The Biggest Unknowns in Functional MRI

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&
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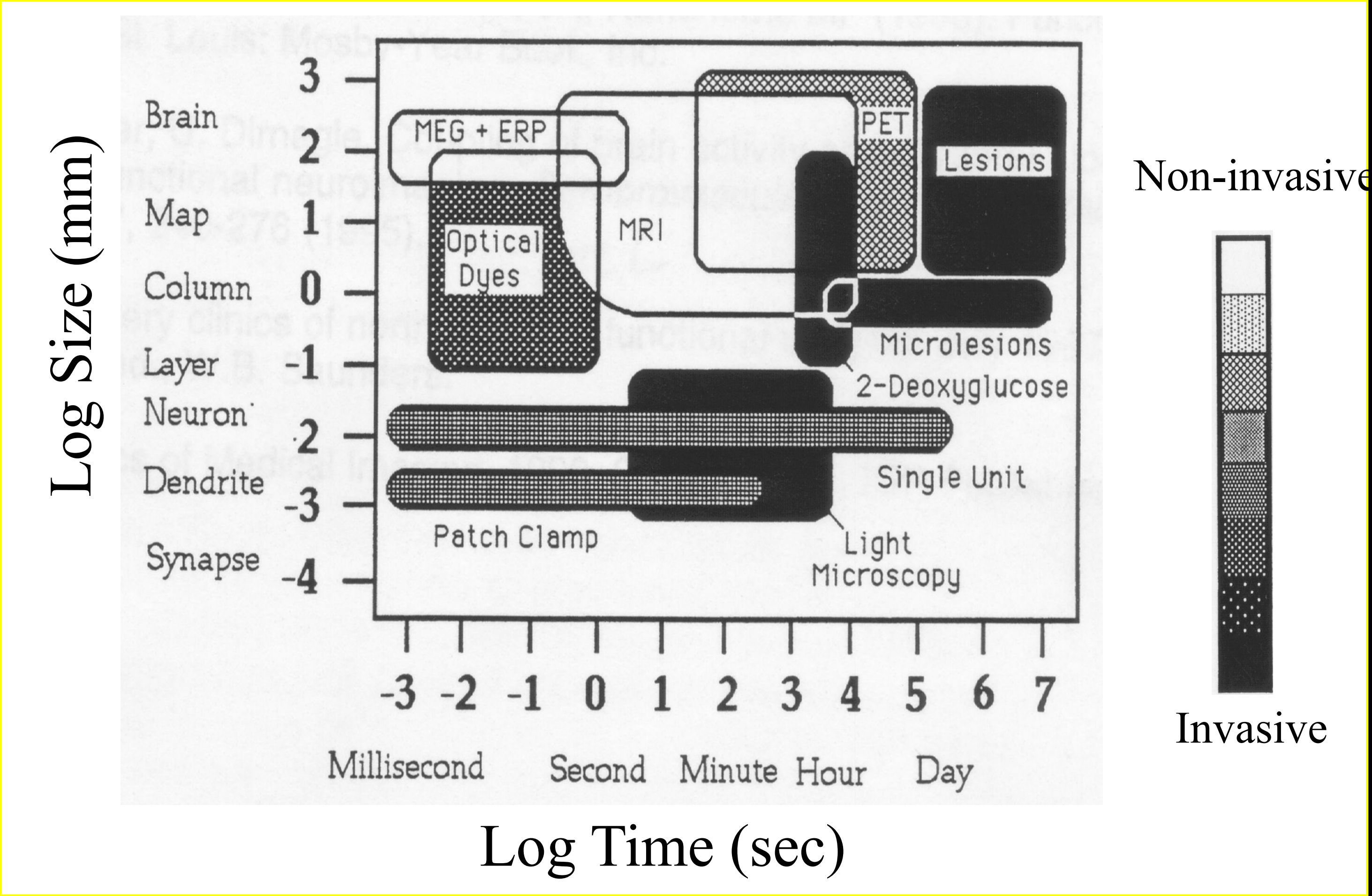
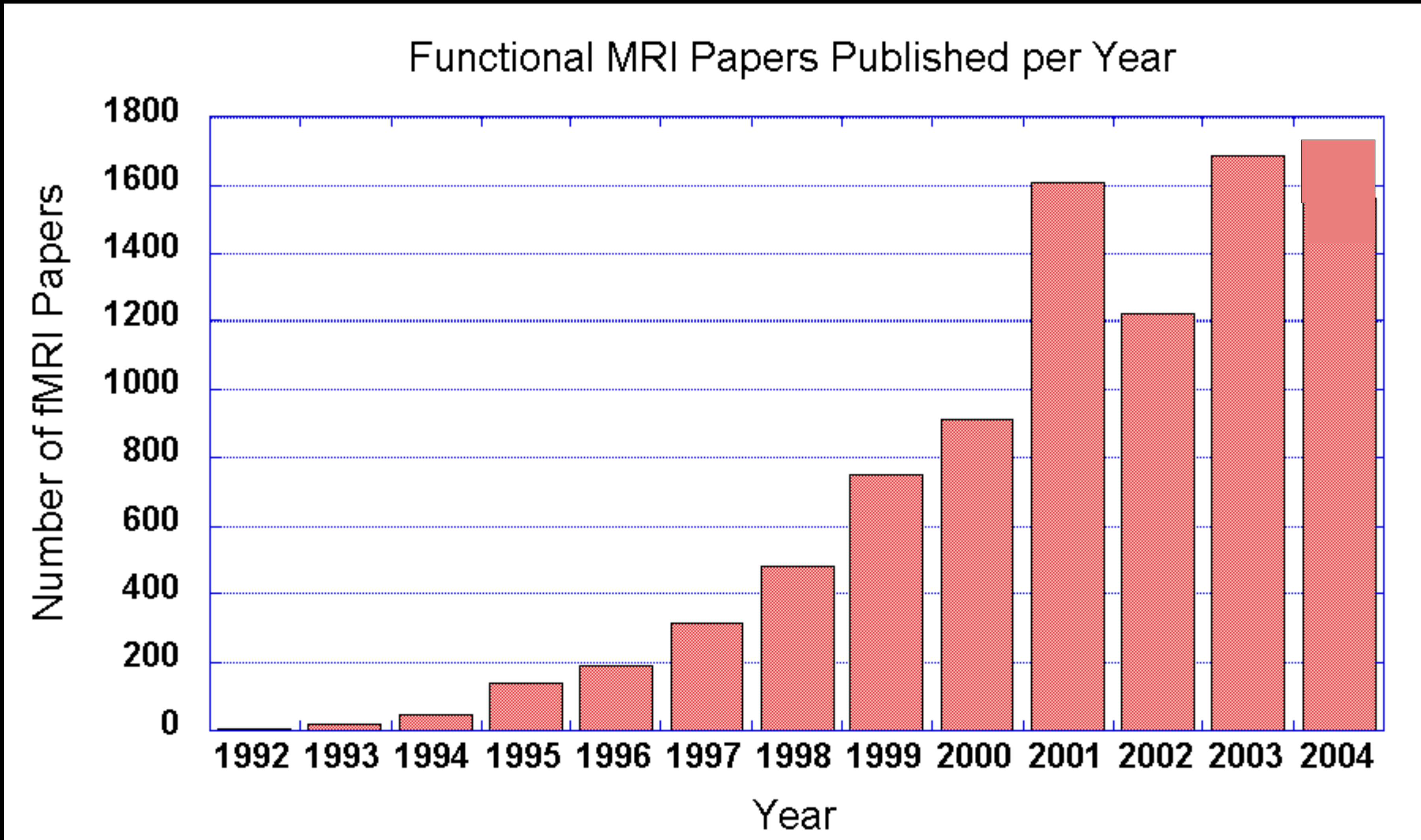
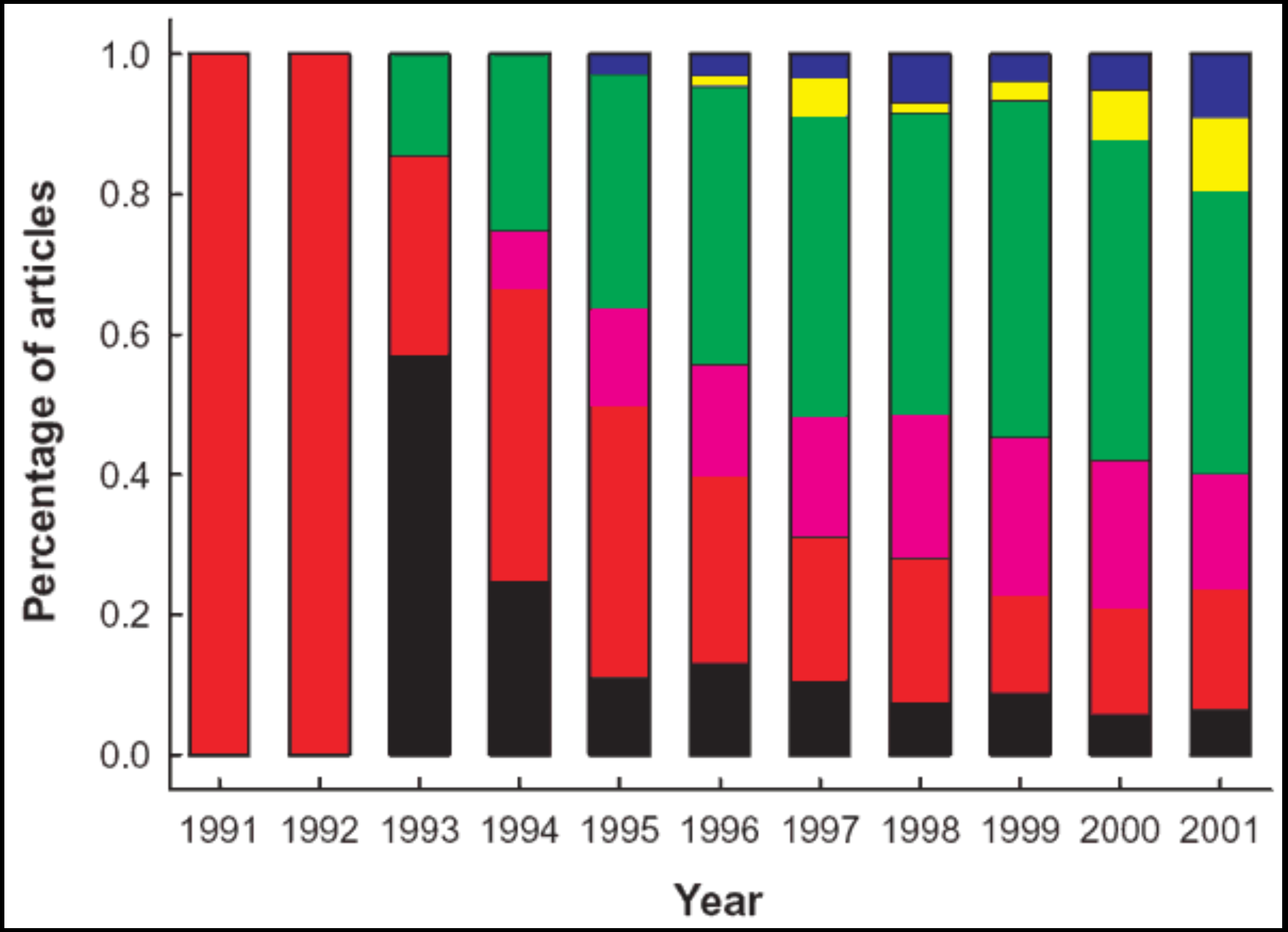
National Institute of Mental Health

Functional Neuroimaging Techniques




Functional MRI Papers Published per Year
Number of fMRI Papers
0
200
400
600
800
1000
1200
1400
1600
1800
1992
1993
1994
1995
1996
1997
1998
1999
2000
2001
2002
2003
2004
Year

Type of fMRI research performed



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, 6 (3) p.205, 2001

Uses

Understanding normal brain organization and changes

-networks involved with specific tasks (low to high level processing)
-changes over time (seconds to years)
-correlates of behavior (response accuracy, performance changes...)

Clinical research

-correlates of specifically activated networks to clinical populations
-presurgical mapping

Future Uses

Complementary use for clinical diagnosis

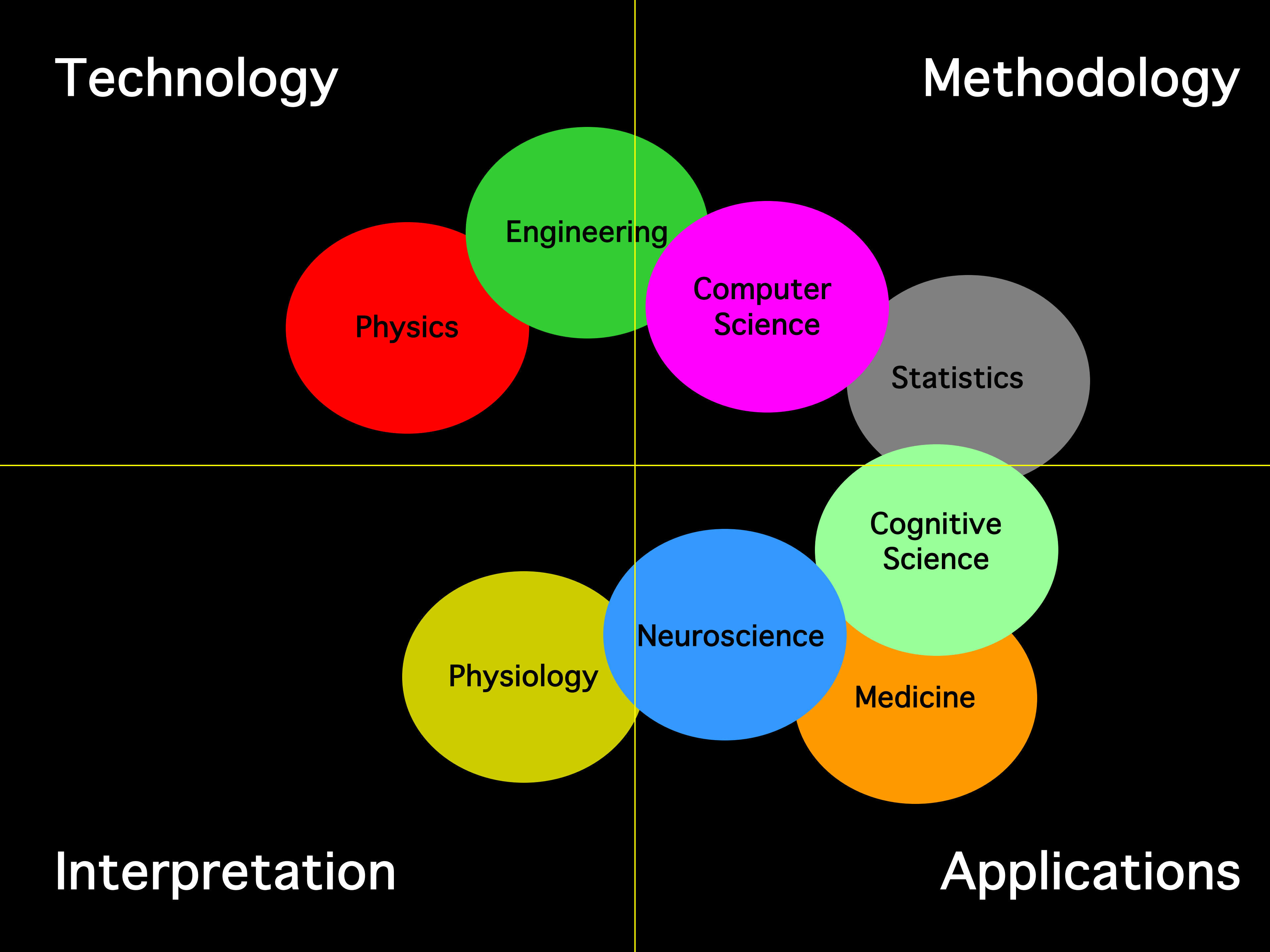
-utilization of clinical research results
-prediction of pathology

Clinical treatment and assessment

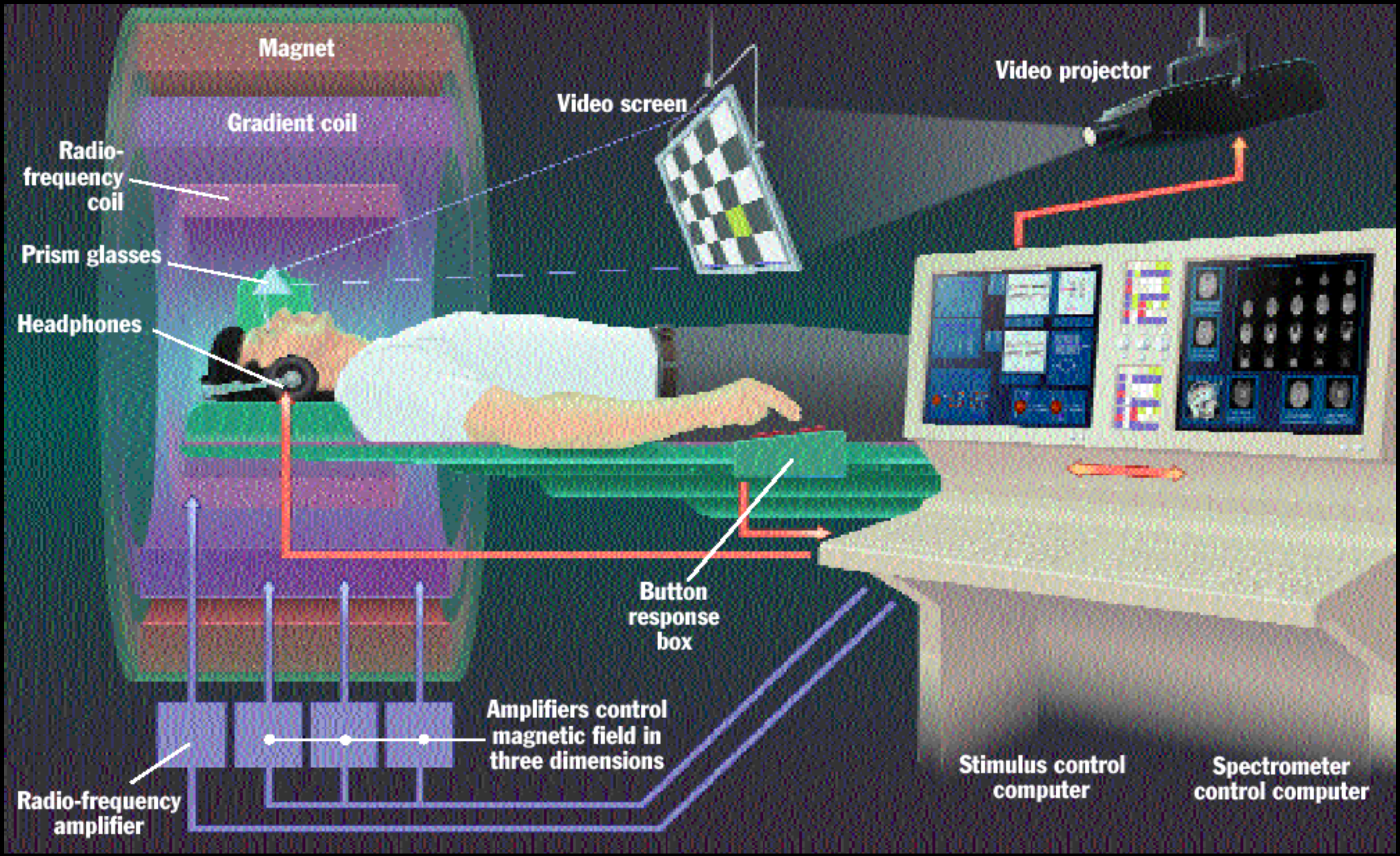
-drug, therapy, rehabilitation, biofeedback
-epileptic foci mapping
-drug effects

Non clinical uses

-complementary use with behavioral, anatomical, other modality results
-lie detection
-prediction of behavior tendencies
-brain/computer interface


Technology
Methodology
Engineering
Physics
Computer Science
Statistics
Cognitive Science
Neuroscience
Physiology
Medicine
Interpretation
Applications

fMRI Setup



Courtesy, Robert Cox, Scientific and Statistical Computing Core Facility, NIMH

MRI vs. fMRI

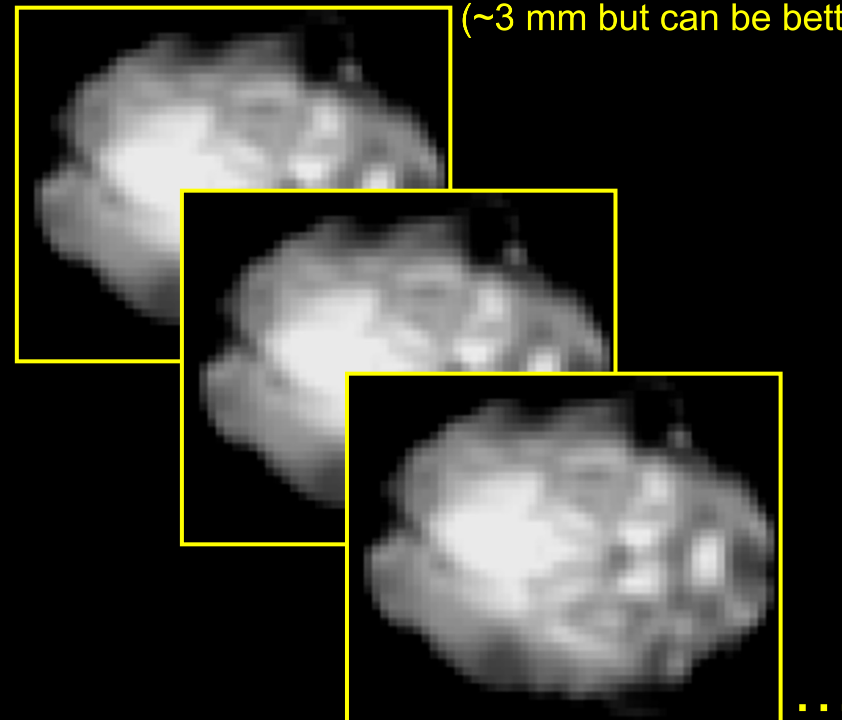
MRI

high resolution
(1 mm)

one image

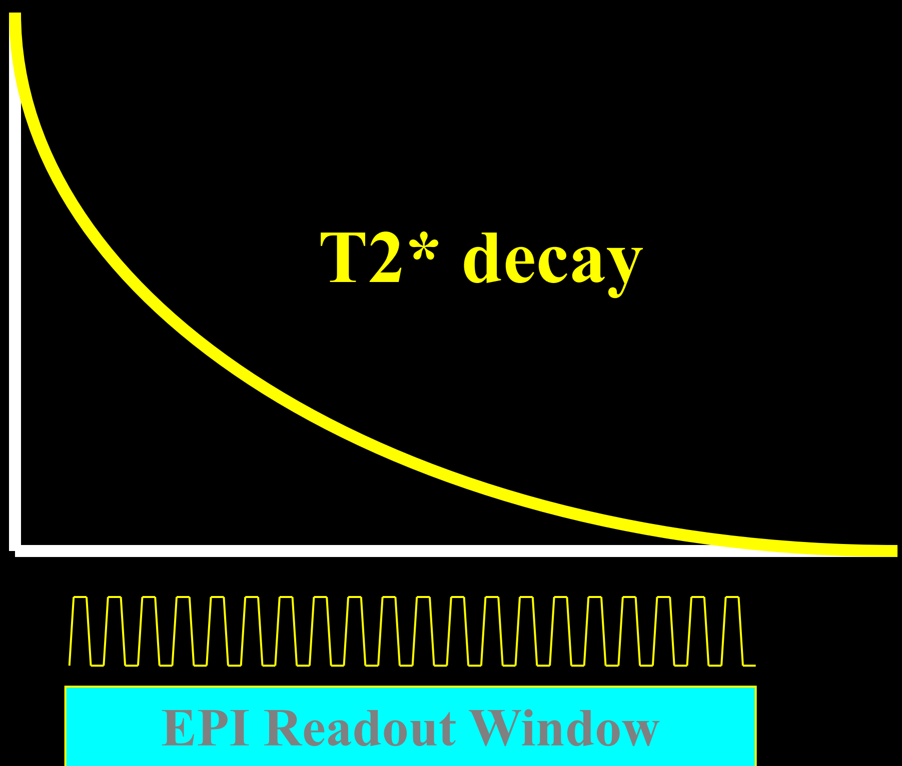
fMRI

low resolution
(~3 mm but can be better)

