Arterial Spin Labeled MR Perfusion Imaging

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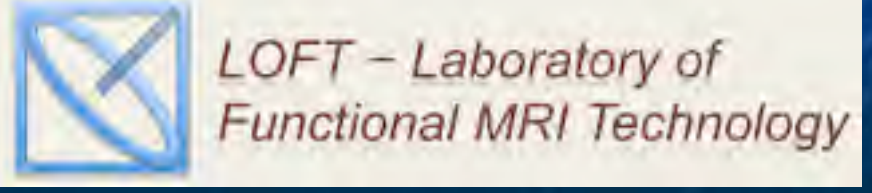


www.loft-lab.org

Outline

- Technical principles of ASL perfusion MRI
  - Pulsed, continuous and pseudo-continuous
  - Perfusion quantification
  - 4D Dynamic flow and perfusion imaging
  - Vessel selective ASL
  - Limitations of ASL perfusion MRI

- Clinical applications of ASL perfusion MRI
  - Neurological disorders: stroke, brain tumor, dementia
  - Functional MRI: comparison with BOLD
  - Neuromodulation and Pharmacological MRI

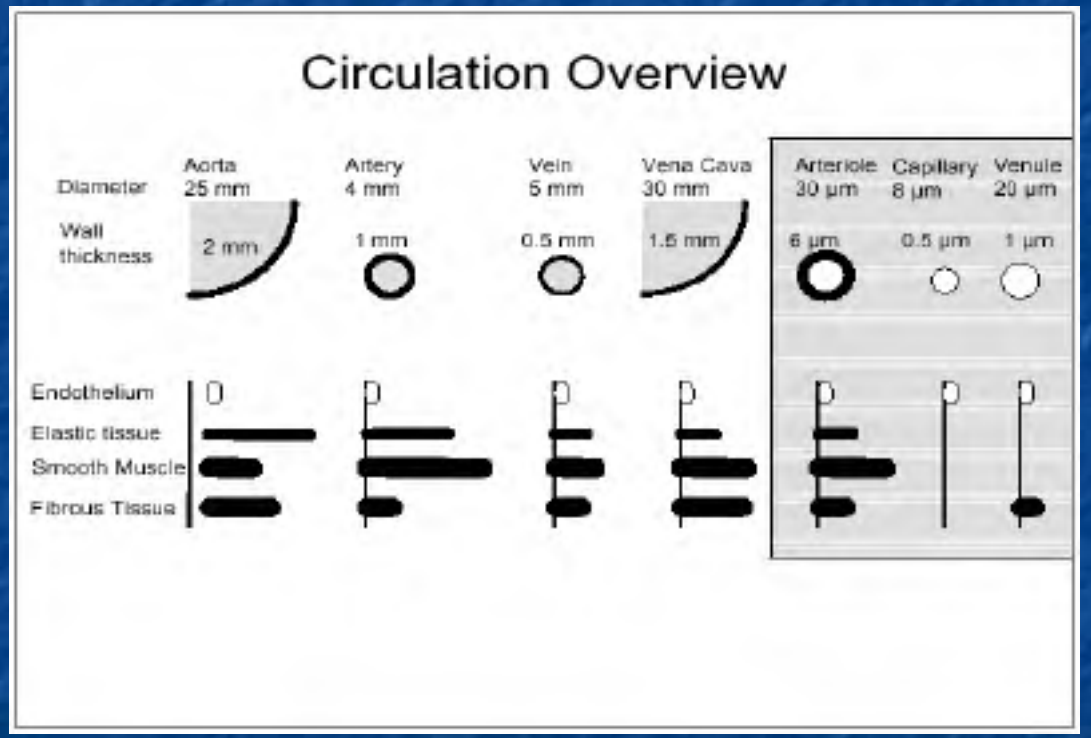
Perfusion

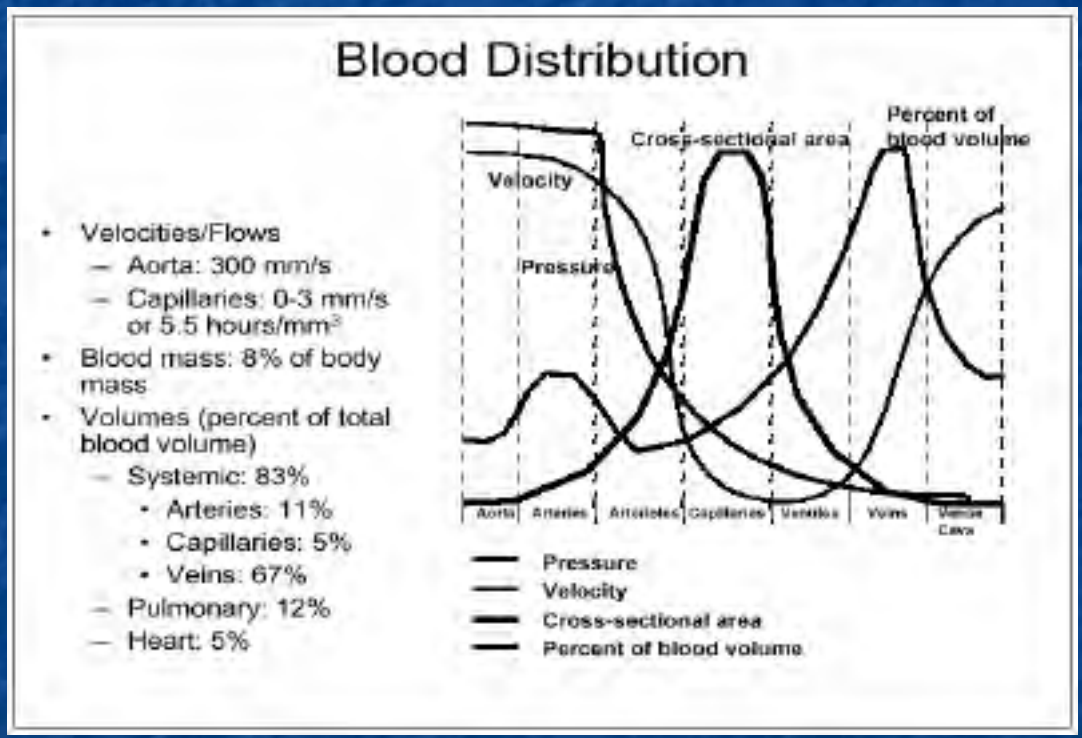
- Perfusion = delivery of nutrients to tissue by means of blood flow
- Definition:
  - The volume of blood that flows through the capillaries of a piece of tissue in a specified period of time
- More regionally specific than arterial or venous blood flow
- Measured in ml / (100g min)

Importance of Perfusion Measurement

- Indicates condition of vascular supply network
- Indirectly reflects metabolic activity of tissue
  - Except in lung, kidneys or when vascular system is injured
- Detects tissue in danger of ischemic damage
- Reflects activity and function of brain and organs (fMRI)

Some Facts of Microvasculature

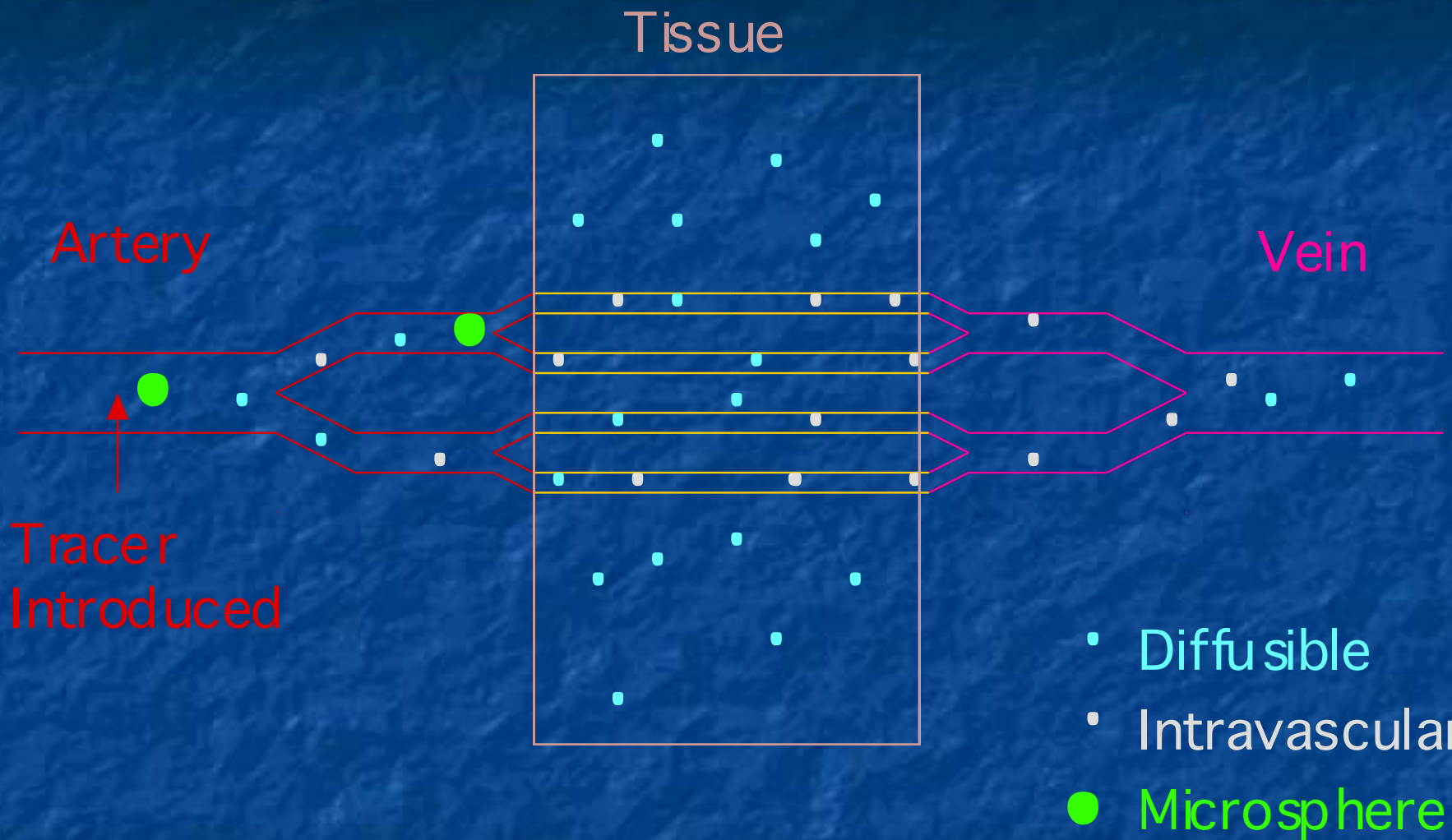




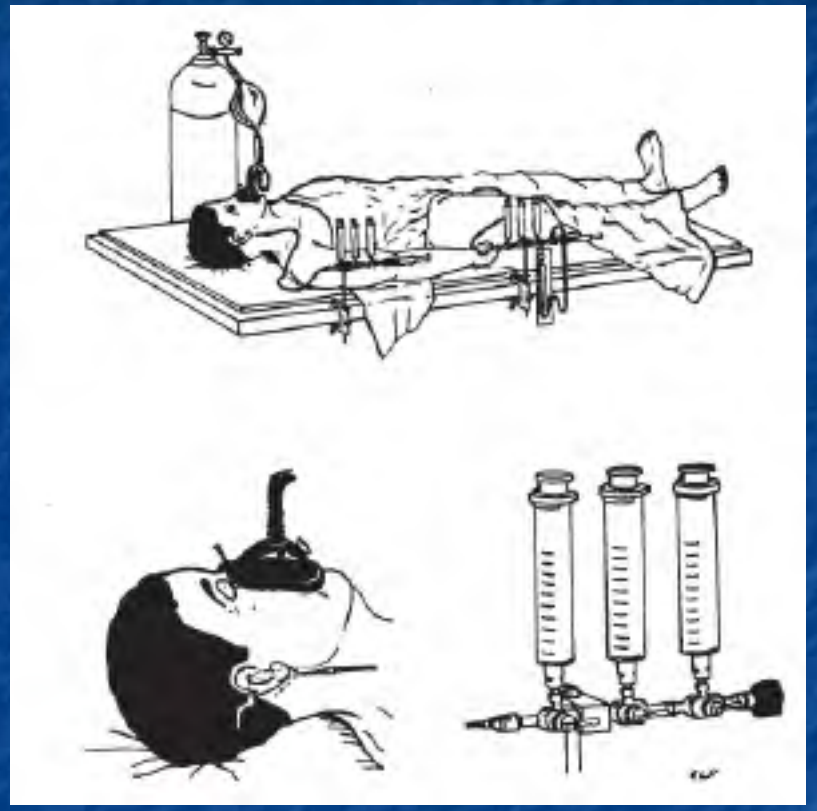
Carpenter MB. *Core text of neuroanatomy*

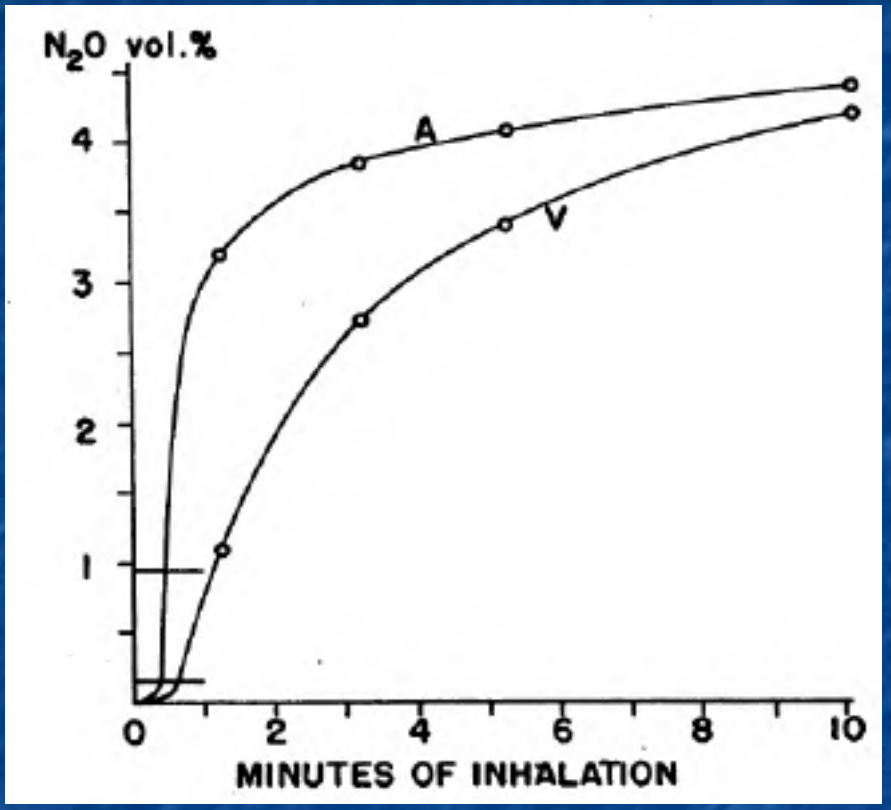
Perfusion is Usually Measured with Tracers

- Tracers vary in transport properties
  - Diffusible tracers
  - Intravascular tracers (blood pool)
  - Microspheres (deposition)
- Tracers vary in stability
  - Radioactive Tracers (PET, SPECT)
  - Nuclear magnetic spins (Hyperpolarization)
  - Stable contrast agents (Gd-DTPA)


Tissue
Artery
Vein
Tracer
Introduced
Diffusible
Intravascular
Microsphere

"Gold Standard" of Perfusion Measurement





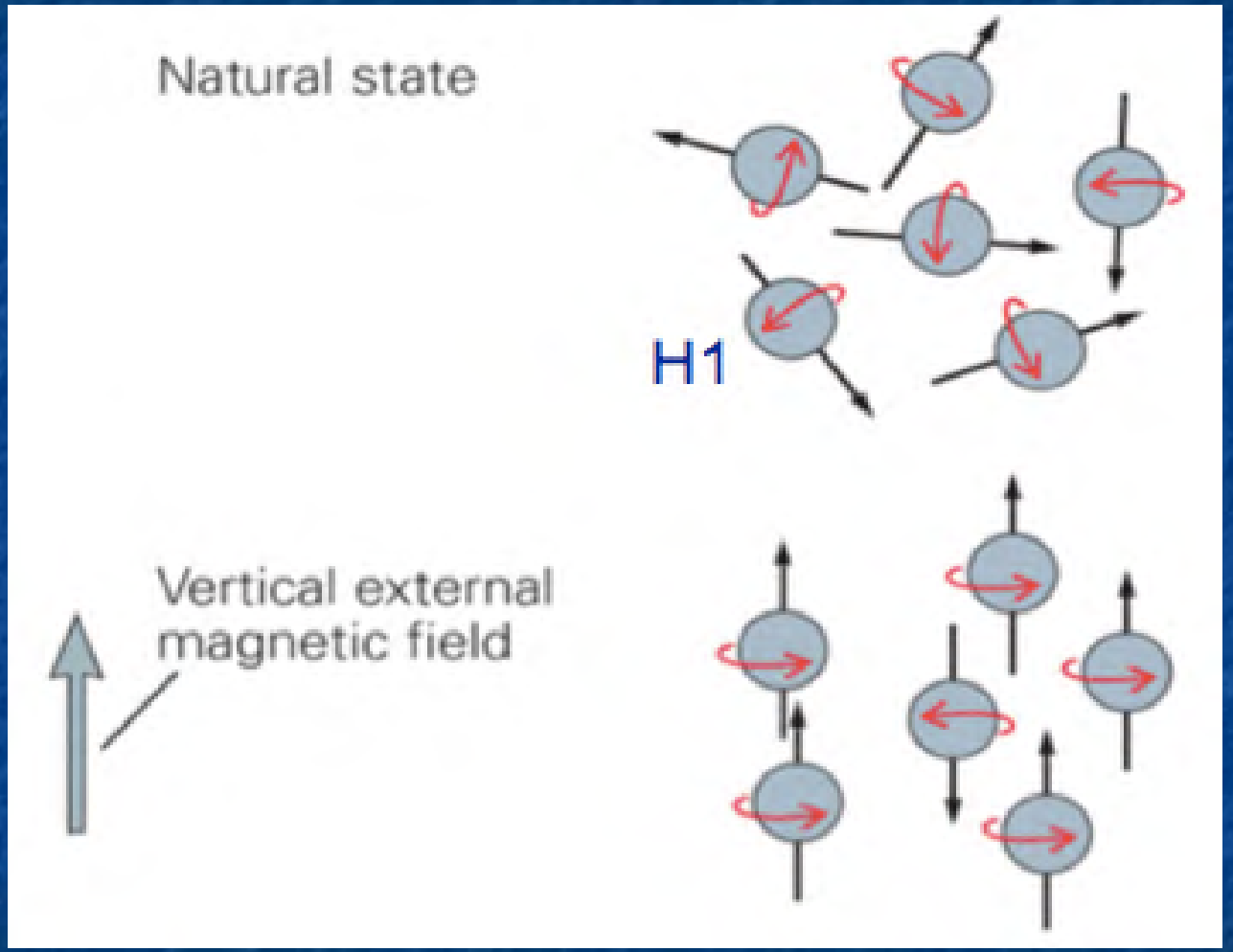
$$(Q_B)_u = TF \int_0^\infty (A-V)dt$$

$$TF = \frac{(Q_B)_u}{\int_0^\infty (A-V)dt}$$

$$CBF = \frac{100 V_u \cdot S}{\int_0^\infty (A-V)dt},$$

Kety & Schmidt (1948)

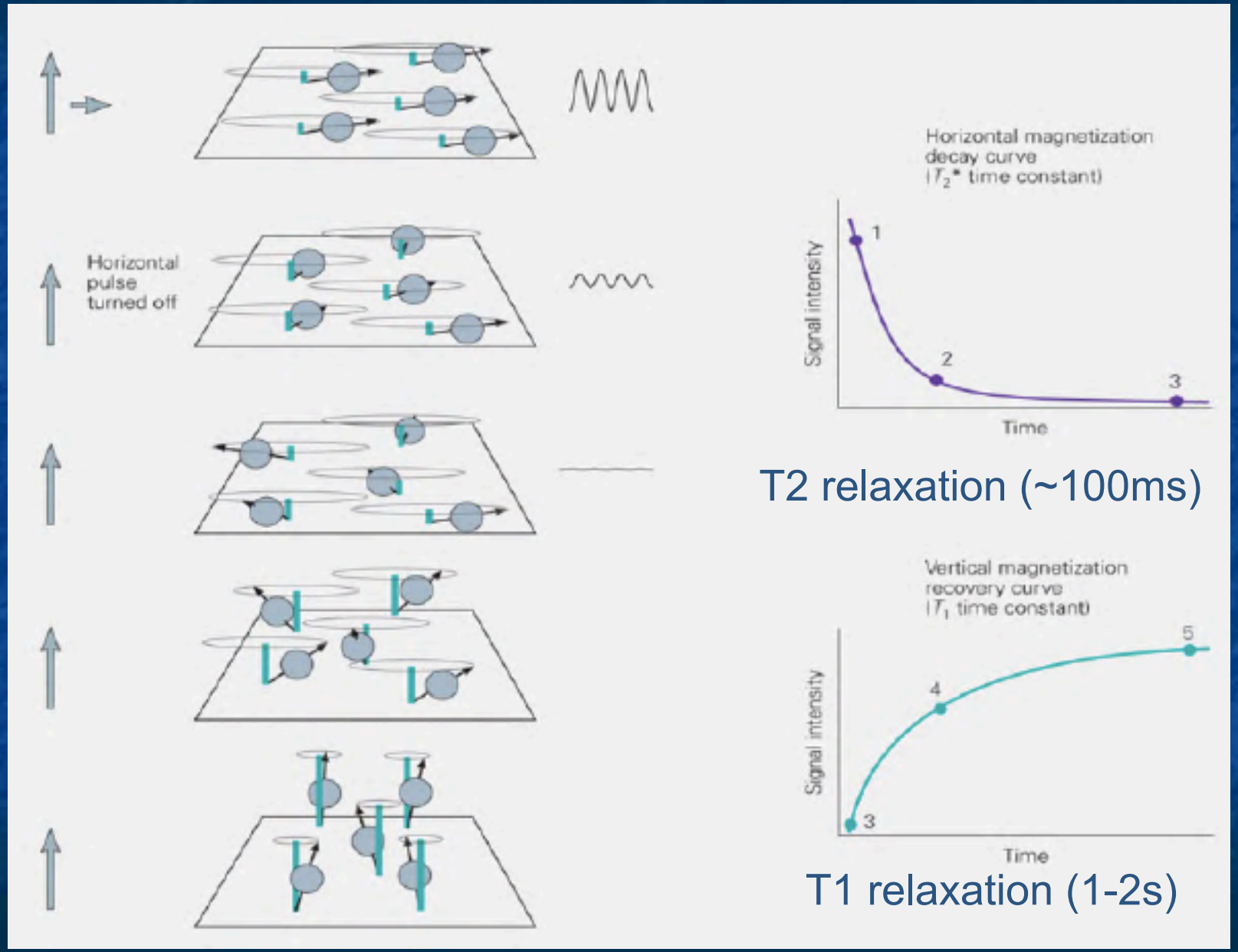
Magnetic Resonance Imaging (MRI)



$$\frac{N+}{N-} = e^{-\Delta E / kT}$$

At 1T, for every million nuclei in the spin-down state, there are about 1 million plus 7 extra nuclei in the spin-up state.

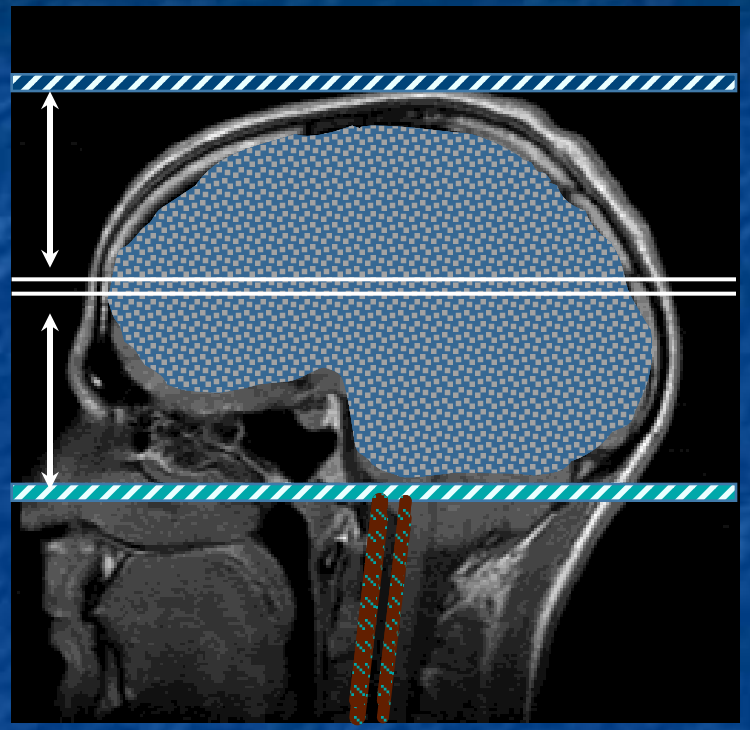
T1 and T2 Relaxation



Arterial Spin Labeling (Tagging)

- Inflowing Blood Spins are Inverted or Saturated Before Entering the Slice
- Imaging is performed after a delay time that allows labeled blood to flow into tissue
- Tagged Image is Subtracted from Control Image with No Tagging

ASL Perfusion MRI



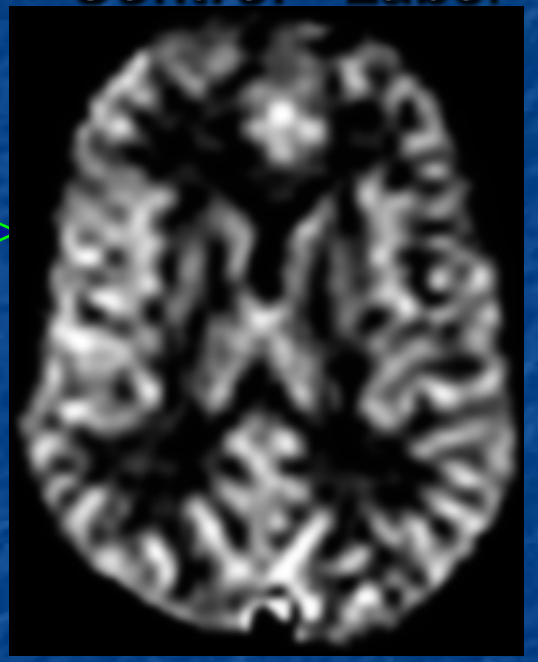
Continuous Adiabatic Inversion Geometry

Control Inversion Plane

Imaging Slice

Arterial Tagging Plane

Control - Label

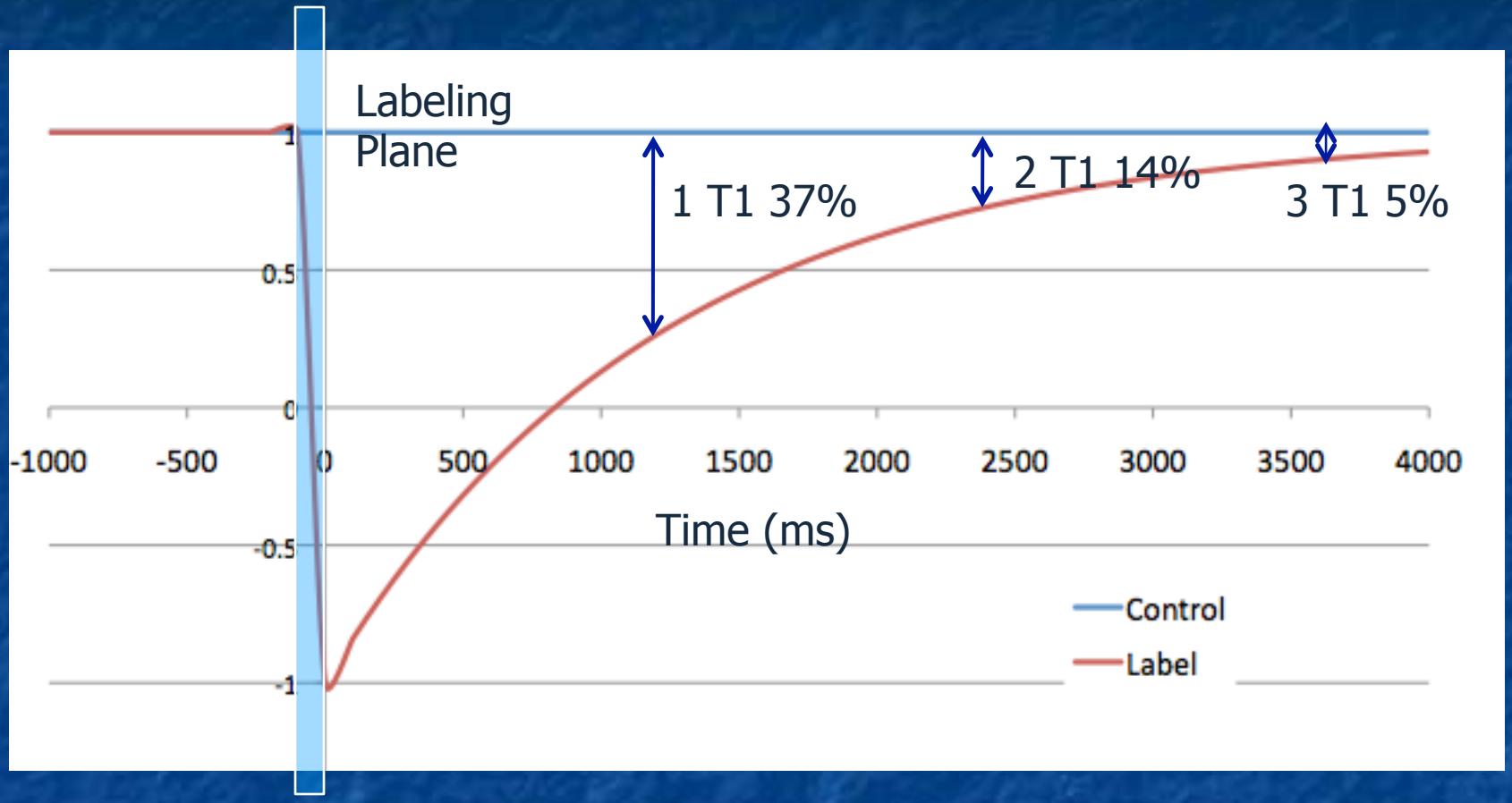


Single Slice Perfusion Image about **1%** effect

CBF in "classical" units of ml/100g/min

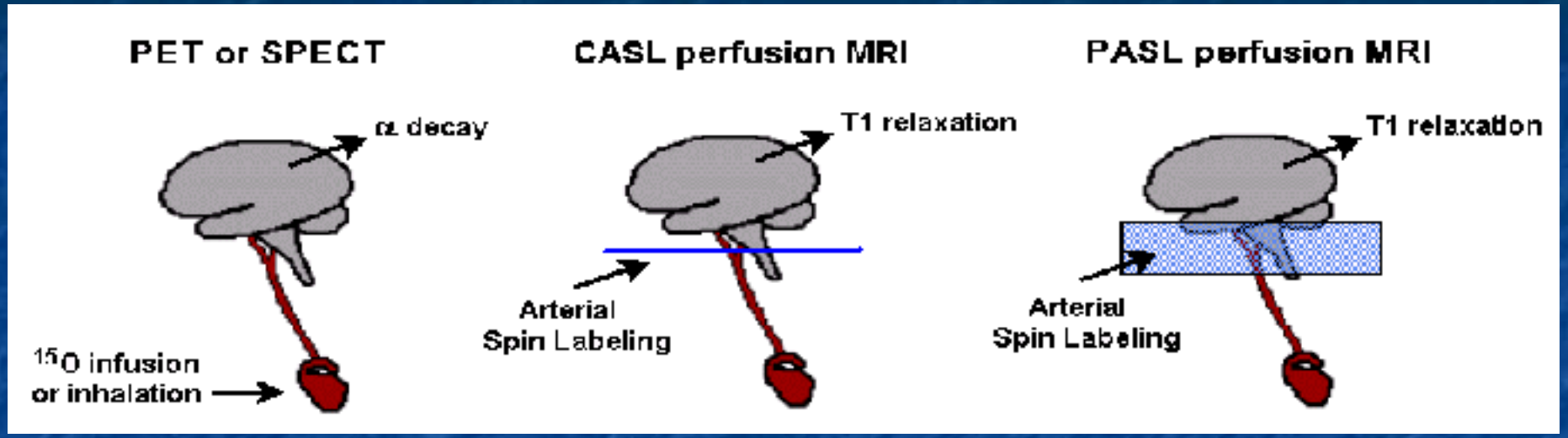
Detre et al. MRM 1992, Williams et al. PNAS 1992

ASL and T1 relaxation



ASL uses magnetically tagged (inverted or saturated) blood water as an endogenous tracer, the tracer half-life is determined by blood T1 (1-2sec) which competes with arterial transit time (ATT).

