Sidi Mohamed Ben Abdellah University

Faculty of Medicine and Pharmacy - Fez

# Neuromatiq 1.0

FACULTE DE MÉDECINE ET DE PHARMACIE
UNIVERSITÉ SIDI MOHAMED BEN ABDELLAH FES

# Dedications

# I dedicate this thesis to:

To **my parents (AbdelHadi Ben Brahim** and **Hibbi Aïcha)** and to my **two sisters (Asma** and **Zineb Ben Brahim)**: I salute your patience and your moral and material support, without which this project would never have been successful.

**To my best friend, Maureen Conner Tenore**, who generously financed this work and has always encouraged me to persevere and give the best of myself. You have always been there for me, and no matter what I asked for, you gave without hesitation. At one point, you were the only one to push forward; I hope that someday I will be able to prove my deep gratitude to you and your family.

**To the memory of the late Hamdoune Hanane**, who left us three years ago, before she could obtain her doctorate in medicine. She fought with patience and courage even in the final stages of her illness. To your soul and to the honor of your family - which is also mine - I dedicate this work.

**To the Qesmi family,** for their support throughout the period of my medical studies in Fez.

**To my professor and thesis rapporteur, Professor Belahsen Mohammed Faouzi**, for the quality of his care in the neurology department of the Hassan II University Hospital in Fez.

To our great master and professor of anatomy, **ALAMI HMIDANE TAYA**, who taught us not only anatomy but also the history and ethics of medical practice.

To the **Dean of the Faculty, Mr. My Hassan Farih,** who supported all the graduating classes of the Faculty of Medicine and Pharmacy of Fez with great care, attentiveness, and kindness.

To all **my friends:** Isam ElMejdi, Issam Jbabri, Ibrahim Lmehjoubi, Zakarya, Lamyae, Rachid, Arlene, Pris, Wendy, Ramona, Che Rhee...

To all **my teachers**, either in medical school or through online training platforms: Thank you for the quality of your presentations and your courses.

To all those **who have supported this project from near and far, around the world**: Thank you for your encouragement, your support, and your warm comments, without which I would not have been able to move forward.

# Acknowledgements

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You supported me even through the hardest and most difficult times. You have always been a great source of inspiration and confidence for me. You taught me the values of honesty, modesty, and honor. You have always fought for me and by my side. You always believed in me, even when you had no idea what I was doing. Without your support, I certainly would never have been able to get here. I am eternally grateful to you.

**My mother, Hibbi Aicha:**

You have borne with me all these years without complaint or dissatisfaction. I remember the years you spent with me, and me alone, during medical school - the joy on your face when I succeeded and the tears flowing down your cheeks every time I failed. So much happiness and so much sorrow, yet you never let me down or stopped believing in me. You afforded me the time to do what I have always dreamed of: dedicating myself to this project. Today, I share with you the fruits of my work and your patience.

**My little sister Zineb:**

"Those who do the real work are often in the shadows." This is true for my little sister Zineb, who takes care of me and the family. Thank you for your kindness, your care, and your support.

**My sister Asma:**

Professional and family commitments have kept you far from us, but know that you are always present in our hearts. Thank you for your support and your help, both you and your husband, Abdelghani Kayfouf. I am very grateful to you.

**My best friend Maureen Conner Tenore:**

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Three years ago, you gave me a lesson that I have never forgotten: that life deserves to be lived with passion and enthusiasm until the very last moment. Your death was a turning point in my life.

You have left us, but I have always kept you in my mind. Never have I seen anyone face death with such courage; I dedicate this work to the honor of your memory. May God keep you in His infinite mercy.

**The Qesmi family:**

You may not be rich in terms of money or wealth, but I found in you a very kind, warm, and generous host family. I will never forget the beautiful moments I spent with you, nor the way you took care of me. I love you all: Salem, Fatima, Mohammed, Merouane, Otman, and Omar. I will always be grateful to you.

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**My professor My Hassan Farih:**

You have been a father to all generations of students at the Faculty of Medicine and Pharmacy in Fez. You have given us advice and support throughout our years of study; all the students of the faculty are very grateful to you.

**My professor and thesis rapporteur Belahsen Mohammed Faouzi:**

I would like to congratulate you, first of all, on the excellence of your teaching and the quality of your courses within the faculty, and also for your perfect care in the neurology department. Your pedagogical method of training has given us, as future doctors, a great deal of self-confidence. In your department, we participated in developing diagnoses and even proposing management plans. I never felt as valued as I did when I was in your department; in other departments, I was often just taking blood pressure and temperatures.

I will never forget the time when, even after I had left the neurology department a year prior, you invited me to see the case of a young child with **myopathy** while explaining her symptoms to me. I will also not forget the day you invited me to the ward to show me what a **Kayser-Fleischer ring** is and how it helped diagnose Wilson's disease in a patient. I felt like a professor of medicine given your interest in explaining these two cases to me, rather than an ordinary extern with nothing better to do than walk the corridors with a stethoscope and a blood pressure monitor in hand.

I have enjoyed collaborating with you on topics such as paraplegia, neurological examination, and especially neurological physiology. I share your view that teaching should be a source of inspiration, motivation, and enthusiasm, rather than mere filler and forced labor.

**My Teachers at the Faculty of Medicine and Pharmacy of Fez:**

Thank you for the quality of your guidance both at the faculty and in the hospital departments. I would like to specifically thank Dr. TIZNITI SIHAM (Head of Radiology), Mr. LOUCHI ABDELLATIF (Head of Surgery B), and Professor HIDA MOUSTAPHA (Head of Pediatrics). Thank you from the bottom of my heart for your kindness and your support.

# Presentation

# Neuromatiq

**Neuromatiq**, or *Audiovisual and Interactive material on Neurological Physiology and its Disorders*, is a medical thesis project carried out by me (**Ben Brahim Mohammed**) and supervised by *Professor* **Belahsen Mohammed Faouzi**, Professor of Neurology at the Faculty of Medicine and Pharmacy of Fez and Head of the Neurology Department at the Hassan II University Hospital.

The purpose of this material is to explain the functioning of the nervous system to medical students and those in related fields by means of 3D animated videos and/or interactive animations.

The world is evolving; our vision of teaching and pedagogy must also evolve. Today, there is a massive technological boom in the field of digital multimedia, and we can achieve a great deal with it in the field of education.

The idea of creating this program came to me five years ago. I regularly watched episodes of the series ***Tous sur orbite***, a series that explains the solar system but is intended for the general public. I was amazed by the simplicity and elegance with which the solar system was presented, sparing the viewers the trouble of superfluous scientific details. As a result, one learns a lot and enjoys it as well.

A few months later, I had the chance to watch a video, ***The Inner Life of the Cell***, produced at Harvard University in the USA, which explains the inner workings of the cell. The scenes are breathtaking; one truly enjoys watching the video while learning about biology. It is even more tangible than a text or a diagram because it is visual, 3D, animated, and beautiful to see.

At the time, I had worked with two medical students on two audiovisual resources in neurology, supervised by Professor Belahsen: one called ***Paraplegia*** and the other ***Neurological Examination***. This latter work was very successful, but it was still amateur work. A realization of the caliber I imagined requires a deep knowledge of the subject, whereas I only had a rudimentary understanding regarding only the *Flash* software.

I took up the subject of neurological physiology with Professor **Belahsen** five years ago without really knowing where it would lead. I have collected a vast number of references: many books on neurophysiology, multimedia materials on physiology with animations, materials with interactive 3D animations, 3D video animations for visual reference, and, above all, collections of videos on the functioning of the nervous system. The series that made the biggest impression on me was certainly the TTC (The Teaching Company) series ***Understanding the Brain***, spread over 36 episodes of 30 minutes each, presented by Professor Jeanette Norden. This series explains how the nervous system works; I have rewatched all the episodes several times and highly recommend it to any medical student.

Before starting the production of the videos, I viewed a huge number of tutorial series on many animation platforms - more than 27,000 videos in the fields of CG (computer graphics) and CGI (computer-generated imagery), animation principles, general computer skills, lighting, color theory, and especially series for specific products like *3ds Max, Photoshop, Flash, ActionScript, HTML/XML/CSS, After Effects, Premiere Pro, Illustrator, Dreamweaver, Soundbooth, Audition, Encore, Bridge***,** and others.

Quality production comes at a high price: four years of relentless work on this project, day and night. It became a real obsession; I did nothing else but train and execute. I learned how to write a script and how to organize and construct sentences in such a way as to produce a succession of coherent scenes. For each subject, I take my time with the writing, collecting the ideas I need to present while eliminating the superfluous. I structure them into a coherent article and make a sketch for each sentence - a rudimentary pencil drawing on a blank page that serves as a preview of what the scene should be in the final product.

Afterward, I create my models in the 3D software, taking care of the colors, textures, lights, cameras, and rendering parameters. I render several sequences for the same scene, each containing a specific piece of information - one for colors, one for ambient light, etc. Sometimes I shoot up to four or five different sequences. An 8-second sequence can take anywhere from 10 minutes to three days to render in 3D, depending on the complexity of the scene; I often use my two local computers to render simultaneously.

Once I have the sequences I need, I import them into *After Effects* to perform compositing (associating different sequences for the same scene) and to add special effects.

I record the sound on *Audition* (sometimes on *Soundbooth*) to eliminate background noise and improve audio quality.

Several other software programs were used in various stages of production; for example, *Illustrator* to plot MRI sections and send the curves to the 3D software to create 3D sections of the brain, *Photoshop* for multiple filters and special effects, and *Premiere Pro* for video editing. *Bridge*, as a DAM (digital asset manager), was very useful for organizing the work, which is a key element in a professional project. On average, there are 28,000 computer-generated images to produce for each video; these must be well-organized in specific folders to avoid chaos.

After the videos were made, *Flash/AS3* (ActionScript 3) programming was used to design the medium and the interface for the videos, images, and animations. The texts are formatted in HTML with CSS style sheets, and the data is organized in XML files.

The interactive animations were made using the *Flare3D* program, an extension of *AS3* that allows for the import and manipulation of 3D models within Flash.

Before beginning the realization of this project, Professor **Belahsen** and **I** concluded that it should not be exhaustive or burdened with unnecessary details. The texts are therefore very brief and concise, containing only the essentials, with reference links provided whenever necessary to dig deeper into questions via *Google Books*, which contains an incredible number of resources on the subject.

The DVD resource of the program is accompanied by another DVD-video material to allow the viewing of the videos on a DVD player in high quality.

# Abbreviations

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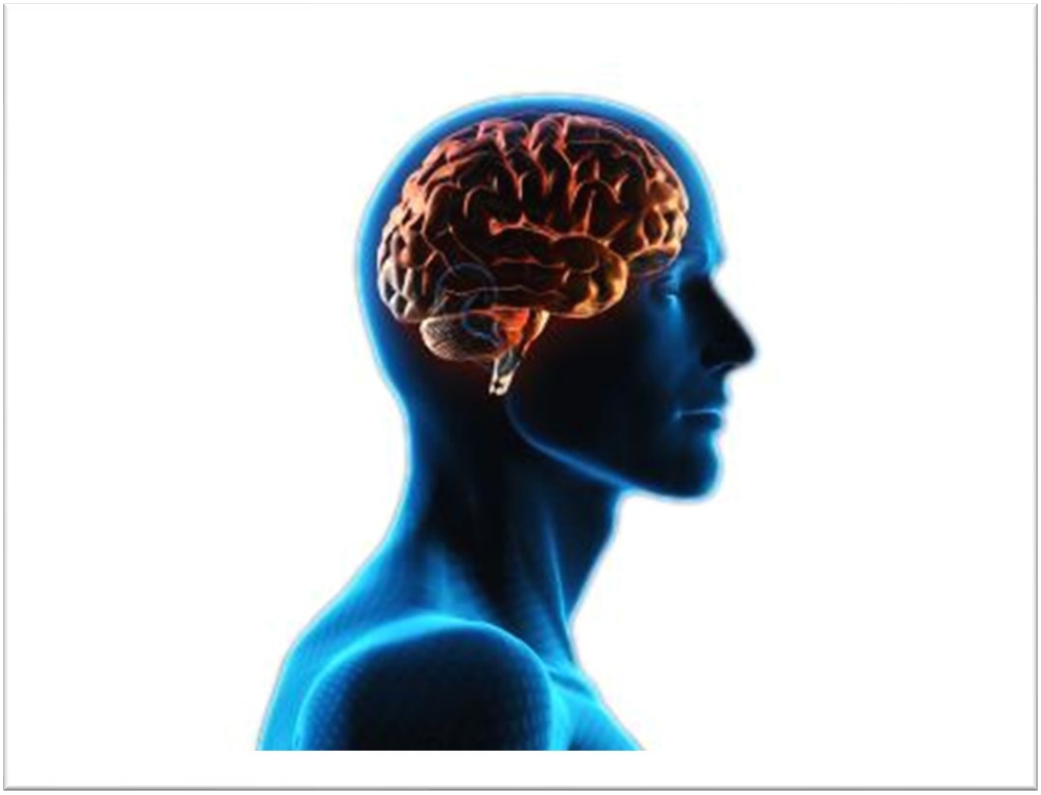
| | |
|---|---|
| **ACh** | Acetylcholine |
| **AChR** | Acetylcholine Receptors |
| **AChE** | Acetylcholinesterase |
| **ACTH** | Adrenocorticotropic Hormone |
| **ADH** | Antidiuretic Hormone |
| **AP** | Action Potential |
| **ARAS** | Ascending Reticular Activating System |
| **ATP** | Adenosine Triphosphate |
| **BBB** | Blood-Brain Barrier |
| **BG** | Basal Ganglia |
| **CNS** | Central Nervous System |
| **CSF** | Cerebrospinal Fluid |
| **CVA** | Cerebrovascular Accident (Stroke) |
| **dB** | Decibels |
| **EEG** | Electroencephalogram |
| **EP** | Evoked Potentials |
| **EPSP** | Excitatory Postsynaptic Potential |
| **FSH** | Follicle-Stimulating Hormone |
| **GABA** | Gamma-Aminobutyric Acid |
| **GH** | Growth Hormone |
| **HLA** | Human Leukocyte Antigen |
| **Hz** | Hertz |
| **Ig** | Immunoglobulin |
| **IHC** | Inner Hair Cells |
| **IPSP** | Inhibitory Postsynaptic Potential |
| **IHT** | Intracranial Hypertension |
| **L2** | Second Lumbar Vertebra |

| | |
|---|---|
| **L-dopa** | Levodopa |
| **LH** | Luteinizing Hormone |
| **LTP** | Long-Term Potentiation |
| **MG** | Myasthenia Gravis |
| **MRI** | Magnetic Resonance Imaging |
| **MS** | Multiple Sclerosis |
| **MSH** | Melanocyte-Stimulating Hormone |
| **NMDA** | N-Methyl-D-Aspartate |
| **NRS** | Numerical Rating Scale |
| **NSAIDs** | Non-Steroidal Anti-Inflammatory Drugs |
| **OHC** | Outer Hair Cells |
| **PET** | Positron Emission Tomography |
| **PNS** | Peripheral Nervous System |
| **REM** | Rapid Eye Movement |
| **S1** | Primary Somatosensory Cortex |
| **S2** | Secondary Somatosensory Cortex |
| **SVS** | Simple Verbal Scale |
| **TIA** | Transient Ischemic Attack |
| **TSH** | Thyroid-Stimulating Hormone |
| **VAS** | Visual Analogue Scale |
| **VPL** | Ventral Posterolateral Nucleus |
| **VPM** | Ventral Posteromedial Nucleus |
| **WHO** | World Health Organization |

# Introduction



# Introduction

"*Education is the kindling of a flame, not the filling of a vessel* ", **Socrates.**

**The nervous system** (human in particular) is arguably the most complex and fascinating structure in the entire known universe to date. It is the foundation of our identity, our thoughts, our memory, our emotions, and all the sensations we experience at every moment. The nervous system allows us to see, hear, smell, and discover the world and environment to which we belong. It also allows us to *act* on this environment: it enables us to build, move, eat, adapt, and expand our faculties in order to apprehend both the most infinitely small particles and the immense and vast structures of the infinitely large universe.

All the rest of the body's organs are **at the service of the nervous system**: the digestive system supplies it with nutrients, the lungs provide it with oxygen, the cardiovascular system ensures the delivery of these resources, and the kidneys purify the blood of toxins that could damage it. Every organ in the body serves the nervous system in one way or another, because if this system fails, all of life goes with it.

Since the dawn of history, humanity has been looking for answers to several questions about thought, language, memory, and emotions. In the absence of resources, the answers were often misguided. Today, with science and technological development at its peak, we have some solid preliminary answers about how this incredible human machine works.

Unfortunately, the nervous system, as extraordinary and fabulous as it is, is not infallible. We sometimes see its functioning altered and its capacities decrease. As paradoxical as it may seem, it is largely **thanks to these abnormalities** that we have been able to discover how the nervous system works. Throughout the history of medicine, researchers and doctors have described neurological diseases and disorders in individuals; after their death, they examined the bodies to see what was missing, because the anatomical abnormalities of certain regions gave many clues about their roles in specific functions - functions such as language, memory, and emotions. However, these were impractical methods, as it was not until the individual died that the anomaly could be identified.

**Comparative physiology** with other animals has also always been a major contributor. But what has undoubtedly most marked modern science in this sense is the development of highly sophisticated methods and means of investigation: optical and electron **microscopy**, **staining** techniques, medical **imaging** (functional imaging in particular), the development of neurophysiology, etc.

All these means, and especially the **dedicated people** who took upon themselves to ask

questions and worked hard to find answers to them, have allowed us to know a great deal about the nervous system today.

Understanding how the nervous system works and the mechanisms of its disorders provides insight into how research can be conducted, or at least in what direction, in order to find effective cures for horrific and devastating neurological diseases such as **Parkinson's** and **Alzheimer's**.

# Anatomical Overview

Anatomically, a distinction is made [160] between the central nervous system (CNS) [95, 225] (or neuraxis) and the peripheral nervous system (PNS) [125].

**Image 1:** The CNS.

## 1. The central nervous system:

### 1.1. The brain :

The brain [157] is located in the skull and contains: the two cerebral hemispheres [224] (which hold the cerebral cortex), the cerebral ventricles [37] where cerebrospinal fluid (CSF) circulates [95], the basal ganglia [4], the thalamus [75], the hypothalamus [4, 50], the cerebellum [4, 54], and the brainstem [32, 38].

### 1.2.The spinal cord :

The spinal cord [38, 160] is the extension of the brainstem outside the skull; it is protected within the spinal canal [43] in the center of the spine. Anterior and posterior roots emerge from it to form the spinal nerves [38, 125].

## 2. The peripheral nervous system :

The **PNS** consists of various nerves and nerve ganglia located outside the neuraxis. It essentially comprises 11 pairs of cranial nerves [64] emerging at the level of the skull (the optic nerve is considered part of the **CNS** [41]), and 31 pairs of spinal nerves [6, 7, 8, 9, 10, 11, 12, 13] which emerge from the **intervertebral foramina** located in the spine.

# The spinal cord

The spinal cord [38, 160] is well protected within the spinal canal [43], which runs through the spine. In adults, it is about 42 cm long in women and 45 cm in men [13, 14, 15, 16, 17, 19]. The spinal cord is the origin of all spinal nerves [38, 125], which number 31 pairs [14].

The spinal cord, like the brain, is surrounded by meninges [43]: the **pia mater** [38, 85], **the arachnoid** [64, 94], and the **dura mater** [43, 69, 94]. It is bathed in **CSF** [95], and it is pierced in the center by a rudimentary canal (the **ependymal canal**) [14, 20].

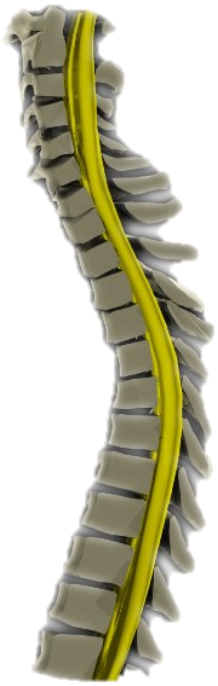


**Image 2**: The spinal cord protected within the spinal canal.

## 1. External Configuration :

Due to the faster intrauterine development of the spine, the nerve roots of the spinal nerves are displaced compared to the intervertebral foramina from which they emerge. This is why the spinal cord ends at the level of the second lumbar vertebra (L2) [21, 22, 23, 24, 25], although it gives off roots extending as far as the fifth sacral or even the first coccygeal roots [26, 27, 28, 29, 30].

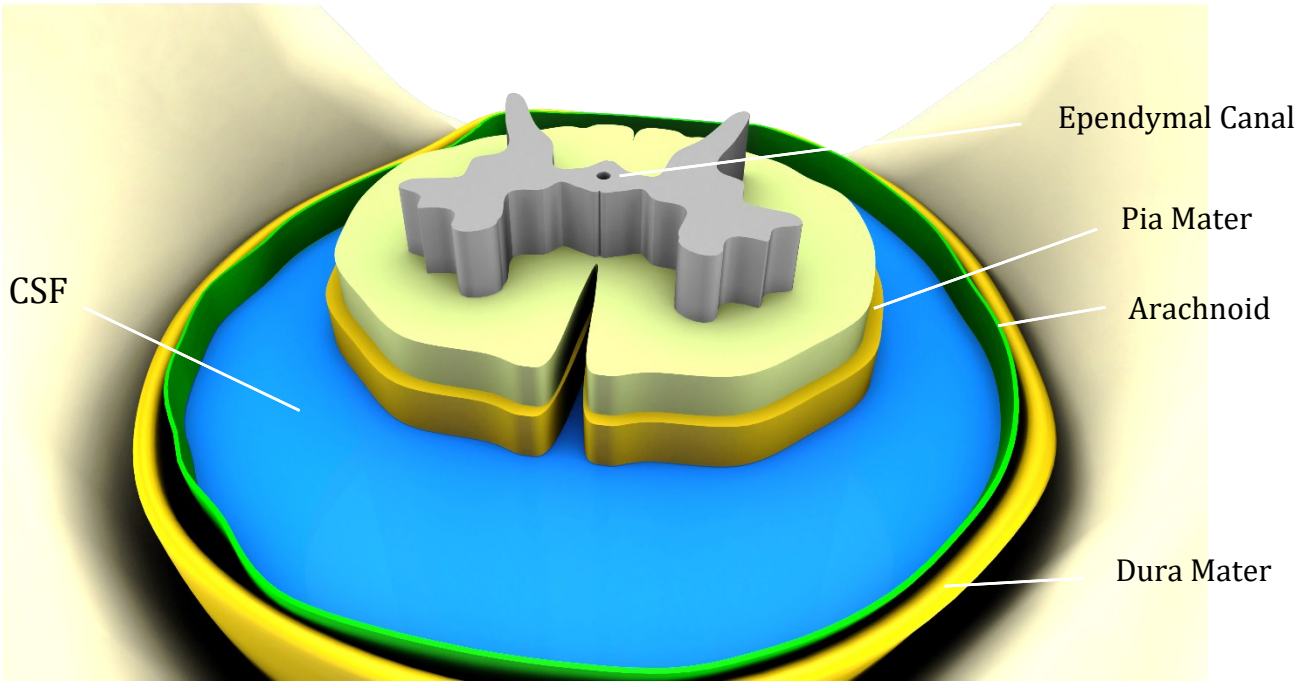



**Image 3:** The spinal cord surrounded by the three meningeal layers.

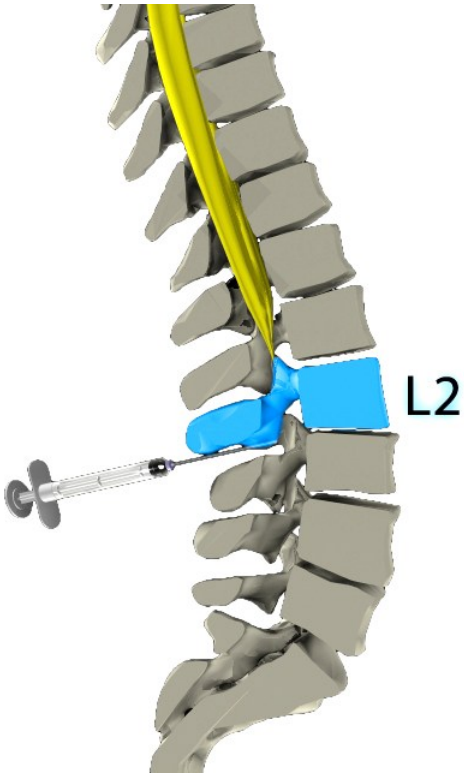



**Image 4:** Lumbar puncture.

When a **lumbar puncture** is to be performed, it is generally done below the second lumbar vertebra so as not to injure the spinal cord [2, 31, 32, 33].

The spinal cord follows the path of the spine, thus describing **two curvatures**: a cervical one with a posterior concavity (**lordosis**) and a thoracolumbar one with an anterior concavity (**kyphosis**) [34].

It also presents two enlargements (**bulges**) [32, 35, 36, 37, 38] : a cervical and a lumbar one, related to the innervation of the upper and lower limbs. It ends at the bottom with the **conus medullaris** [50], which gives rise to the **cauda equina** [91] (a cluster of lumbosacral descending roots).

## 2. Internal Configuration :

On a cross-section [43], the spinal cord has a central region: the **gray matter**, which includes the bodies of nerve cells, and a peripheral part: the **white matter**, which is made up of axonal extensions and their myelin sheaths [104, 113, 124, 125].

The gray matter takes the shape of a butterfly, with two **anterior horns** housing the bodies of the motor neurons and two **posterior horns** which receive the sensory fibers. In the thoracolumbar spinal cord, there are also **lateral horns** for the cell bodies of the **sympathetic fibers** [40, 41, 42].

The white matter is organized into three pairs of columns (**funiculi**) [36, 43, 44, 45] (anterior, posterior, and lateral).

The spinal cord also has a **ventral fissure**, which is the most pronounced, a **posterior sulcus**, and two **lateral sulci** from which two pairs of nerve roots arise: one anterior (**motor**) and the other posterior (**sensory**). These two roots join together to form a spinal nerve.

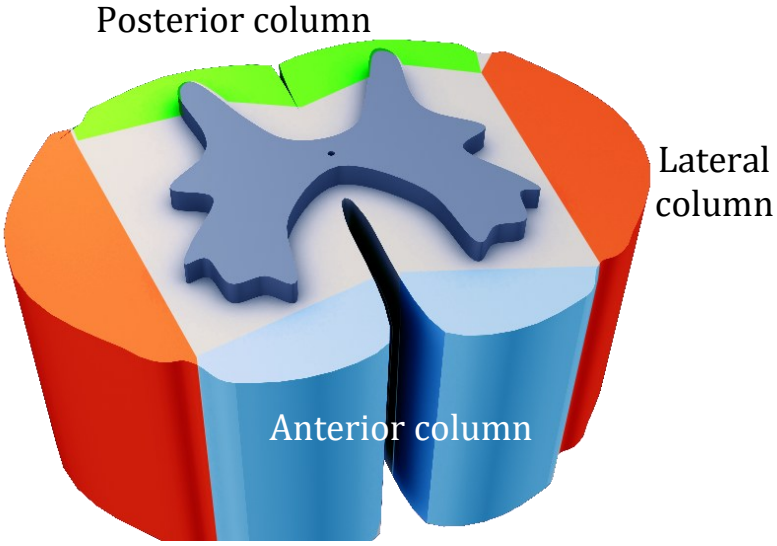



**Image 5:** The columns of the spinal cord

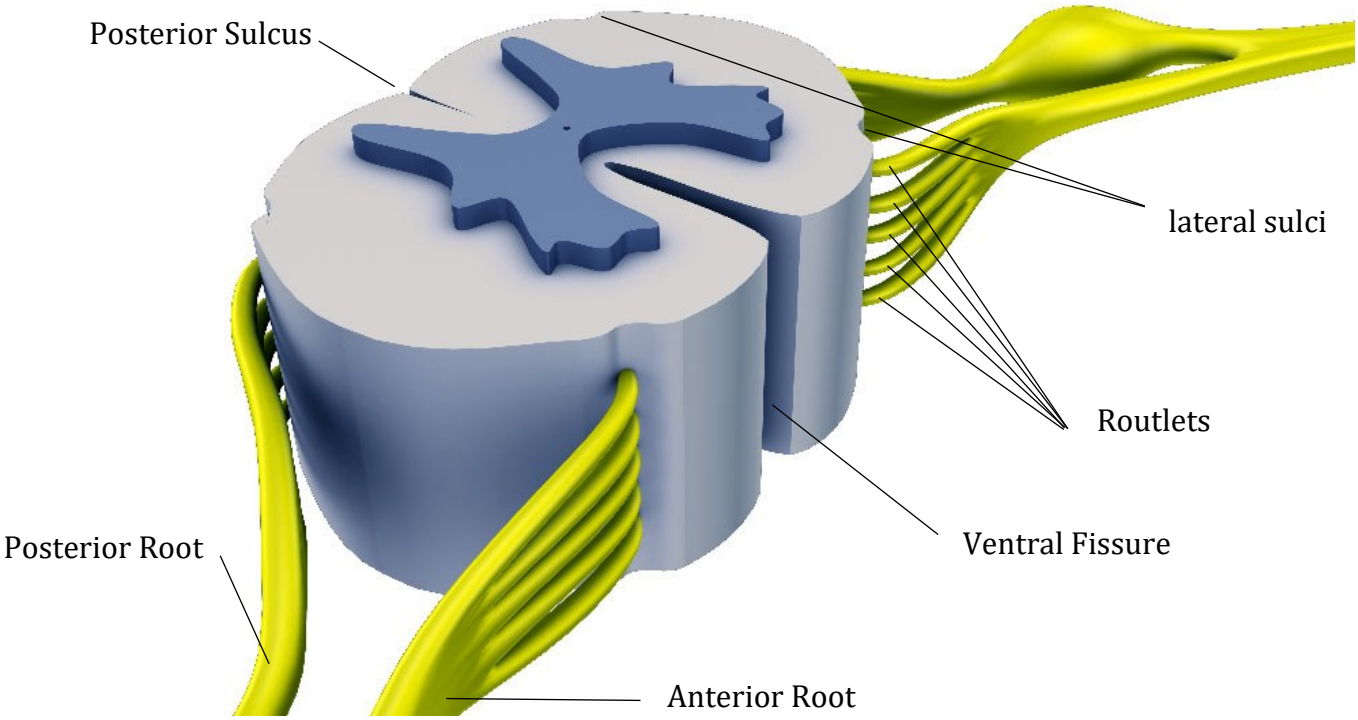



**Image 6:** The emergence of spinal nerve roots.

# The brainstem

**The brainstem** [32, 38] is an anatomical structure of the brain that connects various elements of the nervous system: the **cerebrum**, cerebellum, and spinal cord. It plays a **vital role** [32, 41, 46] due to the essential functions regulated by its nuclei [1], including respiration and heart rate. It is also a transition zone for sensory and motor pathways, as well as a center for **pain control** [47, 48]. Furthermore, it serves as the site of emergence [41] of **the majority of the cranial nerves** [64].

It is divided into three sections [36], which are, from top to bottom: the **midbrain** (**mesencephalon**) [49], the **pons** [181], and the **medulla oblongata** [72].

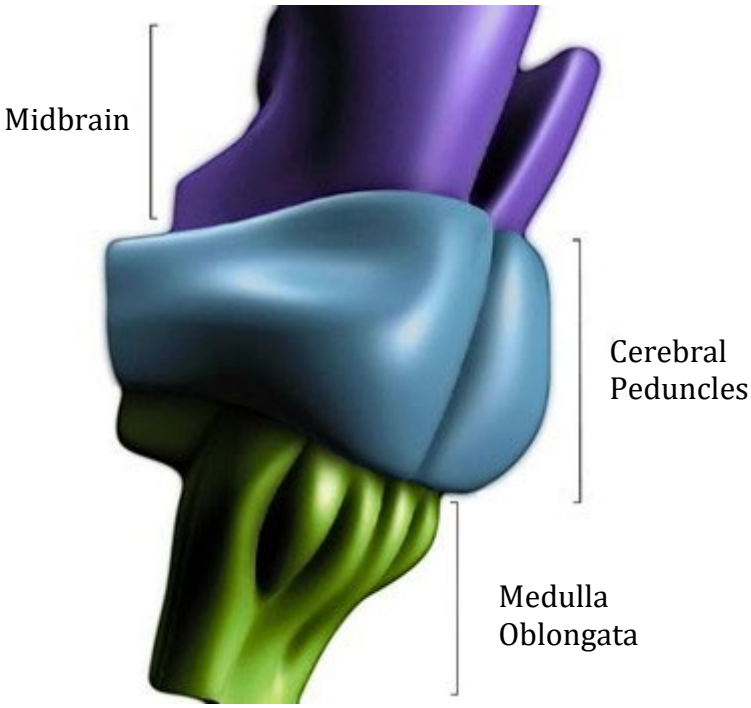



**Image 7:** The three portions of the brainstem.

## 1. The midbrain :

The **midbrain** (or **mesencephalon** [38]) is the part of the brainstem directly connected to the brain via the **cerebral peduncles** [38]. Behind these lies the **tegmentum** [49, 50, 51], which contains the **aqueduct of Sylvius** [41, 43, 72]; the latter connects the **third ventricle** to the **fourth ventricle**. Posteriorly, the midbrain contains the **corpora quadrigemina** [226] (**tectum** [39]), which are essential for functions such as vision and hearing.

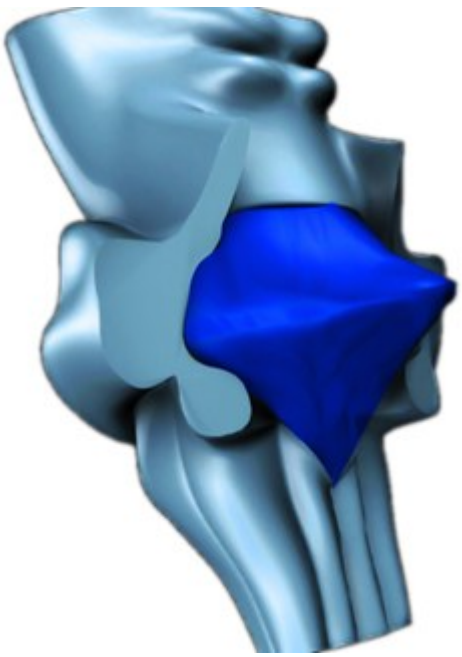


**Image 8:** The Fourth ventricle.

## 2. The Pons :

The **pons** (or **pons Varolii** [38]) is the intermediate part of the brainstem. It plays an important role in motor control, particularly as a relay station between the cerebrum and the cerebellum [52]; it also contributes to autonomic functions and facial sensation (it is at this level that the nucleus and the emergence of the **trigeminal nerve** are located [116]). The **pons** is connected to the cerebellum

by a pair of **middle cerebellar peduncles** [64] and forms the anterior surface (or floor) of the **fourth ventricle** [64].

## 3. The medulla oblongata :

The **medulla** (or *myelencephalon* [38] ) is the part of the brainstem that is continuous with the spinal cord below. It contains the **olivary bodies** [32] as well as the **medullary pyramids** [119] (structures through which the **corticospinal fibers** [39] of the **pyramidal tract** [179, 227] pass).

The *medulla*, or *medulla oblongata* [73] , contains vital autonomic control centers such as the **respiratory centers** [119]. It ends downward at the **pyramidal decussation** [5, 40] , a zone where the fibers of the **corticospinal tract** cross.

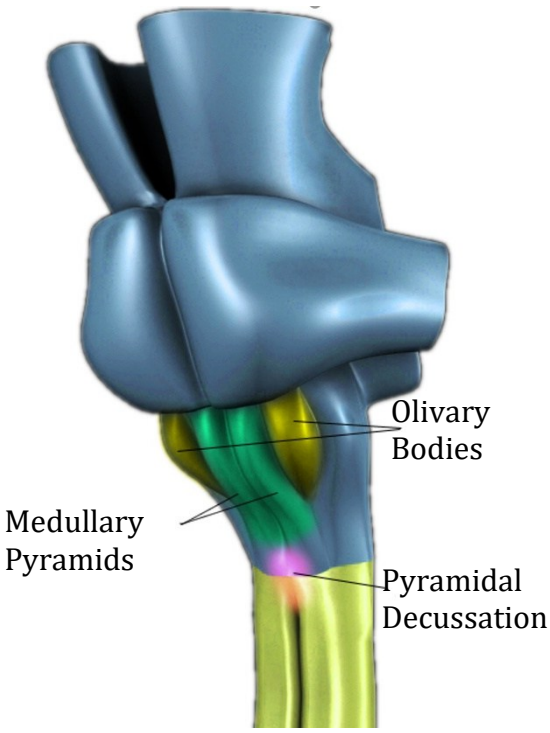



**Image 9:** The medulla oblongata.

# The cerebellum

**The cerebellum** [4, 54] is an organ of the central nervous system located directly behind the brainstem. Together with the brainstem, it occupies the **posterior cranial fossa** [32, 43, 45] below the **tentorium cerebelli** [38].

It is attached to the brainstem by three pairs of **cerebellar peduncles** [43] : superior, inferior, and middle.

The cerebellum contributes primarily to **balance** and **motor coordination** [53]. The concentric grooves that mark its surface give it a foliated appearance.

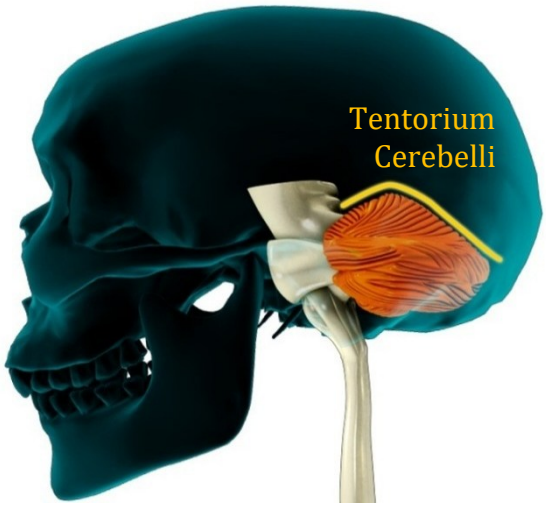



**Image 10:** Location of the cerebellum within the skull.

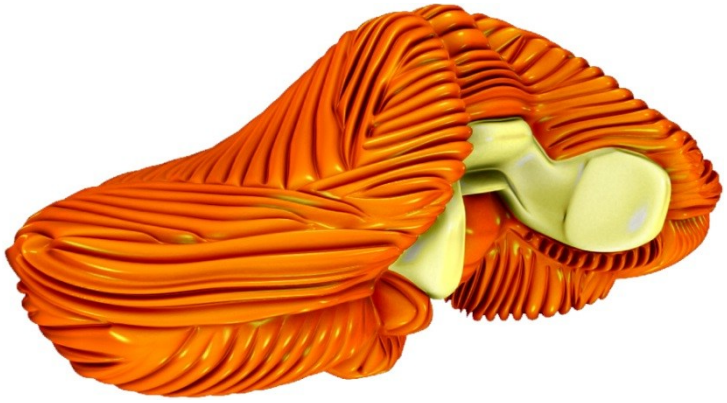


**Image 11:** The cerebellum.

The cerebellum is divided into **three main lobes**: *anterior, posterior, and flocculonodular* [35, 54].

These lobes are further subdivided into **ten lobules** by secondary fissures [4, 43].

The cerebellum is described as having a central (median) region, the **cerebellar vermis** [55, 56] , and three pairs of deep nuclei: **dentate, interposed, and fastigial** [38, 54, 57].

The cerebellum shares many similarities with the cerebrum: it also has a **peripheral cortex** [3, 32, 75] and deep **gray nuclei** that contain neuronal cell bodies. It has two **cerebellar hemispheres** [157] : right and left, as well as several fissures that delineate lobes.

The fissures of the cerebellum are deeper [130] than those of the cerebrum, this vastly increases the surface area of the cerebellar cortex, estimated to be **75%** of that of the cerebral cortex [4].

