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Gender differences of neuropsychological profiles in cognitively normal older people without amyloid pathology

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Abstract

Objective—To investigate the impact of sex on cognition among cognitively normal older people without amyloid pathology.

Methods—The study sample consisted of 83 males (mean age 74 years, ranging from 65 to 88 years) and 111 females (mean age 72 years, ranging from 65 to 89 years) who were cognitively normal without amyloid pathology confirmed by Pittsburgh compound B PET scan. We examined the sex discrepancies in cognition using a comprehensive neuropsychological battery.

Results—Our data showed significantly greater advantage for women than men on the tasks of verbal memory and category fluency while better performance of naming in men than women when age, education and depressive symptoms were considered.

Conclusion—These findings highlight the importance of considering sex differences in the interpretation of cognitive data which contribute to clinical diagnosis of neurodegenerative disorders, such as Alzheimer's disease.

Keywords

amyloid; sex differences; neuropsychological tests

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1. Introduction

Gender differences in cognition occur in healthy older people, showing that women outperformed men in verbal memory consistently [1-3] while men excelled at the tests of attention [3], reaction time [3] and visuospatial ability[2]. This gender difference is substantially important in the diagnosis process because neuropsychological examination is indispensable for the assignment of cognitively normal, mild cognitive impairment (MCI) or dementia and norms for cognitive tests are not sex-adjusted at present. It is a great concern that a correct diagnosis of cognitively normal or cognitively impaired may be missed due to sex differences in the cognitive functions in normative data. For instance, a real amnesic mild cognitive impairment (aMCI) diagnosis is more likely to be delayed in women than men on account of the fact that the women advantage in verbal memory may counteract the effects of Alzheimer's disease (AD) neuropathology, especially in the earlier stages of disease.

AD disproportionately affects women and men. The Framingham Study found that the estimated lifetime risk for AD was one in eleven for men while one in six for women specifically at the age of 65 [4]. In terms of clinical manifestations, men appeared to show more comorbidities, more aggressive behaviors, and higher mortality while women tended to have more disabilities and more depressive symptoms but a longer survival time[5]. It is also noteworthy that a stronger relationship between AD neuropathology and clinical AD was observed in women than in men, indicating AD neuropathology is more prone to be exhibited clinically as dementia in women[6]. In AD patients, men performed better than women in verbal memory [7], naming [7] and verbal fluency [8]. Taken together, AD shows sex differences in multiple aspects.

According to the amyloid cascade hypothesis of AD, amyloid accumulation is the essential cause of compromised cognition in AD and triggering its pathogenesis [9]. However, the proportion of amyloid positive among the healthy population is 26.9%, reported in the HABS dataset[10]. Moreover, previous studies revealed that approximately a quarter of cognitively normal older people over the age of 60 exhibited substantial amyloid deposits in their brains[11]. Interestingly, amyloid deposits were found to be conversely related to cognitive functioning[12], suggesting that amyloid accumulation may produce adverse effects on cognition in non-demented sample of older adults. Therefore, the study sample from previous studies [1-3] investigating the gender differences in cognition among cognitively normal older people were very likely to be “contaminated” by amyloid, leading to the possibility that amyloid might be responsible for some of the variations in cognition between women and men healthy older people. In order to diminish or eliminate the “contaminated” effects of amyloid on cognition, we had chosen a non-demented sample of older adults with no amyloid pathology in our current study, which, to our best knowledge, has not been explored before. Therefore, the main aim of our current study was to determine whether the gender differences in neuropsychological performance exist in cognitively normal older people without amyloid pathology confirmed by carbon-11-labeled Pittsburgh compound B (PiB) PET scan, after controlling for other potentially confounding variables.

2. Material and methods

2.1 Participants and data source

Cross-sectional data used in the preparation of this article were extracted from the Harvard Aging Brain Study (HABS-P01AG036694, <http://nmr.mgh.harvard.edu/lab/harvardagingbrain>), a longitudinal observational study involving demographics, neuropsychological testing, clinical assessment, neuroimaging and biomarker sampling [13]. The overall objective of the HABS has been to further our understanding of aging and preclinical AD. The HABS study was launched in 2010. The initial data freeze (v 1.00), which consists of baseline clinical and cognitive assessments and neuroimaging biomarkers, was released to the entire research community as an open resource.

