Title
Amyloid pathology in the progression to mild cognitive impairment

Authors
Insel, Philip S
Hansson, Oskar
Mackin, R Scott
et al.

Publication Date
2018-04-01

DOI
10.1016/j.neurobiolaging.2017.12.018

Peer reviewed

HHS Public Access

Author manuscript

Neurobiol Aging. Author manuscript; available in PMC 2019 April 01.

Published in final edited form as:

Neurobiol Aging. 2018 April ; 64: 76–84. doi:10.1016/j.neurobiolaging.2017.12.018.

Amyloid pathology in the progression to mild cognitive impairment

Philip S. Insel[a,b,c], **Oskar Hansson**[a,e], **R. Scott Mackin**[b,d], **Michael Weiner**[b,c], **Niklas Mattsson**[a,e,f], and **for the Alzheimer's Disease Neuroimaging Initiative**[g]

[a]Clinical Memory Research Unit, Faculty of Medicine, Lund University, Lund, Sweden

[b]Center for Imaging of Neurodegenerative Diseases, Department of Veterans Affairs Medical Center, San Francisco, CA, USA

[c]Department of Radiology and Biomedical Imaging, University of California, San Francisco, CA, USA

[d]Department of Psychiatry, University of California, San Francisco, CA, USA

[e]Memory Clinic, Skåne University Hospital, Sweden

[f]Department of Neurology, Skåne University Hospital, Sweden

Abstract

The objective of this study was to determine the cognitive and functional decline and development of brain injury in individuals progressing from preclinical (Aβ+ cognitively normal) to prodromal AD (Aβ+ MCI), and compare this with individuals who progress to MCI in the absence of significant amyloid pathology. Seventy-five cognitively-healthy participants who progressed to MCI were followed for 4 years on average and up to 10 years. We tested effects of Aβ on measures of cognition, functional status, depressive symptoms, and brain structure and metabolism. Preclinical AD subjects showed greater cognitive decline in multiple domains and increased CSF p-tau levels at baseline while Aβ-negative progressors showed increased rates of white matter hyperintensity accumuation and had a greater frequency of depressive symptoms at baseline. Aβ-status did not influence patterns of brain atrophy, but preclinical AD subjects showed greater decline of brain metabolism than Aβ-negative progressors. Several unique features separate the transition from preclinical to prodromal AD from other causes of cognitive decline.

[*]Corresponding author: Philip Insel, Center for Imaging of Neurodegenerative Diseases, Department of Veterans Affairs Medical Center, San Francisco, CA 94121, USA. Phone: +1 858 652 8480. philipinsel@gmail.com.

[g]Data used in preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (adni.loni.usc.edu). As such, the investigators within the ADNI contributed to the design and implementation of ADNI and/or provided data but did not participate in analysis or writing of this report. A complete listing of ADNI investigators can be found at: http://adni.loni.usc.edu/wp-content/uploads/how_to_apply/ADNI_Acknowledgement_List.pdf

Drs. Mattsson, Mackin, Hansson, and myself (Insel) have no conflicts of interest.

Ethical review boards at all involved study centers approved the study. All subjects gave written informed consent.
All authors have reviewed and approved this manuscript.

These features may facilitate early diagnosis and treatment of AD, especially in clinical trials aimed at halting the progression from preclinical to prodromal AD.

Keywords

amyloid; cognitively normal; mild cognitive impairment; cognition; MRI

1. Introduction

β-amyloid (Aβ) pathology is a defining pathological hallmark of Alzheimer's disease (AD) detectable by cerebrospinal fluid (CSF) or positron emission tomography (PET) (Mattsson et al., 2014). Cognitively-normal individuals with Aβ pathology (Aβ+) are said to have preclinical AD (Sperling et al., 2011) and have increased risk of cognitive decline (Petersen et al., 2015) and progression to mild cognitive impairment (MCI) compared to those without Aβ pathology (Knopman et al., 2012). However, cognitive decline with progression to MCI also occurs without significant amyloid pathology, for example in depression, cerebrovascular disease (Gorelick et al., 2011) and Lewy body disease (Mckeith, 2006). It is unclear if development of prodromal AD differs from other causes of cognitive decline in terms of specific cognitive or functional deficits, or in measures of brain structure and function. To understand the earliest stages of AD it is essential to study the transition from preclinical to prodromal AD and compare it to other causes of cognitive decline. Knowledge regarding this process may be used to improve the design of clinical trials aimed at preventing the earliest stages of AD.

The optimal cohort to study the transition from preclinical to prodromal AD is a cohort of cognitively-normal individuals, both with and without Aβ pathology, who develop MCI. It might be expected that early-stage AD subjects (subjects with Aβ pathology) would have lower scores on measures of memory function compared to subjects who develop MCI in the absence of Aβ pathology (Aβ− progressors). Aβ− progressors might instead be expected to have a greater incidence of cerebrovascular disease, increased prevalence of white matter lesions (Snyder et al., 2015), frontal lobe atrophy rather than atrophy in the temporoparietal regions associated with AD (Whitwell et al., 2007), and greater impairments in nonmemory cognitive domains (Kramer et al., 2007).

Few studies have been done on individuals progressing from normal cognition to MCI, comparing preclinical AD with Aβ− progressors. Here we present such a study, where we tested if the presence of Aβ affected neuropsychological measures, tau biomarkers, brain atrophy, white matter lesions, depressive symptoms and brain glucose metabolism in 75 cognitively healthy controls who progressed to MCI during up to 10 years of follow-up.

2. Methods

2.1 Participants

Data were obtained from the ADNI database (adni.loni.usc.edu, www.adni-info.org). The population in this study included ADNI-1 and ADNI-2 participants that (1) were enrolled into the cognitively-normal or subjective memory complaint cohorts, (2) progressed to an

MCI diagnosis per site physician and monitor review and captured in the ADNI database, (3) were tested for CSF biomarkers or amyloid PET, and (4) were followed longitudinally for MRI, FDG-PET and neuropsychological testing.

2.2 Amyloid PET

PET Aβ data was acquired by the ligand C11-PiB in ADNI-1 and the ligand F18-florbetapir in ADNI-2. Methods used to acquire and process PET data were described previously (see http://adni.loni.usc.edu/methods/ and (Landau et al., 2012)). We used previously established thresholds for PiB-PET (SUVR > 1.4) and florbetapir-PET (SUVR > 1.1) to identify the presence of Aβ pathology. Amyloid PET scans were available for 60 participants with an average of 2 scans done, 2 years apart (see Supplementary Methods for more details).

2.3 Cerebrospinal fluid biomarker concentrations

For the 15 individuals without Aβ PET scans, amyloid status was determined using CSF amyloid. CSF samples were collected by lumbar puncture and shipped on dry ice to the ADNI Biomarker Core laboratory at the University of Pennsylvania Medical Center for long-term storage at −80°C. CSF $A\beta_{42}$ was measured using the multiplex xMAP Luminex platform (Luminex Corp, Austin, TX) with the INNOBIA AlzBio3 kit (Fujirebio/ Innogenetics, Ghent, Belgium) (Olsson et al., 2005). We used a previously defined threshold of CSF $A\beta_{42}$ < 192 ng/L to identify the presence of Aβ pathology (Shaw et al., 2009). We also compared Aβ progression groups on baseline and longitudinal change of CSF phosphorylated tau (p-tau) and total tau (t-tau), also analyzed using the xMAP Luminex platform with the INNOBIA AlzBio3 kit.

2.4 Cognitive and Functional Outcomes

Cognitive measures assessed were the Mini-Mental State Examination (MMSE) (Folstein et al., 1975), Alzheimer's Disease Assessment Scale-cognitive subscale (Rosen et al., 1984) 13-item version (ADAS13), immediate and delayed logical memory recall from the Wechsler Memory Scale (iMemory, dMemory) (Wechsler, 1987), immediate and delayed Rey Auditory Verbal Learning Test (iAVLT, dAVLT) (Rey, 1958), Trail Making Test parts A and B (Trails A and B) (Reitan, 1958), Boston Naming Test (Williams et al., 1989), Category Fluency (Morris et al., 1989), and the Preclinical Alzheimer's Cognitive Composite, comprising the MMSE, delayed Logical Memory, Trails B, and delayed recall portion of the ADAS13 (Donohue et al., 2017). The functional status measures assessed were the Clinical Dementia Rating Sum of Boxes (CDR-SB) (Morris, 1993) and the Functional Assessment Questionnaire (FAQ) (Pfeffer et al., 1982). Aβ+ progressors and Aβ − progressors were compared on symptoms of depression with the Geriatric Depression Scale (GDS) (Yesavage et al., 1983). Finally, individual items from the CDR-SB and FAQ were assessed.