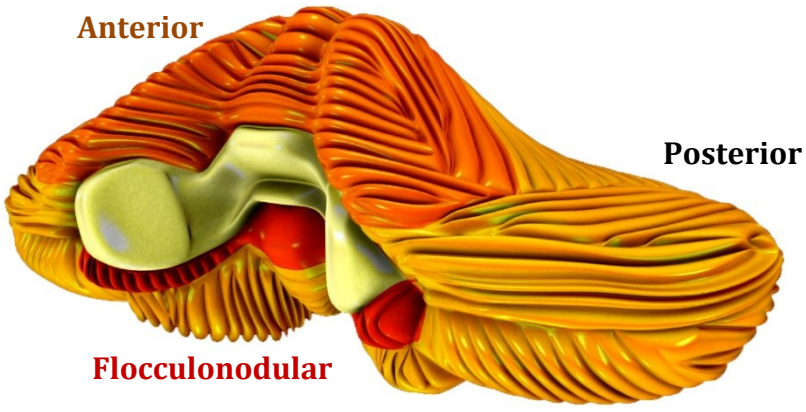



**Image 12:** The lobes of the cerebellum.

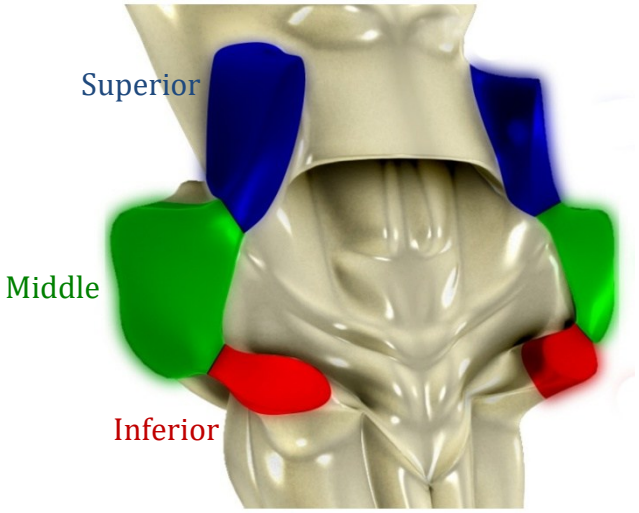



**Image 13:** The Cerebellar Peduncles.

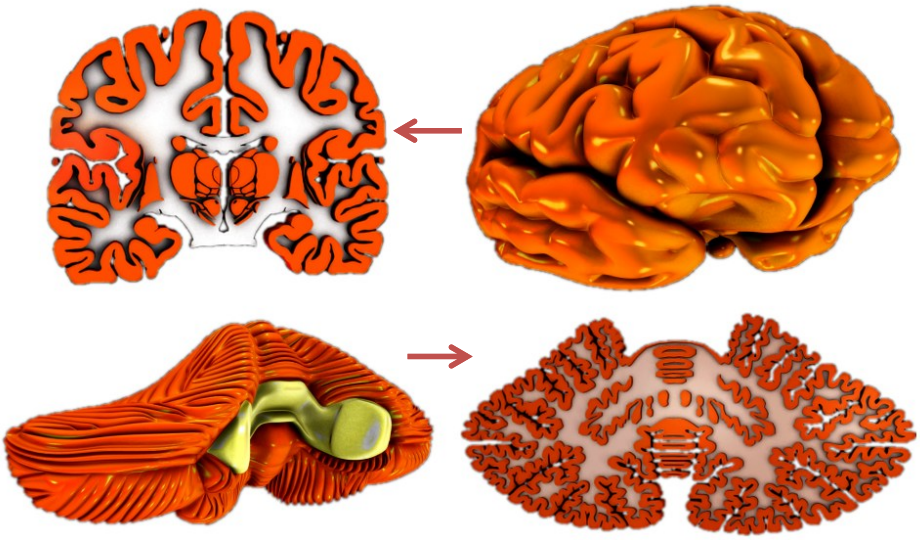


**Image 14:** Comparison between the brain and the cerebellum.

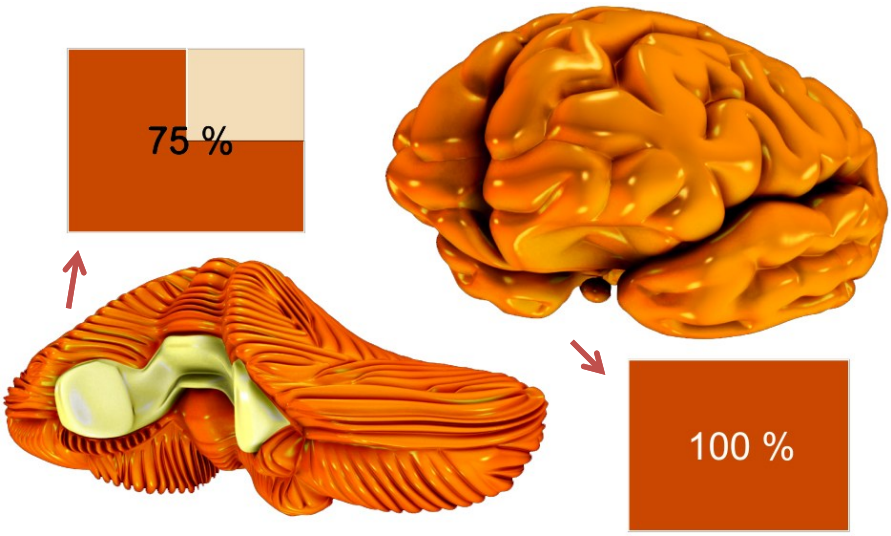



**Image 15:** Comparison between the surface of the cerebellar cortex and cerebral cortex.

The **human brain** [53] (**prosencephalon** [8, 64] , the most prominent part of the encephalon) consists of two nearly symmetrical right and left **cerebral hemispheres** [224] forming the **telencephalon** [58] , in addition to the **diencephalon** [41, 51] - an unpaired, median part covered by the telencephalon - that includes the **thalamus** and **hypothalamus** [8, 59].

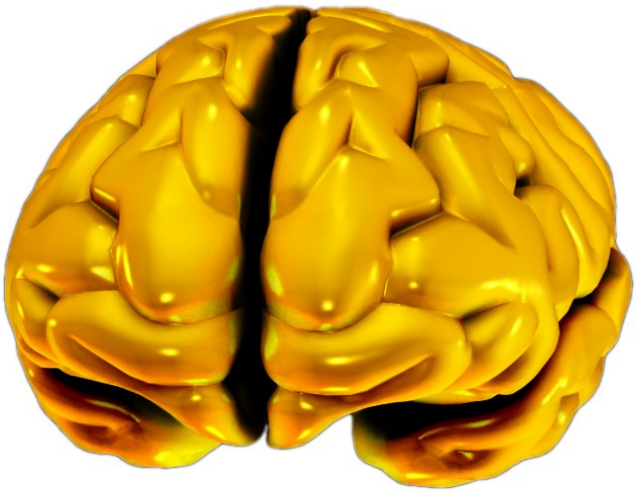


**Image 16:** The brain.

## 1. Internal Configuration :

The cerebral hemispheres constitute the uppermost and largest part of the **central nervous system** [60]; both are linked by nerve commissures, primarily the **corpus callosum** [37, 61, 62].

Each cerebral hemisphere comprises two distinct regions: a peripheral one, the **cortex (gray matter)** [36, 49], containing the cell bodies of the nerve cells; and a central one made of **white matter**, containing essentially the axonal extensions of the neurons as well as their myelin sheaths [39].

Inside each hemisphere are islands of gray matter called the **basal ganglia** [4]. These essentially include the **caudate nucleus** [32, 66] , the **putamen** [32, 51] , the **globus pallidus** [32] , and the **claustrum** [50].

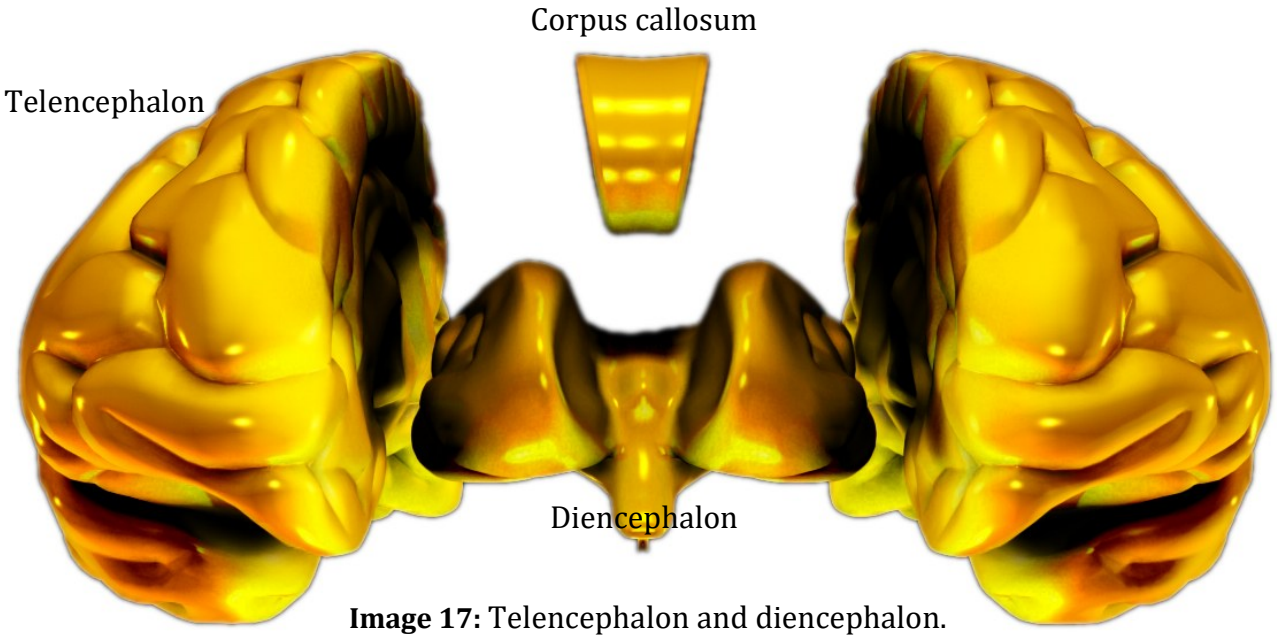



**Image 17:** Telencephalon and diencephalon.

## 2. External Configuration :

Each hemisphere is marked by deep **sulci** [91] that delineate **lobes** [224]. The first is the **lateral sulcus** (or **Sylvian fissure** [91] ), through which the **Sylvian artery** [38] passes; this separates the frontal lobe from the temporal lobe.

The second fissure is the **central sulcus** (or **Rolandic fissure** [63, 72]), which separates the frontal lobe from the parietal lobe.

The third is the **parieto-occipital sulcus** [64] , which separates the occipital lobe from the temporal and parietal lobes.

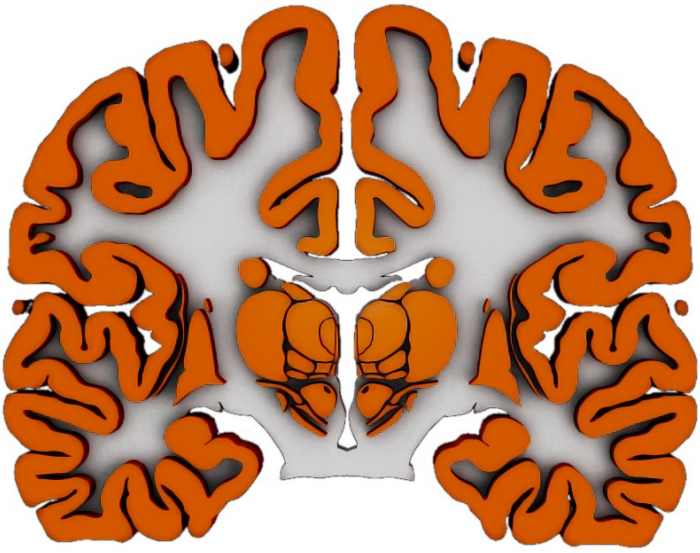


**Image 18:** A frontal section of the brain.

There is also a fifth lobe not visible on the surface: the **insula** [65], which is found by retracting the Sylvian fissure.

Within each lobe, there are shallower sulci that delineate **gyri** (convolutions) [66].

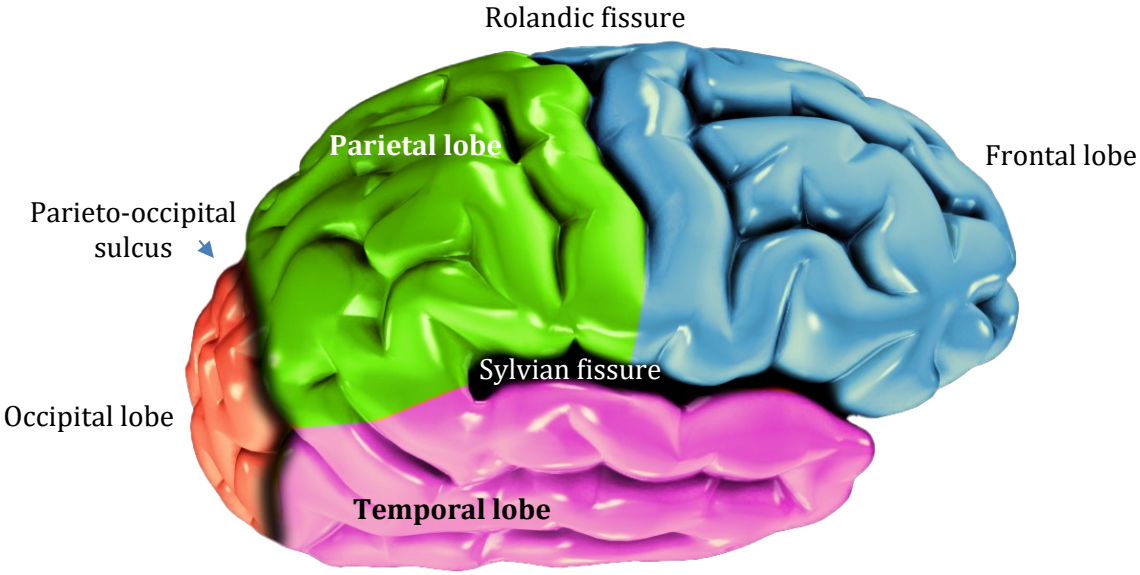



**Image 19:** Side view of the brain.

# Cerebrospinal fluid

The **cerebrospinal fluid** (**CSF**) [3, 5, 50, 71, 91], is the liquid that bathes the central nervous system [45, 67] (brain and spinal cord). It thus provides protection against mechanical shocks and vibrations [5, 31, 42, 68]; it plays a very important role in the regulation of intracranial pressure [42, 69], it participates in cerebral metabolic processes by regulating the exchange of substances [42], and performs many other functions as well [160].

**Image 20:** The cerebrospinal fluid.

The **CSF** circulates in two different compartments: an **intra-encephalic** compartment consisting of ependymal cavities or ventricles, and an **extra-encephalic** compartment corresponding to the **subarachnoid spaces**.

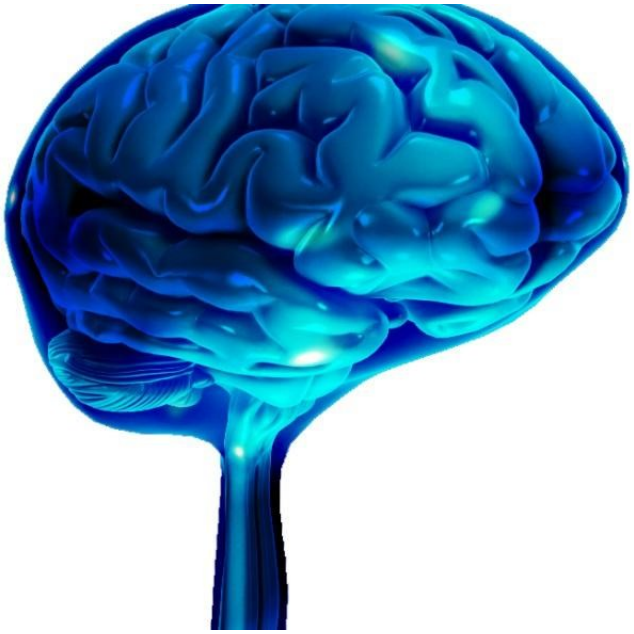


**Image 21:** The extra-encephalic compartment.

The **CSF** is secreted at the level of the **choroid plexuses** [38] : clusters of capillary blood vessels located within the ventricular system [41].

This system, which hollows out the brain, consists of four large cavities [70] (the **cerebral ventricles** [37]) connected to one another by channels. It continues in the spinal cord as the **central canal** [42].

There are two **lateral ventricles** [43, 66], each occupying the center of a cerebral hemisphere. These two lateral ventricles are each connected to the **third ventricle** [38, 224] at the core of the diencephalon via the two **interventricular foramina** (foramina of Monro) [2, 41, 71, 160].

The third ventricle is connected to the **fourth ventricle** [43, 51] at the level of the brainstem by the

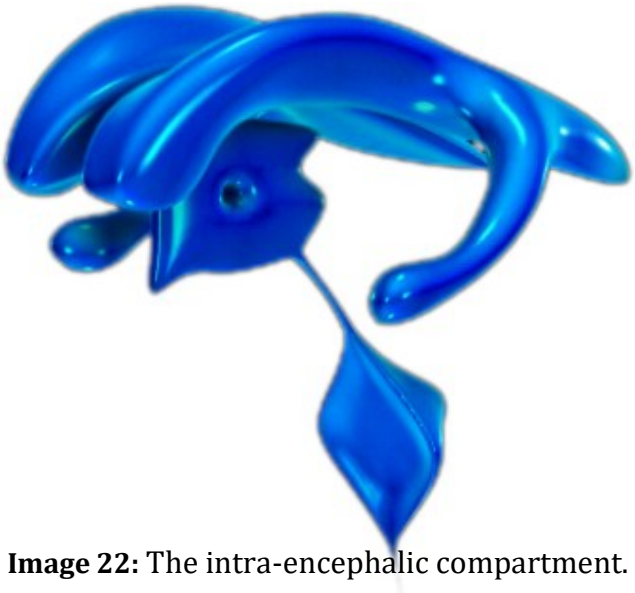


**Image 22:** The intra-encephalic compartment.

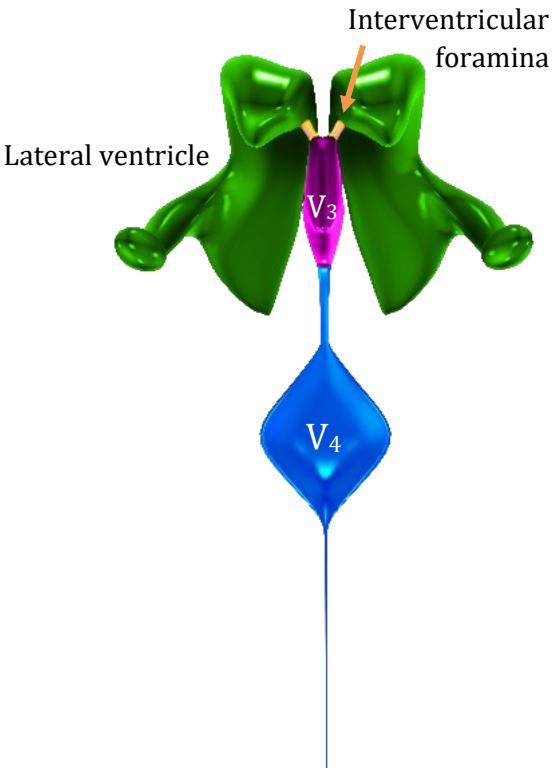



**Image 23:** The ventricular system.

**aqueduct of Sylvius** [41, 43, 72]. From there, the **CSF** exits through the **median aperture** (foramen of Magendie) [32, 38] to occupy the **subarachnoid spaces** [43, 64, 230] between the **pia mater** [38, 85] and the **arachnoid** [64, 94].

The **CSF** is then reabsorbed at the top of the skull through the **arachnoid granulations** (Pacchionian granulations) [160, 183, 226].

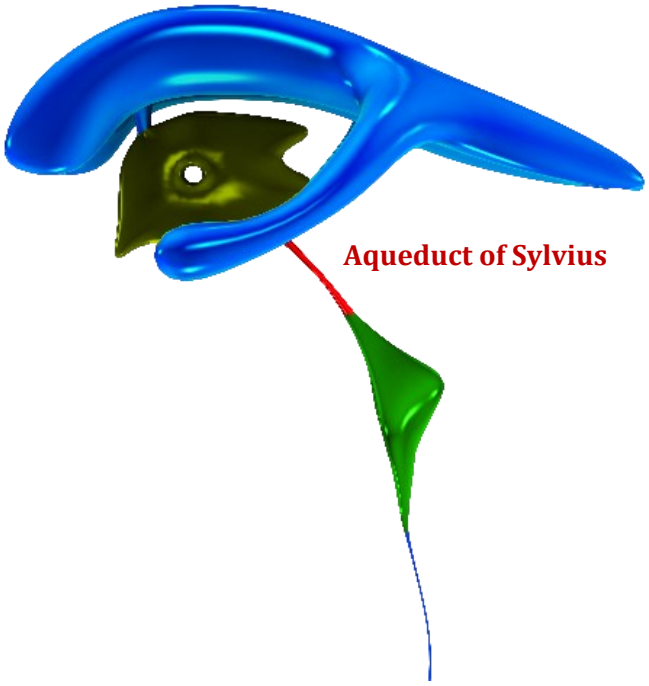



**Image 24:** The aqueduct of Sylvius.

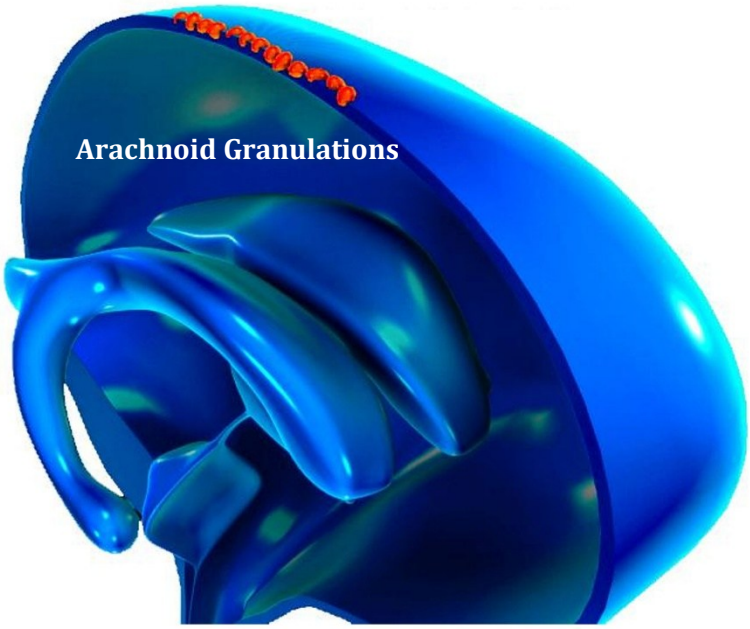



**Image 25:** CSF resorption.

# Thalamus and Hypothalamus

Covered by the two cerebral hemispheres, the **diencephalon** [41, 51] is the central nervous system structure located at the center of the brain.

It contains clusters of gray matter, such as the **thalamus** [42, 75] and **hypothalamus,** that play an extremely vital role in the body.

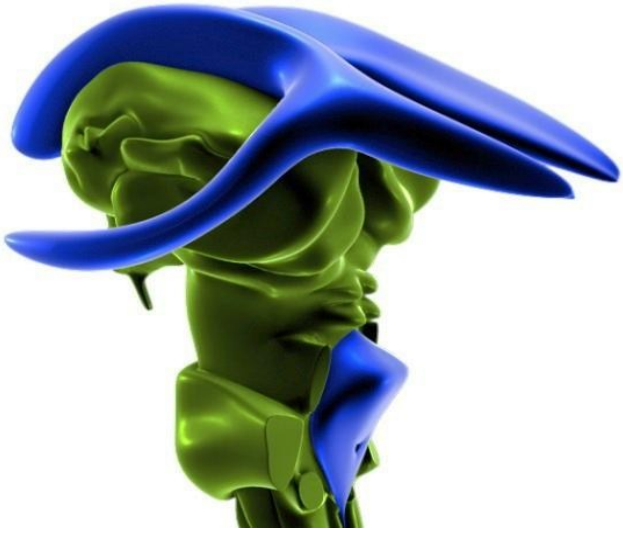


**Image 26:** The diencephalon.

## 1. The thalamus :

The thalamus is a nuclear complex that occupies a large part of the diencephalon [40, 54]. It acts as an essential relay for the vast majority of sensory afferents traveling up to the cerebral cortex [1, 38, 40] , hence its name, which has Greek origins meaning "bed" [40, 119, 140] or "inner chamber" [73] - the one preceding the main room. It also plays a very important role in motor function [40, 75] and the processing of emotions.

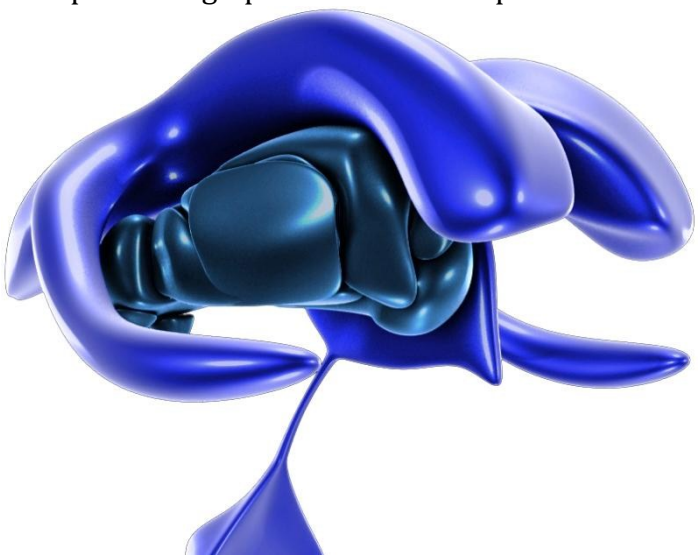


**Image 27:** The thalamus.

The thalamus consists of two masses of gray matter [42] , right and left, each taking an ovoid shape [2, 36, 66]. These two parts are often connected at the center by the **interthalamic adhesion** [38, 43].

The thalamus contains several nuclei [2, 76] , each of which performs a specific role. It forms the lateral wall of the **third ventricle** [38, 224] and is bordered superiorly and anteriorly by the body and frontal horn of each **lateral ventricle** [43, 66].

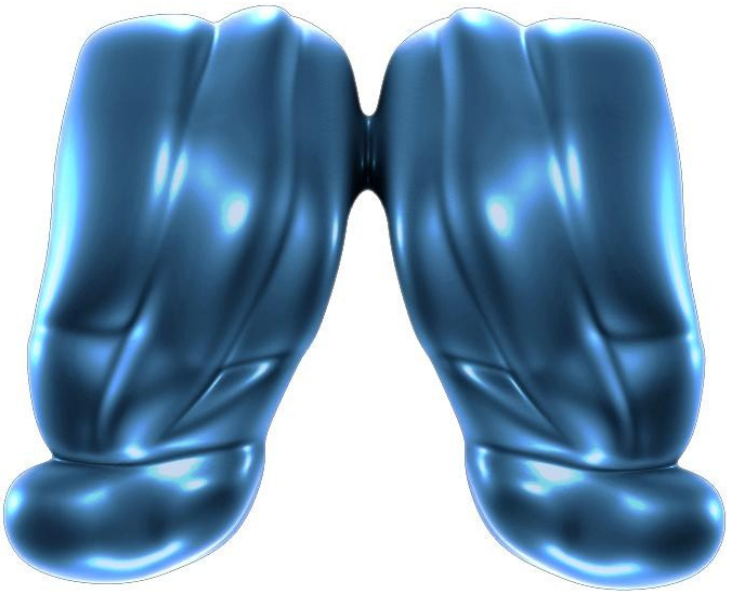


**Image 28:** The two thalami, superior view.

## 2. The hypothalamus :

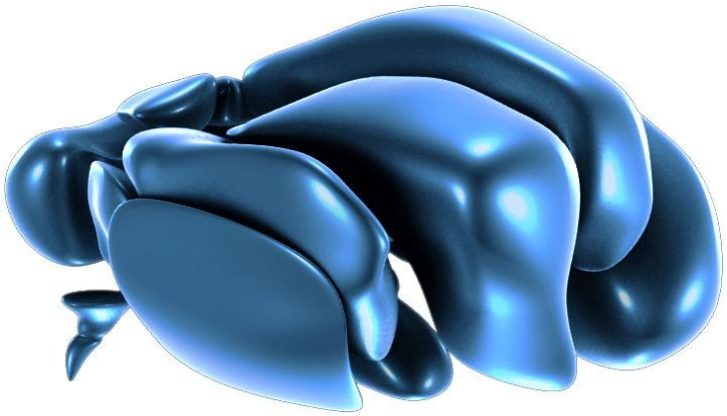


**Image 29:** The nuclei of the thalamus.

The hypothalamus [4, 41, 50] is located directly below [42] and anterior to [54] the thalamus; it is significantly smaller in size and volume than the latter. That said, its role in the body is by no means minor [54, 76].

Indeed, the hypothalamus comprises several distinct nuclei [39] that perform various functions [4, 38], including **thermoregulation** [5, 77], appetite control, and regulation of the sleep-wake cycle. It also plays a vital role in the modulation of the **autonomic nervous system** [4].

The hypothalamus is the primary endocrine driver of the entire body. It controls the secretions of the **pituitary gland**, which produces the body's main hormones [69].

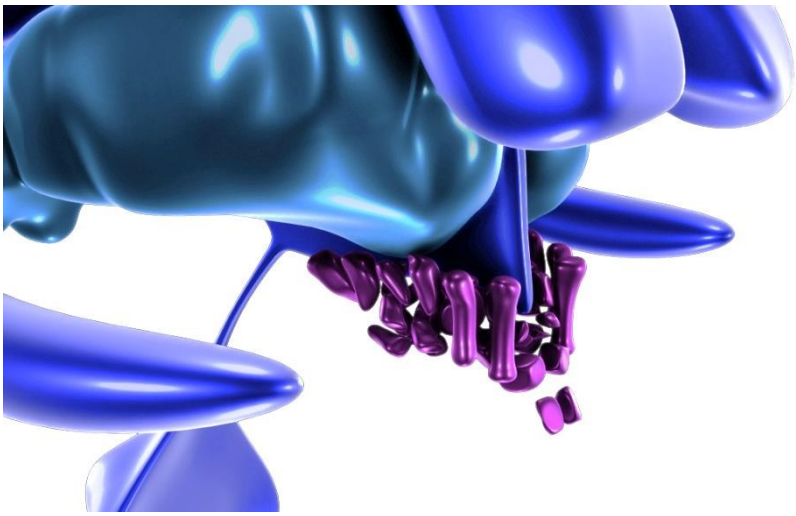


**Image 30:** Location of the hypothalamus.

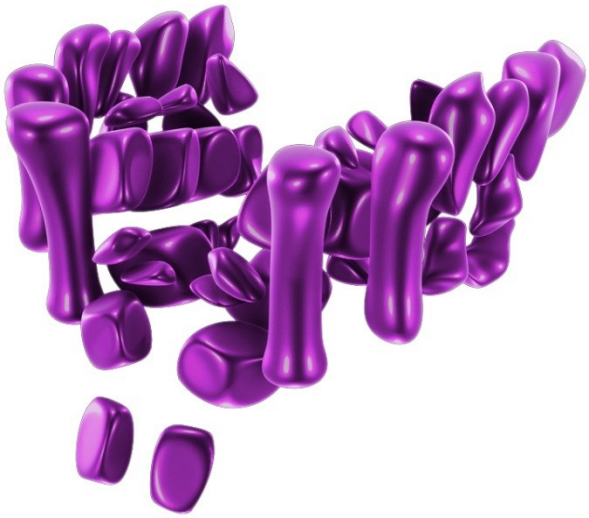


**Image 31:** The nuclei of the hypothalamus.

# Basal ganglia

"*... those dark foundations of the brain...* " **Kinnier Wilson (1925).**

The **basal ganglia (BG)** [4, 54, 91] are a group of richly interconnected subcortical nuclei. They appear gray because they primarily contain neuronal cell bodies. The basal ganglia play a vital role in motor control [53].

There are four primary nuclei: the **striatum** [80], the **pallidum**, the **subthalamic nucleus**, and the **substantia nigra (locus niger)** [4] , in addition to a few other brain structures whose inclusion in the basal ganglia is debated. (Some authors even include the thalamus among the basal ganglia [39, 66] , but most treat it separately).

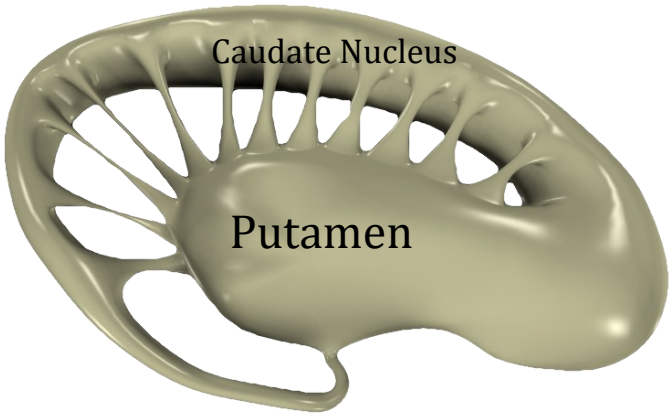



**Image 32:** The striatum.

## 1. The striatum :

It consists of two large nuclei**:**

### 1.1. The caudate nucleus :

The caudate nucleus [32, 66] is a long, lanky, C-shaped structure that "hugs" the lateral ventricles of the brain. You can visualize its three parts like this:

The Head: The thickest part at the front, which forms the wall of the lateral ventricle.

The Body: The middle section that arches over the thalamus.

The Tail: A thin, tapering end that curves all the way down and forward into the temporal lobe, ending near the amygdala.

### 1.2. The putamen :

The putamen [32, 51] is a large, rounded structure that forms the outermost layer of the basal ganglia. Its name comes from the Latin word for "nutshell," which describes its hard, protective appearance. Unlike the elongated caudate, the putamen is more lens-shaped (or lentiform).

## 2. The pallidum :

Also called the **globus pallidus** [32, 64], it comprises an internal and an external part; together with the putamen, it forms the **lenticular nucleus** [2, 37, 66] (so named for its triangular shape on a coronal section).

## 3. The subthalamic nucleus :

The subthalamic nucleus [64] **(body of Luys)** is located below the thalamus and above the midbrain. It is a small structure shaped like a biconvex lens.

## 4. The substantia nigra :

The **substantia nigra** [38] (locus niger) derives its name from the color of its constituent cells, which are rich in black-colored neuromelanin. It plays a very important role in motor function, producing **dopamine** (an essential neurotransmitter) in collaboration with other brain structures. Damage to this area is the primary cause of **Parkinson's disease** [79].

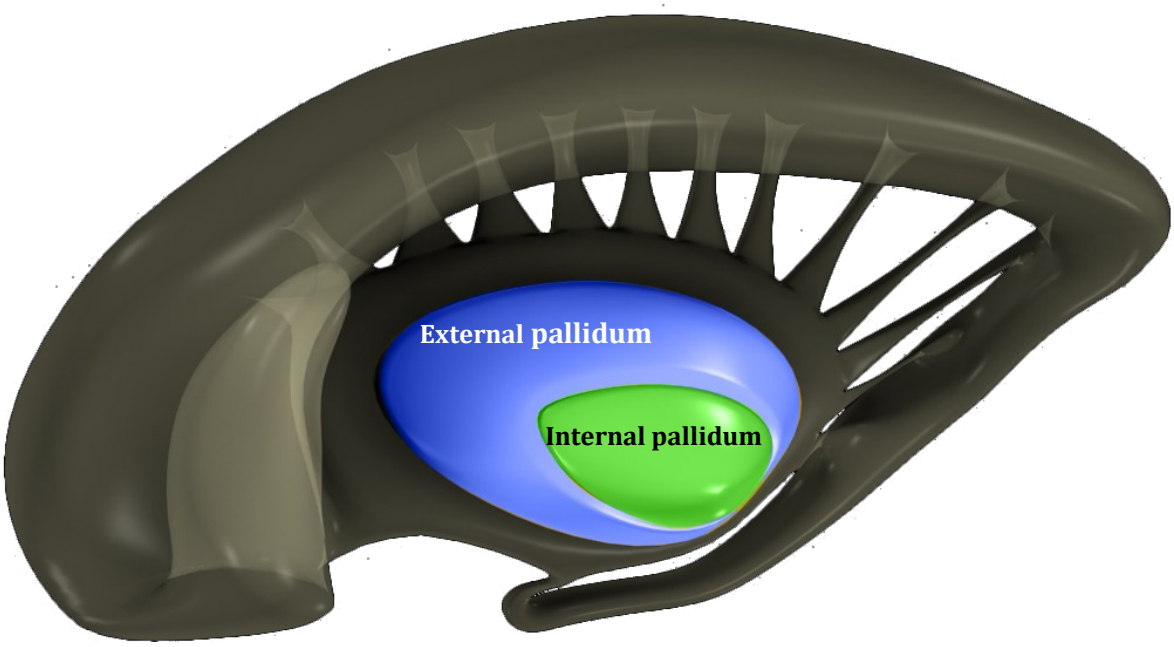



**Image 33:** The pallidum.

# Pituitary and Epiphysis

## 1. The Pituitary gland :

The **pituitary gland** [81,82,83] (hypophysis) is an endocrine gland housed in a bony cavity (the **sella turcica** [84]) and connected to the hypothalamus above by the **pituitary stalk** [64]. It is small in size but plays an extremely important role in the body, given the variety of hormones it produces.

Two parts of the pituitary gland are distinguished and have different embryonic origins: an anterior part, the **anterior pituitary** (adenohypophysis), and a posterior part, the **posterior pituitary** (neurohypophysis).

### 1.1. The anterior pituitary :

The adenohypophysis [42] secretes: growth hormone (**GH**), prolactin, follicle-stimulating hormone (**FSH**), luteinizing hormone (**LH**), adrenocorticotropic hormone (**ACTH**), thyroid-stimulating hormone (**TSH**), and melanocyte-stimulating hormone (**MSH**).

### 1.2. The posterior pituitary :

The neurohypophysis [42] is not composed of glandular cells per se. It contains the nerve endings of neurons originating in the hypothalamus, which release **oxytocin** and **vasopressin** (**ADH** or **antidiuretic hormone**) directly into the bloodstream through **neurosecretion**.

## 2. The pineal gland :

Also called the **epiphysis** [4, 40, 42]**,** is an endocrine gland located behind the third ventricle. It secretes **melatonin**, which plays a fundamental role in regulating the **circadian rhythm**, the body's internal biological clock.

**Descartes** considered this gland to be the "seat of the soul" (origin of the mind) [39].

# Arterial supply

The entire arterial supply [41] of the brain is derived from two arterial systems: the two **internal carotid arteries** [85, 86] anteriorly, and the two **vertebral arteries** [86, 87] (or the **vertebrobasilar system** [88, 89, 90]) posteriorly.

These four major axes are interconnected at several levels, most notably at the base of the brain by the **Circle of Willis** [86, 91]. This anastomotic circle functions as a safety system; if one of the axes becomes deficient, the blood supply from the others compensates for the deficit.

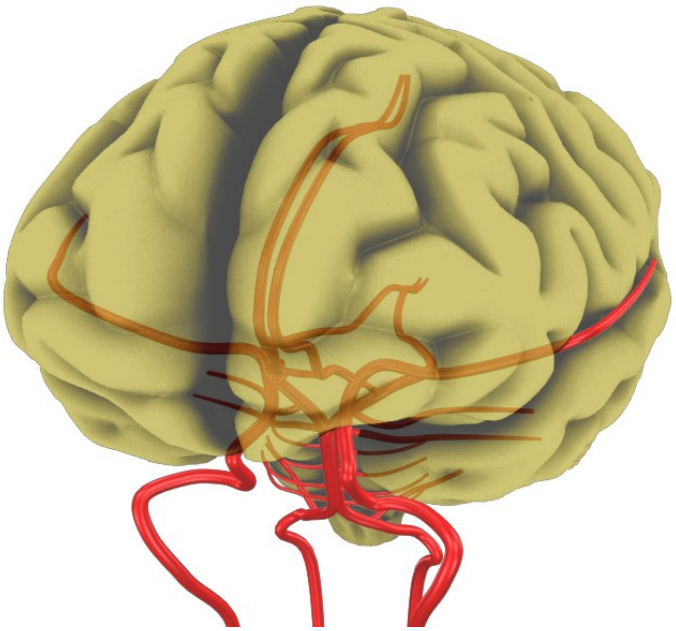


**Image 34:** Arterial supply of the brain.

From this anastomotic circle arise the **main cerebral arteries**.

The internal carotids give off two essential branches: the **anterior cerebral artery** [2], which supplies the medial part of the cerebral hemisphere, and the **middle cerebral artery** [2], which supplies the lateral surface of the hemisphere.

