Characterizing Brain Aging Trajectories in Older Adults with Autism Spectrum Disorder using a Novel Graph Theory Measure

by

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ABSTRACT

Little is known about how cognitive and brain aging patterns differ in older adults with autism spectrum disorder (ASD). However, recent evidence suggests that individuals with ASD may be at greater risk of pathological aging conditions than their neurotypical (NT) counterparts. A growing body of research indicates that older adults with ASD may experience accelerated cognitive decline and neurodegeneration as they age, although studies are limited by their cross-sectional design in a population with strong age-cohort effects. Studying aging in ASD and identifying biomarkers to predict atypical aging is important because the population of older individuals with ASD is growing. Understanding the unique challenges faced as autistic adults age is necessary to develop treatments to improve quality of life and preserve independence.

In this study, a longitudinal design was used to characterize cognitive and brain aging trajectories in ASD as a function of autistic trait severity. Principal components analysis (PCA) was used to derive a cognitive metric that best explains performance variability on tasks measuring memory ability and executive function. The slope of the integrated persistent feature (SIP) was used to quantify functional connectivity; the SIP is a novel, threshold-free graph theory metric which summarizes the speed of information diffusion in the brain. Longitudinal mixed models were using to predict cognitive and brain aging trajectories (measured via the SIP) as a function of autistic trait severity, sex, and their interaction. The sensitivity of the SIP was also compared with traditional graph theory metrics. It was hypothesized that older adults with ASD would experience accelerated cognitive and brain aging and furthermore, age-related changes in brain network topology would predict age-related changes in cognitive performance.

For both cognitive and brain aging, autistic traits and sex interacted to predict trajectories, such that older men with high autistic traits were most at risk for poorer outcomes. In men with autism, variability in SIP scores across time points trended toward predicting cognitive aging trajectories. Findings also suggested that autistic traits are more sensitive to differences in brain aging than diagnostic group and that the SIP is more sensitive to brain aging trajectories than other graph theory metrics. However, further research is required to determine how physiological biomarkers such as the SIP are associated with cognitive outcomes.

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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 conflict of interest related to this research.

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CHAPTER 1

INTRODUCTION

Aging in Autism Spectrum Disorder:

Aging is understudied in autism spectrum disorder (ASD), but emerging evidence suggests that older adults with ASD may be at increased risk for poorer aging outcomes and greater pathological aging. For example, a recent study found that people with ASD are at higher risk for early-onset dementia (Vivanti et al., 2021) as well as other neurodegenerative conditions including Parkinson's disease (Croen et al., 2015; Kern et al., 2013). After adjusting for other risk factors, individuals with ASD were found to have a higher prevalence of dementia compared with the general population, and individuals under age 65 were approximately 2.6 times more likely to be diagnosed with dementia (Vivanti et al., 2021). In general, cognitive aging research in ASD has shown mixed findings with some studies suggesting better, parallel, or worse cognitive aging in ASD (Davids et al., 2016; Geurts et al., 2020; Geurts and Vissers, 2012; Powell, Klinger, and Klinger, 2017; Tse et al., 2019; Abbott, Happé, and Charlton, 2018; Lever and Geurts, 2016; Lever et al., 2015). The discrepancies in these studies may be due to the cross-sectional nature of existing research, which may be confounded by cohort effects (Parner, Schendel, and Thorsen, 2008). Finally, growing evidence in ASD (Stewart, Charlton, and Wallace, 2018; Stewart et al., 2020; Stewart et al., 2021) and the general population (Mason et al., 2021) suggests that higher autistic traits are associated with poorer aging outcomes. Early identification and treatment for age-related neurodegenerative conditions is associated with optimal outcomes (Dubois et al., 2016; Solomon and Murphy, 2005; Boustani et al., 2003). Given that changes in the brain often precede behavioral changes

observed in aging (Benussi et al., 2019), identification of biomarkers predicting atypical aging in ASD will provide a foundation for sample selection in clinical trials or serve as potential prognostic markers in treatment studies. However, there is limited research to date addressing atypical brain aging in ASD and no studies have used longitudinal designs (Mason et al., 2022), which is the gold standard in aging research.

