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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 MRI, and the contribution of age, gender, ApoE ϵ 4 status, intracranial volume, white matter lesions, and β -amyloid (A β) levels to HAR was

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determined using linear regression. Age-related effects of HAR were compared in A β positive (A β +) and A β negative (A β –) participants. Age and A β levels had independent effects on HAR in NC, while gender, ApoE ϵ 4 status, and A β levels were associated with HAR in MCI. In multivariable models, A β levels were associated with HAR in NC; ApoE ϵ 4 and A β levels were associated with HAR in MCI. In MCI, age was a stronger predictor of HAR in A β – versus A β + participants. HAR was higher in A β + participants, but the majority of HAR was due to factors other than A β status. Age-related effects on HAR did not differ between NC versus MCI participants with the same A β status. Therefore we conclude that even when accounting for other covariates, A β status, and not age, is a significant predictor of HAR; and that the majority of HAR is not accounted for by A β status in either NC or MCI.

Keywords

Alzheimer's disease; normal aging; hippocampal atrophy rate; longitudinal study; β -amyloid

1. Introduction

Alzheimer's disease (AD), characterized by plaques of β -amyloid (A β), tangles of tau/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., 2013; Jack et al., 2010; 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 lifespan 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 due to presymptomatic AD pathology. Previous studies have been limited by several factors, including the lack of longitudinal hippocampal volume measurements, the exclusion of brain A β levels from the analyses, and focus on a singular contributing factor such as ApoE ϵ 4 or age without the inclusion of models accounting for multiple variables simultaneously. Since studies 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 non-demented cohort of older adults.

Accumulation of fibrillar brain A β can be directly assessed *in vivo* by positron emission tomography (PET) using the radiotracers Pittsburgh 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 A β 1–42 (CSFA β 1–42) (Shaw et al., 2009). The 20–30% of older adult, cognitively-normal individuals with high levels of brain A β 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 A β 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 non-demented participants. However, sensitivity in linking brain A β 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 apolipoprotein E (ApoE) genotype, gender, white matter lesions (WML), and intracranial volume (ICV). The ϵ 4 allele of ApoE gene is associated with increased risk of AD and increased deposition of A β , and normal older adults ApoE ϵ 4+ homozygotes have a higher rate of brain atrophy (Crivello et al., 2010) and low levels of CSFA β 1–42 (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 A β status, with HAR in NC and MCI participants in ADNI.

2. Participants and Methods

Participants

The ADNI was launched in 2003 by the National Institute on Aging (NIA), the National Institute of Biomedical Imaging and Bioengineering (NIBIB), the Food and Drug Administration (FDA), private pharmaceutical companies and non-profit organizations, as a \$60 million, 5-year public-private partnership. The primary goal of ADNI has been to test whether serial 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 UCSF. ADNI is the result of efforts of many co-investigators 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 three protocols have recruited over 1500 adults, ages 55 to 90, 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 was downloaded from the ADNI database (www.loni.ucla.edu/ADNI). We included ADNI 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 A β 1–42, PIB, or AV45 imaging (Table 1). The number of participants with multiple A β measurements is listed in Table 1.

T1-weighted Magnetic Resonance Imaging (MRI)

Participants underwent a standardized 1.5 Tesla MRI protocol (<http://www.loni.ucla.edu/ADNI/Research/Cores/index.shtml>) 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).

FreeSurfer Longitudinal processing

Automated hippocampal volume measures were performed with FreeSurfer software package version 4.4. To reduce confounding effects of intra-participant morphological variability, each participant's data series was processed by FreeSurfer longitudinal workflow (Fischl et al., 2002; Fischl et al., 2004), and see <http://surfer.nmr.mgh.harvard.edu/fswiki/LongitudinalProcessing>. Details of quality control procedures are posted online (<http://www.loni.ucla.edu/twiki/pub/ADNI/ADNIPostProc/UCSFFreeSurferMethodsSummary.pdf>).

PET Imaging

PIB and AV45 images were collected at multiple sites. Participants were injected with 15 mCi PIB or 10 mCi AV45, four dynamic acquisition frames were obtained 50–70 minutes post injection and coregistered to one another, averaged, interpolated to a uniform image and voxel size (160×106×96, 1.5mm³), and smoothed to a uniform resolution (8mm FWHM). See also: adni.loni.ucla.edu/about-data-samples/image-data. A mean cortical 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).

CSF A β 1–42

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 CSFA β 1–42 measurements are provided in the ADNI procedural manual (www.adni-info.org) and in (Shaw et al., 2009). CSFA β 1–42 was measured using multiplex xMAP Luminex platform (Luminex Corporation, Austin, TX) with Innogenetics (INNO-BIA AlzBio3, Ghent, Belgium) immunoassay kit-based research-use only reagents including monoclonal antibodies 4D7A3 (capture) and 3D6 (detector) for A β 42. All CSFA β 1–42 samples were taken within weeks of the first hippocampal volume measure.