Our study sample included participants who were community dwelling, English-speaking, had good general medical health examined by study physicians, had a score of 25 or higher on the Mini-Mental State Examination (MMSE) [14], a score of 0 on Clinical Dementia Rating (CDR) [15], a score of 11 or lower on Geriatric Depression Scale (GDS-30) [16], no objective memory impairment (measured by scores on the Delayed Recall of the Logical Memory Story A [17]) and a diagnosis of cognitively normal with amyloid negativity (defined by PiB retention, see below). The current study sample consisted of 194 participants, including 83 males and 111 females.

2.2 Clinical and Neuropsychological Assessment

Participants underwent three clinical assessments, including MMSE [14], CDR [15] and GDS-30 [16]. In addition, subjects were administered a comprehensive battery of neuropsychological tests consisting of Verbal fluency (3 categories, F-A-S) [18], Boston Naming Task (BNT-30) [19], Digit Symbol Coding [20], Digit Span [20], Letter Number Sequencing [21], Trail Making Test A and B [22], and Logical Memory I and II [17].

2.3 PiB-PET data

Amyloid burden was measured on a Siemens ECAT EXACT HR + PET scanner at the Massachusetts General Hospital (MGH) PET facility. C^{11} -PiB synthesis and imaging were performed as previously described [23]. Briefly, a 60-min dynamic acquisition was immediately followed after the injection of 8.5-15 mCi [^{11}C]-PiB. The Logan graphical analysis technique with cerebellar grey matter as the reference region was adopted to assess specific PiB retention represented as the distribution volume ratio (DVR), which was calculated for an aggregate of cortical regions, including frontal, temporal, lateral parietal and retrosplenial cortices. PiB retention in these regions is substantial in patients with AD dementia. Using Gaussian mixture modeling, the cutoff value of DVR for the aggregate was established (DVR ≥ 1.20 , A β -; DVR < 1.20 , A β +) [24]. In this analysis, all participants were A β -.

2.4 Statistical analyses

Sociodemographic and clinical variables were compared between sexes using student's t test or Mann-Whitney-U test for continuous variables according to the distribution and χ^2 test for categorical variables. More specifically, sex differences of age, education, MMSE and GDS

scores were examined using Mann-Whitney-U test, for PiB retention using student's t test, and for race using χ^2 test. The cognitive data were transformed into z-scores first. Since the mean level of education of the sample was high (about 16 years), the cognitive data were not normally distributed, being skewed towards high performances. Then we applied the log transformation to make the data normally distributed. After that, we used student's t-test to examine the differences between females and males in cognitive variables. Next, the significant cognitive domains identified in the student's t-test between females and males were then performed in the analyses of covariance (ANCOVA) as dependent variables, with gender as the independent variable and age, education and GDS scores as covariates. IBM SPSS version 20 was used to perform all statistical analyses. A two tailed P value of less than 0.05 was considered to be statistically significant.

1. Results

3.1 Demographic and clinical characteristics by gender

The overall sample comprised 194 cognitively normal older people. Demographics and clinical characteristics of the study sample are demonstrated in Table 1. Briefly, males were older than females (74.1 ± 6.0 versus 72.4 ± 6.1 , $p=0.041$). Other variables were comparable between males and females (all $p > 0.05$).

3.2 Cognitive profiles by gender

Gender differences in neuropsychological profiles in our study sample are summarized in Table 2. As can be seen from this table, men performed better on naming test while women excelled at verbal memory and category fluency. However, we found no sex differences in other cognitive functions (all $p > 0.05$).

3.3 Cognitive profiles by gender after the correction of potential confounding factors

Additionally, the significant cognitive domains (verbal memory, naming and category fluency) identified in the student's t-test between females and males were then performed in the analyses of covariance (ANCOVA) as dependent variables, with gender as the independent variable and age, education and depression (GDS-30) as covariates. We still found significant differences between females and males in verbal memory, naming and category fluency after controlling for age, education and depression (Table 3). In our gender comparisons we calculated effect sizes using Cohen's d (See Table 3), which is defined as the difference between two means divided by a standard deviation for the data. Positive values indicate higher scores for men and negative reflect higher scores for women. The value of 0.20 indicates a small effect, 0.50 a moderate effect and 0.80 a large effect.