Age-related Pathology in ASD

Although there is evidence of increased rates of neurodegeneration in ASD, it is unclear whether ASD might lead to neurodegeneration or if they are part of two separate but comorbid pathways (Kern et al., 2013). Recent evidence suggests that genetic factors may contribute to shared cellular and molecular pathways among neurodevelopmental and neurodegenerative disorders, and neurodevelopmental disorders such as ASD may contribute to an increased risk of neurodegenerative disease later in life (Hickman et al., 2022). Several genes have been proposed in which mutations may contribute to ASD, Alzheimer's disease (AD), and intellectual disability (ID; Ivashko-Pachima et al., 2021). These findings highlight that genes involved in autism may also contribute to neurodegenerative risk later in life, although further studies are needed to characterize aging in ASD and risk factors for cognitive decline and neurodegeneration.

Cognitive Aging in ASD

Other studies have examined cognitive performance and aging in older adults with ASD, given that cognitive declines are a hallmark of normal aging and pathological aging conditions (Bisiacchi et al., 2008; Craik, 2008). However, findings of cross-sectional aging studies in ASD are likely confounded by strong age cohort effects in ASD (Parner. Schendel, and Thorsen, 2008). Findings from several studies examining group

differences indicate that older adults with ASD experience greater cognitive challenges than NT adults in executive function abilities and the time needed to complete daily tasks (Davids et al., 2016; Geurts et al., 2020; Braden et al., 2017). As a group, older adults with ASD also show greater difficulties in attention, working memory, and fluency, but some cross-sectional analyses of age associations suggest steeper cognitive decline with age in NT adults than adults with ASD (Geurts and Vissers, 2012). Conversely, another cross-sectional study found that adults with ASD have greater age-associated deficits in free recall ability and slower processing speeds in both cognitive and motor tasks (Powell, Klinger, and Klinger, 2017). Other cross-sectional studies suggest that adults with ASD have similar or improved cognitive aging outcomes compared with their NT counterparts on tasks involving speed and sequencing (Abbott, Happé, and Charlton, 2018). A group comparison found that adults with ASD scored higher on visual memory tests than NT adults and similarly on verbal memory tests, although they scored lower on generativity and theory of mind measures (Lever and Geurts, 2016). Differences in age trajectories were only observed in visual memory, where a steeper decline in recognition and recall was observed in NT adults compared to adults with ASD (Lever and Geurts, 2016). Similarly, a cross-sectional study on working memory in older adults with ASD reported similar performance between adults with ASD and NT adults, and the results suggested declining working memory ability with age in the NT group but not the ASD group (Lever et al., 2015). In summary, there remains little consensus regarding cognitive aging risk in ASD, and longitudinal designs are needed to control for confounding variables including cohort effects and individual differences.

Aging and Elevated Autistic Traits

A growing body of evidence suggests that elevated autistic traits are associated with poorer aging outcomes, both in ASD and in the general population. A longitudinal study found that higher self-reported autistic traits correlate with a faster aging pace, older facial age, and poorer health as rated by informants, interviewers, and participants themselves (Mason et al, 2021). In a study examining group differences, older adults were grouped by the Broad Autism Phenotype questionnaire as having either low or high levels of autistic traits, and participants with elevated autistic traits performed more poorly on three executive function metrics and an episodic memory test (Stewart et al., 2018). This group also reported poorer executive abilities in everyday life and higher rates of depression and anxiety (Stewart et al., 2018). The authors hypothesized that autistic traits are associated with a higher risk of cognitive decline in aging in both adults with ASD and NT adults (Stewart et al., 2018). A study examining group differences found that older adults with elevated autistic traits have more difficulty with falling asleep, morning drowsiness, and lower sleep quality than the control group (Stewart et al., 2020). A similar study comparing group differences found that older adults with elevated autistic traits have increased rates of psychiatric diagnoses and more self-reported symptoms of anxiety and depression than the control group (Stewart et al., 2021). These studies suggest that the effects of ASD-related genetics and biology on aging may occur on a dimensional scale, where higher severity is linked to worse aging outcomes. Thus, the common paradigm examining diagnostic differences and age-related trajectories may be less sensitive to atypical aging features of ASD, and further

longitudinal work is warranted to determine how elevated autistic traits predict aging trajectories in autistic and non-autistic individuals.

