Early Detection of Alzheimer’s Disease

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11/18/2021
Early Detection of Alzheimer’s Disease
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AHEAD STUDY

ALZHEIMER’S DRUG DONANEMAB

Lilly

The A4 Study

NOW IS THE TIME
Concomitant Pathways to Unhealthy Brain Aging

Alzheimer’s disease and related dementia have multiple underlying pathways.

Prevalence of Pathological Processes at Autopsy in ROS/MAP

Kapasi et al., 2017, Acta Neuropath
Early Detection Tools

- Alzheimer's Disease
- Neurodegeneration
- Small Vessel Disease (micro/macrostructural damage)
- Cerebral Blood Flow

Sensitive to multiple pathologies early within the disease cascade
Early Detection Tools

Sensitive to multiple early pathologies and widely accessible
Subjective Cognitive Decline: Concern, worry, or change in cognition reported by the patient.

Progression of disease pathology and clinical states:
- Preclinical AD
- MCI
- Dementia

Cognitive Performance

Adapted from Jessen et al., 2014, *Alzheimer’s & Dementia*
SCD & Longitudinal Brain MRI
SCD is a Marker of AD

SCD predicts diagnostic conversion in cognitively normal adults

Note: National Alzheimer’s Coordinating Center Data; no complaint n=2967, SCD n=585

Odds Ratio=2.0, p<0.001
Enhance Use of Subjective Cognitive Decline as a Marker of Early Brain Aging

- New SCD Assessment Tool
- Self Complaint (SCD)
- No Complaint

Conversion vs. Age Graph
Early Detection: Merging Clinical with Biomarkers

Early Clinical Symptoms

Early Neuroanatomical and Pathological Changes
New Subjective Cognitive Decline Tool

SCD Survey of 195 Items

Analysis of Endorsement Rates

Exploratory Factor Analysis

Low Factor Loading

Logical Dependence/Double-Barrel

Duplicate Content

Confirmatory Factor Analysis

45 Item SCD Questionnaire

Drop 11 Items with <10% or >90% endorsement

Factor Analysis

Item Response Theory

Drop 9 Items

Drop 91 Items

Drop 41 Items

Factor Analysis

Unidimensionality Confirmed

Gifford et al., 2015 Alz Dem: DADM
Gifford et al., 2019, JINS
### Vanderbilt Subjective Cognitive Decline Questionnaire

<table>
<thead>
<tr>
<th>VMAP SCD Questionnaire</th>
<th>Score Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Score</td>
<td>22-167 (45 items)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>SCD Domain Scores</th>
<th>Example Items</th>
<th>Score Range (# items)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Memory-SCD</td>
<td>Do you think you have problems with your memory?</td>
<td>11-95 (26 items)</td>
</tr>
<tr>
<td></td>
<td>I forget what day of the week it is.</td>
<td></td>
</tr>
<tr>
<td>Executive Functioning-SCD</td>
<td>I have trouble keeping financial records organized.</td>
<td>4-39 (9 items)</td>
</tr>
<tr>
<td></td>
<td>I have trouble thinking things through before acting.</td>
<td></td>
</tr>
<tr>
<td>Language-SCD</td>
<td>I have trouble thinking of the names of objects.</td>
<td>7-33 (10 items)</td>
</tr>
<tr>
<td></td>
<td>I miss the point of what other people are saying.</td>
<td></td>
</tr>
</tbody>
</table>
Utility of the V-SCD Questionnaire: Tool Comparison

Vanderbilt SCD Questionnaire

Everyday Cognition

Memory Functioning Questionnaire

Cognitive Difficulties Scale

SCD Single Item

AUC

Gifford et al., 2019 JINS
SCD is broadly and robustly associated with atrophy in the medial temporal lobe.

Gifford et al., 2020, Alz & Dem; Steinbach 2021, ACN
Utility of the V-SCD Questionnaire: CSF Biomarkers

Note: $A\beta_{42}$ from fasting lumbar puncture of cognitively normal older adults
Utility of the V-SCD Questionnaire: CSF Biomarkers

**SCD & CSF Aβ_42**

- $eta = -7.8$, p<0.001

**SCD & CSF NFL**

- Note: blue line=NC, orange=MCI

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Note: Aβ_42 from fasting lumbar puncture of cognitively normal older adults
Utility of the V-SCD Questionnaire: White Matter Integrity

DTI TBSS

Radial Diffusivity & SCD (Memory and Executive Functioning)

- Cingulum
- Medial Frontal TCATT
- Middle Frontal TCATT
- Inferior Longitudinal Fasciculus (ILF)
- IFG pars triangularis TCATT
- IFG pars opercularis TCATT

Archer, Moore et al., 2021, Neuroimage: Clinical
Utility of the V-SCD Questionnaire: Cerebral Blood Flow

