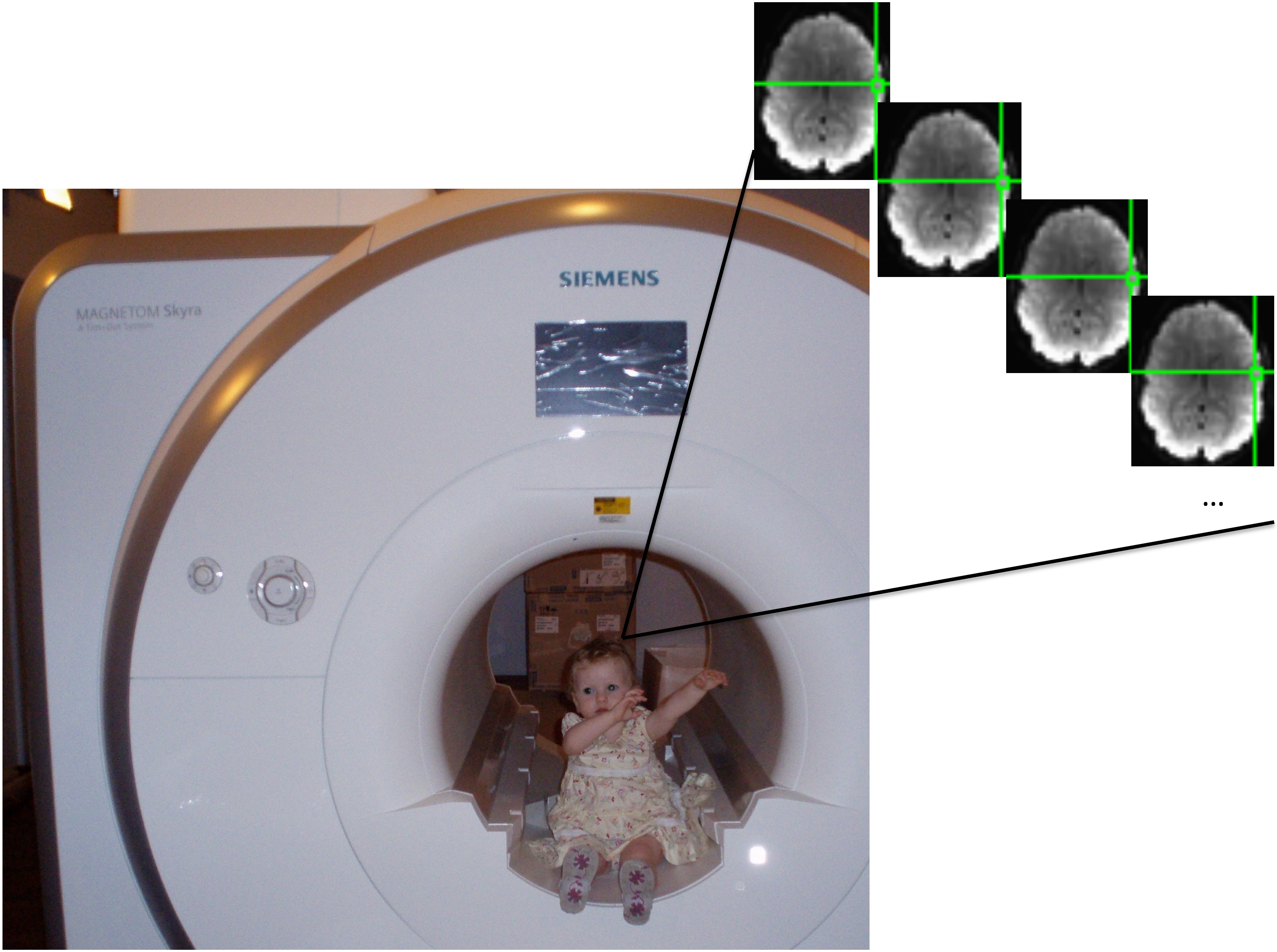
NIH fMRI Summer Course

What’s neuronal and what’s not in fMRI

Daniel Handwerker

June 19, 2017


MAGNETOM Skyra
SIEMENS
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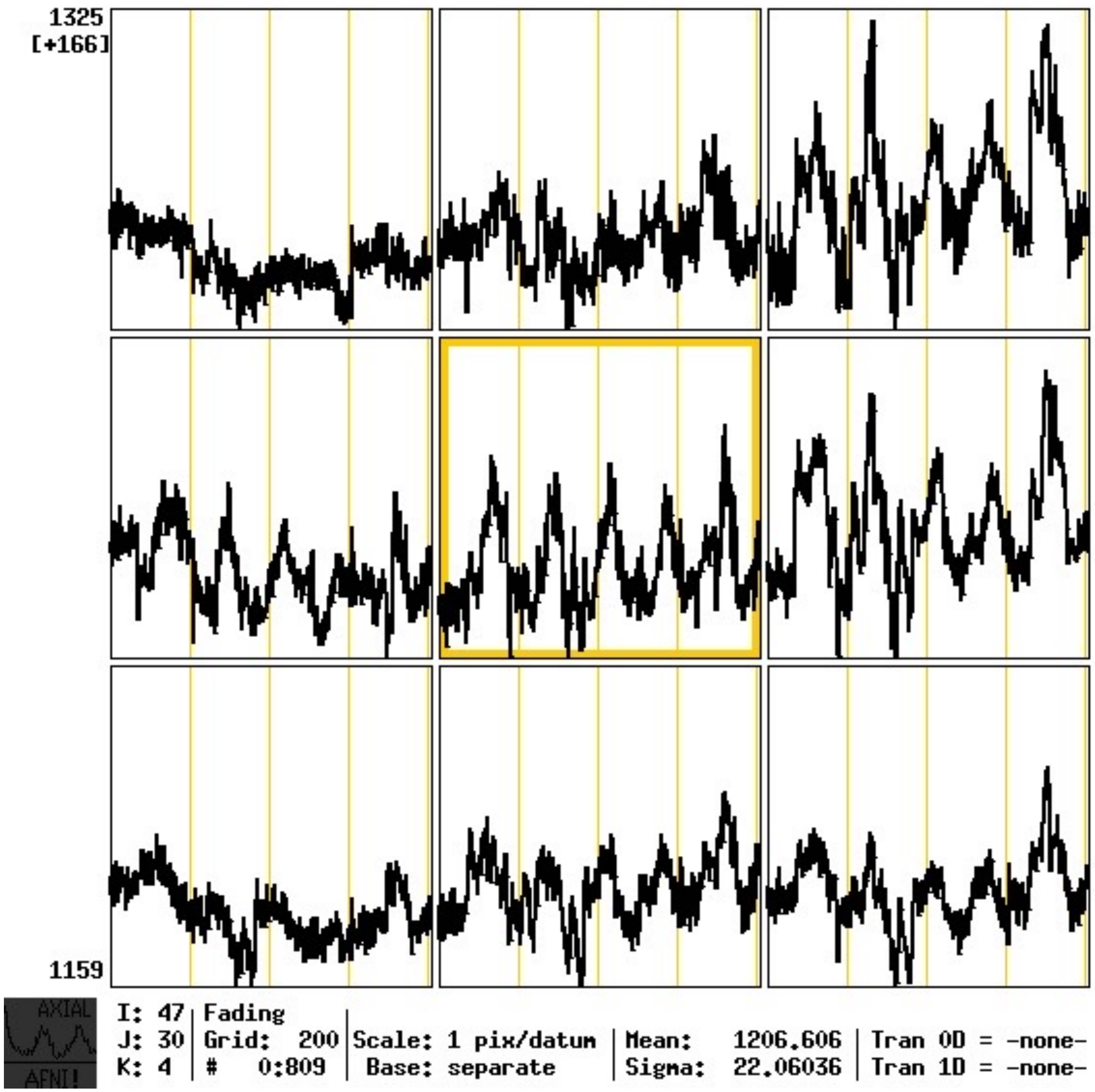
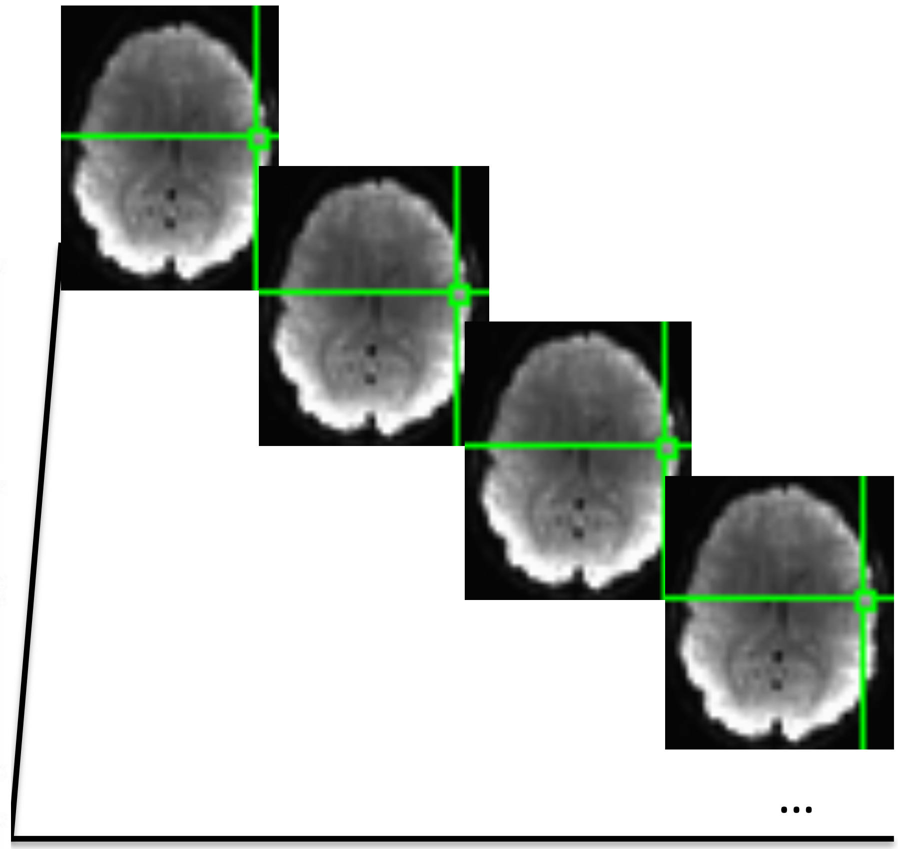
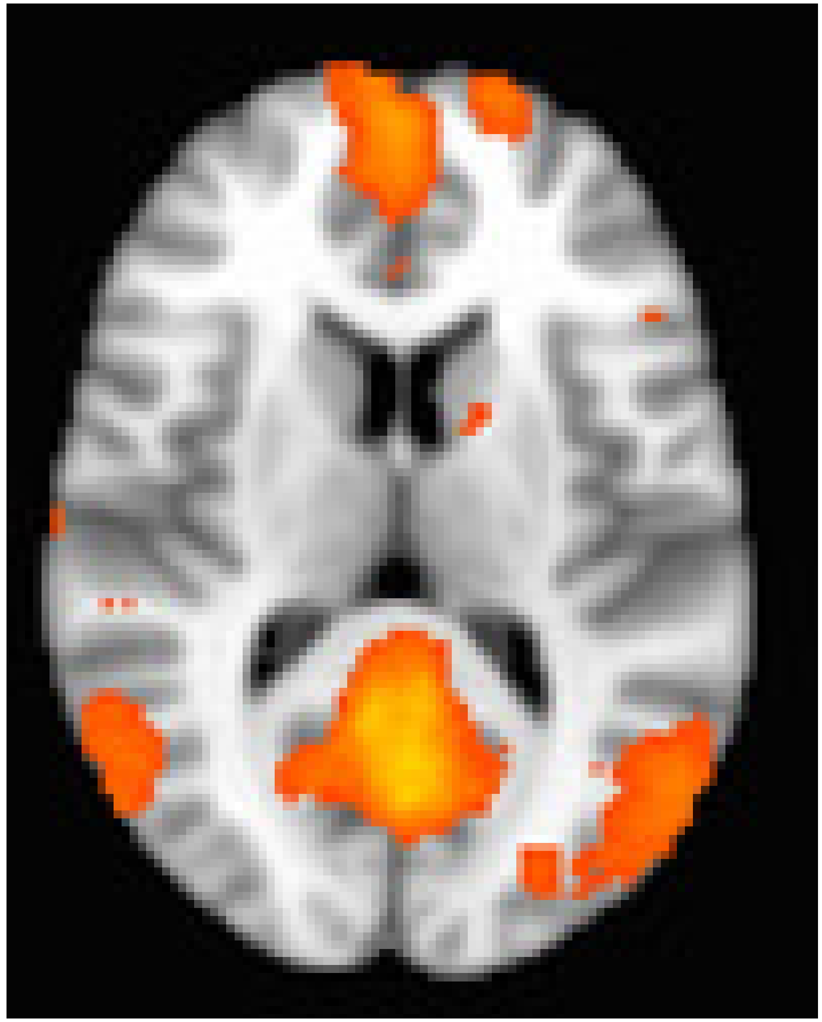
What makes us think this is neural?





5 cycles of a block design task

What makes us think this is neural?



ICA component from a resting state run

Bright & Murphy, *NeuroImage* 2015

What makes us think this is neural?

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

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

Where does this confidence come from?

Confidence for neuroscience as a field

Confidence for an individual study

Where does confidence in fMRI come from?

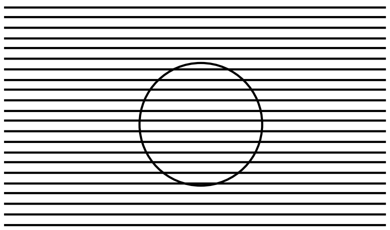
- Confidence for neuroscience as a field
  - A plausible mechanism
  - Results match our understanding of brain function
  - Complementary studies with other measures
- Confidence for an individual finding
  - Appropriate methodlogy
  - Task based fMRI
  - Resting state fMRI
  - A task based case study

