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Variables associated with hippocampal atrophy rate in normal aging and mild cognitive impairment

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ABSTRACT

The goal of this study was to identify factors contributing to hippocampal atrophy rate (HAR) in clinically normal older adults (NC) and participants with mild cognitive impairment (MCI). Longitudinal HAR was measured on T1-weighted magnetic resonance imaging, and the contribution of age, gender, apolipoprotein E (ApoE) ε4 status, intracranial volume, white matter lesions, and β-amyloid (Aβ) levels to HAR was determined using linear regression. Age-related effects of HAR were compared in Aβ positive (Aβ+) and Aβ negative (Aβ−) participants. Age and Aβ levels had independent effects on HAR in NC, whereas gender, ApoE ε4 status, and Aβ levels were associated with HAR in MCI. In multivariable models, Aβ levels were associated with HAR in NC; ApoE ε4 and Aβ levels were associated with HAR in MCI. In MCI, age was a stronger predictor of HAR in Aβ− versus Aβ+ participants. HAR was higher in Aβ+ participants, but most of the HAR was because of factors other than Aβ status. Age-related effects on HAR did not differ between NC versus MCI participants with the same Aβ status. Therefore, we conclude that even when accounting for other covariates, Aβ status, and not age, is a significant predictor of HAR; and that most of the HAR is not accounted for by Aβ status in either NC or MCI.

1. Introduction

Alzheimer's disease (AD), characterized by plaques of β-amyloid (Aβ), tangles of tau and/or phospho tau, and neurodegeneration, begins in the entorhinal cortex and hippocampus (Cardenas et al., 2003; Du et al., 2003; Glenner and Wong, 1984; Jack et al., 2010, 2013; Kosik et al., 1986). AD pathology is accompanied by progressive memory dysfunction leading to a continuum of mild cognitive impairment (MCI) and finally dementia (Grundman et al., 2004; Morris et al., 2001; Petersen et al., 1999). An essential focus of current AD research is identification of biomarkers associated with, and predictive of, AD.

Hippocampal atrophy, a prominent feature of AD that correlates with cognitive decline, is accelerated in AD and associated with AD pathology (Seab et al., 1988) but also occurs across the life span in normal aging (Du et al., 2006; Fjell et al., 2009; Honea et al., 2011; Morra et al., 2009). Because increased hippocampal atrophy rate (HAR) is associated with both normal aging and AD, it is not clear how much HAR in clinically normal older adults (NC) is because of presymptomatic AD pathology. Previous studies have been limited by several factors, including the lack of longitudinal hippocampal volume measurements, the exclusion of brain Aβ levels from the analyses, and focus on a singular contributing factor such as apolipoprotein E (ApoE) ε4 or age without the inclusion of models accounting for multiple variables simultaneously. Because studies

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[1] Data used in preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (adni.loni.ucla.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.ucla.edu/wpcontent/uploads/how_to_apply/ADNI_Acknowledgement_List.pdf.

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aimed at understanding the relationship between HAR, normal aging, and AD are essential for using hippocampal atrophy as a sensitive outcome measure in evaluation of potential AD treatments, the goal of this study was to identify the main factors that contribute to HAR in a nondemented cohort of older adults.

Accumulation of fibrillar brain Aβ can be directly assessed *in vivo* by positron emission tomography (PET) using the radiotracers Pittsburg Compound B (PIB) or (18)Florbetapir (AV45) (Clark et al., 2011; Jack et al., 2008b; Rowe et al., 2007), or indirectly via decreased cerebrospinal fluid levels of Aβ1-42 (CSF Aβ1-42) (Shaw et al., 2009). The 20%–30% of older adult, cognitively normal individuals with high levels of brain Aβ may represent a cohort that will eventually decline to MCI and/or AD (Dickerson et al., 2011; Morris et al., 2009; Rowe et al., 2010). Fibrillar Aβ deposition is associated with whole brain atrophy (Becker et al., 2011; Fagan et al., 2009), including hippocampal atrophy (Mormino et al., 2009) (Fjell et al., 2010; Schott et al., 2010; Storandt et al., 2009; Tosun et al., 2010) in older adult nondemented participants. However, sensitivity in linking brain Aβ to HAR has been limited in previous studies because of small sample sizes and limited longitudinal follow-up.

Additional factors that may be associated with HAR include ApoE genotype, gender, white matter lesions (WML), and intracranial volume (ICV). The ε4 allele of ApoE gene is associated with increased risk of AD and increased deposition of Aβ, and normal older adults ApoE ε4+ homozygotes have a higher rate of brain atrophy (Crivello et al., 2010) and low levels of CSF Aβ1-42 (Schott et al., 2010). Evidence exists for sex differences in brain structure and cognition in normal aging and AD, with differential regional volume reductions in males and females (Cowell et al., 1994; Sowell et al., 2007). In addition to amyloidosis, WMLs and ICV are additional age-associated imaging features which are risk factors for AD that may contribute to outcome measures such as cognition (Carmichael et al., 2010; Constans et al., 1995; Farias et al., 2012; Jagust et al., 2008).

Understanding the relative contribution of multiple factors to HAR is crucial for understanding normal aging and AD disease progression and for designing powerful AD clinical studies that rely on HAR as an outcome measure. Here, we assess the association of multiple variables, especially age and β-amyloid (Aβ) status, with HAR in NC and MCI participants in the Alzheimer's Disease Neuroimaging Initiative (ADNI).

2. Methods

2.1. Participants

The ADNI was launched in 2003 by the National Institute on Aging (NIA), the National Institute of Biomedical Imaging and Bioengineering, the Food and Drug Administration, private pharmaceutical companies and nonprofit organizations, as a $60 million, 5-year public-private partnership. The primary goal of ADNI has been to test whether serial magnetic resonance imaging (MRI), PET, other biological markers, and clinical and neuropsychological assessment can be combined to measure the progression of MCI and early AD. Determination of sensitive and specific markers of very early AD progression is intended to aid researchers and clinicians to develop new treatments and monitor their effectiveness, as well as lessen the time and cost of clinical trials.

