Computerized Cognitive Composite (C3) Performance Differences between Aβ+ and Aβ-normal older adults screened for the A4 (Anti-Amyloid in Asymptomatic AD) Study

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INTRODUCTION

- Computerized cognitive assessments have the potential to significantly reduce participant burden, administration error, and cost in AD secondary prevention trials but validation of these assessments against relevant biomarkers will be required in large multi-site studies of older adults.
- Here we examine group differences in performance on the Computerized Cognitive Composite (C3) between clinically normal older adults classified as either exhibiting elevated PET amyloid (Aβ+) or Aβ- as part of screening procedures for the Anti Amyloid in Asymptomatic AD (A4) study.

METHODS

<table>
<thead>
<tr>
<th>All</th>
<th>Aβ+ n=4486</th>
<th>Aβ- n=3163</th>
<th>Aβ+ n=1323</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (M(SD))</td>
<td>71.29 (4.67)</td>
<td>70.95 (4.53)</td>
<td>72.10 (4.89)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Sex (% female)</td>
<td>59%</td>
<td>60%</td>
<td>59%</td>
<td>0.644</td>
</tr>
<tr>
<td>Education (M(SD))</td>
<td>16.58 (2.84)</td>
<td>16.59 (2.85)</td>
<td>16.54 (2.81)</td>
<td>0.564</td>
</tr>
</tbody>
</table>

- Participants were clinically normal older adults (CDR=0, age 65-85) who screened for the A4 study and underwent florbetapir PET for classification of Aβ status.
- All participants completed the C3 at the first screening visit (Visit1) and an alternate C3 within 90 days at the study eligibility visit (Visit3).
- Differences in performance between Aβ+ and Aβ- on the C3 Composite and individual C3 components at Visit1 and Visit3 were explored while controlling for age, sex, and education.

RESULTS

Performance on C3 Components and Group Differences
- Aβ+ outperformed Aβ- on the overall C3 Composite. Individual measures which differed between groups included BPS-O (p=0.0323), OCL (p=0.005), and ONB (p=0.0002).
- Groups performed similarly on FR, NR, NReg, Detection, and Identification.

The C3 at Two Timepoints
- Effect sizes for Aβ-related cognitive decrements were small (i.e. Cohen’s d<0.2) with the numerically largest effect was observed for the C3 Composite (above). However, this pattern was robust, with equivalent Aβ group findings on the C3 observed at Visit3 as Visit1 (below) and good test-retest reliability (ICC=0.626; 95% CI:0.607-0.644).

CONCLUSIONS

- The C3 composite detects differences in cognition between Aβ+/Aβ-normal older adults with Aβ+ performing worse on measures of memory, working memory, and pattern separation at 2 visits.
- These findings provide preliminary support for the validity and reliability of tablet-based computerized tests in AD secondary prevention trials.
- Future work will determine the sensitivity of the C3 Composite to change over time in the context of a treatment trial.

Correlations Among C3 Components and Demographics
- Greater age was associated with worse performance across all C3 outcomes. Higher education was associated with better performance on all C3 outcomes, with the largest impact on OCL. Women outperformed men on DET.

Predictions for the Utility of the C3 Longitudinally
- Participants will complete the C3 at 6-month intervals for the study duration. The magnitude of the C3 Aβ group difference increased by a factor of 3.6 when restricting the Aβ+ group to the bottom tertile of performers on paper and pencil measures (i.e., the Preclinical Alzheimer’s Cognitive Composite- PACC). This suggests that the C3 will both be feasible for low performers and that C3 performance is related to PACC, the current gold standard in detecting Aβ-related decline.

- The C3 Composite to change over time in the context of a treatment trial.

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