The physics of functional magnetic resonance imaging (fMRI)

Yiming Dong
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Outline

1. Introduction
2. The fMRI experiment
3. The physics basis of fMRI
4. Application
1. Introduction
Phrenology is a pseudomedicine primarily focused on measurements of the human skull, based on the concept that the brain is the organ of the mind, and that certain brain areas have localized, specific functions or modules.

- It used anecdotal, rather than scientific, evidence.

- Nevertheless, its central idea persisted: Localization of Function
fMRI vs. MRI

MRI studies brain anatomy.

Functional MRI (fMRI) studies brain function.
Introduction

- FMRI is a technique for measuring metabolic correlates of neuronal activity.
  - Uses a standard MRI scanner
  - Acquires a series of images (numbers)
  - Uses non-invasive, non-ionizing radiation
  - Can be repeated many times; can be used for a wide range of subjects
  - Combines good spatial and reasonable temporal resolution
1924 - Pauli suggests that nuclear particles may have angular momentum (spin).

1937 – Rabi measures magnetic moment of nucleus. Coins “magnetic resonance”.

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1944 – Rabi wins Nobel prize in Physics.

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1946 – Purcell shows that matter absorbs energy at a resonant frequency.

1946 – Bloch demonstrates that nuclear precession can be measured in detector coils.

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1952 – Purcell and Bloch share Nobel prize in Physics.

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1959 – Singer measures blood flow using NMR (in mice).

1972 – Damadian patents idea for large NMR scanner to detect malignant tissue.

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1973 – Mansfield independently publishes gradient approach to MR.

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1975 – Ernst develops 2D-Fourier transform for MR.

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MRI scanners become clinically prevalent.


1990 – Ogawa and colleagues create functional images using endogenous, blood-oxygenation contrast.

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**BOLD (Blood Oxygen Level Dependent)** contrast results from changing regional blood concentrations of oxy- and deoxy-hemoglobin. Oxyhemoglobin is weakly *diamagnetic*. When oxygen is released to form deoxyhemoglobin, 4 unpaired electrons are exposed at each iron center, causing the molecule to become strongly *paramagnetic* and alters the magnetic *susceptibility* of blood.

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Deoxyhemoglobin is strongly paramagnetic due to 4 unpaired electrons at each iron center.

Paramagnetic deoxyhemoglobin (D) confined to red blood cells causes a local field distortion in and around the vessel.

Pic source: [http://mriquestions.com/bold-contrast.html](http://mriquestions.com/bold-contrast.html)
**Introduction**

Functional magnetic resonance imaging (fMRI) is a methodology for detecting dynamic patterns of activity in the working human brain.

The ability to detect changes in brain activity has a biophysical basis in the magnetic properties of deoxyhemoglobin (produced by haemoglobin losing oxygen), and a physiological basis in the way blood flow increases more than oxygen metabolism when local neural activity increases.

**Cerebral blood flow (CBF)**

**blood oxygenation level dependent (BOLD)**

CBF and BOLD responses in human primary motor cortex to 2 s of finger tapping.
Introduction

Figure Source, Huettel, Song & McCarthy, 2004; Functional Magnetic Resonance Imaging

↑ Neuronal activity  ➔ ↑ blood flow  ➔ ↑ oxy-hemoglobin  ➔ ↑ T2*  ➔ ↑ MR signal
First functional imaging in human.

Flickering Checkerboard
OFF (60 s) - ON (60 s) - OFF (60 s) - ON (60 s) - OFF (60 s)

Kwong et al., 1992
2. The fMRI experiment
The NMR signal

(1) Equilibrium magnetization
(2) Precession

(3) Relaxation  \( T_1 \) and \( T_2 \)  \( T_2^* \) and \( T_2 \)
One of the most common ways for this to occur is for a spin to be located in a molecular environment where it experiences a local static field disturbance \((B_{\text{loc}})\) in addition to the main magnetic field \((B_o)\).
The fMRI experiment

Limits of spatial and temporal resolution for human brain imaging

The human cerebral cortex is a convoluted sheet with an area of \( \approx 2000 \text{ cm}^2 \), a thickness of \( \approx 2.5 \text{ mm} \) and \( \approx 10^5 \) neurons \( \text{mm}^{-2} \). A whole brain image acquisition requires coverage of a three-dimensional (3D) rectangular volume of about \( 200 \times 180 \times 180 \text{ mm}^3 \). For typical whole brain fMRI studies the spatial resolution is usually about \( 3 \times 3 \times 3 \text{ mm}^3 \) with a temporal resolution of about \( 3 \text{ s} \).


“Ultrafast” single-shot imaging with EPI

conventional MRI

Echo Planar Imaging

RF

Echo

$T_2^*$

etc

$k_y$

$k_x$
fMRI experiment design

**Block designs**
Task periods are alternated with periods of rest. Lower BOLD signal during rest periods are digitally "subtracted" from higher BOLD signal during task states to reveal focal areas of cortical activation.