The Principal Investigator of this initiative is Michael W. Weiner, MD, VA Medical Center and University of California, San Francisco (UCSF). ADNI is the result of efforts of many coinvestigators from a broad range of academic institutions and private corporations, and participants have been recruited from over 50 sites across the U.S. and Canada. The initial goal of ADNI was to recruit 800 participants, but ADNI has been followed by ADNI-GO and ADNI-2. To date, these 3 protocols have recruited over 1500 adults, aged 55–90 years, to participate in the research, consisting of cognitively normal older individuals, people with early or late MCI, and people with early AD. The follow up duration of each group is specified in the protocols for ADNI-1, ADNI-2, and ADNI-GO. Participants originally recruited for ADNI-1 and ADNI-GO had the option to be followed in ADNI-2. For up-to-date information, see www.adni-info.org.

All ADNI data were downloaded from the ADNI database (www.loni.ucla.edu/ADNI). We included ADNI-1 participants with successful longitudinal FreeSurfer processing of MRI images (average number of images per participant = 4.6), as well as either valid test result for CSF Aβ1-42, PIB, or AV45 imaging (Table 1). The number of participants with multiple Aβ measurements is listed in Table 1.

2.2. T1-weighted MRI

Participants underwent a standardized 1.5 Tesla MRI protocol (http://adni.loni.usc.edu/methods/mri-analysis/mri-acquisition/) that was previously validated across sites (Jack et al., 2008a). The ADNI MRI quality control center at the Mayo Clinic selected the MP-RAGE image with higher quality and corrected for system-specific image artifacts, as described in Jack et al. (2008a).

2.3. FreeSurfer longitudinal processing

Automated hippocampal volume measures were performed with FreeSurfer software package version 4.4. To reduce confounding effects of intra-participant morphologic variability, each participant's data series were processed by FreeSurfer longitudinal workflow (Fischl et al., 2002, 2004), and see http://surfer.nmr.mgh.harvard.edu/fswiki/LongitudinalProcessing. Details of quality control procedures are posted online (http://adni.loni.usc.edu/methods/mri-analysis/mri-acquisition/).

2.4. PET imaging

PIB and AV45 images were collected at multiple sites. Participants were injected with 15 mCi PIB or 10 mCi AV45, 4 dynamic acquisition frames were obtained 50–70 minutes postinjection and coregistered to one another, averaged, interpolated to a uniform image and voxel size ($160 \times 106 \times 96, 1.5\ mm^3$), and smoothed to a uniform resolution (8 mm FWHM). See also: http://adni.loni.usc.edu/methods/pet-analysis/pet-acquisition/. A mean cortical

Table 1
Demographics of NC and MCI ADNI participants used in this study

	NC	MCI
Number of participants	208	359
Age (mean ± SD)	75.79 ± 5.06	74.61 ± 7.15
Gender (% female)	49%	36.8%*
Years of education (mean ± SD)	16.02 ± 2.87	15.63 ± 3.01
ApoE ε4+ (% of total)	55 (26.4)	198 (55.2)*
Total PIB (% positive)	19 (42.1)	60 (68.3)*
Total AV45 (% positive)	80 (34.0)	94 (64.0)*
Total CSFAβ1-42 (% positive)	108 (38.9)	183 (74.3)*
Number of participants with multiple Aβ measurements	57	79
AV45 and CSF Aβ1-42	46	50
PIB and CSF Aβ1-42	11	32
AV45 and PIB	8	27
AV45, PIB, and CSF Aβ1-42	4	15

Key: Aβ, β-amyloid; ADNI, Alzheimer's Disease Neuroimaging Initiative; CSF, cerebrospinal fluid; MCI, mild cognitive impairment; NC, clinically normal older adults; PIB, Pittsburg Compound B; SD, standard deviation.
* $p < 0.01$ versus NC.

standardized uptake value ratio (SUVR) measure was derived by normalizing average retention values of 9 cortical regions (anterior cingulate, frontal, sensorimotor, lateral temporal, medial temporal, parietal and occipital cortex, occipital pole, and precuneus) to retention value of cerebellar cortex. For each participant, the SUVR was calculated from the average SUVR of scans taken at various time points from initial participant screen. For PIB, scans were performed at baseline (n = 20), month 12 (n = 84), month 24 (n = 78), month 36 (n = 40), and month 48 (n = 2). For AV45, scans were performed at month 36 (n = 7), month 48 (n = 95), month 60 (n = 73), or month 72 (n = 6).

2.5. Cerebrospinal fluid levels of Aβ1-42

CSF samples were obtained by individual centers, then banked and batch-processed using a standardized protocol, under the direction of Drs Leslie Shaw and John Trojanowski of the ADNI Biomarker Core at the University of Pennsylvania School of Medicine. Details regarding CSF collection and CSF Aβ1-42 measurements are provided in the ADNI procedural manual (http://adni.loni.usc.edu/methods/biomarker-analysis/) and in Shaw et al. (2009). CSF Aβ1-42 was measured using multiplex xMAP Luminex platform (Luminex Corporation, Austin, TX, USA) with Innogenetics (INNO-BIA AlzBio3, Ghent, Belgium) immunoassay kit-based research-use only reagents including monoclonal antibodies 4D7A3 (capture) and 3D6 (detector) for Aβ42. All CSF Aβ1-42 samples were taken within weeks of the first hippocampal volume measure.

