Hippocampal atrophy rates and CSF biomarkers in elderly *APOE2* normal subjects

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Editorial, page 1952

Supplemental data at www.neurology.org

ABSTRACT

Objective: To determine whether elderly normal *APOE* E2 (*APOE2*) carriers exhibit slower rates of hippocampal atrophy and memory decline compared to *APOE3/3* carriers. We also determined whether *APOE2* carriers have less Alzheimer pathology as reflected by CSF biomarkers.

Methods: We included longitudinal data from 134 cognitively normal individuals (27 *APOE2/2* or *E2/3*, 107 *APOE3/3*) from the Alzheimer's Disease Neuroimaging Initiative, a prospective cohort study. A linear mixed-effects model was used to determine how *APOE2* affected rates of hippocampal atrophy and cognitive change over time. In a subsample of 72 individuals who also underwent CSF analysis, an ordinary least-squares regression was used to determine whether CSF β-amyloid (Aβ), total tau, and phosphorylated tau-181 (p-tau) differed by *APOE2* status.

Results: *APOE2* carriers demonstrated slower rates of hippocampal atrophy ($p = 0.004$). The mean rate of hippocampal atrophy among *APOE2* carriers was −33 mm^3/year (95% confidence interval −65 to +0.4), or −0.5%/year, compared to −86 mm^3/year (95% confidence interval −102 to −71), or −1.3%/year, in the *APOE3/3* group. No differences in the rates of episodic memory ($p = 0.23$) or overall cognitive change ($p = 0.90$) were detected. In the CSF subsample, *APOE2* carriers had higher levels of CSF Aβ ($p = 0.01$), lower p-tau ($p = 0.02$), and marginally lower tau ($p = 0.12$).

Conclusion: A slower rate of hippocampal atrophy in normal *APOE2* carriers is consistent with the lower risk of Alzheimer disease in these individuals. We hypothesize that the slower atrophy rate is related to decreased preclinical Alzheimer pathology. ***Neurology*® 2010;75:1976–1981**

GLOSSARY

Aβ = β-amyloid; **AD** = Alzheimer disease; **ADAS-Cog** = Alzheimer's Disease Assessment Scale Cognitive Subscale; **ADNI** = Alzheimer's Disease Neuroimaging Initiative; **MCI** = mild cognitive impairment; **MPRAGE** = magnetization-prepared rapid gradient echo; **p-tau** = phosphorylated tau-181; **WMS-R** = Wechsler Memory Scale–Revised.

The association between *APOE* genetic polymorphisms and differing risks of developing Alzheimer disease (AD) has been well-described,[1,2] although the mechanism remains unclear. Approximately 70% of the population carry the common *APOE3/3* genotype, 25% carry at least one *APOE4* allele, and 5% carry an *APOE2* allele.[3] Even before clinical evidence of memory impairment, *APOE4* carriers demonstrate more rapid rates of memory decline.[4-7] On the other hand, carrying an *APOE2* allele is associated with slower rates of memory decline[8] and is considered protective against the development of AD.[2]

e-Pub ahead of print on October 27, 2010, at www.neurology.org.

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Study funding: Supported by the NIH (NIBIB T32 EB001631-05, P41 RR023953, P30 AG010129, and K01 AG030514) and the Dana Foundation. Data collection and sharing for this project was funded by the Alzheimer's Disease Neuroimaging Initiative (ADNI) (National Institutes of Health Grant U01 AG024904). ADNI is funded by the National Institute on Aging, the National Institute of Biomedical Imaging and Bioengineering, and through 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 US Food and Drug Administration. Private sector contributions to ADNI are facilitated by the Foundation for the National Institutes of Health (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 Neuroimaging at the University of California, Los Angeles.

Disclosure: Author disclosures are provided at the end of the article.

