2017-01-06

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Original Publication Citation

Gale, Shawn D., Leslie Baxter, and Juliann Thompson. "Greater Memory Impairment in Dementing Females than Males Relative to Sex-Matched Healthy Controls." Journal of Clinical and Experimental Neuropsychology, vol. 38, no. 5, 2016, pp. 527-533, https://doi.org/10.1080/13803395.2015.1132298.

HHS Public Access

Author manuscript

J Clin Exp Neuropsychol. Author manuscript; available in PMC 2017 January 06.

Published in final edited form as:

J Clin Exp Neuropsychol. 2016 ; 38(5): 527–533. doi:10.1080/13803395.2015.1132298.

Greater Memory Impairment in Dementing Females than Males Relative to Sex Matched Healthy Controls

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Abstract

Previously we demonstrated sex differences in episodic memory in healthy elderly and suggested that normative data be separated by sex. The present study extended the exploration of sex differences on memory measures into two clinical populations, Mild Cognitive Impairment (MCI) and Alzheimer's disease (AD). Seventy-six subjects with MCI and 101 subjects with AD diagnosed by a multidisciplinary team were included. These two groups were also compared to a group of 177 healthy elderly control participants. Sex differences on the Rey Auditory Verbal Learning Test (RAVLT) (total and delayed recall) raw scores and Brief Visuospatial Memory Test-Revised (BVMT-R) were demonstrated within the healthy but not MCI or AD groups. Calculating Z-scores by sex for both dementing groups based on the healthy controls suggested a larger performance gap between healthy and dementing women as compared to healthy and dementing men. MCI females were on average 0.48 standard deviations lower for total verbal learning compared to healthy female controls than were MCI males when compared to healthy male controls. For verbal delayed recall the gap was even larger, 1.09 standard deviations. Similarly, on the BVMT-R, a measure of visual memory, the difference was 0.60 standard deviations for total visual learning and 0.99 standard deviations for delayed recall. This same sex difference, with females showing greater impairment compared to the controls group than did the males, was also present within the AD group. The greater memory impairment in dementing females rather than males when compared to sex matched healthy controls was unlikely to be due to more severe illness since females performed equivalently to males on the Clinical Dementia Rating Scale, Mini-mental Status Examination, Dementia Rating Scale, and were also similar for age, education, and apolipoprotein status. The present study suggested relatively greater memory impairment in females with MCI or AD compared to controls.

Introduction

Previously we demonstrated sex differences on The Rey Auditory Verbal Learning Test (RAVLT) (Rey, 1964) in 172 healthy elderly (Gale, Baxter, Connor, Herring, & Comer, 2007). The effect size (Cohen, 1992) Cohen's *d* for females outperforming males was

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"medium" for total number of words recalled over trials 1 through 5 and "large" for free recall after a twenty minute delay. This effect was not observed on a measure of visuospatial learning and memory, the Brief Visuospatial Memory Test-Revised (BVMT-R) (Benedict, 1997), although the females' average scores were slightly higher. Given the importance of detecting subtle memory impairment in clinical situations it was suggested that normative data for the RAVLT be separated by sex.

Mild cognitive impairment (MCI) has been described as a translational state that occurs prior to the clinical diagnosis of Alzheimer's disease (AD) where memory is impaired but there is often a relative preservation of other cognitive functions, including preservation of functional status (Petersen et al., 2001; Petersen et al., 1999). Whether MCI is simply very early AD and not related to a prodromal process will not be debated here, and this paper will not address the issues related to amnestic MCI versus non-amnestic MCI. However, in a clinical setting one of the most common questions is whether a patient may or may not be demonstrating normal age-related changes in memory. While neuropsychological testing cannot make the definitive diagnosis of dementia, it can be particularly helpful in those cases where functional status appears intact and the only real complaint, often by family members, is that of decreased memory. Previous studies have considered a cognitive memory score that is approximately 1.5 standard deviations (SD) below average, compared to appropriate controls, as a marker of MCI (Petersen et al., 1999). Given that healthy females in our aging database outperformed healthy males on delayed recall by approximately 1 SD, on average, it would be particularly important to compare females to females and males to males in contrast to some studies that choose not to take sex differences into account (Steinberg, Bieliauskas, Smith, Ivnik, & Malec, 2005).

