ONE

ELEMENTARY PARTICLES

Before setting out on our discovery of the brain, we must first understand what makes it such a unique organ (figure 1.1). The brain weighs on average close to 1.5 kilograms (3 pounds, for males, a bit less for females) and is made up of two hemispheres, the left and the right, which play somewhat different roles. It is part of a larger whole, the encephalon, which also includes the brainstem, through which neurons travel to communicate with the spinal cord (some neurons that start at the brain and end at the base of the spinal cord are more than a meter long . . .). Although relatively small in size, the brainstem is crucial because it gathers together vital smaller elements that regulate our life (sleeping, breathing, heartbeats). This is no doubt why it is very protected and difficult to access, because if it is damaged, the result is often fatal. Alongside the brainstem is the cerebellum (the "little brain," which in fact has little in common with the brain). One of its noticeable roles is to smooth out and coordinate our movements; thanks to the cerebellum we are able to walk straight or play the piano.

The human brain is impressive, perhaps less in its size (the brain of an elephant, whose memory is legendary, is larger, at 4 to 5 kilograms [11 pounds]), than in its complexity: the human brain is made up of a large number of folds and bumps, called sulci and gyri, that are not as developed in other animal species, including the great apes. It is to the French surgeon, Paul Broca, that we owe the fundamental discovery that the two hemispheres are not functionally identical, and that the brain is an organ that, although apparently homogeneous, is made up of regions that have different functional speci-

ficities, which is not the case with other such organs (the cells of the liver all do the same work regardless of their location in the organ). This discovery opened the door to modern cerebral physiology and is at the very heart of the goal of neuroimaging: more than just producing images, neuroimaging involves the creation of maps that show the "natural geography" of these regions, and, more important, how they are implicated in the sensory-motor or cognitive functions that they underlie.

Broca's Discoveries

Paul Broca was a surgeon at the Bicêtre hospital (reference 1.1). In 1861 he had a patient, Monsieur Leborgne, who became unintentionally famous. In the hospital M. Leborgne was nicknamed "tan-tan" because he responded to questions (what's your name? what day is it? and so on) with only one syllable, "tan," which in general he repeated twice. This patient had what today is known as aphasia, a sort of "mutism," a disorder affecting the production of language, although he suffered from no paralysis of the "bucco-phonetic" muscles used in speech. After the patient died on April 17 of the same year, Broca did an autopsy and dissection of his brain. He found a lesion on it and drew two major hypotheses from this (figure 1.2), which the next day he presented to the Paris Anthropological Society: the patient's functional disorder must have been owing to the specific localization of the lesion in the brain. That lesion was toward the front, at the base of the third circumvolution of the frontal lobe, in the left hemisphere. Had the lesion been elsewhere, farther back, or in the right hemisphere, M. Leborgne would have perhaps had other symptoms, but he would not have been aphasic. This hypothesis was quickly tested on other patients. Thus was born the principle, which today has been well verified, of a direct link between cerebral localization and function, each cerebral region being associated with a specific function (motor functions, vision, hearing, language, and so on), and this all fitting together on different scales like a set of nesting Russian dolls.

The region that was affected in M. Leborgne's case is today known as Broca's area. Though the role of Broca's area in the production of language is beyond any doubt, we now know that many other cerebral areas (forming a network) are important to language. And inversely, Broca's area is also

implicated in other functions. But it remains true that the postulate of regions of the brain being associated with localized functioning is completely established today.

Broca's second great discovery was that the two hemispheres each have their own areas of specialization: language is mainly seated in the left hemisphere (the twenty or so aphasic patients of Broca all had lesions on the left). Until Broca, the two hemispheres were assumed to have identical functions, like our two kidneys or two lungs, which have exactly the same role. For the first time, then, it appeared that the two cerebral hemispheres were not identical, not functionally interchangeable. In around 85 percent of us, the functions tied to language are predominately located in the left hemisphere; for the others, they are in the right hemisphere, and sometimes the dominance is less clear, with the two hemispheres clearly participating to the same degree in the production of language. At what moment, during the millions of years of evolution, did the lateralization of the human brain appear? Is this predisposition of the left hemisphere for language of genetic origin? Is it present in the brain of the fetus and the baby before they begin to speak? Is it linked to manual dexterity? Studies in neuroimaging are beginning to provide rudimentary answers to those questions.

