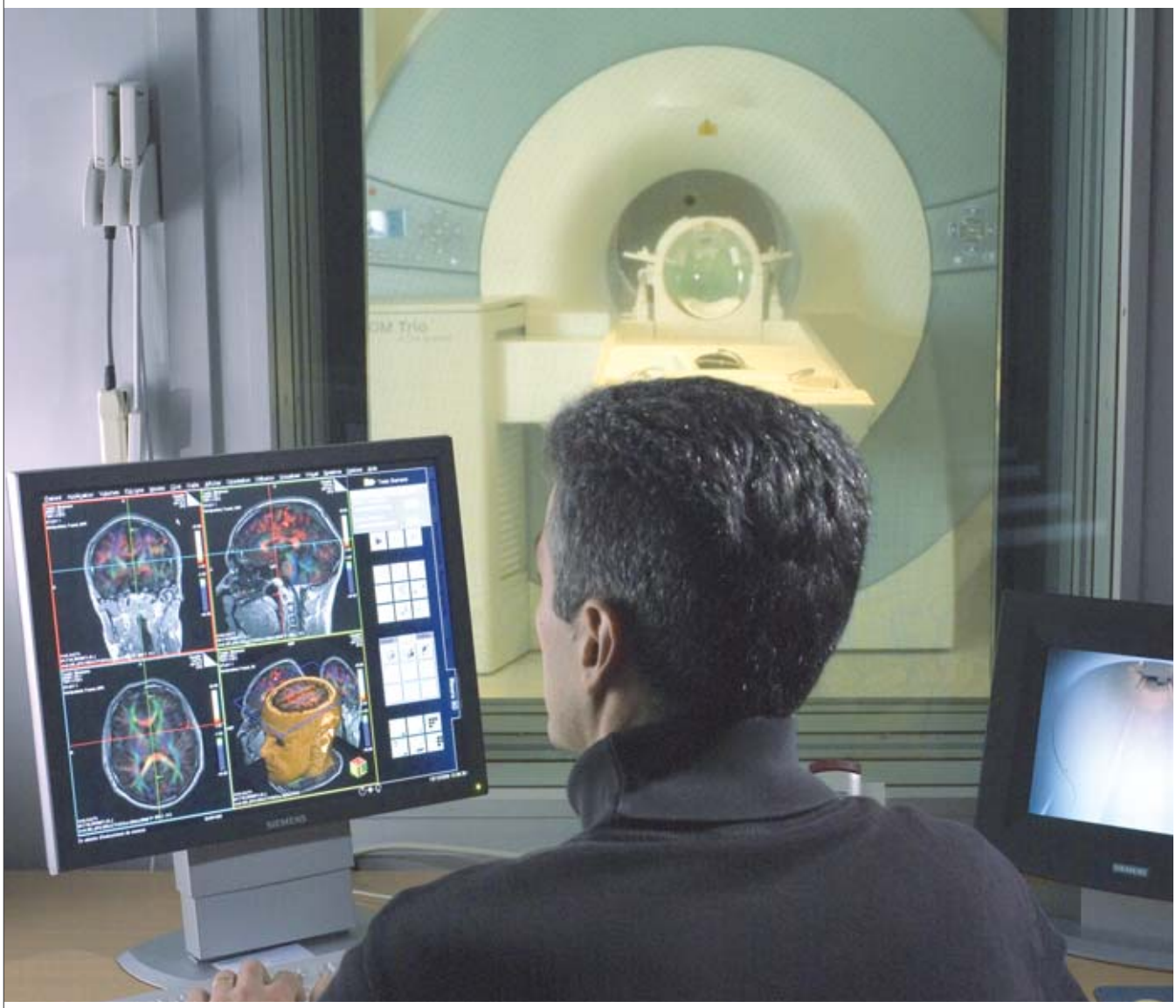
Using **imaging** to understand the **brain**

Structural and functional brain mapping has made huge leaps forward in recent years, driven by developments in imaging technologies, and led by magnetic resonance imaging (MRI). These developments have made it possible to anatomically and functionally map out the brain by imaging the zones activated while a given task is being performed. One of the methods employed to see the brain thinking and provide deeper insight into brain disorders consists in tracking – in real time – the brain activity-related changes in blood flow. It is also possible to measure the movements of water molecules in the brain at the microscopic scale, and thus visualise the detailed architecture of neuronal tissue and its variations. Biological target molecules involved in metabolic processes also offer information on brain disease. Ultra-high-field MRI will make it possible to observe the brain and its diseases with even greater precision, approaching the same scale as the brain processes themselves.



A. Gonin/CEA

3-T MRI system at NeuroSpin. Magnetic resonance imaging techniques are especially well geared to non-invasively studying complex deep organs such as the brain, which have so far proven almost impenetrable.

Clinical applications of magnetic resonance imaging

Magnetic resonance imaging (MRI) has evolved into what is now a major diagnostic and therapeutic follow-up tool for a whole range of diseases, notably brain diseases. It is safe, easy to run, and gives high-precision results, making it suitable for use with all age groups.

Magnetic resonance imaging (**MRI**) is especially well geared to non-invasively studying complex deep organs such as the brain, which have so far proven almost impenetrable (Focus C, ***The main methods of medical imaging***, p. 36). **Anatomical MRI** (**aMRI**) can generate high **spatial resolution** images of the brain's architecture, while **diffusion MRI** (**dMRI**) highlights intra-cerebral connections, **functional MRI** (**fMRI**) tracks brain activity, **magnetic resonance spectroscopy** (**MRS**) and spectroscopic imaging (sMRI) can study biochemical processes (**metabolism**, **neurotransmission**), and magnetic resonance angiography[1] (MRA) can generate pictures of the cerebral vascular system. MRI techniques often employ contrast agents like gadolinium chelates[2] for image enhancement to better characterise certain anomalies. High-**field** (3 **T** and upwards) MRI generates better-quality images and more physiological feedback than more conventional MRI techniques operating at 1.5 T. There have been no reports of adverse effects to date, regardless of magnetic field strength, over the 25-year history of clinical MRI (every year, around 8 million MRI scans are performed in Europe alone), provided there is strict compliance on contraindications, including the absence of any metal object in the patient's body.

P. Stroppa/CEA

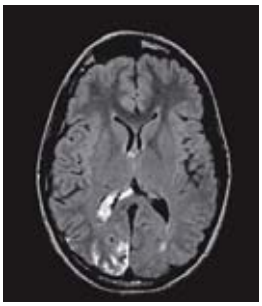
The **SHFJ**'s 3-T MRI system at Orsay (Essonne). Functional neuroimaging is currently unique as a technique, since it is able to provide *in vivo* and *in situ* information on brain function, entirely non-invasively.

Input from MRI driving brain research

The advent of MRI has revolutionised diagnostics in virtually all adult neurological diseases. The breakthroughs driven by MRI extend from *neurodegenerative diseases*, where the progressive atrophy of the deep temporal lobe in Alzheimer's disease and certain deep grey matter nuclei[3] in Huntington's disease have been imaged in detail, through to *stroke*, which can be imaged early on in the first few hours post-insult via diffusion MRI, *brain tumours*, where MRI can help assess how aggressive the tumour is, how likely it will respond to chemotherapy, and potential recurrence, *epilepsy*, where MRI can image microscopic lesions or underlying malformations and help gauge surgical eligibility, *inflammatory and infectious diseases*, where MRI can track the time-course of **white matter** disorders in multiple sclerosis and encephalitis in AIDS, and to *early prognosis of serious head trauma*… and the list goes on.

A first-choice tool for paediatrics

The risk-free versatility of MRI also makes it a first-choice diagnostic tool in paediatrics right from the prenatal period. Fœtal MRI is systematically employed when diagnostic ultrasound indicates potential disorders during pregnancy, as it enables a more detailed analysis of the fœtus, especially the fœtal brain. MRI is routinely used in children, but since the patient has to remain perfectly still, non-cooperative children are often sedated. MRI provides major input on neurological diseases in children, from peri-natal distress (pre- and per-natal injuries) through to genetic diseases of the central nervous system like leukodystrophies – progressive degenerative disorders of the white matter – and any adult disease rooted in childhood.



MRI image of the brain of a woman who has suffered since childhood from epilepsy due to a vascular malformation of the right occipital lobe (shown in white).

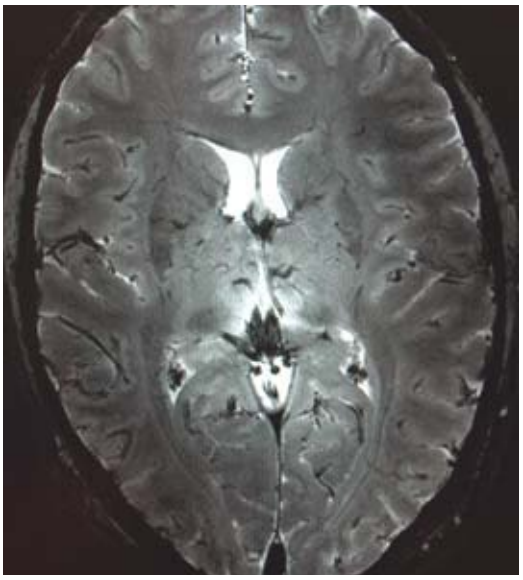
Increasing need for more sensitive instruments

It is important not to lose sight of the fact that the MRI scan can remain 'seemingly' normal in a number of nevertheless highly debilitating diseases, including certain psychiatric disorders like depression, schizophrenia and autism, and even neurological disorders like Parkinson's disease, certain epilepsies,

(1) Angiography: X-ray technique generating images of blood vessels, wherein the subject is administered a contrast agent.

(2) Chelate (from the Greek *khêlê*, meaning claw): chemical complex formed by a **ligand** (the chelating agent) and a metal **cation** (or **atom**) known as a chelate that is bound to the chelating agent by at least two coordinate covalent bonds to form a claw-like group.

(3) Deep grey matter nuclei: clusters of **grey matter** found deep within the depths of the brain and which process information for certain vital functions, as well as for memory.



NeuroSpin/CEA

An image of the human brain acquired with the NeuroSpin centre's 7-T MRI system. Ultra-high-field MRI provides a level of contrast that would be impossible to achieve at lower field strengths.

mental retardation, and others. This has therefore become the focal point of a significant research drive in order to engineer new image acquisition methods – led by ultra-high-field imagers like the 7-T system at **NeuroSpin** and soon the 11.7-T system – or morphometrics-based analyses, which study anatomical variations in the brain that are not visible to the naked eye using statistical **algorithms**, such as CEA-developed BrainVisa software.

Since it first arrived on the scene in late 1970s (at field strengths of 0.5 T!), MRI has continually demonstrated its huge potential as a brain disease diagnostics and therapeutic follow-up tool. This makes it all the more unacceptable that France should continue to lag so far behind in terms of clinical MRI facilities. By enhancing diagnostics, imaging makes it possible to initiate earlier and more effective patient management and thereby cut healthcare costs. The challenge that medicine will soon need to pick up will be to diagnose disease even earlier, actually *before* the onset of clinical signs, and to *prevent* the onset of disease. Medical imaging, in association with other key genetics-based and physiological tools, has already established itself as pivotal to this objective.