Deoxy Hb is an intrinsic MRI contrast agent

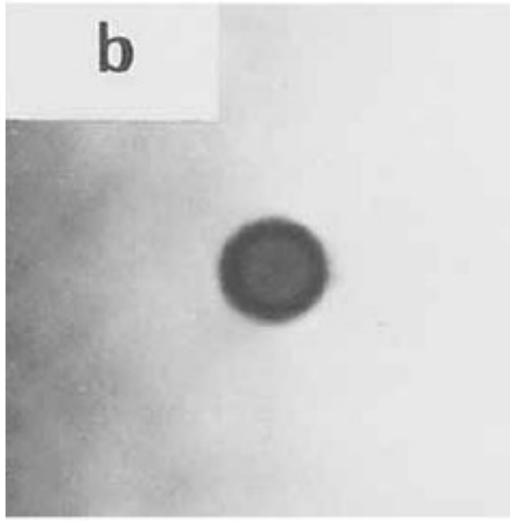
in vitro

in vivo

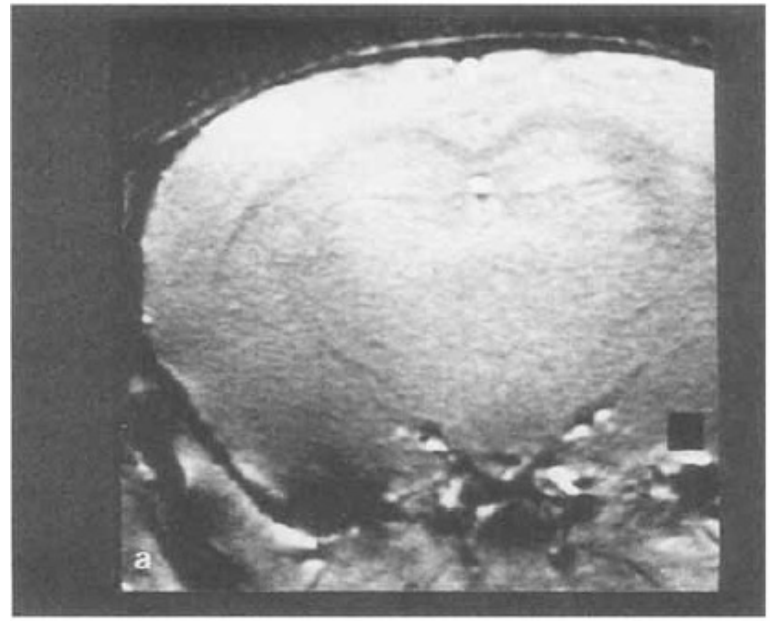
Oxygenated hemoglobin



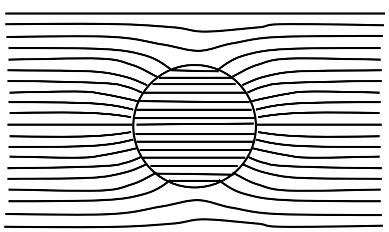
100% oxygenated blood



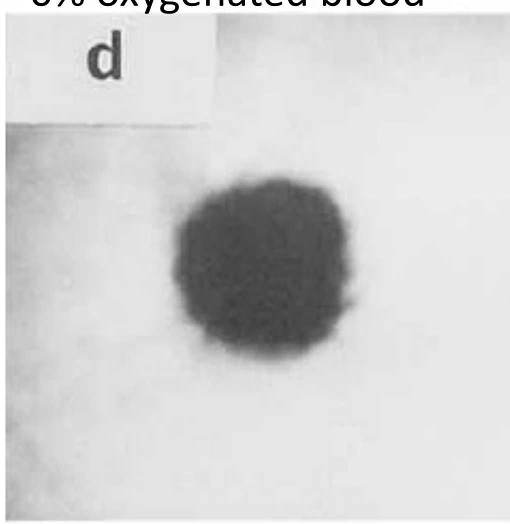
100% O_2



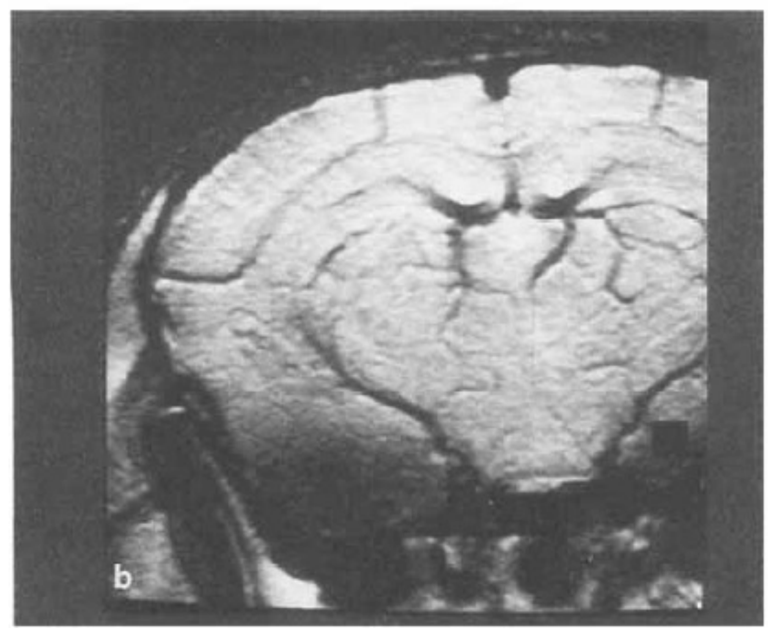
Deoxygenated hemoglobin



0% oxygenated blood



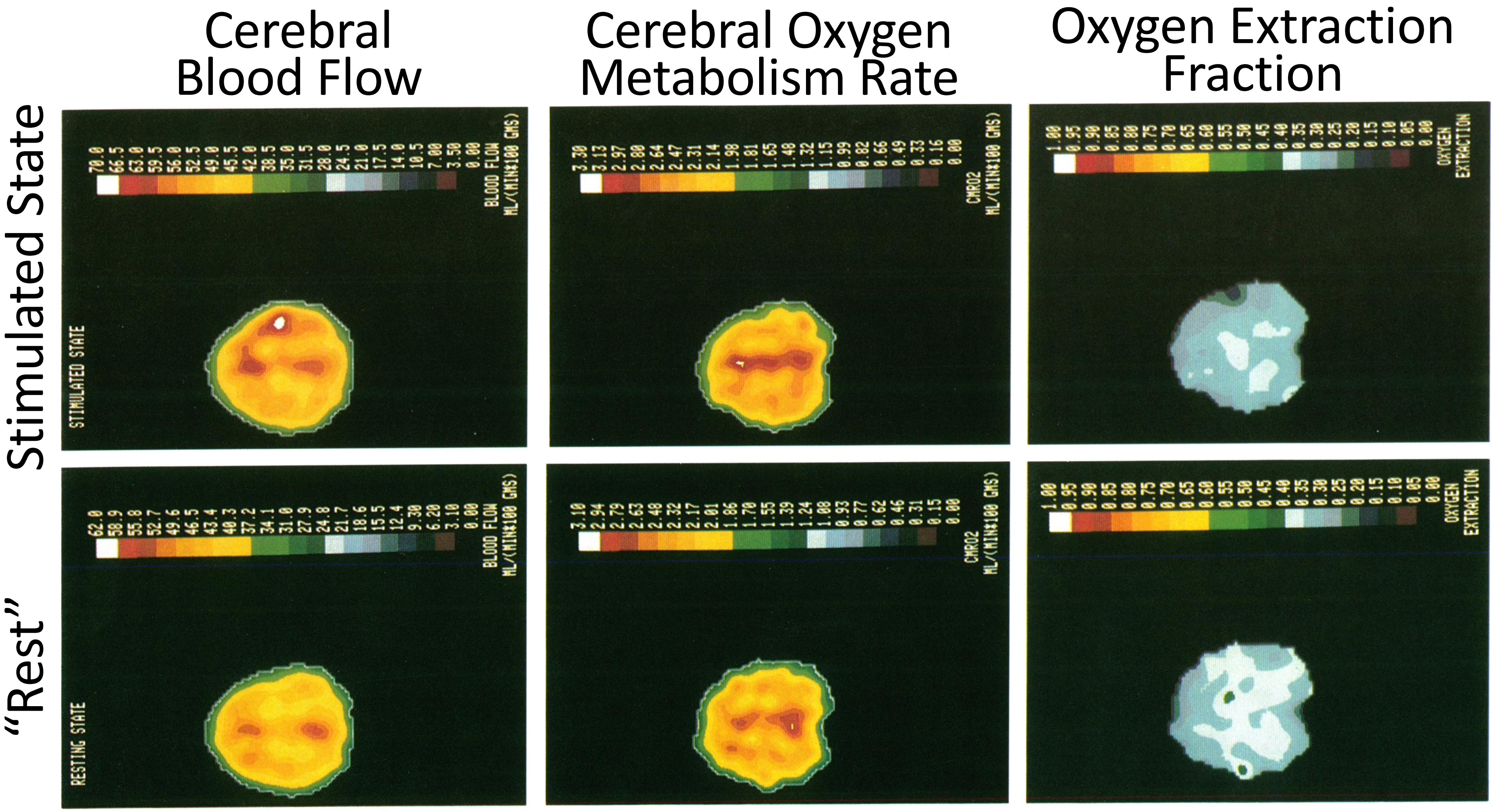
20% O_2



BOLD
Blood Oxygen
Level Dependent

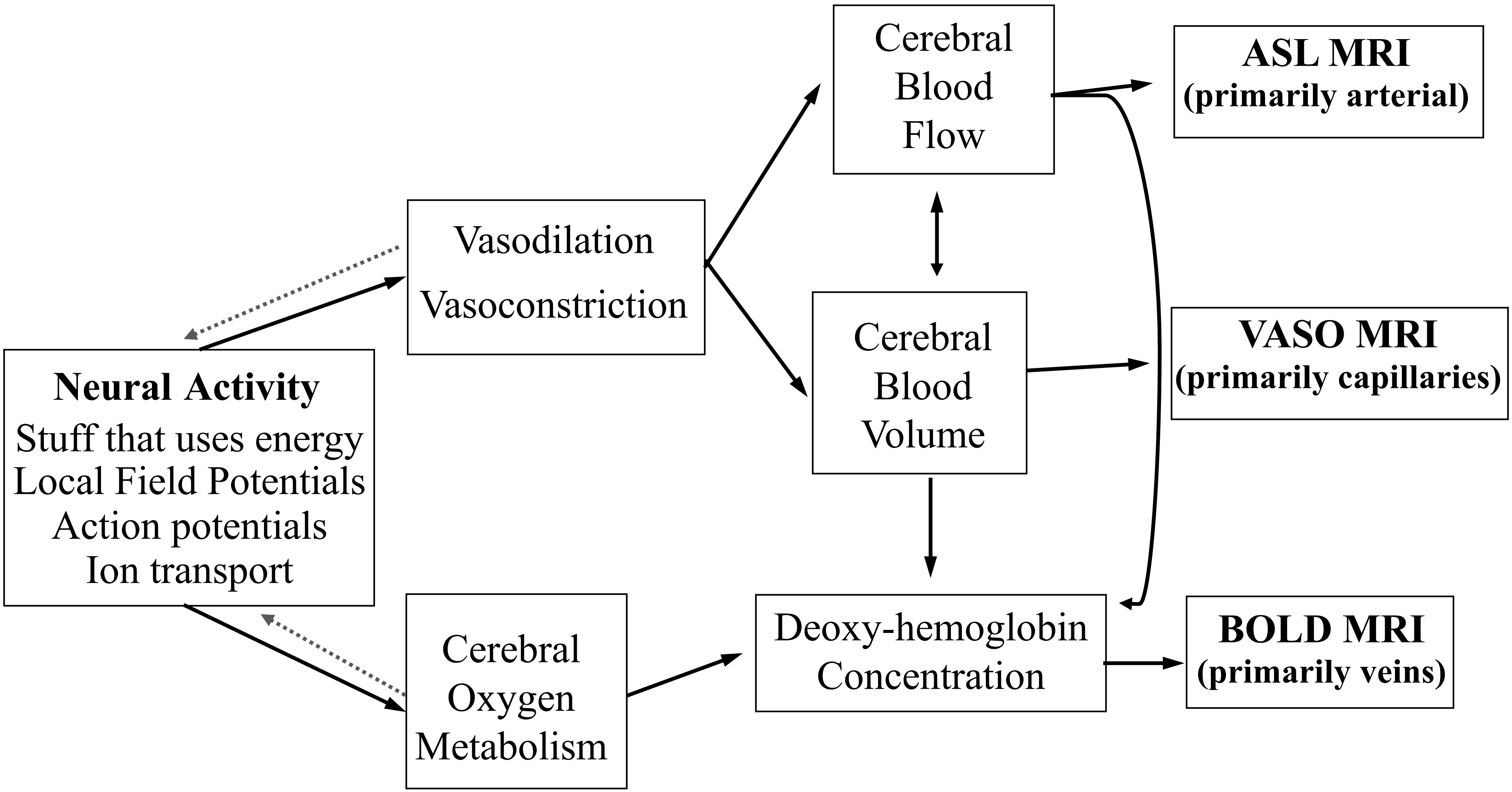
S. Ogawa, T.-M. Lee, A. S. Nayak, P. Glynn, Magn. Reson. Med, 14, 68-78 (1990)

Plausibility: The mechanism behind fMRI



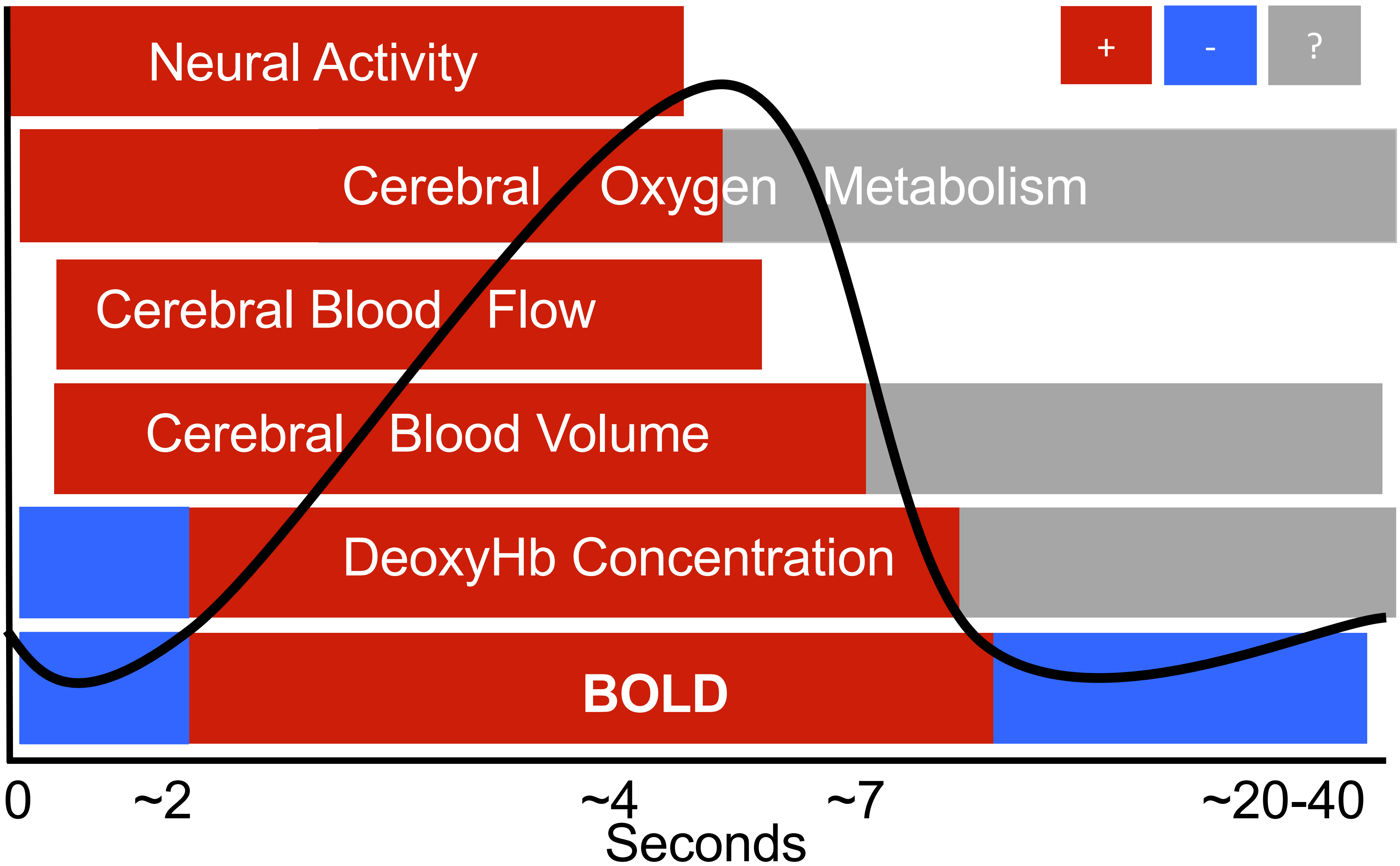
CBF goes up more than CMR_{O2}. This uncoupling produces a highly significant decrease in the local OEF (-19% of mean), indicating that tissue P_{O2} rose during stimulation.

Fox & Raichle, PNAS, Feb, 1986



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

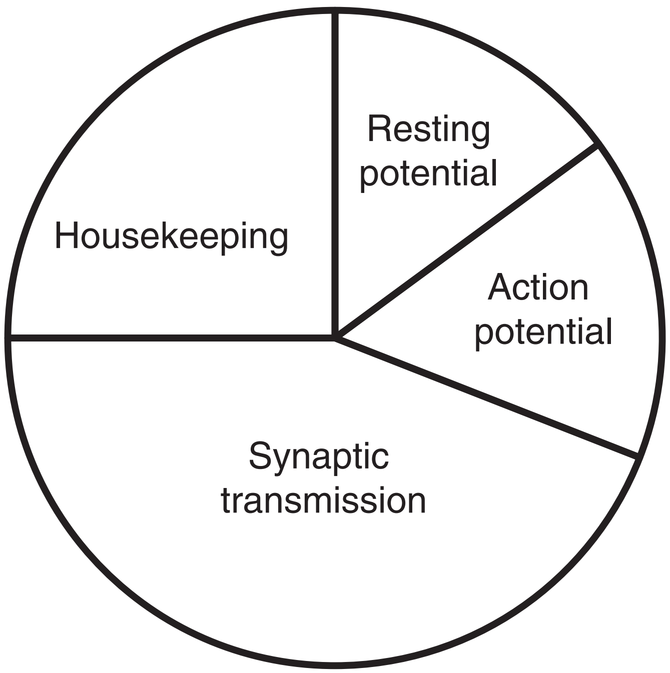
The fMRI BOLD time course



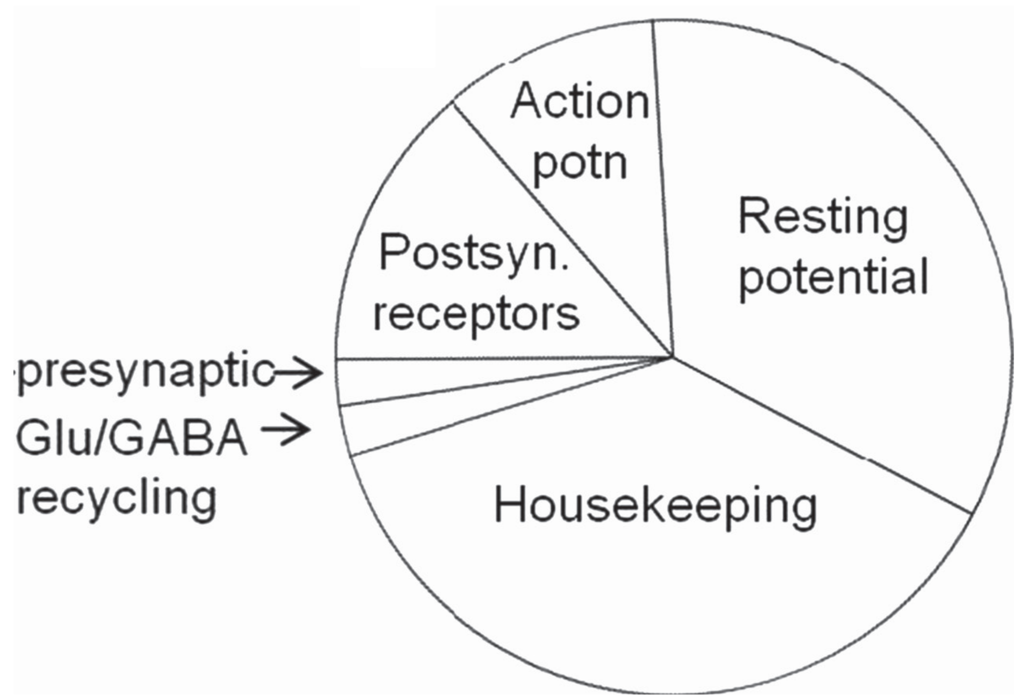
This shows what happens, not why it happens

What types of neural activity use energy?

