The NIA-AA Research Framework: Rationale for a new point of view

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NIA-AA Research Framework: Toward a biological definition of Alzheimer’s disease

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What is Alzheimer’s disease?

- As defined in 1906, Alzheimer’s disease is a pathophysiologic process in the brain.
- AD has an associated clinical continuum that begins with a long asymptomatic or preclinical phase that typically (but not invariantly) progresses to dementia.
- Dementia is a clinical syndrome that can be caused by multiple processes in the brain. Even with the prototypical amnestic progression – may not be AD.
Alzheimer’s Disease
Amyloid and Tau PET Imaging

$\alpha\beta$ (PiB)

Tau (T807)

CN

CN

AD Dementia

Sperling, Mormino, Johnson *Neuron* 2014
NIA-AA Research Framework - Biomarkers

**AT(N) biomarker grouping**

A: Aggregated Aβ or associated pathologic state  
CSF Aβ_{42}, or Aβ_{42}/Aβ_{40} ratio  
Amyloid PET  

T: Aggregated tau (neurofibrillary tangles) or associated pathologic state  
CSF phosphorylated tau  
Tau PET  

(N): Neurodegeneration or neuronal injury  
Anatomic MRI  
FDG PET  
CSF total tau  

Abbreviations: Aβ, β amyloid; CSF, cerebrospinal fluid.  
NOTE. See section 9.4 for explanation of (N) notation.

**AT(N)(C) measures have different roles for definition and staging**

**Definition**

A: Aβ biomarkers determine whether or not an individual is in the Alzheimer’s disease continuum  

T: Pathologic tau biomarkers determine if someone who is in the Alzheimer’s disease continuum has Alzheimer’s disease and are therefore placed in parentheses.  

**Biomarker profiles and categories**

<table>
<thead>
<tr>
<th>AT(N) profiles</th>
<th>Biomarker category</th>
</tr>
</thead>
<tbody>
<tr>
<td>A-T-(N)-</td>
<td>Normal AD biomarkers</td>
</tr>
<tr>
<td>A+T-(N)-</td>
<td>Alzheimer’s pathologic change</td>
</tr>
<tr>
<td>A+T+(N)-</td>
<td>Alzheimer’s disease</td>
</tr>
<tr>
<td>A+T+(N)+</td>
<td>Alzheimer’s disease</td>
</tr>
<tr>
<td>A+T-(N)+</td>
<td>Alzheimer’s and concomitant suspected non-Alzheimer’s pathologic change</td>
</tr>
</tbody>
</table>

**Alzheimer’s continuum**

<table>
<thead>
<tr>
<th>AT(N) profiles</th>
<th>Biomarker category</th>
</tr>
</thead>
<tbody>
<tr>
<td>A-T+(N)-</td>
<td>Non-AD pathologic change</td>
</tr>
<tr>
<td>A-T-(N)+</td>
<td>Non-AD pathologic change</td>
</tr>
<tr>
<td>A-T+(N)+</td>
<td>Non-AD pathologic change</td>
</tr>
</tbody>
</table>
### NIA-AA Research Framework – Clinical

