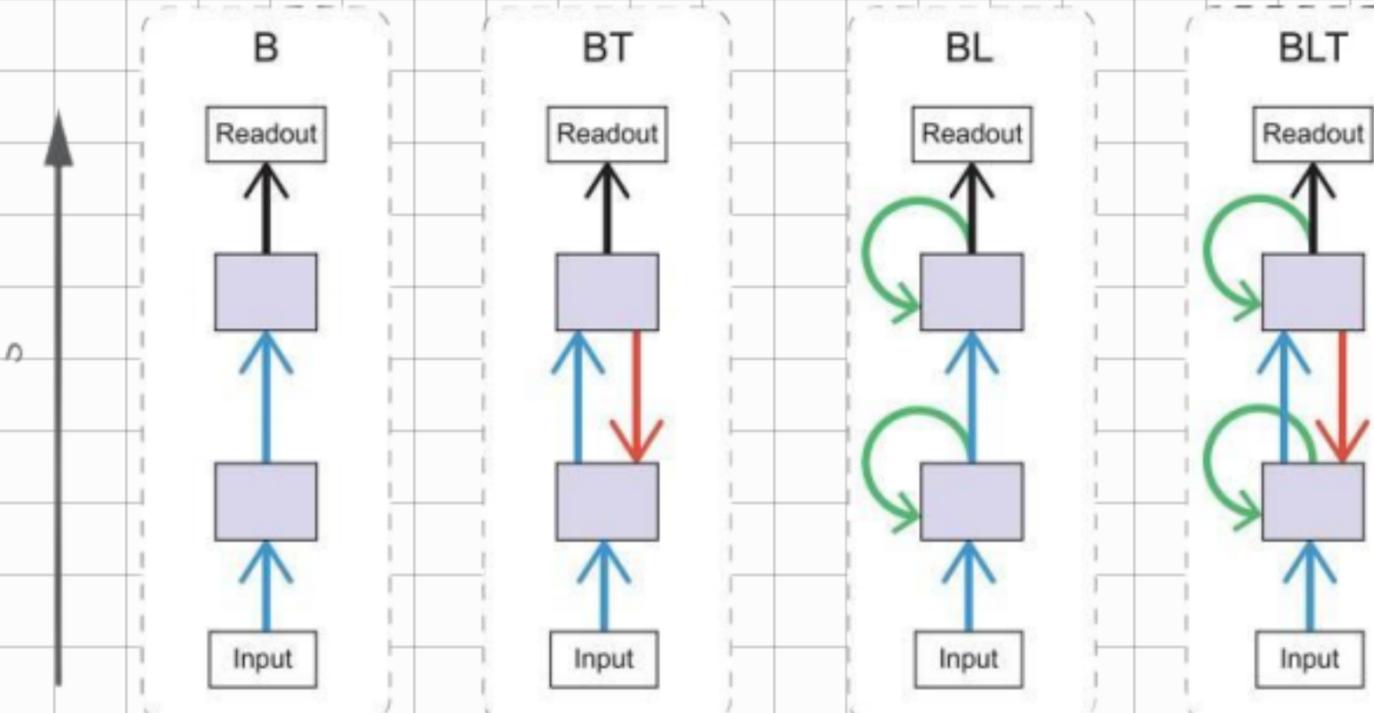
Each column is made of neurons with the same shape and the same function, which react in the same way to the same kind of stimulation.

Columns near each other have similar functions.

Each area has an overall function e.g. vision function, somatosensory function etc

We can move from a function to another with a distance of few centimeters: the more distant the column, the more different the function.

Neurons in the columns form various kinds of networks



*Feedforward*

*Feedback*

*Lateral*

Different kind of network architectures are possible  
The majority of the connections however link neurons  
on the same level, few of them are vertical.

*Feedforward* : directed from regions at the first processing stages to the following ones

*Feedback* : from advanced stages back to previous ones

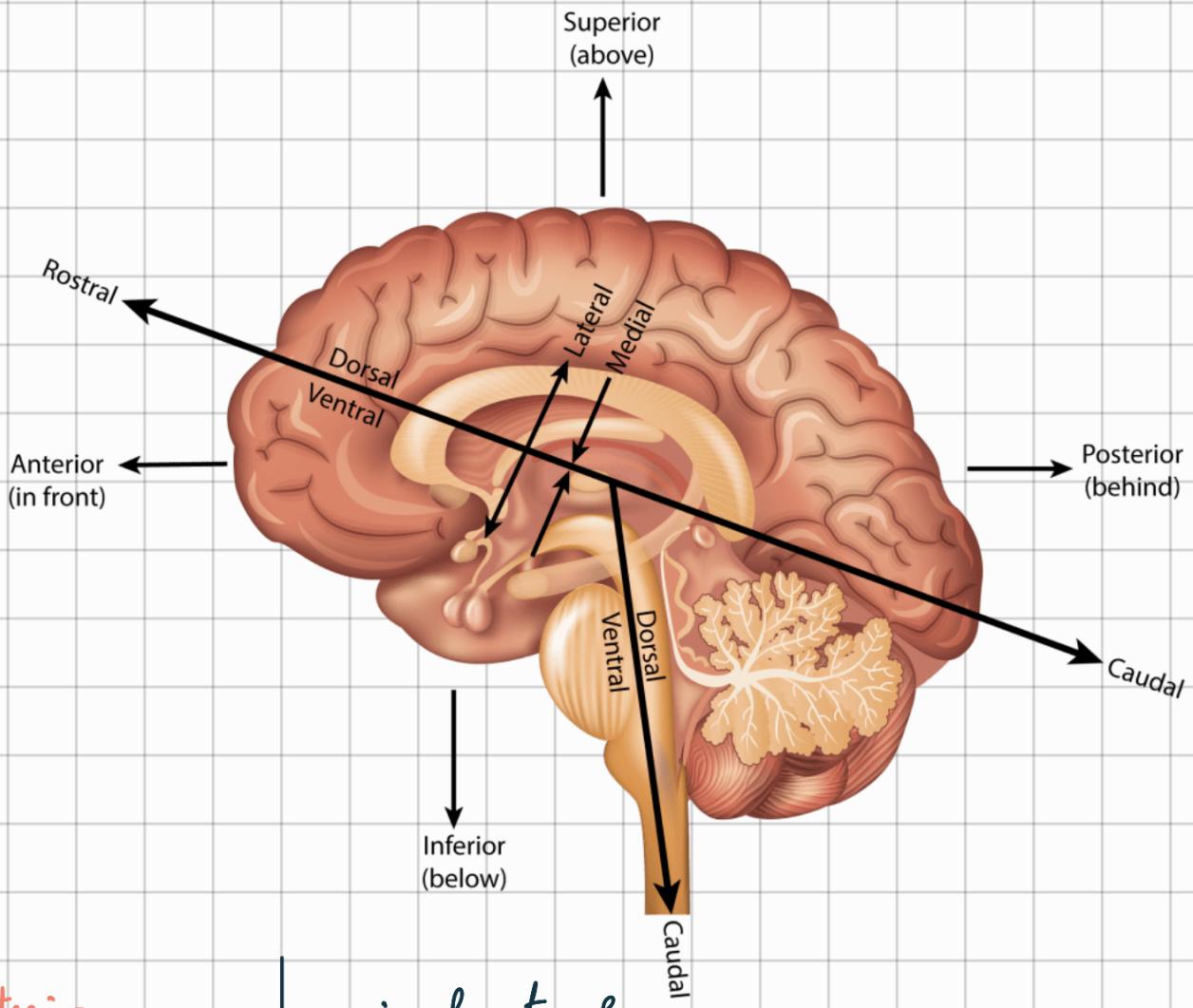
*Lateral* : connections linking same stage regions

