BENEFRI Workshop 2019

Methods in Experimental Neurosciences: From Animal Models to Humans

UNIVERSITÄT BERN

fMRI in Neuroscience
Non-Bold fMRI

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roadmap

9:15-10:00 **Basic concepts of functional Neuroimaging**

fMRI Signal, task-dependent fMRI, resting state fMRI, Functional Network Analysis, processing pipeline, statistical testing, Random Effects, General Linear Model and MRI physics.

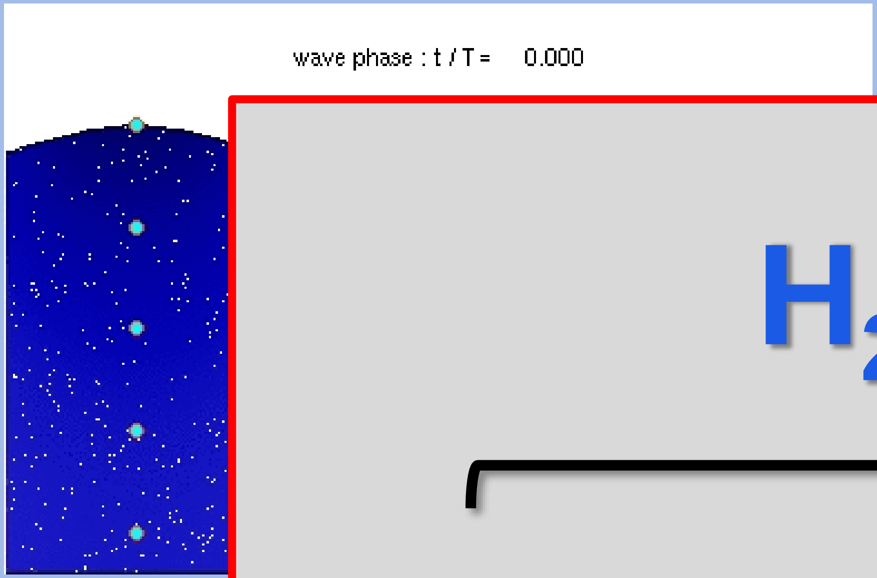
10:15-11:00 **Basic concepts of structural Neuroimaging**

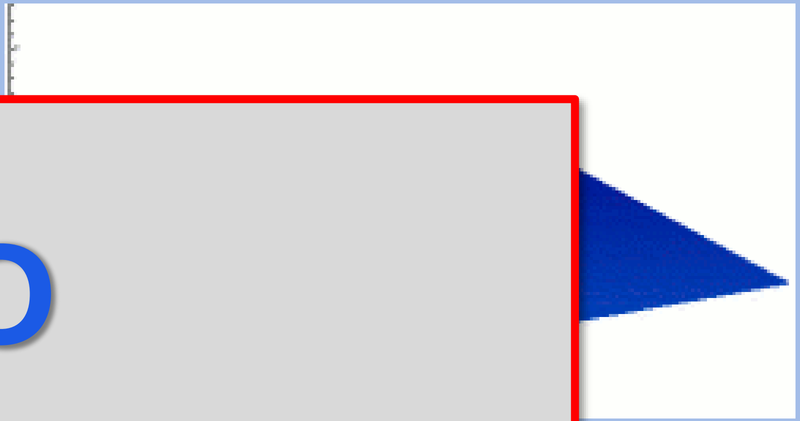
Voxel Based Morphometry, Cortical Thickness, Cortex based inter-subject alignment, Diffusion Tensor Imaging, Tract-Based Spatial Statics.

11:15-12:00 **Advanced Neuroimaging Methods in Neurosciences**

Non-BOLD fMRI, Cerebral Blood flow (CBF), calibrated fMRI, Multimodal Imaging.

Introduction





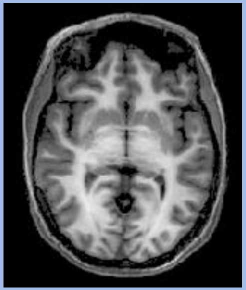
H_2O

MRI PET

http://de.wikipedia.org/wiki/Wasserwelle

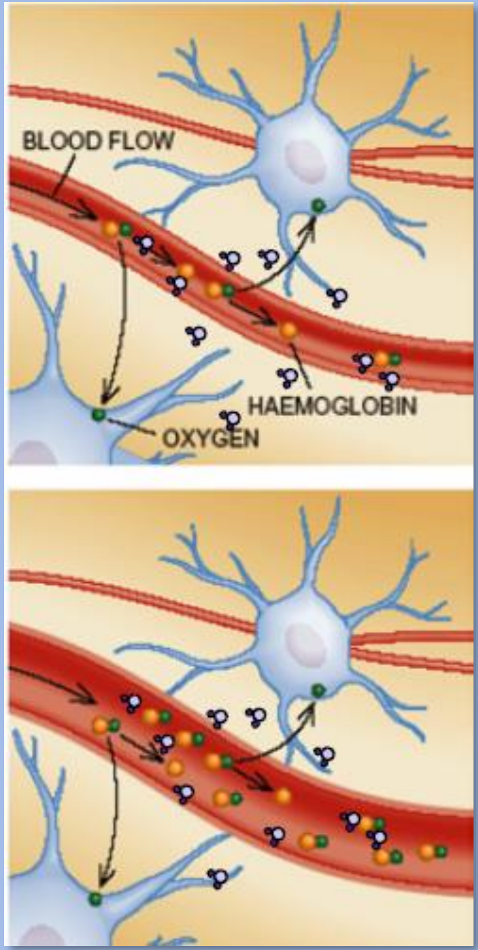
Meachnisms in fMRI

Rest

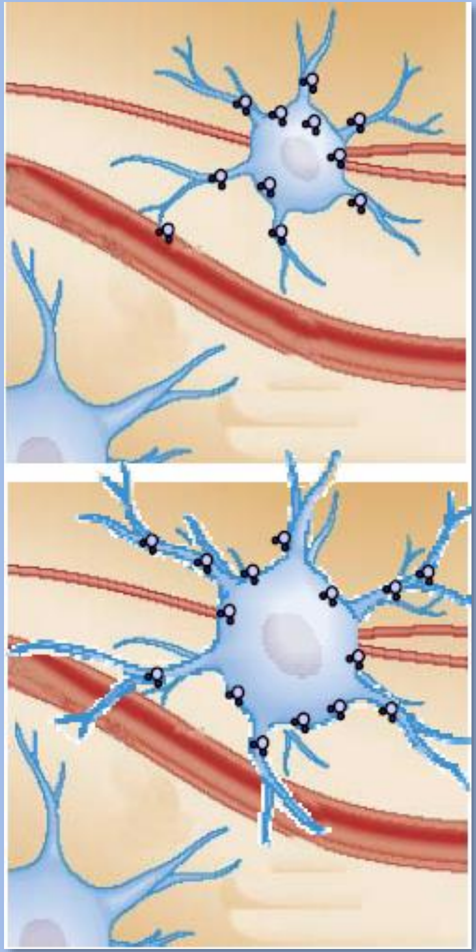


Task

BOLD fMRI

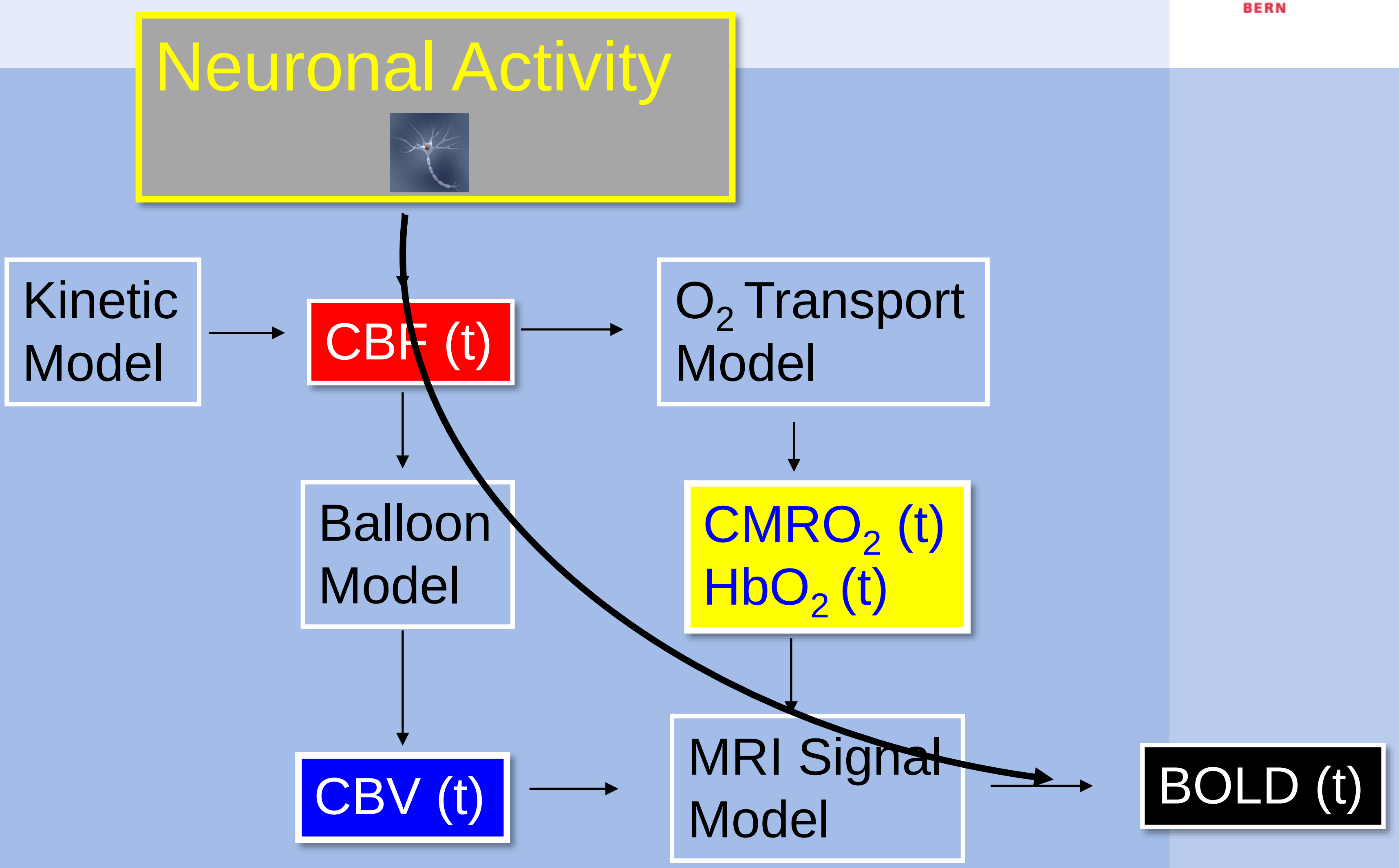


Diffusion fMRI



Le Bihan D. 2007 Phys Med Biol. 52(7):R57-90.

But, what is BOLD realy?



Neuronal Activity

Kinetic Model

CBF (t)

O_2 Transport Model

Balloon Model

$CMRO_2$ (t)

HbO_2 (t)

CBV (t)

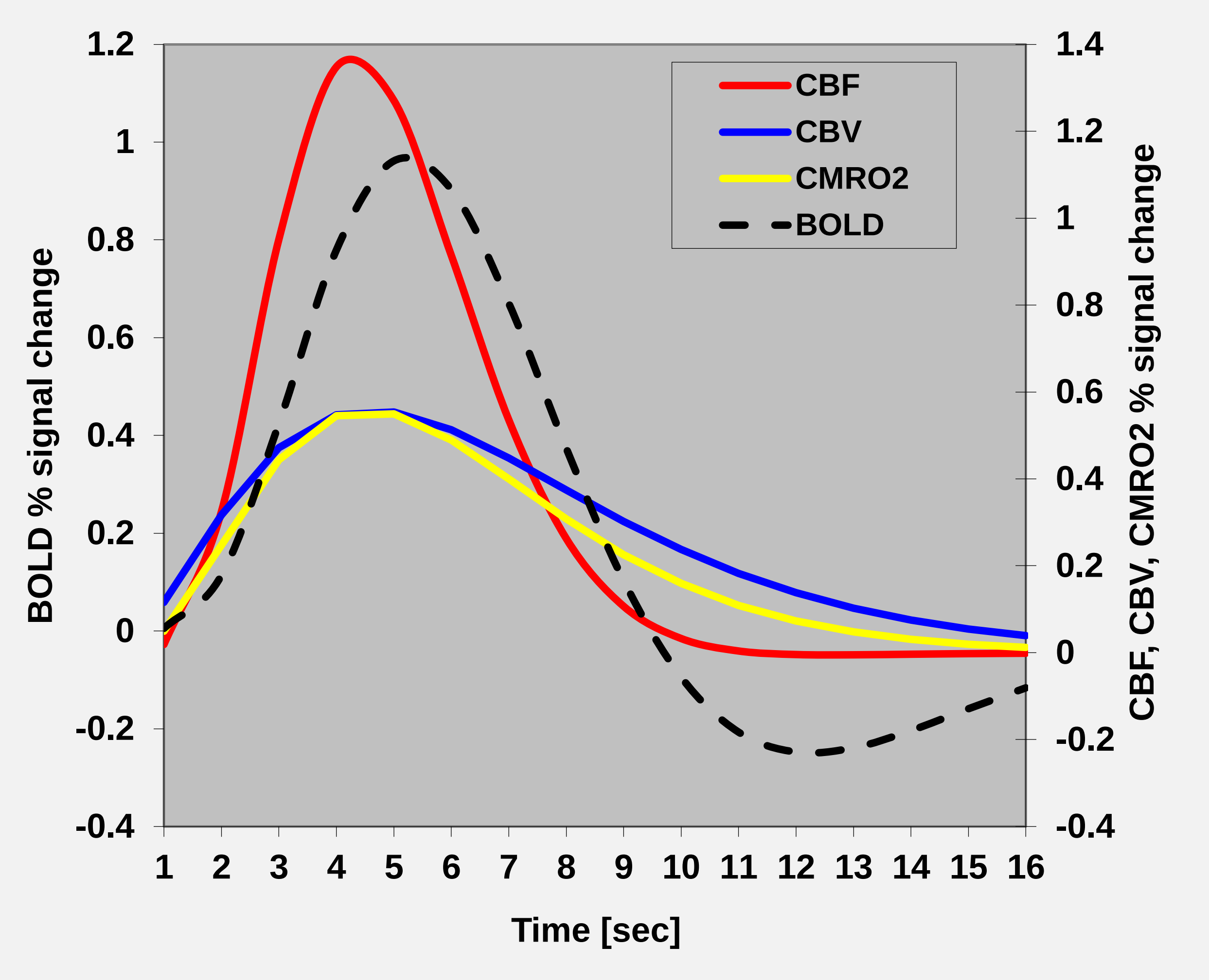
MRI Signal Model

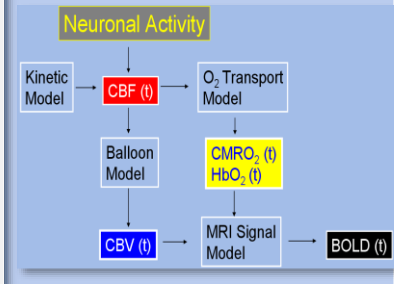
BOLD (t)

Buxton, R.B. et al 1998 *Magn Reson. Med.* 40:383-396.

