How to Map Functional Connectivity Based on Synchronized $CMRO_2$ Fluctuations During the Resting State

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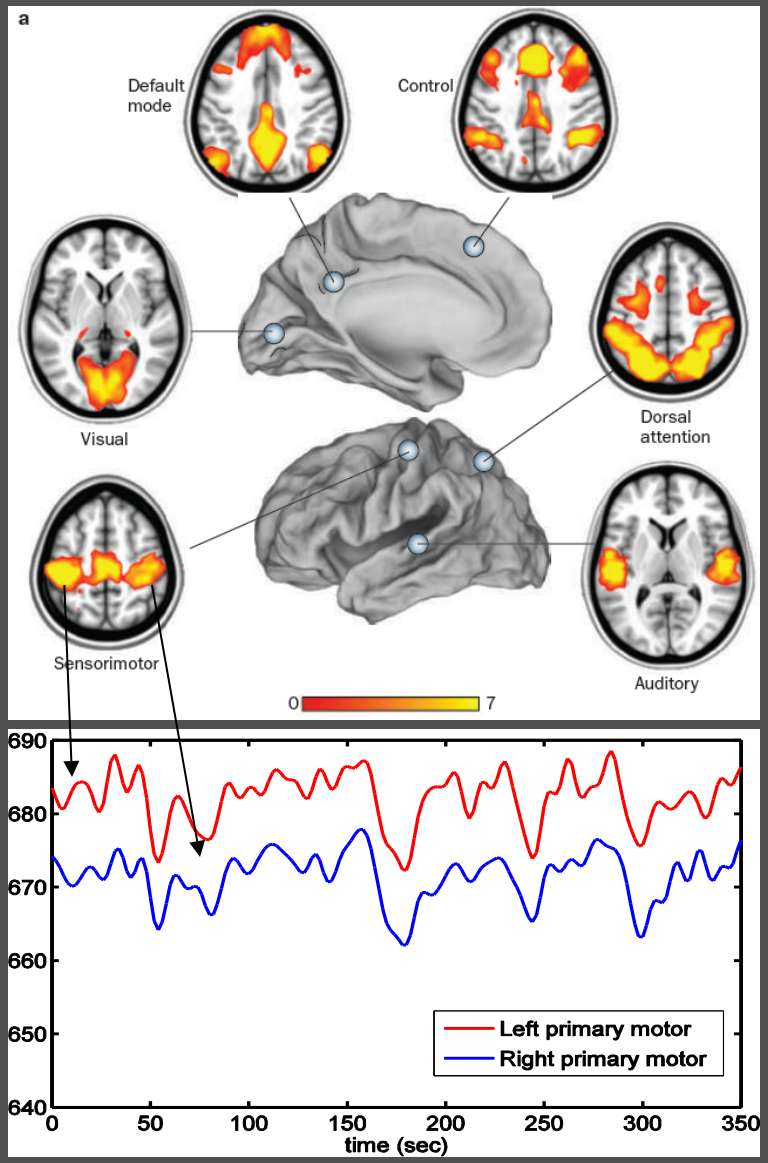
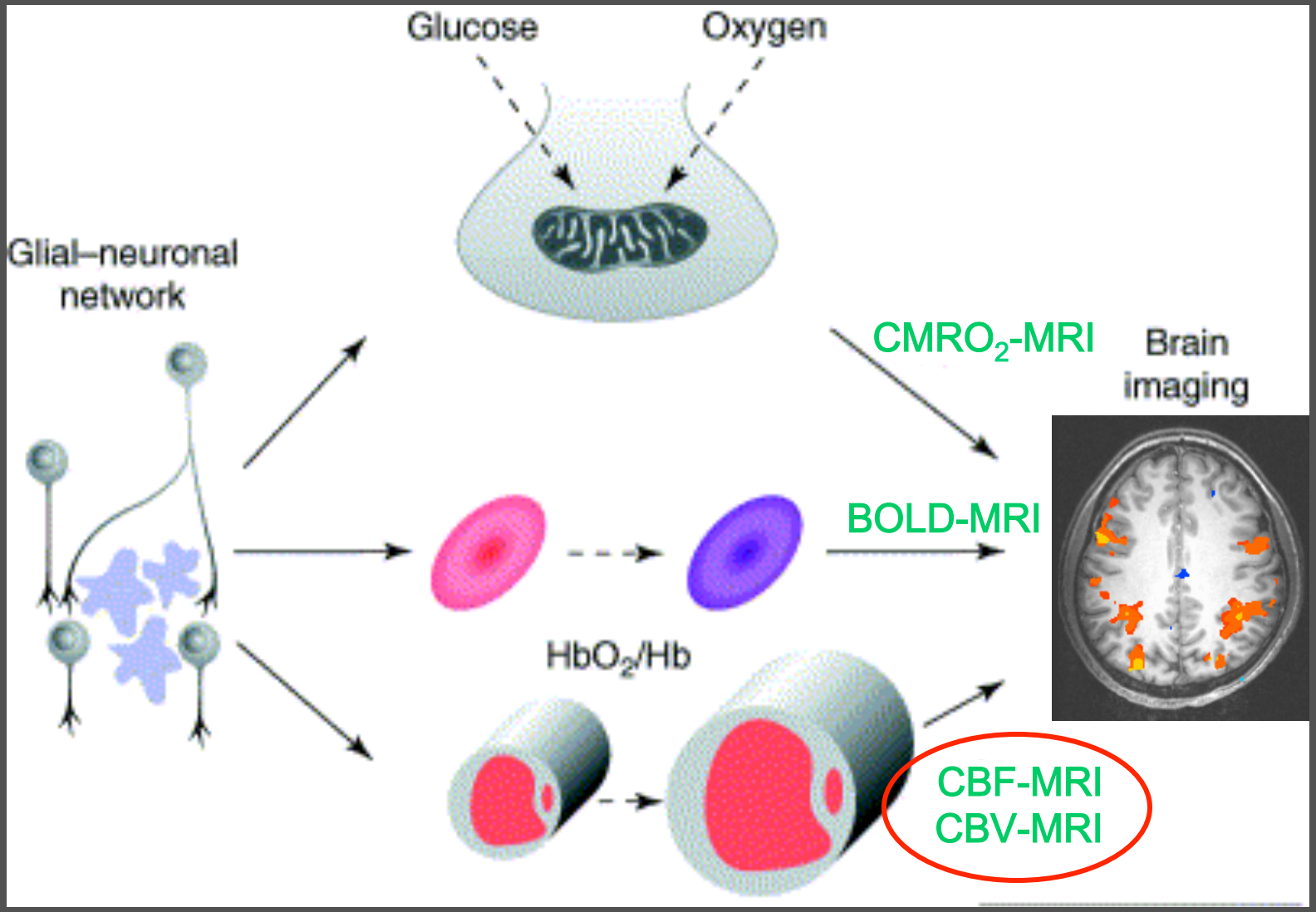
Resting-state functional connectivity

- Spontaneous fluctuations in resting-state fMRI are significantly correlated between brain regions in specific networks.
- These correlations are thought to reflect synchronized neuronal activity, and are called “functional connectivity” of brain regions.



Modified from Zhang & Raichle, Nat. Rev. Neurol, 2010

Neuronal activivity and fMRI detection

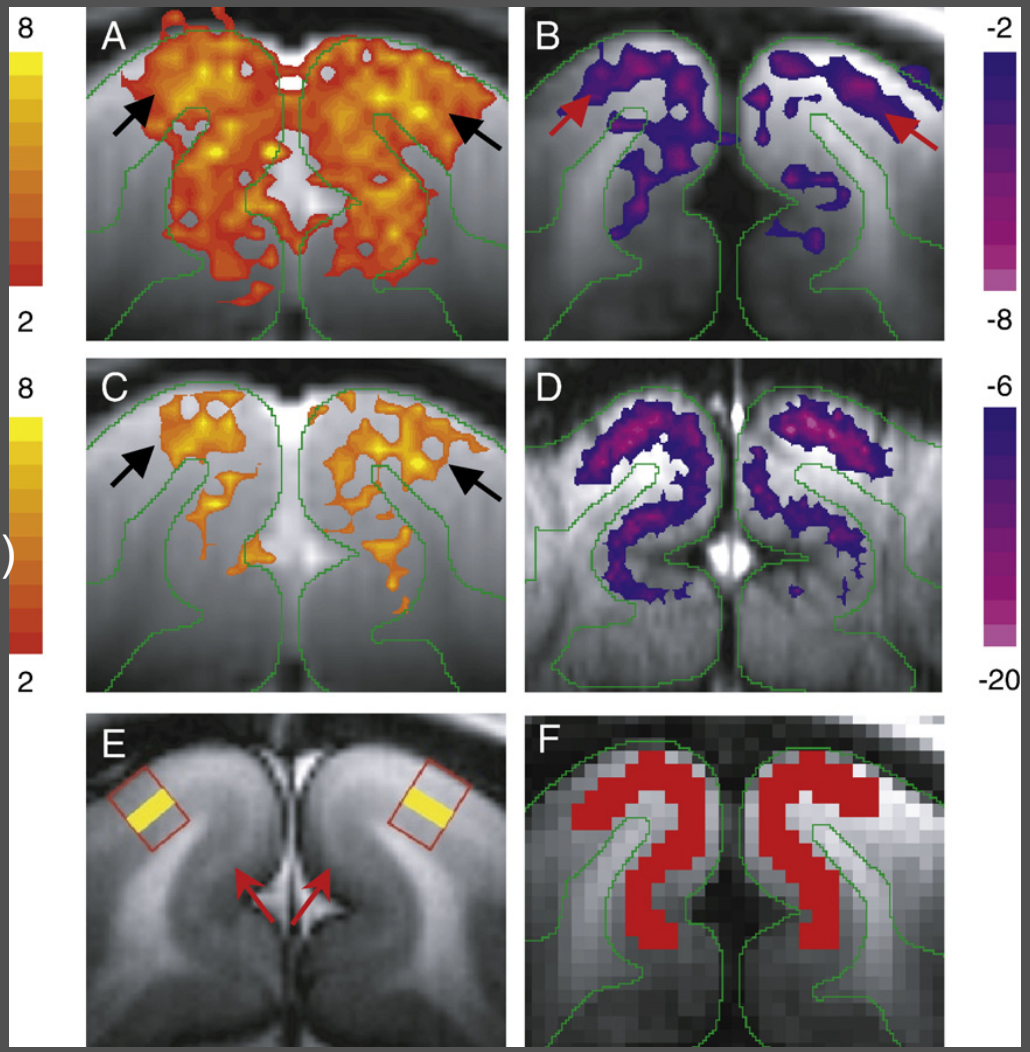


Modified from Bonvento, Sibson & Pellerin, Trends in Neurosciences, 2002

Localization of neuronal activity

SE-BOLD

SE-BOLD
(w/ higher thre.)

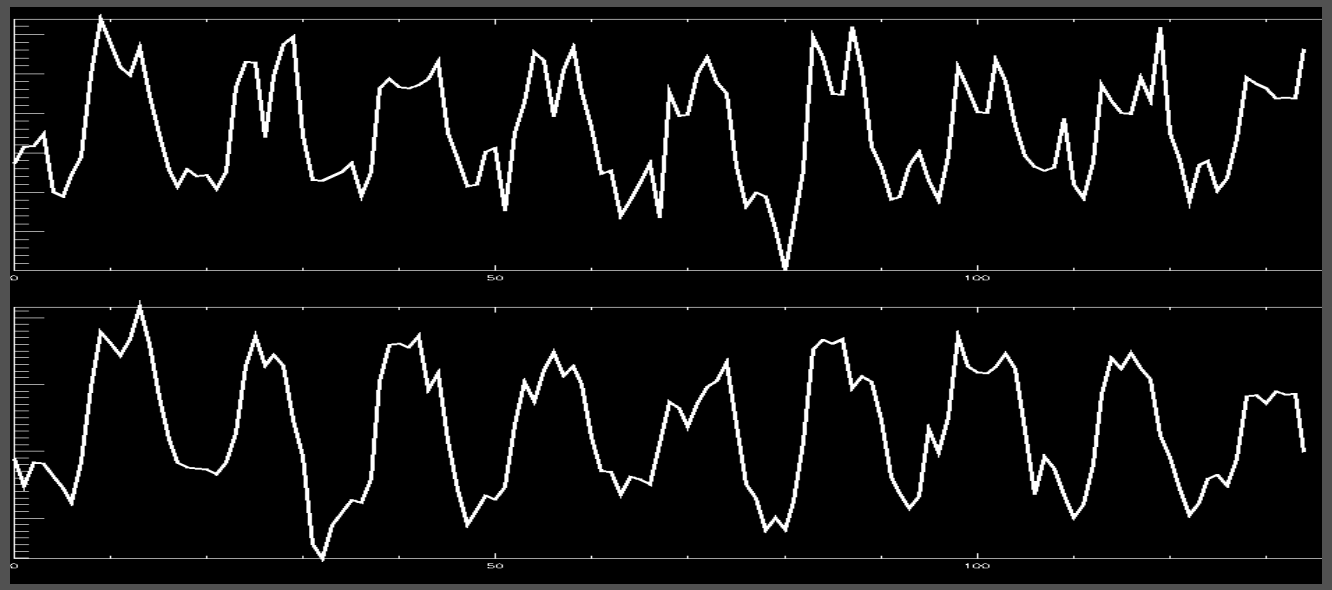


VASO-CBV

MION-CBV

Jin and Kim, NeuroImage, 2008

ph-fMRI using CBF and BOLD: Visual stim. during cocaine injection



Basal CBF	62.6±22.3*	56.9±19.1*	62.0±17.6	*p<0.02
CBF change during visual stimulation	49.4±18.8%	52.6±16.5%	47.4±19.7%	NS

BOLD, or not BOLD…

- BOLD has relatively high sensitivity in detecting oxygenation-related contrast, but limited specificity in localizing neuronal activity.

