BRAIN COMMUNICATIONS

Women can bear a bigger burden: ante- and post-mortem evidence for reserve in the face of tau

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* Data used in preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (adni.loni.usc.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 list of ADNI investigators can be found in Appendix I.

In this study, we aimed to assess whether women are able to withstand more tau before exhibiting verbal memory impairment. Using data from 121 amyloid-β-positive Alzheimer's Disease Neuroimaging Initiative participants, we fit a linear model with Rey Auditory Verbal Learning Test score as the response variable and tau-PET standard uptake value ratio as the predictor and took the residuals as an estimate of verbal memory reserve for each subject. Women demonstrated higher reserve (i.e. residuals), whether the Learning ($t = 2.78$, $P = 0.006$) or Delay ($t = 2.14$, $P = 0.03$) score from the Rey Auditory Verbal Learning Test was used as a measure of verbal memory ability. To validate these findings, we examined 662 National Alzheimer's Coordinating Center participants with a C2/C3 score (Consortium to Establish a Registry for Alzheimer's Disease) at autopsy. We stratified our National Alzheimer's Coordinating Center sample into Braak 1/2, Braak 3/4 and Braak 5/6 subgroups. Within each subgroup, we compared Logical Memory scores between men and women. Men had worse verbal memory scores within the Braak 1/2 (Logical Memory Immediate: $\beta = -5.960 \pm 1.517$, $P < 0.001$, Logical Memory Delay: $\beta = -5.703 \pm 1.677$, $P = 0.002$) and Braak 3/4 (Logical Memory Immediate: $\beta = -2.900 \pm 0.938$, $P = 0.002$, Logical Memory Delay: $\beta = -2.672 \pm 0.955$, $P = 0.006$) subgroups. There were no sex differences in Logical Memory performance within the Braak 5/6 subgroup (Logical Memory Immediate: $\beta = -0.314 \pm 0.328$, $P = 0.34$, Logical Memory Delay: $\beta = -0.195 \pm 0.287$, $P = 0.50$). Taken together, our results point to a sex-related verbal memory reserve.

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Abbreviations: Aβ = amyloid-β; AD = Alzheimer's disease; ADNI = Alzheimer's Disease Neuroimaging Initiative; FTP = flortaucipir; LM = Logical Memory; NACC =National Alzheimer's Coordinating Center; PET = positron emission tomography; preAD = preclinical AD; proAD = prodromal/probable AD; RAVLT = Rey Auditory Verbal Learning Test

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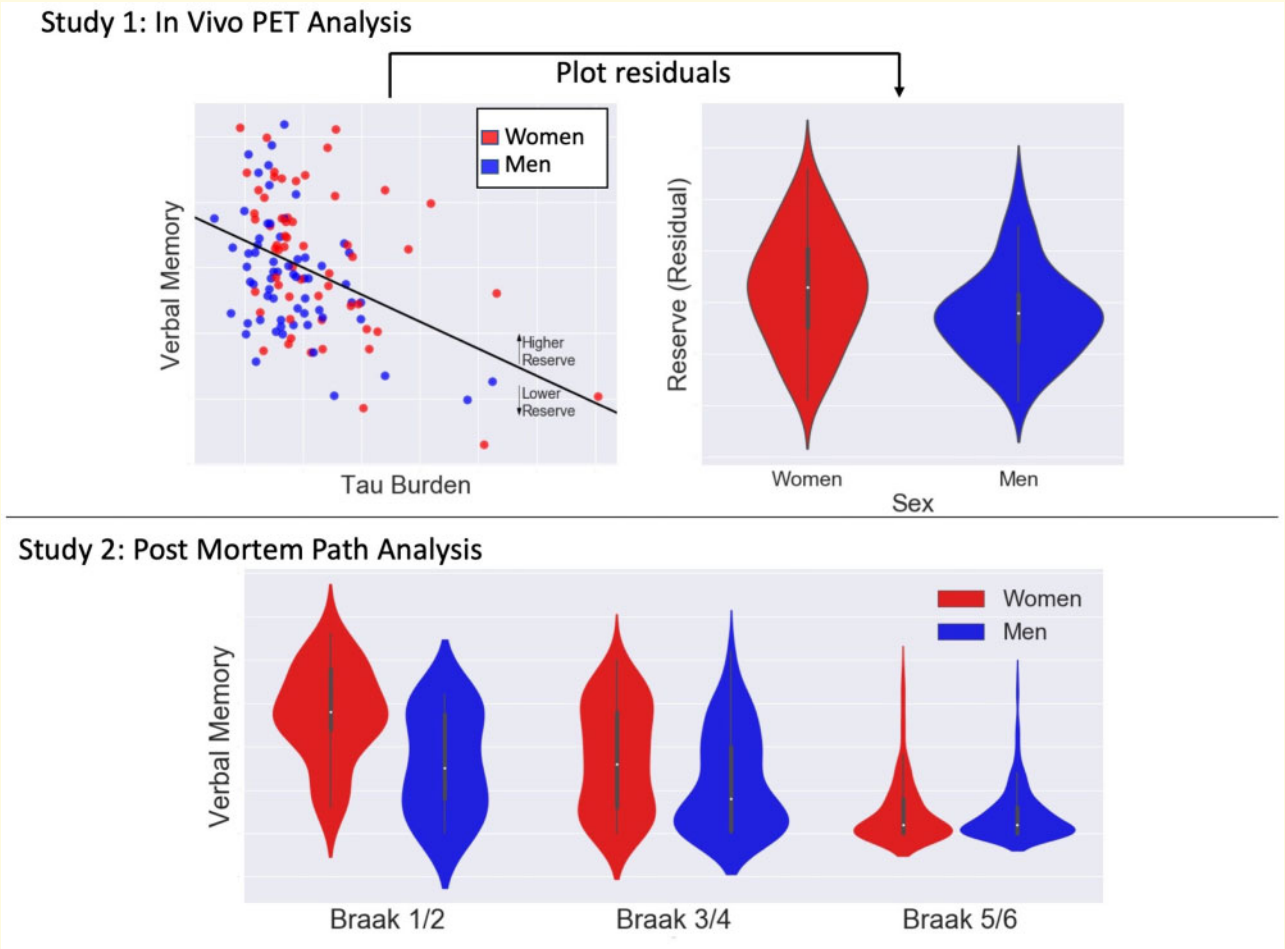
Graphical Abstract