Cerebral Cortex

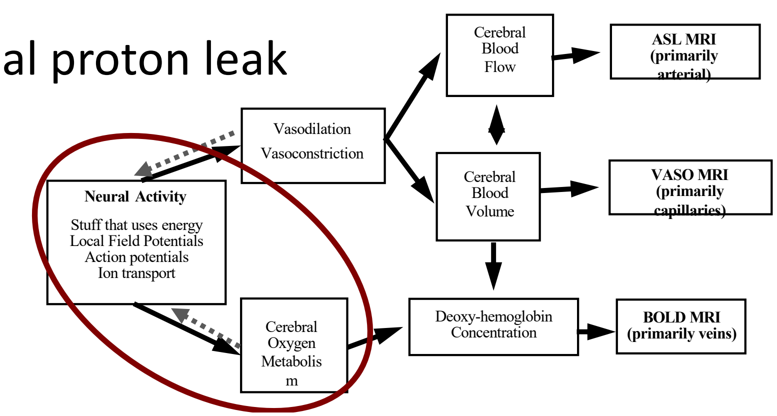


Cerebellar Cortex

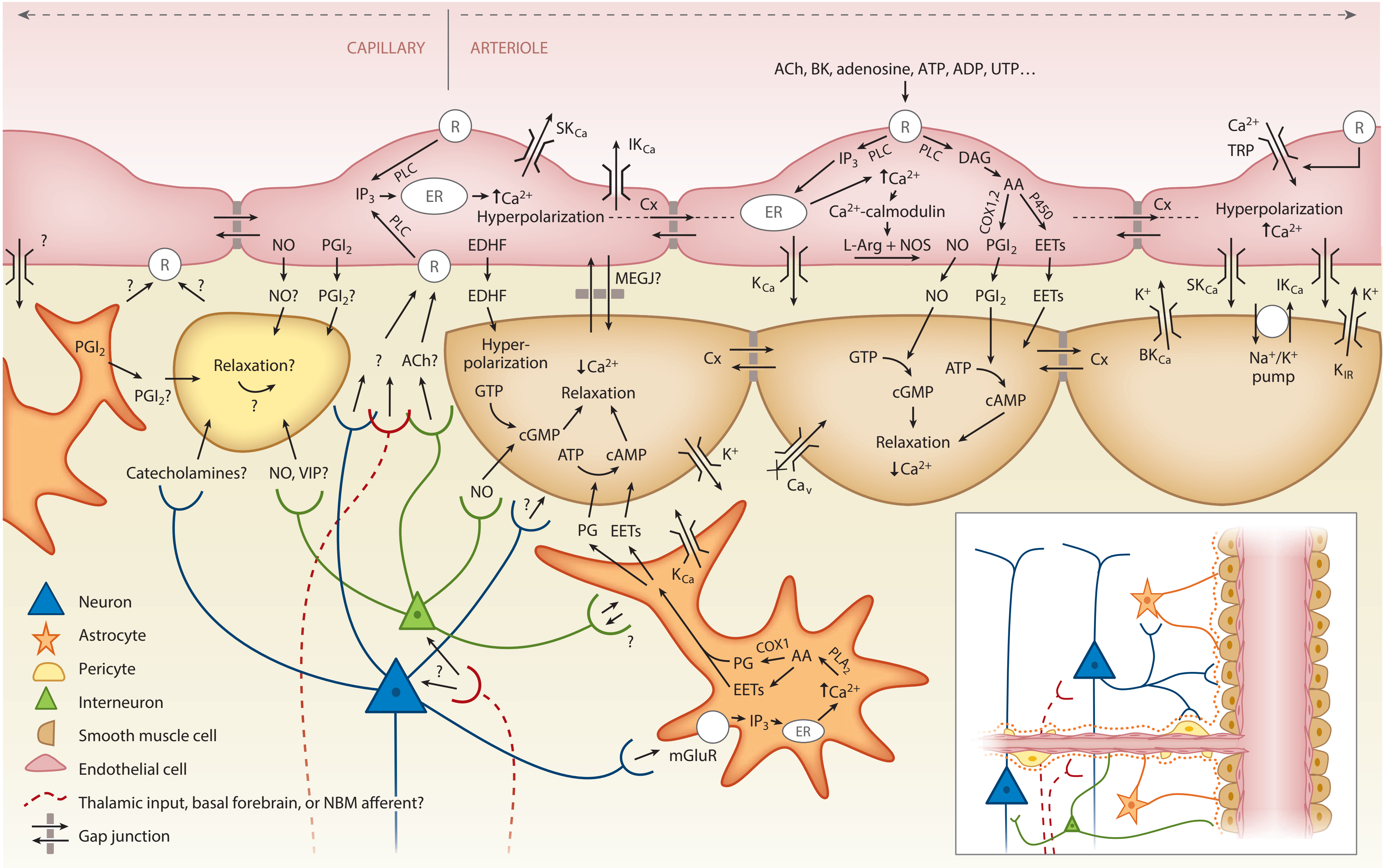


Howarth, Gleeson, & Attwell, JCBFM 2012

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

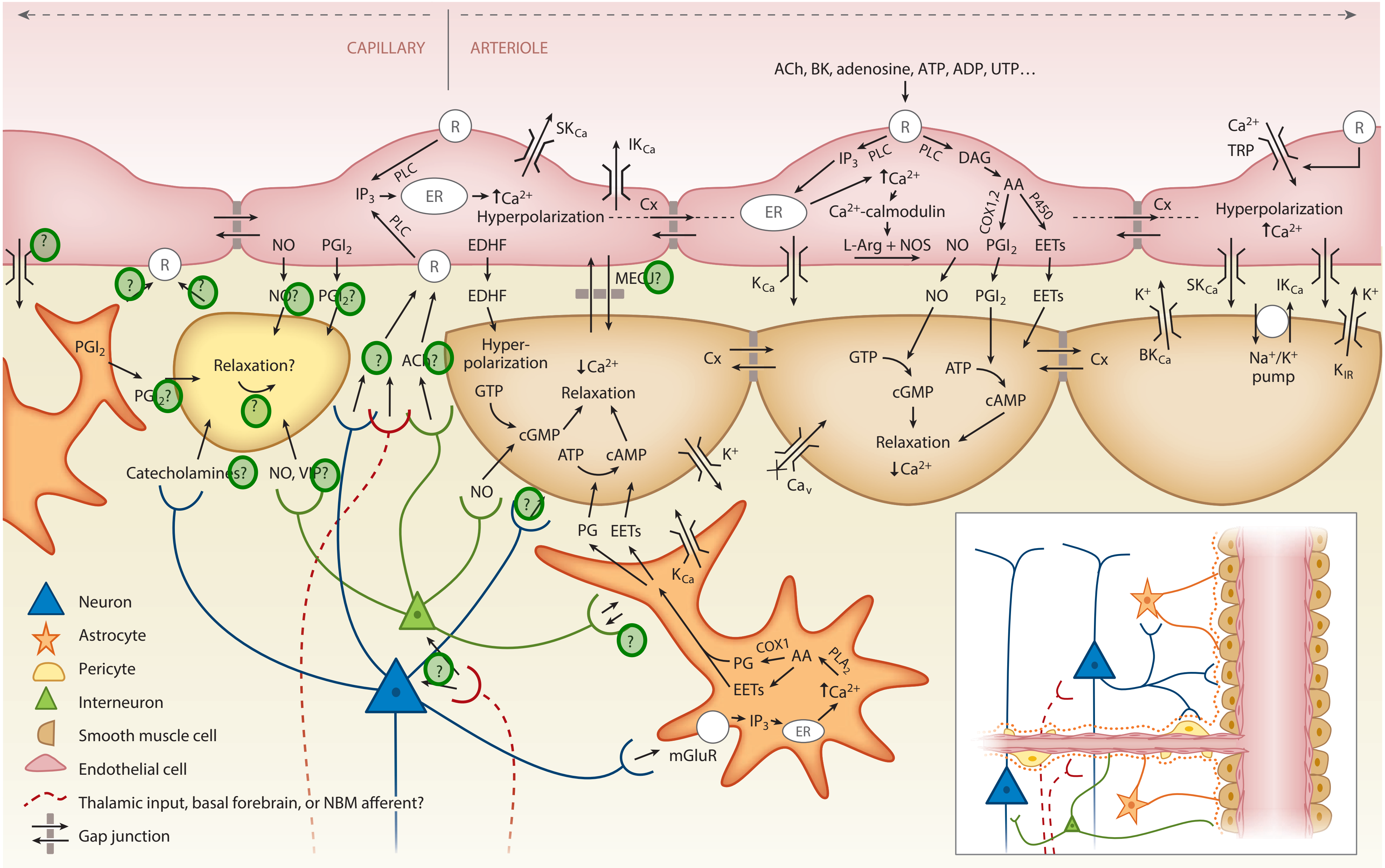


We know a lot about neurovascular coupling
It's not directly driven by oxygen or energy needs



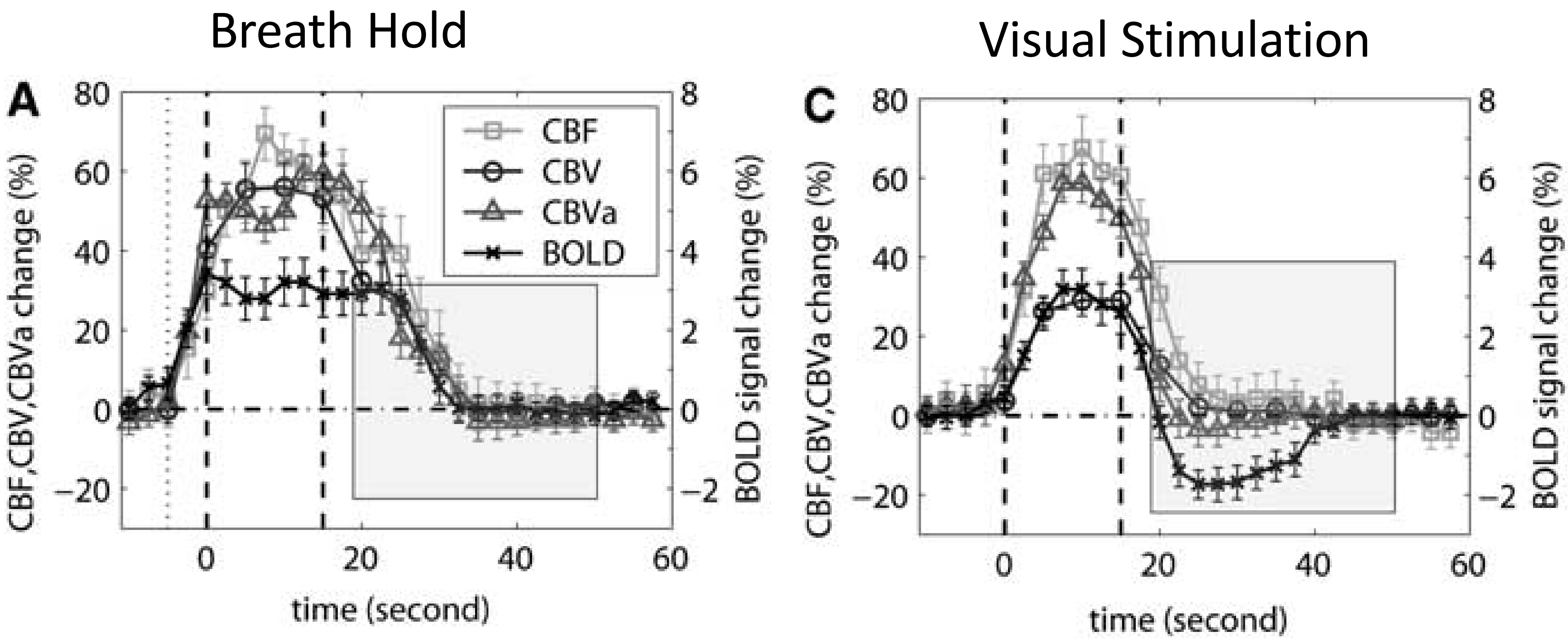
Elizabeth Hillman, Annual Review of Neuroscience 2014. 37:161–81

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



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

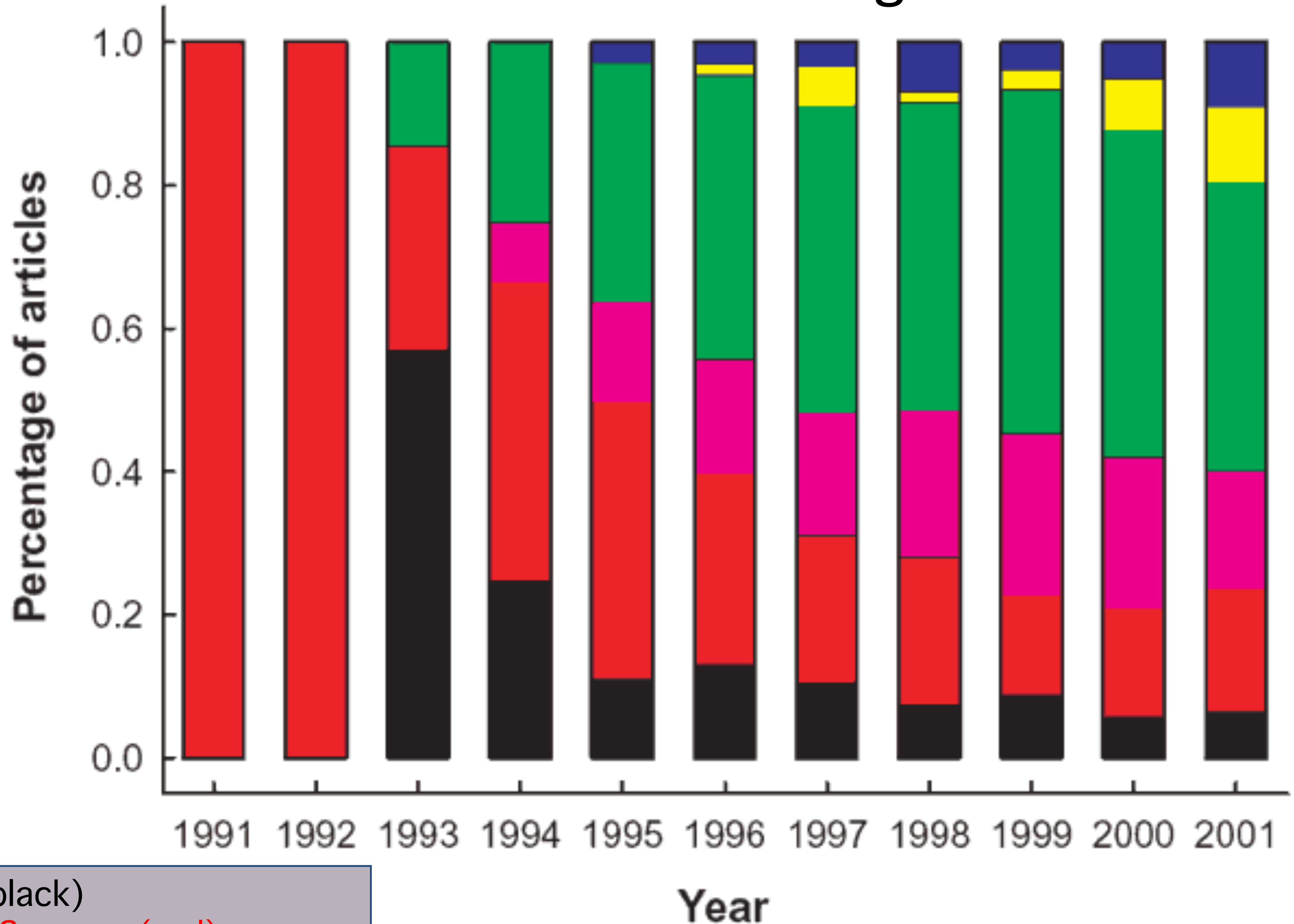
One example of neurovascular coupling complexity



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

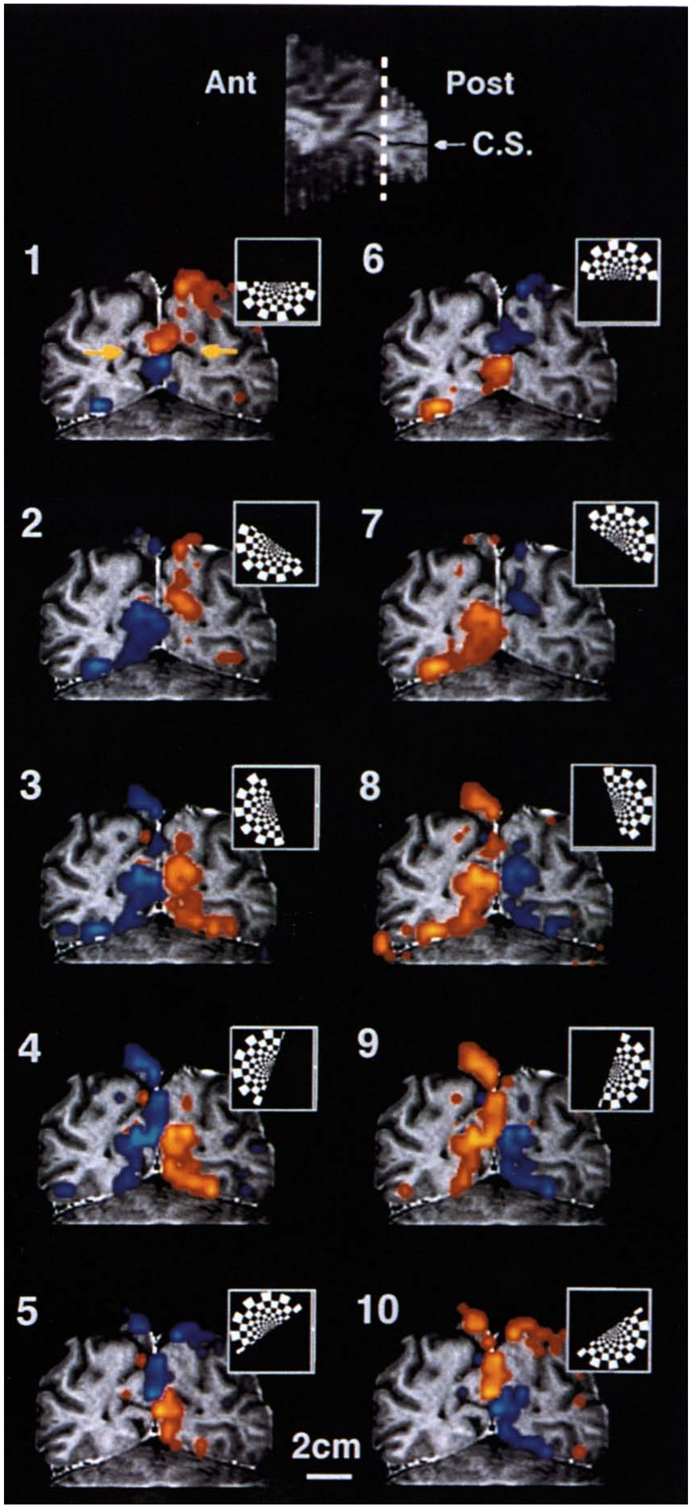
Why believe fMRI is neural?
fMRI results match our understanding of brain function



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

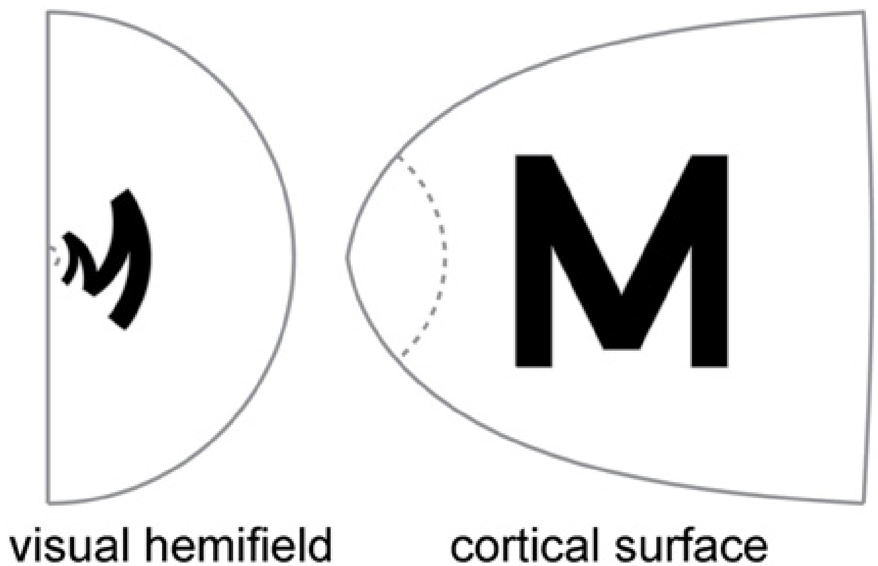
J. Illes, M. P. Kirschen, J. D. E. Gabrielli, Nature Neuroscience, 2003

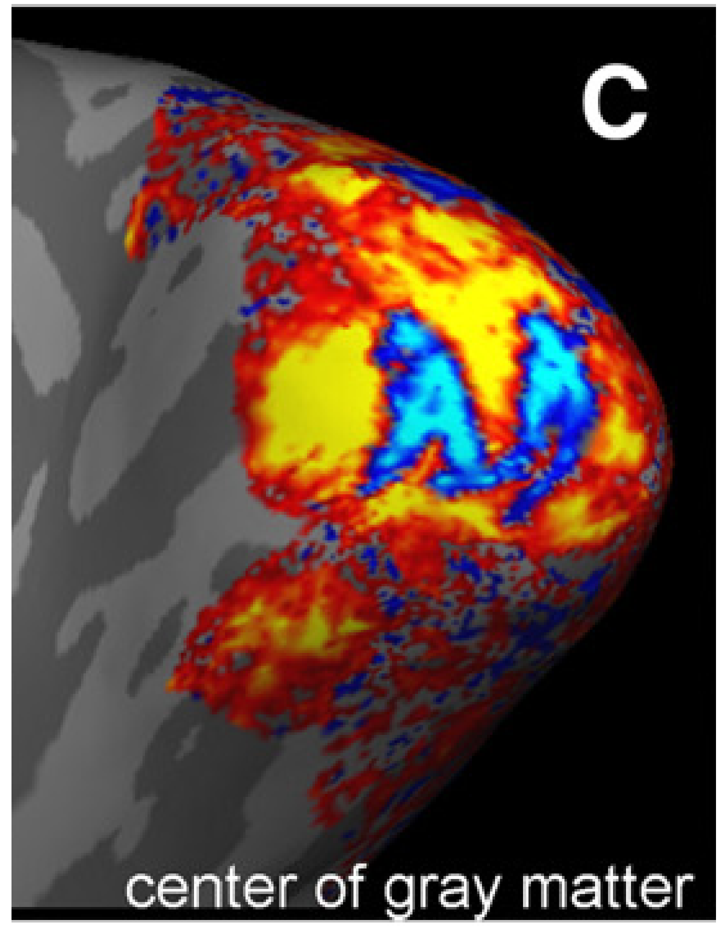
fMRI can show retinotopy in primary visual cortex



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

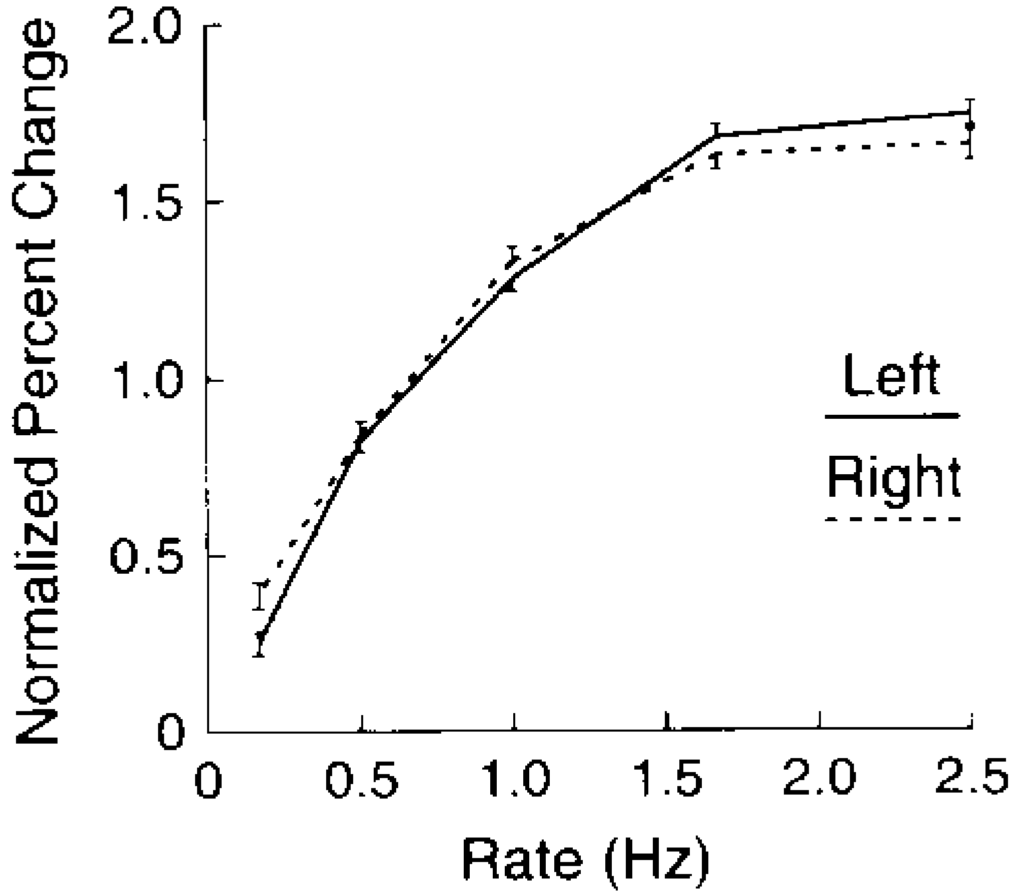
fMRI can have very predictable retinotopic mapping