2.6. Statistical analysis

Repeated measures of hippocampal volumes over 4 years were modeled using linear mixed-effects regression. To determine HAR, hippocampal volume was regressed on time from initial scan with both a random intercept and slope to estimate individual HAR, assuming a compound symmetry correlation structure. In a second step, HAR were then regressed on age, gender, APOE ε4 carrier status, WML, ICV, AV45, PIB, and CSF Aβ1-42 using ordinary least squares regression. The variance of each predictor was estimated using 500 bootstrap samples to account for the initial step of estimating individual HAR. Each predictor was evaluated both separately and in a full model, adjusting for all other predictors. An interaction between Aβ status and age was also considered, using the following thresholds for Aβ positivity: 1.11 SUVR for AV45, 1.5 SUVR for PIB, and 192 pg/mL for CSF Aβ1-42. Ridge regression was performed to evaluate the collective predictive ability of the Aβ measures while adjusting for high correlation between measures; the penalty term was selected via 10-fold cross validation. In the full model, a separate multivariable model was made using each of the Aβ variables because of the high correlation between the 3 measurements. The associations between predictors and HAR were assessed using Wald tests and R^2. Comparisons between MCI and NC participants on baseline variables were done using the Wilcoxon-Mann-Whitney test and Fisher exact test. Model fits were inspected by an analysis of the residuals. All statistics were done using R (v. 2.8.1, The R Foundation for Statistical Computing).

3. Results

3.1. Factors associated with HAR in NC participants

When tested separately in univariable models, only advanced age and increased Aβ levels were significantly associated with HAR in NC participants (Table 2). There was a trend toward a significant association between female gender and increased HAR ($p = 0.07$). Both WM hyperintensities ($p = 0.05$) and hypointensities ($p = 0.07$) also showed strong trends for positive correlation with HAR. Neither ICV nor ApoE ε4 genotype was significantly associated with HAR (Table 2). The 3 Aβ measures were highly correlated with each other (CSF Aβ1-42 vs. AV45 $r = -0.7835$, CSF Aβ1-42 vs. PIB $r = -0.6198$, AV45 vs. PIB $r = 0.7898$), and ridge regression analysis confirmed that including multiple Aβ measures in the multivariable regression did not increase our ability to predict HAR. Therefore, we

Table 2
Factors contributing to HAR in NC and MCI in univariable regression models

	Estimate	Standard error	T-value	*p*-value	R^2
Age					
NC	−8.14	3.457	−2.354	0.02*	0.02619
MCI	−2.92	3.282	−0.089	0.37	0.00222
Gender					
NC	−12.42	6.937	−1.79	0.07	0.01532
MCI	−17.74	6.740	−2.632	<0.001***	0.01904
ICV					
NC	1.89	3.492	0.538	0.591	0.001404
MCI	4.82	3.276	1.47	0.142	0.006019
ApoE ε4+					
NC	−11.42	7.7884	−1.448	0.15	0.01008
MCI	−38.11	6.281	−6.067	<0.001***	0.09347
WM hypointensities					
NC	−6.35	3.475	−1.826	0.07	0.01593
MCI	−1.51	3.285	−0.458	0.65	0.00059
WM hyperintensities					
NC	−6.81	3.472	−1.961	0.05	0.01376
MCI	−2.09	3.284	−0.636	0.53	0.001671
AV45					
NC	−49.14	24.29	−2.023	0.047**	0.08497
MCI	−80.03	22.34	−3.682	<0.001***	0.1829
PIB					
NC	−99.34	29.11	−3.412	<0.001**	0.4065
MCI	−77.40	23.146	−3.344	0.00145**	0.1616
CSF Aβ1-42					
NC	0.21	0.08524	2.460	0.02*	0.05402
MCI	0.39	0.07812	5.00	<0.001***	0.1214

Key: Aβ, β-amyloid; CSF, cerebrospinal fluid; HAR, hippocampal atrophy rate; ICV, intracranial volume; MCI, mild cognitive impairment; NC, clinically normal older adults; PIB, Pittsburg Compound B; WM, white matter.
* $p < 0.05$, ** $p < 0.01$, and *** $p < 0.001$.

Table 3
Factors contributing to HAR in NC and MCI in a multivariable regression model

	Estimate	Standard error	T-value	*p*-value
Age				
NC	−1.113	0.715	−1.557	0.12
MCI	−4.81	0.804	−0.598	0.55
Gender				
NC	−3.03	9.96	−0.332	0.74
MCI	−12.49	11.33	−1.102	0.27
ICV				
NC	0.000	0.000	0.778	0.44
MCI	0.000	0.000	0.781	0.44
ApoE ε4+				
NC	0.126	14.33	0.009	0.99
MCI	−29.74	11.14	−2.70	0.008**
WM hypointensities				
NC	0.000	0.000	−0.736	0.46
MCI	0.000	0.007	−0.018	0.99
CSF Aβ1-42				
NC	0.220	0.093	−2.371	0.02*
MCI	0.256	0.100	2.546	0.01*

Adjusted $R^2 = 0.03072$ for NC, $R^2 = 0.1827$ for MCI.
Key: Aβ, β-amyloid; CSF, cerebrospinal fluid; HAR, hippocampal atrophy rate; ICV, intracranial volume; MCI, mild cognitive impairment; NC, clinically normal older adults; WM, white matter.
* $p < 0.05$, ** $p < 0.01$, and *** $p < 0.001$.

