Limits of BOLD and Beyond: Hemodynamics to Neuronal Currents

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The people who did all the work...

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Natalia Petridou

Jerzy Bodurka

Hemodynamics

-quick overview

-linearity (steady state)

-linearity (dynamic)

-baseline signal

-latency

-width

Neuronal Currents

-model

-approaches

current phantom
cell cultures
human studies

-why there is hope

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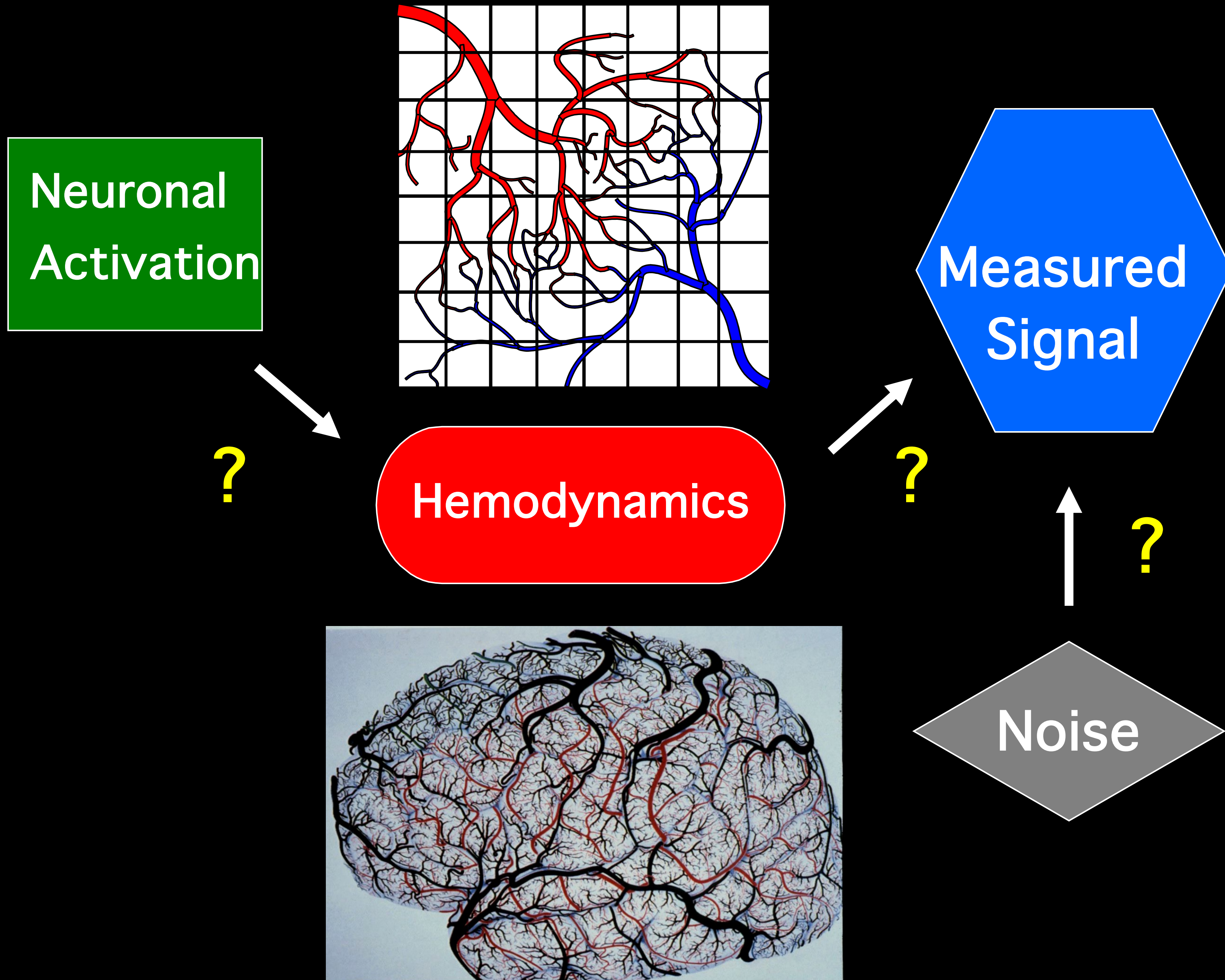
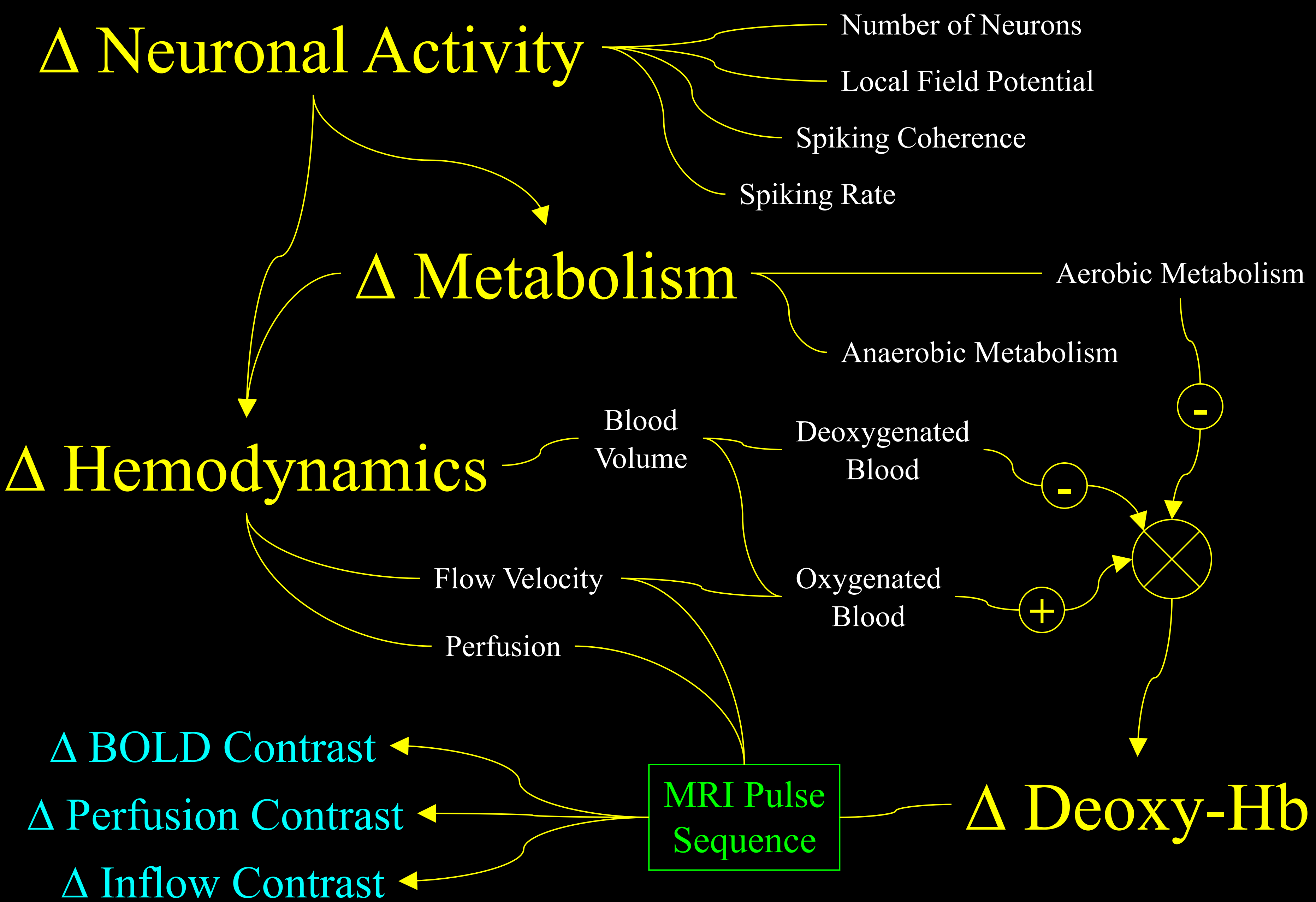
Alternating Left and Right Finger Tapping

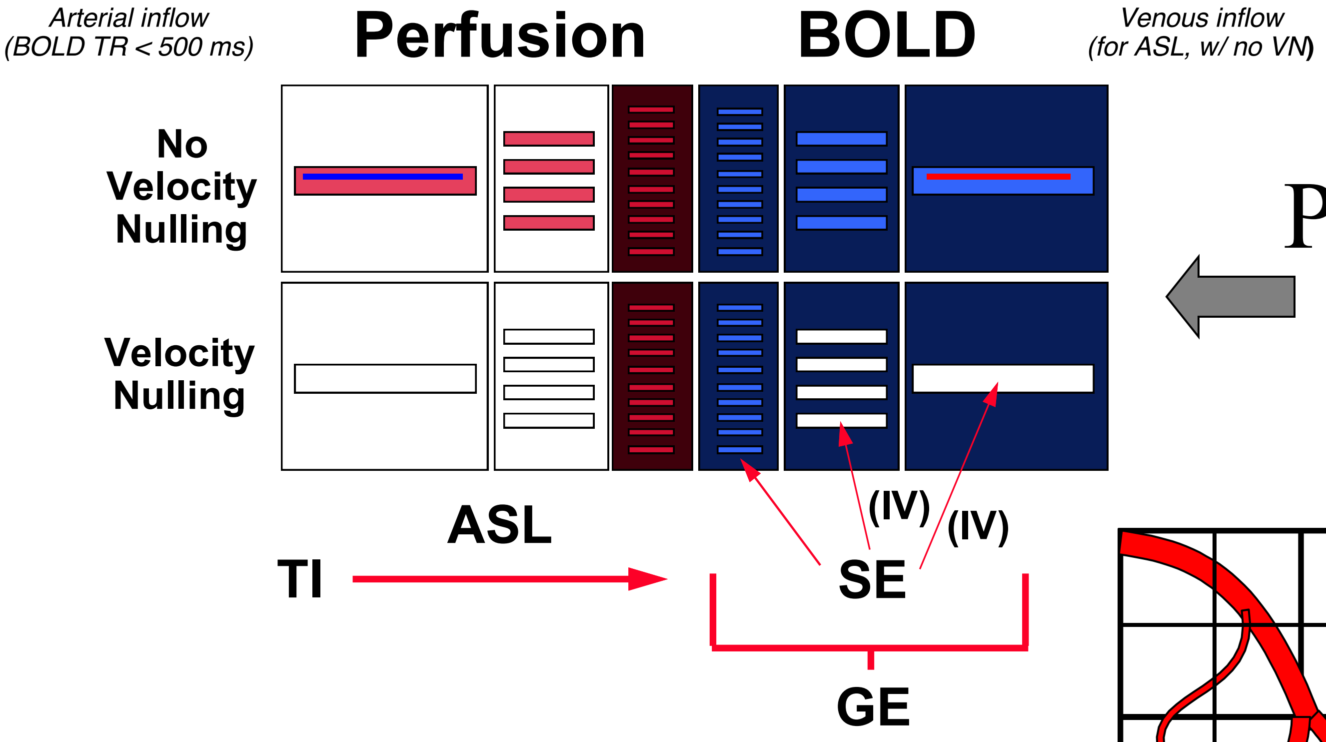
~1992


Neuronal Activation
?
Hemodynamics
?
Measured Signal
?
Noise


Δ Neuronal Activity
Number of Neurons
Local Field Potential
Spiking Coherence
Spiking Rate
Δ Metabolism
Aerobic Metabolism
Anaerobic Metabolism
Δ Hemodynamics
Blood Volume
Deoxygenated Blood
Oxygenated Blood
Flow Velocity
Perfusion
-
-
+
Δ BOLD Contrast
Δ Perfusion Contrast
Δ Inflow Contrast
MRI Pulse Sequence
Δ Deoxy-Hb

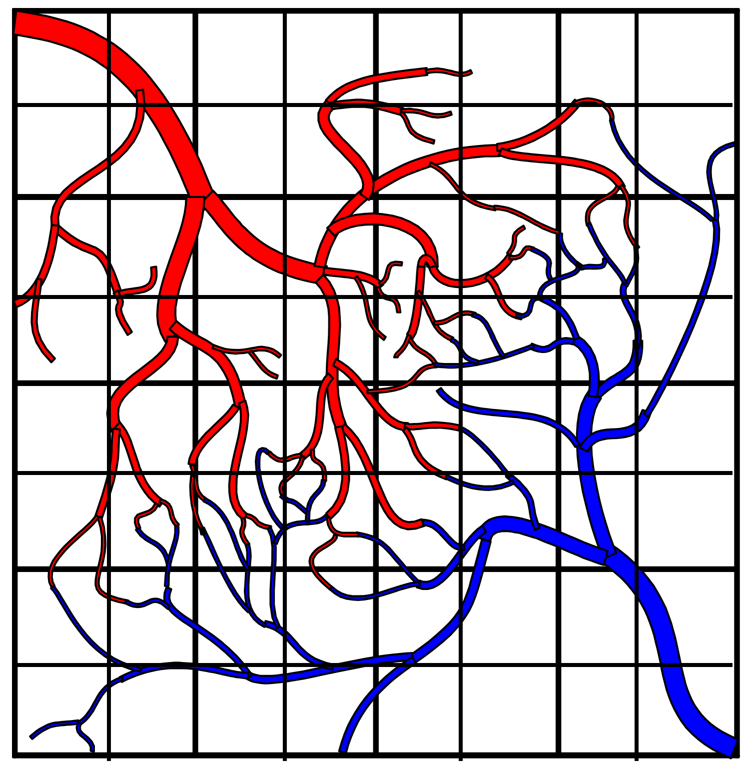
BOLD Contrast:
A Few Strategies for Better Interpretation

- Pulse sequence modulation
- Neuronal activation modulation
- Alternative measurement comparison



Pulse Sequence Sensitivity

Spatial Heterogeneity



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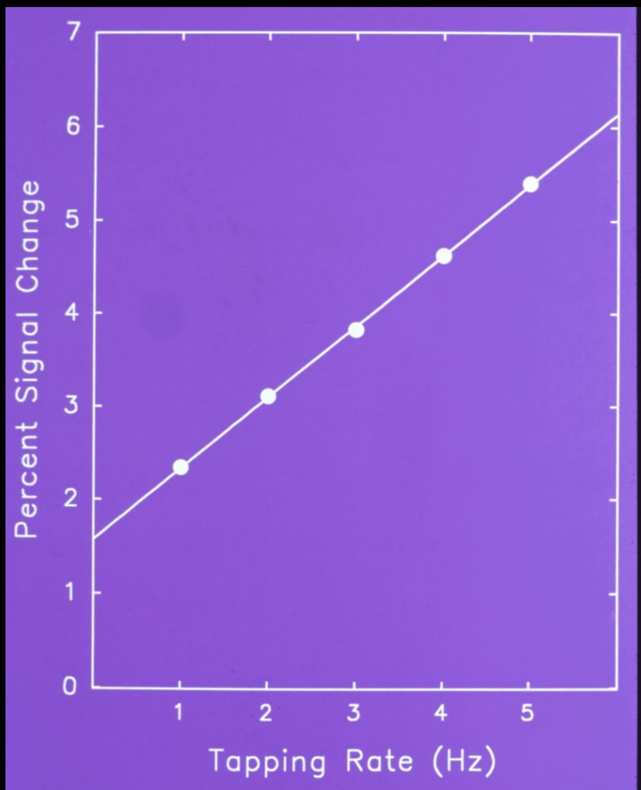
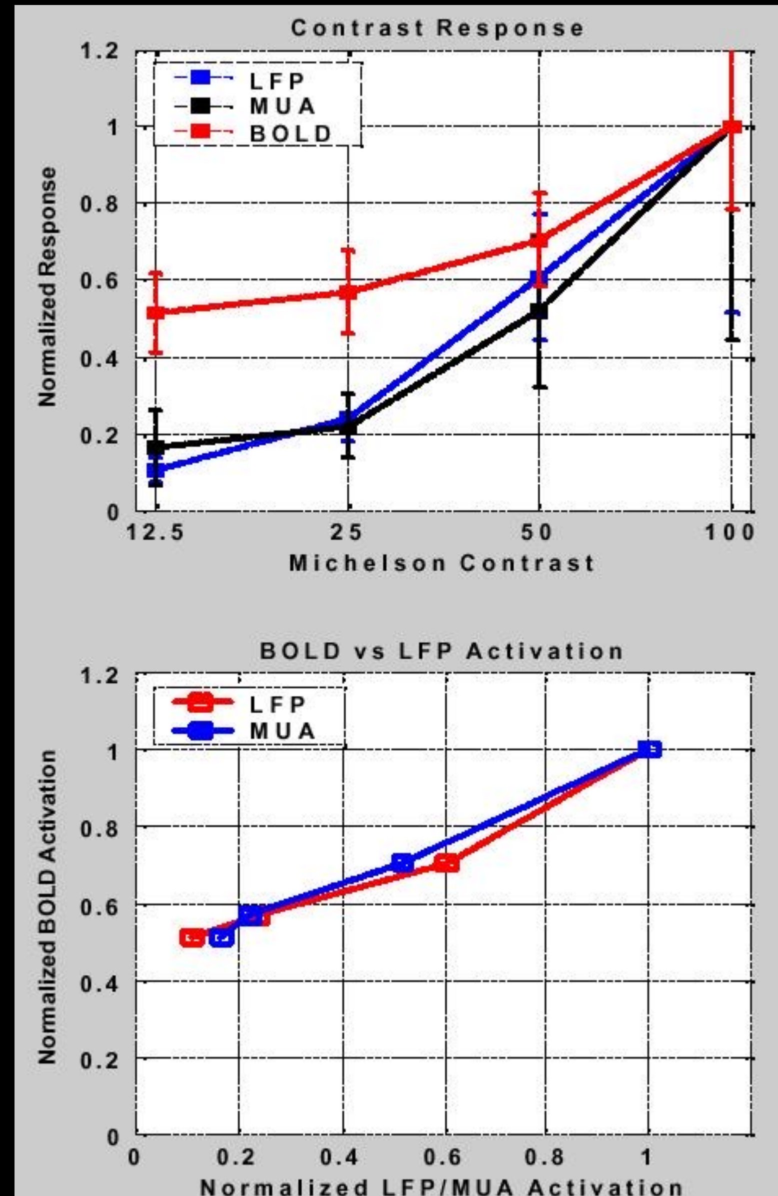


S. M. Rao et al, (1996) "Relationship between finger movement rate and functional magnetic resonance signal change in human primary motor cortex." ***J. Cereb. Blood Flow and Met.*** **16, 1250-1254.**

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



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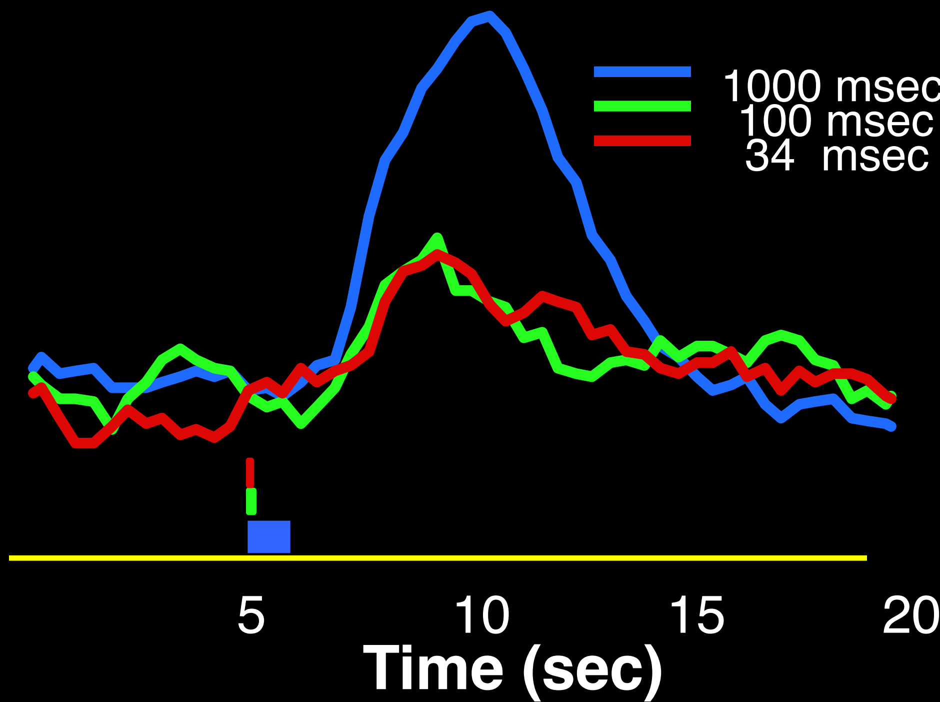
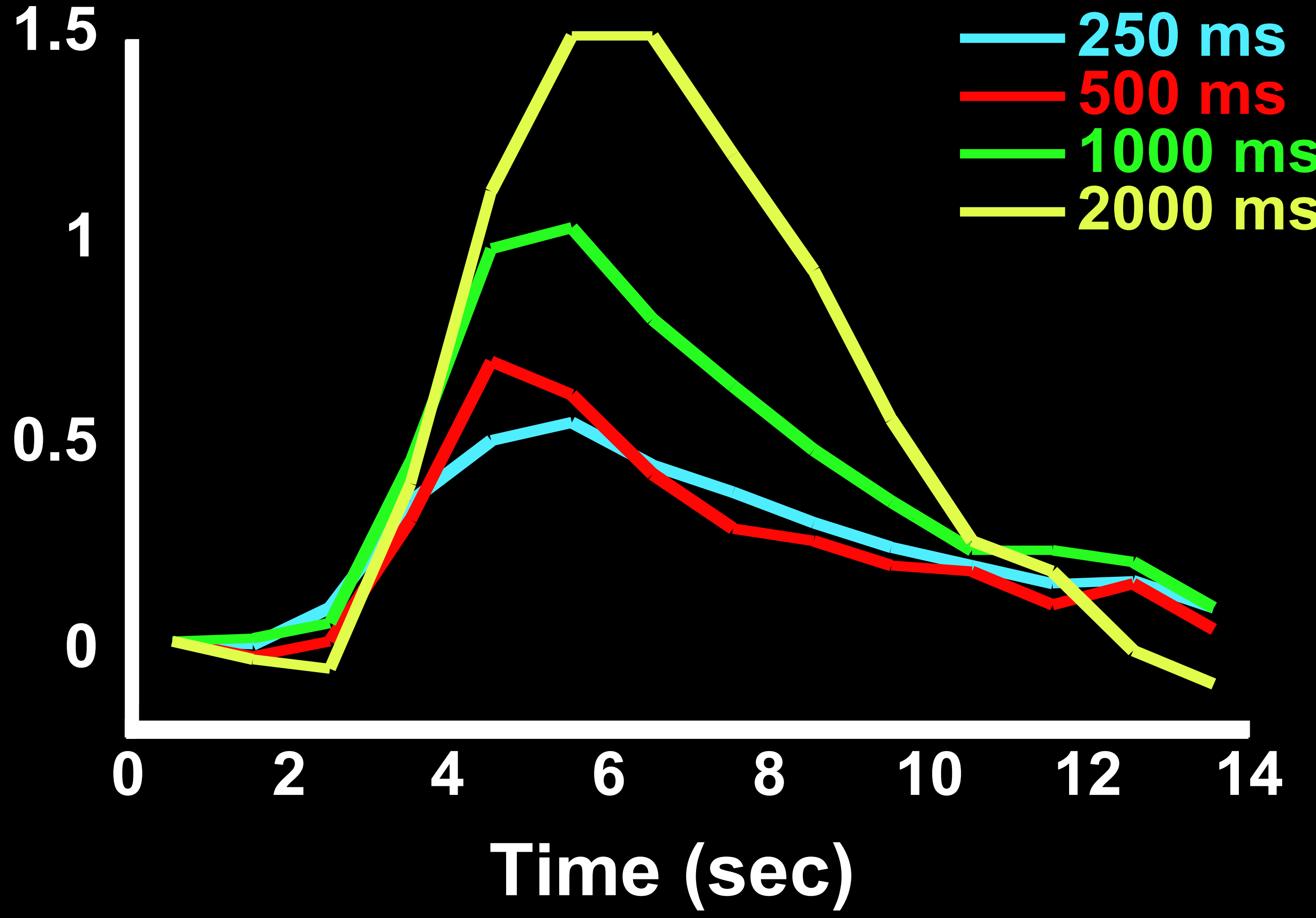
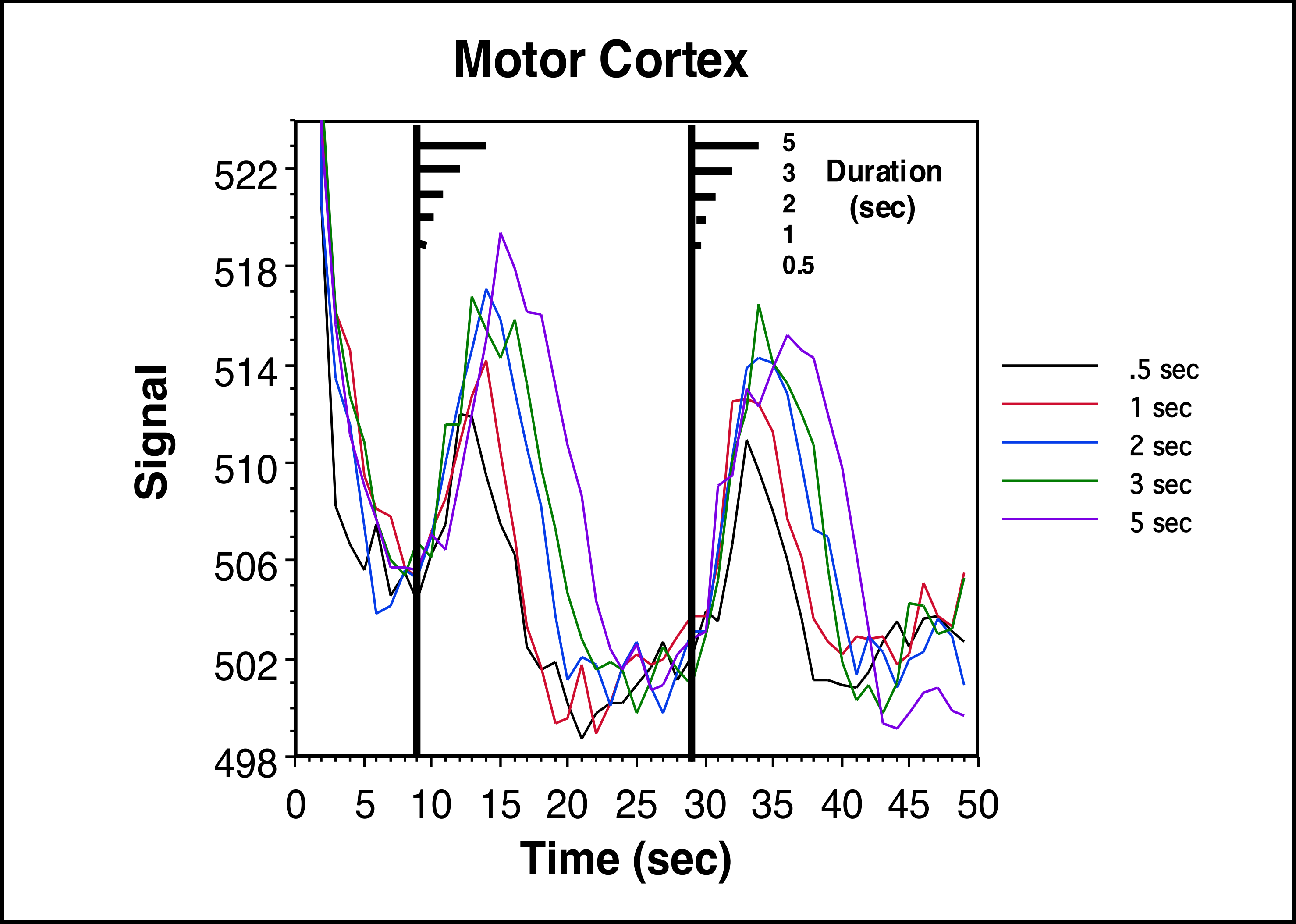


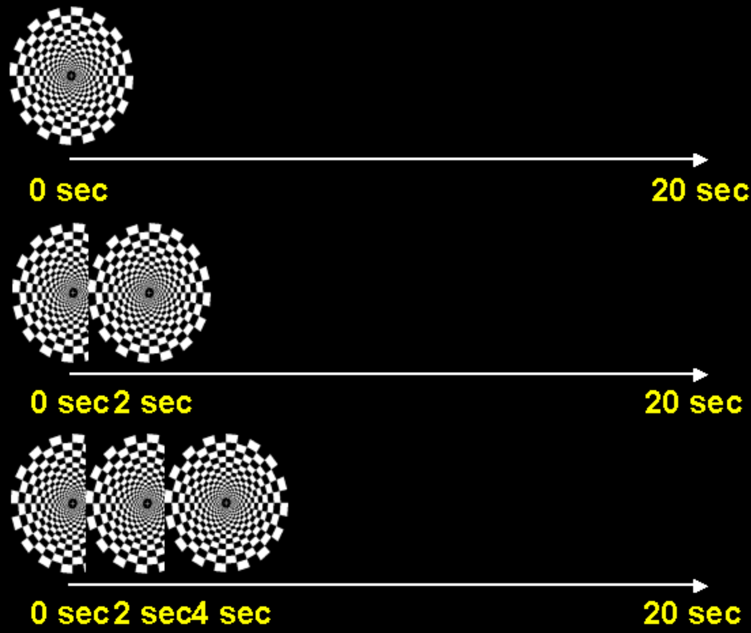
R. L. Savoy, et al., Pushing the temporal resolution of fMRI: studies of very brief visual stimuli, onset variability and asynchrony, and stimulus-correlated changes in noise [oral], 3'rd Proc. Soc. Magn. Reson., Nice, p. 450. (1995).



