

A CENTRAL FRONTIER FOR PHYSICS RESEARCH: THE HUMAN BRAIN STRUCTURE AND FUNCTION

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Nuclear Magnetic Resonance (NMR) is eminently suited for the *in vivo* study of living matter. In this paper, some of the frontier applications of NMR to both the physiological features and pathological alterations of the human brain will be discussed, with special emphasis on the biophysics of brain function.

Physicists, in general, investigate Nature by studying either simple systems or single elements of a system in order to find an easier way for the experimental tests and the theoretical analysis. Living organisms are quite complex and one of their intrinsic features is being structurally heterogeneous. Although a reductionist approach – like studying a part of an organism – can provide insight and help to build up a model for the working of the whole system, it will never provide a direct experimental information about the processes, which occur in the complete organism during its life. Of course the study of man is specially important and in particular that of the human brain, which represents probably the most extraordinary frontier of research for its vast amount of unknown mechanisms and functions, responsible for the human life and for our identity.

Living organisms are of course a special part of the condensed matter that physics has always studied by means of spectroscopic tools. Their heterogeneity requires though that the data are acquired in a spatially resolved way and on time scales shorter than the times characterizing the processes occurring in them. Most of the spectroscopic methods, commonly used in condensed-matter physics research, are not applicable for the investigation of living organisms either because the radiation they use is highly absorbed by the living tissues or due to the impossibility to invent, at the moment, an imaging procedure capable of providing interpretable matrices of data. Moreover these investigation tools, if applied to the study of brain in a living human, must have the fundamental prerequisite of being almost non-invasive and of generating the minimum perturbation.

In the last few decades some new physical techniques, like Positron Emission Tomography (PET), Magnetic Resonance Imaging (MRI), Diffusion Tensor Imaging (DTI) and functional Magnetic Resonance Imaging (fMRI) together with Electro Encephalography (EEG) and Magneto Encephalography (MEG), have opened new investigation lines for the brain structural and functional properties, without substantial perturbation.

Nuclear Magnetic Resonance (NMR) is a very wide field of spectroscopic methods of great versatility, a field from which new original spectroscopic modalities are to be expected. There are some fundamental physical reasons for the extraordinary powers of NMR:

- 1) First of all, due to the range of radiofrequencies used, the spontaneous emission from the excited states is in practice absent and the mechanisms of approach to thermal equilibrium of the nuclear-magnetic-levels populations are very slow (in living tissues the time constant T_1 's are several hundred milliseconds) as they are caused by the interatomic magnetic interactions modulated by molecular dynamics.
- 2) The radiofrequency used is coherent as it is generated electronically and irradiated by solenoids or other sorts of coils.
- 3) The number density of photons in the RF pulses is very high, due to the low energy of each phonon; at 100 MHz (a frequency in the range of those used for *in vivo* NMR) the number of photons is about seven order of magnitude higher than that produced by the same power irradiated at visible frequencies.
- 4) Because of points 1), 2) and 3) the populations on the

nuclear-magnetic-energy levels can be normally inverted (spin thermodynamics has also the negative range of temperatures).

- 5) Due to the fact that different nuclei have quite different gyromagnetic ratios, and that the resonant frequency is given by the product of the magnetic-field intensity and the gyromagnetic ratio, by choosing the proper resonant frequency it is possible to select one subsystem out of all the nuclei; thus in a living organism one can investigate, for example, the magnetization of ^{31}P alone (contained in a few important metabolic compounds), neglecting at the same time the nuclear magnetization of all the other nuclei. Besides the detection of a single nuclear subsystem, naturally existing in the living body, one can introduce metabolites tagged with special non-radioactive isotopes (^{13}C , ^{19}F , ^{15}N , etc). By doing so, it is possible to follow the metabolic processes *in vivo* and their localization.
- 6) The nuclear interactions which characterize the NMR spectrum are those of the nuclear electric quadrupole with the electric-field gradient, the inter-atomic magnetic dipole-dipole interaction, the chemical shift (in practice the diamagnetic electronic shield effect to the intense static field) that nuclei experience, the indirect magnetic dipole-dipole interaction through the electronic polarization (J coupling). Most of these interactions are non-central and thus, having positive and negative values can be partially or totally cancelled either by the molecular motion or by the proper choice of the radiofrequency pulse sequence. This way the interpretation of the spectra is greatly facilitated.
- 7) NMR has the capability of measuring several observables and their spatial dependence (imaging) like: spin density, the spin-lattice relaxation time T_1 (related to molecular dynamics), the spin-spin relaxation time T_2 , the chemical shift (which allows the mapping of several metabolites), the diffusion tensor D (whose imaging provides the axonal cabling of different neuronal areas, flow, the J coupling, etc.)

