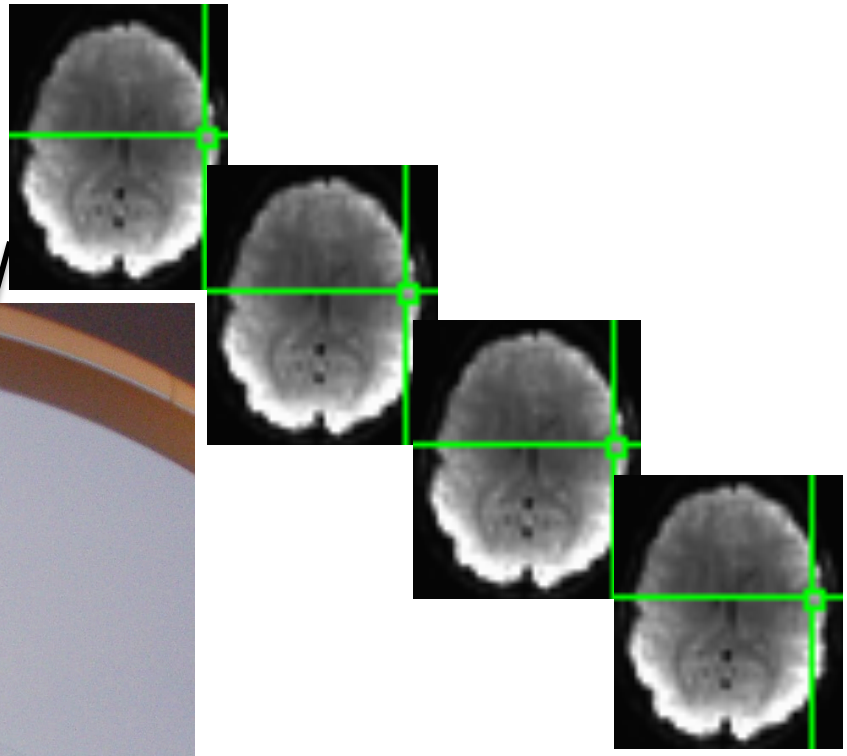
NIH fMRI Summer Course

How do we know what signal is neural and what is not?

Daniel Handwerker

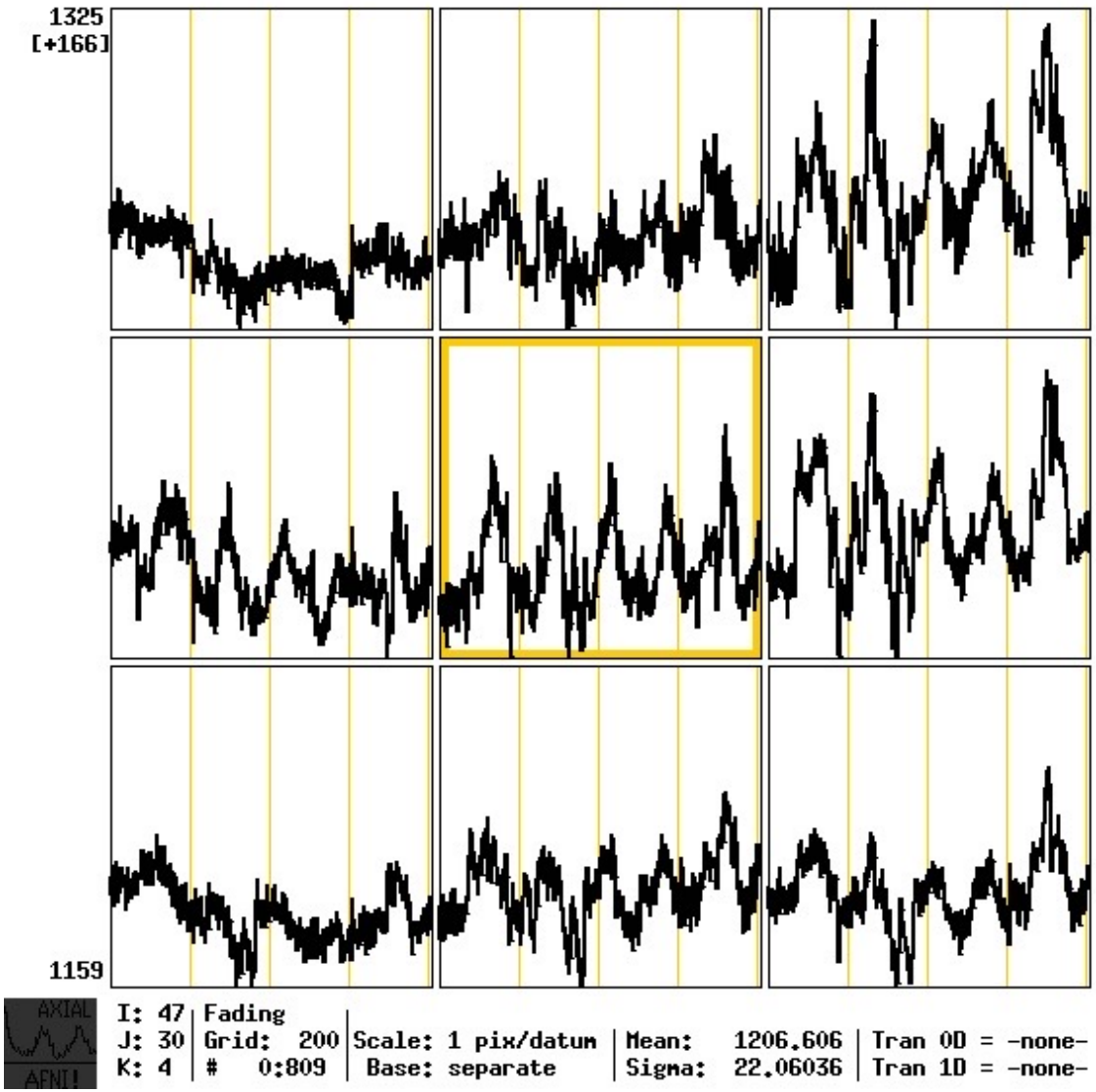
July 13, 2015

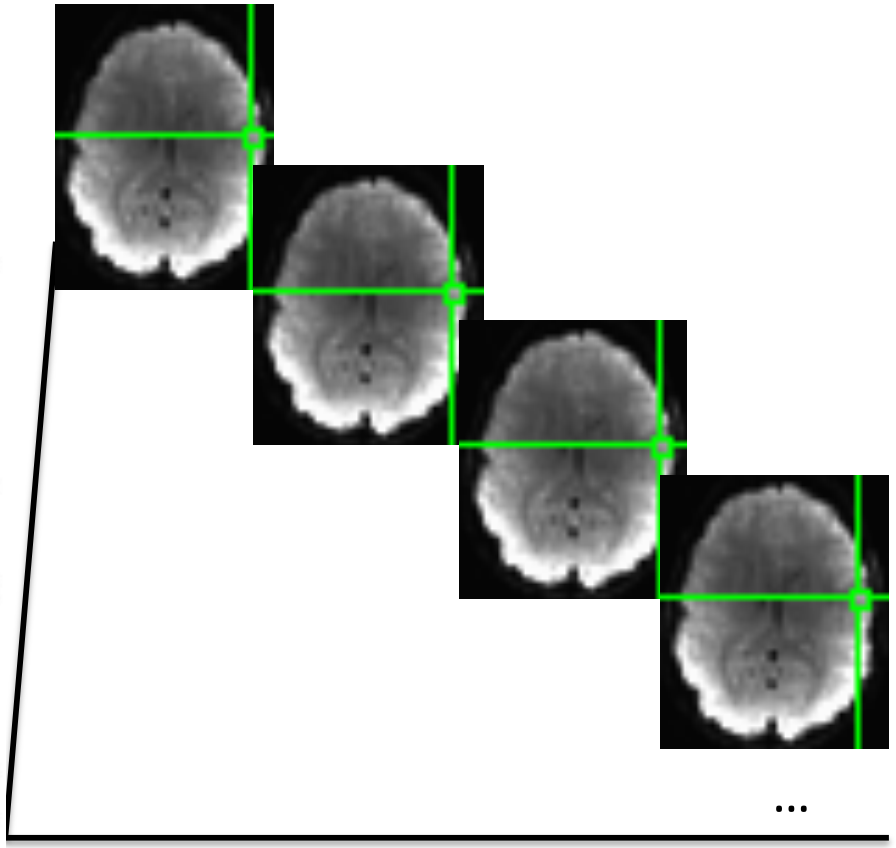

SIEMENS
MAGNETOM Skyra



...

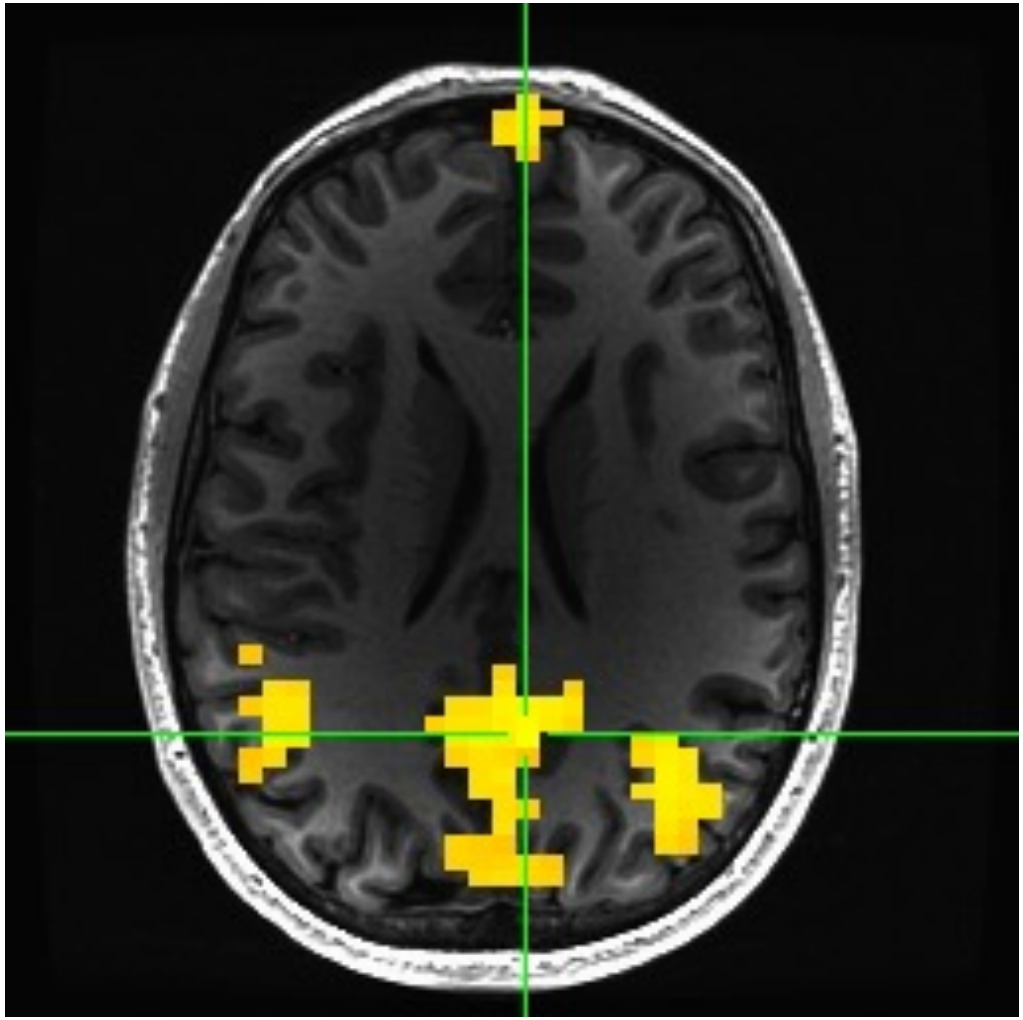
What makes us think this is neural?





5 cycles of a block design task

What makes us think this is neural?



Correlations to a seed voxel

Just because it's published doesn't mean it's neural

This is your brain on…love

Yes, it's possible to *see* that head-over-heels feeling. Anthropologist Helen Fisher, Ph.D., scanned the brains of 17 people who'd been in love for an average of seven months. As they stared at photos of their beloved, certain neural areas lit up on-screen. Says Fisher, "The brain in love reacts in a specific way. It's hard to control." Bottom line: You may think you're following your heart, but it's all in your head. —JO PIAZZA

When you're in love, blood flow increases to a region of the brain that's responsible for motivation. It's illuminated here.

love quickie Is commitmentphobia dead? 75% of single women *and* men are "serious

114

Glamour, March 2004

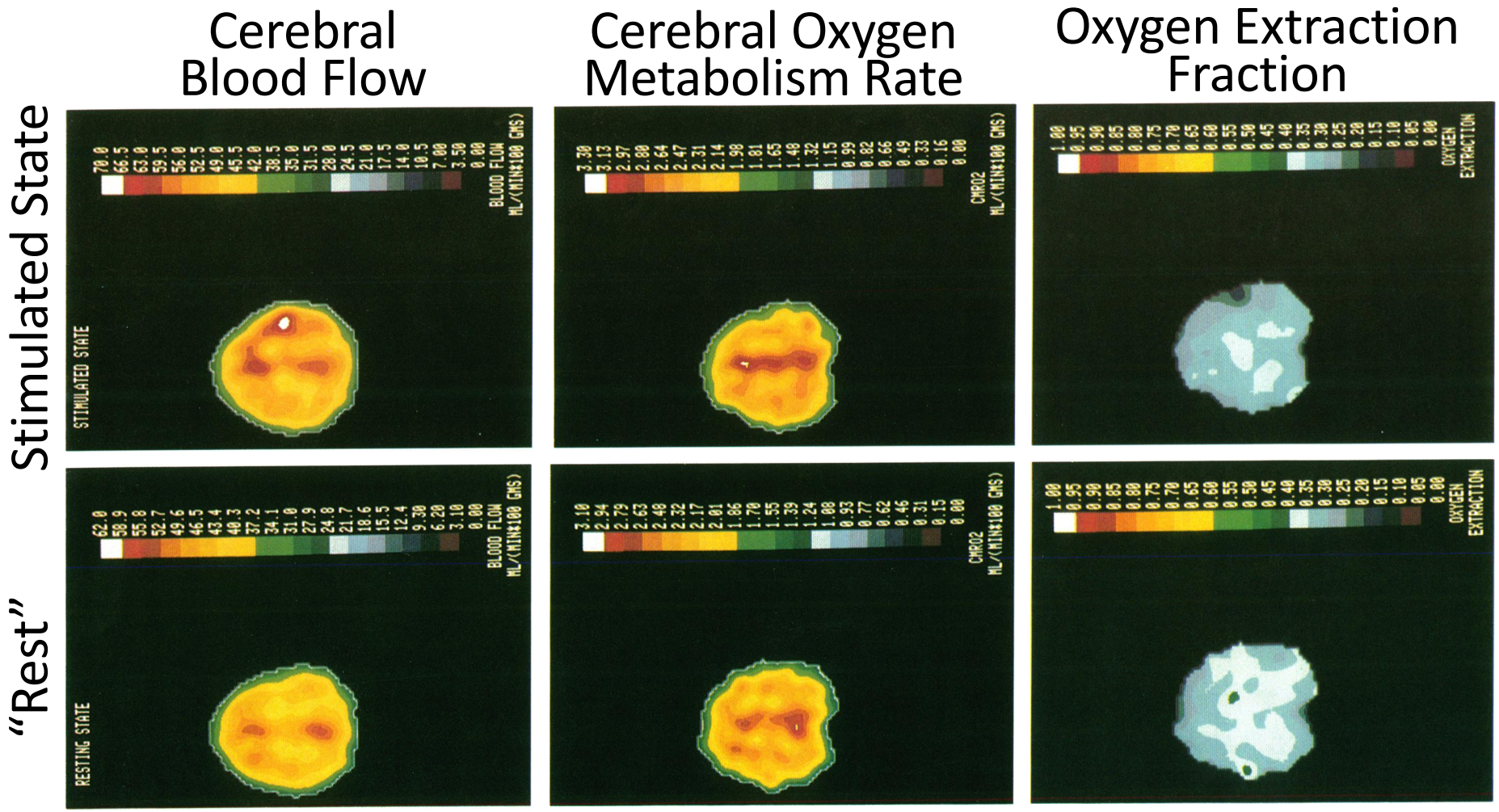
We don’t know any fMRI results are neural

… but, for a well designed and reported study, we can be *reasonably* confident

Objectives

- Why people believe that fMRI measures neural activity?
  - A plausible mechanism
  - Results that match our understanding of brain function
  - Complementary studies with other measures
- Why believe that a specific fMRI study represents neural activity?
  - Task based fMRI
  - Resting state fMRI

Plausibility: The mechanism behind fMRI



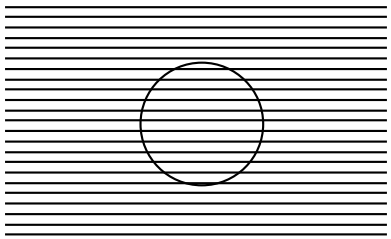
CBF goes up more than CMR_{O2}. This uncoupling produces a highly significant decrease in the local OEF (-19% of mean), indicating that tissue P_{O2} rose during stimulation.

Fox & Raichle, PNAS, Feb, 1986

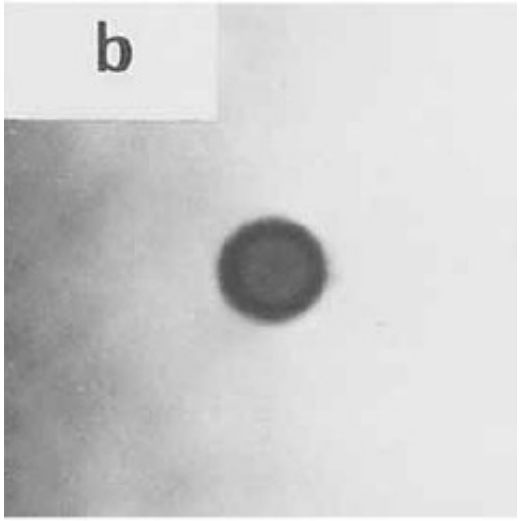
Deoxy Hb is an intrinsic MRI contrast agent