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

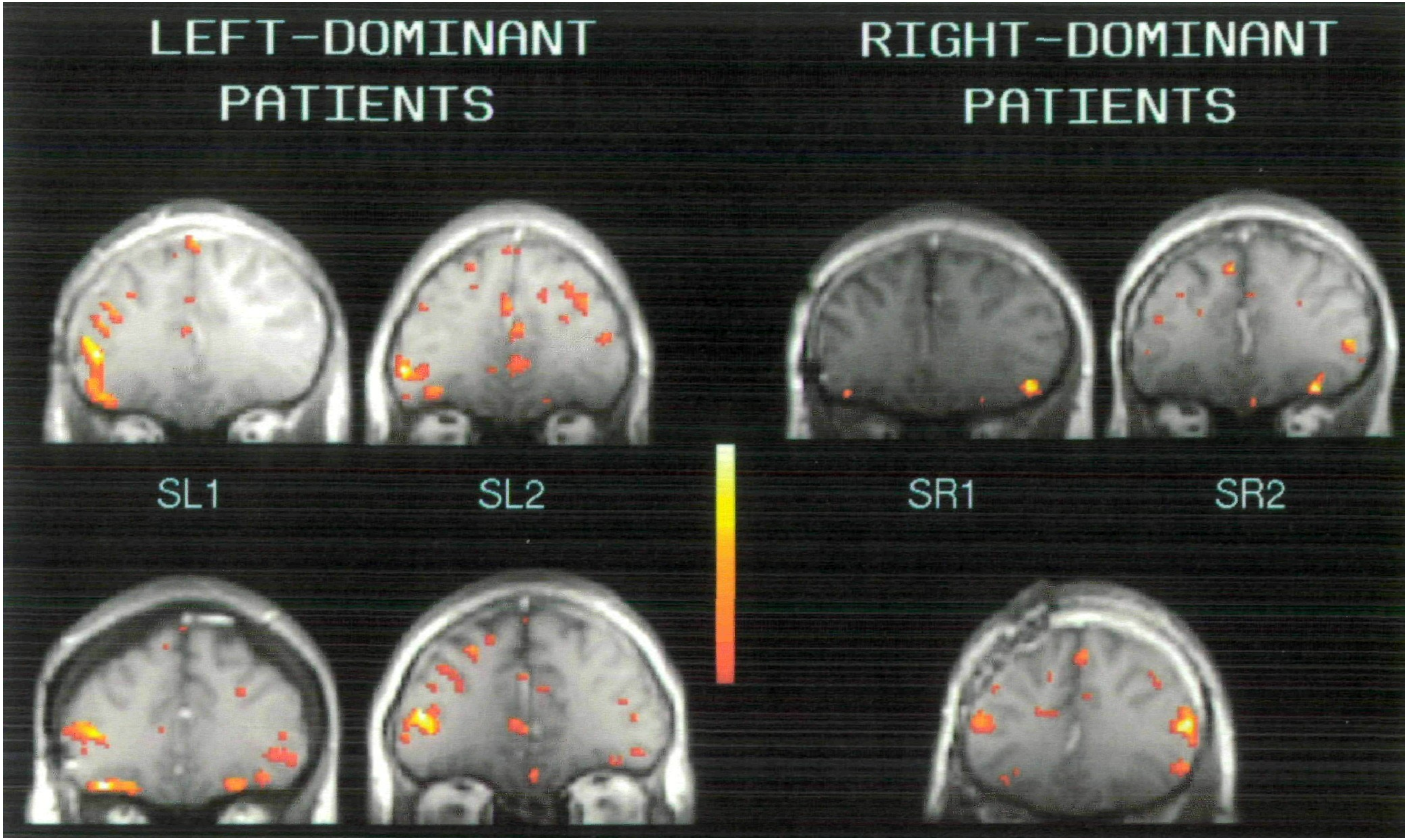
BOLD magnitude scales with auditory stimulus rate



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

Binder et al 1994 Cognitive Brain Research

Language dominance compared to the WADA test

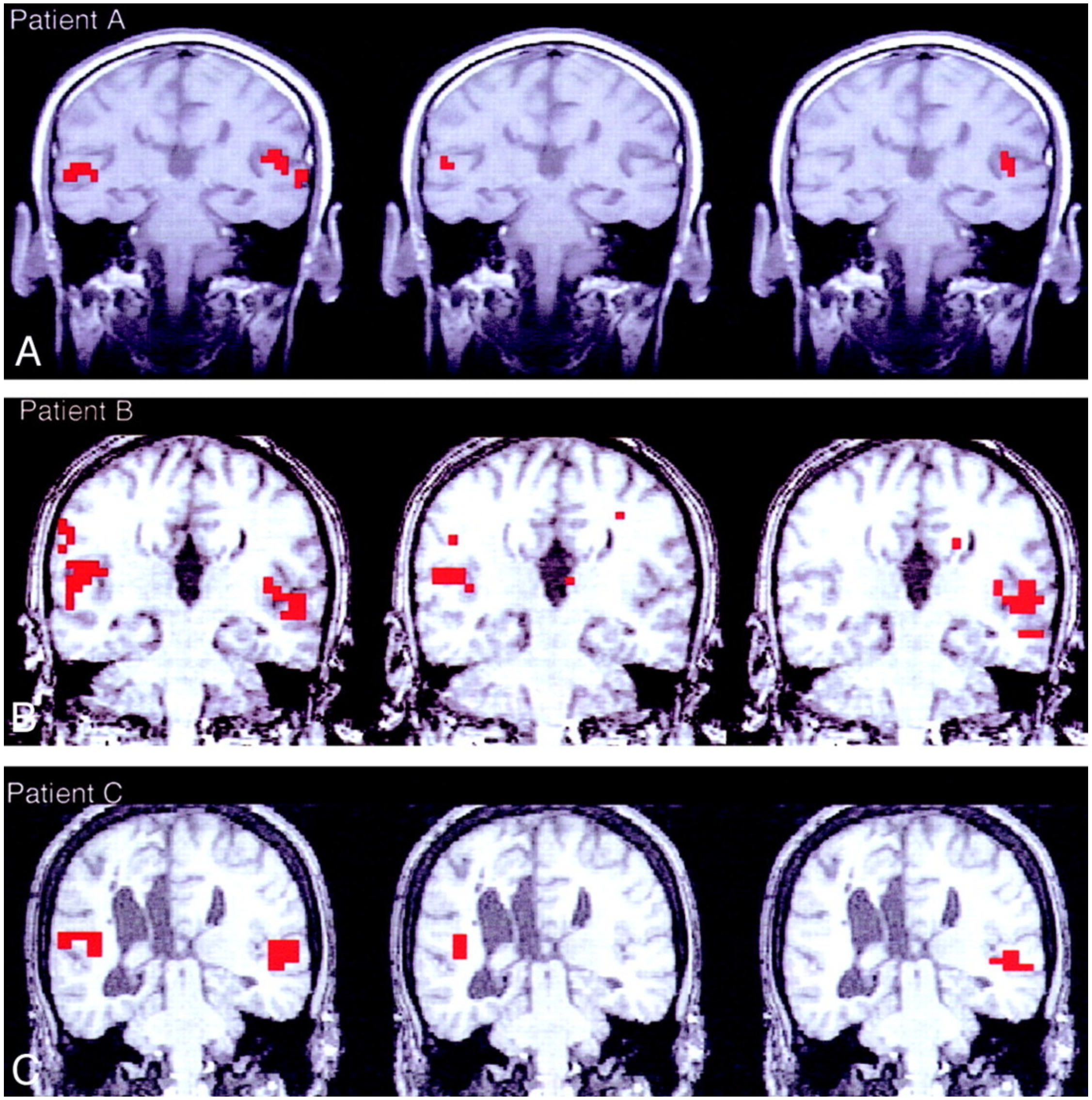


Desmond, et al 1995. Functional MRI measurement of language lateralization in Wada-tested patients. Brain

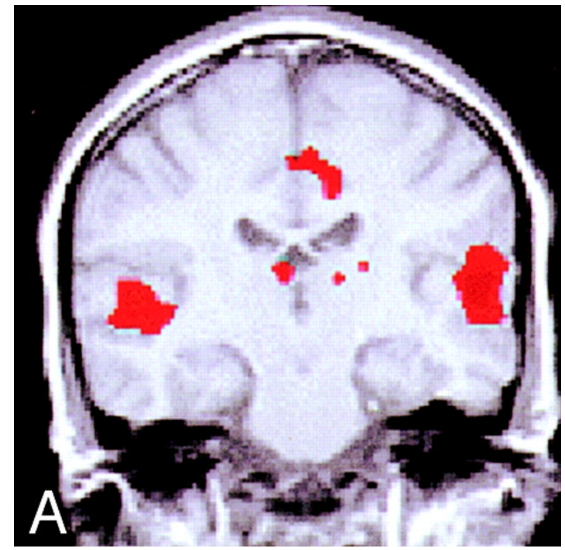
Agenesis of the corpus callosum

Activation from a text listening task

Right and left auditory seeds in resting data



Connectivity map from a healthy volunteer

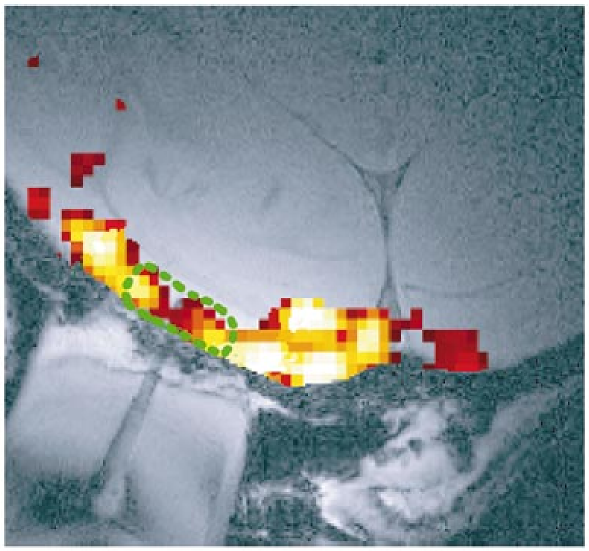


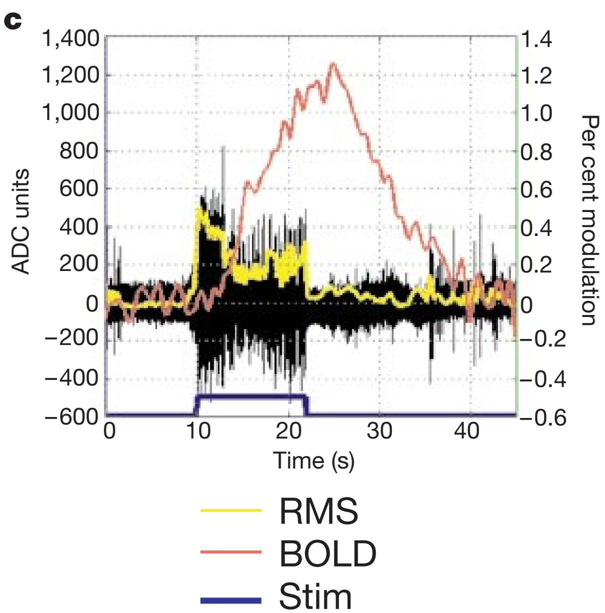
Quigley et al AJNR 2003

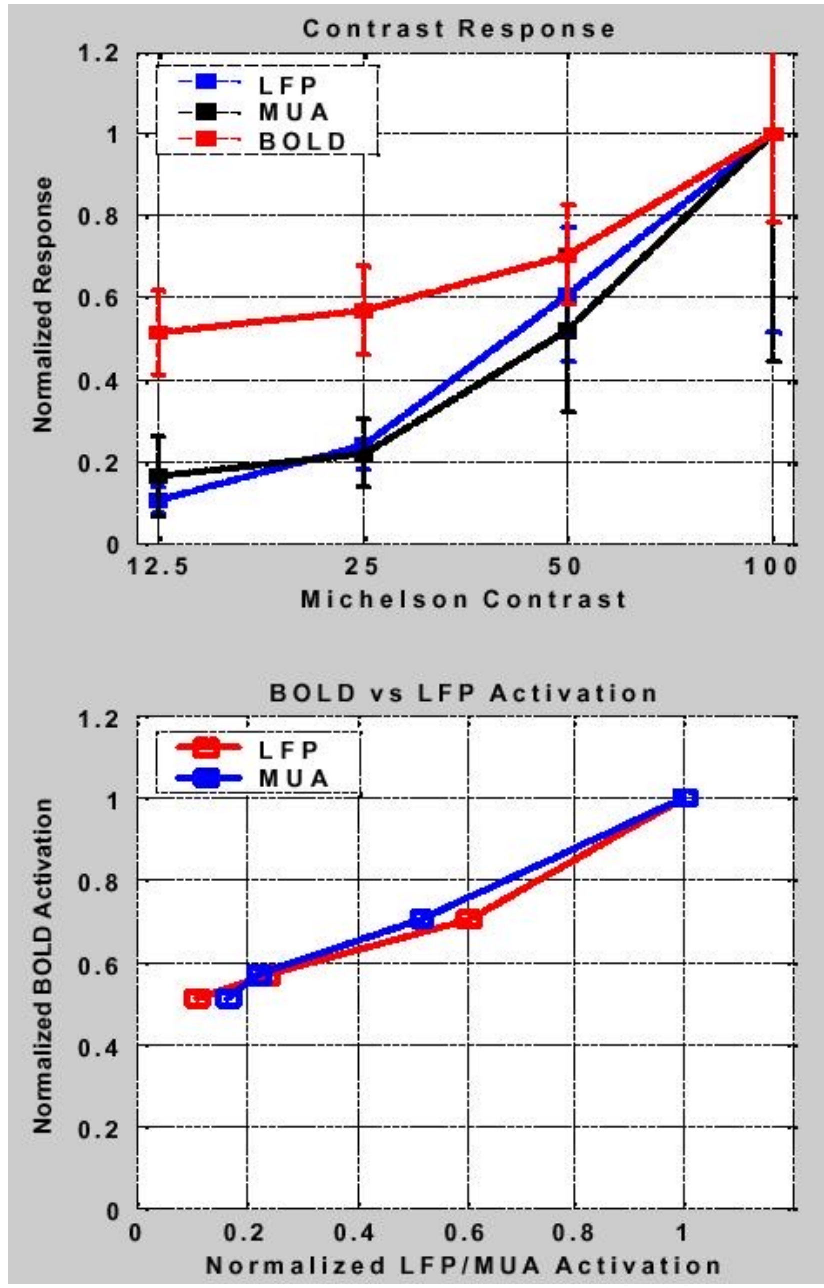
An acallosal patient was first presented by Lowe et al Neuroimage 9:S422 1999

Vasculature is still symmetric, but bilateral neurons are not connected

Why believe fMRI is neural? Complimentary modalities







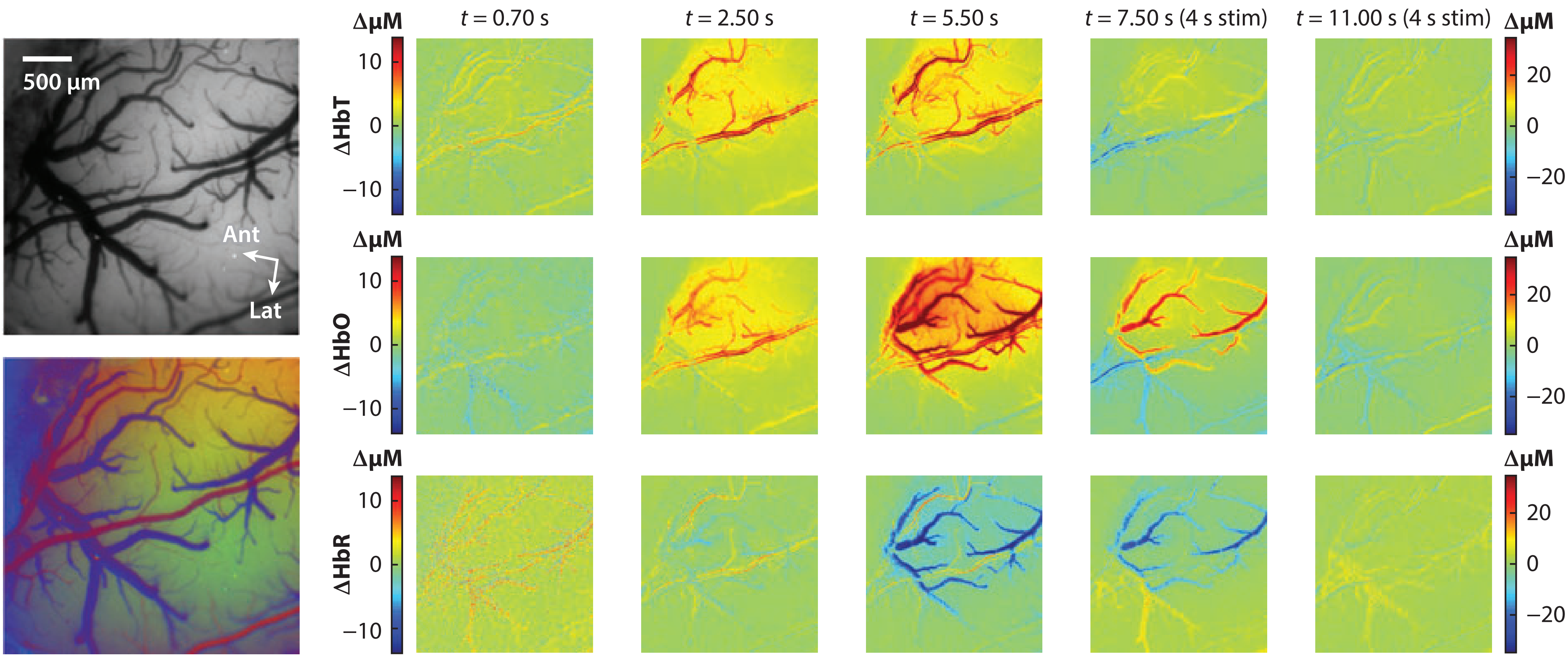
Logothetis also showed that the LFP time courses have a slightly better linear fit than multi-unit spiking activity

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

How is neurovascular coupling studied?