ASL Strategies

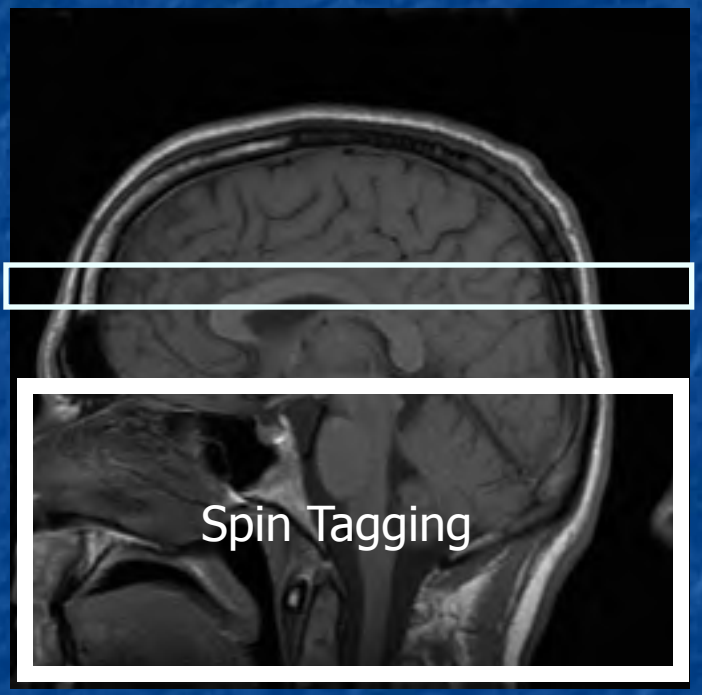


- **Continuous ASL (CASL) vs. Pulsed ASL (PASL)**
  Greater SNR, higher MT effect & SAR, technically challenging

- **Pseudo-CASL (pCASL)**
  Combines advantages of PASL and CASL

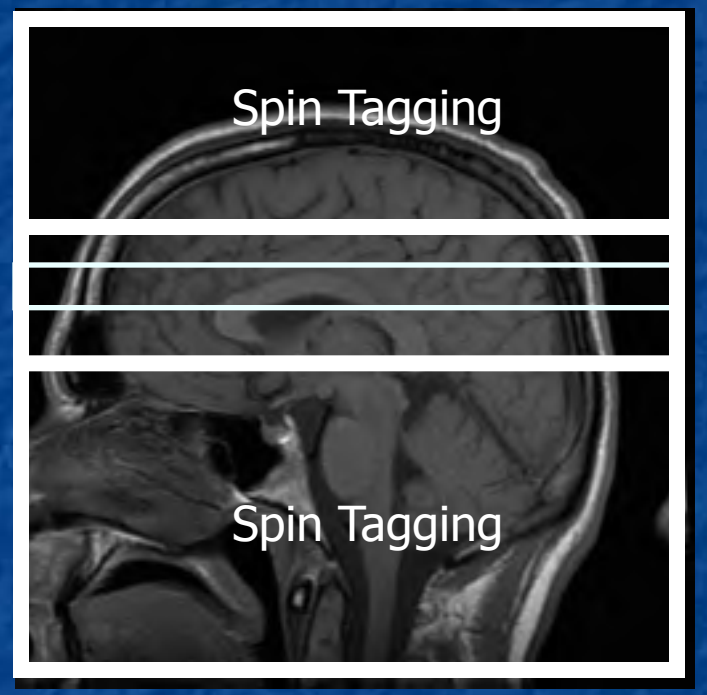
Pulsed ASL (PASL)

EPISTAR



Edelman R et al. (1994)

FAIR



Kim SG (1995)
Kwong KK et al. (1995)

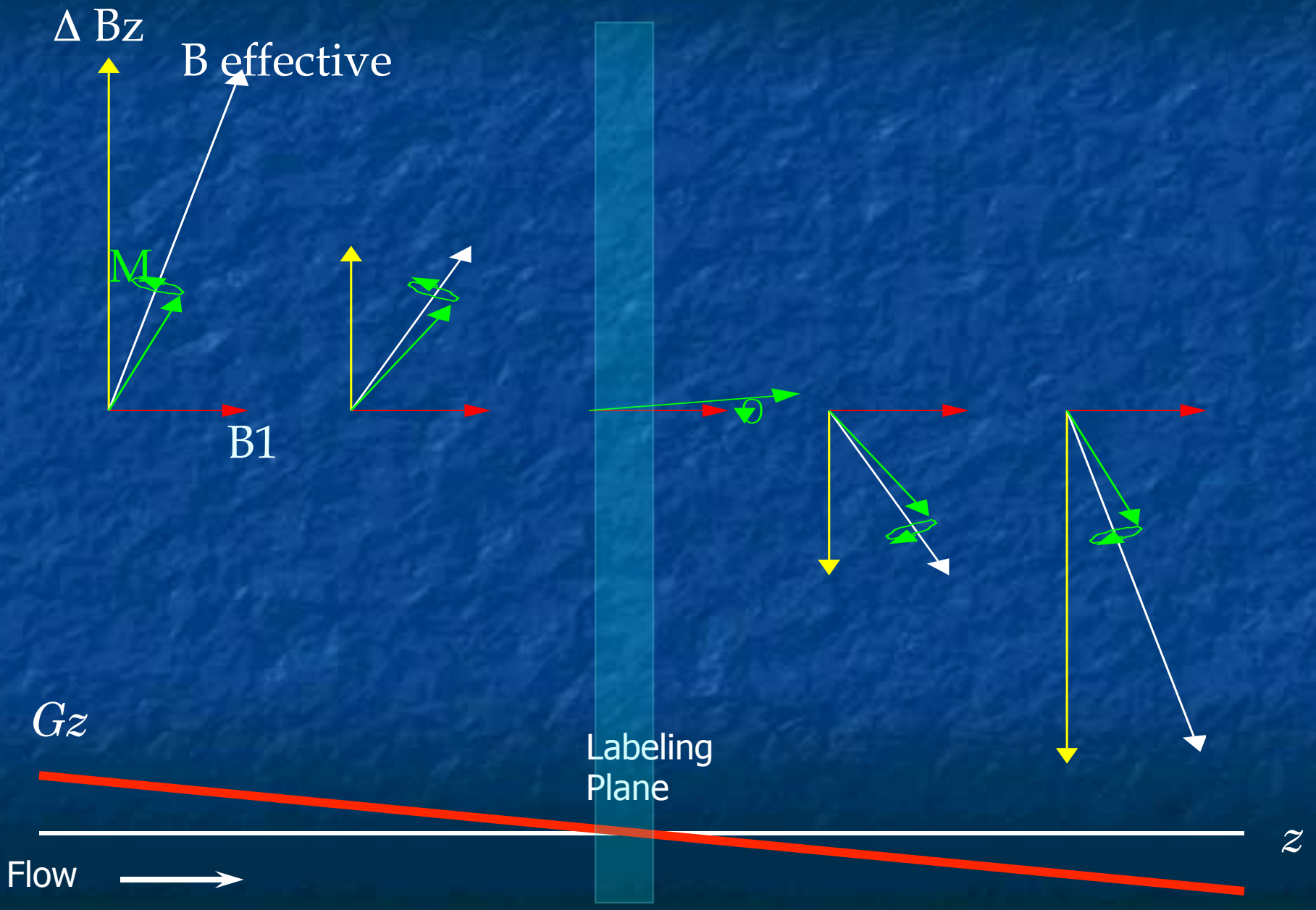
Continuous ASL (CASL)
Flow-driven Adiabatic Inversion

- Constant RF and Gradient Applied
- Spins Rotate with Effective Field
- Must Be Faster than T2

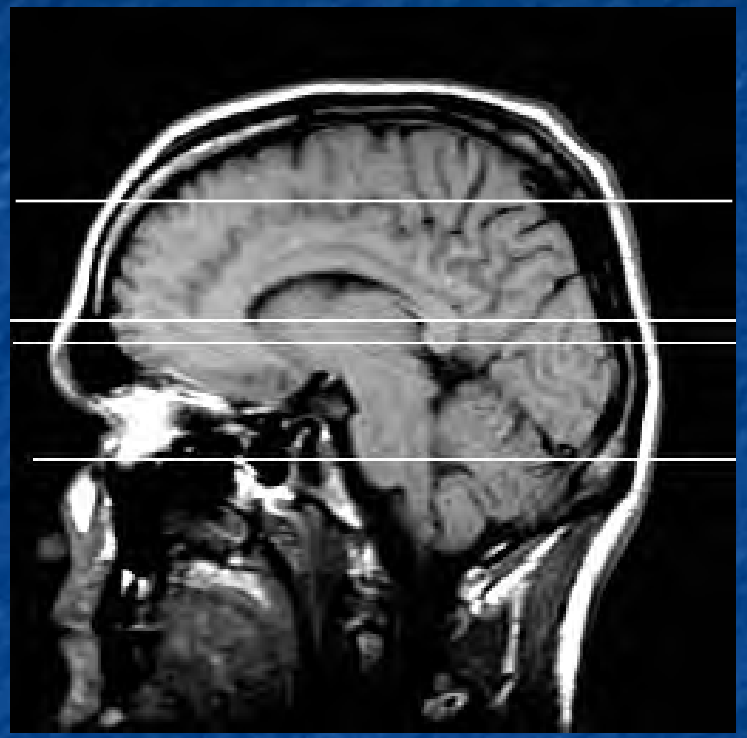
- Must Be Slower Than Precession Around Effective Field

$$\frac{1}{T_2} \ll \frac{G\nu}{B_1} \ll \gamma B_1.$$

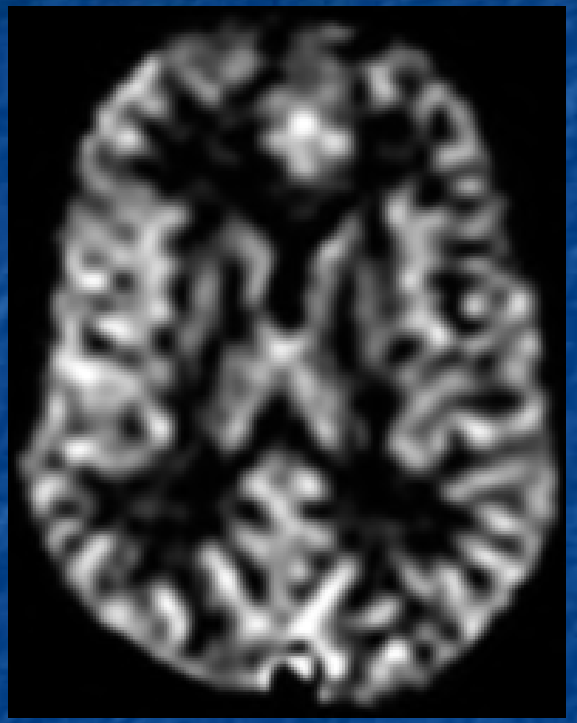
Adiabatic Inversion



Single Slice CASL



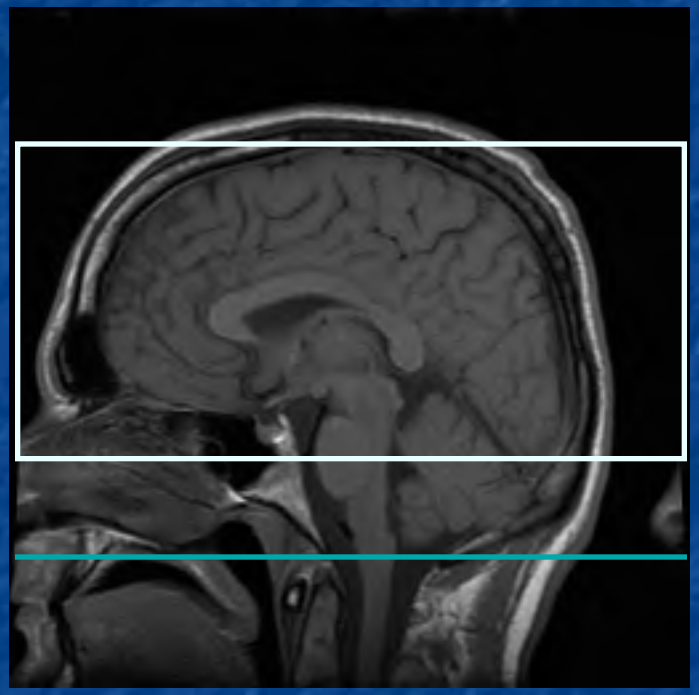
Continuous Adiabatic Inversion Geometry



Single Slice Perfusion Image

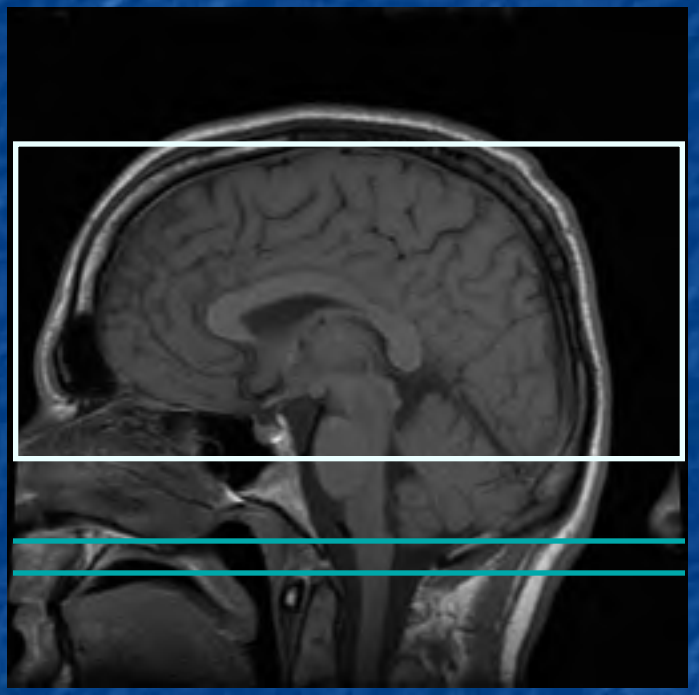
Williams et al. PNAS 1992

Amplitude Modulated Control



Imaged Slab

Labeling Plane

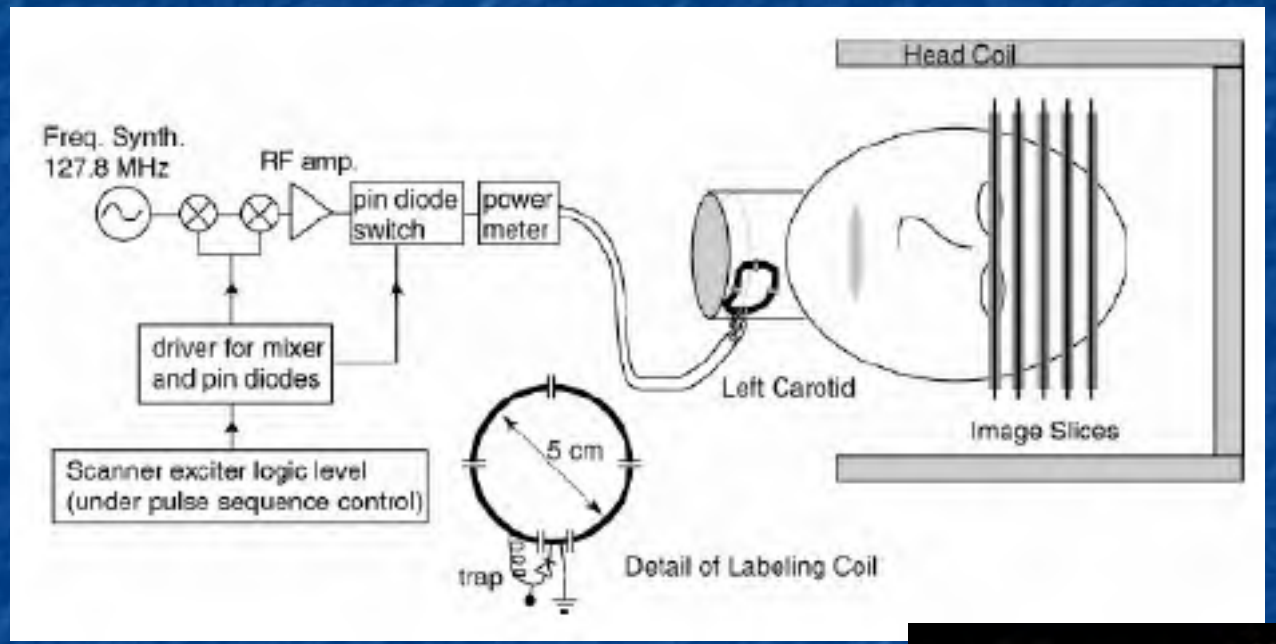


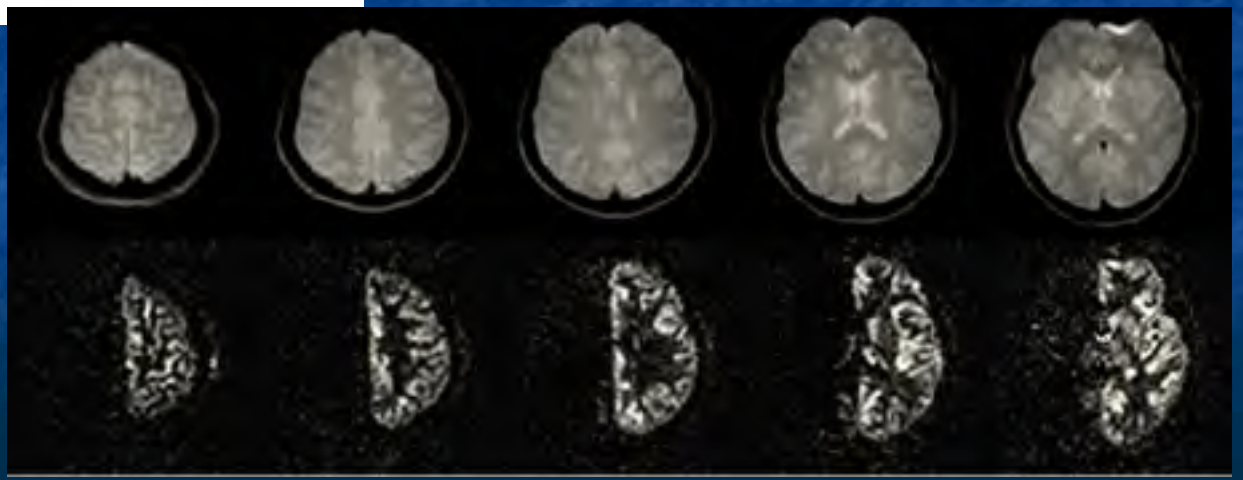
Labeling Geometry

Control Geometry

Alsop DC, Detre JA. Radiology 1998

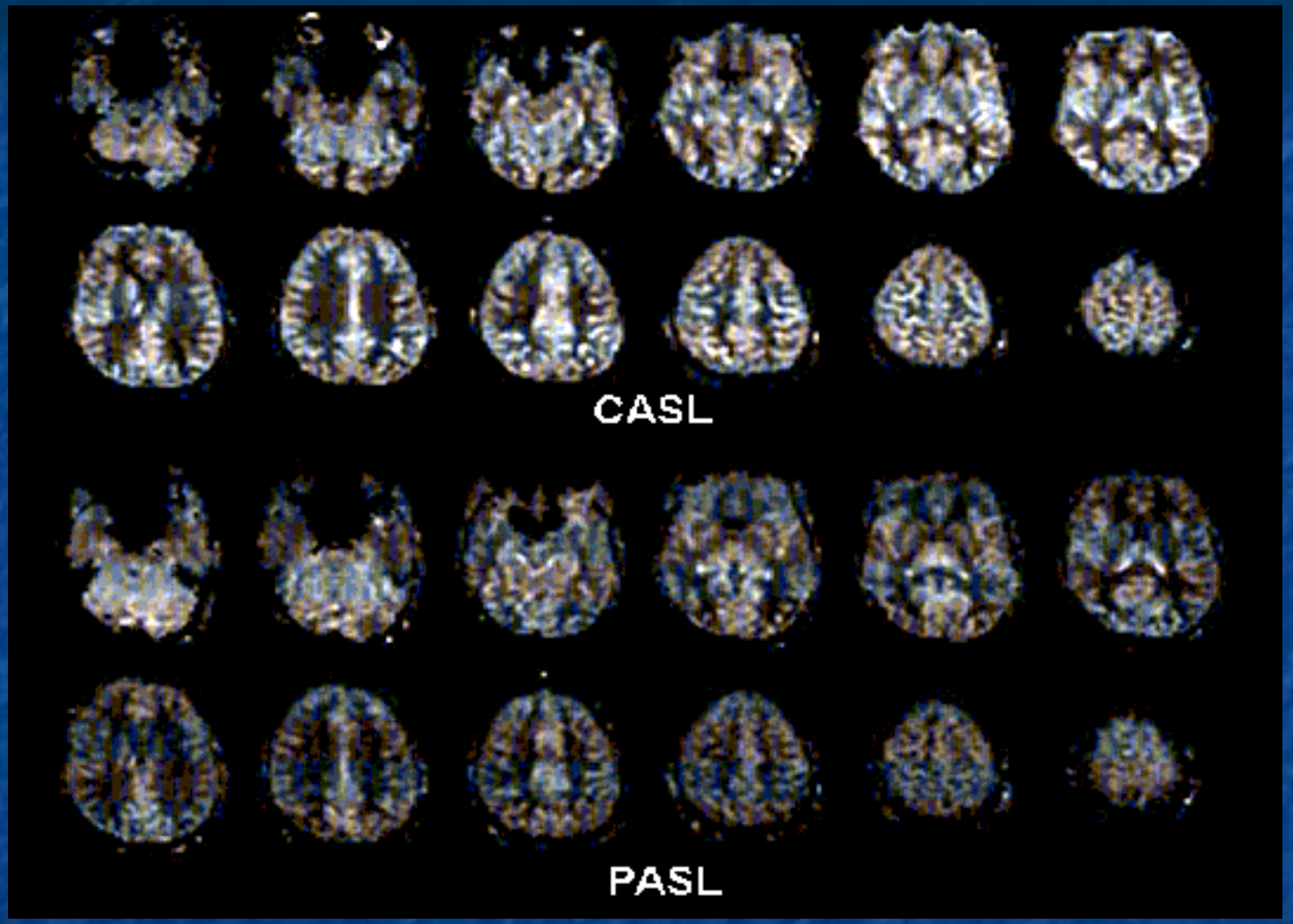
Perfusion Territory Imaging with Separate Labeling Coil





Zaharchuk G et al MRM 1999

Comparison of PASL and CASL at 3T

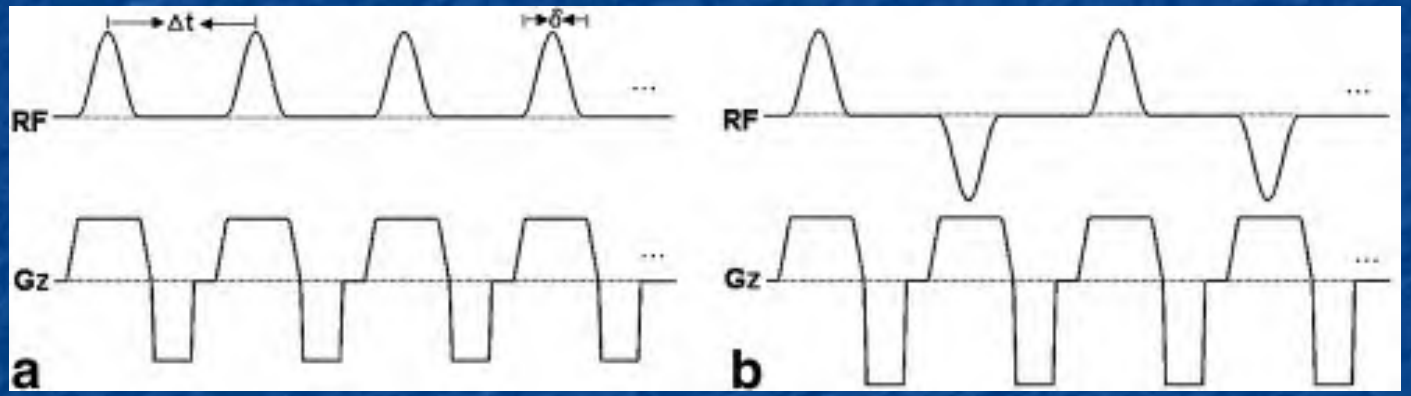


CASL improves SNR by 40% compared to PASL, with higher SAR and duty cycle

Wang et al. Radiology (2005)

Pseudo-continuous Flow Driven Adiabatic Inversion

CASL

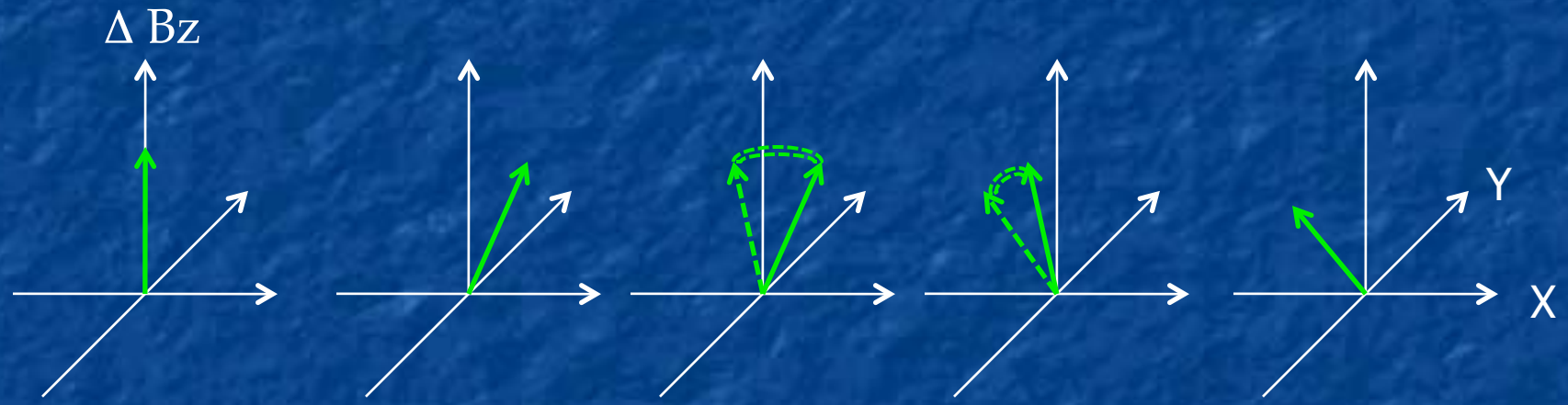


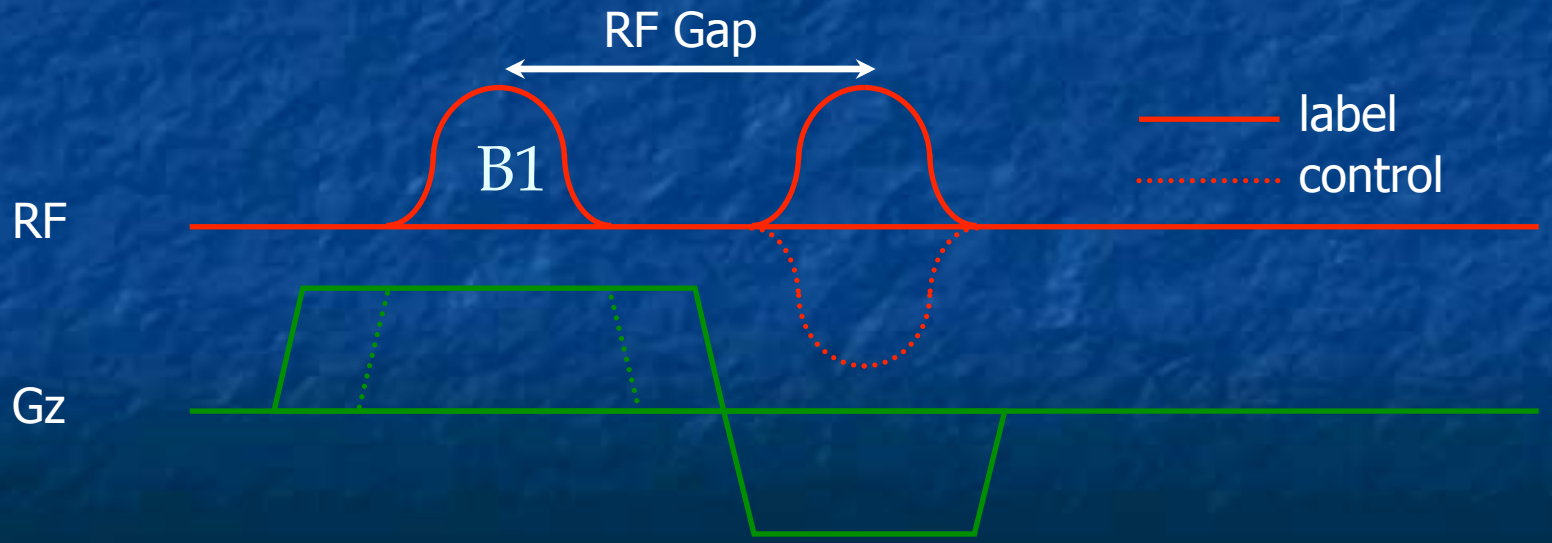
pCASL Label pCASL Control

Use a train of discrete RF and gradient pulses to simulate continuous ASL

Dai et al. MRM 2008; Wu et al. MRM 2007

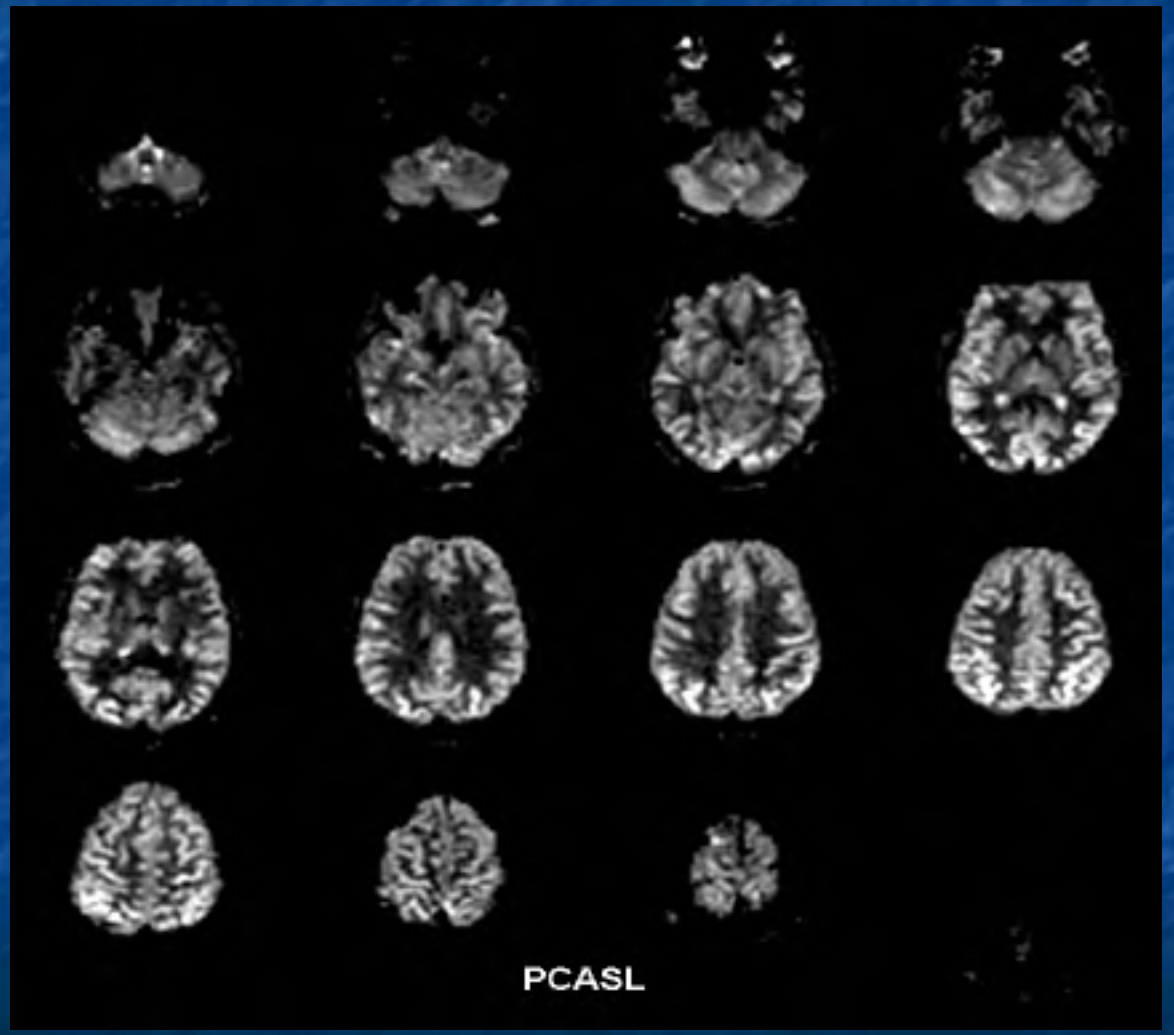
Pseudo-continuous Flow Driven Adiabatic Inversion





Dai et al. MRM 2008; Wu et al. MRM 2007

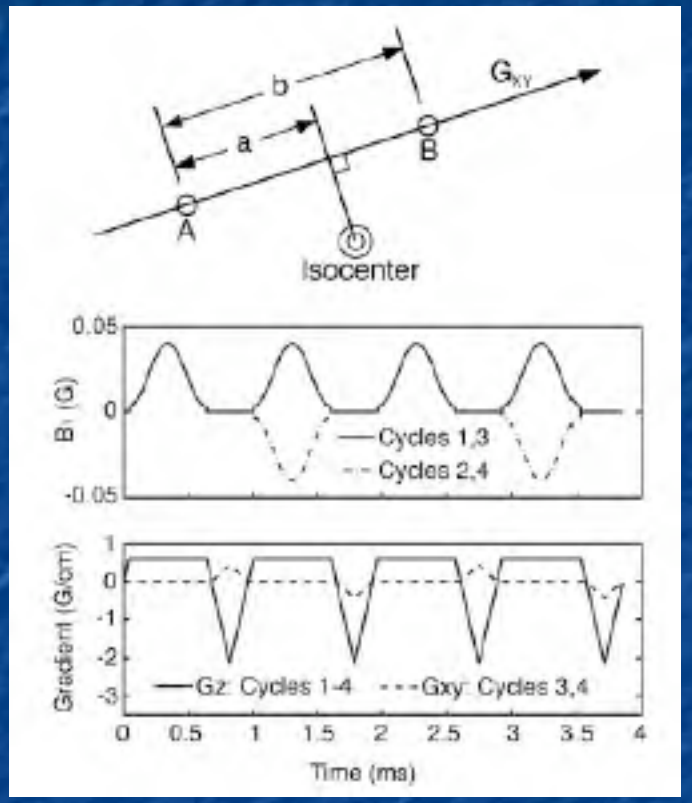
Pseudo-continuous Flow Driven Adiabatic Inversion

