

Martin Lindquist

Department of Biostatistics  
Johns Hopkins  
Bloomberg School of Public Health

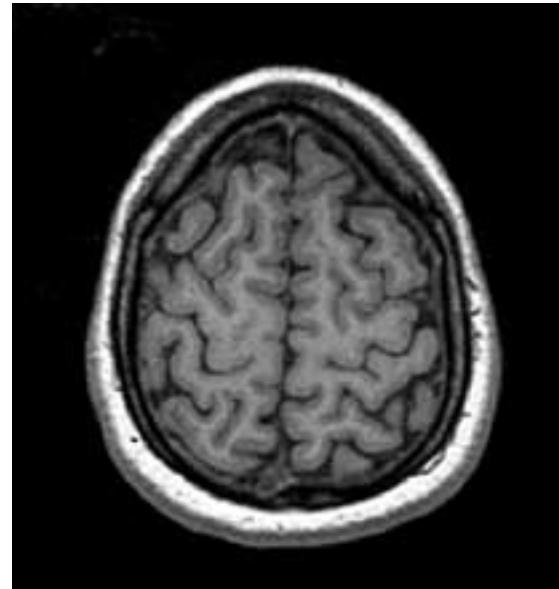
Tor Wager

Department of Psychology and  
Neuroscience and the  
Institute for Cognitive Science  
University of Colorado, Boulder

Signal, noise, and BOLD physiology

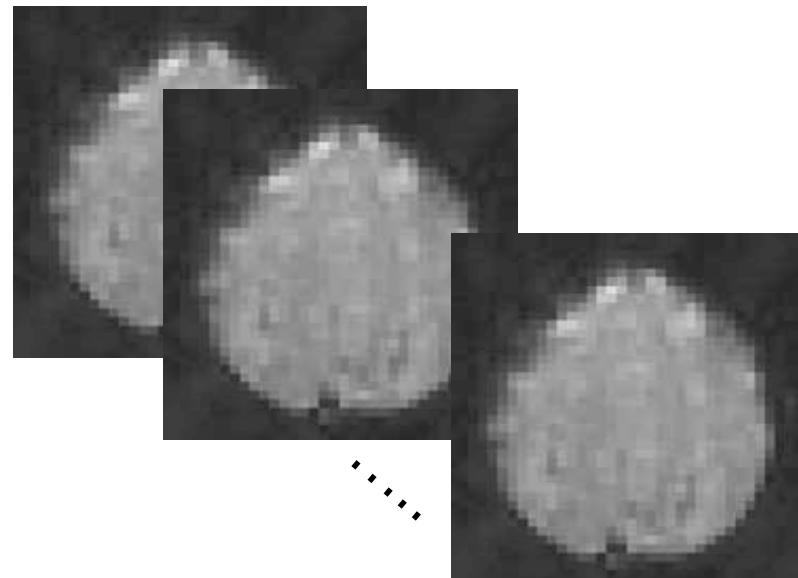
# MRI

- MRI studies brain anatomy.
  - Structural (T1) images
  - High spatial resolution
  - Can distinguish different types of tissue



