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Sex Differences in Cognitive Decline in
Mild Cognitive Impairment and
Alzheimer's Disease

Juliann Thompson

A thesis submitted to the faculty of
Brigham Young University
in partial fulfillment of the requirements for the degree of
Master of Science

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ABSTRACT

Sex Differences in Cognitive Decline in Mild Cognitive Impairment and Alzheimer's Disease

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Alzheimer's disease (AD) is the most common form of dementia and results in progressive cognitive decline, particularly in regards to memory (National Institute on Aging, 2012). Prior research has shown sex differences in brain-atrophy rates of AD patients, with women experiencing a higher rate of progression in volume reduction (Skup et al., 2011). This suggests that there may also be differences in cognitive functioning between sexes, particularly in the rate of cognitive decline with a more rapid disease progression for dementing females compared to dementing males. The current study monitored memory function longitudinally in approximately 200 total participants, 100 with Mild Cognitive Impairment (MCI) or probable AD and 100 healthy controls enrolled in an aging study through the Arizona Alzheimer's Disease Research Consortium. Memory performance was evaluated with two memory tests, the Rey Auditory Verbal Learning Test (RAVLT; Rey, 1941) and the Brief Visuospatial Memory Test-Revised (BVMT-R; Benedict, 1997). Memory function was evaluated in participants with at least three data points over a five-year span. A multivariate regression model was used that includes controls for disease severity, age, age at disease onset, education, ethnicity, and medical comorbidities. Results indicated that females in the MCI and AD groups initially performed better than the males, but that over time, female scores had dropped significantly lower than male scores, suggesting a more rapid decline in females. Significant sex differences in cognitive decline may yield a deeper understanding of the development and progression of AD and aid in more effective and sex-specific treatment.

Keywords: mild cognitive impairment, Alzheimer's disease, sex differences, memory

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Sex Differences in Cognitive Decline in Mild Cognitive Impairment and Alzheimer's Disease

Alzheimer's disease (AD) is the most common form of dementia and results in progressive cognitive decline, particularly in regards to memory (Dai & Yong, 2014). Because AD can only be diagnosed post-mortem by confirming the presence of neurofibrillary tangles and amyloid plaques in the brain (Fan, Batmanghelich, Clark, & Davatzikos, 2008), a workgroup assembled by the National Institute on Aging (NIA) and the Alzheimer's Association recommends dividing AD diagnoses into two categories: probable AD and possible AD (McKhann et al., 2011). The criteria for probable AD includes the following: general criteria for dementia is met, gradual onset of symptoms, clear worsening of cognition as reported by observation, and amnestic or non-amnestic presentation. Amnestic presentation must include deficits in learning or recall, as well as impairment in one of the following domains: ability to acquire and remember new information, reasoning and judgment, visuospatial abilities, language function, or changes in personality or behavior. Non-amnestic presentation typically only includes deficits in language, spatial cognition, or executive dysfunction. Criteria for possible AD is discussed in detail elsewhere (McKhann et al., 2011), as the present study includes only those AD patients with a "probable" diagnosis.

Often considered prodromal AD, mild cognitive impairment (MCI) can be defined as a transitional state between normal aging and meeting criteria for dementia. This often occurs prior to the clinical diagnosis of Alzheimer's disease, where memory is impaired but other cognitive functions are generally intact (Petersen et al., 2001; Petersen et al., 1999). According to the NIA and Alzheimer's Association, criteria for MCI includes a concern regarding a change in cognition, impairment in at least one cognitive domain (e.g. memory, executive function, attention, visuospatial skills, or language), preservation of independence (i.e. general functioning

in everyday life), and the absence of a dementia diagnosis (Albert et al., 2011). Similar to probable AD, MCI can further be divided into amnesic or non-amnesic presentation (Petersen, 2004).

