Applying a Novel Integrated Persistent Feature to Understand Topographical Network Connectivity in Older Adults with Autism Spectrum Disorder

by

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ABSTRACT

Autism spectrum disorder (ASD) is a developmental neuropsychiatric condition with early childhood onset, thus most research has focused on characterizing brain function in young individuals. Little is understood about brain function differences in middle age and older adults with ASD, despite evidence of persistent and worsening cognitive symptoms. Functional Magnetic Resonance Imaging (MRI) in younger persons with ASD demonstrate that large-scale brain networks containing the prefrontal cortex are affected. A novel, threshold-selection-free graph theory metric is proposed as a more robust and sensitive method for tracking brain aging in ASD and is compared against five well-accepted graph theoretical analysis methods in older men with ASD and matched neurotypical (NT) participants. Participants were 27 men with ASD (52 +/- 8.4 years) and 21 NT men (49.7 +/- 6.5 years). Resting-state functional MRI (rs-fMRI) scans were collected for six minutes (repetition time=3s) with eyes closed. Data was preprocessed in SPM12, and Data Processing Assistant for Resting-State fMRI (DPARSF) was used to extract 116 regions-of-interest defined by the automated anatomical labeling (AAL) atlas. AAL regions were separated into six large-scale brain networks. This proposed metric is the slope of a monotonically decreasing convergence function (Integrated Persistent Feature, IPF; Slope of the IPF, SIP). Results were analyzed in SPSS using ANCOVA, with IQ as a covariate. A reduced SIP was in older men with ASD, compared to NT men, in the Default Mode Network [$F(1,47)=6.48$; $p=0.02$; $\eta^2=0.13$] and Executive Network [$F(1,47)=4.40$; $p=0.04$; $\eta^2=0.09$], a trend in the Fronto-Parietal Network [$F(1,47)=3.36$; $p=0.07$; $\eta^2=0.07$]. There were no differences in the non-prefrontal networks (Sensory motor network, auditory network, and medial visual network). The only other graph theory

metric to reach significance was network diameter in the Default Mode Network [$F(1,47)=4.31$; $p=0.04$; $\eta^2=0.09$]; however, the effect size for the SIP was stronger. Modularity, Betti number, characteristic path length, and eigenvalue centrality were all non-significant. These results provide empirical evidence of decreased functional network integration in pre-frontal networks of older adults with ASD and propose a useful biomarker for tracking prognosis of aging adults with ASD to enable more informed treatment, support, and care methods for this growing population.

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Conflict of Interest

The author and committee members of this study have no financial, personal, or other relationships that may pose a potential conflicts of interest related to this research.

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CHAPTER 1

INTRODUCTION

A Primer on Autism Spectrum Disorder and Need

Autism spectrum disorder (ASD) is a developmental neuropsychiatric condition with early childhood onset, thus most research has focused on characterizing brain function in young individuals. Little is understood about brain function differences in middle age and older adults with ASD, despite evidence of persistent and worsening core and cognitive symptoms (Abbott, Happe & Charlton 2018, Happe et al. 2016; Braden et al., 2017; Walsh et al., *in press*). One study found that symptom severity peaks in middle age (Lever & Geurts 2018). Currently, the CDC estimates that 1/59 children have ASD, with the first children diagnosed with ASD now in their elderly years (CDC 2018). The United States is projected to have 700,000 persons over 65 who have been diagnosed with ASD by 2030; thus, there is a clear need for more research in this field (Pivens & Rabins 2011).

Overview of Prior Research

Functional MRI in younger persons with ASD demonstrate that large-scale brain networks containing nodes in the prefrontal cortex are affected (Gilbert 2008, Carper 2005). Further, various graph theoretical analyses have shown disrupted topological organization for young individuals with ASD when compared to neurotypical (NT) individuals (Hill 2004, Gilbert 2008, Barnea-Goraly 2004). However, graph theory-based topological brain organization for older adults with ASD is unknown. The Default Mode Network (DMN) and Executive Networks (EN) are two specific networks of the prefrontal cortex of note in the field of ASD research. Various studies have shown that individuals

with ASD have significant deficits in social-affective processing, explicitly tied to the EN (Lindquist & Barrett 2012). Further, the EN has been recognized as a core network for aberrant functional connectivity in those with ASD (Elton et al 2016), and cognitive difficulties (Solomon, Hogeveen, Libero and Nordahl 2017). The DMN has also been identified as having significant under connectivity for individuals with ASD (Cherkassky 2006). Recent work has demonstrated that the DMN may have aberrant hyperconnectivity between the posterior cingulate and retrospinal cortices and hypoconnectivity between the precuneus and basal ganglia (Lynch 2013). This disparity has been theorized to mean that ASD may have a small-network effect, effecting few but specific networks. This observed atypical functional activity are considered to be prominent neurobiological features of ASD (Padmanabhan 2017). Graph theory metrics have the potential to shed light on this phenomenon. But, traditional graph theory-based methods suffered from the limited generalization because of the difficulty to make a principled choice of threshold values (Chung et al 2015, Choi et al 2014, Lee et al 2017).

Recently, a new methodology for analyzing whole brain network connectivity in Alzheimer's Disease was proposed as a more precise and robust method for detecting differences due to the disease (Kuang & Wang, 2019). This new method is the integration of a prior topological feature (Zeroth Betti number) and an innovative connected component aggregation cost (Christ 2008, Lee et al 2012). This Integrated Persistant Feature (IPF) is a monotonically decreasing convergence function, which when plotted across all possible filtration values, enables one to track the evolution of a network from separate components to a fully connected component. The connected component aggregation cost is produced from the minimum spanning tree of the network, and thus can

be understood as the least amount of 'effort' or 'energy' required for the evolution of the fully connected component. In order to connect more components, more energy would be required, and is related to the length of paths between nodes via a minimum spanning tree (MST). As a fully connected component is the target, then when plotted over the graph filtration, the required energy consumption declines until said target is reached when all components are connected, starting at $\lambda=0$ when all components are loose one can utilize the slope of the resultant plot (SIP) as a rate of convergence. This convergence rate can be thought of as the "rate of information diffusion" within the network due to the encoding of estimated future states as represented by the aggregation cost (Kuang & Wang 2019).

Proposal and Hypotheses

Building on this prior aging neuroscience work, we propose this novel graph theory metric quantifying the rate of information diffusion as a more robust and sensitive method for tracking brain aging in ASD. Moreover, because this metric is free of threshold selection, it has the potential to provide greater generalizability across studies. We will first apply this metric to whole brain analysis in older adults with ASD versus matched neurotypical (NT) adults, as previously done to discriminate between Alzheimer's disease, mild cognitive impairment, and healthy controls (Kuang et al., 2019). However, due to regional specificity of functional brain difference in ASD, we do not expect group differences from the whole brain approach. Rather, we hypothesize group differences will only be present in distinct large-scale brain networks containing nodes within the prefrontal cortex. Lastly, we compare this novel metric against five well-accepted graph theoretical analysis methods, and hypothesize it will provide a larger effect size for group differences.

As this disorder has been primarily investigated in younger individuals, namely children, there is little data demonstrating how aging affects symptoms of ASD, the brain, and future prognosis outlooks. This work serves to not only propose the novel graph theory metric as a potential functional biomarker to understand network organization differences in older adults with ASD but also to orient the field of advanced imaging analytics to a new area of research with a rapidly growing need.

CHAPTER 2

METHODS

Subject Selection

Participants for this study were right handed males, 27 with ASD (52+/- 8.4 years), IQ (109 +/- 2.78) and 21 NT (49.7 +/- 6.5 years), IQ (111 +/- 2.96) for a total of 48 participants that were well age and IQ matched. Subjects were recruited from the greater Phoenix, Arizona area. The cut off for older adults with ASD was 40 years of age based on the only other study of brain connectivity in adults with ASD showing divergent aging trajectories at this age (Koolschijn et al. 2016). There were no significant differences between diagnosis groups. Detailed demographic information can be found in Table 1.

Participants with ASD were recruited via the Southwest Autism Research and Resource Center (SARRC) lifetime database, a voluntarily enrolled database that includes information from all clients who participated in a clinical or research program at SARRC. Other participants with ASD were recruited via grassroots community groups and flyers posted at ASD community events, and their diagnosis was confirmed by SARRC upon enrollment. NT participants were recruited via word of mouth and flyers posted throughout the community.

All participants with ASD reported a clinical or suspected diagnosis of ASD, confirmed with a research reliable psychometrist with a decade of experience via the Autism Diagnostic Observation Schedule-2 (ADOS-2) (Lord et al 2012). ADOS-2 results were reviewed and diagnosis confirmed by a psychologist with 25 years of experience (CJS) who completed the DSM-5 checklist (APA 2013) based on current presentation of

symptoms. NT participants reported no suspected or confirmed diagnosis of ASD, and were administered the Social Responsiveness Scale-2 Adult Self Report (SRS-2; Constantino 2012) in order to confirm. Due to the low level of specificity of the self-report measure (0.60; Mandell et al., 2012) the cutoff for NT participants was set at a *T*-score = 66, in order to accommodate normal variation in social behavior that is unrelated to ASD.

To further increase confidence in NT status, having a first-degree relative with an ASD diagnosis was considered as an exclusionary criteria for NT participants. Other exclusion criteria for all participants were score <70 on the Kaufman Brief Intelligence Test – 2nd Edition (KBIT – 2; Kaufman & Kaufman, 2004) and score ≤26 on the Mini Mental State Exam (MMSE; Folstein, Folstein, & McHugh, 1975).

All participants self-reported their medical history; no participants reported a history of genetic disorders, neurological illness (stroke, dementia), or any head injuries that led to loss of consciousness. As seizures are a common in children with ASD (Volkmar 1990, Theoharides 2011), we did not exclude the small number of our participants who had experienced a single childhood seizure but who were not on anti-seizure medication and who no longer had seizures into their adulthood. We also did not exclude a history of depression or anxiety in the ASD group, as these are common comorbidities in ASD (Lever & Geurts 2016). The NT participants did not report any history of psychiatric mood disorders.

This study was conducted in compliance with Arizona State University's ethical standards for research and the Declaration of Helsinki 2000 revision. All participants provided written consent approved by the Institutional Review Board.

Data Acquisition

Images were collected using a 3-Tesla Philips Ingenia MRI scanner with a maximum gradient strength of 45 mT/m. All participants underwent high-resolution, T1-weighted scans (3D magnetization prepared rapid acquisition gradient echo [MPRAGE]; 170 axial slices, 1.2 mm slice thickness, field of view=240 mm, 256x256 acquisition matrix). Functional blood-oxygen-level dependent (BOLD) signal images were collected via a gradient-echo echo-planar series with whole brain coverage (repetition time=3000ms, echo time=25ms, flip angle=80°, 3mm slice thickness, 24mm field of view, 64x64 acquisition matrix). Resting-state scans were six minutes in duration, during which 120 brain volumes were collected while the participant had their eyes closed. Prior to MRI data acquisition, the option to visit the imaging center and experience the MRI environment was provided to all participants to minimize anxiety-related motion during fMRI acquisition. Padding and headphones were also used to minimize head motion in the scanner.

Pre-Processing

Resting-state fMRI was selected for connectivity analysis as it has shown good reproducibility (Shah et al., 2016), and potential for identification of neurophenotypes in psychiatric disorders (Van Essen & Ugurbil, 2012). Resting-state data were preprocessed using Statistical Parametric Mapping software (SPM-12; Wellcome Department of Cognitive Neurology, Institute of Neurology, London, UK; fil.ion.ucl.ac.uk/spm/) in Matlab (Mathworks, Natick, MA). The first two volumes were removed to account for time needed for scanner magnetization to reach a steady state. Wavelet Despiking using the BrainWavelet toolkit (Patel et al., 2014) was conducted on raw image data to reduce secondary motion artifacts. Slice-time correction and realignment were then performed to correct for differences in slice acquisition timing and motion during scanning,

respectively. The structural images were segmented into gray matter and white matter tissue maps and then skull-stripped to improve co-registration. Each participant's functional image series was co-registered to their skull-stripped T1 image. Using DARTEL Tools implemented in SPM-12, a common template that maximizes inter-participant alignment was generated based on participants' gray and white matter segmented images using an iterative registration process. The common template was then transformed to MNI space, and each participant's DARTEL flow field and MNI transformation parameters were applied to their functional image series. During this step, the data underwent smoothing using a 6-mm full-width half-maximum Gaussian kernel to reduce spatial noise. Images were visually inspected after each step in the preprocessing pipeline. Using the Artifact Detection Tools toolbox, smoothed and normalized images were inspected for high-motion volumes to be censored. However, no volumes exceeded the moderately conservative thresholding criteria (0.9mm) of relative scan-to-scan displacement. Data Processing Assistant for Resting State fMRI (DPARSF) (Yan & Zang 2010) in Matlab (Mathworks) was used for the extraction of 116 regions of interest (nodes, ROI) signals based on the automated anatomical labelling atlas (AAL) (Tzourio-Mazoyer 2002).

