Neuroimaging and Delirium

4th Annual Delirium Boot Camp
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MRI: What Do We Measure?
Historical Perspective

- **500 BC**: “phrenitis” (Hippocrates)
- **1st Century AD**: “delirium” (Celsus)
- **13th Century**: “delirium phrenesis caused by disease of the brain and its membranes” (Bartholomeus Anglicus)
- **1918**: ventriculography and pneumoencephalography (Walter Dandy)
- **1927**: cerebral arteriogram (Moniz)
- **1973**: CT applied to clinical diagnosis (Hounsfield)
- **Mid 1970s**: first MRI (Lauterbur)

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Role of Neuroimaging

- **DELIRIUM (syndrome)**
- **Predisposing Factors**
- **Vulnerability**
- **What Happens During Delirium** (Methodologically Challenging)
- **Long-term Effect**

**CONTROL FOR CONFOUNDING FACTORS**
DELIRIUM

- Global Brain Atrophy
- White Matter Hyperintensities
- Reduced Perfusion of the Frontal, Temporal, Parietal, Occipital, Deep Grey Matter
- Abnormalities in the Corpus Callosum and Internal Capsule

ALZHEIMER’S DISEASE

- Global Brain Atrophy
- Hippocampal Atrophy
- White Matter Hyperintensities
- Reduced Perfusion of the Posterior Cingulate
- Hippocampal Abnormalities

REGIONAL SPECIFICITY

**VISualizing Icu SurvivOrs Neuroradiological Sequelae**

The association between brain volumes, delirium duration, and cognitive outcomes in intensive care unit survivors: The VISIONS cohort magnetic resonance imaging study

Max L. Gunther, PhD; Alessandro Morandi, MD, MPH; Erin Krauskapf, BS; Pratik Pandharipande, MD, MSCI; Timothy D. Girard, MD, MSCI; James C. Jackson, PsyD; Jennifer Thompson, MPH; Ayumi K. Shintani, PhD; Sunil Geervanghese, MD, MSCI; Russell R. Miller II, MD, MPH; Angelo Canonico, MD; Kristen Merkle, BA; Christopher J. Canistraci, MS; Bader P. Rogers, PhD; J. Chris Gatley, PhD; Stephen Heckers, MD, MSCI; John C. Gore, PhD; Ramona O. Hopkins, PhD; E. Wesley Ely, MD, MPH; for the VISIONS Investigation (VISualizing Icu SurvivOrs Neuroradiological Sequelae)

The relationship between delirium duration, white matter integrity, and cognitive impairment in intensive care unit survivors as determined by diffusion tensor imaging: The VISIONS prospective cohort magnetic resonance imaging study

Alessandro Morandi, MD, MPH; Bader P. Rogers, PhD; Max L. Gunther, PhD; Kristen Merkle, BA; Pratik Pandharipande, MD, MSCI; Timothy D. Girard, MD, MSCI; James C. Jackson, PsyD; Jennifer Thompson, MPH; Ayumi K. Shintani, PhD; Sunil Geervanghese, MD, MSCI; Russell R. Miller II, MD, MPH; Angelo Canonico, MD; Christopher J. Canistraci, MS; John C. Gore, PhD; E. Wesley Ely, MD, MPH; Ramona O. Hopkins, PhD; for the VISIONS Investigation (VISualizing Icu SurvivOrs Neuroradiological Sequelae)
Successful AGing after Elective Surgery

Study Participants

- Older Individuals ≥70 years
- Dementia-free
- Non-cardiac Elective Surgery
Successful AGing after Elective Surgery

Study Design and Aims

**DELIRIUM**

N=146 (32 with delirium)

N=126 (28 with delirium)

PREDISPOSING SUBSTRATES

Analysis controlled for Age, Sex, Vascular Comorbidity, Baseline Cognitive Performance

**LONG TERM EFFECT**

T0 (surgery)  
T1 (1 year) 

time

Successful AGing after Elective Surgery

MRI Measures

- **STRUCTURAL (T1, T2, FLAIR)**
  - Global Brain Atrophy
  - Hippocampal Volume
  - White Matter Hyperintensity Volume

- **PERFUSION (Arterial Spin Labeling)**
  - Cerebral Blood Flow

- **DIFFUSION TENSOR IMAGING (DTI)**
  - Microstructural Brain Abnormalities
SAGES Study / MRI Measures

- **STRUCTURAL (T1, T2, FLAIR)**
  - Global Brain Atrophy
  - Hippocampal Volume
  - White Matter Hyperintensity Volume
Brain atrophy and white-matter hyperintensities are not significantly associated with incidence and severity of postoperative delirium in older persons without dementia


### Table 2

<table>
<thead>
<tr>
<th>Quantitative postoperative MRI measures of brain parenchymal damage</th>
<th>All subjects (n = 140)</th>
<th>No delirium (n = 114)</th>
<th>Delirium (n = 32)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>WMH volume (cc)</td>
<td>11.27 ± 6.46</td>
<td>11.55 ± 6.34</td>
<td>10.24 ± 7.58</td>
<td>0.315</td>
</tr>
<tr>
<td>MPV (cc)</td>
<td>1013.61 ± 113.11</td>
<td>1018.71 ± 114.82</td>
<td>996.79 ± 108.68</td>
<td>0.134</td>
</tr>
<tr>
<td>Hypodense area (cc)</td>
<td>3.24 ± 0.43</td>
<td>3.23 ± 0.43</td>
<td>3.23 ± 0.43</td>
<td>0.922</td>
</tr>
<tr>
<td>KVC (cc)</td>
<td>1470.71 ± 158.51</td>
<td>1471.88 ± 163.73</td>
<td>1410.05 ± 138.23</td>
<td>0.803</td>
</tr>
</tbody>
</table>

Data are expressed as mean ± SD. p-value refers to group comparisons of delirium versus delirium by the statistical tests as indicated.

