Published in final edited form as:

Neurobiol Aging. 2016 October ; 46: 32–42. doi:10.1016/j.neurobiolaging.2016.06.003.

Evolution of Neurodegeneration Imaging Biomarkers from Clinically Normal to Dementia in the Alzheimer Disease Spectrum

David S. Knopman, MD^{1,2}, Clifford R. Jack Jr., MD^{2,3}, Emily S. Lundt, MS⁴, Stephen D. Weigand, MS⁴, Prashanthi Vemuri, PhD^{2,3}, Val J. Lowe, MD^{2,3}, Kejal Kantarci, MD^{2,3}, Jeffrey L. Gunter, PhD^{3,5}, Matthew L. Senjem, MS^{3,5}, Michelle M. Mielke, PhD^{1,6}, Mary M. Machulda, PhD^{2,7}, Rosebud O. Roberts, MBChB^{1,6}, Bradley F. Boeve, MD^{1,2}, David T. Jones, MD^{1,2,3}, and Ronald C. Petersen, MD, PhD^{1,2,6}

¹Department of Neurology, Mayo Clinic and Foundation, Rochester, MN

²Mayo Clinic Alzheimer's Disease Research Center, Mayo Clinic and Foundation, Rochester, MN

³Department of Radiology, Mayo Clinic and Foundation, Rochester, MN

⁴Division of Biomedical Statistics and Informatics, Department of Health Sciences Research, Mayo Clinic and Foundation, Rochester, MN

⁵Department of Information Technology, Mayo Clinic and Foundation, Rochester, MN

⁶Division of Epidemiology, Department of Health Sciences Research, Mayo Clinic and Foundation, Rochester, MN

Correspondence to: Dr. DS Knopman, Department of Neurology, College of Medicine, Mayo Clinic, 200 First Street SW, Rochester, MN 55905 USA Telephone 507 538 1038; Fax 507 538 6012; knopman@mayo.edu.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Author Contributions:

Dr. Knopman – Generated first draft and completed final draft. Study concept and design; acquisition of data; analysis and interpretation; critical revision of the manuscript for important intellectual content
Dr. Jack - analysis and interpretation; critical revision of the manuscript for important intellectual content; study supervision
Mr. Weigand - analysis and interpretation; critical revision of the manuscript for important intellectual content
Dr. Vemuri - critical revision of the manuscript for important intellectual content
Dr. Mielke - critical revision of the manuscript for important intellectual content
Dr. Machulda - critical revision of the manuscript for important intellectual content
Dr. Lowe - critical revision of the manuscript for important intellectual content
Dr. Kantarci - critical revision of the manuscript for important intellectual content
Dr. Gunter - critical revision of the manuscript for important intellectual content
Mr. Senjem – analysis, critical revision of the manuscript for important intellectual content
Dr. Jones - critical revision of the manuscript for important intellectual content
Dr. Roberts - critical revision of the manuscript for important intellectual content
Dr. Boeve - acquisition of data; critical revision of the manuscript for important intellectual content
Dr. Petersen - acquisition of data; critical revision of the manuscript for important intellectual content; Study supervision

Disclosures

Mr. Weigand reports no disclosures.
Dr. Gunter reports no disclosures.
Mr. Senjem reports no disclosures.
Dr. Jones reports no disclosures.
Dr. Roberts reports no disclosures.
Dr. Roberts receives research grants from the NIH/NIA.

⁷Department of Psychiatry, Division of Psychology, Mayo Clinic and Foundation, Rochester, MN

Abstract

The availability of antemortem biomarkers for Alzheimer's Disease (AD) enables monitoring the evolution of neurodegenerative processes in real time. Pittsburgh compound B (PIB) positron emission tomography (PET) was used to select participants in the Mayo Clinic Study of Aging and the Mayo Alzheimer's Disease Research Center with elevated β -amyloid, designated as "A+," and hippocampal volume and ¹⁸fluorodeoxyglucose (FDG) positron emission tomography were used to characterize participants as having evidence of neurodegeneration ("N+") at the baseline evaluation. There were 145 clinically normal (CN) A+ individuals, 62 persons with mild cognitive impairment (MCI) who were A+ and 20 with A+ AD dementia. Over a period of 1–6 years, MCI A+N+ individuals showed declines in medial temporal, lateral temporal, lateral parietal, and to a lesser extent, medial parietal regions for both FDG standardized uptake value ratio (SUVR) and grey matter (GM) volume that exceeded declines seen in the CN A+N+ group. The AD dementia group showed declines in the same regions on FDG SUVR and GM volume with rates that exceeded that in MCI A+N+. Expansion of regional involvement and faster rate of neurodegeneration characterizes progression in the AD pathway.

1. Introduction

As recently as a decade ago, disease-course models of the pathophysiological processes that comprised Alzheimer's disease (AD) were constructed by cobbling together antemortem clinical findings and neuropathological observations. While neuropathologically-derived models (Braak and Braak, 1991; Delacourte *et al.*, 1999; Thal *et al.*, 2000; Braak *et al.*, 2006) have been hugely successful in conceptualizing mechanisms in AD, the mapping from neuropathology back to live patients left many aspects of the sequence of events speculative. The recent ability to characterize individuals according to both their degree of β -amyloid burden (Klunk *et al.*, 2004) and degree of neurodegenerative changes (as indexed by either imaging or cerebrospinal fluid biomarkers) has made it possible to establish a sequence of events in the progression of AD pathophysiological processes in living patients in real time. While the availability of Tau-positron emission tomography (PET) imaging (Johnson *et al.*, 2015; Brier *et al.*, 2016; Scholl *et al.*; Schwarz *et al.*, 2016) offers a different route to understanding progression of disease in AD, structural MR and FDG PET might be causally more aligned with cognition than neurofibrillary tangle burden (Gomez-Isla *et al.*, 1997; Savva *et al.*, 2009).

The temporal order of antemortem biomarker changes provides clues about underlying neurobiological mechanisms. Elevated brain β -amyloid has been associated cross-sectionally and longitudinally with changes in neurodegenerative imaging biomarkers in non-demented individuals (Sabuncu *et al.*, 2011; Ewers *et al.*, 2012; Dore *et al.*, 2013; Villemagne *et al.*, 2013; Oh *et al.*, 2014; Araque Caballero *et al.*, 2015; Nosheny *et al.*, 2015). The same has also been reported in persons with AD dementia (Sabuncu *et al.*, 2011). However, while the prior studies (Sabuncu *et al.*, 2011; Ewers *et al.*, 2012; Dore *et al.*, 2013; Araque Caballero *et al.*, 2015; Nosheny *et al.*, 2015) used amyloid biomarkers longitudinally to examine the consequences of elevated brain β -amyloidosis on neurodegenerative biomarkers, none

conditioned the examination on the baseline state of neurodegeneration. Among clinically normal (CN) persons (Knopman *et al.*, 2013) and in those with mild cognitive impairment (MCI) (Knopman *et al.*, 2015), we have reported that those with elevated brain amyloid and abnormal levels of neurodegenerative biomarkers at baseline showed greater progression of atrophy and hypometabolism compared to their cognitively comparable peers without both elevated amyloidosis and neurodegenerative changes. In our prior reports, we were not able to compare across CN and MCI, nor were we able to include an AD dementia (AD DEM) comparison group. Here, we focus on the differences in neurodegeneration imaging biomarkers in persons with elevated brain amyloid across the cognitive spectrum from CN to MCI to AD DEM, to explore the consequences of the intersection of existing neurodegenerative changes and elevated β -amyloid on regional changes in cortical volume and metabolism.

2. Methods

2.1. Participants

We included participants who had at least two PET and MRI scans and a diagnosis of CN, MCI, or AD DEM at baseline. AD DEM and MCI participants were drawn from the Mayo Alzheimer's Disease Research Center (ADRC) and the Mayo Clinic Study of Aging (MCSA), while CN participants were drawn from the latter study only. To be eligible, AD-DEM participants had to have elevated amyloid by PIB PET at baseline. The CN participants reported here included those previously reported (Knopman *et al.*, 2013) plus a much larger group not previously reported; MCI participants were the same ones who were reported previously (Knopman *et al.*, 2015).