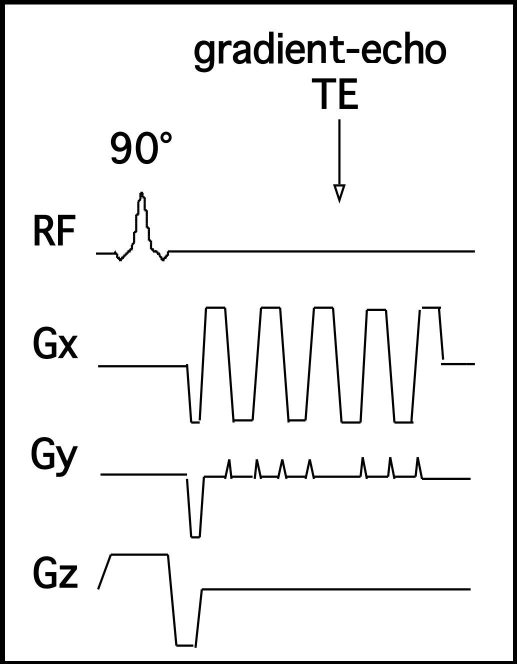


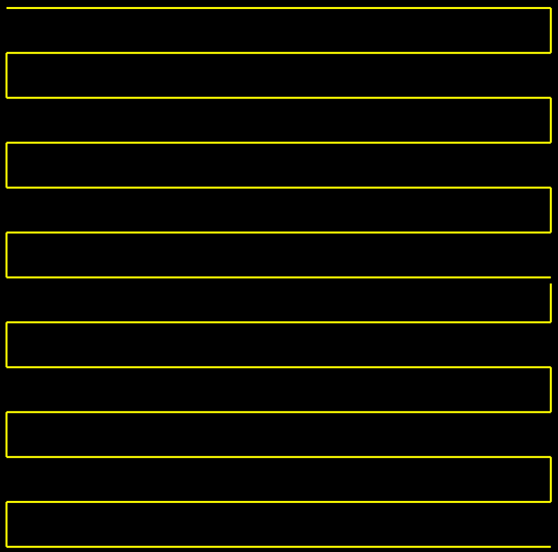
many images
(e.g., every 2 sec for 5 mins)

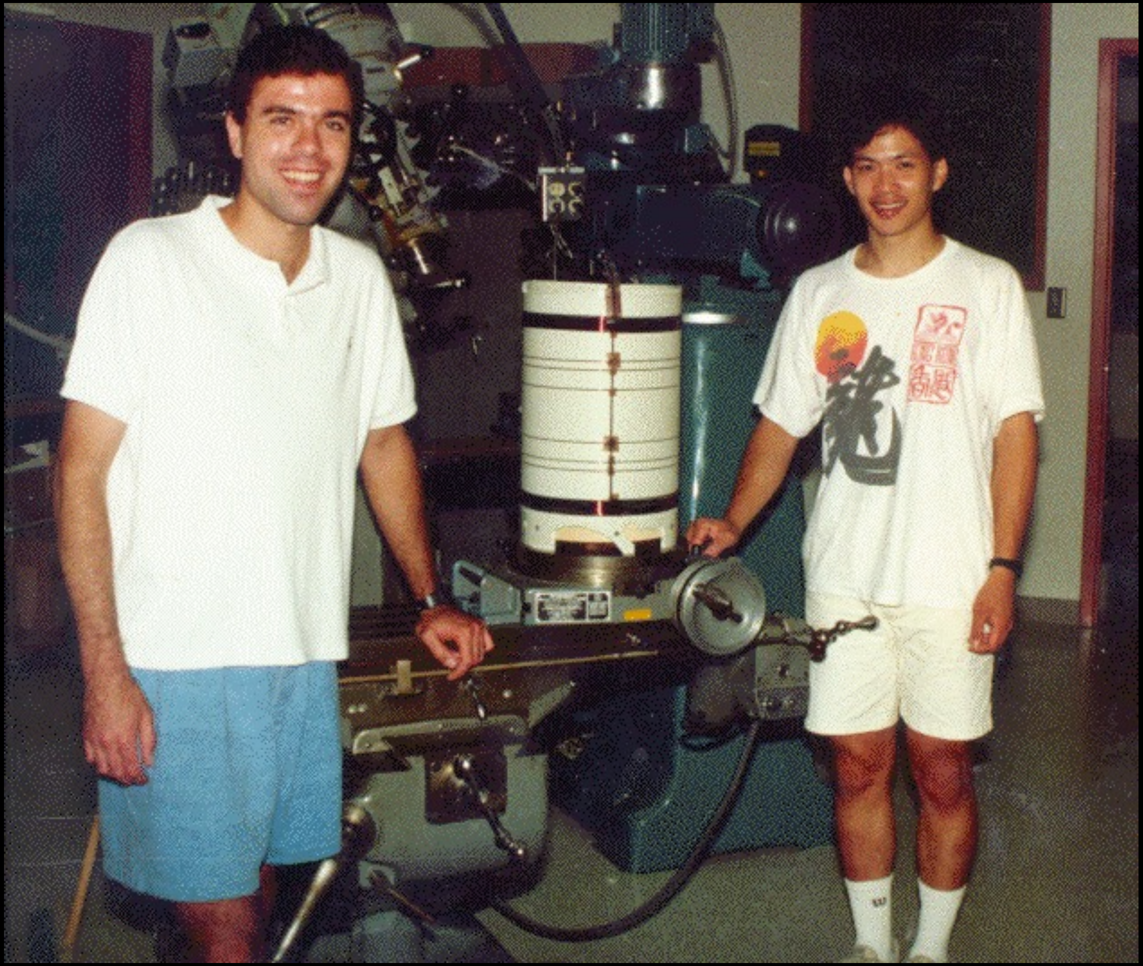
Single Shot EPI



≈ 20 to 40 ms



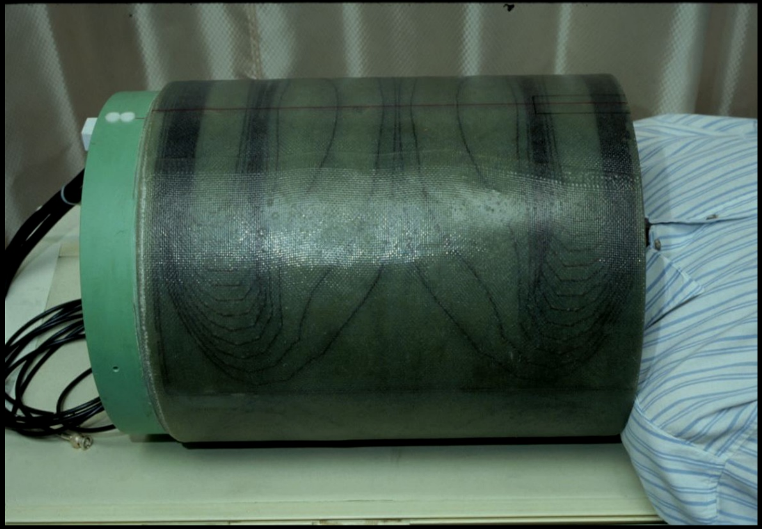




August, 1991

1991-1992

1992-1999



General Electric 3 Tesla Scanner

BOLD

(<u>b</u>lood <u>o</u>xygenation <u>l</u>evel <u>d</u>ependence)

blood flow

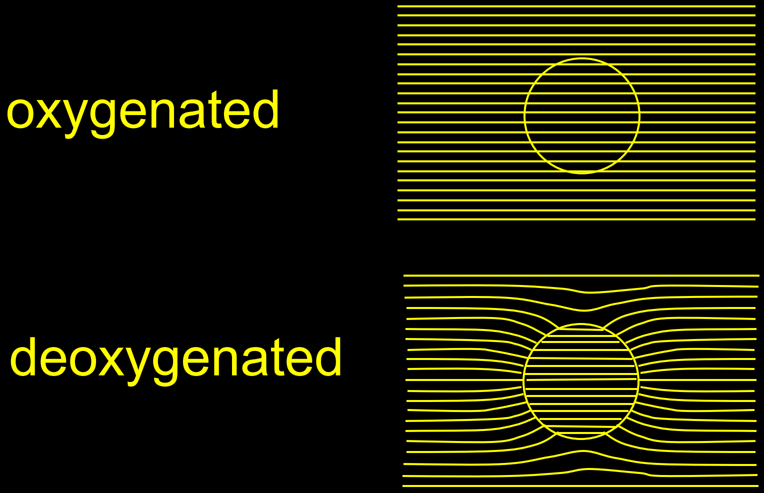
oxygenated-blood

MR signal

Blood Oxygenation Imaging

Oxygenated and deoxygenated red blood cells have different magnetic properties

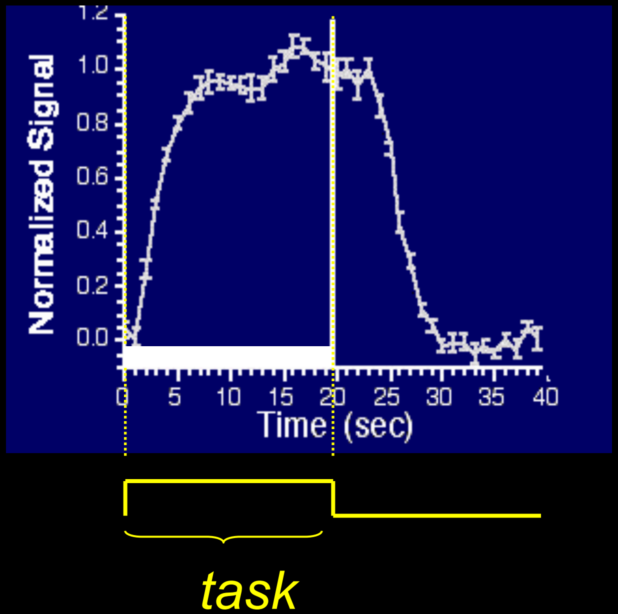
red blood cells

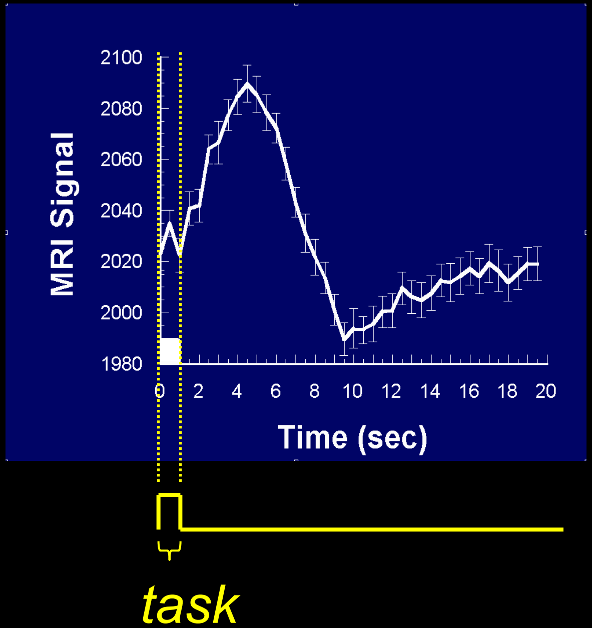


L. Pauling, C. D. Coryell, *Proc.Natl. Acad. Sci. USA 22, 210-216*, **1936**.
K.R. Thulborn, J. C. Waterton, et al., *Biochim. Biophys. Acta. 714: 265-270*, **1982**.
S. Ogawa, T. M. Lee, A. R. Kay, D. W. Tank, *Proc. Natl. Acad. Sci. USA 87, 9868-9872*, **1990**.

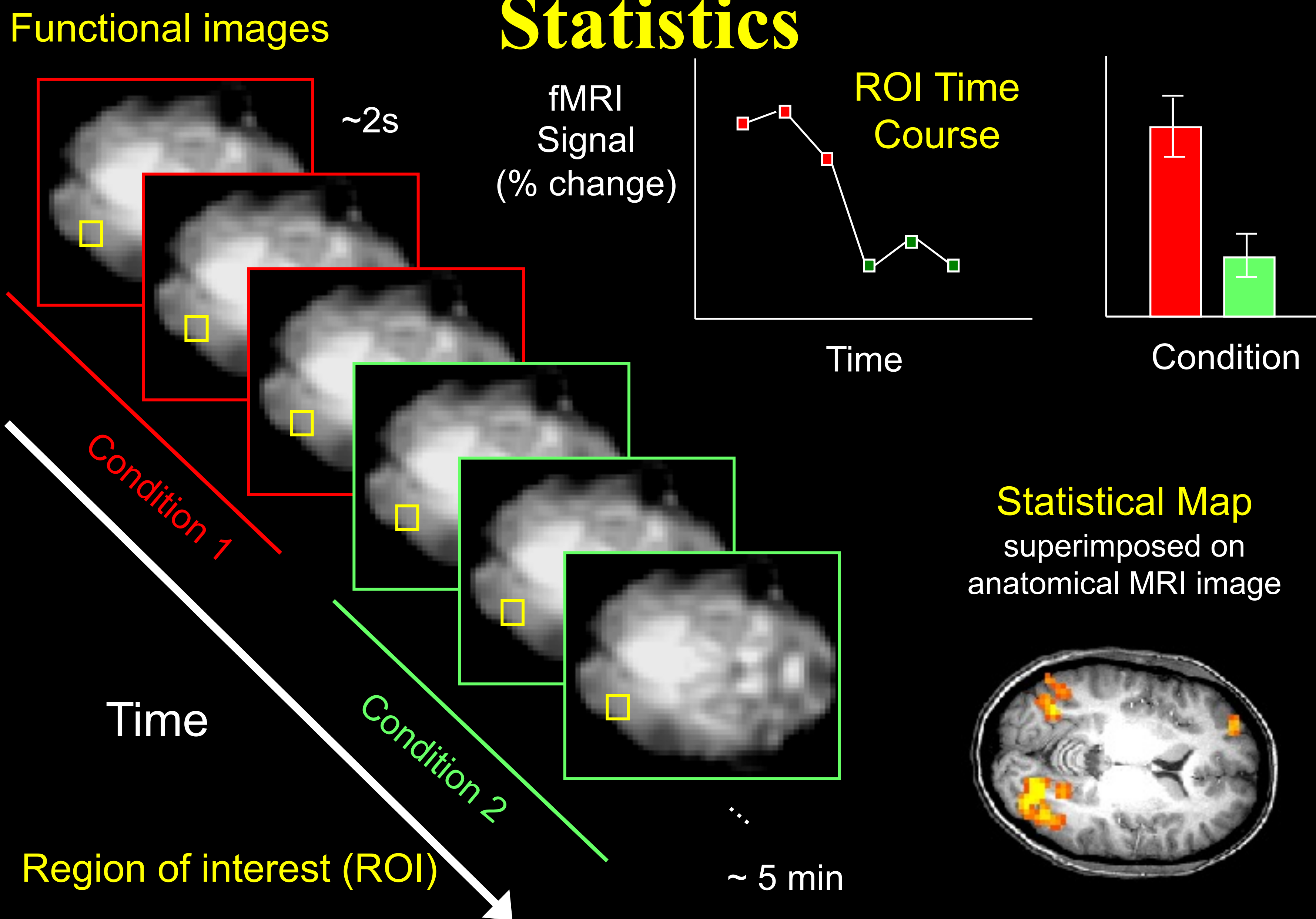
Blood Oxygenation Imaging

- K. K. Kwong, et al, (1992) "Dynamic magnetic resonance imaging of human brain activity during primary sensory stimulation." Proc. Natl. Acad. Sci. USA. 89, 5675-5679.
- S. Ogawa, et al., (1992) "Intrinsic signal changes accompanying sensory stimulation: functional brain mapping with magnetic resonance imaging. Proc. Natl. Acad. Sci. USA." 89, 5951-5955.
- P. A. Bandettini, et al., (1992) "Time course EPI of human brain function during task activation." Magn. Reson. Med 25, 390-397.
- Blamire, A. M., et al. (1992). "Dynamic mapping of the human visual cortex by high-speed magnetic resonance imaging." Proc. Natl. Acad. Sci. USA 89: 11069-11073.