Introduction

Cognitive reserve describes the phenomenon where individuals vary in cognitive performance despite harbouring similar amounts of Alzheimer's disease pathology (Stern, 2002). Cognitive reserve has been attributed to factors such as education (Stern *et al.*, 1992), overall intellectual ability (Alexander *et al.*, 1997), diet (Scarmeas *et al.*, 2006) and social network size (Bennett *et al.*, 2006).

Sex may also play a role in reserve, with women demonstrating higher reserve in verbal memory (Beinhoff *et al.*, 2008, Chapman *et al.*, 2011). This is supported by a pair of recent imaging studies, which reported that women, while expressing similar levels of neurodegeneration (Sundermann *et al.*, 2016*a*, *b*), outperform men in verbal memory. Further evidence comes from an investigation demonstrating that sex can moderate the relationship between amyloid-β (Aβ) and verbal memory performance (Caldwell *et al.*, 2017).

Recent studies have revealed sex differences in tau pathology. Post-mortem data indicate that women have more tau at autopsy (Liesinger *et al.*, 2018; Oveisgharan *et al.*, 2018). Ante-mortem examination of brain tau is now available through positron emission tomography (PET) (Marquié *et al.*, 2015). A recent tau-PET study reported that, among cognitively normal individuals with elevated Aβ, women harboured more tau (Buckley *et al.*, 2019). A potential corollary to these findings is that women can withstand more tau before exhibiting verbal memory impairment. In other words, women may exhibit more reserve, but this hypothesis has not been explored in vivo.

A useful approach for estimating cognitive reserve is the residual framework (Reed *et al.*, 2010; Zahodne *et al.*, 2013; Hohman *et al.*, 2016; van Loenhoud *et al.*, 2017). Under this framework, a model is fitted to the data, where cognitive performance is the response variable and Alzheimer's disease pathology is the predictor. This model provides a predicted level of cognition for a given level of pathology. Those that display higher than predicted cognitive performance (i.e. positive residual) can be characterized as having high cognitive reserve and vice versa.

In this study, we applied this residual approach to PET and verbal memory data from Alzheimer's Disease Neuroimaging initiative (ADNI) to estimate reserve. We then assessed sex differences in reserve, hypothesizing that women would demonstrate higher reserve than men. We further aimed to characterize how women's verbal memory advantage varies by disease stage. For validation, we examined autopsy and verbal memory data subjects from the National Alzheimer's Coordinating Center (NACC).

