The Brain, a Galaxy in Your Head

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FOREWORD

I must have been eight or ten years old... I was accompanying my mother to the grocery store when I came across a small general public book stand. Among these books, there was one that would change my life, no less. Although it had a title such as “The human body” or “The marvellous human body” it’s the illustration on the cover that struck me and captured my attention. On a blood-red background, a semitransparent drawing of a human body revealed different anatomical structures, including the skull and skeleton. Flipping through the book, the inside of the skull was visible, and a diagram of the brain and its blood vessels was illustrated. This image stroke with me. After brief negotiations, my mother agreed to buy the book in question, and that was it. From then on, I wanted to understand and heal the human body. A revelation, no less. Page after page, I was in awe; I had decided what I wanted to do with my life.

Today, at 56, I close my eyes and can still see distinctively the book’s illustrations that I compulsively and religiously browsed through until I had memorized the most minor details. Ultimately, the illustrations of the skull and the brain left the most lasting impressions. I can still see the blood vessels going in and out of the head and the different nerves emerging from the brain. It was such a daunting image!

This period of my life was punctuated by two obsessions: science fiction and the functioning of the human body. More than 40 years later, these two obsessions are still vividly present, one as a hobby, the other as a job. To my great pleasure, the two occasionally intertwine in my medical practice and specific research projects. The quest was initiated by the simple question, “How does the human body work?” and was gradually transformed by my training to become “How does the brain work?”

Interestingly, I know that I will die (the fate that eventually awaits us all!) without having the complete answers to this question. I also know that I will have pursued this grand enigma all my life and will continue to do so as long as my brain allows me to! I would very much like to answer the 8-year-old boy that I was and explain the details in the brain functioning. This book is therefore dedicated to this boy, to his mother, who had the common sense to allow him to develop his curiosity and his obsession, and to his father, who gave him the tools to do so.

I have always doubted my abilities, and this doubt ultimately represented an advantage, a great strength. In high school, this doubt pushed me to do more then necessary to ensure success, allowing me to have the power of my ambitions. I spent most of my evenings studying while many friends were having fun instead. I have no regrets.

I KNEW I wanted to be a surgeon and heal the human body. At the beginning of my medical education, becoming a neurosurgeon represented the ultimate challenge, a path I could never aspire to; and yet! During my training, I developed a marked interest for oncology, hence my specialization in neuro-oncology. I previously said I wanted to work to heal the human body. What disease type causes more damage than cancer, which perverts the programming of our cells, forcing their rebellion against the instructions and rules they should follow? Hence, it would be oncology, neuro-oncology, brain cancer. But that's another story!

The first part of neurosurgery training is called basic sciences. During this period, the acquisition of knowledge related to the anatomy, functioning and physiology of the brain takes place. Unfortunately, after this study block, I discovered, to my great amazement, that there remained many unresolved questions and unexplored mysteries. It is then that the inner child faded, and the adult realized that nothing is that simple and that despite extensive university studies, it is impossible to answer all your questions. A great part of mystery remains! The university's mission is to perfect knowledge. Therefore, it would be one of my missions to deepen my knowledge of the functioning of the brain, tinker with the existing literature to extract conclusions, and try to see a little more clearly.

It was also in this context that I became a university teacher. One of the courses in which I invested the most energy was the neuroanatomy course for medical and postgraduate students. Still obsessed with science fiction, I built a course combining knowledge with extracts from my favourite film, The Matrix. This course was awarded a prize for "the best course at the medical school", "the César Galéano prize", for six consecutive years. After six straight years of winning this award, the faculty authorities removed my course from the candidates for the prize to allow others to win. It was with great pride that year after year, I went to collect my prize at the awards ceremony because, you see, César Galéano had been a fundamental researcher at the University of Sherbrooke, having taught me, many years earlier, neurophysiology! There is no such thing as chance... The book you hold in your hands is, in fact, an adaptation of this neuroanatomy course, without the references to the film The Matrix, of course (I held back!).

It is now directly you, dear readers, that I hail. We all have different subjects of interest: cars, motorcycles, cooking, sports, travel, architecture, aviation, hunting, fishing, fashion, decoration, painting, music, or anything else that might come to your mind. However, these interests have one thing in common: your brain. You know several of these themes, you are interested in the biography of some great characters, artists, comedians or sportsmans, but do you only know yourself? Do you have any idea how your brain works? In other words, do you understand the mechanisms that simply allow you to be?

The answer is probably no. There has always been a schism between scientific publications and accessibility to the uninitiated. I always thought it was part of our mission as scientists to demystify complex topics and inform people. The present text was designed for this very purpose and seeks to fulfill this mission. I hope you find this assignment has been successfully completed after the reading!

The work resulting from this project examines explicitly three questions that have always fascinated me. 1- How does the brain work, to the best of current knowledge. 2- What are the mechanisms producing consciousness? Are these mechanisms exclusive to human beings? Can the mind be considered synonymous with consciousness? In short, what are the more PHILOSOPHICAL implications regarding the functioning of the human brain? 3- And finally, what are the technological impacts on the brain? Will technology help evolve the brain, brain 2.0 style? Will artificial intelligence change the portrait of our civilization?

