Subjective cognitive concerns and biomarker evidence of preclinical AD

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Background

- Previously dismissed as a sign of the “worried well,” emerging evidence suggests that subjective cognitive concerns (SCC) may serve as an early indicator of progression to Alzheimer’s disease (AD).

- In particular, SCC may be most sensitive at the preclinical stage of AD, prior to the onset of clinical impairment on standardized cognitive measures.
Staging Framework for Preclinical AD

Operationalized research criteria for studying preclinical Alzheimer’s disease (AD). As individuals advance along the stages, risk of progressing to MCI and AD dementia increases.

Subjective Cognitive Concerns and AD biomarkers

• If SCC herald initial changes due to AD, it would follow that greater SCC would be associated with greater evidence of Aβ and ND in individuals who are clinically normal.

• Furthermore, SCC would be associated with advancing stages of preclinical AD, such that individuals with both Aβ and ND would show greater SCC than those with Aβ in isolation.
Subjective Cognitive Concerns and Aβ

– We examined 131 CN older individuals from the Harvard Aging Brain Study who had amyloid imaging (PiB-PET)

– PiB PET imaging was measured using an aggregate of cortical regions vulnerable to amyloid deposition

– Participants were given several questionnaires about their subjective memory to create a composite

– Study partner was also given a questionnaire about subjective memory

– Participants were given an extensive cognitive battery
Increased SCC related to increased amyloid burden in CN

Amariglio et al., 2012 *Neuropsychologia*

$r = 0.22, p<0.001$
Relationship between SCC and amyloid stronger in higher education group

Aghjayan et al., in preparation
Association between SCC, Aβ, and ND

• Dichotomized Aβ and ND  (Mormino et al. 2014)
  – Aβ using PiB-PET
  – ND using both hippocampal volume and FDG-PET

• Resulted in 4 groups  (Jack et al., 2012; Knopman et al., 2012)
  – Aβ-/ND- (Stage 0)
  – Aβ+/ND- (Stage 1)
  – Aβ+/ND+ (Stage 2)
  – Aβ-/ND+ (SNAP)
## SCC and preclinical AD staging

Amariglio et al. 2015 *Neurology*

<table>
<thead>
<tr>
<th>Demographic variable</th>
<th>Total, mean SD (total n = 257)</th>
<th>Stage 0 (Aβ−/ND−) (total n = 122)</th>
<th>Stage 1 (Aβ+/ND−) (total n = 32)</th>
<th>Stage 2 (Aβ+/ND+) (total n = 36)</th>
<th>SNAP (Aβ−/ND+) (total n = 67)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>73.7 (6.1)</td>
<td>71.6 (5.7)</td>
<td>73.1 (4.96)</td>
<td>77.1 (6.38)</td>
<td>76.1 (5.67)</td>
</tr>
<tr>
<td>Female, %</td>
<td>57.6</td>
<td>63.1</td>
<td>59.4</td>
<td>61.1</td>
<td>44.8</td>
</tr>
<tr>
<td>Education, y</td>
<td>15.8 (3.0)</td>
<td>15.9 (3.0)</td>
<td>16.4 (2.7)</td>
<td>16.2 (2.8)</td>
<td>15.1 (3.3)</td>
</tr>
<tr>
<td>MMSE</td>
<td>29.0 (1.1)</td>
<td>29.2 (1.0)</td>
<td>28.8 (1.0)</td>
<td>28.7 (1.0)</td>
<td>28.9 (1.1)</td>
</tr>
<tr>
<td>GDS</td>
<td>2.9 (2.6)</td>
<td>2.6 (2.3)</td>
<td>2.4 (2.7)</td>
<td>3.6 (2.8)</td>
<td>3.3 (2.8)</td>
</tr>
<tr>
<td>Memory factor score</td>
<td>5.4 (2.1)</td>
<td>5.5 (2.2)</td>
<td>5.7 (2.3)</td>
<td>4.8 (1.8)</td>
<td>5.1 (2.1)</td>
</tr>
<tr>
<td>SCC composite, z score</td>
<td>0.0 (0.8)</td>
<td>−0.2 (0.7)</td>
<td>0.1 (0.9)</td>
<td>0.3 (0.7)</td>
<td>0.1 (0.8)</td>
</tr>
<tr>
<td>APOE ε4 carriers, %</td>
<td>27.8</td>
<td>16.2</td>
<td>62.1</td>
<td>56.3</td>
<td>18.5</td>
</tr>
</tbody>
</table>
Both $\text{A} \beta^+$ and ND$^+$ independently associated with increased SCC