Following Broca's discovery there was considerable progress, because this concept had opened a true breach in our understanding of the functioning of the brain. For more than a century neurologists (and in particular those of the French school at the beginning of the twentieth century, with Pierre Marie, Jules Déjerine, Joseph Babinksi, and many others) learned a lot from their patients with cerebral lesions. They had only to closely observe the patients and their functional disorders, then "recover" their brains after their deaths to establish a link between the localization of the lesion and the functional deficit. We owe a debt of gratitude to these neurologists, excellent brain sleuths, who, from their careful and detailed observation of sometimes tiny neurological signs (a small anomaly in an eye movement, or subtle cognitive disorders brought to light through complex tests), were able to establish the localization of the lesion within a few centimeters (even a few millimeters in the brainstem). Even if the nature of the problem (for example, the blockage of a small cerebral artery by a blood clot) could sometimes be suggested by symptoms, this rarely resulted in the patient being cured, as therapeutic treatments at that time were quite limited. This conceptual approach in

which functional deficits were associated with cerebral localizations nonetheless had its limits. First, brains had to be retrieved and dissected—and not all patients died! And those that did were not systematically autopsied. In addition, the localization of the lesions was not scientifically controlled in advance but were the work of Mother Nature. Whereas some regions were very often afflicted, others almost never were, and their functional role remained unexplored. This is explained in part by the fact that many lesions are of vascular origin, and that some vessels are more exposed or more fragile than others.

The Birth of Modern Neuroimaging

A radically different approach was taken as neurosurgery began to advance in the 1950s, in particular within the school of the Canadian neurosurgeon Wilder Penfield. During surgical interventions on the brain patients were awakened during the operation (the brain, even though it is the primary nerve center, is not sensitive to pain). By touching or electrically stimulating a cerebral region, the patient could report directly on his or her sensations, such as: "my thumb is asleep." Personalized functional maps of the brain could thus be drawn for each patient to pinpoint the regions to be avoided during the removal of a cancerous tumor, or the source of epileptic seizures, in order to preserve the patient's motor or language functions. This approach for the first time enabled Broca's theories to be proven "positively" (the *expression* of functions), whereas up until then the process was "negative" (a *deficit* of functions in the patients with cerebral lesions), by eliciting expressions of the functional content of healthy cerebral regions.

It was within this context that in the 1970s modern, computerized neuroimaging emerged, a true revolution that forever changed our approach to the brain. Until then neurologists had only cranial radiography at their disposal. X-rays, discovered by Wilhelm Röntgen in 1895, at best enabled the creation of shadowgraphs of the skull upon radiographic film, the shadows being roughly classed into four types depending on their intensity: bone and calcified structures (very opaque in x-rays); water and tissues containing water; fat (not very dense in x-rays); and air (transparent). X-rays of the skull thus showed only fractures of the bone, the appearance of abnormal blood vessels, and sometimes invasive tumors on the skull, occasionally calcified tumors, but not much more. One could go further by injecting a liquid containing

iodine (opaque to x-rays) in the veins or arteries of the patient to display the vascular tree. Beyond direct afflictions of those vessels ("aneurysm": swelling of a fragment of the artery; "angioma": an abnormal proliferation of vessels; shrinking from an atheromatous plaque; blockage from a clot; and so on), one could guess at the presence of otherwise invisible lesions, such as tumors, from the fact that they displaced the normal vascular architecture[1] (figure 1.3). One could also "make opaque" the ventricular cavities, open spaces in the center of the brain that contain cerebrospinal fluid (CSF), by injecting an iodized liquid or a bubble of air (gas encephalography) into the spinal cord at the lower back. By making the patient assume acrobatic positions (to the point of standing on his or her head), the bubble of air would travel to the cerebral ventricles, then into a specific corner of those ventricles. Besides the discomfort of the method and the horrible headaches that often followed, here too, only lesions that displaced or molded the ventricular cavities could be seen. Everything else remained discouragingly invisible.

On the functional side, neurologists were able to record the electrical activity emitted by the brain (electroencephalography, or EEG). Indeed, nerve impulses that enable neurons and brain cells to communicate among each other depend on the movements of ions (atoms that have lost their electrical neutrality) such as sodium, potassium, or calcium. The movements of these charged particles represent little electrical currents that create localized electrical and magnetic fields that can be detected and recorded at a distance using electrodes placed on the scalp. But the signals, whose localization remained very uncertain, above all enabled the detection of electrical occurrences that were abnormal in their intensity, as in the case of epileptic seizures, true cerebral "electrical storms," or in their absence in the case of tumors or a localized affliction of cerebral tissue.