The methods used for participant recruitment and diagnosis have been previously detailed for the MCSA (Petersen, 2004; Roberts *et al.*, 2008; Petersen *et al.*, 2010; Roberts *et al.*, 2012; Roberts *et al.*, 2014). A consensus diagnostic process was used to assign clinical labels of CN, MCI and dementia according to criteria established by the National Institutes on Aging-Alzheimer Association workgroups (Albert *et al.*, 2011; McKhann *et al.*, 2011). We allowed any neuropsychologically-defined MCI subtype. Blood was collected on all participants and *APOE* genotype determined.

These studies were approved by the Mayo Clinic and Olmsted Medical Center institutional review boards. Written informed consent was obtained from all participants. In the case of persons with dementia, a close family member also provided written consent.

2.2 Imaging Methods

All subjects underwent MR imaging, 18 fluorodeoxyglucose (FDG) positron emission tomography (PET) and 11 C-Pittsburgh compound B (PIB) PET with our previously described methodology (Knopman *et al.*, 2013; Jack *et al.*, 2014; Jack *et al.*, 2015; Knopman *et al.*, 2015). Mayo ADRC and MCSA participants who agree to imaging undergo a brain MR on one day and the FDG and PIB PET scans on the following day. A CT scan was performed at the time of PET imaging for attenuation correction. The scans were done within 6 months of a participant's clinical visit.

2.2.1. MR imaging—MR scanning was performed at 3 Tesla and the 3-dimensional magnetization-prepared radiofrequency pulses and rapid gradient echo (MPRAGE) sequences were used for quantitative analyses. The imaging parameters were: TR/TE/T1, 2300/3/900 ms; flip angle 8°; 26-cm field of view (FOV); 256×256 in-plane matrix with a phase FOV of 0.94, voxel dimensions of 1.0156×1.0156×1.2 mm, and number of locations/slab: 170. (Jack *et al.*, 2008).

Hippocampal volume was one of the imaging features used to classify participants at baseline as having abnormal neurodegeneration (“N+”). Hippocampal volume was measured with FreeSurfer (v5.3; <https://surfer.nmr.mgh.harvard.edu/>). Each subject’s raw hippocampal volume was adjusted for TIV to create a total intracranial volume (TIV)-adjusted hippocampal volume (HVa). TIV was measured using the MPRAGE MR scan in which all intracranial contents were identified. HVa was derived by calculating the residual from a linear regression of hippocampal volume versus TIV among a sample of 133 clinically normal participants aged 30 to 59 (Jack *et al.*, 2014)).

Regional grey matter (GM) volume, both at baseline and over time, was one of the outcome measures. The TBM-SyN algorithm was used to derive GM volume estimates (Jack *et al.*, 2014; Vemuri *et al.*, 2015). TBM-SyN computes a symmetric deformation between each pair of scans in a subject’s time series of structural T1 images. For a given serial image pair, the late image is warped to the space of the early image, and a soft mean of the warped late image and the early image is computed, to produce a synthetic early image. In addition, the Jacobian image from the deformation is log-transformed, then annualized to account for the inter-scan interval. The synthetic early image is then parcellated into cortical ROIs, and segmented into GM using SPM unified segmentation (Ashburner, 2009) and a set of custom template, priors and anatomical ROI labels. The ROI masks are then used to quantify the amount of GM in each ROI for the synthetic early image, as well as the mean of the annualized log Jacobian in each ROI. This entire process is repeated in the opposite direction, warping the early image to the late image, to get GM estimates and rates of change in the late image space as well. This pair-wise computation is repeated on all consecutive image pairs for each subject to give estimates of GM at each time point. GM volume estimates from TBM-SyN were averaged at each time point. The values were computed for 14 cortical regions defined by the AAL atlas (Tzourio-Mazoyer *et al.*, 2002); right and left hemisphere values were summed.

2.2.2. PIB PET imaging—PIB PET imaging was used to characterize participants at baseline as having elevated amyloid (“A+”) or not elevated (“A–”). A PIB PET scan consisted of four 5-minute dynamic frames acquired from 40–60 minutes after injection of ¹¹C-PIB. PIB values were grey matter and white matter sharpened. Partial volume correction was performed to account for voxel CSF content. The PIB PET ROIs were derived from an MR template generated from each participant. Median voxel values were extracted from each labeled cortical ROI in the AAL atlas (Tzourio-Mazoyer *et al.*, 2002) modified in-house. A global PIB standardized uptake value ratio (SUVR) was calculated from a group of regions in both hemispheres including parietal, cingulate precuneus, prefrontal, orbito-frontal, temporal, anterior cingulate and posterior cingulate regions, with cerebellar grey matter as the reference region.

2.2.3. FDG PET Imaging—FDG SUVR was used both for baseline classification of neurodegeneration, and also as an outcome measure. FDG PET was obtained on the same day as the PIB PET scan and consisted of four 2-minute dynamic frames acquired from 30–38 minutes after injection of ^{18}F FDG. FDG values were non-sharpened and were not partial-volume corrected. FDG PET regional SUVR values were derived in a similar manner to the PIB PET scans.

Low FDG SUVR in a group of voxels typically impaired in AD was the second imaging feature used to define neurodegeneration (“N+”) at baseline (Jack *et al.*, 2012; Knopman *et al.*, 2013; Jack *et al.*, 2014; Knopman *et al.*, 2015). The voxels were located bilaterally in angular gyrus, posterior cingulate gyrus, and middle/inferior temporal gyrus. For this meta-ROI, values were normalized to the pons and vermis (Landau *et al.*, 2011).

Change in regional FDG SUVR values were used as one of the primary outcome measures. Image values were extracted from a template created from the patient’s own MR using the AAL atlas (Tzourio-Mazoyer *et al.*, 2002) that was modified by us. Regional values were calculated for 14 regions and averaged across hemispheres and weighted to the ROI size. For the outcome measure, FDG SUVR used pons for normalization.

2.3. Baseline Characterization of Participants

Participants were characterized as having elevated brain amyloid (A+) based on a cutpoint of 1.4 for PIB PET SUVR. This value represented the 10th percentile of the distribution of values from a calibration sample of 75 patients with AD dementia who were age 65 or older with MRI and PET data from the Mayo ADRC or MCSA (Jack *et al.*, 2014). A value of PIB SUVR of 1.4 was found to correspond to neuropathological Thal amyloid stage of 2 (Murray *et al.*, 2015). Within the study cohort, 144 of 327 CN participants were A+, 62 of 96 MCI participants were A+, and all AD DEM patients were A+ by design. We also present data from the CN A– (n=183) and MCI A– (n=34) groups for completeness, but the A– groups were not the focus of this report.

The participants were further characterized as having abnormal neurodegenerative changes (N+) based on *either* $\text{HvA} < -2.40 \text{ cm}^3$ *or* FDG SUVR in the meta-ROI affected in AD < 1.32 . The cut-points were derived from the same AD dementia patients described in previous paragraph, and represented the 90th percentile in AD dementia.

2.4. Outcome measures

Baseline and annualized change were examined in GM volume and FDG SUVR in 4 ROIs that are typically abnormal in AD (Whitwell *et al.*, 2008; Dickerson *et al.*, 2011; La Joie *et al.*, 2012): medial temporal (MT), lateral temporal (LT), medial parietal (MP) and lateral parietal (LP). See Supplemental Figure 1 for their locations. The other 10 cortical regions were designated as non-principal ROIs.

2.5. Analyses

Linear mixed-effects regression models were fit in each ROI to assess group differences in baseline FDG SUVR and GM volumes and to assess group differences in changes over time

in FDG SUVR and GM volume. In a secondary analysis, a linear mixed-effects regression model was fit to assess group differences in global PIB SUVR. Each mixed effects model included main effects of time, age at baseline, sex, group and interactions for age at baseline by time and group by time. To account for repeated measures and patient heterogeneity we included random subject-specific intercepts and slopes. In these models group differences at baseline and rates of change were adjusted for age-related baseline differences.