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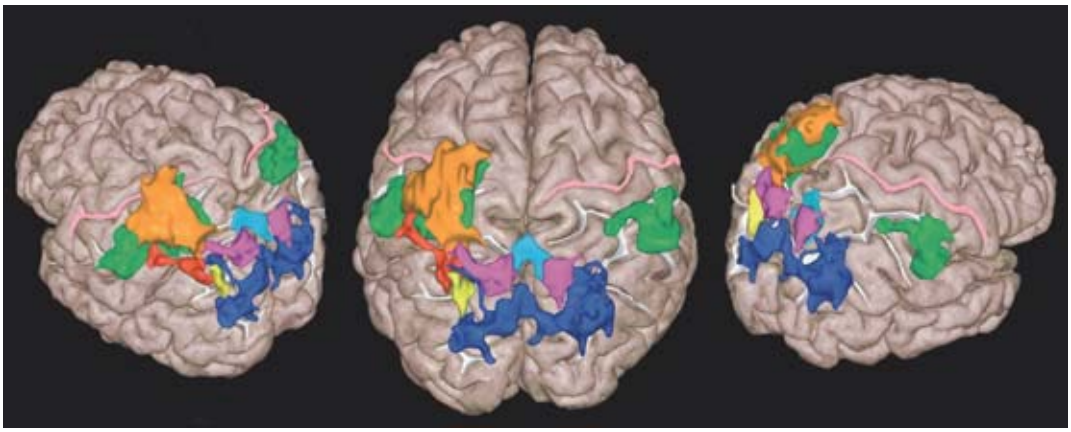
Blood-oxygen-level-dependent functional magnetic resonance imaging

The local, transient increase in blood flow in activated areas of the brain gives an indirect picture of neuron activity that can be used to generate images with high anatomical and temporal precision.

calculation and language
visio-spatial tasks
hand movements
grasping
calculation only
attention alone
saccades only



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Functional magnetic resonance imaging maps the areas of the brain that are activated when performing a given task.

Functional magnetic resonance imaging (**fMRI**) is one of the applications of **magnetic resonance imaging** for studying how the brain works (Focus C, ***The main methods of medical imaging***, p. 36). It works along the principle that there is an increased influx of oxygenated blood in activated brain areas.

Measuring the increase in blood flow

fMRI consists in alternating periods of activity (such as moving the fingers of the right hand) with periods of inactivity while running image acquisitions of the full brain every 1.5 to 6 seconds (which is the average **temporal resolution** conventionally used in research). Active brain areas are mapped out based on the **BOLD** (*Blood-Oxygen-Level-Dependent*) effect, which stems from the **magnetisation** of the **haemoglobin** carried in red blood cells. This haemoglobin comes in two forms. Red blood cells oxygenated in the lungs contain *oxyhaemoglobin*, which as a **molecule** is inactive under **NMR**, whereas the red blood cells deoxygenated by tissues house *deoxyhaemoglobin*, which has **paramagnetic** properties and is therefore visible under NMR.

In the zones that are activated when handling a task, there is a slight increase in **neuron** demand for oxy-

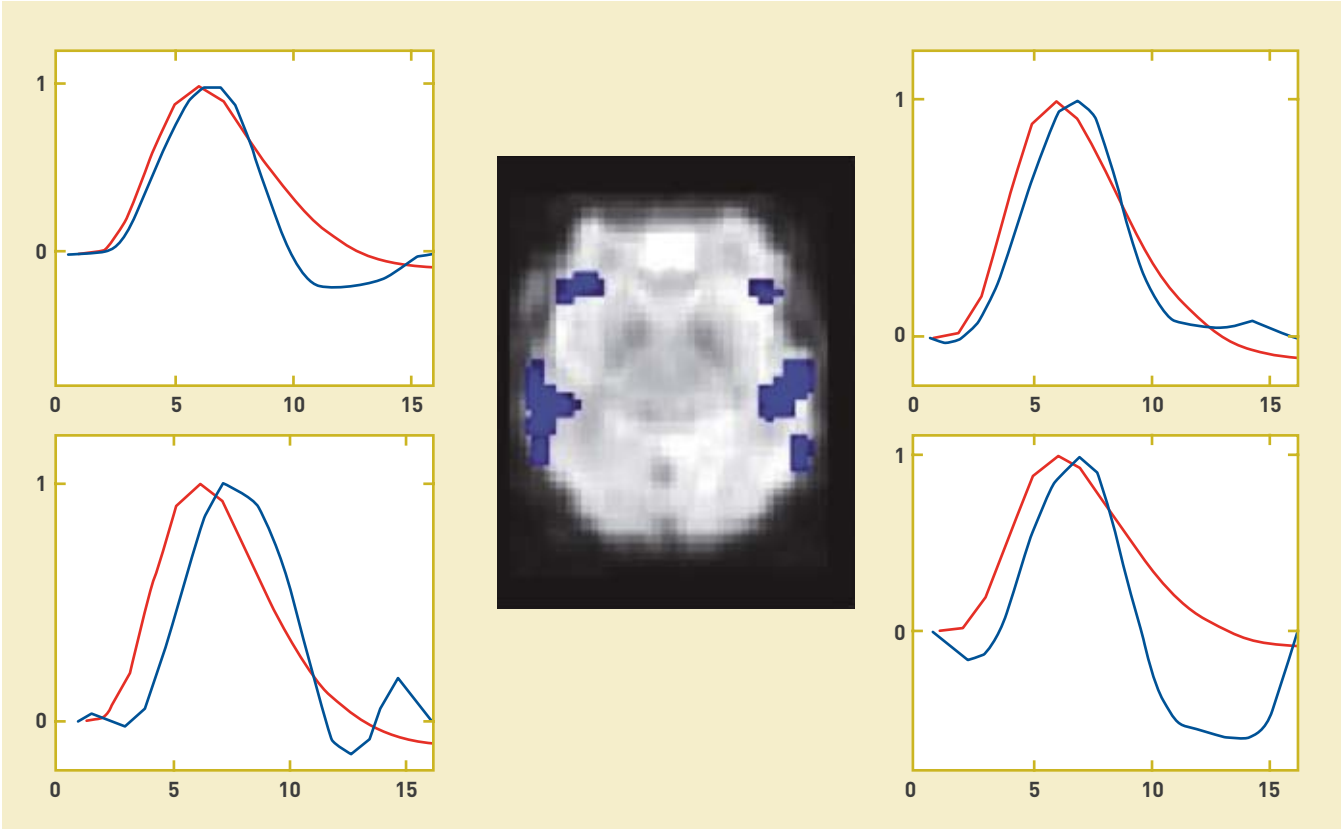

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Figure 1.
Intra-individual spatial variability in the haemodynamic filter.
The blue plot shows regional estimates for the haemodynamic filter in different areas involved in auditory processing (Heschl's gyrus, areas of the primary and secondary auditory cortex, and Broca's area). The red plot shows the canonical form typically used to model the BOLD signal. At centre, a low axial plane slice (z = 0 mm) highlighting bilateral activations in response to auditory stimuli (listening to phrases).

gen that is actually overcompensated by a large increase in blood flow. The net result is a decrease in deoxyhaemoglobin concentration. Since deoxyhaemoglobin is paramagnetic, the MRI signal (the nuclear spin **relaxation** time of the **hydrogen molecules** of water) gets slightly stronger during the periods of activity. It is these slight increases (a few percentage points) in signal that fMRI measures, via fast '*echo-planar*' imaging sequences. The only very slight variations make it difficult to resolve detection and mapping problems, generating the need for powerful statistical methods(1) to highlight the brain activations.

Data pre-processing steps

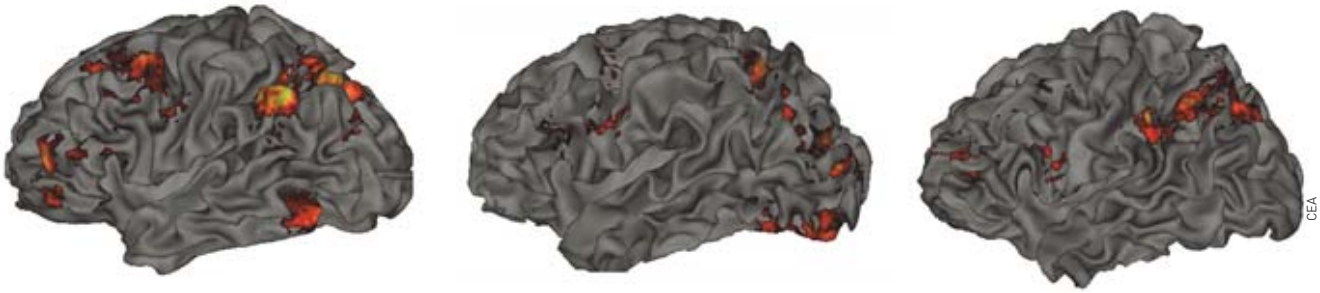
First off, the data obtained has to be pre-processed, which involves making successive corrections for geometric distortion (artefacts of **magnetic susceptibility**), for movement, etc. Since the image shots are acquired at different times (temporal series), the subject lying down in the scanner may move between volumes. Thus, a realignment step can be performed to weigh up the level of movement and align the fMRI images together if there has not been too much movement. These anatomical and functional datasets can then be matched up so that the subject's anatomical image fits with their neurofunctional data. Finally, a pivotal spatial normalisation step allows to factor in inter-subject brain variability and run statistical analyses across multiple human subjects. Indeed, since a number of subjects all participate in the same experiment, their brain scans need to be registered to the same baseline template. The normalisation step warps the brain scans so that they all look like a standard brain.

Modelling the BOLD signal

A parametric **model** to fit the data is adjusted in each **voxel**. To keep the statistics processing simple, this model is linear, in that it is a linear function in relation to the target parameters and describes data variability according to three components: experimental effects induced by the stimulus (effects targeted by the physician), confounding effects (such as physiological artefacts) and residual variability (unexplained by the model and associated with noise from the imaging process). Experimental effects are defined by **convolution** of the neuronal activity putatively evoked in the experimental paradigm(2), with a *haemodynamic filter* representing the typical BOLD response. Since there is a certain level of unknowns in this haemodynamic response, an averaging model has been empirically selected, although pioneering new approaches now make it possible to estimate the response based on data and thus factor in regional and inter-subject differences in the topography of the brain's microvascular network. The general linear model produces an activity map describing the areas of the brain where the experimental paradigm has generated a statistically significant increase in the signal recorded (Figure 1).

(1) Including *Statistical Parametric Mapping* (SPM).

(2) Experimental paradigm: a set of procedures that together form a reference model.



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Inter-subject variability. This image shows brain activity recorded in three subjects during a subtraction task overlaid onto the surface interface between **grey matter** and **white matter**. The illustration reveals not only shape variations between the different brains but also variations in the zones activated during the subtraction task. The issue to be resolved is to understand what these different subjects have in common, how the functional variability is correlated to the anatomical variability, and to what extent these variabilities are explained by genetic, behavioural or demographic factors.

Statistical analysis

The final step in the process is to take data on the subject population and establish which brain regions show an increase in signal. The aim of this analysis is to generalise the results acquired over a sample of ten or twenty subjects to the rest of a population. This analysis will however run up against the widely observed anatomical and functional variability between different brains. Indeed, one of the major challenges for the near future will be to understand where, in terms of behavioural or genetic input, this variability stems from. This understanding is a key stepping stone towards gaining deeper insight into the effects generated by different neurodegenerative or psychiatric brain diseases, the aim being to improve diagnostics.