Network Construction

Analysis was performed at both the whole brain level and specific large-scale network level. Based on Smith et al (2009) and the 116 AAL Atlas, we identified 6 networks which contained a sufficient number of nodes for graph theory analysis. These networks were three prefrontal-containing networks, and three non-prefrontal-containing networks. The prefrontal networks were the DMN, EN, and the Fronto-Parietal Network

(FPN). The three other networks were the sensory motor network (SMN), auditory network (AN), and medial visual network (MVN). Each networks dendrogram (see Results, Figures 9 - 14) denotes which AAL regions were assigned to each network based on Smith et al. (2009).

Integrated Persistent Feature

Each network (including the 116 ROI whole brain) was constructed where each ROI or node represents anatomical brain regions. The Pearson correlation was utilized to determine the distance between nodes, where a larger correlation coefficient implies stronger functional connectivity. In this way we built a hierarchical organization via a dendrogram using the single linkage distance matrix for each subject, and the resting state multiscale network is constructed for every subject in our ASD and NT group. Utilizing the zeroth Betti Number as a persistent homology graph filtration enables us to track the construction of a fully connected component (all nodes connected together of the network) as the filtration value increases (Giuti et al 2016). In this method, plotting the IPF across different filtration values enables us to track the evolution of the network to a fully connected component. The slope of this monotonically decreasing function, the IPF, (SIP) is therefore the rate of connecting components converging over the filtration value λ, which can be thought of as the "rate of information diffusion" within said network. (Kuang et al., 2019).

Traditional Graph Theory Metrics

The IPF has been demonstrated in its initial paper to have greater sensitivity and robustness compared to other widely use graph theoretical network measures when applied to subject-wise Alzheimer's data (Kuang & Wang 2019). In this work, the

authors compared its function against five other graph theoretical metrics; Betti Number Plot (BNP), Characteristic Path Length (CPL), Network Diameter (ND), Eiganvector Centrality (EC) and Modularity (Mod) (Chung et al. 2015, Lee et al 2012, Lee et al 2017). These metrics were obtained through the Brain Connectivity Toolbox for Matlab (Rubinov 2010). Briefly, CPL can be understood as the average shortest distance between all nodal pairs once all nodes are connected, and can be understood as "ease" of data transfer within said network (Brier et al 2014). For example, a low CPL is understood as describing a network with "easily" or quickly" data transfer. ND is how far the furthest nodes of a network are from one another based on a paired path length (Assenov et al 2007). It enables understanding of the size of a network. A large ND and small CP would therefore be considered an efficient network. Mod measures how the communities within a network differ from each other (Sporns & Betzel 2016). EC (Van Duinkerken et al 2017) assigns greater weight or importance to nodes if connected to other highly connected nodes. In this way, a node itself that enables connection between two highly connected nodes is itself a very important node.

Statistical Analysis

The results were analyzed in SPSS (IBM SPSS Statistics for MacOs, Armonk, NY) using an ANCOVA for each graph theory metric for the whole brain or network, with IQ as the covariate due to its influence on cognitive behaviors and network connectivity (Bora and Pantellis 2016, Van Den Heuvel et al 2009).

CHAPTER 3

RESULTS

Whole Brain

As shown in Table 2, the SIP was unable to detect a significant difference between the older ASD group our older NT group ($F(1,47) = 0.360$ $P=0.552$, $\eta^2=0.009$). There were also no significant differences between groups for the five traditional graph theory metrics (Table 2) at the whole brain level.

Prefrontal Networks

The values and statistical information for the SIP and other metrics are found in Table 2. We found a significant difference between older ASD and older NT groups for both the DMN (p=0.02, Figure 2), EN (p=0.04, Figure 3), and a trend approaching significance in the FPN (p=0.07, Figure 4). We also find a significant difference in the DMN for Network diameter (p=0.04), though as shown in Table 2, the effect size for the SIP was stronger. The network diameter was non-significant for the other two prefrontal networks. None of the other graph theory metrics were significant for any prefrontal network (Table 2).

Non-Prefrontal Networks

The values and statistical information for the SIP and other metrics are found in Table 2. As expected, when looking at our other non-prefrontal networks, all measures including the SIP were non-significant between older adults with ASD and older NT adults in the AN, SMN, MVN.

CHAPTER 4

DISCUSSION

Present Findings

The presented study examined the application of novel integrated persistent feature to examine topological network differences in both whole brain analysis and network specific analysis in an older group of adults with ASD than has been traditionally studied. As originally expected, our hypothesis that older individuals with ASD when compared to NT would not have whole brain network differences was confirmed. As the SIP is directly related to network topology, this lack of whole brain convergence rate differences is most likely due to many *unaffected* networks within the brain. Thus, the lack of significant findings at the whole brain level may be a signal to noise issue, as other topological work found differences in local and global efficiency between functional networks in ASD (Rudie 2013). To confirm this, we investigated the prior-identified pre-frontal cortical networks for network differences.

Within these prefrontal networks, we found a reduced SIP in the DMN and EN, and a trend towards significant difference in the FPN. Further, we see from figures 15-17 that the older ASD group specifically had a reduced slope. This is interpreted to mean that within the DMN and EN, older individuals with ASD have reduced network integration when compared to the older NT group. Further, we demonstrate this measures sensitivity in detecting these differences in small sample sizes (Table 2) when compared to the traditional measures as evidenced both by the effect size between groups and that the other five measures were non-significant in the EN (Table 2). However, within the DMN the ND was also significant. Consistent with our findings, others report abnormal

functional connectivity and reduced network recruitment in the DMN in younger groups with ASD as well (Assaf et al 2010, Yerys et al 2015).

Although we did not set out to make inferences about regional within-network connectivity, the dendrograms (Figure 9) provide visually interesting information. Although we are the first to investigate resting-state network dynamics in older adults with ASD our findings largely correlates with previous research in younger groups with ASD. In reference to Figures 9-14, the dendrogram represents the strength of functional connections between nodes and the anatomical features represented by these nodes (Phipps 1971, Lee 2012). For example, as shown in other research with ASD (Lynch 2013), the DMN has strong connections between the posterior cingulate and retrospinal cortices (Figure 9). This strong connection exists in older adults with ASD despite the observed reduced connectivity in the precuneus, hippocampus, and gyrus rectus. Further, this initial connectivity appears different than that of the NT dendrogram (Figure 9) which shows less connectivity between these areas, but stronger connectivity between others, such as the frontal medial and orbital gyri. Looking at our unaffected networks as measured by the SIP (Figures 12, 13, 14) we see that the AN, SMN, and MVN dendrograms are identical between the ASD to NT groups. This may imply differences in network organization in our ASD group that is prefrontal network specific, which is supported by other ASD literature. In one study, network topologies and organization were disrupted in the FPN, DMN, SMN, and occipital network (Itahashi 2014) as measured by a decrease in variety of network techniques (degree centrality, nodal efficiency, betweeness centrality). Functional connectivity analysis of organization also detected differences in networks related to social and emotional processing in the task

negative network (i.e. DMN) despite intact organization of the task positive network (Kennedy 2008), with reduced connective strength being related to worse symptoms. However, many other studies have produced contradicting results on connectivity and organization, potentially due to differences in sample demographics, specifically symptom severity, IQ, and sex (Hull 2017, Gong 2009). Collectively, the dendrograms may provide utility for identifying the most vulnerable anatomical features and component communities for a given neurological condition, which warrants future follow-up.

Previous Application of the SIP

In its introductory paper, the SIP had only been applied to whole brain analysis, though the authors believed its high degree of generalization could enable its application to other network sizes (Kuang et al., 2019). As demonstrated in Table 2, we confirmed that the SIP was a more sensitive measure than the other network measures in the EN and DMN, as evident by effect sizes in ASD versus NT comparison. Specifically, that the ASD group had a reduced SIP over the NT group in both the DMN and EN, and a trend in the FPN (Figure 16, 17). Due to the SIP effect size in the FPN, by the boxplot shown in Figure 17, we believe that increasing the sample size may demonstrate a significant difference in this network as well. Within the DMN and the EN, these results of this novel metric demonstrate that older individuals with ASD have decreased functional integration.

Previous Findings in ASD

Other than the work currently being performed by our research team, there has not been any other study that has investigated rs-fMRI data in older adults with ASD. In a

study performed by Walsh et al. (*in press)*, independent component analysis was applied to investigate network connectivity in younger vs. older adults with ASD. This study demonstrated that the EN in older persons with ASD has significant hypoconnectivity when compared to younger individuals with ASD. Further, reduced connectivity of prefrontal regions within this network to the rest of the network was correlated with worse social cognitive abilities. Despite this, we can look at the broader field of rs-fMRI ASD research and findings for support as to why we only find differences in prefrontal networks. A summary review article of rs-fMRI studies in ASD points to reduced functional coherence in DMN, and a potential compensatory increase in local cortical and sub cortical network connectivity (Rane et al 2015). Findings in young persons with ASD also demonstrate that the DMN specifically has hypoconnectivity (Jung et al 2014). Other work performed with multimodal brain imaging has continued to show differences in network connectivity and topological organization in the prefrontal cortex (Itahashi 2014, Itahashi 2015). As such, these network specific observations in our older populations are consistent with other findings in ASD that demonstrated decreased connectivity in the pre-frontal cortex and specifically in the EN and DMN (Pandhaman 2017, Rudie 2013).

Previous Traditional Graph Theory Applications in ASD

This study is not the first to propose a graph theoretical approach to investigating ASD. In a recent study, differences in the auditory, somatosensory, and subcortical networks were found using community structure analysis using community diversity measures; density, cohesion, and dispersity (Keown et al 2017). However, this study relied on a sample of 174 NT and 111 ASD participants, and only in young adults with no consideration for handedness, sex, or IQ influences on these networks. Other work has

shown increase network size for young individuals with ASD (Malaia 2016), and differences in degree and eigancevtor centrality in the basal ganglia and precuneus (Di Martino 2013). Once again, these studies were done on children with ASD. However, looking at effect sizes (Table 2) for some of these other measures, if a larger population was utilized in our study we may have also seen these differences. It is difficult, however, to find older adults with ASD because of the relative recentness of the diagnosis. The SIP is therefore extremely important over other graph theory metrics due to its sensitivity to detect small differences in smaller sample sizes.

However, no other study has proposed or demonstrated a measurable factor that could be used for tracking age-related changes in topological differences or network integration. In this regard, because the SIP is the more sensitive metric for detecting differences from matched NT older adults, it may also serve as a potential functional biomarker for tracking age-related brain changes . Such a biomarker does not currently exist, and with a growing affected population, could assist in informed treatment and large-scale care methods, while furthering our understand of ASD and its effects on the brain at large.

Limitations and Future Directions

Although this study provided significant contributions to the field of ASD, limitations did exist. First, this study was performed with a relatively small sample size of "high functioning" participants whose diagnosis was determined at different times within their respective lives. Despite our decision to choose the cut-off for our older group based on findings by Koolschijn et al 2016, the chosen range of ages is relatively large. Dividing this population into further age-related groupings would yield small (<5 person) groupings

in some brackets. Future larger sample size studies will be needed to confirm these effects and account for cohort differences. Ideally, longitudinal studies would be performed to verify and validate the SIP as a useful measure of tracking brain aging in ASD. As the group was all "high-functioning", it is limited in its application to the rest of the spectrum for ASD. Further research is warranted to examine the range of intellectual functioning in ASD. Secondly, the population investigated was all male. As sex differences affect neural network connectivity (Ingalhaliker 2014) and organization (Wu 2013), choosing a same sex sample was necessary. Further, it is difficult to find older aged women with ASD due to camouflaging of symptoms (Lai 2017). Future studies are needed to examine if there are any sex differences for this measure.

The full utility of the SIP as a biomarker in older adults with ASD is yet unknown because we have yet to explore relationships with symptoms. These participants are well characterized on an extensive symptom and cognitive battery. Future research will identify which behavioral metrics align most closely with SIP values, and thus estimates of the functional significance of the SIP. Similarly, understanding how the SIP relates to structural brain measures will be necessary to characterize its role in neurobiology. We have extensive structural imaging on these participants as well, and future investigations will examine which structural network metrics (e.g. white vs. gray matter) align most closely with SIP values.

