Arterial Spin Labeling Imaging in Diagnosis and Therapy

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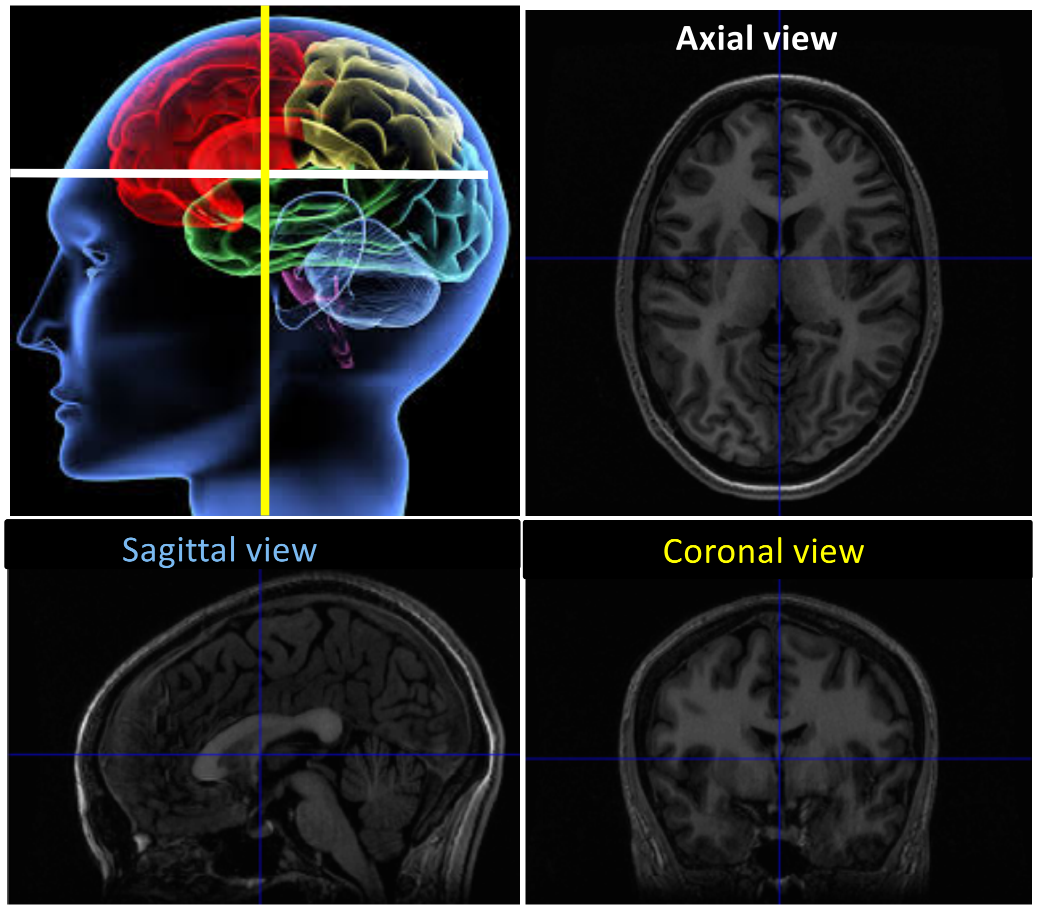
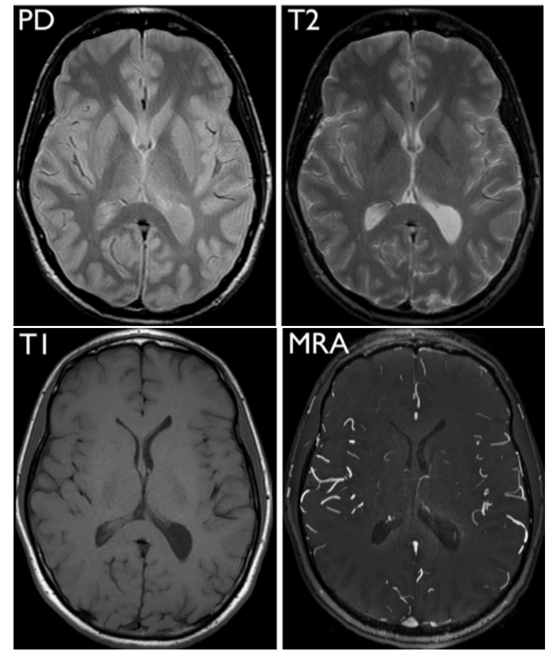
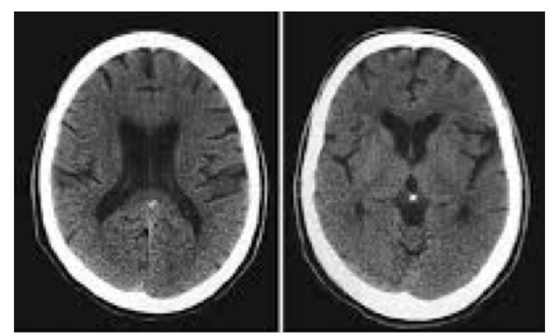
Three-dimension medical imaging



Brain 3-dimension image and Magnetic Resonance images (MRI) in different views (Axial, Sagittal and Coronal views).



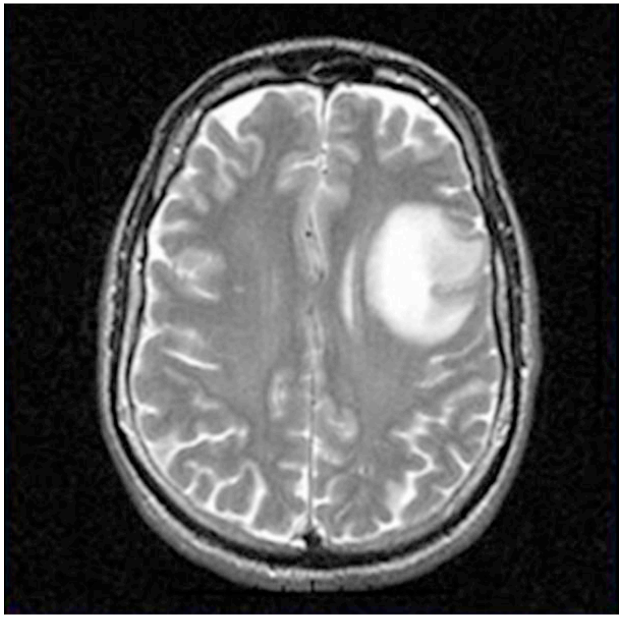
MRI

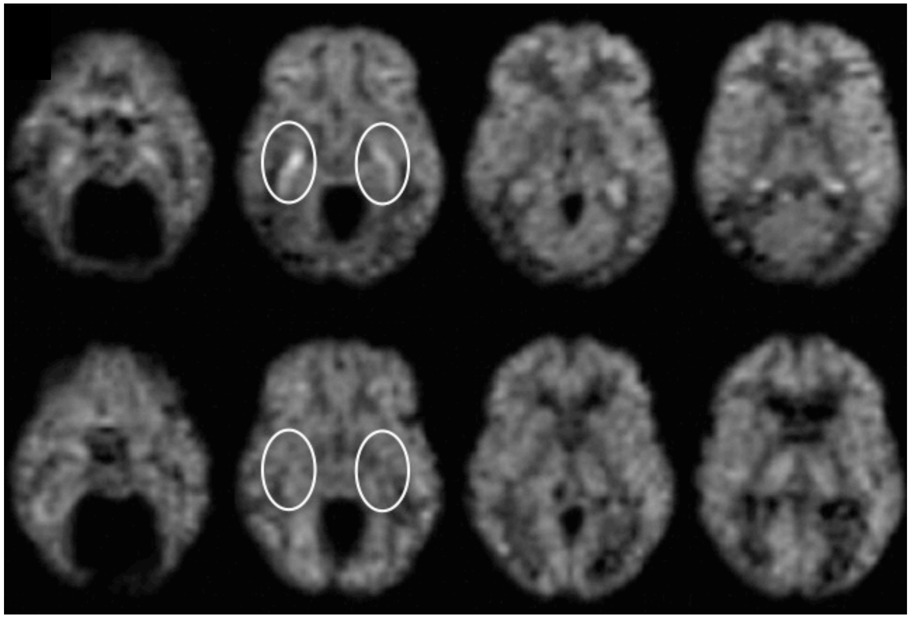


CT

Background *neuroimaging*

- Structural imaging
  - Structure of the brain
  - Diagnosis of large-scale intracranial disease (brain tumor)
- Functional Imaging
  - Metabolism, blood flow, and etc.
  - Diagnosis of lesions on a finer scale (Alzheimer's disease)





Background *Perfusion (blood flow) imaging*

- Perfusion describes the delivery of oxygen and nutrients to tissue by means of blood flow.
  - The volume of arterial blood delivery to a piece of tissue in a specific period of time
  - Measured in ml (blood)/ 100g (tissue).min

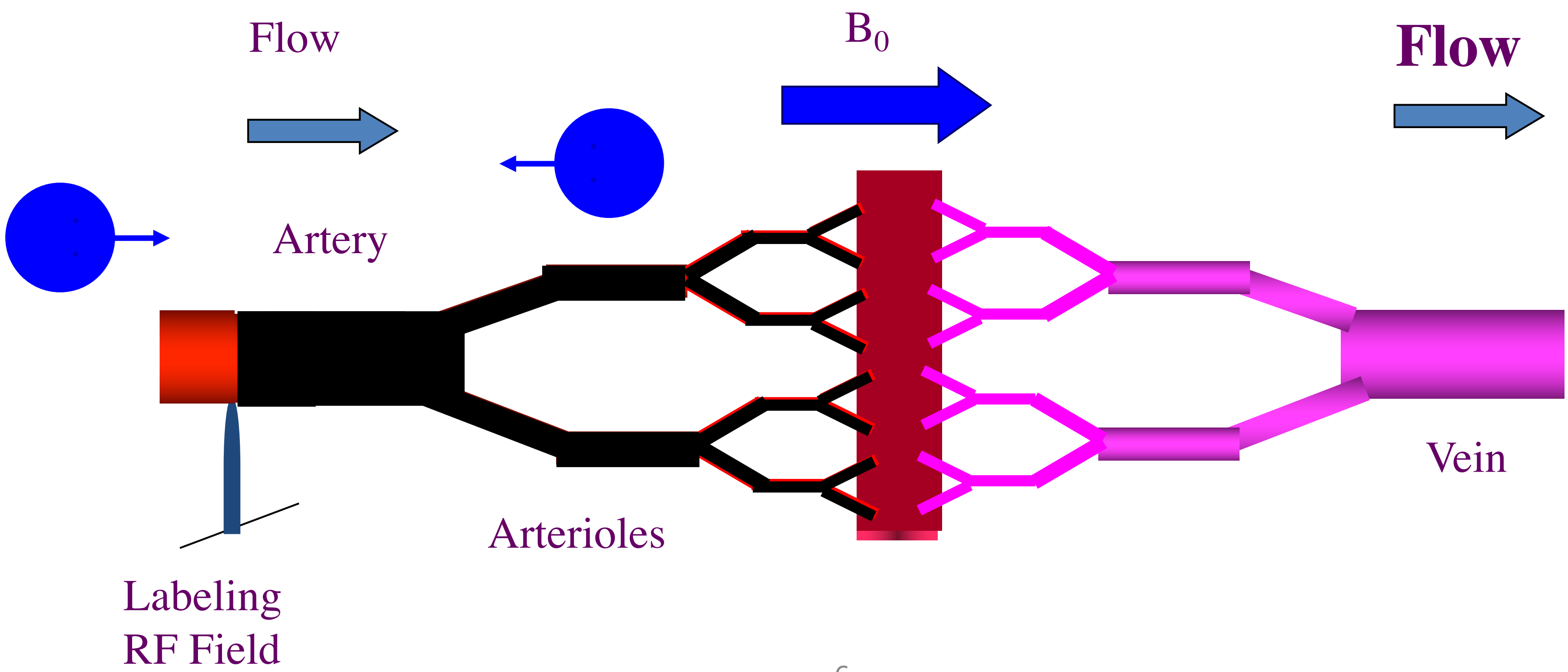
- Perfusion is an important functional measurement.
  - Indicates condition of vascular supply network.
  - Detects tissue in danger of ischemic damage
  - Indirectly reflects metabolic activity of tissue

Background *MR Perfusion imaging*

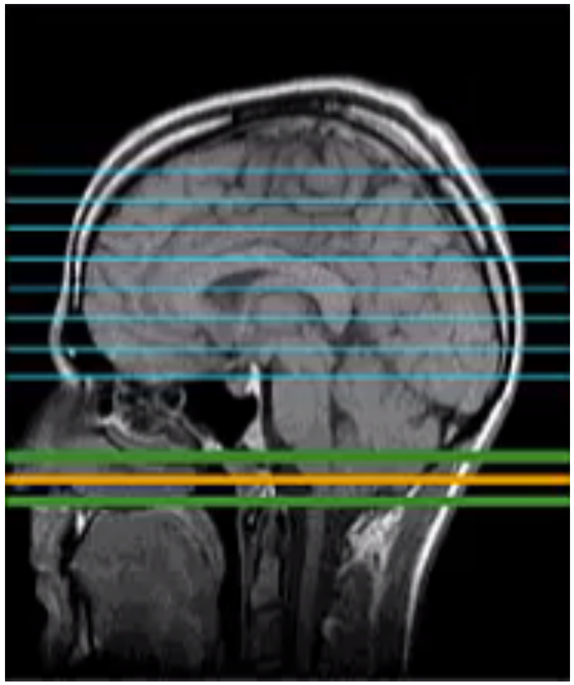
- Advantages
  - Non-invasive
  - Non-ionizing
  - High spatial and temporal resolution
  - Coregistered with high-resolution anatomical MRI data.
  - Quantitative without arterial monitoring
- Approaches
  - Dynamic Susceptibility Contrast (DSC)
  - Arterial Spin Labeling (ASL)