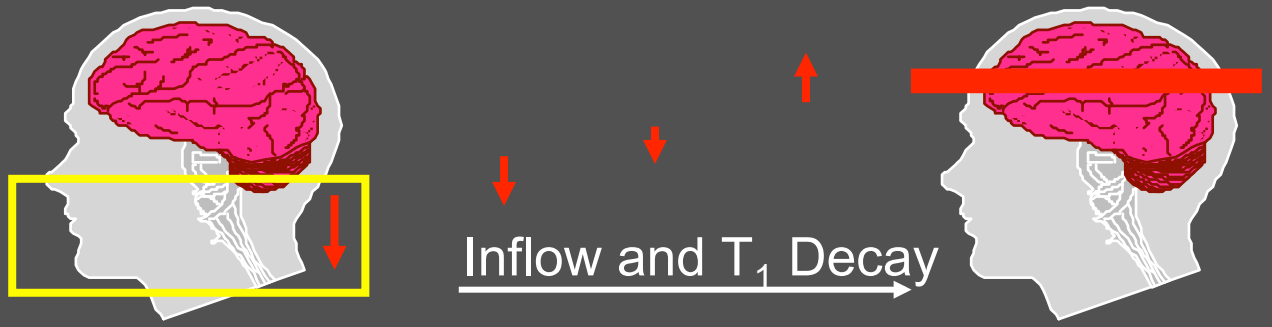
- CBF or CBV based fMRI techniques localize neuronal activity more accurately than BOLD, but have low sensitivity. Be cautious of baseline CBF/ CBV changes in pharmacological fMRI.

- $CMRO_2$ based fMRI techniques should have the best localization of neuronal activity, independent of hemodynamic changes. But its sensitivity might be the lowest.

Beyond-BOLD techniques to detect resting-state functional connectivity

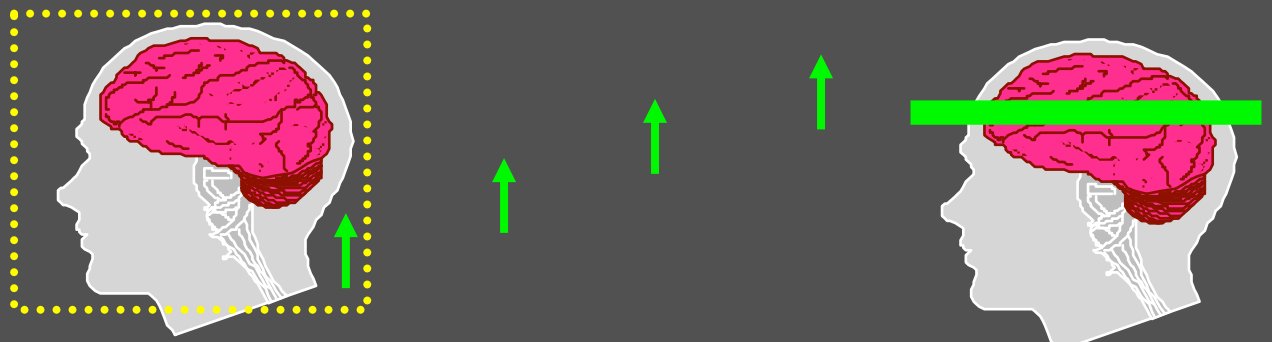
- CBF-based rs-fMRI
  - Arterial spin-labeling (ASL) imaging
- CBV-based rs-fMRI
  - Vascular space occupancy (VASO) imaging
- $CMRO_2$-based rs-fMRI
  - Calibrated fMRI

Arterial Spin Labeling



Label by magnetic inversion

Acquire image of tissue + labeled blood



Control

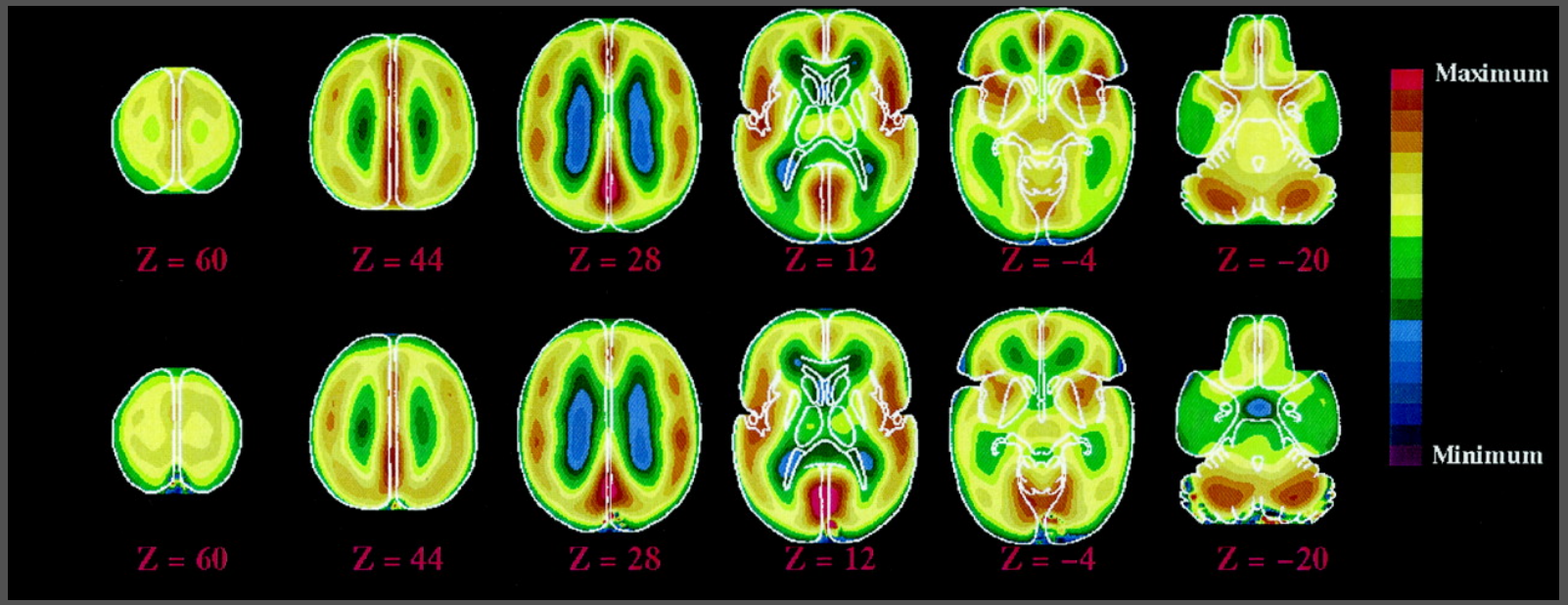
Acquire image of tissue + relaxed blood

Static characteristics of brain activity in the resting state

- PET study showed that a set of brain regions (PCC, MPFC, insula, and thalamus) exhibit higher CBF than the whole brain average at rest (default mode), and CBF in these regions decreases from its baseline level during goal-directed tasks.

CBF

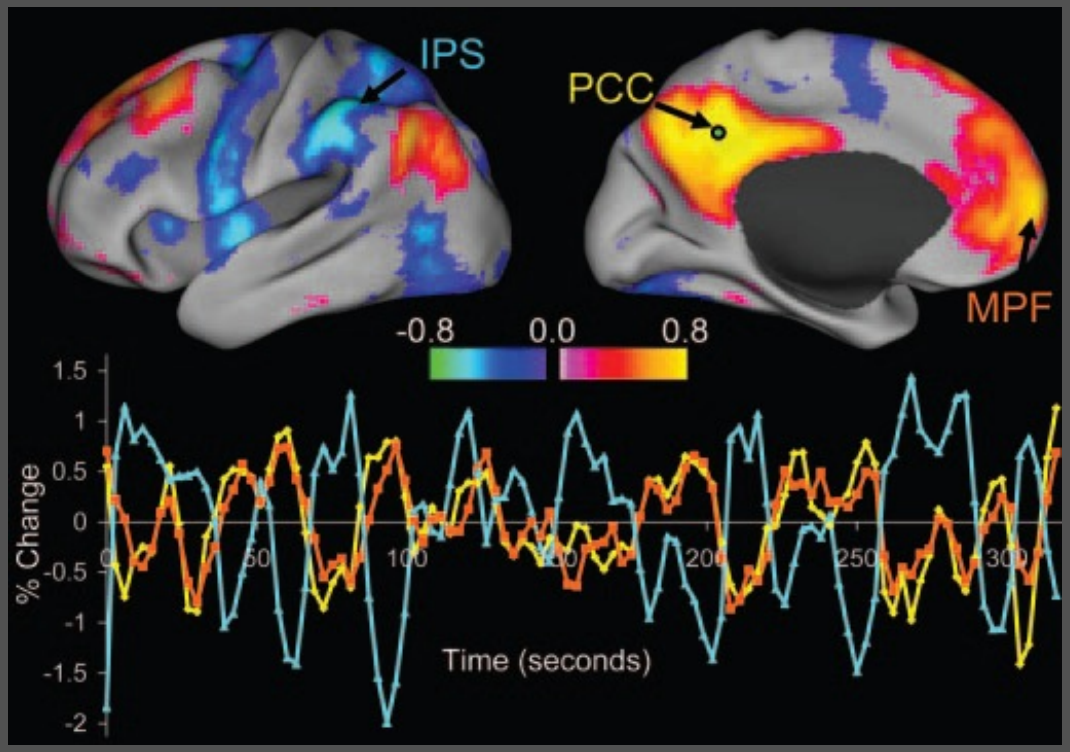
$CMRO_2$



Raichle et al., PNAS, 2001

Dynamic characteristics of brain activity in the resting state

- Dynamic interactions between brain regions have been revealed using resting-state BOLD.



Fox et al., PNAS, 2005.

