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Examining Sex Differences in Markers of Cognition and Neurodegeneration in Autosomal Dominant Alzheimer's Disease: Preliminary Findings from the Colombian Alzheimer's Prevention Initiative Biomarker Study

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Abstract

Background: Growing evidence suggests that there may be a sex-specific biological risk for Alzheimer's disease (AD). Individuals with autosomal dominant AD due to a mutation (E280A) in Presenilin-1 (*PSEN1)* are genetically determined to develop early-onset dementia and thus, have few age-related risk factors for AD that are known to vary by sex (i.e., cardiovascular disease, menopause, life expectancy).

Objective: Investigate sex differences in markers of cognition and neurodegeneration in autosomal dominant AD.

Methods: We conducted a retrospective study in 19 cognitively-unimpaired *PSEN1* mutation carriers (age range 20–44; 11 females), 11 symptomatic carriers (age range 42–56; 8 females), and 23 matched non-carriers family members (age range 20–50; 13 females). We examined hippocampal volume ratio, CERAD Total Score and CERAD Word List (i.e., Learning, Delayed Recall, and Recognition). Mann-Whitney U tests, Spearman correlations and regression models were conducted.

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Conflict of Interest/Disclosure Statement

The authors have no conflict of interest to report.

Results: There were no differential associations between age, CERAD Total Score, CERAD Word List – Learning, Delayed Recall, Recognition, and hippocampal volume ratio in male and female carriers and non-carriers. Cognitively-unimpaired female carriers showed better CERAD Total scores and CERAD Word List – Learning than cognitively-unimpaired male carriers, despite having similar hippocampal volume ratios. The interaction of sex and hippocampal volume ratio did not predict cognitive performance across groups.

Conclusions: Our preliminary findings suggest that cognitively-unimpaired female carriers showed a verbal memory reserve, while, as disease progresses, female carriers did not exhibit a cognitive susceptibility to AD-related neurodegeneration. Future studies with larger samples of autosomal dominant AD are warranted to further understand sex differences in AD-related clinical and pathological markers.

Keywords

sex; Alzheimer's disease; Familial Alzheimer Disease (FAD); cognition; memory; atrophy

INTRODUCTION

Epidemiological studies suggest that females are disproportionately affected by Alzheimer's disease (AD) [1]. Although AD incidence increases with age [2] and more females survive to late-life than males [3], there may also be a sex-specific biological risk for AD. Growing evidence suggests that females have greater AD pathology burden, as evidenced by postmortem studies [4, 5], *in vivo* cerebrospinal fluid (CSF) [6] and neuroimaging studies [7, 8], and that they are more susceptible to AD-related pathology. As levels of AD-related pathology increase, females show greater tau accumulation [7], faster hippocampal volume loss [8], and faster cognitive decline [9] and progression [5] than males. Possible mechanisms underlying sex differences in biological risk have been suggested, including endocrinological [10], cardiovascular [1, 11], or heightened inflammatory responses [12].

However, previous studies investigating sex differences in AD-related pathology and cognitive performance have yielded mixed findings. For instance, Caldwell and colleagues [13] did not find sex differences in hippocampal volume among cognitively normal older adults, while other studies showed that cognitively normal females had greater hippocampal volumes than their male counterparts [14, 15]. Notably, Sundermann and colleagues [15, 16] found that among individuals with mild cognitive impairment, females had better verbal memory than men despite similar levels of medial and inferior temporal glucose metabolism, and hippocampal volume, suggesting that females may have a sex-specific form of cognitive reserve. Thus, sex differences in clinical and pathological manifestations of AD are not well understood.

To our knowledge, no study to date has investigated sex differences in individuals with autosomal dominant AD. Our group follows individuals from the world's largest autosomal dominant AD kindred due to a single mutation (E280A) in the Presenilin1 gene (*PSEN1*). Importantly, this mutation is fully penetrant and not sex-linked, meaning that males and females are equally affected. *PSEN1* mutation carriers are genetically determined to develop early-onset dementia, and although the pathogenesis of autosomal dominant AD is different

from late-onset AD, these conditions have similar clinical, cognitive, and physiological profiles [17]. *PSEN1* mutation carriers have a well-characterized clinical profile, with mild cognitive impairment symptoms emerging at a median age of 44 years old (95% C.I.= 43, 45 years) and dementia at 49 years old (95% C.I.= 49, 50 years) [18, 19]. AD-pathological changes have also been characterized in *PSEN1* mutation carriers, with elevated cortical amyloid accumulation 15 years before clinical symptom onset (i.e., mild cognitive impairment) and elevated levels of tau in medial temporal lobe regions (i.e., entorhinal cortex and inferior temporal lobe) 6 years before clinical symptom onset [17, 20, 21].

