ELSEVIER

Alzheimer's & Dementia 7 (2011) 514–520

Alzheimer's & Dementia

Impact of apolipoprotein ε4–cerebrospinal fluid beta-amyloid interaction on hippocampal volume loss over 1 year in mild cognitive impairment

Gloria C. Chiang[a,b,*], Philip S. Insel[b], Duygu Tosun[a,b], Norbert Schuff[a,b], Diana Truran-Sacrey[b], Sky T. Raptentsetsang[b], Paul M. Thompson[c], Eric M. Reiman[d], Clifford R. Jack, Jr.,[e], Nick C. Fox[f], William J. Jagust[g], Danielle J. Harvey[h], Laurel A. Beckett[h], Anthony Gamst[i], Paul S. Aisen[i], Ron C. Petersen[e], Michael W. Weiner[a,b,g], for the Alzheimer's Disease Neuroimaging Initiative

[a]Department of Radiology, University of California, San Francisco, CA, USA
[b]Department of Veterans Affairs Medical Center, Center for Imaging of Neurodegenerative Diseases, San Francisco, CA, USA
[c]Laboratory of Neuroimaging, University of California, Los Angeles, CA, USA
[d]Department of Psychiatry, University of Arizona, Phoenix, AZ, USA
[e]Department of Neurology, Mayo Clinic College of Medicine, Rochester, MN, USA
[f]Institute of Neurology, National Hospital for Neurology and Neurosurgery, London, England
[g]Department of Neurology, University of California, San Francisco, CA, USA
[h]Department of Public Health Sciences, University of California, Davis, CA, USA
[i]Department of Neurosciences, University of California, San Diego, CA, USA

Abstract

Background: The majority of studies relating amyloid pathology with brain volumes have been cross-sectional. Apolipoprotein ε4 (*APOE* ε4), a genetic risk factor for Alzheimer's disease, is also known to be associated with hippocampal volume loss. No studies have considered the effects of amyloid pathology and *APOE* ε4 together on longitudinal volume loss.

Methods: We evaluated whether an abnormal level of cerebrospinal fluid beta-amyloid (CSF Aβ) and *APOE* ε4 carrier status were independently associated with greater hippocampal volume loss over 1 year. We then assessed whether *APOE* ε4 status and CSF Aβ acted synergistically, testing the significance of an interaction term in the regression analysis. We included 297 participants: 77 cognitively normal, 144 with mild cognitive impairment (MCI), and 76 with Alzheimer's disease.

Results: An abnormal CSF Aβ level was found to be associated with greater hippocampal volume loss over 1 year in each group. *APOE* ε4 was associated with hippocampal volume loss only in the cognitively normal and MCI groups. *APOE* ε4 carriers with abnormal CSF Aβ in the MCI group acted synergistically to produce disproportionately greater volume loss than noncarriers.

Conclusion: Baseline CSF Aβ predicts progression of hippocampal volume loss. *APOE* ε4 carrier status amplifies the degree of neurodegeneration in MCI. Understanding the effect of interactions between genetic risk and amyloid pathology will be important in clinical trials and our understanding of the disease process.

Keywords: Apolipoprotein E4; Hippocampal atrophy; Beta-amyloid; Biomarker; MRI

Data used in the preparation of this article were obtained from the Alzheimer's disease Neuroimaging Initiative (ADNI) database (www.loni.ucla.edu\ADNI). 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. Complete listing of ADNI investigators is available at http://www.loni.ucla.edu/ADNI/Collaboration/ADNI_Authorship_list.pdf.

*Corresponding author. Tel.: +1-415-680-6904; Fax: +1-415-476-0616.

E-mail address: gloria.chiang@radiology.ucsf.edu

1552-5260/$ - see front matter © 2011 The Alzheimer's Association. All rights reserved.
doi:10.1016/j.jalz.2010.12.010

1. Introduction

Fibrillar beta-amyloid (Aβ) plaques, one of the hallmarks of Alzheimer's disease (AD), have been shown to be associated with hippocampal atrophy in multiple cross-sectional positron emission tomography (PET) studies using the amyloid ligand, Pittsburgh compound B (PiB) [1–5]. There are a few studies that have found similar correlations between cerebrospinal fluid (CSF) Aβ, an indirect measure of cerebral amyloid deposition [6,7], and hippocampal atrophy [8,9]. However, results from studies relating Aβ pathology with longitudinal volume loss have been mixed. One PiB-PET study found a strong association between brain Aβ and change in regional magnetic resonance imaging volumes in normal subjects, but only a trend in those with AD [3]. One study reported an association between CSF Aβ and the rate of hippocampal atrophy [10], although CSF p-tau was found to be a better predictor, and two other studies found no correlation between Aβ and the rate of whole brain atrophy [11,12].