250 ms
500 ms
1000 ms
2000 ms
1.5
1
0.5
0
0
2
4
6
8
10
12
14
Time (sec)



Bandettini, et al., The functional dynamics of blood oxygenation level contrast in the motor cortex, 12'th Proc. Soc. Magn. Reson. Med., New York, p. 1382. (1993).

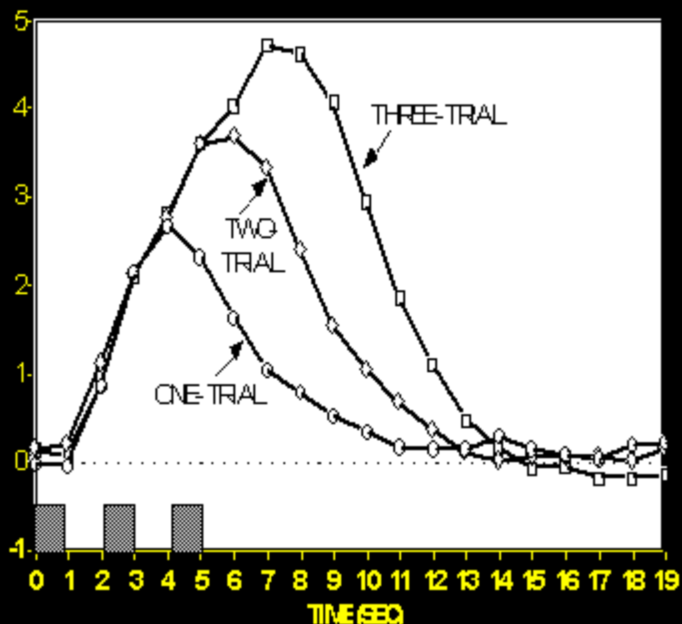


Human Brain Mapping 5:329–340(1997)

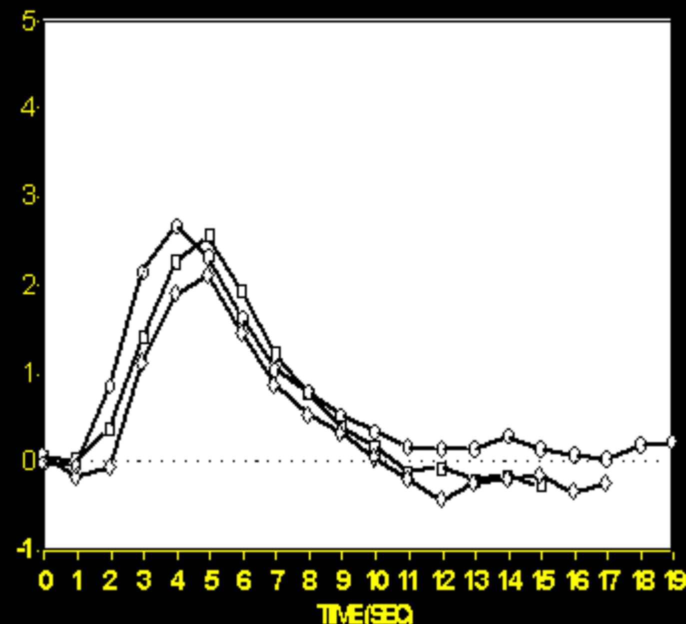
Selective Averaging of Rapidly Presented Individual Trials Using fMRI

Anders M. Dale* and Randy L. Buckner

RAW DATA

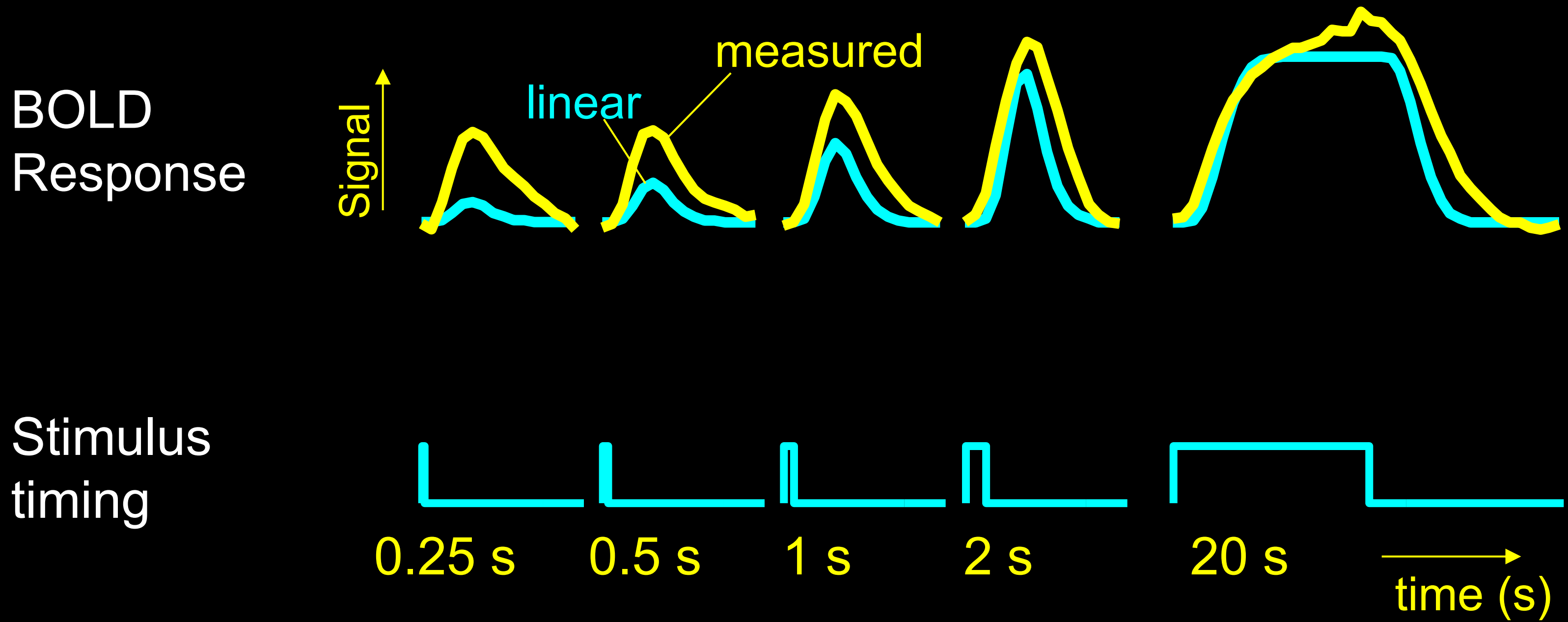


ESTIMATED RESPONSES



Dynamic Nonlinearity Assessment

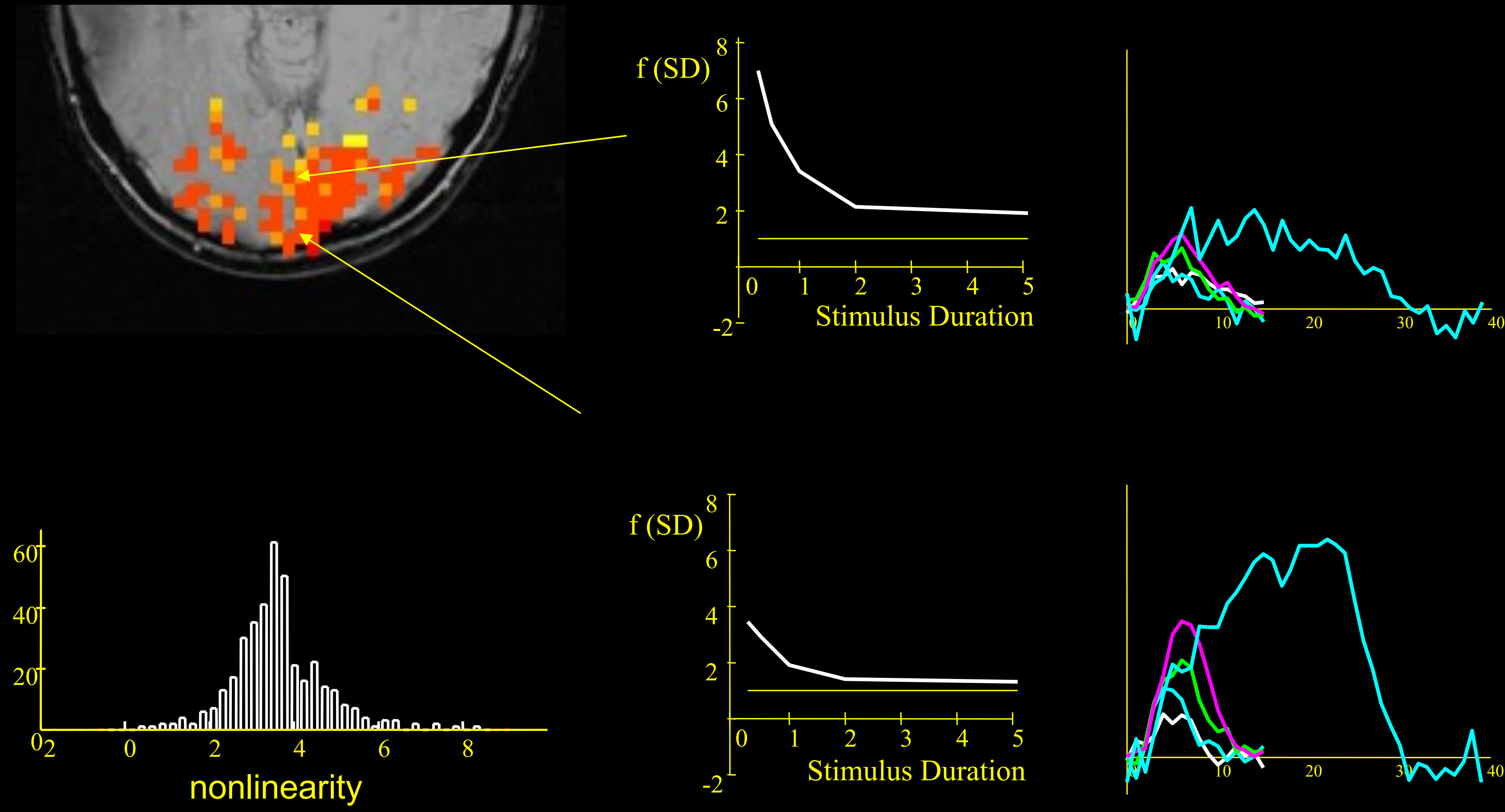
Different stimulus "ON" periods



Brief stimuli produce larger responses than expected

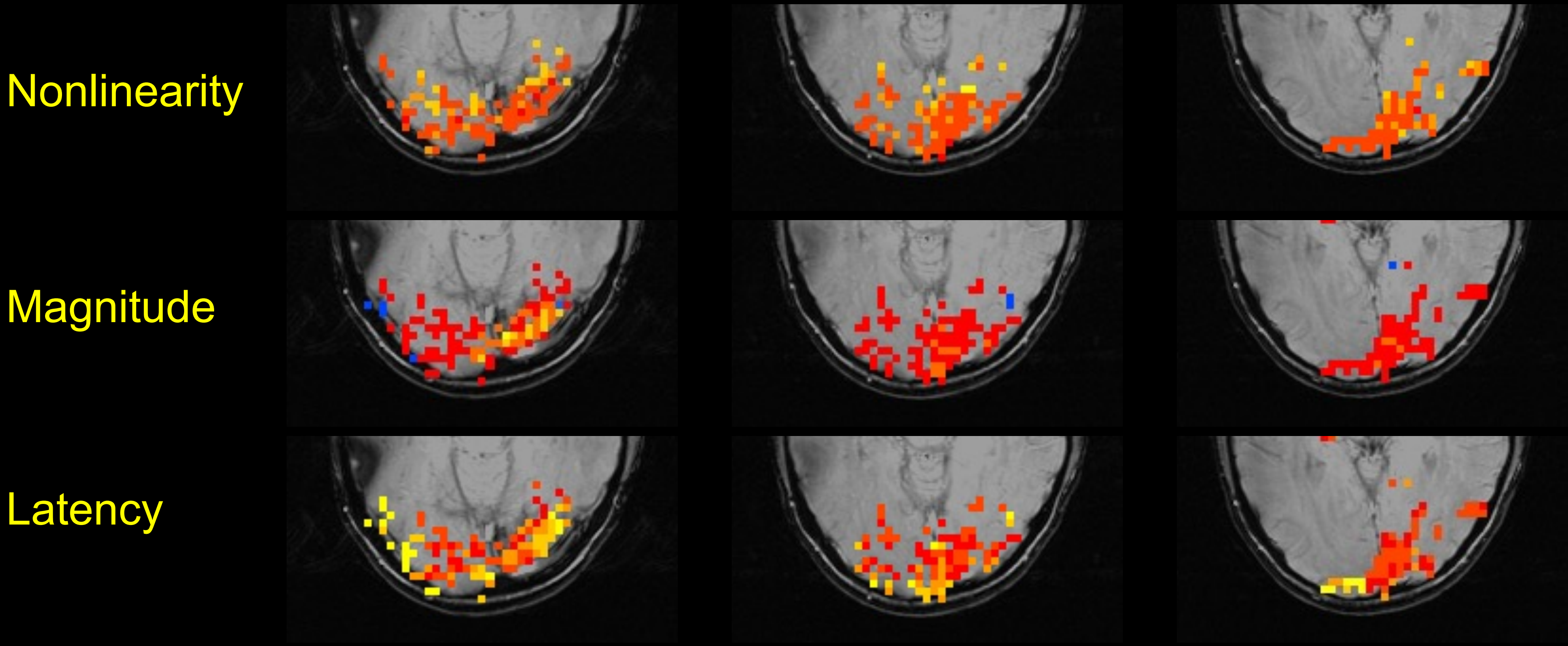
R. M. Birn, Z. Saad, P. A. Bandettini, (2001) "Spatial heterogeneity of the nonlinear dynamics in the fMRI BOLD response." ***NeuroImage*****, 14: 817-826.**

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.

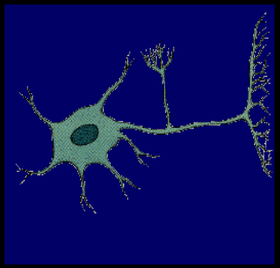
Results – visual task

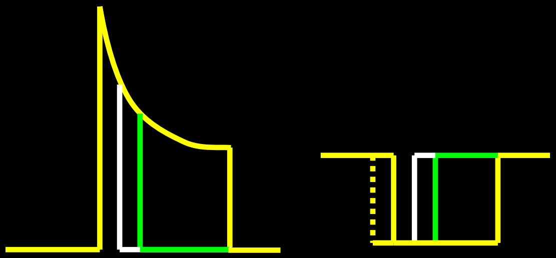


R. M. Birn, Z. Saad, P. A. Bandettini, (2001) "Spatial heterogeneity of the nonlinear dynamics in the fMRI BOLD response." ***NeuroImage*****, 14: 817-826.**

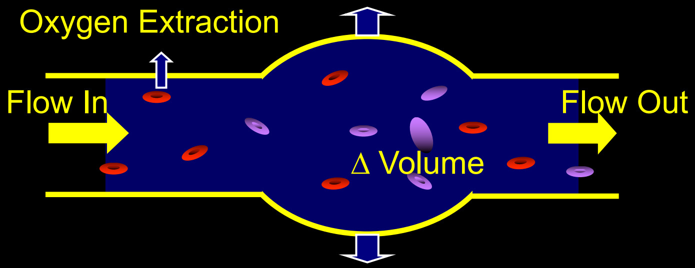
Sources of this Nonlinearity

- Neuronal



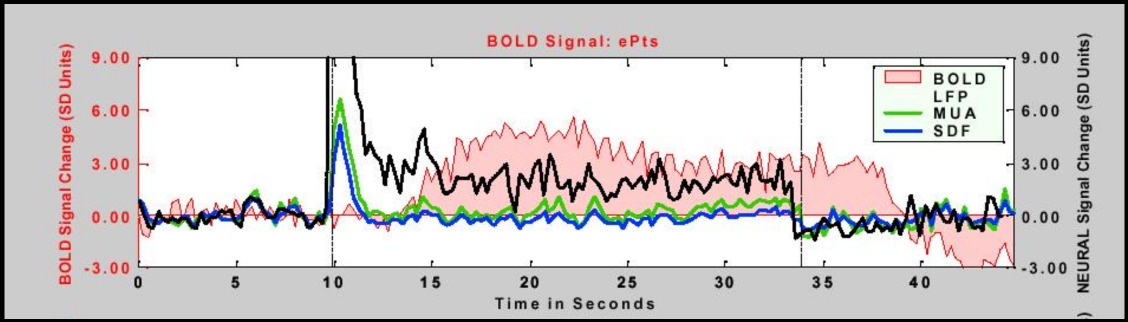


- Hemodynamic
  - Oxygen extraction
  - Blood volume dynamics

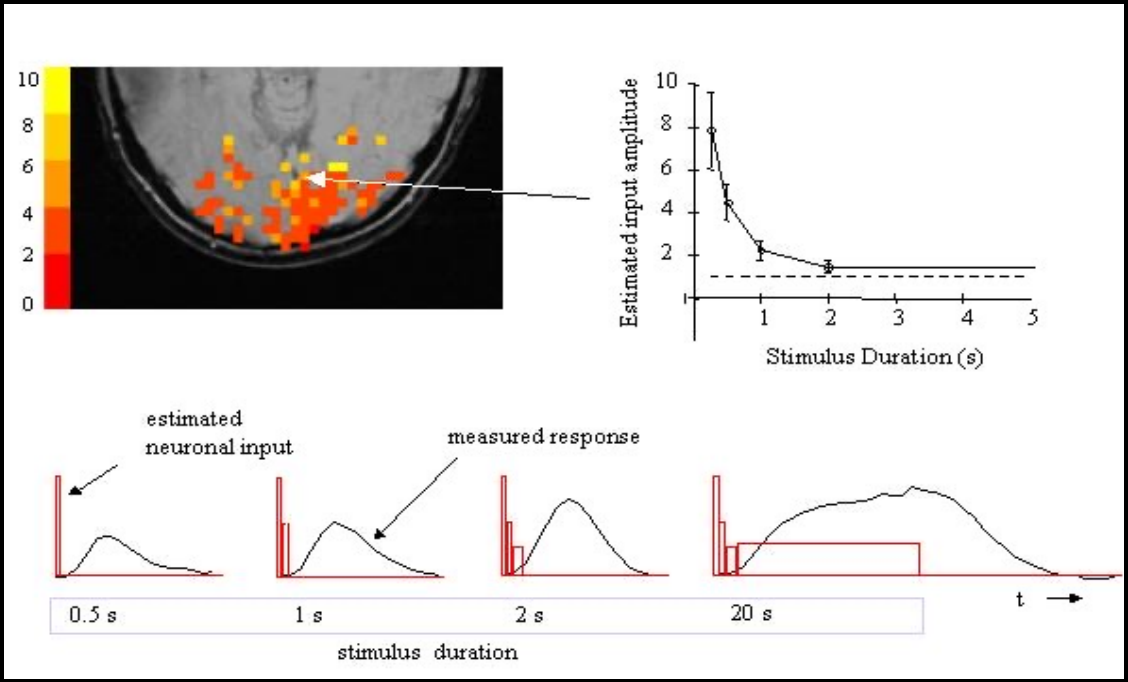


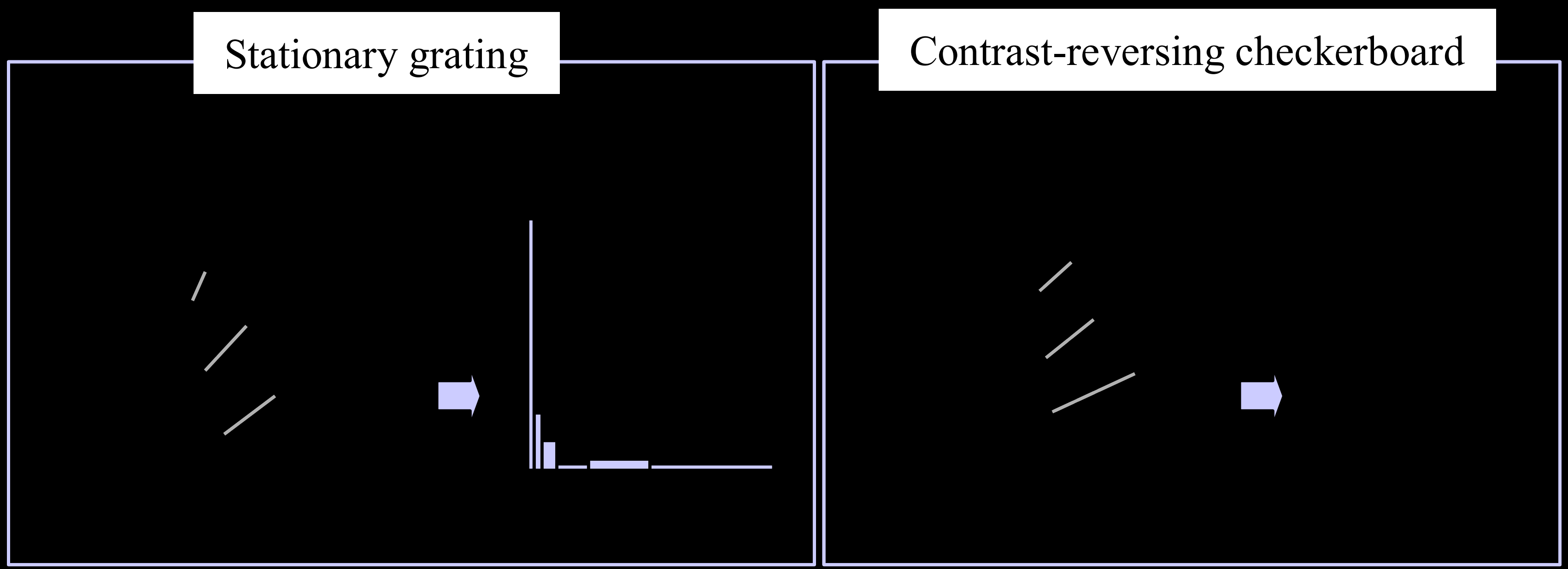
BOLD Correlation with Neuronal Activity

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

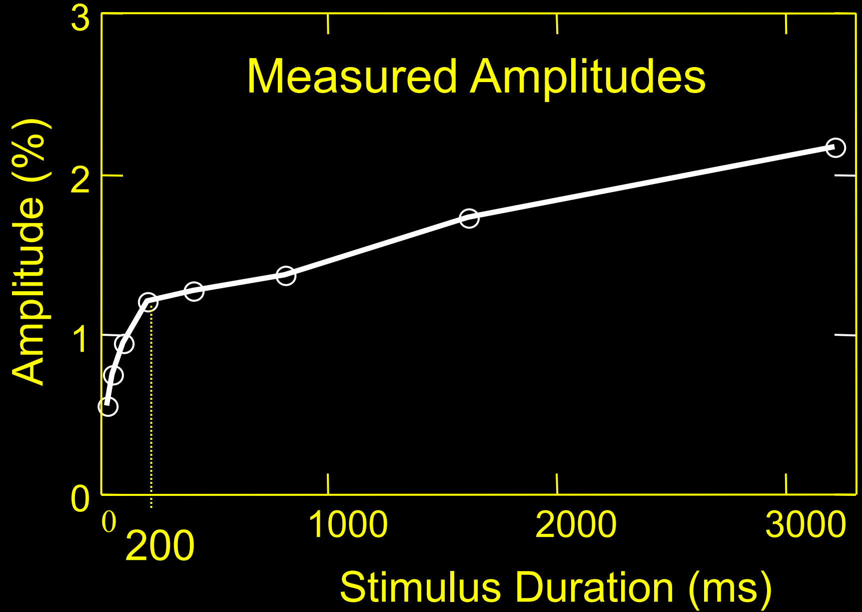


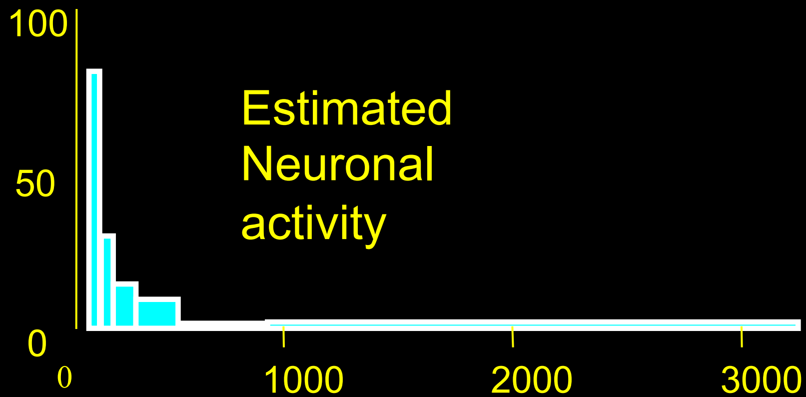
P. A. Bandettini and L. G. Ungerleider, (2001) "From neuron to BOLD: new connections." Nature Neuroscience, 4: 864-866.

