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TITLE: "Cognitive and Neural Correlates of Aging in Autism Spectrum Disorder"

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14. ABSTRACT

Purpose: As the first diagnosed ASD individuals are now reaching old age, it is imperative that we understand the impact of aging on individuals with ASD. We developed a model predicting greater executive dysfunction and frontal lobe susceptibility in ASD beyond normal aging. **Scope:** This study, which is a collaborative study of the Southwest Autism Research and Resource Center the Barrow Neurological Institute and Arizona State University, produces comprehensive cognitive, behavioral, and neuroimaging data on a set of well-characterized older ASD individuals who can be used as a reference for clinical diagnosis, therapeutics, and care plans. The **scope** of the project was to recruit and collect cognitive and neuroimaging data over two time points from a cohort of older adult individuals with ASD and an age-matched neurotypical (NT) group.

Results and significance: We met our goal to recruit and retain our groups. We have had very few withdrawals (3) and have received additional funding to continue our longitudinal data collection in the future and expand our age range and include women. We published 3 papers, have one in review and are preparing several initial longitudinal papers. Based on our findings, we developed a personalized, behavioral intervention program that we submitted for funding via the DoD Clinical Translational Research Award application and received notice that it was recommended for funding (AR190103).

15. SUBJECT TERMS

Autism, aging, functional MRI, fMRI, neuroimaging, executive functioning, memory, cognition, cortical thickness, connectivity, white matter, sparse Bayesian networks, machine learning

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1. INTRODUCTION:

As the first diagnosed Autism Spectrum Disorder (ASD) individuals are now reaching old age, it is imperative that we understand the impact of aging on individuals with ASD. Given the striking parallels in ASD of deficits in executive function, subserved by the frontal lobe, and that the frontal lobe is susceptible to normal age-related changes, we combine neuroimaging, cognitive assessments and behavioral measures to examine aging in ASD compared to Typically Developed (TD) adults. We **hypothesize** that individuals with ASD will have an exacerbation of deficits beyond normal aging, as evidenced in significantly lower scores on tests affected by aging (e.g., executive) along with neuroanatomical markers of dysfunction, and relative preservation of function subserved by more posterior brain regions (memory and local detail processing). Our **objective** is to produce comprehensive cognitive, behavioral, and neuroimaging data on a group of well-characterized older individuals with ASD who can be used as a reference for clinical diagnosis, therapeutics, and care plans. To achieve this goal, our three year project involves longitudinal assessment of aging (40–60 y.o.) ASD individuals versus age-matched TD. In addition to commonly used statistical methods, we will use innovative machine learning and sparse Bayesian networks to combine structure, function, cognition, and symptom profiles to specifically address contributions to accelerated aging in ASD.

2. **KEYWORDS:** Autism, aging, functional MRI, fMRI, neuroimaging, executive functioning, cognition, memory, white matter, cortical thickness, connectivity

3. ACCOMPLISHMENTS:

What were the major goals of the project?

The major goals for the project in the final funding period were:

- A) **To finish obtaining time 2 cognitive and MRI data from ASD and control participants (Major Task 2 and Subtask 3).**
- B) **Analyze and synthesize data to address specific aims (Major Task 3, Milestones 2).**

What was accomplished under these goals?

- A) **Obtaining cognitive and MRI data from ASD and control participants:** This project aimed to collect cognitive and neuroimaging data for 70 participants (35 per group; men 40-60

years of age) for two time points at a 2 year interval. Currently, we have 67 older adult males in this study who have completed the two time points. We have had only 4 older adults from this study withdraw before the second time point; one control/TD participant withdrew because of a change in demands in his job; two ASD adults asked to withdraw after the first time point, and 1 older ASD man was withdrawn by the team because he had significant interval health problems (back problems) that did not allow him to undergo testing and the MRI. We are very pleased with our retention rate. We have developed a foundation of respect within the group of individuals we recruit, and as the PI and a Clinical Neuropsychologist, I offer to all participants to receive feedback from me regarding their findings in order to “give back” to them. We obtained additional funding to continue to follow our cohort, and we have begun to obtain a 3rd time point for our earlier recruits.

This DoD funding helped us build a strong platform that has allowed us to successfully expand our research scope. Dr. Braden has received funding through NIMH K01 and Arizona Biomedical Research Commission grants to expand our study to include aging women with and without ASD who will be used with the data from the DoD study to investigate gender differences in brain, cognition and symptoms. Further, through funding from the State of Arizona and other sources, we have established a young adult ASD cohort (18-25; men and women) who undergo the same procedures as the older cohort. We have 55 young adult males, 38 older adult females and 24 young adult females. Dr. Braden’s graduate student, Melissa Walsh, has received a F31 grant for her work in ASD. Finally, Dr. Braden spearheaded a Mindfulness Based Stress Reduction intervention (no age or gender constraints), based on our findings from our ancillary study examining mood status in ASD, which has just completed. Taken together, we now have recruited **184** individuals who participate in our ASD research program. We recently submitted a DoD Clinical Translational Research Award application and received notice that it was recommended for funding (AR190103) aimed at designing and implementing a unique behavioral intervention for adults with ASD across the lifespan.

