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Sex Differences in the Association between AD Biomarkers and Cognitive Decline

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Abstract

Women are disproportionately affected by Alzheimer's disease (AD) in terms of both disease prevalence and severity. Previous autopsy work has suggested that, in the presence of AD neuropathology, females are more susceptible to the clinical manifestation of AD. This manuscript extends that work by evaluating whether sex alters the established associations between cerebrospinal fluid (CSF) biomarker levels and brain aging outcomes (hippocampal volume, cognition). Participants were drawn from the Alzheimer's Disease Neuroimaging Initiative (ADNI) and included individuals with normal cognition (n=348), mild cognitive impairment (n=565), and AD (n=185). We leveraged mixed effects regression models to assess the interaction between sex and baseline cerebrospinal fluid biomarker levels of amyloid-β42 (Aβ-42) and total tau on cross-sectional and longitudinal brain aging outcomes. We found a significant interaction between sex and Aβ-42 on longitudinal hippocampal atrophy (p=0.002), and longitudinal decline in memory (p=0.017) and executive function (p=0.025). Similarly, we observed an interaction between sex and total tau level on longitudinal hippocampal atrophy (p=0.008), and longitudinal decline in executive function (p=0.034). Women with Aβ-42 and total tau levels indicative of worse pathological changes showed more rapid hippocampal atrophy and cognitive decline. The sex difference was particularly pronounced among individuals with MCI, with lower education, and varied by *APOE* ε4 allele. These results suggest females may be more susceptible to the clinical manifestation of AD.

1. Introduction

Alzheimer's disease (AD) is a neurodegenerative disease which disproportionately affects women (Hebert, Weuve, Scherr, & Evans, 2013). Of the more than 5 million people in the United States afflicted with this disease, two-thirds are women. Although some of this difference between the sexes may be explained by women's longer life expectancies, there may also be biological factors that drive sex differences in the clinical manifestation of AD.

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In addition to prevalence differences between the sexes, differences in the severity and progression of AD have also been documented. Compared to men with AD, women with AD perform worse on a variety of neuropsychological tasks (Henderson & Buckwalter, 1994), have smaller hippocampal volumes (Apostolova et al., 2006), and show more total brain atrophy and temporal lobe degeneration (Hua et al., 2010). At autopsy, women with AD have more neuritic plaques and neurofibrillary tangles than men with AD (Barnes et al., 2005). The clinical effects of plaques and tangles are also more readily apparent in women than men: in this same study, the relation of global AD pathology to clinical diagnosis differed between men and women, with each additional unit of AD pathology associated with a 3-fold increase in the odds of clinical AD in men compared with a more than 22-fold increase in the odds of clinical AD in women (Barnes et al., 2005).

The present manuscript conducts a focused analysis of sex-biomarker interactions in relation to brain aging outcomes of hippocampal volume and two domains of cognitive performance (episodic memory and executive function). To accomplish this, we evaluated the interaction between sex and continuous measures of CSF AD biomarkers (Aβ-42, total tau) to test whether the association between AD biomarkers and brain aging outcomes varies by sex. Our hypothesis was that females would be more susceptible to longitudinal decline in the presence of enhanced AD biomarkers.

2. Materials and Methods

Participants were drawn from the Alzheimer's Disease Neuroimaging Initiative database (ADNI; adni.loni.usc.edu) launched in 2003 as a public-private partnership. The original ADNI study enrolled approximately 800 participants, aged 55–90 years, excluding serious neurological disease other than AD, history of brain lesion or head trauma, and history of psychoactive medication use (for full inclusion/exclusion criteria see http://www.adni-info.org). Informed written consent was obtained from all participants at each site, and analysis of ADNI's publically available database was approved by our local Institutional Review Board prior to data analysis.