Brain Aging in ASD

Several recent studies have used cross-sectional designs to estimate brain aging trajectories in ASD with growing evidence suggesting patterns of exacerbated brain aging in ASD. Studies examining group differences in the brains of older adults with and without ASD generally suggest persistent atypical features, especially in circuits supporting memory (Braden et al., 2017; Koolschijn et al., 2017; Linke et al., 2020). However, only a few studies have examined atypical age-related brain patterns in ASD, all of which have been cross-sectional. For example, a study that utilized diffusion tensor imaging (DTI) to measure white matter integrity found that adults with ASD had greater age-related mean diffusivity and radial diffusivity in white matter tracts than NT adults, suggesting poorer white matter microstructural integrity (Koolschijn at el., 2017). Adults with ASD have a more negative correlation between age and cortical thickness than NT adults (Braden and Riecken, 2019). In another study, our group examined age-group differences in the executive network, with findings suggesting exacerbated declines in network functional connectivity in older adults with ASD relative to NT adults (Walsh et al., 2019). Furthermore, lower functional connectivity in this network was linked to higher autistic traits in older men with ASD, suggesting dimensional sensitivity of autistic traits to detecting atypical brain aging patterns (Walsh et al., 2019). In contrast, less age-related decline was observed in visual network connectivity in adults with ASD, and this finding was supported by attenuated increase in reaction time in older adults with ASD compared with NT adults (Bathelt, Koolschijn, and Geurts, 2020). Besides

variations of MRI analysis, electroencephalography (EEG) has also been used to analyze differences in brain connectivity. A study that examined oscillatory slowing, an indicator of neurophysiological aging, suggested that the brain's peak alpha frequency decreased with age at an increased rate in adults with ASD than NT adults (Dickinson, Jeste, and Milne, 2022). Together, research to date suggests exacerbated brain aging trajectories in ASD, although no studies have used gold-standard longitudinal designs to compare aging trajectories in ASD.

Biomarker Research in Aging and ASD

Resting-state functional connectivity (rs-fMRI) approaches are promising for understanding and informing treatment of neuropsychiatric disease and aging (Fox et al., 2014). However, few studies to date have used rs-fMRI to characterize atypical brain aging trajectories in ASD. One notable study used principal components analysis to derive a graph theory metric based on rs-fMRI to predict aging trajectories in ASD (Ball, Beare, and Seal, 2017). In particular, graph theoretical measures have shown promise as biomarkers in aging research (Kuang et al., 2019; Behfar et al., 2020; Brier et al., 2014; delEtoile and Adeli, 2017). Graph theory is a method of analyzing MRI data to quantify and compare brain network communication features. One challenge in neuroimaging biomarker research is the stringent statistical correction required for whole-brain investigations. Graph theoretical approaches can reduce statistical tests by quantifying network topology features at regional, network, or even the whole brain-level with a single value. For example, instead of comparing group differences in longitudinal trajectories for every voxel or selected regions of the brain, a single value can be produced for each participant to quantify whole-brain communication features, thus

reducing or eliminating multiple comparisons. However, a second challenge associated with graph theory approaches, and generally in rs-fMRI research, is the arbitrary selection of thresholding values to produce subject-level connectivity matrices that are then subject to topological investigation (van den Heuvel et al., 2017). Thresholding makes it difficult to compare findings between studies because the threshold values are subjective and vary based on the study (Chung et al., 2015; Choi et al., 2014; Lee at al., 2017). The Integrated Persistent Feature (IPF) is a metric that eliminates the need for thresholding. When the IPF is plotted across different network states, the slope of the IPF (SIP) is a threshold-free metric which represents the rate of information diffusion, or the speed to fully connect a network (Kuang et al., 2019). The SIP is a promising metric because it summarizes the whole brain with one value, and it has previously shown sensitivity to group differences in Alzheimer's disease, mild cognitive impairment, and healthy participants (Kuang et al., 2019). Thus, novel graph theoretical approaches to quantify functional brain network topology may be promising for biomarker research of aging in ASD.

Sex Differences in Brain Aging:

Research examining sex differences in ASD is lacking, but preliminary evidence suggests that there are sex differences in ASD lifespan brain development (Walsh et al., 2021). One study suggests age-by-sex-by-diagnosis differences in the (cross-sectionally estimated) slope of functional connectivity changes across diffuse brain networks (Kozhemiako et al., 2019). They found similar aging patterns among NT males, ASD males, and ASD females compared with NT females. The authors hypothesized that ASD may follow a "typical male" developmental pattern (Kozhemiako et al., 2019). The same

group later reported that females with ASD have more distinct developmental trajectories of local functional connectivity than other groups, which they concluded to support the female protective effect hypothesis (Kozhemiako et al., 2020). Importantly, a graph theory study examining functional connectivity reported an age-by-sex-by-diagnosis interaction that approached significance for modularity (Henry, Dichter, and Gates, 2018), which measures communication between communities within a network (Sporns and Betzel, 2016). They found that while NT females had quadratic aging trajectories and NT males had flatter aging trajectories, both male and females with ASD had negative quadratic trajectories (Henry, Dichter, and Gates, 2018). Overall, studies examining sex differences in cross-sectionally estimated age trajectories, albeit in younger groups, suggest that sex and ASD may interact to produce distinct neurodevelopmental and aging trajectories in males vs. females with ASD. Thus, sex is a critical variable to consider in brain aging studies in ASD.

