Methodology Development in fMRI
What remains to be done?

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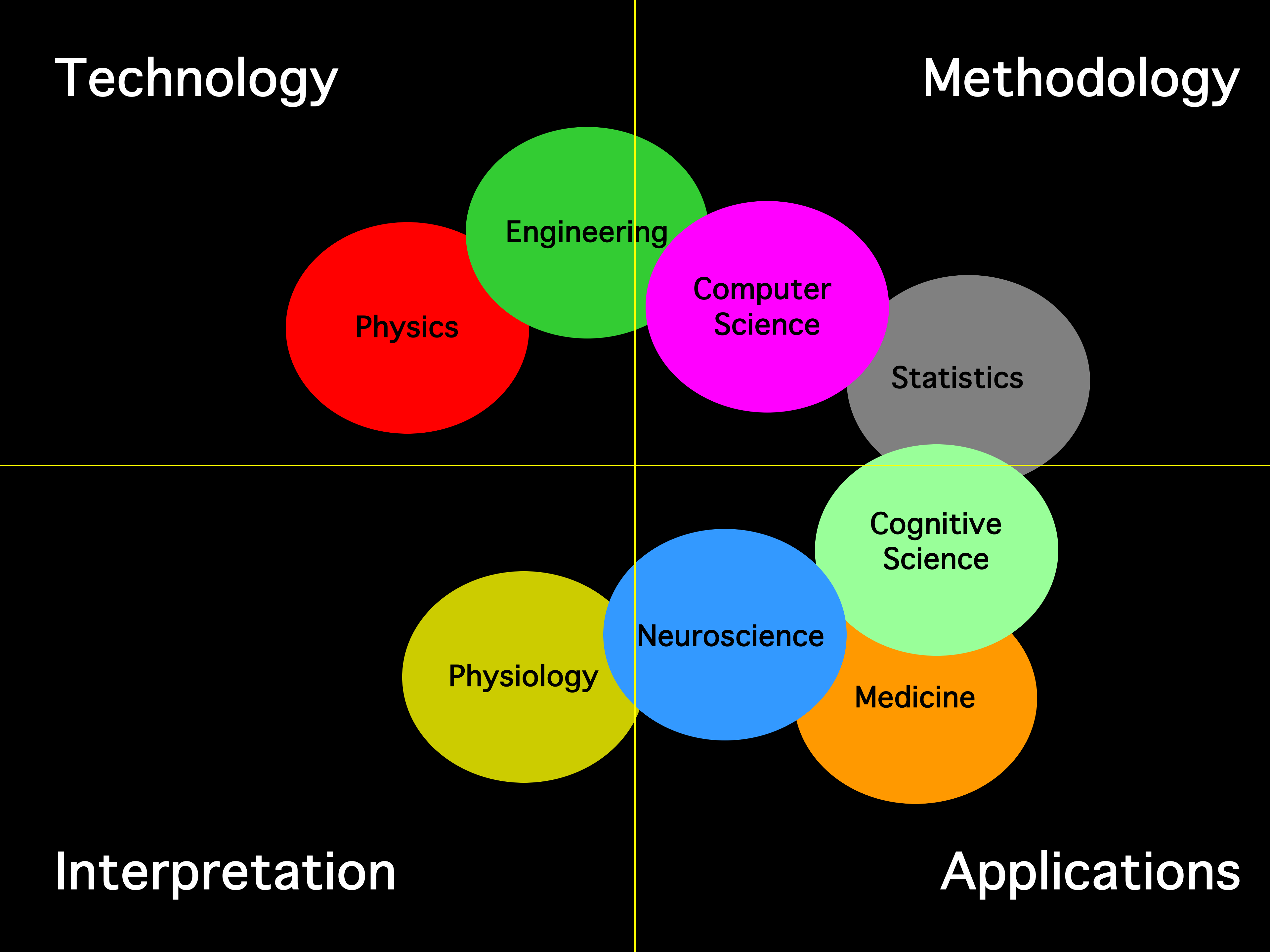
Unit on Functional Imaging Methods

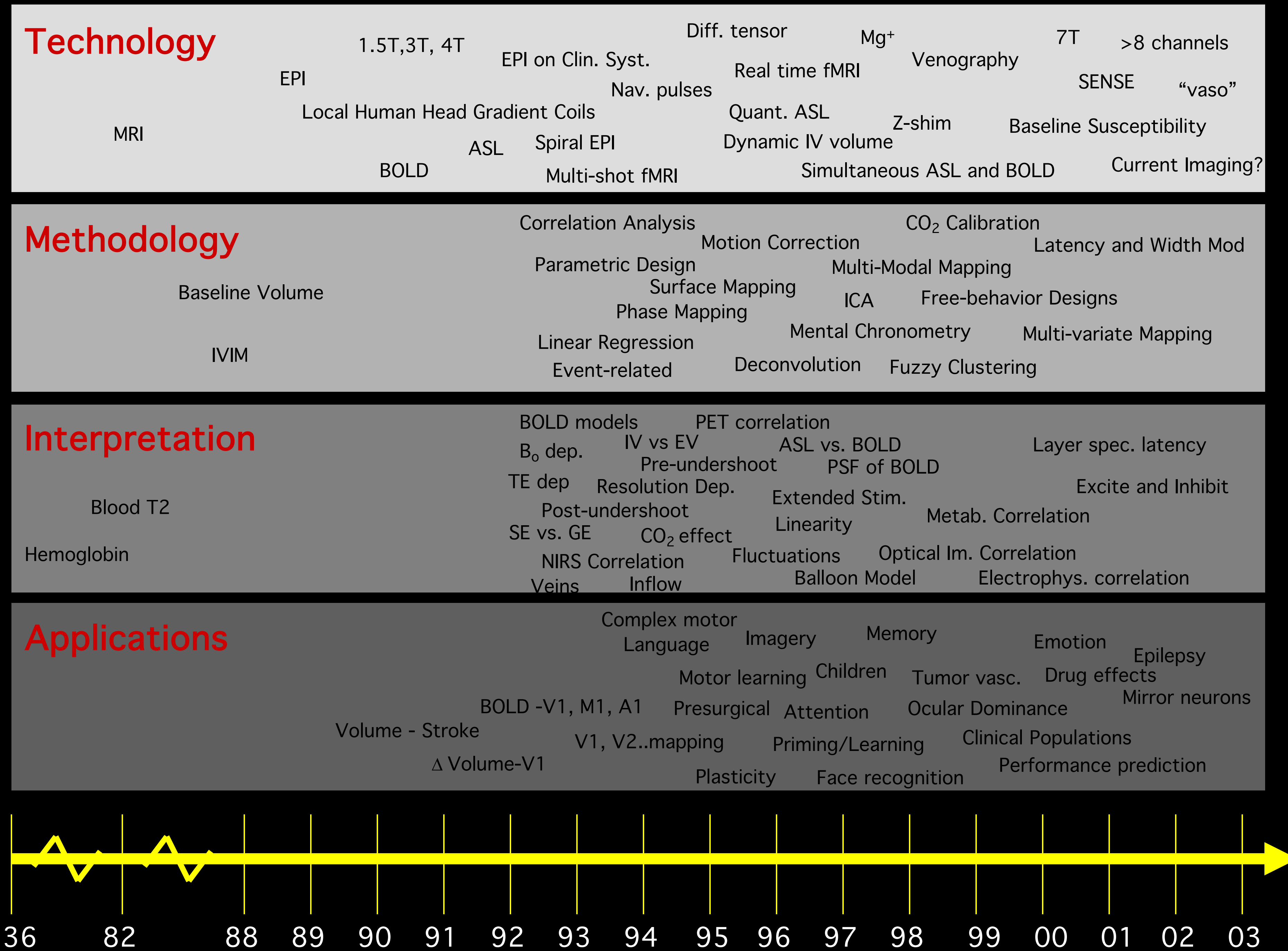
&

Functional MRI Facility

Laboratory of Brain and Cognition

National Institute of Mental Health


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


Technology
MRI
EPI
1.5T,3T, 4T
Local Human Head Gradient Coils
BOLD
ASL
EPI on Clin. Syst.
Spiral EPI
Multi-shot fMRI
Nav. pulses
Diff. tensor
Real time fMRI
Quant. ASL
Dynamic IV volume
Simultaneous ASL and BOLD
Mg+
Venography
Z-shim
7T
SENSE
Baseline Susceptibility
>8 channels
“vaso”
Current Imaging?
Methodology
Baseline Volume
IVIM
Correlation Analysis
Parametric Design
Linear Regression
Event-related
Motion Correction
Surface Mapping
Phase Mapping
Deconvolution
Multi-Modal Mapping
ICA
Mental Chronometry
Fuzzy Clustering
CO_2 Calibration
Free-behavior Designs
Latency and Width Mod
Multi-variate Mapping
Interpretation
Blood T2
Hemoglobin
BOLD models
B_o dep.
TE dep
SE vs. GE
Post-undershoot
NIRS Correlation
Veins
IV vs EV
Pre-undershoot
Resolution Dep.
CO_2 effect
Inflow
PET correlation
ASL vs. BOLD
Extended Stim.
Linearity
Fluctuations
Balloon Model
PSF of BOLD
Optical Im. Correlation
Metab. Correlation
Electrophys. correlation
Layer spec. latency
Excite and Inhibit
Applications
Volume - Stroke
∆ Volume-V1
BOLD -V1, M1, A1
V1, V2..mapping
Complex motor
Language
Motor learning
Presurgical
Plasticity
Imagery
Children
Attention
Priming/Learning
Face recognition
Memory
Tumor vasc.
Ocular Dominance
Clinical Populations
Performance prediction
Emotion
Drug effects
Epilepsy
Mirror neurons
36
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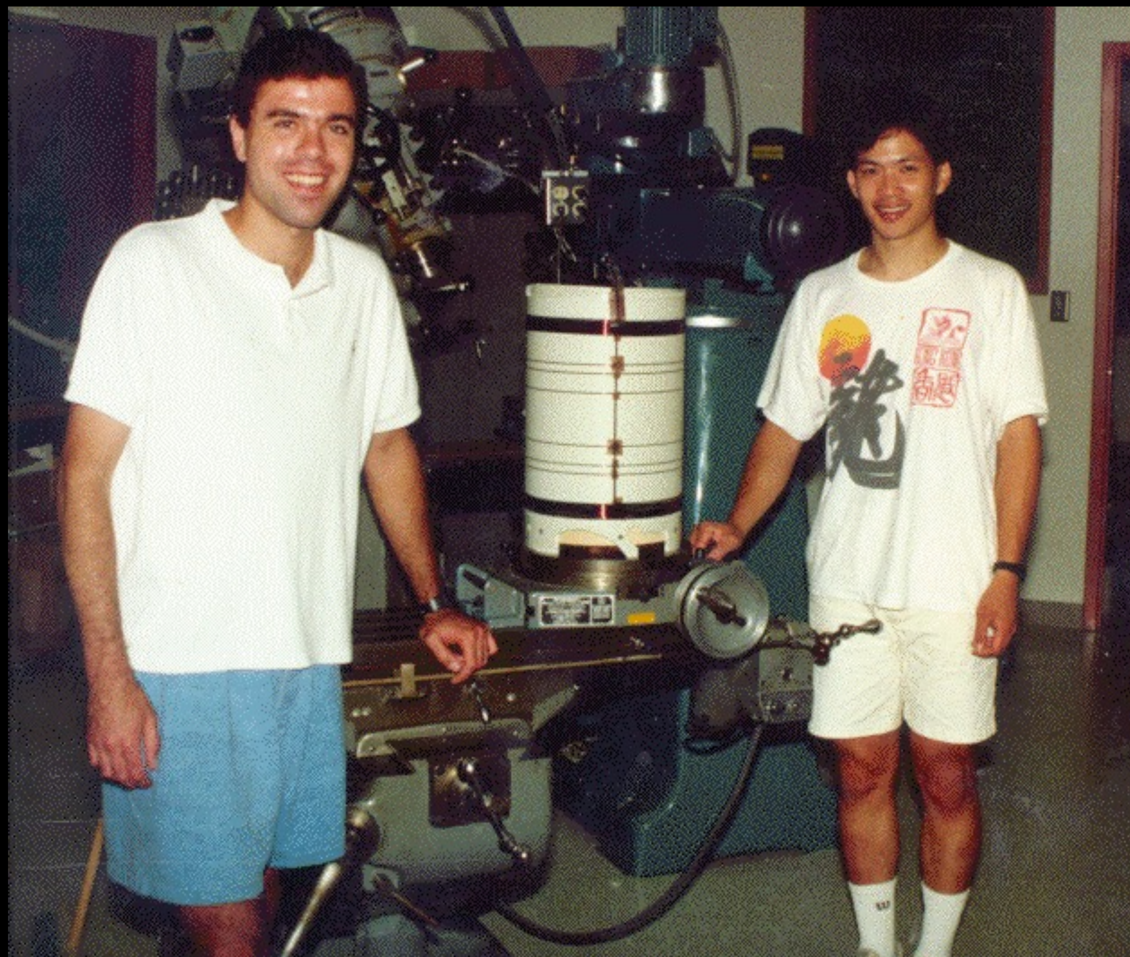
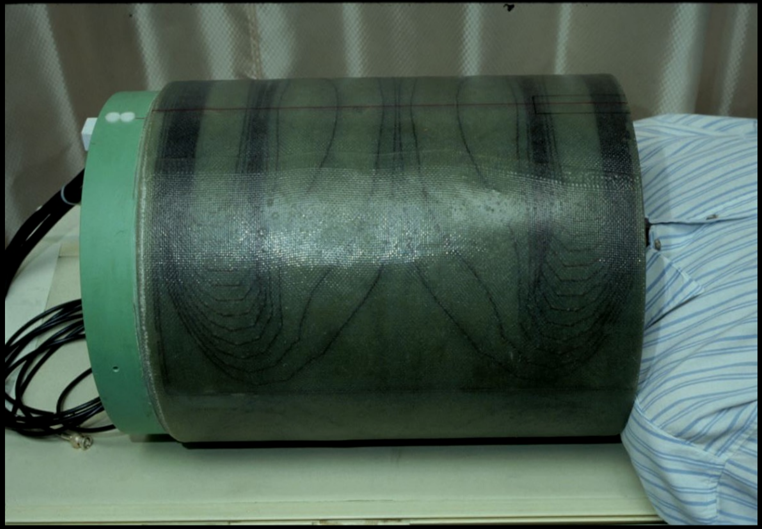


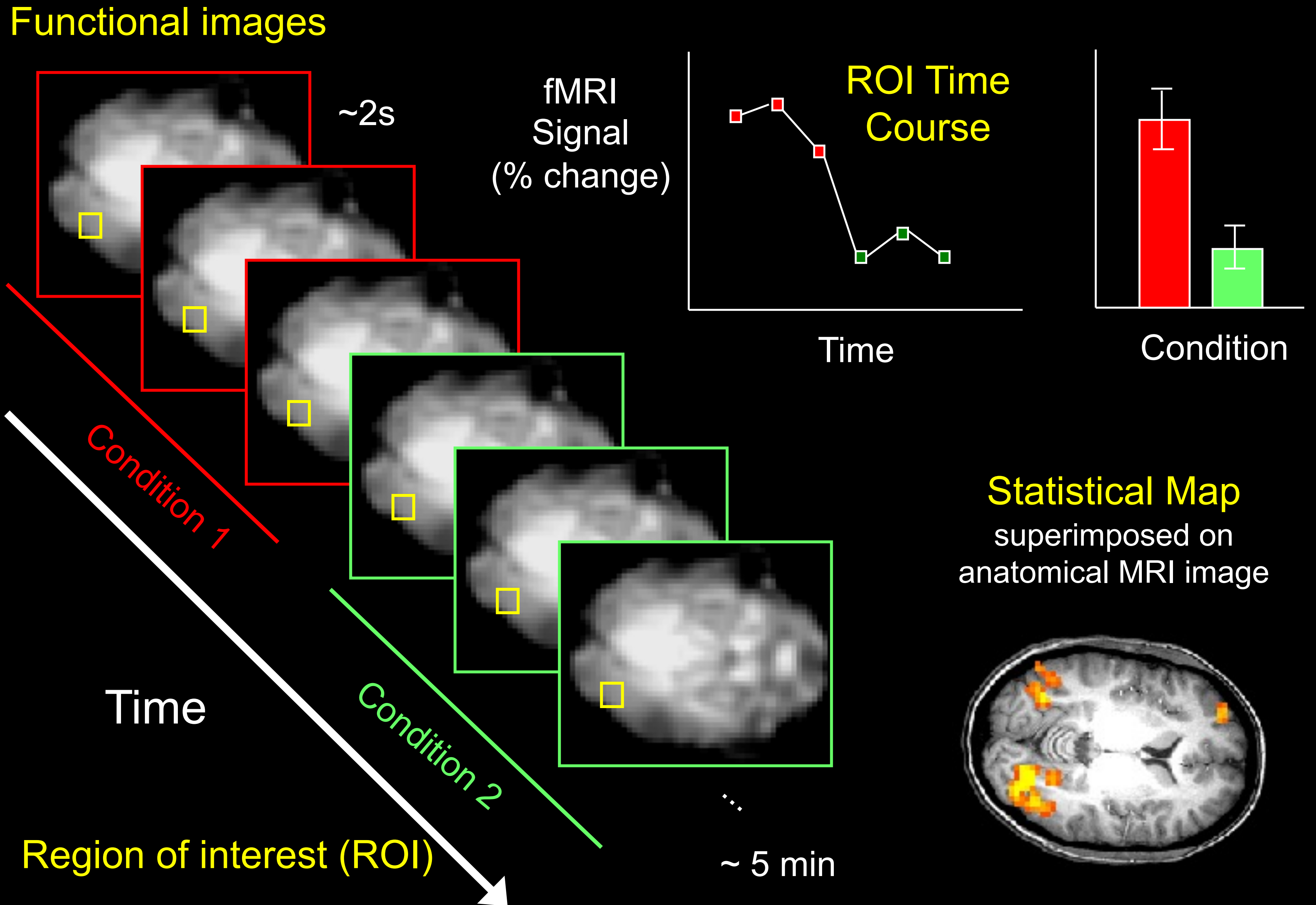
1991-1992

1992-1999



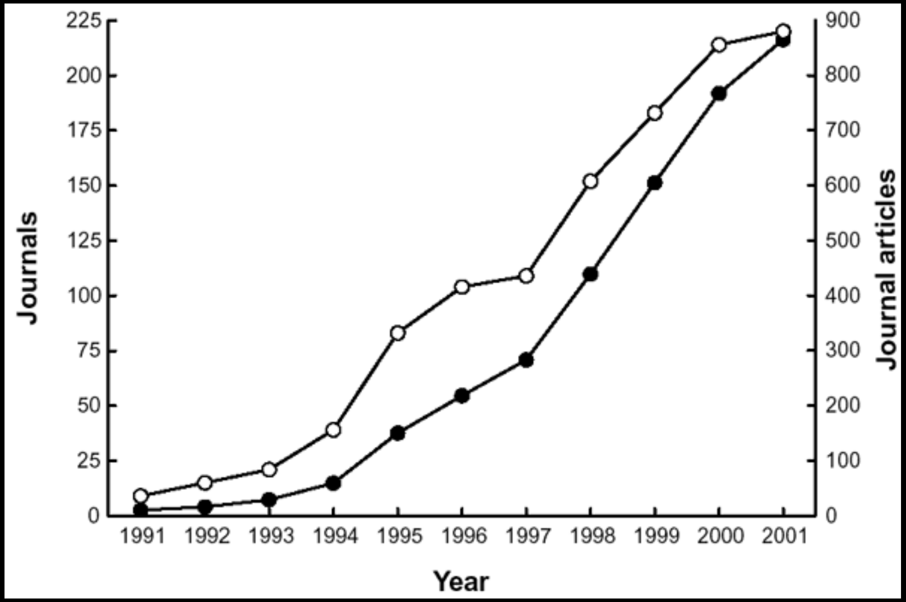
General Electric 3 Tesla Scanner

Activation Statistics

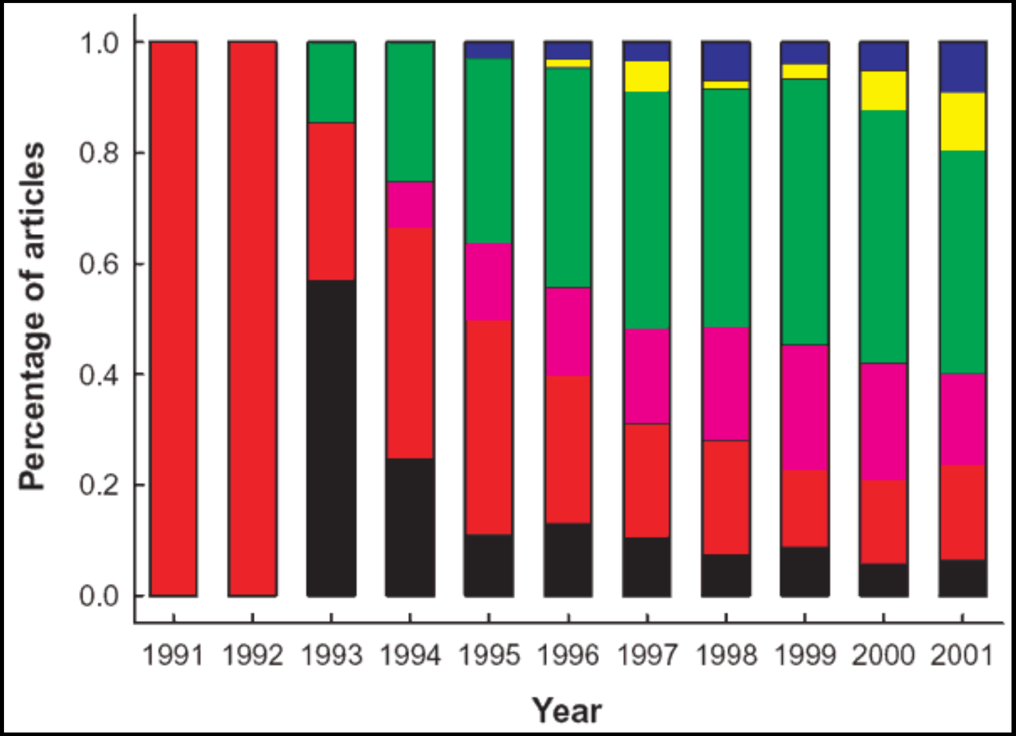


Courtesy, Robert Cox, Scientific and Statistical Computing Core Facility, NIMH

J. Illes, M. P. Kirschen,
J. D. E. Gabrielli,
Nature Neuroscience,
6 (3)m p.205



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



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

Potential 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

Most fMRI studies since 1992:

Minimum necessary:

- Whole Brain EPI
- Field strength of 1.5T or greater
- Basic stimulus delivery and feedback
- Software for image transfer, analysis, and display

Typical advanced features:

- Higher resolution whole brain EPI, spiral, or multi-shot
- Field strength of 3T to 7T
- Quadrature and Surface coils (single, multiple)
- Susceptibility correction
- ASL
- Multiple subject interface devices, including EEG, SCR, eye position.
- Multi-subject analysis, more rigorous statistics, more sophisticated display methods, exploratory analysis

What are the biggest unknowns/challenges?

1. Technology

2. Methods

3. Interpretation

Technology

- Field strength
- Signal to noise
- Resolution
- Shimming

Field strength

Plusses

-SNR proportional to Bo
-Contrast proportional to Bo

Minuses

-Susceptibility effects increase
-RF penetration problems
-SAR problems
-Fluctuations increase

Bottom Line

-SNR buys resolution when technology catches up
-Fluctuations may be increasingly interesting

Signal to noise

Methods to increase

- -Increase Bo
- -Smaller RF coils (arrays)
- -Reduce noise

Issue:

- -Temporal SNR is most important

More SNR…More “signal” is there…

The spatial extent of the BOLD response

Ziad S. Saad,[a,b,*] Kristina M. Ropella,[b] Edgar A. DeYoe,[c] and Peter A. Bandettini[a]

[a] Laboratory of Brain and Cognition, National Institute of Mental Health, NIH, Bethesda, MD 20892-1148, USA
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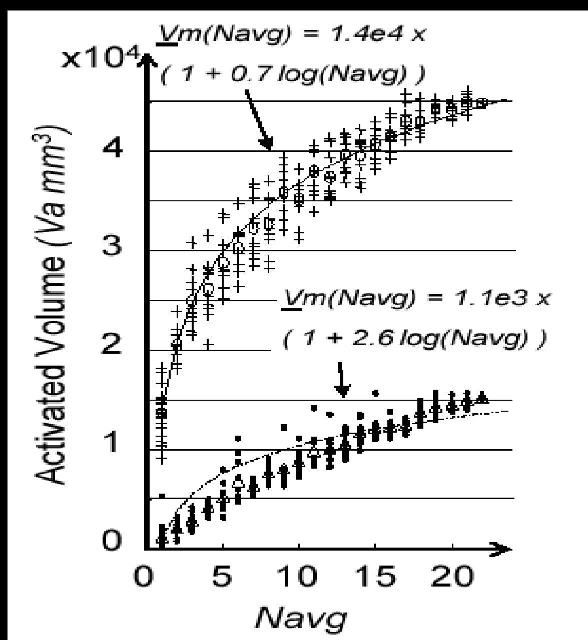
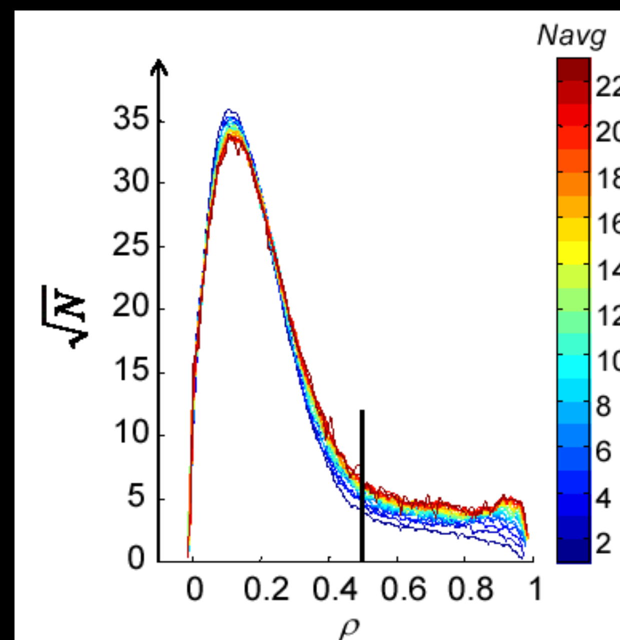
[c] Department of Cell Biology, Neurobiology and Anatomy, Medical College of Wisconsin, Milwaukee, WI 53226, USA