**Event-related Designs**
Event related designs are based on the assumption that neural activity will occur for short and discrete intervals. Such designs attempt to measure transient changes in brain activity. Unlike block designs, stimuli are presented in a random order rather than an alternating pattern offering a higher flexibility in experimental terms.

**Mixed Designs**
Stimuli are displayed in discrete blocks which allows investigating sustained processes and brain responses (state-related processes). Within each block multiple types of events occurs and because there is different types of stimuli, transient responses are also likely to occurs. Therefore, mixed designs can investigate interaction between processes working at different time-scales.
Significant clusters of activation from an audiovisual experiment. The different rows were produced by processing with different spatial scales-filters. Red clusters show visual activation; Blue clusters show auditory activation.
The fMRI experiment

Production of a Color-Coded Activation Map

statistical map → color look-up table transformation → thresholded activation map

Gray Scale → Color Scale (shown here in black and white)

anatomical map → final overlaid activation map

source: Functional Magnetic Resonance Imaging (fMRI), Robert L. Savoy, Ph.D.
Production of a Color-Coded Activation Map

The top and bottom images show the same data, with the top image showing a liberal statistical threshold (Z>2.0), while the bottom image shows a more conservative threshold (Z>5.0). Note that the liberal test identifies more regions, but has a higher incidence of false alarms (suggesting an area is activated when in fact its activity was simply noise).

The right panel illustrates the concept of statistical significance: the L/R and A/P axis show different locations in a slice (from left to right and anterior to posterior) while the color indicates the Z-score at each location. Changing our statistical threshold is analogous to changing the water level, exposing more or fewer peaks.
3. The physiological basis of fMRI
3. The physiological basis of fMRI

physical
$T_2^*$  
Decay time of FID (Free Induction Decay)

$A(t)$  
attenuation factor

$$A(t) = e^{-R_2^*(t)t}$$

$$R_2^* = \frac{1}{T_2^*}$$

If there is no difference between the magnetic susceptibility of the blood vessels and the surrounding tissue, the relaxation rate is assumed to be simply:

$$R_2^* = R_2$$
Now introducing a susceptibility difference between the blood vessels and the surrounding space:

\[ R_2^* = R_2 + \Delta R_2(t) + R_2'(t) \]

The significance of this form is that it breaks the added relaxation into two terms: a part that can be refocused with a spin echo experiment \((R'_2)\) and a part that cannot be refocused \((\Delta R_2)\) and so appears as a change in \(R_2\).
The physical basis of fMRI

The magnetic susceptibility difference is usually taken as

\[ \Delta \chi = (1 - Y) Hct \Delta \chi_0 \]

where \( Y \) is the fractional O\(_2\) saturation of hemoglobin, \( Hct \) is the hematocrit (the volume fraction of blood occupied by red blood cells), and \( \Delta \chi_0 \) is the susceptibility difference that would result if all of the hemoglobin was deoxygenated (\( Y = 0 \)) and the hematocrit is one.

Taken together, the added angular frequency (rad s\(^{-1}\)) distribution around the vessel is:

\[ \delta \omega_0 = 2\pi Y B_0 \Delta \chi_0 (1 - Y) Hct \]

Then we can get the relaxation rate of the extravascular signal in the static dephasing regime (no diffusion):

\[ R_2^' = \frac{2}{3} V \delta \omega_0 \]

Where the \( V \) is blood vessels volume fraction of whole tissue (typically \( \sim 0.05 \)) and the \( 2/3 \) comes from the random orientation of vessels, effectively creating an average scaling frequency of \( \delta \omega_0 \).
Difusion effects

Modeling the effects of diffusion is considerably more complicated, and nearly all studies are limited by the need to assume relatively simple geometries. Several analytical treatments have been proposed, and a number of studies have used Monte Carlo simulations tracking thousands of random walks through a field of randomly oriented vessels to model diffusion.

For example, we can get the diffusion effect parameter by the fast diffusion limit:

\[ \Delta R_2 = \kappa \tau_D V \delta \omega_0 \]

\( \tau_D \sim R^2/D \) is the time required for diffusive motions to be comparable to the spatial scale of the field distortions.

\( \kappa \) is a dimensionless numerical constant (for simplified estimate, \( \kappa=0.25 \))

\( V \) is the blood volume fraction.
The physical basis of fMRI

Modeling the BOLD effect

A full quantitative model of the BOLD effect is important for understanding the basic mechanisms, for optimizing the image acquisition technique to maximize sensitivity, and for calibrating the BOLD signal to measure local $\text{CMRO}_2$ (Cerebral metabolic rate) and CBF (Cerebral blood flow). The basic idea is that the BOLD response depends on both the CBF and $\text{CMRO}_2$ responses. If the BOLD response is measured in conjunction with an ASL experiment to measure the CBF response independently, one can in principle isolate the $\text{CMRO}_2$ response.