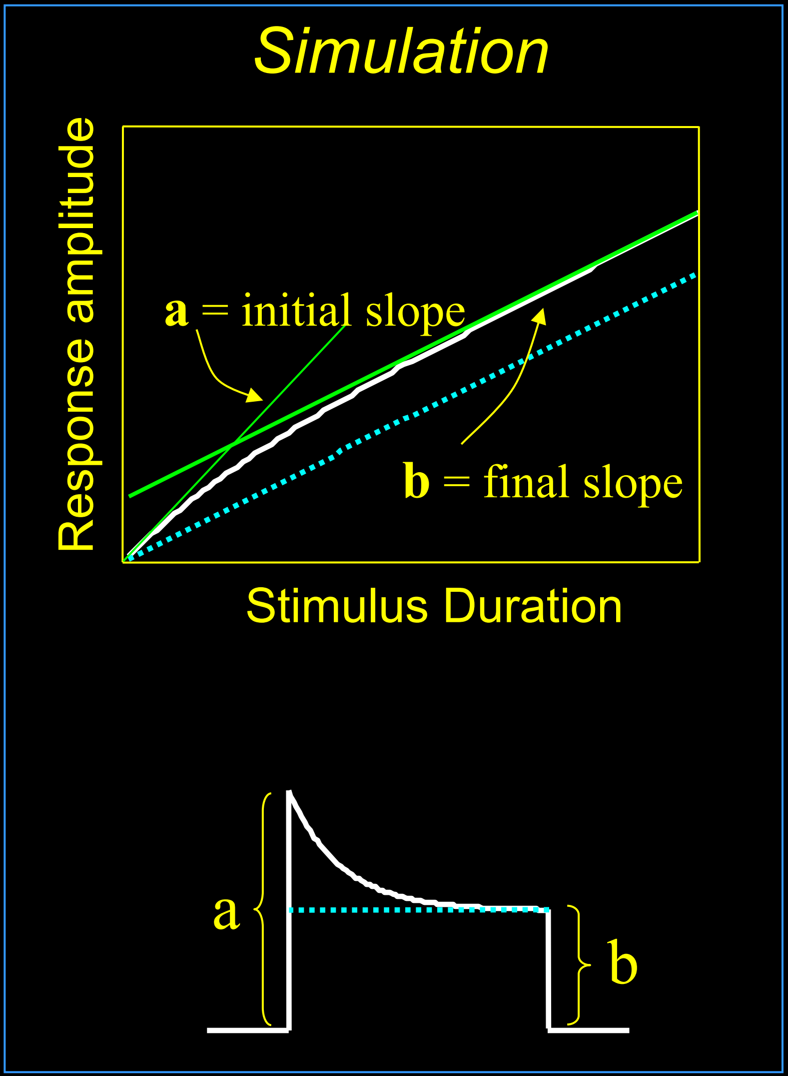



Stationary grating
Contrast-reversing checkerboard

Results – constant gratings

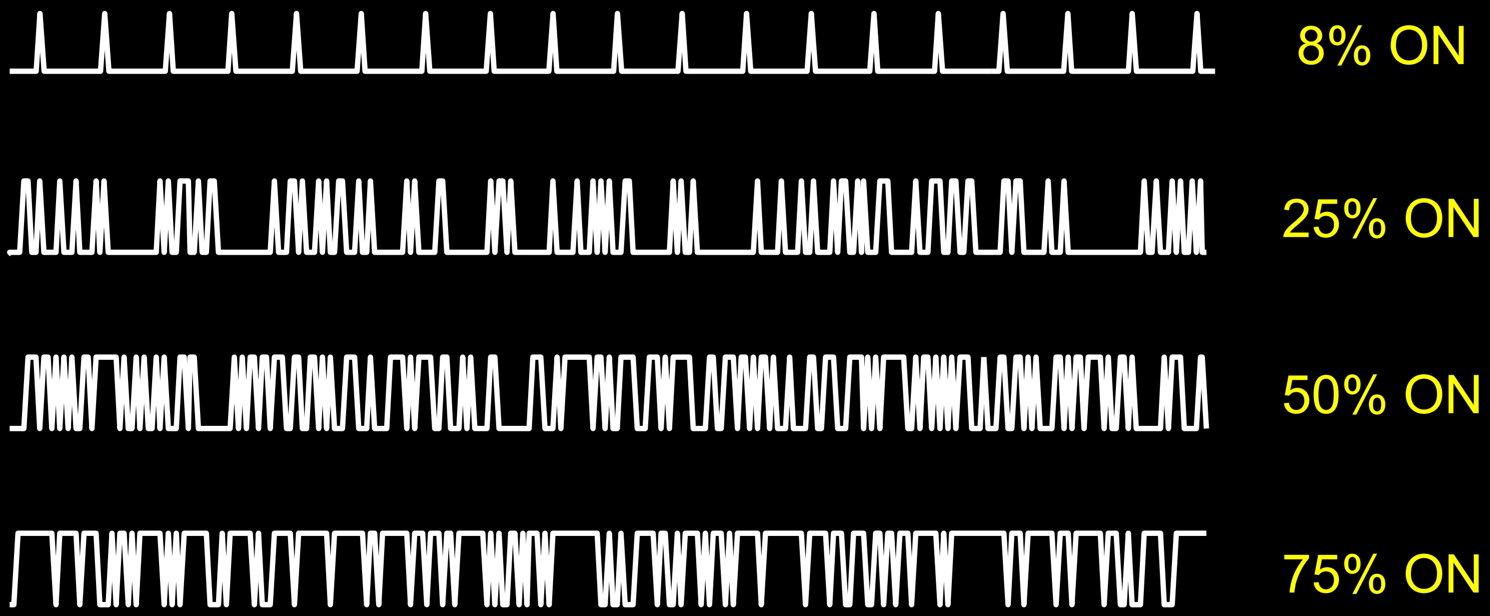






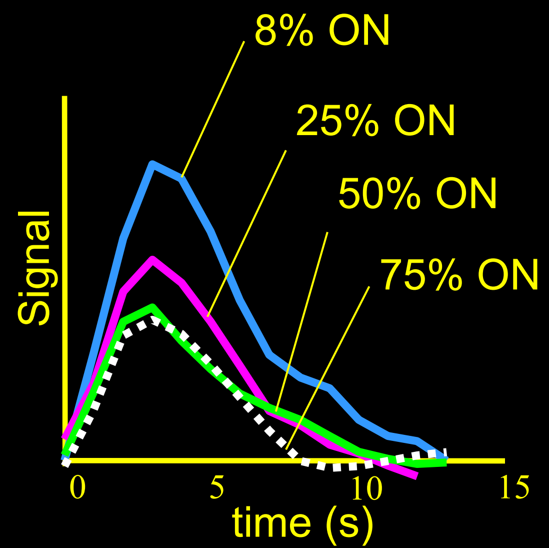
Varying "ON" and "OFF" periods

- *Rapid event-related design with varying ISI*

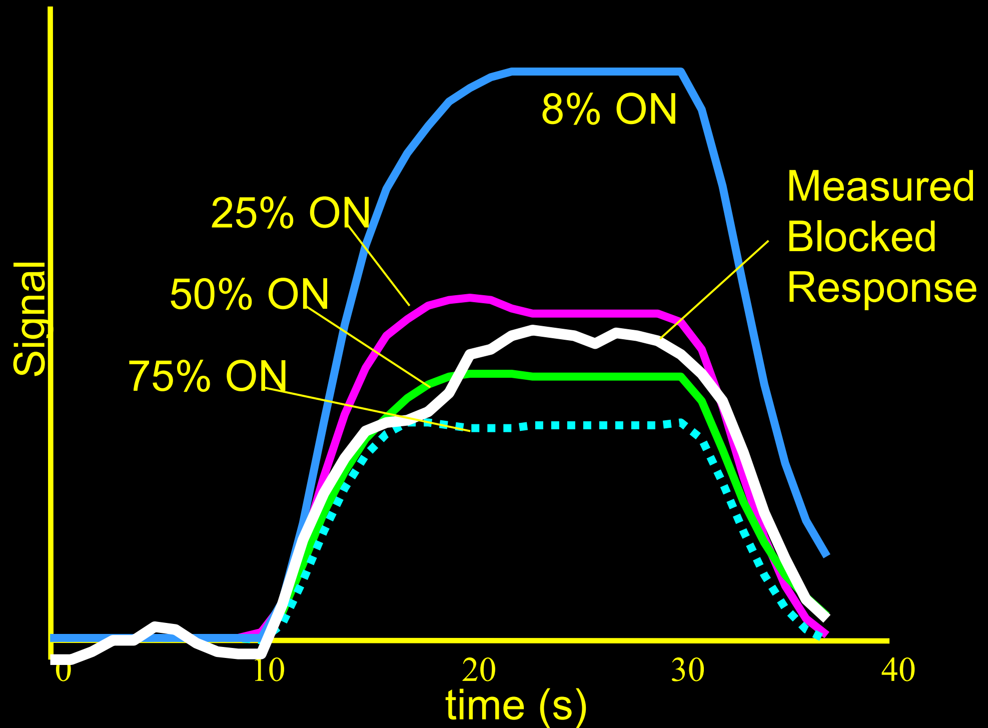


Varying "ON" and "OFF" periods

Estimated Impulse Response



Predicted Responses to 20 s stimulation



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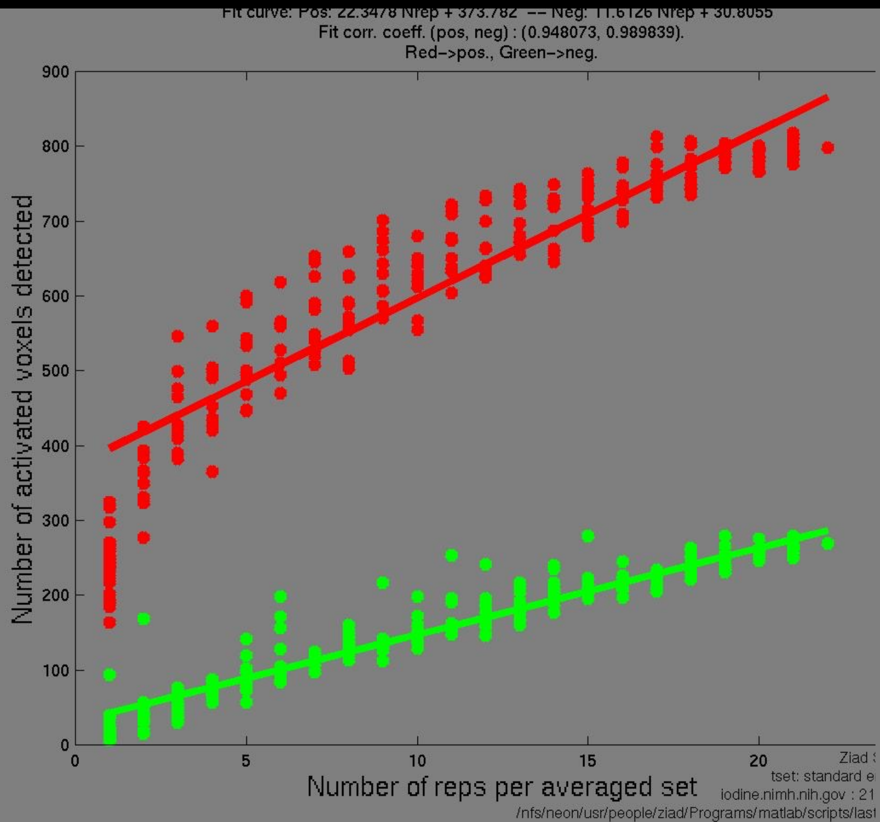
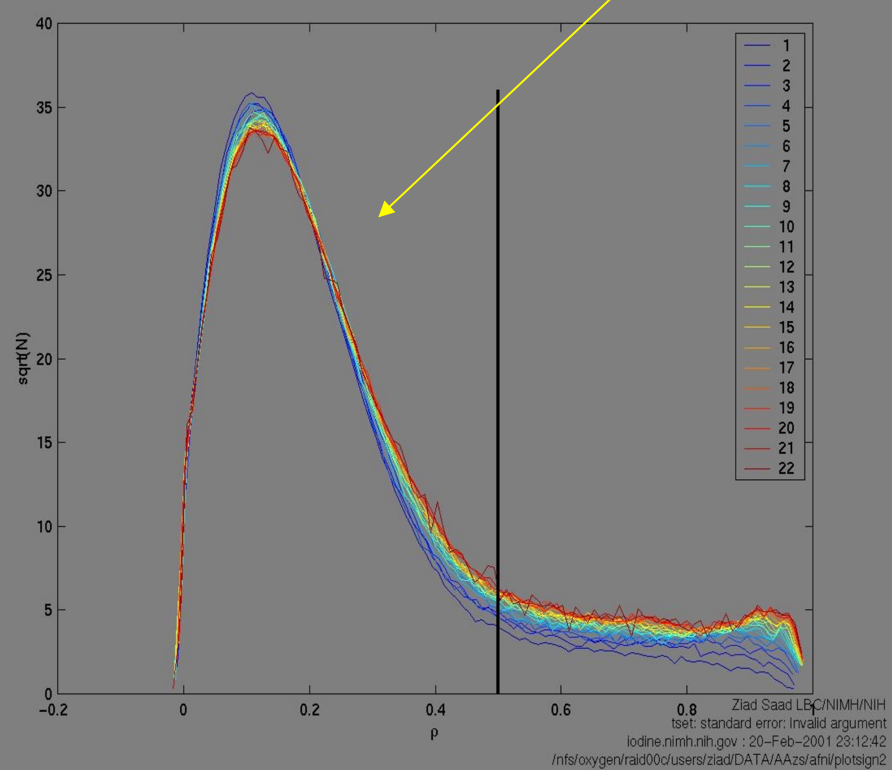
Continuously Growing Activation Area



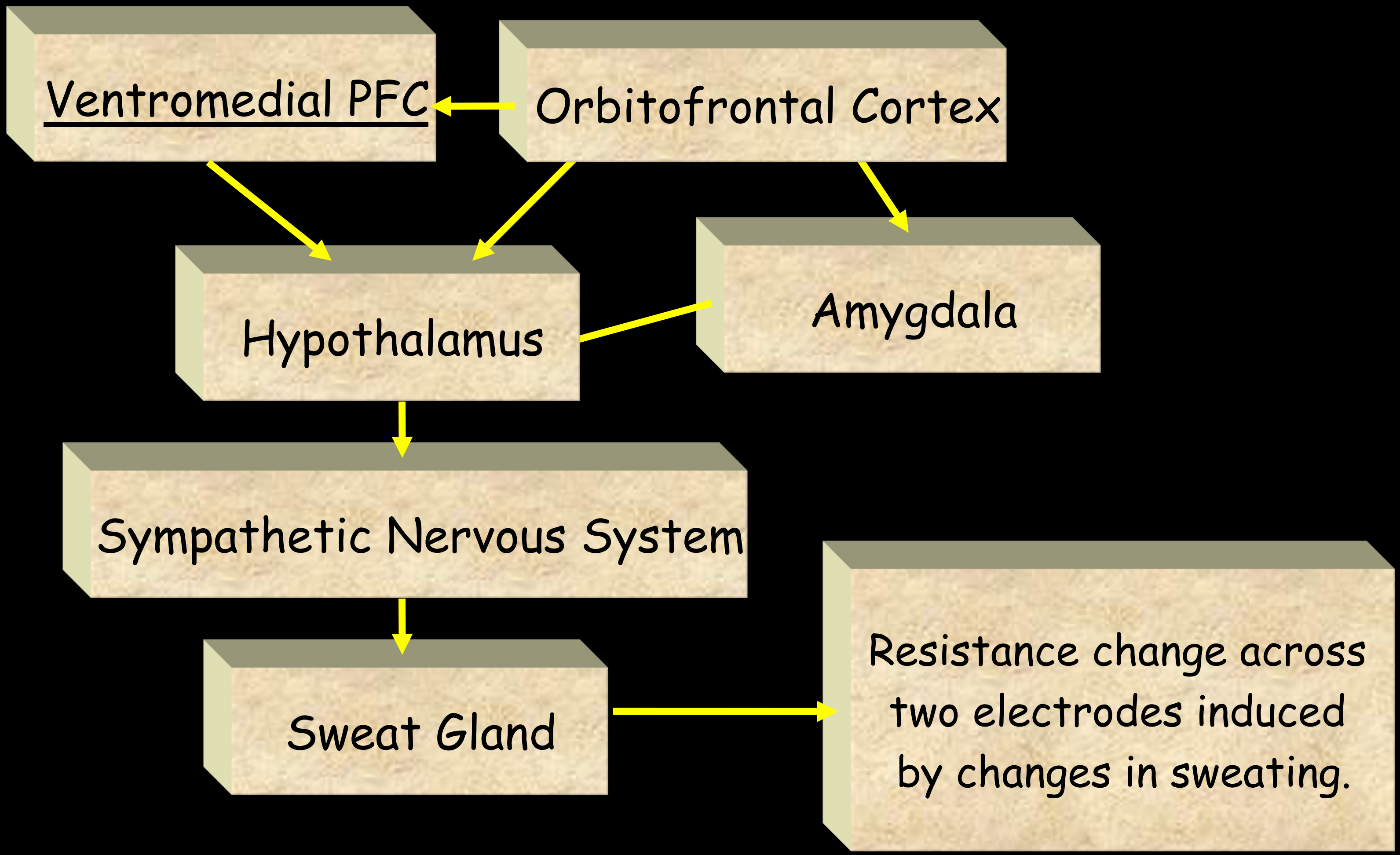
CC Histogram

Inflection Point



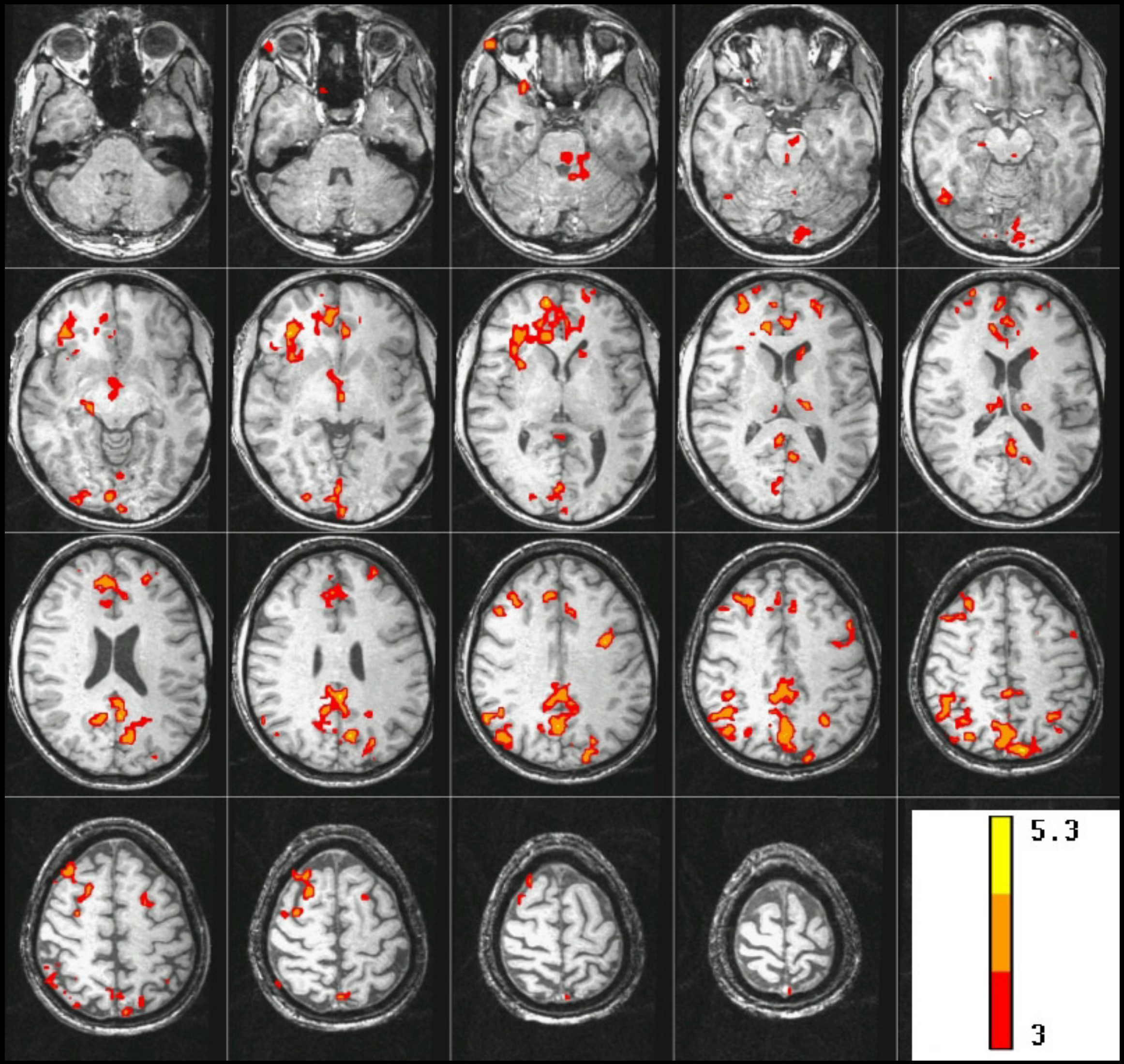
Ziad Saad, Z. S. Saad, K. M. Ropella, E. A. DeYoe, P. A. Bandettini, The spatial extent of the BOLD response. *NeuroImage, (in press).*

The Skin Conductance Response (SCR)



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).

Brain activity correlated with SCR during “Rest”



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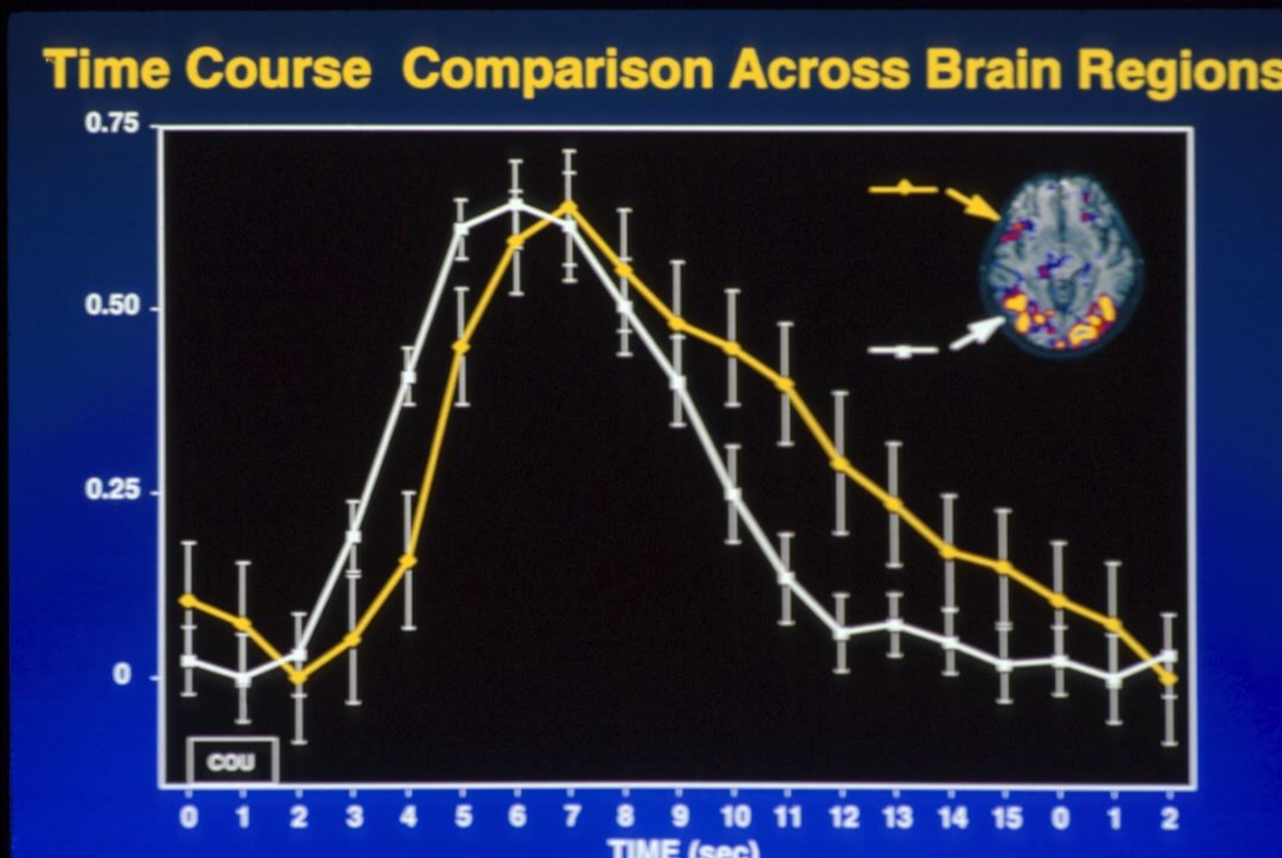
  - *current phantom*
  - *cell cultures*
  - *human studies*
- -why there is hope

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

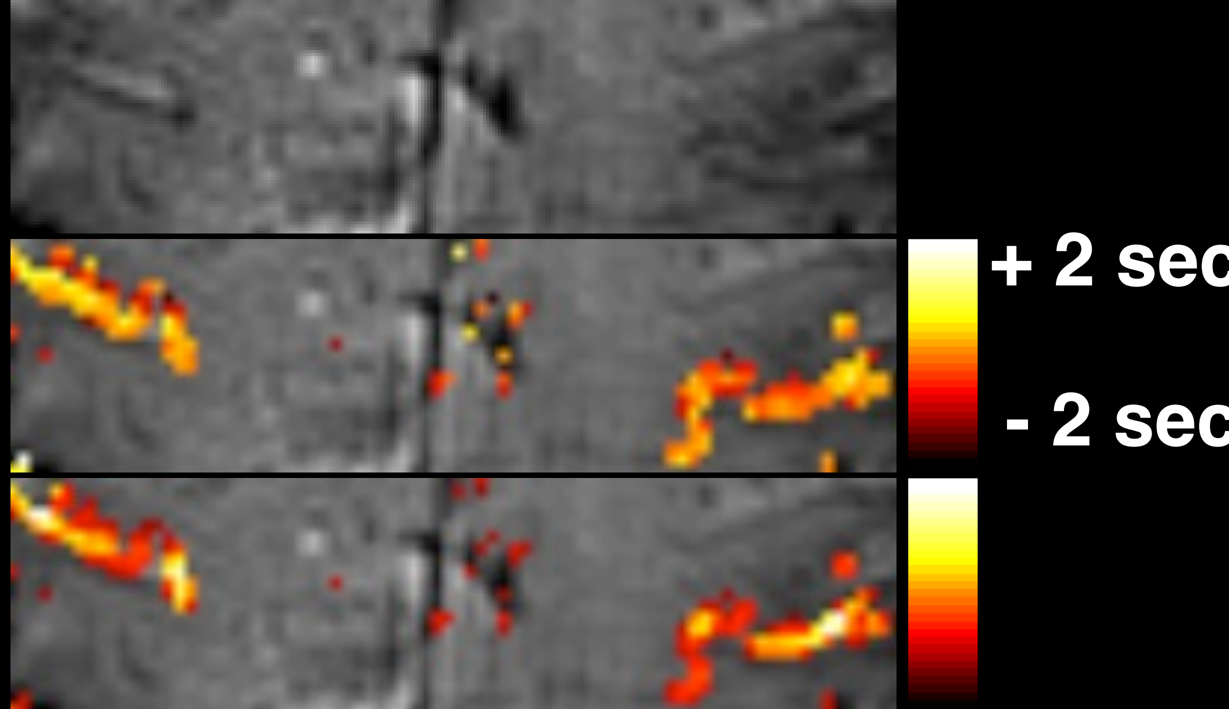
(neuroimaging/single trial/language/prefrontal)