2. Discussion

These findings confirmed significantly greater advantage for women than men on the tasks of verbal memory and category fluency while better performance of naming in men than women among cognitively normal older people without amyloid pathology when age, education and depressive symptoms were considered. However, we found no significant differences between men and women on other cognitive domains. These observations

strengthen the idea that gender discrepancies among cognitively normal older people may pertain only to specific cognitive domains and that these specific domains, when involved in the diagnosis process of cognitive status, could give rise to a misleading outcome if norms are not sex-adjusted.

Gender differences in cognition among healthy older people have been studied extensively. The primary findings were that gender differences in cognitive performance are considered to be few and relatively small[25]. However, the literature provides support for two conclusive differences. Women generally outperform men in episodic memory tasks [26, 27], especially in tasks of verbal episodic memory[28], and tasks of face recognition[29, 30]. Men on the other hand tend to perform better than women in spatial ability tasks[31], especially in tasks of spatial navigation[32]. Further, longitudinal studies indicated that gender differences in cognitive performance were considered to be quite stable across ages, which suggested that men and women seemed to decline in parallel[33-35]. Gender differences in cognitive performance are apparent also in very advanced ages [36]. In our present study, our findings further confirmed gender differences in cognitive performance in normal older people without amyloid pathology, which are largely consistent with previous studies [25-30].

Epidemiological studies reported elevated risk of AD in women[4], although the underlying mechanism remains elusive. However, increasing evidence implicated amyloid as a potential modulator in this sex difference. In transgenic mouse models of AD, female mice exhibited higher amyloid deposits in the brain [37-39], elevated beta-secretase activity and lower levels of neprilysin [39], indicating both up-regulated production and down-regulated clearance of amyloid in females. However, in human study, the results were mixed and inconclusive [6, 40]. Further, approximately a quarter of cognitively normal older people over the age of 60 exhibited substantial amyloid deposits in their brains[11], which were adversely related to cognitive functioning[12]. One may consider the possibility that amyloid, at least in part, could contribute to the observed gender differences in cognition among healthy older people. Thus, in current analysis, we excluded participants who were amyloid positive, and this contributed to the “normality” of the study sample. The results of this study largely supported previous findings as mentioned in the above paragraph, implying that other factors than amyloids may matter for gender differences in cognition among healthy older people. However, the exact mechanism underlying this gender difference remains unknown.

In the past decade, a wealth of biomarkers and technologies advancing our power to early detection of AD have been identified and developed, although neuropsychological examination still remains the essential core in the process of diagnosis. For instance, the diagnosis of aMCI, an intermediate status between normal aging and AD, requires evidence of objective memory impairment, which is typically confirmed by standardized neuropsychological test [41]. Scores on neuropsychological test for aMCI subjects are generally 1 to 1.5 standard deviations (SD) below age and education matched control individuals on normative data[41]. Importantly, these ranges are guidelines but not cutoff scores [41]. It is a bit of a dilemma when physicians encounter subjects with score close to cutoff value. Yet, the sex differences of cognition among healthy elderly could create

another dilemma if norms are not sex-adjusted. For example, a true aMCI diagnosis is more likely to be delayed in women than men, because the women superiority in verbal memory may counteract the effects of AD neuropathology, especially in the earlier stages of disease. Due to our data, conversely, a real non-aMCI (language domain in particular) diagnosis may be delayed more often in men than women because of the men advantage in naming. Taken together, these findings highlighted the importance of considering sex differences in interpretation of cognitive data which contribute to clinical diagnosis.

Ideally, it is important to develop the norms in which individuals were cleared of amyloid pathology as well as all other neuropathologies, and this will be more sensitive in the early detection of MCI or dementia not only due to AD, but also other etiologies, such as tauopathies and Lewy body diseases. However, the cost would be prohibitive, which may limit its generalizability.