Recent literature has shown sex differences in brain atrophy rates and cognitive decline in patients with AD and MCI. Using magnetic resonance imaging (MRI), Hua et al. (2010) found faster atrophic rates in women MCI subjects when compared with male MCI subjects. Additionally, Skup et al. (2011) found greater loss of gray matter in females with probable AD and amnesic MCI (aMCI) in comparison with AD and aMCI males in a longitudinal study investigating atrophy rates. Gray matter atrophy in patients with AD can be up to 20 to 25% greater than that found in healthy controls, and there is a negative correlation between increased cortical atrophy and performance on the Mini Mental Status Exam (MMSE) (Mouton, Martin, Calhoun, Dal Forno, & Price, 1998). This is evidence that because there are marked sex differences in atrophy rates, there may also be sex differences in cognitive decline. For example, the clinical manifestation of Alzheimer's disease is stronger in women than in men (Barnes et al., 2005), and the possession of the ApoE4 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). The aim of the current study is to investigate these effects longitudinally. We hypothesize a larger decline in dementing females' memory scores over time compared to both the healthy controls and dementing males.

Method

Participants

Participants were enrolled in the Arizona Alzheimer's Disease Core Center (ADCC), an NIH-funded longitudinal study of aging, Alzheimer's disease, and related disorders. The Arizona

ADCC is a multi-site consortium consisting of five separate sites including Barrow Neurological Institute, Mayo Clinic Arizona, Sun Health Research Institute, Southern Arizona VA Healthcare System, and University of Arizona Health Science Center. Data was collected longitudinally at annual intervals over a span of ten years. Participants included 75 patients with a diagnosis of MCI (n=46; males=25) or AD (n=29; males=13) and 75 healthy controls (i.e. no degenerative diagnosis; males=36). In order to meet criteria for the current study, clinical participants must have had a diagnosis for MCI or probable AD at the initial neuropsychological assessment and been evaluated at least three times over a five year span. Healthy controls were required to not have met diagnostic criteria for dementia or MCI throughout the entire course of the study. Diagnoses for all participants were made by a multidisciplinary team with members represented from all sites, using the previously discussed diagnostic criteria set forth by the NIA and Alzheimer’s Association.

Table 1

Demographic information and test performance by diagnosis and sex

	Healthy Controls				MCI				AD			
	Male (n = 36)		Female (n = 39)		Male (n = 25)		Female (n = 21)		Male (n = 13)		Female (n = 16)	
	M	SD	M	SD	M	SD	M	SD	M	SD	M	SD
Age	67.8	7.8	67.6	12.3	72.9	6.3	70.9	7.3	77.9	4.7	73.4	10.7
Education	17	1.9	16.4	2.3	15.32	4.7	14.6	2.6	16.2	3.4	12	3.35
MMSE	29.1	0.9	29.3	1.2	26.9	2.1	26.8	1.4	20.1	5.2	18.1	7.8
DRS Total	137.4	2.7	139.7	4.4	129.9	9.3	130.7	5.1	106.6	13.1	103.1	23.2
Age of Onset					70.7	6.2	70	9.2	72.6	4.4	67.9	10.8

MMSE: Mini Mental State Examination

DRS Total: total score on the Dementia Rating Scale.

Materials and Procedure

Memory performance was evaluated with two memory tests, the Rey Auditory Verbal Learning Test (RAVLT; Rey, 1941) and the Brief Visuospatial Memory Test-Revised (BVMT-

R; Benedict, Schretlen, Groninger, Dobraski, & Shpritz, 1997). Tests were administered and scored by each site, and the ADCC has established inter-site reliability of protocol administration and scoring. According to Gale, Baxter, Connor, Herring, & Comer (2007), in this particular ADCC database, no systematic error was observed and a test for homogeneity of variance did not show any statistically significant inter-site differences. Additionally, ANOVA of participant performance between sites did not reveal significant differences.

The RAVLT is a common test for evaluating verbal memory. Participants were administered the test according to standard protocol as outlined in the manual (see Rey, 1941). In step 1 of the RAVLT, patients are presented with auditory presentation of 15-item word list (List A) and asked to immediately, verbally recall them. In step 2, patients are presented with a “distractor” list (List B), and instructed to, again, immediately recall them. Step 3 consists of repeated presentation of List A, and both immediate and delayed recall of the items.

Psychometrically, the RAVLT is a sound test. De Sousa Magalhães, Malloy-Diniz, & Hamdan (2012) reported Cronbach’s alpha for the test, finding an alpha reliability of 0.84, standardized alpha of 0.88, test condition coefficients from 0.78 to 0.82, and retests between 0.81 and 0.86. Participants were administered the RAVLT at each visit and scores were compared annually.