Background *ASL perfusion imaging*

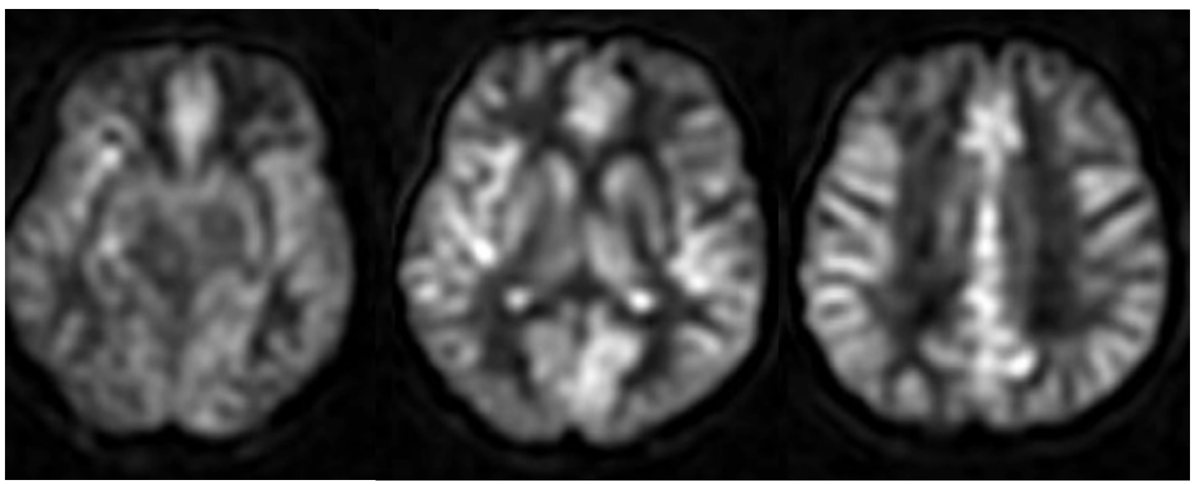
- Use MR scanner to label arterial water spins
- Wait some time until the labeled arterial water freely diffuses into tissue
- Measure the tissue signal and then quantify perfusion in units of ml/100g.min



Background *ASL perfusion images*

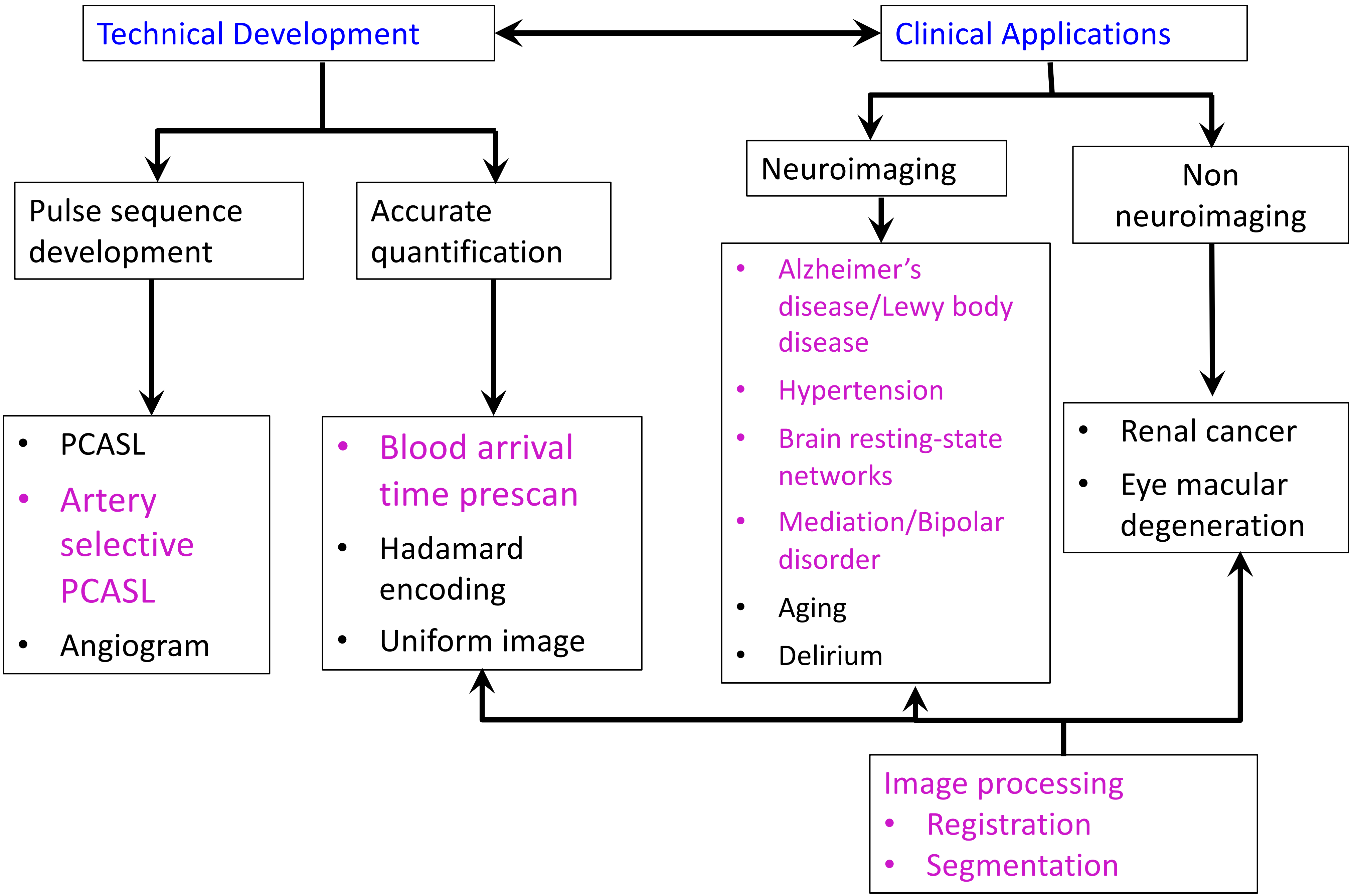


Blood flow Imaging technique: (1) Labeling plane (Yellow) where blood gets labeled. (2) Control plane (Green) where blood gets untouched. (3) Imaging planes (Blue) where blood Flow images are Acquired.



Blood flow images from 3 different axial slices

Overview of my research



Agenda

- **Application of Static ASL Perfusion Imaging**
  - Alzheimer's disease
  - Hypertension
  - Lewy Body disease

- Dynamic ASL Perfusion Imaging
  - Quantifying fluctuations of brain resting state networks
  - Dynamic ASL in bipolar disorder
  - Dynamic ASL in meditation

Image Processing Issues

- **Inadequate Automated Analysis Tools**
  - **Need accurate automated atlas-based analysis for regional analysis.**

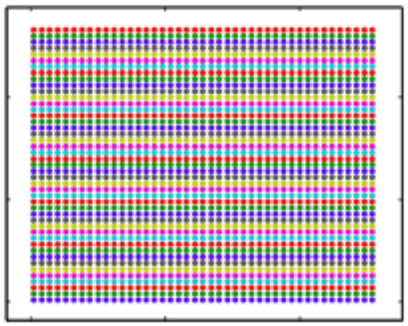
- **Elderly brains pose a challenge to youth-based tools**
  - **Brain volume and atrophy rate of brain local structure differ between elderly and young subjects.**

  - **Globally deformable registration algorithms yield errors.**

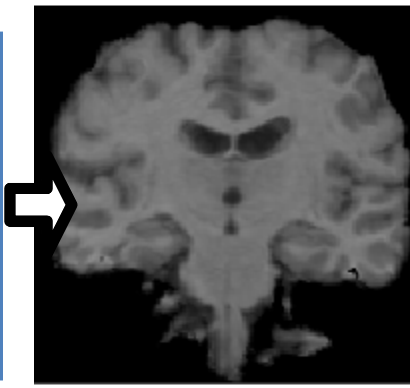
Comparison of Registration Techniques

Geometric Transformation

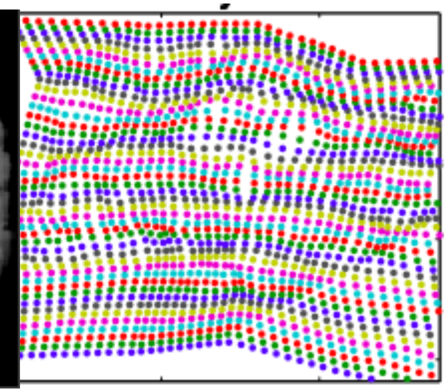
Which ones give accurate transformation?



