Published in final edited form as:

Neuropsychol Dev Cogn B Aging Neuropsychol Cogn. 2020 January ; 27(1): 18–39. doi: 10.1080/13825585.2019.1566433.

Influence of Sex Differences in Interpreting Learning and Memory within a Clinical Sample of Older Adults

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Abstract

Healthy older women typically retain an advantage in verbal memory compared to men (e.g., Zhang, Zhou, Wang, & Zhang, 2017), and men may have an advantage in visuospatial abilities (De Frias, Nilsson, & Herlitz, 2006). Sex is an important factor to consider when evaluating memory with older adults, particularly when using measures that do not provide sex-specific normative data. This present study aimed to examine differences in verbal and nonverbal memory within a clinical sample of older adults (N = 1084). Raw learning and recall scores on the Hopkins Verbal Learning Test, Revised (HVLT-R; Brandt & Benedict, 2001) and Brief Visuospatial Memory Test, Revised (BVMT-R; Benedict, 1997) were compared between sexes within the entire sample and cohorts stratified by age (60 – 69, 70 – 79, and 80 – 89). Within the entire sample, women significantly outperformed men in HVLT-R learning and recall and there were no sex differences in BVMT-R performance. These sex differences, however, were absent or reversed for those with impaired HVLT-R performance and functional deficits, indicating that women retain an early advantage in verbal memory, which is lost with greater indication of disease severity. Sex accounted for a small, but significant portion of variance in HVLT-R learning and recall performance. Overall, the results indicate that women retain an advantage in verbal learning and memory, at least before significant levels of impairment, within a sample of older adults seen at an outpatient neurology clinic, which may have implications for diagnosing memory disorders.

Keywords

memory; sex differences; cognitive impairment; neuropsychology; psychometrics

Sex differences in verbal learning and recall have been a longstanding finding in neuropsychology, with women typically outperforming men in verbal memory (Bleecker, Bolla-Wilson, Agnew, & Meyers, 1988; Kramer, Delis, & Daniel, 1988). Subsequent

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Disclosure Statement
We have no conflicts to disclose.

research has shown that this difference persists into late life, as healthy women continue to exhibit better verbal memory performance than men in the context of normal aging (De Frias et al., 2006; Gerstorf, Herlitz, & Smith, 2006; Lundervold, Wollschläger, & Wehling, 2014; McCarrey, An, Kitner-Triolo, Ferrucci, & Resnick, 2016; Zhang et al., 2017). However, another pattern of findings emerges in the context of mild cognitive impairment (MCI) or dementia related to Alzheimer's disease (AD). Specifically, verbal memory appears to decline more steeply in women with MCI and dementia due to AD as compared to men (Chapman et al., 2011), even after accounting for disease severity, genetic risk factors, and cognitive reserve (Gale, Baxter, & Thompson, 2016). Furthermore, other studies suggest that sex has a moderating effect between AD pathology and memory performance such that women retain an advantage in verbal memory early in the disease process despite hippocampal atrophy (Sundermann et al., 2016a), temporal lobe hypometabolism (Sundermann et al., 2016b), or accumulation of amyloid plaques (Caldwell, Berg, Cummings, & Banks, 2017) but this advantage reverses in the presence of greater disease severity.

In contrast to findings for verbal memory, sex differences in visuospatial abilities have tended to favor men (De Frias et al., 2006; Munro et al., 2012). For example, men typically perform better than women on tasks involving mental rotation and some aspects of navigation (Li & Singh, 2014), but this difference does not consistently translate to a male advantage in memory for nonverbal material. In particular, while healthy older men often outperform healthy older women on measures of nonverbal short-term memory (McCarrey et al., 2016; Proust-Lima et al., 2008), some studies of nonverbal learning and recall in healthy older adults have either found no significant sex differences (Duff, 2016; Kane & Yochim, 2014) or better performance in women than men (Gale, Baxter, Connor, Herring, & Comer, 2007; Gale et al., 2016). In the context of AD, some studies have shown that men retain an advantage in visuospatial skills over women, especially on complex tasks that involve working memory (Laws, Irvine, & Gale, 2016; Millet et al., 2009), but others find no significant differences by sex (Buckwalter et al., 1996; Perneczky, Drzezga, Diehl-Schmid, Li, & Kurz, 2007).

Given known sex differences in verbal memory favoring women and some evidence for differences in visuospatial skills favoring men, some neuropsychological tests utilize normative data that either accounts for this difference or includes separate norms for men and women. For example, Judgment of Line Orientation (Benton, Hamsher, Varney, & Spreen, 1983) has been associated with a male advantage and normative sources suggest adding between one and two points to the raw scores of women to account for this sex difference (Benton et al., 1983; Woodard et al., 1998). Additionally, the California Verbal Learning Test (CVLT; Delis, Kramer, Kaplan, & Ober, 1987) offers separate normative values for men and women, as older women have been shown to consistently perform better than men on CVLT verbal learning and recall (McCarrey et al., 2016).

In contrast, other tests of learning and memory do not include sex-specific norms. The Hopkins Verbal Learning Test, Revised (HVLT-R; Brandt & Benedict, 2001) is a widely used test of verbal memory in clinical settings (Rabin, Paolillo, & Barr, 2016). The measure is particularly useful in assessments with older adults, as it includes a shorter word list,

fewer learning trials, and shorter administration time than the CVLT. Both the HVLT (Brandt, 1991) and HVLT-R have been shown to perform similarly to the CVLT in healthy individuals and older adults with Alzheimer's disease (Lacritz, Cullum, Weiner, & Rosenberg, 2001; Lacritz & Cullum, 1998). While regression-based normative data accounting for many demographic characteristics, including sex, are available for the HVLT-R through interpretive systems such as the Calibrated Neuropsychological Normative System (CNNS; Schretlen, Testa, & Pearlson, 2010), the HVLT-R professional manual does not include sex-specific normative data. The Brief Visuospatial Memory Test, Revised (BVMT-R; Benedict, 1997) is a measure of nonverbal learning and memory designed as analogous to, and co-normed with, the HVLT-R. This measure also does not include separate normative values for men and women.