The First Revolution: The X-Ray CT Scanner

The lives and comfort of these patients (and their neurologists) improved dramatically with the appearance of the x-ray computed tomography (CT) scanner in 1972 (figure 1.4), thanks to the English engineer Godfrey Houns-

[1] Intracerebral angiography is widely used today, but with another objective, within an interventional framework and in connection with therapeutic practices: this is the injection in situ of materials to plug a hemorrhagic break, or of medicine to dissolve a clot, for instance.

field, who, along with Allan McLeold Cormak, received the Nobel Prize in Medicine or Physiology in 1979. This date marks a turning point: the introduction of computers into radiology (reference 1.2). The brain would finally become visible without having to open the skull. First, classic radiographic film was replaced by x-ray-capturing sensors linked to a computer. Thus, instead of the four nuanced shadows detectable by the eye of the radiologist, the computer, through the sensors, could see hundreds. And so nuances between shadows produced by a healthy brain and those coming from lesions, or even different structures of the brain, could then be detected. Above all, instead of projecting a single dimension of shadow, the brain could be scanned under dozens, even hundreds, of different angles. This was made possible by the extreme sensitivity of the sensors and the digitization created by the computer: the dose of x-rays needed for a projection was infinitely reduced compared to classic radiography, which allowed the number of scans to be increased while keeping radiation at a low level.

Cormak showed that it was possible to combine these multiple projections, adding them to the computer's memory, to reconstruct, point by point, the entire picture of what was shown by the x-rays of the skull and its precious contents. The last step was to transform the virtual image into a real image by projecting it onto a screen (this general principle, moreover, was later used in future imaging methods that did not use x-rays). In CT scanning, scanning by x-rays is carried out on a plane (by turning the x-ray scanner around the head of the patient); the image obtained is thus that of a "slice," perpendicular to the axis of the head. In that slice (figure 1.4), one sees cutaneous structures, the bone of the skull with the tiny details of its internal structure, such as the external and internal bony parts of the skull, but above all, and for the first time, the interior of the skull, that is, the brain, the intracerebral ventricles, of course, and any lesions that might be found there—without an autopsy, without dissection, without pain or injury. The patient just lies down for a few minutes in the scanner and his or her brain is virtually dissected into slices by an x-ray beam.

The revolution is complete, and not only on a technological level. Radiologists, used to simple shadows, see much more than they did with their own eyes: and so they must learn to regulate the levels of contrast in the image in order to enhance a given structure. One speaks of "windows" of contrast, for it is indeed a matter of seeing, with the human eye, only a small bit of the

landscape seen by the computer, by choosing the position and the width of the windows. Depending on that choice, the appearance of images can vary enormously, some windows allowing the details of the bones of the skull to appear more clearly, others the cerebral structures. Most important, at the beginning practitioners had to learn to think in terms of slices and rethink the entire three-dimensional (3D) anatomy of the brain learned during long years in anatomy classes and during dissections. Atlases of "tomodensitometry" (another name for computerized x-ray scanning) were created. For neurologists it was also a great surprise, a dream come true, but also from time to time disillusioning when they sometimes discovered that the localization of the lesion revealed from an in-depth analysis of the symptoms of their patient was not at all the same as the one revealed by the scanner . . .

With x-ray CT scanning it became possible, in the treatment of a living patient presenting neurological symptoms, and thus when there was still time to prescribe a treatment, to reveal the presence of a lesion, localize it, and understand its impact on neighboring functional regions, and even sometimes to specify its nature depending on how it was shown in the image. One could also again inject an iodized liquid or another contrasting agent to accentuate the distinction between healthy and abnormal tissue. Such an agent, opaque to x-rays, is distributed in the vascular network, even into the smallest capillaries. A lesion with many vessels, such as a tumor, is thus clearly apparent (figure 1.4). One could also follow the evolution of a lesion in time, in particular to monitor its progression or shrinking following treatment. But the eye of the scanner sometimes sees too much, lesions that one doesn't know what to do with, that one can't explain, fortuitous discoveries during research into another lesion. And some visible lesions, alas, remain without precise diagnosis and remain "nonidentifiable objects," and above all without treatment.

