Twenty Years of Functional MRI

Peter A. Bandettini, Ph.D.

Section on Functional Imaging Methods
Laboratory of Brain and Cognition
http://fim.nimh.nih.gov

&

Functional MRI Facility
http://fmrif.nimh.nih.gov

bandettini@nih.gov

Gadolinium perfusion angiography

Diffusion

metabolic imaging (NAA)

Choline

Creatine

Lactate

Magnetization transfer
Five Key Factors For The Emergence of Functional MRI

1. Magnetic properties of red blood cells
2. Activation related hemodynamic changes
3. Spatial scale of brain activation
4. Echo Planar Imaging
5. Prevalence of MRI scanners

Magnetic Properties of Blood


oxygenated
deoxygenated
red blood cells
Blood $R_2$ proportional to Oxygenation

$R_2$ effect is bulk susceptibility and not dipole-dipole

---

**in vivo**

$100\% \, O_2$

**in vitro**

100% oxygenated blood

0% oxygenated blood


---

“BOLD contrast adds to...functional MRI methodologies that are likely to be complementary to PET imaging in the study of regional brain activity.”

Proceedings of the National Academy of Sciences of the United States of America, 87, 9868-9872.
Five Key Factors For The Emergence of Functional MRI

1. Magnetic properties of red blood cells
2. Activation related hemodynamic changes
3. Spatial scale of brain activation
4. Echo Planar Imaging
5. Prevalence of MRI scanners

Cerebral Tissue Activation

Local Vasodilatation

Increase in Cerebral Blood Flow and Volume

Oxygen Delivery Exceeds Metabolic Need

Increase in Capillary and Venous Blood Oxygenation

Decrease in Deoxy-hemoglobin: paramagnetic

Oxy-hemoglobin: diamagnetic

Decrease in susceptibility-related intravoxel dephasing

Increase in T2 and T2* - weighted sequences

Local Signal Increase in T2 and T2* - weighted sequences
Five Key Factors For The Emergence of Functional MRI

1. Magnetic properties of red blood cells
2. Activation related hemodynamic changes
3. Spatial scale of brain activation
4. Echo Planar Imaging
5. Prevalence of MRI scanners
Orientation Columns in Human V1 as Revealed by fMRI at 7T

Yacoub et al. PNAS 2008
Functional Neuroimaging Techniques

Five Key Factors For The Emergence of Functional MRI

1. Magnetic properties of red blood cells
2. Activation related hemodynamic changes
3. Spatial scale of brain activation
4. Echo Planar Imaging
5. Prevalence of MRI scanners

MRI vs. fMRI

- MRI: high resolution (1 mm), one image
- fMRI: many images (e.g., every 2 sec for 5 mins)

Single Shot Echo Planar Imaging (EPI)

- T2* decay
- EPI Readout Window ≈ 20 to 40 ms
Approximate EPI Timeline

1976 P. Mansfield conceives of EPI
1989 EPI of humans emerges on a handful of scanners
   3 x 3 x 3-10 mm³
1989 ANMR retrofitted with GE scanners for EPI
1991 Home built head gradient coils perform EPI
1996 EPI is standard on clinical scanners
2000 Gradient performance continues to increase
2002 Parallel imaging allows for higher resolution EPI
2006 1.5 x 1.5 x 1.5 mm³ single shot EPI possible
2009 At 7T sub-mm single shot EPI for fMRI is possible
Five Key Factors For The Emergence of Functional MRI

1. Magnetic properties of red blood cells
2. Activation related hemodynamic changes
3. Spatial scale of brain activation
4. Echo Planar Imaging
5. Prevalence of MRI scanners

The Beginnings
The First Functional MRI Results

Susceptibility Contrast agent bolus injection and time series collection of T2 - weighted images


2.5 cm !

TR = 2 sec
TE = 50 ms
One slice
In plane 3.75 x 3.75

Contrast Basics

Perfusion Contrast

**EPISTAR**

**FAIR**

<table>
<thead>
<tr>
<th>TI (ms)</th>
<th>FAIR</th>
<th>EPISTAR</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>200</td>
<td></td>
<td></td>
</tr>
<tr>
<td>400</td>
<td></td>
<td></td>
</tr>
<tr>
<td>600</td>
<td></td>
<td></td>
</tr>
<tr>
<td>800</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1000</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1200</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Functional Contrast

- **Volume (gadolinium)**
- **BOLD**
- **Perfusion (ASL)**
- **CMRO$_2$**
- **Volume (VASO)**
- **Neuronal Currents**
- **Diffusion coefficient**
- **Temperature**
**How fMRI Is Currently Used**

**Research Applications**
- map networks involved with specific behavior, stimulus, or performance
- characterize changes over time (seconds to years)
- determine correlates of behavior (response accuracy, etc.)
- characterization of groups or individuals

**Clinical Research**
- clinical population characterization (probe task or resting state)
- assessment of recovery and plasticity
- attempts to characterize (classify) individuals