Obata, T. et al 2004 *Neuroimage.* 21:144-153.

fMRI Signal overview

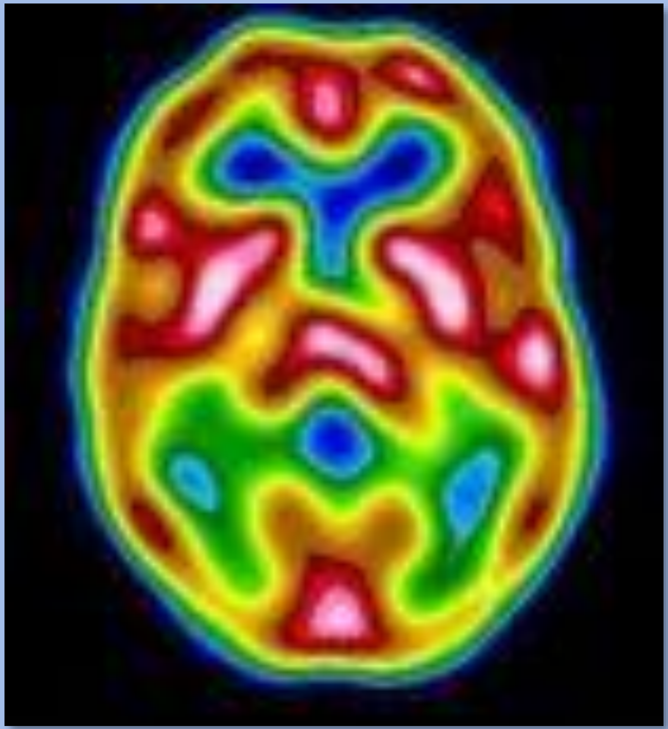




Buxton, R.B. et al 1998 *Magn Reson. Med.* 40:383-396.

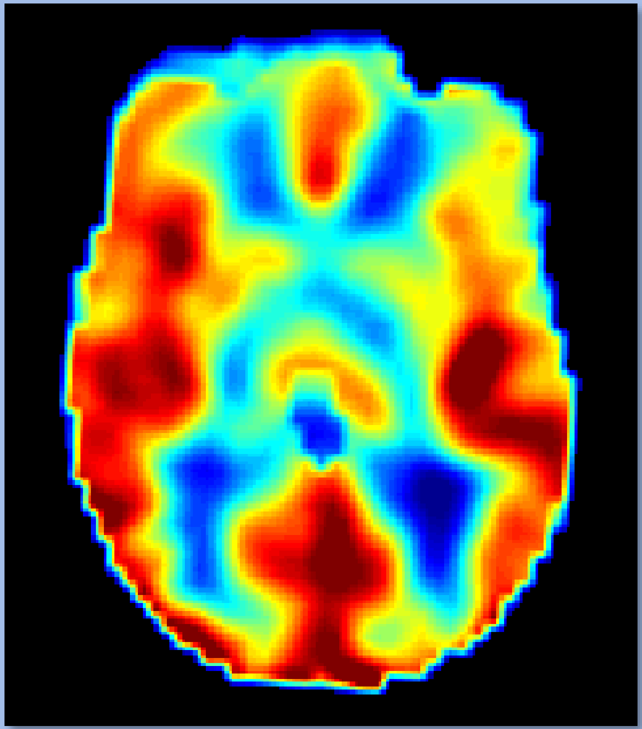
Obata, T. et al 2004 *Neuroimage.* 21:144-153.

Cerebral blood flow (CBF) with Arterial Spin Labeling (ASL)



Ye, F.Q et al. 2000. *Magn Reson. Med.* 44:450-456.

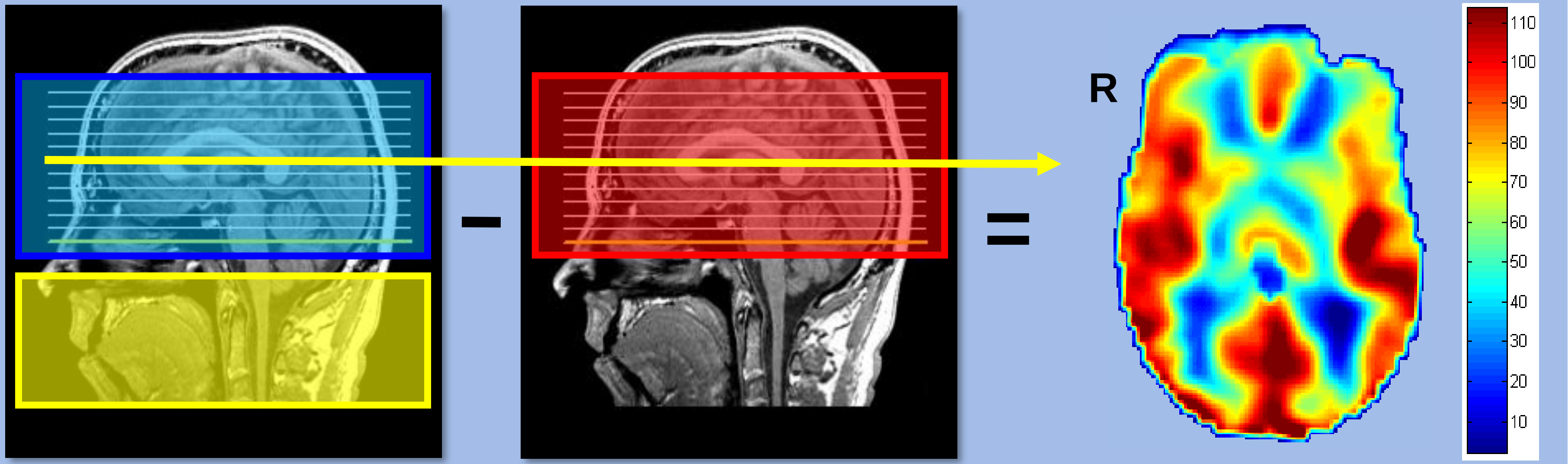
PET: $H_2{}^{15}O$



MR: ASL

Federspiel A. et al., 2008 *ISMRM proceedings.*

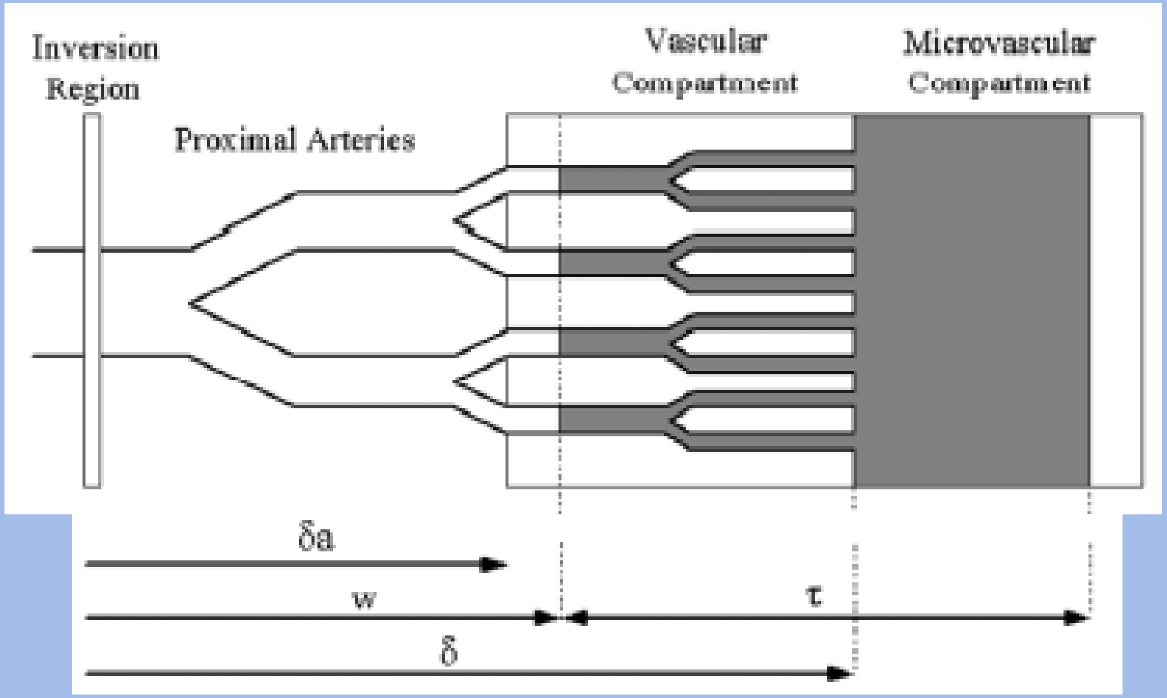
fMRI using ASL



Labeling **Control** **Cerebral blood flow (CBF) [ml/100g/min]**

Federspiel A. et al., 2006 *J Neural Transm*. 13(10):1403-15

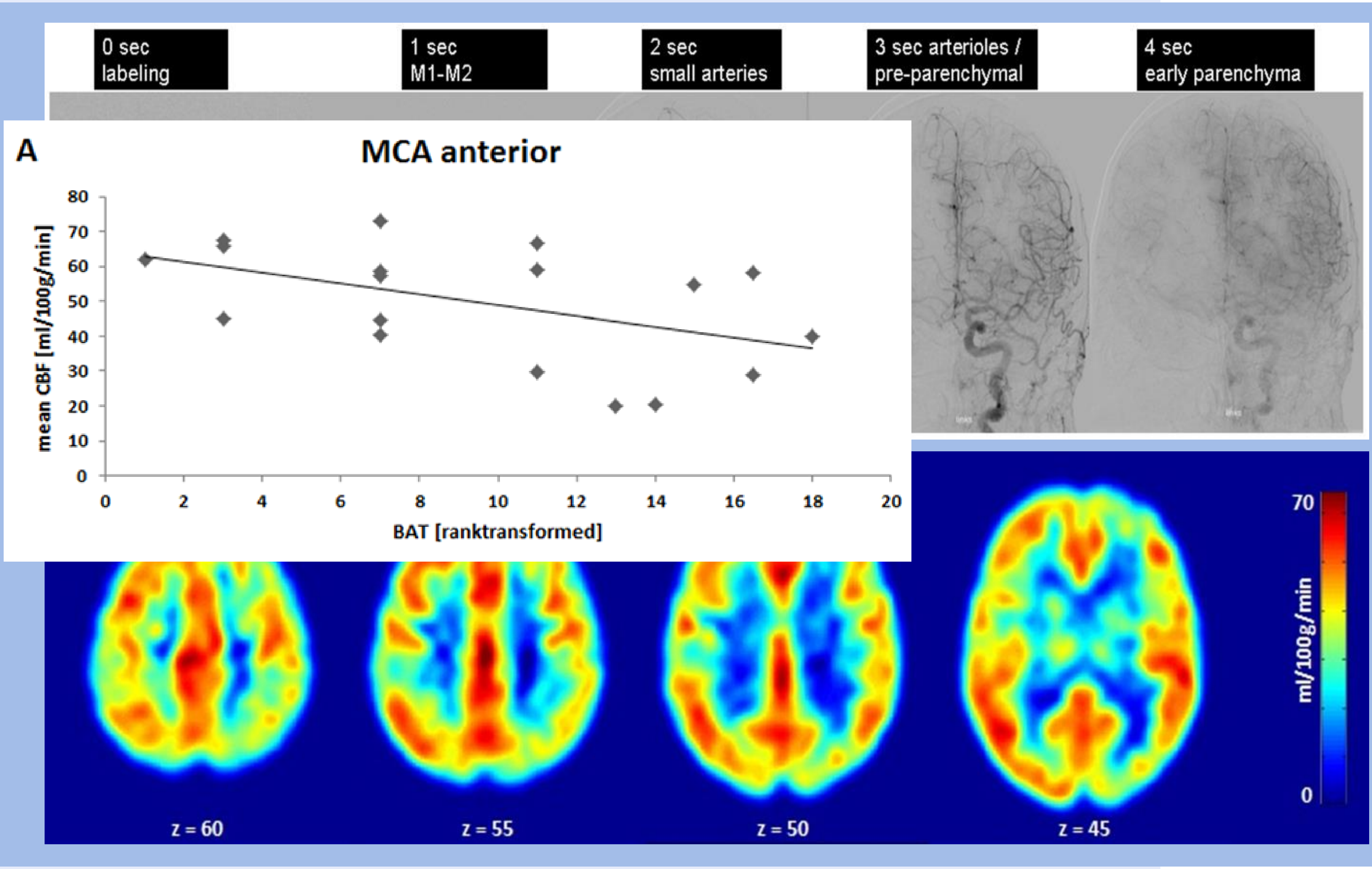
Post label delay



- δ_a **Vascular Transit Time**
- w **Post label delay**
- δ **Tissue transit time**
- τ **Duration of labeling pulse**

Wang J.J. et al 2003 ***Magn Reson. Med.* *5*0:599-607**

CBF timing



Jann K. et al 2012 ***in preparation***

Subtraction strategies

Measurement: **Label image, Control image,…..**

L1, C1, L2, C2, L3, C3, …

Time [Volumes]

Simple subtraction: **C1-L1, C2-L2, ...**

Surround subtraction: **(C1+C2)/2-L1, (C2+C3)/2-L2, ...**

Sinc subtraction: **C3/2-L1, C5/2-L2, ...**

Wong, E.C., Buxton, R.B., Frank, L.R., 1997. Implementation of quantitative perfusion imaging techniques for functional brain mapping using pulsed arterial spin labeling. *NMR Biomed*. 10, 237– 249.

Aguirre, G.K. Detre, J.A. Zarahn, E. Alsop, D.C. 2002. Experimental design and the relative sensitivity of BOLD and perfusion fMRI. *Neuroimage.* **15:**488-500.

ASL processing

- 3-D motion detection and correction.
- Co-registration of 2-D functional and 3-D structural MRI.
- Spatial smoothing with a 8-mm FWHM Gaussian kernel.
- Voxelwise GLM-based correlation of the signal time course with an appropriate reference function.
- Designmatrix: convolution of a standard fixed boxcar function with a gamma-variate hemodynamic response model.
- CBF quantification according to Wang J.J.

Wang J.J. et al., Radiology, 2005. 235(1): p. 218-28.

