Cognition and Hippocampal Volumes in Older Adults with Autism Spectrum Disorder

by

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ABSTRACT

With a growing number of adults with autism spectrum disorder (ASD), more and more research has been conducted on majority male cohorts with ASD from young, adolescence, and some older age. Currently, males make up the majority of individuals diagnosed with ASD, however, recent research states that the gender gap is closing due to more advanced screening and a better understanding of how females with ASD present their symptoms. Little research has been published on the neurocognitive differences that exist between older adults with ASD compared to neurotypical (NT) counterparts, and nothing has specifically addressed older women with ASD. This study utilized neuroimaging and neuropsychological tests to examine differences between diagnosis and sex of four distinct groups: older men with ASD, older women with ASD, older NT men, and older NT women. In each group, hippocampal size (via FreeSurfer) was analyzed for differences as well as correlations with neuropsychological tests. Participants (ASD Female, n = 12; NT Female, n = 14; ASD Male, n = 30; NT Male = 22), were similar according to age, IQ, and education. The results of the study indicated that the ASD Group as a whole performed worse on executive functioning tasks (Wisconsin Card Sorting Test, Trails Making Test) and memory-related tasks (Rey Auditory Verbal Learning Test, Weschler Memory Scale: Visual Reproduction) compared to the NT Group. Interactions of sex by diagnosis approached significance only within the WCST non-perseverative errors, with the women with ASD performing worse than NT women, but no group differences between men. Effect sizes between the female groups (ASD female vs. NT female) showed more than double that of the male groups (ASD male vs. NT male) for all WCST and AVLT measures. Participants with ASD had significantly smaller right hippocampal volumes than NT participants. In addition, all older women showed larger hippocampal volumes when corrected for total

intracranial volume (TIV) compared to all older men. Overall, NT Females had significant correlations across all neuropsychological tests and their hippocampal volumes whereas no other group had significant correlations. These results suggest a tighter coupling between hippocampal size and cognition in NT Females than NT Males and both sexes with ASD. This study promotes further understanding of the neuropsychological differences between older men and women, both with and without ASD. Further research is needed on a larger sample of older women with and without ASD.

DEDICATION

In dedication to my older brother, Daniel, who continues to inspire those around him with his unwavering kindness and passion.

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INTRODUCTION

With normal aging, it is known that cognitive abilities (i.e. executive functioning and memory) decline along with atrophy of the hippocampus. Past studies have suggested that females perform better than males on measures of verbal memory and that sex differences in both verbal learning and memory need to be considered when evaluating the elderly [Gale et al., 2007; Herlitz, Airaksinen, & Nordstrom, 1999]. Cognitive difficulties such as flexible thinking and other aspects of executive dysfunction are observed in younger persons with autism spectrum disorder (ASD) [Russo et al., 2007]. In addition, elderly adults with ASD report more cognitive problems than age-matched neurotypical (NT) adults and continue to experience a low quality of life [van Heijst & Geurts, 2015; Wallace, Budgett, & Charlton, 2016]. Research has also reported that cognitive abilities in older adults with ASD have similar weaknesses compared to that of younger persons with ASD, such as reduced performance in attention, working memory, and fluency tasks compare to age-matched NT controls, but preservation of other cognitive functions such as verbal memory [Geurts & Vissers, 2012; Braden et al., 2017].

Currently, males outnumber females in ASD diagnoses with a 1:3 ratio [Christensen et al., 2012]. Research regarding the specific cognitive differences between adult women with ASD and adult men with ASD is limited. When examining behavioral differences, males with ASD tend to exhibit more externalizing behavior problems than females, such as aggressive behavior, hyperactivity, and increased repetitive behaviors and restricted interests [Werling & Geschwind, 2013]. In addition, research has shown that females with ASD show greater internalizing symptoms than boys, including anxiety, depression, and other emotional symptoms [Werling & Geschwind, 2013]. Research suggests that females with ASD have enhanced abilities to mask ASD traits [Ferri, 2018] through compensatory cognitive

mechanisms. In young adults, males show reduced motor executive function (coordination, inhibition, and planning) and visuospatial performance, compared to NT counterparts, but adult females with ASD are not different from NT females [Lai et al., 2012]. Thus, although the literature on sex differences in ASD are still small, numerous differences related to behavior, neuroanatomy, and presentation of symptoms exist between males and females with ASD and warrant further investigation.

Individuals with ASD have neuroanatomical differences compared to NT counterparts, especially in subcortical structures such as the amygdala and hippocampus. Researchers suggest that hippocampal volumetric differences exist in late childhood, adolescence [Barnea-Goraly et al., 2014], and high-functioning young adults with ASD [Eilam-Stock et al., 2016]. Our lab extended these findings by showing reduced hippocampal volumes in older males with ASD compared to NT males [Braden et al., 2017]. Lastly, older NT women have been shown to have larger hippocampal volumes than NT men [Braden et al., 2016]. Thus, older women with ASD may be protected from the smaller hippocampal size seen in older men with ASD compared to older NT men.

Given this current body of research, we chose to investigate the differences between older men and women with ASD in cognitive performance compared to a matched NT group. We hypothesized that older adult males with ASD would show reduced cognitive performance compared to older females with ASD. In addition, we investigated differences between older men and women with ASD in hippocampal size compared to a matched NT group. For this question, we hypothesized that older men would show greater reduction in hippocampal volume than older females with ASD.