Despite its strengths, some weaknesses in the present study need to be considered. Firstly, individuals in our study sample were highly educated and may not be representative of the general population. Secondly, we cannot exclude the possibility of other cerebral pathologies, such as vascular pathology and tau pathologies, that may also adversely affect cognitive functions. Thirdly, we did not control for other potentially confounding factors, such as estrogen levels, estrogen treatment, APOE genotypes, lifestyles, etc. Fourthly, although all the participants were English speaking, we did not know how many of them were non-English speaking background (NESB). For those NESB participants, maybe their scores on verbal/language-based cognitive tests were different from those native English speakers. In this way, whether they were of NESB could shed some light on the findings of our current study. This shortcoming will be remedied in the future investigation. Fifthly, in our current study, the mean level of education of the sample was high (about 16 years), which had caused the cognitive data to be skewed towards high performances. Thus, our sample is not representative of the normal older population. Finally, small sample size could limit the interpretation of our results.

3. Conclusions

Our findings showed significantly greater advantage for women than men on the tasks of verbal memory and category fluency while better performance of naming in men than women among cognitively normal older people without amyloid pathology. These findings highlight the importance of considering sex differences in the interpretation of cognitive data which contribute to clinical diagnosis of neurodegenerative disorders, such as Alzheimer's disease.

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Table 1
Overall sample characteristics by gender

Variables	Males (n=83)	Females (n=111)	P Value
Age, y	74.1 (6.0)	72.4 (6.1)	0.041 *
Education, y	15.7 (3.2)	15.6 (3.0)	0.832
Race, % White	83.1	76.6	0.264
MMSE	29.1 (1.1)	29.1 (1.1)	0.939
GDS	2.9 (2.7)	3.2 (2.9)	0.585
Cortical PiB aggregate, DVR	1.1 (0.05)	1.1 (0.05)	0.167

Abbreviations: MMSE= Mini-Mental State Examination; GDS= Geriatric Depression Scale; PiB= Pittsburgh compound-B; DVR= Distribution volume ratio.

*
p<0.05

Table 2
Neuropsychological profiles by gender

Measures (median, IQR)	Males (n=83)	Females (n=111)	P Value
Log Boston Naming Test-30	1.45 (.06)	1.43 (0.06)	0.027 *
FAS	43.22 (13.54)	43.75 (14.32)	0.794
3 categories	41.76 (9.97)	45.84 (10.10)	0.006 *
Log Digit forward span	0.85 (0.06)	0.84 (0.07)	0.247
Log Digit backward span	0.69 (0.14)	0.70 (0.11)	0.644
Log Digit symbol Coding	1.65 (0.10)	1.67 (0.11)	0.222
Log Letter number sequencing	0.97 (0.14)	0.97 (0.15)	0.841
Log Logical Memory I	1.14 (0.10)	1.18 (0.10)	0.005 *
Log Logical Memory II	1.09 (0.16)	1.14 (0.11)	0.005 *
Log Trail Making Test-A	1.52 (0.14)	1.54 (0.15)	0.369
Log Trail Making Test -B	1.91 (0.18)	1.93 (0.21)	0.584

Abbreviations: FAS= letters F, A and S; 3 categories= animals, vegetables and fruits; Logical Memory I= Logical Memory-immediate recall; Logical Memory II= Logical Memory- delayed recall.

Cognitive data are summarized as mean (standard deviation).

*
p<0.05.

Table 3
Multiple analysis of covariates of cognitive performance between males and females

Measures	Males (n=83)	Females (n=111)	F (P Value)	Cohen's d
Log Boston Naming Test-30	1.45 (0.06)	1.43 (0.06)	6.8 (0.01) *	0.33
3 categories	41.76 (9.97)	45.84 (10.10)	8.0 (0.005) *	-0.41
Log Logical Memory I	1.14 (0.10)	1.18 (0.10)	9.1 (0.003) *	-0.40
Log Logical Memory II	1.09 (0.16)	1.14 (0.11)	9.8 (0.002) *	-0.36

Abbreviations: 3 categories= animals, vegetables and fruits; Logical Memory I= Logical Memory-immediate recall; Logical Memory II= Logical Memory- delayed recall.

The analysis was adjusted for age, education and depressive symptoms. Cognitive data are summarized as mean (standard deviation).

*
p<0.05.