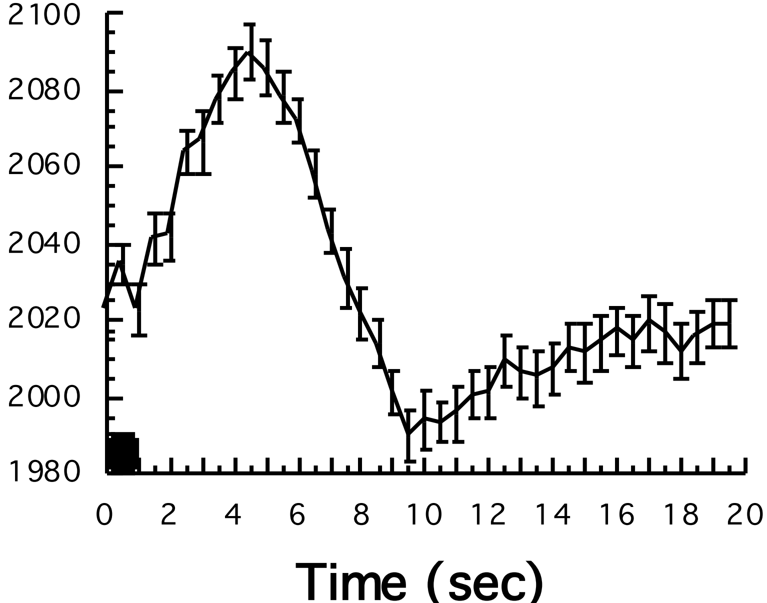
RANDY L. BUCKNER†‡§¶, PETER A. BANDETTINI†‡, KATHLEEN M. O'CRAVEN†‖, ROBERT L. SAVOY†‖,
STEVEN E. PETERSEN**††, MARCUS E. RAICHLE§**††, AND BRUCE R. ROSEN†‡

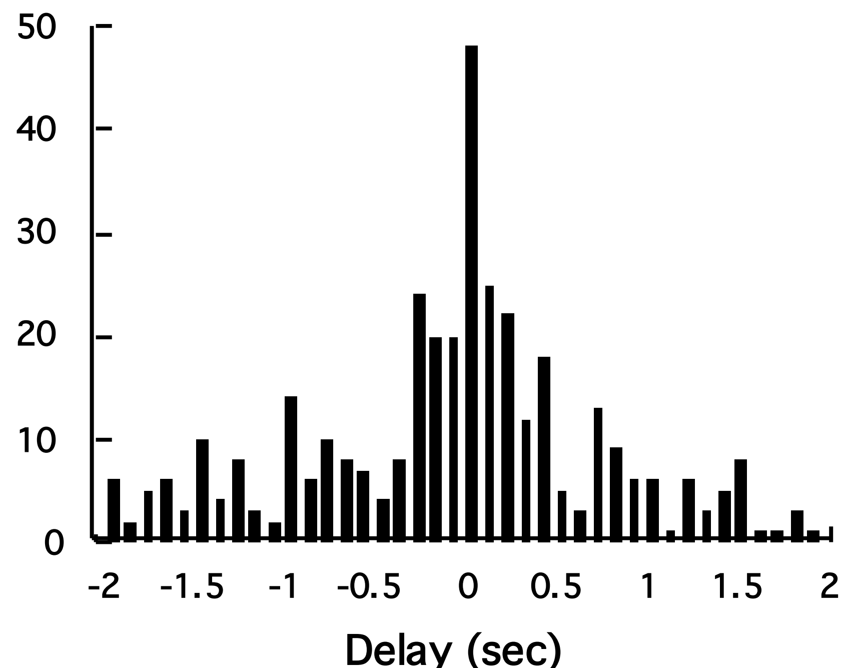


Latency

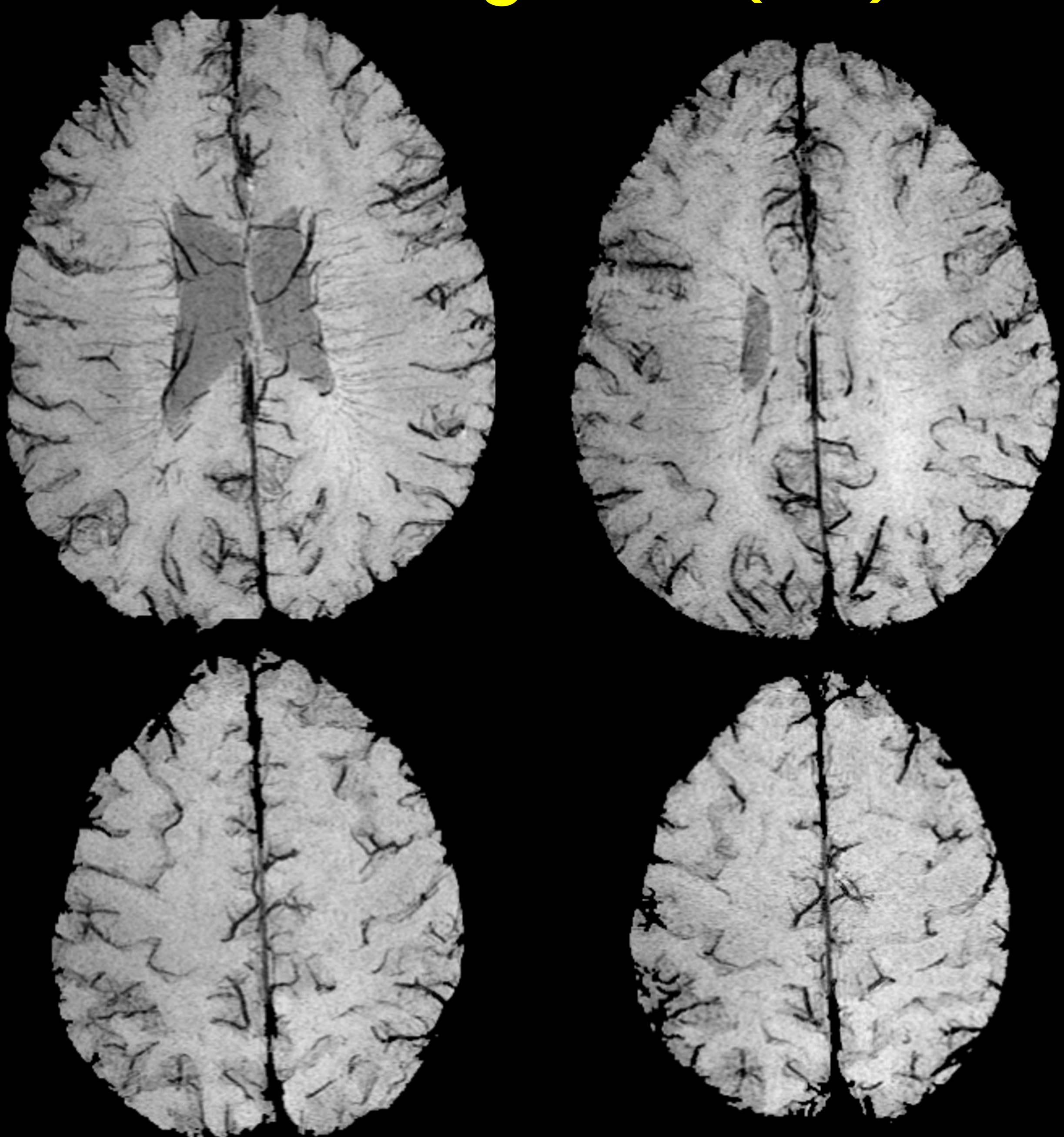
Magnitude

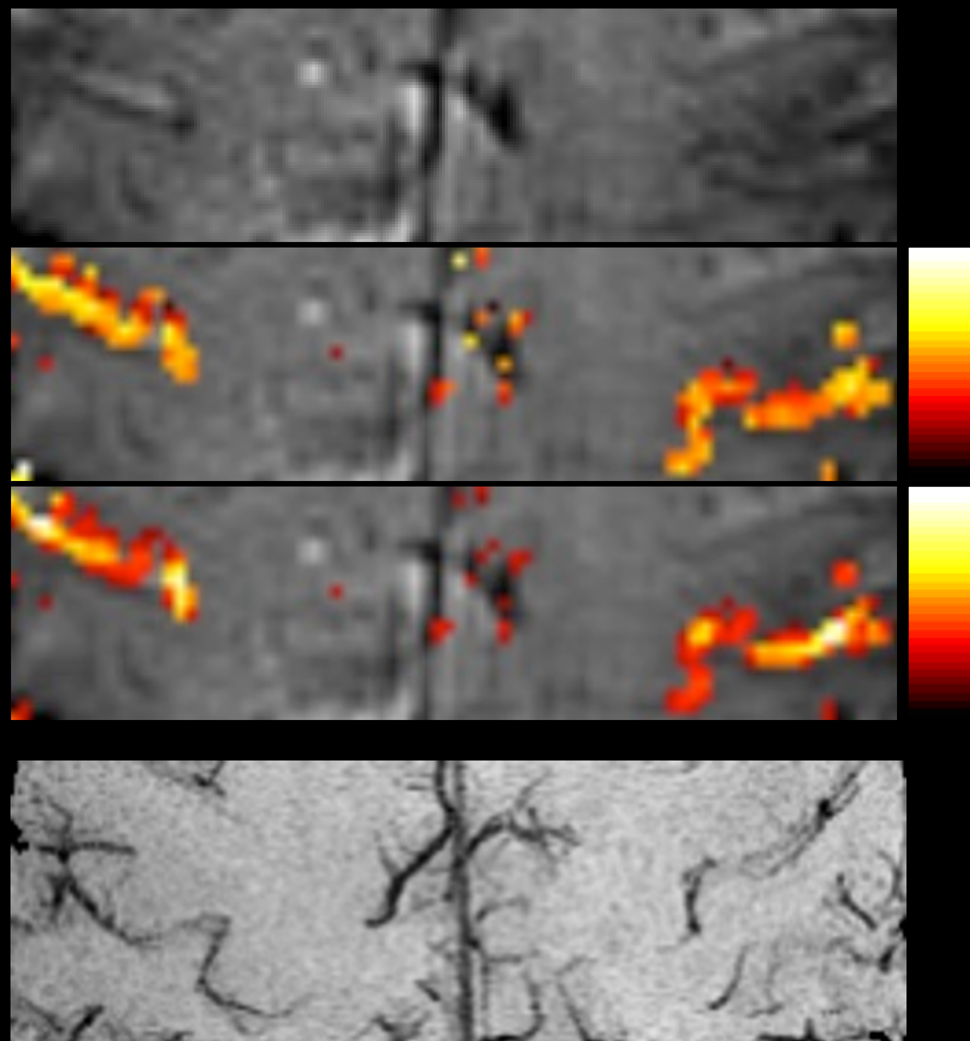






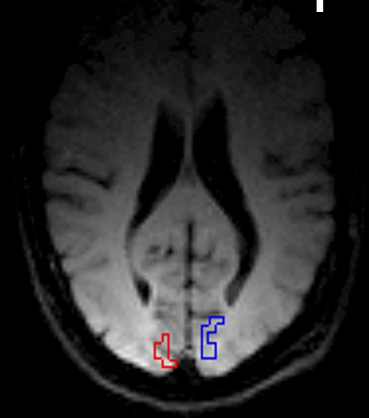
Venograms (3T)



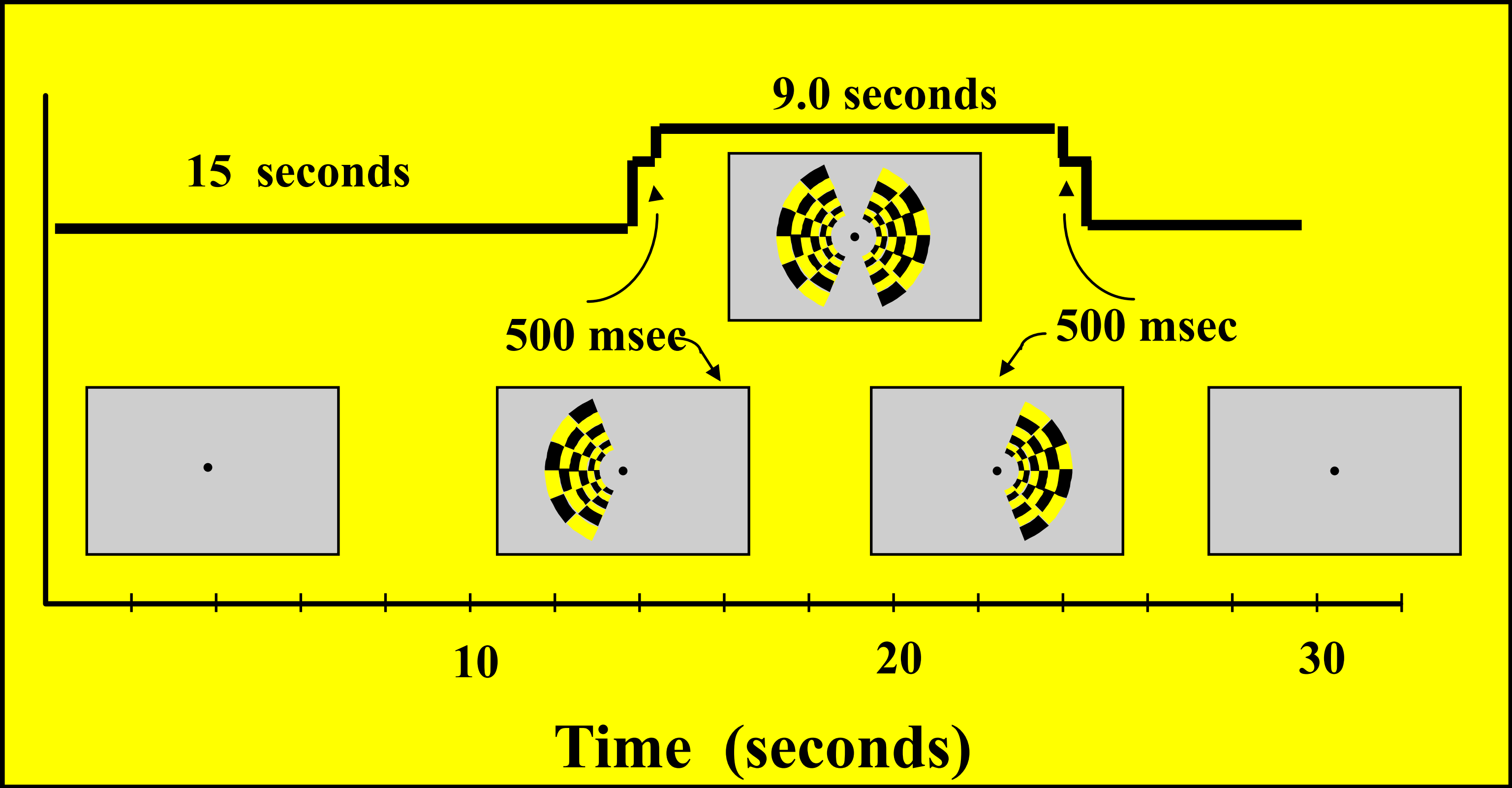


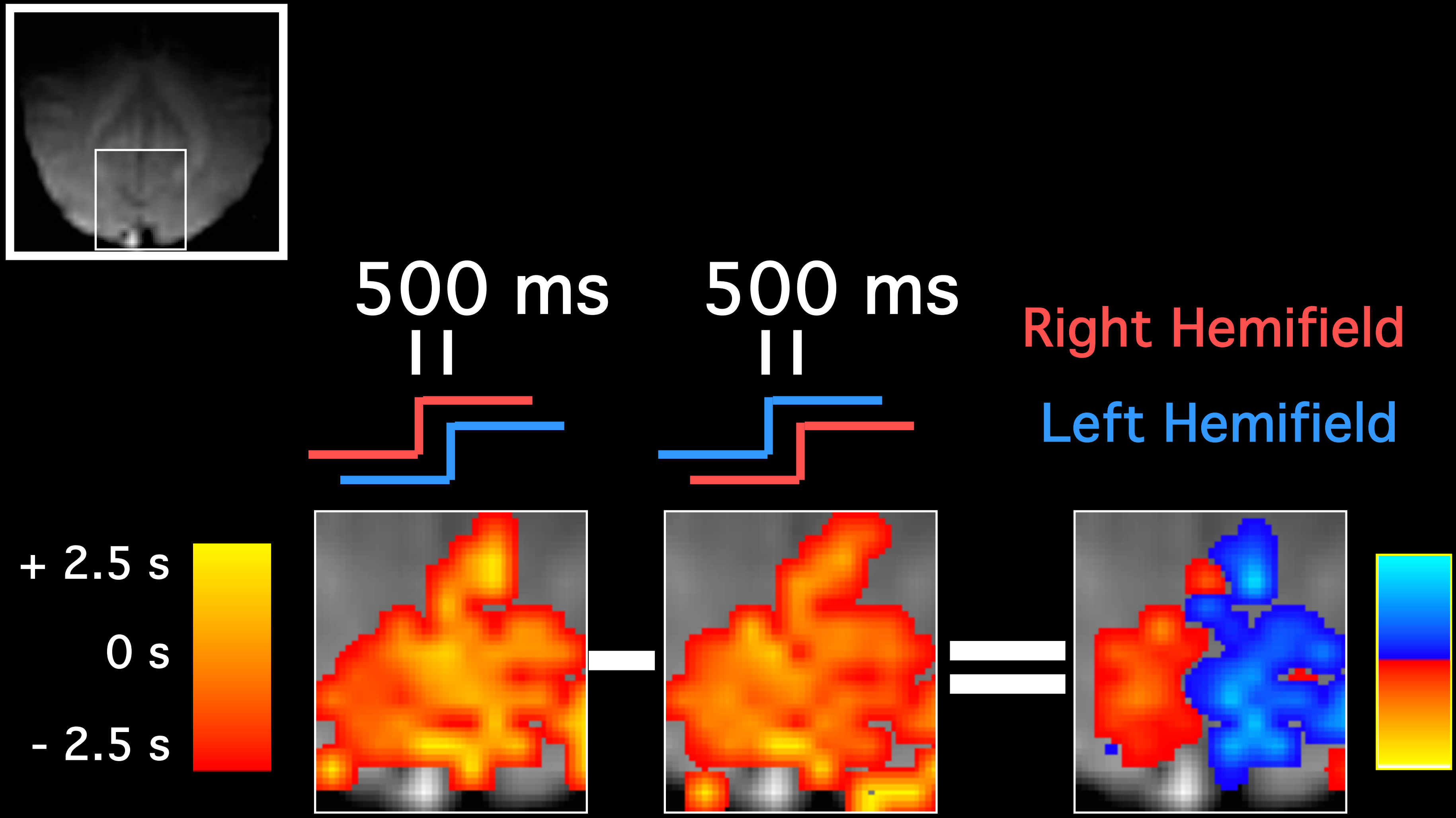
Hemi-Field Experiment

Left Hemisphere



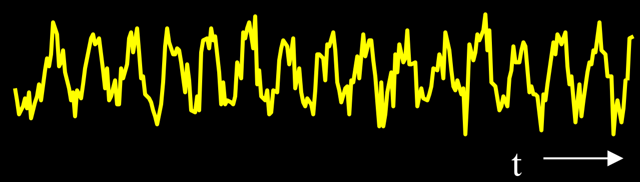
Right Hemisphere

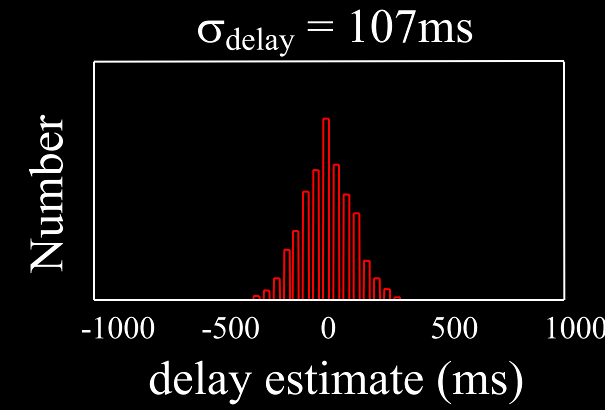



500 ms
=
500 ms
=
Right Hemifield
Left Hemifield
+ 2.5 s
0 s
- 2.5 s
-
=

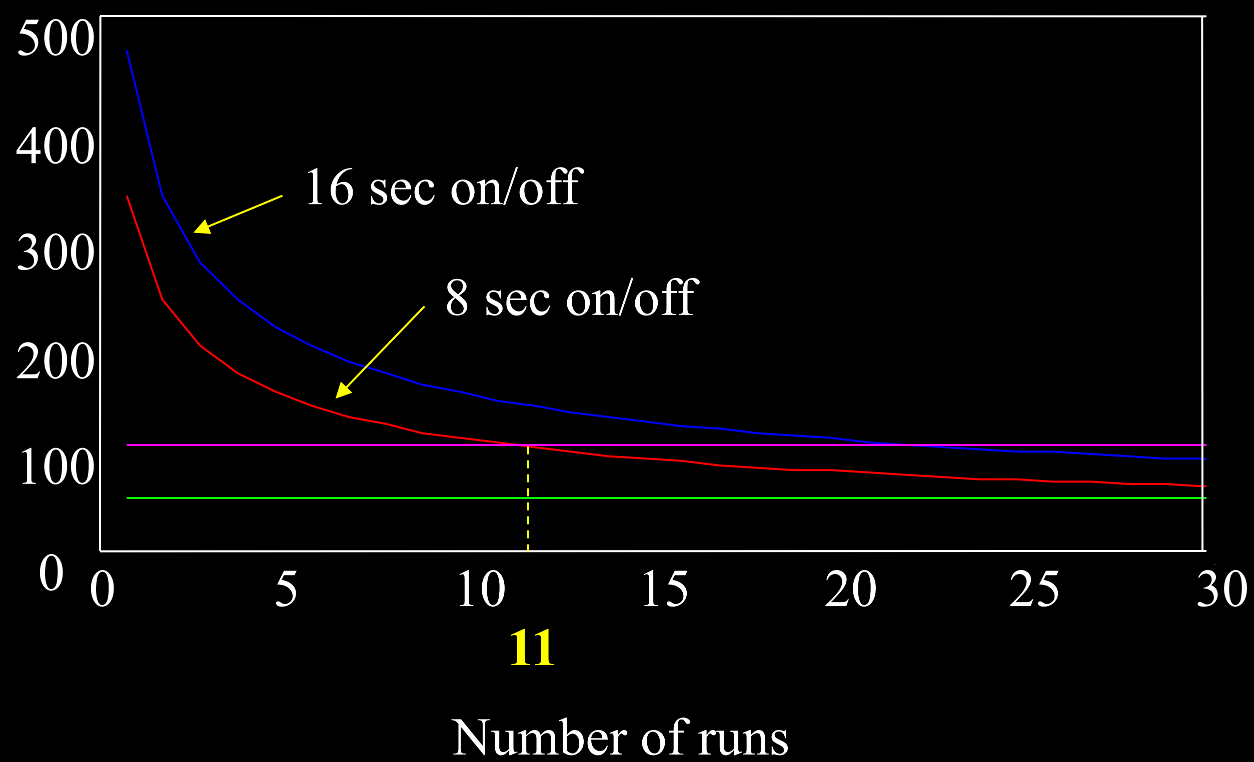
1 run:

1% Noise
4% BOLD
256 time pts /run
1 second TR

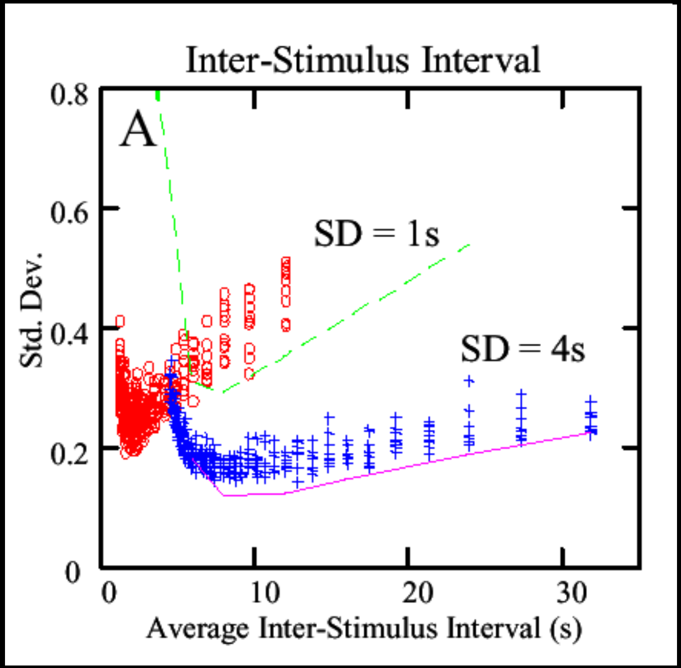


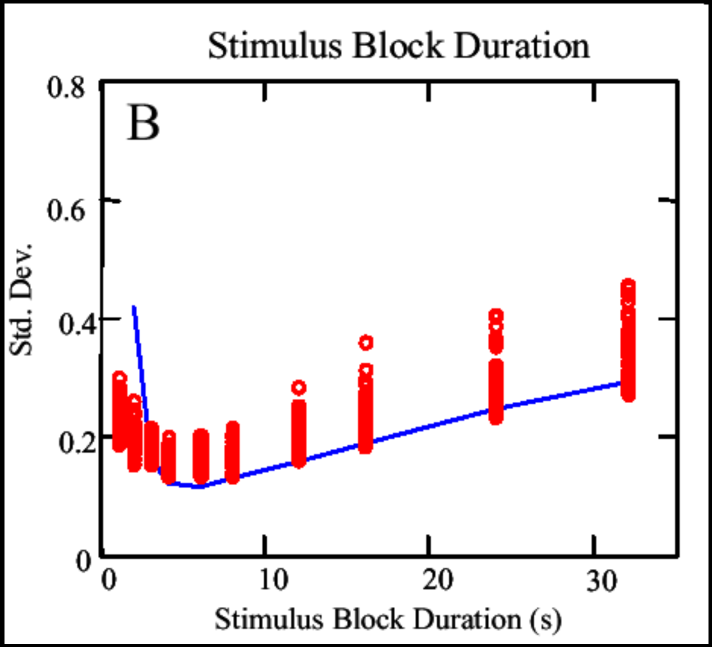


Smallest latency Variation Detectable (ms) ($p < 0.001$)



Optimal Detection of Hemodynamic Latency





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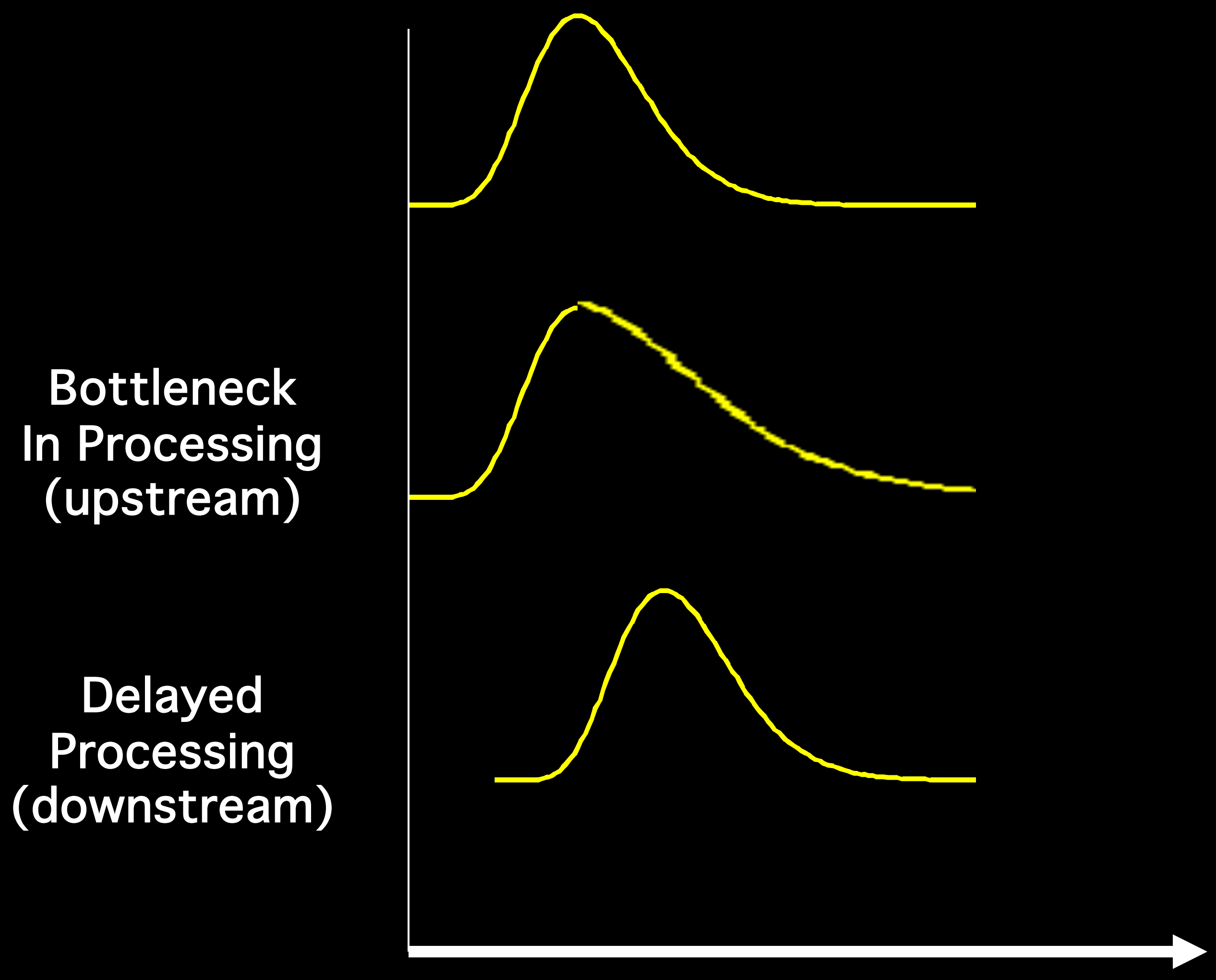
Hemodynamic Response Modulation



Our first attempt to apply this strategy..