2.1 Subjects

We accessed publicly available data from ADNI on 6/12/2015. Participants were enrolled in ADNI based on criteria outlined in the ADNI protocol (http://www.adni-info.org/Scientists/AboutADNI.aspx). For the present analyses, we included all participants with CSF measurement of Aβ-42 and total tau, and the neuroimaging or cognitive outcome of interest. For the neuroimaging analyses, inclusion critieria required a FreeSurfer measure of hippocampal volume derived from 1.5T MRI data, yielding 1098 participants. For the cognitive analyses, participants had to have a composite measure of memory and executive function, yielding 1212 participants. Participant characteristics are presented in Table 1.

2.2 CSF Analyte and Biomarker Processing

ADNI's CSF protocol, including the quantification of Aβ-42 and total tau, has been detailed elsewhere (Jagust et al., 2009; Shaw et al., 2011). For the present analyses, we compiled a

dataset across the UPENN1-UPENN8 data sources available for download and used the first measure of total tau and Aβ-42 available for each participant.

2.3 Neuropsychological Composites

The ADNI neuropsychological protocol, including calculation of episodic memory and executive function composite measures, has been reported previously (Crane et al., 2012; Gibbons et al., 2012). We leveraged a memory (ADNI-MEM) and executive function (ADNI-EF) composite score in the present analyses. ADNI-MEM included a composite z-score based on item level data from the Rey Auditory Verbal Learning Test, the AD Assessment Scale-Cognitive Test, the Mini-Mental State Examination, and Logical Memory I and II. ADNI-EF included item level data from the Trail Making Test Parts A and B, Digit Span Backward, Digit Symbol, Animal Fluency, Vegetable Fluency, and Clock Drawing Test.

2.4 Quantification of Hippocampal Volume and Hippocampal Atrophy

The ADNI neuroimaging protocol has been reported in detail elsewhere (Jack et al., 2008). Images for the current study included original uncorrected 1.5T T1-weighted high-resolution three-dimensional structural data for ADNI-1 and 3T data for ADNI- 2/GO. Cortical reconstruction and volumetric segmentation were performed with the FreeSurfer image analysis suite version 4.3 in ADNI-1 and 5.1 in ADNI 2 (http://surfer.nmr.mgh.harvard.edu/; (Dale, Fischl, & Sereno, 1999; Fischl, Sereno, & Dale, 1999; Fischl, Sereno, Tootell, & Dale, 1999). FreeSurfer processing in ADNI has been described in detail elsewhere (Mormino et al., 2009). An early version of the longitudinal image processing framework was used to process the sequential scans (Reuter, Schmansky, Rosas, & Fischl, 2012). We used left hippocampal volume and right hippocampal volume, as defined by Freesurfer (Desikan et al., 2006), as our primary outcome measurements in brain analyses. All brain volume analyses also included a measurement of intracranial volume (ICV) and a variable for scanner strength as covariates.

2.5 Statistical Analyses

All statistical analyses were performed in R (version 2.15.2; http://www.r-project.org/). Covariates included age, sex, education, cognitive diagnosis, ICV (for neuroimaging analyses) and scanner strength (for neuroimaging analyses). Significance was set a priori as $\alpha=0.05$.

Baseline effects were estimated using a general linear model for each of the four outcomes (left and right hippocampal volume, ADNI-MEM, and ADNI-EF). Longitudinal analyses were performed using mixed effects regression with time modeled as years from baseline for each participant. We evaluated the interaction between sex and CSF AD biomarkers (Aβ-42 or total tau) on the four brain aging outcomes to test the effect of sex in the presence of enhanced AD. Predictors included sex, biomarker level (either Aβ-42 or total tau), and a sex x biomarker interaction term. Longitudinal analyses included a time x sex x biomarker interaction term to evaluate whether sex interacted with biomarker level in association with change in hippocampal volume, memory, or executive function over the follow-up period. All lower order interactions were included in the model.

Additional analyses tested for sex x biomarker x diagnosis interactions, both on cross-sectional and longitudinal outcomes, to assess whether the observed associations differed across the dementia spectrum. All lowed order terms of this three-way interaction term were included in the model. The CSF AD biomarkers were treated as continuous variables for all analyses.

