Chapter 20
How MRI Makes the Brain Visible

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20.1 Progress of Imaging to Investigate the Anatomy of the Brain

It is fair to say that medical imaging started with Roentgen (1896), who got the first Nobel Prize in Physics in 1901 for the discovery of the X-ray. With X-rays, images of the inner body could be obtained for the first time, opening the way to the field of "radiology". However, with radiography mainly bones could be visualized due to their high calcium content, whose many electrons efficiently interact with X-rays. Over time some tissues or organs could be identified on radiographs, such as the lungs, mainly due to improvements in film sensitivity, but radiologists had to deal, rather successfully, with organ shadows more than real images of the organs, sometimes using tricks, such as the injection of iodine-based contrast agents filling vessels or organ cavities to make their shape readily visible.

The second big discovery came when it became possible to really see "wet" tissues, organs of the body, not only dry bones or organ shadows, by combining X-ray systems with sensors and computers, so-called "computed tomography" or CT. It was invented by Dr. Hounsfield (1973) who shared the Nobel Prize in 1979 with Dr. Cormack. The revolution was two-fold. First, the brain became visible within the skull for the first time in patients, completely noninvasively. Second, radiologists had in front of their eyes not projected shadows on a film, but virtual slices of the

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organs which they could manipulate on a computer screen, revealing some contrast features in tissues, normal or diseased. But this also means that radiologists who until then had to mentally reconstruct organ three-dimensional anatomy, most often from antero-posterior body projections, had now to reconstruct space from transverse slices of the body, a real cognitive revolution for them.

That was, however, still not enough. Although it was possible to see some lesions, such as tumors in the brain, the structure of the brain itself could not be seen with great details, nor to say brain function. Along the way came Positron Emission Tomography (PET) which could provide some functional or metabolic images of the brain throughout the injection to the patients of short-live positron emitting tracers made using a nearby cyclotron (Ter-Pogossian et al. 1975). The images were generated using CT mathematical algorithm, but the spatial resolution of the images was too coarse to evaluate brain anatomy, and the making of dedicated radioisotopes was not trivial. Very recently though, PET has undergone a spectacular revival in medicine due to important technical improvements. Ultrasounds can also be used to make precise images of the inner body, but not so much in the brain which has always tried to keep its secrets under the protection of the skull, a serious obstacle to mechanical waves.

Then came Magnetic Resonance Imaging (MRI). With MRI, we can finally see the brain in great details because of a radical shift in the nature of the interaction between the physical mean used to produce images and the biological tissues. With MRI a very strong magnetic field is first used to magnetize water molecules, more precisely, the nuclei (protons) of the water hydrogen atoms. This is a perfect match for medical imaging, compared to X-rays, as our body organs are made of 70% water, even more in the brain. The hydrogen nuclei magnetization properties of water in the brain is not the same for white matter, grey matter or blood vessels. This magnetization can be revealed by using common radiowaves through the Nuclear Magnetic Resonance (NMR) principle, based on quantum mechanics, which was devised by Bloch and Purcell (1952 Nobel Prize) and is commonly used in physics and chemistry. However, the wavelength of the photons associated to those radiowaves is way too large (in contrast to X-ray photons) to allow any fine localization suitable for imaging. The trick to localize the nuclear magnetization is to make the magnetic field to vary in a controlled manner in space (and time) through so-called magnetic field gradients which modulate the frequency of the radiowaves in space (and time) (Lauterbur 1973). Nuclear magnetization, thus, becomes spatially encoded and computer algorithms can produce images showing the spatial distribution of water hydrogen magnetization properties, that is Magnetic Resonance images. Dr. Paul Lauterbur, a chemist, and Sir Peter Mansfield, a physicist, were awarded the Nobel Prize in Medicine in 2003 for their invention of MRI.

By manipulating the magnetization of water molecules, tailoring radiowaves, radiologists are like magicians which can create at will contrasts between tissues within the body and notably the brain. Engineers have greatly improved technical features of MRI scanners, so it is common nowadays to see the blood vessels with amazing details within the brain, or visualize the beating heart or respiration. The brain is finally revealing its detailed anatomical structure with submillimetric reso-

lution in 3 dimensions completely noninvasively. The images can be very impressive, mimicking photos from real brain specimen. We should not forget, however, that those images are only virtual, magnetic avatars of brain water, not real anatomy. Parts of the brain may get heavily distorted or even vanish in some patients when the magnetic field is perturbed, for instance by iron-containing mascara present on eye lids.