in vitro

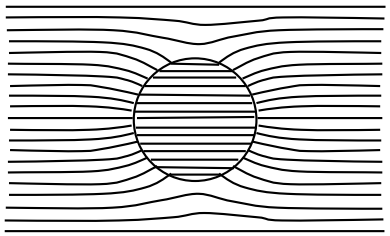
Oxygenated hemoglobin



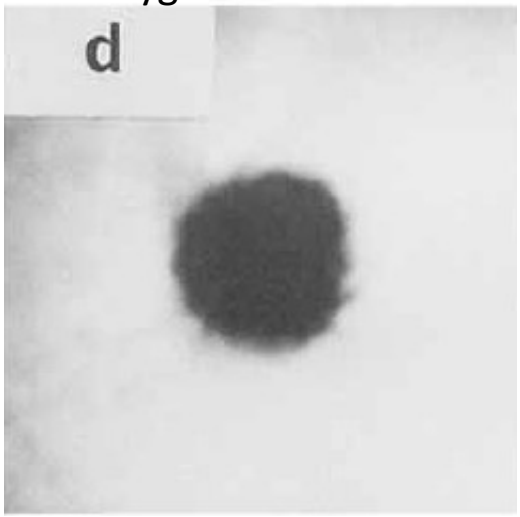
100% oxygenated blood



Deoxygenated hemoglobin

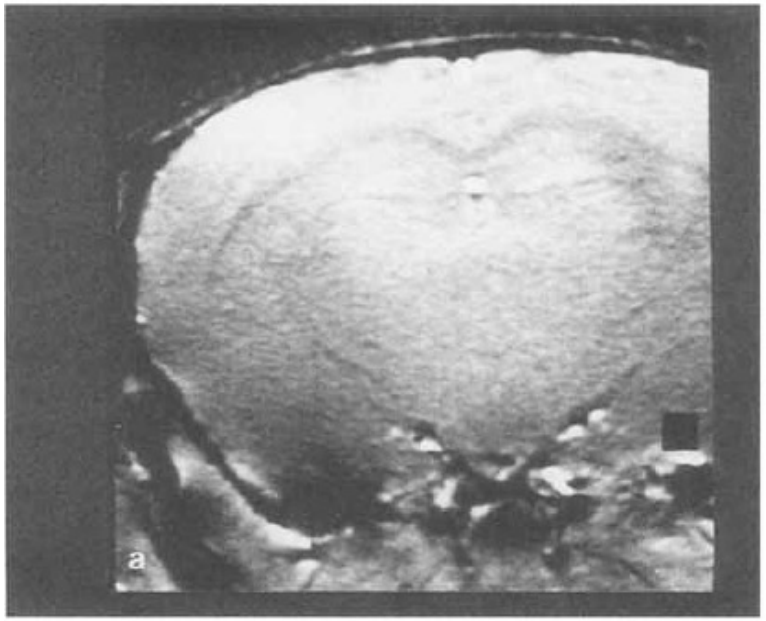


0% oxygenated blood

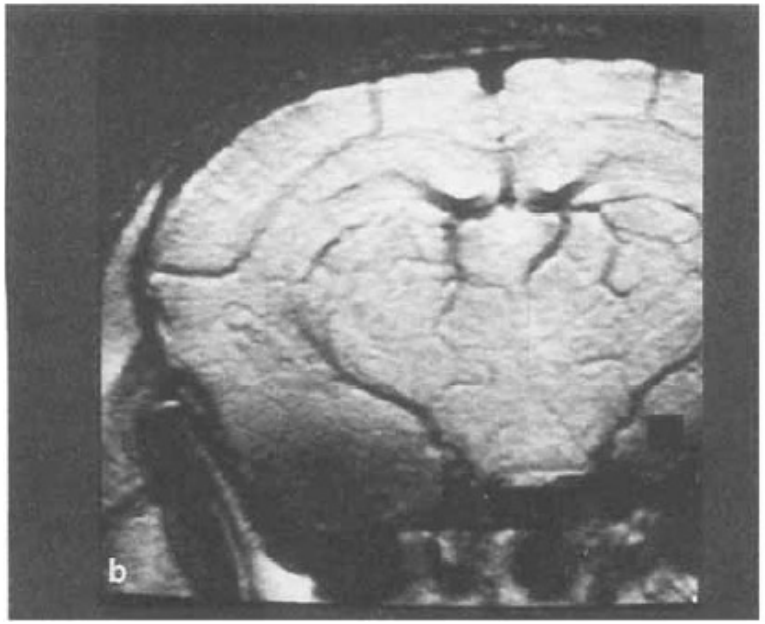


in vivo

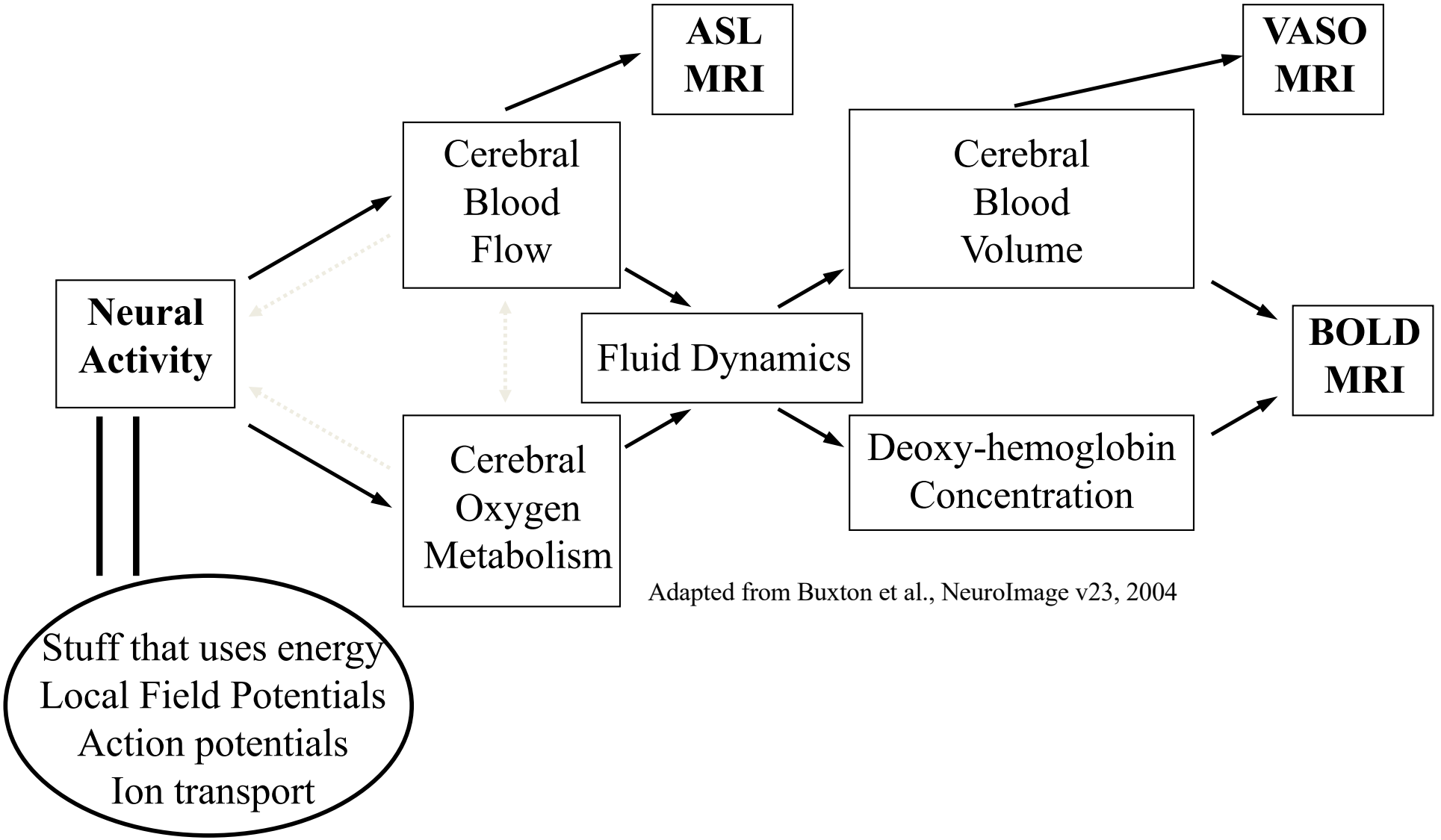
100% O_2



20% O_2

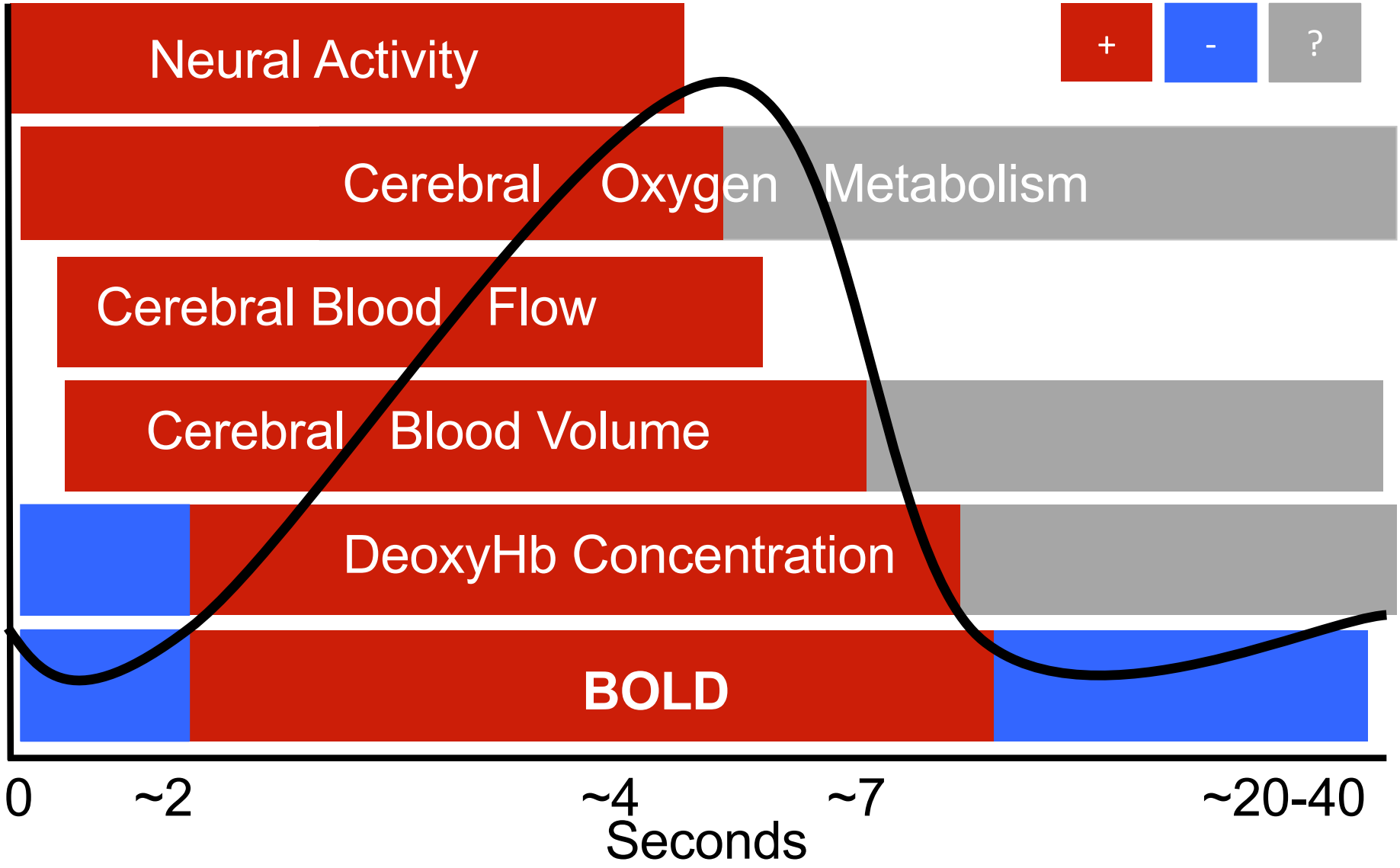


S. Ogawa, T.-M. Lee, A. S. Nayak, P. Glynn, Magn. Reson. Med, 14, 68-78 (1990)



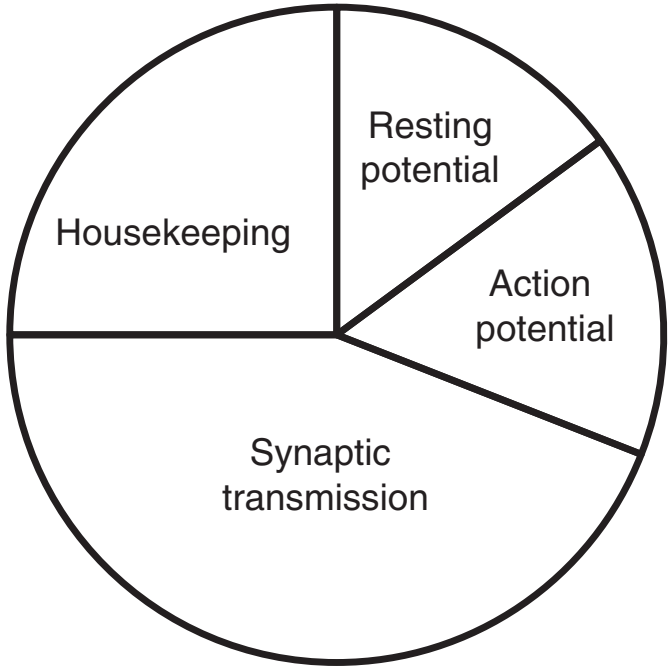
Less deoxyhemoglobin in a voxel (volume) results in a larger Blood Oxygen Level Dependent (BOLD) MRI measurement

The fMRI BOLD time course

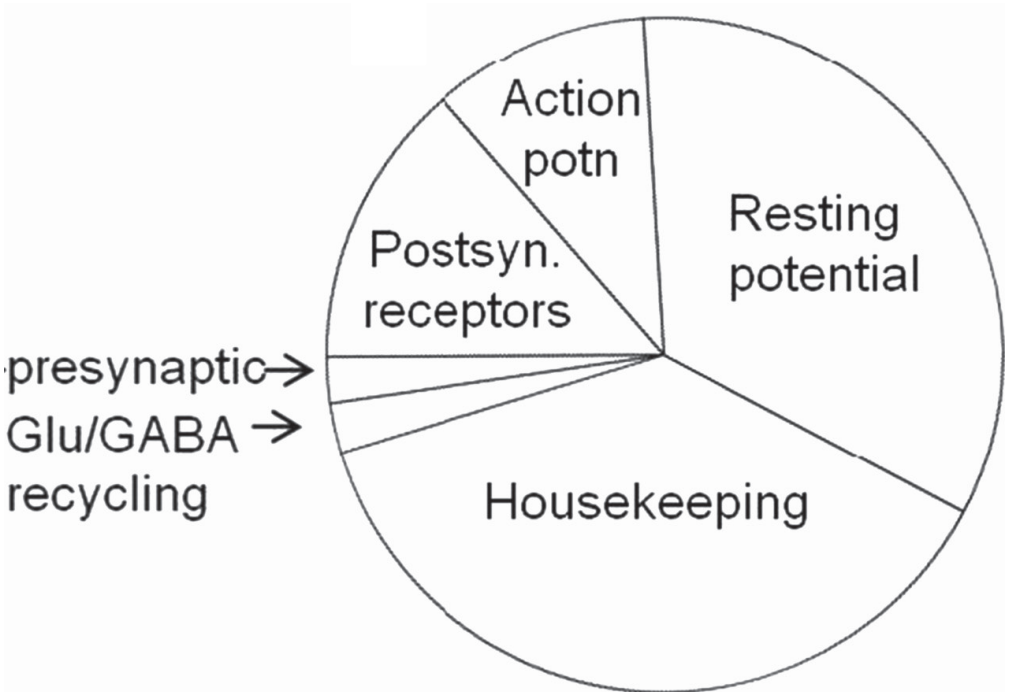


What types of neural activity uses energy?

Cerebral Cortex



Cerebellar Cortex

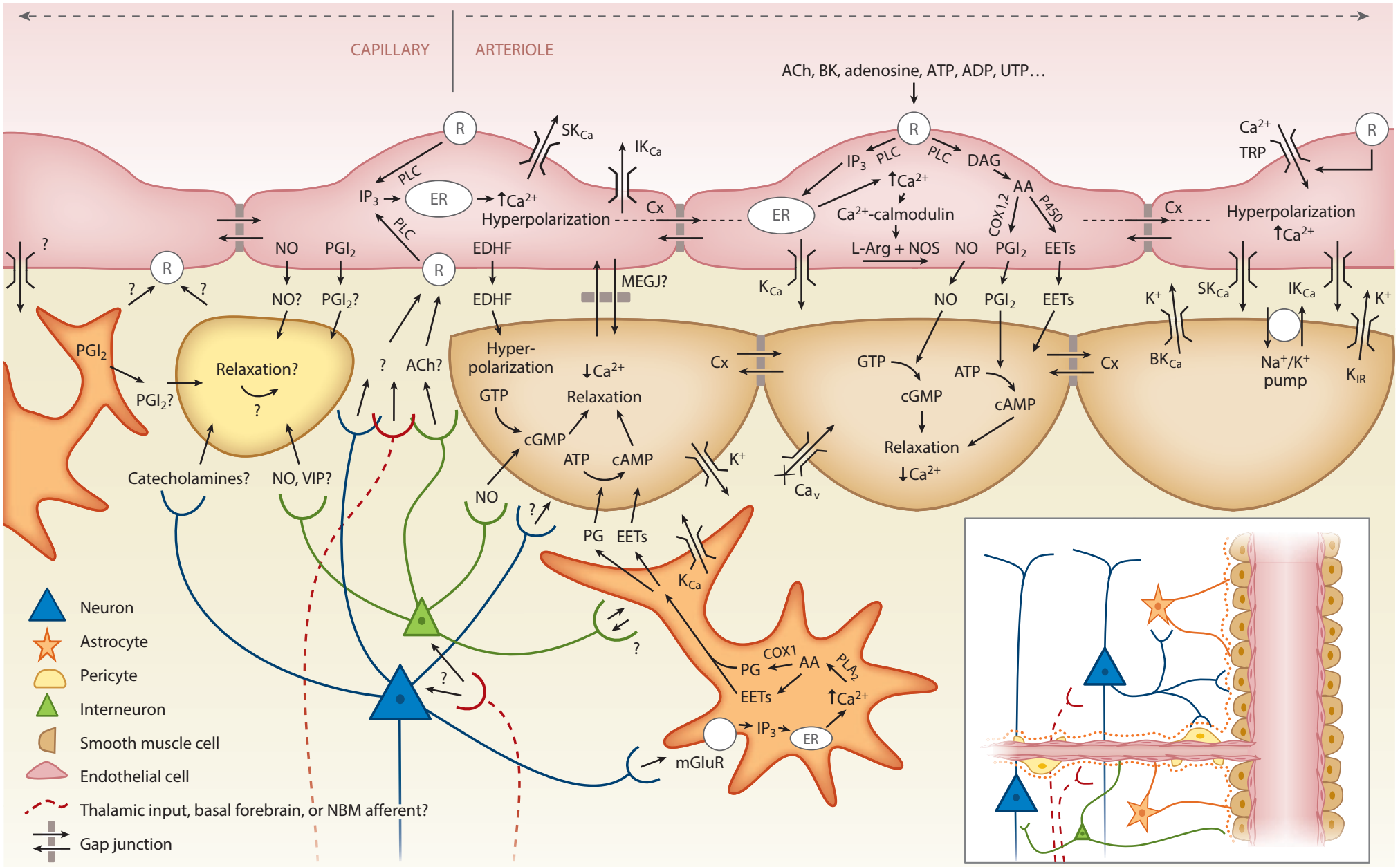


Howarth, Gleeson, & Attwell, JCBFM 2012

Housekeeping: non-signaling tasks, such as turnover of macromolecules, axoplasmic transport and mitochondrial proton leak

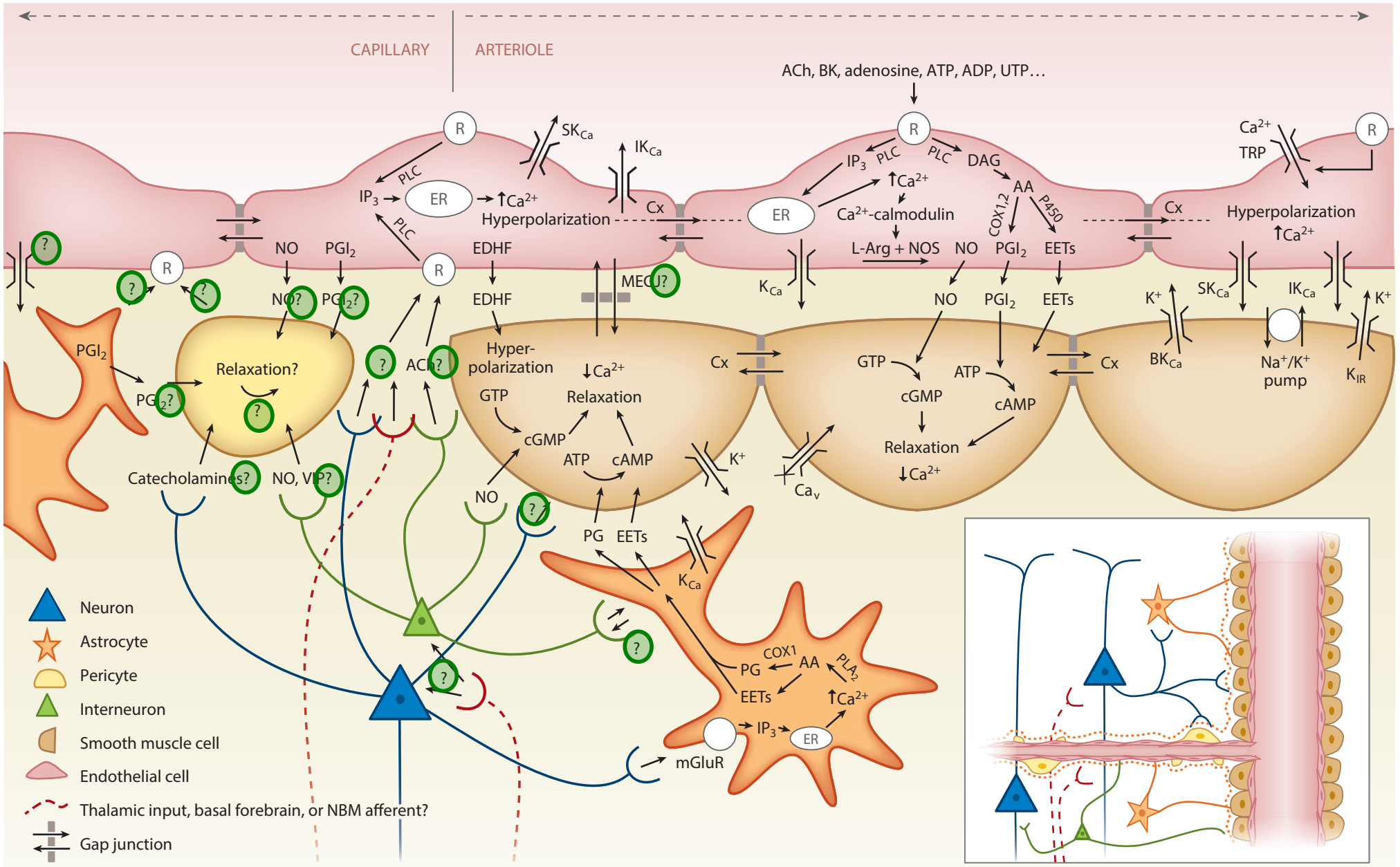
We know a lot about neurovascular coupling