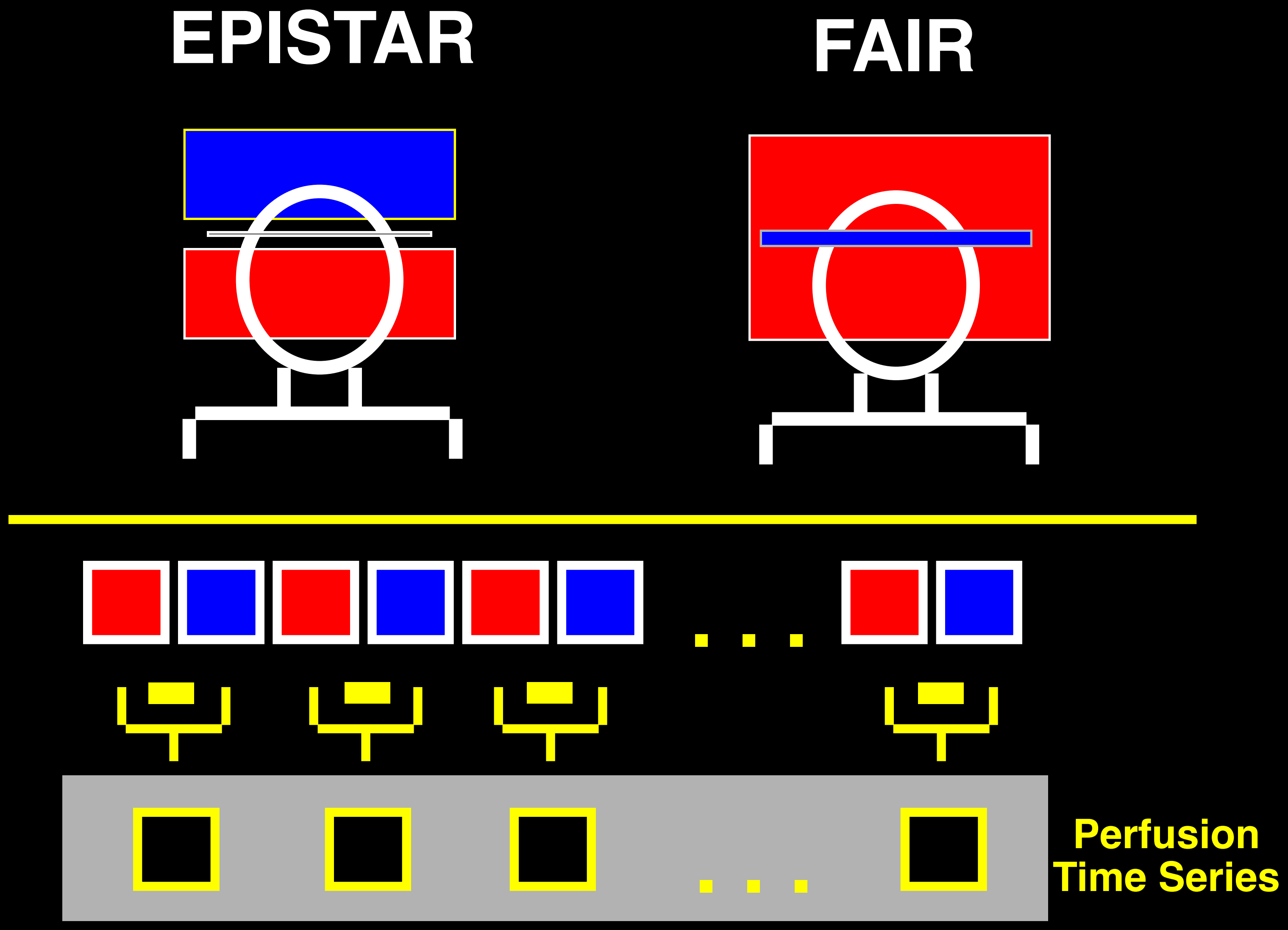


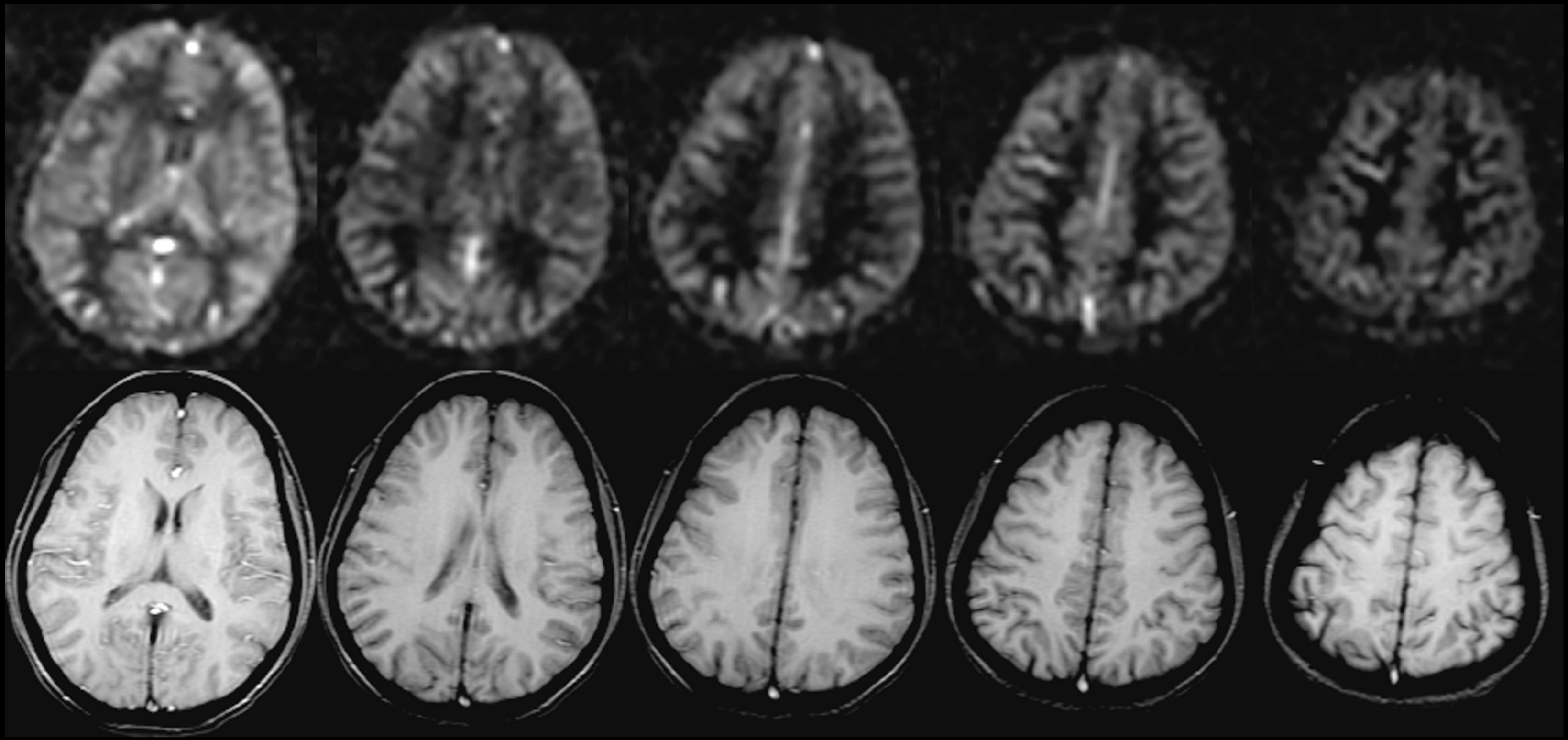
Activation Statistics



Courtesy, Robert Cox, Scientific and Statistical Computing Core Facility, NIMH

Blood Perfusion Imaging





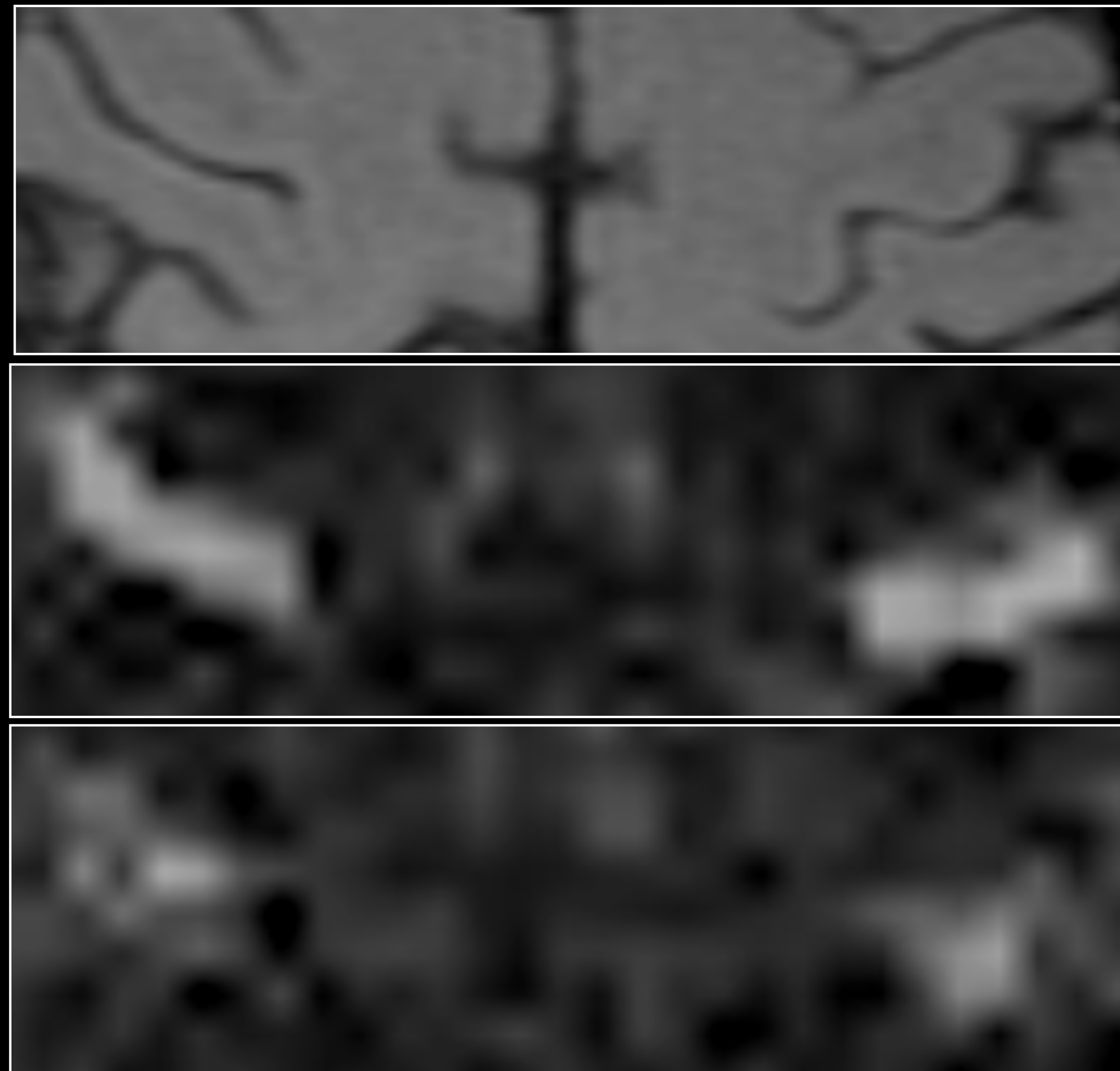
Williams, D. S., Detre, J. A., Leigh, J. S. & Koretsky, A. S. (1992) “Magnetic resonance imaging of perfusion using spin-inversion of arterial water.” Proc. Natl. Acad. Sci. USA 89, 212-216.

Edelman, R., Siewert, B. & Darby, D. (1994) “Qualitative mapping of cerebral blood flow and functional localization with echo planar MR imaging ans signal targeting with alternating radiofrequency (EPISTAR).” Radiology **192**, 1-8.

Kim, S.-G. (1995) “Quantification of relative cerebral blood flow change by flow-sensitive alternating inversion recovery (FAIR) technique: application to functional mapping.” Magn. Reson. Med. **34**, 293-301.

Kwong, K. K. et al. (1995) “MR perfusion studies with T1-weighted echo planar imaging.”Magn. Reson. Med. **34**, 878-887.

Simultaneous BOLD and Perfusion



BOLD

Perfusion

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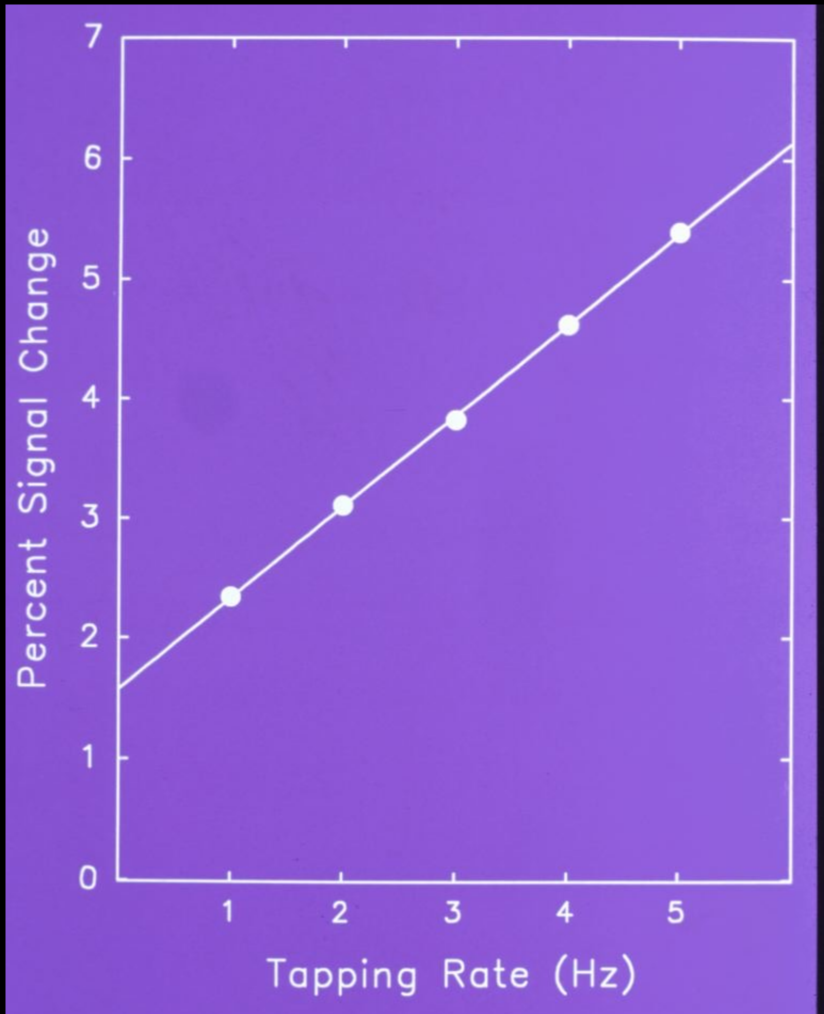
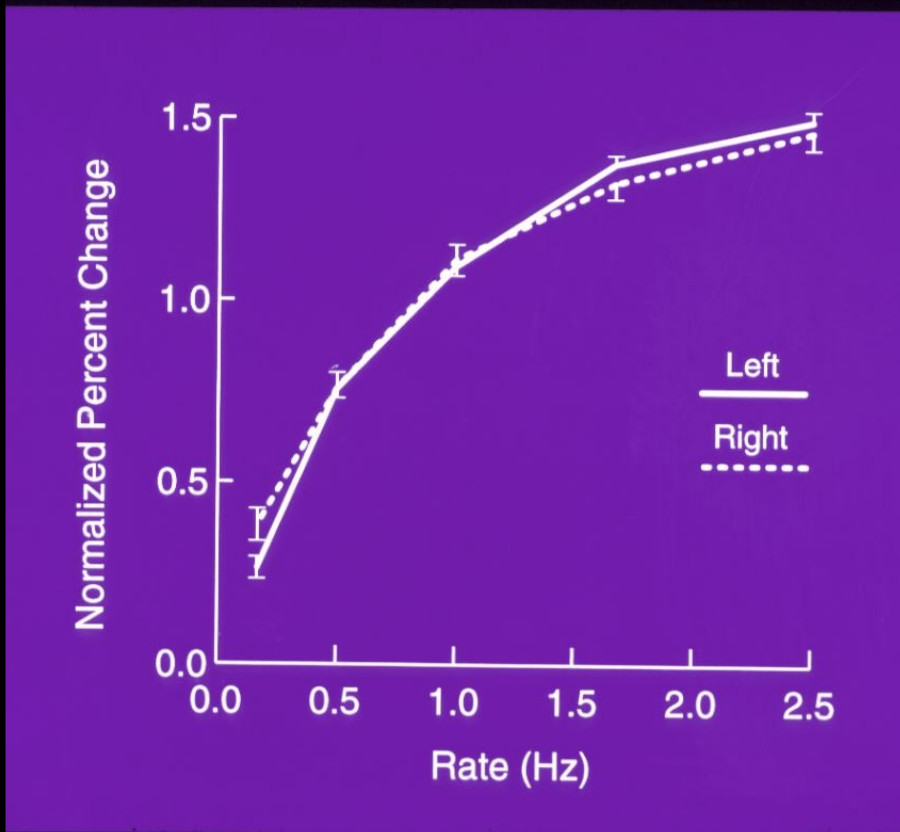
Motor Cortex

Auditory Cortex



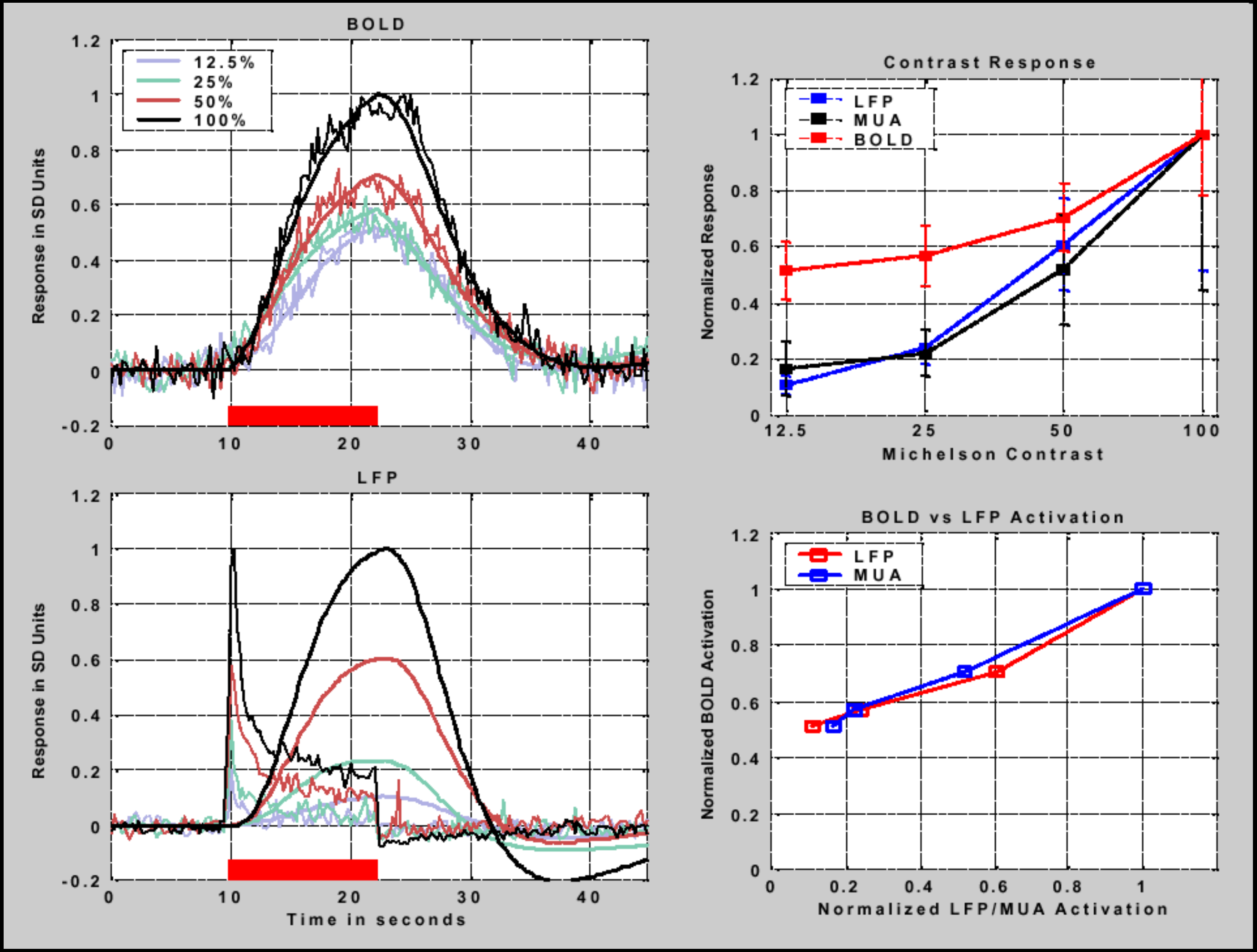


S. M. Rao et al, (1996) “Relationship between finger movement rate and functional magnetic resonance signal change in human primary motor cortex.” *J. Cereb. Blood Flow and Met.* 16, 1250-1254.

J. R. Binder, et al, (1994). “Effects of stimulus rate on signal response during functional magnetic resonance imaging of auditory cortex.” *Cogn. Brain Res.* 2, 31-38

Relationship between neuronal activity and BOLD.

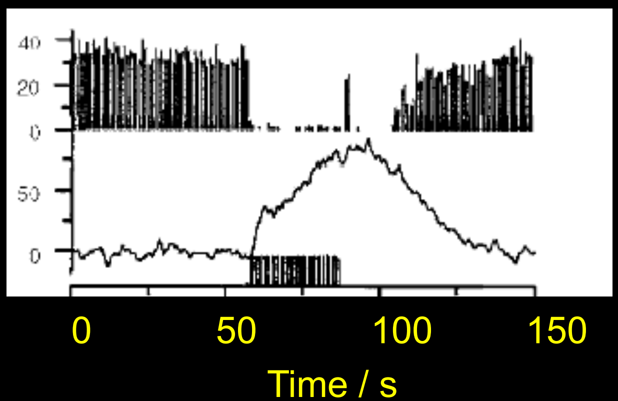
Magnitude



Logothetis et al. (2001) Nature, 412, 150-157

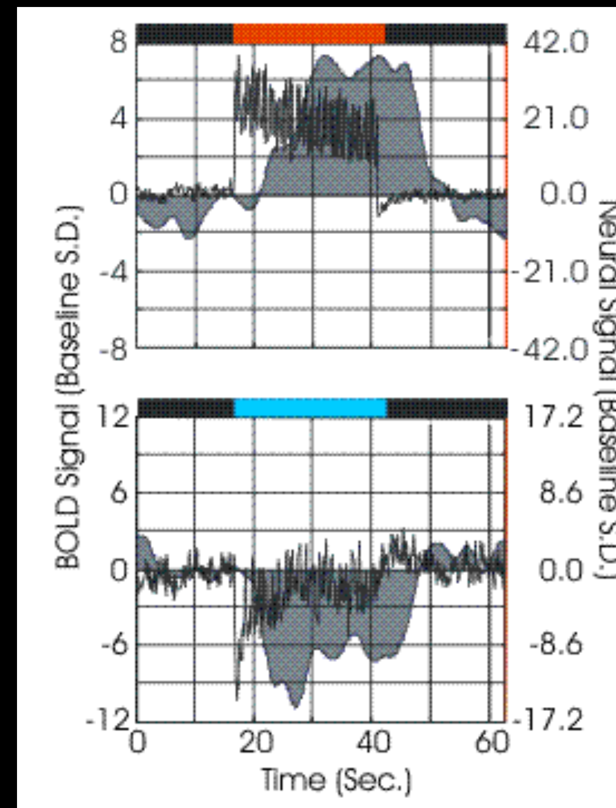
Relationship between neuronal activity and BOLD.

Inhibition



Mathiesen, et al (1998), J Physiol 512.2:555-566

Negative BOLD?



Schmuel et al. (2003) OHBM, 308

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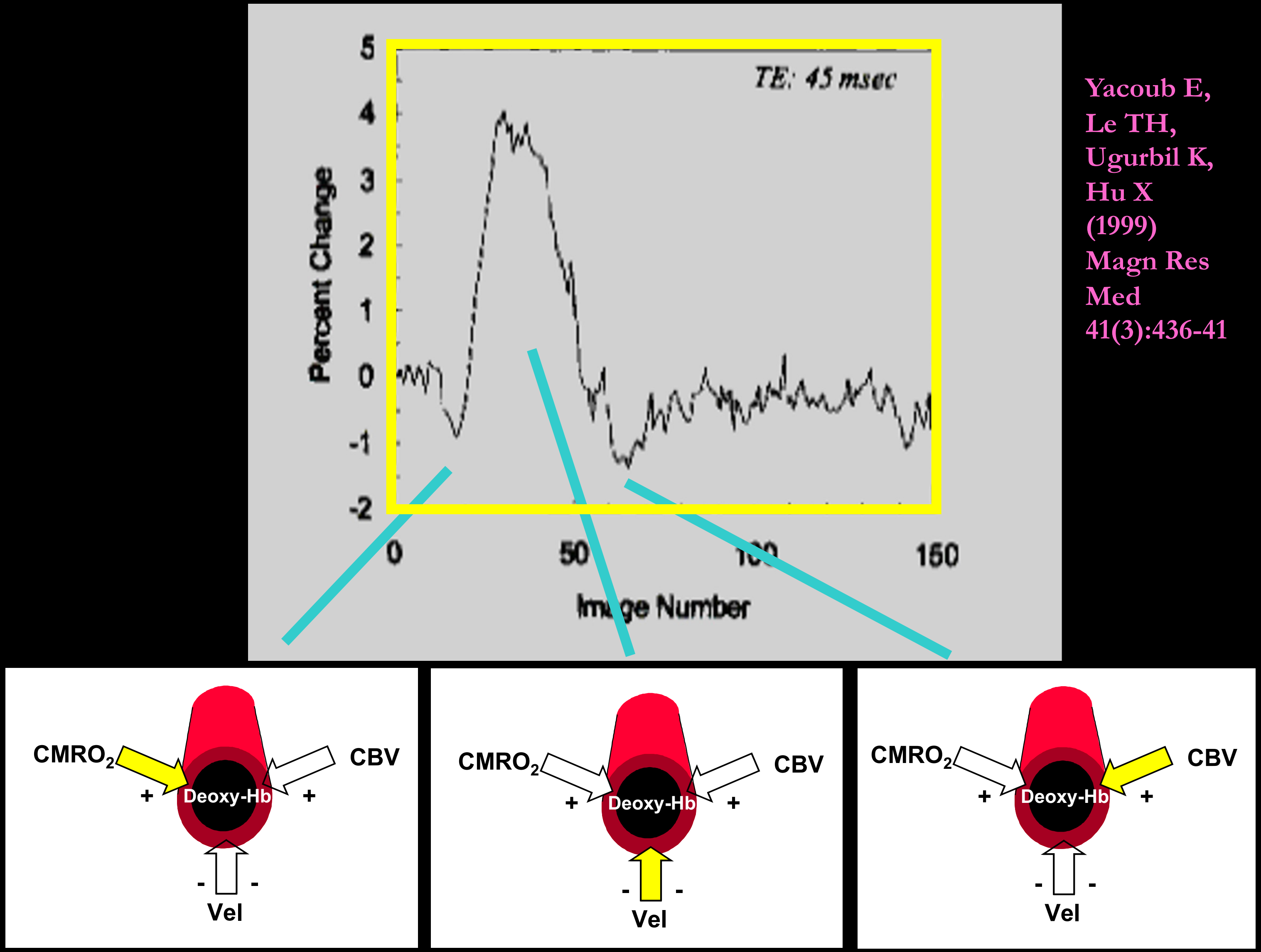
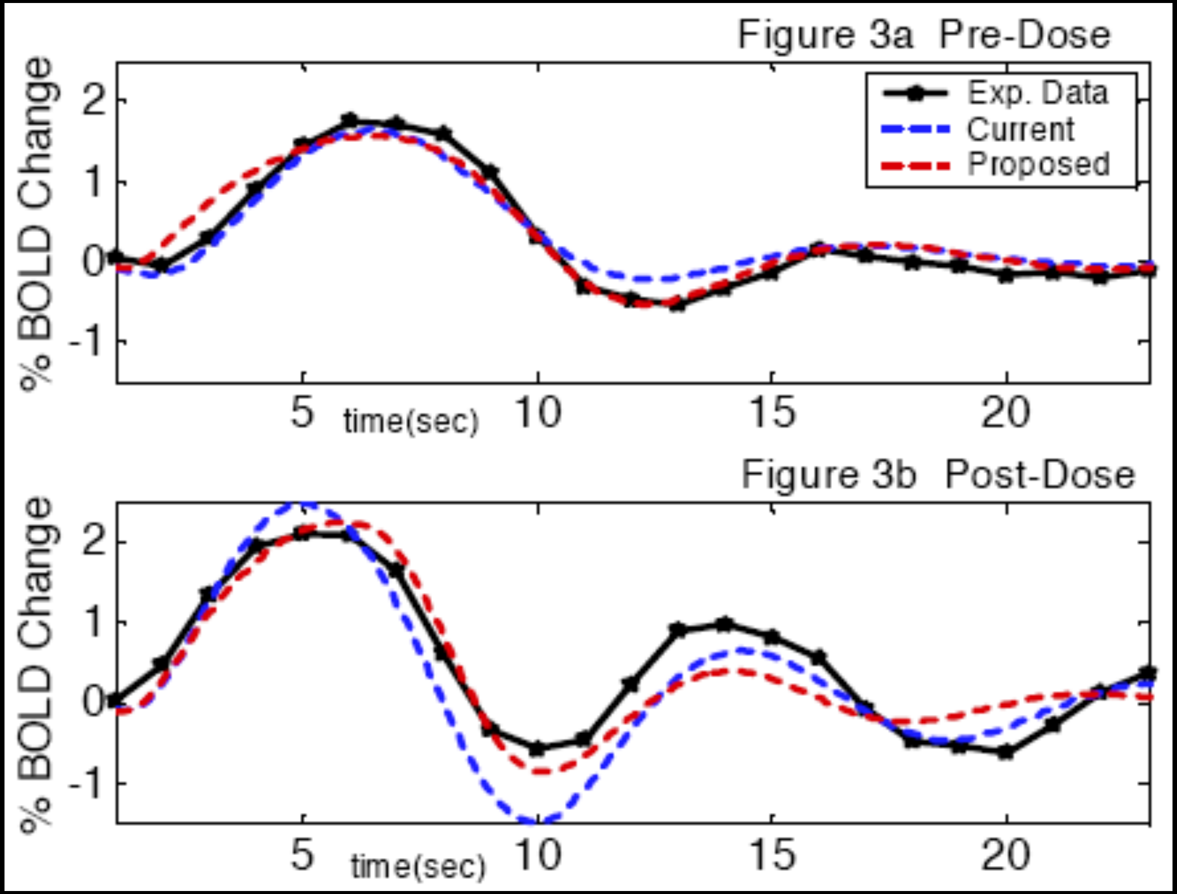
Sources of BOLD dynamic characteristics.