All outcome measures were log-transformed to reduce skewness and to allow for interpretation of slope estimates as approximate annual percent change. We report baseline and change estimates with the usual 95% confidence intervals (CIs), and also used 84% CIs because at that level, non-overlapping intervals correspond to a biomarker group difference that is significant at the $P < 0.05$ level (Knol *et al.*, 2011). We did not correct for multiple comparisons. We used a parametric bootstrap approach with 5000 replicates to simulate baseline and slope coefficients to assess how much support the data provided for an ordering of average values such that $AD\ DEM < MCI\ A+N+ < CN\ A+N+$ (Gelman and Hill, 2007). The percentage of replicates whereby this ordering held can be interpreted as a posterior probability. For example, if the ordering held in 90% of the replicates, the data suggests a high likelihood that on average this ordering is true. We also assessed the correlation between FDG and GM volume at baseline and in terms of rate of change for each of the four principal regions. Valid volumetric estimates could not be obtained for five subjects; they were excluded from all GM volume analyses. All analyses were performed using R Statistical Software (version 3.1.1; R Foundation for Statistical Computing).

3. Results

The 5 A+ groups are described in Table 1. The Supplemental Table 1 includes the A- groups as well. As the CN and MCI groups were not matched on any demographic or clinical features, groups varied to a greater or lesser degree in age, education, sex as well as level of cognitive function and range of imaging abnormalities. Carriage of the *APOE* e4 allele was highest in AD DEM and MCI A+. The MCI A+ group was overwhelming of the amnesic type (57/62, 92%). Forty-seven percent of MCI but only 20% of CN participants were A+N+ (Supplemental Table 2). As expected the AD DEM group had the lowest cognitive test scores. All 20 of the AD DEM participants were A+ by definition and all but one was N+.

Across all A+ participants, baseline values of FDG SUVR and GM volume in the 4 principal ROIs were moderately correlated (rho's 0.32, 0.22, 0.23 and 0.31; $p < 0.001$), and rates of change were similarly or slightly less correlated (rho's 0.32, 0.21, 0.15 and 0.18; $p = 0.002$ for MT, LT, MP and LP, respectively).

Figures 1 to 3 and Tables 2 and 3 illustrate the principal findings. With a much larger sample than in our previous publication on CN, we replicated and extended our prior observations (Knopman *et al.*, 2013) on the extent to which the CN A+N+ group's rate of change in both FDG SUVR and GM volume in the medial temporal ROI exceeded the other CN groups. Our recent report on observations within an MCI group (Knopman *et al.*, 2015) are also reflected in the current analyses. *However, the current report focuses on between-clinical group differences.*

AD DEM versus MCI A+N+

The AD DEM group had significantly lower baseline FDG SUVR in all 4 principal ROIs (MT, $p<0.001$; LT, $p<0.001$; MP, $p=0.003$; LP, $p<0.001$ LP) and lower GM volume in MT and LT ROIs (both $p=0.01$) compared to the MCI A+N+ group (Figure 1). The AD DEM group showed greater metabolic annual percent declines compared to the MCI A+N+ group in 3 of 4 principal ROIs (MT, $p=0.048$; LT, $p=0.01$; MP, $p=0.22$, LP, $p=0.03$), and greater volumetric losses in MT ($p=0.04$), and LT ROIs ($p=0.02$) (Table 2 and Figure 2). The relationship between baseline values and rate of change are depicted in Figure 3.

The AD DEM group's FDG SUVR declines in *non-principal ROIs* did not differ from the MCI A+N+ group. There were also no differences in GM volumes annual percent declines in non-principal ROIs in the AD DEM group compared to the MCI A+N+ group except in insula ($p=0.02$). The values for non-principal ROIs are given in the Supplemental Table 2.

MCI A+N+ versus CN A+N+

At baseline, the MCI A+N+ group had lower MT FDG SUVR ($p=0.045$) and lower MT GM volume ($p=0.006$) compared to the CN A+N+ group but no differences in other principal ROIs (Figure 1). On the other hand, the annual percent declines in FDG SUVR in all 4 principal ROIs ($p<0.001$) and GM volume in 3 of the principal ROIs (MT, $p<0.001$; LT, $p<0.001$; and LP, $p=0.01$) were greater among the MCI A+N+ group than in the CN A+N+ group (Table 2 and Figure 2). The relationship between baseline values and rate of change are depicted in Figure 3.

The MCI A+N+ group showed significantly greater FDG SUVR declines in almost all of *the non-principal ROIs* compared to the CN A+N+ group. The MCI A+N+ group showed significantly greater GM volumetric declines compared to CN A+N+ in insula ($p=0.02$), and precentral gyrus ($p=0.03$). The values for non-principal ROIs are given in the Supplemental Table 2.

Given the differences between AD DEM and MCI A+N+, and between MCI A+N+ and CN A+N+, differences between AD DEM and CN A+N+ were large. The values are given in the Supplemental Table 2.

Summary of CN and MCI A+N+ group and AD DEM differences

The findings are summarized in Table 3. For the 4 principal ROIs we used a bootstrap method with 5000 replicates to evaluate the likelihood that on average AD DEM < MCI A+N+ < CN A+N+ for baseline values of FDG SUVR and GM volume, and that on average AD DEM > MCI A+N+ > CN A+N+ for annual rate of worsening in FDG SUVR and GM volume. Figure 3 and Table 2 summarize the group differences. We found strong evidence for ordering by cognitive severity for baseline FDG SUVR in the MT ROI (98%) and for baseline GM volume in the MT (99%) and LT ROI (96%). The data also indicated moderate support for this ordering for GM volume in the MP ROI (70%) and LP ROI (83%). On rate of decline, there was strong evidence for ordering by cognitive severity across all regions for FDG SUVR (ranging from 89% to 99%) and in the temporal regions for GM volume (99%

for MT and 98% for LT). The data also suggest a relatively high likelihood of ordering for GM volumes in the parietal regions (74% for MP and 85% for LP).

MCI A+N– versus CN A+N–

The CN and MCI A+N– groups also differed. They had similar mean ages but differences in distributions of *APOE* e4 genotype and sex. The MCI group had more elevated PIB SUVR and lower HVa. Whereas there were no baseline differences in FDG SUVR and GM volumes between CN and MCI A+N– groups (Figure 1), the MCI A+N– showed larger declines over follow-up than did the CN A+N– for both FDG SUVR (MT, $p=0.004$; LT, $p=0.008$; LP, $p=0.01$) and GM volume (MT, $p=0.001$; LT, $p<0.001$; LP, $p=0.04$). (Figures 2 and 3).

In the *non-principal ROIs*, the MCI A+N– did not show greater metabolic declines compared to CN A+N–. Volumetrically, the MCI A+N– group showed greater GM volume loss compared to CN A+N– in prefrontal ($p=0.02$), orbitofrontal ($p=0.02$), and insula ($p<0.001$). The values for non-principal ROIs are given in the Supplemental Table 2.

Groups without elevated PIB SUVR

Neither the MCI A–N– nor MCI A–N+ groups showed greater declines in FDG SUVR or GM volume compared to their CN counterparts (see Figure 2).

Differences in PIB SUVR across groups

We compared baseline global PIB SUVR across the A+ groups (Figure 4). As expected, at baseline the AD DEM group had the highest PIB SUVR, the MCI A+ groups the next highest and the CN A+ groups the lowest. However, the rate of increase in PIB SUVR was similar among the A+ CN, MCI and AD DEM groups.

The role of *APOE* e4 genotype

We explored the relationship between carriage of the e4 allele of *APOE* on the progression of structural and metabolic changes across the cognitive spectrum. Because very few *APOE* e4 carriers were found among those who did not have elevated amyloid (Supplemental Table 3), we restricted our analyses to the groups with elevated amyloid. We found that carriers of the *APOE* e4 allele were generally younger, yet had higher PIB SUVR and lower HVa at baseline (Supplemental Table 4 and Supplemental Figure 4). In the regression analyses, there were no baseline group differences based on *APOE* e4 genotype in any ROI. However, in longitudinal analyses carriage of *APOE* e4 was associated with more degeneration in the MT ROI in MCI A+N+ (for FDG SUVR ($p<0.001$) and GM volume ($p=0.01$)) and in AD DEM (for FDG SUVR ($p=0.003$) only). In longitudinal analyses, there were no differences in comparing *APOE* e4 carriers to non-carriers in any other ROI in those two subgroups, and none of the other clinical subgroups showed any *APOE* e4+ effects in any ROIs.

4. Discussion

We found an internally consistent regionally-specific pattern of rate of decline of FDG SUVR and GM volume in A+N+ groups across the spectrum from CN to MCI to dementia.

