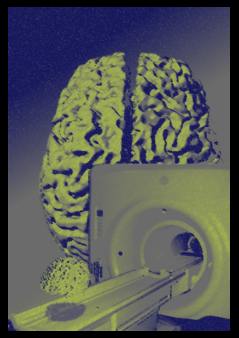
FUNCTIONAL ASL: PERFUSION BASED FUNCTIONAL MRI USING ARTERIAL SPIN LABELING

APPLICATIONS OF ASL IN NEUROSCIENCE

Luis Hernandez-Garcia, Ph.D.

Functional MRI laboratory

University of Michigan

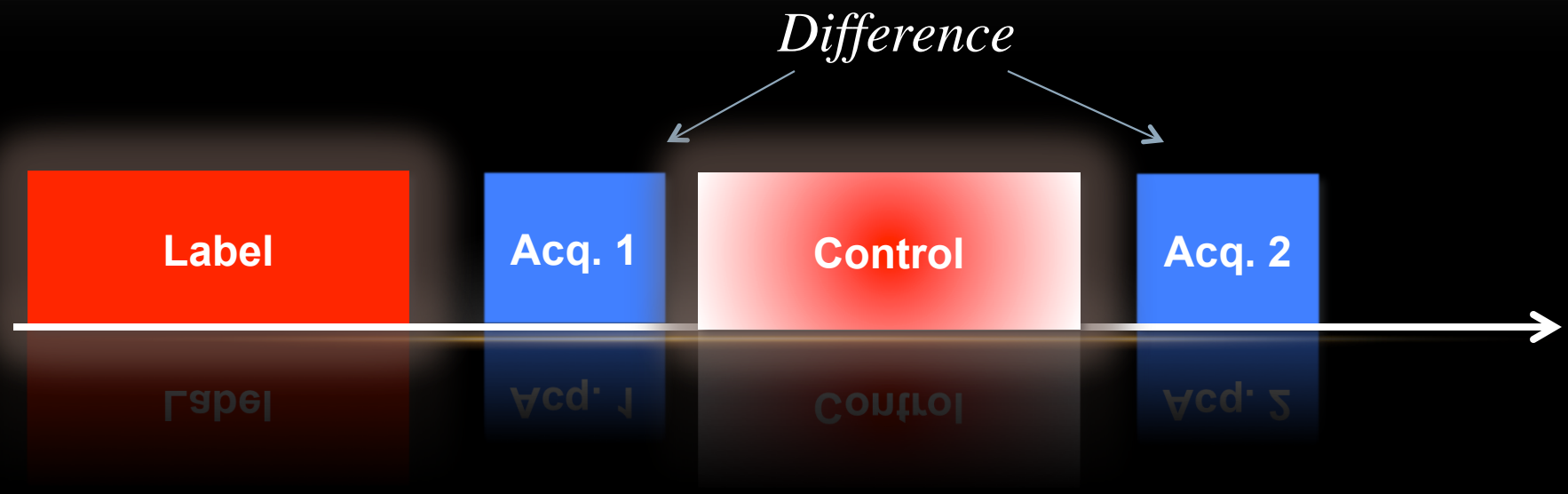


FUNCTIONAL MRI LABORATORY
UNIVERSITY OF MICHIGAN

OVERVIEW

- Quick review of ASL
- The niche for ASL
- Examples of practical applications in literature

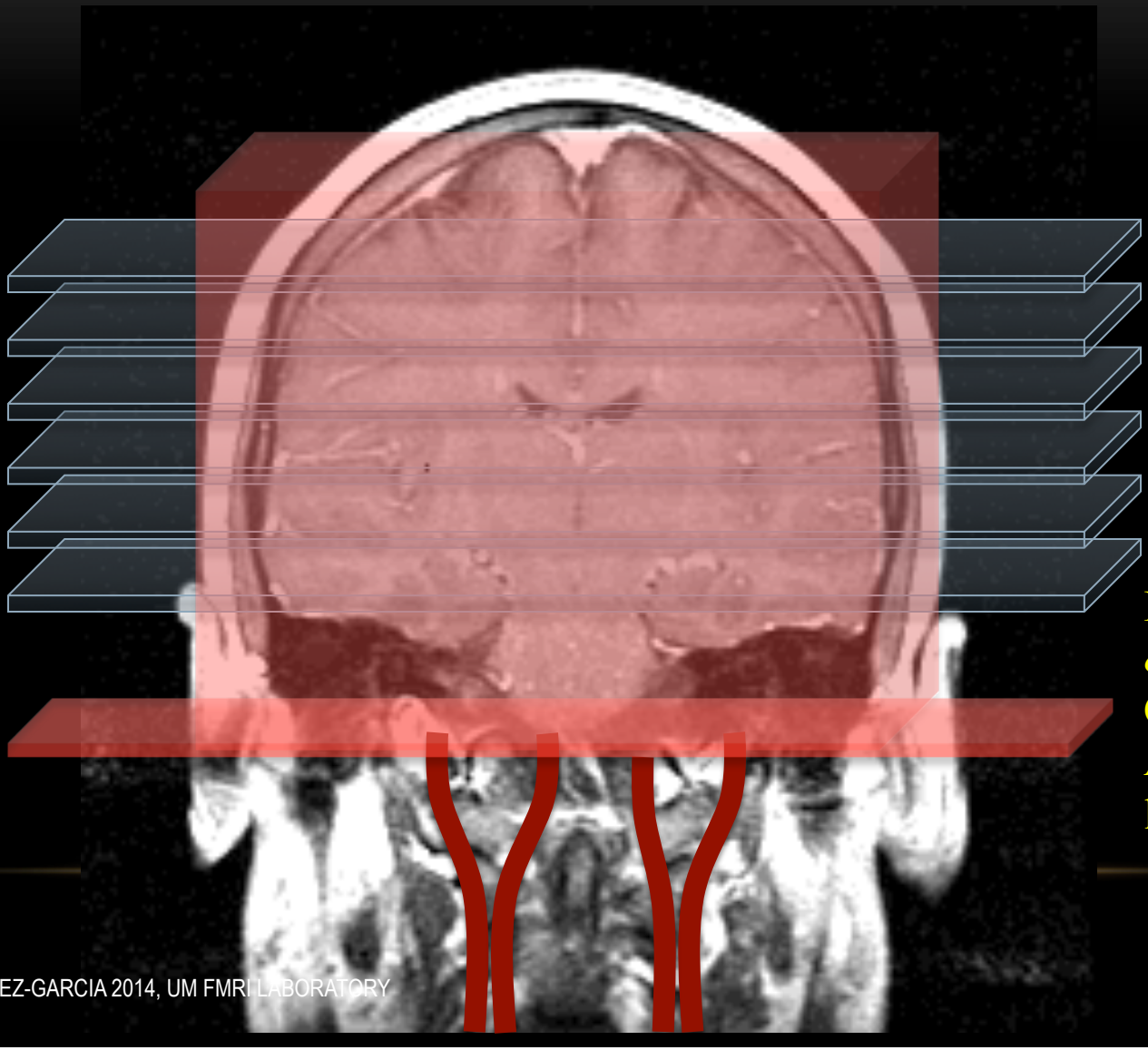
A generic ASL pulse sequence



Some Options

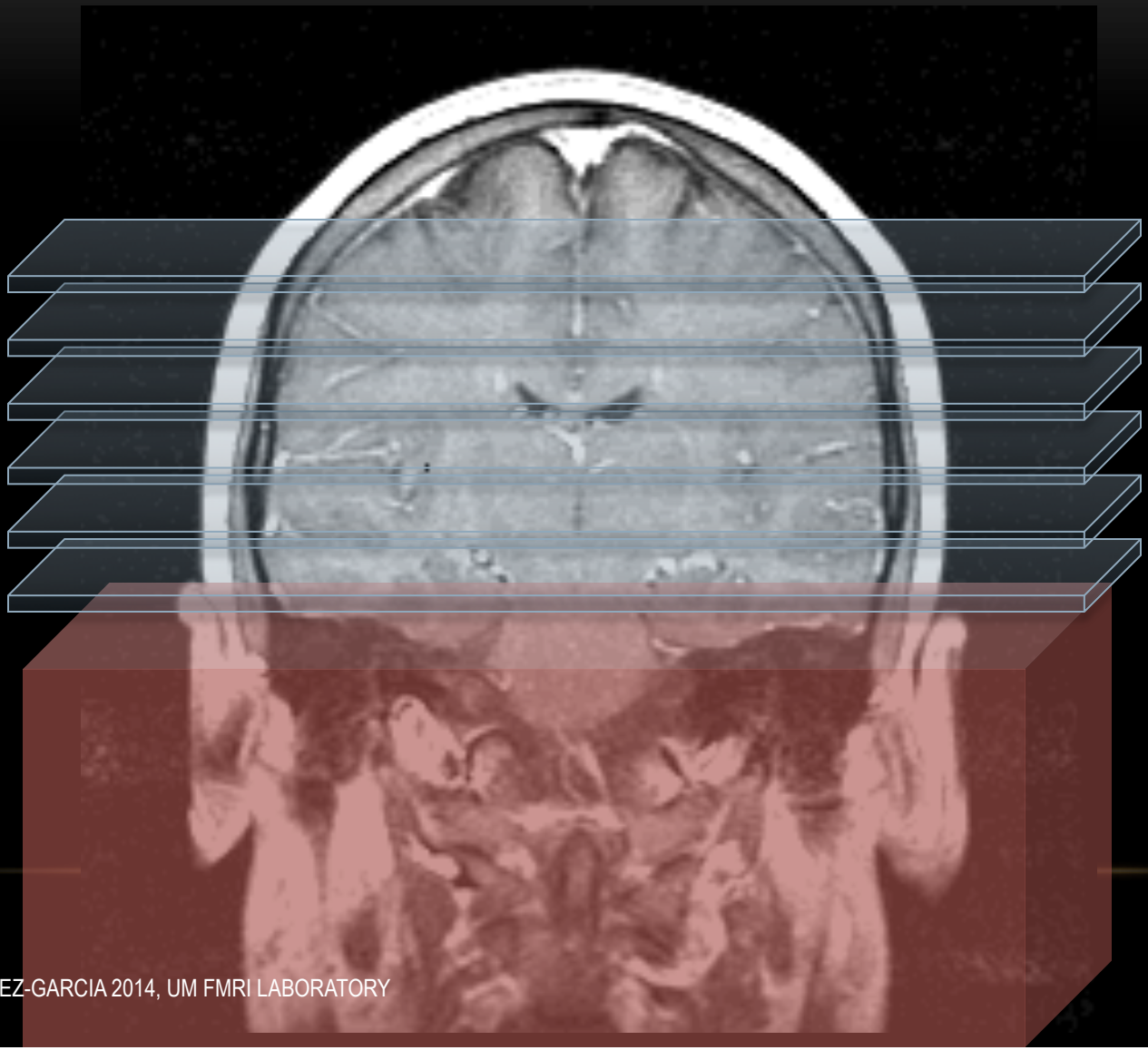
- Pulsed vs. Continuous
- Delays
- Saturation Pulses
- 2D, 3D …

