Contribution of iron and Aβ to age differences in entorhinal and hippocampal subfield volume

Chris M. Foster, PhD, Kristen M. Kennedy, PhD, Ana M. Daugherty, PhD, et al.

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Study question
Do cognitively normal (CN) older adults with both elevated global amyloid-β (Aβ) burden and elevated striatal iron levels have smaller entorhinal cortex (ERC) volumes but normal hippocampal subfield volumes?

What is known and what this paper adds
Researchers have hypothesized that Aβ accumulation promotes oxidative stress, and brain iron accumulation is a known proxy indicator of oxidative stress. This investigation’s results provide evidence for a synergistic relationship between Aβ burden and striatal iron levels as contributors to the preclinical stages of pathologic aging.

Methods
For this cross-sectional study, the investigators recruited 70 CN older adults (mean age, 68.29 ± 10.48 years; age range, 51–94 years) for assessments at an academic center in Dallas, Texas, between 2013 and 2016. These individuals had no histories of neurologic disorders. They underwent [18F]-florbetapir PET scans to assess Aβ burden. They also underwent 3T MRI scans that included a T2*-weighted gradient-recalled echo sequence for assessing striatal iron levels and an ultra-high-resolution T2/proton density-weighted sequence for measuring the volumes of the ERC and 3 hippocampal subfields. The investigators used mixed-effects models to determine whether Aβ burden, striatal iron levels, and age exhibited interactive associations with ERC and hippocampal subfield volumes. Such interactive associations were the primary outcomes.

Results and study limitations
The mixed-effects models revealed a 3-way interaction between Aβ burden, striatal iron levels, and age for ERC volumes, with a negative association between age and ERC volumes existing only in persons with both elevated Aβ burdens and elevated striatal iron levels. The models revealed no such interactive effects on the volumes of any of the 3 hippocampal subfields. The present study’s limitations include the lack of tau pathology assessments, the lack of data concerning other metals with roles in oxidative stress (e.g., copper and zinc), and the reliance on data from a single center, which may limit generalizability.

Study funding and competing interests
This study was funded by Avid Radiopharmaceuticals/Eli Lilly, the NIH, the Alzheimer’s Association, BvB Dallas, and AWARE. The authors report no competing interests. Go to Neurology.org/N for full disclosures.

Table
Strengths of interactions between Aβ burden, striatal iron levels, and age for ERC and hippocampal subfield volumes

<table>
<thead>
<tr>
<th>Region</th>
<th>β coefficient (Z score)</th>
<th>FDR p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ERC</td>
<td>−3.34 (−2.50)</td>
<td>0.029</td>
</tr>
<tr>
<td>Subiculum</td>
<td>0.61 (0.46)</td>
<td>0.711</td>
</tr>
<tr>
<td>CA1/2</td>
<td>−0.79 (−0.59)</td>
<td></td>
</tr>
<tr>
<td>CA3/Dentate gyrus</td>
<td>0.49 (0.37)</td>
<td></td>
</tr>
</tbody>
</table>
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