To assess whether the observed associations differed among *APOE* ε4 carriers and non-carriers, analyses also tested for sex x biomarker x *APOE* ε4 status interactions, both on cross-sectional and longitudinal outcomes. The CSF AD biomarkers were treated as continuous variables for all analyses.

To investigate whether the observed associations were moderated by years of education, analyses tested for sex x biomarkers x education interactions on cross-sectional and longitudinal outcomes. All lower order interactions of this three-way interaction term were included in the model. The CSF AD biomarkers were treated as continuous variables for all analyses.

It is also possible that changes in functional abilities co-occur or drive changes in brain aging, so we evaluated the Functional Activities Questionnaire (FAQ; Pfeffer, Kurosaki, Harrah, Chance, & Filos, 1982), which was collected in all neuropsychological assessments, as an additional cross-sectional and longitudinal outcome.

3. Results

3.1 Sex x Aβ-42 Interaction on Brain Aging

All results are presented in Table 2. Participants were followed for an average of 2.5 years (range: 0 – 9 years) after the baseline visit. At baseline, sex did not interact with Aβ-42 in relation to right or left hippocampal volume ($t(1082)=0.93$, $p=0.35$ and $t(1082)=-0.12$, $p=0.90$, respectively), baseline memory performance ($t(1198)=1.58$, $p=0.11$), or baseline executive function performance ($t(1198)=0.29$, $p=0.77$).

In longitudinal analyses, there was a sex x Aβ-42 interaction in relation to three of the four measured brain aging outcomes including left hippocampal atrophy ($t(2739)=3.07$, $p=0.002$), memory performance ($t(4154)=2.39$, $p=0.02$), and executive function performance ($t(4132)=2.25$, $p=0.02$). As seen in Figure 1, in all cases female sex was associated with worsening outcomes in the presence of a low Aβ-42 level (low CSF Aβ-42 is indicative of higher brain Aβ-42). Sex did not interact with Aβ-42 in relation to right hippocampal atrophy ($t(2739)=1.54$, $p=0.12$).

3.2 Sex x Tau Interaction on Brain Aging

At baseline, sex did not interact with tau in relation to memory performance ($t(1198)=-0.22$, $p=0.83$), executive function performance ($t(1198)=-0.51$, $p=0.61$), right hippocampal volume ($t(1082)=-0.49$, $p=0.62$), or left hippocampal volume ($t(1082)=0.44$, $p=0.66$),

In longitudinal analyses, there was a sex x tau interaction in relation to executive function decline ($t(4132)=-2.11$, $p=0.03$) and left hippocampal atrophy ($t(2739)=-2.61$, $p=0.009$). As

seen in Figure 2, female sex was associated with worsening executive function and hippocampal atrophy in the presence of a high total tau level ("tau positive"). Sex did not interact with total tau level in relation to longitudinal memory performance (t(4154)=−1.20, p=0.23) or right hippocampal atrophy (t(2739)=0.56, p=0.58).

3.4 Diagnosis as an Effect Modifier

At baseline, diagnostic status modified the association between tau and sex on memory (F(2,1192)=5.63, p=0.004), whereby the sex difference was most pronounced among MCI participants. We did not observe any other cross-sectional or longitudinal interactions with diagnosis.

3.5 APOE Status as an Effect Modifier

At baseline, *APOE* ε4 status modified the association between sex and Aβ-42 in relation to right hippocampal volume (t(1079)=2.31, p=0.02), whereby the sex difference was most pronounced among *APOE* ε4 carriers.

In longitudinal analysis, *APOE* ε4 status modified the association between sex and tau in relation to right hippocampal volume (t(2735)=2.24, p=0.03), whereby the sex difference was most pronounced among *APOE* ε4 non-carriers.

3.6 Education as an Effect Modifier

In longitudinal analysis, education modified the association between sex and Aβ-42 in relation to executive function (t(4128)=−1.99, p=0.05), whereby the sex difference was most pronounced among those of lower education level. We did not observe any other cross-sectional or longitudinal interactions with education.