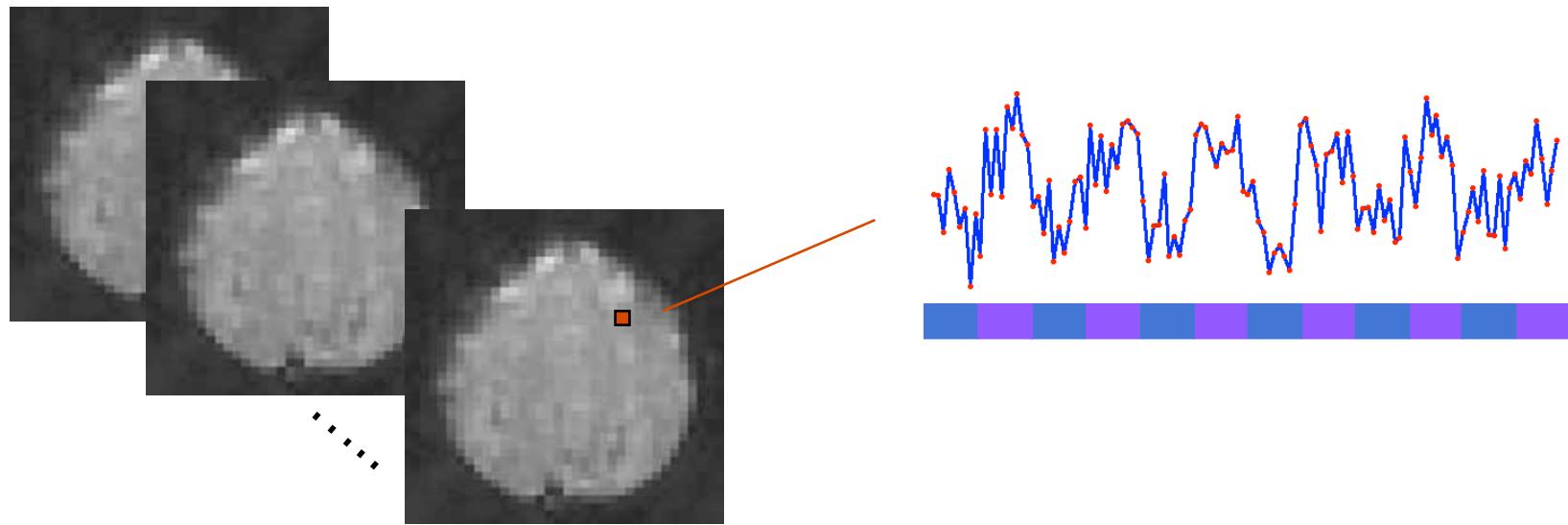
# fMRI

- fMRI studies brain function.
  - Functional ( $T2^*$ ) images
  - Lower spatial resolution/ Higher temporal resolution
  - Relate changes in signal to experimental manipulation



# Functional MRI

- An fMRI experiment consists of a sequence of individual MR images, where one can study oxygenation changes in the brain across time.



# BOLD fMRI

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- The most common approach towards fMRI uses the **Blood Oxygenation Level Dependent** (BOLD) contrast.
- It allows us to measure the ratio of oxygenated to deoxygenated hemoglobin in the blood.
- It doesn't measure neuronal activity directly, instead it measures the metabolic demands (**oxygen consumption**) of active neurons.



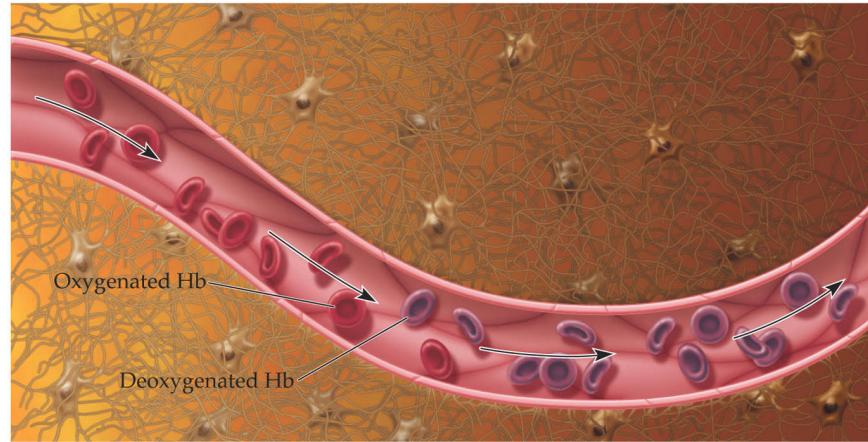
# BOLD Contrast

- Hemoglobin exists in two different states each with different magnetic properties producing different local magnetic fields. (Pauling 1936)
  - Oxyhemoglobin is **diamagnetic**.
  - Deoxyhemoglobin is **paramagnetic**.
- BOLD fMRI takes advantage of the difference in T2\* between oxygenated and deoxygenated hemoglobin.
  - Deoxyhemoglobin suppresses the MR signal.
  - As the concentration of deoxyhemoglobin **decreases** the fMRI signal **increases**.

