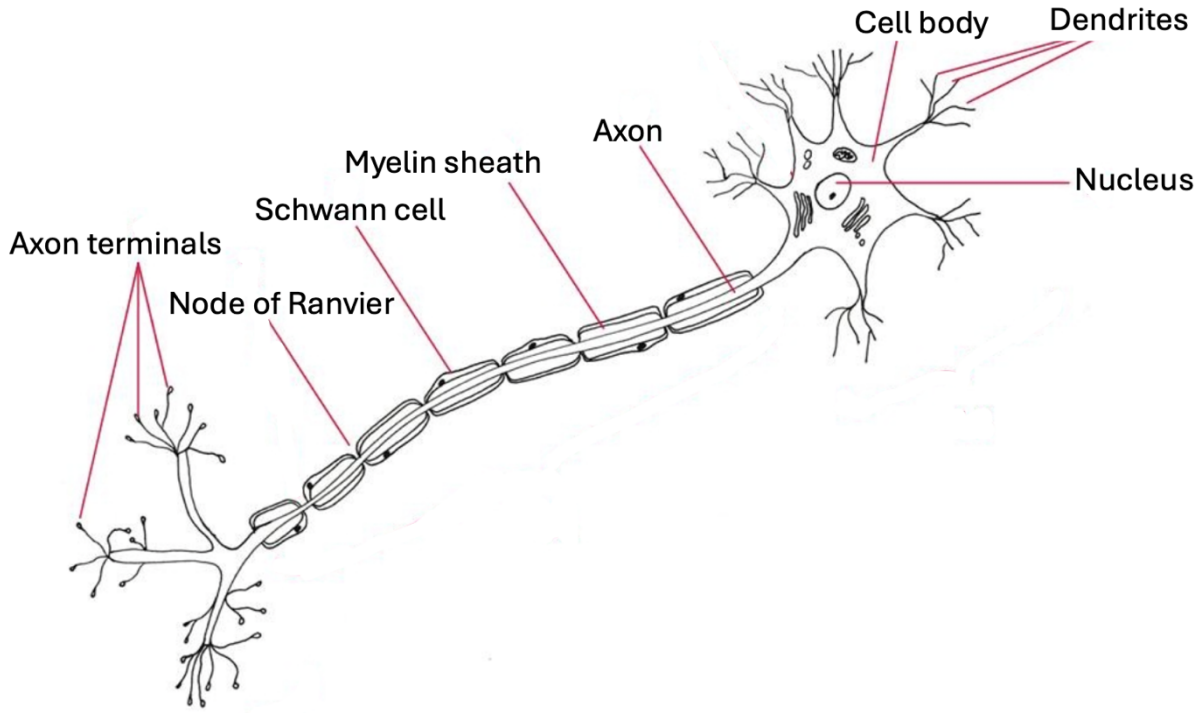
Seeking consciousness

Consciousness is one of the most fascinating phenomena in neuroscience. Everybody agrees that an individual cell has no conscience, and everybody agrees that humans are conscious – and more and more studies show that consciousness is not a specific trait, but a shared trait amongst animals.
Therefore, consciousness must have a biological background…

Constituents of the nervous system

1. The neuron, a highly specialized cell

Neurons are specialized cells in the nervous system, that carry information both within the brain and throughout the body using electrical and chemical signals.
Structure of a neuron:

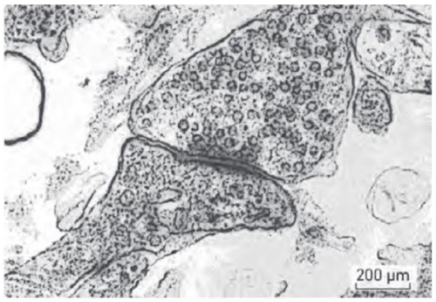


- Cell body (AKA soma): it contains the nucleus and organelles, and integrates incoming signals.
- Dendrites: branch-like extensions that receive signals from other neurons.
- Axon: a long fiber that carries electrical impulses away from the cell body.
- Axon terminals: used to communicate chemically with other neurons or muscles.
- Myelin sheath: fatty insulation that speeds up the transmission of electrical impulses along the axon.

2. The synapse, junction between a neuron and other cells

A synapse is a junction where an axon terminal of one neuron communicates either with the dendrite of another neuron, or with an effector cell, such as a muscle or a gland.
It can be divided in three parts:

- The presynaptic neuron, where the information arrives.
- The synaptic cleft, a 20 to 40 nm wide gap.
- The postsynaptic neuron/cell, where the information will pursue its journey or be processed.



How does information travel inside a neuron?

Note: The description will be done using the example of pain perception.