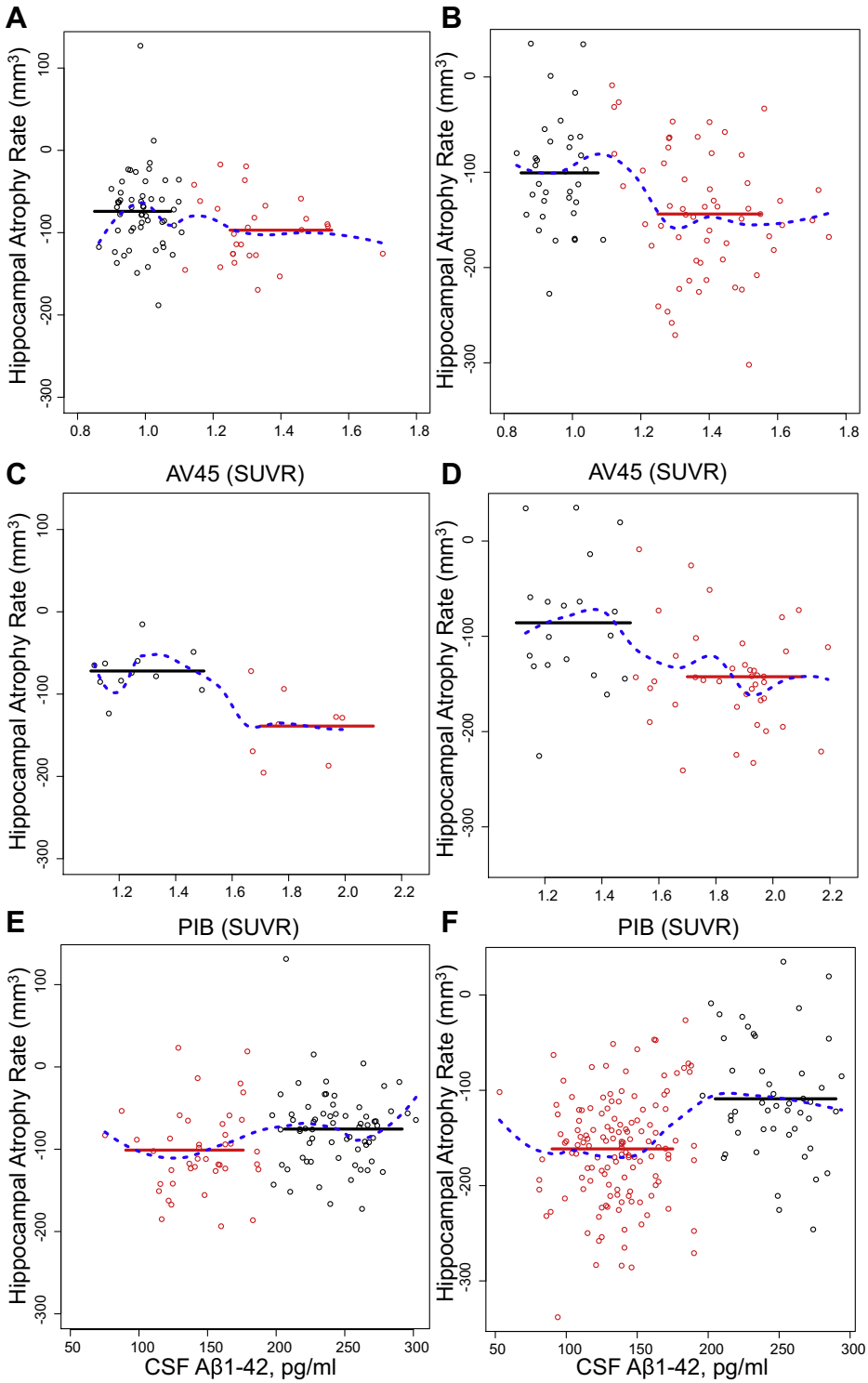

Fig. 1. The effect of Aβ levels on HAR in NC and MCI patients. Scatter plots showing the correlation between 3 different measures of Aβ levels (AV45, A and B; PIB, C and D; CSF Aβ1-42, E and F) and HAR in NC (A–C) and MCI (D–F) participants. Regression analysis (blue dotted line) shows the best fit as a sigmoid that delineates 2 subpopulations of participants, Aβ+ (red circles) and Aβ− (black circles). The threshold values used are 1.11 SUVR for AV45, 1.5 SUVR for PIB, and 192 pg/mL for CSF Aβ1-42. Solid red and black lines represent the mean values for the Aβ+ (red) and Aβ− (black) subgroups. Abbreviations: Aβ, β-amyloid; CSF, cerebrospinal fluid; HAR, hippocampal atrophy rate; MCI, mild cognitive impairment; NC, clinically normal older adults; SUVR, standardized uptake value ratio.

generated a multivariable model using a single Aβ measure, CSF Aβ1-42. In this model, only Aβ levels were positively associated with HAR when adjusting for effects of all variables (Table 3). Thus, the effects of gender, age, and WML are likely confounded by brain Aβ levels because their associations with HAR go away in a multivariable model accounting for Aβ. Further, in separate multivariable models using either PIB or AV45 as the Aβ measure, Aβ levels were significantly associated with HAR when adjusting for effects of all

