Neurophysiological investigation of the basis of the fMRI signal

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Study Goal

- What is the exact relationship between the BOLD signal and the underlying neural activity?

Rationale

- BOLD response can only measure hemodynamic changes such as alterations in flow, blood volume, or intravascular magnetic susceptibility.
- Using other measures simultaneously with fMRI are imprecise
  - Optical imaging: also is looking at hemodynamic response
  - EEG: has poor spatial resolution
- Ideally, one would look at fMRI simultaneously with microelectrode recordings of single-spike responses and local field potentials.

Neurophysiology background

- Multi-Unit Activity (MUA) – reflect the output of a neural population within ~200microns of the electrode tip. This if often referred to as "spike rate."

- Local field potentials (LFP) – reflect the weighted average of synchronized dendrite-soma components of the input signals of a neural population within a few millimeters of the electrode tip. They are often stimulus-locked, and are fast oscillations in the range of 30-150Hz, similar to EEG and MEG.

Method

- 10 Monkeys
- Elicited visual cortical responses to a checkerboard pattern using a block design.
- During this, simultaneously recorded BOLD response, MUA, and LFP.

Neural and BOLD response to pulse stimuli

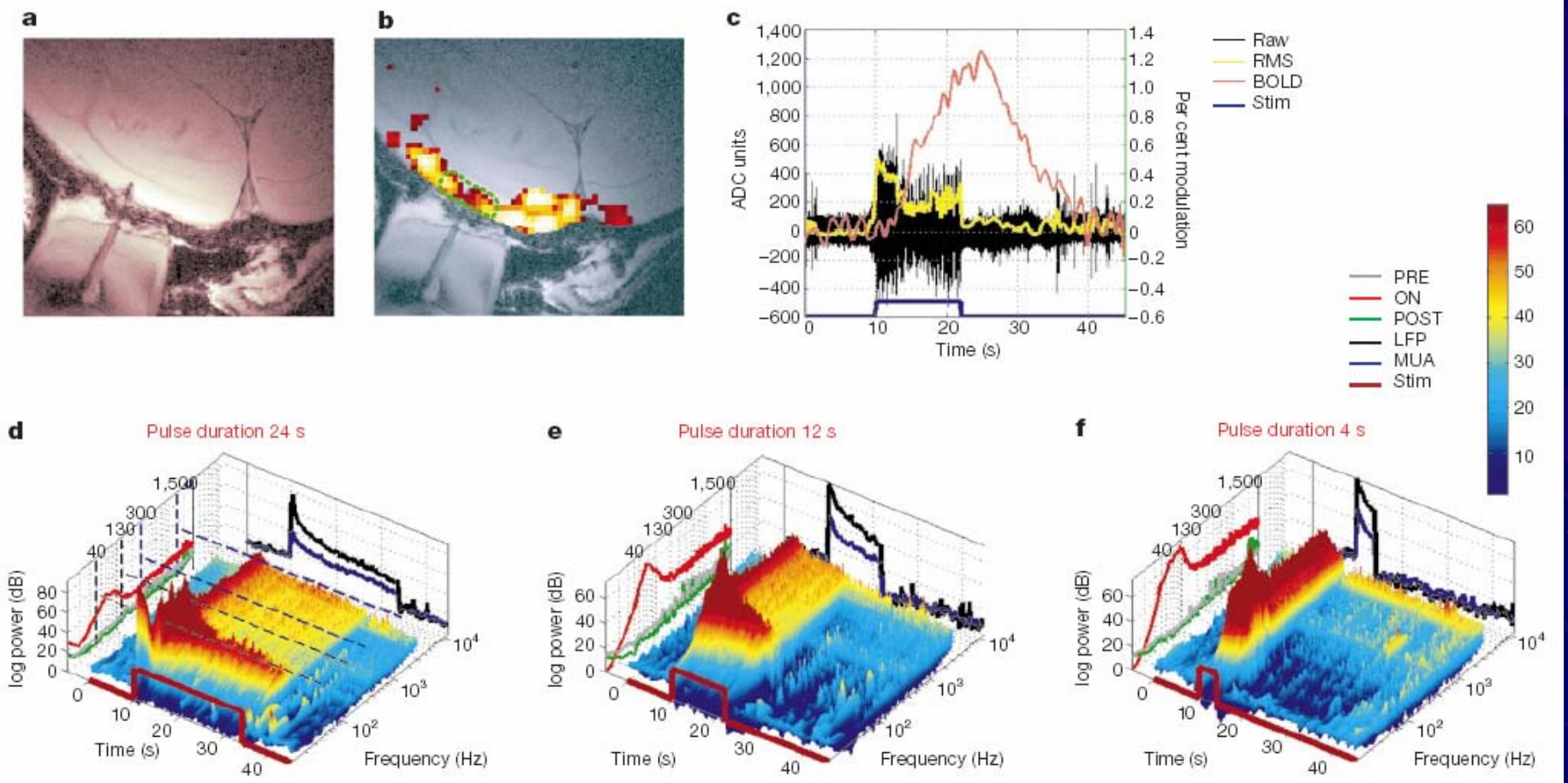

Figure 1 Neural and BOLD responses to pulse stimuli. **a**, FLASH scan (see Methods) showing the location of the electrode tip in primary visual cortex. **b**, BOLD response to rotating chequerboard patterns in striate cortex. Activation can be measured around the electrode tip. **c**, Haemodynamic response (red) superimposed on the de-noised raw neural signal (black). The term 'de-noised raw' denotes that no other signal processing beyond the removal of gradient interference (see Methods) was done. The r.m.s. of the signal is indicated by a thick yellow line. **d**–**f**, Spectrograms for data collected over 24, 12 and 4 s. In each three-dimensional plot, the vertical panel along the time axis shows the average LFP and MUA responses, namely the mean vector of the time series between black and blue dashed lines, respectively. The vertical panel along the frequency axis shows the average spectra for the pre-stimulus, stimulation, and post-stimulus periods. Colour bar shows the logarithm of power. ADC, Analogue to digital converter; STIM, time course of the visual stimulus; PRE, pre-stimulus period; ON, stimulus presentation period; POST, post-stimulus period.

Fig 1 Key points

- Transient increase in power across all frequencies, followed by a lower level of maintained activation.
- LFP always larger than MUA.
- Decrease in neural activity after the termination of the stimulus.