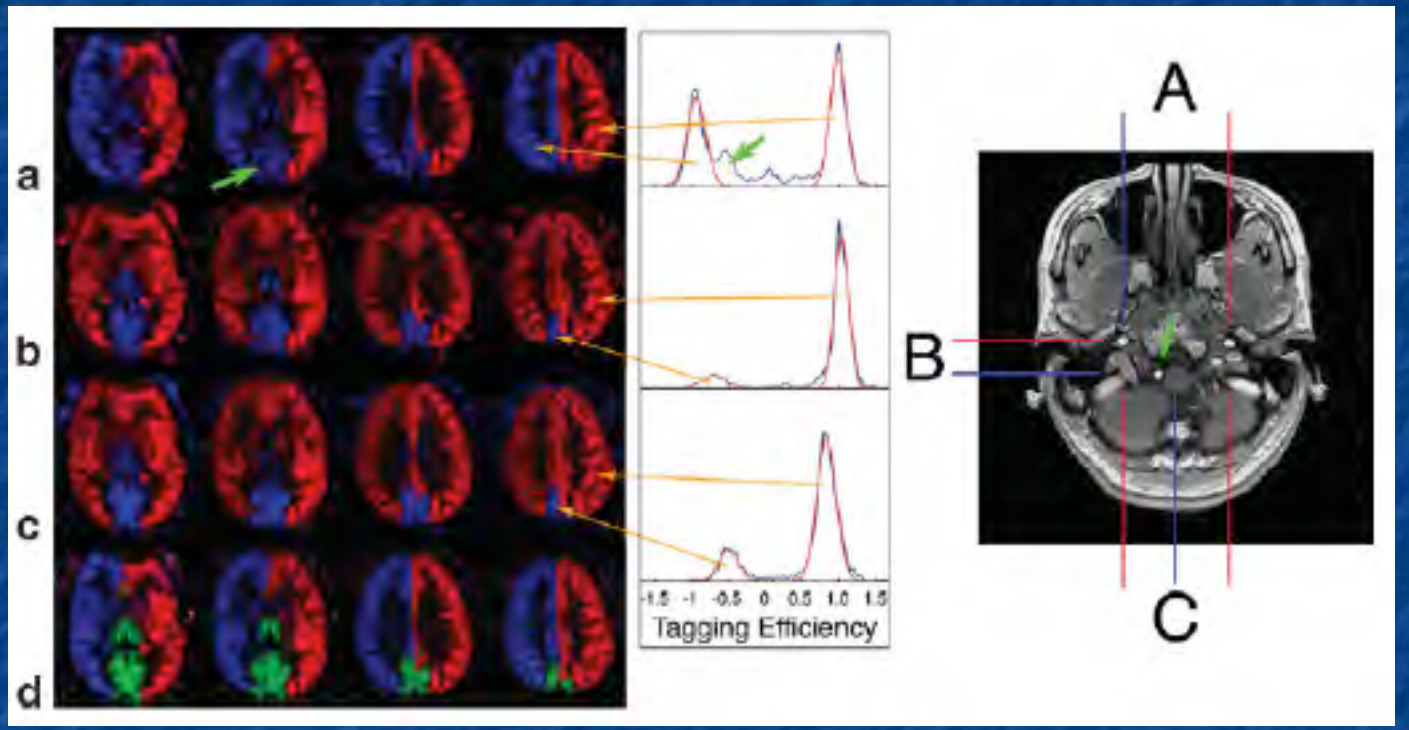


- Repeated vs. continuous RF
- More compatible with current MRI RF amplifiers on
- Allows product body coil excite/ array receive
  - *2-3X SNR improvement*
- Improved efficiency (~80-90% versus ~70% for AM control)
  - *2X SNR improvement*

Dai et al. MRM 2008; Wu et al. MRM 2007

Vessel Encoding pCASL



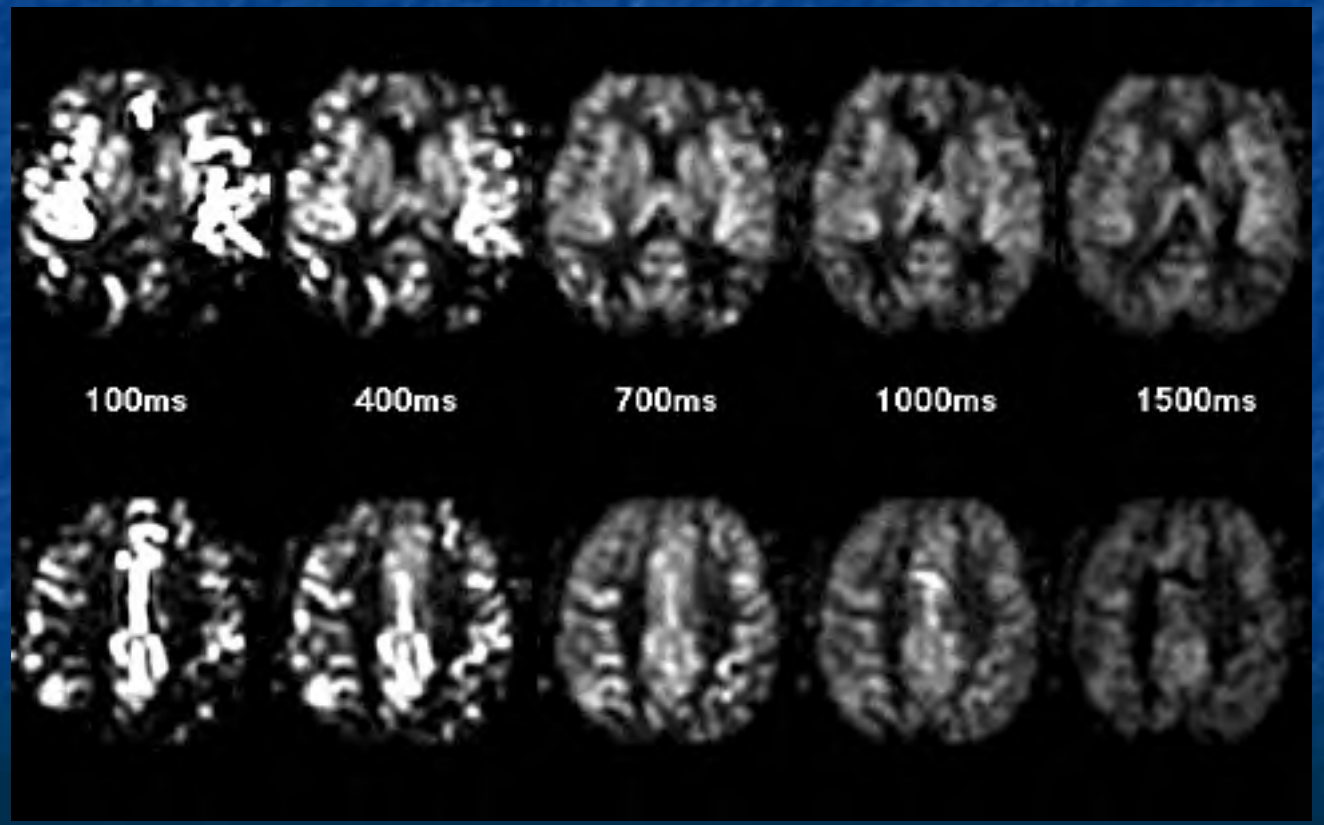


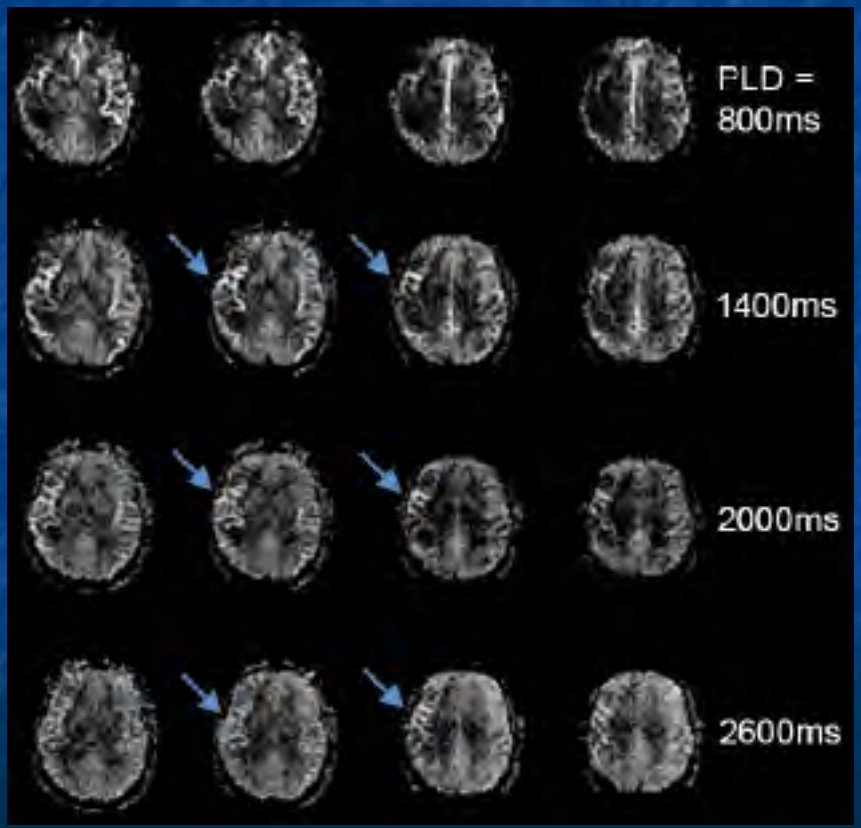
Apply Gx or Gy in pCASL to encode L/R ICA and VA using Hadamard scheme

Wong EC MRM (2007)

Transit Time Effects in ASL

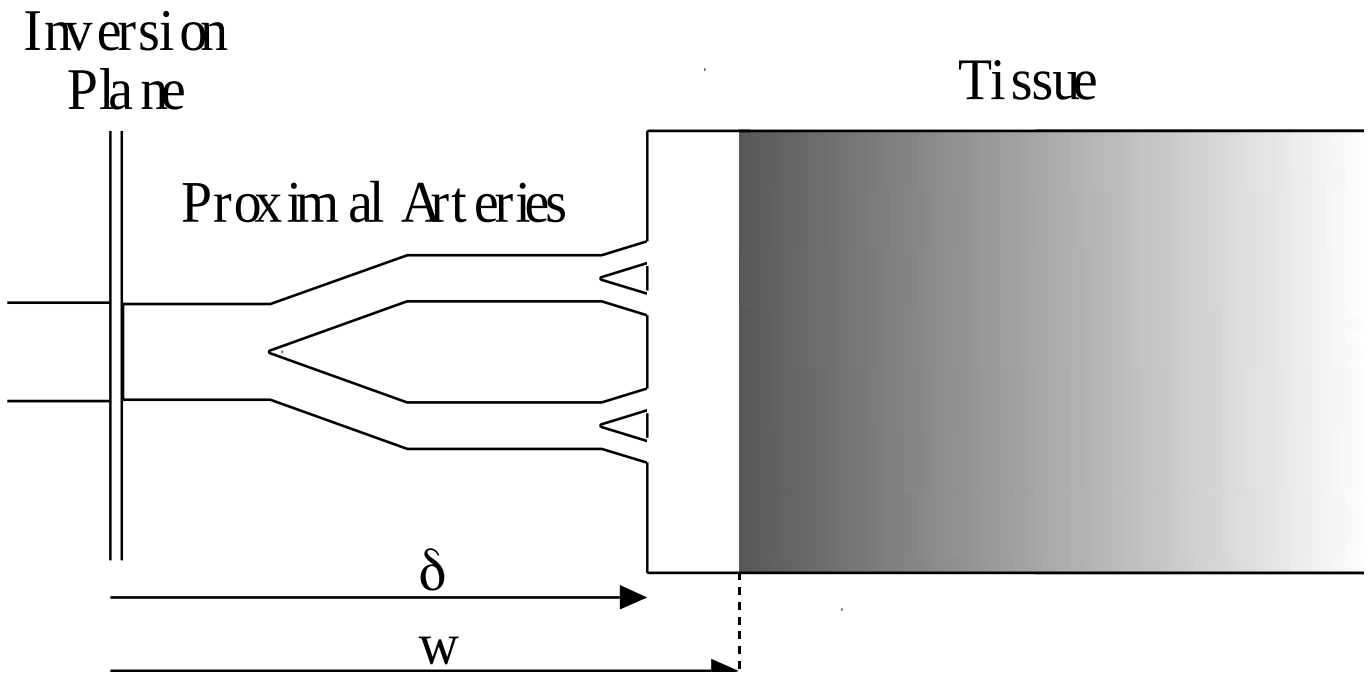
- Flow is exponentially dependent on transit time
- Transit times in human brain are comparable to T1



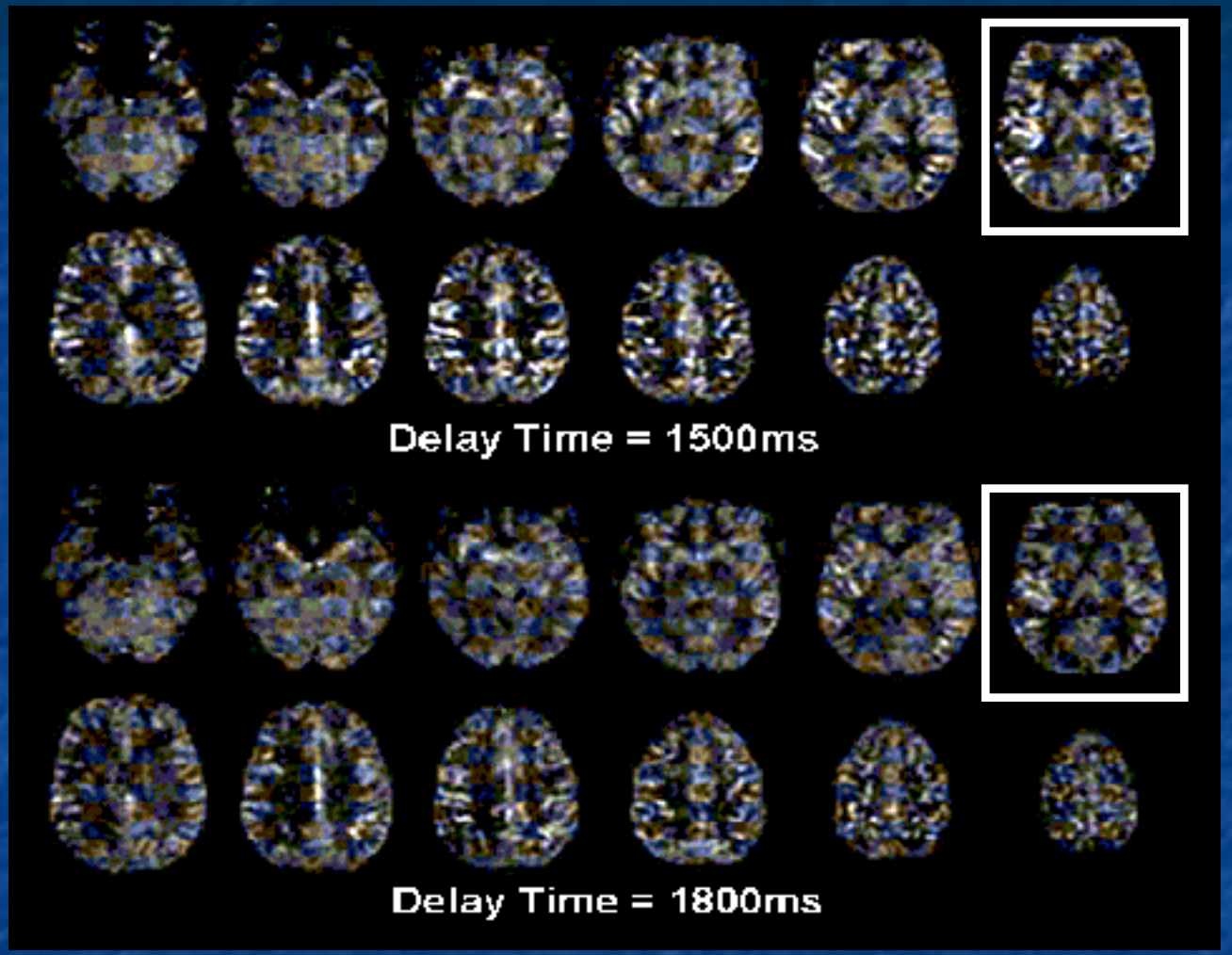


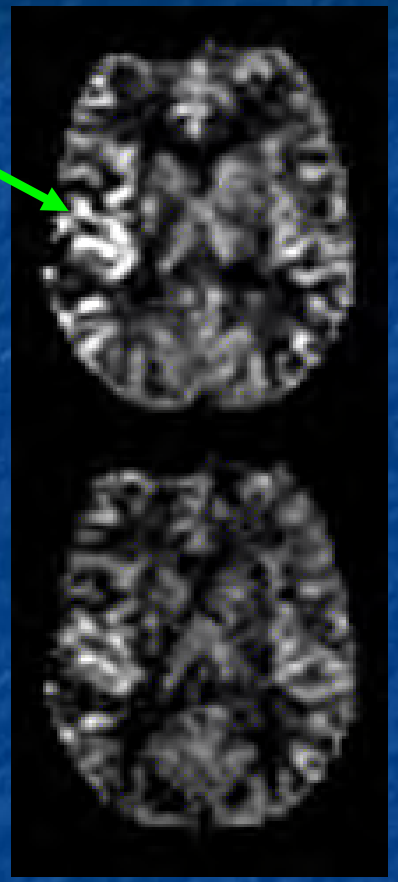
Wang et al MRM 2002

Post-labeling Delay Time to Reduce Transit Effects



Reduced transit artifact with 3T CASL

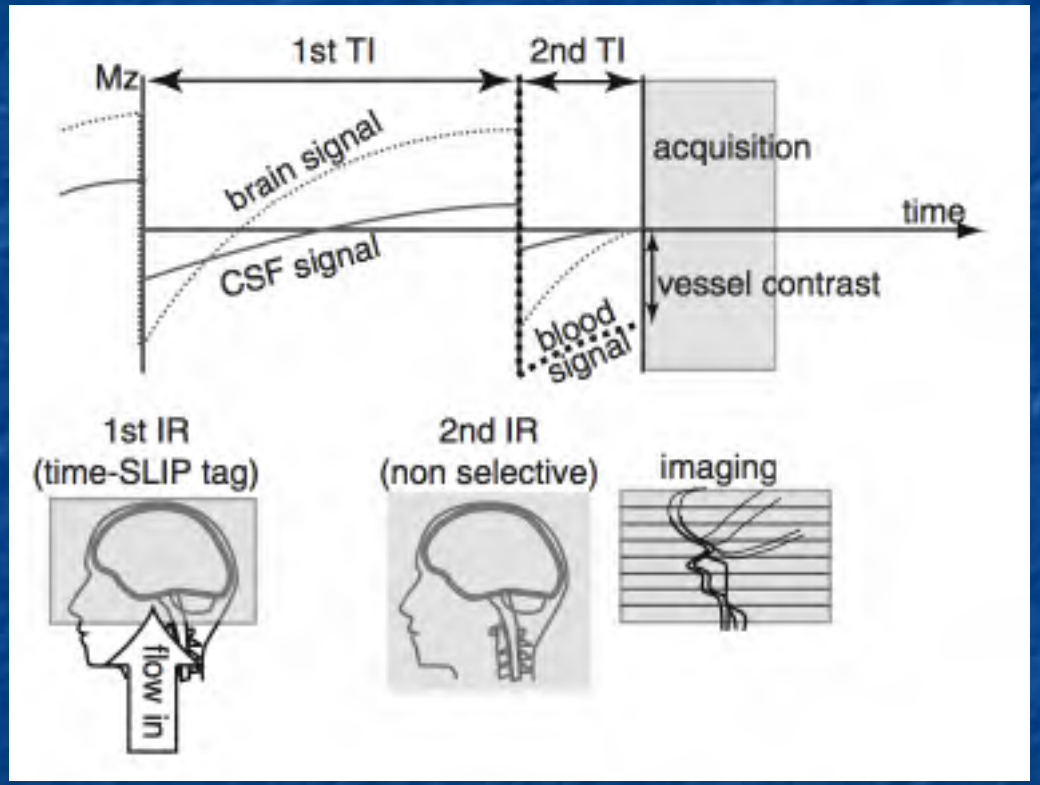




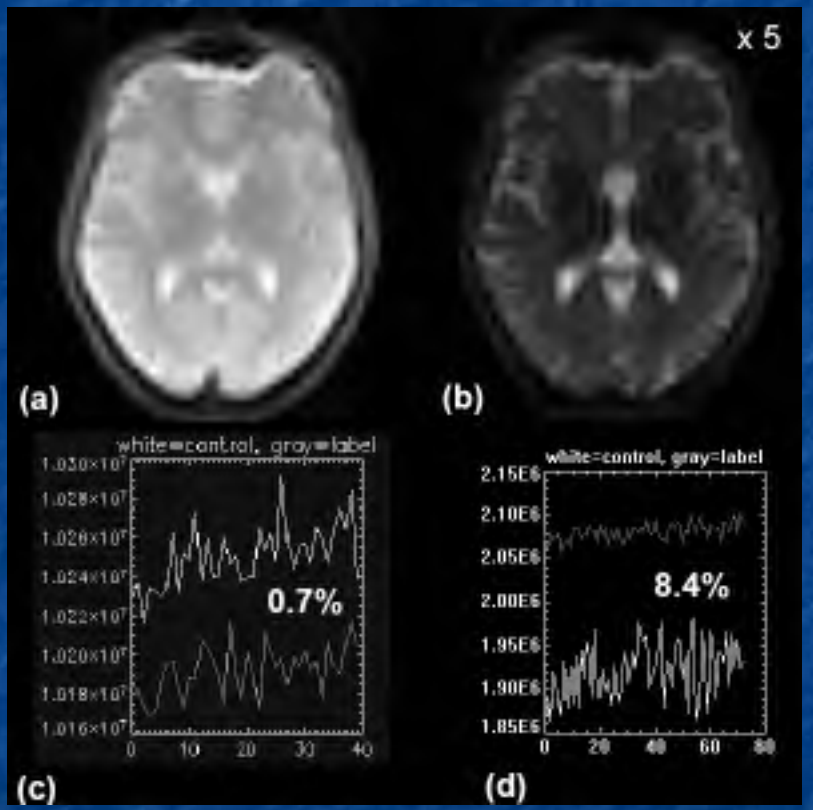
Improved SNR allows increased delay time to measure perfusion with prolonged transit time

Wang et al. Radiology (2005)

Reduce Temporal Fluctuation using Background Suppression

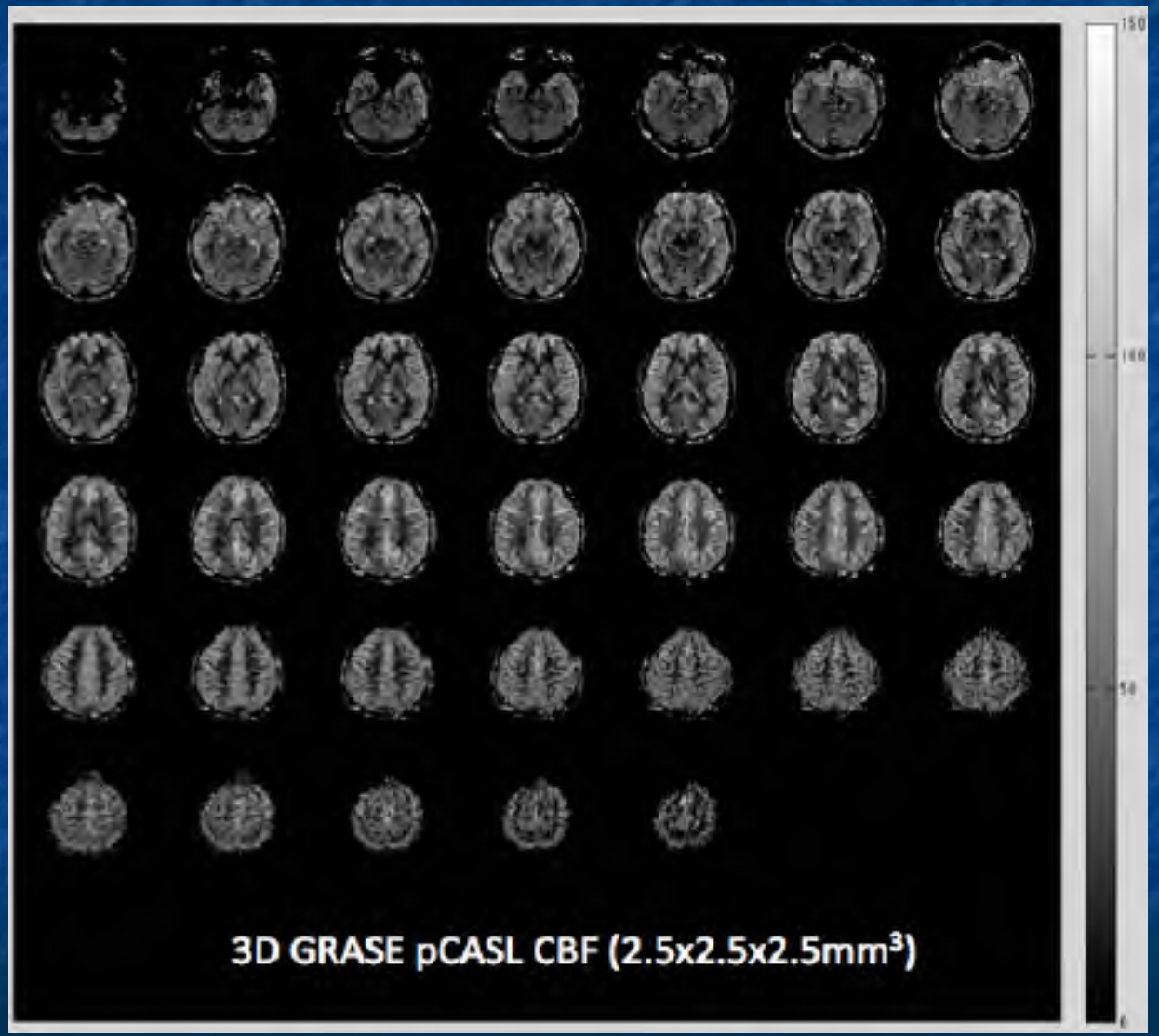


Ishimori et al Radiol Phys Technol 2011



Fernandez-Seara et al. MRM (2008)

Segmented pCASL 3D BS GRASE

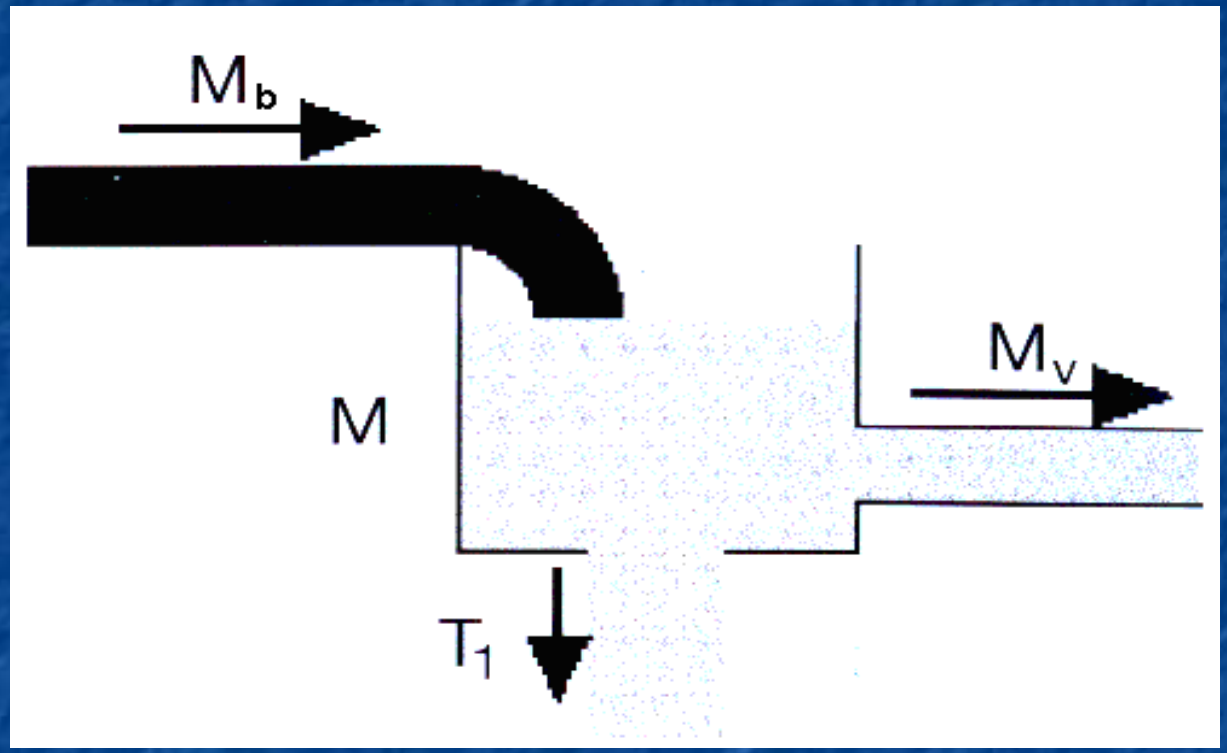


Recommended implementation:

1) pCASL
2) Background suppression
3) Segmented 3D readout without vascular crushing gradients.

Alsop et al *MRM* (2015)
ASL White Paper

Perfusion Model
(Single Compartment Instant exchange)



$$\frac{dM}{dt} = \frac{M_0 - M}{T_1} + fM_b - \frac{f}{\lambda}M$$

Venous outflow

Arterial inflow

Detre & Alsop 1999

Perfusion Model (Tracer Kinetic Modeling)

$$dM(t) = 2M_{0b} f \left\{ C(t) \otimes \left[r(t) \bullet m(t) \right] \right\}$$

Arterial Input Function

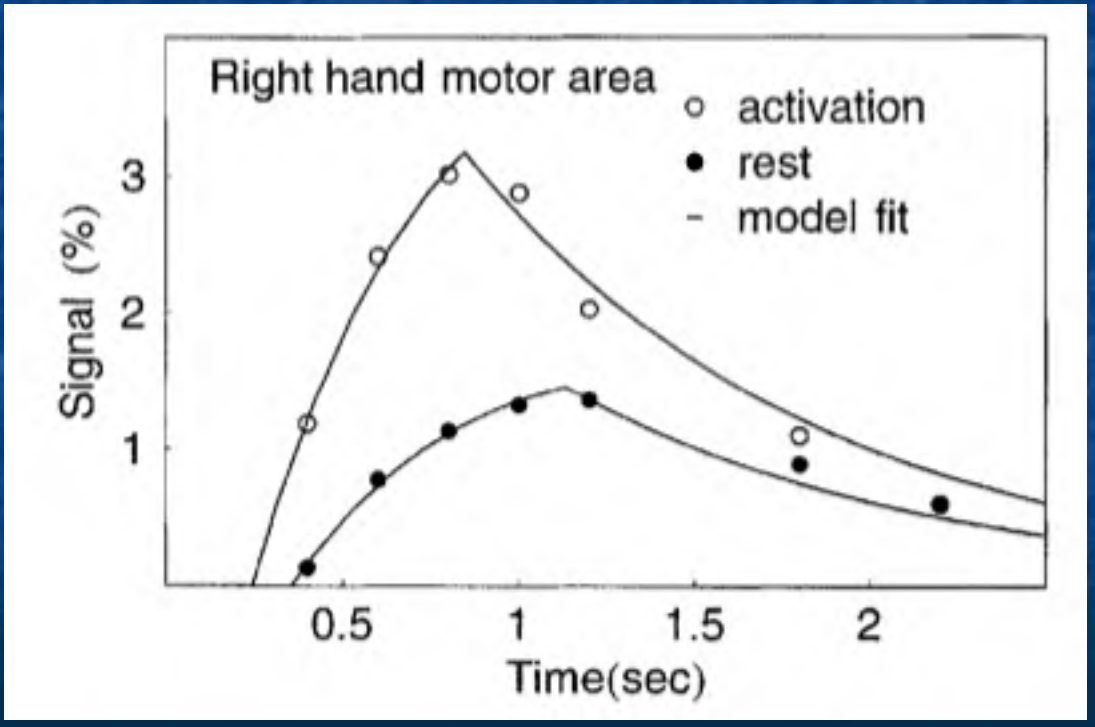
Tissue Residual Function

T1 Relaxation

$$c(t) = \begin{cases} 0 & 0 < t < \Delta t \\ \alpha e^{-t/T_{1b}} \quad \text{(pulsed)} & \Delta t < t < \tau + \Delta t \\ \alpha e^{-\Delta t/T_{1b}} \quad \text{(continuous)} & \\ 0 & \tau + \Delta t < t \end{cases}$$