In not much more than a dozen years the CT scanner began to appear in hospitals, and in another dozen it began to be systematically integrated into the healthcare system. Anecdotally, when I was a medical resident in 1980, it had been strongly recommended that we not speak of the CT scanner in our reports, so we would not be called doctors of science fiction! And yet, at about the same time that the CT scanner appeared, another revolution was brewing, that of magnetic resonance imaging, or MRI, the premises of which

were published in 1973 in the journal *Nature* by the American chemist Paul Lauterbur (reference 1.3). It took this extraordinary technology even longer to penetrate the medical world, as some renowned scientists "didn't believe it." Lauterbur didn't receive the Nobel Prize in Medicine, by the way, until 2003, along with the English physicist Peter Mansfield.

Nuclear Magnetism

The physical principle of MRI is radically different from x-ray CT, because rather than x-rays, a magnetic field and radio waves are used. They still have something in common, however: the marriage of a technology that creates signals in order to expose a contrast between different biological tissues, and computer science, to reconstruct images from those signals, images that are again in the form of slices. An MRI scanner is also a cylinder in which the patient is placed lying down (figure 1.5). The heart of the system is a very large magnet that produces an intense magnetic field, several tens of thousands times greater than the Earth's magnetic field—the one that orients the needles of our compasses.

Why is such magnetic intensity necessary? Because we are dealing with nothing less than the magnetization of the nuclei of atoms. Whereas the x-rays of a CT scanner interact with the electrons that surround atoms, the MRI goes to the atomic nucleus. That nucleus is made up of particles—protons and neutrons. The simplest possible nucleus is made up of a single proton; it is the nucleus of the hydrogen atom, which will be the hero (along with the water molecule in which it is found) of the rest of this book (alongside the brain, of course). Placed in a magnetic field, the proton in question is magnetized. In physical terms, it is said to possess a "magnetic moment," that enables it to be oriented in the direction of the field, a bit like the way the needle of a compass reacts in the Earth's magnetic field. But the analogy stops there. We are in the world of the infinitely small where quantum physics rules,[2] a world very different from our own. In fact, protons can line up in the direction of the field, or in opposing directions, the number of protons in each orientation depending greatly on the intensity of the magnetic

[2] Quantum mechanics is the branch of physics that describes fundamental phenomena at work in physical systems on an atomic and subatomic scale.

Box 1. A Subtle Equilibrium

Nuclear magnetism derives from the movement of charged particles (positive or negative) within atomic nuclei—"quarks." A proton (nucleus of the hydrogen atom) contains three quarks, which give it curious properties. Unlike our compasses, the proton can in fact be oriented in two ways in a magnetic field—in the direction of the field, or in the opposite direction. At very low temperatures, all protons line up in the direction of the field in a stable position of "rest," but as soon as that temperature changes, protons, due to thermic agitation, gradually move into the opposite position, which for them also represents a certain stability. Indeed, the position of rest is very fragile, and it takes only a minor change for the magnetization of the proton to move into the other direction. The balance between the two positions depends on temperature and the intensity of the magnetic field. In the terrestrial field, at the ambient temperature or at 37°C, the temperature of the brain, one finds approximately the same number of protons oriented in each direction, the difference being that two protons in a billion are oriented more in one direction than in the other. The resulting magnetic moment (that is, the overall magnetization of all the nuclei) comes uniquely from that infinitesimal difference, because the protons in opposite orientations reciprocally cancel out their effect. With stronger magnetic fields, that difference is accentuated, and the resulting magnetic moment increases.

field, and the overall magnetization being determined by the difference in the number of protons in those two orientations (see box 1).

In a magnetic field of 1.5 tesla (the "tesla" is the unit of measurement of the magnetic field; 1 tesla representing 20,000 times the strength of the magnetic field in Paris, for example), this difference is 50 protons per 1 billion, and at 3 teslas, it rises to 100 per 1 billion, which is still weak, but begins to make a difference. The first MRI magnets operated at fields of 0.1 to 0.3 tesla, but most of the magnets intended for MRI scanners used in hospitals today produce fields of 1.5 or 3 teslas. Not all atomic nuclei can be magnetized. In particular, those made up of an even number of protons and neutrons do not have a magnetic moment, their magnetic effects are nullified within the atomic nucleus. Unfortunately, included in these are carbon ^{12}C and oxy-

gen ^{16}O, nonetheless key atoms in living matter.[3] This is why we generally resort to the hydrogen atom for MRI, because hydrogen comprises two-thirds of the water molecule (H_2O), which is abundant in the human body: more than 80 percent of the brain mass is comprised of water. Since there are around 30 millions of billions of water molecules, it begins to matter even if only 100 per 1 billion contribute to the observable magnetic moment. MRI is thus above all a story of water.