Static and dynamic characteristics of brain activity in the resting state

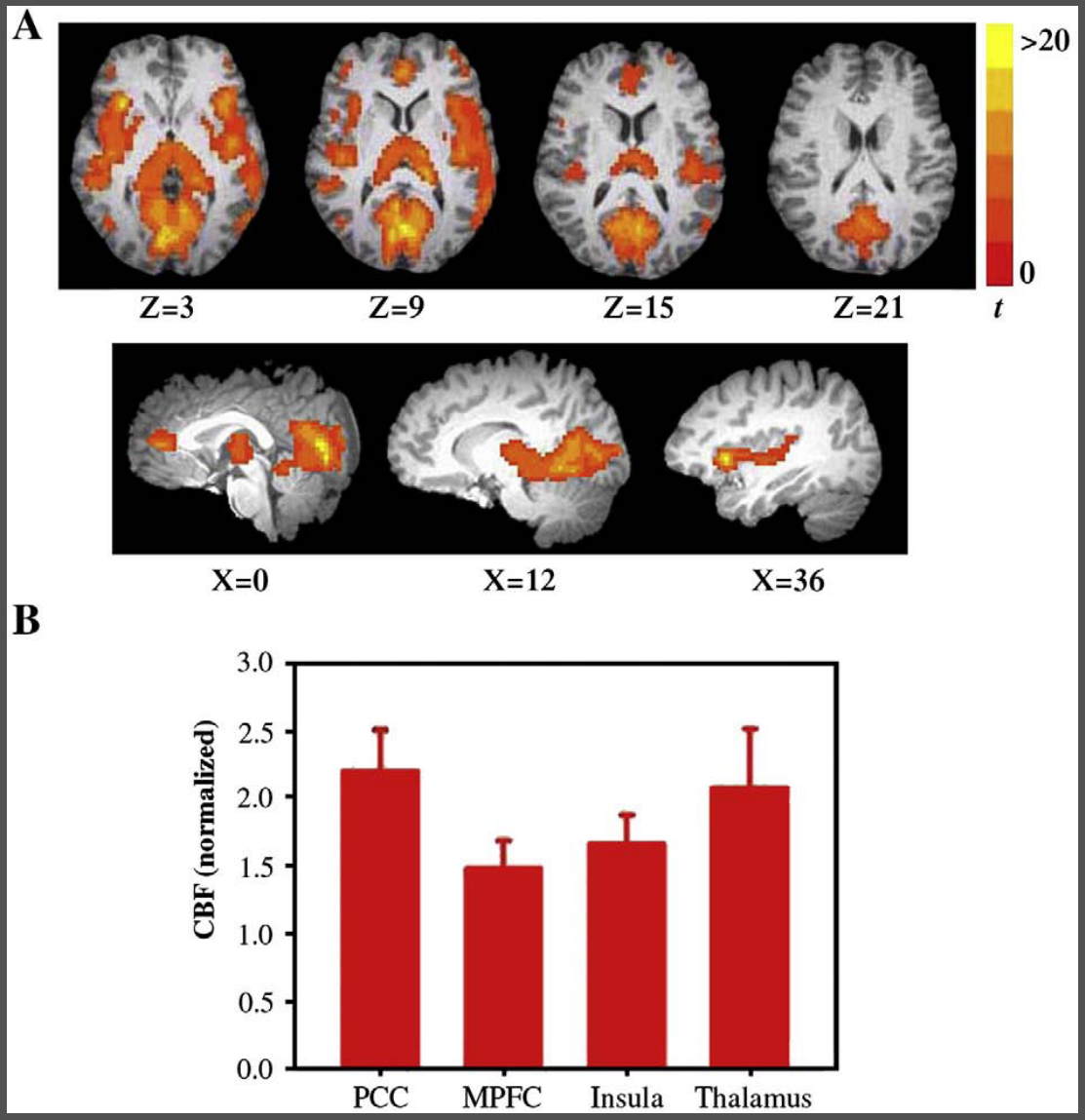
- CBF-based rs-fMRI have the potential to measure the static and dynamic characteristics of resting-state signals under a single modality within the same subjects.

Methodology for CBF-based resting-state fMRI

- **Data acquisition**
  - Pulsed arterial spin labeling (PASL) imaging.

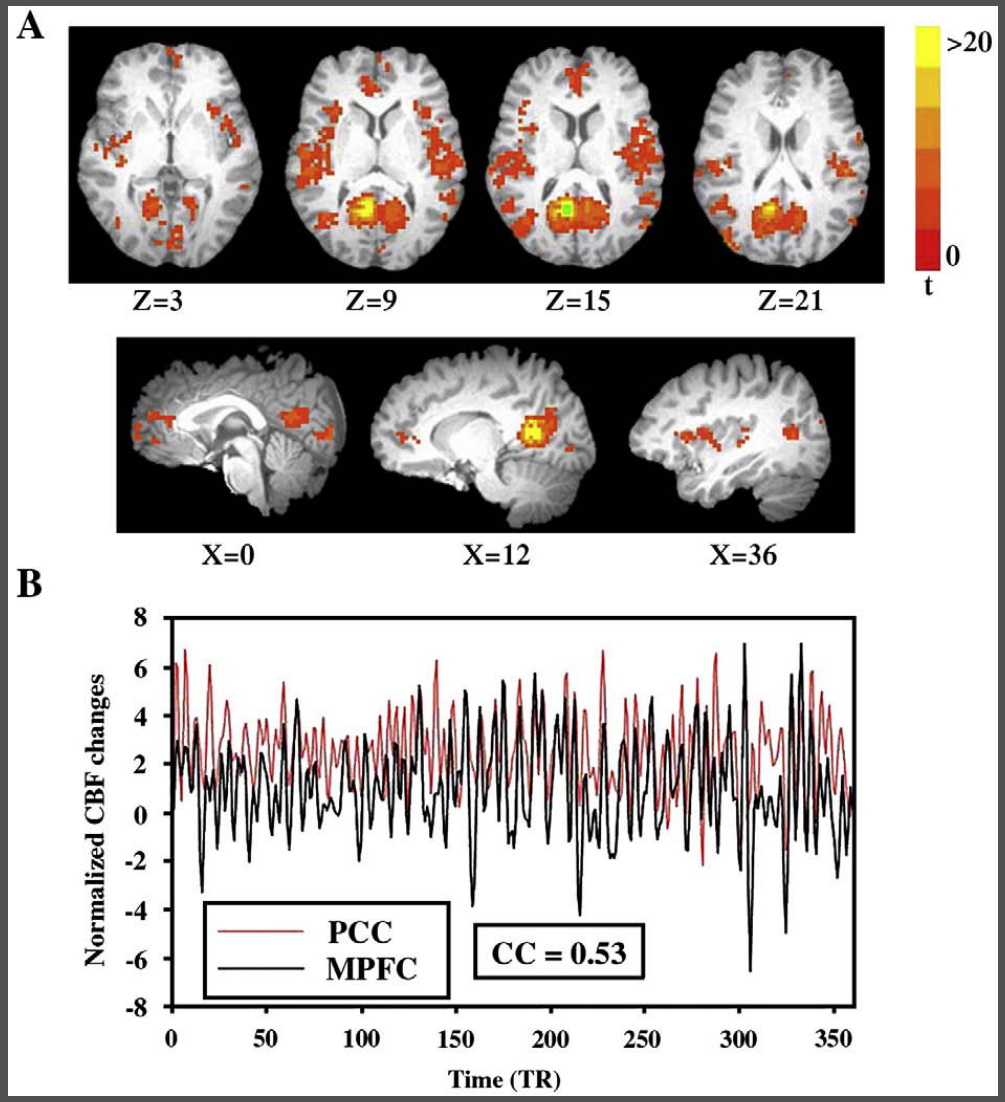
- **Data processing and analysis**
  - Removal of BOLD contribution in the ASL signal (Chuang et al., 2008).
  - Removal of physiological noise using ICA.
  - Seed-based cross correlation analysis (seed in PCC).