Methods and materials

Study 1: ADNI tau-PET analysis

ADNI sample

We included ADNI participants who underwent Aβ-PET, flortaucipir (FTP)-PET and magnetic resonance imaging, completed the ADNI neuropsychological battery and had *APOE* genotyping. Recruitment details for ADNI are detailed elsewhere (Aisen *et al.*, 2010; Weiner *et al.*, 2017). We restricted our sample to Aβ-positive subjects (based on previously derived thresholds; Landau *et al.*, 2012, 2013) to focus on the Alzheimer's disease spectrum.

ADNI neuroimaging processing

For each participant, we downloaded the first available FTP-PET in its most preprocessed form (Joshi *et al.*, 2009) and the magnetic resonance imaging acquired temporally closest to this FTP-PET. Magnetic resonance imaging was processed with FreeSurfer (Dale *et al.*, 1999, Fischl *et al.*, 1999). FTP volumes were first co-registered to each subject's magnetic resonance imaging. Then, standard uptake value ratio volumes were generated by normalizing to average FTP signal in the cerebellar grey. Regional tau values were derived from mean standard uptake value ratio within each Desikan-Killiany region (Desikan *et al.*, 2006). Tau load was defined as the average regional tau from entorhinal, parahippocampal, fusiform, inferior temporal and middle temporal cortex (Jack *et al.*, 2017).

Aβ pathology was assessed using summary cortical standard uptake value ratio (whole cerebellum reference) data generated by the Jagust Lab (Landau *et al.*, 2012, 2013).

ADNI memory measures

To assess verbal memory, we used Rey Auditory Verbal Learning Test (RAVLT) scores acquired closest in time to the FTP-PET (time between FTP-PET and RAVLT date: mean: 0.639 years, SD: 0.783). We used the sum of words across the first five trials (RAVLT Learning) and the number of words recalled after a 30-minute delay (RAVLT Delay).

Statistical analysis

Subject characteristics

We used Welch *t*-tests to assess sex differences in age, education and summary Aβ and χ^2 tests to examine sex differences in ε4 status.

Reserve analyses

We took a residual approach to estimate reserve. First, we fit a linear regression model with RAVLT score as the response variable and age, education, ε4 status and tau load as predictors. This model provides an individual's predicted RAVLT score for a certain level of tau load. Since 'reserve' is defined as having better or worse cognition than is predicted by pathology, we took each individual's residual in the model as an estimation of their reserve. Welch *t*-tests were then performed to test for a difference in residuals (i.e. reserve) between women and men. This procedure was done for two separate models, using either RAVLT Learning or RAVLT Delay as the response variable.

Subgroup stratified analysis

To further explore these sex differences in tau and verbal memory, we stratified our sample into two groups: cognitively normal participants [preclinical Alzheimer's disease (preAD)] and mild cognitive impairment/Alzheimer's disease participants [prodromal/probable Alzheimer's disease (proAD)]. Within each subgroup, we performed the following linear model analyses. First, we assessed sex differences in tau load, RAVLT Learning and RAVLT Delay after correcting for age, education and ε4 status. Then, we tested for sex differences in RAVLT Learning and RAVLT Delay, while controlling for age, education, ε4 status and tau load.

Study 2: NACC post-mortem analysis

NACC sample

For NACC analyses, we utilized data from the December 2018 freeze. We included participants with a clinical diagnosis of normal cognition, amnestic mild cognitive impairment or dementia (with Alzheimer's disease as presumptive etiology) at last clinical visit and autopsy data within 5 years of that visit. Our sample was restricted to individuals 60 years or older at baseline and had at least two visits prior to autopsy. We selected only participants with a Consortium to Establish a Registry for Alzheimer's Disease neocortical neuritic plaque rating of C2 or C3, indicating moderate to frequent plaques (Mirra *et al.*, 1991), to focus on participants on the Alzheimer's disease spectrum and to parallel our ADNI analyses, which included only Aβ-positive individuals.

NACC neuropsychology measures

The NACC neuropsychological battery does not include the RAVLT or similar list-learning task, so we instead used scores from the Logical Memory (LM) test, which assesses immediate (LM Immediate) and 20-minute delayed recall of a brief story (LM Delay). The memory scores from the last test administration prior to death were used.

Statistical analysis

Subject characteristics

To assess sex differences in age, education and time between last clinical visit and death, we used Welch two-sample *t*-tests. To compare carriage of the ε4 allele between men and women, we used χ^2 tests.