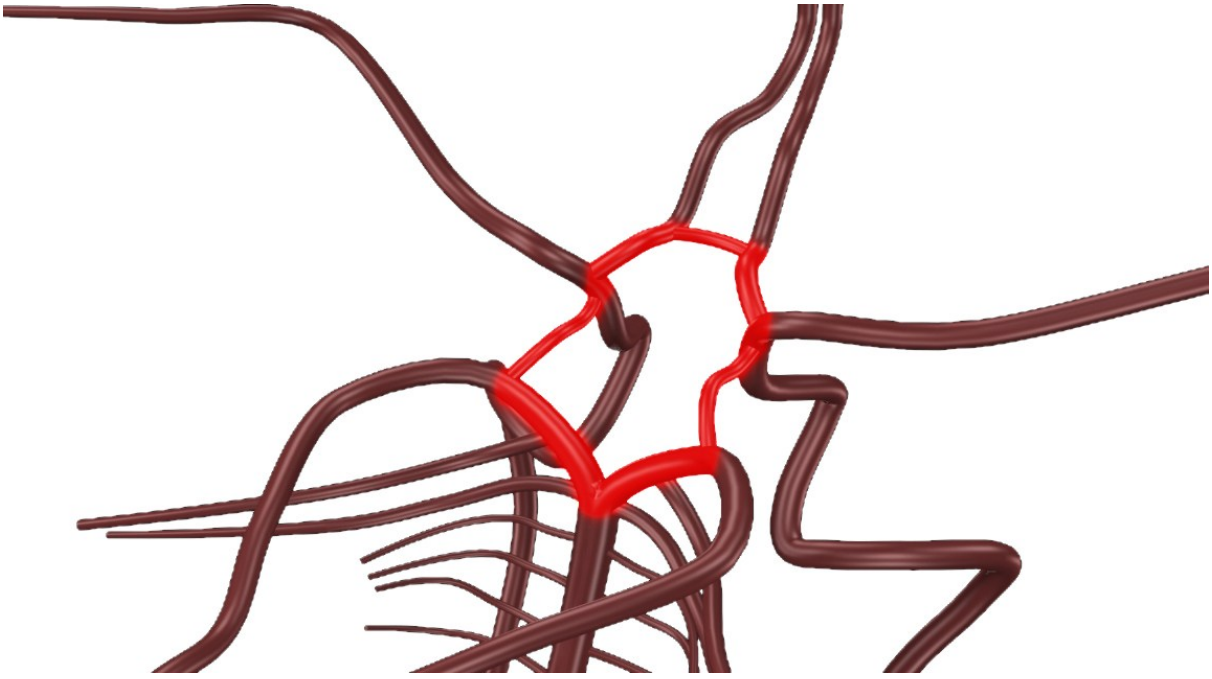


**Image 35:** The Circle of Willis.

The two vertebral arteries merge to form a common trunk (the **basilar artery** [2] ), which gives off branches to the brainstem and the cerebellum. It subsequently divides to form the two **posterior cerebral arteries** [51] , destined for the occipital lobe and the ventral part of the temporal lobe.

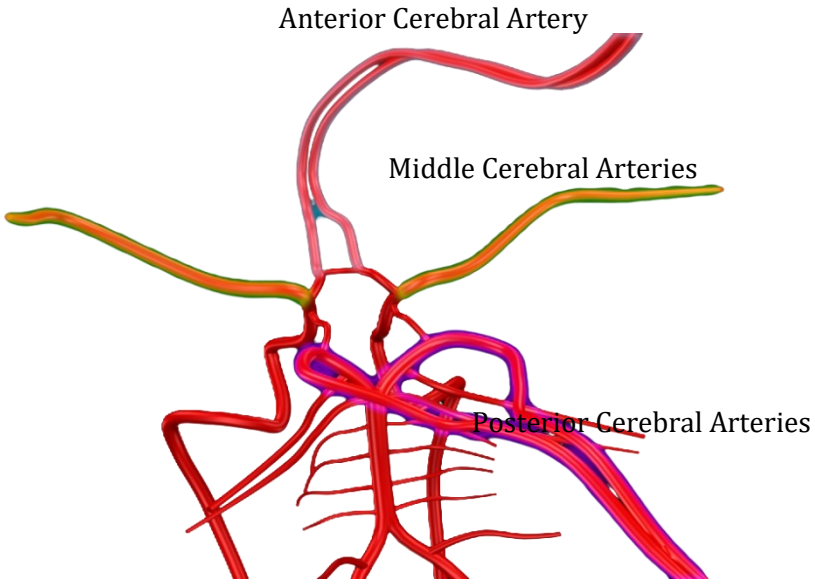



**Image 36:** Cerebral arteries.

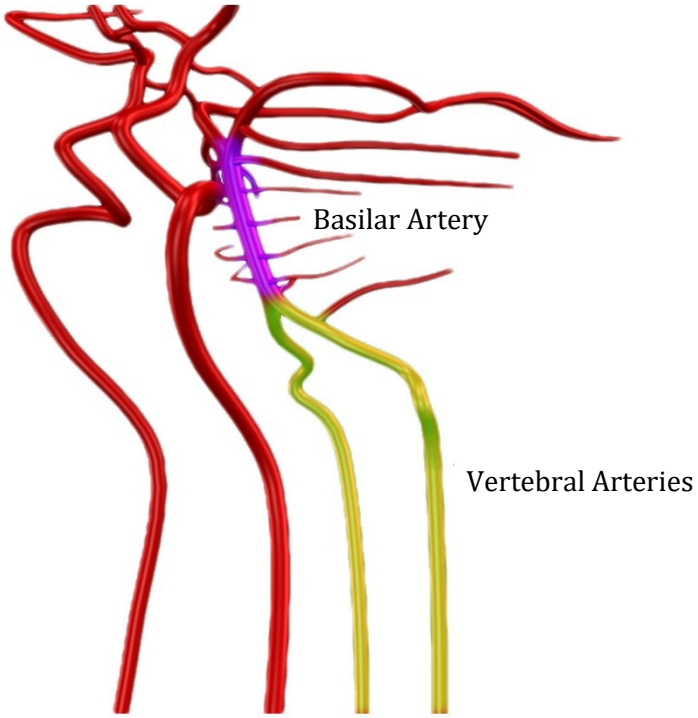
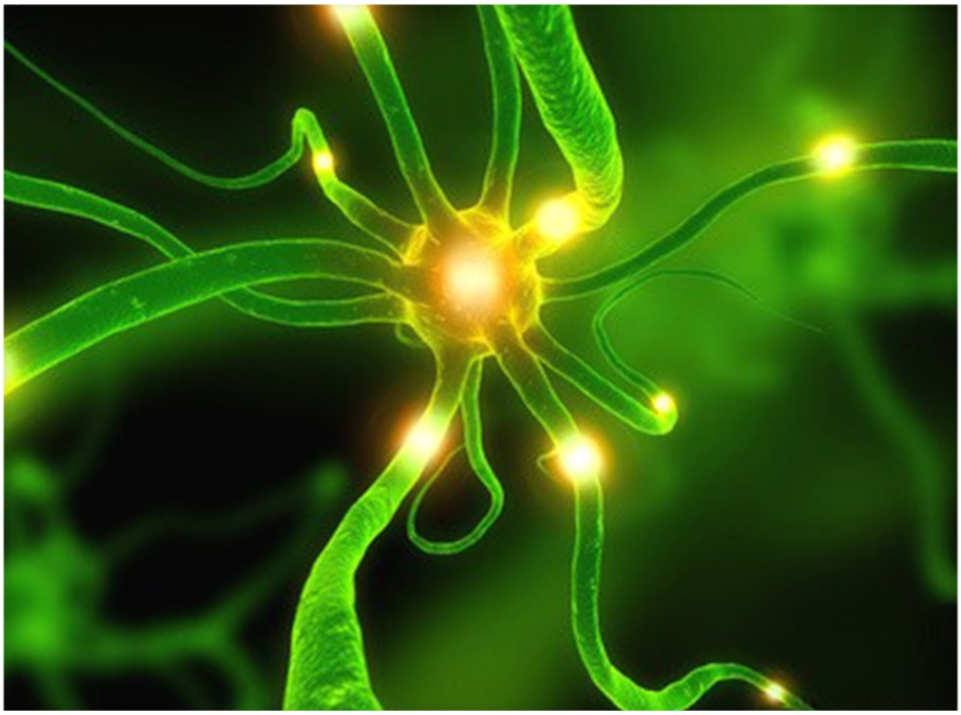



**Image 37:** The vertebrobasilar system.

# Basic Principles



# Basic principles – General Concepts

The nervous system, the most complex tissue in existence [92], is primarily composed of two major categories of cells [52, 93]: **Neurons** [41, 52, 64, 94, 100] (**functional units** [39, 64]) and **Glial cells** [50, 57], which are **support cells** [36, 39]. Without the latter, neurons would be unable to function, or at the very least, would struggle to do so.

Neurons devote nearly all their energy to a single goal: the **transmission of nerve impulses** [39, 75, 95]. It is the glial cells that are responsible for protecting them, nourishing them, and optimizing their function.

The transmission of nerve impulses by nerve cells is due to the electrochemical properties of their **plasma membrane** [96].

Signals are transmitted from one nerve cell to another through junctions called **synapses** [41, 52]. A very specific type of these synapses is the one that connects a neuron to an effector cell, such as a muscle fiber; this synapse is then called a **neuromuscular junction** [4, 40].

Information transfer across a synapse is mediated by chemical messengers called **neurotransmitters** [39, 40, 41, 52].

The proper functioning of the **CNS** is so crucial that it is isolated from the rest of the body by a barrier that limits the passage of potentially harmful substances: the **blood-brain barrier** [3, 41, 42, 70, 81].

Finally, the most extraordinary faculty of the nervous system is its ability to adapt and constantly modify itself according to needs. Thousands of new neural circuits are formed or strengthened every day. This faculty, known as **neuroplasticity** [97, 98], opens up great perspectives for the management of many disorders, particularly those of a sensory nature.

# Neurons

The **nerve cell** [41, 52, 64, 94, 100] or **neuron** is the structural and functional unit of the nervous system [39, 64]. The latter contains approximately 100 billion neurons [1, 4] (Note: Modern

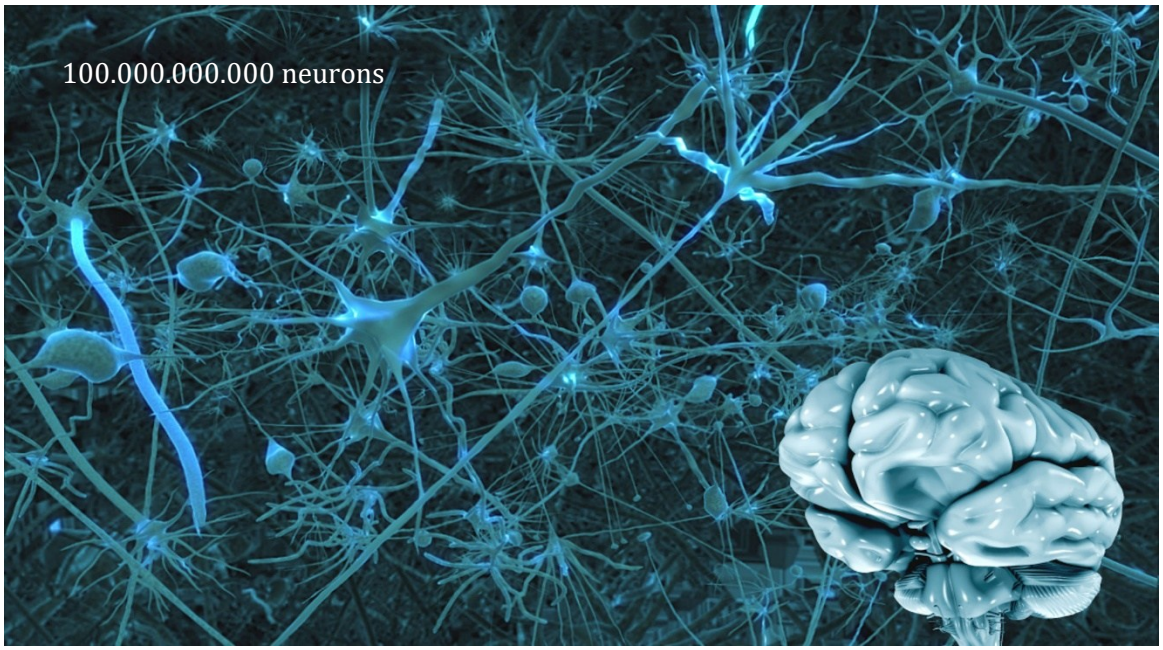



**Image 38:** Nervous tissue.

stereological studies (e.g., Herculano-Houzel, 2009) have established the average human brain contains ~86 billion neurons, not 100 billion).

## 1. Anatomy of a typical neuron:

A typical nerve cell has three distinct regions [1, 40, 99] : the **cell body, dendrites**, and the **axon**.

### 1.1. The cell body :

Also called the **soma** [5, 75] or **perikaryon** [57, 101], it contains the nucleus and the cytoplasm. It includes:

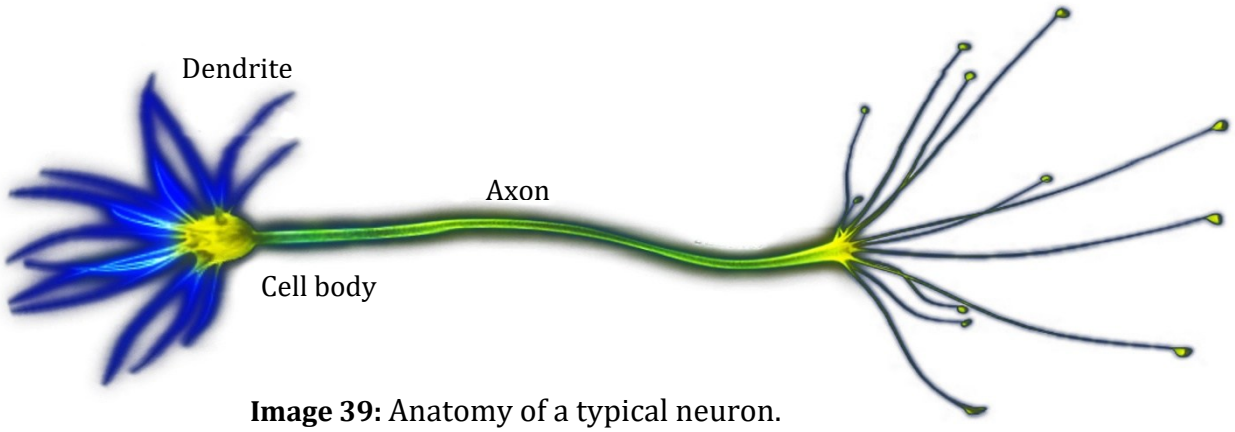



**Image 39:** Anatomy of a typical neuron.

A **rough endoplasmic reticulum**: the site of protein synthesis.

A **Golgi apparatus**: the site of protein storage and maturation. It is the mandatory passage point and regulator of small vesicle traffic.

Several **mitochondria**, which provide the energy essential for cellular metabolism.

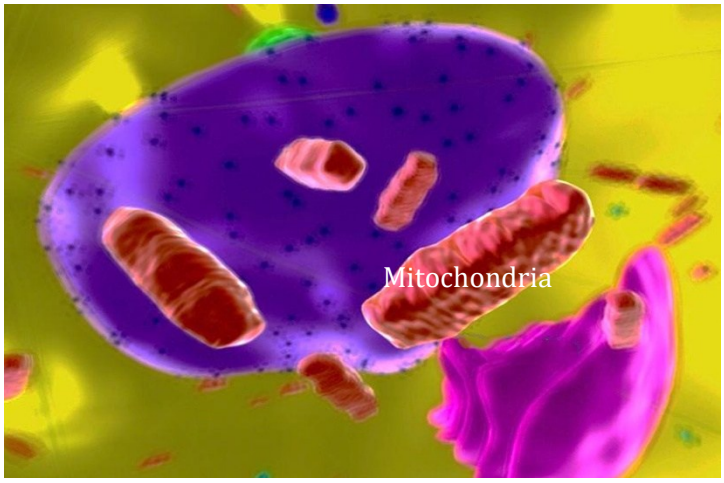



**Image 40:** Mitochondria.

The diameter of the perikaryon varies according to the type of neuron, ranging from 5 to 120 µm [91, 102].

### 1.2. The dendrites :

These are extensions of the perikaryon [5, 96]; they serve primarily to increase the **receptive surface area** for nerve impulses [1, 4, 36]. They are often covered with bud-like structures called **dendritic spines** [41, 74, 103]. A typical neuron contains tens of thousands of dendritic spines [103], each forming a synapse [74].

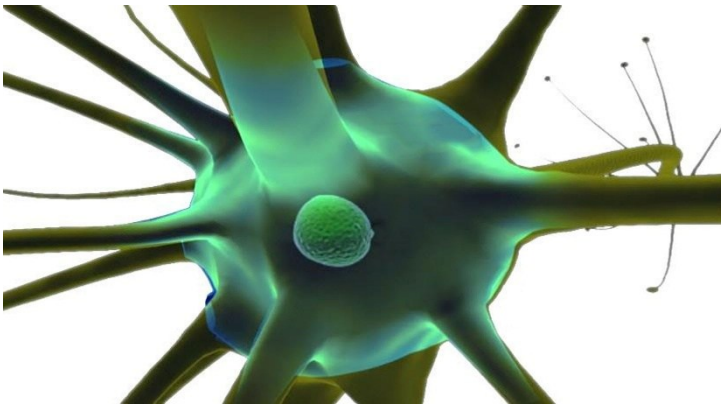


**Image 41:** The cell body of a neuron.

### 1.3. The axon :

The axon [5, 91, 96] emerges from the perikaryon, starting at the **axon hillock** [81, 104], an area extremely rich in microtubules, also called the **trigger zone** [40, 81] because it is the usual starting point of nerve impulses [40].

Perikaryon
Soma

The axon follows a path of varying length before ending in a **terminal arborization** (**telodendria** [75]). This gives rise to several nerve endings, at the tip of each there is a swelling: the **terminal button** or **synaptic knob** [101], which contains several synaptic vesicles filled with neurotransmitters.

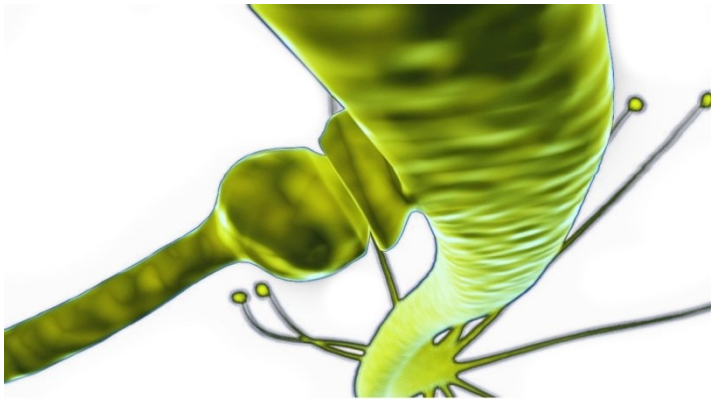


**Image 42:** An axo-axonal synapse.

Before the terminal arborization, a neuron may give off side branches called **axon collaterals** to distribute the nerve impulse to other targets. [105].

The axon membrane (**axolemma** [106])

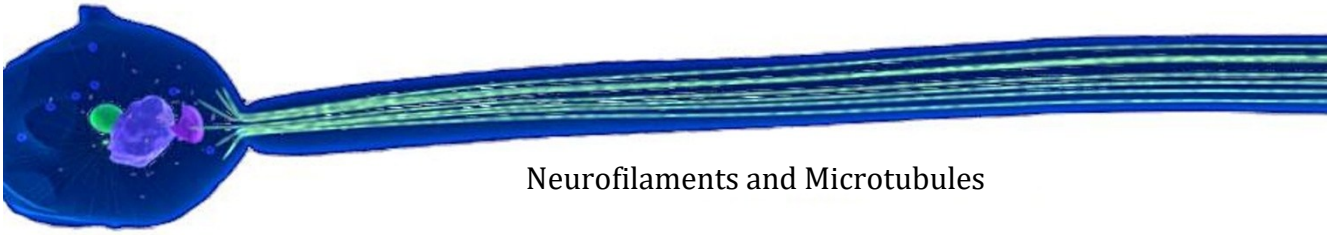



**Image 43:** The cytoskeleton of neurons.

encloses the **axoplasm** [91] (an extension of the perikaryon's cytoplasm), which is traversed throughout its length by neurofilaments and microtubules that stabilize the structure of the axon and ensure the bidirectional transfer of substances between the perikaryon and the axonal terminals [74].

## 2. Axonal transport :

There are **four types of** axonal transport [35, 50,107]**:**

- Two **rapid transports** (anterograde and retrograde) that carry the vesicles at a speed of **10** to **40** cm/day [108] from the perikaryon to the nerve ending and vice versa.
- **Slow anterograde transport** with a speed of **0.1** to **2** mm/day [57].
- A **mitochondrial transport** [104] that continuously renews the mitochondria in the nerve endings at a speed of **1 to 4 cm/day** [5].

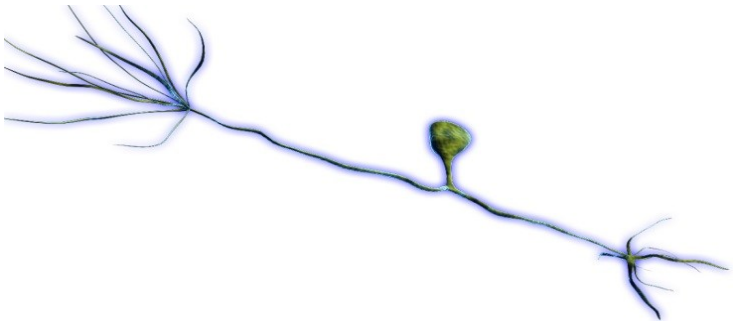


**Image 44:** Pseudo-unipolar neuron.

## 3. Features of the nerve cell:

The neuron possesses **several characteristics** that set it apart from other cells in the body.

### 3.1. It is an excitable cell:

The neuron receives and transmits electrochemical signals thanks to the presence in its membrane of specific proteins that regulate the transfer of ions into or out of the cell [42,110].

### 3.2.It is a secretory cell:

The nerve cell **secretes neurotransmitters**, sometimes even hormones, at the level of its axonal terminal [109].

### 3.3.It is an amitotic cell:

With the exception of a few nerve zones where low levels of neuronal mitosis occur (notably in the **hippocampus**) [40], mature neurons are arrested in interphase and [110], as post-mitotic cells, no longer undergo division, making them cells with **extreme longevity** [110]. This also explains the rarity of brain tumors of neuronal origin.

**Image 45:** Bipolar neuron.

Every day, tens of thousands of neurons are lost [111], yet this depletion rarely results in a notable disorder because of neural **plasticity**; surviving neurons compensate by reorganizing their connections and strengthening existing circuits.

### 3.4.It is a polarized cell:

There are two essential poles: the **somatodendritic tree**, which receives the signal, and the **axonal pole**, which propagates it [112]. However, the axon can receive a signal directly at the level of an **axo-axonal synapse** [75].

### 3.5. It is a cell with a very high metabolism:

Indeed, the neuron requires a constant and abundant supply of oxygen and glucose [110], which explains cerebral death within minutes in the event of **cerebral anoxia**.

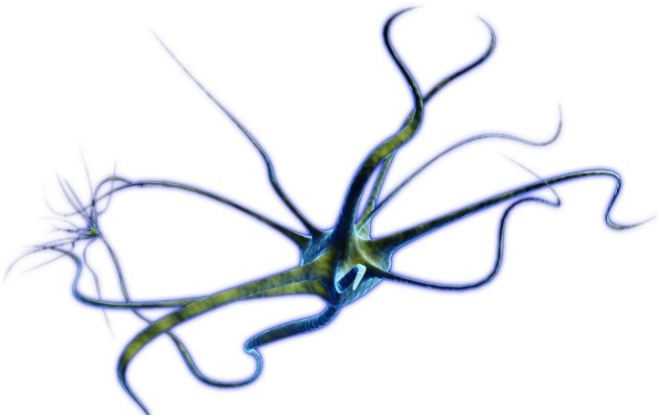


**Image 46:** Multipolar neuron.

### 3.6.Neurons are characterized by extraordinary polymorphism:

More than 150 types are distinguished [Jeanette Norden, *Understanding the Brain*] according to their size, polarity, structure, function, and location [35]. However, based on their shape, we can distinguish between three main (non-exclusive) categories [40, 49]**:**

- **Unipolar** or **pseudo-unipolar** neurons (often sensory).
- **Bipolar** neurons (e.g., certain interneurons).
- **Multipolar** neurons (e.g., motor neurons).

On a functional level, we distinguish between **sensory neurons**, which conduct impulses

toward the CNS, and **motor neurons**, which conduct impulses away from the CNS. Between the two are other neurons called **interneurons**.

Nerve fibers are organized into **tracts** within the CNS and nerves within the PNS. As for the cell bodies: they gather in the cortex and nuclei within the CNS, and in **ganglia** within the PNS.

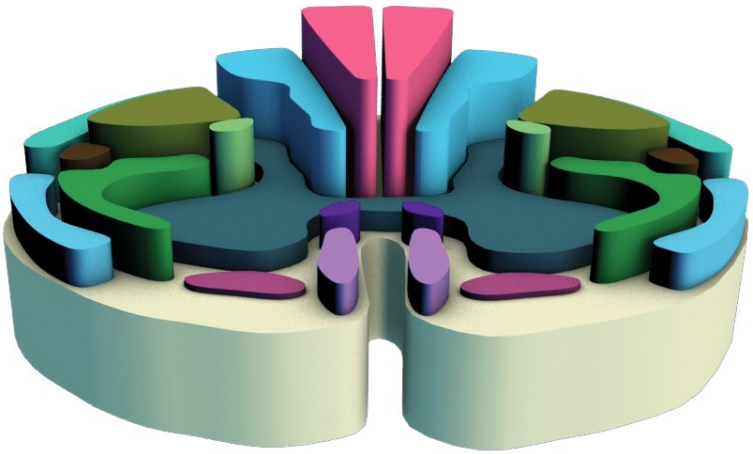


**Image 47:** Tracts within the CNS.

### 3.7.Neurons are the longest cells in the body:

They can reach up to **1 meter** in length in humans [113]. If the cell body were the size of a grapefruit, the dendrites would be **2** to **5 cm** long, and the axon would be **1 km** long.

# Glial cells

Despite the complexity and cellular density of the nervous tissue, it mainly consists of two large categories of cells [52, 93] : neurons [41, 52, 64, 94, 100] , which are the major and ultimate players in the transmission of nerve impulses, and **glial cells** [50, 57, 114] - also called **gliocytes** or **neuroglia** [116] - which act as "baby-sitters" for the nerve cells, among other roles.

**Image 48:** Gliocytes.

While the nervous system contains about 100 billion neurons [1, 4], gliocytes are nearly 10 times more numerous [114, 115]; this proves the undoubtedly important role these cells play (Note: The 10:1 glia-to-neuron ratio is a historical myth; recent research indicates a ratio of roughly 1:1 in the human brain).

Upon their discovery in the second half of the 19th century [100, 116, 117] , it was thought that glial cells (from "glia," meaning "glue") primarily served as a glue to bind nerve cells together (hence their name) [40, 118]. Over time, many fundamental functions crucial to the operation of neurons have been attributed to them [40, 57].

Unlike neurons, which are mostly amitotic, glial cells can and do reproduce [36, 119].

There are two categories of gliocytes [120]:

**Neuroglia**: including the four types of gliocytes in the central nervous system: astrocytes, oligodendrocytes, ependymal cells, and microglia.

Gliocytes of the peripheral nervous system: including **satellite** cells and **Schwann** cells.

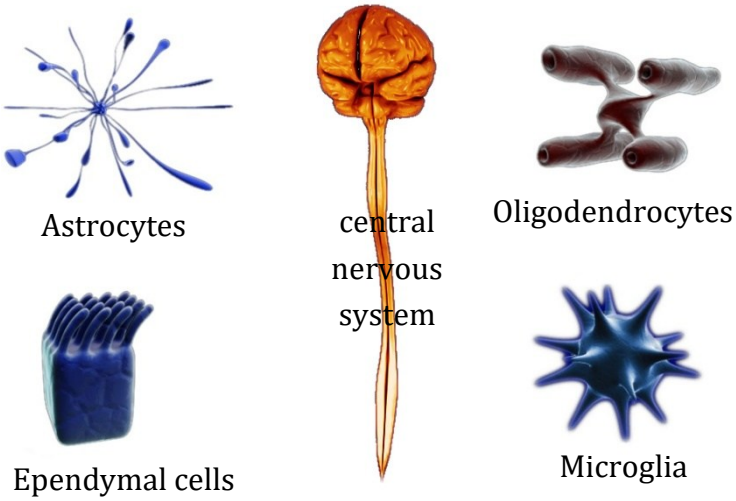



**Image 49:** Neuroglia.

## 1. Astrocytes :

These are the most abundant and largest gliocytes [1,35, 94,121]; they are star-shaped with several processes. A distinction is made between: **Type I** astrocytes [35, 70] , which are in contact

**Image 50:** Type I astrocytes surrounding blood capillaries.

with blood capillaries, and **Type II** astrocytes [35, 70] , which surround neurons and synaptic clefts, thereby preventing the dispersion of neurotransmitters.

Astrocytes have many functions [104] , several of which are still under investigation. For instance:

They play a vital role in the formation of the **blood-brain barrier** [39].

They ensure the supply of oxygen and nutrients to neurons [40].

They help maintain an appropriate chemical environment for the production of action potentials by neurons [40, 116].

They capture excess neurotransmitters in the synaptic cleft and participate in their metabolism [57, 116].

They provide structural support by forming a network that maintains the architecture of the nervous tissue [2].

They form **glial scars** in damaged areas of the brain [50].

They guide the migration of neurons to their final locations during development [120], and perform many other functions…

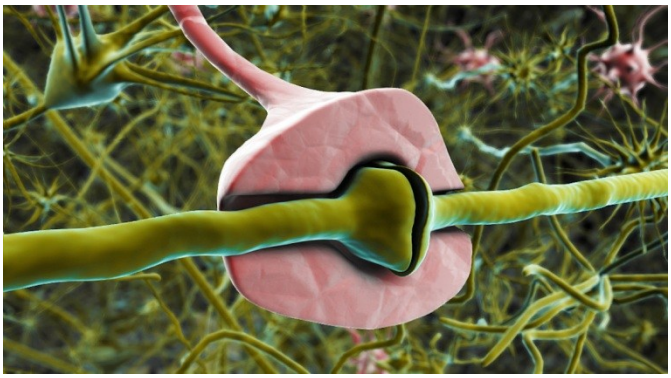


**Image 51:** Type II astrocyte surrounding a synapse.

## 2. Oligodendrocytes :

Oligodendrocytes [1, 49, 81, 100, 104, 122] are smaller and have fewer processes than astrocytes. They also serve as a support network for CNS neurons but primarily provide their **myelination** [100, 123].

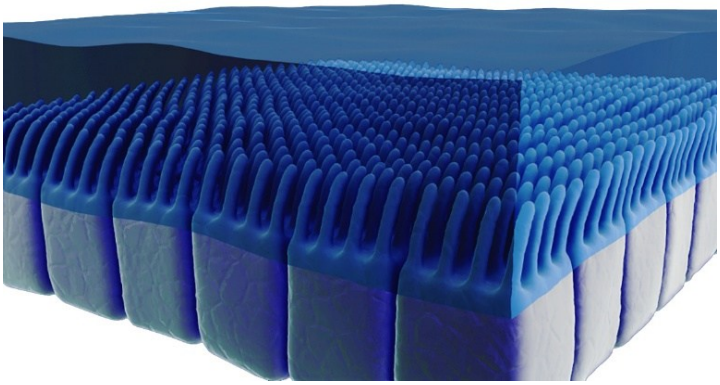


**Image 52:** Ependymal cells.

Each oligodendrocyte gives off several processes that wrap around axons, which then become surrounded by a large number of concentric layers (30 to 100) [40, 100]. These layers form the **myelin sheath** [104, 113, 124, 125] : a substance composed mainly of lipids that insulates and protects axons, similar to the plastic around electrical wires. Most importantly, this myelin sheath serves to accelerate the speed of nerve impulses [125]. An oligodendrocyte can myelinate up to 30 or even 50 adjacent axons [4, 100].

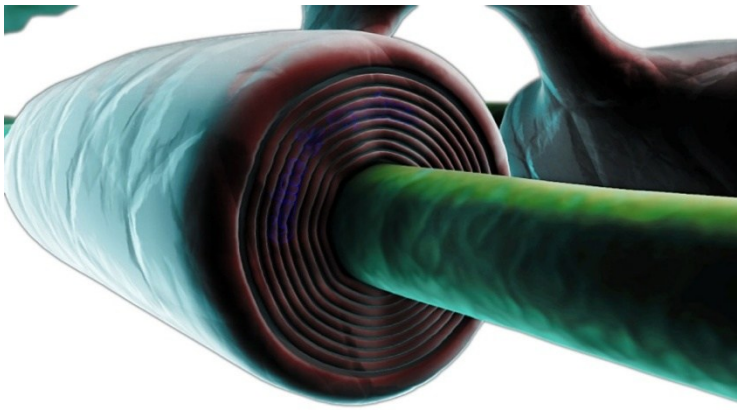


**Image 53:** The myelin sheath.

## 3. Ependymal cells :

Ependymal cells [126] are cuboidal (cube-like) or columnar (tall); they are often ciliated and form a simple epithelium that lines the internal cavities of the CNS. They ensure the secretion of **cerebrospinal fluid** and facilitate its circulation.

## 4. Microglia :

Microglia [104] are small, star-shaped cells with few processes; they share the same embryonic origins as monocytes and macrophages.

Microglia protect the cells of the central nervous system against infectious and toxic attacks. They can migrate to injured regions and eliminate debris from dead cells. Their protective role is of great importance because the cells of the immune system do not have access to

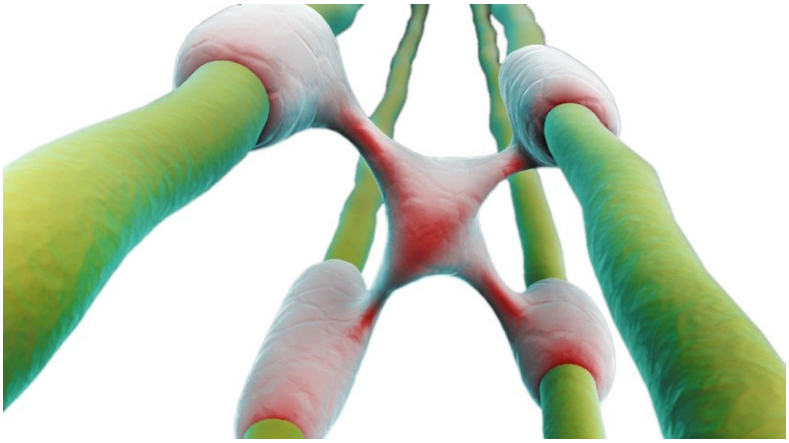


**Image 54:** An oligodendrocyte.

the central nervous system.

## 5. Satellite cells :

These flattened cells surround neuronal cell bodies within the ganglia, performing regulatory functions analogous to those of astrocytes [40,128,129].

## 6. Schwann cells :

Schwann cells [39,124,127], also known as **neurolemmocytes** [128, 129], are flattened cells that envelop axons in the peripheral nervous system to form the myelin sheath.

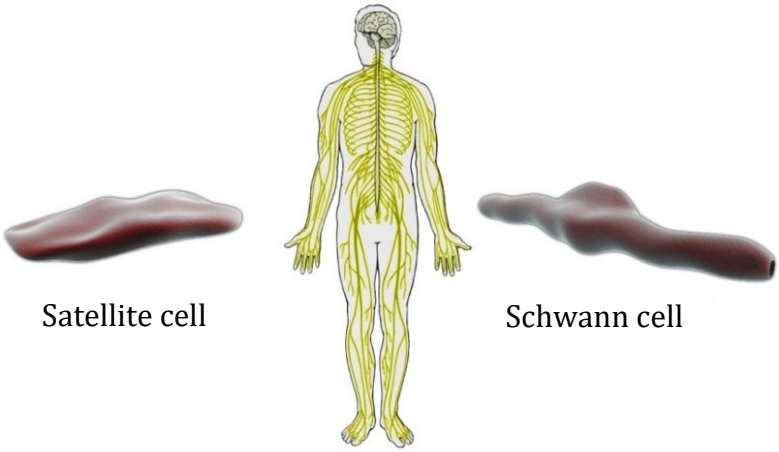



**Image 55**: PNS Gliocytes

Each Schwann cell myelinates a portion of a single axon [40, 124, 126, 130]. Occasionally, a neurolemmocyte may surround axons without forming a myelin sheath; these axons are then said to be **unmyelinated** [131].

Several neurolemmocytes are organized in a chain around a single axon; the constriction defined by each Schwann cell and its neighbor is called a **node of Ranvier** [81, 94]. It is at this level that collaterals can emerge from the axon [99]. The zone between two nodes of Ranvier is called the **internodal segment**.

Schwann cells play a trophic and nourishing role for peripheral axons. They can accelerate the speed of nerve impulses by up to 100 times [132] , and they also play a very important role in the regeneration of peripheral nervous system axons in the event of injury [100]...

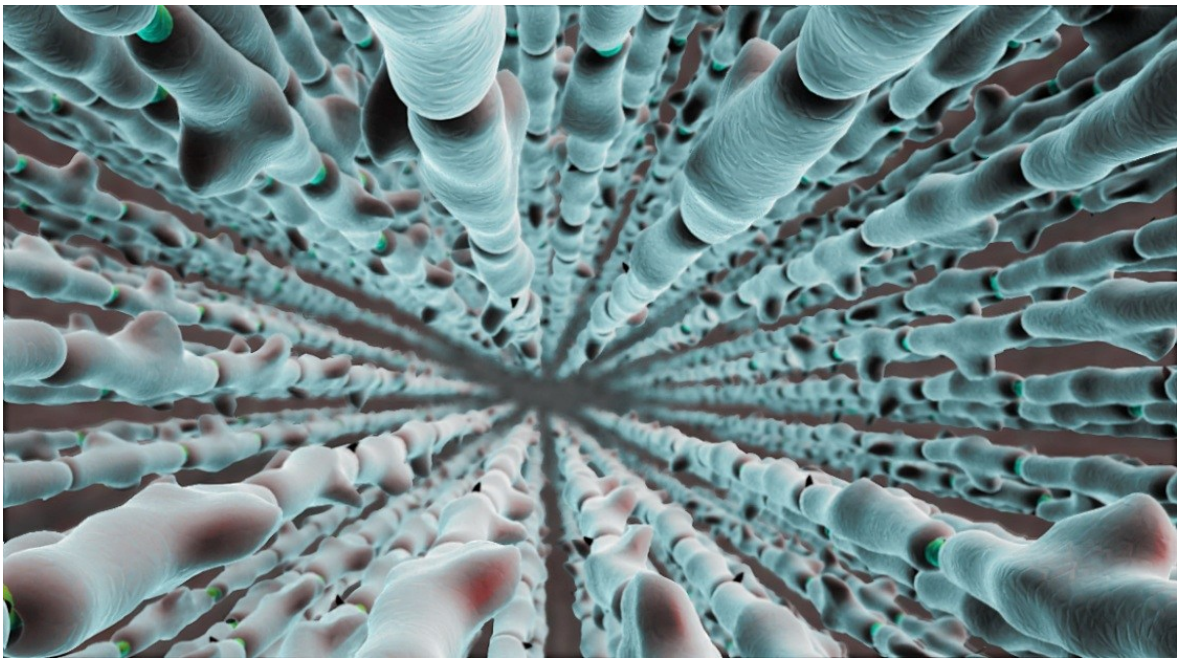


**Image 56:** Nerve fibers within the PNS.

# The Nerve Impulse

The fundamental role of a neuron is to receive, propagate, and transmit nerve signals. Its plasma membrane possesses specific electrochemical properties that allow it to react to a stimulus and propagate its action to the nerve ending.

The plasma membrane of neurons contains channels and pumps capable of regulating the distribution of ions on either side of the membrane according to their electrical charge and concentration. We will see that this regulation plays a primary role in the transmission of nerve impulses.

Unlike an electrical wire, it is not the flow of electrons that conducts the signal [96], but a wave of ionic exchanges occurring across the membrane. This propagation is therefore electrochemical in nature.

## 1. Fundamental Notions :

Two notions are very important to take into account: the **concentration gradient** [39] and the **electrical gradient** [39].

Indeed, in biological systems, molecules tend to diffuse from areas of high concentration toward areas of low concentration; they are then said to follow their **concentration gradient**.

Charged molecules also follow an electrical gradient (**potential gradient**); thus, positively charged molecules will diffuse toward negatively charged areas and vice versa.

However, these molecules are often shared between different, and sometimes even opposite, electrical and concentration gradients. They will then diffuse in a balanced manner according to these two gradients, following an **electrochemical gradient** [100].

## 2. The resting potential :

The diffusion of ions across the plasma membrane occurs through specific channels [5, 75]. Potassium channels are highly permeable [113], which is not the case for sodium channels. Indeed, at rest, the membrane is poorly permeable to sodium; it is even considered impermeable to it.

On the plasma membrane, there is a **$Na^+$-$K^+$-$ATP_{ase}$ pump** that actively moves - with each consumption of an ATP molecule (the universal currency of cellular energy) - 3 sodium ions out of the cell for every 2 $K^+$ ions moved inside. This pump consumes so much energy that some have attributed 30% or even 50% of all the energy consumed by the brain to it.

Overall, the $Na^+$-$K^+$-$ATP_{ase}$ pump fills the cell with potassium and empties it of sodium; with

each intervention, it moves a net positive charge toward the outside of the cell.

Intracellular $K^+$ ions follow their chemical gradient and exit toward the extracellular milieu, bringing more and more positive charges with them. The intracellular side of the membrane thus becomes negatively charged, which limits the further diffusion of potassium ions.