Here is the complete menu, which will be served in 3 acts. Happy tasting!

To my mother, who knew how to light the first spark,

To my father, whose consciousness now merges with the cosmic radiation background,

To my children, a virtually infallible source of joy and pride,

And to my life partner, Caroline, with whom I share the same curiosity….

Finally, to all my brain tumour patients, I salute your courage and resilience; you are my motivation, my driving force, and you never leave my thoughts…

INTRODUCTION

Writing a text on the brain accessible to all seemed a relatively simple task at the start of the project several years ago. Indeed, the plan was to adapt some of the courses I teach at university for medical and postgraduate students. However, while embarking on such a project, I convinced myself to add content to make it as a complete and up-to-date guide as possible on the scale of current knowledge. This is how the project gradually reached an unexpected scale, and the task I faced became gargantuan.

Indeed, certain chapters required detailed research to produce a balanced text on complex subjects. Such complexity required me to overlook certain details, obscured in favour of information I considered essential. Some of these editorial choices were made for the sake of conciseness and clarity, to keep the reader invested, to avoid burying them under an avalanche of information. There remains much to say on this subject; I hope I captured the essentials for you. The same goes for references; thus, several of the references consulted but not providing additional information of interest were left aside, so as not to weigh down the text unnecessarily.

This book is divided into 11 chapters that follow an intuitive approach regarding function and anatomy. The text can be divided into four main sections:

1) The history of neuroscience (chapter 1).
2) The study of the brain (chapters 2 to 8) which is, strictly speaking, the essence of the work.
3) Diseases affecting the brain (chapter 9).
4) In conclusion, a more philosophical discussion on consciousness and the mind (chapter 10), as well as artificial intelligence and the impacts of digital technologies on the brain (chapter 11).

It seemed ill-advised to begin exploring the brain without firstly summarizing the major historical events that have punctuated the discoveries leading to the current understanding of the organ. Therefore, the first chapter focuses on the history of the landmark discoveries about the brain.

Once we have completed this historical exploration, we will begin learning about the brain in Chapter 2 by using a simple but valuable comparison as a blueprint to affix our new knowledge: the computer. Here, we will deconstruct a computer according to its main components and then substitute the main anatomical modules that form the brain. Chapters 3 through 6 follow this plan. However, we will see later that this analogy, which is very useful as an introduction, will eventually be abandoned because pushing our knowledge further will make it obvious that the brain is not a modular organ, but instead functions as an integrated whole.

Hence, chapter 3 will allow us to discuss the casing of our computer, namely the skull and the different layers of protection of the brain, the meninges. The general anatomical organization of the brain will also briefly be described, emphasizing the various compartments inside the brain.

We will then be ready to jump straight into the subject. In Chapter 4, we begin a more in-depth exploration of the brain, using the plan we developed in Chapter 2 during our analogy with the computer. We will thus detail what the processors are in our brain and how these processors are connected. They are called neurons and are mainly concentrated in the cerebral cortex, this thin envelope on the surface of our brain. The connections between these neurons are axons, which are so numerous that they form most of the volume of the brain under the cortex; we call this "white matter".

Once this exploration is completed, we leave the brain's surface (cortex) to dive inside the white matter. In Chapter 5, we will discuss certain groups of neuronal nuclei that provide integration tasks that are specific and highly specialized. We will see that these groups of neurons are hubs, essential relays for certain specific functions, and these deep nuclei form loops with the cerebral cortex. These are 1) the basal ganglia, essentially involved in the motor system; 2) the thalami, a fundamental component of the sensory system and the system of consciousness; 3) the hippocampi, nuclei associated with the limbic system and whose essential function involves the consolidation of memories; and 4) the hypothalamus, a nucleus regulating the automatic functions of our brain, our thermostat. 5) the amygdala, which is also a component of the limbic system, and act as a an integrator for memory encoding and for emotions.

Continuing our descent towards the depth of the brain in Chapter 6, we reach its most fundamental and elementary component, the brainstem. Akin to the trunk of a tree, the brainstem is a complex structure of the brain that represents the support for the integration of our brain's functions. We will also see that this brainstem is the transit of information between the brain and the spinal cord, which goes down and up the spine. This spinal cord ensures the passage of information from the periphery of our body to our brain and vice versa. Finally, we will conclude this chapter by presenting a structure finely attached to the posterior aspect of the brainstem, a module of incredible complexity: the cerebellum.

At this stage of our learning, we will have completed our overview of the general anatomy of the brain. But the journey will not yet be over! We will still have to cover some important themes.

In chapter 7, we will focus on a complex and fascinating subject: the brain vasculature. It is, in fact, impossible to dissociate the brain from its vascularization; the latter is abundant to the point where the total length of blood vessels in the brain is estimated at 650 km! As if that was not enough, these blood vessels are different from those in the rest of the body and have properties that deserve attention. In particular, we will see that the brain's blood vessels form an exclusive barrier to the different molecules circulating in our body. Another property is closely linked to the function of the brain: thanks to a device that we call the "neurovascular unit," the small cerebral blood vessels will dilate preferentially in brain areas that are activated during specific activities. Given its uniqueness and complexity, the cerebral vasculature practically forms an "organ within an organ."