CONTINUOUS ASL

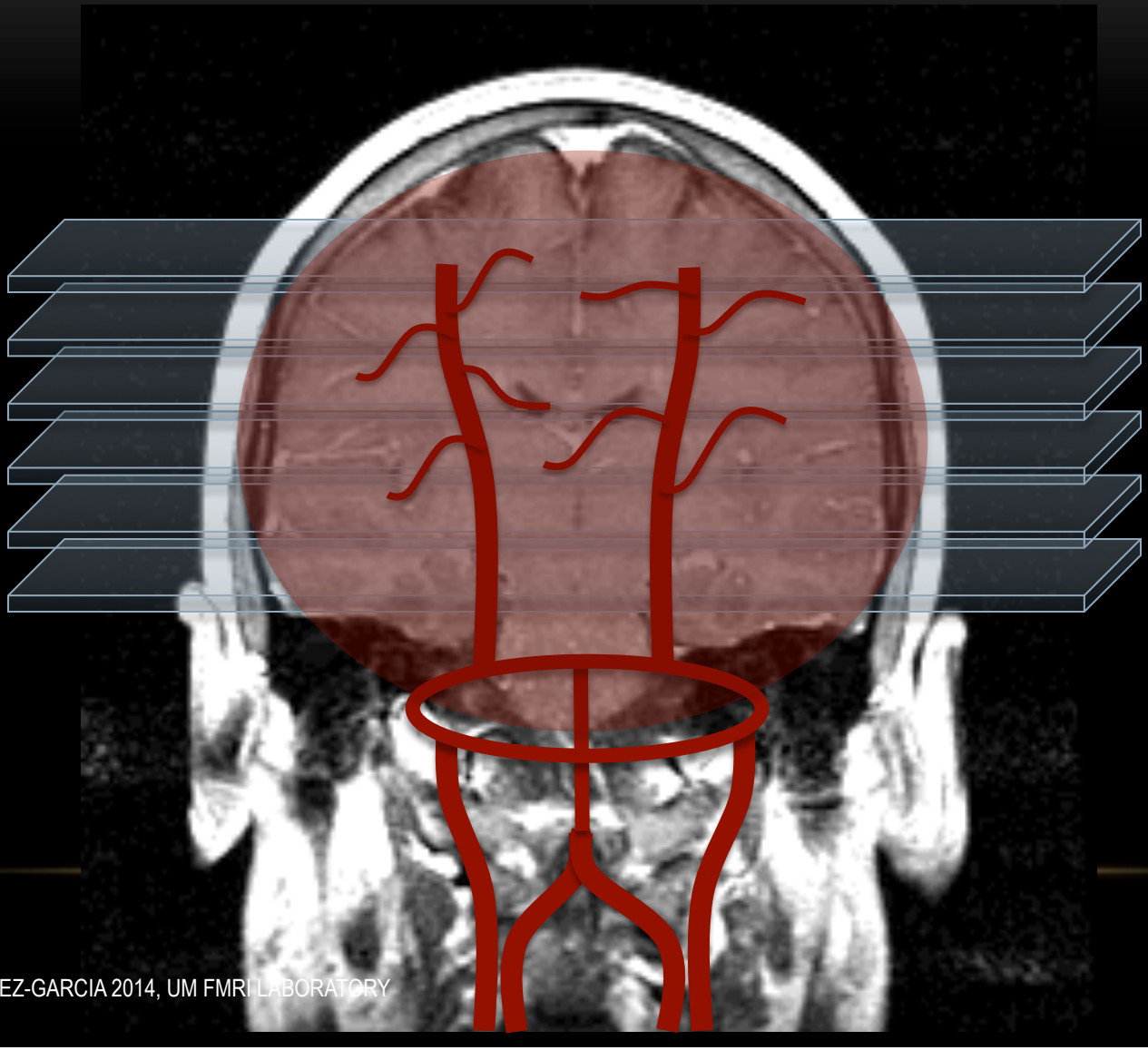


Inversion
&
Control
At the same
location

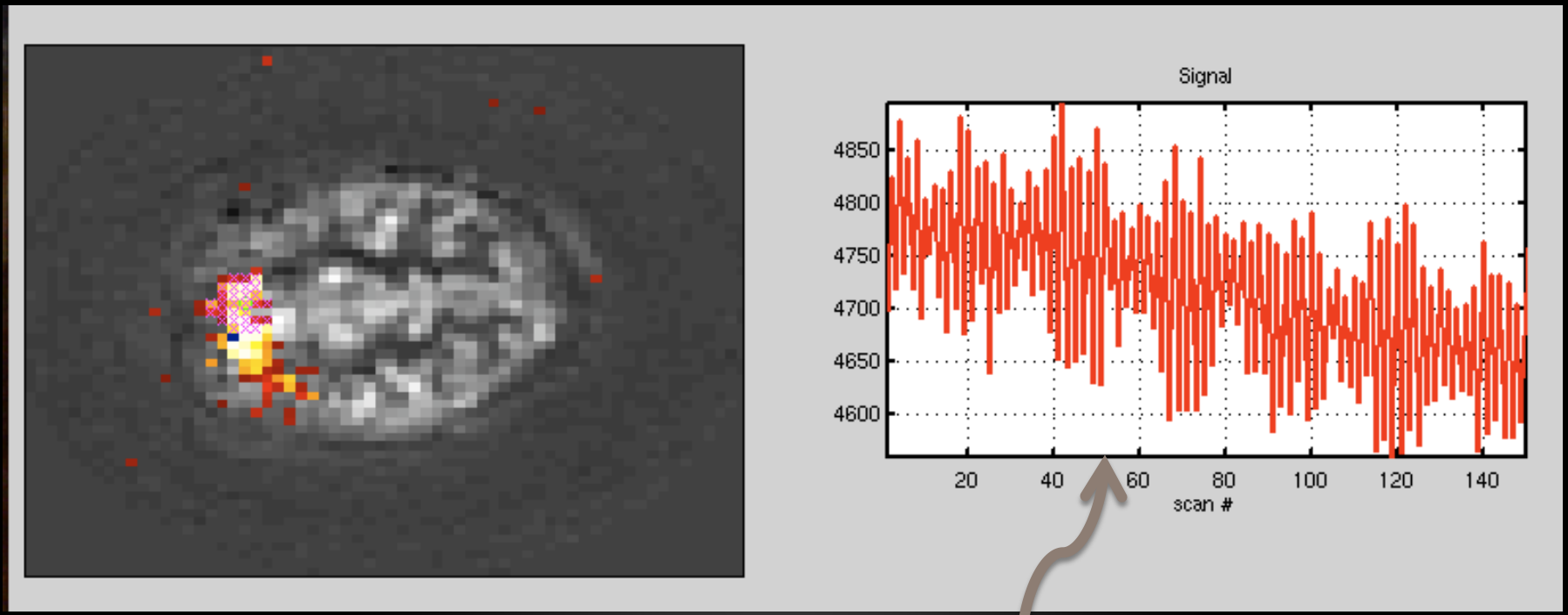
PULSED ASL SCHEMES



VELOCITY SELECTIVE ASL



ASL-BASED FUNCTIONAL MRI



Raw (unsubtracted) time course

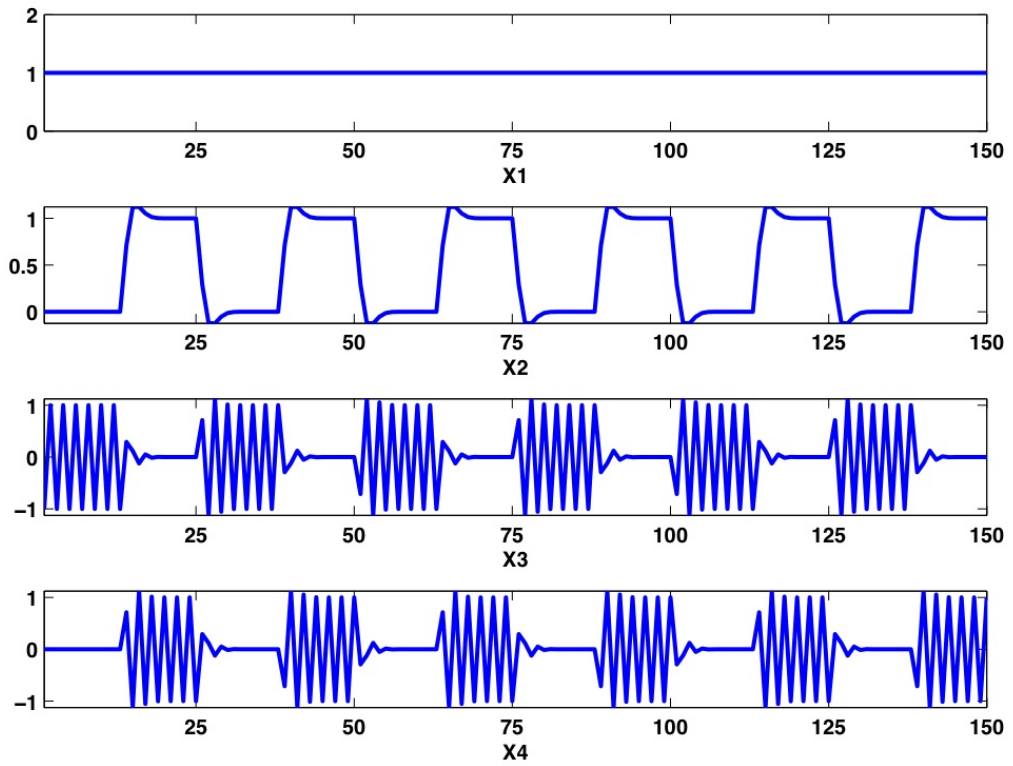
A LINEAR MODEL FOR ASL

Base image

BOLD effects

ASL at rest

ASL during activation



QUANTIFYING *DYNAMIC* PERFUSION CHANGES

Traditional Approach:

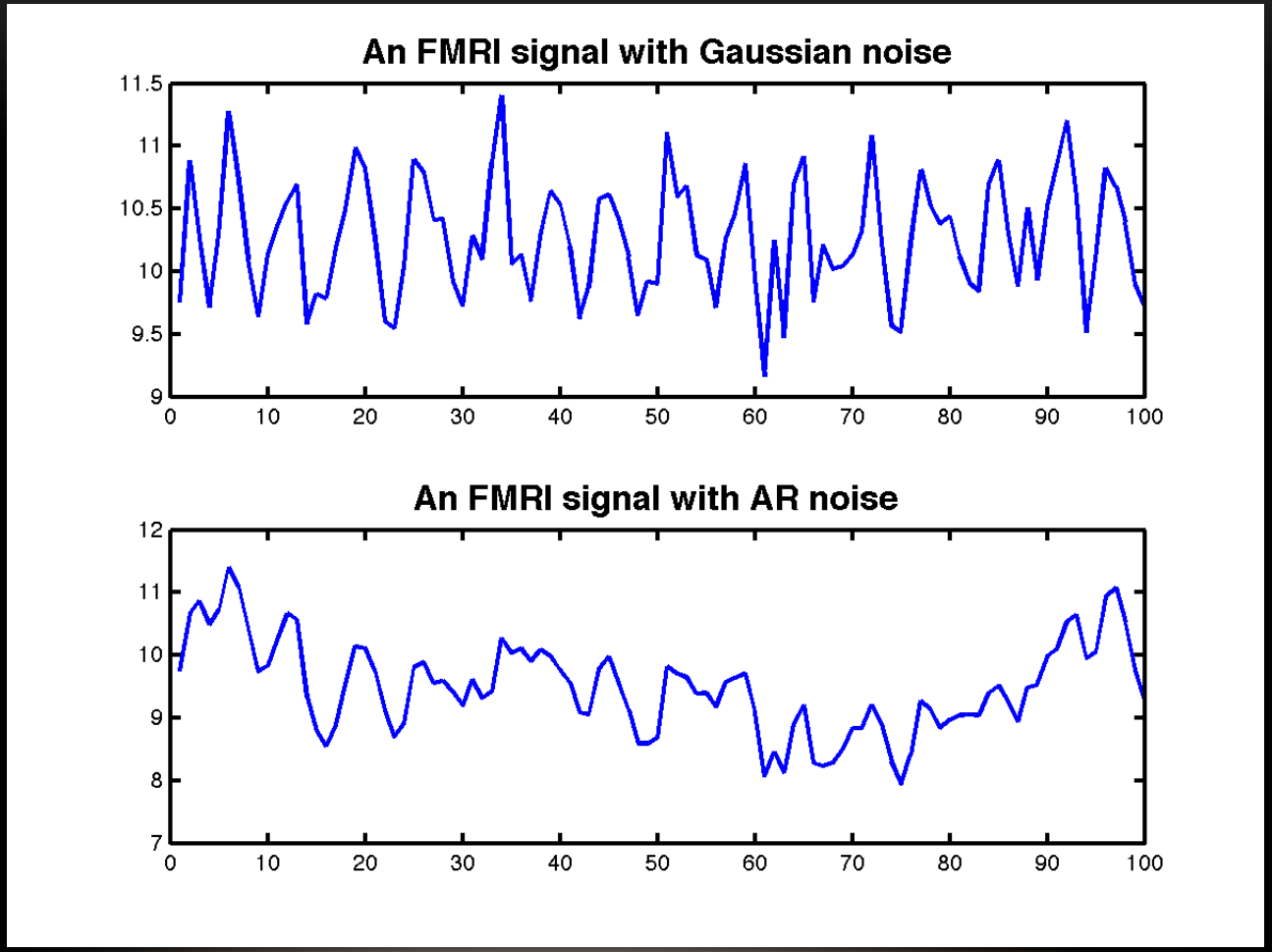
1. Calculate perfusion from each subtraction pair using tracer kinetics Wang J, et al. (2002). Magn. Reson. Med., vol. 48, no. 2, pp. 242-254.
2. Calculate difference in perfusion between conditions.
3. Calculate means and variances

GLM Approach:

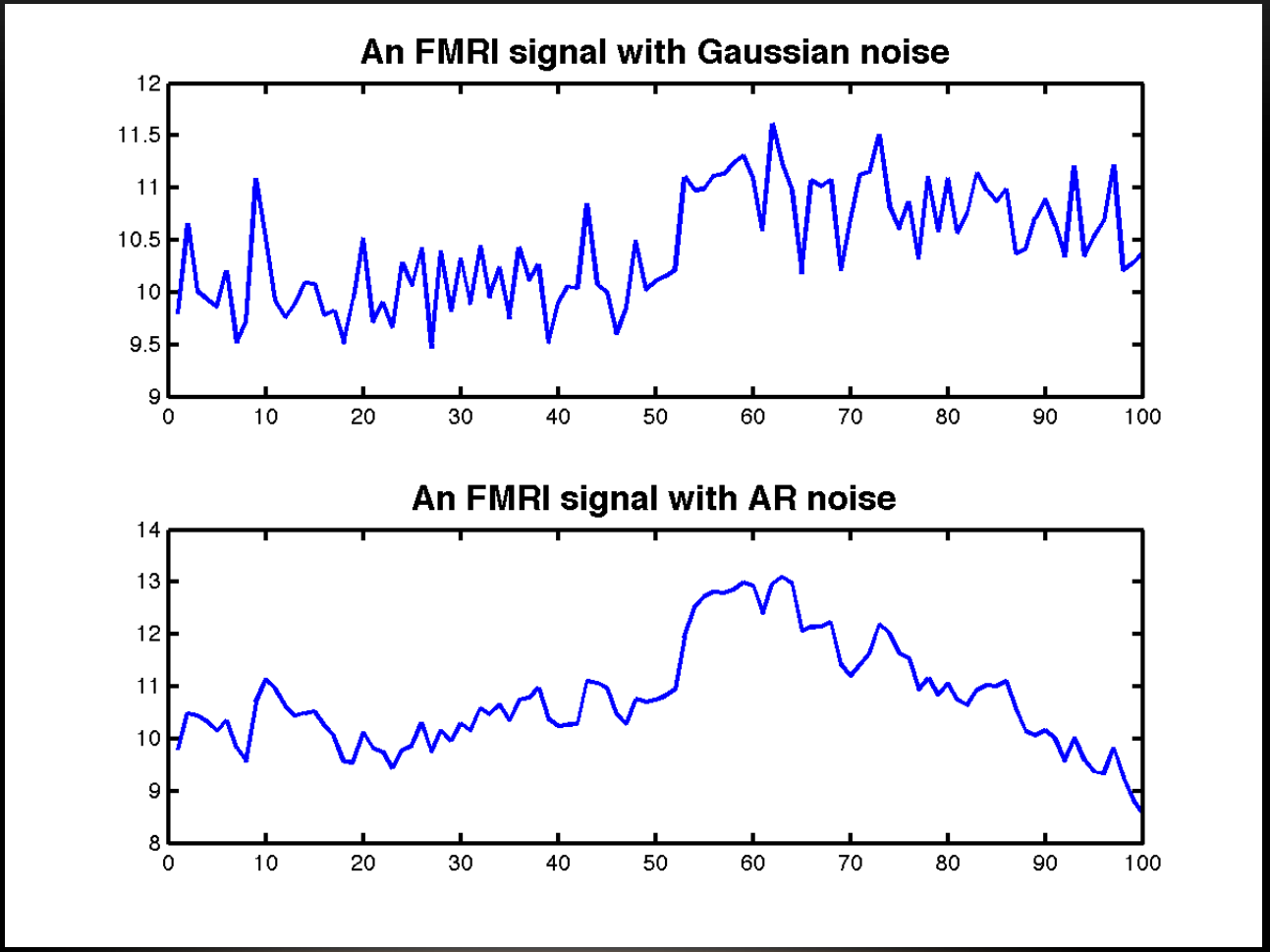
1. Translate GLM parameters (betas) into perfusion.
2. Translate variance estimates (sigmas) into perfusion effects variance

Hernandez-Garcia L, et al. (2010), Magn. Res. Imaging, 28 (7), Pages 919-927.