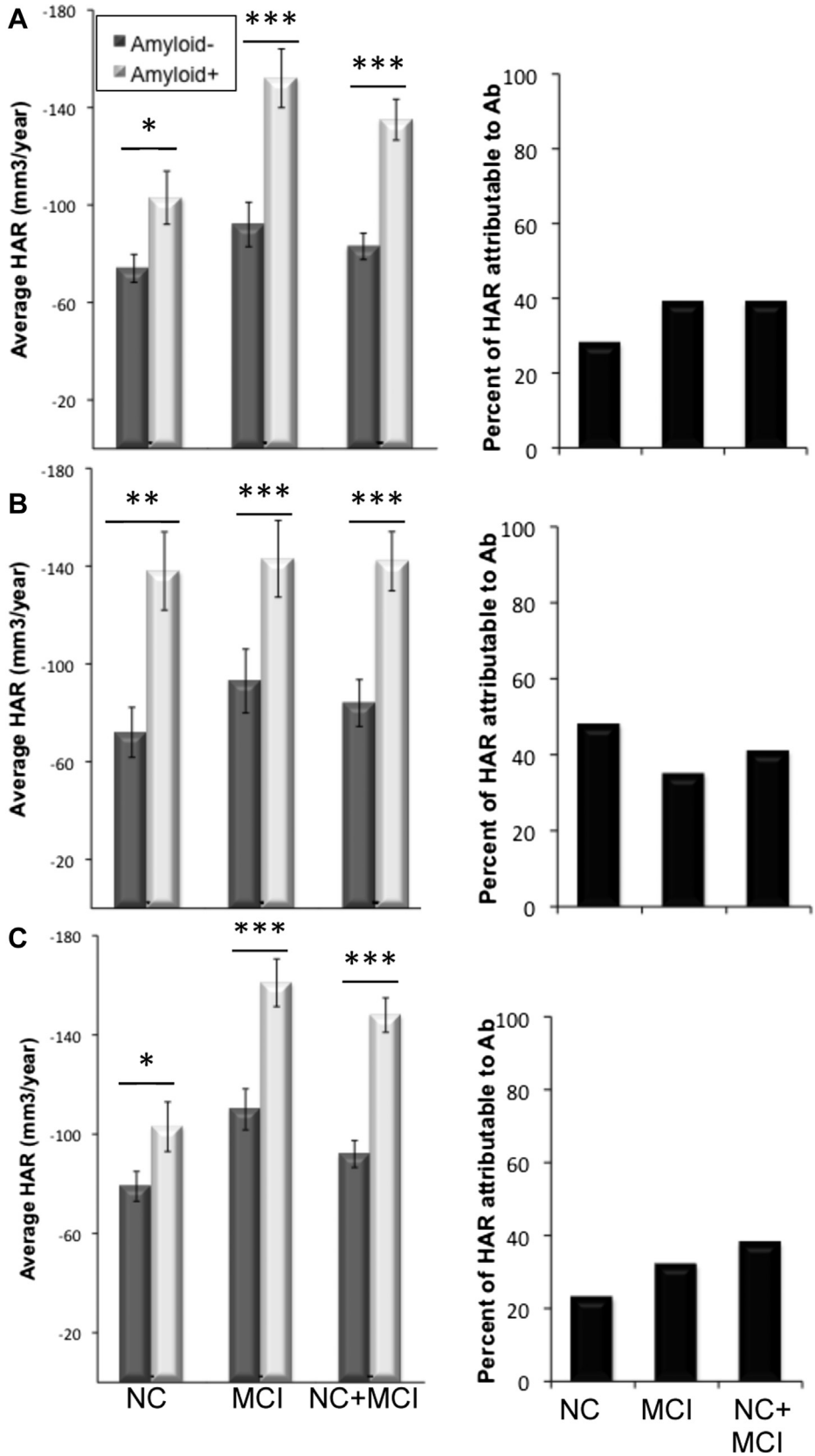

Fig. 2. HAR attributable to Aβ in NC and MCI patients. Bar plots showing average HAR in Aβ+ (dark bars) and Aβ− (light bars) subgroups of NC, MCI, and the combined cohorts (NC + MCI) for AV45 (A), PIB (B), and CSF Aβ1-42 (C). Black bars show the percentage of total HAR attributable to Aβ for each Aβ measure. * $p < 0.01$, ** $p < 0.001$, and *** $p < 0.0001$. Abbreviations: HAR, hippocampal atrophy rate; MCI, mild cognitive impairment; NC, clinically normal older adults.