# BOLD Physiology

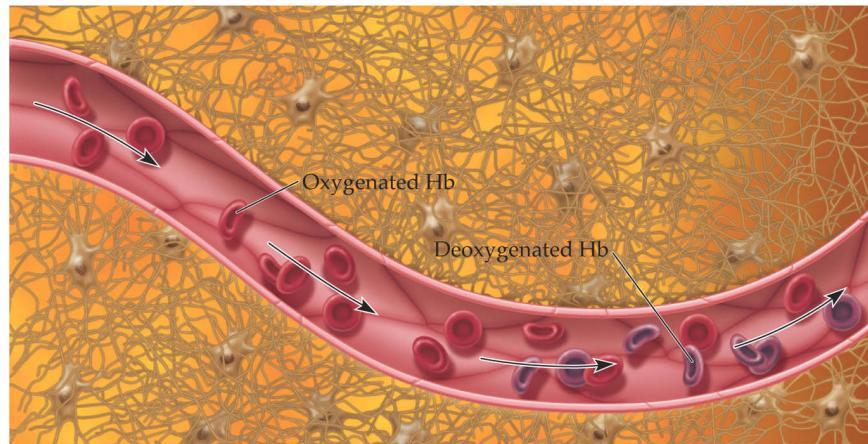
## Rest

- Normal flow (rCBF)
- Normal  $T_2^*$ -weighted signal



## Active

- Increased flow (rCBF)
- Decreased Deoxy-Hb
- Increased CBV
- Increased  $T_2^*$ -weighted signal



