Basic tradeoffs and constraints in fMRI methodology and applications

Jennifer Evans
fMRI in temporal – spatial perspective

Grinvald A. PNAS (2005)
FMRI data pipeline

- Experiment Design
- Scanning
- Preprocessing
- Individual Analysis
- Group Analysis
- Interpretation
• Limitations based on the biophysical constraints
  • voxel contents
  • neurovascular coupling
  • hemodynamic response

• Limitations based on imaging constraints
  • Space – time tradeoffs (optimal voxel size)
  • Pulse sequence contrasts

• Summary
What's in a voxel?

- Neurons
- Synapses
- Axons
- Dendrites

- Vasculature
- Capillaries
- Aterioles/venules
- Arteries/Veins

Logothetis NK, Nature (2008)
Average size of fMRI voxels

- In plane resolution of 9-16 mm\(^2\) (3x3, 4x4)
- Slice thickness 5-7 mm
- Average voxel size: 55 mm\(^3\)

5.5 million neurons
2.2-5.5 \(10^{10}\) synapses
22 km of dendrites
220 km of axons
And vasculature ...
Spatial inhomogeneity of vasculature
Back to BOLD ...

Neural activity → Neurovascular coupling → Vascular response

- Synaptic signalling
- Metabolic signalling
- Glia

- Arteriole
- Capillary bed
- Venules
- Oxidative metabolism
- Blood flow
- $[\text{dHb}]$
- BOLD signal

BOLD FMRI

Ianetti & Wise JMRI (2007)
From neurons to fMRI / metabolic pathway

Temporal: neural speed, hemodynamic response

- **Temporal**
  - Neural speed: Instantaneous changes in neural activity.
  - Hemodynamic response: Induced changes in blood flow due to neural activity.

- **Graphs**
  - **Neuronal response**:
    - Graph showing spikes per second over time (sec).
  - **Hemodynamic response**:
    - Graph showing hemodynamic changes over time (sec).
Extra- and intra-vascular responses to stimulus

A

Baseline

Stimulus

Artery
Vein

Oxyhemoglobin
Deoxyhemoglobin

B

Expected stimulus-induced changes in MR-related parameters

<table>
<thead>
<tr>
<th></th>
<th>Arterial Blood</th>
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BOLD effect
Hemodynamic Response speed

- Slow response, delayed 4-6 s, lasts ~ 4-6 s, returns to baseline much later
- Post and pre stimulus undershoot, vascular variation

Glover, GH Neuroimage (1999)
Minimum time between stimuli

Henson, 2007; http://imaging.mrc-cbu.cam.ac.uk/imaging/DesignEfficiency
Hemodynamic response as a filter

(a) Stimulus (“Neural”) $\times$ HRF $\Rightarrow$ Predicted fMRI Data

(b) $\Rightarrow$ Fourier Transform

(c) Magnitude $\times$ Magnitude $\Rightarrow$ Magnitude
fMRI acquisition

Functional

Anatomic

One image / 2 s for 5 min

BOLD signal time series

One image / 3-5 min

Courtesy of Catie Chang NINDS
Filling k-space, one line at a time

Courtesy of Nick Bock, McMaster
Filling k-space, center out

Courtesy of Nick Bock, McMaster
Standard pulse sequences

Glover, Neuroimage (2012)
Example EPI/Spiral images … susceptibility

(A) EPI R/L

(B) EPI A/P

(C) Spiral

Glover, Neuroimage (2012)
(C) Spiral-in/out

Glover, Neuroimage (2012)
Susceptibility reduction

Glover, Neuroimage (2012)
Voxel size

- In going smaller voxel size is primarily limited by SNR
- smaller is usually desirable to reduce partial volume effects, physiological noise

Voxel SNR is given by

$$SNR \propto p^2 w \sqrt{T_{acq} N}$$

Where $p$ is the voxel size, $w$ is the slice thickness, $T$ is the acquisition time, and $N$ is the number of time frames

$T_{acq}$ is about 20-30ms for single shot EPI.

Triantafyllou et al, Neuroimage (2005)
fMRI acquisition

Anatomic

One image / 3-5 min

Functional

BOLD signal time series

One image / 2 s for 5 min

Courtesy of Catie Chang NINDS
Whole brain vs. Partial coverage

**Increasing number of slices:**
- Decreased temporal **or**
- Decreased in-plane resolution

**Increasing slice thickness:**
- Increased partial voluming
- Increased susceptibility artifacts

**Useful for:**
- Cognitive studies
- Resting state

**Useful for:**
- Specific ROIs

**Thinner slices for short TRs**
- Increased in-plane resolution
- Shorter TR
Single shot EPI

T2* decay

EPI Readout Window

≈ 20 to 40 ms

Courtesy of Peter Bandettini
Multi-shot EPI

- All lines acquired in a single "shot" with one RF pulse
  - Pros: Fast
  - Cons: Long readout => distortions

- Split the acquisition into parts
  - Pros: acquire higher resolution
  - Cons: phase errors, ghosting, requires more time
- Undersample k-space by acceleration factor $n$
- Reconstruct either in k-space (GRAPPA) or image space (SENSE)
- Maximum acceleration limited by number of coils and SNR reduction
Multi-slice or multi-band excitation

Multi-slice or multi-band excitation

- Excites multiple slices at once,
- Uses coil sensitivity profiles to unmix the images
- Sub TR whole brain images are achievable
- Loss in SNR
- Long reconstruction times

What is the optimal voxel size?