In a study of episodic memory in 84 subjects (42 controls) Chapman et al. (2011) reported control women outperformed control men, while the opposite was true for subjects diagnosed with AD. The 21 women with AD scored lower than the 21 men with AD in tests of both immediate and delayed memory, suggesting that disease progression may affect the female brain differently than the male brain. This study did not include subjects diagnosed with MCI so it was unclear if a similar sex difference would be present in earlier stages of dementia. Similarly, a meta-analysis conducted by Irvine et al. (2012) addressed sex differences in cognition in subjects diagnosed with AD. They found that cognitive deterioration appeared to be greater in women than men with AD. While the mechanism for this finding is unclear, it is possible that there are sex differences in how AD affects the brain. For example, Skup et al. (2011) found greater loss of gray matter in females with probable AD and amnestic MCI (aMCI) compared to males with AD and aMCI in a longitudinal study investigating rates of atrophy. Taken together, we hypothesized that the sex differences seen on measures of memory in healthy elderly may be absent in dementia, which if true, may reflect greater cognitive impairment in females than males compared to healthy elderly. Our aim was to extend our previous findings, and those reported by Chapman et al. (2011), by analyzing a much larger sample as well as including both a group of subjects with probable AD and those with MCI. Thus, the current study will extend the exploration of sex differences in patients with MCI and later stages of AD progression.

Method

Participants and Procedures

A total of 354 (181 females, 173 males) participants from the Arizona Alzheimer's Disease Core Center (ADCC) were included in this study. The Arizona ADCC is a consortium that draws participants from the following sites in Arizona: Mayo Clinic, Barrow Neurological Institute, University of Arizona Health Science Center, Banner Sun Health Research Institute, and the Southern Arizona VA Healthcare System. A multidisciplinary team, which represents all sites, makes the diagnosis of each participant enrolled in the database. Only those participants with all data points of interest were included in this study. Ethnic background of the participants was as follows: 90.7% White, 8.2% Hispanic, 0.6% Native American, 0.3% Black, and 0.3% Asian.

The Arizona ADCC confers participant diagnosis based on several criteria a) history of symptomology b) Clinical Dementia Rating scores (Morris, 1993) (0=Cognitively normal, 0.5=MCI and 1.0-3.0=Dementia), and number of cognitive domains falling below normative cutoff scores (e.g. 0 for controls, 1 for MCI, > 1 for AD) (McKhann et al., 2011). Therefore, subjects diagnosed with MCI and Alzheimer's disease will have impaired scores on cognitive tests, but the extent of impairment is not used to guide diagnosis.

All neuropsychological measures analyzed in this study were administered at the same testing session in a standardized fashion to all participants, as outlined in the included references: RAVLT including a 20 minute delay and recognition trial (Geffen, Moar, O'Hanlon, Clarck, & Geffen, 1990; Lezak, 1995), form 4 of the BVMT-R (Benedict, 1997), Dementia Rating Scale (DRS) (Mattis, 1988), Controlled Oral Word Association Test (COWAT) from the Multilingual Aphasia Examination (Benton & Hamsher, 1976), the Mini-Mental State Examination (MMSE) (Folstein, Folstein, & McHugh, 1975), and the Vocabulary subtest from the Wechsler Adult Intelligence Scale-3rd edition (WAIS-III) (Wechsler, 1997). Inter-site reliability of test scoring and administration has been established and confirmed through statistical analyses.

Statistical Analyses

Analyses were carried out by grouping participants according to diagnostic group (Cognitively healthy, MCI and AD) and sex (M/F) resulting in a total of 6 groups. Between group analyses of the following dependent variables were carried out utilizing a multivariate analysis of variance (MANOVA): RAVLT total number of words recalled over trials 1-5 (RAVLT total) and the number of words recalled after a long delay (RAVLT delay), BVMT-R total score over trials 1-3 (BVMT-R total) and the score after a delay (BVMT-R delay), total score on the MMSE, total score on the DRS, total raw score on the Vocabulary subtest of the WAIS-III, and the total number of words generated over three one-minute trials on the COWAT. Post-Hoc comparisons were carried out using the Bonferroni correction for multiple comparisons. Statistical analyses were carried out in IBM SPSS 23 (IBM Corp., Armonk, New York). First we carried out an omnibus MANOVA with all groups and dependent variables. Next we carried out MANOVAs between males and females by diagnostic group (i.e., controls, MCI, and AD). Finally, we compared the Z-scores from the

RAVLT and BVMT-R between the males and females within the MCI and AD groups using independent t-tests.

Results

Demographic information and test performance by diagnostic group and sex is presented in Table 1.