2.5 MRI

Structural magnetic resonance imaging brain scans were acquired using 1.5T MRI for ADNI-1 subjects and 3.0T MRI for ADNI-2 subjects. We used a standardized protocol including T1-weighted MRI scans using a sagittal volumetric magnetization prepared rapid

gradient echo (MP-RAGE) sequence (Jack et al., 2008). Automated volume measures were performed with FreeSurfer (FS). Our primary analysis included data on lateral ventricle volume and combined volumetric measures from different FS ROIs. These combined regions are described in Supplementary Table 1. In an exploratory analysis, we estimated group differences on all FS regions, separately. P-values from the analysis of FS regions were adjusted using a false discovery rate correction. We also analyzed white matter hyperintensity volumes estimated based on run-time PD (proton density)-, T1-, and T2-weighted structural magnetic resonance images of the brain (Schwarz C, Fletcher E, DeCarli C, 2009).

2.6 Brain metabolism

FDG-PET image data were acquired and processed as described previously (Landau et al., 2012). We used mean FDG-PET counts of the temporal region, angular region and cingulate regions.

2.7 Statistical analysis

Subjects were classified as Aβ+ if they were positive for any amyloid measurement taken during follow-up. Two subjects became Aβ+ during follow-up, while all other Aβ+ subjects were positive at the initial Aβ measurement. Baseline associations between demographics, medical history, neuropsychiatric inventory (NPIQ) (Kaufer et al., 2000) and Aβ status were assessed. Continuous variables were evaluated using the Wilcoxon rank-sum test and categorical variables with Fisher's Exact test.

Subjects were followed for up to 10 years for neuropsychological testing and up to four years for imaging measures (MRI and FDG-PET). Longitudinal measures were modeled using linear mixed-effects regression with a spline function to capture departures from linearity in the trajectory of the outcomes (Hastie and Tibshirani, 1990). Because ADNI-1 used 1.5T MRI scanners and ADNI-2 used 3T scanners, we evaluated MRI differences both within each study separately and also together, while adjusting for scanner type. MRI models were adjusted for intracranial volume, scanner type, age and gender. We also evaluated clustering subjects within scanner type as part of the mixed-models. Responses were converted to z-scores for comparability. Likelihood ratio tests were used to evaluate longitudinal trajectory differences. All models were adjusted for demographics (age, gender and education), depression symptoms, APOE ε4 allele status and intracranial volume for MRI models.

Individual items from the CDR-SB and FAQ were also assessed. For additional details on the FAQ items, see Supplementary Table 3. Survival regression was used to model the effect of Aβ on the time to the initial endorsement of CDR-SB and FAQ items, separately. Time to progression to MCI was modeled with survival regression, assuming a Weibull distribution. Significance of tests was reported using two sided p-values. All analyses were preformed in R v3.3 (www.r-project.org). See the Supplementary Methods for full statistical analysis details.

2.8 Ethics

Ethical review boards at all involved study centers approved the study. All subjects gave written informed consent.

3. Results

3.1 Study population

We included 75 subjects who progressed to MCI during a median follow-up of 4 years (IQR: 2.0, 5.8) in the Aβ+ group and 3 years (IQR: 1.7, 5.3) in the Aβ− group, (p=0.49). Detailed information on follow-up sample sizes is included in Supplemental Table 2. Forty subjects (53.3%) were Aβ+ and 35 (46.7%) were Aβ−. There was no relationship between the modality used to measure Aβ (CSF or PET) and Aβ-positivity. For those whose CSF was used to determine Aβ status, 53% were Aβ+; similarly for PET, 53% were Aβ+ (p>0.99). Aβ+ progressors were older on average compared with Aβ− progressors (78 vs 75 years old, p=0.015) and had a higher frequency of APOE ε4 alleles (47.5% vs 20%, p=0.02). There were no significant group differences in education (p=0.44), gender (p=0.35), or proportion of subjects with subjective memory complaints (p=0.46). There were no group differences on history of psychiatric (p=0.28), neurological (p=0.41), cardiovascular (p=0.46), hypertensive (p>0.99), hepatic (p>0.99) or endocrine/metabolic (p=0.82) symptoms. There were no group differences on the NPIQ total (p=0.16) or individual items (p>0.17), with the exception of the depression/dysphoria item (p=0.007), where 18% of the Aβ− progressors endorsed symptoms of depression/dyphoria compared to 0% of the Aβ+ progressors, at baseline. Aβ+ progressors also had a lower frequency of depressive symptoms at baseline compared to Aβ− progressors on the GDS (p=0.03), but longitudinal development of depressive symptoms did not differ by Aβ status (χ^2=0.32, p=0.85).

3.2 Progression to MCI

Time to MCI did not differ between the groups (β = 0.07, p = 0.73, Supplementary Figure 1). The median time to progression was approximately 2.5 years for both groups. Thirty (85.7%) Aβ− and 36 (90%) Aβ+ subjects were clinically diagnosed with MCI due to AD. The remaining Aβ− progressors were diagnosed with MCI due to corticobasal degeneration (N=2), normal pressure hydrocephalus (N=1), vascular disease (N=1), and unknown (N=1). The remaining Aβ+ progressors were diagnosed with MCI due to Parkinson's disease (N=1), vascular disease (N=2) and a pituitary macro adenoma (N=1).

3.3 Cognition

Cognitive measures are shown in Figure 1. There were no group differences at baseline. There were no longitudinal differences in MMSE, ADAS13, dAVLT, iAVLT, or category fluency. Aβ+ progressors showed significantly worse decline on the PACC, dMemory, iMemory, BNT, Trails A and Trails B. Estimates are summarized in Table 1.

3.4 CDR-SB and FAQ

Functional measures are shown in Figure 2. There were no significant group differences at baseline or over time in CDR-SB. Aβ+ progressors tended toward faster decline in FAQ (p=0.09). Estimates are summarized in Table 1.

We also assessed the individual items from the CDR-SB and FAQ (Figure 3). CDR-SB items were modeled assuming a Weibull distribution, while FAQ items were best modeled assuming a Gaussian distribution. FAQ items were more frequently endorsed (answered yes to the item) at baseline, and as such were left-censored at baseline, resulting in a better fit when assuming a Gaussian distribution. CDR-SB items were almost never endorsed at baseline. There were no significant differences between Aβ− and Aβ+ progressors on any CDR-SB item. Estimates, confidence intervals and p-values are summarized in Table 2.

There were no significant differences between Aβ− and Aβ+ progressors on any FAQ item, although Aβ+ progressors tended toward shorter time to endorsement on the Event (keeping track of current events) item.

3.5 Brain structure

MRI measures of brain structure are shown in Figure 4. There were no group differences at baseline or over time in any MRI ROI, p>0.13). There were no differences in the results when the 1.5T and 3T scans were analyzed separately or when the scanner type adjustment was removed from the model. There was faster accumulation of white matter hyperintensities in Aβ− progressors, (β=0.14, p=0.05).

3.6 Brain glucose metabolism

FDG-PET measures of brain glucose metabolism are shown in Figure 4. Aβ+ progressors showed faster decline in metabolism in the temporal lobe (β=−0.11, p=0.02) and the cingulate gyrus (β=−0.15, p=0.003), and tended toward faster decline in the angular gyrus (β=−0.09, p=0.07). There were no differences in FDG-PET in any region at baseline (p>0.23).

