Joint Morphometric and Perfusion Brain Changes in Aging

Michael Ewers
Duygu Tosun & Michael Weiner
University of California, San Francisco
VA Medical Center
Brain Changes in Normal Aging

• Cross-sectional and longitudinal estimates converge on 0.5% of global brain volume decline per year \(^\text{1}\) \(^{\text{Fotenos et al., Neurol, 2005}}\)
  – Decline starts as early as 30 yrs of age
  – Rate doubles (about 1% p.a.) in subjects with very mild AD (age > 70 yrs)
  – Linear + quadratic association for GM and WM

\(^{\text{1}}\) Fjell et al. Cereb Cortex, 2009
Perfusion Changes in Aging

• Perfusion brain changes more variable, although frontal decline has been observed as well
• Hypoperfusion may lead to increased brain atrophy
  – Age related vascular pathology
• Regional hyperperfusion may have compensatory function and be predictive of cognitive changes in aging
• Perfusion changes in aging poorly established
Aims of current study

- Trajectory of perfusion changes within the whole brain
- Comparison to changes in brain structure
- Association of perfusion changes in large-scale networks in association with regional brain atrophy
- Life-span perspective
Multimodal Assessment of Perfusion and DBM

• 77 non-demented controls
  – Abnormal on none or 1 standard neuropsychol. test battery
  – Age range: 21-85 yrs, average = 56 yrs
  – Multimodal assessment: T1 weighted MRI & continuous arterial spin labeling on 4T scanner
  – Deformation based morphometry via large deformation fluid registration
  – Spatial Normalization applied to grey matter corrected ASL images
Statistical design

Univariate Regression Analysis

\[ Y = \beta_0 + \text{Age} \times \beta_1 + \text{Age}^2 \times \beta_2 \]

Partial least squares analysis:
Functional Connectivity w/in Modalities

DBM (Jacob Det.) ASL

DBM

ASL

DBM (Jacob Det.) ASL

SPM Maps

PLS Maps

Predict Cognitive Decline

Parallel ICA:
Inter-modal connectivity

Corr of Mixing Coeff.
Univariate: Linear and Quadratic Age Effects on DBM

\[
\text{Jacob. Det.} = \beta_0 + \text{Age} \times \beta_1
\]

\[
\text{Jacob. Det.} = \beta_0 + \text{Age} \times \beta_1 + \text{Age}^2 \times \beta_2
\]

p-value cluster level < 0.05, voxel level = \( p < 0.01 \)
Statistical design

Univariate Regression Analysis

\[ Y = \beta_0 + \text{Age} \times \beta_1 + \text{Age}^2 \times \beta_2 \]

Partial least squares analysis:
Functional Connectivity w/in Modalities

DBM (Jacob Det.) → ASL → SPM Maps

DBM (Jacob Det.) → ASL → PLS Maps
Behavioral Partial Least Squares

1. \[
\begin{bmatrix}
\text{Age} \\
25 \\
61 \\
\vdots \\
\vdots
\end{bmatrix}
\leftrightarrow
\begin{bmatrix}
\text{DBM/ASL Images}
\end{bmatrix}
\rightarrow
\text{Cross-correlation of X and Y Matrix S}
\]

Behavioral Matrix X  
DBM/ASL Images Matrix Y

2. Singular Value Decomposition

3. Brain Score computation

Adopted from MacIntosh et al, Neuroimage, 1996
Partial Least Squares Analysis of Age on DBM

Linear & quadratic Age effects, thresholded at $p = 0.005$ (bootstrapped)
PLS DBM Brain Scores vs. Age

Linear and quadratic age associations for LV1

LV1: Correlation coefficient for gender: $r = 0.01$
LV2: Age (linear): $r = -0.08$, Age (quadratic): $r = 0.08$, gender: $r = -0.68$
LV3: n.s.
Association between DBM and Age within PLS-derived ROI

Average Jacob Det. In neg. PLS-ROI

Average Jacob Det. in pos. PLS-ROI
Univariate: Linear and Quadratic Age Effects on ASL-Perfusion

Jacob. Det. = $\beta_0 + \text{Age} \times \beta_1$

Jacob. Det. = $\beta_0 + \text{Age} \times \beta_1 + \text{Age}^2 \times \beta_2$

p-value cluster level < 0.05, voxel level = $p < 0.01$
Partial Least Squares Analysis of Age on Perfusion

Linear & quadratic Age effects, thresholded at $p = 0.005$ (bootstrapped)
PLS Perfusion Brain Scores vs. Age

LV1, \( p = 0.005 \)

\[ r = 0.6 \]

LV2: Correlation coefficient for gender: \( r = 0.33 \)

LV2: Age (linear): \( r = 0.07 \), Age (quadratic): \( r = 0.06 \), gender: \( r = -0.52 \)

LV3: n.s.
Association between Perfusion and Age within PLS-derived ROI

- Average Perfusion in ROI with neg. BSR
- Average Jacob Det. in neg. PLS-ROI

- Average Perfusion in ROI with pos. BSR
- Average Jacob Det. in pos. PLS-ROI
Statistical design

**Univariate Regression Analysis**

\[ Y = \beta_0 + \text{Age} \times \beta_1 + \text{Age}^2 \times \beta_2 \]

**Partial least squares analysis:**
Functional Connectivity w/in Modalities

DBM (Jacob Det.)    ASL

DBM (Jacob Det.)    ASL

SPM Maps

DBM (Jacob Det.)    ASL

ASL

PLS Maps

**Parallel ICA:**
Inter-modal connectivity

Predict Cognitive Decline

Corr of Mixing Coeff.
Parallel ICA of DBM and Perfusion

A  Mixing coefficients

B  DBM

C  Perfusion
Mixing Coefficient of DBM Predict Delayed Recall

$r = -0.34$
$p = 0.005$
Summary

• Univariate and multivariate largely overlap in findings on age-associated changes
  – DBM: increase in ventricles and widely distributed cortical atrophy
  – ASL: perfrontal and temporal increase but mostly posterior decrease in perfusion
  – Associations are linear plus quadratic in nature

• Multimodal associations: Spatially divergent association between ventricular expansion and medial temporal perfusion increase
Conclusions

• Age-related increase in perfusion associated with atrophy may be abnormal (compensatory)
• Ventricular expansion associated with aging associated with increased MTL perfusion may be especially sensitive for predicting memory decline
• Caution: Mediation needs to be shown (Age Effect on Cognitive Decline by DBM)
Perspective

• Scalar statistics like PLS-derived brain score or ICA derived mixing coefficient may have utility to predict cognitive decline and clinical outcome

• Joint functional and structural changes may be more predictive than uni-modal changes

• DTI to analyze neuronal network specific changes across modalities