The primary goal of our study was to determine whether baseline CSF Aβ level is associated with longitudinal hippocampal volume loss, incorporating data from the multicenter Alzheimer's Disease Neuroimaging Initiative (ADNI; www.loni.ucla.edu\ADNI). Because apolipoprotein ε4 (*APOE* ε4), a well-documented genetic risk factor for developing AD [13,14], is known to be associated with increased brain Aβ [15–18] and hippocampal atrophy [19–21], we further explored whether *APOE* ε4 modifies the relationship between abnormally low CSF Aβ and hippocampal volume loss.

2. Methods

2.1. Participants

The participants in this study were recruited through the ADNI between 2005 and 2008, a longitudinal study including 56 centers in the United States and Canada was conducted with the purpose of identifying biomarkers of early AD for clinical trials (www.adni-info.org). The ADNI was funded by the National Institute on Aging (NIA), the National Institute of Biomedical Imaging and Bioengineering (NIBIB), the Food and Drug Administration, private pharmaceutical companies, and nonprofit organizations, as a 5-year public–private partnership.

2.2. APOE *genotyping and clinical assessment*

All participants underwent *APOE* genotyping at the baseline visit. Approximately 6 mL of blood were collected from each participant in an ethylenediamine tetraacetic acid-containing tube, gently mixed by inversion, and shipped at an ambient temperature to a single designated laboratory within 24 hours of collection for analysis.

Participants ranged in age from 55 to 90 years, did not have major depression or severe systemic illnesses that would interfere with participation, and did not take investigational or psychometric medications. The normal control (NC) subjects had no memory complaint, had preserved activities of daily living, scored between 26 and 30 on a baseline Mini-Mental State Examination (MMSE) [22], scored a 0 on the Clinical Dementia Rating (CDR) scale [23], and scored within the normal range on the Logical Memory II subscale (delayed paragraph recall) from the Wechsler Memory Scale-Revised [24]. Subjects with mild cognitive impairment (MCI) had a memory complaint that was verified by a study partner, had preserved activities of daily living, and scored between 24 and 30 on the MMSE, 0.5 on the CDR, and below the normal range on the Logical Memory II subscale (delayed paragraph recall) from the Wechsler Memory Scale-Revised. Subjects with AD scored between 20 and 26 on the MMSE, between 0.5 and 1 on the CDR, and met National Institute of Neurological and Communicative Diseases and Stroke/Alzheimer's Disease and Related Disorders Association criteria for probable AD [25]. Written consent was obtained from all subjects participating in the study, and the study was approved by the institutional review board at each participating site.

2.3. CSF analysis

As described in the ADNI protocol (www.adni-info.org), all 56 participating centers were asked to perform lumbar punctures on a minimum of 20% of their participants. Approximately one-half of the participants recruited at each center underwent lumbar puncture for CSF analysis. CSF samples were banked and batch-processed at a single laboratory, as described previously [26]. Briefly, lumbar puncture was performed with a 20- or 24-gauge spinal needle at the baseline visit after an overnight fast. The CSF samples were then transferred to polypropylene transfer tubes, frozen on dry ice within an hour after collection, and shipped on dry ice overnight to a single designated laboratory. After thawing for 1 hour at room temperature and gentle mixing, 0.5 mL aliquots were prepared from these samples. The aliquots were then stored in bar code-labeled polypropylene vials at −80°C and measured using the xMAP Luminex platform (Luminex Corp, Austin, TX) with Innogenetics (INNOBIA AlzBio3, Ghent, Belgium) immunoassay kit-based reagents, which included the monoclonal antibody specific for $A\beta_{1\text{-}42}$ (4D7A3).

In our analysis, the baseline CSF Aβ level was dichotomized as either abnormal (i.e., reflective of underlying AD pathology) or normal (Fig. 1). It was previously published that using a threshold CSF Aβ value of 192 pg/mL yielded a sensitivity of 96% for detecting AD, on the basis of a sample of non-ADNI NC subjects and subjects with AD using the same CSF assay [27]. Furthermore, this cutoff value showed 91% agreement with evidence of brain amyloid using PiB in PET imaging [28].

2.4. MRI acquisition

Participants underwent the following standardized 1.5-T MRI protocol (http://www.loni.ucla.edu/ADNI/Research/