It's not directly driven by oxygen or energy needs



Elizabeth Hillman, Annual Review of Neuroscience 2014. 37:161–81

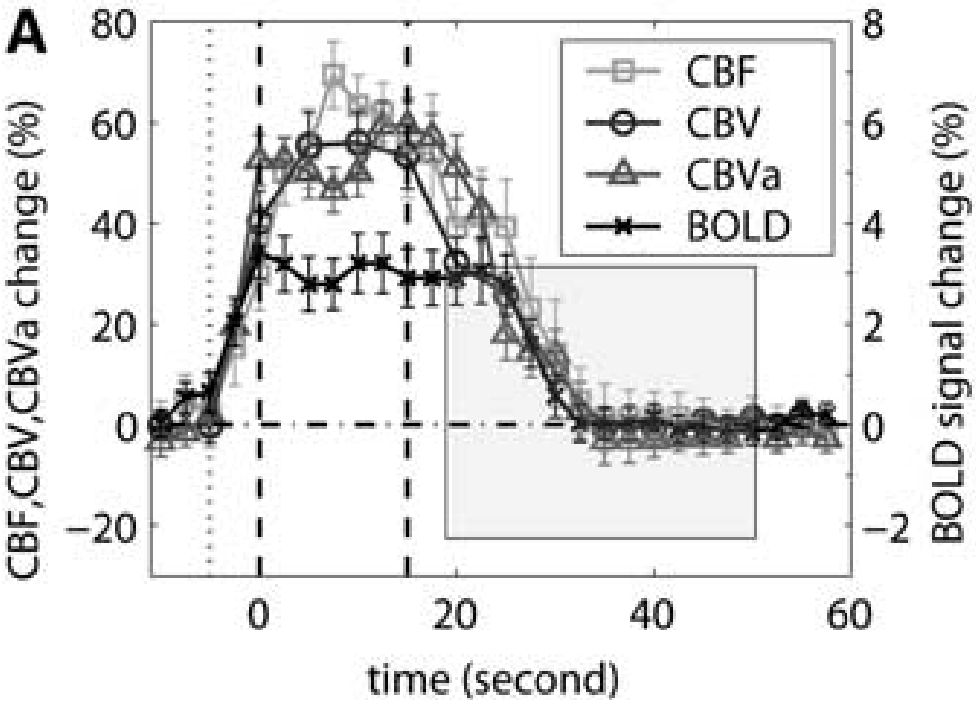
There's still a lot we don't know about neurovascular coupling



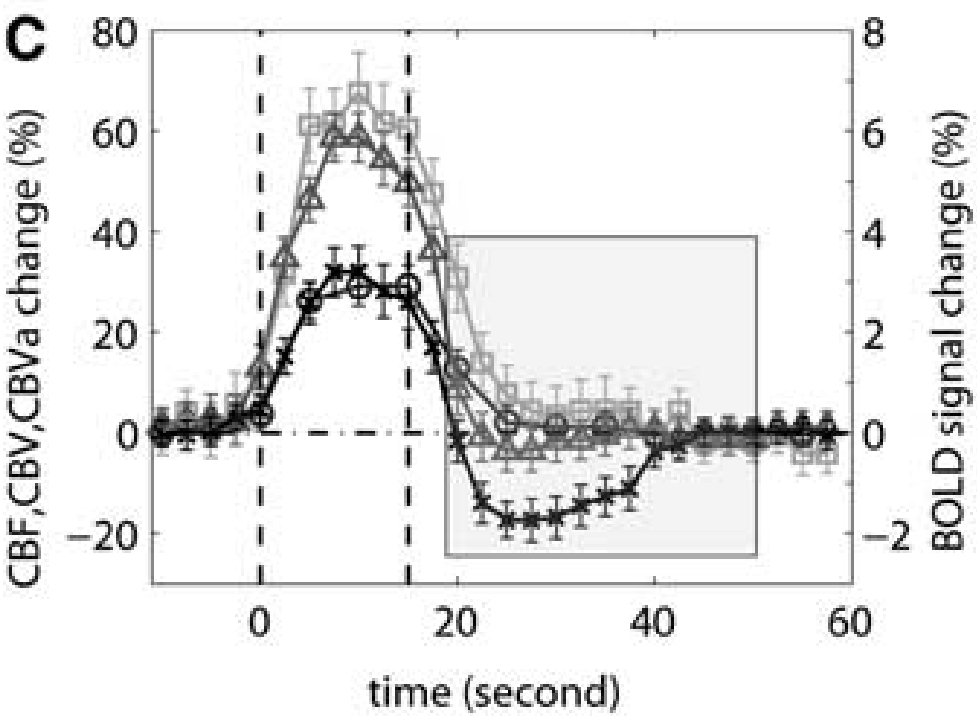
Elizabeth Hillman, Annual Review of Neuroscience 2014. 37:161–81

One example of neurovascular coupling complexity

Breath Hold



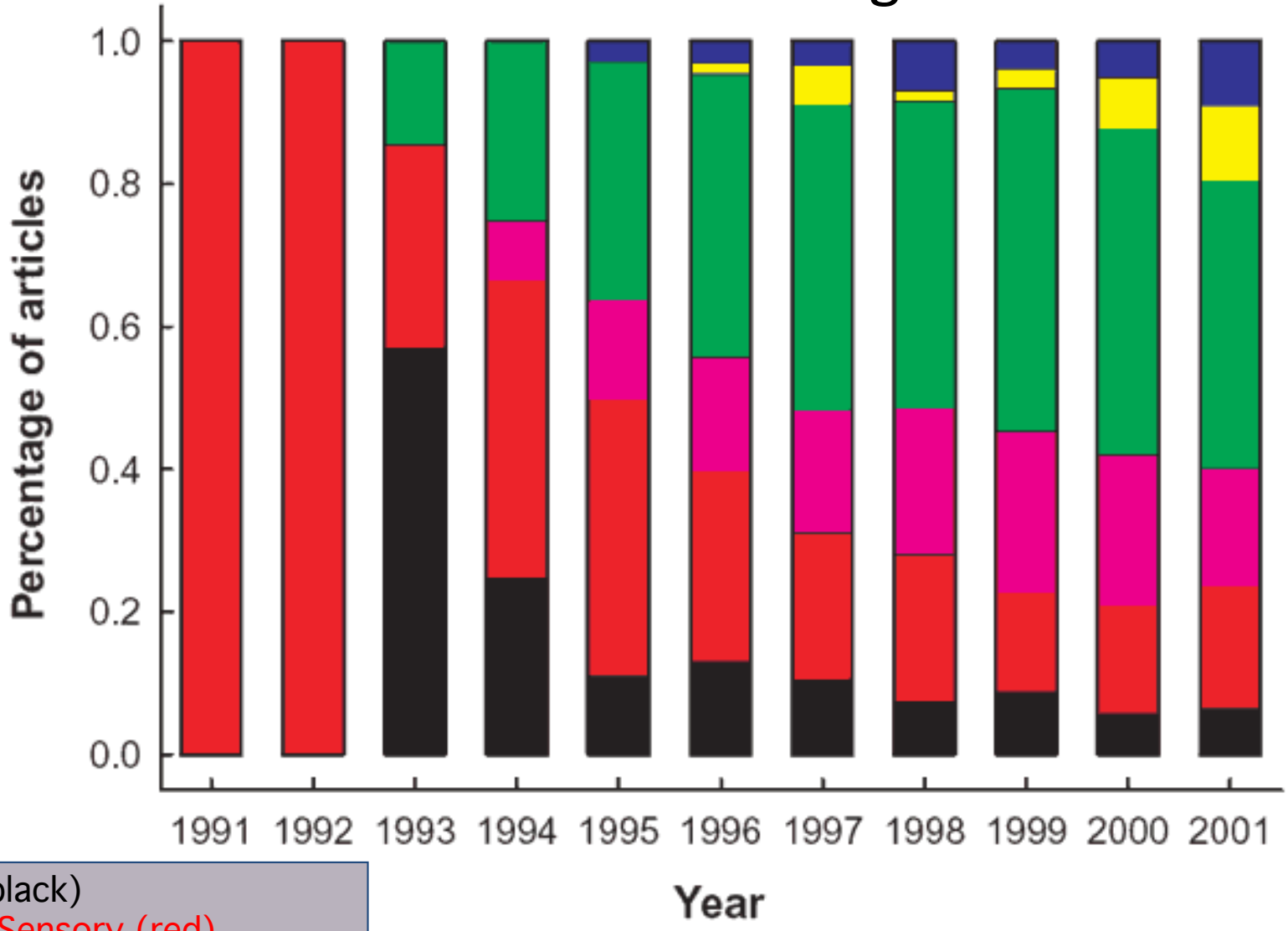
Visual Stimulation



Is the BOLD undershoot after stimulation from continued oxygen metabolism or vascular changes?

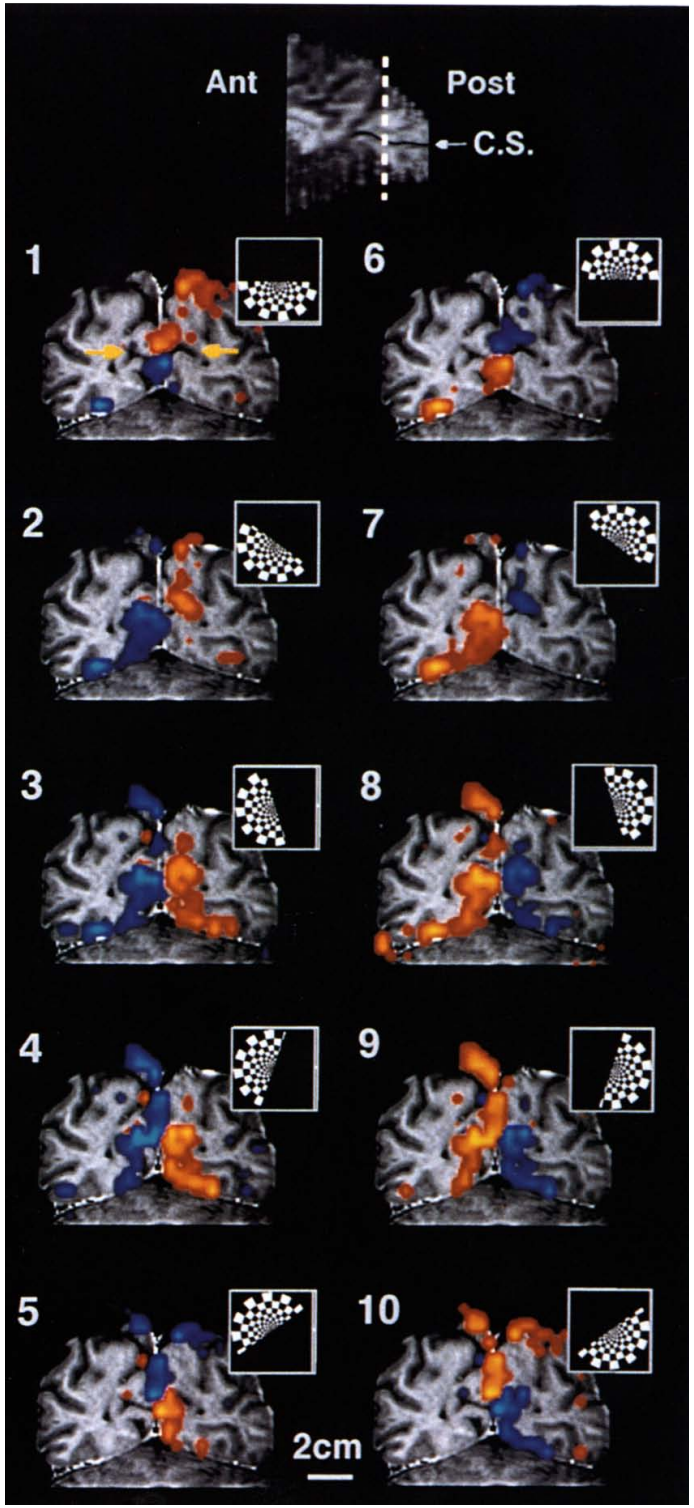
Hua et al “Physiological origin for the BOLD poststimulus undershoot in human brain: vascular compliance versus oxygen metabolism” JCBFM 2011

Why believe fMRI is neural?
fMRI results match our understanding of brain function



Motor (black)
Primary Sensory (red)
Integrative Sensory (violet)
Basic Cognition (green)
High-Order Cognition (yellow)
Emotion (blue)

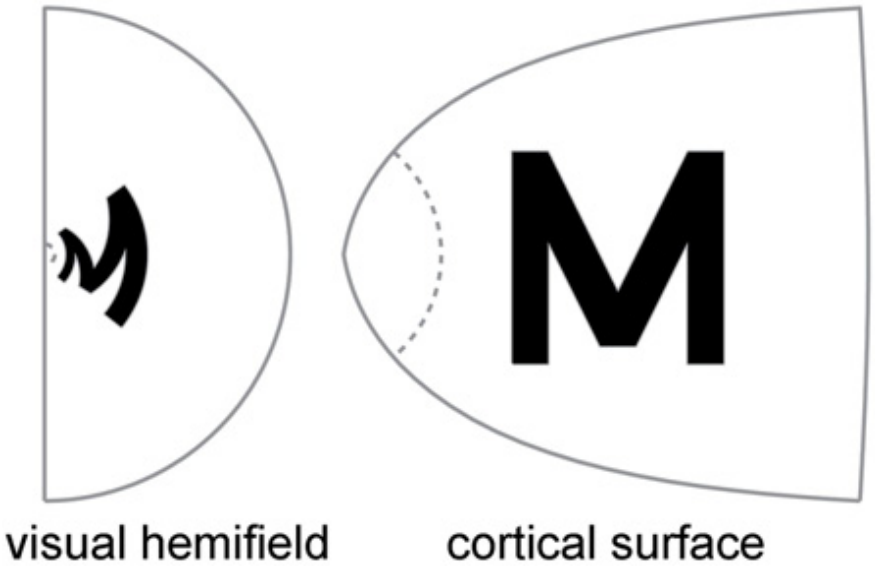
J. Illes, M. P. Kirschen, J. D. E. Gabrielli, Nature Neuroscience, 2003

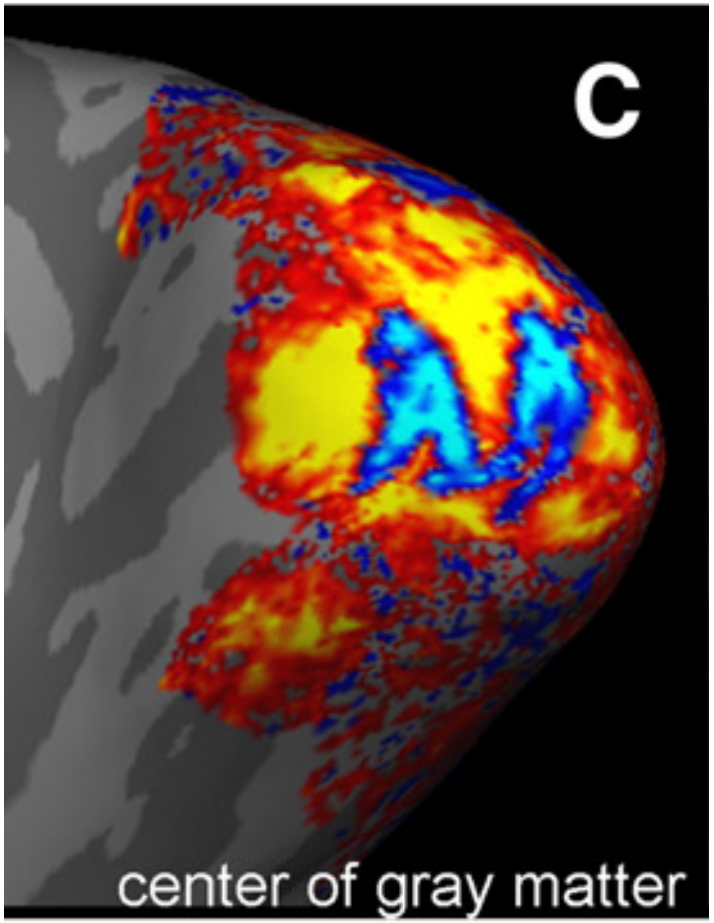


fMRI can show retinotopy in primary visual cortex

DeYoe, E.A., et al., 1994. Functional magnetic resonance imaging (FMRI) of the human brain. Journal of Neuroscience Methods 54, 171–187.

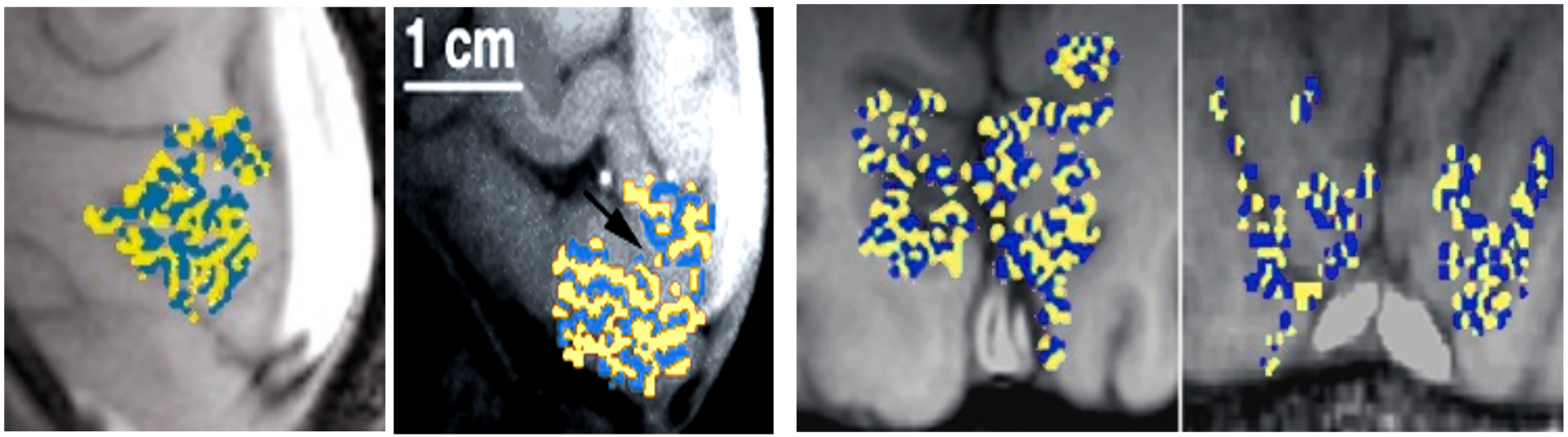
fMRI can have very predictable retinotopic mapping





Polimeni, et al 2010. Laminar analysis of 7T BOLD using an imposed spatial activation pattern in human V1. NeuroImage

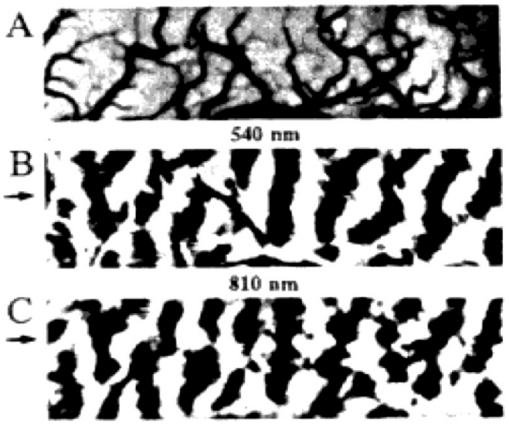
fMRI can map ocular dominance columns



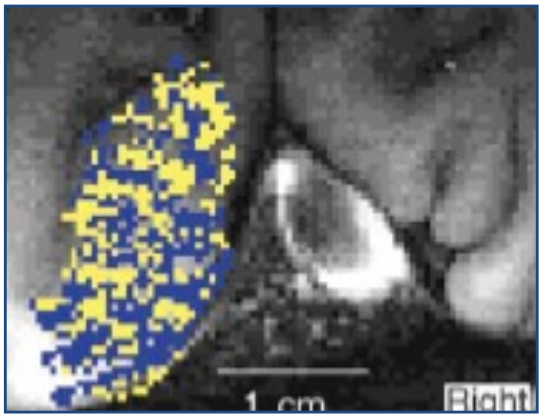
Menon, R. S., S. Ogawa, et al. (1997). J Neurophysiol 77(5): 2780-7.