Therefore, outside of any transmission, the equilibrium established by all these elements creates an electrical potential difference between the positively charged extracellular medium and the negatively charged intracellular medium. This transmembrane potential is called the **resting potential**, and it is often situated between -50 and -75 mV.

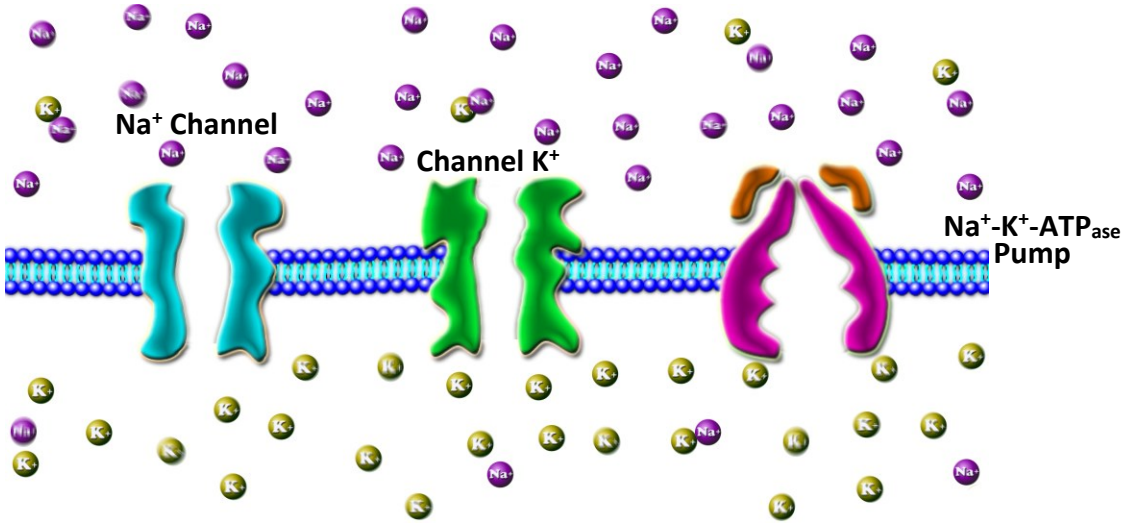



**Image 57:** Channels and pumps on the plasma membrane of neurons.

There are other molecules and other intervening elements that have not been detailed here to simplify the phenomenon; otherwise, it is much more complicated [39, 41, 100, 133].

## 3. The action potential :

There is a **voltage-gated sodium channel** on the membrane that only opens during a variation in electrical potential between the two sides of the membrane [39, 41]. When the membrane potential exceeds a threshold value, the voltage-gated sodium channels open and cause a massive influx of $Na^+$ ions into the cell (approximately 1 million/second [96, 134]) until the polarity of the membrane reverses (**depolarization phase**).

Potassium can then follow its concentration gradient and exit the cell; this gradually brings the membrane potential back to its resting state (**repolarization phase**). During this phase, sodium channels are inactivated and cannot be opened during a **refractory period**.

Sodium continues to be actively pumped out of the cell as potassium ions rejoin the interior.

The delay in potassium returning to the cell is responsible for a **hyperpolarization** that

gradually regresses.

## 4. Signal propagation :

When membrane depolarization occurs for one reason or another - most often at the level of the **axon hillock** [113], where the concentration of voltage-gated sodium channels is most pronounced - nearby channels are activated, and so on.

This wave of depolarization continues until the membrane depolarization signal traverses the entire axonal length and ends at the **terminal button**.

The **refractory period** of voltage-gated sodium channels prevents the signal from moving backward [135]; thus, the signal always propagates in only one direction. This wave of action potentials is called the **nerve impulse**. The propagation of this impulse obeys the **all-or-none law**: either the transmembrane potential exceeds a threshold value and results in an action potential, or it is simply ignored.

On a single nerve fiber, the amplitude of the action potential does not vary; the encoding of signal intensity is determined by the **frequency** of the action potentials - the more action potentials there are, the more intense the signal.

The speed of nerve impulse transmission varies from one neuron to another. Indeed, the larger the diameter of the axon, the faster the signal propagates.

The speed of the nerve impulse also depends on the **myelination** of the axon [100]: in myelinated fibers, the action potential jumps from node to node; this is referred to as **saltatory** transmission, which is very fast (up to 120 m/s [75, 119]), as opposed to the **continuous** propagation in unmyelinated fibers, which is slower.

In myelinated fibers, $Na^+$ channels are concentrated at the nodes; the action potential recorded at this level is so significant that it can rapidly influence the sodium channels in the next node, and so on.

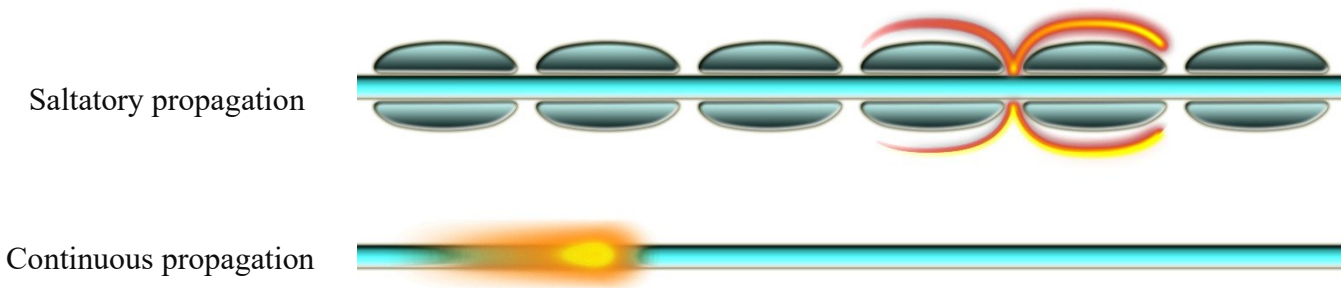



**Image 58:** Saltatory and continuous propagation of nerve impulses.

# Synapses

In 1897, the English neurophysiologist **Charles Sherrington** [74] observed that the speed of the nerve impulse from the cortex to the limbs was lower than that of its propagation within a single nerve fiber. He concluded that there must be some sort of interruption slowing down the transmission of the impulse. Thus, he introduced the concept of the **synapse** (from the Greek *syn*, meaning "together," and *haptein*, meaning "to touch" or "to grasp"; i.e., "connection") [52].

Indeed, neurons communicate with each other through synapses. A single neuron can have between 1,000 and 10,000 synapses [109] (approximately 300,000 on cerebellar **Purkinje cells** [57]). Multiply this number by 100 billion neurons to get an idea of the sheer number of communications within the nervous system!

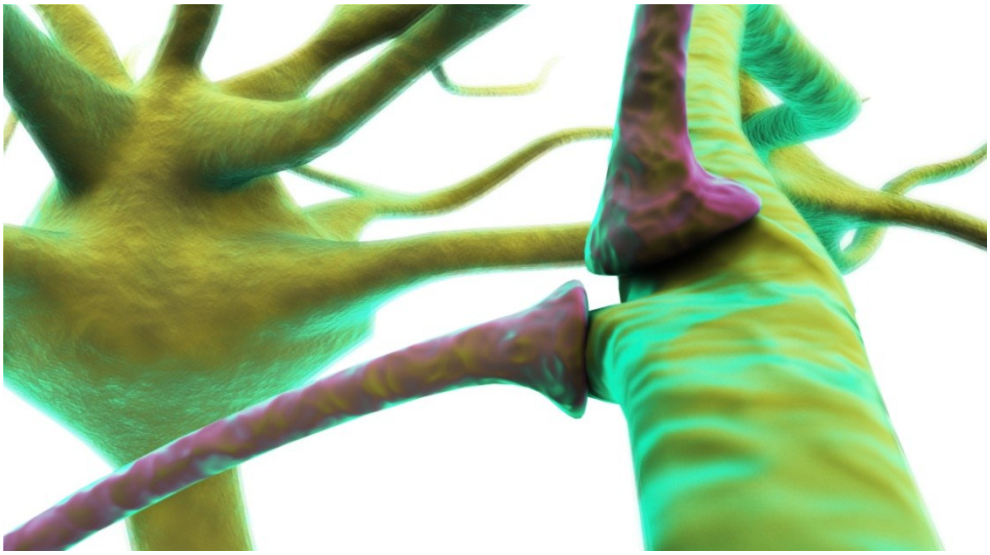


**Image 59:** A chemical synapse.

## 1. Classification :

Synapses can be classified according to their location, structure, function, or the nature of the neurotransmitter released [39, 71].

### 1.1. According to location :

Axonal terminals can be in contact with dendrites (**axodendritic** synapse), the perikaryon (**axosomatic** synapse), or even end on another axon (**axo-axonic** synapse) [4].

### 1.2. According to their nature :

There are two main categories of synapses [41]**:**

**Electrical** synapses [42] , which form gap junctions between certain neurons; they play an

important role during development and often transform into chemical synapses later. In adults, they are limited to a few regions of the brain.

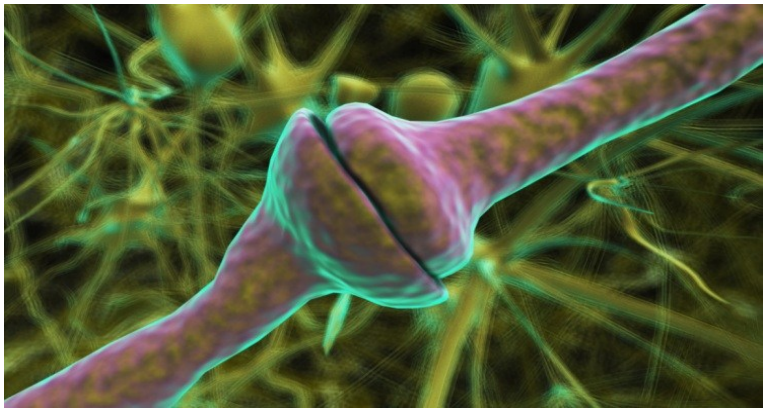


**Image 60:** A chemical synapse.

**Chemical** synapses [52] are by far the most widespread; the signal travels via the secretion of chemical mediators called **neurotransmitters** or **neuromediators**. These neurotransmitters can have an excitatory effect (e.g., acetylcholine, glutamate) or an inhibitory effect (e.g., GABA). A neuron may secrete more than one type of neurotransmitter [38, 39, 41].

### 1.3. According to the postsynaptic cell:

Synapses can connect neurons with other neurons or with **effector** cells [2]: glandular (**neuroglandular** junction) or muscular (**neuromuscular** junction).

## 2. Anatomy of a synapse :

A synapse consists of three parts [5] : a **presynaptic** region, which corresponds to the terminal button of the presynaptic axon; a **postsynaptic** region (the area opposite the terminal button); and an intervening space called the **synaptic cleft**.

The terminal button contains synaptic vesicles filled with neurotransmitters and several mitochondria (an energy source). The postsynaptic part does not contain synaptic vesicles, which makes signal propagation unidirectional at this level.

The postsynaptic part contains receptors, most often of the channel-linked type, which open in response to the action of the released neurotransmitters.

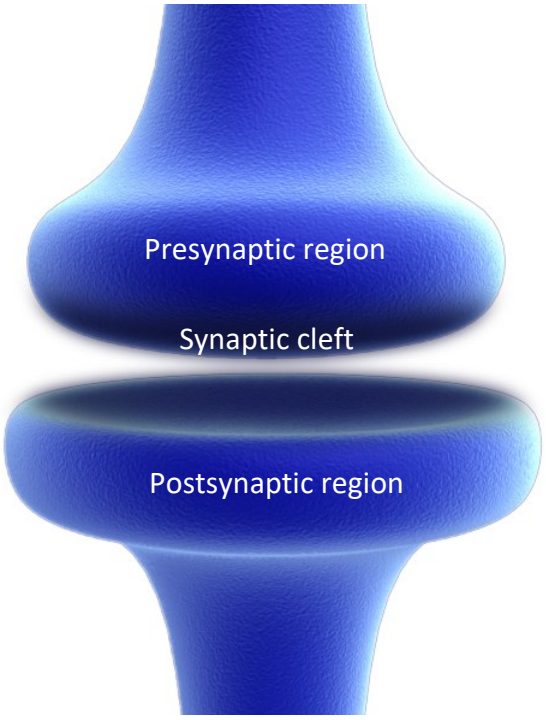



**Image 61:** Anatomy of a chemical synapse.

## 3. Process :

When a train of action potentials (a succession of action potentials) arrives at the terminal button, it triggers the opening of voltage-gated **calcium** channels. Calcium then enters the cell massively and, through a cascade of chemical reactions [39, 57], stimulates the fusion of synaptic vesicles with the plasma membrane. On average, 300

synaptic vesicles are released with each action potential [57]. The greater the number of action potentials, the more vesicles are released.

The neurotransmitters diffuse toward the postsynaptic region to activate their receptors and are then rapidly eliminated [57], either by diffusion out of the synaptic cleft (where they are captured by gliocytes) or by degradation by a specific enzyme and reabsorbed by the terminal button to produce more neurotransmitters (**reuptake** [100]).

# 4. Post-Synaptic potentials :

## 4.1. Excitatory post-synaptic potential :

In an excitatory synapse, the neurotransmitter causes sodium channels to open, allowing sodium to enter the cell and creating a local depolarization called an Excitatory Post-Synaptic Potential **(EPSP)** [4, 39, 41].

This rarely triggers an action potential in the dendrites or perikaryon, as these two regions are very sparse in voltage-gated sodium channels. It is therefore a **graded potential** whose amplitude decreases over time and distance from the excitatory synapse to the **axon hillock** (an area extremely rich in voltage-gated sodium channels and the usual site of action potential initiation).

## 4.2. Inhibitory Post-Synaptic Potential :

In an inhibitory synapse, the neurotransmitter (e.g., GABA) causes the opening of chloride channels (allowing chloride to enter the cell) or potassium channels (allowing potassium to exit the cell) in the postsynaptic region.

In both cases, there is a local hyperpolarization of the plasma membrane called an Inhibitory Post-Synaptic Potential **(IPSP)** [4]. This hyperpolarization diffuses in the same way as the **EPSP** to the axon hillock, where it makes it more difficult to generate an action potential. Inhibitory synapses are often located near the axon hillock, where their inhibitory action can be most effective.

# 5. Integration :

In real time, it is rare for a single stimulation to generate an **AP**. The neuron receives multiple stimuli simultaneously. The processing of these stimuli occurs at the axon hillock through spatial and temporal summation of the various potentials received [38, 39, 54].

In **spatial summation** [1]: if the sum of excitatory and inhibitory potentials from different synapses arriving at the axon hillock at the same time exceeds a threshold value, it will trigger an

action potential; otherwise, it will be ignored.

In **temporal summation** [52]: if many excitatory potentials occur close together in time, they add up and can also reach the depolarization threshold to trigger an action potential.

The axon hillock then acts as a neural integrator [96], deciding - based on the various potentials gathered - whether or not to trigger an action potential.

# The neuromuscular junction

Body movements are performed by muscles. By contracting, a muscle shortens and thus manages to bring the two bones to which it is attached closer together. However, it is the nervous system that controls this muscular contraction via the nerves.

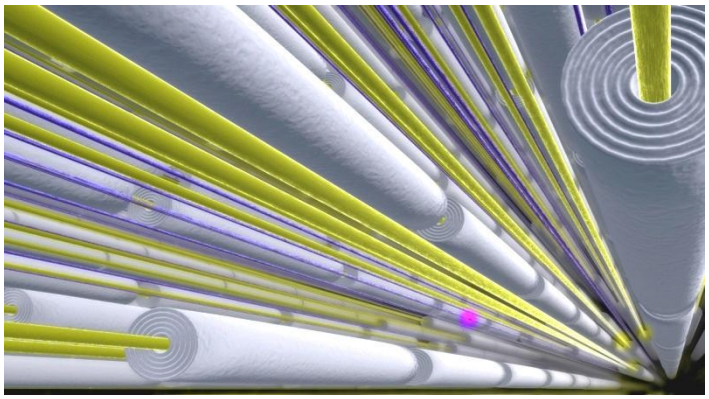


**Image 62:** Nerve fibers of the PNS.

Each nerve contains thousands of nerve fibers [51, 75] organized into sensory axons (peripheral processes) that carry sensory information and motor axons that convey motor impulses

## 1. The motor unit :

Each motor neuron innervates several muscle fibers; this association defines what is called a motor unit [41, 54, 107, 109].

In general, the fewer muscle fibers there are in a motor unit, the more precise the movement. For example, in the temporal muscle, there are about 1,000 muscle fibers per motor unit [1, 3], whereas in the **extraocular muscles**, there are only five, which reflects the high degree of precision in eye movements [4, 41].

As for the intensity of the muscle contraction, it is proportional to the number of motor units **recruited**.

## 2. The neuromuscular junction :

A motor neuron gives off several branches that sometimes spread throughout the entire thickness of a muscle. Each ending is intended to stimulate a single muscle fiber at a very specific location: **the neuromuscular junction** [2, 4, 54].

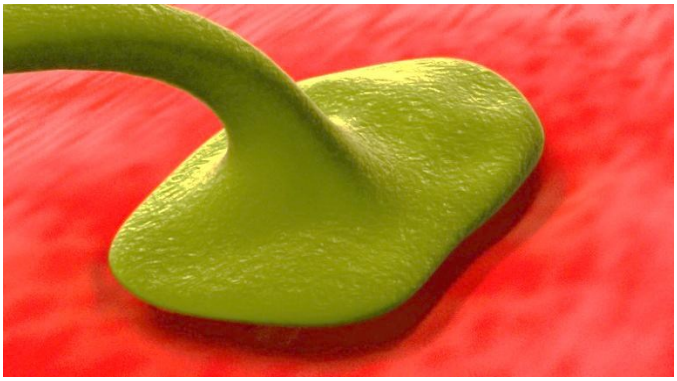


**Image 63:** A neuromuscular junction.

### 2.1. The terminal button :

Just before the axonal termination, the motor neuron loses its myelin sheath and forms a **terminal button**. The latter contains many mitochondria, to ensure an energy supply, and several synaptic vesicles. Each vesicle contains approximately 10,000 molecules of acetylcholine (the exclusive neurotransmitter of the

neuromuscular junction) [4, 100, 136].

### 2.2. The motor end plate :

On the muscle fiber side, there is the motor end plate, which is the area directly opposite the terminal button. Even though these two regions (**synaptic knob** and motor end plate) are very close to each other, there is no actual physical contact between them.

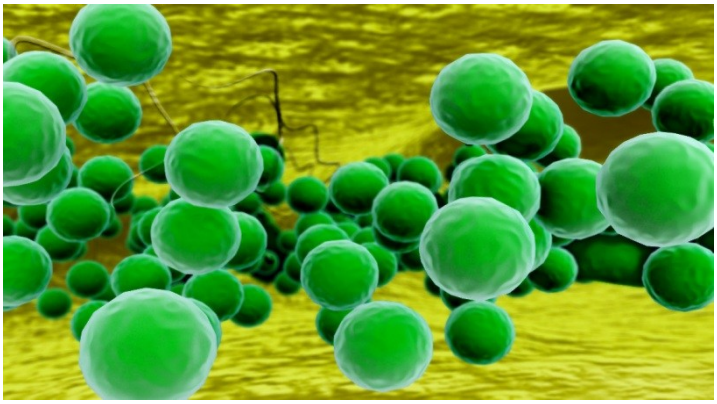


**Image 64:** Synaptic vesicles.

The motor end plate [39, 109, 135] , which is thick and electrically non-excitable, forms junctional folds that increase the synaptic contact surface area.

## 3. Process :

Upon reaching the nerve ending, the motor impulse triggers the opening of calcium channels, leading to a massive influx of calcium ions into the cell. Calcium promotes the fusion of acetylcholine vesicles with the cell membrane [39, 57] , releasing their entire neurotransmitter content into the synaptic cleft.

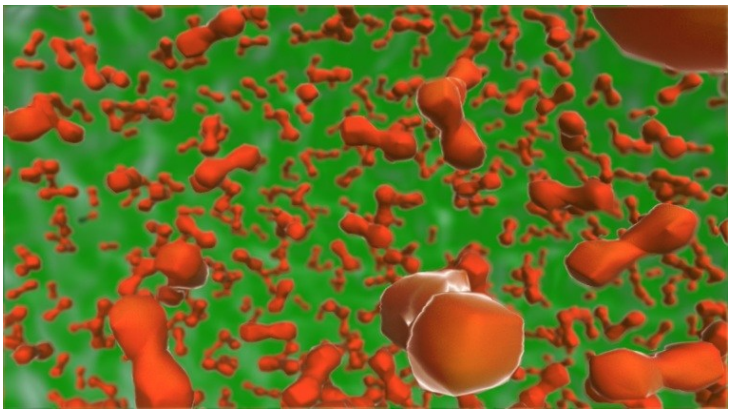


**Image 65:** Acetylcholine molecules.

The acetylcholine molecules then diffuse across to the cholinergic receptors, which are primarily concentrated within the folds.

The binding of two **ACh** molecules to a receptor [5, 100, 113, 136] triggers the opening of a sodium channel, facilitating the entry of sodium ions into the muscle fiber, thereby depolarizing the postsynaptic membrane and creating an **end-plate potential** [4].

Depending on the number of activated receptors, this potential can exceed a threshold value and thus trigger a muscle action potential that will spread across the entire muscle membrane and cause the muscle fiber to contract.

There may be a minimal release of **ACh** by spontaneous exocytosis into the

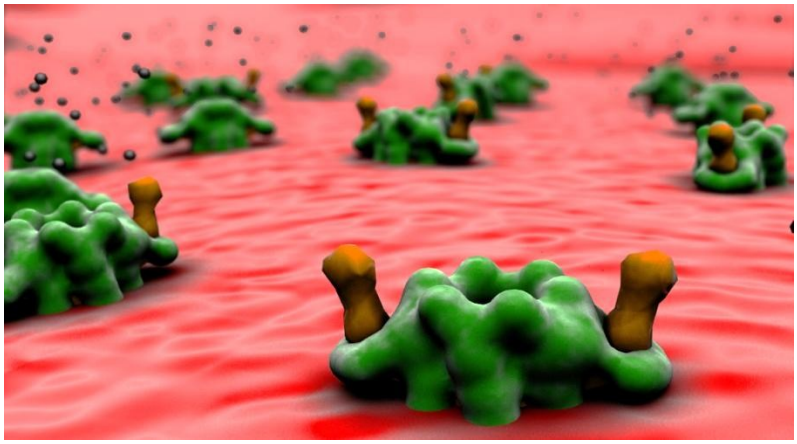


**Image 66:** ACh receptors at the motor end plate.

synaptic space in the absence of any nerve stimulation. However, the number of receptors activated in this way is far from sufficient to trigger a muscle action potential [136].

## 4. Elimination of acetylcholine :

Acetylcholine molecules are rapidly broken down by an enzyme (**acetylcholinesterase** [1, 12]) present in the synaptic space. This degradation produces two molecules: **acetate** and **choline**, the latter of which is taken up to the nerve ending to form new acetylcholine molecules.

The rapid destruction of acetylcholine thus prevents prolonged muscle contraction.

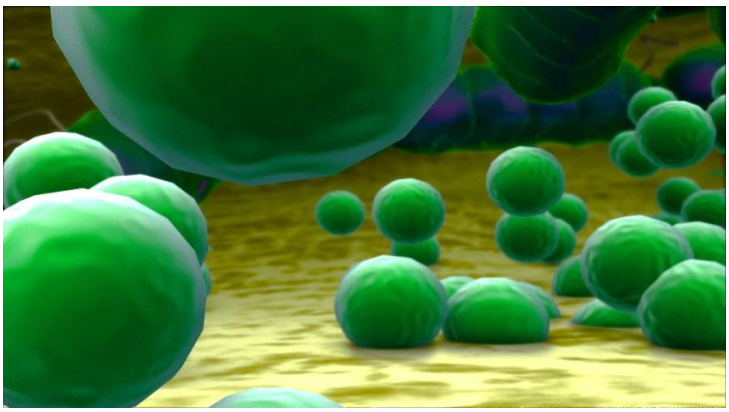


**Image 67:** Vesicle fusion with the membrane.

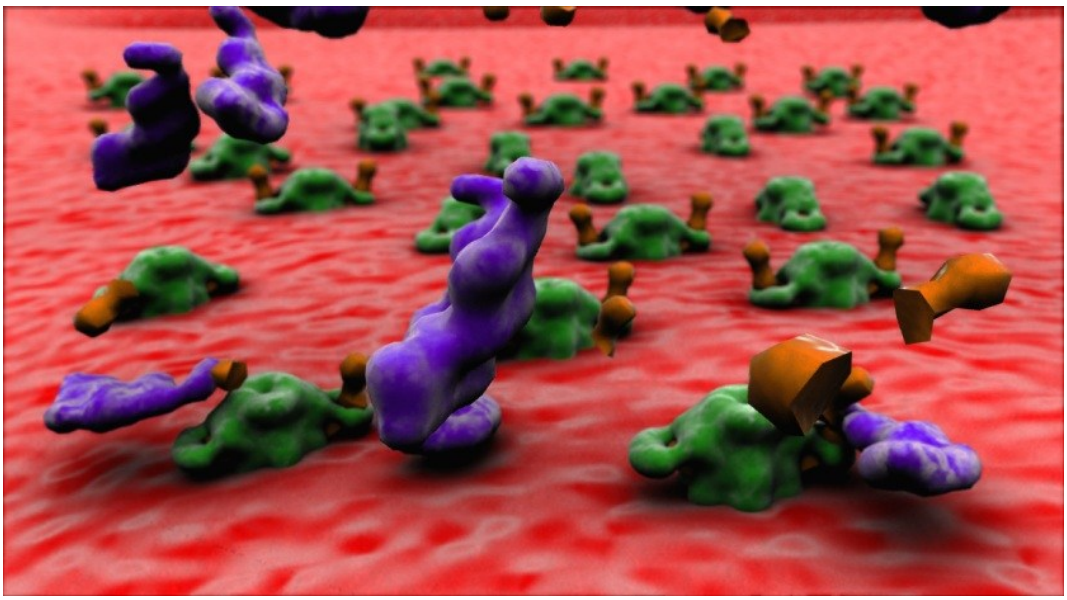


**Image 68:** Breakdown of ACh molecules by acetylcholinesterase.

# Neurotransmitters

Nerve cells communicate with each other and with other cells through the secretion of biochemical substances called **neurotransmitters** [5, 38, 41, 54].

Many neurons secrete more than one type of neurotransmitter [38, 39, 41].

Certain neurotransmitters can have different actions on the same target cell. The response time is also variable.

Each terminal button contains several thousand vesicles [1], each of which is filled with approximately 10,000 neurotransmitter molecules [4, 100, 136].

## 1. Neurotransmitters :

### 1.1. Neurotransmitter criteria :

Today, more than 50 substances that meet the criteria for neurotransmitters [52, 82] have been identified. These main criteria are as follows [38, 39, 41]:

- A neurotransmitter must be ***present*** in the ***presynaptic neuron***.
- Its release must occur in response to presynaptic depolarization.
- There must be specific receptors ***for this neurotransmitter*** in the postsynaptic neuron.

Other molecules widespread in the body, such as ATP and nitric oxide, have been considered neurotransmitters [57, 110], although they possess atypical properties.

### 1.2. Classification of neurotransmitters :

There are several classifications of neurotransmitters based on their biochemical structure and their action [10].

#### a. According to their structure :

Two main categories are generally distinguished according to their structure [38, 41, 52]: neuropeptides and small molecules.

**Neuropeptides** [2, 57] consist essentially of amino acid chains; they include a wide range of molecules with diverse effects, such as *endorphins* [76] and *somatostatin* [5]. They are synthesized in the soma.

**Small molecules** [38] group together the majority of classic neurotransmitters, such as *acetylcholine* [41], *glutamate* [38], *GABA* [48], and *catecholamines* [52]. They are primarily synthesized

in the nerve endings and have a much faster action than neuropeptides.

Regardless of the site of neurotransmitter synthesis, the required enzymes are always synthesized in the cell body [80].

### b. According to their action :

Neurotransmitters can be excitatory or inhibitory; they can also have a direct or indirect action on their receptors.

## 2. Neuromodulators :

While the primary role of neurotransmitters is to transmit nerve impulses from one nerve cell to another, *neuromodulators* [1] (which are also secreted by neurons) function to modify the operation and metabolism of the target cell over a significant duration. These neuromodulators generally affect a population of neurons and harmonize their functioning.

## 3. Neurohormones :

*Neurohormones* [1], such as certain catecholamines (epinephrine and norepinephrine), are substances released by nerve cells into the bloodstream; they thus act at a distance on target cells spread throughout the entire body.

A neurotransmitter can also function as a neuromodulator or neurohormone depending on its site of production and its diffusion.

## 4. Neurotransmitter receptors :

The neurotransmitters can only take effect at sites capable of binding them: **receptors**. [41].

Receptors are specific macromolecular structures found in particular regions of the plasma membrane of target cells.

Molecules that bind to and activate a receptor are called **ligands** or **agonists**. Substances capable of binding to a receptor and blocking it are called **antagonists**.

There are **two types** *of receptors* [41]**:**

**Channel-linked receptors** (also called **ionotropic**) [4, 39], which allow for the direct and rapid action of neurotransmitters. These receptors open a channel, causing specific ionic diffusion and a direct, rapid change in the potential of the postsynaptic membrane.

**Metabotropic receptors** (**G-protein coupled**) [4, 39], which determine slow synaptic responses produced by the G-protein and by intracellular second messengers.

The combination of receptors and the chemical substances that activate or inactivate them

constitutes a major target for therapeutic drugs [38, 41] and most recreational drugs.

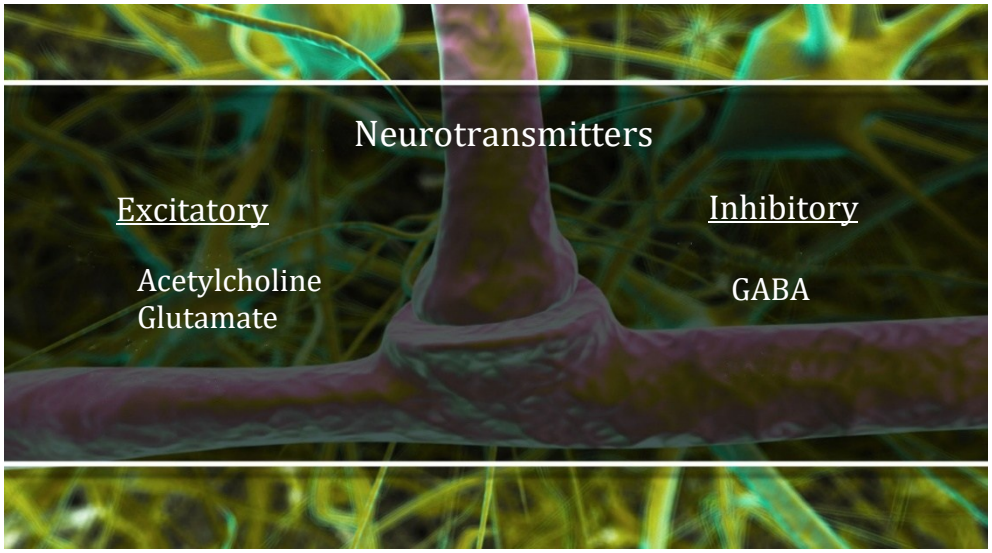



**Image 69:** Major neurotransmitters.

# The blood-brain barrier

The human brain, which weighs about 2% [137] of the body's mass, requires more than 20% [138] of the total body's energy supply; thus, it alone receives 16% [5] of the arterial irrigation.

The **CNS** has no real reserves of energy or oxygen [109], and neurons are incapable of functioning anaerobically [52]. It is therefore an organ entirely dependent on continuous perfusion and a sufficient supply of oxygen and nutrients. Consequently, after 10 seconds without oxygen, consciousness is lost, and after a few minutes, neurons begin to die [105].

Conversely, the nervous system requires a stable environment for optimal functioning. It cannot tolerate massive and sudden fluctuations in molecular and ionic composition within the interstitial spaces. For this reason, the nervous system is almost totally isolated from the blood by a barrier that acts as a mandatory and extremely selective filter between the contents of the capillaries and the extracellular environment of the nervous tissue. This barrier is called the *blood-brain barrier* [41, 70] **(BBB).**

Before the discovery of microglia and their immune role within the CNS, it was thought that the latter relied on the **blood-brain barrier** as its only means of passive defense against toxic and infectious attacks.

## 1. Anatomy:

The **BBB** consists of three essential elements [70]**:**

The **tight junctions** of the endothelial cells that line the interior of the blood capillaries. In the brain, these junctions have a structure that is significantly more impermeable than in the rest of the body, and the number of mitochondria in these endothelial cells is 5 to 10 times higher than elsewhere [91]; this is a response to the very high energy demand of active transport processes at this level.

The **basal membrane** of the arterial capillaries.

The **astrocytic end-feet** of type I astrocytes [41, 70] form (by joining together) a continuous sheath that serves as a selective barrier against the entry of pathogens and neurotoxic substances into the nervous tissue."

## 2. Physiology:

In addition to their relatively passive participation in the formation of the blood-brain barrier, astrocytes are also capable of controlling the contraction and dilation of blood vessels [96], thereby regulating blood flow to manage the uptake of substances according to needs.

The blood-brain barrier plays both a physiological and an anatomical role; gases (oxygen and carbon dioxide), as well as fat-soluble substances and alcohol [91], can freely cross it according to their concentration gradient (from higher to lower concentration). In contrast, polar molecules (ionized, hydrophilic) can only diffuse through active transport mechanisms involving specific channels and pumps, which operate only according to requirements.

## 3. Therapeutics:

The blood-brain barrier constitutes a real obstacle to the passage of drugs [41] targeting neurological conditions such as brain tumors. Several research projects are currently being conducted to address this problem.

This constraint can be bypassed either by the injection of high doses of drugs, the administration of an agonist or a precursor that crosses the barrier (as in the case of **L-dopa** vs. *dopamine* [1, 41]), or by the **intrathecal injection** [42] of the drug (directly into the **CSF**).

## 4. Pathology:

In newborns and infants, the blood-brain barrier is not as effective as in adults; it allows the passage of certain neurotoxic molecules, such as bile pigments, which can damage the brain (**kernicterus**) [42].

In certain pathological cases, such as meningitis, there is a breakdown of the **BBB**, which fortunately facilitates the passage of antibiotics, such as penicillin, into the central nervous system [42].

"*Human beings are genetically programmed, programmed to learn*" (**F. Jacob, 1981**).

## 1. Brain vs Computer :

The functioning of the nervous system and that of a computer system have several similarities [118, 228, 229]**:**

Both utilize a basic **binary signal (0–1).** In computers, current either flows or it does not. In the nervous system, this corresponds to the **all-or-none law** of action potentials.

Both consist of a **hardware** component (physical equipment for the computer and organs for the nervous system) and a software component [229] (programs for computer systems and higher cognitive functions for the nervous system) [228].

However, the nervous system is infinitely more powerful on several levels**:**

If we compare a *transistor* (the basic element of a microprocessor, which is the center of calculation and data processing in a computer) to a *synapse*, as both perform similar functions, we find that the highest-performance microprocessors designed today contain only about 3 billion transistors [*Wikipedia*, *Transistor count*]. In contrast, the nervous system possesses approximately *100 trillion synapses* (100,000,000,000,000) [4, 57], a number of neural connections within the human body that is as fascinating as it is extraordinary.

Our brain is a supercomputer that not only manages this vast number of neurons and synapses but does so at a **minimal energy cost**: approximately what is required to power an ordinary light bulb. If we were to build a supercomputer with the same number of transistors, it would require at least 100 megawatts of energy to operate - enough to power an entire city [139].

Not only is the brain superior in its number of connections and low energy consumption, but it is also far more efficient in managing those connections. In the brain, these operate in **parallel:** billions of pieces of information circulate simultaneously at any given moment. In contrast, microprocessors typically operate in **serial** mode, processing one piece of information after another.

Yet, the most extraordinary faculty of the nervous system is certainly not its raw power. The true and undeniable force of the nervous system is, and will always be, its **flexibility and plasticity**. Every day, we lose approximately 100,000 neurons [111], yet we continue to live as if nothing has changed. This is due to the formation of new connections that compensate for the deficit. Conversely, a microprocessor would possibly fail following the loss of a single transistor.

## 2. Discovery :

In 1890, the famous Russian physiologist **Ivan Pavlov** [76] noticed that dogs tended to salivate before actually coming into contact with food. He decided to investigate this "**psychic secretion**" thoroughly although he was a physiologist. He conducted a series of experiments in which he signaled every meal to a dog with a sound. After a few days, the dog began to salivate whenever it heard the signal. Pavlov concluded that physiological reflexes could be triggered by specific conditioning of the brain, and he introduced the concept of the **conditioned reflex** [54].

This experiment had a major impact on modern neurology and psychology. Later, the term **neuroplasticity** was coined by his student, **Jerzy Konorski**, who further developed Pavlov's research. We know today that conditioned reflexes are merely variations of a fundamental and essential property of the nervous system: neuroplasticity [97].

Neuroplasticity is the most remarkable and striking cerebral faculty; it is the power to change and adapt to environmental conditions and experience. It is thanks to neuroplasticity that we can memorize, forget, learn, develop, and recover from brain injuries that can sometimes be devastating.

Pavlov's discovery is just one example of what the nervous system is capable of. Indeed, the nervous system is in a state of perpetual change and development, and research in this field continues to amaze us every day with the incredible potential of neuroplasticity.

Thanks to modern techniques such as **PET** (positron emission tomography [67]) and **functional MRI** [76], which allow for the localization of brain regions responsible for specific functions, it has been shown that every person possesses a unique distribution of functional areas within their brain. While there are broad correspondences, there are nonetheless differences based on each individual's past and experience.

For example, a violinist has a brain region that is more developed for the muscles controlling the pinky finger compared to the other fingers. Similarly, an individual blind from birth or childhood who uses Braille to read develops significant activity in the **visual cortex**, even though they are unable to see.

Whenever a brain region becomes non-functional due to damage to a sensory or effector apparatus, it reallocates its neural resources to other functions. **In the brain, nothing remains idle.**

This explains how the blind can possess highly refined hearing and touch, how those who are deaf and mute develop impressive sign language communication skills, and how other individuals with disabilities manage to compensate by developing other aptitudes. Neuroplasticity also explains how we can become more intelligent over time, even though we lose tens of

thousands of neurons every day without them being replaced.

## 3. Mechanisms :

Where does this flexibility and plasticity of the nervous system come from? In fact, there are several underlying mechanisms, occurring at both local and global scales.

### 3.1. At the synaptic level (synaptic plasticity):

If an action potential is triggered in a presynaptic neuron and the same stimulation is repeated several times [52], it is noted that the response of the postsynaptic neuron increases in intensity over time; thus, there is an improvement in **synaptic efficiency**. If, after a few days, the same presynaptic neuron is restimulated, the same intense response will be recorded postsynaptically.

This phenomenon is called **Long-Term Potentiation (LTP)** [3, 38, 39]. Whenever a synapse is repeatedly used, it becomes more reactive and efficient over a long duration. This may be due to:

- Increased secretion of neurotransmitters.
- An increase in the number of postsynaptic receptors or changes in their properties (**phosphorylation**), causing them to stay open longer.
- A decrease in neurotransmitter reuptake.

### 3.2. At the cellular level (neuronal plasticity):

A neuron can create new synapses (**synaptogenesis**) [74] or modify the structure of **dendritic spines**, which impacts the amplitude of synaptic excitation. The excitability threshold at the **axon hillock** can also vary according to several factors, particularly hormonal ones; a higher threshold makes it more difficult to generate an action potential.

Furthermore, though exceptional, low levels of **neurogenesis** can occur, most often in the *hippocampus*, where new neurons are born with new functions.

### 3.3. On a global scale (cerebral plasticity):

There can be a reorganization of neural networks and a redefinition of their connections [141]. We recall the famous phrase by **Donald Hebb** [140] (considered the father of neuroplasticity in the 1950s): "*Neurons that fire together wire together*" [140]. Whenever a neural circuit is repeatedly activated, it forms a robust network dedicated to a specific function.

## 4. Applications :

An increasing number of studies focus on neuroplasticity to elucidate its mechanisms, limits,

and - most importantly - its potential. Today, neurosurgeons possess the knowledge to predict whether a function will be recovered following a surgical procedure on the brain.