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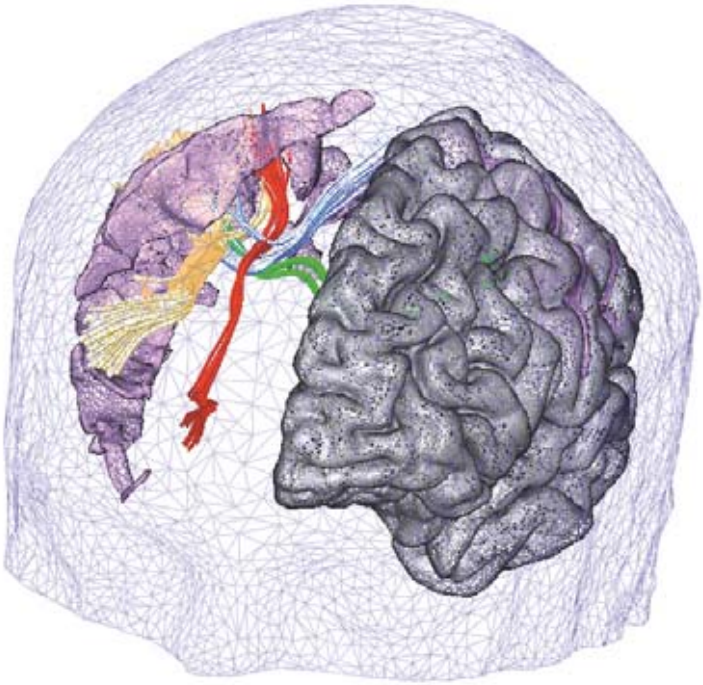
Diffusion magnetic resonance imaging: from Brownian motion to imaging of the mind

The diffusion of water molecules (Brownian motion) in brain tissue can be measured to quickly detect neural activation.



J.-F. Mangin, V. El Kouby, M. Perrin, Y. Cointepas and C. Poupon, SHFJ/CEA

dMRI now makes it possible to map the brain's 'information highways': large bundles of fibers (yellow, red, green, blue) that enable neurons in different regions of the brain to communicate together.

Over the last thirty years, functional neuroimaging has firmly established itself as an indisputable approach to study the brain, primarily through **positron emission tomography** (**PET**) and **magnetic resonance imaging** (**MRI**) – see Focus C, ***The main methods of medical imaging***, p. 36. Although these two methods are based on radically different physical principles – **beta + radioactive decay** in PET and **nuclear magnetisation** in MRI – they both share water **molecules** to produce images of brain activity. This is not really surprising, given that water accounts for 80% of the weight and 90% of the molecules in the brain. PET and MRI-based functional imaging has so far been based on the relationship between **neuronal** activation and blood flow. There is a local increase in blood flow in activated brain regions. With PET, water made radioactive (H_2O^{15}) using a cyclotron(1) is injected into the blood circulation of a patient or a healthy volunteer. The increased blood flow in areas activated by a **cognitive** or

(1) Cyclotron: a circular **particle accelerator** inside which particles placed in a magnetic field are accelerated under vacuum by an ac electric field. Cyclotrons produce the **radioisotopes** oxygen-15, carbon-11, nitrogen-13 and fluorine-18 that are used in nuclear medicine.

sensorimotor task results in a local increase in emitted radiation in the brain tissue that can be detected using the PET camera. With MRI, the **hydrogen nuclei** in water molecules are magnetised by a very strong **magnetic field** (*nuclear* ***paramagnetism***). The increased blood flow in activated regions is accompanied by a local change in blood oxygenation and blood volume. Since the **haemoglobin** in red blood cells contains an iron **atom** whose **electrons** present magnetic susceptibility (*electron paramagnetism*), a change in the magnetic field surrounding vessels is triggered by the flow of red blood cells, changing, in turn, the magnetisation properties (relaxation) of the water molecules surrounding the blood vessels. This change, although very slight, can be detected by the MRI scanner, in a method called *Blood-Oxygen-Level-Dependent* (**BOLD**) fMRI. However, in both of these systems, water is only an indirect indicator of the local haemodynamic response to brain activity (Figure 1).

Research teams the world over – including at **NeuroSpin** – are now using BOLD MRI to map the cerebral networks involved in cognitive processes like language, calculation, mental imagery or even awareness, in order to understand how the brain works and why disorders can occur (Figure 2). However, there are a number of well-known limits to the method. Although the principle of coupling between neuronal activity, **metabolism** and blood flow has in most cases been verified, there is still uncertainty as to the degree of this correlation and the mechanisms involved. Indeed, the correlation is sometimes broken in certain pathological conditions or in the presence of certain drugs: a region may activate normally without a concomitant increase in blood flow, and therefore go undetected. Furthermore, there are unavoidable limits to the spatial precision of brain activation images, since the blood vessels responsible for the haemodynamic response irrigate or drain brain regions containing huge numbers of **neurons** that may have different functions. Similarly, the physiological mechanisms that trigger the increase in blood flow have a relatively long temporal response that intrinsically places limits on the **temporal resolution** of the methods used (the blood flow increase peaks several seconds after neural activity begins).

However, a new, fundamentally different approach recently developed produces images of brain activity by tracking the *molecular diffusion* patterns of water. It has shown that there is a slowdown in water diffusion in activated brain regions.

Diffusion MRI for probing down to microscopic scale

One of the four groundbreaking articles published by Albert Einstein in 1905 has unwittingly given birth to a powerful method for exploring the human brain and how it works. Einstein studied and explai-

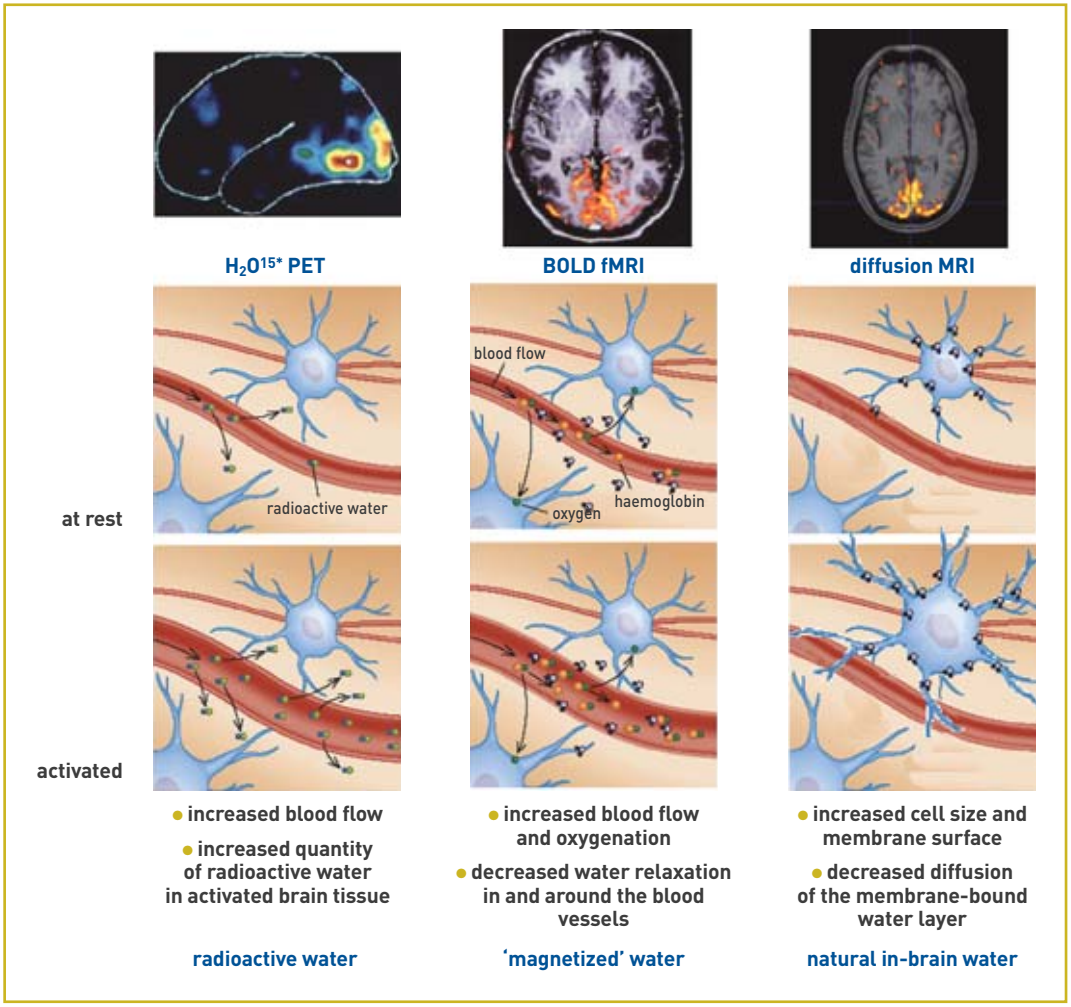


Figure 1.
The general principles of PET and MRI for functional neuroimaging. Left; PET imaging of brain activation. Radioactive water (H_2O^{15}) is used as a **tracer** to detect the increase in blood flow caused by neural activation. Middle; BOLD fMRI imaging of brain activation in the visual cortex. The magnetisation of water in and around blood vessels is modulated by the flow of red blood cells containing deoxyhaemoglobin (which, due to its iron atom, is paramagnetic). Right; diffusion MRI imaging of brain activation in the visual cortex. The decrease in water diffusion that occurs during activation likely stems from the swelling of activated cells and the resulting expansion of the membrane-bound water layer. While PET and BOLD fMRI simply use water as an indirect means of enabling the imager to detect changes in blood flow, diffusion MRI detects changes in the properties of water that could play an integral part of the activation process itself.

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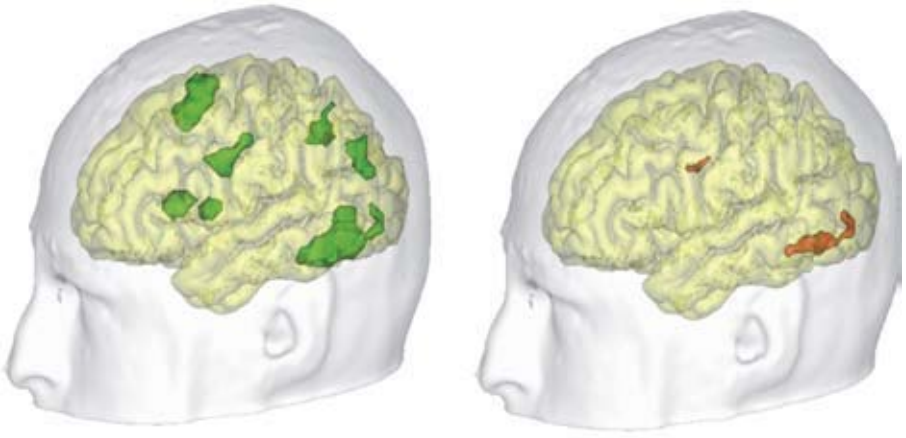

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Figure 2. Brain imaging confirms the hypothesis of the subliminal perception of words. **Functional MRI** can be combined with **electroencephalography** to show that a subset of the regions activated during the conscious reading process is also unconsciously active when words are presented subliminally.

ned molecular diffusion as the random motion of molecules (known as Brownian motion) that results from the kinetic energy they carry. Molecular diffusion is a ubiquitous process universally manifested, including in human cells and brains. Midway through the 1980s, we demonstrated for the first time that it was possible to image the molecular movement of water diffusion in the human brain via MRI. This was achieved by making the magnetic field variable in space (field gradient) for a short instant. The field change experienced by molecules in diffusion-driven motion over this short interval was expressed as a slight variation in **resonance** frequency together with phase dispersion. The statistical distribution of the phase dispersion for the full set of water molecules in each image **voxel** produces slight but measurable signal attenuation, thereby giving a quantitative reflection of the diffusion process.