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 since 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 ϵ 4 carrier status, WML, ICV, AV45, PIB, and CSFA β 1–42 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 A β status and age was also considered, using the following thresholds for A β positivity: 1.11 SUVR for AV45, 1.5 SUVR for PIB, and 192 pg/ml for CSFA β 1–42. Ridge regression was performed to evaluate the collective predictive ability of the A β 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 A β variables due to 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's 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

Factors associated with HAR in NC Participants

When tested separately in univariable models, only advanced age and increased A β levels were significantly associated with HAR in NC participants (Table 2). There was a trend towards 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 ϵ 4 genotype was significantly associated with HAR (Table 2). The three A β measures were highly correlated with each other (CSFA β 1–42 versus AV45 $r=-0.7835$, CSFA β 1–42 versus PIB $r=-0.6198$, AV45 versus PIB $r=0.7898$) and ridge regression analysis confirmed that including multiple A β measures in the multivariable regression did not increase our ability to predict HAR. Therefore, we generated a multivariable model using a single A β measure, CSFA β 1–42. In this model, only A β 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 A β levels since their associations with HAR go away in a multivariable model

accounting for A β . Further, in separate multivariable models using either PIB or AV45 as the A β measure, A β levels were significantly associated with HAR when adjusting for effects of all variables ($p=0.05$ for AV45, $p=0.006$ for PIB), confirming that the association of A β and HAR holds up when accounting for other variables that may affect HAR.

Factors associated with HAR in MCI Participants

In MCI participants, female gender, ApoE $\epsilon 4+$ status, and all three A β measures were significantly associated with increased HAR (Table 2) in univariable models. As with NC participants, A β levels measured by all 3 A β 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 CSFA $\beta 1-42$ as the A β measure, only ApoE $\epsilon 4$ status and A β level retained a significant association with HAR (Table 3). Thus, the effect of gender on HAR is likely confounded by only ApoE $\epsilon 4$, and/or A β levels in MCI participants. We also found the significant association between A β and HAR in multivariable regression models using each of the other A β measures ($p=0.03$ for AV45, $p=0.02$ for PIB).

In summary, although multiple variable are associated with HAR in univariable models, only A β levels are significantly associated with HAR in both NC and MCI in a model adjusting for effects of age, gender, WMLs, and ICV in a single model. In MCI, ApoE $\epsilon 4+$ genotype is also 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 variables as age and gender on HAR can be accounted for by brain A β levels in NC and MCI participants, and additionally by ApoE $\epsilon 4$ status in MCI participants. In both NC and MCI, A β levels, measured by PIB, AV45, or CSF A $\beta 1-42$, showed the strongest association with HAR. Thus, in both NC and MCI participants, A β levels show the most robust association with HAR even when multiple demographic and neuroimaging factors are taken into account.

The effect of age and A β status on HAR

We next tested for differential age-related effect on HAR in participants classified as A β positive (A $\beta+$) or A β negative (A $\beta-$) 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 A $\beta+$ and A $\beta-$ subgroups, with higher age-adjusted HAR in the A $\beta+$ cohort for both NC and MCI (Figure 1). Next, we calculated the percent of HAR that was accounted for by A β status as the difference in HAR between the A $\beta+$ and A $\beta-$ subgroups, and found that the majority of HAR was not attributable to A β status in NC, MCI, or a combined cohort (Figure 2). In MCI alone, or a combined cohort of NC+MCI, there was a significant interaction between age and A β status, with a stronger association between age and HAR in the A $\beta-$ subgroup ($p=0.007$ for AV45 and CSFA $\beta 1-42$, $p=0.03$ for PIB) (Figure 3). In fact, for A $\beta+$ participants, there was a slight decrease in HAR associated with increased age (Figure 3). Thus, the association between age and HAR depends on A β 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 two-year clinical trial using HAR as an outcome measure for testing drug effect, with HA measurements performed every 6 months. We found that 1591 NC participants per arm would be required to detect a 25% slowing of A β -related HAR. However, detecting a 25% slowing of total HAR only in A β + or A β - NC would require 84 or 210 participants per arm, respectively. Thus, the use of A β status as inclusion criterion in a NC cohort confers adequate statistical power using fewer participants.