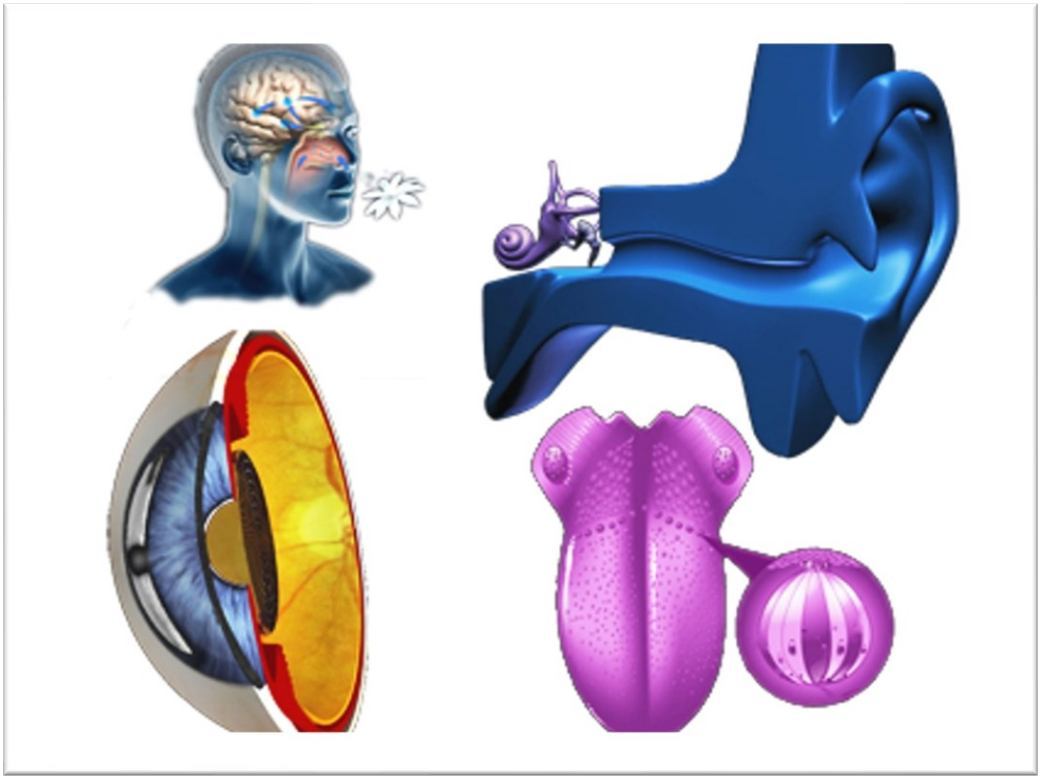
This cerebral flexibility has begun to be exploited in recent years, particularly in the field of sensory loss.

For instance, devices now exist that allow people with certain forms of blindness to "**see**" using their tongue [97, 141]: cameras mounted on the forehead transmit visual data to a device placed on the tongue, where light signals are converted into mechanical signals. Because the tongue is highly sensitive, it allows the patient to discriminate between these "mechanical pixels." Over time, the brain adapts to this new function, and the **visual cortex** takes over the perception of this new sensory modality.

Another example involves a patient who lost her sense of balance due to **labyrinthine toxicity** caused by antibiotics. She was fitted with a device that sends regular vibratory signals to the floor of the mouth based on her spatial orientation. Gradually, her brain adapted to this new form of signal and integrated its function in the same way it integrates neurological data from the inner ear.

These practical applications of neuroplasticity in sensory loss prove once again that sensory organs are for the most part means of extracting data from the world. While they are very powerful and elaborate on their own, their peripheral failure can be bypassed through artificial means (**sensory substitution** [97] ), and the brain will successfully adapt to these new modalities.

# Sensory Systems



# Sensory Systems – General Principles

Senses play a fundamental role in our lives. Sensory systems provide the primary interface between the individual and the environment, facilitating a constant awareness of external stimuli.

It is estimated that every second, our brain receives more than a billion pieces of information from different sensory modalities [142]. This incredibly vast number demonstrates the extent to which the nervous system is continuously bound to the environment.

Like many other species, we possess several sensory modalities that detect various physical and chemical properties. For instance, we possess an extraordinary visual system sensitive to light. Through this system, we perceive electromagnetic waves as meaningful images. We also have an auditory system that detects even the slightest variations in air pressure and converts them into understandable sound. Two other chemical systems - olfactory and gustatory - allow us to detect chemical particles and assign them a smell and a taste. Another balancing system informs us (consciously or not) of our position and movements in space.

And above all, we possess an impressive sensory entity: the **somatosensory system**, which is as vital as vision or hearing, if not more. This system, diffuse and ubiquitous throughout the body [39], constantly provides information about our own body, what touches it, and, above all, what threatens it.

Sensory systems are often composed of a receptor organ, a transmission pathway, and a cortical reception and perception area within the brain. Signal **transduction** occurs at the receptor organ - that is, the conversion of physicochemical properties into electrical signals that can be transmitted by neurons.

The arrival of these electrical signals in the primary cortical areas represents only the first stage of information assimilation within the brain. Indeed, other regions, known as associative cortical areas, are required for the information to acquire meaning; this process is what we call **perception**.

# Somesthesia

**Somesthesia** [2, 5, 72] (also called Somatosensation, body sensitivity, general sensitivity, or somatic sensitivity) differs from other sensory systems. Indeed, its receptor organs are distributed all over the body [39], and it corresponds to completely different sensory modalities [5].

## 1. Somatosensory Modalities :

Somatosensation is, in fact, a multisensory system that provides information on:

- *Fine touch* (*epicritic*) [36]: detection of delicate shapes and fine textures of objects.
- *Coarse touch* (*protopathic*): gives a global idea of the geometry of objects.
- *Pressure*.
- *Vibration* (*pallesthesia*) [107].
- *Temperature* [4].
- *Pain* (nociception) [5].
- And the sense of *limb position* in space (*statokinesia*).

In general, three major categories of general sensitivity are distinguished [5, 96]:

- ***Exteroception:*** Sensitivity related to the outside world.
- ***Proprioception*** [4]: Perception of the relative position of body parts (***deep sensitivity***).
- ***Interoception*** [74]: Sensitivity of the viscera and vegetative systems.

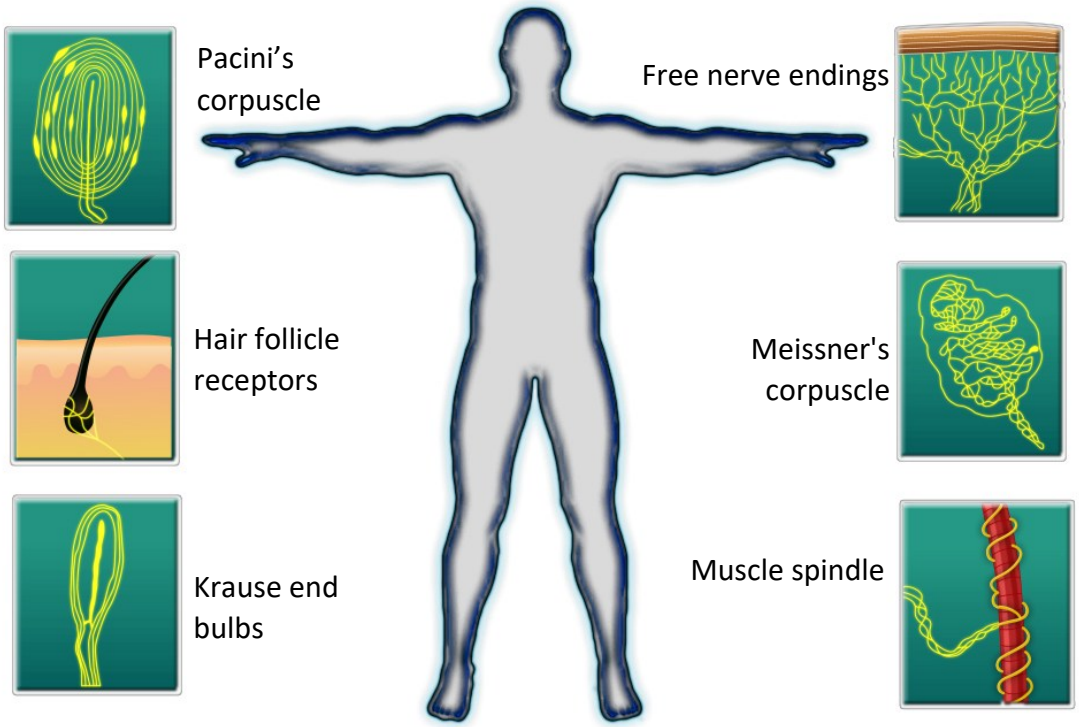



**Image 70:** Somesthetic receptors.

## 2. Receptors :

There are several types of receptors [41, 57] involved in converting different signals (mechanical, thermal, and chemical) into action potentials: the language understood by neurons. Thus, we distinguish:

- **Mechanoreceptors** (which react to pressure),
- **Chemoreceptors** stimulated by chemical substances,
- **Thermoreceptors** (sensitive to heat),
- And **nociceptors** (which collect data on pain) [57].

In the category of mechanoreceptors [5], several varieties exist based on discriminative power (the ability to distinguish between two close points of stimulation) and adaptation time to the stimulus (the delay after which the receptor ceases to emit action potentials).

We thus distinguish: **Hair receptors** [44], **Merkel discs** [38, 41], **Meissner corpuscles** (very important for fine touch) [38], and **Ruffini corpuscles** [143].

There are two types of temperature receptors [36]: **heat** receptors and **cold** receptors.

For proprioceptive sensitivity, there are three varieties of receptors: **Golgi tendon organs** [54, 109], **neuromuscular spindles** [3, 38, 109], and **joint receptors** [54, 109].

There are also **polymodal receptors** [57, 144] and **free nerve endings** [41] that primarily provide information on pain.

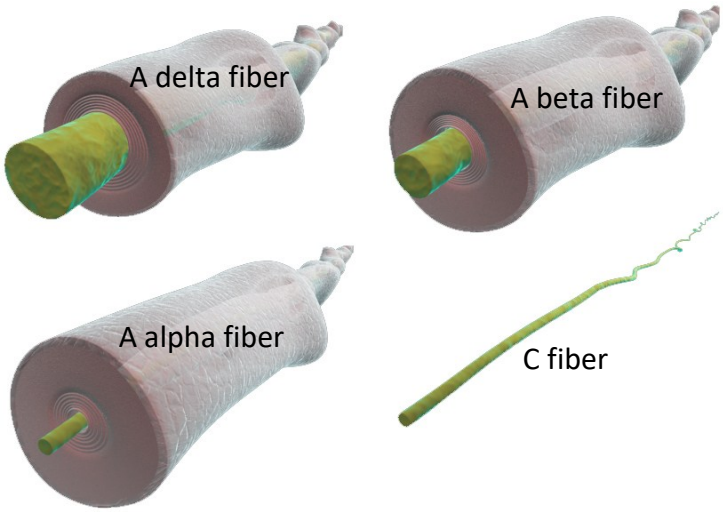



**Image 71:** Somesthetic nerve fibers.

## 3. Transmission :

### 3.1. Peripheral pathways of Somatosensory transmission:

Receptors are linked to nerve fibers that carry sensory information from the receptors to the **CNS**. Four types of fibers are distinguished by their diameter and myelination [57]**:**

- **A-alpha fibers** are large-diameter myelinated fibers: (proprioception)**.**
- **A-beta fibers,** medium-diameter myelinated fibers: (mechanoreception).
- **A-delta fibers**, small-diameter myelinated fibers**.**

- And unmyelinated **C fibers** of small diameter: (for nociception and thermoception) [3].

The cell bodies (pseudo-unipolar) of these fibers are located in the **spinal ganglia** for spinal nerves, and in the **Gasserian ganglion** (trigeminal ganglion) [45] for the trigeminal nerve, which is responsible for facial sensitivity.

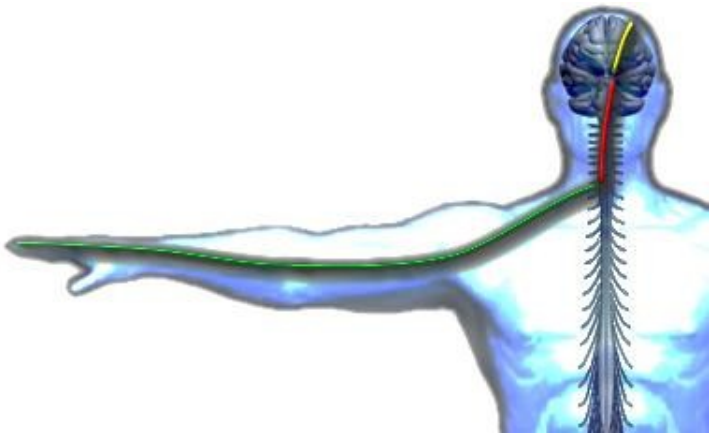


**Image 72:** The chain of three neurons of somatosensory transmission.

### 3.2. Receiving fields :

A **receptive field** [5] is the anatomical area innervated by the dendritic processes of a single nerve cell. These regions are smaller and more numerous at the extremities (fingertips, lips, tongue), which explains the high sensitivity in these regions.

### 3.3. Dermatomes :

Each sensory root contains sensory fibers linked to a specific area of the skin called a **dermatome** [41]. There are 31 pairs of spinal nerves; however, there are only 30 pairs of dermatomes. This is because the first spinal nerve root, **C1**, often does not contain sensory fibers [13, 18].

### 3.4. Central pathways of somatosensory transmission:

There is classically a chain of three neurons that ensures the conduction of the sensory signal to the cerebral cortex. Within the **CNS**, sensory fibers are organized into two main tracts: the **lemniscal system** (dorsal column pathway) and the **extralemniscal system** (spinothalamic or anterolateral pathway).

The **lemniscal system** [41] fibers carry information regarding fine touch, vibration, and proprioception. They constitute the **posterior columns** of the spinal cord and ascend to the **gracile and cuneate nuclei** [36] in the medulla oblongata. At this level, they synapse with the second neurons, which cross the midline (**decussation**) and ascend along the **medial lemniscus** to the thalamus, where they make a second synapse.

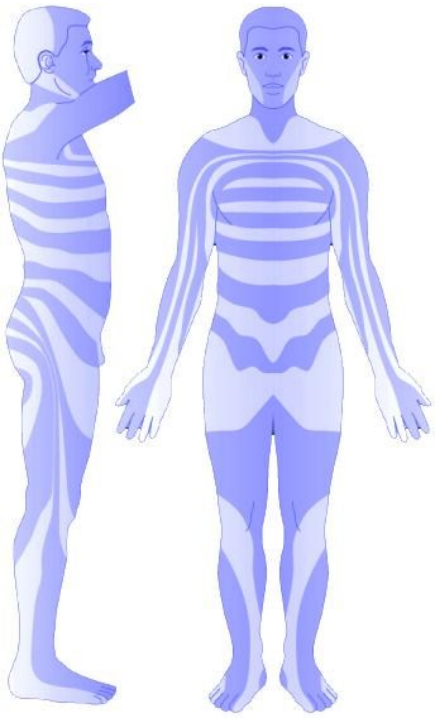


**Image 73:** Dermatomes.

The **extralemniscal system** [145] carries afferents for pain, thermoception, and coarse touch. The first neurons of this system synapse directly upon entering the spinal cord at the level of the **substantia gelatinosa**; the second neurons cross the midline and form the **anterolateral tract**, which reaches the thalamus, where these fibers make a second synapse. Fibers of this system also relay at various brainstem nuclei, notably the **reticular formation** and the **periaqueductal gray**.

There is also a third system that connects the cerebellum to fibers carrying information on unconscious proprioception (**spinocerebellar tract**) [38, 75].

Both systems (lemniscal and extralemniscal) reach the thalamus at the **ventrobasal complex** [50]. At this level, there is a somatotopic map of different body parts: the head at the *ventral posteromedial* **(VPM)** nucleus [71] and the rest of the body at the *ventral posterolateral* **(VPL)** nucleus [2].

From the thalamus, third-order neurons carry the signal to the primary somatosensory cortex.

## 4. Perception :

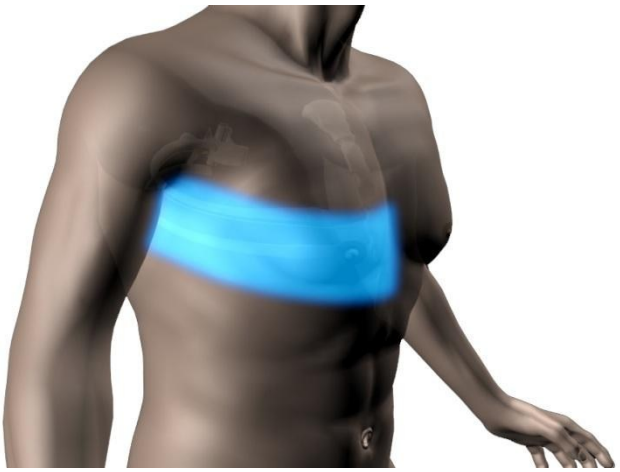


**Image 74:** A dermatome.

The **primary somatosensory cortex (S1)** is located in the **postcentral gyrus** and corresponds to areas 3, 1, and 2 of **Brodmann's classification** [38].

At this level, there is also a somatotopic representation [57] of all body parts. This representation is disproportionate, based on sensory finesse and the distribution of receptive fields in each body part. This somatotopy is illustrated by the famous **Penfield homunculus** [119], which has giant hands and a giant mouth but a tiny trunk.

Fibers from the primary somatosensory cortex **S1** project to the **secondary somatosensory cortex (S2)** [38], which is involved in memory processes. Others join the **associative somatosensory cortex** posteriorly in the **posterior parietal cortex** (areas 5 and 7) [57], where the integration of sensory information with visual information occurs to construct a coherent reality. Ultimately, each side of the brain processes sensory information from the opposite side of the body.

# Vision

*"We do not see with our eyes; we see with our brain."* ***Jeanette Norden***

Of all the sensory systems available to us, vision [52, 57, 133] is undoubtedly the most impactful. It allows us to observe, analyze, and interact effectively with our surroundings. Without it, our primary window to the world would be closed.

## 1. Reception :

### 1.1. Anatomy :

The receptor organ for vision is the **eye** (eyeball) [43, 45]. This spherical organ is composed of three layers [42], which are, from the exterior to the interior: the **sclera**, the **choroid**, and the **retina**.

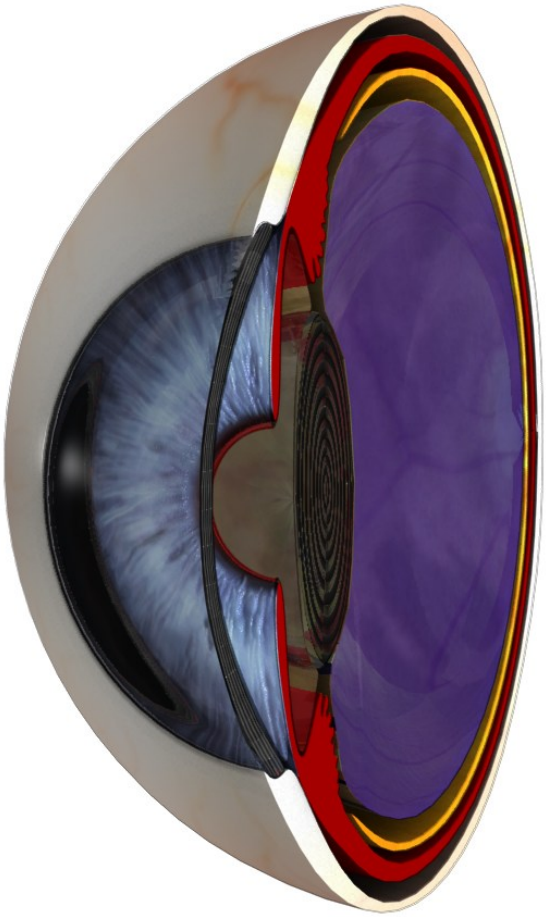


**Image 75:** A section of the eyeball.

The **sclera** (the white of the eye) [146] is a white, tough envelope that maintains internal pressure and protects the eye against mechanical damage. It continues anteriorly as a thin, transparent, non-vascularized, and richly innervated envelope: the **cornea** [64]. The cornea bulges at the front of the eyeball.

The **choroid** [5, 64, 146] : A black, richly vascularized envelope that nourishes the photoreceptor cells of the eye and maintains the interior of the eye as a dark chamber. The choroid continues anteriorly as the **ciliary body** [94, 122, 147] and the **iris** [133] , which gives us our eye color and delineates an opening: the **pupil**. Together, these vascular structures form the **uvea** [72].

The **retina** [57]: A thin membrane of about 0.5 mm [154] that is highly vascularized. This is the nervous tissue that continues as the **optic nerve** at the level of the **optic disc (optic papilla)**. The retina is the sensory part that contains the **photoreceptor cells** [39, 94].

Behind the iris lies the **lens (crystalline lens)** [99, 148], a transparent, biconvex structure involved in focusing light beams onto the retina.

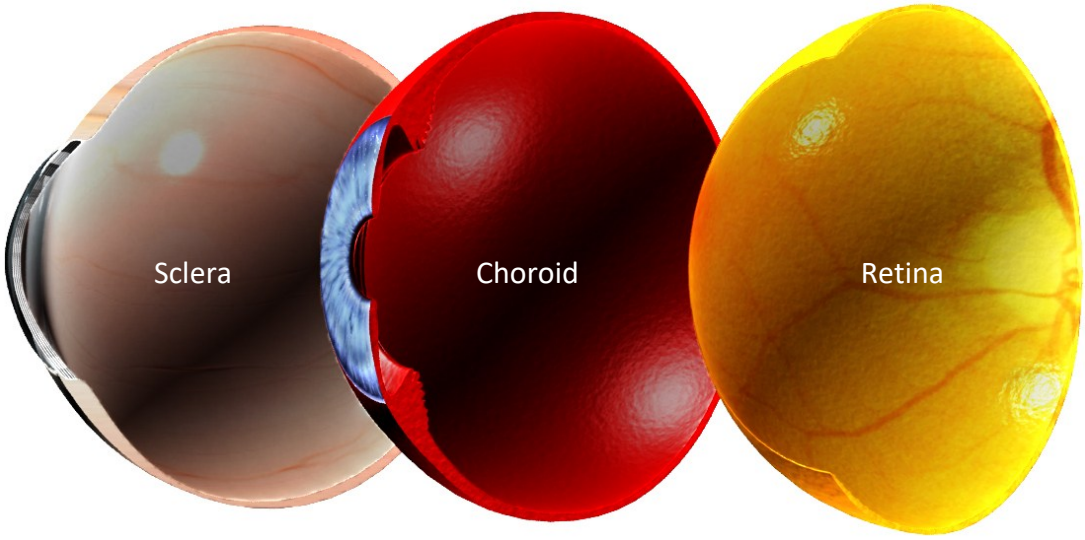



**Image 76:** The three tunics of the eye.

The interior of the eye is filled with substances that maintain its globular shape: in front of the lens is the **aqueous humor** [104, 148] , a transparent liquid of low viscosity that nourishes the cornea. Behind the lens is the **vitreous body** [116, 148, 149] , a transparent gelatinous substance that holds the retina in place against the ocular wall and absorbs a large amount of ultraviolet rays.

### 1.2. Optics :

The cornea is the first surface that light must pass through to reach the retina; it is curved and therefore contributes significantly to the convergence of light rays.

The **pupil** is the diaphragm of the eye [52]; it regulates the amount of incoming light by changing its diameter in response to light intensity, thanks to the antagonistic muscular system of the iris [150]: radial fibers dilate the pupil, and circular fibers constrict it.

The **lens** is the objective of the eye [43]. Its biconvex shape and flexibility allow it to modify its curvature to focus on objects at various distances; this phenomenon is called **accommodation** [3].

The eye thus functions like a camera [43] with a diaphragm (the pupil) [52] for automatic exposure control, an objective (cornea and lens) [43] in autofocus mode, and a photosensitive surface (the retina). The resulting image is focused on the retina (in an emmetropic eye), where it is reduced and inverted.

### 1.3. The retina :

#### a. Retinal cells :

The retina [3] (nervous tissue originating from the diencephalon during development [41, 72]) consists essentially of three layers of nerve cells [1, 70, 151]. Moving from the inner surface of the eye toward the back, we first find the **ganglion cells** [4, 99, 152]. Their axons bundle together to form the

optic nerve, totaling about 1 million fibers per eye [75, 96, 133, 149, 152].

Behind them are the **bipolar cells** [153], which bridge the gap between photoreceptors and ganglion cells, forming the intermediate layer. Paradoxically, the **photoreceptor neurons** [99], the cells that actually detect light, form the deepest layer at the very back of the eye, sitting against the choroid.

Two other types of neurons also exist in the retina: **horizontal cells** and **amacrine cells** [99]. These interpose between the three layers of the retina and help improve the contrast and definition of the image transmitted to the brain.

### b. Photoreceptors :

There are two types of photoreceptor cells: **cones** and **rods**. Each human eye contains about 125 million photoreceptors [99], of which only 5 million [75] are cones.

- **Cones :**

Although they are far fewer in number than rods, **cones** determine our **visual acuity** [48]. In fact, the central area of the retina (**macula**) [154] contains a central region (**fovea** [4, 39, 148]) that is completely devoid of rods [38, 39]; only cones exist at this place.

Cones provide us with **color vision** [1, 39] thanks to three pigments (**opsins** [38] ) sensitive to blue, green, and red. Each cone contains only one of these pigments. Cones allow us to perceive image details [1, 39] because each cone is linked to a single bipolar cell, which in turn is linked to a single ganglion cell [41]. So, each cone has its own dedicated "line" to the brain.

**Image 77**: A cone.

- **Rods :**

Rods [153] are extremely sensitive to light [1]; a single rod can absorb and react to a single photon [5, 41]. They contain an essential pigment (**rhodopsin** [57]); each rod contains about 1,000 discs with 40 million rhodopsin pigments [155].

Rhodopsin contains a molecule (**retinal**, a derivative of vitamin A [4, 42]) that changes shape whenever it absorbs light, triggering a chain reaction that hyperpolarizes the membrane and stimulates a bipolar cell.

Rods are distributed mainly at the periphery of the retina and allow us to detect the **movement** of objects [149]. Their high sensitivity enables us to see in the dark (**scotopic vision**) [41], unlike cones, which provide **photopic vision**.

### c. The optic disc (optic papilla):

In a fundus examination [67], the area where all the nerve fibers gather to form the optic nerve is clearly visible; this area is called the **optic disc (optic papilla)** [148]. Since there are no photoreceptors at this level, it is a **blind spot** [41]. Why then do we not notice any gap in our visual field? The answer is that the brain fills in the missing information by using data collected from the surrounding areas [39].

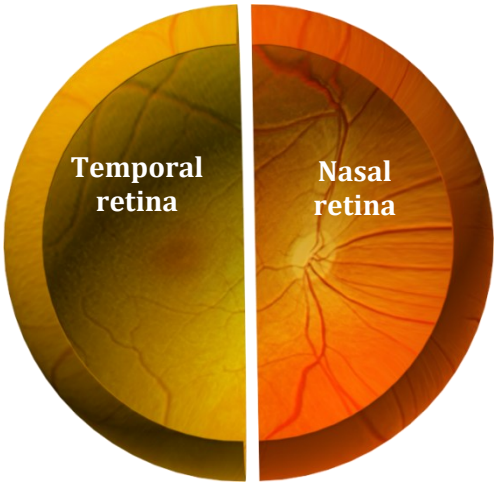



**Image 78:** Nasal retina and temporal retina.

### d. Retina and visual hemifields :

The retina is divided into two parts [72]: the **nasal retina** and the **temporal retina**. The visual field is also divided into two hemifields, each corresponding to the region of the retina that receives it [41]. Light from the right visual field strikes the nasal retina of the right eye and the temporal retina of the left. For the left visual field, the opposite is true.

## 2. Transmission :

All the nerve fibers from the ganglion cells form the optic nerve [41, 116]. This is the only nerve in the body that belongs to the **CNS** and not the **PNS** [41].

From an anatomical point of view, it is the only nerve surrounded by the three layers of the meninges [64]. Embryologically, it develops from the **diencephalon** [50]. At the cellular level, it does not contain Schwann cells but rather **oligodendrocytes**, which is why it is often affected in multiple sclerosis.

The optic nerve originates behind the eye and terminates at the **optic chiasm**, just above the pituitary gland.

The optic chiasm [119] is a crossover point where fibers from each nasal retina cross the midline to join fibers from the temporal retina of the contralateral eye, thus forming a pair of **optic tracts**. Each optic tract contains information from the **contralateral visual hemifield** [50].

**Image 79:** A rod.

The two optic tracts curve around the brainstem (cerebral peduncles) and reach the **lateral geniculate nuclei** of the thalamus. From there, several bundles of fibers (**optic radiations**) [41, 149] project onto the *primary visual cortex* in the occipital lobe, as well as other structures like the **superior colliculi** in the brainstem, where certain reflex phenomena are processed.

## 3. Perception :

The *primary visual cortex* **(V1, Brodmann area 17)** [49, 73], located in the occipital cortex, is the first cortical relay for the nerve fibers of the visual system. It receives visual information and handles its primary processing.

Each visual cortex analyzes the **contralateral visual hemifield**. There is a **retinotopy** [5] with a very large area of the visual cortex corresponding to the fovea (the central area of the macula).

From the primary visual cortex, other nerve fibers project to other regions of the cerebral cortex known as the **secondary visual cortex** [57]: **V2, V3, V4, V5, MT...** [57] in order to analyze visual properties such as color, shape, texture, movement, and depth.

Other fibers project to distant regions of the cortex called **associative areas** [57]. There are two main types of these projections [57]**:**

The **dorsal stream** (the "where," or occipito-parietal pathway): this system analyzes movement, depth, and spatial orientation, allowing for the localization of objects.

The **ventral stream** (the "what," or occipito-temporal pathway): it analyzes shape and color, allowing for the recognition and perception of objects.

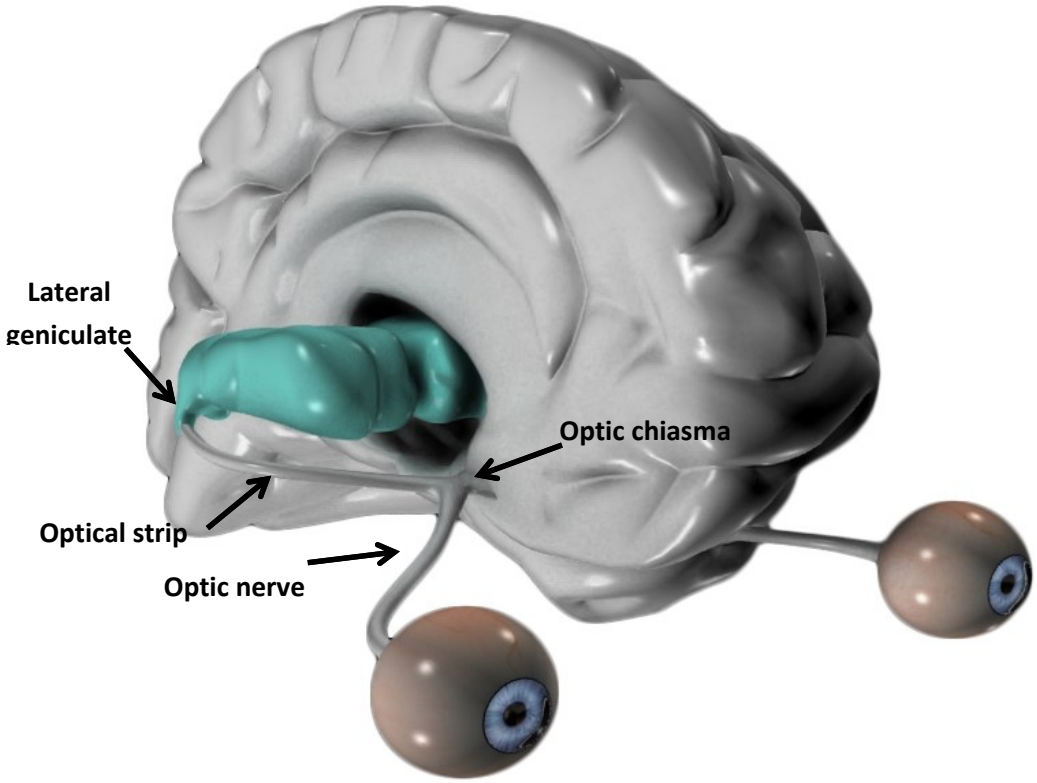



**Image 80:** Visual transmission pathways.

# Hearing

What is known as sound [3, 39] is actually just a perception of a succession of high- and low-pressure zones in the air. This succession forms a sound wave [141]. Each sound wave is characterized by a *frequency* [39] - the number of cycles per second, expressed in **hertz (Hz)** - and an **amplitude** [39] - the sound intensity, expressed in **decibels (dB)**.

The decibel is a logarithmic unit; this means that every time the sound level increases by ten decibels, the sound wave carries ten times more power. To our ears, we perceive this as the sound being roughly twice as loud.

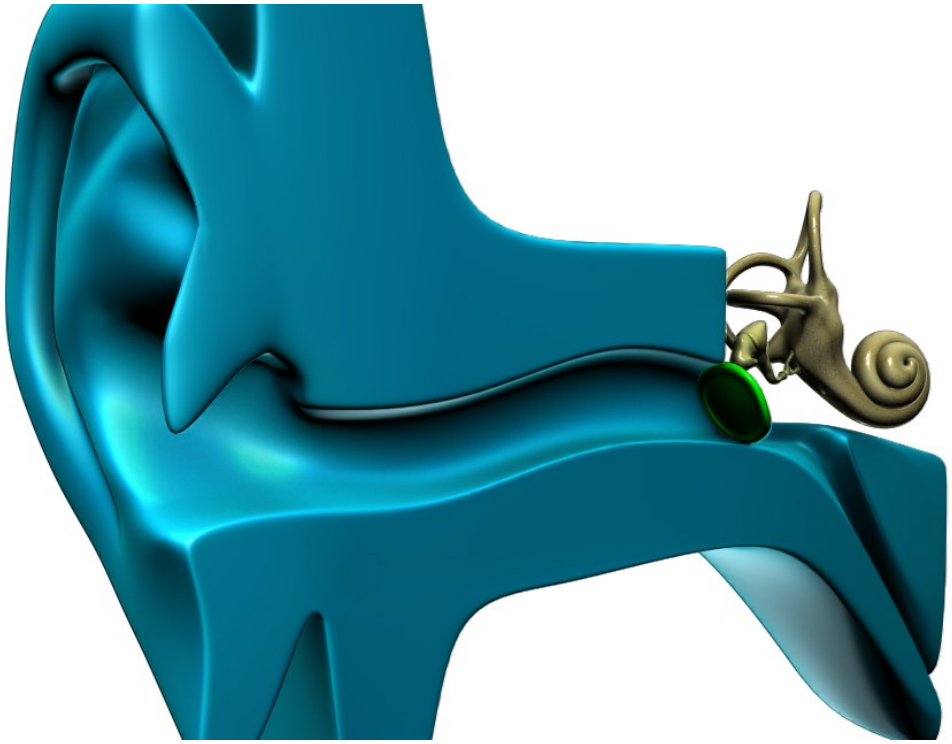


**Image 81:** The auditory system.

## 1. Reception :

The receptor organ for sound is the **ear** [57], it consists of three parts: the outer ear, the middle ear, and the inner ear.

### 1.1. The outer ear :

The outer ear [38] includes the **pinna** (auricle), which, thanks to its trumpet-like shape, amplifies sound intensity and buffers the abrupt transition of air from the open environment to the confined **external auditory canal**. The latter (about three centimeters long) directs sound waves to the **eardrum** (tympanic membrane) [5], a thin membrane that constantly vibrates in response to sound impacts.

### 1.2. The middle ear :

The middle ear [41] contains three essential bones: the **malleus** (hammer), which is attached to the eardrum by its handle; the **incus** (anvil); and the **stapes** (stirrup). This complex, known as the **ossicular chain** [84], acts as a sound mediator between the air medium outside the eardrum and the fluid medium of the inner ear beyond the **oval window**.

When a sound wave passes from air into a liquid medium, its power is reduced by 99.9%; this is known as resistance or, more commonly, **acoustic impedance** [52]. The very high ratio of the tympanic diameter to the diameter of the oval window allows, among other mechanisms, to bypass this loss [3] and amplify the vibration intensity by 30 dB.

To protect the inner ear from damage, the middle ear uses the **stapedial reflex** [72], which automatically dampens any sounds louder than 70 decibels. This protective mechanism involves the **stapedius muscle** and the **tensor tympani muscle**. The ossicular chain then becomes more rigid, weakening the sound intensity.

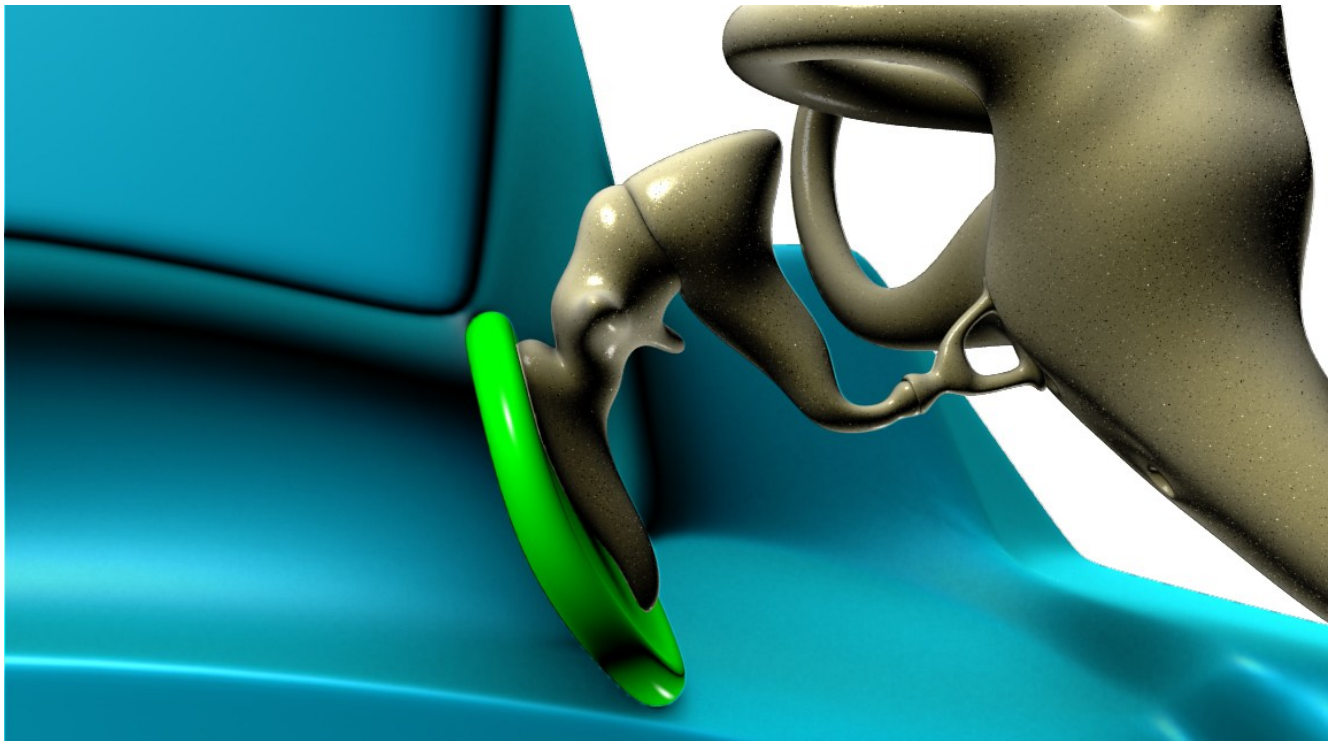


**Image 82:** The ossicular chain.

### 1.3. The inner ear :

The inner ear [5, 41] contains the **cochlea** [57], the actual organ for the **transduction** of mechanical signals (**vibrations**) into electrical signals (**action potentials**), the language of neurons. The cochlea has a conical, spiral shape similar to a snail shell, with two and a half turns [133] around a bony pillar called the **modiolus**.

The interior of the cochlea is divided along its length into three cavities: the **scala vestibuli** at the top, the **scala tympani** at the bottom, and the **cochlear duct** (scala media) between them. The scala vestibuli is in contact with the vestibule and the oval window; it communicates at the apex with the scala tympani through an opening called the **helicotrema**. Both of these chambers contain **perilymph**.

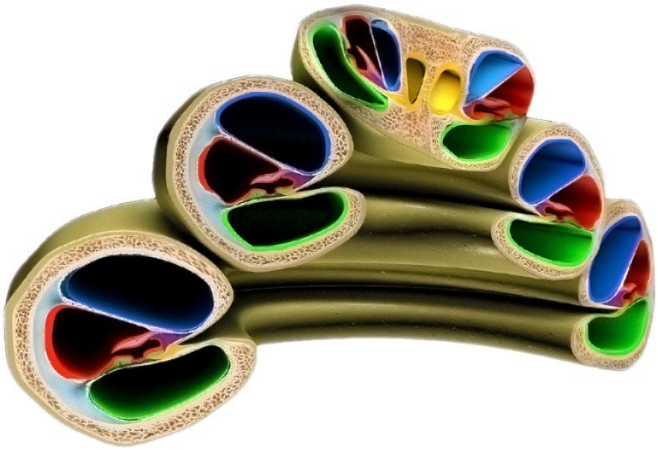


**Image 83:** A section of the cochlea.

The cochlear duct contains **endolymph** as well as the **organ of Corti** [41, 57], which is the structure responsible for converting vibrations into electrical signals. The cochlear duct is separated from the scala tympani by the **basilar membrane** and from the scala vestibuli by **Reissner's membrane**.