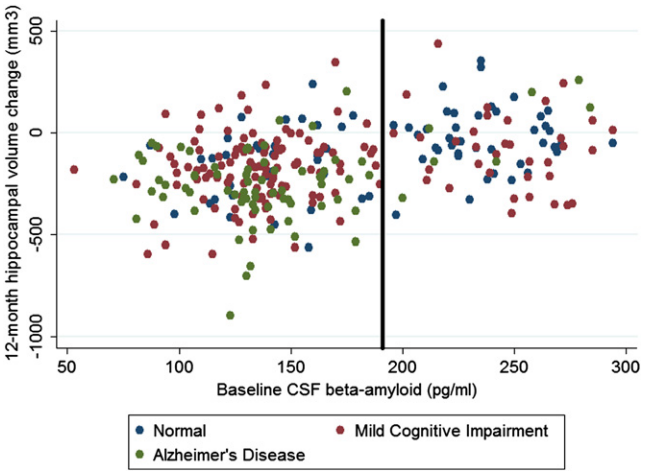

Fig. 1. Association between baseline cerebrospinal fluid beta-amyloid level and 1-year change in hippocampal volumes. The cerebrospinal fluid beta-amyloid level of <192 pg/mL (as delineated by the solid line) is considered abnormal in this study, which is reflective of underlying AD pathology. Conversely, a level of >192 pg/mL is considered normal.

Cores/index.shtml): two T_1-weighted MRI scans, using a sagittal volumetric magnetization-prepared rapid gradient echo sequence, with an echo time of 4 ms, repetition time of 9 ms, flip angle of 8°, and acquisition matrix size of 256 × 256 × 166 in the *x*-, *y*-, and *z*-dimensions with a nominal voxel size of 0.94 × 0.94 × 1.2 mm^3 [29].

2.5. MRI post-processing

The raw Digital Imaging and Communications in Medicine MRI data were downloaded from the Laboratory of Neuro Imaging Image Database Archive (http://www.loni.ucla.edu/ADNI/Data/index.shtml). The images were aligned, skull-stripped, and segmented using FreeSurfer software, version 4.3 (http://surfer.nmr.mgh.harvard.edu/) [30]. Bilateral hippocampal volumes, obtained from this segmentation, were averaged in the analyses. The change in hippocampal volumes over 1 year was calculated by subtracting the baseline hippocampal volume from the volume at follow-up and normalized by the time difference.

2.6. Statistical analyses

We excluded 33 subjects who carried a minimum of one *APOE* ε2 allele to avoid confounding the analysis because *APOE* ε2 is believed to be protective against development of AD and associated with slower rates of hippocampal atrophy [31,32]. Thus, our final cohort included 297 subjects who underwent a lumbar puncture and a minimum of two MRI scans, spaced 1 year apart—77 NC subjects, 144 with MCI, and 76 with probable AD (Table 1).

All statistical analyses were programmed in R, version 2.9.2 (www.r-project.org). Model assumptions were assessed with plots of residuals. *APOE* genotype was dichotomized into *APOE* ε4 carriers (ε3/ε4 or ε4/ε4) and noncarriers (*APOE* ε3/ε3). Age, baseline hippocampal volume, gender, and years of education were included as covariates in every model.

We first determined whether an abnormal baseline CSF Aβ level and *APOE* ε4 carrier status were independently associated with 1-year change in hippocampal volumes in all stages, after adjusting for covariates, using ordinary least squares regression. If both risk factors were significantly associated with volume loss, we then tested for interaction between *APOE* ε4 and CSF Aβ. For this, we centered CSF Aβ on its mean to reduce collinearity and included an interaction term between *APOE* ε4 and CSF Aβ, which was considered significant at the $\alpha = 0.05$ level.

3. Results

3.1. Group characteristics

The group characteristics are summarized in Table 1. Mean CSF Aβ was significantly lower in *APOE* ε4 carriers as compared with noncarriers at each clinical stage, consistent with previously published data [15–18]. The *APOE* ε4 MCI group was slightly younger and included more women. No significant differences in MMSE were seen between carriers and noncarriers within each clinical stage. Without adjusting for covariates, the change in raw hippocampal volumes over 1 year was found to be significantly different by *APOE* ε4 status in the NC and MCI groups, but not in AD.

3.2. Association between CSF Aβ and 1-year change in hippocampal volumes

Participants with an abnormally low CSF Aβ level had greater volume loss in all groups. In the NC group, participants with a low CSF Aβ level had a 138 mm^3 greater 1-year volume loss than those with a normal CSF Aβ level ($P < .001$). In the MCI group, participants with a low CSF Aβ level had a 71 mm^3 greater volume loss than those with a normal CSF Aβ level ($P = .03$). In the AD group, participants with a low CSF Aβ level had a 300 mm^3 greater 1-year volume loss than those with a normal CSF Aβ level ($P < .001$).

3.3. Association between APOE ε4 and 1-year change in hippocampal volumes

Participants who carried a minimum of one *APOE* ε4 allele had greater volume loss in the NC and MCI groups. In the NC group, *APOE* ε4 participants had a 121 mm^3 greater 1-year volume loss than those without an *APOE* ε4 allele ($P < .007$). In the MCI group, *APOE* ε4 participants had a 76 mm^3 greater volume loss than those without an *APOE* ε4 allele ($P = .01$). In the AD group, *APOE* ε4-positive and *APOE* ε4-negative participants demonstrated no difference in 1-year volume loss ($P = .66$).

