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Memory decline accompanies subthreshold amyloid accumulation

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Memory decline accompanies subthreshold amyloid accumulation

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Abstract

Objective

Extensive cortical beta-amyloid (A beta positivity) has been linked to cognitive decline, but the clinical significance of elevations in A beta within the negative range is unknown.

Methods

We examined amyloid and cognitive trajectories (memory, executive function) in 142 cognitively normal older individuals enrolled in the Alzheimer's Disease Neuroimaging Initiative who were A beta-negative at baseline and who had at least 2 (F-18)-florbetapir PET scans over 3.9 +/- 1.4 years. We determined whether A beta accumulation was associated with longitudinal changes in memory or executive function.

Results

Among baseline-negative individuals, florbetapir slope (mean annual increase 0.002 +/- 0.008 standardized uptake value ratio units/yr) was not related to age, sex, education, APOE4 status, baseline memory or executive function, temporoparietal glucose metabolism, baseline hippocampal volume, or hippocampal volume change; but it was related to higher baseline cortical florbetapir, indicating that A beta accumulation was ongoing at baseline in those who accumulated during the study. Over the course of follow-up, 13 individuals converted to florbetapir+ and 14 nearly nonoverlapping individuals converted to mild cognitive impairment or Alzheimer disease. Amyloid accumulation among baseline-negative individuals was associated with poorer longitudinal memory performance (p = 0.019), but it was not associated with changes in executive function. Reducing the sample to individuals with at least 3 timepoints to estimate the florbetapir slope strengthened the relationship further between florbetapir accumulation and memory decline (p = 0.007).

Conclusions

Memory decline accompanies A beta accumulation in otherwise healthy, A beta-negative older adults. Amyloid increases within the negative range may represent the earliest detectable indication of pathology with domain-specific cognitive consequences.

Keywords

KeyWords Plus: NEUROIMAGING INITIATIVE ADNI; MILD COGNITIVE IMPAIRMENT; WHITE-MATTER ATROPHY; ALZHEIMER DISEASE; AGING; COGNITIVE FUNCTION; AGING; NEUROIMAGING;
REFERENCE; ALZHEIMER'S-DISEASE; COMPOSITE SCORE; COMPOUND B-PET; NEURODEGENERATION; DYSFUNCTION; TRIALS

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### Cited References: 33

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<table>
<thead>
<tr>
<th>ID</th>
<th>Title</th>
<th>Times Cited</th>
<th>Authors and Details</th>
</tr>
</thead>
</table>
| 1  | Stability of the preclinical episodic memory deficit in Alzheimer's disease | 225         | Backman, L; Small, B.J; Fratiglioni, L  
BRAIN Volume: 124  Pages: 96-102  Part: 1  Published: JAN 2001 |
| 2  | Human amyloid-beta synthesis and clearance rates as measured in cerebrospinal fluid in vivo | 302         | Bateman, Randall J.; Munsell, Ling Y.; Morris, John C.; et al.  
NATURE MEDICINE Volume: 12  Issue: 7  Pages: 856-861  Published: JUL 2006 |
| 3  | Clinical and Biomarker Changes in Dominantly Inherited Alzheimer's Disease | 1109        | Bateman, Randall J.; Xiong, Chengjie; Benzinger, Tammie L. S.; et al.  
NEW ENGLAND JOURNAL OF MEDICINE Volume: 367  Issue: 9  Pages: 795-804  Published: AUG 30 2012 |
| 4  | Improved longitudinal [F-18]-AV45 amyloid PET by white matter reference and VOI-based partial volume effect correction | 39          | Brendel, Matthias; Hoegenauer, Marcus; Delker, Andreas; et al.  
GROUP Author(s): Alzheimer's Dis Neuroimaging  
NEUROIMAGE Volume: 108  Pages: 450-459  Published: MAR 2015 |
| 5  | Improved Power for Characterizing Longitudinal Amyloid-beta PET Changes and Evaluating Amyloid-Modifying Treatments with a Cerebral White Matter Reference Region | 36          | Chen, Kewei; Roontiva, Auttawut; Thiyagura, Pradeep; et al.  
GROUP Author(s): Alzheimer's Dis Neuroimaging  
JOURNAL OF NUCLEAR MEDICINE Volume: 56  Issue: 4  Pages: 560-566  Published: APR 2015 |
| 6  | Development and assessment of a composite score for memory in the Alzheimer's Disease Neuroimaging Initiative (ADNI) | 107         | Crane, Paul K.; Carle, Adam; Gibbons, Laura E.; et al.  
GROUP Author(s): Alzheimer's Dis Neuroimaging  
BRAIN IMAGING AND BEHAVIOR Volume: 6  Issue: 4  Pages: 502-516  Published: DEC 2012 |
| 7  | Association Between Elevated Brain Amyloid and Subsequent Cognitive Decline Among Cognitively Normal Persons | 29          | Donohue, Michael C.; Sperling, Reisa A.; Petersen, Ronald; et al.  
GROUP Author(s): Alzheimer's Dis Neuroimaging  
JAMA-JOURNAL OF THE AMERICAN MEDICAL ASSOCIATION Volume: 317  Issue: 22  Pages: 2305-2316  Published: JUN 13 2017 |
| 8  | MINI-MENTAL STATE - PRACTICAL METHOD FOR GRADING COGNITIVE STATE OF PATIENTS FOR CLINICIAN | 48,292      | FOLSTEIN, MF; FOLSTEIN, SE; MCHUGH, PR  
JOURNAL OF PSYCHIATRIC RESEARCH Volume: 12  Issue: 3  Pages: 189-198  Published: 1975 |
9. **A composite score for executive functioning, validated in Alzheimer's Disease Neuroimaging Initiative (ADNI)**
   By: Gibbons, Laura E.; Carle, Adam C.; Mackin, R. Scott; et al.
   Group Author(s): Alzheimer's Dis Neuroimaging
   BRAIN IMAGING AND BEHAVIOR Volume: 6 Issue: 4 Pages: 517-527 Published: DEC 2012