<table>
<thead>
<tr>
<th>Biomarker Profile</th>
<th>Cognitive stage</th>
<th>Mild Cognitive Impairment</th>
<th>Dementia</th>
</tr>
</thead>
<tbody>
<tr>
<td>A(^+) T(^-(N))</td>
<td>normal AD biomarkers, cognitively unimpaired</td>
<td>normal AD biomarkers with MCI</td>
<td>normal AD bio dementia</td>
</tr>
<tr>
<td>A(^+) T(^-(N))</td>
<td>Preclinical Alzheimer’s pathologic change</td>
<td>Alzheimer’s pathologic change with MCI</td>
<td>Alzheimer’s pathologic change with dementia</td>
</tr>
<tr>
<td>A(^+) T(^+(N))</td>
<td>Preclinical Alzheimer’s disease</td>
<td>Alzheimer’s disease with MCI (Prodromal AD)</td>
<td>Alzheimer’s disease with dementia</td>
</tr>
<tr>
<td>A(^+) T(^-(N))</td>
<td>Alzheimer’s and concomitant suspected non Alzheimer’s pathologic change, cognitively unimpaired</td>
<td>Alzheimer’s and concomitant suspected non Alzheimer’s pathologic change with MCI</td>
<td>Alzheimer’s and concomitant suspected non Alzheimer’s pathologic change with dementia</td>
</tr>
<tr>
<td>A(^+) T(^-(N))</td>
<td>non-Alzheimer’s pathologic change, cognitively unimpaired</td>
<td>non-Alzheimer’s pathologic change with MCI</td>
<td>non-Alzheimer with dementia</td>
</tr>
</tbody>
</table>

**Numeric clinical staging—Applicable only to individuals in the Alzheimer’s continuum**

**Stage 1**
- Performance within expected range on objective cognitive tests. Cognitive test performance may be compared to normative data of the investigator’s choice, with or without adjustment (the choice of the investigator) for age, sex, education, etc.
- Does not report recent decline in cognition or new onset of neuropsychiatric symptoms of concern.
- No evidence of recent cognitive decline or new neuropsychiatric symptoms by report of an observer (e.g., study partner) or by longitudinal cognitive testing if available.

**Stage 2**
- Performance within expected range on objective cognitive tests.
- Transitional cognitive decline: Decline in performance of cognitive function, which may involve any cognitive domain(s), i.e., not exclusively memory.
- May be documented through subjective report of cognitive decline that is of concern to the participant.
- Repetition of change from individual baseline within past 1-3 years, and persists for 6 months or longer.
- May be corroborated by informant but not required.
- Or may be documented by evidence of subtle decline on longitudinal cognitive testing but not required.
- Or may be documented by both subjective report of decline and objective evidence on longitudinal testing.
- Although cognition is the core feature, mild neuropsychiatric changes—for example, changes in mood, anxiety, or motivation—may coexist. In some instances, the primary complaint may be neuropsychiatric rather than cognitive. Neuropsychiatric symptoms should have a clearly defined onset, which persists and cannot be explained by life events.

**Stage 3**
- Performance in the impaired/abnormal range on objective cognitive tests.
- Evidence of decline from baseline, documented by the individual’s report or by observer (e.g., study partner) report or by change on longitudinal cognitive testing or neuropsychiatric behavioral assessments.
- May be characterized by cognitive presentations that are not primarily amnestic.
- Performs daily life activities independently, but cognitive difficulty may result in detectable but mild functional impact on the more complex activities of daily life, that is, may take more time or be less efficient but can still complete, either self-reported or corroborated by a study partner.

**Stage 4**
- Mild dementia
- Substantial progressive cognitive impairment affecting several domains, and/or neuropsychiatric disturbance. Documented by the individual’s report or observer (e.g., study partner) report or change on longitudinal cognitive testing.

**Stage 5**
- Moderate dementia
- Progressive cognitive impairment or neuropsychiatric changes. Extensive functional impact on daily life with impairment in basic activities. No longer independent and requires frequent assistance with daily life activities.

**Stage 6**
- Severe dementia
- Progressive cognitive impairment or neuropsychiatric changes. Clinical interview may not be possible.
- Complete dependency due to severe functional impact on daily life with impairment in basic activities, including basic self-care.
What the NIA-AA Framework IS and IS NOT

- Intended to be a research framework – explicitly stated this is NOT ready for use in the clinic
- Is applicable to both observational and clinical trials
- Is NOT a mandate for biomarker only research
- Does NOT devalue importance of clinical syndrome
- Testable hypotheses - generate alternative approaches
- Help learn “What we don’t know that we don’t know”
Why is it important to define AD as a biological entity?