METHODS

Participants

For this study, recruited participants consisted of: 12 women with ASD, 14 NT women, 30 men with ASD, and 23 NT men. All participants were middle-aged to older adults with a range of ages from 40 to 71 years with IQ scores ranging from 70 to 141 (all participants with ASD were free from intellectual disability). Male and female participants with ASD were recruited via the Southwest Autism Research & Resource Center (SARRC) lifetime database. This voluntarily enrolled database which contained information from all individuals who participated in a clinical or research program at the SARRC. Through grassroots community groups and flyers posted at ASD college and community events, other participants with ASD were recruited and their diagnosis was confirmed by SARRC upon enrollment. Both male and female NT participants were recruited via word of mouth, postings on social media, and flyers posted throughout the community [Braden et al., 2017].

Inclusion/Exclusion Criteria

In order to participate in the study, participants with ASD required a diagnosis based on the Diagnostic and Statistical Manual of Mental Disorders 4th or 5th Edition, otherwise known as the DSM IV or DSM V [American Psychiatric Association, 2000, 2013]. The process for this diagnosis included each ASD participant to self-report a life-long pattern of social impairment and early developmental history to verify age of symptom onset. For this study, we confirmed the current presentation of symptoms with the Autism Diagnostic Observation Schedule-2, module 4 [ADOS-2; Lord et al., 2012]. The ADOS-2 was administered by a research-reliable psychometrician at SARRC. Diagnosis was confirmed if the participant reached a threshold score (Communication + Social Interaction Total ≥ 7).

This data is part of a larger study that includes a functional MRI language task, thus all participants were right-handed for the purpose of homogeneity in hemisphere language dominance. Due to the strong influence of genetics in ASD, NT participants had no first degree relative with an ASD diagnosis and all participants were screened for presence of ASD symptoms with the Social Responsiveness Scale-2 [SRS-2; Constantino, 2012]. All participants were given the Kaufman Brief Intelligence Test 2nd edition [Kaufman & Kaufman, 2004] to provide an estimate of full-scale IQ (>70 required) and similar intelligence between each group. As common with ASD, a small percentage of our participants had experienced a single childhood seizure, but none continued to experience seizures in adulthood nor took seizure medication. No participants reported head injuries with loss of consciousness or any known genetic disorders. The NT participants did not demonstrate a history of psychiatric disorders in order to achieve a diagnosis-free comparison group. However, since depression and anxiety are common comorbidities with an ASD diagnosis, these were not exclusionary for any of the ASD participants. Therefore, recruiting a reasonably sized group of middle-age adults without a history of depression or anxiety would be difficult and overly restricted to a unique set of individuals with ASD. No participants had current or past history of other Axis I diagnoses such as schizophrenia or bipolar disorder. All participants provided written consent approved by the Institutional Review Board [Braden et al., 2017].

Cognitive Measures

The participants were given four cognitive tests to measure aspects of executive functioning and memory across the older adult groups. Assessments included the Wisconsin Card Sorting Test (WCST), Rey Auditory Verbal Learning Test (RAVLT), Wechsler Memory

Scale-Fourth Edition (WMS-IV): Visual Reproduction (VR) subtests I & II, and Trail Making Test (TMT) Parts A and B. The WCST is a task often used to measure executive functioning in areas such as perseveration, flexibility, working memory, set-shifting skills, and inhibition [Hill, 2004; Milner, 1963]. Within the WCST, participants matched 128 stimulus cards to one of four key cards with limited and changing instructions with a maximum of six categories. The WCST was used to measures various aspects of participant's executive functioning by examining general errors, perseverative errors, non-perseverative errors, and number of categories completed. In order to assess verbal learning and memory participants were given the RAVLT [Rey, 1964]. This assessment involves the examiner reading an initial list of 15 words (i.e. List A) for the examinee to repeat back immediately (A1). Following this, the examinee free recalls List A four additional times (A2-A5). The examiner gives a distracting list of 15 new words (List B) followed by free recall once again (B1). Without reading List A again, the examiner then asks for List A to be recalled (A6). After 20 minutes, the examinee is asked to recall as many words as possible from List A (A7). From these lists, learning over trials (LOT) is calculated by taking the total number of words recalled from all five trials minus five times the number of words obtained in the first trial. The WMS-IV (Pearson, Inc.) is composed of seven subtests used to assess someone's ability to store and retrieve information. For this study, we were interested in examining visual memory in the immediate- and delayed-recall conditions through the VR subtests I & II. The VR I subtest requires the examinee to recreate an image immediately after being shown the nonverbal visual stimuli (i.e. simple geometrical-like shapes). In comparison, the VR II subtest is the long-term visual spatial memory portion of the task where the examinee draws the image from memory following a delay. In total, the VR II score consists of how the examinee did recreating the images and recognizing and matching the designs presented

in the immediate condition [Maccow, 2011]. The TMT Parts A & B [Reitan, 1958] is frequently used to test processing speed and other executive functioning areas such as attention, visual scanning, sequencing and shifting, psychomotor speed, abstraction, and flexibility [Salthouse, 2011]. In Part A, the participant must draw lines to connect circled numbers in numerical order (i.e. 1-2-3) as quickly and efficiently as possible. In Part B, the participant must draw lines connecting circled numbers and letters in an alternating numeric and alphabetic order (i.e. 1-A-2-B, and so on) also as rapidly as possible. Participants were timed during each part and scored on how many errors were made.