10. **Memory impairment, executive dysfunction, and intellectual decline in preclinical Alzheimer's disease**
    By: Grober, Ellen; Hall, Charles B.; Lipton, Richard B.; et al.
    JOURNAL OF THE INTERNATIONAL NEUROPSYCHOLOGICAL SOCIETY Volume: 14 Issue: 2 Pages: 266-278 Published: MAR 2008

11. **Microglial dysfunction and defective beta-amyloid clearance pathways in aging Alzheimer's disease mice**
    By: Hickman, Suzanne E.; Allison, Elizabeth K.; El Khoury, Joseph
    JOURNAL OF NEUROSCIENCE Volume: 28 Issue: 33 Pages: 8354-8360 Published: AUG 13 2008

12. **Serial PIB and MRI in normal, mild cognitive impairment and Alzheimers disease: implications for sequence of pathological events in Alzheimers disease**
    By: Jack, Clifford R., Jr.; Lowe, Val J.; Weigand, Stephen D.; et al.
    Group Author(s): Alzheimer's Dis Neuroimaging Initi
    BRAIN Volume: 132 Pages: 1355-1365 Part: 5 Published: MAY 2009

13. **Tracking pathophysiological processes in Alzheimer's disease: an updated hypothetical model of dynamic biomarkers**
    By: Jack, Clifford R., Jr.; Knopman, David S.; Jagust, William J.; et al.
    LANCET NEUROLOGY Volume: 12 Issue: 2 Pages: 207-216 Published: FEB 2013

14. **Prevalence of Cerebral Amyloid Pathology in Persons Without Dementia A Meta-analysis**
    By: Jansen, Willemijn J.; Ossenkoppele, Rik; Knol, Dirk L.; et al.
    Group Author(s): Amyloid Biomarker Study Grp

15. **Amyloid deposition, hypometabolism, and longitudinal cognitive decline**
    By: Landau, Susan M.; Mintun, Mark A.; Joshi, Abhinay D.; et al.
    Group Author(s): Alzheimer's Dis Neuroimaging Ini
    ANNALS OF NEUROLOGY Volume: 72 Issue: 4 Pages: 578-586 Published: OCT 2012

16. **Measurement of Longitudinal beta-Amyloid Change with F-18-Florbetapir PET and Standardized Uptake Value Ratios**
    By: Landau, Susan M.; Fero, Allison; Baker, Suzanne L.; et al.
    JOURNAL OF NUCLEAR MEDICINE Volume: 56 Issue: 4 Pages: 567-574 Published: APR 2015