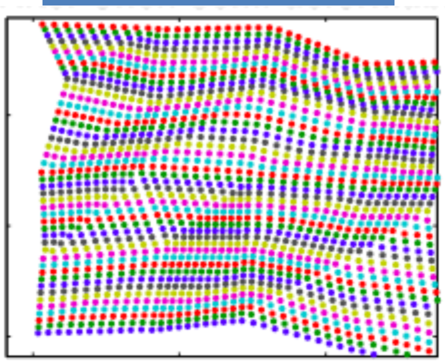
Geometric Transformation



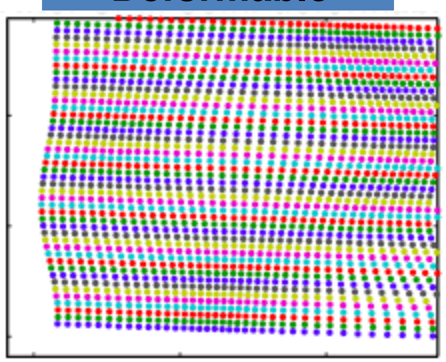
Chen Fully-Deformable



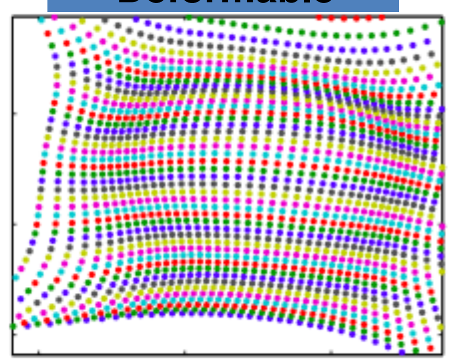
Chen Semi-Deformable



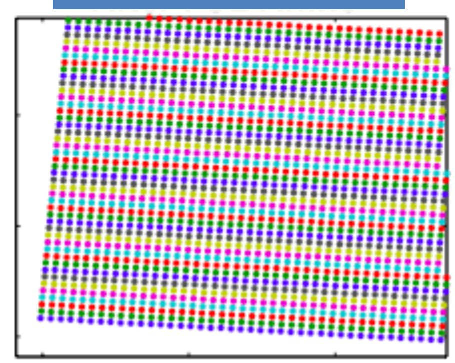
SPM Semi-Deformable



AIR Semi-Deformable



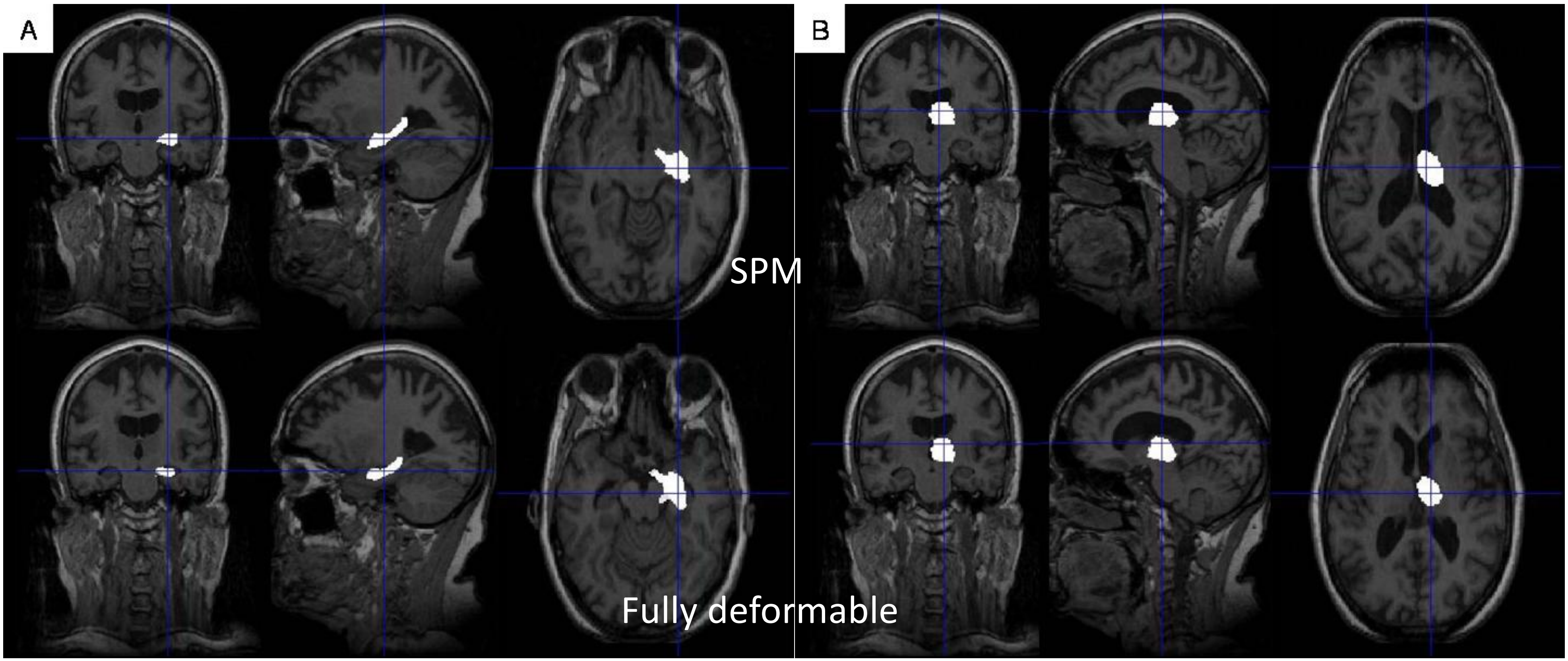
FLIRT Affine



Chen M. Doctoral dissertation in Carnegie Mellon University. 1999

Validation of Fully deformable registration

Comparisons of SPM normalization vs Fully deformable registration



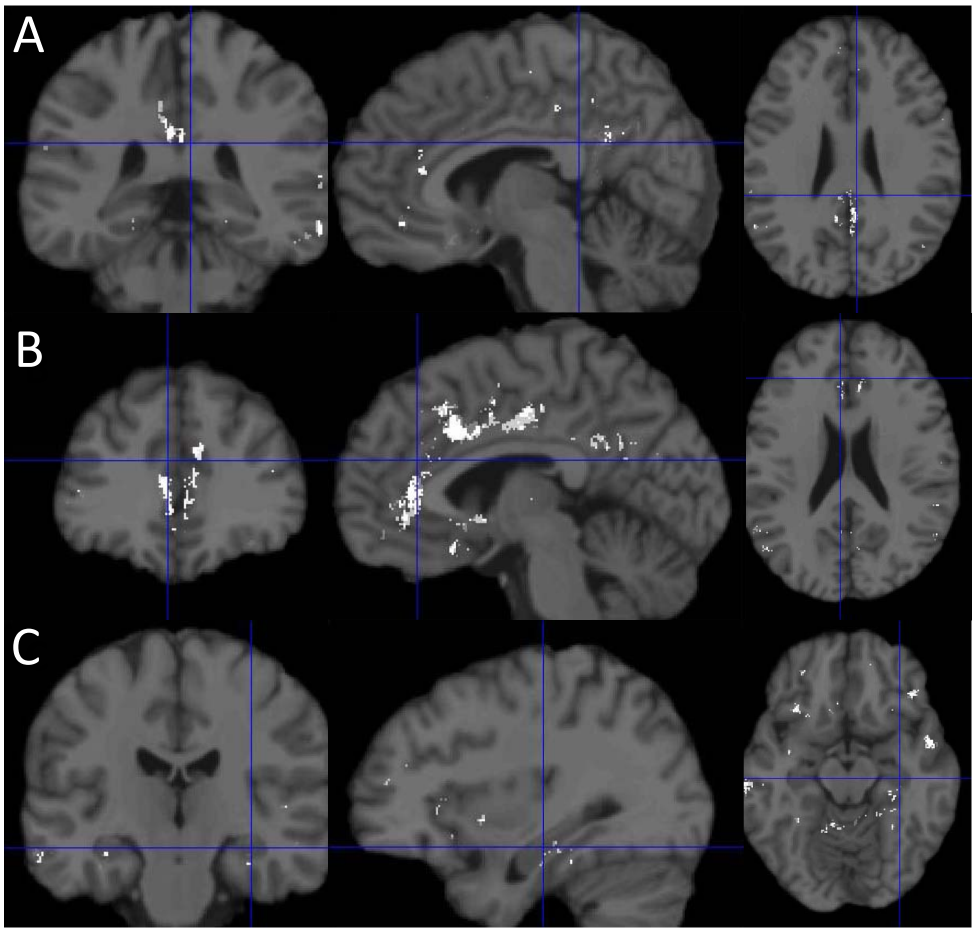
Hippocampus

Thalamus

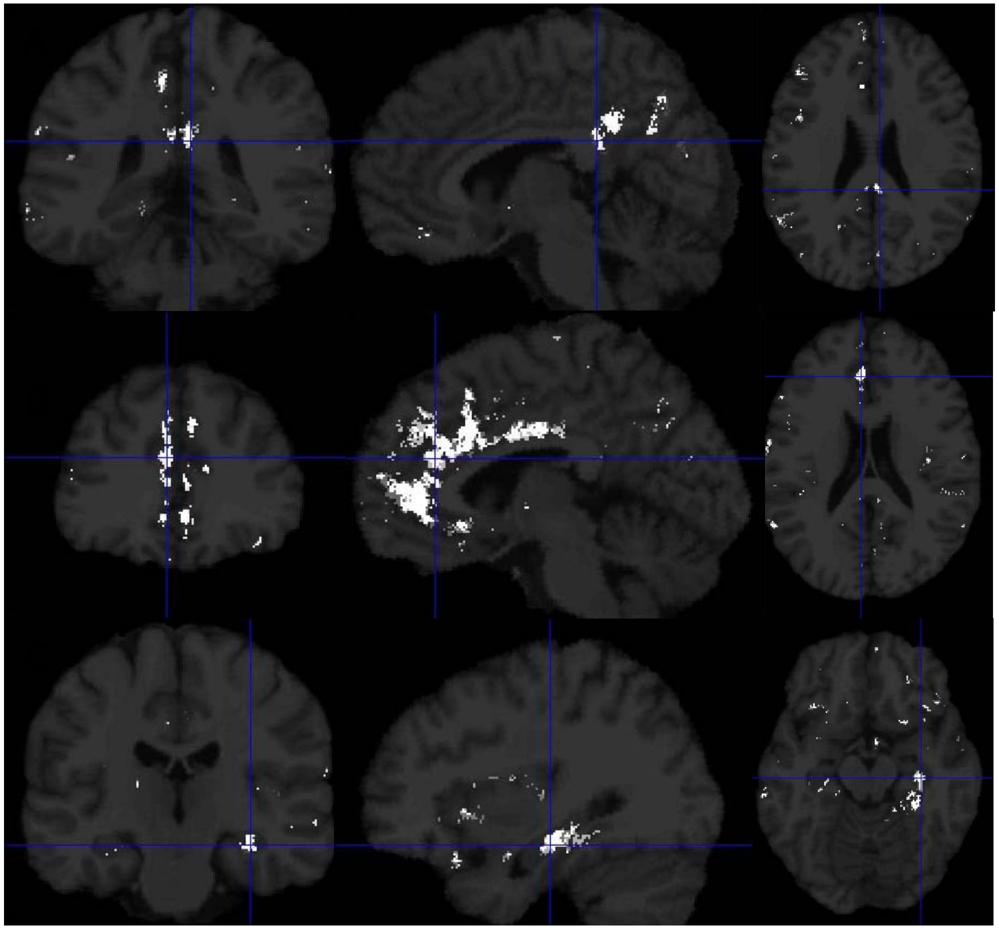
Significant differences of Gray matter perfusions

Comparisons of SPM normalization vs. Fully Deformable Registration

SPM normalization



Fully deformable registration



A. Control > MCI (Top Row)

B. AD > MCI (Middle Row)

C. MCI >Control (Bottom Row)

[1]Dai et al, JMRI 2008;28(6):1351-60.

General Linear Model

- Brain signals from different subjects are modeled as a linear combination of disease effects and covariates.

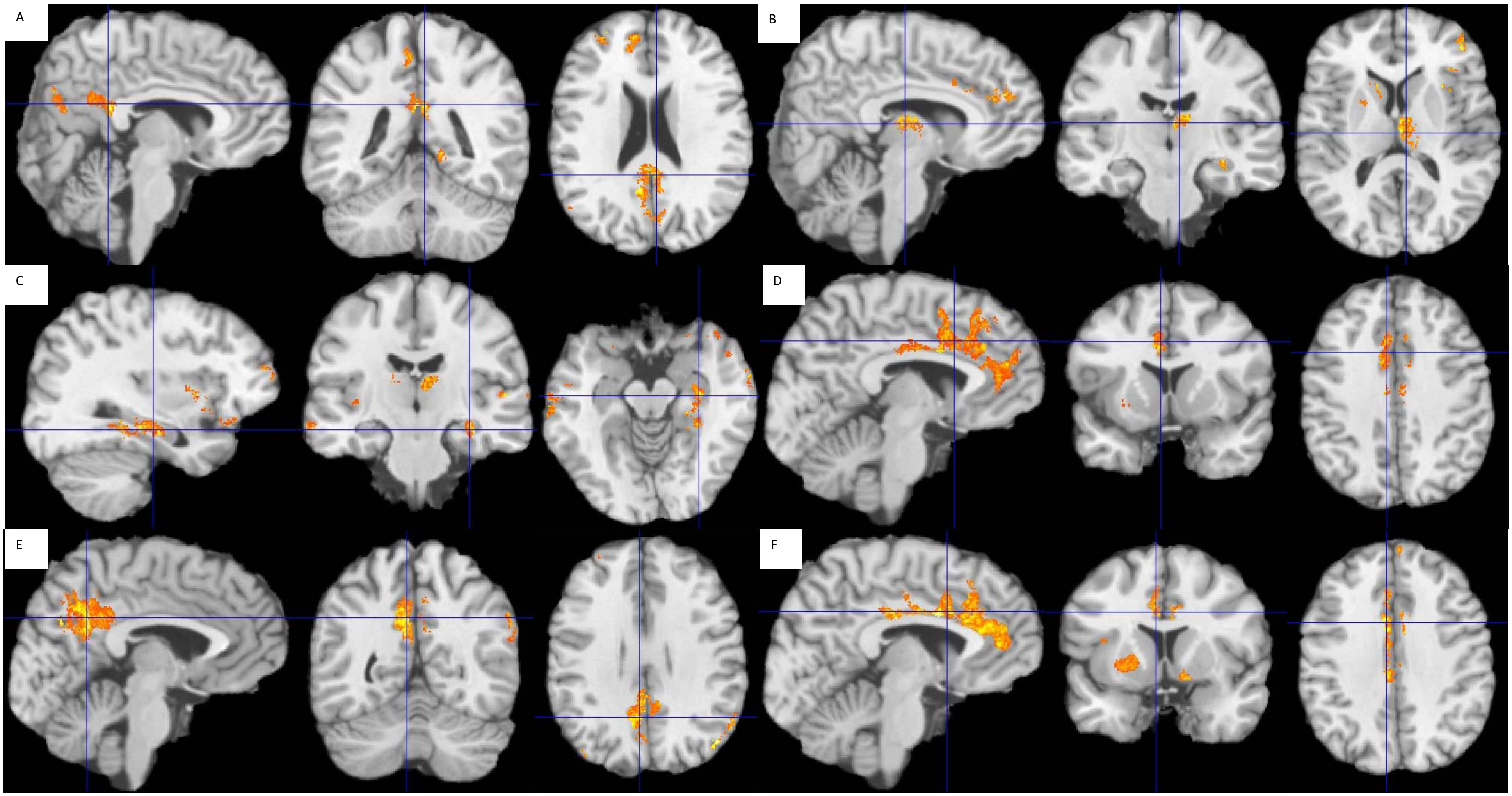
$$y = X\boldsymbol{\beta} + \boldsymbol{\varepsilon}.$$

$$\underbrace{\overset{1}{\begin{bmatrix}60\\75\\50\\55\\\vdots\\63\\58\\71\end{bmatrix}}}_{y}{}_{m} = {}_{m}\underbrace{\overset{p}{\begin{bmatrix}1&64&0&1\\1&62&0&1\\1&55&1&1\\1&65&0&1\\\vdots&\vdots&\vdots&\vdots\\0&57&1&1\\0&69&1&1\\0&59&0&1\end{bmatrix}}}_{X} \times {}_{p}\underbrace{\overset{1}{\begin{bmatrix}\beta_1\\\beta_2\\\beta_3\\\beta_4\end{bmatrix}}}_{\beta} + \underbrace{\boxed{\text{Error}}}_{\varepsilon}$$

Fig. 1. Brain signals from all the subjects at a single voxel expressed as a general linear model. m is the number of subjects, p is the number of explanatory variables, X is the design matrix with the columns from left to right as disease state, age, gender and constant term, β is the coefficient associated with the explanatory variables, and ε is the error term.