Present Study:

The goal of this study is to use a longitudinal design to characterize cognitive and brain aging trajectories in ASD as a function of either diagnosis or autistic trait severity. First, to reduce multiple comparisons, we will use principal components analysis (PCA) to derive a single cognitive component metric explaining maximal variability in performance on a comprehensive cognitive battery of memory and executive functioning. We will examine how autistic traits, sex, or the interaction of sex and autistic traits predict longitudinal aging trajectories for this cognitive component. Then, we will explore the ability of a novel graph theoretical metric, the SIP, to predict distinct trajectories as a function of autistic traits, sex, and the interaction of sex and autistic traits

in a sample of ASD and NT adults. We will further compare the sensitivity of the SIP to traditional graph theory metrics (Betti number plot [BNP], characteristic path length [CPL], network diameter [ND], Eigenvector centrality [EC], and modularity [MOD]) to characterize atypical brain aging trajectories in ASD. We will also validate that autistic trait severity shows more sensitivity to atypical aging trajectories than diagnosis in an analysis of diagnosis, sex, and sex-by-diagnosis differences in cognitive and SIP trajectories. Finally, we will confirm links between brain trajectories and changes in cognitive ability over time, as summarized by the PCA component. We hypothesize that higher ASD trait severity will predict poorer cognitive and brain aging outcomes in men with ASD. Furthermore, we expect that the SIP will show greater sensitivity than the other graph theory metrics to atypical brain aging trajectories in ASD. Finally, we predict that changes in brain network topology with age will predict changes in cognitive performance with age in men with ASD.

CHAPTER 2

METHODS

Participants

Participants for this study with ASD were recruited through the Southwest Autism Research and Resource Center (SARRC) and with flyers posted throughout the community. NT participants were recruited through flyers and via word of mouth. Participants with ASD had their diagnoses confirmed at SARRC by a psychometrist with the Autism Diagnostic Observation Schedule-2 (ADOS-2; Lord et al., 2012) to determine if DSM-V criteria for an ASD diagnosis was met. Participants in either group with a score <70 on the Kaufman Brief Intelligence Test – 2nd Edition (KBIT-2) and scores <26 on the Mini Mental State Exam (MMSE) were excluded from the study (Kaufman and Kaufman, 2004; Folstein, Folstein, and McHugh, 1975). NT participants were excluded if they had any suspected or confirmed ASD diagnosis, t-scores > 66 on the Social Responsiveness Scale – 2 Adult Self Report (SRS-2), or if they had a first-degree relative with a confirmed ASD diagnosis (Constantino, 2012). Participants in either group were also excluded if they had a history of neurological disorders or a head injury which resulted in loss of consciousness. Participants who had one childhood seizure but who are not taking anti-seizure medication and have not had any seizures in adulthood were not excluded, because children with ASD have a high frequency of seizures (Theoharides and Zhang, 2011). Participants were tested at baseline and at 2-, 4-, and 6-year follow-up visits.

Quantifying Symptom Severity

Self-reported ASD traits were measured with the Social Responsiveness Scale-2nd Edition Adult Self-Report (SRS-2A; Constantino, 2012). The SRS-2A consists of 65 questions regarding social behaviors related to ASD. The scale reports both a summary T-score and subscale scores, which include Social Awareness (8 items), Social Cognition (12 items), Social Communication (22 items), Social Motivation (11 items), and Restricted Interests/Repetitive Behaviors (12 items). Total T scores are grouped by their reflection of ASD-related behaviors as follows: Mild (60-66), Moderate (67-75), and Severe (76+). Scores of 59 or below indicate minimal to no reported ASD-related behaviors. Total raw scores were used for the analysis.