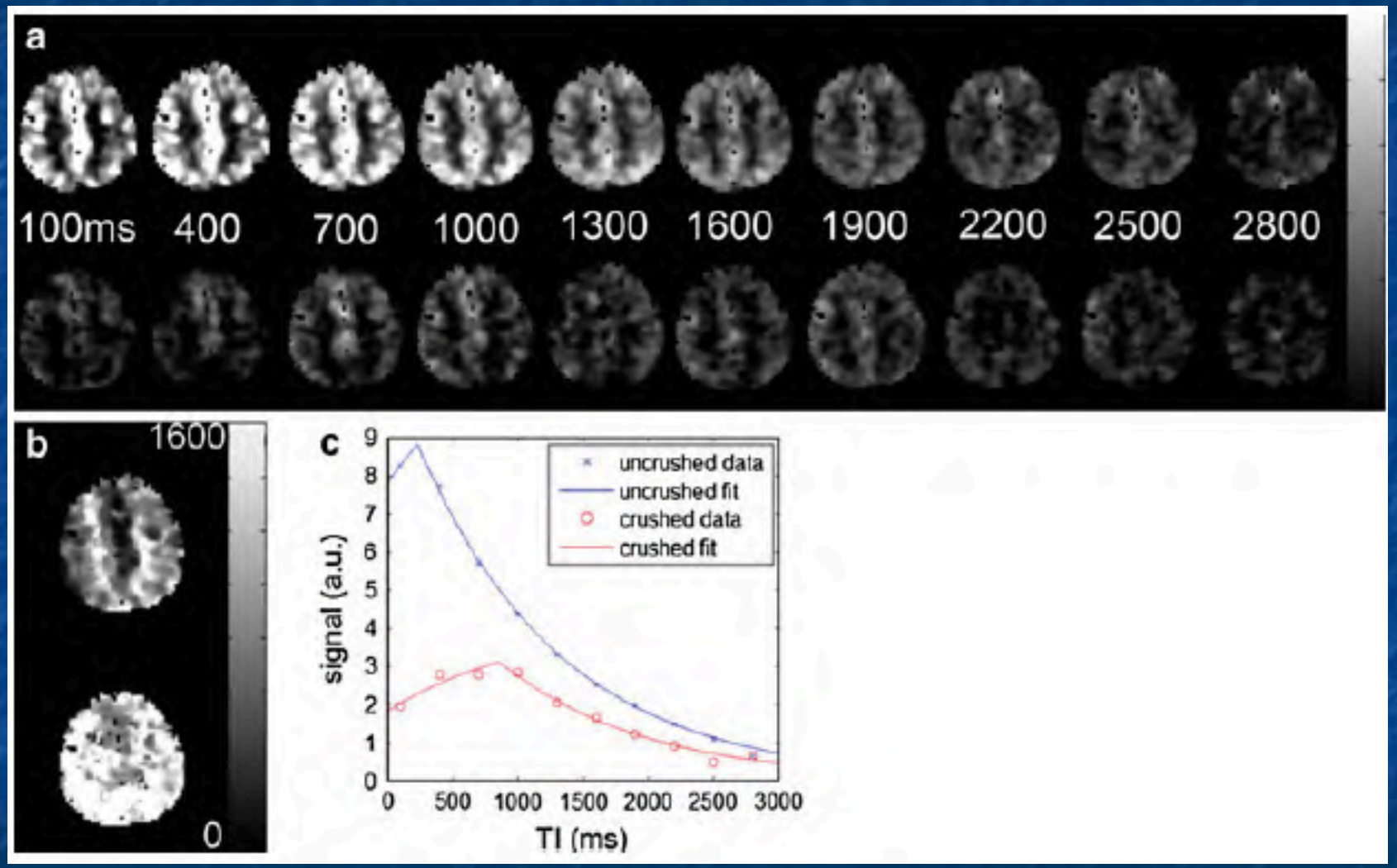
$$r(t) = e^{-f t/\lambda}$$

$$m(t) = e^{-t/T_1}$$



Buxton R et al MRM 1999

Dynamic ASL using Look-Locker Sampling

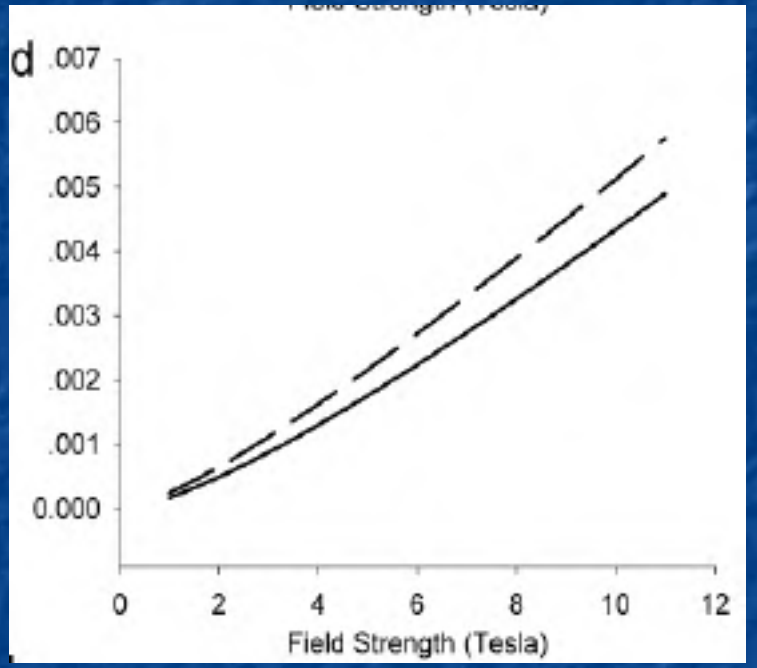


Chen et al. MAGMA (2012)

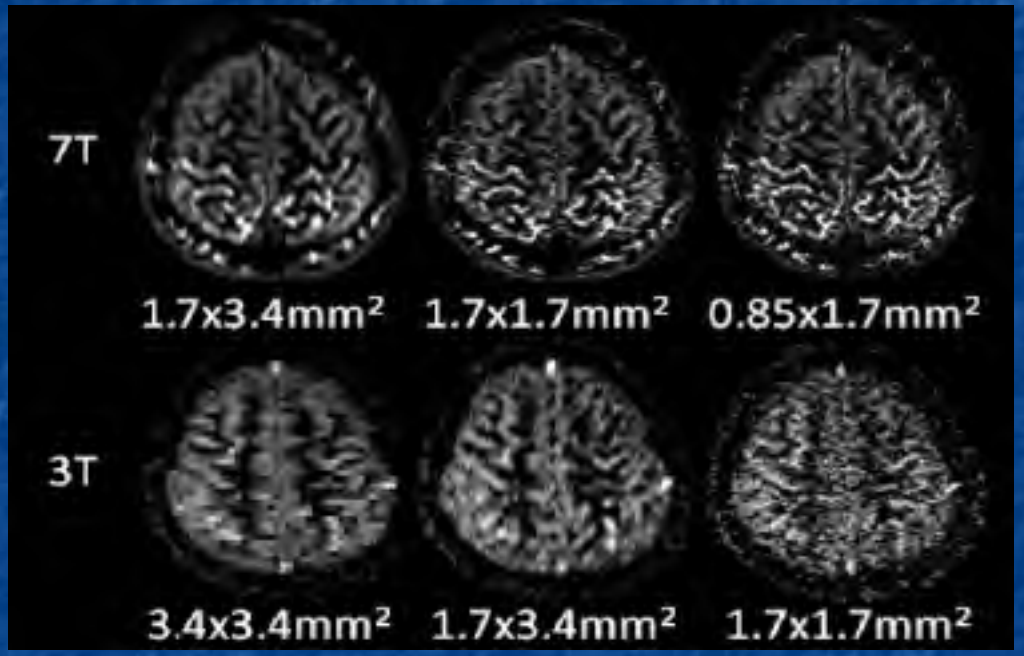
Limitations of ASL

- Relatively low SNR
  - ~1% arterial blood signal which relaxes during arterial transit
- Arterial transit effects
  - focal vascular signals and underestimation of tissue perfusion

ASL Benefits from High Fields



ASL Signal as a function of field strength

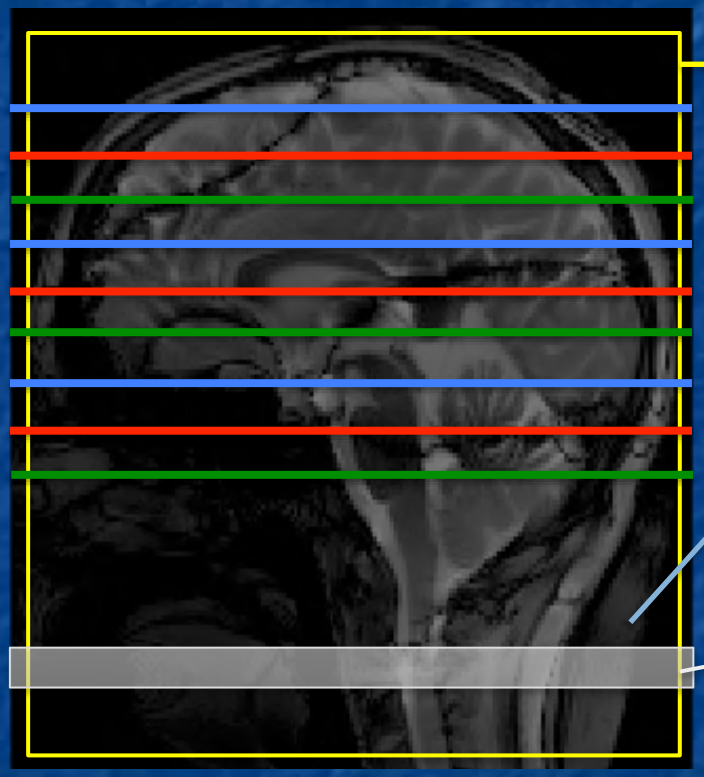


Turbo-FLASH based pCASL

ASL benefits from both increased SNR and prolonged T1 at high field

Zuo et al PLoS One 2013

SMS TFL pCASL with CAIPIRINHA at 3 and 7T

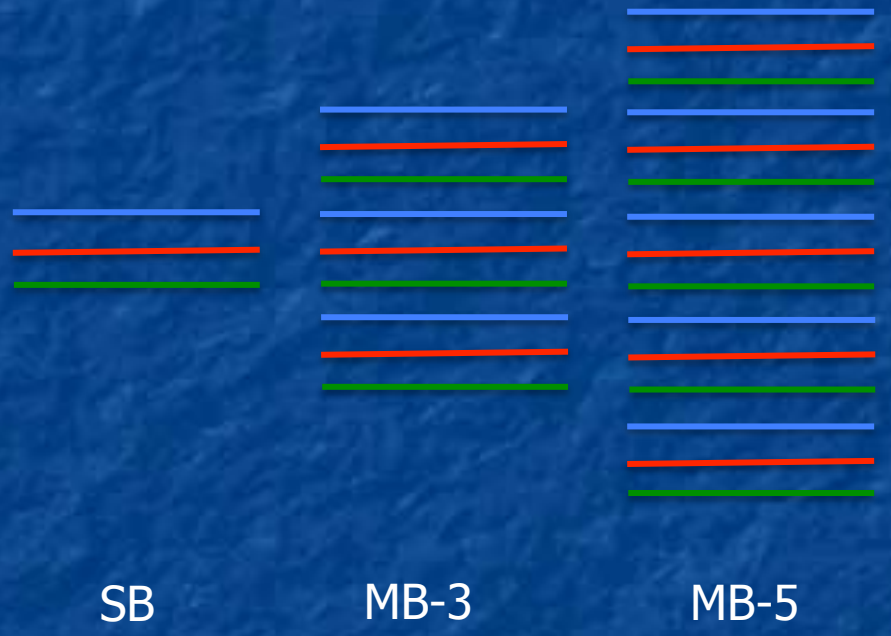


Third-order shimming volume

Imaging slices

Dielectric pad

Labeling plane



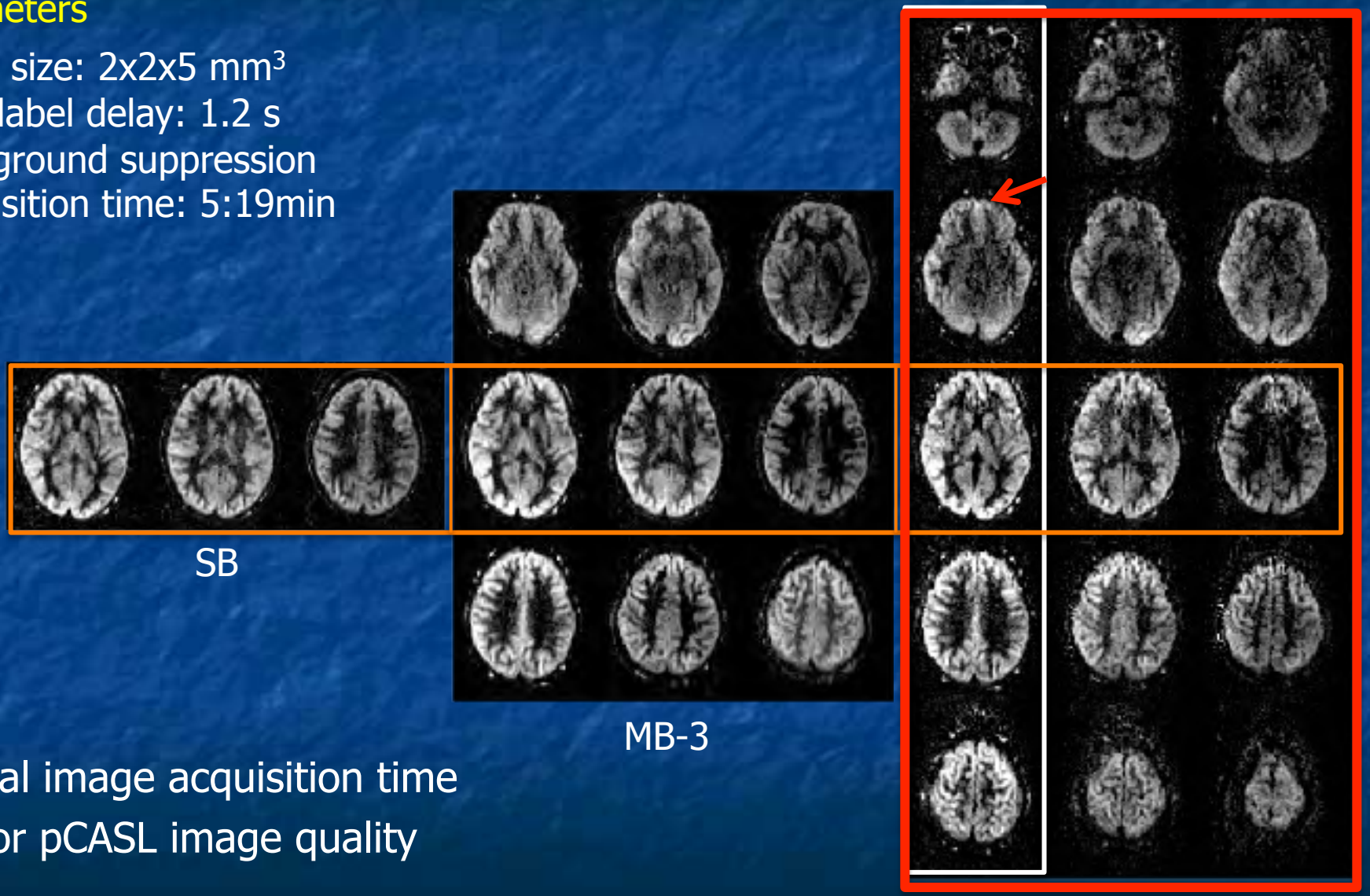
FOV/3 CAIPIRINHA shift

Y. Wang, et al, *NeuroImage* 113, 2015

SMS TFL pCASL images at 3T

Key parameters

- voxel size: 2x2x5 mm^3
- post label delay: 1.2 s
- background suppression
- acquisition time: 5:19min



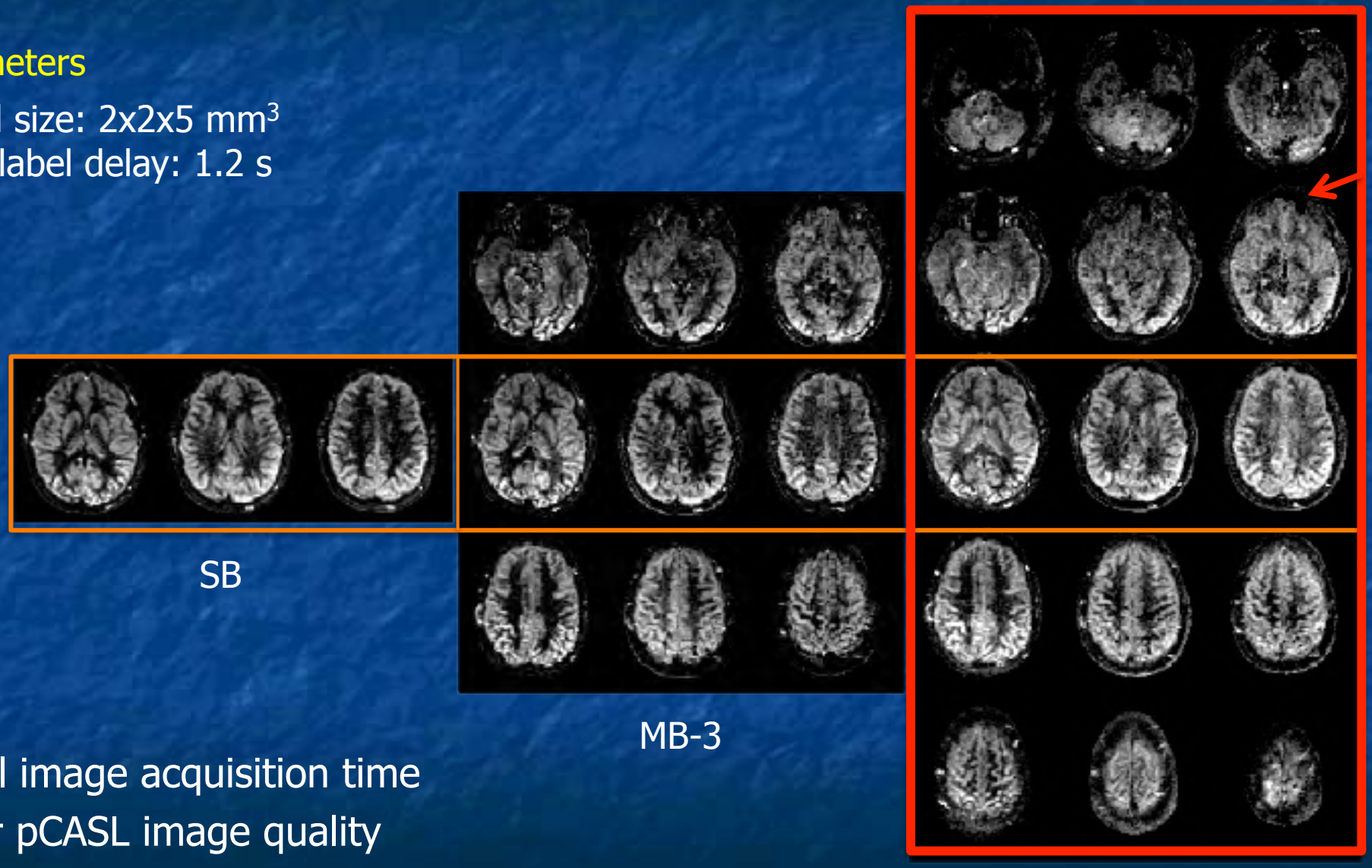
- Identical image acquisition time
- Superior pCASL image quality

Y. Wang, et al, *NeuroImage* 113, 2015

SMS TFL pCASL images at 7T

Key parameters

- Voxel size: 2x2x5 mm^3
- post label delay: 1.2 s



SB

MB-3

MB-5

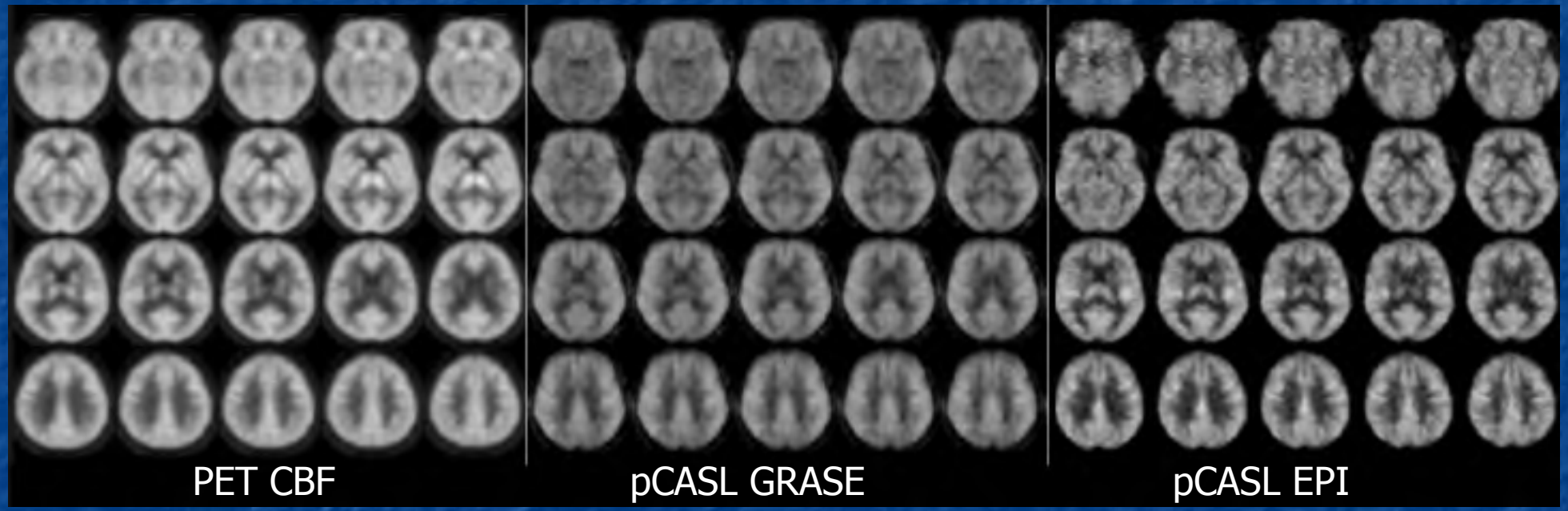
- Identical image acquisition time
- Superior pCASL image quality

Y. Wang, et al, *NeuroImage* 113, 2015

Applications of ASL

- Neurological disorders: stroke, brain tumor, dementia
- Neurodevelopment and genetic effects
- Functional and pharmacological MRI: comparison with BOLD
- Neuromodulation

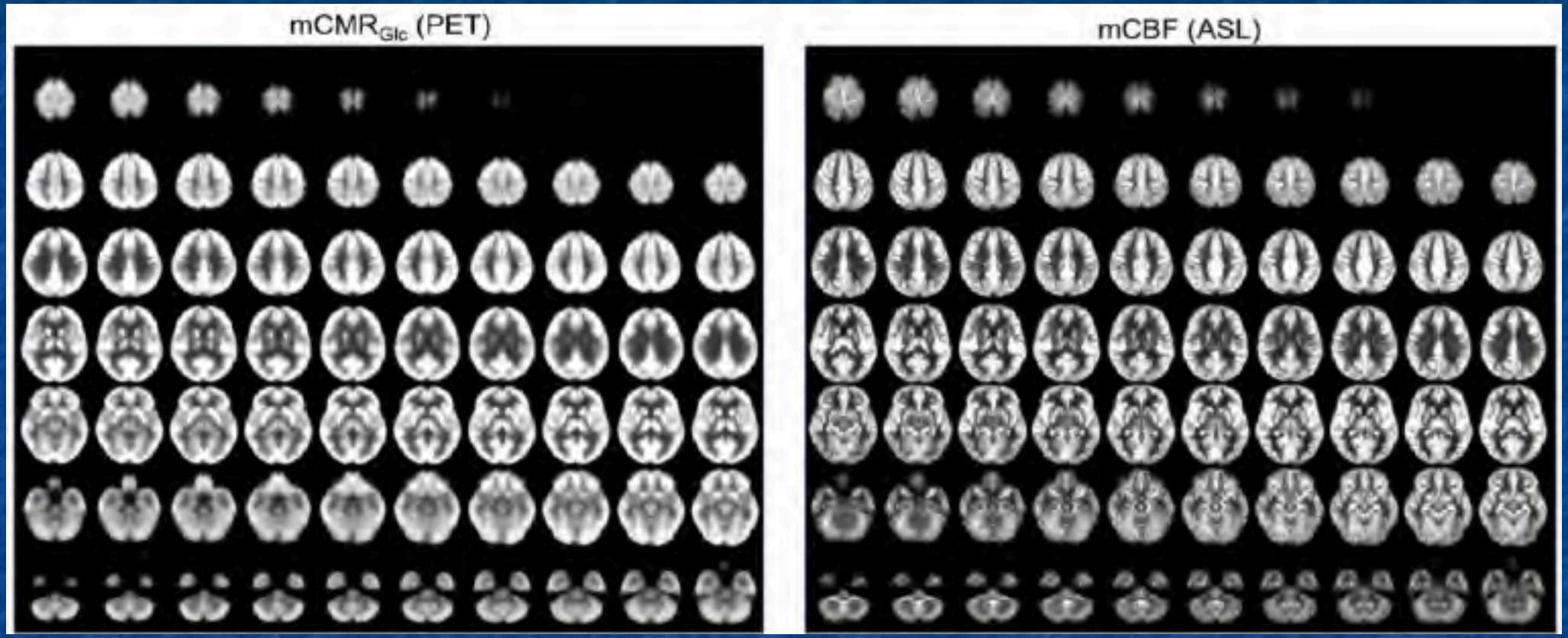
Comparison of 15O-PET and pCASL CBF



Average Pearson correlation ($r=0.53$, $p<0.001$) between PET and pCASL CBF

Kilroy et al JMRI (2013)

Comparison of ASL and FDG-PET

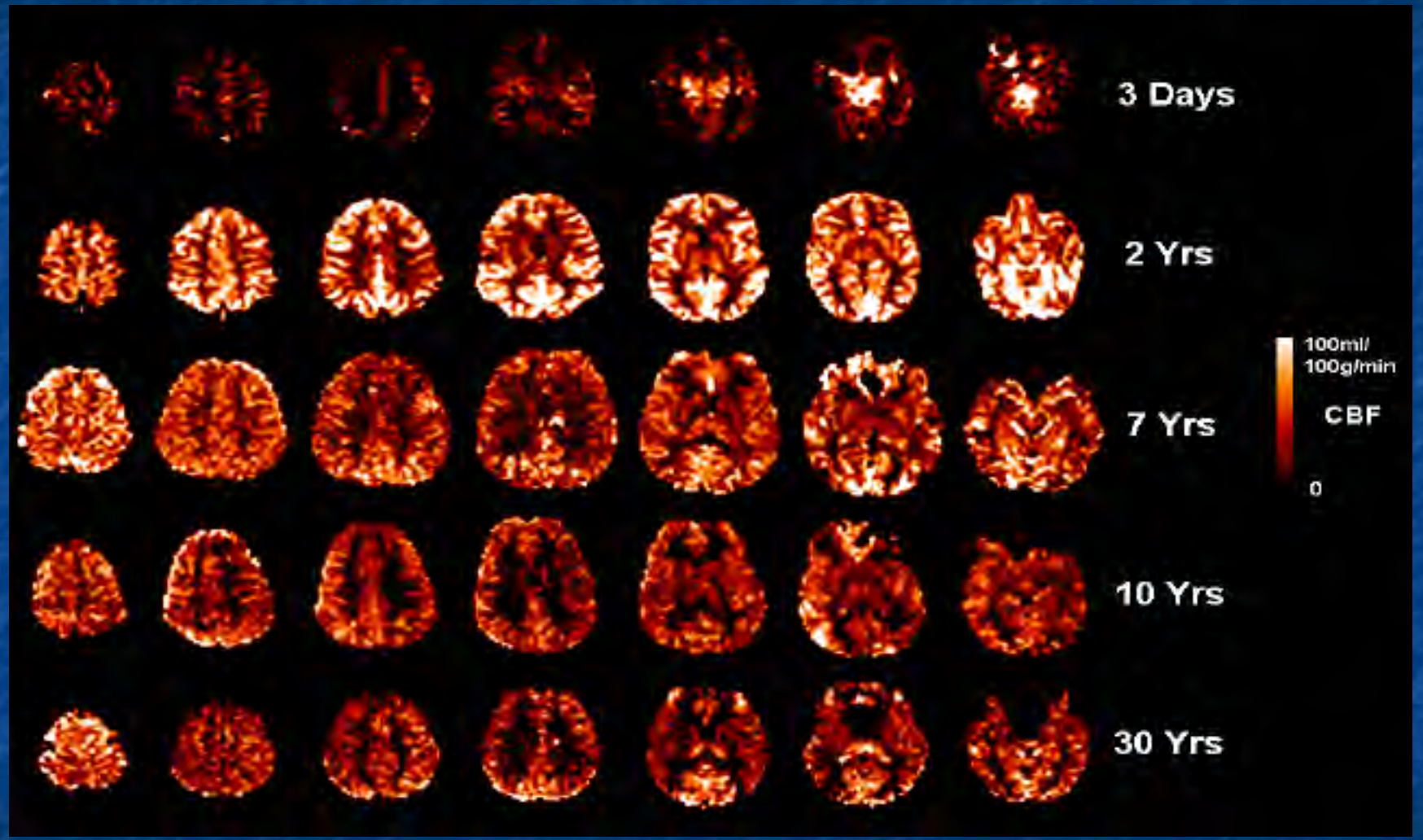


CBF (pCASL) CMRglc (FDG-PET)

20 healthy volunteers (23-59yrs) participated both ASL MRI and FDG-PET scans

Cha et al. JCBFM (2013)

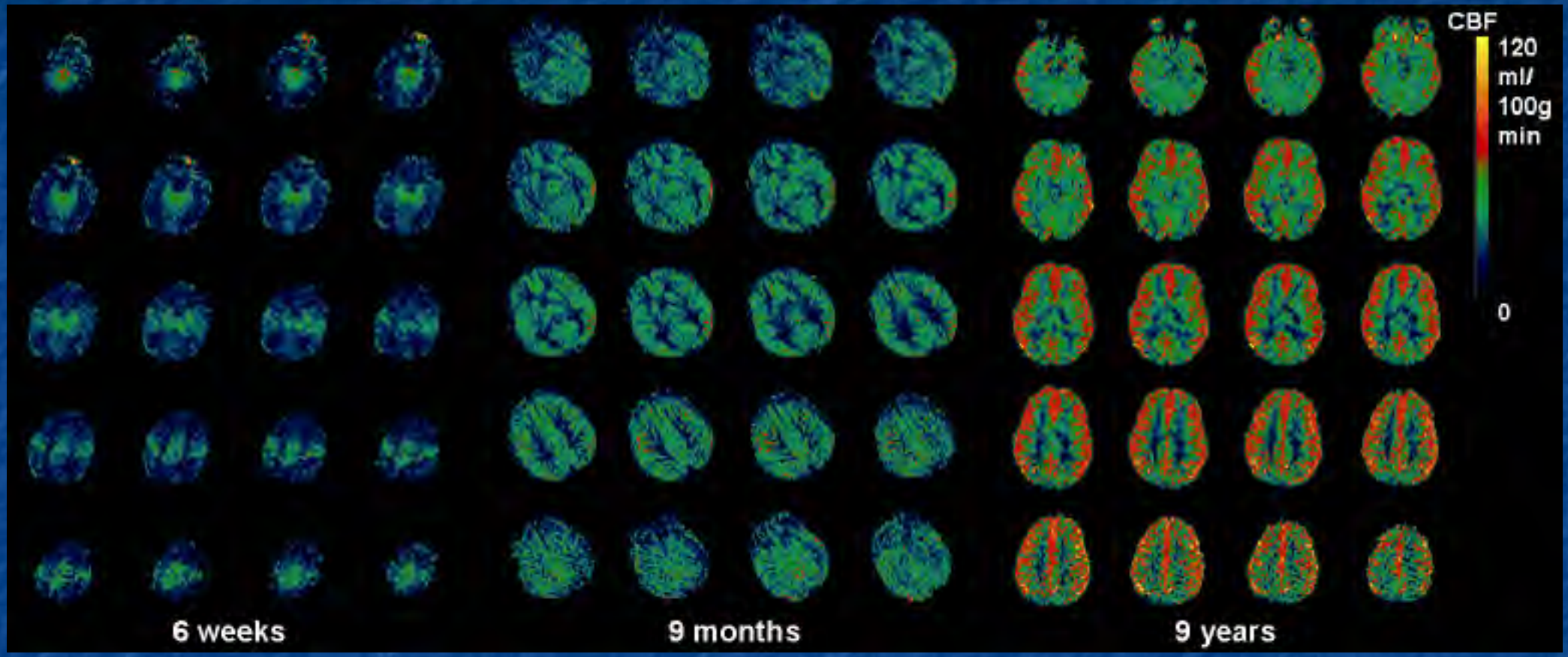
Developmental Change of CBF



Representative CBF images across the age span from 3 days to 30yrs acquired using a PASL technique at 1.5T.

Wang et al Clin Dev Neurosci (2009)

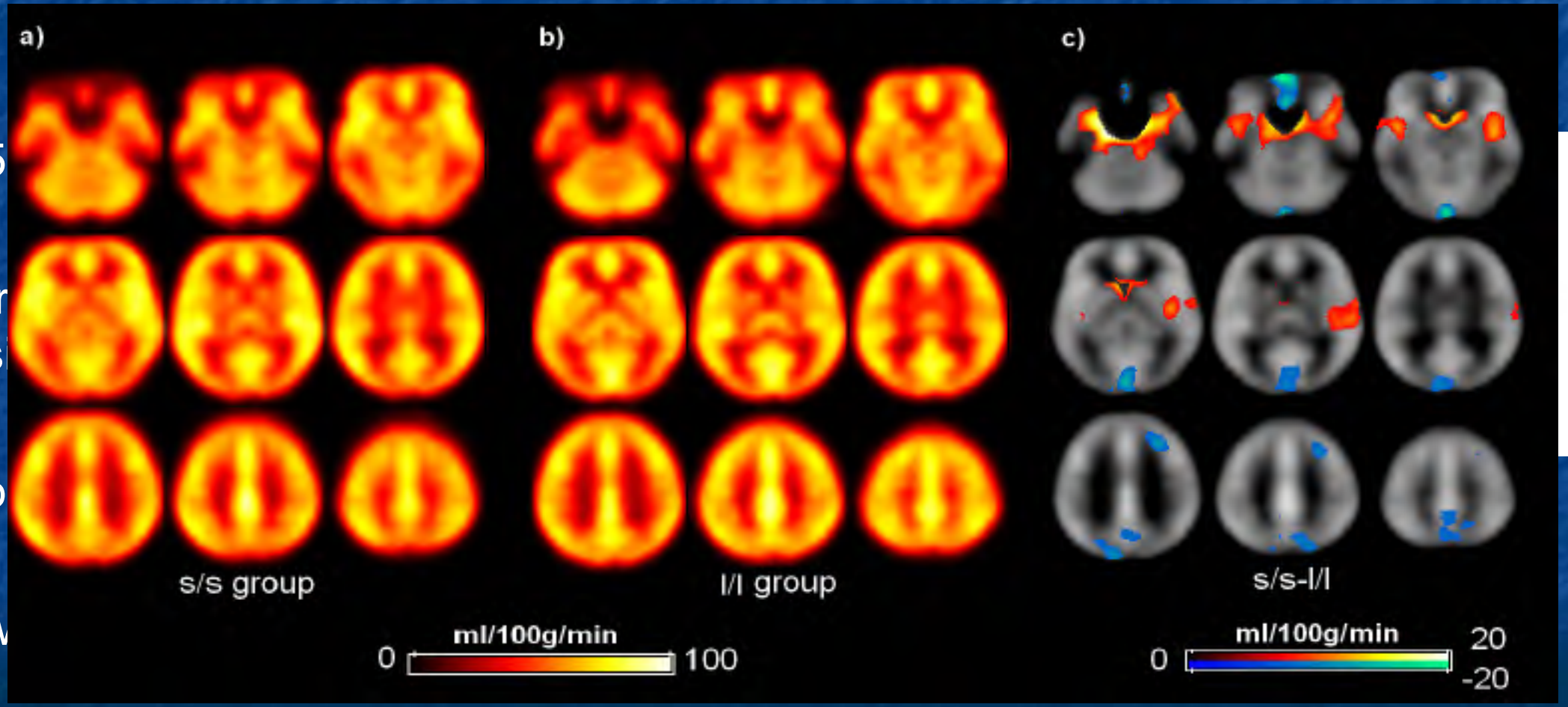
3D pCASL GRASE of Infants and Children



Representative CBF maps acquired using pCASL 3D BS GRASE in high risk infants aged 6 weeks and 9 months, and an ASD boy 9yr old.

