Neural basis of fMRI signals

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From sensory stimuli to fMRI maps

Stimulus

$T_2^* / T_2 / \text{CBF}$
From sensory stimuli to fMRI maps

Stimulus  Neuronal activity  Change in CBF  \( T_2^* / T_2 / CBF \)
From sensory stimuli to fMRI maps

Stimulus | Neuronal activity | Change in CBF | $T_2^*/T_2/\text{CBF}$

[Images and graphs illustrating the relationship between sensory stimuli, neuronal activity, changes in CBF, and MRI/PET/OI measurements]
From sensory stimuli to fMRI maps

Stimulus → Neuronal activity → Change in CBF → MRI / PET / OI measurement

Neurovascular coupling

T₂* / T₂ / CBF
From sensory stimuli to fMRI maps

Stimulus  Neuronal activity  Change in CBF  \( T_2^* / T_2 / CBF \)

Neurovascular coupling  MRI / PET / OI measurement
Overview: Thursday’s lecture

- Neuronal mechanisms underlying less conventional fMRI responses
Thursday’s lecture: Neuronal activity underlying resting state BOLD

Shmuel and Leopold (2008)
Thursday’s lecture: Negative BOLD Responses

Shmuel et al., Neuron (2002)
Overview

- Basics of intra-cranial neurophysiology
- Vascular mechanisms of BOLD response

Quantitative relationship and neuronal mechanisms:

- Metabolic response and Spiking activity
- Positive BOLD response and spiking activity
- Positive BOLD response and synaptic activity
From sensory stimuli to fMRI maps

Stimulus  Neuronal activity  Change in CBF  \( T_2^* / T_2 / \text{CBF} \)

Neurovascular coupling

MRI / PET / OI measurement
Locally measured neuronal activity: extracellular recordings (majority of studies)

A neuron is considered to be embedded in an extracellular medium that acts as a volume conductor (Lorente de Nó 1947; Freeman 1975).
Locally measured neuronal activity: extracellular recordings

When the membrane potential between two separate regions of such a neuron is different, there is a flow of current in the neuron matched by a return current through the extracellular path.
Local Field Potentials and Multi-Unit Activity

- The potential measured by an electrode with respect to a distant site reflects action potentials, superimposed on other waves of lower frequency.

- A filter cut-off is used in most recordings to obtain MUA (above 400 Hz) and LFPs (below 150 Hz).

- LFPs can be further classified to frequency bands used in EEG - delta, theta, alpha, beta, and gamma.

Logothetis, 2002
The Mean Extracellular Potential & its Components

Freq < 150Hz

Freq > 400Hz

MUA

LFP
Components of the Mean Extracellular Potential

**MUA**
- Single event duration: Approx 1 msec, Spatial summation: Radius of 100-200 microns
- Represents: Mainly activity of the projection neurons that form the output of a cortical area

**LFPs**
- Single event duration: 10 - 100 msec, Spatial summation: Radius of 1-2 mm
- Represent:
  - Population Synaptic Potentials (PSPs)
  - Voltage-gated membrane oscillations
  - Represent the input of a given cortical area as well as its local intra-cortical processing (including the activity of excitatory and inhibitory neurons)

Logothetis, 2002
fMRI signal is an indicator of overall activity of very many neurons and processes

Density of neurons in cerebral cortex

\[ 12 \times 10^4 \; / \; \text{mm}^3 \]
\[ 1 \times 10^6 / 2 \times 2 \times 2 \; \text{mm}^3 \]

Density of synapses in cerebral cortex

\[ 9 \times 10^8 \; / \; \text{mm}^3 \]
\[ 7.2 \times 10^9 / 2 \times 2 \times 2 \; \text{mm}^3 \]

Shuez A and Briatenberg V, 1998
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Stimulus  Neuronal activity  Change in CBF  \( T_2^* \), \( T_2 \), CBF

Neurovascular coupling  MRI measurement
Blood Oxygenation Level Dependent: BOLD functional MRI signal

- indirect detection of neuronal activity
  - magnetic properties of hemoglobin
    - deoxyhemoglobin acts as a *contrast agent*

\[
\begin{align*}
\text{Deoxyhemoglobin} & \quad \chi \sim 1.6 \\
\text{Oxyhemoglobin} & \quad \chi \sim -0.3
\end{align*}
\]

from B. Pike, MNI

From B. Pike, MNI
Cortical blood vessels

- Duvernoi et al., 1981
Cortical blood vessels: control of blood flow

Peppiatt, Attwell et al., 2006. Harrison et al., 2002.

Potential control sites of cerebral hemodynamic response: arteriolar smooth muscle, and pericytes on capillaries.
- BOLD is inversely proportional to deoxyHb in capillaries and veins

Physiological parameters influencing BOLD signal:

- CMRO2
- CBF
- CBV

DeoxyHb

BOLD
Mechanisms of the positive BOLD response

neural activity $\uparrow \rightarrow$ oxygen consumption $\uparrow \rightarrow$ blood flow $\uparrow \uparrow \rightarrow$

oxy-Hb $\uparrow \uparrow \rightarrow$ deoxy-Hb $\downarrow \rightarrow$ T2* $\uparrow \rightarrow$ MR signal $\uparrow$

- normal flow
- basal level [deoxy-Hb]
- basal CBV
- normal MR signal

- increased flow
- decreased [deoxy-Hb]
- increased CBV
- increased MR signal
Time course of BOLD signal

Question on BOLD Signal:

What is the origin of the signal: arteries, arterioles, capillaries, venules or veins?
Question on BOLD Signal:

What is the origin of the signal: arteries, arterioles, capillaries, venules or veins?