Thus, this extraordinary cohort allows us to investigate sex differences along the AD trajectory from preclinical to clinical stages. Moreover, *PSEN1* carriers are virtually destined to develop early-onset dementia and thus, have few age-related factors that confer risk for AD and are known to vary by sex such as cardiovascular disease [1, 11, 22], or hormonal changes [10, 23]. Lastly, examining sex differences in autosomal dominant AD limits common methodological challenges that may confound research into sex differences in sporadic AD, such as survival bias due to differences in mortality among males and females [24].

For the purpose of this study, we leveraged data from the Alzheimer's Prevention Initiative Biomarker study [20] to retrospectively examine sex differences in global cognition, verbal memory (i.e., learning, delayed recall and recognition in a list-learning task), and hippocampal volume ratio in *PSEN1* mutation carriers. We hypothesized that cognitively intact female and male mutation carriers would not differ in hippocampal volume or global cognition, while cognitively intact female mutation carriers would exhibit better verbal memory. When examining sex differences across disease stages by also including symptomatic carriers, we further hypothesized that female mutation carriers would exhibit worse global cognition, verbal memory delayed recall, and lower hippocampal volume than male mutation carriers.

METHODS

Participants

Thirty *PSEN1* mutation carriers (age range: 20–56, mean age: 37.8 +/− 10.6 years; 63% females) and twenty-three matched non-carrier family members (age range: 20–50, mean age: 32.9 +/− 8.8 years; 61% females) from the Alzheimer's Prevention Initiative Biomarker study [20] were retrospectively analyzed. Individuals were recruited from the Alzheimer's Prevention Initiative registry, an effort to locate, enroll, genotype, and perform medical and cognitive evaluations of *PSEN1* E280A family members living in the region of Antioquia, Colombia [25].

Inclusion criteria included an age range of 18 to 60 years. To ensure a broad age distribution among cognitively unimpaired mutation carriers and non-carriers, individuals were enrolled into 18–34 years and 35–60 years age groups. Mutation carriers and non-carriers were matched for sex, age, and educational level within the two age groups [17, 20]. Cognitively unimpaired participants (n=19 carriers) had to show no cognitive impairment on a standard cognitive battery as defined by cutoff scores on the Spanish version of the Consortium to

Establish a Registry for AD battery (CERAD) [26], a Clinical Dementia Rating (CDR) global score of zero and a Mini-Mental State Examination (MMSE) score of at least 28. Symptomatic mutation carriers were defined as having a CDR of ≥ 0.5 and MMSE score between 27 and 18, indicating a clinical diagnosis of mild cognitive impairment (7 carriers, 5 females; mean age: 46 +/− 4.8 years) or mild dementia (4 carriers, 3 females, mean age: 50.5 +/− 1.9 years) according to the National Institute on Aging-Alzheimer's Association diagnostic criteria terminology [27, 28]. Demographic and clinical characteristics of the sample are described in Table 1.

Procedure

All participants or their legal representatives provided informed consent before enrollment into the registry. Ethics approval was obtained from the University of Antioquia Ethics Committee Review Board. Participants and investigators acquiring data were blind to genetic status.

Clinical and Neuropsychological Test

Clinical and neuropsychological evaluations were performed in Spanish at the Universidad de Antioquia (Colombia), which included the MMSE [29], CDR [30], and the Spanish version of the CERAD battery [26] that was previously adapted for this Colombian population. The CERAD Word List task is divided into learning, delayed recall, and recognition. First, participants are shown 10 cards with a word. CERAD Word List – Learning is calculated as the sum of words correctly recalled over three trials (30 points possible for total score). After a 7-minute delay, participants are asked to recall the 10 words shown (CERAD Word List – Delayed Recall; 10 points possible for total score). Finally, participants are shown a list of 20 words (10 target words and 10 distractors). CERAD Word List – Recognition is calculated as the sum of correctly identified targets and distractors minus 10. We also calculated a CERAD Total score, as previously reported [31], by aggregating six CERAD subtests including semantic fluency (Animals), Boston Naming Test (15 items), Word List- Learning, World List - Delayed Recall, Word List - Recognition, and Constructional Praxis Copy.