The two-way between groups MANOVA (diagnostic group by sex) was performed on the demographic and cognitive variables. Box's M test was statistically significant ($p < .01$), so we used Pillai's trace to evaluate multivariate effects, Pillai's trace = .147, [$F(20,680) = 2.703$, $p < 0.001$]. Chi-square analyses confirmed no difference ($p > 0.05$) in the proportion of APOE-ε4 carriers vs. non-carriers between males and females within each diagnostic group. Of note, the identical superscript letters next to the means in Table 1 indicate which groups are being compared.

Within the MCI group MANOVA revealed no differences between MCI females and MCI males in age, education, MMSE, COWAT, DRS score, WAIS-III Vocabulary, RAVLT total score, RAVLT delayed recall, BVMT-R total score, or BVMT-R delayed recall score [$F(10,65) = 1.425$, $p > 0.10$]. There was also no difference in global CDR score between sexes ($p > .05$). Similarly, MANOVA demonstrated no statistically significant sex differences on these cognitive or demographic measures within the AD group [$F(10,90) = 1.039$, $p > 0.10$]. Within the AD group there was no difference in global CDR score between sexes ($p > .05$). In contrast to no sex differences in the MCI and AD groups, within the healthy controls the overall MANOVA comparing males and females was significant, [$F(10,166) = 6.461$, $p < 0.001$]. Univariate analyses demonstrated no sex differences in age, COWAT, or WAIS-III Vocabulary. However, the healthy males had approximately one more year of education than the females ($p = 0.022$). Although there were statistical differences between healthy males and females on the MMSE ($p=0.030$) and DRS ($p=0.046$) with females scoring slightly higher, these differences would not be considered to be clinically significant (e.g. MMSE of 29.2 for males vs. 29.5 for females) (see Table 1). In contrast, there were significant sex differences in performance on the memory measures, which would likely be considered clinically significant, with the females outperforming the males on RAVLT total score, RAVLT delayed recall, BVMT-R total score, and the BVMT-R delayed recall score even though male controls had approximately one additional year of education than females.

Sex Differences in Episodic Memory and the Effect of Dementia

We converted the memory scores of each subject with MCI or AD to Z-scores based on the same sex healthy controls in this study (i.e. using our controls as normative data for our subjects with MCI or AD). We found sex differences in the extent of memory impairment (e.g. a negative Z-score) in the dementia groups. Specifically, the performance gap between healthy and dementing women was consistently larger than the gap between healthy and dementing men. This sex difference was present in both the MCI and AD groups. Results are provided in Table 2.

Independent t-tests indicated statistically significant differences in Z-scores from memory tests between the male and female MCI subjects. Similarly, the differences in Z-scores between male and female AD subjects was also statistically different. T-statistics are presented in Table 2.

Discussion

Sex differences in RAVLT raw scores were demonstrated within the healthy control but not MCI or AD groups. Calculating Z-scores based on healthy (i.e. non-demented) controls illustrated that, in general, women in the MCI and AD groups had much lower memory scores compared to the healthy control range than did male MCI or AD subjects. The greater difference in memory function in women was not simply due to more severe illness since women and men were equivalent for level of dementia severity as indicated by CDR, MMSE, and DRS. Sex differences were also unlikely to be related to premorbid function or cognitive reserve in that male and females were equivalent within diagnostic groups on Vocabulary score from the WAIS-III, a measure of verbal intelligence, and performance on the COWAT, a measure of verbal fluency. Thus, better memory performance in the healthy females compared to healthy males was not related to higher verbal intellectual function or verbal fluency. Finally, sex differences were unlikely to be due to age and APOE-ε4 status as these were also equivalent between groups.

In contrast to our prior study (Gale et al., 2007) here we find sex differences in healthy controls on the BVMT-R. Previous research suggests sex differences on tasks of visuospatial memory may be found when active rather than passive visuospatial manipulation is required (Lewin, Wolgers, & Herlitz, 2001; Millet et al., 2009). Since the BVMT-R essentially requires no visuospatial manipulation and the stimuli can be somewhat easily verbalized, this may explain the female advantage in our control group. In other words, the control females had better verbal memory than control males and may have been able to verbalize the figures on the BVMT-R resulting in better visuospatial memory.

While some studies have not found sex differences in the incidence or pattern of cognitive impairment in AD (Barnes et al., 2003), others have suggested increased incidence in women (Gao, Hendrie, Hall, & Hui, 1998; Mielke, Vemuri, & Rocca, 2014) or differences in the level of impairment in specific cognitive domains such as language function (Ripich, Petrill, Whitehouse, & Ziol, 1995) and memory (Chapman et al., 2011). Our findings were based on relative (to a control group), not absolute, differences between women and men. This finding could potentially reflect differences in the disease process between the sexes. Furthermore, this effect was present in the early stages of illness (e.g. MCI) when memory is typically the most salient issue.