Cognition

Given that little is known about cognitive aging in ASD to derive hypotheses about cognitive domains most vulnerable to aging, we used principal components analysis on measures from a comprehensive cognitive battery. PCA derives a single measure of cognitive performance that explains maximum variability in this sample. In brief, measures included in the PCA analysis included: 1) Wisconsin Card Sorting Task (WCST) Perseverative Errors, 2) Rey Auditory Verbal Learning Task Short Term (AVLT A1) and Long-Term (AVLT A7) verbal memory scores, 3) Wechsler Memory Test Visual Reproduction Task Short Term (WMS-VR-I) and Long Term (WMS-VR-II) scores, 4) Tower of London total correct, 5) Trails A and B total time, and 6) Stroop interference scores. SPSS 26 was used to generate the cognitive component; PCA was implemented using maximum likelihood estimation with 100 iterations. While the top component was of primary interest as it explains maximum variability in the sample's

cognitive performance, a second component with an eigenvalue greater than one was also produced and examined in an exploratory manner in subsequent longitudinal analyses.

Data Acquisition

A 3-Tesla Philips Ingenia MRI scanner was used for all of the scans, and the maximum gradient strength was 5 mT/m. A three-dimensional magnetization prepared rapid acquisition graduate echo (MPRAGE) was used to acquire the T1 weighted structural images (170 axial slices, 1.2 mm thickness, 240mm FOV, 256x256 acquisition matrix). A gradient-echo echo-planar series with whole brain coverage was used to obtain resting state images (TR=3s, echo time=25ms, flip angle=80°, 3mm slices, 24mm FOV, 64x64 acquisition matrix). Participants had the opportunity to visit the scanner before their scans in an attempt to reduce any stress or anxiety related to the MRI process. They were also provided with ear plugs, head phones, and padding to make the scanner more comfortable and to minimize motion. The participants were instructed to lay in the scanner with their eyes closed for six minutes (120 volumes) and to "clear their mind."

Image Pre-Processing

Statistical Parametric Mapping software (SPM-12) was used to preprocess the resting-state data in MATLAB (Wellcome Department of Cognitive Neurology, Institute of Neurology, London, UK; fil.ion.ucl.ac.uk/spm/; Mathworks, Natick, MA). The structural T1 images were preprocessed with image segmentation and skull-stripping. For rs-fMRI images, Wavelet Despiking was done with the BrainWavelet toolkit (Patel et al., 2014). The next steps were functional image realignment, anatomical image segmentation, skull-stripping, functional image co-registration, and DARTEL normalization to the MNI space with 8mm FWHM smoothing. Functional outliers were

removed at a 0.5 mm framewise displacement threshold. A CompCor confound regression was conducted, including realignment parameters/first order derivatives, scrubbing, linear detrending, and bandpass filtering [.008 .1]. The images were visually inspected after preprocessing for quality assurance. Then, Data Processing Assistant for Resting State fMRI (DPARSF; Chao-Gan and Yu-Feng, 2010) was used to extract denoised timecourses for 116 regions of interest based on the automated anatomical labelling atlas (AAL; Tzourio-Mazoyer et al., 2002).

Graph Theory Metric Calculations

Graph theoretical analysis of rs-fMRI images is an approach where the brain is represented by networks in a mathematical graph. The graph is made up of intersections (nodes) and edges between regions. The elements of the matrix are composed of coefficients representing the functional communication between regions (Medaglia, 2017). However, it is common to threshold graphs by choosing the strength of edges that form the graph where the network organization is evaluated (van den Heuvel et al., 2017). The Integrated Persistent Feature (IPF) is a metric that eliminates the need for thresholding. It is derived from the zeroth Betti number and the Connected Component Aggregation Cost. The zeroth Betti number is a homology-based topological feature (Kuang et al., 2019). Persistent homology quantifies topological features for a given state of a network, but it does not give information about future states of the network. The Connected Component Aggregation Cost measures the energy that would be required to fully connect a network from its current state. When the IPF is plotted across different network states, the slope (SIP) is a threshold-free metric which represents changes in network connectivity (Kuang et al., 2019). The SIP is a decreasing convergence function,

and a steeper negative slope can be interpreted as more efficient information diffusion in a network.

Methodology from Kuang et al. (2019) was replicated to construct networks and calculate the IPF at each network scale filtration value. In summary, the mean time series of ROIs were extracted for AAL regions, and the observed distance matrix was calculated through Pearson correlation. Single linkage dendrogram was used to obtain the predicted distance matrix. The single linkage distance matrix was used to construct a multiscale resting state network (RSN) for each subject, and the IPF was plotted against different filtration values. The slope of the IPF (SIP) was calculated for each participant.