P.S.F. Bellgowan, Z. S. Saad, P. A. Bandettini, Understanding neural system dynamics through task modulation and measurement of BOLD amplitude, latency, and width. *Proc. Nat'l. Acad. Sci. USA (in press).*

Use of Task Timing Modulation to Extract Processing Streams

Stimuli – Six-letter English words and pronounceable non-words.
Each word or non-word was rotated either 0, 60,or 120 degrees

Task – Lexical Decision (word / non-word).

Dependent Measures – Percent Correct and Reaction Time.

Hypotheses :

1) **Stimulus rotation of 120 degrees will result in:**

a) Longer Reaction Times

b) Stimulus rotation demands a change in perceptual perspective prior to linguistic processing, resulting in a delayed IRF onset in areas involved in Lexical and Pre-Lexical processing.

2) **Lexical discrimination will result in :**

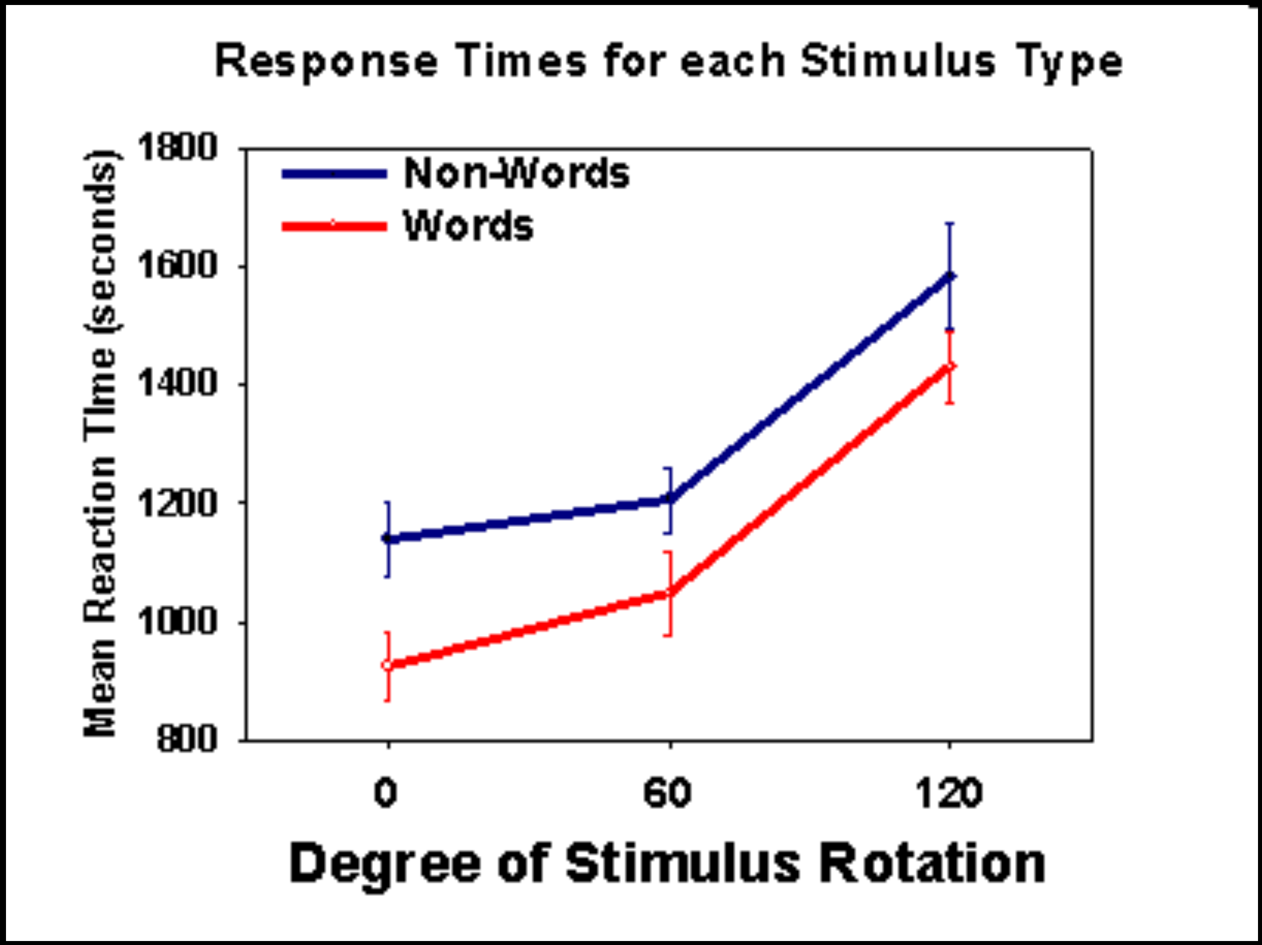
a) Longer Reaction Times for non-words due to increased Pre-Lexical processing demands.

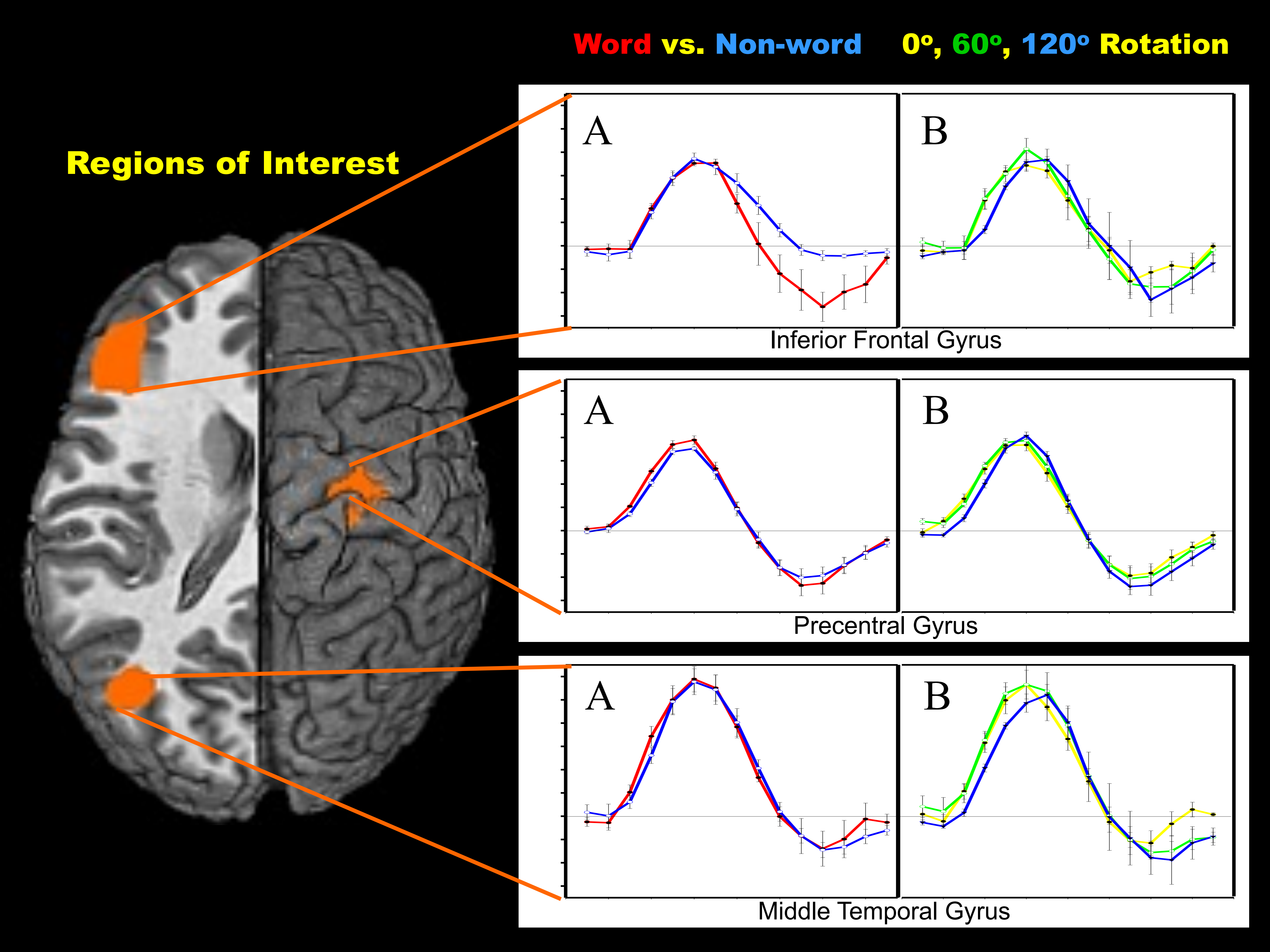
b) Wider IRF in Inferior Frontal cortex for non-words

c) Delayed IRF onset in Left Middle Frontal Cortex

Lexical Delay

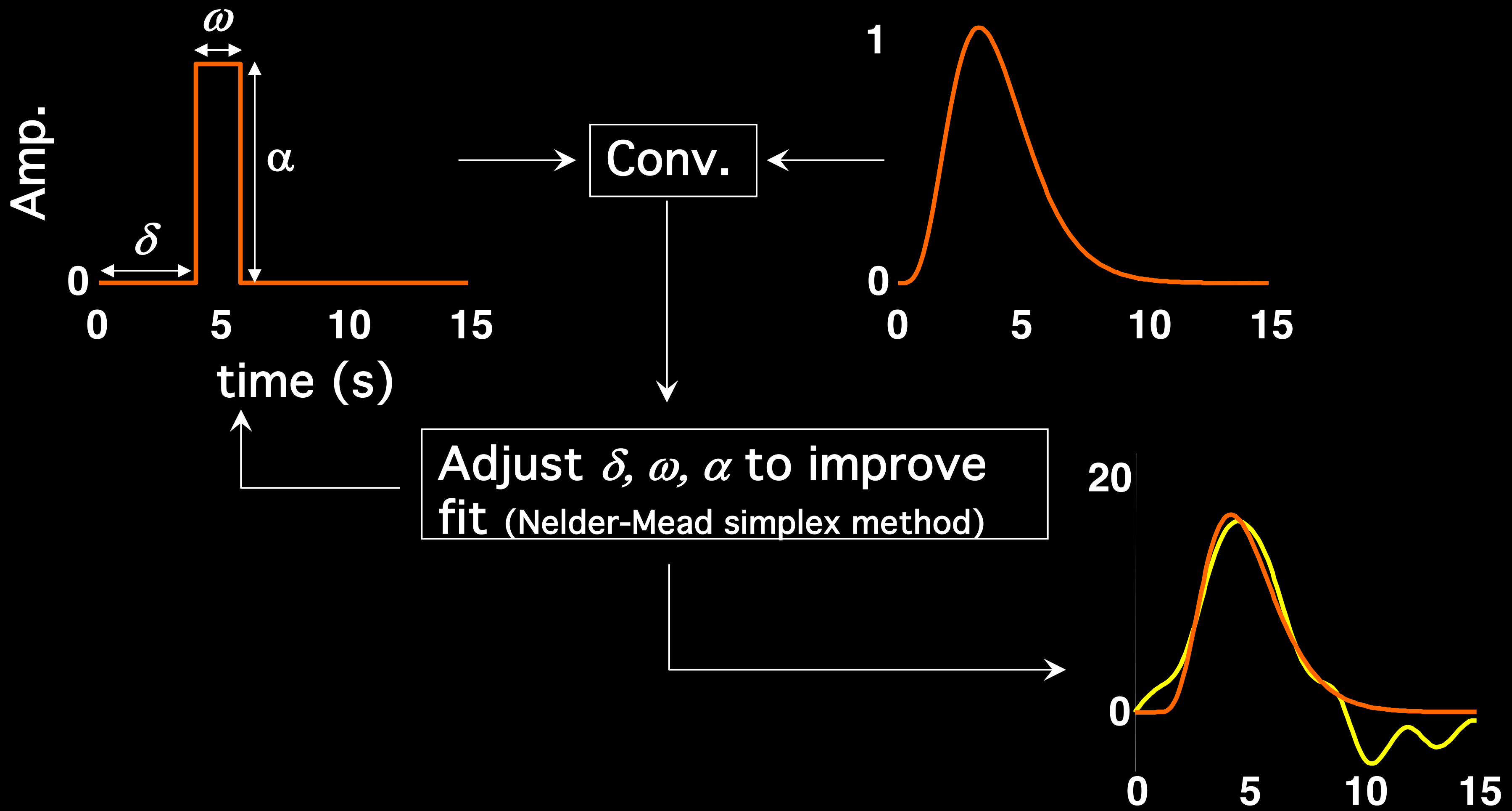
Rotational Delay	Words	Non-Words	Mean Reaction Time
0^0	smudge	dierts	823 ms
60^0	frolic	cuhlos	891 ms
120^0	slouch	gedmus	1446 ms
Mean Reaction Time	986 ms	1219 ms	


Response Times for each Stimulus Type
Non-Words
Words
1800
1600
1400
1200
1000
800
Mean Reaction TIme (seconds)
0
60
120
Degree of Stimulus Rotation

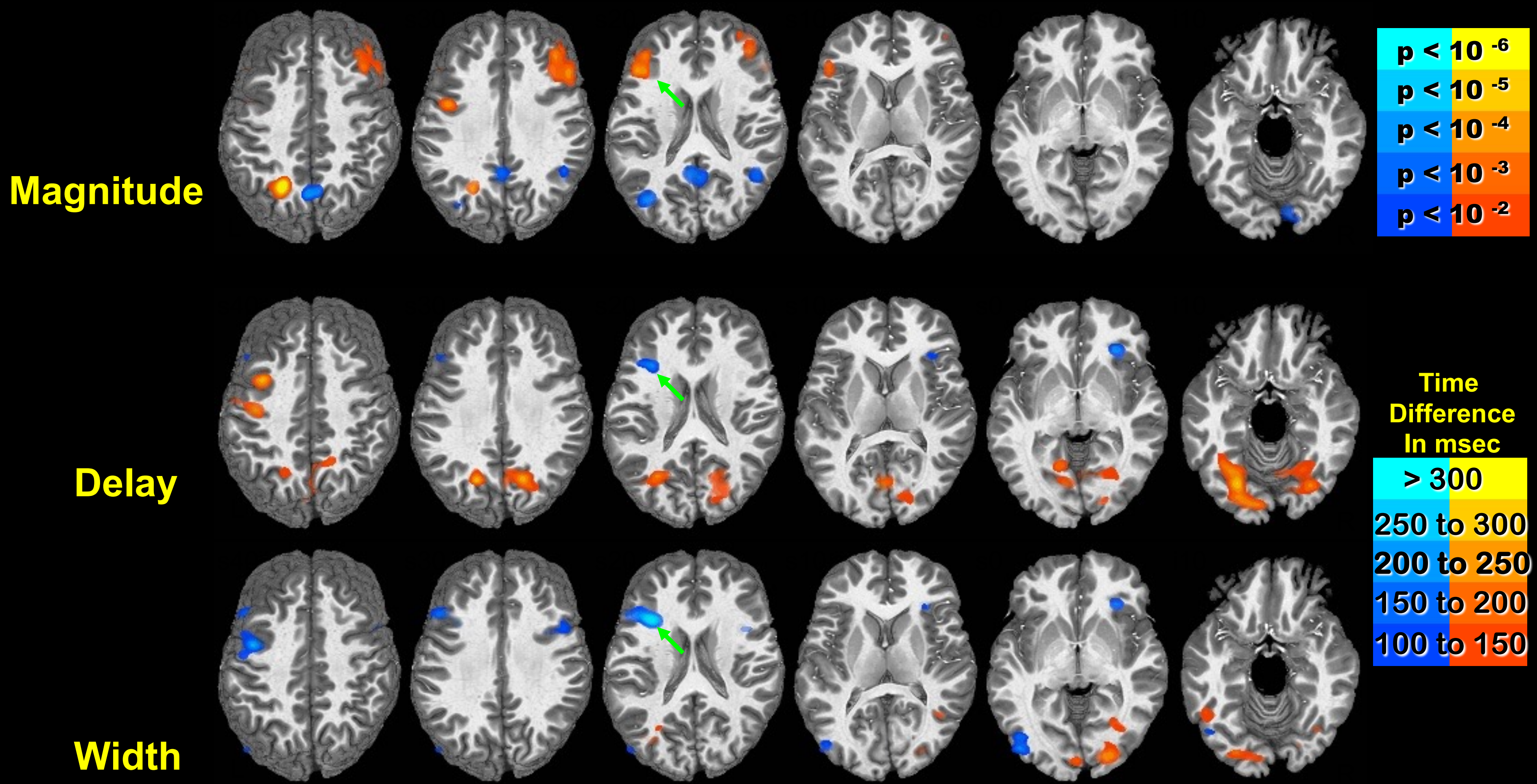


Word vs. Non-word
0º, 60º, 120º Rotation
Regions of Interest
A
B
Inferior Frontal Gyrus
A
B
Precentral Gyrus
A
B
Middle Temporal Gyrus

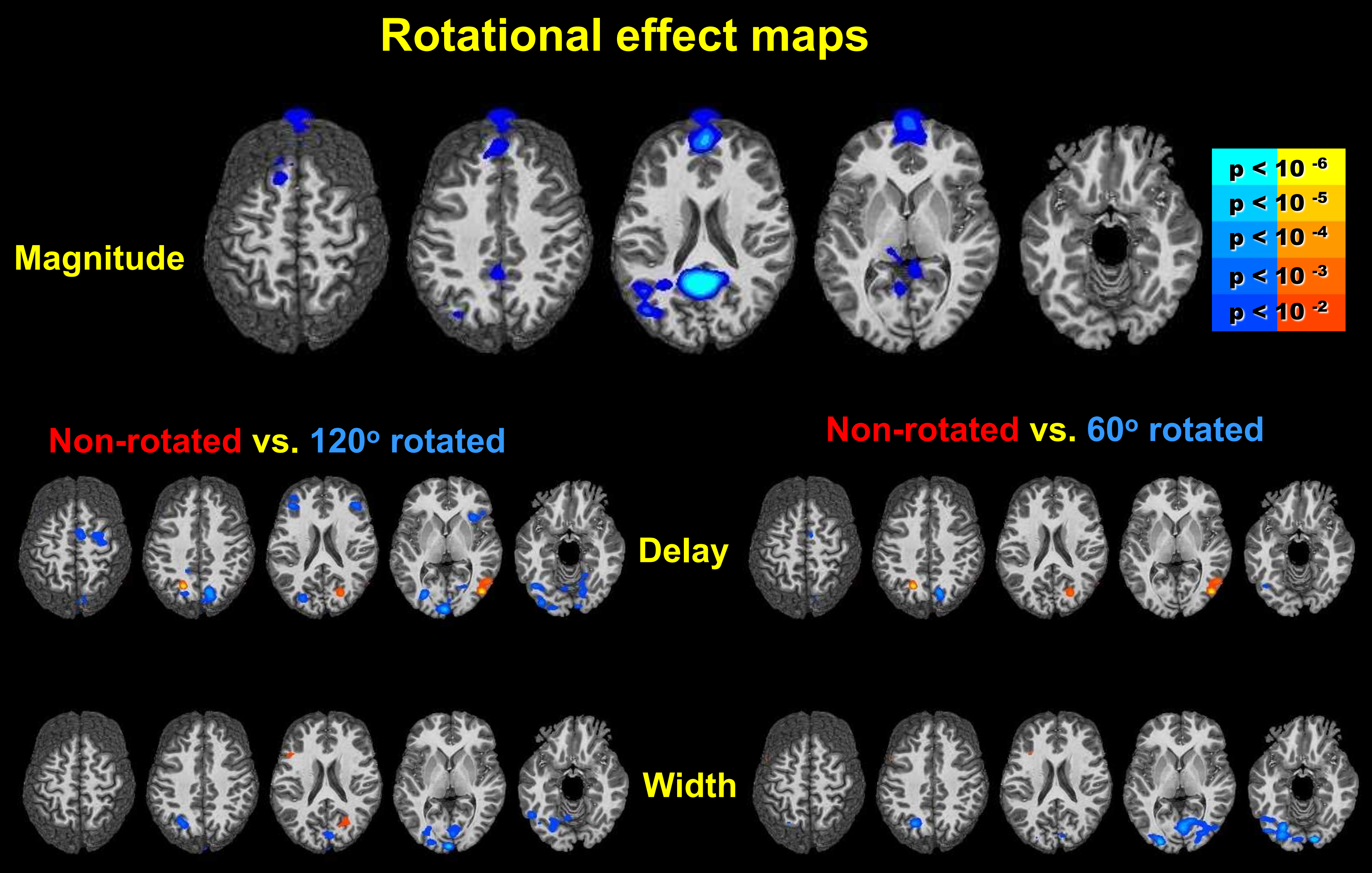
Estimation of Delay, Width & Amplitude



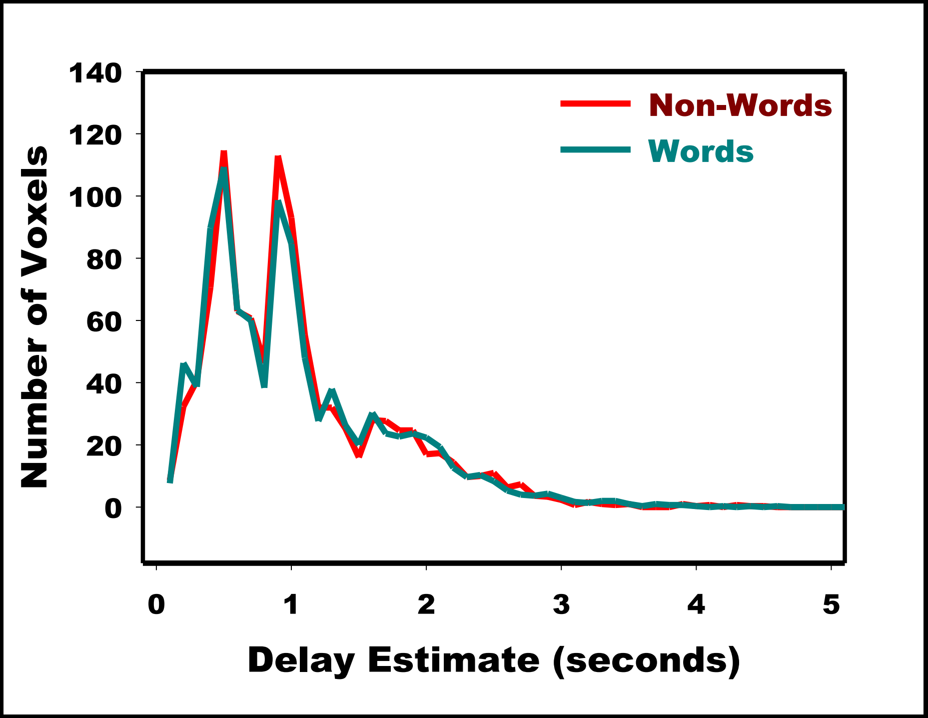
Lexical effect maps

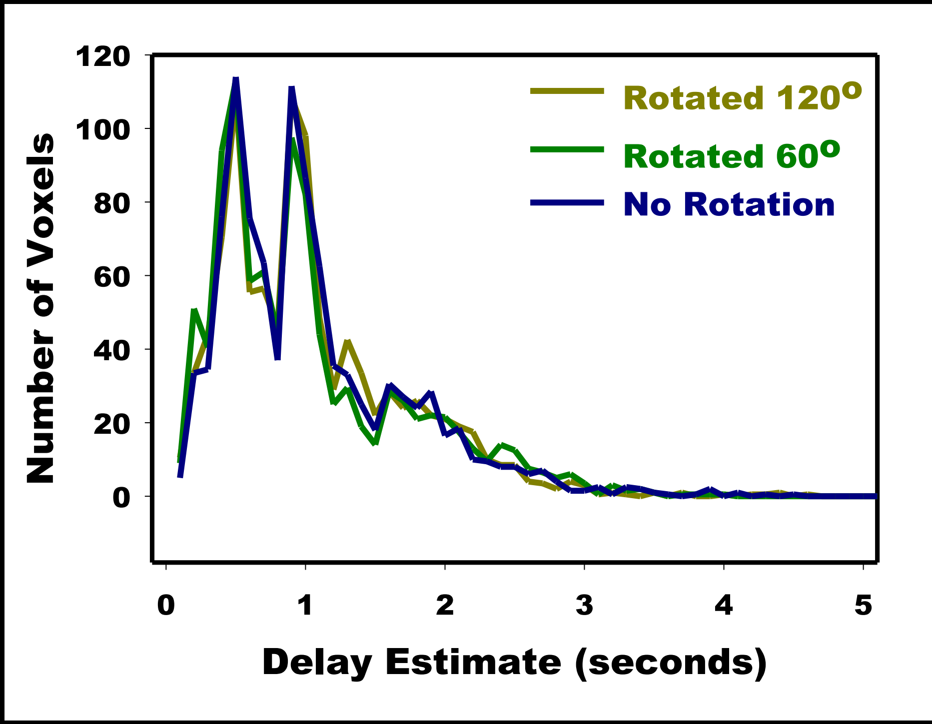


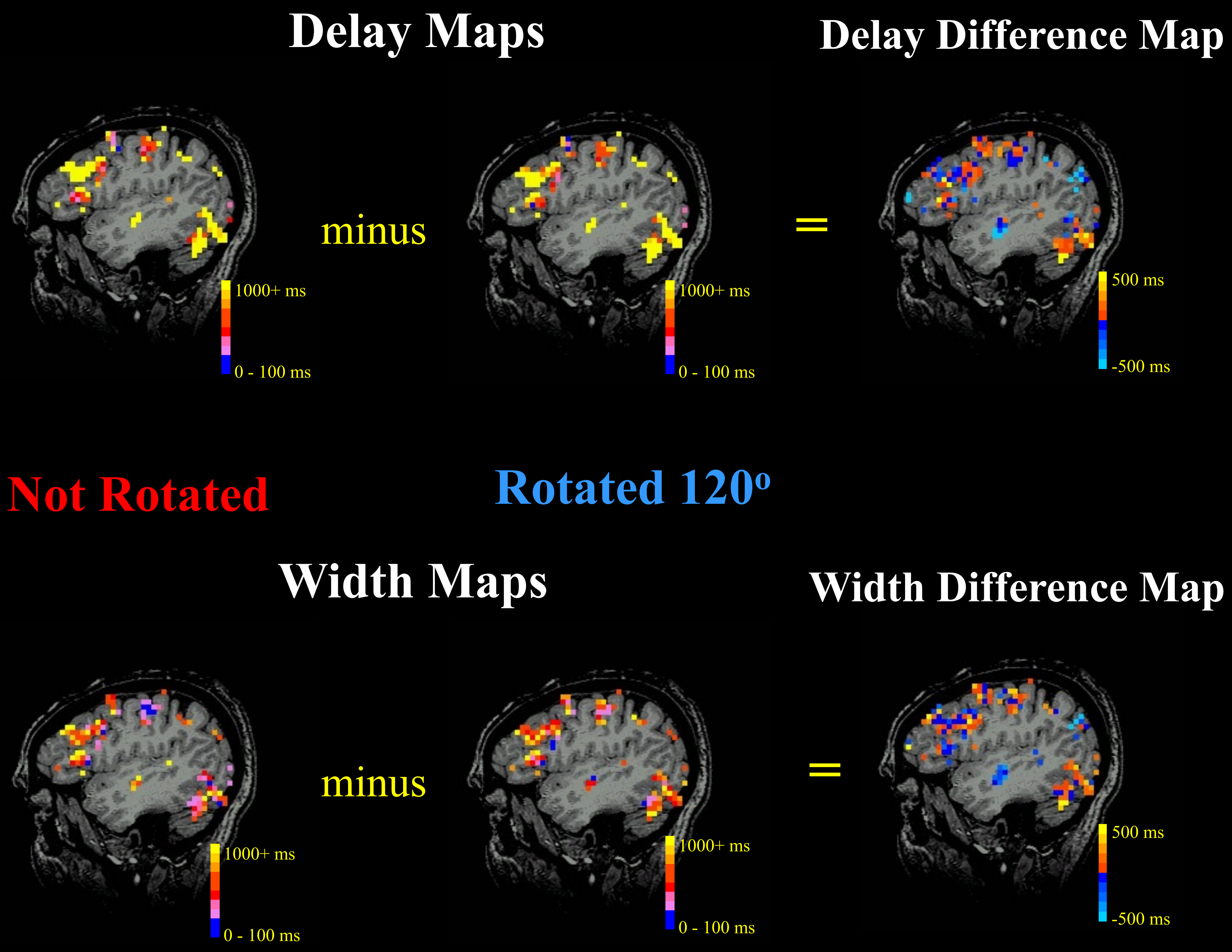
Warm colors are areas where Words > Non-words. Cool colors (blues) are areas Where Non-words > words. The Left hemisphere is toward the left margin. The green arrows highlight the inferior frontal gyrus.