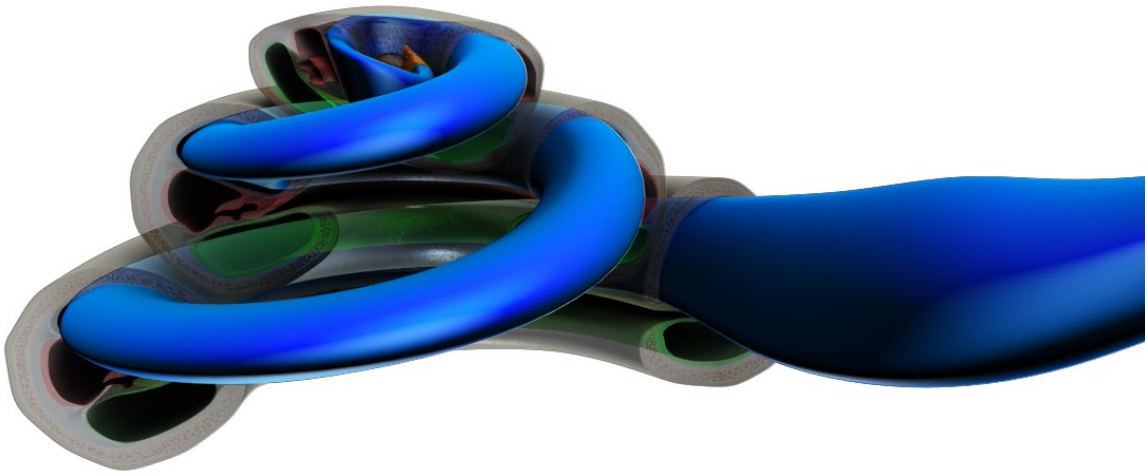


**Image 84**: The scala vestibuli.

### 1.4. The organ of Corti :

The **organ of Corti** [41] comprises two types of sensory cells: the **inner hair cells (IHCs)** arranged in a single row (there are about 3,500 IHCs in the cochlea), and the **outer hair cells (OHCs)** arranged in three V-shaped rows [38]. These cells contain cilia that are attached to a membrane called the **tectorial membrane**.

When the hair cells slide relative to the tectorial membrane, they depolarize and release neurotransmitters [41] that stimulate

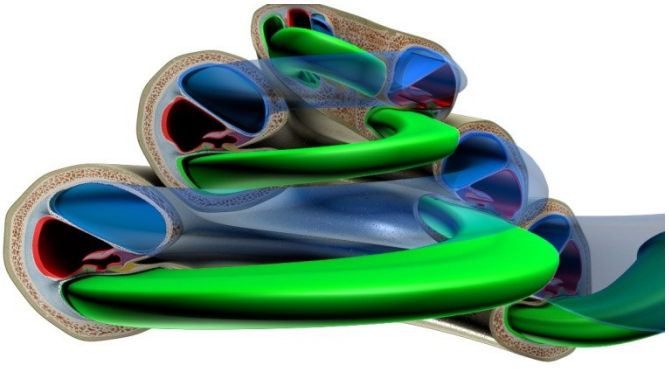


**Image 85:** The scala tympani.

nerve fibers. These fibers follow the basilar membrane to the modiolus, where their cell bodies form the **spiral ganglion**. From this ganglion, the axonal fibers gather to form the **cochlear nerve** at the center of the cochlea.

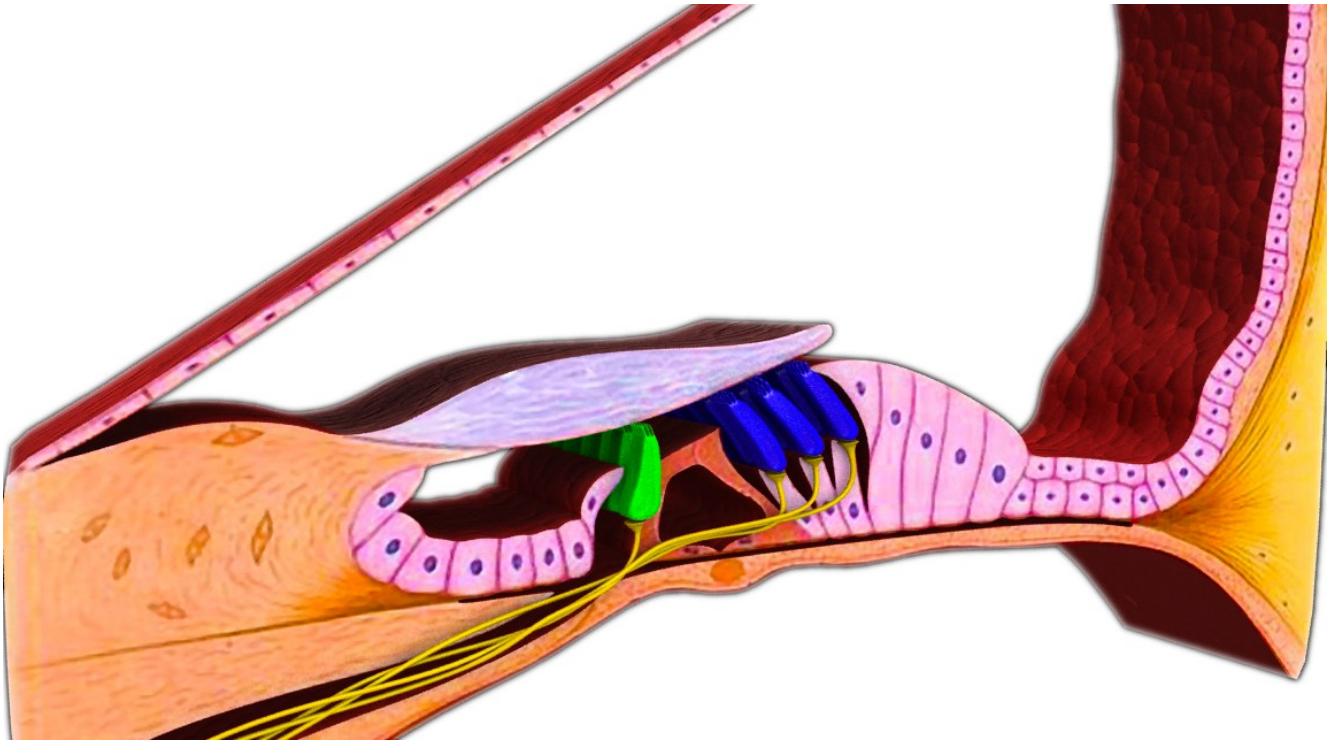


**Image 86:** The organ of Corti.

### 1.5. Functioning :

When sound vibrations reach the eardrum, they are amplified and transmitted via the ossicular chain to the oval window. This causes the perilymph inside the scala vestibuli to vibrate [39].

Depending on the frequency of the sound wave, the **basilar membrane** (which is gradually more flexible and wider from the base to the apex [5]) will vibrate preferentially at a specific zone [39]. This zone is located near the oval window for **high-pitched sounds** and near the apex for **low-pitched sounds** [41].

In the zone of preferential vibration, the hair cells slide against the tectorial membrane [5] , depolarize, and send a nerve signal via the afferent nerve fibers to the brainstem.

The main function of the **OHCs** is to contract to amplify the vibration of the basilar membrane at the point of stimulation [96], allowing the **inner hair cells** to depolarize at low amplitudes. The inner hair cells play the most prominent role in auditory reception [38]; the outer hair cells act more as "**tuners**" that amplify vibrations where necessary. This is illustrated by the fact that 95% of afferent fibers are dedicated to the inner hair cells.

## 2. Transmission - Perception :

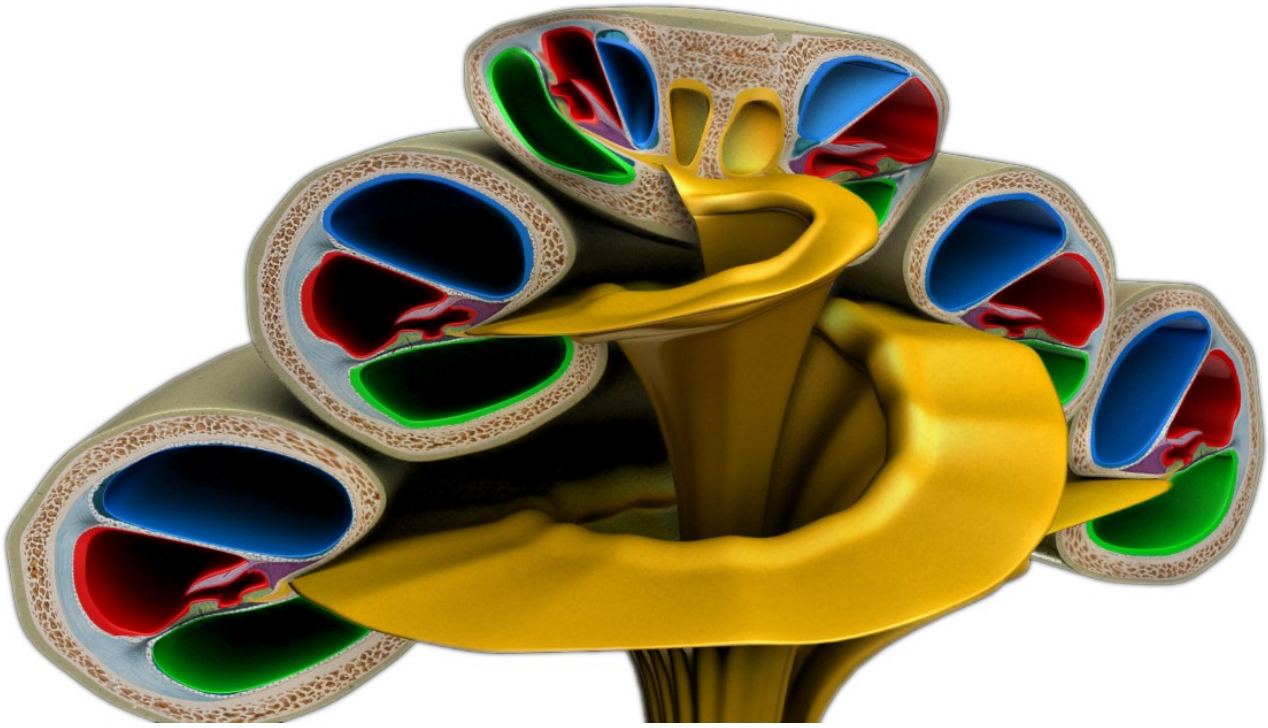


**Image 87:** The cochlea and the spiral ganglion.

When the inner hair cells depolarize, they stimulate the associated nerve fibers, which carry the nerve signal to the **spiral ganglion**. From there, an action potential travels along the cochlear nerve to the **ipsilateral cochlear nucleus** in the brainstem [50].

The central relays of the auditory system are more complex than those of the visual system. Indeed, processing the sounds the ear receives requires the extraction of vast amounts of data: information on intensity, frequency, spatial localization [3], duration, and the filtering of background noise.

Two main auditory pathways are distinguished [5] within the **CNS**: the *primary auditory pathway* [41, 49, 133] and the *non-primary auditory pathway*.

The ***primary auditory pathway*** (dedicated exclusively to auditory perception) begins at the ipsilateral cochlear nucleus and reaches the **superior olivary complex** (contralateral in 80% of cases). These fibers ascend to reach the nuclei of the **lateral lemniscus**, then the **inferior colliculus**, and the thalamus at the **medial geniculate body**. From there, fibers reach the **primary auditory cortex** in **Brodmann areas 41** [39] surrounded by a secondary auditory area. It should be noted that a **tonotopy** [5] exists within the primary auditory cortex, with a graduated distribution of different sound frequencies [39].

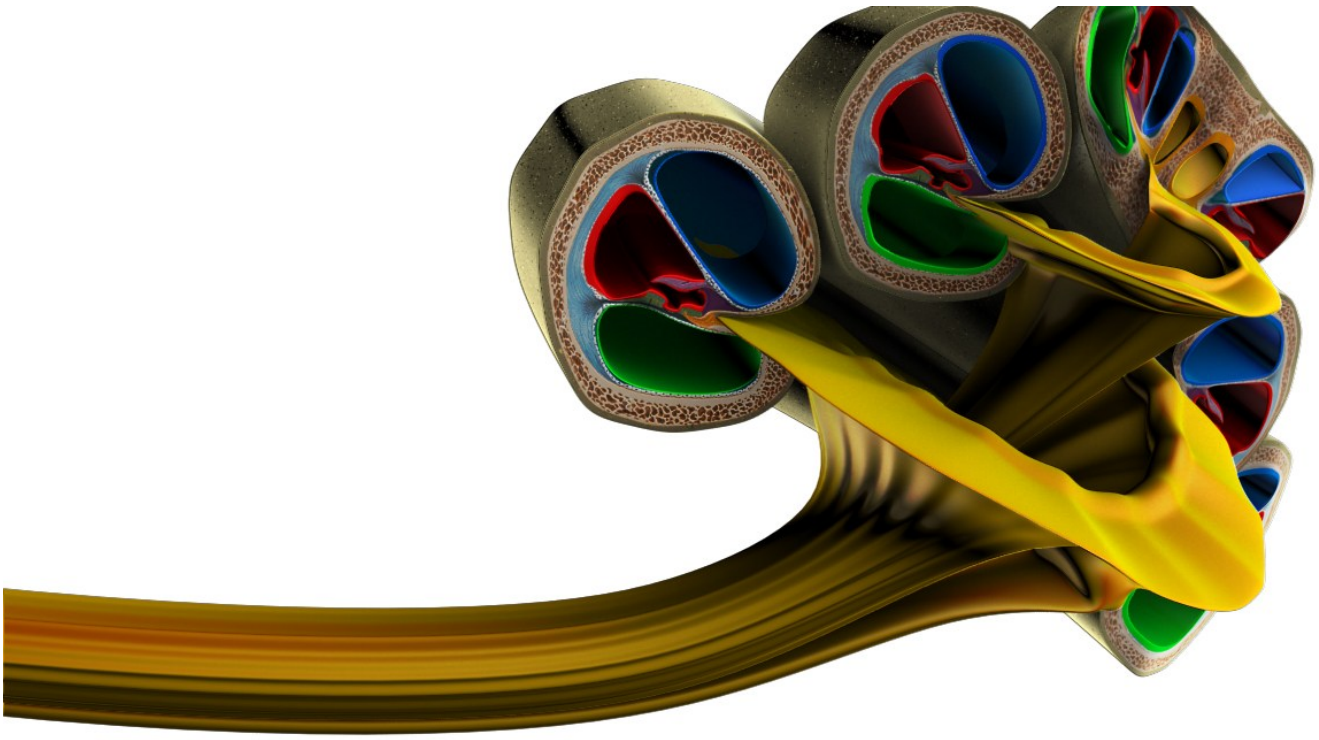


**Image 88:** The cochlear nerve.

The ***non-primary auditory pathway*** is a *non-specific* and polymodal pathway; it makes ipsilateral and contralateral relays in the **reticular formation** and then the reticular center of the thalamus. From there, its fibers project to the **polysensory associative** cortex.

# Balance

**Balance** [42, 130] plays a vital role in our lives. It is thanks to this ability that we can stand, walk, and orient ourselves in space.

Balance is the set of mechanisms that stabilize the body during **standing** and during active or passive movement. These mechanisms help maintain a reference posture and allow the body to return to it regardless of the circumstances.

Maintaining static and dynamic balance requires mechanisms involving a motor component made of neuromuscular elements, but also, and most importantly, mechanisms that constantly inform the **CNS** of the position of different body parts and their movements.

## 1. Sensory modalities of balance :

The sense of balance is a unique system. First, it's a system that functions mostly unconsciously, and second, it involves several sensory modalities [96].

Among the organs participating in the sensory system of balance are**:**

- The ***vestibular system*** [67]**:** a specific organ of balance.
- The ***visual system***.
- Deep sensitivity (***proprioception***).
- And the superficial sensitivity of the **soles of the feet**.

All these systems synchronize their afferent signals to constantly inform the **CNS** of the position or movements of different body parts so that it can react in the most appropriate manner.

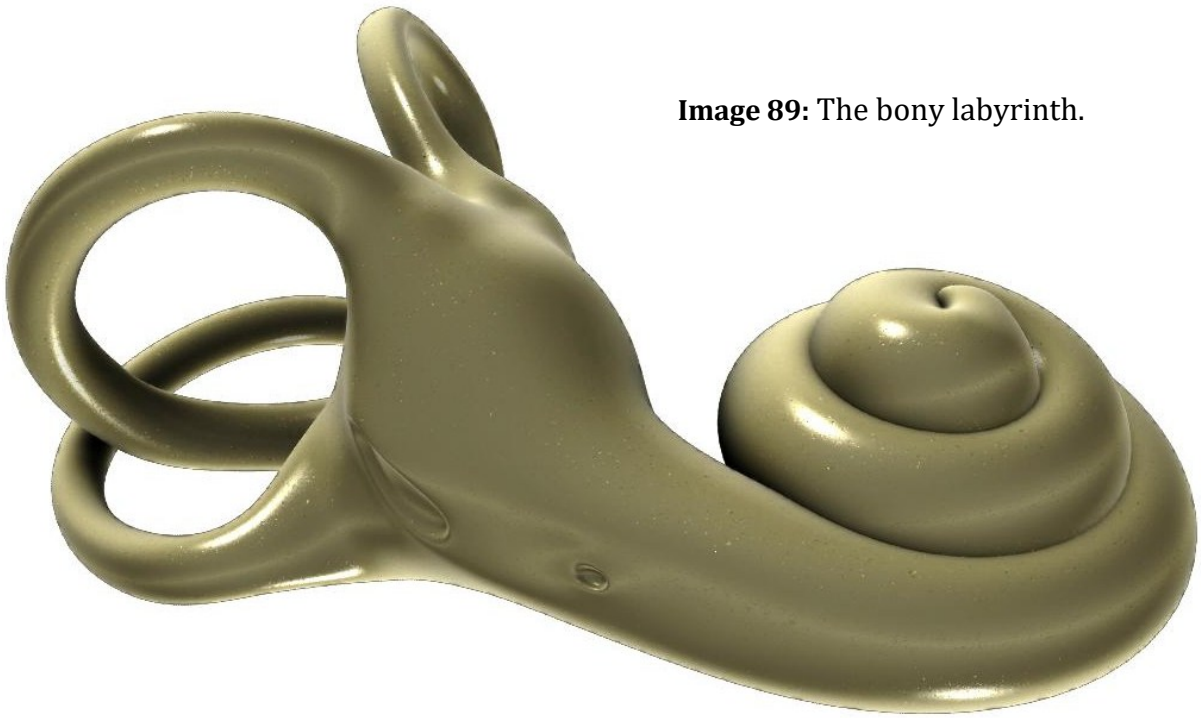


**Image 89:** The bony labyrinth.

## 2. Reception :

The inner ear consists of a **bony labyrinth** filled with a fluid called **perilymph**. Floating within this fluid is the **membranous labyrinth**, which is filled with its own separate fluid called **endolymph**. The membranous labyrinth is divided into an anterior auditory component (**cochlear duct**) and a posterior **vestibular system** [38, 39], the specific organ for balance.

The vestibular system is about 1 cm in diameter and comprises two chambers: the **utricle** and the **saccule**, as well as three **semicircular canals**.

### 2.1. Otolithic organs :

The utricle and the saccule are called **otolith organs** [38] because they contain **otoliths** (calcium carbonate crystals). They are specialized in detecting the movements and linear accelerations of the head, as well as its static position relative to the axis of **gravity**.

The utricle is oriented horizontally [38]; its sensory cells detect all movements occurring in the horizontal plane. The saccule, on the other hand, has a vertical orientation; it provides sensory information on vertical movements. These two systems constantly inform the **CNS** about the position of the head and the displacement movements it undergoes in all directions.

The sensory cells of the vestibular system are similar to the hair cells of the cochlea [41]; they are embedded in the epithelium with cilia on their apical pole: **stereocilia** and **kinocilia**. These cilia are bathed in a gelatinous layer (the **cupula**) [52] which, in the utricle and saccule, is peppered with microcrystals (**otoliths**) that increase its consistency.

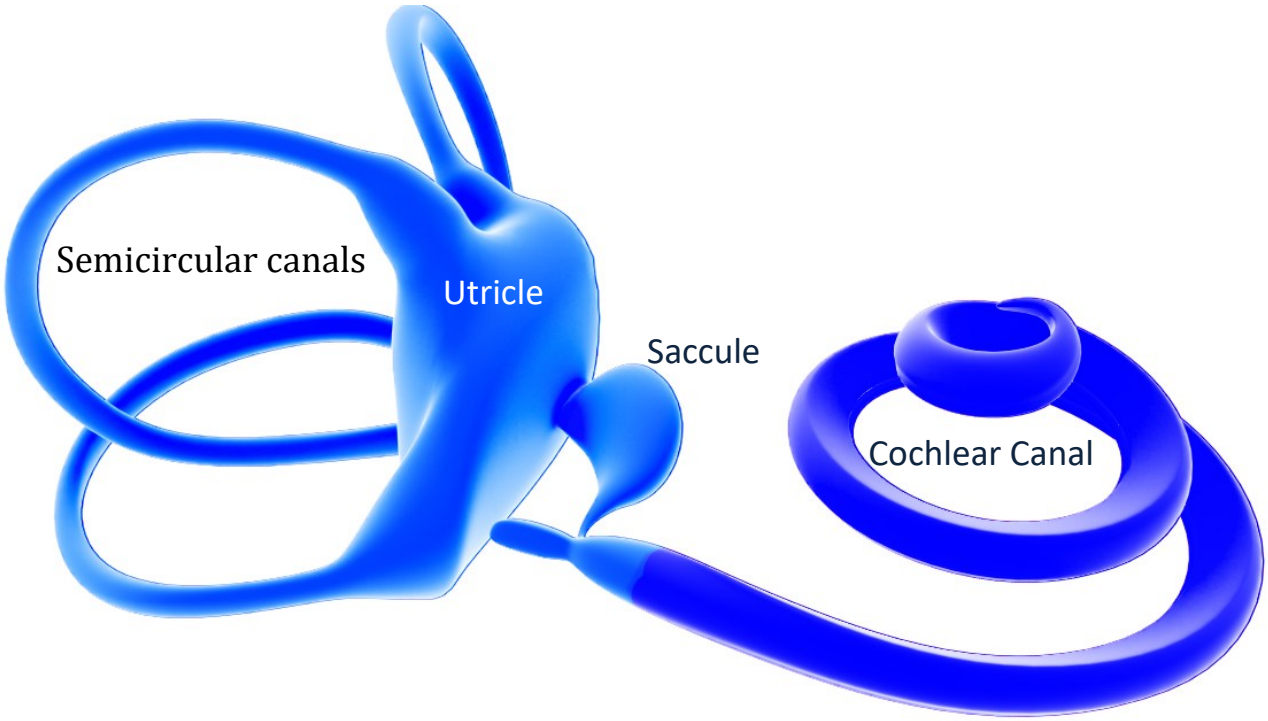



**Image 90:** The membranous labyrinth.

When the head moves, the endolymph (due to its inertia) takes time to follow, and thus pushes the **cupula** in the opposite direction of the movement. This carries the cilia of the sensory cells with it, causing them to **depolarize** [41] and activate the associated afferent neurons.

### 2.2. Semicircular canals :

The three semicircular canals are each arranged in one of the planes of space [38, 52]; there is an anterior, a posterior, and a lateral canal. Each canal ends near the utricle with a swelling (the **ampulla** of the canal). The latter contains sensory cells that function according to the same mechanism [38] as those in the saccule and utricle, except that the **cupulae** at this level do not contain otoliths.

Due to their circular arrangement, the semicircular canals signal the **rotational movements** of the head.

## 3. Transmission – Perception :

The nerve fibers originating from the hair cells of the vestibular system have their cell bodies in **Scarpa's ganglion** (**vestibular ganglion**) [50]. From this, the vestibular nerve emerges and joins the cochlear nerve to form the **vestibulocochlear nerve (CN VIII)**.

After reaching the *vestibular nucleus* [38] in the brainstem, the fibers of the vestibular branch of nerve VIII relay with other neurons that reach different regions of the central nervous system: the **thalamus** [41], the cerebellum, the cerebral cortex, the spinal cord, the reticular formation, and the **oculomotor nuclei**, which enable the **vestibulo-ocular reflex** [50]. This reflex stabilizes images on the retina during movement.

# Olfaction

Just like taste, **olfaction** [5, 133, 141] is a sense whose stimuli are chemical in nature. It is through this sense that we can detect and analyze volatile chemical substances present in the air, these molecules are what we perceive as **odors**.

While this sense is of vital importance in other species, in humans, its significance is secondary. Indeed, in humans, the sense of smell is less developed compared to other animals [5] and is subject to great subjectivity, making it difficult to study.

## 1. Reception :

The receptor organ for olfaction is located in the upper part of the nasal cavities. This is the **olfactory mucosa** [94, 130], it contains olfactory sensory cells - 10 million in humans compared to 200 million in dogs for reference [141]. These cells are bipolar neurons equipped with olfactory cilia; they have the capacity to detect odors at the tips of their dendrites.

Olfactory neurons are unique: they continue to proliferate in adults (**neurogenesis**) [4, 116]. The lifespan of a primary olfactory neuron is approximately 30 to 60 days [99].

We are able to smell between 4,000 and 10,000 different odors [5] ; each odor preferentially activates a specific group of receptor neurons [5]. The mucus of the olfactory mucosa captures molecules that bind to receptor proteins on the ciliary membrane of the olfactory receptors. This binding triggers a cascade of biochemical reactions that ultimately depolarize the membrane and lead to the generation of an **action potential** [38, 41].

## 2. Transmission :

The axons of the receptor neurons cross the **cribriform plate** of the ethmoid bone, forming the **olfactory nerve** [41, 50, 116].

The olfactory nerve is a very peculiar nerve. First, it is the **shortest** nerve, as its length barely exceeds the thickness of the cribriform plate; second, it does not have an anatomically solid and firm structure like the rest of the body's nerves, but is instead a collection of nerve fiber bundles that traverse the cribriform plate at various points.

Some authors confuse the olfactory nerve with the **olfactory tract** [83] between the bulb and the olfactory striae, whereas the majority of authors agree that the olfactory nerve is simply the set of nerve fibers between the olfactory mucosa and the **olfactory bulb** [116].

The **olfactory bulb** [4, 38, 41] is characterized by the presence of **glomeruli** [38, 96] - spherical structures containing the synaptic junctions of receptor neurons-, **mitral cells** (the main relay

neurons of the olfactory bulb) [5], and local interneurons. There are approximately 1,000 glomeruli in the olfactory bulb [5], each averaging 25,000 synaptic junctions.

Olfactory neurons that possess the same affinity for a specific odor group together in the same glomerulus, where they synapse with the relay mitral cells. These pass through the ***olfactory tract*** [116] and then the ***lateral olfactory stria*** [45], terminating directly in the **piriform and prepiriform cortex** (primary olfactory cortex) [50] without first relaying through the thalamus.

## 3. Perception :

From the primary olfactory cortex, several fibers project to the hypothalamus, thalamus, amygdala, hippocampus, and **orbitofrontal cortex** [38].

Fibers projecting to the **limbic system** (the hippocampus and amygdala in particular) trigger emotional reactions and induce the formation of memories.

Certain odors, such as those of smoke, gas, or skunk, stimulate the sympathetic nervous system.

Appetizing smells stimulate salivation, while unpleasant odors trigger defense reflexes such as sneezing, choking, or vomiting.

# Taste

The **tongue** is a musculo-membranous organ made of 17 very powerful muscles [116], all controlled by **the hypoglossal nerve** [107]. It plays a fundamental role in speech and eating. The tongue also acts as the primary sensory receptor for a chemical sense [36]: **gustation (taste)** [38, 72].

## 1. Reception :

Numerous protrusions called **lingual papillae** [99] are found on the lingual mucosa. These include: *circumvallate* [4, 72], *fungiform* [41], and *filiform papillae* [72]. The *circumvallate* and *fungiform papillae* are the structures responsible for gustation [99].

Unlike rudimentary olfactory receptors, which are essentially the nerve endings of sensory cells, taste relies on more specialized structures: the **taste buds** [41]. These buds are located on the mucosa of the *circumvallate* and *fungiform papillae* [99]; they are composed of support cells (**basal cells**) surrounding the receptor cells, which are arranged concentrically.

Each bud contains 50 to 150 receptor cells [38]. Each receptor cell possesses a ciliated **apical pole** responsible for capturing chemical substances and a **basal pole** that synapses with the sensory neuron.

Four fundamental tastes are distinguished: *sweet*, *bitter*, *sour*, and *salty* [1]. Other flavors add to this list: *astringent* (cranberries, tea, tannins), *pungent* (chili, ginger), *metallic* (ferrous sulfate hydrate), *fatty*, and *starchy*...

Chemical substances must be soluble in saliva to be detected by the gustatory cells. It is commonly said that specific regions of the tongue exist for each taste, but this is not true. In fact, these different tastes can be detected across the entire surface of the tongue [41].

Once bound to the cell membrane, the chemical substances trigger a cascade of biochemical reactions that ultimately depolarize the receptor cell [41].

## 2. Transmission :

Once depolarized, the gustatory cell secretes neurotransmitters that act on the affiliated sensory neuron, triggering an **action potential** that propagates along the nerve fiber to the brainstem [5].

The **facial nerve** [3] carries taste from the front two-thirds of the tongue. In this same region, the **trigeminal** nerve handles touch and temperature sensitivity. For the back third, the glossopharyngeal nerve [3] provides both taste and touch sensation.

The cell bodies of these nerve fibers are located in the **geniculate ganglion** (VII) [116] and the **petrosal ganglion** (IX). The postganglionic fibers enter the brainstem and terminate in the corresponding nuclei, where they relay with other neurons that reach the ventral and posterior parts of the thalamus.

At this level, these neurons relay with fibers that travel through the *internal capsule* to terminate in the *primary gustatory cortex* [5] in the parietal lobe, near the postcentral gyrus.

## 3. Perception :

From the primary gustatory cortex, fibers project to the *secondary gustatory cortex* [5] in the temporal lobe, as well as to the hypothalamus, the amygdala, and the **insula**, providing an affective component to taste.

Finally, it should be noted that the nerve fibers for gustation *do not cross the midline*; consequently, the left primary gustatory cortex receives and analyzes gustatory information from the left side of the tongue, and vice versa [38].

# Motor Systems

# Motor Systems - Overview

While sensory systems provide us with information about our own bodies and the environment, **motor systems** allow us to interact with that environment. Every movement, no matter how simple, is achieved through mechanisms that are most often very complex [130].

In fact, at every moment, the systems we are about to examine – **pyramidal system**, **extrapyramidal system**, and the **cerebellum** - synchronize their actions to produce fluid and correct movement [3].

The *pyramidal system* is at the heart of voluntary actions, the *extrapyramidal system* is composed of circuits and tracts that allow for the automation of movements, and the *cerebellum* ensures their coordination and any necessary correction.

The **autonomic nervous system**, as its name suggests, is not subject to voluntary control. Through its two branches - **sympathetic** and **parasympathetic** - it is responsible for controlling various internal organs in order to adapt their function to the different situations the organism may face.

**Reflexes** are motor shortcuts that also escape voluntary control. They allow us to avoid a threat even before we identify it, which is highly practical and often vital.

The *autonomic nervous system* and *reflexes* are somewhat unique in that they require both sensory and motor components.

# The pyramidal system

A voluntary movement [5], regardless of its nature, must go through several stages and numerous neural circuits before being executed [3, 130].

The gathering of sensory information is important before, during, and even after the movement is performed [39]. Constant feedback is essential for correcting our movements while they are happening [75]; This is why the primary motor cortex sits directly in front of the primary somatosensory cortex, with numerous nerve fibers physically linking the two regions [75].

## 1. Cortical areas :

The planning of voluntary movement takes place largely in the **prefrontal cortex (area 8)** [39]. Movement programming occurs in the **premotor cortex (area 6)** [32], which comprises two distinct regions: the **supplementary motor area** [38] and the **premotor area** [74, 75].

The execution of movements is performed by the **primary motor cortex (area 4)** [4, 39], which occupies the entire precentral gyrus. Like its somatosensory counterpart, it is characterized by a somatotopic distribution of the various body parts. This distribution is disproportionate; regions where the musculature is responsible for fine movements are overrepresented in the cortex compared to other regions. This representation is illustrated by the **Penfield homunculus** [4, 41], which has hands and a face that are large relative to the rest of the body.

Deep in the brain, structures like the basal ganglia act as a quality control center. They use feedback loops to fine-tune our actions, making sure every movement is smooth, accurate, and coordinated [5].

## 2. The pyramidal tract :

The fibers originating from the primary motor cortex form what is known as the **pyramidal tract**. It is so called because the neurons forming it have pyramidal cell bodies in the cerebral cortex (layer 5) [157]. Another plausible explanation is that the main path of the pyramidal tract (the **corticospinal tract**) forms the two pyramids in the medulla oblongata [32]; this definition excludes the corticonuclear tract.

The **pyramidal tract** [179] is the main pathway for voluntary motor activity [130, 227]. It should be noted that this pathway also includes fibers from the premotor areas and the somatosensory and associative cortices [31]. Indeed, only 40% of the fibers of the pyramidal tract originate from the primary motor cortex [3].

The pyramidal tract consists of two bundles: the **corticospinal** and the **geniculate** (also called

**corticonuclear** or **corticobulbar**) tracts.

## 2.1. The corticospinal tract :

The **corticospinal tract** [39] travels from the cortex, passing through the **corona radiata** (the white matter of the cerebral hemispheres), then through the **posterior limb of the internal capsule** [4], the middle part of the cerebral peduncle, and the **pons**.

In the medulla oblongata, the corticospinal tract forms the two **medullary pyramids**. At the lower limit of the medulla (**pyramidal decussation**), 80% [44, 57, 75] of the fibers of this tract cross the midline to form the **lateral corticospinal tract** [5] tract descends along the **lateral column** of the spinal cord [38]. The remaining fibers form the **anterior corticospinal tract** [5].

In the **ventral horn** of the spinal cord, the fibers of the lateral corticospinal tract connect either to interneurons or directly to motor neurons for the muscles involved in fine movements [39].

The fibers of the anterior corticospinal tract continue directly down the **ventral column** of the spinal cord. They cross the midline at each segment in the **anterior commissure** to connect to the corresponding interneurons located in the anterior horns of the cord. These fibers provide bilateral innervation of the axial musculature [41].

Together, these two corticospinal tracts - the anterior and the lateral - provide what is known as contralateral control. This simply means that each side of your brain manages the movements of the opposite side of your body.

## 2.2. The corticonuclear tract :

The **corticonuclear tract** [31, 157] also originates from the cortex. It passes through the **genu** of the internal capsule (hence its name), then provides fibers to the various cranial nerve nuclei in the brainstem. From there, the fibers may or may not cross the midline, depending on the target musculature.

# Extrapyramidal system

"*In spite of the great degree of motor weakness and helplessness, in a pure case* [of hepatolenticular degeneration] *the abdominal reflexes are preserved and a double flexor response is obtained ... in other words, this affection, where it occurs in an uncomplicated form, is an extrapyramidal motor disease*" **Kinnier Wilson, 1912.**

Alongside the pyramidal tract, there are numerous pathways and circuits involved in involuntary motor activity (notably posture and balance), in the automation of gestures, and in motor coordination.

These pathways are highly complex as they involve several components of the nervous system: the cerebral cortex, cerebellum, basal ganglia, brainstem, and spinal cord. They therefore involve many neural relays that are very difficult to study.

## 1. Definition :

The term extrapyramidal poses a terminological problem. Indeed, a distinction must be made between two uses of the term: the **extrapyramidal system**, which often refers to the motor system regulated by the **basal ganglia** [79], and the **extrapyramidal tracts**, which comprise the motor pathways descending into the spinal cord independently of the pyramidal tract.

## 2. Extrapyramidal system :

The notion of the extrapyramidal system [75] was introduced in 1912 by Kinnier Wilson [158]. He proposed that there was a distinct entity regulating motor function alongside the pyramidal tract.

It later became obvious that this system is so complex that the concept of "extrapyramidal" itself is beginning to lose some of its relevance in the field of neurophysiology [4] in favor of the concept of the **basal ganglia** system [158], although it remains important in the field of neuropathology [91]. Indeed, a lesion in any of the nuclei involved in this system leads to specific motor abnormalities [41].

The **extrapyramidal system** involves the *basal ganglia* [38, 39, 78, 79]. It acts as a control system for voluntary movements. When a movement is executed through the pyramidal system, collaterals branch off toward the basal ganglia to inform the extrapyramidal system of the nature of the movement to be performed [41].

This system analyzes the target movement and provides a neurological scenario (a series of excitations and inhibitions of the pyramidal neurons in the primary motor cortex) to execute the

movement in the most appropriate and fluid manner.

The extrapyramidal system has no direct motor projection to the spinal cord. It is a system consisting of a large number of circuits that utilize various types of feedback to function, but the result of this analysis always terminates at the primary motor cortex to command the movement [41].

## 3. Extrapyramidal tracts :

The extrapyramidal tracts comprise four main bundles :

The **rubrospinal tract** [38, 41], which originates in the red nucleus and follows a path parallel to the lateral corticospinal tract. It is involved in the motor control and coordination of the large distal muscles of the upper and lower limbs. The red nucleus is linked to the cerebellar system and receives no afferents from the basal ganglia system [31].

The **vestibulospinal tract** [3] is involved in the control of balance.

The **reticulospinal tract** [41] plays a role in muscle tone, gait, and automatic postural adjustments.

The **colliculospinal tract** (or **tectospinal tract**) [38] connects the tectum of the midbrain with the spinal cord. It controls head movements in response to visual and auditory stimuli.

# Role of the cerebellum

The **cerebellum** (or "little brain") plays an extremely important role in our lives. It alone contains more than half of the neurons of the entire brain [54], with over 50 billion neurons [159].

## 1. Functions of the cerebellum :

The cerebellum plays a vital role in voluntary motor function, posture, the maintenance of balance, the coordination of complex movements, motor learning, and many other roles recently highlighted, including autonomic and cognitive-emotional functions [36, 41].

No matter how simple the movements to be performed, the cerebellum is always there to control and coordinate them. Without the cerebellum, it would be impossible for us to walk or even stand upright. It would be impossible to perform the simplest daily activities that require any degree of precision, and without the cerebellum, we would be unable to learn how to carry out even the simplest tasks.

## 2. Cerebellar cortex :

The cerebellar cortex differs from its cerebral counterpart; while the latter consists of various cell layers whose number varies by cortical region (reaching up to six and defining the Brodmann areas), the cerebellar cortex contains three cell layers throughout [75]; therefore, there are no Brodmann areas in the cerebellum.

Even though the cerebellum looks small, it is packed with incredibly tight folds. If you were to unfold the cerebellar cortex, its surface area would actually cover about 75% of that of the much larger cerebral cortex [4].

## 3. Purkinje cells :

Of all 50 billion cerebellar cells, only the **Purkinje cells** (numbering approximately 15 million [3]) project outside the cerebellum [32] (accounting for only 0.03% of all cerebellar neurons).

Each Purkinje cell can have up to 300,000 synapses with other neurons [57], demonstrating the high degree of integration that occurs within the cerebellum [82].

Patients with cerebellar damage often show signs similar to alcohol intoxication. This is because alcohol is highly toxic to Purkinje cells - the most critical neurons in the cerebellum for coordinating movement.

## 4. Cerebellar pathways :

To work its magic, the cerebellum acts like a high-speed processor, constantly gathering data from almost every corner of the nervous system. It monitors your intentions from the brain and combines them with proprioceptive information from the spinal cord to track your body's position. At the same time, it processes visual and vestibular signals to maintain your balance. By integrating all of this with input from the basal ganglia and brainstem, the cerebellum ensures your every move is smooth and perfectly coordinated.

Through the **pons**, the cerebellum receives collateral relays from the fibers of the pyramidal tract [41], allowing it to be constantly aware of intended movements and to monitor their execution in real-time through a set of sensory feedback mechanisms, particularly visual and proprioceptive ones.

The cerebellum thus possesses all information regarding the circumstances of movement execution. From there, it ensures control of these movements through relay control loops that terminate in the **contralateral** primary motor cortex to join the pyramidal tract [41]. Since this tract also crosses the midline, the cerebellar hemispheres ultimately exert **ipsilateral** control over motor function [5].

# The autonomic nervous system

Alongside the **somatic** *nervous system* [160], which governs our interaction with the external world and of which we are largely aware, there is another entirely involuntary system that ensures the internal functioning of the body's various organs. This is the **autonomic** *nervous system* [3, 4, 42, 50, 104, 107, 160], also known as the **vegetative** *nervous system*.

This system regulates the functioning of the heart, lungs, glands, digestive system, and blood vessels [133] - in short, many organs over which we have no voluntary control.

The autonomic nervous system is divided into two major systems that usually have antagonistic actions [3, 52, 133] on their various targets: the **sympathetic (orthosympathetic)** *nervous system* and the **parasympathetic** *nervous system*.