C) Analyze and synthesize data to address all specific aims (Major Task 3, Milestones 2).

- i. Our first publication from our initial cross-sectional analyses in Autism Research, the official journal of the International Society for Autism Research (Impact factor: 3.765; ranked 5/51 for Behavioral Sciences and 9/70 for Psychology Developmental journals) was published on September 21, 2017. There have been 19 citations since this article was published, including demonstrating a strong interest in our research among the ASD research community. Citations are from papers in JAMA Psychiatry, Journal of Autism and Developmental Disorders, Brain Sciences, among others.

Citation: Braden BB, Smith CJ, Thompson A, Glaspy TK, Wood E, Vatsa D, Abbott AE, McGee SC, Baxter LC. Executive function and functional and structural brain differences in

middle-age adults with autism spectrum disorder. *Autism Res.* 2017 Dec; 10 (12):1945-1959 Epub 2017 Sept 21 PMID: 28940848 DOI: 10.1002/aur.1842

- ii. Baxter LC, Nespodzany A, Walsh MJ, Wood E, Smith CJ, Braden BB. The influence of age and ASD on verbal fluency networks. *Research in Autism Spectrum Disorder.* 2019. 63: 52-62. DOI:10.1016/j.rasd.2019.03.002 (RASD 5 Year Impact Factor: 2.252 (2018))

We have previously investigated cross-sectional differences in executive functioning but other cognitive domains, especially language, also depend on frontal lobe networks. We included in our study an fMRI fluency task in our study to determine if a language task subserved in part by the frontal lobe would show a larger aging effect in ASD individuals than TDs. In this study, we used a network approach to investigate the influence of age and the diagnosis of ASD on language networks. The integrity and connectivity of the frontal lobe, which subserves fluency, may be compromised by both ASD and aging. Alternate networks often integrate to help compensate for compromised functions during aging. We used network analyses to study how compensation may overcome age-related compromised in individuals with ASD. We analyzed fluency networks from both middle-aged (40-60) and young (18-25) men who have a diagnosis of ASD, and age- and IQ-matched TDs. We first used group individual component analysis (ICA) for each of the 4 groups to determine whether different networks were engaged. An SPM analysis was used to compare activity in the network nodes from the ICA analyses. Figure 1 shows the networks generated when the participants were silently generating words to letter prompts. The default network, involved in the rest condition was also extracted. Figure 2 shows the group and age differences for these network nodes. Both age and group differences were observed. Strong age-related changes were observed for regions associated with speed of response (left thalamus and BA 6/Supplementary Speech Area). The large, age-related decreases in these regions suggest possible weakening in frontal-subcortical connectivity in older adults, or differences in processing efficiency of internally directed task demands. We found that both young and middle-aged adults with ASD showed less “deactivation” during the word generation condition compared to the NT groups. There is considerable interest in gaining a better understanding of how individuals with ASD transition between fMRI conditions because activation patterns during the low-level, or baseline condition is often more telling than the more demanding condition. This failure to release from the active condition may be related to behavioral difficulties with flexible thinking. Interestingly, the superior temporal lobe (left BA 22) showed increased engagement during word generation for all older adults, suggesting that the older individuals may have relied more heavily on lexical processing than younger adults as speed of processing decreases. This differential engagement of brain regions beyond the LIFG was observed in light of similar performance in all groups, suggesting that the challenges associated with aging, and possibly ASD, results in recruitment of neural networks to support effective performance. These findings are in alignment with the model of the

“adaptive brain” described by Park and Reuter-Lorenz (the STAC model; 2009). Based primarily on working memory and executive functioning **compensatory mechanisms**, they hypothesize that maintaining behaviors at a higher level in older adults (and other conditions that involve neural challenges, like ASD) are related to the brain’s ability to use compensatory scaffolding, or “recruitment of additional circuitry that shores up” against neural changes that can negatively affect functioning.