The HVLT-R manual specifies that sex was not a clinically-relevant predictor of any learning or memory indices and the BVMT-R manual states that sex was not a significant predictor of learning or memory scores. Thus, the normative data for these measures is not separated by sex. The BVMT-R normative sample was meant to closely resemble the US Census with regard to age, but no descriptive statistics are offered that specify the percentage of men and women in the sample. The manual for the HVLT-R has more detailed description of the normative sample, which consisted predominantly of women (i.e., 75.2%) ranging in age from 16 to 92 years old (Brandt & Benedict, 2001). The sex distribution is most skewed within the older adult sample, particularly the cohort of 70 to 79 year olds, which is 90% women.

The HVLT-R manual describes the results of a step-wise multiple regression demonstrating that sex was a small but statistically significant contributor to the variance in all learning and memory scores, accounting for 1.7% of the variance in total learning score and 1.4% of the variance in delayed recall performance. In contrast, age accounted for 18.8% of the variance in total learning score and 12.2% of delayed recall performance, and education accounted for 5.1% of the variance in total learning and 3.3% of the variance in delayed recall. Even though sex was a significant predictor of HVLT-R learning and memory in their normative sample, it was not considered clinically meaningful compared to the contributions of these other demographic variables.

Research into sex differences in HVLT-R and BVMT-R performance has been somewhat mixed. Although several studies did not find sex differences using these measures (Hester, Kinsella, Ong, & Turner, 2004; Gale et al., 2016; Kane & Yochim, 2014), other studies have found significant differences. Vanderploeg et al. (2000) found that women outperformed men on all HVLT-R subtests and that sex accounted for 8.5% of the variance in HVLT-R verbal learning (sum of trials 1 to 3) in a sample of healthy older adults. The authors offered a formula to account for this difference, suggesting for example, that for women aged 60 to 79, two points be deducted from the raw sum of the learning trials and one point be deducted from the delayed recall raw score. Duff (2016) did not find significant sex differences in BVMT-R performance but showed that healthy older women outperformed men on all HVLT-R learning and recall indices. He provided equations that demographically adjust normative scores accounting for sex. Munro et al. (2012) found that healthy older women outperformed men on both HVLT-R learning and delayed recall indices with the largest sex

difference observed for total learning score. While there were not significant overall sex differences found within a Latino/Latina population using a Spanish version of the HVLT-R, there was a small effect found in a Guatemalan sample, with women outperforming men in both verbal learning and recall (Arango-Lasprilla et al., 2015). In a sample of African American and Caucasian adults, Norman et al. (2011) found that women outperformed men in HVLT-R learning but significant sex differences in delayed recall were only observed within the Caucasian adults. In contrast, when examining BVMT-R performance, they found that women outperformed men on BVMT-R total learning and delayed recall score within the sample of African American adults but this sex difference was not observed in Caucasian adults. When examining healthy older African American adults, Friedman, Schinka, Mortimer, and Graves (2002) found that sex had a significant, moderately-sized effect on most HVLT-R indices and offered gender-based corrections to account for this difference. Finally, Gale and colleagues (2007) found that healthy older women outperformed men on BVMT-R learning and memory indices, although the effect sizes were mostly small or negligible, particularly in the 70 to 89 year old age cohort.

Research into sex differences in HVLT-R and BVMT-R performance in clinical samples has been limited. Within a sample of older adults diagnosed with either MCI or AD, Gale and colleagues (2016) did not find significant sex differences in BVMT-R performance for either diagnostic group. Performance on the original HVLT was examined in a mixed sample of older adults with dementia syndromes (primarily AD and vascular dementia) and sex did not significantly contribute to learning and memory indices (Hogervorst et al. 2001).

The nature and persistence of sex differences in learning and memory in the context of neurodegenerative disease remains unclear and may be an important variable in the interpretation of memory performance in older adults. Thus, the present study sought to examine sex differences in both verbal and nonverbal learning and memory within a large clinical sample of older adults with varying levels of cognitive impairment. Patients were seen at an outpatient neurology clinic specializing in neurodegenerative and movement disorders. Even though healthy older women appear to outperform men on verbal learning and memory tasks, it is unclear whether this female advantage will be present in a clinical sample that includes individuals with varying degrees of cognitive impairment and diverse neurological conditions. Given the evidence for stronger verbal memory performance in healthy older women, and some evidence that this effect persists into at least early AD, we hypothesized that we would find a similar pattern within our clinical sample of older adults, with women retaining an advantage in verbal learning and memory. While extant research into sex differences in nonverbal memory is less conclusive, the prior studies examining nonverbal memory in healthy older adults contained smaller sample sizes than our current study and several consisted of a majority of female participants. Thus, with our large sample of older adults, with roughly equal numbers of men and women, we expected men to outperform women on the BVMT-R.

Methods

Participants

Data were gathered from archival medical records of patients who underwent neuropsychological evaluation at a specialty neurology clinic as part of their routine clinical care. Patients are typically referred for diagnostic clarification or to establish a baseline of functioning in order to aid in treatment planning. Typical diagnoses include AD, Lewy body disease, movement disorders including Parkinson's disease, and rarer degenerative diseases (e.g., frontotemporal dementia). Records of patients between the ages of 60 and 89 who had HVLT-R, BVMT-R, and Geriatric Depression Scale (GDS; Yesavage et al., 1982) data available were selected from the broader clinic sample of patients seen between 2011 and 2017. The total sample consisted of 1,084 older adults with a mean age of 73.65 (SD = 6.37). Within the entire sample, there were 577 men (53.2%) and 507 women (46.8%) with an average of 14.75 years of education (SD = 2.77). The majority of patients were Caucasian (84.4%), with 6% being African American, 1.7% Asian, and 1.5% Hispanic. Individual age cohorts were also examined and each cohort contained roughly equivalent numbers of men and women (49.5% women in the 60 - 69 cohort, 44.9% women in the 70 - 70 cohort, and 47.4% women in the 80 – 89 cohort). See Table 1 for detailed sample characteristics and covariates by sex.

Measures

The Hopkins Verbal Learning Test, Revised (HVLT-R; Brandt & Benedict, 2001) was used to measure verbal learning and memory and the Brief Visual Memory Test, Revised (BVMT-R; Benedict, 1997) was used to measure nonverbal learning and memory. For both tasks, primary measures of interest were the raw total learning score (total points earned across three learning trials) and the raw delayed recall score (points earned on the free recall trial after a 20 to 25-minute delay). The Wide Range Achievement Test, Fourth Edition (WRAT-4; Wilkinson & Robertson, 1993) reading subtest was used as an estimate of premorbid intellectual functioning (Strauss, Sherman, & Spreen, 2006). Of note, WRAT-4 data was missing for a small portion of the sample (n = 32).