3.7 CSF p-tau and t-tau

CSF tau information was available for 30 Aβ+ and 28 Aβ− subjects. Of these, 23 Aβ+ and 17 Aβ− subjects had longitudinal CSF data available. Aβ+ progressors had significantly higher CSF p-tau concentrations at baseline (β=0.55, p=0.05). There were no significant group differences in change over time in CSF p-tau (χ^2=2.10, p=0.35). There were no significant differences in baseline CSF t-tau (β=0.23, p=0.47) or change over time (χ^2=2.14, p=0.34).

4. Discussion

We examined the role of Aβ pathology in the progression from normal cognition to MCI, with regard to function, cognition, CSF tau, symptoms of depression, brain structure and metabolism. The main findings include 1) Aβ− and Aβ+ progressors had similar time to MCI, despite Aβ+ progressors declining significantly faster on tests of memory, executive

function, processing speed and language. 2) Aβ− and Aβ+ progressors showed similar rates of decline on the CDR-SB, although there was some evidence for accelerated functional decline on the FAQ. 3) Aβ− and Aβ+ progressors had similar rates of brain atrophy, although Aβ− progressors demonstrated a significantly faster rate of white matter lesion accumulation over time, and Aβ+ progressors showed greater decline in temporal and cingulate brain metabolism. 4) Aβ+ progressors had elevated levels of CSF p-tau at baseline. 5) Aβ− progressors endorsed more baseline depressive symptoms. 6) Aβ− and Aβ+ progressors were classified as MCI due to AD to the same degree by the diagnosing physicians. Our findings show that progression from preclinical to prodromal AD differs substantially from other causes of early cognitive decline both in terms of specific cognitive domains and also imaging and biomarker characteristics. Still, several commonly used tools to monitor progression to MCI do not readily identify Aβ− associated decline and careful selection of neuropsychological and biomarker assessments should be used to facilitate identification and follow-up of preclinical AD in screening programs and clinical trials.

Several studies have shown that increased age, shorter education, presence of APOE ε4, subtle cognitive decline, and cognitive complaints are risk factors for progression to MCI (Oulhaj et al., 2009). Further, AD-like combinations of CSF biomarkers (Li et al., 2007) or increased brain atrophy rates may also predict progression to MCI, although baseline CSF biomarkers or brain structure may not always predict progression to MCI (Vemuri et al., 2009).

Aβ+ progressors declined faster than Aβ− progressors on the PACC, a cognitive composite designed to capture early decline associated with Aβ deposition. Aβ+ progressors also declined faster on individual domains including immediate and delayed memory recall, executive function (Trails B), processing speed (Trails A) and language (BNT), indicating that these domains are more specific to cognitive decline in preclinical AD, compared with the decline seen in the Aβ− progressors. The Aβ groups did not differ significantly on more general measures of cognition (MMSE and ADAS13), which is convergent with the findings from the functional scales, and highlights the difficulties in identifying early-stage clinical AD by general cognitive scoring instruments. In contrast, the immediate and delayed recall of the AVLT test (list learning) did not differ between the groups. These results have implications for the design of clinical trials aimed at people with early-stage AD. First, the fact that logical memory tests, but not AVLT, differentiated between Aβ+ and Aβ− progression is consistent with our previous finding that logical memory produced higher power estimates than AVLT when used as an outcome measure in a hypothetical trial of preclinical AD (Insel et al., 2015) and points to the importance of selecting specific instruments to achieve a high specificity for Aβ-associated cognitive decline during the progression to MCI. Further, the disconnect between the CDR memory item, which was not associated with Aβ, and the logical memory test, which was strongly associated with Aβ, suggests that specific functional tests should be used in clinical trials in order to optimize the chance of detecting functional changes that are related to the cognitive changes of early-stage AD. Assessments could consist of a composite of specific functional items, perhaps preferably from the FAQ scale or another sensitive functional measure like the Amsterdam ADL scale. More research is needed on the specific functional items that are associated with the early stages of AD.

The findings that Aβ− and Aβ+ progressors had similar time to MCI, and similar overall functional decline (measured by CDR-SB and FAQ, although the groups were marginally divergent on FAQ), indicate that the overall degree of functional impairment did not differ substantially between early-stage AD and other causes of decline from normal cognition. Further, the groups did not differ significantly on individual CDR items (including the memory item) or FAQ items.

The finding that progressors had a similar burden of brain atrophy, while preclinical AD subjects had greater decline in temporal and cingulate brain metabolism, fits with a disease model where changes in metabolism precede brain atrophy during the development of AD. This is in agreement with a recent study where we found (in MCI subjects) that changes in metabolism (and cognition) appeared at earlier stages of Aβ pathology compared to changes in brain structure (Insel et al., 2016). The fact that the pattern of brain atrophy did not differ between the groups also fits with a previous study where Aβ− cognitively-normal people had considerable overlap with the atrophy seen in preclinical AD (Fjell et al., 2013). The increased rates of white matter hyperintensity volume in Aβ− is consistent with their increased depressive symptoms (de Groot et al., 2000). The magnitude of this effect may have been mitigated by ADNI inclusion criteria limiting inclusion to subjects with a Hachinski score ≤4, which may have excluded Aβ− individuals with a high likelihood of developing white matter lesions.

The finding that CSF p-tau was increased already at baseline in Aβ+ progressors is in line with previous findings of increased CSF p-tau in preclinical AD (Mattsson et al., 2017) and suggests that these subjects were in a state of tau-related neuronal injury or vulnerability already at baseline. Furthermore, the Aβ+ progressors did not change over time in CSF p-tau levels, despite that they likely accumulated increasing amounts of brain tau pathology during this time, given the known correlation between tau pathology and clinical symptoms of AD (Nelson et al., 2017). The lack of longitudinal increases in CSF p-tau is in line with previous studies showing only very modest correlations between CSF p-tau and the total amount of brain tau load visualized by tau PET in AD (Gordon et al., 2016; Mattsson et al., 2017). Increased CSF p-tau may therefore primarily indicate a presence of tau related pathology, rather than being a measure of the total amount of tau in the brain. We also note that CSF t-tau was not increased in Aβ+ progressors. Together, this may suggest that CSF p-tau is a more sensitive marker than CSF t-tau for the effects of very early stage AD pathology on tau metabolism.

The finding that endorsement of depressive symptoms was more common in Aβ− progressors suggests that subsyndromal depression may precede and exacerbate cognitive decline in a subgroup of Aβ− progressors (Sacuiu et al., 2016).

Finally, the finding that progressors from both groups were classified as MCI due to AD to the same degree by experts blinded to the Aβ data stresses the difficulties in identifying early-stage AD by clinical characteristics alone, even in a selected group of amnestic MCI patients. This further supports the use of biomarkers to identify AD in early stages of the disease.

This study systematically examines the role of Aβ in the progression from normal cognition to MCI. The strengths of the study include a relatively large sample size, given the difficulty of observing normal to MCI progression prospectively, a long follow-up time, and inclusion of a broad array of neuropsychological tests and biomarker modalities that are potentially dynamic during the early stages of AD. However, the study also has some limitations. Despite rather large and clinically meaningful differences between the Aβ groups, such as ADAS13 and FAQ, which both show 0.75 SDs of additional decline in the Aβ+ group, these estimates remained nonsignificant. These comparisons were likely underpowered. Although ADNI subjects are extremely well characterized, they come from a selected sample, which may affect the generalizability of the findings. For most subjects, we used PET imaging to identify Aβ pathology, but a proportion of PET Aβ negative subjects may have positive CSF biomarkers of Aβ pathology (Mattsson et al., 2015). Those subjects may in fact have early stages of Aβ pathology (Palmqvist Natu Comm 2017), and including them in the Aβ− group may therefore reduce the difference between the Aβ− and Aβ+ groups. However, by using the standard thresholds for Aβ positivity we make our results more applicable to the general community of AD researchers and clinical trial designers. The fact that Aβ− progressors were younger than Aβ+ progressors may reflect the fact that incipient Aβ pathology is strongly associated with higher age (Jansen et al., 2015) and also suggests that causative factors in Aβ− progressors (which may include subsyndromal depression and unidentified genetic risk factors) are less age-dependent. All main analyses were adjusted for age, which makes it unlikely that the detected group differences were driven by age. Tau burden is of central interest and may explain some of the observed differences in cognitive trajectories. Tau pathology may be estimated by either CSF or PET biomarkers. CSF tau biomarkers may be elevated early in the disease process, but also plateau quite early, while tau PET measures may continue to increase in intensity throughout the clinical stages of the disease (Mattsson et al., 2017).Unfortunately, tau PET was not available for these individuals.