At this stage of our journey, we would now be expected to have an excellent understanding of how the brain works. However, as we will see throughout this text, nothing is that simple, and the brain's structure does not easily reveal its function. Chapter 8 will attempt to illuminate what we know about human cognitive functioning. Here we will explore what is most complex and abstract in brain functioning; whether it be language, memory, judgment, attention, working memory, we will see how these functions are distributed in vast, complex networks extending throughout the brain.

We will now have a reasonably complete knowledge of the anatomy and functioning of the brain. Now will be the time to focus on what goes wrong when the brain is sick. Chapter 9 will give us a quick and concise overview of the different classes of diseases that can affect the brain and the type of symptoms they produce.

Technically, this is where the initially planned project was to reach its conclusion and where the text was to conclude. But my curiosity got the better of me, and I chose to continue exploring the brain, in a decidedly more philosophical mission. Chapter 10 is the result of this quest. Implicitly, the initial question, "What is consciousness?" was to be transformed into an in-depth exploration of the different hypotheses claiming to provide an answer to this question. As you will see, there is no definitive answer, and perhaps never will be. The narrative process of this chapter, just as will be the case for the following chapter, stands out from the rest of the work. While the first part of this book presents undeniably factual information, chapters 10 and 11 are written in the form of an essay. Indeed, chapter 11 continues the exploration launched in chapter 10 on consciousness with a technological aim. In this chapter, we will explore the promises of artificial intelligence and the impact of new technologies on the brain.

Initially, this chasm between the book's two sections, chapters 1 to 9 (factual) and chapters 10 and 11 (essay), made me uncomfortable. However, the more I reread, the more I think about it, the more it seems to me that this split in form represents a logical progression towards two fundamental questions for which a firm answer does not exist: 1) what are the mechanisms responsible for the production of consciousness, and 2) is technological evolution going too far, too fast? Thus, after reading about the evolution of knowledge about the brain since the birth of humanity (chapter 1), we explored the brain to the limit of what is reasonable in the context of a layman text (Chapters 2 to 9). The logical continuation of our approach requires us to leave the path of facts to walk the path of speculation to explore the elements of response to these two questions. I learned a lot while putting together the last two chapters and trying to answer these two questions. I am satisfied with the route that these two trails took me on. I hope the ride will be as pleasant and profitable for you! Happy reading…

Before embarking on our exploration of the brain, and more particularly before beginning our historical journey in the first chapter, which explores the acquisition of knowledge on the subject since the beginnings of humanity, certain generalities regarding the organization of the brain must first be clarified here to allow a fair understanding of the concepts that will follow…

Thus, we describe the central nervous system as all the nervous system components in the skull or the vertebral column (brain and spinal cord). The brain is made up of two hemispheres, the left and the right. For sensory functions (perception), motor skills, and visual information processing, the information is processed in the hemisphere opposite (contralateral) to the source of the signals. When I move my left arm, the initial information producing the movement, or the command, comes from my right hemisphere. When someone touches my right hand, the information is transmitted to my left hemisphere and processed there. Likewise, visual information entering my eyes and stimulating the retina (membrane receiving visual information at the back of the eye) on the left side will be analyzed FOR BOTH EYES in my right hemisphere.

The brain's hemispheres are composed of a thin outer layer called the cortex, in which neurons reside. This cortex is formed of numerous folds that we call gyri (convolutions). Neurons in the cortex relay long extensions to communicate with each other, which we call axons. These axons occupy most of the subcortical space (under the brain's cortex) and form the white matter.

Now equipped with these basic notions, we can begin our journey.

CHAPTER 1

A BRIEF SUMMARY OF THE HISTORY OF NEUROSCIENCE

The twilight of humanity, the appearance of the first human beings, dates back 200,000 years (Groucutt, Petraglia, Bailey, Scerri et al., 2015, 149-150). However, it was not until 2600 BC that the first mention of the brain as an organ appeared in an archaeological document (Elsberg, 1931, 272). We are therefore in the Pharaonic era in ancient Egypt, under the reign of King Djoser. His principal advisor was named Imhotep, an exceptional and unusual character. He is considered the first architect, engineer and doctor in the history of humankind. He would be the author of a medical treatise discussing the brain for the first time, as well as describing several cases of head injuries. However, nowhere is the role of the brain discussed in the manuscript; it is essentially a descriptive document. The functions of the brain were neither known nor necessarily suspected at that time. Nevertheless, the skull appears to have been the anatomical site of the first documented and performed surgeries in human history. Indeed, skulls specimens dating back to prehistoric times, from the Mesolithic onwards, have been recovered. Closer analysis revealed traces of a neurosurgical procedure in the form of a craniotomy, i.e. the surgical opening of the skull (Rawlings and Rossitch, 1994, 507-513). Furthermore, we know that some of the subjects operated at the time survived their procedure: the contours of the bone opening ossified in some of the skull specimens found, supporting the fact that the 'patient' survived several years following surgery. But the neurosurgeons of the time probably didn't know which organ they were dealing with! It would also be interesting to know the indications justifying these procedures. At this point in history, the role played by the brain was still unsuspected.