All these features, together with the negligible interaction of the radiofrequency with the living tissues, make NMR of absolute primary relevance for the investigation of biological systems.

Among the areas of research on biological systems, the human brain structure and function represents an extraordinary potential source of knowledge. Of course we refer to a Galileian approach to this target, by making use of new physical methods. In fact the physics research on human brain structure and function will be both

- i) a way to contribute to the solution of some of the fundamental questions of knowledge concerning memory, logic, conscience, the definition of the border

between life and death, etc.;

- ii) a crucial contribution towards understanding the causes and the evolution of the neurodegenerative diseases, a dramatic emergency hitting several million human beings.

Our research for over a decade has exploited the great versatility of NMR to investigate the human brain function. Physical methods related to NMR in which we were strongly involved are the following:

- brain energetics and the resting brain,
- the water diffusion in the brain,
- multimodal approaches,
- neurocurrents imaging and Ultra Low Field MRI.

1 Brain energetics and the resting brain

The energetics of the human brain, namely the study of the energetic expenditure on brain function, as well of the strategies the brain exploits in order to restore its chemical energy charge, is an emerging field in neurosciences. This is basically related to the underlying fundamental biochemical principle linking function and metabolic regulation, which applies to the cellular as well as to the organ and organism level. In particular, metabolism is not a mere collection of reactions subserving the provision of energy substrates to a tissue in order to realize its function. In fact, metabolism poses severe limitations on the modality in which energy is consumed by the different processes of cell physiology [1]. This is especially relevant for the brain, which utilizes nearly 20% of the total energy of the organism even if it accounts for only 2% of the body weight. In spite of a massive vascularisation, and of a very high aerobic capacity, the energetic needs of primates brain is barely satisfied in ordinary conditions, as is clearly shown by the degree of damage a short deprivation of blood supply can induce. Furthermore, metabolism itself can influence brain activity through metabolic cascades resulting in the formation of a multitude of chemical signals. In fact, in the last decades it has been demonstrated that several byproducts of cerebral metabolism, notably of possible non-neuronal origin, can modulate the excitability of neurons and their firing patterns [2].

Besides these general facts, there is a number of practical reasons that make neuroenergetics important for the study of the brain. Several pathologies, including epilepsy, and neurodegenerative diseases, are related (not necessarily in a cause-effect fashion) to alteration to the metabolic rates or equilibriums. Considering future developments, the realization of interfaces brain-computer are tightly related to this issue, in particular considering the local energetic limitations of the human brain. Any kind of interface should comply with these limitations, that are currently unknown

from a quantitative point of view. It is perfectly possible, for instance, that an external input carries a quantity of information requiring an energy too high to be elaborated. This “energetic overflow” is something that can be predicted on theoretical bases and should not be overlooked.

The available estimates of the energy expenditure of individual neuronal processes are still incomplete, thus preventing us from fully understanding how resources are quantitatively allocated by the brain, while resting and signaling. This is thought to be essential in the understanding of adaptive changes that have molded both the effect of metabolism on function and vice versa. Moreover, it is possible that astrocytes have a crucial energetic role [3, 4]. Astrocytes are non-excitabile brain cells that actually outnumber neurons, albeit being comparable in total volume. It has been hypothesized that astrocytes participate in a tight metabolic partnership with neurons, via a neurotransmitter-dependent lactate trafficking between astrocytes and neurons. While this latter hypothesis is debated, the partnership between neurons and astrocytes is supposed to be crucial in several features of brain function. In particular, they are involved in potassium homeostasis, neurotransmitters recycling, vascular control, and modulation of synaptic signaling [5]. The latter two features directly link astrocytes to the generation of the fMRI signal, while lactate trafficking can be studied with proton and ^{13}C magnetic-resonance spectroscopy.

In this regards, neurovascular coupling and neurometabolic coupling (*i.e.* the coupling between neural activity and vascular response or metabolism modulations, respectively) allow the indirect study of brain function, via well-established fMRI techniques based on the assessment of cerebral blood flux, or on the BOLD (Blood-oxygenation level dependent) contrast (fig. 1), or via spectroscopic techniques.