Perfusion Group Comparison of Early AD

Results of Voxel-Based Analysis



(A, B) **Control vs. MCI (Top Row)**

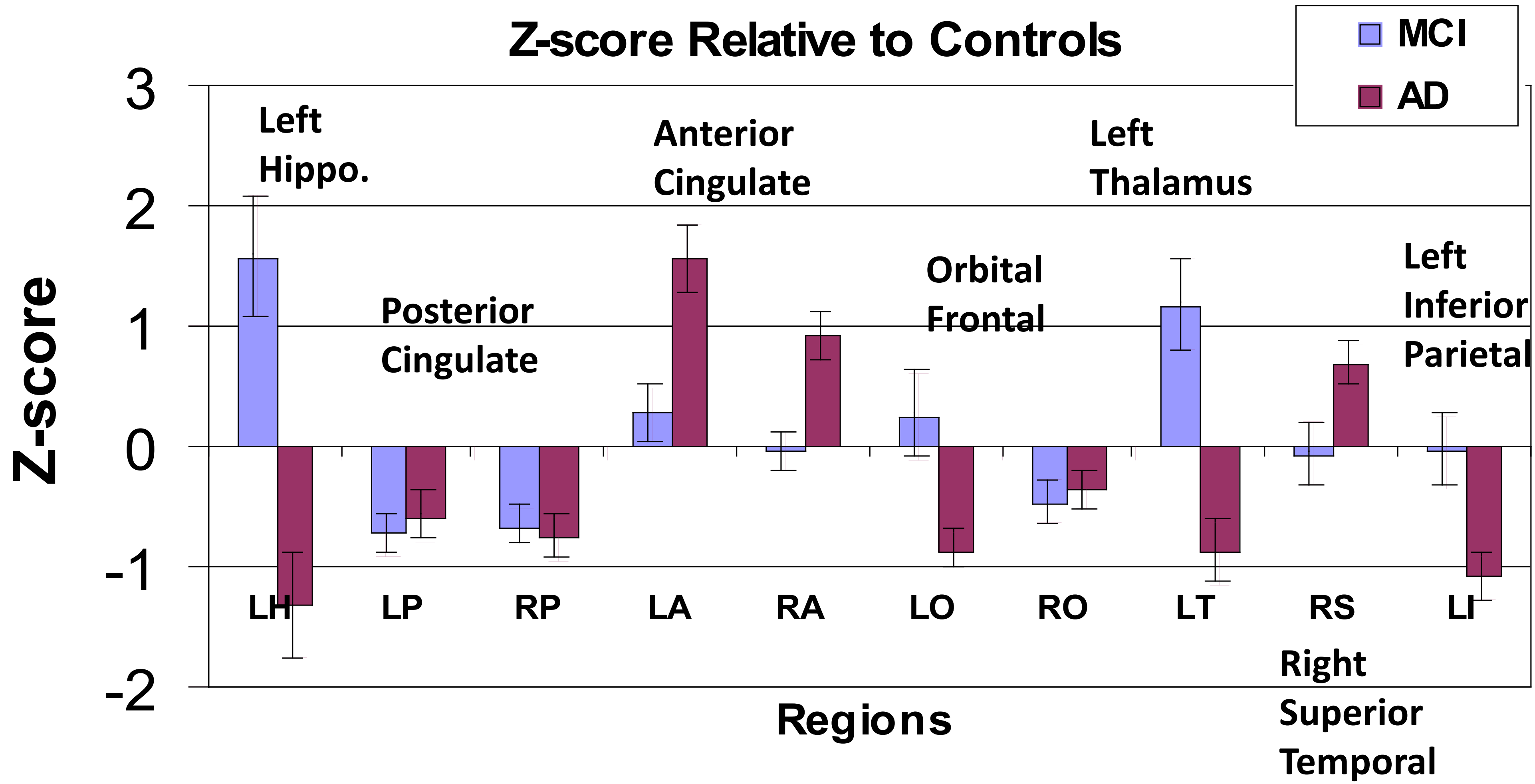
(C, D) Control vs. AD (Middle Row)

(E, F) MCI vs. AD (Bottom Row)

Dai W et al, Radiology 2009;250:856-866.

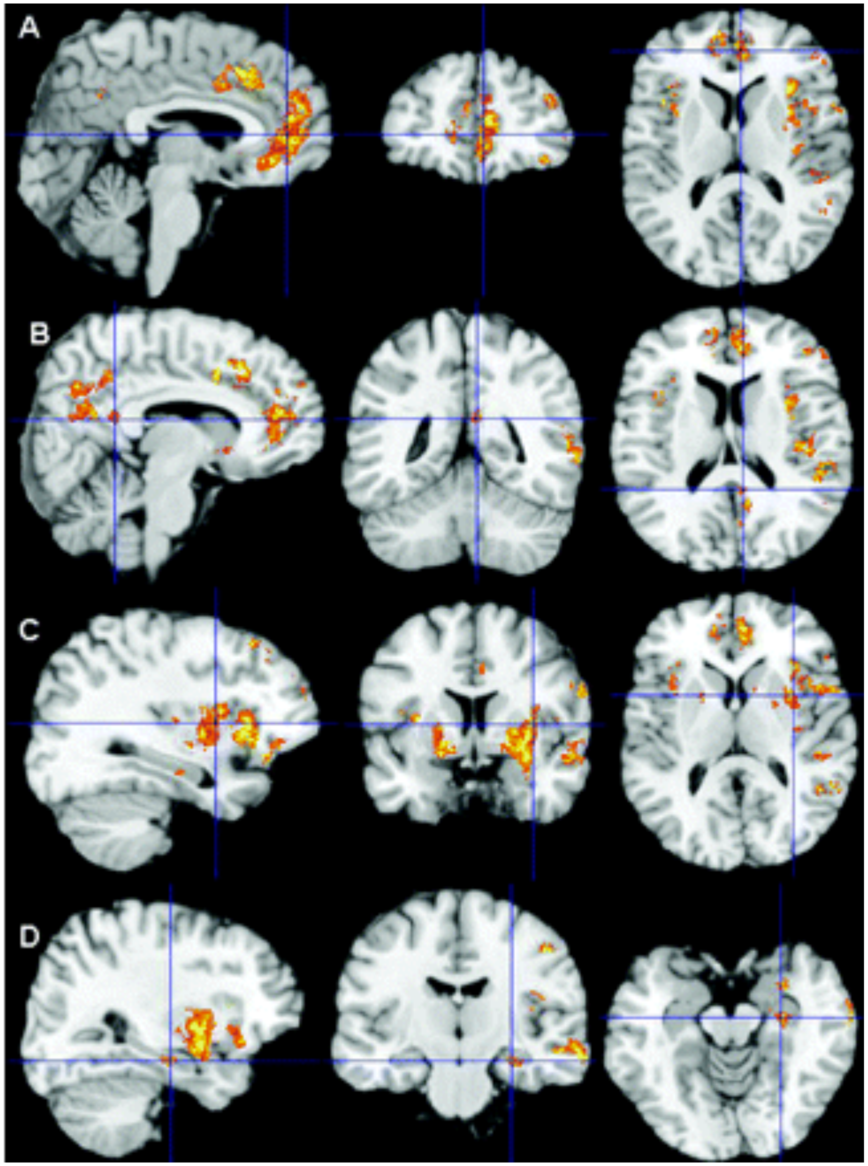
Perfusion Group Comparison of Early AD

Results of Region-Based Analysis



Comparison of standard Z-score of CBFs for regions in normal controls, MCI, and early AD subjects. Error Bars represent standard error from the mean (SEM).

Perfusion Group Comparison of Hypertension

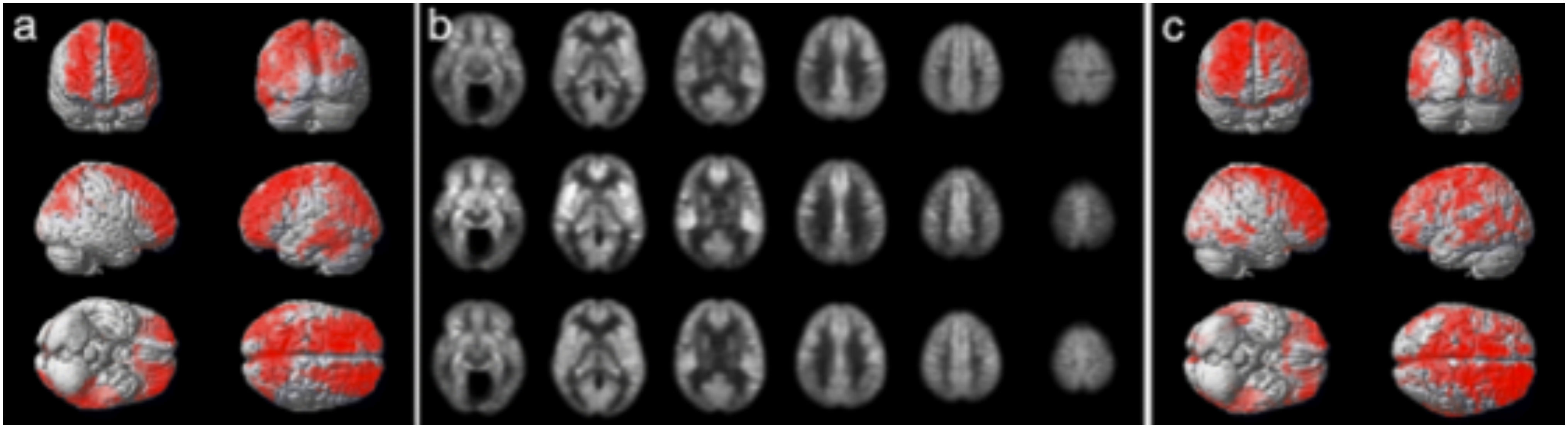


Hypertension vs. Controls

- Perfusion is affected not only in the subcortical regions, but also in limbic and paralimbic structures.
- HTN creates a vulnerability state for the development of neurodegenerative disorders, especially Alzheimer disease.

Dai W et al, Stroke. 2008; 39: 349-354

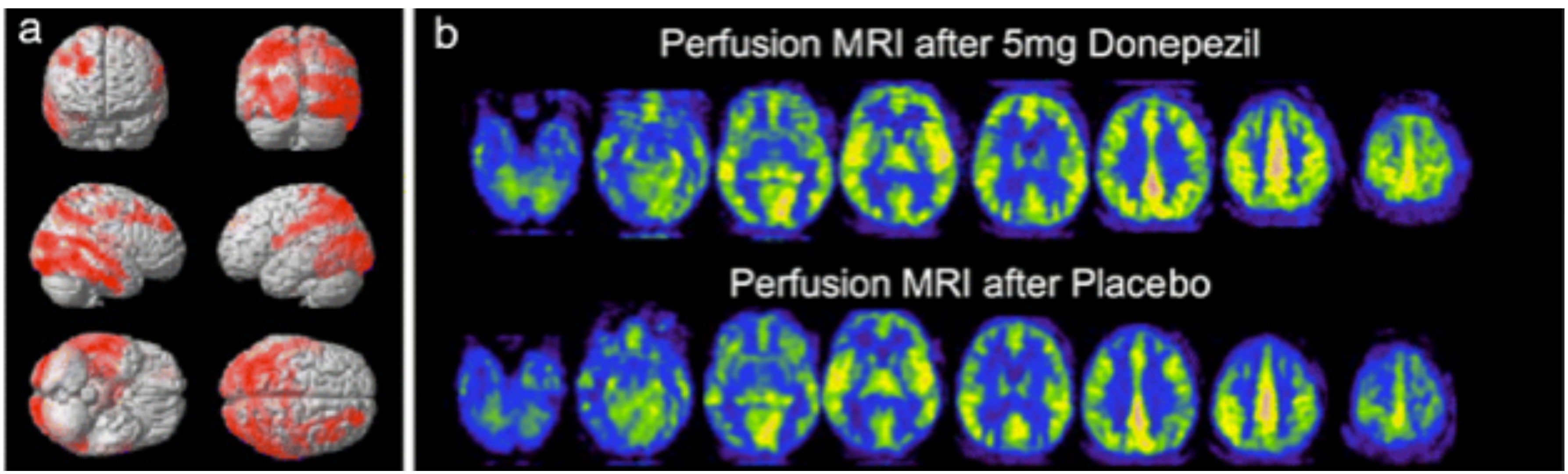
Perfusion comparison with Lewy body disease



Control>LB

Control (top): n=16
AD (middle): n=16
LB (bottom): n=10

AD>LB



Fong et al, Brain Imaging Behav. 2011; 5(1):25-35

Summary of perfusion application

- Fully deformable registration was proven to be more accurate to detect the local brain perfusion changes.
- Voxel-based analysis of ASL perfusion can detect significant group changes without priori hypothesis.
- The AD findings may imply a compensatory mechanism, at the capillary level, accompanied the neurodegenerative process.
- HTN creates a vulnerability state for the development of neurodegenerative disorders, especially AD.
- Lewy body patients exhibit pronounced decrease of perfusion. A single dose of Donepezil increases both perfusion and cognitive performance.