CHAPTER 5

CONCLUSION

Results demonstrate that this novel network measure maintains its statistical power and robustness when applied to ASD group difference studies, but is specific to prefrontal-containing networks. Understanding the full value of this functional imaging biomarker will come from future investigations of relationships with symptoms in ASD and sensitivity to age-related changes in our longitudinal study. Ultimately, we aim to determine if one time point analysis of the SIP can predict future symptom decline in aging adults with ASD.

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APPENDIX A

ALL REFERENCED FIGURES

Figure 1: Plot of the IPF for the Whole Brain

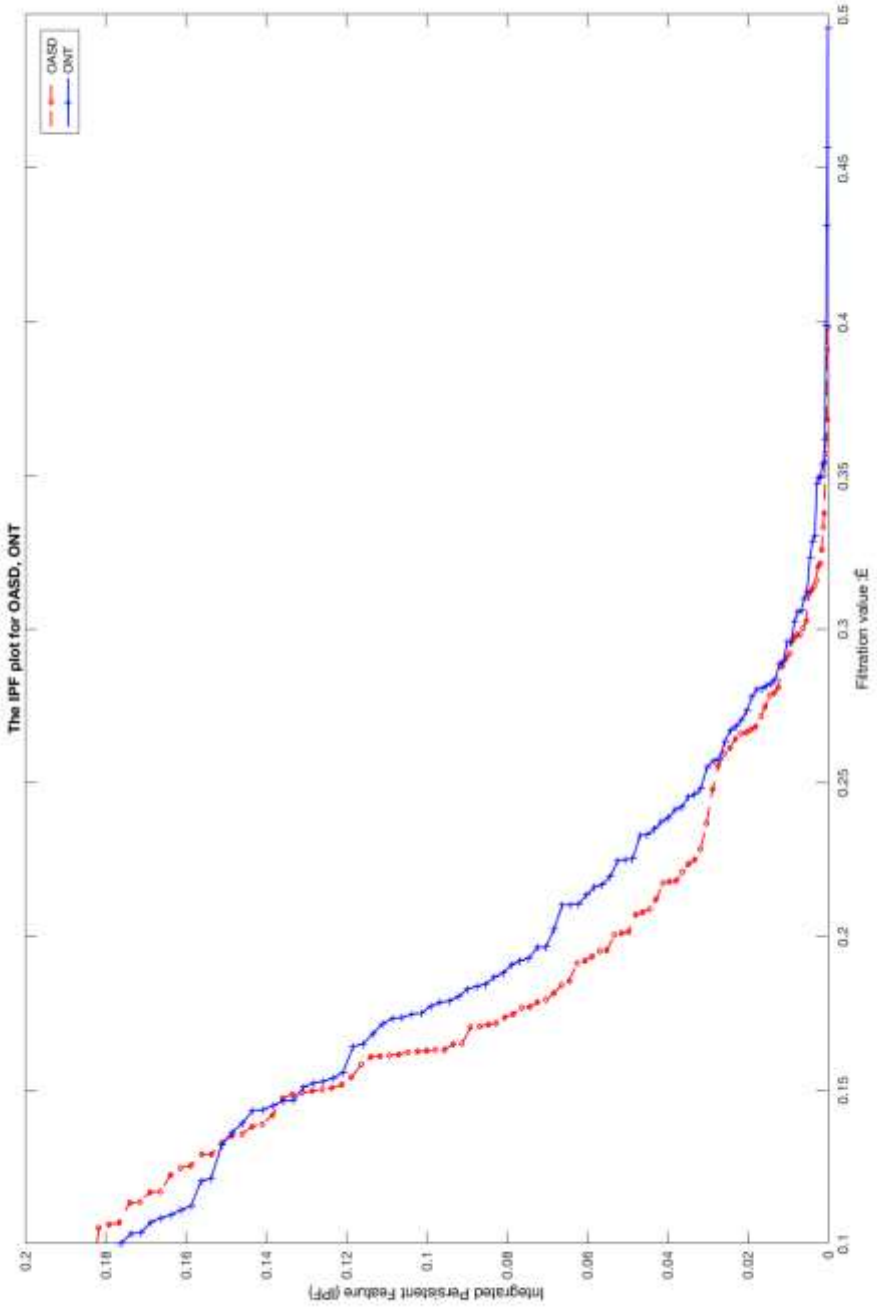


Figure 2: Plot of the IPF in the Default Mode Network

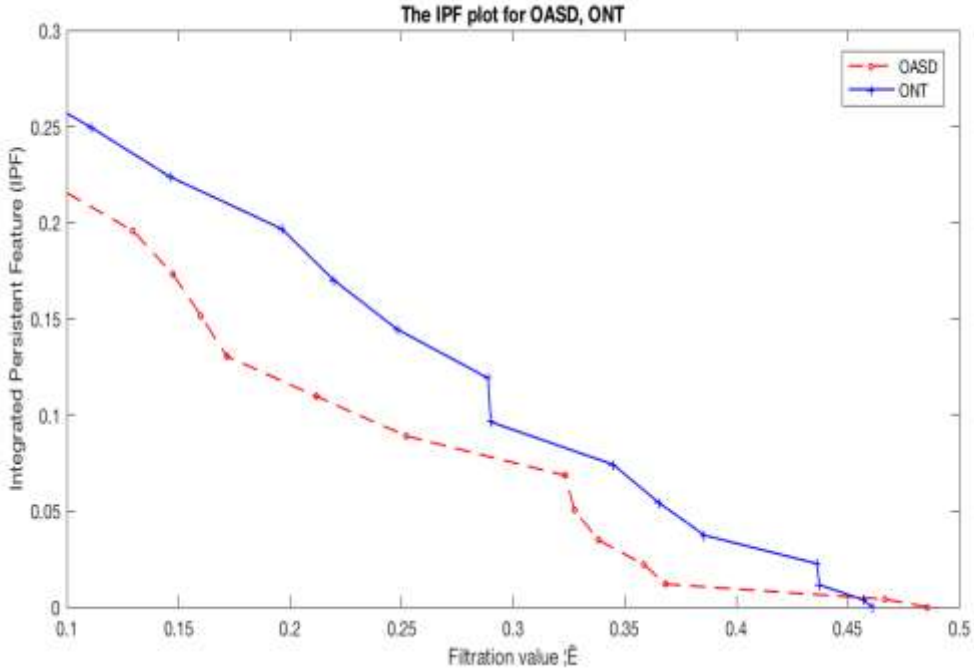


Figure 3: Plot of the IPF in the Executive Network

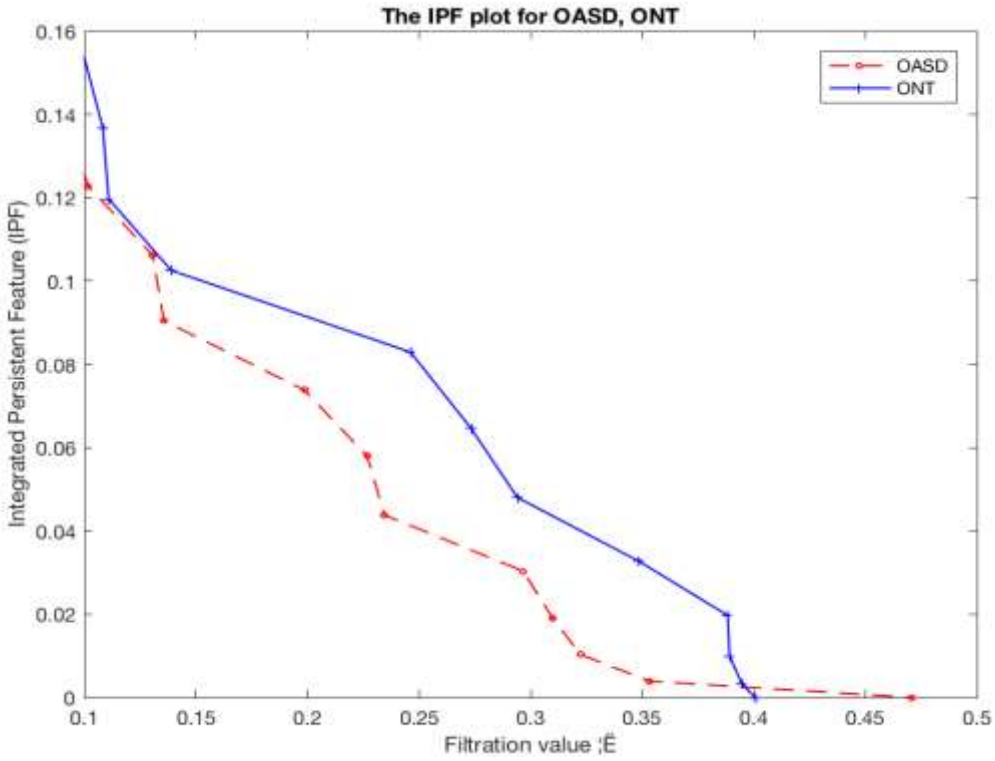


Figure 4: Plot of the IPF in the Fronto-Parietal Network

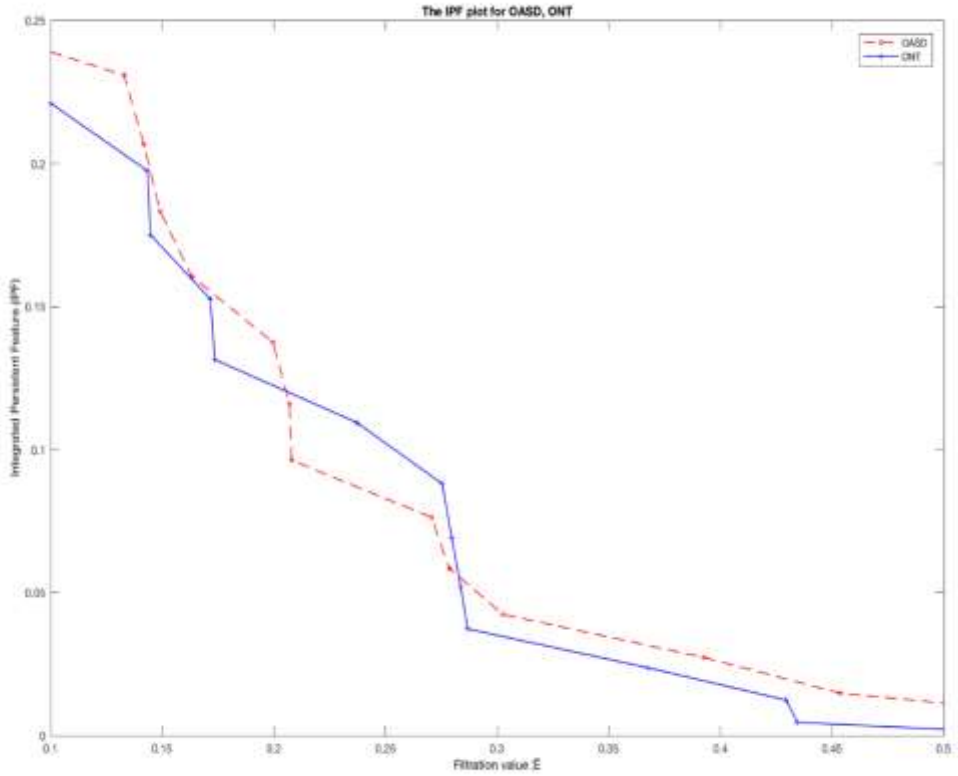


Figure 5: Plot of the IPF in the Auditory Network

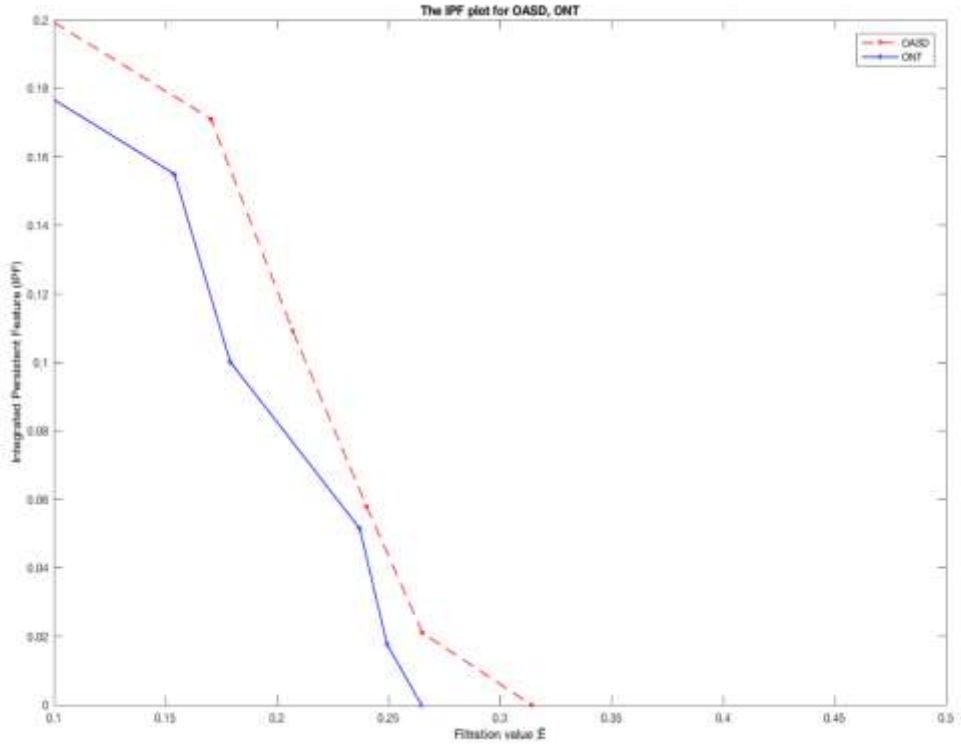


Figure 6: Plot of the IPF in the Medial Visual Network

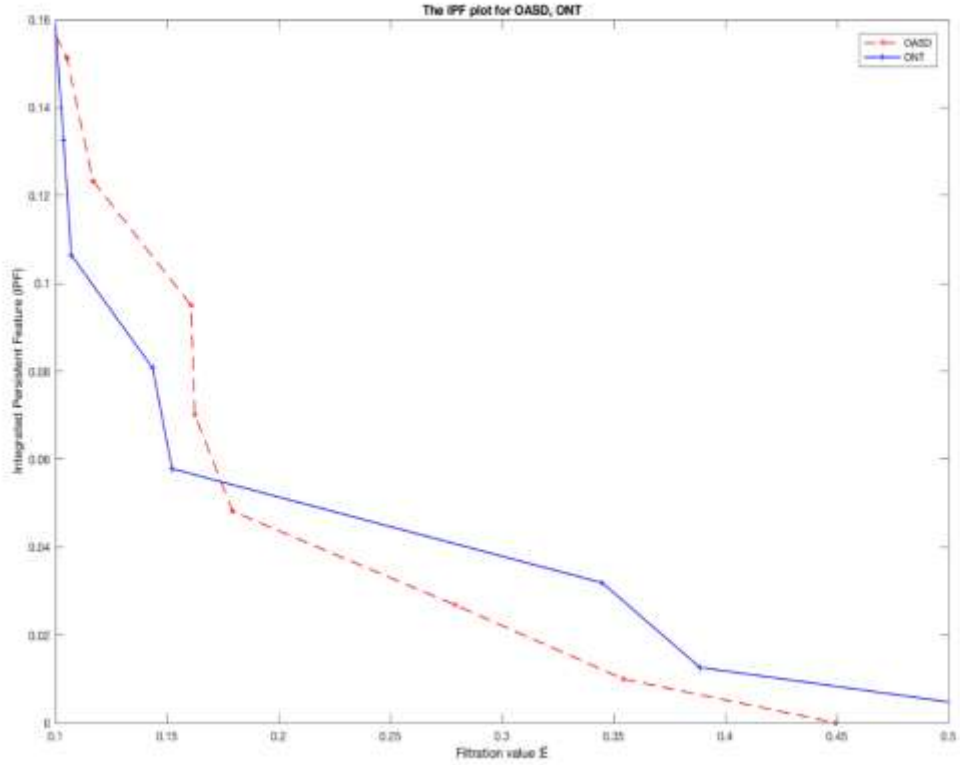


Figure 7: Plot of the IPF in the Sensory Motor Network

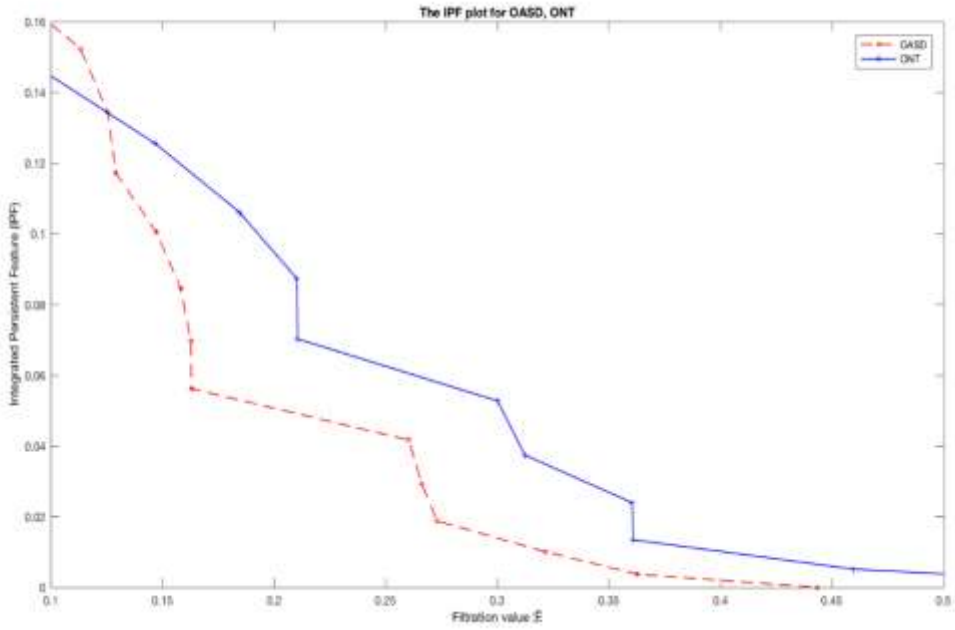


Figure 8: Dendrogram of Connectivity between Anatomical Regions for the Whole Brain