The features themselves of the energetic brain demand, and in particular the relative low regional increase of this demand during strong neural activity, have triggered a growing branch of fMRI and metabolic studies aimed at understanding how is the basal energy used. It is well known that neuronal and astrocytic membranes are imperfect dielectrics, thus making extremely expensive the maintenance of the resting membrane potentials because of ions leakage, even in the absence of any electrical stimulation. Nonetheless, a significant energy expenditure is related to fluctuations of neural activity, that induce slow fluctuations of the fMRI signal. These fluctuations

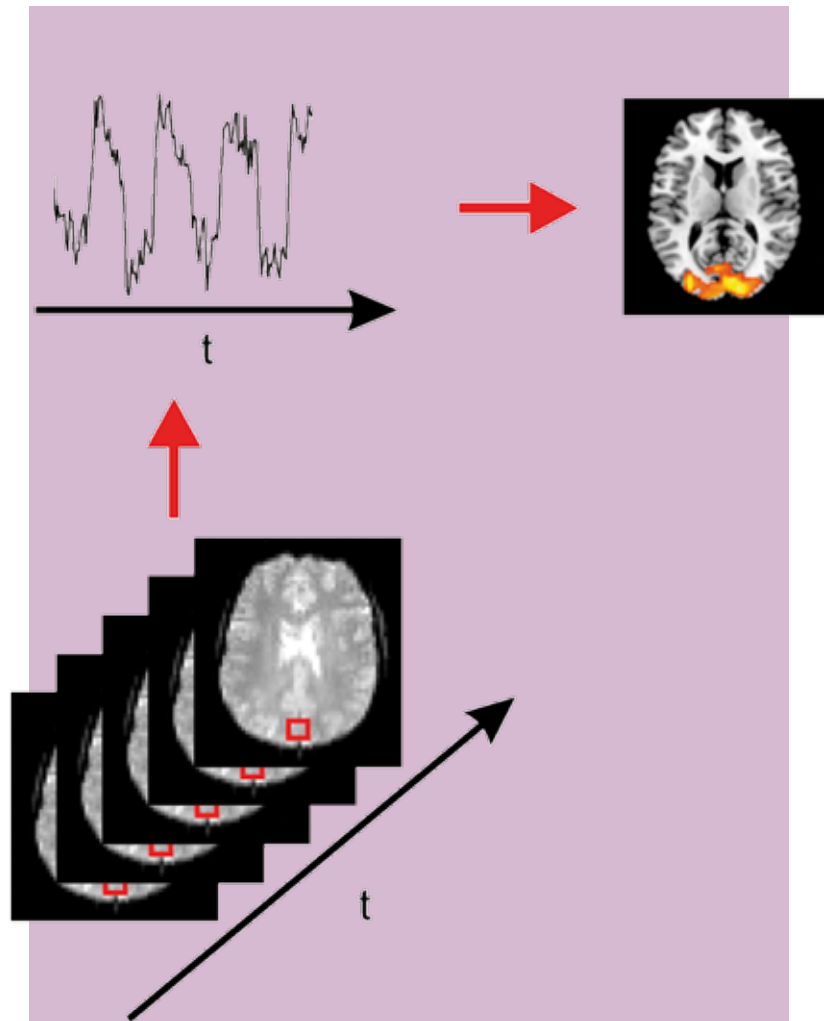


Fig. 1 Typical BOLD-based experiment.

Bottom: a series of fast images is acquired while the subject performs a task. A whole brain image can be acquired in about 1-2 seconds with EPI (Echo Planar Images) approaches. These EPI are intrinsically sensitive to T_2^* , a parameter that is affected by tissue paramagnetism. Given that deoxyhaemoglobin, but not oxyhaemoglobin, is paramagnetic, the intensity of each voxel (element of volume) of the images is modulated by the local degree of blood oxygenation, that in turn depends on the brain activity. In particular, the activity induces a transient hyperoxygenation, that results in a longer T_2^* , hence in a slightly more intense voxel.

Top left: the time course of each voxel is examined. Voxels in

regions responding to the task show a time course correlated with the task, with an amplitude modulation depending on the magnetic field, but in the order of 1-5% over the baseline. Voxels in regions not responding to the task carry only noise.