1. The initial stimulus

Specialized sensory neurons, called nociceptors, are found in the upper layers of the skin, especially in the epidermis. Having free nerve endings, (no capsule or specialized structure), they are capable of detecting pain (nociception), temperature, and sometimes mechanical stimuli.
A painful stimulus (pressure, cut, extreme temperature, both hot or cold) activates the free nerve endings:

- The neuron's membrane is at about -70 mV (inside negative relative to outside). This resting potential is maintained by sodium-potassium ion pumps and potassium ion leak channels.
- When the potential due to the stimulus reaches the threshold (about -55 mV), the voltage-gated Na^+ channels open, allowing Na^+ ions to rush into the cell. The inside becomes more positive, rising to around +30 mV) – The membrane is depolarized.
- After a brief delay, Na^+ channels close and voltage-gated K^+ channels open. K^+ ions flow out of the neuron, restoring the negative charge inside. The membrane potential moves back toward the resting level – The membrane is repolarized.
- K^+ channels may remain open slightly longer than needed, causing the membrane to become slightly more negative than resting potential (about -75 mV) – The membrane is hyperpolarized.
- Finally, sodium-potassium pumps and leak channels restore the original ion concentrations, returning the neuron fully to -70 mV.

An action potential has been generated.

Note: This action potential and the resting potential before and after can be visualized on the screen of an oscilloscope.

2. From an action potential to a nerve impulse

The action potential is very localized, in a small region around the stimulated end.

- This region has a positive charge inside and negative charge outside, relative to adjacent resting regions. An electric disequilibrium has been generated.
- Na^+ ions flow along the inside of the axon from the stimulated region toward the adjacent, still-resting regions to re-uniformize charge repartition – a current is created. Outside the axon, the current has to flow back along the extracellular fluid to complete the circuit.
- The local inward flow of positive ions depolarizes the adjacent resting membrane. When the depolarization reaches the threshold, the same action potential is created – It has moved from one segment to another, creating a nerve impulse.

Note: The previous segment if the axon has a refractory period, during which cation channels are temporarily inactive. This prevents the action potential from moving backward – The impulse moves unidirectionally along the axon.

3. Speed of the nerve impulse

a. Factors linked to the axon.

The speed of a nerve impulse is not uniform along the axon. It depends on different parameters:

- Axon diameter: a larger diameter opposes less resistance to ion flow, leading to faster impulse.
- Temperature: Higher temperatures generally increase the speed of nerve impulses (up to a physiological limit).
  Note: Very low temperatures can slow or block conduction.
- Ion concentration: Any disruption, due to disease or toxins, can slow or block impulses.
- Health of the nerve: Axonal damage reduces conduction efficiency.

On average, the speed of a nerve impulse in an axon would be around 0.5 to 2 m/s… Much slower than how we feel pain…

b. How come?

An axon is structured in different segments separated by Nodes of Ranvier. Each segment is covered with a myelin sheet, a fatty insulation which protects it, but not only. It also prevents ion flow across the membrane in the myelinated regions.
The nodes of Ranvier are not wrapped with myelin. This is where voltage gated Na+ and K+ channels are concentrated.

- When an action potential is generated at an end of an axon, local currents flow inside the axon to the next node of Ranvier.
- It is only there that the time-consuming depolarization/repolarization process can occur, and a new action potential can be generated.

The impulse "jumps" from node to node rather than traveling continuously along the membrane – it travels through Saltatory conduction.
This allows a much faster impulse transmission (up to 120 m/s), a higher energy efficiency (fewer ions being exchanged, less ATP is used by the sodium-potassium pump), and maintains signal strength over long distance.

Note: Without this very high transmission speed, life wouldn't be very efficient, if possible at all. Pain is there to let you know that you have to move/change… A delay of a second or more could be problematic/dangerous/life threatening.

4. Transmission of the pain signal

The nerve impulse travels along afferent sensory neurons:

- Peripheral axons bring the signal from the skin to the cell body in the dorsal root ganglion.
- Central axons bring the signal from the dorsal root ganglion into the spinal cord.
- Second-order neurons carry the signal from the spinal cord to the brain.

From one neuron to the other

To allow a flexibility in the transmission of messages, the nervous system is not continuous, but made of multiple neurons separated by tiny gaps – synapses.
An action potential is not susceptible to cross a synapse: another mean of transmission of the information is therefore needed.

1. The presynaptic neuron releases neurotransmitters.

- When an action potential reaches the axon terminal of the presynaptic neuron, it causes voltage gated calcium channels in the presynaptic membrane to open. The concentration gradient creates a calcium influx inside the presynaptic terminal.
- The excess calcium ions cause synaptic vesicles to move toward and fuse with the presynaptic membrane. This exocytosis frees neurotransmitters stored in the vesicles into the synaptic cleft.

2. The postsynaptic neuron receives the neurotransmitters.

- The neurotransmitters diffuse across the synaptic cleft. The gap being very small, they bind to receptors on the postsynaptic membrane. The process seen in chemical signaling then leads to a depolarization – an excitatory postsynaptic potential (EPSP).
- An EPSP being usually small, multiple EPSPs need to add together to reach the threshold for an action potential:
    - Either EPSPs arriving from the same synapse in rapid succession – temporal summation
    - Or EPSPs arriving from multiple synapses, at the same time – spatial summation.
- The formation of a new action potential, which then turns into a nerve impulse… And the story repeats towards the next synapse.