3.7 Sex x CSF Biomarkers on Functional Abilities

As noted in Table 2, we did not observe any sex differences in the association between AD biomarkers and FAQ scores. In longitudinal analyses, there was a trend towards an interaction between Aβ-42 and sex (p = 0.055) whereby females showed a greater increase in functional deficits over time in the presence of low Aβ-42 (low CSF Aβ-42 is indicative of higher brain Aβ-42).

4. Discussion

The present manuscript evaluated whether sex modifies the association between AD biomarkers and brain aging outcomes in older adults. Female sex was associated with greater hippocampal atrophy and longitudinal cognitive decline in the presence of enhanced AD biomarkers. The sex difference was particularly pronounced in the presence of low education and appeared to vary by *APOE* genotype. These results suggest that women may be more susceptible to the downstream effects of the AD neuropathological cascade.

Our primary research finding was that female sex was associated with greater left hippocampal atrophy and faster decline in memory and executive function performance in the presence of a low CSF Aβ-42 level (indicating higher levels of Aβ-42 in the brain).

Similarly, we observed that females showed greater right hippocampal atrophy and longitudinal decline in executive function performance in the presence of high CSF total tau levels. This finding is consistent with autopsy reports highlighted in the introduction that demonstrated that an increase in AD pathology was associated with a greater increase in the odds of clinical AD in women compared to men (Barnes et al., 2005). Similarly, Barnes et al. (2005) observed a tighter coupling between level of neuropathological burden and cognitive performance in women whereby women showed twice the reduction in global cognitive performance compared to men for every one unit increase in global AD pathology. Our results and the previous autopsy findings suggest that females may be more susceptible to the clinical manifestation of AD.

The mechanism of the observed sex difference in the clinical manifestation of AD remains unclear, but it certainly could be driven by age-related changes in estrogen levels during older adulthood. The association between higher levels of estradiol and better cognitive performance is well established (see (Luine, 2014) for review), and there are some models suggesting estrogen may directly regulate levels of Aβ (Anastasio, 2013) and tau hyperphosphorylation (Alvarez-de-la-Roza et al., 2005). Moreover, estrogen has been shown to reduce neural vulnerability to apoptosis in the presence of Aβ, particularly in the hippocampus (Nilsen, Chen, Irwin, Iwamoto, & Brinton, 2006). The protective effect of estrogen in the hippocampus appears to be driven by alterations in calcium homeostasis that reduce the apoptotic response to Aβ. The possibility of a calcium-dependent alteration in apoptotic signaling provides potential for target candidate gene and protein analyses to assess whether alterations in genes driving calcium signaling exacerbate the observed susceptibility in females. However, additional work is needed to understand whether such estrogen mediated effects actually drive the observed sex-difference in susceptibility to the clinical manifestation of disease.

One interesting observation from previous work is that females with AD appear to show more rapid cognitive decline than males with AD (Tschanz et al., 2011), likely driven by the tighter coupling of cognition and neuropathology previously highlighted. Although our primary analyses only statistically adjusted for diagnosis, we also evaluated diagnostic interactions. We observed a three-way interaction between tau, diagnosis, and sex whereby the most pronounced sex difference was among MCI participants. The three-way interaction results seem to indicate that sex differences in the clinical manifestation of disease may vary across the cognitive diagnostic spectrum, but additional longitudinal work is needed to better understand this dynamic process.

Previous work has also demonstrated that the *APOE* ε4 risk allele has a more potent effect in females than in males (Farrer et al., 1997). Similarly, previous reports from ADNI suggest the largest sex difference in cognitive trajectories is observed in *APOE* ε4 carriers (Lin et al., 2015). Our primary findings covaried for *APOE*, suggesting that *APOE* is not driving the observed gender differences. However, we also observed two interesting interactions among *APOE*, biomarker levels, and sex. In the case of amyloid, the sex difference in the association between Aβ-42 levels and left hippocampal volume was most pronounced among the *APOE* ε4 carriers. In the case of tau, the sex difference in the association between total tau levels and right hippocampal volume was most pronounced among *APOE*