Static perfusion in the resting state



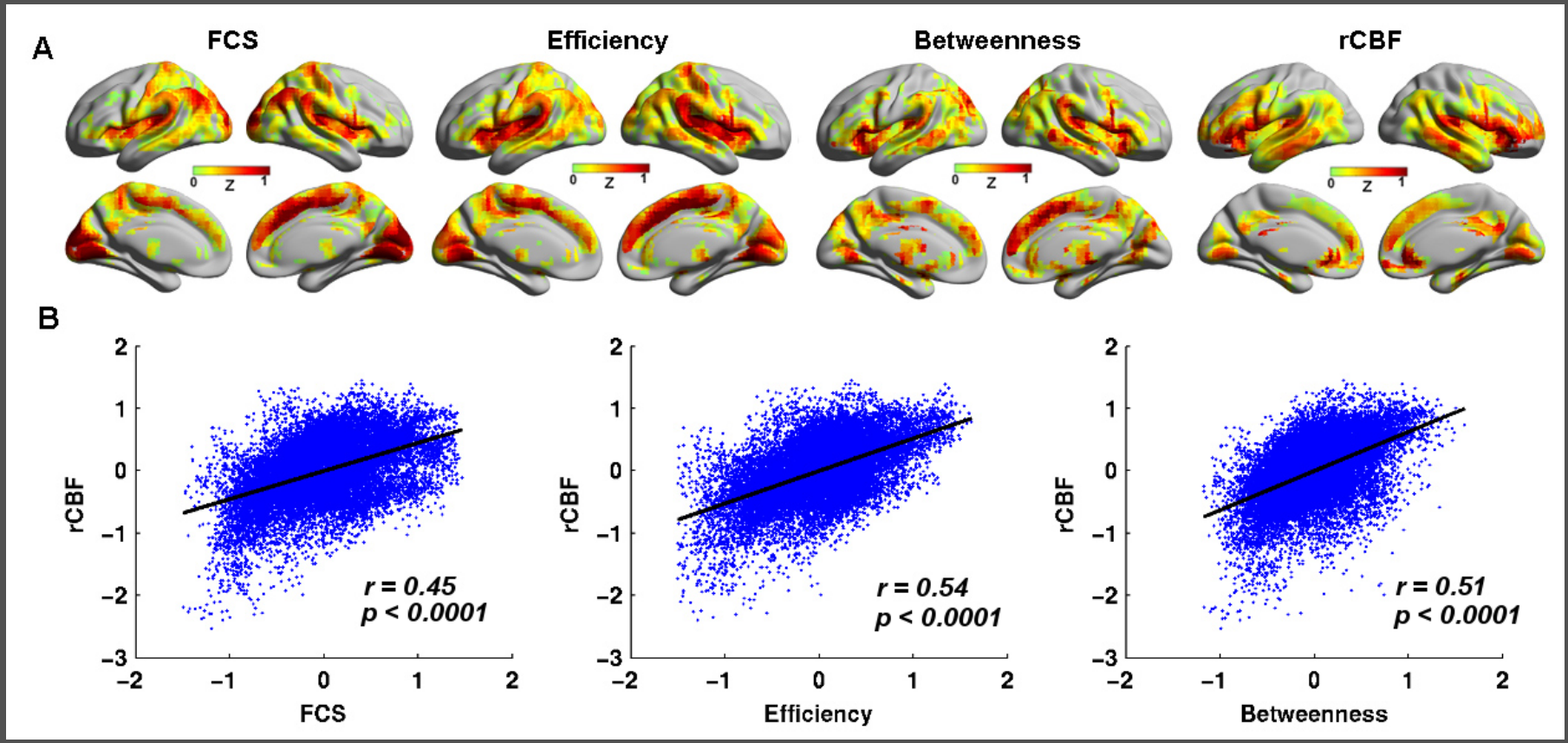
Zou et al., NeuroImage, 2009

Dynamic perfusion in the resting state - Functional connectivity



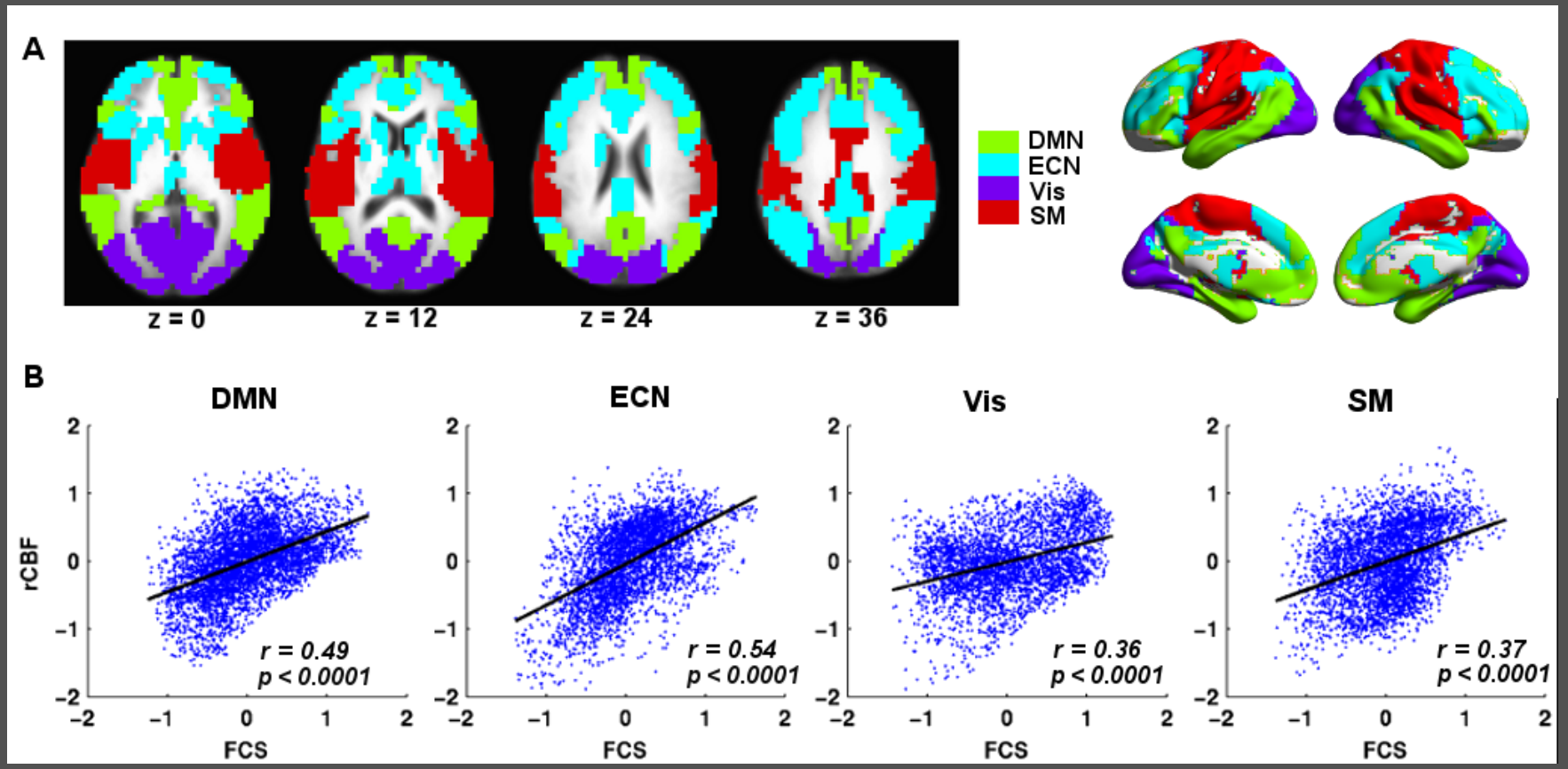
Zou et al., NeuroImage, 2009

Functional connectivity strength vs. CBF



Liang et al., PNAS, 2013

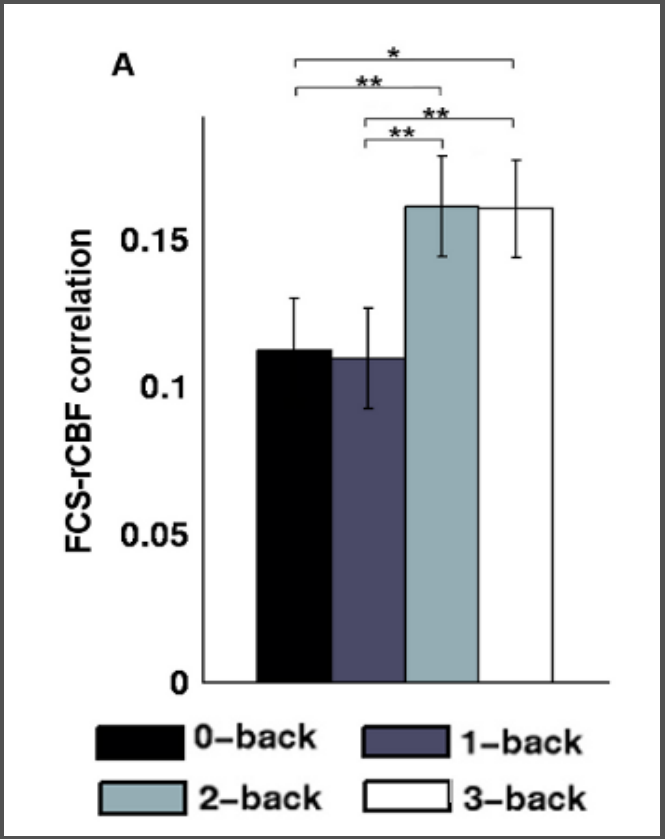
Functional connectivity strength vs. CBF in four brain networks



Liang et al., PNAS, 2013

N-back working memory task state

- FCS-rCBF relationship was strengthened at higher task load



Liang et al., PNAS, 2013

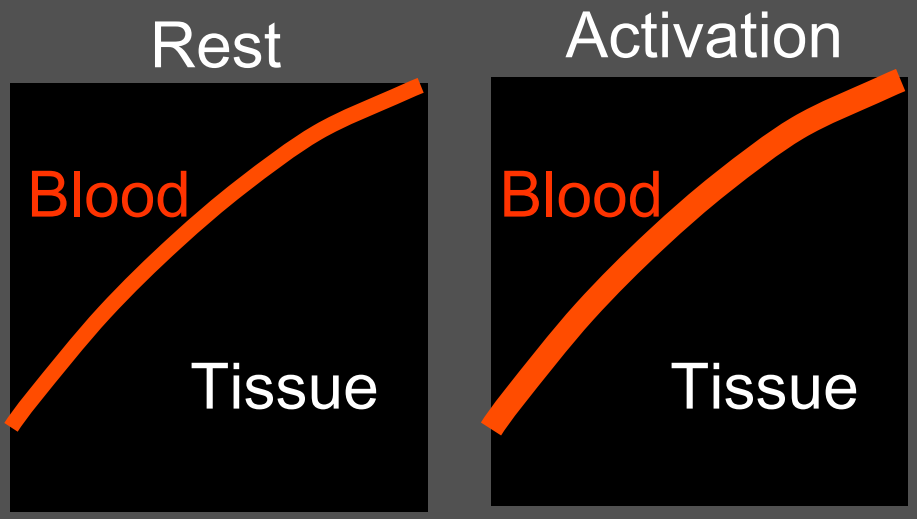
Summary of CBF-based rs-fMRI

- ASL can simultaneously assess the static and dynamic brain activity using the same imaging modality within the same subject.

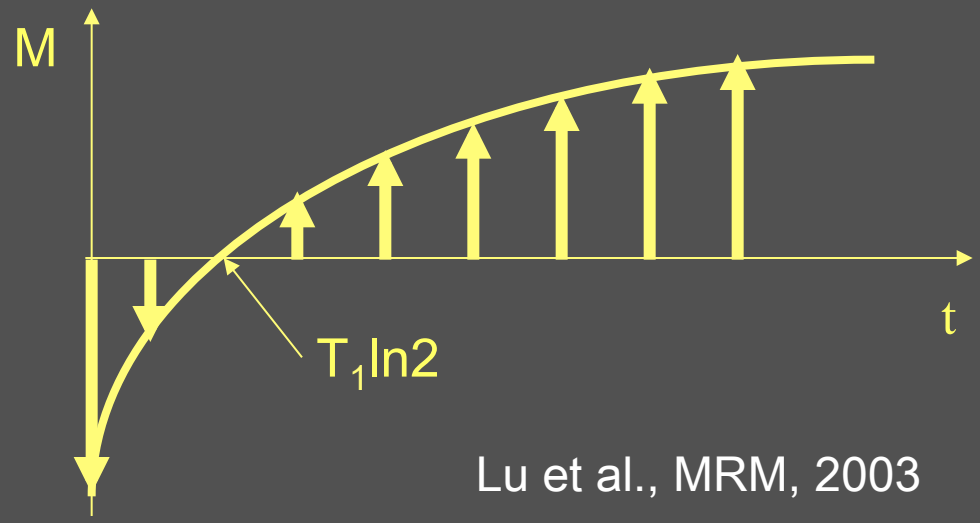
- Static CBF was significantly higher in PCC, MPFC, insula, and thalamus than the global brain average, consistent with previous PET observations. Dynamic analyses showed that these brain regions are highly correlated with PCC.

- Functional connectivity strength is closely coupled with regional CBF at rest and is modulated by cognitive load, suggesting a physiological basis of functional hubs in the brain.