0.54 x 0.54 in plane resolution

Optical Imaging



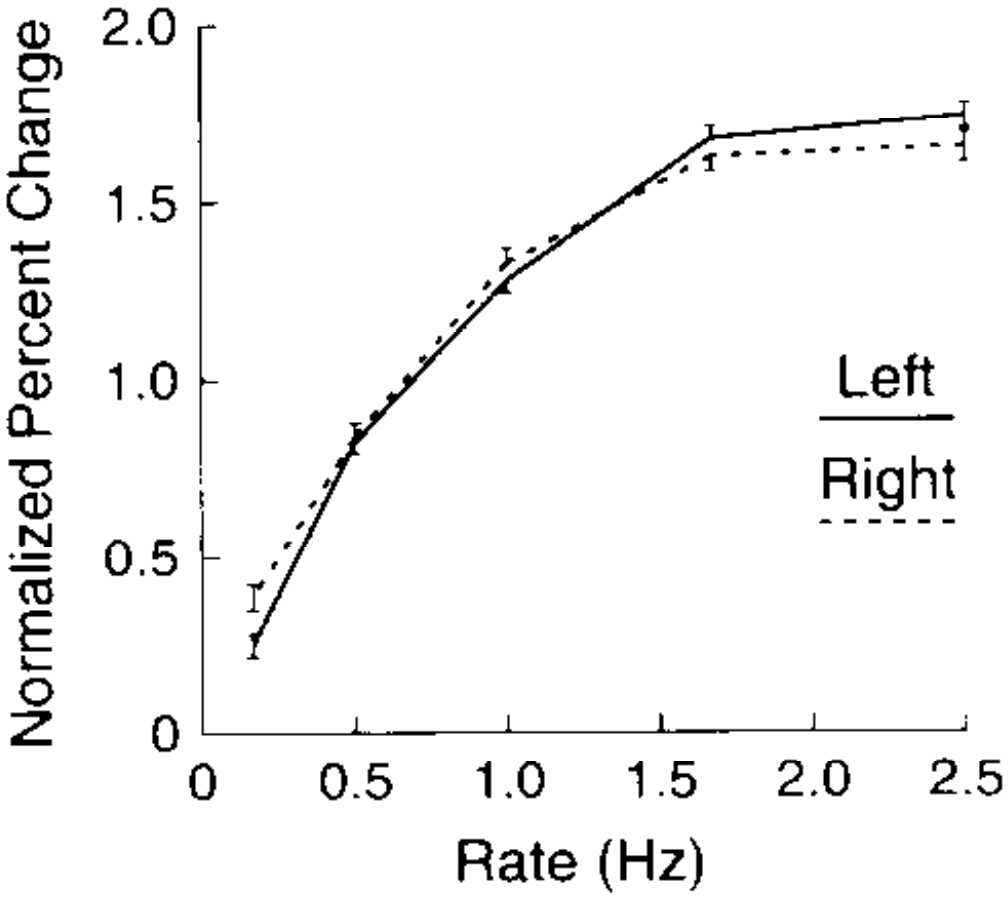
R. D. Frostig et. al, PNAS 87: 6082-6086, (1990).



Cheng, et al. (2001)
Neuron,32:359-374

0.47 x 0.47 in plane resolution

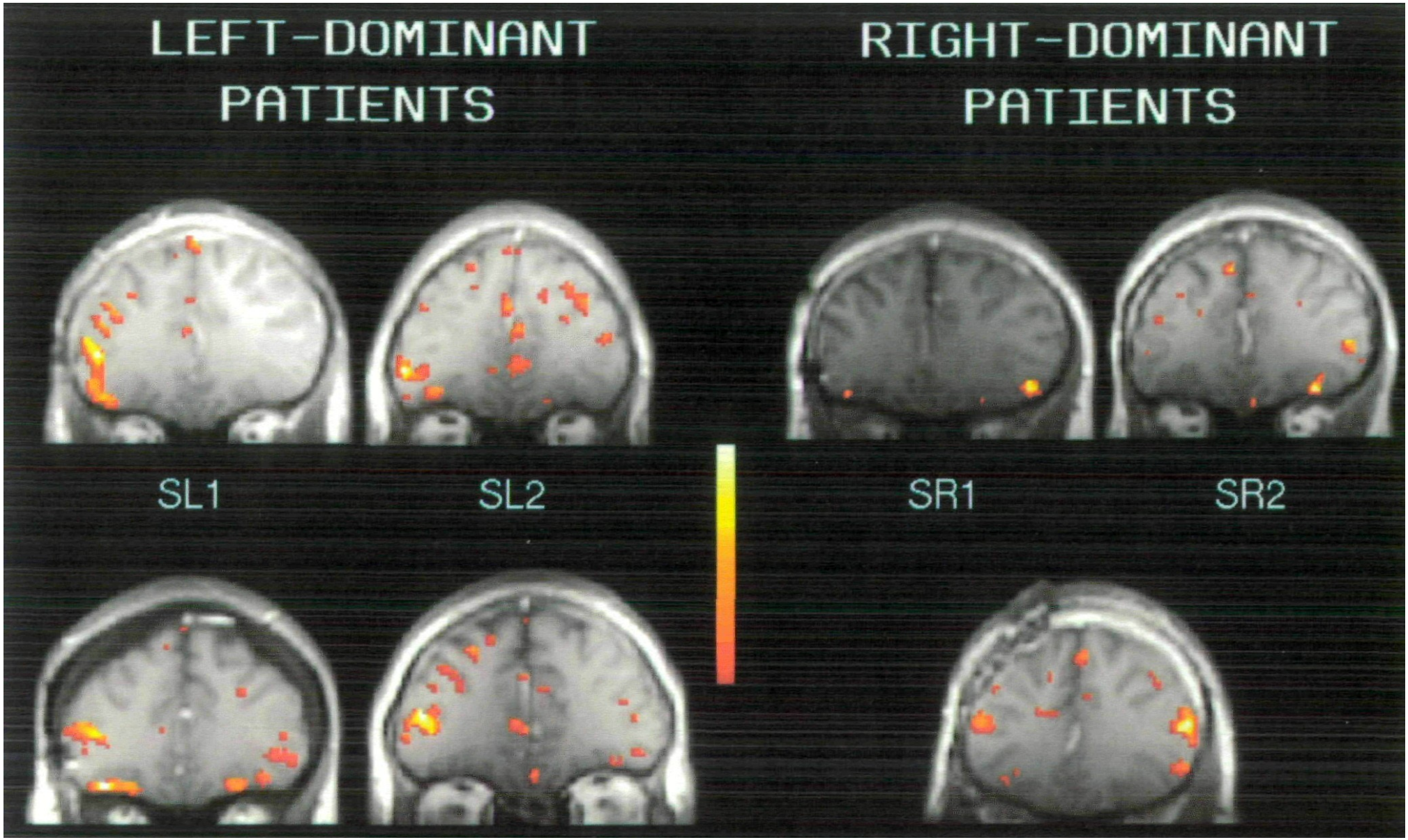
BOLD magnitude scales with auditory stimulus rate



Average responses of 5 subjects' voxels in Heschl's Gyrus

Binder et al 1994 Cognitive Brain Research

Language dominance compared to the WADA test

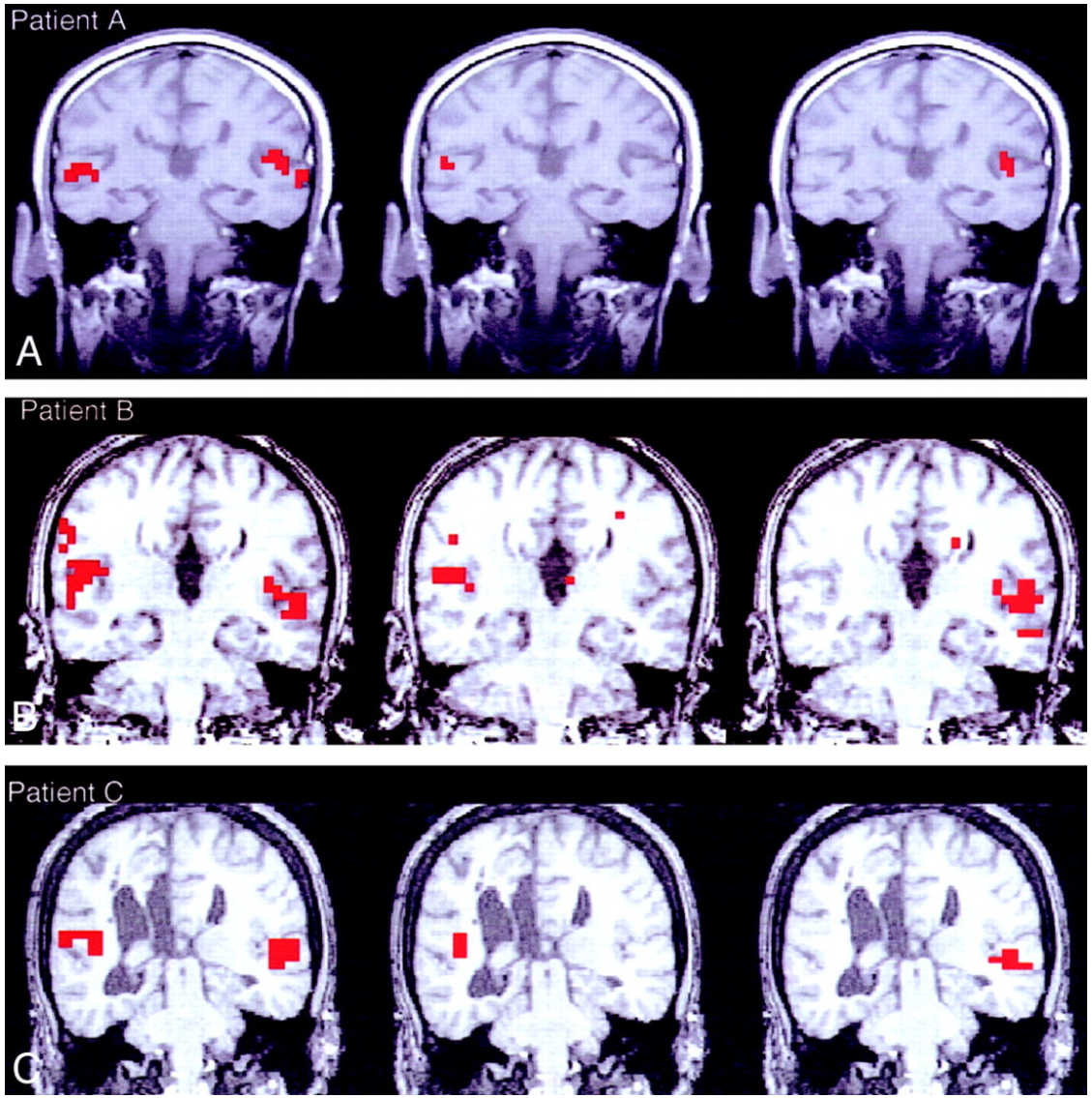


Desmond, et al 1995. Functional MRI measurement of language lateralization in Wada-tested patients. Brain

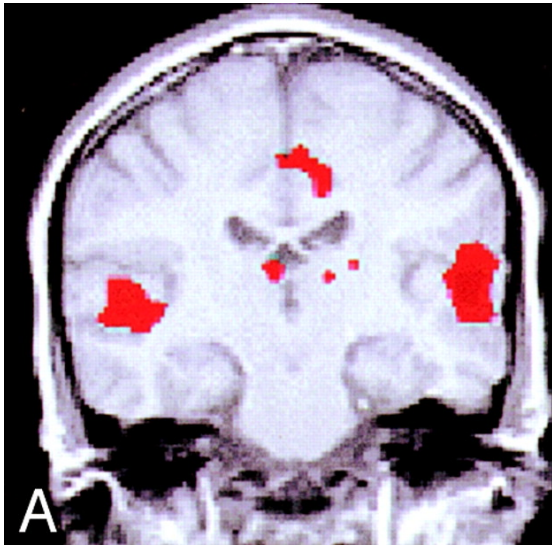
Agenesis of the corpus callosum

Activation from a text listening task

Right and left auditory seeds in resting data



Connectivity map from a healthy volunteer

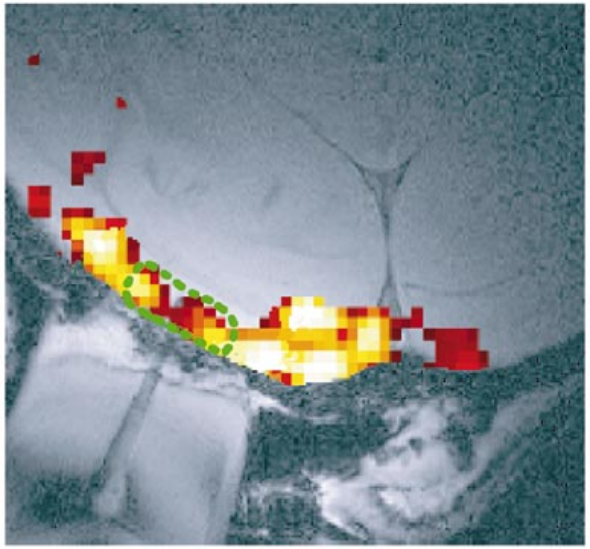


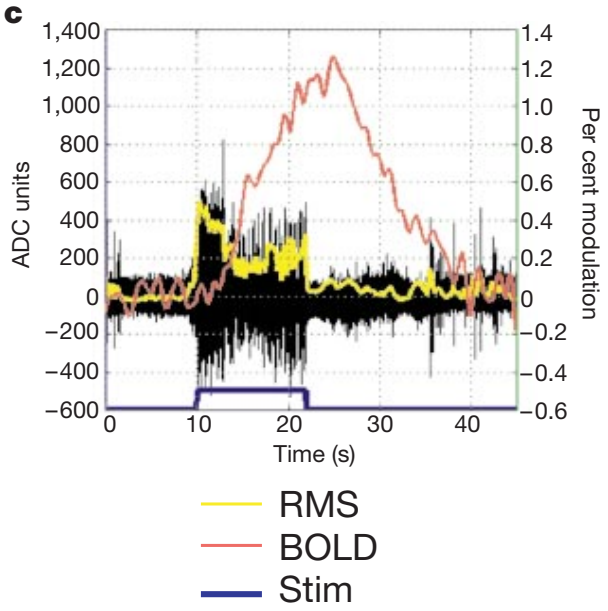
Quigley et al AJNR 2003

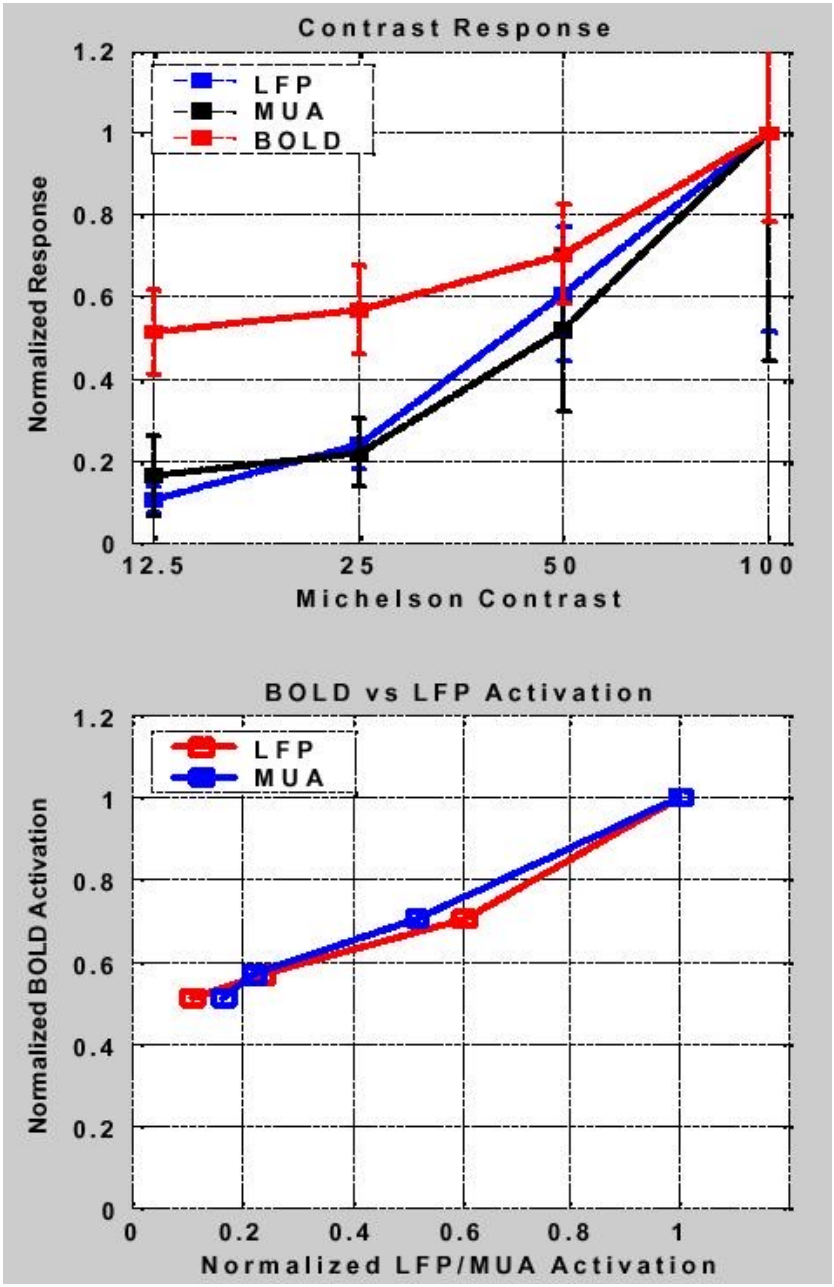
An acallosal patient was first presented by Lowe et al Neuroimage 9:S422 1999

Vasculature is still symmetric, but bilateral neurons are not connected

Why believe fMRI is neural? Complimentary modalities



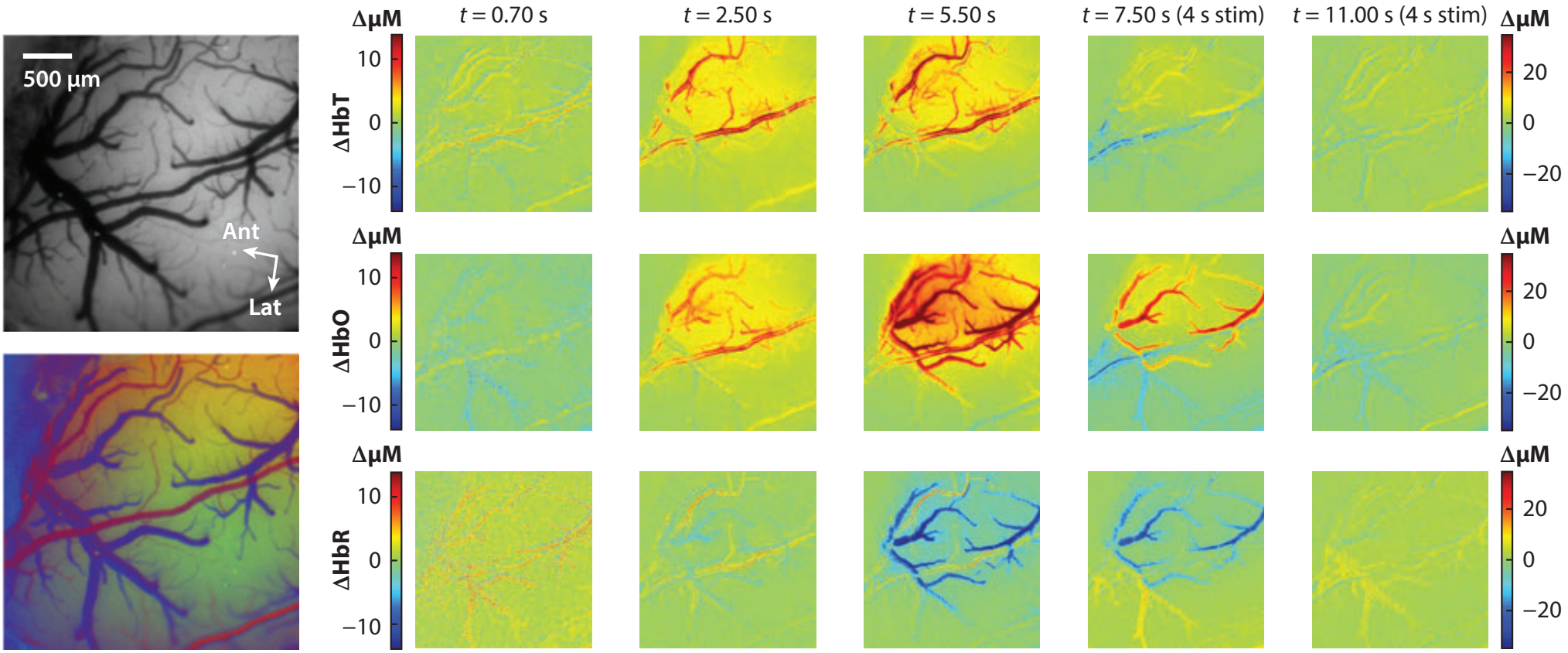




Logothetis also showed that the LFP time courses have a slightly better linear fit than multi-unit spiking activity