All these connection can either be *excitatory* or *inhibitory*:

*excitatory* : induces more and more activity in the output neurons

*inhibitory* : mitigates the activity of the output neurons

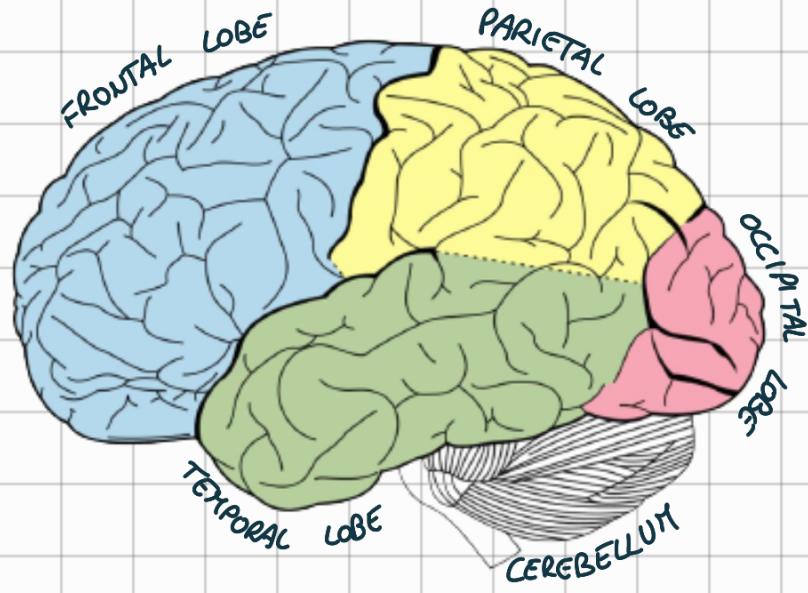
# Parts of the Brain



Anterior  
Posterior  
Superior  
Inferior  
Rostral  
Caudal  
Ventral  
Dorsal  
Proximal  
Distal  
Medial  
Lateral  
Contralateral  
Ipsilateral

in front of  
behind  
above  
below  
towards the front of the brain  
towards the back of the brain  
towards the belly  
towards the back  
closer to a set point  
farther from a set point  
towards midline of body  
towards appendages  
on the opposite side  
on the same side