## 1. The sympathetic system :

The primary neurons of the **sympathetic** *nervous system* [3] have their cell bodies in the lateral horn of the spinal gray matter [44]. They give off **preganglionic fibers** that terminate either in a sympathetic chain ganglion or in a peripheral ganglion [160]. From these ganglia, other fibers, called **postganglionic fibers**, emerge to reach the target organs [3, 4].

As in the parasympathetic system [133], the preganglionic neurons are **cholinergic** (their neurotransmitter is acetylcholine) [133]. In contrast, the postganglionic neurons are very often **noradrenergic** [71] (secreting norepinephrine) or **adrenergic** (secreting epinephrine); both of these molecules belong to the catecholamine family [52].

The sympathetic nervous system plays a primary role in stressful and threatening situations, where physical effort is required and focus and energy are needed [82].

Thus, this system dilates the pupils, dilates the pulmonary bronchioles, and increases the respiratory rate. It also increases heart rate and cardiac output, raises blood pressure, and stimulates the secretion of **epinephrine** (stress hormone) by the **adrenal medulla** [133]. It inhibits digestion, directs blood toward the muscles, stimulates the release of glucose by the **liver** into the blood, and inhibits urination from the bladder.

There are several types of **catecholaminergic receptors** [136], distinguished by their preferential response to one catecholamine or another. These include **alpha-1, alpha-2, beta-1, beta-2, and beta-3** receptors.

## 2. The parasympathetic system :

The parasympathetic system [3] is often called the 'Craniosacral' system because of where it

begins. It starts in the brainstem with four specific cranial nerves: the oculomotor **III**, facial **VII**, glossopharyngeal **IX**, and - most importantly – the vagus nerve **X**.

The vagus nerve is the 'super-highway' of this system, carrying about 75% of all parasympathetic signals to your heart, lungs, and gut. The system then picks up again at the very base of the spine, using the S2 through S4 sacral nerves to manage the lower organs, like the bladder and bowels.

Both the preganglionic and postganglionic neurons of the parasympathetic system are **cholinergic** [107]. Acetylcholine stimulates **nicotinic** *receptors* in the autonomic ganglia and **muscarinic** *receptors* in the target tissues [3].

The parasympathetic nervous system is involved in situations of calm, rest [82], and energy conservation [136]. Its action opposes the sympathetic system almost point by point [3, 52, 133].

Thus, the general effects of parasympathetic stimulation are: **bradycardia** (the vagus nerve being responsible for **vasovagal syncope**), increased intestinal peristalsis, increased gastric, salivary, and intestinal secretions, relaxation of most sphincters of the gastrointestinal tract, and **miosis** (constriction of the iris) ...

# Reflexes

A **reflex** [4] is defined as any behavior of the organism that occurs in response to a particular stimulus without the intervention of consciousness. Most often, this reactionary behavior is motor (muscular) in nature, but it can also be of a different nature, such as glandular.

## 1. Roles of reflexes :

Reflexes are essential behaviors for the organism, given that they are, in most cases, extremely rapid and stereotyped. They allow us to adapt to various situations, particularly those where the physical integrity of the organism is threatened. This is notably the case when one immediately and involuntarily withdraws their hand even before realizing it has been burned [82].

## 2. Nature of the reflexes :

Reflexes can be innate or acquired through various life experiences [1]. The reflexes we possess are numerous and varied, but they all obey the same principle: few synaptic relays, which guarantees the speed of the reaction.

A reflex requires a sensory receptor that captures the signal and an afferent fiber that carries the signal to the **CNS**, often the spinal cord or the brainstem. From there, a motor impulse arises and travels along a motor neuron to stimulate an effector organ (often a muscle), which then reacts. This sequence of events is called the **reflex arc** [1, 54].

## 3. The reflex arc :

There is no voluntary control over the *reflex arc.* That said, there are sometimes fibers that ascend to the cerebral cortex to keep us informed of what has occurred.

When a physician strikes the **patellar ligament** [57] (during a physical examination), this percussion causes an elongation of the quadriceps muscle. The **neuromuscular spindles** [3, 38, 109] located within it stretch and send a signal to the spinal cord via proprioceptive nerve fibers (Type A-alpha). These fibers terminate in the **anterior horn** of the spinal cord [1] on the dendrites of the motor neurons that contract the quadriceps.

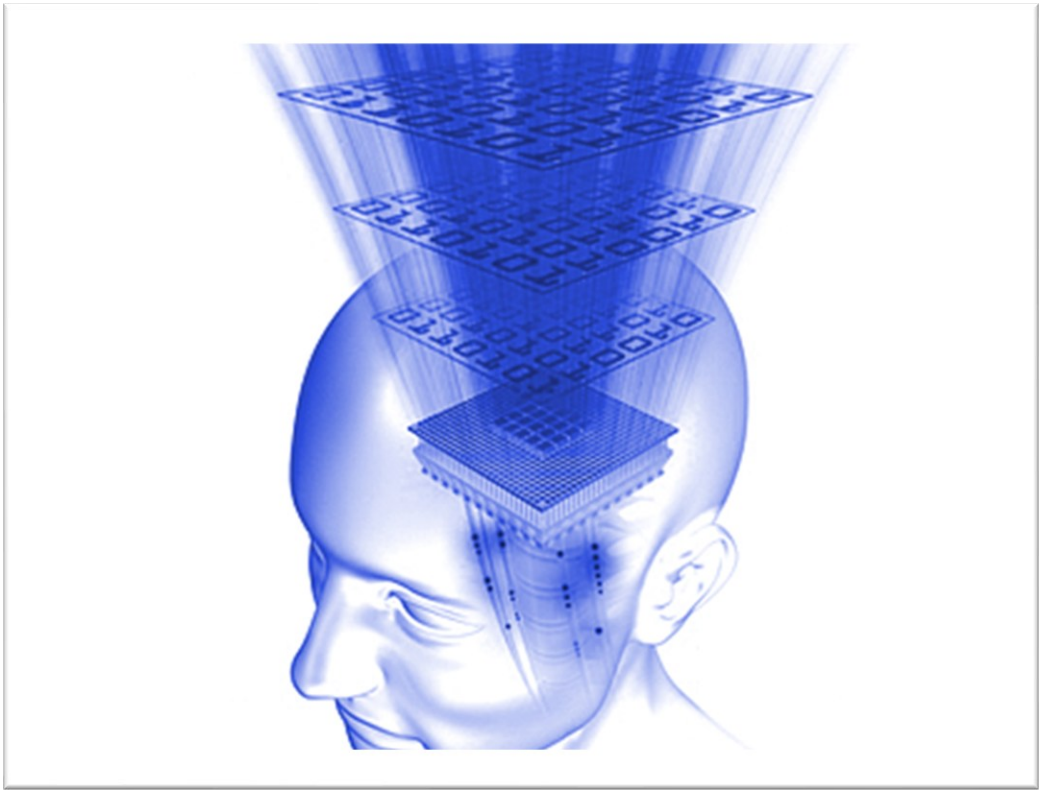
The proprioceptive fibers also activate interneurons that inhibit the motor neurons of the antagonist muscle [130, 133]. This results in a knee extension reaction.

## 4. Reflexes in medicine :

Reflexes are widely utilized in clinical practice; they often provide information about the

nature and site of a nervous system lesion. Thus, if the patellar reflex is absent, it indicates a peripheral failure. If, on the other hand, it is exaggerated and **brisk**, it is concluded that there is a loss of central control over the reflex arc, indicating a central lesion [67].

# Higher Functions



# Higher Functions – Overview

Apart from the afferent (sensory) and efferent (motor) functions we have studied, the **CNS** (the brain in particular) is responsible for developing highly complex and difficult-to-study functions generally referred to as **higher functions** [42].

This entity encompasses highly complex processes such as memory and learning, language, consciousness, judgment, and other functions of the mind.

In this chapter, we will discuss consciousness - what it is and from where it might emerge. Discussing consciousness automatically leads us to describe sleep: why do we sleep? And what does the brain do in its waking state?

We will explore language, one of the most fascinating functions of the human race; without this faculty, it would not have been possible to transmit knowledge from generation to generation, and thus, any kind of progress would have been impossible.

We will also discuss memory and learning, two functions that are completely linked, interconnected, and vital.

Finally, we will address the **limbic system** and its role in elaborate functions such as memory, emotions, and executive functions [161, 162].

# Memory and learning

Memory plays a decisive role in our lives [3]. **In fact**, without memory, life would have no meaning. Memory is the **means by which we locate ourselves** in time; it is the fabric that shapes each individual's history.

## 1. Definitions :

Memory is defined as the capacity to **capture, encode, store, and retrieve** information [4].

Memory is often confused with learning. Even though these two processes are closely linked, it is worth mentioning that **learning** [1] primarily applies to the phase of acquisition and storing of memories.

**Recall** involves the active retrieval of information, while **recognition** requires only deciding whether an item among others has been previously encountered [119].

## 2. Classifications :

The concept of memory, while in common usage, is actually more complex than it appears. In fact, a distinction is made between several types of memory [38, 135]:

### 2.1. Based on duration :

#### a. Sensory memory :

This is of extremely short duration; it is nothing other than our perception of things and events. It is the echo and internal resonance of sensory information that persists for a few fractions of a second within our consciousness [145].

#### b. Short-term memory :

Also called **working memory** [163], this constitutes a level of selective filtering for information gathered by our senses, lasting for up to one minute [164]. It allows us to retain a few items - on average, seven pieces of data, such as a phone number [42] - data with which we **work** (hence its name). Depending on their importance, these items may or may not move to a longer-term level storage [161].

#### c. Long-term memory :

Long-term memory [165] ensures the preservation of memories over a long period: months, years, or even a lifetime.

### 2.2. Based on the type of information stored:

Depending on the type of data to be memorized [39], it may be:

#### a. Explicit memory :

Also known as **declarative memory** [167], this concerns data that can be expressed in words. A distinction is made between [165]:

**Semantic memory** [164], which involves the memorization of specific objects and facts.

**Episodic memory** [145], which concerns events clearly situated in time.

#### b. Implicit memory [166] :

Also called **procedural memory** [165], this is an essentially motor memory that concerns "know-how." It consists of sensorimotor automatisms so well integrated that we are unaware of them. For example, someone who knows how to perform sutures would find it difficult to explain the method using only words. Many of our emotional responses and conditioned reflexes are also part of implicit memory.

## 3. Memory efficiency :

### 3.1. Nature of memory :

Our memory is **associative** [119], meaning it is more effective when we link the data to be memorized with items already stored in our memory; one thing reminds us of another, which reminds us of yet another, and so on.

Memory is the result of a reconstruction of different elements. We do not store entire scenes in our brains. Furthermore, no memory is truly identical to its origin, **like a photograph**; that would require too much to memorize, and our skull is, unfortunately, **non-expandable**. We retain only a few pieces of the puzzle - a few breadcrumbs that later help us reconstruct and retrieve memories from various key elements.

### 3.2. Factors influencing memory :

Several factors influence memory efficiency [168]:

- The degree of vigilance, arousal, attention, and concentration at the time of memorization.
- Interest, motivation, need, or the necessity of the items to be remembered.
- Repetition.
- Location, lighting, smell, noise... in short, the entire context present during memorization is

recorded along with the data.

- The effort of memorization, hence the term **working memory**. Developing one's memory means giving meaning to the elements to be memorized and making logical connections with what has already been acquired. The more a memory is encoded, elaborated, organized, and structured, the easier it will be to retrieve.

## 4. Mechanisms of memory :

Several neural structures play a vital role in memory:

The **hippocampus** [54] plays a key role in episodic memory. It constantly gathers data from different sensory areas (visual, auditory, somatosensory, etc.), selects the most significant ones, links them into a single episode of events rather than a collection of separate memories, and redistributes them to the appropriate areas.

Individuals who have undergone the removal of both hippocampi can no longer store new memories in their long-term memory [167], but they retain the ability to recall old memories from before the surgery.

Certain highly intense personal memories involve what is called **emotional memory** [169]. In addition to the hippocampus, this involves another structure of the limbic system: the **amygdala** [39], a region known for managing our fear responses. Several other limbic system structures contribute to encoding our memories in a lasting way.

The path of information to be stored in long-term memory follows the **Papez circuit** [38, 50], which connects the hippocampus, fornix, mammillary bodies, anterior thalamus, and cingulate gyrus.

Procedural memory does not involve the hippocampus at all. It is instead associated with changes in the **cerebellum** [1], the basal ganglia, and the motor cortex.

The prefrontal cortex plays a vital role in working memory [1]. It acts as the brain's "mental scratchpad" holding information in our minds while we actively use it.

No single neuron contains within itself the information necessary to retrieve a memory. The brain retains data through the formation of new networks. These networks are modifiable through the formation of new synapses or the strengthening of existing ones. These may have existed before, but their functioning was previously ineffective.

**Long-term potentiation (LTP)** [3, 38, 39], which is the primary mechanism of neurological plasticity, plays an essential role in the formation and efficiency of these synapses.

# Consciousness

"*Consciousness is to the psychologist what gravity is to the physicist: inevitable*" (**Baars**).

## 1. Problems of consciousness :

Consciousness [73, 119, 133] is a very difficult subject to study for several reasons [119]. First, there are several definitions of consciousness - the word is used in many different contexts [164] - and second, it involves many brain structures [166] and other higher functions such as memory [73] and language [170].

Another factor adding to the complexity is that consciousness is a purely subjective experience [166] and is therefore only accessible to the person experiencing it; thus, its study must be conducted through human subjects. Animal models contribute very little because it is not yet known with certainty what form of consciousness to attribute to them [41].

## 2. General Overview :

### 2.1. Definition :

Consciousness can define several things:

- The power to focus one's attention;
- The state of wakefulness ;
- The faculty of abstraction;
- The faculty of verbalization - that is, expressing events through words;
- The ability to develop projects and establish new mental relationships based on past experiences;
- Self-awareness ;
- The faculty to establish values...

### 2.2. The unconscious :

To truly understand consciousness, we must also consider the hidden world of the **unconscious**. Indeed, the brain possesses a multitude of specialized circuits that process approximately 1 billion pieces of data per second regarding various aspects of our environment [142]. Only an infinitely small portion of this data emerges into our consciousness.

### 2.3. Sleep :

Not every state of disrupted consciousness is pathological; unlike comas [57], syncope, or lipothymia, which certainly have pathological origins, sleep constitutes a state of physiological disruption of consciousness that is, moreover, very interesting to study [91, 119].

## 3. Classification :

A distinction is made between two forms of consciousness: **primary consciousness** [170], responsible for vigilance or the state of wakefulness - which is defined primarily by its opposite (loss of consciousness) - and **higher-order consciousness** [171], such as the definition and distinction of the "self," which is more difficult to study and explain.

The approach to the "self" has historically been the work of philosophers and psychologists; more recently, it has been the subject of several studies that have yet to reach a consensus on their conclusions. It is therefore necessary to clearly define which level of consciousness is being discussed when attempting to associate it with brain structures.

## 4. Mechanisms :

Consciousness utilizes short-term memory; processes developing in long-term memory only enter consciousness after passing through short-term memory [133].

Several brain structures that control consciousness in terms of wakefulness are well known. First is the **reticular formation** [38, 42, 57], the activity level of which influences our state of vigilance, wakefulness, and sleep. Indeed, being awake requires an interaction between the reticular formation and other brain structures, notably the cerebral cortex. For this reason, the ascending pathways of the reticular formation are named the **Ascending Reticular Activating System (ARAS)** [45].

Next is the **thalamus**, the "relay station" for all signals originating from the body [38]. Finally, the **cerebral cortex** [44], whose importance is crucial for all forms of sensory perception and control of voluntary movements [73].

The **pons** [166], the **raphe nuclei**, and the **locus coeruleus** are also structures involved in maintaining primary consciousness [41]. For consciousness to emerge, it appears there must be an exchange or resonance between different regions of the brain. Thanks to functional brain imaging techniques, we can observe the stages that lead to the emergence of a conscious mental image.

## 5. Split-brain syndrome :

The most significant experience in the history of the study of consciousness is undoubtedly

the study of **split-brain syndrome** (callosal disconnection syndrome) [133].

In forms of epilepsy resistant to medical treatment that spread to both cerebral hemispheres, a section of the **corpus callosum** is sometimes performed. Even though this involves cutting approximately 200 million nerve fibers [39, 80], patients notice no significant deficit after the operation. However, elaborate experiments reveal something fascinating: each hemisphere develops its own consciousness, independent of the other hemisphere [73].

If an object is placed in the left hand of the subject while they are blindfolded, they cannot identify the object because the language region - located in the left hemisphere - does not have access to the sensory information, which, in the case of the left hand, reaches the right hemisphere. Nevertheless, the subject is able to draw the object with their left hand [39, 166].

# Sleep

**Sleep** [91, 119] is a physiological loss of consciousness that is distinguished from coma by its reversibility. Indeed, even in the deepest stages of sleep, a sufficiently strong stimulus can be perceived by the brain and wake the sleeper [1].

The **sleep-wake cycle** corresponds to one of the fundamental cycles in humans and practically all animals: the **circadian rhythm** [38, 119].

## 1. Duration of sleep :

We sleep for at least **one-third of our lives** [41]; this alone is enough proof of the importance of sleep. In a normal adult, the average duration of sleep is 7 to 8 hours per day [42]. **Long sleepers** may need 10 hours of sleep, while **short sleepers** may be satisfied with only 5 [168].

There is no truly "optimal" sleep duration; the only criterion for a good amount of sleep is feeling energetic during the following day. The duration of sleep varies with age [145]. In general, from birth to death, it only decreases.

## 2. Phases of sleep :

Far from being uniform, our sleep fluctuates between different **stages** (or phases) [38, 41, 57] occurring in a characteristic order during the night.

**Electroencephalography** (EEG) [41] is the most widely used examination for studying sleep. A **hypnogram** (sleep EEG) [5, 136] records the activity of cortical neurons using electrodes placed in specific locations on the scalp.

The EEG has distinguished two essential phases of sleep [80]: **slow-wave** sleep and **paradoxical** sleep [166]. Based on their frequency and amplitude, EEG waves allow for the distinction of four stages of slow-wave sleep [1, 72]: **Stage I** corresponds to falling asleep or drowsiness, **Stage II** to light sleep, and **Stages III and IV** correspond to deep sleep.

During **paradoxical sleep**, the EEG trace [4] closely resembles that of wakefulness, with its rapid rhythm and low amplitude. For this reason, the neurobiologist **Michel Jouvet** named it "paradoxical sleep" in 1959 [119]. In English-speaking literature, it is referred to as **REM** (for Rapid Eye Movement [32]) because this type of sleep is characterized by numerous rapid eye movements under closed eyelids.

The different phases of sleep proceed as follows: 1 - 2 - 3 - 4 - 3 - 2 - 1 - REM - 1 - 2 - 3 - 4 - 3 - 2 - 1 - REM... etc. Each **descent** into deep sleep is followed by an **ascent** leading to a period of paradoxical sleep [5].

Although similar in duration, the cycles evolve during the night. In the first third, slow-wave sleep dominates [39]. In fact, the first two cycles consist mainly of deep slow-wave sleep [57], which explains the great physical recovery benefits associated with the first hours of sleep. Conversely, light slow-wave sleep and paradoxical sleep are proportionally more significant at the end of the night [57].

## 3. Sleep and activity :

Sleep is far from a mere **passive standby** of our physical and mental activity. It is an altered state as varied and complex as the waking state [57], accompanied by important physiological changes (temperature, hormonal secretions, heart and respiratory rates, etc.) [41].

### 3.1. During slow-wave sleep :

Muscles are more relaxed, and the rare movements serve only to adjust body position. The overall metabolism of the organism decreases: temperature, energy consumption, heart rate, respiration, and kidney function all slow down in accordance with the predominance of the **parasympathetic system** during this phase. The slow rhythms of the EEG during slow-wave sleep indicate that the brain also appears to be at rest.

### 3.2. During paradoxical sleep :

Cerebral oxygen consumption (which reflects energy consumption) is very high - sometimes even higher than that of an awake brain reflecting on a complex cognitive problem. There is a near-total loss of muscle tone, leaving us **literally paralyzed**, which prevents the body from **acting out dreams**. However, the respiratory and cardiac muscles ensure vital functions. The eye muscles remain active and produce the famous rapid eye movements, while heart and respiratory rates increase irregularly under the influence of the **sympathetic system**.

## 4. Role of sleep :

There is very little certainty regarding the exact role of sleep [1]. Slow-wave sleep and paradoxical sleep appear to have completely different roles. While the body rests during slow-wave sleep - which is why deep sleep is also called **restorative sleep** - the role of paradoxical sleep is much more debated. It appears to serve to consolidate **memory** and **learning processes** [163]; it also plays a role in emotions and personality traits, and finally, it is the primary stage for dreams.

The role of dreams is also debated [5]: Freud described dreams as the "**royal road to the unconscious**" [76]. Their scenarios are thought to be constructed from impressions experienced during the day and old memories that are transformed or disguised to escape the control of consciousness. Other scientists attribute an arbitrary nature to them, stemming from the brain's

**misinterpretation** of external signals due to the state of consciousness being disrupted by sleep. Dreams do not only occur during paradoxical sleep, but it is in this phase that the clearest scenes and most coherent events are experienced [57]; deep sleep is the typical ground for **nightmares** and **night terrors** [166].

## 5. Mechanisms of sleep :

The mechanisms of wakefulness and sleep are highly complex [5, 95], involving several anatomical structures and chemical molecules.

### 5.1. Anatomical structures involved :

Broadly speaking, the components of the modulatory systems of the sleep-wake cycle can be grouped into two main pathways, both originating from part of the **reticular nucleus of the medulla oblongata**.

- The **ventral pathway** [172], which projects toward the posterior hypothalamus and the **nucleus basalis of Meynert** [119, 172] (cholinergic neurons). This is the reticulo-hypothalamo-cortical pathway. Stimulation of the posterior hypothalamus produces a state of wakefulness comparable to that obtained by stimulating the reticular formation of the brainstem.
- The **dorsal pathway** [172], which activates the cholinergic mesopontine nuclei [119], the mesencephalic reticular formation (aspartate/glutamate neurons), and the thalamus. This is the reticulo-thalamo-cortical pathway.

A key structure of the sleep-wake cycle is the **suprachiasmatic nucleus** [57]; it belongs to the hypothalamus, located directly above the optic chiasm [119]. The activity of the neurons in this nucleus increases and decreases over a 24-hour period, making it a key element in the regulation of the **circadian rhythm**.

The suprachiasmatic nucleus receives signals from the optic nerves, allowing it to **calibrate the biological clock** [1, 39, 119] based on day-night cycles. It also influences the secretion of **melatonin** (the key hormone of the nycthemeral cycle) by the pineal gland [57].

The **locus coeruleus** [38] (a nucleus located in the pons) also plays a major role in the sleep-wake cycle through its connections with the **raphe nuclei** [38] (involved in falling asleep), the paraventricular nuclei of the hypothalamus, and the cerebral neocortex. These projections are **adrenergic**, making the locus coeruleus a center for stress [80], motivation, and arousal. The complete destruction of this nucleus suppresses dreaming and paradoxical sleep.

## 5.2. Biology of sleep :

Two processes must overlap correctly in the body for us to fall asleep:

- The **circadian rhythm**, regulated by our biological clock, which orchestrates the cyclic secretion of several hormones, including **melatonin** [1], which is involved in sleep.

- The accumulation of **hypnogenic substances** during the day, which induce an urge to sleep that only dissipates with sleep - such as **serotonin**, which is secreted by the anterior hypothalamus and inhibits the posterior hypothalamus [136].

One of the most studied hypnogenic factors is **adenosine** [136], a small molecule resulting from the degradation of ATP. Adenosine also acts as a neuromodulator at many synapses in the brain. Natural antagonists of adenosine receptors, such as the **caffeine** in coffee or the **theophylline** in tea, are well-known stimulants.

The activity of the posterior hypothalamus naturally decreases during sleep, releasing less **histamine** [41]. **Antihistamines** taken for allergies often cause drowsiness by decreasing histamine activity [74].

# Language

" *By limiting oneself to the purely physiological study of language, one risks never penetrating to that internal faculty of which language is the manifestation or the external sign*" **Müller, 1861**.

**Language** [3, 4, 57] is the function that allows us to communicate with others. Whether spoken, written, or signed, communication plays a vital role in our lives. Indeed, through language, we can express our thoughts, needs, and desires; we can inform others and inform ourselves about potential threats or dangers. Without language, there would be no history or progress... In short, language is at the heart, if not at the pinnacle, of the cognitive functions most important to humans [5].

## 1. Language and languages :

Language is our faculty to encode and decode abstract or concrete elements through a sequence of signs and symbols understood by others. These signs are structured in a precise way to form meaningful expressions. The set of these signs and the rules of their structure constitute a language. Today, there are more than 6,000 languages across the planet [173] - 1,000 languages in New Guinea alone [174].

The number of symbols and words in a any language is not infinite. However, through their various combinations into sentences, one can form an infinite number of expressions. This shows just how powerful language really is.

The brain's ability to recognize particular words in someone's verbal stream is remarkable. One only needs to listen to a foreign language to realize the difficulty of isolating its constituent elements. A person speaking their native language does not isolate words with silences, like the spaces separating written words, and yet our brain recognizes them individually and assigns them meaning.

## 2. Phonatory apparatus :

To be able to speak, we possess a highly sophisticated **phonatory apparatus** [175]. The human vocal apparatus can be compared to a wind and string musical instrument [175]. It includes a wind source: the lungs (the generator); a vibrating structure: the vocal cords in the larynx (the vibrator); and a series of resonance chambers formed by the pharynx, the mouth, and the nasal cavities (resonator or amplifier). The transformation of laryngeal sound into speech is then completed by the position of the soft palate, tongue, lips, and teeth, which act as **modulators** of the emitted sound.

## 3. Cerebral language areas :

There are two brain regions strongly involved in language: **Wernicke's area** and **Broca's area** [41, 74].

### 3.1. Wernicke's area :

This area is located in the temporal lobe, just beside the primary and secondary auditory cortex. It ensures the comprehension of language elements. Wernicke's area receives information from the auditory area for spoken language, analyzes it, and sends impulses to Broca's area via the **arcuate fasciculus**.

### 3.2. The arcuate fasciculus :

Recent studies have shown that the **arcuate fasciculus** actually connects Wernicke's area to the region of the primary motor cortex [198] located behind Broca's area, rather than terminating directly on it. It is the lateral portion of the superior longitudinal fasciculus that communicates between Wernicke's area and Broca's area via the **supramarginal gyrus** [198].

### 3.3. Broca's area :

Located in the frontal lobe, **Broca's area** is responsible for language expression. It is connected to the primary motor area that controls the contractions of various body muscles, particularly those of the larynx involved in speech.

## 4. Cerebral lateralization :

Language is most often under the control of only one of the two brain hemispheres [41], referred to as the **dominant hemisphere** [50]. This phenomenon is one aspect of the general asymmetry of brain function known as **cerebral lateralization** [166].

The dominant hemisphere is almost always the left (in 90% of cases [96]) in right-handed people. In left-handed people, brain physiology is both more variable and less understood; the dominant hemisphere is often the left, but sometimes the right. In other cases, lateralization seems less distinct, and the two hemispheres appear more balanced [4].

However, this categorical view of a dominant hemisphere for language is far from absolute. Recent studies have demonstrated the important role of the right hemisphere in intonation (**prosody**) [41] - the faculty by which one can formulate the same sentence in various ways to convey completely different meanings. It allows for the transformation of a statement into an order, a wish, or a question.

# The limbic system

" *Is emotion a magical product, or is it a physiological process that depends on an anatomical mechanism?* " **James Papez.**

## 1. History :

The term **limbic** (**Limbus**, meaning "border" or "edge" in Latin [39]) was first introduced by the French physician and anatomist **Paul Pierre Broca** in 1878 [74]. He used the term "**great limbic lobe**" to designate a supplemental lobe particularly involved in emotion, consisting of the olfactory bulb and tract, the hippocampus, and the **cingulate gyrus** (**cingulum**, meaning "belt" in Latin) [75]. Of course, the **limbic system** [32, 41] is not currently recognized as a **true lobe** [38].

In 1937, the American neuroanatomist **James Papez** published his research [80] on an emotional circuit now known as the **Papez circuit** [38, 50]. This circuit includes the hippocampus, the **cingulate gyrus** [41], the thalamus, the hypothalamus, and some of their interconnections.

A few years later, in 1949, **Paul MacLean** [39] expanded on Papez's ideas and integrated them with the concept of the "great limbic lobe" proposed by Paul Broca, leading to the notion of a **limbic system** [80]. Since then, other anatomical structures have gradually been added to this system, such as the **prefrontal cortex** and the **orbitofrontal region** [71].

## 2. Functions of the limbic system:

The limbic system is a group of brain structures that play a very important role [39] in behavior, particularly in emotions, memory, learning, and some of the **executive functions** [161, 162].

In the field of neurophysiology, "**emotion**" does not mean "**feeling,**" which is the internal and purely subjective experience a person has in response to a particular situation. Emotions are instead the physiological reactions that accompany these feelings - changes in behavior or the functioning of organs [176].

The limbic system is often called the "**visceral brain**" or "**emotional brain**" [119] because it plays a significant role in a series of emotions, including pain, pleasure, docility, affection, anger, aggression, fear, and pleasure...

**Executive functions** include skills related to planning, **working memory**, anticipation, initiative, organization, problem-solving, logical reasoning, cognitive control, abstract thinking, rule learning, selective attention, the selection of motor responses, and motivation. Executive functions are primarily linked to the functioning of the **prefrontal cortex** and the **orbitofrontal region** [177]. The limbic system also influences the endocrine system and the **autonomic nervous**

**system** [166].

## 3. Anatomy of the limbic system:

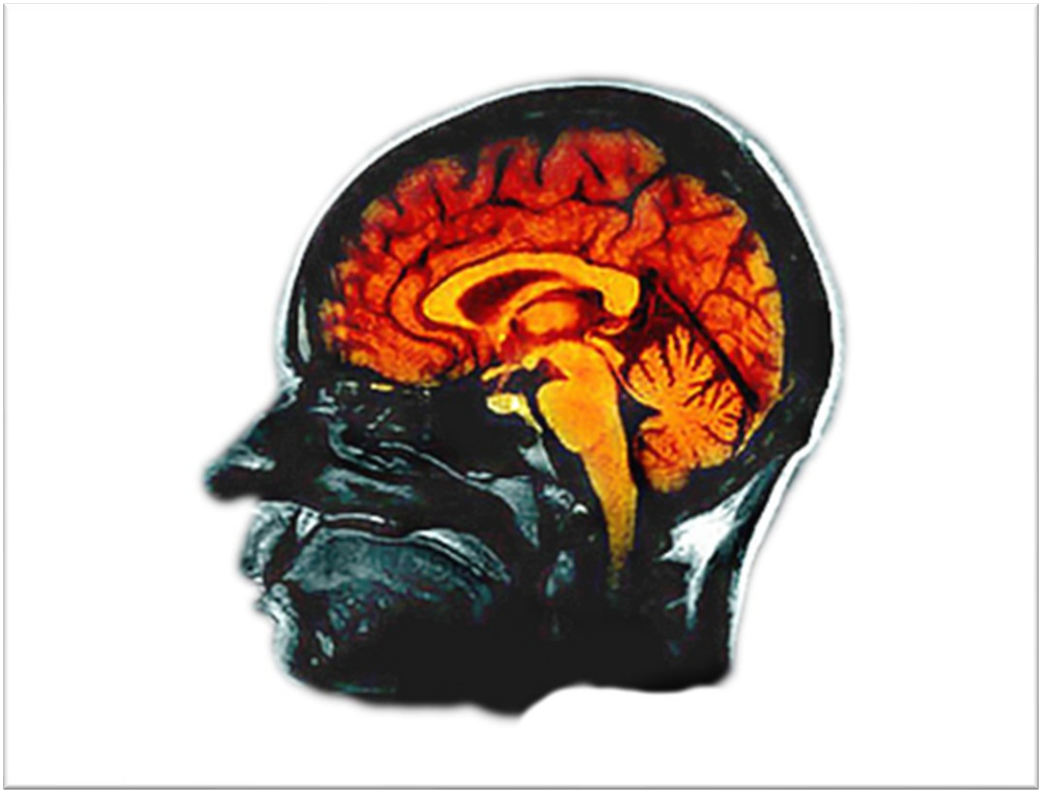
The limbic system comprises several cortical and subcortical structures located around the thalamus [80]. All these structures form an integrated system that ensures the survival of the individual through the implementation of visceral responses and adaptive behaviors.

Since the 1950s, the list of brain structures defining the limbic system has continuously expanded; among these essential structures are: the **cingulate gyrus** [32], the hypothalamus, the **anterior nuclei of the thalamus**, the olfactory apparatus, the hippocampus, and the **amygdaloid nuclei**...

At the heart of this system is the **Papez circuit**, which is very important for memory. In this circuit, information circulates in a loop from the hippocampus to the **mammillary bodies** of the hypothalamus (via the **fornix**), then passes to the **anterior nuclei of the thalamus**, then to the **anterior cingulate cortex**, before returning to the hippocampus.

The **amygdaloid complex** [38] plays several roles: it is involved in olfaction, emotions, and especially in the development of appropriate responses to danger [96]. The classic experiment of a mouse with both amygdalae destroyed shows that it no longer tends to flee from a potential predator.

# Neurological disorders



# Neurological disorders - Overview

The study of neurophysiology would be of no practical interest if it did not help solve real-world human struggles. The nervous system, as noble and protected as it is, can be subject to a multitude of diseases and pathologies.

Prior knowledge of the anatomical structures affected and their functioning makes it possible not only to explain "failures" but also, and above all, to propose and devise effective and high-performance therapeutic strategies and preventive measures to repair or, at least, avoid them.

In this chapter, we will see how an interruption of blood flow in a cerebral artery produces harmful consequences, not only for the affected region but also for the surrounding areas.

We will discuss pain and explain why, when an individual has a cardiac problem, they may feel pain elsewhere.

We will discuss **myasthenia gravis** and describe how the primary therapeutic methods act to compensate for the defect in acetylcholine receptors at the motor end plate.

We will discuss the pathophysiological basis of epilepsy, multiple sclerosis, and aphasia, as well as two degenerative diseases whose consequences are horrific and devastating: **Parkinson's disease** and **Alzheimer's disease**.

# 1. General Overview :

The brain represents less than **2%** [137] of human body weight. However, it alone receives more than **16%** [5] of the body's total blood supply. It is an organ with very high metabolic activity, requiring more than **20%** [138] of the entire body's energy intake.

Unfortunately, the brain has very small energy reserves (oxygen and glucose) [109]. Neurons die within a few minutes in the absence of a continuous energy supply [105]. If a neuron dies, there is a very low probability of it being replaced. For this reason, maintaining cerebral vascular supply is of paramount importance.

A **stroke** [4, 178] (**cerebrovascular accident - CVA**) is a sudden interruption of blood flow to a region of the brain, resulting in neurological deficits [179].

These disruptions, or strokes, manifest as two distinct entities, each with its own devastating mechanism: **ischemic stroke**, caused by the obstruction of a blood vessel (80% of all strokes), and **hemorrhagic stroke**, which causes bleeding within the brain (20% of strokes) [180].

# 2. Ischemic stroke :

## 2.1. Causes :

An **ischemic stroke** [69] is the consequence of the occlusion of an artery supplying the brain (cerebral artery, internal carotid, or vertebrobasilar system). This leads to a cerebral infarction (or **cerebral softening** [181]).

This obstruction can have several origins:

- Obstructive atheroma,
- The lodging of a clot formed locally or of cardiac origin (embolism),
- A tear in the arterial wall (dissection)
- Compression by a tumor...

## 2.2. Clinical Presentation :

The resulting deficit affects a well-defined cerebral territory; it is said to be **systematized**. The clinical manifestations [69] depend on the territory affected.

For instance, if the left posterior cerebral artery is affected, the subject will develop right homonymous hemianopia. If, on the other hand, the left middle cerebral artery is affected, the

subject will develop a sensory-motor deficit of the right side of the body, most often associated with aphasia.

An ischemic event can be transient (**Transient Ischemic Attack** or **TIA** [31]), with a rapid return to normal without sequelae. The deficit can also be permanent, as in the case of an **established ischemic stroke** [184].

### 2.3. Pathophysiology :

A severe and prolonged interruption of cerebral blood flow, even in a small region of the brain, leads to tissue hypoxia [183, 185], resulting in:

- Metabolic changes (anaerobic glycolysis, lactic acid formation),
- Excessive release of glutamate, a neurotransmitter that is highly toxic to nerve cells at high concentrations [41],
- Dysfunction of the **$Na^+/K^+$ pumps** [86], leading to an intracellular influx of **$Ca^{++}$** [183] ...

Together, these disturbances trigger a cascade of enzymatic activations and an accumulation of acidic metabolites and cytotoxic free radicals [69], leading to irreversible cellular damage. This is why initial symptoms may be minor; but without early intervention, the clinical picture can rapidly deteriorate.

Membrane anomalies and capillary permeability disorders are complicated by **cerebral edema** observed in the ischemic zone. In addition to the direct impact of cerebral hypoperfusion on the ischemic region, these metabolic complications extend to the surrounding area, known as the **penumbra zone** [183].

Cerebral softening of ischemic origin may be complicated secondarily by bleeding within the lesion; this is referred to as **hemorrhagic transformation** [182].

## 3. Hemorrhagic stroke :

**Hemorrhagic stroke** [69] is caused by the rupture of a blood vessel that is often already damaged (an **arteriovenous malformation** or an **aneurysm** [38]) and subjected to excessive blood pressure. Tobacco and alcohol are factors that significantly weaken the blood vessels.

During a hemorrhagic stroke, a hematoma forms rapidly, causing sudden-onset focal neurological signs related to the brain structures destroyed or compressed.

The edema that develops around the hematoma worsens the compression of the brain within the skull and leads to or increases **intracranial hypertension**. As the skull is non-expandable, nerve structures under pressure may herniate under the **falx cerebri** or through the **foramen magnum**,

an immediate life-threatening emergency.

Occasionally, during a hemorrhagic stroke, there is a massive release of calcium ions, which induces a sudden **vasospasm** [69], that can trigger further ischemic events.

# Epilepsies

"*The history of epilepsy can be summarized as 4,000 years of ignorance, superstition, and stigmatization, followed by 100 years of knowledge, superstition, and stigmatization*" **Rajendra Kale, 1997** [190].

## 1. General Overview :

The term **epilepsy** is derived from Greek; it means "to be seized" or "taken by surprise" [186].

Epilepsy [41, 69, 179, 185] is a neurological condition characterized by recurrent seizures that involve:

**Clinically:** Tonic-clonic motor manifestations, sensory and autonomic disturbances, and/or an alteration of consciousness.

**Electroencephalography:** A characteristic tracing of paroxysmal electrical activity [187].

Epilepsy is the most frequent chronic neurological condition after migraine [187]. It is a relatively benign pathology in most cases, but its psychological, familial, and social impacts are often far greater than the severity of the disease itself.

It should be noted that epilepsy is not a **mental illness** [69], contrary to popular belief, even though it may be accompanied in some cases by certain behavioral and cognitive disorders.

## 2. Pathophysiology :

An epileptic seizure is the clinical consequence of excessive, hypersynchronous, and self-sustaining paroxysmal discharges from a more or less extensive population of cerebral neurons [75].

This synchronized discharge results from an imbalance between inhibitory and excitatory mechanisms [188], leading to intense and disordered neuronal activity. This activity, which sometimes originates from a small cortical area (**epileptogenic zone**) [187], spreads gradually through the cerebral cortex.

Seizures manifest in very diverse ways, depending on the area of the brain where the discharge begins and its mode of propagation. For example, a partial seizure localized in the occipital lobe will result in abnormal visual perception; if it propagates forward, it may lead to motor or sensory phenomena. If it spreads to the entire brain, it may transform into a **generalized tonic-clonic seizure** [31] **(grand mal)** [75].

An epileptic seizure is a highly dynamic phenomenon that abnormally and successively

involves various brain structures and, consequently, their functions (language, motor or sensory phenomena, eye movements, etc.).

The initial clinical signs have significant localizing value. Often, an (**aura**) [187] may occur - a phenomenon that is almost always identical for the same person, announcing the imminence of the seizure. Being able to describe it helps to specify the origin of the seizure. Usually, the discharge follows the same pathway, so the signs remain consistent for the same individual.

## 3. Classification :

Several types of epileptic seizures can be distinguished. For example, there are convulsive and non-convulsive seizures; they can be partial or generalized; they may or may not involve loss of consciousness; they can be purely motor or sensory, and occur while fully conscious.

### 3.1. According to origin :

- **Symptomatic epileptic seizure:** Secondary to a well-defined cause (trauma, tumors, etc.) [187].
- **Essential epilepsy** [107]**:** The most widespread form, idiopathic, without a notable organic cause. This refers to the epileptic disease itself.
- **Cryptogenic epilepsy:** Has an underlying organic cause [145] that remains undetected despite investigation [187].