The advent of CT and more importantly of MRI was a revolution because it became possible, for the first time, to investigate the brain of patients where they were still alive, and not through dissection post-mortem, a tremendous revolution for health care, of course. Those images have confirmed the existence of a strong link between a lost function and the localization of a lesion, as first envisioned at the end of the nineteenth century by French surgeon Paul Broca with his famous patient suffering from aphasia (Broca 1861). Brain MRI has completely changed the way we can study the brain, normal or diseased.

Because MRI does not use any ionizing radiation, we can obtain images without any danger of fetuses during pregnancy and get images of the developing brain. Neurons are produced at a very high rate during pregnancy, up to 250,000 neurons per minute, to reach a capital of about 100 billion neurons at birth. MRI reveals how the brain shape evolves when neurons produced at the center of the fetal brain migrate to the future brain surface which becomes more and more complex, with sulci and gyri, as it must accommodate such a large number of neurons. MRI studies can thus be used to collect large amount of data which can infer or confirm theories about brain development, and the interactions between genes and environment. Indeed, although humans share many features in the brain anatomy there are large differences between people if we look at their brain in details.

For example, the location, length and shape of the central sulcus can vary a lot, sometimes by as much as 1.5 cm. We do not understand yet the exact mechanisms (and reasons) of this variability. Our genes are probably partly responsible, but there could also be mechanical reasons occurring during brain development. Another famous example is the brain of taxi drivers, at least London taxi drivers, where a study was carried out. London taxi drivers are trained hard for 2 years, navigating in the streets of London. Amazingly, the size of the hippocampus, our inner GPS, is bigger in those taxi drivers than in the common population (Maguire et al. 2000). It means that by practicing navigation, taxi drivers shape and increase the size of their hippocampus. Pianists for whom coordination between the two hands is very important have a little more gray matter (which is interpreted as containing more neurons) in the related parts of the brain (Gaser and Schlaug 2003, Parsons et al. 2005). Of course, those changes are tiny, not directly visible on the images at naked eye, but revealed by artificial intelligence computer algorithms which compare the MRI images of those brains with databases of MRI images collected in large cohort of normal subjects or patients. Time may come in the near future when such "phrenology" algorithms may reveal to us or others some intimate features of our personal life or genetic imprints on our brain from MRI images, which rises important ethical issues. From those studies, it is easy to see that that we deeply and specifically modify our brains depending on our life and history. Indeed, plasticity can change

the anatomy of our brain very rapidly. A study has shown that in young subjects who got trained to juggle balls for a few weeks some parts of the brain had already developed, mainly in the regions of the brain involved when visualizing movement in space (Draganski et al. 2004).

20.2 Imaging Brain Function with Functional MRI (fMRI)

Plain MRI reveals exquisite details about brain's anatomy, but what about brain function? For many years, one way to see the brain working was through awake patients in the neurosurgery suit, simulating parts of the brain through electrodes. This approach is still currently used today by neurosurgeons after awakening their patients to very precisely determine the location where they have to perform their surgery to avoid functional damages. Looking at the activity of brain regions without opening the skull has been a dream. This dream has come true with functional MRI. Brain activity and blood flow are closely linked (neurovascular coupling hypothesis) as was suggested at the end of the nineteenth century by Roy and Sherrington (1890): Regions of the brain where there is activity have an increased energy demand and increased blood flow: If we have a way to see local changes in blood flow in the brain, we will have a chance to see its activity. Indeed, MRI can be made very sensitive to blood flow variations. Blood are made of red blood cells which contain hemoglobin, a complex molecule which hold an atom of iron. The magnetization status of the iron atom within the strong magnetic field of the MRI scanner depends on the oxygen load of hemoglobin. In short, one may consider that hemoglobin-filled red blood cells travelling in small blood vessels become tiny flowing magnets in the magnetic field of the MRI magnet, which will change locally the magnetic field around those vessels. The nearby water molecules are sensitive to those changes in the magnetic field, and their magnetization will change. The effect is tiny, but again, with dedicated computer software, one can produce images reflecting those changes in the water magnetization near the vessels occurring in the regions where the brain has been activated (Ogawa et al. 1992; Kwong et al. 1992; Bandettini et al. 1992). This is really a wonderful discovery which was made by Seiji Ogawa who called his method "BOLD" for Blood Oxygen Level Dependent (Ogawa et al. 1990).