# Lobes



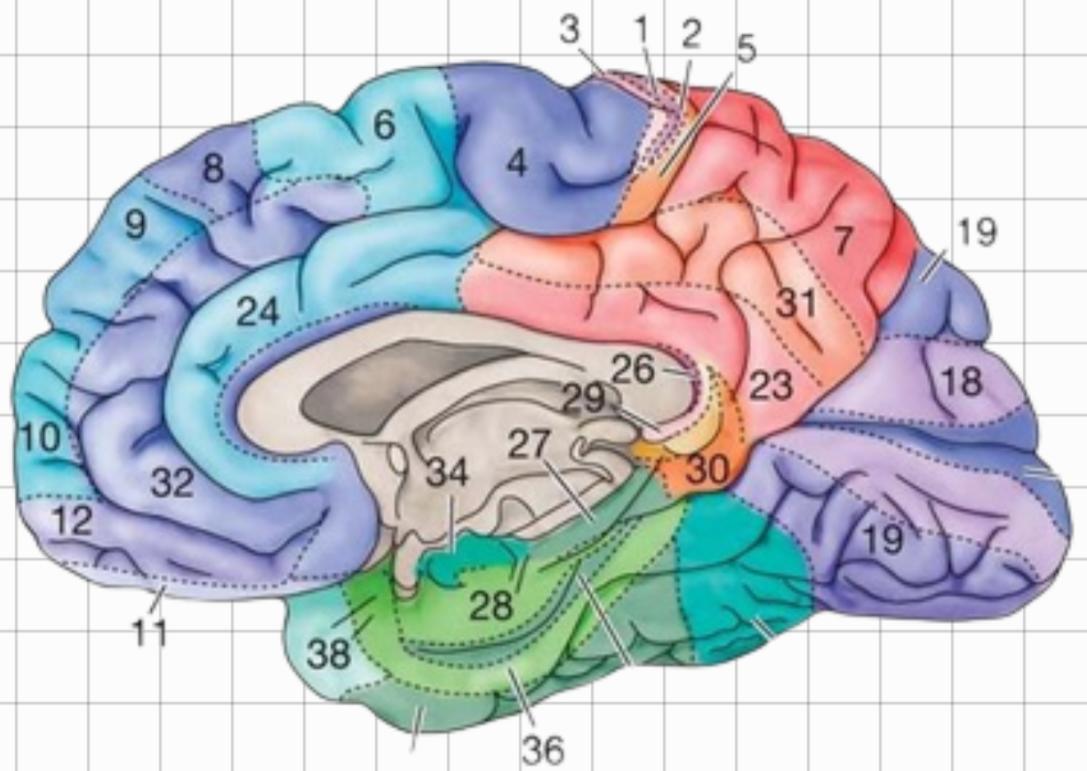
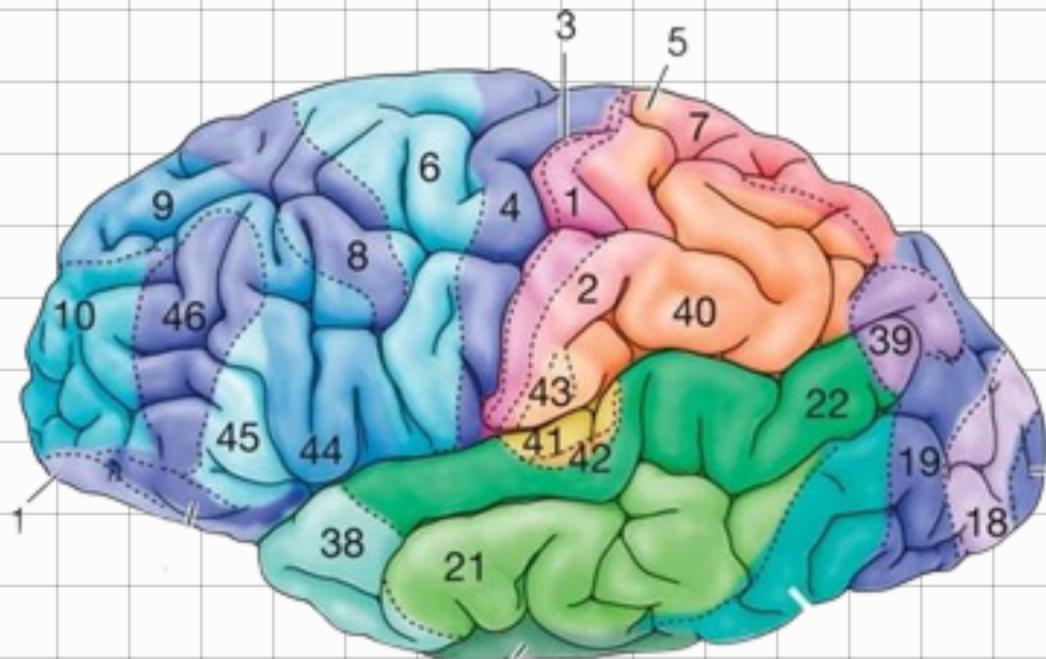
**Frontal :** reasoning  
decision making  
expressive language  
planning and execution of movement  
orientation  
higher level cognitive processes

**Parietal :** primary and secondary somatosensory cortex  
spatial navigation  
touch, pressure, temperature and pain (external stimuli)

**Occipital :** primary visual cortex  
processing and interpretation of visual information

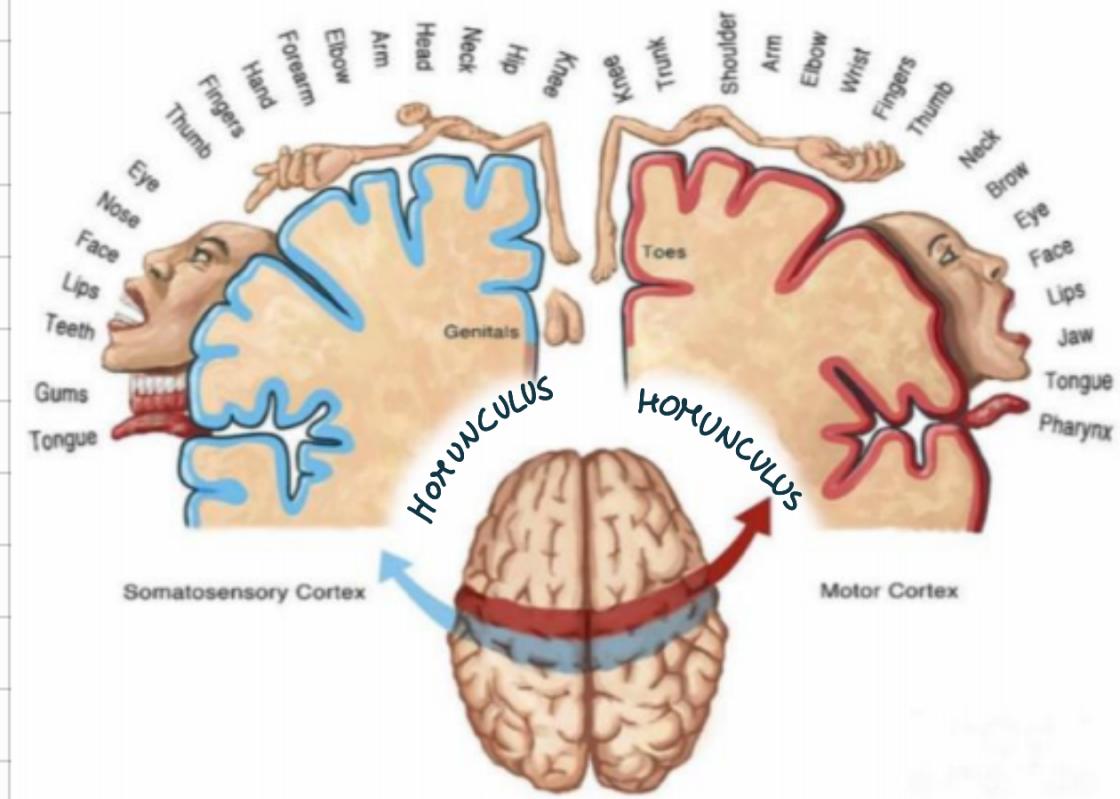
**Temporal :** auditory cortex  
center for receptive language  
hippocampus (memory formation and emotion)

## Brodmann areas



We can further divide and classify each lobe in multiple areas based on cytoarchitecture (neural cells type and organization). Multiple areas/tissue types may participate to the same function.