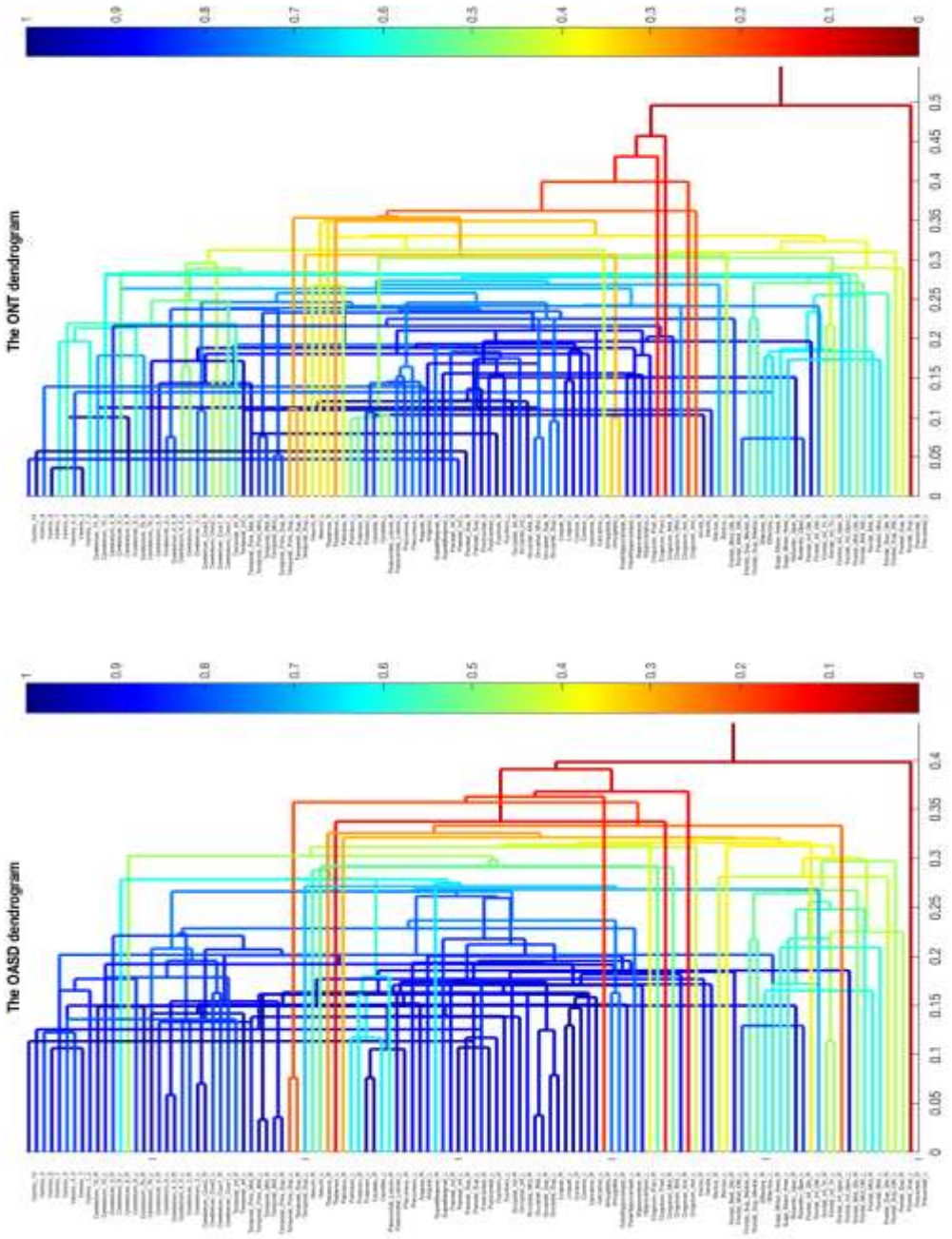


Figure 9: Dendrogram of Connectivity between Anatomical Regions for the DMN

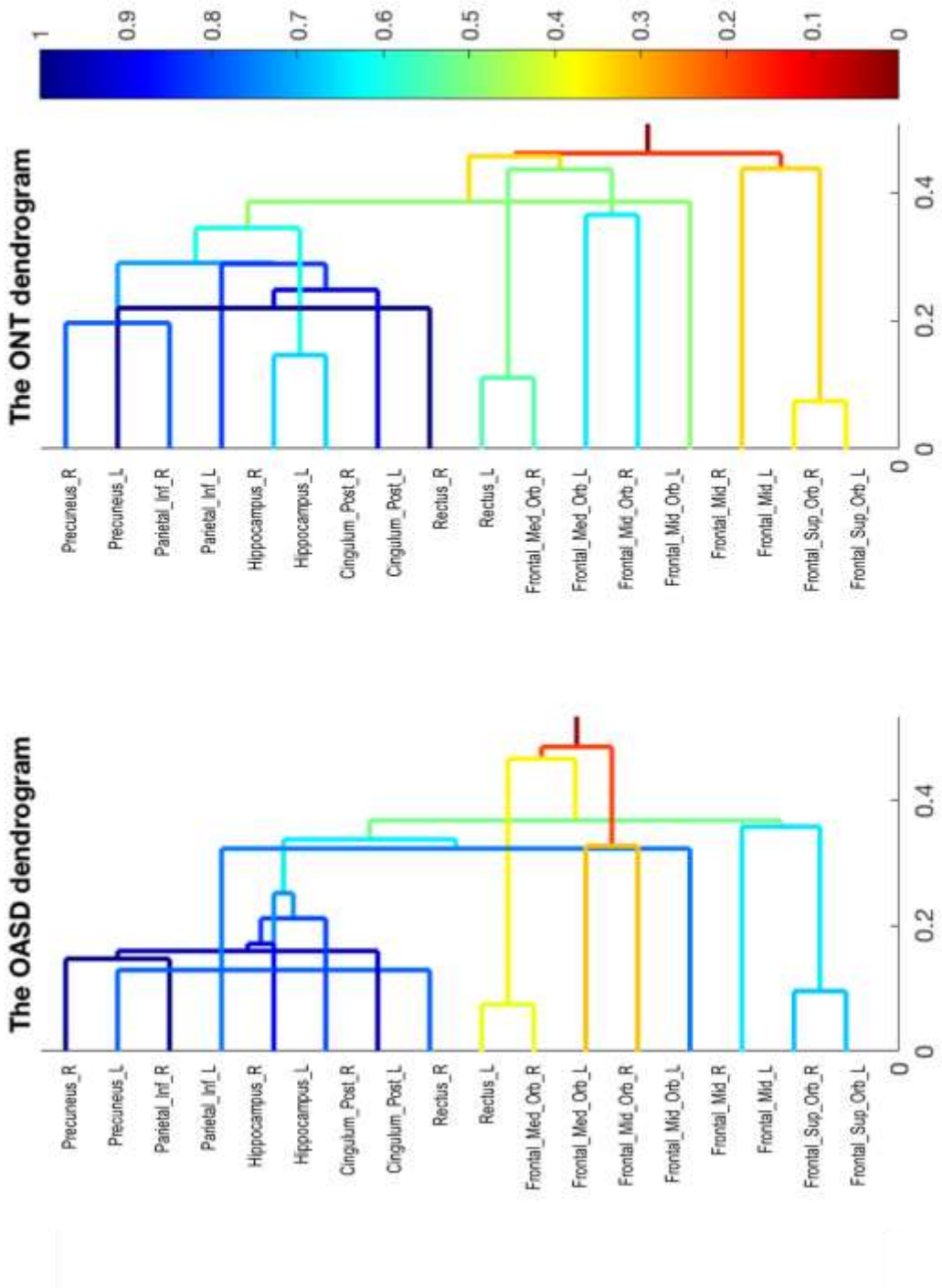


Figure 10: Dendrogram of Connectivity between Anatomical Regions for the EN

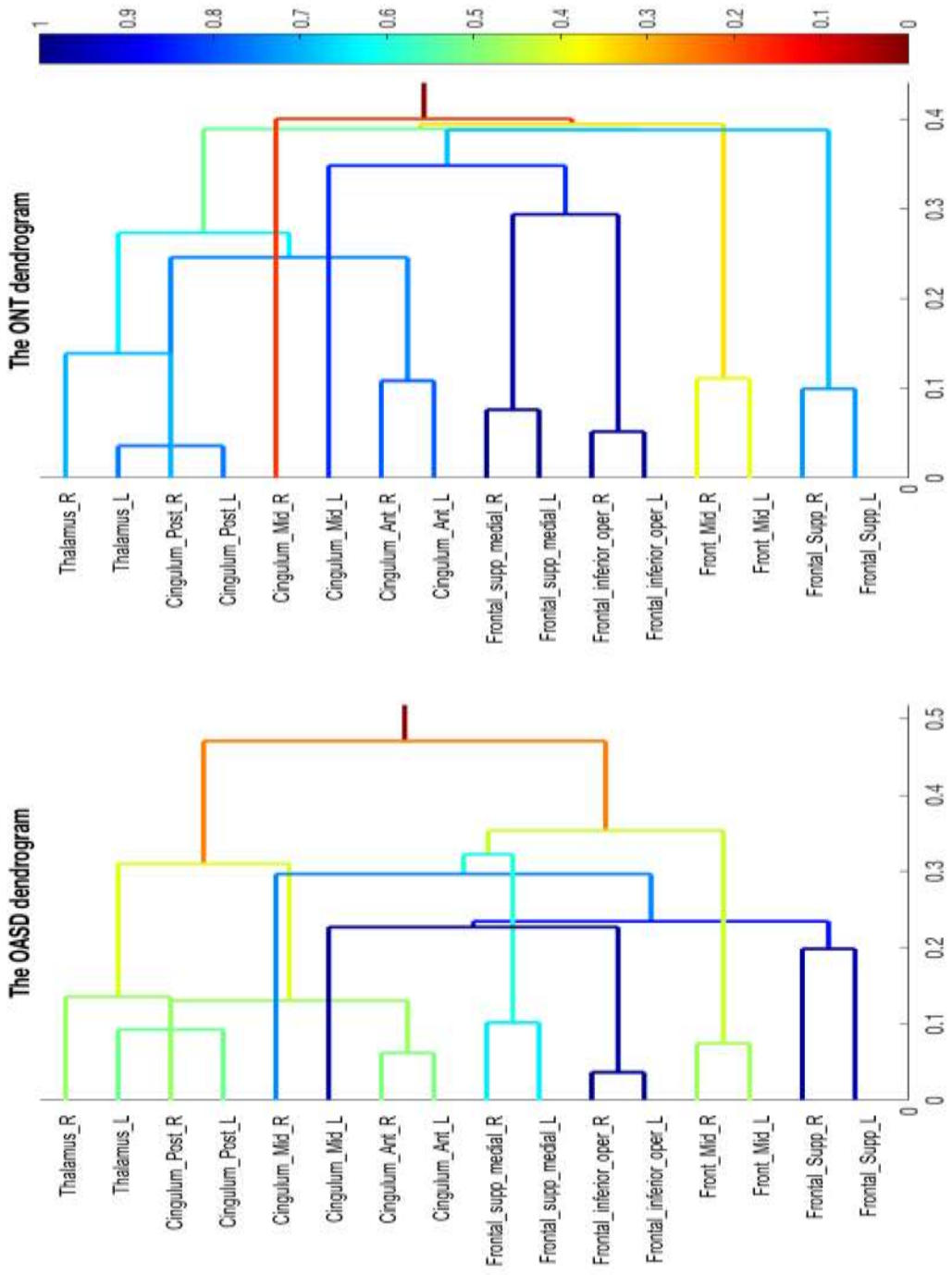


Figure 11: Dendrogram of Connectivity between Anatomical Regions for the FPN

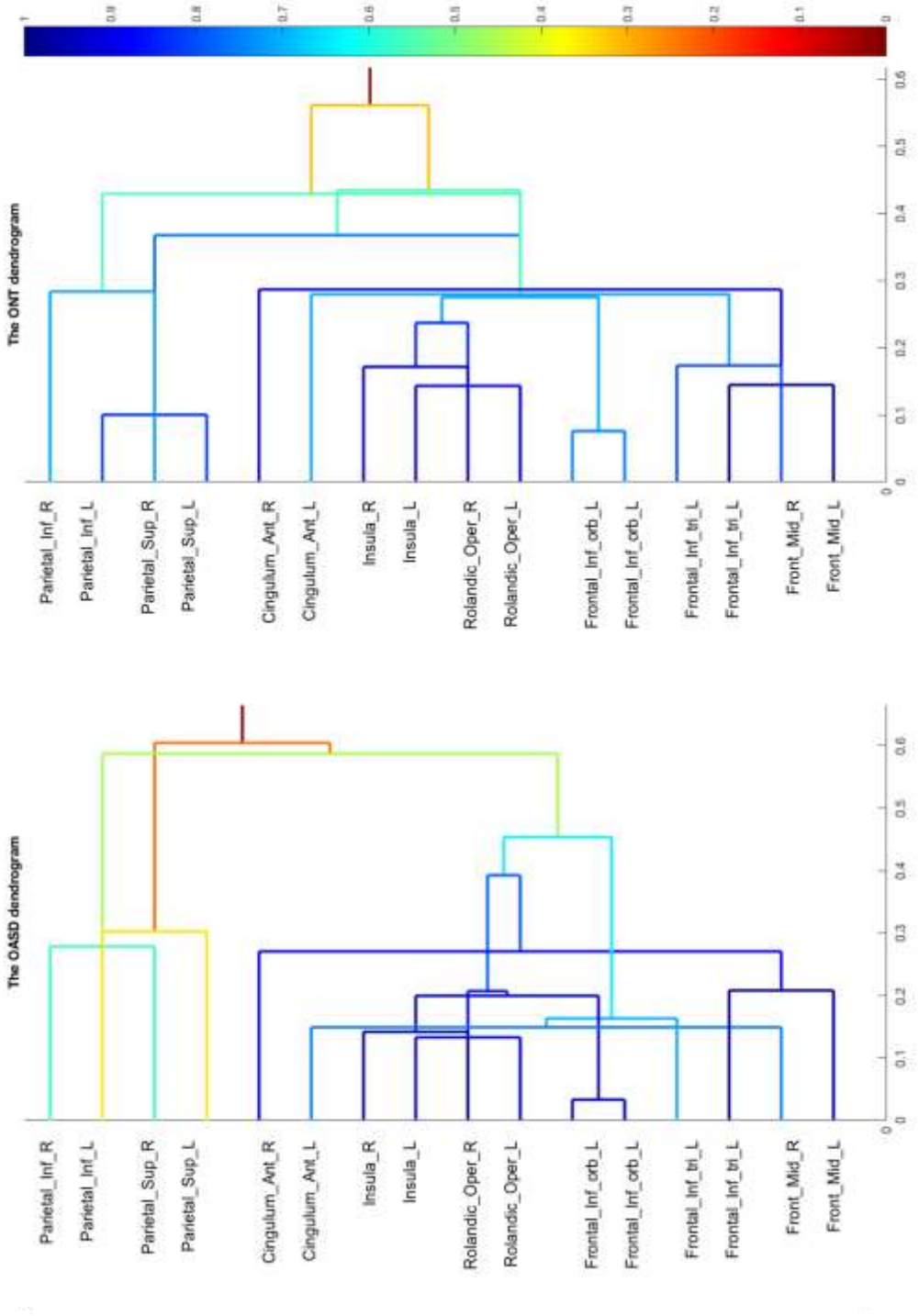


Figure 12: Dendrogram of Connectivity between Anatomical Regions for the AN

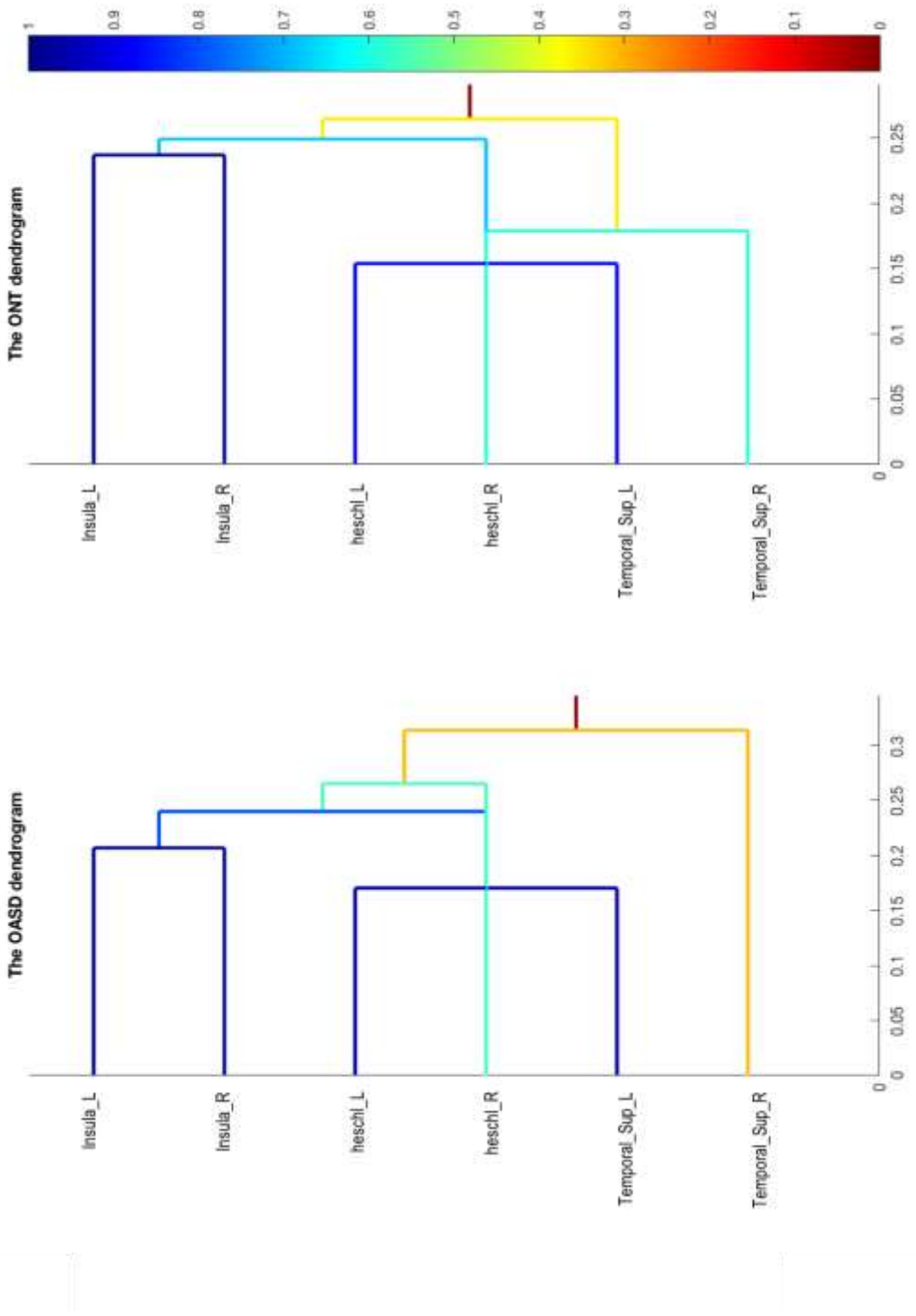


Figure 13: Dendrogram of Connectivity between Anatomical Regions for the MVN

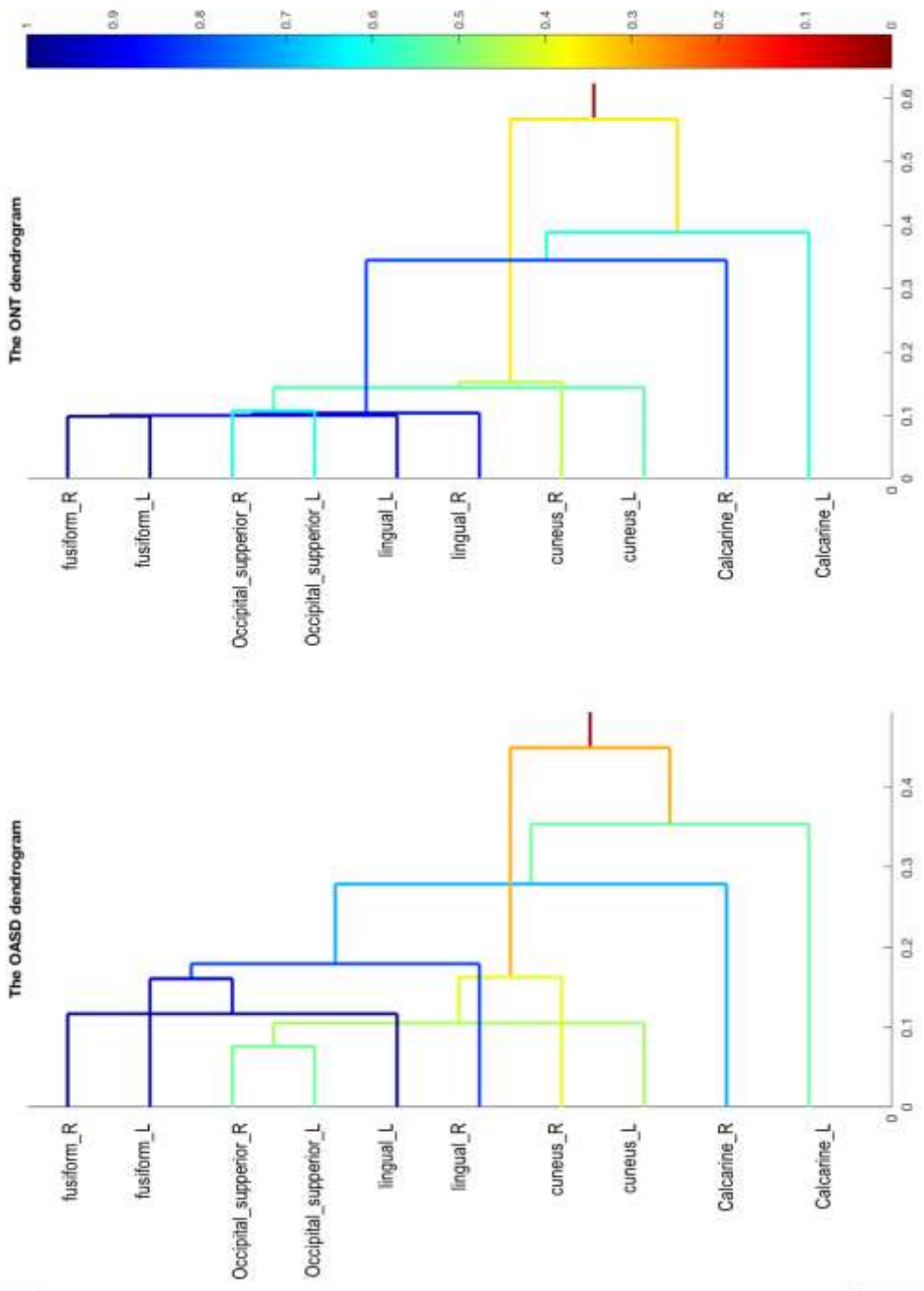


Figure 14: Dendrogram of Connectivity between Anatomical Regions for the SMN

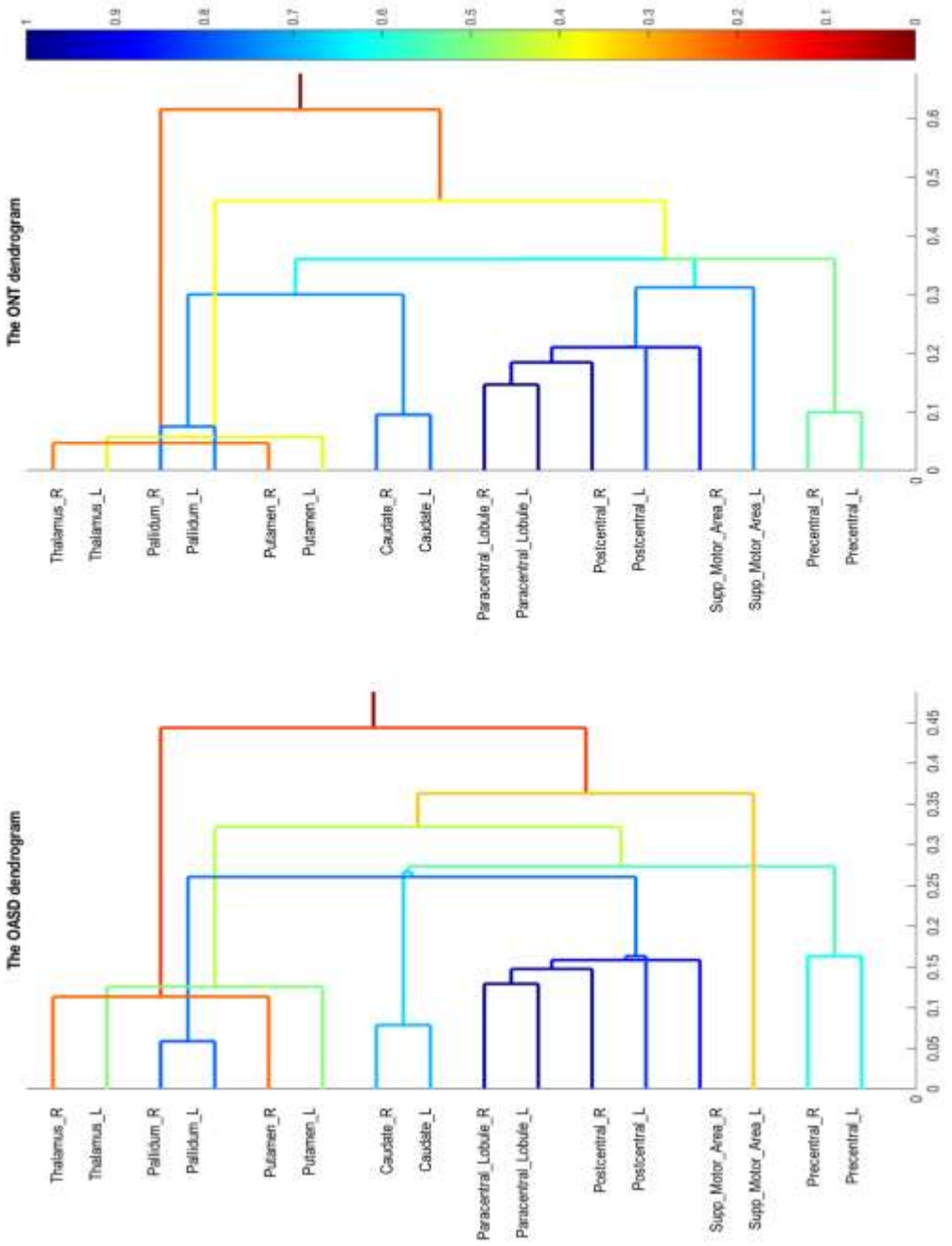


Figure 15: Box Plot of the SIP in the DMN

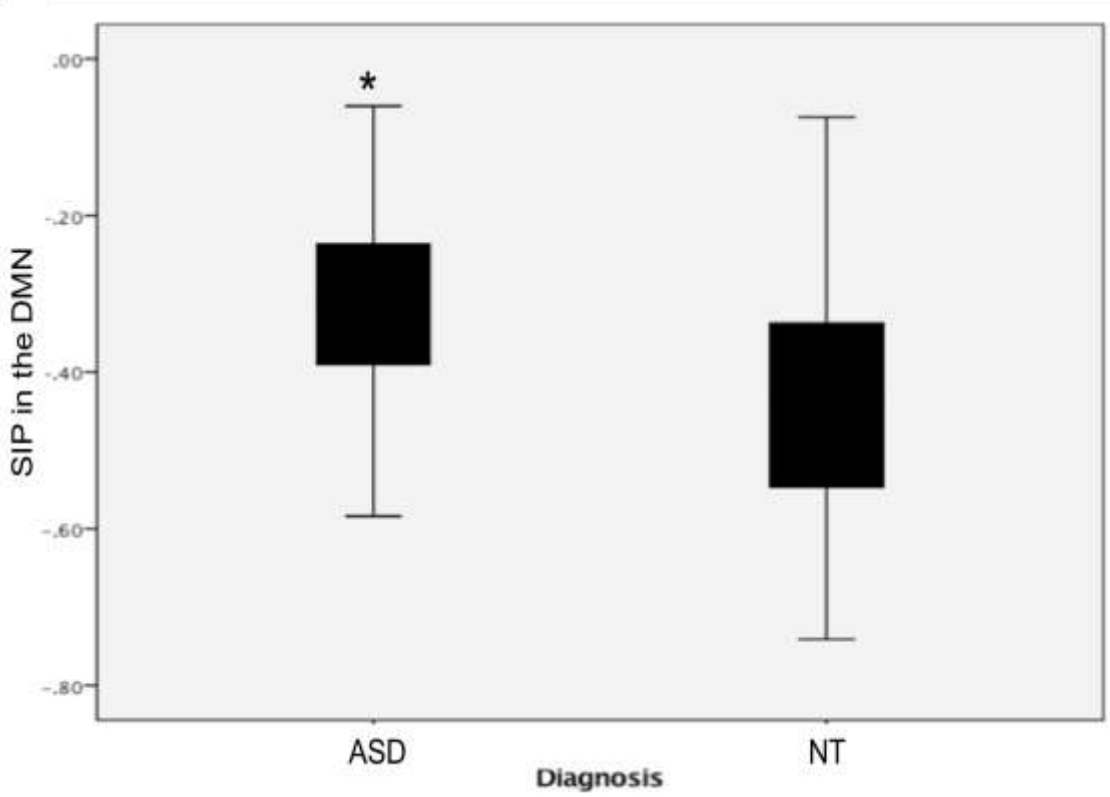


Figure 16: Box Plot of the SIP in the EN

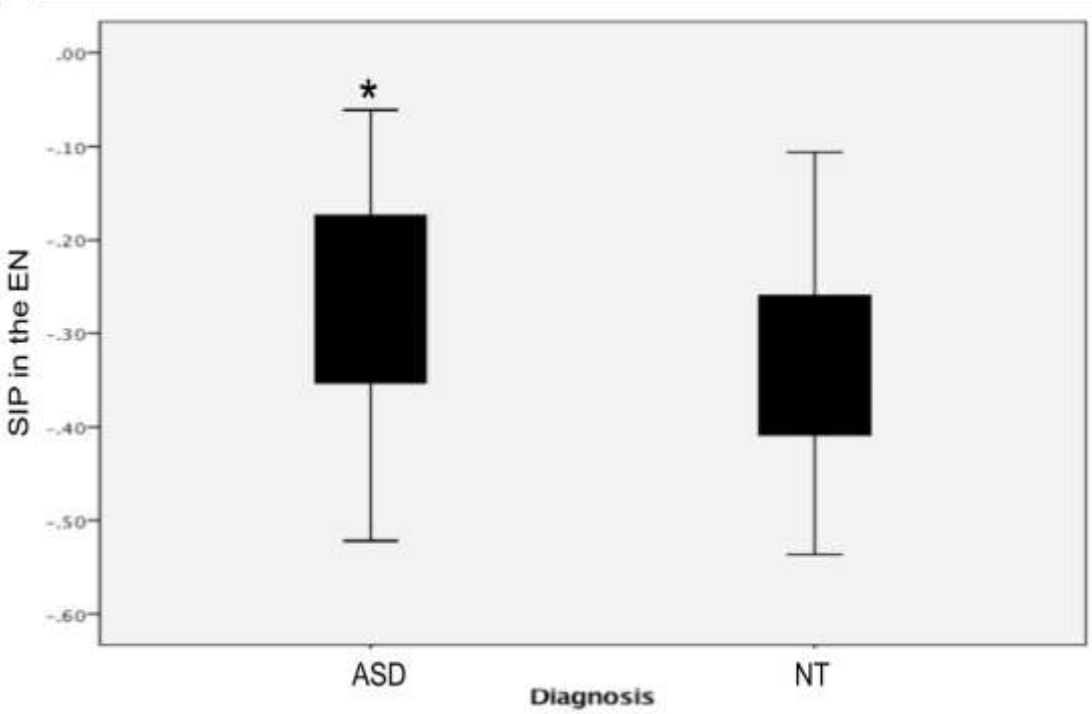
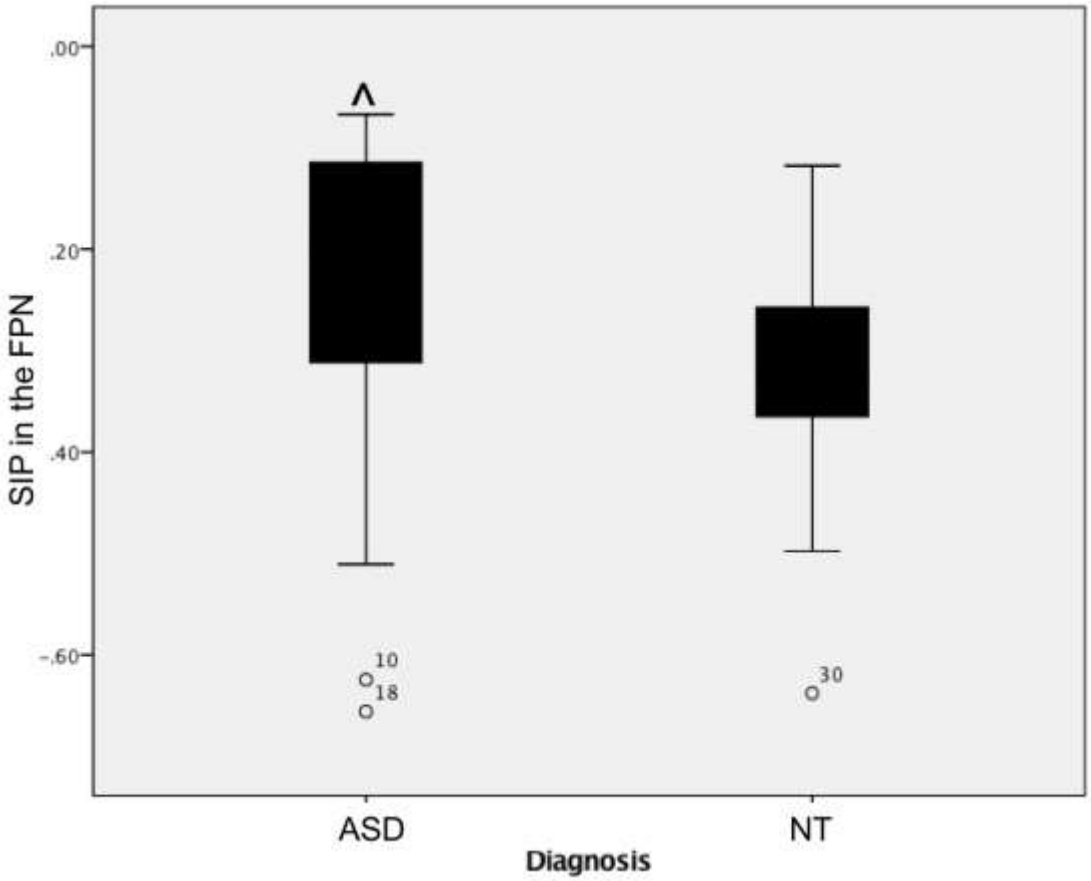


Figure 17: Box Plot of the SIP in the FPN



APPENDIX B

ALL REFERENCED TABLES

Table 1: Subject Demographic Data

	ASD	NT
AGE (YEARS)	52+/- 8.4 years	49.7 +/- 6.5 years
RANGE	40-70	40-64
IQ	109 +/- 2.78	111 +/- 2.96
RANGE	70-131	89-141
YEARS EDUCATED	15.5 +/- 2.7	16 +/- 2.4
RANGE	11-20	9-20
SRS-2	73.2 +/- 10	45.7 +/- 6.3
RANGE	56-89	37-60
ADOS-2	10.6 (3.0)	----
RANGE	7-19	

Table 2: Statistical Analysis Results (F, P, $\eta^{2)}$ for All Networks and All Measures

Network	**SIP**	**BNP**	**CPL**	**ND**	**EC**	**Mod**
Bold –	Trend					
Bold/UL	Significant					
Whole						
F	0.360	0.613	0.481	0.118	2.08	0.00
P	0.552	0.438	0.492	0.733	0.157	0.99
η^2	0.01	0.015	0.12	0.003	0.48	0.00
DMN						
F	5.968	0.004	2.198	4.502	0.979	1.767
P	**0.019**	0.949	0.145	**0.040**	0.979	0.191
η^2	0.13	0.00	0.048	0.093	0.328	0.039
EN						
F	4.398	2.139	0.032	0.001	0.308	0.032
P	**0.042**	0.151	0.859	0.981	0.581	0.859
η^2	0.089	0.045	0.001	0.00	0.007	0.001
FPN						
F	3.357	3.783	0.595	0.00	1.575	0.009
P	**0.074**	0.058	0.445	0.993	0.216	0.925
η^2	0.071	0.078	0.013	0.00	0.034	0.00
AN						