Molecular diffusion refers to the random translational movement of molecules that results from the heat energy they carry. In a free medium, and for a given time interval, these three-dimensional molecular movements follow Gauss' law(2). The statistical distance travelled by the molecules is related to their diffusion coefficient. This diffusion coefficient is solely dependent on the size (or mass) of the molecules, temperature, and the **viscosity** of the medium. For example, water molecules that diffuse freely at 37 °C have a diffusion coefficient of $3 \cdot 10^{-9}$ m^2/s, which translates to a statistical distance of diffusion of 17 **µm** in 50 milliseconds. Around 30% of the molecules will have at least covered this distance, while only 5% have gone beyond 34 µm.

The powerful driving concept underlying **diffusion MRI** (**dMRI**) is therefore based on the fact that the water molecules, via their diffusion patterns, will probe biological tissues at a microscopic scale, i.e. well below the millimetre scale of most MRI images. In practice, diffusion time is in the 50-100 millisecond bracket, while the water molecules diffuse through the brain over distances of around 1-15 µm, where they rebound from or interact with a number of barriers, such as cell membranes, fibers, organelles(3), **macromolecules**, etc. This means that diffusion distance is lower than the 'free' diffusion, and movement distribution is no longer Gaussian. In other words, while local viscosity is the predominant effect for very short diffusion windows, barriers become the predominant effect at longer diffusion windows, i.e. those used in medical MRI. Ultra-precise **modelling** of water molecule motion in tissue remains a thriving focus of research, but non-invasively tracking water molecule motion in tissue has already provided precious detailed information on the structure of cerebral tissue and its spatial organisation, as well as on physiological or pathology-induced structural changes.

Major clinical applications

The greatest and most impressive application of dMRI thus far has been to image acute cerebral ischaemia(4) (or 'stroke'; Figure 3). The breakthrough discovery was that water diffusion slows immediately after the onset of acute ischaemic stroke (triggered for example when a blood clot migrates into a cerebral artery), while the neurons begin to suffer and die from this interruption in local blood circulation. dMRI is currently the only technique capable of identifying, flagging and gauging the extent of acute stroke. This information means that certain patients can be given targeted emergency treatment in the first few hours post-trauma, when the condition of the cerebral tissue can still be reversed, thus preventing debilitating permanent sequelae like hemiplegia or speech loss.

A further discovery was that in-brain water diffusion was **anisotropic**. Water diffusion in **white matter** varies according to the direction it is measured in. White matter is composed of **axonal** extensions of neurons clustered in parallel myelinated fiber

(2) Gauss's law: in probability, general law that governs the distribution of a random variable, the graphical representation of which is a bell-shaped curve (Gauss curve).

(3) Organelle: general term for a specialised membrane-bound cell structure in the eukaryote cell cytoplasm.

(4) Ischaemia: drop in the arterial blood supply to an organ, causing lowered oxygenation of its tissues.

bundles. Water diffuses faster along the fibers than perpendicular to them. In recent years, this property has been exploited to determine the spatial orientation of the white matter fiber bundles and thereby reveal how the brain is 'cabled'. This technique is called diffusion tensor imaging, or DTI. This has made it possible to produce the first 3D images of the connective networks interfacing brain regions in any given person, rather than just by statistical modelling (Figure 3). This leap forward is currently revolutionising the neurosciences, and has already been used to study certain diseases that could be linked to damaged brain connections, such as schizophrenia.

Another vastly important potential clinical application of dMRI is as a cancer detection and therapeutic follow-up tool (Figure 3). Here again, water diffusion is slower in cancerous lesions and metastases. Studies are in progress to validate dMRI as an alternative to FDG-PET (FDG, or fluorodeoxyglucose, is a radiation-emitting 'false' sugar that hyperactive cells capture and accumulate), which can detect cancerous lesions according to hyper**metabolism**. dMRI would offer a far more direct analysis, as the slowdown in diffusion is likely caused by cell proliferation and the associated increase membrane density. Moving into therapy, dMRI can provide evidence of whether anti-cancer treatments have been efficient after just days, rather than weeks or months (as water diffusion re-increases in treatment-sensitive tumour areas), thereby saving precious time if the therapy proves inefficient and needs to be changed.

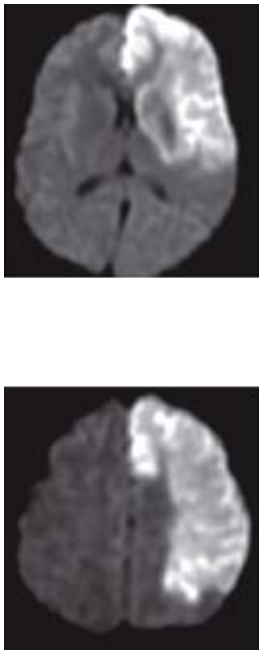
Water diffusion and brain activity

The fact that water diffusion is non-Gaussian in biological tissue like the brain clearly stems from interactions between water and the cell components, cytoplasm and membrane. Prompted by recent discoveries on the physics of water and water diffusion, particularly in biological tissue, researchers are working with a new model stating that there are two *pools* of water. One is a "fast diffusion" pool (containing 70% water and around 2.5 times slower than the diffusion of free water) corresponding to tissue bulk water in fast exchange with the water hydration shell around **proteins** and macromolecules. The second is a "slow diffusion" pool (containing 30% water and around 10 times slower than the diffusion of free water) originating from a layer of highly-structured water molecules running along the membrane surface. This water structure system results from the spatial distribution of electrical charges at the membrane protein surface and the cytoskeleton(5) attached to it, leading to decreased density and diffusion mobility. Given that most cells have a high surface-to-volume ratio, it is perfectly logical that any increase in cell volume (swelling) or density (proliferation) would result in a tangible increase in the membrane-bound water pool, and thus a drop in the global diffusion coefficient measured.

The slight slowdown in water diffusion in activated brain areas occurs several seconds *before* the haemodynamic response detected by BOLD fMRI. It can be described in terms of a phase transition of the water molecules from the 'fast' diffusion pool to the 'slow' diffusion pool. This phase transition may well be due to an expansion in the membrane surface and therefore cell swelling during brain activation (Figure 1). A large body of research, particularly from optical imaging, has demonstrated that cell swelling is one of the physiological responses associated with neural activation, coinciding with the peak of the action potential.

This mechanism of diffusion, if validated, would

(5) Cytoskeleton: the structural scaffolding of a cell cytoplasm, formed of organic **polymers**, and that lends the cell its mechanical properties.



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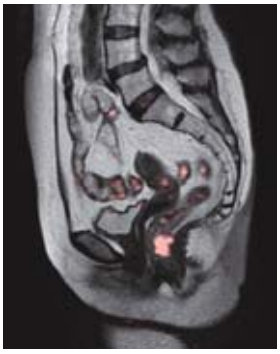
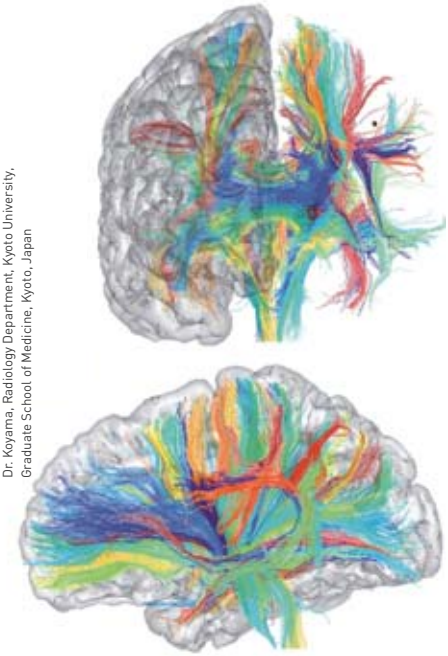


Dr. Koyama, Radiology Department, Kyoto University, Graduate School of Medicine, Kyoto, Japan



V. El Kouby, Y. Cointepas, M. Perrin, C. Poupon and J.-F. Mangin, SHFJ/CEA

Figure 3.
Left; dMRI and acute cerebral ischaemia (stroke).
The high-signal region presents a slowdown in water diffusion resulting from the blood inflow stoppage and the following cytotoxic oedema (cell swelling).
Middle; dMRI and cancer.
Colour highlights the regions where there is a slowdown in water diffusion, areas identified as containing cancer cells (primary lesions or metastases).
Right; brain dMRI and tractography. White matter water diffusion is anisotropic. The fastest direction of diffusion indicates point-to-point fiber direction in the image. Post-processing software is able to interconnect the points and generate colour images mapping the topography of the white matter bundles.

mark a major turning point, since the fact that is more tightly and more directly linked to neural activity means that it potentially offers improved temporal and **spatial resolution**. However, on a conceptual level, this approach goes further still. In contrast with classical PET or MRI-based detection approaches which rely on *artificially* changing the physical properties of water (by radiation emission and magnetisation), the new water diffusion-based approach simply uses MRI as a means to reveal *intrinsic* changes in the properties of water during cortex activation. Water is certainly not a passive actor in cell physiology, and these changes may well be an integral active part of the mechanisms of activation, since water homeostasis and water movement almost certainly play a central role in brain physiology and the interactions with membrane events. Indeed, there has recently been a flurry of literature on the physical properties of water in biological tissue and the cell events underlying brain activation, but word has not yet got around.

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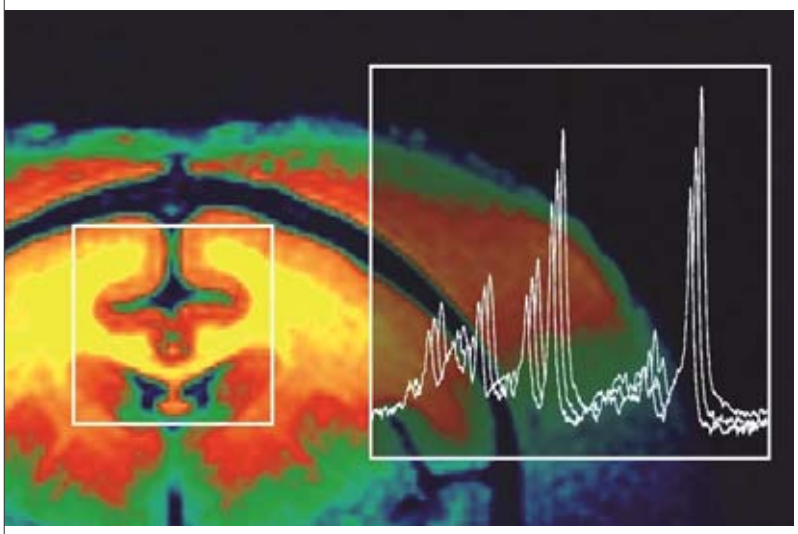
The contribution of NMR spectroscopy to the study of brain metabolism

Although *in vivo* nuclear magnetic resonance spectroscopy (MRS), in contrast to MRI, is not yet widely employed in routine clinical practice, partly due to its limited sensitivity, it remains a highly promising clinical tool for research into the regulatory mechanisms of brain energy metabolism.



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MRS, which analyses the molecules involved in brain chemistry, is a very promising tool for the early screening of brain disease.

Nuclear magnetic resonance spectroscopy (**MRS**) appeared in the wake of the discovery of **nuclear magnetic resonance** (**NMR**) 60 years ago, and has since proven unique among physico-chemical analysis techniques for characterising chemical compounds *in vitro*. Over the last twenty years, MRS has been used to explore biological tissue *in vivo* (Focus C, ***The main methods of medical imaging***, p. 36). MRS makes it possible to measure brain energy **metabolism**.