Received 16 August 2002; revised 29 October 2002; accepted 21 November 2002

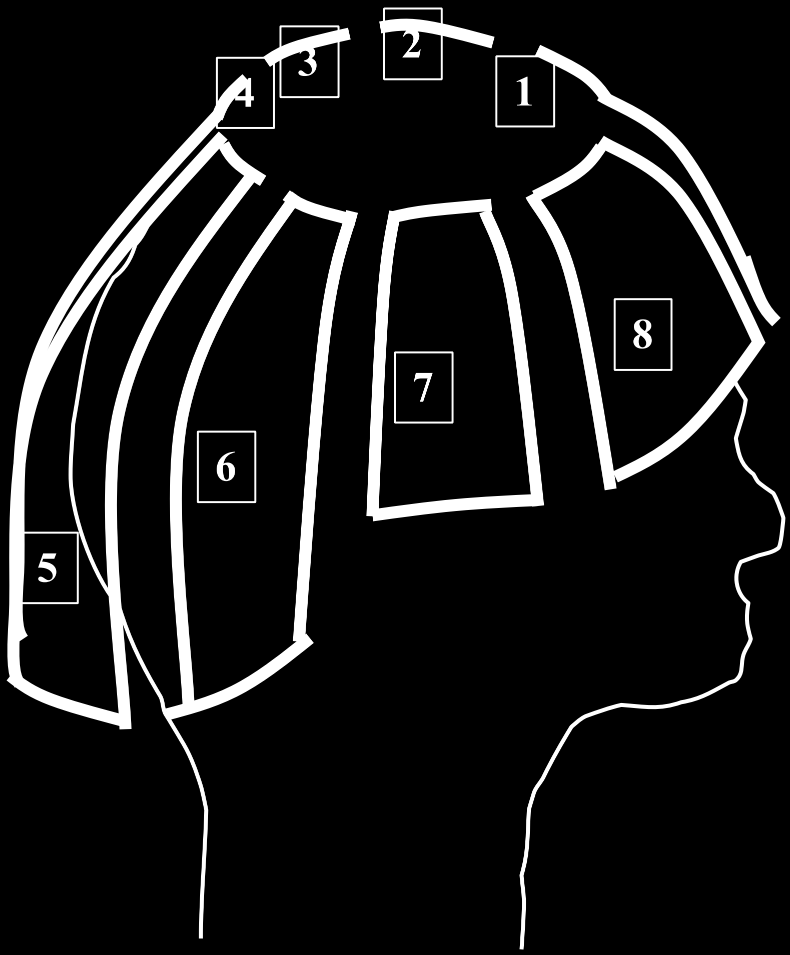
NeuroImage





Introduction

General concept



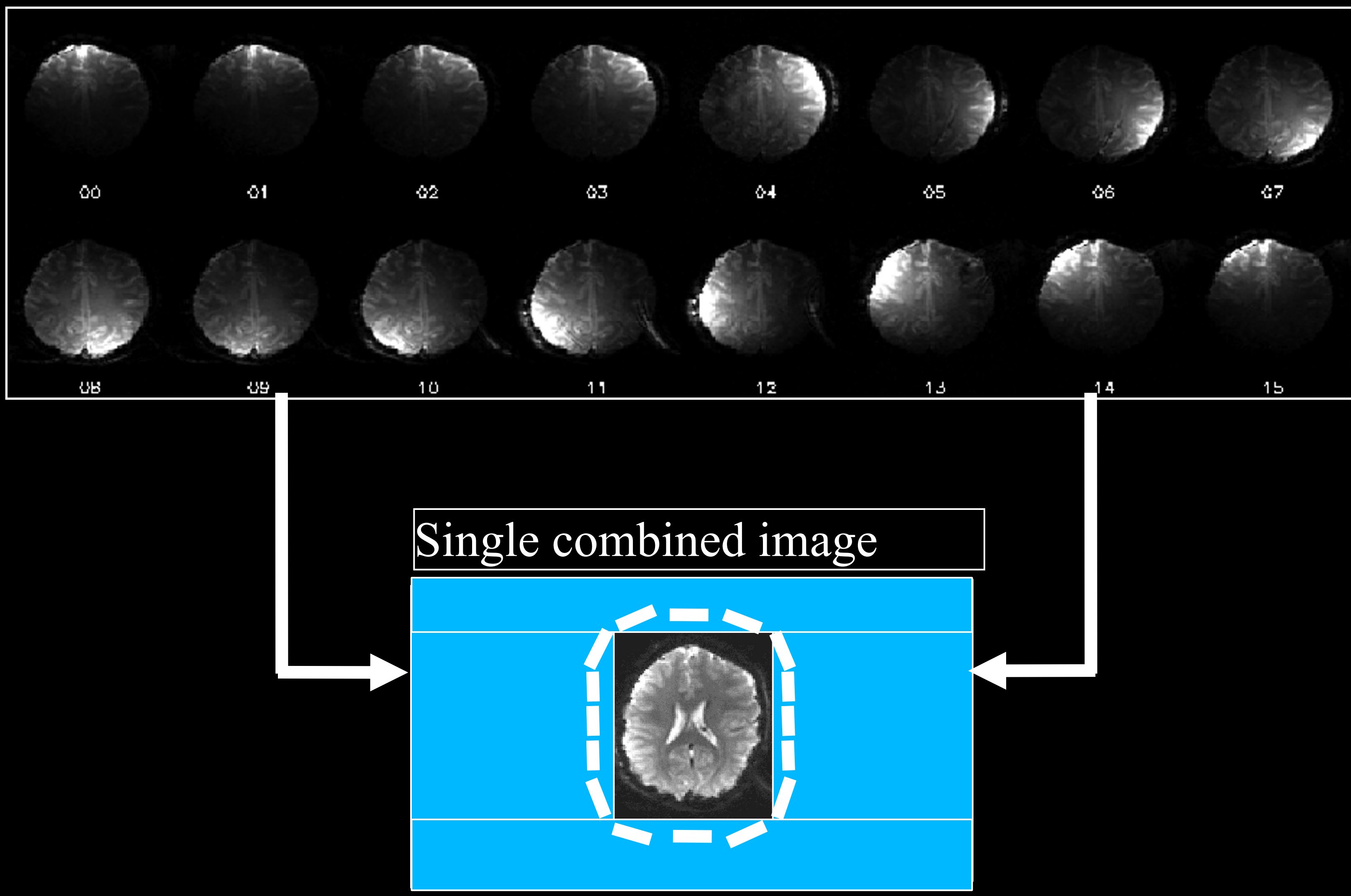
de Zwart et al. MRM 47:1218 (2002).

MRI Reception Hardware – 16 channels

Built by Nova Medical Inc.

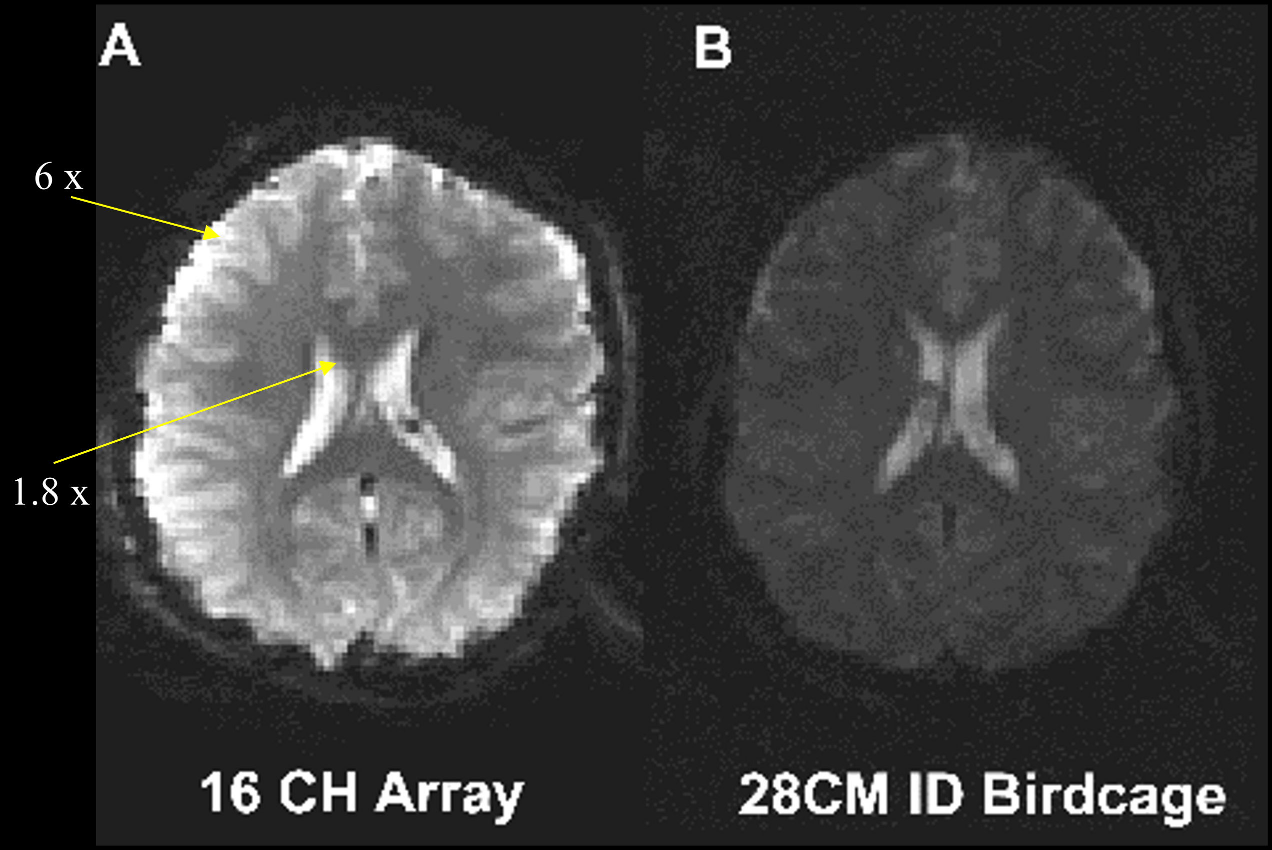
de Zwart et al. MRM 51:22 (2004).

Individual coil images



Experimental Data

SNR comparison



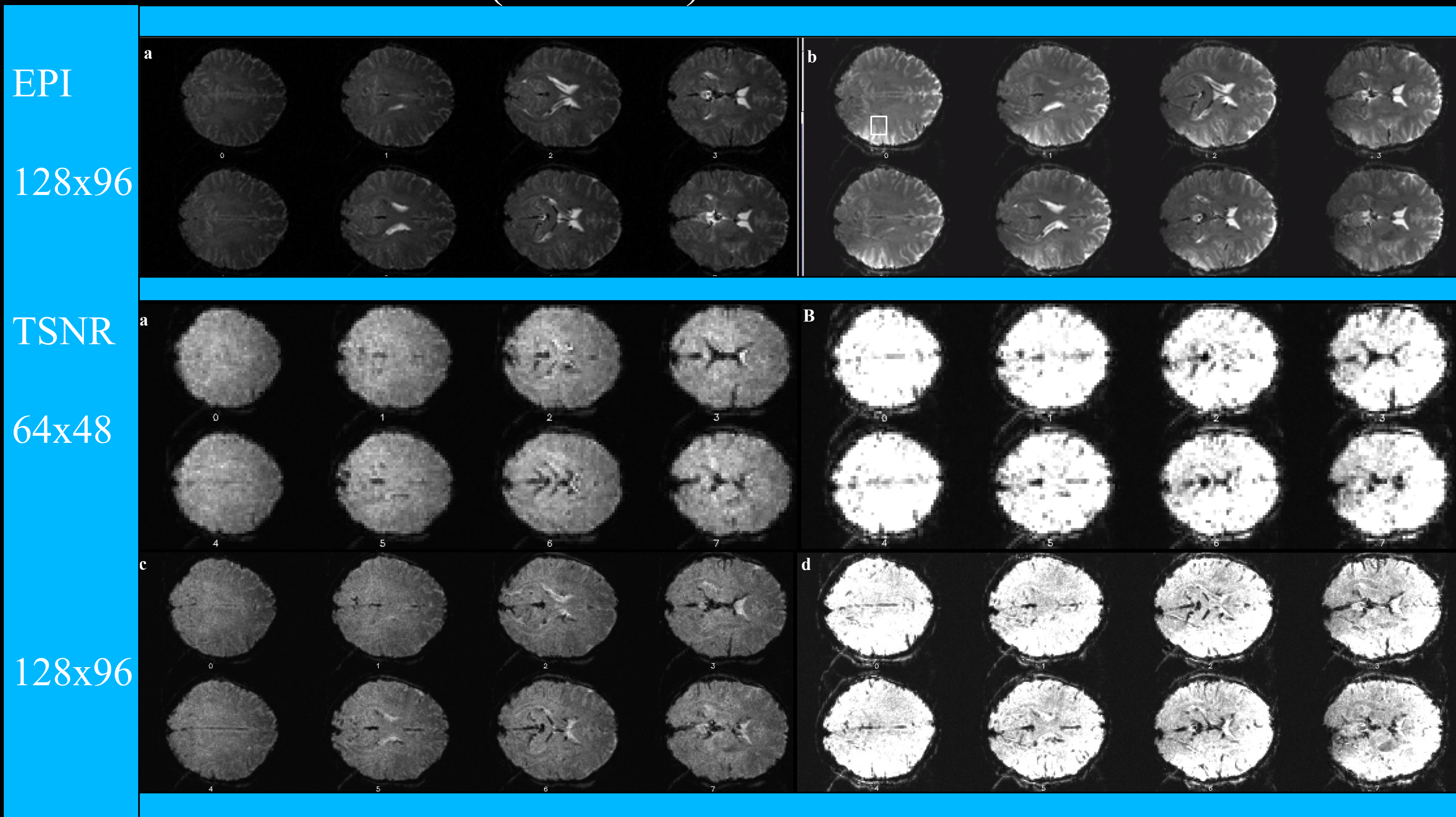
Both images are in the same scale.
Relative intensity corresponds to SNR.

3-fold SNR improvements

Experimental Data

TSNR comparison

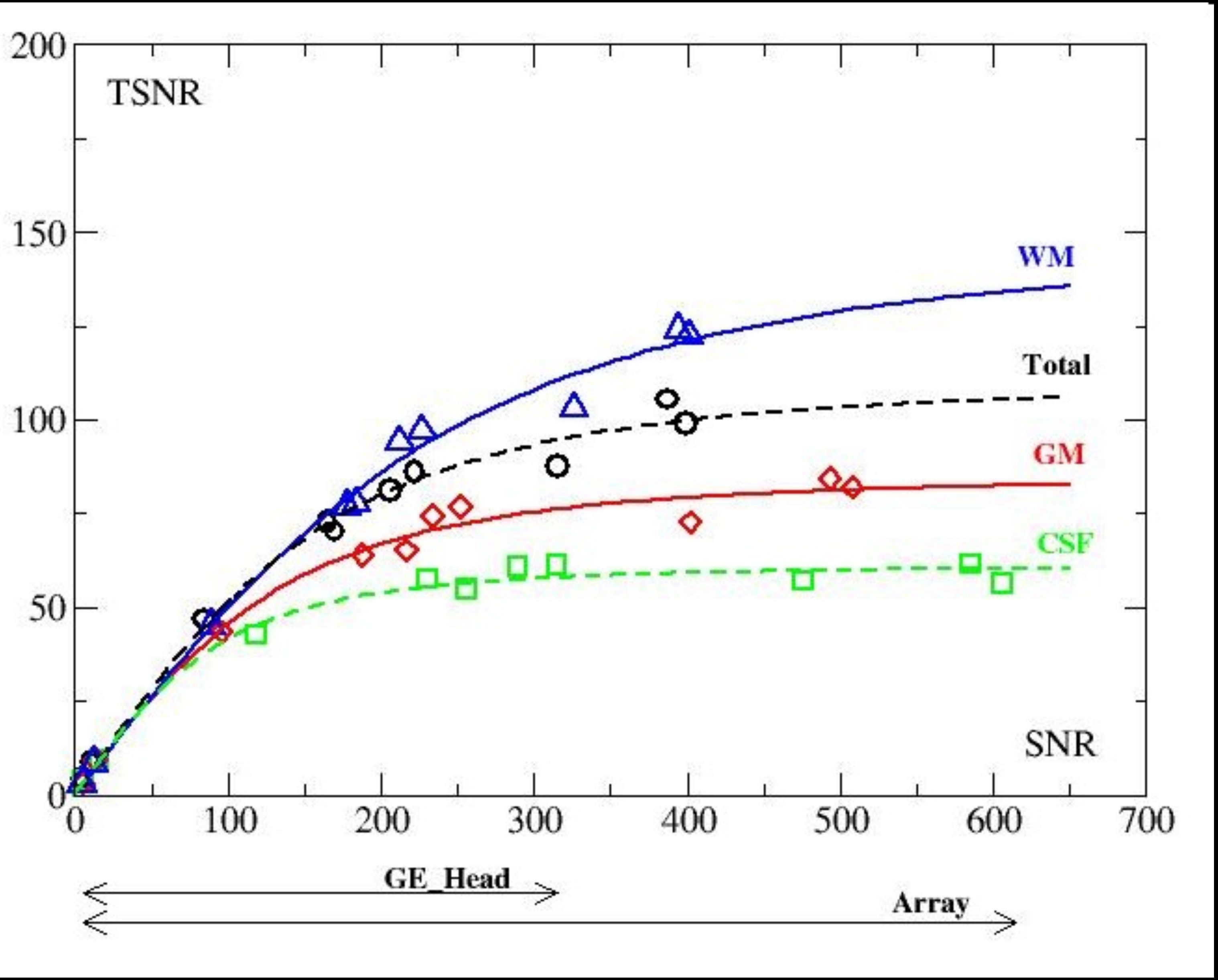
1 channel (MAI coil) 16 channel



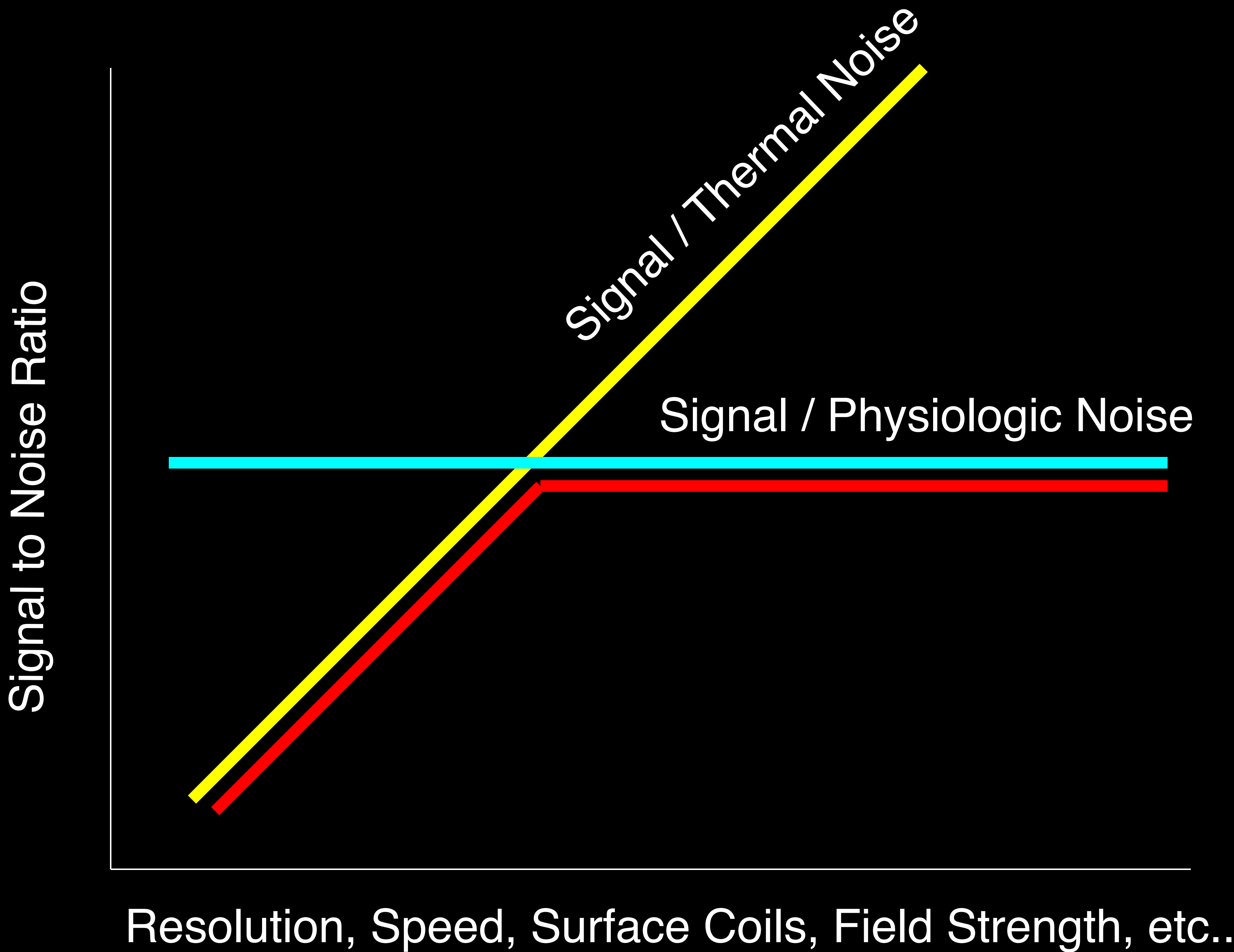
$TSNR_{16}/TSNR_{1}$:

ROI: 64x48 -> 1.98 +/- 0.52 128x96 -> 2.2 +/- 0.53

An average over all slices for both resolutions -> 1.7 +/- 0.3



Bodurka et al.


Signal / Thermal Noise
Signal / Physiologic Noise
Signal to Noise Ratio
Resolution, Speed, Surface Coils, Field Strength, etc..

Resolution

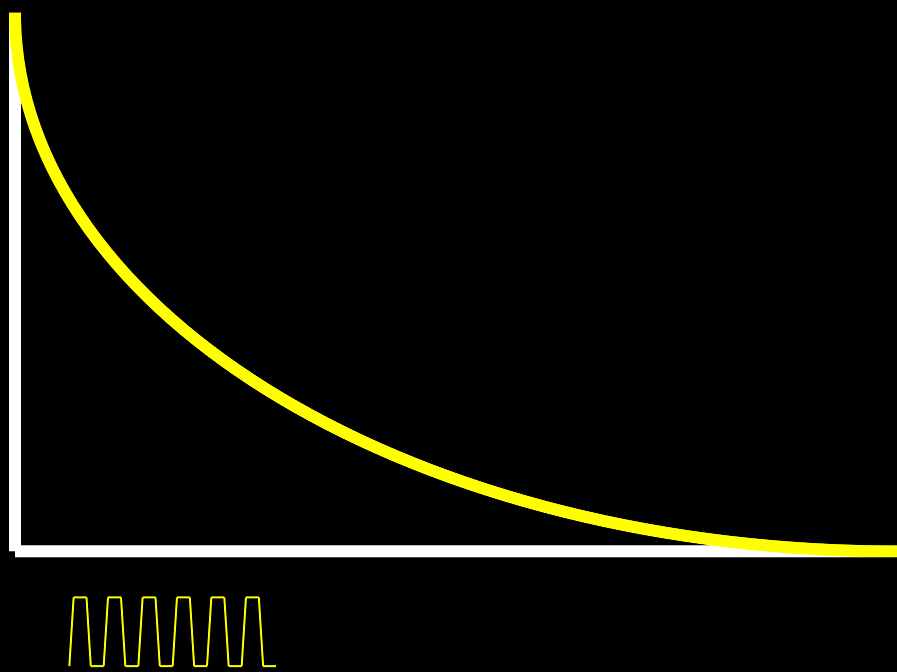
Methods to increase:

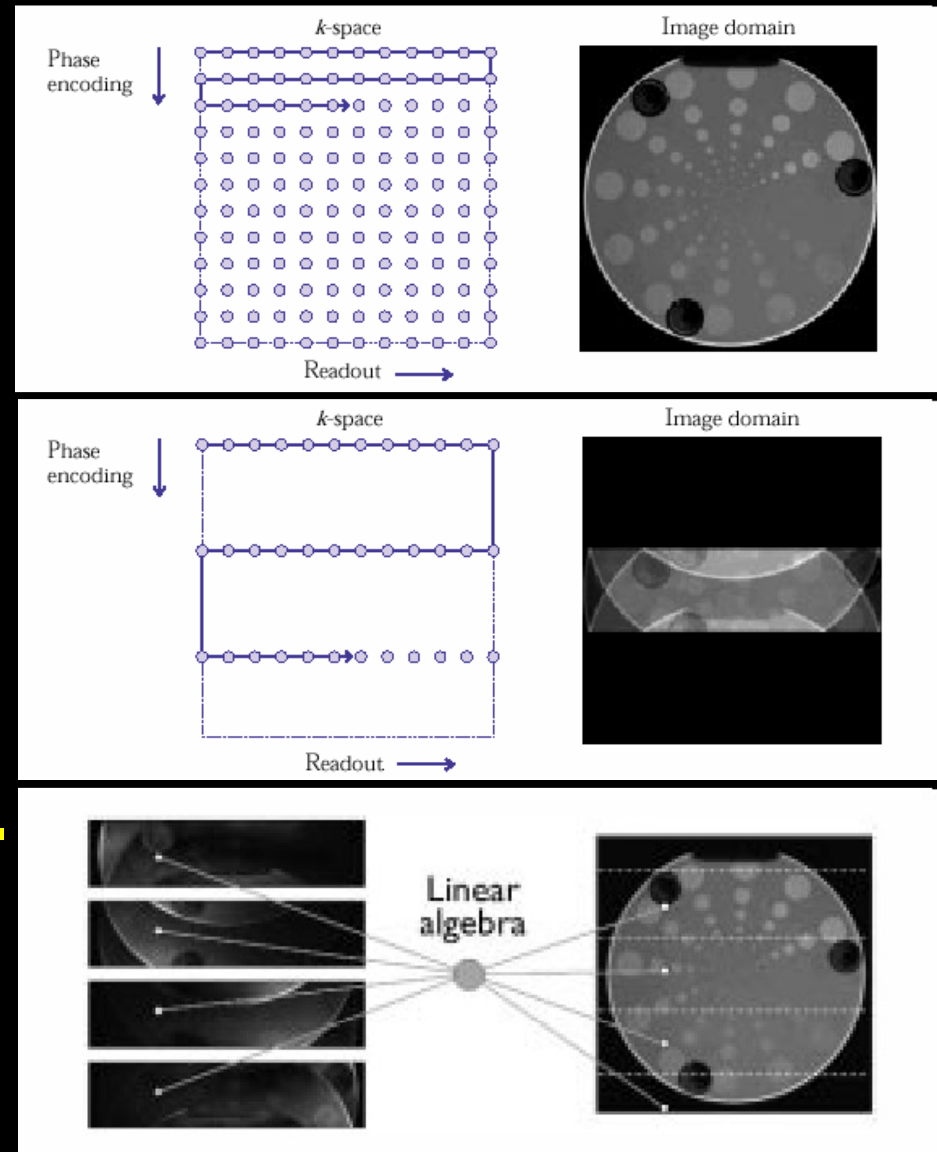
- -Faster sampling rate per image
- -Faster gradient switching
- -Longer readout window
- -Partial k-space
- -Multi-shot techniques
- -Parallel Imaging

Bottom Line:

- -Up against limits in most methods
- -Multi-shot still problematic (time, stability)
- -Parallel imaging is most promising

SENSE Imaging





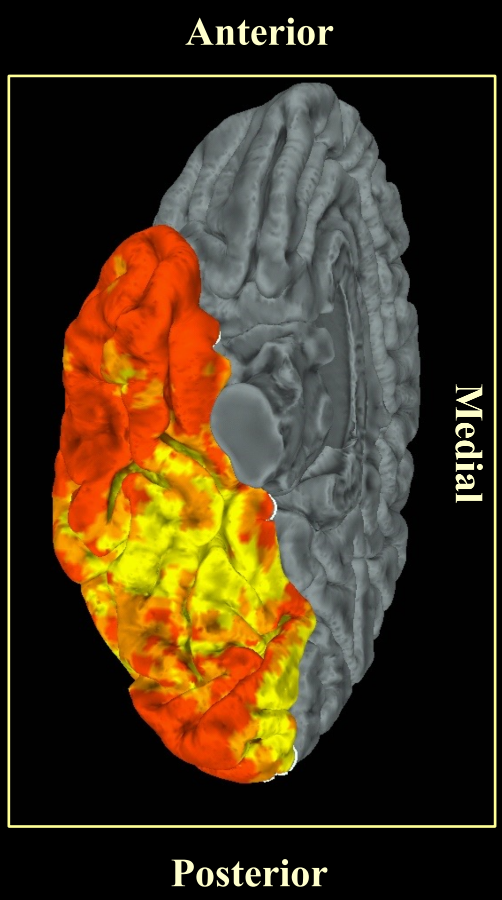
≈ 5 to 30 ms

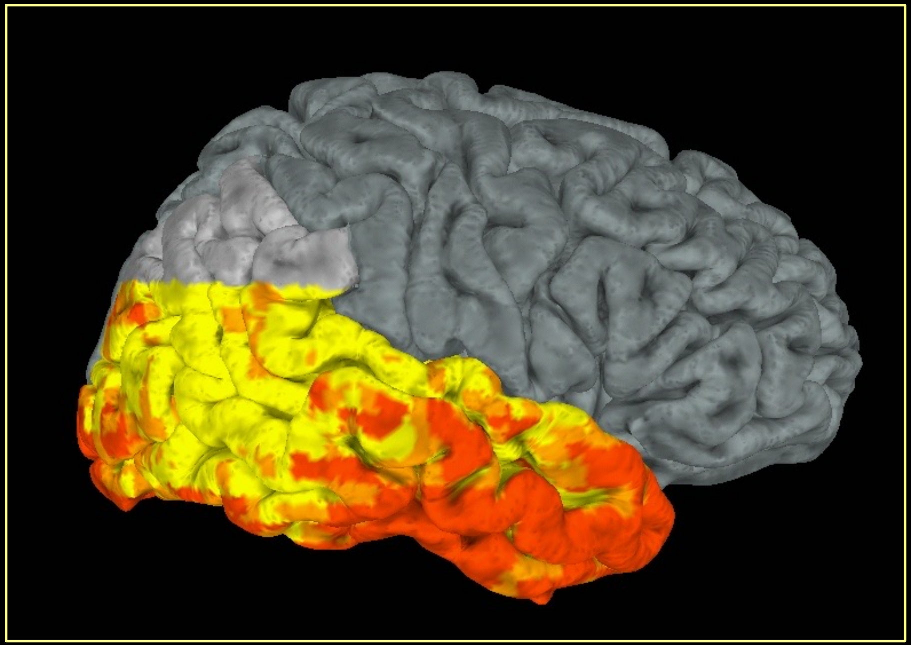
Pruessmann, et al.