Structurally, numerous studies have reported decreased hippocampal volumes and accelerated rates of hippocampal atrophy among cognitively normal *APOE*4 carriers.[9-12] Relatively little has been reported regarding structural differences associated with the *APOE*2 allele. To our knowledge, only one study has described a "protective" morphology among *APOE*2 carriers, manifested by greater entorhinal cortical thickness among adolescents.[13] Counterintuitively, 2 cross-sectional studies report detrimental effects of *APOE*2, by decreasing hippocampal volumes[10] and increasing hippocampal sulcal cavities.[14]

The primary aims of this study were to test our hypotheses that cognitively normal *APOE*2 carriers demonstrate reduced rates of hippocampal atrophy and episodic memory decline compared to *APOE*3/3 carriers. We further tested the hypothesis that differences in hippocampal atrophy rates could be related to differences in underlying Alzheimer pathology.

METHODS

Participants. The participants in this study were recruited between 2005 and 2008 through the Alzheimer's Disease Neuroimaging Initiative (ADNI), a longitudinal study of 819 individuals from 56 centers in the United States and Canada (229 cognitively normal, 398 with mild cognitive impairment [MCI], 192 with probable AD) designed to identify biomarkers of early AD for clinical trials.[15] The ADNI was funded by the National Institute on Aging, the National Institute of Biomedical Imaging and Bioengineering, the Food and Drug Administration, private pharmaceutical companies, and nonprofit organizations, as a 5-year public-private partnership. Briefly, subjects were between the ages of 55 and 90, without clinical or structural evidence of a significant neurologic or psychiatric disease, and without systemic medical illness or laboratory abnormalities that would interfere with follow-up. Further details regarding inclusion and exclusion criteria can be found at www.adni-info.org.

In addition to the inclusion and exclusion criteria described above, the cognitively normal subjects had no memory complaints, had preserved activities of daily living, scored between 24 and 30 on a baseline Mini-Mental State Examination,[16] scored a 0 on the Clinical Dementia Rating scale,[17] and scored within the normal range on the Logical Memory II subscale (delayed paragraph recall) from the Wechsler Memory Scale–Revised (WMS-R).[18]

Standard protocol approvals, registrations, and patient consents. 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.

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

The participants also underwent neuropsychological assessment at baseline and every 6 months with the Alzheimer's Disease Assessment Scale Cognitive Subscale (ADAS-Cog)[19] and at baseline and every 12 months with the WMS-R.[18] The ADAS-Cog was used as a measure of overall cognitive function. The 30-minute delayed paragraph recall score of the WMS-R, in which a participant recounts a story that was told to him or her after the time delay, was used as a measure of episodic memory.

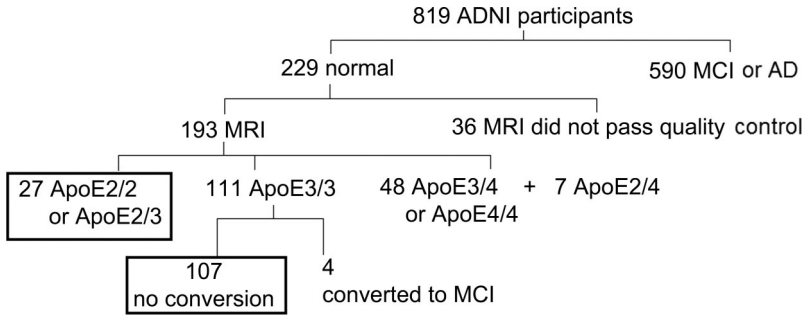
MRI acquisition and hippocampal volume estimation. MRI was performed at the baseline visit, after 6 months, after 12 months, and after 24 months. The participants underwent the following 1.5-T MRI protocol (http://www.loni.ucla.edu/ADNI/Research/Cores/index.shtml), which was standardized across all sites: 2 T1-weighted MRI scans, using a sagittal volumetric magnetization-prepared rapid gradient echo (MPRAGE) sequence, with an echo time of 4 msec, repetition time of 9 msec, 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. A single quality control center was designated to select the MPRAGE image with higher quality, which was corrected for system-specific image artifacts, and used for hippocampal volume estimation.[20] Scans that demonstrated severe motion artifacts or field inhomogeneity were excluded from the analysis.

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 longitudinal FreeSurfer software, version 4.3 (http://surfer.nmr.mgh.harvard.edu/).[21] The segmented volumes were visually rated for accuracy by experienced staff and excluded from the analysis as appropriate. Bilateral hippocampal volumes, obtained from this segmentation, were summed in the analyses.