### 3.2. According to clinical manifestations :

When seizures originate in a localized area of the brain, they are called **partial** [188]. When they involve the entire brain, they are called **generalized** [67, 187].

#### a. Generalized seizures :

- **The tonic-clonic seizure (grand mal):**

This is the most well-known because it is the most spectacular [107]. It manifests as a fall, loss of consciousness, tonic-clonic convulsions, tongue biting, and sometimes loss of bladder or bowel control. It carries a risk of more or less serious injury and usually stops after about a minute.

**Status epilepticus** [69] is a sequence of generalized epileptic seizures without interruption and without a return to consciousness; the coma is deep, and severe autonomic disturbances occur, threatening the patient's life. The status epilepticus is a medical emergency.

- **Absence :**

**Absence** [188] is a type of generalized seizure involving a brief suspension of consciousness without motor, sensory, or autonomic symptoms. The gaze is blank, and communication is

interrupted for a few seconds. Absence seizures are usually repeated throughout the day and correspond to what was formerly called **petit mal** [75].

- **Other forms of generalized seizures :**

Clonic, myoclonic, tonic and atonic seizures.

### b. Partial (focal) seizures :

- **Simple partial seizures :**

In the motor form, known as **Bravais-Jacksonian** [189], the seizure begins with localized motor signs that spread gradually according to progression across the contralateral primary motor cortex [185].

Other types of simple partial seizures are non-motor, involving sensory, autonomic, or psychic disturbances.

- **Complex partial seizures :**

With disturbances of consciousness, which may or may not be associated with automatisms [187].

- **Partial seizures with secondary generalization** [183]**.**

Begin as a localized focal discharge - often felt as a brief aura - before rapidly evolving into a global electrical storm that engulfs both hemispheres.

## 4. Diagnosis :

First, confirm the diagnosis of epilepsy and identify its underlying cause. Exclude all non-epileptic mimics to ensure an accurate diagnosis. [188]: hysteria, vasovagal syncope, breath-holding spells, syncope, tetany, or spasmophilia, using appropriate examinations.

The diagnosis of epilepsy relies on:

### 4.1. Electroencephalogram (EEG) :

The **EEG** [5, 185] helps highlight interictal abnormalities (between seizures) and sometimes records the seizures themselves. Ideally, the EEG should be coupled with a video recording [187].

A normal EEG does not formally rule out the diagnosis of epilepsy [69], and it may need to be repeated. In cases of severe epilepsy, a long-term recording coupled with video over one or several days in a specialized center may be necessary.

### 4.2. Neuroimaging :

These are not always indispensable [188]. If a lesion is suspected, an **MRI** (Magnetic Resonance Imaging) can show abnormalities that simple X-rays or CT scans cannot detect. Other imaging techniques may be proposed, especially if surgery is considered.

## 5. Treatment :

The treatment of epilepsy often requires a multidisciplinary approach (pharmacological, psychological, social, and sometimes even surgical) [31].

The two imperatives of anti-epileptic treatment are total seizure control and the absence of side effects. Therapeutic choices depend on a precise evaluation of the seizure type. They also depend on the patient's psychological profile and medical-social condition.

Therapeutic management relies primarily on **anti-epileptic drugs** [31] (or anticonvulsants): barbiturates (e.g., phenobarbital), benzodiazepines (diazepam, clonazepam), sodium valproate, phenytoin, carbamazepine, etc. Each product is preferentially active against one or a few varieties of epilepsy, and its goal is to prevent new seizures or reduce their frequency.

**Benzodiazepines** are the first-line emergency medications for epileptic seizures (convulsions) or status epilepticus.

For certain forms of drug-resistant epilepsy, primarily partial ones, surgical intervention may be considered [188] (cortectomies or disconnections).

# Parkinson's Disease

**Parkinson's disease** [54, 79, 187] was first described in 1817 by the English physician **James Parkinson** [74], after whom it is named. It is a neurodegenerative disorder of the central nervous system characterized by progressive, primarily motor disturbances. Its causes are poorly understood.

The clinical picture of this disease is the consequence of neuron loss in the **locus niger** [38] and impairment of the **nigrostriatal tracts** [31]. The disease usually begins between the ages of 45 and 70 [74]. It is the second most common neurodegenerative disease [79, 91] after Alzheimer's disease.

**Parkinson's disease** is distinguished from **Parkinsonian syndromes** [191], which arise from various origins, are generally more severe, and respond inconsistently to treatment.

## 1. Pathophysiology :

It is a neurodegenerative condition characterized by the premature death of neurons, essentially those in the **substantia nigra (locus niger)** [187]. This part of the brain, located at the midbrain-diencephalon junction, is involved in movement control, partly through the secretion of a neurotransmitter: **dopamine** [41].

The loss of dopaminergic neurons results in an insufficient quantity of dopamine within the **striatum**; the progressive nature of the disease explains why it remains undetected for many years. Initial clinical signs only appear after the destruction of approximately 70% of the neurons [192] in the locus niger.

Over time, other neural structures may be affected, involving other neurotransmitters responsible for controlling other faculties such as memory, emotions, balance, blood pressure, sphincters, and sexuality [191].

## 2. Diagnosis :

The symptoms of Parkinson's disease are diverse. They are not always highly specific, and the disease may begin with vague disturbances such as peri-articular pain, depression, or fatigue. At the onset of the disease, symptoms are characterized by their **unilateral** nature [79, 91]. These symptoms include:

- **Tremors** [69]: These manifest primarily at rest, persist even during sleep, and worsen with emotion. They mainly affect the upper limbs, particularly the hands; the head does not shake. They often cause social embarrassment but rarely result in major disability.

- **Akinesia** [185]**:** Difficulty initiating or continuing a movement, and the loss of automatic movements.

- **Body rigidity** [187]**:** Excessive muscle tension results in permanent stiffness, increased resistance to movement, a short-stepped gait, falls, loss of balance, and forward curvature of the spine.

- **Loss of facial expression:** The face becomes inexpressive.

## 3. Treatment :

The treatment of Parkinson's disease has seen considerable progress in recent years.

### 3.1. Medications :

No drug has demonstrated efficacy in stopping the progression of Parkinson's disease [193, 194]; there is no curative treatment. Current medicinal protocols remain purely **symptomatic** [96].

**Levodopa** or **L-dopa** [187] is a dopamine precursor used therapeutically because dopamine itself does not cross the blood-brain barrier [1, 41]. L-dopa provides symptomatic relief for many patients. It is converted into dopamine in the brain to meet the needs of regions lacking it. However, after several years of treatment, Levodopa gradually becomes less effective [31].

Other drugs may be administered alone or alongside L-dopa: **dopamine agonists** [79], enzymes that inhibit dopamine degradation [178], or enzymes that inhibit the breakdown of Levodopa in the blood. Other treatments may be administered to reduce tremors, such as **anticholinergic** medications [185], which are prescribed alone or in combination with the previously mentioned treatments.

Certain symptoms, such as loss of balance, drops in blood pressure, mood disorders, or memory impairment, respond poorly to antiparkinsonian drugs because they are caused by damage to other brain circuits that do not involve dopamine, thus requiring other types of medication.

### 3.2. Deep brain stimulation :

When medications no longer provide the expected benefits, it is possible for certain patients to have electrodes implanted in specific brain regions, connected to a stimulator (pacemaker), to improve the functioning of the damaged areas [69].

### 3.3. Physical rehabilitation :

Alongside drug treatments, physical rehabilitation (**physiotherapy** [193], **occupational therapy** [191] , and **speech therapy** [195] ) is an indispensable complement. It helps maintain the flexibility

necessary to pursue motor activities.

# Alzheimer's Disease

" *I have lost my self* " **Auguste D, 1901.**

## 1. General Overview :

**Alzheimer's disease** [69, 196, 197] is a **neurodegenerative pathology** [138, 198] that affects various regions of the brain. It is the **primary** [140, 199] cause of **dementia** [197] (an acquired, progressive, profound, and irreversible decline in cognitive functions) in the elderly.

This disease is named after **Dr. Alois Alzheimer** who, in 1907 [196], first described the anatomical alterations observed in the brain of a 51-year-old patient, **Auguste D.** [201].

In 1901 [200], Dr. Alzheimer asked the patient to state her name; Auguste tried to remember it but could not, then she looked up at the doctor and said, "*I have lost myself*" [202].

## 2. Pathophysiology :

The neurodegenerative process responsible for the disease involves the formation of **amyloid plaques** [113] (senile plaques) between neurons and, inside the neurons, aggregates of tau proteins that form **neurofibrillary tangles** [196].

These two phenomena cause massive neuronal destruction, which manifests macroscopically as **cortical atrophy** [185, 196]. In patients with Alzheimer's disease, the brain can lose 8 to 10% of its weight every ten years, compared to 2% in a healthy subject [203]. Cortical atrophy is accompanied by a dilation of the cerebral ventricles and cortical sulci.

Neuronal loss particularly affects **cholinergic systems** [80] (neocortex, entorhinal cortex, amygdala, hippocampus, nucleus basalis of Meynert [50, 119, 172]), noradrenergic systems (**locus coeruleus**), and serotonergic systems (**raphe nuclei**) [63].

## 3. Risk factors :

The exact causes of Alzheimer's disease remain unknown [39], but it is hypothesized that environmental factors (**aluminum and heavy metals, including mercury** [204]) and genetic factors [196, 197] contribute to it. Mutations in at least four genes predisposing to Alzheimer's disease have been identified.

Risk factors for developing Alzheimer's disease include:

- **Age** is the most significant risk factor [196]. As we age, the body's natural repair mechanisms become less effective.

- **Cardiovascular disease :** All risk factors for cardiovascular disease [204] (such as hypertension and hypercholesterolemia) are also risk factors for Alzheimer's disease.
- **Family** and **genetic** history [196, 197].
- The **ApoE4 gene** [197].
- **Female sex** [196].
- **Diabetes** [205].
- **Head trauma** [196, 197, 204] ...

## 4. Clinical Presentation :

The first symptom of Alzheimer's disease is the loss of memory of recent events (**amnesia**) [201]; this initially manifests as minor lapses that progressively worsen as the disease advances, while long-term memories are relatively preserved.

Subsequently, cognitive deficits extend to the fields of language (**aphasia**) [198], the organization of movements (**apraxia**) [205], visual recognition (**visual agnosia**) [197], and **executive functions** (such as decision-making and planning) [206]. These latter symptoms specifically reflect the pathological degenerative process affecting the frontal lobes of the brain.

These psychological changes affect essential human qualities, and for this reason, Alzheimer's is sometimes described as a disease in which victims suffer the loss of the qualities that form the essence of human existence.

## 5. Treatment :

There is currently no treatment that can cure Alzheimer's disease [206] or even stop its progression. However, some medications slow its advancement by alleviating the loss of memory, language, and reasoning.

### 5.1. Specific treatments :

These are medications prescribed specifically for Alzheimer's disease [207]**:**

- **Acetylcholinesterase inhibitors:** They inhibit the breakdown of acetylcholine, aiming to correct the acetylcholine deficit observed in the brains of those affected by this disease.
- **NMDA antagonists:** N-methyl-D-aspartate (NMDA) neuronal receptors play an important role in memorization processes.

### 5.2. Non-specific treatments :

These modify the patient's behavior without addressing the disease itself [206].

- **Psychotropic drugs** reduce anxiety, aggression, or states of agitation. Anticholinergics should be avoided as they worsen the disease.
- Medications targeting the risk factors of the disease: certain statins, antioxidants (such as vitamin E or melatonin), and anti-inflammatories.

In all cases, addressing the disruptions caused by cognitive impairment in the personal and relational lives of patients is essential, as is providing support to their families. Cognitive rehabilitation techniques and certain psychotherapies are often helpful.

# Pain

**Pain** [3, 4, 57] is a distressing and unpleasant sensation perceived by the organism usually in response to a harmful stimulus. It usually serves as a warning signal from the body to indicate a threat to its physical integrity.

Pain can also refer to emotional suffering (for example, following a death); however, this type of pain will not be addressed here. Even though it is an unpleasant experience, pain circuits play a vital role in our survival [48, 187], as this sensation forces us to act, often instinctively, to escape potential danger.

Pain is the primary symptom in most diseases [208, 209]. Its clinical description is of major interest for reaching an **accurate diagnosis** and, subsequently, an appropriate remedy. However, pain can be so excessive and intolerable that it becomes a disease in itself. It is essential to implement targeted interventions that alleviate patient distress.

## 1. Pathophysiology of pain :

### 1.1. From the Periphery to the CNS:

The **nociceptive message** [107] (painful) results from a painful stimulus at the nerve endings of cutaneous [69], muscular, articular, or visceral structures. This message is then carried by afferent nerve pathways to the **CNS** [1, 4].

Polymodal nociceptors (activated by mechanical, thermal, and chemical stimuli) and **unmyelinated C fibers** play a major role in detecting, encoding intensity, and transmitting cutaneous pain. These C fibers are unmyelinated with a diameter <1 µm [3] and a slow conduction velocity <2 m/s. Other types of fibers also participate in the conduction of nociceptive signals, such as **A-delta fibers** (thinly myelinated) [57].

After traveling through the peripheral nerves, the nociceptive afferent fibers reach the central nervous system [41] at the level of the posterior roots of the spinal cord or, for cranial nerves, at the brainstem. **Substance P** (the primary neurotransmitter of pain) and glutamate excite the neurons of the dorsal horn of the spinal cord [1, 38, 107]. The nociceptive impulse then follows the **spinothalamic (extralemniscal) pathway** [145], which is specific to thermo-nociception.

### 1.2. Modulation of nociceptive messages :

Once the nociceptive message is transmitted from the periphery to the **CNS**, it is modulated by different control mechanisms [35].

Afferent fibers (**A-alpha** and **A-beta**) that transmit tactile messages inhibit nociception at the spinal level. This explains our tendency to touch the hurt area immediately after the accident. These inhibitory phenomena can be presynaptic or postsynaptic (**Gate Control Theory** [39]).

In the brainstem, there are neurons that give rise to **descending inhibitory pathways** [38, 107] (for example, those in the **periaqueductal gray** [3]). By blocking nociceptive pathways, these neurons induce analgesia in the painful area.

## 2. Different types of pain [69]:

### 2.1. According to the Mechanism of Pain:

#### a. Nociceptive pain :

This represents the classic model of reception, transmission, and perception of pain according to the mechanisms mentioned above.

#### b. Neurogenic pain :

This refers to pain that does not result from tissue damage but is due to an interruption of nociceptive pathways, leading to a disturbance in the transmission system [207].

#### c. Psychogenic pain :

This refers to pain for which there is no organic explanation [207].

#### d. Referred Pain :

The fibers of the spinothalamic pathway sometimes receive convergent afferents from both the skin and certain viscera. When a nociceptive impulse is received, the brain attributes the source of the stimulus to the skin, which is more frequently stimulated. This is the case, for example, during a **myocardial infarction** "heart attack", where pain is felt in the left hand and the mandible, even though there is no injury there [3, 209].

### 2.2. Depending on the course of the pain:

- Acute pain [48].
- Chronic pain [69].

## 3. Pain Assessment :

### 3.1. Simple Verbal Scale (SVS) :

The patient is asked verbally to evaluate their pain according to 4 or 5 categories, resulting

in a score: 0: No pain, 1: Mild, 2: Moderate, 3: Severe, 4: Extremely severe [210].

### 3.2. Numerical Rating Scale (NRS) :

This allows the patient to rate their pain on a scale where the minimum score is 0 and the maximum, representing intolerable pain, is 10 [208].

### 3.3. Visual Analog Scale (VAS) :

This is a ruler featuring a subjective line on one side and a 100 mm scale on the other. The patient draws a line or moves a slider according to the intensity of the pain, ranging from (**no pain**) to (**worst imaginable pain**). The healthcare provider matches the notation on the back to the displacement of the slider [91, 179].

### 3.4. Other Multidimensional Methods :

This category includes several types of questionnaires and behavioral scales. While subjective, these assessment tools are essential for clinical orientation and monitoring pain progression [208].

## 4. Analgesic treatments :

Therapeutic measures must primarily target the source of the pain but must also aim for patient relief [69]. The **World Health Organization (WHO)** has classified different analgesic substances into three levels based on their activity. It is recommended to follow this **step-by-step strategy** in pain management [91].

### 4.1. Level 1 :

***Paracetamol*** and ***non-steroidal anti-inflammatory drugs (NSAIDs)*** such as aspirin, ibuprofen, and noramidopyrine. For pain judged as mild or moderate by a physician, these drugs should be prescribed first. They act primarily by inhibiting **cyclooxygenase**, an enzyme responsible for a cascade of chemical reactions that lead to pain. The most frequent side effects of these drugs are gastric, though other very serious disorders can occur in cases of overdose.

### 4.2. Level 2 :

**Weak opioid analgesics** [211], which are derivatives of opium and morphine, such as codeine, dihydrocodeine, dextropropoxyphene, and tramadol. Codeine and dextropropoxyphene are often combined with Step 1 analgesics because their modes of action are different and complementary, creating a **synergistic effect**. These substances act on the **CNS** via specific receptors responsible for pain suppression. The primary side effects include constipation, drowsiness, nausea, vomiting,

and respiratory difficulties. These compounds carry a risk of physical dependence.

### 4.3. Level 3 :

**Strong opioid analgesics**, such as **morphine** [48, 211] and its derivatives. These drugs have the same characteristics and the same mode of action as the previous ones but are more powerful. They are used for severe pain or pain resistant to Step 2 analgesics. They share the same side effects as weak opioid analgesics and can lead to the same issues with dependence.

# Myasthenia Gravis

**Myasthenia gravis** [39, 41, 212], from the Latin [219] (meaning "grave muscle weakness"), is a relatively rare chronic autoimmune disease that preferentially affects women [178].

Myasthenia is linked to a defect in the transmission of nerve impulses between the nerve endings of motor neurons and muscle fibers [219]. It manifests as muscle weakness that worsens with activity and improves with rest. Its severity lies in the risk of respiratory complications [69] that can be life-threatening for the patient.

## 1. Pathophysiology :

The neuromuscular transmission defect results from the blocking of **acetylcholine receptors (AChR)** at the motor end plate by anti-acetylcholine receptor autoantibodies (**anti-AChR antibodies**) [218].

Alongside this humoral factor, it is established that the **thymus** plays an important role in the pathogenesis of myasthenia [187]. Approximately 10% of patients with myasthenia have a thymoma, and two out of three patients have thymic hyperplasia [185].

These immune abnormalities may have a genetic basis [220]; myasthenia appears to be linked to a different HLA phenotype depending on whether it is an early-onset form in young women or a late-onset form.

## 2. Diagnosis :

In half of the cases, the first signs are ocular, with **diplopia** (double vision) or **ptosis** (drooping of the upper eyelids) [107]. In other cases, the onset is marked by difficulty with phonation, chewing, or weakness in the limb muscles.

In myasthenia, muscle weakness increases with exertion [187] and can lead to partial paralysis of the affected muscle. Rest improves muscle strength [75]. However, in severe forms of the disease, muscle strength is permanently reduced and does not improve, even after prolonged rest.

The clinical examination must be supplemented by an **anticholinesterase test** (Prostigmin), for which a positive result is a significant diagnostic argument in favor of myasthenia, although a negative result does not rule out the diagnosis [207].

## 3. Treatment :

Myasthenia can be treated with **cholinesterase inhibitor** medications. These drugs prevent the breakdown of acetylcholine and thus prolong its action on the receptors of the motor end plate

[212].

In the case of a thymoma, a **thymectomy** is performed. Immunomodulators are sometimes used, such as intravenous polyvalent immunoglobulin infusions and corticosteroids.

# Multiple sclerosis

**Multiple sclerosis** [41, 69, 86, 187, 212] **(MS)** is a chronic autoimmune inflammatory neurological disease. It is a multifactorial pathology whose clinical manifestations are linked to the **demyelination** [213] of nerve fibers in the white matter of the central nervous system (comprising the brain, spinal cord, and optic nerve, the latter being part of the **CNS** [41]). The definition of **MS** is primarily anatomical; the description of the lesions is what gave the disease its name [74].

## 1. Pathophysiology :

It is a demyelinating pathology; its symptoms are linked to the destruction of myelin [107, 185] while sparing the axons (myelin-axonal dissociation [31, 36, 107, 179]). Early lesions confirm its inflammatory nature [182], showing edema and inflammatory infiltrates alongside active myelin disintegration [31]. In older lesions, inflammation is found at the periphery - in the zones of progression - consisting of T lymphocytes (CD4), followed by macrophages and B lymphocytes that secrete immunoglobulins (IgM and then IgG) [74].

Older lesions are the site of astrocytic proliferation, which characterizes the sclerosis of nerve tissue (plaques). What Charcot described in 1868 [214] is only the scarring phase of the lesions. These multiple plaques are disseminated throughout the central nervous system. They can affect any part of the white matter, but they have sites of predilection: the brainstem and periventricular zones [36].

The unique feature of this disease is its progression, marked by phases of **relapses** [178] (during the formation of a new zone of demyelination) and **remission** (when the plaque heals), with partial remyelination [107] and sometimes dramatic improvement in symptoms. During a relapse, the myelin sheath is destroyed. This demyelination leads to an alteration in electrical conduction within the axon, resulting in various clinical signs that appear over a few days.

Unfortunately, over time, new relapses heal less effectively, and neurological alterations eventually stop regressing, forming permanent lesions. The rhythm of the **relapsing-remitting** phases varies significantly from one individual to another; for some, the disease remains without major impact outside of relapses for a long time, while for others, a rapid deterioration in quality of life occurs due to frequent relapses with poor recovery.

There is also a progressive form that consists of a permanent worsening. In patients suffering from **MS**, heat impairs nerve conduction and thus worsens symptoms during relapses (**Uhthoff's phenomenon**) [215].

## 2. Causes :

There is likely no single cause of **MS**; rather, it is recognized as a multifactorial disease for which several factors are being identified: autoimmunity, genetic factors, and environmental factors [213] ...

It is an autoimmune disease linked to the abnormal activity of certain antibodies directed against the myelin sheath of nerve fibers, triggered by a likely viral event [75] in an individual genetically predisposed to the disease [216]. **MS** has an increased incidence among women and young adults.

## 3. Diagnosis :

Often, the first signs of the disease include a temporary decrease in visual acuity and paresthesia (tingling or "pins and needles") in the arms. After a few days, these symptoms disappear, only for diplopia and balance disorders to set in later.

Patients with **MS** may present with motor disorders (muscle weakness, muscle contractions and spasms, paralysis of one or more limbs, ataxia, and speech or writing disorders) sometimes associated with sensory disturbances (tingling, abnormal sensations in a part of the body, extremities, hands, feet, or face, pain, diffuse headaches, dizziness and imbalance).

There is no specific test for **multiple sclerosis** [212]. Modern examinations allow for early diagnosis, but clinical data are often sufficient: a progression through successive relapses is highly suggestive of the diagnosis. A duration of 24 hours is necessary to qualify an event as a relapse.

**Dissemination in space** is the second criterion [212]; this involves demonstrating that the patient has at least two lesions in the central nervous system. The ideal clinical situation for diagnosis is the concomitant involvement of the neuraxis and the optic nerve. In other cases, recourse to complementary examinations is necessary to demonstrate this multifocality. It should be noted that the identified lesions are often more disseminated than clinical symptoms suggest.

Analysis of the **cerebrospinal fluid (CSF)** [91, 215] provides valuable diagnostic evidence when it highlights inflammation.

**Evoked potentials (EP)** [31, 216] - visual, auditory, sensory, and more recently motor EPs - allow for the detection of subclinical distress in the corresponding axonal pathways. The goal is to demonstrate the multifocality of the lesions; if clinical data alone achieve this, these tests are unnecessary.

**Magnetic Resonance Imaging (MRI)** [183] is the second examination of choice; it allows for the early detection of lesion multifocality, even before the onset of symptoms [215].

## 4. Treatment :

The treatment of **multiple sclerosis** aims for two objectives: to slow the progression of the disease and to relieve the patient. However, it is still impossible to cure **MS** [217]. Treatment is therefore symptomatic [216], although it can influence the course of the disease: corticosteroids, immunosuppressants, antispasmodics, muscle relaxants, antidepressants, and interferon-beta…

Medical treatment is accompanied by rest, physiotherapy sessions, therapeutic massage, and rehabilitation (**occupational therapy** and **physiotherapy**). However, one must remain critical regarding the efficacy of treatments, especially at the beginning of the disease, while taking into account the naturally regressive nature of relapses. For individuals with the disease, it is possible to slow the onset of symptoms by getting enough rest [212], avoiding stress, heat and sunlight, exercising regularly, and maintaining a healthy, balanced diet.

# Aphasia

**Aphasia** [75, 185, 198, 221] is a term of Greek origin meaning "loss of speech" [222]. It refers to a partial or total acquired loss of the ability to express and/or understand language, whether spoken or written, despite the anatomical and functional integrity of the phonatory organs (tongue, larynx) and independent of any neurological impairment of sensory origin (without hearing or visual difficulties) or motor origin (primary motor cortex) [185].

## 1. Pathophysiology :

Aphasia occurs following a lesion of the dominant left hemisphere for language. This lesion appears as a result of brain injury: a tumor, head trauma, or most commonly, a **stroke (CVA)** [198].

Most people with aphasia do not completely lose the use of speech. Aphasia is a language disorder that can present significant nuances: some patients show only slight hesitation in finding their words, while others have almost entirely lost the ability to express themselves, understand what is being said to them, read, and/or write, even while other faculties such as memory or orientation remain well-preserved.

## 2. Classification :

There are several types of aphasia, depending on the underlying mechanisms and the clinical manifestation of the cerebral abnormalities [50]. Classically, aphasia can be classified into three main categories [212]**:**

### 2.1. Sensory aphasia, or Wernicke's aphasia:

This type of aphasia is characterized by a deficit in language comprehension and difficulty interpreting the meaning of words and sentences [5, 198]. It is characterized by severe comprehension impairment and by verbal expression using inappropriate words, including the use of new vocabulary (**neologisms** [50]).

The patient is often unaware of their impairment [223]. This type of aphasia primarily occurs during a lesion in the left hemisphere affecting **Wernicke's area**.

### 2.2. Motor aphasia or Broca's aphasia:

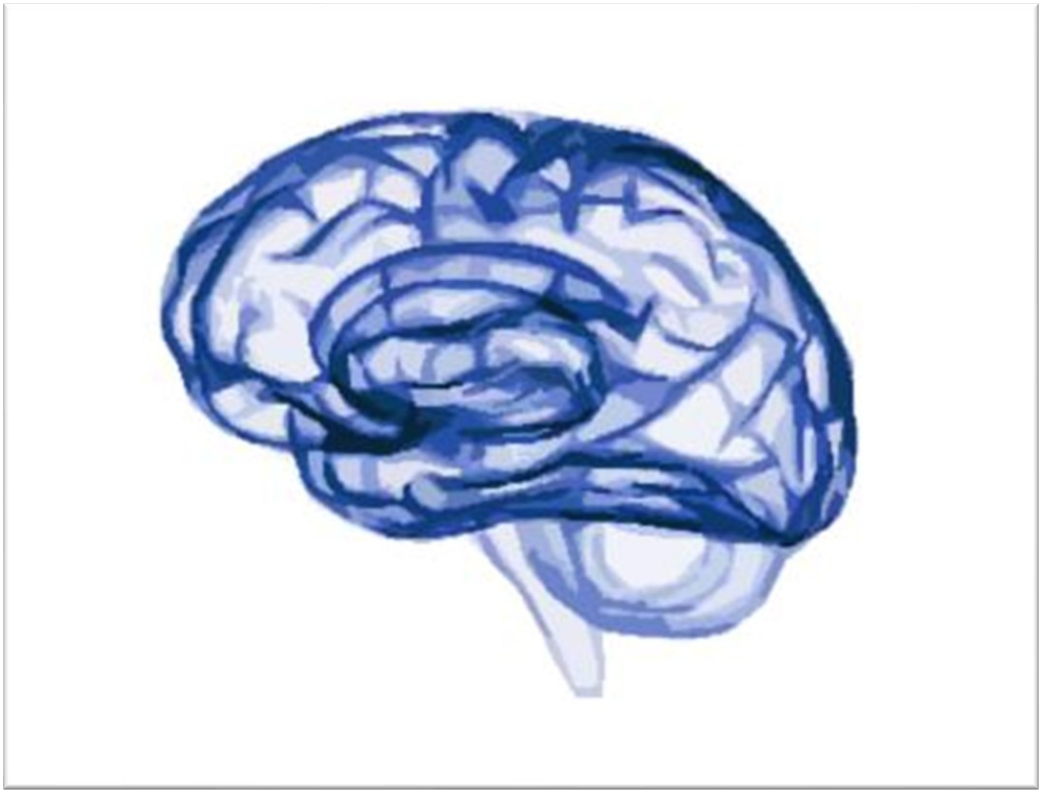
Loss of speech, difficulty expressing ideas [49]. It is characterized by oral and written impairments, whereas comprehension remains relatively good. The patient generally exhibits various degrees of articulation problems and uses non-structured sentences. They have difficulty finding the exact words to express themselves, and the words used are often inappropriate. This

type of aphasia is generally seen during a **right hemiplegia** (paralysis affecting the right half of the body) in which **Broca's area** is affected.

## 2.3. Conduction aphasia:

This type of aphasia [198] often occurs during a lesion involving the **arcuate fasciculus** [221], which connects Wernicke's area to Broca's area. Conduction aphasia is characterized by difficulties in both the expression and reception of language. The management of this type of aphasia is often very difficult, especially when the impairments are severe.

# Conclusion



# Conclusion

"*The Art is long, life is short, opportunity fleeting, experience delusive, judgment difficult.*" **Hippocrates - The First Aphorism.**

The nervous system remains shrouded in enigma; for every mechanism we decipher, a thousand new questions emerge.

How can a thought be developed, an idea forged, and a consciousness and profound sense of individuality constructed from an inert mass such as the brain? How do electrical circuits provide us with this massive subjective illusion of the self? How does this 1.3 kg mass manage to make us - humans - beings that are so exceptional and so powerful?

There is an enormous amount to say about the nervous system, and what has been discussed in this medium is certainly very little, if not nothing, compared to what is known today; in fact, the sum of human knowledge in this field today is likely only a tiny fraction of what remains to be discovered.

Understanding the functioning of the nervous system requires a multidisciplinary approach encompassing biology, psychology, neurology, philosophy, sociology, and history... and even computer science, as the operation of computer systems presents many similarities with the functioning of the nervous system.

# Abstract

# Summary

Neuromatiq or Audiovisual and Interactive material on Neurological Physiology and its Disorders is a medical thesis project intended for the medical student among others. The objective of this thesis is to present the functioning of the nervous system in a simplified and concise manner.

Understanding the functioning of the nervous system is a very difficult task, and despite the availability of many masterpieces on neurological physiology in particular, they rarely go beyond the tradition of a book based on text and images or diagrams. I hope through Neuromatiq to present the nervous system from a different angle, based on 3D videos and interactive animations.

In this project, the subjects are presented according to increasing levels of complexity, starting with the anatomical overview, then the basics of neurophysiological functioning, then sensory and motor systems to finish with the higher functions that present the most difficult aspect of neurological physiology.

It would be pointless to discuss neurological physiology in a medical thesis without dealing with pathological cases. That's why a chapter on neurological disorders exposes the pathophysiological aspects of the most common diseases in neurology.

No volume and no book would suffice alone to understand the functioning of the nervous system; it is for this reason that the text of the thesis is full of links to references allowing the user to read more about each question we omitted to detail further.

# Feed-back

# Feed-back

Despite the negative comments around me like "*... You're wasting your time...*" or "*... it's useless...*"... The videos of this material that have been published on the internet have been received with great interest and admiration from medical professors, teachers, students, researchers and others around the world.

I had thousands of messages and thousands of emails that pushed me to continue in this direction, I will just quote here the ones that impressed me the most otherwise it is impossible to include all the comments.

*"Mohammed, Thank you for making these medical videos that are informative yet presented in such a way that allows for people who are not trained in medicine to understand the way the human body functions.*

*The combination of the audio and visual presentation provided a format that kept the material not only educational, but entertaining and enjoyable as well. By watching your videos I learned about the amazingly complex and precise way the human being functions in a way I never would have had the opportunity to know.*

*Your work is an inspiration. "* ***Maureen Conner Tenore***, *United States*.

*" There are many hours of work. These are very well done animations with explanations in French. They are very rare thank you for everything. I am doing my bachelor's degree in nursing and it has been extremely useful to me, I am visual. Thank you and continue your involvement in medicine. "* ***Jacobin***, *Canada*.

*" Hello Sir,*

*I am a teacher in a vocational training center located in Quebec City, province of Quebec in Canada. I would like to know if you would give me permission to use some of the videos you have created on nerve cells to present to students who will eventually become nurses. Thank you for your answer. Have a nice day. "* ***Jean - François Deschênes***, *Canada*.

*" I'm studying psychology and these animations in French are really magnificent and help to retain each area. There are already a lot of things in English and these videos in French*

*on Youtube are a really nice rarity. Thank you. "*

***Musiinfsk**, France.*

*" Bravo! I also studied psychology 25 years ago... If these wonders had existed, it would have really made our lives easier.... It's a fantastic piece of work and I'm proud to watch it in French and to be able to share it with my 16 - year - old daughter, who will be able to understand much faster than I could. Thank you so much. "*

***Mirabilis**, France.*

*" I feel like I've found a treasure. you don't know how much your animations will help me in my work as a SVT teacher. I am proud of you.*

*PS: SVT (life and earth sciences).in Morocco, it is the new name of natural sciences. "*

***Life and Earth Science Teacher**, Morocco.*

*" I am in my first year, in Kinesiology, at the University of Montreal. I just wanted to at Congratulate you for all your work, A big THANK YOU! for these educational videos in French... My teacher liked this video too because he shared it with us in his lecture notes! "* ***Melyssa**, Canada.*

*" Hello! Taking my mid - term in neurobiology in 2 days, I have to thank you for this work which allowed me to understand the 3/4 of the courses and slides that I did not grasp! Thank you! "*

***Student**, France.*

*" Hello, Thank you very much for this wonderful work and for your generosity in sharing it. I work in the field of psychology and psychotherapy, your presentations are precious to me. "*

***Thildeswingout**, France.*

*" Hello Medbenmedben, I have been working as a speech therapist for 20 years. When I did my studies, I really struggled to imagine everything you show in 3D... I salute a work that I find very visually beautiful, playful, and which makes learning much simpler. I have forwarded the links to your videos to people currently studying speech therapy. They will certainly be grateful to you. When passion helps... Thank you so much. Long live Morocco! "* ***Speech Language Pathologist**, France.*

*" It's true that your videos are very well made and pleasant to watch, we understand much better the way you explain. Bravo and thank you!! It's really great!! "*

**Beehyenneprod**, *France*.

*" Thank you very much, your video has been very useful to me and my colleague for our revisions. Congratulations on this 12 - minute summary!*

*We just wanted to have a little more precision about the mechanisms inducing hyperpolarization during AP but it's already great! "* **Raitomea**, *France*.

*" It's an excellent job... The structure is clear, the information precise and, in addition, a true artist in the presentation. I would also like to be able to read the text in French for your video "neuromuscular transmission". Thank you and respect. "* **ferrc75**, *France*.

*" It's really great! it helps me a lot because I couldn't locate the different structures in 3D, now everything is clear! :). It's very well done! I think you help a lot of students! "* **SnowMarine**, *Belgium*.

*" But this video is simply amazing. Thank you!!! I have a bio test tomorrow and it makes for a good review. "* **Carlos**, *Canada*.

*" It's perfect! I am a student at the Paris School of Speech Therapy, and this is exactly our program, but more synthetic. The images are really great for finding your way in space, much better than an unreadable flat diagram! "* **Budget**, *France*.

*" This is an excellent video!! I'm in nursing school and this was very very helpful!! Many thanks! "* **native1910**, *United States*.

*" Thank you so much. I finally understood the process of the Neuromuscular Junction. Thank You. Please post more videos related to Anatomy and Physiology.*

*Great explanation. "* **Telugu**, *United States*.

*" An exceptional video. 5/5. It's not too simple that it avoids detail, but not so complicated that it's hard to understand. A well rounded video. "* **Urbanfire**, *Australia*.

*" Very nice explanation. Helped me a lot with my studies and visualizing the process. Thank you! "* **Pikesbeach**, *United States*.

*“ Great video (description) Could you please continue download them in English.... truly understand and follow you teaching method. Thank you! ”* ***Paopats***, *United States*.

*“ This was an absolutely amazing video. I too was looking for something that explained in a 3 - dimensional way that was detailed enough that I would walk away with the whole picture but not too difficult to understand. ”* ***Kcj***, *United States*.

*“ It is one of the best and didactic explanation that define a neuromuscular junction. Thank you very much.*

*A great and prosperous future is waiting for you. ”* ***Mizrahi***, *Palestine*.

*“ This is superb. I am taking a course in the brain, and this is the only video I've seen that explains the whole process, and it does so with beautiful visuals and beautiful and patient narration. Also the fact that it describes muscles makes it so much more tangible to me, so I can easily make the leap to neurons. ”* ***Omu***, *United States*.

*“ Simply AWESOME! Very well explained and schematized I am 7 hours away from my contest and your videos are one by one allowing me to make a difference! Everything is much clearer! Thank you very much! ”* ***Amfibiun***, *France*.

*“ Thank you for these videos!! I have so much trouble imagining these abstract things, this is a very precious help. Keep going, it's great!! ”* ***Arsen***, *France*.

*" Great job sir. I understand the system better now. "*

***Rukash***, *Sénégal*.

*" Great! Thank you for these very useful explanations for my nursing training! "*

***Huddypowa***, *Suisse*.

*“ Your work is excellent, it's exactly what I dreamed of to visualize my neuroanatomy classes. Thank you very much!!! ”* ***Chicatube***, *France*.

*" Hello, I find your videos very interesting. I am looking for documentation on different subjects, because I am a teacher for nurses in Canada. Your videos are complete and easy to understand. Is it*

*possible to use your videos in my course on the cell, genetics and the neurosensory system?*

*I congratulate you again on your work, it is very interesting. Hoping for a statement from you soon... "* ***Valérie Perreault***, *Canada*.

*" I am proud of you ! You do such good work masha'allah. I am proud to be Moroccan, and I learn great things about medicine by watching your videos. A professor is using your video to show us structures of certain cells. Keep up the good work ! "* ***Solidus***, *France*.

*" Good evening, I just watched your animation on the description of the LCR. Congratulations on your pedagogical creation, I will now offer it in my classes. I am a teacher - researcher on the dynamics of the CSF and its involvement in brain pathologies. If you are interested, I can provide you with animations representing the dynamic aspect of this vital fluid is still mysterious. Don't hesitate.*

*Respectfully! "* ***Olivier Balédent***, *France*.

*" Just to thank you for your videos. I'm preparing for the medical exam and I'm struggling a little but thanks to your videos I understand better. Thank you so much. "*

***Madelinxs***, *France*.

*" Good evening, thank you very much for submitting these videos, it is really an excellent work on your part, and of course on our dear Professor Belahsen. This is how our Faculty will shine with the knowledge of its professors and students. By the way, I'm Naidal, a 2nd year student in the FMPF. Kind regards. "*

***Naidal***, *Morocco*.

*" Salam, Your videos are very rich and well done. Bravo for this work. My wife wants to use some passages for educational purposes. Is there a method to copy some snippets. Thank you in advance and good luck. "*

***Hechmi M'NASRI***, *France*.

*" Dear Ben Brahim Mohammed, I found your animation and would like to inquire if we can use parts of it in an educational DVD about the human muscular functions, of course with credits? Thank you for a quick answer. "* ***BriggiV***, *Germany*.

*" Hi , My Name Is Allan and I'm a student of Sport Science, I Saw some Of your Videos And they Are amazing and well explained. I would like to ask your permission to translate them into my*

*Language (Hebrew) so it could help others with the same interest. I would make sure to make comment as to the source of the videos and their origin. Greetings. "*

***Allan**, Australia.*

*" First of all, I would like to congratulate you on the quality of your work. It is precisely on this subject that I would like to ask you. Would you allow me to use your work in the context of my intervention with student nurses?*

*I thank you in advance for the attention you will give to my request and wish you an excellent continuation. "*

***Scarabunta**, France.*

*" Hello Mohammed, My name is Erez and I am the manager of a non - profitable educational website for teenagers. I would like, with your permission, to post your video - "neuromuscular junction - motor unit" on my website, and to add Hebrew subtitles (translation only). I will give you proper acknowledgment and add a link to your website.*

*Many thanks. "*

***Erez**, Palestine.*

*" Dear colleague, I was heavily impressed by your marvelous video animation on the neuromuscular junction. I would really be eager to show this video to my medical and neuroscience students. Is there a possibility to get the video for teaching purposes ? Looking forward to your answer, kind regards. "*

***Hannsjörg Schröder**, MD, Professor of Anatomy / Neuroanatomy, Department of Anatomy, University of Köln, Kerpener Straße 62, 50924 Köln. Germany.*

*" Hello, I saw your video online and I think it's very good. Would you agree to give it to me or loan, I am a trainer in sport.*

*Thank you for a friendly answer. "*

***Boxingsavate**, France.*

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