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

Bruno Maraviglia
Department of Physics, University of Rome “Sapienza”
Enrico Fermi Centre, Rome, Italy
• Physicists, in general, investigate Nature by studying Simple Systems, easier for experimental tests and theoretical analysis.

• Living organisms are quite complex, in particular human brain is probably the most extraordinary frontier of research for its vast amount of unknown mechanisms and functions, responsible of the human life.
The Physics Research on Human Brain Structure and Function will be both:

1) 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.

2) a crucial contribution to understand the causes and the evolution of the neurodegenerative diseases, a dramatic Emergency hitting several million human beings.
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.
NMR = WIDE AREA OF METHODS continuously expanding.

Absolute relevance in biological systems.

Why: - no spontaneous emission
     - coherent radiation
     - high number of photons
     - inversion of energy levels populations is normal
     - subsystems of nuclei (different Gamma)
     - several interactions (most non central)
     - detects several parameters
My Group of research for over a decade has exploited the great versatility of NMR to investigate the Human Brain Function.

The power of NMR is much greater than that of other modalities, due to its capability of measuring several observables and their spatial dependence (imaging) like: spin density, the spin-lattice relaxation time T1, (related to molecular dynamics), the spin-spin relaxation time T2, the chemical shift (which allows the mapping of several metabolites), the J coupling, the diffusion tensor D (whose imaging provides the axonal cabling of different neuronal areas), flow, etc.
AXONS AND SYNAPSES

1. Action potential travels down axon
2. Action potential depolarizes presynaptic membrane, opening voltage-dependent Ca\(^{2+}\) ion channels
3. Ca\(^{2+}\) flows into cell, causing vesicles to fuse with presynaptic membrane
4. Neutrotransmitter (e.g., glutamate) is released into synapse
5. Neutrotransmitter binds with receptor on postsynaptic ion channels, opening them
6. Ions (e.g., Na\(^{+}\)) flow into postsynaptic cell, changing its potential
7. The resulting potential change is known as an EPSP or IPSP

FONDAZIONE SANTA LUCIA
ISTITUTO DI RICOVERO E CURA A CARATTERE SCIENTIFICO
Ospedale di riferimento nazionale e di alta specializzazione per le riabilitazioni neuromotorie

CENTRO I. L. FERMI
OXYGEN SUPPLY
Oxy-hemoglobin is diamagnetic
Deoxy-hemoglobin is paramagnetic
Blood Oxygen Level Dependent MRI (BOLD MRI)

Academic Press 2004
Physical Methods related to NMR in which my group is strongly involved:

1) Dynamics of metabolites concentration under brain stimulation; brain energetics

2) Combination of fMRI and EEG,

3) Resting state fMRI, Diffusion Tensor Imaging (DTI)

4) Ultra-low field MRI-MEG, neurocurrents imaging, etc.
1) Dynamics of metabolites concentration under brain stimulation
Lactate dynamics

Neuroenergetics: experimental


2) Combination of fMRI and EEG
Simultaneous fMRI and Evoked Potentials
Improved EEG source localization by constraining with fMRI clusters (spontaneous & evoked activity)

Improved prediction of time fMRI signal changes in order to localize with increased sensitivity:

- unpredictable spontaneous activity (epilepsy, sleep, brain rhythms, drug effects)
- unpredictable changes in evoked activity
1. Degradation of fMR image quality

- Local image artefacts due to the magnetic susceptibility and conductivity of EEG electrode assemblies (signal drop-outs and geometric distortions)

- Decreased SNR (RF interactions with conductors & increased noise due to RF em radiation emitted by the EEG recording equipment)

2. Patient safety issues

- Local heating
- Low-impedance conducting loops through tissue
3. Degradation of EEG data quality

- Pulse sequence artefact (due to MR gradient switching and RF pulses)

- Ballistocardiogram artefact (induced by small body movements due to cardiac pulse and blood flow effects within B₀)

- Artefact-free EEG trace
Pulse sequence artefact (PSA)

- A precise relationship between MR sequence parameters and PSA can be established in both the temporal and spectral domain.
- PSA shows high temporal stability and affects only certain spectral frequencies.
Solutions for pulse sequence artefact (PSA)

• Select appropriately experimental designs and acquisition protocols (frequency of stimulation or interleaved protocols)

• PSA filtering via
  - low-pass filtering
  - subtraction of an estimated PSA template

![Graph showing artifact peak amplitude against frequency with a peak at 4.6mV at 200 Hz]
epilepsy, FOS
MRS&EEG

Concentration Glu+Gln (mmol)

Stimulus

Spectrogram PO8

Component 2-3 Hz (typical frequency of FOS spike) of the spectrogram, block averaged

Metabolism ↔ long time: visual stimulus / rest
EEG Signal ↔ short time: alternate ON/OFF
3) Resting state fMRI, Diffusion Tensor Imaging (DTI)
The brain accounts for 20% of the oxygen, and hence calories, consumed by the body

In the average adult human, the brain represents 2% of the body weight

Only less than 20% of brain energy consumption is due to its interaction with the external world (stimulated activity), all the rest (80%) is due to autonomous, almost unexplored activity.
About 80% of Brain Energy consumption is due to autonomous almost unexplored activity.
Resting state
Low frequency intrinsic correlations during rest the default mode network(s)

Greicius M et al, PNAS 2003; 100, 253-258
The network connectivity in its dynamical, functional manifestation is just at an early stage of investigation.