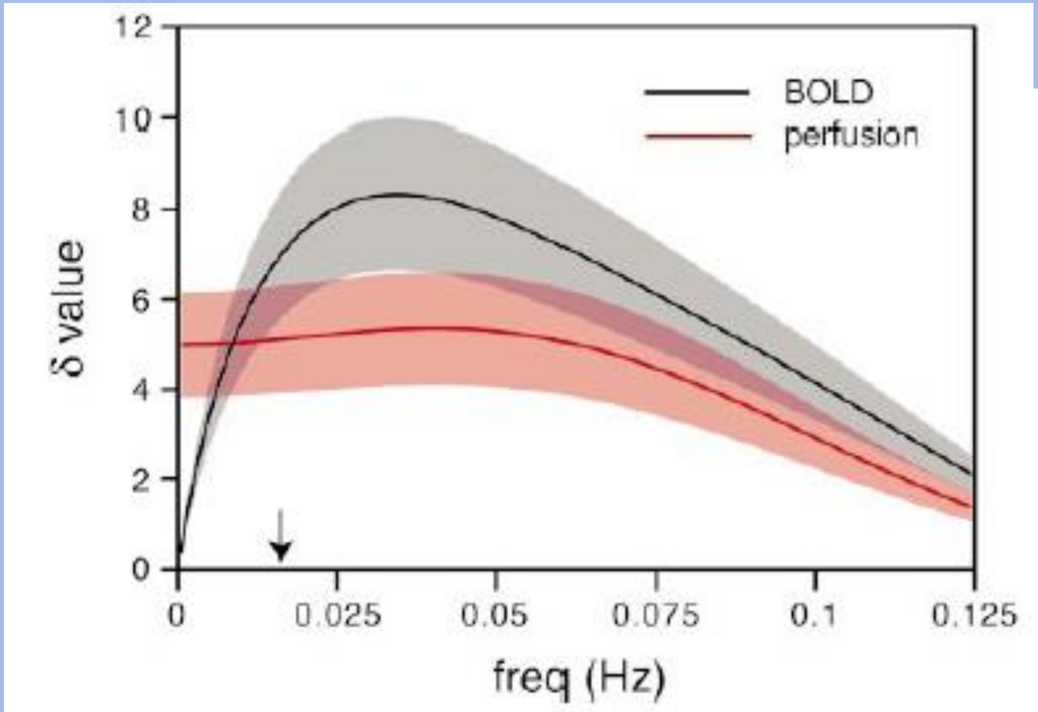
Perfusion quantification CASL

$$CBF = \left(\frac{\lambda \cdot \Delta M}{2 \cdot \alpha \cdot \langle M_{control} \rangle \cdot T_{Lb}} \right) \cdot \left(\frac{1}{e^{-(\frac{D_{t,slice}}{T_{Lb}})} - e^{-(\frac{(D_{t,slice}+L_t)}{T_{Lb}})}} \right)$$

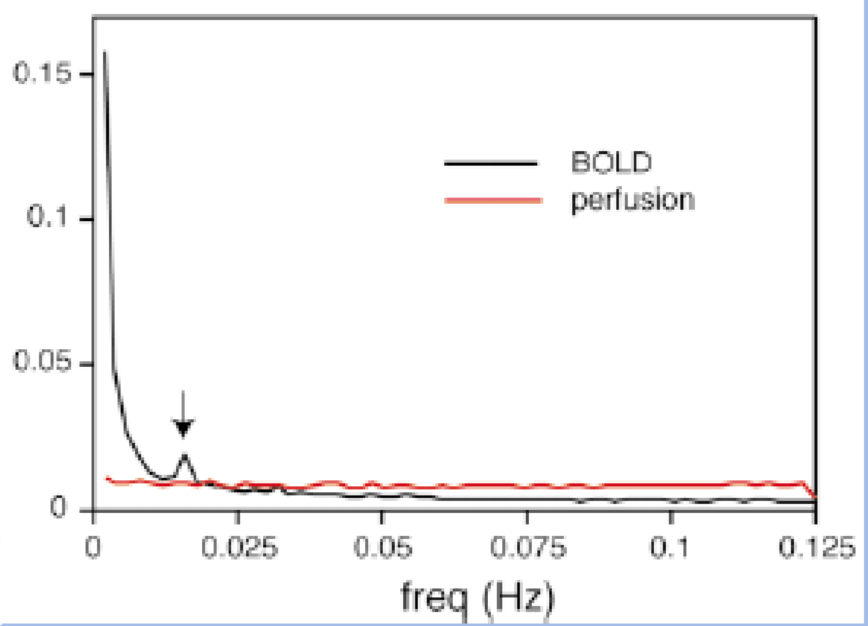
ΔM	**Control-Label image**
$\langle M_{control} \rangle$	**Average control images, or M_0 equilibrium Magnetization**
$D_{t,slice}$	**post-labeling delay + slice time**
L_t	**Label time**
λ	**blood/tissue water partition coefficient [ml/g]**
α	**tagging efficiency**
T_{Lb}	**Relaxation time of blood**

ml/100 g /min

Relative SNR for BOLD and Perfusion



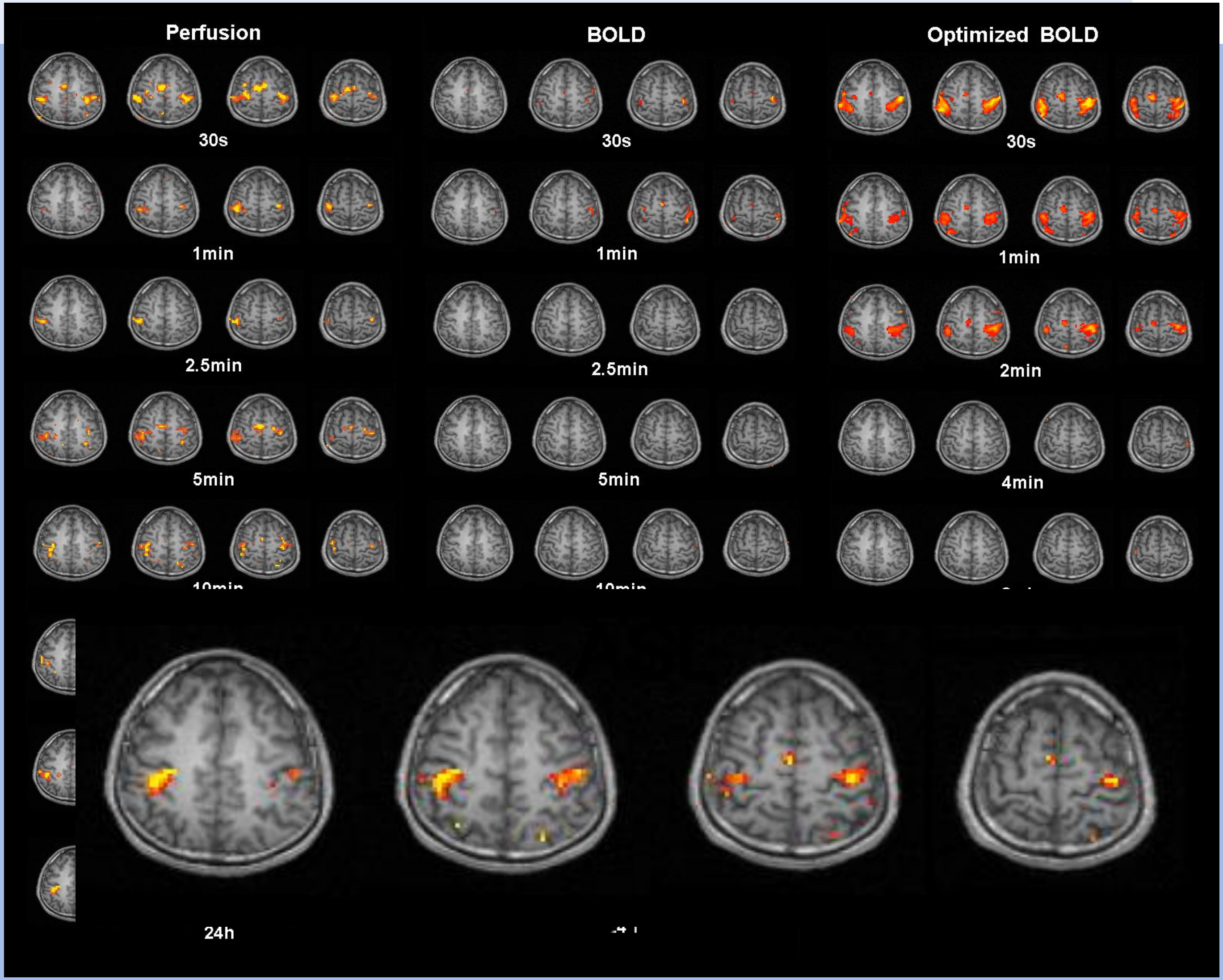
1/f distribution of power



Aguirre, G.K. Detre, J.A. Zarahn, E. Alsop, D.C. 2002.
Experimental design and the relative sensitivity of BOLD and perfusion fMRI.
Neuroimage. **15:**488-500.

Validated: Wang, J. Aguirre, G.K. Kimberg, D.Y. Roc, A.C. Li, L. Detre, J.A. 2003.
Arterial spin labeling perfusion fMRI with very low task frequency.
Magn Reson. Med. 49:796-802.

Temporal Characteristics of Perfusion and BOLD FMRI



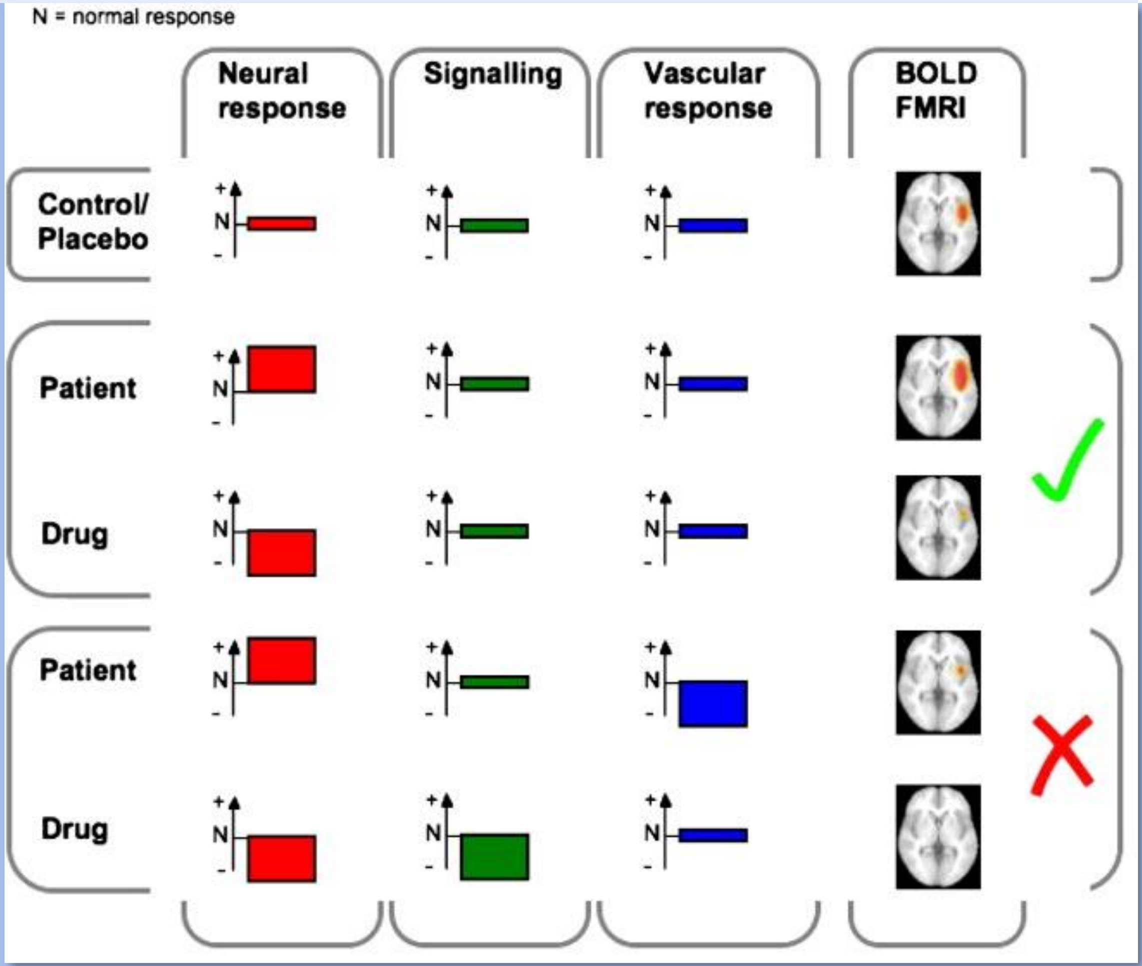
Wang et al. MRM (2003)

CBF-ASL applications in clinical setting

- Acute and chronic cerebrovascular disease / Stroke
- Tumor and Angiogenesis
- CNS neoplasms
- Epilepsy
- Aging and Development / Pediatry
- Neurodegenerative diseases
- Neuropsychiatric disorders
- Addiction, Stress, etc.

not complete list…

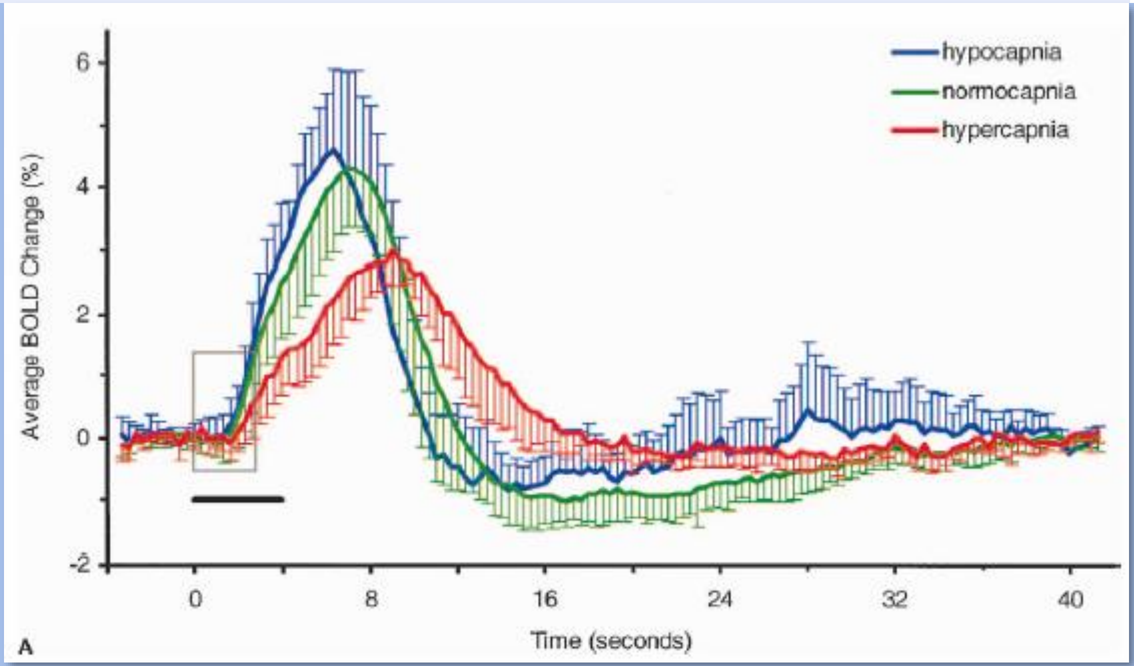
BOLD fMRI in Patient/Drug



Interpretation of BOLD results sometimes ambiguous!