As our sample included a spectrum of patients, ranging from normal cognition with subjective complaints to those with dementia, the Activities of Daily Living Questionnaire (ADLQ; Johnson, Barion, Rademaker, Rehkemper, & Weintraub, 2004) was used where available to measure level of impairment in daily abilities to account for severity of functional impairment in an effort to account for disease severity. The questionnaire is used to rate changes in daily skills (such as self-care, household care, travel, and communication) and is completed by a caregiver (typically a spouse or other family member). The total score on the ADLQ ranges from 0 to 100%, with higher scores indicating greater levels of functional impairment. A score of <34% reflects minimal impairment, scores ranging from 34 to 66% reflect moderate impairment, and scores greater than 67% indicate severe impairment (Johnson et al., 2004). These data were unavailable for 310 patients (29% of the total sample).

As depression is more prevalent in women than men, and can impair verbal learning (Elderkin-Thompson, Moody, Knowlton, Hellemann, & Kumar, 2011; Kessler, 2003), total score on the Geriatric Depression Scale (GDS; Yesavage et al., 1982) was also included. Scores on the GDS range from 0 to 30 and scores above 10 indicate clinically meaningful depression (Yesavage et al., 1982). All patients selected for this study had available GDS data.

Analyses

All data were analyzed using IBM SPSS version 23 (IBM Corp., 2015). Independent samples t-tests were used to determine group differences between sexes in demographic and clinical characteristics (age, education, premorbid IQ, functional impairment, and depression severity). As noted, not all patients had WRAT-4 or ADLQ data available. Therefore, subsamples of patients in which data from these covariates were available were analyzed to measure sex differences between estimated premorbid IQ and functional impairment. In addition to the full sample, analyses were also conducted within three subsamples stratified by age, corresponding to the HVLT-R and BVMT-R normative groups (ages 60 – 69, 70 – 79, and 80 – 89). Chi-square analyses were used to determine if there were significant differences in missing data between sexes, within the entire sample, and within each age cohort individually. Variables that significantly differed between sexes were used as covariates in subsequent group analyses. Analyses of covariance (ANCOVA) were used to compare raw total learning and recall scores on the HVLT-R and BVMT-R in men and women, to determine sex differences in verbal and nonverbal learning and memory. Specifically, four ANCOVA models were computed to compare learning and memory between men and women in the overall sample, using verbal learning (HVLT-R total learning), verbal recall (HVLT-R delayed recall), nonverbal learning (BVMT-R total learning), and nonverbal recall (BVMT-R delayed recall) as dependent variables. These analyses were conducted within the entire sample and for each age cohort individually.

In post-hoc analyses individuals were classified as impaired (falling below 1.5 standard deviations from the mean) or unimpaired on HVLT-R and BVMT-R learning and recall scores using the normative tables in the respective manuals. However, as the BVMT-R normative sample only extends up to age 79, normative values were obtained for patients aged 80 to 88 using other published norms (Kane & Yochim, 2014). Sex differences were then examined with ANCOVA analyses within the impaired groups and unimpaired groups for the entire sample.

Additional post-hoc analyses were conducted grouping individuals into approximations of diagnostic categories using HVLT-R or BVMT-R performance and level of functional impairment (ALDQ total score). For example, individuals with unimpaired learning or recall scores (as defined above) with minimal functional impairment (an ADLQ score of 0 to 33) were classified as “memory normal.” We also examined individuals with impaired learning or recall scores and minimal functional impairment, similar to a mild cognitive impairment (MCI) level of severity. Finally, individuals with impaired learning or recall scores and moderate to severe functional impairment (an ADLQ score above 33) were examined, similar to dementia-level impairment. Sex differences in HVLT-R and BVMT-R learning and

recall scores were then examined within each diagnostic category approximation with ANCOVA analyses.

Finally, following significant group differences determined in ANCOVA analyses, hierarchical multiple regression analyses were conducted to estimate the unique contribution of sex to learning and memory scores. Demographic characteristics (age, education, premorbid IQ) and depression severity (GDS score) were entered in a first step followed by sex in a second step with the raw verbal learning and recall scores used as dependent variables. These regression models were used to identify predictors of learning and memory in the entire sample and, following significant outcomes identifying sex differences within the age cohort analyses, the same regression model was used to identify predictors of learning and memory performance within the 70 to 79 age cohort. To account for multiple comparisons, p values were adjusted using the Holm's sequential Bonferroni procedure within each family of analyses (see Eichstaedt, Kovatch, & Maroof, 2013 for a review).

Results

Within the entire sample, men and women did not significantly differ in age, $t(1082) = .57$, $p = .57$. Among individuals with available WRAT-4 and ADLQ data, men and women did not significantly differ in estimated premorbid intelligence, $t(1050) = 1.08$, $p = .28$, or functional impairment rating, $t(722) = 1.25$, $p = .90$. Additionally, the presence of missing data for the WRAT-4 and ADLQ did not significantly differ between the sexes within the entire sample or within any age cohort. Education level and depression severity significantly differed between sexes, as men had one additional year of education on average, compared to women, $t(1082) = 4.67$, $p < .001$, and women obtained higher scores on the GDS compared to men, $t(1082) = 5.21$, $p < .001$. Within the entire sample 33.9% of individuals were characterized as endorsing clinically significant depression (GDS total score greater than 9). Education level and depression severity were used as covariates within the subsequent ANCOVA. After accounting for education and depression severity, within the entire sample, women exhibited better HVLT-R total learning performance, $F(1, 1080) = 24.62$, $p < .001$, and HVLT-R delayed recall, $F(1, 1080) = 7.50$, $p = .018$, but there were no significant sex differences in BVMT-R total learning, $F(1, 1080) = 22.00$, $p = .52$, or BVMT-R delayed recall, $F(1, 1080) = 0.12$, $p = .73$. The effect sizes of the sex difference in HVLT-R total learning (Cohen's $d = 0.27$) and HVLT-R recall (Cohen's $d = 0.16$) within the entire sample were small.