Experimental Data

Axial-oblique single shot rate-2 SENSE EPI using 16-channel reception. Rate-2 SENSE allowed an image matrix of 192x144 (nominal resolution : 1.25x1.25x2 mm^3) with relative little EPI distortions.

Average Temporal Signal-to-Noise ratio Comparison Between Coils





16 Element Array > GE coil

Shimming

A solvable problem:

- -more shim coils and/or coil designs
- -increased shim currents
- -higher resolution (fixes dropout)
- -shorter readout window (fixes distortion)
- -shim inserts
- -z-shim methods

Methods

- Temporal resolution
- Magnitude Calibration
- Multi-subject averaging/normalization at very high resolution
- Motion (very slow and motion correlated)
- Scanner noise effect removal
- Individual Map "Classification"
- Local pattern effect mapping and classification
- Exploratory analysis techniques (ICA, PCA..)
- Paradigm design
- Temporal fluctuations (removal and use)
- Baseline susceptibility mapping
- Non-invasive blood volume imaging
- Multimodal integration
- Simultaneous measures with fMRI
- Functional Connectivity mapping
- Real time fMRI
- Neuronal Current MRI

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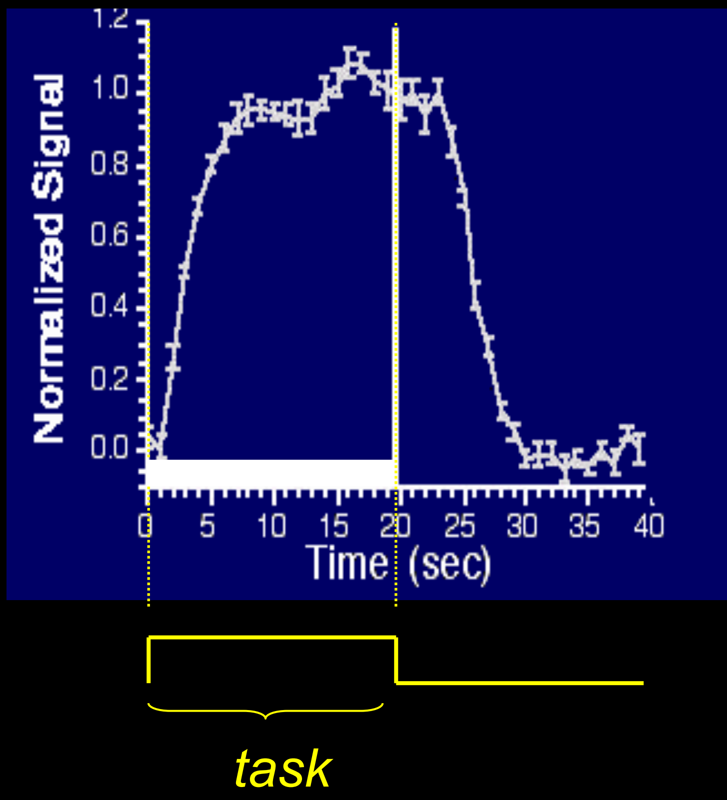
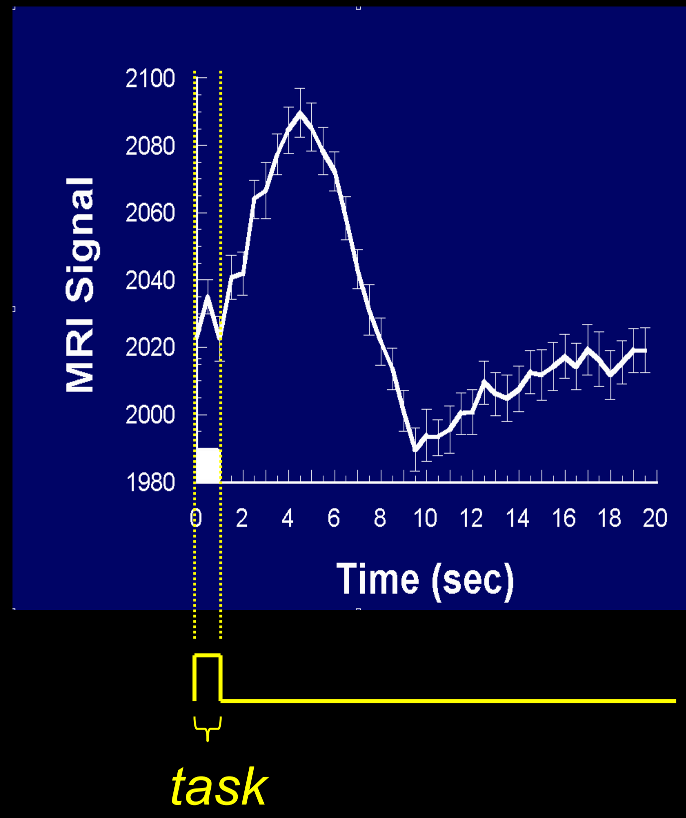
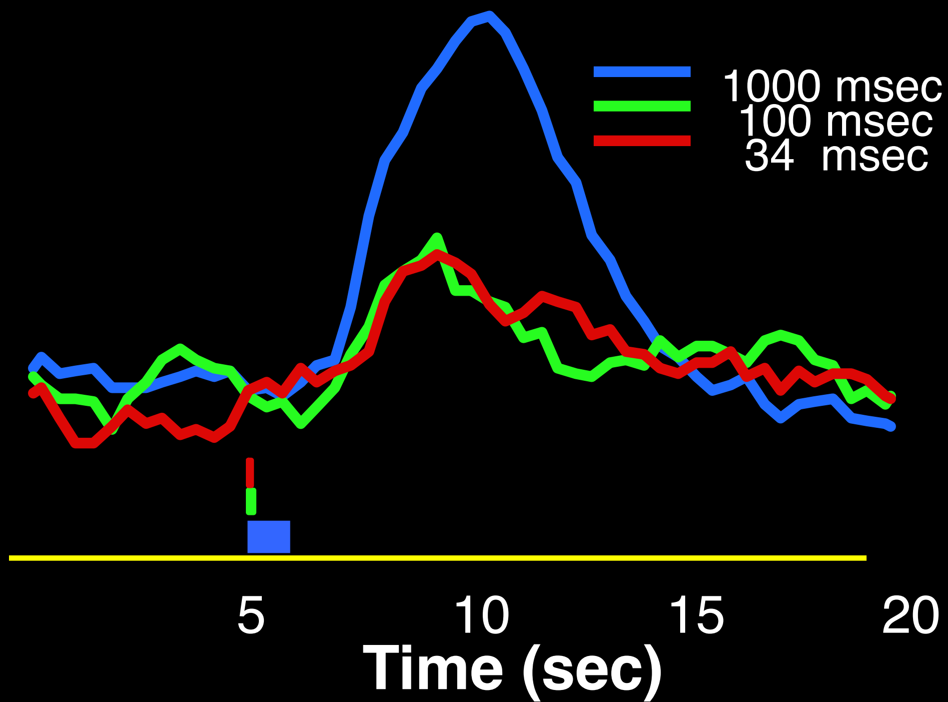
Temporal resolution







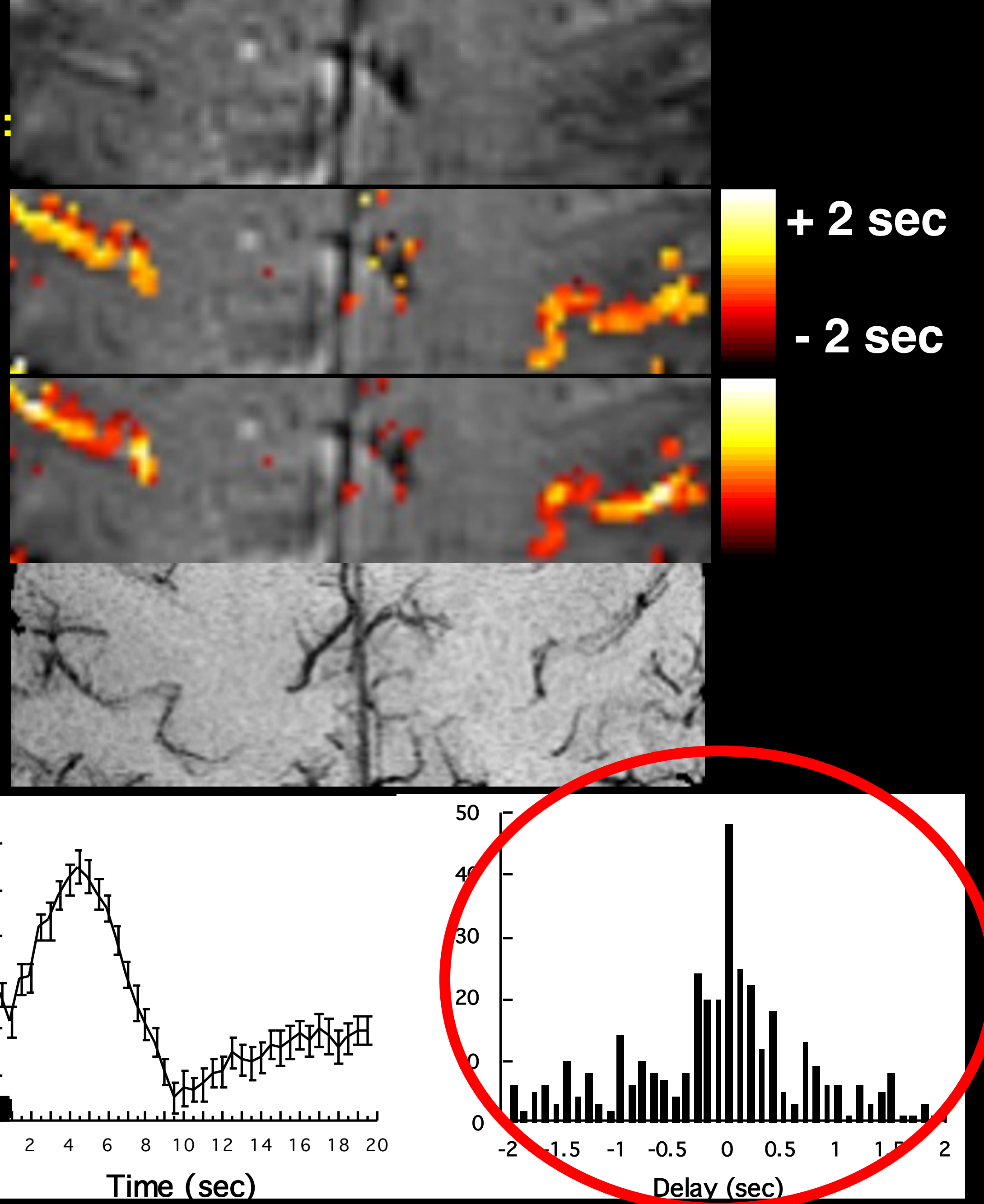
R. L. Savoy, et al., Pushing the temporal resolution of fMRI: studies of very brief visual stimuli, onset variability and asynchrony, and stimulus-correlated changes in noise [oral], 3'rd Proc. Soc. Magn. Reson., Nice, p. 450. (1995).

The major obstacle in BOLD contrast temporal resolution:

Latency

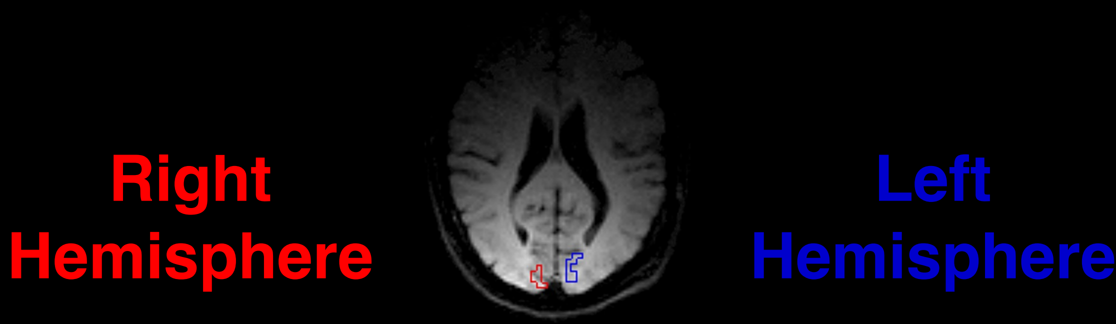
Magnitude

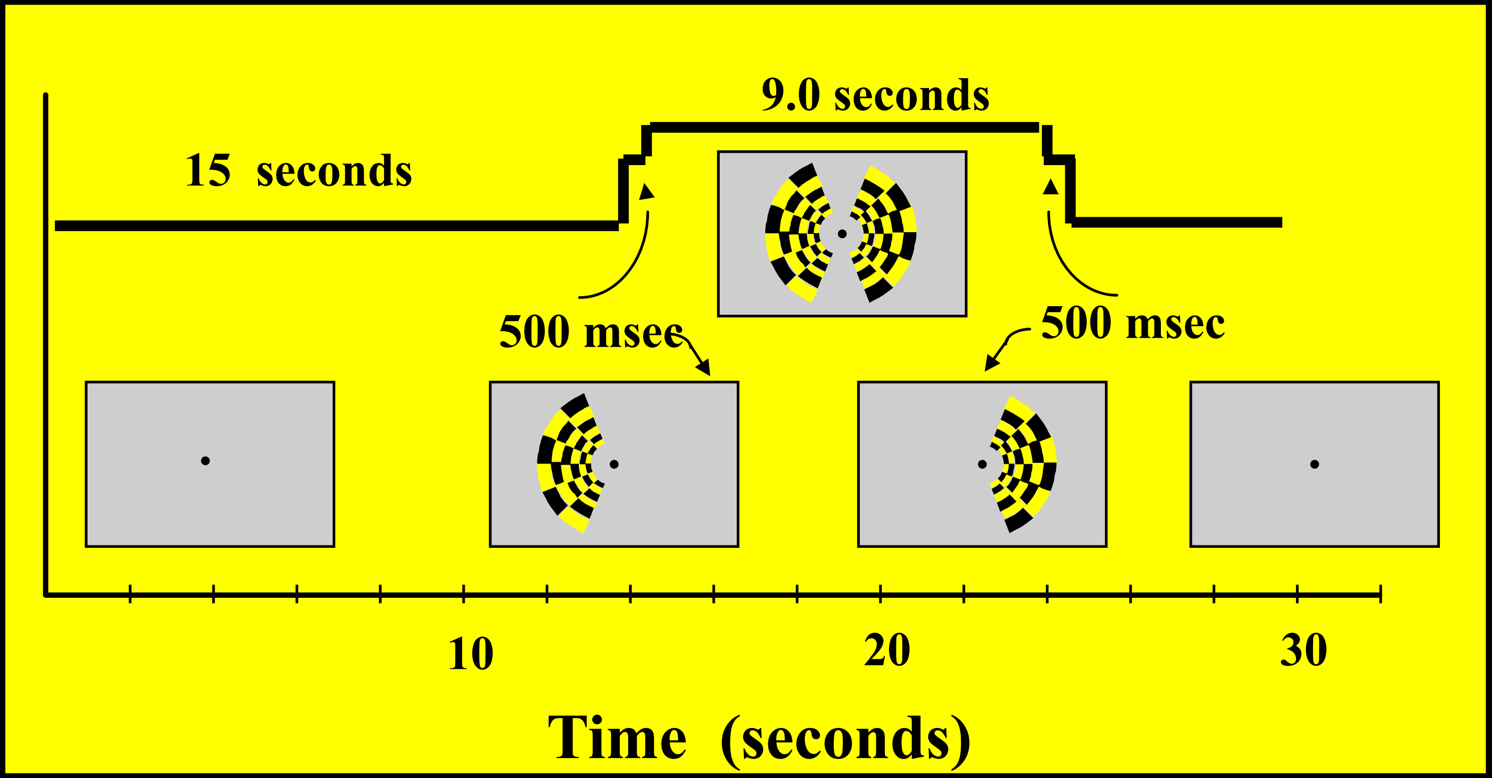
Venogram

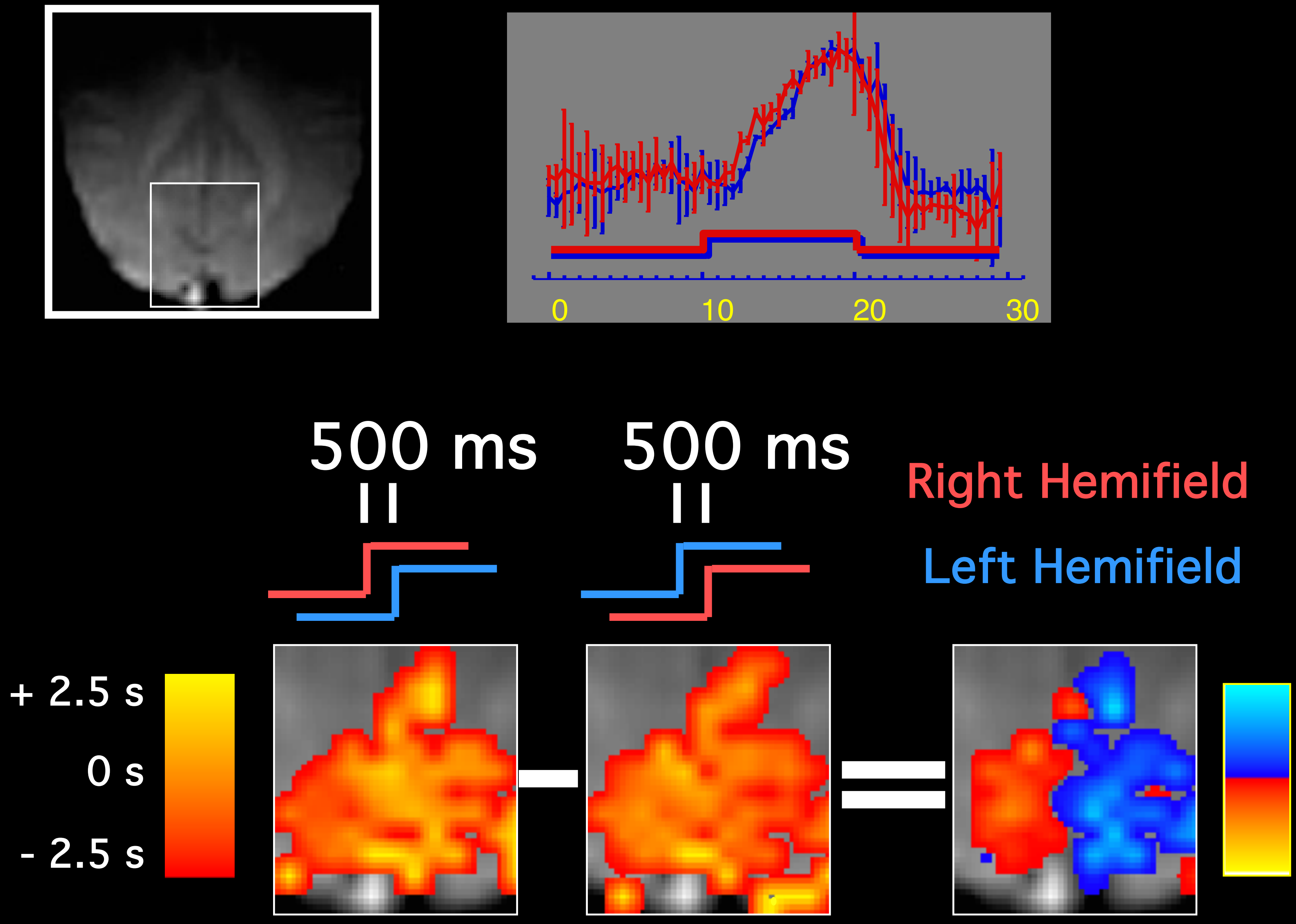


P. A. Bandettini, The temporal resolution of Functional MRI *in* "Functional MRI" (C. Moonen, and P. Bandettini., Eds.), p. 205-220, Springer - Verlag,. 1999.

Hemi-Field Experiment






0
10
20
30
500 ms
=
500 ms
=
Right Hemifield
Left Hemifield
+ 2.5 s
0 s
- 2.5 s

Cognitive Neuroscience Application:

Understanding neural system dynamics through task modulation and measurement of functional MRI amplitude, latency, and width

PNAS

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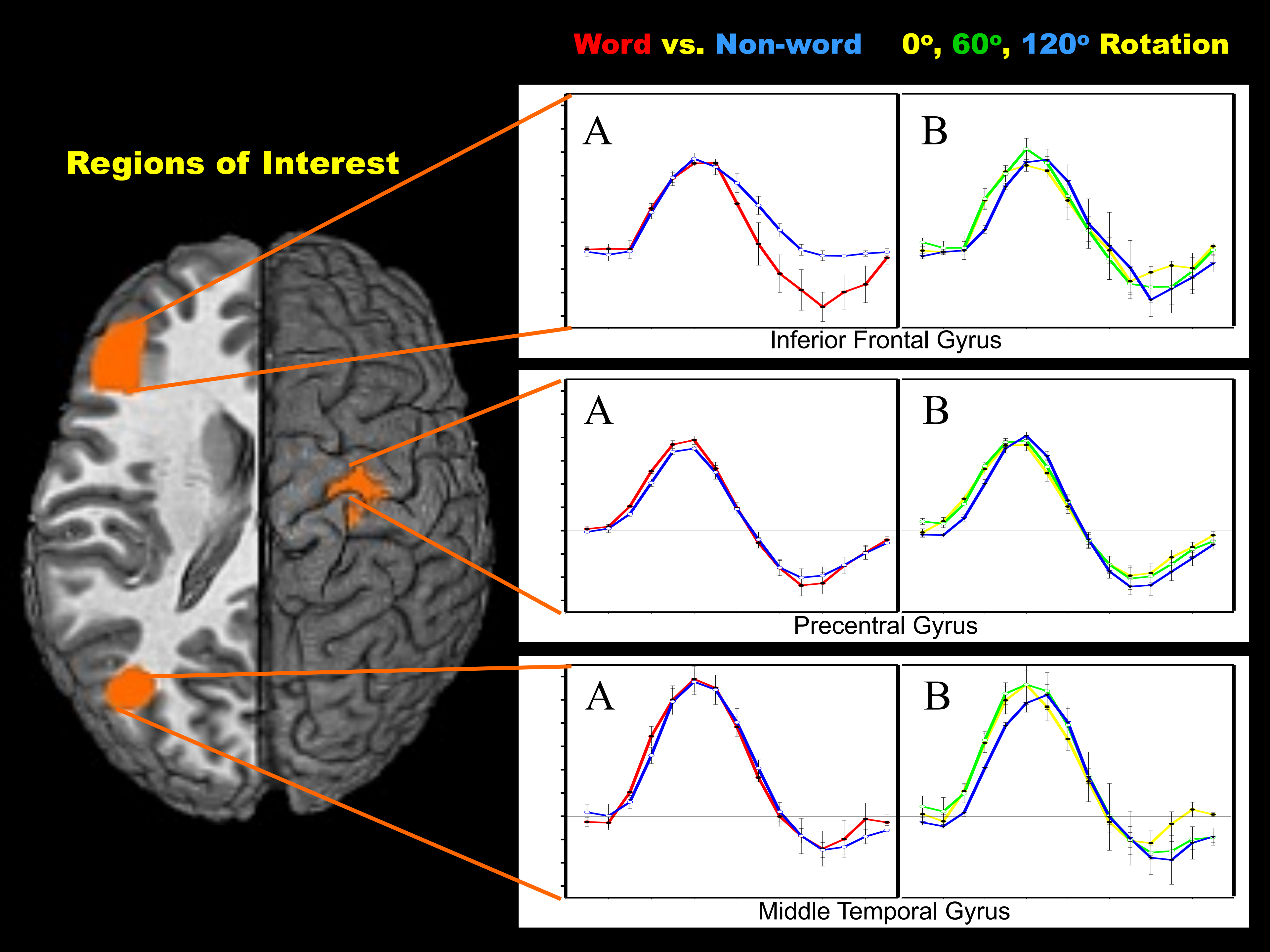
*Laboratory of Brain and Cognition and ‡Scientific and Statistical Computing Core, National Institute of Mental Health, Bethesda, MD 20892