ε4 non-carriers. Previous reports have highlighted *APOE* x sex interactions on brain structure and function (Sampedro et al., 2015), indicating that the impact of *APOE* on neural deficits is more potent in females than in males. Our results build on this literature by reinforcing that sex differences in amyloid-related deficits in brain structure may be driven by *APOE* ε4 carriers, whereas sex differences in tau-related deficits do not appear to be driven by the *APOE* ε4 carrier effect. Additional work targeting sex differences in the molecular alterations downstream of amyloid and tau will be necessary to understand the mechanisms of the observed *APOE* interactions.

Education is another critical factor when considering sex differences in the clinical manifestation of disease. Previous work found that low education was a stronger risk factor for AD in females than in males (Launer et al., 1999). Interestingly, we observed a modest three-way interaction between Aβ-42 levels, education, and sex whereby the most pronounced sex difference in the association between Aβ-42 and executive function was observed among those with lower levels of education.

The present findings provide additional evidence that females are more susceptible to the clinical manifestation of AD, particularly in the presence of enhanced AD biomarkers. However, it is difficult to conclude whether the observed sex difference is driven by differences in the etiology and pathophysiology of the AD cascade, or a more general sex-difference in susceptibility to a variety of late-life risk factors of poor brain aging. Our secondary analyses highlighting functional activities were inconclusive, but certainly a more thorough study of sex differences in the functional, cognitive, and neural changes that occur across the AD spectrum is warranted. Importantly, the results also highlight the need to pursue sex-stratified analyses of genetic risk to better assess potential sex differences in the genomic pathways that drive the clinical manifestation of disease.

The present results must be interpreted within the framework of our statistical models and the ADNI cohort. In all analyses, we included covariates adjusting for disease status and progression including age, diagnosis, education, and *APOE* ε4 carrier status. While we found significant sex interactions with *APOE*, education, and diagnosis it should be noted that the observed effects were small, and the sample sizes within contingency table cells for such 3-way interactions were limited. Future work aimed at better teasing apart these variables will be critical to understanding how sex differences in AD relate to other age-related diseases. While the ADNI cohort provides an ideal dataset to perform a comprehensive analysis of sex differences using a variety of risk factors and brain aging outcomes, it does also present some clear sample limitations. The participants have higher levels of education on average than the general population, likely have lower levels of overt cerebrovascular disease due to the Hachinski cut-off score applied during screening, and were predominantly Caucasian. Moreover, many of the clinical and demographic characteristics were not matched between males and females (Table 3), leaving open the possibility that we may not have been able to adequately adjust for confounding factors in our analyses. While there was not a statistically significant difference in conversion rates between men and women, it is interesting that men had a slightly higher rate than women. These results, and previous results in autopsy samples, highlight the need for a carefully

matched cohort that is built to specifically evaluate sex differences in the clinical manifestation of AD.

These results highlight the need for clinicians to carefully monitor patient cognition, as even early subtle changes in relatively high performing individuals may be a harbinger of future cognitive decline. If confirmed in a more carefully matched sample, the heightened association between AD biomarkers and brain aging outcomes suggests screening for AD biomarkers may be especially important in post-menopausal women when treatments become available. However, it is difficult to draw definitive conclusions without a more thorough understanding of the mechanism driving the observed sex differences.

In conclusion, the present manuscript provides evidence of a novel sex x biomarker interaction that is consistent with previous autopsy findings and suggests that females may be more susceptible the damaging clinical effects of AD neuropathology.

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The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

6. Compliance with Ethical Standards

This research was supported in part by the Building Interdisciplinary Research Careers in Women's Health program (K12 HD043483), the Vanderbilt Medical Scientist Training Program (T32 GM07347), and the Vanderbilt Memory & Alzheimer’s Center. The authors report no conflicts of interest. Informed consent was obtained from all participants included in the study.