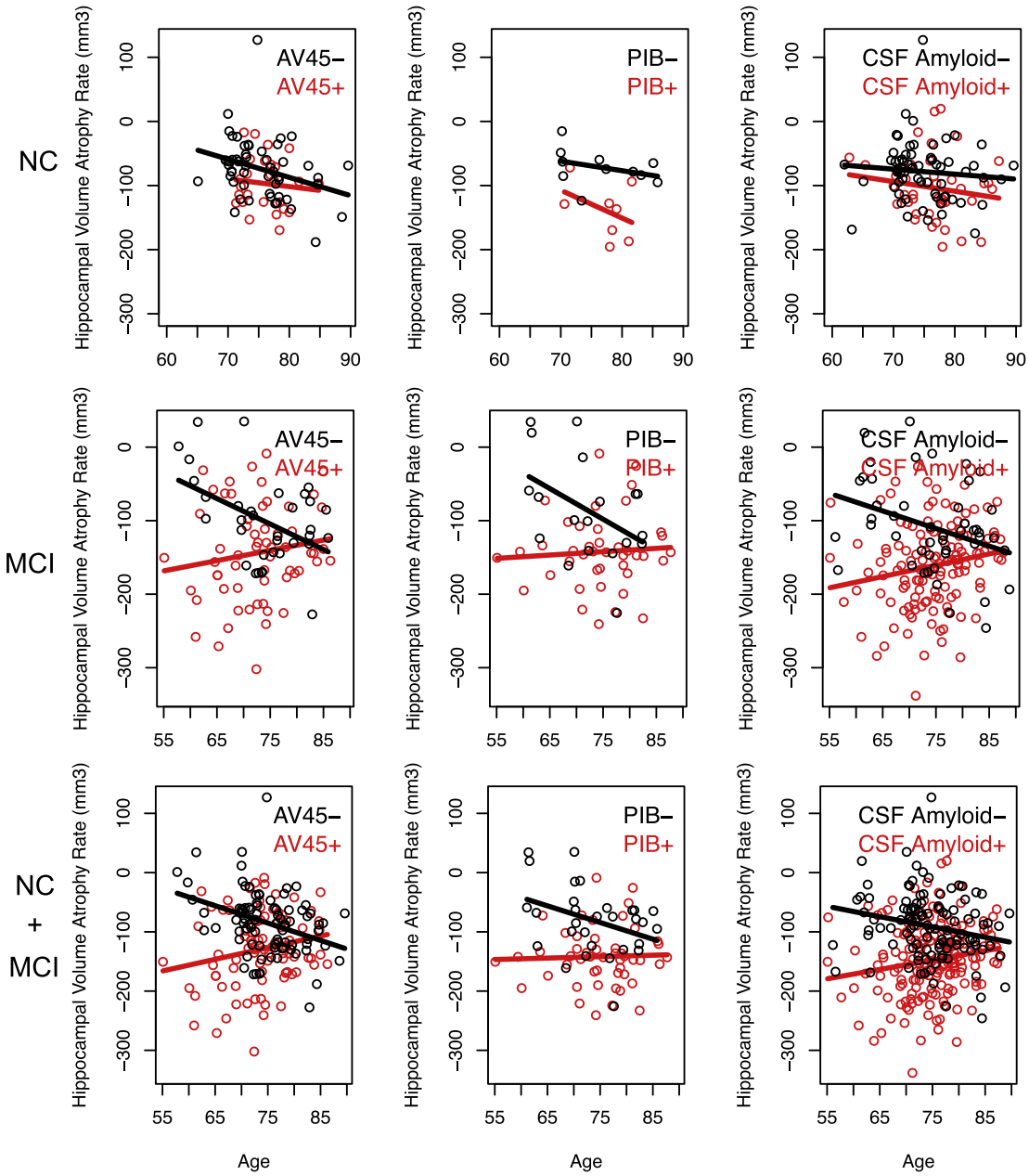

Fig. 3. The effect of age and Aβ status on HAR. Scatter plots showing the effect of age on HAR in a cohort of NC, MCI, or NC + MCI participants classified as Aβ+ (red circles) or Aβ− (black circles) according to levels of AV45, PIB, or CSF Aβ1-42. Linear regression analyses (solid black and red lines) show a significant interaction between age and Aβ status in MCI participants ($p = 0.007$ for AV45, $p = 0.03$ for PIB, and $p = 0.001$ for CSF Aβ1-42) as well as in the combined cohort of NC + MCI ($p < 0.001$ for AV45, $p = 0.07$ for PIB, and $p = 0.002$ for CSF Aβ1-42) but not in NC participants ($p = 0.56$ for AV45, $p = 0.44$ for PIB, and $p = 0.70$ for CSF Aβ1-42). Abbreviations: Aβ, β-amyloid; CSF, cerebrospinal fluid; HAR, hippocampal atrophy rate; MCI, mild cognitive impairment; NC, clinically normal older adults; PIB, Pittsburg Compound B.

variables ($p = 0.05$ for AV45 and $p = 0.006$ for PIB), confirming that the association of Aβ and HAR holds up when accounting for other variables that may affect HAR.

3.2. Factors associated with HAR in MCI participants

In MCI participants, female gender, ApoE ε4+ status, and all 3 Aβ measures were significantly associated with increased HAR (Table 2) in univariable models. As with NC participants, Aβ levels measured by all 3 Aβ measures showed the strong association with HAR (Table 2). In the MCI cohort, there was no significant association between HAR and age, ICV, or WML (Table 2). Using a multivariable regression model, with CSF Aβ1-42 as the Aβ measure, only ApoE ε4 status and Aβ level retained a significant association with HAR (Table 3). Thus, the effect of gender on HAR is likely confounded by ApoE ε4 and/or Aβ levels in MCI participants. We also found a significant association between Aβ and HAR in multivariable regression models using each of the other Aβ measures ($p = 0.03$ for AV45 and $p = 0.02$ for PIB).

In summary, although multiple variable are associated with HAR in univariable models, only Aβ levels are significantly associated with HAR in NC in a model adjusting for effects of age, gender, WMLs, and ICV in a single model. In MCI, Aβ levels and ApoE ε4+ genotype are significantly associated with HAR in both the univariable and multivariable models. Thus, a comparison of univariable and multivariable models reveals that the effects of such

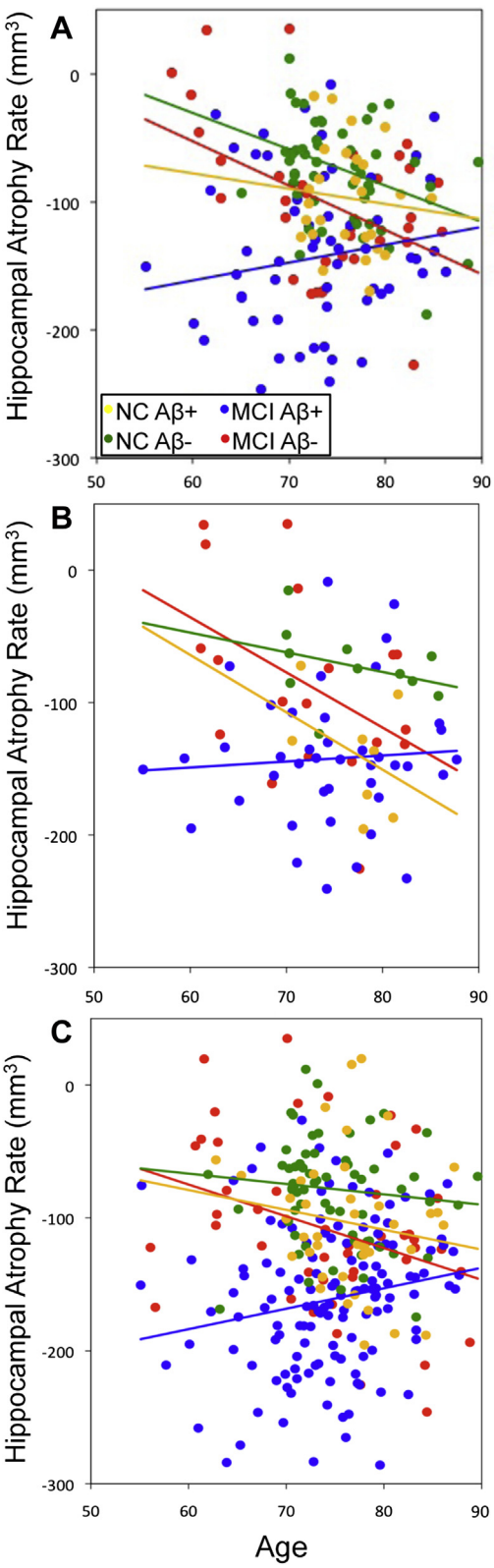

Fig. 4. The effect of diagnosis on age-related HAR in Aβ+ and Aβ− subpopulations. Scatter plots showing the effect of age on HAR in NC and MCI participants dichotomized into Aβ+ and Aβ− subgroups using AV45 (A), PIB (B), or CSF Aβ1-42 (C) levels. Regression analyses for each subgroup are represented by solid lines. Abbreviations: Aβ, β-amyloid; CSF, cerebrospinal fluid; HAR, hippocampal atrophy rate; MCI, mild cognitive impairment; NC, clinically normal older adults; PIB, Pittsburg Compound B.