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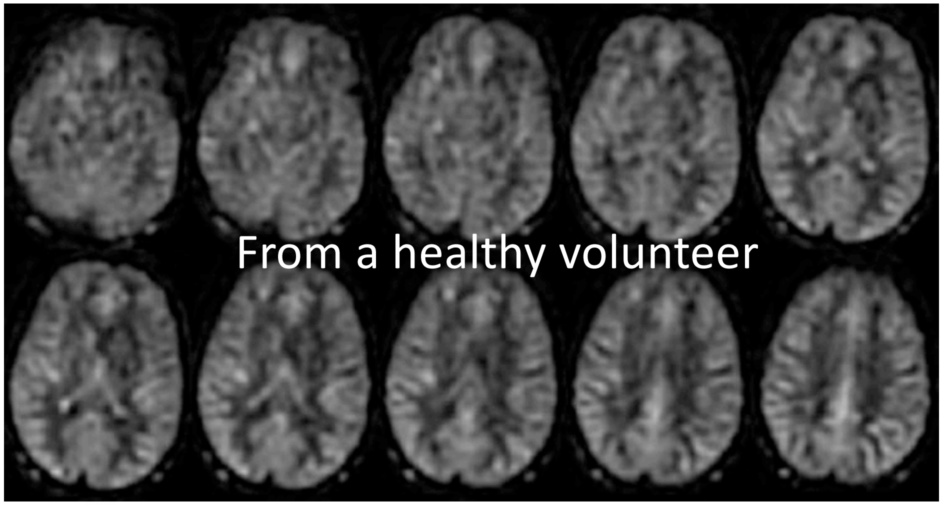
- **Dynamic ASL Perfusion Imaging**
  - Quantifying fluctuations of brain resting state networks
  - Dynamic ASL in bipolar disorder
  - Dynamic ASL in meditation

ASL Perfusion image



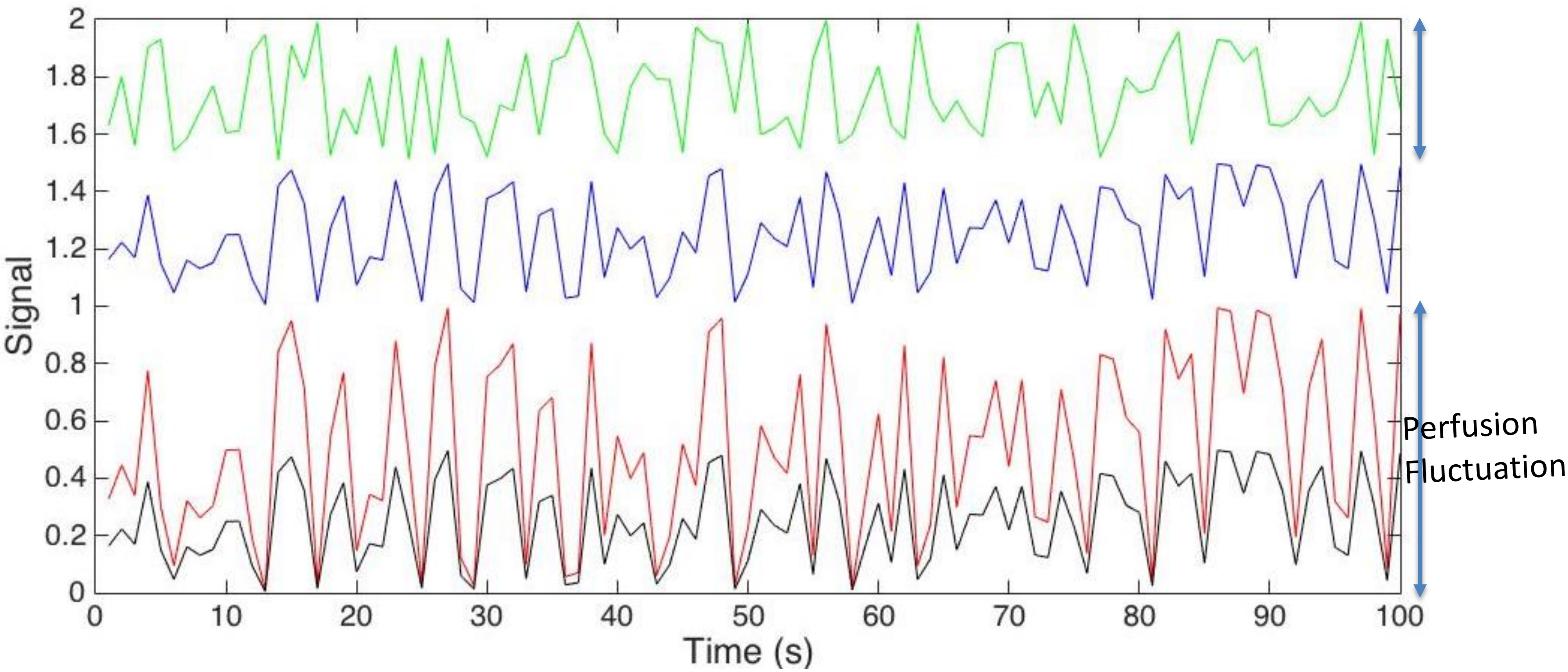
Dai W et al, *Magnetic Resonance in Medicine* 60:1488–1497 (2008).

- Static behavior

(mean perfusion)

- Dynamic behavior

(Perfusion fluctuation & functional connectivity)



Background

- Another neuroimaging technique (BOLD) can determine the regions of the brain more active during a task.
- Brain activity is present even in the absence of an explicit task.
- BOLD has revealed a number of resting state brain networks.
  - brain regions that have spontaneous fluctuations
  - Non-neural coherent noise

Dynamic ASL

- BOLD fMRI can determine the activated regions during a task and resting state networks.
- Characterize resting-state networks using ASL
  - A 3D ASL image
  - Strong suppression of background tissue
- Compare resting state networks between ASL and BOLD
- Quantify the magnitude of signal fluctuations in resting state networks

Dai et al, Journal of Cerebral Blood Flow & Metabolism, 2016; 36(3):463-473.

Methods *sequences & protocol*

- Pulsed-continuous arterial spin labeling technique (PCASL)[1]
  - Labeling duration of 2 s and post-labeling delay of 1.8 s
- Background suppression pulses[2]
  - Pulse timing to achieve 0.3% of background tissue signal
- Vessel suppression preparation pulse[3]
- ASL Imaging Sequence
  - 3D Stack of Spiral imaging: 4 mm cubic resolution, TR of 5 s.
  - Forty resting-state PCASL volumes collected in 20 minutes
- BOLD imaging sequence
  - 2D GE EPI: 28 slices with 4 mm thickness, TR of 2 s
  - Three hundred resting state BOLD volumes collected in 10 minutes
- T1-weighted MPRAGE images
- Twenty healthy subjects (30.3 $\pm$ 4.6 years old) on GE 3 Tesla scanner

1. Dai et al, Magn Reson Med 2008;60:1488-97. 2. Maleki et al, MAGMA 2012;25:127-33.
3. Dai et al, 17th ISMRM 2009:1512.

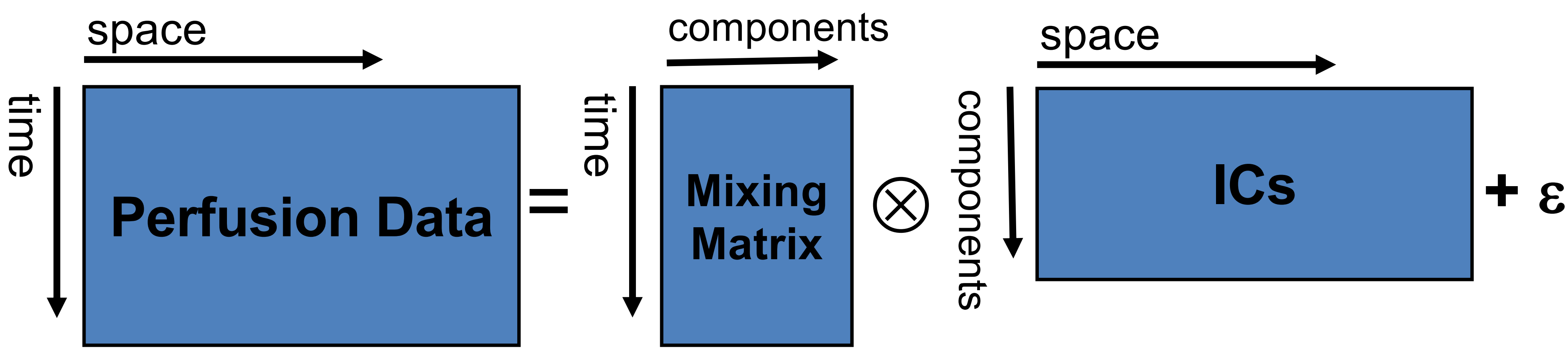
Methods *image analysis*

- Preprocessing
  - Motion correction, removal of nonbrain structures
  - 6 mm FWHM spatial smoothing, 4D grand mean scaling by the same factor
  - No temporal filtering for ASL data but high pass filtering (FWHM=100 s) for BOLD
  - Normalized to MNI152 standard space
- Statistical Analysis
  - Use independent component analysis (ICA) implemented by FSL MELODIC software[1]
  - ICA performed on the whole group of data formed by temporal concatenation
  - Number of components was set as 10,15,20 due to unstable automatic dimension[2]

1. Beckmann et al,Phil. Tran. R. Soc. B 2005;360:1001-13. 2.Huvarine et al, IEEE Trans. Neural Netw. 1999.

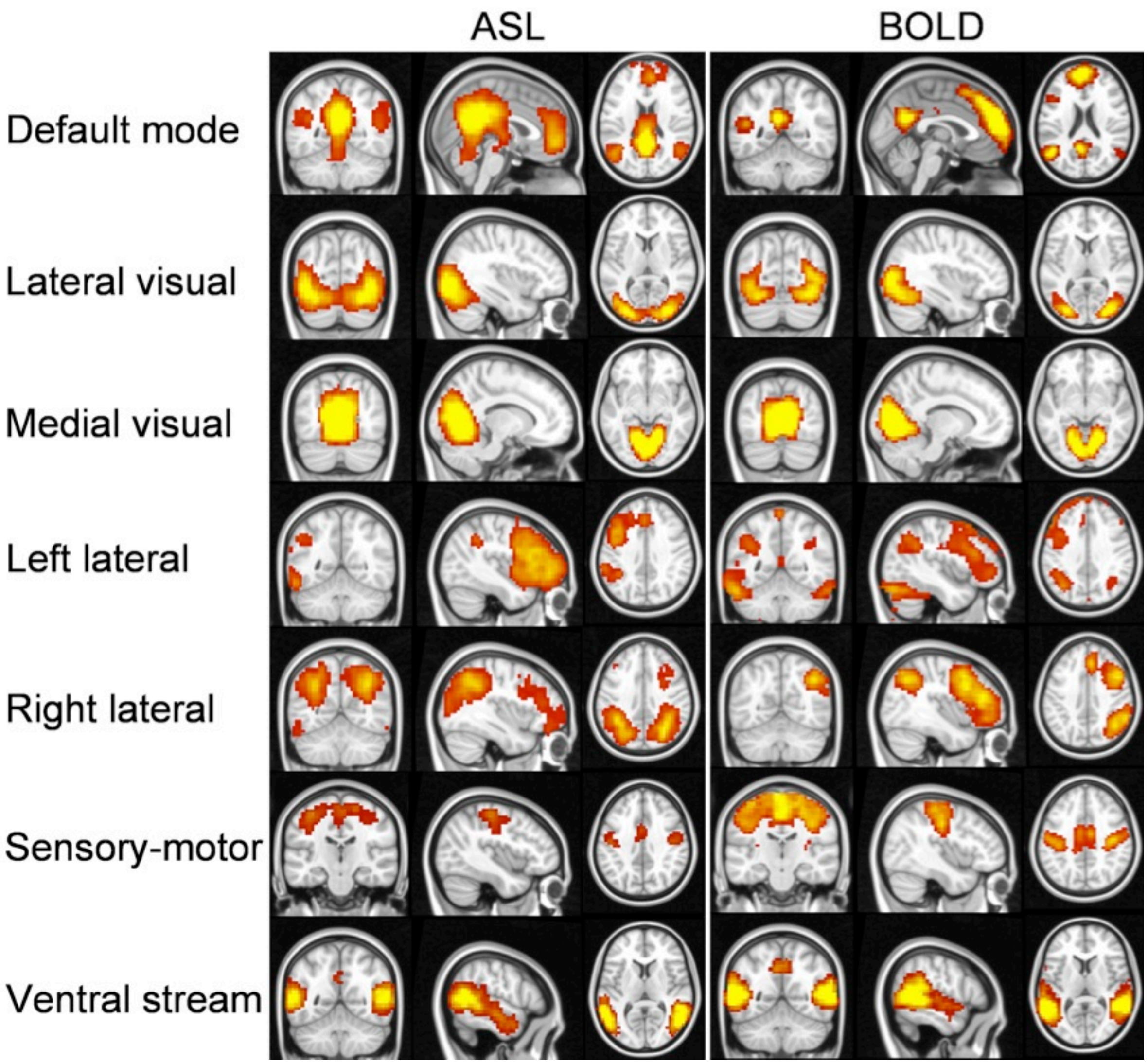
Methods *Quantification of ICs*

- ICA program using *infomax* algorithm[1]
  - Hard to convert from the ICs to the perfusion signals within MELODIC
  - Calculate the perfusion signals represented by the ICs.
    - Obtain the signal fluctuation map of the ICs
    - Obtain the fluctuation map of residual noise (ε)
  - Calculate the perfusion signal represented by each IC.
    - Obtain the signal fluctuation map of each IC