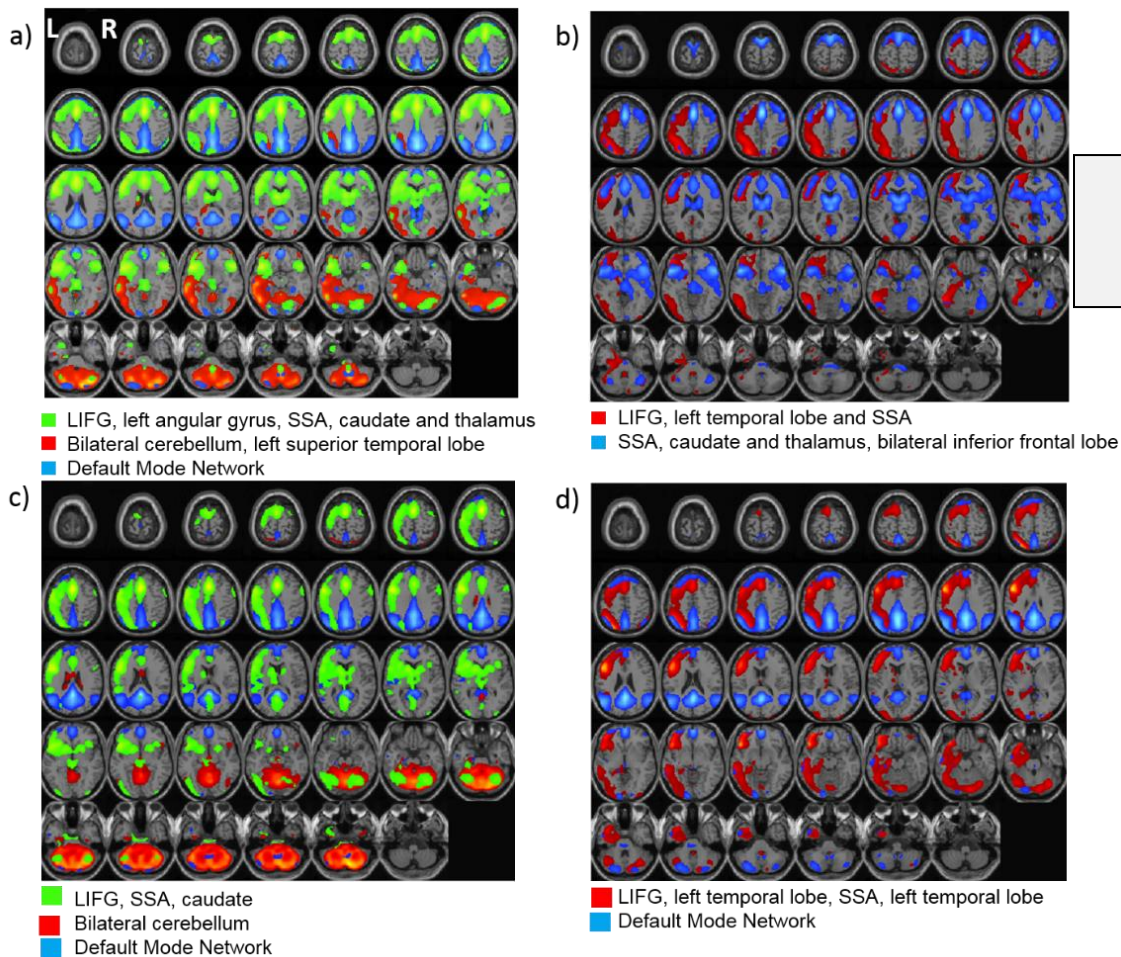


Figure 1 a) Young NT; b) Young ASD; c) Middle-aged NT; d) Middle-aged ASD.