Brain Imaging

Structural magnetic resonance imaging was performed at Hospital Pablo Tobon Uribe in Medellín, Colombia. As previously described [17], volumetric magnetic resonance imaging data were acquired on a 1.5-T imaging system (Avanto; Siemens) with a T1-weighted, magnetization-prepared, rapid-acquisition, gradient-echo pulse sequence (echo time, minimum full; flip angle, 8°; number of excitations, 1; field of view, 22 cm; imaging matrix, 192 × 192 pixels; and section thickness, 1.2 mm). All images were reviewed for quality and compliance in accord with the Alzheimer's Disease Neuroimaging Initiative recommendations [32]. All images were visually inspected to verify ROI characterization. Hippocampal volume to total intracranial volume ratios were characterized from bilateral hippocampus volumes in each participant's T1-weighted magnetic resonance image using a software package (FreeSurfer 5.1; http://surfer.nmr.mgh.harvard.edu) [33, 34].

Statistical Analyses

Analyses were carried out using SPSS Version 24. Nonparametric Mann-Whitney U test and Spearman correlations were conducted, as data were not normally distributed. Fisher's Z-test was used to compare correlation coefficients. We used regression analyses to characterize associations between sex, hippocampal volume, and the interaction term of sex by hippocampal volume as the predictor variables and cognitive performance as the dependent variable in cognitively unimpaired *PSEN1* mutation carriers. We then conducted the same regression analyses in all *PSEN1* mutation carriers (i.e., cognitively unimpaired and symptomatic carriers) to characterize these associations along the disease trajectory. All analyses were also conducted in non-carriers.

RESULTS

Markers of cognition and neurodegeneration in male and female carriers

Table 1 shows demographic, cognitive and clinical characteristics. Among cognitively unimpaired carriers, males and females did not differ on age, years of education, MMSE scores or hippocampal volume ratio. Cognitively unimpaired females showed better CERAD Total scores and CERAD Word List – Learning than cognitively unimpaired males, while there were no other differences in cognitive measures. There were no sex differences in demographics, cognitive measures or hippocampal volume ratio among symptomatic male and female carriers and male and female non-carriers.

Association of age with markers of cognition and neurodegeneration in male and female carriers

In this population, age is commonly used as a proxy to measure disease progression because carriers get closer to the estimated age of symptom onset as they age [18, 19]. We found that, among cognitively unimpaired male and female carriers, age was not associated with hippocampal volume ratio, CERAD Word List- Learning, Delayed Recall, Recognition, or CERAD Total scores (Table 2).

Across all carriers, greater age in both male and females was associated with lower hippocampal volume (Males: $\boldsymbol{r_s} = -.71$, $p = .015$; Females: $\boldsymbol{r_s} = -.66$, $p = .002$). Older age was significantly associated with worse CERAD Word List – Learning ($\boldsymbol{r_s} = -.76$, $p = .000$), Delayed Recall ($\boldsymbol{r_s} = -.66$, $p = .002$), Recognition ($\boldsymbol{r_s} = -.62$, $p = .005$), and CERAD Total score ($\boldsymbol{r_s} = -.68$, $p = .001$) in female carriers. In contrast, while greater age was also associated with worse CERAD Word List – Learning, Delayed Recall, Recognition, or CERAD Total score in male carriers, these associations did not reach significance. The difference between the magnitudes of these associations was not statistically significant.

Among male and female non-carriers, age was not correlated with hippocampal volume ratio, CERAD Word List – Learning, Delayed Recall, Recognition, and CERAD Total score.

Sex, and markers of cognition and neurodegeneration

Among cognitively unimpaired carriers, hippocampal volume ratio, sex and the interaction term of sex and hippocampal volume ratio did not predict performance on the CERAD Word

List- Learning, Delayed Recall, Recognition, or CERAD Total score (Table 3). Sex showed a trend towards significance in predicting CERAD Total scores (β = .58, p = .072), wherein cognitively unimpaired female carriers showed higher scores than cognitively unimpaired male carriers.

Across all carriers, lower hippocampal volume ratio predicted worse performance on the CERAD Word List- Learning, Delayed Recall, Recognition, and CERAD Total scores (Table 3). Sex did not predict performance on the CERAD Word List- Learning, Delayed Recall, Recognition or CERAD Total scores across all carriers. The interaction term of sex and hippocampal volume ratio did not predict performance on the CERAD Word List- Learning, Delayed Recall, or CERAD Total scores, while it showed a trend towards significance in predicting CERAD Word List- Recognition scores ($\beta = .33$, $p = .078$).