Huettel et al. 2009

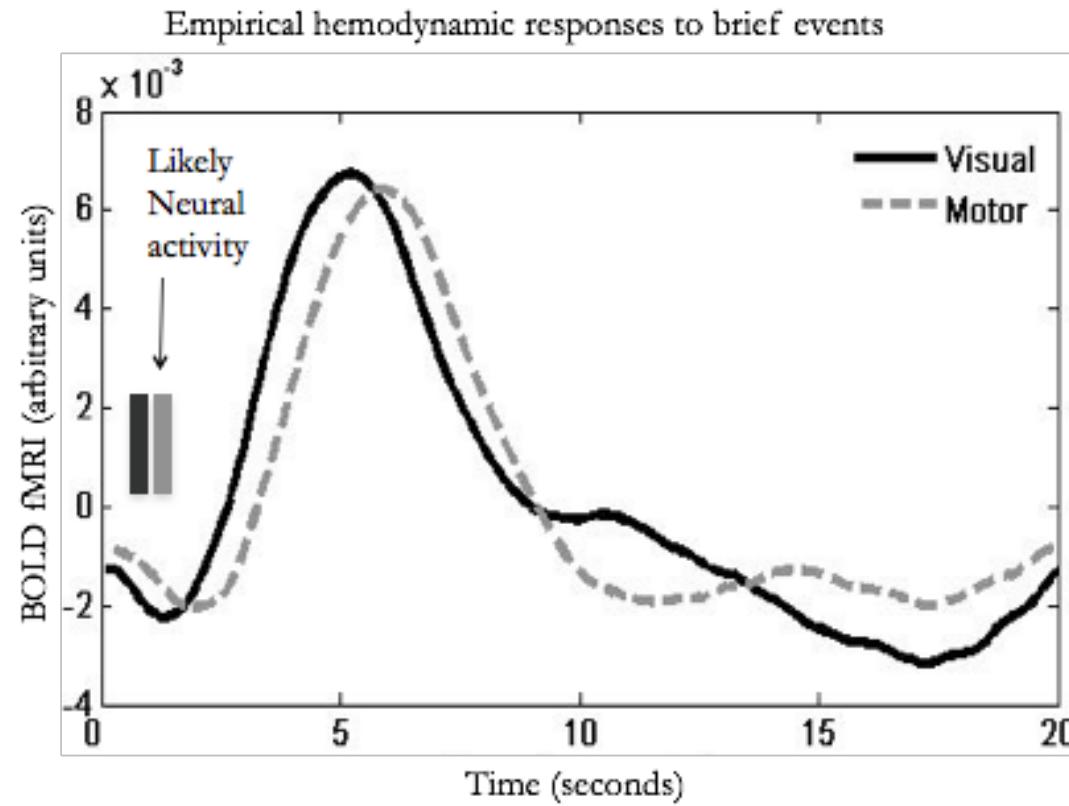
# BOLD Signal

- The change in the MR signal triggered by instantaneous neuronal activity is known as the **hemodynamic response function**.
- As neural activity increases, so does metabolic demand for oxygen and nutrients.
- As oxygen is extracted from the blood, the hemoglobin becomes paramagnetic which creates distortions in the magnet field that cause a T2\* decrease (i.e. a faster decay of the signal).

# BOLD Signal

- Initial increases in deoxyhemoglobin can lead to a decrease in BOLD signal (“initial dip”).
- An over-compensation in blood flow dilutes the concentration of deoxyhemoglobin and tips the balance towards oxyhemoglobin.
  - This leads to a peak in BOLD signal about 4-6 s following activation.
- After reaching its peak, the BOLD signal decreases to an amplitude below baseline level.
  - This poststimulus undershoot is due to a combination of reduced blood flow and increased blood volume.

# HRF



Lindquist et al., 2008

The strongest signal appears 5-6 seconds after activation.