Yacoub E, Le TH, Ugurbil K, Hu X (1999) Magn Res Med 41(3):436-41

An example of dynamics modulation

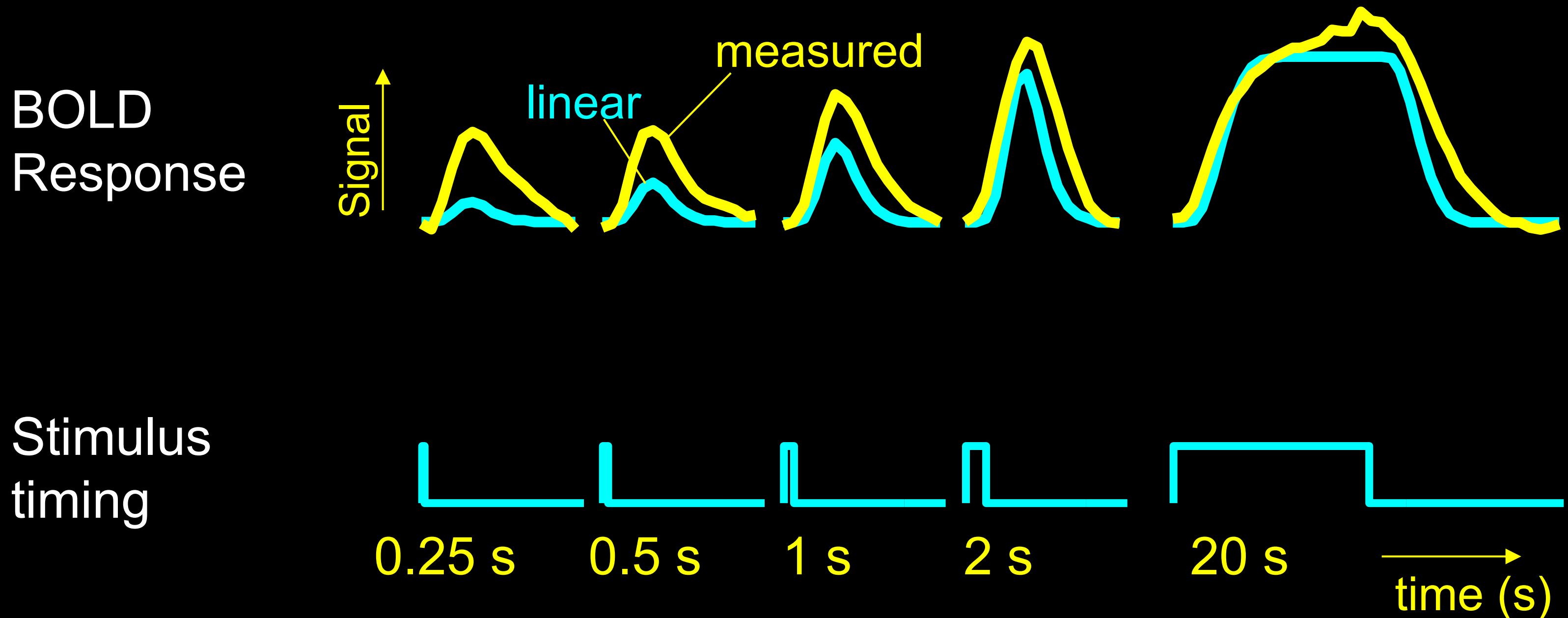
Effects of Caffeine



Behzadi, et al (2004), ISMRM 279

Dynamic Nonlinearity Assessment

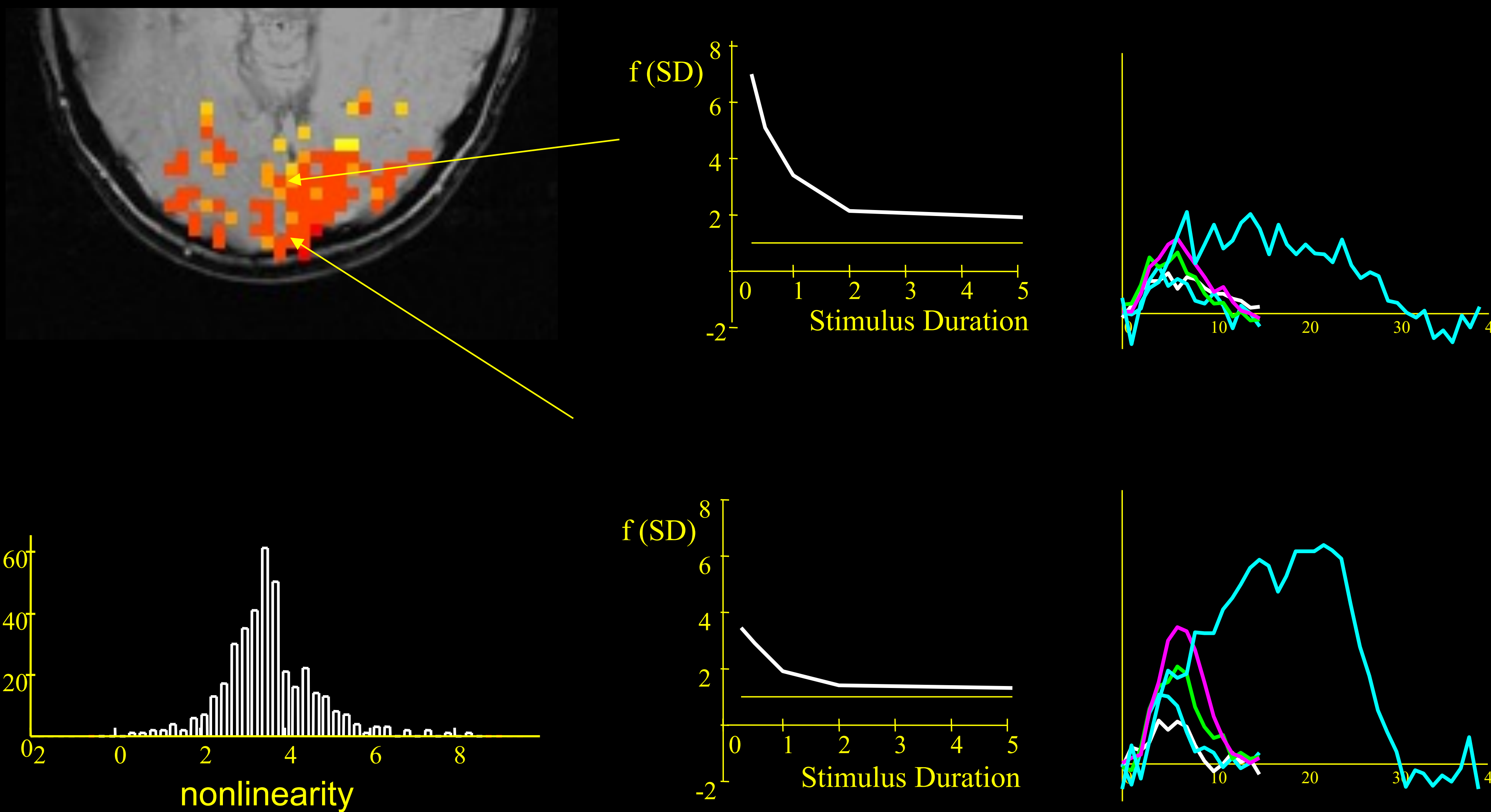
Different stimulus "ON" periods



Brief stimuli produce larger responses than expected

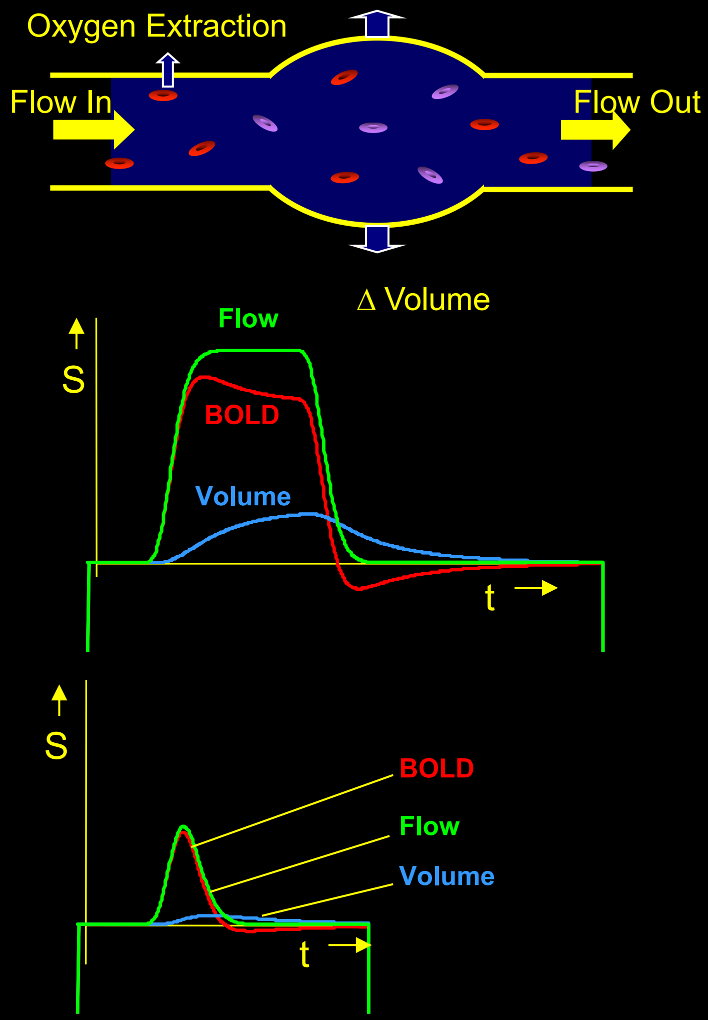
R. M. Birn, Z. Saad, P. A. Bandettini, (2001) "Spatial heterogeneity of the nonlinear dynamics in the fMRI BOLD response." ***NeuroImage*****, 14: 817-826.**

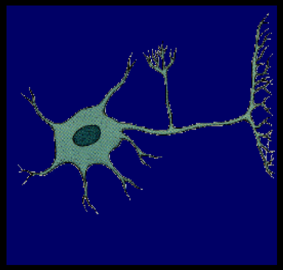
Spatial Heterogeneity of BOLD Nonlinearity

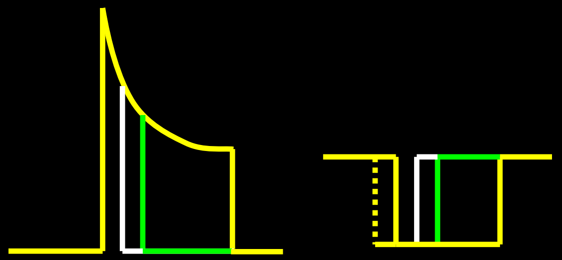


R. M. Birn, Z. Saad, P. A. Bandettini, (2001) "Spatial heterogeneity of the nonlinear dynamics in the fMRI BOLD response." *NeuroImage*, 14: 817-826.

Sources of this Nonlinearity



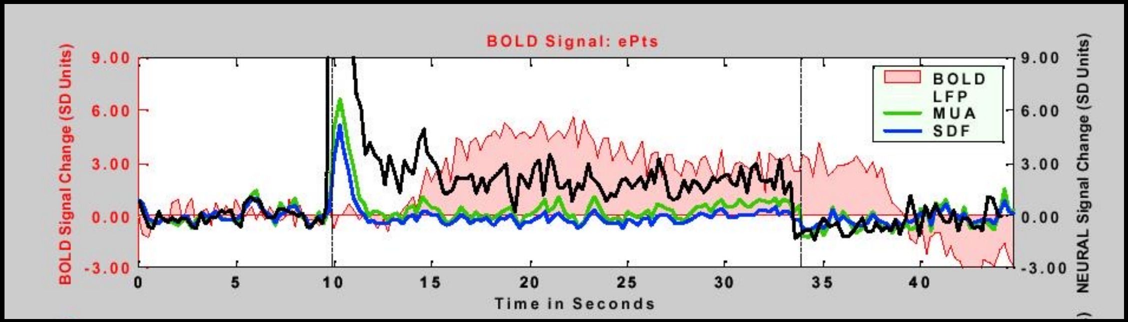




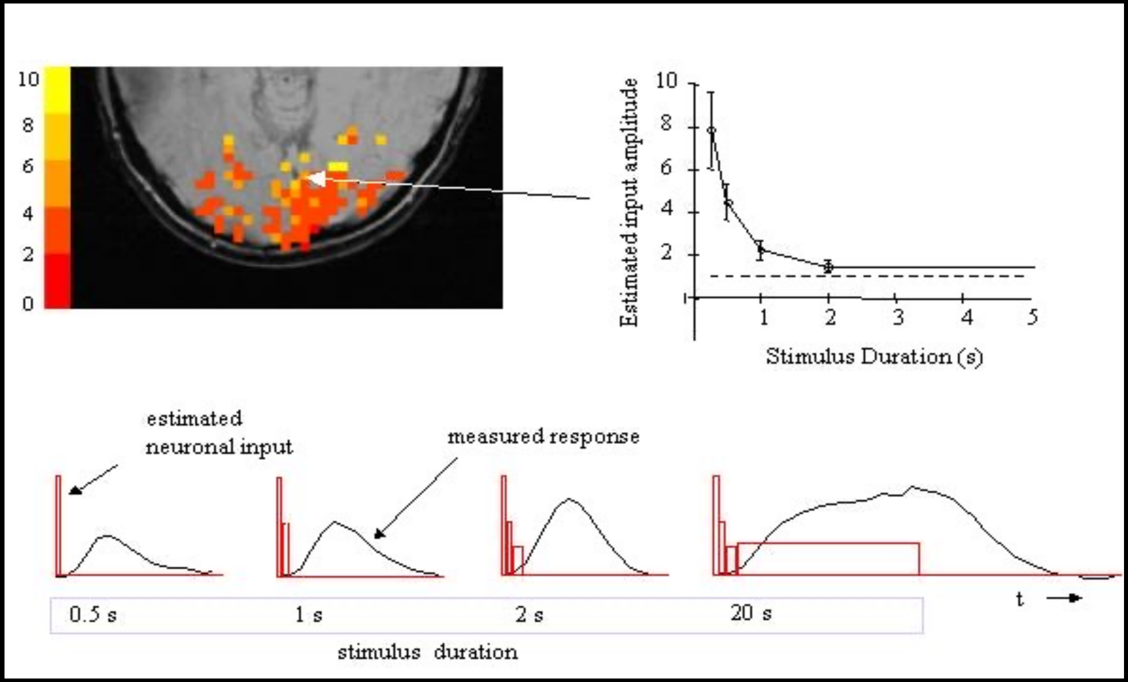
Vasquez et al. (1998) NeuroImage, 7, 108-118

BOLD Correlation with Neuronal Activity

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



P. A. Bandettini and L. G. Ungerleider, (2001) "From neuron to BOLD: new connections." Nature Neuroscience, 4: 864-866.



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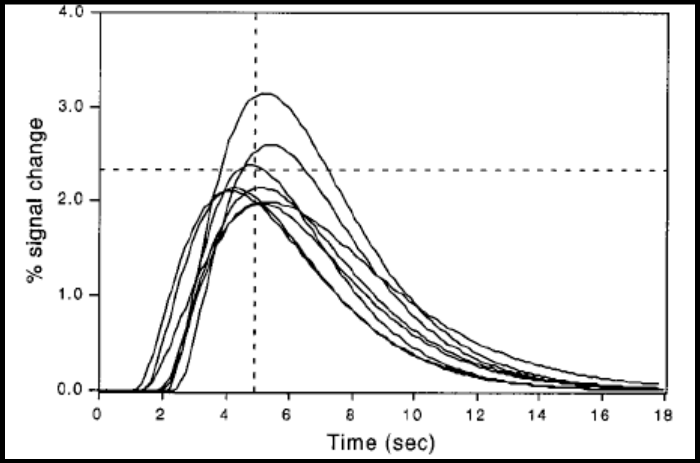
Sources of spatial and temporal variability.

Latency and Magnitude

From Subject to Voxel….

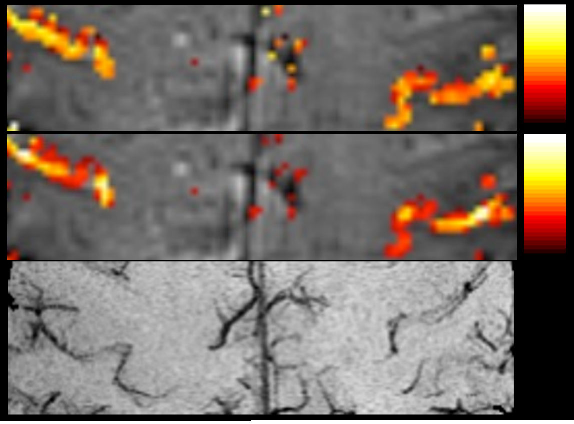


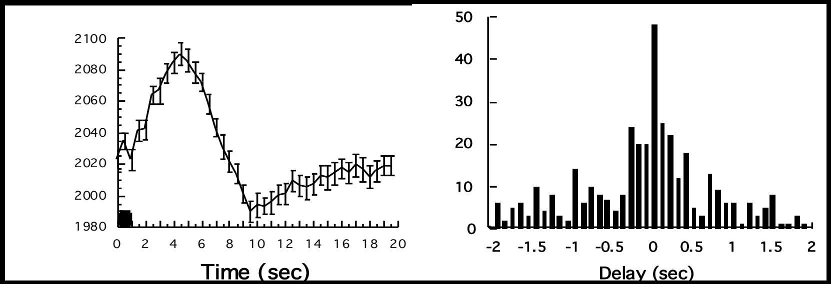
Miezin, et al (2000), NeuroImage 11, 735-759

Latency

Magnitude

Venogram

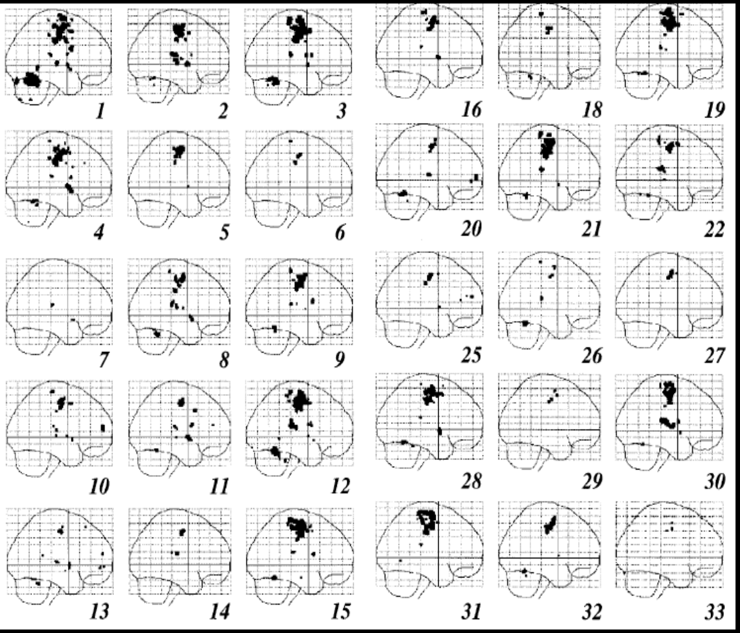




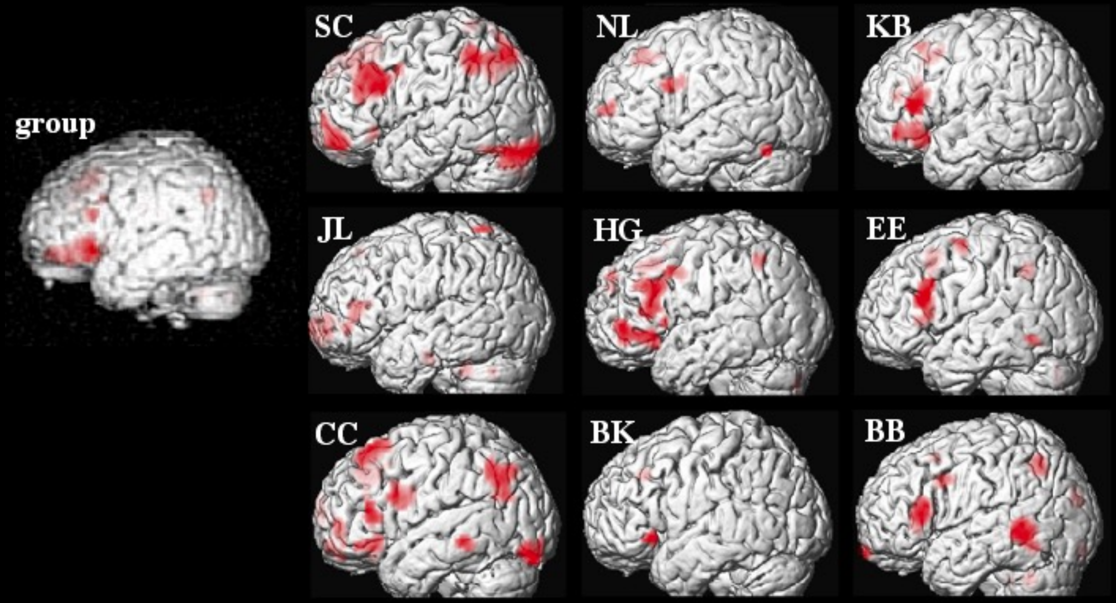
P. A. Bandettini, (1999) "Functional MRI" 205-220.

Sources of spatial and temporal variability.