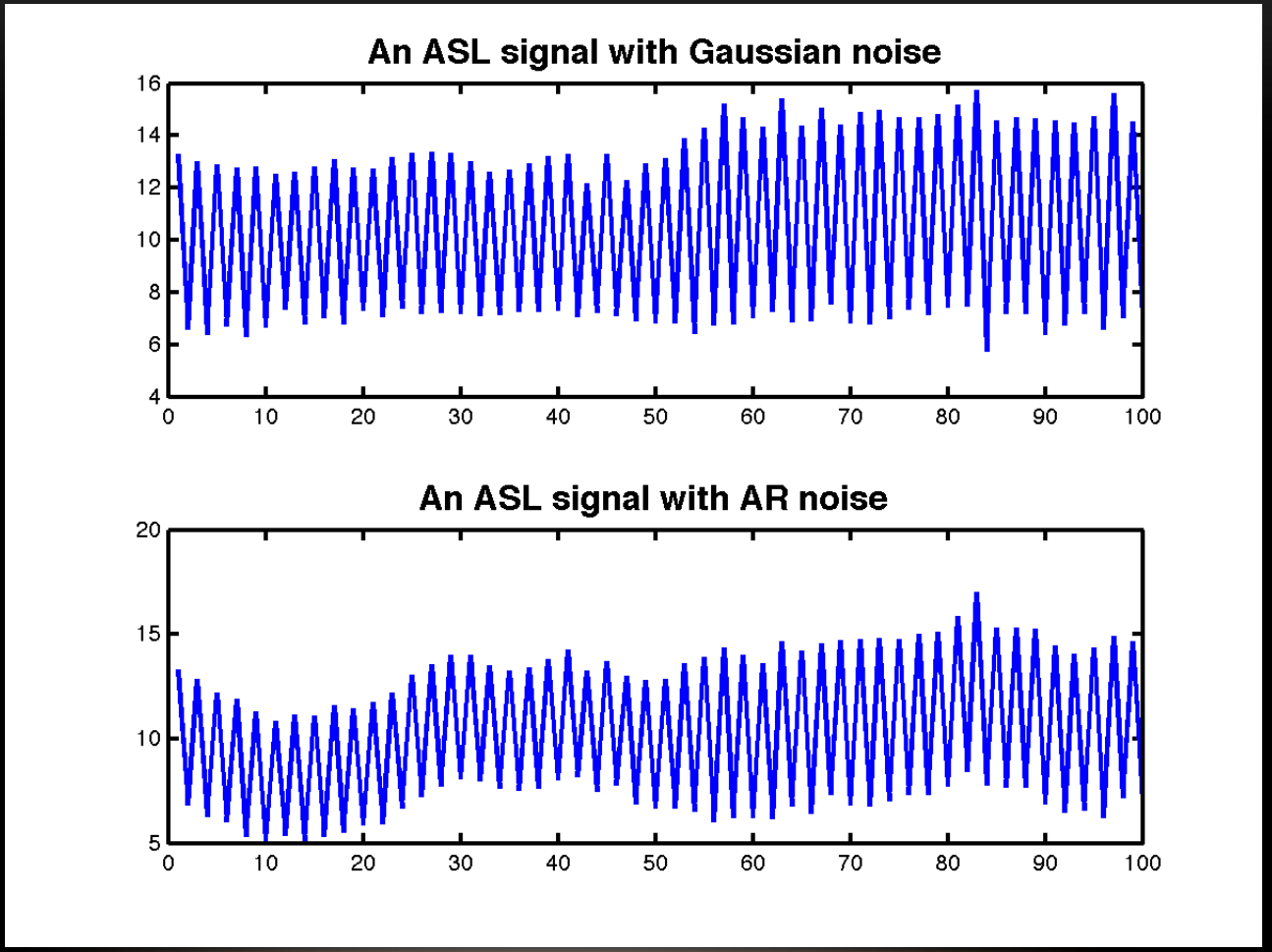
EVENT RELATED BOLD



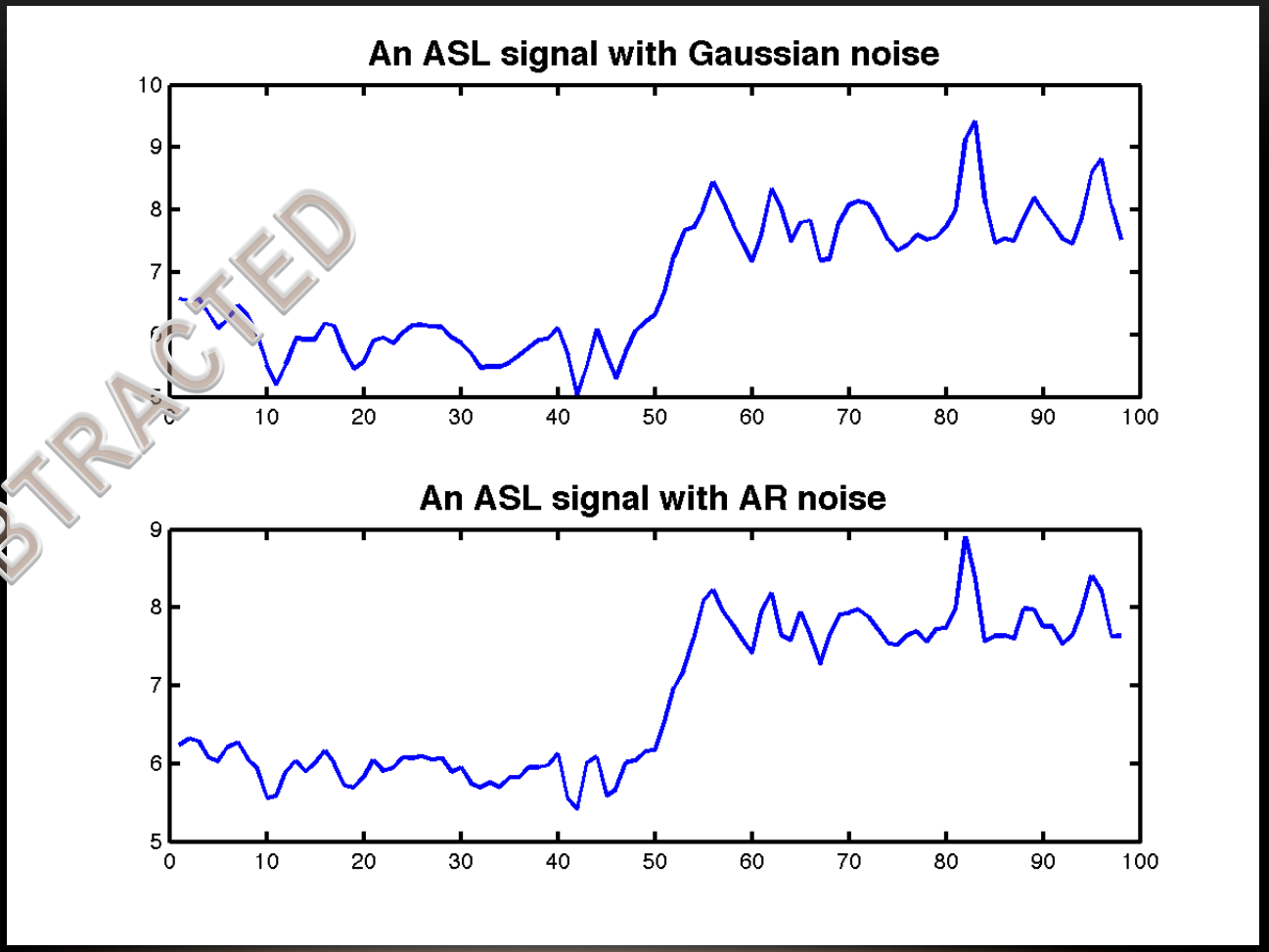
BLOCKED DESIGN BOLD: SLOW PARADIGM



BLOCKED DESIGN FASL: SLOW PARADIGM

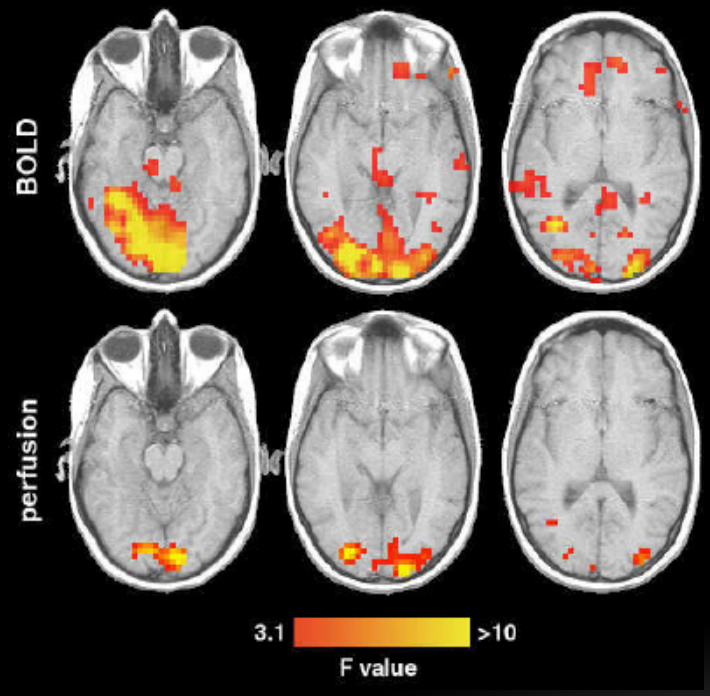


BLOCKED DESIGN FASL: SLOW PARADIGM

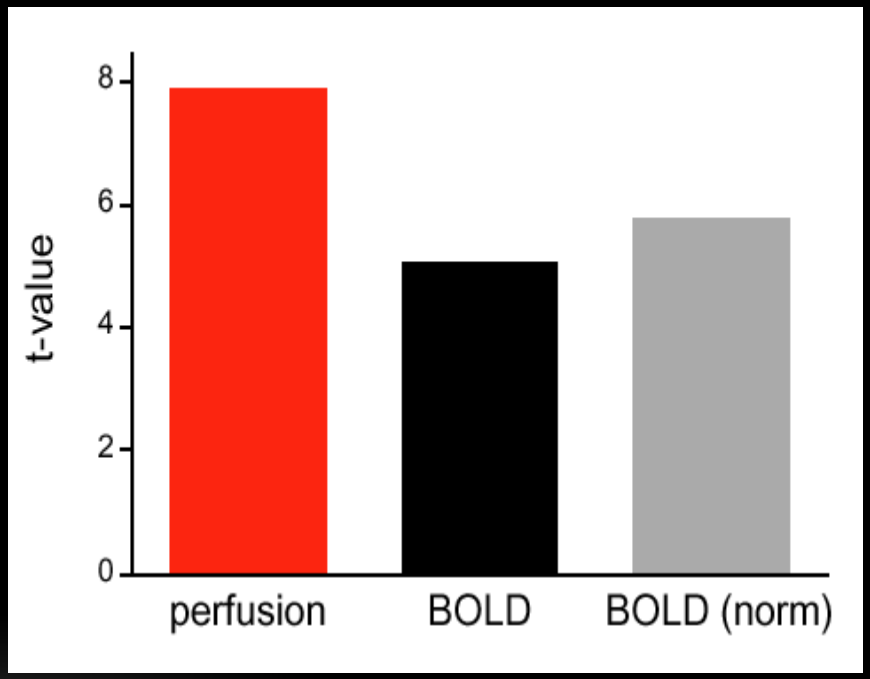


ASL PERFUSION FMRI VS. BOLD (SENSITIVITY)

*Aguirre, G., J. Detre, et al. (2002). "Experimental design and the relative sensitivity of BOLD and perfusion fMRI." Neuroimage **15**(3): 488-500.*