MRI and Hippocampal Volumes

Neuroanatomical MRI data were taken utilizing a 3-Tesla Philips Ingenia MRI scanner with maximum gradient strength of 45 mT/m . The participants all had high-resolution, T1-weighted anatomical scans (3D magnetization prepared rapid acquisition gradient echo (MPRAGE) 256 3 256 in-plane resolution, 240 mm field of view (FOV); 170 sagittal slices 1.2 mm). In order to ease potential anxiety around having an MRI scan, participants had the option of visiting the imaging center and experience the MRI environment prior to the data collection. In addition, participants were provided with headphones and padding to minimize head motion in the scanner. Hippocampal volume was measured in mm3 based on brain segmentation [Fischl et al., 2002; Fischl et al., 2004] via the FreeSurfer (surfer.nmr.mgh.harvard.edu) program automated parcellation and divided by total intracranial volumes (TIV) mm3 to correct for variation in brain size [Braden et al. 2017].

Statistical Analyses

Cognitive measures of interest were WCST: errors, perseverative errors, non-perseverative errors, and categories; RAVLT: total correct of A1 list, total correct of A7 list, total words overall, learning over trials score; WMS: Visual Reproduction I & II scores; and TMT: total time form A, total time form B. Two-way analysis of variances (ANOVAs) in SPSS determined main effects of and interactions between diagnosis and sex. In addition, one-way ANOVAs were conducted on the demographic variables across the four groups (i.e. ASD male and female; NT male and female). Within group correlational analyses were conducted between hippocampal volumes and all cognitive measures.

RESULTS

Demographics

All groups of older adults were similar across the domains of age, IQ, and education, and participants did not differ in these areas (Table 1). It is important to note that our study consisted primarily of men at the beginning and only began investigating women two years after initiation, thus the total number of females (n=26) is less than males (n=52). However, the total number of participants with ASD (n=42) and without ASD (n=36) are closer in number.

Table 1. Demographic Variables

	ASD Female (n = 12) Mean (±SD) Range	**NT Female** (n = 14) Mean (±SD) Range	**ASD Male** (n = 30) Mean (±SD) Range	**NT Male** (n = 22) Mean (±SD) Range	**Statistical Comparison**
Age (years)	55.6 (±9.6) 42-71	56 (±7.9) 42-70	52.4 (±8.6) 40-70	50.1 (±6.7) 40-64	F(3, 75) = 2.07 p = 0.11
IQ[a]	113 (±14.1) 88-134	108.3(±11.3) 85-132	107.9 (±15) 70-131	111.21 (±13) 89-141	F(3, 74) = 0.41 p = 0.75
Education (years)	16.3 (±2.4) 12-20	17.32 (±2.2) 12-20	15.46 (±2.6) 11-20	16.08 (±2.4) 9-20	F(3, 75) = 1.90 p = 0.14

[a]Kaufman Brief Intelligence Test-2

Cognitive Differences in Diagnosis and Sex

When examining differences across diagnosis, the older ASD group as a whole performed worse than the older NT group on the majority of cognitive measures including WCST: errors, perseverative errors, non-perseverative errors, categories; RAVLT: learning over trials; WMS: VR I, VR II; and TMT time A. Trends approaching significance for diagnosis as a factor included the RAVLT A7 and RAVLT total words. Across the two sexes, the women performed better on RAVLT total words; however, the men performed significantly better when assessing processing speed in TMT A. There was a trend approaching significance for RAVLT learning over trials where females performed relatively better than the males. Interactions of diagnosis and sex approached significance on the WCST non-perseverative errors measure (see Table 2). Across diagnosis comparisons within sex show that females had twice the effect sizes compared to men on tasks of WCST: errors, perseverative errors, non-perseverative errors, number of categories and RAVLT: learning over trials; whereas across the male groups, the effect sizes were small-to-medium comparatively. In contrast, the male group had slightly larger effect sizes on the WMS: VR I & II and TMT: time A, time B.

Table 2. 2 x 2 ANOVA Results of Cognitive Test Scores

	Significant factor				
	Diagnosis p-value	Sex p-value	Sex by Diagnosis p-value	**Female Effect Size (d)**	**Male Effect Size (d)**
WCST[a] Errors	0.001*	0.588	0.129	1.23	0.43
WCST PE[b]	0.006*	0.413	0.426	1.38	0.44
WCST NPE[c]	0.006*	0.941	0.072[#]	1.11	0.22
WCST Categories	0.020*	0.787	0.205	0.85	0.27
RAVLT[d] A1	0.536	0.227	0.728	0.27	0.06
RAVLT A7	0.055[#]	0.235	0.502	0.64	0.31
RAVLT TotWords[e]	0.062[#]	0.009*	0.606	0.64	0.32
RAVLT LOT[f]	0.001*	0.072[#]	0.246	1.13	0.51
WMS VR[g] I	0.032*	0.904	0.702	0.51	0.62
WMS VR II	0.013*	0.643	0.965	0.58	0.64
TMT[h] Time A	0.043*	0.037*	0.412	0.29	0.72
TMT Time B	0.163	0.338	0.502	0.25	0.45

[a]Wisconsin Card Sorting Test
[b]Perseverative Errors
[c]Non-perseverative errors
[d]Rey Auditory Verbal Learning Test
[e]Total words
[f]Learning over trials
[g]Wechsler Memory Scale – Visual Reproduction
[h]Trails Making Test
*Significance $p<0.05$
[#]Trend approaching significance $p<0.10$

