Basics of fMRI Part 2
BOLD Dynamics, Resting State, Perfusion, and Volume

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Center for Multimodal Neuroimaging

National Institute of Mental Health

FMRIF

What Accompanies Brain Activation?
Metabolic, Hemodynamic, and Other Measurables

Effect	Increase	Decrease	Underlying Mechanism	Magnetic Resonance Measure	Relative Detectability
Deoxyhemoglobin		10 - 30%	Oxygen Delivery Exceeds Metabolic Need	Blood Oxygen Sensitive Dependent Contrast (BOLD)	100
CBF	30-50%		Vasodilatation & Capillary Perfusion	Arterial Spin Labelling (ASL)	25
CBV	10-15%		Dilatation & Capillary Recruitment	Vascular Space Occupancy (VASO)	25
Middle cerebral artery (MCA) flow velocity	10-15%		Global autoregulation	Phase Contrast or Inflow Sensitive MRI	10
CMRO2	10-15%		Oxidative metabolism	Ratio of change in CBF/BOLD, calibrated by global stress of change in CBF/BOLD	10
Venous Oxygen Saturation	10-15%		Decresed oxygen extraction fraction	Possible T1 change in blood & tissue (Zero-TE sequences)	8
Glucose		5-12%	Increased Glucose metabolism	1H MRS	5
Lactate	10-30%		Increased glycolysis in Astrocytes	1H MRS	5
Glutamate (excitatory neurotrasmitter)	2-5%			1H MRS	5
GABA (inhibitory neurotrasmitter)	occasionally	5-10%		1H MRS	4
Cerebral Spinal Fluid (CSF) volume	small		displacement by increase blood volume	T1-wieghting	2
Cerebral Spinal Fluid (CSF) flow	small		displacement by increase blood volume	Phase Contrast MRI, T1-weighting	2
Elasticity Change	6-10%		increased blood volume	MR Elastography	2
Na+ moves intracellularly			Action potential	Na+ fMRI	1
Aspartate		3-4%		1H-MRI	1
Creatine Kinase (CK)	30%			31P magnetization transfer MRS	1
Nicotinamide adenine dinucleotide (NAD)		reduced NAD+	electron shuttle in glycolosys	31P MRS and 1H MRS	1
Temperature	0.1 degree Celsius			MR Phase or Diffusion Coefficient	0.5
Cell Swelling	3%		Ion flux draws water into neuons	Decrease in Diffusion Coefficient	0.5
Neuronal Currents?	transient/small		Dendritic currents with spiking	MR magntude or phase	0.01?

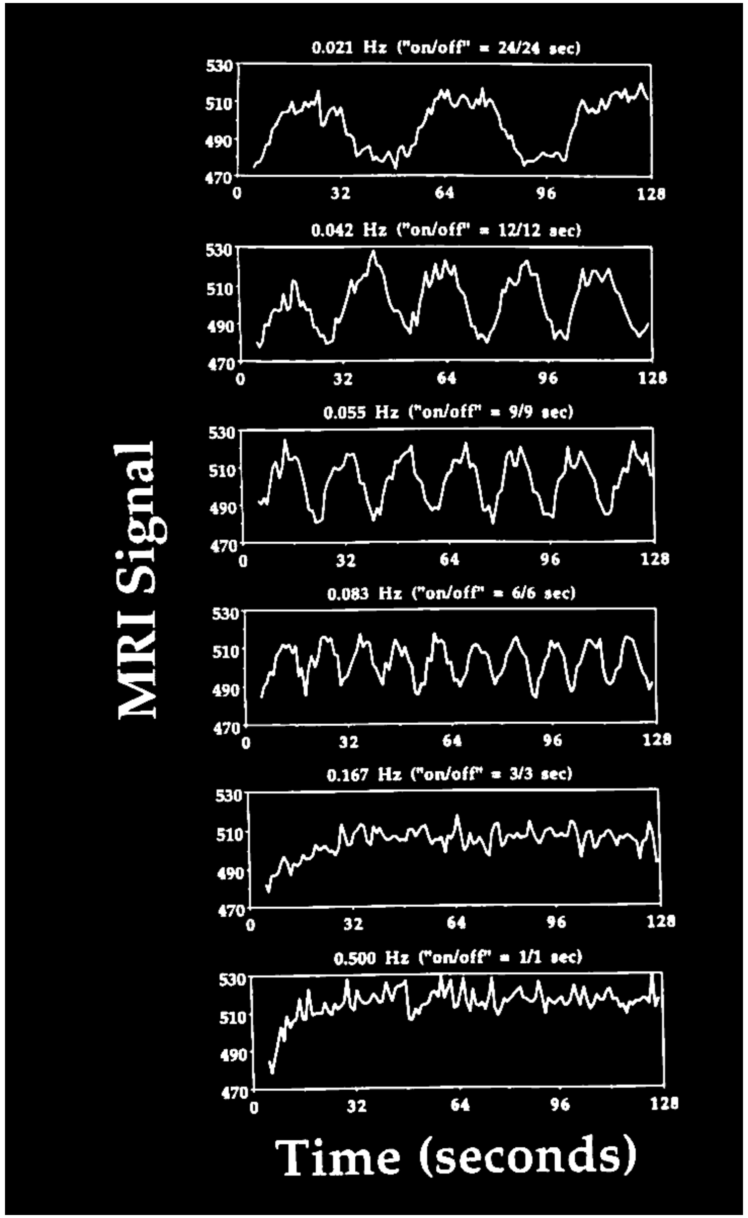
Previous Lecture:

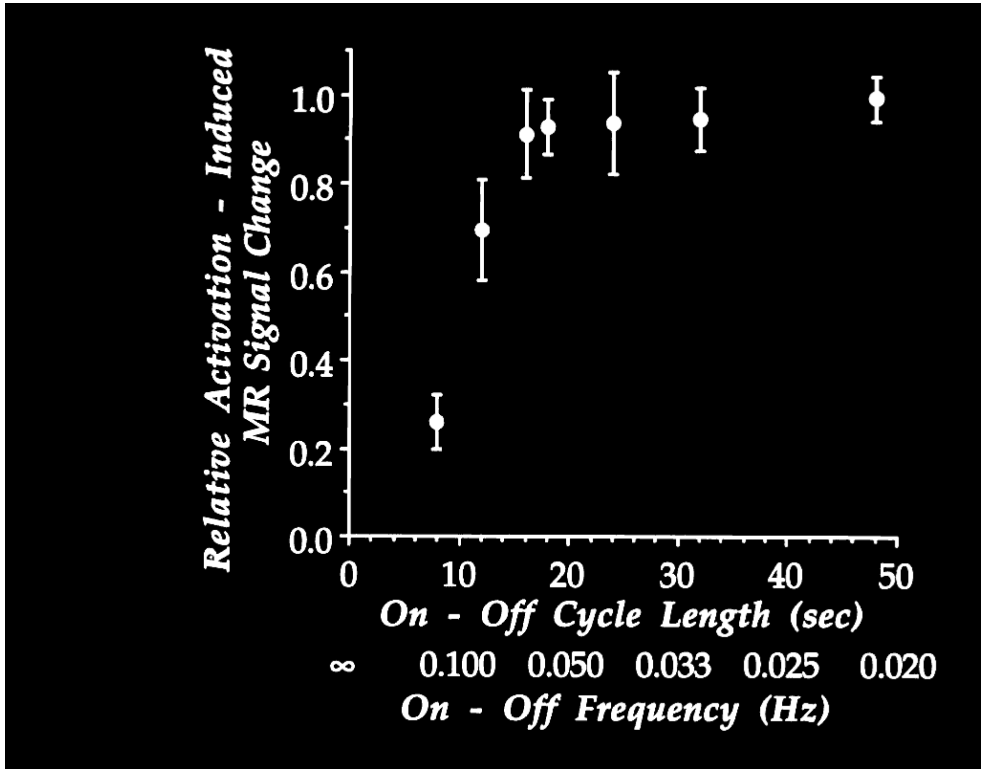
- Overview of physiology that accompanies brain activation.
- Basics of BOLD Contrast and Acquisition
- Vein effects and Spin-echo vs Gradient-echo fMRI
- Effects of Respiration and Blood Pressure

This Lecture:

- Dynamics, Nonlinearities, and Latencies of BOLD Contrast
- Resting State fMRI
- Perfusion Imaging (Arterial Spin Labelling)
- $CMRO_2$ Imaging
- Blood Volume Imaging (Vascular Space Occupancy)

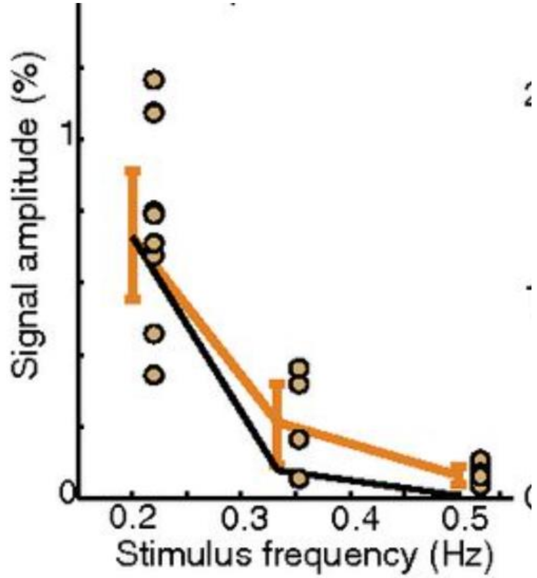
Duty Cycle (on/off rate)

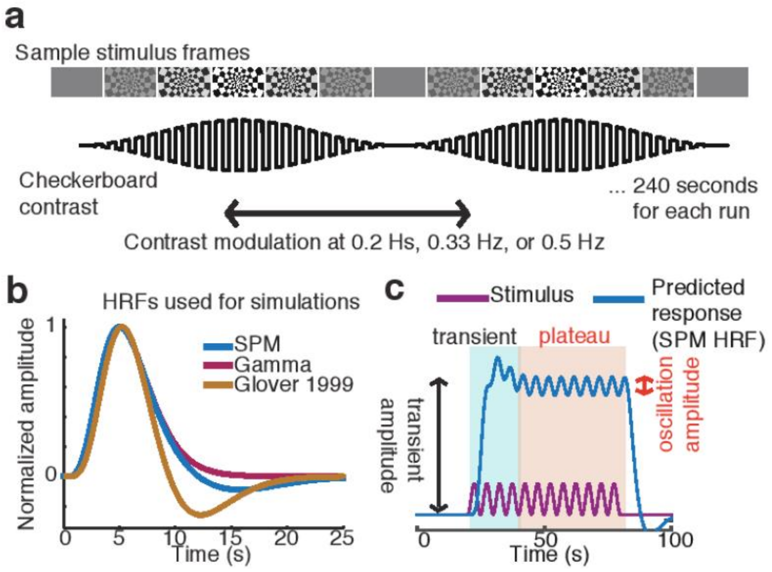


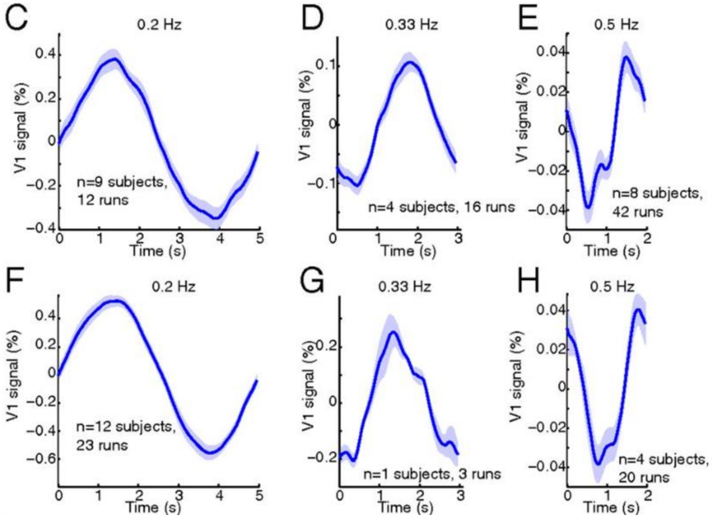


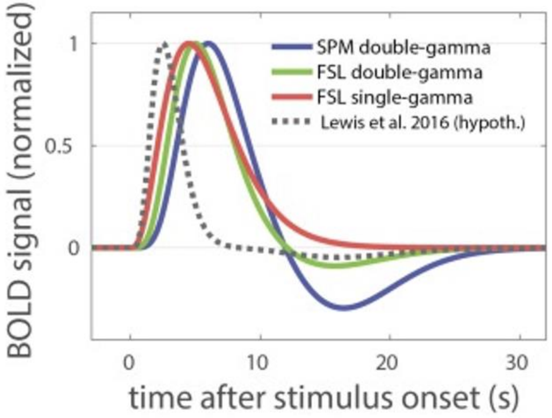
P.A. Bandettini,, Functional MRI using the BOLD approach: dynamic characteristics and data analysis methods, in "Diffusion and Perfusion: Magnetic Resonance Imaging" (D. L. Bihan, Ed.), p.351-362, Raven Press, New York, 1995.

Duty Cycle







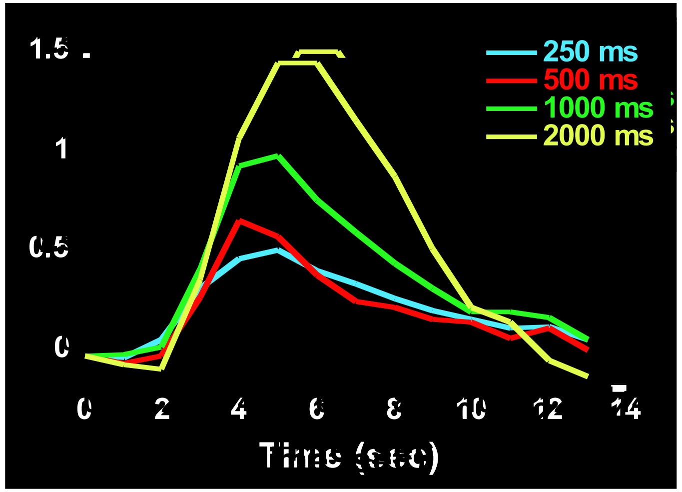


Higher amplitude at high duty cycle than predicted by a linear system

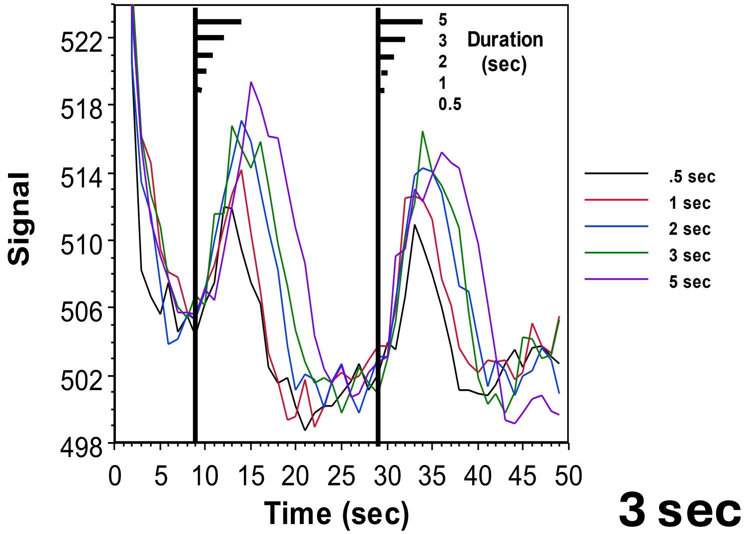
L.D. Lewis, K. Setsompop, B.R. Rosen, J.R. Polimeni.
Fast fMRI can detect oscillatory neural activity in humans, *Proc. Natl. Acad. Sci. U.S.A.* 113 (43) E6679 E6685, https://doi.org/10.1073/pnas.1608117113 (2016).

Stimulation Duration

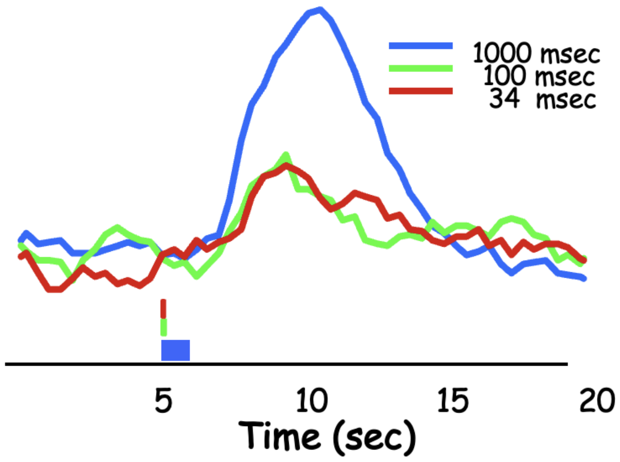
Visual Cortex



Motor Cortex



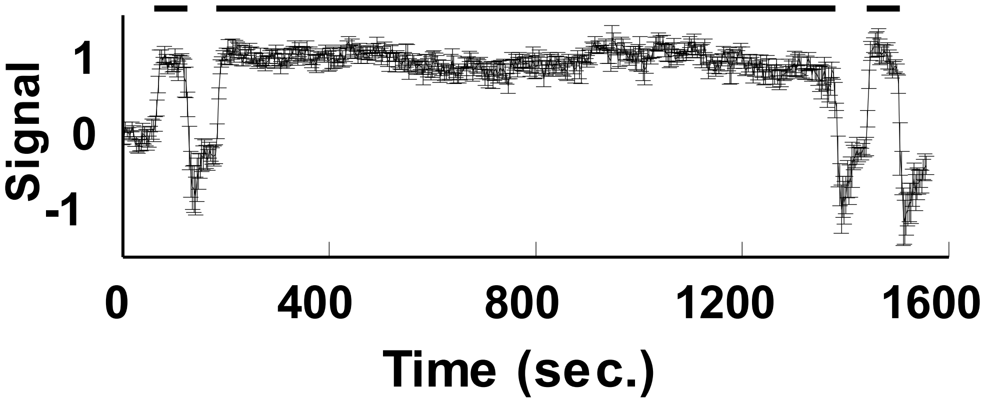
Visual Cortex



R. L. Savoy et al SMR 1995

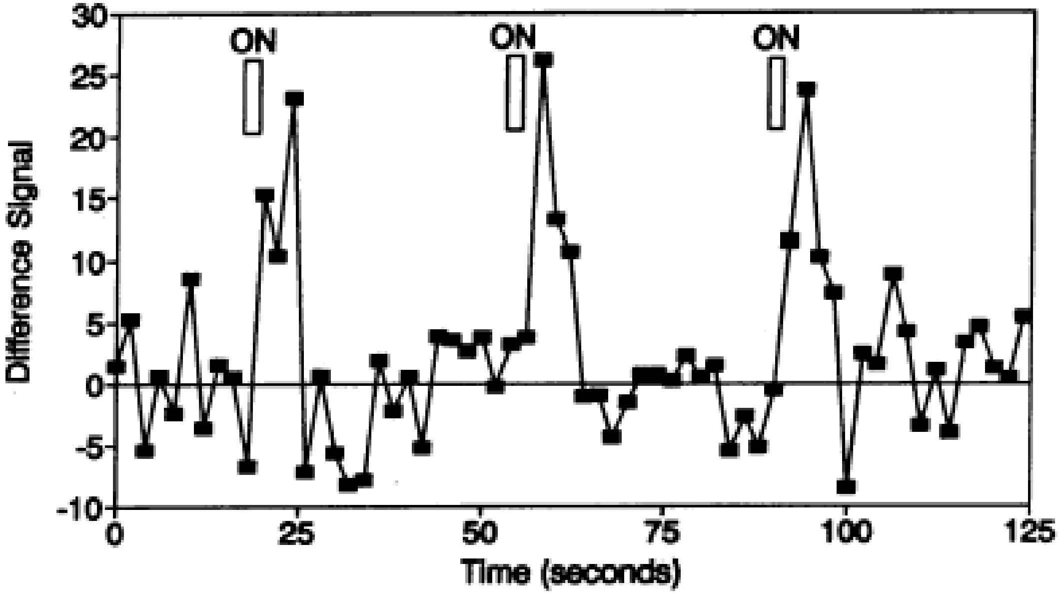
20 minutes continuous activation

T2* - Weighted



P. A. Bandettini, (1997) *Human Brain Mapping* 5, 93-109.

3 seconds activation



Blamire, A. M., et al. (1992). Proc. Natl. Acad. Sci. USA 89: 11069-11073.