Rotational effect maps
Magnitude
p < 10 -6
p < 10 -5
p < 10 -4
p < 10 -3
p < 10 -2
Non-rotated vs. 120o rotated
Non-rotated vs. 60o rotated
Delay
Width

Distribution of Delay Estimates for Subject BP







Delay Maps
Delay Difference Map
minus
=
1000+ ms
0 - 100 ms
1000+ ms
0 - 100 ms
500 ms
-500 ms
Not Rotated
Rotated 120º
Width Maps
Width Difference Map
minus
=
1000+ ms
0 - 100 ms
1000+ ms
0 - 100 ms
500 ms
-500 ms

Hemodynamics

-quick overview

-linearity (steady state)

-linearity (dynamic)

-baseline signal

-latency

-width

Neuronal Currents

-model

-approaches

current phantom

cell cultures

human studies

-why there is hope

Toward direct mapping of neuronal activity: MRI detection of ultra weak and transient magnetic field changes.

Jerzy Bodurka

Natalia Petridou

Peter A. Bandettini

Introduction

- Neuronal activity is directly associated with ionic currents.

- These bio-currents induce **spatially distributed and transient** magnetic flux density (B_c) changes and magnetic field gradients (dB_c/dr).

- In the context of MRI, these currents therefore alter **the magnetic phase** ($\Delta\phi$) of surrounding water protons.

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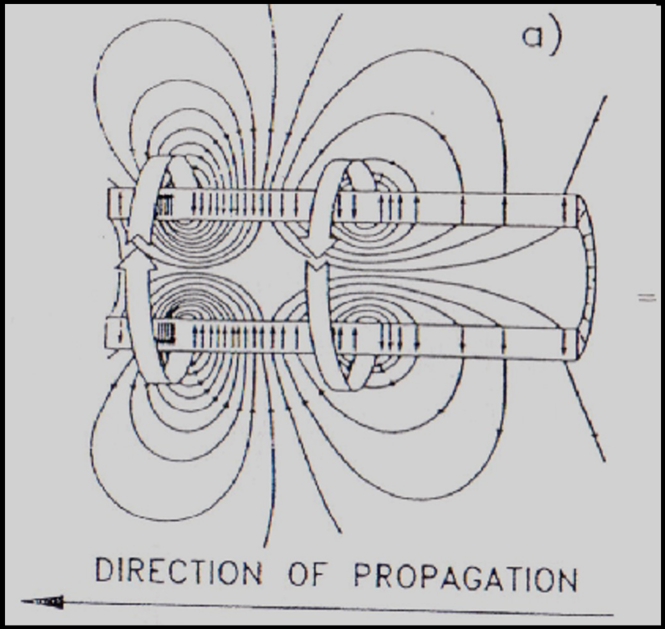
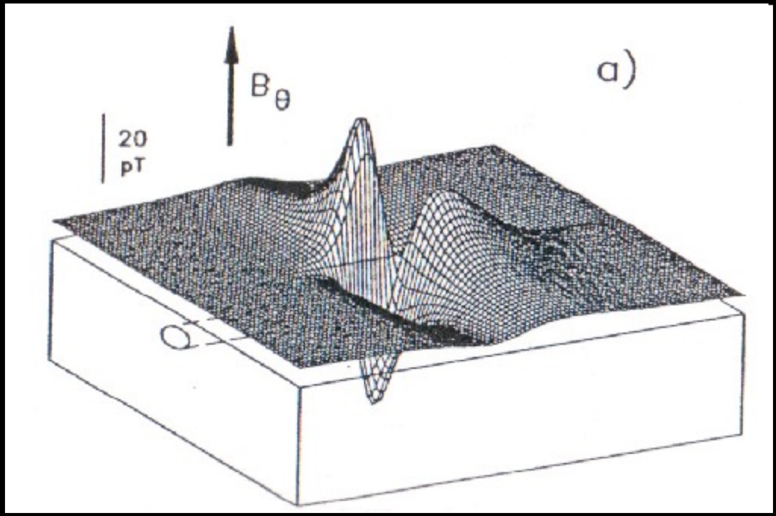
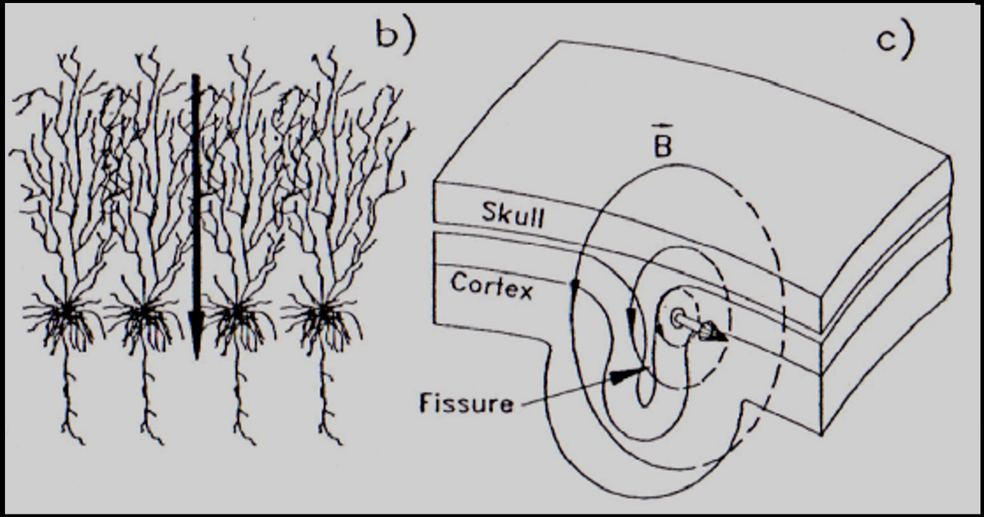
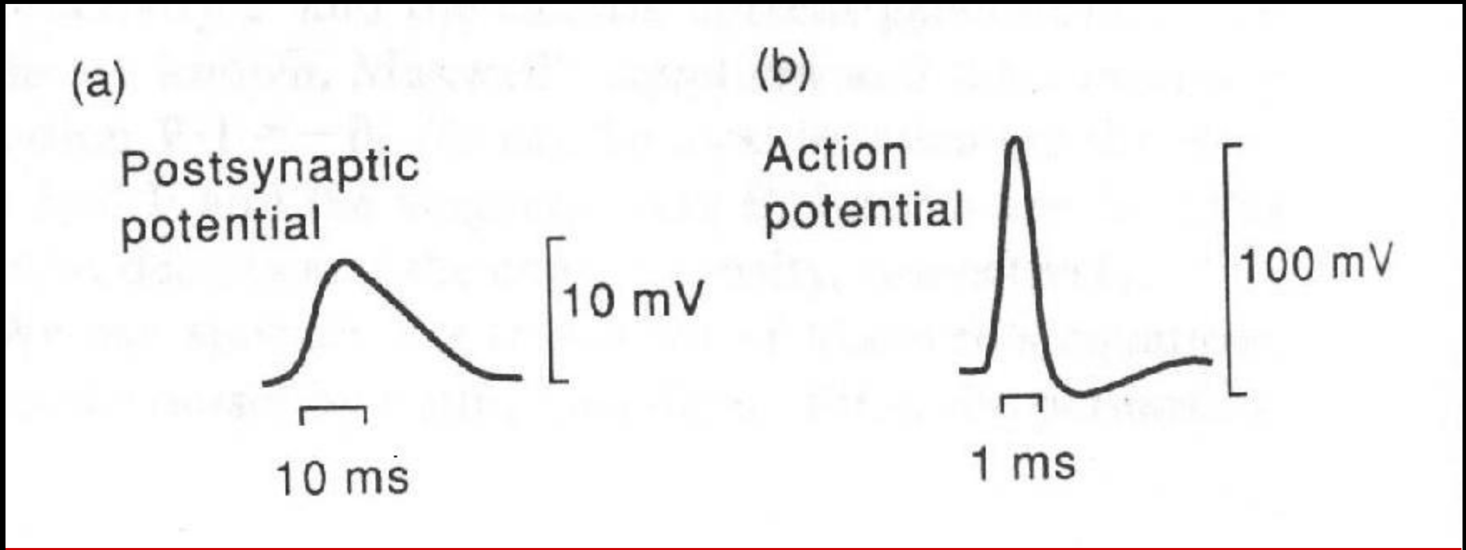






J.P. Wikswo Jr et al. *J Clin Neuronphy* 8(2): 170-188, 1991

Synchronous activity among large neuronal populations produce **small transient** magnetic field changes which are typically detected on the scalp with Magnetoencephalography (MEG).



Schematic representation of (a) a postsynaptic potential and (b) an action potential as a function of time.

The post synaptic potential lasts for 10ms or more, allowing integration of individual fields to create

MEG detectable > 100 fT field on surface of skull

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Derivation of B field generated in an MRI voxel by a current dipole

Single dendritic tree 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 = 4μm, $\sigma \approx 0.25\ \Omega^{-1}\ m^{-1}$, V = 10mV and

r = 4cm (measurement distance when using MEG) the resulting value is: **B≈0.002 fT**

Because $\mathbf{B_{MEG}}$**=100fT** (or more) is measured by MEG on the scalp, a large number of 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:

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

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

Can MRI Detect transient B_0 changes

On the order of 0.2 nT?

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Frequency shift associated with 0.2 nT field shift = 0.01 Hz.
At TE = 30 ms, $\Delta\phi$ = 0.09 deg.

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-latency

-width

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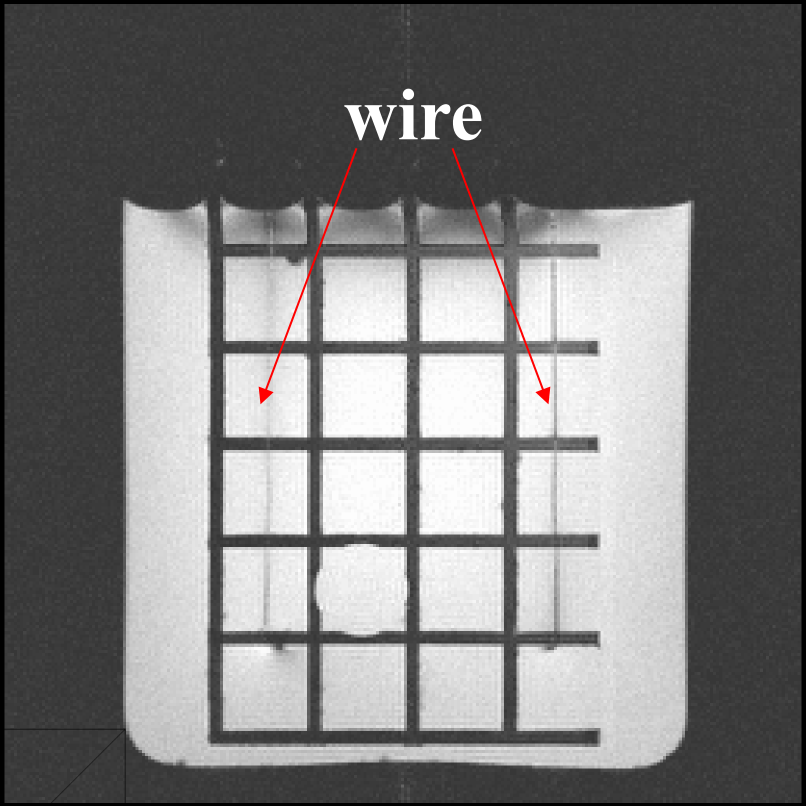
-model

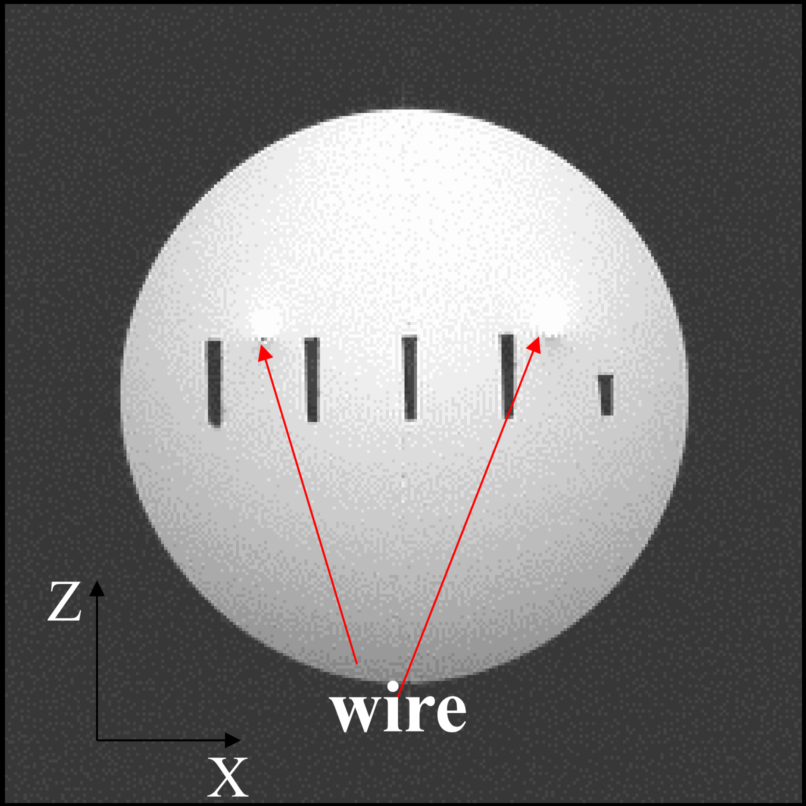
-approaches

current phantom
cell cultures
human studies

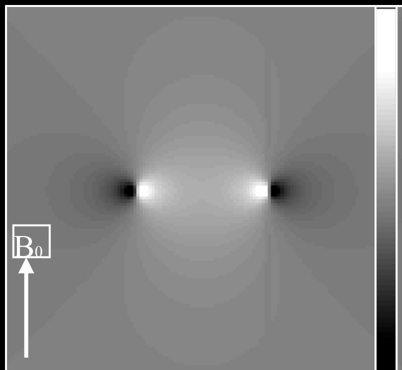
-why there is hope

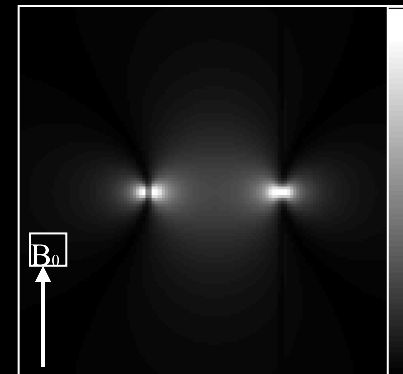
Current Phantom Experiment





Simulation

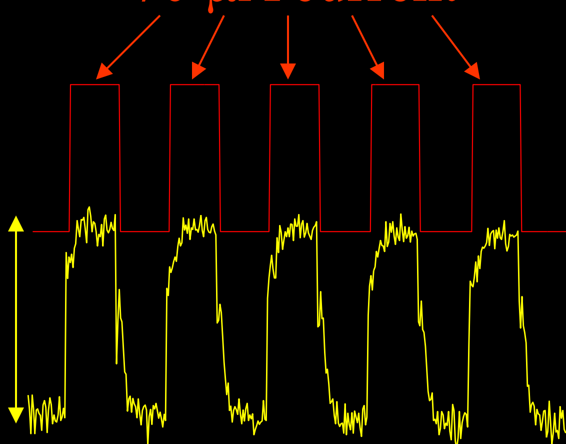




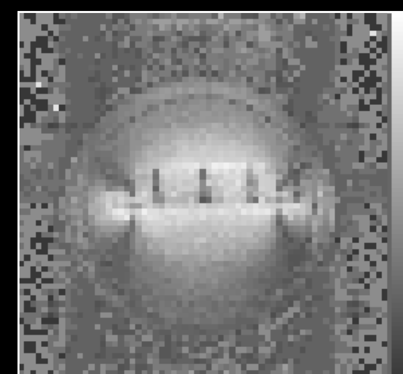
Measurement

$\Delta\phi \cong 20^0$

Correlation image

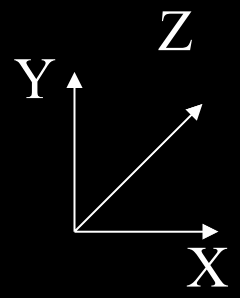


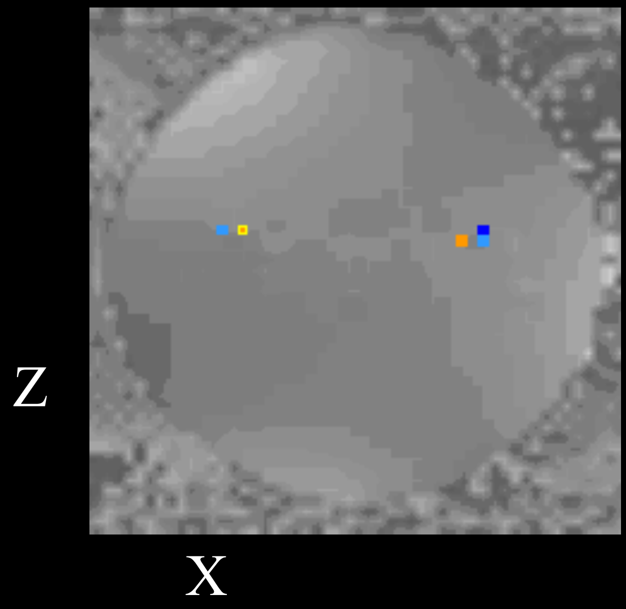
Single shot GE EPI

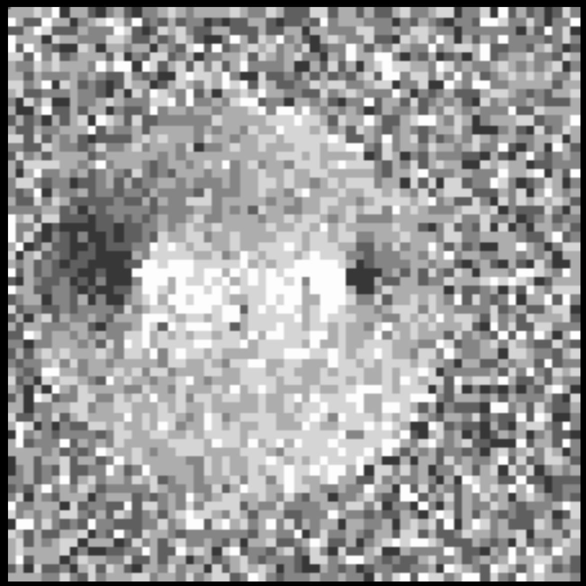


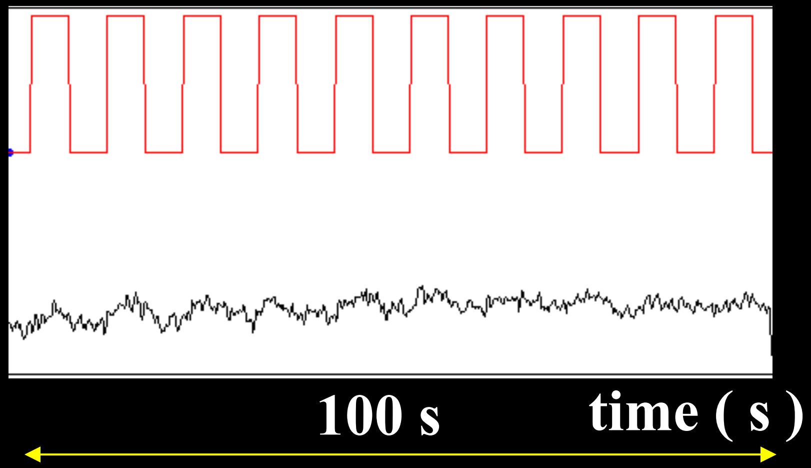
Spectral image

$B_0 \parallel Z$









$\Delta B = \Delta\phi / (\gamma \ TE)$

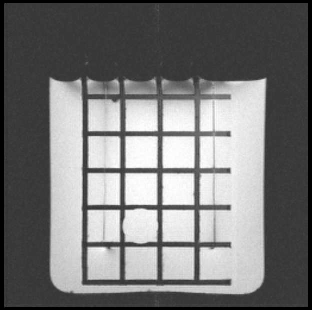
SD of phase noise was $\sigma_\phi = 0.016$ rad

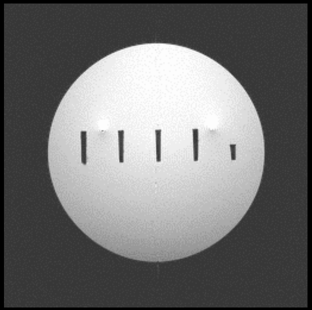
$\Delta B_\phi = 2.2$ nT

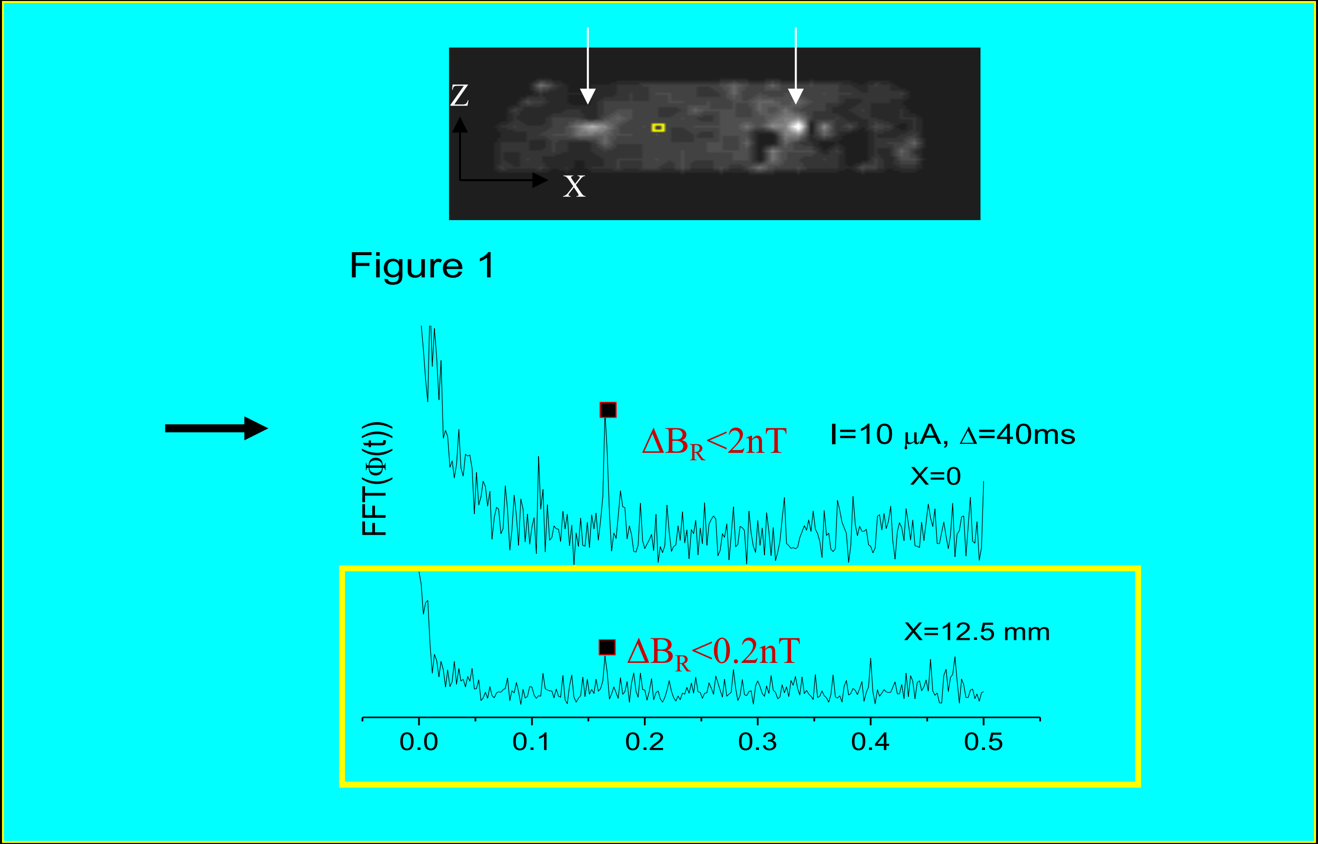
Sensitivity:

$\Delta B = (1.7 \pm 0.3)$ nT

Single shot GE EPI,
TR=54ms, TE=27ms,
FOV=12cm, 64x64







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).

Conclusions of phantom studies:

While many unknowns about neuronal-induced current magnitudes and spatial scales remain, the combination of a SE EPI sequence with precisely synchronized stimulation protocol optimizes the ability to detect small and transient magnetic field changes.

Transient or periodic flux density changes as small as 200 pT can be detected using MRI.