Given baseline differences in education and depression severity between men and women all following analyses include education and GDS score as covariates. Within the entire sample, 39.7% had impaired HVLT-R learning scores. Within this group, there were no sex differences in HVLT-R learning performance, $F(1, 426) = 1.33$, $p = .249$. Within the entire sample, 50.8% had impaired HVLT-R delayed recall performance and within this group men outperformed women on HVLT-R delayed recall performance, $F(1, 547) = 7.70$, $p = .006$, $d = 0.19$. In contrast, within the group with unimpaired HVLT-R learning scores (60.3%) women outperformed men in HVLT-R learning, $F(1, 650) = 8.68$, $p = .003$, $d = 0.18$. Within the group with unimpaired recall performance (49.2%) women also outperformed men on HVLT-R delayed recall, $F(1, 529) = 19.00$, $p < .001$, $d = 0.32$. Within the entire sample

(excluding $n = 7$ patients aged 89 as there were no available published norms for this age group), 45.0% had impaired BVMT-R learning performance. Within this group there were no sex differences in BVMT-R learning score, $F(1, 481) = 0.01$, $p = .929$. Within the entire sample (again excluding patients aged 89) 45.2% had impaired BVMT-R delayed recall performance. Within this group there were no sex differences in BVMT-R recall score, $F(1, 483) = 0.165$, $p = .685$. Within the patient group with unimpaired BVMT-R learning performance there were no sex differences in BVMT-R learning, $F(1, 588) = 0.77$, $p = .381$. Within those with unimpaired BVMT-R delayed recall performance there were no sex differences in BVMT-R recall, $F(1, 586) = 1.81$, $p = .179$.

Within the memory normal group women outperformed men in HVLT-R learning, $F(1, 317) = 6.64$, $p = .010$, and HVLT-R recall, $F(1, 260) = 5.97$, $p = .015$. For those in the MCI approximation group there were no significant sex differences in HVLT-R learning, $F(1, 193) = 1.32$, $p = .252$, or HVLT-R recall, $F(1, 250) = 0.04$, $p = .841$. Within the dementia approximation group there were no sex differences in HVLT-R learning, $F(1, 147) = 0.04$, $p = .844$, and men exhibited significantly better HVLT-R recall performance than the women, $F(1, 180) = 4.34$, $p = .039$. There were no sex differences in BVMT-R learning or recall within any of the diagnostic approximation groups.

60 – 69 Age Cohort

When stratifying by age cohort, within the 60 – 69 year age group, there were significant sex differences in GDS score only, with women obtaining higher scores than men, $t(315) = -3.11$, $p = .010$. Within this age cohort 40.4% of individuals endorsed clinically significant symptoms of depression (GDS total score greater than 9). Education level did not significantly differ between sexes in this age cohort. There were no significant sex differences in any learning or memory performances after accounting for depression severity.

The mean HVLT-R total learning score for women in this age cohort, rounding to the nearest whole number, was at the 7th percentile for age and the mean total learning score for men was at the 5th percentile for age. The mean HVLT-R delayed recall score for women was at the 9th percentile and men performed at the 5th percentile. Within this age cohort 46.1% were classified as having impaired HVLT-R learning scores and 53.3% were classified as having impaired HVLT-R delayed recall performance. Within this age cohort, the mean BVMT-R learning score for both men and women fell within the 12th to the 16th percentile for age and the mean delayed recall score for both sexes fell within the 14th to the 16th percentile for age. Within this cohort, 43.2% were classified as having impaired BVMT-R learning scores and 40.4% exhibited impaired delayed recall performance.

70 – 79 Age Cohort

Within the 70-79 age group, men had significantly more education than women, $t(552) = 4.20$, $p < .001$, and women obtained significantly higher GDS scores, $t(552) = -3.66$, $p < .001$. Within this age cohort 32.3% of individuals endorsed clinically significant symptoms of depression. When accounting for both education and depression severity, women outperformed men on HVLT-R total learning, $F(1, 550) = 17.76$, $p < .001$; $d = 0.30$. Within

this cohort women also exhibited significantly better performance on HVLT-R delayed recall, $F(1, 550) = 8.18$, $p = .012$; $d = 0.23$. There were no significant sex differences in BVMT-R total learning, $F(1, 550) = 0.10$, $p = .76$, or BVMT-R delayed recall, $F(1, 550) = 0.11$, $p = .75$; both depression severity and education level were used as covariates.

The mean HVLT-R learning score within this age cohort for women was at the 21st percentile for age and men performed at the 16th percentile for age. The mean HVLT-R delayed recall score for women was at the 13th percentile for age and men performed at the 6th percentile for age. Within this cohort, 31.4% of individuals exhibited impaired HVLT-R learning scores and 45.8% of individuals exhibited impairment in HVLT-R delayed recall. The mean BVMT-R learning score for both men and women fell within the 8th to 12th percentile for age and the mean BVMT-R delayed recall score for both sexes fell within the 12th to 14th percentile for age. Within this cohort, 47.5% of individuals exhibited impaired BVMT-R learning performance and 47.5% exhibited impaired delayed recall.

80 – 89 Age Cohort

Within the 80-89 age group, after accounting for multiple comparisons, there were no significant differences in age, education, premorbid IQ, or GDS between men and women. Within this age cohort, 28.2% of individuals endorsed clinically significant symptoms of depression. Sex differences in HVLT-R total learning initially emerged but did not survive correction for multiple comparisons, $F(1, 211) = 5.18$, $p = .10$. Additionally, there were no significant differences in HVLT-R delayed recall, $F(1, 210) = 1.41$, $p = .24$, BVMT-R total learning, $F(1, 210) = 0.21$, $p = .65$, or BVMT-R delayed recall, $F(1, 210) = 0.11$, $p = .74$.

Within this age cohort, the mean HVLT-R learning score for women was at the 9th percentile for age and the mean learning score for men was at the 7th percentile for age. The mean HVLT-R delayed recall score for both sexes was measured at the 5th percentile. Within this age cohort, 51.6% exhibited impaired HVLT-R learning performance and 60.1% exhibited impaired delayed recall performance. With regard to nonverbal learning and memory, the mean BVMT-R learning score for both sexes was at the 16th percentile for age (excluding individuals aged 89). The mean BVMT-R delayed recall score for women aged 80 to 88 fell at the 8th percentile for age and men within this age range performed at the 7th percentile for age. Table 5 presents memory performance data for the entire sample and within each age cohort.