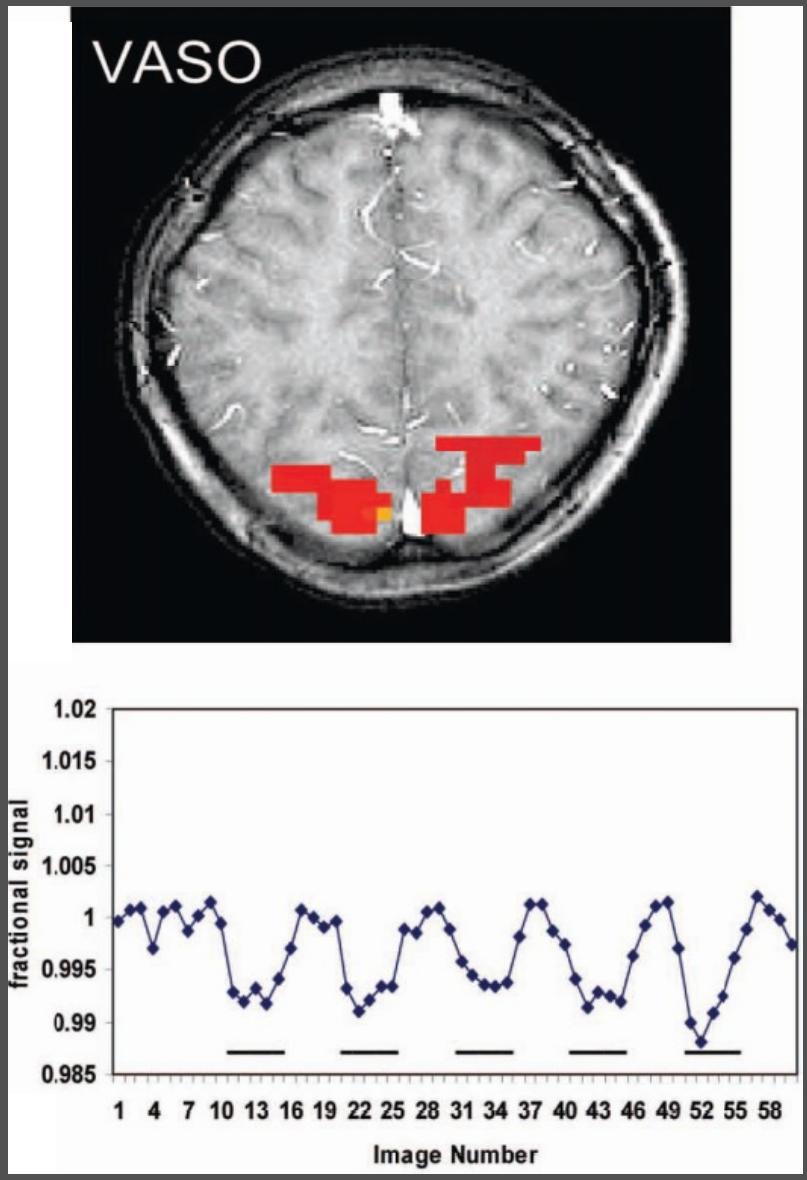
VASO – Vascular space occupancy



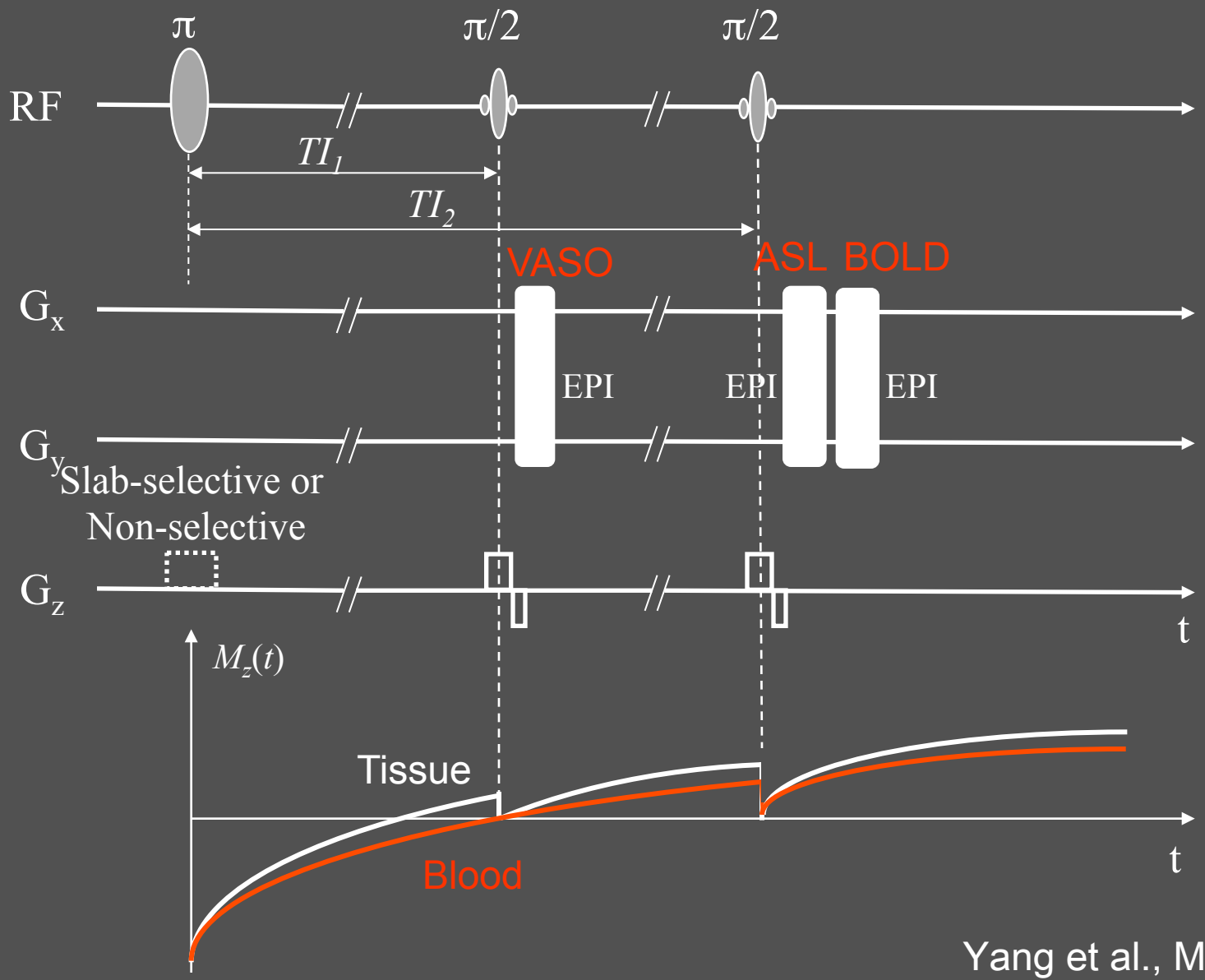
CBV change ~ 20-30%



Lu et al., MRM, 2003



Simultaneous VASO, ASL and BOLD

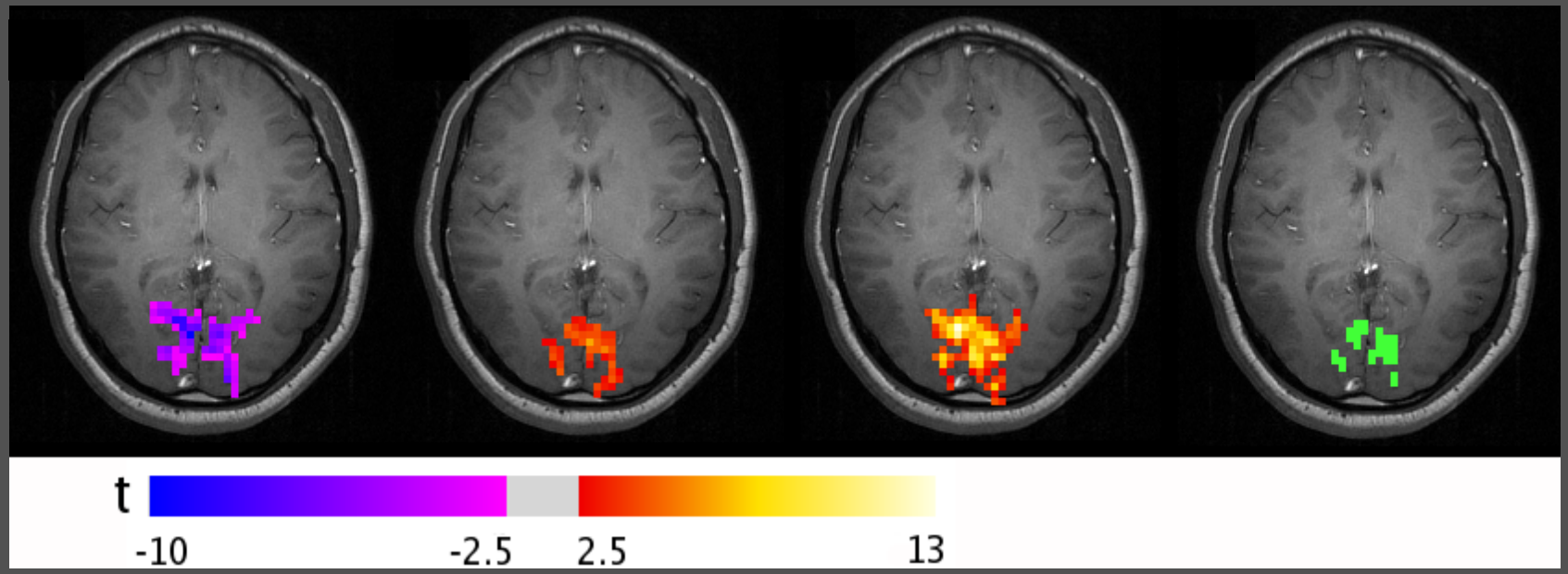


Yang et al., MRM, 2004

Simultaneous VASO, ASL and BOLD:

2 and 8 Hz Visual Stimulation

VASO ASL BOLD Common ROI

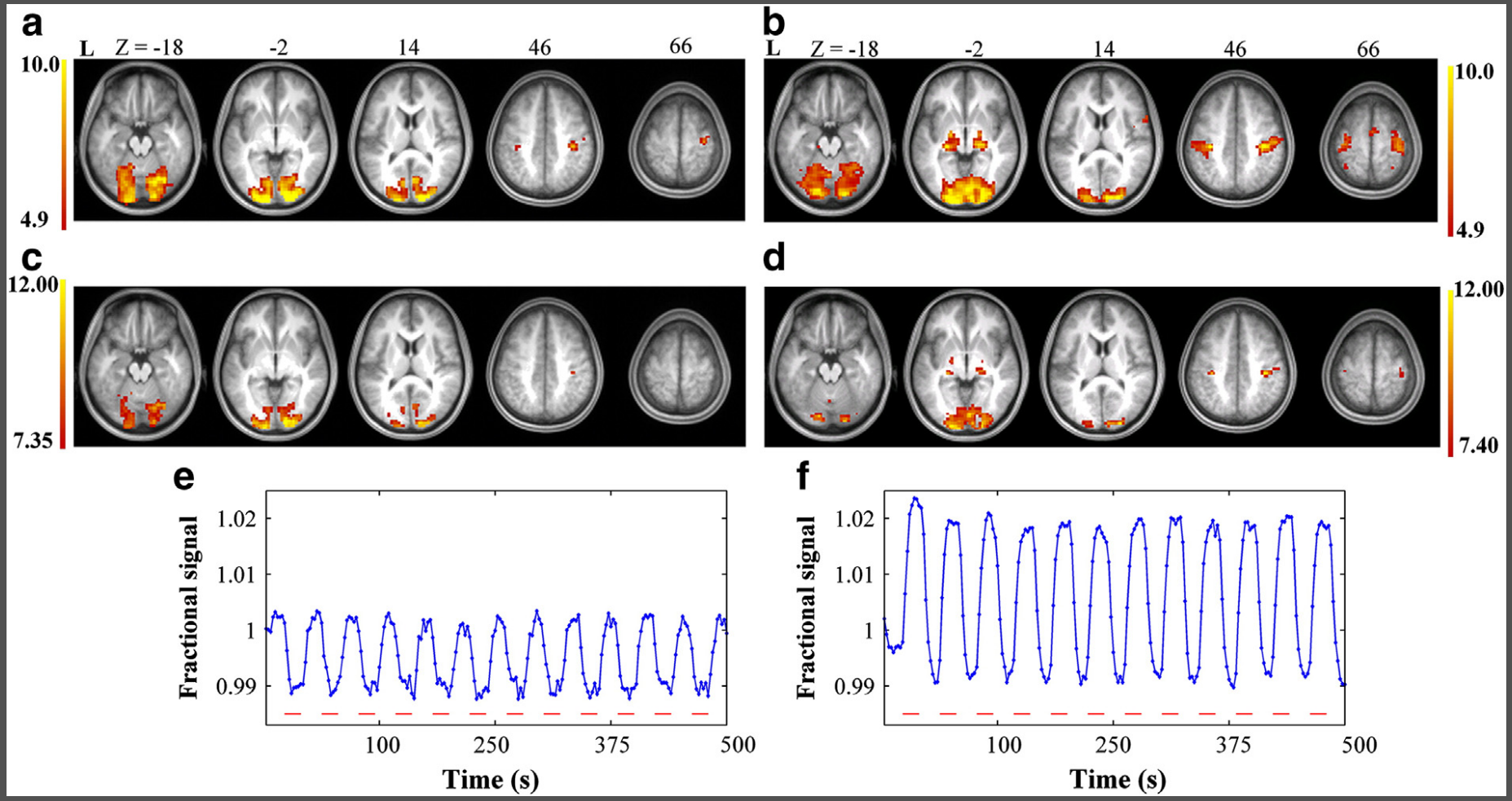


	VASO(%)	ASL (%)	BOLD	$CMRO_2$
2 Hz	-1.42±0.50	42.8±12.2	1.28±0.28	15.9±9.80
8 Hz	-2.48±0.40	68.2±13.0	1.94±0.56	21.4±12.2

CBV-based fMRI for detecting resting-state brain activity

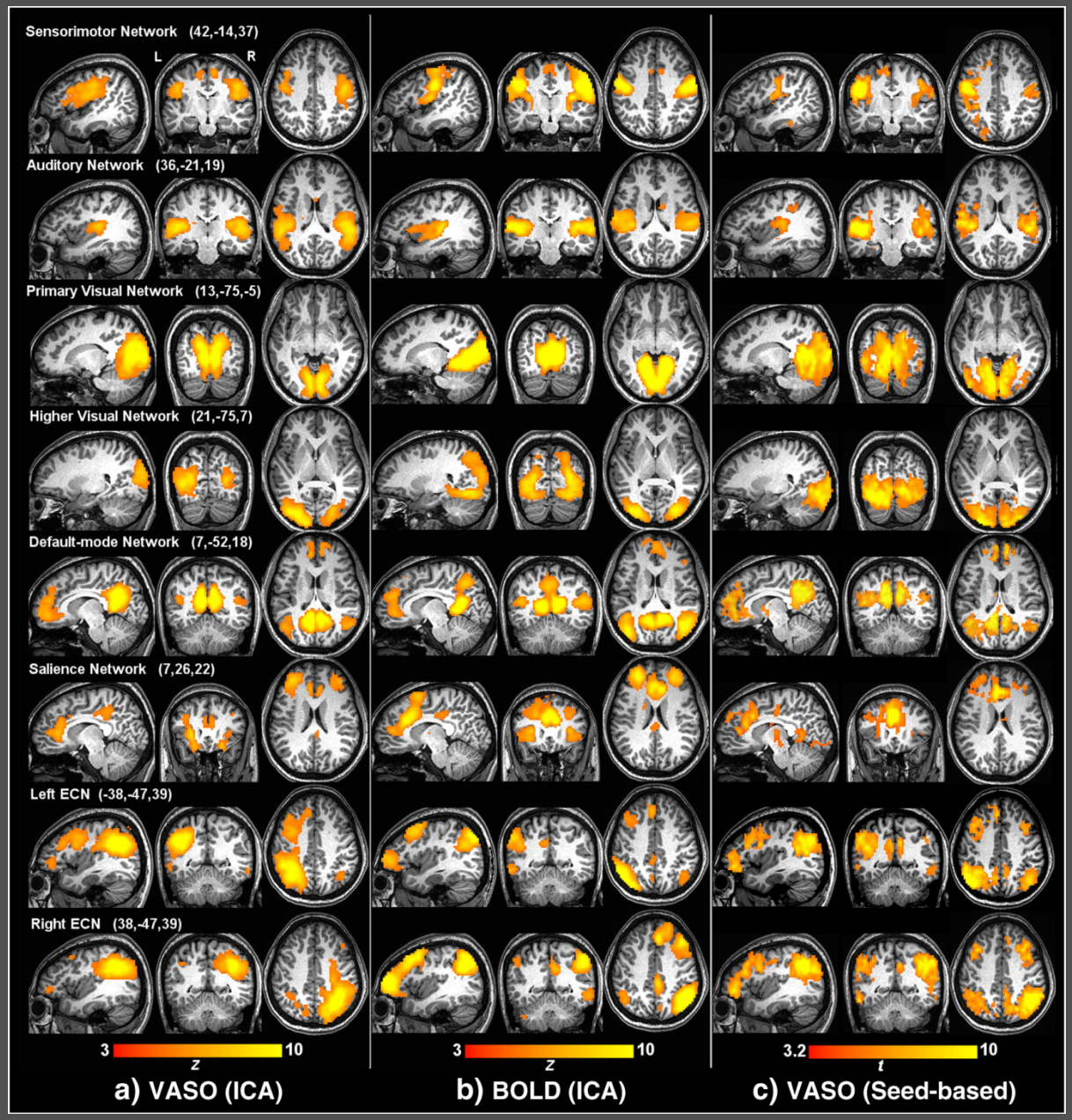
- Developed a 3D-VASO sequence covering the whole brain in a single shot.
- Evaluated the feasibility of the sequence in detecting resting-state brain activity.