Optimization of Phase Detection

1. Increase image S/N
2. Reduce Temporal Phase Noise
3. Selectively tune sequence to frequency of NMR phase change

Sources of Phase Noise

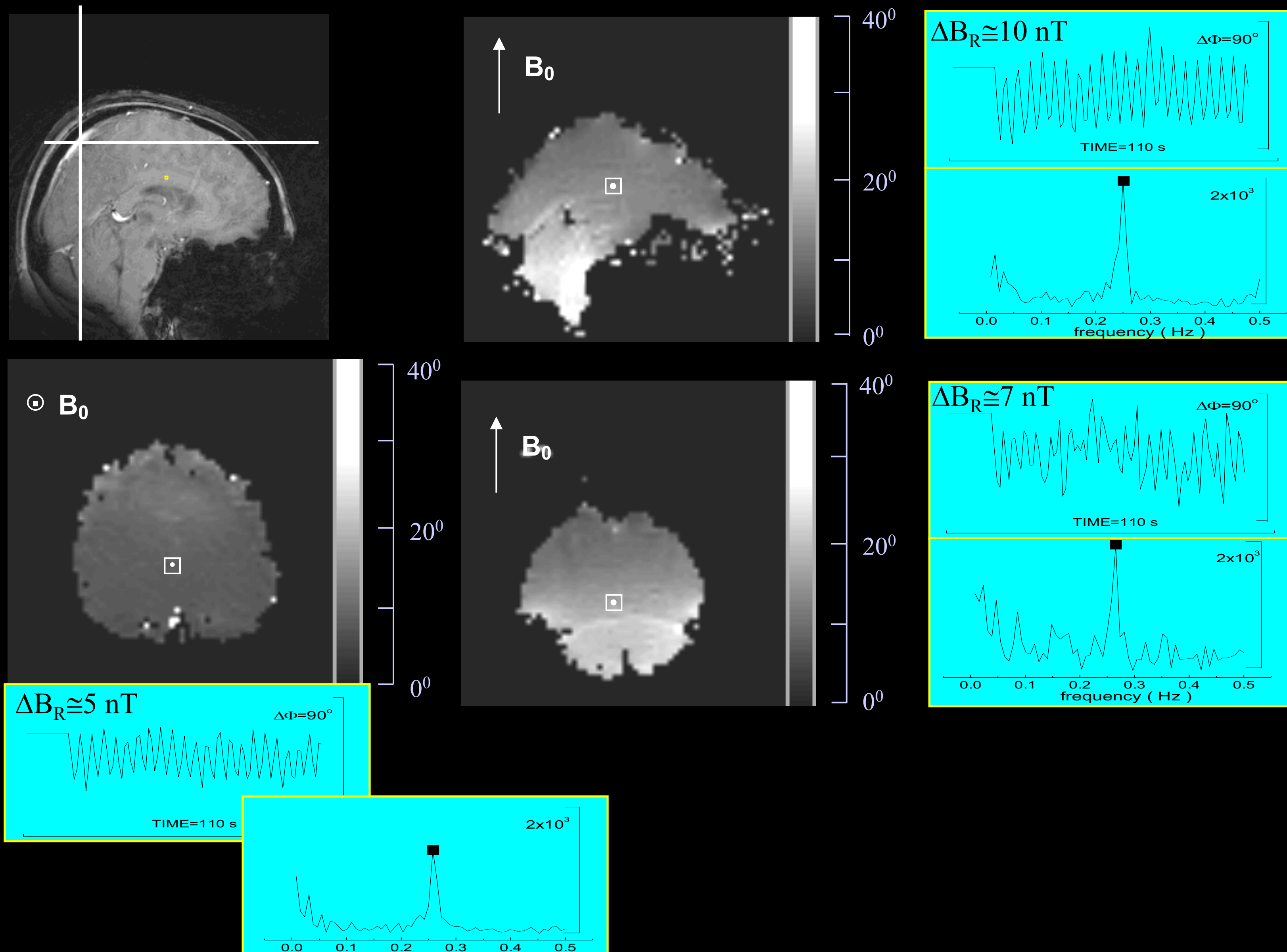
- Respiration (chest wall movement)

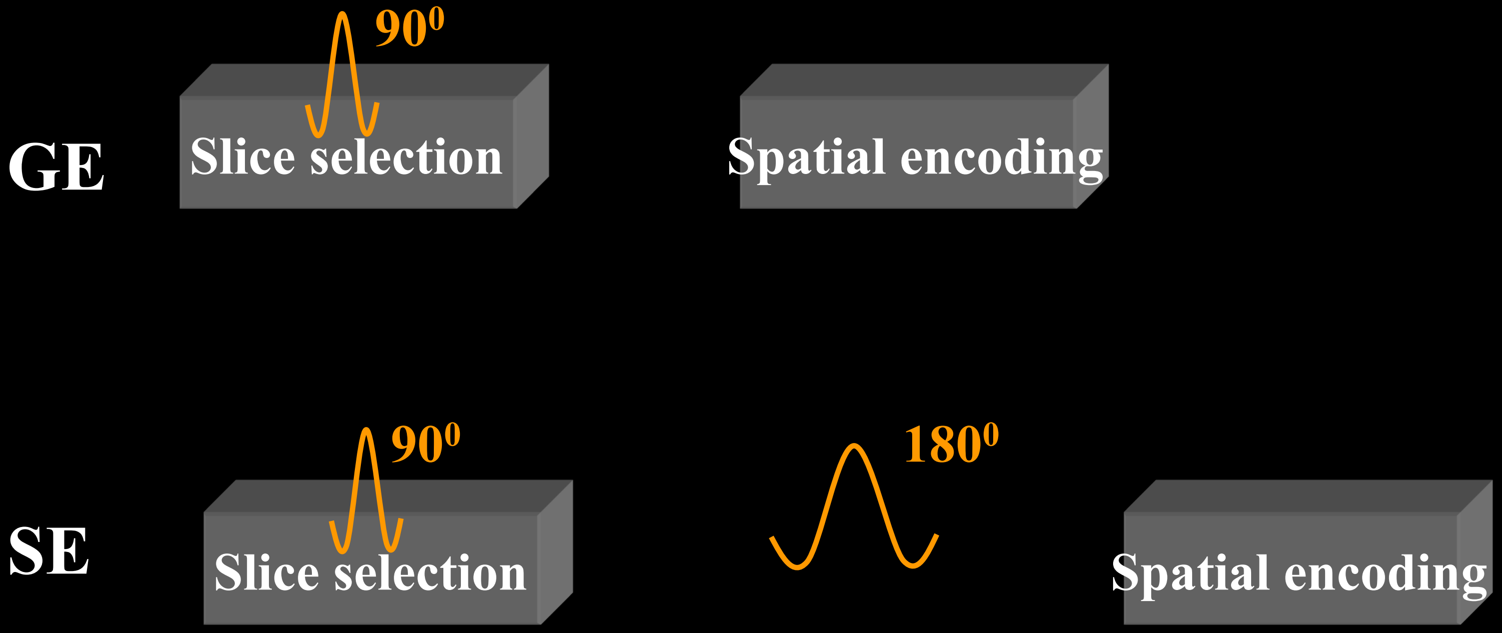
- cardiac pulsation

- eye movement

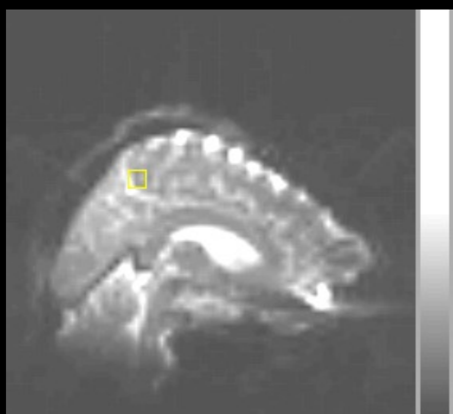
-system instabilities (including eddy currents)

Experiment (human respiration)



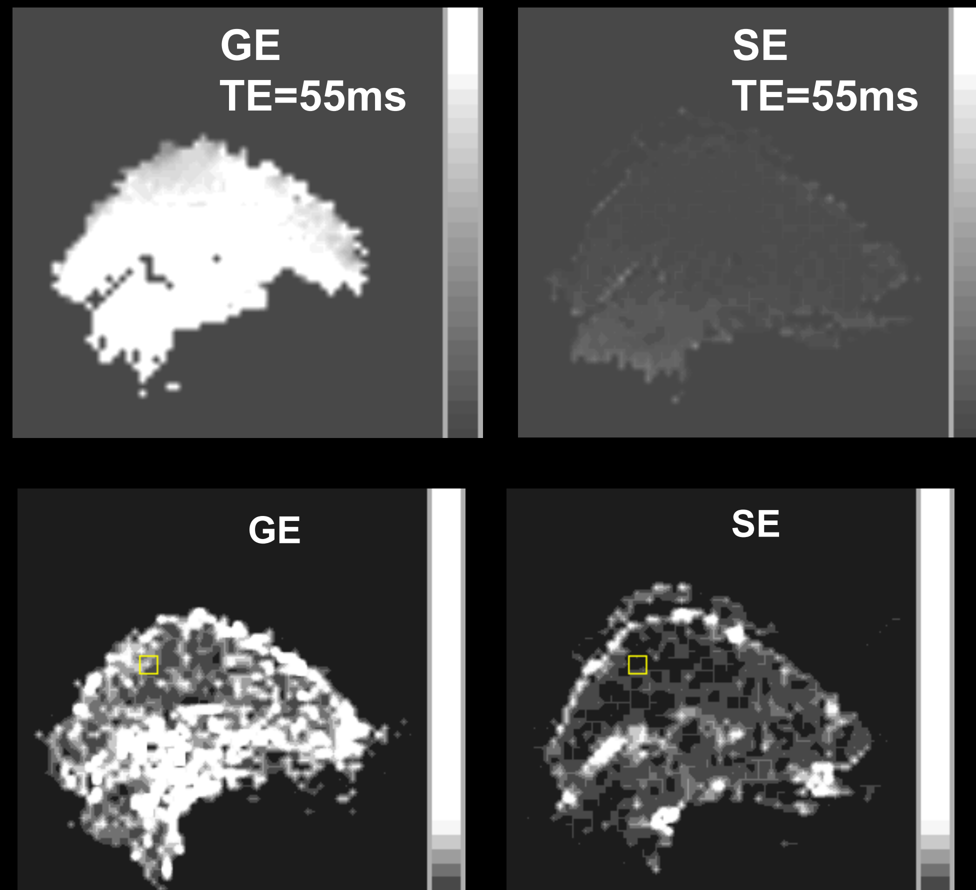

GE
Slice selection
90⁰
Spatial encoding
SE
Slice selection
90⁰
180⁰
Spatial encoding

Experiment (human respiration)

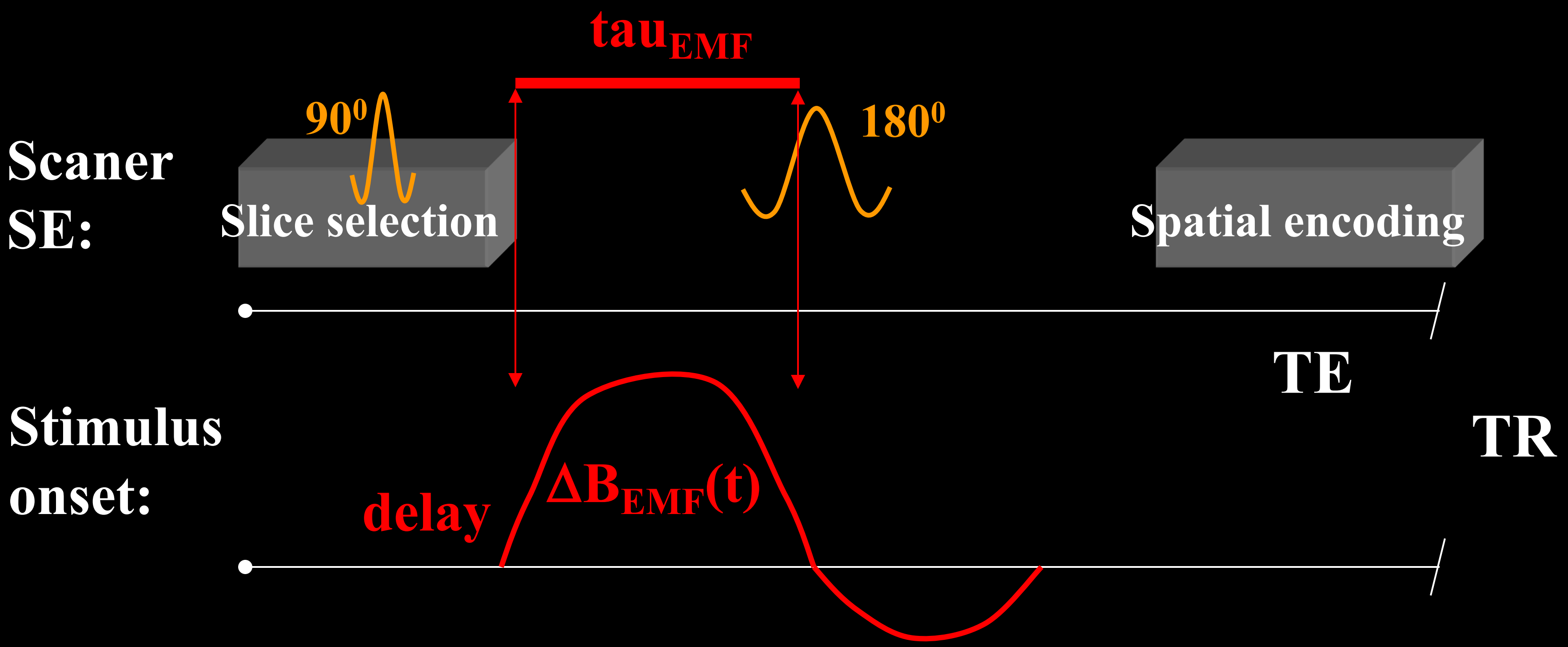


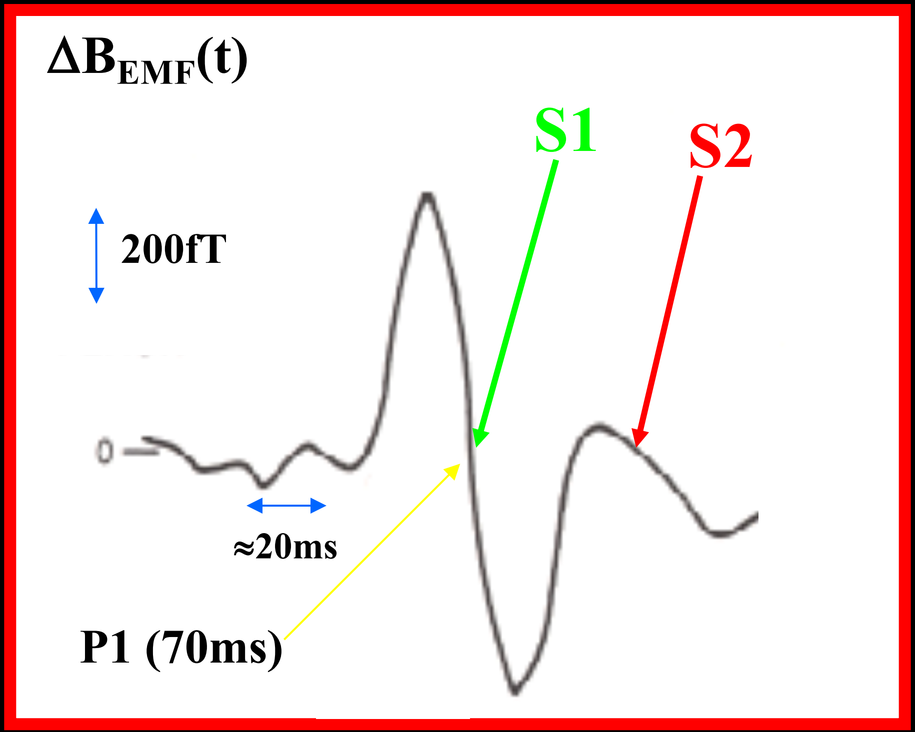
Spectral images

TR =1.0 sec



Spin-echo sequence advantages:





S1: Optimal temporal position for 180 pulse; net phase shift induce by EMF>0

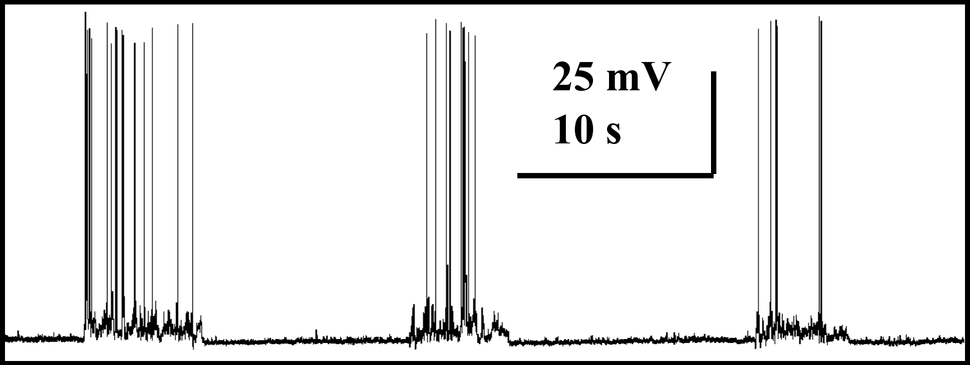
S1: For this 180 pulse temporal position net phase shift induce by EMF is close to zero

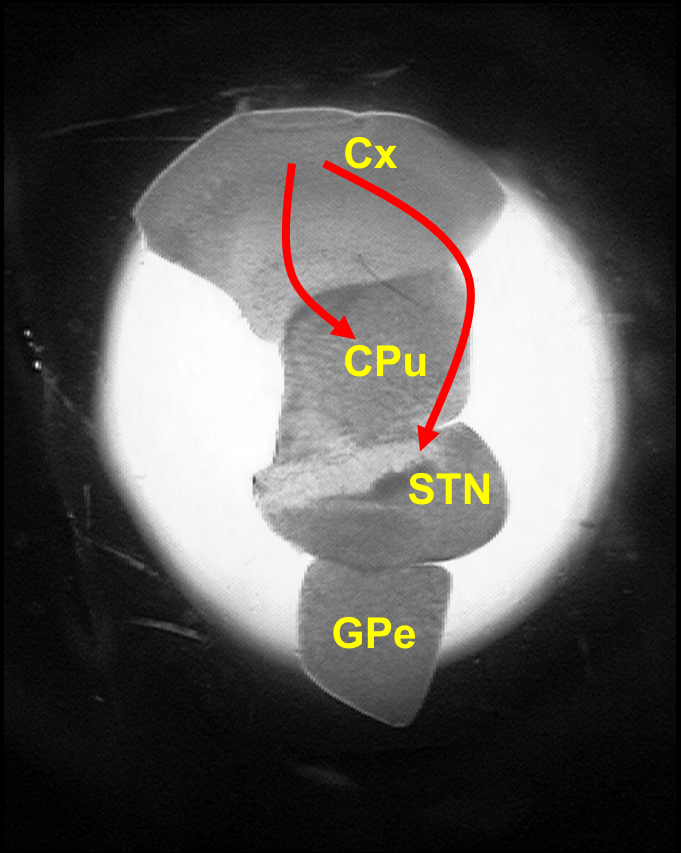
detection of neuronal currents in vitro

physiological model

Tissue Cultures

- Coronal sections of newborn-rat brains (in-plane:0.3-1mm^2 thickness:~60µm)





D. Plenz *NNP, NIMH, NIH*

detection of neuronal currents in vitro

methods

Setup

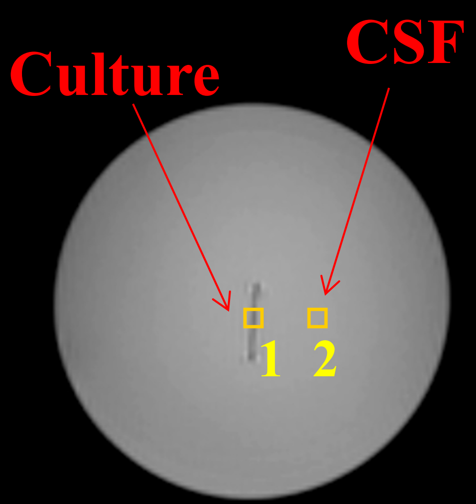
- 10cm diameter CSF-filled glass container
- 3T GE scanner (Milwaukee, WI)
- 10” surface coil (Nova Medical Inc)

Imaging

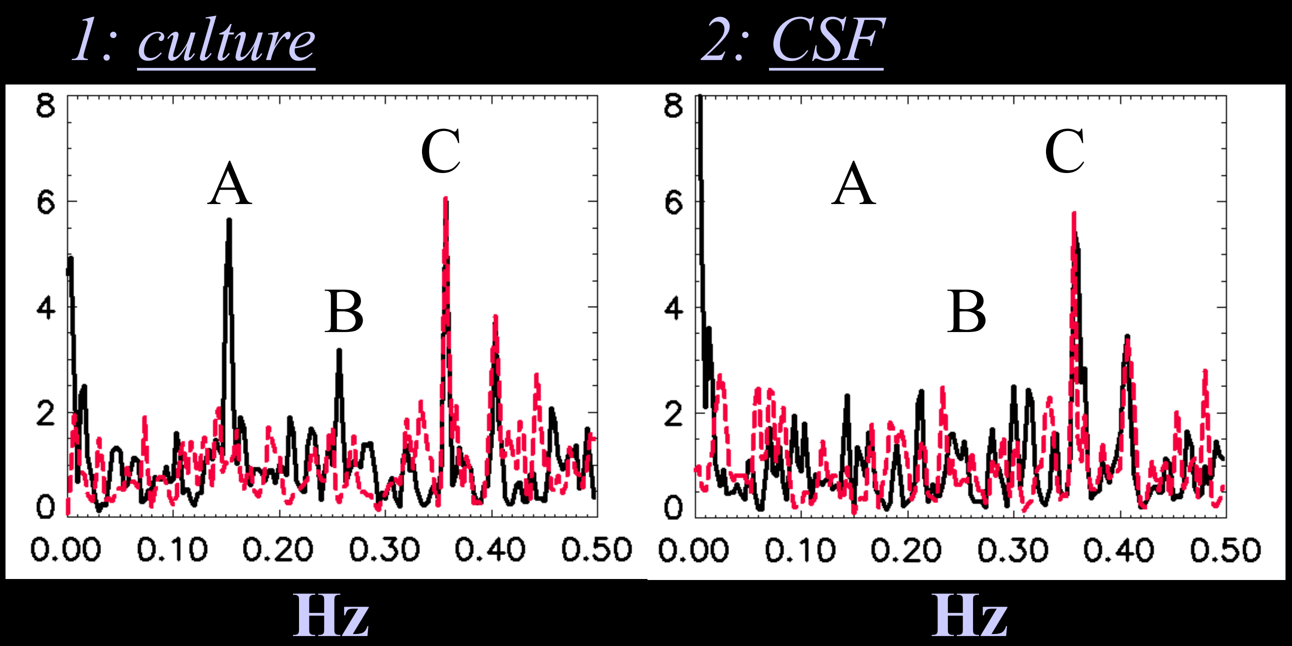
- FSE structural images (256x256)
- SE EPI single shot, TE: 60ms, TR:1s, flip angle: 90^0,
  FOV: 18cm, 64x64, 4 slices (3mm). Images: 1200 (20 min)
  - Active: 10 min activity
  - Inactive: 10 min after TTX administration

detection of neuronal currents in vitro

results



FSE image



Active state: black line, Inactive state: red line

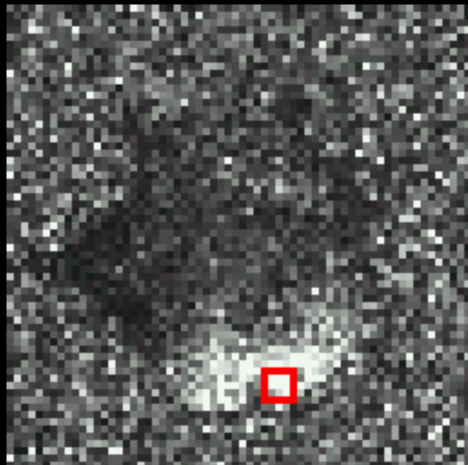
A: activity, on-off frequency (appx. 7 sec)
B: activity
C: scanner noise (cooling-pump)