Regression Results within the Full Sample

Following the significant results from ANCOVA analyses showing sex differences in HVLT-R learning and recall within the entire sample, multiple regression analyses were conducted. Within the full sample (excluding those without WRAT-4 reading data, $n = 32$), a multiple regression model predicting HVLT-R total learning was significant using age, education, premorbid IQ, depression severity, and sex as independent variables, $F(5, 1046) = 32.36$, $p < .001$, $r^2 = .13$. The regression analysis revealed that sex contributed significant, unique variance to HVLT-R total learning, 1.9%, $p < .001$, after accounting for the effects of age, education, estimated premorbid IQ, and depression severity. The results of a second multiple regression analysis predicting HVLT-R delayed recall within the entire sample (again

excluding those without WRAT-4 data, $n = 32$) was significant with age, education, premorbid IQ, depression severity, and sex as independent variables, $F(5, 1046) = 24.56$, $p = .01$, $r^2 = .10$. The regression results revealed that the unique variance explained by sex was relatively small, but significant, 0.6%, $p = .030$.

Regression Results within the 70 – 79 Age Cohort

As the largest sex differences in ANCOVA analyses occurred within the 70 – 79 year age cohort, additional regression analyses were run in this subsample. The multiple regression analysis with age, education, premorbid IQ, depression severity, and sex predicting HVLT-R total learning was significant, $F(5, 536) = 8.89$, $p < .001$, $r^2 = .07$. The regression results revealed that sex contributed a significant amount of variance beyond the effect of age, education, estimated premorbid IQ, and depression severity, 2.4%, $p < .01$. The multiple regression model using age, education, estimated premorbid IQ, depression severity, and sex as independent variables was significant in predicting HVLT-R delayed recall, $F(5, 536) = 5.52$, $p < .001$, $r^2 = .04$. The variance in HVLT-R delayed recall explained by sex was weaker than the variance explained in HVLT-R total learning (1.1%) and did not remain significant after correcting for multiple comparisons, $p = .052$.

Discussion

In a sample of 1,084 older adults between the ages of 60 and 89 presenting in a memory clinic setting, we found that women significantly outperformed men on verbal learning and memory measures. Within the age cohorts, sex differences only emerged for verbal learning and memory in the 70 – 79 age cohort. There were no significant sex differences in nonverbal learning or memory across the sample as whole, or in any of the age-defined cohorts. While this was a clinical sample, only about half of the patients exhibited impaired learning and memory performances, with a slightly larger proportion of individuals in the 70 – 79 cohort exhibiting unimpaired verbal learning and memory performance. When the subset of patients with impaired verbal learning and memory scores was examined, there were no sex differences in verbal learning and men actually showed an advantage in verbal delayed recall compared to women. In contrast, when examining the subset of patients with unimpaired verbal learning and memory scores, sex differences emerged that were consistent with the overall sample, with women outperforming men on both verbal learning and delayed recall. There were again no sex differences in nonverbal learning or recall within either the impaired or unimpaired groups.

Similarly, when subsets of patients approximating diagnostic groups (memory normal, mild cognitive impairment, and dementia) were examined, sex differences emerged for those without impairment in verbal learning or memory and only minimal functional impairment. Specifically within the group with normal learning and memory performance without significant functional impairment the women exhibited better verbal learning and memory ability than the men. In contrast, within the groups approximating mild cognitive impairment and dementia women appear to lose this advantage and men in the group approximating dementia actually performed better on verbal delayed memory than the women. There were

also no sex differences in nonverbal learning or recall within any of the approximated diagnostic groups.

The sex differences observed within the entire sample are consistent with prior research that has found that healthy older women outperform healthy older men in verbal memory (De Frias et al., 2006; McCarrey et al., 2016; Zhang et al., 2017). The sex differences in our sample appear driven by those without significant memory impairment and at most minimal functional impairment, which indicates that in a mixed clinical sample women show an early advantage in verbal learning and memory but lose this advantage as markers of clinical impairment (i.e., cognitive and functional changes) advance. This is consistent with prior research that suggested the verbal memory advantage in women is attenuated in the setting of more extensive cognitive impairment (e.g., Alzheimer's dementia), or have found negligible sex differences in older adults with MCI, AD, and those with vascular dementia (Buckwalter et al., 1996; Gale et al., 2016; Sundermann et al., 2016b). Additionally, Chapman et al. (2011) found that the verbal memory advantage observed in healthy older women was reversed in patients with AD, as men with AD exhibited better story recall than women with AD. This is consistent with our finding in which men exhibited better verbal recall than women in patients with memory and functional impairment. This finding within our dementia approximation group is also consistent with recent research showing that women exhibit a more rapid trajectory of memory decline in the setting of AD pathology (Buckley et al., 2018).

Our finding that women exhibit better verbal learning and memory within a clinical population, at least for those without significant memory or functional impairment, may have implications for interpreting neuropsychological test performances in older adults with varying degrees of cognitive impairment. As the HVLT-R normative sample consists primarily of women, this normative source may not provide the most accurate reflection of a male patient's performance. The normative age group of 70 to 79 year olds is the most skewed in sex distribution within the HVLT-R normative sample, which was primarily (90%) female (Brandt & Benedict, 2001). Within our clinical sample of older adults, this is also the age cohort in which we found the biggest sex differences in verbal learning and memory.

Where present, the effects of the verbal memory advantage in women were small, although consistent with the size of the effect of sex differences found in healthy older adults using the same verbal learning and memory measure (Munro et al., 2012). However, these effects are smaller than others reported using different measures. For example, in healthy, highly educated older adults the sex difference in learning and memory using the CVLT and Rey Auditory Verbal Learning Test (RAVLT; Schmidt, 1996) were medium to large with women outperforming men in both learning and memory indices (Gale et al., 2007; McCarrey et al., 2016). However, these effects are attenuated in clinical samples as small to medium sex effects were observed in a sample with MCI using the RAVLT but were small or negligible (i.e., non-significant) within a sample with dementia (Sundermann et al., 2016a). Thus, differences in the verbal learning and memory measure used and the nature of our mixed clinical sample may account for the smaller effect sizes observed.