- Also need to take into account noise fluctuations over time
- Thermal sources, physiological noise

\[ \sigma = \sigma_{thermal} + \sigma_{physio} \]

- TSNR is the ratio over the average voxel time course signal over the time course standard deviation.

\[ tSNR = \frac{\bar{S}}{\sqrt{\sigma_{thermal}^2 + \sigma_{physio}^2}} \]

- TSNR has a nonlinear relation with image SNR

\[ \sigma_{thermal} \propto B_0 \]
\[ \sigma_{physio} \propto S \]

Triantafyllou et al, Neuroimage (2005)
Optimal voxel size?

\[ \sigma_{\text{thermal}} = \sigma_{\text{physio}} \]

Has been suggested as a guide to choosing voxel size given a particular image SNR. Based on tissue types and imaging parameters.

Pros
- Higher SNR (1.6 times at 7t v 4t )
=> potential increased resolution / specificity

Cons
- shorter T2*
=> faster readout/ acceleration needed
- long TR
=> longer repetition time to get signal
- larger field perturbations/ inhomogeneities
- SAR limitations
What's the effective spatial resolution?

- Imaging limit ~0.5 mm, easily 2mm, standard 3 ish mm
- Hemodynamic PSF 3.5 mm (Engel, 1997)
- Higher at 7T ~2.3 mm
- Smoothing improves reproducibility, alignment between subjects ~10mm (Strother 2005)
Contrast Options

Different pulse sequences:

- Spin echo
- Diffusion weighted
- Arterial spin labeling
- Multi-echo
Pulse sequences

Spin Echo

Gradient Echo

Transverse magnetization

T2

T2*

90° 180°

180°
Increased specificity with SE

\[ \Delta R^*_2 \]

\[ \Delta R_2 \]

Vessel Radius

<3 \( \mu m \)

3 to 15 \( \mu m \)

> 15 \( \mu m \)

Kim, Methods (2003)
And vasculature ...
GE BOLD fMRI (A) has the highest percent signal change at the cortical surface, where large pial vessels are located (green contours).

Large vessel contributions are suppressed in SE BOLD.

The highest CBV change is at the middle of the visual cortex in layer 4 that has the highest metabolic and CBF responses.

## Spin echo summary

### Pros

- Increased specificity (esp at high fields where IV signal is low)
- Less sensitive to rapidly flowing blood
- Less signal dropout.

### Cons

- Fewer slices per TR
- Lower fCNR by x 2 to 4.
- Acquisition window still T2*
- Very large IV signal still present at most field strengths.

Courtesy of Peter Bandettini
High field applications of GE, SE

Cortical layers using GE

Optical orientation columns using SE

Yacoub E et al. PNAS 2008;105:10607-10612

Polimeni JR et al, Neuroimage (2010)
Diffusion weighting

- add diffusion gradients to help separate out the intra and extra vascular components

Lee SP et al, MRM (1999)
- Intravascular contribution decreases as magnetic field strength increases.

<table>
<thead>
<tr>
<th>Magnetic field (T)</th>
<th>MR technique, echo time (ms)</th>
<th>b value (s/mm²)</th>
<th>Subject, brain region</th>
<th>Intravenous fraction</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.5</td>
<td>ASE, 165</td>
<td>10–690</td>
<td>Human, V1</td>
<td>0.5–0.7</td>
<td>Boxerman et al (1995)</td>
</tr>
<tr>
<td></td>
<td>SE, 125</td>
<td>200–700</td>
<td>Human, V1</td>
<td>0.6–1.0</td>
<td>Zhong et al (1998) (Figure 4B)</td>
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<tr>
<td>3.0</td>
<td>GE, 82</td>
<td>165–660</td>
<td>Human, M1</td>
<td>0.6–0.9</td>
<td>Song et al (1996)</td>
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<tr>
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<td>GE, 33–93</td>
<td>100</td>
<td>Human, V1</td>
<td>0.46–0.62</td>
<td>Donahue et al (2011)</td>
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<td>SE, 96.5</td>
<td>14–454</td>
<td>Human, V1</td>
<td>~0.5</td>
<td>Jochimsen et al (2004)</td>
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<td>Human, V1</td>
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<td>40–400</td>
<td>Human, V1</td>
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<td>Human, V1</td>
<td>0.08–0.16</td>
<td>Donahue et al (2011)</td>
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<td></td>
<td>SE, 40</td>
<td>30–500</td>
<td>Rat, S1</td>
<td>~0</td>
<td>Lee et al (1999)</td>
</tr>
<tr>
<td></td>
<td>SE, 16–70</td>
<td>200</td>
<td>Cat, V1</td>
<td>0–0.6</td>
<td>Jin et al (2006)</td>
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A. Baseline and Stimulus