Across non-carriers (Table 4), hippocampal volume ratio, sex, and the interaction term of sex and hippocampal volume ratio did not predict CERAD Word List- Learning, Delayed Recall, Recognition, or CERAD Total scores.

DISCUSSION

Growing evidence suggests that females may be more susceptible to AD-related pathology [5, 7–9, 35]. However, sex differences in clinical and pathological manifestations of AD remain poorly understood. To our knowledge, this is the first study to investigate sex differences in markers of cognition and neurodegeneration in carriers of an autosomal dominant Alzheimer's disease mutation who are destined to develop early-onset AD by midlife [18, 19]. We leveraged data from the world's largest kindred with a single mutation (E280A) in the Presenilin1 gene (*PSEN1).* Importantly, *PSEN1* carriers develop mild cognitive impairment at a median age of 44 years and dementia at a median age of 49 years [18], and thus have few age-related risk factors for AD at symptom onset that are known to vary by sex (i.e., life expectancy, cardiovascular disease, hormonal changes).

In autosomal dominant AD, age is commonly used as a proxy of disease progression, because as carriers age, they get closer to their age of estimated symptom onset. Therefore, we examined the relationship between age and markers of cognition and neurodegeneration. We found that among cognitively unimpaired male and female carriers, age was not associated with markers of cognition or neurodegeneration, perhaps due to limited age range in this group. When examining this relationship across all carriers, older age was associated with lower hippocampal volume in both male and female carriers, while older age was associated with worse global cognition and verbal memory in female carriers only. Of note older age was also associated with worse cognition and verbal memory in male carriers but these associations did not reach significance. Nonetheless, the magnitude of these associations was not statistically different among male and female carriers. This finding may be driven by the larger number of symptomatic female carriers that result in a greater range of cognitive performance.

We examined sex differences in markers of cognition and preliminary findings show that cognitively unimpaired female carriers showed better global cognition and verbal memory

learning than cognitively unimpaired male carriers. This finding is consistent with previous extensive literature showing a verbal memory advantage for females [36]. However, we did not find a difference in word list delayed recall or recognition variables, perhaps due to restricted range in performance. With regard to the sex difference on global cognition, it is important to note that global cognition was measured using the CERAD total score, an aggregate of six CERAD subtests that also includes word list learning, thus likely contributing to the effect found. Non-carrier females also showed slightly better cognitive performance than non-carrier males, although differences were not statistically significant. Again, restricted range of performance in the CERAD may have limited our ability to detect differences, particularly among cognitively unimpaired individuals. In contrast, when examining all carriers by also including symptomatic carriers, cognitive performances did not differ among males and females. This may suggest that this verbal memory advantage may only be present in earlier stages of the disease, as previously shown [37], although further examination in samples with larger number of symptomatic carriers is required.

We also examined sex differences in markers of neurodegeneration and found that males and females had similar levels of hippocampal volume ratio among cognitively unimpaired and symptomatic carriers. This finding does not support our hypothesis, as we posited that as disease progresses and pathology accumulates, female carriers would exhibit worse levels of neurodegeneration. However, it is consistent with previous reports that found no sex-specific differences in hippocampal volume preservation among cognitively normal individuals [13]. Nonetheless, it is important to highlight that previous studies show great variability in findings wherein some studies found that females showed greater brain resilience to tau deposition [38], while others found that females showed lower brain resilience [35]. Further research is needed to clarify whether females show greater resilience or susceptibility to AD-related pathology than males, and whether this effect varies across disease stages.

With regard to the effect of sex moderating the relationship between neurodegeneration and cognitive performance, we found that there was no interaction between sex and hippocampal volume ratio in predicting cognitive performance among cognitively unimpaired carriers. Similarly, across all carriers, sex by hippocampal volume interaction did not predict verbal memory learning, delayed recall, or global cognition. However, there was a trend towards significance, wherein female carriers with lower hippocampal volume ratio had worse verbal memory recognition than male carriers. Overall, contrary to our hypotheses, our findings show no evidence that females with this autosomal dominant AD mutation have greater cognitive susceptibility to AD-related neurodegeneration compared to male carriers. Our ability to detect such an effect may have been limited by the relatively low number of symptomatic carriers, particularly with mild dementia. Alternatively, the sex differences previously found in sporadic AD may be linked to factors that are not relevant in this unique cohort of autosomal dominant AD, such as older age [2, 19], cardiovascular disease [1, 11, 22], menopause [10, 23], or survival bias (i.e., mortality differences in males and females) [24].