• Most importantly to find an effective treatment!
• Focus on 2 specific issues:
  – We do not always get the diagnosis right clinically
  – Disease exists prior to clinically evident symptoms
PET Amyloid Imaging Across the Spectrum of AD

Harvard Aging Brain Study

Sperling, Mormino, Johnson  Neuron 2014
We do not always get it right clinically

- Recent clinical trials with 9-24% of clinically diagnosed mild-moderate AD dementia and up to 50% of MCI do not have evidence of Aβ pathology.
- Similar results from autopsy studies of “blue ribbon” AD mild-moderate dementia patients from ADRC’s - 14% did not show evidence of elevated amyloid plaque, 59% of those were Braak stage 0-II (Serrano-Pozo et al. *Annals of Neurology* 2014)
Does misdiagnosis matter?

- Amyloid negative dementia patients do not decline at the same rate

Salloway, Sperling et al. AAIC 2014

Landau et al Neurology 2016
Does misdiagnosis matter in large epi studies?

• If 10-20% of “AD dementia” do not have AD pathology and 30% of “normal controls” do have AD pathology - may contribute noise to even large studies

• Attempts to replicate GWAS hits from clinical cohorts confirmed only 12 out of 21 loci in autopsy cohort (Beecham et al. *PLoS Genet* 2014)

• Misattribute risk factors – Example diabetes contributes to cerebrovascular pathology rather than AD (Abner E et al. *Alz & Dem* 2016)
Need for biomarkers in large studies!

- Need to validate less expensive biomarkers (blood, eye, etc) and sensitive computerized cognitive tests using “Gold Standard” biomarker confirmed samples
- Diversity is critical – both for race/ethnicity and for range of socio-economic status
  - Relatively little biomarker data in non-white or non-highly educated individuals - Data in African-Americans thus far suggest that multiple pathologies may play greater role
- Consider biomarkers in representative subsets
Biologic definition should enhance understanding of clinical syndrome

• Of course the clinical syndrome associated with AD is important – this is what matters to patients and families

• Many complex contributing factors to cognitive decline and dementia beyond AD pathology, we must define what we can and investigate the unexplained variance

• Important to elucidate all contributing factors to cognitive impairment and target appropriate treatments
Hypothetical Scenario 1

• A 78 year old woman has been followed for 1 year with progressive amnestic cognitive impairment

• She has a follow-up clinic visit - diagnosed with dementia due to Alzheimer’s disease

• She is hit by a bus on the way home from clinic. The autopsy reveals minimal evidence of amyloid plaque and neurofibrillary tangles, (A1 B1 C1), with hippocampal sclerosis

• Did this patient have Alzheimer’s disease?
Alzheimer’s disease begins prior to clinically evident impairment

- Very consistent evidence from imaging, biomarker, and autopsy studies in both genetic-at-risk and age-at-risk cohorts that Aβ and NFTs accumulate more than a decade prior to symptoms.
- Cognitively unimpaired older individuals who are Ab+, and especially those who are T+ are at very high risk for cognitive decline.
The continuum of Alzheimer’s disease

Cognition

Years

“Normal” Aging

Preclinical

MCI
Prodromal AD

Dementia

Sperling R et al 2011
NIA-AA Preclinical Workgroup
Cognitive Decline in Amyloid Positive “Normals”

Preclinical Alzheimer Cognitive Composite

\[ \chi^2 = 46.4 \]
\[ P < .001 \]

Donohue M et al. *JAMA* 2017
Prediction of progression to symptomatic AD by preclinical stages

Washington University CSF - Vos et al *Lancet Neurology* 2013
Prospective Longitudinal Memory Decline Associated with Higher Tau PET in Ab+ Normals

Harvard Aging Brain Study n=140
Mean follow-up 2.01 +/- .77 years

Sperling, Mormino et al Under Review
# Lifetime Risk of Dementia stratified by AD biomarkers

Table 3: Lifetime risks (%) of AD dementia for males based on screening for amyloidosis (A), neurodegeneration (N), and mild cognitive impairment (MCI) by age.