In conclusion, we found that progression from preclinical to prodromal AD is different from progression to MCI due to other causes of decline in terms of cognition, development of brain hypometabolism, and accumulation rates of white matter lesions, but not in terms of overall longitudinal function or other measures of brain structure. These results differ, in part, from previously described hypothetical models of the sequence of biomarker changes in AD (Jack et al., 2013) in that in this analysis, we see differences in glucose metabolism and cognitive functioning in the absence of structural brain differences between the two Aβ pathology groups. This has implications for both the etiology of progression and clinical trial design. People with preclinical AD are currently recruited into clinical trials of novel treatments where the goal is to achieve disease-modification and reduce decline in cognition and function. Our results may be used to tailor outcome measurements in such clinical trials, and may also be used in screening programs or online registries to facilitate identification of subjects who are in preclinical stages of AD.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Data collection and sharing for this project was funded by the Alzheimer's Disease Neuroimaging Initiative (ADNI). ADNI is funded by the National Institute on Aging, the National Institute of Biomedical Imaging and Bioengineering, and through generous contributions from the following: Alzheimer's Association; Alzheimer's Drug Discovery Foundation; BioClinica, Inc.; Biogen Idec Inc.; Bristol-Myers Squibb Company; Eisai Inc.; Elan Pharmaceuticals, Inc.; Eli Lilly and Company; F. Hoffmann-La Roche Ltd and its affiliated company Genentech, Inc.; GE Healthcare; Innogenetics, N.V.; IXICO Ltd.; Janssen Alzheimer Immunotherapy Research and Development, LLC.; Johnson and Johnson Pharmaceutical Research and Development LLC.; Medpace, Inc.; Merck and Co., Inc.; Meso Scale Diagnostics, LLC.; NeuroRx Research; Novartis Pharmaceuticals Corporation; Pfizer Inc.; Piramal Imaging; Servier; Synarc Inc.; and Takeda Pharmaceutical Company. The Canadian Institutes of Health Research is providing funds to support ADNI clinical sites in Canada. Private sector contributions are facilitated by the Foundation for the National Institutes of Health (www.fnih.org). This research was also supported by The Strategic Research Area MultiPark at Lund University. The grantee organization is the Northern California Institute for Research and Education, and the study is coordinated by the Alzheimer's Disease Cooperative Study at the University of California, San Diego. ADNI data are disseminated by the Laboratory for Neuro Imaging at the University of Southern California. This research was also supported by National Institutes of Health (NIH) grants P30 AG010129 and K01 AG030514, the Strategic Research Area MultiPark (Multidisciplinary Research in Parkinson's disease) at Lund University, The Swedish Alzheimer foundation, The Greta and Johan Kock Foundation for Medical Research, The Thelma Zoega foundation for medical research, The Swedish federal government under the ALF agreement, the Bundy Academy, and the Magnus Bergwall foundation.

Dr. Weiner has served on the Scientific Advisory Boards for Pfizer, BOLT International, Neurotrope Bioscience, Eli Lilly, U. of Penn's Neuroscience of Behavior Initiative, National Brain Research Centre(NBRC), India, LEARN Program at University of North Carolina, and ADNI. He has provided consulting to Synarc, Pfizer, Janssen, KLJ Associates, Easton Associates, Harvard University, University of California, Los Angeles (UCLA), Alzheimer's Drug Discovery Foundation (ADDF), Neurotrope Bioscience, Avid Radiopharmaceuticals, Clearview Healthcare Partners, Perceptive Informatics, Smartfish AS, Decision Resources, Inc., Araclon, Merck, Defined Health, and Genentech. The following entities have provided funding for travel; Pfizer, Paul Sabatier University, MCI Group France, Travel eDreams, Inc., Neuroscience School of Advanced Studies (NSAS), Danone Trading, BV, CTAD Ant Congres, Kenes, Intl., ADRC, UCLA, UCSD, Sanofi-Aventis Groupe, University Center Hospital, Toulouse, Araclon, AC Immune, Eli Lilly, New York Academy of Sciences (NYAS), National Brain Research Center, India for Johns Hopkins Medicine, Consortium for Multiple Sclerosis Centers (CMSC), Northwestern University, and University of Pennsylvania. He served on the Editorial Boards for Alzheimer's and Dementia and MRI. He received honoraria from Pfizer, Tohoku University, and Danone Trading, BV. He received research support from Merck, Avid, the Veterans Administration (VA) and Department of Defense (DOD).

The data contained in this manuscript have not been previously published, have not been submitted elsewhere and will not be submitted elsewhere while under consideration at Neurobiology of Aging.

References

de Groot JC, de Leeuw F-E, Oudkerk M, Hofman A, Jolles J, Breteler MMB. Cerebral White Matter Lesions and Depressive Symptoms in Elderly Adults. Arch. Gen. Psychiatry. 2000; 57:1071.doi: 10.1001/archpsyc.57.11.1071 [PubMed: 11074873]

Donohue MC, Sperling RA, Petersen R, Sun C-K, Weiner MW, Aisen PS. Association Between Elevated Brain Amyloid and Subsequent Cognitive Decline Among Cognitively Normal Persons. JAMA. 2017; 317:2305–2316. DOI: 10.1001/jama.2017.6669 [PubMed: 28609533]

Fjell AM, McEvoy L, Holland D, Dale AM, Walhovd KB. Brain Changes in Older Adults at Very Low Risk for Alzheimer's Disease. J. Neurosci. 2013; 33:8237–8242. DOI: 10.1523/JNEUROSCI.5506-12.2013 [PubMed: 23658162]

Folstein MF, Folstein SE, McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. J. Psychiatr. Res. 1975; 12:189–198. DOI: 10.1016/0022-3956(75)90026-6 [PubMed: 1202204]

Gordon BA, Friedrichsen K, Brier M, Blazey T, Su Y, Christensen J, Aldea P, Mcconathy J, Holtzman DM, Cairns NJ, Morris JC, Fagan AM, Ances BM, Benzinger TLS. The relationship between cerebrospinal fluid markers of Alzheimer pathology and positron emission tomography tau imaging. 2016; :1–12. DOI: 10.1093/brain/aww139

Gorelick PB, Scuteri A, Black SE, Decarli C, Greenberg SM, Iadecola C, Launer LJ, Laurent S, Lopez OL, Nyenhuis D, Petersen RC, Schneider JA, Tzourio C, Arnett DK, Bennett DA, Chui HC, Higashida RT, Lindquist R, Nilsson PM, Roman GC, Sellke FW, Seshadri S. Vascular contributions

to cognitive impairment and dementia: A statement for healthcare professionals from the American Heart Association/American Stroke Association. Stroke. 2011; 42:2672–2713. DOI: 10.1161/STR.0b013e3182299496 [PubMed: 21778438]

Hastie TJ, Tibshirani RJ. Generalized Additive Models. Monogr. Stat. Appl. Probab. 1990; doi: 10.1016/j.csda.2010.05.004

Insel PS, Mattsson N, Mackin RS, Kornak J, Nosheny R, Tosun-Turgut D, Donohue MC, Aisen PS, Weiner MW. Biomarkers and cognitive endpoints to optimize trials in Alzheimer's disease. Ann. Clin. Transl. Neurol. 2015; 2:534–47. DOI: 10.1002/acn3.192 [PubMed: 26000325]

Insel PS, Mattsson N, Mackin RS, Schöll M, Nosheny RL, Tosun D, Donohue MC, Aisen PS, Jagust WJ, Weiner MW. Accelerating rates of cognitive decline and imaging markers associated with β-amyloid pathology. Neurology. 2016; 86:1887–1896. DOI: 10.1212/WNL.0000000000002683 [PubMed: 27164667]