This study has limitations and thus, findings should be interpreted with caution. First, this is a retrospective, cross-sectional study with a small sample size and relatively few symptomatic carriers, which may have resulted in limited power to detect sex differences,

particularly in later stages of the disease. Additionally, there were a larger number of females in the sample and a greater number of symptomatic female carriers. The generalizability of these findings to others at risk for autosomal dominant AD or late-onset sporadic AD requires further investigation. However, despite the small sample size/power limitations, which are generally inherent in autosomal dominant AD research, this cohort offers a unique opportunity to examine sex differences using neuroimaging methods with fewer age- and sex-related confounds than in research with sporadic AD (i.e., mortality/life expectancy, cardiovascular disease, or menopause).

Summary

In conclusion, this is the first study to investigate sex differences in autosomal dominant AD due to a single mutation (E280A) in the *PSEN1* gene. We examined the effect of sex on markers of cognition and neurodegeneration. Our findings suggest that cognitively unimpaired female carriers had better global cognition and verbal memory learning than males, despite having similar hippocampal volume ratios. Moreover, there was no evidence that, as disease progresses, female carriers had a cognitive susceptibility to AD-related neurodegeneration. Notably, these findings are preliminary and interpretation warrants caution. Future studies with larger samples of autosomal dominant AD and longitudinal time points are warranted to further understand sex differences in AD-related clinical and pathological markers to inform detection, prevention, and development of AD treatments.

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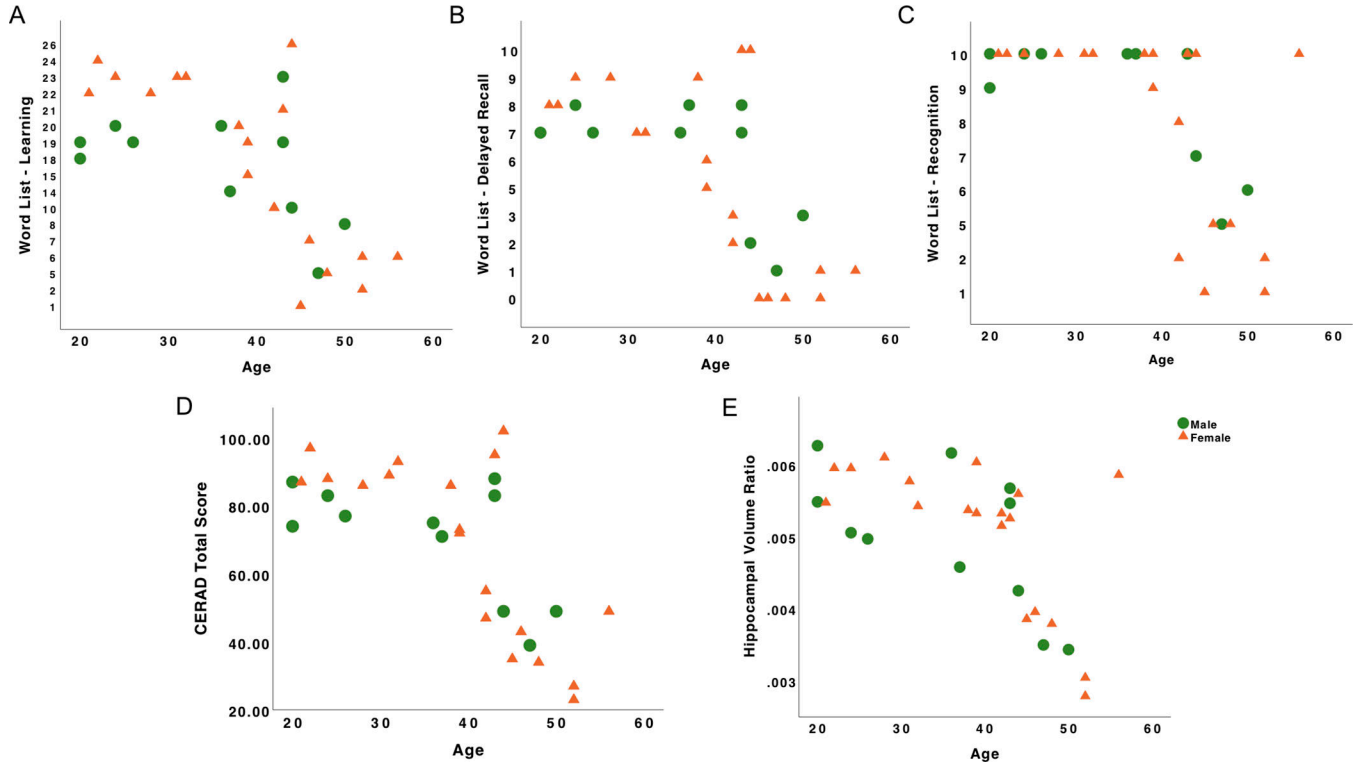