Pathology analyses

We first stratified our NACC cohort into three subgroups: Braak 1/2, Braak 3/4 and Braak 5/6 subgroups. We then used linear models to examine sex differences in LM Immediate and LM Delay scores within each subgroup. In these models, we corrected for time between last clinical visit and death, age at clinical visit and ε4 status.

Data availability

The ADNI demographic, genetic, neuroimaging and neuropsychology data that were used in our analyses are available for eligible users for access and download at the ADNI data repository (adni.loni.usc.edu). The NACC demographic, genetic, neuropathology and neuropsychology data that were used can be accessed freely by eligible researchers through the NACC website (alz.washington.edu).

Table 1 Demographic characteristics and memory tests scores of participants included in ADNI tau-PET analyses

Variable	Women	Men
Number (% of ADNI sample)	58 (47.9)	63 (52.1)
Age (years)*	76.7 (6.80)	79.7 (6.98)
Education (years)*	15.4 (2.41)	16.9 (2.46)
Number of (%) *APOE* ε4 carriers	32 (55)	36 (57)
Race (% white)	94.8	96.8
Number of preAD	26	23
Number of proAD (MCI/Alzheimer's disease)	32 (17/15)	40 (27/13)
RAVLT Learning	38.1 (14.1)	34.2 (12.0)
RAVLT Delay	5.14 (5.01)	3.97 (4.63)

Cells are formatted as mean (SD) unless otherwise noted.
MCI = mild cognitive impairment.
*Significant difference ($P < 0.05$) between women and men across the entire sample.

Results

Study 1: ADNI tau-PET analysis

Subject characteristics

A total of 121 ADNI participants met criteria for our study. Summary statistics are displayed in Table 1. Across the sample, women were younger [$t(119) = -2.37$, $P = 0.02$] and had fewer years of education [$t(119) = -3.40$, $P < 0.001$]. No sex difference in ε4 status [χ^2 (1) = 0.0476; $P = 0.83$] was observed. In our preAD group (23 men and 26 women), the women were not different with respect to age [$t(44) = -1.50$, $P = 0.14$], education [$t(47) = -1.35$, $P = 0.18$] or ε4 status [$\chi^2(1) = 0.0137$; $P = 0.91$]. In the proAD group (40 men and 32 women), the men were marginally older than women [$t(65) = -1.77$, $P = 0.08$] and had higher education than proAD women [$t(73) = 3.21$, $P = 0.002$] but were not different with respect to ε4 status [χ^2 (1) < 0.001; $P > 0.99$]. We observed no sex differences in summary Aβ standard uptake value ratio across the whole group [$t(115) = 0.946$, $P = 0.35$], within the preAD [$t(46) = 1.298$, $P = 0.20$] or within proAD [$t(65) = 0.376$, $P = 0.71$].

Reserve analysis

We first fit a linear regression model with RAVLT Learning as the response variable and with age, education, ε4 status and tau load as predictors. In this model (*R*-squared of model: 0.258), age ($\beta = -0.591$, SE = 0.156, $P < 0.001$), ε4 status ($\beta = -5.03$, SE = 2.19, $P = 0.02$) and tau load ($\beta = -21.6$, SE = 3.86, $P < 0.001$) were independently associated with RAVLT Learning. Education was not significantly associated with RAVLT Learning ($\beta = 0.681$, SE = 0.414, $P = 0.10$). Analysing the residuals with Welch's *t*-tests revealed that women had significantly higher residuals (i.e. more reserve) than men in the RAVLT Learning [$t(111) = 2.78$, $P = 0.006$] (Fig. 1B).

When this analysis was repeated with RAVLT Delay as the response variable, rather than RAVLT Learning, similar results were observed (*R*-squared of model: 0.262). Tau load ($\beta = -5.57$, SE = 1.449, $P < 0.001$), age ($\beta = -0.256$, SE = 0.0574, $P < 0.001$), ε4 status ($\beta = -2.41$, SE = 0.804, $P = 0.003$) and education ($\beta = 0.338$, SE = 0.152, $P = 0.03$) were related to RAVLT Delay. Furthermore, analysis of the residuals demonstrated that women also had higher reserve in this model [$t(114) = 2.14$, $P = 0.04$] (Fig. 1D).

The significant age difference between men and women in our ADNI sample may have potentially confounded the results of our reserve analysis. Thus, we re-performed this analysis using a subset of our ADNI participants ($N = 106$; 53 women, 53 men) that were matched for age across sexes. In these age-matched analyses, we found similar results.