Table 1
Patient characteristics by clinical stage and *APOE* ε4 status

Characteristics	NC			MCI			AD		
	APOE ε3/ε3	*APOE* ε3/ε4 or ε4/ε4*	*P* value	*APOE* ε3/ε3	*APOE* ε3/ε4 or ε4/ε4*	*P* value	*APOE* ε3/ε3	*APOE* ε3/ε4 or ε4/ε4*	*P* value
N	55	22		65	79		24	52	
Age (years)	76 (5.0)	76 (6.3)	.37	76 (8.5)	73 (6.5)	.03†	77 (9.1)	74 (7.1)	.19
Female (%)	55	36	.21	26	44	.04†	42	42	.91
Education (years)	16 (2.4)	16 (3.4)	.84	16 (2.9)	16 (2.9)	.82	15 (5.3)	14 (4.0)	.14
CSF Aβ (pg/mL)	209 (48.8)	147 (43.5)	<.001†	188 (59.8)	141 (38.8)	<.001†	169 (53.6)	130 (29.3)	.001†
Baseline hippocampal volume (mm^3)	6752 (731.5)	6691 (724.2)	.70	5904 (1072.9)	5599 (923.8)	.06	5433 (1466.4)	5073 (792.0)	.50
MMSE	29 (1.0)	29 (0.9)	.45	27 (1.8)	27 (1.8)	.49	23 (2.0)	24 (1.8)	.68
Unadjusted 1-year change in hippocampal volume (mm^3)	−57.8 (179.2)	−160.5 (150.9)	.01†	−103.5 (176.0)	−199.9 (166.2)	.003†	−231.0 (227.3)	−252.1 (174.1)	.80

Abbreviations: NC, normal control; MCI, mild cognitive impairment; AD, Alzheimer's disease; MMSE, Mini-Mental State Examination; *APOE*, apolipoprotein E; Aβ, beta-amyloid.

NOTE. Data shown are means (SD).

*Number of (*APOE* ε3/ε4, *APOE* ε4/ε4) carriers in each group: NC (20, 2), MCI (63, 16), AD (34, 18).

†Significant at the $\alpha = 0.05$ level.

3.4. *Testing for an* APOE *ε4–CSF Aβ interaction in NC and MCI*

Because both *APOE* ε4 and a low CSF Aβ level were associated with greater volume loss in the NC and MCI groups, we then tested for an *APOE* ε4–CSF Aβ interaction in these groups. No significant *APOE* ε4–CSF Aβ interaction was seen in the NC group ($\beta = 138$, $P = .19$). There was however a significant interaction between *APOE* ε4 and CSF Aβ in the MCI group ($\beta = -181$, $P = .02$). As compared with *APOE* ε4-noncarriers with normal CSF Aβ, *APOE* ε4-carriers with abnormal CSF Aβ had 88 mm^3 greater volume loss over 1 year ($P = .02$). Additionally, as compared with *APOE* ε4-noncarriers with abnormal CSF Aβ, *APOE* ε4-carriers with abnormal CSF Aβ had 97 mm^3 greater volume loss over 1 year ($P = .004$).

4. Discussion

The major findings of this study are: (1) an abnormally low baseline CSF Aβ level, suggestive of underlying AD pathology, predicted greater 1-year change in hippocampal volumes in all groups; (2) *APOE* ε4 carriers demonstrate greater hippocampal volume loss only in the NC and MCI groups; and (3) *APOE* ε4 and low CSF Aβ are synergistic risk factors, such that *APOE* ε4 carrier status amplifies the predicted 1-year volume loss beyond that predicted by a low CSF Aβ level alone.

The finding that an abnormally low CSF Aβ level predicted 1-year hippocampal volume loss is consistent with the predominantly cross-sectional literature, which describes an association between amyloid pathology and hippocampal atrophy [1–5,8–10]. Some have postulated that the large extracellular amyloid plaques disrupt cortico-hippocampal pathways, leading to neurodegeneration [2]. Another hypothesis is that insoluble plaques detected in CSF are an indirect marker of soluble Aβ oligomers, which may be the inciting agent in AD, by disrupting hippocampal synapses and promoting volume loss [33,34].

The second finding that *APOE* ε4 is associated with greater longitudinal hippocampal volume loss in the NC and MCI groups is also compatible with previously published data. Numerous studies suggest that *APOE* ε4 carriers demonstrate increased vulnerability to developing AD, which is manifested through neurodegeneration [35–38]. A reason for the lack of increase volume loss among *APOE* ε4 carriers in the AD group may be that, although *APOE* ε4 carriers develop AD at an earlier age [13], after the disease is clinically apparent in an individual, *APOE* ε4 no longer alters the course of the disease. The lack of a significant difference in hippocampal volumes among *APOE* ε4 carriers and noncarriers with AD has also been reported in previous studies [39,40].