Traditional graph theory metrics include Betti Number Plots (BNP), Characteristic Path Length (CPL), Network Diameter (ND), Eigenvector Centrality (EC), and Modularity (Mod) (De Silva and Ghrist, 2007; Watts and Strogatz, 1998; Assenov et al., 2008; Lohmann et al., 2010; Sporns and Betzel, 2016). These metrics were also calculated using the Brain Connectivity Toolbox for the purpose of comparing their sensitivity with the SIP (Rubinov and Sporns, 2010). BNPs quantify how the number of connected components varies throughout different filtration values, or spatial states. CPL measures the efficiency of information transfer throughout a network, and it is the average shortest distance between all nodal pairs (Rubinov and Sporns, 2010). Lower CPL values are associated with more efficient information transfer. The ND measures network size by calculating the distance between the farthest paired nodes in a network (Assenov at al., 2008). Mod measures communication between communities within a network (Sporns and Betzel, 2016). A high Mod value indicates high communication within a region but low communication between regions. EC assigns each node a value

based on the number of other nodes it is connected to, so a node that is highly connected has a greater weight (Lohmann et al., 2010).

Longitudinal Analyses

Longitudinal analyses examined the influence of autistic traits, sex, and the interaction of sex and autistic traits on cognitive and brain aging. We also explored the same models, but instead investigated diagnosis group effects rather than autistic traits for a comparison of sensitivity (e.g., autistic traits vs. diagnosis). All longitudinal modeling was conducted in SAS 9.4 using proc mixed. For cognitive variables, our primary dependent measure was the first PCA-derived component, which loaded strongly and positively onto memory variables. However, we explored longitudinal trajectories for all components with an eigenvalue greater than one (which consisted of one other component that loaded more positively onto executive functioning variables). For brain variables, our primary dependent measure of interest was the SIP. However, we also explored longitudinal trajectories for traditional graph theory measures including BNP, CPL, EC, ND, and Mod for a comparison of sensitivity with the SIP. For the primary brain (SIP) and cognitive (PCA component 1) longitudinal analyses, alpha was set at $p=0.05$ without correction. Given the exploratory nature of the other brain/cognitive analyses, alpha was also set at $p=0.05$. Models included the following fixed effects: age, autistic traits, sex, age*autistic traits, age*sex, and age*sex*autistic traits. Continuous predictors were mean-centered and categorical predictors were dummy coded. Using Aikake Information Criterion (AIC) for model selection, we compared the following models separately for the primary dependent measures: 1) fixed effects only, 2) mixed effects with random slopes, 3) mixed effects with random slopes/intercepts. When

random effects were included, an unstructured covariance pattern model was used. The optimal fixed effects covariance pattern model was selected using AIC comparing two parsimonious (autoregressive with and without constrained variances) vs. two unstructured models (unstructured with and without constrained variances). The model of best fit was selected separately for cognitive vs. brain analyses. For exploratory analyses, the same model was used as the corresponding primary cognitive or brain analysis (e.g., fixed vs. mixed and covariance patterns). All models used maximum likelihood estimation. Exploratory post-hoc investigations of significant three-way interactions were conducted for men and women separately to determine the sex group driving significant effects. These models were the same as the full group model, except the sex variable was eliminated from the analysis and restricted maximum likelihood estimation was used to adjust for the smaller sample. Figures were generated using proc sgplot to display predicted SIP values as a function of age, with a gradient legend coloring participants according to autistic trait severity.

We also conducted a post-hoc exploratory investigation of cognitive-brain trajectory associations in the group showing the most vulnerable brain trajectories (men with ASD). For this analysis, we included only men with ASD. The dependent measure in this model was the memory-loading PCA component. Fixed effects included age, subject-mean SIP values, and SIP residuals (from the subject mean) to investigate whether trait or state-level SIP values influenced cognitive performance. Random intercepts and slopes were modeled using an unstructured covariance pattern model. Given the small sample, a simple, parsimonious autoregressive covariance pattern model with constrained variances was used to model repeated measures for fixed effects.

Furthermore, given the small sample, restricted maximum likelihood estimation was used.

CHAPTER 3

RESULTS

Demographics

At 2-year follow-up, there were a total of 70 participants (13 ASD females, 23 ASD males, 14 NT females, 19 NT males). Twenty participants were tested at a 4-year follow-up (1 ASD female, 9 ASD males, 2 NT females, 11 NT males), and 11 participants were tested at a 6-year follow- up (4 ASD males and 7 NT males). The ages of the participants and their follow-up intervals are displayed in Figure 1, and the demographic information for the participants is listed in Table 1. There were no significant differences between groups in terms of age, average interval between visits, MMSE score, KBIT-2 composite score, or the ADOS-2 score. There was a significant difference in the number of visits between males and females ($p=0.001$) because recruitment of female participants began several years after males. As expected, there was also a significant difference in SRS-2 scores between diagnostic groups ($p<0.001$).