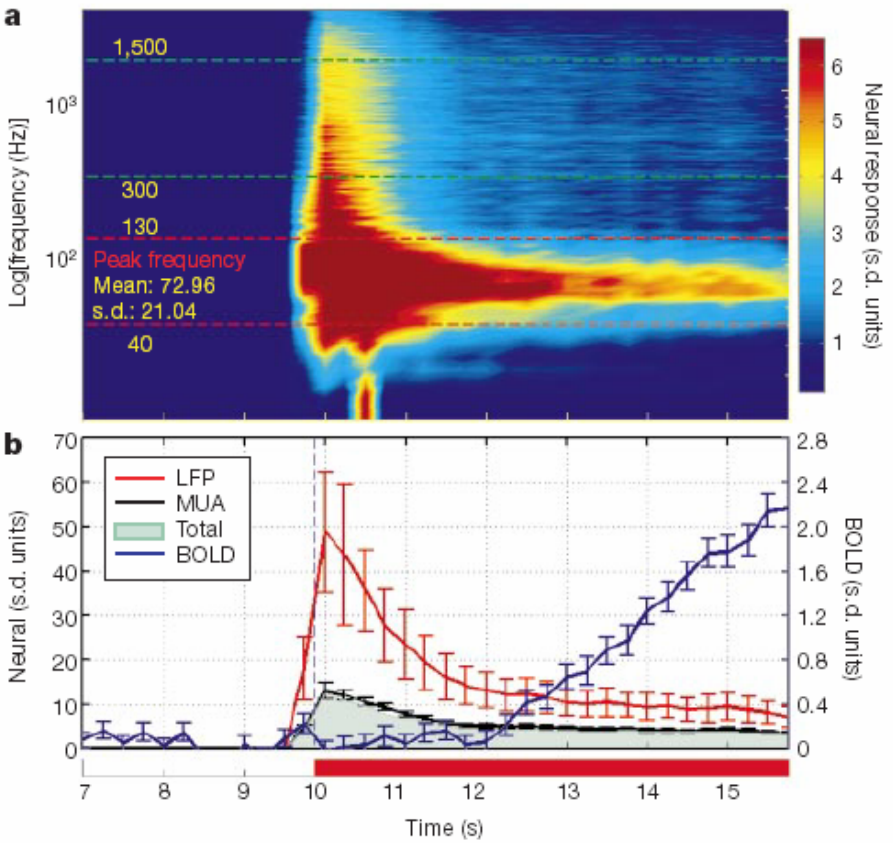

Figure 2 Time-dependent frequency analysis for population data. **a**, Spectrogram of the first 6 s of the neural response averaged over all data collected during 24, 12.5, 12 and 6 s of stimulus presentation (10 monkeys, 619 experiments). Each time course is expressed in units of the standard deviation of the pre-stimulus period. Colour (and thus the colour bar) encodes the reliability of signal change for each frequency (signal-to-noise ratio) rather than the magnitude of the power spectrum. Red and black dashed lines show the LFP and MUA frequency bands, respectively. **b**, Mean LFP (red), MUA (black) and total (green surface) neural response (average across all frequencies), together with the BOLD signal (blue). The total signal is very similar to the MUA signal as the LFP represents a small frequency range (note the logarithmic scale of the frequency axis in **a**). The figure shows the significantly higher LFP activation for both the transient and the sustained portion of the response. Error bars are 1 s.d. with $N = 10$ (number of monkeys).

Time-dependent frequency analysis for all data

Fig 2. Key points

- Maximum increase in power is at 72.96Hz, or in the gamma range of the LFPs.
- 2b – marked difference in SNR between neural and BOLD signals.
- Hence, could result in statistical rejection of an activation despite the fact that the underlying neural activity is highly robust and significant.
- Higher LFP for both the transient and sustained portion of the response.