Jack CR, Bernstein MA, Fox NC, Thompson P, Alexander G, Harvey D, Borowski B, Britson PJ, Whitwell JL, Ward C, Dale AM, Felmlee JP, Gunter JL, Hill DLG, Killiany R, Schuff N, Fox-Bosetti S, Lin C, Studholme C, DeCarli CS, Krueger G, Ward HA, Metzger GJ, Scott KT, Mallozzi R, Blezek D, Levy J, Debbins JP, Fleisher AS, Albert M, Green R, Bartzokis G, Glover G, Mugler J, Weiner MW. The Alzheimer's Disease Neuroimaging Initiative (ADNI): MRI methods. J. Magn. Reson. Imaging. 2008; 27:685–691. DOI: 10.1002/jmri.21049 [PubMed: 18302232]

Jack CR, Knopman DS, Jagust WJ, Petersen RC, Weiner MW, Aisen PS, Shaw LM, Vemuri P, Wiste HJ, Weigand SD, Lesnick TG, Pankratz VS, Donohue MC, Trojanowski JQ. Tracking pathophysiological processes in Alzheimer's disease: An updated hypothetical model of dynamic biomarkers. Lancet Neurol. 2013; 12:207–216. DOI: 10.1016/S1474-4422(12)70291-0 [PubMed: 23332364]

Jansen WJ, Ossenkoppele R, Knol DL, Tijms BM, Scheltens P, Verhey FRJ, Visser PJ, Aalten P, Aarsland D, Alcolea D, Alexander M, Almdahl IS, Arnold SE, Baldeiras I, Barthel H, van Berckel BNM, Bibeau K, Blennow K, Brooks DJ, van Buchem MA, Camus V, Cavedo E, Chen K, Chetelat G, Cohen AD, Drzezga A, Engelborghs S, Fagan AM, Fladby T, Fleisher AS, van der Flier WM, Ford L, Förster S, Fortea J, Foskett N, Frederiksen KS, Freund-Levi Y, Frisoni GB, Froelich L, Gabryelewicz T, Gill KD, Gkatzima O, Gómez-Tortosa E, Gordon MF, Grimmer T, Hampel H, Hausner L, Hellwig S, Herukka S-K, Hildebrandt H, Ishihara L, Ivanoiu A, Jagust WJ, Johannsen P, Kandimalla R, Kapaki E, Klimkowicz-Mrowiec A, Klunk WE, Köhler S, Koglin N, Kornhuber J, Kramberger MG, Van Laere K, Landau SM, Lee DY, de Leon M, Lisetti V, Lleó A, Madsen K, Maier W, Marcusson J, Mattsson N, de Mendonça A, Meulenbroek O, Meyer PT, Mintun MA, Mok V, Molinuevo JL, Møllergård HM, Morris JC, Mroczko B, Van der Mussele S, Na DL, Newberg A, Nordberg A, Nordlund A, Novak GP, Paraskevas GP, Parnetti L, Perera G, Peters O, Popp J, Prabhakar S, Rabinovici GD, Ramakers IHGB, Rami L, Resende de Oliveira C, Rinne JO, Rodrigue KM, Rodríguez-Rodríguez E, Roe CM, Rot U, Rowe CC, Rüther E, Sabri O, Sanchez-Juan P, Santana I, Sarazin M, Schröder J, Schütte C, Seo SW, Soetewey F, Soininen H, Spiru L, Struyfs H, Teunissen CE, Tsolaki M, Vandenberghe R, Verbeek MM, Villemagne VL, Vos SJB, van Waalwijk van Doorn LJC, Waldemar G, Wallin A, Wallin ÅK, Wiltfang J, Wolk DA, Zboch M, Zetterberg H. Prevalence of Cerebral Amyloid Pathology in Persons Without Dementia: A Meta-analysis. Jama. 2015; 313:1924–1938. DOI: 10.1001/jama.2015.4668 [PubMed: 25988462]

Kaufer DI, Cummings JL, Ketchel P, Smith V, MacMillan A, Shelley T, Lopez OL, DeKosky ST. Validation of the NPI-Q, a brief clinical form of the Neuropsychiatric Inventory. J. Neuropsychiatry Clin. Neurosci. 2000; 12:233–239. DOI: 10.1176/appi.neuropsych.12.2.233 [PubMed: 11001602]

Knopman DS, Jack CR, Wiste HJ, Weigand SD, Vemuri P, Lowe V, Kantarci K, Gunter JL, Senjem ML, 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. DOI: 10.1212/WNL.0b013e3182563bbe [PubMed: 22551733]

Kramer JH, Mungas D, Reed BR, Wetzel ME, Burnett MM, Miller BL, Weiner MW, Chui HC. Longitudinal MRI and cognitive change in healthy elderly. Neuropsychology. 2007; 21:412–418. DOI: 10.1037/0894-4105.21.4.412 [PubMed: 17605574]

Landau SM, Mintun MA, Joshi AD, Koeppe RA, Petersen RC, Aisen PS, Weiner MW, Jagust WJ. Amyloid deposition, hypometabolism, and longitudinal cognitive decline. Ann. Neurol. 2012; 72:578–586. DOI: 10.1002/ana.23650 [PubMed: 23109153]

Li G, Sokal I, Quinn JF, Leverenz JB, Brodey M, Schellenberg GD, Kaye Ja, Raskind Ma, Zhang J, Peskind ER, Montine TJ. CSF tau/Amyloid-beta 42 ratio for increased risk of mild cognitive impairment: A follow-up study. Neurology. 2007; 69:631–639. DOI: 10.1212/01.wnl.0000267428.62582.aa [PubMed: 17698783]

Mattsson N, Insel PS, Donohue M, Landau S, Jagust WJ, Shaw LM, Trojanowski JQ, Zetterberg H, Blennow K, Weiner MW. Independent information from cerebrospinal fluid amyloid-β and florbetapir imaging in Alzheimer's disease. Brain A J. Neurol. 2015; 138:772–783. DOI: 10.1093/brain/awu367

Mattsson N, Insel PS, Landau SM, Jagust WJ, Donohue MC, Shaw LM, Trojanowski JQ, Zetterberg H, Blennow K, Weiner M. Diagnostic accuracy of CSF Ab42 and florbetapir PET for Alzheimer's disease. Ann. Clin. Transl. Neurol. 2014; 1:534–543. DOI: 10.1002/acn3.81 [PubMed: 25356425]

Mattsson N, Schöll M, Strandberg O, Smith R, Palmqvist S, Insel PS, Hägerström D, Ohlsson T, Zetterberg H, Jögi J. F-AV- 1451 and CSF T-tau and P-tau as biomarkers in Alzheimer ' s disease. 2017; 9:1212–1223. DOI: 10.15252/emmm.201707809

Mckeith IG. Diagnosis and management of dementia with Lewy bodies: third report of the DLB Consortium. Neurology. 2006; 66:1455. author reply 1455. doi: 10.1212/01.wnl.0000224698.67660.45

Morris JC. The Clinical Dementia Rating (CDR): current version and scoring rules. Neurology. 1993; 43:2412–2414. DOI: 10.1212/WNL.43.11.2412-a

Morris JC, Heyman a, Mohs RC, Hughes JP, van Belle G, Fillenbaum G, Mellits ED, Clark C. The Consortium to Establish a Registry for Alzheimer's Disease (CERAD). Part I. Clinical and neuropsychological assessment of Alzheimer's disease. Neurology. 1989; 39:1159–1165. DOI: 10.1212/WNL.41.4.479 [PubMed: 2771064]

Nelson PT, Braak H, Markesbery WR. Neuropathology and Cognitive Impairment in Alzheimer Disease : A Complex but Coherent Relationship. 2017; 68:1–14.