CSF analysis. As described in the ADNI protocol (www.adni-info.org), all 56 participating centers were asked to perform lumbar punctures on at least 20% of their participants. Approximately 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.[22] 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 into 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. Monoclonal antibodies specific for β-amyloid (Aβ), total tau, and p-tau phosphorylated at threonine-191 (p-tau) were used as reagents, which have been found to be useful in predicting AD.[23]

Statistical analyses. The process of selecting the sample of 134 participants for our primary analysis is shown in figure 1 (table 1). Group differences in baseline characteristics were assessed using the Wilcoxon rank sum and Fisher exact tests. *APOE*2/4 participants were excluded to eliminate potential confounding of the *APOE*2 effect by the presence of *APOE*4. Four *APOE*3/3 subjects who converted to MCI clinically during the

Figure 1 Sample selection process from the Alzheimer's Disease Neuroimaging Initiative (ADNI) cohort



AD = Alzheimer disease; MCI = mild cognitive impairment.

study period were also excluded from the analysis. Comparison of the 193 subjects whose MRI passed quality control with the remaining 36 of the normal cohort and comparison of the 134 in our sample with the other 91 of the normal cohort yielded no differences in age, gender, years of education, or Mini-Mental State Examination scores ($p > 0.05$). Furthermore, approximately half of these participants (n = 72) underwent lumbar puncture for CSF biomarker analysis. Comparison of the 72 participants in this subsample who underwent CSF analysis with the remainder of the normal cohort (n = 157) also yielded no differences in age, gender, years of education, or Mini-Mental State Examination scores ($p > 0.05$).

Table 1 Baseline group characteristics[a]

	APOE2/2 or APOE2/3	*APOE3/3*	*p* Value
Total sample			
No.	27	107	
Age, y	76 (4.6)	76 (5.2)	0.37
Male/female	14/13	57/50	0.53
Education, y	16 (3.5)	16 (2.6)	0.78
ADAS-Cog	5.4 (2.3)	5.8 (2.7)	0.52
Mini-Mental State Examination	29 (1.3)	29 (0.9)	0.32
Baseline hippocampal volume, mm^3	6,765 (1002)	6,686 (785)	0.88
CSF biomarker subsample[b]			
No.	17	55	
Age, y	75 (4.0)	76 (5.0)	0.60
Male/female	8/9	25/30	0.56
Education, y	15 (3.3)	16 (2.4)	0.40
ADAS-Cog	5.5 (2.6)	6.1 (2.9)	0.41
Mini-Mental State Examination	29 (1.2)	29 (0.9)	0.06
Baseline hippocampal volume, mm^3	6,539 (691.6)	6,762 (724.9)	0.21
CSF β-amyloid, pg/mL	242.2 (33.8)	209.4 (49.2)	0.01[c]
CSF total tau, pg/mL	58.3 (18.1)	69.9 (26.6)	0.13
CSF p-tau, pg/mL	17.1 (4.8)	25.2 (12.5)	0.003[c]

Abbreviation: ADAS-Cog = Alzheimer's Disease Assessment Scale Cognitive Subscale; p-tau = phosphorylated tau-181.
[a] Data are mean (SD).
[b] CSF available for 72 of 134 participants (54%).
[c] Significance by Wilcoxon rank sum test.

A linear mixed-effects model was used to assess the rate of change of hippocampal atrophy and cognition, as well as their association with *APOE*2, while accounting for within-subject variation. The mixed-effects model was designed to separate random variations of hippocampal volumes across subjects at baseline from the fixed effects of change over time and *APOE*2 carrier status. All statistical analyses were programmed in STATA version 11 (StataCorp, College Station, TX).