Nuclei of biological interest

The main NMR-detectable **nuclei** of biological interest are **hydrogen** ^{1}H, i.e. **protons**, phosphorous-31, or ^{31}P, and carbon-13, or ^{13}C. ^{1}H NMR offers relatively high sensitivity and can measure between 5 and 15 **metabolites** in the human brain depending on the performance of the NMR system used. These metabolites include N-acetylaspartate, creatine and choline, as

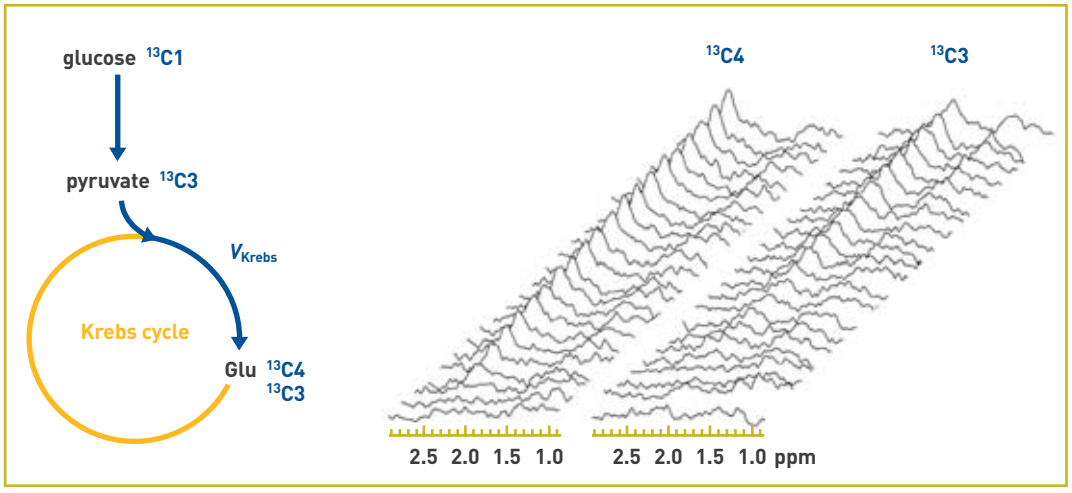

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Figure 1. Cerebral oxidative metabolism labelled by perfusing ^{13}C glucose. Left; the ^{13}C is incorporated from blood glucose up to glutamate (Glu). Right; NMR-detected labelling of the 4th and 3rd glutamate-driven carbon atoms in the rodent brain during a 90-minute perfusion of ^{13}C glucose.

well as certain **neurotransmitters** and **amino acids** including glutamate, GABA, aspartate and glutamine. ^{31}P NMR will detect a shorter list of between 3 and 5 metabolites, again depending on the system deployed. However, what makes ^{31}P NMR so useful is that it detects **molecules** (like ATP, P_i, PCr)[1] that are directly involved in cellular energy metabolism.

Measuring brain energy metabolism

In addition to the quantification of metabolites, MRS also offers the possibility of measuring the rate of biosynthesis or degradation of certain metabolites. There are two technical approaches for this dynamic measurement: ^{13}C **isotopic** labelling and ^{31}P **saturation** transfer.

Importantly, ^{13}C isotopic labelling is able to measure the rate of the Krebs cycle [2] (V_{Krebs}) *in vivo*. The ^{13}C-labelled glucose is the premium precursor for brain measurements, since it drives around 90% of cerebral oxidative metabolism. Isotopic labelling is achieved through intravenous perfusion of ^{13}C glucose. ^{13}C-MRS is able to detect the incorporation of ^{13}C in the highest-concentration intermediates in the Krebs cycle, particularly glutamate Glu, Figure 1. The kinetics of ^{13}C incorporation serves as a basis for calculating Krebs cycle turnover rate. Alternative substrates like ^{13}C-labelled acetate can be used to measure other metabolic pathways in the brain (Figure 2).

Metabolic flux can also be gauged *in vivo* via ^{31}P NMR, using the "magnetisation transfer" technique. This protocol involves detecting the transfer of ^{31}P **magnetisation** between the substrate and the product of a chemical reaction. This method, when applied to the $P_i \leftrightarrow$ATP reaction, consists in selectively irradiating the terminal ^{31}P of ATP. Chemical exchange effects mean that this irradiation causes an attenuation of P_i magnetisation, an attenuation measured in order to deduce ATP synthesis rate.

A tool for studying brain disease

In vivo metabolic flux measurements applied in a disease setting can provide evidence on whether there has been a change in energy metabolism, the extent of the change, and its time-course. NMR measurements of metabolic flux could go beyond providing information on the biochemical mechanisms underlying the disease to become a tool for therapy assessment and follow-up. The CEA, in tandem with the **CNRS** (URA 2210) has heavily researched Huntington's disease – a hereditary neurodegenerative disorder characterised by abnormal body movements – via MRS. Animal models of the disease have been developed and then studied using both ^{13}C and ^{31}P NMR. The research then moved on to study groups of human patients, thereby providing some insight into the mechanisms underlying the neurodegeneration involved.

The NMR techniques and their applications outlined here offer only a partial illustration of the potential heralded by MRS. Ultra-high-**field** NMR systems to be developed over the next few years are expected to yield more highly localised spectroscopic measurements, and thereby create fully-fledged 'metabolic MRI' systems.

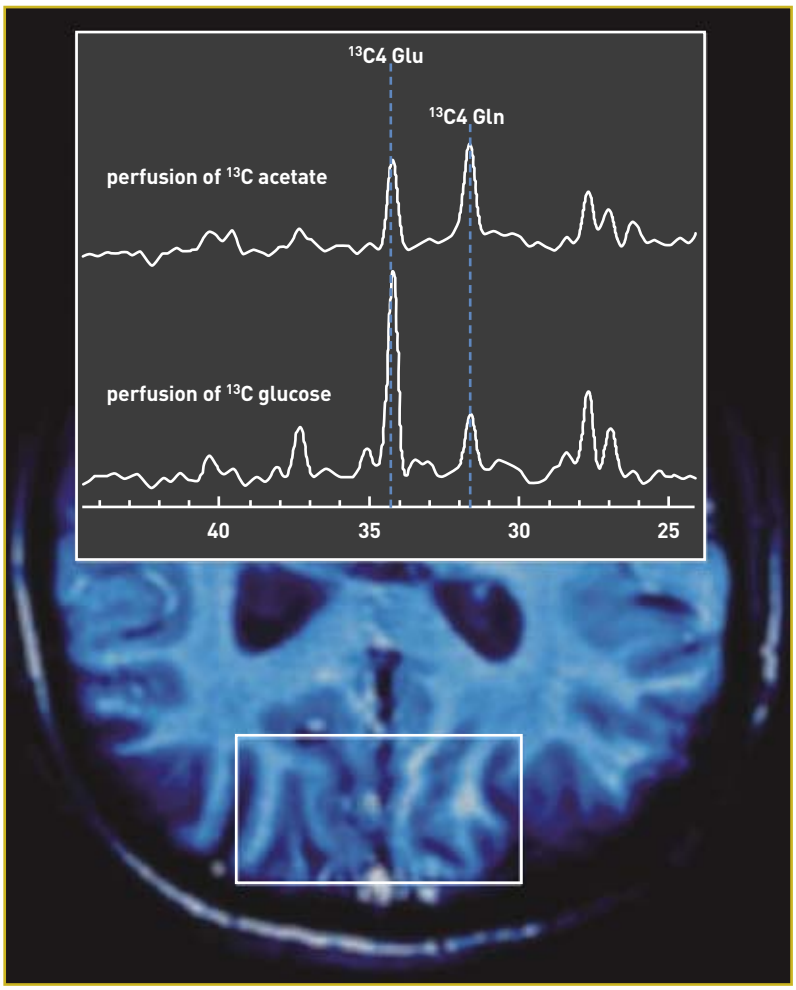

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Figure 2.
^{13}C NMR spectra of the human brain, which were acquired during ^{13}C acetate and ^{13}C glucose perfusions. These spectra were recorded in the region-of-interest bounded by a white rectangle on this NMR image of the brain generated through the same protocol. The perfusion of ^{13}C acetate (top spectrum) leads to a stronger glutamine peak (^{13}C4 Gln) than glutamate peak (^{13}C4 Glu), whereas the perfusion of ^{13}C glucose leads to a stronger glutamate enrichment. Since glutamine is compartmented in the astrocytes[3], the preferential labelling of glutamine during ^{13}C-acetate perfusion illustrates that the astrocytes preferentially oxidise the ^{13}C acetate substrate.

(1) ATP (adenosine triphosphate): a molecule that transfers energy from 'high-fuel' molecules for cell functions.

P_i (inorganic phosphate): an **ionised** compound of phosphoric acid that plays a role in cellular energy processes.

PCr (phosphorylcreatine): molecule that acts as an energy "buffer" in the ATP system.

(2) Krebs cycle: the final step of oxidative *catabolism* (a series of **enzymatic** reactions that breaks down large organic molecules like carbohydrates, fats and **proteins**, releasing energy as ATP) that in eukaryotic cells occurs in the *mitochondria*. It is the Krebs cycle that covers the majority of a cell's energy requirements.

(3) Astrocytes: glial cells (central nervous system cells that form a separate group from **neurons** and which can reproduce by *mitosis*) that play an active role in providing metabolic support and glucose nutrients to neurons (*type I astrocytes*), or in neurotransmission, where they act on the release and reuptake of neurotransmitters (*type II astrocytes*).

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FOCUS C

The main methods of medical imaging

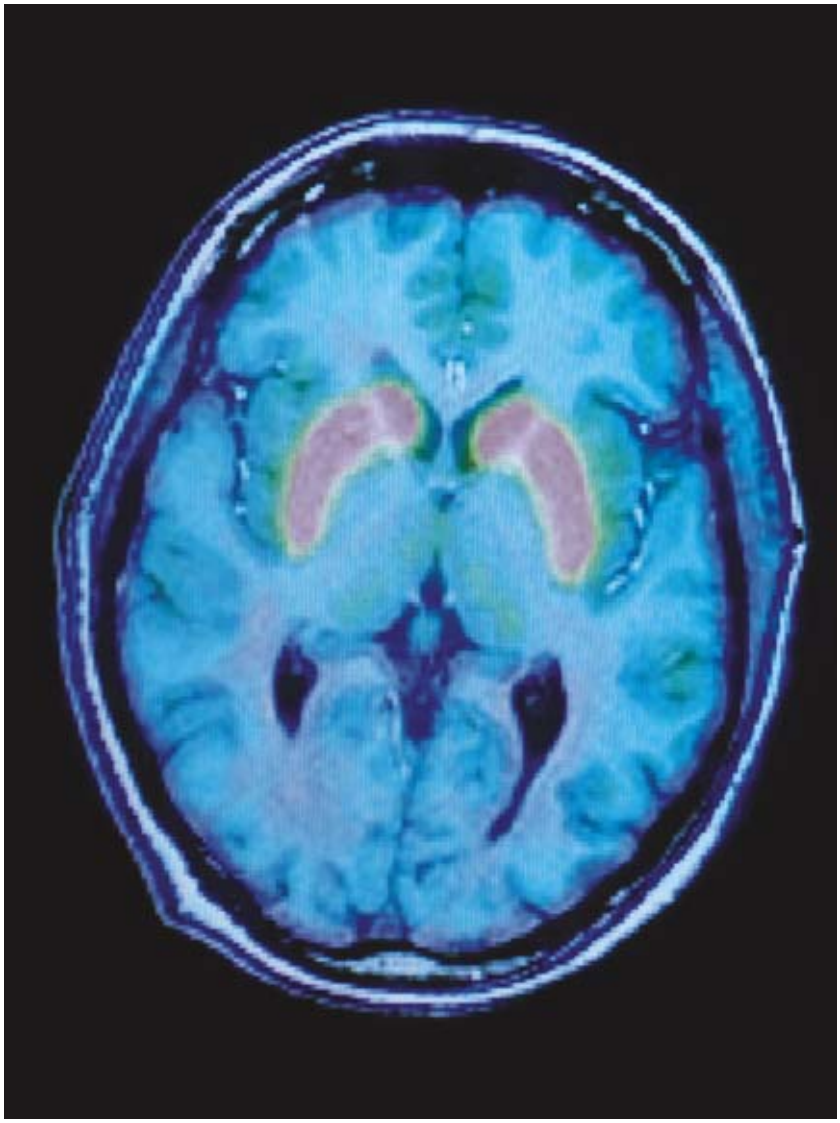
Medical imaging is a unique, non-invasive set of techniques that make it possible to visualise biological processes actually within living organisms themselves. It is a key means for providing insight into physiology and pathology, and ultimately for disease diagnosis, prognosis and therapy. Imaging is therefore the first-choice investigative tool in several branches of medicine and biology.