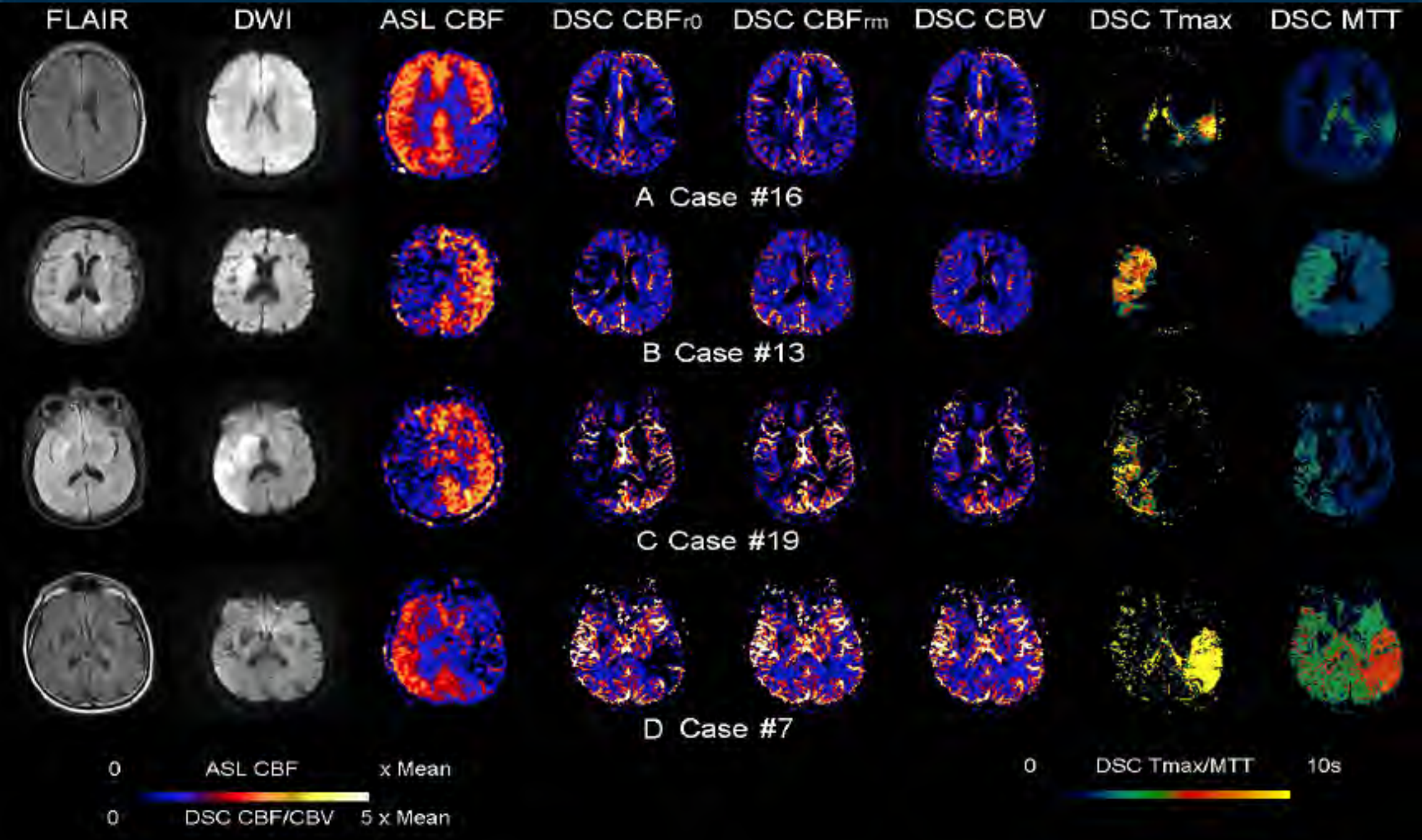
Serotonin transporter-linked polymorphic region (5-HTTLPR)

- 5
- tr
s
- p
- w



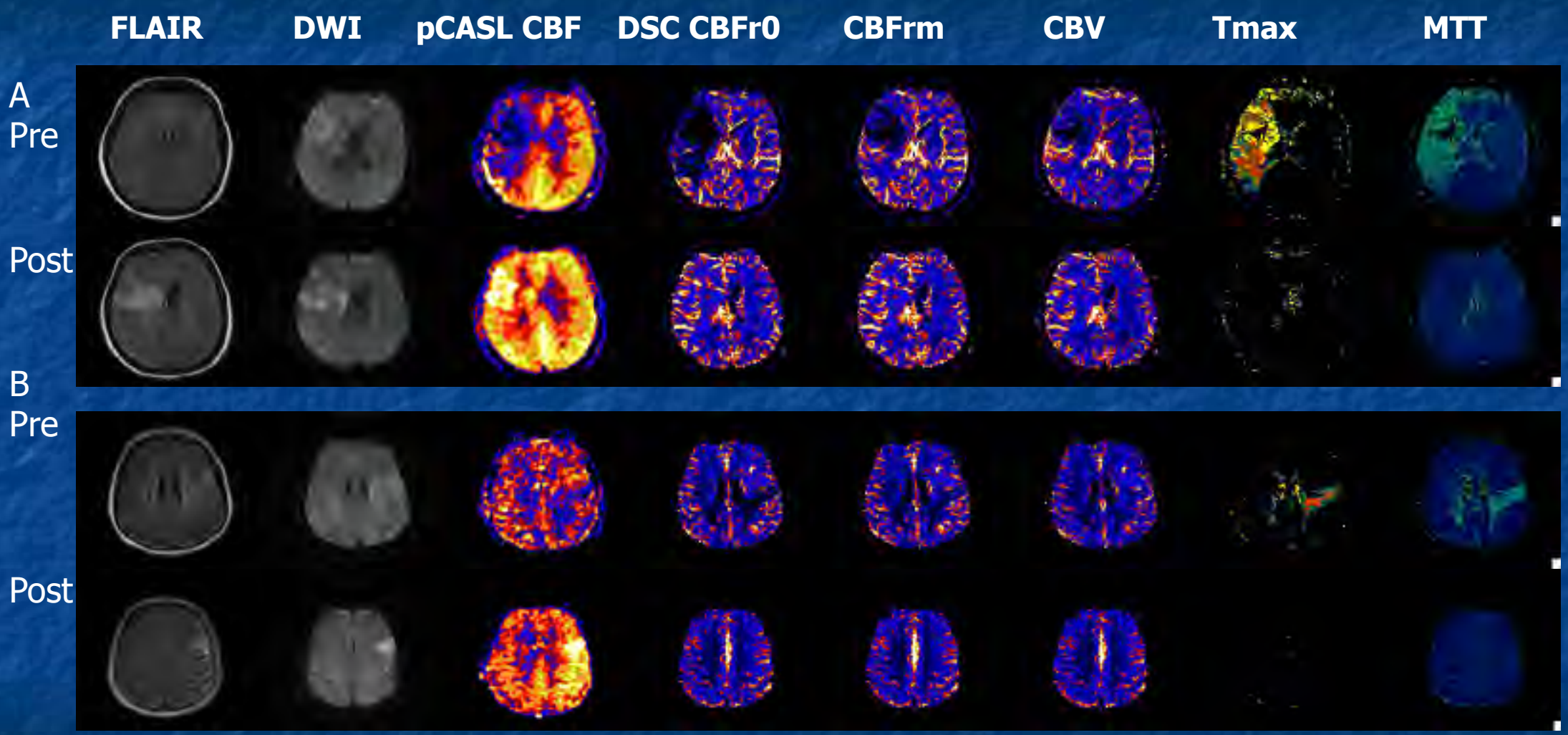
Rao et al. Bio Psych (2007)

Representative AIS cases showing hypo-perfusion lesions



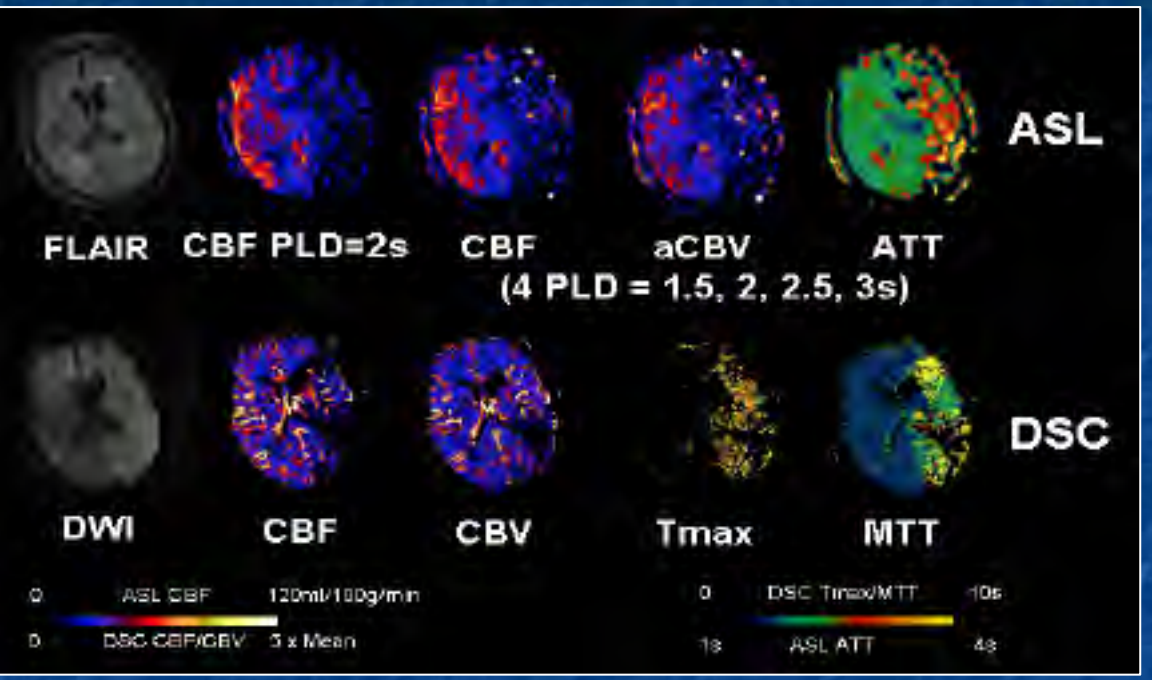
Wang et al Stroke (2012)

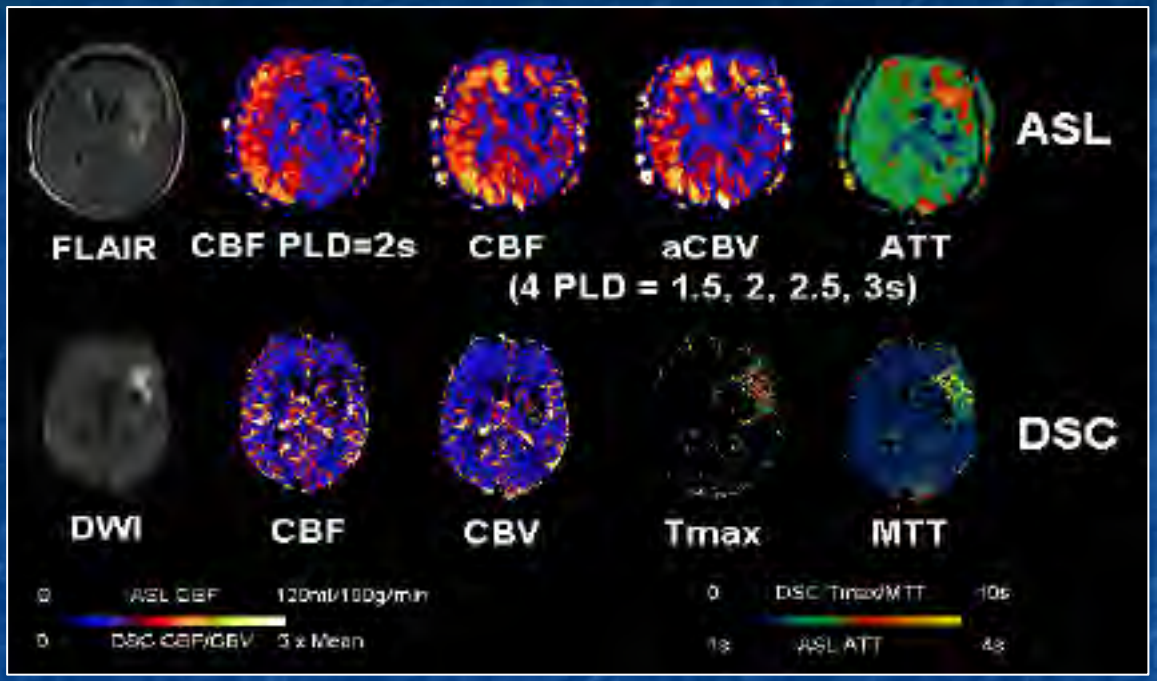
Representative AIS cases pre and post endovascular intervention



Wang et al Stroke (2012)

Multi-delay multi-parametric ASL in AIS

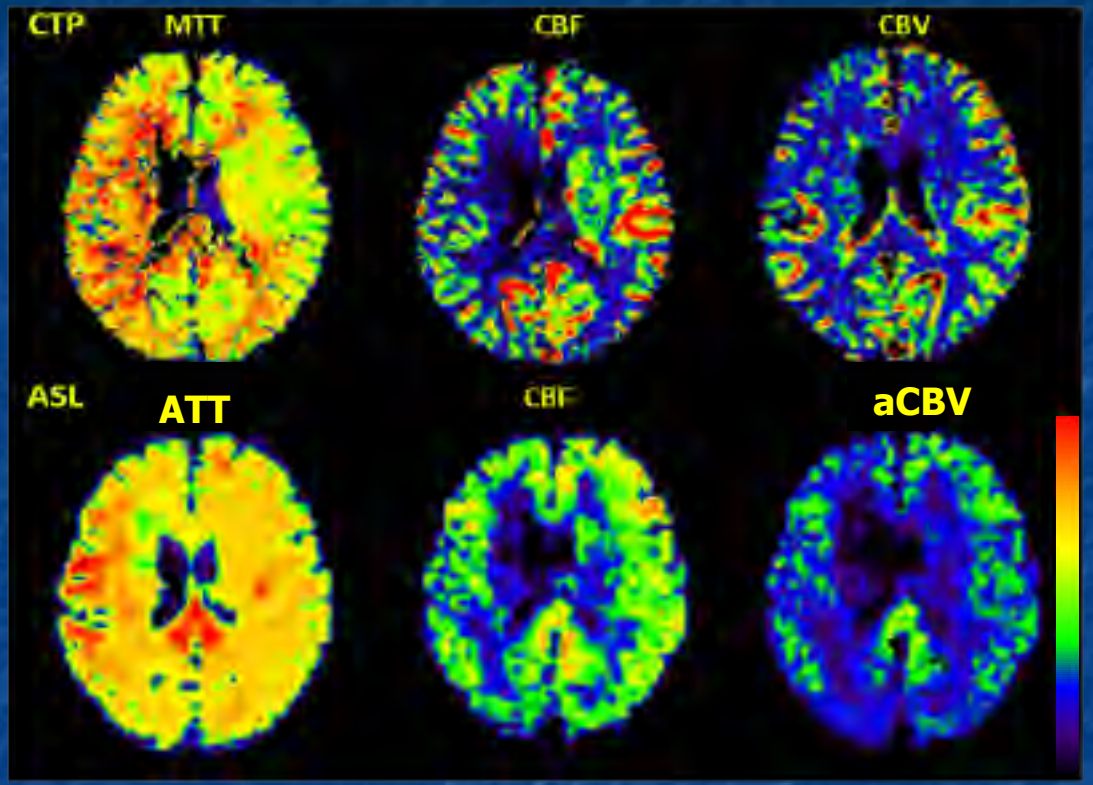




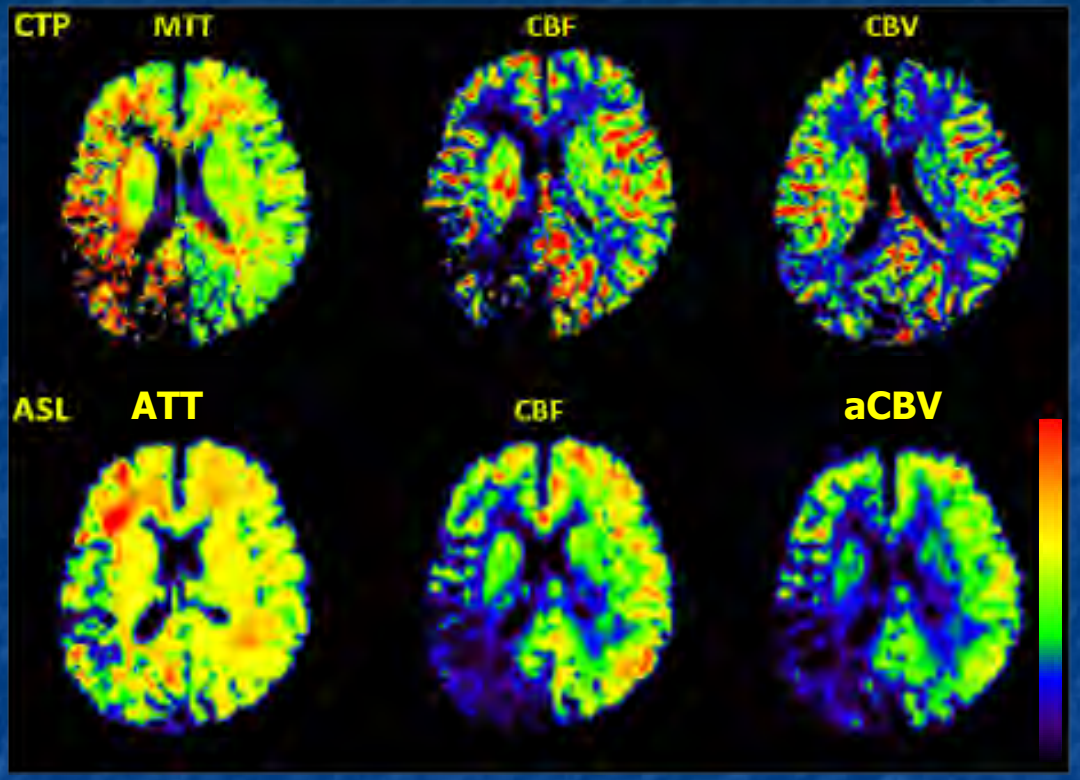
PCASL GRASE with 4 delays (1.5, 2, 2.5, 3s) allows estimation of ATT, CBF and arterial CBV (aCBV)

Wang et al NI: Clinical (2013)

Multi-parametric ASL VS. CTP in moya moya disease



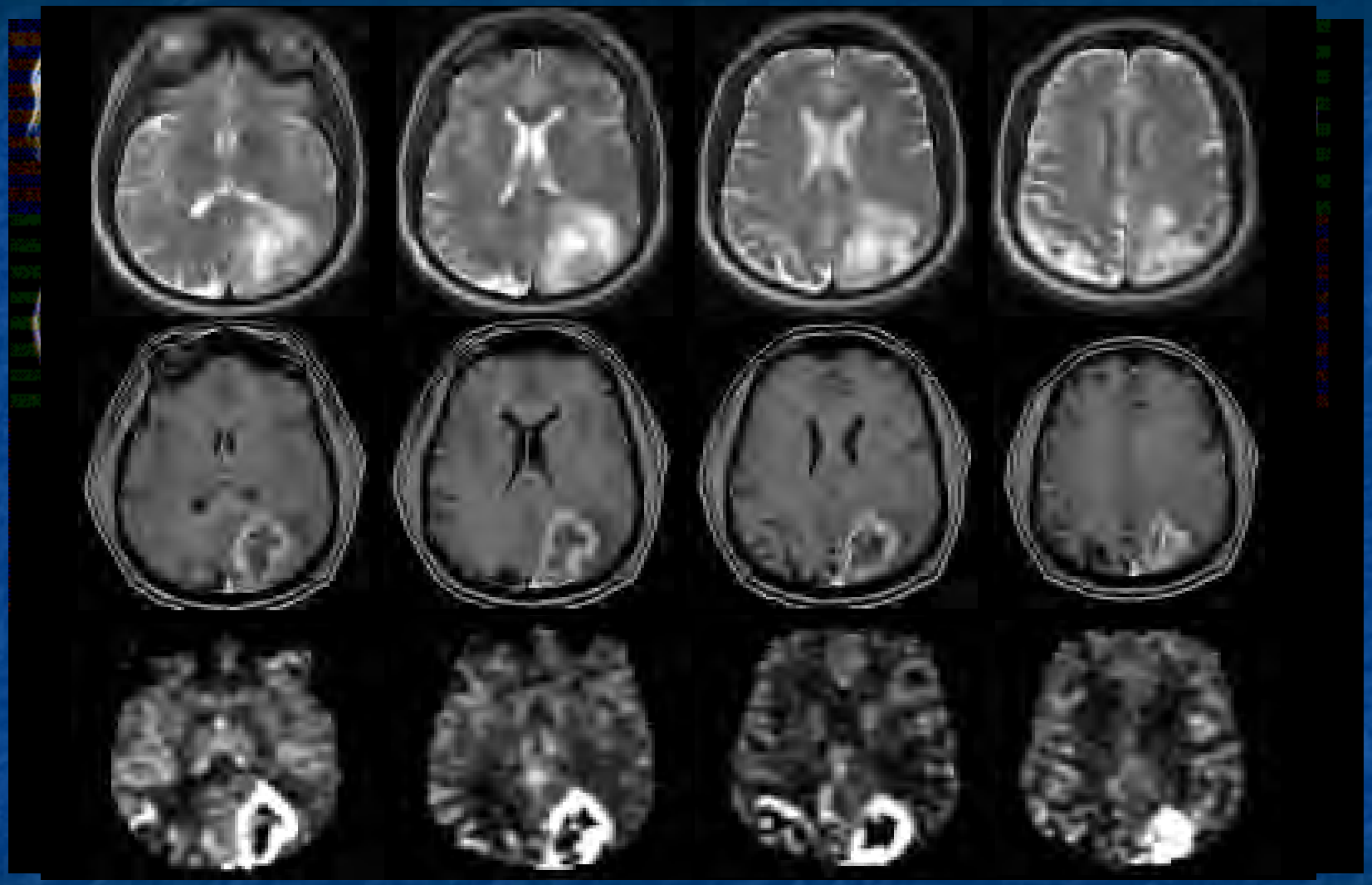
Case 1. CTP shows low perfusion areas in right temporo-patietal lobe with decreased CBF values and elevated MTT and CBV.ASL is in concordance with the results of CTP.



Case 2. ASL CBF show hypoperfusion in the right frontal, occipital,temporal-parietal lobes. CTP MTTrha and ASL ATT were prolonged with hypoperfusion on CBF images. ASL aCBV map shows larger hypoperfusion region than CTP CBV.

Wang et al Eur Radio (2014)

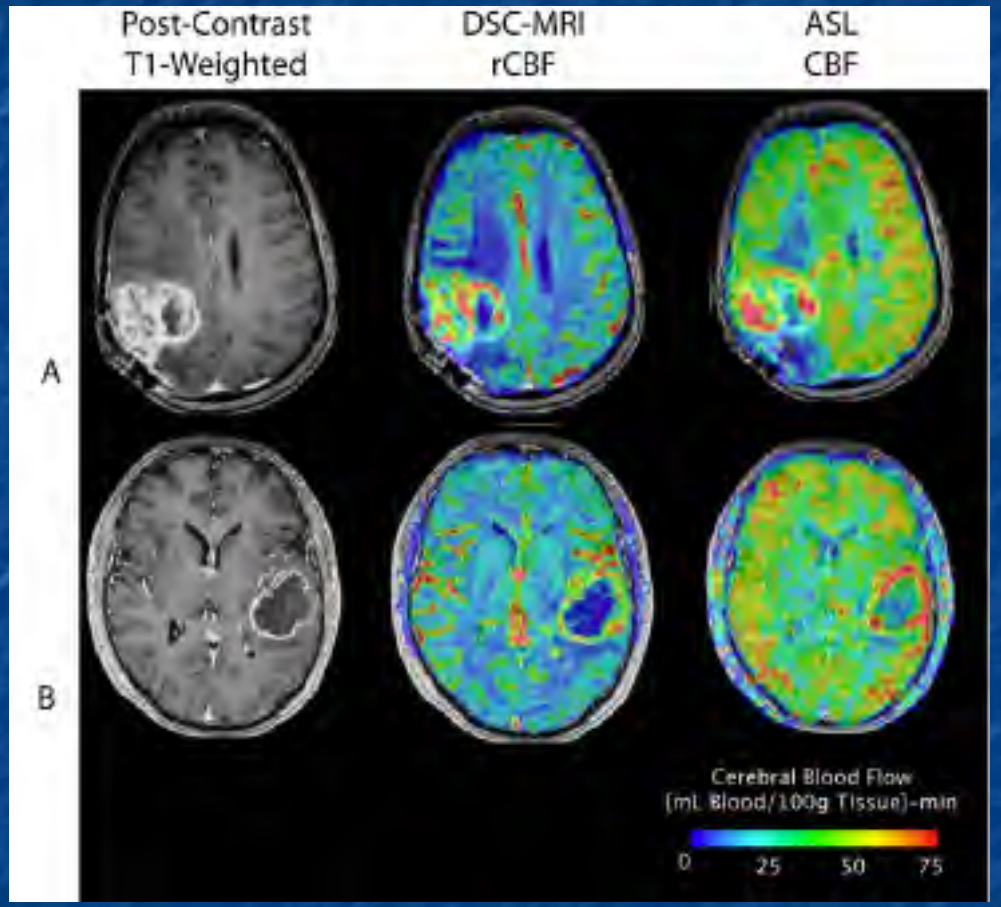
3T CASL in Brain Tumor

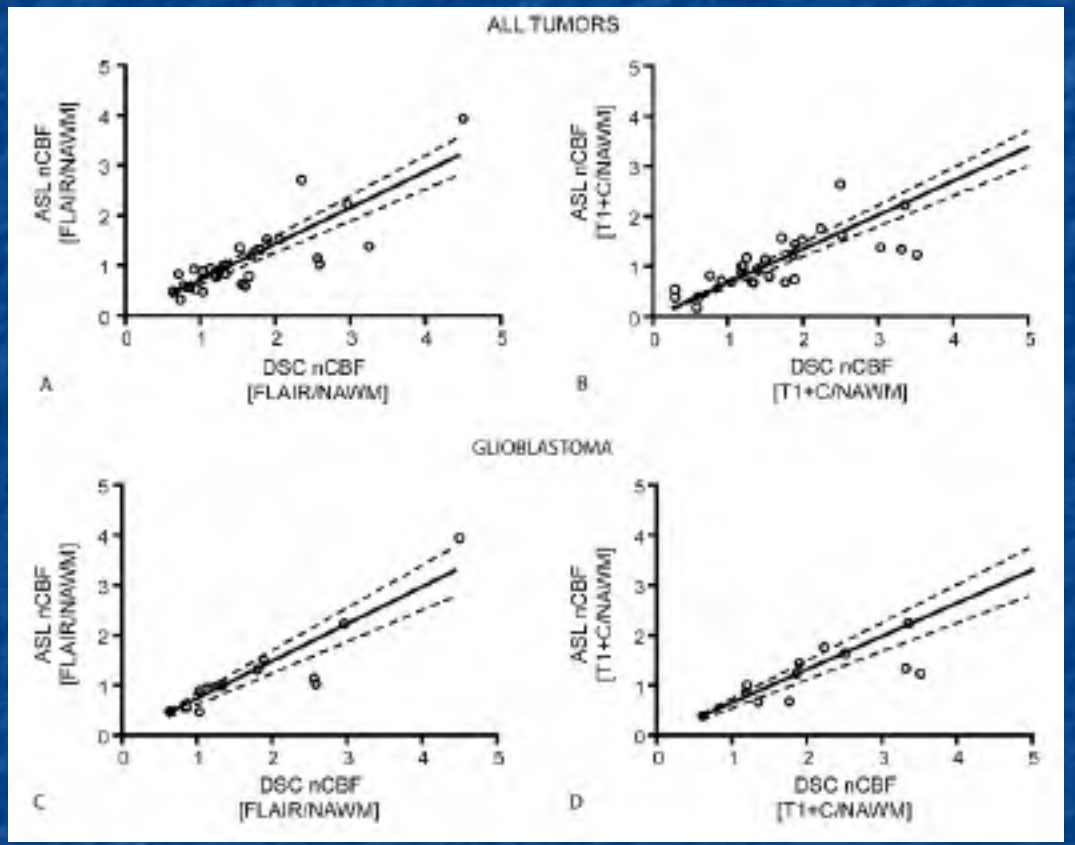


Tumor grading and biopsy guiding

Wolf et al. JMRI (2005)

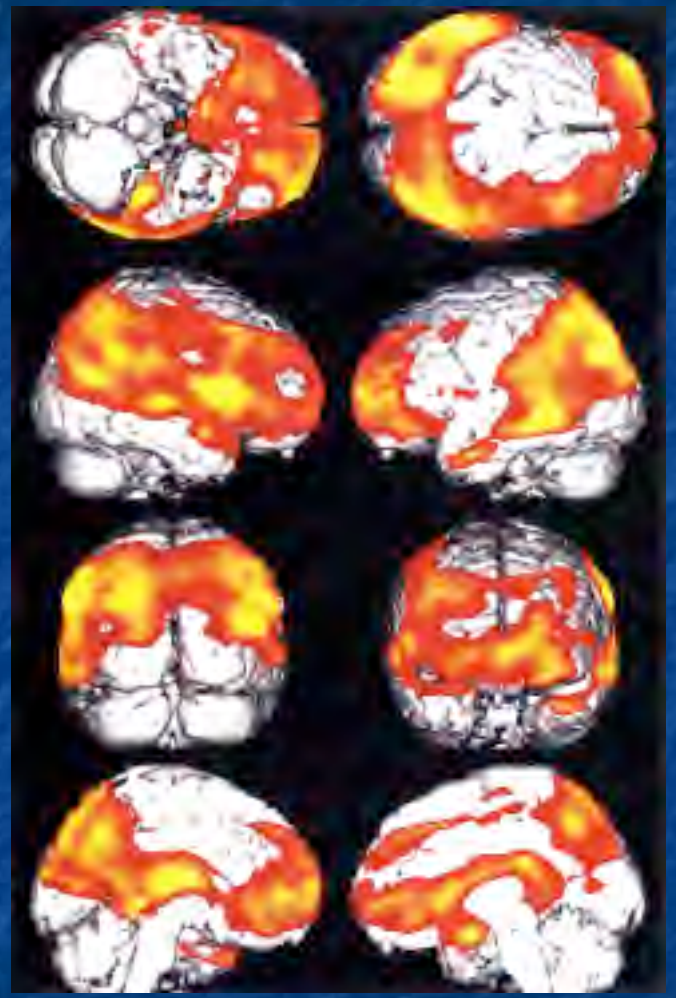
Comparison of ASL and DSC in Brain Tumor Grading





White et al J Neuroimag (2014)

Perfusion MRI in Alzeimer's Dementia



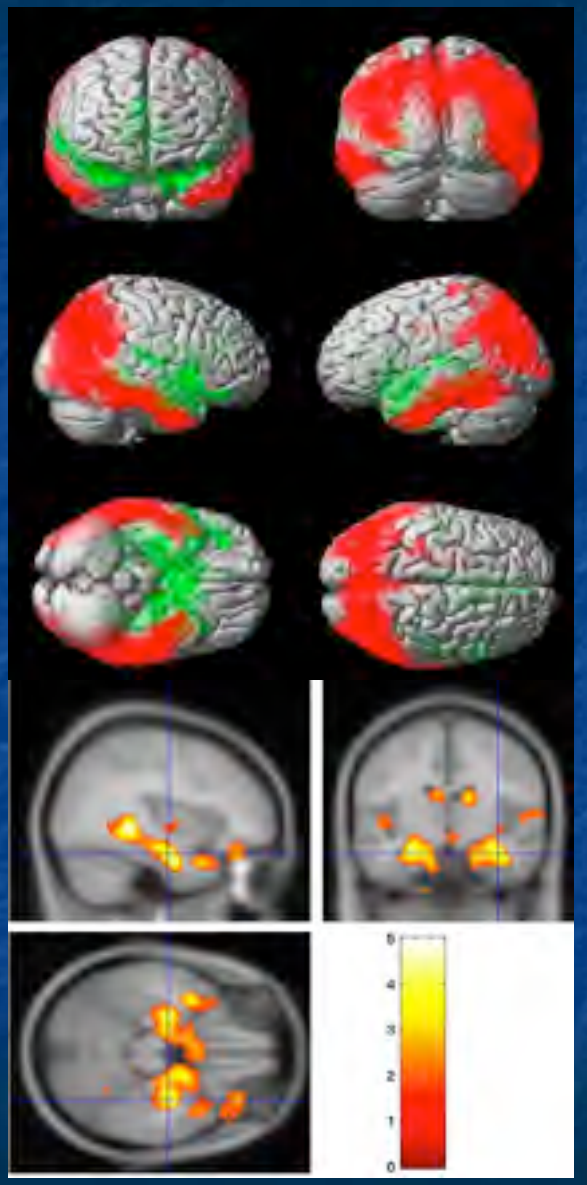
AD vs. CONTROL

Alsop et al Ann Neuroloy (2000)