F	1.004	0.614	0.136	0.554	1.661	0.320
P	0.322	0.437	0.714	0.460	0.204	0.575
η^2	0.022	0.013	0.003	0.012	0.036	0.007
MVN						
F	0.154	0.074	0.015	0.099	0.132	0.045
P	0.697	0.787	0.903	0.754	0.718	0.832
η^2	0.003	0.002	0.00	0.002	0.003	0.001
SMN						
F	0.008	0.811	1.830	1.778	0.831	0.003
P	0.928	0.373	0.183	0.189	0.367	0.957
η^2	0.00	0.018	0.039	0.038	0.018	0.00

Table 3: AAL Atlas Regions

116	Vermis_10	87	Temporal_Pole_Mid_L	58	Postcentral_R	29	Insula_L		
115	Vermis_9	86	Temporal_Mid_R	57	Postcentral_L	28	Rectus_R		
114	Vermis_8	85	Temporal_Mid_L	56	Fusiform_R	27	Rectus_L		
113	Vermis_7	84	Temporal_Pole_Sup_R	55	Fusiform_L	26	Frontal_Med_Orb_R		
112	Vermis_6	83	Temporal_Pole_Sup_L	54	Occipital_Inf_R	25	Frontal_Med_Orb_L		
111	Vermis_4_5	82	Temporal_Sup_R	53	Occipital_Inf_L	24	Frontal_Sup_Medial_R		
110	Vermis_3	81	Temporal_Sup_L	52	Occipital_Mid_R	23	Frontal_Sup_Medial_L		
109	Vermis_1_2	80	Heschl_R	51	Occipital_Mid_L	22	Olfactory_R		
108	Cerebelum_10_R	79	Heschl_L	50	Occipital_Sup_R	21	Olfactory_L		
107	Cerebelum_10_L	78	Thalamus_R	49	Occipital_Sup_L	20	Supp_Motor_Area_R		
106	Cerebelum_9_R	77	Thalamus_L	48	Lingual_R	19	Supp_Motor_Area_L		
105	Cerebelum_9_L	76	Pallidum_R	47	Lingual_L	18	Rolandic_Oper_R		
104	Cerebelum_8_R	75	Pallidum_L	46	Cuneus_R	17	Rolandic_Oper_L		
103	Cerebelum_8_L	74	Putamen_R	45	Cuneus_L	16	Frontal_Inf_Orb_R		
102	Cerebelum_7b_R	73	Putamen_L	44	Calcarine_R	15	Frontal_Inf_Orb_L		
101	Cerebelum_7b_L	72	Caudate_R	43	Calcarine_L	14	Frontal_Inf_Tri_R		
100	Cerebelum_6_R	71	Caudate_L	42	Amygdale_R	13	Frontal_Inf_Tri_L		
99	Cerebelum_6_L	70	Paracentral_Lobule_R	41	Amygdale_L	12	Frontal_Inf_Oper_R		
98	Cerebelum_4_5_R	69	Paracentral_Lobule_L	40	ParaHipposcampal_R	11	Frontal_Inf_Oper_L		
97	Cerebelum_4_5_L	68	Precuneus_R	39	ParaHipposcampal_L	10	Frontal_Mid_Orb_R		
96	Cerebelum_3_R	67	Precuneus_L	38	Hippocampus_R	9	Frontal_Mid_Orb_L		
95	Cerebelum_3_L	66	Angular_R	37	Hippocampus_L	8	Frontal_Mid_R		
94	Cerebelum_Crus2_R	65	Angular_L	36	Cingulum_Post_R	7	Frontal_Mid_L		
93	Cerebelum_Crus2_L	64	SupraMarginal_R	35	Cingulum_Post_L	6	Frontal_Sup_Orb_R		