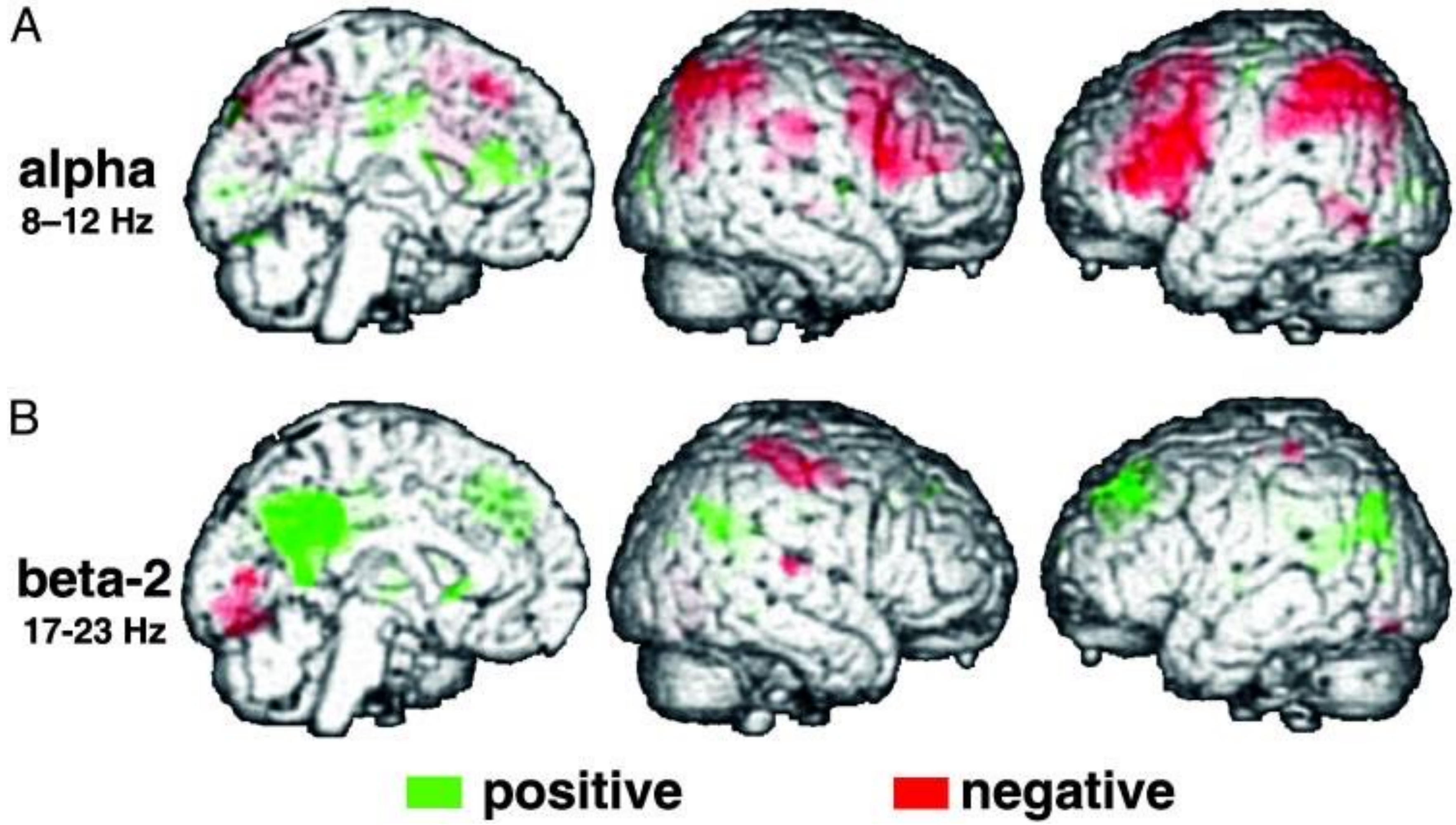
- Humans, non-human primate, rodents…
- Mostly in alive animals but:
  - Awake/asleep, Task/Rest
  - With/without anesthesia
- Imaging tools:
  - two-photon imaging, laser dopler, other optical imaging, MRI, EEG, electrophysiology, ...
- Systemic manipulations
  - Manipulations for visualization (i.e. Calcium imaging)
  - Manipulations for perturbing the system: Changing inhaled gases, disrupting cellular pathways, changing local or global neural activity

Optical measures



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

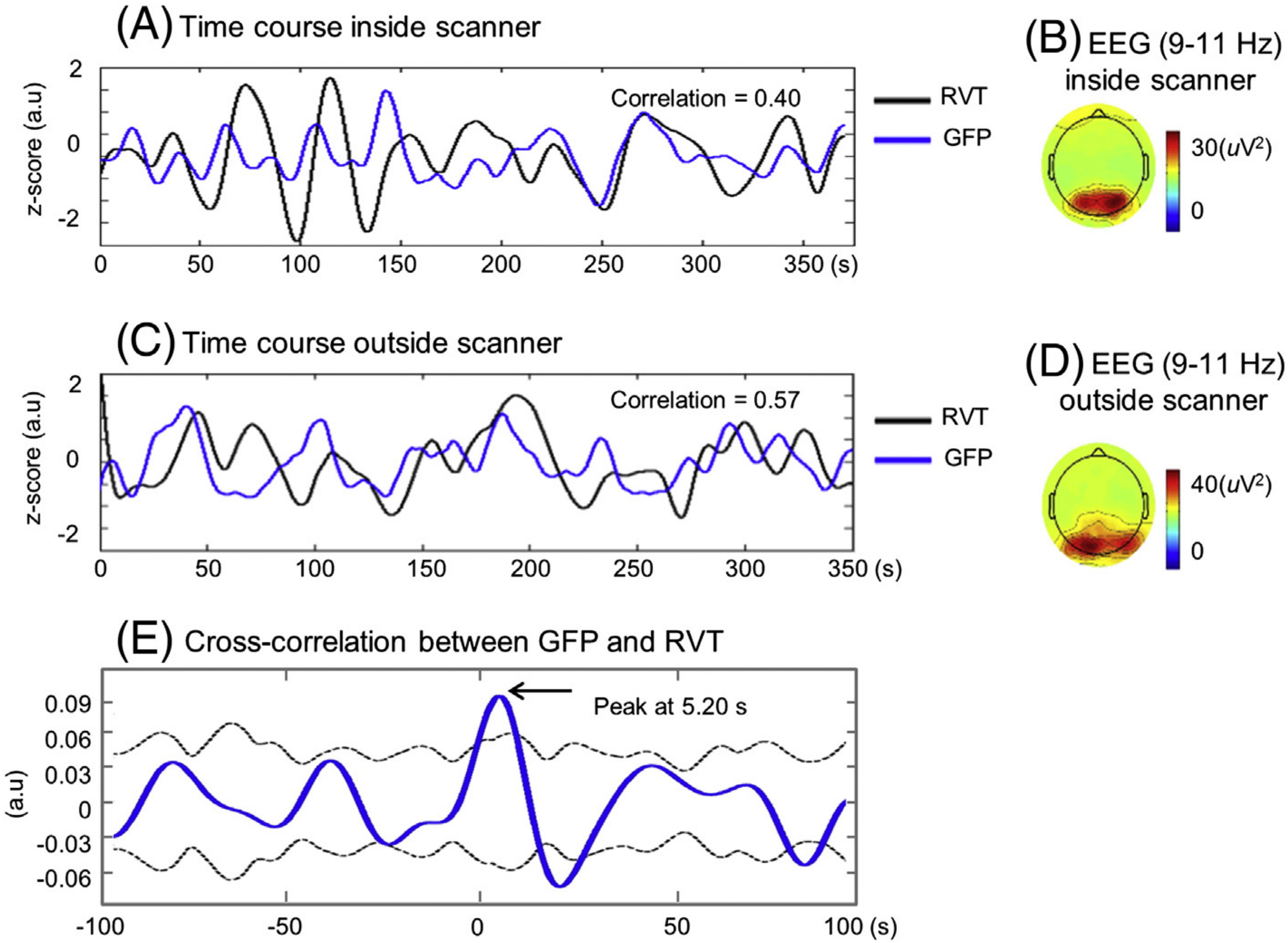
fMRI relationship to EEG



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

Laufs et al PNAS 2003

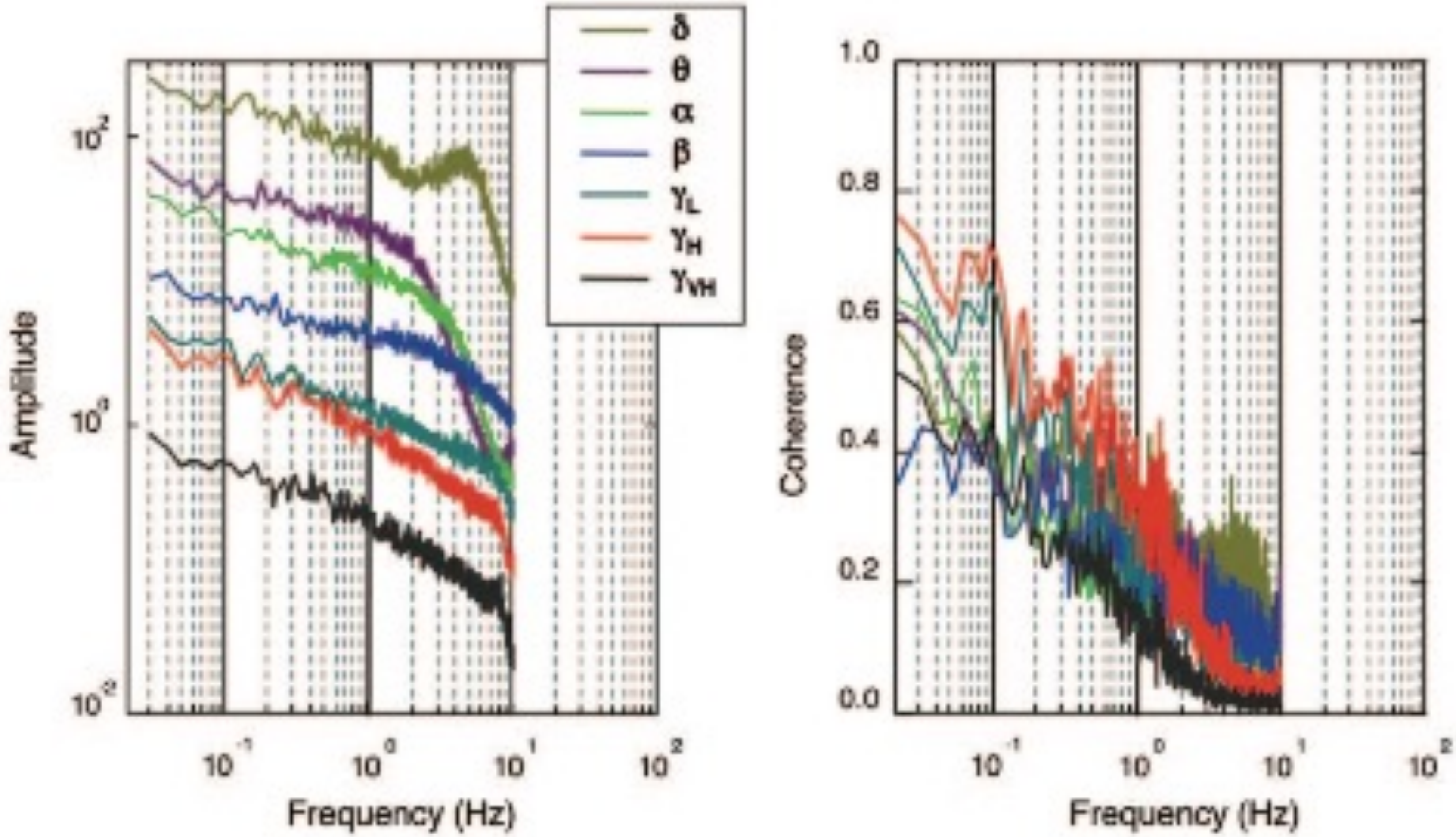
The EEG/fMRI rest relationship isn't simple



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

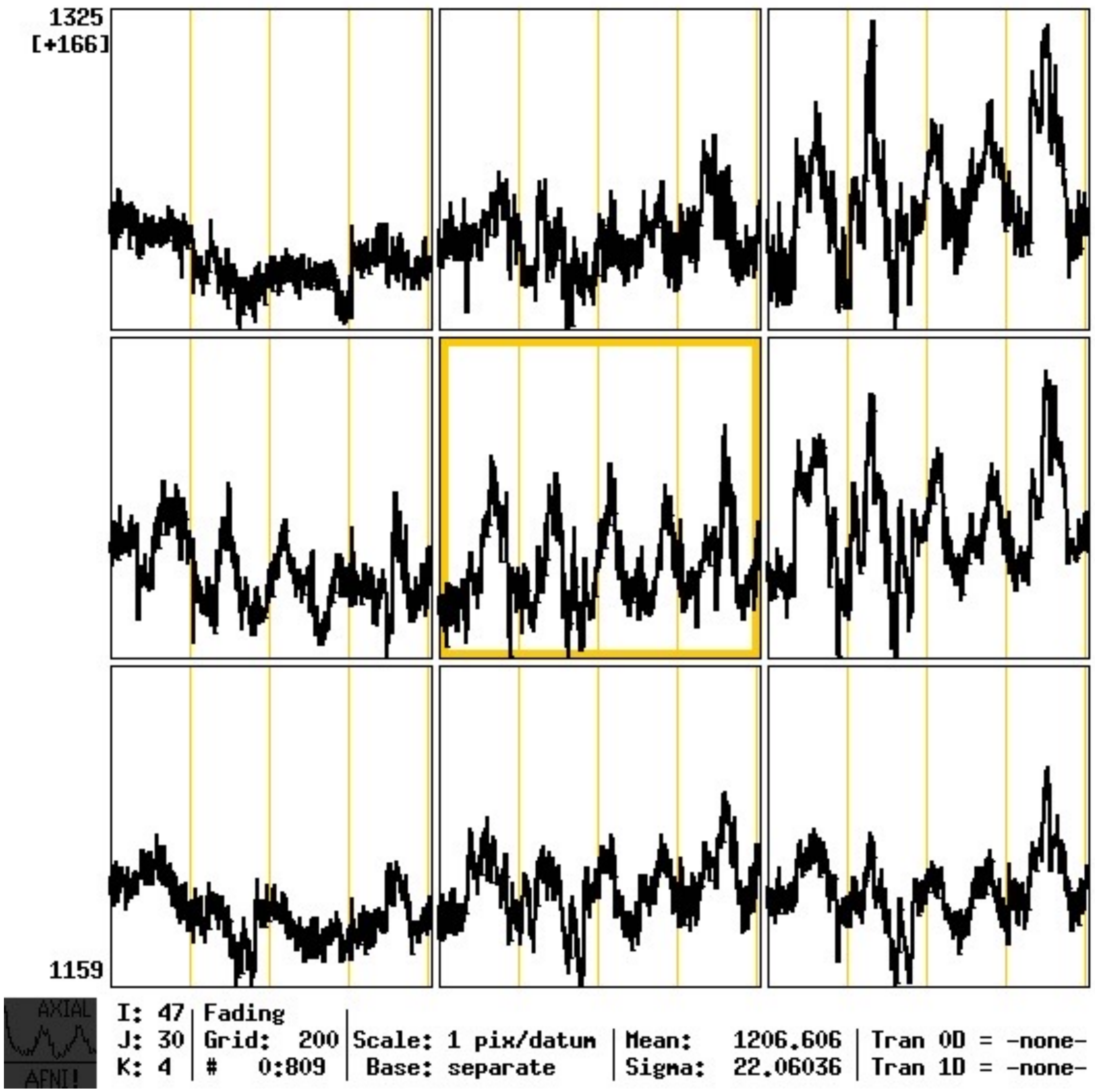
Based on a slide from M Lowe

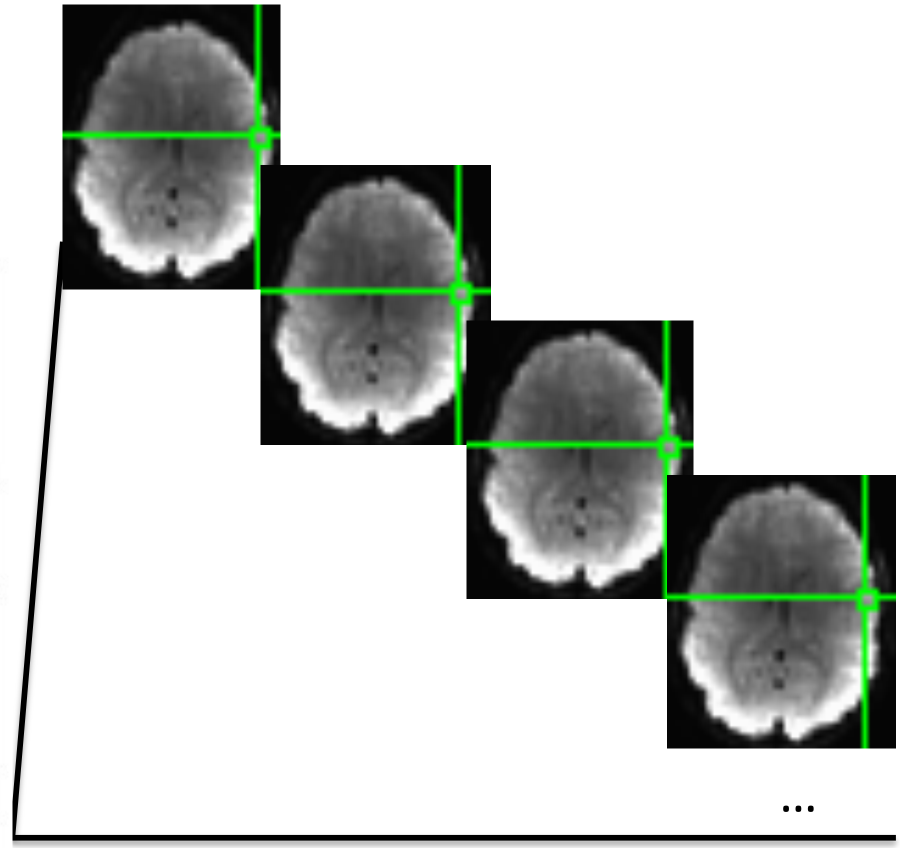
Why believe that a specific fMRI study represents neural activity?

Where does confidence in fMRI come from?

- Confidence for neuroscience as a field
  - A plausible mechanism
  - Results match our understanding of brain function
  - Complementary studies with other measures
- Confidence for an individual study
  - Task based fMRI
  - Resting state fMRI
  - A task based case study

How do we know this is neural?

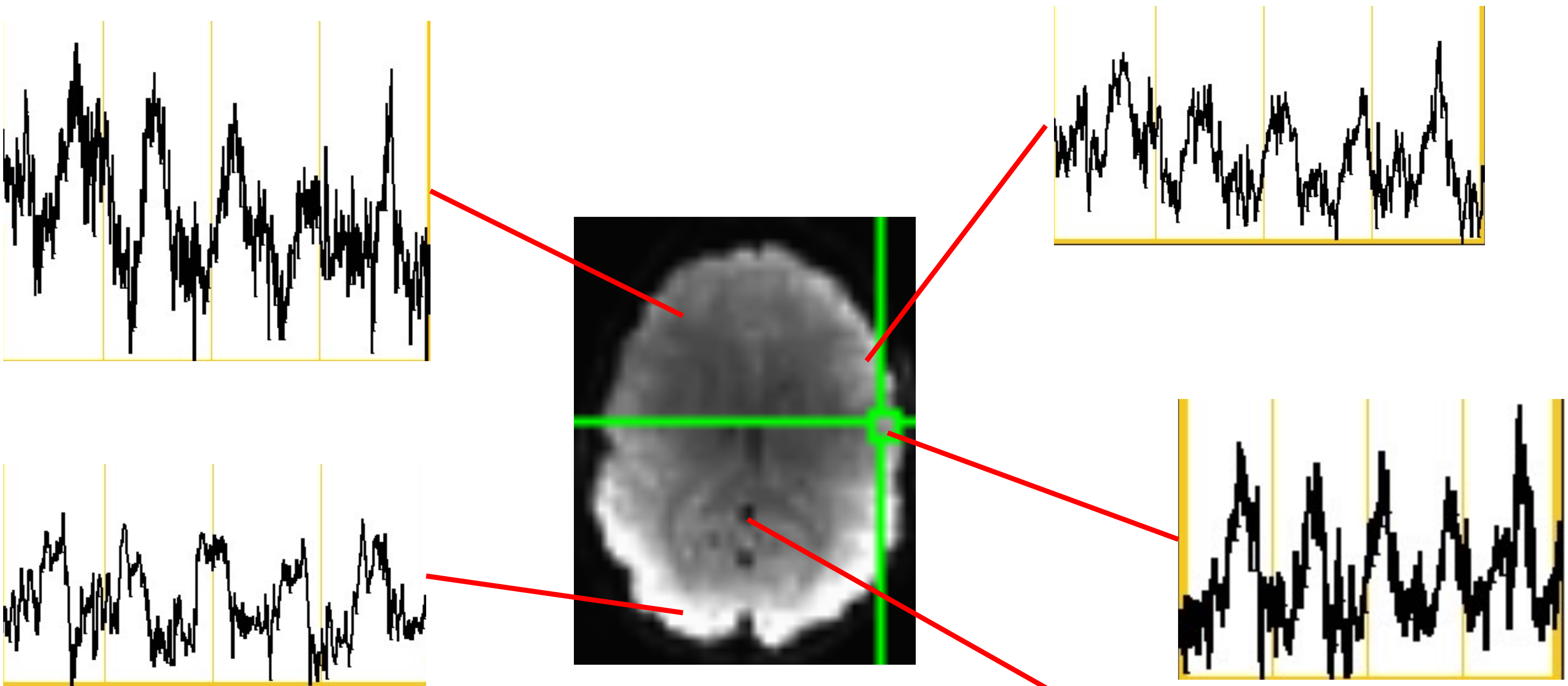


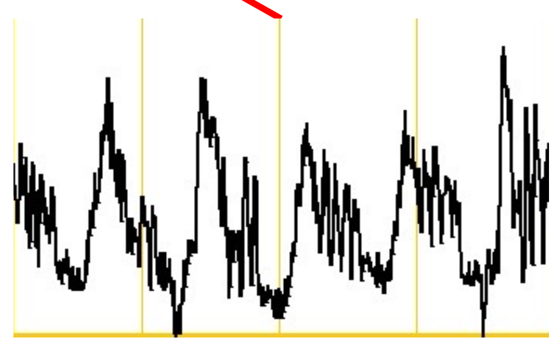


5 cycles of a block design task

How do we know this's is neural?