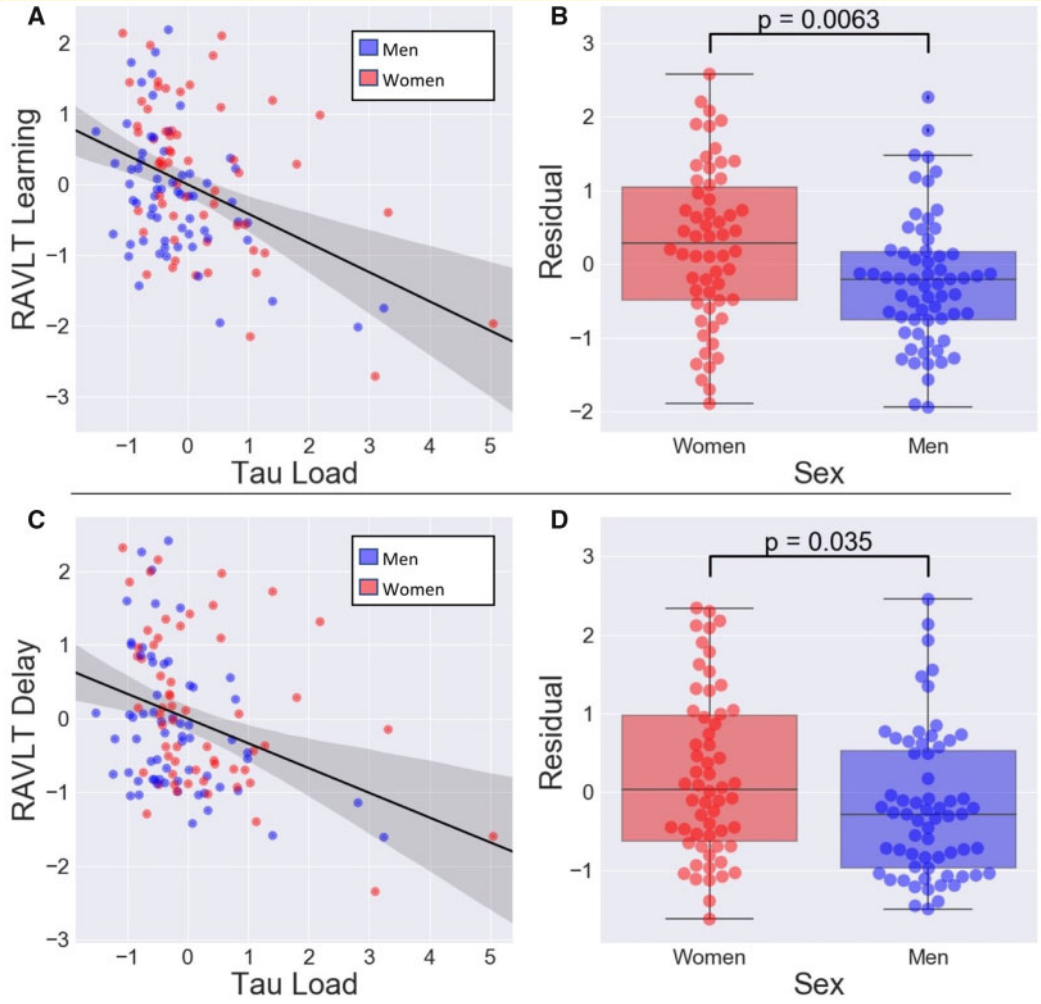


Figure 1 Women demonstrate higher reserve to tau than men. Scatter plots (**A**) between RAVLT Learning and tau load or (**C**) between RAVLT Delay and tau load. RAVLT Learning, RAVLT Delay and tau load were regressed onto age, years of education and ε4 status before plotting. Here, tau load is the average of regional SUVRs from a set of Alzheimer's disease-vulnerable regions in temporal cortex. The boxplots with swarm plot overlays are residuals from a linear model predicting (**B**) RAVLT Learning or (**D**) RAVLT Delay from tau load, age, years of education and ε4 status. Women have significantly higher residuals than men. SUVRs = Standard uptake value ratios.

Subgroup stratified analysis

After correcting for age, education and ε4 status, men in the preAD group performed worse on RAVLT Learning ($\beta = -6.75$, SE = 3.16, $P = 0.04$) than women, but comparably on RAVLT Delay ($\beta = -1.74$, SE = 1.41, $P = 0.23$). In addition, preAD men had less tau load than women ($\beta = -0.0921$, SE = 0.0362, $P = 0.01$), after accounting for age, education and ε4 status. Lastly, after correcting for age, education, ε4 status and tau load, men performed marginally worse on RAVLT Learning ($\beta = -6.54$, SE = 3.42, $P = 0.06$) but comparably on RAVLT Delay ($\beta = -1.76$, SE = 1.53, $P = 0.26$).