# HRF Properties

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- Magnitude of signal changes is quite small
  - 0.1 to 5%
  - Hard to see in individual images
- Response is delayed and quite slow
  - Extracting temporal information is tricky, but possible
  - Even short events have a rather long response
- Exact shape of the response has been shown to vary across subjects and regions.



# How well does BOLD signal reflect increases in neuronal activity?

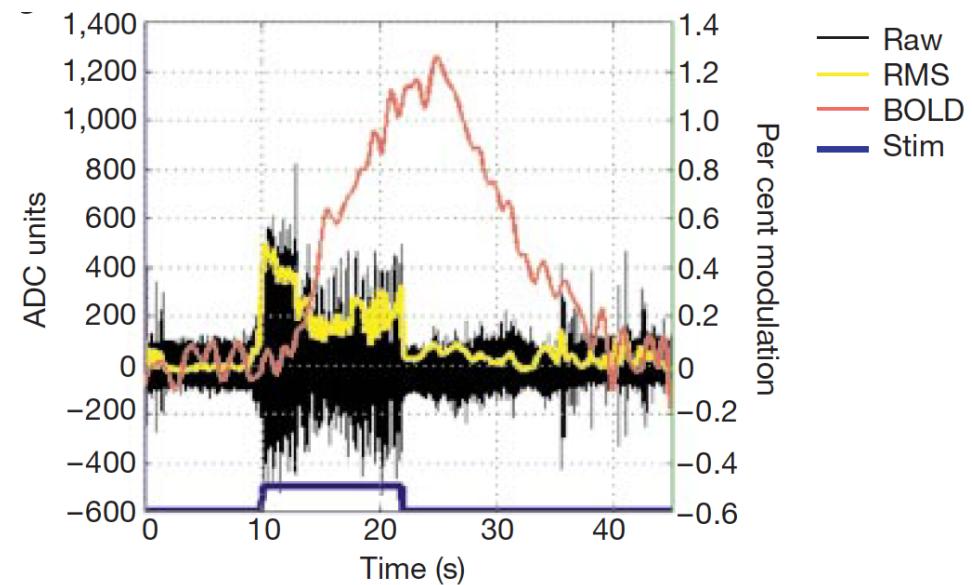
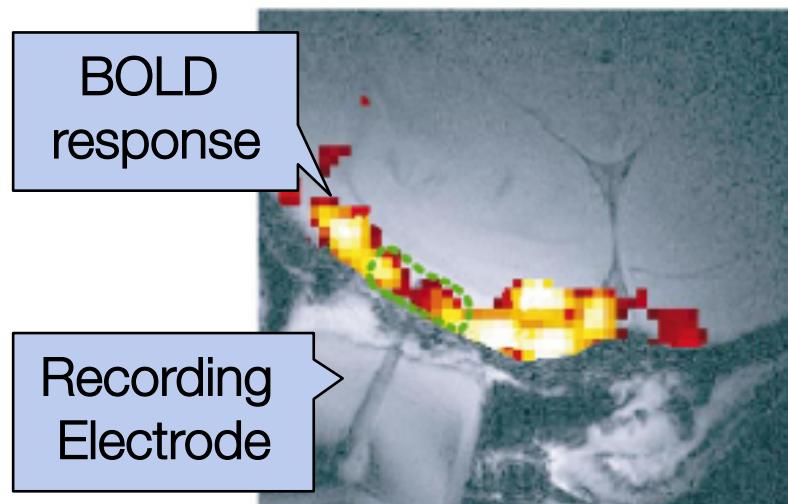
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- The BOLD signal often corresponds relatively closely to the local field potential, the electrical field potential surrounding a group of cells.
- Reflects integrated post-synaptic activity, under many conditions.
- Localization of BOLD signal to areas of increased neural activity improves with field strength: Reduced point-spread function and large-vessel contribution
- Does not always reflect changes in neuronal activity
  - Anticipatory vasodilation (Sirotin & Das 2009)
  - Vascular interactions: ‘blood steal’ (Shmuel et al., Nature 2006)