Finally, the finding that the presence of a genetic risk factor, *APOE* ε4 amplifies the association between CSF Aβ and progressive hippocampal volume loss in MCI is novel. One possible explanation for this is that the *APOE* ε4 carriers with low CSF Aβ are more likely to have AD pathology. Although an abnormally low CSF Aβ level is highly sensitive for detecting brain amyloid associated with AD, it is not entirely specific for AD [27]. Some of the participants with low CSF Aβ levels may have frontotemporal dementia and would not demonstrate the same degree of hippocampus-specific volume loss as compared with patients with prodromal AD

[41]. However, this argument would also be true among NC subjects, in whom no interaction was demonstrated.

A second explanation for the *APOE* ε4–CSF Aβ interaction in MCI could be explained by a temporal progression of pathologic mechanisms resulting from the *APOE* ε4 genotype. Early on when subjects demonstrate normal cognition, the predominant effect of *APOE* ε4 seems to be to increase brain amyloid deposition, as reported by numerous previous studies [15–18]. Because both *APOE* ε4 carrier status and a low CSF Aβ level, as defined by our cutoff value, reflect greater brain amyloid, no interaction was seen in our NC group. However, after cognitive impairment is evident clinically, as in the MCI group, the effects of Aβ and *APOE* ε4 on pathogenesis of AD may diverge, thus resulting in disproportionately greater volume loss in those with both risk factors. Indeed, *APOE* ε4 has been found to be associated with an inability to repair synaptic damage; more rapid promotion of other neurotoxic species, such as tau; susceptibility to oxidative stress; and promotion of inflammatory cascades [17], beyond simply increasing levels of brain amyloid. Further work examining this interaction is warranted.

A third possible explanation is that both *APOE* ε4 and a low CSF Aβ level are markers of disease progression. According to previously published data, only 10% to 15% of individuals with MCI will progress to AD each year [42]. The other 85% to 95% of individuals with stable MCI may be more likely have higher levels of CSF Aβ and be *APOE* ε4-negative, thus resulting in slower hippocampal volume loss.

Several study limitations deserve to be mentioned. First, the ADNI was designed to mimic a trial population, so participants were more educated, more Caucasian, and had fewer comorbidities, as compared with a community-based cohort [43]. The generalizability of our conclusions is thus controversial, and the length of follow-up was short. Second, this was a secondary analysis of the cohort, thus there were different proportions of *APOE* ε4-carrier individuals at each clinical stage. Overall, the NC and AD groups had about one-half the number of participants as the MCI group, resulting in reduced power to detect differences. Rather than take a sample with balanced proportions, we wanted to include all available data. Furthermore, an allelic dose-dependent effect of *APOE* ε4 could not be explored because only two NC subjects were homozygous for *APOE* ε4, and the MCI and AD had imbalanced proportions of heterozygotes and homozygotes. Third, we only included hippocampal volumes as a marker of structural change to limit the number of comparisons. Inclusion of other limbic or whole brain markers would potentially detect more *APOE* ε4 effects not described in our analysis. Further prospective studies are needed to validate our findings.

In summary, we demonstrated that baseline CSF levels of Aβ are predictive of near-term hippocampal volume loss. The strengths of this study include the recruitment of participant from multiple centers, longitudinal follow-up, and consideration of all three clinical stages. We further raised the possibility of an *APOE* ε4–CSF Aβ interaction effect on longitudinal hippocampal atrophy among participants with MCI. As interest grows in using hippocampal atrophy as an outcome in clinical trials, it will be important to consider how varying risk factors and biomarkers interact and influence the progression of neurodegeneration.

Acknowledgments

This work was funded by the National Institutes of Health (NIH), NIBIB (T32 EB001631-05).

Dr. Fox also receives funding from the Medical Research Council, the Alzheimer's Research Trust (ART), and the National Institute for Health Research.

Data collection and sharing for this project was funded by the ADNI (NIH Grant U01 AG024904). ADNI is funded by the NIA, the NIBIB, and through generous contributions from the following: Abbott, AstraZeneca AB, Bayer Schering Pharma AG, Bristol-Myers Squibb, Eisai Global Clinical Development, Elan Corporation, Genentech, GE Healthcare, GlaxoSmithKline, Innogenetics, Johnson and Johnson, Eli Lilly and Co., Medpace, Inc., Merck and Co., Inc., Novartis AG, Pfizer Inc, F. Hoffman-La Roche, Schering-Plough, Synarc, Inc., and Wyeth, as well as nonprofit partners, the Alzheimer's Association and Alzheimer's Drug Discovery Foundation, with participation from the U.S. Food and Drug Administration. Private sector contributions to ADNI are facilitated by the Foundation for the NIH (www.fnih.org). 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 California, Los Angeles.

This research was also supported by NIH grants P30 AG010129, K01 AG030514, and the Dana Foundation.