<table>
<thead>
<tr>
<th>Age</th>
<th>Normal state 1</th>
<th>A state 2</th>
<th>N state 3</th>
<th>A &amp; N state 4</th>
<th>MCI &amp; A &amp; N state 5</th>
<th>MCI &amp; N state 6</th>
</tr>
</thead>
<tbody>
<tr>
<td>60</td>
<td>13.9 (6.9–25.1)</td>
<td>23.1 (14.9–33.0)</td>
<td>23.1 (11.4–44.3)</td>
<td>33.6 (24.4–43.5)</td>
<td>92.9 (91.7–93.9)</td>
<td>71.7 (64.3–79.2)</td>
</tr>
<tr>
<td>65</td>
<td>12.9 (6.3–23.6)</td>
<td>21.9 (13.9–31.4)</td>
<td>20.8 (10.3–39.4)</td>
<td>32.9 (23.8–42.7)</td>
<td>90.4 (88.6–91.7)</td>
<td>64.9 (57.1–73.2)</td>
</tr>
<tr>
<td>70</td>
<td><strong>11.3 (5.4–21.2)</strong></td>
<td><strong>19.9 (12.5–29.0)</strong></td>
<td><strong>18.2 (9.0–34.0)</strong></td>
<td><strong>31.3 (22.5–40.7)</strong></td>
<td><strong>86.0 (83.6–87.8)</strong></td>
<td><strong>56.3 (48.6–65.0)</strong></td>
</tr>
<tr>
<td>75</td>
<td>9.3 (4.3–17.8)</td>
<td>17.2 (10.6–25.4)</td>
<td>15.2 (7.5–28.2)</td>
<td>28.6 (20.3–37.5)</td>
<td>79.5 (76.5–82.0)</td>
<td>46.6 (39.4–55.2)</td>
</tr>
<tr>
<td>80</td>
<td>6.8 (3.0–13.5)</td>
<td>13.6 (8.2–20.6)</td>
<td>11.7 (5.7–21.9)</td>
<td>24.5 (17.1–32.5)</td>
<td>69.9 (66.1–73.0)</td>
<td>36.0 (29.8–43.8)</td>
</tr>
<tr>
<td>85</td>
<td>4.4 (1.9–9.2)</td>
<td>9.5 (5.6–14.8)</td>
<td>8.1 (3.9–15.5)</td>
<td>18.9 (13.0–25.5)</td>
<td>56.7 (52.6–60.2)</td>
<td>25.3 (20.6–31.7)</td>
</tr>
<tr>
<td>90</td>
<td>2.4 (1.0–5.2)</td>
<td>5.4 (3.1–8.8)</td>
<td>4.7 (2.2–9.2)</td>
<td>12.4 (8.3–17.0)</td>
<td>40.2 (36.4–43.5)</td>
<td>15.6 (12.5–20.0)</td>
</tr>
</tbody>
</table>

Abbreviation: AD, Alzheimer’s disease.

NOTE. Lower and upper bounds are given in brackets.
Amyloid biomarkers associated with increased risk of clinical progression

Donohue M et al JAMA 2017
Impact of Secondary Prevention in Preclinical AD

Brookmeyer R et al *Alz & Dem* 2018A
Results: A4 Study Screening
Preclinical Alzheimer Cognitive Composite