<table>
<thead>
<tr>
<th></th>
<th>Estimate</th>
<th>Std. Error</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ND group</td>
<td>0.284</td>
<td>0.127</td>
<td>0.026</td>
</tr>
<tr>
<td>$\text{A} \beta$ group</td>
<td>0.396</td>
<td>0.133</td>
<td>0.003</td>
</tr>
<tr>
<td>Age</td>
<td>-0.007</td>
<td>0.010</td>
<td>0.503</td>
</tr>
<tr>
<td>Education</td>
<td>-0.016</td>
<td>0.020</td>
<td>0.433</td>
</tr>
<tr>
<td>Sex</td>
<td>-0.097</td>
<td>0.116</td>
<td>0.406</td>
</tr>
</tbody>
</table>
SCC is associated with advancing stages of preclinical AD

Amariglio et al. 2015 *Neurology*
Conclusions

• Greater self-reported subjective cognitive concerns is related independently to both Aβ and ND in clinically normal older individuals

• Evidence of both Aβ and ND is associated with greater subjective cognitive concerns than Aβ in isolation

• Additional variables, such as education, may modify the relationship between SCC and AD biomarkers
The continuum of Alzheimer’s disease

Cognitive function

Years

Asymptomatic
Preclinical
Early symptomatic

“Normal” Aging
MCI
Dementia

Sperling R et al Alzheimer & Dementia 2011
## Preclinical and MCI groups

<table>
<thead>
<tr>
<th></th>
<th>Total</th>
<th>Cognitively normal</th>
<th>Mild Cognitive Impairment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Aβ -</td>
<td>Aβ +</td>
</tr>
<tr>
<td>N</td>
<td>286</td>
<td>191</td>
<td>62</td>
</tr>
<tr>
<td>Age, y</td>
<td>73.3 (6.4)</td>
<td>72.7 (6.1)</td>
<td>75.0 (6.2)</td>
</tr>
<tr>
<td>Female, %</td>
<td>56.7</td>
<td>59.1</td>
<td>59.7</td>
</tr>
<tr>
<td>Education, y</td>
<td>15.8 (3.1)</td>
<td>15.5 (3.1)</td>
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</tr>
<tr>
<td>MMSE</td>
<td>28.7 (1.5)</td>
<td>29.0 (1.1)</td>
<td>28.8 (1.0)</td>
</tr>
<tr>
<td>AMNART</td>
<td>120.4 (9.7)</td>
<td>120.0 (9.6)</td>
<td>122.4 (8.4)*</td>
</tr>
<tr>
<td>GDS total</td>
<td>1.4 (1.5)</td>
<td>1.2 (1.3)</td>
<td>1.2 (1.3)</td>
</tr>
<tr>
<td>Subjective, score 1-7</td>
<td>5.2 (0.9)</td>
<td>5.3 (0.9)</td>
<td>4.9 (0.9)</td>
</tr>
<tr>
<td>Objective, score 0-25</td>
<td>12.6 (4.4)</td>
<td>13.5 (3.5)</td>
<td>13.9 (3.0)</td>
</tr>
</tbody>
</table>
Self-awareness along preclinical/prodromal AD

Vannini et al., in review
Subjective vs. objective memory along preclinical/prodromal AD

Vannini et al., in review
Conclusions

• During the preclinical stage Aβ+ individuals may demonstrate greater cognitive concerns, despite normal memory performance

• At the stage of MCI, individuals demonstrate a discrepancy between objective memory performance and subjective report, particularly in Aβ+ individuals
Importance

- SCC may be one approach in identifying individuals at greater risk for progression to MCI and AD dementia
- More practically, findings may help to identify subjects appropriate for secondary prevention trials
- SCD may also serve as outcome measures in drug trials that are looking to demonstrate clinical benefit
- SCD should not be dismissed and may become particularly important as treatments become available
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