# Cortical features map - cortical and somatosensory



Somatosensory cortex : corteccia sensoriale, gestisce stimuli esterni.  
È parietal lobe  
L'estensione di ciascuna area è proporzionale alla quantità di recettori sensitivi che deve gestire.

Motor cortex : corteccia motoria; controlla tutte le cellule muscolari del corpo e gestisce le contrazioni volontarie o involontarie. L'estensione di ciascuna area è proporzionale alla quantità di muscoli da controllare.

Le due cortece sono molto simili sebbene le loro funzioni siano molto diverse. Per entrambe abbiamo una corrispondenza 1 a 1 tra la parte del corpo controllata e la parte della corteccia che la controlla. Possiamo mappare tutto il corpo interamente su queste zone.

Homunculus: the organization of the cortex in this region maps the entire body; the extension of the area in the cortex is proportional not to the physical extension but to the number of muscles/receptors it needs to control.

The left hemisphere is linked to the right part of the body

The right hemisphere is linked to the left part of the Body

contralateral

## Subcortical areas

## Subcortical areas



difficult to reach,  
more primitive but  
not less complex  
nor less interesting  
than the cortex

most informations from  
the outside world needs to  
go through the thalamus  
before reaching the cortex

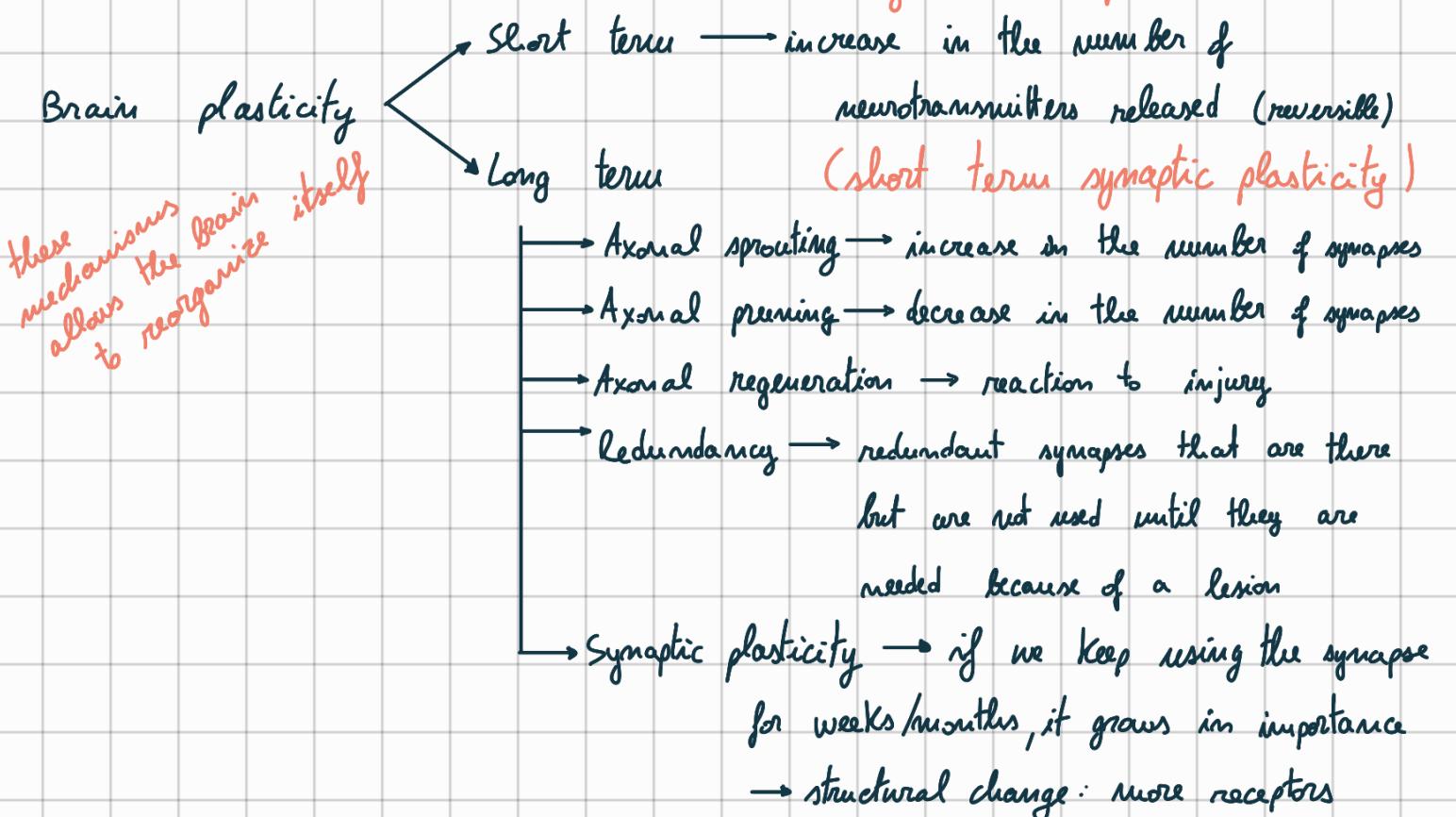
# Brain plasticity

"the phenomena of habit in living beings are due to the plasticity of the organic materials of which their bodies are composed" - William James, 1890

"two cells or systems that are repeatedly active at the same time will tend to become associated so that activity in one facilitates activity in the other" - Donald Hebb,  
↳ mechanism that leads to plasticity 1969

"neurons that fires together, wires together"

they produce ← synchronized ↓ physically associated, meaning that their action potential synapses will be strengthened by the repeated activation



# Recordings

## Recordings

### → Single-cell Recordings

→ Intracellular → only method that directly **measures** the brain activity (not a correlate). Must be done *in vitro*.

sharp electrodes

patch electrodes

actual membrane potential

→ Extracellular → Electrodes are placed near the membrane but do not penetrate it.