VASO and BOLD in a visual-task fMRI

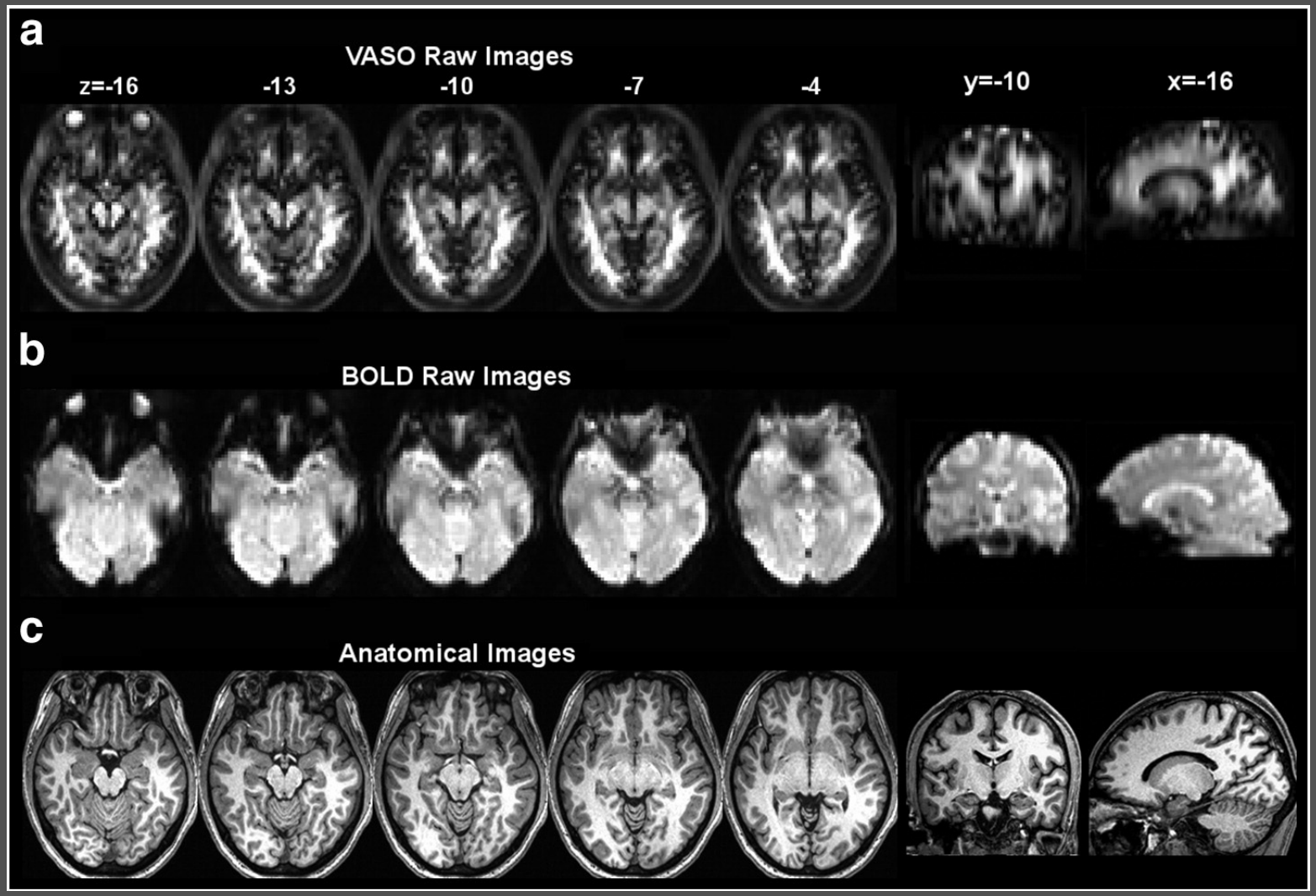


Miao et al., NeuroImage, 2014

VASO and BOLD in resting-state fMRI



Susceptibility artifacts in VASO and BOLD



Miao et al., NeuroImage, 2014

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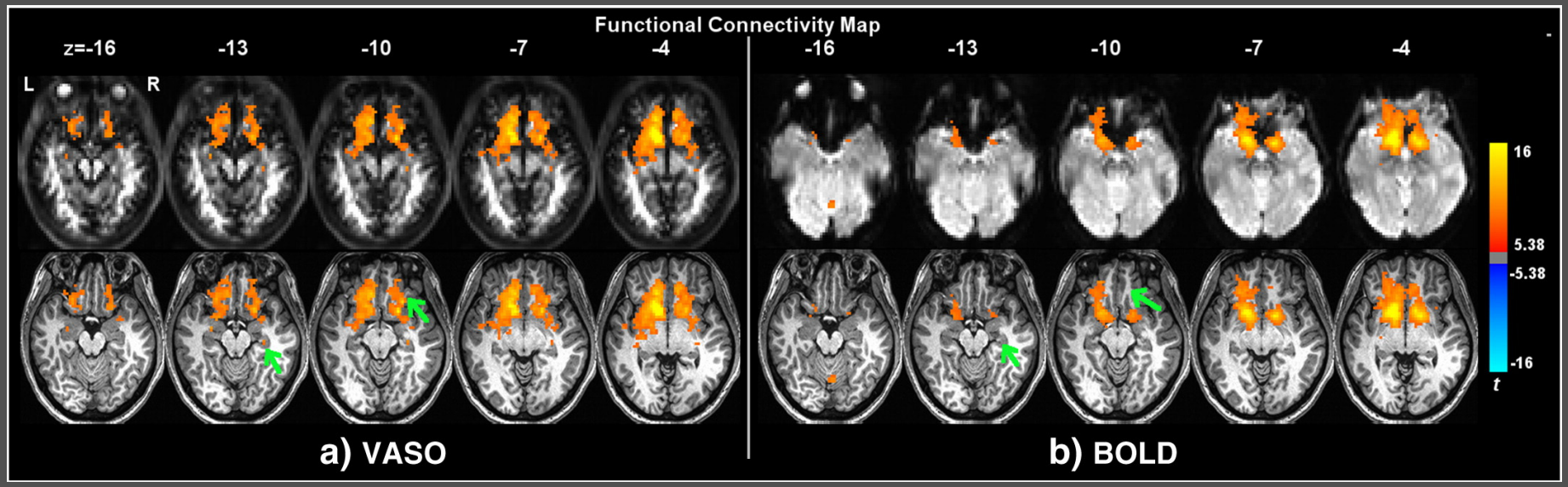
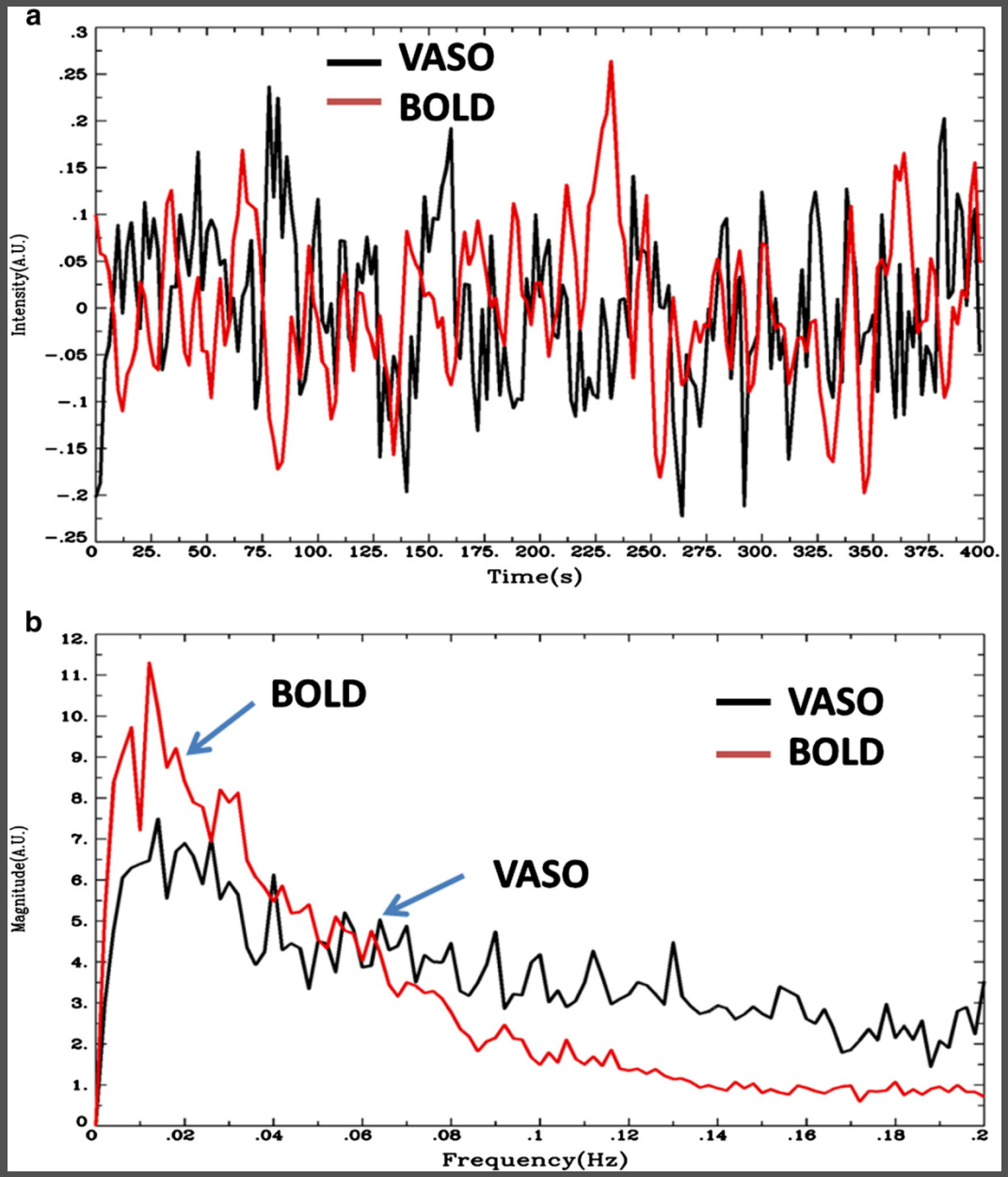


Miao et al., NeuroImage, 2014

Frequency specificity of VASO and BOLD



Summary of CBF-based rs-fMRI

- 3D-VASO imaging can measure resting-state brain activity in the whole brain.
- Intrinsic brain networks detected by the 3D-VASO imaging are very consistent with those by BOLD in the human brain. Improved localization of neuronal activity is expected with high resolution (≤ 1 mm).
- 3D-VASO imaging is less sensitive to susceptibility-induced artifects, and therefore will be useful in brain regions (such as OFC) that suffer from signal loss in BOLD.

Motivations for metabolism-based resting-state fMRI

- The underlying mechanism of rs-fMRI has not been fully understood yet.
- Physiological noise (cardiac and respiratory) and non-neuronal hemodynamic oscillations are potential confounds in rs-fMRI signal.
- Metabolism fluctuations (e.g. $CMRO_2$) are closely related to neuronal activities, but independent to physiological and hemodynamic changes.