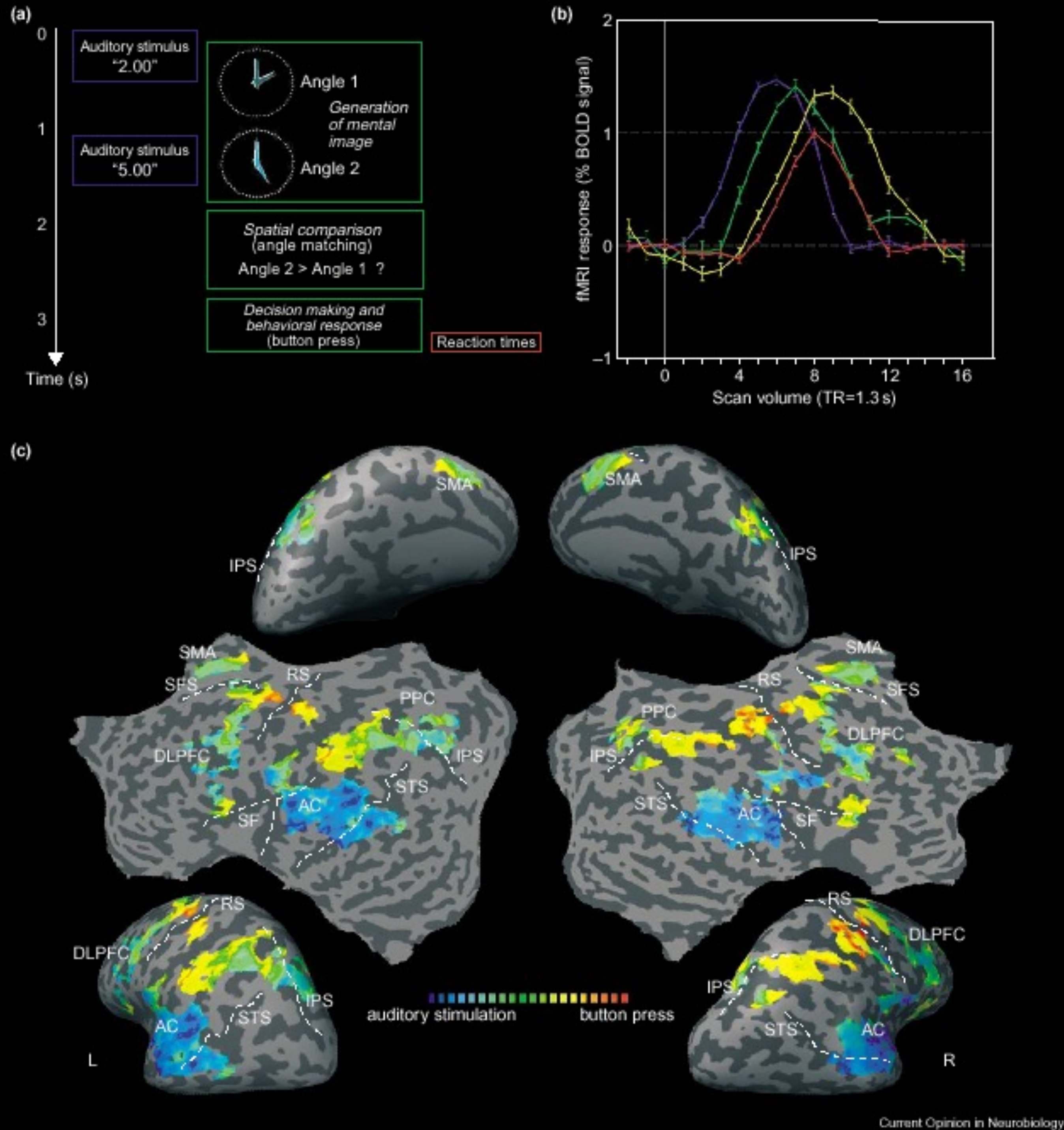
Communicated by Leslie G. Ungerleider, National Institutes of Health, Bethesda, MD, December 19, 2002 (received for review October 31, 2002)

Rotational Delay	Lexical Delay: Words	Lexical Delay: Non-Words	Mean Reaction Time
0⁰	smudge	dierts	823 ms
60⁰	frolic	cuhlos	891 ms
120⁰	slouch	gedmus	1446 ms
Mean Reaction Time	986 ms	1219 ms	



Word vs. Non-word
0º, 60º, 120º Rotation
Regions of Interest
A
B
Inferior Frontal Gyrus
A
B
Precentral Gyrus
A
B
Middle Temporal Gyrus

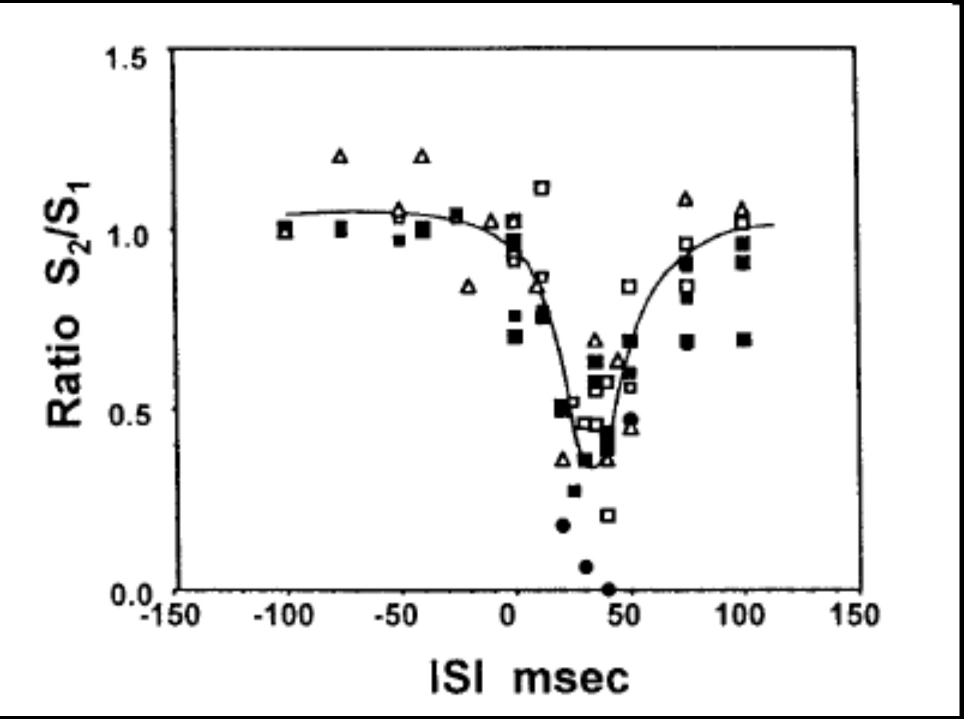
No calibration



Formisano, E. and R. Goebel, *Tracking cognitive processes with functional MRI mental chronometry.* Current Opinion in Neurobiology, 2003. **13**: p. 174-181.

An approach to probe some neural systems interaction by functional MRI at neural time scale down to milliseconds

Seiji Ogawa[†‡], Tso-Ming Lee[†], Ray Stepnoski[†], Wei Chen[§], Xiao-Hong Zhu[§], and Kamil Ugurbil[§]



11026–11031 PNAS **September 26, 2000** vol. 97 no. 20

Magnitude Calibration
Or
Extraction of $CMRO_2$ changes

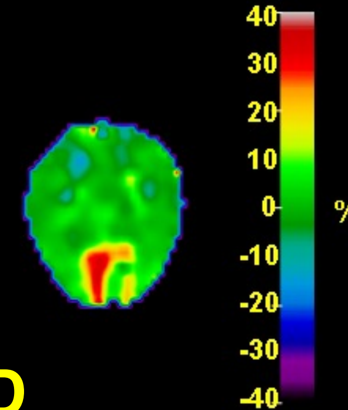
	Flow	CMRO2	BOLD
Activation	↑	↑	↑
Hypercapnia	↑	→	↑↑

Proc. Natl. Acad. Sci. USA
Vol. 96, pp. 9403–9408, August 1999
Neurobiology

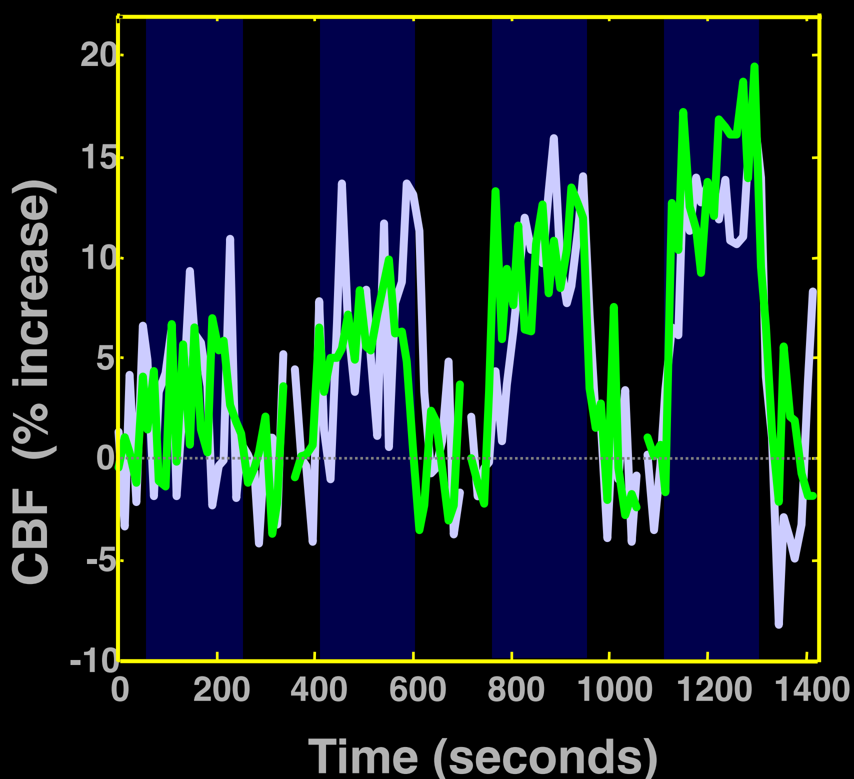
Linear coupling between cerebral blood flow and oxygen consumption in activated human cortex

RICHARD D. HOGE*†, JEFF ATKINSON*, BRAD GILL*, GÉRARD R. CRELIER*, SEAN MARRETT‡, AND G. BRUCE PIKE*

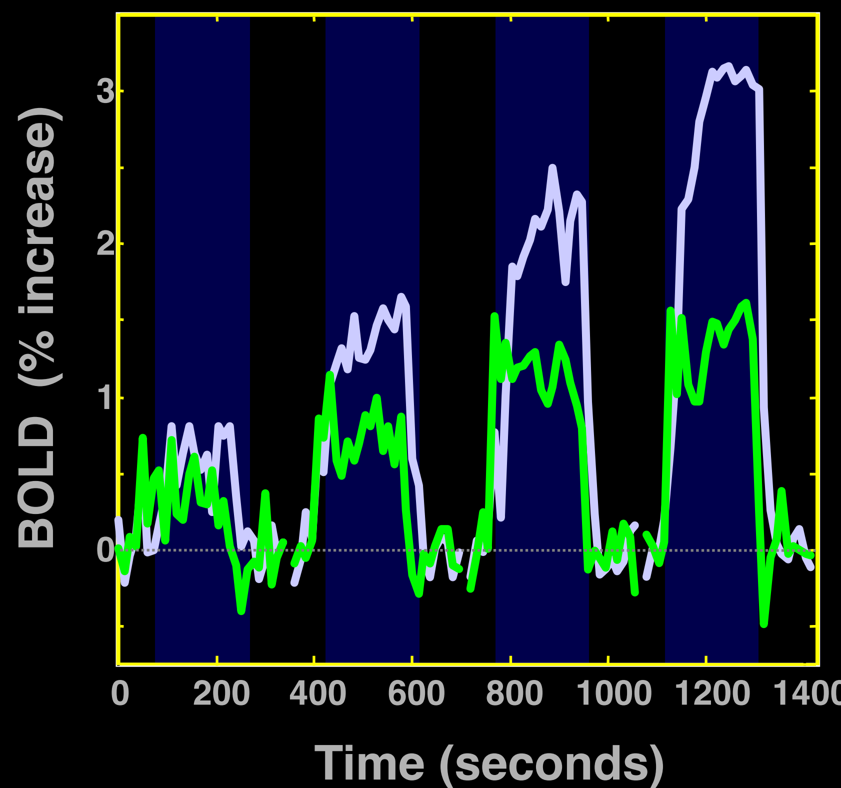
*Room WB325, McConnell Brain Imaging Centre, Montreal Neurological Institute, Quebec, Canada H3A 2B4; and ‡Nuclear Magnetic Resonance Center, Massachusetts General Hospital, Building 149, 13th Street, Charlestown, MA 02129



CBF



BOLD



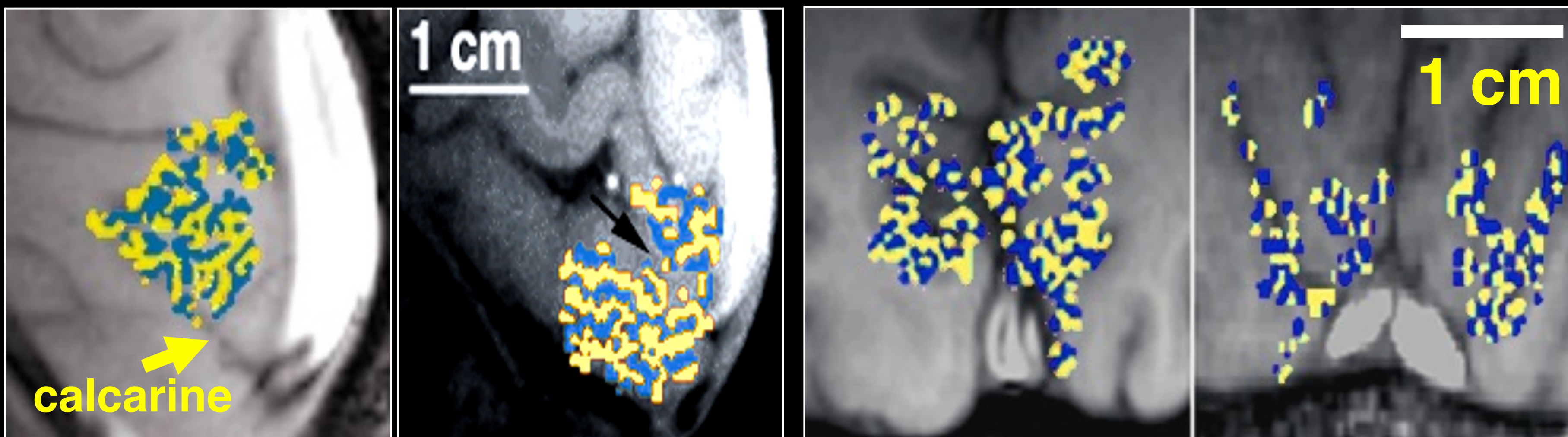
Simultaneous Perfusion and BOLD imaging during graded visual activation and hypercapnia

N=12

Multi-subject averaging/normalization at very high resolution

Current spatial normalization techniques have a large intrinsic (up to 10 mm) variability. This issue will become more problematic at higher resolutions.

Multi-subject averaging/normalization at very high resolution



Menon et al.

Motion (very slow and activation correlat

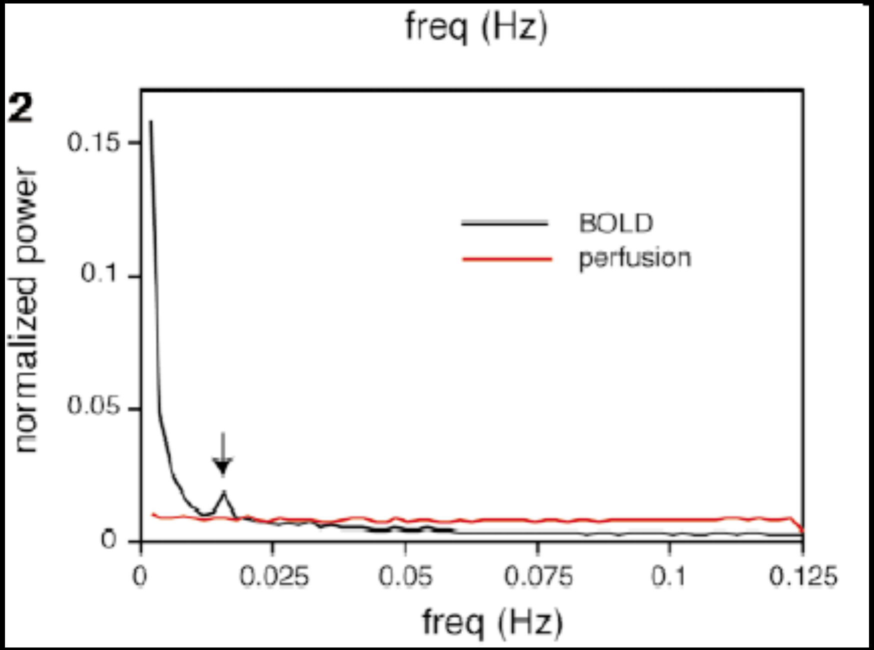
Very slow:

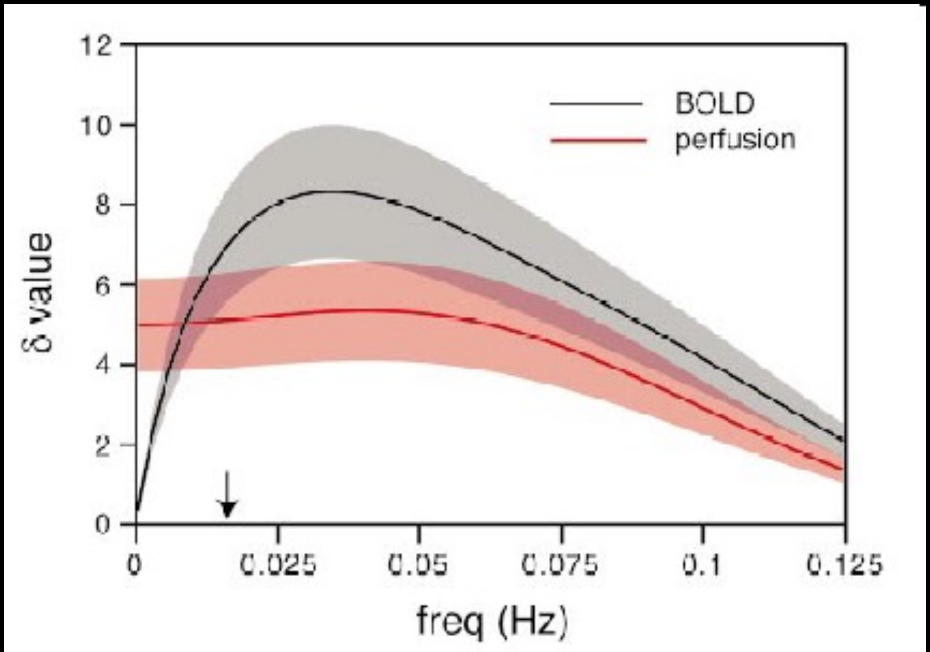
- -a problem when looking at slow state changes
- -one solution: ASL techniques

Activation correlated:

- -separable from hemodynamic response

ASL Techniques show more temporal stability

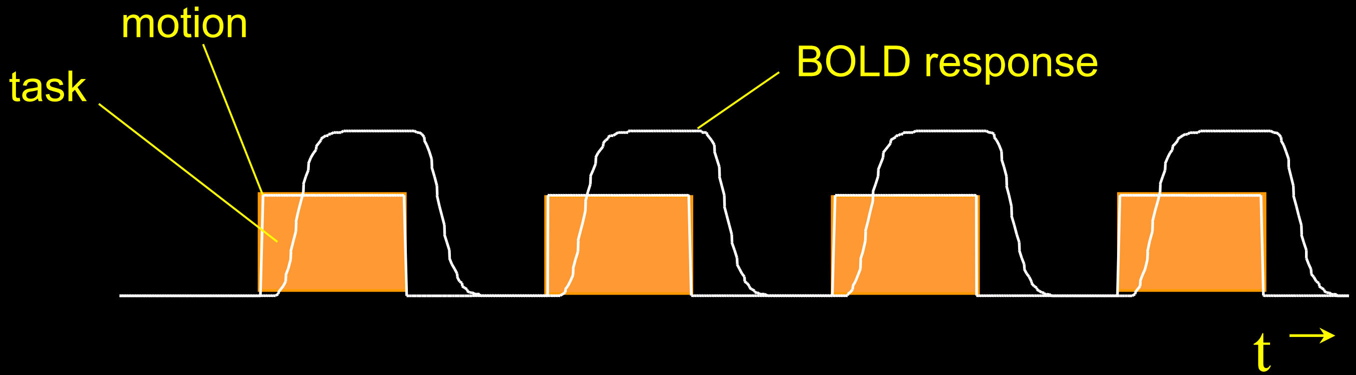




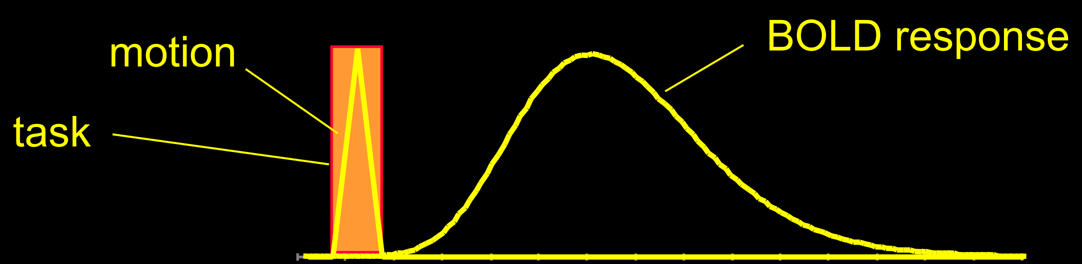
Experimental design and the relative sensitivity of BOLD and perfusion fMRI Aguirre GK, Detre JA, Zarahn E, Alsop DC, **NEUROIMAGE** 15 (3): 488-500 MAR 2002

fMRI during tasks that involve brief motion

Blocked Design

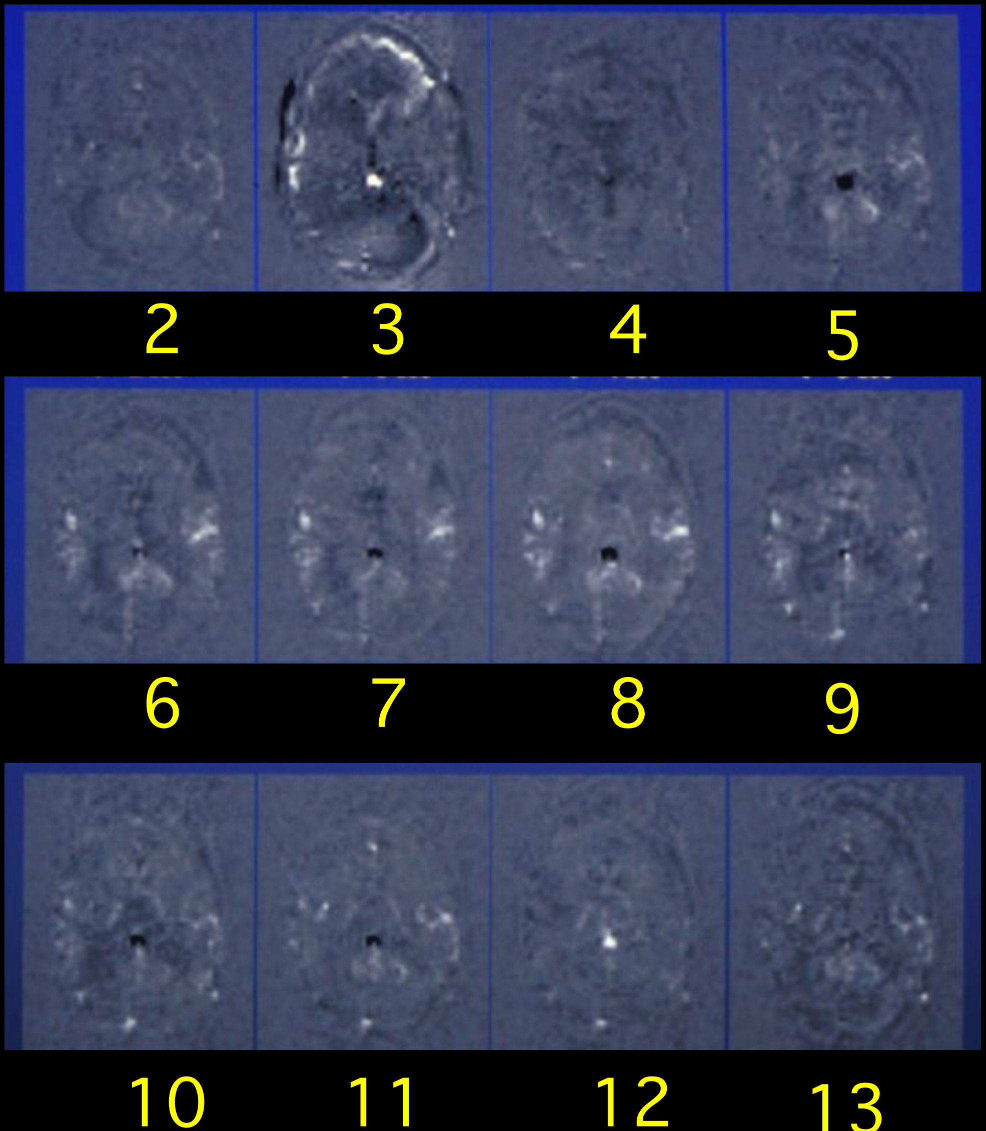


Event-Related Design



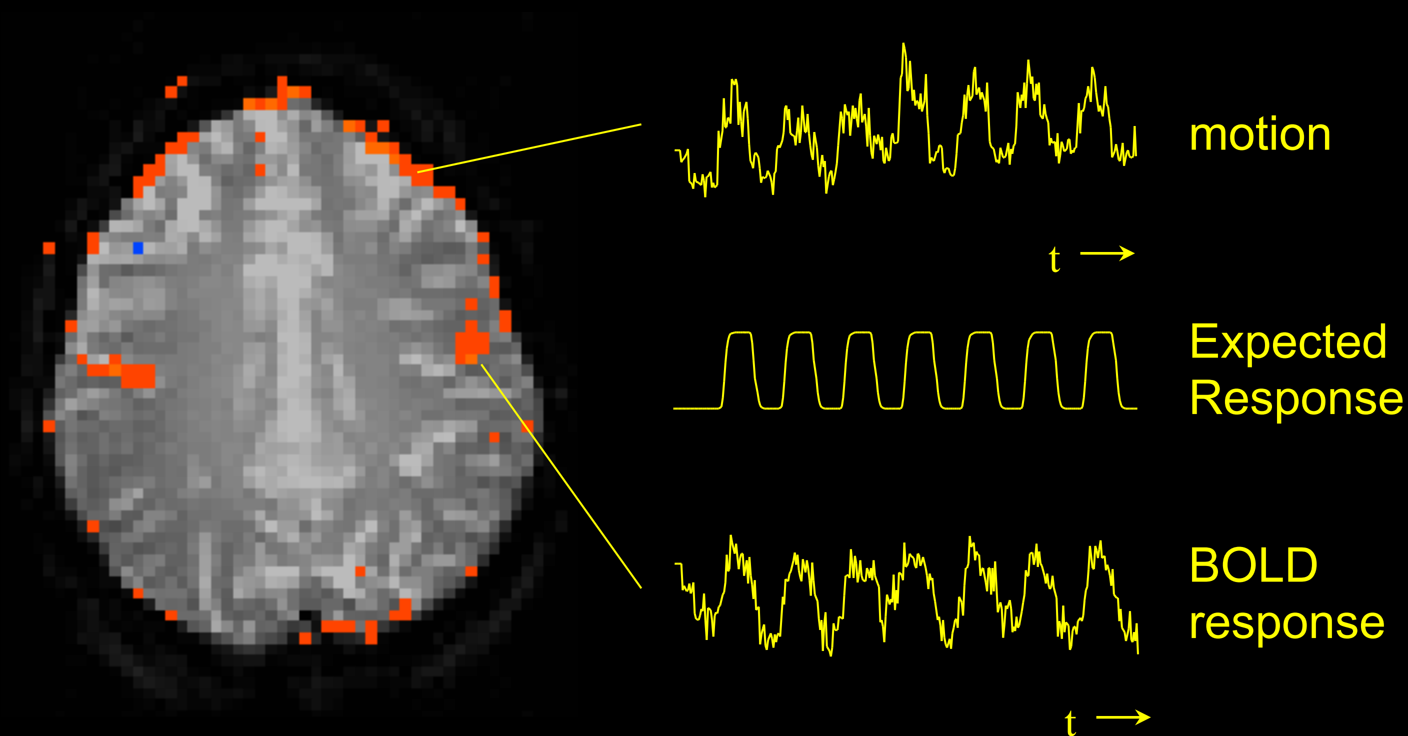
R. M. Birn, P. A. Bandettini, R. W. Cox, R. Shaker, Event - related fMRI of tasks involving brief motion. *Human Brain Mapping* 7: 106-114 (1999).