The AD-DEM group, which was A+ by design and definition, showed both lower baseline values and higher rates of neurodegenerative processes in the 4 principal ROIs plus insula compared to MCI A+N+ and to CN A+N+ (as well as to all other MCI and CN subgroups). The MCI A+N+ group also exhibited a neurodegenerative process that spread into lateral temporal and both parietal ROIs (but mainly lateral parietal). The MCI A+N+ group had less structural or metabolic impairment at baseline and marginally less worsening over time compared to the AD DEM group, but more metabolic and structural deterioration than CN A+N+. Among persons with elevated brain β -amyloid, the transition from clinically normal status to MCI to dementia mapped logically onto the progression of neurodegenerative imaging biomarkers. While clinical – neuropathological studies (Braak and Braak, 1991; Duyckaerts *et al.*, 1997; Delacourte *et al.*, 1999; Braak *et al.*, 2006) have told us that disease expands regionally in temporal isocortex, parietal isocortex and insula as cognition declines, a unique contribution of antemortem serial imaging was the demonstration of an *increasing rate* of neurodegenerative change as cognitive decline worsened from CN to MCI to AD DEM. As we have previously reported in both CN (Knopman *et al.*, 2013) and MCI (Knopman *et al.*, 2015), CN A+N+ or MCI A+N+ groups showed greater declines compared to their other biomarker-defined peers. Our findings go beyond prior work (Sabuncu *et al.*, 2011; Ewers *et al.*, 2012; Dore *et al.*, 2013; Araque Caballero *et al.*, 2015; Nosheny *et al.*, 2015), in showing that the combination of elevated β -amyloidosis and substantial neurodegeneration were jointly required for progression to occur across the AD spectrum.

While global brain β -amyloid levels rose across the spectrum from CN to MCI to AD DEM, there were no group differences in rate of change of β -amyloid accumulation. In contrast to the regional expansion of neurodegeneration from CN to MCI to dementia, the lack of difference in rate of change in brain amyloid levels once again (Jack *et al.*, 2009) makes the point that β -amyloidosis is not proximate to cognition in the sequence of pathophysiological events in the AD pathway. To be sure, we have observed differences in the rate of amyloid accumulation (Jack *et al.*, 2013) as a function of baseline PIB SUVR levels, but as shown here, it was neurodegeneration, and not β -amyloid, that changed in synchrony with declining clinical status.

*APOE*e4 carriage had a large effect on whether an individual had elevated β -amyloid, consistent with much prior work, eg (Morris *et al.*, 2010; Vemuri *et al.*, 2010). However, except for an association with greater metabolic and volumetric losses in the medial temporal ROI in the MCI A+N+ group, carriage of the *APOE*e4 allele did not impact MCI A+N– participants and had no impact on any CN group including the A+N+. To the extent that *APOE*e4 carriage is associated with the appearance of β -amyloid elevations roughly 7 years earlier than non-carriers (Jack *et al.*, 2015), it seems plausible that the excess neurodegenerative changes in MT in MCI A+N+ *APOE*e4 carriers reflected their longer exposure to elevated β -amyloidosis and earlier neurodegenerative changes. That a role for *APOE*e4 carriage was not evident in the CN A+N+ group is somewhat enigmatic, but is consistent with prior studies showing a negligible effect of e4 carriage on hippocampal volume in normals, but a consistent effect in AD dementia (Jack *et al.*, 1999; Lemaitre *et al.*, 2005; Schuff *et al.*, 2009).

Stratifying our groups by baseline neurodegeneration provided some insights into the A+N– groups. Those who were MCI A+N– entered the period of observation with less hypometabolism and volume loss (see Supplemental Figure 3 for scatterplots) than the MCI A+N+ group but showed generally similar rates of neurodegeneration. We are uncertain whether the MCI A+N– group represented persons in whom our neurodegenerative biomarkers failed to capture a salient amyloid (AD)-related process, or whether they were simply at an earlier stage of progression in the AD pathway. In contrast, the CN A+N– group showed less progression of neurodegeneration than the CN A+N+ group, again suggesting that the synergy between amyloidosis and neurodegeneration is critical.

Our method of defining neurodegeneration reflected a strategy that we have previously followed (Jack *et al.*, 2012; Knopman *et al.*, 2013; Jack *et al.*, 2014; Knopman *et al.*, 2015) that allowed abnormalities in either HVa or FDG SUVR as the definition. We have found that the modality or modalities used to define neurodegeneration had little impact on age-related prevalence of abnormality (Jack *et al.*, 2015). We have previously shown that our approach to defining neurodegeneration with either HVa or FDG SUVR successfully predicts clinical progression from CN to MCI or dementia (Knopman *et al.*, 2012) or from MCI to dementia (Petersen *et al.*, 2013). Those observations were replicated in the current analyses, in which the CN A+N+ group experienced a 3-fold greater number of persons who progressed compared to the CN A+N– group, and the MCI A+N+ group experienced nearly a doubling of the number who progressed to dementia.

The joint presence of elevated β -amyloid and evidence for neurodegeneration as shown here was mirrored in clinical progression both from CN to MCI (Knopman *et al.*, 2012; Roe *et al.*, 2013; van Harten *et al.*, 2013; Vos *et al.*, 2013; Wirth *et al.*, 2013; Mormino *et al.*, 2014; Toledo *et al.*, 2014) or from MCI to dementia (van Rossum *et al.*, 2012; Petersen *et al.*, 2013; Prestia *et al.*, 2013; Caroli *et al.*, 2015; Vos *et al.*, 2015). It is hard to escape the conjecture that elevated β -amyloid levels plays a necessary role in promoting or accelerating neurodegeneration – once it reaches a certain threshold – during the CN and MCI stages of the AD process. The conjecture does not imply that β -amyloid initiates the process in sporadic AD, but rather that β -amyloid plays an essential role in promoting neurodegeneration at some point between the time that a person is cognitively normal into the symptomatic phase of AD. Recent work with mouse models of β -amyloidosis and tauopathy also support the role of β -amyloidosis as an accelerant of tauopathy and neurodegeneration (Pooler *et al.*, 2015). In sporadic AD, the distinction between accelerant and initiator may seem subtle, but the implications are profound, and could account in part for disappointing therapeutic adventures with anti-amyloid agents to date.

These analyses have some limitations because the groups were not matched demographically. The AD DEM group was slightly younger and slightly better educated than the CN and MCI A+N+ groups. Sex differences might reflect differential survival or sex-specific risk factors. Matching has some appeal but it induces other group differences that are artificial (eg, CN and MCI groups generally differ in age). Ideally the analyses here should also be performed with incident MCI and AD DEM cases to demonstrate more clearly the evolution of AD neurodegeneration on an individual level, but the rate of progression from CN to MCI is slow enough that we would need a decade, if not more, of

longitudinal experience for sufficient numbers of originally CN persons to develop MCI. And over that length of time, attrition, comorbidity and mortality from other causes would greatly compromise analyses. We chose to perform these analyses by defining categorical clinical groups rather than using cognitive function as a continuous variable. There are several reasons for our choice. First, such an analysis can be mapped to clinical situations. Second, to the extent that the different sample sizes of CN, MCI and DEM groups do not match the distribution in the population, the proportions of participants at different levels of cognitive dysfunction could skew clinical-imaging relationships. Finally we used both FDG SUVR and GM volume to assess change. There were similar regional outcomes for both FDG SUVR and GM volume changes, but the two biomarkers of neurodegeneration were not measuring the same thing as shown by their modest correlations. In CN individuals such differences have been previously reported (La Joie *et al.*, 2012). It was not our goal to determine if FDG PET or volumetric MR was superior to the other; rather we found that they both provided unique information.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Funding: This work was supported by NIH grants P50 AG16574, U01 AG06786, R01 AG41851, and R01 AG11378, the Elsie and Marvin Dekelboum Family Foundation and the Robert H. and Clarice Smith and Abigail Van Buren Alzheimer's Disease Research Program of the Mayo Foundation.

Dr. Knopman serves on a Data Safety Monitoring Board for Lundbeck Pharmaceuticals and for the DIAN study; is an investigator in clinical trials sponsored by Biogen, TauRX Pharmaceuticals, Lilly Pharmaceuticals and the Alzheimer's Disease Cooperative Study; and receives research support from the NIH.

Dr. Jack serves on scientific advisory board for Eli Lilly & Company; receives research support from the NIH/NIA, and the Alexander Family Alzheimer's Disease Research Professorship of the Mayo Foundation; and holds stock in Johnson & Johnson.