They **detect** (do **NOT measure**) the action potentials. Can be done *in vivo*. They detect **side effects**, not the phenomenon.

Can measure only **strong** variations

action potential (AP)

$\sim 100 \text{ mV}$

post synaptic potential (PSP)

$\sim 10 \text{ mV}$

We don't need to measure the amplitude of an action potential since it's always the same. We measure the time interval between spikes

### Recordings from Neural Populations (**behaviour of a group of cells**)

→ **collective methods**)

→ Local Field Potential (LFP)

→ Electroencephalography (EEG)

→ Stereo-Electroencephalography (S-EEG)

→ Electrocorticography (ECOG)

→ Scalp EEG

## Recordings from Neural Populations (behaviour of a group of cells)

### → Local Field Potential (LFP)

measures the collective activity of all the cells (Post Synaptic Potentials) from outside

### → Electroencephalography (EEG)

↳ originates from synchronous postsynaptic cortical currents

Volume conduction: tissue contains water, ion currents can spread

This effect is visible at a large distance (cm) but is instantaneous

↳ Amplitude on the scalp =  $\mu\text{V}$

↳ Temporal resolution = ms (high)

Can be either

↳ Stereo-electroencephalography (S-EEG) → needles (even in subcortex)

↳ Electrocorticography (ECoG)

→ electrode arrays (intracranial)

↳ Scalp EEG (SEEG)

→ electrodes on the scalp

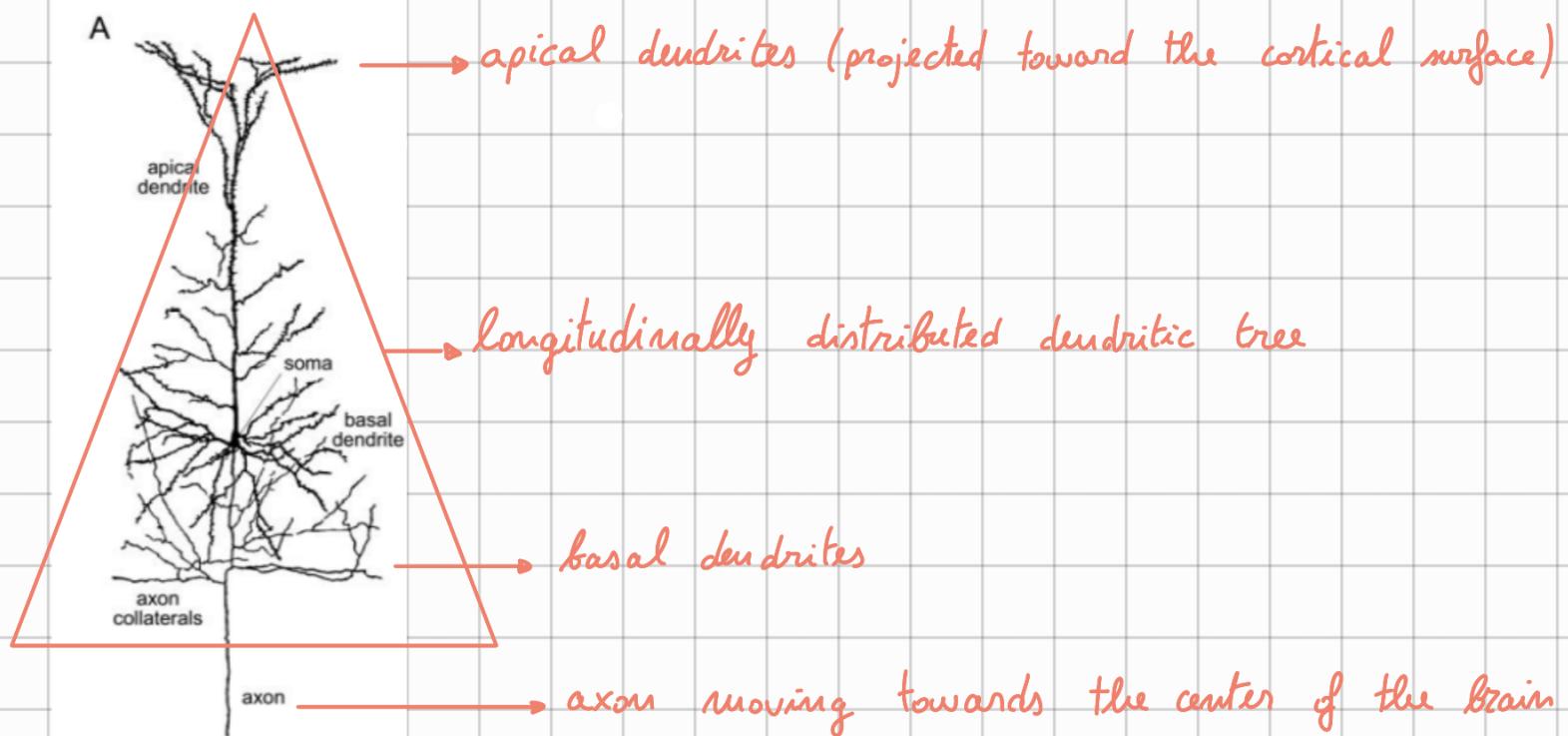
## Invasiveness

invasiveness

1. intracellular recordings
2. extracellular recordings
3. local field potentials
4. stereo-electroencephalography
5. electrocorticography
6. scalp EEG (totally non invasive)

