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eFigure 78. Association between Aβ amplitude and linear rise with mean cortical binding potential

This supplementary material has been provided by the authors to give readers additional information about their work.
eMethods. Equation

\[
\frac{\text{Aβ42 PR}}{\text{Aβ40 PR}} = \frac{[\text{Aβ42}]}{[\text{Aβ40}]} \left( \frac{\text{FTR Aβ42}}{\text{FTR Aβ40}} \right)
\]

Complementary associations between β-amyloid fractional turnover rates, concentrations, production rates, and cosinor parameters are expected since the kinetic parameters are interrelated based on this equation.
### eTable 1. Participant demographic information

<table>
<thead>
<tr>
<th></th>
<th>Amyloid Negative</th>
<th>Amyloid Positive</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of participants</td>
<td>39</td>
<td>38</td>
</tr>
<tr>
<td>Age, years*</td>
<td>71.8 ± 5.8 (62.2-87.7)</td>
<td>73.4 ± 7.3 (60.4-85.8)</td>
</tr>
<tr>
<td>Weight, kg*</td>
<td>79.8 ± 16.4 (53.1-122.5)</td>
<td>75.4 ± 15.3 (42.2-106.6)</td>
</tr>
<tr>
<td>BMI, kg/m²*</td>
<td>27.4 ± 5 (20.1-39.9)</td>
<td>25.8 ± 4.8 (16.5-40.3)</td>
</tr>
<tr>
<td>Sex</td>
<td>20M/19F</td>
<td>26M/12F</td>
</tr>
<tr>
<td>ApoE4 status</td>
<td>5 ApoE4+</td>
<td>27 ApoE4+</td>
</tr>
<tr>
<td>PET PiB status</td>
<td>11 no PET PiB imaging</td>
<td>22 no PET PiB imaging</td>
</tr>
<tr>
<td>MCBP*</td>
<td>0.046 ± 0.047 (-0.04-0.15)</td>
<td>0.69 ± 0.29 (0.26-1.24)</td>
</tr>
<tr>
<td>CSF [Aβ42]:[Aβ40]*</td>
<td>0.168 ± 0.035 (0.07-0.21)</td>
<td>0.096 ± 0.017 (0.061-0.13)</td>
</tr>
<tr>
<td>CDR-SB status</td>
<td>0=27, &gt;0=12</td>
<td>0=6, &gt;0=32</td>
</tr>
</tbody>
</table>

*Mean ± standard deviation (range)

kg: Kilogram
m: Meter
M: male
F: female
ApoE4: apolipoprotein E4
PET: Positron emission tomography
PiB: Pittsburgh Compound B
MCBP: Mean cortical binding potential
CSF: Cerebrospinal fluid
Aβ: Amyloid-beta
CDR-SB: Clinical dementia rating-sum of boxes

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**Table 2.** SDs of the residuals for straight line and cosine wave

<table>
<thead>
<tr>
<th></th>
<th>Aβ40</th>
<th>Aβ42</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean SDR</td>
<td>SD SDR</td>
</tr>
<tr>
<td>Straight line</td>
<td>MS</td>
<td>10.45*</td>
</tr>
<tr>
<td></td>
<td>ELISA</td>
<td>17.52</td>
</tr>
<tr>
<td>Cosine wave</td>
<td>MS</td>
<td>9.67*#</td>
</tr>
<tr>
<td></td>
<td>ELISA</td>
<td>17.1#</td>
</tr>
</tbody>
</table>

Aβ: Amyloid-beta  
SDR: Standard deviation of the residuals  
SD: Standard deviation  
MS: mass spectrometry  
ELISA: enzyme-linked immunosorbent assay  
*p<0.0001 for MS vs. ELISA comparison by paired two-tailed t-test  
#p<0.0001 for straight line vs. cosine wave comparison by paired two-tailed t-test
**eTable 3.** Effect of age on $\text{A}\beta 42$ amplitude and linear rise

<table>
<thead>
<tr>
<th>Age 60.4-67.6 years</th>
<th>Mean Difference (pM)</th>
<th>Standard Error</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>16.77</td>
<td>5.45</td>
<td>0.007</td>
</tr>
<tr>
<td>Age 67.7-72.9 years</td>
<td>7.46</td>
<td>3.51</td>
<td>0.046</td>
</tr>
<tr>
<td>Age 73.0-78.3 years</td>
<td>6.71</td>
<td>4.58</td>
<td>0.163</td>
</tr>
<tr>
<td>Age 78.4-87.7 years</td>
<td>3.3</td>
<td>2.04</td>
<td>0.125</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Age 60.4-67.6 years</th>
<th>Mean Difference (pM/hr)</th>
<th>Standard Error</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2.16</td>
<td>0.974</td>
<td>0.041</td>
</tr>
<tr>
<td>Age 67.7-72.9 years</td>
<td>0.942</td>
<td>0.391</td>
<td>0.025</td>
</tr>
<tr>
<td>Age 73.0-78.3 years</td>
<td>0.466</td>
<td>0.415</td>
<td>0.279</td>
</tr>
<tr>
<td>Age 78.4-87.7 years</td>
<td>0.203</td>
<td>0.25</td>
<td>0.428</td>
</tr>
</tbody>
</table>

Mean difference in $\text{A}\beta 42$ amplitude or linear rise between amyloid-negative and amyloid-positive individuals divided by age quartiles
Two-tailed independent samples t-test
Bold: $p<0.05$