Dr. Vemuri receives research grants from the NIH/NIA.

Dr. Mielke receives research grants from the NIH/NIA, Alzheimer Drug Discovery Foundation, Lewy Body Dementia Association, and the Michael J Fox Foundation.

Dr. Machulda receives research support from the NIH/NIA & NIDCD.

Dr. Lowe serves on scientific advisory boards for Bayer Schering Pharma, Piramal Life Sciences and receives research support from GE Healthcare, Siemens Molecular Imaging, AVID Radiopharmaceuticals and the NIH (NIA, NCI)

Dr. Kantarci receives research grants from the NIH/NIA.

Dr. Boeve receives royalties from the publication of *Behavioral Neurology of Dementia* and receives research support from Cephalon, Inc., Allon Therapeutics, GE Healthcare, the NIH/NIA, and the Mangurian Foundation.

Ronald C. Petersen serves on data monitoring committees for Pfizer, Inc., Janssen Alzheimer Immunotherapy, and is a consultant for Biogen, Roche, Inc., Merck, Inc. and Genentech, Inc.; receives publishing royalties from *Mild Cognitive Impairment* (Oxford University Press, 2003), and receives research support from the National Institute of Health.

Abbreviations

A–N–	amyloid not elevated and neurodegeneration absent
A+N–	amyloid elevated and neurodegeneration absent
A+N+	amyloid elevated and neurodegeneration present
A–N+	amyloid not elevated and neurodegeneration present.
APOE	apolipoprotein E
AD	Alzheimer's disease
ADRC	Alzheimer's Disease Research Center
CN	Clinically Normal
FOV	field of view
FDG PET	¹⁸ fluorodeoxyglucose positron emission tomography
GM	grey matter
HVa	adjusted hippocampal volume
IQR	interquartile range
LP	lateral parietal
LT	lateral temporal
MCSA	Mayo Clinic Study of Aging
MPRAGE	magnetization-prepared radiofrequency pulses and rapid gradient echo
MP	medial parietal
MT	medial temporal
MR	magnetic resonance imaging
MCI	mild cognitive impairment
PiB PET	Pittsburgh compound B positron emission tomography
ROI	region of interest
SUVr	standardized uptake value ratio
TIV	total intracranial volume.

References

Albert M, DeKosky ST, Dickson D, Dubois B, Feldman H, Fox NC, Gamst A, Holtzman D, Jagust WJ, Petersen RC, Snyder PJ, Phelps CH. The diagnosis of mild cognitive impairment due to Alzheimer's disease: recommendations from the National Institute on Aging– Alzheimer's

- Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimer's & Dementia: Journal of the Alzheimer's Association*. 2011; 7:270–279.
- Araque Caballero MA, Brendel M, Delker A, Ren J, Rominger A, Bartenstein P, Dichgans M, Weiner MW, Ewers M. Mapping 3-year changes in gray matter and metabolism in Abeta-positive nondemented subjects. *Neurobiol Aging*. 2015; 36:2913–2924. [PubMed: 26476234]
- Ashburner J. Computational anatomy with the SPM software. *Magn Reson Imaging*. 2009; 27:1163–1174. [PubMed: 19249168]
- Braak H, Alafuzoff I, Arzberger T, Kretschmar H, Del Tredici K. Staging of Alzheimer disease-associated neurofibrillary pathology using paraffin sections and immunocytochemistry. *Acta Neuropathol*. 2006; 112:389–404. [PubMed: 16906426]
- Braak H, Braak E. Neuropathological staging of Alzheimer-related changes. *Acta Neuropathol (Berl)*. 1991; 82:239–259. [PubMed: 1759558]
- Brier MR, Gordon B, Friedrichsen K, McCarthy J, Stern A, Christensen J, Owen C, Aldea P, Su Y, Hassenstab J, Cairns NJ, Holtzman DM, Fagan AM, Morris JC, Benzinger TL, Ances BM. Tau and Abeta imaging, CSF measures, and cognition in Alzheimer's disease. *Sci Transl Med*. 2016; 8:338ra366.
- Caroli A, Prestia A, Galluzzi S, Ferrari C, van der Flier WM, Ossenkoppele R, Van Berckel B, Barkhof F, Teunissen C, Wall AE, Carter SF, Scholl M, Choo IH, Grimmer T, Redolfi A, Nordberg A, Scheltens P, Drzezga A, Frisoni GB. Mild cognitive impairment with suspected nonamyloid pathology (SNAP): Prediction of progression. *Neurology*. 2015; 84:508–515. [PubMed: 25568301]
- Delacourte A, David JP, Sergeant N, Buee L, Wattez A, Vermersch P, Ghzali F, Fallet-Bianco C, Pasquier F, Lebert F, Petit H, Di Menza C. The biochemical pathway of neurofibrillary degeneration in aging and Alzheimer's disease. *Neurology*. 1999; 52:1158–1165. [PubMed: 10214737]
- Dickerson BC, Stoub TR, Shah RC, Sperling RA, Killiany RJ, Albert MS, Hyman BT, Blacker D, Detorledo-Morrell L. Alzheimer-signature MRI biomarker predicts AD dementia in cognitively normal adults. *Neurology*. 2011; 76:1395–1402. [PubMed: 21490323]
- Dore V, Villemagne VL, Bourgeat P, Fripp J, Acosta O, Chetelat G, Zhou L, Martins R, Ellis KA, Masters CL, Ames D, Salvado O, Rowe CC. Cross-sectional and longitudinal analysis of the relationship between Abeta deposition, cortical thickness, and memory in cognitively unimpaired individuals and in Alzheimer disease. *JAMA Neurol*. 2013; 70:903–911. [PubMed: 23712469]
- Duyckaerts C, Benneicib M, Grignon Y, Uchiyama T, He Y, Piette F, Hauw JJ. Modeling the relation between neurofibrillary tangles and intellectual status. *Neurobiol Aging*. 1997; 18:267–273. [PubMed: 9263190]
- Ewers M, Insel P, Jagust WJ, Shaw L, Trojanowski JQ, Aisen P, Petersen RC, Schuff N, Weiner MW. CSF biomarker and PIB-PET-derived beta-amyloid signature predicts metabolic, gray matter, and cognitive changes in nondemented subjects. *Cereb Cortex*. 2012; 22:1993–2004. [PubMed: 22038908]
- Gelman, A.; Hill, J. *Data Analysis Using Regression and Multilevel/Hierarchical Models*. New York, NY: Cambridge University Press; 2007.
- Gomez-Isla T, Hollister R, West H, Mui S, Growdon JH, Petersen RC, Parisi JE, Hyman BT. Neuronal loss correlates with but exceeds neurofibrillary tangles in Alzheimer's disease. *Ann Neurol*. 1997; 41:17–24. [PubMed: 9005861]
- Jack CR Jr, Knopman DS, Weigand SD, Wiste HJ, Vemuri P, Lowe V, Kantarci K, Gunter JL, Senjem ML, Ivnik RJ, Roberts RO, Rocca WA, Boeve BF, Petersen RC. An operational approach to National Institute on Aging-Alzheimer's Association criteria for preclinical Alzheimer disease. *Ann Neurol*. 2012; 71:765–775. [PubMed: 22488240]
- Jack CR Jr, Lowe VJ, Senjem ML, Weigand SD, Kemp BJ, Shiung MM, Knopman DS, Boeve BF, Klunk WE, Mathis CA, Petersen RC. 11C PiB and structural MRI provide complementary information in imaging of Alzheimer's disease and amnesic mild cognitive impairment. *Brain*. 2008; 131:665–680. [PubMed: 18263627]
- Jack CR Jr, Lowe VJ, Weigand SD, Wiste HJ, Senjem ML, Knopman DS, Shiung MM, Gunter JL, Boeve BF, Kemp BJ, Weiner M, Petersen RC. Serial PIB and MRI in normal, mild cognitive impairment and Alzheimer's disease: implications for sequence of pathological events in Alzheimer's disease. *Brain*. 2009; 132:1355–1365. [PubMed: 19339253]