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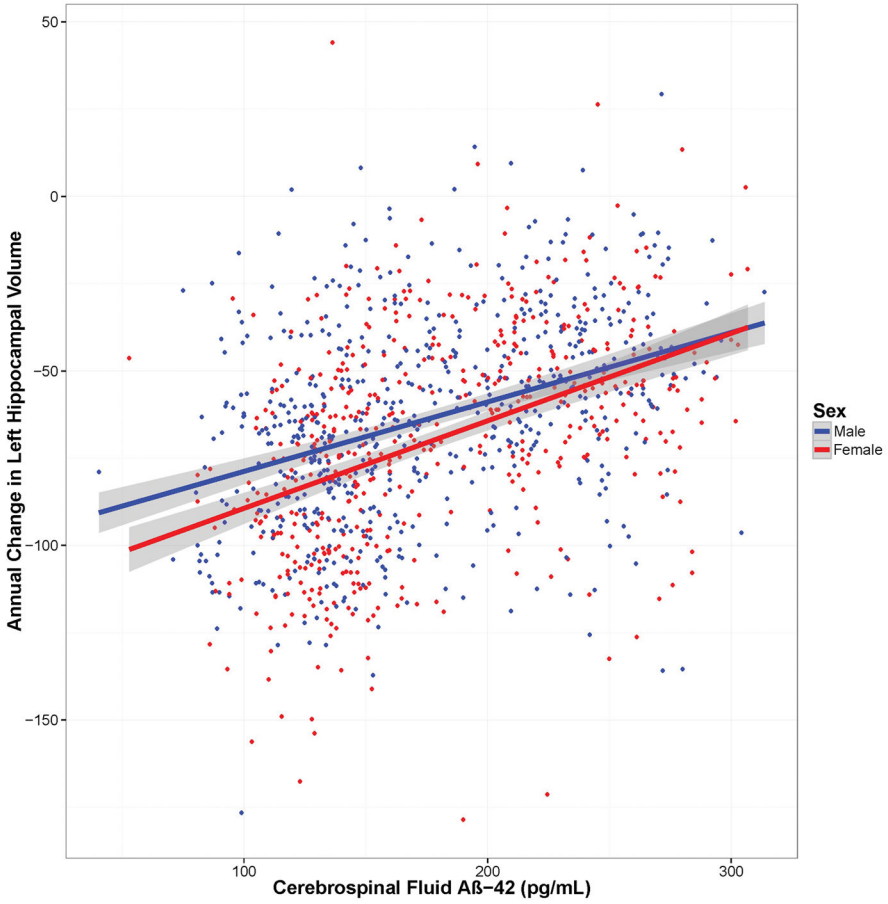

Figure 1. Females show a faster rate of hippocampal atrophy in the presence of enhanced (low levels) of CSF Aβ-42. (IMAGE FOR REVIEW PURPOSES ONLY)

CSF Aβ-42 levels are along the x-axis. Annual change in left hippocampal volume is along the y axis. Sex is differentiated by color with males in red and females in blue. The gray shading around the regression line represents the standard error.