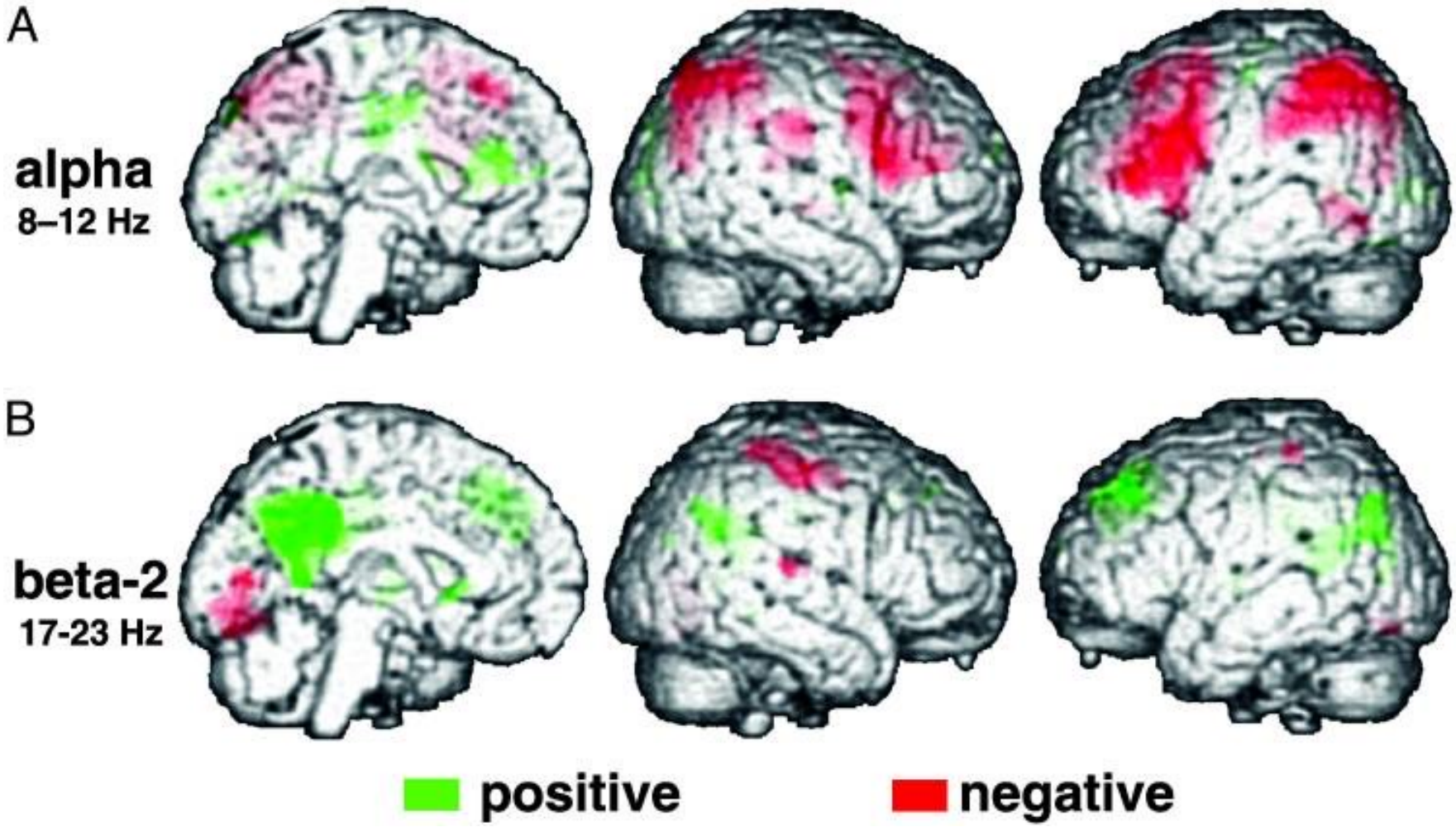
Logothetis et al. (2001) "Neurophysiological investigation of the basis of the fMRI signal" Nature, 412, 150-157

Optical measures



Elizabeth Hillman, Annual Review of Neuroscience 2014. 37:161–81

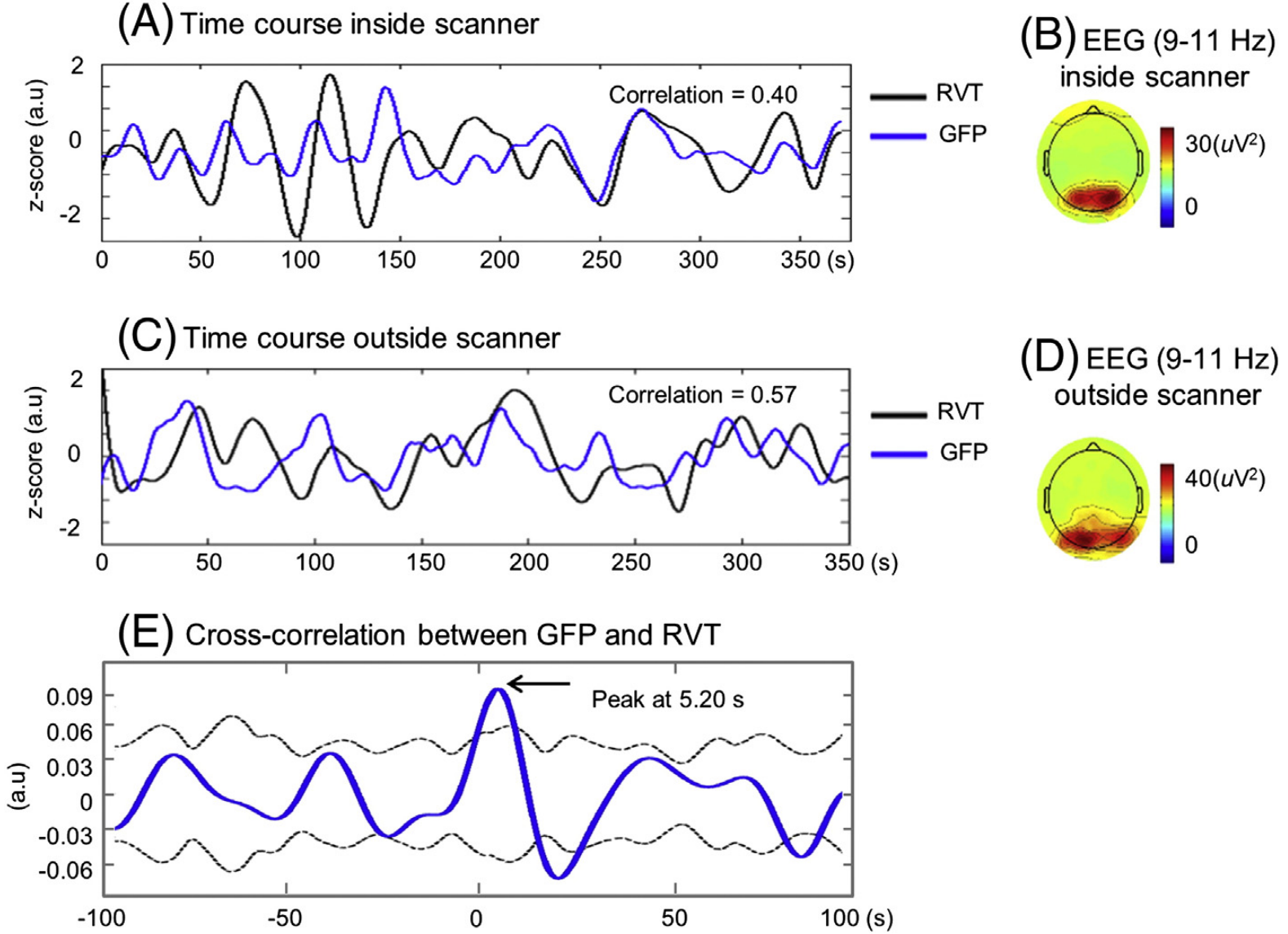
fMRI relationship to EEG



Activation and deactivation maps of EEG signals convolved with a hemodynamic response

Laufs et al PNAS 2003

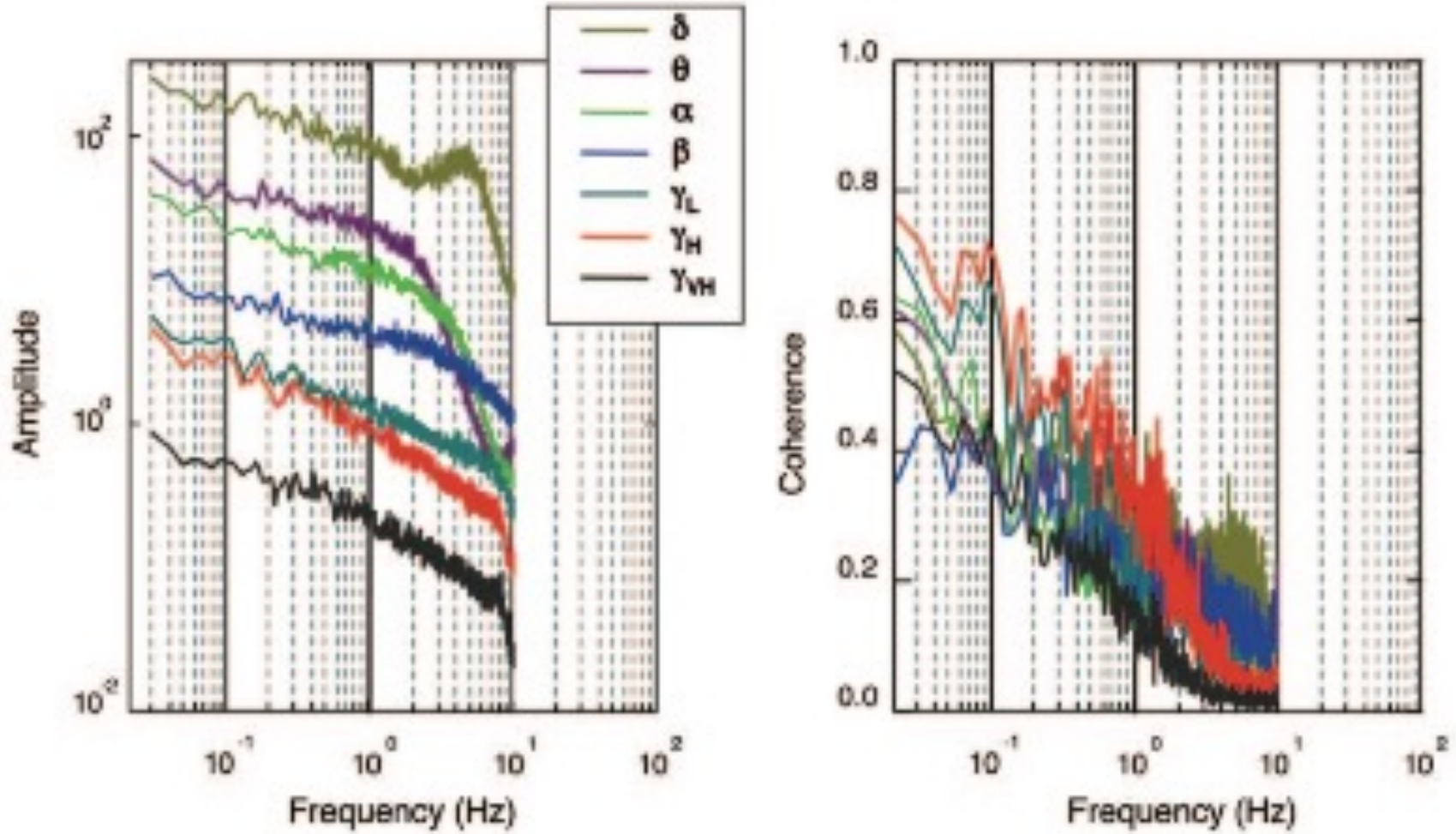
The EEG/fMRI rest relationship isn't simple



EEG alpha (GFP) also correlates with breathing (RVT)

Yuan, Zotev, Phillips, Bodurka *Neuroimage*, 2013

Relationships similar to resting state in electrical recordings



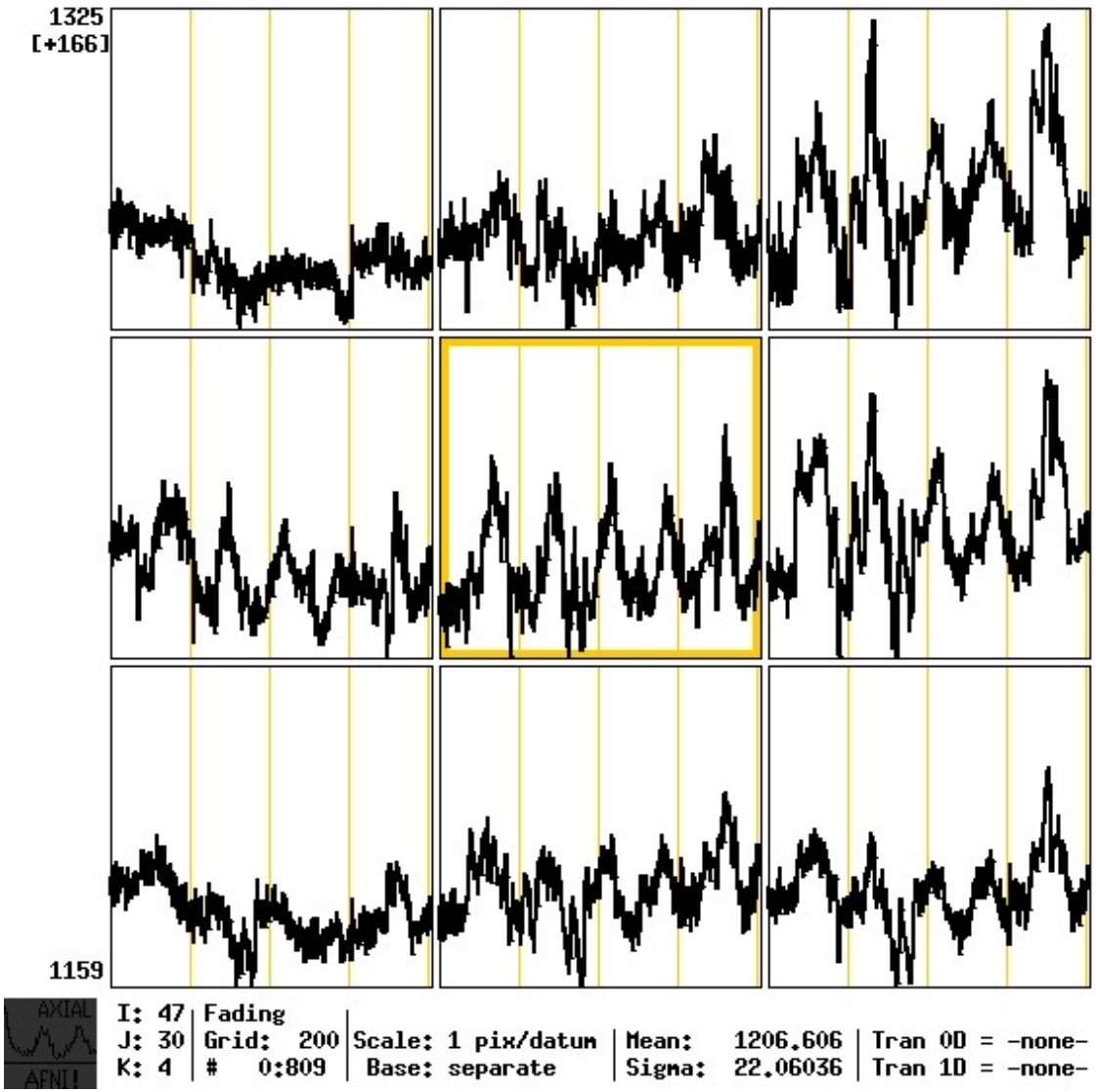
There is a high power signal and a coherence across electrodes in multiple LFP frequency bands.

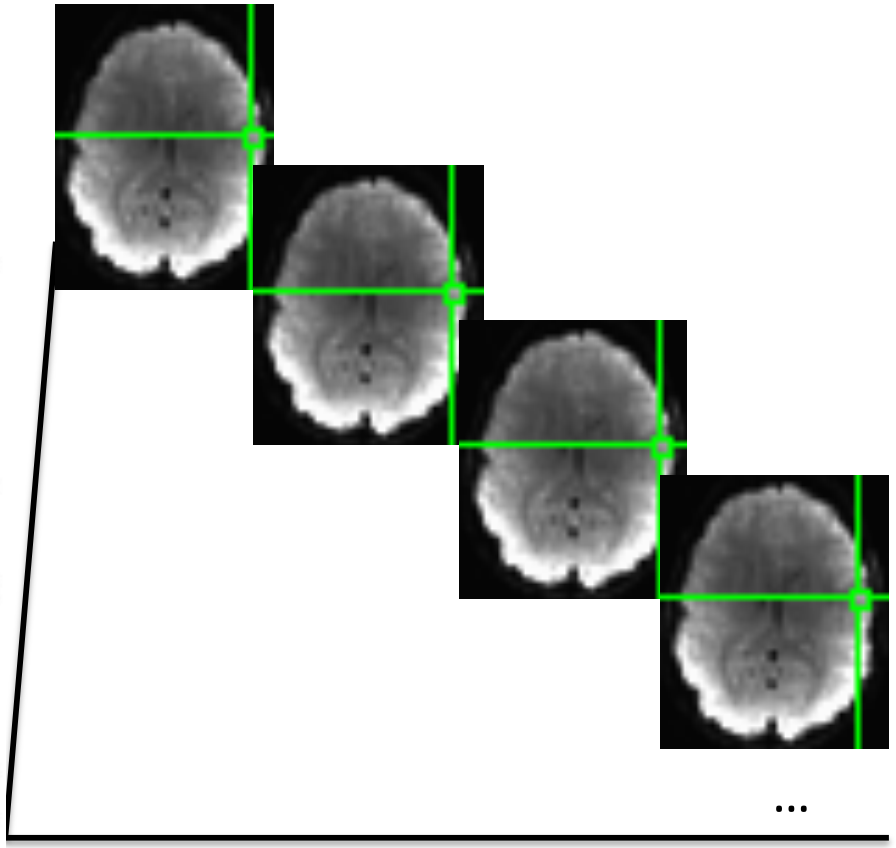
Leopold et al Cerebral Cortex 2003

Based on a slide from M Lowe

Why believe that a specific fMRI study represents neural activity?

How do we know this is neural?

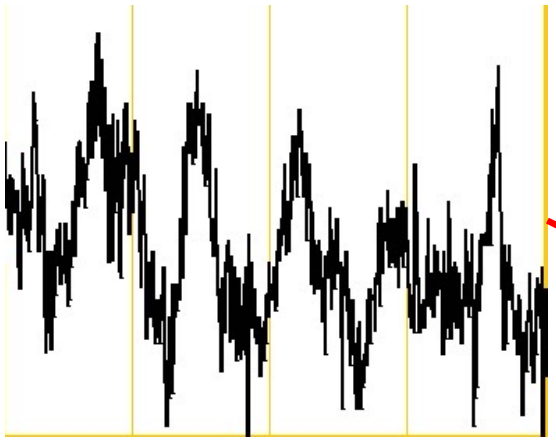


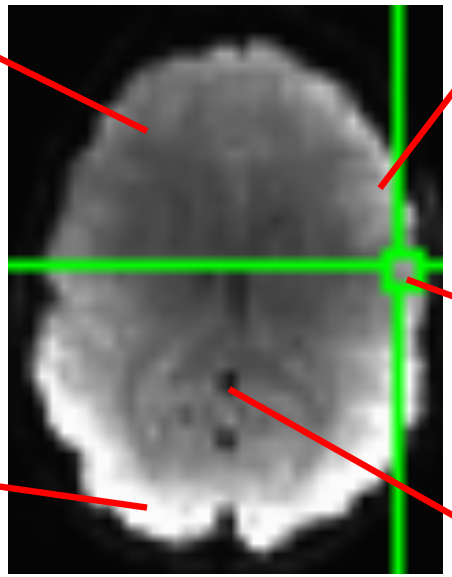


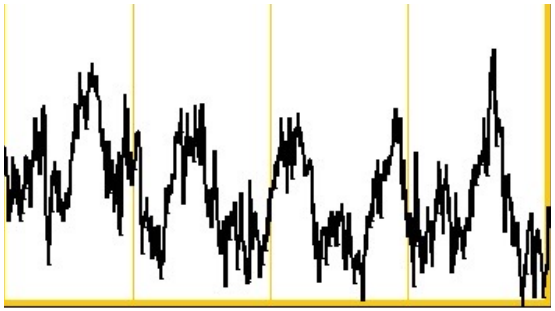
5 cycles of a block design task

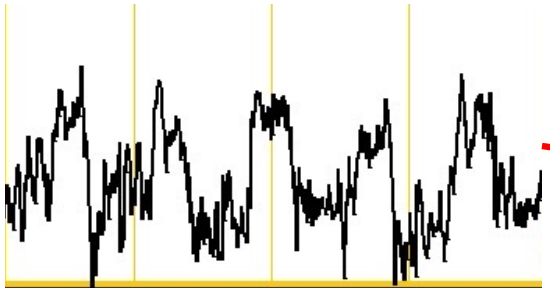
How do we know it's neural?