Spatial Variation



McGonigle, et al (2000), NeuroImage 11, 708-734



Courtesy, Mike Miler, UC Santa Barbara and Jack Van Horn, fMRI Data Center, Dartmouth

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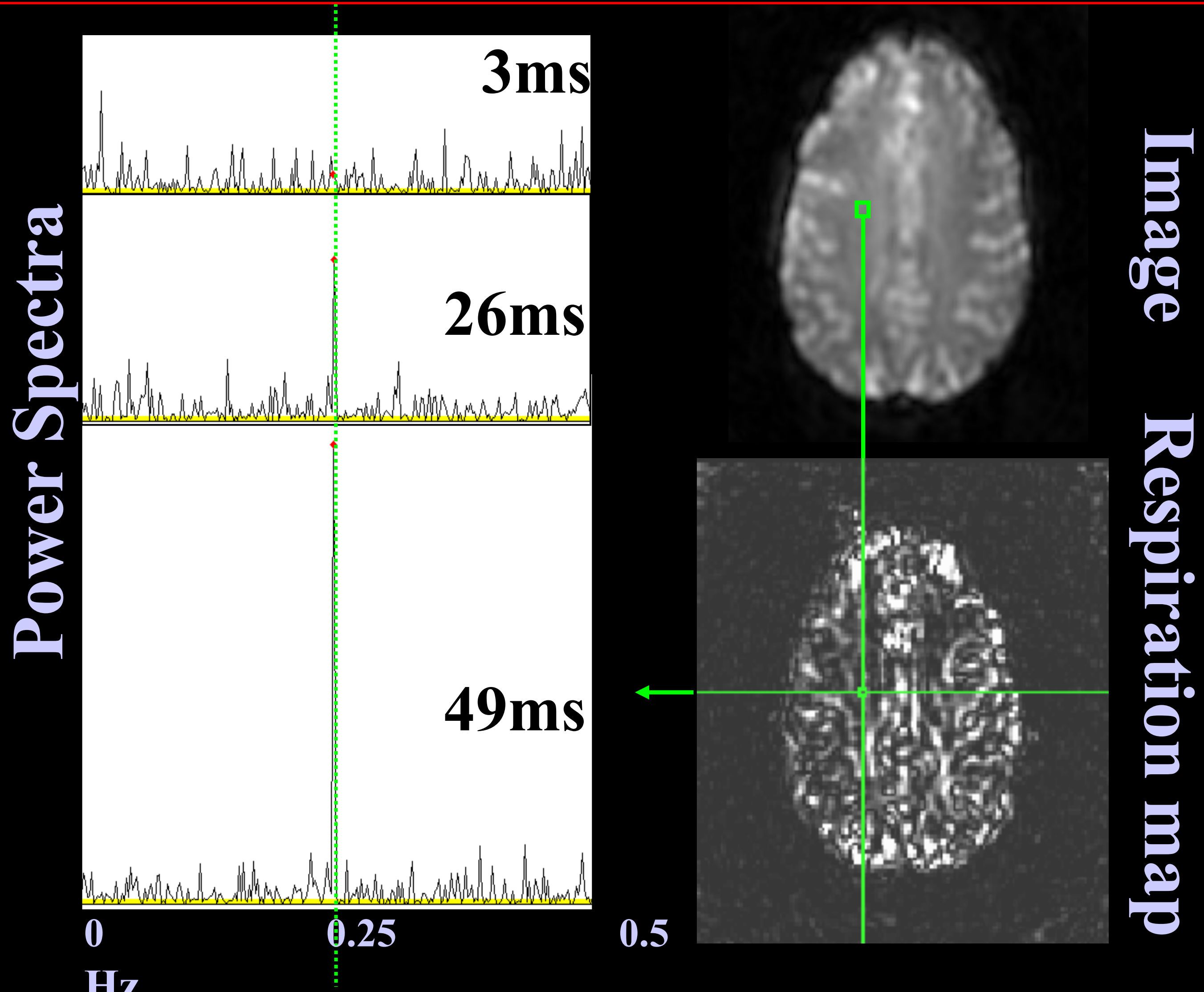
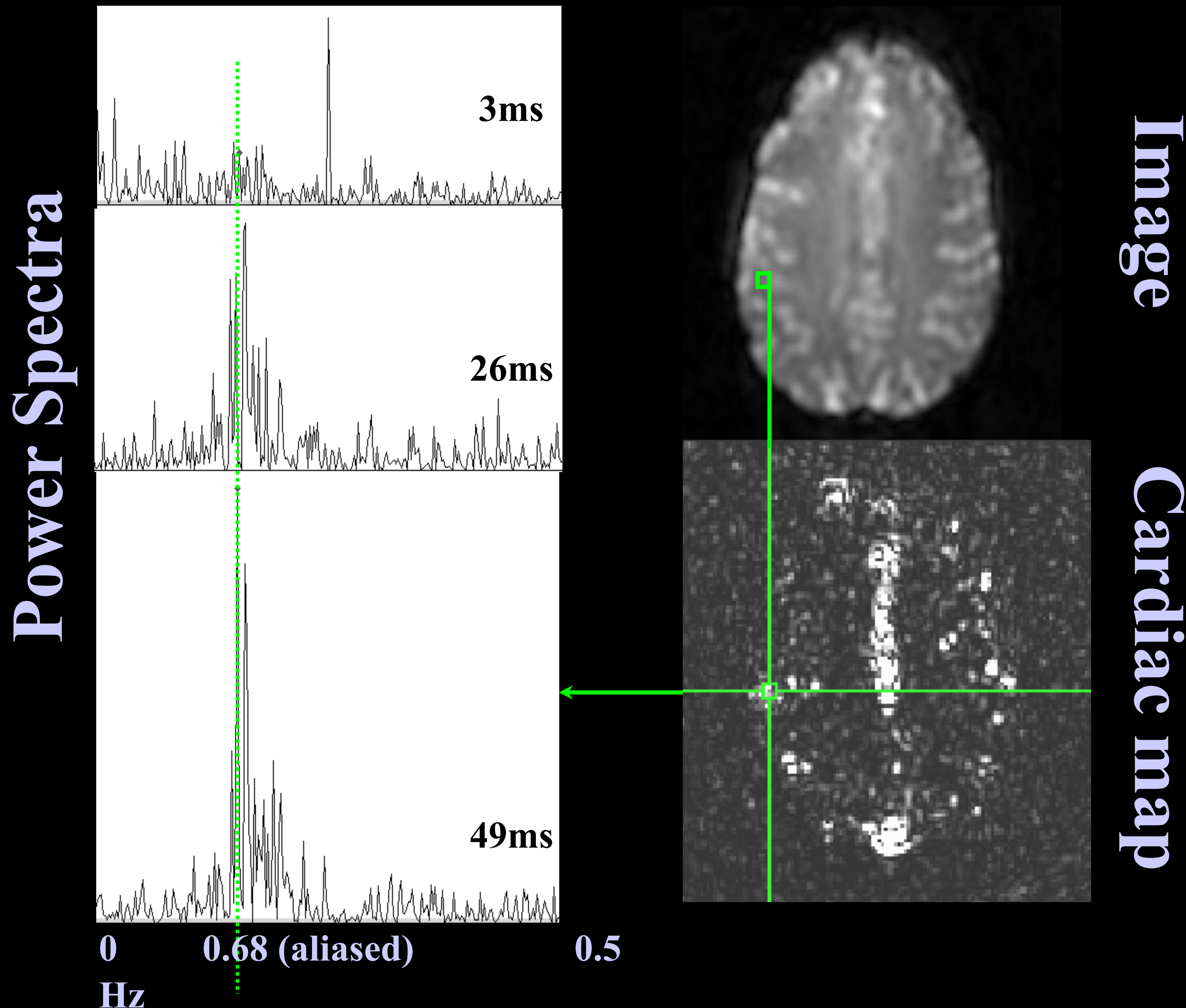
0.25 Hz Breathing at 3T

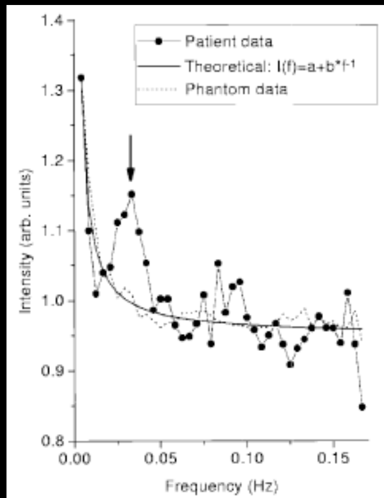


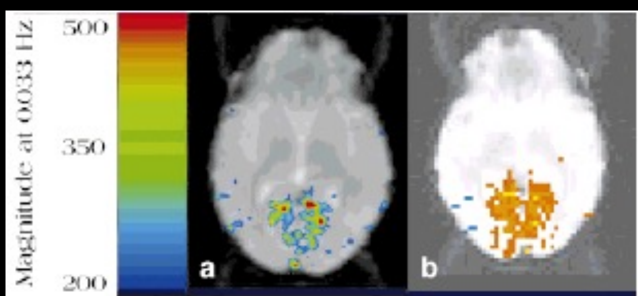
0.68 Hz Cardiac rate at 3T



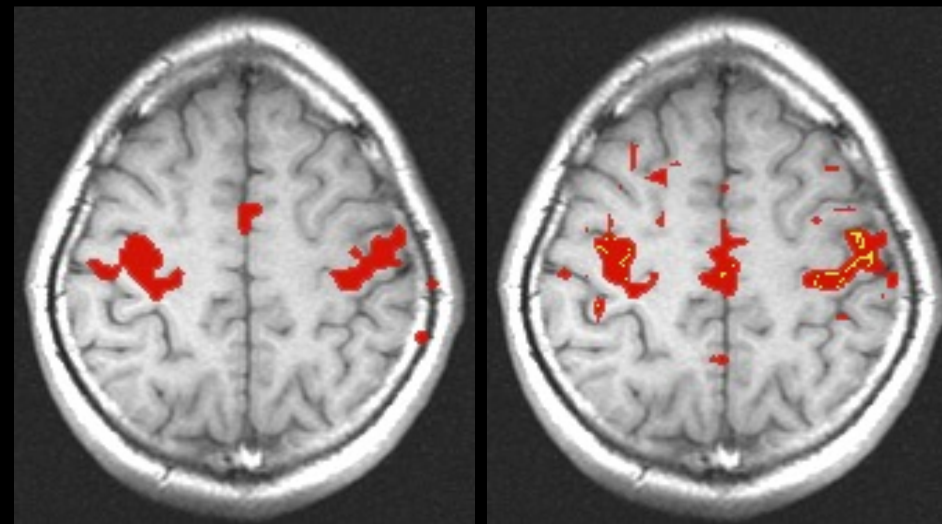
What's really in the noise?

Spontaneous Fluctuation Correlation

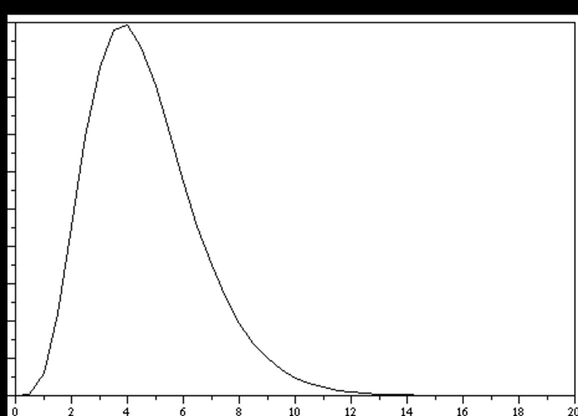




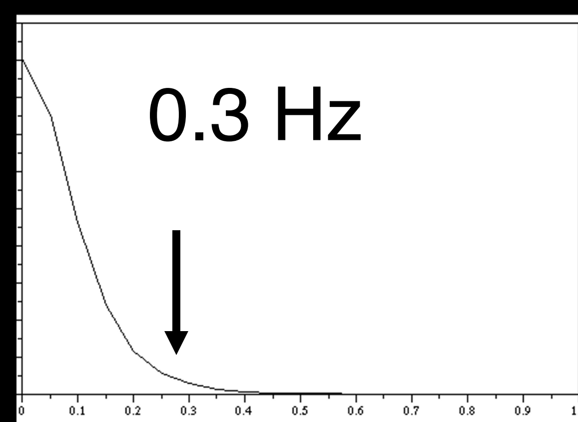
Kiviniemi, et al (2000), MRM 44, 373-378



Biswal, et al (1995), MRM 34, 537-541

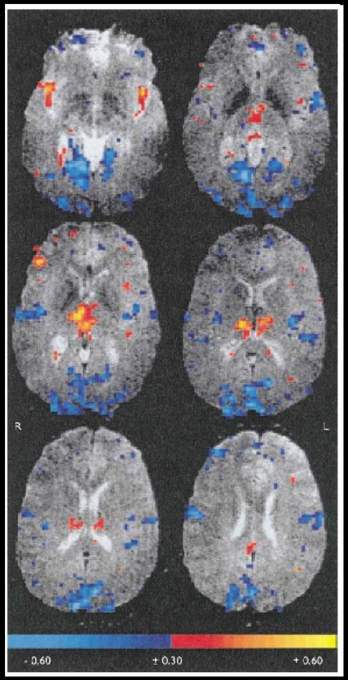


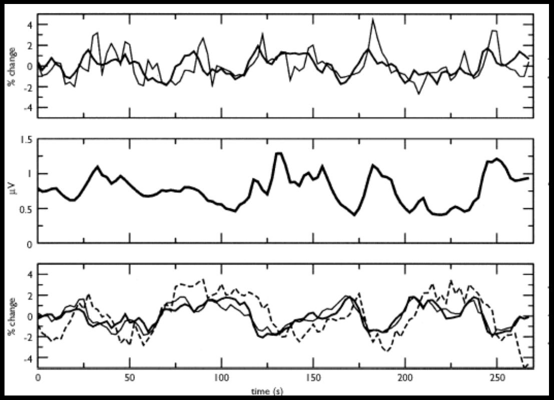
FFT



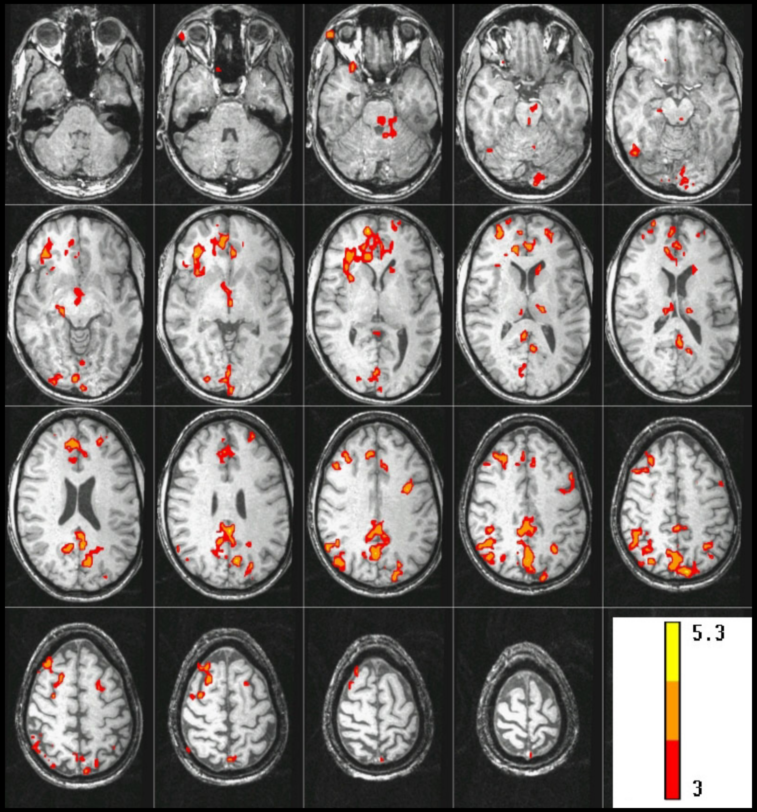
What's really in the noise?

Correlation with External Measures





Goldman, et al (2002), Neuroreport



Patterson, et al (2002), NeuroImage 17, 1787-1806

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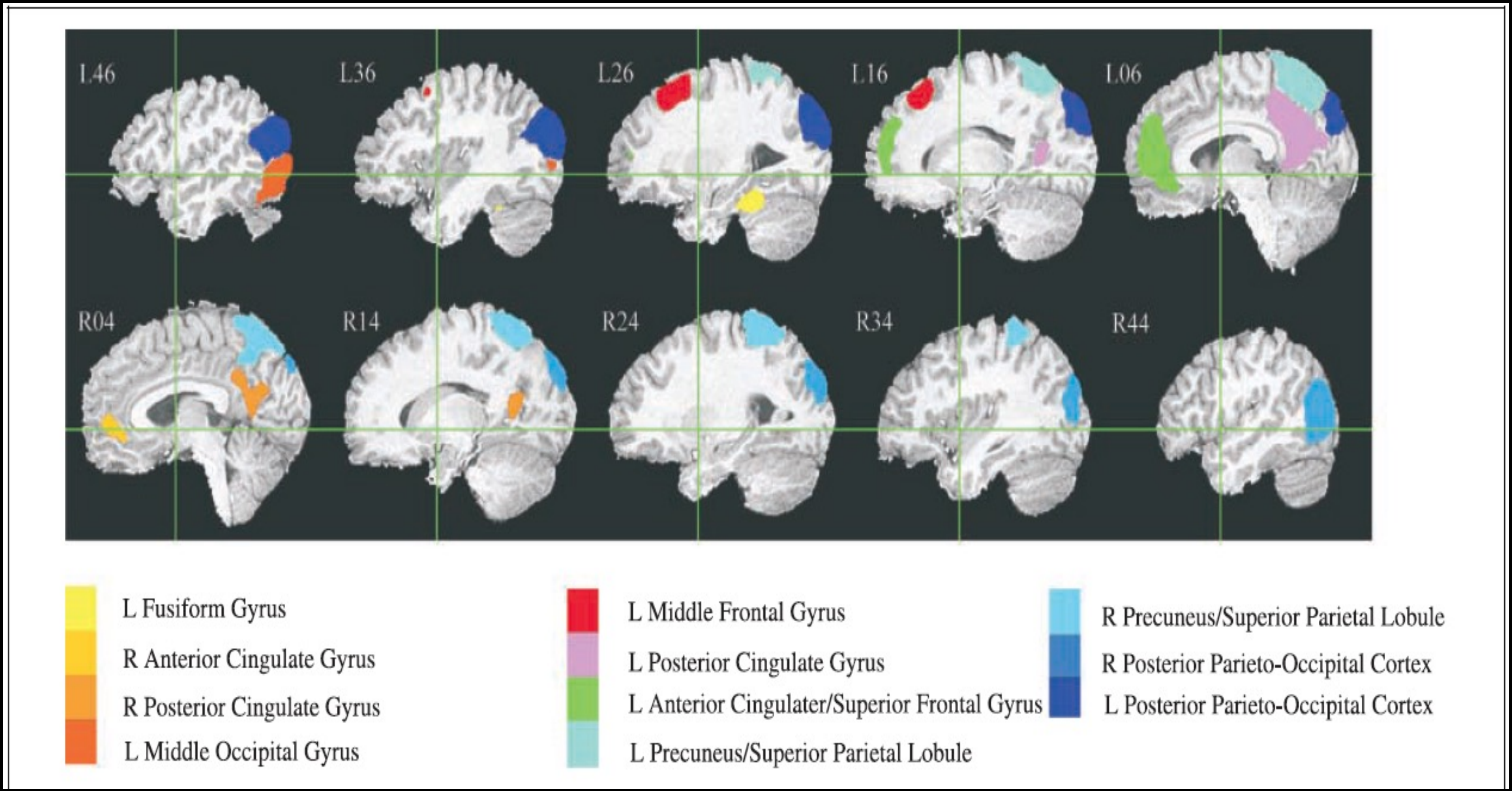

McKiernan, et al (2003), Journ. of Cog. Neurosci. 15 (3), 394-408

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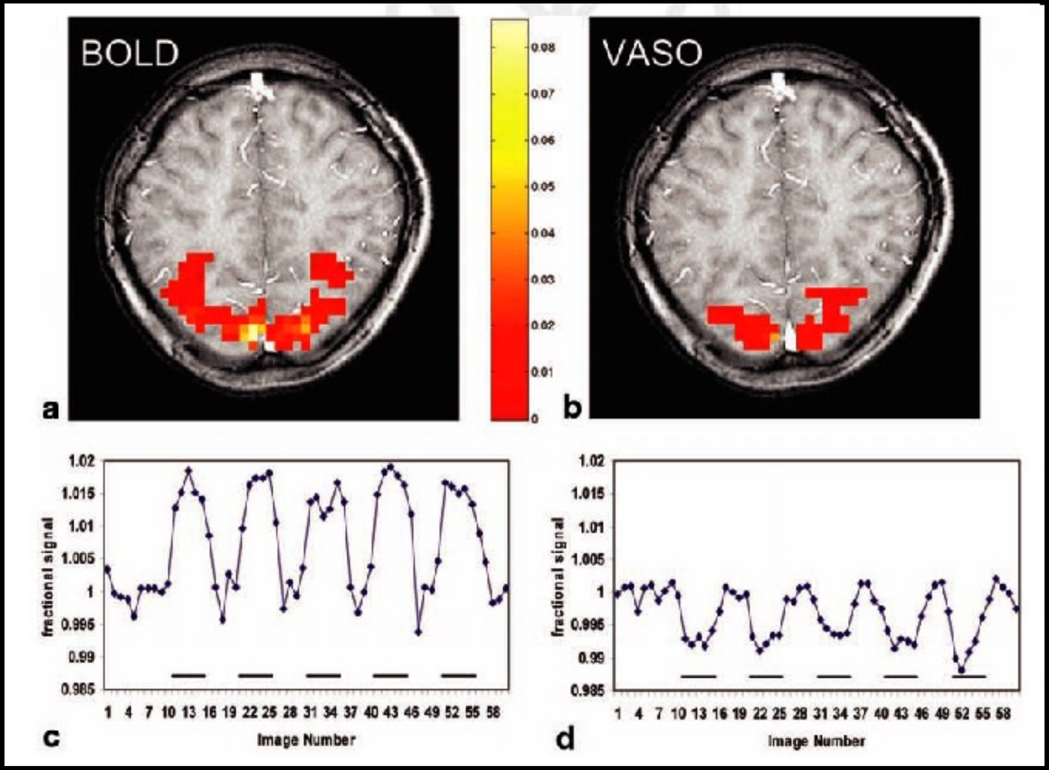
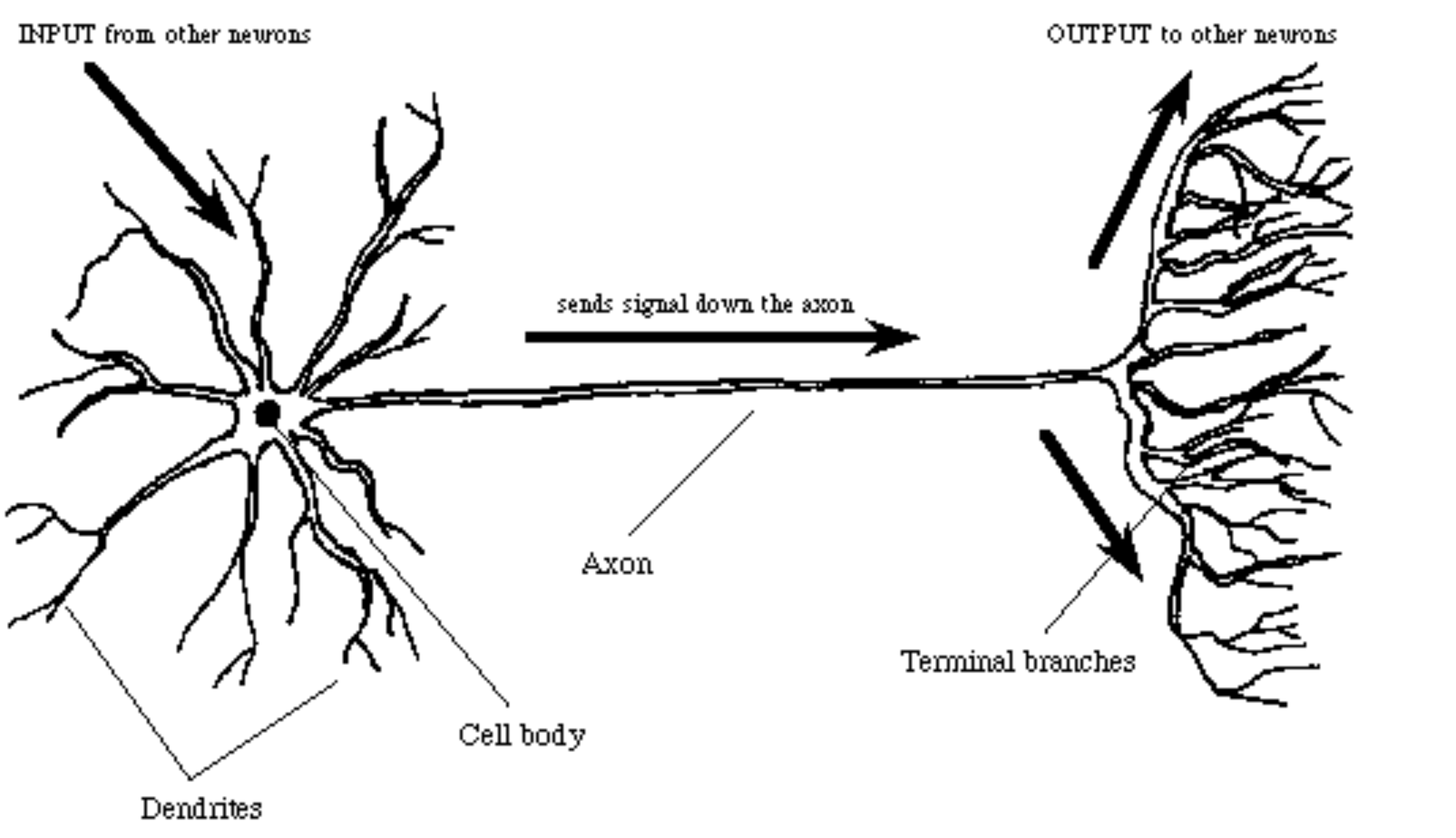
Other sources of functional contrast?