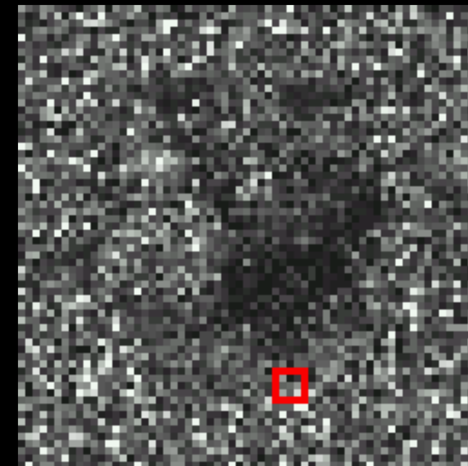
Preliminary Human Studies

Phase v=0.12Hz

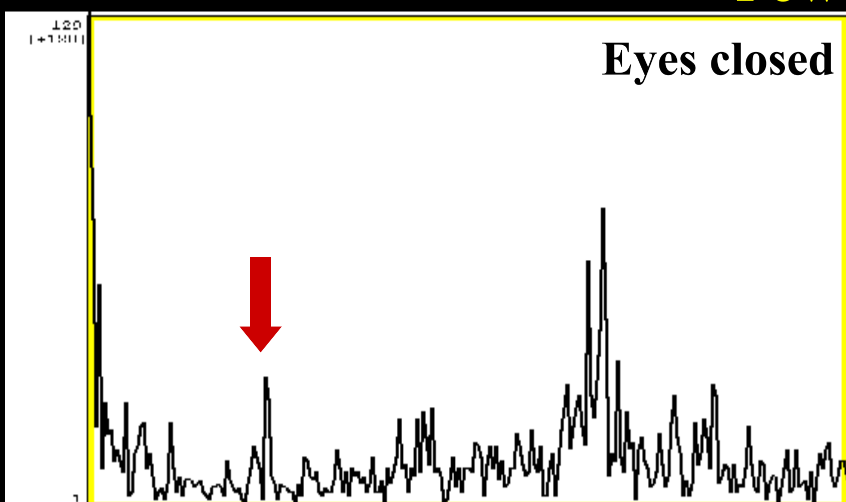
Closed

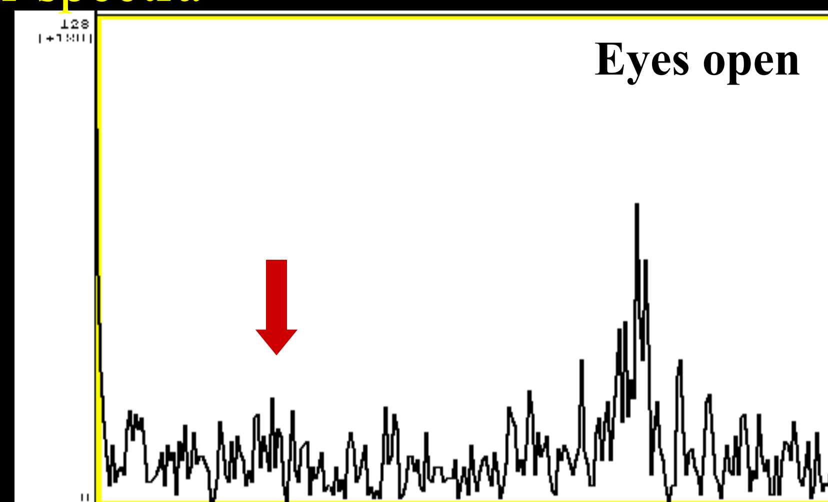
Open





Power spectra





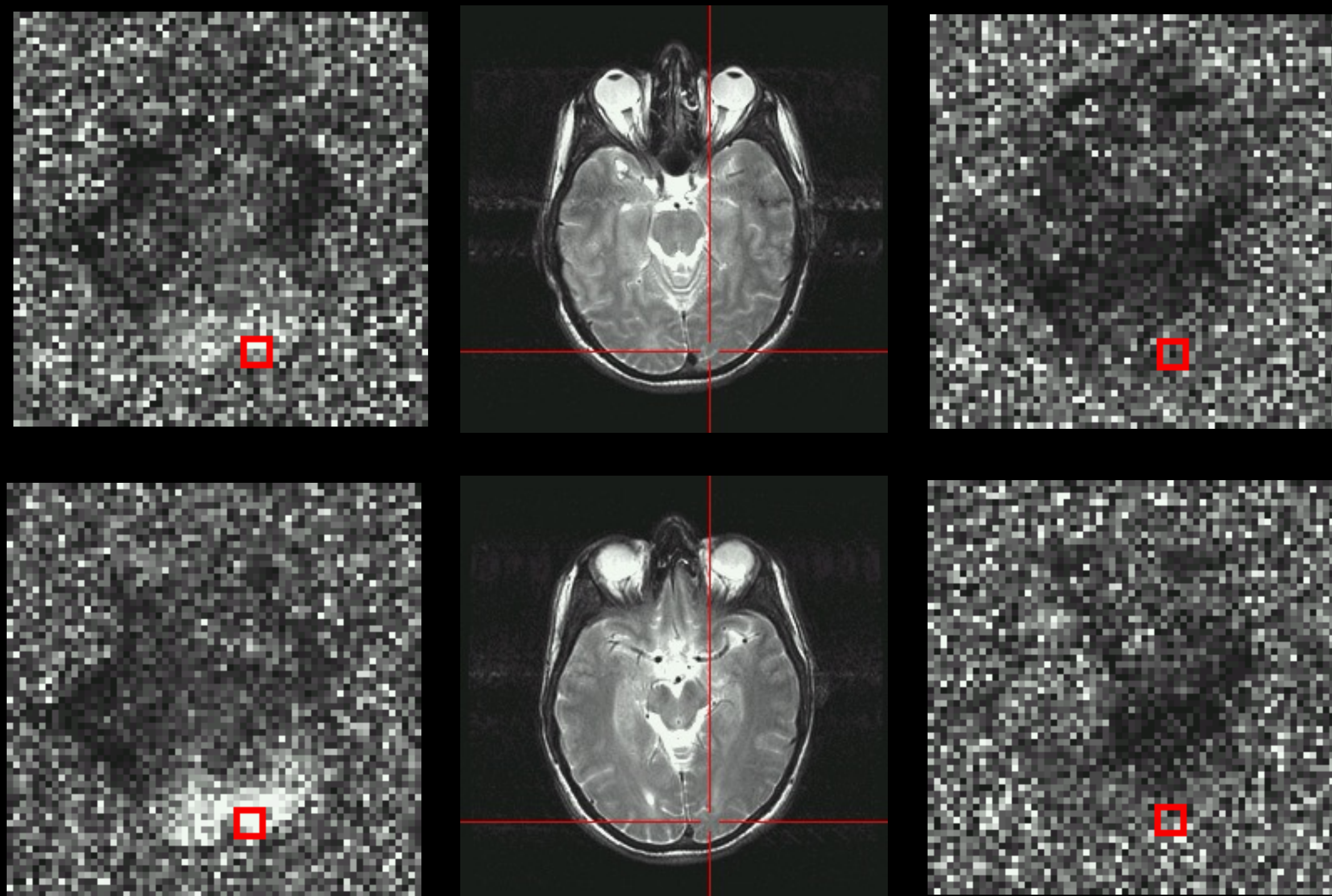
0.5 Hz

0.5 Hz

Phase v=0.12Hz

Closed

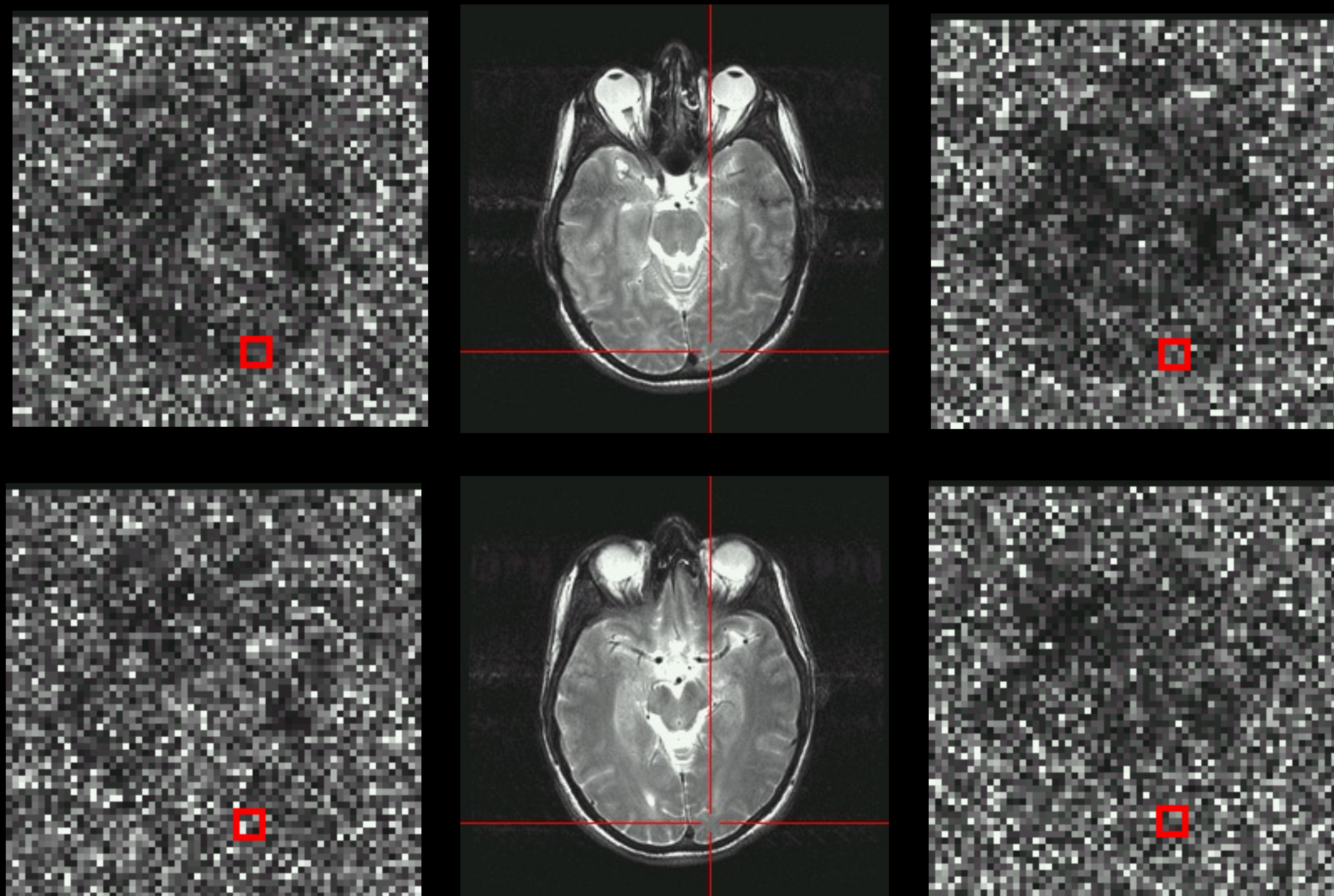
Open



Magnitude v=0.12Hz

Closed

Open



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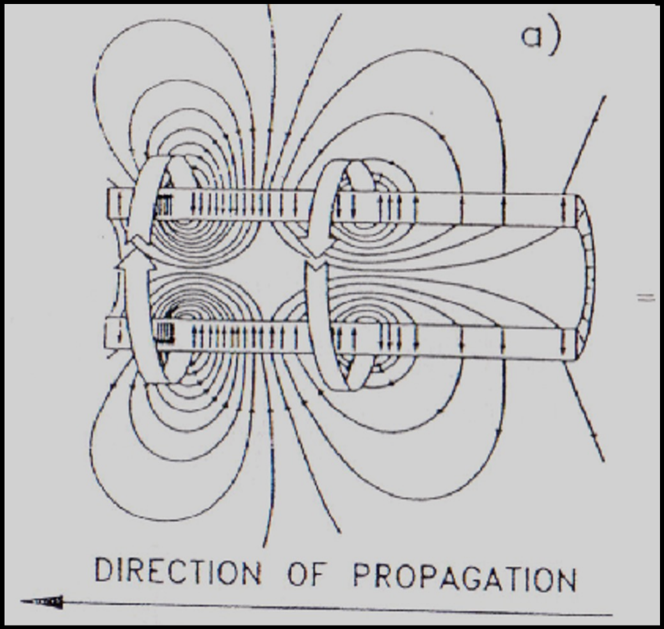
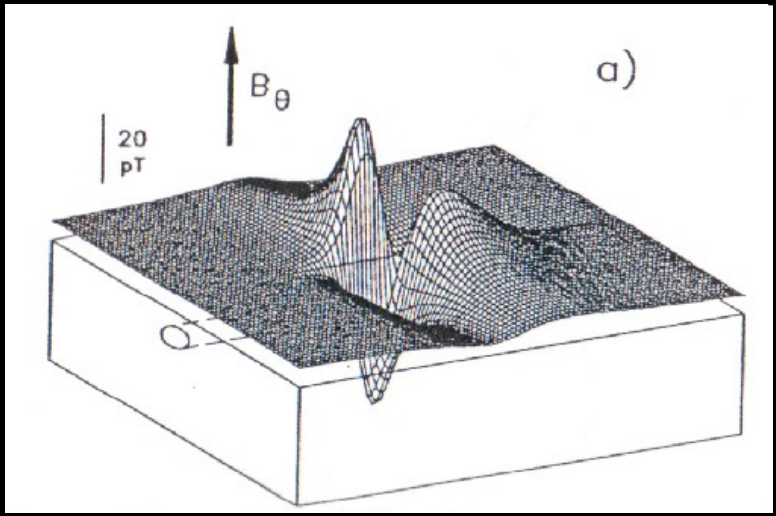
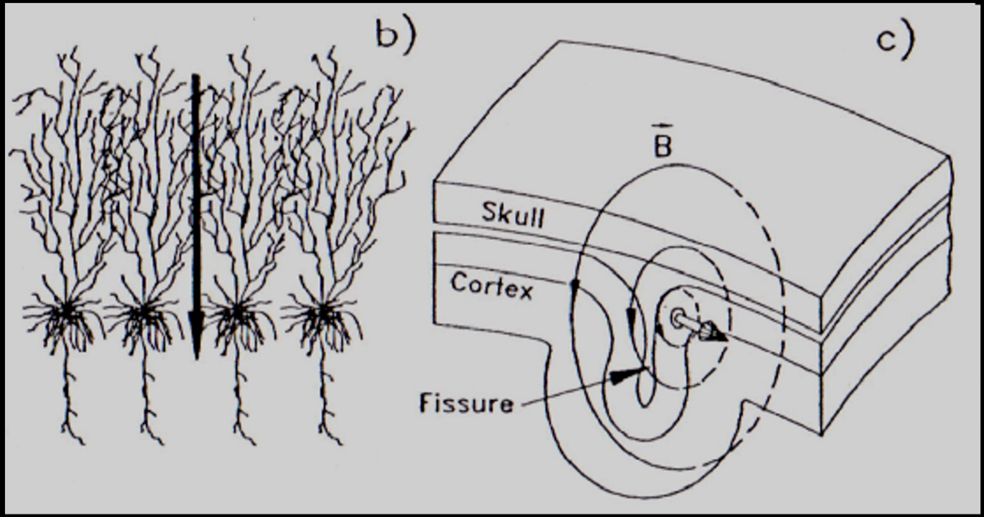
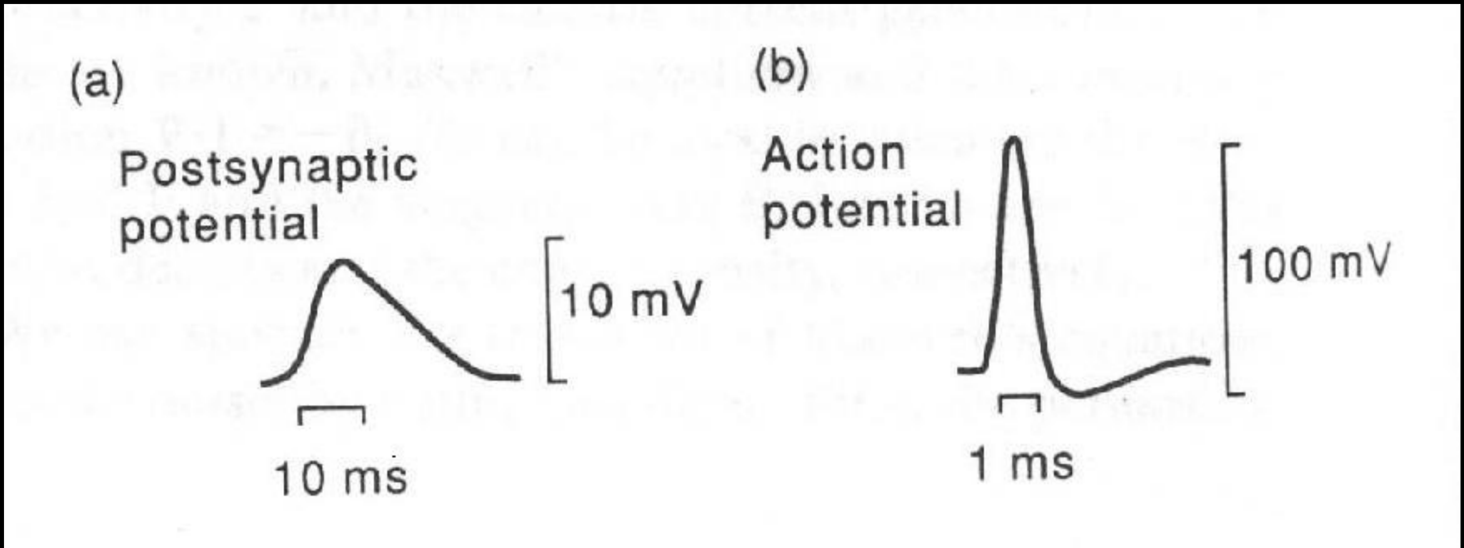






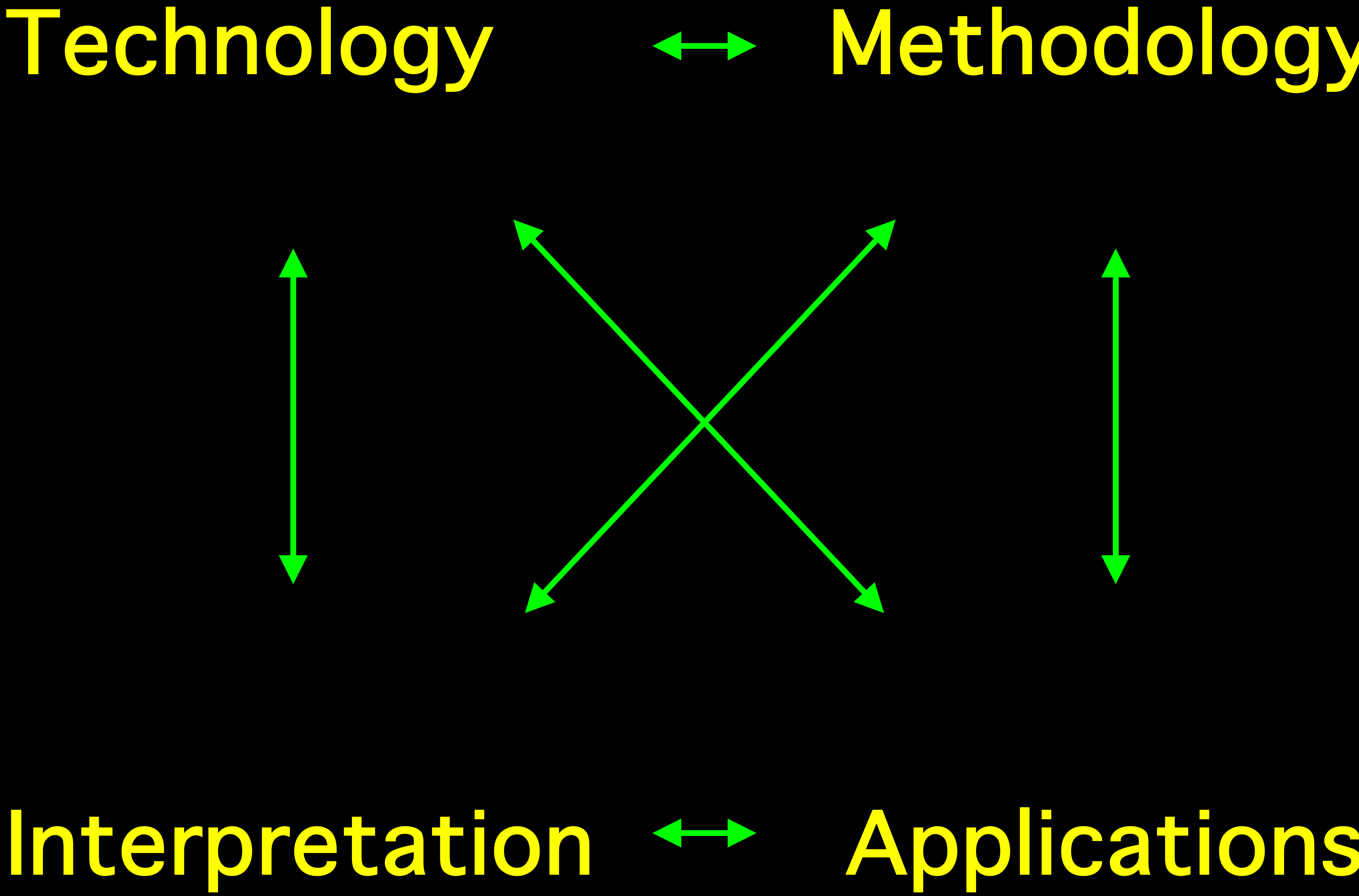
J.P. Wikswo Jr et al. ***J Clin Neuronphy*** **8(2): 170-188, 1991**

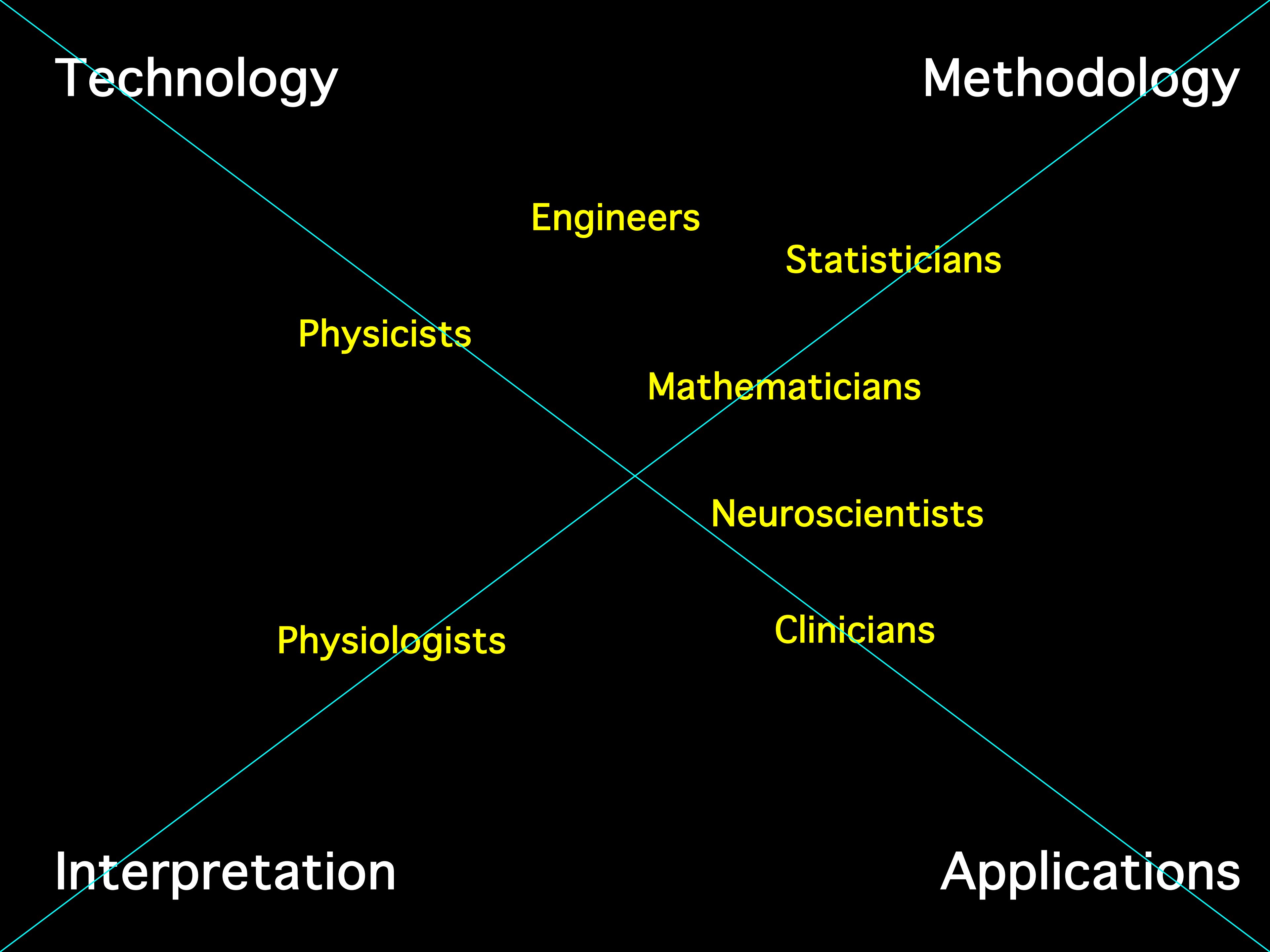


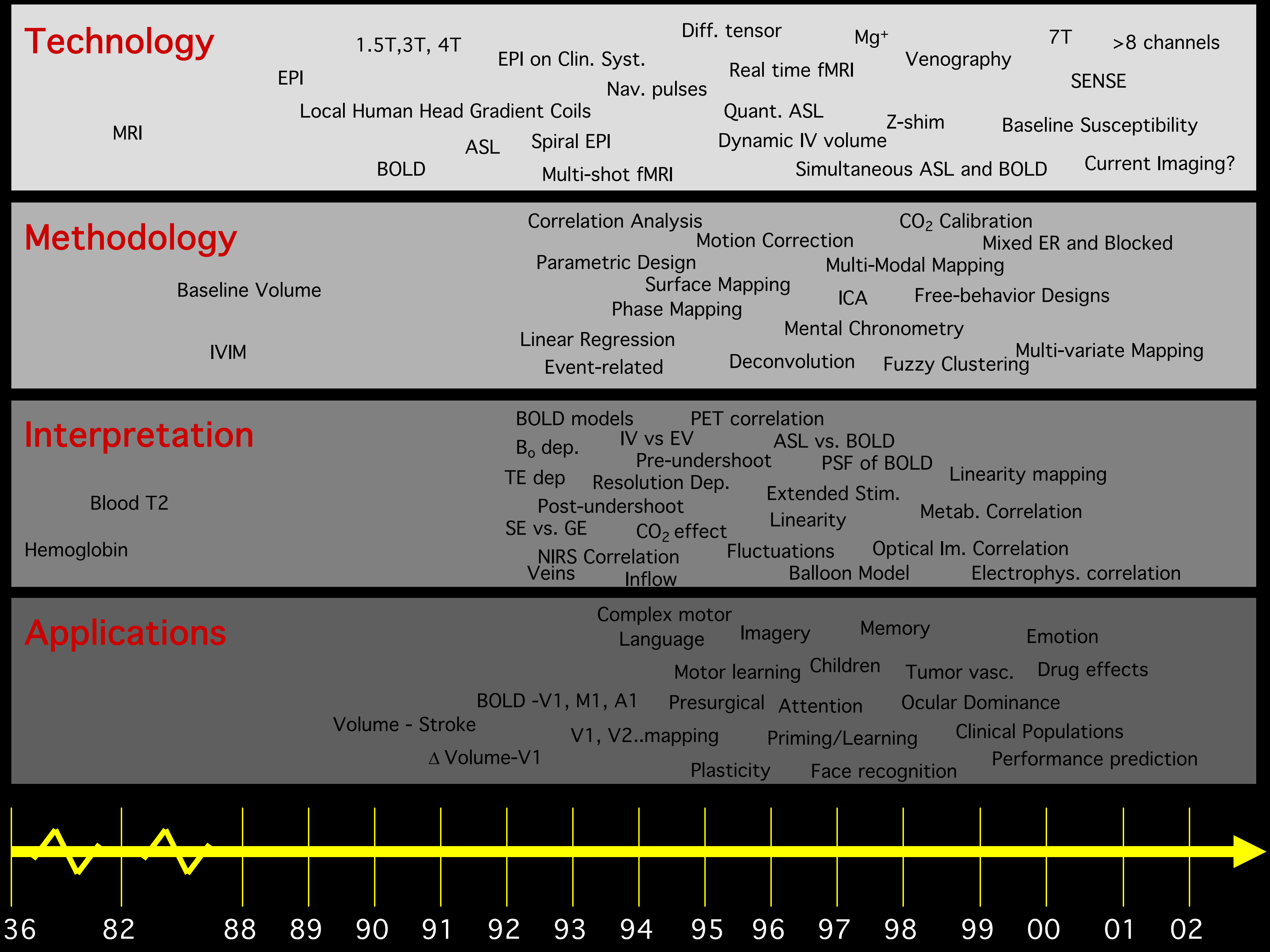
Schematic representation of (a) a postsynaptic potential and (b) an action potential as a function of time.

The post synaptic potential lasts for 10ms or more, allowing integration of individual fields to create

MEG detectable > 100 fT field on surface of skull


Technology
Methodology
Interpretation
Applications


Technology
Methodology
Engineers
Statisticians
Physicists
Mathematicians
Neuroscientists
Physiologists
Clinicians
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
Mg+
Z-shim
Simultaneous ASL and BOLD
Venography
7T
SENSE
Baseline Susceptibility
>8 channels
Current Imaging?
Methodology
Baseline Volume
IVIM
Correlation Analysis
Parametric Design
Surface Mapping
Phase Mapping
Linear Regression
Event-related
Motion Correction
Multi-Modal Mapping
ICA
Mental Chronometry
Deconvolution
CO2 Calibration
Mixed ER and Blocked
Free-behavior Designs
Fuzzy Clustering
Multi-variate Mapping
Interpretation
Blood T2
Hemoglobin
BOLD models
Bo dep.
IV vs EV
TE dep
Resolution Dep.
Pre-undershoot
Post-undershoot
SE vs. GE
CO2 effect
NIRS Correlation
Veins
Inflow
PET correlation
ASL vs. BOLD
PSF of BOLD
Extended Stim.
Linearity
Fluctuations
Balloon Model
Linearity mapping
Metab. Correlation
Optical Im. Correlation
Electrophys. correlation
Applications
Volume - Stroke
Δ 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
Emotion
Drug effects
Performance prediction
36
82
88
89
90
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93
94
95
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99
00
01
02

FIM Unit & FMRI Core Facility

Director:
Peter Bandettini

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

Computer Specialist:
Adam Thomas

Post Docs:
Rasmus Birn
Hauke Heekeren
David Knight
Patrick Bellgowan
Ziad Saad

Graduate Student:
Natalia Petridou

Post-Back. IRTA Students:
Elisa Kapler
August Tuan
Dan Kelley

Visiting Fellows:
Sergio Casciaro
Marta Maieron
Guosheng Ding

Clinical Fellow:
James Patterson

Psychologist:
Julie Frost

Summer Students:
Hannah Chang
Courtney Kemps
Douglass Ruff
Carla Wettig
Kang-Xing Jin

Program Assistant:
Kay Kuhns

Scanning Technologists:
Karen Bove-Bettis
Paula Rowser