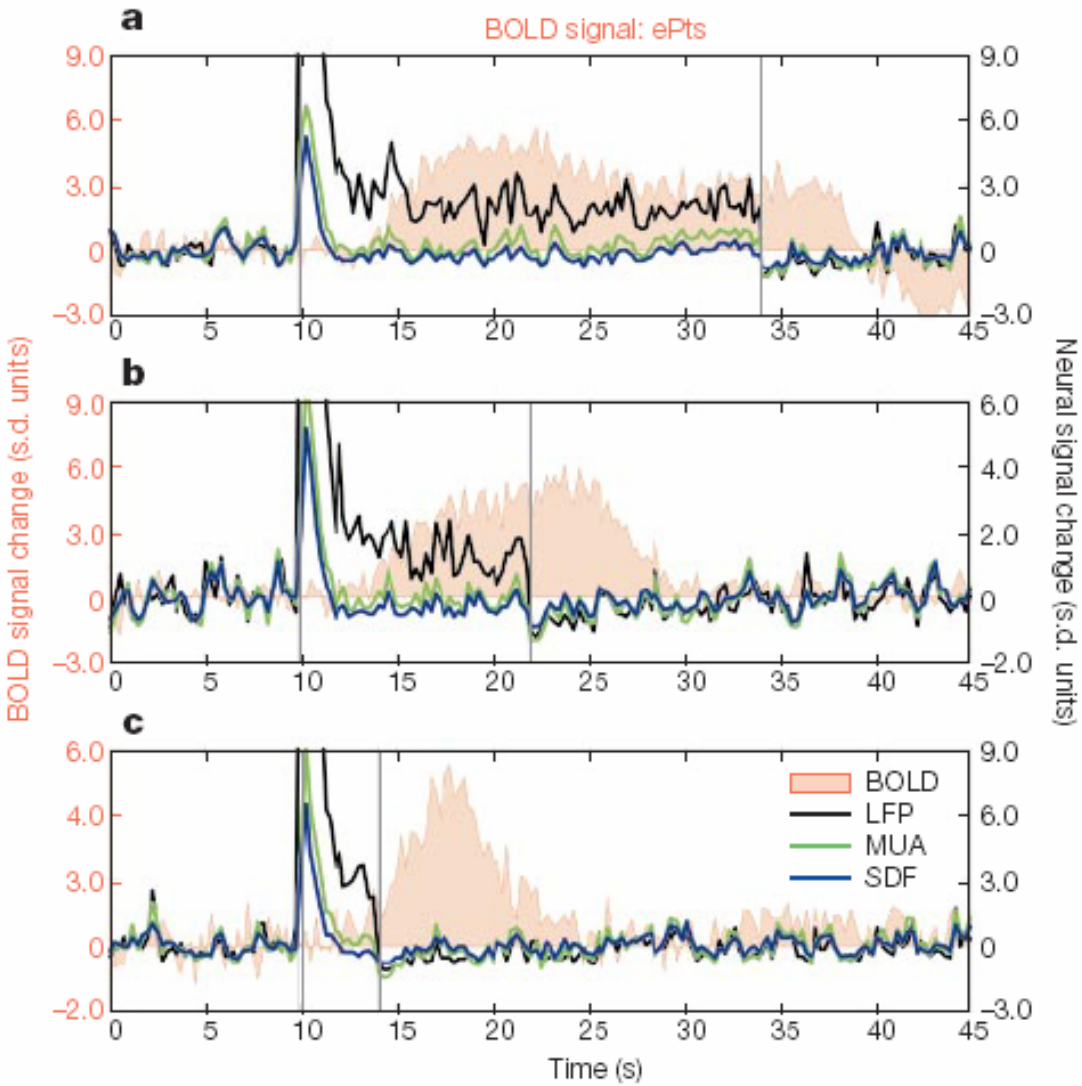

Figure 3 Simultaneous neural and haemodynamic recordings from a cortical site showing transient neural response. **a**–**c**, Responses to a pulse stimulus of 24, 12 and 4 s. Both single- and multi-unit responses adapt a couple of seconds after stimulus onset, with LFP remaining the only signal correlated with the BOLD response. SDF, spike-density function (see text); ePts, electrode ROI—positive time series.

Neurons with transient response

Fig 3. Key points

- 25% of MUA show a transient response returning to baseline after 2-4s.
- Conversely, LFP was always elevated for the duration of the stimulus.
- Suggests that BOLD may reflect more the neural activity related to the input and local processing in any given area, rather than the spiking activity commonly thought of as the output of an area.