Figure 1: Participants' ages and follow-up intervals

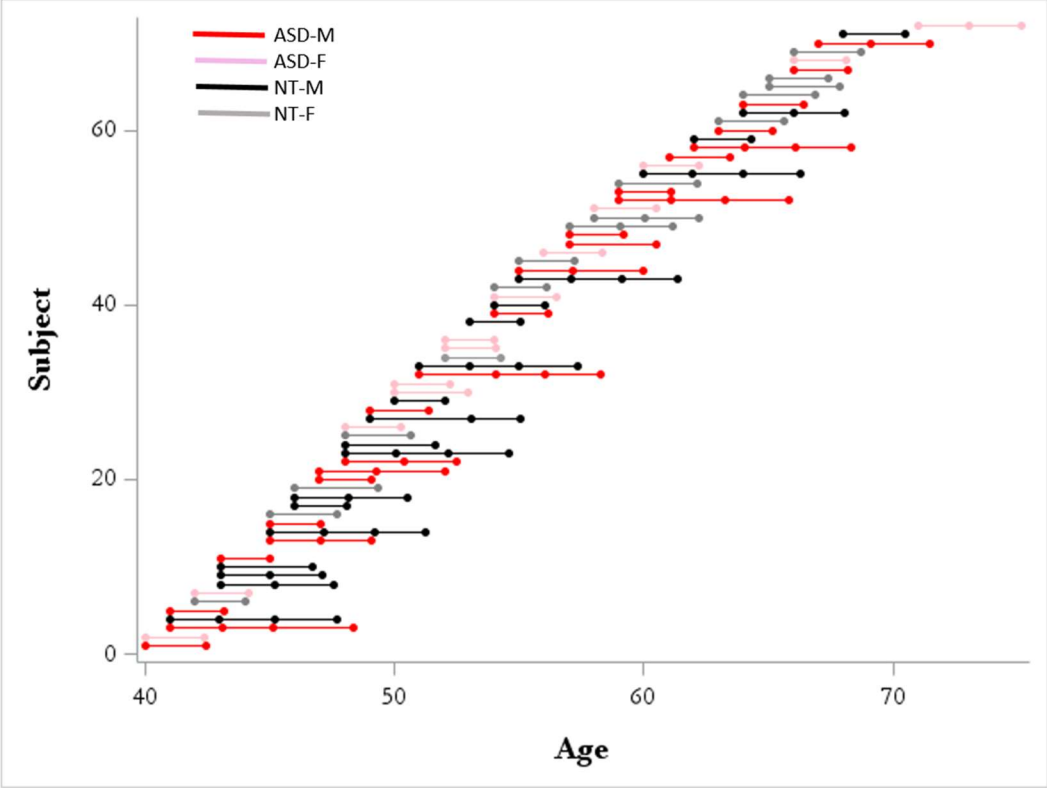

Fig. 1. Participants' ages and follow-up intervals. Each participant is represented by an individual line, and each dot represents one visit.

Table 1: Demographics for participants

	ASD M (n=23) Mean (±SD) Range	ASD F (n=13) Mean (±SD) Range	NT M (n=19) Mean (±SD) Range	NT F (n=14) Mean (±SD) Range	Statistics
Age (baseline, years)	53.09 (±8.64) 40-67	53.77 (±8.68) 40-71	51.00 (±7.78) 41-68	56.21 (±8.20) 42-66	n/a
Average interval (years)	2.31 (±0.35) 1.99-3.48	2.27 (±0.26) 1.97-2.95	2.28 (±0.49) 1.96-4.05	2.50 (±0.43) 2.00-3.35	n/a
Number of visits	2.57 (±0.79) 2-4	2.08 (±0.28) 2-3	2.89 (±0.88) 2-4	2.14 (±0.36) 2-3	Sex: $F_{df}=12.65_{1,66}$ P=0.001
SRS-2	93.90 (±26.76) 56-138	98.15 (±25.45) 44-134	31.44 (±18.16) 7-70	19.79 (±13.10) 3-46	Diagnosis: $F_{df}=166.96_{1,62}$ P<0.001
MMSE	29.30 (±1.02) 26-30	29.23 (±1.01) 27-30	29.26 (±0.99) 26-30	29.64 (±0.63) 28-30	n/a
KBIT-2	112.00 (±14.80) 70-131	108.54 (±11.38) 88-127	113.00 (±12.65) 94-141	109.64 (±12.41) 85-132	n/a
ADOS-2	10.48 (±3.13) 7-19	9.46 (±1.56) 7-13	n/a	n/a	n/a

Table 1. The demographic information for participants. There were no significant differences between groups for age, average interval, Mini Mental State Exam scores (MMSE), Kaufman Brief Intelligence Test- 2nd Edition scores (KBIT-2), or Autism Diagnostic Observation Schedule- 2 scores (ADOS-2). Females had significantly fewer visits than males because the female study began after the male study, and participants with ASD had higher Social Responsiveness Scale- 2 Adult Self Report (SRS-2) scores than NT adults due to the social symptoms associated with ASD.