The effect of diagnosis on age-related HAR in A β + and A β - subgroups

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

4. Discussion

The major findings are (1) In NC participants, only A β levels were significantly correlated with HAR when adjusting for age, gender, Apo $\epsilon 4$ genotype, WMLs and ICV in a multivariable model; (2) In MCI participants, both A β levels and ApoE $\epsilon 4$ genotype were significantly associated with HAR in the multivariable model; (3) There was significant HAR in both the A β + and A β - NC and MCI subgroups, and A β + participants had significantly higher HAR than A β -; (4) In MCI or the combined cohort of NC+MCI, there was a significant interaction between age and A β status, with a stronger association between age and HAR in the A β - subgroup, indicating that age had a significantly higher association with HAR in A β - participants than in A β + participants in MCI but not NC; (5) Less than half of age-related HAR was attributable to A β 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 time period in a linear regression model allowed us to capture volume changes over a longer time period than many other studies, while better controlling for random variations in volume measurement over time. Compared to 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 A β 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: (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 A β 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 two cohorts is due to 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, A β , and/or ApoE ϵ 4 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 A β -altering therapies in NC and MCI individuals, as also discussed in (Holland et al., 2012a; Holland et al., 2012b). We found that, although age-adjusted HAR is higher in the A β + group for both NC and MCI, less than half of HAR is attributable to A β status. Furthermore, subsetting participants into A β + and A β - subgroups can drastically reduce the number of participants needed to achieve adequate statistical power. According to our sample size analysis, compared to a study using a general NC cohort, a study using only A β + participants would require a greater than 18 fold reduction in the number of participants (84 verses 1591 participants per arm), and a study using only A β - participants would require a greater than 7 fold reduction in the number of participants (210 verses 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 A β + and A β - subgroups. It demonstrates that the majority of hippocampal atrophy is accounted for by variables other than A β and/or age. Since treatments directed at reducing A β would not be expected to slow the non-A β -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 controls (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, while 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 A β measurement in relation to the structural MRIs used to calculate HAR. The A β measure is a single snapshot taken at variable intervals with respect to hippocampal volume measurements. In our study, all CSF A β 1–42 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 A β 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 percent of HAR attributable to A β status. Finally, because we calculated HAR using a linear model, we may have overestimated contributions of A β 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 A β 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 A β 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 A β 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-A β therapeutics for AD.

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Highlights

- We examine effects of multiple variables on longitudinal HAR in NC and MCI.
- Multivariable linear regression analysis revealed novel associations with HAR.
- In MCI there was a significant interaction between age and A β status.
- Less than half of age-related HAR was attributable to A β levels in NC and MCI.
- Our findings can inform the design of clinical trials of anti-A β therapies for AD.

Figure 1. The effect of A β levels on HAR in NC and MCI

Scatter plots showing the correlation between 3 different measures of A β levels (AV45, **A and D**; PIB, **B and E**; CSFA β 1–42, **C 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 two subpopulations of participants, A β + (red squares) and A β – (black squares). The threshold values used are 1.11 SUVR for AV45, 1.5 SUVR for PIB, and 192 pg/ml for CSFA β 1–42. Solid red and black lines represent the mean values for the A β + (red) and A β – (black) subgroups.

Figure 2. HAR attributable to Aβ in NC and MCI

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, ***p<0.0001.

Figure 3. The effect of age and A β status on HAR

Scatter plots showing the effect of age on HAR in a cohort of NC, MCI, or NC+MCI participants classified as A β + (red circles) or A β - (black circles) according to levels of AV45, PIB, or CSFA β 1–42. Linear regression analyses (solid black and red lines) show a significant interaction between age and A β status in MCI participants ($p=0.007$ for AV45, $p=0.03$ for PIB, and $p=0.001$ for CSFA β 1–42) 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 A β 1–42), but not in NC participants ($p=0.56$ for AV45, $p=0.44$ for PIB, and $p=0.70$ for CSF A β 1–42).

Figure 4. The effect of diagnosis on age-related HAR in A β + and A β - subpopulations
 Scatter plots showing the effect of age on HAR in NC and MCI participants dichotomized into A β + and A β - subgroups using AV45 (A), PIB (B), or CSF A β 1–42 (C) levels. Regression analyses for each subgroup are represented by solid lines.

Table 1

Demographics of NC and MCI ADNI participants used in this study

	NC	MCI
Number of participants	208	359
Age (mean $\pm$ SD)	75.79 $\pm$ 5.06	74.61 $\pm$ 7.15
Gender (% Female)	49%	36.8% *
Years of Education (mean $\pm$ SD)	16.02 $\pm$ 2.87	15.63 $\pm$ 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 CSF Aβ1–42 (% 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

*
p<0.01 versus NC

Table 2

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

	Estimate	Std. 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 Hypo					
NC	-6.35	3.475	-1.826	0.07	0.01593
MCI	-1.51	3.285	-0.458	0.65	0.00059
WM Hyper					
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

* p<0.05,
** p<0.01,
*** p<0.001

Table 3

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

	Estimate	Std. 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 Hypo				
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.*
p<0.05,**
p<0.01,***
p<0.001