- Jack CR Jr, Wiste HJ, Knopman DS, Vemuri P, Mielke MM, Weigand SD, Senjem ML, Gunter JL, Lowe V, Gregg BE, Pankratz VS, Petersen RC. Rates of beta-amyloid accumulation are independent of hippocampal neurodegeneration. *Neurology*. 2014; 82:1605–1612. [PubMed: 24706010]
- Jack CR Jr, Wiste HJ, Lesnick TG, Weigand SD, Knopman DS, Vemuri P, Pankratz VS, Senjem ML, Gunter JL, Mielke MM, Lowe VJ, Boeve BF, Petersen RC. Brain beta-amyloid load approaches a plateau. *Neurology*. 2013; 80:890–896. [PubMed: 23446680]
- Jack CR Jr, Wiste HJ, Weigand SD, Knopman DS, Vemuri P, Mielke MM, Lowe V, Senjem ML, Gunter JL, Machulda MM, Gregg BE, Pankratz VS, Rocca WA, Petersen RC. Age, Sex, and APOE ϵ 4 Effects on Memory, Brain Structure, and beta-Amyloid Across the Adult Life Span. *JAMA Neurol*. 2015; 72:511–519. [PubMed: 25775353]
- Jack CR Jr, Wiste HJ, Weigand SD, Rocca WA, Knopman DS, Mielke MM, Lowe VJ, Senjem ML, Gunter JL, Preboske GM, Pankratz VS, Vemuri P, Petersen RC. Age-specific population frequencies of cerebral beta-amyloidosis and neurodegeneration among people with normal cognitive function aged 50–89 years: a cross-sectional study. *Lancet Neurol*. 2014; 13:997–1005. [PubMed: 25201514]
- Jack CR, Petersen RC, Xu YC, O'Brien PC, Smith GE, Ivnik RJ, Boeve BF, Waring SC, Tangalos EG, Kokmen E. Prediction of AD with MRI-based hippocampal volume in mild cognitive impairment. *Neurology*. 1999; 52:1397–1403. [PubMed: 10227624]
- Jack CRJ, Wiste HJ, Weigand SD, Knopman DS, Mielke MM, Vemuri P, Lowe V, Senjem ML, Gunter JL, Reyes D, Machulda MM, Roberts R, Petersen RC. Different definitions of neurodegeneration produce similar frequencies of amyloid and neurodegeneration biomarker groups by age among cognitively non-impaired individuals. *Brain*. 2015; 138:3747–3759. [PubMed: 26428666]
- Johnson KA, Schultz A, Betensky RA, Becker JA, Sepulcre J, Rentz D, Mormino E, Chhatwal J, Amariglio R, Papp K, Marshall G, Albers M, Mauro S, Pepin L, Alverio J, Judge K, Philiossaint M, Shoup T, Yokell D, Dickerson B, Gomez-Isla T, Hyman B, Vasdev N, Sperling R. Tau PET imaging in aging and early Alzheimer's disease. *Ann Neurol*. 2015
- Klunk WE, Engler H, Nordberg A, Wang Y, Blomqvist G, Holt DP, Bergstrom M, Savitcheva I, Huang GF, Estrada S, Ausen B, Debnath ML, Barletta J, Price JC, Sandell J, Lopresti BJ, Wall A, Koivisto P, Antoni G, Mathis CA, Langstrom B. Imaging brain amyloid in Alzheimer's disease with Pittsburgh Compound-B. *Ann Neurol*. 2004; 55:306–319. [PubMed: 14991808]
- Knol MJ, Pestman WR, Grobbee DE. The (mis)use of overlap of confidence intervals to assess effect modification. *Eur J Epidemiol*. 2011; 26:253–254. [PubMed: 21424218]
- Knopman DS, Jack CR Jr, Lundt ES, Wiste HJ, Weigand SD, Vemuri P, Lowe VJ, Kantarci K, Gunter JL, Senjem ML, Mielke MM, Machulda MM, Roberts RO, Boeve BF, Jones DT, Petersen RC. Role of beta-Amyloidosis and Neurodegeneration in Subsequent Imaging Changes in Mild Cognitive Impairment. *JAMA Neurol*. 2015; 72:1475–1483. [PubMed: 26437123]
- Knopman DS, Jack CR Jr, Wiste HJ, Weigand SD, Vemuri P, Lowe V, Kantarci K, Gunter JL, Senjem M, Ivnik RJ, Roberts RO, Boeve BF, Petersen RC. Short-term Clinical Outcomes for Stages of NIA-AA Preclinical Alzheimer disease. *Neurology*. 2012; 78:1576–1582. [PubMed: 22551733]
- Knopman DS, Jack CRJ, Wiste HJ, Weigand SD, Vemuri P, Lowe VJ, Kantarci K, Gunter JL, Senjem ML, Mielke MM, Roberts RO, Boeve BF, Petersen RC. Selective Worsening of Brain Injury Biomarker Abnormalities in Cognitively Normal Elderly with β -amyloidosis. *JAMA Neurol*. 2013; 70:1030–1038. [PubMed: 23797806]
- La Joie R, Perrotin A, Barre L, Hommet C, Mezenge F, Ibazizene M, Camus V, Abbas A, Landeau B, Guilloteau D, de La Sayette V, Eustache F, Desgranges B, Chetelat G. Region-Specific Hierarchy between Atrophy, Hypometabolism, and beta-Amyloid (Abeta) Load in Alzheimer's Disease Dementia. *J Neurosci*. 2012; 32:16265–16273. [PubMed: 23152610]
- Landau SM, Harvey D, Madison CM, Koeppe RA, Reiman EM, Foster NL, Weiner MW, Jagust WJ. Associations between cognitive, functional, and FDG-PET measures of decline in AD and MCI. *Neurobiol Aging*. 2011; 32:1207–1218. [PubMed: 19660834]
- Lemaitre H, Crivello F, Dufouil C, Grassiot B, Tzourio C, Alperovitch A, Mazoyer B. No epsilon4 gene dose effect on hippocampal atrophy in a large MRI database of healthy elderly subjects. *Neuroimage*. 2005; 24:1205–1213. [PubMed: 15670698]