<table>
<thead>
<tr>
<th>SCD Outcomes</th>
<th>Total SCD</th>
<th>Memory-SCD</th>
<th>Language-SCD</th>
<th>Executive Functioning-SCD</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total CBF</strong></td>
<td>β</td>
<td>p-value</td>
<td>β</td>
<td>p-value</td>
</tr>
<tr>
<td><strong>Frontal Lobe CBF</strong></td>
<td>β</td>
<td>p-value</td>
<td>β</td>
<td>p-value</td>
</tr>
<tr>
<td><strong>Parietal Lobe CBF</strong></td>
<td>β</td>
<td>p-value</td>
<td>β</td>
<td>p-value</td>
</tr>
<tr>
<td><strong>Occipital Lobe CBF</strong></td>
<td>β</td>
<td>p-value</td>
<td>β</td>
<td>p-value</td>
</tr>
<tr>
<td>Total SCD</td>
<td>-0.01</td>
<td>0.04*</td>
<td>-0.01</td>
<td>0.05</td>
</tr>
<tr>
<td>Memory-SCD</td>
<td>-0.02</td>
<td>0.07</td>
<td>-0.02</td>
<td>0.08</td>
</tr>
<tr>
<td>Language-SCD</td>
<td>-0.04</td>
<td>0.05</td>
<td>-0.04</td>
<td>0.09</td>
</tr>
<tr>
<td>Executive Functioning-SCD</td>
<td>-0.07</td>
<td>0.003</td>
<td>-0.07</td>
<td>0.006</td>
</tr>
</tbody>
</table>

Note: *Results attenuated and non-significant in sensitivity analyses excluding statistical outliers
Summary

Pathological & Neuropsychiatric Pathways

- Alzheimer's Disease
- Neurodegeneration
- Small Vessel Disease
- Neuropsychiatric Symptoms

Subjective Cognitive Decline Profiles
• Penalized regression models (least absolute shrinkage and selection operator (LASSO))
  • Extraction of SCD items that predict specific pathways known to drive SCD → SCD profiles
Leveraging the Heterogeneity of SCD

### LASSO Results: Items Selected & Weights

<table>
<thead>
<tr>
<th>SCD Item</th>
<th>CSF Aβ42 (n=45)</th>
<th>GDS* (n=93)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Weight</td>
<td>Weight</td>
</tr>
<tr>
<td>I fail to recognize people I know.†</td>
<td>-0.069</td>
<td></td>
</tr>
<tr>
<td>Change in finding my way around a familiar neighborhood.§</td>
<td>-0.039</td>
<td></td>
</tr>
<tr>
<td>I need a written list when I do errands to avoid forgetting things.†</td>
<td>-0.005</td>
<td></td>
</tr>
<tr>
<td>How often is losing the thread of thought in public speaking a problem?‡</td>
<td>0.006</td>
<td></td>
</tr>
<tr>
<td>How often is going to the store and forgetting what you wanted to buy a problem?‡</td>
<td>0.008</td>
<td></td>
</tr>
<tr>
<td>How is your memory compared to the way it was 1 year ago?‡</td>
<td>-0.402</td>
<td></td>
</tr>
<tr>
<td>I forget steps in recipes I know well and have to look them up.†</td>
<td>-0.387</td>
<td></td>
</tr>
<tr>
<td>I don't remember things as well as I used to.†</td>
<td>-0.223</td>
<td></td>
</tr>
<tr>
<td>When interrupted reading, I have trouble finding my place again.†</td>
<td>-0.042</td>
<td></td>
</tr>
<tr>
<td>How often do directions to places present a problem?‡</td>
<td>-0.025</td>
<td></td>
</tr>
<tr>
<td>How often does doing a test present a problem?‡</td>
<td>-0.016</td>
<td></td>
</tr>
<tr>
<td>Change in understanding the point of what others are trying to say.§</td>
<td>0.007</td>
<td></td>
</tr>
<tr>
<td>I forget right away what people say.†</td>
<td>0.018</td>
<td></td>
</tr>
<tr>
<td>Change in recalling conversations a few days later.§</td>
<td>0.025</td>
<td></td>
</tr>
<tr>
<td>Change in remembering appointments, meetings, or engagements.§</td>
<td>0.081</td>
<td></td>
</tr>
<tr>
<td>I make mistakes in writing, typing, or operating a calculator.†</td>
<td>0.185</td>
<td></td>
</tr>
<tr>
<td>How often do phone numbers you use frequently present a problem for you?‡</td>
<td>0.250</td>
<td></td>
</tr>
<tr>
<td>I have trouble with my memory, paying attention, or understanding what others are saying to me.†</td>
<td>0.457</td>
<td></td>
</tr>
<tr>
<td>Change in following a story in books or TV.§</td>
<td>0.477</td>
<td></td>
</tr>
<tr>
<td>Do you have difficulty in remembering to turn off the stove or lights?¶</td>
<td>0.714</td>
<td></td>
</tr>
<tr>
<td>I find it hard to keep my mind on a task/job.†</td>
<td>1.112</td>
<td></td>
</tr>
</tbody>
</table>