BOLD fMRI is easy to perform and very powerful. For instance, when asking someone placed in complete darkness in a MRI scanner to just think about a cat or another animal we can see on the fMRI images that their primary visual cortex gets activated from the changes in the magnetization of the water molecules there, revealing the implication of the primary visual cortex not only to see the real world but also our mental images (Klein et al. 1990). Consequently, it was observed by Sadato et al. (1998) that congenitally blind people reading Braille with their fingers also activate their primary visual cortex. This means that literally they "see" and read with their fingers. From this result, one may consider that there are local circuits in the brain that are genetically programmed to perform generic, low-level

basic tasks used to process information coming from various inputs. Yet, the way we use them varies from person to person, depending on how those basic circuits are connected. Blind people have the visual circuits, but they are connected differently because they do not receive visual inputs. For normal people, the connections are mainly with the eyes (but not specifically, as activation from fingers appears after a few days of Braille reading practice), while for blind people the connections are with other senses, touch from the fingers or audition from the ears.

We can see even further into our brain. The visual cortex is retinotopic: If we look at a vertical flashing bar, we activate the visual cortex in a particular way, different from the way activated by looking at a horizontal object, and this is visible on fMRI images. As it has been shown that real and mental vision shares some circuits it is not so surprising to see that similar pattern differences are observed in fMRI images when subjects in total darkness just think about a vertical or horizontal bar. Indeed, we can predict with high success which orientation subjects were thinking about, horizontal or vertical, when the MRI images were acquired. With high resolution fMRI it has now become possible to "read" on the visual cortex of volunteers the activation patterns produced by their imagination of alphabetic letters. With little training computer algorithms can decode such patterns and reveal those letters with incredible accuracy.

The potential of this "mind reading" ability is enormous. Owen et al. have shown amazing fMRI images obtained in a young lady who was in a vegetative state because of a car accident (Owen et al. 2006). Once installed in the scanner the team asked the patient "What is your name?" While, of course, no response could be observed physically, the fMRI images revealing that her language Broca's area became clearly activated, implying that this lady had understood the question and responded in her mind. To the question "Could you think that you are playing tennis?" or "Could you imagine you are navigating into your house" fMRI showed activation of regions which are activated in normal people performing the same thinking tasks. Similar results have been found in 15–20% of the patients in a similar state, opening the way to cognitive interactions with those patients.

20.3 Imaging Brain Tissue Microstructure with Diffusion MRI (dMRI)

Diffusion MRI is a specific imaging modality on its own, which has its early roots in the 1905 physics PhD thesis of Einstein on molecular diffusion (Einstein 1956). Einstein showed that the diffusion process, known macroscopically from the Fick laws, was, indeed, the results of microscopic Brownian motion of atoms and molecules, proving indirectly the existence of those atoms and molecules, the existence of which was only a hypothesis at the time. In 1985 it was shown that MRI could be used to produce images of Brownian motion and water molecular diffusion (Le Bihan and Breton 1985). The spatial resolution of MRI images is around

millimeters, far from the scale which would be necessary to get information on the nature of tissues and lesions from individual cells which are 100 to 1000 times smaller. According to Einstein's diffusion equation, at the brain temperature (37 °C), water molecules diffuse on distances in the order of 15 μm during 50 milliseconds (typical time interval used with MRI). By measuring water diffusion, even at the MRI image scale, one could get precious information on what water molecules have encountered in the tissue, such as cell membranes, fibers, etc., acting as probes for us of the microscopic scale. In order to encode diffusion-driven molecular motion in MRI images one has to rely on the magnetic field gradients used for MRI, but pushed to a much greater level. The magnetic field is changed in space for very short time intervals, based on a method which was introduced for NMR, before the advent of MRI, by Stejskal and Tanner (1965). The problem was to combine the spatial encoding at microscopic (diffusion) and macroscopic (MRI) level which was solved in 1985, leading to the first "diffusion MRI" images of the brain of normal subjects and patients (Le Bihan et al. 1986). Those images revealed a completely new kind of contrast, not available with standard MRI, giving insight into the microstructure of tissues.