$D = 0.32$
$p < 0.0001$
$\text{Adj}^* p < 0.0001$

*p value adjusted for age, gender, and education

$N = 3163$  $N = 1323$

Sperling R et al
AAIC 2018
A4 Screening Results: PACC Components

**MMSE**
- $D = .11$
- $p = 0.013$
- $\text{Adj } p = 0.097 \text{ (ns)}$

**Digit Symbol**
- $D = .27$
- $p < 0.0001$
- $\text{Adj } p < 0.0001$

**LM Delayed**
- $D = .17$
- $p = 0.0002$
- $\text{Adj } p = 0.0028$

**FCSRT96**
- $D = .26$
- $p < 0.0001$
- $\text{Adj } p < 0.0001$
Results: A4 Screening
Cognitive Function Index

<table>
<thead>
<tr>
<th>CFI-Pt</th>
<th>CFI-SP</th>
<th>CFI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Self Report</td>
<td>Study Partner</td>
<td>Combined</td>
</tr>
</tbody>
</table>

- CFI-Pt
  - D = 0.31
  - p < 0.0001
  - Adj p < 0.0001

- CFI-SP
  - D = 0.23
  - p < 0.0001
  - Adj p < 0.0001

- CFI
  - D = 0.33
  - p < 0.0001
  - Adj p < 0.0001

Amyloid Status

Aβ−  | Aβ+  |
---   | ---   |
Self Report | Study Partner | Combined
Disease does not require clinical symptoms
Which of the below is NOT considered disease?

• Asymptomatic 80% stenosis of the left main coronary artery detected on cardiac catheterization
• Asymptomatic HIV infection with CD4 count <200
• Asymptomatic invasive ductal carcinoma detected on mammogram

Cannot simultaneously be at risk for a disease and have the disease, instead “at risk for symptoms”
Caveats

• Amyloid is necessary but not sufficient to predict imminent cognitive decline in preclinical AD

• Not everyone with preclinical AD will progress to clinical dementia – Need to study resilience, and develop predictive models for individuals

• Current biomarkers may not fully capture the toxic forms of Aβ and tau proteinopathies

• Need biomarkers for other contributing pathologies, especially TDP-43, α-synuclein, and more vascular
Hypothesis Testing - NIA-AA Framework

Fig. 6. Hypothesis testing using the research framework. In this figure, we outline various possible mechanistic pathways that involve A, T, (N), and (C). We believe current evidence most strongly supports the “modified amyloid cascade hypothesis” pathway denoted in (A), and this is reflected in the terminology in Table 2. However, we illustrate several alternatives that could be tested using the research framework. These are discussed in the text. This is not intended to represent an exhaustive list of all possible pathways but rather an illustration of some possible mechanistic pathways where A and T are and are not causal in AD pathogenesis. In each of these models, the final common pathway is (N) → (C), which is based on the assumption that in neurodegenerative diseases, neuronal/synaptic damage is the histopathologic feature that is most proximate to cognitive impairment. Abbreviations: AD, Alzheimer disease.

Jack C et al
Alz & Dem 2018
Why defining AD as a biologic entity for research is critically important

• We must move into the 21st century in defining AD as a biologic entity rather than a clinical syndrome
• We would never run clinical trials or observational risk studies for cancer without confirmation of pathology
• The optimal time for intervention (at least with anti-amyloid and perhaps even anti-tau therapeutics) may be prior to clinical symptoms!
Hypothetical Scenario 2

- A 72 year old woman enrolls in an observational study
- She has no memory complaints and performs in the normal cognitive range
- She is found to have abnormal Aβ and Tau on CSF
- After 2 years, she reports she has noticed a slight decline in her memory. At Year 4, she progresses to MCI. At 7 years, she has progressed to dementia.
- At what point did she “get” Alzheimer’s disease?
Gratitude

• Keith Johnson, Dorene Rentz, Beth Mormino, Aaron Schultz from the Harvard Aging Brain Study
• Paul Aisen, ACTC and A4 Teams at Lilly, Avid, MNI, ATRI, ADCS, Mayo, CogState
• Collaboration for Alzheimer Prevention
• Alzheimer’s Association, GHR Foundation, Gates Ventures, and Fidelity Biosciences, AMP FNIH
• National Institute on Aging
Rebuttal
**Figure 4. Leading causes of death for persons ages 65 years and older by sex, 2002**