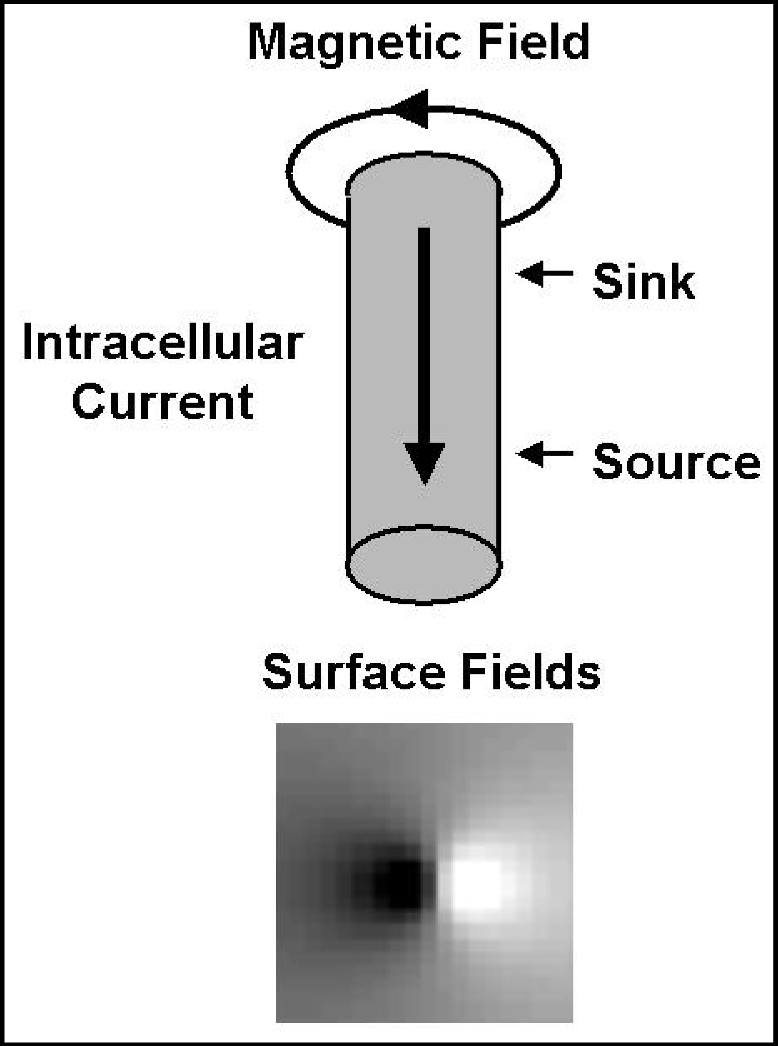
Blood Volume

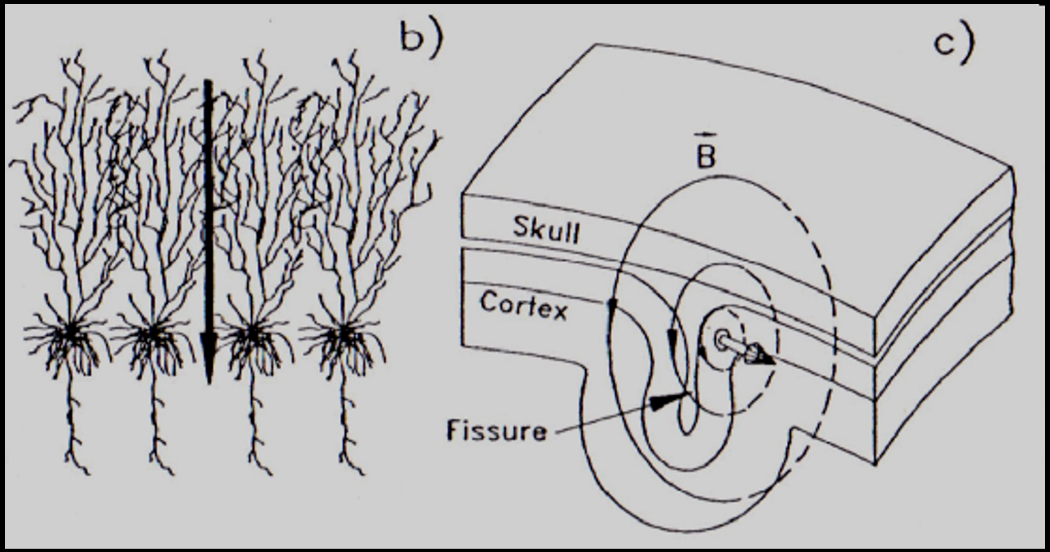


Lu, et al (2003) MRM 50 (2): 263-274

Neuronal Current MRI?

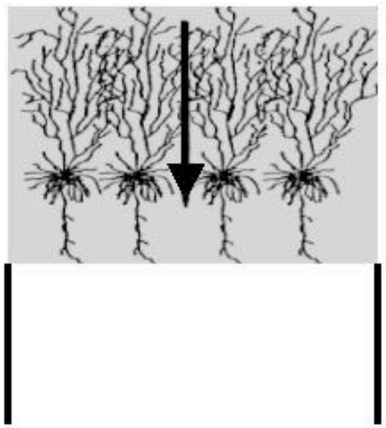




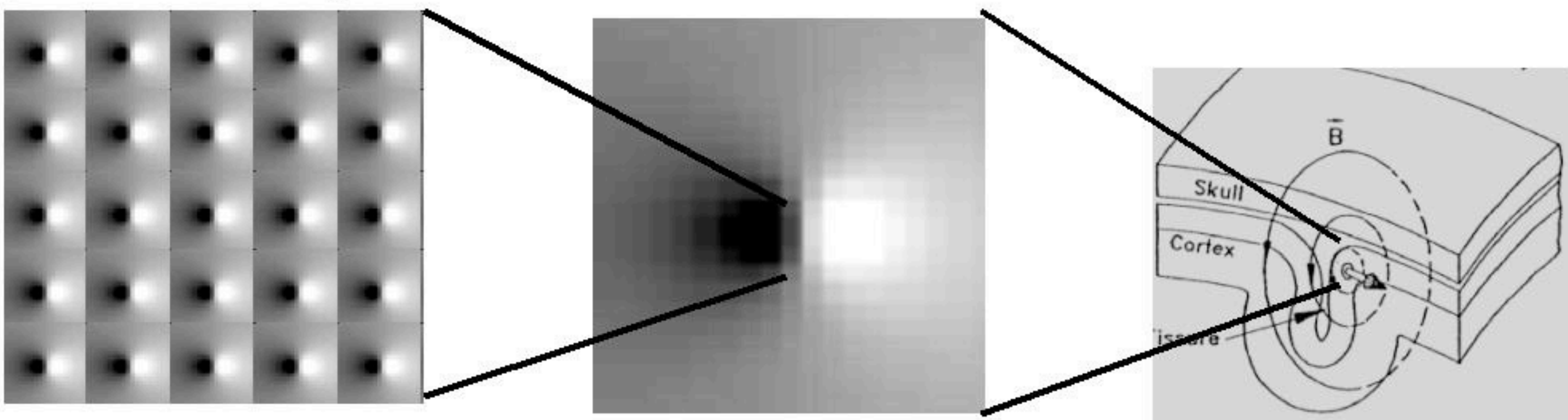


100 fT at on surface of skull

J.P. Wikswo Jr et al. *J Clin Neuronphy* 8(2): 170-188, 1991



Surface Field Distribution Across Spatial Scales



Magnetic field associated with single dendrite

Single dendrite having a diameter d, and length L behaves like a conductor with conductivity σ. Resistance is R=V/I, where $R=4L/(\pi d^2 \sigma)$. From Biot-Savart:

$$B = \frac{\mu_0}{4\pi}\frac{Q}{r^2} = \frac{\mu_0}{16}\frac{d^2 \sigma V}{r^2}$$

by substituting $d = 4\mu m$, $\sigma \approx 0.25\ \Omega^{-1}\ m^{-1}$, $V = 10mV$ and $r = 4cm$

(typical measurement distance when using MEG)

the resulting value measured at the surface of a skull is:

$B \approx 0.002$ fT

J. Bodurka, P. A. Bandettini. *Toward direct mapping of neuronal activity: MRI detection of ultra weak transient magnetic field changes.* **Magn. Reson. Med. 47: 1052-1058, (2002).**

Magnetic field associated with bundle of dendrites

Because $\mathbf{B_{MEG}=100fT}$ is measured by MEG on the scalp, at least 50,000 neurons (0.002 fT x 50,000 = 100 fT), must coherently act to generate such field. These bundles of neurons produce, within a typical voxel, 1 mm x 1 mm x 1 mm, a field of order:

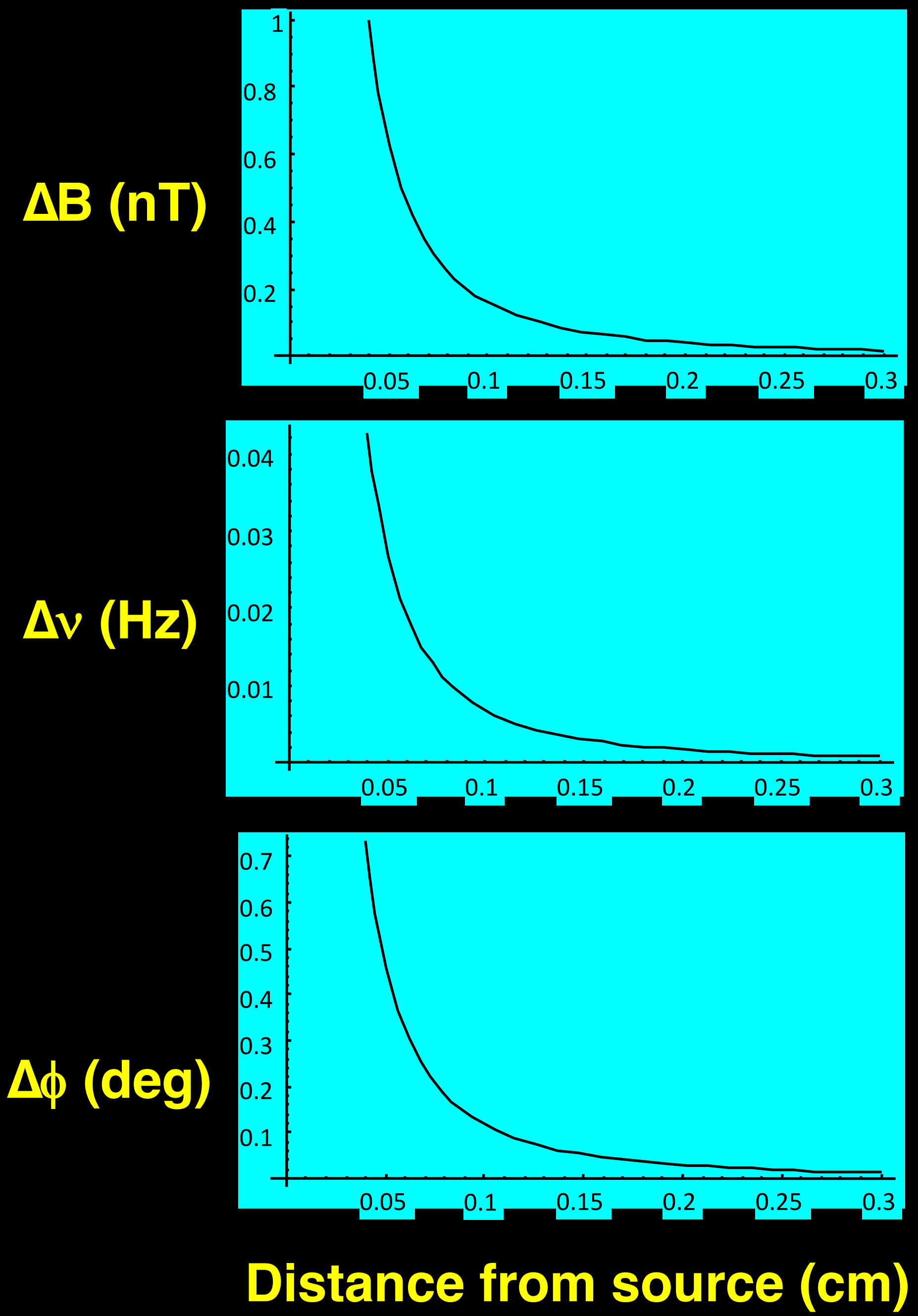
$$B_{MRI} = B_{MEG}\left(\frac{r_{MEG}}{r_{MRI}}\right)^2 = B_{MEG}\left(\frac{4\,cm}{0.1\,cm}\right)^2 = 1600\,B_{MEG}$$

$\mathbf{B_{MRI} \approx 0.2nT}$

$\Delta B = 100fT * (4cm/x)^2$

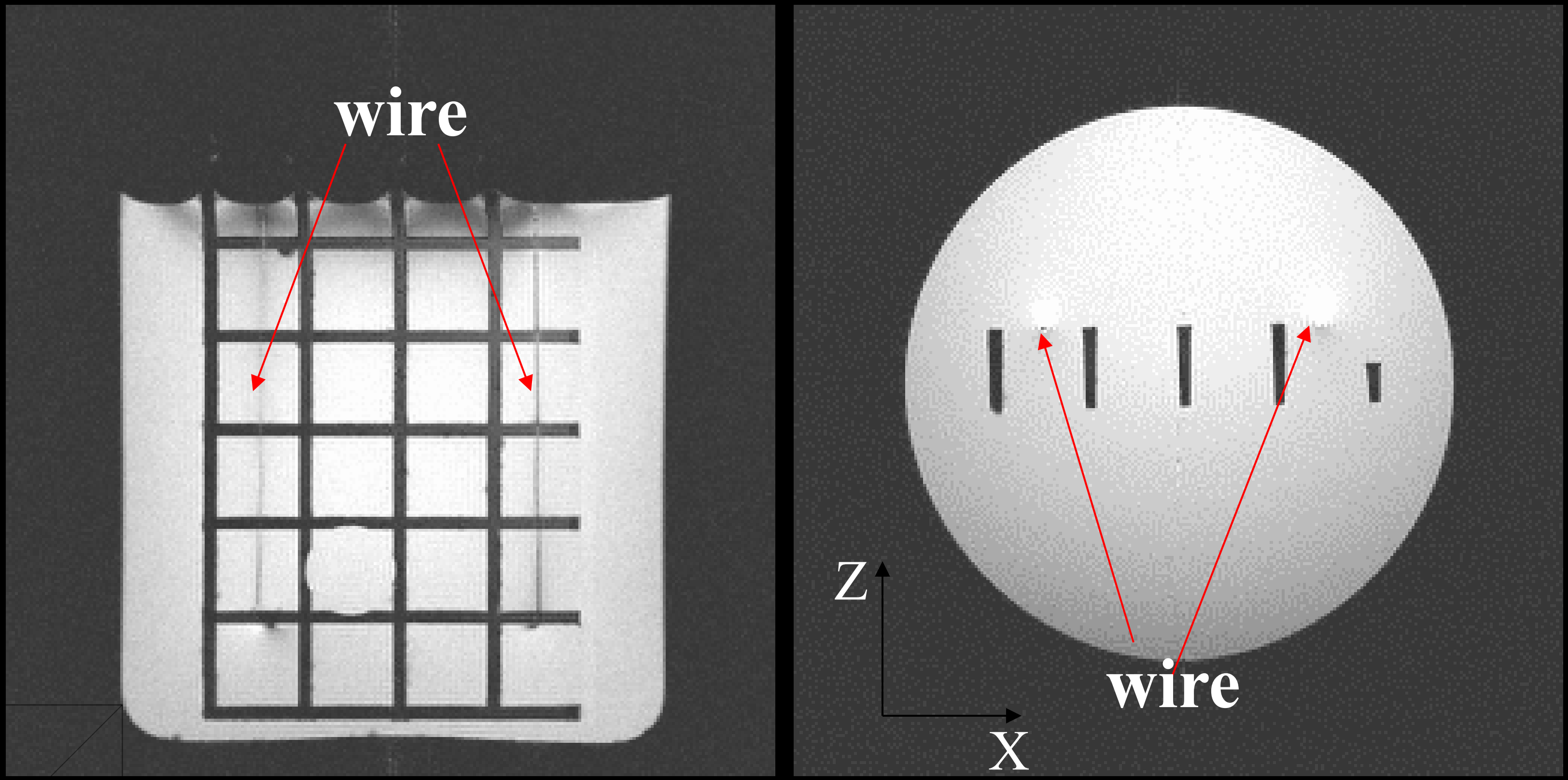
$\Delta\nu = \gamma * \Delta B$

$\Delta\phi = \Delta\nu * TE * (\square\square\square/\pi)$

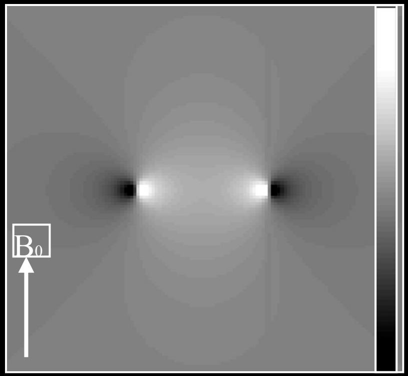


Is 0.2 nT detectable?

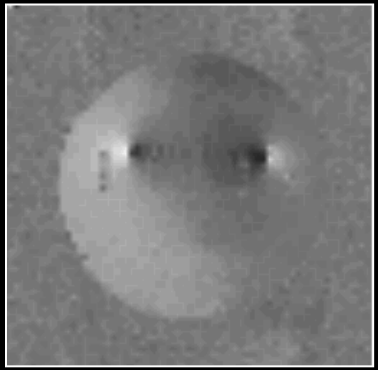
Current Phantom Experiment



calculated $B_c \parallel B_0$



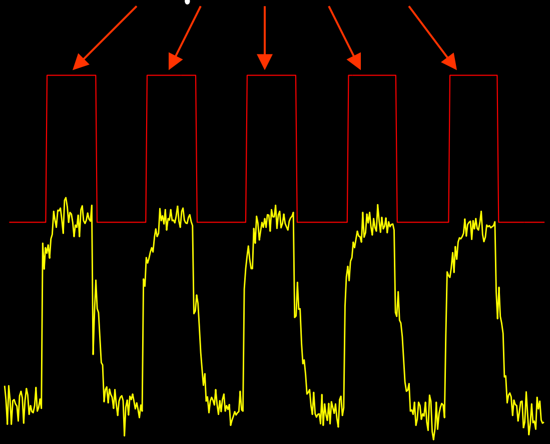
$\Delta\phi \cong 20^0$



Correlation image

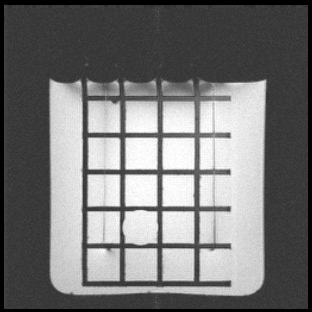
Measurement

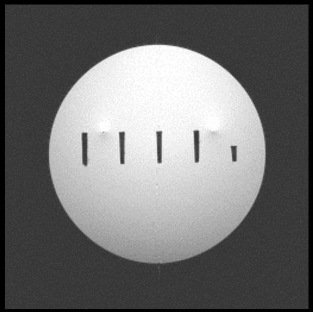
70 μA current

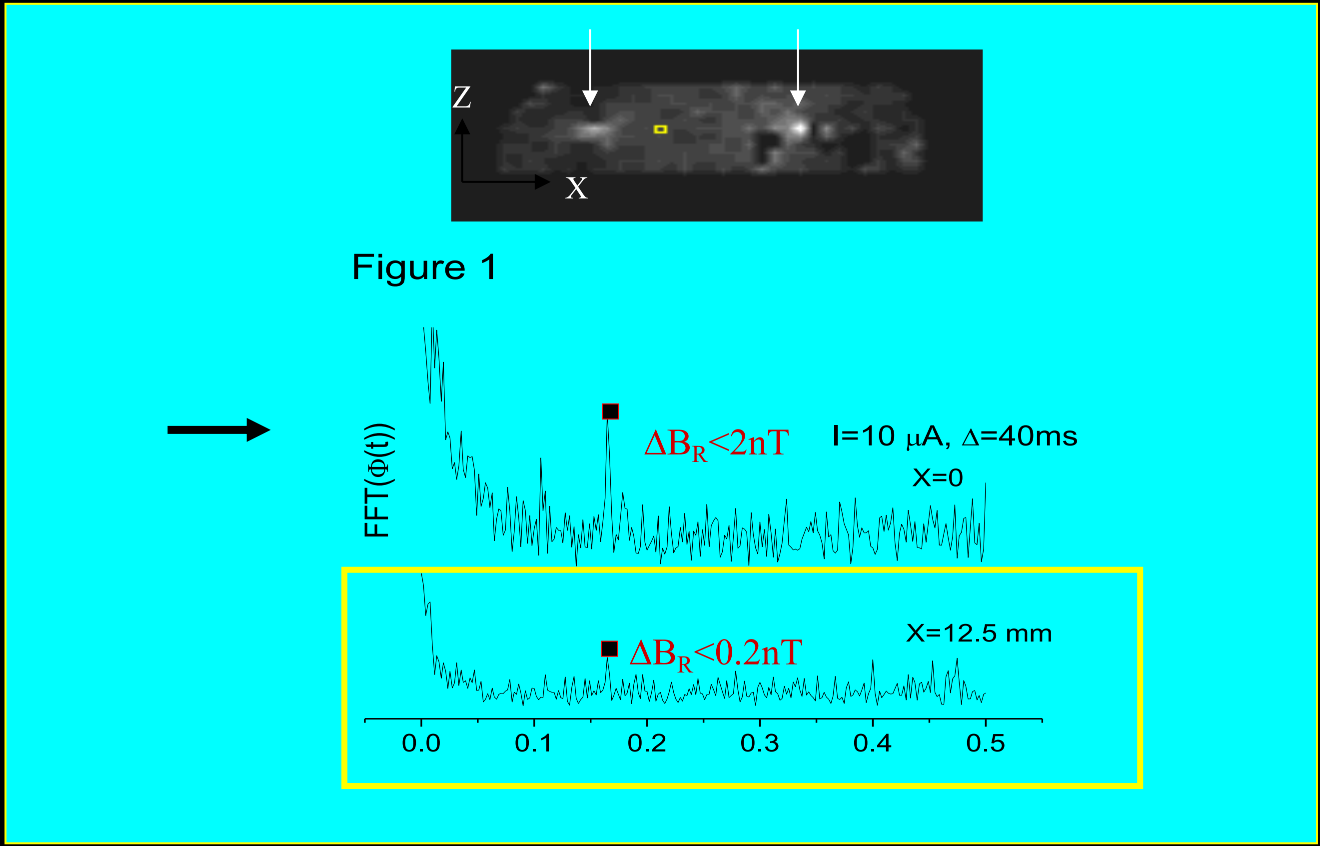


Single shot GE EPI

J. Bodurka, P. A. Bandettini. Toward direct mapping of neuronal activity: MRI detection of ultra weak transient magnetic field changes, Magn. Reson. Med. 47: 1052-1058, (2002).