Overt Word Production



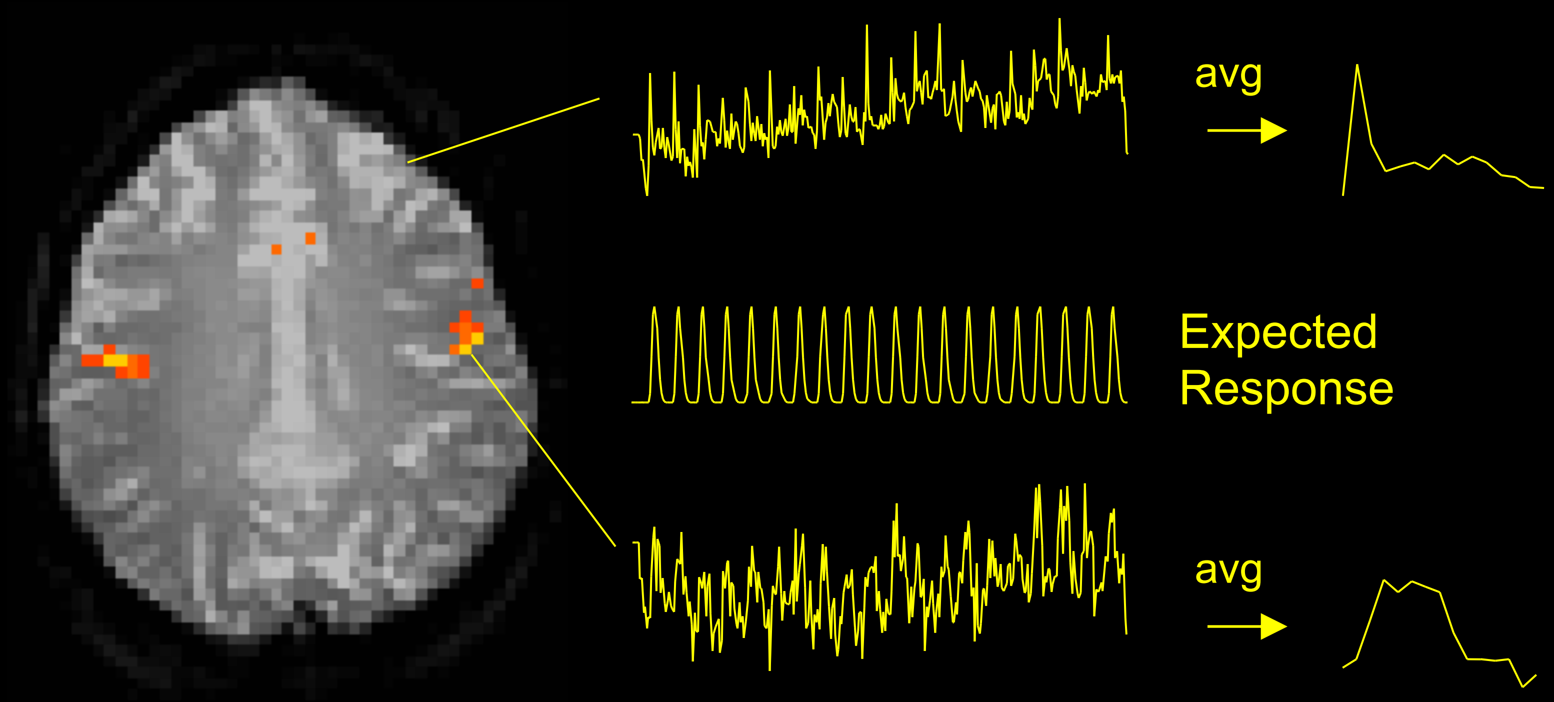
R. M. Birn, P. A. Bandettini, R. W. Cox, R. Shaker, Event - related fMRI of tasks involving brief motion. *Human Brain Mapping* 7: 106-114 (1999).

Speaking - Blocked Trial

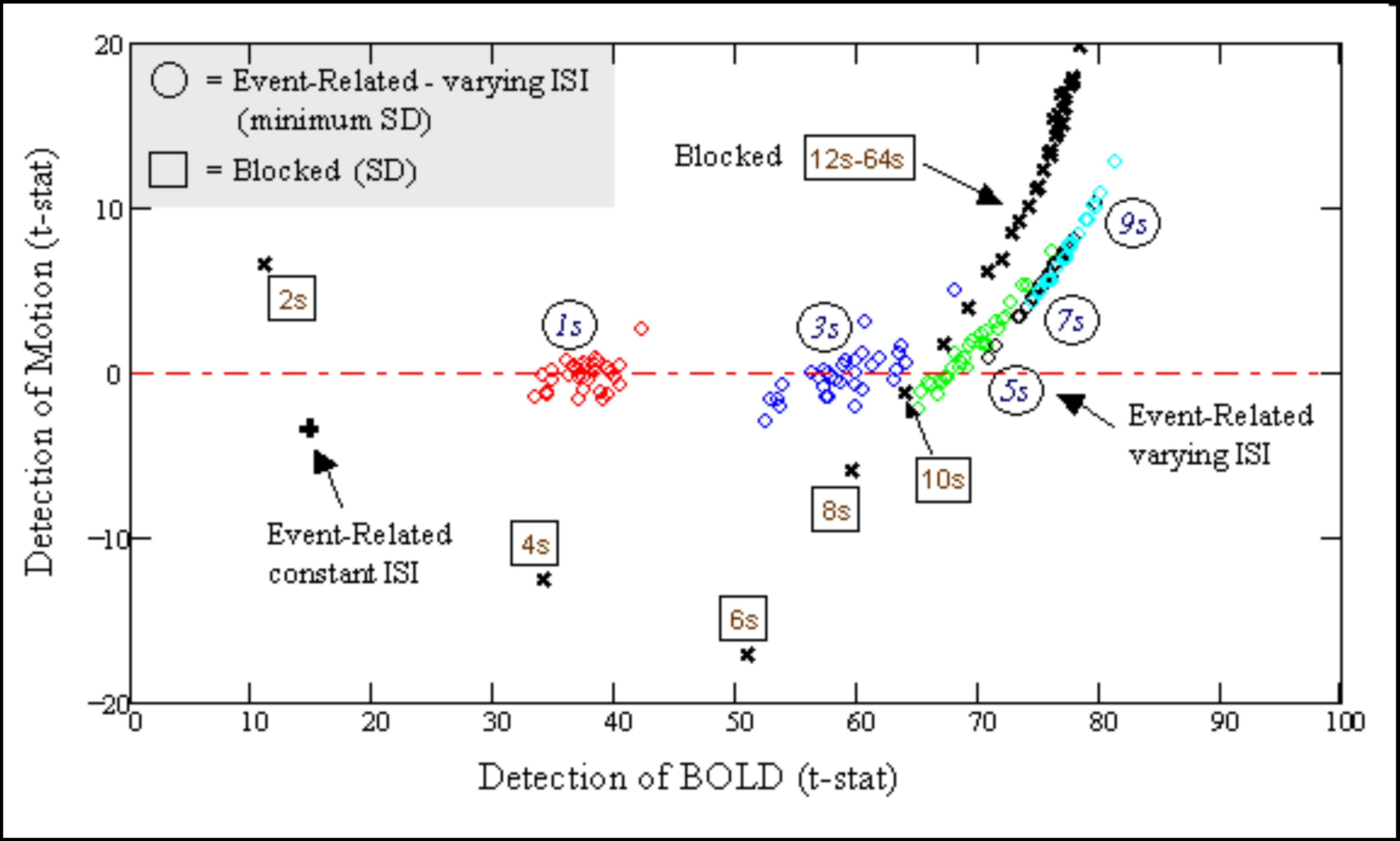


R. M. Birn, P. A. Bandettini, R. W. Cox, R. Shaker, Event - related fMRI of tasks involving brief motion. *Human Brain Mapping* 7: 106-114 (1999).

Speaking - ER-fMRI



R. M. Birn, P. A. Bandettini, R. W. Cox, R. Shaker, Event - related fMRI of tasks involving brief motion. *Human Brain Mapping* 7: 106-114 (1999).



= Event-Related - varying ISI (minimum SD)
= Blocked (SD)
Blocked
12s-64s
2s
1s
3s
9s
7s
5s
Event-Related varying ISI
Event-Related constant ISI
4s
6s
8s
10s
Detection of Motion (t-stat)
Detection of BOLD (t-stat)
20
10
0
-10
-20
0
10
20
30
40
50
60
70
80
90
100

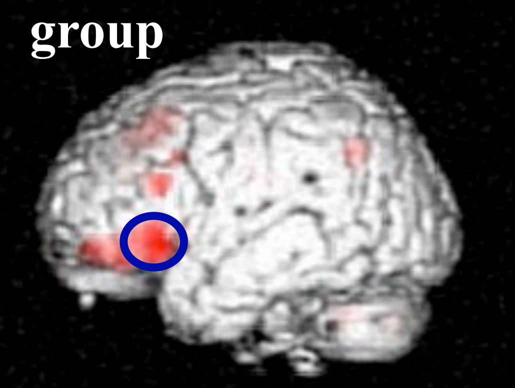
Individual Map "Classification"

The issue: We can make inferences about groups when averaging individual maps, but can we make inferences which group an individual belongs to?

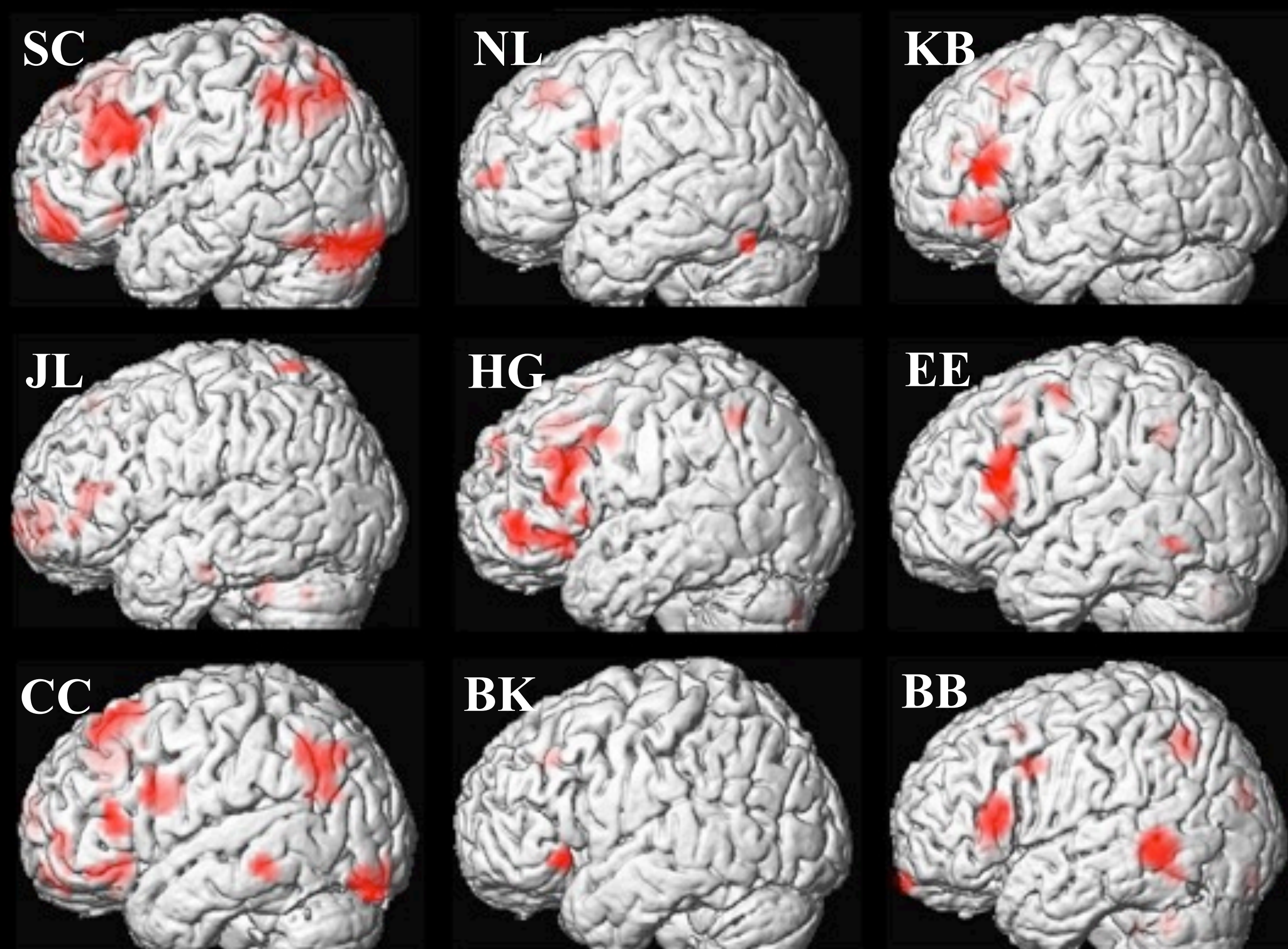
Not yet. Requires extensive classification techniques.

Extensive Individual Differences in Brain Activations During Episodic Retrieval

Miller et al., 2002



Individual activations from the left hemisphere of the 9 subjects



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

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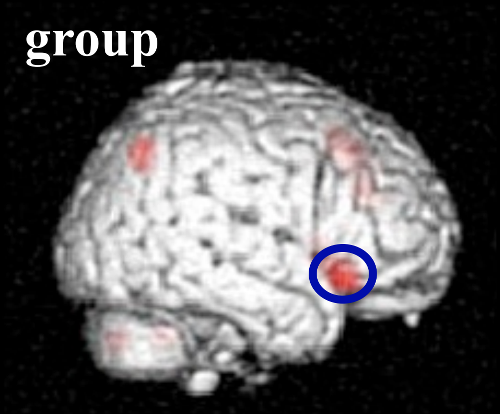
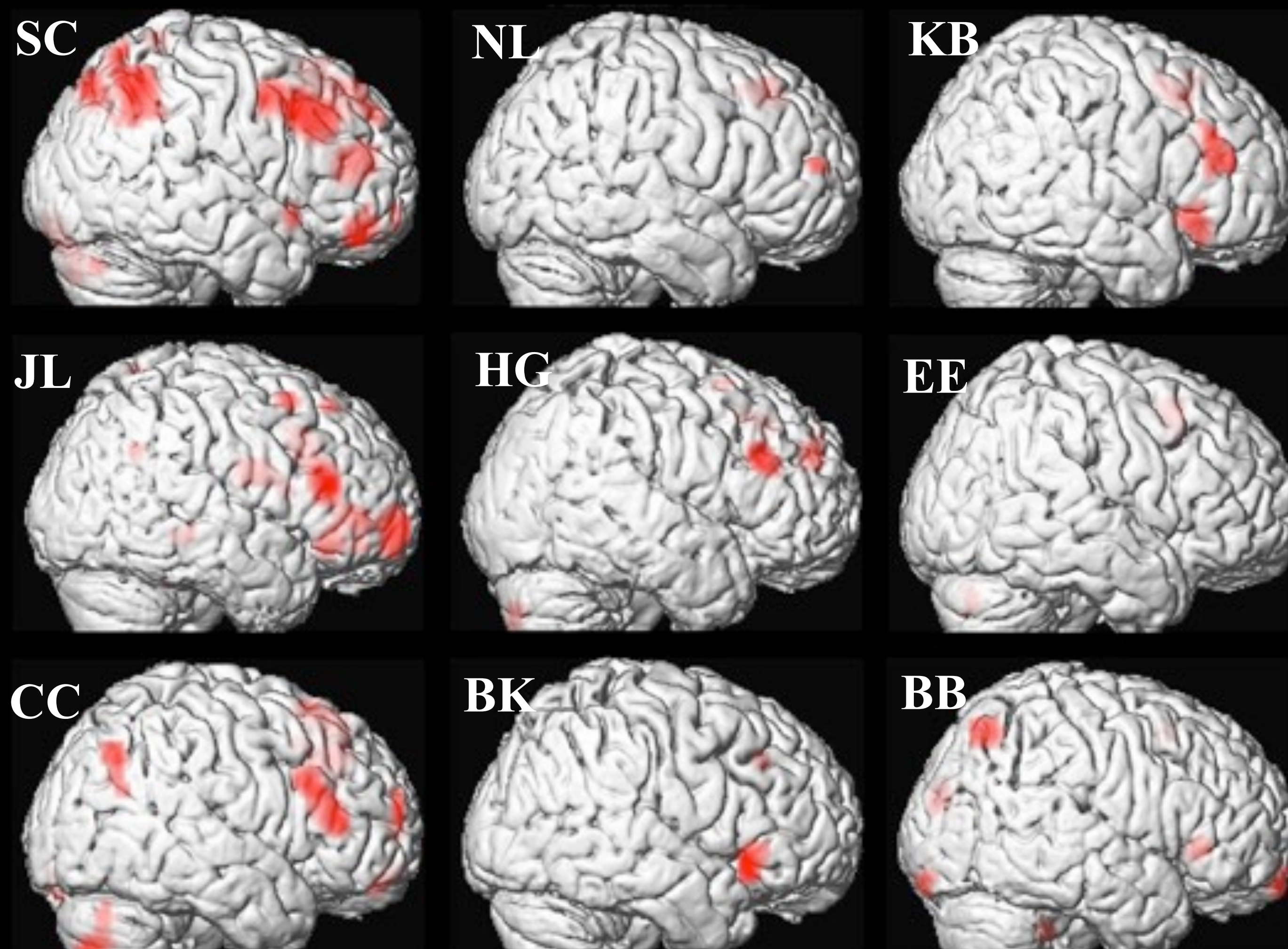
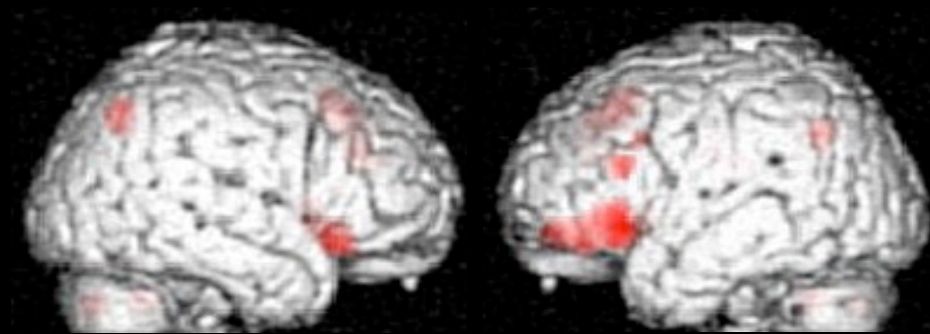


Individual activations from the right hemisphere of the 9 subjects

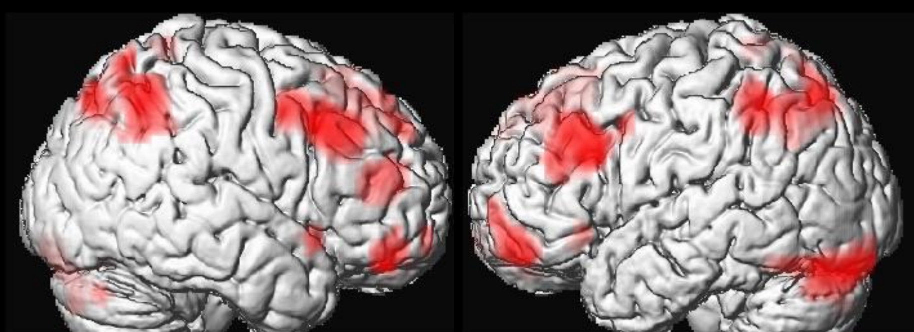


Courtesy, Mike Miler, UC Santa Barbara and Jack Van Horn, fMRI Data Center, Dartmouth University

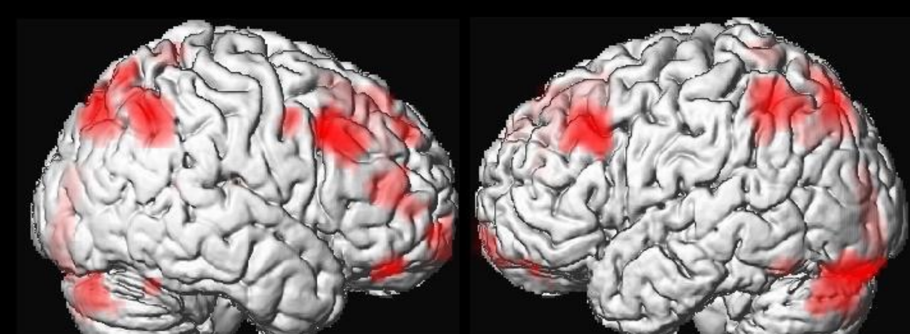
These individual patterns of activations are stable over time



Group Analysis of Episodic Retrieval



Subject SC

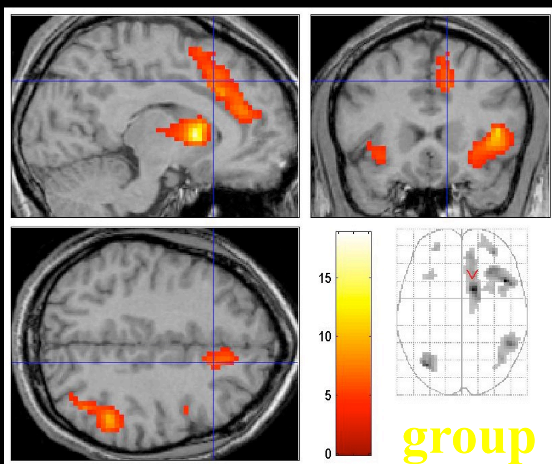


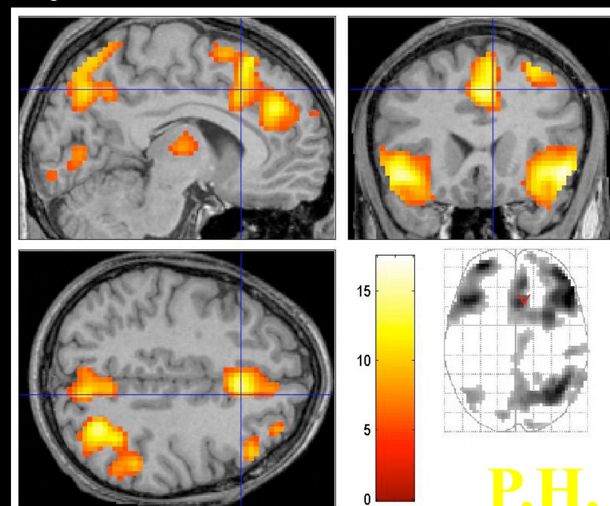
Subject SC 6 months later

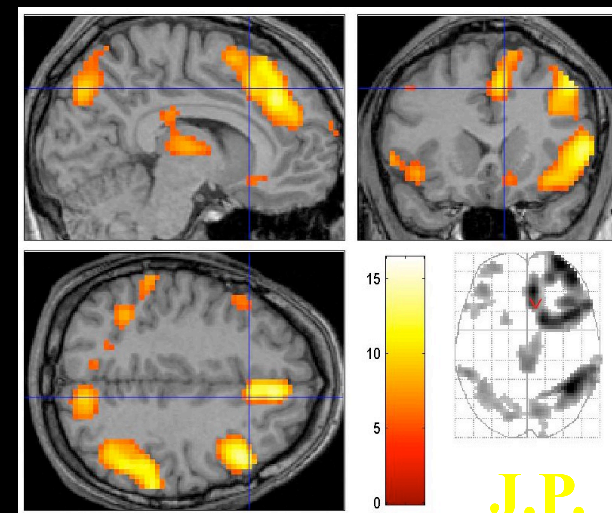
Courtesy, Mike Miler, UC Santa Barbara and Jack Van Horn, fMRI Data Center, Dartmouth University

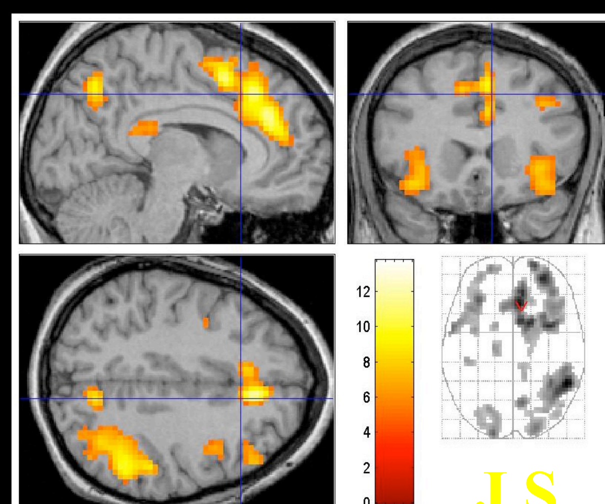
Individual patterns of activity are much more consistent across subjects for other retrieval tasks.