Diffusion MRI is now installed on almost all MRI scanners and widely used in the clinical field. The first major application of diffusion MRI has been acute stroke, but applications are now extending to oncology, psychiatry, etc. Ischemic brain stroke, caused by the obliteration of a cerebral blood vessel by a clot, is the third common cause of death and the first cause of long-term disability by far. After stroke, 30% patients who survive need daily assistance, and 70% have impaired occupational capacity. The cognitive and societal cost is huge for healthcare, but also for productivity loses. In 1990, Moseley et al. (1990a), working on a model of acute stroke in the cat and using the new diffusion MRI method discovered that the diffusion coefficient of water was going quickly (minutes) and sharply down during stroke at the acute phase following the obliteration of a brain blood vessel. In short, in the regions of the brain where neurons were dying due to a lack of blood irrigation, the diffusion of water molecules was slowing down in relation to the swelling of dying brain cells (cytotoxic edema). For the first time, an objective marker of acute stroke was available, showing at the acute phase (within minutes and hours after the stroke onset) that a stroke had occurred and where exactly in the brain. Stroke can now get instantaneously cured if diagnosed in emergency by dissolving the clots that caused the ischemic event using thrombolytic agents, saving the fate or even the life of many patients worldwide. The health problem now is to get enough stroke centers disposing of MRI scanners available to emergencies and to educate the public to the early symptoms, as millions of neurons are dying every minute after the stroke onset.

Diffusion MRI is also now making a big impact in oncology, as it can accurately detect malignant lesions completely noninvasively. In regions of the body where cells proliferate, as in cancer, water Brownian motion decreases. Sensitivity to malignant lesions has been shown to be very high. Because the diffusion MRI images are very crisp and accurate, this method is increasingly being used, especially in the breast and prostate, as a method to detect cancer, sometimes automati-

cally using artificial intelligence algorithms. Diffusion MRI can also be used for monitoring treatment efficacy, giving information on whether therapy is effective or not at an early stage, before actual changes to the tumor size can be detected, saving several weeks or months if a switch to another treatment has to be made, as has been shown for brain glioblastoma.

Another major and unexpected breakthrough of diffusion MRI has been to give access, for the first time as there is no other approach available, to the brain connections. Brownian motion of water molecules seen with diffusion MRI is faster along the white matter fibers than perpendicular to them (Moseley et al. 1990b). In the early 1990s it was shown that by measuring water diffusion in two perpendicular directions the orientation of the white matter fibers in the brain could be determined. The images were very crude at that time, but it was the first demonstration that images of the orientation of the connection fibers in the brain could be obtained (Douek et al. 1991). Soon after, with P. Basser and J. Mattiello we developed the concept of diffusion tensor imaging (DTI) which fully exploits the sensitivity of diffusion MRI to orientation in space (Basser et al. 1994), allowing the orientation of the brain white matter fibers to be determined accurately for each point of the image. By connecting all those points together using dedicated mathematical algorithms one gets stunning 3D images of the connections themselves (Poupon, 1998; Mori et al. 1999; Conturo et al. 1999). Those images are now found in anatomy textbooks and atlas of the human brain connections in adults and children have been made available from DTI. It takes just a few minutes of brain scanning to get those connectivity maps, and applications are growing in neuroscience and medicine, revealing some unchartered territories. For instance, one can see that 2–4 months old babies have already connection fibers more developed in the arcuate fasciculus of the left hemisphere, before they acquire language skills (Dubois et al. 2009). Pianists also develop connections in specific areas of the brain depending on the number of hours spent practicing in their life (Bengtsson et al. 2005). During childhood a few thousand hours are enough to deeply modify those connections. Between 11 and 17 years of age, it takes more hours of practice to another set of regions. By adult age, other regions are affected, but at the price of a great many hours of practice, even in professional pianists. In dyslexia, it has been shown that some connections could be faulty in regions of the temporal lobe implied in reading (Klingberg et al. 2000). When dyslexic patients improve their reading abilities through some rehabilitation, one can observe improvements in those connections with dMRI. Indeed, brain connectivity seems to play a major role is some psychiatric illnesses, such as schizophrenia, as faulty connections have been found in some patients between frontal regions where thoughts originate and temporal auditory regions (Skelly et al. 2008), resulting in time asynchrony and explaining perhaps why “inner voices” (like mental images in the visual cortex) are perceived by those patients, as if watching a movie with the sound and the images out of synchrony, which is very uncomfortable.

