Cerebrospinal fluid and PET measures of tau pathology may indicate different stages of AD pathological progression.

**Background**

Alzheimer’s disease (AD) is characterized by a decades-long period of pathological changes leading to the onset of dementia. At the dementia stage, the brain is likely to be too seriously affected for any intervention to meaningfully alter the disease process. As a result, some in the research field have suggested to shift from a cognitive-based to a biology-based definition of the disease. Criteria for disease definition include measures of pathological hallmarks (amyloid-β [Aβ] and tau) and neurodegeneration.

Owing to the availability of cerebrospinal fluid (CSF) and imaging markers, either magnetic resonance imaging (MRI) or positron emission tomography (PET), of disease processes, modalities are often used interchangeably. However, investigations of CSF and PET measures of AP pathology suggest that these two modalities provide both overlapping and complementary information. Some investigators have suggested that CSF Aβ abnormality may occur earlier than PET.

With the availability of novel PET tracers we can now investigate whether CSF (P-tau) and PET (Flortaucipir; FTP) measures of tau pathology are indicative of different pathophysiological stages.

**Participants and Methods**

1659 ADNI participants with at least one FTP-PET scan or one follow-up assay of CSF AD biomarkers

322 ADNI participants (213 unimpaired, 98 with MCI and 11 with AD) with a FTP-PET scan (FTP-PET SUVRs in AD metaROI, cerebellum grey normalized) and a CSF biomarker assessment (P-tau) within a 23-month period.

**Cross-sectional Results**

Demographics: Increased proportion of at risk individuals with tau positivity

<table>
<thead>
<tr>
<th>Group</th>
<th>CSF+PET+</th>
<th>CSF+PET-</th>
<th>CSF-/PET+</th>
<th>CSF-/PET-</th>
<th>τFFP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>(75.84)</td>
<td>(74.50)</td>
<td>(75.84)</td>
<td>(74.50)</td>
<td></td>
</tr>
<tr>
<td>Male (%)</td>
<td>0.21</td>
<td>0.22</td>
<td>0.21</td>
<td>0.22</td>
<td></td>
</tr>
<tr>
<td>Educational level (%)</td>
<td>0.19</td>
<td>0.19</td>
<td>0.19</td>
<td>0.19</td>
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</tr>
<tr>
<td>Neurodegeneration (c/s)</td>
<td>0.23</td>
<td>0.24</td>
<td>0.23</td>
<td>0.24</td>
<td></td>
</tr>
<tr>
<td>FTP+ (SUVR)</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>FTP- (SUVR)</td>
<td>0.62</td>
<td>0.62</td>
<td>0.62</td>
<td>0.62</td>
<td></td>
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<tr>
<td>Cognitively unimpaired (%)</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>Cognitive follow-up prior to PET (months)</td>
<td>12 (10-24.61)</td>
<td>12 (10-24.89)</td>
<td>12 (10-24.61)</td>
<td>12 (10-24.89)</td>
<td></td>
</tr>
<tr>
<td>Executive function composite (c/s)</td>
<td>0.10</td>
<td>0.10</td>
<td>0.10</td>
<td>0.10</td>
<td></td>
</tr>
</tbody>
</table>

**Retrospective analysis**

CSF: CSF tau+ persons have increased retrospective CSF P-tau accrual

Cognition: tau CSF+/PET+ experienced decline in memory and executive function for at least 5 years

**Conclusions**

Among 322 ADNI participants categorized according to their levels of tau pathology as measured by PET and CSF we found that:

- CSF-/PET+ occurred less frequently than CSF+/PET-, CSF-/PET- or CSF+/PET+
- Participants with at least one positive tau biomarker had increased Aβ pathology
- Only CSF+ showed retrospective change in CSF tau levels spanning at least 5 years
- CSF+/PET+ participants were more likely to have worse cognitive performance
- CSF+/PET+ persons had retrospective cognitive decline for at least 5 years

Results are consistent with the notion that CSF P-tau is an early indicator of AD pathophysiological changes. Given the reduced inference from the CSF+/PET+ group, it is unclear whether this stage is artifactual or represents an alternate pathogenetic route. Prospective CSF/PET studies will improve our understanding of this phenomenon.

**References**

3. Palmqvist et al. Brain (2016);139:1226-1236
5. Osenkoppete et al. JAMA (2018);320:1151-1162

**Acknowledgments**

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