Stimulation Duration

Proc. Natl. Acad. Sci. USA
Vol. 93, pp. 14878–14883, December 1996
Neurobiology

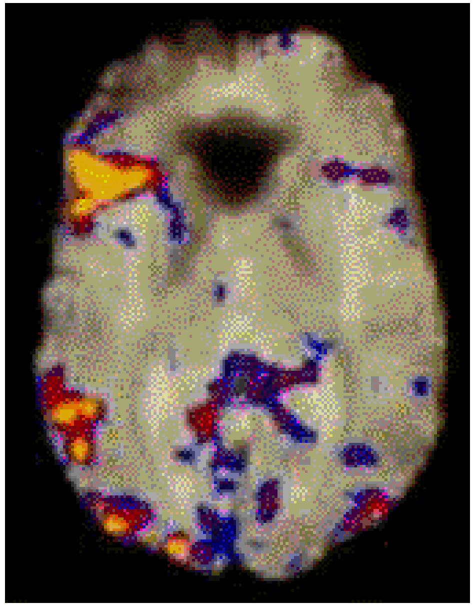
Detection of cortical activation during averaged single trials of a cognitive task using functional magnetic resonance imaging

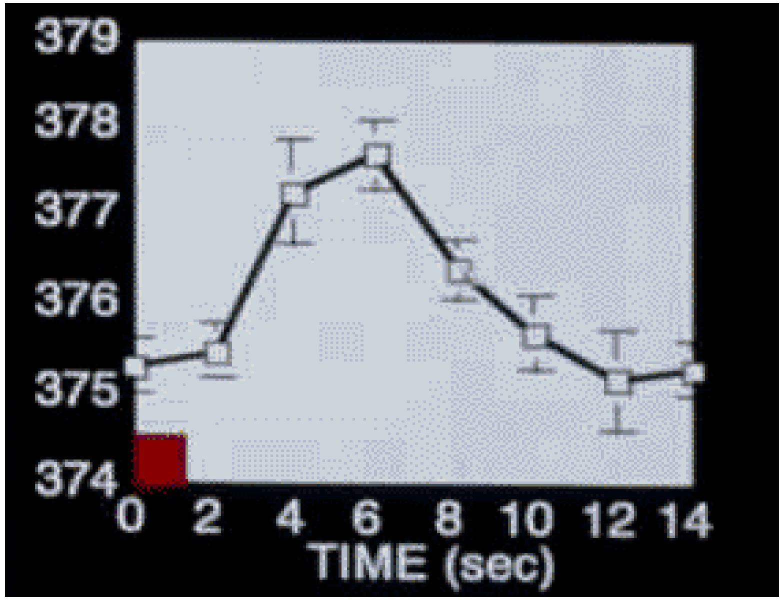
(neuroimaging/single trial/language/prefrontal)

RANDY L. BUCKNER[†‡§¶], PETER A. BANDETTINI[†‡], KATHLEEN M. O'CRAVEN[†||], ROBERT L. SAVOY[†||], STEVEN E. PETERSEN[**††], MARCUS E. RAICHLE[§**††], AND BRUCE R. ROSEN[†‡]

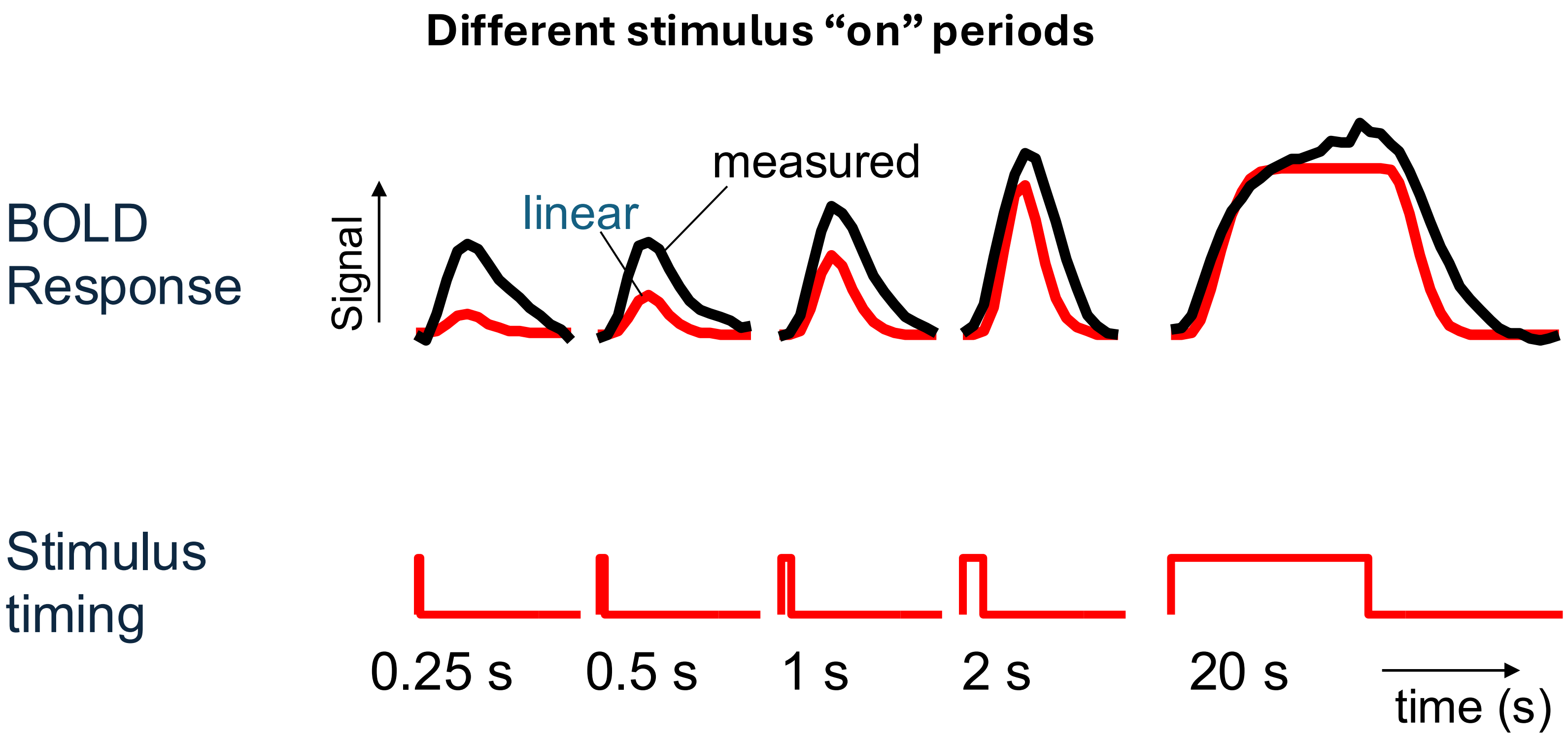
[†]Department of Radiology, Massachusetts General Hospital Nuclear Magnetic Resonance Center, Charlestown, MA 02129; [‡]Harvard University Medical School, Boston, MA 02115; [||]Rowland Institute, Cambridge, MA 02142; and [**]Departments of Neurology and Neurosurgery and McDonnell Center for the Study of Higher Brain Function, and Departments of [§]Radiology and [††]Anatomy and Neurobiology, Washington University Medical School, St. Louis, MO 63110

Contributed by Marcus E. Raichle, September 4, 1996





Stimulation Duration Effects

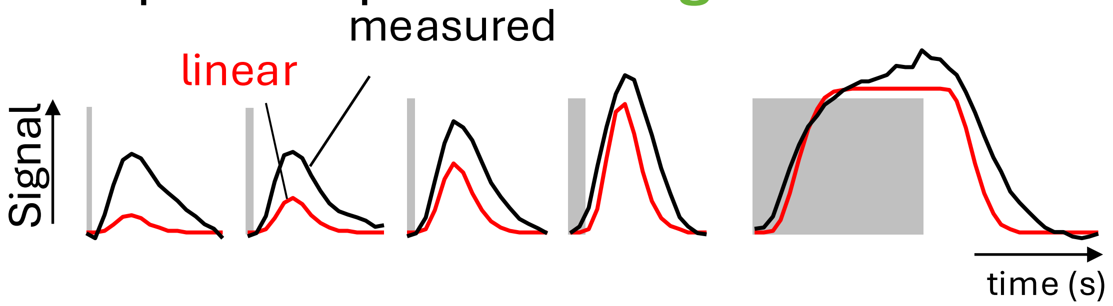


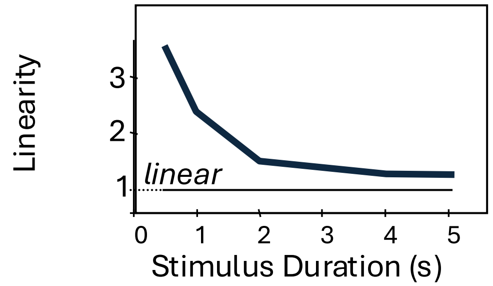
Brief stimuli produce larger responses than expected

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

Stimulation Duration Effects

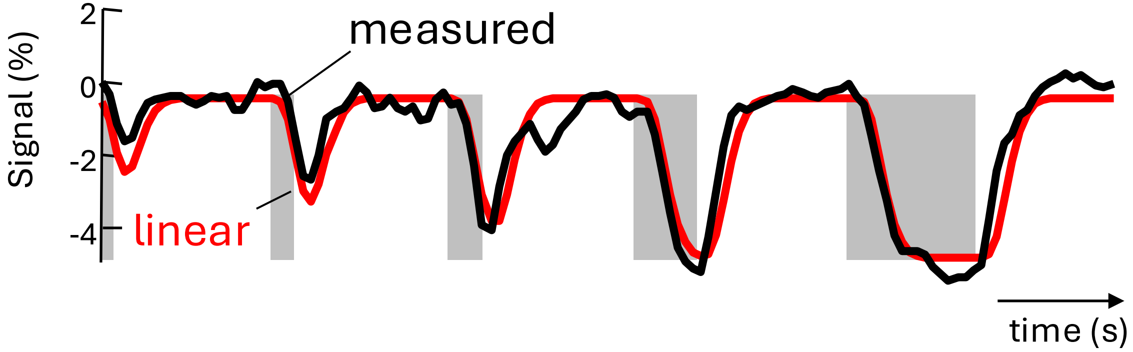
Brief “on” periods produce **larger** increases than expected.

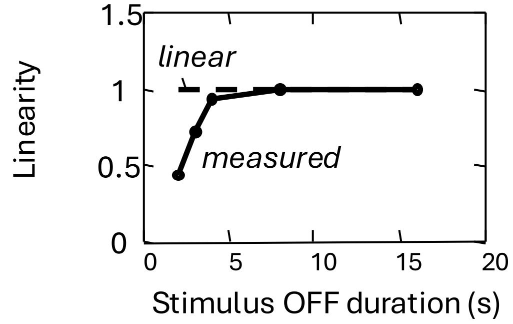




R. M. Birn, Z. Saad, P. A. Bandettini, NeuroImage, 14: 817-826, (2001)

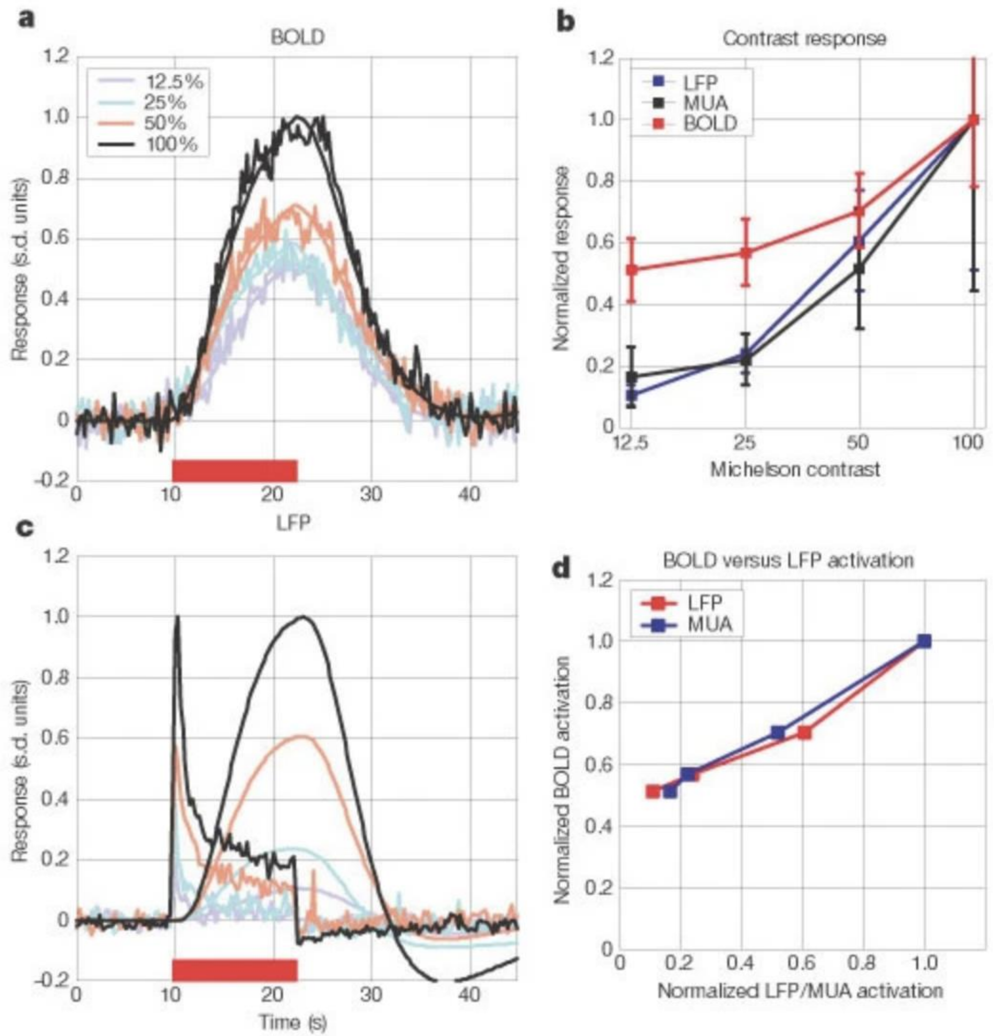
Brief “off” periods produce **smaller** decreases than expected.



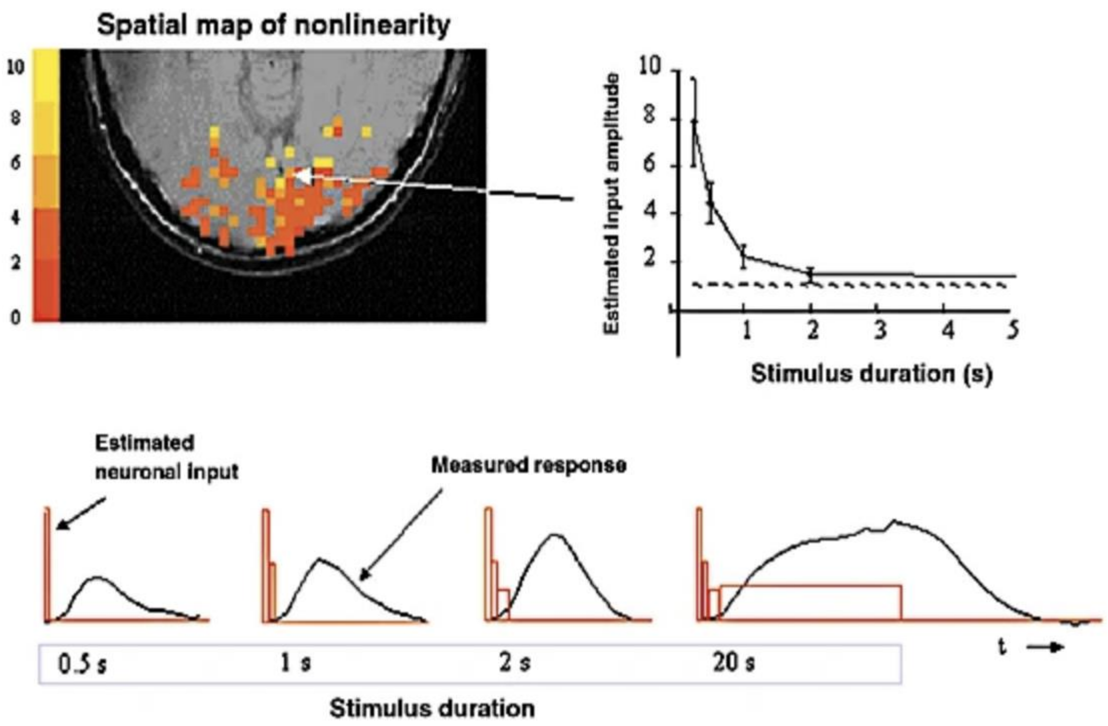


R.M. Birn, P. A. Bandettini, NeuroImage, 27, 70-82 (2005)

(Non-) Linearity of the BOLD Response: Neuronal in Origin?



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

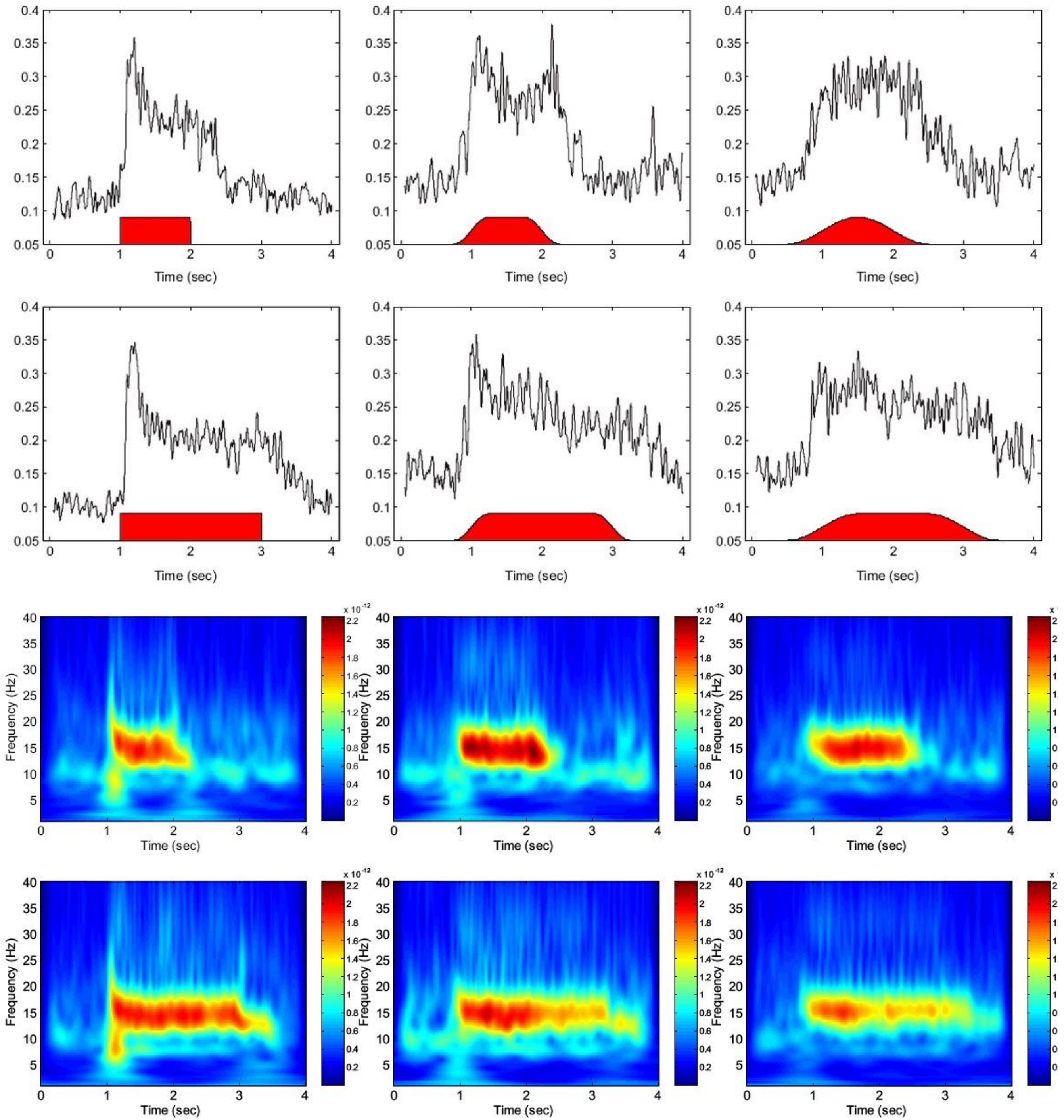


Bandettini & Ungerleider, Nature Neuroscience 4, 864-866 (2001)

Are Nonlinearities Neuronal or Hemodynamic?

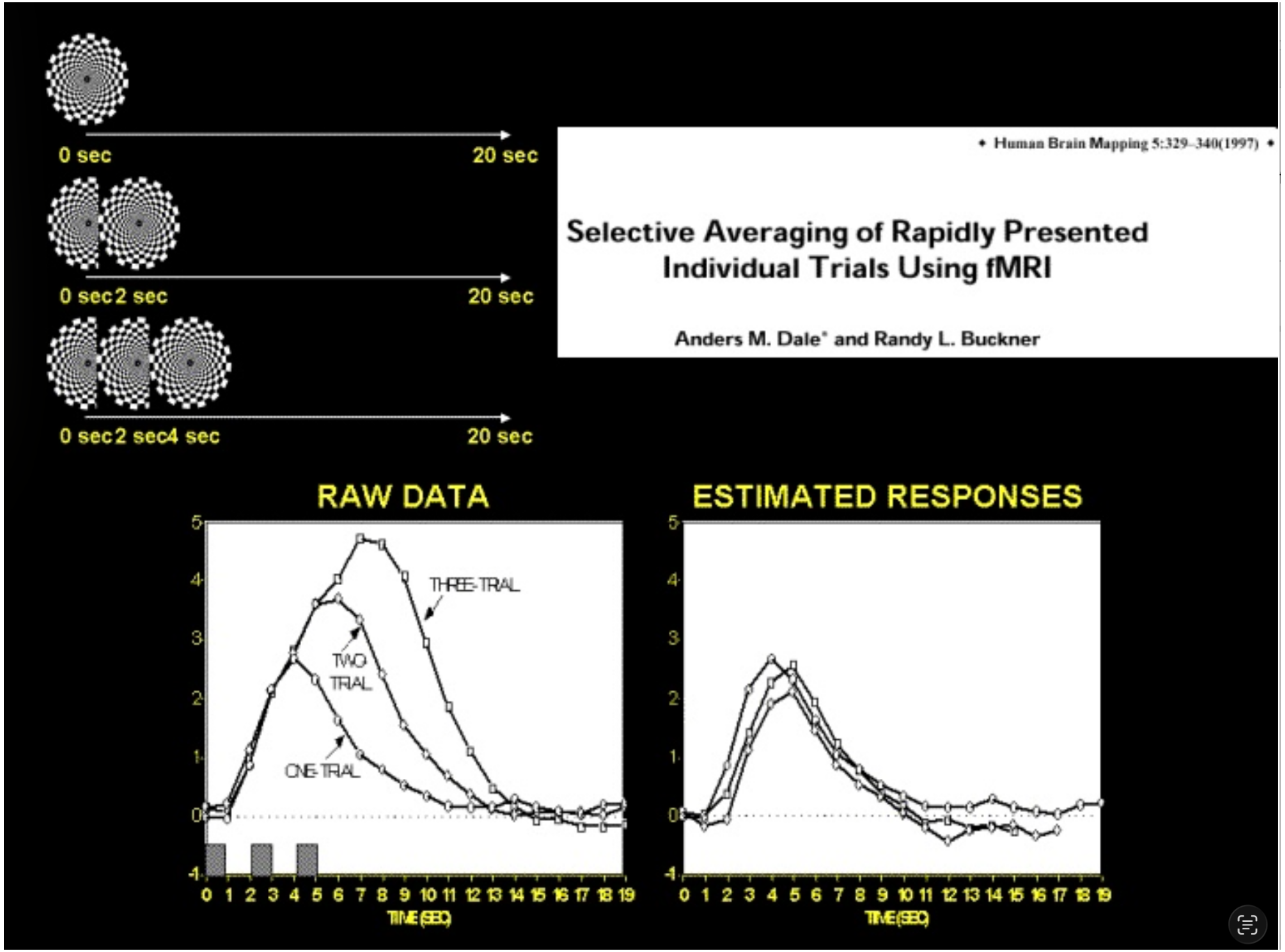
Early Evidence for Neuronal Source of Nonlinearity

MEG vs fMRI: varying from sharp to smooth onset and cessation



Tuan, A. S.; Birn, R. M.; Bandettini, P. A.; Boynton, G. M. Differential Transient MEG and fMRI Responses to Visual Stimulation Onset Rate. *International Journal of Imaging Systems and Technology* 2008, *18* (1), 17–28.