Iannetti & Wiese 2007 *Magn Reson Imaging*. 25(6):978-88

Effect of hypo/hypercapnia

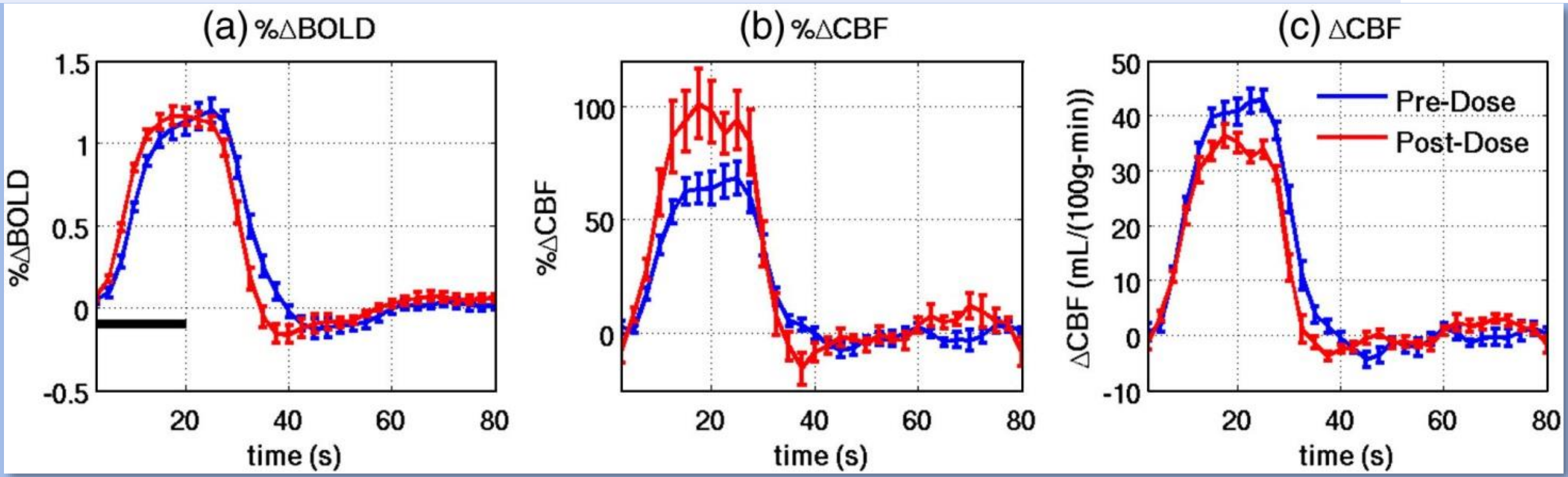


↓ CO2 **Hypocapnia** Faster BOLD signal / higher BOLD signal

↑ CO2 **Hypercapnia** slower BOLD signal / lower BOLD signal

Coehen E.R. et al. 2002 *J Cereb Blood Flow Metab.* 22(9):1042-53.

Effect of Caffein

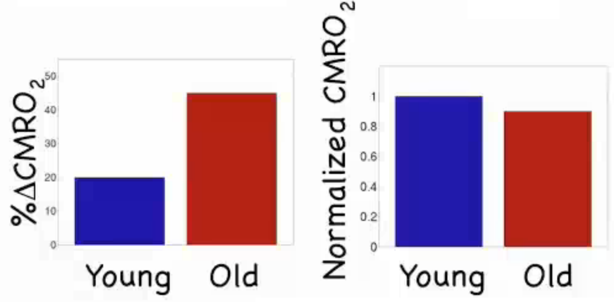


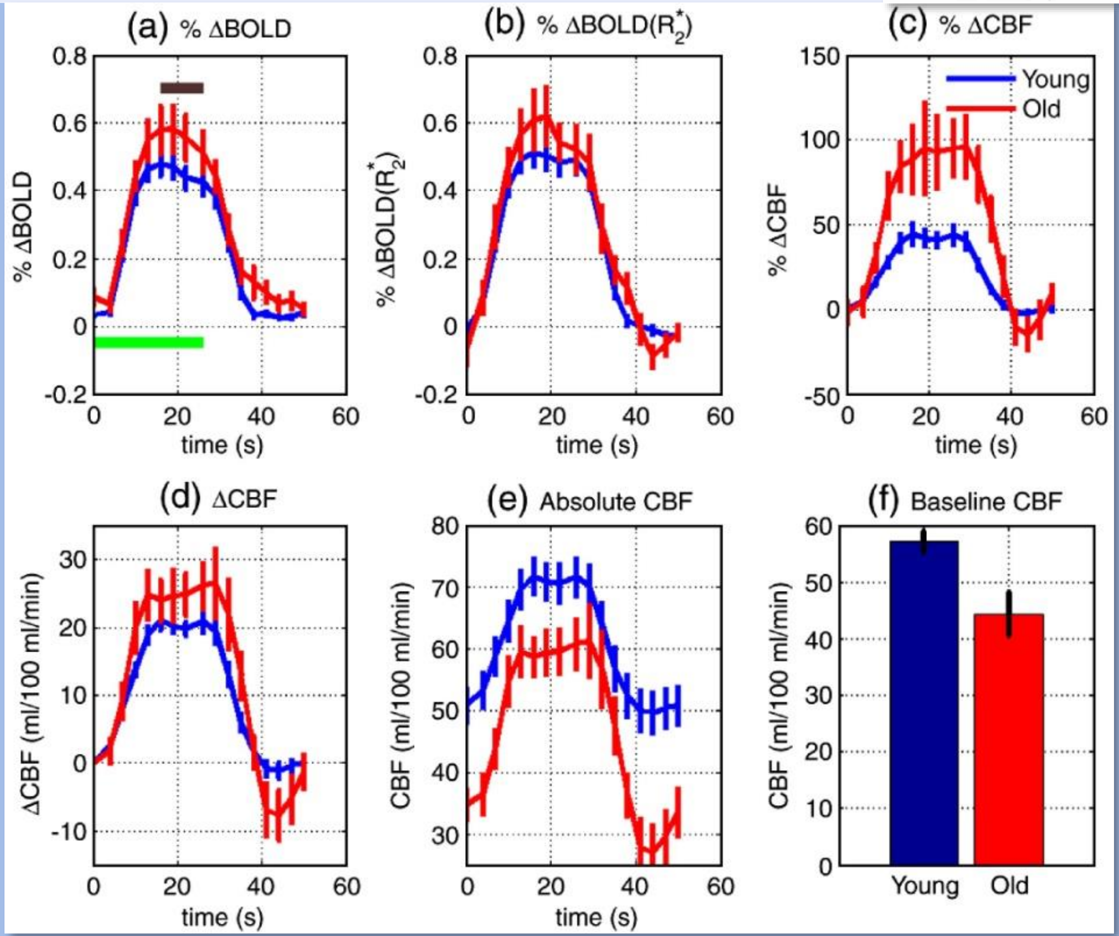
Caffein has similar effect on CBF like hypercapnia

But, no detection with BOLD !

Liau J. et al. 2008 ***Neuroimage.*** **42(1):296-305**

Effect of Age



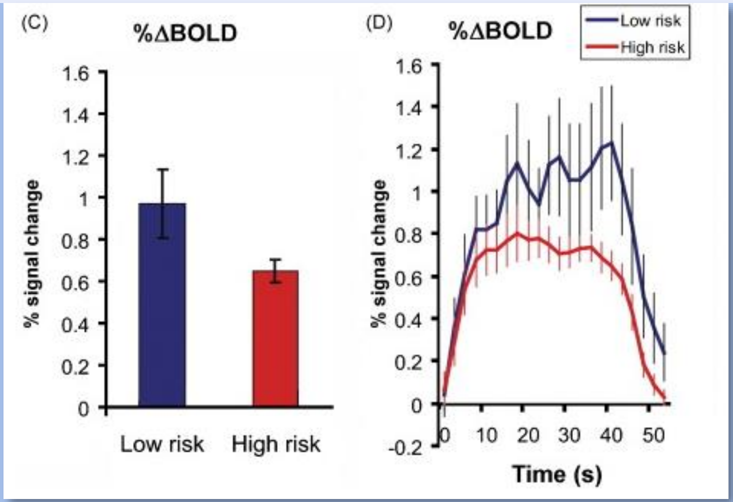


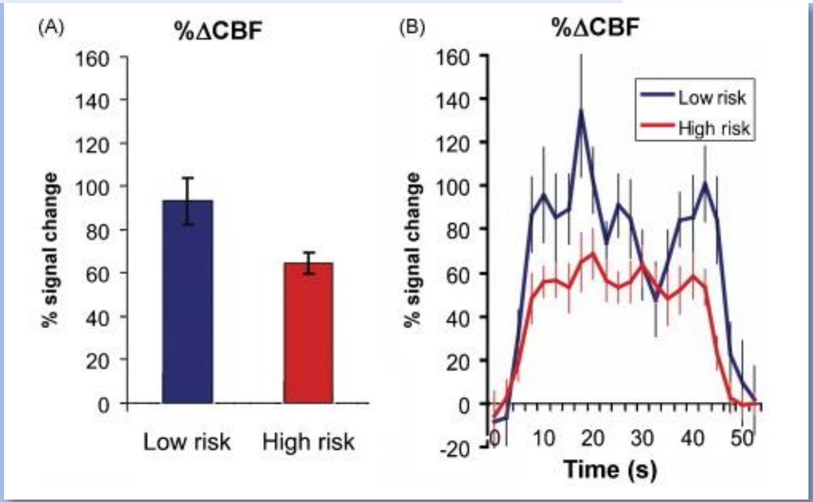
No significant differences in BOLD between young/old

Significant differences in CBF between young/old

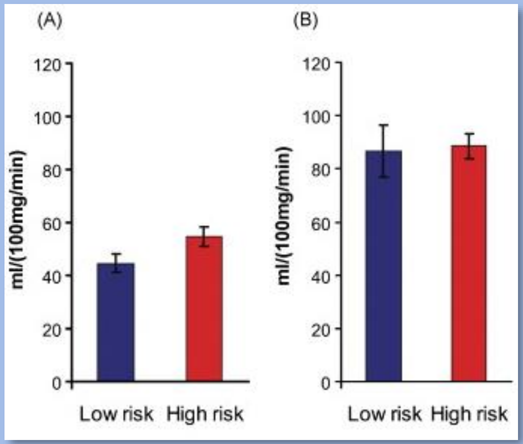
Restom K. et al. 2007 *Neuroimage.* 37(2):430-9.

Effect of Alzheimer‘s disease risk





Rest



Task (memory task)

Medial temporal Lobe activation

Fleisher A.S. et al. 2009 *Neurobiol Aging.* 30(11):1737-48.

Conclusion

> BOLD signal is a complex function of baseline state and changes in CBF, CBV; CMRO2

> May reflect differences in baseline vasculature or metabolic state

> Calibrated fMRI may be useful in presence of disease, medication, age...

> BOLD activations should be interpreted with caution, and do not necessarily reflect differences in neuronal activation.

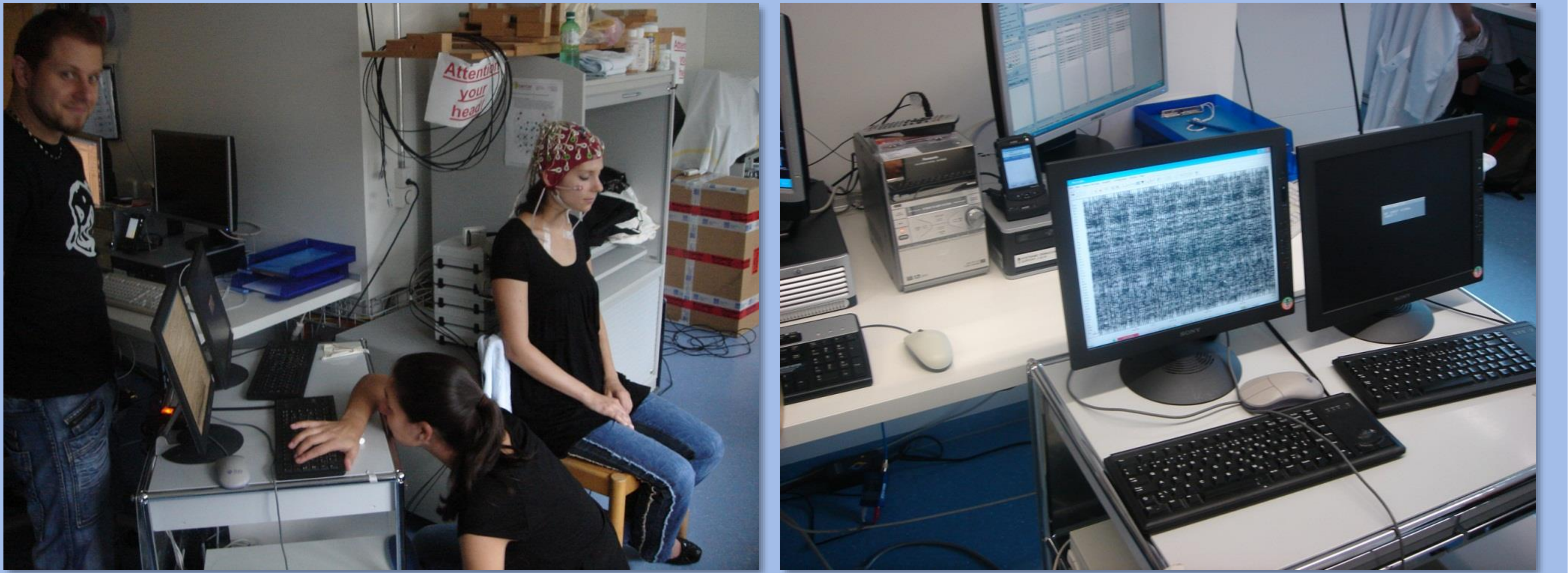
Hypothesis

- During CO_2 administration we expect no significant changes in total amount of neuronal activation in the human brain.

- Therefore, within the same subject and with the same recording setup, during resting state we expect to observe no changes in EEG (frequency bands) under hypercapnia.

- We expect $CMRO_2$ to remain constant during this setting

EEG setting



EEG resting test outside MR scanner………..and EEG simultaneous during BOLD recoding.

EEG /fMRI simultaneous recording

Mounting EEG trough head coil

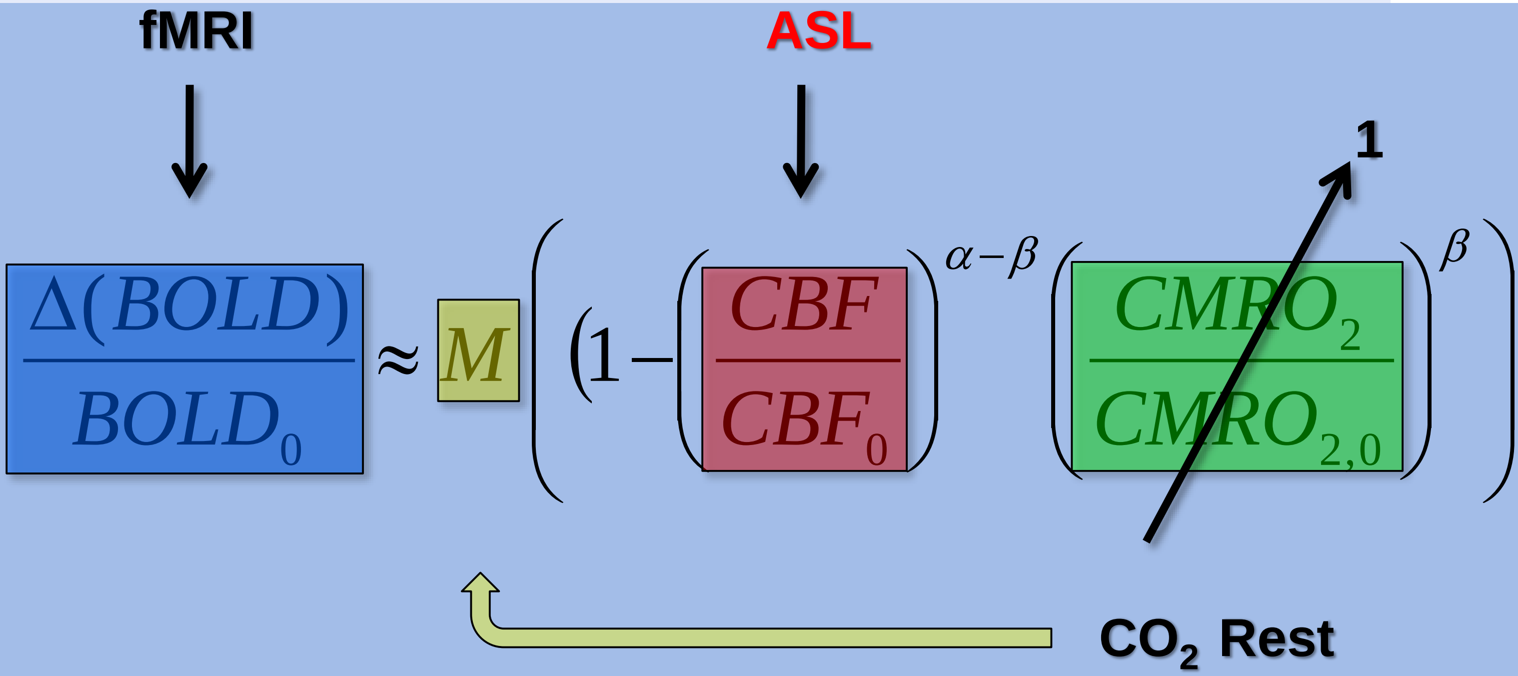
Visible are CO_2 face mask, LCD goggles, hart rate meter and expiration recoding capno-meter.