92	Cerebelum_Crus1_R	63	SupraMarginal_L	34	Cingulum_Mid_R	5	Frontal_Sup_Orb_L		
91	Cerebelum_Crus1_L	62	Parietal_Inf_R	33	Cingulum_Mid_L	4	Frontal_Sup_R		
90	Temporal_Inf_R	61	Parietal_Inf_L	32	Cingulum_Ant_R	3	Frontal_Sup_L		
89	Temporal_Inf_L	60	Parietal_Sup_R	31	Cingulum_Ant_L	2	Precentral_R		
88	Temporal_Pole_Mid_R	59	Parietal_Sup_L	30	Insula_R	1	Precentral_L		

APPENDIX C

INSTITUTIONAL REVIEW BOARD DOCUMENTATION

Institutional Review Board Study ID

ASU IRB IRB # STUDY00006088 | Approval Period 1/8/2019 – 1/7/2020

APPENDIX D

SUBJECT INFORMED CONSENT FORM

Subject Informed Consent Form

ASU Arizona State University

Subject Informed Consent Form

Cognitive and Neural Correlates of Aging in Autism Spectrum Disorder: Interactions with Sex

Investigator: ***B. Blair Braden, PhD***
Autism Brain Aging Laboratory Director
Department of Speech and Hearing Sciences
Arizona State University
976 S Forest Mall, Tempe, AZ 85281
(480)727-3970
abalab@asu.edu

Why am I being invited to take part in a research study?

You have been identified as a possible participant in a clinical research study called "Cognitive and Neural Correlates of Aging in Autism Spectrum Disorder: Interactions with Sex." This study is funded by the Arizona Department of Health Services, the National Institute for Mental Health Research, and Arizona State University's Speech and Hearing Science Departmental Funds. A research study is done when physicians, scientists, and others try to find new ways to diagnose and/or treat different illnesses. Since this research study is experimental and the future results have not been proven, you need to know enough about the risks and benefits to decide if you want to participate. This process is called informed consent.

Doctor B. Blair Braden, the Principal Investigator for this research study, or a member of the study team, will discuss this study with you in great detail. This "Informed Consent" document explains what will be expected of you and what risks or benefits you may experience if you agree to participate. You should read this document very carefully and ask as many questions as you need to fully understand what participating in this study means. Please understand that by signing this document you agree to participate in this experimental study.