**Amyloid Profile**

<table>
<thead>
<tr>
<th>SCD Profile</th>
<th>CSF Aβ42 (n=26)</th>
<th>GDS* (n=51)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$R^2$</td>
<td>$R^2$</td>
</tr>
<tr>
<td>Amyloid Profile</td>
<td>0.19</td>
<td>0.002</td>
</tr>
<tr>
<td>Neuropsychiatric Profile</td>
<td>0.03</td>
<td>0.20</td>
</tr>
</tbody>
</table>

**Validation of Selected SCD Items & Profiles**

Note: $R^2$ from linear regression including age, education, and APOE-ε4 status with fixed beta of item weights from Table 3; GDS=Geriatric Depression Scale total score minus 4 cognitive items.

**Performance of Selected SCD Items & Profiles**

<table>
<thead>
<tr>
<th>SCD Profile</th>
<th>CSF Aβ42 (n=83)</th>
<th>GDS* (n=160)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$R^2$</td>
<td>$R^2$</td>
</tr>
<tr>
<td>Amyloid Profile</td>
<td>0.13</td>
<td>0.10</td>
</tr>
<tr>
<td>Neuropsychiatric Profile</td>
<td>0.09</td>
<td>0.12</td>
</tr>
</tbody>
</table>

Note: $R^2$ from linear regression including age, education, and APOE-ε4 status with fixed beta of item weights from Table 3; GDS=Geriatric Depression Scale total score minus 4 cognitive items.
How does including SCD enhance detection of amyloid positivity beyond other accessible tools?

<table>
<thead>
<tr>
<th>Predictor</th>
<th>p-value</th>
<th>C-Index</th>
<th>Change in C-Index</th>
</tr>
</thead>
<tbody>
<tr>
<td>MoCA*</td>
<td>0.44</td>
<td>0.75</td>
<td></td>
</tr>
<tr>
<td>SCD Score</td>
<td>0.01</td>
<td>0.79</td>
<td>0.04</td>
</tr>
<tr>
<td>Plasma Tau</td>
<td>0.38</td>
<td>0.76</td>
<td>0.015</td>
</tr>
</tbody>
</table>

*Base model with MoCA, age, education, sex, race. Each predictor added to base model.
Vanderbilt Memory & Alzheimer’s Center
Angela Jefferson, PhD
Timothy Hohman, PhD
Matthew Schrag, MD, PhD
Kimberly Pechman, PhD
Logan Dumitrescu, PhD
Derek Archer, PhD
Corey Bolton, PsyD
Maxim Turchan
Hailey Kresge
Francis Cambronero
Corey Bown
Elizabeth Moore
Ujwala Pamidimukkala
Niranjana Shashikumar
Humza Ahmed
Varuna Jasodanand
Vaibhav Janve

Vanderbilt University – Biostatistics
Dandan Liu, PhD
Omair Khan, MAS

Vanderbilt University – Cardiovascular Medicine
Deepak Gupta, MD
Yan Ru Su, MD

Vanderbilt University – Radiology
Manus Donahue, PhD
L. Taylor Davis, MD

Funding Sources
K23-AG045966 (Paul B. Beeson Career Development Award)
R01-AG062826
NIRG-13-283276
K12-HD043483
IIRG-08-88733
R01-AG034962
UL1-TR000445 (VICTR)
K24-AG046373
R01-HL111516
T32-MH064913
K23-AG030962 (Paul B. Beeson Career Development Award)
The John Hartford Foundation
Atlantic Philanthropies
American Federation for Aging Research
Vanderbilt & Aging Project (VMAP) Renewal & Expansion

Cohort Enrollment & Follow-Up Timeline

- Original (Legacy) Cohort (n=335)
  - Baseline
  - 18 Month
  - 3 Year
  - 5 Year

- Legacy Cohort Follow-Up
  - 7 Year
  - 9 Year
  - 11 Year

- New Expansion Cohort (n=650)
  - Baseline
  - 18 Month
  - 3 Year

Multiple Data Types
- Demographics
- Clinical History
- Bloodwork
- Genetics
- Cardiac Imaging
- Cognitive Testing
- Neuroimaging
- Molecular Biomarkers

New Areas of Emphasis
- Younger Age Band
- Cognitively Unimpaired
- Outreach & Engagement
- Universal CSF Collection