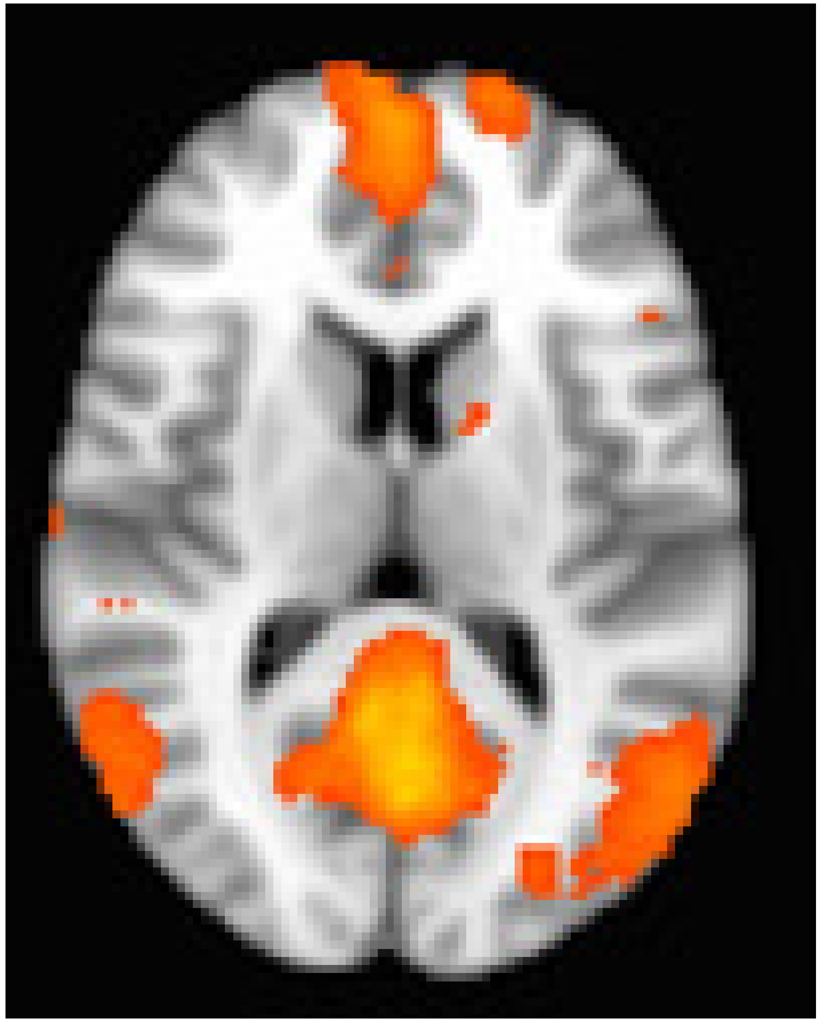
This probably isn't neural





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

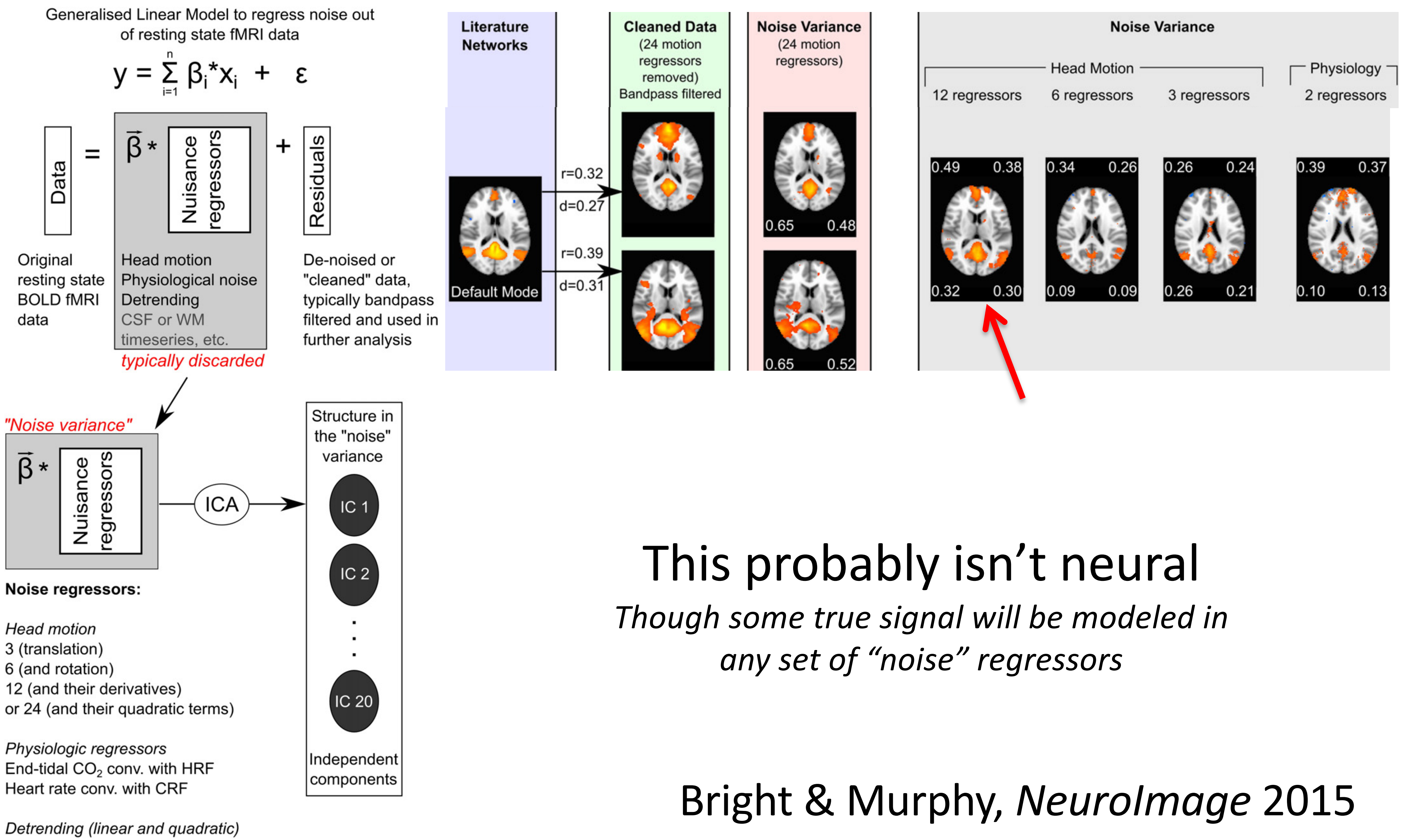
How do we know that this is neural?