The Nuclei Enter into Resonance: From NMR to MRI

What are we going to do with this magnetized water (via its protons), which nature graciously puts at our disposal? This is where the concept of nuclear magnetic resonance (NMR) comes in, a concept that was introduced independently by the Americans Felix Bloch and Edward Mills Purcell in 1946, which earned them the Nobel Prize in 1952. The idea that is hidden behind NMR is that one can voluntarily "force" the orientation of the magnetic moment of atomic nuclei by entering into resonance with them, and thus modify their overall magnetization, by giving them the necessary energy in the form of radio waves of a very precise frequency (see box 2).

NMR continues to be enormously useful in physics and chemistry because nuclei inform us about their local environment, on an atomic scale. Indeed, these nuclei belong to atoms found in molecules (water for the hydrogen nucleus, but also many other complex molecules that contain hydrogen, such as amino acids, proteins, or DNA, to cite only molecules of biological interest). This environment upsets the local magnetic field perceived by the nuclei (mainly due to electrons present in the molecules, also carriers of magnetic moments), which is translated by small variations in the frequency of resonance of the waves reemitted by the nuclei. By carefully analyzing these waves, we can identify the frequencies, and deduce the molecules in which the nuclei are found, in what quantity, indeed even in what part of those molecules, at what distance from other nuclei, and so on. Last, with NMR spectroscopy we can reconstruct the three-dimensional structure of molecules as well as their temporal dynamics, a technology that earned Richard Ernst the Nobel Prize in Chemistry in 1991. NMR spectroscopy quickly appeared as

[3] "Exotic" variations (isotopes) such as carbon 13 (^{13}C: 6 protons, but 7 neutrons) or oxygen 17 (^{17}O: 8 protons and 9 neutrons) are magnetizable, but they are found in nature only in trace amounts.

Box 2. Atomic Tuner

The equilibrium between two orientations can be upset by an effect of resonance with radio waves—this is the principle of NMR. Radio waves, like light, are electromagnetic, but they can also be described by an elemental particle, the photon, carrier of a very determined amount of energy depending on the frequency (like a "color" for visible light). When an oriented proton absorbs a photon that has the right quantity of energy, it becomes "excited," and shifts to the opposite orientation. For the proton, the frequency of resonance is 42.6 megahertz (MHz) in a magnetic field of 1 tesla. All of this of course involves a very large number of protons. In this process, the energy absorbed is in large part restored, again in the form of photons—that is, radio waves of the same frequency that one must capture by means of an antenna and a radio receiver. The signal received is then amplified. Initially, its intensity directly reflects the number of magnetizable nuclei present—in this case, the number of protons and thus water molecules. Because the wave frequency depends on the nuclei, one can simply set the radio receiver at the right frequency to change the nucleus—if it is no longer hydrogen (and water) that one wants to study—exactly like choosing one's favorite station on a radio! At 1 tesla, the frequency is 42.6 MHz for the hydrogen nucleus, 40 MHz for the fluorine nucleus, and 17.2 MHz for the phosphorus nucleus. After a short time (called "relaxation" time), nuclei are de-excited and return to their original orientation. The energy is dissipated in the medium and the signal disappears.

an extremely powerful technology for physicists, chemists, and biochemists, more recently for biologists, and ultimately for physicians.

The principle of MRI (imaging through NMR) took root much later in the mind of Paul Lauterbur, in a fast-food restaurant in Pittsburgh, and became concrete through his scribbling on a paper tablecloth. Lauterbur, who had started his career as a chemist at home with a "junior chemist" set, had become familiar with NMR during his military service, which, thanks to his chemistry degree, he fulfilled as a member of the scientific staff. In an attempt to be transferred to a laboratory other than the one where he had first been assigned (developing chemical weapons . . .) he claimed that he knew about NMR. Lucky for him—and for us—that he did. Since the frequency of the