17. **Amyloid-beta Imaging with Pittsburgh Compound B and Florbetapir: Comparing Radiotracers and Quantification Methods**
    By: Landau, Susan M.; Breault, Christopher; Joshi, Abhinay D.; et al.
    Group Author(s): Alzheimer's Dis Neuroimaging
    JOURNAL OF NUCLEAR MEDICINE Volume: 54 Issue: 1 Pages: 70-77 Published: JAN 2013
19. **Associations between cognitive, functional, and FDG-PET measures of decline in AD and MCI**
   By: Landau, Susan M.; Harvey, Danielle; Madison, Cindee M.; et al.
   Group Author(s): Alzheimer’s Dis Neuroimaging Initi
   NEUROBIOLOGY OF AGING Volume: 32 Issue: 7 Pages: 1207-1218 Published: JUL 2011

20. **The Alzheimer's Disease Assessment Scale.**
    By: Mohs, R C
    International psychogeriatrics Volume: 8 Issue: 2 Pages: 195-203 Published: 1996

21. **Development of cognitive instruments for use in clinical trials of antidementia drugs: Additions to the Alzheimer's disease assessment scale that broaden its scope**
    By: Mohs, RC; Knopman, D; Petersen, RC; et al.
    ALZHEIMER DISEASE & ASSOCIATED DISORDERS Volume: 11 Supplement: 2 Pages: S13-S21 Published: 1997

22. **Synergistic Effect of beta-Amyloid and Neurodegeneration on Cognitive Decline in Clinically Normal Individuals**
    By: Mormino, Elizabeth C.; Betensky, Rebecca A.; Hedden, Trey; et al.
    JAMA NEUROLOGY Volume: 71 Issue: 11 Pages: 1379-1385 Published: NOV 2014

23. **THE CONSORTIUM TO ESTABLISH A REGISTRY FOR ALZHEIMERS-DISEASE (CERAD) .4. RATES OF COGNITIVE CHANGE IN THE LONGITUDINAL ASSESSMENT OF PROBABLE ALZHEIMERS-DISEASE**
    By: Morris, J C; Edland, S; Clark, C; et al.
    NEUROLOGY Volume: 43 Issue: 12 Pages: 2457-2465 Published: DEC 1993

24. **Title: [not available]**
    By: Reitan, R. M.; Wolfson, D.
    The Halstead-Reitan Neuropsychological Test Battery: Theory and clinical interpretation Published: 1985
    Publisher: Neuropsychology Press, Tucson, AZ

25. **Longitudinal cognitive decline is associated with fibrillar amyloid-beta measured by [C-11]PiB**
    By: Resnick, S. M.; Sojkova, J.; Zhou, Y.; et al.
    NEUROLOGY Volume: 74 Issue: 10 Pages: 807-815 Published: MAR 2010

26. **Title: [not available]**
    By: Rey, A.
    L'examen Clinique En Psychologie Published: 1964

27. **C-11-PiB PET assessment of change in fibrillar amyloid-beta load in patients with Alzheimer's disease treated with bapineuzumab: a phase 2, double-blind, placebo-controlled, ascending-dose study**
    By: Rinne, Juha O.; Brooks, David J.; Rossor, Martin N.; et al.
    LANCET NEUROLOGY Volume: 9 Issue: 4 Pages: 363-372 Published: APR 2010

28. **Two Phase 3 Trials of Bapineuzumab in Mild-to-Moderate Alzheimer's Disease**
    By: Salloway, Stephen; Sperling, Reisa; Fox, Nick C.; et al.
    Group Author(s): Bapineuzumab 301 302 Clinical
    NEW ENGLAND JOURNAL OF MEDICINE Volume: 370 Issue: 4 Pages: 322-333 Published: JAN 23 2014

29. **The A4 Study: Stopping AD Before Symptoms Begin?**
    By: Sperling, Reisa A.; Rentz, Dorene M.; Johnson, Keith A.; et al.
    SCIENCE TRANSLATIONAL MEDICINE Volume: 6 Issue: 228 Article Number: 228fs13 Published: MAR 19 2014

30. **Amyloid beta deposition, neurodegeneration, and cognitive decline in sporadic Alzheimer's disease: a prospective cohort study**
    Times Cited: 599