Within the proAD group, women and men did not perform differently on RAVLT Learning ($\beta = -0.861$, SE = 2.64, $P = 0.75$) or RAVLT Delay ($\beta = 0.281$, SE = 0.833, $P = 0.74$) after controlling for age, education and ε4 status. However, proAD men had lower tau ($\beta = -0.191$, SE = 0.0819, $P = 0.02$) than women. In models controlling for age, education, ε4 status and tau load, we found no sex differences in RAVLT Learning ($\beta = -1.96$, SE = 2.46, $P = 0.43$) or RAVLT Delay performance ($\beta = -0.436$, SE = 0.811, $P = 0.59$).

Study 2: NACC post-mortem analysis

Subject characteristics

There were 662 subjects in the NACC database who met criteria for our study and had complete data. The summary statistics are presented in Table 2. There were no sex differences in any demographic variables within the Braak 1/2 group or within the Braak 3/4 group. In the

Table 2 Demographic characteristics and memory tests scores of participants included in NACC post-mortem analyses

	Braak 1/2, N = 46		Braak 3/4, N = 153		Braak 5/6, N = 463	
	Women	Men	Women	Men	Women	Men
Number (% of Braak subgroup)	24 (52)	22 (48)	67 (44)	86 (56)	198 (43)	265 (57)
Age (years)[c]	84.9 (7.6)	84.4 (7.9)	85.9 (7.9)	83.7 (7.5)	82.9 (8.3)*	80.2 (8.1)
Education (years)[c]	15.0 (2.2)	15.1 (3.7)	15.1 (2.6)	15.5 (3.3)	14.2 (2.7)	16.0 (3.0)*
Number of (%) *APOE* ε4 carriers	6 (25)	6 (27)	32 (48)	41 (48)	114 (58)	165 (62)
Race (% white)	100	95.5	98.5	93.0	89.9	95.5
Time between last clinical visit and death (years)	1.0 (0.8)	0.9 (0.8)	1.0 (0.9)	1.3 (0.9)	1.9 (1.4)	1.8 (1.3)
LM Immediate[a,b]	13.8 (5.3)*	8.0 (5.7)	8.7 (6.0)*	6.0 (5.7)	2.5 (3.7)	2.2 (3.0)
LM Delay[a,b]	12.5 (6.0)*	7.1 (6.3)	7.4 (6.2)*	4.9 (5.8)	1.3 (3.3)	1.2 (2.6)

Cells are formatted as mean (SD) unless otherwise noted.
[a]Significant sex difference ($P < 0.05$) in the Braak 1/2 subgroup.
[b]Significant sex difference ($P < 0.05$) in the Braak 3/4 subgroup.
[c]Significant sex difference ($P < 0.05$) in the Braak 5/6 subgroup.
*Asterisk indicates higher value for women than men in that Braak category.

Braak 5/6 subgroup, there were differences in age [$t(419) = 3.447$, $P < 0.001$] and education [$t(446) = -6.570$, $P < 0.001$], with women being older and men having more educational attainment.

Pathology analysis

In the Braak 1/2 group, men had lower scores on both the LM Immediate ($\beta = -5.960$, SE = 1.517, $P < 0.001$) and LM Delay ($\beta = -5.703$, SE = 1.677, $P = 0.001$) after controlling for age at clinical visit, time between last clinical visit and death date, education and ε4 status. In a similar model within the Braak 3/4 group, we observed similar results. Men had lower scores on both LM Immediate ($\beta = -2.900$, SE = 0.938, $P = 0.002$) and LM Delay ($\beta = -2.672$, SE = 0.955, $P = 0.006$) (Fig. 2B and D). In contrast, there were no sex differences in LM Immediate ($\beta = -0.314$, SE = 0.328, $P = 0.34$) or LM Delay ($\beta = -0.195$, SE = 0.287, $P = 0.50$) performance within the severe Alzheimer's disease group.

Discussion

We examined the relationship between sex, tau and verbal memory in two different cohorts. Using ADNI data, we applied a residual approach to estimate verbal memory reserve to tau pathology for each subject. We found that women demonstrate higher verbal memory reserve. These findings were validated using data from the NACC, where we found that, among individuals within Braak 1/2 or Braak 3/4, women had superior verbal memory. Taken together, our findings point to a sex-related verbal memory reserve in the face of tau pathology.