Since only 2 individuals were homozygous for the *APOE*2 allele, *APOE*2 carrier status was dichotomized to represent both *APOE*2/2 and *APOE*2/3 genotypes. The *APOE*3/3 carriers were considered the reference group for comparison. In addition, age, gender, and education in years were used as covariates in the model. Accordingly, the following mixed effects model was used:

$$V_{ij} = (B_0 + \beta_0) + \beta_1 APOE2_i + (\beta_2 + \beta_3 APOE2_i)\, t_{ij} + \text{covariates} + \epsilon_{ij}$$

Here, V_{ij} represents the hippocampal volume of subject i at timepoint j, $APOE2_i$ represents the carrier status of each subject, and t_{ij} represents the time interval between MRI scans. $(B_0 + \beta_0)$ are the coefficients for the random and fixed variations in baseline volumes. The coefficient β_1 represents the fixed effects of *APOE*2 carrier status at baseline. Finally, $(\beta_2 + \beta_3)$ are the coefficients for time-dependent changes in hippocampal volumes, irrespective (β_2) and respective (β_3) of *APOE*2 carrier status. The error term ϵ_{ij} represents random noise.

A similar model was used to evaluate rates of memory and cognitive decline. The assumption of linearity was assessed visually using plots of the mean hippocampal volumes over time and by including a quadratic term for time, which was found to be nonsignificant.

In our subgroup with CSF data, we used ordinary least squares regression to determine whether the level of each biomarker differed by *APOE*2 carrier status. Age, gender, and years of education were again used as covariates. Model assumptions were not violated, as assessed by plots of residuals.

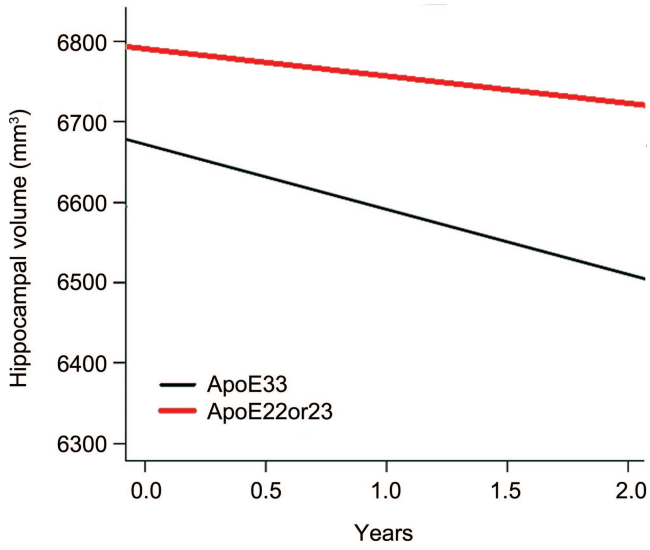
RESULTS

The group characteristics are summarized in table 1. There were no significant differences in age, gender, years of education, or baseline cognition. Unadjusted levels of CSF Aβ and p-tau differed between groups at baseline.

***APOE*2 is associated with a reduction in hippocampal atrophy rates.** The results of the mixed effects models are shown (figure 2, table 2). Overall, hippocampal volume decreased over time ($p < 0.001$), and *APOE*2 carrier status was associated with slower rates of hippocampal atrophy compared to noncarriers ($p = 0.004$). The rate of hippocampal atrophy for *APOE*2 carriers was -33 mm^3/year (95% CI -65 to $+0.4$) or -0.5% per year, compared to -86 mm^3/year (95% CI -102 to -71) or -1.3% per year for the *APOE*3/3 group. Of note, *APOE*2 carriers did not have larger hippocampal volumes at baseline ($p = 0.93$).

***APOE*2 is not associated with differences in rates of change of cognitive scores.** WMS-R delayed paragraph recall scores increased marginally over time ($p = 0.06$), whereas ADAS-Cog did not change over time

Figure 2 Linear mixed-effects model of hippocampal atrophy rates by group



($p = 0.28$). No difference in rates of memory or cognitive change was detected by *APOE*2 status.

***APOE*2 is associated with decreased Alzheimer pathology.** In the subsample with CSF biomarkers, the cross-sectional models, adjusting for covariates, demonstrated that *APOE*2 carriers had 34 pg/mL higher baseline levels of CSF Aβ ($p = 0.01$, 95% CI +7 to + 60) and 8 pg/mL lower levels of p-tau ($p = 0.02$, 95% CI −14 to −1), compared to *APOE*3/3 carriers. Furthermore, *APOE*2 carriers had 11 pg/mL lower levels of total tau, although this did not reach statistical significance ($p = 0.12$, 95% CI −25 to +3).