- McKhann GM, Knopman DS, Chertkow H, Hyman BT, Jack CRJ, Kawas CH, Klunk WE. The diagnosis of dementia due to Alzheimer's disease: Recommendations from the National Institute on Aging and the Alzheimer's Association workgroup. *Alzheimer's & Dementia: Journal of the Alzheimer's Association*. 2011; 7:263–269.
- Mormino EC, Betensky RA, Hedden T, Schultz AP, Amariglio RE, Rentz DM, Johnson KA, Sperling RA. Synergistic effect of beta-amyloid and neurodegeneration on cognitive decline in clinically normal individuals. *JAMA Neurol*. 2014; 71:1379–1385. [PubMed: 25222039]
- Morris JC, Roe CM, Xiong C, Fagan AM, Goate AM, Holtzman DM, Mintun MA. APOE predicts amyloid-beta but not tau Alzheimer pathology in cognitively normal aging. *Ann Neurol*. 2010; 67:122131.
- Murray ME, Lowe VJ, Graff-Radford NR, Liesinger AM, Cannon A, Przybelski SA, Rawal B, Parisi JE, Petersen RC, Kantarci K, Ross OA, Duara R, Knopman DS, Jack CR Jr, Dickson DW. Clinicopathologic and 11C-Pittsburgh compound B implications of Thal amyloid phase across the Alzheimer's disease spectrum. *Brain*. 2015; 138:1370–1381. [PubMed: 25805643]
- Nosheny RL, Insel PS, Truran D, Schuff N, Jack CR Jr, Aisen PS, Shaw LM, Trojanowski JQ, Weiner MW. Variables associated with hippocampal atrophy rate in normal aging and mild cognitive impairment. *Neurobiol Aging*. 2015; 36:273–282. [PubMed: 25175807]
- Oh H, Madison C, Villeneuve S, Markley C, Jagust WJ. Association of gray matter atrophy with age, beta-amyloid, and cognition in aging. *Cereb Cortex*. 2014; 24:1609–1618. [PubMed: 23389995]
- Petersen RC. Mild cognitive impairment as a diagnostic entity. *J Intern Med*. 2004; 256:183–194. [PubMed: 15324362]
- Petersen RC, Aisen P, Boeve BF, Geda YE, Ivnik RJ, Knopman DS, Mielke MM, Pankratz VS, Roberts R, Rocca WA, Weigand S, Weiner M, Wiste HJ, Jack CR. Mild Cognitive Impairment Due to Alzheimer's Disease: Criteria in the Community. *Ann Neurol*. 2013; 74:199–208. [PubMed: 23686697]
- Petersen RC, Roberts RO, Knopman DS, Geda YE, Cha RC, Pankratz VS, Boeve BF, Tangalos EG, Ivnik RJ, Rocca WA. Prevalence of mild cognitive impairment is higher in men than in women. The Mayo Clinic Study of Aging. *Neurology*. 2010; 75:889–897. [PubMed: 20820000]
- Pooler AM, Polydoro M, Maury EA, Nicholls SB, Reddy SM, Wegmann S, William C, Saqran L, Cagsal-Getkin O, Pitstick R, Beier DR, Carlson GA, Spires-Jones TL, Hyman BT. Amyloid accelerates tau propagation and toxicity in a model of early Alzheimer's disease. *Acta Neuropathol Commun*. 2015; 3:14. [PubMed: 25853174]
- Prestia A, Caroli A, van der Flier WM, Ossenkoppele R, Van Berckel B, Barkhof F, Teunissen CE, Wall AE, Carter SF, Scholl M, Choo IH, Nordberg A, Scheltens P, Frisoni GB. Prediction of dementia in MCI patients based on core diagnostic markers for Alzheimer disease. *Neurology*. 2013; 80:1048–1056. [PubMed: 23390179]
- Roberts RO, Geda YE, Knopman D, Cha R, Pankratz VS, Boeve B, Ivnik R, Tangalos E, Petersen RC, Rocca WA. The Mayo Clinic Study of Aging: Design and Sampling, Participation, Baseline Measures and Sample Characteristics. *Neuroepidemiology*. 2008; 30:58–69. [PubMed: 18259084]
- Roberts RO, Geda YE, Knopman DS, Cha RH, Pankratz VS, Boeve BF, Tangalos EG, Ivnik RJ, Rocca WA, Petersen RC. The incidence of MCI differs by subtype and is higher in men: The Mayo Clinic Study of Aging. *Neurology*. 2012; 78:342–351. [PubMed: 22282647]
- Roberts RO, Knopman DS, Mielke MM, Cha RH, Pankratz VS, Christianson TJ, Geda YE, Boeve BF, Ivnik RJ, Tangalos EG, Rocca WA, Petersen RC. Higher risk of progression to dementia in mild cognitive impairment cases who revert to normal. *Neurology*. 2014; 82:317–325. [PubMed: 24353333]
- Roe CM, Fagan AM, Grant EA, Hassenstab J, Moulder KL, Maue Dreyfus D, Sutphen CL, Benzinger TL, Mintun MA, Holtzman DM, Morris JC. Amyloid imaging and CSF biomarkers in predicting cognitive impairment up to 7.5 years later. *Neurology*. 2013; 80:1784–1791. [PubMed: 23576620]
- Sabuncu MR, Desikan RS, Sepulcre J, Yeo BT, Liu H, Schmansky NJ, Reuter M, Weiner MW, Buckner RL, Sperling RA, Fischl B. The dynamics of cortical and hippocampal atrophy in Alzheimer disease. *Arch Neurol*. 2011; 68:1040–1048. [PubMed: 21825241]
- Savva GM, Wharton SB, Ince PG, Forster G, Matthews FE, Brayne C. Age, neuropathology, and dementia. *N Engl J Med*. 2009; 360:2302–2309. [PubMed: 19474427]

- Scholl M, Lockhart SN, Schonhaut DR, O'Neil JP, Janabi M, Ossenkoppele R, Baker SL, Vogel JW, Faria J, Schwimmer HD, Rabinovici GD, Jagust WJ. PET Imaging of Tau Deposition in the Aging Human Brain. *Neuron*. 2016; 89:971–982. [PubMed: 26938442]
- Schuff N, Woerner N, Boreta L, Kornfield T, Shaw LM, Trojanowski JQ, Thompson PM, Jack CR Jr, Weiner MW. MRI of hippocampal volume loss in early Alzheimer's disease in relation to ApoE genotype and biomarkers. *Brain*. 2009; 132:1067–1077. [PubMed: 19251758]
- Schwarz AJ, Yu P, Miller BB, Shcherbinin S, Dickson J, Navitsky M, Joshi AD, Devous MD Sr, Mintun MS. Regional profiles of the candidate tau PET ligand 18F-AV-1451 recapitulate key features of Braak histopathological stages. *Brain*. 2016
- Thal DR, Rub U, Schultz C, Sassin I, Ghebremedhin E, Del Tredici K, Braak E, Braak H. Sequence of Abeta-protein deposition in the human medial temporal lobe. *J Neuropathol Exp Neurol*. 2000; 59:733748.
- Toledo JB, Weiner MW, Wolk DA, Da X, Chen K, Arnold SE, Jagust W, Jack C, Reiman EM, Davatzikos C, Shaw LM, Trojanowski JQ. Neuronal injury biomarkers and prognosis in ADNI subjects with normal cognition. *Acta Neuropathol Commun*. 2014; 2:26. [PubMed: 24602322]
- Tzourio-Mazoyer N, Landeau B, Papathanassiou D, Crivello F, Etard O, Delcroix N, Mazoyer B, Joliot M. Automated anatomical labeling of activations in SPM using a macroscopic anatomical parcellation of the MNI MRI single-subject brain. *Neuroimage*. 2002; 15:273–289. [PubMed: 11771995]
- van Harten AC, Smits LL, Teunissen CE, Visser PJ, Koene T, Blankenstein MA, Scheltens P, van der Flier WM. Preclinical AD predicts decline in memory and executive functions in subjective complaints. *Neurology*. 2013; 81:1409–1416. [PubMed: 24049134]
- van Rossum IA, Vos SJ, Burns L, Knol DL, Scheltens P, Soininen H, Wahlund LO, Hampel H, Tsolaki M, Minthon L, L'Italien G, van der Flier WM, Teunissen CE, Blennow K, Barkhof F, Rueckert D, Wolz R, Verhey F, Visser PJ. Injury markers predict time to dementia in subjects with MCI and amyloid pathology. *Neurology*. 2012; 79:1809–1816. [PubMed: 23019259]
- Vemuri P, Senjem ML, Gunter JL, Lundt ES, Tosakulwong N, Weigand SD, Borowski BJ, Bernstein MA, Zuk SM, Lowe VJ, Knopman DS, Petersen RC, Fox NC, Thompson PM, Weiner MW, Jack CR Jr. Accelerated vs. unaccelerated serial MRI based TBM-SyN measurements for clinical trials in Alzheimer's disease. *Neuroimage*. 2015; 113:61–69. [PubMed: 25797830]
- Vemuri P, Wiste HJ, Weigand SD, Knopman DS, Shaw LM, Trojanowski JQ, Aisen PS, Weiner M, Petersen RC, Jack CR Jr. Effect of apolipoprotein E on biomarkers of amyloid load and neuronal pathology in Alzheimer disease. *Ann Neurol*. 2010; 67:308–316. [PubMed: 20373342]
- Villemagne VL, Burnham S, Bourgeat P, Brown B, Ellis KA, Salvado O, Szoëke C, Macaulay SL, Martins R, Maruff P, Ames D, Rowe CC, Masters CL. Amyloid beta deposition, neurodegeneration, and cognitive decline in sporadic Alzheimer's disease: a prospective cohort study. *Lancet Neurol*. 2013; 12:357–367. [PubMed: 23477989]
- Vos SJ, Verhey F, Frolich L, Kornhuber J, Wiltfang J, Maier W, Peters O, Ruther E, Nobili F, Morbelli S, Frisoni GB, Drzezga A, Didic M, van Berckel BN, Simmons A, Soininen H, Kloszewska I, Mecocci P, Tsolaki M, Vellas B, Lovestone S, Muscio C, Herukka SK, Salmon E, Bastin C, Wallin A, Nordlund A, de Mendonca A, Silva D, Santana I, Lemos R, Engelborghs S, Van der Mussele S, Freund-Levi Y, Wallin AK, Hampel H, van der Flier W, Scheltens P, Visser PJ. Prevalence and prognosis of Alzheimer's disease at the mild cognitive impairment stage. *Brain*. 2015; 138:1327–1338. [PubMed: 25693589]
- Vos SJ, Xiong C, Visser PJ, Jasielec MS, Hassenstab J, Grant EA, Cairns NJ, Morris JC, Holtzman DM, Fagan AM. Preclinical Alzheimer's disease and its outcome: a longitudinal cohort study. *Lancet Neurol*. 2013; 12:957–965. [PubMed: 24012374]
- Whitwell JL, Josephs KA, Murray ME, Kantarci K, Przybelski SA, Weigand SD, Vemuri P, Senjem ML, Parisi JE, Knopman DS, Boeve BF, Petersen RC, Dickson DW, Jack CR Jr. MRI correlates of neurofibrillary tangle pathology at autopsy: a voxel-based morphometry study. *Neurology*. 2008; 71:743–749. [PubMed: 18765650]
- Wirth M, Oh H, Mormino EC, Markley C, Landau SM, Jagust WJ. The effect of amyloid beta on cognitive decline is modulated by neural integrity in cognitively normal elderly. *Alzheimers Dement*. 2013; 9:687–698. e681. [PubMed: 23474040]

