The impact of amyloid and tau accumulation on prospective structural and memory change in cognitively normal older adults

Tyler N. Toueg1, Xi Chen2, Theresa M. Harrison3, Corrina Fonseca1, Suzanne L. Baker2, William J. Jagust1,2
1Helen Wills Neuroscience Institute, University of California, Berkeley
2Lawrence Berkeley National Laboratory

Objective

In Alzheimer’s disease (AD), tau pathology is related to prospective longitudinal atrophy. Relationships between tau and structure have been explored in cognitively normal older adults (CN), showing that early tau is related to decreased cortical thickness. Most of these analyses have only related tau to brain structure cross-sectionally or retrospectively. However, tau seems to predict different structural changes depending on whether the analysis is retrospective versus prospective. Therefore, using voxel-wise analyses, we explored whether and where tau deposition at baseline was associated with prospective longitudinal changes in brain structure and memory in CN.

Aim: The goal of this project was to investigate if elevated levels of AD biomarkers at baseline are associated with prospective changes in brain structure and memory in CN.

Methods

Subject Demographics

<table>
<thead>
<tr>
<th>CN Aβ-</th>
<th>CN Aβ+</th>
<th>CN Aβ Unknown</th>
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<tbody>
<tr>
<td>N</td>
<td>72</td>
<td>51</td>
</tr>
<tr>
<td>Age @ tp1</td>
<td>77.23 ± 6.82</td>
<td>77.33 ± 4.22</td>
</tr>
<tr>
<td>Sex M / F</td>
<td>31 / 41</td>
<td>19 / 32</td>
</tr>
<tr>
<td>Education (Y)</td>
<td>17.18 ± 1.82</td>
<td>16.37 ± 1.89</td>
</tr>
<tr>
<td>APOEe4</td>
<td>6</td>
<td>25</td>
</tr>
<tr>
<td>Avg time b/w MRI (Y)</td>
<td>1.76 ± 0.62</td>
<td>1.87 ± 0.77</td>
</tr>
<tr>
<td>Avg time b/w cog (Y)</td>
<td>1.4 ± 0.6</td>
<td>0</td>
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</tbody>
</table>

• CN subjects were recruited from the Berkeley Aging Cohort Study (BACS), a biomarker study of normal aging.
• Aβ+ status was determined by PiB PET global DVR > 1.065.
• 18F-Flortaucipir (FTP) was used to measure tau PET SUVRs 80-100 min post-injection.
• Inferior cerebellar gray was used as the reference region to calculate FTP SUVRs.
• Partial volume correction was applied for ROI-based tau measures.

Number of Prospective Timepoints for Volume (MRI) and Memory

Prospective change measured using slope measurements

• Slope estimated from linear mixed-effects model based on random effect of time predicting volume and memory
• Structure:
  • 1.5T MP RAGE images processed with FreeSurfer v6.0 using the longitudinal pipeline
  • Structural measures adjusted for ICV using residual in linear regression
  • ROIs = EC and Hippocampus volume
• Memory:
  • Standardized composite score focused on memory (short-delay free-recall, long-delay free-recall of the CVLT and Visual Reproduction, and total score of Logical Memory)

Results

Relating structural change to voxelwise tau PET at baseline

Model 1: 
• L/R structure change slope + Age + Sex + Edu + APOEe4
• L Hippocampus Slope + R Hippocampus Slope

Model 2: 
• L/R structure change slope + Age + Sex + Edu + APOEe4 + Aβ status
• L Hippocampus Slope + R Hippocampus Slope

Model 3: 
• L/R structure change slope + Age + Sex + Edu + APOEe4 + Aβ status
• L Hippocampus Slope + R Hippocampus Slope

Model 4: 
• L/R structure change slope + Age + Sex + Edu + APOEe4 + Aβ status
• L Hippocampus Slope + R Hippocampus Slope

Conclusions

1) Prospective atrophy in left and right hippocampus was related to elevated tau PET signal in parahippocampal cortex (PHC) voxels.
2) Prospective memory decline was related to elevated tau signal that was most prominent in left medial temporal and posterior parietal regions, driven by the Aβ+ group.
3) In PHC, tau was related to both prospective hippocampal atrophy and memory decline.
4) An exploratory analysis of ROI-based tau measures found that baseline tau, especially in entorhinal cortex, predicted prospective atrophy in multiple temporal regions, with strongest predictions in Aβ+ participants.

Discussion

Our findings suggest that early tau accumulation in CN has structural and cognitive consequences. Tau in PHC predicting both memory decline and hippocampal atrophy suggests that PHC may be an important area to monitor in preclinical AD.