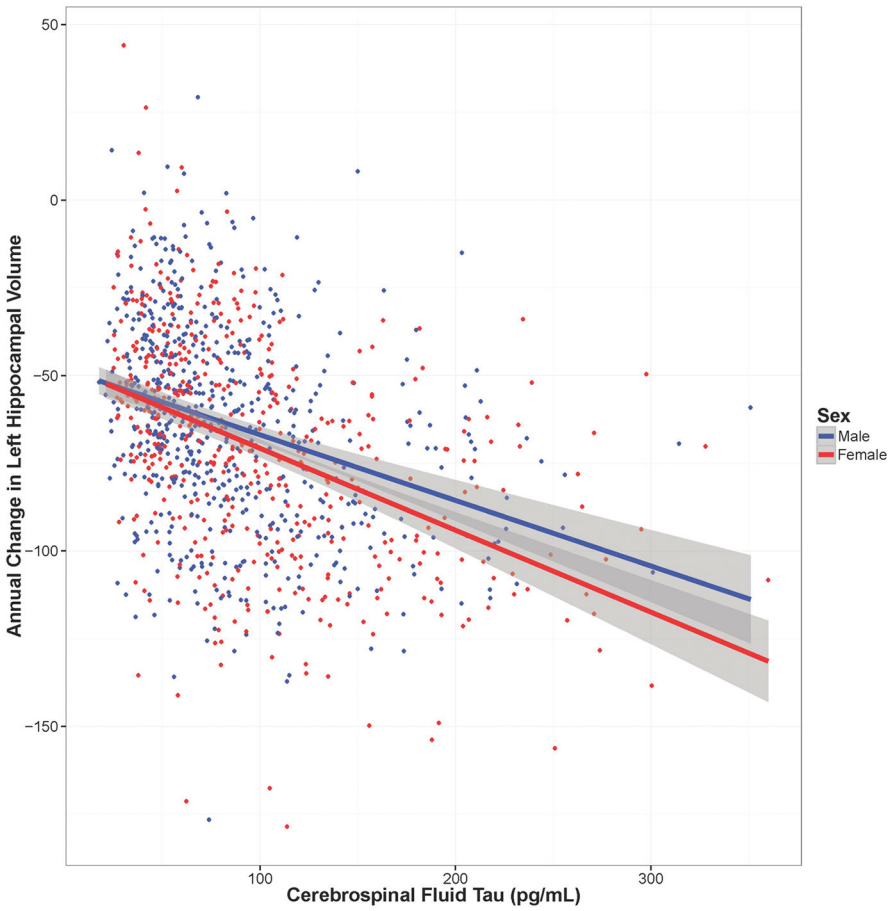

Figure 2. Females show a faster rate of hippocampal atrophy in the presence of enhanced CSF tau levels

CSF Aβ-42 levels are along the x-axis. Annual change in right hippocampal volume is along the y axis. Sex is differentiated by color with males in red and females in blue. The gray shading around the regression line represents the standard error.

Table 1

Sample Characteristics

Brain Volume Dataset	Baseline Clinical Diagnosis[#]			
	Normal Control	Mild Cognitive Impairment	Alzheimer's Disease	Statistical Test
Sample Size, n	348	565	185	
APOE ε4 Carriers, %	27%	50%	69%	$\chi^2(2) = 89.1$, p<0.001
Females, %	53%	42%	46%	$\chi^2(2) = 9.3$, p=0.003
Baseline Age, years	74 ± 6	72 ± 8	74 ± 8	F(2,1095)=7.7,p<0.001
Education, years	16 ± 3	16 ± 3	15 ± 3	F(2,1095)=6.5,p=0.002
CSF Total Tau, pg/mL	67 ± 30	90 ± 54	132 ± 62	F(2,1095)=105,p<0.001
CSF Aβ-42, pg/mL	200 ± 52	173 ± 53	140 ± 41	F(2,1095)=88,p<0.001
Left Hippocampus, mm^3	3763 ± 463	3442±609	2932 ± 580	F(2,1095)=150,p<0.001
Right Hippocampus, mm^3	3707 ± 439	3362 ± 603	2881 ± 536	F(2,1095)=146,p<0.001
Cognitive Dataset				
Sample Size, n	374	612	226	
APOE ε4 Carriers, %	27%	49%	67%	$\chi^2(2) = 93.6$, p<0.001
Females, %	53%	42%	42%	$\chi^2(2) = 11.3$, p=0.001
Baseline Age, years	74 ± 6	73 ± 8	75 ± 8	F(2,1209)=10.1,p<0.001
Education, years	16 ± 3	16 ± 3	15 ± 3	F(2,1209)=8.2,p<0.001
CSF Total Tau, pg/mL	67 ± 32	90 ± 53	127 ± 62	F(2,1209)=103,p<0.001
CSF Aβ-42, pg/mL	200 ± 52	172 ± 54	140 ± 39	F(2,1209)=101,p<0.001
Memory, z-score	0.94 ± 0.5	0.2 ± 0.6	−0.71 ± 0.5	F(2,1209)=634,p<0.001
Executive Function, z-score	0.78 ± 0.7	0.22 ± 0.8	−0.83 ± 0.8	F(2,1209)=296,p<0.001