ICA component from a resting state run

Bright & Murphy, *NeuroImage* 2015

The map is from the motion-correlated noise

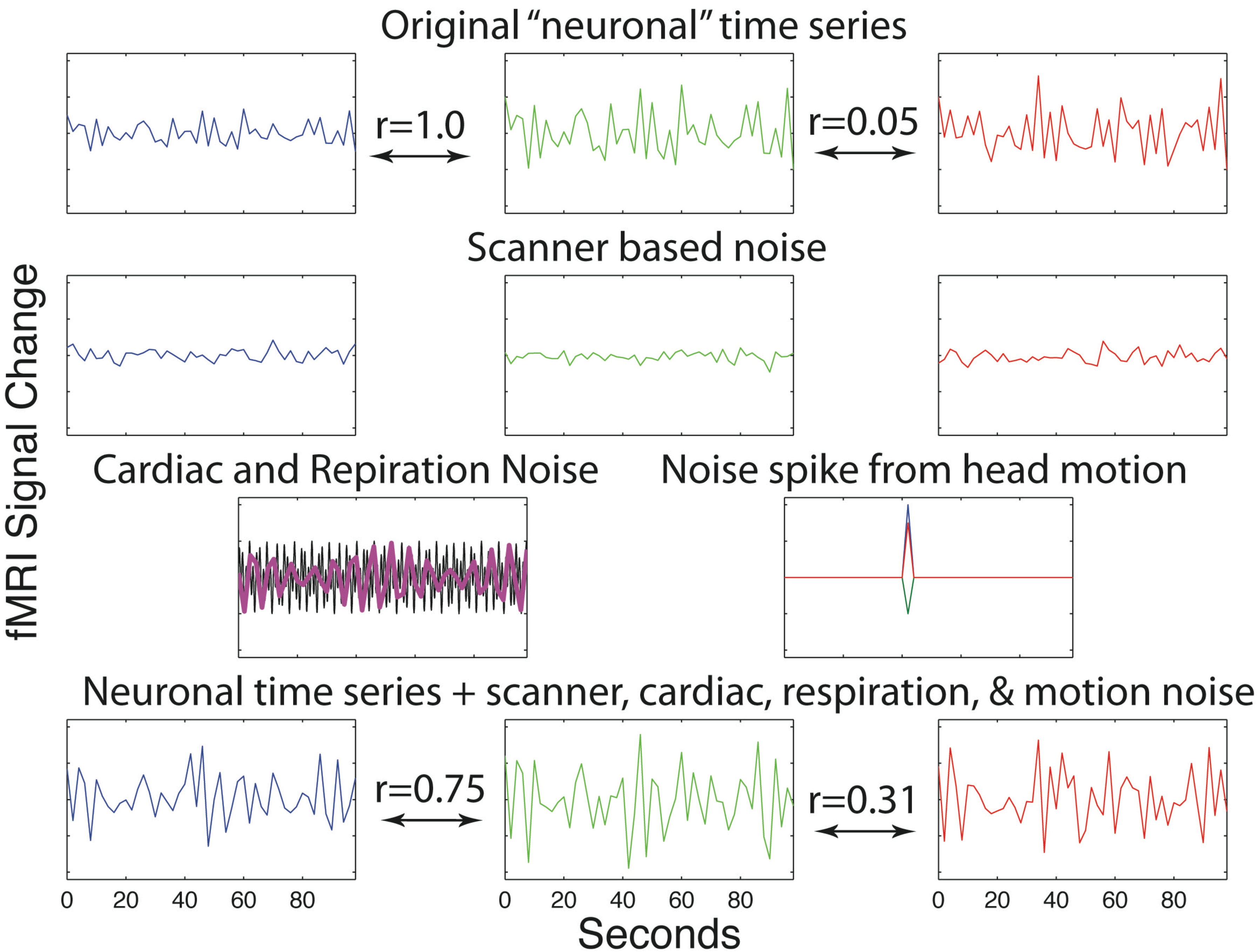


This probably isn't neural

Though some true signal will be modeled in any set of "noise" regressors

Bright & Murphy, *NeuroImage* 2015

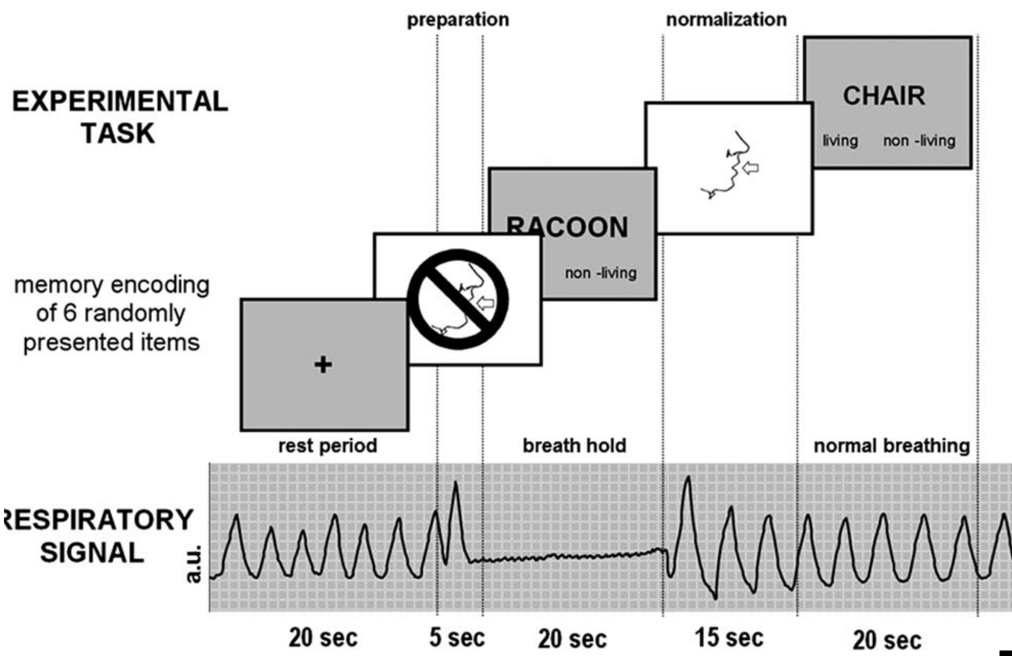
Isolating the neural signal

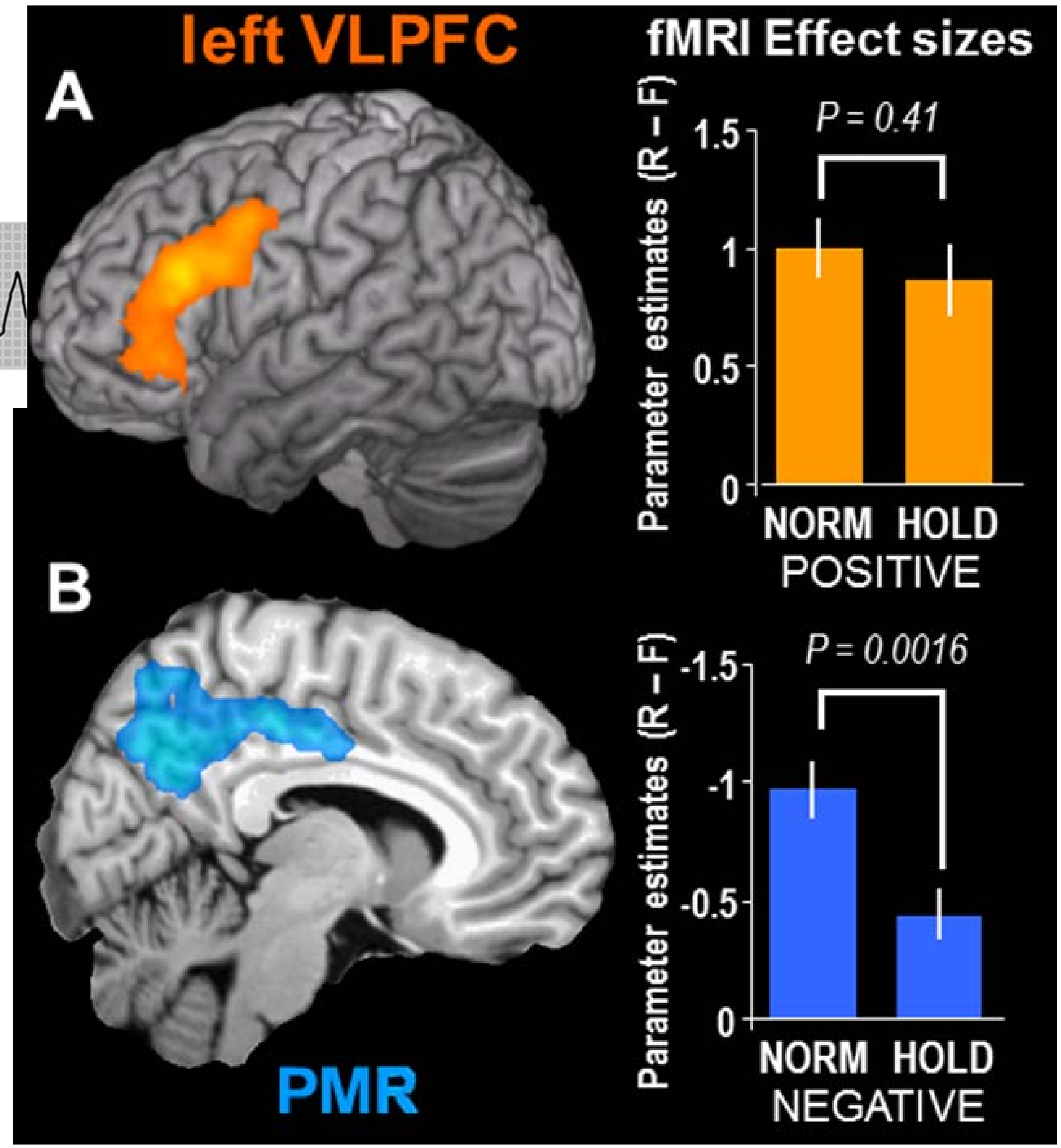


Challenges

- 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

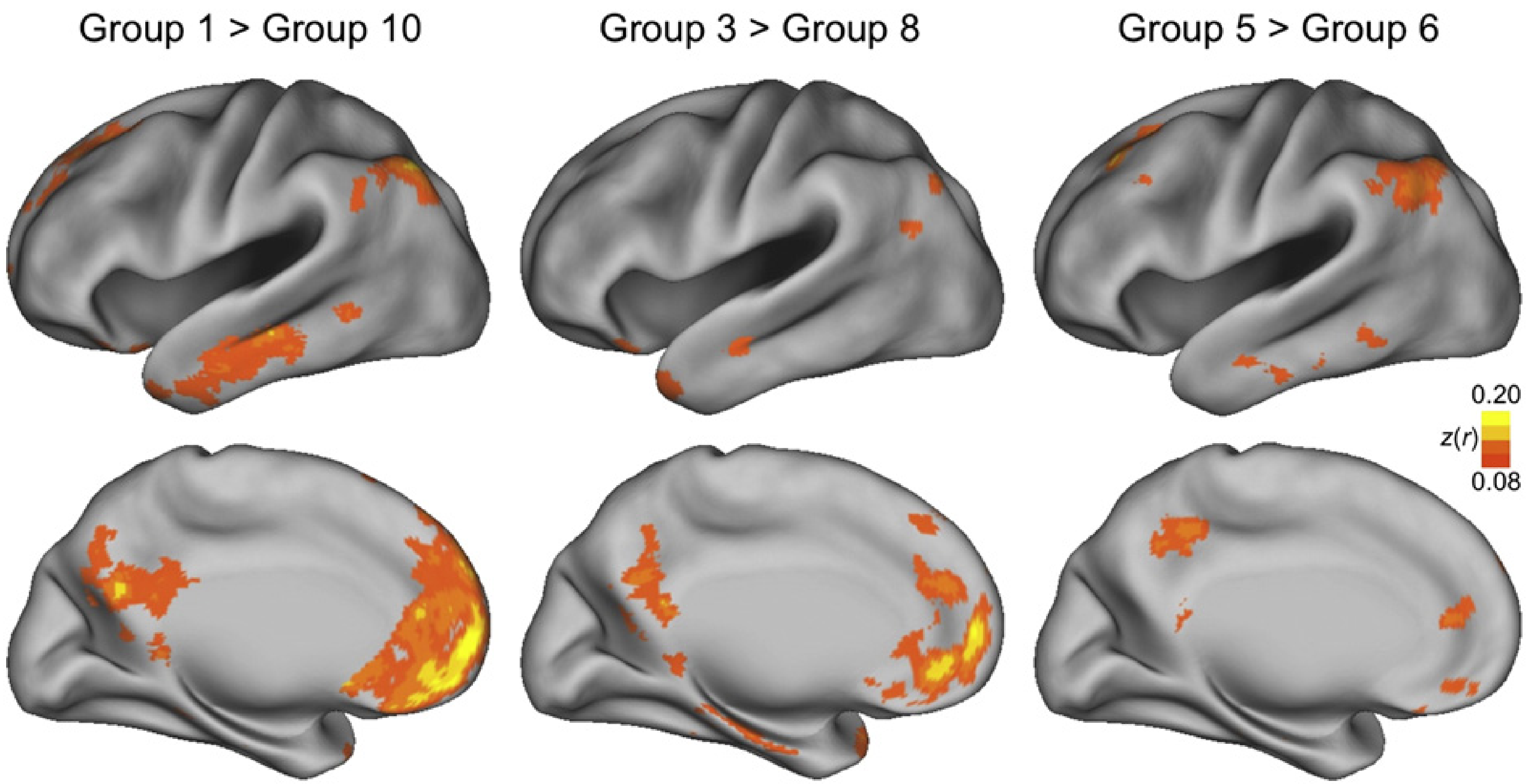
Respiration can bias fMRI task results





Huijbers et al Hum Brain Mapping 2014

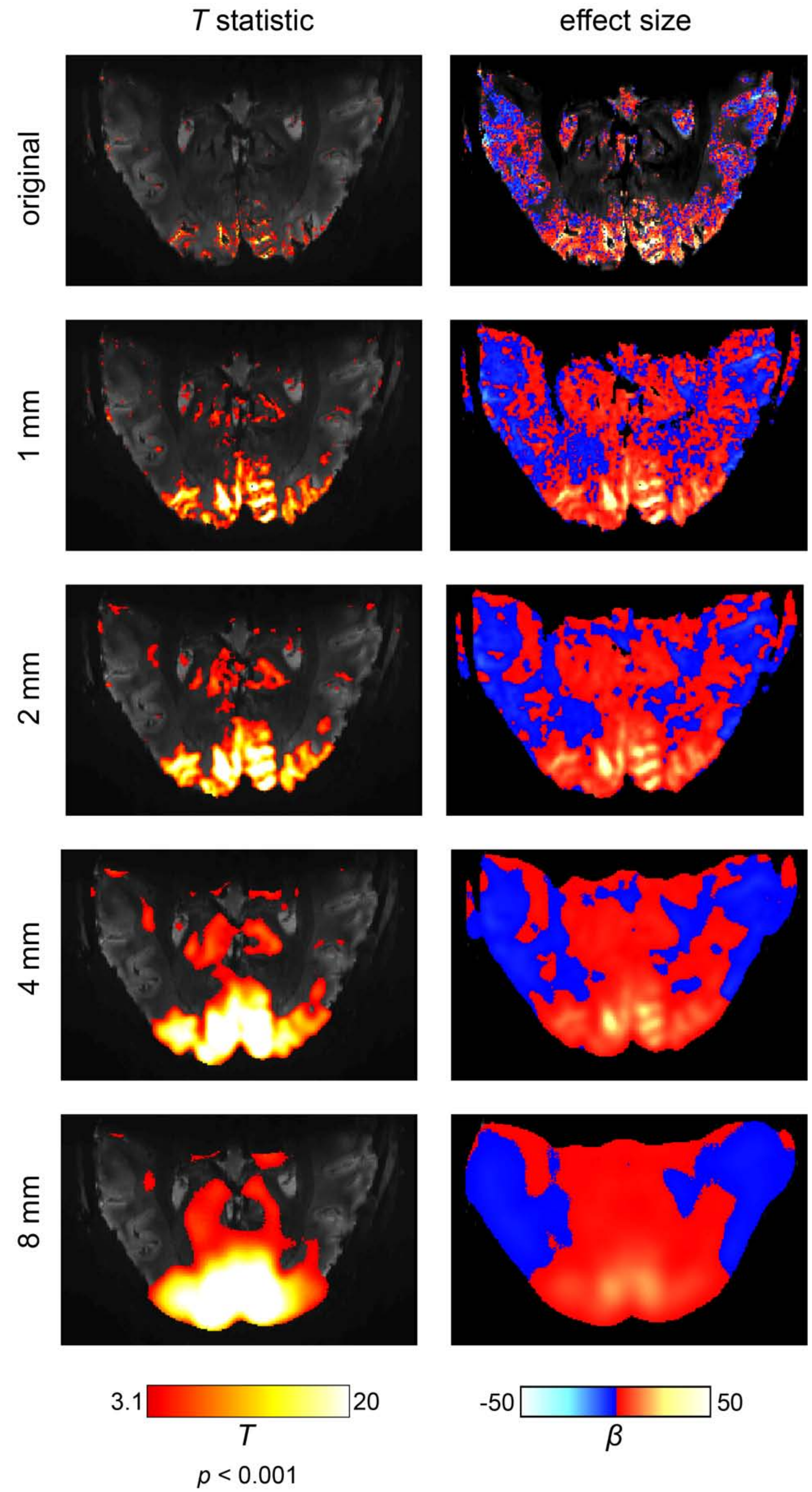
Connectivity differences based on head motion



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

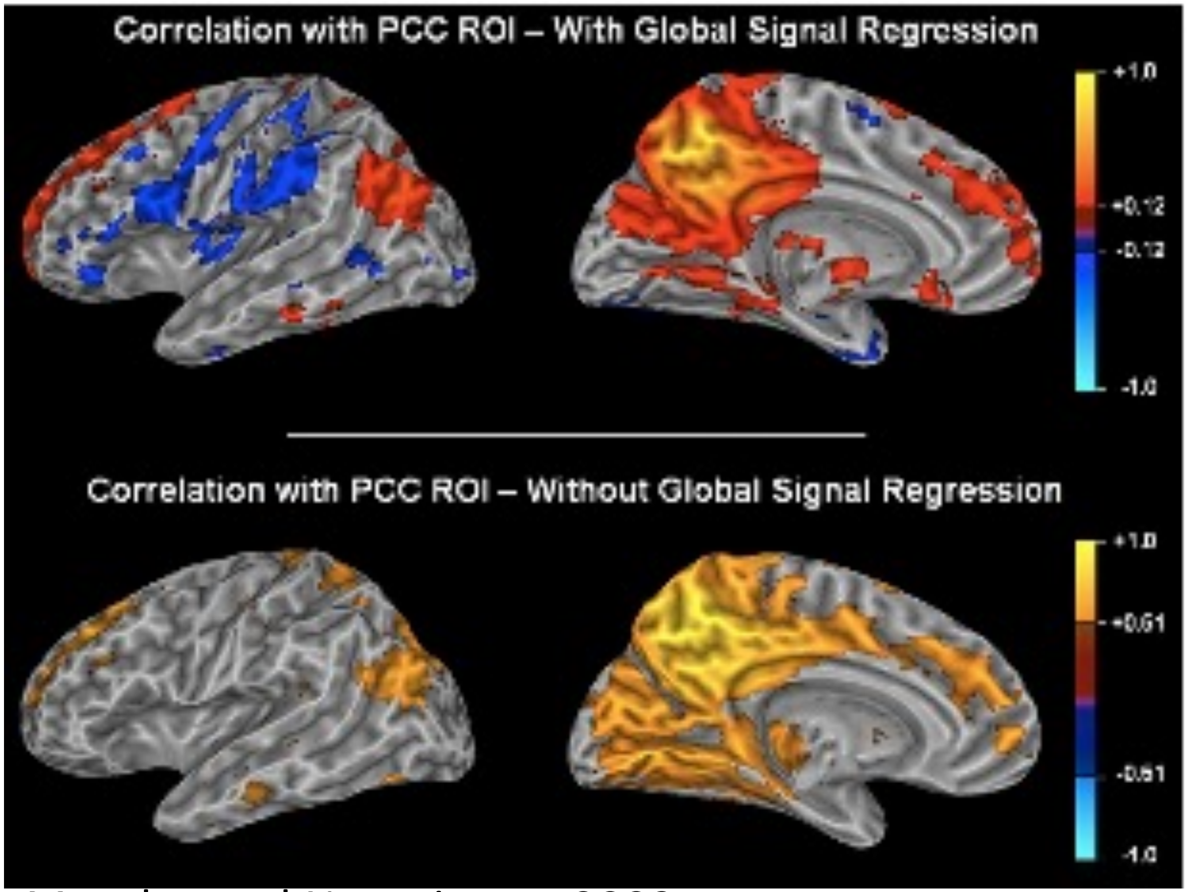


Stelzer, J., et al, Front Hum Neurosci, 2014

Data processing matters:

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

Correlations to the Posterior Cingulate

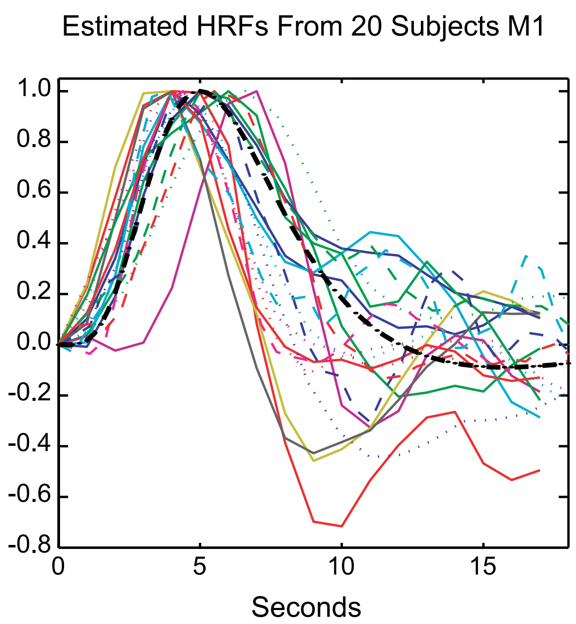


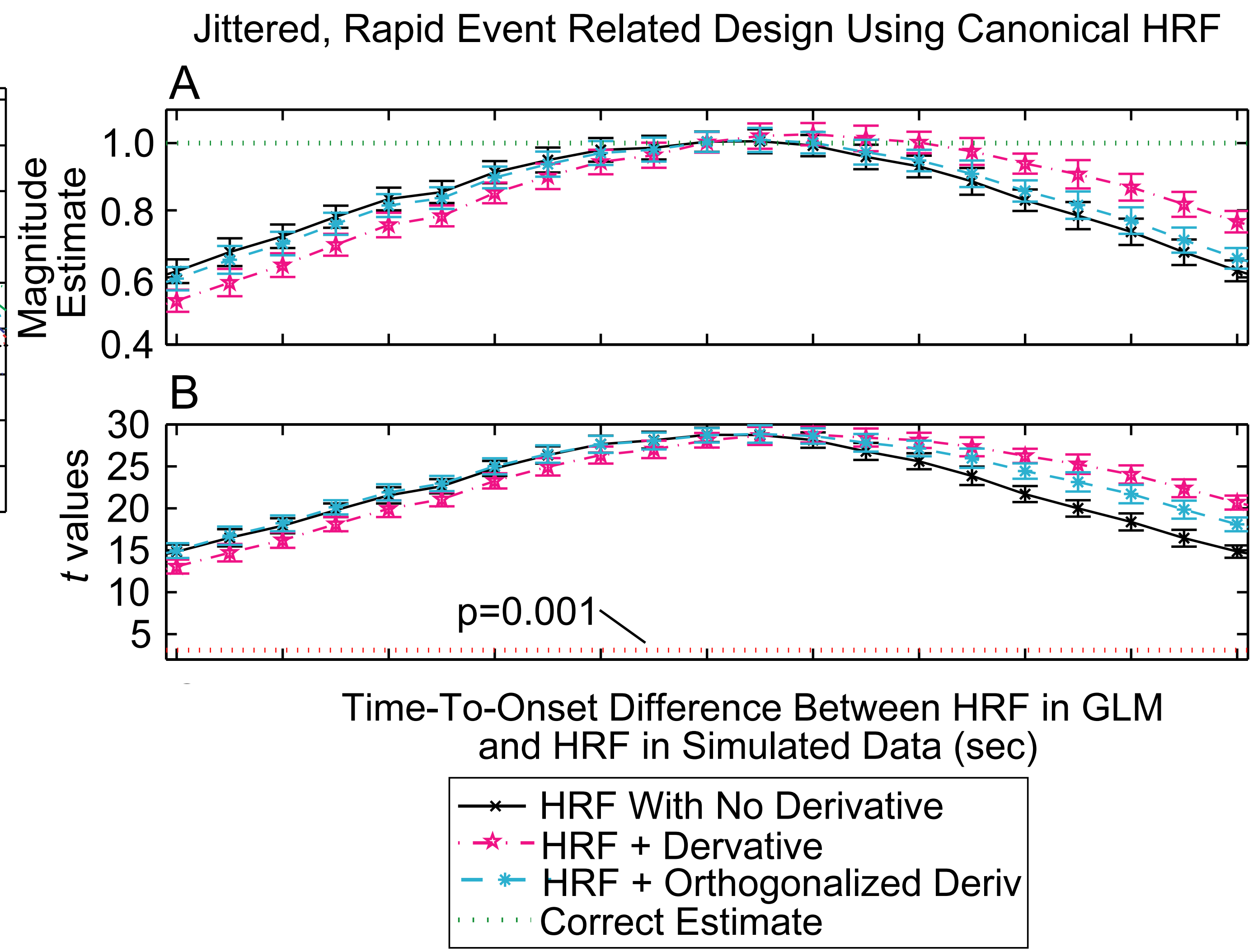
Murphy et al Neuroimage 2009

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

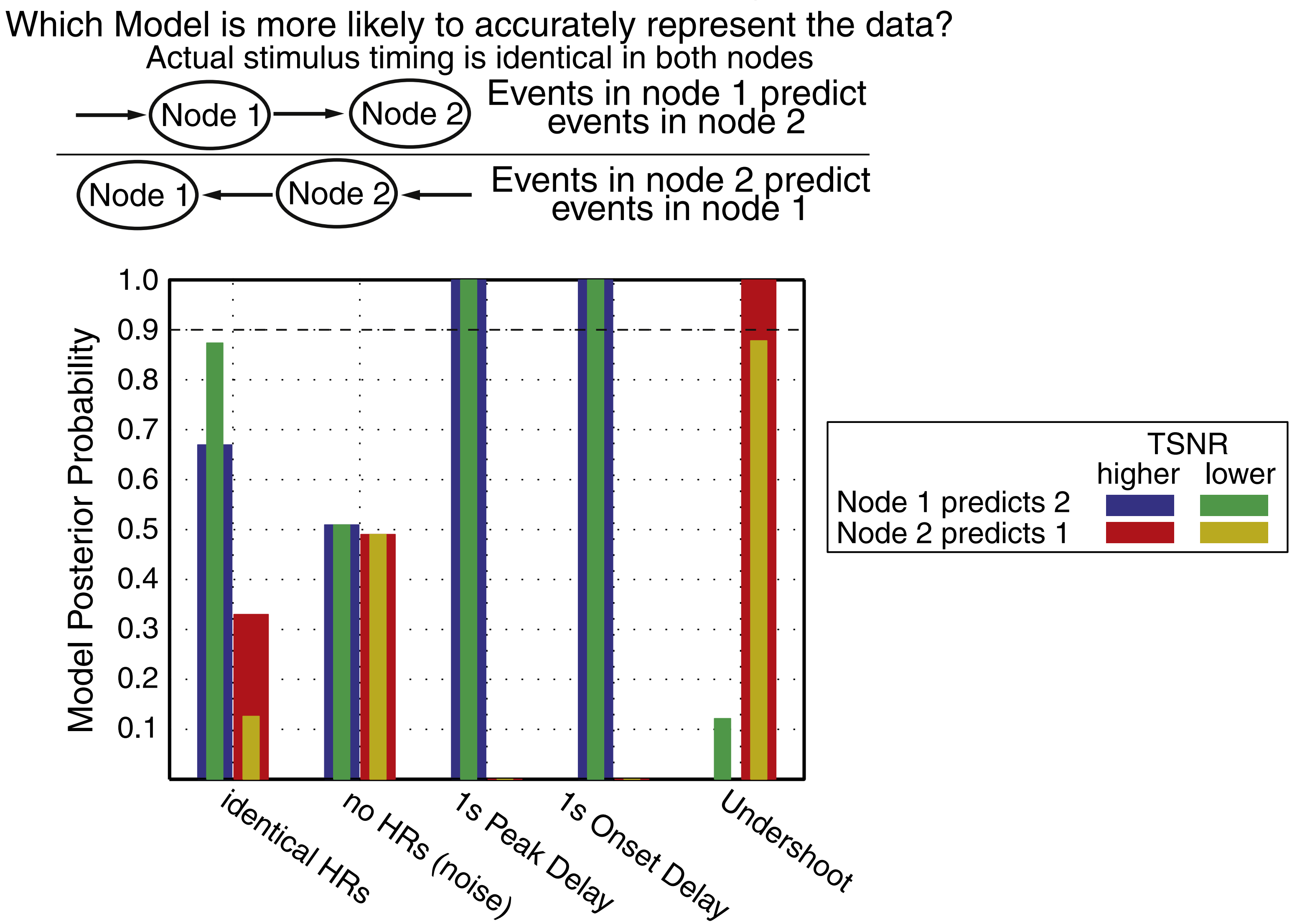




Handwerker et al, Neuroimage 2014

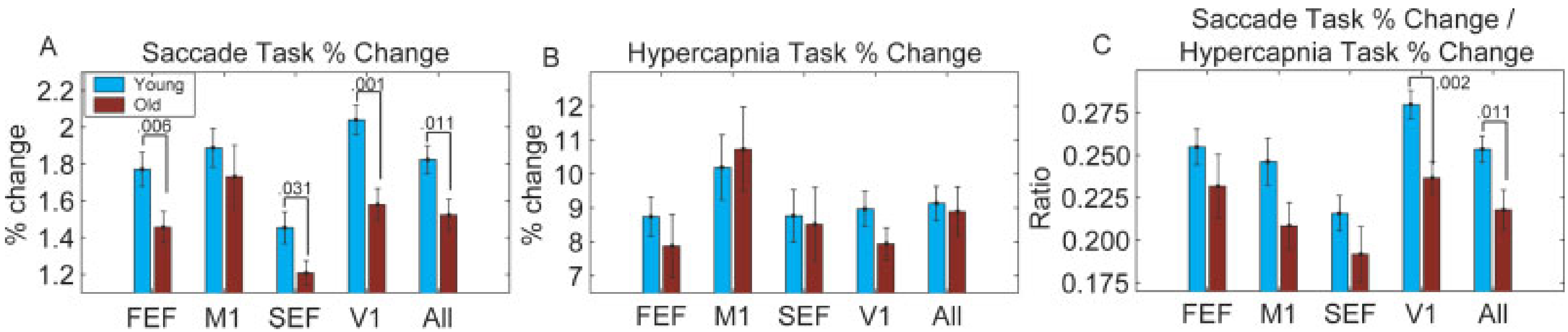
Modeling the order of neural events with fMRI is dicey