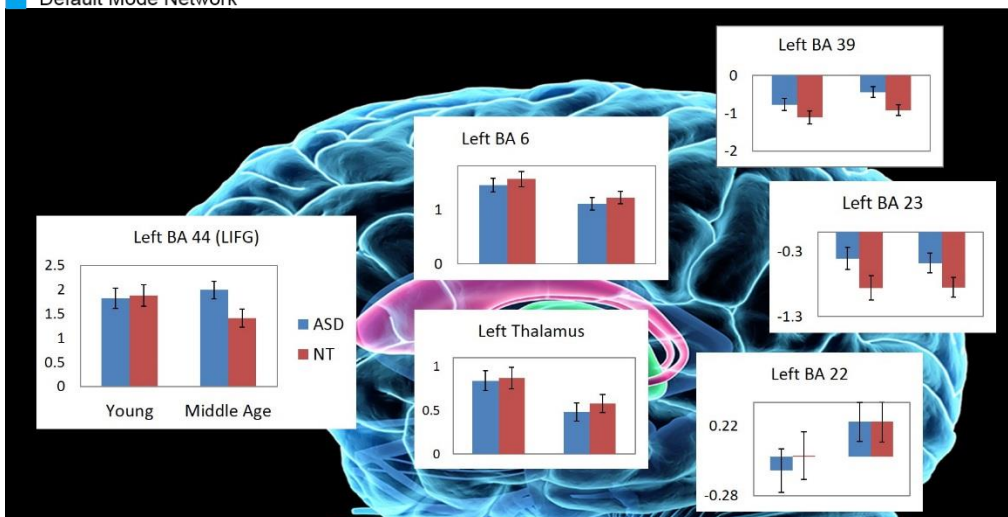
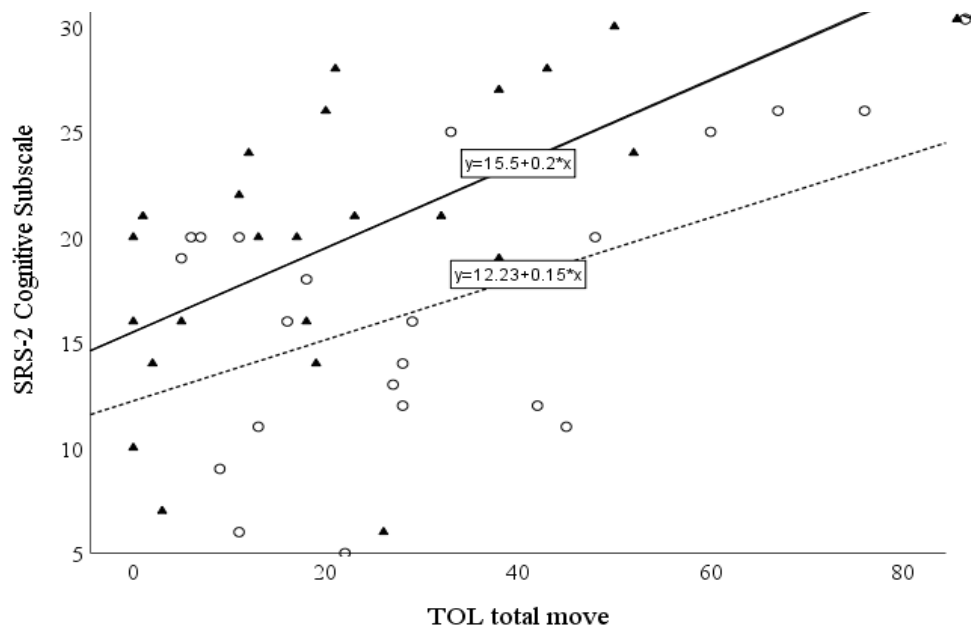
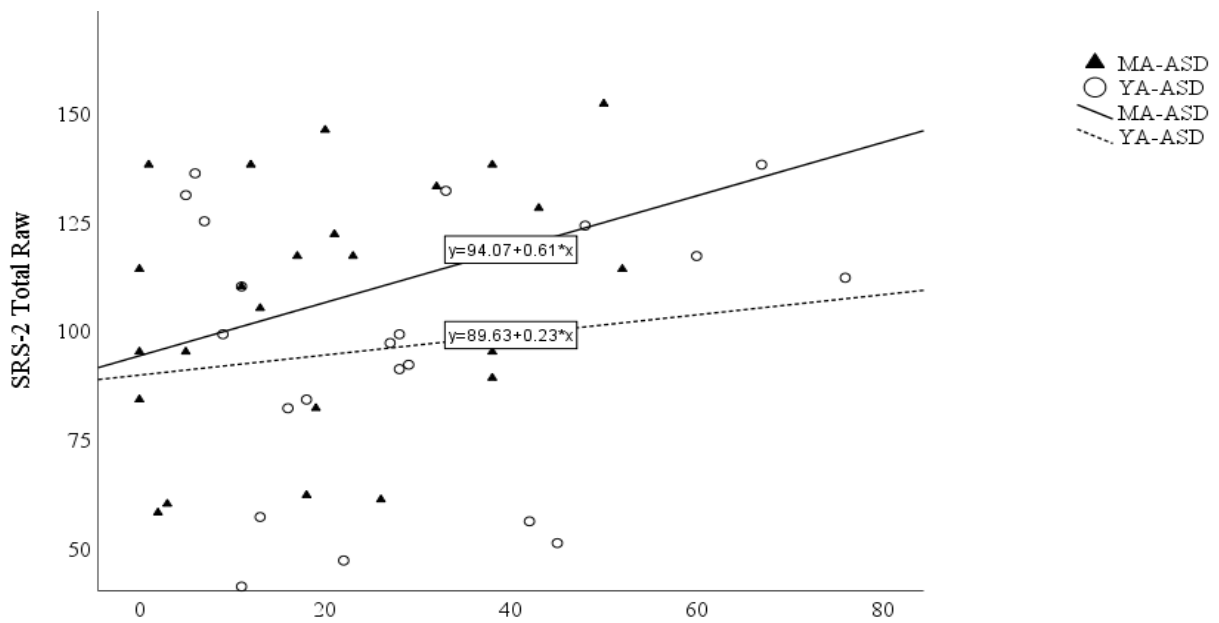


Figure 2

- iii. Walsh M, Baxter LC, Smith CJ, Braden BB. Age group differences in executive network functional connectivity and relationships with social communication impairments in Autism Spectrum Disorder. *Research in Autism Spectrum Disorder*. 2019 63: 63-77.
DOI:10.1016/j.rasd.2019.02.008

The first author is the graduate student of Dr. Braden. Dr. Baxter was a member of her graduate student committee for this project. Ms. Walsh examined the how social communication abilities may be altered with aging in ASD, and to better understand the neural basis for these changes.