[#]Diagnostic groups were defined according to the ADNI protocol. Normal Control subjects had a Mini-Mental Status Examination (MMSE) score between 24 and 30, a Clinical Dementia Rating (CDR) score of 0, and were not depressed (Geriatric Depression Scale score <6). Mild Cognitive Impairment subjects had a MMSE score between 24 and 30, objective memory impairment, subjective memory impairment, and a CDR score of 0.5. Alzheimer's Disease subjects met clinical criteria for dementia, had an MMSE of between 20 and 26, and had CDR score of .5 or 1.

[*]ICV corrected values are for illustration purposes only, however ICV was entered into all statistical models as a covariate.

Table 2

Associations Between Sex and Brain Aging Variables

	Sex x Aβ-42		Sex x Tau	
Cross-Sectional Outcomes	β	**p-value**	β	**p-value**
Right Hippocampal Volume	0.48	0.35	−0.26	0.62
Left Hippocampal Volume	−0.06	0.90	0.23	0.66
Episodic Memory Composite	0.0009	0.11	−0.0001	0.827
Executive Function Composite	0.0002	0.77	−0.0004	0.61
Functional Activities Questionnaire	−0.003	0.45	0.005	0.27
Longitudinal Outcomes	β	**p-value**	β	**p-value**
Right Hippocampal Volume	0.14	0.12	0.06	0.58
Left Hippocampal Volume	**0.29**	**0.002** *	**−0.28**	**0.009**
Episodic Memory Composite	**0.0005**	**0.017**	−0.0003	0.23
Executive Function Composite	**0.0006**	**0.02**	**−0.0006**	**0.03**
Functional Activities Questionnaire	−0.004	0.055	0.003	0.29

Boldface signifies effects that are significant at $p < 0.05$.

* Signifies effect is significant when correcting for multiple comparisons (Bonferroni).

Table 3

Sex Differences in Clinical and Demographic Variables

	Sex		
Brain Volume Dataset	**Male**	**Female**	**Statistical Test**
Sample Size, n	665	547	
APOE ε4 Carriers, %	46%	46%	$\chi^2(1) = 0.01$, p=0.933
Conversion, %[#]	19%	16%	$\chi^2(1) = 3.5$, p=0.062
Baseline Age, years	74 ± 07	72 ± 07	F(1,1210) = 20.8,p<0.001
Education, years	17 ± 03	15 ± 03	F(1,1210) = 41.5,p<0.001
Number of Visits	4.50 ± 2.13	4.36 ± 2.05	F(1,1210) = 1.4,p=0.235
Follow Up Period, Years	2.54 ± 1.93	2.44 ± 1.93	F(1,1210) = 0.7,p=0.402
CSF Total Tau, pg/mL	86 ± 49	95.64 ± 58.45	F(1,1210) = 10.0,p=0.002
CSF Aβ-42, pg/mL	172 ± 55	178 ± 54	F(1,1210) = 3.5,p=0.063
Memory, z-score	0.12 ± 0.74	0.43 ± 0.81	F(1,1210) = 49.3,p<0.001
Executive Function, z-score	0.12 ± 0.94	0.29 ± 0.96	F(1,1210) = 9.9,p<0.001
Left Hippocampus, mm^3 [*]	3442 ± 628	3329 ± 582	F(1,1095) = 9.5,p=0.002
Right Hippocampus, mm^3 [*]	3529 ± 633	3374 ± 607	F(1,1095) = 17,p<0.001

[#]Conversion calculated among individuals with normal cognition (NC) and mild cognitive impairment (MCI) where a conversion was defined as: NC → MCI, NC → AD, or MCI → AD over the course of the study period.

[*]Left and Right Hippocampus presented for the neuroimaging subgroup (see Table 1)