Patients were also evaluated with the BVMT-R, a measure of visuospatial memory. During administration of the BVMT-R, participants are presented various visual designs for 10 seconds each and instructed to reproduce as many designs as possible. Immediately following this trial, identical designs are repeatedly presented twice, and patients are instructed to attempt to improve their performance. After a 25 minute delay, participants are asked to reproduce the previously viewed matrix strictly from memory. This trial is typically followed by a delayed recognition task that includes 6 target and 6 non-target figures. Patients are instructed to respond

yes or no to whether they have previously seen the item. One major strength of the BVMT-R for neuropsychological assessment is that it is available in six different forms, and inter-form reliability has been demonstrated (Benedict, Schretlen, Groninger, Dobraski, & Shpritz, 1996). Multiple test forms are ideal in longitudinal studies such as ours to reduce practice effects, as participants were tested annually. Benedict et al. also report criterion coefficients between 0.52 – 0.80 when compared with similar measures of visual-spatial memory, and high between- and within-subjects reliability.

Statistical Analyses

Analysis of the test score data was conducted using a latent growth curve model. This model is particularly useful in studies like ours because it allows for analysis of longitudinal data by defining an intercept, or baseline measure, and tracking the slope, or change over time. Similar to hierarchical linear models, latent growth curves allow both within- and between-individual variations. This is accomplished by looking at two distinct models: one modeling relationships within each of the lower level units, and a second modeling how these relationships vary between units (Hofmann, 1997). In lower levels, each individual's data are fitted to a regression line, acting as estimates based on data from the individual and the entire population. Then, data are weighted by the number of data points and the reliability of the regression (Terracciano, McCrae, Brant, & Costa, 2005). According to Terracciano et al., this approach “tends to shrink the individuals' coefficients toward the population means.” In the current study, level one will consist of the repeated test scores for each participant, and level two will represent each participant. This will allow us to create a growth curve and more accurately estimate differences within each individual over time. RAVLT and BVMT total learning scores and long-term memory scores over the three epochs will be compared between genders as well as disease

severity (AD vs. MCI). This will give us an accurate view of differences between clinical and control populations, sex differences in the clinical population, as well as possible differences between distinct stages of disease progressions (i.e. MCI vs. AD). We will also enter education, presence of ApoE4 allele, and age of disease onset as covariates.

Results

Statistical Assumptions

Preliminary analysis of the data showed that all assumptions of structural equation modeling were met. First, data were assessed in terms of missing values, normality, and multicollinearity. On average, there were 6 missing values for AVLT total and long-term and BVMT total scores. Data were examined manually for potential patterns of missingness as well as total number of missing values. Because no obvious patterns were detected and missing data represented a small portion of total scores (<5%), it was concluded that the data was likely missing at random, with no clear connection between the missing values and the dependent and independent variables. Further, scores for each participant in the remaining variables were near the mean, and did not show any extremely high or low values that may indicate impairment or outliers. Due to the random nature of the data, and after examining other variables, maximum likelihood was used for missing value imputation. A power correlation assessing the significance of impact of the missing variables ($p > .05$) confirmed that missing data likely did not have an effect on analyses. Next, we looked at the normality of the data. Results indicate that our model is normally distributed with no significant skew or kurtosis. Multicollinearity was assessed using Stata 13.1 software, and results indicated low collinearity between variables ($r^2 = 0.09 - 0.12$; mean VIF = 1.98).

Latent Growth Curve Modeling

Results were analyzed using latent growth curve modeling (LGCM), due to the longitudinal nature of the data and hypotheses. LGCM is appropriate in situations where both individual and group differences are being examined over time. According to De Fraine, Van Damme, & Onghena (2007), LGCM is useful when researchers want to view a typical path and how individuals or groups differ from the average trajectory. Goodness of fit was examined and the model was adequate ($\chi^2 > 0.07$; RMSEA=0.10; CFI=0.86), but after reviewing modification indices for the model, we decided it would make theoretical sense as well as increase model fit to covary the error terms for AVLT and BVMT long-term memory scores. Following this change, fit improved to $\chi^2 > 0.207$; RMSEA=0.08; CFI 0.96).