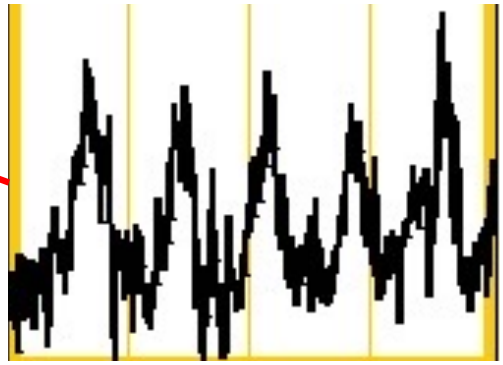
This probably isn't neural

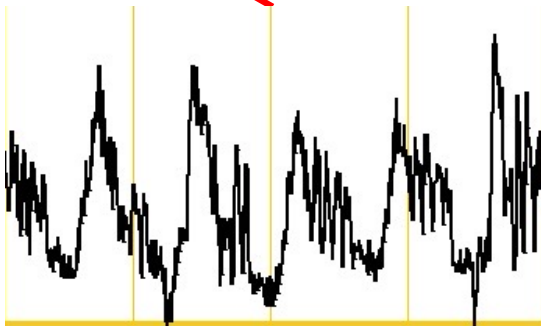






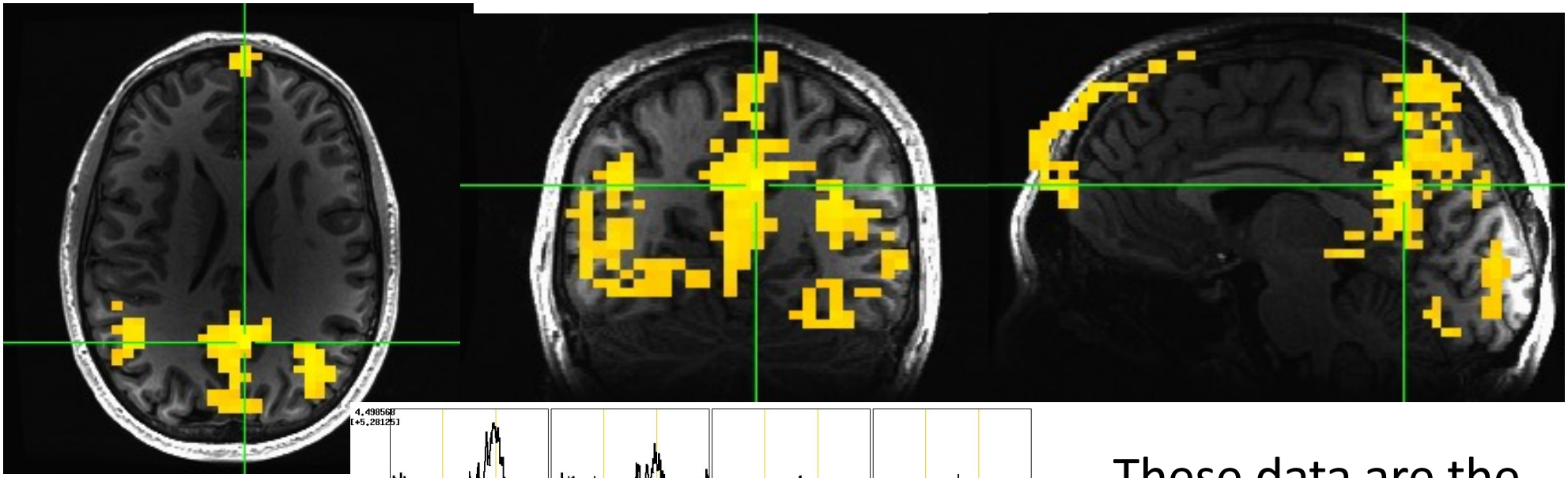


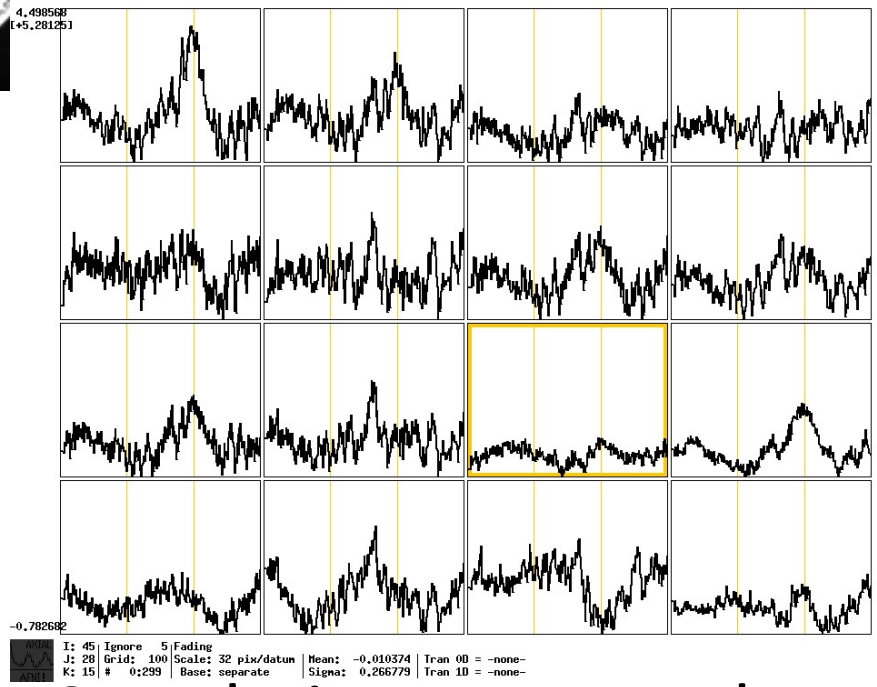




5 cycles of a block design
breath holding task
BOLD changes primarily because
of a global blood flow change

How do we know this is neural?

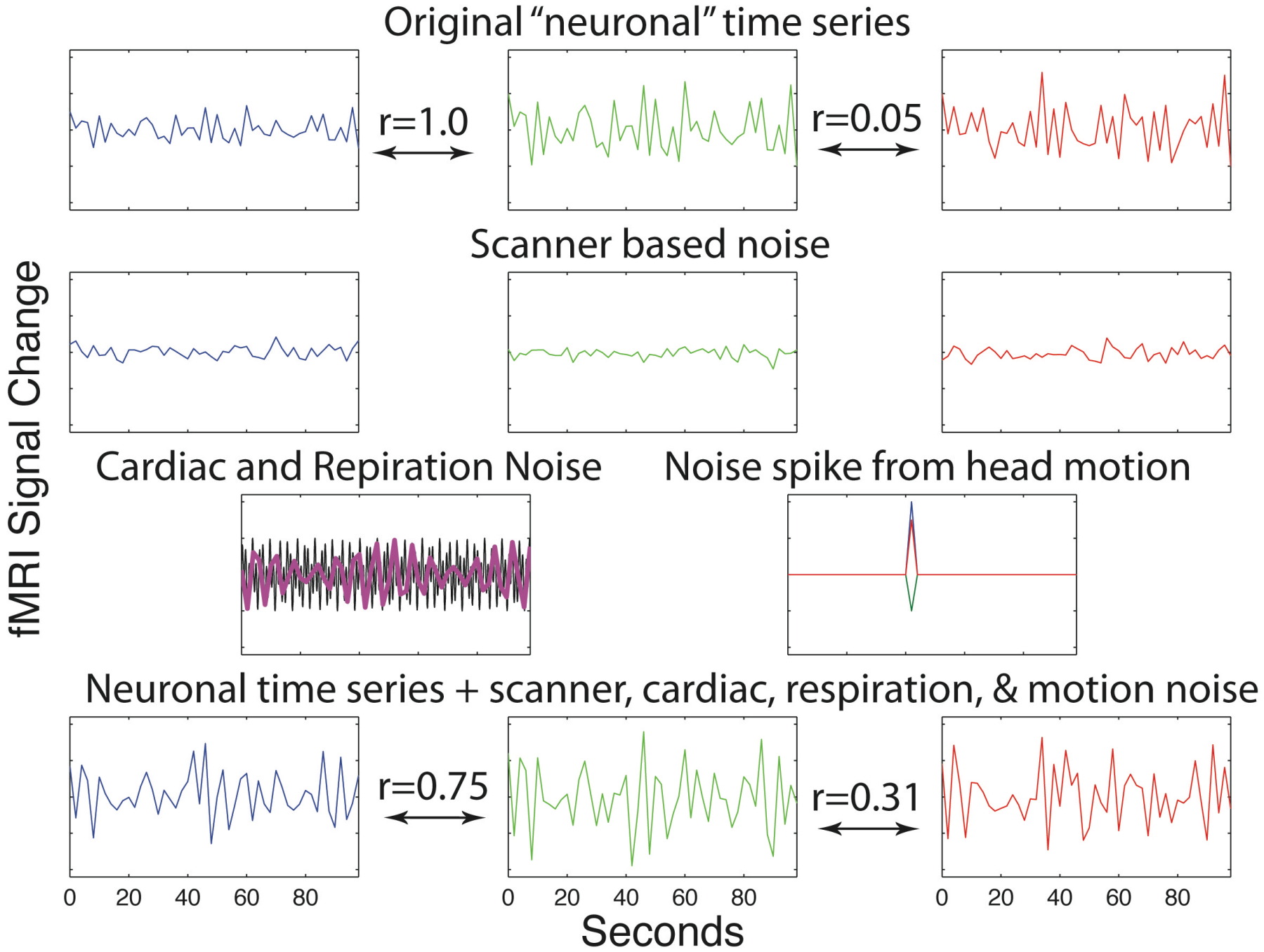




Correlations to a seed voxel

These data are the breathing and motion noise from a resting state scan (with a nice looking axial slice very selectively chosen)

Isolating the neural signal

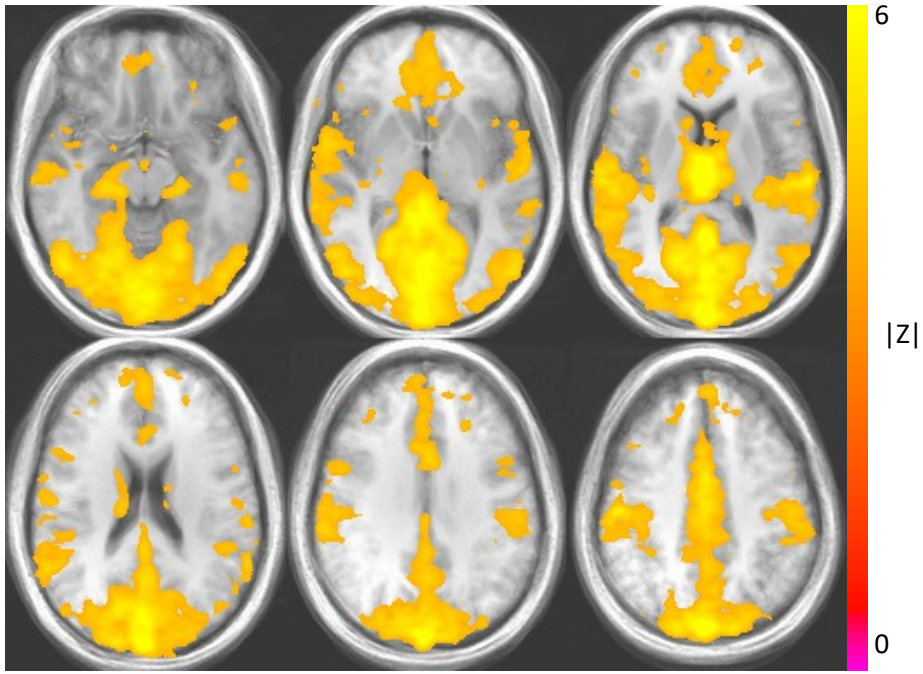


Challenges

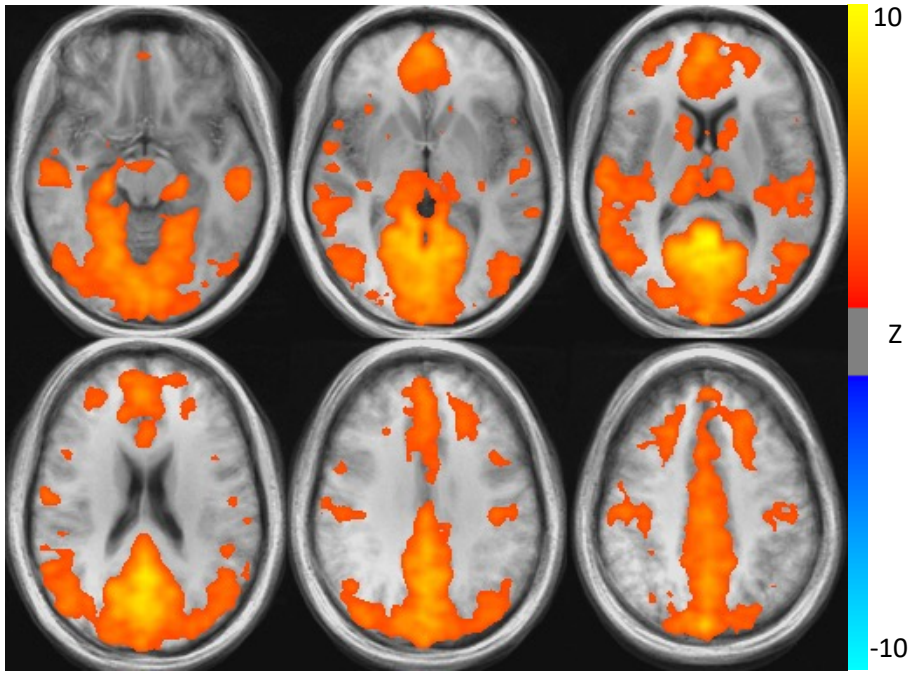
- Non-neural partially BOLD fluctuations: Respiration, Cardiac pulsation
- Head Motion
- Bad Task Design
- Understanding the effects of data collection choices
- Understanding the effects of data processing choices

Unmodeled respiration & cardiac noise WILL cause problems with resting connectivity

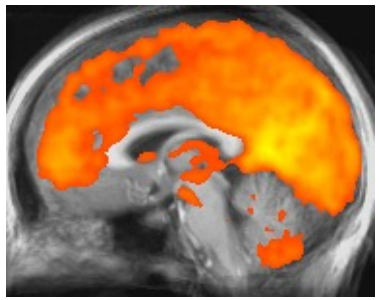
Respiration changes using RVT



Correlation (of PCC) at Rest



Group (n=10)

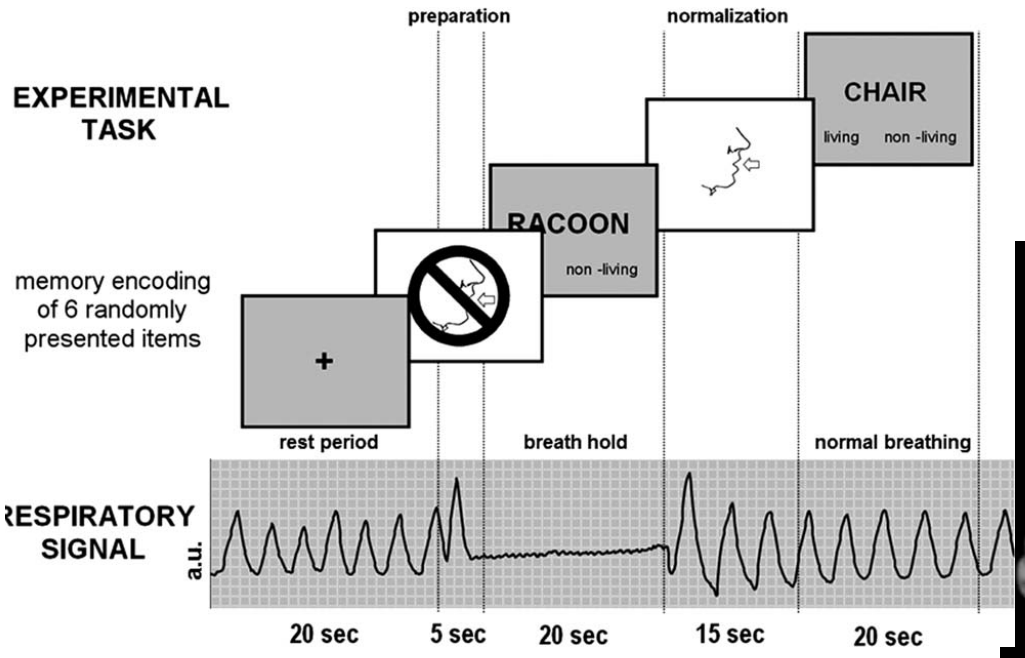


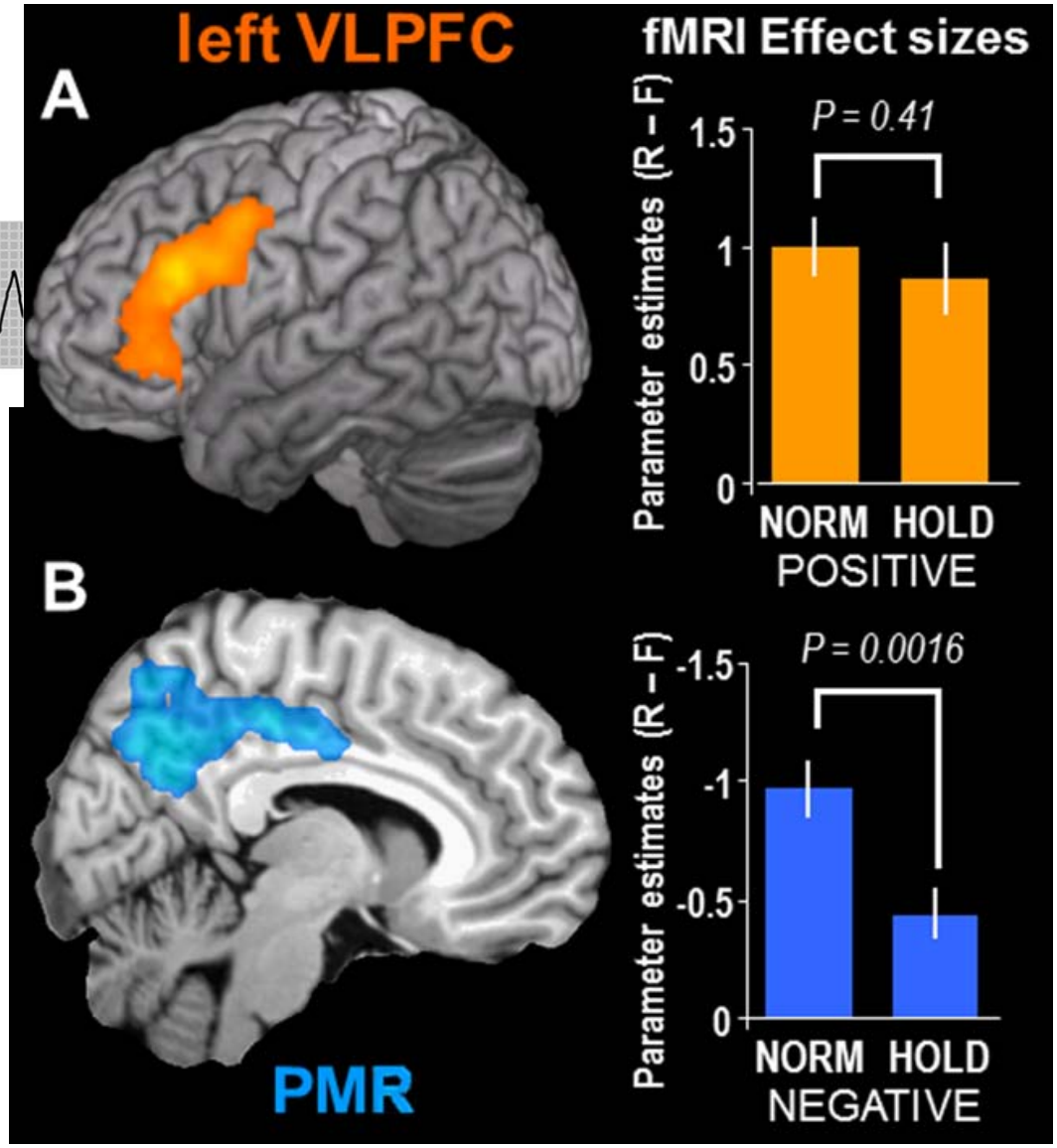
RVT = measuring and tracing (Respiration Volume)/time and removing it from the time series