Above about 1s stim, HRF is linear, allowing deconvolution



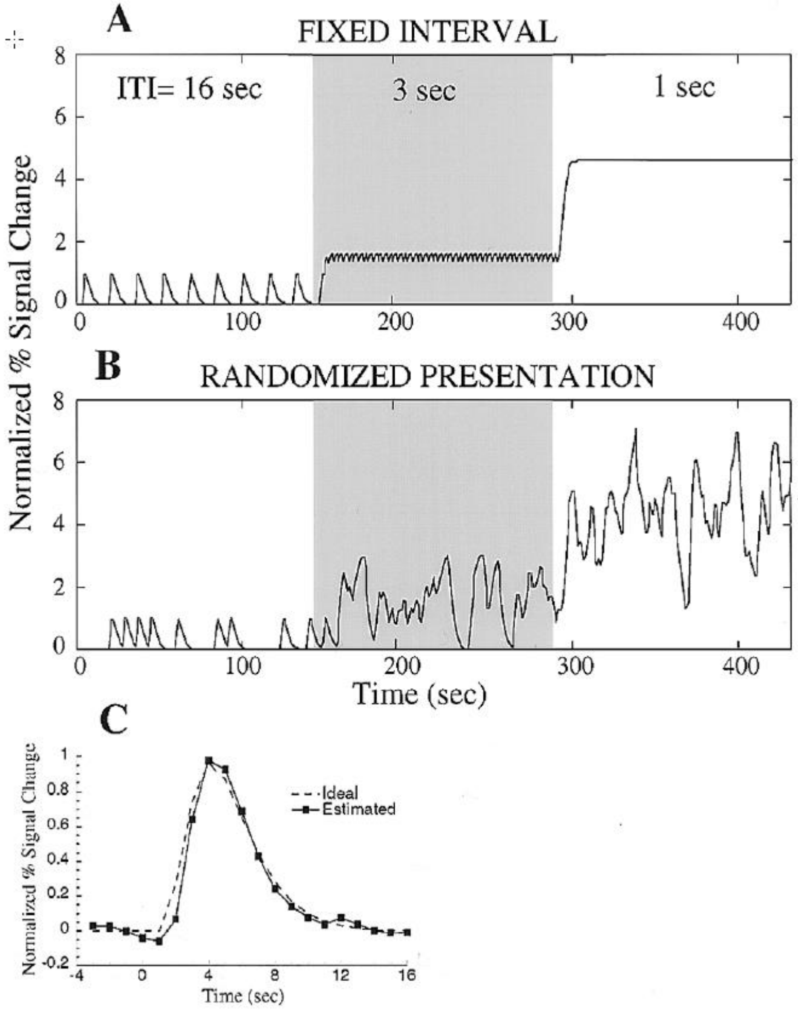
Jittered Event-Related Designs

NeuroRepor t9, 3735–3739 (1998)

Randomized event-related experimental designs allow for extremely rapid presentation rates using functional MRI

Marc A. Burock,[1,2] Randy L. Buckner,[3] Marty G. Woldorff,[4] Bruce R. Rosen[1] and Anders M. Dale[1,CA]

[1]Massachusetts General Hospital, Nuclear Magnetic Resonance Center, Bldg 149, 13th Street, Charlestown, MA 02129; [2]Harvard-MIT Division of Health Sciences and Technology, Cambridge, MA 02129; [3]Washington University, Department of Psychology, St. Louis, MO 63130; [4]University of Texas Health Science Center, Research Imaging Center, San Antonio, TX 78284, USA



NeuroImage 15, 252–264 (2002)
doi:10.1006/nimg.2001.0964, available online at http://www.idealibrary.com on IDEAL

RAPID COMMUNICATION

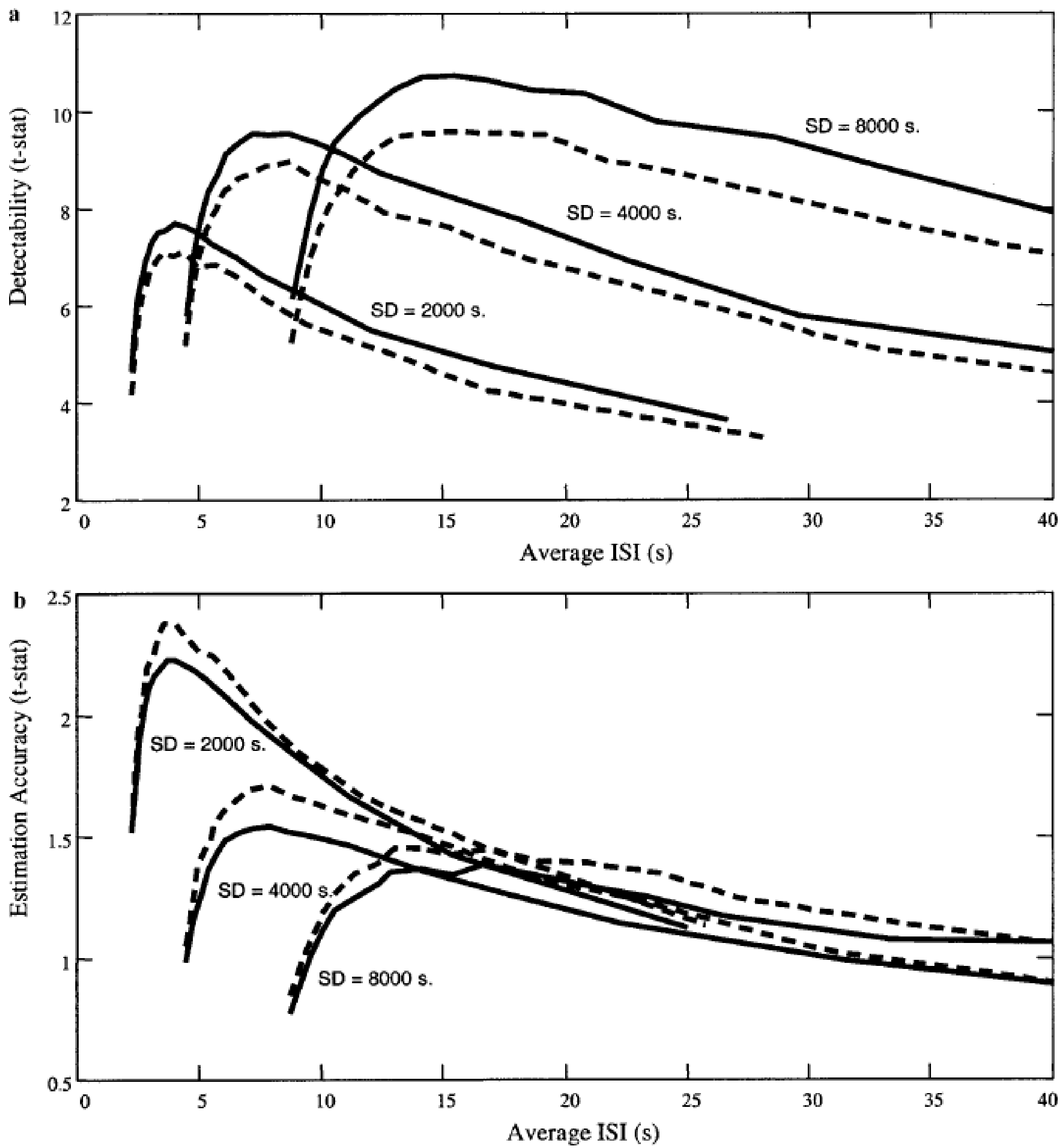
Detection versus Estimation in Event-Related fMRI: Choosing the Optimal Stimulus Timing

Rasmus M. Birn, Robert W. Cox,* and Peter A. Bandettini

3T Functional Neuroimaging Core, National Institute of Mental Health, and *Scientific and Statistical Computing Core, National Institute of Mental Health, Bethesda, Maryland

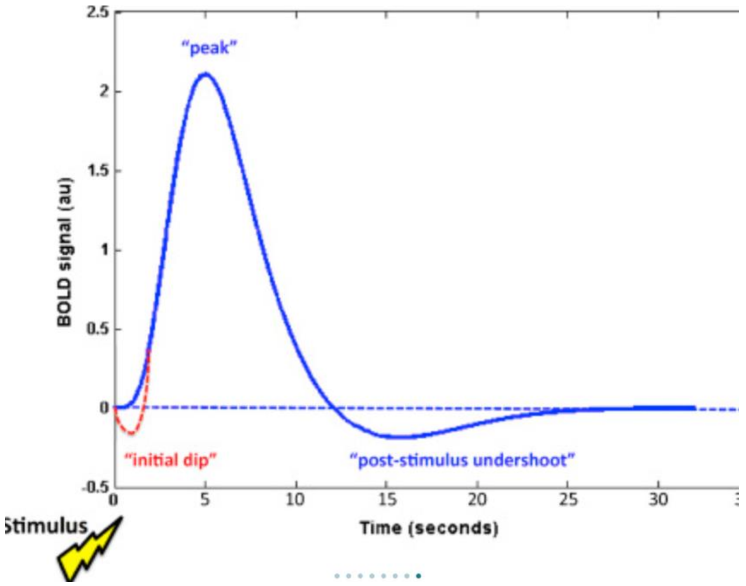
Received December 28, 2000

- **For detection and mapping, sensitivity increases with Average ISI -> block design.**
- **For Estimating the event related response shape from an ROI, sensitivity increases with shorter SD.**

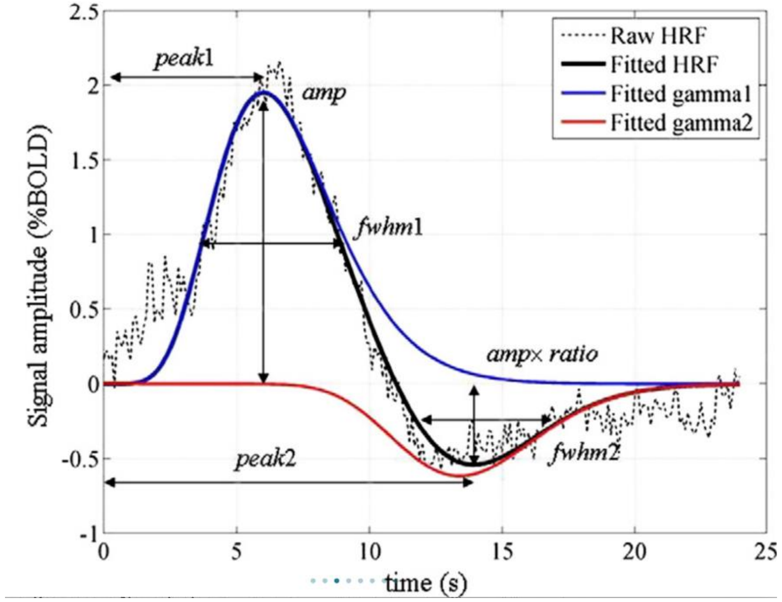


Undershoots

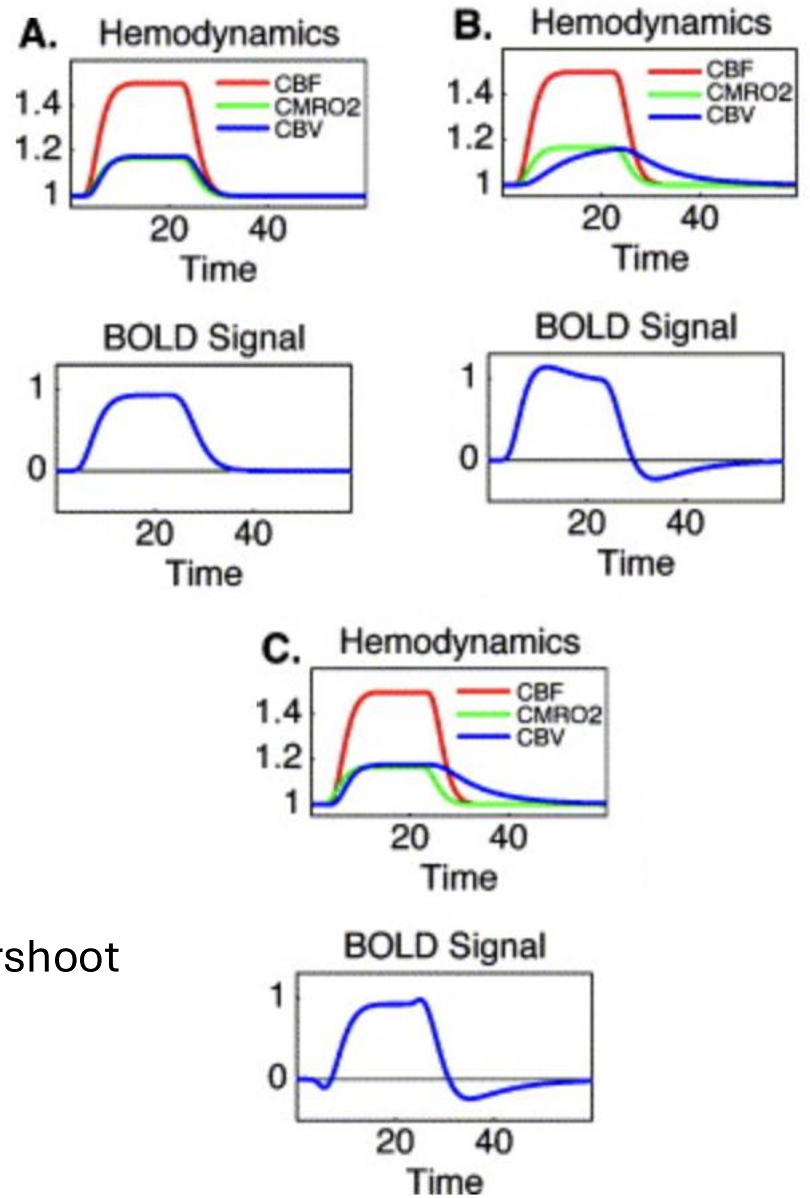
The HRF



Mathematical Models…

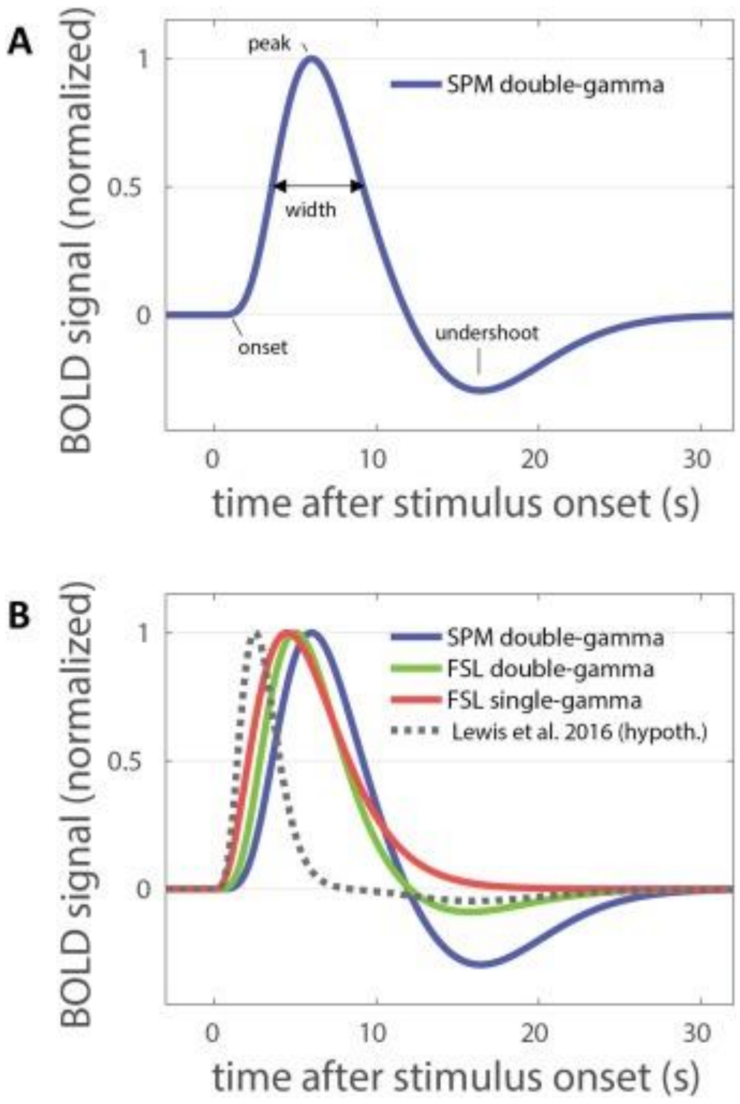


Physiologic models..



The pre-undershoot issue lost appeal (not repeatable), but the post undershoot was heavily debated…flow, CMRO2, volume? Still not fully resolved.

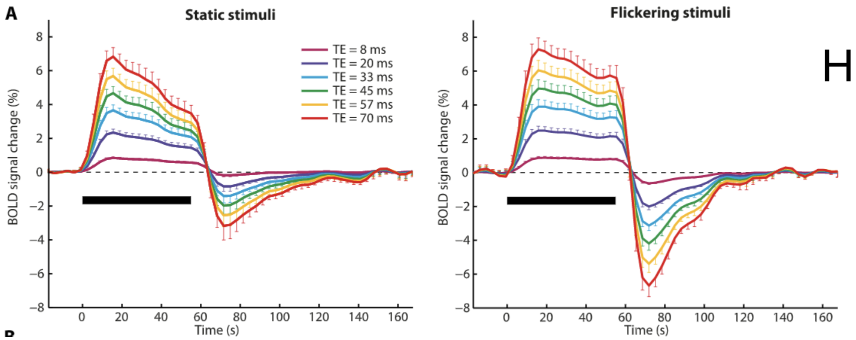
Mysteries of linearity, undershoots, transients



Task timing

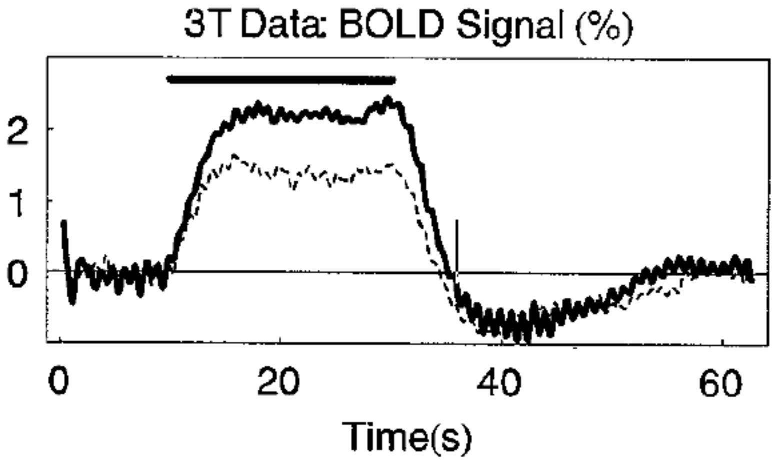
Polimeni and Lewis, Progress in Neurobiology, (2021)

-depends on location, task, timing, and pulse sequence



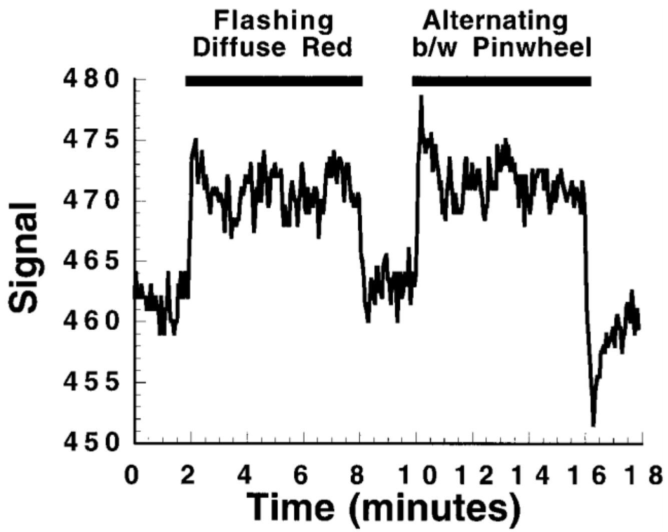
Havlicek et al, NeuroImage, (2017)

Stimulus & Echo Time



Diffusion weighting

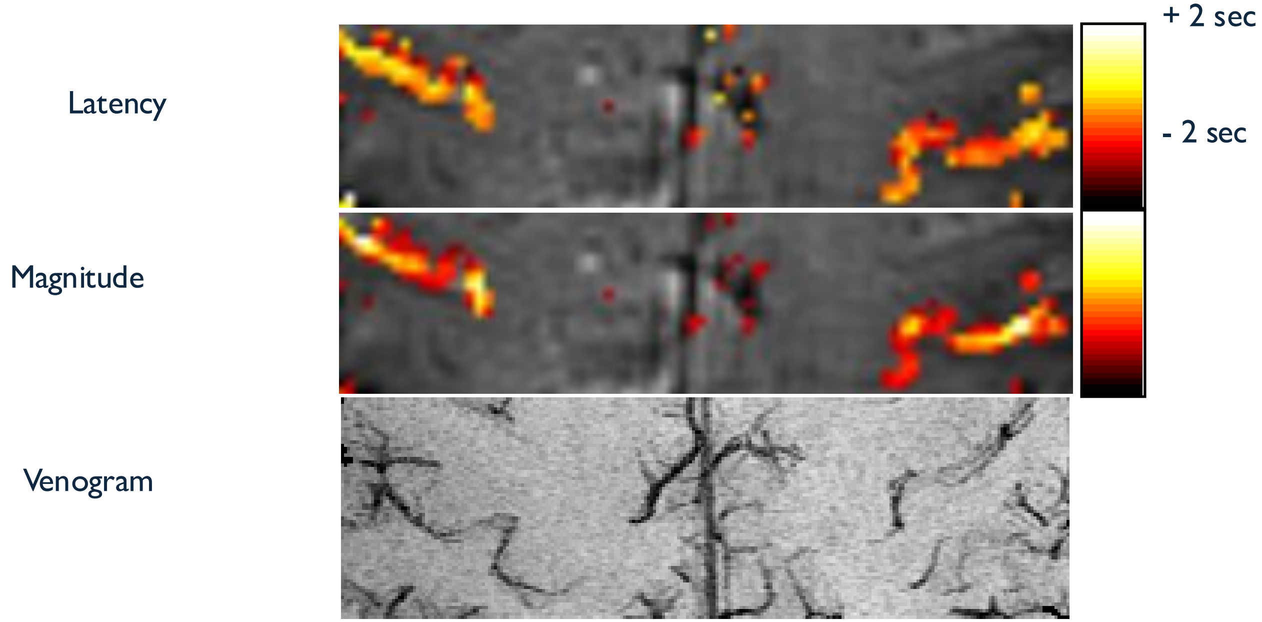
Buxton et al, ISMRM (1996)