DISCUSSION Our study demonstrated that cognitively normal *APOE*2 carriers, compared to *APOE*3/3 carriers, exhibit 1) slower rates of hippocampal atrophy and 2) a CSF biomarker profile suggestive of decreased underlying Alzheimer pathology.

Table 2 Summary of the mixed-effects models[a]

Rate of change in:	Group	Estimated rate (95% CI)	Mean % change	*p* Value
Hippocampal volume (mm^3/y)	*APOE*2	−33 (−65 to 0.4)	−0.5	0.004
	*APOE*3	−86 (−102 to −71)	−1.3	
WMS-R delayed recall (units/y)	*APOE*2	0.51 (0.06 to 0.96)	+4.0	0.23
	*APOE*3	0.21 (−0.01 to 0.42)	+1.6	
ADAS-Cog (units/y)	*APOE*2	−0.12 (−0.47 to 0.23)	−2.1	0.90
	*APOE*3	−0.09 (−0.25 to 0.09)	−1.5	

Abbreviations: ADAS-Cog = Alzheimer's Disease Assessment Scale Cognitive Subscale; CI = confidence interval; WMS-R = Wechsler Memory Scale–Revised.
[a] Models were adjusted for age, gender, and education. Mean percent change was calculated by dividing the annual rate of change by the mean baseline value.

The first major finding is that *APOE*2 carriers have slower rates of hippocampal atrophy, compared to carriers of the common *APOE*3/3 genotype. Moreover, the slower rates in *APOE*2 carriers cannot be explained by variations in baseline hippocampal volumes, since this was accounted for in our model. Prior literature on structural abnormalities among *APOE*2 carriers has been scarce and inconsistent, with only one study demonstrating increased entorhinal cortical thickness among *APOE*2 carriers.[13] The 2 other studies assessing cross-sectional volumetric differences among *APOE*2 carriers used manual tracings of the hippocampi[10] and sulcal cavities as an indirect measure of hippocampal differences,[14] which could have played a role in finding a detrimental effect of the *APOE*2 allele. None of the previous studies demonstrated longitudinal change. Our finding that the *APOE*2 allele reduces hippocampal atrophy rates is thus consistent with prior population-based evidence of this allele being protective.[2]

The finding of a CSF biomarker profile reflective of decreased Alzheimer pathology among *APOE*2 carriers may explain the observed reduction in hippocampal atrophy rates. Several in vitro and animal studies have reported that *APOE*2 isoform binds Aβ more efficiently than *APOE*3, promotes decreased Aβ polymerization into amyloid filaments, and transports Aβ across the blood–brain barrier more quickly, suggesting an overall role in decreasing Aβ accumulation.[24] Decreased Alzheimer neuropathology associated with *APOE*2 has also been described in elderly normal subjects postmortem[25] and using imaging and CSF biomarkers.[26] Although only about half of our sample underwent CSF analysis, we also found evidence for increased CSF Aβ, decreased p-tau, and marginally total tau. Since hippocampal volumes have been shown to reflect Alzheimer pathology[27] and predict future development of AD,[28] it is conceivable that decreased Alzheimer pathology related to cellular mechanisms of *APOE*2 could explain decreased hippocampal atrophy rates. On the other hand, a recent postmortem study among a population greater than the age of 90 found increased Alzheimer pathology among *APOE*2 carriers, despite a reduced risk of clinical dementia.[29] It is likely that other compensatory mechanisms for maintaining cognition among *APOE*2 carriers exist, and further follow-up of the ADNI population is required to assess how these findings may change with older age.

Since the rates of change in memory and cognitive scores were relatively minimal in the duration of follow-up, it is not surprising that the effects of *APOE*2 carrier status were not significant.