The first author of this study is Dr. Braden's graduate student. She conducted her study under the supervision of Dr. Braden, her primary mentor, and Dr. Baxter, who is a member of her



graduate school committee). She examined the correlation of social communication abilities (Social Responsiveness Scale-2; SRS-2) and executive function (Tower of London; ToL) and found a stronger relationship between these two factors in the older adults with ASD.

Figure 1. Correlation between Tower of London Total Moves and SRS-2 (a) Total and (b) Cognitive Subscale Raw scores. * $p < 0.05$; Middle-Age (MA); Young-Adult (YA)

Comparing the resting state fMRI-derived EN of young (YA) and older adult (OA) TD and ASD individuals, there was a greater degree of hypoconnectivity in OA vs YA ASD than was observed for OA vs YA TDs, suggesting an exacerbated age-related decline in functional connectivity of the left dorsolateral prefrontal cortices in adults with ASD. There was a significant correlation between hypo-connectivity of the EN and higher SRS-2 scores in middle-aged adults with ASD.

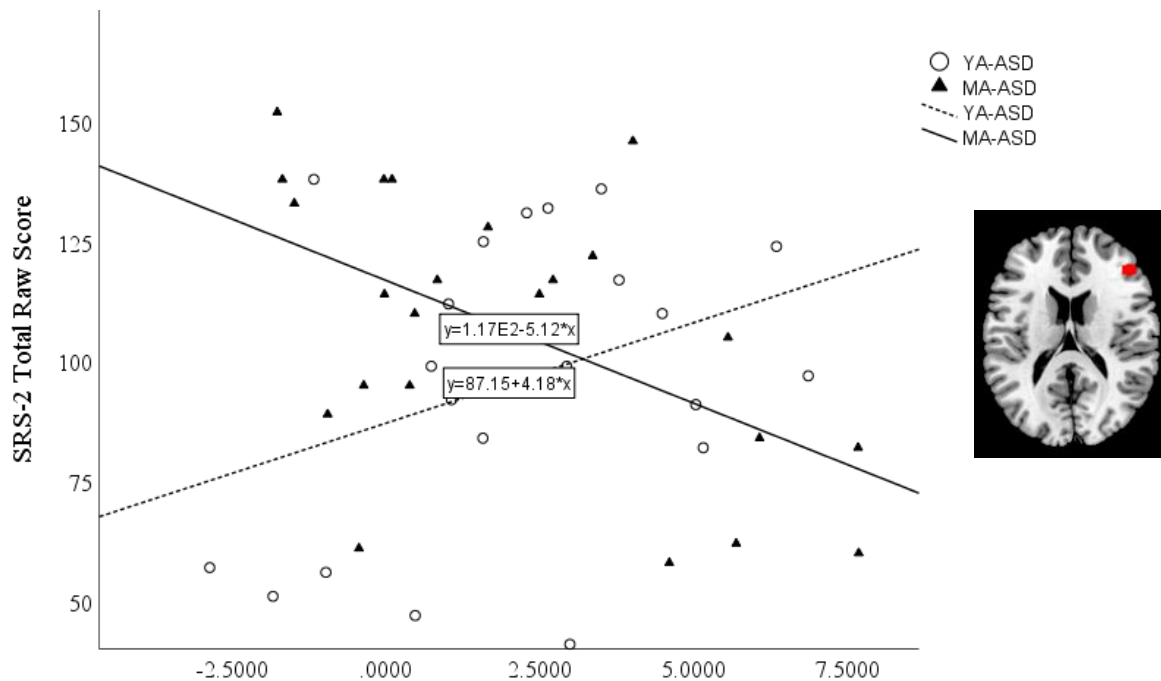


Figure 2. Correlation between functional connectivity of the right Dorsolateral Prefrontal Cortex (ROI inset) and SRS-2 scores.

This study suggests that executive control and planning plays a role in social communication problems in ASD, and that these abilities and the underlying hypoconnectivity of the Executive Network may explain why these abilities may become more troublesome with age in adults with ASD.

iv. Manuscripts in process: “Taking Time to Prepare: Planning and Efficiency on the Tower of London Test in ASD” Ashley Nespodzany, MS, B. Blair Braden, PhD, Christopher J. Smith, PhD, Brief Summary: The first author is a research assistant in the Baxter Lab. This study investigates planning abilities in ASD. Planning—defined as identifying goals, formulating strategies to achieve them, and then organizing and monitoring the implementation of those strategies to reach those goals—is a particular EF subdomain that may be compromised in ASD. The current literature on planning abilities in ASD is predominantly on child and adolescent populations and inconsistently find lower performance by ASD individuals on these tasks. The aim of this study was to examine differences in planning ability between ASD and TD adults. We examined group differences in planning performance between ASD and TD groups in a sample of young adults and middle-aged adults using a Tower of London (ToL) task. While we predicted that the group with ASD would be outperformed by the TD on ToL performance, we examined the mediating and moderating effects of time spent planning, learning rates, trial complexity, processing speed, and working memory to explain differences in ToL measures between ASD and TD adults. ToL performance from 41 Adult NT and 56 Adults with ASD were used. The ToL test measures of total moves, initiation time (time spent planning), execution time, and total number of correct trials were recorded. Linear modeling was used to compare the relationship between initiation time and number of trials completed correctly for each group.