While the effects of sex on verbal learning and recall indices were small, sex was a significant, independent predictor of verbal learning and memory. For example, with the 70 to 79 age cohort, sex explained 2.4% of the variance verbal learning, which is greater than the effect described in the HVLT-R manual (1.7%), although the variance explained in verbal recall was non-significant (1.1%) and similar to the HVLT-R manual results (1.4%). These percentages are smaller than some that have been reported in the literature, for example Vanderploeg et al. (2000) found that sex accounted for 8.5% of the variance in HVLT-R learning and Norman et al. (2011) found that sex accounted for 3% of the variance in HVLT total learning and 5% of the variance in delayed recall. These differences in variance explained by sex may be accounted for by sample characteristics as these prior studies included only healthy younger or older adults and did not examine a clinical sample. In our clinical sample sex did not account for a large portion of the variance in HVLT performance. However, to put variance accounted for by sex into perspective, in our subsample of 70 – 79 year olds the variance explained by age, education level, premorbid IQ, and depression all together accounted for 5.2% of verbal learning and 3.8% of verbal recall. The total variance explained in verbal learning and recall from these demographic and mood measures known to be related to memory only accounts for twice as much variance as sex, indicating that sex is also an important independent contributor. Taken together, these findings suggest that sex is an important variable to consider in the interpretation of verbal learning and memory performance in older adults seen in a clinical setting and suggests that there may be a role for sex-specific normative sources, particularly for the HVLT-R.

Accurate classification of memory performance also has important implications for the diagnosis of memory disorders including Alzheimer's disease (AD). Evidence of memory impairment is included in the diagnostic criteria for AD, which relies on objective cognitive testing (Dubois et al., 2014). Women in the 70 to 79 age cohort recalled almost one more word than the men, which corresponds to almost six percentile points when converted to a standard score using the HVLT-R normative tables. The importance of this difference is illustrated by the fact that the mean delayed recall performance for women in this age group fell within the low-average range while the mean performance for men was in the impaired range. While it is not likely that a clinician's diagnosis of AD will hinge on the ability of a patient to recall one additional word on the HVLT-R, there are some settings in which this could translate to a clinically meaningful difference, which may impact patient care and diagnosis. For example, inclusion in clinical trial research often relies on cut-off scores on cognitive screening or memory measures and thus not accounting for this sex difference could result in misclassification of participants into diagnostic groups in clinical research or inappropriate exclusion of a potential participant. For example, Hogervorst et al. (2001) suggested cut-off scores based on sensitivity and specificity of the original HVLT for detecting dementia generally as well as AD. Using such cut-offs for screening purposes to identify individuals needing further evaluation or treatment or for inclusion in research could result in incorrect decisions given the sex differences in verbal memory that we describe in the present study. We recognize that in a clinical evaluation a patient's performance on memory measures are interpreted in the context of many variables and that neuropsychological test scores merely serve as one piece of a comprehensive diagnostic

assessment. Here we argue that sex is also an important variable to consider in the evaluation of older adults seen at a memory clinic.

In contrast to the sex differences observed in the cohort of 70-79 year olds, these sex differences were absent in the 60 – 69 and 80 – 89 age cohorts. Within the 80 – 89 year age cohort, a female advantage in verbal learning initially emerged but did not survive correction for multiple comparisons and there were no sex differences in verbal recall. There was a greater proportion of individuals with impaired verbal learning and memory performance within this age cohort and given the relatively advanced age of the individuals in this cohort, there may be a greater prevalence of AD and the absence of sex differences would therefore be consistent with prior research describing the loss of the verbal memory advantage in women with AD (Sundermann et al., 2016b).

Within the 60 – 69 year age cohort the mean verbal learning and memory performance for women fell into the borderline range whereas the mean performance for men fell into the impaired range. This difference illustrates the impact that sex differences may pose in the interpretation of verbal memory performance. However, it should be noted that because the mean verbal learning and memory scores for each sex were rounded to the nearest whole number in order to obtain normative values, this magnified the difference between the scores, thus artificially inflating the sex differences present. In fact, sex differences within the 60 – 69 year old age cohort were not statistically significant, with men and women exhibiting roughly equivalent performance on learning and memory measures. It is unclear why sex differences were not evident in this age cohort. Prior research has shown that healthy older women exhibit stronger verbal memory abilities and rates of cognitive decline tend to be consistent between men and women into healthy aging (Ferreira, Ferreira Santos-Galduróz, Ferri, & Fernandes Galduróz, 2014; Gestorf et al., 2006; Lundervold et al., 2014). However, there is some evidence that women’s memory abilities may decline more sharply in the context of neurological disease (Chapman et al., 2011; Laws et al., 2016; Mielke et al., 2014). Additionally, roughly half of the individuals in this age cohort performed in the impaired ranged on learning and memory tasks. Thus, given these two competing patterns, and the mixed clinical nature of the present sample, with participants ranging in severity of cognitive dysfunction, this subgroup finding may reflect an averaged effect of these two patterns, and consequently no observable sex differences in memory. In other words, the 60 – 69 year old age cohort may contain women with early onset neurodegenerative disease, where memory abilities begin to decline at a steeper trajectory than men, along with women with subjective cognitive complaints or incipient MCI who retain a sex advantage in verbal memory resulting in a null, averaged effect.

Contrary to our hypothesis, we did not find evidence for a nonverbal memory advantage in men. In fact, we did not find any significant sex differences in BVMT-R learning or recall within the full sample or within any individual age cohort. This finding is consistent with some prior studies that also did not find an advantage for men in nonverbal learning or memory, using the same neuropsychological measure. For example, Kane and Yochim (2014) also did not find an advantage for men in BVMT-R performance in a sample of healthy older adults and Gale and colleagues (2007) actually found that healthy women outperformed men on nonverbal learning and memory and found no sex differences in

BVMT-R performance in samples of older adults with MCI or AD. Additionally, the BVMT-R manual itself reported no significant contribution from sex in any learning or recall scores within their normative sample (Benedict, 1997). The literature describing sex differences in nonverbal memory is fairly inconsistent. For example, several studies utilize a measure that relies more on immediate or working memory, such as the Benton Visual Retention Test (BVRT; Benton, 1945; McCarrey et al., 2016; Proust-Lima et al., 2008). Other studies have not included men as old as those in our sample (e.g., Pauls, Petermann, & Lepach, 2013) and some studies focus on pure diagnostic groups (e.g., Tensil et al., 2017). Thus these differences in methodology may account for our null finding. Additionally, men appear to exhibit an advantage for measures that involve visual rotation (McCarrey et al., 2016) or visuospatial construction (De Frias et al., 2006) and thus the BVMT-R, involving immediate and delayed visual memory, may not capture nonverbal abilities that best differentiate men and women.