Olsson A, Vanderstichele H, Andreasen N, De Meyer G, Wallin A, Holmberg B, Rosengren L, Vanmechelen E, Blennow K. Simultaneous measurement of beta-amyloid(1–42), total tau, and phosphorylated tau (Thr181) in cerebrospinal fluid by the xMAP technology. Clin Chem. 2005; 51:336–45. [PubMed: 15563479]

Oulhaj A, Wilcock GK, Smith AD, de Jager CA. Predicting the time of conversion to MCI in the elderly. Neurology. 2009; 73:1436–1442. DOI: 10.1212/WNL.0b013e3181c0665f [PubMed: 19794124]

Petersen RC, Wiste HJ, Weigand SD, Rocca WA, Roberts RO, Mielke MM, Lowe VJ, Knopman DS, Pankratz VS, Machulda MM, Geda YE, Jack CR Jr. Association of Elevated Amyloid Levels With Cognition and Biomarkers in Cognitively Normal People From the Community. JAMA Neurol. 2015; 55905:1–8. DOI: 10.1001/jamaneurol.2015.3098

Pfeffer RI, Kurosaki TT, Harrah CH, Chance JM, Filos S. Measurement of functional activities in older adults in the community. J. Gerontol. 1982; 37:323–329. DOI: 10.1093/geronj/37.3.323 [PubMed: 7069156]

Reitan R. Validity of the Trail Making Test as an indicator of organic brain damage. Percept. Mot. Skills. 1958; 8:271–276. DOI: 10.2466/PMS.8.7.271-276

Rey, A. L'examen clinique en psychologie., Lexamen clinique en psychologie. 1958. doi:CRJ Alz lib Copy2 #618; CRJ Alz lib Copy2-Converted #618; CRJ Alz Library 2 shared lib-Converted #1017; MMM Master_Reference_List-Converted #21; JLW MCI-Converted #22; JLW PCA-Converted #58; JLW VBMprediction-Converted #87

Rosen WG, Mohs RC, Davis KL. A new rating scale for Alzheimer's disease. Am. J. Psychiatry. 1984 doi:6496779.

Sacuiu S, Insel PS, Mueller S, Tosun D, Mattsson N, Jack CR, DeCarli C, Petersen R, Aisen PS, Weiner MW, Scott MacKin R. Chronic depressive symptomatology in mild cognitive impairment is associated with frontal atrophy rate which hastens conversion to Alzheimer dementia. Am. J. Geriatr. Psychiatry. 2016; 24:126–135. DOI: 10.1016/j.jagp.2015.03.006 [PubMed: 26238228]

Schwarz C, Fletcher E, DeCarli CCO. Fully-automated white matter hyperintensity detection with anatomical prior knowledge and without flair. Inf. Process. Med. Imaging. 2009; 21:239–251. [PubMed: 19694267]

Shaw LM, Vanderstichele H, Knapik-Czajka M, Clark CM, Aisen PS, Petersen RC, Blennow K, Soares H, Simon A, Lewczuk P, Dean R, Siemers E, Potter W, Lee VMY, Trojanowski JQ. Cerebrospinal fluid biomarker signature in alzheimer's disease neuroimaging initiative subjects. Ann. Neurol. 2009; 65:403–413. DOI: 10.1002/ana.21610 [PubMed: 19296504]

Snyder HM, Corriveau RA, Craft S, Faber JE, Greenberg SM, Knopman D, Lamb BT, Montine TJ, Nedergaard M, Schaffer CB, Schneider JA, Wellington C, Wilcock DM, Zipfel GJ, Zlokovic B, Bain LJ, Bosetti F, Galis ZS, Koroshetz W, Carrillo MC. Vascular contributions to cognitive impairment and dementia including Alzheimer's disease. Alzheimer's Dement. 2015; 11:710–717. DOI: 10.1016/j.jalz.2014.10.008 [PubMed: 25510382]

Sperling RA, Aisen PS, Beckett LA, Bennett DA, Craft S, Fagan AM, Iwatsubo T, Jack CR, Kaye J, Montine TJ, Park DC, Reiman EM, Rowe CC, Siemers E, Stern Y, Yaffe K, Carrillo MC, Thies B, Morrison-Bogorad M, Wagster MV, Phelps CH. Toward defining the preclinical stages of Alzheimer's disease: Recommendations from the National Institute on Aging and the Alzheimer's Association workgroup. Alzheimer's Dement. 2011; 7:1–13. DOI: 10.1016/j.jalz.2011.03.005 [PubMed: 21255738]

Vemuri P, Wiste HJ, Weigand SD, Shaw LM, Trojanowski JQ, Weiner MW, Knopman DS, Petersen RC, Jack CR. MRI and CSF biomarkers in normal, MCI, and AD subjects: diagnostic discrimination and cognitive correlations. Neurology. 2009; 73:287–93. DOI: 10.1212/WNL.0b013e3181af79e5 [PubMed: 19636048]

Wechsler D. Manual for Wechsler Memory Scale - Revised, The Psychological Corporation. 1987 doi:PCA-Converted #56.

Whitwell JL, Weigand SD, Shiung MM, Boeve BF, Ferman TJ, Smith GE, Knopman DS, Petersen RC, Benarroch EE, Josephs KA, Jack CR. Focal atrophy in dementia with Lewy bodies on MRI: A distinct pattern from Alzheimer's disease. Brain. 2007; 130:708–719. DOI: 10.1093/brain/awl388 [PubMed: 17267521]

Williams BW, Mack W, Henderson VW. Boston naming test in Alzheimer's disease. Neuropsychologia. 1989; 27:1073–1079. DOI: 10.1016/0028-3932(89)90186-3 [PubMed: 2797414]

Yesavage JA, Brink TL, Rose TL, Lum O, Huang V, Adey M, Leirer VO. Development and validation of a geriatric depression screening scale: a preliminary report. J. Psychiatr. Res. 1983; 17:37–49. DOI: 10.1016/0022-3956(82)90033-4

- Longitudinal decline in Aβ+ MCI progressors was compared to decline in Aβ − MCI progressors
- Aβ+ progressors showed greater decline in brain metabolism, logical memory, executive funtion, processing speed and language.
- Aβ− progressors showed faster rates of white matter hyperintensity accumulation and more depressive symptoms at baseline
- Aβ− and Aβ+ progressors did not differ in time to MCI diagnosis