Our findings suggest that sex differences in cognitive outcome in both MCI and AD could reflect sex differences in the extent or course of the disease. Consistent with this possibility, Hua et al. (2010) found faster whole brain and temporal lobe atrophic rates in women with MCI compared to males with MCI. Skup et al. (2011) also found sex differences in patterns of atrophy in both AD and MCI. However, not all studies have found sex differences (Bai et al., 2009). And a recent meta-analysis evaluating the prevalence of amyloid pathology in

persons without dementia from ages 50-90 did not find a sex difference though pathology was associated with cognitive impairment, age, and APOE genotype (Jansen et al., 2015). Still, there may also be sex differences in relation to modifying factors of the disease. For example, the association between the clinical manifestation of Alzheimer's disease and the underlying neuropathology may be more robust in women than in men (Barnes et al., 2005). The presence of the APOE-ε4 allele has also been shown to have detrimental effects on episodic memory in women, but not in men (Lehmann et al., 2006; Mortensen & Hogh, 2001). Damoiseaux et al. (2012) found an interaction between APOE-ε4 and sex in healthy older adults with women but not men demonstrating significantly reduced functional connectivity in the default mode network. In another sample they found an interaction between APOE-ε4 and cerebrospinal measurements of tau levels with healthy women having higher levels than APOE-ε4 males. Taken together, these findings demonstrate an APOE-ε4 by sex interaction that may clarify dementia-related sex differences and associated changes in both functional neural networks and contributors to the underlying neuropathology. Similarly, Heise et al (2014) found reduced connectivity in otherwise healthy APOE-ε4 carrier females between the hippocampus and precuneus/posterior cingulate cortex compared to APOE-ε4 carrier males, ε3 homozygote females, and ε3 homozygote males. Finally, it may also be that the disease itself is not different between the sexes but that premorbid differences between the sexes in regional brain function and structure interact with the disease differently. For example, Yoshizawa et al. (2014) studied older (not elderly) healthy adults and demonstrated sex differences in cerebral glucose metabolism, with females demonstrating increased metabolism mainly in frontal and parietal areas while men demonstrated increased metabolism mostly in temporal regions, and that these differences were associated with cognitive performance even after adjustment for age, education, and MMSE. Furthermore, sex differences in regional hippocampal morphology have been found to be associated with the onset of puberty, which reduced hippocampal volume in males but not females (Satterthwaite et al., 2014). Thus, perhaps sex differences in underlying brain structures/function interact differentially with the MCI/AD disease process.

Limitations of this study include the cross-sectional rather than longitudinal nature of the data. Although we did not find evidence that the women with MCI or AD had greater disease severity than the men, and they were compared to a well-defined control cohort, it is possible that other unknown factors could have influenced our findings. For example, since we only included participants with all data points this could have biased who was included in the study. Also, because this was a cross-sectional study we cannot address causation. Secondly, we did not distinguish between potential MCI subgroups (e.g. amnestic versus other) or APOE genotype, though there were no group differences in the proportion of APOE-ε4 carriers, and further studies may shed light on more complex interactions between genotype, sex and cognitive impairment. Finally, our sample, including the controls, was mostly white and highly educated making our findings less generalizable. Still, strengths of this study include a large sample size and control group, well-documented diagnosis, and thorough cognitive assessment.

We found sex differences in cognition from the healthy to early and late dementing stages. Given the implications of this finding future researchers may want to address both the timing and mechanism of greater cognitive decline in females through longitudinal analyses.

Acknowledgments

This research was funded in part by the Barrow Neurological Foundation, the Arizona Alzheimer's Disease Core Center (NIA P30 AG19610-03) and the State of Arizona (Arizona Alzheimer's Consortium).