For this study, we are enrolling adults with and without autism spectrum disorder (ASD) between the ages of 18 and 89 years to help us better understand how the brain changes in adults with ASD as they age.

Why is this research being done?

Adults with ASD often experience symptoms that can affect their quality of life and ability to live independently, and these may get worse with age. We are conducting this research study to better understand brain function in adults with ASD during aging. This information will allow us to find brain areas vulnerable to aging. Identifying these areas may help us develop interventions for adults that will promote independent living and improved health.

How long will the research last?

We plan to have you participate in this study every two years through 2023, with the potential for future years depending on funding. If you are a participant with ASD, the first time you participate you will go to the Southwest Autism Research and Research Center (SARRC) for a 2 hour visit to complete interviews and assessments about ASD. These interviews and assessments will determine your eligibility to participate in the study.

All eligible participants will be scheduled for a time to go to the Autism Brain and Aging Laboratory at Arizona State University for a 3 hour visit to complete assessments, cognitive testing, and questionnaires, as well as optional collection of a saliva sample. Participants will also be scheduled for a time to go to Barrow Neurological Institute (BNI) for another 2 hour visit to collect MRI scans of your brain.

All visits can be scheduled for the same day, and in most cases, the same location, if more convenient.

Every two years, you will come back to ASU and BNI to repeat the cognitive testing and have another MRI scan. These visits will last about 5 hours total.