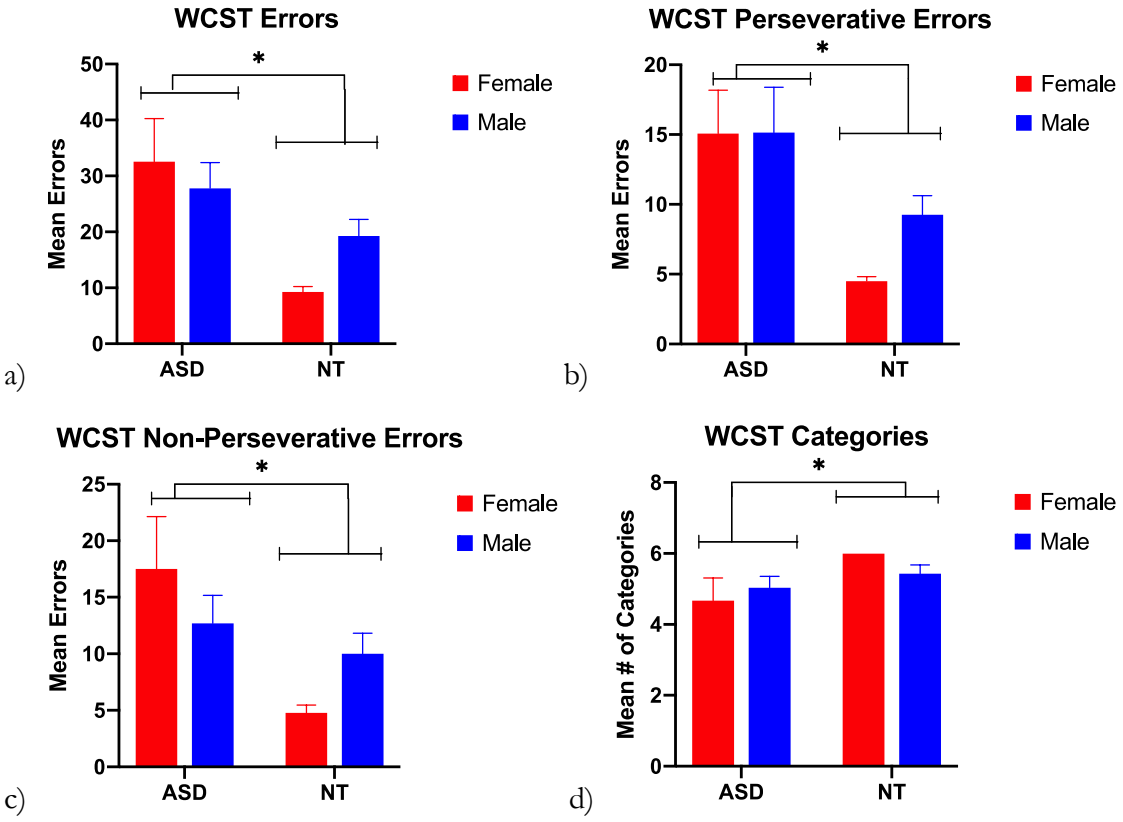

Figure 1. Results on executive functioning tasks. (a) Average amount of errors made on WCST (±SE). (b) Average amount of perseverative errors on WCST (±SE). (c) Average amount of non-perseverative errors on WCST (±SE) with trend approaching significance for sex by diagnosis interactions. (d) Average amount of categories completed in WCST (±SE). *$p<0.05$ for diagnosis across areas of measure; ASD participants performed significantly worse than NT participants on this executive functioning task.

