Overview II

- Neuronal activity underlying negative BOLD

- Resting-state networks:
  - Definition of a resting state network
  - Neuronal activity underlying resting state BOLD
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.
Does BOLD always reflect correctly changes in neuronal activity?

Perhaps not…

Negative fMRI BOLD response
Beyond the stimulated regions in human visual cortex: **Negative BOLD response**

**Fixation task**

**Stimulus:**
flickering checkers

**Control:**
blank gray

**GE-EPI**
2 sagittal slices

![Image of brain scans with color coding and scale](image)

- **Dorsal**
- **Anterior**

**P < 7×10⁻⁴**

-0.8 **Negative corr.**   -0.17  0.17  0.8 **Positive corr.**
The negative BOLD response is associated with negative blood flow response.

BOLD (GE-EPI) vs. Cerebral blood flow (FAIR)

Spatial cluster reproducibility: $p < 3.2 \times 10^{-6}$

Subject: S8
(ss-nss)/nss

GE-EPI/FAIR
1 axial slice

One shot
2\( \times \)2\( \times \)8 mm\(^3\)

TR: 6 sec/vol
TE: 20 msec.
cerebral blood flow

vascular

cerebral blood flow

neuronal activity
cerebral blood flow

neuronal activity

cerebral blood flow

neuronal activity
Negative BOLD response

GE-EPI 8 segments TR / TE: 250 / 20 ms
5 oblique slices .75×.75×2 mm³ TR / vol 2 sec

Shmuel et al., Nature NS 2006
BOLD response from the ROI

Overlapping stimulus
Non-overlapping stimulus
Mean ± SEM over all data-sets
Neuronal signal: mean power

Mean ± SEM

Baseline S.D. units

Mean ± SEM

time (sec.)
Neuronal signal: action potentials

Mean ± SEM

Spikes / 2 sec.

Spike frequency over time (sec.)

-10 0 10 20 30

Mean ± SEM
cerebral blood flow

neuronal activity

?
cerebral blood flow
neuronal activity
vascular
metabolic
neuronal activity
Blood steal $\Rightarrow$ ???

hypoxia $\Rightarrow$ ???

decreases in neuronal activity ???

Q: Is the origin of the decreases in neuronal activity vascular (e.g. from hypoxia due to vascular blood steal) or neuronal?
Normalized BOLD and neuronal response
Coupling of the **negative** BOLD response to the decreases in neuronal activity

\[ \text{BOLD} = f(\text{Neuronal}) \]

\[ r = .42, \ p < 10^{-3} \]

\[ r = .43, \ p < 10^{-5} \]
The **negative BOLD response** is associated and correlated with decreases in neuronal activity.
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Spontaneous fluctuations in fMRI signals

- Large amplitude fluctuations in spontaneous fMRI signals in the resting state in human cerebral cortex (Biswal et al., 1995; Fox et al., 2006).

- Note the slow temporal scale of the fluctuations: 0.01 - 0.1 Hz (one cycle is 10 s long or even longer).
Spontaneous fluctuations in fMRI signals
The human somato-motor resting state network

Functional connectivity (correlated functional MRI signals) in the resting state

Analysis: seed based correlation

Biswal et al., 1995; Fox and Raichle, 2007
Measure of functional connectivity: similarity of time-courses (measured with Pearson’s correlation coefficient)

\[-1 \leq r \leq 1; \text{ a measure of linearity}\]
The human somato-motor resting state network

Functional connectivity (correlated functional MRI signals) in the resting state

Analysis: seed based correlation

Biswal et al., 1995; Fox and Raichle, 2007
Connections of V1 in tangential sections through flat mounted mouse cerebral cortex. (a, b) Darkfield image of anterogradely labeled axonal projections (yellow; high density clusters are marked by red-brown centers) after injection of BDA into V1 (arrow).

From Wang et al., JNS (2012).
Anatomical (or structural) connectivity and functional connectivity are 2 different concepts

- Structural connectivity refers to axonal projection from one area (A) to another (B).

- Functional connectivity refers to statistical dependence (e.g. correlation) between the time-courses of activities in areas A and B.

- Two areas that show functional connectivity are not necessarily anatomically connected.
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Non-neurophysiological contributions

- Part of these fluctuations and correlations could be of subject movement, MRI noise, or physiological noise origin (Wise et al., 2004; Birn et al., 2006, 2008, Shmueli et al., 2007).

Respiration-Induced Signal Changes

The respiration volume per time correlates with functional MRI signal (precuneus, cuneus, superior temporal gyrus, fusiform gyrus, and occipital cortex).
Methods

- 9 sessions

Uniform gray: 7 sessions

In darkness: 2 sessions

Neurophysiology simultaneously with fMRI
(Logothetis et al., 2001)

Methods
Methods

[Graph showing BOLD (% change) vs time (s) and broadband neuro. vs time (s) with frequency (Hz) on the right side.

Graph labels:
- BOLD (% change) on the y-axis
- broadband neuro. on the y-axis
- time (s) on the x-axis
- frequency (Hz) on the right side of the graph.
Methods
Methods

BOLD (% change)

BOLD signal showing fluctuations over time.

Frequency (Hz)

Spectral analysis showing frequency bands.

Power (% change)

Graph illustrating power changes over time for different frequency bands.
Correlation between BOLD and neurophysiology

- Multiple non-overlapping time-course segments (15 s each) of neuronal-activity and BOLD were tested for correlation, with lags from 0 to 15 s.