Indeed, the brain has not always been considered the seat of consciousness. The heart and circulatory system were believed to be the medium housing the mind. This belief held for a long time. Empedocles, a Greek philosopher of the pre-Socratic era, developed in the 5th century BC a hypothesis according to which all body elements were composed of variable proportions of the four fundamental elements of nature (fire, air, water and earth). According to him, the ingredients of the blood determined intelligence, and therefore, most of the intellect must lay within the heart and the circulatory system (Biès, 1969, 101-103). Democritus modified this view somewhat, asserting that the mind could only be associated with the fastest particles and that these particles resided in the brain (Wismann, 2010, 51-66). At that time, two opposing visions had 'logical' arguments supporting them. On the one hand, the proponents of the cardiocentric hypothesis, who considered that the heart housed intelligence and consciouness, relied on the fact that the heart was a dynamic organ, always in movement, unlike the brain, which seemed inert. Furthermore, it had been noticed that when the heart stopped beating, the individual became inanimate permanently: this observation supported the argument that the heart was the seat of consciousness.

Advocates of the 'craniocentric' position, for their part, considered the skull to be the seat of consciousness. In support of their thesis, they argued instead that a solid blow to the head produced unconsciousness and that this state could be transitory or permanent, which was just as true, obviously. This debate continued unabated until Plato's intervention (Damasio, 1995, 17-21). The latter took hold of these concepts and modified them according to the geometric theories dear to him. With his intervention, the debate ended, at least for a while. He argued that 'the soul could only be attached to the bodily receptacle by geometric shapes, and that this link was made at the level of 'the marrow,' this substance which we now know under the term 'central nervous system' (the brain and the spinal cord). Hence, it appears here, for the first time, around 400 years BC, the notion of a soul that was separated from the body but that resided essentially at the level of the brain. As we will see, Descartes will take up this body-mind duality much later. But the historic march towards the refinement of knowledge about the central nervous system would, unfortunately, stop here for a long while.

If the scientists and philosophers of the time had continued their research and reasoning on the foundations laid by Plato, it is safe to say that knowledge on the brain would be much more advanced today. But that was without considering the contribution to the debate of Plato's most famous student, Aristotle, who muddied the waters for nearly 2000 years (Aubenque, 1983)!

The history of humanity is full of fascinating twists and turns, steps forward then backward in a long choreography of knowledge acquisition…. We are about to take a giant step backwards in the narrative that interests us! Indeed, Aristotle, who sometimes had a tumultuous relationship with his master, set the scientists of the time on a false trail by developing theories radically opposed to those of Plato. He claimed that each organ had its own independent, autonomous psyche. For him, the importance of an organ is immediately apparent and proportional to the action it materially performs. Incidentally, as most organs seem attached to the body's core and, by extension, to the heart which occupies a central location, Aristotle postulated that the heart must necessarily be the organ controlling the human body rather than the brain. For him, the brain is only a thermal machine whose purpose is to cool the blood, heated at the level of the heart by emotions. Hence, we are back to cardiocentrism. In this new conception of biological functioning, the brain is reduced to the rank of a standard thermostat! However, this new ideological incursion will be strengthened by Aristotle with a new concept to fill the scientific deficiencies of the time: the ether. The ether, an invisible element, a primordial component of the universe, the stars and paradise, is drawn in by our lungs, transmitted to our heart, and constitutes the central element of each organ's psyche. This design will be immediately retained and accepted. Indeed, the connection between the ether, a fundamental element of stellar origin, and the psyche, the intangible element of the human being, was probably considered an irresistible concept to scientists of the time. The notion of an ether made it possible to equalize the two terms of the metaphysical equation. The ether will occupy a central role in physics, as in biology, until the contribution of great physicists at the beginning of the 20th century. It was, in fact, Einstein who definitively deconstructed the concept of the ether, but that's another story! As for ours, we will have to wait for the contribution of Descartes, 2000 years after Aristotle, to find back the trail initially laid by Plato and return to a craniocentric conception of the human mind.

Although Descartes will be the one who breaks the cardiocentric dogma constructed by Aristotle, we cannot obscure the role of another great character, whose discoveries are at the very basis of the founding of neuroscience and of whom several scientists, Descartes included, will be inspired by: Galen. Galen of Pergamon (129 to 210 BC) was a Greek physician and scientist who studied in Alexandria. As for the conception of the nervous system that he developed, Galen was inspired by the precepts of Aristotle using an interesting angle (Freemon, 1994, 263-269). Indeed, he conceptualized a model based on an in-depth study of the respiratory system, the central subject of his studies. According to Aristotle's vision, the ether, once gathered by the lungs, was transformed into 'pneumavitale' in the heart, then circulated to the organs through the blood vessels. However, Galen affirmed that when the 'vital pneuma' reached the brain, it changed into 'psychic pneuma' and then circulated along the nerves. The brain again becomes an organ of consciousness under Galen, in the same way the heart was. For the first time in the history of humanity, we note a direct anatomical link between the brain and the nerves, the first mention of a functional system, the nervous system. It was under Galen that, for the first time, the brain was dissected and studied anatomically. Thus, it will essentially unveil the following anatomical components:

1. the brain, seat of sensations;
2. the cerebellum, centre of muscular action
3. the nerves, arising from the brain, in which the 'psychic pneuma' circulates
4. the ventricles, cavities found in the brain, the seat of the 'psychic pneuma'
5. The rete mirabile, a network of blood vessels located at the base of the brain.