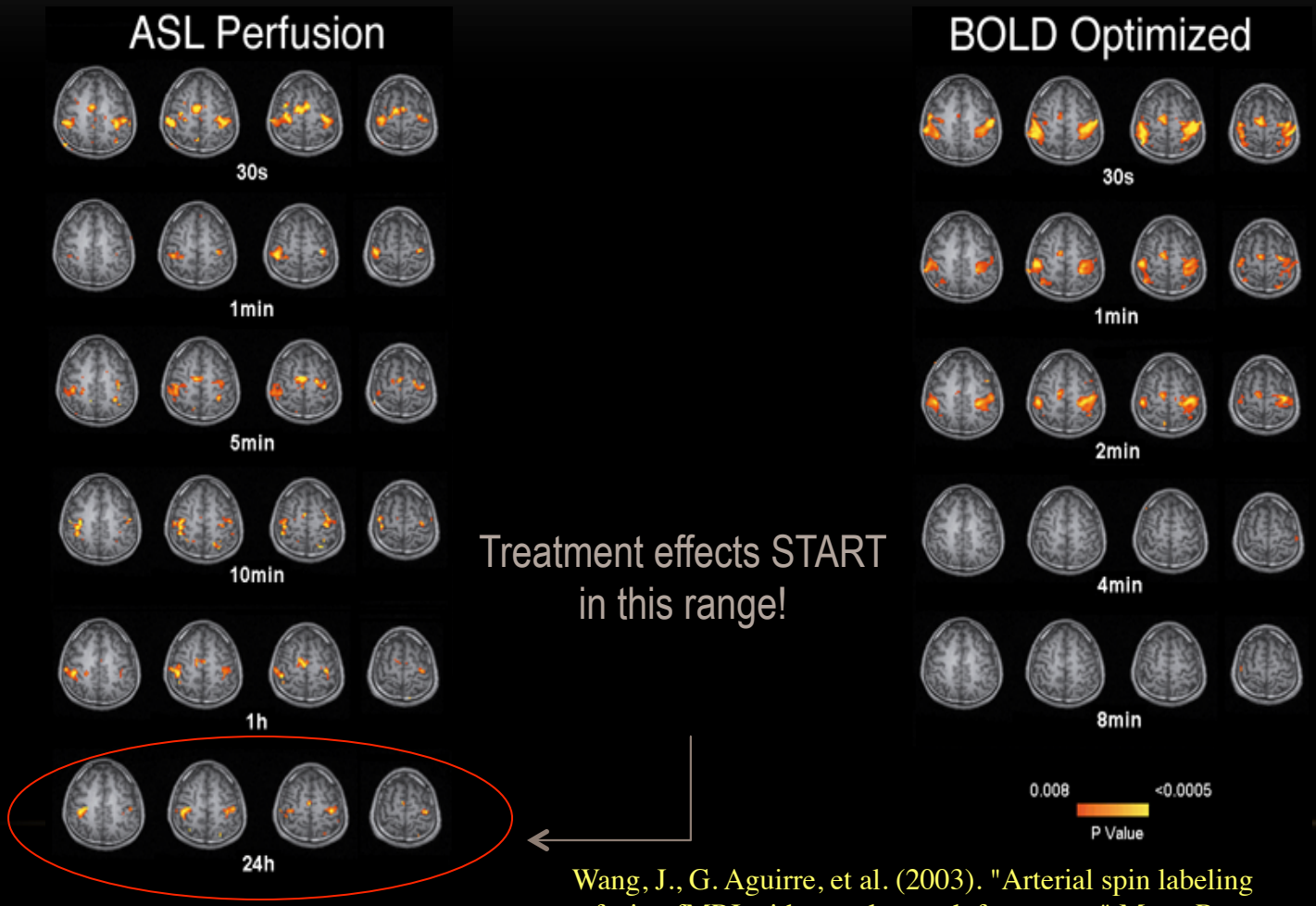


Single Subject



Group Analysis (Random Effects)

ASL PERFUSION VS. BOLD
VERY LOW TASK FREQUENCY

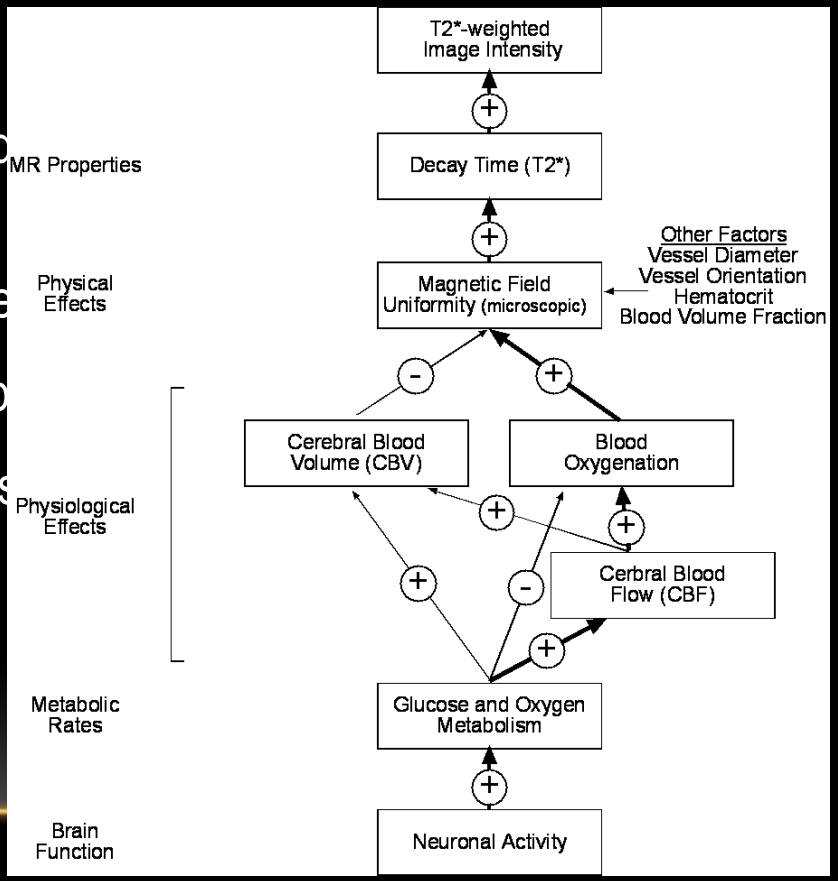


Treatment effects START in this range!

Wang, J., G. Aguirre, et al. (2003). "Arterial spin labeling perfusion fMRI with very low task frequency." Magn Reson Med **49**(5): 796-802.

WHY ASL?
QUANTIFICATION.

- BOLD : a complicated mix of parameters.
- Calibrated (quantitative) BOLD requires add
  them)
- ASL can yield perfusion directly with simple
- Perfusion is well correlated with local field p
- Perfusion is fairly stable from person to pers
  - Multi-center studies
  - Longitudinal studies …



WHY ASL?
THE BOLD SIGNAL DRIFT

- Autoregressive structure of MRI noise
- BOLD signals are inherently “drifty” because:
  - Physiological effects
    - Respiration
    - Heart beat
  - Scanner effects
  - Temperature

WHY **NOT** ASL?

- *Current ASL techniques have lower SNR than BOLD!*
  - *(the ASL signal is about 1 % of the total signal in a voxel)*
- *Current ASL techniques are significantly slower than BOLD!*
  - *BOLD can collect one volume every second*
  - *ASL requires a labeling period and a PAIR of images (3 seconds at the very best)*

ASL'S NICHE

- Real time neurofeedback
- Drug Studies
- Attention
- Cognitive Training
- Low frequency paradigms
- Mental State studies
- Population Studies
- … anything SLOW or requiring Quantification!

SOME ASL STUDIES IN NEUROSCIENCE

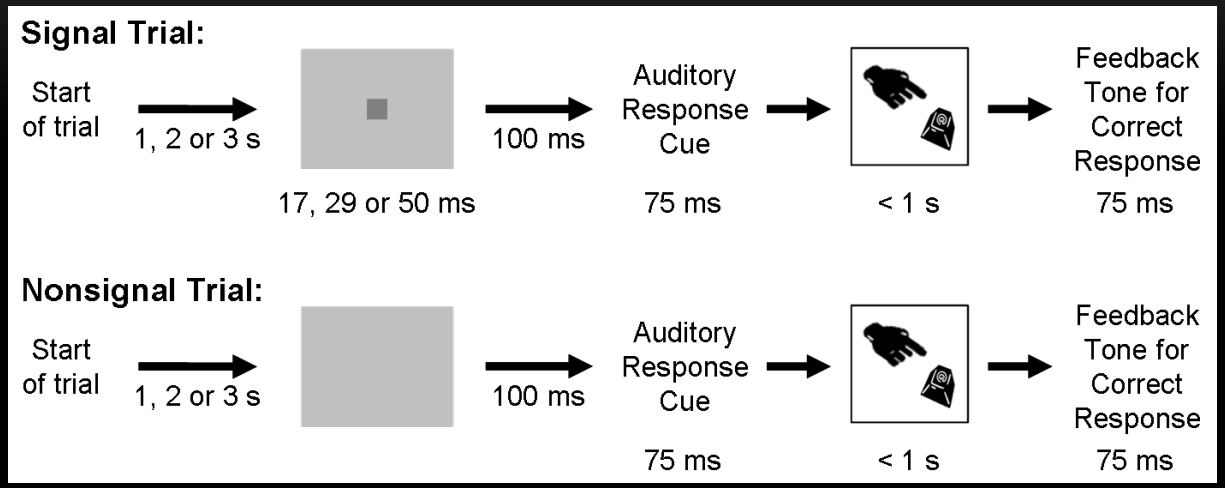
- Cognitive neuroscience
  - Attention
  - Working memory
- Clinical applications
  - Schizophrenia
  - Multiple sclerosis
  - Alzheimers

EXAMPLE #1: SUSTAINED ATTENTION STUDY

Demeter, E. et al: "Challenges to attention: a continuous arterial spin labeling (ASL) study of the effects of distraction on sustained attention."
Neuroimage, vol. 54, no. 2, pp. 1518–1529, 2011.

- What are the neural substrates of sustained attention?
- What does distraction do to your ability to sustain attention?
- How does this relate to existing animal work (measures of cholinergic activity)?