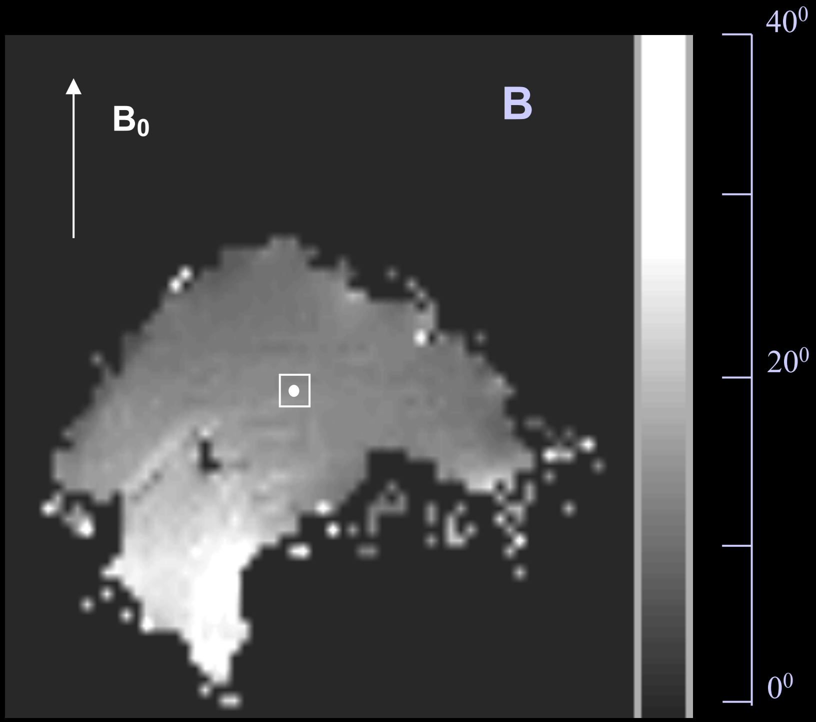


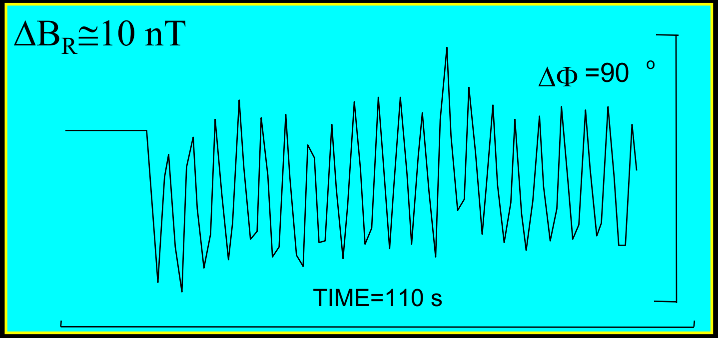
J. Bodurka, P. A. Bandettini. Toward direct mapping of neuronal activity: MRI detection of ultra weak transient magnetic field changes, Magn. Reson. Med. 47: 1052-1058, (2002).

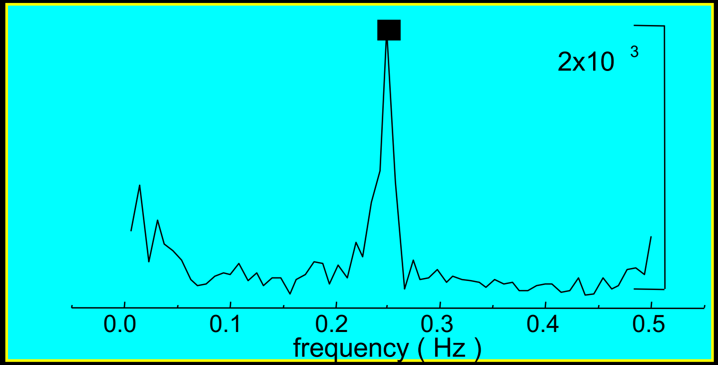
Main issues/obstacles:

- The effect is small
- Artifactual changes (respiration, cardiac) are order of mag larger
- The effect itself depends on geometry (phase/magnitude)
- The timing of the effect is variable
- BOLD still ubiquitous…

Human Respiration

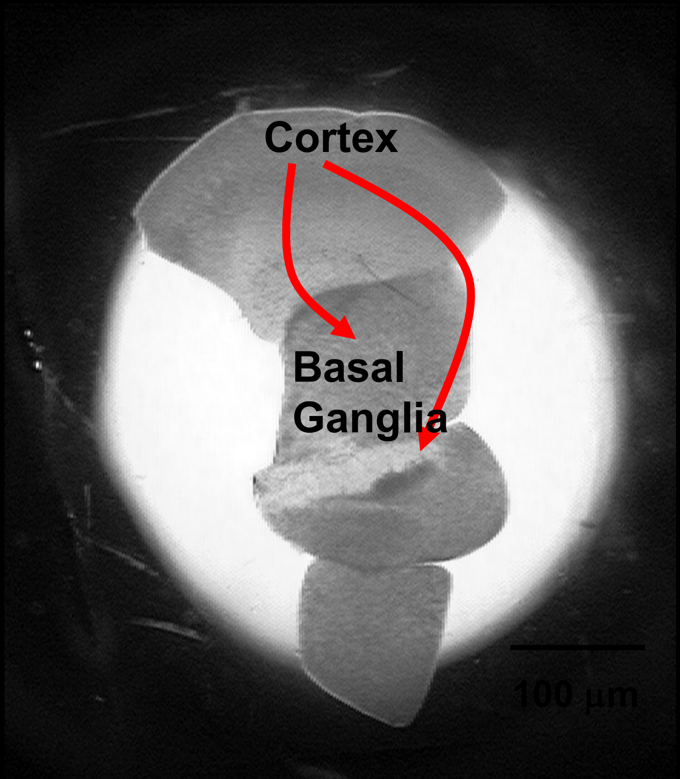






in vitro model

Organotypic (*no blood supply or hemoglobin traces*) sections of newborn-rat somato-sensory Cortex, or somato-sensory Cortex & Basal Ganglia



Plenz, D. et al. *Neurosci* 70(4): 861-924, 1996

- Size: in-plane:~1-2mm^2, thickness: 60-100µm
- Neuronal Population: 10,000-100,000

- Spontaneous synchronized activity < 2Hz
- Epileptiform activity
- Spontaneous beta freq. activity (20-30Hz)
- Network Activity Range: ~ 0.5-15µV

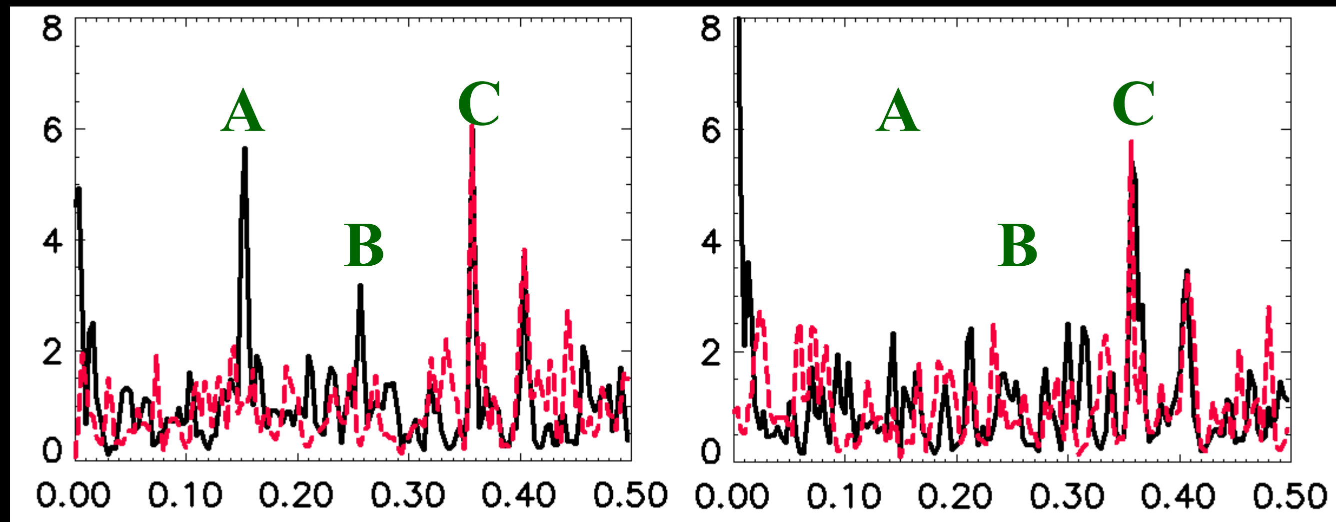
3 Tesla data

Culture ACSF

FSE image

0.15Hz map

1: culture *2: ACSF*



Hz Hz

Active condition: black line

Inactive condition: red line

A: 0.15 Hz activity, on/off frequency

B: activity

C: scanner noise (cooling-pump)

The Biggest Unknowns in Functional MRI

1. Relationship between neuronal activity and fMRI.
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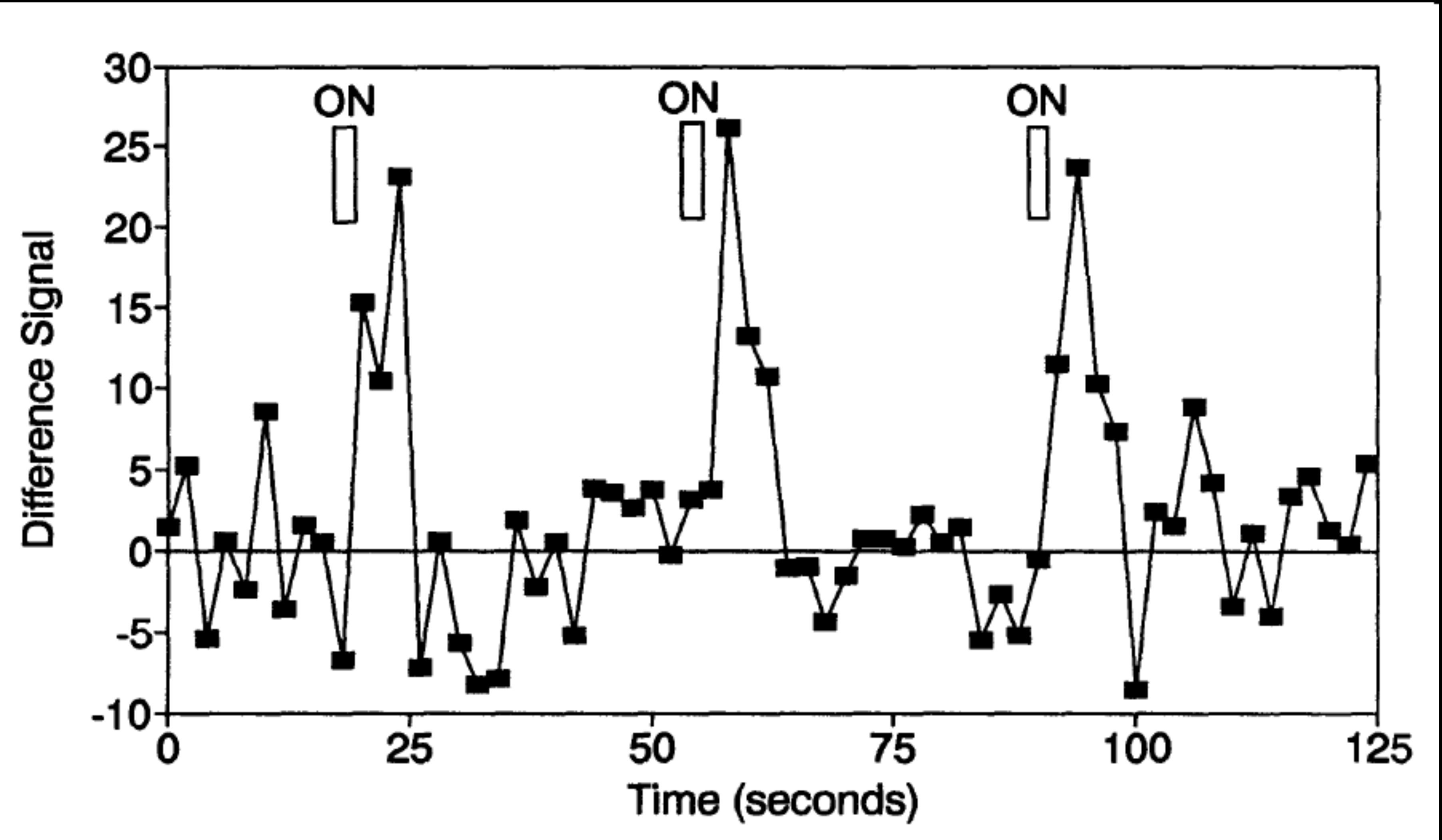
4. What’s really in the noise?
5. What’s “resting” state?
6. Other sources of functional contrast?
7. Ultimate temporal resolution?
8. Ultimate spatial resolution?
9. Ultimate clinical utility?
10. Best processing and display methods?
11. Optimal field strength?

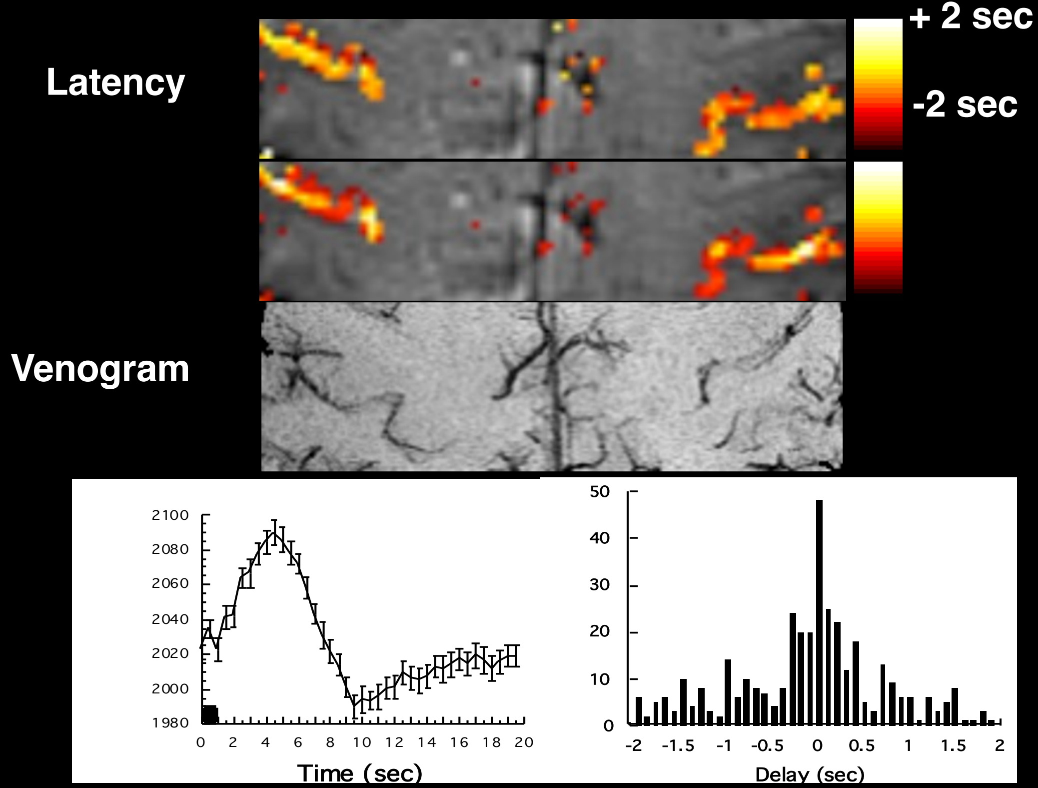
First Event-related fMRI Results



Blamire, A. M., et al. (1992). "Dynamic mapping of the human visual cortex by high-speed magnetic resonance imaging." Proc. Natl. Acad. Sci. USA 89: 11069-11073.

Ultimate temporal resolution?

Voxel-wise hemodynamic variation

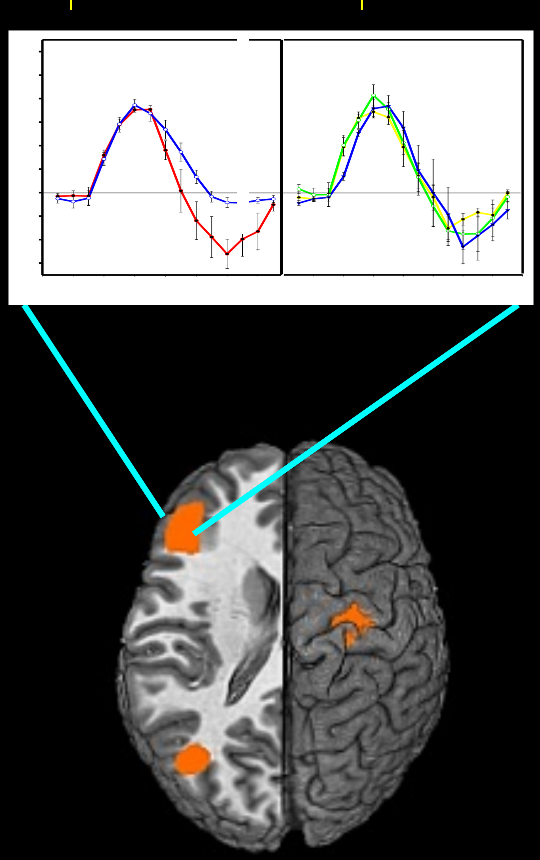


P. A. Bandettini, (1999) "Functional MRI" 205-220.

Ultimate temporal resolution?
Task Timing Modulation

Word vs. Non-word

0°, 60°, 120° Rotation



Bellgowan, et al (2003), PNAS 100, 15820–15283

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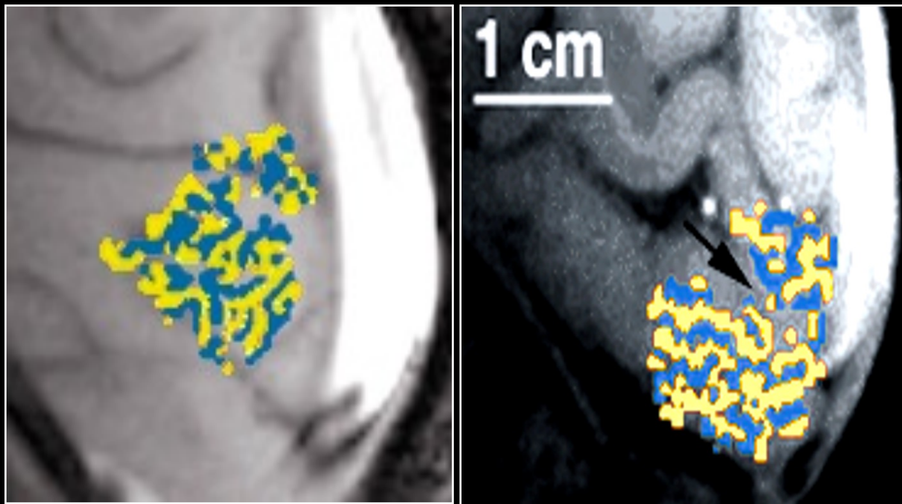
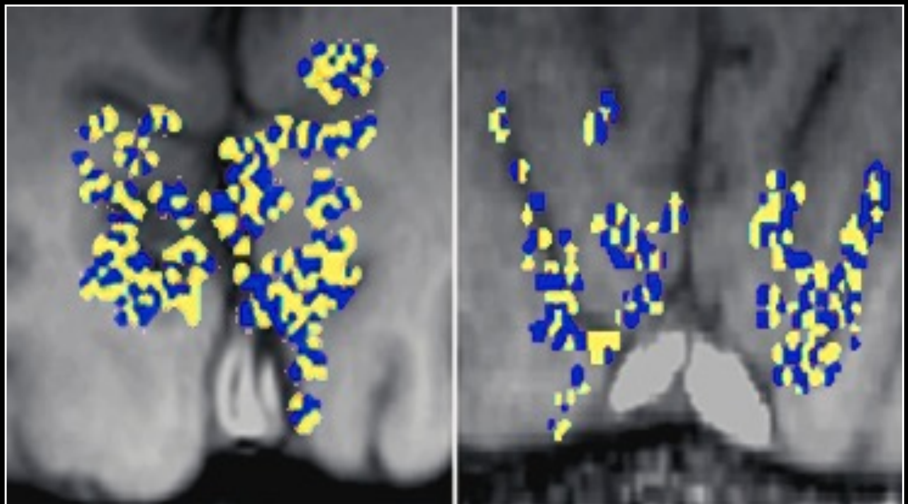
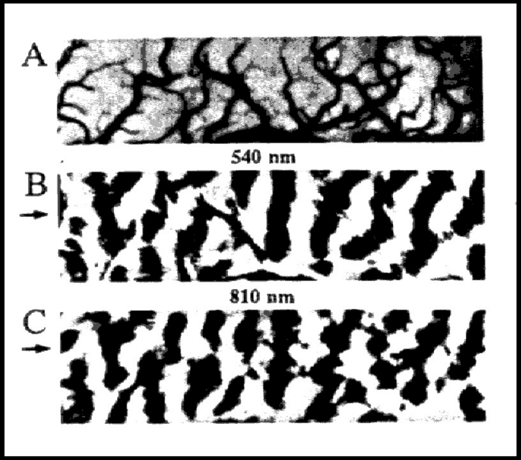
Ocular Dominance Column Mapping using fMRI





Menon, R. S., S. Ogawa, et al. (1997). "Ocular dominance in human V1 demonstrated by functional magnetic resonance imaging." J Neurophysiol 77(5): 2780-7.