Figure 1 shows that the ASD group required more moves to solve the test and had fewer correct trials; however, no differences were observed for initiation or execution times. Interestingly, Figure 2 shows that the ability to perform the test well depends on the amount of time taken to plan the move. Even though both groups had similar ranges of times to plan moves, this factor has little effect on how well TD individuals do, but greatly affects the ASD group. Those individuals in the ASD group that quickly make a move without consideration have worse scores than those that take time to plan the move. In fact, there are no group differences in those individuals who have the longest planning time. These results are important for developing interventions that will help improve executive functioning in ASD individuals. We expanded our prior analyses to include women. Interestingly, the findings for the men are not observed in the group of women, suggesting there are some sex-mediated interactions in the approach to this test.

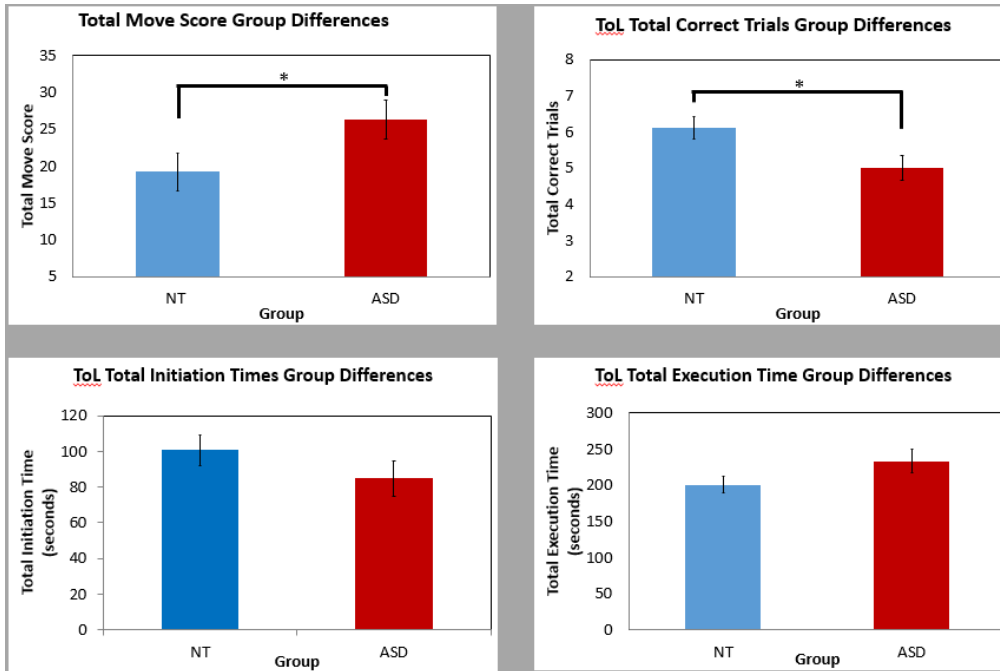
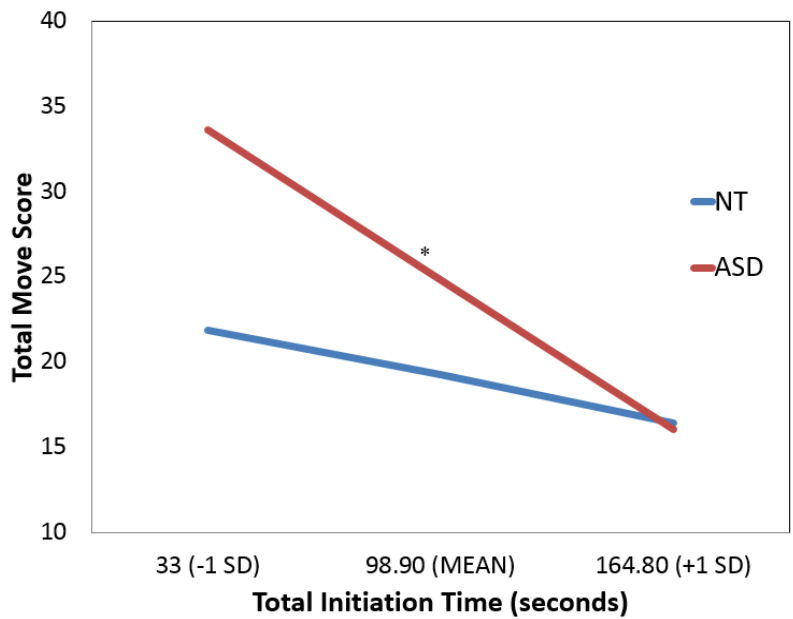


Figure 1: Findings from men. Group Differences on common measures of ToL test.