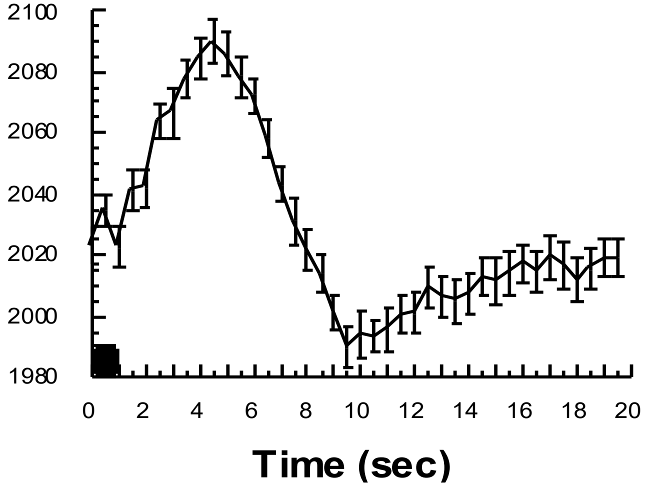


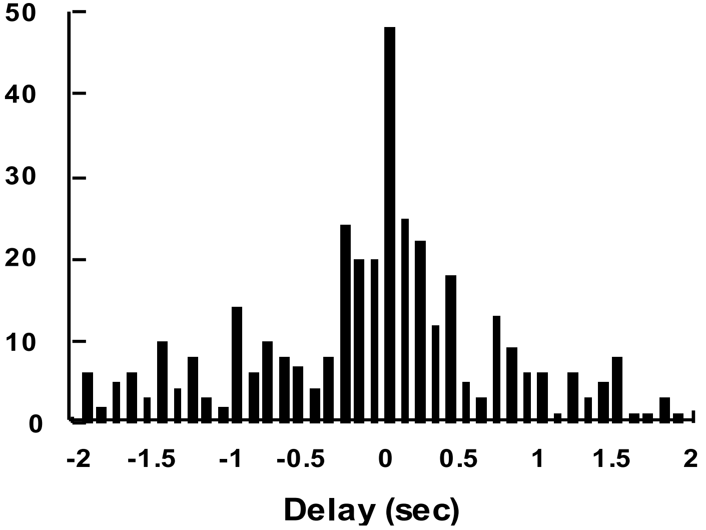
Stimulus

Bandettini et al, HBM (1997)

Latency Across the Brain

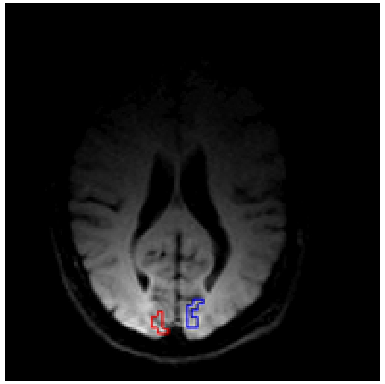


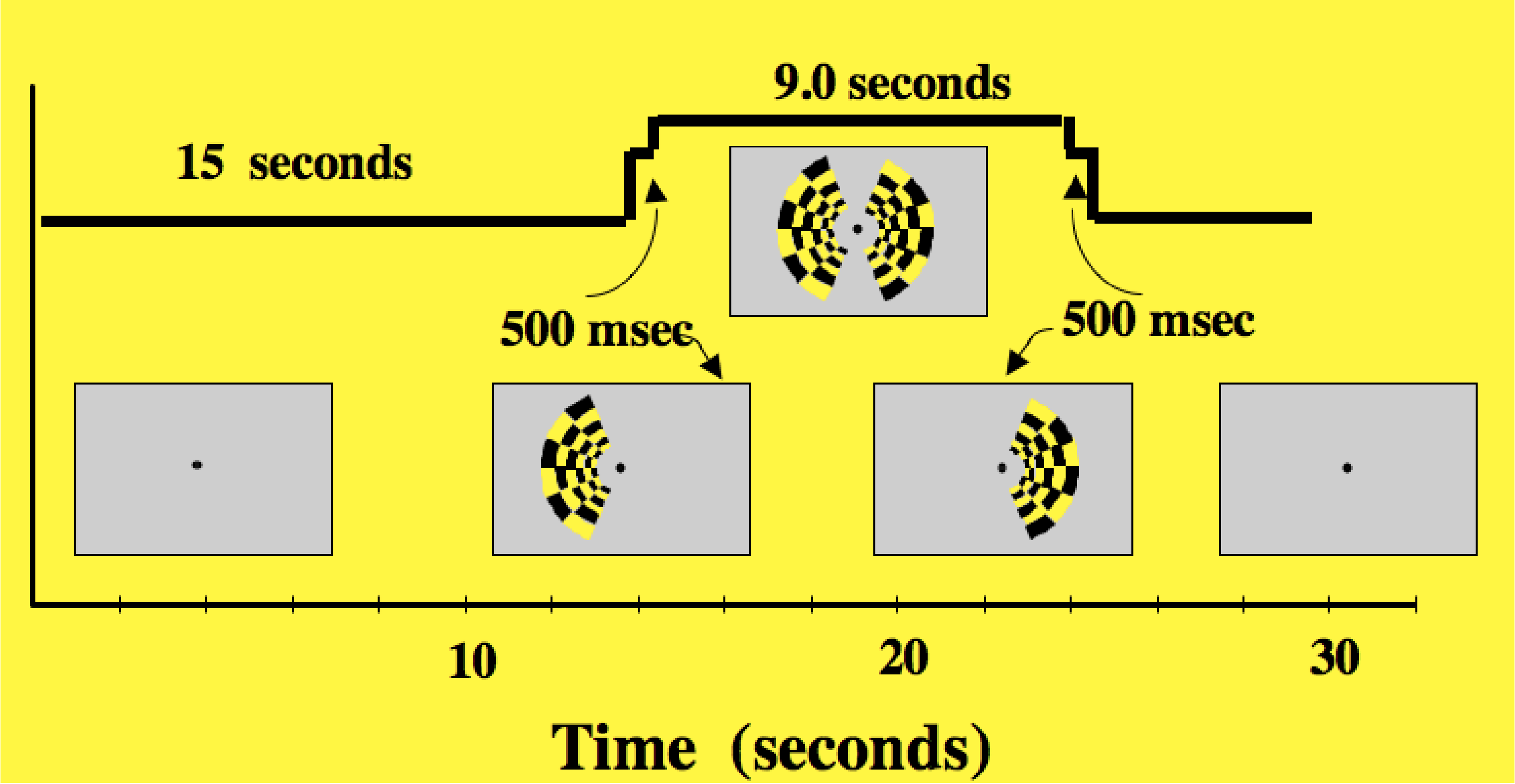




P.A. Bandettini, (1999) "Functional MRI" 205-220.

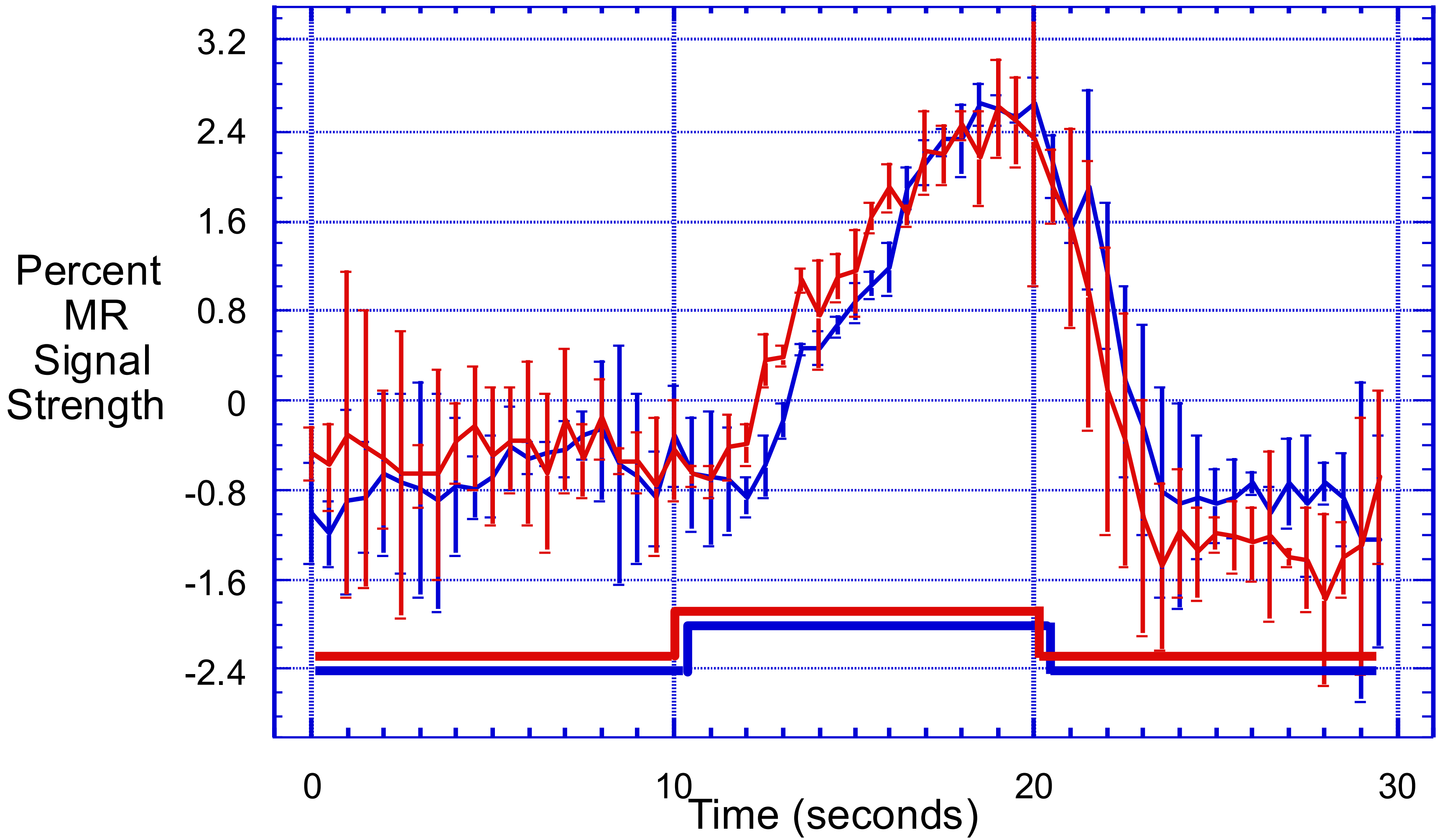
Latency Across the Brain





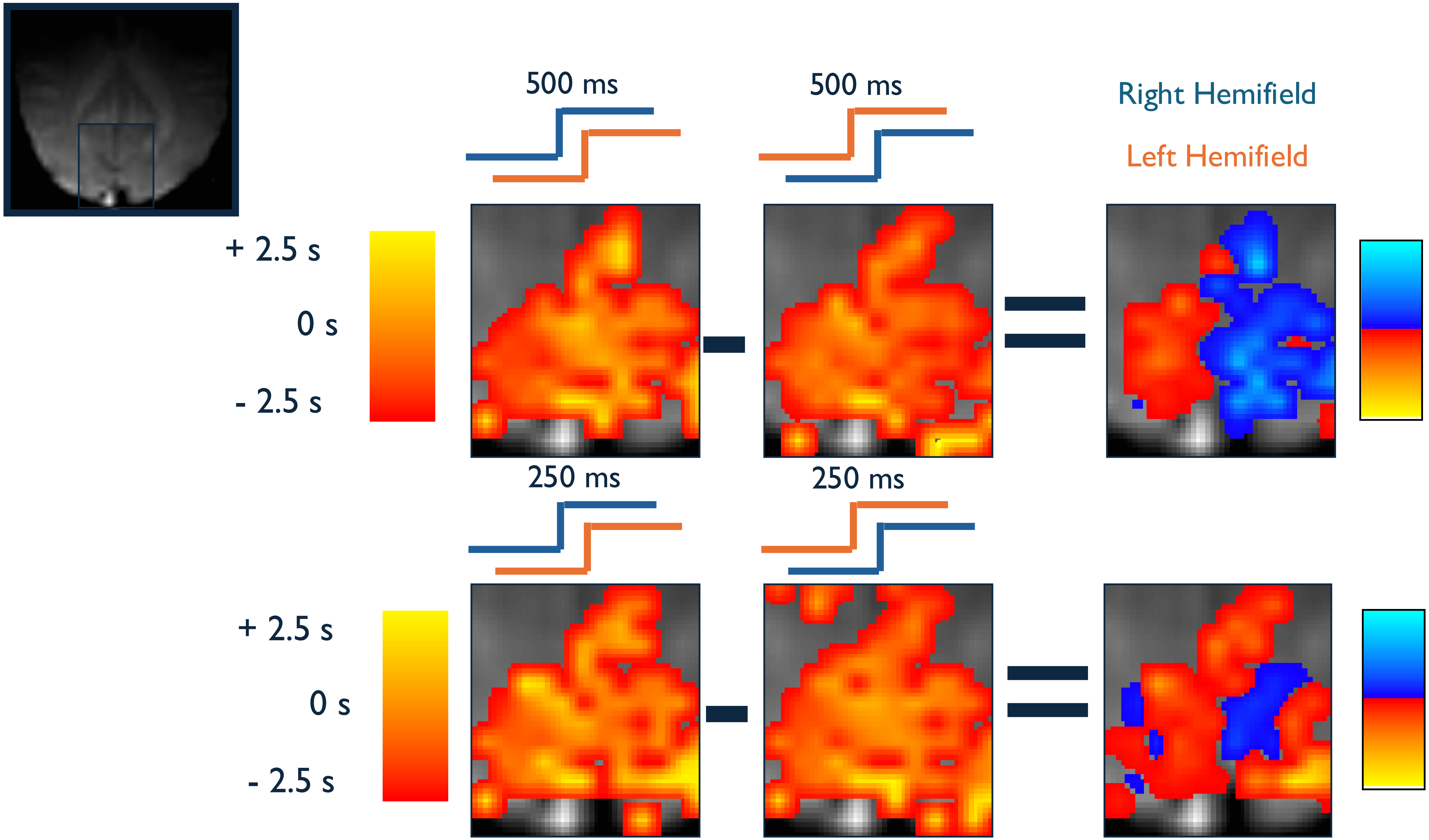
Latency Across the Brain

Hemi-field with 500 msec asynchrony



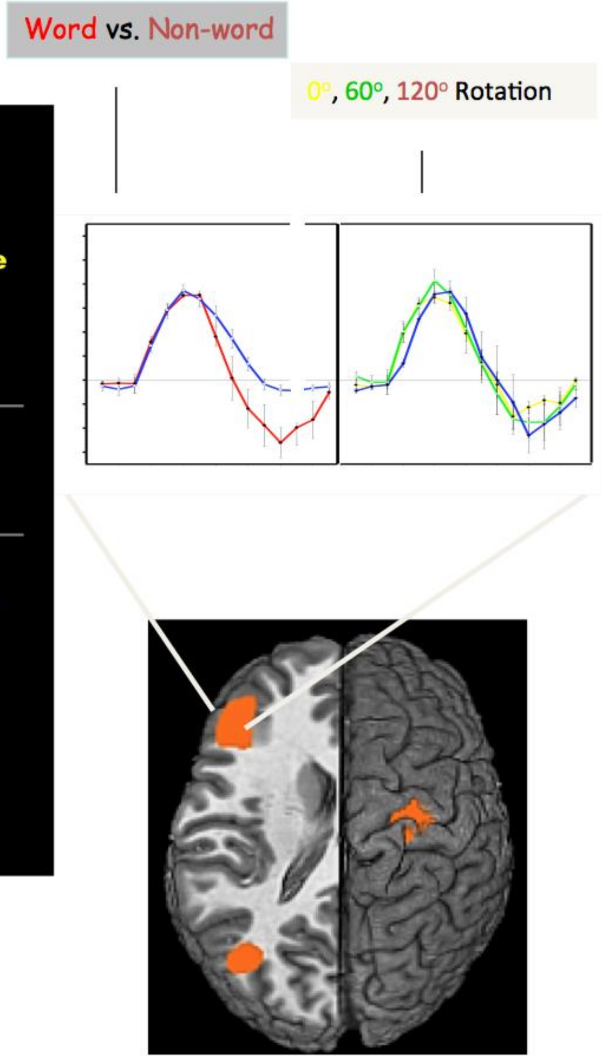
Average of 6 runs

Latency Across the Brain



Exploiting Dynamics for a Cognitive Task

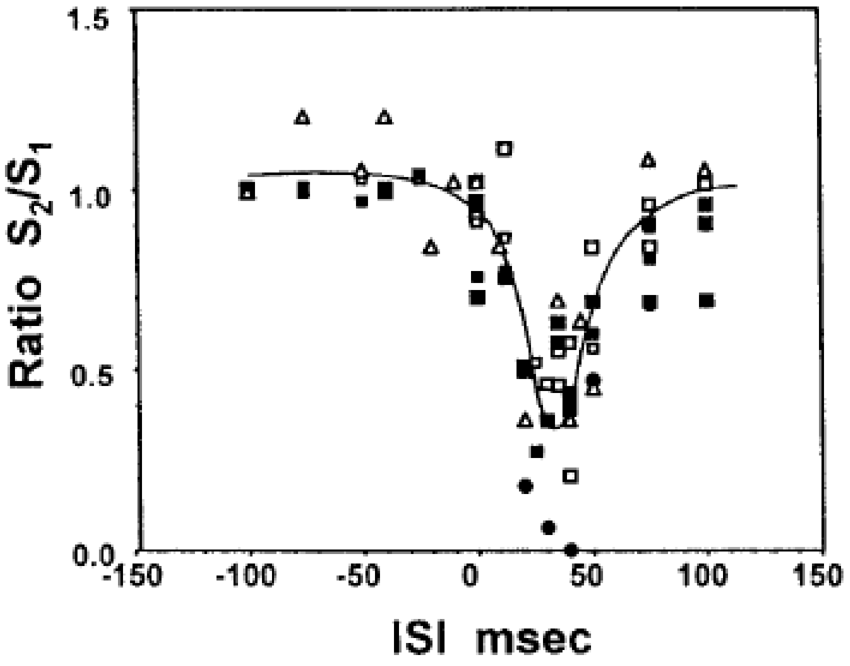
Rotational Delay	Lexical Delay: Words	Lexical Delay: Non-Words	Mean Reaction Time
0°	smudge	dierts	823 ms
60°	frolic	cuhlos	891 ms
120°	slouch	gedmus	1446 ms
Mean Reaction Time	986 ms	1219 ms	



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

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[§]



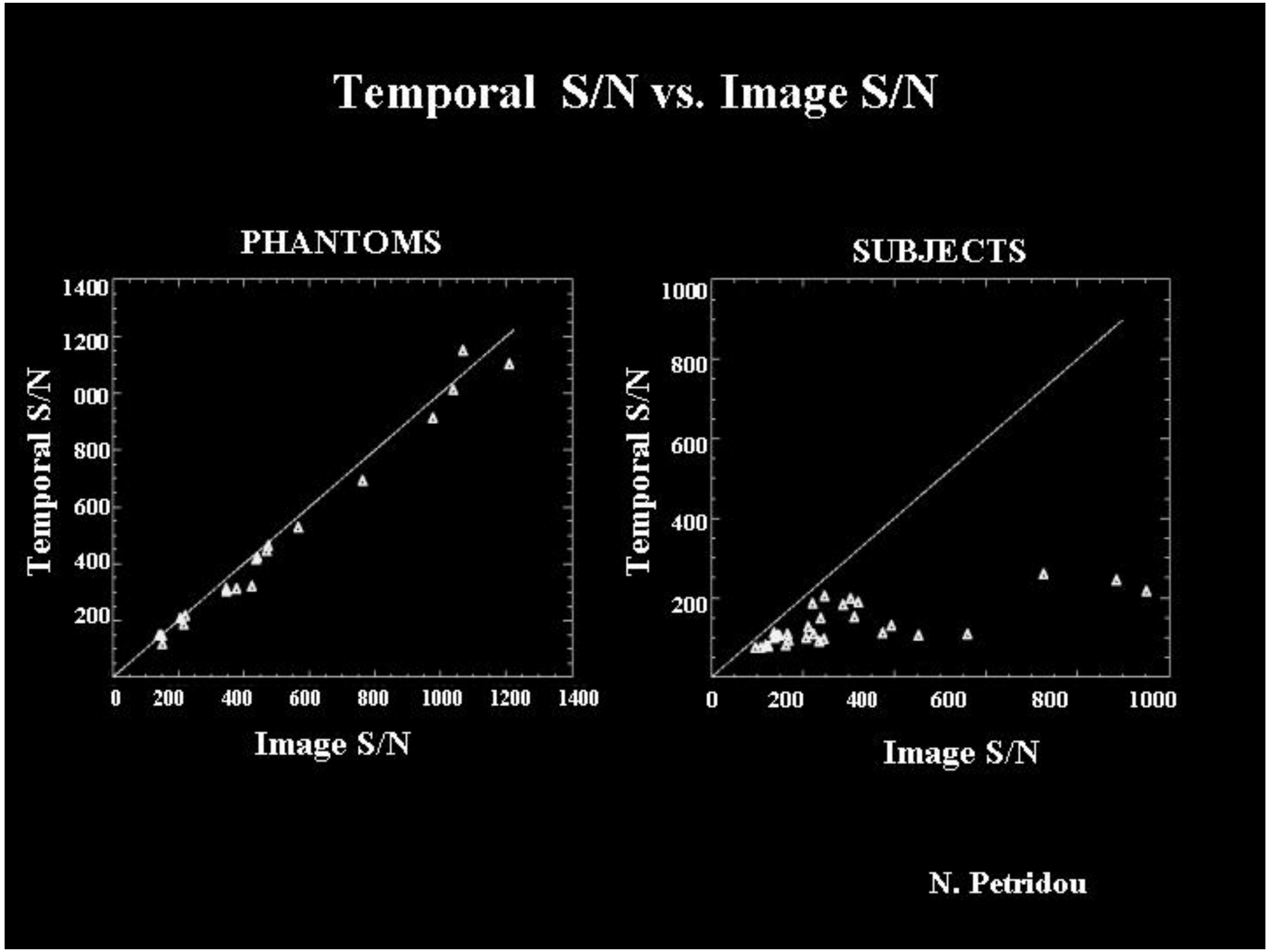
11026–11031 PNAS September 26, 2000 vol. 97 no. 20