Slide from Rasmus Birn

Related findings are in Bright & Murphy, *NeuroImage* 2015

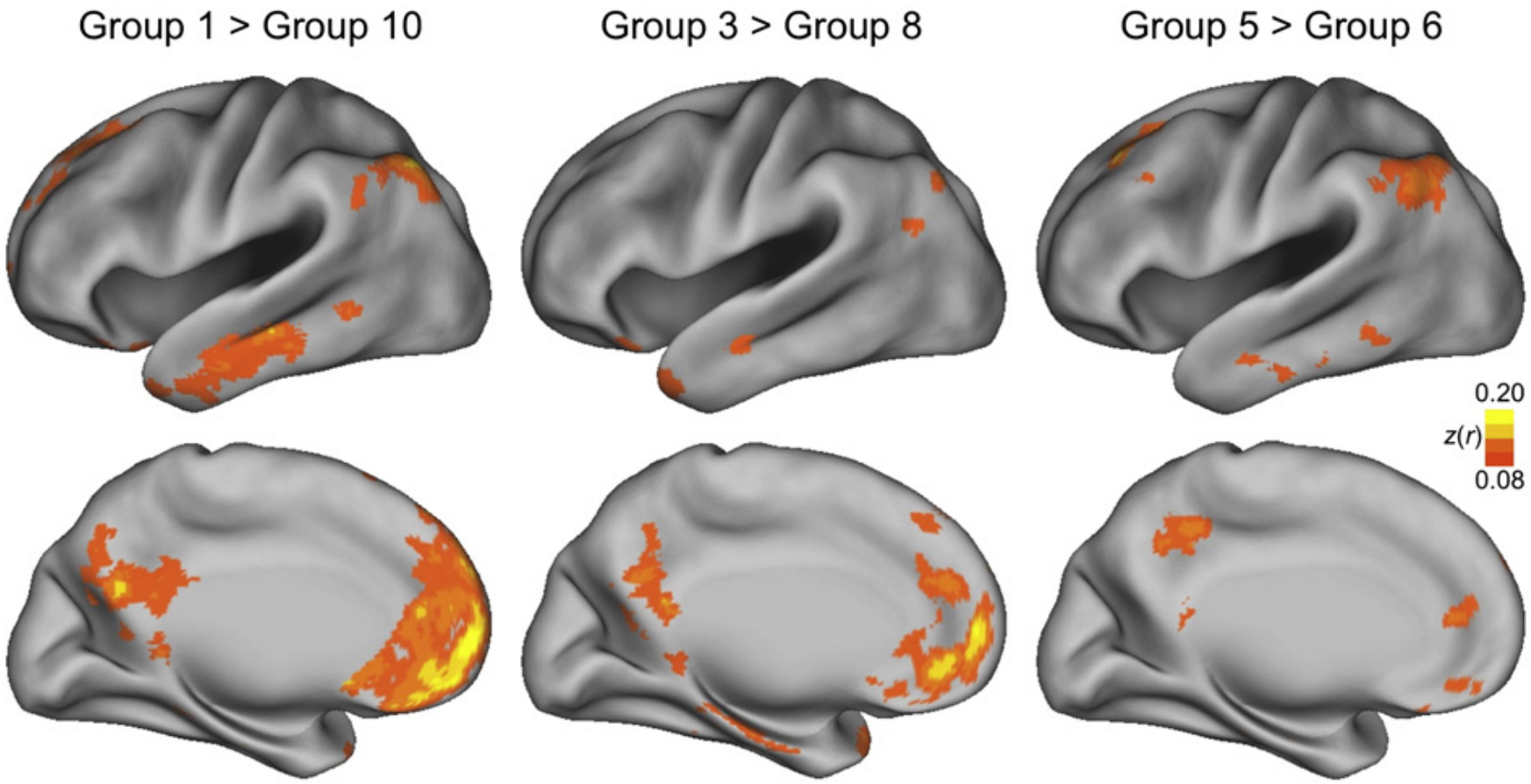
Respiration can also bias fMRI task results





Huijbers et al Hum Brain Mapping 2014

Connectivity differences based on head motion

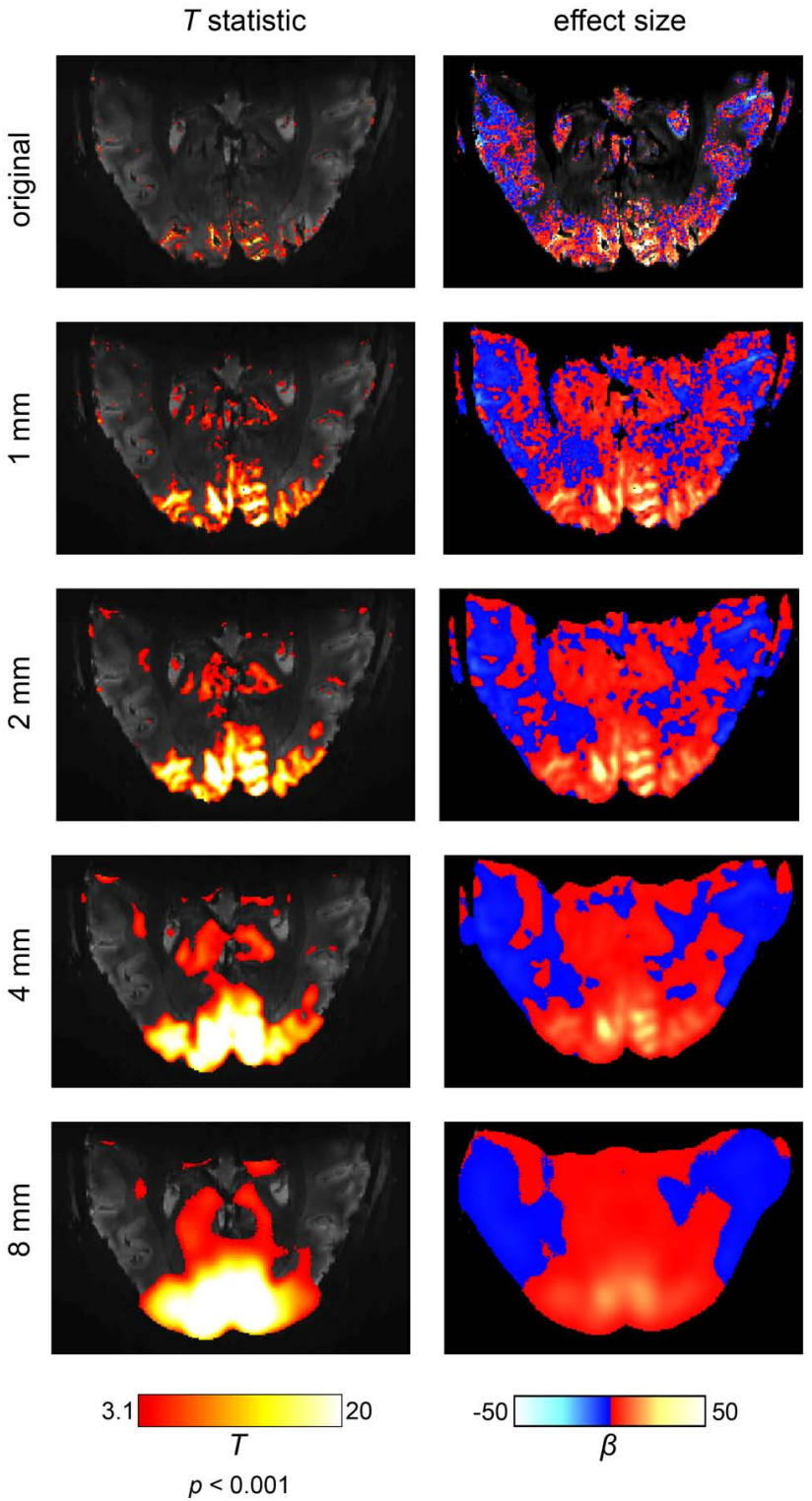


Each group is 100 Subjects

Group 1 had the least motion and group 10 had the most motion

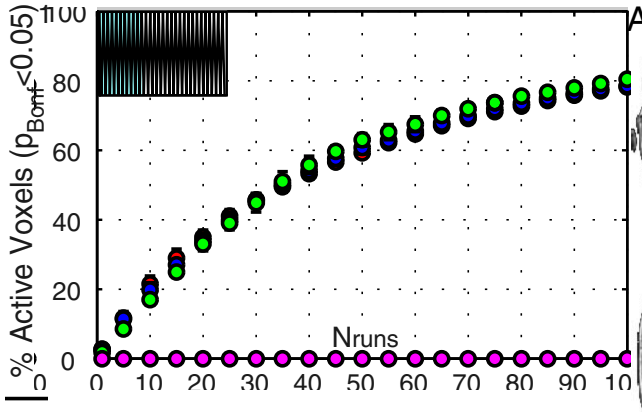
Van Dijk et al, Neuroimage 2012

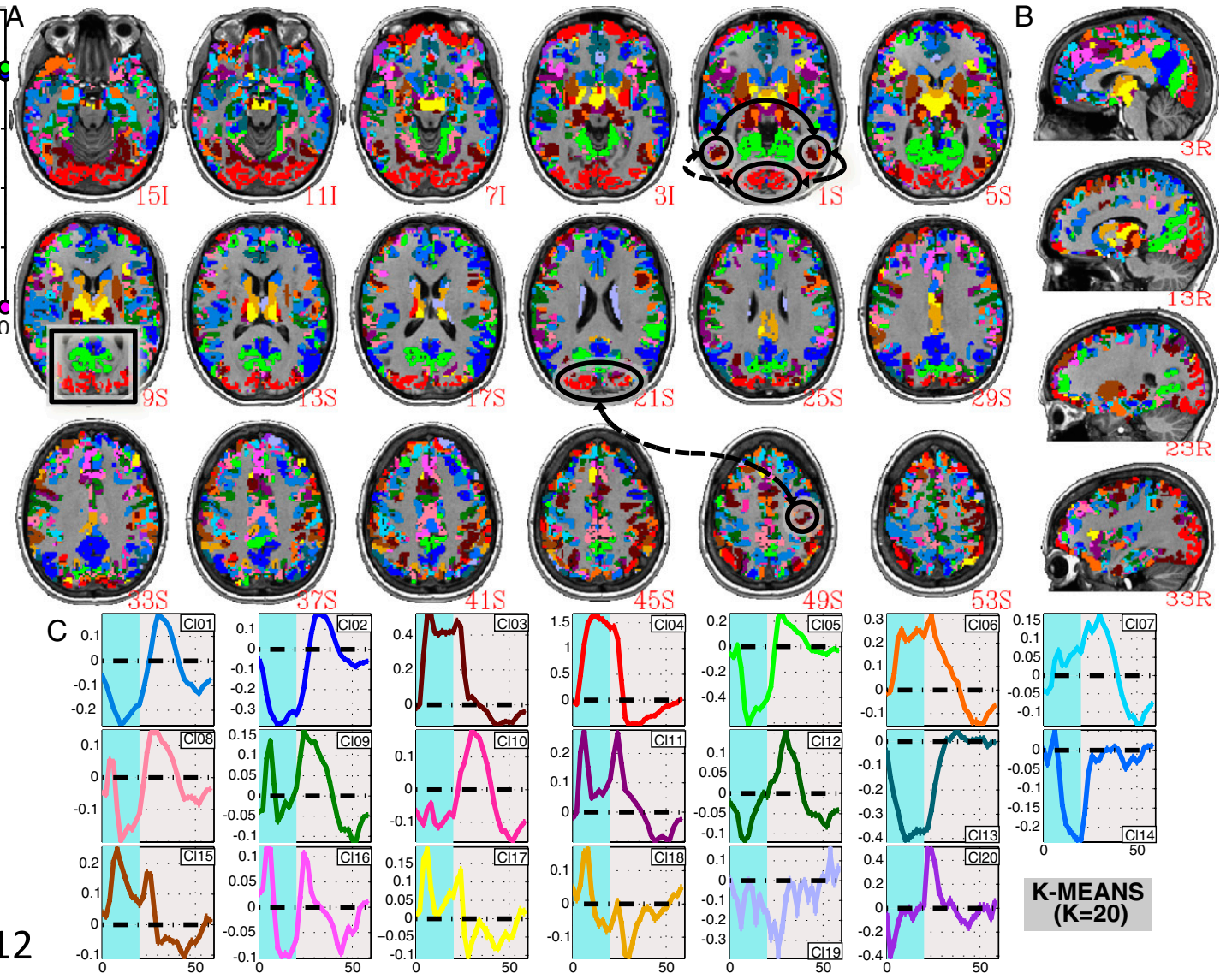
Data collection matters
Spatial resolution



Stelzer, J., et al, Front Hum Neurosci, 2014

The amount of data matters



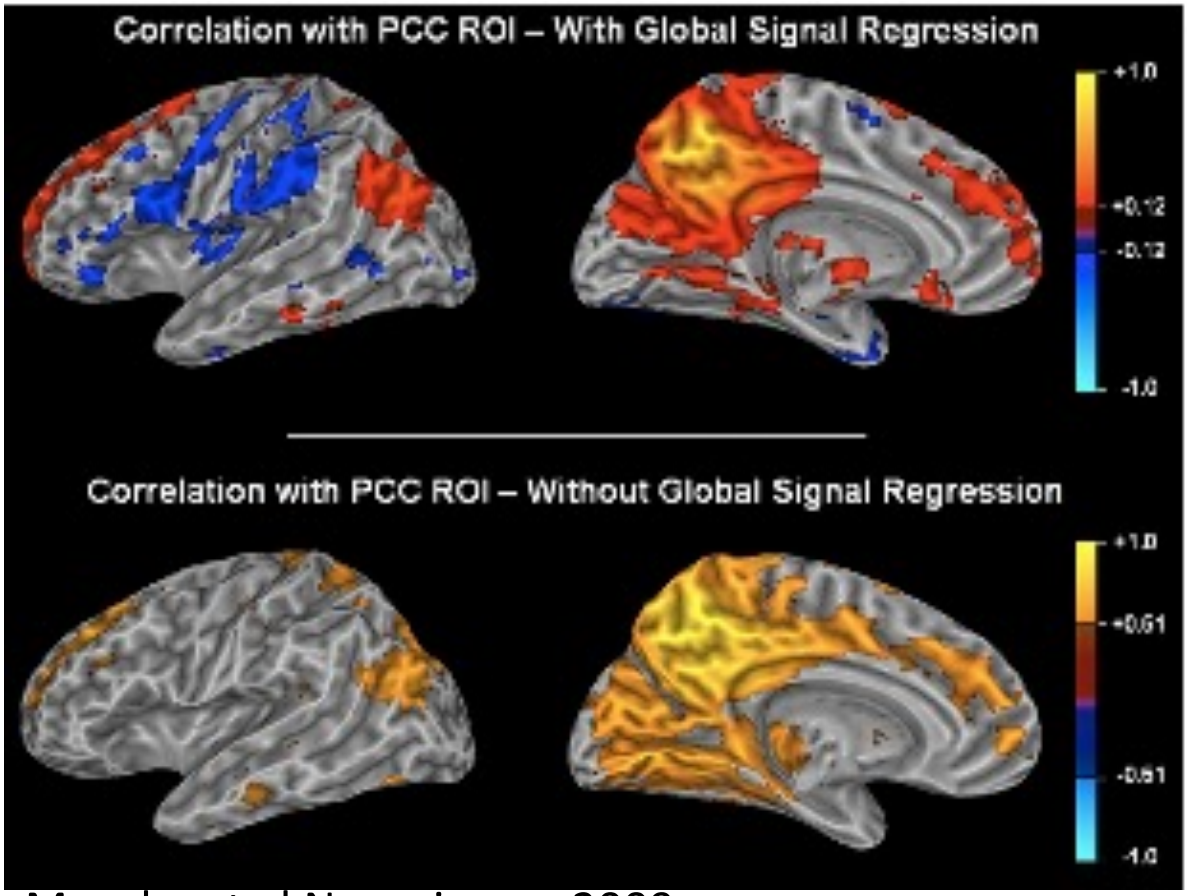


Gonzalez-Castillo, PNAS 2012

Data processing matters:

A common preprocessing step will always result in anti-correlated networks

Correlations to the Posterior Cingulate

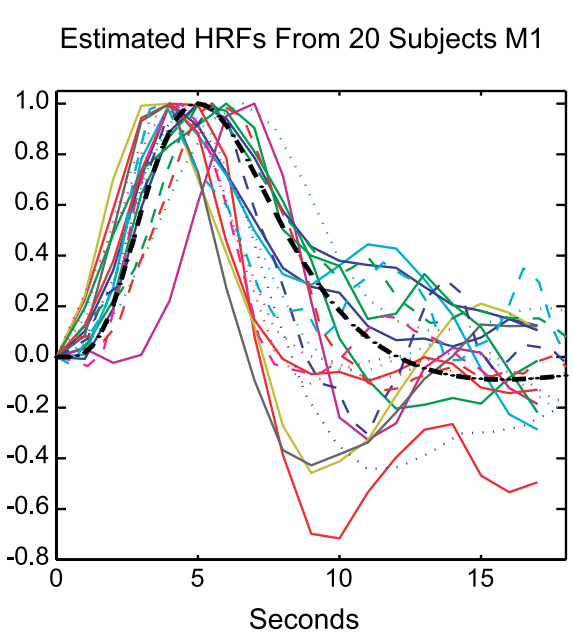


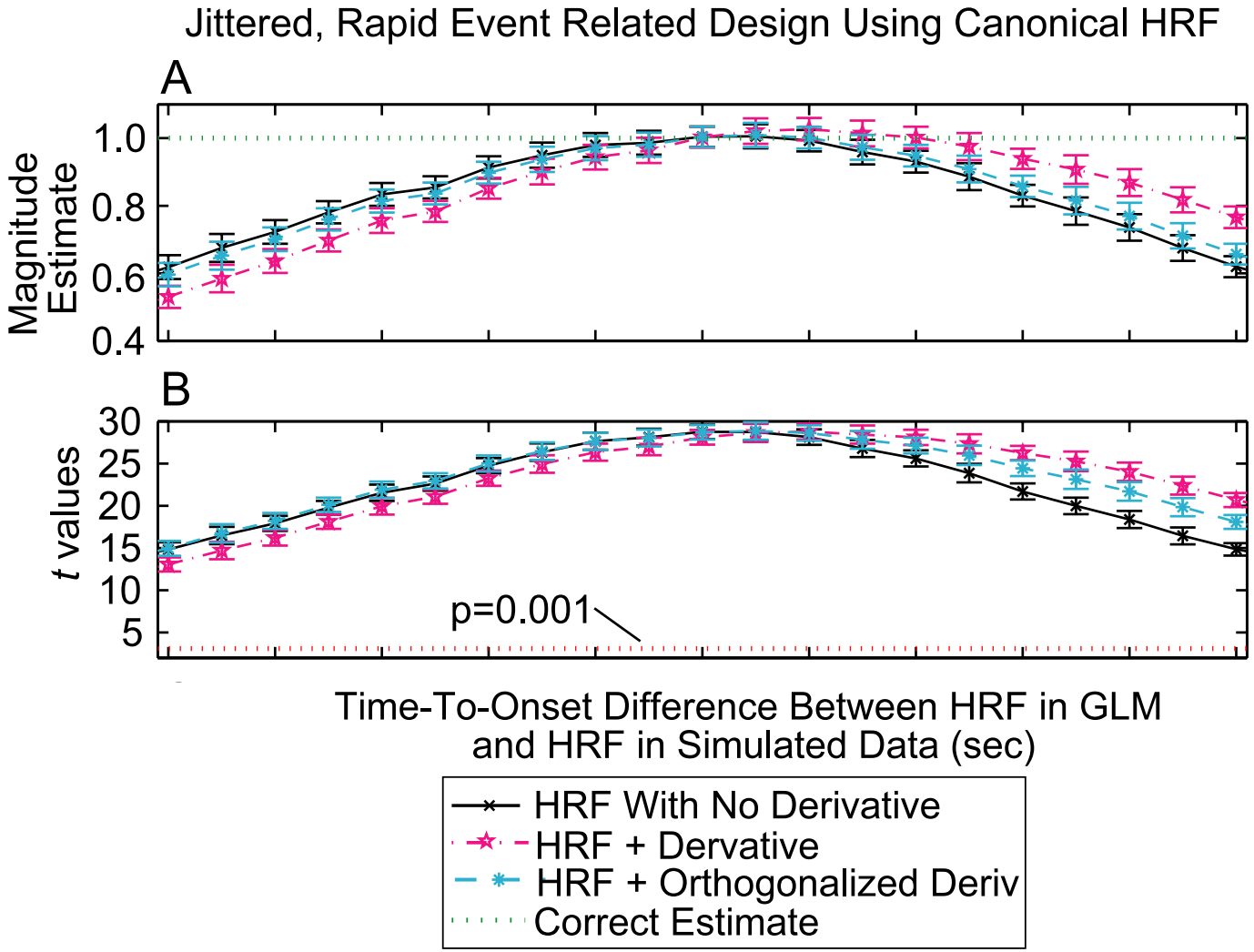
Murphy et al Neuroimage 2009

Removing the global signal was supposed to remove non-neural fluctuations, but it also induces anti-correlations