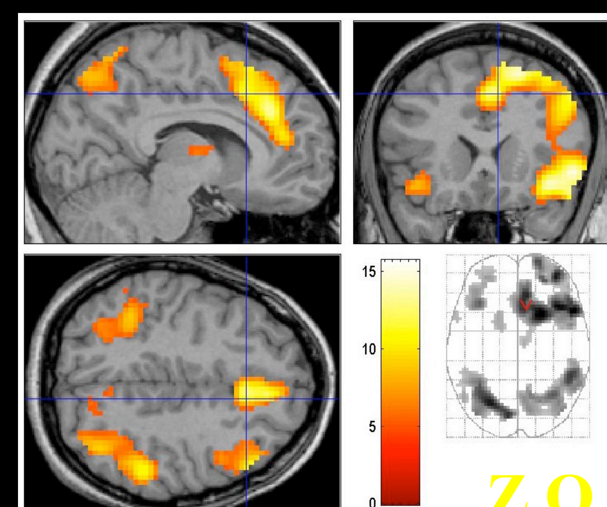
spatial working memory











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

Local Pattern Effect Mapping and Classification

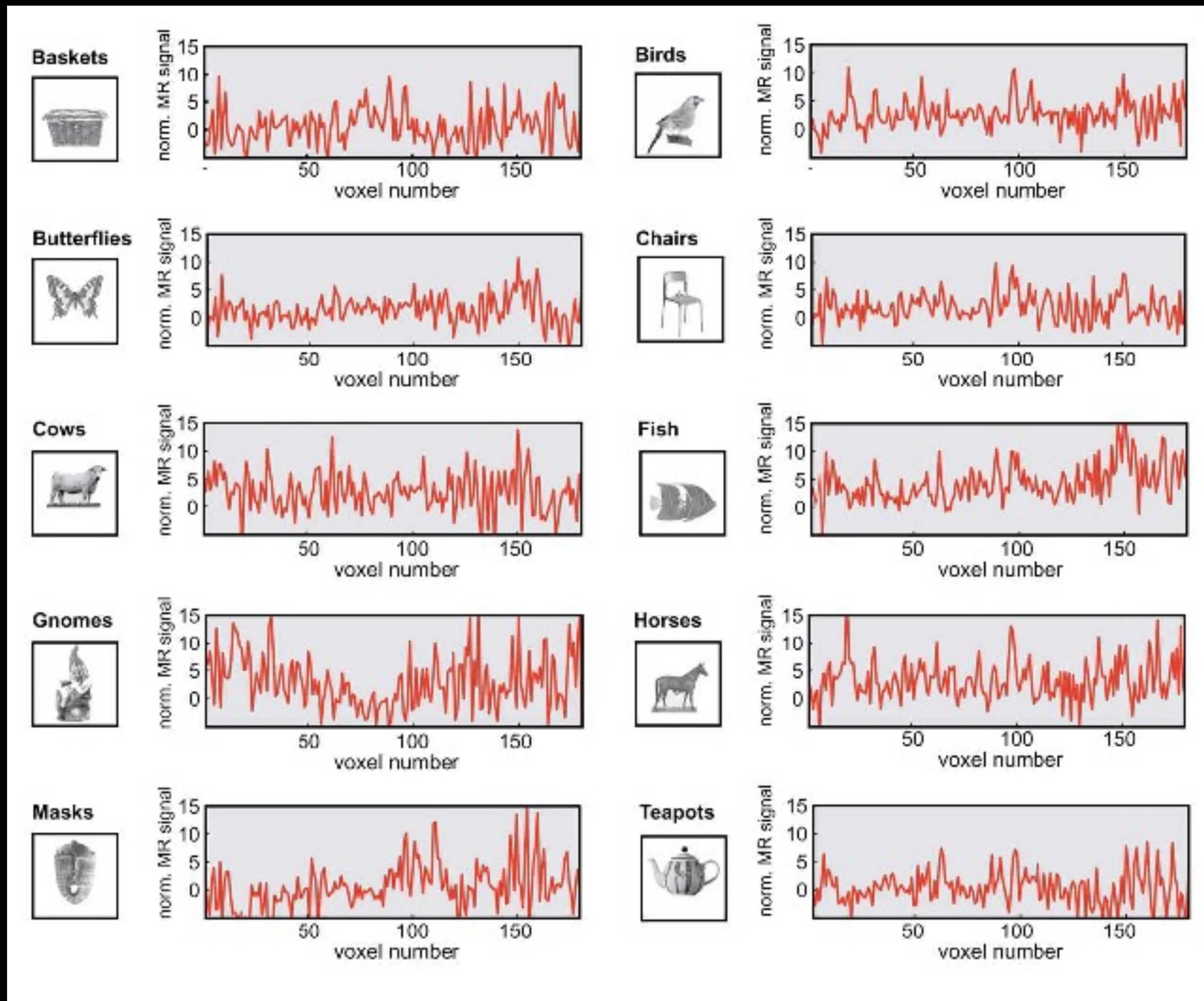
Functional magnetic resonance imaging (fMRI) "brain reading": detecting and classifying distributed patterns of fMRI activity in human visual cortex

David D. Cox[a,b,*] and Robert L. Savoy[a,b,c]

[a] Rowland Institute for Science, Cambridge, MA 02142, USA
[b] Athinoula A. Martinos Center for Structural and Functional Biomedical Imaging, Charlestown, MA 02129, USA
[c] HyperVision, Inc., P.O. Box 158, Lexington, MA 02420, USA

Received 15 July 2002; accepted 10 December 2002

NEUROIMAGE 19 (2): 261-270 Part 1 JUN 2003



Temporal fluctuations (removal and use)

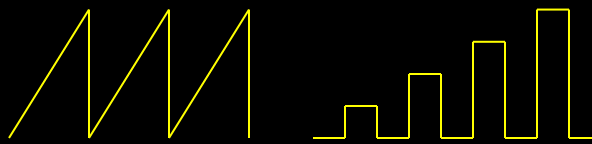
Time series contains many sources of noise.
-cardiac, motion, respiratory, blood oxygenation

A goal is to extract the oxygenation fluctuations to the extent that they indicate resting state or spontaneous activity.

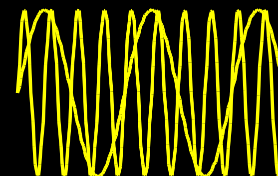
Paradigm Design

1. Block Design

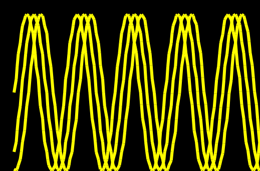
2. Parametric Design



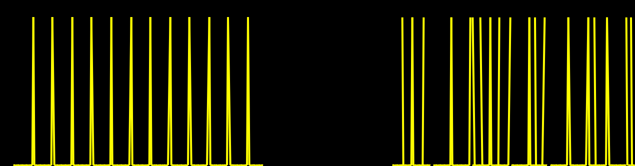
3. Frequency Encoding



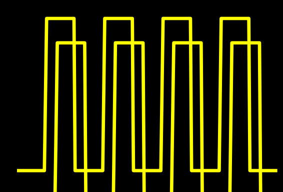
4. Phase Encoding



5. Event Related

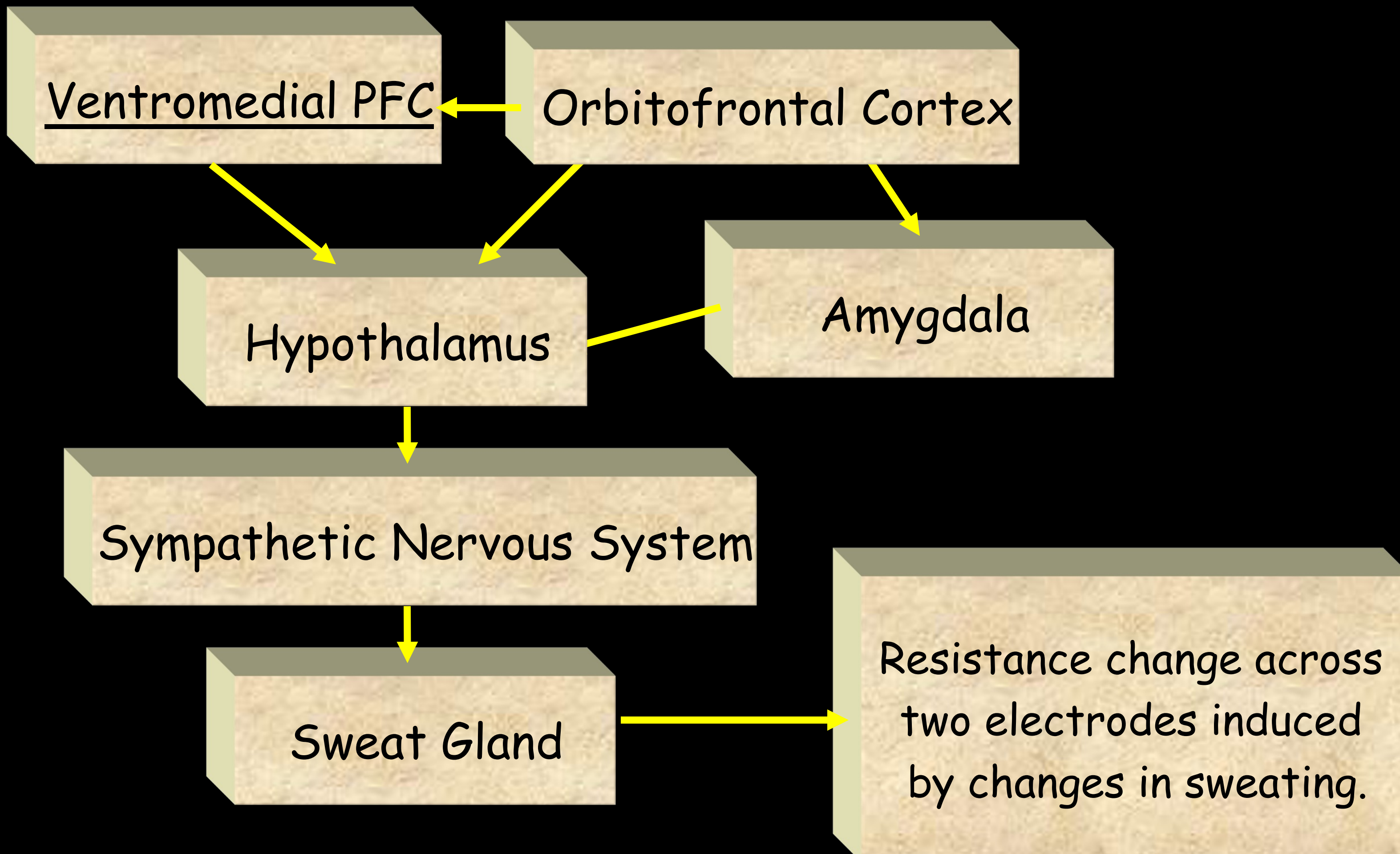


6. Orthogonal Design

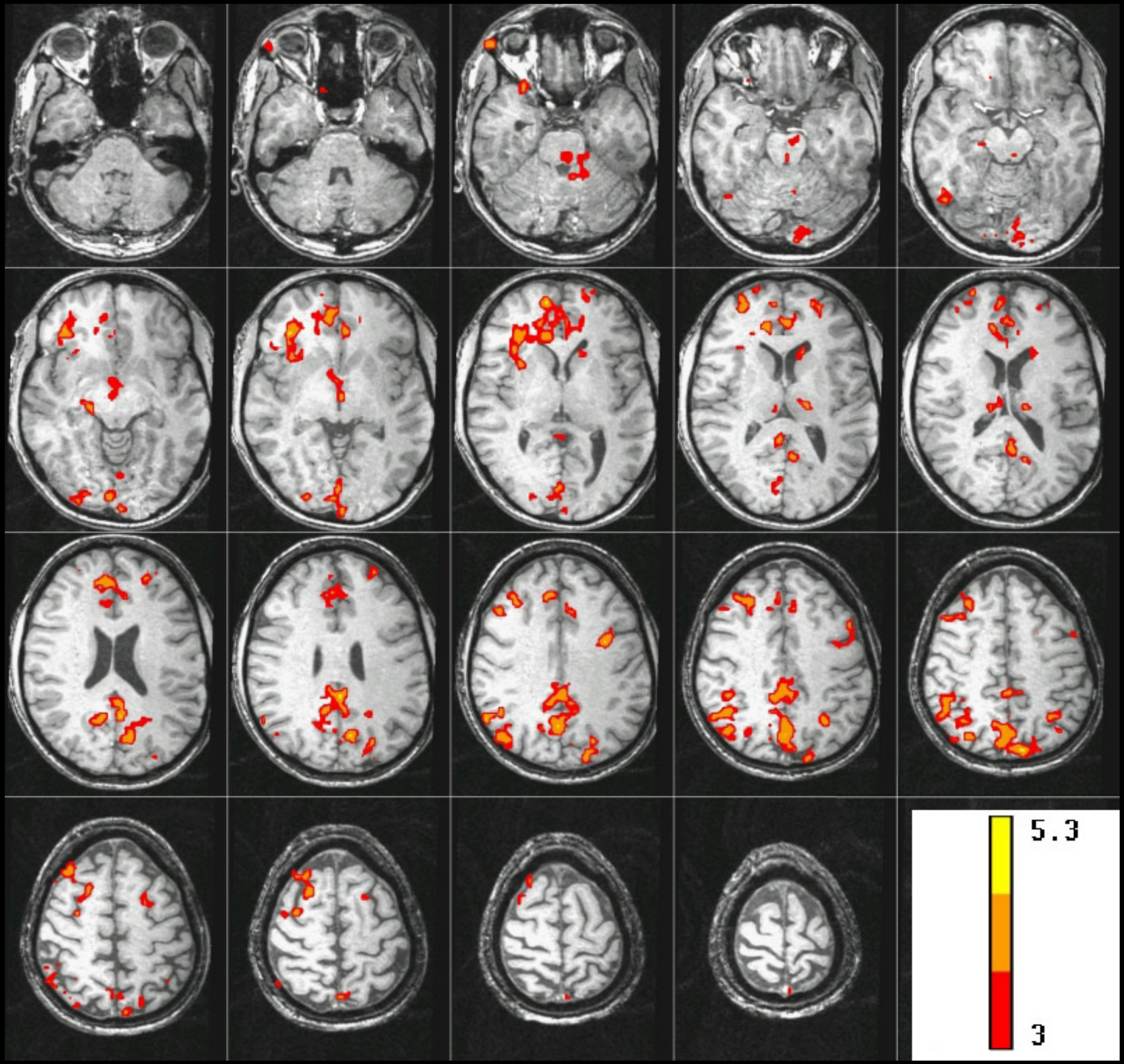


7. Free Behavior Design

The Skin Conductance Response (SCR)



Brain activity correlated with SCR during "Rest"



J. C. Patterson II, L. G. Ungerleider, and P. A Bandettini, Task - independent functional brain activity correlation with skin conductance changes: an fMRI study. *NeuroImage 17: 1787-1806, (2002).*

Simultaneous EEG and fMRI of the alpha rhythm

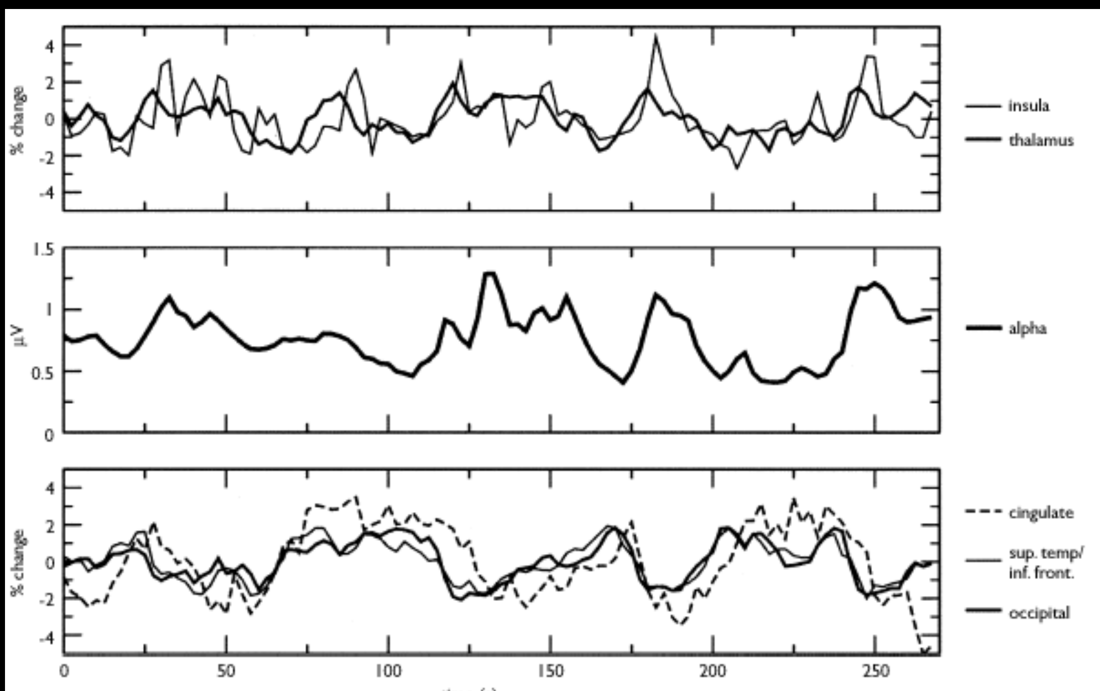
Robin I. Goldman,[2,CA] John M. Stern,[1] Jerome Engel Jr[1] and Mark S. Cohen

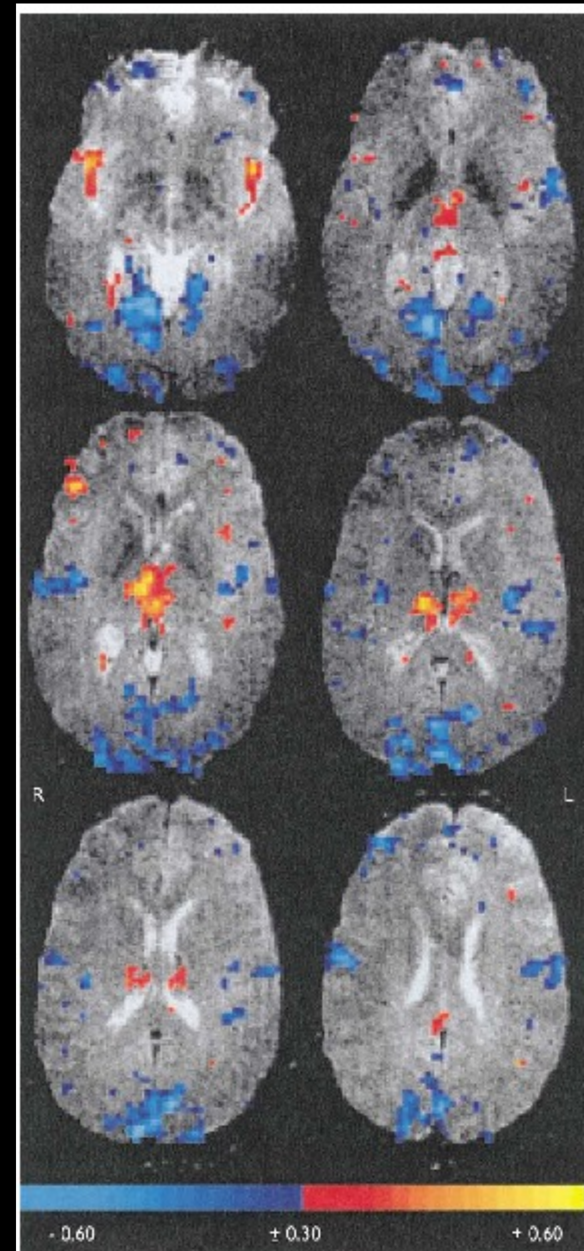
Ahmanson-Lovelace Brain Mapping Center, UCLA, 660 Charles Young Drive South, Los Angeles, CA 90095; [1]Department of Neurology, UCLA School of Medicine, Los Angeles, CA; [2]Hatch Center for MR Research, Columbia University, HSD, 710 W. 168th St., NIB-1, Mailbox 48, NY, NY 10032, USA

[CA,2]Corresponding Author and Address: rg2146@columbia.edu

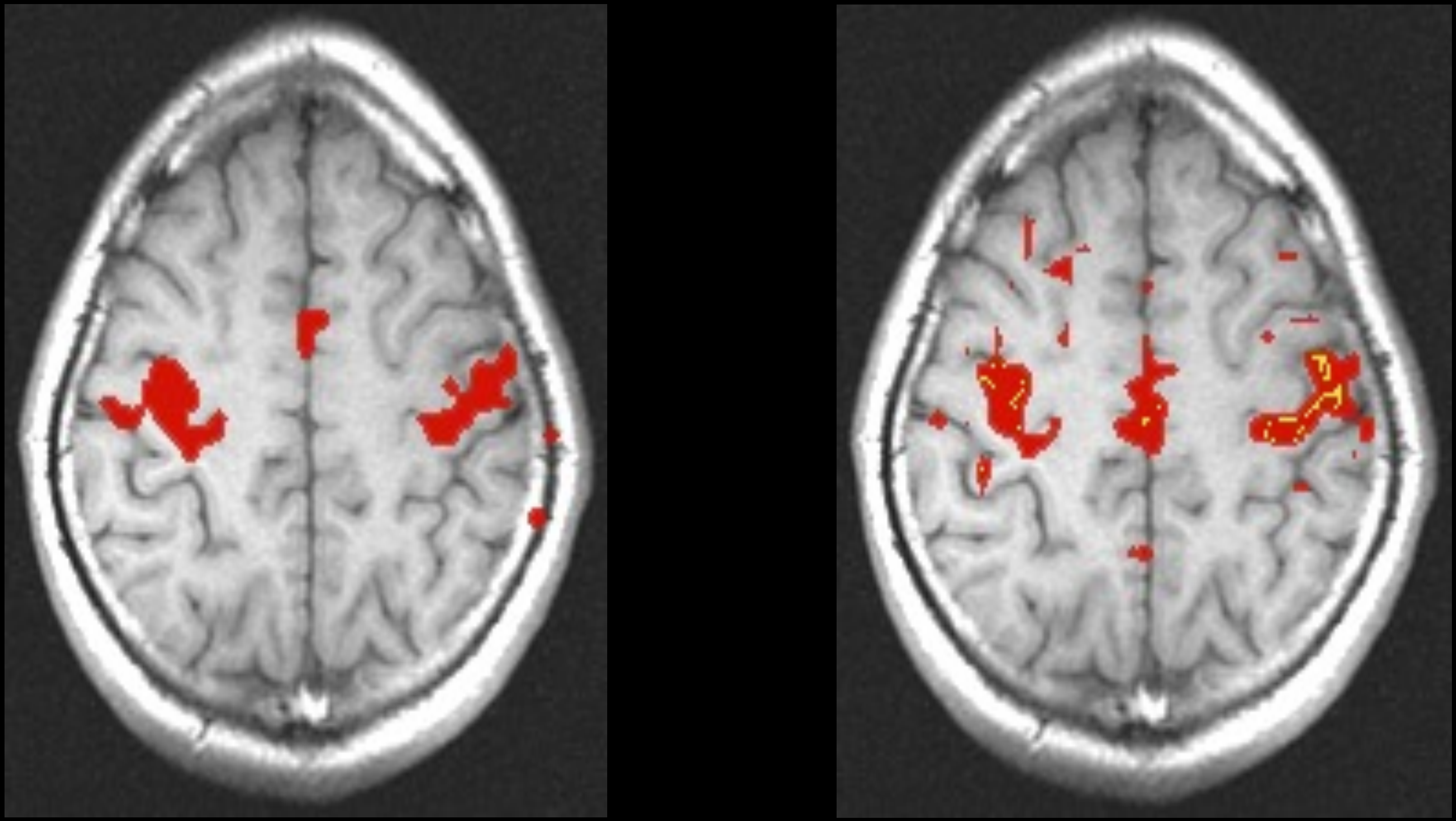
Received 28 October 2002; accepted 30 October 2002