Galen, a successful writer, documented his discoveries with dedication, resulting in a collection of manuscript estimated at around 12,000 pages (Kuhn, Ackermann, Asmann 1821). This work will then become the text of reference in medicine and form the basis of medical knowledge taught throughout the Middle Ages. Although Galen's model complements and refines that of Aristotle, we nevertheless remain essentially in a cardiocentric biological system. Indeed, the functional contribution of the brain remains limited despite a more important role than that hypothesized by Aristotle.

The Middle Ages, or the medieval era, represents a period of history essentially characterized by the importance of monotheistic religions that consider the body sacred and inviolable. Therefore, it will be a time of prohibitions and taboos regarding scientific experiments. This era of immobility is also characterized as a 'dark age' by certain authors (the Dark Ages, in Anglo-Saxon literature). Although most serious historians do not favour such a designation, considering it simplistic and reductive, I will allow myself to use it since it seems particularly appropriate in the context of the history we tell here and of science more generally. Let us say that progress in science and medicine will be particularly modest during this period due to a lack of experimentation and openness (Gingras, Limoges, Keating, 1998, 115-141). The dogmatism imposed by the clergy prevailed over curiosity and flexibility of thought. As such, there will obviously be no question of carrying out human cadaveric dissections and anatomical knowledge will remain essentially frozen until the advent of the Renaissance. Regardless of the event(s) that we consider to be the instigator of this period, most historians agree that the Renaissance originated in Italy, and more precisely, Florence as its epicentre. Although the causes of this revolution were essentially economic, the resulting consequences would ultimately be cultural and scientific. The massive arrival of Byzantine scholars in Italy following the fall of Constantinople had a catalytic effect on the development of medical knowledge. Indeed, these academics brought a vast 'forgotten' Greek literature, as well as the Arabic interpretations resulting from it, which would serve as a natural catalyst for an ideological upheaval. The conjunction between new printing techniques, the discovery of these 'lost' manuscripts and innovative artistic approaches culminated in a revolution in unravelling medical knowledge in general and human anatomy in particular.

We have all assimilated the works of Leonardo da Vinci (1452-1519) as prototypical of the Renaissance. Leonardo is the 'renaissance man'! Leonardo, a multidisciplinary investigator, eloquently symbolizes the most accomplished representative of the Renaissance. Indeed, he touched on all aspects of this intellectual revolution simultaneously as an artist, an accomplished painter, an engineer, an architect, and even an anatomist. He carried out numerous anatomical dissections and collected his observations on the subject. I often tell myself we can't master everything, and Leonardo is an eloquent example. Indeed, his anatomical sketches are rather simplistic, particularly when we focus on his portrayal of the central nervous system.

We would rather have to wait for the work of Andreas Veaslius (1515-1564) to really see the appearance of the first great anatomist in the history of humanity (Margoscsy, Taniloiu, 2018, 718-730). Born in Brussels, he studied in Paris and Padua (near Venice, Italy). After completing numerous human cadaveric dissections, he methodically deconstructed Galen's anatomical observations and precepts. He quickly understood that Galen, who had not carried out human dissections because of prohibitions at the time, had instead used great apes for his work and had transposed his observations to humans without validation. He then undertook to correct Galen's errors. He embarked on a systematic study of the human body by cadaveric dissection which culminated, after four years of hard work, in the publication of a monumental text entitled "De Humani corporis fabrica libri septem" (The Structure of the Human Body). This text, published in 1543 in Basel, Switzerland, spans more than 700 pages in 7 volumes and is considered a true revolution in the history of medicine. It is genuinely the first detailed descriptive work on human anatomy. The quality of the engravings found in this work was previously unprecedented. Vesalius accurately described the structures and components of the brain for the first time and made extremely precise illustrations of them. However, his work remains descriptive. He studied little and did not describe the function of any organs. In the case of the brain, as we will see a little later, this represents a significant deficiency. Vesalius' illustrations were nevertheless light years ahead of Leonardo's in refinement.

But let's get back to our story. The work carried out by Vesalius was meticulous but descriptive which limited the author to highlight the morphology of the brain. He deconstructed specific anatomical observations falsely conveyed by Galen but did not spend any time analyzing their functional or philosophical consequences. In other words, the functioning of consciousness as described by Aristotle and later refined by Galen remained. Enters René Descartes (1596-1650). After carrying out several cadaveric dissections of his own and probably inspired by the work of Galen and Vesalius, he noticed an anatomical phenomenon that had otherwise gone unnoticed by the scientific community until then: the nerves seemed connected to the brain! Galen had mentioned it without attaching the slightest importance to it. For Descartes, it was a revelation (Carter, 1983). He concluded that the nerves were 'tubes', which he believes to be hollow and probably the mediators of the transmission of information to the muscles and the organs. Descartes' reasoning was as follows: as these nerves are responsible for movements and are connected to the brain, the latter must be the mediator of consciousness, the human body's controller, and hence the soul's receptacle. Hence, Descartes dismantled Aristotle's precept, recognized the probability of a physical-psychic duality mentioned earlier in the history of humanity by Plato, and restored the brain to its rightful place. He is indeed the first, after Plato, to consider that a human being has a single and unique soul and that this soul is a distinct and metaphysical entity somehow joined to the body. Although this theory would not be embraced by all scientists of the time, we can proclaim without hesitation that it was a bold and insightful statement, and one that still animates many conversations today! In the last chapter of this work, we will attempt to address the delicate question surrounding the relationship between the soul and the brain.