Figure 1. Relations among age, cognition and neurodegeneration in *PSEN1* male and female carriers

Note. A, Verbal memory learning as a function of age. B, Verbal memory delayed recall as a function of age. C, Verbal memory recognition as a function of age. D, CERAD Total score as a function of age. E, Hippocampal volume ratio as a function of age. Green dots represent male *PSEN1* mutation carriers and orange triangles represent female *PSEN1* mutation carriers.

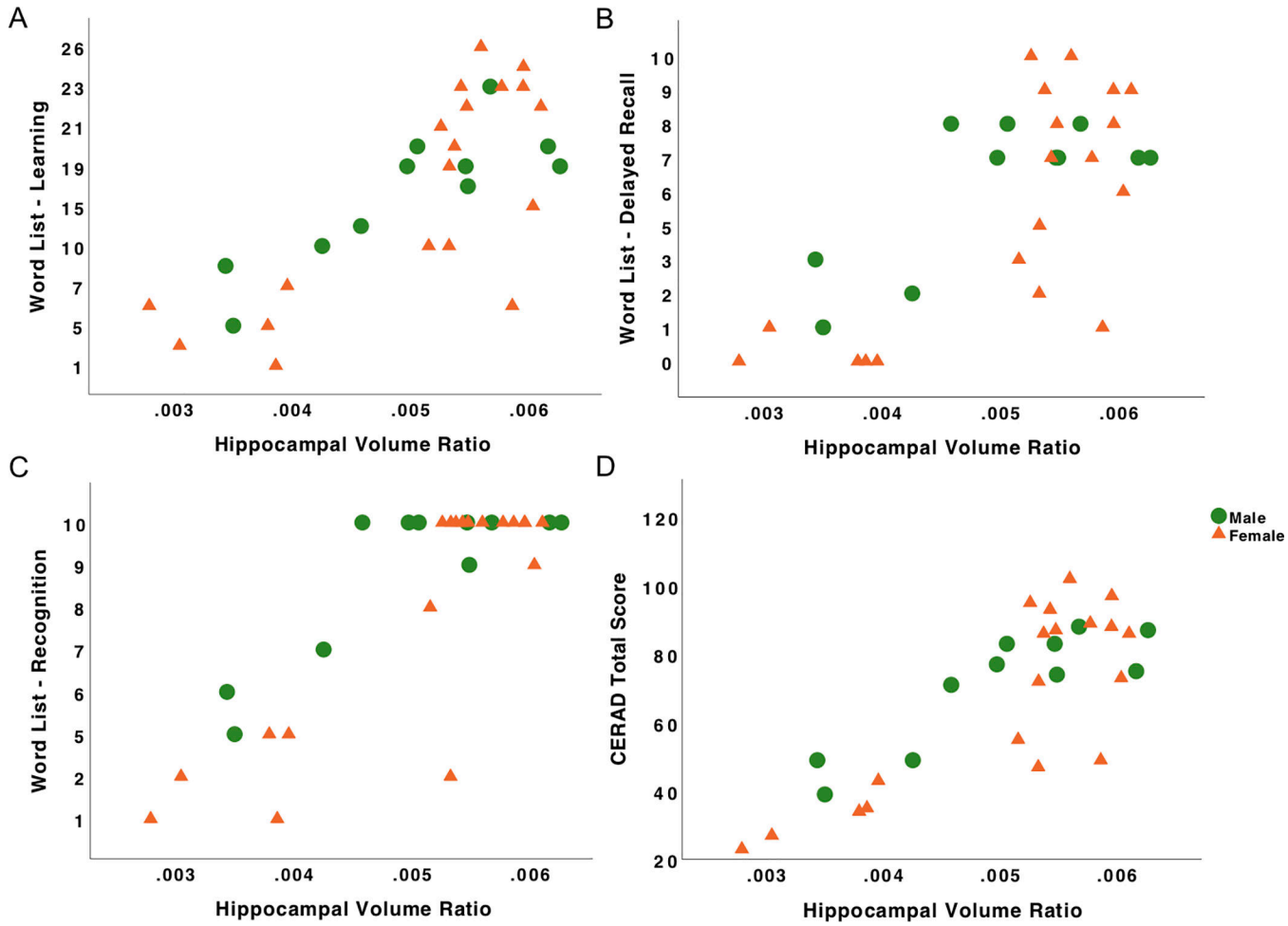

Figure 2. Relations among neurodegeneration and cognition in *PSEN1* male and female carriers