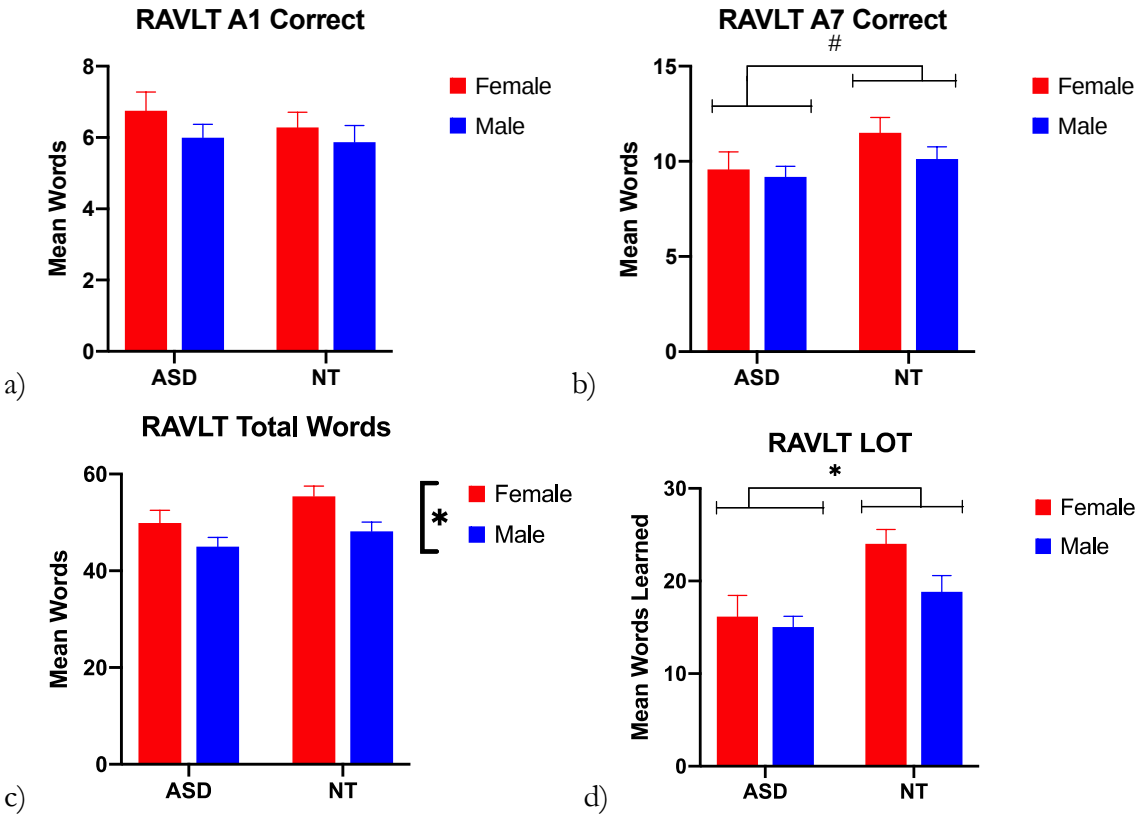

Figure 2. Comparing across diagnosis and sex for measures on verbal learning and memory tasks. (a) AVLT Immediate recall. Average number of words during first trial (±SE); no significant differences across diagnosis or sex. (b) AVLT delayed recall. Average number of words recalled during 7th trial of list A (±SE). NT participants performed relatively better than ASD participants. (c) AVLT Total number of correct words A1-A5 (±SE). Females recalled more words than the males. (d) AVLT Learning over trials (±SE). NT participants performed significantly better on learning portion. * = $p<0.05$; # = $p<0.10$.

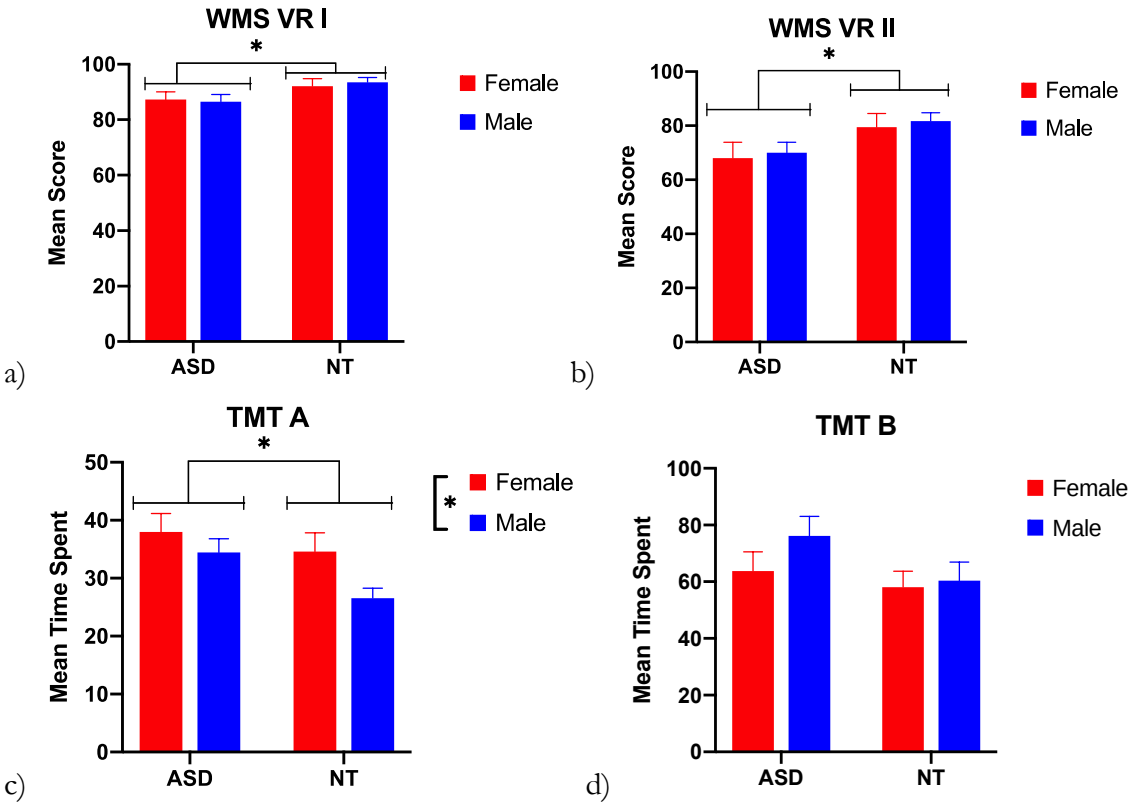

Figure 3. Results on visual memory and processing speed tasks. (a) Average scores on immediate visual-memory recall (±SE) where those with ASD performed significantly worse than the NT group. (b) Average scores on delayed visual-memory recall (±SE) where those with ASD performed significantly worse than the NT group. (c) Average time spent (seconds) on Part A of TMT (±SE) showed that those with ASD performed significantly slower than NT group; females as a whole took longer to complete the task. (d) No significant difference across diagnosis or sex for average time spent (seconds) on Part B of TMT (±SE). * = $p<0.05$.