How many people will be studied?

We expect about 280 adults will participate in this research study, including 140 adults with ASD and 140 Non-ASD, neuro-typical adults.

What happens if I say yes, I want to be in this research?

You are free to decide whether or not you wish to participate in this study and complete the study procedures described below. If you choose not to participate in this study, it will not affect your treatment at ASU, SARRC, or BNI, nor will it influence the professionals who work with you.

If you choose to participate in this study, you will be asked to undergo the procedures described and outlined below:

Visit*	**First Visit**			**2-year Follow-Up Visits**	
Study Procedures	• Diagnostic interview for adults in ASD group	• Cognitive testing • Self-report questionnaires • Informant-report questionnaires (optional) • Saliva sample (optional)	• MRI	• Cognitive testing • Self-report questionnaires • Informant-report questionnaires (optional)	• MRI
Visit Duration	2 hours	3 hours	2 hours	2 ½ hours	1 ½ hours
Visit Location	SARRC	ASU	BNI	ASU	BNI

* Visit procedures may be scheduled for the same day and, in some case, at the same location for your convenience.

Screening Procedures: You will be asked interview questions using standardized questionnaires to confirm a diagnosis of ASD (Autism Diagnostic Observation Schedule; Social Responsiveness Scale-2) or, if you are in the Non-ASD group, to make sure you do not meet ASD diagnosis criteria (Social Responsiveness Scale-2). These are simple and general questions about your current and past behaviors, like employment, social relationships, etc. You will also be given a test to understand your basic thinking skills (Kaufman Brief Intelligence Test-II). These assessments will only be done during the first time you come for the study.

Cognitive Testing: You will undergo cognitive testing, usually paper-and-pencil tasks or answering questions, which assess thinking abilities like memory, attention, and visual abilities. This will take about 2 ½ hours. These tasks will be done the first time you come for the study and then again during the follow-up visits.

Self-Report Questionnaires: You will be asked to complete questionnaires assessing things like mood, anxiety, social network, and quality of life. This will take about 20 minutes to complete. These

questionnaires will be done the first time you come for the study and then again during the follow-up visits.

Optional Informant-Report Questionnaires: If you are willing, we would like for you to ask someone who knows you well to fill out questionnaires regarding your symptoms. These additional questionnaires will help us to better understand the different ways adults experience ASD. Having an informant report is optional and you may still participate in the study even if you choose not to identify an informant. In some cases, an informant may be present with you during your visit and can complete the measures during the visit. Alternatively, you can give the informant report questionnaires to someone at a later time to be returned in a pre-addressed envelope. These questionnaires will be offered the first time you come for the study and then again during the follow-up visits.

MRI Exam: An MRI helps us look at the brain. The full name for an MRI is magnetic resonance imaging. An MRI allows us to see parts of the brain that are difficult to see otherwise. MRI uses a magnetic field and radio waves to make pictures of the brain tissue, neither of which are painful or harmful to people. There are no injections or radiation used in this MRI procedure. You will lie on a table that will be moved into a donut-shaped magnet (like a tunnel). When the imaging starts, you will hear a thumping sound, which is made by the movement of the magnetic fields but is not harmful.

Using the MRI, we will take detailed, high quality pictures of your brain. We will also take pictures that measure changes in blood flow to different parts of your brain while you perform thinking tasks. This is called functional MRI. The special techniques used for functional MRI are not yet used for clinical diagnosis or other clinical uses and are primarily for the purposes of research, as in this study.

You will wear goggles to see the tasks we will ask you to do while you are in the MRI scanner. These tasks will be explained to you in detail. During each scan it is very important for you to stay as still as possible to keep from blurring the images. Foam padding may be used to help you keep your head still during the scan. The amount of time you will spend in the MRI scanner is about 1 hour. The MRI will be done the first time you come for the study and then again during the follow-up visits.

Optional saliva sample: A small amount of saliva will be collected to be used for two possible purposes. You will choose how your sample will be used. The first purpose is a genetic test (called "apolipoprotein E or APOE") to be used for THIS study. Some studies have suggested that APOE may be related to memory problems or other cognitive problems as we age. There is no evidence that APOE can be important in diagnosing neurological diseases. Given the previous research on APOE, we are interested to know if there is an association between APOE and aging with ASD. Because APOE is not used for regular medical care, you will not be told the results of the test. The test results will not be put in your medical record either. The second purpose is to store the sample for future, currently unspecified research. If, for example, an important discovery is made two years from now that will help us to better understand memory problems or other cognitive problems in aging, your sample might be used for such a study. Alternatively, it may never be used for any research again. You may still participate in the study even if you choose not to provide a saliva sample.

What happens if I say yes, but I change my mind later?

Your participation in this research study is voluntary and you are free to withdraw from this study at any time and we will not hold it against you. If you decide you no longer want to participate, please email or call Dr. Braden and the ABA Lab to let them know of your decision.

Is there any way being in this study could be bad for me?

Screening and cognitive assessments, and fMRI task:

These tests are not dangerous, but may be mildly stressful. The cognitive assessments ask questions regarding your thinking abilities which can be mildly tiring for people.

Self-report questionnaires:

The mood assessment questionnaires ask questions regarding feelings of depression and anxiety, which can be mildly upsetting for some people. You may leave specific questions blank that cause you to become too upset or anxious.

MRI:

Metal - Although MRI has no known harmful effects, there are certain situations where an MRI would not be safe. As part of the screening process we will ask you safety questions to make sure you are safe to be scanned. Metal objects within the body such as pacemakers, aneurysm clips, other metallic implants, or shrapnel may be affected by the magnetic field. If you have metal within your body or in your eyes, this study may not be safe for you; please discuss this with Dr. Braden or someone on the research team. Metal objects in your pockets or elsewhere on your body will need to be removed before you enter the scanning room. They may create a safety hazard in the powerful magnetic field.

Claustrophobia – The MRI tube is a small space and may cause a feeling of claustrophobia or increased anxiety. If this is difficult for you, let the researchers know and you can stop participating in the study immediately. The scan operator will help you out of the scanner.

Loud noises – The MRI scanner makes a lot of noise when it is taking pictures. This is not dangerous, nor will not cause any damage to your ears, but may be uncomfortable. You will be wearing earplugs and headphones to decrease the noise.

Reproductive risks - MRI has no known effects on pregnancy or fertility. However, since we are not 100% sure MRI has no effects on a developing fetus, women who are pregnant may not participate in this study. You must state that to the best of your knowledge, you are not now pregnant.

Genetic Testing:

Genetic test results may create risks for you. The results may cause you to become emotionally upset, affect insurance, influence job discrimination, and/or create family conflicts from learning unknown information about your parents or blood relatives. To protect you from these risks, these results will only be used for research purposes and will not be entered into the medical record or given to you or family members. In addition, the samples and results will only be labeled with a subject ID code and will not contain any of your identifiable information.

Will being in this study help me in any way?

We cannot promise any benefits to you or others from your taking part in this research. However, participants may gain a better understanding of their own ASD symptoms, cognitive strengths and weaknesses, and depressive and anxious symptoms while completing the tests and questionnaires. Participants may also appreciate receiving an image of their brain from the MRI.

Is there compensation for participating?

If you complete all study requirements during the initial study visits, including the cognitive testing, questionnaires, and MRI, you will be compensated (paid) $100. If you complete all study requirements in future two year follow-up visits, you will again be compensated with another $100 at each follow-up.

If you will be receiving payments from ASU in addition to the compensation for this study (e.g. compensation for other studies, employee, independent contractor) that when combined meet or exceed

$600 in a calendar year, ASU is subject to tax reporting requirements for these payments. In this case, any personal information (e.g. name, mailing address, SSN, tax ID) collected to process your compensation will be safeguarded and only used for mandatory reporting purposes. You may choose to waive compensation if it will increase your payment total from ASU above $600 and you do not wish to provide identifying information for tax reporting purposes. Please let us know if you have any questions about the ASU human subject payment policies.

How will I be informed of additional information or new findings

If you decide to participate, we will tell you of any new scientific findings during this study. The MRI pictures we take are not the same as those that are taken for clinical purposes; however, a neuroradiologist at Barrow Neurological Institute will look at the pictures. If anything is found that requires follow-up with a physician, Dr. Braden will contact you and tell you to contact your physician.

What happens to the information collected for the research?

Efforts will be made to limit the use and disclosure of your personal information, including research study records, to people who have a need to review this information. We cannot promise complete secrecy. The research team, authorized ASU personnel, and regulatory entities such as the Office of Human Research Protections (OHRP) may have access to your study records to protect your safety and welfare. Any information derived from this research project that personally identifies you will not be voluntarily released or disclosed by these entities without your separate consent, except as specifically required by law. Research records provided to authorized, non-ASU entities will not contain identifiable information about you. Publications and/or presentations that result from this study will not include identifiable information about you.

All electronic data will be stored on a secure server at Arizona State University. All other data will be stored in locked cabinets in a locked lab at Arizona State University. If you choose to provide a saliva sample, your sample will be stored safely in locked cabinets at the Autism and Brain Aging Laboratory at Arizona State University. Access to all data will be limited to approved research staff. Data analysis will be conducted on de-identified datasets with all identifiable information removed. De-identified datasets may be shared and the researchers intend to keep these datasets indefinitely.

Optional Data Sharing

ASD is a complex disorder. One way to facilitate scientific discoveries related to ASD is for researchers to share data. If you are willing, we would like to be able to share your data with other researchers through data exchanges like the Autism Brain Imaging Data Exchange (ABIDE) and the National Database for Autism Research. Your data will be completely anonymous, with no protected health information included.

You have the right to refuse to allow your data to be shared. You will not be able to withdraw your data once it has been shared because your data will receive a new anonymous code and we will no longer know which data is yours.

Please indicate if you would like to participate in the optional data sharing:

☐ Yes, my data may be shared with other researchers to facilitate scientific discoveries related to ASD.

Who can I talk to?

If you have questions, concerns, or complaints now or at any time during your participation in the study, please talk to the research team. You may contact Dr. B Blair Braden and the Autism Brain Aging Laboratory at Arizona State University at (480)727-3970, abalab@asu.edu, 975 S. Myrtle Ave. Tempe, Arizona 85287-0102.

This research has been reviewed and approved by the Social Behavioral IRB. You may talk to them at (480) 965-6788 or by email at research.integrity@asu.edu if:

- Your questions, concerns, or complaints are not being answered by the research team.
- You cannot reach the research team.
- You want to talk to someone besides the research team.
- You have questions about your rights as a research participant.
- You want to get information or provide input about this research.

Are you interested in providing the optional saliva sample?

As noted above, you will have the option of providing a small sample of your saliva and you may choose how your sample is used. You can participate in the cognitive testing and MRI parts of the study without participating in the saliva collection.

- Your sample will be labeled with a subject ID code (rather than your name).
- Your sample will be stored safely at the Autism and Brain Aging Laboratory at ASU.
- There will be no cost to you for any tissue collected or analyzed.
- Your sample will only be used for research and will not be sold.
- Some of the future studies may or may not be for testing the genes that you inherited from your parents (also known as genetic testing).
- There is a very small chance that some commercial value may result from the use of your saliva sample. If that would happen, you agree that you or your family will not share in any potential profits.
- To protect you from the risks of genetic testing, results will only be used for this research study and will not be entered into the medical record or given to you or family members.

Please select how you would like your sample used by checking ALL boxes below that apply:

☐ Yes, my saliva sample may be used in THIS research study to learn about a risk factor for cognitive problems.

☐ Yes, my saliva sample may be stored and used in future research studies.

If you want your biospecimen and genetic testing destroyed at any time, please contact to Dr. Braden and the ABA Lab. We have the right to end storage of your sample and genetic testing without telling you. If you move, please send us your new address.

Are you interested in learning about future studies?

If you are interested in being contacted in the future to learn about new studies that may be suitable for you, please mark the appropriate box(es) below. There is no obligation to actually participate in any study you may be contacted about.

☐ Yes, please contact me for future studies and store my contact information in a confidential manner.

☐ Yes, please share my contact information with other researchers who have currently approved IRBs for studies investigating aging or autism.

You are voluntarily deciding whether or not to participate in the research study described in this consent form. Your signature below indicates that you have read and understand the information provided, and that you have decided to participate. You will receive a copy of the signed informed consent document.

Signature of participant	Date
Printed name of participant	

Investigator Statement:

I attest that I, or my representative, discussed this study with the above named participant. This person had enough time to consider this information, had an opportunity to ask questions, and voluntarily agreed to participate in this study.

Signature of person obtaining consent	Date
Printed name of person obtaining consent	