The residual framework has been used extensively to estimate reserve in the presence of brain changes associated with Alzheimer's disease, such as neurodegeneration and Aβ (Hohman *et al.*, 2016). We are aware of no prior tau imaging studies that have explored sex-related reserve. However, a series of recent studies suggested that for similar levels of neurodegeneration, women performed better on the RAVLT (Sundermann *et al.*, 2016*a*, *b*). Furthermore, another study found that the relationship between Aβ and RAVLT performance can be moderated by sex (Caldwell *et al.*, 2017). Our findings, in combination with these studies, indicate that women can sustain more Alzheimer's disease-related brain insult before showing impaired RAVLT performance.

Apart from these imaging investigations, our results are compatible with clinical and neuropsychological studies. The verbal memory advantage for cognitively normal women over men that we observed is consistent with prior clinical investigations (Beinhoff *et al.*, 2008, Chapman *et al.*, 2011). Furthermore, these studies, like ours, showed that the advantage disappears with the progression of disease into dementia. Taken together, these observations are congruent with the following interpretation of how Alzheimer's disease may progress in men and women. Women start with a premorbid (i.e. prior to the onset of Alzheimer's disease pathology) advantage in verbal memory abilities. During the early phases of tau accumulation, memory abilities begin to decline in both men and women, but the premorbid advantage for women persists during this early phase, such that women still perform superiorly in verbal memory for a given level of tau (consistent with the apparent reserve that we found in our study). Then, after a critical point in the Alzheimer's disease course, women begin to show a faster decline in memory abilities and ultimately 'catch up' to the memory impairment of men (in line with our lack of verbal memory sex differences in the later AD stages). The notion that women begin to decline more rapidly is supported by *in vivo* studies showing that women progress faster from mild cognitive impairment to Alzheimer's disease and exhibit greater rates of