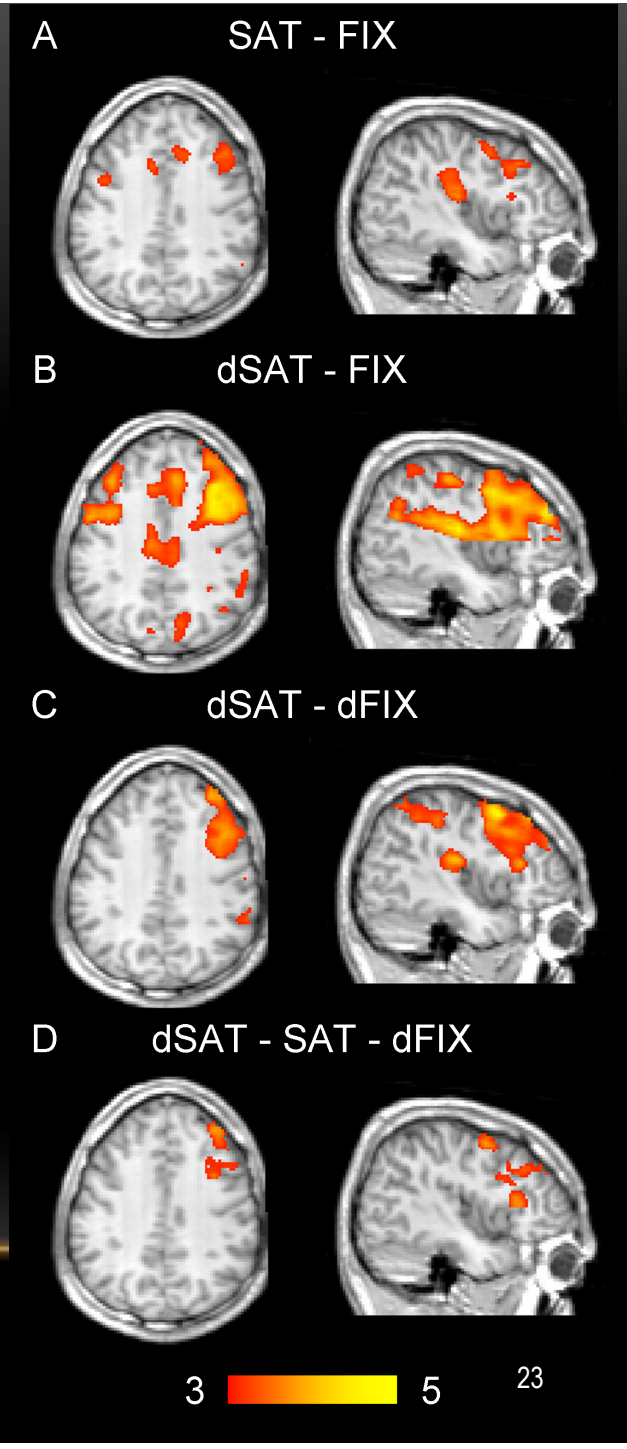
SUSTAINED ATTENTION STUDY: THE EXPERIMENT



- Task paradigm:
  - Long period of time on task: 140 and 160 second blocks
  - Detect the presence of a short visual cue (< 50 ms).
  - Sometimes in the presence of a distracting flashing light.
- Imaging:
  - continuous ASL with separate labeling coil
  - No arterial signal suppression.

SUSTAINED ATTENTION STUDY: FINDINGS

- The distractor impaired behavioral performance.
- Increase in activation in right fronto-parietal regions.
- Recruitment of the mechanisms to maintain attention.
- But … RDLPFC correlates with worse performance.
- These results mirrored findings in rat studies of cholinergic system.



SUSTAINED ATTENTION STUDY:

- ✓ Slow Paradigm (0.005 Hz)
  Intervention
  Longitudinal
  Baseline activity
  Quantification (relative)

EXAMPLE #2: WORKING MEMORY TRAINING STUDY

M. Buschkuehl, et al “Neural effects of short-term training on working memory.”

Cogn. Affect. Behav. Neurosci., pp. 147–160, 2014.

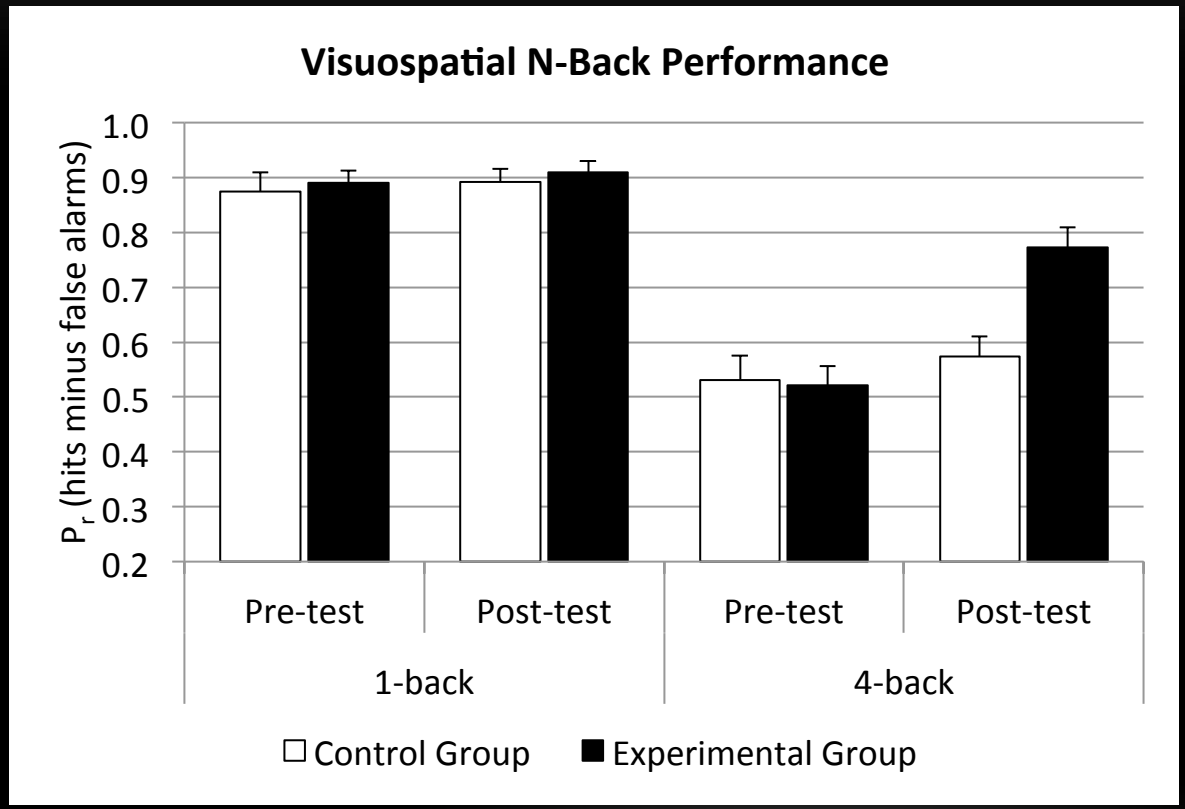
- How does cognitive training affect performance?
- What happens to your brain when you practice?
  - Resting
  - Activation

WORKING MEMORY TRAINING STUDY: THE EXPERIMENT

Visual N-back tasks: 4-back and 1-back
Imaging with pseudo-continuous ASL

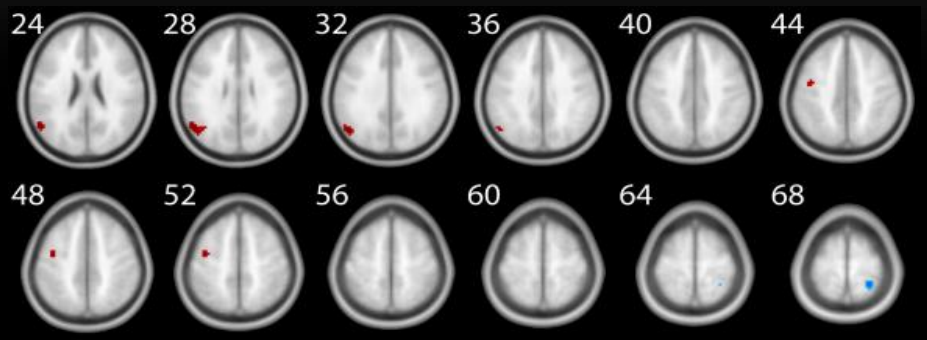
1. Test Performance (while collecting ASL images)
2. Train for one week, 20 mins. per day
3. Test Performance (while collecting ASL images)

WORKING MEMORY TRAINING STUDY: FINDINGS



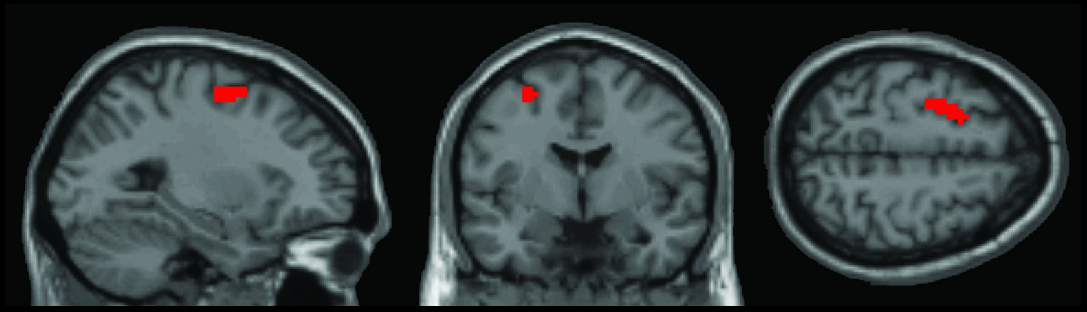
Effect of training:
They get better at it

WORKING MEMORY TRAINING STUDY: FINDINGS



Effect of training:
Resting Perfusion Change

Effect of training:
Activation Perfusion Change



WORKING MEMORY TRAINING STUDY:

- ✓ Intervention
- ✓ Longitudinal
- ✓ Baseline activity
- ✓ Quantification (relative)

EXAMPLE #3: SCHIZOPHRENIA STUDY

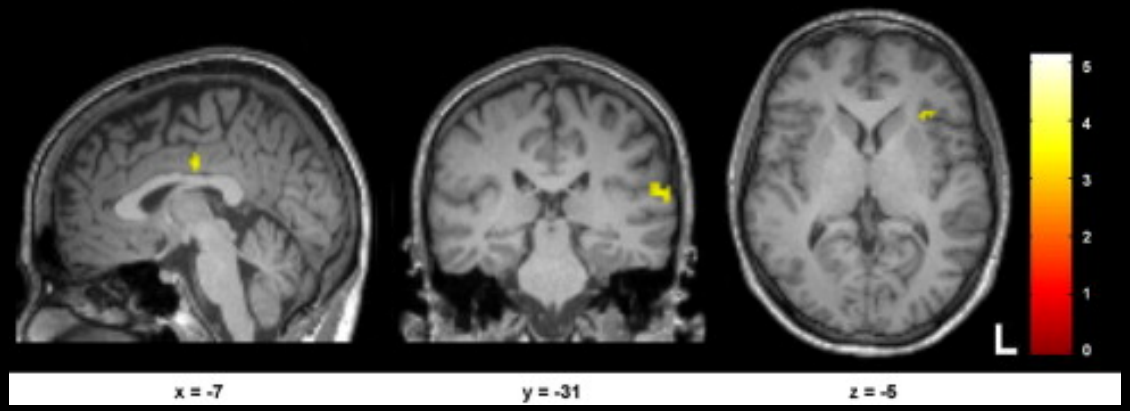
Kindler J, et al: "Reduced neuronal activity in language-related regions after transcranial magnetic stimulation therapy for auditory verbal hallucinations."
Biol Psychiatry. 2013 Mar 15;73(6):518-24.