See also: Fried et al. 2005 Ann Rev Psych; Logothetis et al, 2001; Mukamel et al. 2005; Chaimow et al. 2011

# Example: Correspondence between BOLD and neuronal activity



BOLD response [usually] reflects pooled local field potential activity



Logothetis et al, 2001, Fig. 1

# Basic Quality Control: Assessing SNR

- Signal-to-noise ratio (SNR)
  - The strength of a signal divided by its variability.
  - A basic measure of effect size
- Contamination
  - Tissue segmentation
  - Correcting for motion
  - Interpolating missing data
- Temporal quality control
  - Measures the consistency of the signal in the data across time points.
  - Calculated at each voxel in an image -> SNR maps

# Basic Quality Control: Assessing SNR

## Basic definitions

- Signal-to-noise ratio (SNR)
  - The strength of a signal divided by an estimate of noise variability
  - A basic measure of effect size
- Contrast-to-noise (CNR)
  - The difference between two signals divided by an estimate of noise variability (for more definitions see Welvaert & Rosseel 2013)

Spatial: Calculated across one image

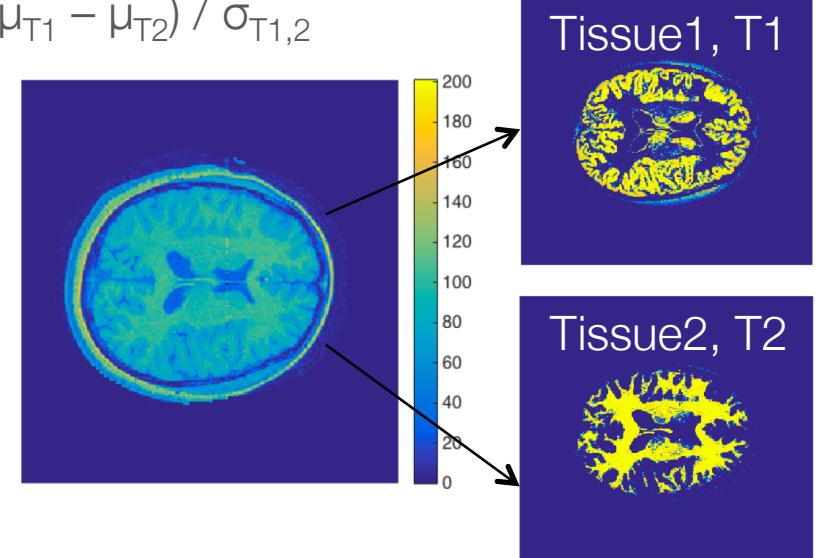
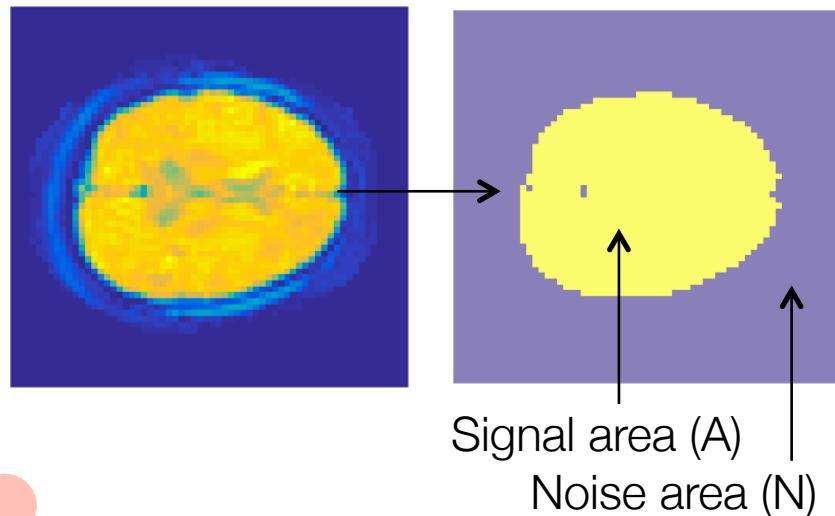
Temporal: Calculated at each voxel across time



# Basic Quality Control: Assessing SNR

## Single-image measures

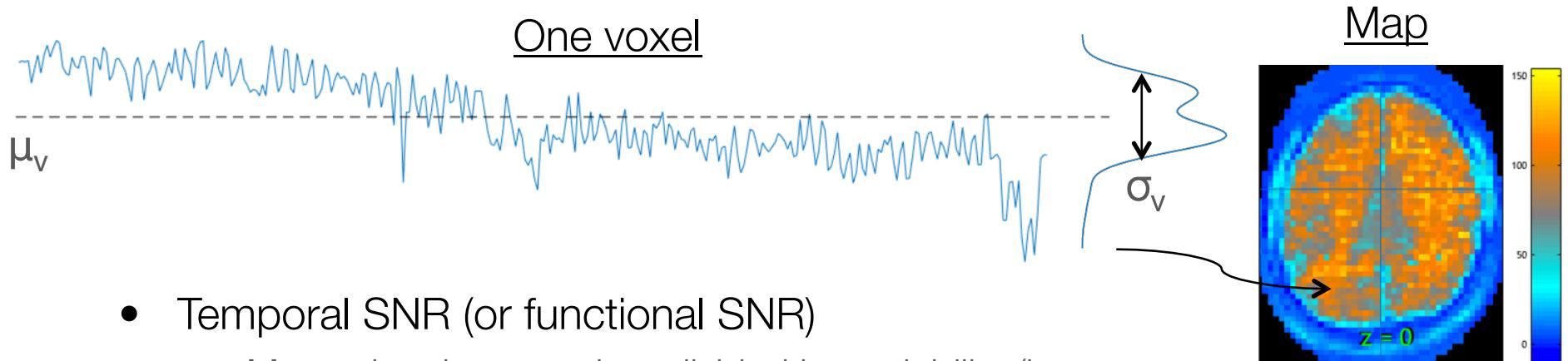
- Calculated on a single image, one statistic value per image
- Spatial SNR:
  - Mean intensity within signal area of interest ( $\mu_A$ ) divided by standard deviation outside signal area ( $\sigma_N$ )
- Spatial contrast-to-noise ratio (CNR)
  - The difference in intensity between two tissue types divided by the variability in their measurements:  $(\mu_{T1} - \mu_{T2}) / \sigma_{T1,2}$