Note: If the threshold is not reached at the axon hillcock, the EPSPs decay, without firing an action potential – the signal doesn't exist anymore.

3. Internal regulation.

A nervous impulse systematically leads to EPSPs. However, this can produce over-depolarised neurons, thus over-excitation, leading to seizures, anxiety or hyperexcitability.
To ensure a controlled and precise neural signalling, EPSPs are constantly balanced between by Inhibitory PostSynaptic Potentials (IPSPs):

- The presynaptic terminal contains vesicles storing excitatory neurotransmitters, but also vesicles storing inhibitory neurotransmitters.

  Ex: GABA and adenosine in the brain, glycine and endorphins in the spinal cord and in the brain.

  They are released continuously, with an increased production when the action potential arrives at the presynaptic terminal.
- They bind to specific ligand-gated ions channels on the postsynaptic membrane, creating a hyperpolarization, an IPSP. The postsynaptic membrane then becomes less likely to reach threshold for firing an action potential, counterbalancing the depolarization due to EPSPs.
- Such as for EPSPs, the response to IPSPs is cumulative. The response of the postsynaptic neuron is therefore a sum of all potentials received:
    - If the net effect of all EPSPs and IPSPs reaches the threshold, an action potential is fired.
    - If the net effect is below the threshold, no action potential forms.

Thanks to the combination of both EPSPs and IPSPs, synapses act as decision-making units.

- EPSPs produce the excitation. With them alone, neurons would fire continuously, and neural circuits would become overexcited.
- IPSPs counterbalance the EPSPs, to allow neurons to ignore weak or irrelevant excitatory inputs: it will fire only when excitation is strong and relevant. They also prevent delay firing or prevent it at specific times, which is crucial for coordination of the networks and the maintaining of rhythms involved in cognition, movement and perception, thus allowing flexibility and learning.

Note: Disruption of this balance can be linked to several disorders, such as epilepsy, anxiety or ASDs.

4. "Treating pain"

Exogenous chemicals – chemicals introduced from outside the body – can alter synaptic transmission. They can act in several ways:

- In acting on the neurotransmitter release.

  Exs: Botulinum toxin blocks acetylcholine release, causing muscle paralysis.
  Amphetamines increase dopamine and norepinephrine release, enhancing stimulation of the postsynaptic neuron.
- In inhibiting the neurotransmitter reuptake, thus prolonging their action.

  Exs: Selective Serotonin Reuptake Inhibitors increase the amount of serotonin in the synaptic cleft, producing a mood elevation.
  Cocaine blocks the reuptake of dopamine, leading to prolonged excitation.

- In acting on neurotransmitter degradation.
  Ex: Acetylcholinesterase inhibitors (e.g. nerve gases) prevent breakdown of acetylcholine, leading to excessive stimulation of muscles or neurons.
- In acting on postsynaptic receptors.
  Some chemicals can mimic or block neurotransmitters.
  - Agonists will bind to receptors and activate them.
    Ex: Opioids (e.g. morphine, codeine or fentanyl) have a structure similar to endorphins. They bind to these receptors in the brain and spinal cord and act similarly to endorphins, thus increase the inhibitory signalling – the pain transmission is reduced.
  - Antagonists will bind to receptors and block them.
    Ex: Glutamate is an excitatory with specific receptors in the post-synaptic neuron. Ketamine has a structure similar to glutamate, and therefore can bind to these receptors. It will then block them, leading to decreased EPSPs. It is used as a drug to reduce severe or chronic pain.
    Note: Antagonists can also be used to "increase pain". In the case of an overdosis of analgesia, drugs such as naloxone are injected in the body. They bind to the endorphin receptors and block them, thus reducing the IPSPs.

And what about consciousness, at the end?

Individual neurons are specialized cells, processing and transmitting information through electrical impulses and chemical signals:

- Synapses allow signals to converge and diverge – Connectivity
- Neural connections change with experience, shaping "conscious" experience - Plasticity
- Multiple inputs (both excitatory and inhibitory) are summed in postsynaptic neurons, allowing sophisticated decision-making – Integration
- Coordinated activity across large populations of neurons can be associated with awareness and attention – Synchronization

Consciousness is an emerging property – it is not the sum of the properties of each individual neuron, but takes in account their interactions: it depends on how neurons process and combine information from multiple sources, and must be fluid, changing from moment to moment, depending on attention, sensory input and internal states.

Note: It is agreed on the fact that consciousness is located in the brain:

- *The cerebral cortex (prefrontal cortex, parietal cortex and temporal lobes) is the place for perception, decision-making and self-awareness.*
- *The thalamus acts as a relay station, integrating sensory information.*
- *A Default Mode Network (DMN) exists, active during introspection and daydreaming.*
- *Other attention and sensory-motor networks also contribute to conscious perception.*