You will have noticed, dear readers, that at this time of our narrative, the study of the brain was essentially limited to its morphology, appearance, and very little to its function. Aside from the different theories on the overall functioning of the brain and the mind, as put forward by Plato, Aristotle, Galen, Descartes and several other investigators, we are still very far from a coherent theory of the brain's functioning. This is because the scientists of the time still did not have the theories and technologies allowing them to initiate the type of studies which would make it possible to resolve the impasse. They were missing certain tools that are about to make their appearance. Indeed, despite the magnificent frescoes of Vesalius, which admirably reproduced the anatomical details of the brain, we still do not understand to the slightest how the brain works at this time in history. However, nothing is lost; we must start with the basics, and this base is anatomy.

Thus, the detailed anatomical study of the brain allowed Marcello Malpighi (1628-1694) to describe that it is essentially composed of white matter made up of fibres (Malpighi and Fracassati, 1665). Subsequently, several scientists studied this white matter by perfecting brain dissection techniques (Niels Stensen (1638-1686), Raymon de Vieussens (1641-1716) and Félix Vicq d'Azur (1748-1794)) (Patten, 1992, 3-14). Let's not forget that the brain is a soft tissue without rigidity, which dramatically complicates its dissection and study post-mortem (after death). You also must see a fresh brain sample to understand the extent to which brain tissue presents a substantial macroscopic homogeneity, making any research based on morphology obsolete when trying to elucidate its functioning. We must also remember that at this stage of history, neurons had not been yet discovered; hence, we had no idea of this white matter's role. The first mention of a cell located in the cortex of the brain is attributed to Antony Van Leeuwenhoek (1623-1723), who identified 'globules' in his studies of the brain's outer layer using rudimentary microscopy techniques (van Leeuwenhoek,1674,178-182). These 'globules' were none other than neurons, more precisely their cellular body!

We are now about to reach the dawn of the 19th century in our history, and a true revolution in neuroscience is about to blossom. This revolution will be launched by Franz Josef Gall (1758-1828) and his assistant Johann Spurzheim (1776-1832). Both were renowned and accomplished neuroanatomists, but that is not what history remembers them for (Ackernecht, 1958). Indeed, their first interest was directed toward the cerebral convolutions, the folds on the surface of the brain that seem practically random and, until then, devoid of any functional interest by previous investigators. After in-depth embryological studies on the shape of the brain and the convolutions, they concluded that these folds were, in fact, the seat of the different psychological abilities of the human being and that these functions were distributed according to a very precise and reproducible map, from one individual to another. For them, the brain was a collection of several modules, each representing a motor or psychological function. A 'pseudo-science' had just been born: phrenology (Greenblatt, 1995, 346-370).

Gall believed that all brain functions were REGIONALLY located in the convolutions. As the shape of the skull is closely related to the shape of the brain (we will see why later), it was hence possible to study the shape of the skull to predict the strengths and weaknesses of each person. Thus, someone displaying a particularly developed ability would have an outgrowth in the skull corresponding to the cortical representation of said ability. This is where the French expression la bosse des mathématiques comes from (literally 'the math bump'). This theory was obviously wrong. Not only was it inaccurate, but it was also used for nefarious purposes throughout the 20th century. Indeed, 'expert' morphologists in phrenology used this 'science' to classify the skulls of individuals into different social and racial subtypes. The theory of the 'born criminal' proposed by Lombroso in 1876 indeed claims an association between the 'primitive' form of the facial features and the skull and a propensity for vagrancy and criminal activities. But the most heinous application of phrenology and skull anthropometry rightfully belongs to the Nazis. Indeed, a doctrine developed by Alfred Rosenberg suggested that pure Aryans possessed distinct morphological characteristics. As such, under the leadership of Henrich Himmler, Hitler's right-hand man, anthropometry was put at the service of the Office for Racial Policy, the search for Aryan origins. The nazis, therefore, proceeded to examine and measure the skull (craniometry) to classify individuals as Aryan or non-Aryan (Finger and Eling, 201, chapter 9). What nonsense...a perfect display that science is not always used wisely!

However, this new approach still had the merit of aiming scientists onto a new path: the regionalization of brain functions. Let's not forget that until now, under the leadership of Aristotle, Galen and Descartes, the brain was still considered an organ with global functioning. Inspired by the work of Gall and Spurzheim, Pierre Paul Brocas (1824-1880) initiated a series of events which led to the development of the modern theory of the localization of cerebral functions. Broca was a surgeon and an anatomist. A practical minded man, he firmly believed that a precise anatomical structure must perform A PRECISE FUNCTION. An expert in anthropology, it was somewhat by accident that he was involved in this fascinating odyssey (Broca, 1861, 330-357). In April 1861, Broca took care of a 51-year-old patient, a man named Leborgne, who was transferred to him for terminal gangrene of the right leg.