Simultaneous EEG/fMRI recoding is ready.

Visible are capno-meter and hart rate meter device (left)

LCD goggle device (bottom, right).

Calibrated fMRI „Davis Model“



fMRI

ASL

$$\frac{\Delta(BOLD)}{BOLD_0} \approx M\left((1-\left(\frac{CBF}{CBF_0}\right)^{\alpha-\beta}\left(\cancelto{1}{\frac{CMRO_2}{CMRO_{2,0}}}\right)^{\beta}\right)$$

CO_2 Rest

$$\left(\frac{CBV}{CBV_0}\right)=\left(\frac{CBF}{CBF_0}\right)^{\alpha}$$

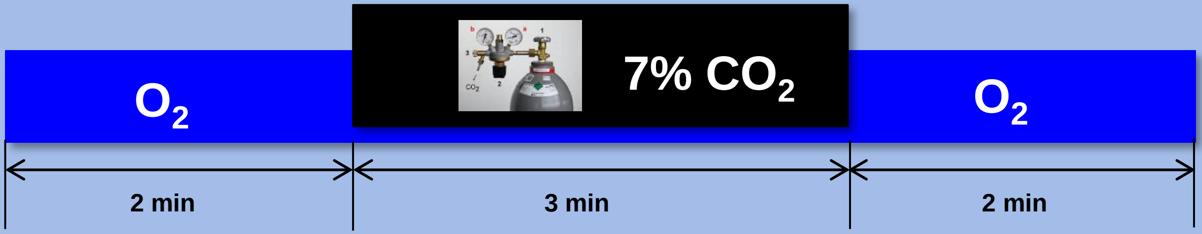
α = 0.38

β ~ 1.0 @ 3 T

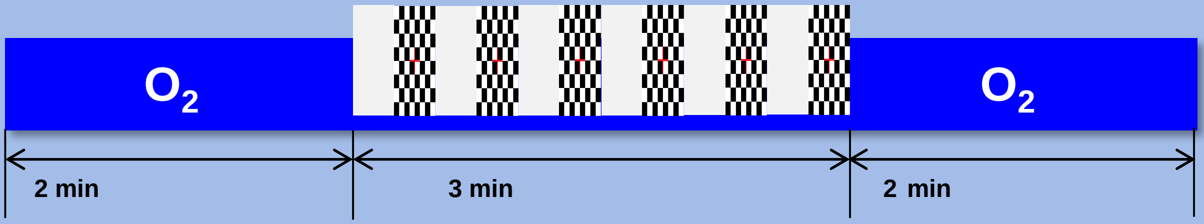
Davis T.L. et al 1998 PNAS 95:1834-39; Brown G.G. et al 2007 Neuropsych. Rev. 17: 107-25

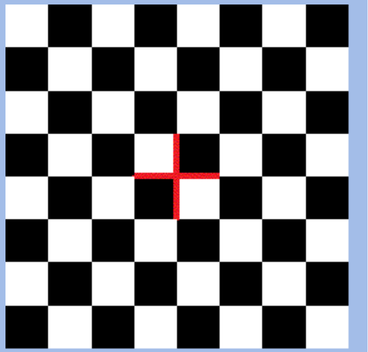
CO_2 administration / Visual stimulus

- ASL / BOLD / EEG scan during CO_2



- ASL / BOLD / EEG scan during visual stimulation





2 Hz full-field flashing checkerboard pattern with fixation cross

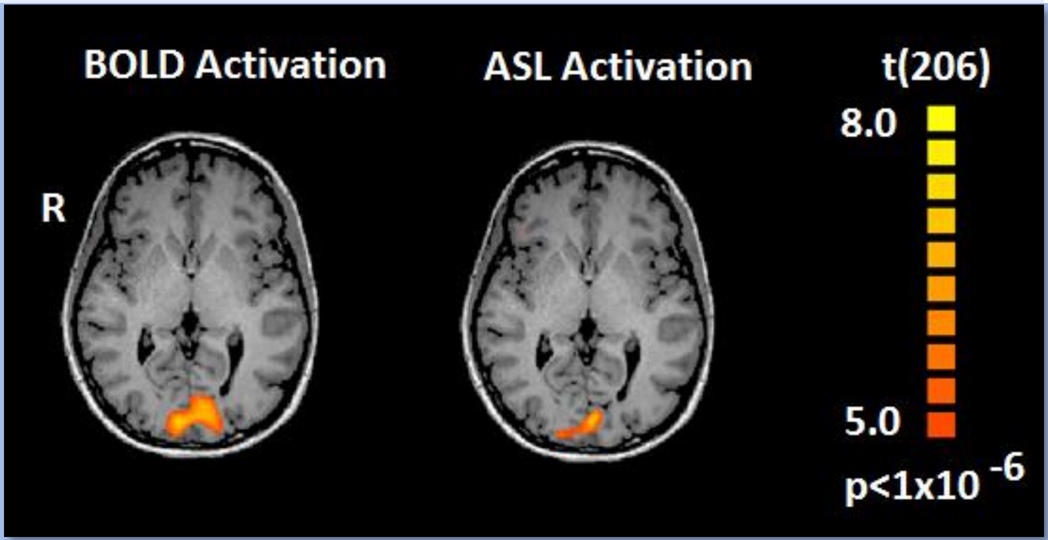
Visual display over LCD MR compatible goggles

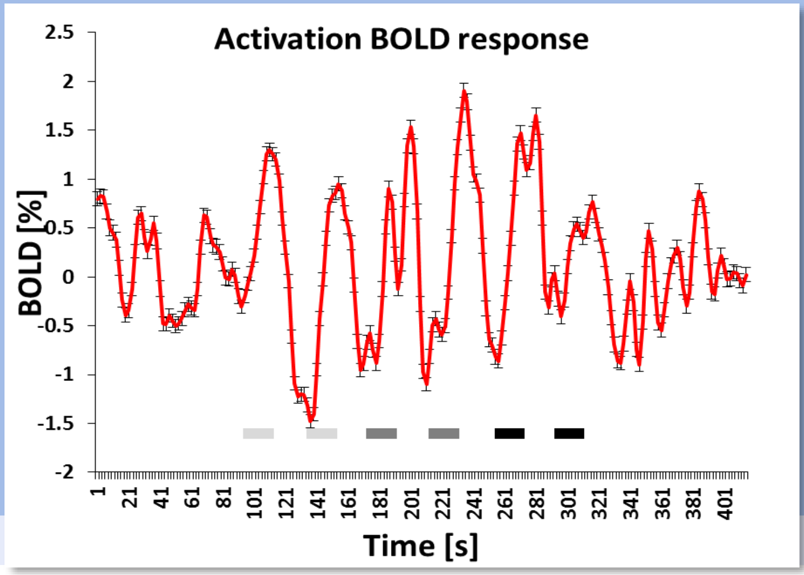
Results

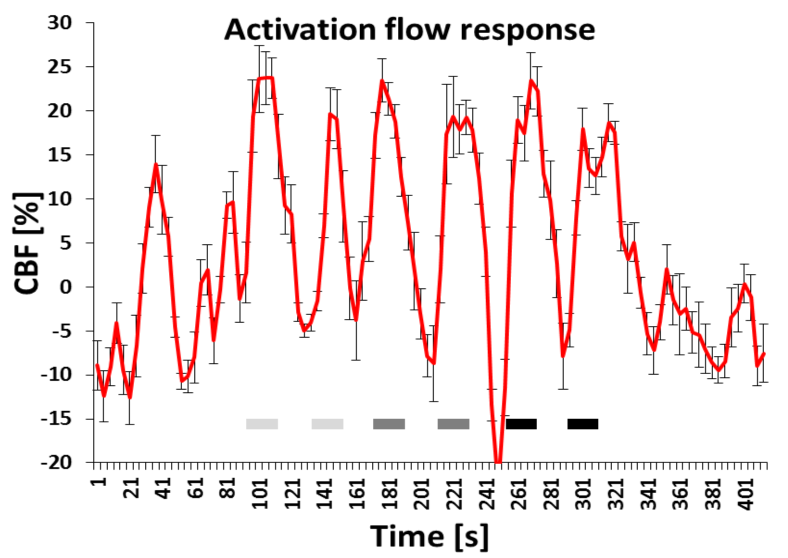
- End-tidal CO_2 ↑ 6 mm Hg during CO_2
- Heart rate (HR) ↑ 7 units during CO_2

	AIR		CO_2
> Whole brain CBF	54.30 [ml/100g/min]	↑	60.69 [ml/100g/min]

fMRI results: air + visual stimulus

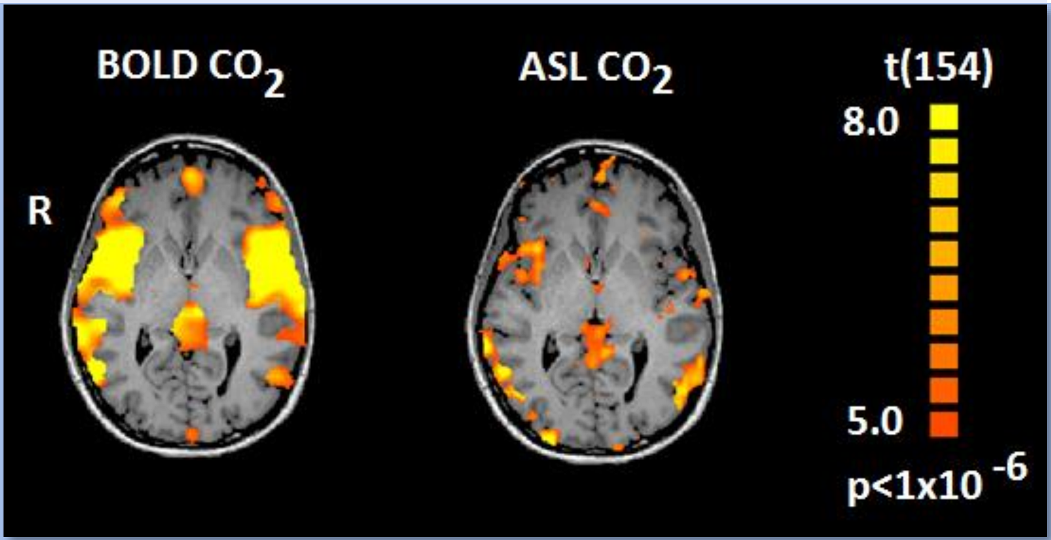


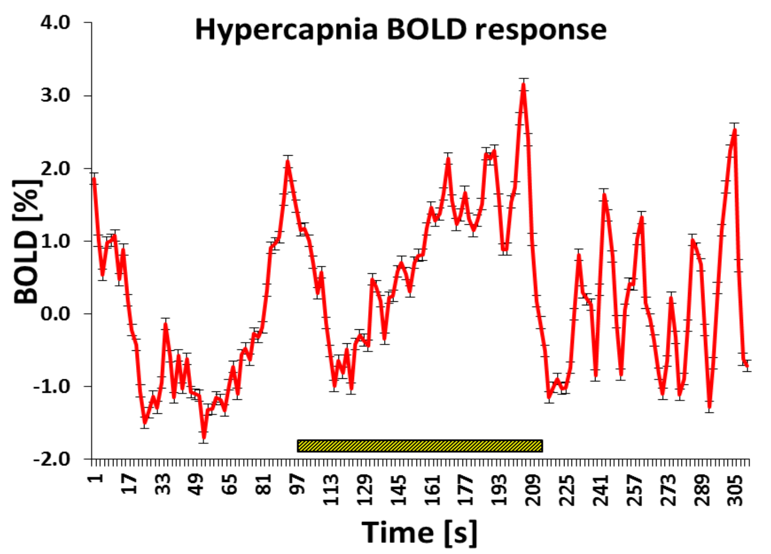


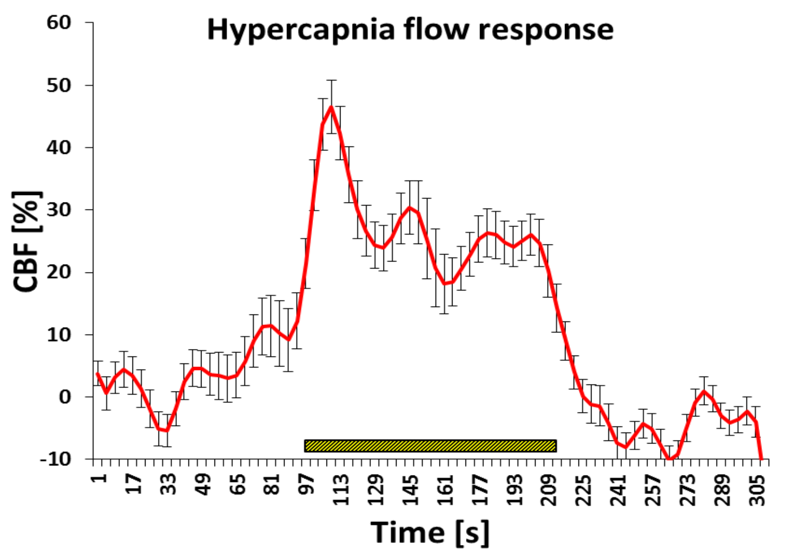


fMRI results: hypercapnia

ROI







Estimation of M and $CMRO_2$

	Rest	Stimulus	Estimation
BOLD Air		**0.48 ± 0.72**	
BOLD 7 % CO_2	**0.71 ± 0.87**		
ASL Air		**13.57 ± 9.72**	
ASL 7 % CO_2	**26.86 ± 7.40**		
M			**5.02 ± 0.56**
$CMRO_2$			**25.62 ± 0.05**

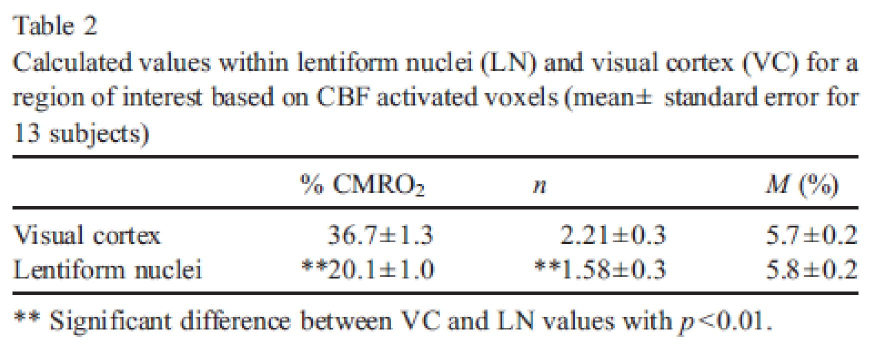


Table 2

Calculated values within lentiform nuclei (LN) and visual cortex (VC) for a region of interest based on CBF activated voxels (mean± standard error for 13 subjects)