1. Bell et al,Neural Computation 1995;7:1129-59.

Brain networks *ASL vs. BOLD*



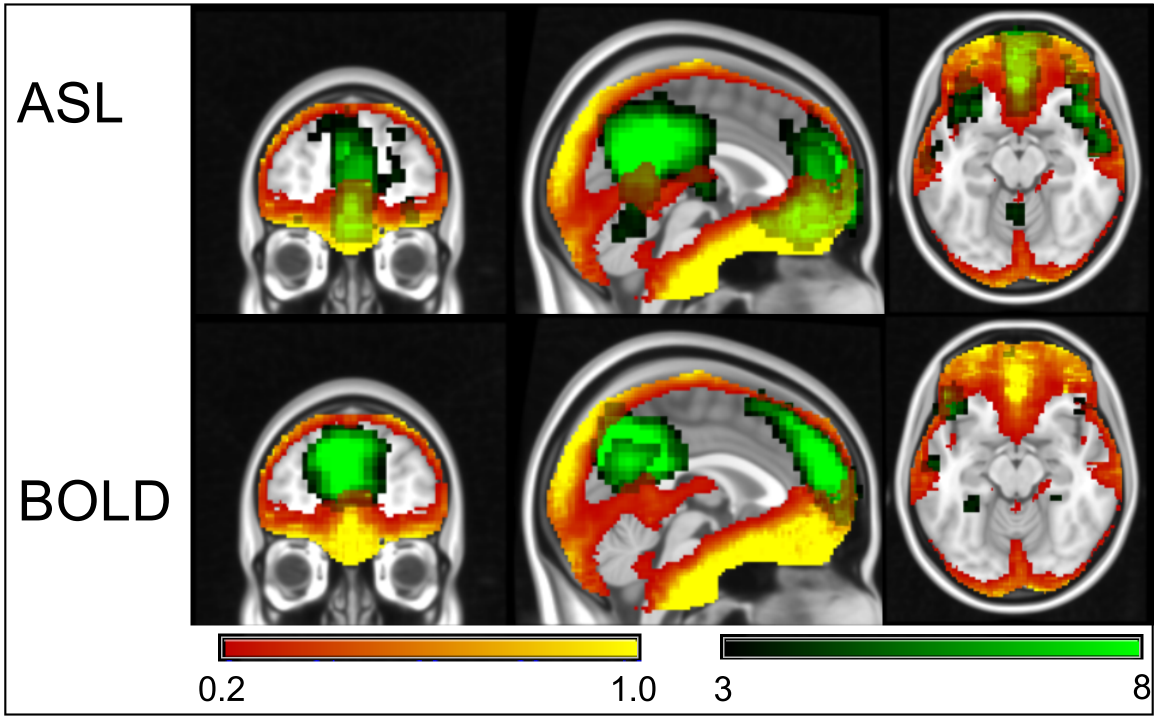
- ASL had fewer artifactual ICs than BOLD.
    - ASL required 15 ICA, only 2 are non-neural artifacts.
    - BOLD required 20 ICA, 8 are non-neural artifacts.

- ASL data show similar resting state networks to BOLD data[1-2].

1. Beckmann et al, Phil. Tran. R. Soc. B 2005;360:1001-13.
2. Damoiseaux et al, PNAS 2006; 12848-53.

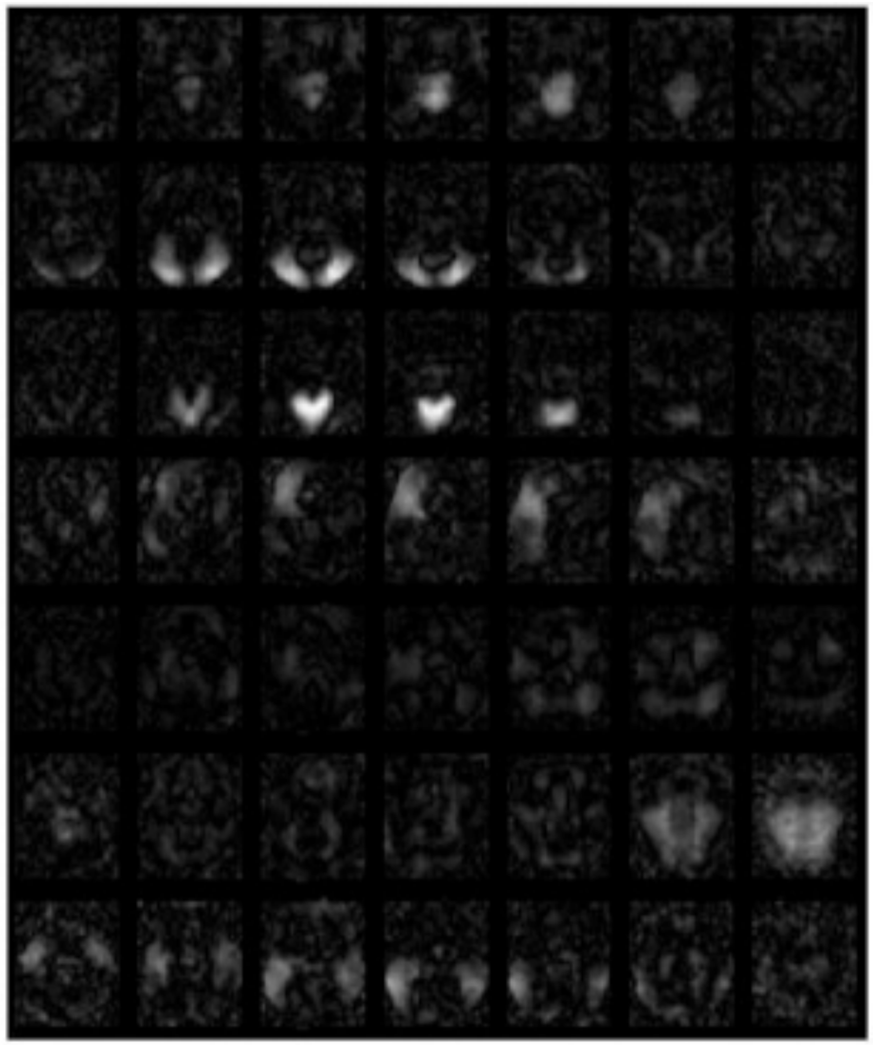
Susceptibility *ASL vs. BOLD*

Default mode network overlaid on BOLD high-variation regions



- BOLD Group-level CV map (Red-yellow color)
  - ➢ showed high variability in high-susceptibility regions and brain edges.
- Default mode network (Green color)
  - ➢ ASL data showed larger extent within susceptibility regions than BOLD.

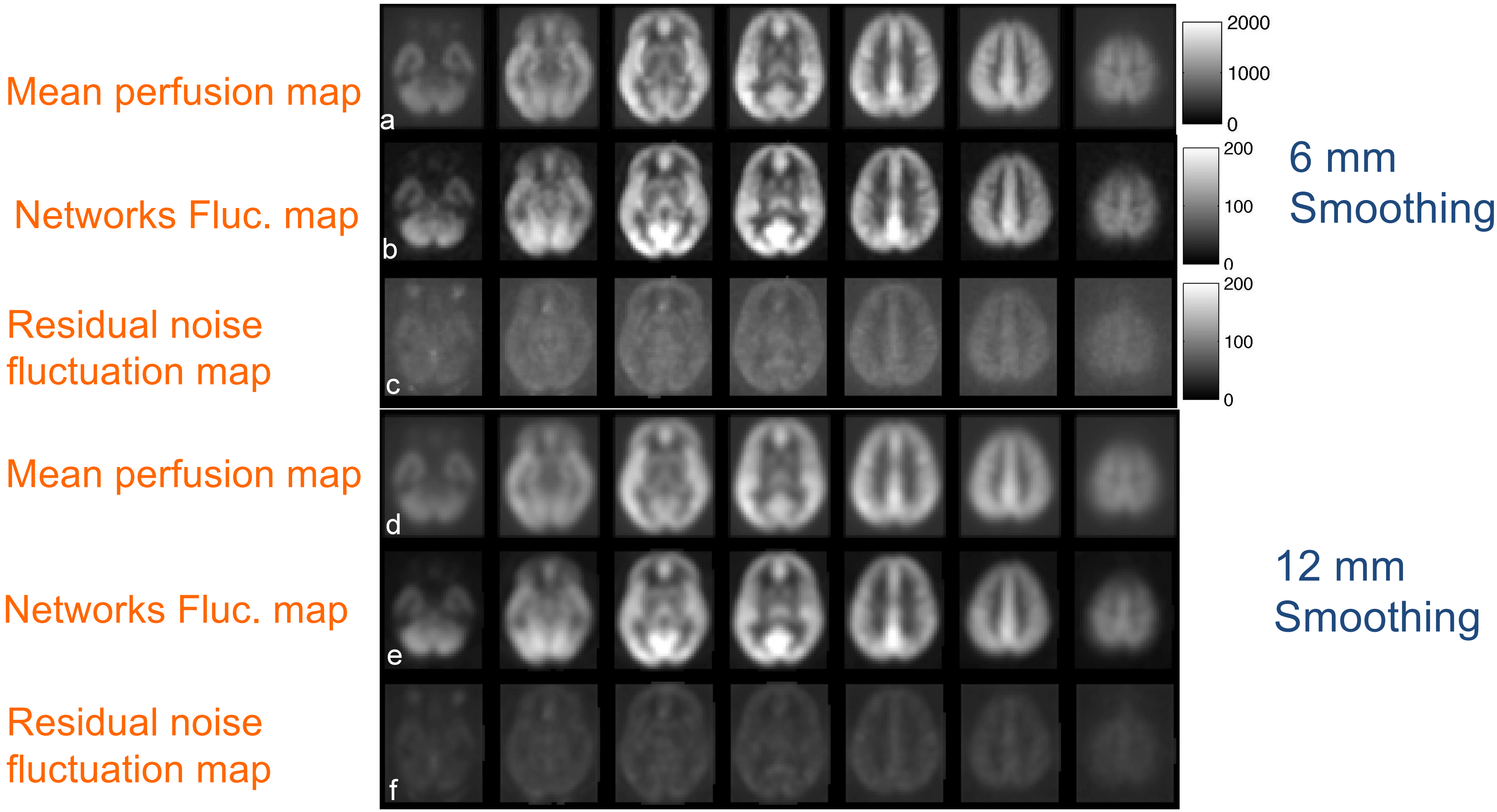
Individual network fluctuations



	network fluctuations
Default Mode	4.43%
Lateral Visual	6.42%
Medial Visual	6.71%
Left Lateral	3.63%
Right Lateral	2.96%
Sensory-motor	4.42%
Ventral stream	3.50%

- Perfusion signal fluctuations vary across different brain networks.
- The lateral and medial visual ICs showed the largest fluctuations.

brain networks vs. residual noise



- IC fluctuations are much larger than residual noise fluctuations.
- With larger smoothing kernel, residual noise fluctuations can be reduced by 39.75% but IC fluctuations can be reduced by 7.77%.

Summary of resting-state networks

- 3D ASL perfusion data can reliably extract resting-state networks.
- ASL perfusion data have fewer artifactual components and less vulnerability to susceptibility artifacts.
- ASL perfusion data can provide a quantitative measurement of signal fluctuations within the IC networks.
- Global and network fluctuations are the dominant structured noise sources in ASL perfusion data.
- This capability may be used for improved noise reduction and statistical analysis of future ASL studies.

1. Dai et al, Journal of Cerebral Blood Flow & Metabolism, 2016; 36: 463-473.

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- Application of Static ASL Perfusion Imaging
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- **Dynamic ASL Perfusion Imaging**
  - Quantifying fluctuations of brain resting state networks
  - Dynamic ASL in bipolar disorder
  - Dynamic ASL in meditation

Dynamic ASL in bipolar disorder

- Bipolar disorder (BD) is a fluctuating psychiatric disorder of mood that can severely affect quality of life and social functioning of patients.

- Neuroimaging studies reported functional alterations in various brain regions and abnormal functional connectivity, limited power and high variability are common.

- OFC abnormalities may play an important role in the neuropathology of BD.

- We use the dynamic ASL technique to investigate whether the perfusion measures are altered in BD patients

Methods *subjects & protocols*

- Forty-five subjects (19 BD patients, 26 controls) were imaged on a GE 3 Tesla scanner using an 8-channel head coil receive array.
- T1- weighted magnetization prepared rapid gradient echo (MPRAGE) images.
- Resting state PCASL images
  - Twenty-seven 3D ASL volumes collected in 9 minutes
  - Each PCASL image was acquired with a 3D stack of spirals RARE sequence (two spiral interleaves and control-label pairs).