DOI: 10.1097/01.wnr.0000047685.08940.d0



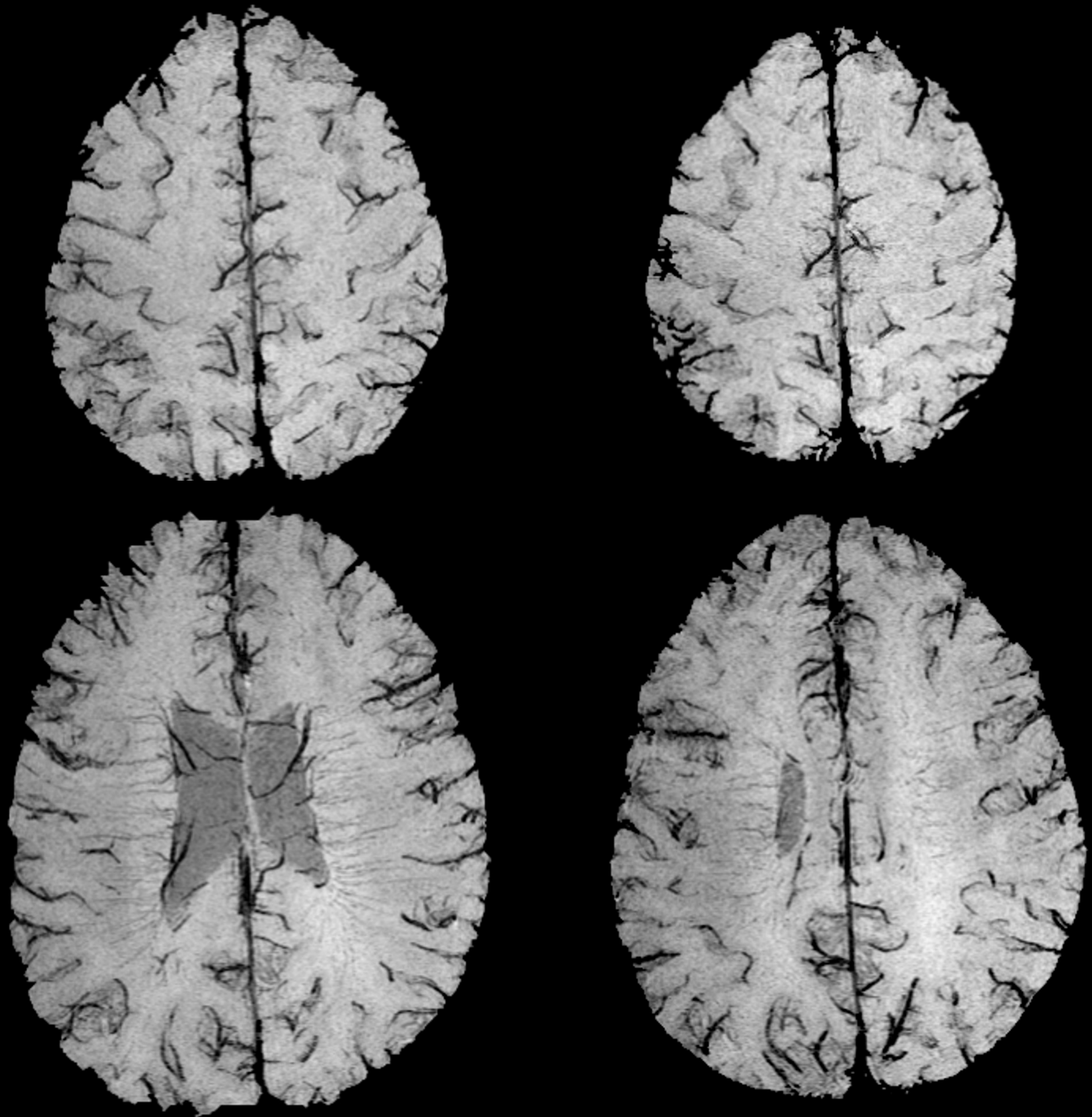


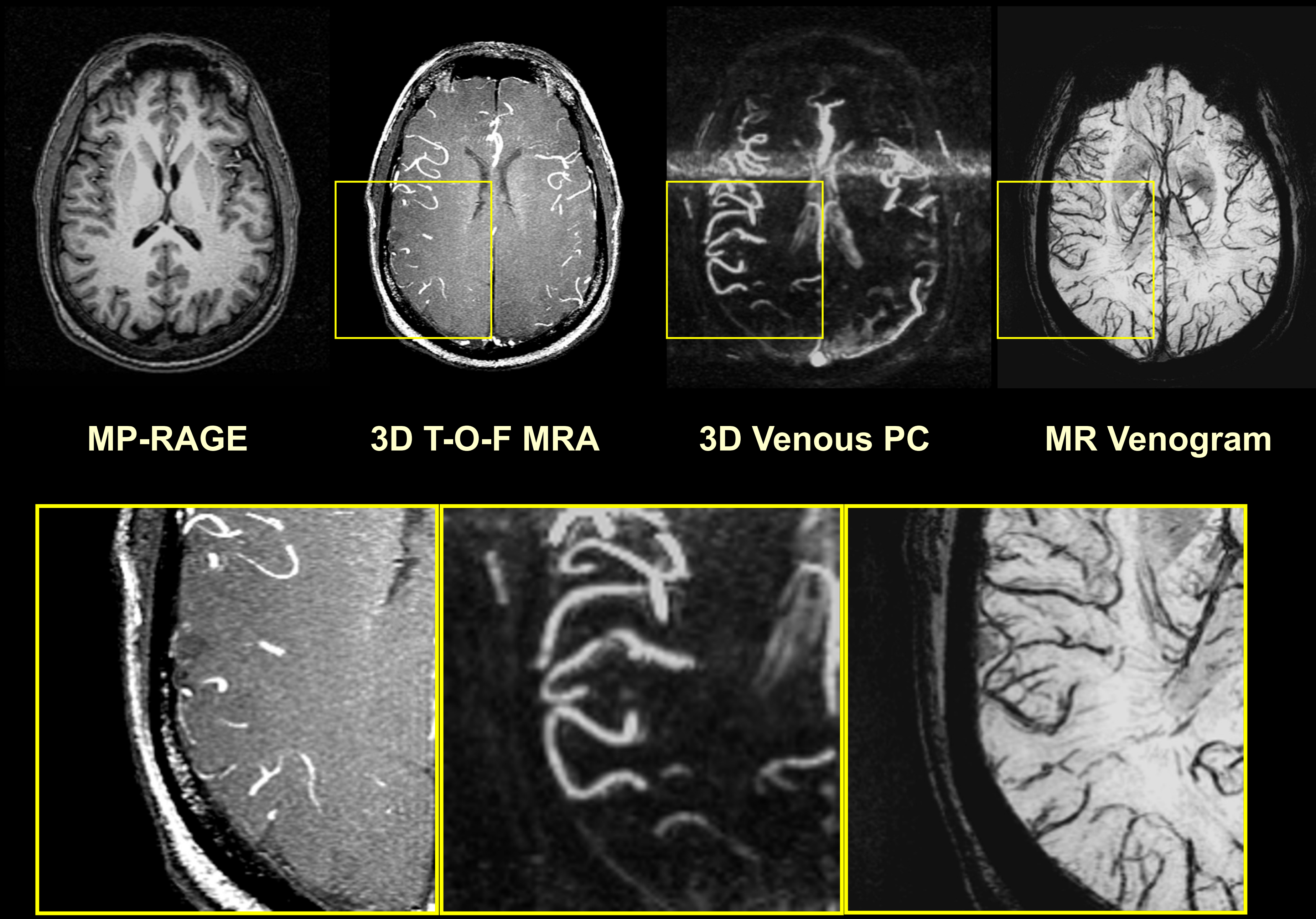
Resting State Fluctuations

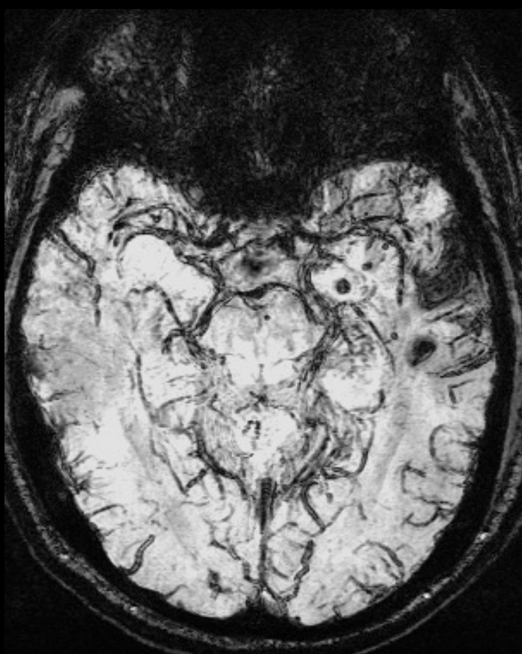


B. Biswal *et al*., MRM, 34:537 (1995)

Baseline susceptibility mapping




MP-RAGE
3D T-O-F MRA
3D Venous PC
MR Venogram

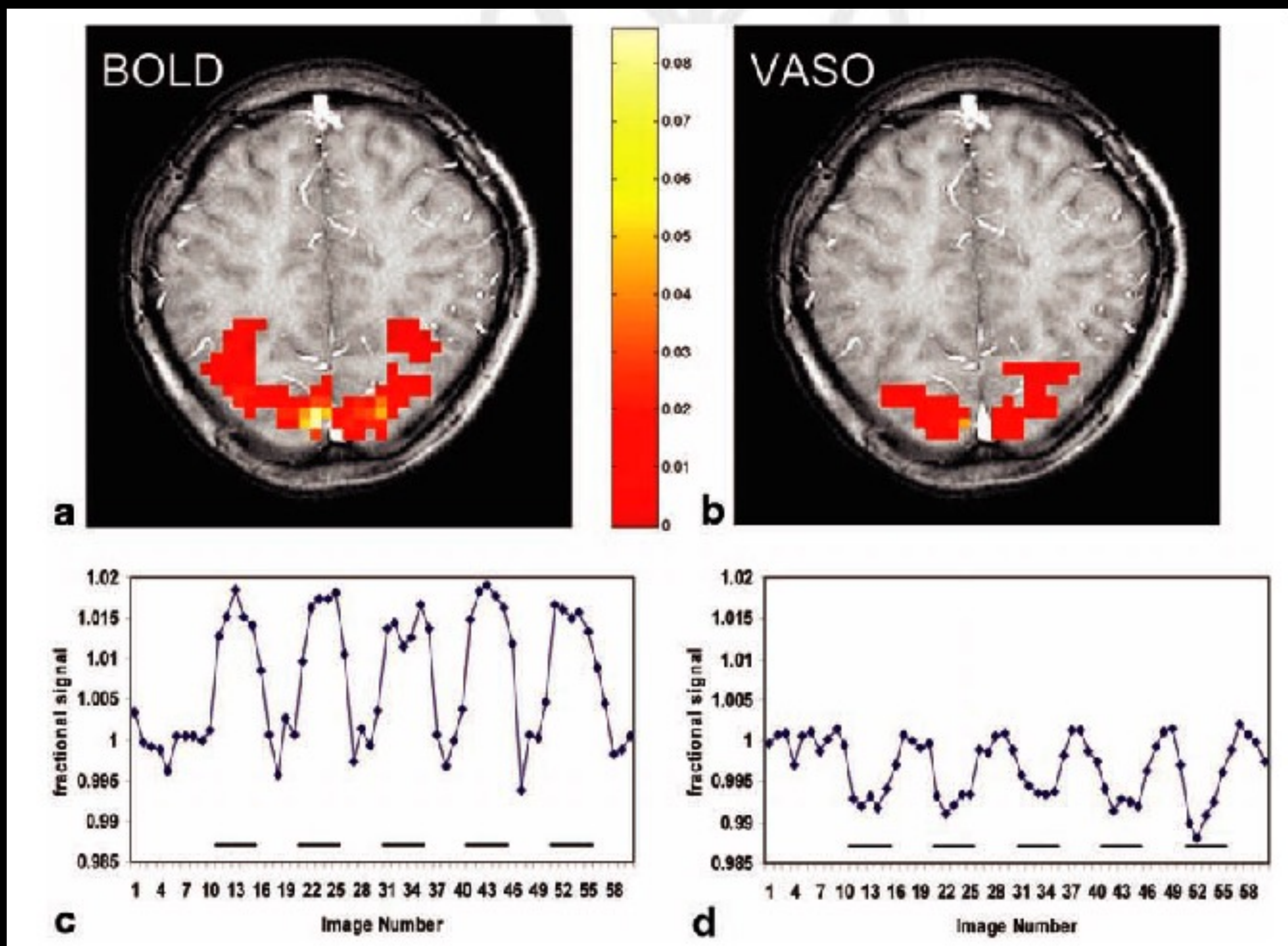


Non-invasive blood volume mapping

Functional Magnetic Resonance Imaging Based on Changes in Vascular Space Occupancy

Hanzhang Lu,[1–3] Xavier Golay,[1,3] James J. Pekar,[1,3] and Peter C.M. van Zijl[1,3*]

MAGNET RESON MED 50 (2): 263-274 AUG 2003



Direct Neuronal Current Imaging?

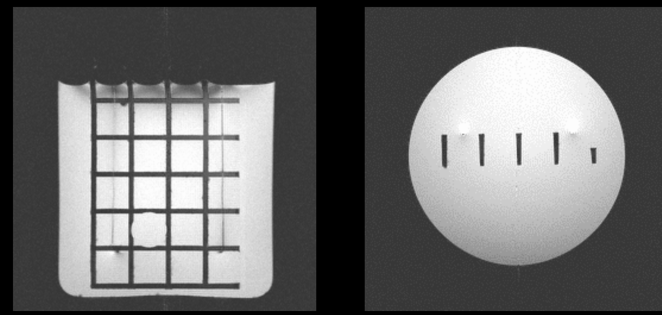
Toward Direct Mapping of Neuronal Activity: MRI Detection of Ultraweak, Transient Magnetic Field Changes

Jerzy Bodurka[1*] and Peter A. Bandettini[1,2]

- Preliminary models suggest that magnetic field changes on the order of 0.1 to 1 nT are induced (at the voxel scale) in the brain.

- These changes induce about a 0.01 Hz frequency shift or 0.09 deg (@ TE = 30 ms) phase shift.

- Question: Is this detectable?



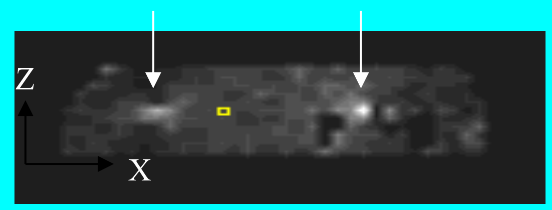
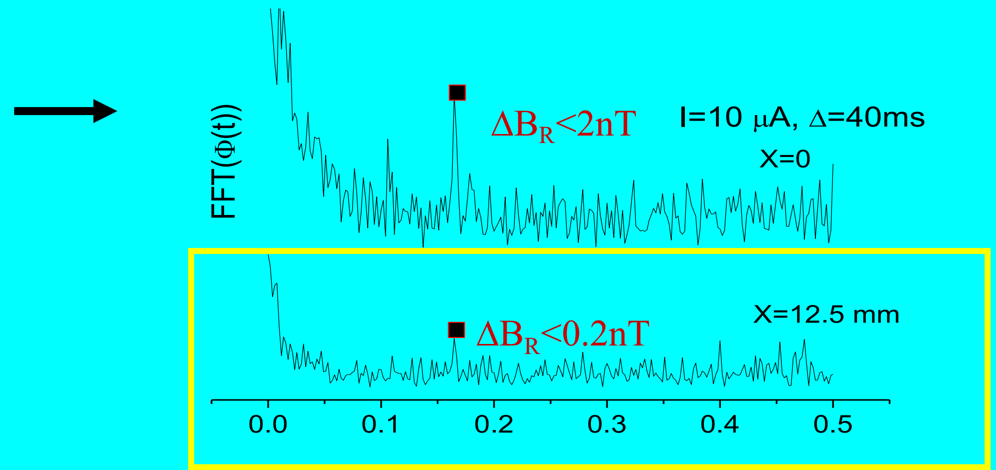
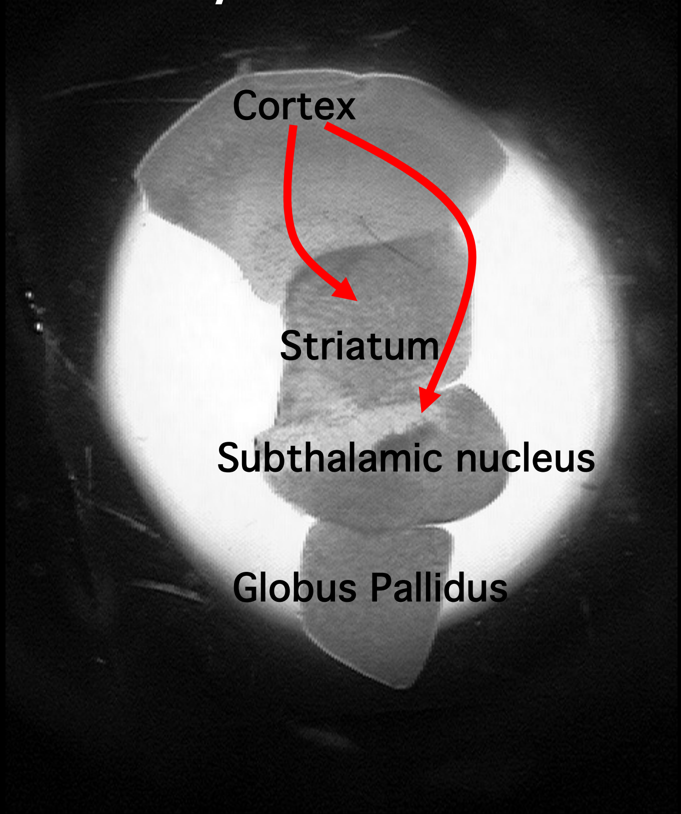

Z
X

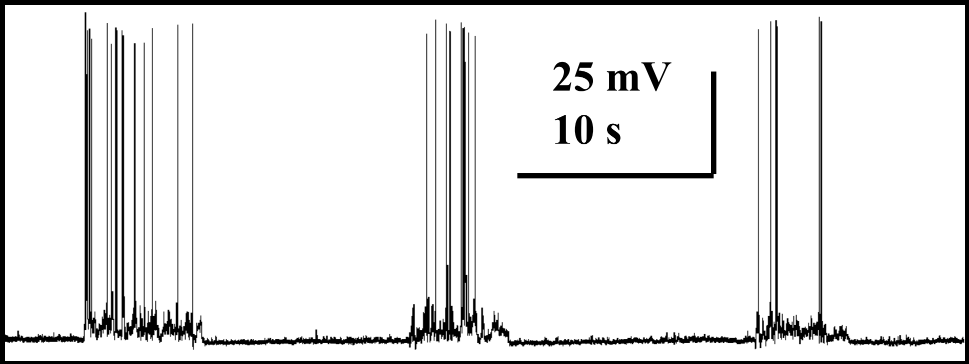
Figure 1


FFT(Φ(t))
ΔB_R<2nT
I=10 μA, Δ=40ms
X=0
ΔB_R<0.2nT
X=12.5 mm
0.0
0.1
0.2
0.3
0.4
0.5

In Vitro Results

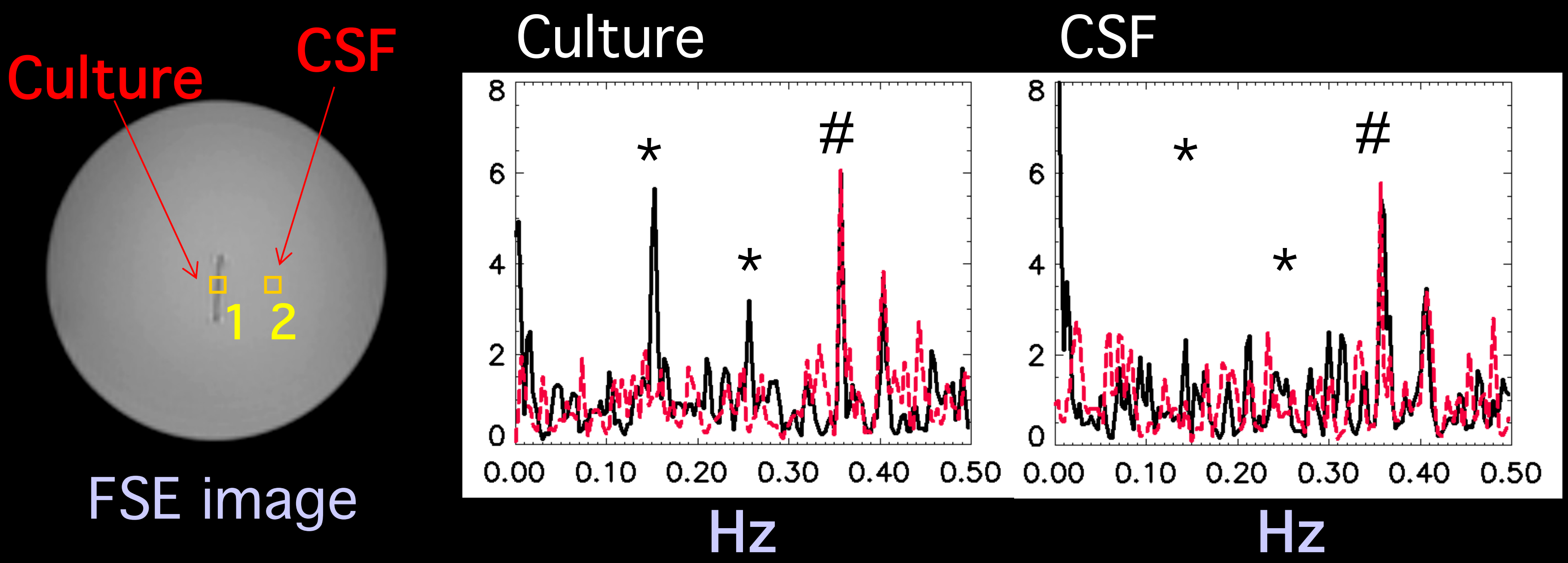
Newborn rat brains have been found to exhibit spontaneous and synchronous firing at specific frequencies





Plenz, D. and S.T. Kital. Nature, 1999. **400**: p. 677-682.

Results



Active state: 10 min, Inactive state: 10 min after TTX admin.

*: activity

#: scanner pump frequency

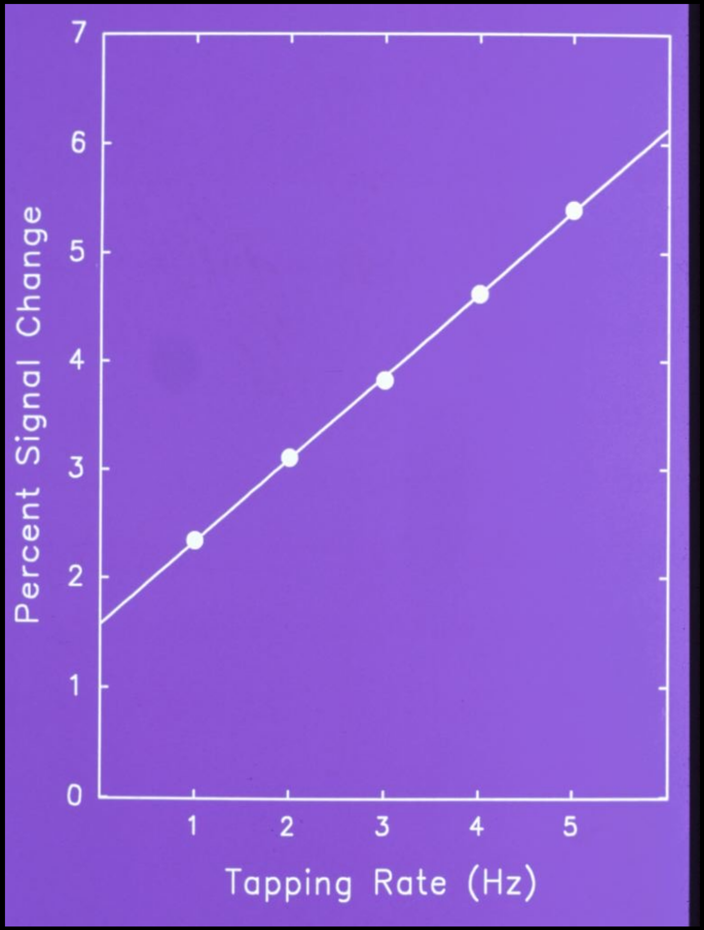
Petridou et al.

Interpretation

- Linearity / proportionality
- Hemodynamic vs. Neuronal effects
- Resting state (fluctuations and DC)
- Neuronal inhibition / excitation effects
- Negative signal changes
- HRF latency, magnitude, pre and post undershoot
- T2, T2*, T1, diffusion, and Mo changes
- Differences across modalities (location, timing)

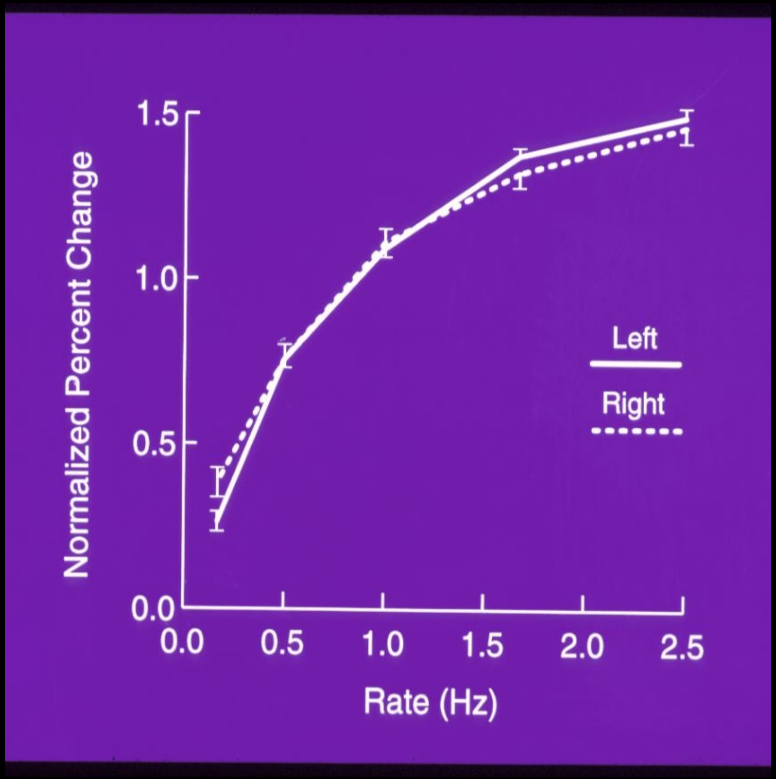
Linearity / proportionality

Motor Cortex



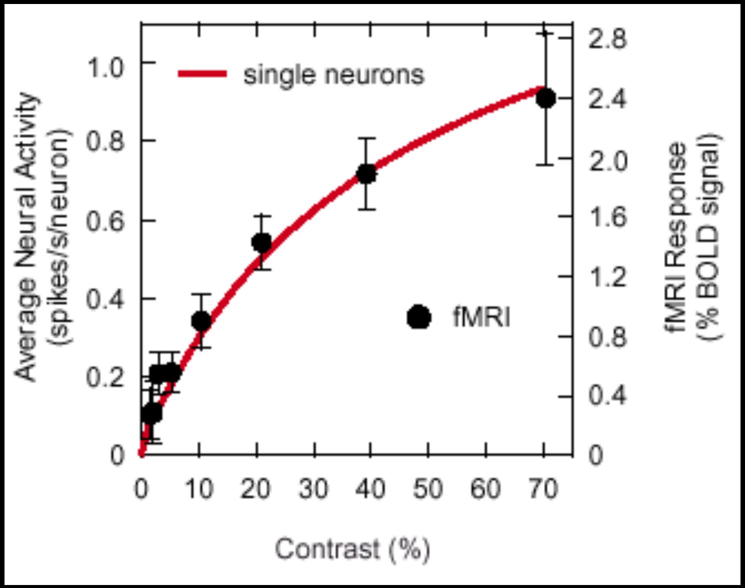
S. M. Rao et al, (1996) "Relationship between finger movement rate and functional magnetic resonance signal change in human primary motor cortex." *J. Cereb. Blood Flow and Met.* 16, 1250-1254.

Auditory Cortex



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

fMRI responses in human V1 are proportional to average firing rates in monkey V1



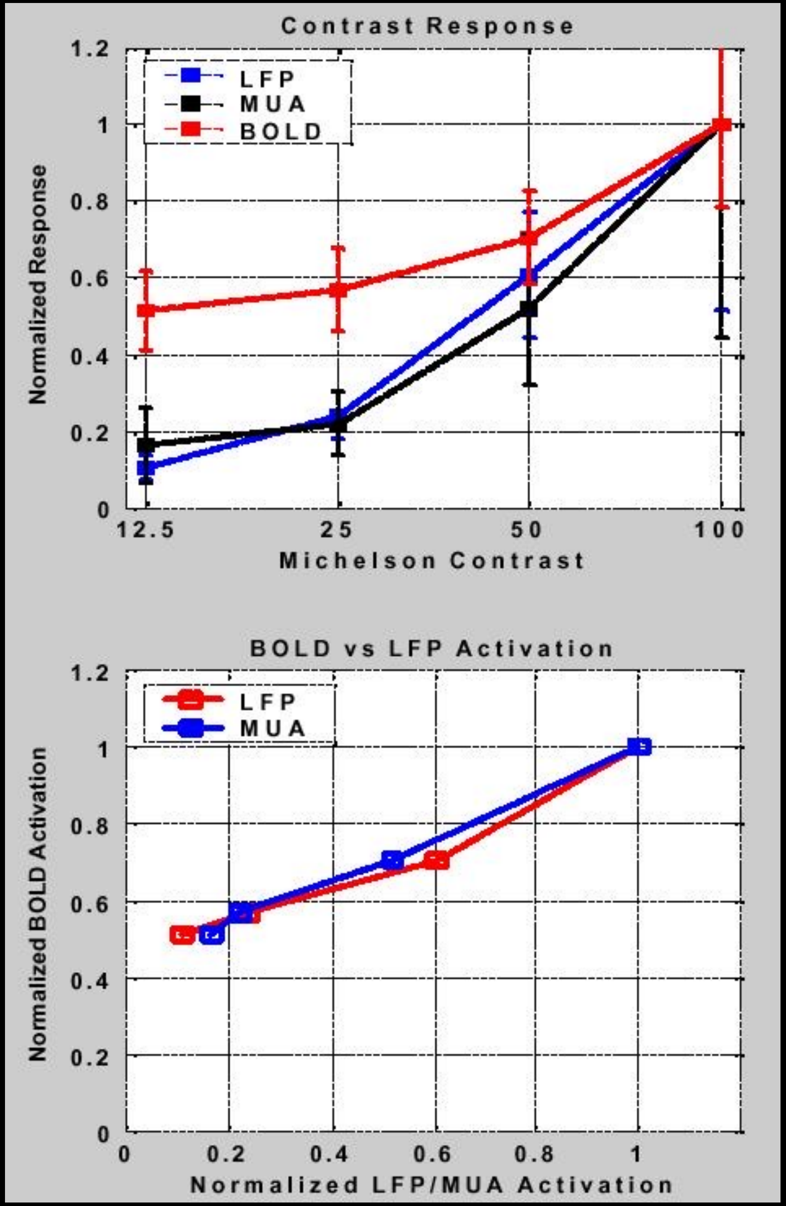
Heeger, D. J., Huk, A. C., Geisler, W. S., and Albrecht, D. G. 2000.Spikes versus BOLD: What does neuroimaging tell us about neuronal activity? *Nat. Neurosci.* **3:** 631–633.

0.4 spikes/sec -> 1% BOLD

Rees, G., Friston, K., and Koch, C. 2000. A direct quantitative relationship between the functional properties of human and macaque V5. *Nat. Neurosci.* **3:** 716–723.