Removing uncharacterized signals can cause uncharacterized population differences

Modeling response shape can matter

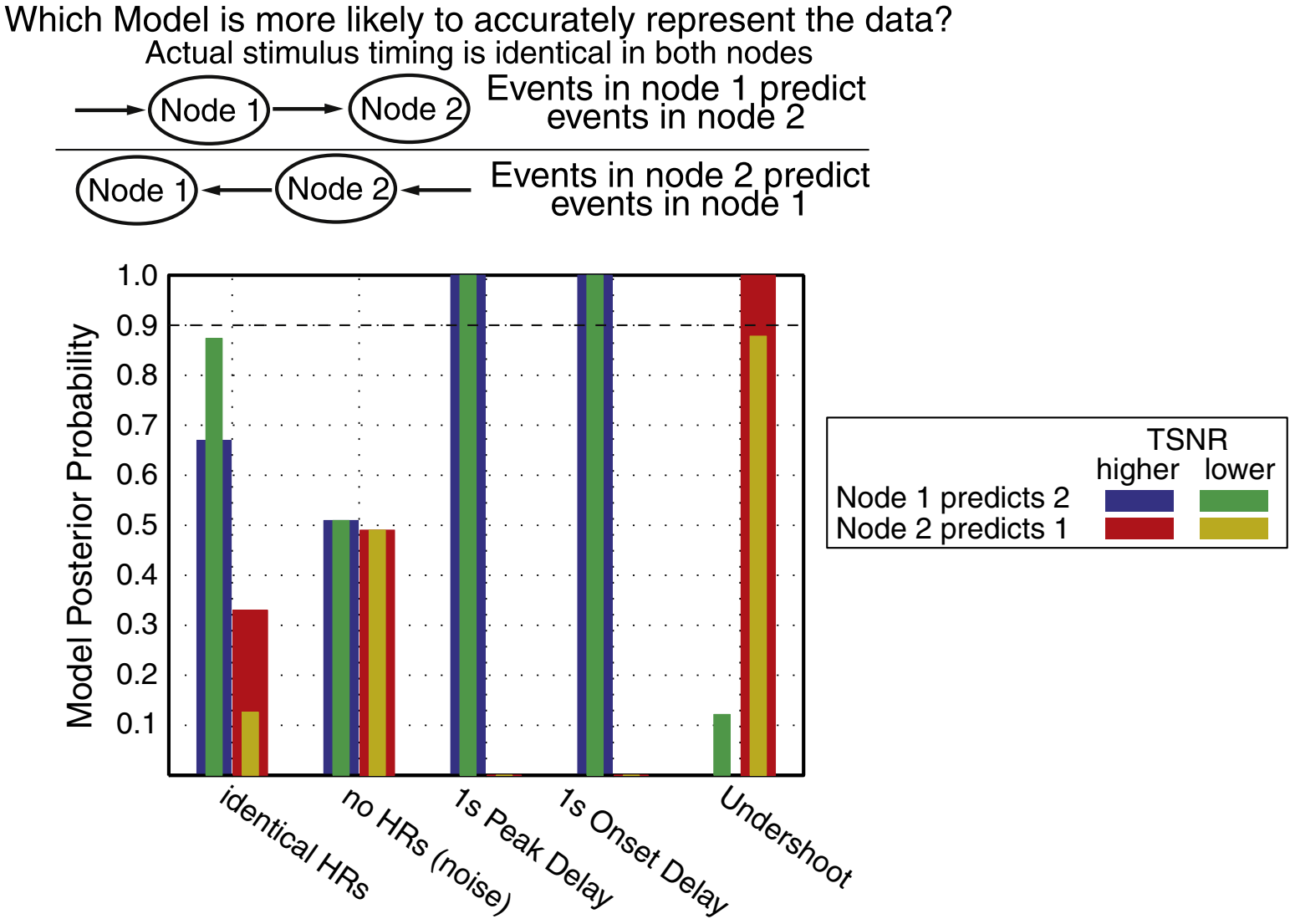




Handwerker et al, Neuroimage 2014

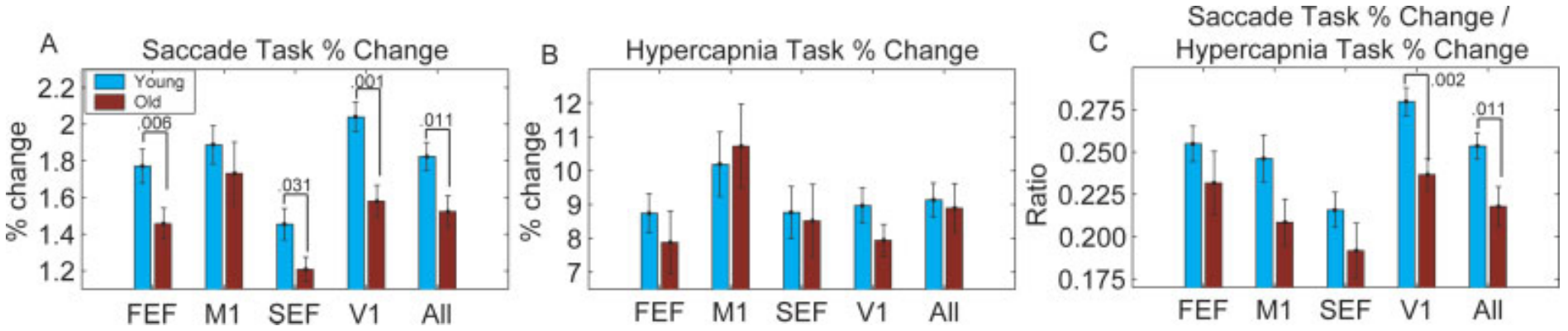
Modeling the order of neural events with fMRI is dicey

An example using Dynamic Causal Modeling



Handwerker et al *NeuroImage* 2012

Population differences can occur from non-neural variation

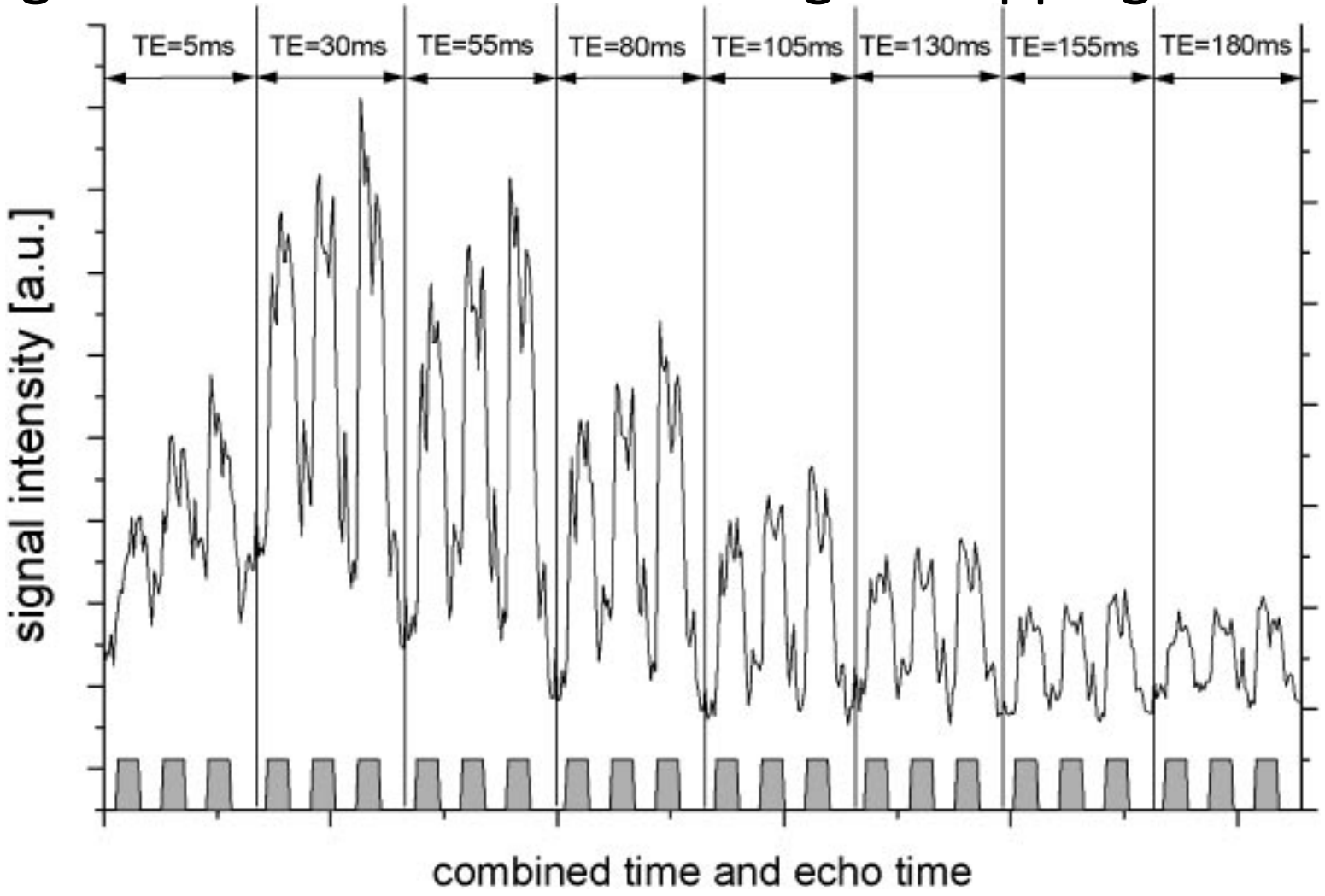


Response magnitudes in several brain regions vary during a cognitive task and a primarily vascular breath holding task.

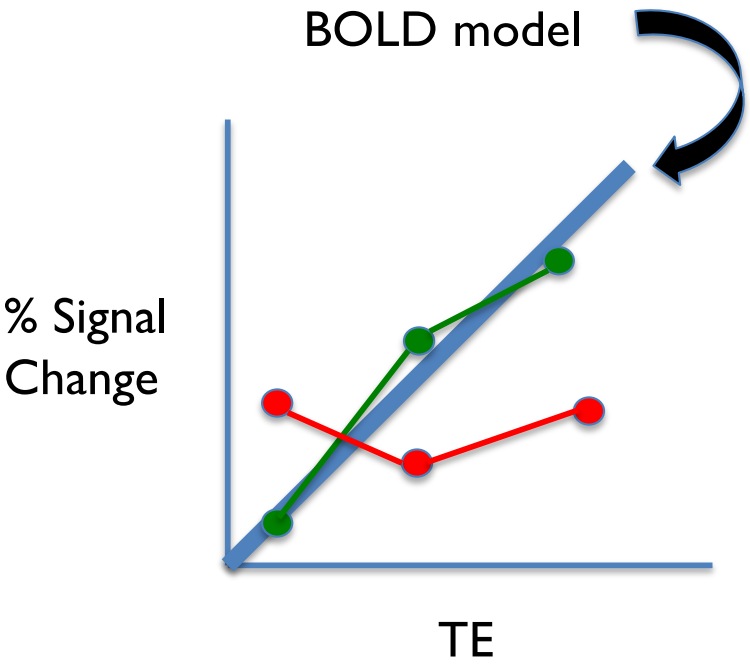
Handwerker et al, Human Brain Mapping 2007

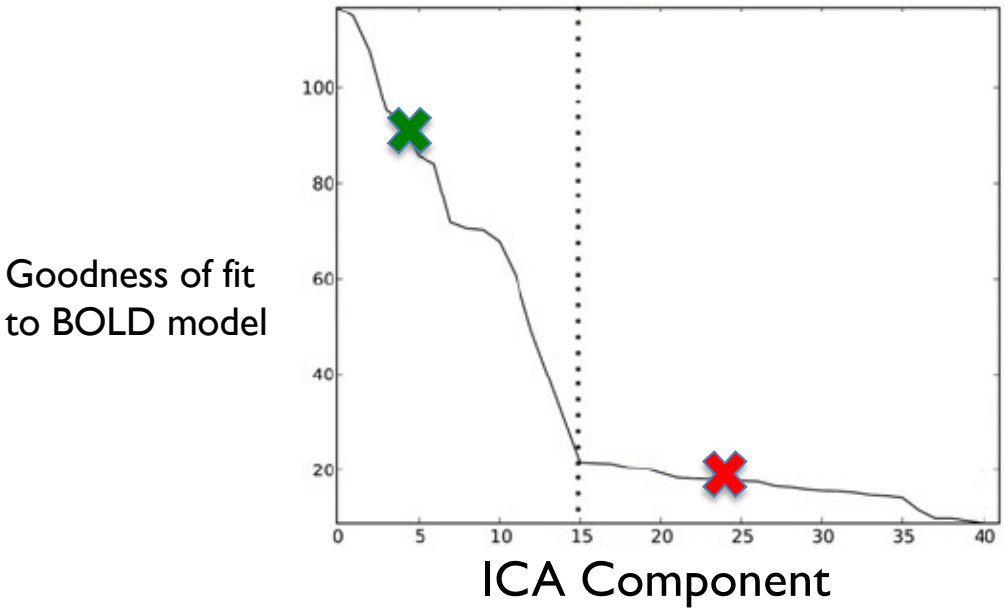
Using multi-echo fMRI to increase confidence that responses are BOLD

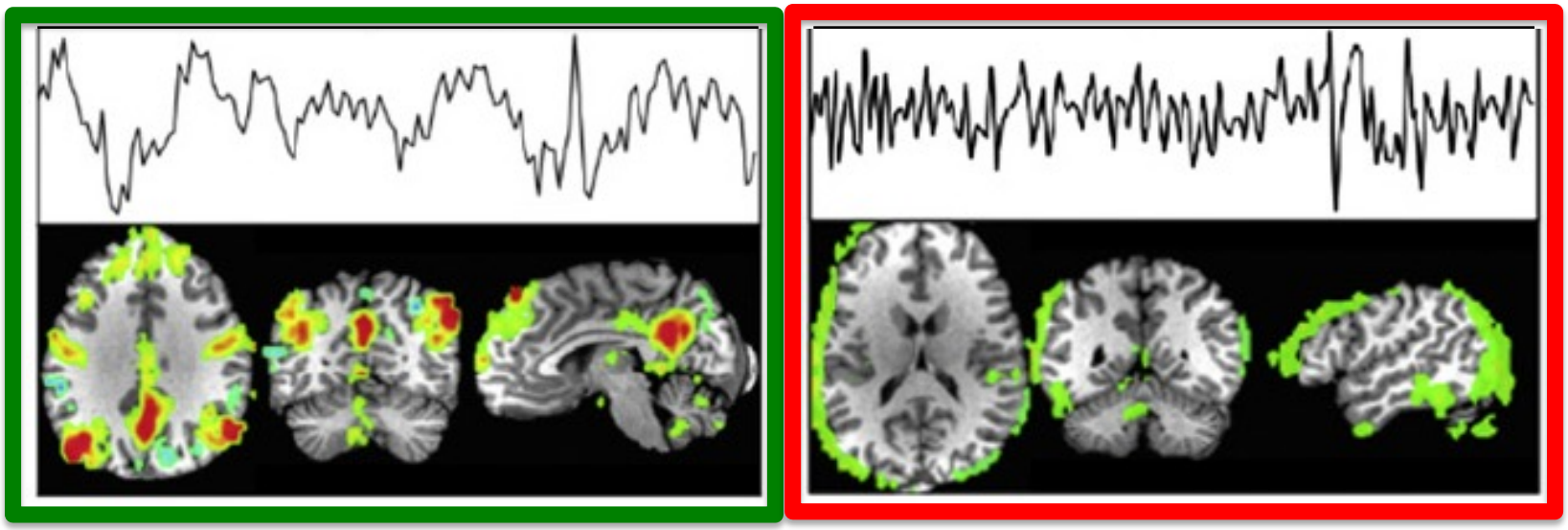
Average across active voxels in a figure tapping task at 3T



Barth et al NMR Biomed 2001, p484


BOLD model
% Signal Change
TE


Goodness of fit to BOLD model
100
80
60
40
20
0
5
10
15
20
25
30
35
40
ICA Component



Multi-echo-ICA denoising

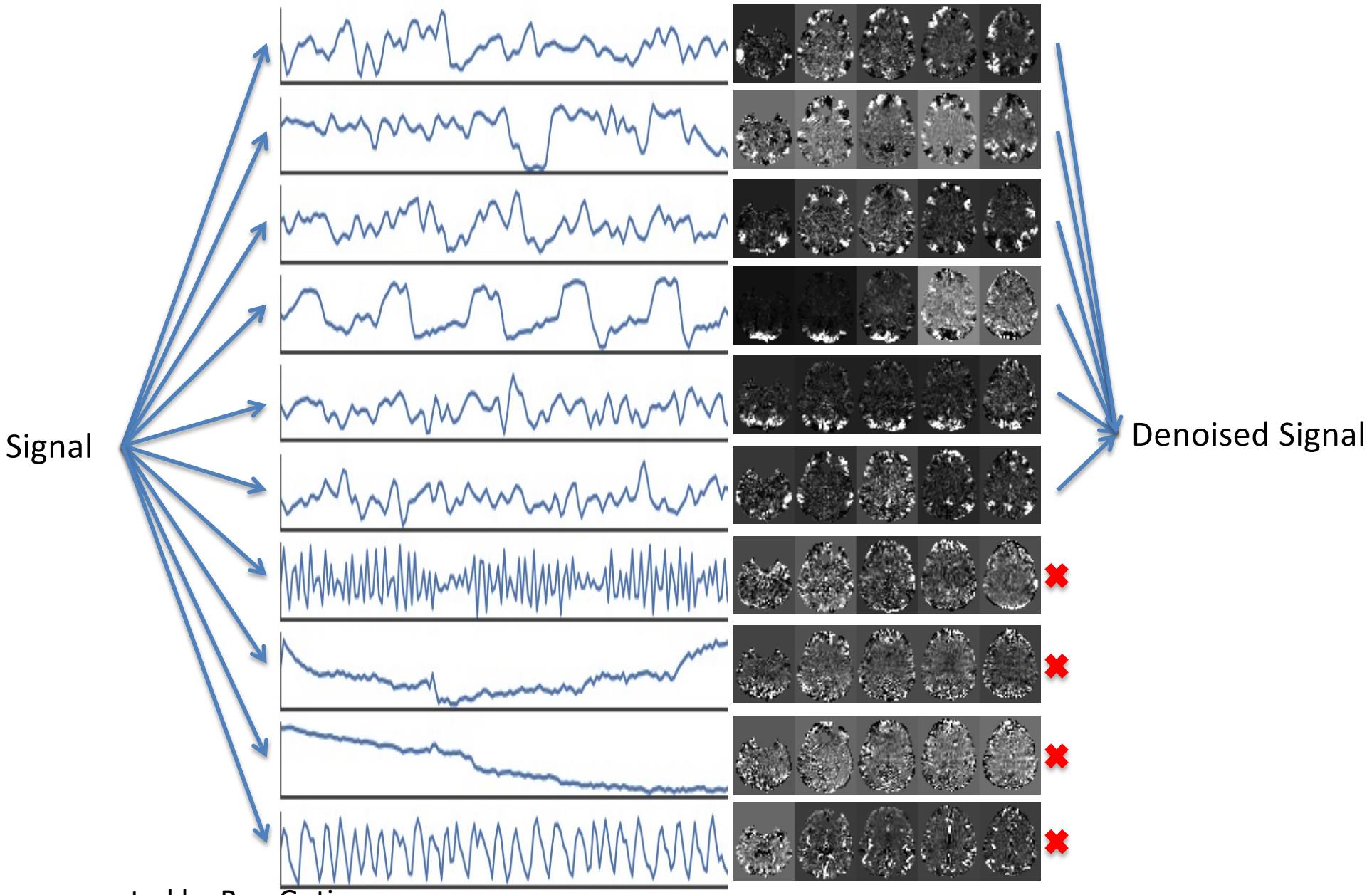


Image created by Ben Gutierrez

Summary

- fMRI helps us understand the brain!
- Even though we measure an indirect signal, it can be quite specific
- There are many ways to confuse artifacts with neural signals if you're not careful
- Think about choices from data collection through analysis
- Look carefully at your data