BOLD

Neuronal

Lag 0 s
Correlation between BOLD and neurophysiology

- Multiple non-overlapping time-course segments (15 s each) of neuronal-activity and BOLD were tested for correlation, with lags from 0 to 15 s.
Correlation between BOLD and neurophysiology

- Multiple non-overlapping time-course segments (15 s each) of neuronal-activity and BOLD were tested for correlation, with lags from 0 to 15 s.
Correlation between BOLD and neurophysiology

- Multiple non-overlapping time-course segments (15 s each) of neuronal-activity and BOLD were tested for correlation, with lags from 0 to 15 s.

BOLD

............................

..........................

Neuronal

Lag 3 s
Correlation between BOLD and neurophysiology

- Multiple non-overlapping time-course segments (15 s each) of neuronal-activity and BOLD were tested for correlation, with lags from 0 to 15 s.
Spontaneous fluctuations in BOLD correlate with the underlying neuronal activity: Broadband.

Simultaneously acquired

Shuffled

Peak: approx. 6 s lag
Spontaneous fluctuations in BOLD correlate with the underlying neuronal activity: Gamma

Peak: approx. 6 s lag
Spontaneous fluctuations in BOLD correlate with the underlying neuronal activity: MUA

Simultaneously acquired

Shuffled

Peak: approx. 6 s lag
Spontaneous fluctuations in BOLD correlate with the underlying neuronal activity: Spike rate

Simultaneously acquired

Shuffled

Peak: approx. 6 s lag
Spatial extent of the correlation – case 1

- Anterior
- Midline
- Specificity to gray matter regions
Spatial extent of the correlation – case 1

Anterior

1 cm

Midline

0 s

Electrode
Spatial extent of the correlation – case 1

1 cm

Anterior

Midline

3 s

Electrode
Spatial extent of the correlation – case 1

Midline

Anterior

1 cm

Electrode

4 s
Spatial extent of the correlation – case 1

Anterior

1 cm

Midline

Electrode

5 s
Spatial extent of the correlation – case 1

1 cm

Anterior

Midline

Electrode

6 s
Spatial extent of the correlation – case 1

1 cm

Anterior

Midline

Electrode

7 s
Spatial extent of the correlation – case 1

1 cm

Anterior

Midline

Electrode 8 s
Spatial extent of the correlation – case 1

1 cm

Anterior

Midline

9 s

Electrode
Spatial extent of the correlation – case 1

1 cm

Anterior

Midline

10 s

Electrode
Anterior

1 cm

Midline

Electrode

0 s

Spatial extent of the correlation – case 2
Spatial extent of the correlation – case 2
Spatial extent of the correlation – case 2
Spatial extent of the correlation – case 2
Spatial extent of the correlation – case 3

Gamma

30 continuous min of spontaneous activity, in darkness
Spatial extent of the correlation – case 3

Gamma

Correlation in both hemispheres with neurophysiology in one site of V1
Spatial extent of the correlation – case 3

Gamma

- Origin is not vascular
- Polysynaptic pathways, possibly involving higher visual areas or the thalamus
Summary

- Spontaneous fluctuations in fMRI signals in V1 correlate with the locally measured fluctuations in the underlying neuronal-activity.

- Fluctuations in BOLD correlate with fluctuations in the LFP Gamma activity, MUA, and in spike rate.

- The neuronal and hemodynamic signals are correlated over large regions of the visual cortex.
Cross-correlation between the fMRI (ROI data) and LFP power time courses as a function of LFP constituent frequency.

Schölvinck M L et al. PNAS 2010;107:10238-10243
Spatial extent of the correlation between the neural signal in V1 and spontaneous fMRI fluctuations.

Schölvinck M L et al. PNAS 2010;107:10238-10243
Overview

- Definition/quantification of a resting-state network

- Does fMRI-based spontaneous activity reflect neurophysiological activity?

- Do resting state networks reflect functionally identified networks?
The human somato-motor resting state network

Functional connectivity (correlated functional MRI signals) in the resting state

Analysis: seed based correlation

Biswal et al., 1995; Fox and Raichle, 2007
Which other resting state networks exist?

Medial visual     Occipital pole visual     Lateral visual     Default mode network     Cerebellum

Sensori-motor     Auditory     Executive control     Fronto-parietal perception–somesthesis–pain     Fronto-parietal language-cognition

Smith S M et al. PNAS 2009;106:13040-13045
- Talairach coordinate system is defined by making two points on the mid-sagittal plane, the anterior and posterior commissures, lie on a straight horizontal line.
- Distances are measured from the anterior commissure.
- This coordinate system makes it possible to spatially warp an individual brain image obtained through MRI onto a model prototypical brain.
Correspondence of the brain’s functional architecture during activation and rest

- BrainMap: a data-base describing which brain coordinates are activated by specific tasks.
- 36-subject resting FMRI dataset
- 29,671-subject BrainMap activation database
- 3 most informative orthogonal slices
- (Left column of each pair) Resting FMRI data
- (Right column of each pair) Corresponding network from BrainMap, shown superimposed on the MNI152 standard space template image.
- The networks were paired automatically by using spatial cross-correlation, with mean $r = 0.53$
Correspondence of the brain’s functional architecture during activation and rest

medial visual     occipital pole visual     lateral visual    default mode network    cerebellum

sensory-motor             auditory           executive control     fronto-parietal
perception–somesthesis–pain language-cognition

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