Medical imaging started with X-ray radiation and then developed further with the discovery of artificial radioactivity and the allied screening techniques. The next leaps forward, first to Nuclear Magnetic Resonance (NMR) and then to superconducting magnets, led to technological breakthroughs in Magnetic Resonance Imaging (MRI).

One of the key dynamic human brain imaging methods is Electroencephalography (EEG) which uses electrodes fitted on the scalp to measure the electrical activity produced by the brain through synaptic currents generated in neurons. EEG gives information on the time-locked neurophysiological activity of the brain, and in particular the cerebral cortex. This information is used in neurology for diagnostics, or in cognitive neuroscience for research.

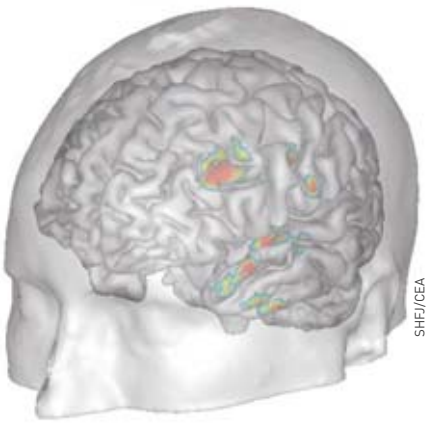
Magnetoencephalography (MEG) records the magnetic fields produced by the currents generated by neurons in the brain, using sensors fitted close to the head. MEG is employed in clinical settings by neurologists, especially when the focus is on epilepsy, and for cognitive neuroscience research. MEG can also be used to study developmental disorders like dyslexia, psychiatric disorders like schizophrenia and neurodegenerative disorders like Parkinson's and Alzheimer's.

Positron Emission Tomography (PET) consists in intravenously administering a tracer molecule labelled with a radioactive isotope and using external detection techniques to track how a normal or diseased organ functions. Radioactive tracers present the same physico-chemical properties as their non-radioactive counterparts, with the exception that they are able to emit radiation. This means that they act as a marker that is followed, using appropriate detection methods, to track the previously-labelled molecule's kinetics through the body. The data gathered is then analysed and transformed using a mathematical model to generate a screen image showing where the radiotracer settles in the body. PET is a widespread technique in physiological or pathophysiological studies on cognition and behaviour and is commonly used to study central nervous system disorders



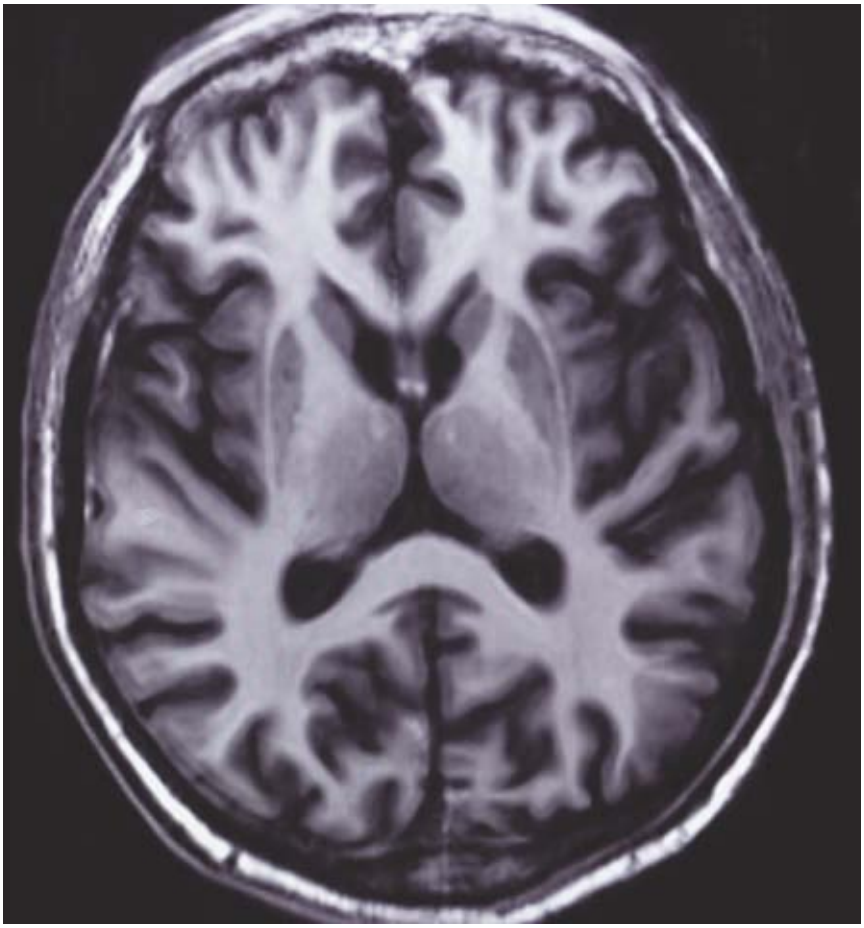
P. Stroppa/CEA

A PET image. The PET camera detects the positrons emitted by radioactive tracers previously injected into the living subject, and 3D images of the target organ are reconstructed by computer analysis.



SHFJ/CEA

Melancholic depression. PET images measuring regional energy activities merged with the aMRI image of the patient's brain. Areas of hypoactivation are individually detected.



P. Stroppa/CEA

Image acquired through the SHFJ's 3-T MRI system at Orsay (Essonne). This technique provides extremely high-precision analysis of infectious or inflammatory lesions, brain vessel damage, and tumours.

such as epilepsy, cerebral ischaemia, stroke, and neurodegenerative disorders (Parkinson's disease, Huntington's disease).

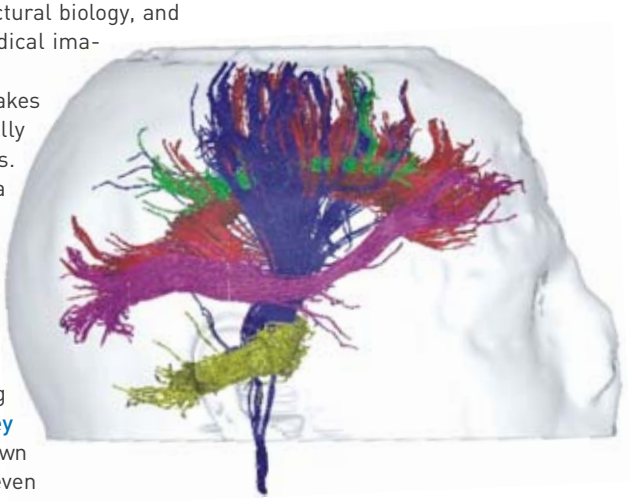
Magnetic Resonance Imaging (MRI) is a non-invasive *in vivo* imaging method. MRI is capable of studying 'soft' tissue such as the brain, bone marrow, or muscle, for example. It can be used to map anatomic structure (anatomical MRI, or aMRI), monitor organ function (functional MRI, fMRI) and track various processes of metabolism (Magnetic Resonance Spectroscopy, MRS). After its first developments in 1946, MRI uses the physical phenomenon of NMR that exploits the magnetic properties of atomic nuclei. Certain nuclei, such as the hydrogen nuclei for example, have a weak magnetic moment, or spin. NMR works by detecting variations in the magnetisation of atomic nuclei in response to an extremely powerful magnetic field and electromagnetic wave-driven excitation. When an electromagnetic wave is applied at the right frequency, i.e. the *resonance frequency*, these nuclei change alignment and emit signals as they return to their initial position. Technological advances in computing and magnetic fields have taken NMR from condensed matter physics on to chemical analysis and then structural biology, and more recently into medical imaging.

Anatomical MRI. MRI makes it possible to visually display all body organs. The resonance, under a very-high magnetic field, of water molecules, which are naturally abundant in most biological tissues, is used to generate cross-sectional images detailing brain structures (grey matter, white matter) down to the millimetre and even less. Radiologists use 'anatomical' imaging to detect and localize brain lesions.

Functional MRI. The recent acceleration in data acquisition and processing has led to the advent of 'functional' MRI, which is able to show neural activity in different brain regions. Indeed, speaking, reading, moving or thinking all activate certain areas in the brain. This neuronal activation triggers a local increase in blood flow in the brain regions concerned. Although it cannot directly detect neuronal activity, fMRI is able to detect the local, transient increase in blood flow that neuronal activity causes, which it does by gauging the magnetization of the haemoglobin contained in red blood cells.

Diffusion MRI (dMRI). Diffusion MRI is a powerful tool for measuring the movements of water molecules at the microscopic scale, thereby providing a precise architecture of the neuronal tissue and its variations. It offers a more direct method of measuring than other conventionally used imaging techniques. Diffusion MRI makes it possible to investigate tissue structure at a much finer scale than the millimetre scale offered by MRI image resolution, with the added advantage of being much faster.

This array of medical imaging technologies is rounded off by nuclear magnetic resonance spectroscopy (MRS), a non-invasive method of gaining biochemical and metabolic information on the central nervous system. MRS, which is based on the same principles as MRI, can be used to provide precise quantitative data on dozens of different molecules.



V. El Kouby, M. Perrin, C. Poupon and J.-F. Mangin, SHFJ/CEA

dMRI can diagnose certain pathologies very early on and provide images of the connective fiber clusters (white matter) that network the various brain regions together.

Superconductivity and superconductors

P. Stroppa/CEA

One of the main fields of application of superconductivity is medical imaging. This is the 3-tesla magnetic resonance imager at the SHFJ hospital in Orsay (Essonne).

Some historical background

Trains "flying" above the track using magnetic levitation, electricity storage finally resolved using giant magnetic coils, electrotechnical instruments and electric power transmission cables with no joule losses, magnetic fields that can be used to explore the human body and deliver even higher resolution images. People have been marvelling at the potential uses of superconductivity since 1911 when Dutch physicist Heike Kammerlingh-Onnes first discovered the extraordinary property exhibited by superconducting materials; their electrical resistance drops to zero below a certain critical temperature (which varies with their isotopic mass). This discovery won him the Nobel Prize in Physics in 1913.

Apart from zero electrical resistance and optimal electrical conductivity, the superconductors discovered by Kammerlingh-Onnes (later named type I superconductors) possess another remarkable property manifested by the Meissner effect, discovered in 1933 by German physicists Walter Meissner and Robert Ochsenfeld. If we ignore the London penetration depth[1], superconductors can be said to exhibit perfect diamagnetism, i.e. the superconducting material fully expulses its internal magnetic field up to a certain critical field value whereas, in theory, the magnetic field of a material with perfect conduction of electricity should equal that of the externally applied field.