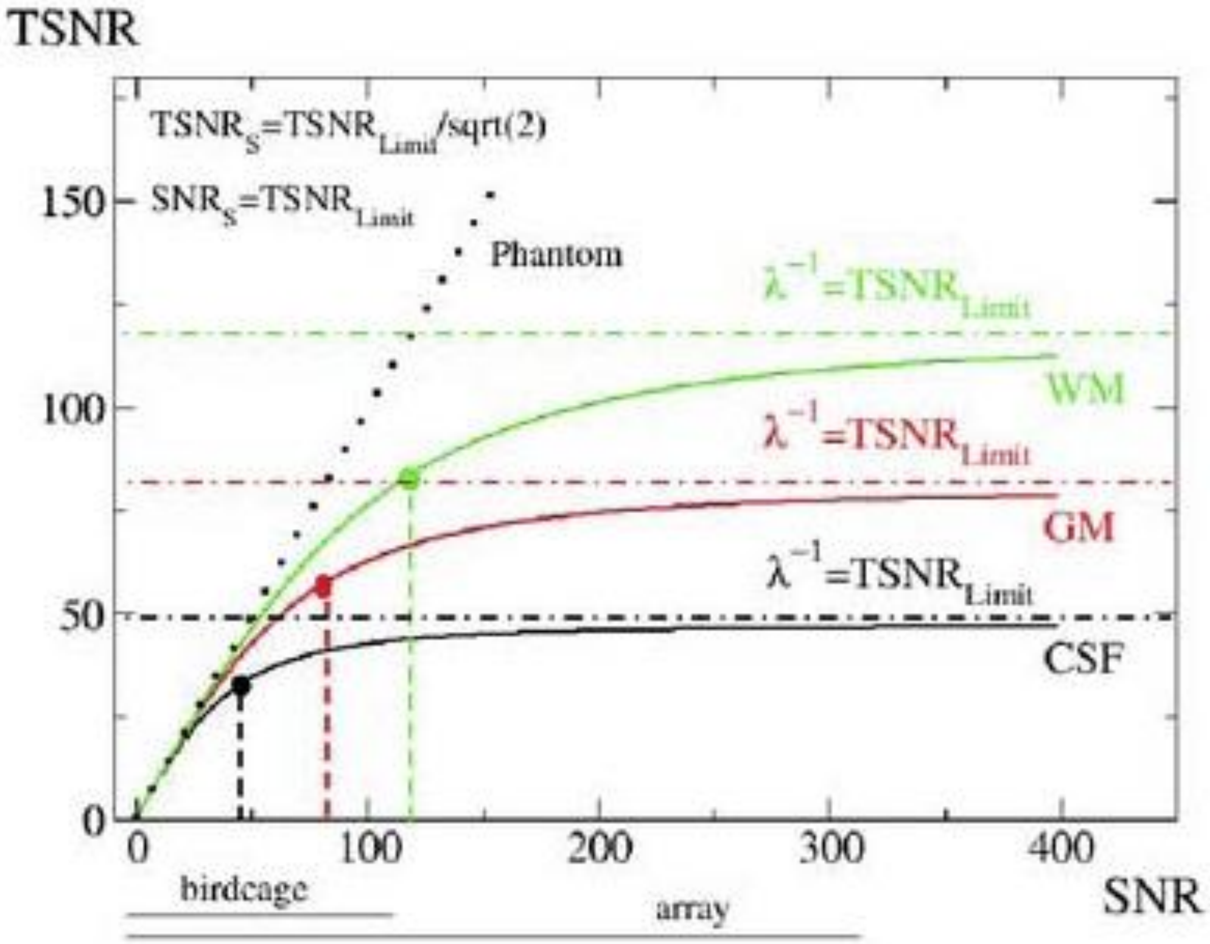
Kinds of Temporal Resolution

Temporal resolution factors	Values for each factor
Fastest image acquisition rate	MREG: 100 images/s
Minimum time for signal to significantly deviate from baseline	≈3 s
Fastest on-off rate in which amplitude-is not compromised	≈8 s on, 8 s off
Fastest on-off rate in which hemodynamic response keeps up	1 s on, 1 s off
Minimum activation duration	≈30 ms (no limit determined yet, but the response behaves similarly below 500 ms)
Standard deviation of baseline signal	≈1% (less if physiological fluctuations and system instabilities are filtered out)
Standard deviation of onset time estimation	≈450 ms
Standard deviation of return to baseline time estimation	≈1250 ms
Standard deviation of entire on-off response time estimation	≈650 ms
Range of latencies over space	± 2.5 s

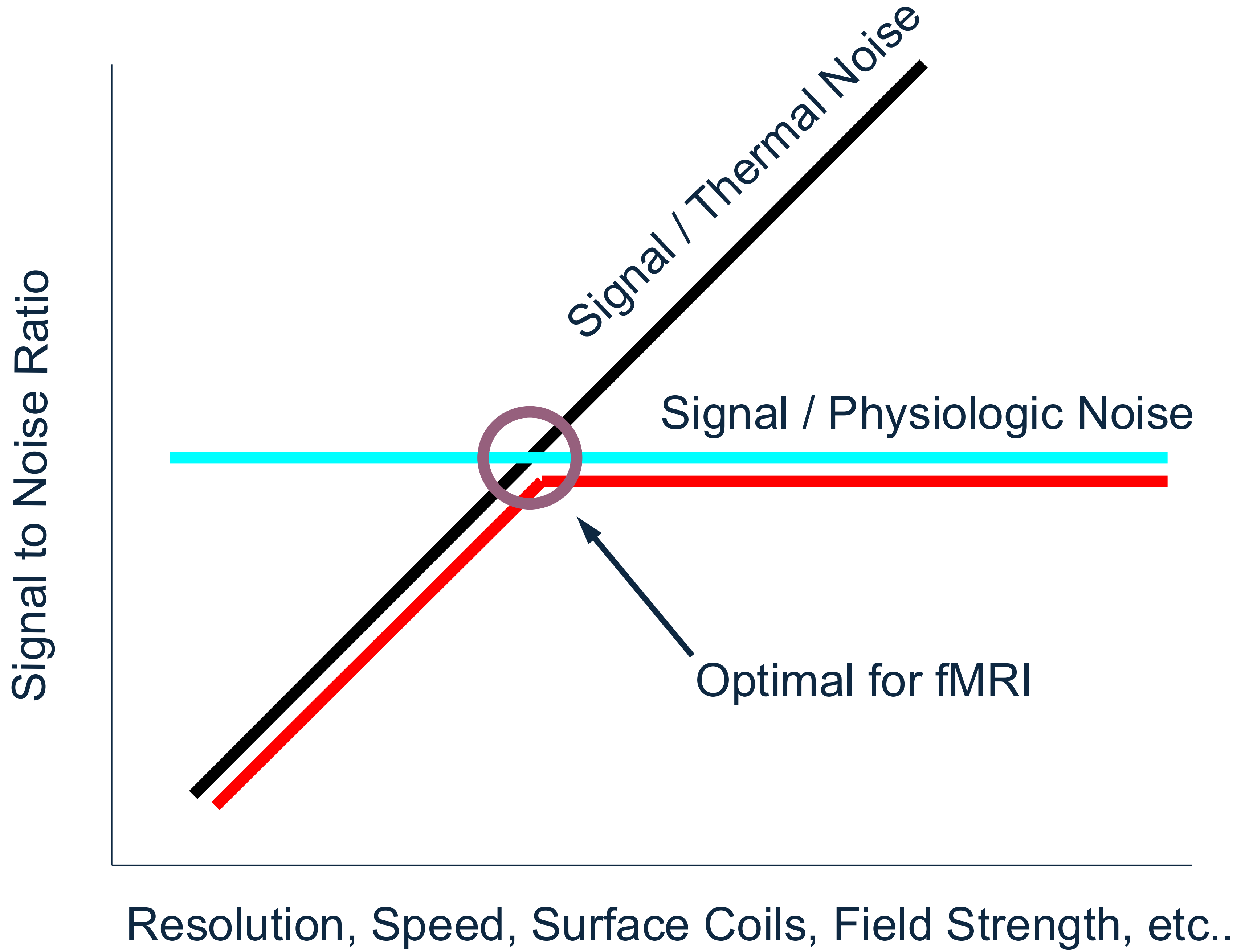
P. A. Bandettini, (1999) "Functional MRI" 205-220.

Temporal vs. Image SNR in a phantom and human





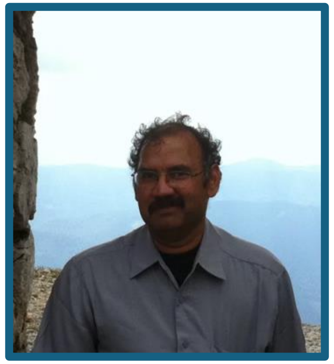
J. Bodurka, F. Ye, N Petridou, P. A. Bandettini, Mapping the MRI voxel volume in which thermal noise matches physiological noise – implications for fMRI. *NeuroImage,* 34, 542-549 (2007)


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

Resting State fMRI

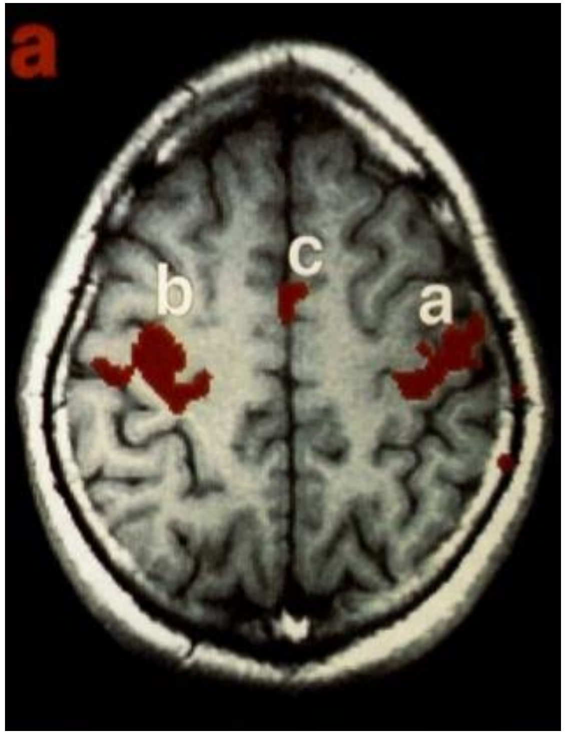
Functional Connectivity in the Motor Cortex of Resting Human Brain Using Echo-Planar MRI

Bharat Biswal, F. Zerrin Yetkin, Victor M. Haughton, James S. Hyde

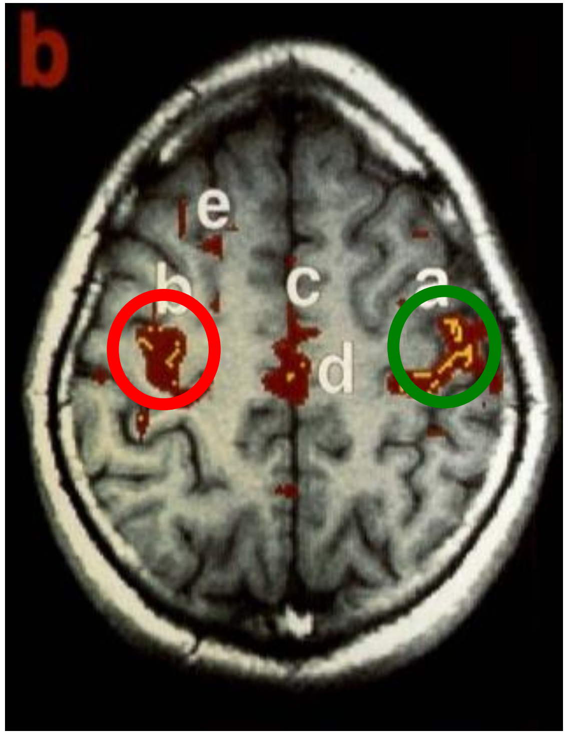


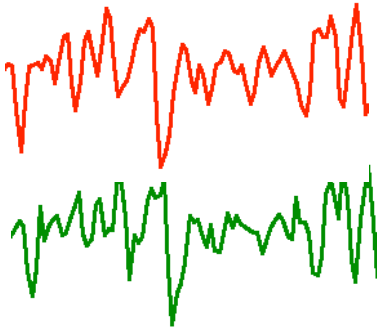
Mag. Res. Med. 1995,

task *activation*

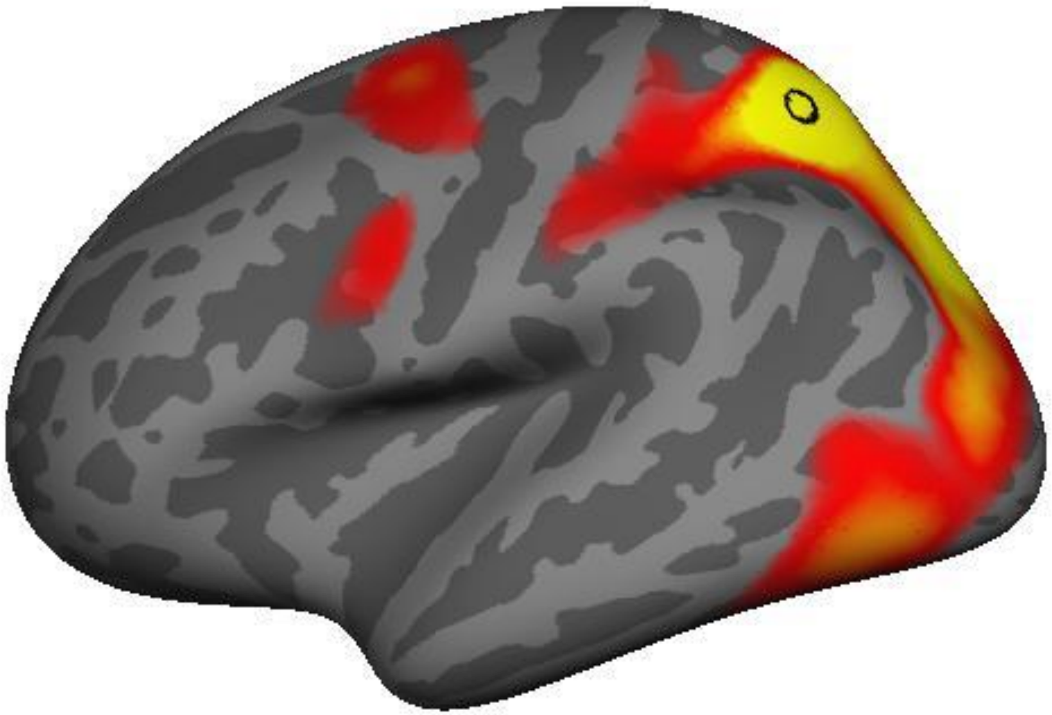


resting state *correlation*



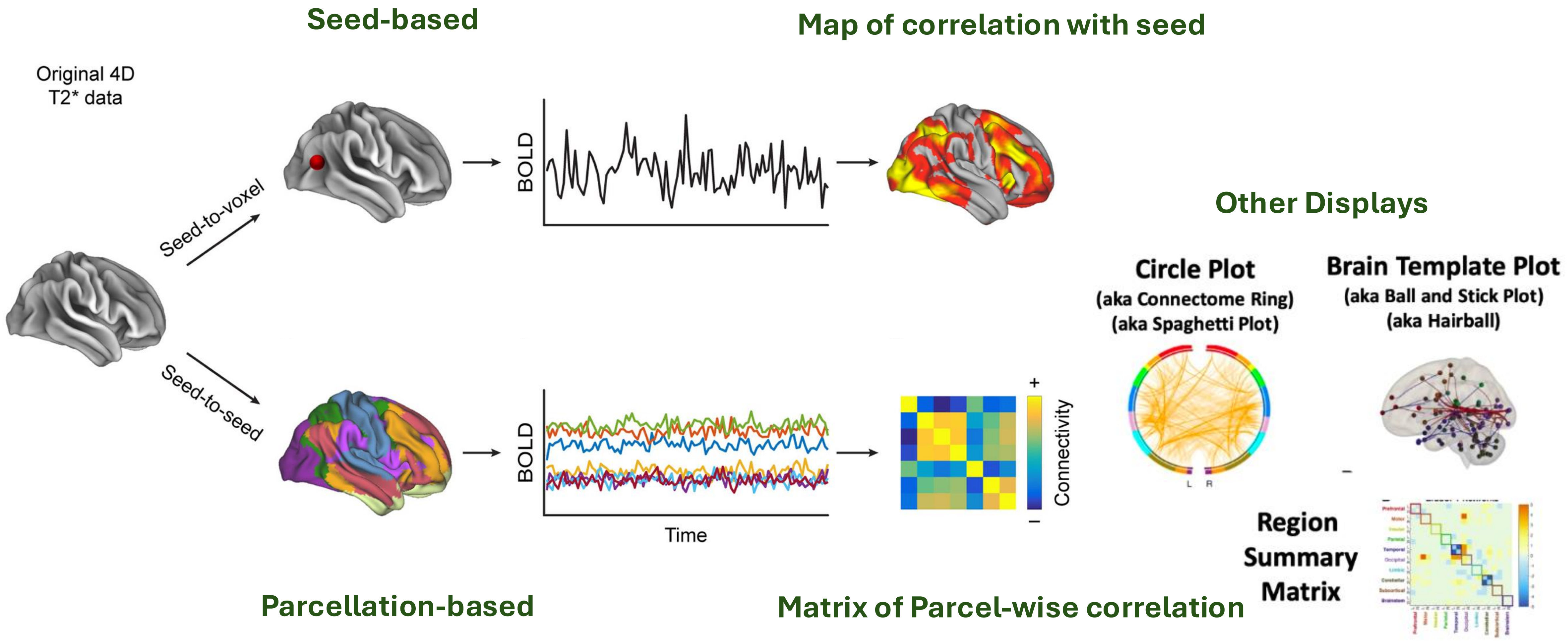


Seed-based Correlation



Buckner et al. 2013

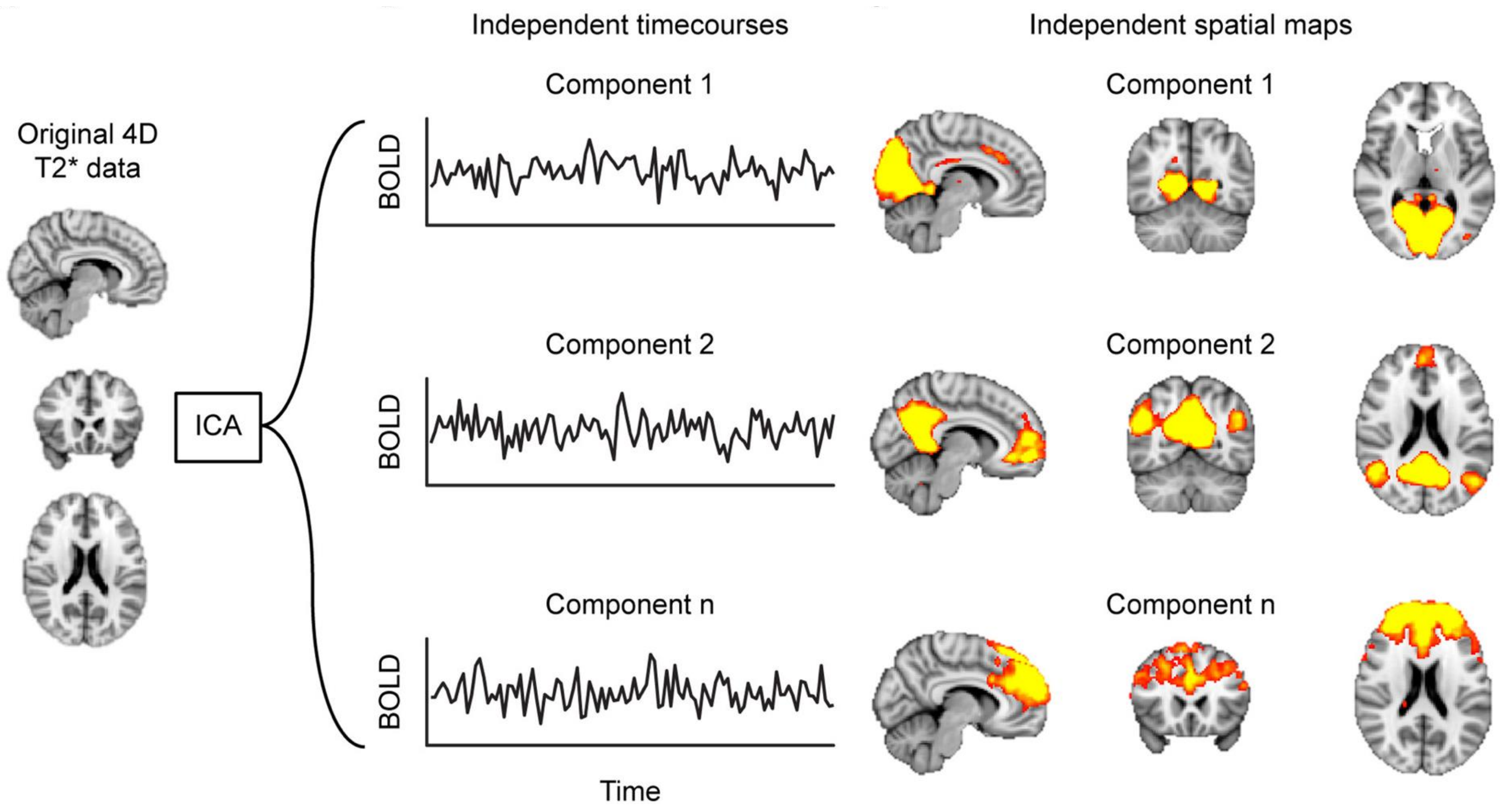
How is functional connectivity measured?