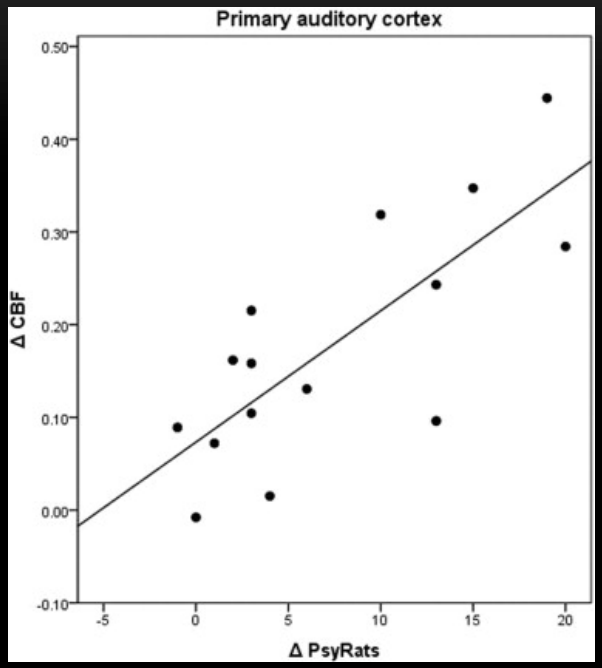
- Pharmaco-resistant auditory verbal hallucinations (AVH)
- People with AVH show increased activity in areas responsible for speech perception and production.
- What are the effects of repetitive TMS treatment ?

SCHIZOPHRENIA STUDY: THE EXPERIMENT

- Neuronavigation (BOLD imaging of language processing)
- TMS treatment:
  - 10 day course
  - 1-Hz or theta-burst stimulation (TBS)
  - Neuronavigation with frameless stereotaxic system.
- Control group received usual (pharmacological) treatment
- Measure CBF before and after
- Measure psychotic symptom rating scale (psyRATS) before and after

SCHIZOPHRENIA STUDY: FINDINGS





ROI analysis: Reduced CBF in:

- primary auditory cortex
- Broca's area
- cingulate

Clinical: significant reduction in psyRATS with rTMS

SCHIZOPHRENIA STUDY:

- ✓ Intervention
- ✓ Longitudinal
- ✓ Baseline activity
- ✓ Quantification

EXAMPLE #4 : MULTIPLE SCLEROSIS

D'haeseleer, M et al: "Cerebral hypoperfusion in multiple sclerosis is reversible and mediated by endothelin-1"
Proc Natl Acad Sci U S A. 2013 Apr 2;110(14):5654-8

- We know CBF is reduced in MS
- Chronic hypoperfusion can produce neuronal degeneration similar to MS
- Endothelin-1 (ET1) is a vasoconstrictor
- Inflammatory response in astrocytes : source of ET1.
- Is ET1 responsible for CBF reduction and neuronal damage?
- Therapy?

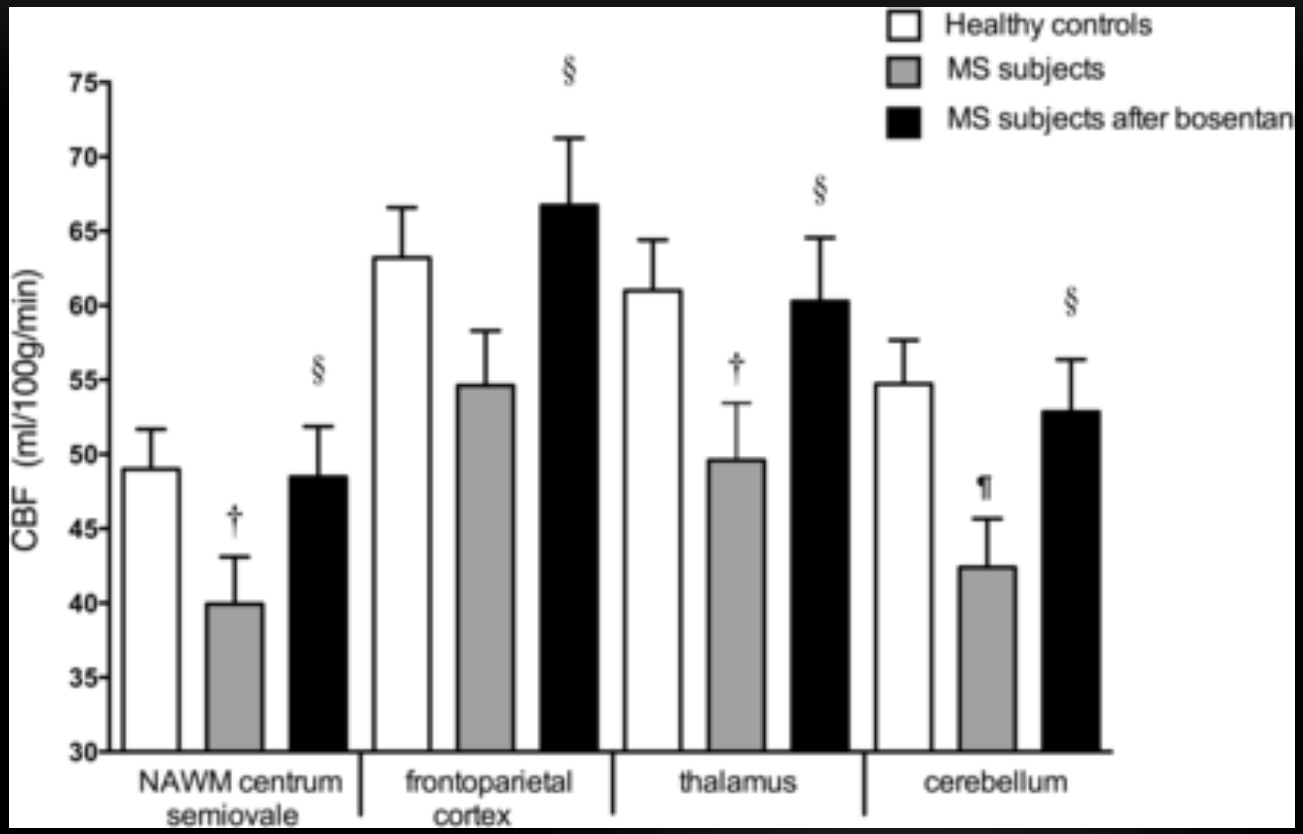
MULTIPLE SCLEROSIS STUDY: THE EXPERIMENT

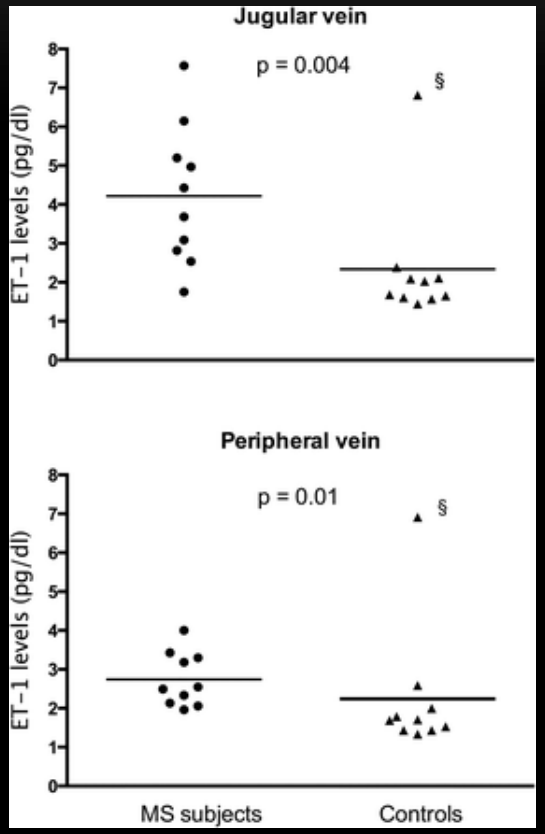
Protocol:

1. Measure CBF with pulsed ASL (EPISTAR)
2. Measure ET1 levels in internal Jugular vein
3. Administer ET-1 receptor antagonist : 'bosentan'
4. Measure CBF with pulsed ASL (EPISTAR)
5. Measure ET1 levels in internal Jugular vein

Post-mortem histology in white matter samples from separate cohorts of controls and MS patients (ET-1 tests)

MULTIPLE SCLEROSIS STUDY: FINDINGS





MULTIPLE SCLEROSIS STUDY:

- ✓ Intervention
- ✓ Longitudinal
- ✓ Baseline activity
- ✓ Quantification (relative)