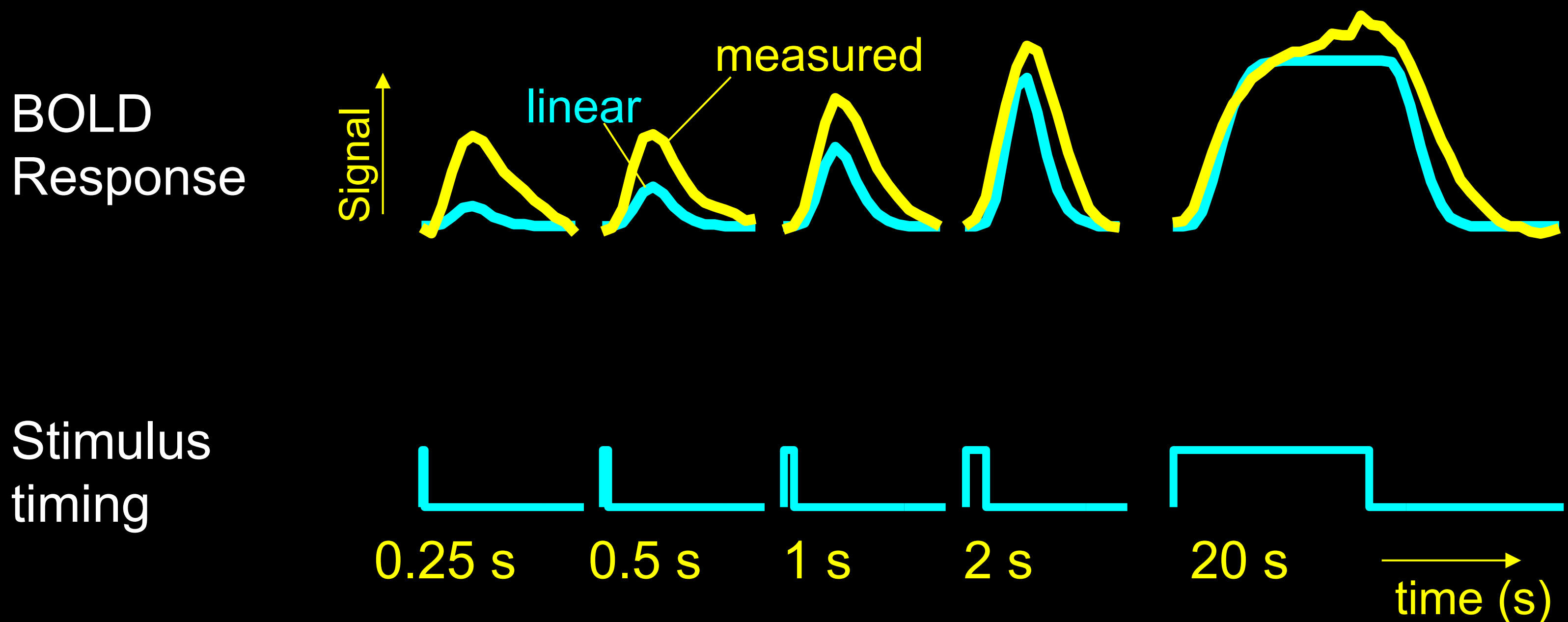
9 spikes/sec -> 1% BOLD

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



Dynamic Nonlinearity Assessment

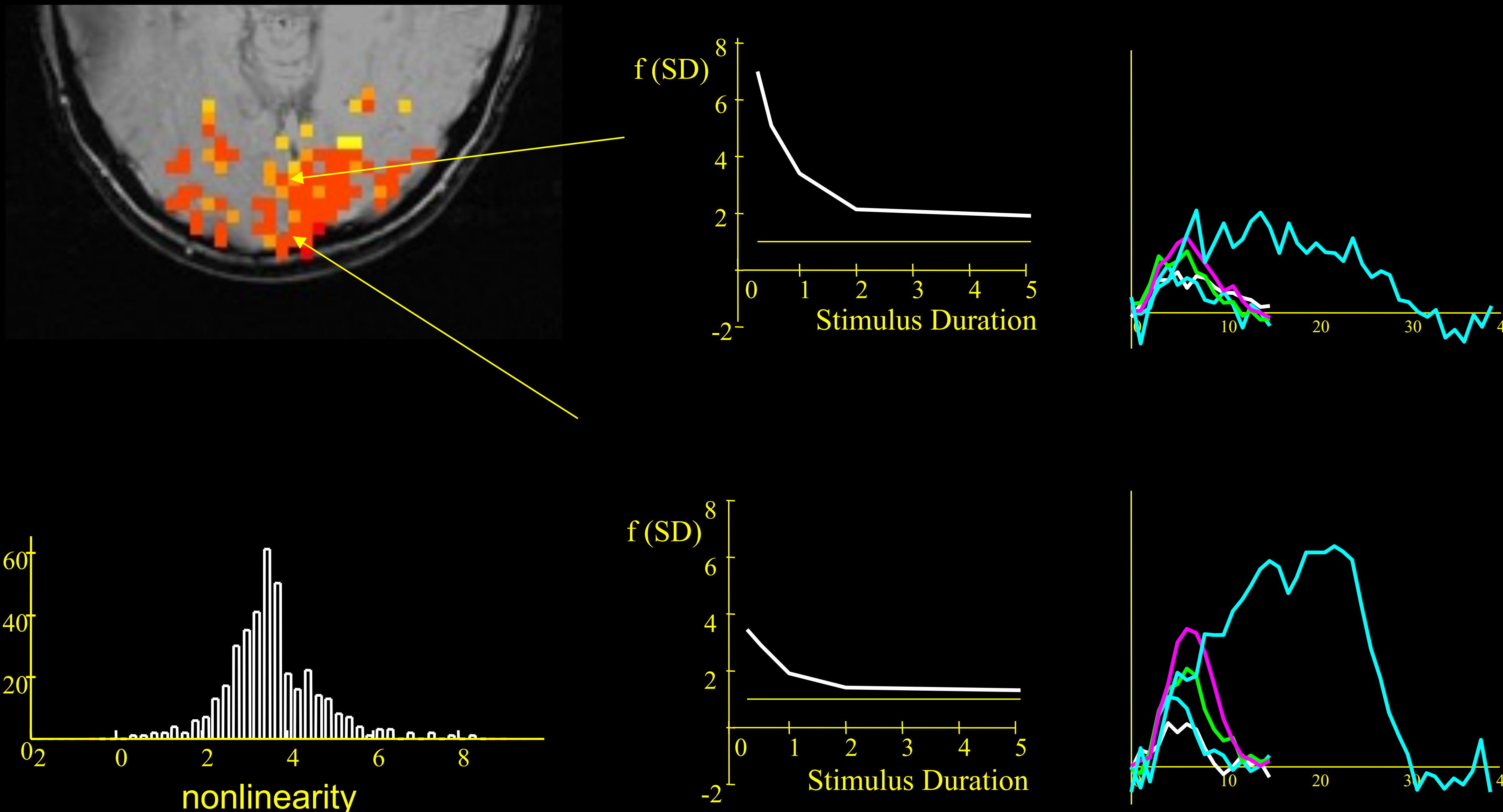
Different stimulus "ON" periods



Brief stimuli produce larger responses than expected

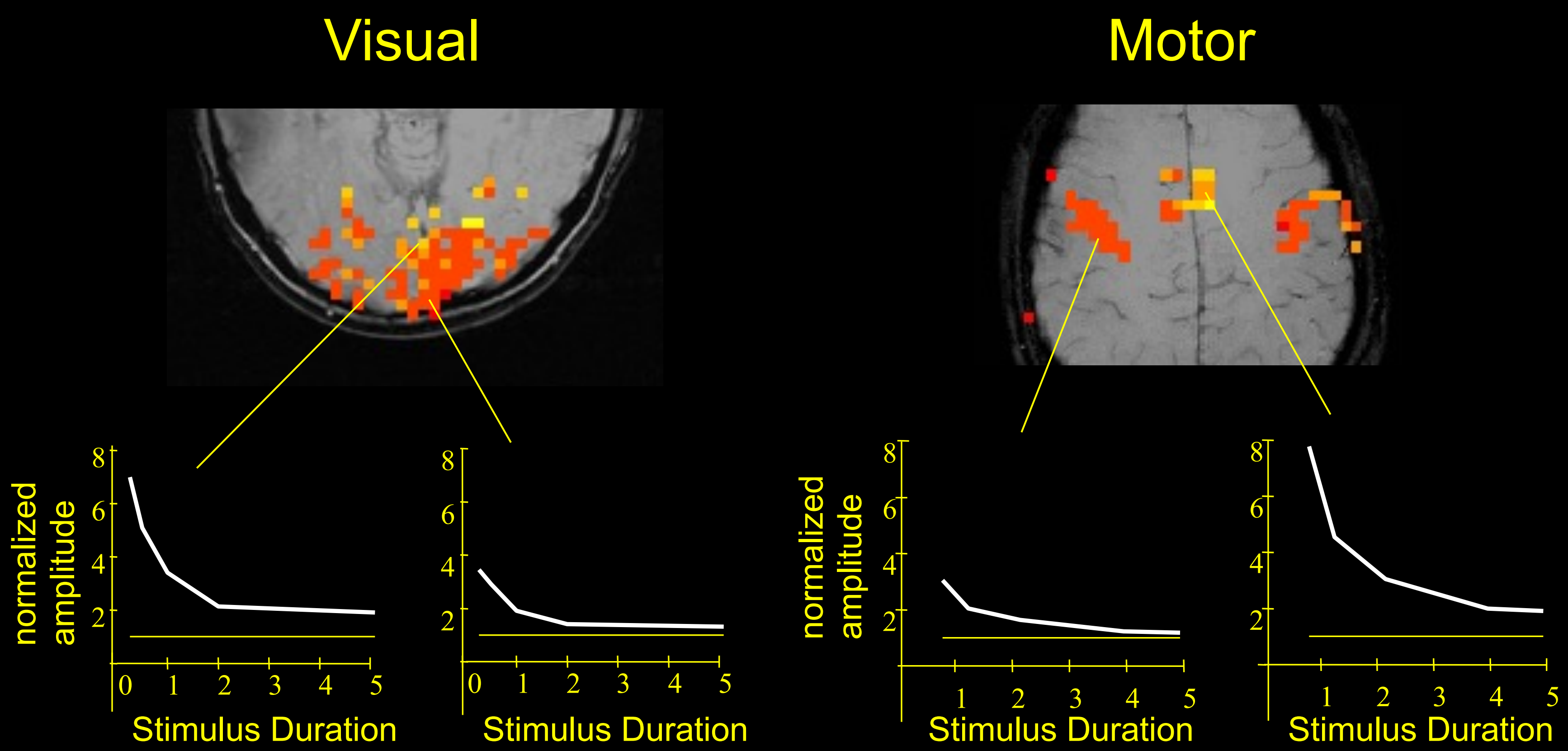
R. M. Birn, Z. Saad, P. A. Bandettini, (2001) "Spatial heterogeneity of the nonlinear dynamics in the fMRI BOLD response." ***NeuroImage*****, 14: 817-826.**

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.

Spatial variation of linearity



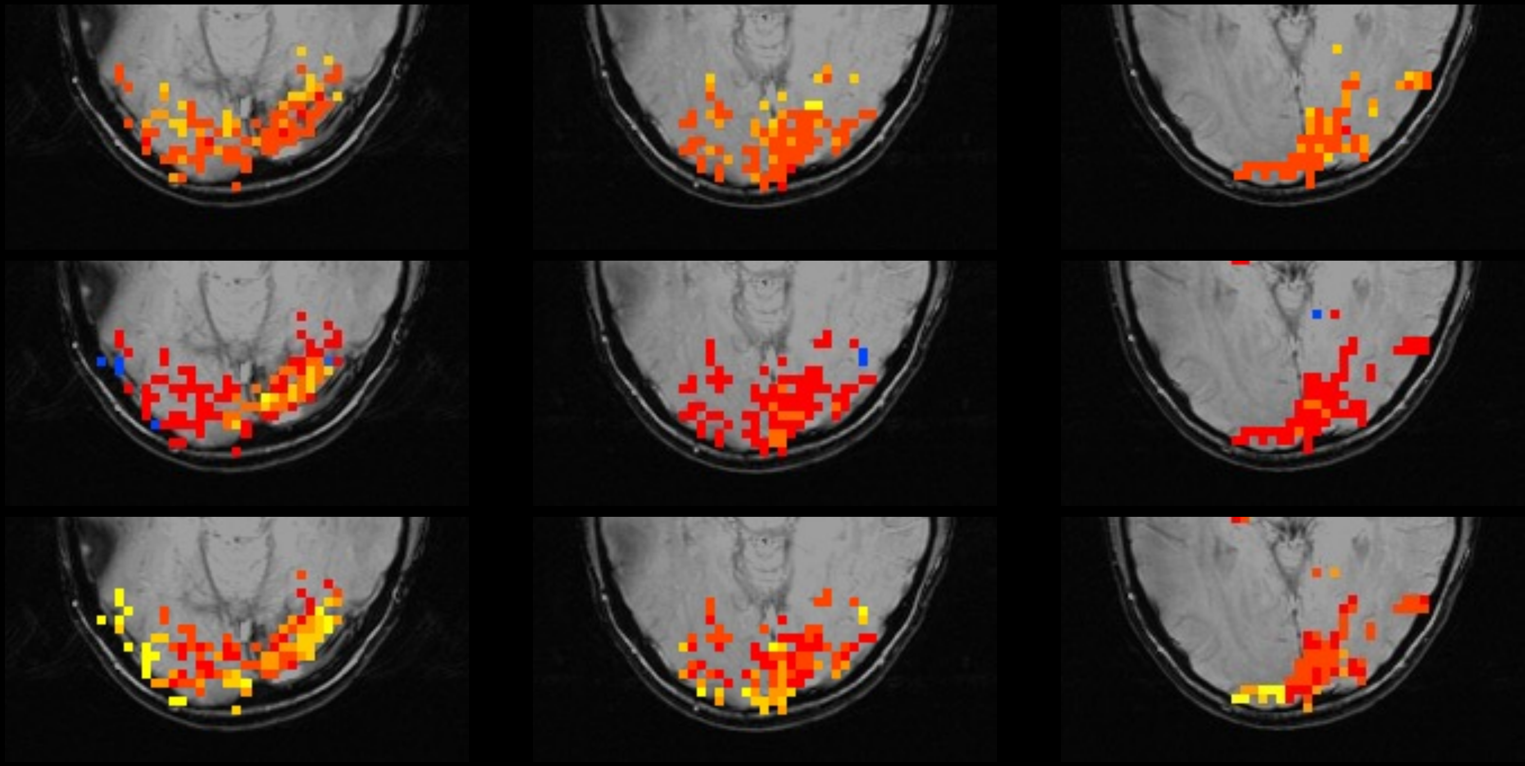
R.M. Birn, et al. Neuroimage 14, 817-26, 2001

Results – visual task

Nonlinearity

Magnitude

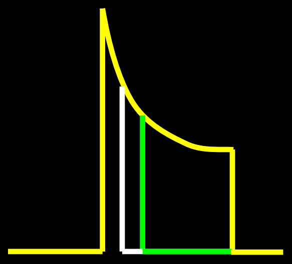
Latency



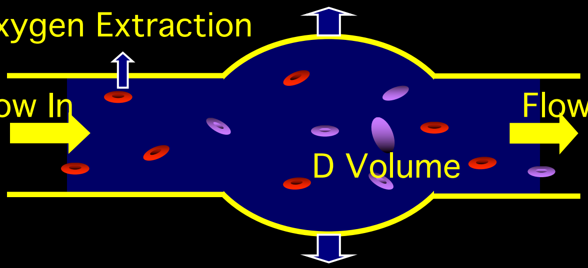
R. M. Birn, Z. Saad, P. A. Bandettini, (2001) "Spatial heterogeneity of the nonlinear dynamics in the fMRI BOLD response." *NeuroImage*, 14: 817-826.

Sources of this Nonlinearity

- Neuronal

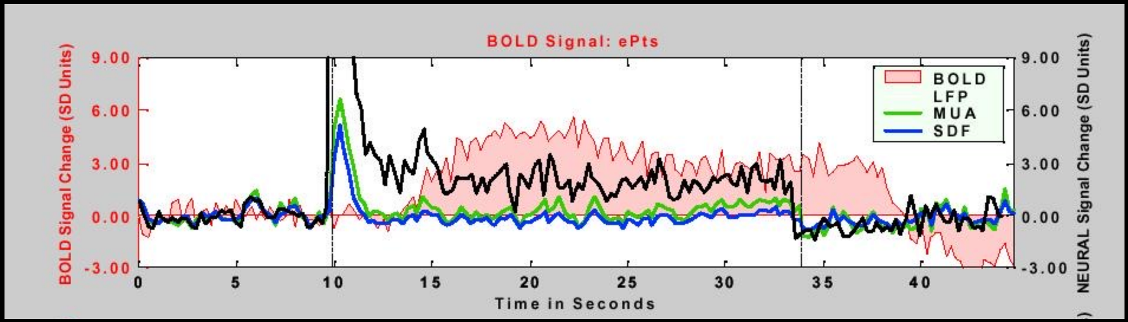


- Hemodynamic
  - Oxygen extraction
  - Blood volume dynamics

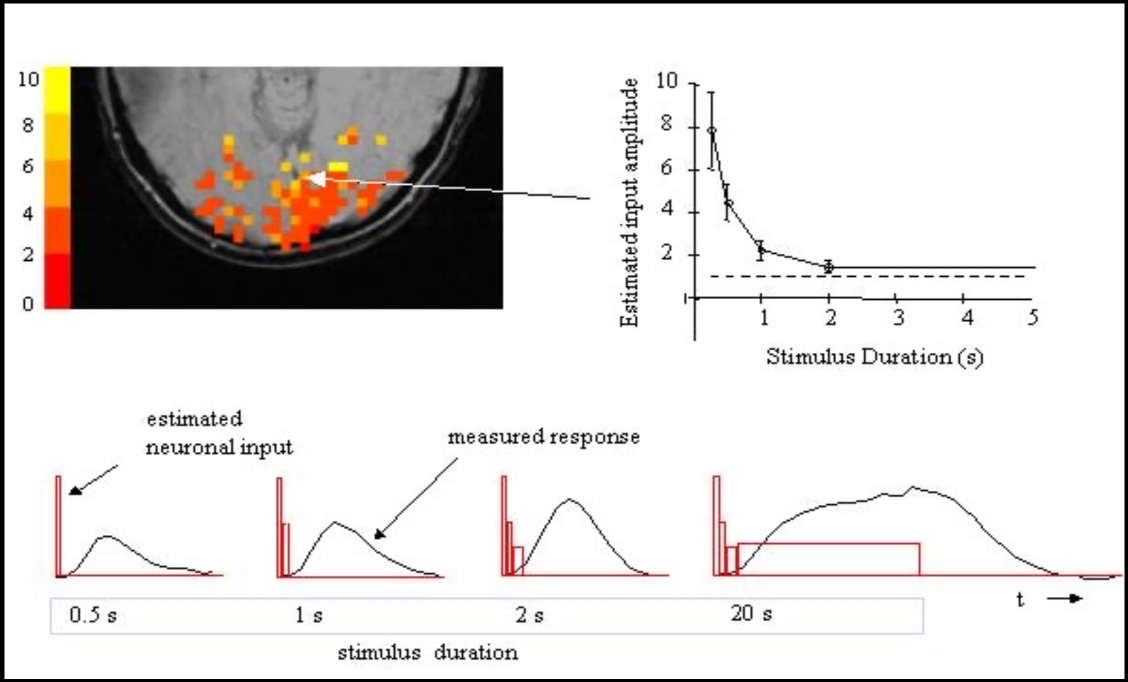


BOLD Correlation with Neuronal Activity

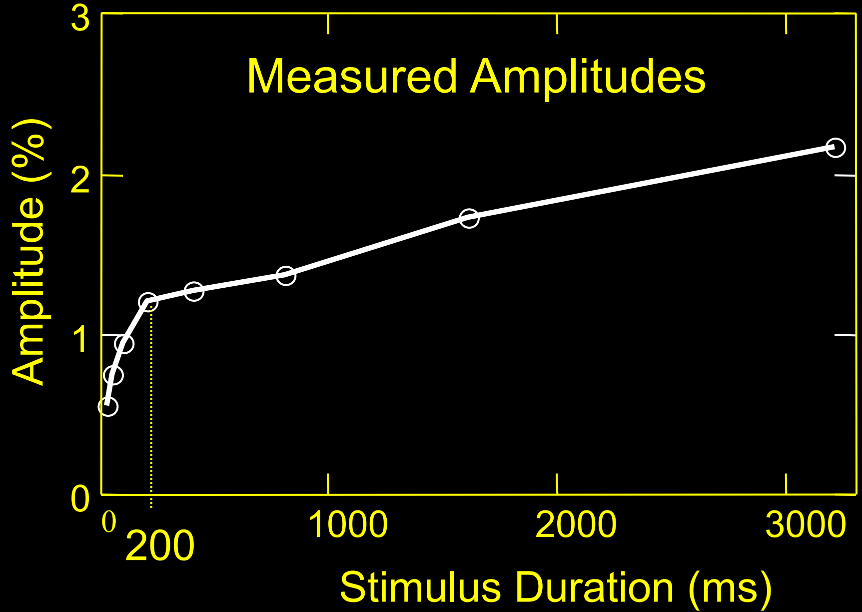
Logothetis et al. (2001) “Neurophysiological investigation of the basis of the fMRI signal” Nature, 412, 150-157.

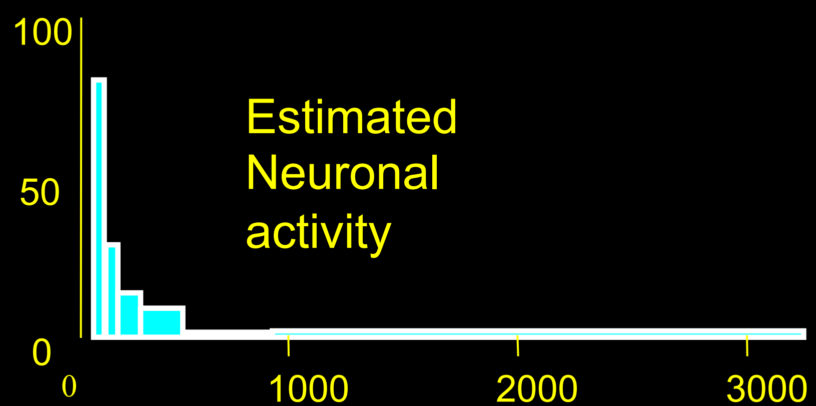


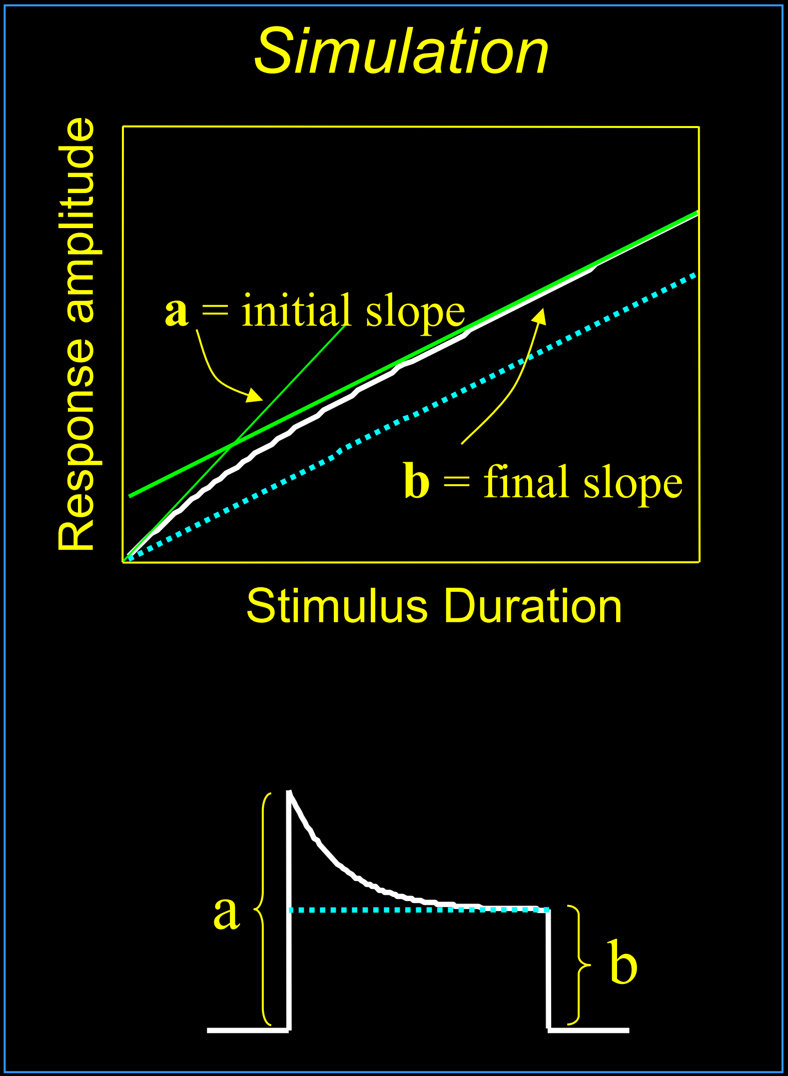
P. A. Bandettini and L. G. Ungerleider, (2001) “From neuron to BOLD: new connections.” Nature Neuroscience, 4: 864-866.

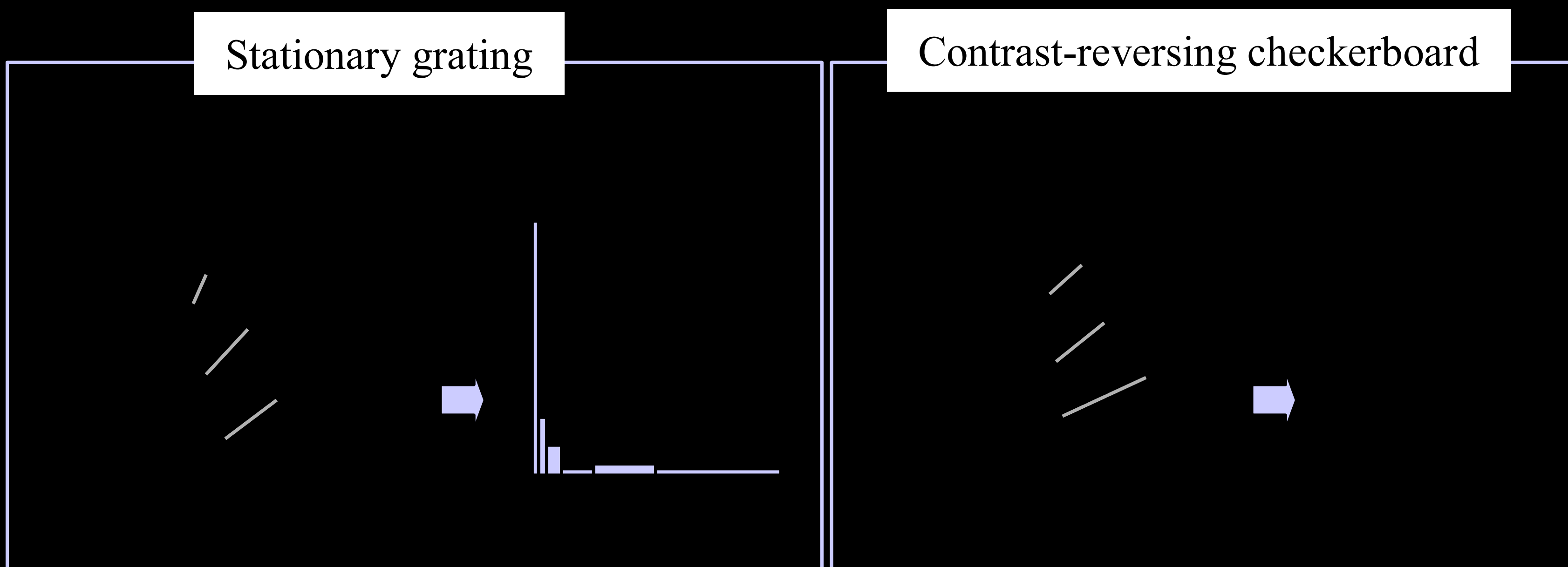


Results – constant gratings








Stationary grating
Contrast-reversing checkerboard

FIM Unit & FMRI Core Facility

Director:
Peter Bandettini

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

Computer Specialist:
Adam Thomas

Post Docs:
Hauke Heekeren
David Knight
Anthony Boemio
Patrick Bellgowan
Ziad Saad

Graduate Student:
Natalia Petridou

Post-Back. IRTA Students:
Hanh Ngyun
Ilana Levy
Elisa Kapler
August Tuan
Dan Kelley

Visiting Fellows:
Sergio Casciaro
Marta Maieron
Guosheng Ding

Clinical Fellow:
James Patterson

Psychologist:
Julie Frost

Summer Students:
Allison Sanders
Julia Choi
Thomas Gallo
Jenna Gelfand
Hannah Chang
Courtney Kemps
Douglass Ruff
Carla Wettig
Kang-Xing Jin

Program Assistant:
Kay Kuhns

Scanning Technologists:
Karen Bove-Bettis
Paula Rowser
Alda Ottley