	% $CMRO_2$	*n*	*M* (%)
Visual cortex	36.7±1.3	2.21±0.3	5.7±0.2
Lentiform nuclei	**20.1±1.0	**1.58±0.3	5.8±0.2

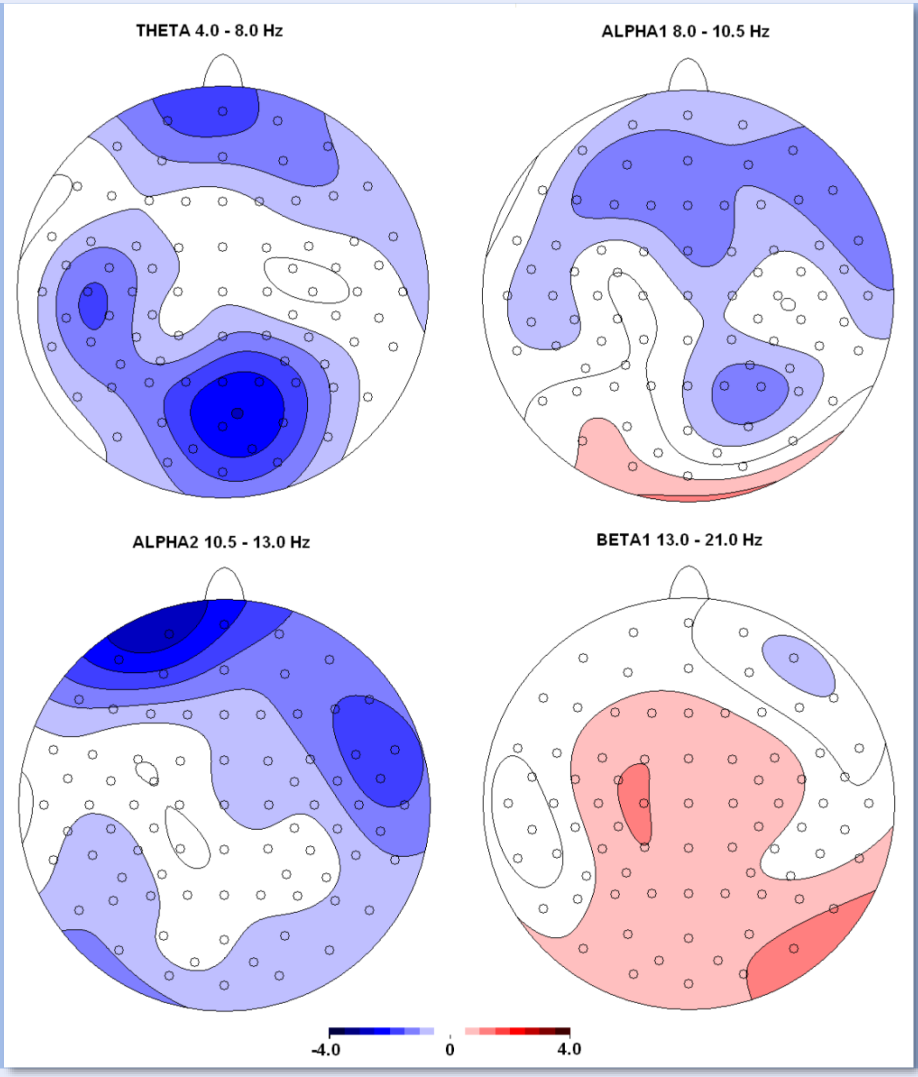
** Significant difference between VC and LN values with $p<0.01$.

Ances B.M. et al. 2008 Neuroimage. 39(4):1510-1521.

EEG spectral results: t-test CO_2 vs Air

during CO_2 ↓ θ

during CO_2 ↓ α

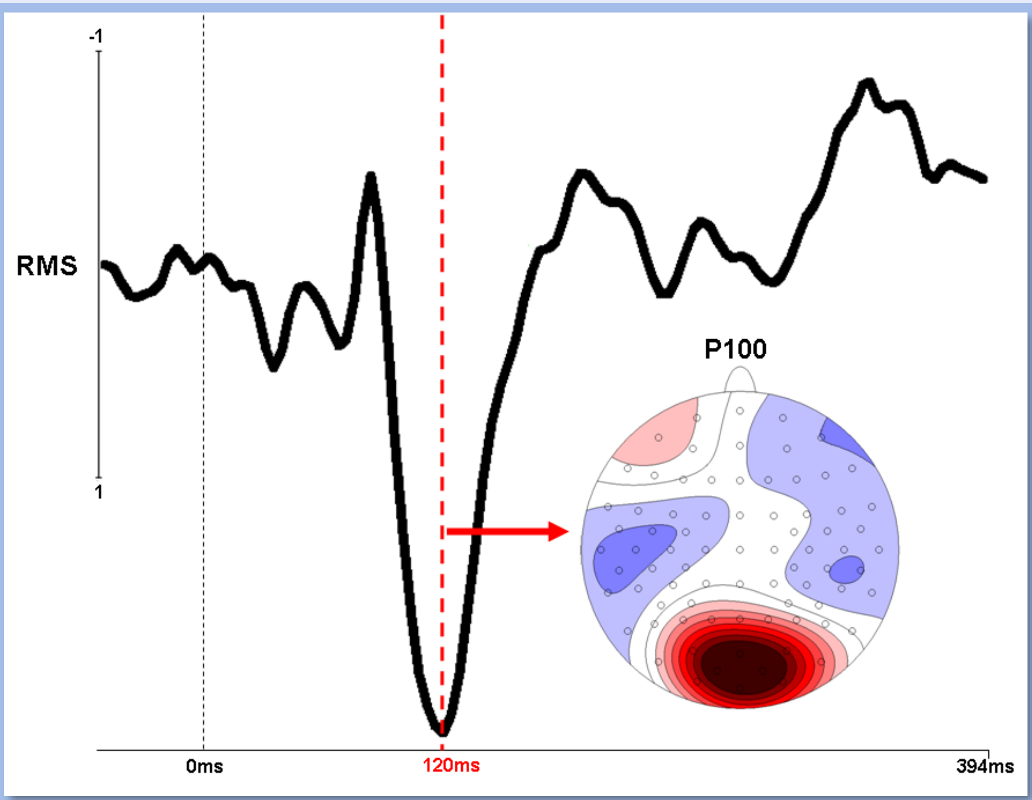


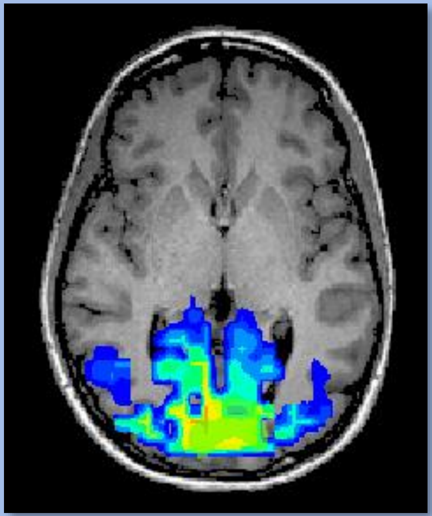
	Air	CO_2
θ	**0.71**	**0.68**
α1	**0.57**	**0.56**
α2	**0.57**	**0.53**
β	**0.47**	**0.51**

Mean RMS [μV]

Only resting periods are included

EEG results: P100 ERP





Current density estimation (sLORETA).

Pascual-Marqui, R.D., Methods Find Exp Clin Pharmacol, 2002. 24 Suppl D: p. 5-12.

„Davis Model“ and EEG

$$\frac{\Delta(BOLD)}{BOLD_0} \approx M\left(\left(1-\left(\frac{CBF}{CBF_0}\right)^{\alpha-\beta}\left(\frac{CMRO_2}{CMRO_{2,0}}\right)^{\beta}\right)\right.$$

Frequency	$\Delta(CMRO_2)/CMRO_2$
θ	$\frac{\Delta(CMRO_2)}{CMRO_2} \approx \frac{\Delta v}{v} = \frac{0.71}{0.68} = 1.044$
α2	$\frac{\Delta(CMRO_2)}{CMRO_2} \approx \frac{\Delta v}{v} = \frac{0.57}{0.53} = 1.075$

Neuronal energy <-> additional work (spiking frequency)

Davis T.L. et al 1998 PNAS 95:1834-39; Hyder F. et al 2004 Stroke 35: 2635-41; Hyder F. et al 2010 Front Neuroeneg 2: 18; Maandag N.J. et al 2007 PNAS 104: 20546-51; Shulman R.G. et al 2007 Neuroimage 36: 277-81;

$CMRO_2$ under CO_2 and EEG

$$\frac{\Delta(CMRO_2)}{CMRO_2} \approx \frac{\Delta v}{v} \neq const$$

This Pilot Study shows a dependency on frequency and a shows distinct topographic distribution.

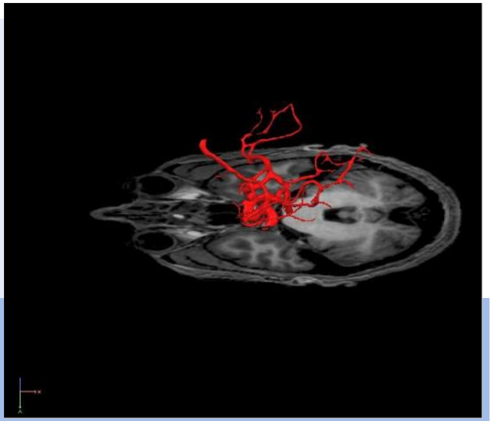
$$\frac{\Delta(CMRO_2)}{CMRO_2} \neq const$$

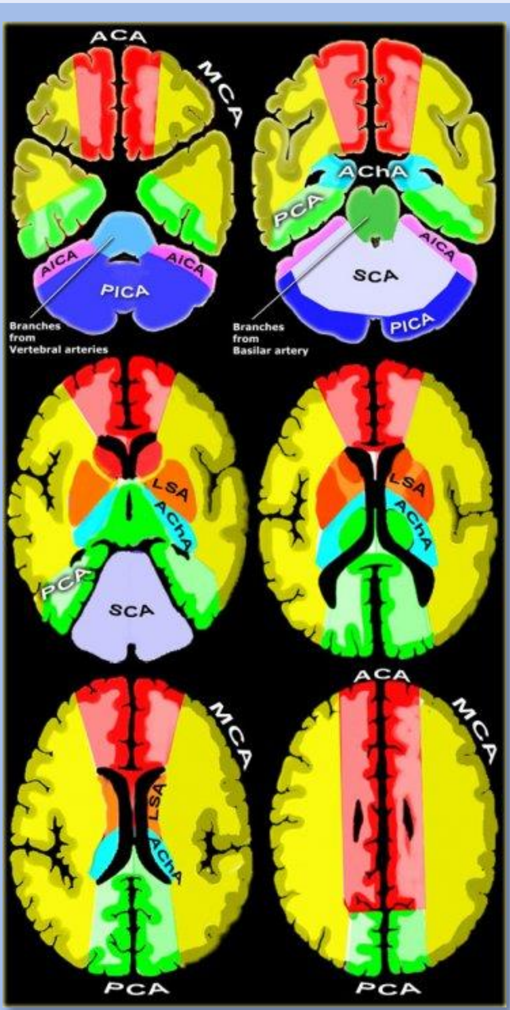
Xu, F., et al., J Cereb Blood Flow Metab, 2011, 31: 58-67.

$$\frac{\Delta(CMRO_2)}{CMRO_2} = const$$

Chen, J.J. and G.B. Pike, J Cereb Blood Flow Metab, 2010, 30: 1094-9.

Cerebral Arterial Territory

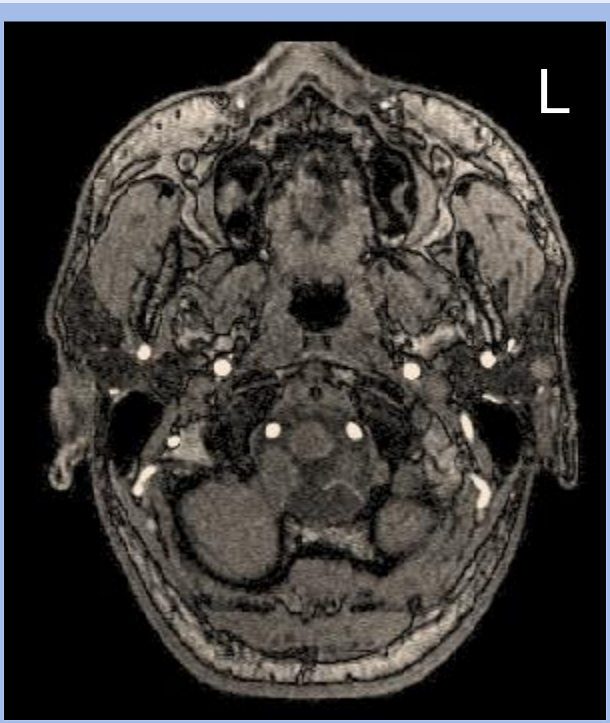




🟦 Posterior Inferior Cerebellar Artery (PICA)
⬜ Superior Cerebellar Artery (SCA)
🟦 Branches from vertebral and basilar artery
Anterior Choroideal artery (AchA)
🟧 Lenticulo-striate arteries (LSA)
🟥 Anterior cerebral artery (ACA)
🟨 Middle cerebral artery (MCA)
🟩 Posterior cerebral artery (PCA)

Adapted from: Savoiardo M. 1986 *Ital J Neurol Sci*. 7(4):405-9.

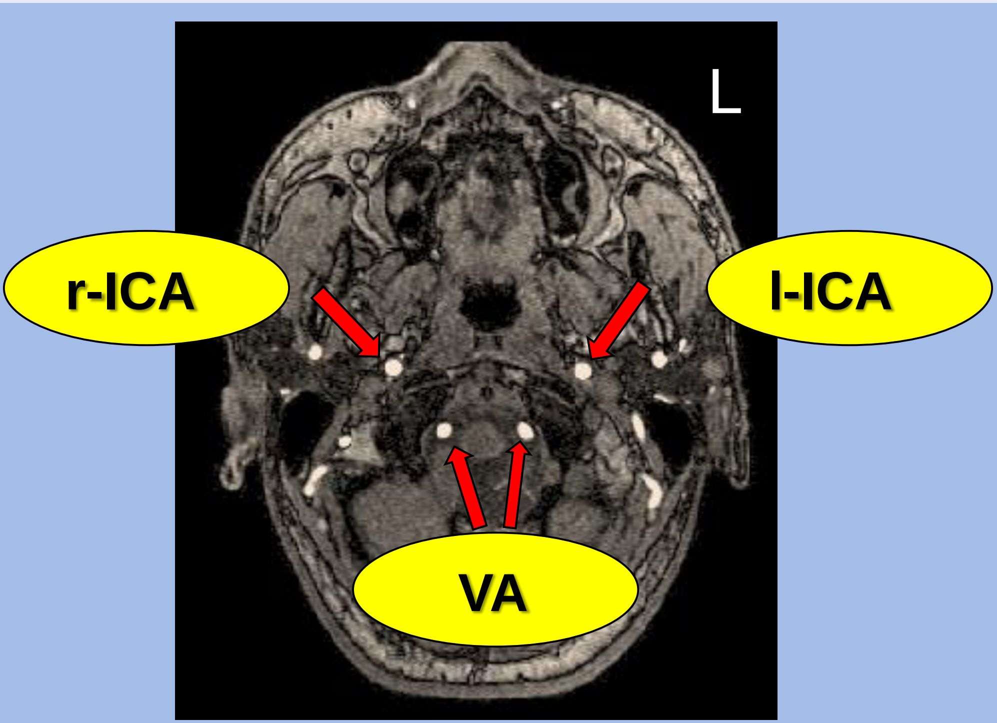
Selective ASL (sASL): visualization of cerebral arterial territory



1) perform TOF	~ 5 min
2) perform “selective ASL”	~ 7 min

Davies NP Jezzard P. 2003 *Magn reson Med*. 49(6):1133-42. Wong E.C. 2007 *Magn reson Med*. 58(6):1086-91.