Tahedl et al, Frontiers in Neurology, 2018

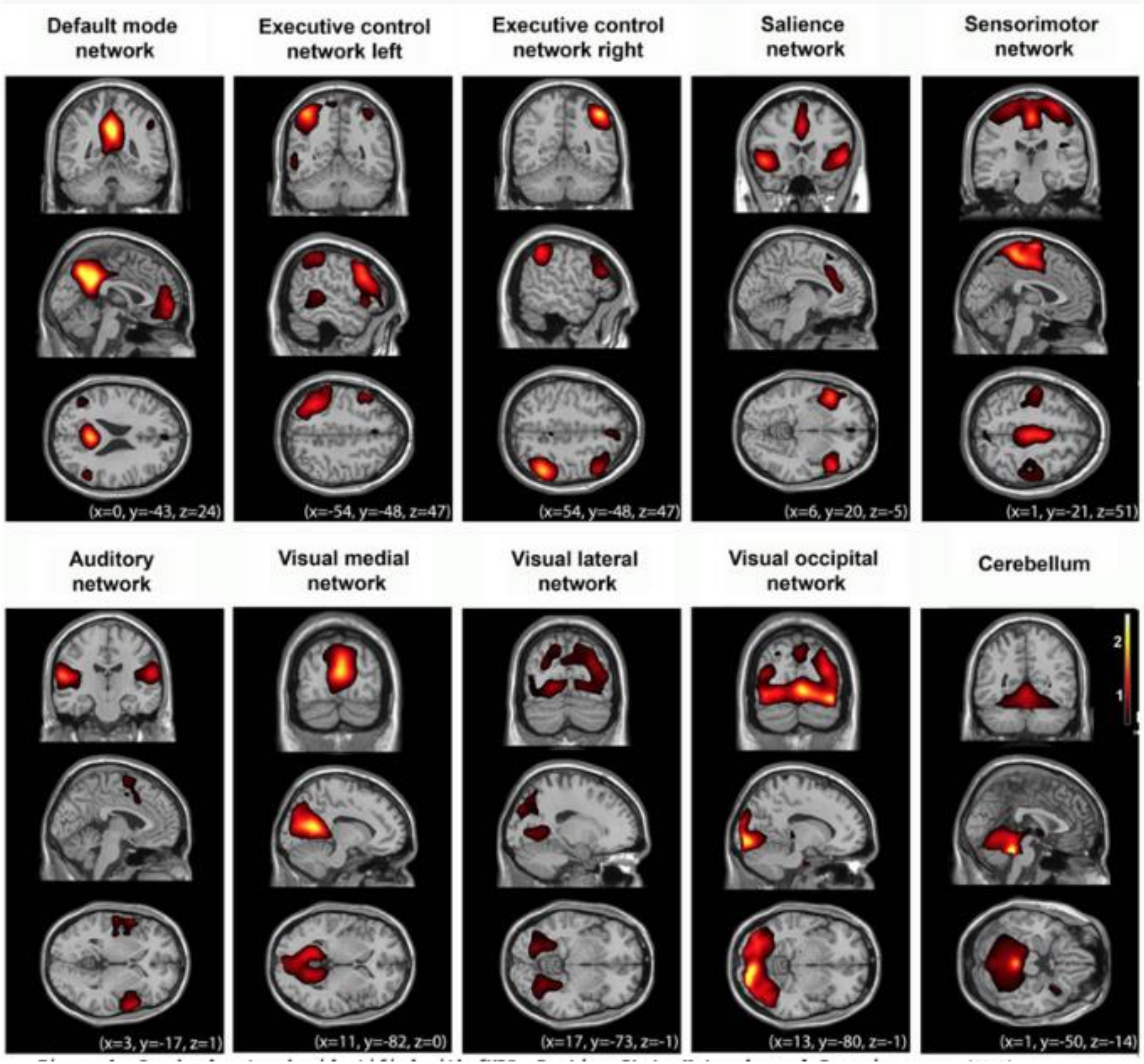
How is functional connectivity measured?

Independent Component Analysis



Tahedl et al, Frontiers in Neurology, 2018

Example of Networks Derived Using ICA



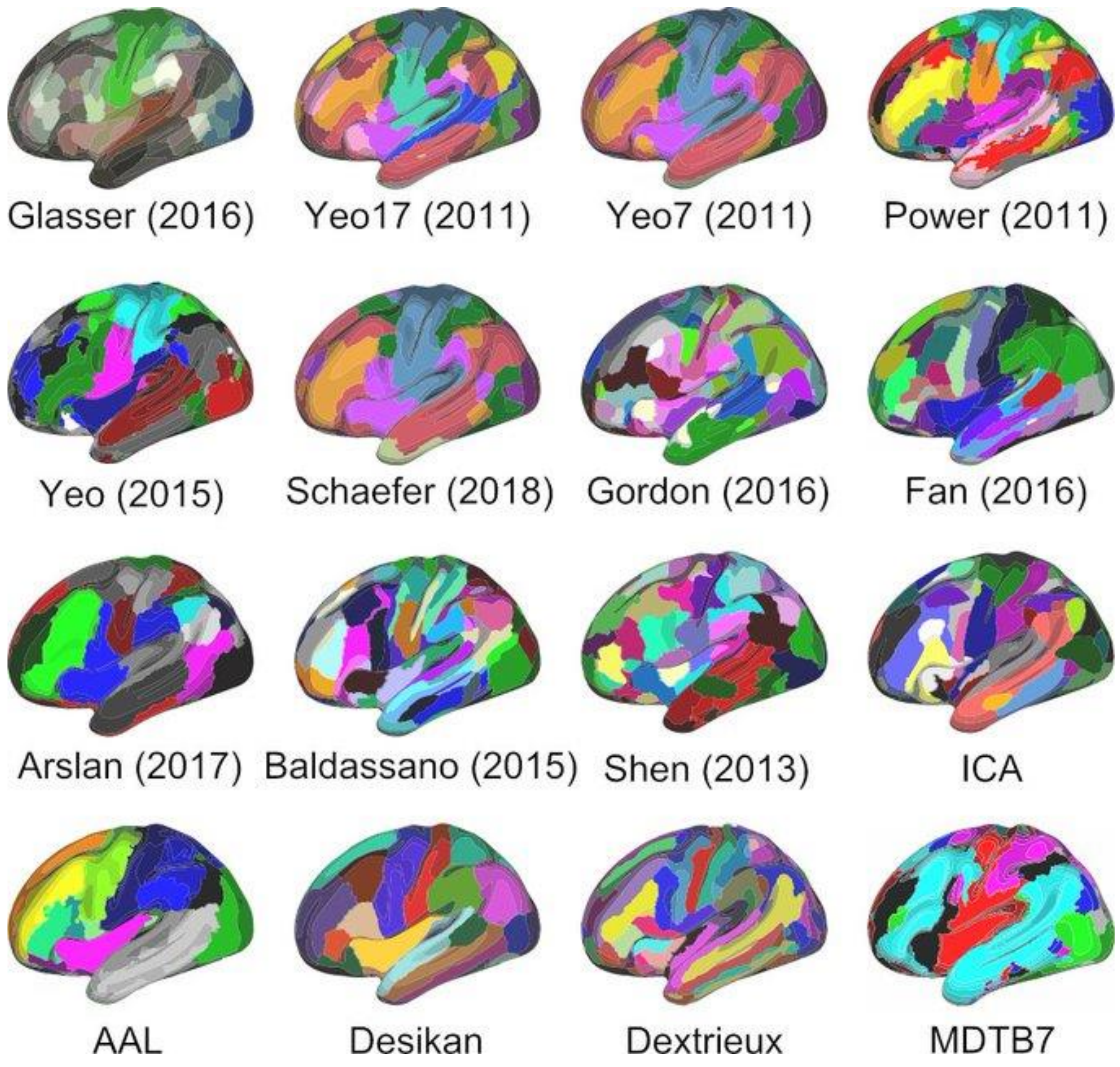
L. Heine, et al, Frontiers in Psychology, 2012

Diverse Functional Parcellation Approaches

Heirarchical clustering
K-means clustering
Ward's linkage
Region growing
Euclidean distance
Principle Component Analysis
Spectral clustering
Eigenvector discretizing
...

https://biomedia.doc.ic.ac.uk/brain-parcellation-survey/

D. Zhi, et al, HBM, 2022



What contributes to spontaneous fluctuations?

Spontaneous Neuronal Activity
- -conscious thought
- -unconscious processes*
- -arousal, vigilance

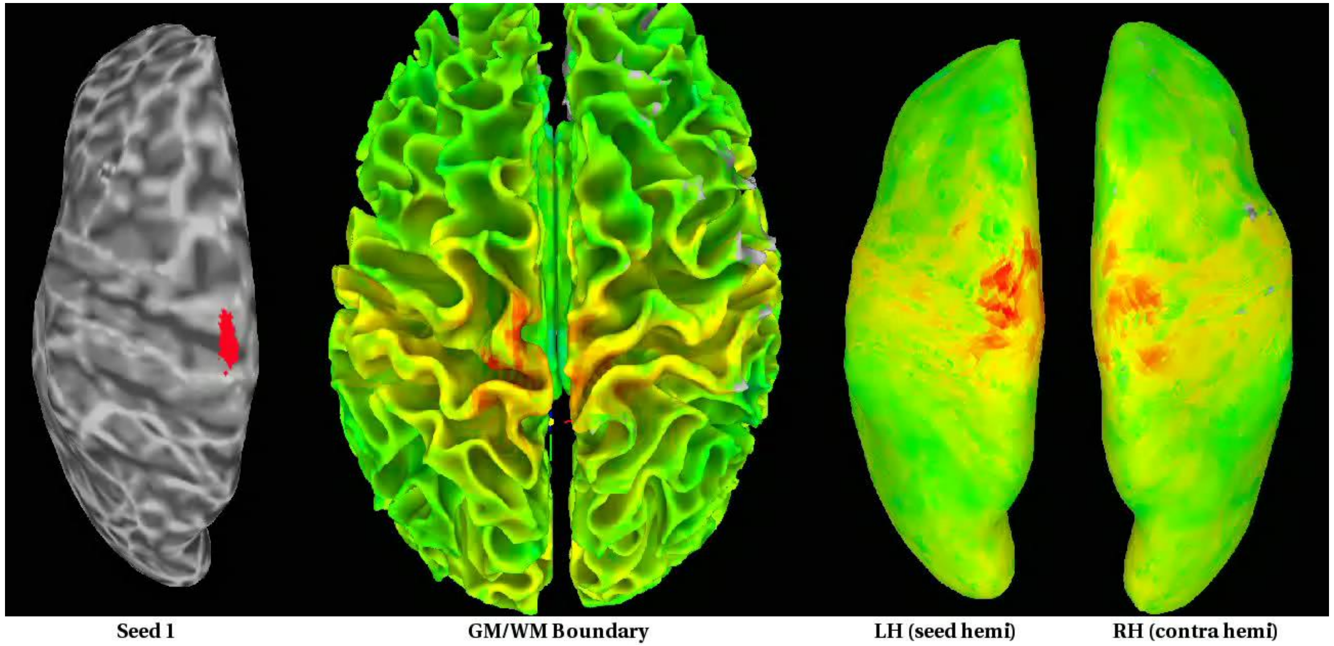
Respiration
- -chest wall B_0
- -variable end tidal CO_2 related flow/BOLD changes

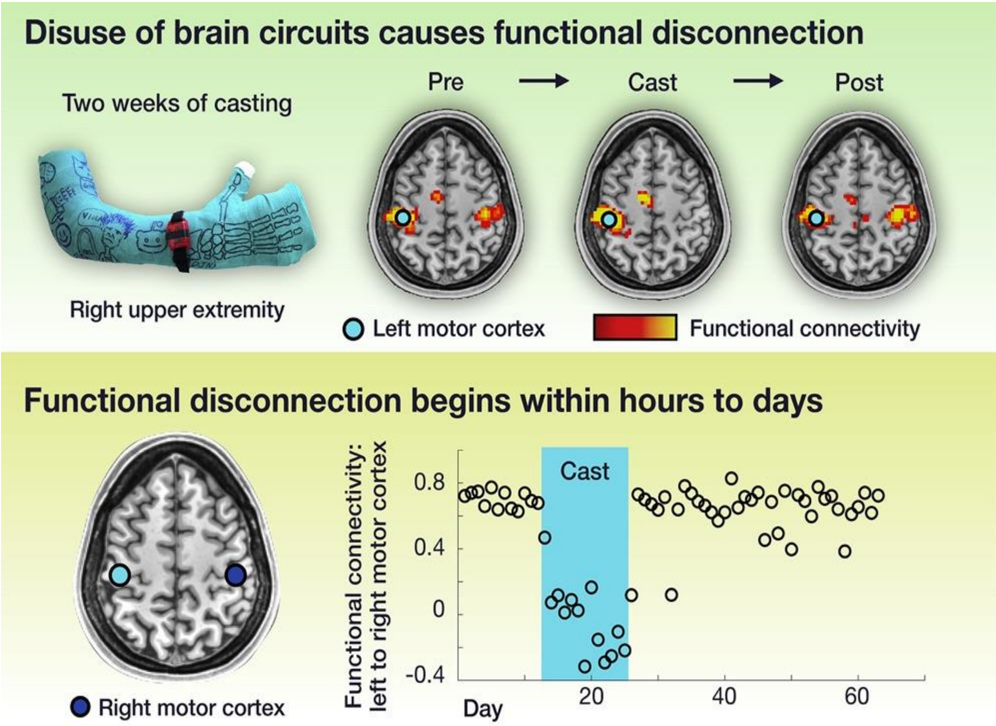
Cardiac Pulsation

Thermal Noise
Motion
Scanner Instability

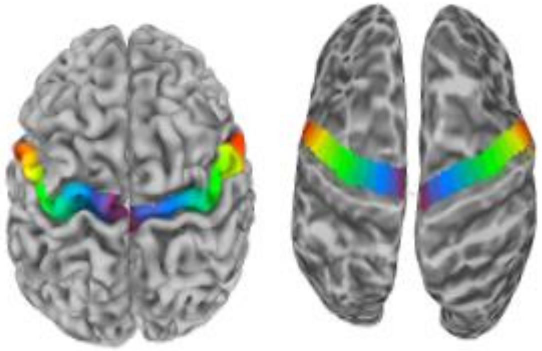
* "...low dimensionality of spontaneous neural patterns may reflect slow transitions between generic priors tuned for low dimensional, general-purpose, behavioral patterns. ... dynamics across sequences of brain states may reflect the maximization of the entropy of explanations (or ...the *exploration of the brain's dynamic repertoire*) that generative models use in the absence of data, to explain, to remain flexible." ***G. Pezzulo et al. TICS 2021***

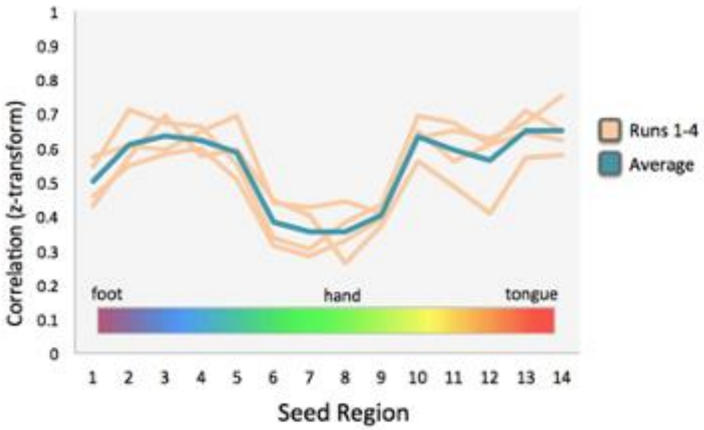
Unconscious Processes





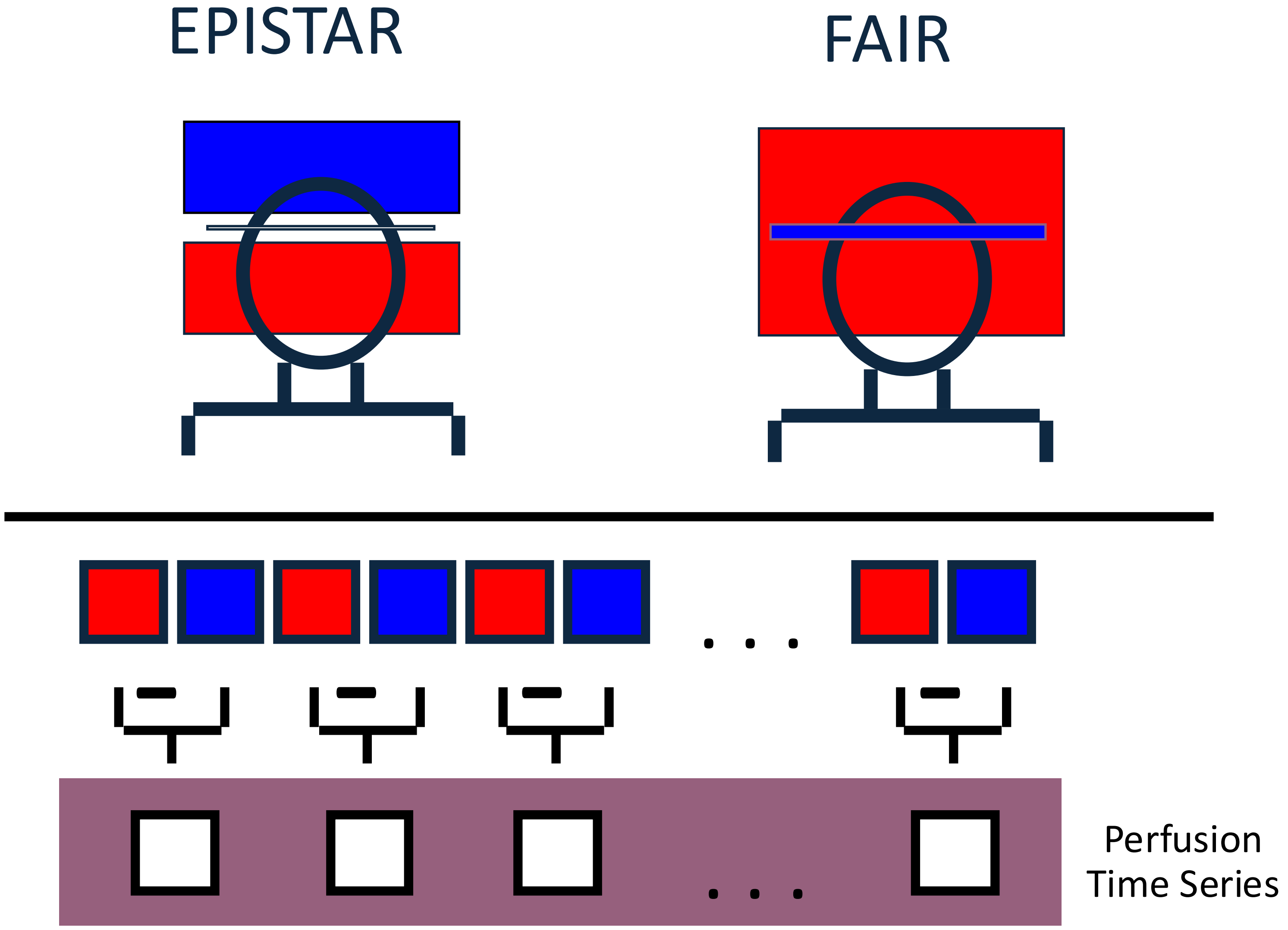
Motor cortex mostly in left-right sync, but hands are not

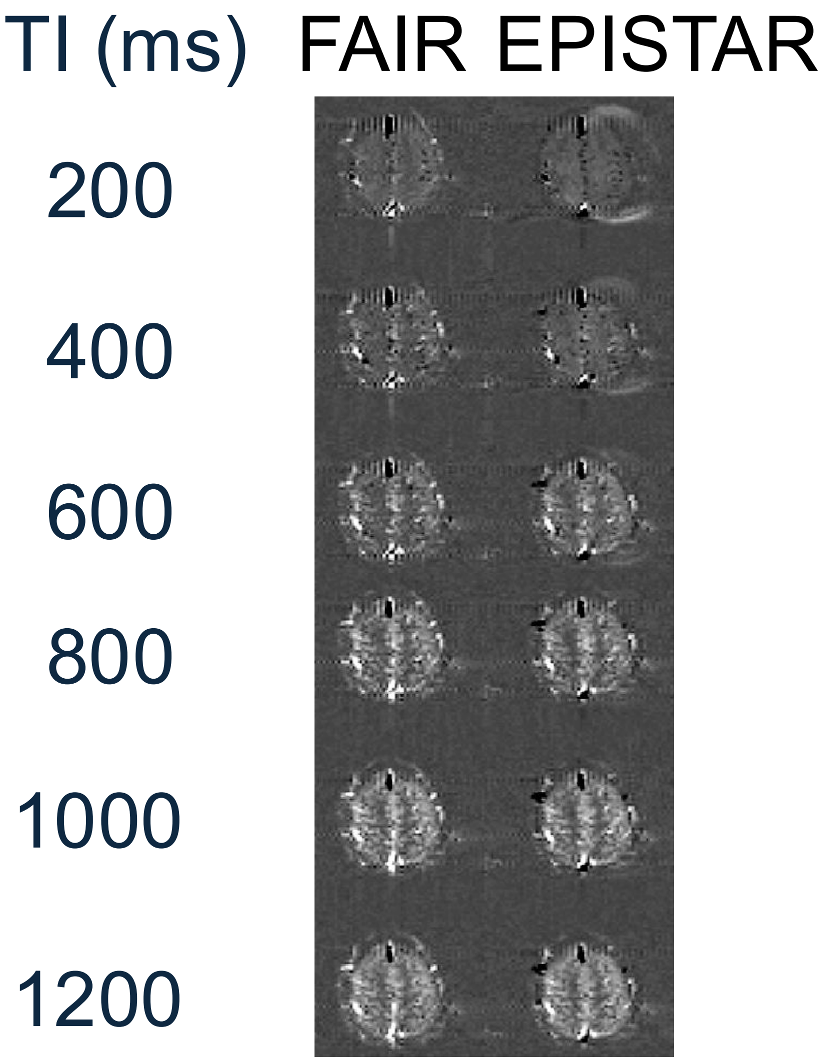




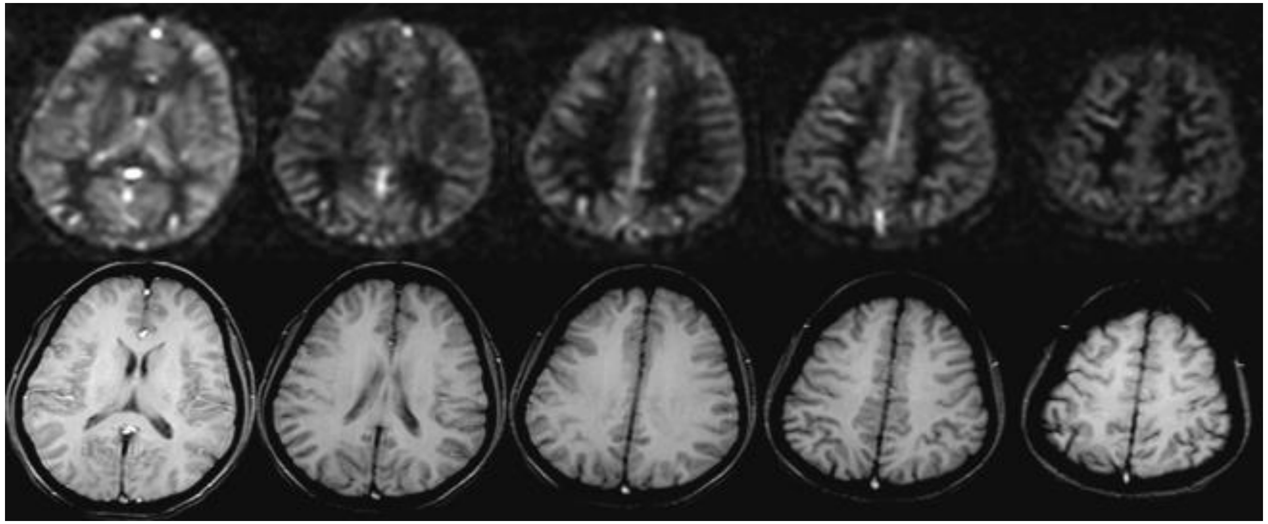
D. J. Newbold et al. Neuron, 2020

Blood Perfusion





Blood Perfusion



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.