EXAMPLE #5: ALZHEIMER'S DISEASE

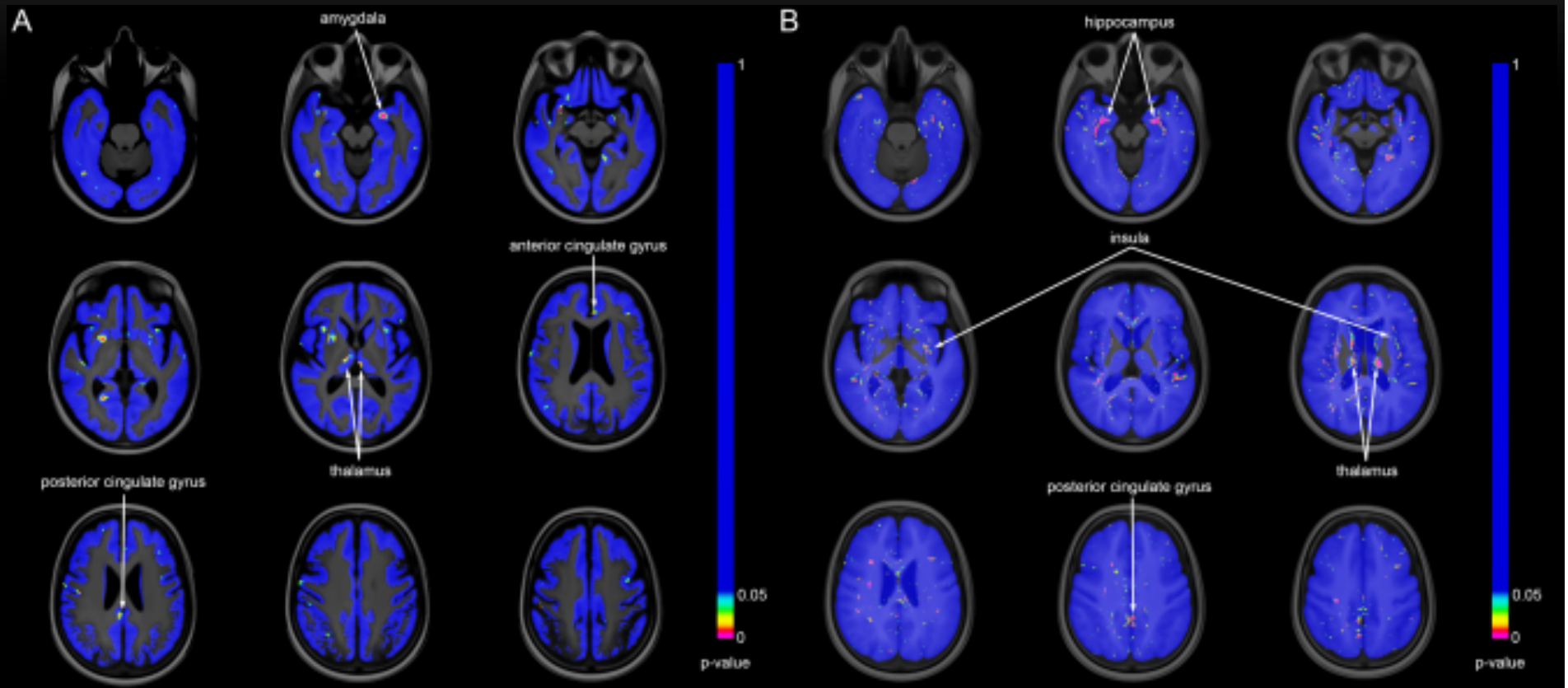
Bron, E. E., et al (2014): " Diagnostic classification of arterial spin labeling and structural MRI in presenile early stage dementia" Hum. Brain Mapp.. doi: 10.1002/hbm.22522

- Hypo-perfusion precedes atrophy and dementia
- Find biomarker to predict outcomes: ASL and machine learning.
- ASL data and/or morphometry (GM atrophy) ?

ALZHEIMER'S DISEASE STUDY: THE EXPERIMENT

- Two groups:
- pre-senile patients with early stage dementia
- ADNI cohort (elderly AD patients)
- pCASL imaging
- T1 weighted structural imaging
- Can we differentiate patients from controls using…
  - CBF?
  - GM volume?
  - Combination of the two?
- Compare several SVM classification methods

ALZHEIMER'S DISEASE STUDY: FINDINGS



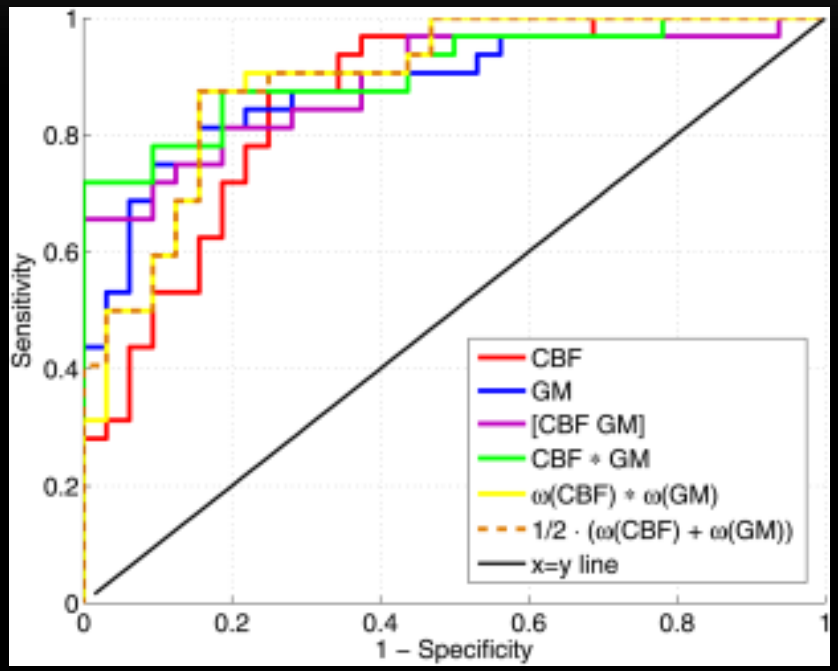
CBF differences

GM volume differences

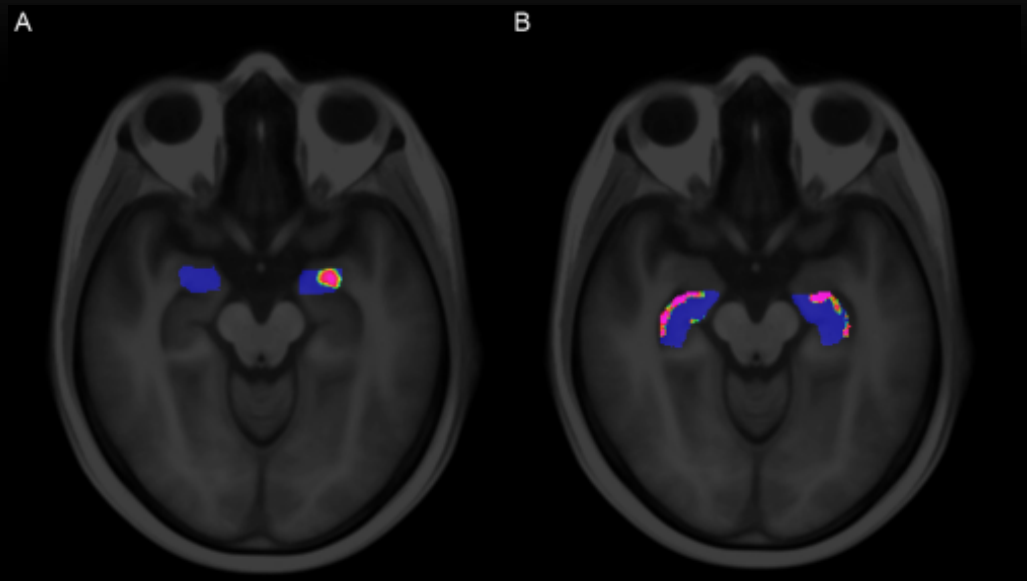
ALZHEIMER'S DISEASE STUDY: FINDINGS

- CBF could be used as a marker for diagnosis by itslef
- No real added value in using CBF data *for classification purposes*

Classification ROC



ALZHEIMER'S DISEASE STUDY: FINDINGS



CBF differences

GM volume differences

Some interesting observations:

- CBF differences in amygdala
- -GM differences in hypocampus

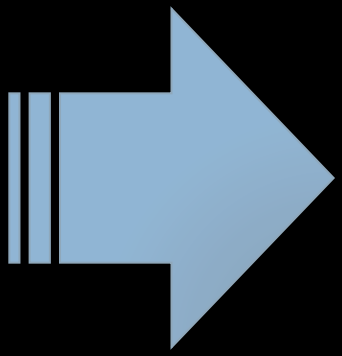
ALZHEIMER'S DISEASE STUDY:

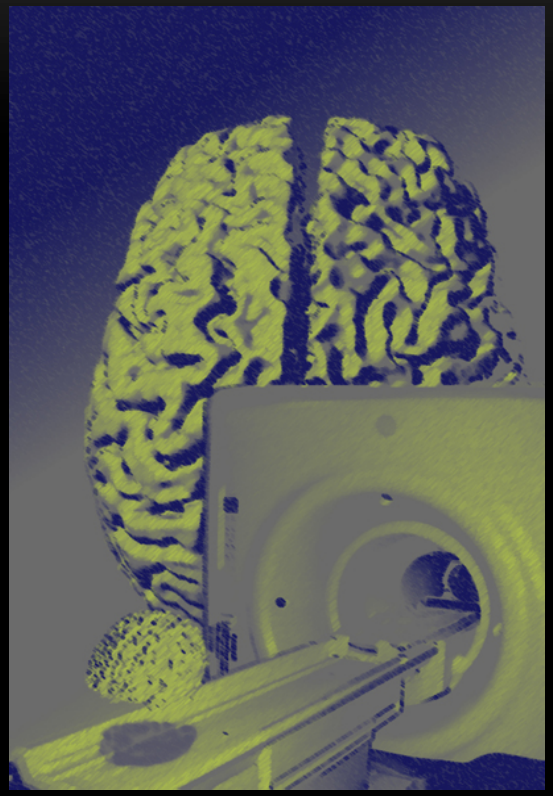
Intervention

- ✓ Longitudinal
- ✓ Baseline activity
- ✓ Quantification (relative)

RECALL:

- *Current ASL techniques have lower SNR and Speed than BOLD*
- *BOLD breaks down in slow paradigms because of drifts (autoregressive noise)*



- Neurofeedback
- Drug Studies
- Attention
- Cognitive Training
- Slow paradigms
- Mental State studies
- Population Studies
- … anything SLOW or requiring Quantification!

QUESTIONS?