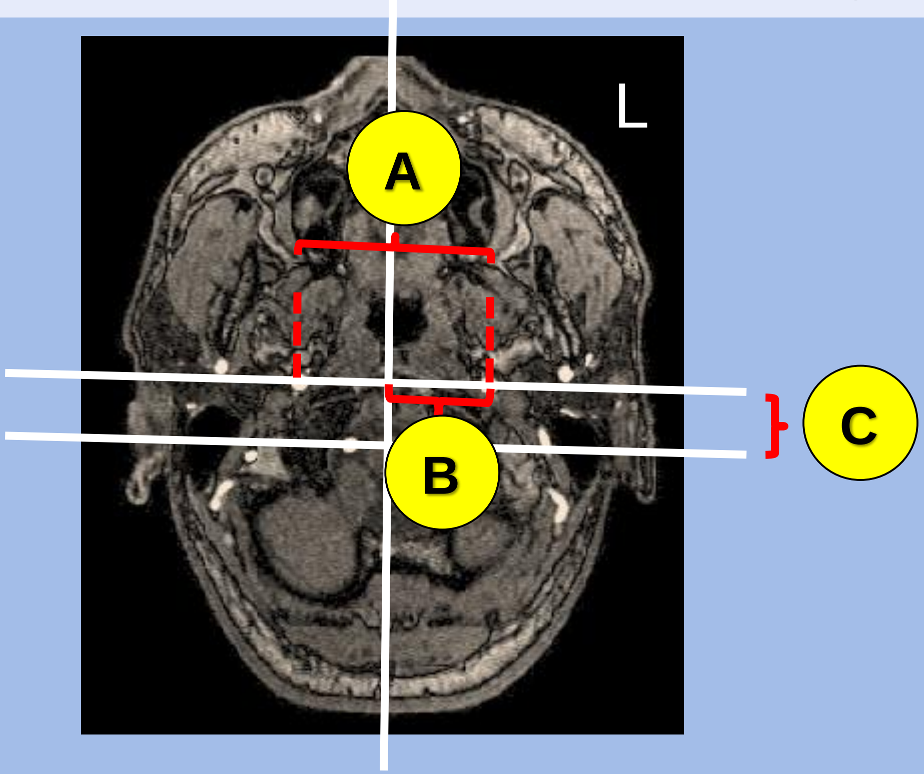
Selective ASL: visualization of cerebral arterial territory



- Identification left/right Internal Carotid Artery (ICA)
- Identification left/right Vertrebral Artery (VA)

Wong E.C. 2007 *Magn reson Med*. 58(6):1086-91. Wu W.C. 2007 *Magn reson Med.* 58(5):1020-7.

Selective ASL:
visualization of cerebral arterial territory



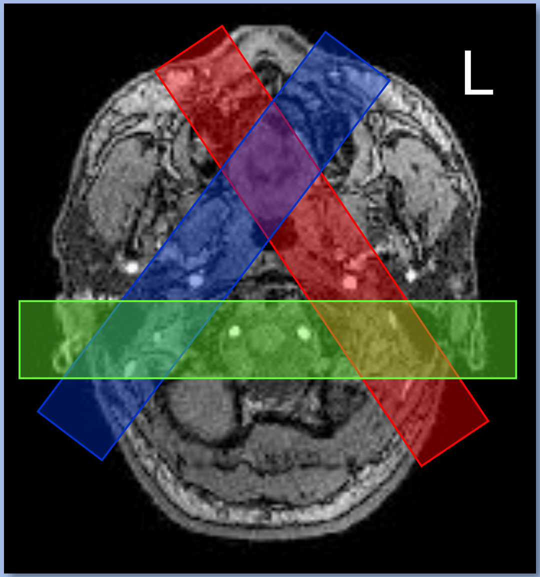
- Distance between left and right ICA
- Distance between left ICA and Isocenter
- Distance between line of Isocenter and Basilar Artery

A
B
C

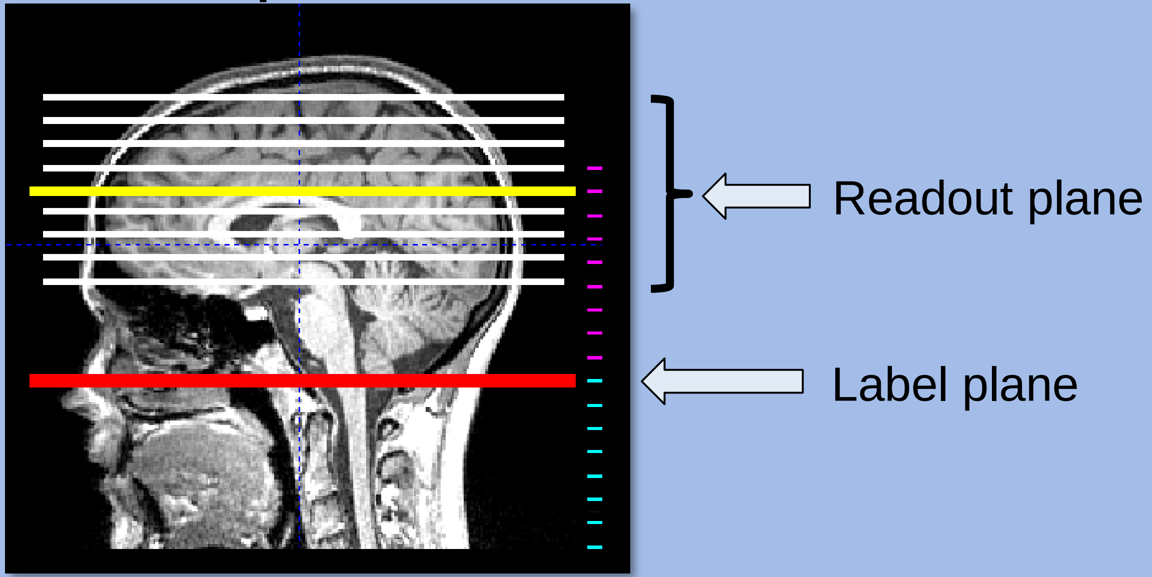
Wong E.C. 2007 *Magn reson Med*. 58(6):1086-91. Wu W.C. 2007 *Magn reson Med.* 58(5):1020-7.

sASL: setting

TOF



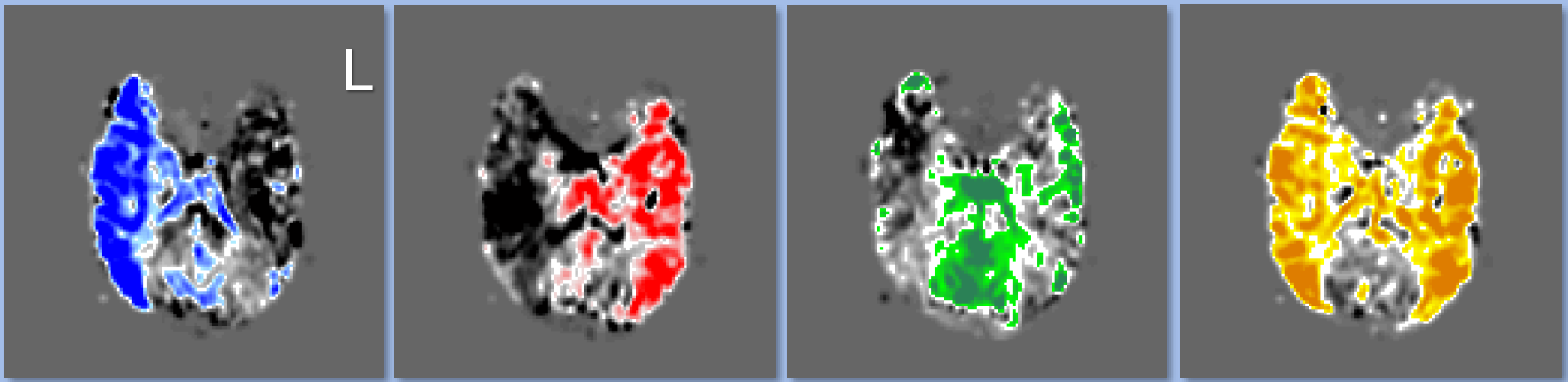
slice position



Repeat cycle of Label, Control, L-ICA, R-ICA, Anterior, Posterior.

Wong E.C. 2007 *Magn reson Med*. 58(6):1086-91. Wu W.C. 2007 *Magn reson Med.* 58(5):1020-7.

Average sASL Maps



Right

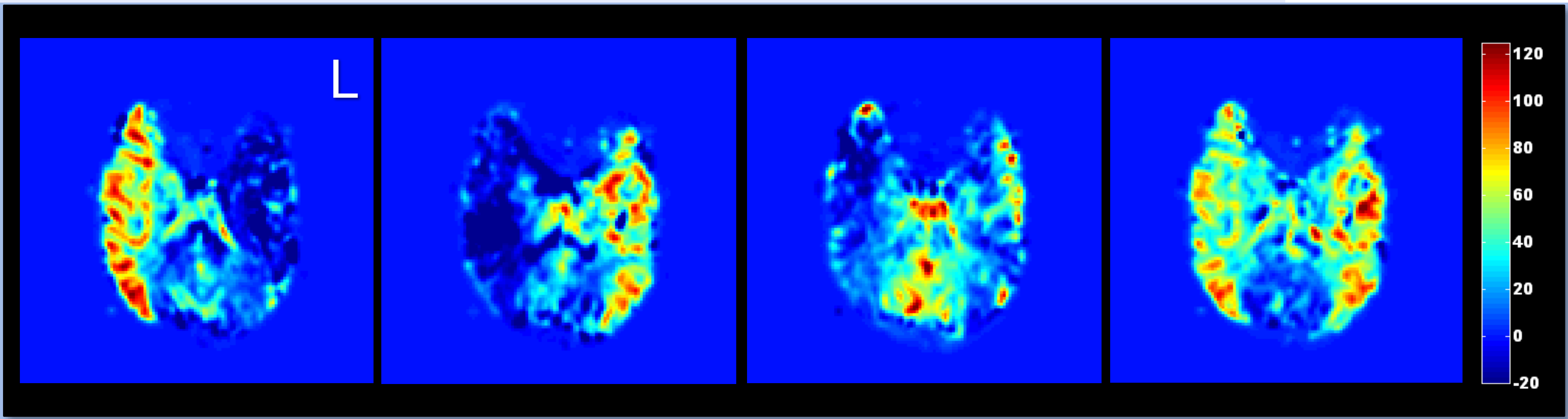
Left

Posterior

Anterior

Federspiel A., Wiest R., Jann K., Gralla J., Mattle H., Dierks T. @ 3T Magnetom Trio Bern

Average sASL Maps in units [ml/100g/min]

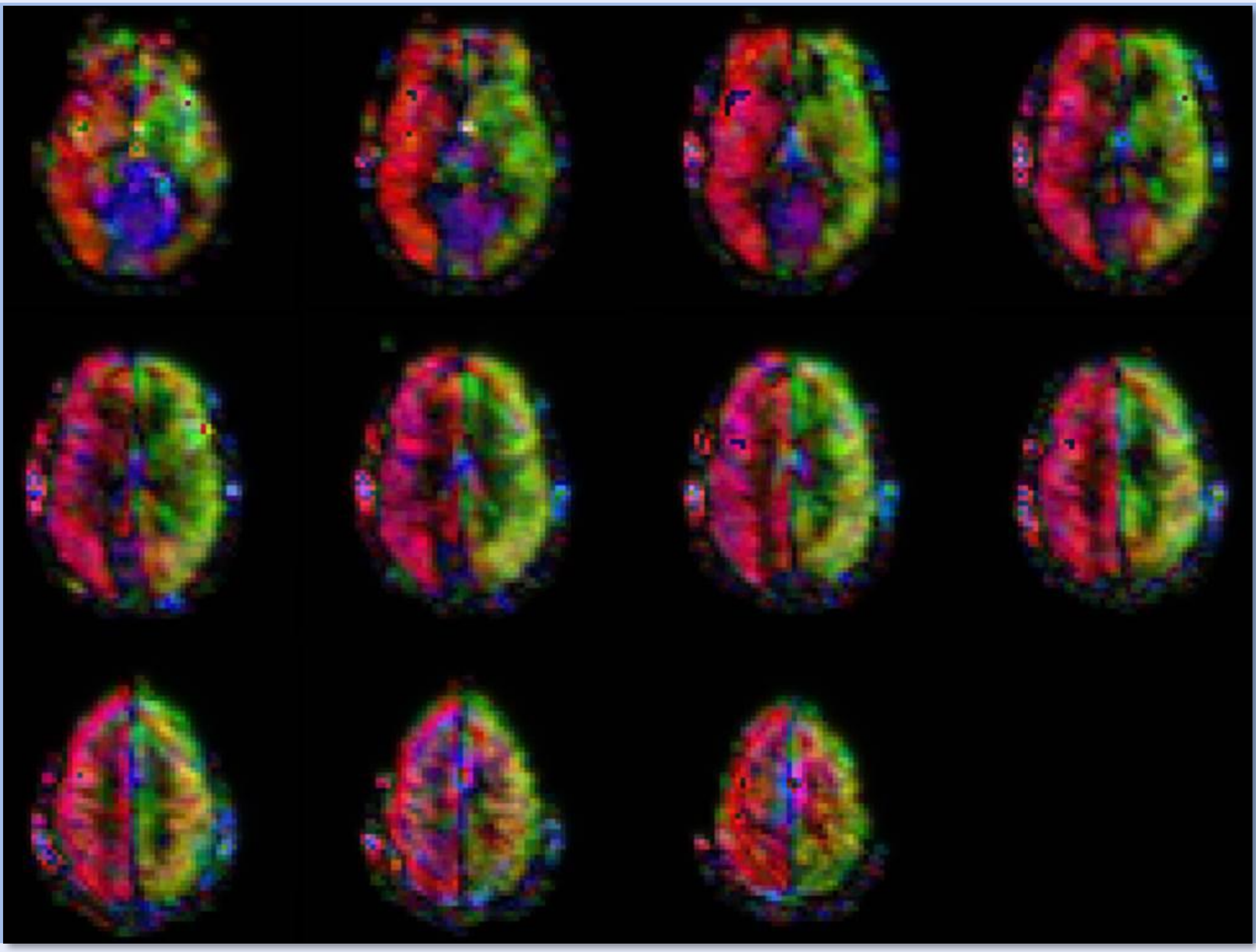


Right Left Posterior Anterior

$$CBF = \left(\frac{\lambda\cdot\Delta M}{2\cdot\alpha\cdot\langle M_{control}\rangle\cdot T_{Lb}}\right)\cdot\left(\frac{1}{e^{-(\frac{D_{t,slice}}{T_{Lb}})} - e^{-(\frac{(D_{t,slice}+L_t)}{T_{Lb}})}}\right)$$