Highlights

- MCI A+N+ group had more metabolic and structural deterioration than CN A+N+.
- AD-DEM had more metabolic and structural deterioration than MCI A+N+.
- Specificity of amyloid related neurodegeneration for temporo-parietal isocortex
- *Increasing rate* of neurodegenerative change from CN A+N+ to MCI A+N+ to AD DEM.

Figure 1. Baseline FDG SUVR and GM Volume

Group mean (SE) estimates at baseline for FDG SUVR (A) and GM volume (B) estimates with 95% confidence interval (CI) estimates (thin gray lines) and 83.5% CI estimates (thicker black lines) by biomarker group **for primary ROIs**: medial temporal, medial parietal, lateral temporal, and lateral parietal. The 83.5% CI allows for visual comparisons between groups where any amount of overlap indicates a lack of significance at the 0.05 level. Estimates are from a linear mixed model for a male participant age 80 years.

Figure 2. Annual Percent change in FDG SUVR and GM Volume

Group mean (SE) estimated annual percentage change for FDG SUVR (A) and GM volume (B) with 95% confidence interval (CI) (thin gray lines) and 83.5% CI (thicker black lines) by biomarker group for **primary ROIs**: medial temporal, medial parietal, lateral temporal and lateral parietal. The 83.5% CI allows for visual comparisons between groups where any amount of overlap indicates a lack of significance at the 0.05 level. Estimates are from a linear mixed model for a male participant age 80 years.

Figure 3. Trajectory over time, by group

Regression plots for the 4 **primary ROIs** showing trajectories of FDG SUVR (top panels) and grey matter (GM) (bottom panels) over time for biomarker defined groups for a hypothetical male 80 years of age. The x-axis is time from baseline. The time scale was limited to 2 years for illustrative purposes. See Figures 1 and 2 for confidence intervals of baseline values and slopes. Color coding: CN (orange), MCI (blue), AD Dementia (green); A+N+ (solid lines); A+N- (dashed lines).

Figure 4. Global PIB SUVR at Baseline and Annual Percent Change

Group mean (SE) estimates for global PIB PET estimates at baseline (left panel) and estimated annual percentage change (right panel) with 95% confidence interval (CI) estimates (thin gray lines) and 83.5% CI estimates (thicker black lines) by biomarker and clinical diagnostic group. The 83.5% CI allows for visual comparisons between groups where any amount of overlap indicates a lack of significance at the 0.05 level. Estimates are from a linear mixed model for a male participant age 80 years.

Table 1

Participant characteristics

Statistics shown are of the form mean (SD) unless otherwise specified.

	CN A+/N- (n = 79)	MCI A+/N- (n = 17)	CN A+/N+ (n = 65)	MCI A+/N+ (n = 45)	AD DEM A+ (n = 20)
Male, no. (%) ^a	39 (49%)	11 (65%)	51 (78%)	29 (64%)	14 (70%)
Age, yrs ^a	80 (5)	79 (5)	80 (5)	81 (5)	78 (6)
Age, Min, Max	72 to 94	71 to 90	70 to 93	72 to 90	71 to 92
Education, yrs ^b	14 (3)	14 (4)	15 (3)	14 (3)	16 (2)
APOE e4 genotype N, (%) ^c	30 (38%)	10 (59%)	27 (42%)	23 (51%)	14 (70%)
PIB SUVR	1.74 (0.33)	1.95 (0.33)	1.82 (0.37)	2.11 (0.48)	2.44 (0.42)
FDG SUVR AD sign regions	1.46 (0.10)	1.44 (0.10)	1.27 (0.10)	1.25 (0.14)	1.12 (0.23)
Adj. Hippocampal Volume (HVa)	-1.13 (0.54)	-1.75 (0.55)	-2.12 (0.84)	-2.81 (0.82)	-3.14 (0.90)
Total Intracranial Volume, Liters	1.5 (0.14)	1.5 (0.14)	1.6 (0.14)	1.5 (0.13)	1.5 (0.12)
MMSE ^d	28 (1.4)	26 (2.0)	28 (1.2)	25 (2.7)	21 (5.2)
Global Cognitive Z-score ^e	0.75 (0.81)	-0.29 (0.42)	0.35 (0.76)	-0.74 (0.84)	-1.20 (0.82)
No. of visits /imaging	2 (0.5)	2 (0.5)	2 (0.5)	2 (0.7)	3 (0.9)
Range	2 to 4	2 to 3	2 to 4	2 to 6	2 to 5
No. (%) having					
2 imaging visits	62 (78%)	10 (59%)	52 (80%)	33 (73%)	13 (65%)
3+ imaging visits	17 (22%)	7 (41%)	13 (20%)	12 (27%)	7 (35%)
Time in study ^f , yrs	2.6 (1.19)	2.2 (0.99)	2.6 (1.19)	2.1 (1.10)	1.9 (1.11)
Range	1 to 5	1 to 4	1 to 6	1 to 5	1 to 4

^a Z-scores 70+ CN & MCI, MCSA

^d Converted from STMS scores

^e No differences in sex or age across CN (A+N- and A+N+ combined), MCI (A+N- and A+N+ combined) and AD DEM groups.

^b Compared to AD DEM, CN and MCI groups had lower education (p=0.02), but there were no differences between CN and MCI groups.

^c AD DEM group had higher proportion of APOE e4 carriage than CN group (p=0.01) but not MCI group (p=0.07). There were no differences in APOE e4 carriage between CN and MCI.

^f Time in study refers to the period between the first and last imaging studies.

Table 2
Effect size and 95% confidence intervals for paired group differences in annual rate of change*

	FDG SUVR MCI A+N+ minus CN A+N+	GM Volume MCI A+N+ minus CN A+N+	FDG SUVR AD DEM minus MCI A+N+	GM Volume AD DEM minus MCI A+N+
Medial Temporal	-1.0 (-1.5, -0.5)	-0.8 (-1.1, -0.4)	-0.8 (-1.5, -0.01)	-0.6 (-1.2, -0.1)
Lateral Temporal	-1.3 (-2.0, -0.6)	-0.8 (-1.2, -0.4)	-1.3 (-2.3, -0.3)	-0.7 (-1.3, -0.03)
Medial Parietal	-1.6 (-2.5, -0.8)	<i>-0.4 (-0.9, 0.1)</i>	<i>-0.8 (-2.1, 0.5)</i>	<i>-0.4 (-1.2, 0.5)</i>
Lateral Parietal	-1.6 (-2.5, -0.7)	-1.0 (-1.7, -0.2)	-1.4 (-2.7, -0.1)	<i>-0.6 (-1.8, 0.5)</i>

* All **bolded** contrasts were significant at an uncorrected $p < 0.05$. Contrasts in yellow boxes were significant at $0.001 < p \leq 0.01$, and contrasts in orange boxes were significant at $p < 0.001$.

Table 3
Percent of 5000 bootstrap replicates with the ordering AD DEM < MCI A+N+ < CN A+N
+ at baseline and AD DEM > MCI A+N+ > CN A+N+ declines over time

	FDG SUVR	GM volume
Baseline		
Medial Temporal	98%	99%
Lateral Temporal	26%	96%
Medial Parietal	29%	70%
Lateral Parietal	20%	83%
Rate of change		
Medial Temporal	97%	99%
Lateral Temporal	99%	98%
Medial Parietal	89%	74%
Lateral Parietal	99%	85%