Note. A, Verbal memory learning as a function of hippocampal volume ratio. B, Verbal memory delayed recall as a function of hippocampal volume ratio. C, Verbal memory recognition as a function of hippocampal volume ratio. D, CERAD Total scores as a function of hippocampal volume ratio. Green dots represent male *PSEN1* mutation carriers and orange triangles represent female *PSEN1* mutation carriers.

Table 1.

Demographic, cognitive and clinical characteristics of sample.

	Non-carriers			Cognitively Unimpaired Carriers			Symptomatic Carriers		All Carriers		
	M(SD)		p^a	M(SD)		p^b	M(SD)		M(SD)		p^c
	Male n = 9	Female n = 13		Male n = 8	Female n = 11		Male n = 3	Female n = 8	Male n = 11	Female n = 19	
Age (years)	30.89 (8.81)	34.21 (8.88)	.449	31.13 (9.75)	32.82 (8.33)	.545	47.00 (3.00)	47.87 (5.08)	35.45 (11.10)	39.16 (10.34)	.838
Education (years)	12.00 (3.16)	10.83 (3.41)	.498	12.13 (3.23)	12.36 (2.06)	.075	6.00 (2.65)	9.75 (3.58)	10.45 (4.11)	11.26 (3.02)	.121
MMSE	29.67 (.50)	29.77 (.44)	.459	29.88 (.35)	29.91 (.30)	.904	25.00 (1.00)	23.88 (4.05)	28.55 (2.34)	27.37 (3.97)	1.00
CERAD Total	79.44 (6.08)	80.79 (7.14)	.430	79.75 (6.34)	88.00 (9.18)	.047*	45.67 (5.77)	39.12 (11.19)	70.45 (16.98)	67.42 (26.65)	.303
CERAD Word List – Learning	18.56 (2.51)	19.79 (3.21)	.280	19 (2.51)	21.64 (2.91)	.030*	7.67 (2.52)	5.88 (3.27)	15.91 (5.80)	15 (8.53)	.469
CERAD Word List – Delayed Recall	7.00 (1.32)	7.43 (1.50)	.496	7.38 (.52)	8.00 (1.61)	.230	2.00 (1.00)	.88 (1.13)	5.91 (2.59)	5.00 (3.87)	.138
CERAD Word List – Recognition	9.78 (.67)	9.86 (.53)	.747	9.88 (.35)	9.91 (.30)	.816	6.00 (1.00)	4.25 (3.37)	8.82 (1.89)	7.53 (3.56)	.301
Hippocampal Volume × 10^3	5.52 (.19)	5.68 (.48)	.378	5.46 (.58)	5.66 (.31)	.56	3.72 (.45)	4.22 (1.11)	4.98 (.96)	5.05 (1.03)	.540

Note: M = Mean; SD = Standard Deviation; MMSE = Mini Mental State Exam; CERAD = Consortium to Establish a Registry for Alzheimer's Disease.

[a] p-value calculated for Mann-Whitney test for males versus females in matched non-carriers.

[b] p-value calculated for Mann-Whitney test for males versus females in cognitively intact PSEN1 mutation carriers.

[c] p-value calculated for Mann-Whitney test for males versus females across all *PSEN1* mutation carriers (including cognitively unimpaired and symptomatic carriers).

* $p<0.05$.*. Group differences significant at the 0.05 level (2-tailed).

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Table 2.

Correlation of age, cognitive measures and neurodegeneration in cognitively unimpaired *PSEN1* mutation carriers, across all *PSEN1* mutation carriers and non-carriers.