Box 3. The Brain Practices Scales

Resonance is also at the heart of MRI imaging. Here, one chooses the frequency of a nucleus (in general the hydrogen nucleus), but the magnetic field is varied slightly in a given direction. This "gradient" in the field induces a gradient in the frequency of resonance along a given direction, a bit like how the notes of a piano keyboard go from low to high. In each spatial position there thus corresponds a given frequency, just as with each key of the piano there corresponds a note. If a chord of several notes is played, we can, by listening to the sound (and being a bit of a musician), make out the keys (notes) that were played in the chord, and even the respective intensity with which they were struck. This is exactly what is achieved with MRI: the radio waves reemitted by the brain are made up of a superposition of multiple resonance frequencies of protons, according to their localization in the brain. One can find these frequencies, and for each one of them, their intensity linked to the number of implicated protons, by decomposing the global signal received with a mathematical operation called "Fourier's transformation" (what our ear naturally does for piano chords!). To obtain an "image" (that is, the number of protons implicated for each position in a slice of the brain, and no longer a projection in one direction), it is necessary to carry out the operation many times, by varying the direction of the gradient in space within the slice. We can then combine these signals to obtain an image representing the magnetization of the protons at each point of the brain. This is the fundamental principle of MRI, although many variants and improvements are used today to advance the method.

resonance of waves emitted by the nuclei depends on the magnetic field, his idea was to have the magnetic field vary progressively and in a controlled space (we speak of "gradients" in the field) to determine the spatial origin of the radio waves emitted by the nuclei of the object under study: for each position along the gradient of the field there is a corresponding frequency (figure 1.5); we can then obtain a map of the magnetization of the nuclei at each point in space—that is, an image (see box 3).

The first objects Lauterbur studied were a shell that his daughter had found on Long Island, a pepper, and tubes filled with water. The article he then wrote was rejected by the famous journal *Nature* because the images

were too blurry. Lauterbur fought with the editors, and the article, which became a great classic, was finally published. Lauterbur later wrote that the entire history of science of the last fifty years could be written with the articles rejected by the prestigious scientific journals *Nature* and *Science*. Moreover, the idea of these "gradients" in the field had already been introduced by the French scientist Robert Gabillard twenty years earlier, but his work had remained unknown. Lauterbur was unable to convince his university (New York University at Stony Brook) to patent his invention (which he called "zeugmatography") in order to market it, which was a huge strategic mistake (the MRI market was estimated at close to 5 billion dollars in 2011). It took him almost ten years to obtain funds from the American government to construct a first prototype. During that time other processes to encode the spatial origin of NMR signals in an object, and thus to create images, were developed, without having to "turn" the gradient in a great number of directions. In particular Peter Mansfield of the University of Nottingham borrowed Lauterbur's idea and improved it by introducing a process of very rapid encoding and localization of signals. It then took another fifteen years for that improvement to be routinely available, but his university had taken out patents, and Mansfield, who became rich, was knighted by Her Majesty.

We must emphasize the real weakness of the energy from radio waves that creates the resonance of atomic nuclei. Those waves have nothing to do with nuclear energy, even if they involve atomic nuclei, and also remain very inferior to those associated with x-rays and radioactivity. Since there is no radioactivity or radiation involved, and in order to avoid any confusion in the public's mind, our legislators proposed dropping the term "nuclear." Thus was born "magnetic resonance imaging," or MRI.

The Anatomy of an MRI Scanner

The key to MRI is thus this "gradient," this spatial variation of the field, which enables us to record, to encode the spatial origin of NMR signals. It is obtained through coils of copper wire through which a very intense current passes in a very short amount of time. The position of these coils enables the superimposition on the main field (intense and very spatially homogeneous, created by the main magnet) of another, much smaller field, but one that

can be varied in three spatial directions. A basic MRI scanner is thus made up of a large magnet (in general in the shape of a cylinder) within which are placed the coils, and antennae to emit and receive radio waves. It is an assemblage whose dimensions are optimized to diminish the related costs. In other words, in the machine there is only the room necessary to place the object of study—in this case, the head of the patient (figure 1.5).

In order to produce intense magnetic fields over a large volume, a specific technology is required. Permanent magnets (like the ones we find on our refrigerator doors) can produce only limited fields (at most one- or two-tenths of a tesla) and are rarely used for MRI. Therefore, one resorts to the technology of superconducting electromagnets. Superconducting materials, such as an alloy of niobium and titanium, enable the passing of very intense currents (several hundred amperes are necessary to reach fields on the order of tesla over large volumes) because they offer no resistance to the current if they are cooled to a temperature of –269°C, which can be done by plunging the magnet into a bath of liquid helium. Superconductivity is also a recent discovery in the quantum properties of matter (it has generated no fewer than twenty Nobel Prizes since its discovery by Kamerlingh Onnes in 1911). It enables the current to circulate without any loss of energy: provided the magnet is cooled in liquid helium, it can produce its magnetic field *ad eternam*. Thus, the field is present even when the scanner is off, which necessitates some precautions when someone enters the room where it is located.

