Significance of White Matter Hyperintensities in MCI

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MCI is Early AD

AD Process → Hippocampal Injury → MCI → AD

Petersen et al, Arch Neurol, 2001
White Matter Hyperintensities

T1

PD

T2
Vascular Risk Factors Predict WMH

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Diabetes</td>
<td>0.0113</td>
</tr>
<tr>
<td>Heart Disease</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Systolic Blood Pressure</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Left Ventricular Hypertrophy</td>
<td>0.0001</td>
</tr>
<tr>
<td>Treated Hypertension</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Jeerakathil, et al. Stroke, 2004
WMH Quantification
## White Matter Hyperintensities and MCI

<table>
<thead>
<tr>
<th>Predictor Variable</th>
<th>Adjusted RR and 95% CL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>1.18 [1.03, 1.35]</td>
</tr>
<tr>
<td>WMH</td>
<td>5.34 [1.80, 15.9]</td>
</tr>
<tr>
<td>ApoE4</td>
<td>3.54 [1.43, 8.78]</td>
</tr>
<tr>
<td>Diastolic BP</td>
<td>1.70 [1.07, 2.71]</td>
</tr>
</tbody>
</table>

*DeCarli et al; Arch Neurol, 2001*
WMH are Associated with Episodic Memory Deficits

- DeCarli et al, Arch Neurol, 2001
- Wu et al, Neurology, 2002
- Lopez et al, Arch Neurol, 2003
- Petkov et al, J Int Neuropsychol Soc, 2004
Role of AD and WMH In MCI

AD Process

Hippocampal Injury

White Matter Injury

Executive Control Deficit

MCI

CVD
Different Mechanisms of Episodic Memory Failure in MCI

Christine Wu Nordahl, Charan Ranganath, Andrew Yonelinas, Charles DeCarli, Bruce Reed, William J. Jagust
Neuropsychologia 43(11) 1688-1697; 2005
aMCI Subtypes

Based on SALSA dataset, n=122
## Subject Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Controls</th>
<th>MCI-HA</th>
<th>MCI-WMH</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>n</strong></td>
<td>20</td>
<td>11</td>
<td>11</td>
</tr>
<tr>
<td><strong>Age</strong></td>
<td>78.65 (6.34)</td>
<td>74.55 (5.65)</td>
<td>77.64 (3.56)</td>
</tr>
<tr>
<td><strong>Education</strong></td>
<td>15.6 (2.79)</td>
<td>15.8 (3.46)</td>
<td>13.5 (1.51)</td>
</tr>
<tr>
<td><strong>Gender (M/F)</strong></td>
<td>5/15</td>
<td>4/7</td>
<td>5/6</td>
</tr>
<tr>
<td><strong>MMSE</strong></td>
<td>29.63 (0.49)</td>
<td>27.46 (1.81)*</td>
<td>27.27(2.45)*</td>
</tr>
<tr>
<td><strong>Left HC</strong></td>
<td>.150 (.03)</td>
<td>.102 (.03)*</td>
<td>.148 (.02)</td>
</tr>
<tr>
<td><strong>Right HC</strong></td>
<td>.152 (.02)</td>
<td>.107 (.03)*</td>
<td>.147 (.01)</td>
</tr>
<tr>
<td><strong>WMH load</strong></td>
<td>13.15 (15.185)</td>
<td>7.66 (2.93)</td>
<td>34.38 (12.2)*</td>
</tr>
<tr>
<td><strong>Hypertension</strong></td>
<td>47%</td>
<td>45%</td>
<td>82%</td>
</tr>
<tr>
<td><strong>Type II Diabetes</strong></td>
<td>12%</td>
<td>0%</td>
<td>27%</td>
</tr>
</tbody>
</table>

* differs from other groups, p < .05
Behavioral Tasks

1. Episodic Memory Task: Object-Color Association

study
18 red/18 green

delay
~60m

test
red or green?
MCI-HA and MCI-WMH are equally impaired on the color association episodic memory task.

* Differs from controls and MCI-HA $p < .01$
Behavioral Tasks

2. Working Memory Task: Item Recognition
   2, 4, 6 - item verbal
   4 - item spatial

study
+ 
B R

delay
2 sec

probe
b
MCI-WMH are impaired on the item recognition task

* Differs from controls and MCI-HA p < .01
** Differs from controls p < .01, Differs from MCI-HA p = .08
3. Working Memory Task: N-back
   - 1-back
   - 2-back
MCI-WMH are also impaired on the n-back working memory tasks

* Differs from controls and MCI-HA p < .01
Summary of Behavioral Data

• MCI-HC and MCI-WMH are equally impaired on the episodic memory task

• MCI-WMH are impaired on working memory, both in simple maintenance as well as a more complicated task involving manipulation and maintenance
White Matter Changes Compromise Prefrontal Cortex Function in Healthy Elderly

Christine Wu Nordahl, Charan Ranganath, Andrew Yonelinas, Charles DeCarli, Evan Fletcher, William J. Jagust
In Press: Journal Cognitive Neuroscience
Behavioral Tasks

Episodic Retrieval

Study (prior to scanning)
18 red/18 green

Test (during scanning)
red or green?

Working memory:
Low and high loads

A D
B R
study

+ delay
~60m

+ delay
2 sec

b probe
Working memory activations

- Bilateral dorsal prefrontal cortex activations
- Bilateral ventral prefrontal cortex activations
**Working memory task:**
Dorsal prefrontal cortex function is negatively correlated with WMH severity

Consistent with evidence suggesting that dorsal PFC is more affected in aging
Working memory task:
Anterior cingulate cortex function is negatively correlated with WMH severity

Anterior cingulate activity is associated with cognitive control (i.e., ability to guide thought and action in accordance with internal intentions)

Functional connectivity between anterior cingulate and PFC mediates successful task performance (Kondo et al 2004)
Summary of fMRI Data

• WMH a presumed indicator of cerebrovascular brain injury is associated with working memory impairment

• Executive control processes are likely involved and related to amount of WMH
Disconnection of Working Memory Processes by White Matter Hyperintensities

Adriane Mayda
Graduate Student, IDeA Lab
University of California at Davis
Disconnection Hypothesis

Vascular Factors

White Matter Injury

WMH

Cognitive Deficits

? FA
Anisotropy Mapping
Location of WMH in MCI

Normal Controls (n=30)  MCI (n=29)
Location of WMH and ROI
Correlations

- Log WMH (% TCV) vs Accuracy: $R^2 = 0.20$
- Fractional Anisotropy vs Accuracy: $R^2 = 0.62$

**Total WMH**

**FA within WMH**
Summary

• aMCI has at least 2 subtypes
  – Hi WMH
  – Small Hippocampi

• Amnesia in MCI-WMH results from
  – Impairments in executive control
  – Reduced prefrontal activation
  – Disconnection from posterior targets
Conclusions

• WMH are common to the elderly
• WMH alone can be associated with episodic memory impairments
• WMH likely contribute to susceptibility to late life cognitive impairment and dementia
• WMH are potentially modifiable
• Adriane Mayda
• Christine Nordahl
• Evan Fletcher
• Owen Carmichael
• IDeA Lab

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http://neuroscience.ucdavis.edu/idealab/