Recording	PROS	CONS
Intracellular	max accuracy	can only be done in-vitro
Extraacellular	can be done in-vivo	detect side effects, not the phenomenon
Local Field Potentials	detailed: spacial resolution is very high, we can measure small portions of the cortex; measure the field close to the neurons	invasive: electrodes put inside the cortex
Stere- Electroencephalography	high spatial resolution; can measure the activity in subcortical regions; reduced amount of noise	electrodes deeply implanted in the brain; can potentially bring damage, infections, ...
Electrocorticography	high temporal resolution;	low spatial resolution; intracranical, so high invasiveness
Scalp - ElectroEncephalography (EEG)	totally non invasive; high temporal resolution	low spatial resolution

## Cortical pyramidal neurons



Cortical pyramidal neurons are particularly useful to understand the generation of EEG signals as they are responsible for the signals that we gather on the scalp



neurons are organized in a parallel fashion and oriented the same way, normally to the cortical surface.

Columns of neurons are called **palisades** and each of them is formed by 6 layers

A single neuron can be modeled as a current dipole

Current dipoles: dipoles are defined as a separation of charge over distance, fundamental to measuring and recording activity using EEG

PSPs do more than merely excite or inhibit a neuron.

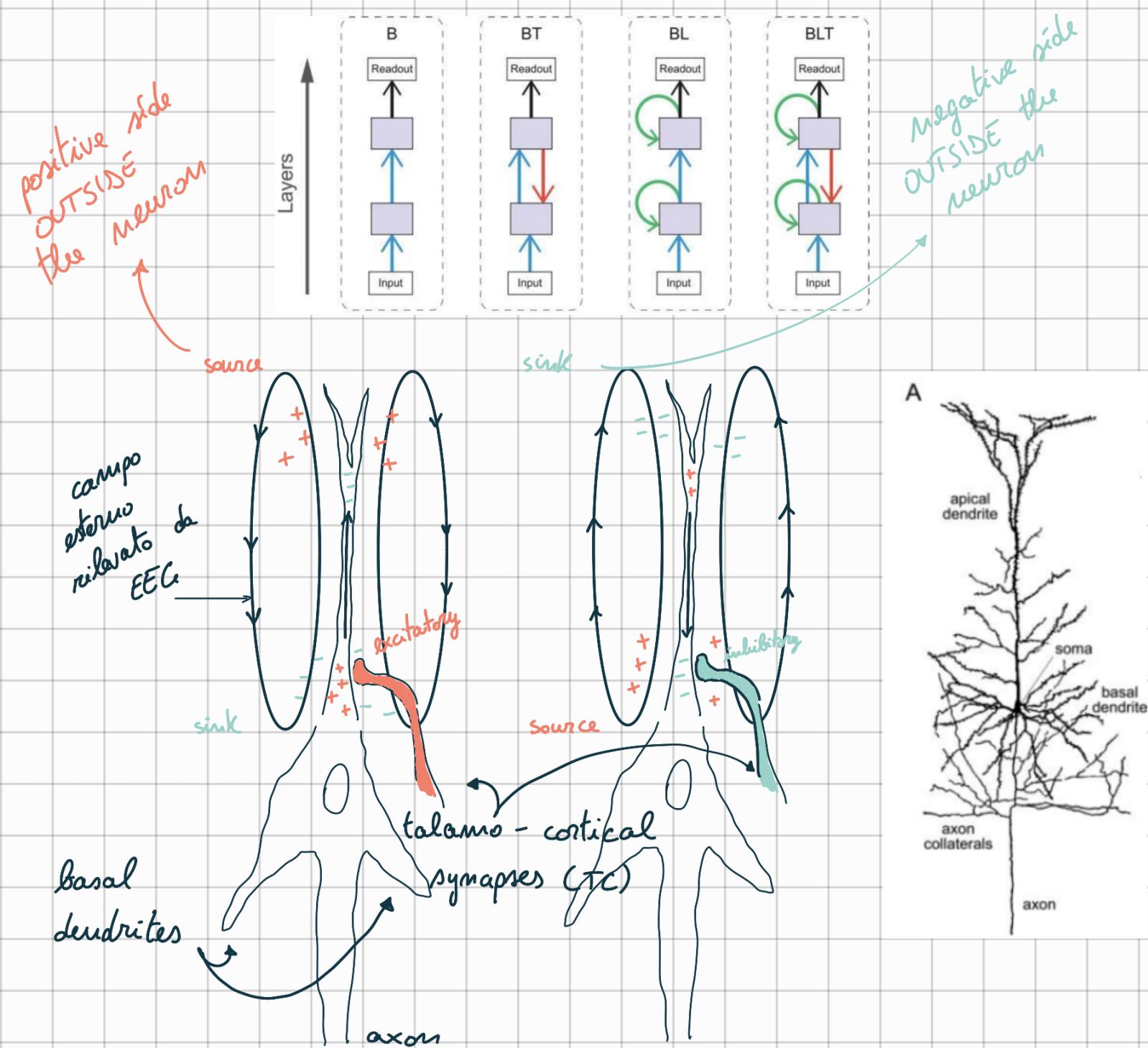
An Excitatory Post Synaptic Potential (EPSP) increases the likelihood that a neuron will fire since it is depolarizing (lets positive ions flow into the cell).

Alternatively, an Inhibitory Post Synaptic Potential (IPSP) decreases the likelihood that a neuron will fire, hyperpolarizing the cell by making the membrane potential more negative.

Despite they lead to an action potential or not, both EPSP and IPSP generates a separation of charges known as a dipole.