**Clinical Applications**
- presurgical mapping (CPT code in place as of Jan, 2007)

---

**Top 10 Most Significant Developments in fMRI**

1. “Resting state” correlations
2. SPM, FSL, AFNI, Brain Voyager processing platforms
3. Fast even related designs with deconvolution
4. Multi-modal integration / comparison (animal and human)
5. Hemodynamic response models
6. High field / high resolution results
7. Parallel acquisition / reconstruction (SENSE/SMASH)
8. Detailed retinotopic mapping
9. FMRI Decoding / Multivariate / Machine Learning
10. Robust motion correction or ICA analysis or real time fMRI or fMRI-adaptation
Overview of fMRI

Functional Contrast:
- Blood volume
- Blood flow/perfusion
- Blood oxygenation

Spatial resolution:
- Typical: 3 mm^3
- Upper: 0.5 mm^3

Temporal resolution:
- Minimum duration: < 16 ms
- Minimum onset diff: 100 ms to 2 sec

Sensitivity:
- tSNR = 40/1 to 120/1
- fCNR = 1/1 to 6/1

Interpretability issues:
- Neurovascular coupling, vascular sampling, blood, physiologic noise, motion and other artifacts, etc..

What fMRI Can’t Do

What some would argue are shortcomings with fMRI

• Too low SNR vs subject/patient limits of compliance (about 2 hours)
• Requires motivated subjects/patients (motion sensitivity)
• Too low spatial resolution (each voxel has several million neurons)
• Any higher resolution than 3 mm^3 lost with subject averaging.
• Too low temporal resolution (hemodynamics are variable and sluggish)
• Too inconsistent activation patterns
• Anatomical images for fMRI are of low quality (dropout/distortion)
• Requires a task (BOLD cannot look at baseline maps).
• Too confined space and high acoustic noise (environment non-optimal).
• Too many physiologic variables influence signal.

Exciting Trends

• FMRI Decoding / Multivariate Analysis / Machine Learning
• Resting State Fluctuations (Connectivity)
• High Field / High Temporal & Spatial Resolution (input/output layers)
• Longitudinal fMRI / MRI studies across time scales
• Clinical inroads (default mode, genetic correlations, connectivity)
• Multi-modal integration
• Individual assessment
• Multi-band sequences...short TR whole brain connectivity.
Parametric manipulation of brain activation demonstrated that BOLD contrast approximately followed the level of brain activation: visual system (Kwong et al., 1992), auditory system (Binder et al., 1994), and motor system (Rao et al., 1996).

The use of continuous variation of visual stimuli parameters as a function of time was proven a powerful method for fMRI-based retinotopy: (Engel et al., 1994, Deyoe et al., 1994, Sereno et al., 1995).

Event-related fMRI was first demonstrated (Biemire et al., 1992).

Application of event-related fMRI to cognitive activation was shown (Buckner et al., 1996, McCarthy et al., 1997).

Development of mixed event-related and block designs was put forward: (Donaldson et al., 2002).

Paradigms were demonstrated in which the activation timing of multiple brain systems was orthogonal, allowing multiple conditions to be cleanly extracted from a single run (Courtney et al., 1997).

High resolution maps were created: For spatial resolution: ocular dominance columns (Menon et al., 1997, Cheng et al., 2001) and cortical layer activation maps were created (Logothetis et al., 2002).

Extraction of information at high spatial frequencies within regions of activation was demonstrated (Haxby et al., 2001).

For temporal resolution: Timings from ms to hundreds of ms were extracted (Ogawa et al., 2000, Menon et al., 1998, Henson et al., 2002, Bellgowan et al., 2003).

The development of “deconvolution” methods allowed for rapid presentation of stimuli (Sole and Buckner, 1997).

Early BOLD contrast models were put forward: (Ogawa et al., 1993, Burton and Frank, 1997).

More sophisticated models were published that more fully integrated the latest data on hemodynamic and metabolic changes (Buxton et al., 2004).

The development of “clustered volume” acquisition was put forth as a method to avoid scanner noise artifacts (Buston et al., 2004).

The findings of functionally related resting state correlations: (Biswal et al., 1995) and regions that consistently show deactivation (Binder et al., 1999, Raichle et al., 2001) were described.

Observation of the pre-undershoot in fMRI (Hennig et al., 1997, Menon et al., 1995, Hu et al., 1997) and correlation with optical imaging was reported (Malonek and Grinvald, 1996).

Simultaneous use of fMRI and direct electrophysiological recording in non-human primate brain during visual stimulation elucidated the relationship between fMRI and BOLD contrast. (Logothetis et al., 2001). Simultaneous electrophysiological recordings in animal models provided evidence that inhibitory input could cause an increase in cerebral blood flow (Matheissen et al., 1998).

Structural equation modeling was developed in the context of fMRI time series analysis: (Buchel and Friston, 1998).

---

**How most fMRI studies are performed**

**MRI parameters:**
1.5T - 3T, 64 x 64 matrix, 3mm x 3mm x 5mm voxel size, whole brain, TR = 2 sec.

**Paradigm:**
Block design or event-related, single or multiple conditions.

**Analysis:**
Motion correct, multi-regression, spatial smoothing and spatial normalization, standard classical statistical tests, multi-subject averaging.