Hippocampal Volume Analyses

Between the two hippocampi, the right hippocampus showed significantly smaller volume between the ASD and NT groups (Table 3). Women as a whole had significantly larger left and right hippocampi sizes. No significance was found when investigating sex by diagnosis interactions. The hippocampal volume differences between male groups had a slightly larger effect size than female groups

Table 3. 2 x 2 ANOVA Hippocampal Volume by %TIV

	Significant factor				
	Diagnosis p-value	Sex p-value	Sex by Diagnosis p-value	**Female Effect Size (d)**	**Male Effect Size (d)**
Left	0.067[#]	0.014*	0.940	0.42	0.48
Right	0.043*	0.002*	0.702	0.41	0.48

*Significance $p<0.05$
[#]Trend approaching significance $p<0.10$

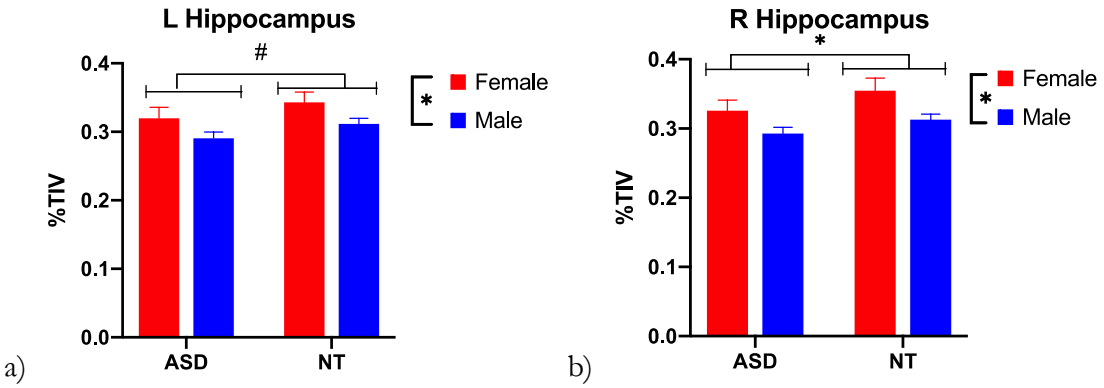

Figure 4. (a) All female participants showed significantly larger left hippocampus volumes than all male participants. NT participants showed relatively larger left hippocampus volumes with only approaching significance. (b) Female participants had significantly larger right hippocampal volumes than all male participants. Overall, participants with ASD showed significantly smaller right hippocampus volumes than NT participants. * = $p<0.05$; # = $p<0.10$.

Correlations Between Hippocampal Volumes & Cognitive Variables

Due to group differences in cognitive and hippocampal measures, correlations were evaluated within group. For NT females, bilateral hippocampi volumes correlated with the following measures WCST: errors, perseverative errors, non-perseverative errors, categories completed; RAVLT: total words; WMS: Visual Reproduction I; and TMT: time from side A, time from side B. NT males showed a correlation between left hippocampal volume and the WCST perseverative errors measure. Neither ASD group showed any significant correlations between hippocampal volumes and any cognitive area (Table 4).

Table 4. Correlations Between Cognitive Measures and Hippocampal Volume

	Hippocampal Volume (Left & Right Hemisphere)							
	ASD Female		**NT Female**		**ASD Male**		**NT Male**	
	Left p-value r value	Right p-value r value	Left p-value r value	Right p-value r value	Left p-value r value	Right p-value r value	Left p-value r value	Right p-value r value
WCST Errors	0.812 -0.089	0.809 -0.085	0.002* -0.727	0.002* -0.724	0.438 0.154	0.493 0.136	0.065 -0.400	0.329 -0.22
WCST PE	0.927 -0.032	0.906 -0.042	0.008* -0.665	0.009* -0.652	0.466 0.145	0.448 0.136	0.027* -0.464	0.193 -0.29
WCST NPE	0.741 -0.116	0.748 -0.113	0.004* -0.700	0.004* -0.702	0.645 0.092	0.794 0.052	0.165 -0.308	0.529 -0.143
WCST Categories	0.601 0.183	0.611 0.178	>0.99[a] --	>0.99[a] --	0.301 -0.204	0.358 -0.184	0.099 0.362	0.327 0.221
RAVLT A1	0.611 0.178	0.745 0.115	0.127 0.43	0.140 0.417	0.786 0.053	0.642 -0.091	0.747 -0.074	0.838 -0.047
RAVLT A7	0.290 -0.357	0.288 -0.358	0.176 0.386	0.197 0.37	0.154 0.273	0.348 0.184	0.199 0.286	0.578 0.127
RAVLT TotWords	0.581 -0.192	0.505 -0.232	0.037* 0.556	0.042* 0.546	0.951 -0.012	0.608 -0.10	0.878 -0.035	0.507 -0.151
RAVLT LOT	0.188 -0.434	0.225 -0.404	0.549 0.178	0.541 0.182	0.594 -0.104	0.914 -0.021	0.792 0.061	0.652 -0.103
WMS VR I	0.304 0.348	0.399 0.289	0.004* 0.695	0.003* 0.716	0.451 0.147	0.707 0.073	0.207 0.282	0.545 0.138
WMS VR II	0.979 -0.009	0.898 -0.045	0.083 0.479	0.081 0.482	0.254 0.22	0.809 0.047	0.352 0.21	0.912 0.025
TMT Time A	0.258 -0.38	0.193 -0.43	0.002* -0.740	0.002* -0.739	0.412 -0.159	0.161 -0.268	0.216 -0.277	0.652 -0.103
TMT Time B	0.167 0.453	0.106 0.516	0.028* -0.579	0.023* -0.595	0.738 -0.066	0.654 -0.088	0.309 -0.229	0.659 -0.101