The CBF normalized to its baseline value ($f$) and the $\text{CMRO}_2$ normalized to its baseline value ($r$)

$$\frac{\Delta S}{S} = M \left( 1 - f^{\alpha-\beta} r^\beta \right)$$

With the constant $\beta = 1.3$ (compromise between the effects of large and small vessels) and $\alpha = 0.38$ (based on experiments comparing total CBV with CBF), which are commonly used recently.
# The physical basis of fMRI

<table>
<thead>
<tr>
<th>Variable</th>
<th>Description</th>
<th>Typical baseline value</th>
<th>Example change with activation</th>
</tr>
</thead>
<tbody>
<tr>
<td>CBF (F)</td>
<td>Cerebral blood flow (ml arterial blood per ml tissue per min)</td>
<td>0.5 min&lt;sup&gt;-1&lt;/sup&gt;</td>
<td>0.65 min&lt;sup&gt;-1&lt;/sup&gt; (+30%)</td>
</tr>
<tr>
<td>OEF (E)</td>
<td>Oxygen extraction fraction (dimensionless)</td>
<td>0.4</td>
<td>0.34 (-15%)</td>
</tr>
<tr>
<td>CMRO&lt;sub&gt;2&lt;/sub&gt; (R)</td>
<td>Cerebral metabolic rate of oxygen (micromoles O&lt;sub&gt;2&lt;/sub&gt; per ml tissue per min, or mM min&lt;sup&gt;-1&lt;/sup&gt;)</td>
<td>1.6 mM min&lt;sup&gt;-1&lt;/sup&gt;</td>
<td>1.8 mM min&lt;sup&gt;-1&lt;/sup&gt; (+12%)</td>
</tr>
<tr>
<td>CMRGl&lt;sub&gt;c&lt;/sub&gt;</td>
<td>Cerebral metabolic rate of glucose (micromoles glucose per ml tissue per min, or mM min&lt;sup&gt;-1&lt;/sup&gt;)</td>
<td>0.3 mM min&lt;sup&gt;-1&lt;/sup&gt;</td>
<td>0.4 mM min&lt;sup&gt;-1&lt;/sup&gt; (+30%)</td>
</tr>
<tr>
<td>CBV</td>
<td>Cerebral blood volume (dimensionless fraction of tissue volume)</td>
<td>0.05</td>
<td>0.055 (+10%)</td>
</tr>
<tr>
<td>[O&lt;sub&gt;2&lt;/sub&gt;]&lt;sub&gt;a&lt;/sub&gt;</td>
<td>Arterial oxygen concentration (micromoles O&lt;sub&gt;2&lt;/sub&gt; per ml blood)</td>
<td>8 mM</td>
<td>8 mM (——)</td>
</tr>
</tbody>
</table>
4. Application of fMRI
Applications of fMRI

fMRI of Visual System

BOLD/fMRI of visual cortex by checkerboard pattern. Also note activation of lateral geniculate nucleus (green arrow).
Applications of multimodal MRI to brain lesion characterization.

These images were acquired from a 52-year-old patient with a right solitary metastatic tumour in the post-central gyrus, associated with paresis of the left foot.

c. Functional MRI (fMRI) during finger tapping identifies the brain regions associated with hand movement. Injury to these regions during tumour resection could be expected to lead to functional impairments of the left hand.

d. fMRI with sensory stimulation of the left foot identifies regions that, if injured during tumour resection, could be expected to lead to greater functional impairments of the left foot.
Applications of multimodal MRI to brain lesion characterization.

Pharmacological functional MRI (phMRI) allows drug effects in the brain to be defined from their modulation of activity.

In this example, brain activity with a noxious thermal stimulus applied to the skin relative to that with a non-painful warmth was mapped during the infusion of increasing concentrations of remifentanil (an opiate analgesic saline placebo) (a); 0.5 ng/ml (b); 1.0 ng/ml (c); 2 ng/ml (d). The decrease in the functional MRI signal provides an objective measure of decreasing central pain response with higher doses of the drug. This provides a tool for both pharmacokinetics and pharmacodynamic studies.

Applications of fMRI in translational medicine and clinical practice. Matthews PM1, Honey GD, Bullmore ET. Nat Rev Neurosci. 2006 Sep;7(9):732-44.
1. Introduction
   Functional MRI (fMRI) studies brain function
   BOLD (Blood Oxygen Level Dependent)

2. The fMRI experiment
   MRI experiment $T_2^*$ and $T_2$
   technique
   experiment design
   Visualization

3. The physics basis of fMRI

4. Applications


III. Functional Magnetic Resonance Imaging (fMRI), Robert L. Savoy, Ph.D.,

IV. Applications of fMRI in translational medicine and clinical practice. Matthews PM1, Honey GD, Bullmore ET. Nat Rev Neurosci. 2006 Sep;7(9):732-44.

V. The physics of functional magnetic resonance imaging (fMRI), Richard Buxton, Department of Radiology, University of California, San Diego, USA

VI. http://mriquestions.com, Allen D. Elster

VII. An introduction to functional MRI, Bianca de Haan and Chris Rorden

VIII. fMRI visualization and methods, James Shuang Gao
THANK YOU!