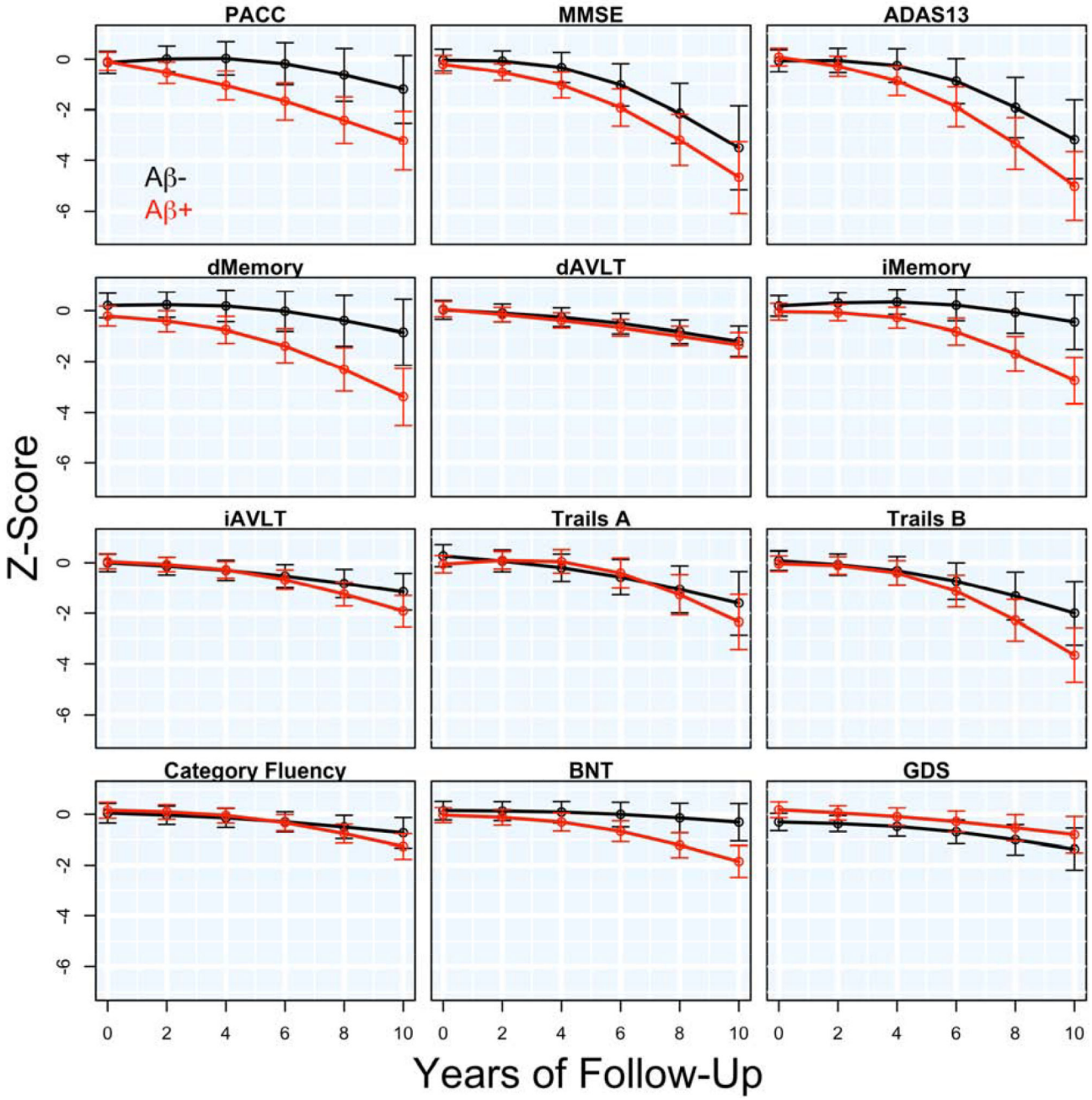

Figure 1. Cognition

Estimated trajectories and 95% confidence intervals of cognitive outcomes by Aβ group over 10 years of follow-up.

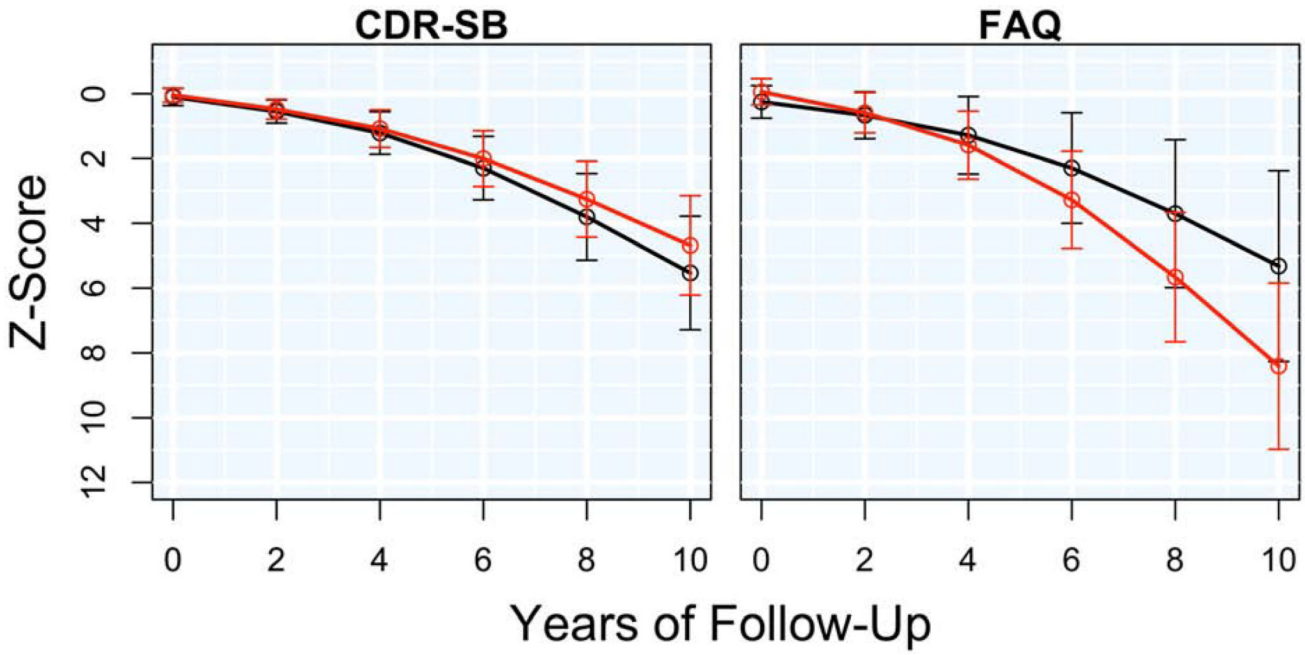

Figure 2. CDR-SB and FAQ

Estimated trajectories and 95% confidence intervals of functional outcomes by Aβ group over 10 years of follow-up. CDR-SB was not scaled to the baseline mean and SD due to nearly zero variance at baseline. Instead, CDR-SB was scaled to the mean and SD across all observations.

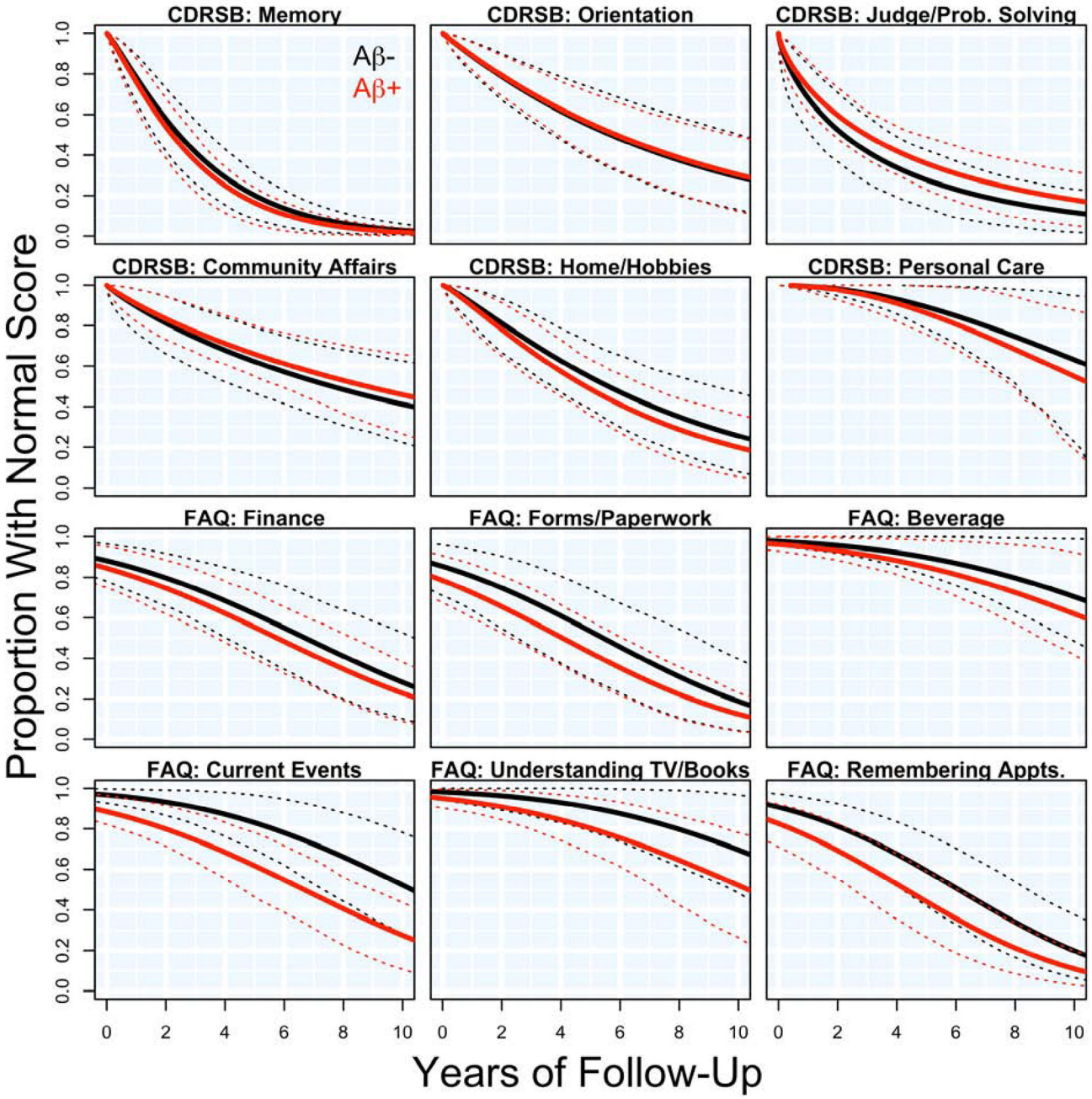

Figure 3. CDR-SB and FAQ Items

Survival curves of the time to initial FAQ or CDR-SB item endorsement over 10 years of follow-up.