variables as age and gender on HAR can be accounted for by brain Aβ levels in NC and MCI participants, and additionally by ApoE ε4 status in MCI participants. In both NC and MCI, Aβ levels, measured by PIB, AV45, or CSF Aβ1-42, showed the strongest association with HAR. Thus, in both NC and MCI participants, Aβ levels show the most robust association with HAR even when multiple demographic and neuroimaging factors are taken into account.

3.3. The effect of age and Aβ status on HAR

We next tested for differential age-related effects on HAR in participants classified as Aβ positive (Aβ+) or Aβ negative (Aβ−) according to previously established thresholds (Aizenstein et al., 2008; Jack et al., 2008a; Johnson et al., 2013; Joshi et al., 2012; Mormino et al., 2012; Shaw et al., 2009; Weigand et al., 2011). We found significant HAR in both the Aβ+ and Aβ− subgroups, with higher age-adjusted HAR in the Aβ+ cohort for both NC and MCI (Fig. 1). Next, we calculated the percentage of HAR that was accounted for Aβ status as the difference in HAR between the Aβ+ and Aβ− subgroups, and found that most of the HAR was not attributable to Aβ status in NC, MCI, or a combined cohort (Fig. 2). In MCI alone, or a combined cohort of NC + MCI, there was a significant interaction between age and Aβ status, with a stronger association between age and HAR in the Aβ− subgroup ($p = 0.007$ for AV45 and CSF Aβ1-42 and $p = 0.03$ for PIB) (Fig. 3). In fact, for Aβ+ participants, there was a slight decrease in HAR associated with increased age (Fig. 3). Thus, the association between age and HAR depends on Aβ status in MCI participants, likely because this represents a group in which disease accelerates HAR and eclipses the effect of age alone.

Based on our results, we conducted a power analysis of a hypothetical 2-year clinical trial using HAR as an outcome measure for testing drug effect, with hippocampal volume measured every 6 months. We found that 1591 NC participants per arm would be required to detect a 25% slowing of Aβ-related HAR. However, detecting a 25% slowing of total HAR only in Aβ+ or Aβ− NC would require 84 or 210 participants per arm, respectively. Thus, the use of Aβ status as inclusion criterion in an NC cohort confers adequate statistical power using fewer participants.

3.4. The effect of diagnosis on age-related HAR in Aβ+ and Aβ− subgroups

To assess the contribution of participant diagnosis to age-related HAR, we determined whether participants who share the same Aβ status differ in the effect of age on HAR by testing for an age × diagnosis interaction separately in the Aβ+ and Aβ− subgroups (Fig. 4). As stated previously, we found no significant association between age and HAR using the full model. Furthermore, we found no significant interaction between age and diagnosis in Aβ+ participants ($p = 0.44$) or Aβ− participants ($p = 0.64$) (Fig. 4). To confirm whether participant diagnosis is significantly associated with overall HAR, we performed linear regression on the Aβ+ and Aβ− subgroups separately, using diagnosis, age, gender, and ApoE ε4 status as explanatory variables and HAR as the outcome variable. In the Aβ+ cohort, ApoE ε4+ status ($p = 0.02$), MCI diagnosis ($p < 0.001$), and female gender ($p = 0.05$) were all associated with increased HAR, whereas in the Aβ− cohort, only age and MCI diagnosis ($p < 0.001$) were significantly associated with increased HAR. We conclude that Aβ status, regardless of diagnosis, is the variable that determines the trajectory of age-related HAR. This finding supports the use of Aβ

status as a defining criteria for assessing features of neurodegeneration in subpopulations of participants in future studies.

4. Discussion

The major findings are as follows: (1) in NC participants, only Aβ levels were significantly correlated with HAR when adjusting for age, gender, Apo ε4 genotype, WMLs, and ICV in a multivariable model; (2) in MCI participants, both Aβ levels and ApoE ε4+ genotype were significantly associated with HAR in the multivariable model; (3) there was significant HAR in both the Aβ+ and Aβ− NC and MCI subgroups, and Aβ+ participants had significantly higher HAR than Aβ−; (4) in MCI or the combined cohort of NC + MCI, there was a significant interaction between age and Aβ status, with a stronger association between age and HAR in the Aβ− subgroup, indicating that age had a significantly higher association with HAR in Aβ− participants than in Aβ+ participants in MCI but not NC; and (5) less than half of age-related HAR was attributable to Aβ levels in NC, MCI, or a combined cohort of NC and MCI participants.

These findings have important implications for the design of future studies examining the association between brain volume, aging, and AD related biomarkers. Modeling HAR using multiple volume measurements over a 4-year period in a linear regression model allowed us to capture volume changes over a longer period than many other studies, while better controlling for random variations in volume measurement over time. Compared with previous cross-sectional studies that reported an association of age and hippocampal volume in older adult NC (Brickman et al., 2008; Jack et al., 1997), we find no association between HAR and age in an adjusted multivariable model. Our work confirms that of previous studies showing a correlation between Aβ levels and HAR in older adult NC (Fjell et al., 2010; Schott et al., 2010), and extends these findings using HAR measured longitudinally over a longer time span, with multiple data points per participant.

Our inclusion of multiple variables in a single, multivariable regression model reveals novel associations between the variables used and HAR. For NC participants, the difference between the univariable and multivariable models were as follows: (1) age is only significantly associated with HAR in the univariable model; and (2) the trend-level associations of gender and WML found in the univariable models do not hold up in the multivariable model. Thus, future studies examining associations between gender, age, and WML and HAR are likely to overestimate these associations if they do not account for Aβ levels and other variables in their analyses.