Another fact about MRI scanners is that the room where the magnet is placed must be shielded with copper, a Faraday cage: as we know, a simple shield or screen (such as that in a concrete tunnel) is enough to ruin the reception of our car radios. It is not like a lead screen used to limit the *escape* of x-rays from an x-ray scanner beyond a room to avoid any unwanted irradiation; rather it is an electromagnetic screen that prevents radio waves from *entering* the room and polluting the MRI signals. Indeed, the energy in play is very weak, and the signals produced by the protons of the brain are of the same order, if not inferior, to those emitted by hertzian radio, television, or telephone waves, and so on: at 1.5 tesla, the waves emitted by hydrogen nuclei have a frequency of 64 megahertz (MHz), and at 3 teslas, 125 MHz—a range of waves similar to those emitted in radiophonic transmission. If we don't want to transform the MRI scanner into a very expensive radio, we

must protect its antennae from neighboring waves in order to capture exclusively the waves emitted by the atomic nuclei of the brain—and not the greatest hits.

In practice, an MRI exam consists of sending small bursts of radio waves into the hydrogen nuclei of the brain, then "listening" to the signals reemitted by those nuclei (by storing them in a computer memory), while alternately pulses of current are periodically sent to the gradient coils to localize the signals within the brain, all of this being organized extremely precisely and rapidly (dozens, indeed hundreds, of times per second). It is thus a true musical score (one speaks moreover of a MRI *sequence*) that the computer must play with the electronic equipment of the MRI scanner, after programming by the technical team.

Those who have already undergone an MRI exam know how noisy the scan is. Indeed, the very intense magnetic field produced by the main magnet contrasts with the small fields of localization produced by the gradient coils and subjects them to very great force. They are then subjected to mechanical vibration, which generates a sometimes very intense noise against which the subject must be protected. The type of noise generated depends on the MRI sequence; it goes from jack-hammering to more musical sounds of variable frequencies, because the sequence is very rapid. Some of my colleagues have even managed, temporarily, to convert MRI scanners into true (but unpleasant) musical instruments.

The Crystal Skull

In short, MRI involves placing our precious brain in the center of this gigantic magnet so that the brain's atomic nuclei can be instantaneously magnetized. The technician in charge expertly plays with the magnetization of the hydrogen nuclei by means of appropriate bursts of radio waves, and captures the resulting waves emitted in return by those nuclei in the central memory of the scanner's computer. There, "reconstruction" software sorts the waves in function of their original localization (the computer knows the map of the magnetic field programmed by the technician). We then have a latent image, a map of the magnetization of the hydrogen nuclei of the brain, which remains only to be projected onto a screen.

The x-ray scanner had trained the radiologist to see many details in the structures of bones. Indeed, x-rays interact with the electrons of atoms, and bone is very rich in calcium which, with its twenty electrons, greatly inhibits x-rays. Soft tissue such as the brain, 80 percent of which is water, is almost transparent to x-rays (hydrogen has only one electron). In MRI, it is just the opposite: one sees "soft" tissue very well, since the signal comes almost exclusively from the magnetization of the hydrogen atom of water. Bone gives little or no signal because it contains very little hydrogen. With MRI, it is thus the skull that becomes transparent . . . a crystal skull that suddenly lays bare the brain it protects and whose secret it has guarded up to now, offering its deepest recesses to our indiscreet look (we will see later that this term is not inappropriate!) with unprecedented precision.

Fat, such as that contained in the scalp or between the internal and external walls of the skull, rich in hydrogen atoms, also emits a strong signal. The MRI image is indeed foremost an image of the density of the tissue's hydrogen atoms. The images are extraordinary, very detailed and very contrasted (figure 1.6). For the first time we can clearly distinguish the gray matter that covers the brain from the deeper white matter, a distinction that is very difficult to make with the x-ray scanner. The difference in the density of hydrogen (or in the amount of water) between these two tissues is, however, very small—less than 10 percent. What is the origin of this new contrast, then?