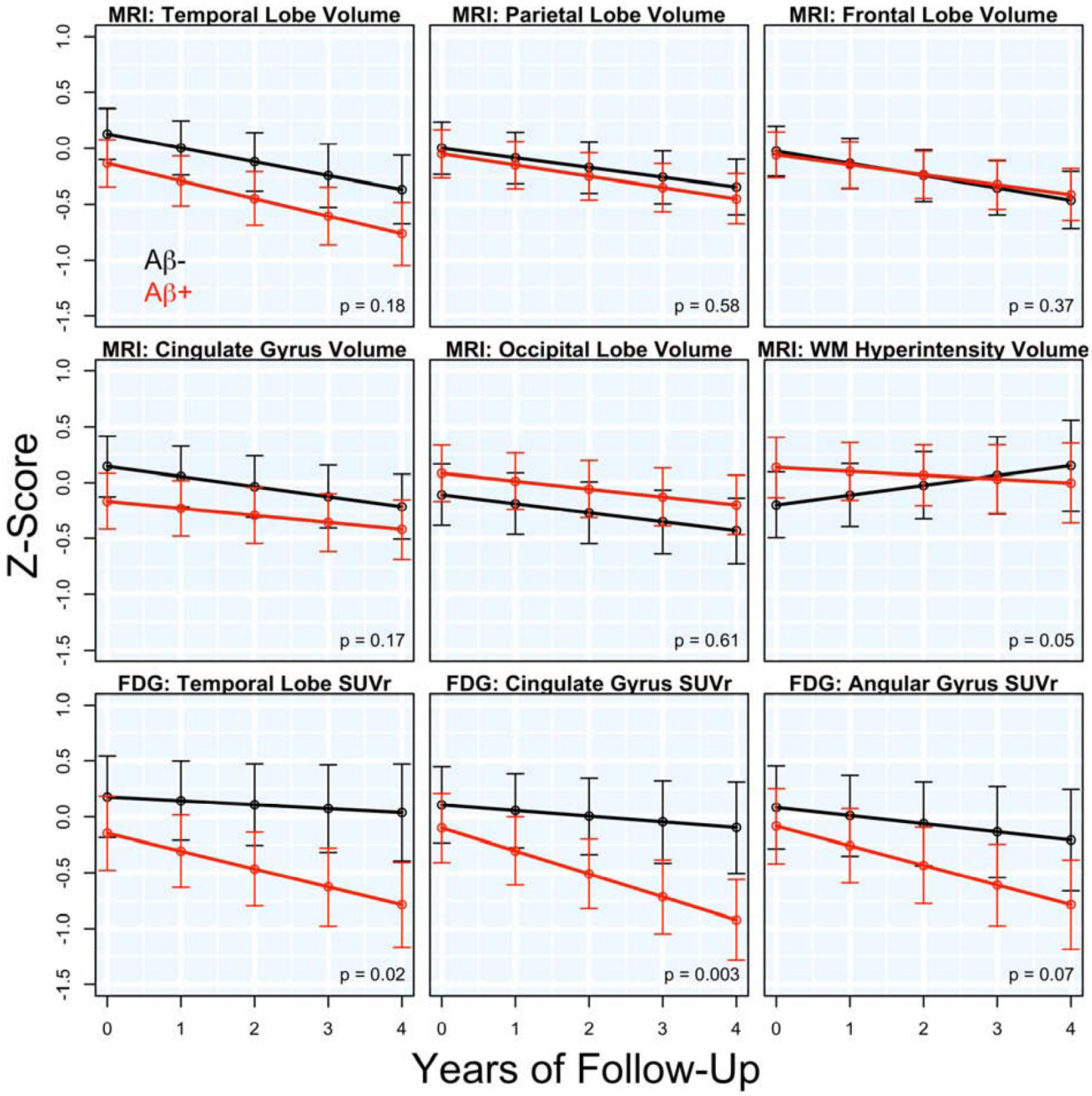

Figure 4. MRI, white matter hyperintensity volume, FDG-PET

Estimated trajectories and 95% confidence intervals of brain volume and glucose metabolism by Aβ group over 4 years of follow-up. P-values for longitudinal group differences are shown in the lower right.

Table 1

Cognition and Function: Baseline and Longitudinal differences

Outcome	**Aβ+ vs Aβ− Progressors**	
	Baseline	
	$Z_{Aβ+} - Z_{Aβ-}$ (SE)	**p**
PACC	0.03 (0.27)	0.90
MMSE	−0.17 (0.27)	0.52
ADAS13	−0.15 (0.27)	0.58
dMemory	−0.42 (0.30)	0.16
iMemory	−0.23 (0.25)	0.36
dAVLT	0.03 (0.23)	0.91
iAVLT	0.05 (0.21)	0.83
Trails A	0.33 (0.26)	0.21
Trails B	0.12 (0.23)	0.61
Boston Naming Test	−0.18 (0.23)	0.43
Category Fluency	0.11 (0.24)	0.64
CDR-SB	−0.40 (1.21)	0.74
FAQ	−0.31 (0.30)	0.31
	Longitudinal Change	
	χ^2	p
PACC	10.92	0.004
MMSE	1.34	0.51
ADAS13	4.32	0.12
dMemory	6.85	0.03
iMemory	9.33	0.01
dAVLT	1.02	0.60
iAVLT	4.46	0.11
Trails A	7.43	0.02
Trails B	7.15	0.03
Boston Naming Test	10.99	0.004
Category Fluency	3.46	0.18
CDR-SB	1.04	0.60
FAQ	4.71	0.09

The χ^2 statistic tests the magnitude of the longitudinal trajectory differences.

Table 2

CDR-SB and FAQ Items

	Aβ+ vs Aβ− Progressors		
CDR-SB			
	β	**95% CI**	**p**
Memory	0.91	(0.58, 1.37)	0.61
Orientation	1.03	(0.50, 2.07)	0.92
Judgement/Problem Solving	1.35	(0.70, 3.33)	0.37
Community Affairs	1.16	(0.48, 1.46)	0.70
Home/Hobbies	0.86	(0.55, 3.42)	0.54
Personal Care	0.88	(0.31, 1.67)	0.68
FAQ			
	β	95% CI	
Finance	−0.96	(−4.84, 2.83)	0.58
Forms/Paperwork	−1.38	(−4.90, 2.14)	0.41
Shopping	−1.35	(−5.21, 1.98)	0.43
Beverage	−1.58	(−8.67, 3.70)	0.58
Games	−1.48	(−4.82, 1.05)	0.29
Meal	−1.61	(−5.04, 1.21)	0.30
Current Events	−3.65	(−7.51, −0.20)	0.10
Understanding TV/Books	−2.88	(−9.17, 2.26)	0.30
Remembering Appts.	−1.77	(−5.05, 0.61)	0.19
Travel	−0.81	(−3.58, 1.80)	0.56

CDR-SB estimates result from survival models assuming a Weibull distribution. βs are the ratio of the time to endorsement in Aβ+ compared to Aβ−. For example, β = 0.96 indicates that the mean time to endorsement for Aβ+ progressors was 1 – 0.96 = 4% shorter compared to Aβ− progressors. β=1 indicates that the time to endorsement was the same in both groups. Confidence intervals excluding 1 would indicate a significant difference at p = 0.05. FAQ estimates result from models assuming a Gaussian distribution. Unlike the CDR-SB estimates, βs are the difference in time to endorsement between the two groups. For example, β = −0.35 indicates that the mean time to endorsement for Aβ+ progressors was 0.35 years shorter compared to Aβ− progressors. β = 0 indicates that the time to endorsement was the same in both groups. Confidence intervals excluding 0 would indicate a significant difference at p = 0.05.