Herein lies the second obstacle that continues to hamper superconductor applications: superconductivity is lost at above a critical magnetic field strength. For many years physicists thought there was only one type of superconductivity and that the magnetic anomalies observed in some samples were due solely to the presence of impurities. In the 1950s, however, Russian physicists Vitaly L. Ginzburg and Lev Davidovitch Landau came up with the theory that there were actually two types of superconductors.

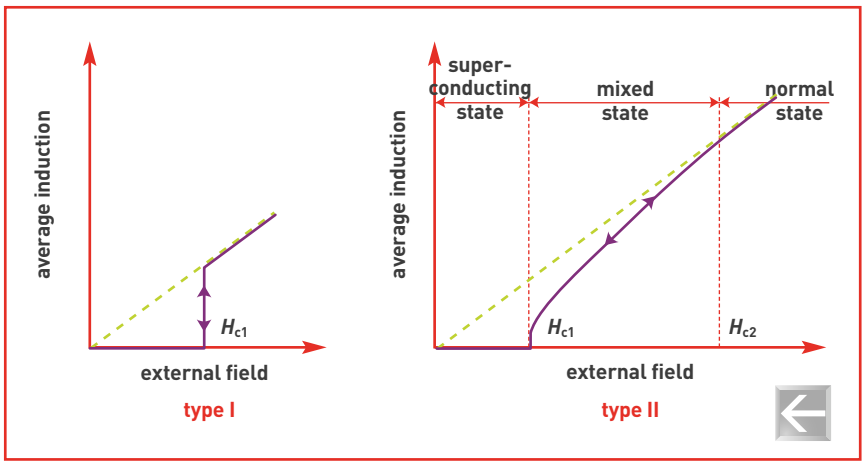
In 1957, the Russian-American physicist Alexei A. Abrikosov finally confirmed type II superconductivity. Type II superconductors exhibit a completely different type of magnetisation characterised by a mixed state that allows them to retain their superconducting state even in intense magnetic fields. This means they are not subject to the Meissner effect. In 2003, Abrikosov, Ginzburg and the Anglo-American physicist Anthony J. Leggett were awarded the Nobel Prize in Physics for their research into superconductors.

It was also in 1957 that American physicists John Bardeen, Leon N. Cooper and John R. Schrieffer published their theory of superconductivity, which won them the 1972 Nobel Prize in Physics. This BCS theory (named after the first letter of their surnames) postulates that electrons move through a conductor as Cooper pairs (two electrons with opposite spin). These pairs act like spin-zero bosons and condense into a single quantum state via a phonon interaction, which

(1) In 1935, Fritz and Heinz London proposed another explanation for the Meissner effect by claiming that the magnetic field decreases with depth from the surface of a superconducting material over a characteristic length λ_L known as the penetration depth.

is also a quantized mode of vibration. It is this electron-phonon interaction that underpins **resistivity** and superconductivity. **Ions** move in response to the ultra-fast passage of an electron (10^6 m/s), thereby creating an area of positive electrical charge which is held after the passage of the electron. This attracts another electron that pairs up with the first electron thereby resisting the **Coulomb repulsion** but not **thermal agitation**, which explains why temperature has such an adverse effect on superconductivity.

The BCS theory, which applies to **'conventional' superconductors**, did not however provide for the appearance of superconductivity at fairly high temperatures, i.e. higher than the temperature of liquid nitrogen (77 **K**, i.e. – 196 °C), and *a fortiori* at ambient temperature. This 77 K threshold was reached by using compounds such as Y-Ba-Cu-O (current records stand at around 165 K, at high pressure, and 138 K, i.e. – 135 °C, at standard pressure). German physicist Johannes Georg Bednorz and Swiss physicist Karl Alexander Müller were awarded the Nobel Prize in Physics in 1987 for their work on **unconventional superconductors**. They discovered a lanthanum-based copper oxide **perovskite** material that exhibited superconducting properties at a temperature of 35 K (- 238 °C). By replacing lanthanum with yttrium, particularly in $YBa_2Cu_3O_7$, they were able to significantly raise the critical temperature thus developing the cuprate family of superconductors. Although these are highly effective superconductors, the fact that they are ceramics makes them difficult to use in electrotechnical applications. All **high-critical-temperature superconductors** are type II superconductors.



(taken from Lavoisier, "*Matériaux supraconducteurs*")

Figure 1.
Average induction in type I and type II superconductors under an externally applied magnetic field.

The strange magnetic properties of type II superconductors

In the presence of a magnetic field, type II superconductors exhibit perfect diamagnetism up to certain field H_{c1} just like type I superconductors. Beyond H_{c1}, however, type II superconductors enter a mixed state that allows partial field penetration up to H_{c2} (Figure 1), thereby permitting a material to be superconducting under a high magnetic field.

This mixed state resembles an array of normal-state cores that start to fill the superconducting material at H_{c1} and over. Each region contains a flux quantum ($2.07 \cdot 10^{-15}$ **weber**) and is surrounded by a vortex of superconducting currents (Figure 2). When the magnetic field increases, the network densifies until it completely fills the superconducting material at H_{c2}.

The distinction between the two types of superconductivity is coupled to the concepts of coherence length ξ and penetration depth λ_L, which characterise the interface between a normal region and a superconducting region. ξ represents the spatial variation of the superconducting state (i.e. the density of the superconducting electrons) and λ_L the London penetration depth of the magnetic field. It is the ratio of these two characteristic lengths, known as the *Ginzburg-Landau parameter* and written as κ ($\kappa = \lambda_L/\xi$), that determines which type of superconductivity is involved. If $\kappa < \sqrt{2}/2$, the superconductor is type I, and if $\kappa > \sqrt{2}/2$, the superconductor is type II.

At the interface, the penetration of the magnetic field, as defined by λ_L, corresponds to an increase in free energy in the superconducting material, while the formation of the superconducting state, characterised by the coherence length, is related to a decline in free energy. The interface's energy balance varies with the ratio κ. In type II superconductors, the

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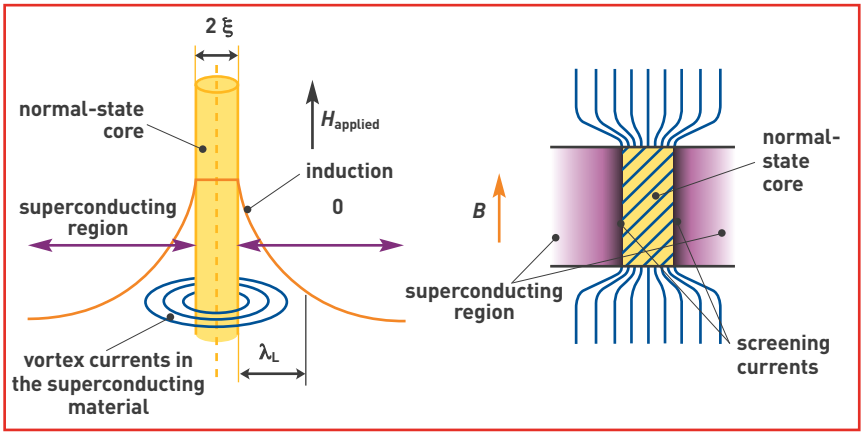

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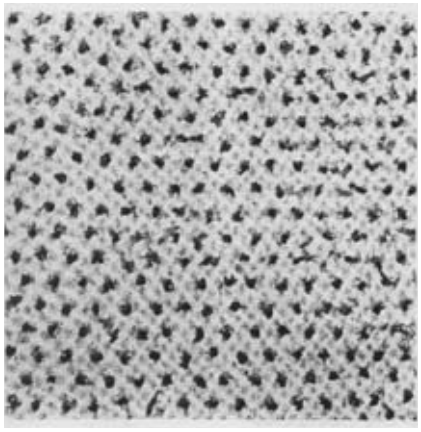
Figure 2.
Diagram of a vortex illustrating penetration depth and coherence length.



U. Essmann and H. Träuble

Magnetic pattern on the surface
of a superconductor in mixed state.

material		ξ (µm) 0 K	λ_L (µm) 0 K	κ	T_c (K)	$\mu_0 \cdot H_{c1}$ (teslas) 0 K	$\mu_0 \cdot H_{c2}$ (teslas) 0 K
type I	Al	1.36	0.05	0.04	1.18	0.010 5	
	Pb	0.083	0.037	0.5	7.18	0.080 3	
type II	NbTi	0.005	0.3	60	9.25	0.01	14
	Nb_3Sn	0.003 6	0.065	18	18	0.017	25.5
	YBaCuO	plane 0.003	plane 0.8	≈ 300	93		140
		axis *c* 0.000 6	axis *c* 0.2				

Table.
Characteristics of some type I and type II superconductors. $\mu_0 \cdot H_{c1}$ and $\mu_0 \cdot H_{c2}$ represent magnetic inductions, where μ_0 is the magnetic permeability of a vacuum (and of the material in this particular case).

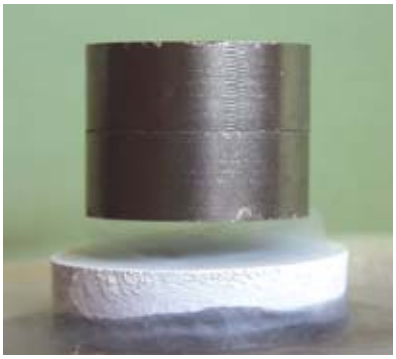
page 17 cont'd
mixed state therefore results from the creation of a large number of interfaces, with each interface corresponding to a negative energy balance conducive to superconductivity above the H_{c1} field (Table).

Potential avenues for application

Type I superconductivity does not present any great potential for new areas of application. Unfortunately, the critical temperature that limits superconductivity applications is very low in the two superconducting materials that currently offer real-world applications i.e. niobium-titanium, NbTi (9.2 K) - the first superconducting cables in niobium-titanium alloy were developed in the early 1960s - and niobium-tin, Nb_3Sn (18 K). These materials have to be cooled to the temperature of liquid helium (4.2 K)[2] in order to activate their superconducting properties. This temperature was the first important milestone towards achieving superconductivity at ambient temperature, which is the ultimate goal.

Type II superconductors can withstand very strong magnetic fields, and are also able to carry extraordinarily high current densities, up to another critical value that varies with the magnetic field (Figure 3). This fact heralded the development of the first superconducting magnets. The current densities that can be generated under these conditions are huge in comparison with what can be achieved with domestic or industrial electrotechnical applications (around 10 A/mm²).

Since the 1970s, the CEA has been focusing its research on the production of large-scale intense permanent magnetic fields (magnetic confinement of fusion plasmas, particle physics, medical imaging). In fact, these are the predominant applications of type II superconductors, mainly NbTi[3], where superconductivity significantly cuts down on electric power consumption despite the cryogenic efficiency of the facilities - in fact, one watt dissipated at 4.2 K requires a minimum consumption of 300 W at ambient temperature in the largest industrial power plants. While researchers the world over still dream of developing superconducting materials that function at room temperature, it would seem that applied superconductivity will still have to rely on the use of very low temperature cooling for the foreseeable future.



LEG Grenoble

The discovery of high-critical-temperature superconductivity made it possible to see how superconductivity manifests in the open air in the form of a magnet floating above a pellet of liquid-nitrogen cooled YBaCuO, which is now a famous example of the effect.