For MCI but not NC participants, we found a significant association between gender and HAR in the univariable model but not the multivariable model. However, the difference in effect size in NC ($r^2 = 0.014$) versus MCI ($r^2 = -0.019$) for this association is negligible, and there is a trend-level ($p = -0.07$) association between gender and HAR in NC. Therefore, it is possible that the difference in significance between the 2 cohorts is because of the fact that the MCI cohort is 73% larger than the NC cohort (Table 1), conferring greater statistical power to analyses done in the MCI group. Further studies using a larger NC cohort are needed to confirm this finding. The effect of gender on HAR goes away when adjusting for the other variables in the multivariable models (Table 2), suggesting it is confounded by age, Aβ, and/or ApoE ε4 genotype. We conclude that gender has no significant influence, and this finding emphasizes the importance of controlling for confounding variables in future studies examining links between gender and brain atrophy.

Another important implication of our findings is for the design of clinical trials that test the efficacy of Aβ-altering therapies in NC and MCI individuals, as also discussed in (Holland et al., 2012a, 2012b). We found that, although age-adjusted HAR is higher in the Aβ+ group for both NC and MCI, less than half of HAR is attributable to Aβ status. Furthermore, subsetting participants into Aβ+ and Aβ− subgroups can drastically reduce the number of participants needed to achieve adequate statistical power. According to our sample size analysis, compared with a study using a general NC cohort, a study using only Aβ+ participants would require a greater than 18-fold reduction in the number of participants (84 vs. 1591 participants per arm), and a study using only Aβ− participants would require a greater than 7-fold reduction in the number of participants (210 vs. 1591 participants per arm) to obtain the same level of statistical power. Our study extends previous findings by measuring the effect of age on HAR separately in Aβ+ and Aβ− subgroups. It demonstrates that most of the hippocampal atrophy is accounted for by variables other than Aβ and/or age. Because treatments directed at reducing Aβ would not be expected to slow the non-Aβ-related HAR, our results can inform future clinical trials on expected levels of HAR reduction NC and MCI participants.

Although this study provides important new information about the factors contributing to HAR, it has some limitations. First, the ADNI cohort may not accurately reflect the population in terms of HAR in normal control subjects (Whitwell et al., 2012). ADNI exclusion criteria limit the range of values available for some variables we studied here. For example, ADNI does not include participants with cerebrovascular disease, which biases the WML values to a narrow range of values. This type of selection bias could lead us to underestimate the significance of the association of some variables with HAR. Thus, although these findings are highly relevant to the AD field and those conducting clinical research on an AD-focused aging population, it limits our ability to generalize to a population of older adults. Furthermore, the smaller cohort size of NC versus MCI participants used in our study increases the risk that we will overestimate the contributions of specific variables to HAR in MCI or underestimate the same associations in NC.

Another limitation is the timing of the brain Aβ measurement in relation to the structural MRIs used to calculate HAR. The Aβ measure is a single snapshot taken at variable intervals with respect to hippocampal volume measurements. In our study, all CSF Aβ1-42 samples were taken before the initial volume measurement, all AV45 scans were done after the final volume measurement, and PIB measurements were taken at variable intervals within the same timeframe as the volume measurements. However, the different Aβ measurements were still highly correlated with each other in terms of their association with HAR and showed a high level of consistency in terms of the percentage of HAR attributable to Aβ status. Finally, because we calculated HAR using a linear model, we may have overestimated contributions of Aβ and age to the extent that accelerated and/or nonlinear HAR were present in the data (Schuff et al., 2012).

In conclusion, this study shows that the presence of brain Aβ is a major predictor of HAR in older adults, but that most HAR in older adult NC and MCI participants is not associated with the presence of Aβ and is likely to be a consequence of aging and other unknown factors. The findings emphasize the importance of including longitudinal volume measurements in studies of brain atrophy and of simultaneously accounting for the contributions of multiple variables to brain atrophy. Our results demonstrate the importance of accounting for brain Aβ accumulation when designing clinical studies of AD drugs, and therefore have important implications for the design and statistical powering of future clinical trials testing the efficacy of anti-Aβ therapeutics for AD.

Disclosure statement

To fully address any financial relationships of the coauthors that may lead to a perceived conflict of interest, we would like to make the following disclosures. Dr Shaw reports grants from NIA/NIH during the conduct of the study. Dr Shaw previously was consultant for Innogenetics and collaborates on quality assessment activities as part of the Alzheimer's Disease Neuroimaging Initiative. Dr Aisen has been a consultant for NeuroPhage; 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, Astellas, Dainippon, Biomarin, Solvay, Otsuka, Daiichi, AstraZeneca, Janssen, Medivation, Inc, Ichor, Toyama, Lundbeck, Biogen Idec, iPerian, Probiodrug, Somaxon, Biotie, Anavex, and Kyowa Hakko Kirin Pharma. In addition, Dr Aisen has grants or pending grants from Lilly, Baxter, NIA, and FNIH. Dr Weiner has been on scientific advisory boards for Pfizer and BOLT Inter-national; has been a consultant for Pfizer Inc, Janssen, KLJ Associates, Easton Associates, Harvard University, inThought, INC Research, Inc, University of California, Los Angeles, Alzheimer's Drug Discovery Foundation and Sanofi-Aventis Groupe; has received funding for travel from Pfizer, AD PD meeting, Paul Sabatier University, Novartis, Tohoku University, MCI Group, France, Travel eDreams, Inc, Neuroscience School of Advanced Studies (NSAS), Danone Trading, BV, CTAD ANT Congres; serves as an associate editor of Alzheimer's & Dementia; has received honoraria from Pfizer, Tohoku University, and Danone Trading, BV; has research support from Merck, Avid, DOD, and VA; and has stock options in Synarc and Elan.

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