- Artery
- Vein
- Oxyhemoglobin
- Deoxyhemoglobin

B. Expected stimulus-induced changes in MR-related parameters

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ASL vs. BOLD

Detre JA et al., Clinical Neurophysiology (2002)
# ASL vs. BOLD

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<tr>
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<th><strong>BOLD</strong></th>
<th><strong>ASL</strong></th>
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<tbody>
<tr>
<td><strong>Signal Mechanism</strong></td>
<td>Blood flow, Blood volume, Oxygenation consumption</td>
<td>Blood flow</td>
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<tr>
<td><strong>Contrast parameter</strong></td>
<td>T2*</td>
<td>T1</td>
</tr>
<tr>
<td><strong>Spatial specificity</strong></td>
<td>Venules and draining veins</td>
<td>Capillaries, arterioles</td>
</tr>
<tr>
<td><strong>Typical signal change</strong></td>
<td>0.5-5 %</td>
<td>&lt; 1 %</td>
</tr>
<tr>
<td><strong>Imaging methods</strong></td>
<td>Gradient-echo, spin-echo</td>
<td>Spin-echo</td>
</tr>
<tr>
<td><strong>Sample rate (TR)</strong></td>
<td>1-3 s per image</td>
<td>&lt; 3-8s per perfusion image</td>
</tr>
<tr>
<td><strong>Optimal task frequency</strong> (block design)</td>
<td>0.01 – 0.06 Hz (100 s - 16 s)</td>
<td>&lt; 0.01 Hz</td>
</tr>
<tr>
<td><strong>Intersubject variability</strong></td>
<td>High</td>
<td>Low</td>
</tr>
<tr>
<td><strong>Imaging coverage</strong></td>
<td>Whole brain</td>
<td>Most of brain cortex</td>
</tr>
<tr>
<td><strong>Major artifacts</strong></td>
<td>Susceptibility, motion, baseline drift</td>
<td>Vascular artifact</td>
</tr>
<tr>
<td><strong>Relative CNR</strong></td>
<td>&gt; 2 high task frequency &lt; 0.5 low task frequency</td>
<td>1</td>
</tr>
</tbody>
</table>

Detre JA et al., Clinical Neurophysiology (2002)
Long duration stimulation: ASL vs. BOLD

Separating BOLD from non-BOLD
Signal scaling

a Multi-echo EPI images

b Multi-echo EPI time courses for task (V1)

C Multi-echo EPI time courses for rest (precuneus)
κ spectrum

spontaneous brain activity

- default mode network
- lingual visual network
- auditory network
- basal ganglia
- motor network

TE-Dependence Maps of ICA Functional Networks

κ

component rank by κ

sinus flow
subject motion
cardiac pulsation
field fluctuation
noise
Temporal limits

- Create a functional image within 2 s for more robust activation or in less than 1 s using acceleration.
- Limited by filtering lag of hemodynamic response function 4-6 s.
- Long (> 2 min) duration stimuli are hampered by baseline changes.
- Can detect differences in the onset of hemodynamic responses down to 100 ms.

Spatial limitations

- At 3 T: ~ 1.5 mm$^3$ resolution
  - The functional point spread function is about 3.5 mm.
- At 7 T, ~ 0.5 mm$^3$ resolution
  - The functional point spread function can be has high as 1.5 mm.
- At 7 T, using spin-echo sequences, the smallest resolved functional unit was orientation columns (on the order of 0.5-mm width).
- Practically limited by smoothing kernels, template alignment in group studies.

Yacoub E et al. PNAS 2008; 105:10607-10612
Hemodynamic Specificity

Arterial inflow (BOLD TR < 500 ms)

Venous inflow (Perf. No VN)

Perfusion

BOLD

TI

ASL

GE

SE

Courtesy of Peter Bandettini
Sensitivity

- Limited to a temporal signal-to-noise ratio of about 100:1 across all field strengths by physiologic fluctuations that occur over time.
- Better modeling of the physiological fluctuations required.

• BOLD signal change is not a quantitative measure.
  - Hemodynamic factors (baseline blood volume, neurovascular coupling) influence location, magnitude, and dynamics.

• Use of multi-echo, combination of contrasts

• Multimodal studies are needed to firmly establish the relationship between BOLD signal and neural activity.

• Developing techniques to measure neuronal currents (small signals...)
Acknowledgements

Thanks to:

Catie Chang
Peter Bandettini