Dr. Reiman serves on the scientific advisory boards of Accera, AstraZeneca, Elan Pharmaceuticals, Eli Lilly, GlaxoSmithKline, and Siemens; serves as a consultant to Amnestix/Sygnis; holds US Patent Number 6,374,130, issued April 16, 2002; and receives research support from Kronos Life Sciences, GlaxoSmithKline, AstraZeneca, Avid, the NIA (9R01 AG031581-10 [PI]), and the State of Arizona.

Dr. Jack is an investigator in clinical trials sponsored by Pfizer; serves as a consultant for Elan Pharmaceuticals; and receives research support from the NIH (R01-AG11378) and the Alexander Family Alzheimer's Disease Research Professorship of the Mayo Foundation.

Dr. Fox has served on the scientific advisory boards of Alzheimer's Research Forum, Alzheimer's Society, and ART, and editorial boards of *Alzheimer's Disease and Associated Disorders*, *Neurodegenerative Diseases*, and *BioMed Central: Alzheimer's Research and Therapy*. He holds a patent for QA Box that may accrue revenue. In the last 5 years, his research group has received payment for consultancy or for conducting studies from Abbott Laboratories, Elan Pharmaceuticals, Eisai, Eli Lilly, GE Healthcare,

IXICO, Lundbeck, Pfizer Inc, Sanofi-Aventis, and Wyeth Pharmaceuticals. He receives research support from the Medical Research Council (G0801306 [PI], G0601846 [PI]), NIH (U01 AG024904 [Co-investigator {sub contract}]), ART (ART/RF/2007/1 [PI]), and the National Institute for Health Research (as a Senior Investigator).

Dr. Jagust serves on a scientific advisory board of Genentech; has served as a consultant to Synarc, Elan Pharmaceuticals, Genentech, Ceregene, Schering-Plough, and Merck & Co.; and receives research support from the NIH (AG027859 [PI], AG027984 [PI], and AG 024904 [Coinvestigator]) and the Alzheimer's Association (ZEN-08-87090 [PI]).

Dr. Aisen serves on a scientific advisory board for NeuroPhage; serves as a consultant to Elan Corporation, Wyeth, Eisai Inc., Schering-Plough Corp., Bristol-Myers Squibb, Eli Lilly and Company, NeuroPhage, Merck & Co., Roche, Amgen, Genentech, Inc., Abbott, Pfizer Inc, Novartis, and Medivation, Inc.; receives research support from Pfizer Inc, Baxter International Inc., and the NIH (NIA U01-AG10483 [PI], NIA U01-AG024904 [Coordinating Center Director], NIA R01-AG030048 [PI], and R01-AG16381 [Co-I]); and has received stock options from Medivation, Inc. and NeuroPhage.

Dr. Petersen serves as a consultant to Elan Pharmaceuticals, Wyeth Pharmaceuticals, and GE Healthcare; receives royalties from publishing Mild Cognitive Impairment (Oxford University Press, 2003); and receives research support from the NIA (AG 06786 [PI] and AG 16574 [PI]).

Dr. Weiner serves on scientific advisory boards for Bayer Schering Pharma, Eli Lilly, Nestle, CoMentis, Neurochem, Eisai, Avid, Aegis, Genentech, Allergan, Lippincott, Bristol Meyers Squibb, Forest, Pfizer, McKinsey, Mitsubishi, and Novartis. He has received non–industry-supported funding for travel; serves on the editorial board of *Alzheimer's & Dementia*; received honoraria from the Rotman Research Institute and BOLT International; receives research support from Merck & Co, Avid, NIH (U01AG024904 [PI], P41 RR023953 [PI], R01 AG10897 [PI], P01AG19724 [Coinvestigator], P50AG23501[Coinvestigator], R24 RR021992 [Coinvestigator], R01 NS031966 [Coinvestigator], and P01AG012435 [Coinvestigator]), the Department of Defense (DAMD17-01-1-0764 [PI]), and the Veterans Administration (MIRECC VISN 21 [Core PI]); and holds stock in Synarc and Elan Pharmaceuticals.

References

[1] Frisoni GB, Lorenzi M, Caroli A, Kemppainen N, Nagren K, Rinner JO. In vivo mapping of amyloid toxicity in Alzheimer disease. Neurology 2009;72:1504–11.

[2] Mormino EC, Kluth JT, Madison CM, Rabinovici GD, Baker SL, Miller BL, et al. Episodic memory loss is related to hippocampal-mediated beta-amyloid deposition in elderly subjects. Brain 2009; 132:1310–23.

[3] Scheinen NM, Aalto S, Koikkalainen J, Lotjonen J, Karrasch M, Kemppainen N, et al. Follow-up of [11C]PIB uptake and brain volume in patients with Alzheimer disease and controls. Neurology 2009; 73:1186–92.