The hospital staff called this patient "tan tan" because those were his only words. Indeed, Leborgne had been admitted to the same hospital 21 years earlier for a sudden speech impairment. Although this condition persisted, over the years, the patient gradually began to deteriorate, exhibiting weakness in right his arm and then his leg. At the time Broca received him for his gangrenous episode, Leborgne was in a deteriorated neurological state but nevertheless retained an understanding of language despite his severe expressive deficit. The patient died five days later, and understanding the interest of this 'case,' Broca immediately carried out the autopsy and the retrieval of his brain. He discovered a focal lesion involving the 'left inferior frontal convolution' (this region is now called Broca's area). Cautious, he nevertheless waited to confirm this association between a circumscribed deficit and a precise location in another patient. Being attentive to similar cases, he did not have to wait long. Six months later, a second patient, this one aged 84 and suffering from a speech deficit identical to Leborgne, was admitted under his care for a fractured femur. The latter survived his fracture for 12 days, and it was obviously with haste that Broca recovered his brain shortly after his death. Interestingly, he discovered a lesion localized in the same brain area (Broca, 1861, 330-357). Broca went on to accumulate eight similar cases in the following years, presenting kindred lesions. This methodical collection allowed him to conclude that "we speak with the left hemisphere," thanks to a cerebral area located in the inferior frontal circonvolution, which we now call Broca's area. Thus, the strongest argument for a focal distribution of functions within the brain via specialized regions was born. But that's not all.

Around the same time, in England, an English doctor named Hughlings Jackson became interested in a curious phenomenon which made him famous. Dr. Jackson was studying epilepsy and its manifestations. In some of his patients, he noticed the stereotypical pattern with which certain epileptic seizures manifest themselves, producing symptoms spreading in a wave of predictable manifestations that he called 'the march'. We now call it the Jacksonian March. (Greenblatt, 1977, 412-414). This walk describes the sequential appearance of motor manifestations linked to an epileptic seizure in the form of involuntary and repetitive movements slowly propagating from one contiguous region of the cerebral cortex to another (the cortex is the outer layer of the brain, but we will come back to this in detail in the next chapter). In doing so, the clinical manifestations of these seizures affect different body parts in an orderly and sequential pattern. Hence, the attack can start in the face, then spreads to the hand, arm and leg, or vice versa. Based on this observation, Jackson understood that this wave of propagation in symptoms reflected the inherent organization of the cerebral motor cortex (Greenblatt, 1977, 414-428). It somewhat was as if the motor cortex was organized like a reproducible map in all human beings, and those suffering from epilepsy revealed the organization of this map. Although his major contribution was in the understanding of epilepsies (we will return to this in chapter 9), he also helped to establish the notion of localization of cerebral functions. He made it possible to suspect a correspondence between the initiating site of certain epilepsies, and the arising symptoms in question. Therefore, here was a second irrefutable argument for the value of the doctrine of localization of cerebral functions. However, we remain at an anecdotal stage regarding knowledge, observing the stereotypical consequences of certain diseases and specific lesions. In order to go further than these observations, which correlated a clinical deficit with a brain lesion, certain advances and scientific refinements were still missing, but we are about to get there!

And so, towards the end of the 19th and the beginning of the 20th century, a series of observations led to a real revolution in knowledge relating to the central nervous system. First of all, the improvement of the microscope will allow the study of human tissues on a microscopic scale never before achieved. This progress will also lead to innovations in how the observed samples are dyed prior to their microscopic observation. Indeed, anyone who looks under the microscope at an uncoloured slice of any tissue specimen will understand that the interest of such an observation is somewhat limited. It is challenging to differentiate and perceive the underlying structures constituting the tissue without any contrast. This predicament in microscopy pushed certain researchers of the time to develop new colouring techniques, allowing more 'contrasted' microscopic exploration. Thus, towards the end of 1890, Camillo Golgi (1843-1926), an Italian scientist, created a colouring technique using silver salt. This technique was subsequently used by a Spanish scientist, Santiago Ramon y Cajal (1852-1934), to observe the tissues of the central nervous system. By perfecting the Golgi technique, Cajal changed perceptions regarding the function of the central nervous system forever. He was the first to observe a neuron as a distinct cell and to identify this cell as the functional constituent unit of the central nervous system (Anctil, 2015, 3-12). From there, he laid the foundation to what we now call the neural doctrine (Finger, 2001, 22-45). These two pioneers were both awarded the Nobel Prize for Medicine in 1906 for this essential discovery. The ideology of the neural doctrine places the neuron at the centre of the functioning of the central nervous system. It makes the neuron the basic unit of the neurological system. Each neuron represents the original brick forming the masterful edifice that is the brain. With this cell type now identified and described, it hence becomes possible to go further in understanding the functional organization of the brain. The neural doctrine remains the cornerstone in the application of new knowledge about how the brain functions to this day.