1. Dai W et al., J Cereb Blood Flow Metab, 2016;36(3):463-73

Methods *Image Analysis*

- PCASL time series were motion-corrected and normalized to the standard template space using SPM8.

- For each subject
  - Perfusion were quantified as the average image.
  - Perfusion fluctuation were quantified as standard deviation image.
  - Perfusion connectivity were quantified as Pearson correlation coefficient image with a seed in orbitofrontal cortex (OFC) respectively across the 26 time points by removing the first perfusion image.

Methods *Image Analysis*

- Factor analysis were used to categorize the psychiatric symptoms into four dimensions (positive, negative, maniac, and depressive dimensions).
- SPM and Statistical non-Parametric Mapping (SnPM) was used to compare the difference of perfusion, perfusion fluctuation, perfusion connectivity maps between BD patients and controls.
- One-thousand random permutations were performed to calculate the distribution of the largest supra-threshold cluster size (voxel-level threshold of 0.01) and maximum t values.
- Perfusion maps, perfusion fluctuation maps, and perfusion connectivity maps were correlated with each of four dimensions.

Abnormal perfusion fluctuation and connectivity in bipolar disorder

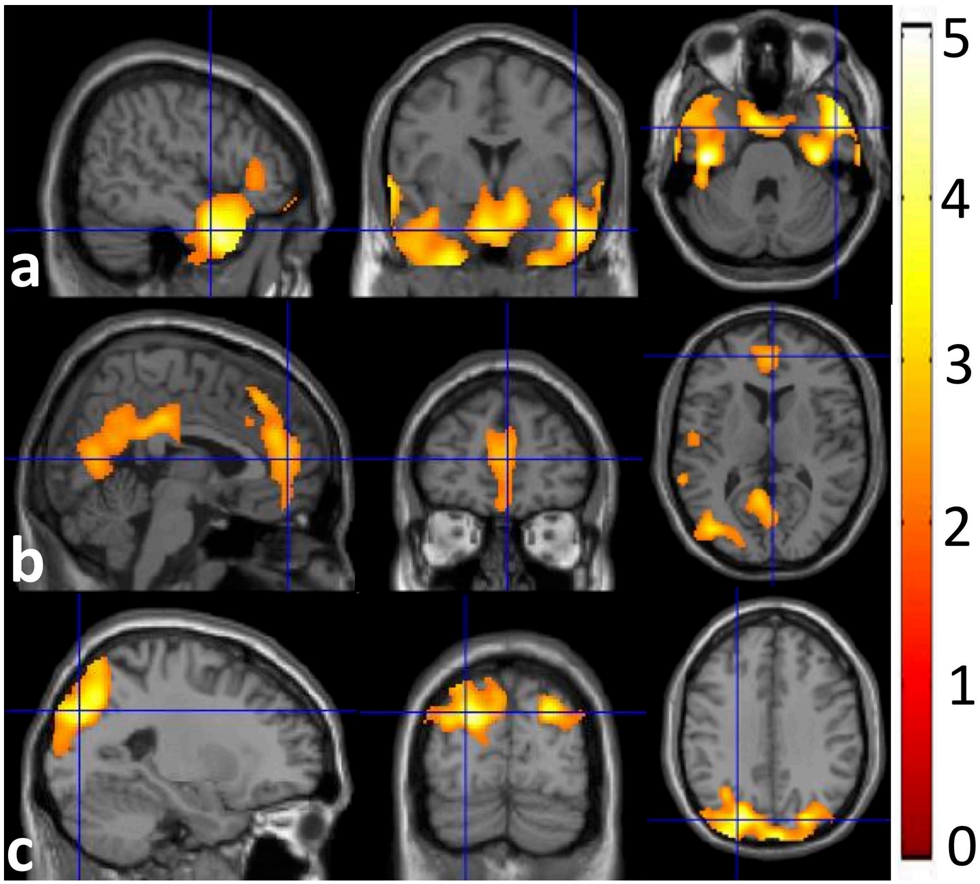

Fig. 1

- Significant increase of perfusion fluctuations in the lower salience network (Fig. 1a).
- Significant decrease of perfusion fluctuation of perfusion fluctuation in default mode network (Fig. 1b).
- Significant increase of perfusion connectivity in dorsal attention network (Fig. 1c).

Symptom-specific deficits in bipolar disorder

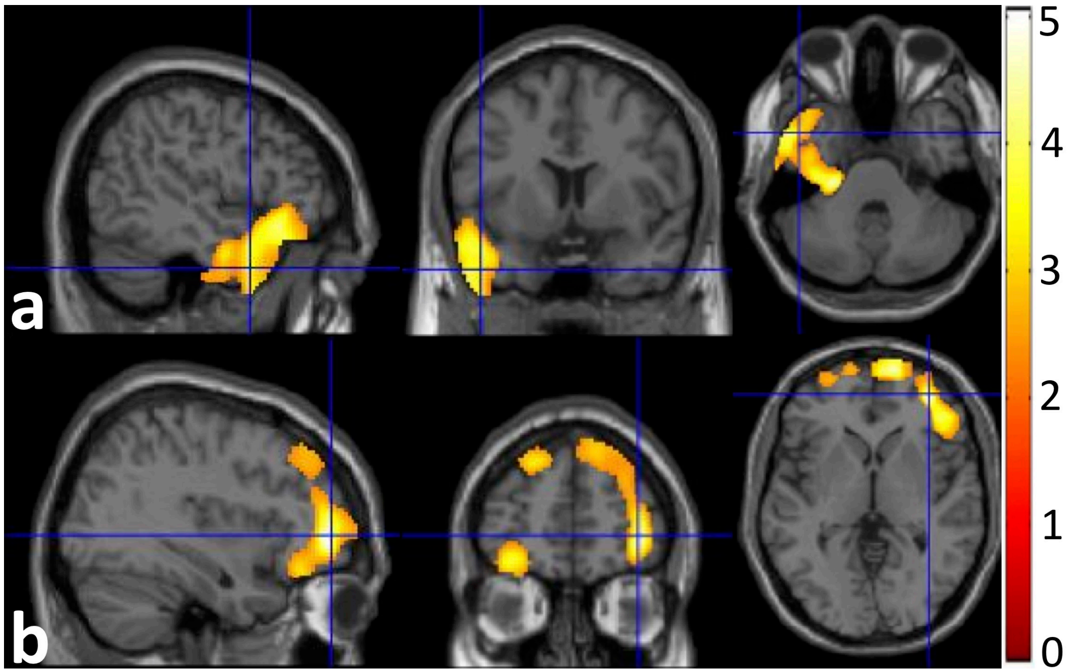

Fig. 2

- Significant positive correlation of perfusion fluctuation with maniac dimension in temporal pole/OFC regions (Fig. 2a).
- Significant negative correlation of perfusion connectivity with positive dimension in frontoparietal control network (Fig. 2b),

Summary of bipolar disorder ASL study

- Dynamic ASL is sensitive to perfusion-related alterations in BD patients relative to controls, especially to perfusion fluctuation and connectivity.
- Resting-state ASL is capable of detecting symptom-specific deficits of brain networks.
- Resting-state ASL-related measures may serve as novel neuroimaging biomarkers for BD, if confirmed in a large study.

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Dynamic ASL on Meditation

- Focused meditation has been shown to influence human brain networks, especially the default mode network (DMN) and dorsal attention network (DAN).
- Most of these studies were performed using traditional fMRI techniques and concentrated on the functional connectivity (FC) difference between experienced meditators and nonmeditators during meditation.
- Explore the sustained change in brain FC during rest following 2-month meditation practice using dynamic ASL.

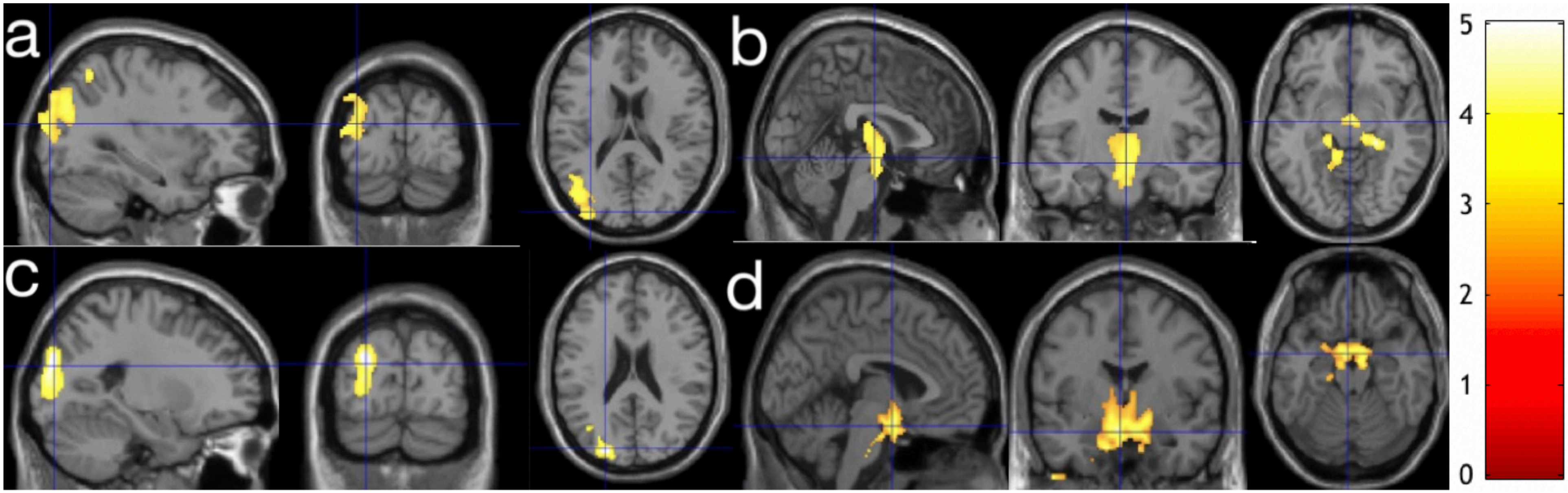
Dynamic ASL on Meditation Methods

- 3D pseudo-continuous arterial spin labeling (PCASL) sequence with 50 repetitions (11 subjects at baseline & 10 subjects at follow-up)
- The mean ASL signal from time series was used to derive the absolute CBF map using the flow kinetic model
- Divided by the whole-brain CBF to produce the relative CBF map
- Relative CBF map and ASL image time series were transformed to the standard brain space

Dynamic ASL on Meditation Methods

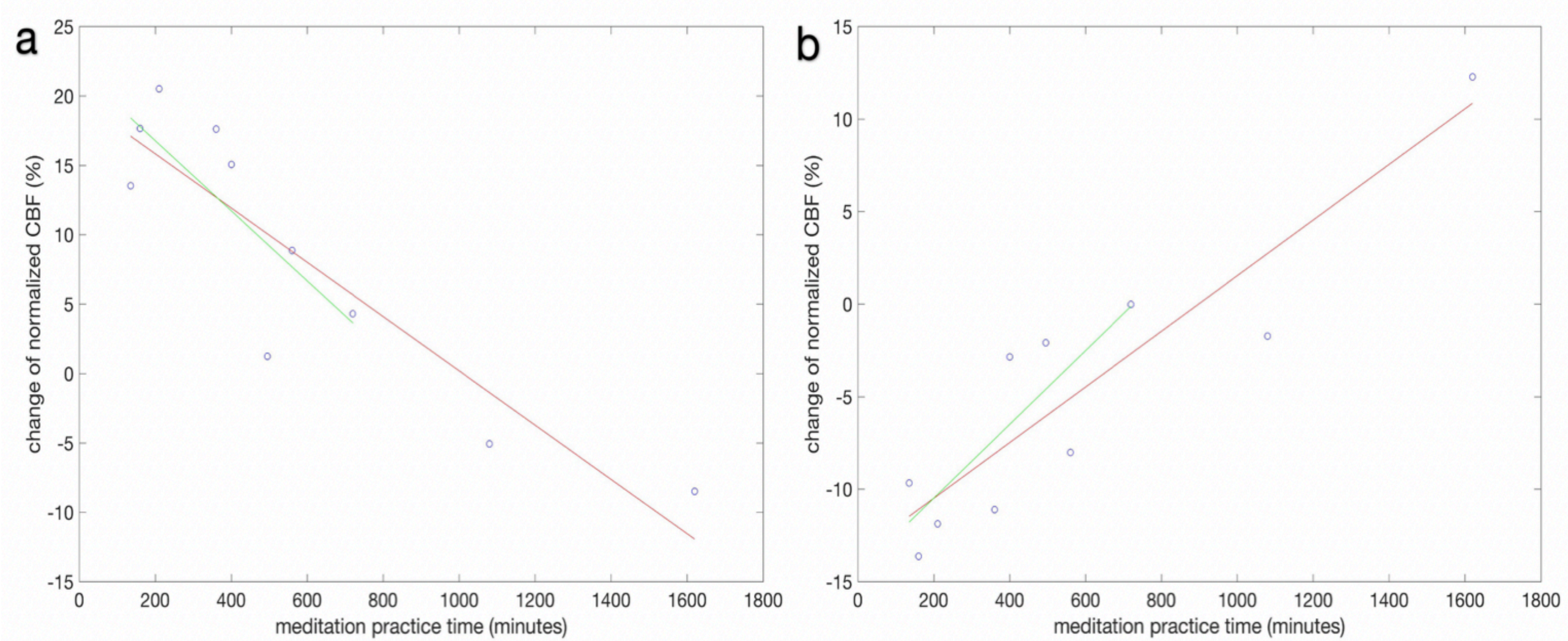
- Five seed regions of interest were chosen from DMN and DAN
- Individual FC maps were calculated from ASL image time series using Pearson correlation
- Individual FC maps were transformed into z score maps by a Fisher z transformation and smoothed with a 6mm Gaussian kernel.
- The CBF and FC maps before and after practicing meditation were compared using SPM8 via a paired t test with gender as a covariate
- The difference of the CBF and FC maps before and after meditation practice was modeled via multiple linear regression with gender and practice time as covariates

Dynamic ASL on Meditation CBF Results



(a) follow-up CBF> baseline CBF, (b) baseline CBF> follow-up CBF, (c) the more practice time is associated with the less increase of perfusion, and (d) the more practice time is associated with less decrease of perfusion. Color bar shows the range of t values.

