Brain Changes in 676 ADNI subjects: Summary of 10 Studies using Tensor Based Morphometry & Automated Hippocampal Maps

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http://www.loni.ucla.edu/~thompson/ADNI/adni.html
Overview

Mapped brain changes in 676 ADNI subjects

- Tensor-based morphometry (gives 3D maps of rates of tissue loss)
- Automated Hippocampal/Ventricular Mapping
- 1000s of scans, no manual intervention

Only need ~40 AD and 80 MCI subjects to detect 25% slowing of disease (10x better than best clinical score)

Which MRI measures correlate best with clinical decline, and with CSF biomarkers (A-beta/Tau)?
What is the best numeric summary of change from a 3D image?
Is 3T better than 1.5T? How is power affected by pooling?
Detecting Anatomical Change

4-year Interval 2 weeks
Mapping Growth and Loss

- Growth
- Loss
- No Change
AD (N=104) versus Normal (N=157)
- Mean Atrophy Rates -

Hua, X. and Thompson, P.M. et al., 2009
MCI (N=254) versus Normal (N=157) - Mean Atrophy Rates -

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MCI Converters Lose Tissue Faster

What are these loss rates correlated with?

For drug trials, want to summarize change in a Region-of-interest (ROI)

Anatomical ROI based on temporal lobes

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

Statistical ROI reduces sample size by 15-50%; most helpful in MCI

- Statistically-defined ROI outperforms the anatomically-defined temporal lobe ROI; extremely helpful in MCI, as it focuses on the part of the brain that is changing most*

<table>
<thead>
<tr>
<th>TBM Designs</th>
<th>AD Stat-ROI</th>
<th>AD Temporal-ROI</th>
<th>MCI Stat-ROI</th>
<th>MCI Temporal-ROI</th>
</tr>
</thead>
<tbody>
<tr>
<td>sKL-MI S6L8</td>
<td>48</td>
<td>55</td>
<td>88</td>
<td>99</td>
</tr>
<tr>
<td>sKL-MI S9L5</td>
<td>52</td>
<td>72</td>
<td>85*</td>
<td>132</td>
</tr>
</tbody>
</table>

(better for MCI)

Sample size estimates for a drug trial (= 48AD, 88 MCI)

- does it matter what statistical threshold is used to define the region with greatest effect sizes for change?

Hua, X. and Thompson, P.M. et al., 2009
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

- Sum-of-boxes Clinical Dementia Rating (CDR) gives best power among the clinical scores, but the TBM method is 10 times better

<table>
<thead>
<tr>
<th>Loss Rate %/yr</th>
<th>AD</th>
<th>MCI</th>
</tr>
</thead>
<tbody>
<tr>
<td>CDR-SB</td>
<td>408</td>
<td>796</td>
</tr>
<tr>
<td>ADAS-Cog</td>
<td>619</td>
<td>6797</td>
</tr>
<tr>
<td>MMSE</td>
<td>1078</td>
<td>3275</td>
</tr>
</tbody>
</table>

Is power better at 3T?

1.5T

3 T
More of the brain showed AD-accelerated tissue loss at 3T than at 1.5 T but with slightly weaker effect size (24 AD vs. 35 CTLs scanned at both field strengths)
Generated a statistical ROI for each field strength (slightly smaller at 3T)
MCI: Power slightly worse at 3T, similar in AD

<table>
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<tr>
<th></th>
<th>AD</th>
<th>MCI</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.5 Tesla</td>
<td>37</td>
<td>107</td>
</tr>
<tr>
<td>3 Tesla</td>
<td>48</td>
<td>159</td>
</tr>
</tbody>
</table>

Very similar in AD  
Worse for MCI

N80 = Minimal Sample Sizes, per diagnostic group, to detect 25% slowing of the mean atrophic rate (with 80% power, alpha = 0.05).

Mixing 3T and 1.5T scanners -
Power did not degrade at all when
25% of the scanners were 3T

MIX IS OK
Comparison of AdaBoost and Support Vector Machines for Detecting Alzheimer’s Disease through Automated Hippocampal Segmentation


AD effect

MMSE correlation

HP Loss Rates (980 scans)

ApoE4+ atrophied 2-3% faster
AT BASELINE, GROUP DIFFERENCES ARE MAPPED:

Normals vs. AD

Top View

Right

Left

Significance Maps

Normals vs. MCI

Top View

Right  Left

P value
BASELINE ATROPHY CORRELATES WITH:

MMSE Score

Top View

Right

Left

P value
Sum of Boxes CDR Score
Top View
Right
Left

P value
Depression
Top View
Right    Left

P value
Carrying the ApoE 4 Gene
MCI only  \( N = 186 \)

Top View

Right  \hspace{1cm} \text{Left}
Carrying the ApoE 2 Gene
Normals & MCI  N = 158
Top View
Right  Left

P value
Change in MMSE Score
Top View
Right
Left

P value
Change in Sum of Boxes
CDR Score
Top View
Right
Left
Change in Diagnosis
(MCI to AD)
Top View
Right
Left

P value
Significant Maps for CSF Biomarkers

$A\beta_{1-42} \ (N = 141)$

$pTAU_{181P}/A\beta_{1-42} \ (N = 141)$

$pTAU_{181P} \ (N = 138)$

$TAU/A\beta_{1-42} \ (N = 138)$

$TAU \ (N = 138)$

Summary

All MRI measures correlate well with CSF biomarkers, clinical decline, and predict future conversion to AD.

TBM needs 50 AD and 75 MCI subjects to detect 25% slowing of disease (10x better than best clinical score)

All maps show focal effects - interesting that these statistically guided ROIs will give much better numeric summaries of change (15-50% reductions in sample size)

Mixing 1.5T and 3T scanners is not a problem; but 3T was slightly worse for tracking change in MCI