Metabolism-based resting-state fMRI

- Simultaneous acquisition of BOLD and ASL signals (dual-echo acquisition).

- Determination of $CMRO_2$ from the BOLD and perfusion signals, based on a biophysical model.

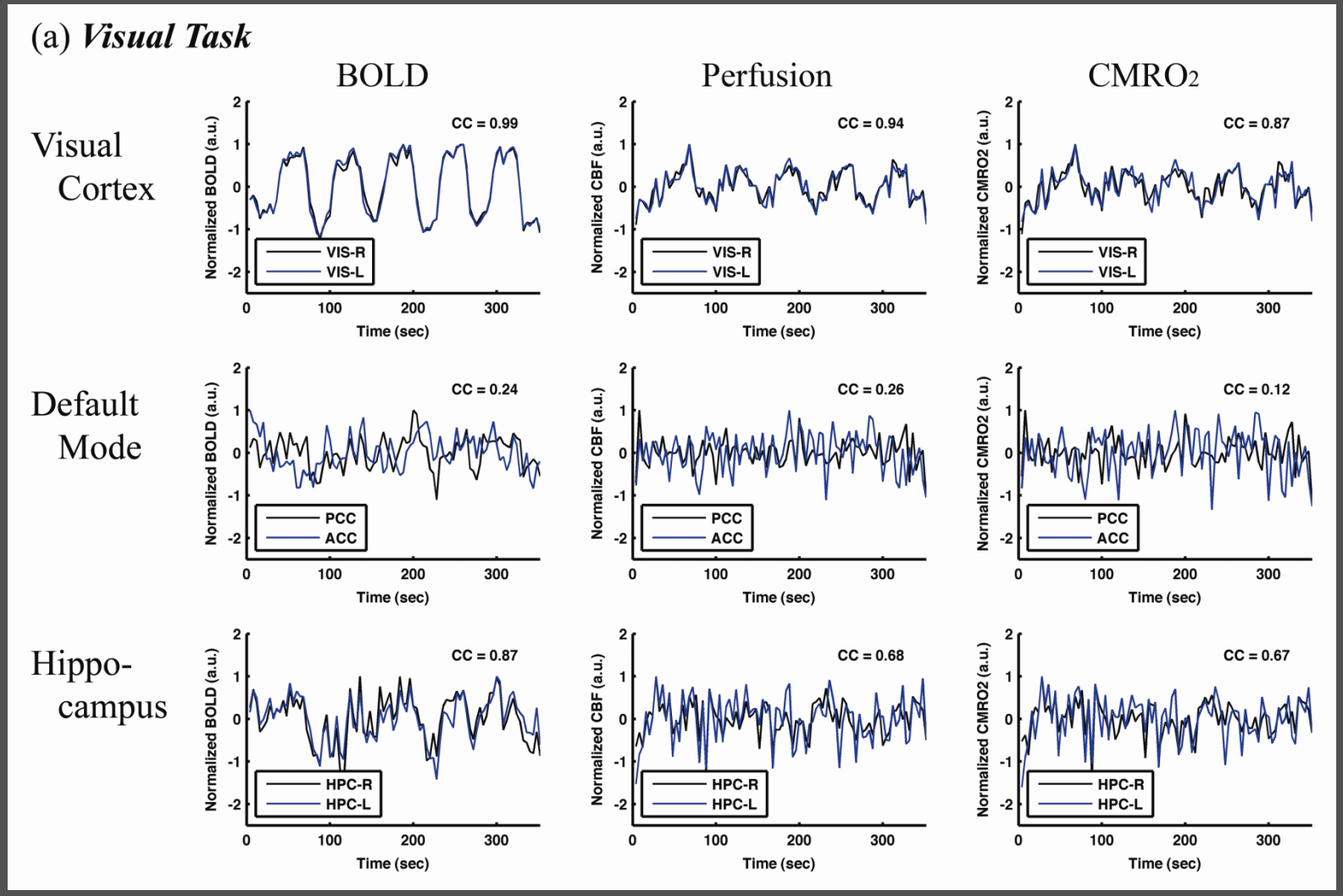
$$S_{CMRO_2} = (1 - \frac{S_{BOLD\%}}{M})^{1/\beta} (S_{CBF})^{1-\alpha/\beta}$$

M, α and β are constants, which can be determined from experiments or literature.

- **Data analysis**

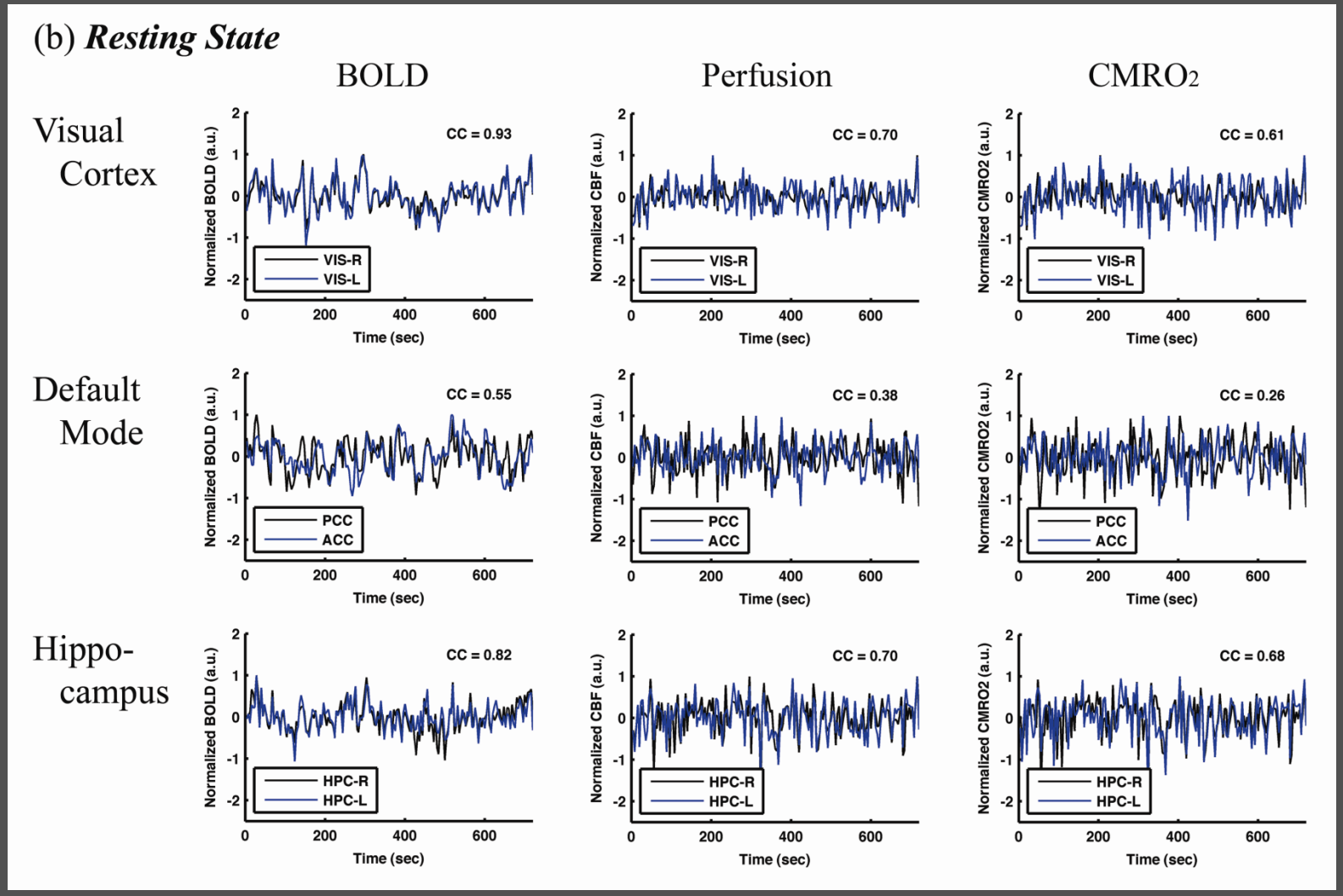
➢ Seed-based cross correlation analysis (Seeds in PCC, visual, and hippocampus).

