White matter hyperintensity burden in elderly cohort studies.

The Sunnybrook Dementia Study, Alzheimer Disease Neuroimaging Initiative, and Three-City Study.

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Background

Given the recent acknowledgement of the complex mixed pathologies that contribute to the clinical expression of dementia, various cohort studies have aimed to examine Alzheimer’s disease (AD) and cerebrovascular disease as comorbid pathologies, with neuroimaging playing a central role in these studies.

Objective

Using white matter hyperintensities (WMH) as a biomarker of cerebrovascular disease, we compared WMH burden between the Sunnybrook Dementia Study (SDS), the Alzheimer’s Disease Neuroimaging Initiative (ADNI), the Three-City Study (3C), and various other studies around the world.

Results

<table>
<thead>
<tr>
<th>Study Location</th>
<th>Sample (n)</th>
<th>WMH Volume Ranges for SDS &amp; ADNI1 study samples</th>
</tr>
</thead>
<tbody>
<tr>
<td>SDS Canada</td>
<td>AD (216)</td>
<td>23.0 (2.1)</td>
</tr>
<tr>
<td>ADNI N. America</td>
<td>AD (347)</td>
<td>27.0 (2.1)</td>
</tr>
<tr>
<td>3C France</td>
<td>AD (189)</td>
<td>27.7 (1.7)</td>
</tr>
</tbody>
</table>

Table 1: MMSE, Age, and WMH volumetrics by Dx group and study sample.

**Table 2: Comparison of WMH volumetric reports from various studies around the world**

Gaps in diagnostic criteria: Probable vs. Possible AD?

Based on our findings, it was evident that ADNI1 had minimal WMH burden relative to other large studies that examine aging and dementia.

This low WMH burden in ADNI1 may be considered as both an advantage, representing a relatively ‘pure’ sample with little confounding vasculopathy, and a disadvantage, as it limits generalizability to ‘real world’ patient populations with mixed pathologies and to non-demented groups with baseline vascular disease.

Possible reasons for this distinction include a potential selection bias towards people with well managed vascular risk factors and gaps in diagnostic criteria.

Discussion

Methods

**Table 2: Comparison of WMH volumetric reports from various studies around the world**

**Fig. 1** Scatterplots showing the distribution of WMH volume by age for AD patients, MCI, and NC, comparing the ADNI1 (RED circles) and the SDS (BLUE triangles). Head sizes are corrected for total intracranial volume. NC ADNI1 patients were also matched by disease severity using the HoN. Dotted line represents the 10cc cognitive threshold for WMH originally proposed by Roizen and colleagues. 

**Fig. 2** Pie chart showing WMH volume ranges for the Sunnybrook Dementia Study (SDS, left) and the Alzheimer’s Disease Neuroimaging Initiative (ADNI1, right).

**Fig. 3** Structural MRI (left), middle PD, right T2) of a 71 year-old woman living with Alzheimer’s disease. T1 voxel analysis revealed that she had 16cc of WMH. Should this be considered moderate or severe WMH burden? Should this patient’s diagnosis be probable or possible AD dementia based on NIA-AA criteria? [3,11]

**Fig. 4** Proton density (PD) and T2-weighted structural MRI showing white matter hyperintensities of presumed vascular origin (WMH [15]) segmentation in red, WMH volumetrics for SDS, ADNI1, and 3C were obtained from PD/T2 based segmentations.

Several other large studies were used for additional comparison demonstrating similar WMH results:

- Leukoaraisis and Disability Study (LADIS) [4]
- Rotterdam Study [5]
- Personality & Total Health (PATH) Through Life [6]

References

4. Frisoni et al. (2009), NeuroImage.
5. Voschenholt et al. (2010), ArchNeurol.
6. Chen et al. (2009), Neurology.
7. Non et al. (2014), Stroke.

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