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.
Diffusion

\[ \vec{J} = - D \vec{\nabla} c \]

Fick’s Law

\[ \frac{\partial}{\partial t} c = - \vec{\nabla} \cdot \vec{J} \]

Mass conservation law

\[ \frac{\partial}{\partial t} c = \vec{\nabla} ( D \vec{\nabla} c ) \]

Diffusion equation
Diffusion Tensor Imaging

\[ S(t) = f(N, T_1, T_2, CS, J, D, \ldots) \]

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

\[ P(r'' - r', t) \quad R = r'' - r' \]

\[ P(R, t) \]

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

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

\[ \langle R^2 \rangle = \int_{-\infty}^{+\infty} R^2 P(R, t) \, dR = 6Dt \]
Diffusion Tensor Imaging

Axon in successive stages of myelinization

Axon mean diameter ≈ 7µm
Microtubulus ≈ 20nm

< r² > = 6 D t
< r² > = 40µm

Where: D=2.3x10⁻⁹ m²/s

t = Δ = 80ms
Diffusion Tensor Imaging

Diffusion weighted imaging:

**DWI**

\[ S(b) = S(0) \exp \left( -bD \right) \]

\[ b = \gamma^2 G^2 \delta^2 (\Delta - \frac{\delta}{3}) \]

*Function of gradient amplitude, duration and distance*

**Signal**

(a.u.)

\[ S(0) \]  

\[ S(b) \]

**b factor**

(s/mm²)
\[ \frac{S(t)}{S_0} = \exp \left( -\sum_{i,j=1}^{3} b_{ij} D_{ij} \right) \]

\[ D = \begin{pmatrix} D_{xx} & D_{xy} & D_{xz} \\ D_{yx} & D_{yy} & D_{yz} \\ D_{zx} & D_{zy} & D_{zz} \end{pmatrix} \]

\[ D = \begin{pmatrix} D_1 & 0 & 0 \\ 0 & D_2 & 0 \\ 0 & 0 & D_3 \end{pmatrix} \]

Main Ellipsoid Axis

At least six independent parameters are required. At least six no-complanar DWI + one T2w

\( S_{\text{exp}} = \sum \)
Diffusion Tensor Imaging

Eigenvectors

Principal directions of diffusion
(fiber orientation)
From the eigenvectors to white matter tracts: Fibers tractography
Diffusion Tensor Imaging (DTI)
Anomalous Diffusion

From gaussian diffusion to anomalous diffusion

Conventional DWI and DTI

Gaussian propagation

$$< r^2 > = 6 \, Dt$$

$$S(b) = S(0) \exp(-bD)$$

In living systems:

Anomalous diffusion

$$< r^2 > = 6 \, Dt^\gamma$$

$$0 < \gamma < 1$$

subdiffusion

Stretched exponential model
Anomalous diffusion tensor vs DTI

Conventional DTI

Anomalous Diffusion Tensor

MD

FA

$M_\gamma$

$A_\gamma$
4) Ultra-low field MRI-MEG, neurocurrents imaging, etc
ULF-fMRI: Direct Detection of Neuronal Currents

Need to find NMR solutions to imaging the early stages of the neuronal activity when BOLD signal is still absent or alternatives to the BOLD-fMRI.
Neuronal current MRI

**ULTRA-LOW FIELD NMR PROTOCOL**

Two different magnetic fields. One strong for prepolarization, $B_p=10\text{mT}$, and a weaker one for readout $B_0=100\text{uT}$.

**HIGH FIELD NMR PROTOCOL**

One magnetic field for both the prepolarization and the readout.
Ultra-low field MRI Properties

Coregistration of NMR and biomagnetic signals


Fig. 4. (a), (b) Two cross sections at different positions of a forearm; thickness of one slice is 24 mm. (c) Same image as (b) with amplitude correction.

Ultra-Low Field MRI and Brain Images

Acquisition Parameters

**ULF**
- $B_0 = 46 \mu T$ (measurement)
- $B_p = 30$ mT (polarization)
- $(\Delta x, \Delta y) = 3mm \times 3mm$
- $T_{prep} = 1$ s (prepolarizing time)

**HF**
- $B_0 = 1.5$ T (measurement & polar)
- $(\Delta x, \Delta y) = 1mm \times 1mm$
- $TE = 64$ ms
- $TR = 9000$ ms

<table>
<thead>
<tr>
<th>Name</th>
<th>$T1 (ms)$</th>
<th>$T2 (ms)$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gray Matter</td>
<td>$103 \pm 5$</td>
<td>$106 \pm 11$</td>
</tr>
<tr>
<td>CSF</td>
<td>$344 \pm 9$</td>
<td>$355 \pm 15$</td>
</tr>
<tr>
<td>Scalp</td>
<td>$124 \pm 7$</td>
<td>$120 \pm 7$</td>
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I have presented to you some of the results and of the targets of my 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 components 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 inforcing 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 in deed 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 phylosophers.

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
Border between life and death
Conscience = *Arousal*  + *awareness*

( vigilant, awake) + (conscious of self and of the environment)
Fig. 1. We observed supplementary motor area (SMA) activity during tennis imagery in the patient and a group of 12 healthy volunteers (controls). We detected parahippocampal gyrus (PPA), posterior parietal-lobe (PPC), and lateral premotor cortex (PMC) activity while the patient and the same group of volunteers imagined moving around a house. All results are thresholded at $P < 0.05$ corrected for multiple comparisons. $X$ values refer to distance in mm from the midline in stereotaxic space (SOM text).
New 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.
MARBI Lab, Magnetic Resonance for Brain Investigation Laboratory

Full data storage and processing facilities

Site & manutention granted by Fondazione Santa Lucia
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