Neuroimaging biomarkers track brain degeneration in 676 subjects with Alzheimer’s disease, mild cognitive impairment, and healthy controls

Laboratory of Neuro Imaging
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and the Alzheimer's Disease Neuroimaging Initiative
Alzheimer's Disease Neuroimaging Initiative (ADNI)

• ADNI is a large five year research project
• 200 AD, 400 MCI and 200 elderly controls
• http://www.adni-info.org/
• http://www.loni.ucla.edu/ADNI/
Tensor-Based Morphometry (TBM) - Cross-sectional Design -

MDT $\rightarrow$ Jacobian Map $\rightarrow$ Individual Scan

$\begin{pmatrix}
\frac{\partial(x-u)}{\partial x} & \frac{\partial(y-u)}{\partial y} & \frac{\partial(z-u)}{\partial z} \\
\frac{\partial(x-u)}{\partial y} & \frac{\partial(y-u)}{\partial y} & \frac{\partial(z-u)}{\partial y} \\
\frac{\partial(x-u)}{\partial z} & \frac{\partial(y-u)}{\partial z} & \frac{\partial(z-u)}{\partial z}
\end{pmatrix}$

$\det J(r) > 1$ Volume Expansion

$\det J(r) < 1$ Volume Loss
Tracking brain degeneration in 676 subjects with AD (N=165), MCI (N=330), and healthy controls (N=181)

- AD vs. CTL
- MCI vs. CTL
- AD vs. MCI

Baseline TBM correlate with Sum-of-Boxes CDR

Baseline TBM correlate with FUTURE CHANGES in Sum-of-Boxes CDR

Baseline TBM correlate with MMSE

Association between Jacobian values and conversion to AD in a year

MCI (n = 186)

40 MCI subjects became AD after a year, corresponding to a conversion rate of 21.5%

ApoE and brain structure

Tensor-Based Morphometry (TBM) - Longitudinal Design -

$\begin{vmatrix}
\frac{\partial(x-u_x)}{\partial z} & \frac{\partial(y-u_y)}{\partial z} & \frac{\partial(z-u_z)}{\partial z} \\
\frac{\partial(x-u_x)}{\partial y} & \frac{\partial(y-u_y)}{\partial y} & \frac{\partial(z-u_z)}{\partial y} \\
\frac{\partial(x-u_x)}{\partial x} & \frac{\partial(y-u_y)}{\partial x} & \frac{\partial(z-u_z)}{\partial x}
\end{vmatrix}

\det J(r) > 1 \text{ Volume Expansion}

\det J(r) < 1 \text{ Volume Loss}
AD (N=104) versus Normal (N=157)
- Mean Atrophy Rates -

MCI (N=254) versus Normal (N=157)

- Mean Atrophy Rates -

Region-of-interest (ROI)

Temporal lobes

Statistical ROI derived from an independent training sample of 22 AD patients

Estimated sample sizes (n80)

- needed to detect a 25% reduction in the mean annual change with a two-sided test and $\alpha=0.05$ at 80% power, for a two-arm study

$$n = \frac{2\sigma^2_D \left( z_{1-\alpha/2} + z_{\text{power}} \right)^2}{\left(0.25 \bar{\beta}\right)^2}$$

➢ Sum-of-boxes Clinical Dementia Rating (CDR) gives best power among the clinical scores, but the TBM method is 9 times better

<table>
<thead>
<tr>
<th></th>
<th>AD</th>
<th>MCI</th>
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<tbody>
<tr>
<td>TBM</td>
<td>48</td>
<td>88</td>
</tr>
<tr>
<td>CDR-SB</td>
<td>408</td>
<td>796</td>
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<td>ADAS-Cog</td>
<td>619</td>
<td>6797</td>
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<tr>
<td>MMSE</td>
<td>1078</td>
<td>3275</td>
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</tbody>
</table>

The rates of temporal lobe atrophy correlate with the levels of CSF biomarkers- A longitudinal study of 100 subjects (20 AD, 40 MCI and 20 controls)

Summary

• TBM as a neuroimaging marker
  – Correlate with clinical decline, CSF biomarkers, and predict future conversion to AD

• Using TBM as a potential surrogate marker, only 48 AD and 88 MCI subjects are needed to detect 25% slowing of disease in clinical trials (9x better than best clinical score)
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