[a]All NT women reached ceiling number of categories
*Significance $p<0.05$

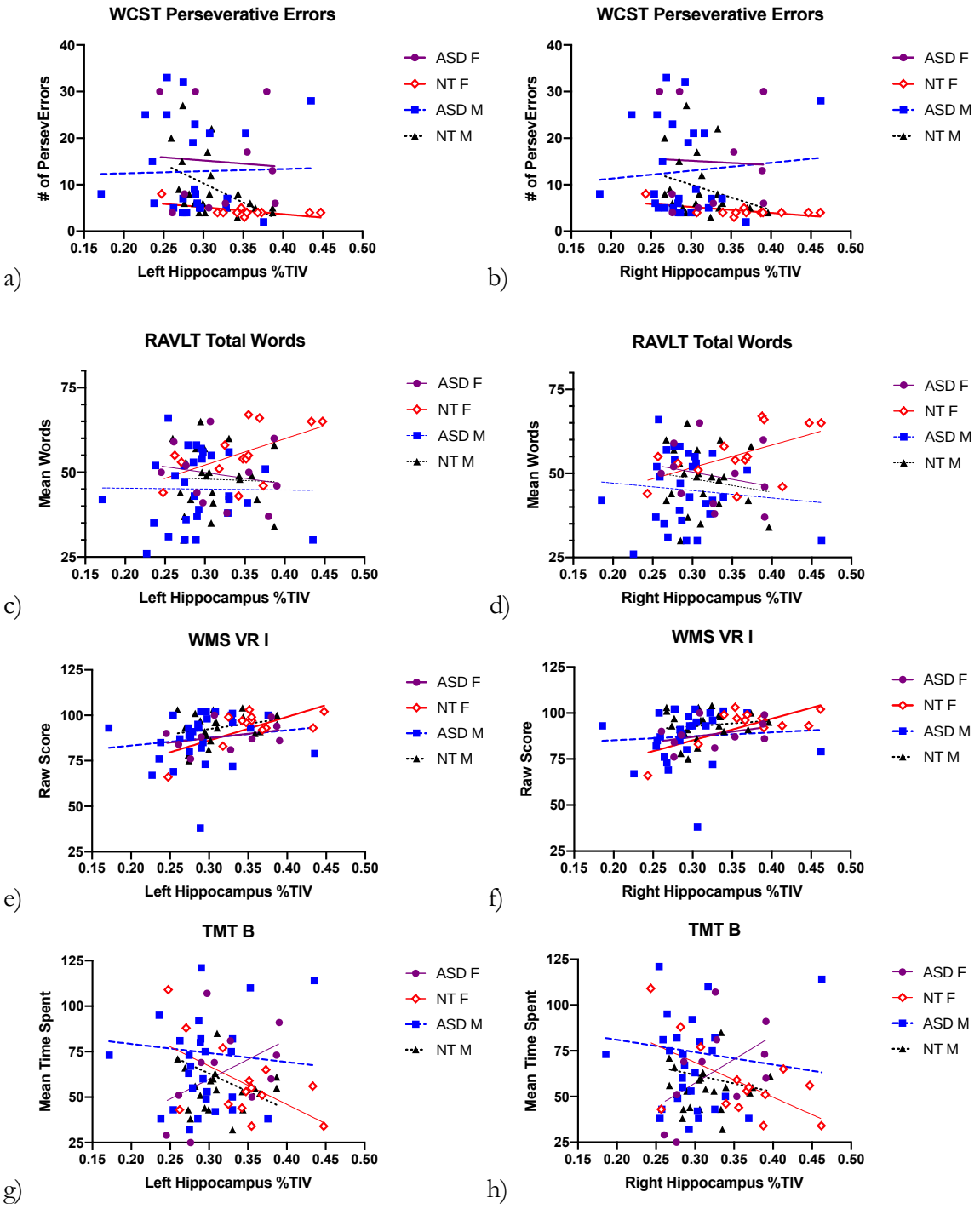

Figure 5. Correlations between cognitive measures and hippocampal volumes across the four groups: ASD Females (ASD F), NT Females (NT F), ASD Males (ASD M), and NT Males (NT M). Bilateral hippocampal volumes significantly correlated for NT F with all areas of WCST (errors, PE, NPE), RAVLT - total words recalled, WMS VR I - immediate recall, and TMT Parts A and B time spent (in seconds).

DISCUSSION

Diagnosis Group Differences

This study provides one of the first examinations into differences in cognitive functions and hippocampal volume sizes in older men and women, with and without ASD. We hypothesized that older adult males with ASD would show reduced cognitive performance compared to older adult females with ASD. In addition, we anticipated that older adult males with ASD would show greater reduction in hippocampal volume than older females with ASD. The results of the analyses showed that older adults with ASD have significantly weaker skills related to executive function (WCST), learning (RAVLT: LOT), visual immediate and delayed memory (WMS: VR I & II), and processing speed (TMT: Time A). This is consistent with other research showing that cognitive abilities in older adults with ASD are similar to that of younger persons with ASD and that verbal memory is relatively intact compared to other areas of cognition [Geurts & Vissers, 2012; Braden et al., 2017].