Diffusion functional MRI (DfMRI) (Le Bihan et al. 2006) can also be used as an alternative for BOLD-fMRI. BOLD-fMRI, as we have seen, relies on the neurovascular coupling hypothesis and does not reflect neuronal activity directly, which may

fail in certain conditions which impair neurovascular coupling. On the other hand, DfMRI is thought to be more directly linked to neuronal activation, as the diffusion MRI signal is exquisitely sensitive to minute changes occurring in the tissue microstructure upon various physiological or pathological changes (Le Bihan 2014). Studies on rodents have evidenced that while the BOLD fMRI response is abolished by blocking the neurovascular response the DfMRI response is maintained, strongly suggesting that the DfMRI signal is not of vascular origin and that its mechanism differs from that of BOLD (Tsurugizawa et al. 2013). In addition, the DfMRI response is faster (time to reach the activation peak and time to return to baseline) than the hemodynamically driven BOLD signal response, as revealed by visual stimulation experiments in human subjects (Le Bihan et al. 2006). Based on earlier reports that the water apparent diffusion coefficient (ADC) decreases in relation to cell swelling and that neural swelling is one of the responses associated with neural activation, it has been hypothesized that the decrease in the water ADC observed during neural evoked responses would originate from the dynamic swelling of neurons or neuron parts, in line with a neuromechanical coupling hypothesis. This hypothesis is supported by the observation with microscopic MRI in *Aplysia* neuronal preparations that water diffusion decreases at the tissue level, while increasing inside neuron bodies, when cells of are exposed to swelling inducers, such as hypotonic solution or ouabain (an inhibiter of Na^+/K^+ pumps) and after neuronal activation induced by perfusion with a solution containing dopamine (Abe et al. 2017a). During activation neural cell swelling can be evidenced from optical microscopy imaging. Furthermore, water diffusion increases in specific brain regions in anesthetized rats, reflecting the decrease neuronal activity observed with local field potentials (LFPs), especially in regions involved in wakefulness (Abe et al. 2017b). In contrast, BOLD signals showed non-specific changes reflecting systemic effects of the anesthesia on overall brain hemodynamics status. Electrical stimulation of the central median (CM) thalamus nucleus where this anesthesia-induced water diffusion increase has been observed leads the animals to transiently wake up. Infusion in CM of furosemide, a specific neuronal swelling blocker, leads water diffusion to increase further locally and increases the current threshold necessary for the awaking of the animals under CM electrical stimulation. Oppositely, induction of cell swelling in CM through infusion of a hypotonic solution (−80 mOsm aCSF) leads to a local water diffusion decrease and a lower current threshold to wake up the animals. Strikingly, the local water diffusion changes produced by blocking or enhancing cell swelling in CM are also mirrored remotely in areas functionally connected to the CM, such as the cingulate and somatosensory cortex. Together, those results strongly suggest that neuronal swelling, possibly at the dendritic spine level is a significant mechanism underlying DfMRI and likely brain function at an elementary level.

20.4 Future of MRI

By gaining an order of magnitude in the spatial and temporal resolution of the images obtained by MRI we should be able not only to "better" see inside our brain, confirming or invalidating our current assumptions on how it works, but also to generate new assumptions, today impossible to anticipate, and perhaps to reach a holy grail: decoding the functioning of our brain. As suggested by MRI studies in animals at ultra-high magnetic fields (> 10 Tesla), the sensitivity and, thus, the spatial and temporal resolution of the images increase together with the magnetic field. New contrast mechanisms could also be explored. There is no physical limit to this increase in magnetic field, only technical challenges which can be solved. With such an ultra-high field (UHF) MRI system in hands one would be within reach to acquire with timescales compatible within human tolerances images at a scale of one hundred micrometers at which everything remains to discover.