Answer: mainly capillaries, venules, and veins, because in arteries and arterioles there is almost no deoxy-hemoglobin.
BOLD and neurophysiology:

1. Time lag
2. Which blood vessels do we get our BOLD signals from?
- Optical imaging of Intrinsic Signals

Bonhoeffer and Grinvald (1996)
- Optical imaging of Intrinsic Signals

Bonhoeffer and Grinvald (1996)

605 nm

Absorption spectra
- Time-course of Intrinsic Signals

Bonhoeffer and Grinvald (1996)

Shtoyerman et al. (2000)
- Optical imaging of Voltage Sensitive Dyes

Shoham et al. (1999)
Intracellular recording vs. Voltage Sensitive Dyes Imaging

Modified from Cohen L et al., 1972
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Neurovascular coupling  MRI / PET / OI measurement
Estimating neuronal activity based on hemodynamic & metabolic signals

- Quantitative relationship

- Which type of neuronal activity is reflected in these signals: spikes or synaptic activity?
Time course of BOLD signal

Overview

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Quantitative relationship and neuronal mechanisms:
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Quantitative relationship of BOLD and neurophysiology:

Are metabolic responses proportional to changes in neurophysiological activity?
Optical imaging of intrinsic signals

Diagram:
- Computer
- Digital Camera Controller
- Visual Stimulator
- Light Guide Illuminator
- CCD Camera
- Image Display
- Video-projector
- Projection-screen
- 605nm
Optical imaging of intrinsic signals

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Optical imaging (deoxyHB – oxyHb) & targeted electrical recording: the ‘dip’

Shmuel and Grinvald, 1996
Metabolic response vs. multi-unit spikes

\[ r = 0.79 \]

\[ \text{Var(intrinsic)} = 0.46 \times 10^{-7} \]

Shmuel and Grinvald, 1996
Metabolic response vs. multi-unit spikes

$r = 0.76$

$\text{Var(intrinsic)} = 0.77 \times 10^{-8}$

Shmuel and Grinvald, 1996
Quantitative relationship of BOLD and neurophysiology:
Are positive BOLD responses proportional to changes in neurophysiological activity?
Time course of BOLD signal

Positive BOLD responses in human V1 are proportional to average firing rates in monkey V1

Conclusions

- The initial oxygen consumption deoxyHb – OxyHb response in the visual cortex is ~proportional to the local spiking activity

- Positive BOLD responses in human V1 are proportional to average firing rates in the corresponding areas of the monkey cortex
Conclusions

- The initial deoxyHb – OxyHb response in the visual cortex is ~ to the local spiking activity

- Positive BOLD responses in human V1 are proportional to average firing rates in the corresponding areas of the monkey cortex

- So – does BOLD reflect spiking activity?
Conclusions

- The initial deoxyHb – OxyHb response in the visual cortex is ~ to the local spiking activity

- Postive BOLD responses in human V1 are proportional to average firing rates in the corresponding areas of the monkey cortex

- So – does BOLD reflect spiking activity? The detected linearity does not imply on the origin of the hemodynamic response (spikes vs. synaptic activity: correlation ≠ causation).
Quantitative relationship of BOLD and neurophysiology:
Are hemodynamic responses proportional to changes in Local Field Potentials?
Cerebella Blood Flow versus LFPs

CBF versus $\Sigma LFP$ during climbing fibre stimulation

CBF versus $\Sigma LFP$ during parallel fibre stimulation

Cereberral Blood Flow versus LFPs:
Increasing, linear and non-linear responses

CBF versus $\sum LFP$ during climbing fibre stimulation

CBF versus $\sum LFP$ during parallel fibre stimulation

Which type of neuronal activity is reflected by BOLD: spikes or synaptic activity?
Activity-dependent CBF increases evoked by stimulation of cerebellar parallel fibres are dependent on synaptic excitation, including excitation of inhibitory interneurons, whereas the net activity of Purkinje cells, the principal neurons of the cerebellar cortex, is unimportant for the vascular response.

Conclusions

The hemodynamic response is in many instances ~ **linear** with the underlying neuronal spike activity.

Non-linearities between the hemodynamic response and LFP / spiking activity have been observed.

Cerebrellar Blood Flow does not depend on spiking activity.
fMRI & Recordings: Cerebral Cortex, V1

Electrode Position

BOLD Activation

Logothetis et al.
Nature (2001)
BOLD ~ neuronal activity

SNR for Neural & Hemodynamic Signals

![Graph showing NEURAL SD Units and BOLD SD Units over Time in Seconds]
Dissociation of MUA and BOLD-Signal

Conclusions

• The BOLD response directly reflects a local increase in neural activity assessed by the mean Extracellular Field Potential signal.

• The Signal to Noise Ratio (SNR) of the neural signals is much higher than that of the fMRI signals. Thresholding methods are likely to underestimate a great deal of actual neural activity related to the stimulus or task.

• The BOLD response reflects changes in LFP / synaptic activity / input to- and local processing in a region, more than MUA / output of a region.