AD vs. CONTROL

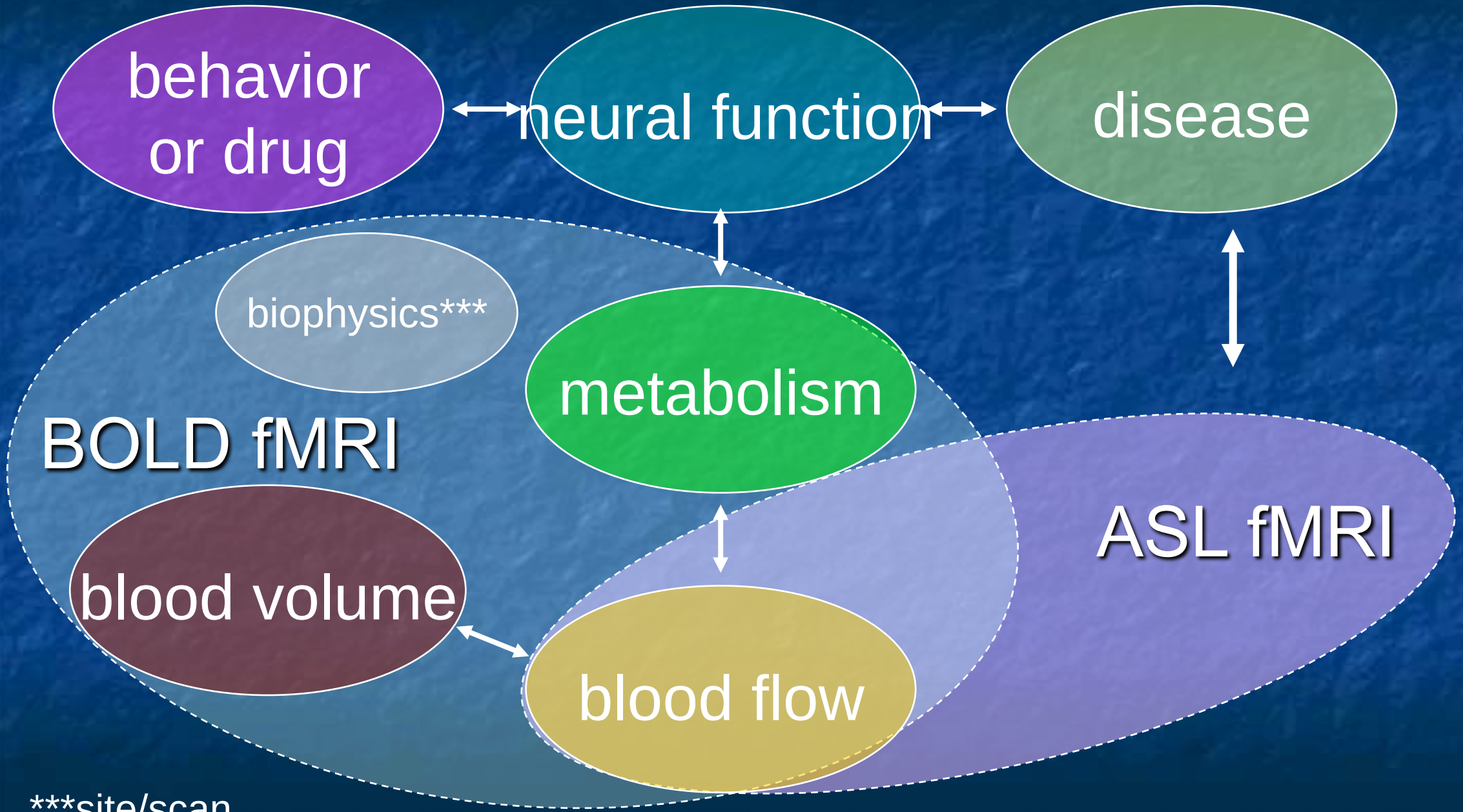
MCI vs. CONTROL

Johnson et al Radiology (2005)



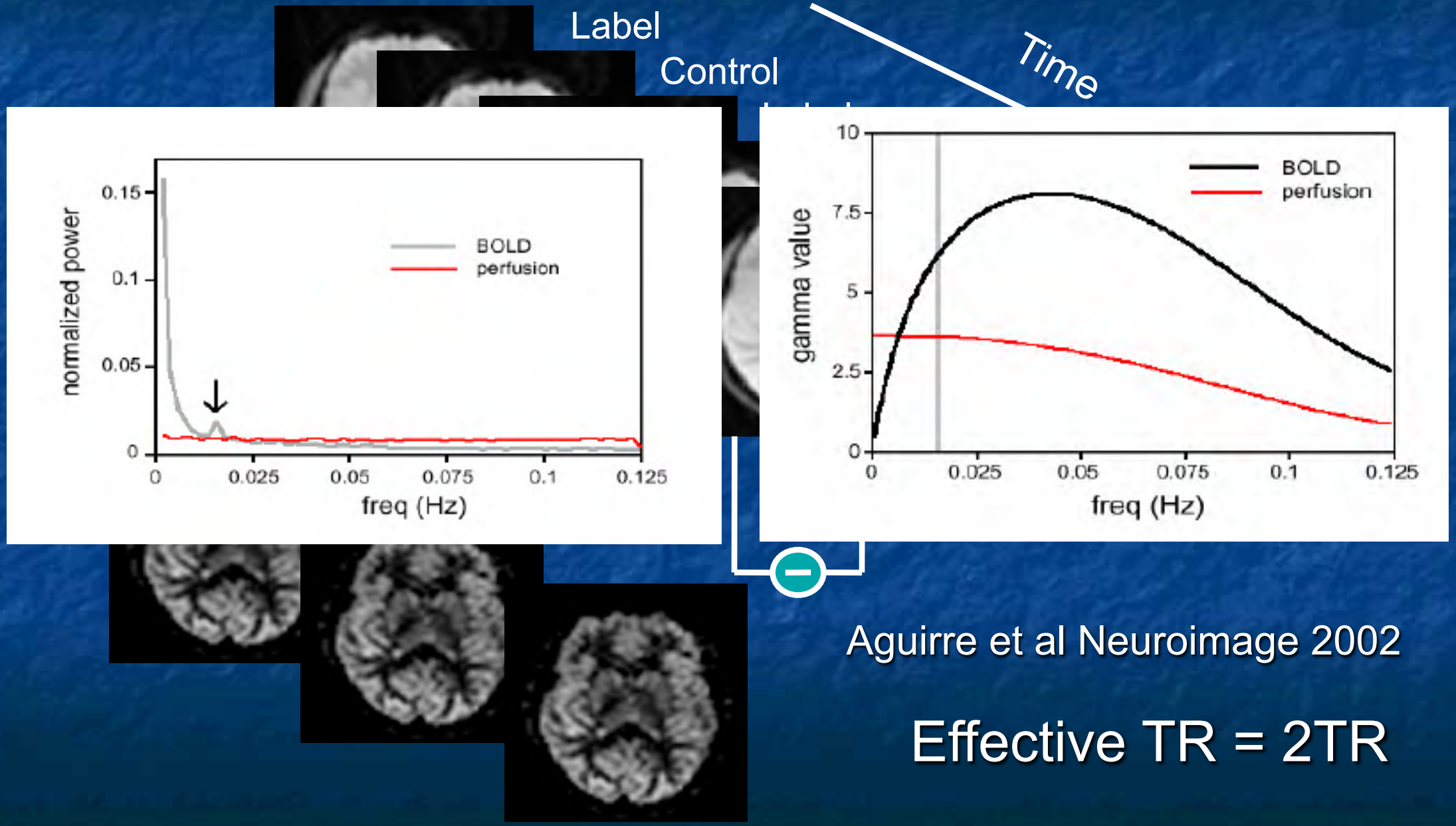
Alsop et al Neuroimage (2008)

Physiological Basis of fMRI/phMRI



***site/scan effects

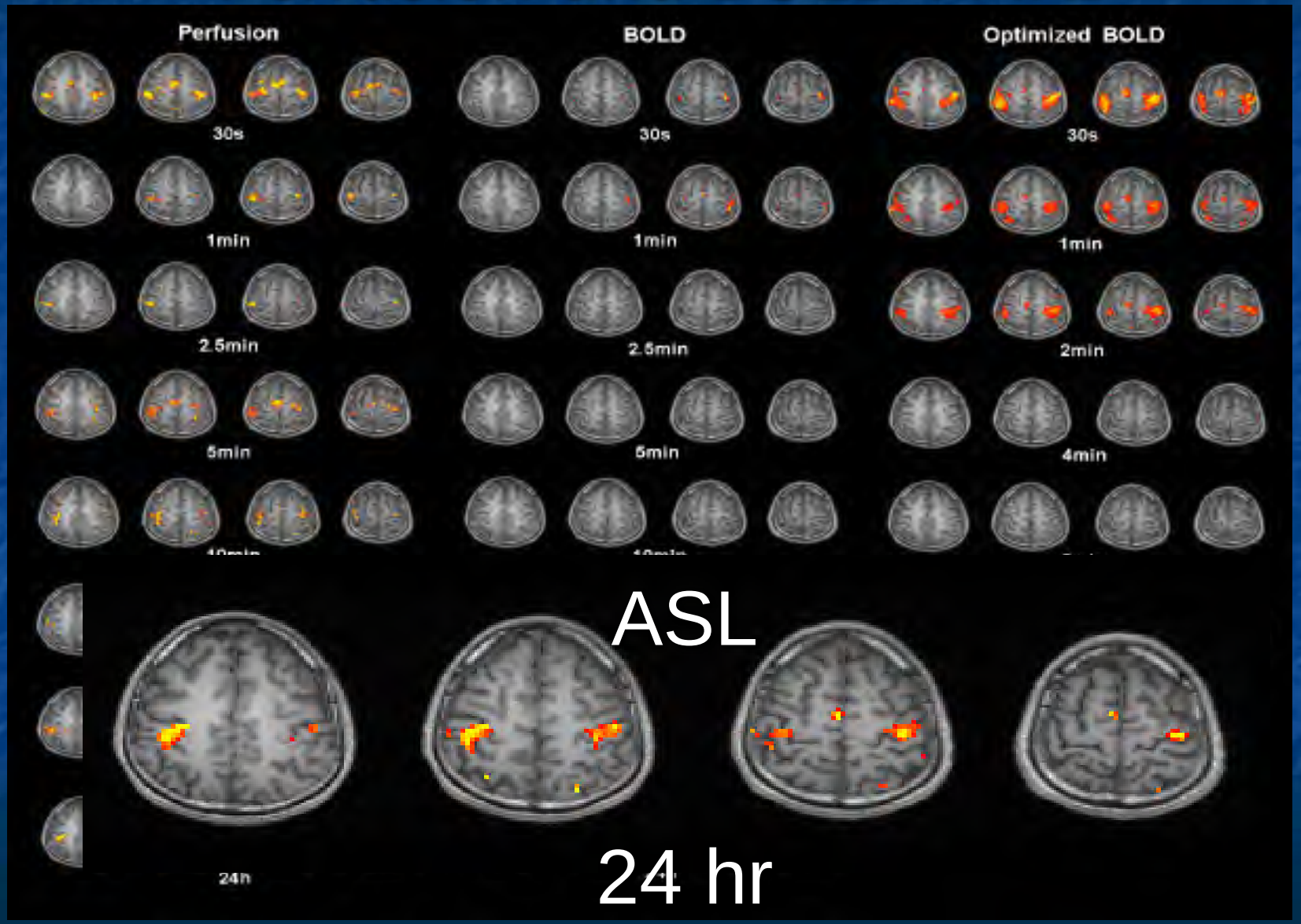
ASL Perfusion fMRI



Aguirre et al Neuroimage 2002

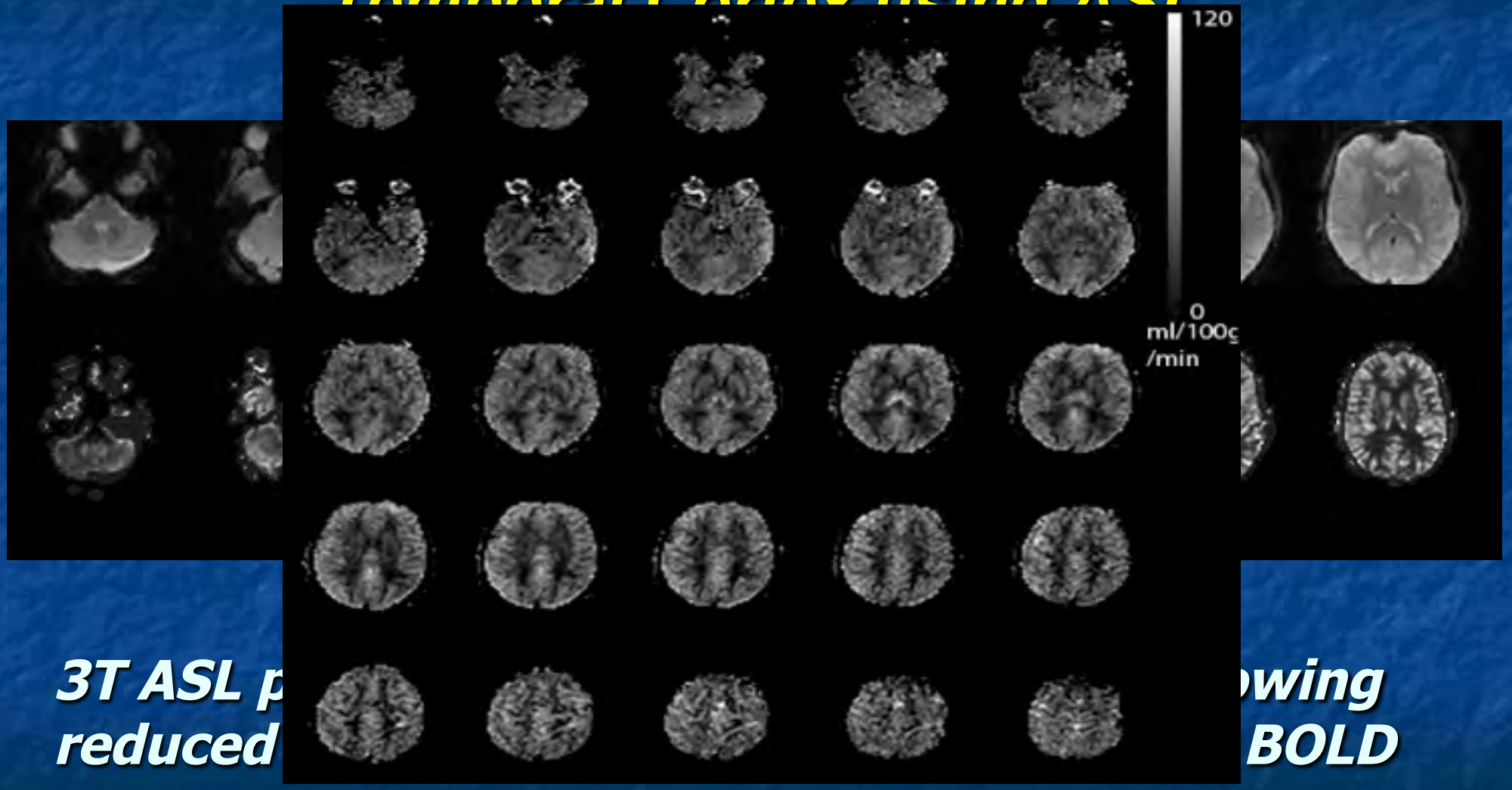
Effective TR = 2TR

Temporal Characteristics of Perfusion and BOLD FMRI



Wang et al. MRM (2003)

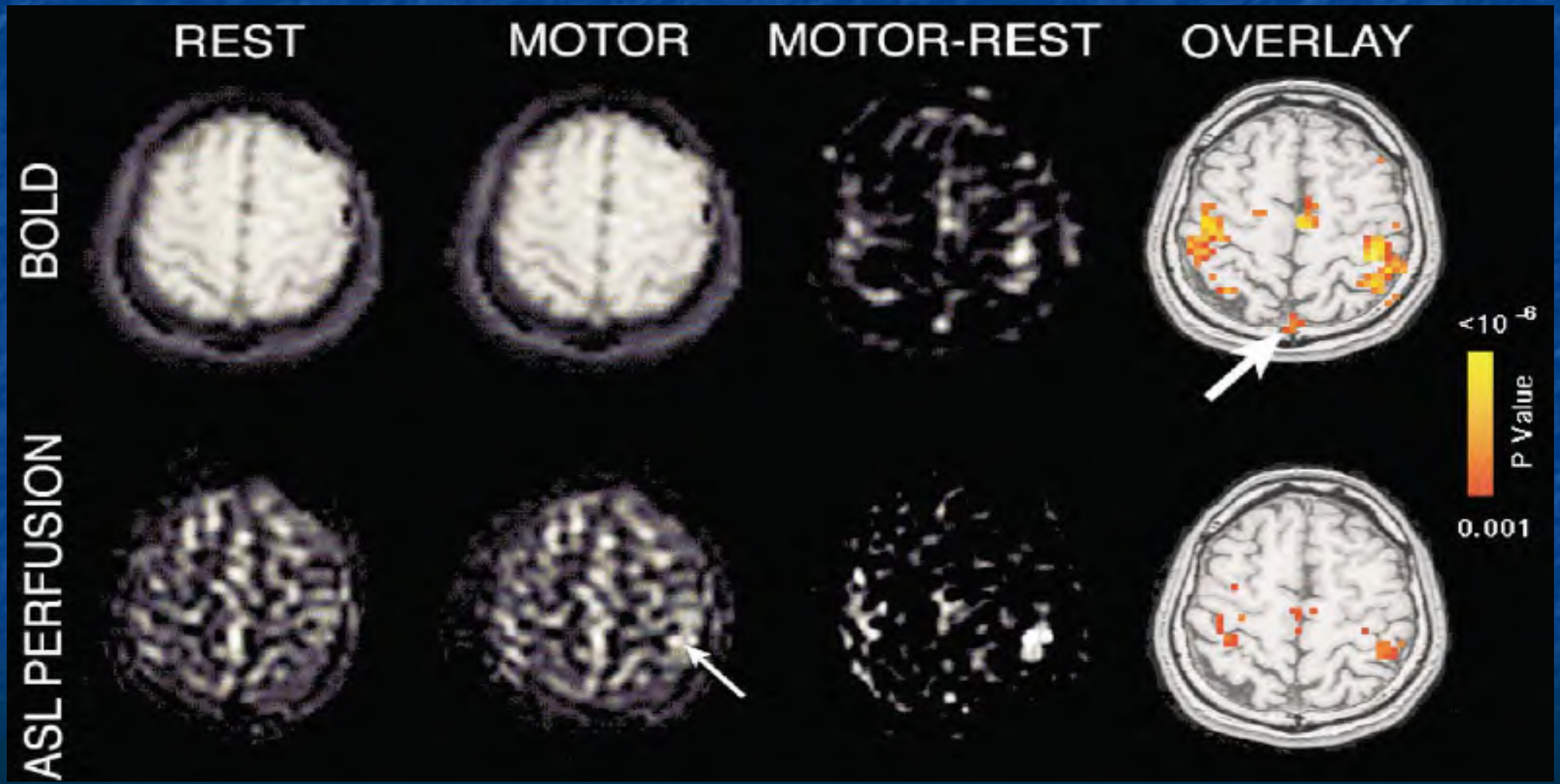
Improved Coverage in Orbitofrontal and Temporal Cortex using ASL



3T ASL p… …owing reduced … BOLD

Wang et al Dev Clin Neurosci (2008)

Spatial Localization Using ASL vs. BOLD fMRI



Detre & Wang, Clinical Neurophysiology 2002

Perfusion fMRI of cigarette-induced craving

Imaging Session Tim

Smoke Break (-

- **Scan 1** **Locali**

Pre - (

CASL

Post -

High I

Smoke Break (-

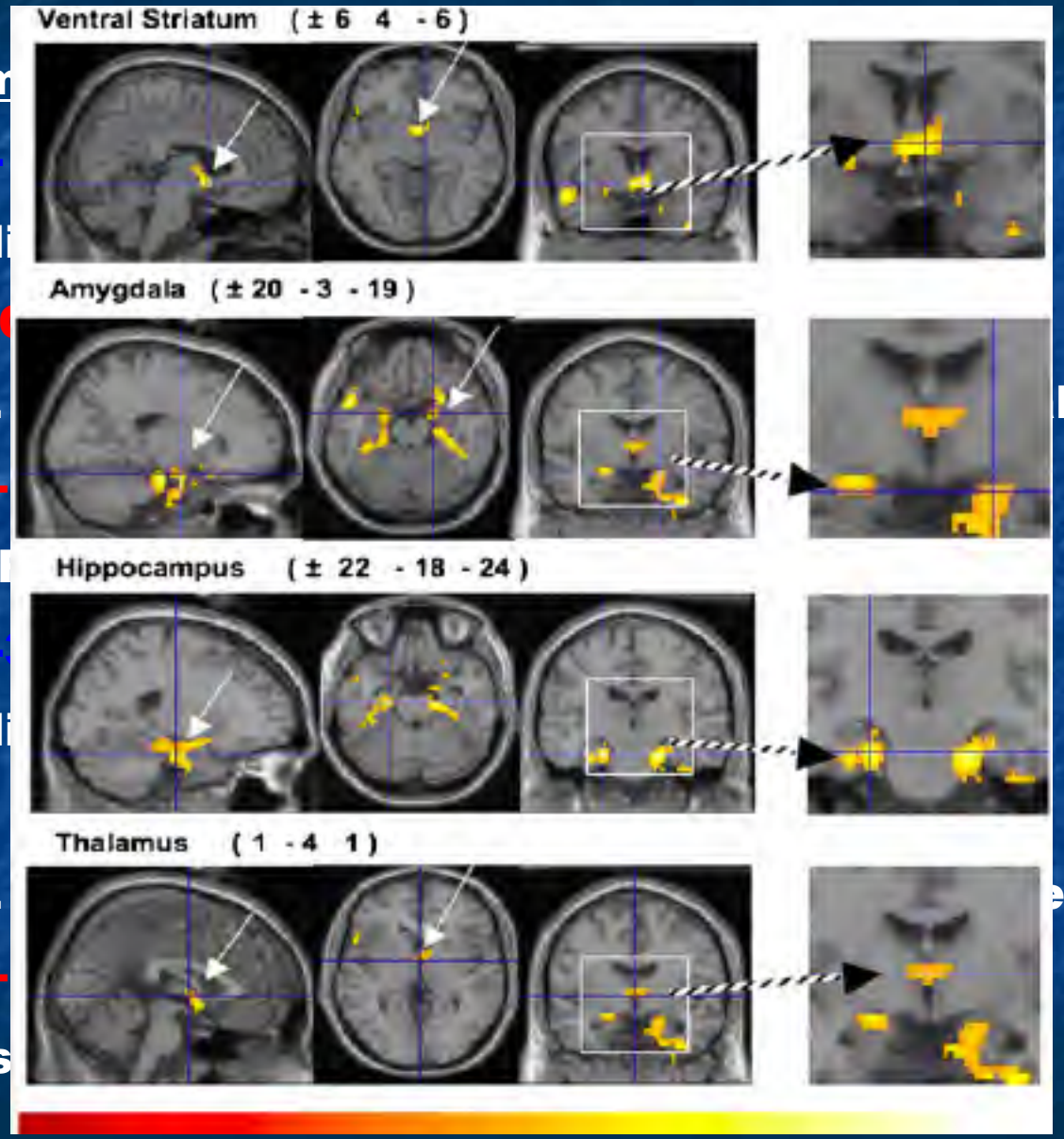
- **Scan 2** **Locali**

Pre -

CASL

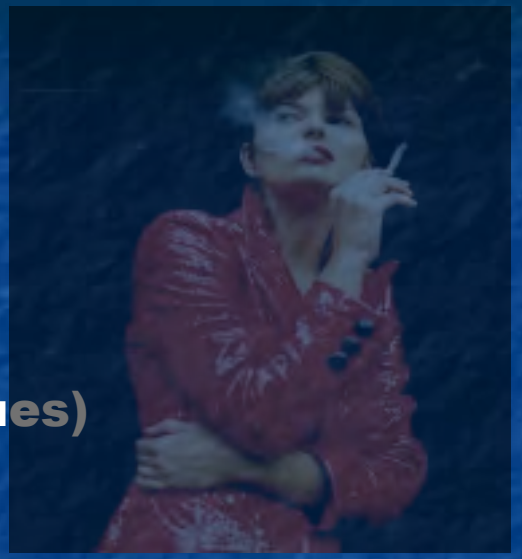
Post -

Diffus



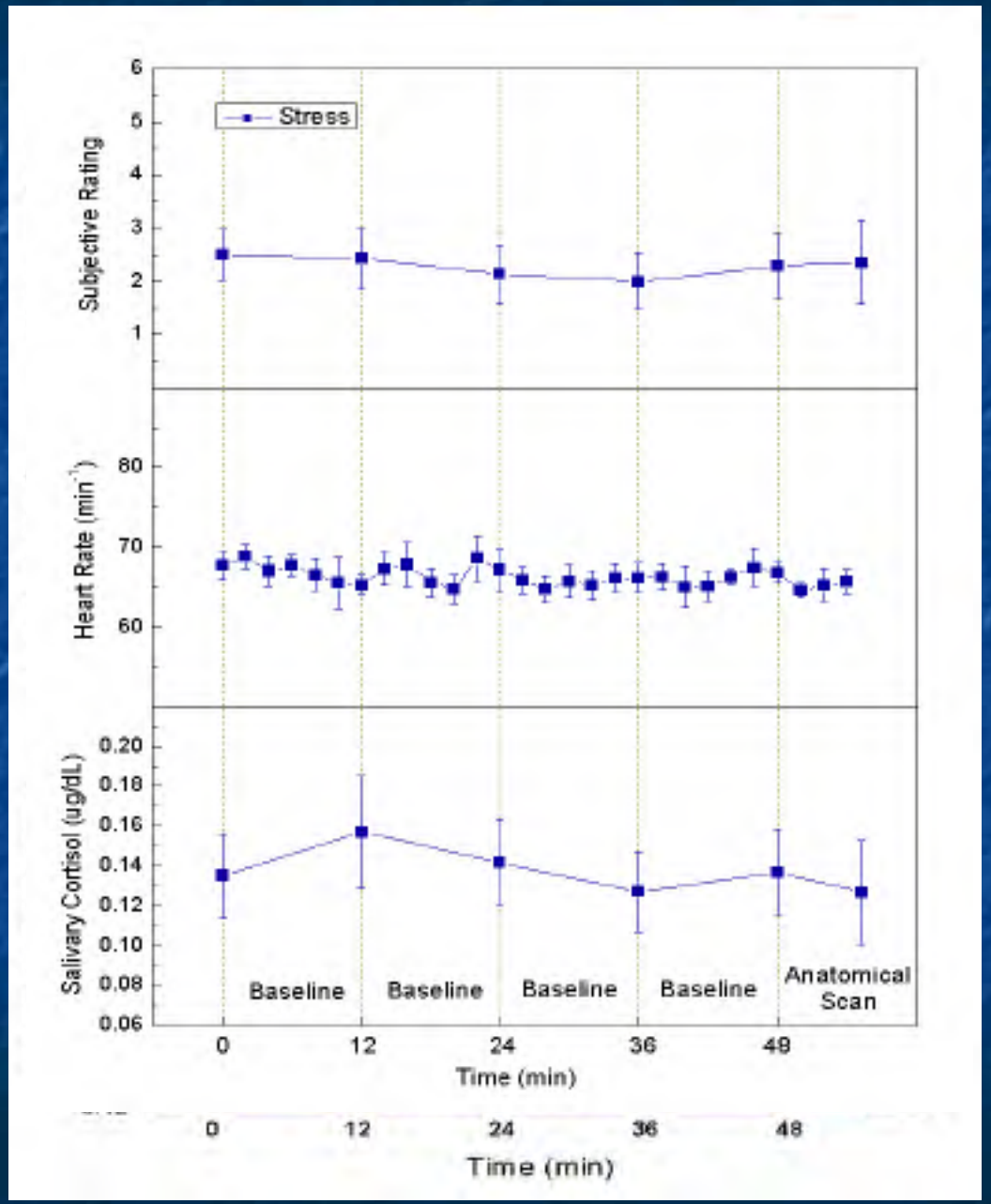
l Cues)

eutral Cue)



Franklin et al. NPP 2007

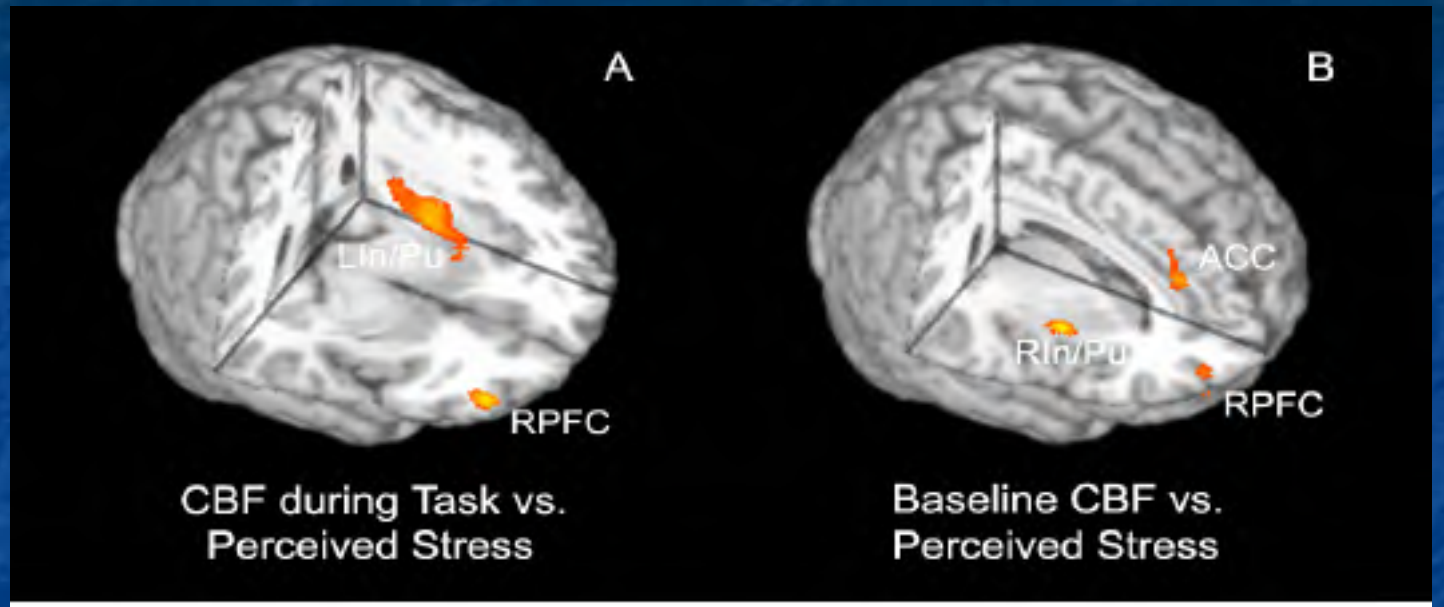
Neural Substrate of Psychological Stress

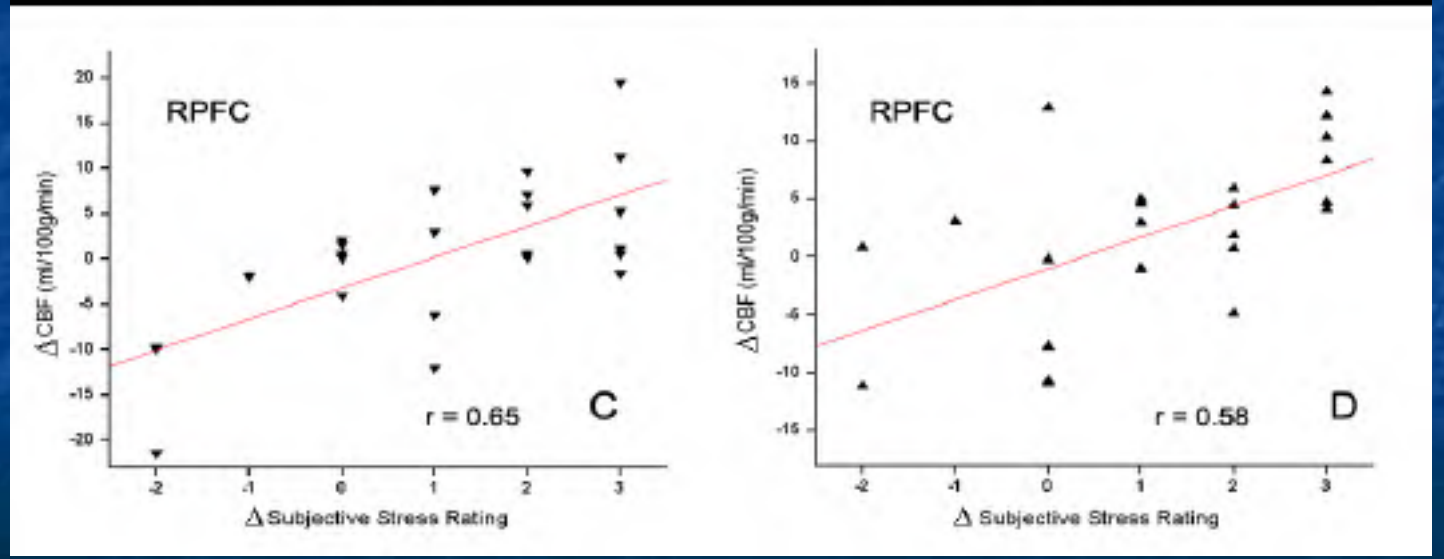


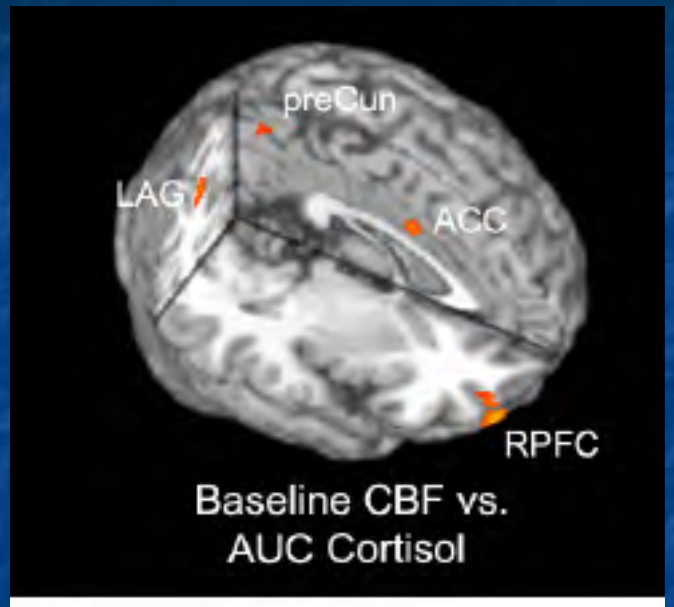
- Pressured subtraction task
- 23 Subjects (25.5 ± 2.5 y, 11F)
- 7 Control subjects (4F)
- 3T CASL, AMC, PLD=1sec
- 4 X 8 min scans
  - Baseline
  - Low stress
  - High stress
  - Baseline
- Self rating of stress and anxiety
- Salivary cortisol
- Heart rate