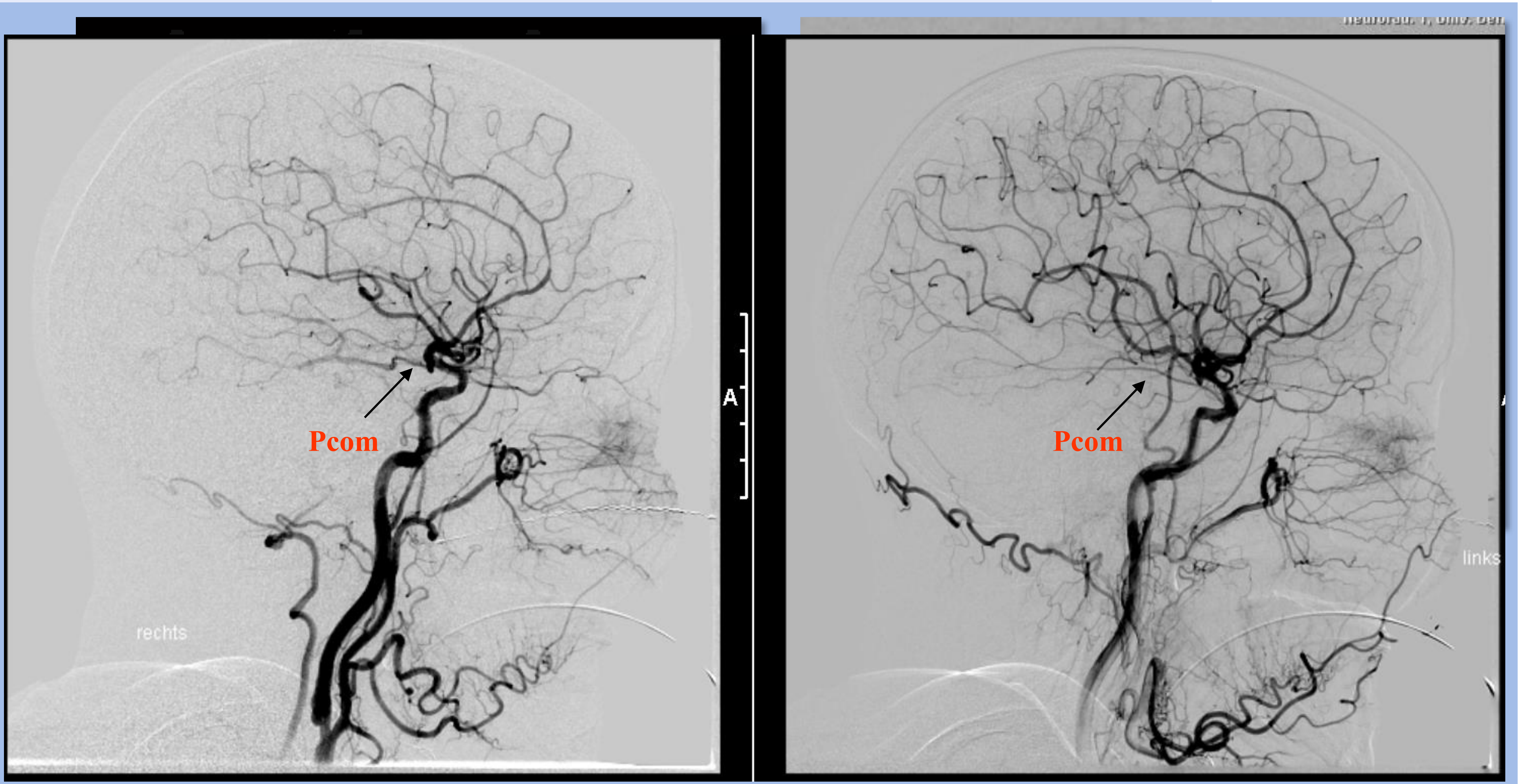
Federspiel, A. Wiest R., Jann K., Gralla J., Mattle H., Dierks T. @ 3T Trio Bern **Wang J.J. et al. *Magn reson Med*. 50(3):599-607**

Mapping of cerebral vascular territories



Federspiel, A. Wiest R., Jann K., Gralla J., Mattle H., Dierks T. @ 3T Magnetom Trio Bern

Clinical application of selective ASL

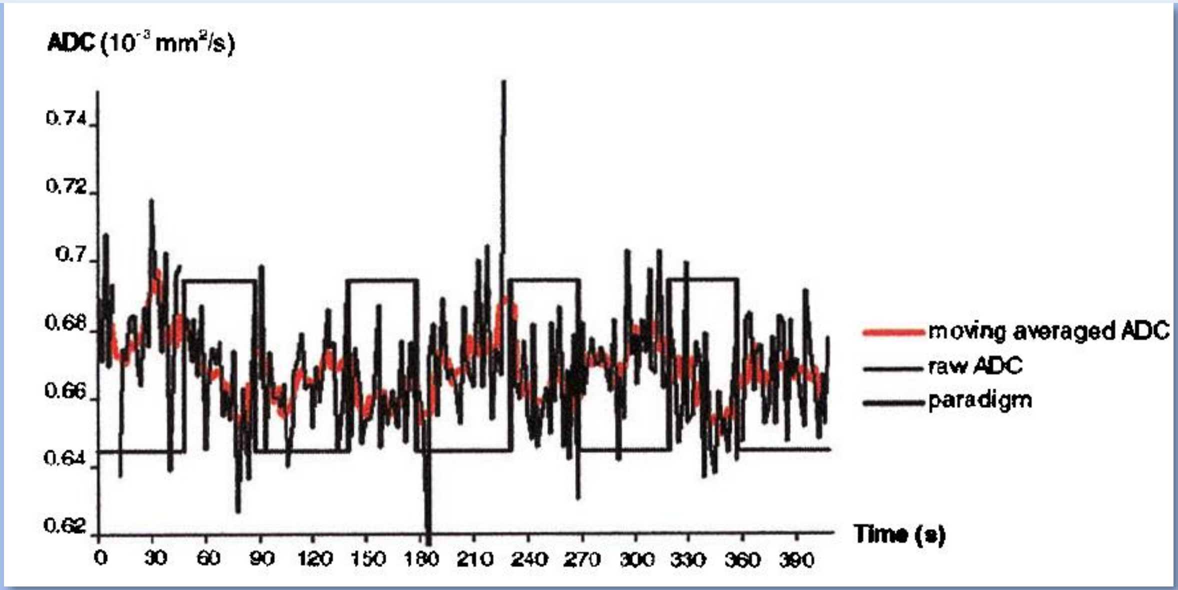


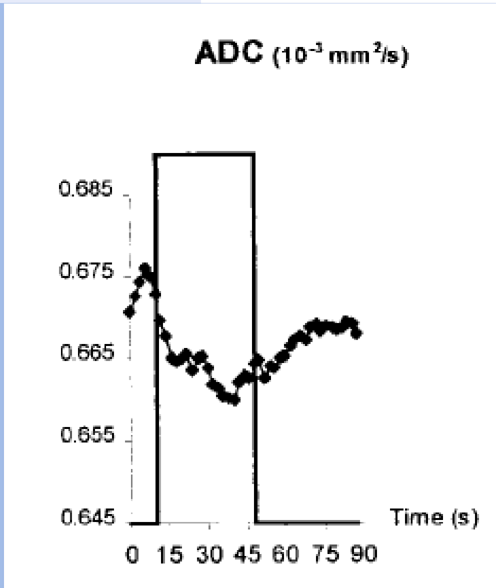
Federspiel, A. Wiest R., Jann K., Gralla J., Mattle H., Dierks T. @ 3T Magnetom Trio Bern

Indirect measure of Neuronal Activity

Metabolism	↑ Neuronal Activity ↑ CBF ↑ CBV ↑ $CMRO_2$ ↓ deoxyHb ↑ BOLD
EEG	Electrical signal (postsynaptic potentials) from a large number of neurons
mechanical ?	Cell swelling when Action Potential is generated

Diffusion fMRI

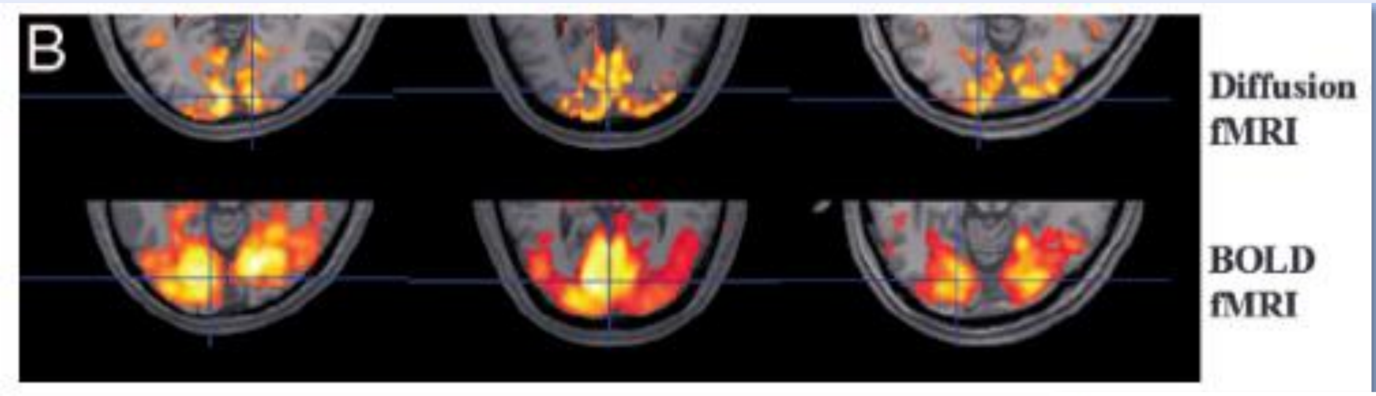




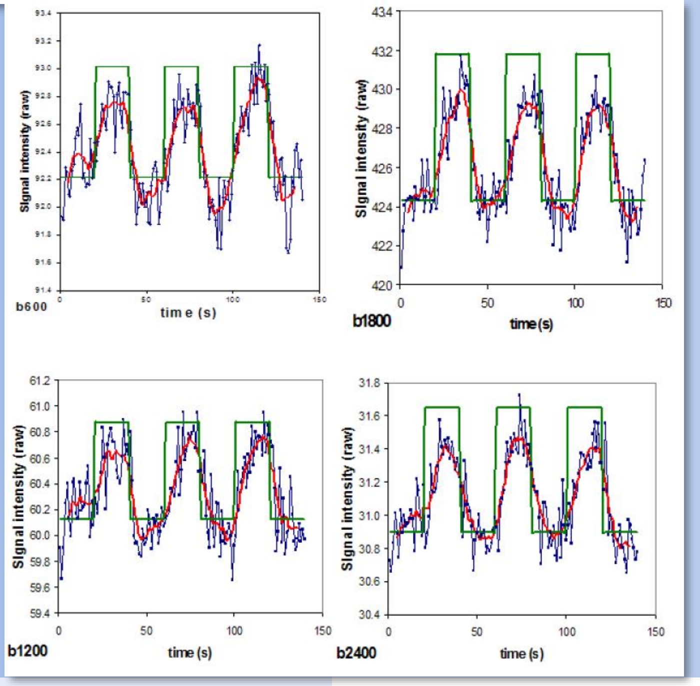
↓ ADC	**linked to transient swelling of cortical cells** **or** **transient microstructural changes of neurons or glial cells during activation**

Darquie A. et al. 2001 *PNAS.* 98(16):9391-5.

fDTI

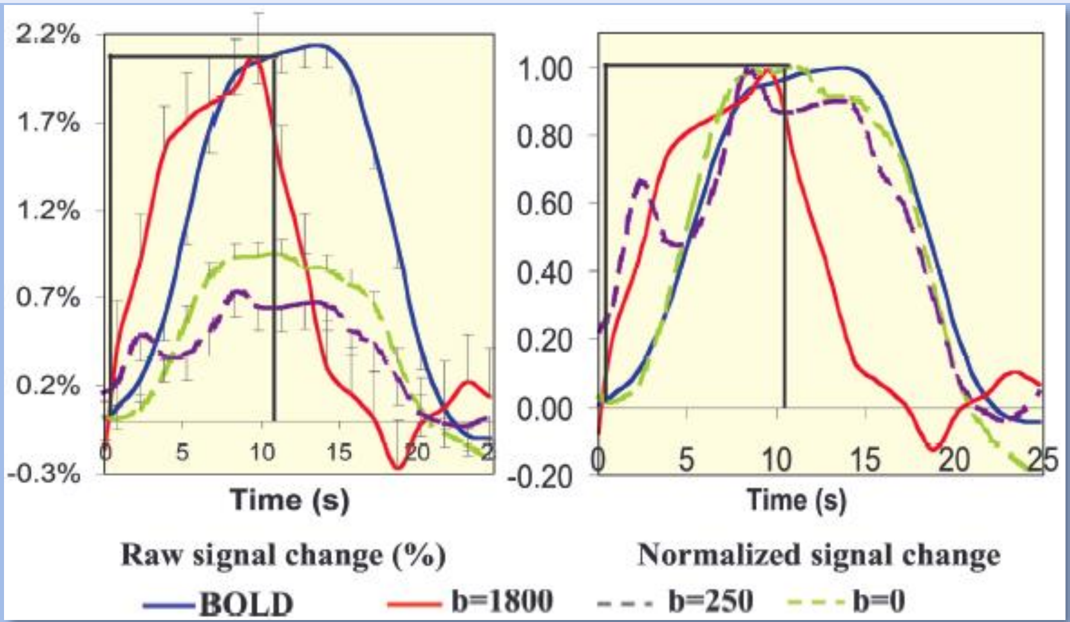


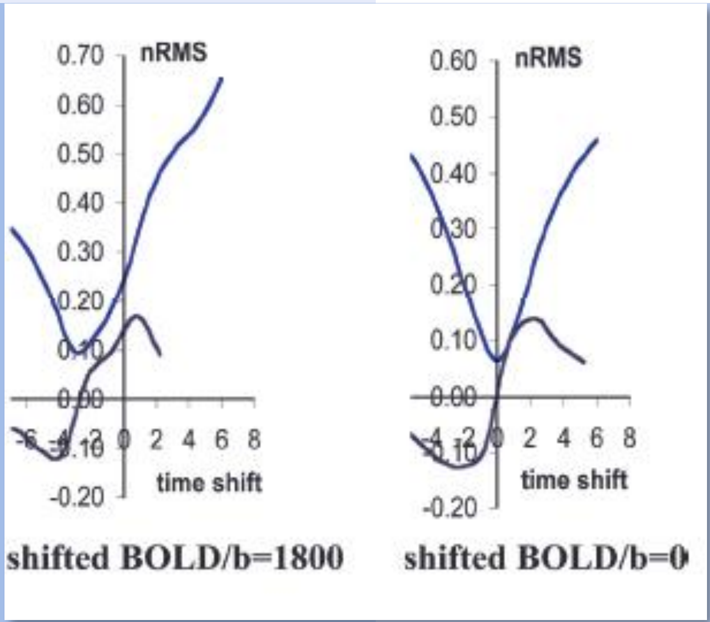
Comparison of BOLD and fDTI
SPM for b=1800 s/mm^2



Le Bihan D. et al. 2006 *PNAS.* 103(21):8263-8

fDTI and BOLD signal





BOLD = SDP expansion time course (b=0)

But for b>0

SDP expansion time course always ahead of BOLD

Conclusion

> BOLD signal is a complex function of baseline state and
changes in CBF, CBV; CMRO2

> May reflect differences in baseline vasculature or metabolic state

> Calibrated fMRI may be useful in presence of disease, medication, age...

> BOLD activations should be interpreted with caution, and do not
necessarily reflect differences in neuronal activation.

>Diffusion changes and BOLD changes refers to
different physiological events

>Observed signal changes originated by diffusion
The mechanism of diffusion is not vascular