And it is here that another scientist, a German, will seize the opportunity and make a lasting contribution to clarify the structure and functioning of the brain. Enters Korbidian Brodmann (1868-1918), who published his detailed work on the cytoarchitecture of the cortex in 1909 (Garey LJ, 2006, 59-98). "Cyto" refers to cells and, therefore, to the architecture of the organization of cells in the different layers of the cerebral cortex. The cortex has several layers (six, usually). By precisely studying the distribution and shape of cells in each layer of the human (and monkey) cerebral cortex, Brodmann masterfully described 52 structurally distinct regions. He will postulate, without ever being able to prove it, that these regions all play a different role, serve functions that are unique and specific to them, and therefore constitute a functional map of the brain that is highly reproducible from one individual to another. This assertion will later be successfully confirmed by other investigators, at least in part. His lasting contribution to the field remains and is recognized every day in neuroscience: we still use the term 'Brodmann areas' to define certain functional areas of the brain. But how were defined these functional areas? Until now, as you have noticed, we have been limited to a descriptive study of the brain, even if this description is more and more thorough, microscopic, and precise. But what about function? How does the brain work? How is it organized? Apart from the work of Broca and Jackson, we are still far from a study of brain function, and the conjunction between a brain region and a precise function remains speculative.

This is all about to change. Neuroscience is about to enter the modern era and move to the next level, thanks largely to the neuronal doctrine, the recognition that the neuron is the fundamental unit in the functioning of the nervous system. Indeed, once the neuron has been identified, all that remains is to understand and define its function. Luigi Galvani (1737-1798) was the first to demonstrate that electricity could stimulate muscle contraction (Hoff, 1936, 157-170). In doing so, without knowing it, he founded a new field of study, bioelectricity. However, when these experiments were carried out, the neuron still had to be discovered. So, after the description of the neuron and referring to Galvani's past work, it was rationalized that the neuron was an electrically excitable cell; this had the effect of inaugurating a whole new field of research and investigation, that of functional neuroanatomy ...

Enters David Ferrier (1843-1928). As is often the case in science, Ferrier's contribution will not be the result of isolated work on his behalf but rather the logical continuation of work undertaken by other scientists (Young, 1970). Indeed, in 1870, the Germans Fritsch and Hitzig were the first to apply an electric current to the surface of the brain of living dogs to investigate the consequences (Fritsch and Hitzig, 2009, 123-130). They will thus conduct these stimulation experiments on multiple occasions, with Frau Hitzig's kitchen table as their laboratory, and in doing so, will identify and annotate the cortical sites which, when stimulated, produced stereotypical movements in their poor canine subjects. Although the work of these two young investigators was initially met with great skepticism, a young Scottish doctor of the time took it up. Using a similar cerebral cortex stimulation technique, Ferrier applied it to the study of the brains of cats, dogs, rabbits, guinea pigs, and finally monkeys (Ferrier, 1874, 766). He reported his first results in 1873, but his most significant contribution to neuroscience was published in 1876 in the work "The Functions of the Brain." In this text, he made certain inferences, comparing the monkey brain to that of a human, and extrapolated his findings to the human brain (Ferrier, 1876, 138-162).

But one can ask whether is it adequate to claim that the human brain is sufficiently similar to that of the monkey to allow such a comparison? Can we allow ourselves such comparisons and inferences? Not without objectifying the findings, at least in the spirit of the scientific method. There is only one way to know: to test it on human subjects! All that remains is to use this technique for the benefit of human brain surgery.

Here, a digression: It is interesting to mention that although the surgical discipline evolved relatively gradually throughout human history, brain surgery, for its part, took its very first step relatively late. The central nervous system (brain and spinal cord) is surrounded by several protective envelopes (chapter 3). The most important of these envelopes is undoubtedly the dura mater, a rigid layer ensuring protection of the nervous tissue against infections, among other things. At the time, if there was one certainty regarding the dura mater, it was that if a surgeon opened it, accidentally or at its initiative, this would almost invariably lead to an infection and the death of the patient. We therefore understand well the reluctance to carry out brain surgery on the part of doctors of the time. *Primum non nocere*, after all!

Consequently, the only cases operated on were those of patients suffering from significant trauma (head trauma) requiring some form of intervention. Hardly any choice in this situation. However, these interventions were rarely to the benefit of the patient and most often ended in death or some form of severe morbidity.

It was really in 1879 that the actual first neurosurgery was carried out by a Scottish surgeon named William Macewen. What did he do that was so exceptional? First, he put into practice what he had learned from one of his mentors, a certain Joseph Lister, also Scottish; he used an antiseptic technique to reduce the risk of infection. Then, based on the discoveries of Ferrier and Jackson, he did use the patient's symptoms (motor impairments and seizures) to plan his approach and the opening of the skull to remove the lesion (a benign meningioma-like tumour). This is the first reported neurosurgery combining a 'modern' localization technique, anesthesia and an antiseptic technique (Macewen, 1881, 581-583). Thus, two years after this remarkable feat (August 1881), an international medical convention took place in London. There are events that irremediably and drastically change the course of history. This gathering is undoubtedly a convincing example (Jefferson, 1950). Bringing together some of the most prominent players in emerging neuroscience of the time (Ferrier, Charcot, Osler, Jackson, Keen, Macewen, Godlee, Horsley, Lister, Pasteur, Virchow, etc.), the discussions during this meeting catalyzed a paradigm shift in the clinical approach to neuroscience, and the