Top right: the time course of each voxel is compared to the expected response with statistical approaches, against the null hypothesis that the voxel does not respond to the task. Based on the result of the statistical tests, parametrical maps are obtained, showing statistical parameters (*e.g.* z-value) or physiological parameters (*e.g.* the percent variation of signal). Statistical maps are usually superimposed to high-resolution anatomical images in order to match activated areas with the corresponding anatomical structures.

are coherent, and are organized in networks consistent across subjects, supposed to constitute the brain ongoing activity during the resting state, and reflecting long range functional connectivity between distinct brain areas [6]. The functional role of these oscillations is highly controversial. It has been related to random silent thought, to the balance between internal state and external environment, or even to high-level concepts, as self-referential behaviour, or consciousness. Whatever the meaning and the mechanisms, recent studies highlighted that steady-state networks are modulated, but generally not suppressed by brain steady state activity, as well as by many neurological or psychiatric diseases, suggesting that BOLD-fMRI oscillations are an integral part of the brain function.

2 The water diffusion in the brain

The connectivity obviously requires the existence of a physical connection, which is represented by bundles of axons detectable by the use of Diffusion Tensor Imaging (DTI). This imaging method, although already in use, is still in continuous evolution.

The time dependent NMR signal $S(t)$ is a function of several observables, as we said before, among which there is the diffusion tensor D , that can be accurately measured as a function of spatial coordinates. The equations which govern the diffusion process in homogeneous systems are

$$\vec{J} = -D\vec{\nabla}c, \text{ Fick's law,}$$

$$\frac{\partial}{\partial t}c = -\vec{\nabla}\vec{J}, \text{ Mass conservation law.}$$

where J is the mass flow and c the concentration of the diffusing particle, which in our case is in general the water molecule.

From the combination of the two equations one gets the diffusion equation:

$$\frac{\partial}{\partial t}c = \vec{\nabla}(D\vec{\nabla}c), \text{ Diffusion equation.}$$

This equation can be in general rewritten as

$$\frac{\partial C}{\partial t} = D \left(\frac{\partial^2 C}{\partial x^2} + \frac{\partial^2 C}{\partial y^2} + \frac{\partial^2 C}{\partial z^2} \right) = D\nabla^2 C,$$

if one assumes that the diffusion coefficient does not depend directly on spatial coordinates. The dependence of the NMR signal S on D is reported in fig. 2. Of course in heterogeneous systems like the brain tissue the diffusion coefficient tensor components change from voxel to voxel and their determination requires several measurements, as is shown in fig. 2.

This diffusion is commonly called Gaussian diffusion; in fact

if one writes the equations in terms of probability rather than concentration (P the probability that one water molecule moves from r' to r'' in a time t),

$$P(r'' - r', t),$$

that, setting

$$R = r'' - r',$$

becomes

$$P(R, t),$$

the diffusion equation

$$\frac{\partial P}{\partial t} = D\nabla^2 P$$

has the Gaussian solution

$$P(R, t) = \frac{1}{\sqrt{4D\pi t}} \exp\left(-\frac{R^2}{4Dt}\right),$$

which gives for the mean square displacement the well-known result

$$\langle R^2 \rangle = \int_{-\infty}^{+\infty} R^2 P(R, t) dR = 6Dt.$$

This is the principle on which the Diffusion Tensor Imaging is based. However the real diffusion of the water molecule within the complex and variably organized cerebral tissue does not respect a Gaussian law. Several boundaries limit the free diffusion, which is thus restricted by different structures which characterize the tissue. Some empirical models have been proposed, and research to connect parameters contained in new expressions to the microscopic structure of the tissue is carried out in different places, besides our group.

3 Multimodal approaches

In vivo imaging of the brain function based on the BOLD contrast offers significant advantages, including completely non-invasive nature, excellent spatial resolution (1 mm³, or less, is the current state of the art), wide availability on commercial MRI scanners. However, it is an indirect technique, being based on a complex interplay between haemodynamic and metabolic events, that in turn depend on neural activity. This intrinsic limitation can be at least partially overcome by multimodal approaches, mainly based on the combined acquisition of functional MRI and electrophysiological signals, that allow to directly correlate the BOLD signal with the underlying electrical activity [7].