1992...Perfusion using Arterial Spin Labeling

Proc. Natl. Acad. Sci. USA
Vol. 89, pp. 212–216, January 1992
Biophysics

Magnetic resonance imaging of perfusion using spin inversion of arterial water

(cerebral blood flow/adiabatic fast passage/hypercarbia/rat brain/cold injury)

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Communicated by Mildred Cohn, September 19, 1991

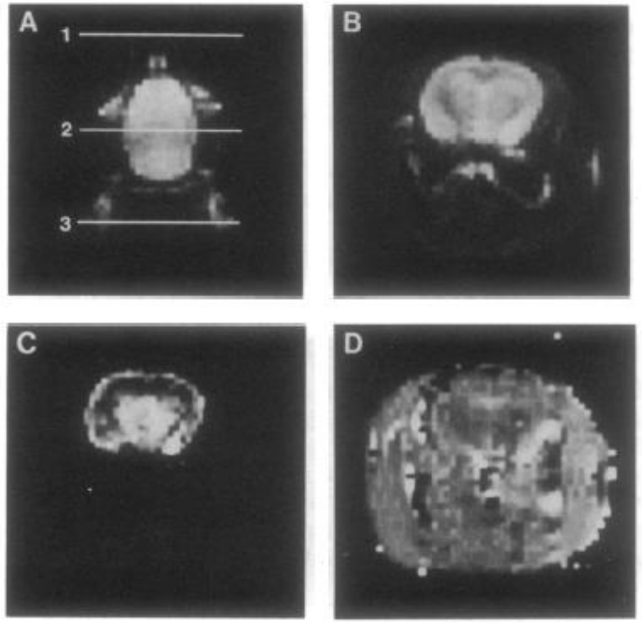


FIG. 2. (*A*) Coronal image of a rat head. The resonance planes for radiofrequency used for spin inversion by AFP for control and inversion images are indicated by 1 and 3, respectively, and plane 2 is the detection plane. (*B*) Control transverse image from the detection plane (plane 2 in *A*). (*C*) Difference image between control and inversion images. (*D*) T_{1app} image.

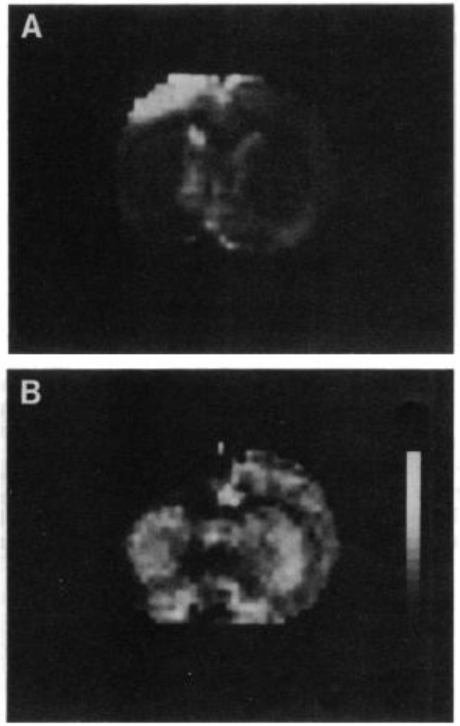
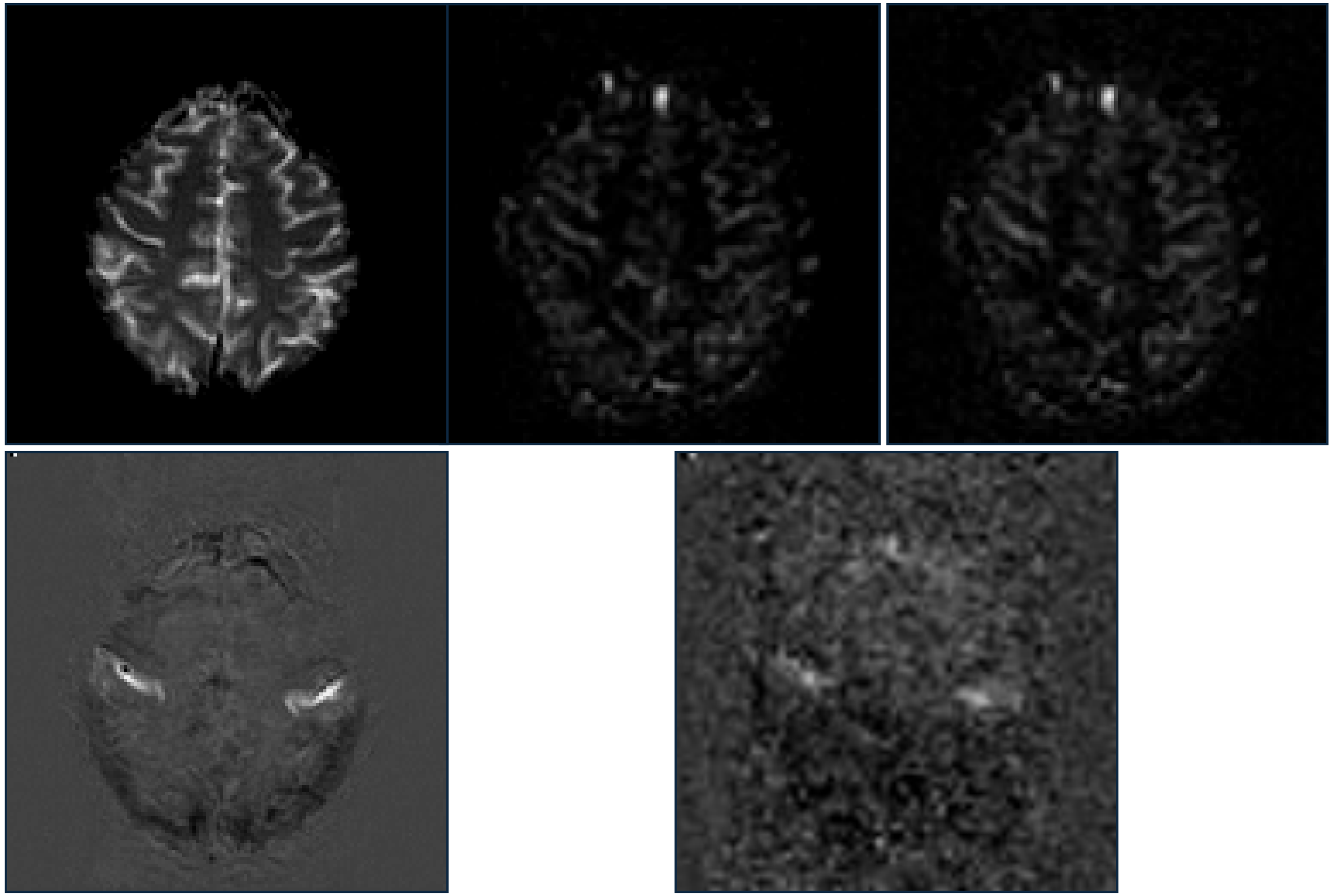


FIG. 5. Comparison of conventional MRI and perfusion imaging of a rat brain subjected to a regional cold injury. (*A*) Conventional T_2-weighted image (TE = 60 ms, TR = 2 s). The injured region shows up as hyperintensity due to a longer T_2. (*B*) Perfusion image of the same slice. The grey scale is from 0 to 6 ml·g^{-1}·min^{-1}. The injured region is dark due to low flow.

Perfusion

BOLD *Rest* *Activation*

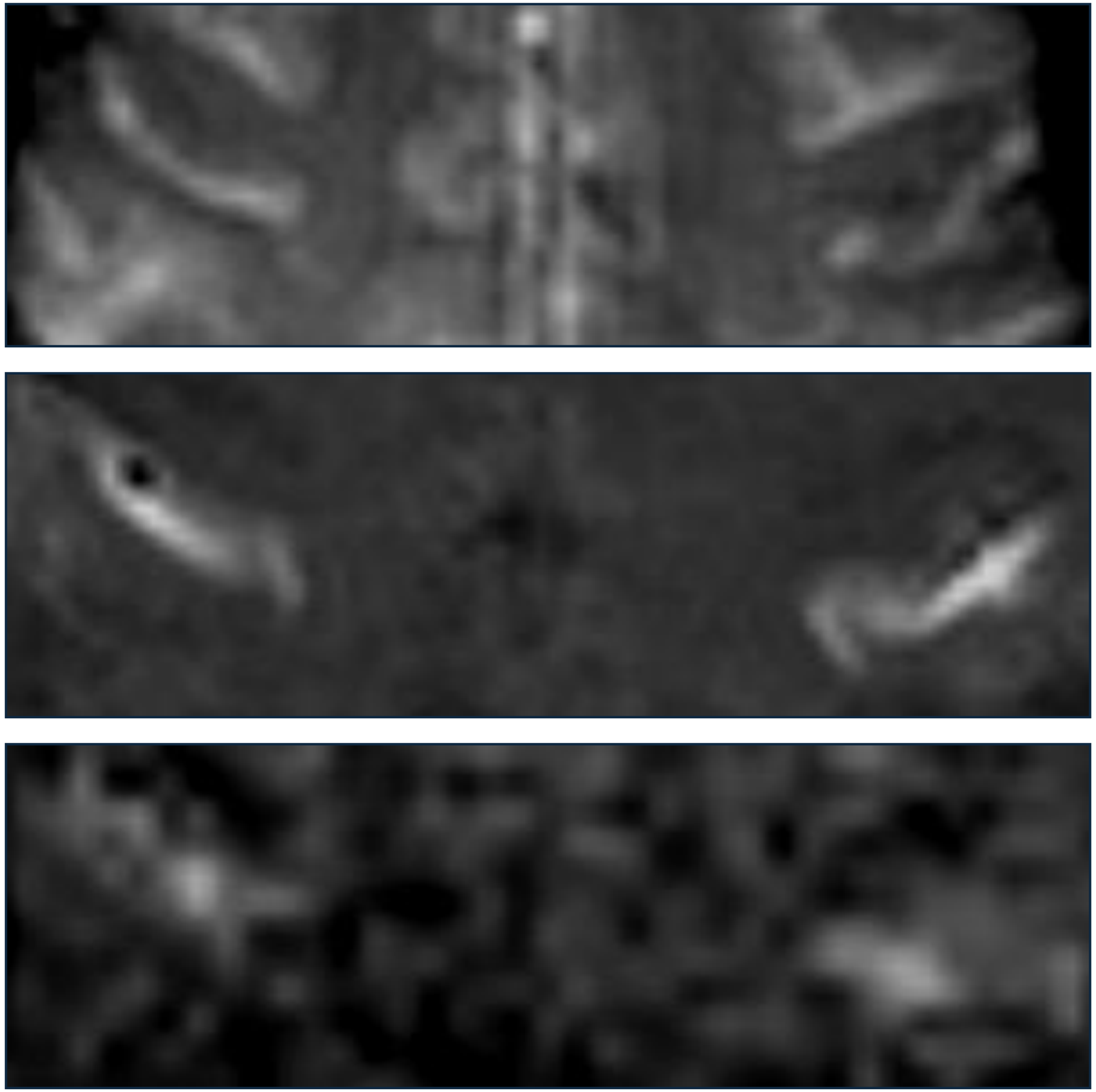


P. A. Bandettini, E. C. Wong, Magnetic resonance imaging of human brain function: principles, practicalities, and possibilities, *in* "Neurosurgery Clinics of North America: Functional Imaging" (M. Haglund, Ed.), p.345-371, W. B. Saunders Co., 1997.

Anatomy

BOLD

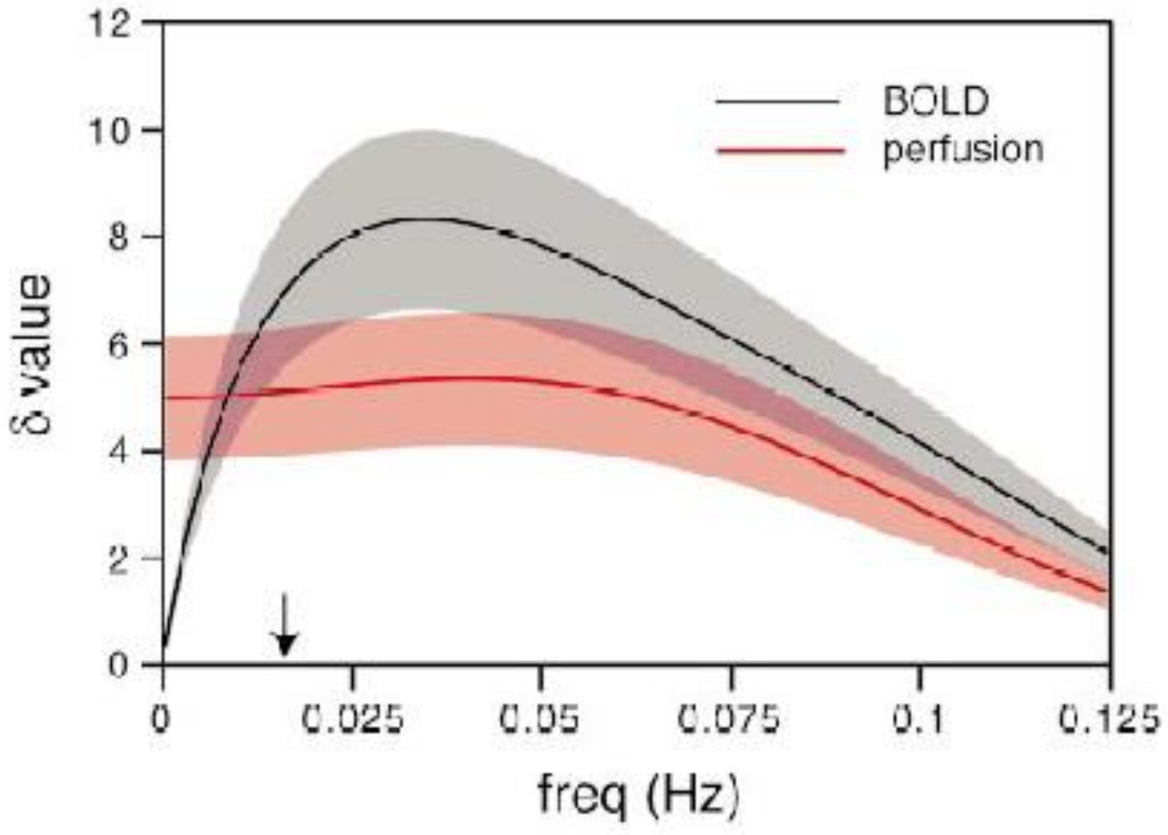
Perfusion



P. A. Bandettini, E. C. Wong, Magnetic resonance imaging of human brain function: principles, practicalities, and possibilities, *in* "Neurosurgery Clinics of North America: Functional Imaging" (M. Haglund, Ed.), p.345-371, W. B. Saunders Co., 1997.

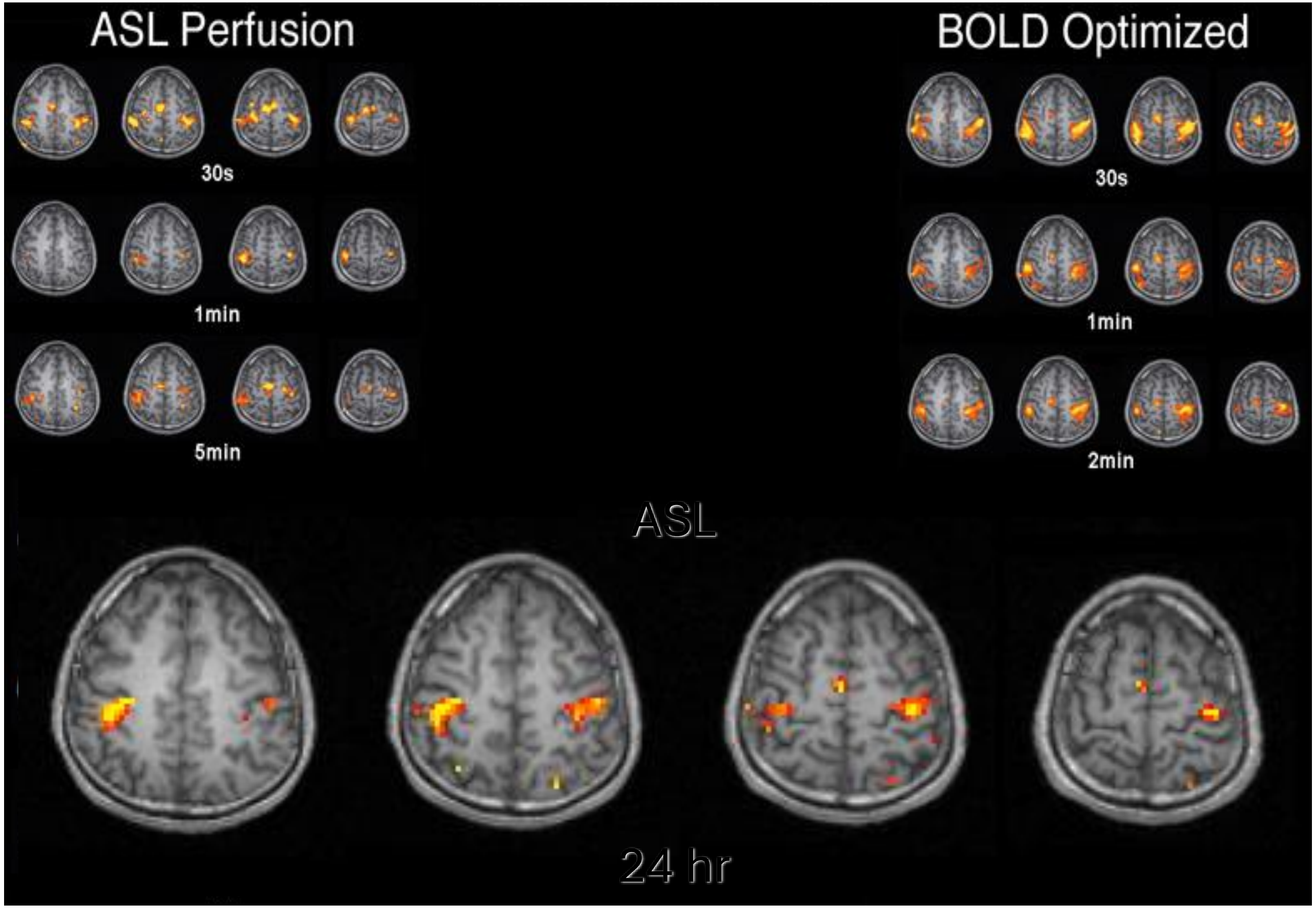
Blood Perfusion

Better than BOLD for long duration activation...



GK Aguirre et al, (2002) NeuroImage 15 (3): 488-500

Perfusion vs. BOLD: Low Task Frequency

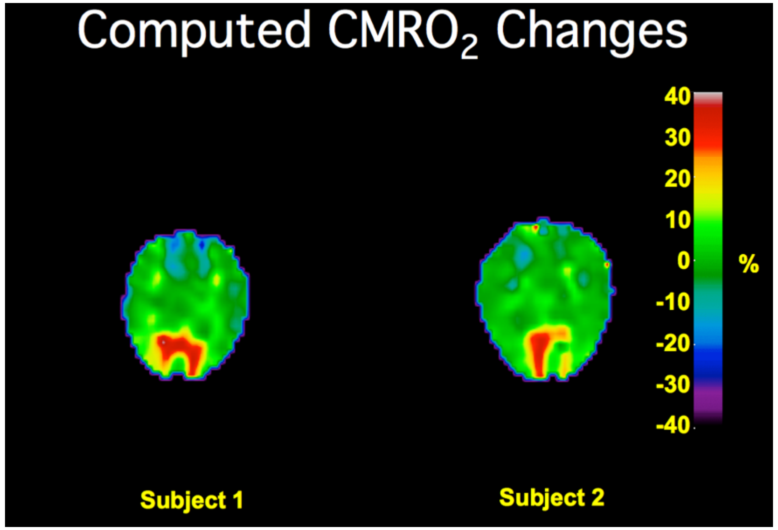


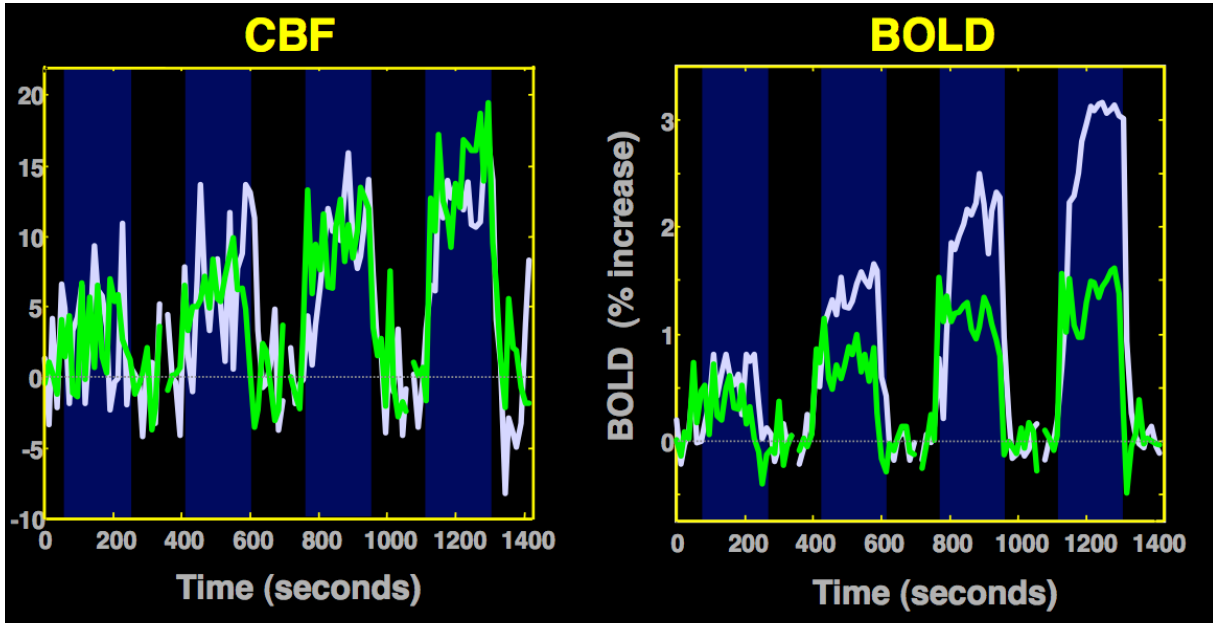
GK Aguirre et al, (2002) NeuroImage 15 (3): 488-500

Activation-induced $CMRO_2$ Changes

Basic Idea:

- BOLD during Activation < BOLD during comparable flow change with no activation (i.e. global CO_2 stress).
- The reason is the during activation $CMRO_2$ increases, pulling oxygen from blood.
- From the above difference, one can calculate activation-induced $CMRO_2$ changes.