We must look to another of the MRI pioneers, Raymond Damadian. This professor at the State University of New York (SUNY) Downstate Medical Center recounts how he was suffering from stomach pain and that he feared it was cancer. He thus sought a means to reveal the cancer in his abdomen, without having to be opened up, by using NMR. At the beginning of the 1970s MRI had not yet been born, nor had the x-ray CT scanner. However, Damadian had an interesting hypothesis (reference 1.4). An NMR study of samples of cancerous tissue had revealed an intriguing phenomenon. NMR signals are ephemeral: after having been rattled by radio waves, the magnetization of hydrogen atoms of water in tissues "relaxes"—that is, it spontaneously returns to its initial value of equilibrium. The time of that return is called "time of relaxation T1."

Now, it seemed at that time that the magnetization of cancerous tissue returned more slowly to a state of equilibrium than did normal tissue, having

a longer T1 than that of healthy tissue. Roughly, the time of relaxation T1 reflects the interactions between the magnetization of the nuclei under study and the chemical environment in which they are found. In pure water, the molecules don't have much to encounter and their T1 is very long (a few seconds). In biological tissue that contains a large number of diverse molecules, the T1 of water is around 3 to 6 times shorter, but cancerous tissue in general has a longer T1 (that tissue swelling with water due to edema), whence Damadian's idea to measure the T1 of the hydrogen nuclei of his stomach. In 1972 he applied for a patent for a machine based on that principle, but one that used a procedure of localization of the NMR signal through focalization and scanning of the area point by point, which was much different and much less effective than Lauterbur's method that led to MRI. Seven years later he obtained a first image with his scanner (which he called *Indomitable*—nothing to do with the French nuclear submarine of the same name), but this was after Lauterbur and Mansfield. However, Damadian always considered himself one of the inventors of MRI (his machine is on display at the National Inventors Hall of Fame in Ohio and his supporters were extremely disappointed to see that the Nobel Prize for the MRI was not granted to him in 2003). However, in the meantime he had founded the company FONAR to exploit his patent and make MRI scanners, fighting with other builders whom he accused of stealing his patent. He thus won $129 million in the famous lawsuit that he brought against General Electric in 1997.

Today we know that the lengthening of T1 in cancerous tissue is not specific to cancer, that lengthening translates rather as an inflammation of the tissue and its infiltration by water (edema), which infuses the tissue with more liquid, thus accounting for a longer T1. But it remains true that the incredible contrast that one can see in MRI images comes principally from the difference in the time of relaxation between the tissue, in function of its composition. Thus, the times of relaxation of cerebral gray matter and white matter are very different, due to their different compositions, even if we are today incapable of explaining exactly why that is so by means of physical or mathematical models. Images produced by MRI scanners do not depend so much on the tissue's content in protons (and thus in water), but rather on the time of relaxation of that tissue, T1, but also T2, another time of relaxation that translates the duration during which the waves emitted by the hydrogen nuclei remain synchronous, which also depends on the nature of the tissue.

The technician in charge of the exam can thus adjust and manipulate this contrast as needed by altering the magnetization and demagnetization of the nuclei.

The so-called white matter can easily appear grayer or whiter than the so-called gray matter! The names "white" and "gray" were first assigned due to the way the tissue looked under the microscope after it had been altered with the chemical fixers of the time—they lose all meaning with MRI. Other structures, such as the small blood vessels or the clusters of neurons at the center of the brain or in the spinal cord (called "gray" nuclei) (figure 1.6), appear clearly, with unequal precision, the resolution of images today reaching a fraction of a millimeter. Compared to the brain sections obtained through dissection, MRI images often appear even a bit more detailed, but with this very great difference: the owner of the brain has spent only a short time lying in the magnetic field of the scanner . . . and has left with his or her brain intact!

Thanks to the progress achieved in the technology of the antennae used in MRI, the gradient coils and the memory capacity of computers, images can be acquired in great numbers and very quickly, at the rhythm of several images per second, which enables us to study dynamic processes, such as the beating of the heart or the movement of the intestines. These images are now routinely obtained in hospitals (at present more than 30,000 MRI scanners have been installed around the world, around 30 for 1 million inhabitants in the United States), and several million exams are performed every year.

In seeing the fantastic images of the brain provided by MRI, it is easy to forget that they are not real sections, but indeed virtual sections emanating from an ephemeral magnetization of the water of the brain, revealed by its passage through an MRI scanner (upon exiting the scanner, the magnetization disappears immediately and entirely, of course), images of very subtle and sustained magnetization of the protons that make up its water molecules. But those protons and water molecules, by being magnetized infinitesimally and then relaxing, reveal many secrets of the structure and the functioning of our brains, as we will discover in the following chapters.