Dynamic ASL on Meditation CBF Results

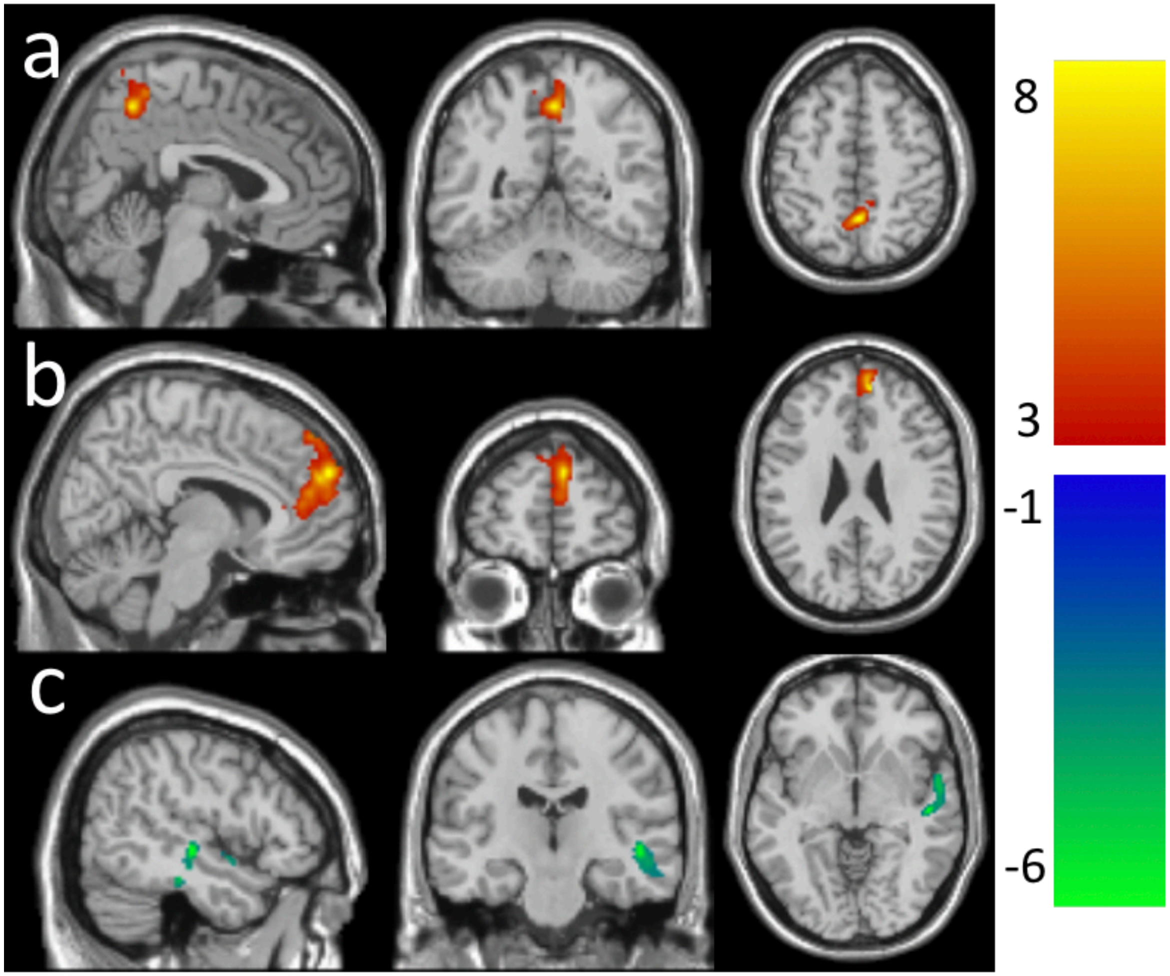


More practice time of meditation was associated with (a) less CBF increase in the left occipital region and (b) less CBF decrease in the left thalamus region.

Summary of cerebral blood flow

- The baseline CBF increase in the occipital/parietal region and decrease in the thalamus region after 2-month meditation practice agrees with the baseline CBF change in a SPECT study after 8-week meditation practice of patients with memory issues
- The baseline CBF increase in the occipital/parietal region has been related to tension, supporting the neural change of meditation in handling emotional stress.
- The association of CBF change in the occipital/parietal and thalamus regions indicates a complex neural pathway of meditation.

Dynamic ASL on Meditation FC Results



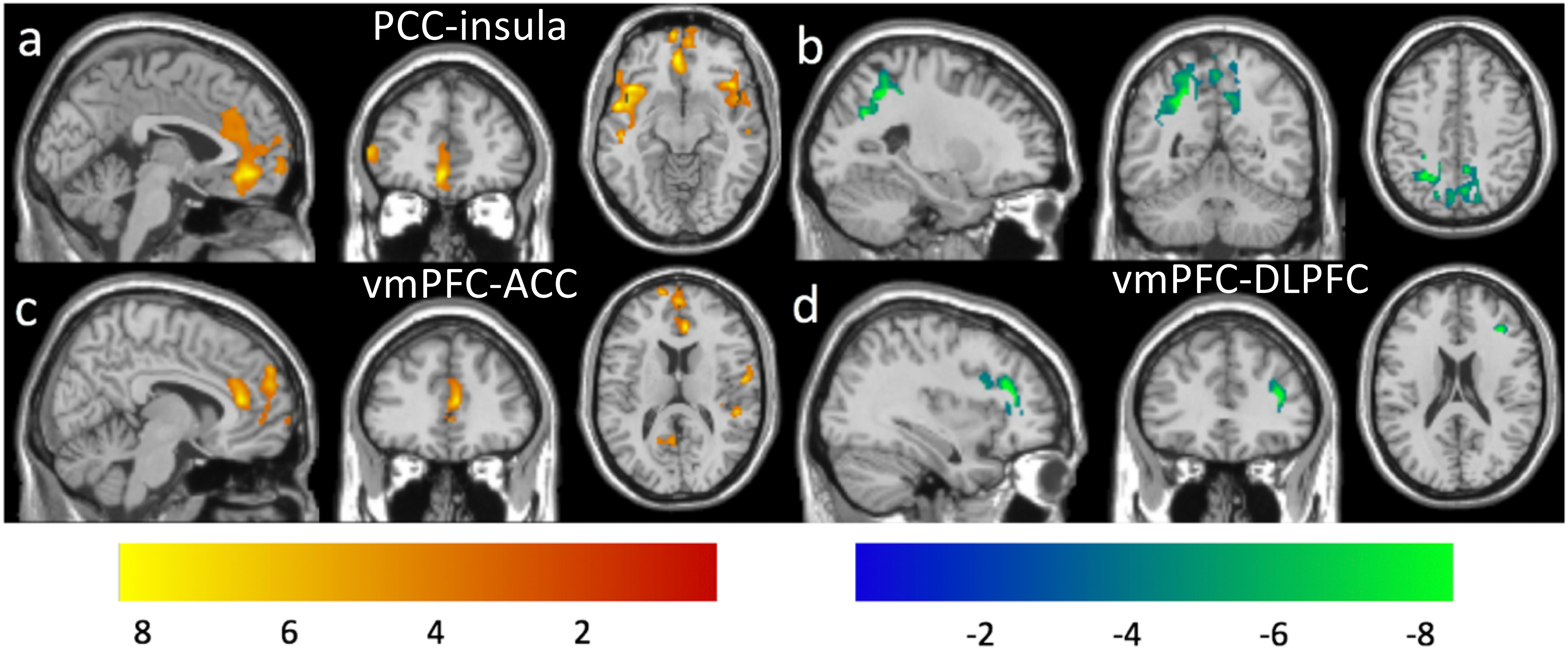
LMT-precuneus

RFE-superior frontal

LMT-superior temporal

between DMN and DAN

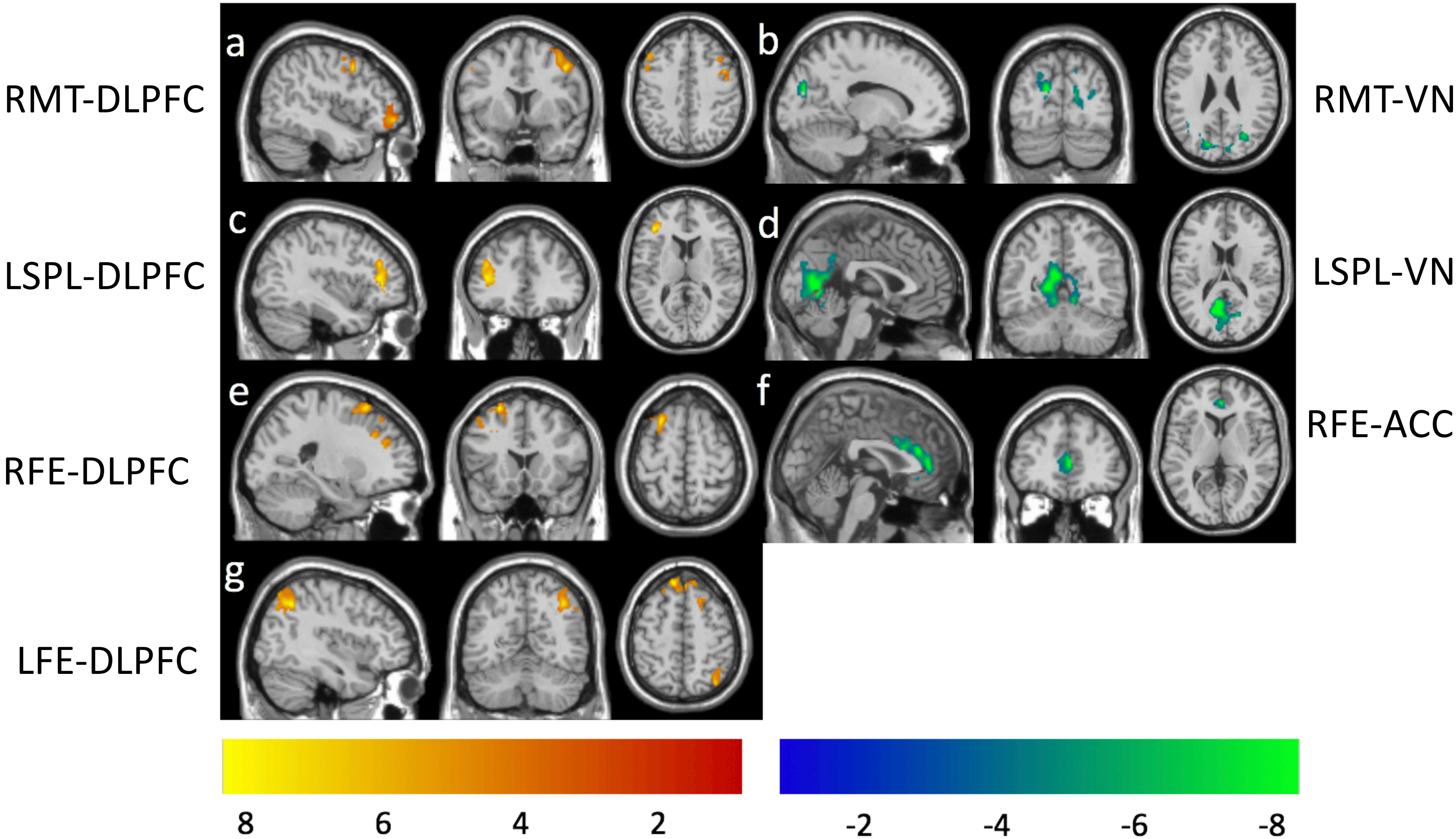
Dynamic ASL on Meditation FC Results



between DMN and SAN

between DMN and FPN

Dynamic ASL on Meditation FC Results



between DAN and FPN

between DAN and VN

Summary of Meditation ASL study

- Our significant findings using dASL support further investigation into the power of the technique in meditation studies.

- Two-month meditation is associated with the changes of rsFC and the changes of rsFC are associated with practice time.

- The meditation practice can strengthen the efficient control of FPC on fast switching between DMN and DAN.

- The meditation practice improves the utilization of attentional resources with reduced focus on visual processing.

Thank you for your attention!