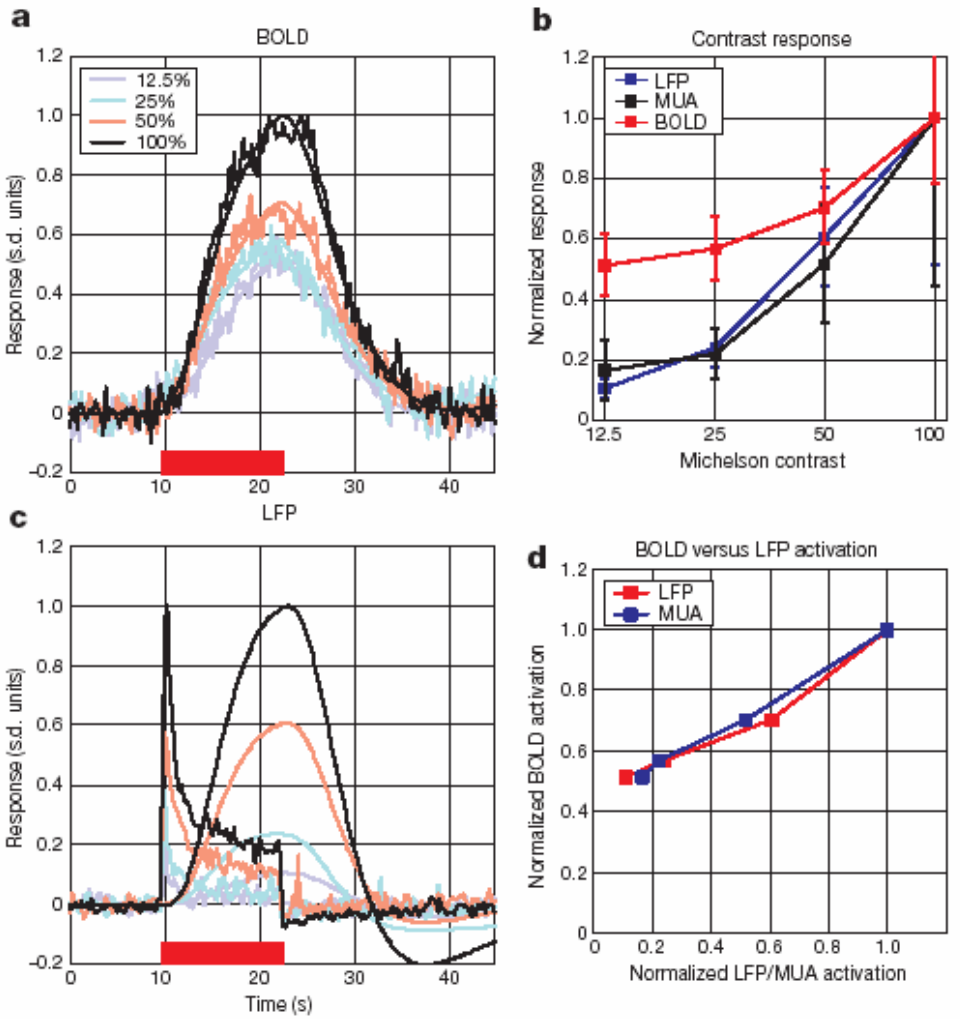

Figure 5 fMRI responses to pulse stimuli at four different contrasts (12.5, 25, 50 and 100%). **a**, Mean fMRI response superimposed with a model estimated with nonlinear curve fit. The scale parameter of the model was taken as the response amplitude. **b**, Normalized response amplitude of LFP and MUA against contrast. Data from five sessions with a pulse duration of 12.5 s. **c**, LFP responses for four different contrasts. Smooth lines are the result of convolution of the neural responses with the impulse response estimated by correlation analysis. **d**, Normalized BOLD response as a function of LFP and MUA. Responses were normalized by dividing each response by the maximum response.

fMRI response to 4 different visual pattern contrasts

Fig 5. Key points

- BOLD, LFP, and MUA all increase with stimulus contrast, but not linearly.
- BOLD response has a threshold type of nonlinearity.

Summary

- BOLD unequivocally reflects an increase in neural activity.
- Increase in LFPs during stimulation is significantly stronger than that of MUA.
- 25% of MUAs show transient activity and return to baseline, while LFP are sustained throughout the stimulus duration.
- LFP response gives a better estimate of BOLD response than the MUA (modeling data).
- SNR of neural signal was at least 10X higher than BOLD SNR, suggesting the fMRI analyses probably underestimate actual neural activity.
- There is a linear relationship between the neural activity and BOLD response.
- BOLD seems to reflect incoming input and local processing in an area rather than spiking activity.
- Consequentially, fMRI may reveal activation in areas where there is no single-unit activity.