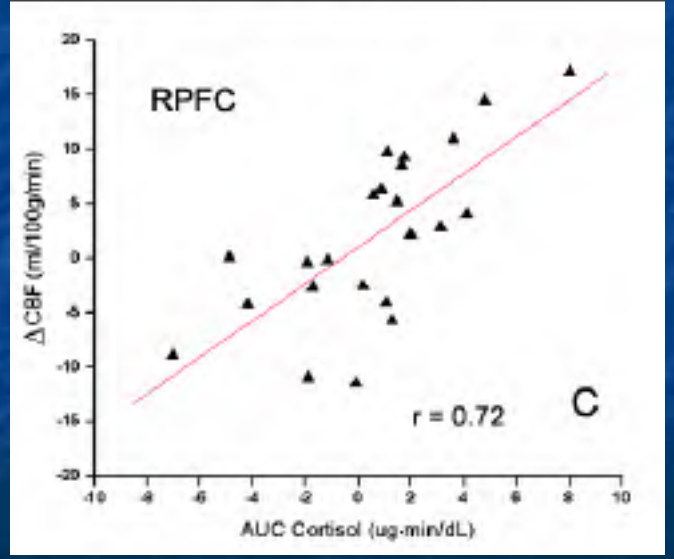
Wang et al. PNAS 2005

Correlation of CBF and Stress: RPFC



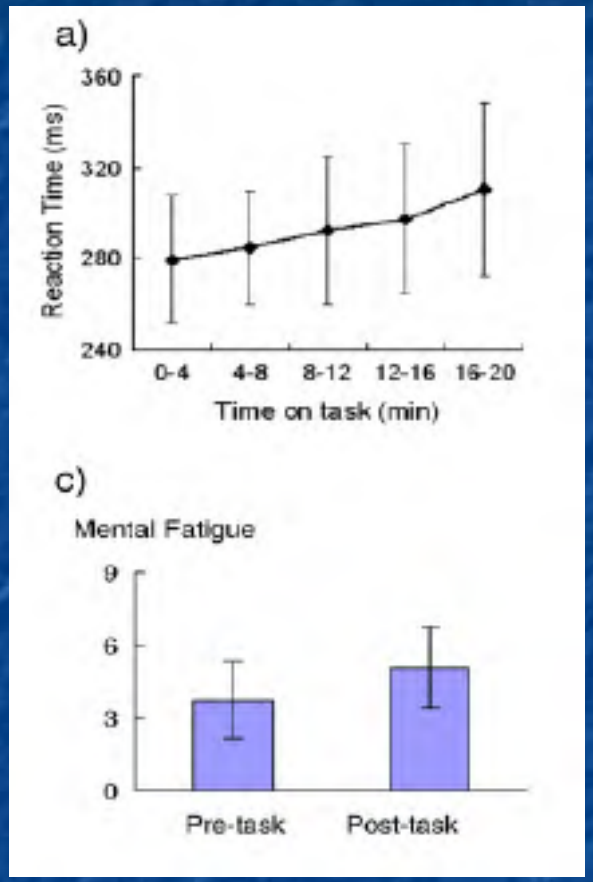




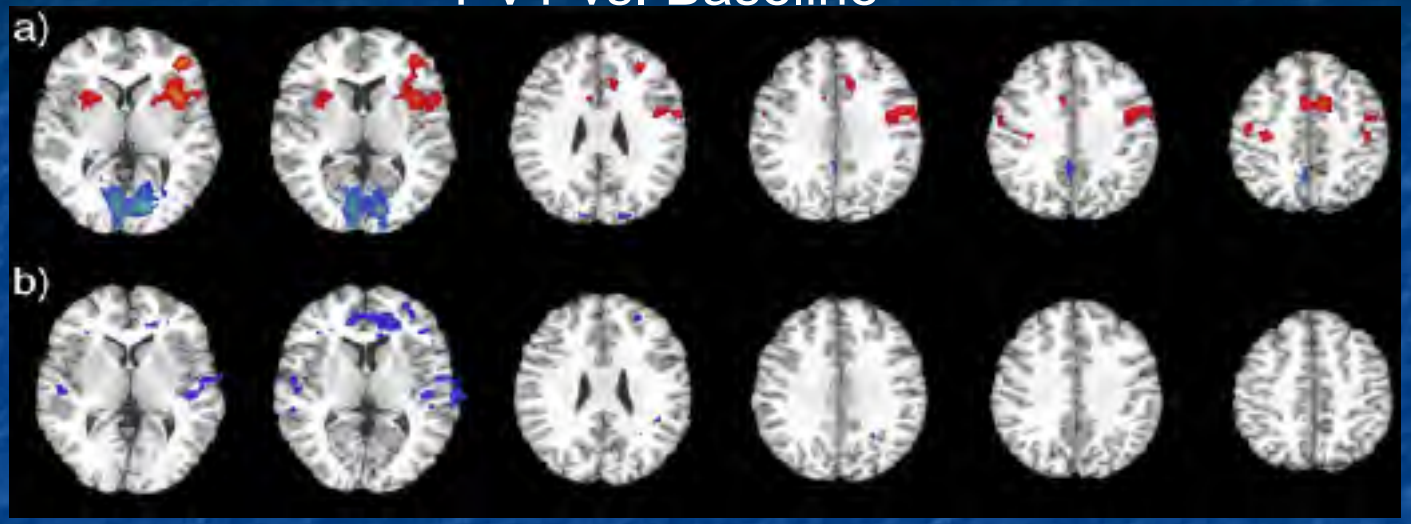


Wang et al. PNAS 2005

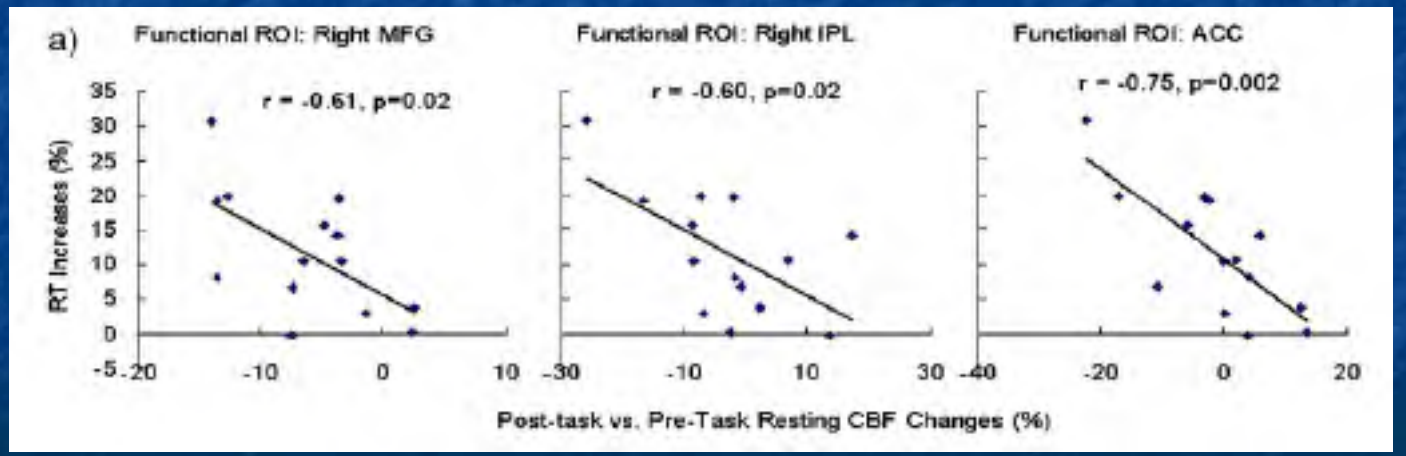
Neural Correlates of Mental Fatigue



PVT vs. Baseline

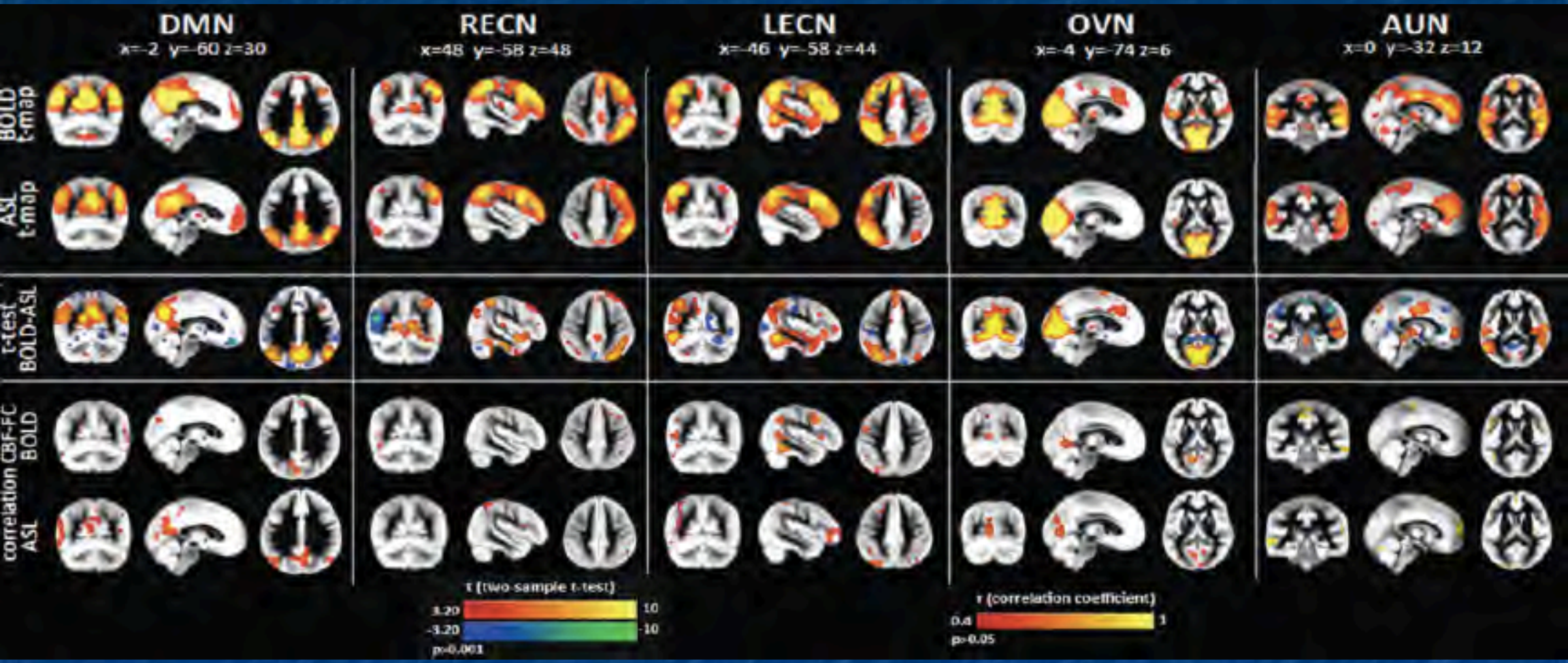


Post-task CBF vs. Pre-task CBF



Lim et al. Neuroimage 2010

Similarity and Reliability of Resting Brain Networks in ASL and BOLD rs-fMRI



Test-retest analyses indicated more reliable networks in BOLD (average ICC: 0.905±0.033 between sessions; 0.885±0.052 between scanners) than ASL (0.545±0.048 / 0.575±0.059). ASL provided highly reproducible network-specific CBF measurements (average ICC: 0.956±0.010 / 0.939±0.026).

Jann et al. *NeuroImage* (2015)

Altered Perfusion and Functional Connectivity in Autism Spectrum Disorders

Brain and Behavior

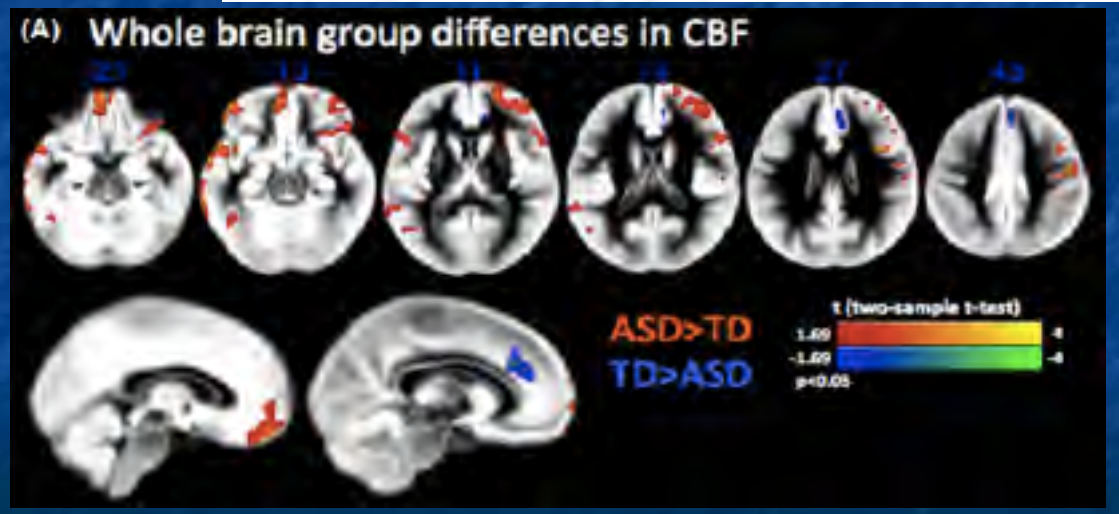
Open Access

Altered resting perfusion and functional connectivity of default mode network in youth with autism spectrum disorder

Kay Jann[1], Leanna M. Hernandez[2], Devora Beck-Pancer[2], Rosemary McCarron[2], Robert X. Smith[1], Mirella Dapretto[2] & Danny J. J. Wang[1]

[1]Laboratory of FMRI Technology (LOFT), Ahmanson-Lovelace Brain Mapping Center, Department of Neurology, University of California, Los Angeles, California

[2]Department of Psychiatry and Biobehavioral Sciences, University of California, Los Angeles, California

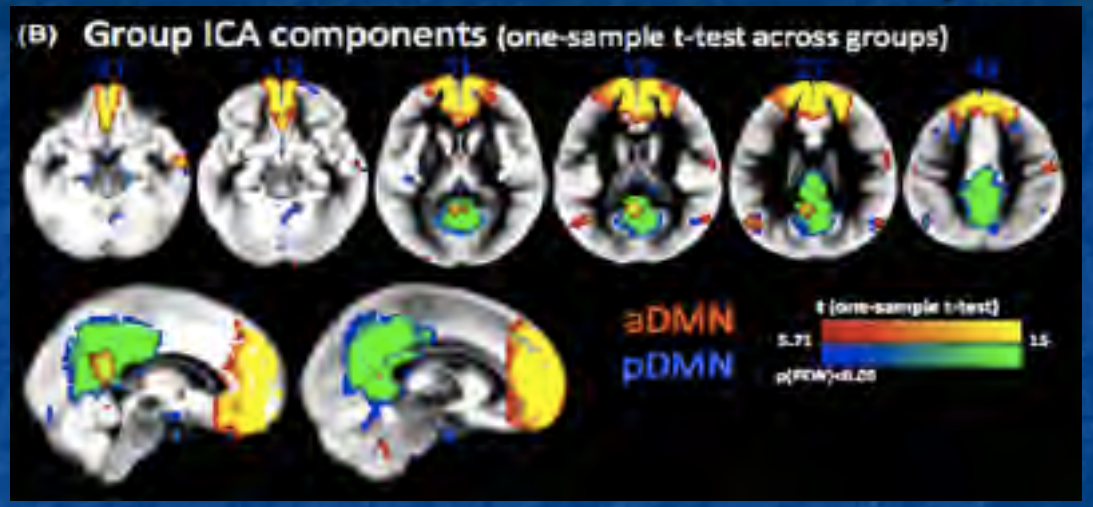


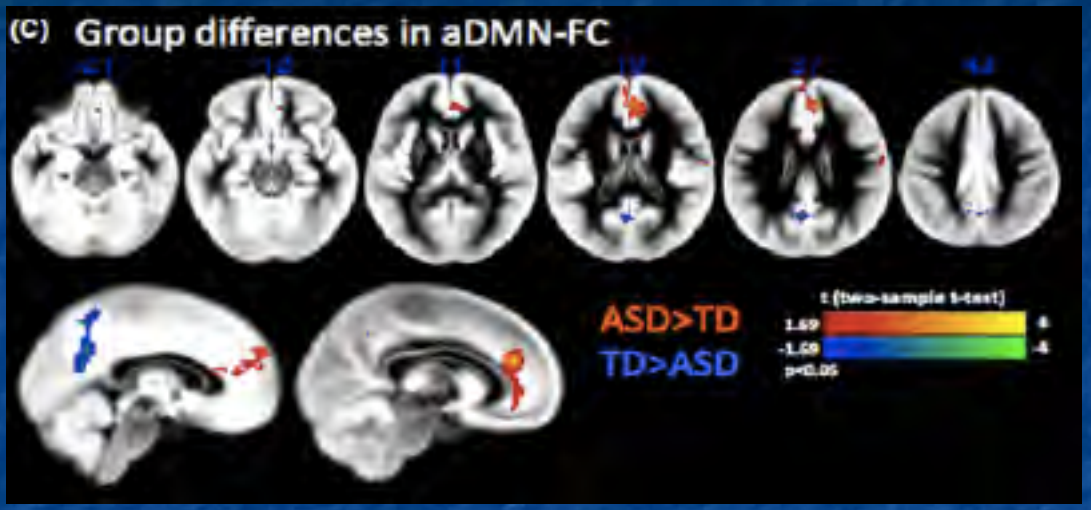
- Frontotemporal hyperperfusion and hypoperfusion in the dorsal anterior cingulate cortex.
- Suggest delayed development of frontotemporal regions

17 youth with ASD (13.8±2.0yrs; 4F) and 22 matched typically developing (12.8±3.6yrs; 3F) children.

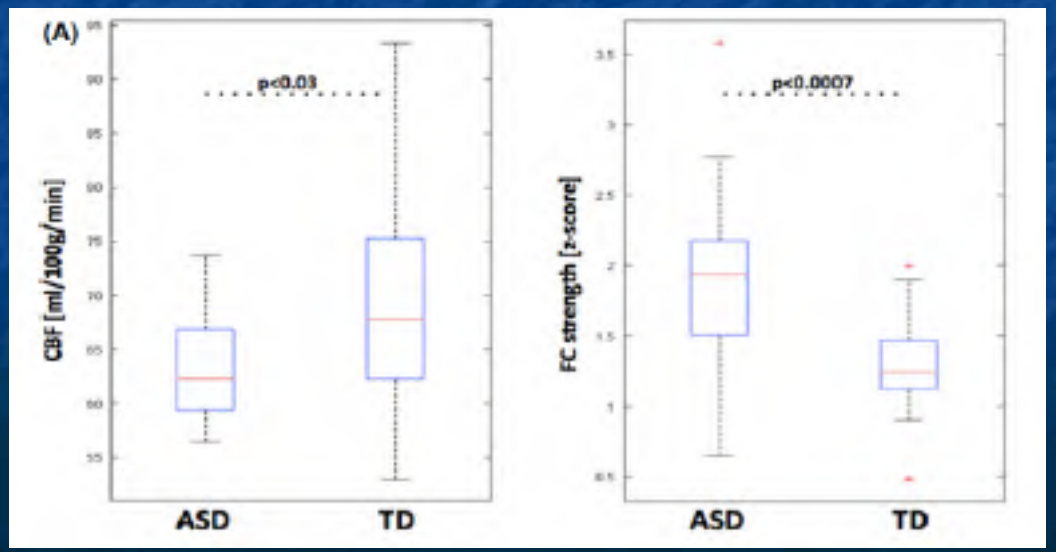
Jann et al. *Brain & Behavior* (2015)

Altered Perfusion and Functional Connectivity in Autism Spectrum Disorders





Increased local FC in the anterior module of the default mode network (DMN) accompanied by decreased CBF in the same area.



ASD exhibits increased functional connectivity (FC) along with reduced cerebral blood flow (CBF) in the dorsal anterior cingulate cortex (dACC)

Jann et al. *Brain & Behavior* (2015)

Advantages of ASL perfusion for phMRI

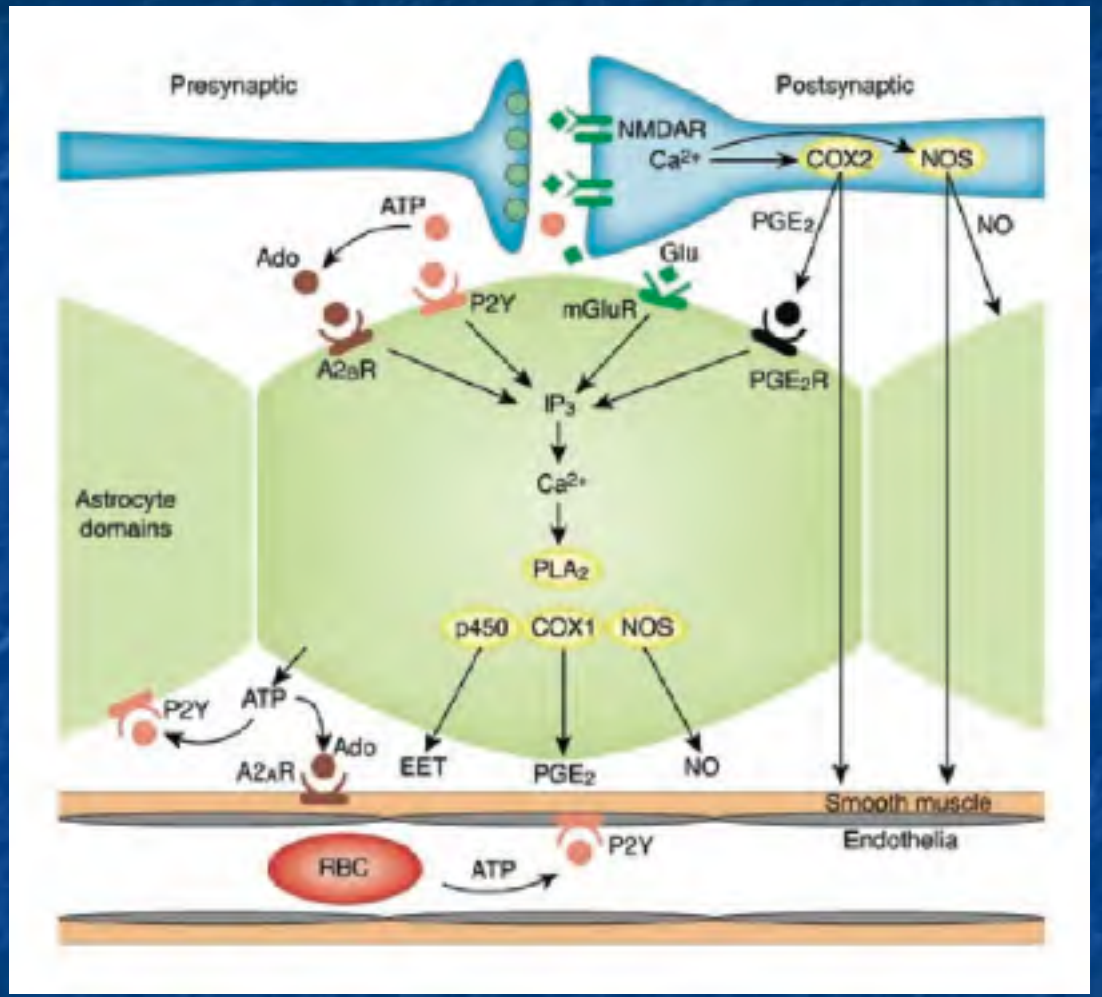


Diagram of Neurovascular Coupling
Iadecola & Nedergaard, Nat Neurosci 2007

- CBF is a quantitative physiological parameter
- Coupled to neuronal activity through neurovascular coupling
- BOLD reflects complex interplay of CBF, CBV and CMRO2
- ASL CBF can quantify brain activity both during resting state baseline **(trait)** and task activation **(state)**
- BOLD lacks absolute quantification of the "baseline" state.

Cortical responses to amphetamine exposure studied by pCASL MRI

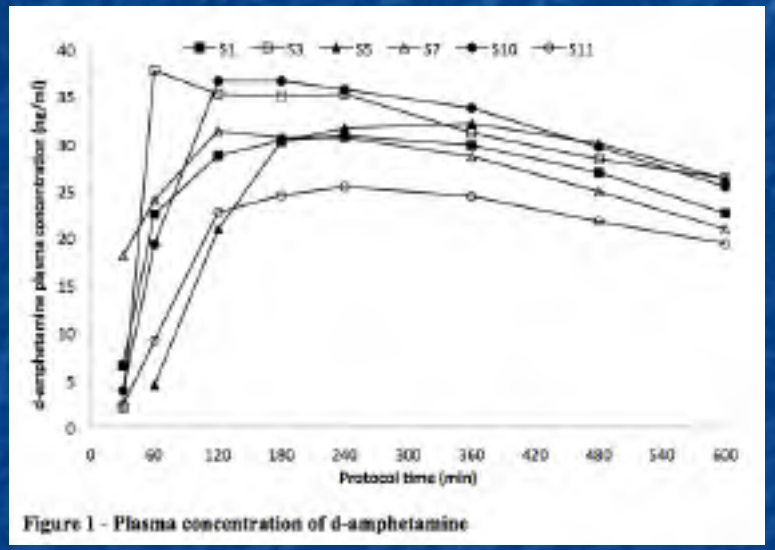
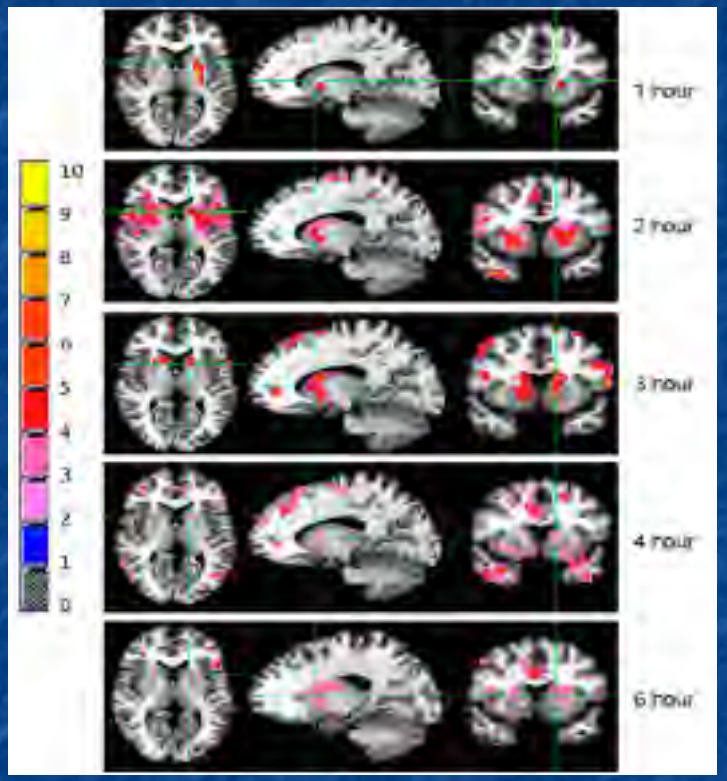
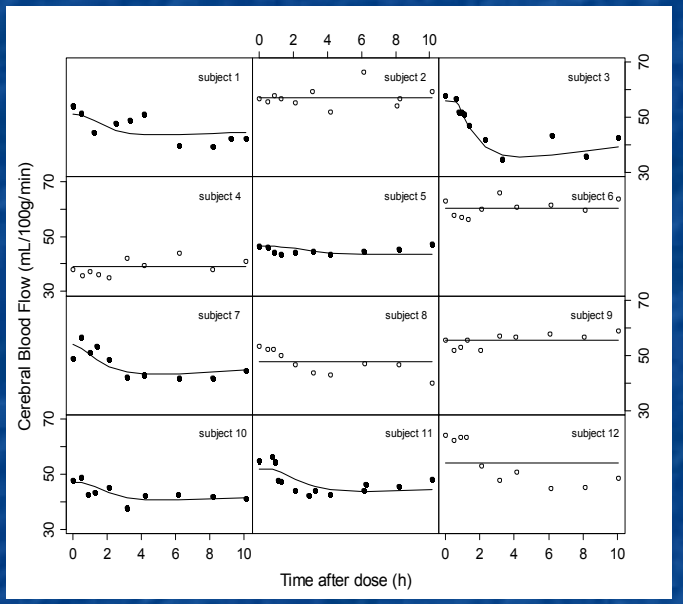


Figure 1 - Plasma concentration of d-amphetamine

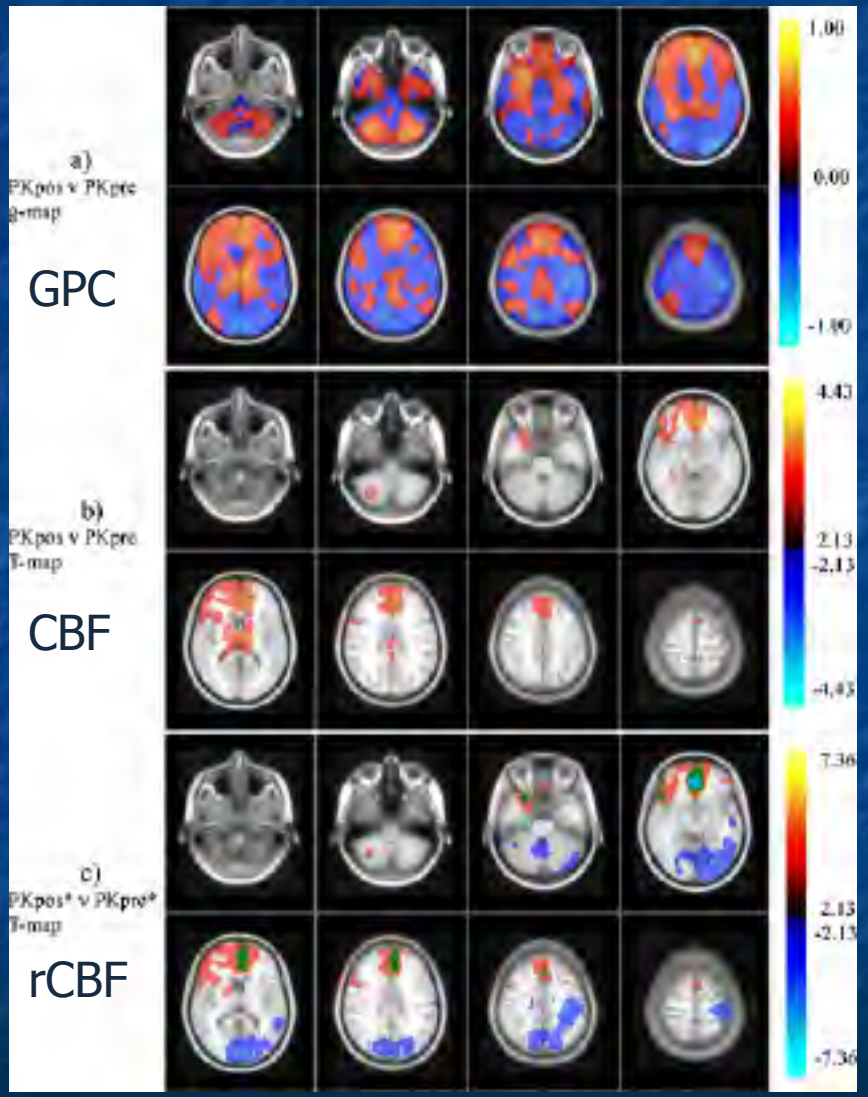




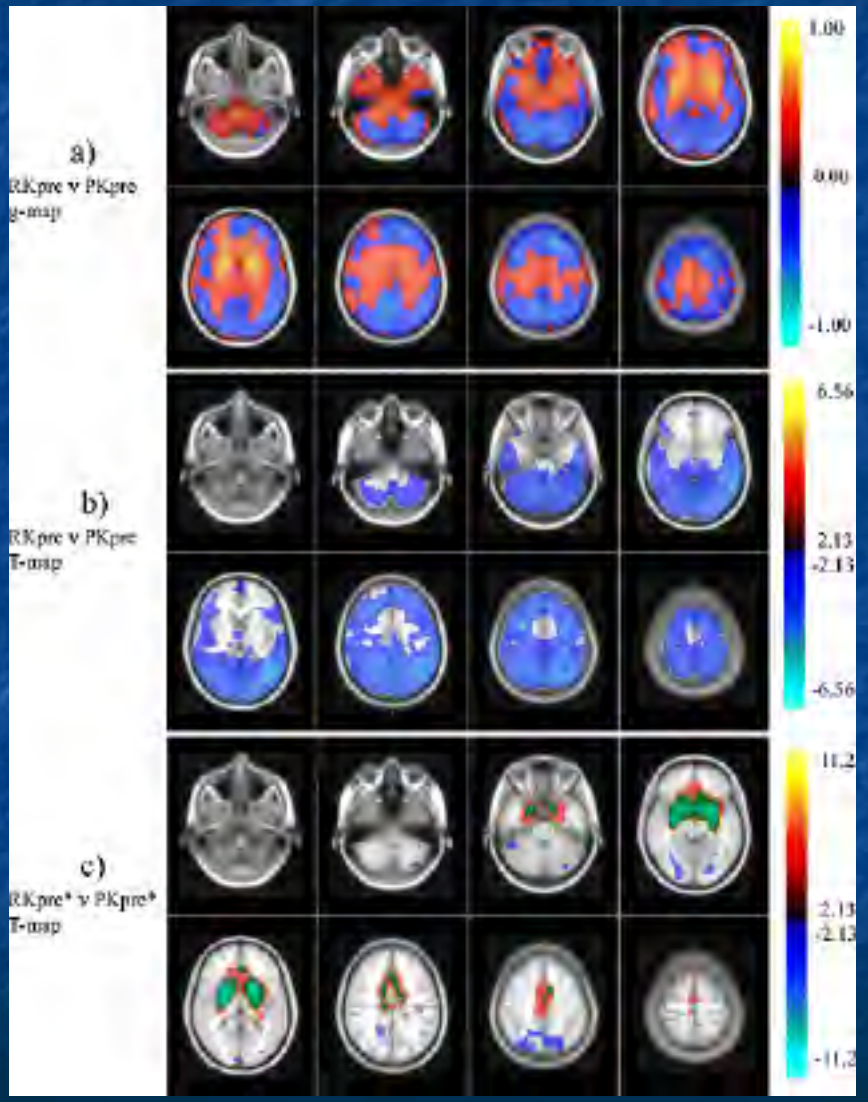
- 12 healthy subjects double blinded design
- 6 20mg d-amphetamine; 6 placebo
- ASL and blood samples were collected 10 time points during 10hr after dose