# Basic Quality Control: Assessing SNR

## Time series measures

- Calculated at each voxel across a time series



- Temporal SNR (or functional SNR)
  - Mean signal across time divided by variability (i.e., standard deviation) across time,  $\mu_v / \sigma_v$
  - With temporally detrended data, also called Signal-to-Fluctuation-Noise Ratio (SFNR); Friedman & Glover 2006
- Temporal CNR (or signal sensitivity)
  - Difference in intensity for “on” vs. “off” states divided by variability
  - Related to sensitivity to task (e.g., BOLD sensitivity)

# Scaling: Issues with quantifying BOLD responses

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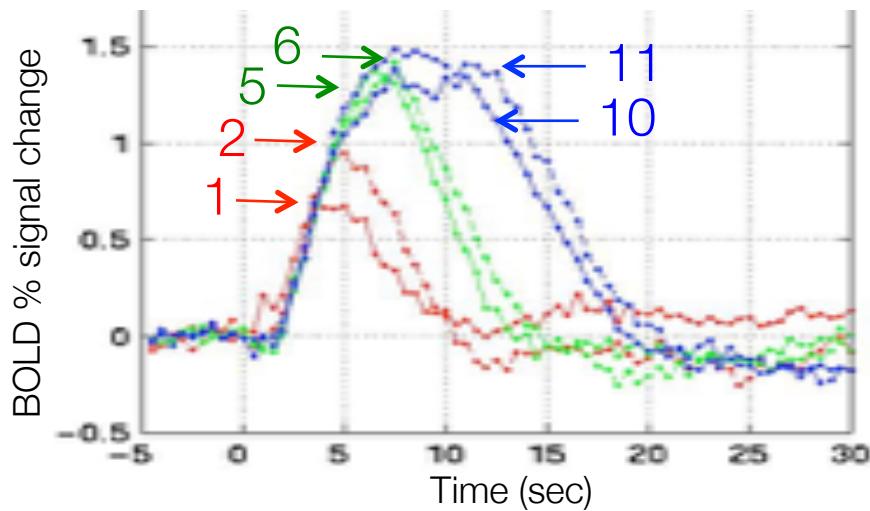
- The absolute scaling of BOLD responses is arbitrary
- Depends on acquisition variables:
  - field strength
  - Pulse sequence and gain o amplifiers
  - Acquisition parameters: TR, TE, voxel size, and flip angle
  - Tissue type: Local concentration of water
- Also depends on analysis variables (more on this later)
- Implications
  - Most values reported in arbitrary units (A.U.s) or % signal change
  - Not a problem when comparing conditions (e.g., tasks) and participants acquired with the same scanner and parameters

# Non-linearity

- Studies have shown that the BOLD response is roughly linear, with some departures from linearity.
- There is some evidence of **refractory effects**, or **saturation**, which are reductions in amplitude of a response as a function of inter-stimulus intervals.
- There is evidence of non-linearity if the stimulus are spaced closer than 5-6 s apart (e.g., Meizin et al. 2000; Wager et al. 2005).
- Difficult to account for in analysis, can produce confounds. Best to minimize with appropriate experimental design (more on this later).

# Example: Nonlinearity

- Series of 1, 2, 5, 6, 10 or 11 visual “flashing checkerboard” events (125 msec duration).
- Without nonlinearity, response to **two** events would be about twice as high as **one** event.
- Response to **five** events would be about 3 times as high, (less than 5 due to shifting in time)
- Actual responses are close to  $\frac{1}{2}$  the predicted amplitude. This is nonlinear ‘saturation.’



Wager et al. 2005

# End of Module



@fMRIstats