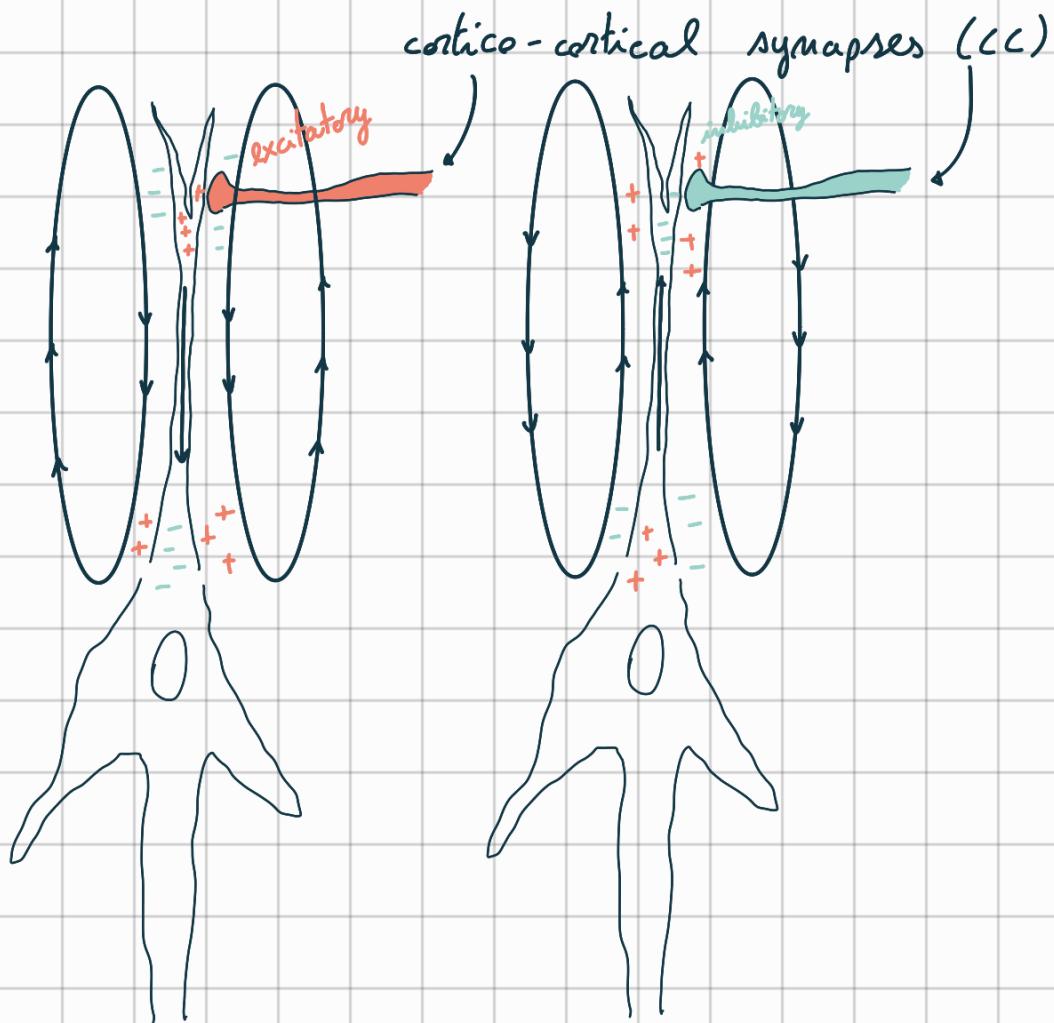
EEG signals are primarily generated from a type of neuron called pyramidal neurons in the cortex (pyramidal neurons have a pyramidal shaped dendritic tree facing the external of the head and consequently an axon facing down towards the subcortical areas).

When a post synaptic signal receives an excitatory signal from an active axon terminal, positive ions flow into the dendrites, depolarizing the interior of the cell; the surrounding extracellular space becomes relatively more negative (at the reception site). The extracellular space at the opposite end of the dendritic tree is now relatively more positive than the extracellular space at the reception site. This pair of equal and oppositely charged poles, spanning across the dendrites and the cell body become the conduction medium for a dipole. The current flows from the positive side (**source**) into the negative reception site (**sink**). An IPSP is the opposite.



**Sink** and **source** are relative to the **positive current** on the outside of the cell body. Current ( $\rightarrow$ ) flows from the positive another side (**source**) to the negative another side (**sink**)

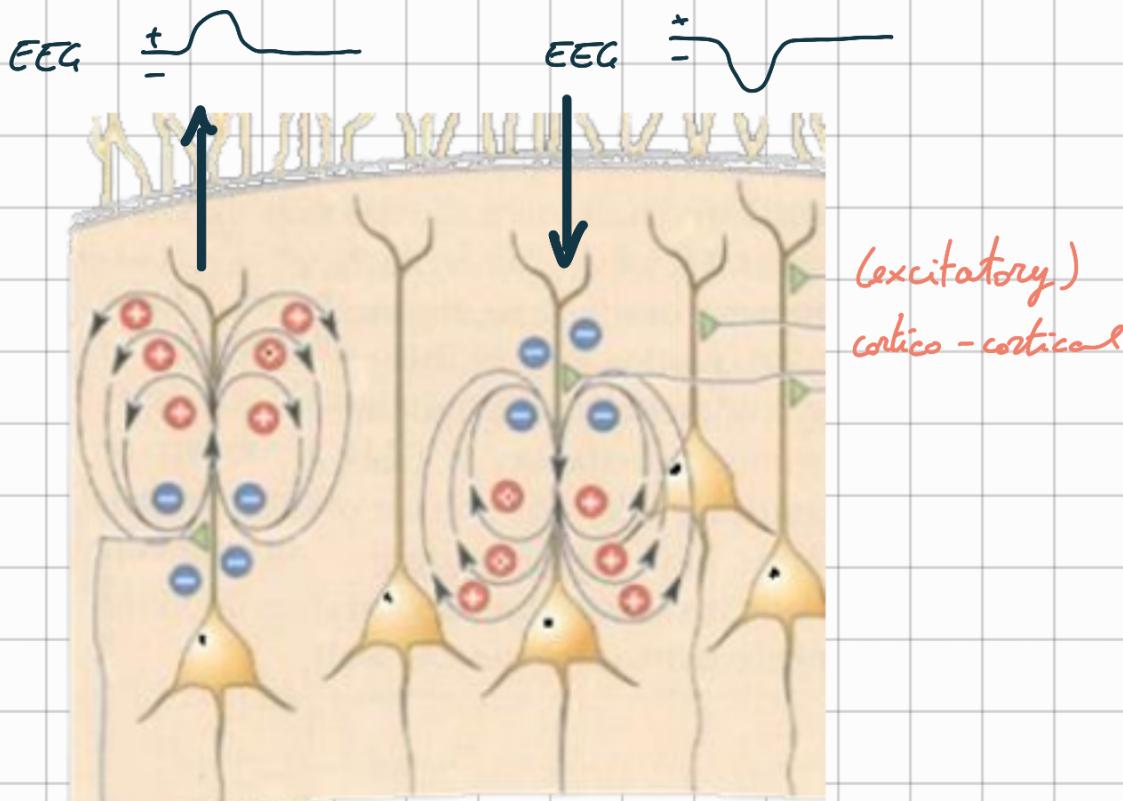
EEG measures the slower Post Synaptic Potential, not the action potential, which is more likely to be picked from the sensors