	Cognitively Unimpaired Carriers					
	Male n = 8		**Female n = 11**			
	r_s	p^a	r_s	p^b	Z	p^c
CERAD Total	.15	.720	.05	.894	.18	.859
CERAD Word List – Learning	.27	.512	−.27	.427	.97	.331
CERAD Word List – Delayed Recall	.34	.407	.16	.644	.34	.735
CERAD Word List – Recognition	.50	.206	.16	.644	.68	.496
Hippocampal Volume	−.23	.586	−.43	.189	.40	.692
	All Carriers					
	Male n = 11		**Female n = 19**			
	r_s	p^a	r_s	p^b	Z	p^c
CERAD Total	−.55	.081	−.68	.001*	.49	.626
CERAD Word List – Learning	−.52	.103	−.76	.000*	.97	.332
CERAD Word List – Delayed Recall	−.51	.107	−.66	.002*	.53	.595
CERAD Word List – Recognition	−.58	.060	−.62	.005*	.14	.885
Hippocampal Volume	−.71	.015*	−.66	.002*	−.22	.827
	Non-Carriers					
	Male n = 9		**Female n = 14**			
	r_s	p^a	r_s	p^b	Z	p^c
CERAD Total	−.01	.983	−.02	.931	.02	.984
CERAD Word List – Learning	.23	.558	.23	.427	.00	1.00
CERAD Word List – Delayed Recall	−.23	.553	.06	.825	−.58	.562
CERAD Word List – Recognition	.00	1.00	−.38	.181	.78	.430
Hippocampal Volume	−.13	.732	−.19	.507	.12	.903

Note: CERAD = Consortium to Establish a Registry for Alzheimer's Disease; Hippocampal Volume = Hippocampal Volume Ratio; r_S = Spearman's rho coefficient; Z = Z statistics.

[a] p-value calculated for Spearman correlation in males.

[b] p-value calculated for Spearman correlation in females.

[c] p-value calculated for Fisher exact test comparing Spearman's rho in males and females.

* $p<0.05$.*. Group differences significant at the 0.05 level (2-tailed).

Table 3.

Regression estimates of the effect of sex and neurodegeneration on cognition in *PSEN1* mutation carriers

		Cognitively Unimpaired Carriers n = 19			All Carriers n = 30		
Outcome Variable	**Predictors**	**β**	***p*[a]**	**Effect Size (*Cohen's f*)**	**β**	***p*[b]**	**Effect Size (*Cohen's f*)**
CERAD Word List - Learning	Hippocampal Volume	.35	.215	.27	3.33	.003*	1.27
	Sex	.54	.093	.53	−.58	.568	.10
	Sex × Hippocampal Volume	−.26	.468	.19	.44	.661	.09
CERAD Word List- Delayed Recall	Hippocampal Volume	−.15	.617	.12	2.60	.015*	1.09
	Sex	.23	.510	.26	−.97	.341	.19
	Sex × Hippocampal Volume	.08	.845	.05	.17	.476	.14
CERAD Word List-Recognition	Hippocampal Volume	−.02	.958	.17	.53	.007*	1.52
	Sex	.31	.382	.06	−.18	.096	.39
	Sex × Hippocampal Volume	−.37	.362	.24	.33	.078	.36
CERAD Total Score	Hippocampal Volume	.25	.372	.16	.65	.002*	1.45
	Sex	.59	.072	.55	−.06	.586	.12
	Sex × Hippocampal Volume	−.27	.460	.20	.20	.315	.20

Note. CERAD= Consortium to Establish a Registry for Alzheimer's Disease; Hippocampal Volume = Hippocampal Volume Ratio.

[a] p-value calculated for regression model in cognitively unimpaired *PSEN1* mutation carriers.

[b] p-value calculated for regression model across all *PSEN1* mutation carriers (including cognitively unimpaired and symptomatic carriers).

* p<0.05.*. Group differences significant at the 0.05 level (2-tailed).

Table 4.

Regression estimates of the effect of sex and neurodegeneration on cognition in non-carriers.

Outcome Variable	Predictors	β	p^a	Effect Size (*Cohen's f*)
CERAD Word List - Learning	Hippocampal Volume	.23	.772	.03
	Sex	.28	.465	.21
	Sex × Hippocampal Volume	−.24	.793	.06
CERAD Word List- Delayed Recall	Hippocampal Volume	−.31	.698	.04
	Sex	.00	.994	.15
	Sex × Hippocampal Volume	.42	.648	.11
CERAD Word List- Recognition	Hippocampal Volume	−.83	.306	.04
	Sex	−.23	.541	.07
	Sex × Hippocampal Volume	.93	.310	.24
CERAD Total Score	Hippocampal Volume	−.03	.968	.14
	Sex	.00	.991	.10
	Sex × Hippocampal Volume	.20	.824	.05

Note. CERAD= Consortium to Establish a Registry for Alzheimer's Disease; Hippocampal Volume = Hippocampal Volume Ratio.

[a] p-value calculated for regression model in non-carriers.

[*] $p<0.05$.*. Group differences significant at the 0.05 level (2-tailed).