Electrophysiological approaches can be broadly divided into two classes: invasive, and non-invasive. Invasive approaches include the use of single microelectrodes, grids, or arrays, that can be used for individual spikes recording, as

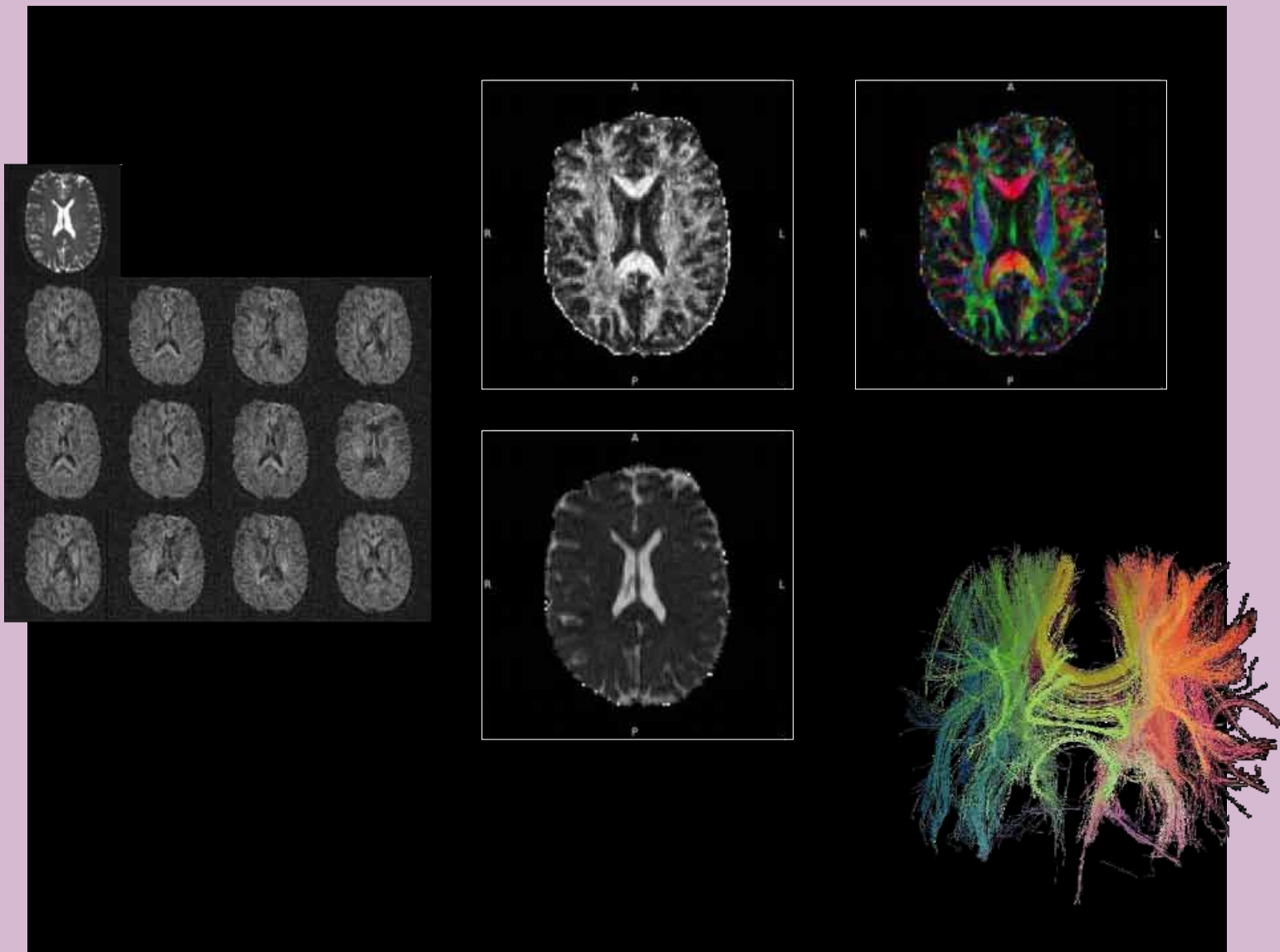


Fig. 2 Example of a DTI acquisition and processing. Left: At least one image without diffusion weighting (S_0 , top) and six images with diffusion weighting in different directions (S_b , bottom, 12 are shown) are needed, because the tensor is symmetric. The diffusion weighting is given by the application of diffusion gradients in different directions. Note that the diffusion weighted images have a lower SNR. The cerebrospinal fluid (where diffusion is essentially free) shows the higher attenuation. White matter shows less attenuation, but the attenuation is modulated by the direction of the gradient: the effect is particularly evident, for instance, in the splenium (posterior part) of the corpus callosum, that