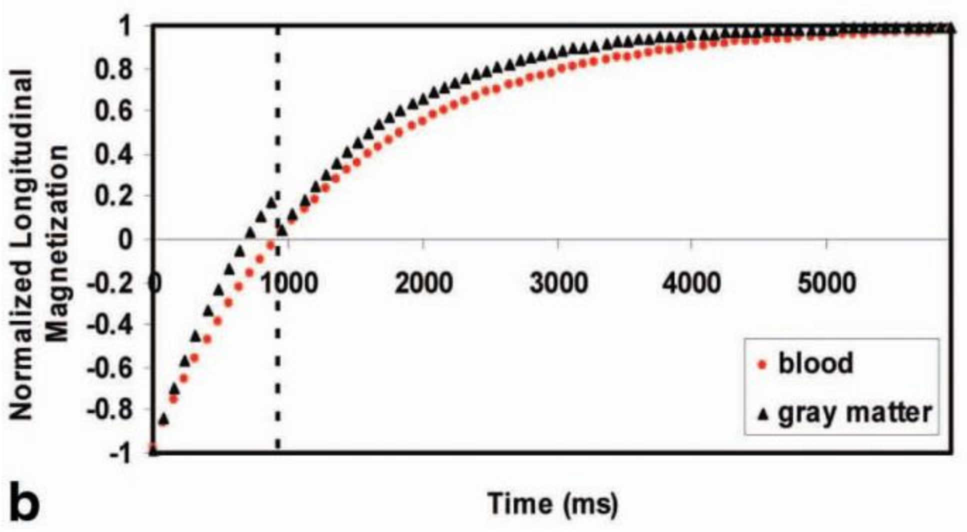


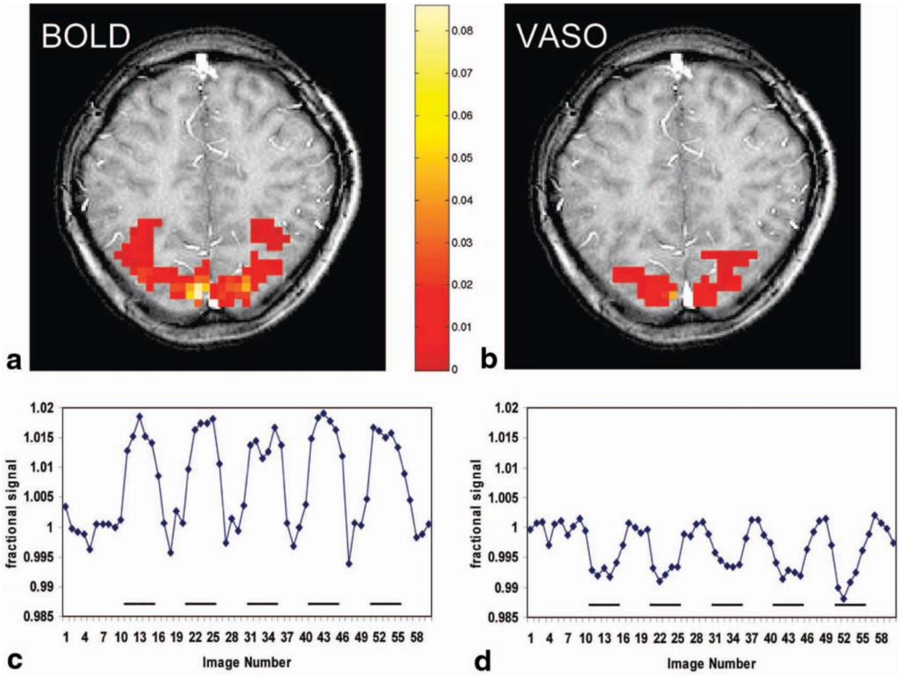
Visual Activation = green
Hypercapnia = white

R. D. Hoge, et al, PNAS 96: 9403-9408, 1999

Blood Volume Changes:
Vascular Space Occupancy “VASO” fMRI

H. Lu, et al, MRM 50: 263-274, 2003



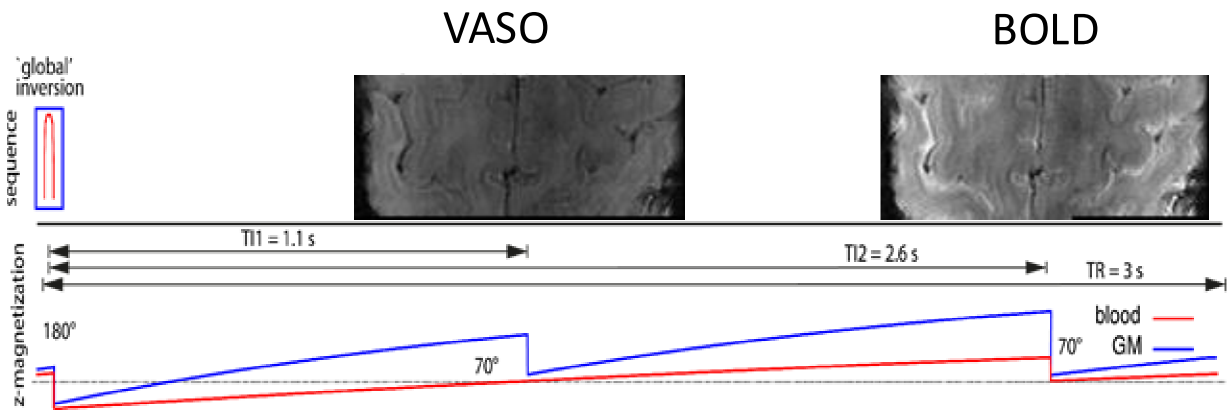


Null blood based on T1 difference between blood and tissue
..more blood -> less signal.

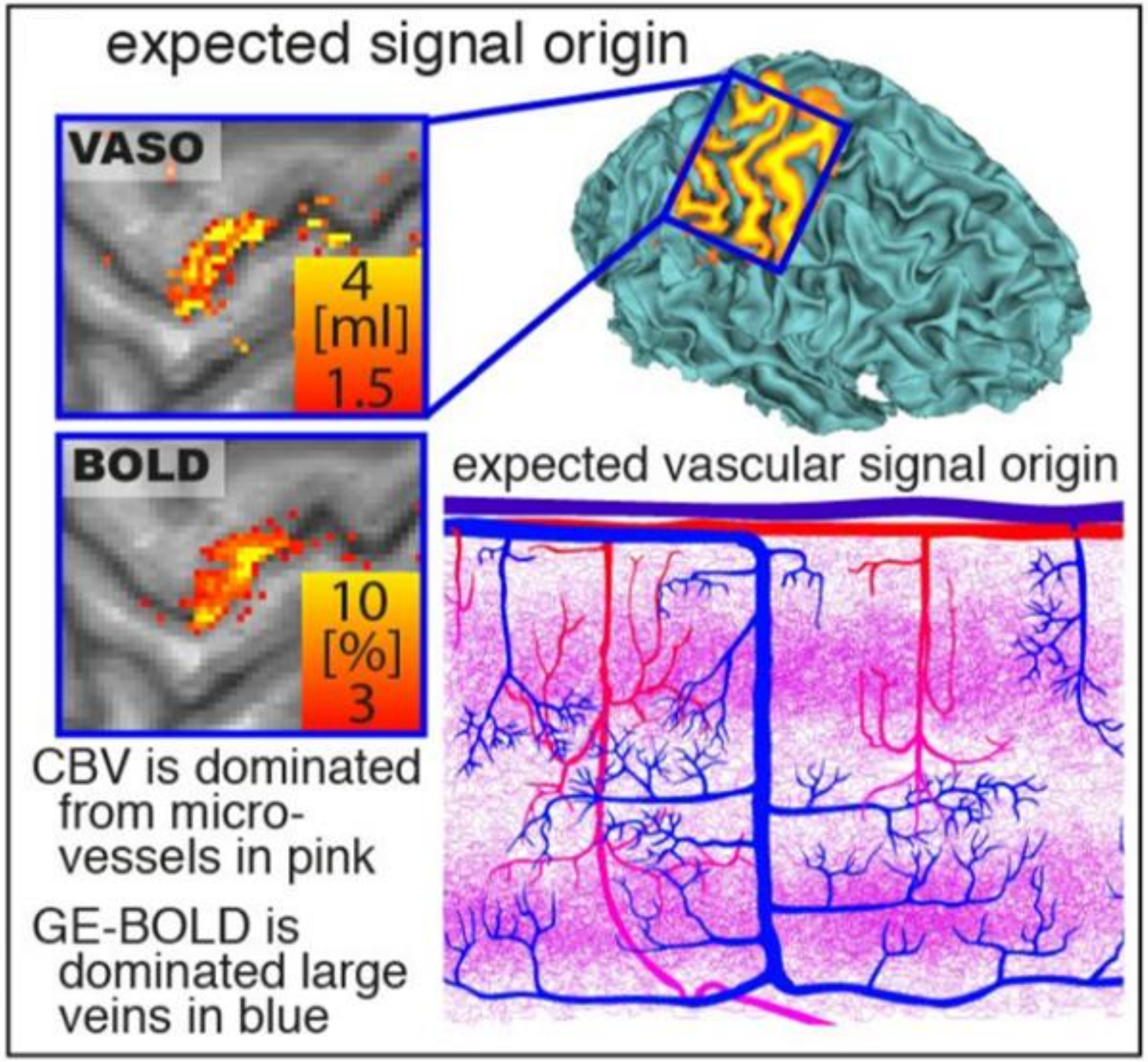
Simultaneous VASO and BOLD

VASO: Vascular space imaging (blood volume changes)
BOLD: blood oxygenation level dependent (amount of doxy-Hb)

Simultaneous VASO & BOLD:
Our primary pulse sequence for high-res fMRI:



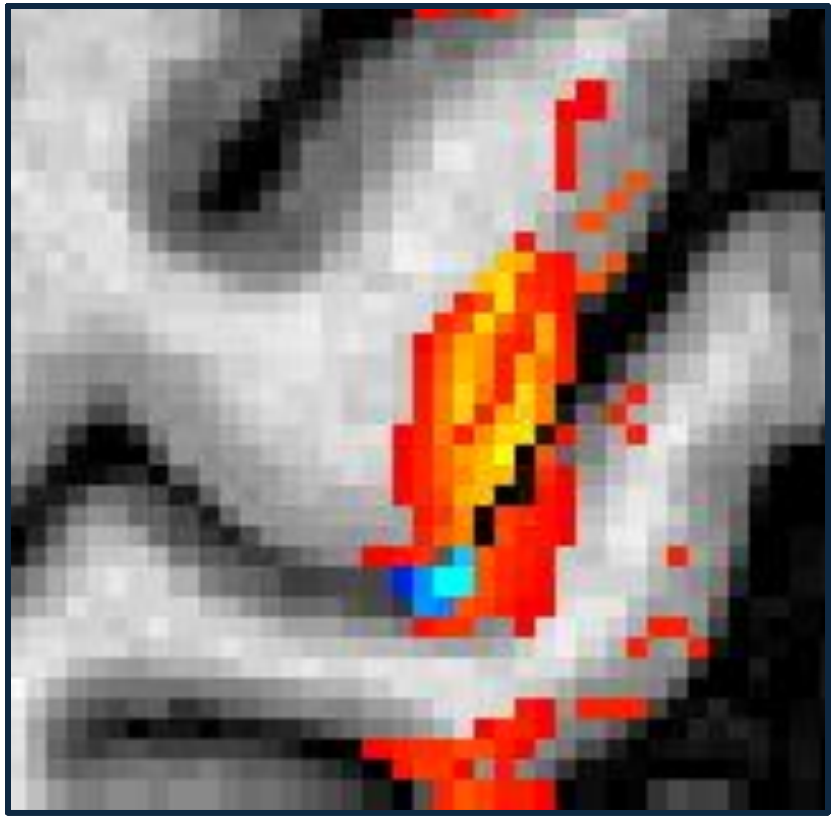
Lu et al. MRM 2003
Huber et al., MRM, 2014



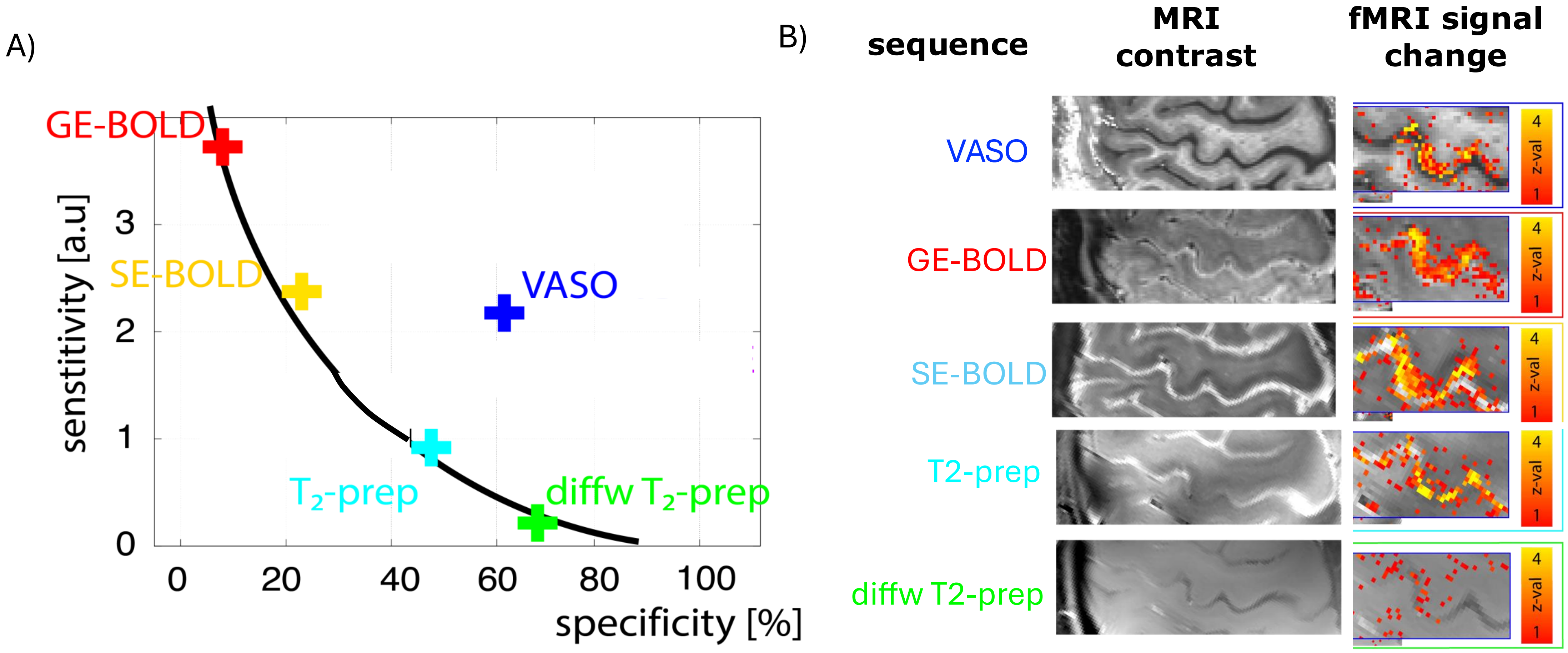
Functional Structure Changes < 0.8 mm

right tapping

resol. 0.75mm



fMRI Sensitivity vs Specificity



P.A. Bandettini, L. Huber, E. S. Finn, Current Opinion in Behavioral Sciences, 2021

What Accompanies Brain Activation?
Metabolic, Hemodynamic, and Other Measurables

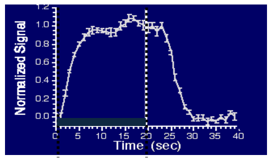
Effect	Increase	Decrease	Underlying Mechanism	Magnetic Resonance Measure	Relative Detectability
Deoxyhemoglobin		10 - 30%	Oxygen Delivery Exceeds Metabolic Need	Blood Oxygen Sensitive Dependent Contrast (BOLD)	100
CBF	30-50%		Vasodilatation & Capillary Perfusion	Arterial Spin Labelling (ASL)	25
CBV	10-15%		Dilatation & Capillary Recruitment	Vascular Space Occupancy (VASO)	25
Middle cerebral artery (MCA) flow velocity	10-15%		Global autoregulation	Phase Contrast or Inflow Sensitive MRI	10
CMRO2	10-15%		Oxidative metabolism	Ratio of change in CBF/BOLD, calibrated by global stress of change in CBF/BOLD	10
Venous Oxygen Saturation	10-15%		Decresed oxygen extraction fraction	Possible T1 change in blood & tissue (Zero-TE sequences)	8
Glucose		5-12%	Increased Glucose metabolism	1H MRS	5
Lactate	10-30%		Increased glycolysis in Astrocytes	1H MRS	5
Glutamate (excitatory neurotrasmitter)	2-5%			1H MRS	5
GABA (inhibitory neurotrasmitter)	occasionally	5-10%		1H MRS	4
Cerebral Spinal Fluid (CSF) volume	small		displacement by increase blood volume	T1-wieghting	2
Cerebral Spinal Fluid (CSF) flow	small		displacement by increase blood volume	Phase Contrast MRI, T1-weighting	2
Elasticity Change	6-10%		increased blood volume	MR Elastography	2
Na+ moves intracellularly			Action potential	Na+ fMRI	1
Aspartate		3-4%		1H-MRI	1
Creatine Kinase (CK)	30%			31P magnetization transfer MRS	1
Nicotinamide adenine dinucleotide (NAD)		reduced NAD+	electron shuttle in glycolosys	31P MRS and 1H MRS	1
Temperature	0.1 degree Celsius			MR Phase or Diffusion Coefficient	0.5
Cell Swelling	3%		Ion flux draws water into neuons	Decrease in Diffusion Coefficient	0.5
Neuronal Currents?	transient/small		Dendritic currents with spiking	MR magntude or phase	0.01?

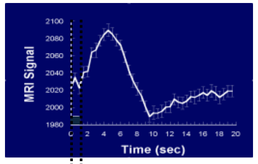
Inhibition / Excitation
Oscillations
Transient / Tonic
Spontaneous
Feedforward / Feedback

Neuronal Activity

Physiology

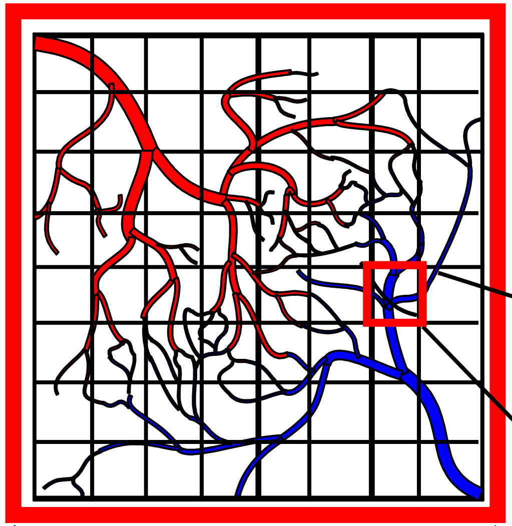
Hematocrit
Blood pH
Blood flow/perfusion
Blood Volume
Blood Oxygenation
Blood pCO_2
Blood Pressure
Neurovascular coupling
$CMRO_2$

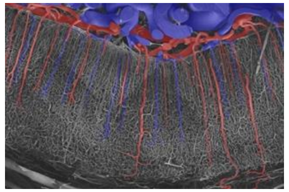




Hemodynamics

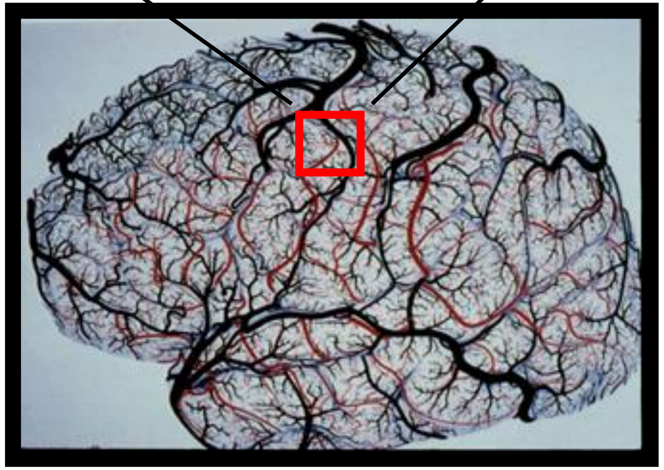
voxel





layers

regions



Gradient-echo
Spin-echo, asymmetric spin-echo
Multi-echo
Perfusion
BOLD
Diffusion gradients
Inflow weighting
Resolution Dependence
Field strength

MR Parameters

Noise

Thermal
System
Motion
Physiologic
Respiration
Cardiac

Magnitudes
Latencies
Shape
Transients
Undershoot
NMR Phase
Location

Measured Signal

ELSEVIER

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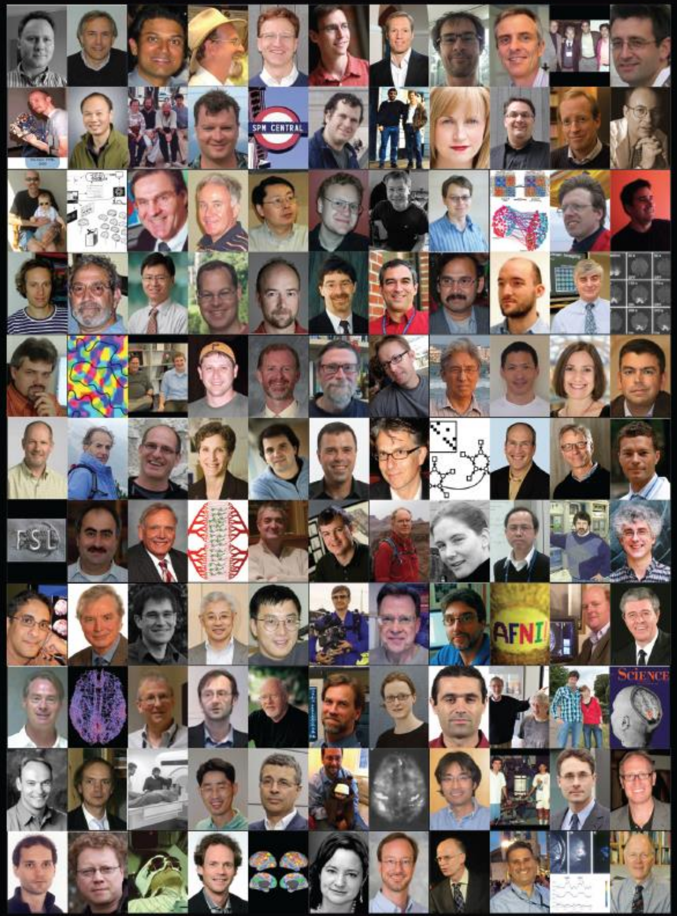
NeuroImage

Editor-in-Chief
Peter Bandettini



Special Issue

**20 Years of fMRI:
The Science
and the Stories**

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