<table>
<thead>
<tr>
<th>Cause of death</th>
<th>All</th>
<th>Male</th>
<th>Female</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Percent all deaths</td>
<td>Percent all deaths</td>
<td>Percent all deaths</td>
</tr>
<tr>
<td></td>
<td>Rank</td>
<td>Rank</td>
<td>Rank</td>
</tr>
<tr>
<td>Heart disease</td>
<td>31.8</td>
<td>31.8</td>
<td>31.8</td>
</tr>
<tr>
<td>Cancer</td>
<td>21.6</td>
<td>25.0</td>
<td>18.8</td>
</tr>
<tr>
<td>Stroke</td>
<td>7.9</td>
<td>6.5</td>
<td>9.1</td>
</tr>
<tr>
<td>Chronic lower respiratory diseases</td>
<td>6.0</td>
<td>6.5</td>
<td>5.6</td>
</tr>
<tr>
<td>Influenza and Pneumonia</td>
<td>3.2</td>
<td>3.1</td>
<td>3.4</td>
</tr>
<tr>
<td>Alzheimer's disease</td>
<td>3.2</td>
<td>2.1</td>
<td>4.1</td>
</tr>
<tr>
<td>Diabetes</td>
<td>3.0</td>
<td>2.9</td>
<td>3.1</td>
</tr>
<tr>
<td>Nephritis, nephrotic syndrome, and nephrosis</td>
<td>1.9</td>
<td>2.0</td>
<td>1.8</td>
</tr>
<tr>
<td>Accidents</td>
<td>1.9</td>
<td>2.1</td>
<td>1.7</td>
</tr>
<tr>
<td>Septicemia</td>
<td>1.5</td>
<td>1.4</td>
<td>1.5</td>
</tr>
</tbody>
</table>

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**Survival rates for prostate cancer**

According to the most recent data, when including all stages of prostate cancer:

- The 5-year relative survival rate is 99%
- The 10-year relative survival rate is 98%
- The 15-year relative survival rate is 96%
Encouraging history from other fields

• Cholesterol Wars in Cardiology in the 70’s
  • Secondary prevention trials in familial hypercholesterolemia and in post-MI with intact cardiac function
  • Reduction of cholesterol estimated to have reduced cardiac morbidity and mortality by 28%
  • As in “A3” rationale, recommendations for treating cholesterol have steadily evolved to lower LDL

• Amyloid does not have to be “the” cause of AD, merely “a” critical factor that can be impacted at the optimal time
Greater Amyloid Associated with Greater Tau Burden
(A4 Study Baseline Data)

FTP PET Vertex correlations with cortical FBP SUVR (n=239)

Left Fusiform
Sperling R et al HAI 20
A4 Tau PET and Cognitive Performance

\begin{align*}
\beta &= -0.18 \\
\text{[-0.27, -0.09]} \\
p &< 0.001
\end{align*}

\begin{align*}
\beta &= -0.17 \\
\text{[-0.26, -0.08]} \\
p &< 0.001
\end{align*}

\begin{align*}
\beta &= -0.17 \\
\text{[-0.26, -0.07]} \\
p &< 0.001
\end{align*}

\begin{align*}
\beta &= -0.19 \\
\text{[-0.28, -0.09]} \\
p &< 0.001
\end{align*}

Johnson K et al AAIC 2018
Preclinical Alzheimer Cognitive Composite

Harvard Aging Brain Study (n=277)

Mormino E et al. Alz & Dementia 2017
Hypothetical Interaction of Amyloid and Tau in Preclinical AD

Sperling, Mormino, Johnson *Neuron* 201
Change in Tau PET associated with change in cognition

\[ R^2 = 0.23, \ p = 0.0001 \]

Covariates: Age, Sex, and Education

Hanseeuw B et al. Under Review
The relationship between A and T

Harvard Aging Brain Study Data          Aaron Schultz and Keith Johnson