Key: BPV, brain parenchymal volume; KVC, intracerebral cavity volume; MRI, magnetic resonance imaging; WMH, white-matter hyperintensity.

1 Analyze-Wein test,
2 Student's t test.

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### White-Matter Hyperintensities Predict Delirium After Cardiac Surgery

Takahisa Hatano, M.D., Jin Narumoto, M.D., Ph.D., Keisuke Shibata, M.D., Ph.D., Teruyuki Matsumoto, M.D., Shogo Taniguchi, M.D., Yuzuru Hata, M.D., Koit Nomura, M.D., Ph.D., Hitoshi Yabo, M.D., Ph.D., Kenji Fuhui, M.D., Ph.D.

Association of pre-operative brain pathology with post-operative delirium in a cohort of non-small cell lung cancer patients undergoing surgical resection

James C. Rosa, Jian C. Hsu, Robert Downey, Jun Ai, Marcus L. David, Andre Haschke, Reena Kar-Grodzicki, and Tim Antiel

The association between brain volumes, delirium duration, and cognitive outcomes in intensive care unit survivors: The VISIONS cohort magnetic resonance imaging study


Pre-existing cerebral infarcts as a risk factor for delirium after coronary artery bypass graft surgery

Sunti Otome, Kengo Makiwa, Tomoko Goto, Tomoko Baba, and Atsushi Yoshitake

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**RETROSPECTIVE Design CONFOUNDERS**

**NO CONTROL Group**

**NO Pre-Delirium MRI**

**NO Association with Global WMH score**
SAGES Study / MRI Measures

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  - Global Brain Atrophy
  - Hippocampal Volume
  - White Matter Hyperintensities Volume

- **PERFUSION** (Arterial Spin Labeling)
  - Cerebral Blood Flow

- **DIFFUSION TENSOR IMAGING** (DTI)
  - Microstructural Brain Abnormalities

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**Cerebral blood flow MRI in the nondemented elderly is not predictive of post-operative delirium but is correlated with cognitive performance**

Tammy T Hsieh<sup>1,2</sup>, Weiying Dai<sup>1,4</sup>, Michele Cavallari<sup>3</sup>, Charles RG Guttman<sup>1</sup>, Dominik S Meier<sup>6</sup>, Eva M Schmitt<sup>1</sup>, Bradford C Dickerson<sup>4</sup>, Daniel Z Presk<sup>1</sup>, Edward R Marcantonio<sup>2</sup>, Richard N Jones<sup>2,4</sup>, Yun Ray Gou<sup>2</sup>, Thomas G Traynor<sup>2,5</sup>, Tamara G Fong<sup>2,6</sup>, Long Ngo<sup>1</sup>, Sharon K Inouye<sup>2,3,4</sup>, David C Alsp<sup>3,4</sup> and on behalf of the SAGES Study Group
• Reduced flow and metabolism in the posterior cingulate is the earliest functional predictor of cognitive impairment and Alzheimer’s disease

• The absence of an association between blood flow in this region and delirium argues against a role for incipient AD in the risk of delirium in elderly subjects without dementia.

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**SAGES Study / MRI Measures**

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- **DIFFUSION TENSOR IMAGING (DTI)**
  - Microstructural Brain Abnormalities
DTI Abnormalities Indicate Brain Microstructural Damage

Neural substrates of vulnerability to postsurgical delirium as revealed by presurgical diffusion MRI

Delirium Severity
(age, gender, vascular comorbidity)

Delirium Severity
(age, gender, vascular comorbidity, GCP)
What We Learned

- Microstructural tissue damage captured by Diffusion MRI underlies the occurrence of delirium.
- The spatial distribution and predominance of diffusion findings over dementia sensitive techniques like gray matter atrophy and perfusion suggest that delirium is associated more with age related decline in white matter pathways than neuronal loss and reduced perfusion or metabolism.
- Implications regarding the pathogenesis of delirium can come from the regional specificity of the abnormalities associated with delirium.
  - Baseline DTI abnormalities predisposing to delirium showed two separate phenomena (AD-like, and frontal/parietal)
  - Longitudinal DTI abnormalities seem more diffused, but the observed effect was too small to localize abnormalities with confidence
IMPORTANT FACTORS

- **Baseline scan**
- **Control for confounders** to isolate the relationship between brain abnormalities and delirium.
- **Inclusion/exclusion criteria**: implications for generalizability and sensitivity/specificity

Future Work

- Relationship between **delirium and dementia**: AD-like vs. Age-like abnormalities
- **Other MRI measures and techniques** to further explore the relationship between brain damage and delirium
  - Cortical Thickness
  - Regional WMH
  - Structural/Functional Connectivity (DTI Tractography, Resting-State fMRI)