An example using
Dynamic Causal Modeling



Handwerker et al *NeuroImage* 2012

Population differences can occur from non-neural variation

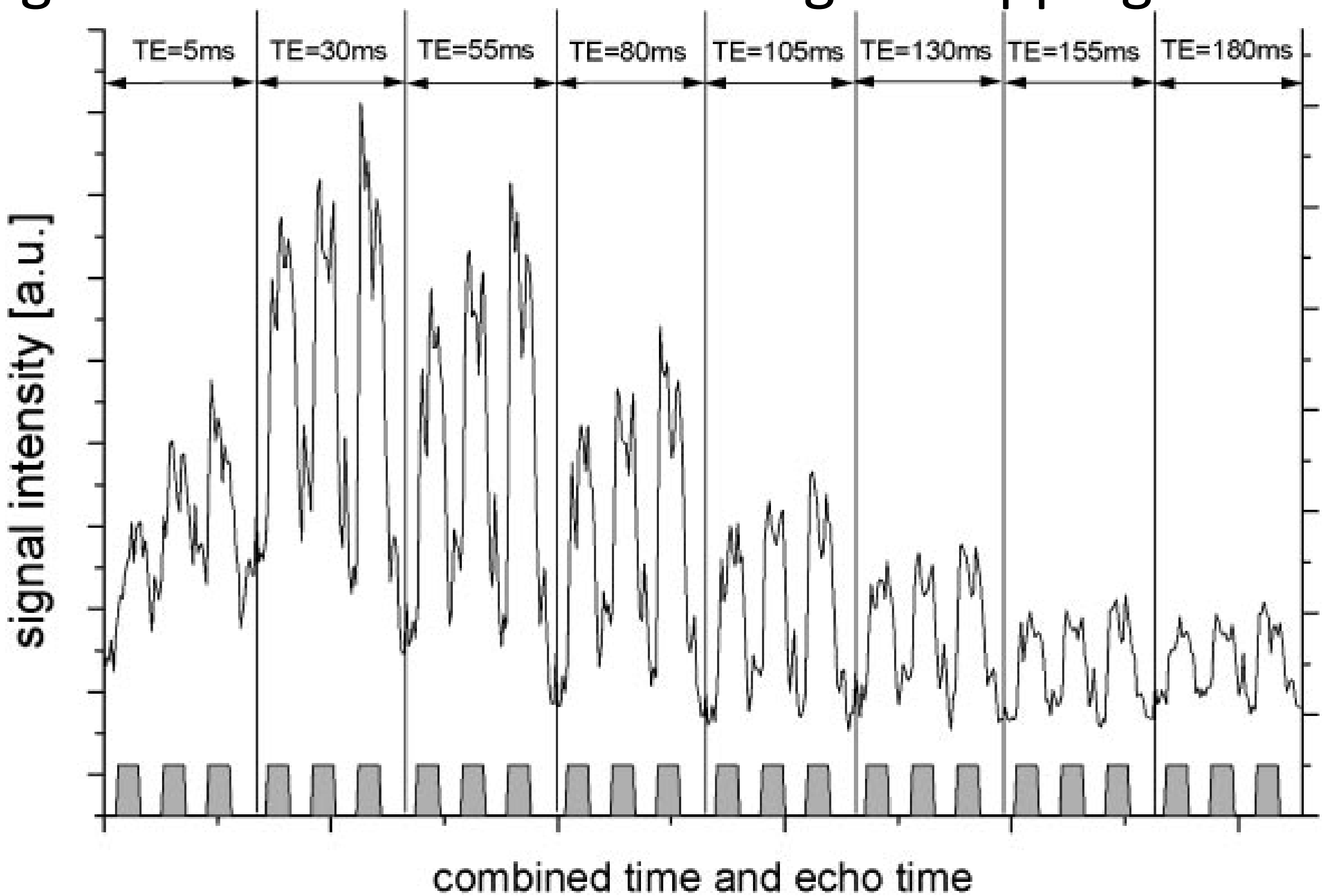


Response magnitudes in several brain regions vary during a cognitive task and a primarily vascular breath holding task.

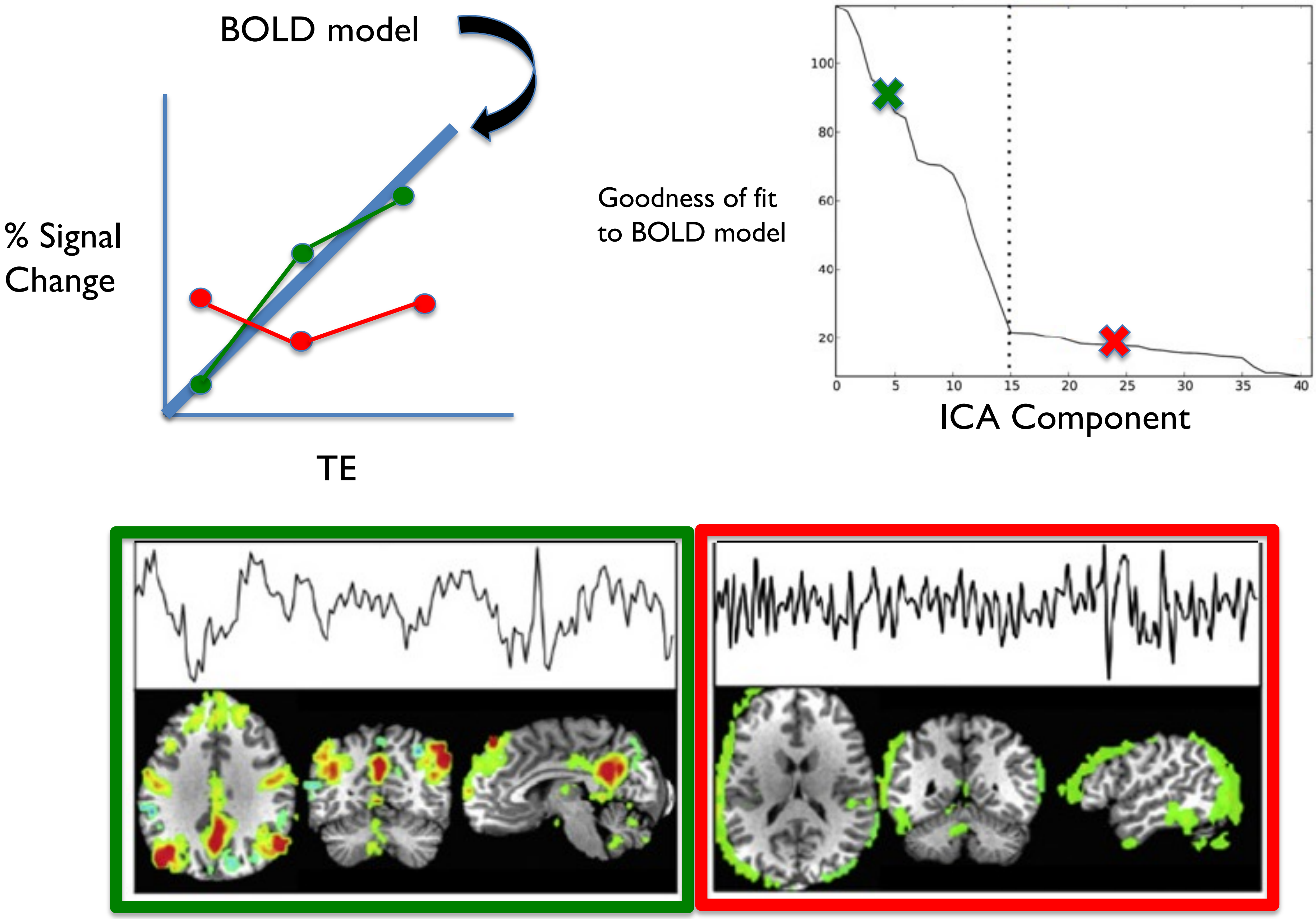
Handwerker et al, Human Brain Mapping 2007

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
ICA Component

Multi-echo-ICA denoising

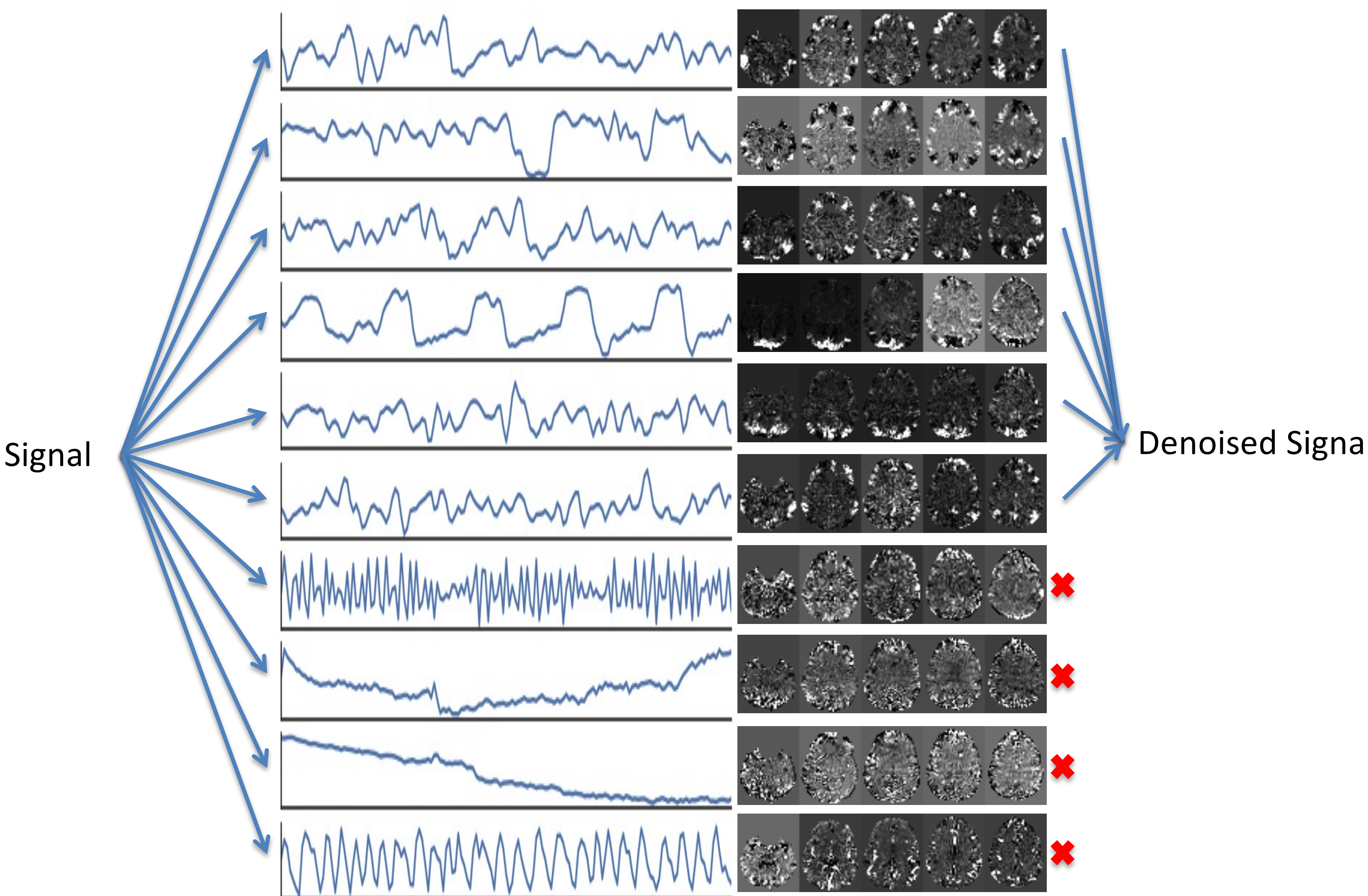
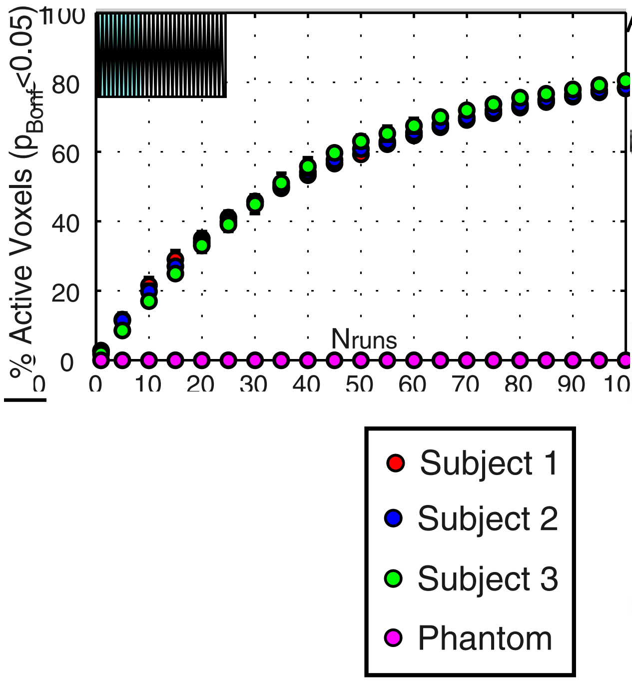
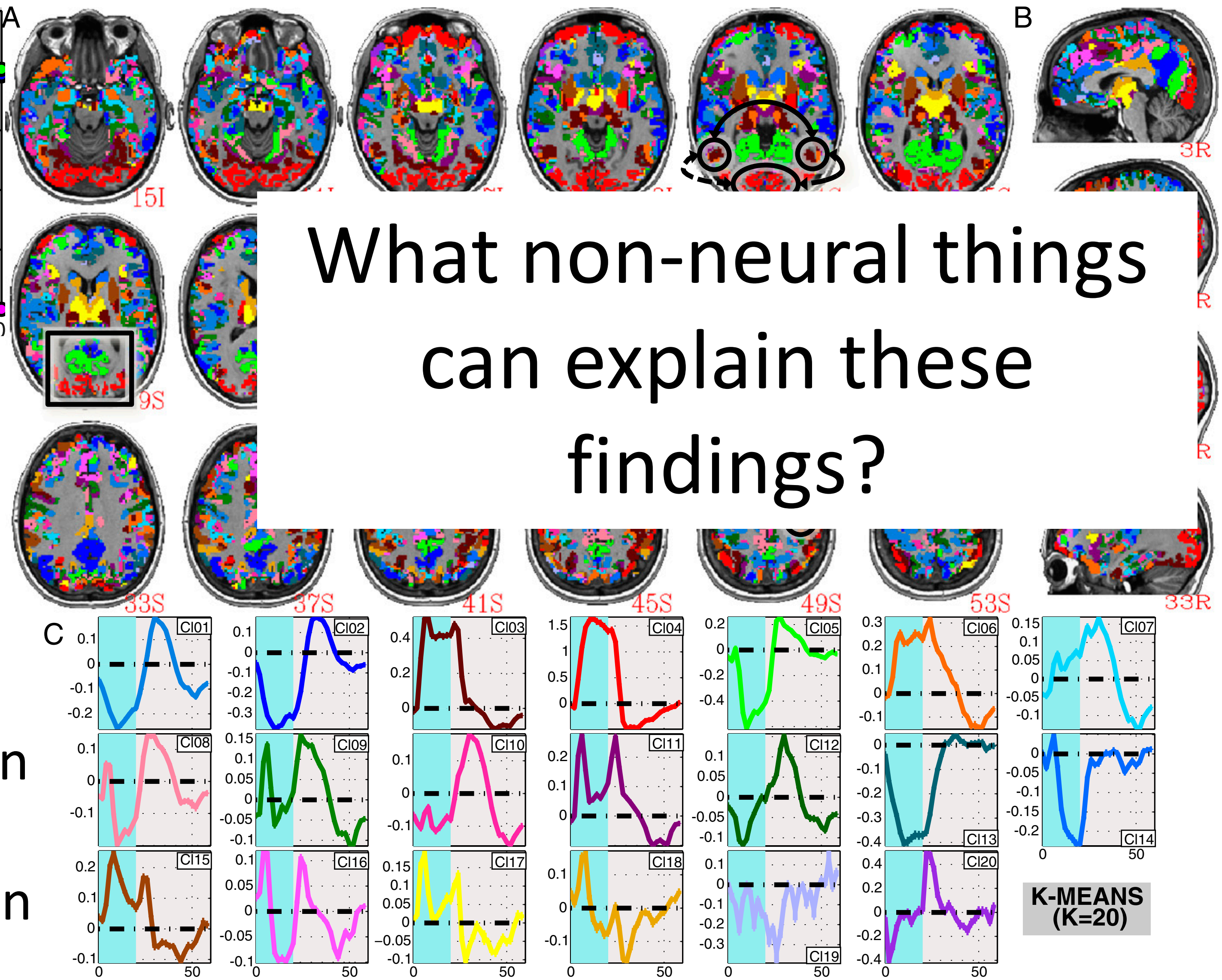


Image created by Ben Gutierrez

A case study





What non-neural things can explain these findings?

- More data -> more significant activation
- Response shapes vary across the brain

Gonzalez-Castillo, PNAS 2012

What non-neural things can explain these findings?

- Luck
- Specific Analysis Decisions
- Head motion
- Voxel size (Partial voluming)
- Global blood flow dynamics (blood steal)

What non-neural things can explain these findings?

Luck & specific analysis decisions

- Replication
  - Same results in 3 volunteers
  - Follow-up study showed same results in 3 more volunteers
- Several variants of the analyses (i.e. different models and different clustering methods) were done & either didn't affect the results or altered them in predicted ways

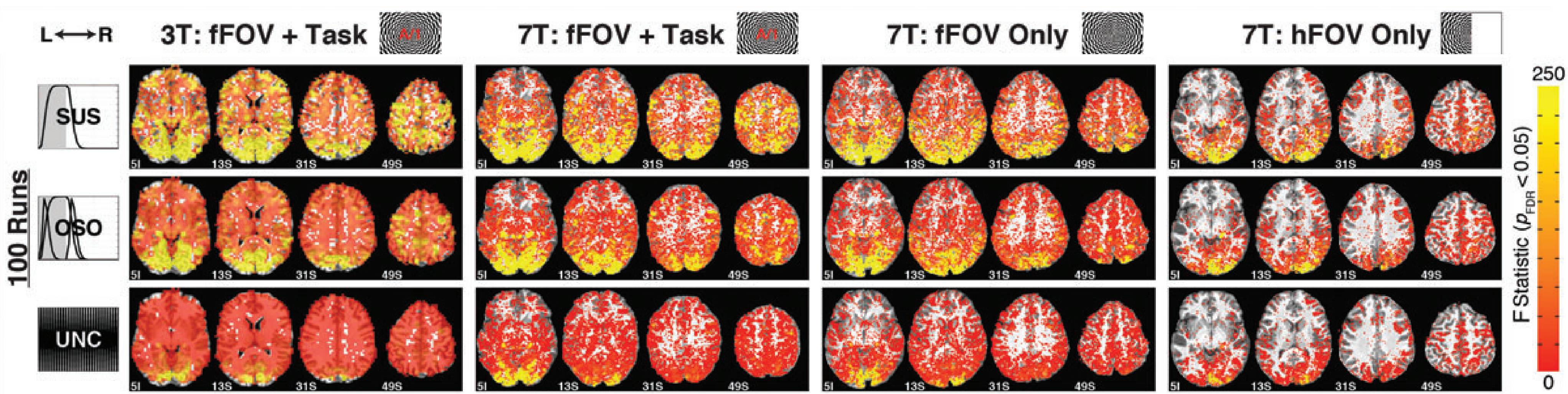
What non-neural things can explain these findings?

- Head motion
  - There was minimal head motion across these data and the head motion causes some predictable activation artifacts that we didn’t see
- Global blood flow dynamics (blood steal)
  - The spatial variation of response shapes doesn’t match what we’d expect blood steal to look like
  - A follow-up study showed widespread activation with the response shapes changing depending on task

What non-neural things can explain these findings?

Voxel-size (partial voluming)

Global blood flow dynamics (blood steal)



Gonzalez-Castillo, Cerebral Cortex 2014

What non-neural things can explain these findings?

- Luck: No
- Specific Analysis Decisions: Very unlikely
- Head motion: Very unlikely
- Voxel size (Partial voluming): Probably not
- Global blood flow dynamics (blood steal): Might be a factor that does affect the specific results, but probably doesn't explain the big-picture finding

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