[4] Storandt M, Mintun MA, Head D, Morris JC. Cognitive decline and brain volume loss as signatures of cerebral amyloid-beta peptide deposition identified with Pittsburgh compound B: cognitive decline associated with Abeta deposition. Arch Neurol 2009;66:1476–81.

[5] Bourgeat P, Chetelat G, Villemagne VL, Fripp J, Raniga P, Pike K, et al. Beta-amyloid burden in the temporal neocortex is related to hippocampal atrophy in elderly subjects without dementia. Neurology 2010;74:121–7.

[6] Strozyk D, Blennow K, White LR, Launer LJ. CSF Abeta 42 levels correlate with amyloid-neuropathology in a population-based autopsy study. Neurology 2003;60:652–6.

[7] Tapiola T, Alafuzoff I, Herukka SK, Parkkinen L, Hartikainen P, Soininen H, Pirttila T. Cerebrospinal fluid {beta}-amyloid 42 and tau proteins as biomarkers of Alzheimer-type pathologic changes in the brain. Arch Neurol 2009;66:382–9.

[8] Herukka SK, Pennanen C, Soininen H, Pirttila T. CSF Abeta42, tau and phosphorylated tau correlate with medial temporal lobe atrophy. J Alzheimers Dis 2008;14:51–7.

[9] Fjell AM, Walhovd KB, Amlein I, Bjornerud A, Reinvang I, Gjerstad L, et al. Morphometric changes in the episodic memory network and tau pathologic features correlate with memory performance in patients with mild cognitive impairment. Am J Neuroradiol 2008;29:1183–9.

[10] Henneman WJ, Vrenken H, Barnes J, Sluimer IC, Verwey NA, Blankenstein MA, et al. Baseline CSF p-tau levels independently predict progression of hippocampal atrophy in Alzheimer disease. Neurology 2009;73:935–40.

[11] Josephs KA, Whitwell JL, Ahmed Z, Shiung MM, Weigand SD, Knopman DS, et al. Beta-amyloid burden is not associated with rates of brain atrophy. Ann Neurol 2008;63:204–12.

[12] Sluimer JD, Bouwman FH, Vrenken H, Blankenstein MA, Barkhof F, van der Flier WM, et al. Whole brain atrophy rate and CSF biomarker levels in MCI and AD: a longitudinal study. Neurobiol Aging 2010; 31:758–64.

[13] Corder EH, Saunders AM, Strittmatter WJ, Schmechel DE, Gaskell PC, Small GW, Roses AD, Haines JL, Pericak-Vance MA. Gene dose of apolipoprotein E type 4 allele and the risk of Alzheimer's disease in late onset families. Science 1993;261:921–3.

[14] Seshadri S, Drachman DA, Lippa CF. Apolipoprotein E epsilon 4 allele and the lifetime risk of Alzheimer's disease: what physicians know, and what they should know. Arch Neurol 1995;52:1074–9.

[15] Schmechel DE, Saunders AM, Strittmatter WJ, Crain BJ, Hulette CM, Joo SH, et al. Increased amyloid β-peptide deposition in cerebral cortex as a consequence of apolipoprotein E genotype in late-onset Alzheimer disease. Proc Natl Acad Sci USA 1993;90:9649–53.

[16] Reiman EM, Chen K, Liu X, Bandy D, Yu M, Lee W, et al. Fibrillar amyloid-beta burden in cognitively normal people at 3 levels of genetic risk for Alzheimer's disease. Proc Natl Acad Sci USA 2009;106: 6820–5.

[17] Bu G. Apolipoprotein E and its receptors in Alzheimer's disease: pathways, pathogenesis and therapy. Nat Rev Neurosci 2009;10:333–44.

[18] Small GW, Siddarth P, Burggren AC, Kepe V, Ercoli LM, Miller KJ, et al. Influence of cognitive status, age, and APOE-4 genetic risk on brain FDDNP-PET binding in non-demented persons. Arch Gen Psychiatry 2009;66:81–7.

[19] van de Pol LA, van der Flier WM, Korf ES, Fox NC, Barkhof F, Scheltens P. Baseline predictors of rates of hippocampal atrophy in mild cognitive impairment. Neurology 2007;69:1491–7.

[20] Morra JH, Tu Z, Apostolova LG, Green AE, Avedissian C, Madsen SK, et al. Automated mapping of hippocampal atrophy in 1-year repeat MRI data from 490 subjects with Alzheimer's disease, mild cognitive impairment, and elderly controls. Neuroimage 2009;45:S3–15.

[21] Schuff N, Woerner N, Boreta L, Kornfield T, Shaw LM, Trojanowski JQ, et al. MRI of hippocampal volume loss in early Alzheimer's disease in relation to ApoE genotype and biomarkers. Brain 2009;132:1067–77.

[22] 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;12:189–98.