Our study has several limitations. First, the ADNI was intended to mimic a trial population, so

the duration of follow-up was relatively short. In addition, this cohort consisted of more Caucasians, was more highly educated, and had fewer comorbidities than a community population at this age.[15] As a result, generalization of these findings should be approached with caution and further validation in prospective population-based cohorts is required. The hippocampal atrophy rates among our cohort, however, are similar to that of a recent meta-analysis which estimated a rate of −1.41%/year among normal controls.[30] Furthermore, an association between *APOE*2 and cerebral amyloid angiopathy, which can lead to lobar hemorrhages, has been described.[31] These would have been excluded from the ADNI with an abnormal screening MRI, thus removing a potential source for a detrimental effect of *APOE*2. Finally, while we used WMS-R delayed paragraph recall as a measure of verbal memory, it is known to be confounded by practice effects, which could explain the overall upward trend in memory scores over time. Nevertheless, 52 (39%) of the subjects in our sample did demonstrate at least a 1-point decline in the paragraph recall score. Whether measuring verbal memory or practice effects, no group differences in this longitudinal measure over time were detected.

This study provides evidence that the protective effect of the *APOE*2 genetic polymorphism is detectable in vivo, before there is evidence of cognitive impairment. We hypothesize that slower rates of neurodegeneration could be related to decreased underlying Alzheimer neuropathology.

AUTHOR CONTRIBUTIONS

Statistical analysis was conducted by Philip Insel and Dr. Gloria Chiang.

ACKNOWLEDGMENT

Data used in the preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (www.loni.ucla.edu\ADNI). 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.

DISCLOSURE

Dr. Chiang, P.S. Insel, and Dr. Tosun report no disclosures. Dr. Schuff serves as a consultant for the Michael J. Fox Foundation; has received honoraria from the British Research Council and Elsevier; and receives research support from Synarc, the Michael J. Fox Foundation, the US Department of Defense, and the NIH (P41 RR023953 [coinvestigator]; P50AG23501 [coinvestigator]). D. Truran-Sacrey and S.T. Raptentsetsang report no disclosures. Dr. Jack serves as a consultant for Elan Corporation and GE Healthcare; receives research support from Pfizer Inc., the NIH (NIA R01-AG11378 [PI] and U01 AG024904-01 [coinvestigator]), and the Alexander Family Alzheimer's Disease Research Professorship of the Mayo Foundation; and holds stock in GE Healthcare and Johnson & Johnson. Dr. Aisen serves on a scientific advisory board for NeuroPhage; serves on the editorial advisory board of *Alzheimer's Research & Therapy*; 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, Bayer Schering Pharma, Medivation, Inc., Daiichi Sankyo, Astellas Pharma Inc., Dainippon Sumitomo Pharma Company Limited, BioMarin Pharmaceutical Inc., Solvay Pharmaceuticals, Inc., Otsuka Pharmaceutical Co., Ltd., AstraZeneca, and Janssen; 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 [coinvestigator]); and has received stock options from Medivation, Inc. and NeuroPhage. Dr. Petersen serves on scientific advisory boards for Elan Corporation, Wyeth, and GE Healthcare; receives royalties from publishing *Mild Cognitive Impairment* (Oxford University Press, 2003); and receives research support from the NIH/NIA (P50-AG16574 [PI], U01-AG06786 [PI], R01-AG11378 [coinvestigator], and U01–24904 (coinvestigator)]. Dr. Weiner serves on scientific advisory boards for Bayer Schering Pharma, Eli Lilly and Company, Nestlé, CoMentis, Inc., Neurochem Inc., Eisai Inc., Avid Radiopharmaceuticals Inc., Aegis Therapies, Genentech, Inc., Allergan, Inc., Lippincott Williams & Wilkins, Bristol-Myers Squibb, Forest Laboratories, Inc., Pfizer Inc., McKinsey & Company, Mitsubishi Tanabe Pharma Corporation, and Novartis; has received funding for travel from Nestlé and Kenes International and to attend conferences not funded by industry; serves on the editorial board of *Alzheimer's & Dementia*; has received honoraria from the Rotman Research Institute and BOLT International; serves as a consultant for Elan Corporation; receives research support from Merck & Co., Avid Radiopharmaceuticals Inc., the NIH (U01AG024904 [PI], P41 RR023953 [PI], R01 AG10897 [PI], P01AG19724 [coinvestigator], P50AG23501 [coinvestigator], R24 RR021992 [coinvestigator], R01 NS031966 [coinvestigator], and P01AG012435 [coinvestigator]), the US Department of Defense, the Veterans Administration, and the State of California; and holds stock in Synarc and Elan Corporation.

Received April 28, 2010. Accepted in final form August 3, 2010.

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