	excitatory cortico-cortical	inhibitory talamo-cortical
E	CC	TC
I		
EEG		
EEG		

Dipole direction depends on :

1. synapse nature (EPSP or IPSP)
2. synapse position
  1. apical cortico-cortical (CC)
  2. basal talamo-cortical (TC)

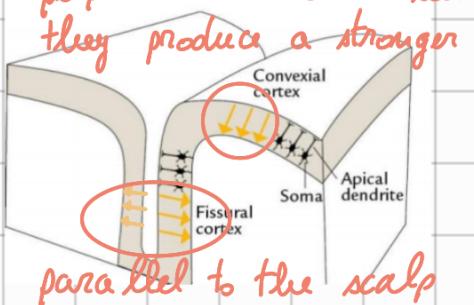


(excitatory)  
talamo-cortical

(excitatory)  
cortico-cortical

Pyramidal neurons are perpendicular to the cortical surface. Gyri are more efficient generators of EEG than sulci for three reasons:

- favorable orientation of the isopotential lines with respect to the scalp;
- the dipole layers in opposing sulci cortices tend to cancel each other → mutual cancellation
- palisade dipole sources line up in parallel, creating large dipole layers.



parallel to the scalp

perpendicular to the scalp:  
they produce a stronger signal

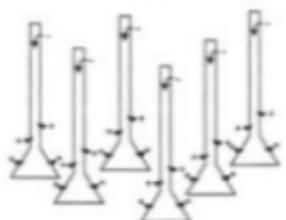
ElectroEncephalography (EEG) measures the *synchronous* electrical activity of *neural populations*. It depends on the orientation of the neurons (*gyri* produce most of the EEG, *sulci* produce little to no EEG).

The amplitude of the signal is:

- linearly proportional to the amount of *synchronous neurons*;
- proportional to the square root of the amount of *asynchronous neurons* (because of *intracortical cancellation* ↑↓)

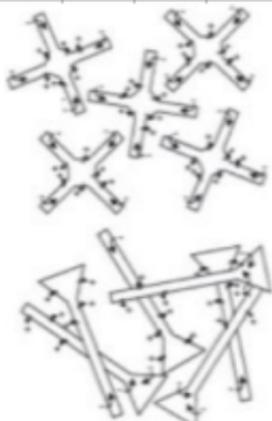
*Open fields* (currents sum and conduct to the electrodes)

They are generated by aligned, synchronous neurons. Only neurons that produce an open field contribute to the EEG



*Closed fields* (cancellation before it reaches the electrodes)

- Radially symmetric neurons
- Randomly oriented neurons
- Asynchronously activated neurons



Mainly constituted by *post-synaptic potentials* because they are *slower* and can sum up more easily in large groups of neurons.

Action potentials are fast and *more difficult* to add up in time.

# EEG

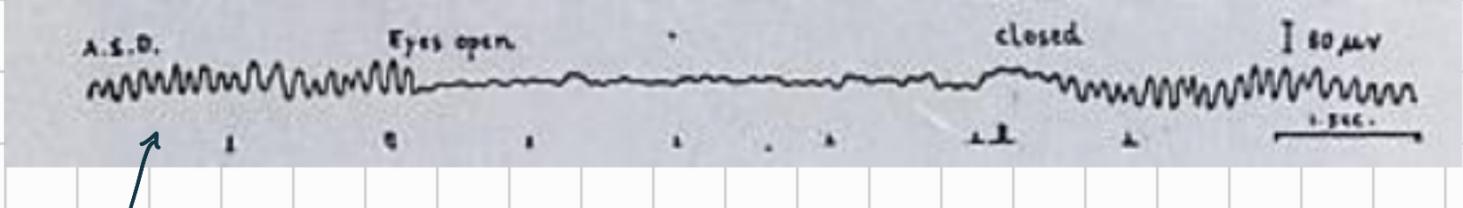
## ADVANTAGES

1. Non invasive
2. Easy to use
3. Portable
4. Inexpensive
5. Covers the entire cortical surface
6. Excellent temporal resolution

## LIMITATIONS

1. **Spatial blur** (attenuation and spread of the potential with distance).
2. **Low signal-to-noise ratio.**
3. **Multiple sources** contribute to the single electrode signal.
4. Near electrodes record **partially overlapped (correlated) signals**.
5. **Reference choice.**

When the neurons are not involved in producing any information, they synchronize with the thalamus.



idling oscillations: oscillations that we have at rest, when the neurons are not involved in the processing of any information and are all synchronized with the thalamus.

We have a stronger signal not because the brain is more active, but because it is at rest. When resting it oscillates around 10 Hz.

When the neurons get involved in the processing of something they desynchronize and the resulting spectrum will stabilize since many signals will cancel each other.

10 Hz  $\rightarrow$   $\alpha$  rhythm