Two models were used for analyses; first, investigating gender changes in immediate memory (RAVLT and BVMT total scores) and long-term memory (RAVLT and BVMT long-term scores). The second model used the same immediate and long-term memory scores, but included sex differences with the varying levels of impairment (i.e. control, AD, or MCI).

Sex Differences

Results indicate that female participants in both the AD and MCI groups tended to start at a lower initial score, show decreased scores over time on measures of both the RAVLT and the BVMT long-term memory trial, and have an overall worse trajectory when compared to male participants with AD, significant at a $p < 0.001$ level. Female scores on total learning showed a similar path; however, females tended to begin at a slightly higher initial score, but showed a more rapid decline over the three epochs, ending with significantly lower scores than male counterparts ($p < 0.05$). In other words, although women in the MCI and AD groups initially performed better than the men, by the third visit, scores had dropped significantly lower than

male scores in the third epoch. This demonstrates differences for gender between clinical populations, but no significant effects were found when comparing AD vs. MCI samples. So, although clinical males consistently outperformed clinical females, with females showing more impairment over time, effects were not significantly more severe in female AD. This partially supports our hypotheses that females tend to decline more rapidly than males, even in the early stages of cognitive decline. As expected, female control significantly outperformed female clinical participants in measures of both immediate and long-term memory. Although male clinical participants also performed more poorly than both the female and male control participants, differences were not as large, indicating again that female clinical participants generally showed more impairment than males both at baseline and over time.

Discussion

Sex differences in both RAVLT and BVMT-R total learning and long-term memory raw scores were demonstrated in the MCI and AD groups when compared with healthy controls, but were not significantly different when divided by diagnoses. This suggests that, in general, women in the clinical groups achieved lower average scores and declined more rapidly over the 3-year interval than both the dementing males and the healthy controls. Because verbal memory is typically one of the first detectable signs of cognitive decline, and visuospatial memory is often fairly preserved in initial stages of the disease, it makes sense that female participants performed consistently lower on the RAVLT, compared to initially high scores that dropped over time on the BVMT-R. However, because there were no noticeable differences between the women in the AD and MCI groups, we cannot say whether disease severity plays a role in how quickly or severely participants are declining. Additionally, the greater cognitive cannot be

attributed to greater disease severity since women and men scored similarly on dementia rating scales measuring severity (i.e. MMSE, DRS, and age at symptom onset; see Table 1).

There are several limitations in our study design, most of which arise due to the use of archival data. Because we do not currently have access to the exact protocol used for administration and scoring of tests and recruitment of participants, specifically the healthy controls, we are unable to address confounds related to the selection of participants. This is an obvious threat that will need to be addressed before conclusions can be made about the study.

The longitudinal nature of the research also introduces limitations due to repeated testing at multiple sites. Because the database includes participants at five different sites over a span of ten years, it is impossible to confirm that administration and scoring of the tests was standardized with every participant. Those conducting the neuropsychological evaluations likely changed frequently at each site during the decade this data was collected, and even small variations between (or within) experimenters has the ability to introduce error. Additionally, mortality rates may influence results as several patients in the ADCC database passed away before the completion of the study. Because Alzheimer's disease is a fatal condition (though prognosis depends on severity), it is expected that mortality rates in a study such as ours will be higher than average. Even as we attempt to control for this possible confound, we acknowledge that it may be a major threat. For example, if the more severe cases of Alzheimer's disease (and therefore greater cognitive decline) are not included in our study because they pass away, it may skew the results to look less severe or less differentiated than they actually are. Mortality will need to be assessed and addressed as we receive more information from the ADCC protocol. Lastly, any results obtained in this study are limited to a very specific population. We are only looking at patients with MCI and AD, and only measuring abilities in verbal and visuospatial memory.

Although significant results may have a large impact on this specific subset of clinical patients, we recognize that conclusions cannot be generalized beyond this small selected population.

Although there are several limitations to this study that need to be considered and addressed, there are several strengths that we believe will aid future research in this area.

Although investigation of sex differences is not new to our populations of interest, ours is the first of our knowledge to address the speed of cognitive decline progression between the sexes. Significant sex differences in the rapidity of cognitive decline may yield a deeper understanding of the development and progression of MCI and AD and aid in more effective and sex-specific treatment.

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