include large bundles of fibres coherently orientated. In case of Gaussian diffusion, the signal is attenuated following the law $\frac{S}{S_0} = e^{-\sum_{i=1}^S \sum_{j=1}^S b_{ij} D_{ij}}$, where D is the diffusion tensor and the matrix b characterizes the MRI diffusion gradients, and hence the diffusion weighting. From a least-square fitting, the diffusion tensor is derived. For practicality and easy quantitative comparison, some scalar quantities can be derived from the tensor: fractional anisotropy (top) expresses the degree of anisotropy of D , while mean diffusivity (bottom) expresses the overall degree diffusion, invariant for rotations (actually, mean diffusivity is defined as the trace

of the tensor). Right: in order to preserve directional information, the RGB representation is a common choice (top). In this case, the colour represents the direction of the eigenvector of the tensor corresponding to the larger eigenvalue (*i.e.* the direction of maximum diffusion, code is: red right-left, green anterior-posterior, blue superior-inferior), while brightness represents fractional anisotropy (*i.e.* how much the direction of maximum diffusion is privileged compared to perpendicular directions). Finally, the DTI data can be used by specific algorithms to reconstruct the fibres bundles (tractography, bottom).

well as for integrated signals (mainly Local Field Potentials, LFP, and Multiple Unit Activity, MUA, that reflect the spatial integration of postsynaptic potentials and spiking activity, respectively). Invasive approaches are restricted to use on animals (where implants can be chronic, allowing longitudinal studies), or on humans, in those cases that require preoperative cortical EEG (electroencephalogram acquired on the cortical surface). Non-invasive approaches include EEG and MEG, and are currently adopted in humans.

While substantial information can be obtained even with deferred recordings, *i.e.* the acquisition on the same subject, but in different sessions, of MRI and electrophysiological signals, this method does not allow the study of unexpected activity (*e.g.* due to unpredictable phenomena, like epileptic events). Even worse, the deferred recording allows the multimodal data combination only in terms of global parameters, like average amplitude, or variance, but impedes the direct correlation of time courses, that is perfectly feasible, and rich of information, being limited only by the temporal resolution of fMRI (about a second).

The direct combination of electrophysiological and fMRI data, simultaneously acquired during the same session, is a feasible, but technically challenging proposition. Electrophysiological instrumentation can worsen the quality of fMRI data because of induced noise, radiofrequency shielding, and susceptibility artefacts, but the main issue is the complete obscuration of electrophysiological traces caused by the MR electrical noise: radiofrequency pulses are picked up by the electrodes, but the most severe interference is caused by the fast-switching field gradients during fMRI, that induce in the closed loops created by cables and subject head a strong potential, much higher than electrophysiological signals. Fortunately, the artefacts are stereotyped, and several methods have been developed to cope with them [8].

Currently, simultaneous electrophysiological and fMRI measurements are widely exploited and capitalize on both the high spatial resolution of fMRI and the direct nature of electrophysiological signals. These multimodal studies have been initially focused on the research on the neurophysiological origin of the fMRI signal, but have been later applied to a wide range of topics, both in the neurosciences and in clinical sciences, allowing unambiguous interpretation of fMRI-based activation maps, and, more in general, a deeper understanding of the dynamic functioning of the brain.

4 Neurocurrents imaging and Ultra Low Field MRI

Beyond the exploitation of multimodal approaches, it has been suggested that the tiny time-dependent alteration to the magnetic field induced by the neuronal currents themselves can induce measurable effects on MR images.

However, this effect is really hard to observe. It has been calculated that the alteration to the magnetic field induced by neuronal currents (NC) is in the order of a fraction of a nT [9]; moreover, the orientation and coherence of the currents have an impact (making the effect proportional not only to the magnitude of the currents), and finally the BOLD signal itself is based on the alteration of the magnetic field homogeneity induced by deoxyhaemoglobin, and this effect, that is quite larger, introduces a significant confound [10].

Although specific technical optimizations can improve the sensitivity to NC, it is very likely that their effects are of at least an order of magnitude too little to be directly observed with conventional MR. In fact, *in vivo* MRI observation of NC has been sporadically reported, especially in conditions (like anomalous epileptic activity) that are likely to increase the amplitude and spatial coherence of neuronal currents [10].