**Aβ:** Amyloid-beta

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**Table 4.** Spearman correlations between cerebrospinal fluid β-amyloid concentrations, fractional turnover rates, and production rates

<table>
<thead>
<tr>
<th></th>
<th>Aβ40</th>
<th>Aβ42</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Production rate</td>
<td>FTR</td>
</tr>
<tr>
<td>Concentration</td>
<td>0.90**</td>
<td>-0.08</td>
</tr>
<tr>
<td>FTR</td>
<td>-0.06</td>
<td></td>
</tr>
</tbody>
</table>

FTR: fractional turnover rate  
Aβ: Amyloid-beta  
*=p<0.05  
**=p<0.0001
**eTable 5. Summary of serial cerebrospinal fluid β-amyloid sampling human studies**

<table>
<thead>
<tr>
<th>Study</th>
<th>Participants (n)</th>
<th>Cognitive Status</th>
<th>Aβ Assay</th>
<th>CSF Sampling Frequency and Volume</th>
<th>Linear Rise</th>
<th>Amplitude</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bateman <em>et al.</em> 2007</td>
<td>15</td>
<td>Normal</td>
<td>ELISA</td>
<td>6 ml every hour for 36 hours</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Huang <em>et al.</em> 2012</td>
<td>46</td>
<td>Mixed</td>
<td>ELISA</td>
<td>6 ml every hour for 36 hours</td>
<td>Attenuated with amyloid deposition</td>
<td>Attenuated with age</td>
</tr>
<tr>
<td>Li <em>et al.</em> 2012</td>
<td>21</td>
<td>Normal</td>
<td>Multiple x</td>
<td>Variable CSF Aβ variability affected by draw frequency and volume</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Moghekar <em>et al.</em> 2012</td>
<td>10</td>
<td>Impaired</td>
<td>ELISA, xMAP</td>
<td>40 ml every 6 hours for 24 or 36 hours</td>
<td>No linear rise</td>
<td>No time-of-day fluctuations</td>
</tr>
<tr>
<td>Slats <em>et al.</em> 2012</td>
<td>12</td>
<td>Mixed</td>
<td>ELISA, xMAP</td>
<td>6 ml every hour for 36 hours</td>
<td>Results confounded by use of bacterial filter on lumbar catheter</td>
<td></td>
</tr>
<tr>
<td>Roh <em>et al.</em> 2012</td>
<td>12</td>
<td>Mixed</td>
<td>ELISA</td>
<td>6 ml every hour for 36 hours</td>
<td>Attenuated with amyloid deposition and AD mutation</td>
<td></td>
</tr>
<tr>
<td>Dobrowolska <em>et al.</em> 2014</td>
<td>49</td>
<td>Mixed</td>
<td>ELISA</td>
<td>6 ml every hour for 36 hours</td>
<td>Attenuated with age and amyloid deposition</td>
<td></td>
</tr>
</tbody>
</table>

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<table>
<thead>
<tr>
<th>Study</th>
<th>n</th>
<th>Group</th>
<th>Assay</th>
<th>Time Points</th>
<th>Concentrations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ooms et al. 2014*</td>
<td>26</td>
<td>Normal</td>
<td>ELISA, xMAP</td>
<td>6 ml at 7 time points for 19 hours</td>
<td>Control: 6 ml at 7 time points for 19 hours, SD: 6 ml at 11 time points for 19 hours, Concentrations increased in the SD group compared to control</td>
</tr>
<tr>
<td>Lucey et al. 2015#</td>
<td>178</td>
<td>Mixed</td>
<td>Variable</td>
<td>Rate affected by frequency of CSF draws</td>
<td>Varied between studies, most with diurnal pattern</td>
</tr>
<tr>
<td>Van Broeck et al. 2016</td>
<td>18</td>
<td>Normal</td>
<td>Multiplex</td>
<td>Variable</td>
<td>CSF Aβ variability affected by draw frequency and volume</td>
</tr>
<tr>
<td>Lucey et al. (current manuscript)</td>
<td>77</td>
<td>Mixed</td>
<td>MS</td>
<td>6 ml every hour for 36-48 hours</td>
<td>Aβ42 amplitude attenuates with amyloidosis and faster aggregation rates (FTR ratio). Aβ40 by MS not affected by amyloidosis</td>
</tr>
</tbody>
</table>

Aβ: amyloid-β; AD: Alzheimer’s disease; ELISA: enzyme-linked immunosorbent assay; MS: mass spectrometry; SD: sleep-deprived; FTR: fractional turnover rate
*: intervention trial with sleep-deprived and control groups
#: pooled analysis of 17 indwelling lumbar catheter studies
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eFigure 78. Association between Aβ amplitude and linear rise with mean cortical binding potential

A. Aβ42 amplitude (pM) vs. MCBP. The horizontal dashed line is at 15 pM. B. Aβ42 linear rise (pM/hr) vs. MCBP. C. Aβ40 amplitude (pM) vs. MCBP. The horizontal dashed line is at 200 pM. D. Aβ40 linear rise (pM/hr) vs. MCBP. The vertical dashed line is MCBP=0.18, the cutoff for amyloid-negative (<0.18) or amyloid-positive (>0.18). Amyloid-negative (blue) and amyloid-positive (red) participants are shown. Aβ: amyloid-beta; MCBP: mean cortical binding potential; pM: picomolar; hr: hour.