Figure 2: The relationship between TOL Initiation Time and Total Move Score Moderated by Presence of ASD Diagnosis



Other related activities:

As noted in prior reports, we received a grant from the Institute for Mental Health Research to study emotional aspects of aging and ASD. The literature indicates that ASD individuals have greater rates of comorbid anxiety and depression. Our assessment includes self-report measures of anxiety and depression self-report at the time of cognitive testing and MRI scanning. Data from the baseline assessment of some of our participants showed that 88% of the middle-age ASD group reported significant levels of anxiety and 44% reported significant depression, as compared to 45% of a group of 8 young-adult ASD for both anxiety and depression. Social network measures did not significantly correlate with mood measures in either middle-age or young-adult ASD, and the report of caregivers was not correlated with the symptom severity reported by the participants. Participants from our group of TDs are not part of these analyses since our exclusion criteria for TDs includes current or past psychiatric illness or symptoms. Interestingly, anxiety and depression symptoms correlated with several cognitive measures for the young ASD group, but there was no correlation in the older ASD group with cognition. This suggests that the cognitive deficits observed in the older ASD participants are not due to the presence of anxiety and depression but instead anxiety and depression may independently be affected in aging. In this study, we recruit the same participants who contributing to the MRI/cognition study. To date, we have evaluated 21 participants using a combination of clinical interview by a psychiatrist structured interview (via the Structured Clinical Interview for DSM Disorders (SCID for DSM-IV) and self-report measures to better understand how individuals with ASD express/self-report anxiety and depression. By far, the most common symptom that is observed in these ASD individuals is anxiety. Interestingly, many have difficulties articulating their emotional state, raising the question of difficulties with interoception. Interoception, or the ability to sense the internal state of the body, has been implicated as an area of impairment in autism. We plan on using these data to help guide the mood component of our proposed intervention trial.

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b. What opportunities for training and professional development has the project provided?

Training and professional development was not a major goal of this project; however, this project provided the environment to train and promote Dr. Baxter’s post-doctoral resident, Dr. Blair Braden, who is one of the key personnel in this study. She has transitioned to a tenured-track position at Arizona State University and has established a lab in Autism and Aging. She has obtained a K-01 award and other external funding in Autism. We will continue to collaborate on this project together. Furthermore, her graduate student, Melissa Walsh, has received an F31 grant.

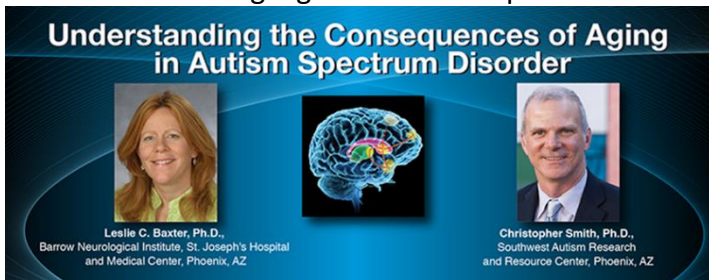
c. How were the results disseminated to communities of interest?

Autism Brain Imaging Data Exchange: The Autism Brain Imaging Data Exchange II is large-scale data repository of ASD and TD controls from 17 sites. Our contribution of 58 samples (which includes participants that are part of the DoD study) include the oldest sample in the group (aged 64 years old) and represents the first substantial set of older adults in the exchange. Our contribution to this high-profile, international group of researchers helps us to disseminate our study to the ASD research community. We will continue to contribute to this data exchange.

i. ***Aging in Autism Special Interest Group, International Society for Autism Research (INSAR).***

Both Drs. Baxter and Braden are members of the group of Autism researchers dedicated to the study of older individuals with Autism. The group was formed by Hilde Geurts, PhD of the University of Amsterdam to work towards common goals for studying older adults with ASD. Both Drs. Baxter and Braden are part of the founding members and will contribute to the establishment of a core set of cognitive tests and other data that can be collated across studies from around the world.

ii. Our research was highlighted on the Department of Defense website in the past year.



iii. Dr. Baxter and Dr. Smith were speakers at a Autism Speaks event on 8/3/18, discussing new frontiers in research (Phoenix, Arizona). Event attended by family members and professional caregivers.

d. **What do you plan to do during the next reporting period to accomplish the goals?**

- e. Continue second time point evaluations of those participants who are two years from their original study.

B) **IMPACT:**

a. **What was the impact on the development of the principal discipline(s) of the project?**

We have significantly increased the number of older adults to a national data exchange. Our study is complementing the established cognitive studies in older individuals with Autism to emphasize the importance of developing a greater understanding of aging in Autism to inform treatment. We recently submitted a DoD Clinical Translational Research Award application and received notice that it was recommended for funding (AR190103) aimed at designing and implementing a unique behavioral intervention for adults with ASD across the lifespan.