The brain is a spatially very inhomogeneous organ. A key question is to understand how the specific three-dimensional organization of our brain cells, neurons and glial cells, in clusters or networks within the layers of the brain cortex, and their short- and long-term dynamic interactions via their short and long range connections, are responsible for the emergence of a genetically determined set of elementary operations which, combined together and under the effect of exposure to environment result in higher order function, language, calculus, or even consciousness. Infants can today learn to manipulate cell phones with some success in a few hours, though, there are certainly no "cell phone" brain areas, nor to say "cell phone" genes. The segregation of cells in a set of functional areas along the cortical surface separated with abrupt boundaries has been known since Brodmann gave an account of his observation under a microscope of the single half-brain of an old lady at the onset of the twentieth century, and found out the existence of about 60 distinct areas which he labeled by numbers (for instance, area 17 is the primary visual cortex). A recent MRI study has extended this set of brain regions to almost 200 (Glasser et al. 2016). In some way, this is conceptually equivalent to the discovery of our 46 chromosomes and their link to heredity in the mid-1880s. At a more microscopic level it was later discovered that the vector of heredity was the DNA molecule, an assembly of nucleotides, present in the chromosomes. Similarly, we know neurons (as well as glial cells) compose Brodmann's areas and support brain function. But it was not until Crick and Watson had the vision that information was hidden at an intermediate spatial scale, between DNA's nucleotides and chromosomes scales, in the three-dimensional organization (double helix) of the DNA molecule that the existence of the genetic code emerged. Could there be a "neural code" carried by the three-dimensional organization of brain cells?

To find out we must explore this "mesoscale" which is today out of reach. We can explore the human brain in vivo roughly at millimeter resolution (hundreds of thousands of cells at best) and, at the other extremity of the spectrum, we can record the

activity of a limited set of neurons in animals, which can be used in feed theoretical models of small neural networks. But what really happens between those two scales, around clusters of a few thousands of cells, remain Terra Incognita, and it would be naive to assume the landscape at this scale is a mere sum of what is visible at an inferior scale. Synergies across scales is in order and this quest for a "neural code" is one of the major challenges of contemporary science, together with the exploration of matter, of the universe, or the control of thermonuclear fusion. Key questions are: "How do neuron clusters work and exchange information? How is information stored? What are the respective role of genes and environment in the cortical localization, genesis and functioning of those clusters? How are they formed and maintained or altered during the brain development stage and after?" Obviously, this intimate knowledge of normal brain functioning mechanisms will lead to a better understanding of its dysfunctions, neurological or psychiatric pathologies in a broad sense, which will probably open new therapeutic possibilities (such as brain reprogramming).

Those challenging views led in the early 2000s the French Atomic Energy Commission (CEA) to launch a program to conceive and build a "human brain explorer", the first human MRI scanner operating at 11.7 T (Le Bihan and Schild 2017). This scanner was envisioned to be part of an ambitious project aimed at pushing the limits of neuroimaging, from mouse to man, using UHF MRI. With such a unique instrument brain connections and brain activity could be seen at a resolution of hundreds of micrometers, ions, metabolites, neurotransmitters could be detected and measured, giving access in vivo and noninvasively to brain chemistry or genes at work in the developing brain. This 11.7 T magnet was designed by the physicists and engineers of CEA based on specifications defined by teams at NeuroSpin. The magnet was part of a larger endeavor to develop Molecular Imaging at Ultra-High Field financed through a French-German initiative (hence the name "Iseult" for the project) involving academic (CEA and Julich University), industrial (Siemens, Bruker, Guerbet and Alstom MSA) and governmental organizations across both countries (AII, then Oséo and BPI for France, BMBF for Germany). The 11.7 T magnet has been finalized at the Alstom-GE facility in Belfort and delivered to NeuroSpin in Saclay in May 2017 for a commissioning in 2019. The first images of the human brain at 11.7 T might not be obtained until a few years later, however, due necessary developments in MRI technology to accommodate issues associated with the increase in frequency (the system will operate at 500 MHz) and approval for safety by regulatory agencies. Nonetheless, this prototype 11.7 T MRI scanner dedicated to advanced brain research, with the unprecedented resolution and new contrasts it will allow, will certainly open a new window of opportunities to make the brain even more visible and better understand some brain disorders, develop new disease biomarkers or novel therapeutic means.

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