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Table 1

Demographic information and test performance by diagnosis and sex

	Controls		Mild Cognitive Impairment		Alzheimer's Disease	
	Male (n = 64)	**Female (n = 113)**	**Male (n = 46)**	**Female (n = 30)**	**Male (n = 63)**	**Female (n = 38)**
Age	76.7 (8.2)	75.5 (8.0)	77.5 (6.5)	77.1 (7.0)	77.7 (5.7)	75.8 (8.3)
Education	16.1 (2.7)[a]*	15.2 (2.7)[a]*	15.0 (3.4)	14.0 (3.0)	14.4 (4.0)	13.9 (3.3)
% APOE ε4	29.6	19.0	54.1	66.7	71.9	84.3
CDR	.07 (.18)	.02 (.10)	.49 (.13)	.55 (.16)	1.03 (.58)	1.21 (.61)
MMSE	29.2 (.98)[b]*	29.5 (.73)[b]*	27.4 (1.8)	26.6 (2.2)	21.1 (4.4)	20.3 (5.7)
DRS Total	138.5 (3.5)[c]*	139.6 (3.4)[c]*	128.8 (7.9)	130.0 (5.6)	107.7 (18.2)	104.2 (23.9)
Vocabulary	52.0 (8.6)	51.2 (8.1)	45.4 (10.6)	44.3 (10.3)	32.7 (14.3)	36.1 (13.2)
COWAT	38.5 (10.8)	40.9 (11.5)	36.8 (11.0)	32.4 (10.8)	22.8 (11.5)	24.8(13.0)
RAVLT TOT	40.3 (8.4)[d]**	48.9 (9.4)[d]**	27.7 (6.8)	30.0 (6.5)	18.2 (6.5)	18.1 (9.1)
RAVLT Del	7.6 (2.8)[e]**	10.4 (2.7)[e]**	2.7 (2.8)	2.8 (2.5)	.67 (1.3)	.42 (1.0)
BVMT-R TOT	13.8 (5.8)[f]**	17.5 (6.2)[f]**	7.9 (4.1)	7.4 (5.6)	2.8 (2.0)	2.7 (2.7)
BVMT-R Del	6.1 (2.8)[g]**	7.5 (2.5)[g]**	2.8 (2.4)	2.1 (2.5)	.30 (.69)	.42 (1.0)

Note. Mean and Standard Deviation (SD) are provided for each variable.

[a]Identical superscript letters (e.g.) represent a significant group difference between sexes.

*indicates $p<0.05$,

**indicates $p<.01$

The lack of superscripts between the sexes on any measures within the MCI or AD groups indicates no statistically significant differences were found.

APOE E4 is proportion of sample with presence of an Apolipoprotein-ε4 allele

CDR is the Clinical Dementia Rating global score

MMSE is the total raw score on the Mini Mental State Examination

DRS total is the total raw score on the Dementia Rating Scale

Vocabulary is the total raw score from the WAIS-III Vocabulary subtest

COWAT is total raw score on Controlled Oral Word Association Test

RAVLT TOT is the total number of words recalled over trials 1-5 on the Rey Auditory Verbal Learning Test

RAVLT Del is the number of words recalled after the delay on the Rey Auditory Verbal Learning Test

BVMT-R TOT is the total raw score over trials 1-3 on the Brief Visuospatial Memory Test-Revised

BVMT-R Del is the total raw score after the 25′delay on the Brief Visuospatial Memory Test-Revised

Table 2

Z-scores (separately based on male or female healthy controls), *t*-statistics, and effect sizes between males and females on memory test performance in the MCI and AD groups

	MCI					
	Male (n = 46)		**Female (n = 30)**			
	M	**SD**	**M**	**SD**	***t***	**Cohen's *d* effect size**
RAVLT TOT	-1.51	0.82	-1.99	0.70	2.66*	0.63
RAVLT Del	-1.74	0.99	-2.83	0.94	4.81**	1.13
BVMT-R TOT	-1.02	0.70	-1.63	0.90	3.25**	0.76
BVMT-R Del	-1.17	0.84	-2.16	1.01	4.65**	1.07
	AD					
	Male (n = 63)		Female (n = 38)			
	M	SD	M	SD	*t*	Cohen's *d* effect size
RAVLT TOT	-2.64	0.77	-3.25	0.97	3.45**	0.70
RAVLT Del	-2.47	0.48	-3.73	0.38	13.74**	2.91
BVMT-R TOT	-1.90	0.35	-2.38	0.44	6.08**	1.21
BVMT-R Del	-2.05	0.24	-2.83	0.40	12.13**	2.36

*$p < 0.05$,

**$p < .01$

MCI = mild cognitive impairment

AD = Alzheimer's disease

M = mean, SD = standard deviation, *t* = t-statistic

RAVLT TOT is the total number of words recalled over trials 1-5

RAVLT Del is the number of words recalled after the delay

BVMT-R TOT is the total score over trials 1-3

BVMT-R Del is the total score after the 25′delay.

J Clin Exp Neuropsychol. Author manuscript; available in PMC 2017 January 06.