MRI biomarkers of small vessel disease

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Detecting small vessel disease pathologies

- Arteriolosclerosis
- Atherosclerosis
- Microinfarcts
- Cerebral Amyloid Angiopathy (CAA)

Most are not visible in MRI.

Visible effects on the brain, but some are not specific.

Less visible effects on the brain.

Mixed pathologies are common.

Charidimou et al., Brain 2017
Kapasi et al., Acta Neuropathol. 2017
Mission: Identify and validate biomarkers for the small vessel diseases of the brain that produce vascular contributions to cognitive impairment and dementia (VCID).
MRI in MarkVCID

- Developed **uniform MRI acquisition protocol.**
  - **T₁w 3D MPRAGE:** TE=1.65 ms, TR=9.4 ms, 176 sag slices, af=2, 1x1x1 mm³
  - **T₂w 3D FLAIR:** TE=271 ms, TR=4.8 s, TI=1.65 s, 176 sag slices, af=3, 1x1x1 mm³
  - **T₂w 3D FSE:** TE=252 ms, TR=2.5 s, 176 sag slices, af=2 in both phase encoding and slice encoding directions, 1x1x1 mm³
  - **Multi-echo 3D GRE:** 8 echoes with TE=n × 2.4 ms, where n=1-8, TR=27 ms, 146 sag slices, af=2, 1.2x1.2x1.2 mm³
  - **Spin-echo echo-planar DTI:** TE=76 ms, TR=9.2 s, 80 axial slices, b=1000 s/mm² for 40 diffusion directions, 6 b=0 s/mm² volumes, af=2, 2x2x2 mm³
  - **2D GRE-EPI:** TE=21 ms, TR=1.5 s, 36 axial slices, 281 timepoints, af=2, 3.4x3.4x3.8 mm³
- Developed **QC protocol:** including MPRAGE, DTI and EPI on the ADNI phantom.
MRI biomarkers tested in MarkVCID (1\textsuperscript{st} wave)

White matter hyperintensities (cross-sectional) Category: Stratification

Total volume of white matter hyperintensities.
MRI biomarkers tested in MarkVCID (1\textsuperscript{st} wave)

White matter hyperintensities (longitudinal)

Change in the total volume of white matter hyperintensities in one year (including expansion or regression of penumbra).

Time-point 1  WMH difference  Time-point 2

courtesy of Drs. Wilcock D. and Jicha G.
MRI biomarkers tested in MarkVCID (1st wave)

**Peak Skeletonized Mean Diffusivity (PSMD)**

PSMD measures the width of the peak of the histogram of mean diffusivity after projection onto the WM skeleton.

Baykara et al., Ann Neurol 2016
MRI biomarkers tested in MarkVCID (1st wave)

Cerebrovascular reactivity (CVR)

Whole brain CVR value. Measured with BOLD MRI by modulating blood CO₂ level (inhaling 5% CO₂ for 50s periods).

Category: Susceptibility/Risk

courtesy of Dr. Lu H.

Peng et al., Neuroimage 2018
MRI biomarkers tested in MarkVCID (1st wave)

**Arteriolosclerosis**

Classifier trained to identify moderate to severe arteriolosclerosis (machine learning)

*Category: Risk*

- **Biomarker**
- **Score representing the likelihood of arteriolosclerosis**
- **WMH maps**
- **Diffusion anisotropy maps**
- **Demographics**
1) Study how ex-vivo brain MR properties relate to those in-vivo.

2) Extract ex-vivo MRI signatures of SVD pathologies in a large community-based cohort of older adults with and without dementia.

3) Develop classifiers of SVD pathologies based on ex-vivo multimodal MRI.

4) Translate ex-vivo classifiers to in-vivo and test using in-vivo MRI data.
General procedures

- Participants of the Memory and Aging Project (MAP), Religious Orders Study (ROS), Minority Aging Research Study (MARS), African American Core, Latino Core.
Ex-vivo MRI data can be linked to in-vivo data

Kotrotsou et al., Magn Reson Med 2014

dawew et al., Neurobiol Aging, 2014

Evia et al., PLoS One, 2017
Neuropathologic correlates of white matter hyperintensities

- N=603
- Ex-vivo MRI and pathology
- Ordinal logistic regression

Dependent variable:
WMH burden

Independent variables:
Neuropathologic correlates of white matter hyperintensities

- N=275
- Ex-vivo MRI and pathology
- Multiple linear regression

Dependent variable:
WMH regional volume

Independent variables:
Neuropathologic correlates of T2, QSM, etc.

Arteriolar sclerosis
CAA
Micro-infarcts
Atherosclerosis
Amyloid plaques
PHF-tau tangles

N=200

N=223
Constructing biomarkers of SVD pathologies

- WMH maps
- # of micro-bleeds
- Presence of superficial siderosis
- # of EPVS
- # and volume of infarcts
- Regional brain volumes
- Diffusion anisotropy maps
- T2 relaxation maps
- Magnetic susceptibility maps

Machine learning → Biomarker → Score for SVD pathologies
Classification of arteriolosclerosis based on ex-vivo MRI

- Support vector machine (SVM)
- 132 participants (~90 years old)
- Features: demographics + WMH maps + DTI maps
- 100 repeats of stratified shuffle split cross-validation (80% training, 20% testing)
- Average AUC = 0.74

![ROC curve graph]
In-vivo testing of arteriolosclerosis biomarker

- 439 non-demented participants (~80 years old)
- Biomarker score is correlated with change in:
  - **perceptual speed:** -0.17 (p=0.0004)
  - **visuospatial ability:** -0.11 (p=0.02)
  - semantic memory: -0.09 (p=0.052)
  - episodic memory: -0.07 (p=0.15)
  - working memory: -0.07 (p=0.17)
Classification of arteriolosclerosis/atherosclerosis based on ex-vivo MRI

• Logistic regression classifier
• 727 participants (~90 years old)
• Features: demo + WMH risk score (Random Forests) + R2 risk score (Random Forests)
• 100 repeats of stratified shuffle split cross-validation (80% training, 20% testing)
• Average AUC = 0.73

![Receiver operating characteristic curve](image)

- Eval MRI
- Eval MRI
- Eval MRI
- Eval MRI
- Death
- Autopsy
- 1st Ex-vivo MRI
- 2nd Ex-vivo MRI
- Histopathology
In-vivo testing of arteriolosclerosis/atherosclerosis biomarker

- 428 non-demented participants (~80 years old)
- Biomarker score is correlated with change in:
  - working memory: \(-0.13 (p=0.004)\)
  - semantic memory: \(-0.10 (p=0.016)\)
  - perceptual speed: \(-0.08 (p=0.051)\)
  - episodic memory: \(-0.06 (p=0.12)\)
Take home messages

- MRI-based SVD biomarkers are undergoing multi-site validation at MarkVCID.

At Rush / IIT

- We combine ex-vivo MRI and histopathology to:
  - Identify the neuropathologic correlates of brain characteristics.
  - Develop MRI biomarkers of SVD neuropathologies.

- Combination of ex-vivo MRI and pathology:
  - Minimizes interval between imaging and autopsy.
  - Imaging independent of frailty level.

- Community-based cohorts. Large N. Multiple MR modalities. Multiple pathologies.

- Rush / IIT (wave 1): Arteriolosclerosis kit
  Biomarker score is correlated with decline in perceptual speed and visuospatial abilities 2 years after MRI.

- Rush / IIT (wave 2): Arteriolosclerosis/Atherosclerosis kit
  Biomarker score is correlated with decline in working memory and semantic memory 2 years after MRI.
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