[23] Morris JC. The Clinical Dementia Rating (CDR): current version and scoring rules. Neurology 1993;43:2412–4.
[24] Wechsler D, Wms- R. Weschsler Memory Scale—revised manual. New York, NY: The Psychological Corporation, Harcourt Brace Jovanovich, Inc; 1987.
[25] McKhann G, Drachman D, Folstein M, Katzman R, Price D, Stadlan EM. Clinical diagnosis of Alzheimer's disease: a report of the NINCDS Alzheimer's disease RDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's disease. Neurology 1984;34:939–44.
[26] Shaw LM. PENN biomarker core of the Alzheimer's disease Neuroimaging Initiative. Neurosignals 2008;16:19–23.
[27] Shaw LM, Vanderstichele H, Knapik-Czajka M, Clark CM, Aisen PS, Petersen RC, et al. Cerebrospinal fluid biomarker signature in Alzheimer's disease Neuroimaging Initiative subjects. Ann Neurol 2009;65:403–13.
[28] Jagust WJ, Landau SM, Shaw LM, Trojanowski JQ, Koeppe RA, Reiman EM, et al. Relationships between biomarkers in aging and dementia. Neurology 2009;73:1193–9.
[29] Jack CR, Bernstein MA, Fox NC, Thompson P, Alexander G, Harvey D, et al. The Alzheimer's disease Neuroimaging Initiative (ADNI): MRI methods. J Magn Reson Imaging 2008;27:685–91.
[30] Fischl B, Salat DH, Busa E, Albert M, Dieterich M, Haselgrove C, et al. Whole brain segmentation: automated labeling of neuroanatomical structures in the human brain. Neuron 2002;33:341–55.
[31] Corder EH, Saunders AM, Risch NJ, Strittmatter WJ, Schmechel DE, Gaskell PC, et al. Protective effect of apolipoprotein E type 2 allele for late onset Alzheimer disease. Nat Genet 1994;7:180–4.
[32] Chiang GC, Insel PS, Tosun D, Schuff N, Truran-Sacrey D, Raptentsetsang S, et al. Hippocampal atrophy rates and CSF biomarkers in elderly APOE2 normal subjects. Neurology 2010;75:1976–81.
[33] Walsh DM, Klyubin I, Fadeeva JV, Cullen WK, Anwyl R, Wolfe MS, et al. Naturally secreted oligomers of amyloid β protein potently inhibit hippocampal long-term potentiation in vivo. Nature 2002;416:535–9.
[34] Kayed R, Head E, Thompson JL, McIntire TM, Milton SC, Cotman CW, et al. Common structure of soluble amyloid oligomers implies common mechanism of pathogenesis. Science 2003;300:486–9.
[35] Moffat SD, Szekely CA, Zonderman AB, Kabani NJ, Resnick SM. Longitudinal change in hippocampal volume as a function of apolipoprotein E genotype. Neurology 2000;55:134–6.
[36] Farlow MR, He Y, Tekin S, Xu J, Lane R, Charles HC. Impact of APOE in mild cognitive impairment. Neurology 2004;63:1898–901.
[37] Fleisher A, Grundman M, Jack CR, Petersen RC, Taylor C, Kim HT, et al. Sex, apolipoprotein E epsilon4 status, and hippocampal volume in mild cognitive impairment. Arch Neurol 2005;62:953–7.
[38] den Heijer T, Oudkerk M, Launder LJ, van Duijin CM, Hofman A, Breteler MM. Hippocampal, amygdalar, and global brain atrophy in different apolipoprotein E genotypes. Neurology 2002;59:746–8.
[39] Jack CR, Petersen RC, Xu YC, O'Brien PC, Waring SC, Tangalos EG, et al. Hippocampal atrophy and apolipoprotein E genotype are independently associated with Alzheimer's disease. Ann Neurol 1998;43:303–10.
[40] Drzezga A, Grimmer T, Henriksen G, Muhlau M, Perneczky R, Miederer I, et al. Effect of APOE genotype on amyloid plaque load and gray matter volume in Alzheimer disease. Neurology 2009;72:1487–94.
[41] Riemenschneider M, Wagenpfeil S, Diehl J, Lautenschlager N, Theml T, Heldmann B, et al. Tau and Aβ42 protein in CSF of patients with frontotemporal degeneration. Neurology 2002;58:1622–8.
[42] Grundman M, Petersen RC, Ferris SH, Thomas RG, Aisen PS, Bennett DA, et al. Mild cognitive impairment can be distinguished from Alzheimer disease and normal aging for clinical trials. Arch Neurol 2004;61:59–66.
[43] Petersen RC, Aisen PS, Beckett LA, Donohue MC, Gamst AC, Harvey DJ, et al. Alzheimer's Disease Neuroimaging Initiative (ADNI): clinical characterization. Neurology 2010;74:201–9.