**Hypothesis:**
A region or network of regions show modulation with a task. This modulation is unique to the task and/or population.

---

**How fMRI might be be performed**

**MRI parameters:**
3T - 11.7T, 256 x 256 matrix, 0.5 x 0.5 x 0.5 voxel size, whole brain TR = 1sec or select slab TR = 100 ms.

**Paradigm:**
Natural, continuous, fMRI-adaptation, or no stimuli/task. Simultaneous multi-modal, or multiple contrast measurements.

**Analysis:**
Motion correct, dynamic Bo-field correction, no spatial or temporal smoothing, machine learning algorithms, pattern classification, resting state connectivity assessment, hemodynamic parameter assessment - calibration, correlation with behavior.

**Hypothesis:**
Similar to previous but using the high resolution patterns, fluctuations, dynamics, and contrast mechanisms that we are still figuring out how to interpret and extract.
What fMRI Might Do

Clinical Research Complementarity
- usage of clinical research findings for more effective diagnoses, prediction, characterization, and/or intervention

Clinical treatment and assessment of therapy
- better understanding of the specific pathology mechanism
- drug effect assessment
- assessment of therapy progress, biofeedback
- epileptic foci mapping
- neurovascular physiology assessment

Non clinical uses
- lie detection
- prediction of behavior tendencies
- brain/computer interface

Orientation Columns in Human V1 as Revealed by fMRI at 7T

Real time fMRI feedback from Anterior Cingulate Cortex to reduce chronic pain

Control over brain activation and pain learned by using real-time functional MRI, R. C. deCharms, et al. PNAS, 102; 18626-18631 (2005)
Individual Differences in Brain Activations During Episodic Retrieval
Miller et al., 2002

Individual activations from the left hemisphere of the 9 subjects

Individual activations from the right hemisphere of the 9 subjects

These individual patterns of activations are stable over time

Group Analysis of Episodic Retrieval

Finger Movement

Left

Right

Subject SC

Subject SC 6 months later

Courtesy, Mike Miller, UC Santa Barbara and Jack Van Horn, fMRI Data Center, Dartmouth University
Listening to Spoken Words

$\approx 5 \text{ to } 30 \text{ ms}$

Pruessmann, et al.

3T single-shot SENSE EPI using 16 channels: $1.25 \times 1.25 \times 2\text{mm}$

Ocular Dominance Column Mapping

Menon, R. S., S. Ogawa, et al. (1997). J Neurophysiol 77(5): 2780-7. 0.54 x 0.54 in plane resolution


Optical Imaging

Cheng, et al. (2001) Neuron, 32:359-374 0.47 x 0.47 in plane resolution
**Orientation Columns in Human V1 as Revealed by fMRI at 7T**


-Yacoub et al. PNAS 2008

Scalebar = 0.5 mm

-Yacoub et al. PNAS 2008

**Visual Activation Paradigm:** 1, 2, & 3 Trials

-0 sec

-2 sec

-4 sec

-20 sec
**Randomized event-related experimental designs allow for extremely rapid presentation rates using functional MRI**

Marc A. Burock,1,2 Randy L. Bucetner,3 Marty G. Woldeff,1 Bruce R. Rosen1 and Anders M. Dale1,2

1Massachusetts General Hospital, Nuclear Magnetic Resonance Center, Bentley 320 12th Street, Charlestown, MA 02129; 2Harvard-MIT Division of Health Sciences and Technology, Cambridge, MA 02139; 3Washington University, Department of Psychology, St. Louis, MO 63130; 4University of Texas Health Science Center, Research Imaging Center, San Antonio, TX 78284, USA.

**Resting State Correlations**

**Activation:** correlation with reference function

**Rest:** seed voxel in motor cortex

---


---

B. Biswal et al., MWM, 34:537 (1995)
BOLD correlated with 10 Hz power during "Rest"

Positive

10 Hz power

Negative

Goldman, et al. (2002), Neuronreport

Patterns

Ventral temporal category representations

Object categories are associated with distributed representations in ventral temporal cortex

Haxby et al. 2001

1991
Pattern-recognition analysis of fMRI activity patterns

- Haxby et al. (2001)
- Carlson et al. (2003)
- Kamitani & Tong (2005)
- Haynes & Rees (2005)
- Kriegeskorte et al. (2006)

Logothetis et al. (2001)
"Neurophysiological investigation of the basis of the fMRI signal" Nature, 412, 150-157

Ocular Dominance Column Mapping

≈ 5 to 30 ms

Pruessmann, et al.

3T single-shot SENSE EPI using 16 channels: 1.25x1.25x2mm


0.54 x 0.54 in plane resolution

Optical Imaging


Ocular Dominance Column Mapping


0.47 x 0.47 in plane resolution

Orientation Columns in Human V1 as Revealed by fMRI at 7T