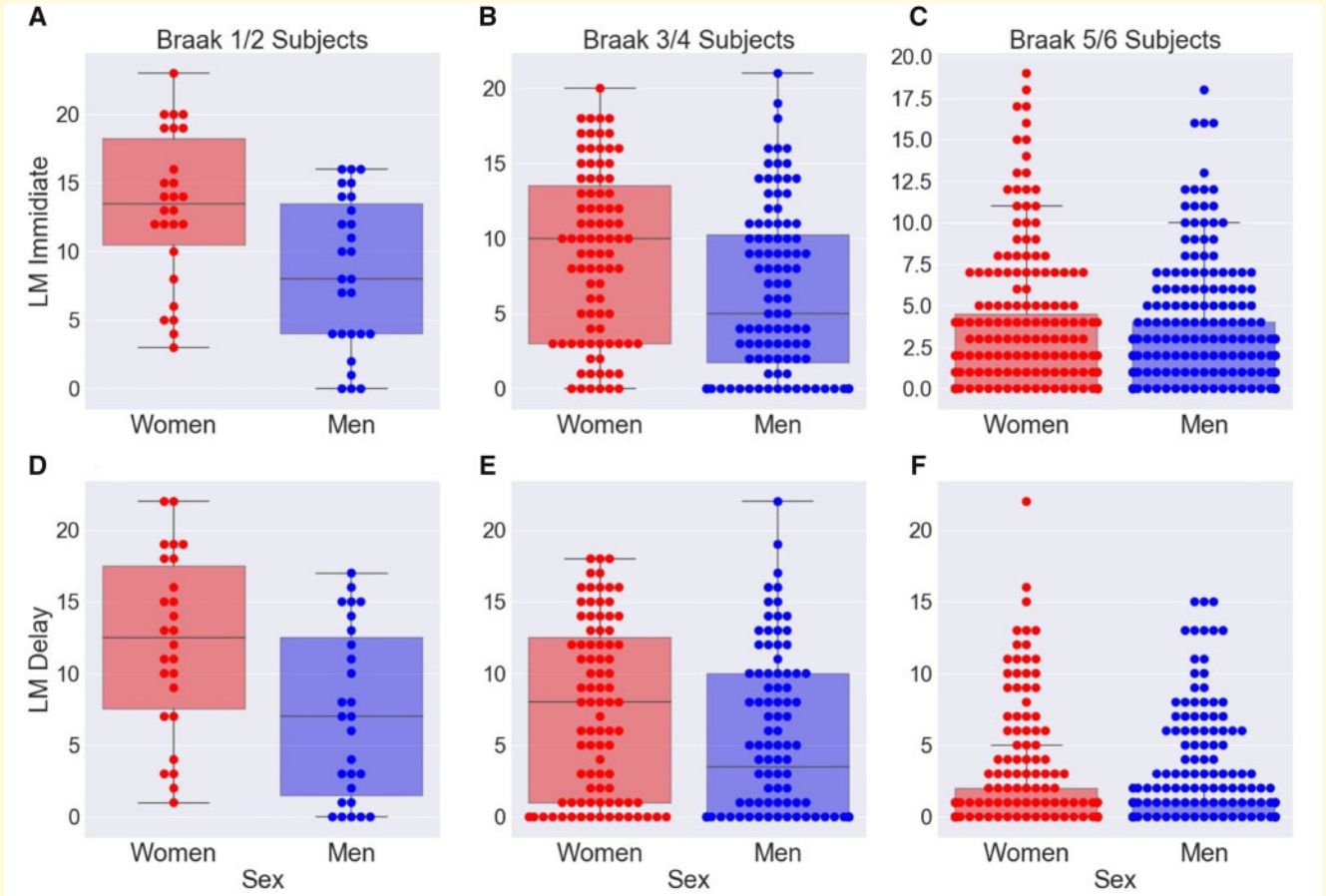


Figure 2 Among participants with similar levels of Alzheimer's disease-related pathology, women perform better on verbal memory tests. On the *y*-axis are raw scores for (**A**–**C**) LM Immediate and (**D**–**F**) LM Delay. Within the Braak 1/2 group and within the Braak 3/4 group, women had significantly higher scores on both LM Immediate and LM Delay. We observed no significant differences in LM score in the Braak 5/6 group.

Alzheimer's disease-related cognitive decline (Lin *et al.*, 2015, Koran *et al.*, 2017). Even further evidence comes from a *post-mortem* study indicating that women are more likely than men to express Alzheimer's disease pathology as dementia (Barnes *et al.*, 2005). Lastly, it was recently reported that women are more susceptible to tau-related hypometabolism (Ramanan *et al.*, 2019), proposing a potential underlying mechanism for this rapid decline seen in women. Despite this burden of evidence, however, our finding of a lack in verbal memory sex differences among the more progressed stages of Alzheimer's disease can alternatively be attributed to a floor effect in the verbal memory scores rather than a rapid decline in women.

Our results from the NACC post-mortem analyses bolster our conclusions from the ADNI tau-PET analyses. First, the finding that, within Braak 1/2 and Braak 3/4 subgroups, women performed better on verbal memory is consistent with our interpretation of a sex-related reserve that we derived from ADNI results. Furthermore, for our NACC analyses, we used scores from a different memory test. The harmony in results across ADNI and NACC analyses indicates that the sex-related reserve is not specific to RAVLT or LM but reserve in verbal memory abilities in general.

The sex-related verbal memory reserve would have several implications for clinical research. Much of our understanding about the evolution of Alzheimer's disease is garnered from large observational cohorts, such as ADNI and NACC. These cohorts often rely heavily on assessing memory with verbal tests. Our findings contribute to the mounting evidence that it is critical to take into account sex differences when considering cut points for verbal memory tests (Sundermann *et al.*, 2019). They also endorse the use of additional non-verbal memory tests in cohort studies of aging to better characterize the memory changes associated with Alzheimer's disease.

Although the residual approach has been shown to be a suitable proxy for reserve by many groups, it clearly does not account for all variability in cognition. For example, men might have worse cognition than predicted by tau because they have more co-morbidities, working in concordance with tau, to impair cognition. Incorporating in vivo markers for pathologies that

commonly co-occur with Alzheimer's disease would be helpful to further characterize sex differences in the ability to tolerate tau.

Though this study is unable to fully explain the underpinnings of reserve, it demonstrates that sex plays a role in conferring apparent cognitive reserve in the face of tau. As such, we feel these results and others call for the end of treating sex as a variable of no interest and, instead, suggest thoughtful consideration into the role of sex in the expression of Alzheimer's disease.

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Competing interests

J.B.B. has served on advisory boards for Elan, Bristol-Myers Squibb, Avanir, Novartis, Genentech and Eli Lilly and holds stock options in CorTechs Labs, Inc., and Human Longevity, Inc. The terms of these arrangements have been reviewed and approved by UCSD in accordance with its conflict of interest policies.

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