Nortin et al, Neuroimage, 2012

Modulatory effects of ketamine, risperidone and lamotrigine on resting brain perfusion



Ketamine

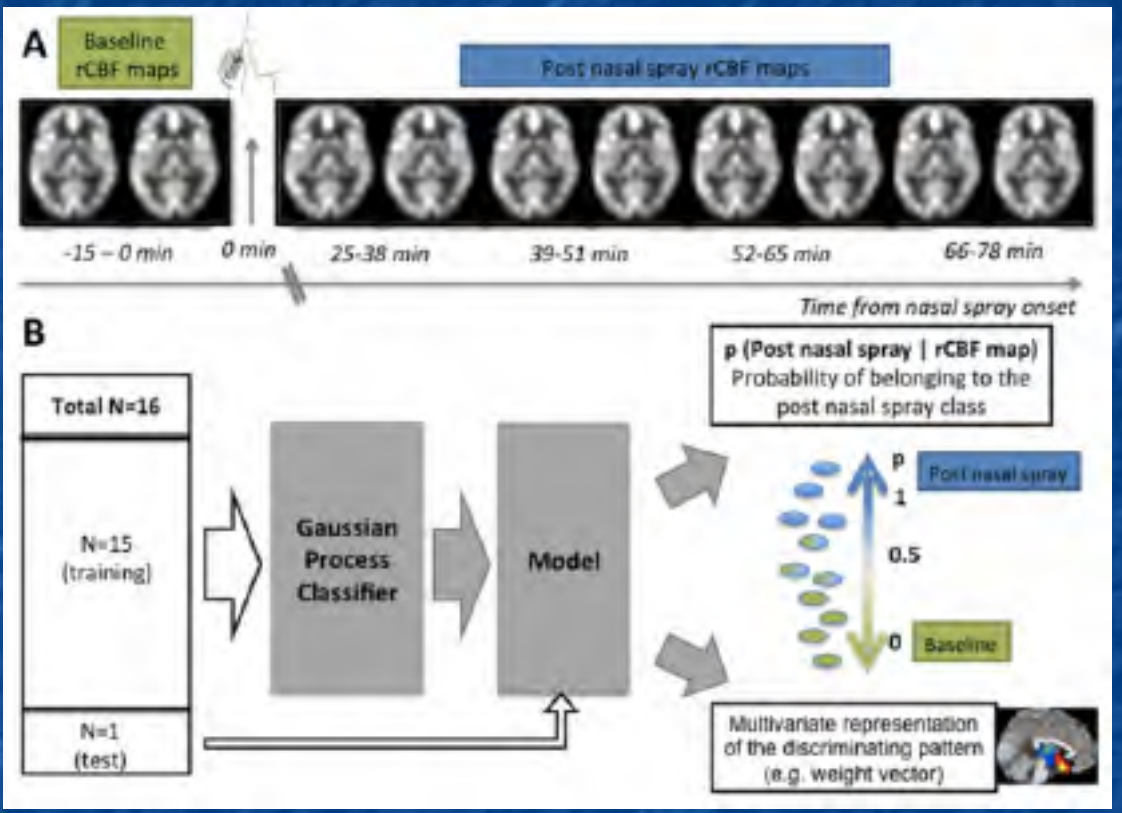


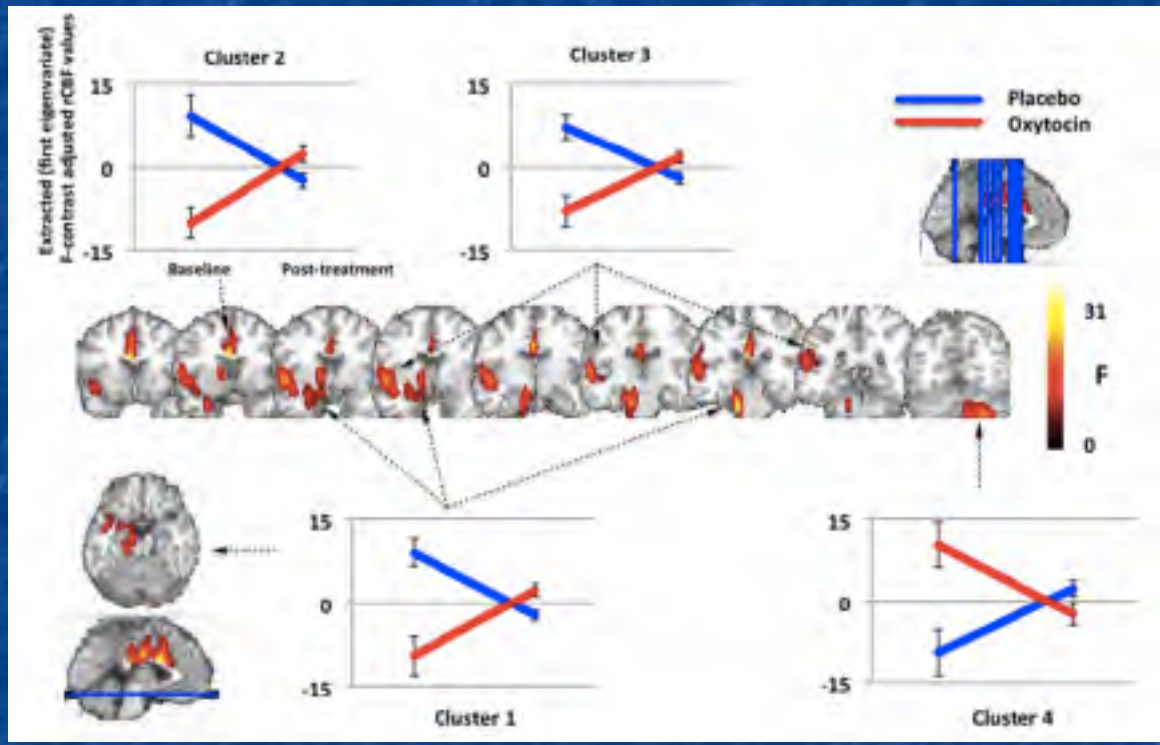
Risperidone

- 16 healthy subjects double blinded design
- Ketamine infusion paired with Risperidone, Lamotrigine, or placebo

Shcherbinin et al, Psychopharmology, 2015

Cerebral Blood Flow Changes Following Intranasal Oxytocin

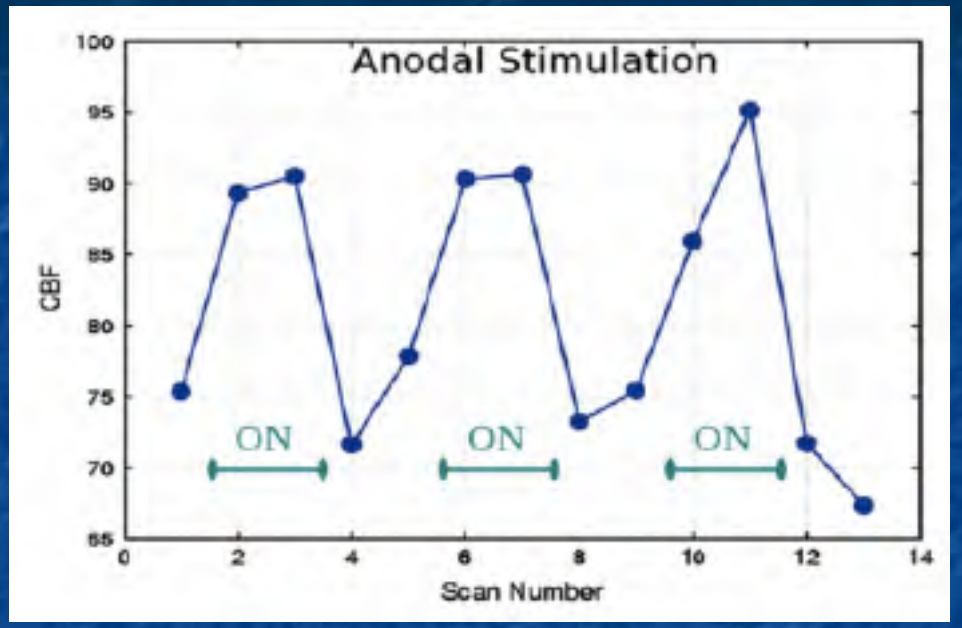


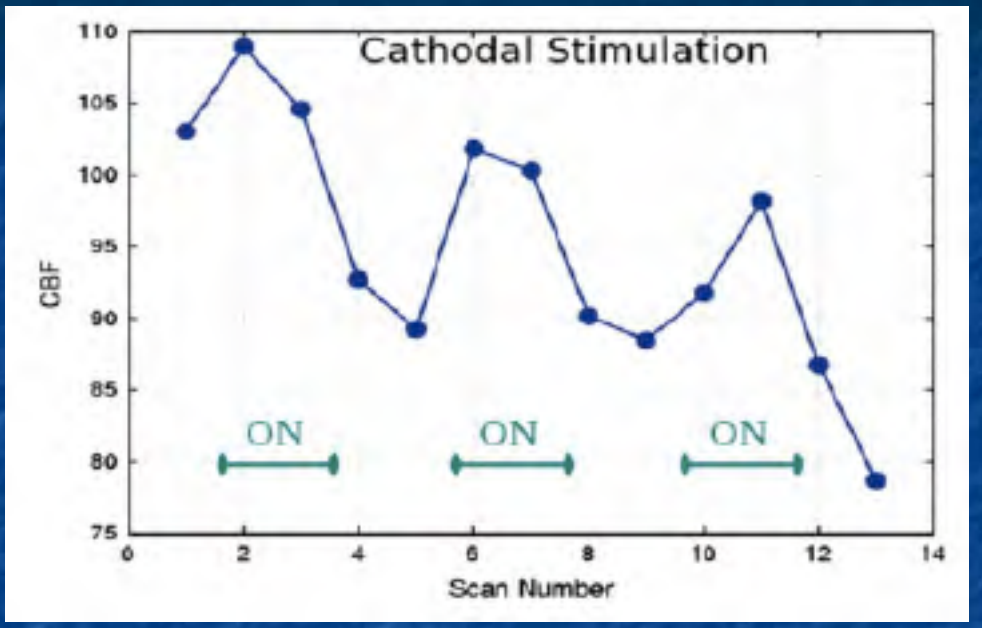


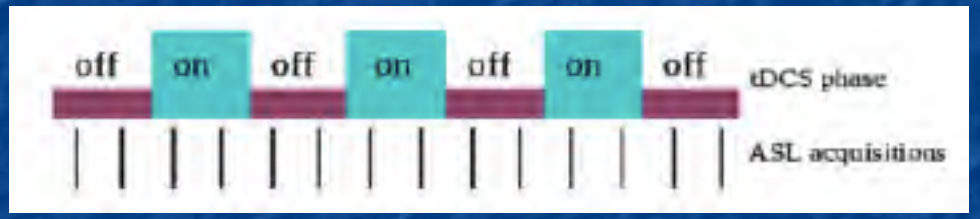
- 32 healthy men double blinded design
- 16 intranasal oxytocin (IN-OT); 16 placebo

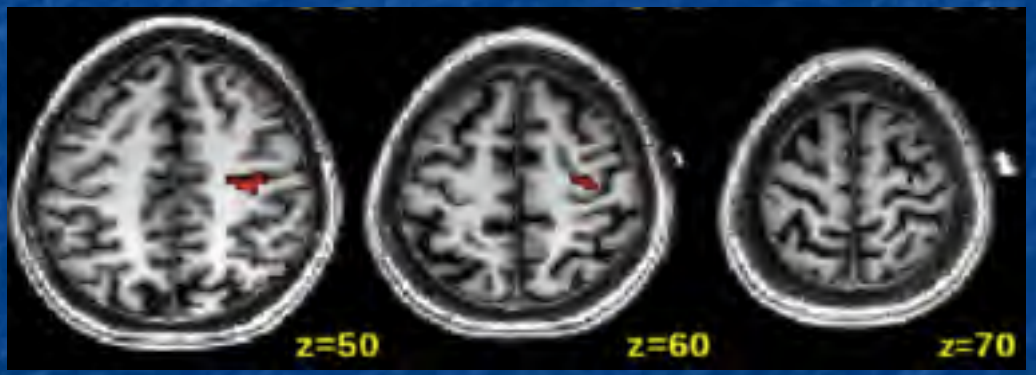
Paloyelis et al, Biol Psych, 2014

CBF changes of tDCS





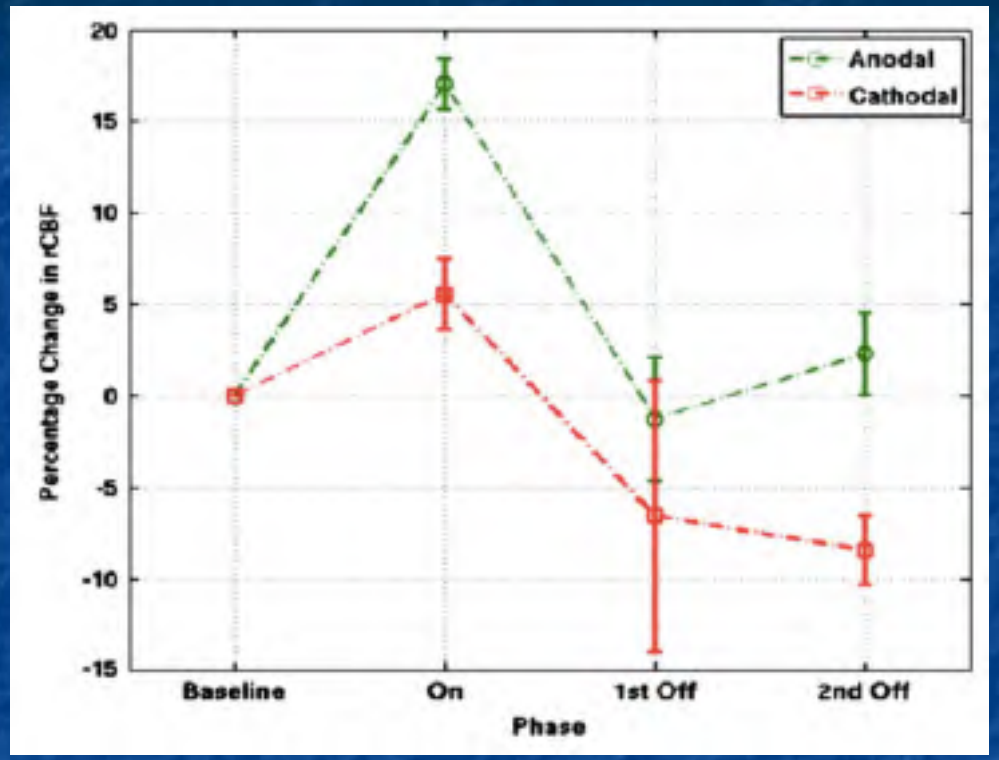


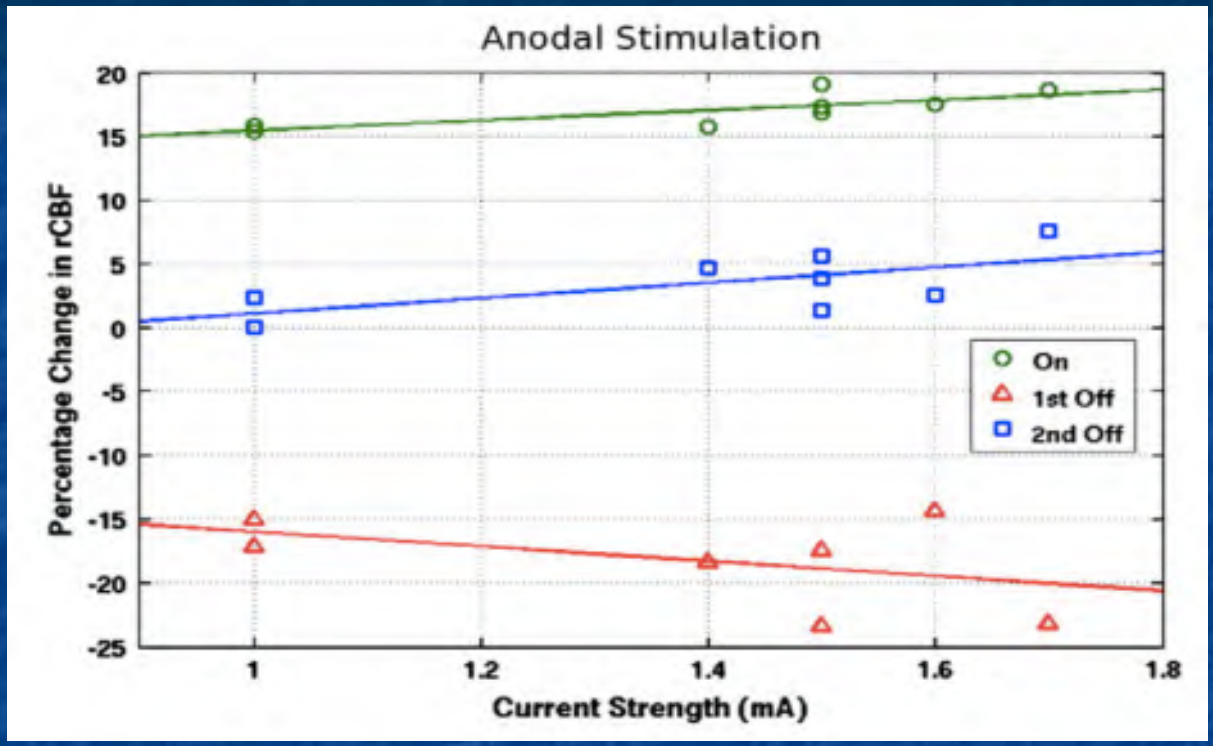


Anodal tDCS increased 17.1% in rCBF during stimulation and increase during off, while cathodal tDCS increased 5.6% in rCBF during stimulation but decrease during post-stimulus period.

Zheng et al Neuroimage 2012

CBF changes of tDCS

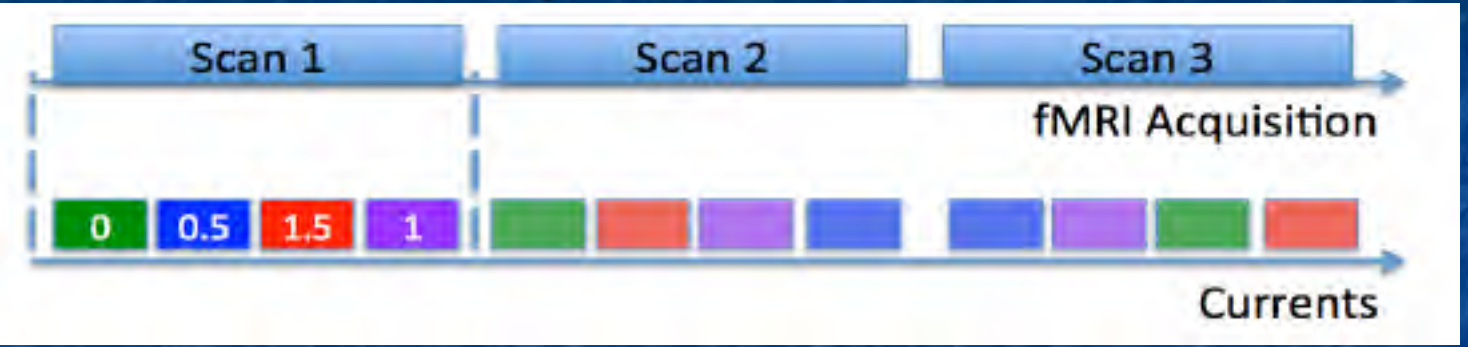


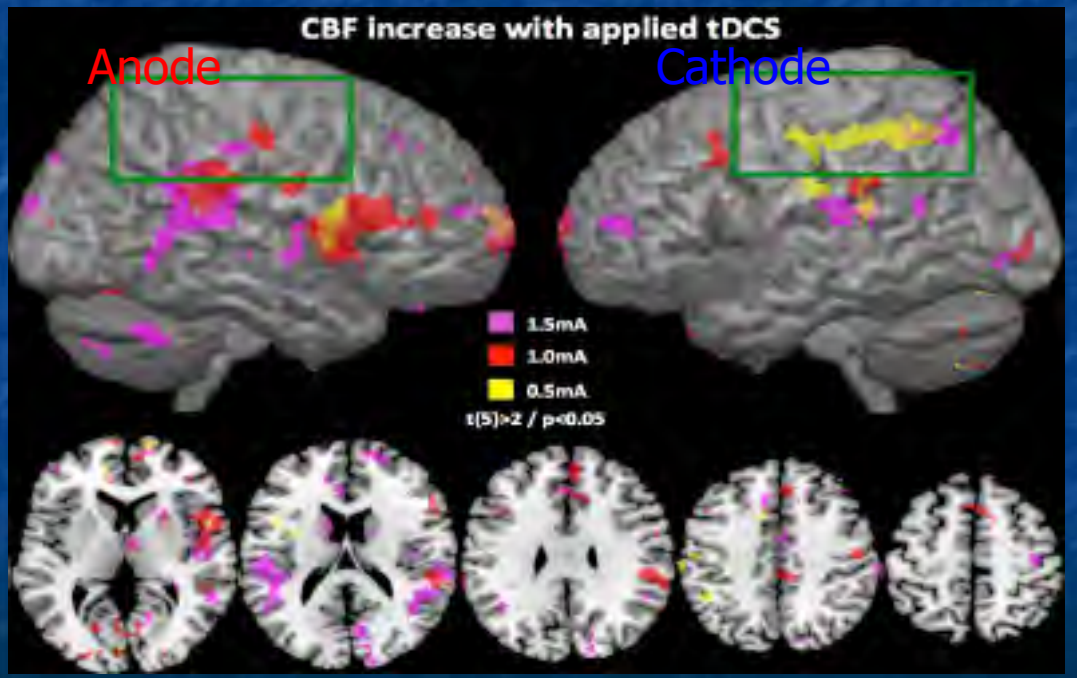


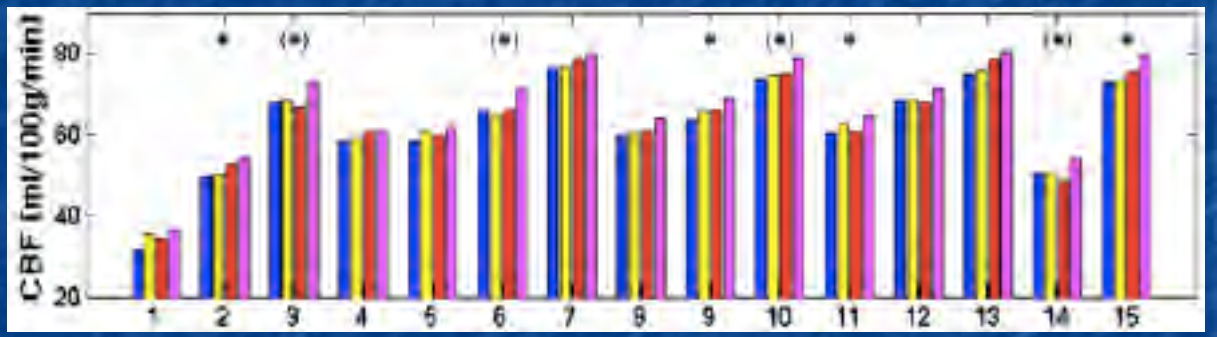
Anodal tDCS induced CBF changes are correlated with current intensity while cathodal tDCS induced CBF are not correlated with current

Zheng et al Neuroimage 2012

Neurophysiological Effect of tDCS Assessed by ASL Perfusion MRI



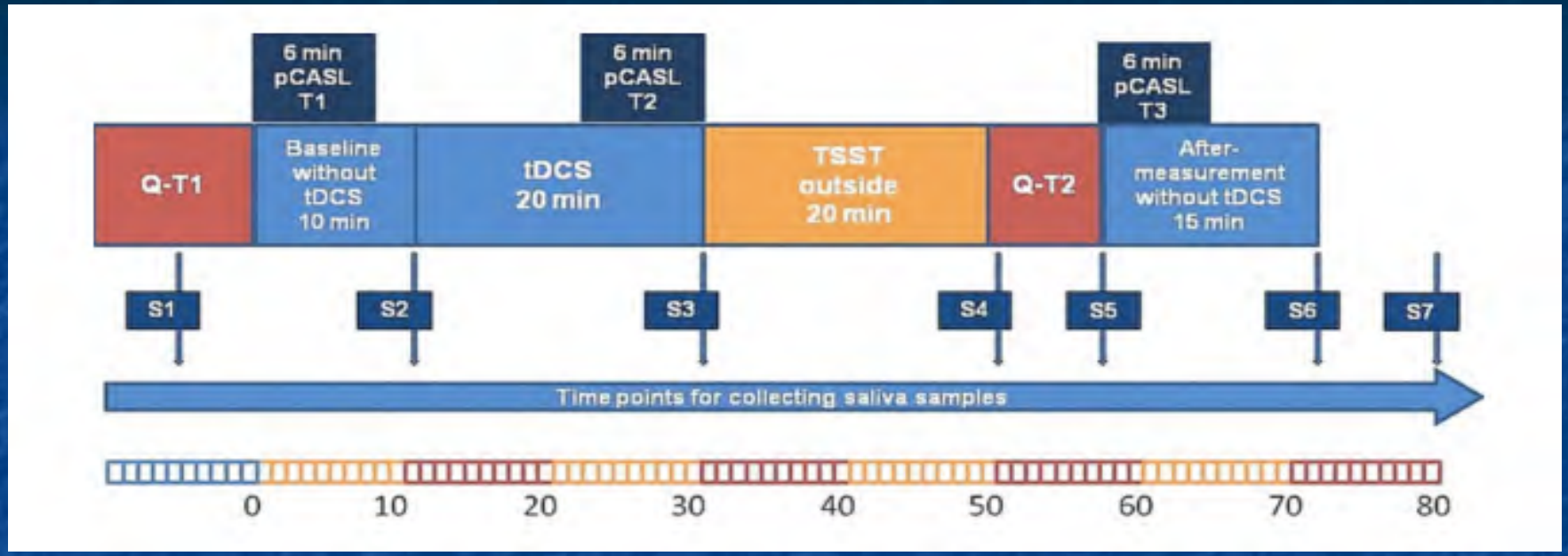


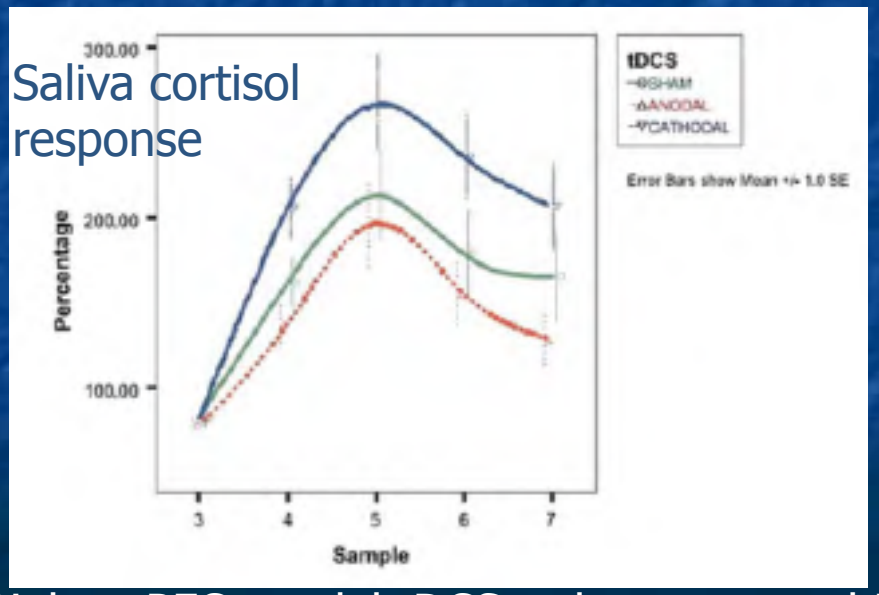


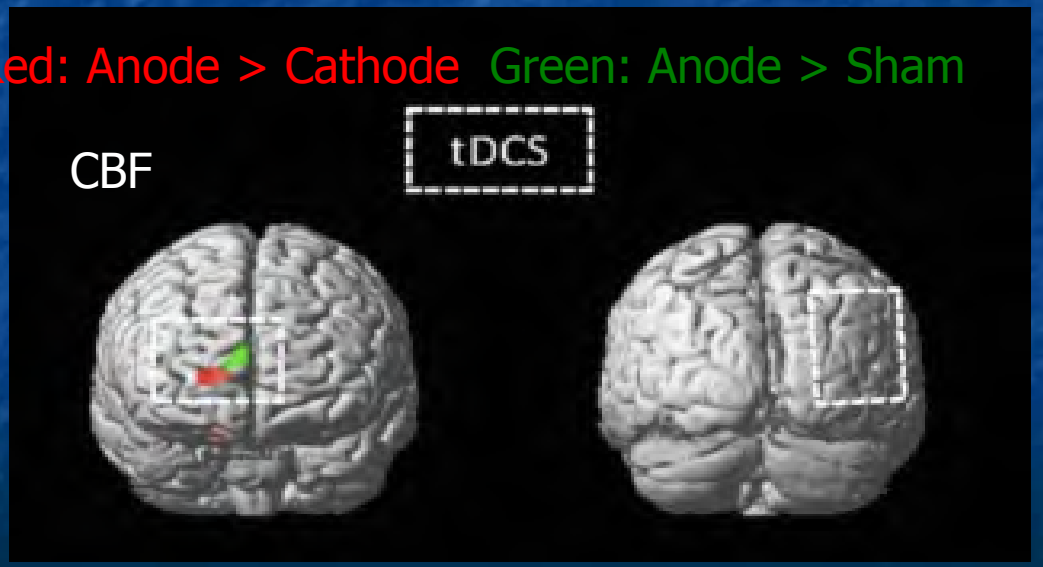
Dose response curves of increased CBF induced by tDCS
* Indicates significant ANOVA
(*) indicates trend

Jog et al ISMRM 2016

tDCS Effects on Stress



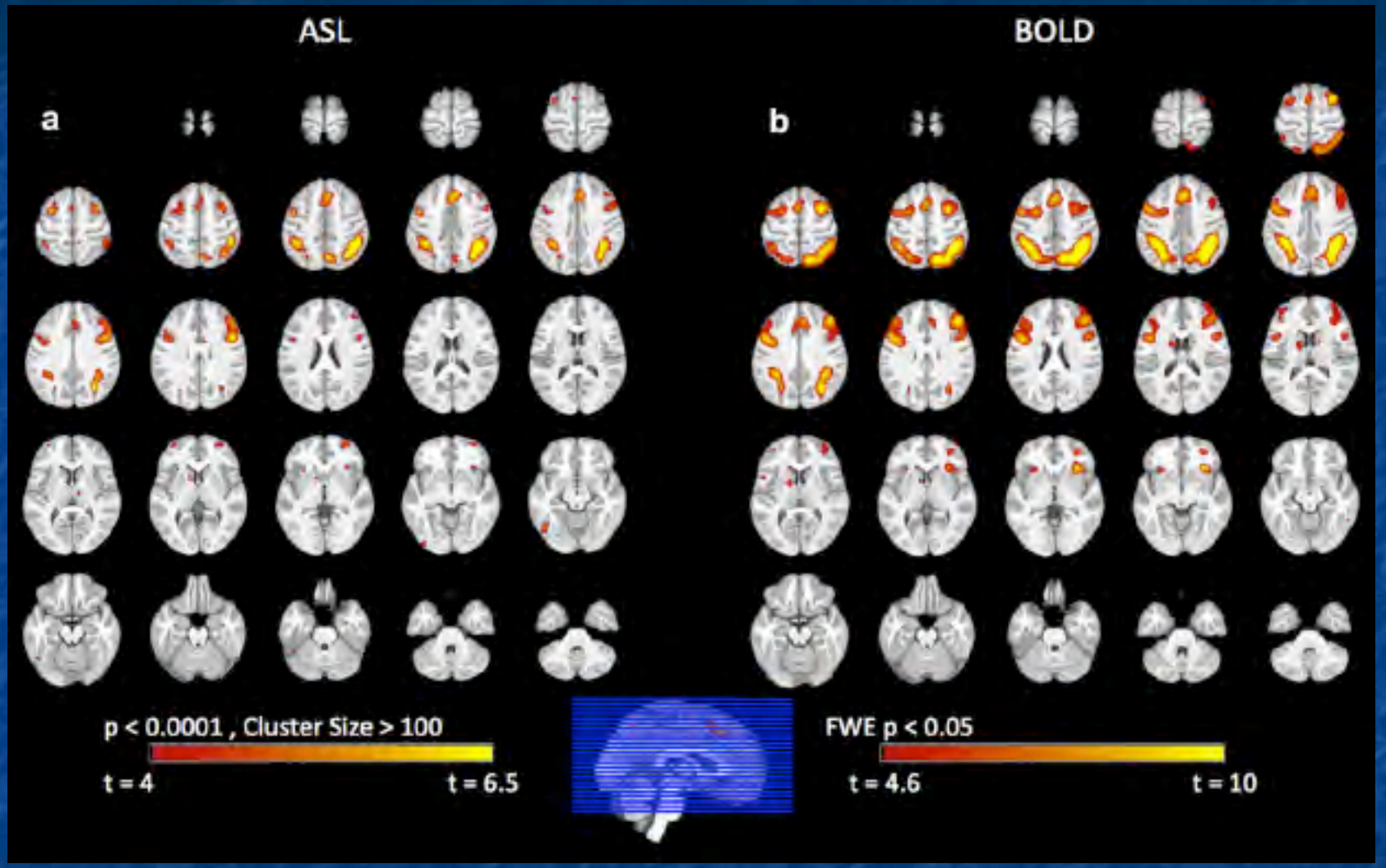




Right mPFC anodal tDCS reduce stress while cathodal increase stress responses

Antel et al HBM 2014

Concurrent ASL/BOLD fMRI



Dual-echo pCASL fMRI of 2-back working memory in 91 children 7-17yrs age

Yan, Jog et al NeuroImage (Under revision)

Take Home Messages

- ASL white paper recommends pCASL with background suppressed 3D acquisitions
- ASL perfusion fMRI is an important quantitative tool complementing BOLD fMRI
- ASL perfusion fMRI has unique value in characterizing state/trait effects and pharmacological and neuromodulation
- Further technical developments allow increased sensitivity and spatiotemporal resolution