Optical Imaging

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

Neuron, Vol. 32, 359–374, October 25, 2001, Copyright ©2001 by Cell Press

Human Ocular Dominance Columns as Revealed by High-Field Functional Magnetic Resonance Imaging

Kang Cheng,[1] R. Allen Waggoner, and Keiji Tanaka
Laboratory for Cognitive Brain Mapping
RIKEN Brain Science Institute and
CREST
Japan Science and Technology Corporation
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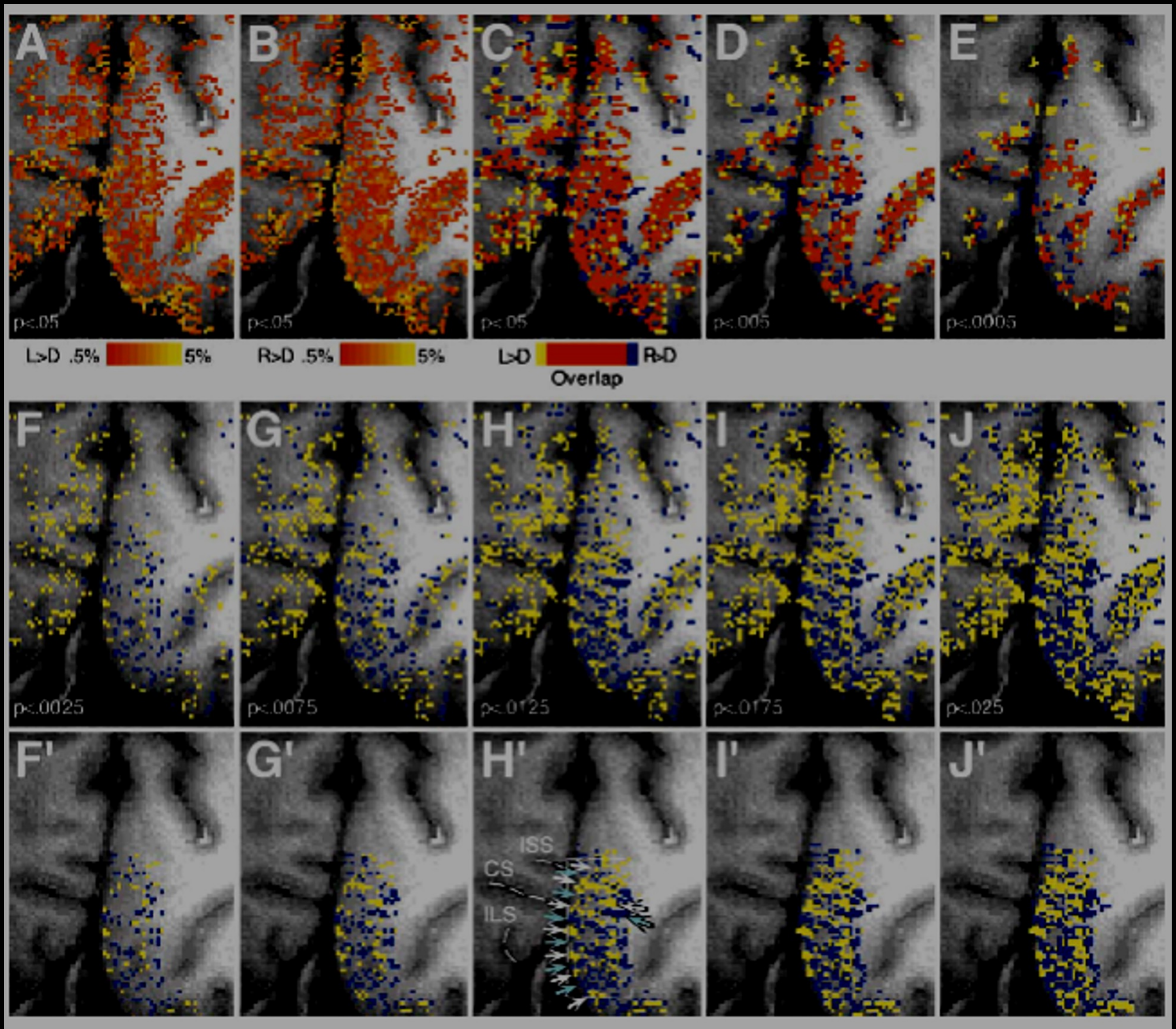
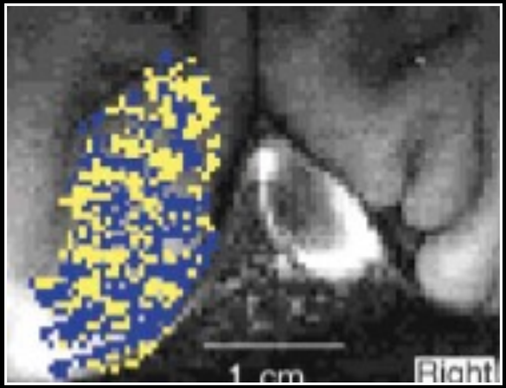


Ultimate spatial resolution?

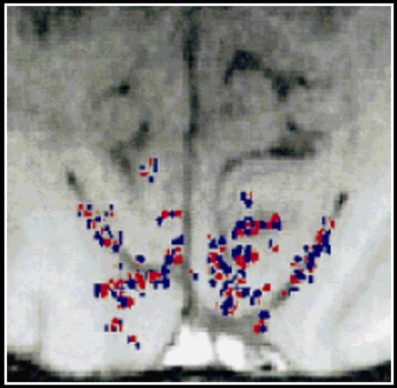
Resolving columns with single shot EPI is a goal..

0.47 x 0.47 in plane resolution



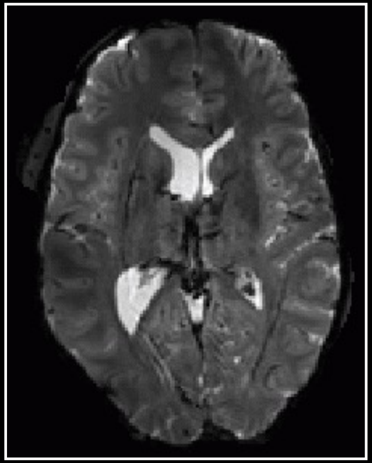
Cheng, et al. (2001) Neuron,32:359-374

0.54 x 0.54 in plane resolution



Menon et al, (1999) MRM 41 (2): 230-235

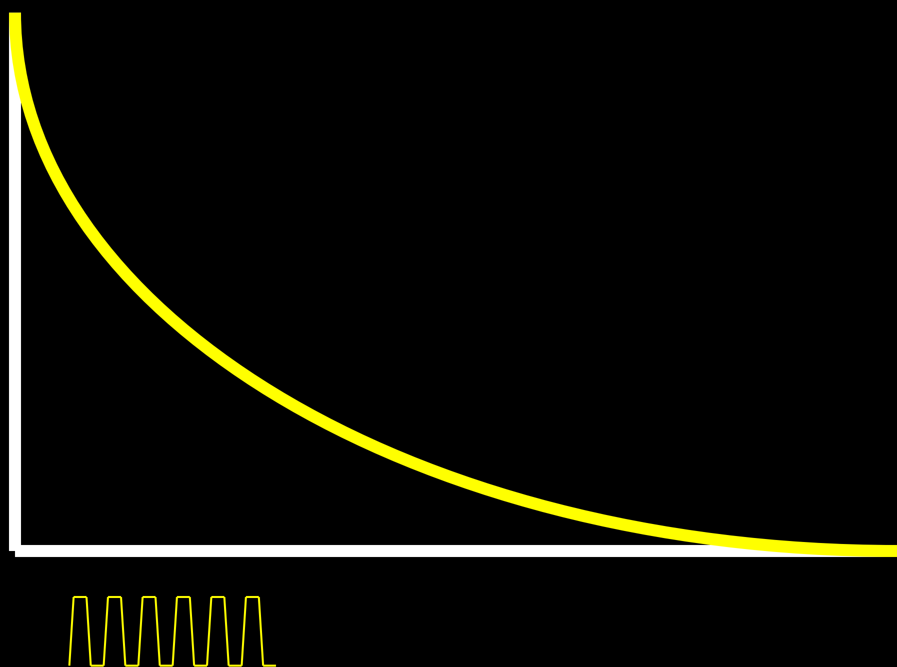
Multi-shot with navigator pulse



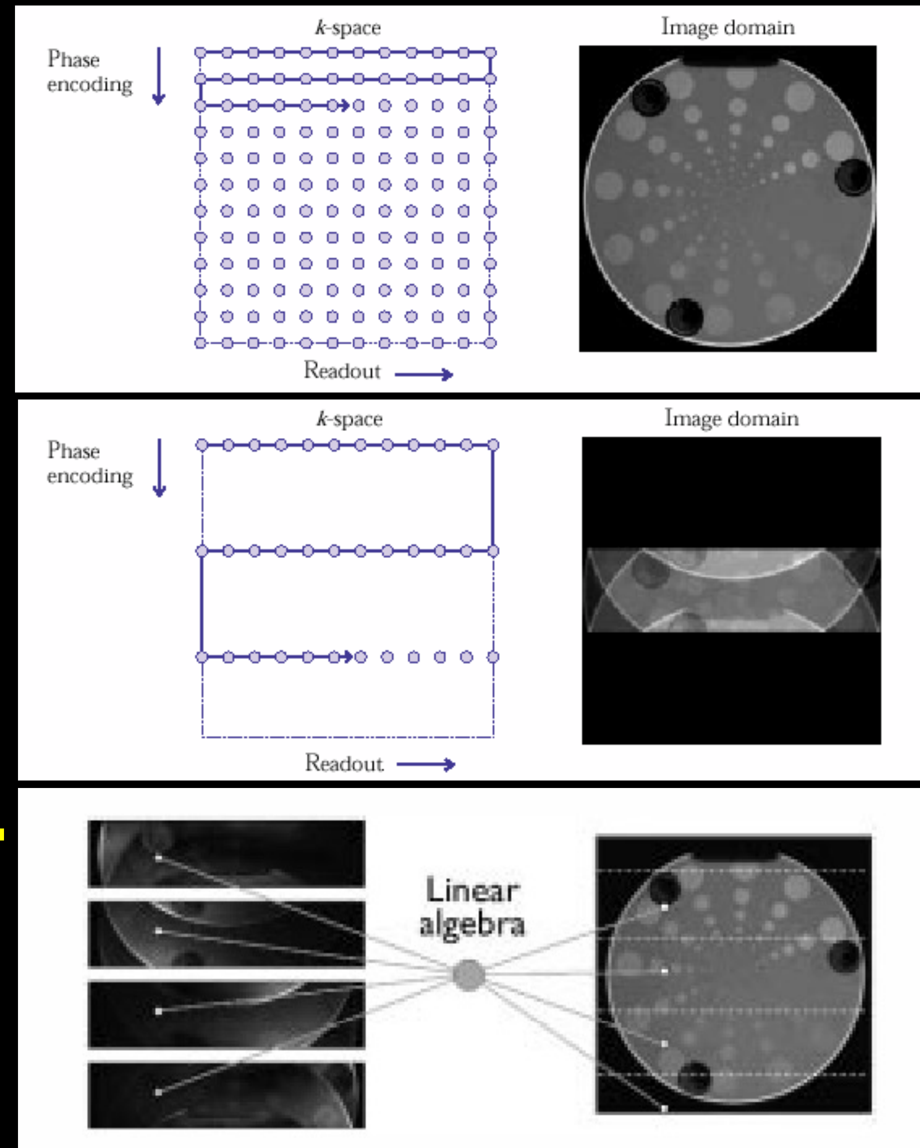
3T single-shot SENSE EPI using 16-channels:1.25x1.25x2mm

…using SENSE, 32 channels, 7T,
and perhaps partial k-space we might get to 0.5 mm^3

SENSE Imaging



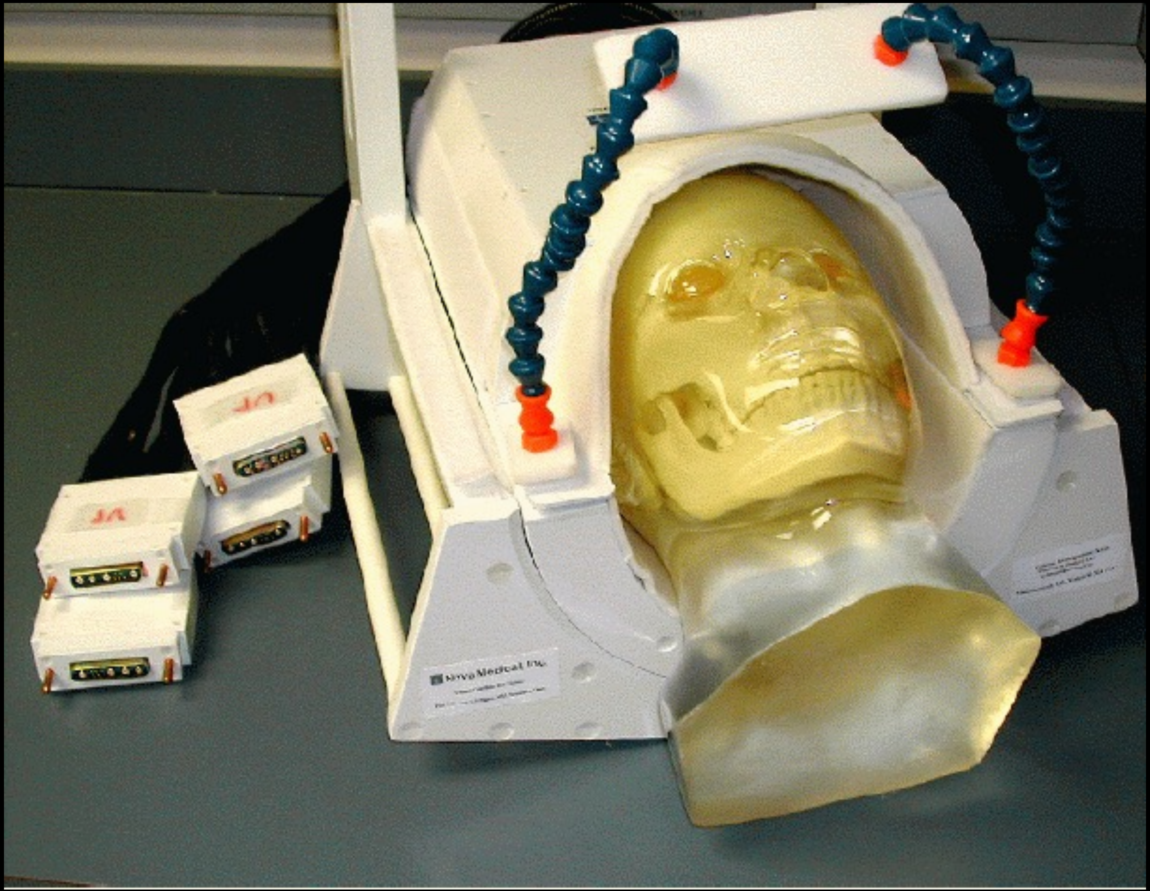
≈ 5 to 30 ms



Pruessmann, et al.

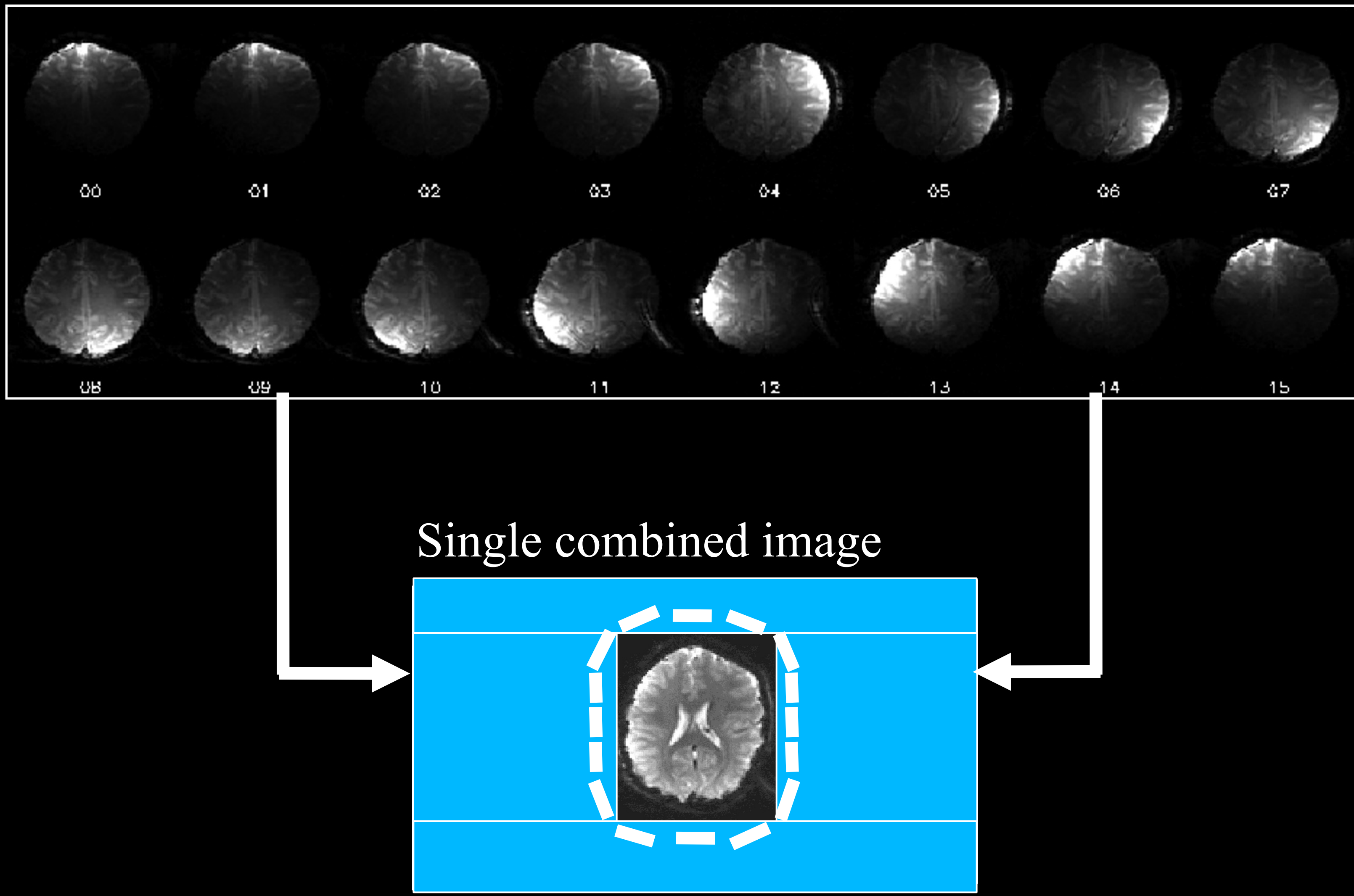
Parallel acquisition (16 radio frequency channels)

Custom-built
Radio-frequency
(RF) coil



Nova Medical, Inc.

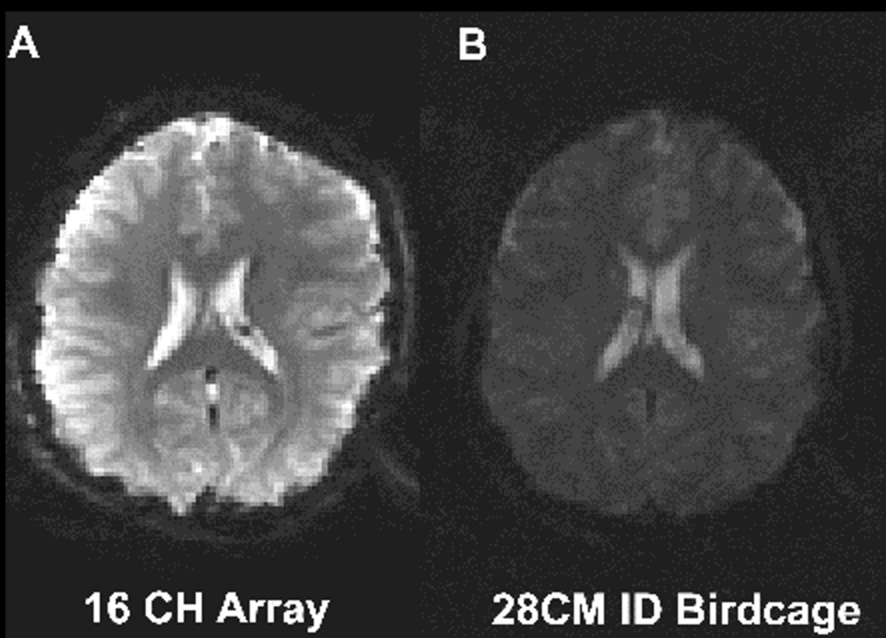
Individual coil images



Single combined image

Parallel acquisition (16 radio frequency channels)

Large improvement in signal-to-noise ratio (SNR)



- Increased resolution
- Increased imaging speed
- Increased sensitivity

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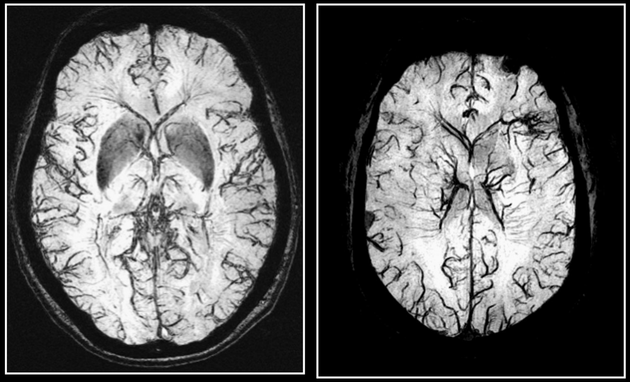
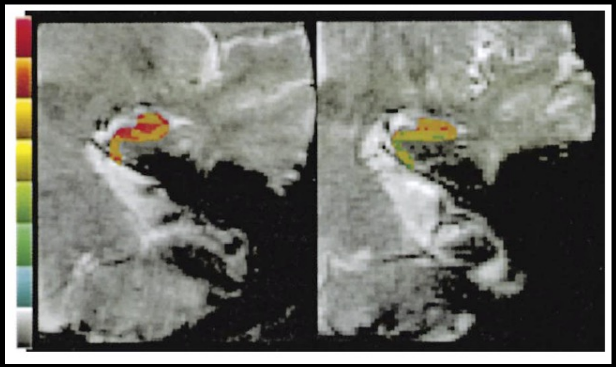
Ultimate clinical utility?

Needs:

- Real time feedback
- Characterization of confounding effects
- Robust yet incisive set of probe tasks
- Baseline information?

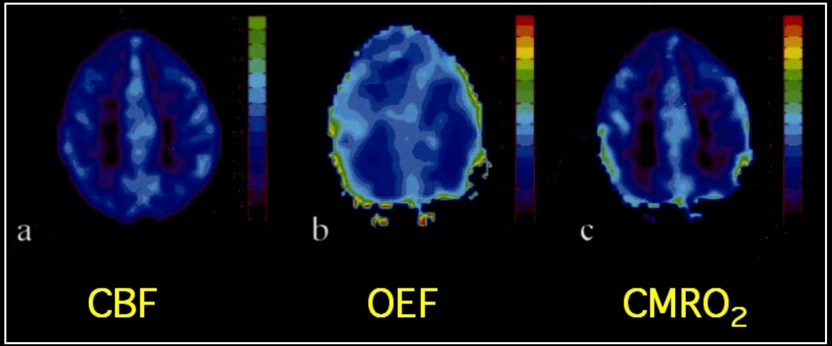


Bove-Bettis, et al (2004), SMRT



Small, et al (2001), Neuron 28:853-664

Bartha, et al (2002), MRM 47:742-750



An, et al (2001), NMR in Biomedicine 14:441-447

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Best processing and display methods?

Processing

fMRI data, and noise is time and space varying in predictable and unpredictable ways over several temporal and spatial scales…

Signal and noise models…
Model free, open ended, methods?

Classification methods?
Multivariate methods?
Connectivity (across time and space scales?)

Best processing and display methods?

Display

To convey:

-collapsed multidimensional data
-sense of data quality

Surface
Glass brain
ROI
Time courses
Example slices
Connectivity maps?
“Quality” index?

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Optimal Field Strength?

Utility vs. Difficulty

Difficulty:

Shimming (generally lower T2 and T2*)
RF penetration effects
Stability

Utility:

Higher SNR
Better susceptibility contrast
Better ASL perfusion contrast (longer T1)

Functional Imaging Methods Unit
&
Functional MRI Facility

fim.nimh.nih.gov

fmrif.nimh.nih.gov

Computer Specialist:
Adam Thomas

Staff Scientists:
Sean Marrett
Jerzy Bodurka
Frank Ye
Wen-Ming Luh
Rasmus Birn

Post Docs:
Hauke Heekeren
David Knight
Anthony Boemio
Niko Kriegeskorte

Scanning Technologists:
Karen Bove-Bettis
Paula Rowser
Alda Ottley
Ellen Condon

Program Assistant:
Kay Kuhns

Graduate Student:
Natalia Petridou

Unit on Functional Imaging & FMRI Core Facility

http://sodium.nimh.nih.gov/upload

T165.ppt