Participants with ASD as a whole had significantly smaller right hippocampi compared to NT participants. This relates to previous research stating that hippocampal volume differences are present in young persons with ASD. It is also consistent with our recent study that found hippocampi in older males with ASD were smaller than NT males. Late adulthood is associated with increased hippocampal atrophy and dysfunction [Erickson, 2012] and these results imply that this change in hippocampal volume may be exacerbated in those with ASD. Future longitudinal research is warranted to determine age-related hippocampal trajectories in ASD. ASD groups did not show correlations between hippocampal size and memory tasks or any other cognitive task which is unexpected. Executive functioning and memory are cognitive functions that are essential for living

independently and contributes greatly to level of quality of life. Identifying neural correlates of cognitive functions will be important to developing biologically-informed interventions.

Sex Group Differences

For sex differences, older adult women as a whole recalled more total words in the RAVLT showing greater verbal learning compared to older men. This relates well to past research has found that elderly women performed better on all aspects of the RAVLT and recalled more total words than males [Gale et al., 2007]. However, the older men performed significantly better on the TMT Part A task suggesting better overall visuo-spatial, processing speed and psychomotor function. These results were consistent with findings that state women do not perform as well on visuospatial and arithmetic tasks when processing speed is involved [Goldstein et al., 1990]. Overall, older women also have larger bilateral hippocampi compared to older men. This is consistent with recent research emphasizing the NT women have significantly larger hippocampi sizes compared to matched-NT men [Braden et al., 2016]. The NT female group's hippocampal volume sizes correlated with nearly all of the cognitive tests, whereas the other three groups did not. These results suggest that NT older women have a tighter relationship between hippocampal size and complex cognitive abilities compared to ASD adults and NT men. It also suggests that hippocampi size has a significant impact for NT females on cognitive performance in areas other than short-term and long-term memory, which is unexpected. This could be due to the nature of the NT older women having larger hippocampi overall, meaning they are recruiting it while completing cognitive tasks because it is more intact.

Sex by Diagnosis Interactions

Based on the data and results, our hypotheses of 1) older men with ASD having worse cognition than females with ASD and 2) older men with ASD having smaller

hippocampi were not supported. One reason why these hypotheses did not line up with our results could be because women may be exerting greater neural resources for camouflaging autistic traits across their lives that contributes to exacerbated cognitive decline [Livingston et al., 2017]. Another possible reason could be due to the theory of extreme male brain in ASD, which states that men and women with ASD have a hypermasculinized version of the male brain [Baron-Cohen et al., 2005]. Thus, being a woman with ASD may not confer the same cognitive benefits over men with ASD as being a NT woman does over NT men. In one of the measures, the WCST non-perseverative errors, there was a trend approaching significance with sex by diagnosis interactions showing differences between women with ASD and the NT women, but not men with ASD vs. NT men. WCST non-perseverative errors measure has been thought of to relate to working memory due to the nature of switching mindsets in the task and remembering past moves and because it does not include any errors made purely out of perseveration. This suggests slightly worse working memory in women with ASD, compared to their NT counterparts, than men. Interestingly, differences in effect size were considerably larger between the female groups than the male groups on all of the WCST measures and RAVLT total words. This suggests that there were greater differences in cognition related to executive functioning and some memory between females with and without an ASD diagnosis compared to the males. Whereas the male groups showed slightly greater effect sizes than females on measures of WMS: visual reproduction I & II and TMT: time A and time B suggesting somewhat better visual memory and processing speed skills in NT men. All in all, data suggests executive function in older women with ASD is likely more affected than in men, but limited significance for sex by diagnosis interactions was achieved with this sample size.

LIMITATIONS

First, the sample size of the older female group was fairly modest and potentially lacked the statistical power of the older male group. Because this was an initial analysis on an important yet unexplored area in ASD, we did not correct for multiple comparisons. Future work with larger sample sizes will incorporate statistical correction. In addition, the distribution of ages in the females and males are not entirely matched, as the female group had more relatively older participants. Recruitment of more middle-age women with ASD and some older male matches is in progress. Another limitation related to the older women is that we did not take menopause or hormone use into account, which may have made differences in cognitive scores. However, we are actively collecting this data and will incorporate it into future stats as the sample size grows. As our project continues on, a longitudinal study is in progress for comparing cognition and brain differences in those with and without ASD across the lifespan; therefore, interpretations of these results are limited to a cross-sectional snap shot. Finally, our current results are not representative of the 30% of individuals with ASD who also have intellectual disability. Future research across the continuum of ASD is warranted.

CONCLUSION

In conclusion, we examined cognitive and hippocampal volume size differences between older participants with and without ASD and across sexes. Overall, we found that those with ASD performed worse than the NT participants on a range of cognitive assessments and that they generally had smaller hippocampal volumes than the NT group. Differences between females and males were also evident across some cognitive measures and both hippocampal volumes consistent with previous NT literature. By identifying how cognitive difficulties manifest across age and sexes in adults with ASD, intervention can be more focused on assisting these individuals by capitalizing on their strengths and helping to improve their weaknesses to achieve and/or sustain independence. Further research with a larger sample size in each group and across ages is warranted to establish the relationship between the aging brain and cognitive functions across the genders with ASD.

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