Limitations and Future Directions

Our sample consisted of a large sample of older adults seen at a specialty outpatient neurology clinic but specific diagnostic information was not available. We classified individuals into groups approximating diagnostic status using information about level of learning and memory impairment as well as severity of functional impairment using a measure completed by caregivers (ADLQ; Johnson et al., 2004). However, using the ADLQ may not be the most accurate way to capture disease severity for the purpose of diagnostic classification as this measure relies on caregiver ratings of functional difficulties in daily life and is not specific to severity of cognitive decline. However, the authors of this measure found that the ADLQ is moderately correlated with the Mini Mental State Examination (MMSE; Folstein, Folstein, & McHugh, 1975), which is often used as a proxy for disease severity (Johnson et al., 2004).

Additionally, our sample was predominately Caucasian with above-average education, which may limit the generalizability of these findings. The education level of our sample is similar to the HVLT-R normative sample overall but slightly higher than the 70 – 79 normative group (12.95 years on average). Raw HVLT-R learning and memory scores were utilized to examine sex differences and thus deviations from the normative sample characteristics were not likely to impact the sex differences findings. Furthermore, without specific diagnostic information our findings may be applied to other outpatient memory disorders clinics where diagnostic information is unknown, the sex differences observed in our clinical sample may not generalize to a specific diagnostic group or to other settings.

Future directions include examining sex differences in subsamples of older adults in specific diagnostic groups and level of cognitive impairment (e.g., MCI, dementia, Alzheimer's disease, movement disorders) as well as incorporating neuroimaging markers and examining cognitive strategy approach in our study of sex differences within this clinical sample. Prior studies have found evidence that hippocampal volumes, adjusted for total brain volume, are larger in women than men as they age (Braden et al., 2016; Jack et al., 2015). There is also evidence that women may utilize both internal and external memory strategies to a greater extent than men, which has been put forth as an explanation for the observed sex differences

in memory, at least in healthy older adults (Kramer, Delis, & Daniel, 1988; McDougall, Pituch, Stanton, & Chang, 2014; Sunderaraman, Blumen, DeMatteo, Apa, & Cosentino, 2013). Future studies within our clinical sample aim to examine differences in hippocampal volumes as well as learning and memory strategies, specifically semantic clustering, and their relationships to the observed sex differences in verbal learning and memory.

Conclusion

In a large, clinical sample of older adults seen at a memory disorders center, we found that sex differences in verbal memory emerge in a relatively similar fashion to those seen in healthy older adults. These sex differences appear driven by those without significant verbal learning or memory impairment with at most minimal functional decline, consistent with the hypothesis that women have an early memory advantage, which is lost when markers of disease burden (i.e., memory and functional impairment) advance. This sex difference in verbal memory has relevance for interpreting neuropsychological performances of older men and women seen in a clinical or research setting, especially when the memory test does not provide separate norms by sex. The results also highlight the importance of developing well-characterized clinical norms, as neurological disease may differentially impact men and women.

Acknowledgments

This work was supported by an Institutional Development Award (IDeA) from the National Institute of General Medical Sciences of the National Institutes of Health under grant number 5P20GM109025; and The Women's Alzheimer's Movement.

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Table 1

Sample Characteristics and Covariates by Sex

	Total Sample ***N*** **= 1084**		**Age 60 – 69** ***n*** **= 317**		**Age 70 – 79** ***n*** **= 554**		**Age 80 – 89** ***n*** **= 213**	
	Female ***n*** **= 507**	**Male** ***n*** **= 577**	**Female** ***n*** **= 157**	**Male** ***n*** **= 160**	**Female** ***n*** **= 249**	**Male** ***n*** **= 305**	**Female** ***n*** **= 101**	**Male** ***n*** **= 112**
Age	73.53 (6.53)	73.75 (6.23)	66.26 (2.30)	66.16 (2.49)	74.11 (2.69)	74.44 (2.80)	83.39 (2.80)	82.71 (2.33)
Education (Years)	14.33 * (2.60)	15.11 (2.78)	14.75 (2.53)	15.14 (2.62)	14.13 * (2.55)	15.12 (2.90)	14.19 (2.76)	15.07 (3.14)
WRAT-4 [a]	103.07 (10.57)	102.30 (12.38)	100.54 (10.91)	99.14 (12.46)	102.77 (9.73)	102.41 (12.63)	107.76 (10.66)	106.49 (10.21)
ADLQ [b]	27.13 (20.67)	27.30 (18.09)	23.47 (19.32)	27.26 (17.98)	25.98 (20.65)	25.97 (18.02)	34.97 (20.81)	31.40 (17.97)
GDS [c]	9.37 * (6.38)	7.45 (5.77)	10.36 * (7.02)	8.06 (6.12)	9.22 * (6.28)	7.35 (5.77)	8.19 (5.34)	6.84 (5.18)

Note: Data presented in mean (standard deviation). Analyses presented compared females and males within the total sample and with each age cohort separately.

[a] Wide Range Achievement Test, 4th Edition reading subtest standard score; Missing data for $n = 32$ patients.

[b] Activities of Daily Living Questionnaire percentile score; Missing data for $n = 310$ patients.

[c] Geriatric Depression Scale total score; no missing data.

* $p < .01$

Table 2

Mean Sex Differences for Patients with Impaired Learning and Memory Performance

	Impaired Verbal Learning		Impaired Verbal Recall		Impaired Nonverbal Learning		Impaired Nonverbal Recall	
	Female *n* = 166	**Male *n* = 264**	**Female *n* = 238**	**Male *n* = 313**	**Female *n* = 224**	**Male *n* = 261**	**Female *n* = 231**	**Male *n* = 256**
Verbal Learning[a]	12.45 (3.37)	12.74 (3.17)						
Verbal Recall[b]			1.08 (1.77)	1.43* (1.93)				
Nonverbal Learning[c]					7.02 (3.06)	6.94 (3.09)		
Nonverbal Recall[d]							1.70 (1.37)	1.61 (1.34)

Note: Learning and memory impairment was defined by performing below 1.5 standard deviations from the mean using published normative values.