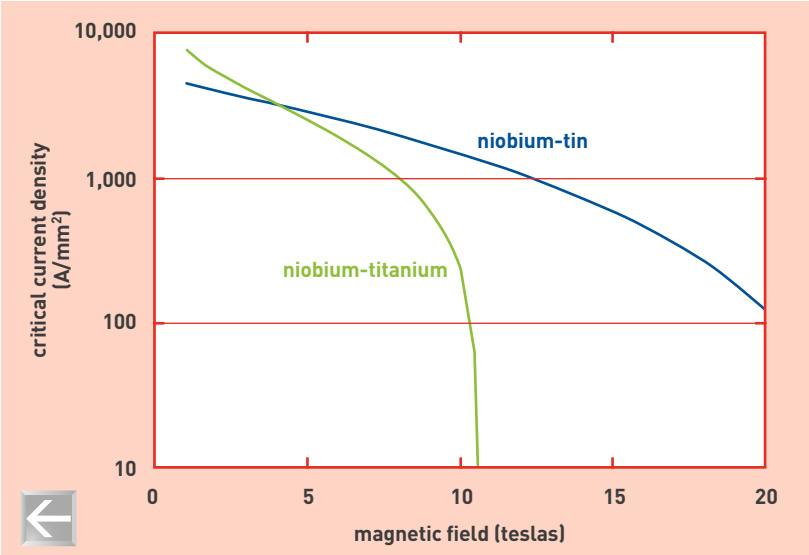


Figure 3.
Characteristic critical current densities in relation to a 4.2-K magnetic field for the two superconducting materials most widely used, particularly in the manufacture of superconducting magnets.

(2) The history of superconductivity actually goes as far back as William Ramsay who, in 1895, was the first person to isolate helium. Indeed, where would the science of superconductivity be today if it wasn't for helium which is the key component of the ultra-low cooling process? Note also that Kammerlingh-Onnes finally succeeded in producing liquid helium in 1908 following unsuccessful attempts by James Dewar in the late 19th century, thus paving the way to the discovery of superconductivity.

(3) Produced in quantities of around 1,500 to 2,000 tons per year.

FOCUS A

The different types of magnetism

The origins of magnetism lie in the properties of electrons as explained by the laws of quantum physics. Part of an electron's magnetic properties (*spin magnetism*) results from its quantum-mechanical spin state, while another part results from the orbital motion of electrons around an atom's nucleus (*orbital magnetism*) and from the magnetism of the nucleus itself (nuclear magnetism). This is put to use, in particular, for nuclear magnetic resonance imaging in the medical field. Magnetism is therefore produced by electric charges in motion. The force acting on these charges, called the Lorentz force, demonstrates the presence of a magnetic field.

Electrons have an intrinsic magnetic dipole moment (the magnetic quantum state being the Bohr *magneton*), which can be pictured as an electron's rotational motion of spin around itself in one direction or another, oriented either upwards or downwards. The *spin quantum number* (one of the four numbers that 'quantifies' the properties of an electron) equals 1/2 (+ 1/2 or - 1/2). A pair of electrons can only occupy the same *orbital* if they have opposite magnetic dipole moments.

Each atom acts like a tiny magnet carrying an intrinsic magnetic dipole moment. A nucleus (the neutron and proton individually have a half-integer spin) will have a half-integer spin if it has an odd atomic mass number; zero spin if the atomic mass number and charge are even, and an integer spin if the atomic mass number is even and the charge odd.

On a larger scale, several magnetic moments can together form magnetic domains in which all these moments are aligned in the same direction. These spatial regions are separated by domain walls. When grouped together, these domains can themselves form a macroscopic-scale magnet (Figure E1).

The type of magnetism that comes into play is determined by how these elementary constituents are ordered, and is generally associated with three main categories of material: *ferromagnetic*, *paramagnetic* and *diamagnetic*.

Any material that is not diamagnetic is by definition paramagnetic provided that its magnetic susceptibility is positive. However, ferromagnetic materials have particularly high magnetic susceptibility and therefore form a separate category.

1. Ferromagnetic materials are formed of tiny domains inside which atoms exhibiting parallel magnetisation tend to align themselves in the direction of an external magnetic field like elementary dipoles. In fact, the magnetic moments of each atom can align themselves spontaneously within these domains, even in the absence of an external magnetic field. Applying an external field triggers domain wall movement that tends to strengthen the applied field. If this field exceeds a certain value, the domain most closely oriented with the direction of the applied field will tend to grow at the expense of the other domains, eventually occupying the material's whole volume. If the field diminishes, the domain walls will move, but not symmetrically as the walls cannot fully reverse back to their original positions. This results in remanent magnetisation, which is an important feature of naturally occurring magnetite, or of magnets themselves.

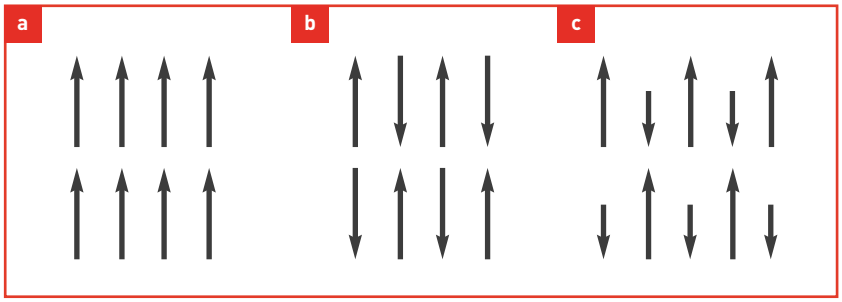


Figure E1.
Intrinsic magnetic dipole moments have parallel alignment in ferromagnetic materials (a), anti-parallel alignment but zero magnetisation in antiferromagnetic materials (b), and anti-parallel alignment with unequal moments in ferrimagnetic materials (c).

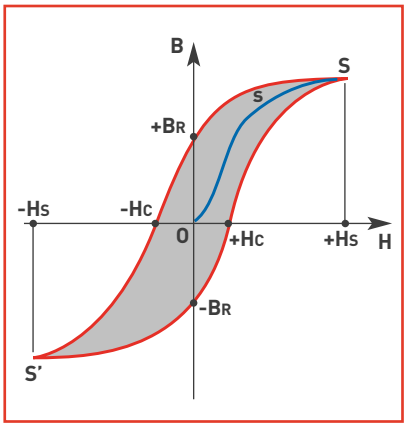


Figure E2.
The induction B of a magnetic material by a coil is not proportional to its magnetic excitation (*field H*). While the initial magnetisation forms an OsS-type curve, shown in blue in the figure, it reaches saturation at point s. Only a partial induction is retained if the field approaches zero; this remanent induction can only be cancelled out by reversing the magnetic field to a "coercive" field value. This hysteresis loop illustrates the losses due to "friction" between the magnetic domains shown on the area bounded by the magnetisation and demagnetisation curves.

The whole process forms a hysteresis loop, i.e. when the induced field is plotted against the applied field it traces out a *hysteresis curve* or *loop* where the surface area represents the amount of energy lost during the irreversible part of the process (Figure E2). In order to cancel out the induced field, a coercive field has to be applied: the materials used to make artificial permanent magnets have a high coercivity.

Ferromagnetic materials generally have a zero total magnetic moment as the domains are all oriented in different directions. This ferromagnetism disappears above a certain temperature, which is known as the Curie Temperature or Curie point.

The magnetic properties of a given material stem from the way the electrons in the metallic cores of a material or of a transition metal complex collectively couple their spins as this results in all their spin moments being aligned in the same direction.

Materials whose atoms are widely distributed throughout their crystal structure tend to better align these elementary magnets via a coupling effect. This category of materials, which is characterised by a very high positive magnetic

Stoiber Productions, München

A Transrapid train using magnetic levitation arriving at the Long Yang bus station in Shanghai (China). This German-built high-speed, monorail train was commissioned in 2004 to service the rail link to Pudong international airport.

susceptibility, includes iron, cobalt and nickel and their alloys, steels in particular, and some of their compounds, and, to a lesser extent, some rare earth metals and alloys with large crystal lattices, and certain combinations of elements that do not themselves belong to this category. In ferrimagnetic materials, the magnetic domains group into an anti-parallel alignment but retain a non-zero magnetic moment even in the absence of an external field. Examples include magnetite, ilmenite and iron oxides. Ferrimagnetism is a feature of materials containing two types of atoms that behave as tiny magnets with magnetic moments of unequal magnitude and anti-parallel alignment. Antiferromagnetism occurs when the sum of a material's parallel and anti-parallel moments is zero (e.g. chromium or haematite). In fact, when atoms are in a close configuration, the most stable magnetic arrangement is an anti-parallel alignment as each magnet balances out its neighbour so to speak (Figure E1).

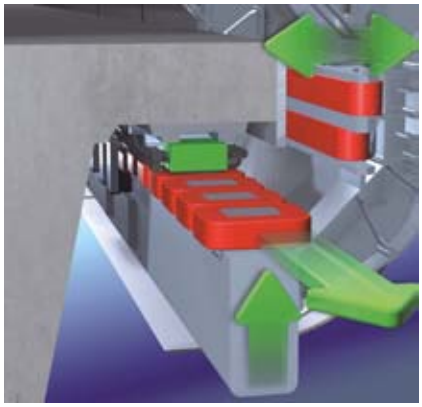
2. Paramagnetic materials behave in a similar way to ferromagnetic materials, although to a far lesser degree (they have a positive but very weak magnetic susceptibility of around 10^{-3}). Each atom in a paramagnetic material has a non-zero magnetic moment. In the presence of an external magnetic field, the magnetic moments align up, thus amplifying this field. However, this effect decreases as temperature rises since the thermal agitation disrupts the alignment of the elementary dipoles. Paramagnetic materials lose their magnetisation as soon as they are released from the magnetic field. Most metals, including alloys comprising ferromagnetic elements are paramagnetic, as are certain minerals such as pegmatite.

3. Diamagnetic materials exhibit a negative and an extremely weak magnetic susceptibility of around 10^{-5}. The magnetisation induced by a magnetic field acts in the opposite direction to this field and tends to head away from field lines towards areas of lower field strengths. A perfect diamagnetic material would offer maximum resistance to an external magnetic field and exhibit zero permeability. Metals such as silver, gold, copper, mercury or lead, plus quartz, graphite, the noble gases and the majority of organic compounds are all diamagnetic materials.

In fact, all materials exhibit diamagnetic properties to a greater or lesser extent, resulting from changes in the orbital motion of electrons around atoms in response to an external magnetic field, an effect that disappears once the external field is removed. As Michael Faraday showed all that time ago, all substances can be "magnetised" to a greater or lesser degree provided that they are placed within a sufficiently intense magnetic field.

Electromagnetism

It was the Danish physicist Hans Christian Ørsted, professor at the University of Copenhagen, who, in 1820, was first to discover the relationship between the hitherto separate fields of electricity and magnetism. Ørsted showed that a compass needle was deflected when an electric current passed through a wire, before Faraday had formulated the physical law that carries his name: the magnetic field produced is proportional to the intensity of the current. Magnetostatics is the study of static magnetic fields, i.e. fields which do not vary with time.



Close-up of the magnets used to guide and power the train.

Magnetic and electric fields together form the two components of electromagnetism. Electromagnetic waves can move freely through space, and also through most materials at pretty much every frequency band (radio waves, microwaves, infrared, visible light, ultraviolet light, X-rays and gamma rays). Electromagnetic fields therefore combine electric and magnetic force fields that may be natural (the Earth's magnetic field) or man-made (low frequencies such as electric power transmission lines and cables, or higher frequencies such as radio waves (including cell phones) or television.

Mathematically speaking, the basic laws of electromagnetism can be summarised in the four Maxwell equations (or Maxwell-Lorentz equations) which can be used to provide a coherent description of all electromagnetic phenomena from electrostatics and magnetostatics to electromagnetic wave propagation. James Clerk Maxwell set out these laws in 1873, thirty-two years before Albert Einstein incorporated the theory of electromagnetism in his *special theory of relativity*, which explained the incompatibilities with the laws of classical physics.