Time courses of BOLD, perfusion, and $CMRO_2$ – Visual stimulation



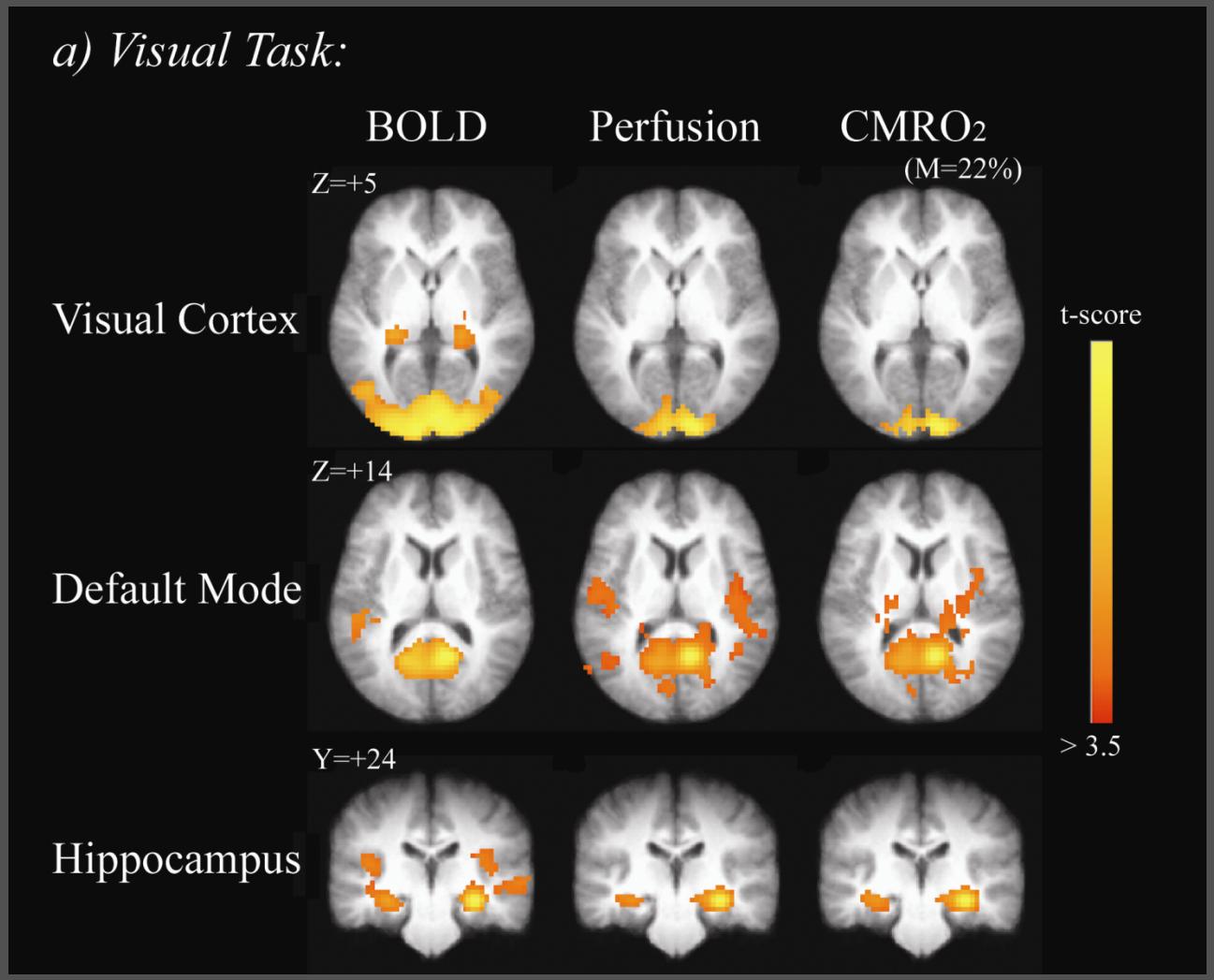
Wu et al., NeuroImage, 2009

Time courses of BOLD, perfusion, and $CMRO_2$ – Resting state



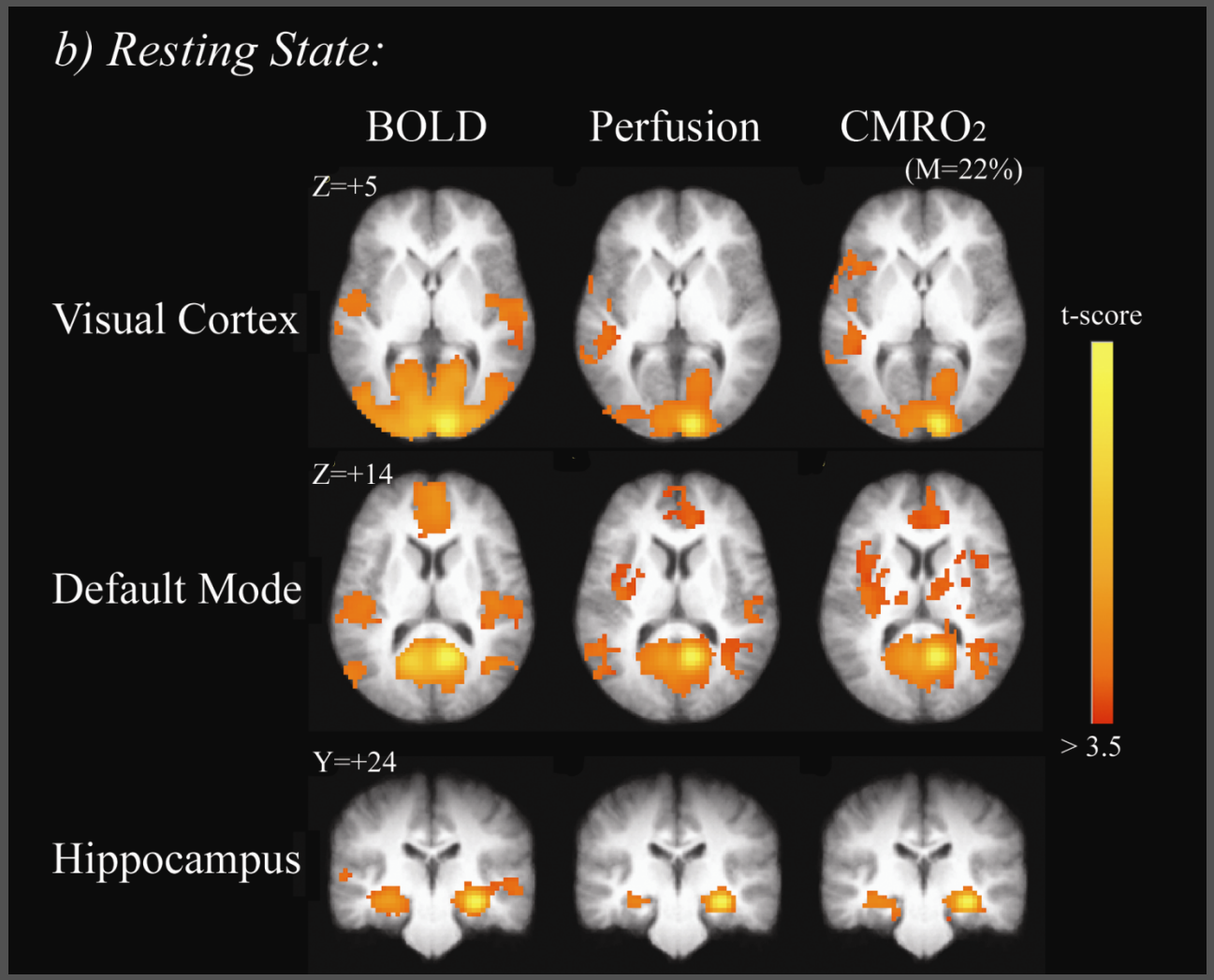
Wu et al., NeuroImage, 2009

Connectivity maps of BOLD, perfusion, and $CMRO_2$ – Visual stimulation



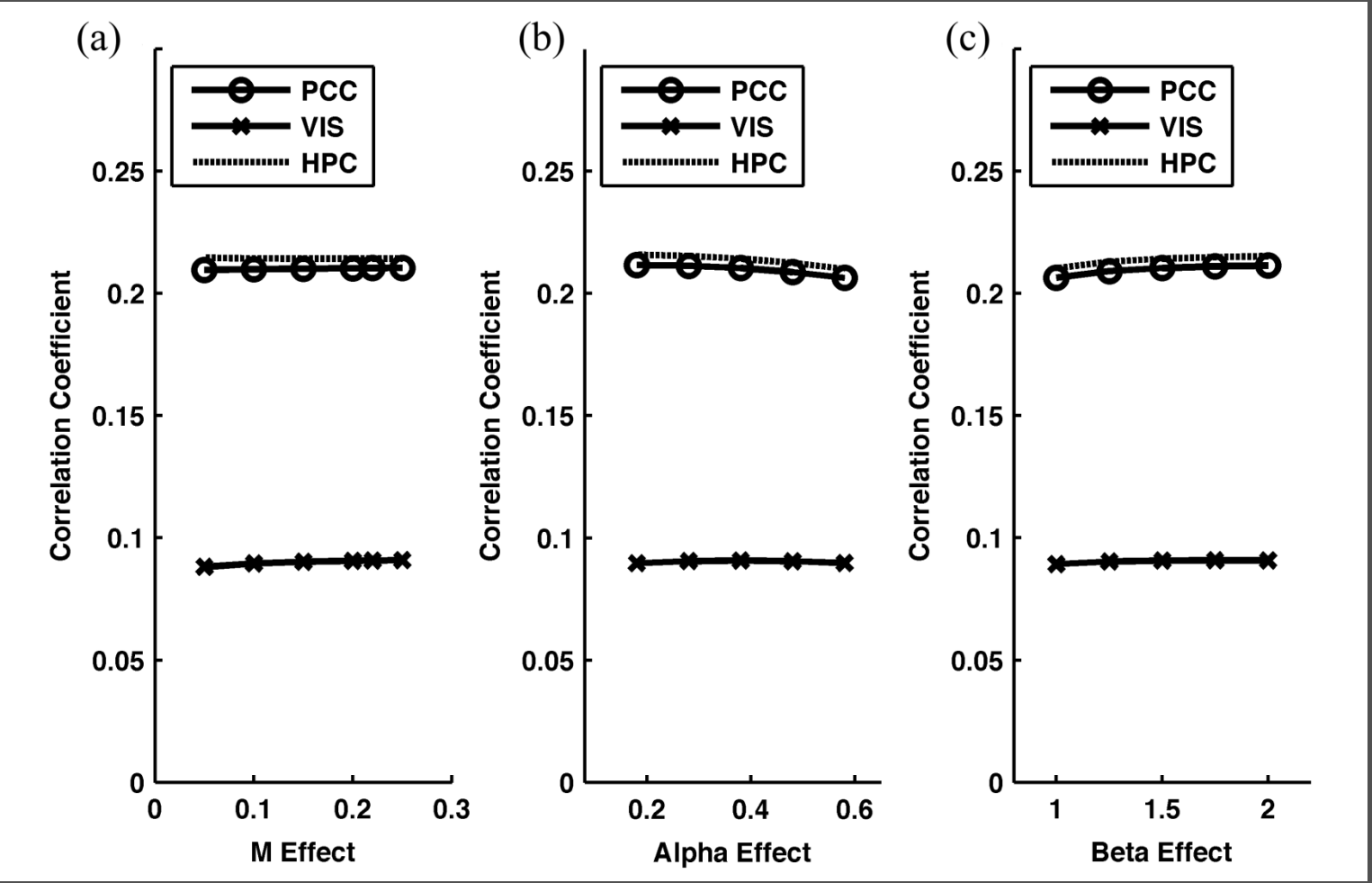
Wu et al., NeuroImage, 2009

Connectivity maps of BOLD, perfusion, and $CMRO_2$ – Resting state



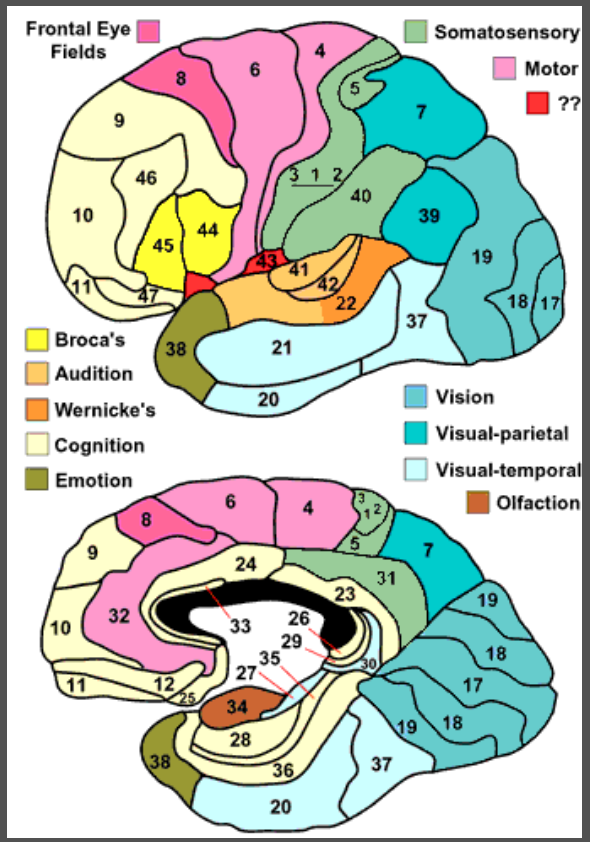
Wu et al., NeuroImage, 2009

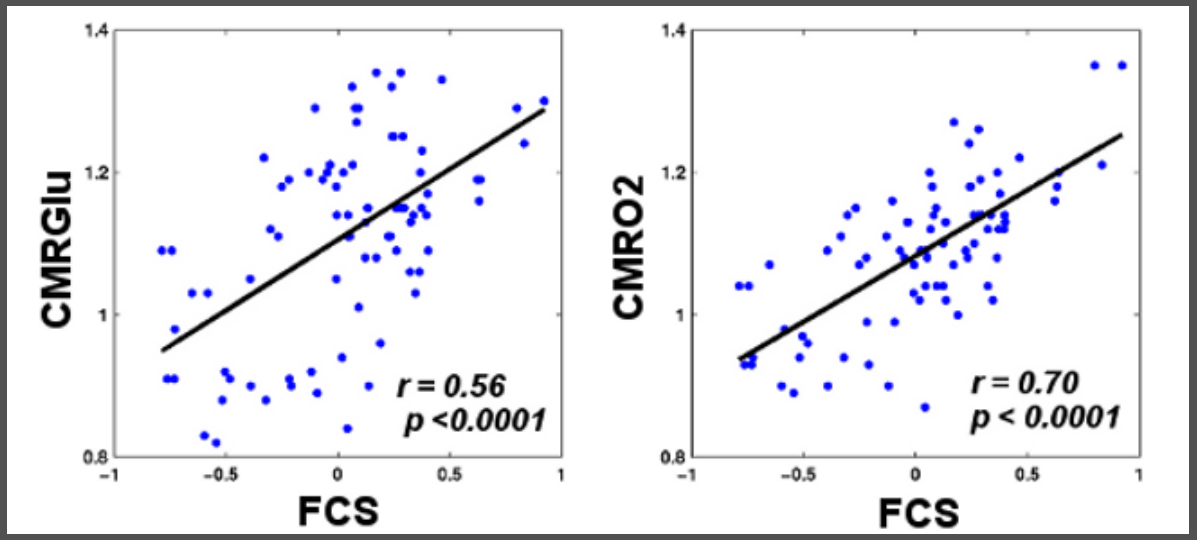
Sensitivity to the parameters in the biophysical model



Wu et al., NeuroImage, 2009

Functional connectivity strength vs. metabolism across Brodmann areas





Liang et al., PNAS, 2013

Summary of Metabolism-Based rs-fMRI

- Functional connectivity of the brain can be detected not only from BOLD and perfusion, but also $CMRO_2$.
- This observation provides direct evidence supporting the hypothesis that spontaneous fMRI signal fluctuations have a metabolic origin.
- Since regional metabolism is closely coupled with local neuronal activity, the fMRI fluctuations are likely associated with ongoing neuronal activity.

Summary – $CMRO_2$, CBF/CBV, and BOLD

	$CMRO_2$	CBF & CBV	BOLD
Quantifying brain activity	good	good-fair	limited
Sensitivity	Low	fair	high
Spatial specificity	good	good-fair	fair-poor
Temporal resolution	poor	poor-fair	good
Spatial coverage	poor	good-fair	good
Data interpretation	good	good-fair	limited
Implementation	hard	hard-fair	easy