What was the impact on other disciplines?

Nothing to Report.

b. What was the impact on technology transfer?

Nothing to Report.

What was the impact on society beyond science and technology?

- i. An intent of our study is to develop a plan of action to help keep older adults with ASD as independent as possible for as long as possible. We foresee that the results of our study, which is one of the first of its kind, will be able to inform state agencies and community aging programs to develop interventions that will help keep older ASDs independent. We plan on continuing to publish our results, and becoming a voice for the older ASD population, to help form effective and meaningful supports and treatments for this group.

- C) **CHANGES/PROBLEMS:** *The Project Director/Principal Investigator (PD/PI) is reminded that the recipient organization is required to obtain prior written approval from the awarding agency Grants Officer whenever there are significant changes in the project or its direction. If not previously reported in writing, provide the following additional information or state, "Nothing to Report," if applicable:*

a. Changes in approach and reasons for change

Nothing to Report

b. Actual or anticipated problems or delays and actions or plans to resolve them

Obtaining institutional and HRPO approval for the study took longer than expected, so recruitment of our cohort was somewhat behind schedule. However, we have had excellent retention of participants in our study.

Changes that had a significant impact on expenditures

Our expenditures for MRI scans and patient reimbursement is less than expected over the grant period because of the delays in obtaining institutional approval, and patient recruitment.

c. Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents

- i. We changed our local consent and HIPAA forms to allow us to share anonymized data with the Autism Brain Imaging Data Exchange (detailed above). This was approved by our institution. We informed the HRPO, who also approved this. Current approval dates are: Informed Consent: 4/20/16; HIPAA: 3/02/16

- d. **Significant changes in use or care of human subjects:** Nothing to Report
- e. **Significant changes in use or care of vertebrate animals.** N/A
- f. **Significant changes in use of biohazards and/or select agents** N/A
- D) **PRODUCTS:** *List any products resulting from the project during the reporting period. If there is nothing to report under a particular item, state "Nothing to Report."*
 - a. **Publications, conference papers, and presentations**
Nothing to Report
 - i. **Journal publications.** Nothing to Report
 - ii. **Books or other non-periodical, one-time publications.** Nothing to Report
 - b. **Other publications, conference papers, and presentations.** Nothing to Report
 - c. **Website(s) or other Internet site(s)**
Website/link to our media coverage: <http://abc7.com/health/adult-men-with-autism-participate-in-one-of-a-kind-study/1429782/>
 - d. **List the URL for any Internet site(s) that disseminates the results of the research activities. A short description of each site should be provided.** Nothing to report
 - e. **Technologies or techniques**
None to report
 - f. **Inventions, patent applications, and/or licenses**
None to report
 - g. **Other Products**
None to report

E) PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

a. What individuals have worked on the project?

Name:	<i>Leslie C. Baxter, PhD</i>
Project Role:	<i>PI</i>
Researcher Identifier (e.g. ORCID ID):	<i>0000-0002-3971-863X</i>
Nearest person month worked:	<i>2</i>
Contribution to Project:	<i>Dr. Baxter oversaw data collection, analysis and interpretation</i>
Funding Support:	National Institute on Aging NIA 5 P30 AG019610-03 (Reiman, PI; Baxter, Site PI) State of Arizona, Arizona Alzheimer's Consortium

Name:	<i>Brittany Blair Braden, PhD</i>
Project Role:	<i>Assistant Professor (ASU)</i>
Researcher Identifier (e.g. ORCID ID):	<i>0000-0001-6842-9784</i>
Nearest person month worked:	<i>4</i>
Contribution to Project:	<i>Dr. Braden oversaw data analysis and manuscript prep</i>
Funding Support:	<i>1K01MH116098, National Institute for Mental Health (PI: Braden)</i>

	ADHS16-00005488, Arizona Biomedical Research Commission (PI: Braden)
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- b. **Has there been a change in the active other support of the PD/PI(s) or**
- c. **Change in key personnel since the last reporting period?** Yes, Dr. Braden has obtained a K-01 award and an Arizona Biomedical Research Committee award.
- d. **What other organizations were involved as partners?** SARRC, ASU (see below)
 - 1. **Organization Name:** Southwest Autism Resource and Research Center
 - 2. **Location of Organization:** 2225 N 16th Street Phoenix, AZ 85006
 - 3. **Partner's contribution to the project** Partnering PI
 - 4. **Collaboration** Recruitment of participants, collaboration with data interpretation and manuscript preparation
 - 5. **Organization Name:** Arizona State University
 - 6. **Location of Organization:** 975 S Myrtle Ave P.O. Box 870102, Tempe, AZ 85287
 - 7. **Partner's contribution to the project** Co-investigator
 - 8. **Collaboration** Collaboration with data interpretation and manuscript preparation