It has been suggested that Magnetic Resonance Imaging at Ultra Low Field (precession field in the range from a μT to a mT) can have some advantages over conventional MR for the study of direct magnetic effects induced by NC [11]. Ultra Low Field MRI (ULF MRI) is not a novel concept, but it had significant advances in recent years with the improvement of SQUID-based detection.

ULF MRI is grounded on the use of 2 magnetic fields: a pre-polarization field, and a significantly lower precession field. The pre-polarization field is dynamically switched on before and off during each acquisition, thus allowing the precession field to exploit a magnetization far higher of what would be determined by the thermal equilibrium.

Bare MRI signal is twofold dependent on the magnetic field, because of the increased polarization induced by higher magnetic fields, and because of the higher FID current induced at higher Larmor frequencies. However, also the noise (and in particular the physiological noise) increases with magnetic field. It is usually accepted that Signal-to-Noise Ratio (SNR) at low fields scales as $B_0^{7/4}$. In ULF MRI, this is partially overcome by the effective "hyperpolarization" effect that is created by the pre-polarization field.

ULF MRI has a number of potential practical applications in areas where conventional MRI is unpractical, uneconomical, or hardly feasible (field/transportable applications, security and health screening, presence of metallic implants), however a really interesting property is that the precession field can be made similar to the magnetic fields induced by NC (that is independent of B_0). This property makes feasible new imaging methodologies, that exploit the NC-generated magnetic field to flip the local magnetization, instead of perturbing the spin coherency (as happens in conventional MRI-based NC imaging). There is some theoretical evidence that this resonant approach can offer significant advantages in SNR [11]; other advantages of ULF MRI for NC detection include the drastic reduction of confounds that scale as B_0 : namely, BOLD effect and susceptibility artefacts of

physiological origin. Although SNR is still the main issue, it is possible that direct detection of NC is a feasible proposition with ULF MRI.

Finally, the use of SQUID detection allows the combined registration of ULF MRI signal and MEG with the same instrument, given that MEG is conventionally performed with SQUIDs. MEG is capable of directly measuring the magnetic fields generated by NC, however an anatomical reference is needed in order to fully exploit the information carried by the MEG signal. Co-registration between MEG data and anatomical images is cumbersome and prone to errors larger than the intrinsic spatial resolution of MEG (*e.g.* for the localization of magnetic sources). While the integration of SQUIDs for MEG acquisition in a high-field scanner is impossible, it has been shown that it is possible to use the SQUID-based ULF MR hardware for recording the MEG traces. In this case, the ULF images are intrinsically co-registered with the MEG acquisition. Currently, the straightforward approach of directly using as anatomical reference the ULF images acquired during the same session of a MEG seems a suboptimal strategy, because of the long time needed for gathering enough anatomical details at ULF fields. However, poor-resolution ULF images, acquired in reasonable time, still contain enough details to drive a fine co-registration between high-resolution images conventionally obtained (for instance, at high field) and the MEG data [12].

5 Conclusions

We have proposed here some of the results and of the targets of our Group. It is clear that the main objective is to develop some methods capable of imaging, with high resolution, directly the processes responsible of the neuro-activation, *i.e.* the neurocurrents and possibly the metabolic dynamics associated to it. The integration of PET with functional NMR Imaging Methods is work in progress in some laboratories, confirming the crucial role that the different fields of Physics must play in the future.

The frontier of brain function is however so complex that fundamental new ideas and methods must necessarily be invented in parallel with theoretical modelization and interpretation. Most of these results will be eventually reached by enforcing a coordinated action of physicists, with obvious interaction with neurobiologists, neurologists, etc.

These lines of research are usually considered by physicists, in a very reductive way, as part of "Medical Physics". Of course some important applications of these results are indeed devoted to Medicine. However the vast amount of unknown questions concerning our mind have a profound appeal for our knowledge. Without the crucial contribution of physicists, most of this field will remain a subject for psychologists or philosophers.

After all the target of understanding, by physical means, the

brain architecture and the way it operates is just a humble but Galileian approach to: *nosce te ipsum*.

New MRI physical methods can be used, in vegetative states, to detect perception and even conscious awareness. This perspective will be relevant for diagnosis, medical-decision making, besides for the fundamental questions about the nature of consciousness, thought and will.

Among the brain dysfunctions the neurodegenerative diseases cannot, in general, be objectively diagnosed; the mechanisms which generate them are unknown and medical treatments in practice are not existing.

New insight, with the support of original physical methods, is dramatically needed in order to discover the causes of these modern plagues.

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