[a] Hopkins Verbal Learning Test –Revised (HVLT-R) trials 1-3 total raw score, the range of possible scores is from 0 to 36

[b] HVLT-R delayed recall raw score, the range of possible scores is from 0 to 12

[c] Brief Visuospatial Memory Test -Revised (BVMT-R) trials 1-3 total raw score, the range of possible scores is from 0 to 36

[d] BVMT-R delayed recall raw score, the range of possible scores is from 0 to 12

* $p < .01$

Table 3

Mean Sex Differences for Patients with Unimpaired Learning and Memory Performance

	Unimpaired Verbal Learning		Unimpaired Verbal Recall		Unimpaired Nonverbal Learning		Unimpaired Nonverbal Recall	
	Female *n* = 507	**Male *n* = 577**	**Female *n* = 269**	**Male *n* = 264**	**Female *n* = 277**	**Male *n* = 315**	**Female *n* = 270**	**Male *n* = 320**
Verbal Learning[a]	22.26* (4.00)	21.52 (4.03)						
Verbal Recall[b]			8.04* (1.97)	7.40 (2.06)				
Nonverbal Learning[c]					18.57 (5.51)	18.30 (5.62)		
Nonverbal Recall[d]							7.58 (2.17)	7.36 (2.58)

Note: Unimpaired learning and memory was defined by performing at or above 1.5 standard deviations below the mean using published normative values.

[a] Hopkins Verbal Learning Test –Revised (HVLT-R) trials 1-3 total raw score, the range of possible scores is from 0 to 36

[b] HVLT-R delayed recall raw score, the range of possible scores is from 0 to 12

[c] Brief Visuospatial Memory Test -Revised (BVMT-R) trials 1-3 total raw score, the range of possible scores is from 0 to 36

[d] BVMT-R delayed recall raw score, the range of possible scores is from 0 to 12

* $p < .01$

Table 4

Mean Sex Differences within Diagnostic Approximation Groups

	Normal Learning and Functioning		Impaired Learning and Normal Functioning		Impaired Learning and Functioning	
	Female *n* = 151	Male *n* = 170	Female *n* = 79	Male *n* = 118	Female *n* = 61	Male *n* = 90
Verbal Learning[a]	22.40 * (3.84)	21.39 (3.97)	12.46 (3.30)	12.90 (3.20)	12.38 (3.25)	12.14 (3.14)
	Female *n* = 124	Male *n* = 173	Female *n* = 106	Male *n* = 115	Female *n* = 78	Male *n* = 86
Nonverbal Learning[b]	18.40 (5.49)	18.36 (5.38)	7.28 (2.96)	7.22 (3.12)	5.74 (2.93)	6.65 (3.10)
	Normal Recall and Functioning		**Impaired Recall and Normal Functioning**		**Impaired Recall and Functioning**	
	Female *n* = 121	Male *n* = 143	Female *n* = 109	Male *n* = 145	Female *n* = 83	Male *n* = 101
Verbal Recall[c]	7.91 * (1.90)	7.39 (1.90)	1.24 (1.92)	1.26 (1.92)	1.04 (1.64)	1.42 * (1.90)
	Female *n* = 124	Male *n* = 175	Female *n* = 106	Male *n* = 113	Female *n* = 81	Male *n* = 89
Nonverbal Recall[d]	7.44 (2.28)	7.47 (2.82)	1.68 (1.36)	1.54 (1.33)	1.54 (1.37)	1.61 (1.36)

Note: Normal memory or learning defined by performing at or above 1.5 standard deviation below the mean using published normative values. Impaired memory or learning defined by performance below 1.5 standard deviations below the normative mean. Normal functioning defined by a total score of 0 to 33 on the Activities of Daily Living Questionnaire (ADLQ) and impaired functioning was defined as a total ADLQ score above 33.

[a] Hopkins Verbal Learning Test –Revised (HVLT-R) trials 1-3 total raw score, the range of possible scores is from 0 to 36

[b] Brief Visuospatial Memory Test -Revised (BVMT-R) trials 1-3 total raw score, the range of possible scores is from 0 to 36

[c] HVLT-R delayed recall raw score, the range of possible scores is from 0 to 12

[d] BVMT-R delayed recall raw score, the range of possible scores is from 0 to 12

* $p < .05$

Table 5

Mean Sex Differences within each Age Cohort

	Total Sample ***N*** **= 1084**		**Age 60 – 69** ***n*** **= 317**		**Age 70 – 79** ***n*** **= 554**		**Age 80 – 89** ***n*** **= 213**	
	Female ***n*** **= 507**	**Male** ***n*** **= 577**	**Female** ***n*** **= 157**	**Male** ***n*** **= 160**	**Female** ***n*** **= 249**	**Male** ***n*** **= 305**	**Female** ***n*** **= 101**	**Male** ***n*** **= 112**
Verbal Learning[a]	19.05 * (5.97)	17.50 (5.71)	20.30 (6.01)	19.19 (6.00)	19.30 * (5.85)	17.60 (5.37)	16.49 (5.50)	14.82 (5.17)
Verbal Recall[b]	4.78 * (3.95)	4.16 (3.58)	5.51 (4.09)	5.24 (3.73)	5.03 * (3.81)	4.18 (3.51)	3.00 (3.54)	2.57 (2.92)
Nonverbal Learning[c]	13.31 (7.37)	13.17 (7.28)	15.76 (8.25)	15.71 (7.98)	13.09 (6.87)	13.10 (6.85)	10.04 (5.56)	9.76 (5.88)
Nonverbal Recall[d]	4.83 (3.46)	4.80 (3.56)	5.73 (3.71)	5.79 (3.51)	4.84 (3.30)	4.83 (3.62)	3.42 (3.97)	3.30 (2.96)

Note: Analyses presented compared the mean learning and memory performance between females and males within the total sample and each age cohort separately.

[a] Hopkins Verbal Learning Test –Revised (HVLT-R) trials 1-3 total raw score, the range of possible scores is from 0 to 36

[b] HVLT-R delayed recall raw score, the range of possible scores is from 0 to 12

[c] Brief Visuospatial Memory Test -Revised (BVMT-R) trials 1-3 total raw score, the range of possible scores is from 0 to 36

[d] BVMT-R delayed recall raw score, the range of possible scores is from 0 to 12

* $p < .01$