Cognitive PCA Component Derivation

The first cognitive PCA component loaded most positively onto memory variables (see Table 2). The positive loadings were in the following order: 1) verbal long-term memory (AVLT A7), 2) visual short-term memory (WMS-VR-I), 3) visual long-term memory (WMS-VR-II), 4) verbal short-term memory (AVLT A1), and 5) Tower of London (ToL). The top negative loadings were in the following order: 1) Trails B, 2) Trails A, 3) Wisconsin Card Sorting Task (WCST) Perseverative Errors, and 4) Stroop. This component may be more representative of memory processes. The second PCA component also had an eigenvalue greater than one. This component loaded positively onto most variables, but with the strongest positive loadings ordered as follows: 1) Stroop and 2) Trails A. This component may be more representative of cognitive control/attention and/or processing speed.

Table 2: Cognitive principal components derivations

	Component	
	1	**2**
WCST	-0.403	0.067
AVLT A1	0.595	0.273
AVLT A7	0.795	0.244
WMS-VR-I	0.737	0.302
WMS-VR-II	0.712	0.397
ToL	0.327	-0.056
Trails A	-0.609	0.515
Trails B	-0.717	0.369
Stroop	-0.335	0.709

Table 2. The results from the cognitive principal component derivation. The first component loaded most positively onto memory variables, and the second component loaded most positively onto variables measuring executive function and processing speed. Abbreviations: Wisconsin Card Sorting Task Perseverative Errors (WCST), Rey Auditory Verbal Learning Task Short Term (AVLT A1) and Long-Term (AVLT A7) verbal memory scores, Wechsler Memory Test Visual Reproduction Task Short Term (WMS-VR-I) and Long Term (WMS-VR-II) scores, Tower of London total correct (ToL), Trails A and B total time, and Stroop interference scores.

Cognition: Longitudinal Trajectories

For the memory-loading cognitive component, there was a significant autistic traits-by-sex-by-age interaction. Specifically, greater autistic traits predicted greater cognitive reductions over time, but female sex attenuated this effect (Table 3; Fig. 2). Post-hoc analysis of sex groups separately showed that, for men, autistic traits approached significance for predicting the intercept ($t23.3$=-2.04, p=.052) and slope ($t_{43.1}$=-1.84, p=.072) for the memory-loading PCA component trajectory. Specifically,

higher autistic traits predicted lower intercepts and more negative slopes. For women, autistic traits trended toward predicting the intercept (t_{28}=-1.89, p=.071) but not the slope (t_{28}=0.20, p=.843) of the memory-loading PCA component growth curve, although power was more limited in this group. Higher autistic traits also predicted lower intercepts in women. There were no other significant effects of autistic traits, sex, or lower order interactions. For the cognitive control-loading PCA component, there were no significant effects of any predictor or interaction. There were no significant effects for diagnostic group for either the memory-loading PCA component or the cognitive control-loading PCA component.

Table 3: Memory loading PCA component

Solution for Fixed Effects					
Effect	**Estimate**	**Standard Error**	**DF**	**t Value**	**Pr > |t|**
Intercept	-0.0051	0.17	48.9	-0.03	0.98
Age	-0.027	0.017	103	-1.61	0.11
SRS Baseline	-0.0071	0.0038	50.2	-1.90	0.06
Age x SRS Baseline	0.00038	401	94.5	0.94	0.35
Sex	0.034	0.21	49.7	0.16	0.87
Age by Sex	-0.0040	0.021	111	-0.19	0.85
SRS Baseline by Sex	-0.00038	0.0049	49.8	-0.08	0.94
Age by SRS Baseline by Sex	-0.00096	0.00049	99.4	-1.95	**0.05**

Table 3. The solution for fixed effects analysis of the cognitive memory-loading principal components analysis. There is a significant effect for the interaction between age, autistic traits, and sex.

Figure 2: Age trajectories of memory-loading PCA component

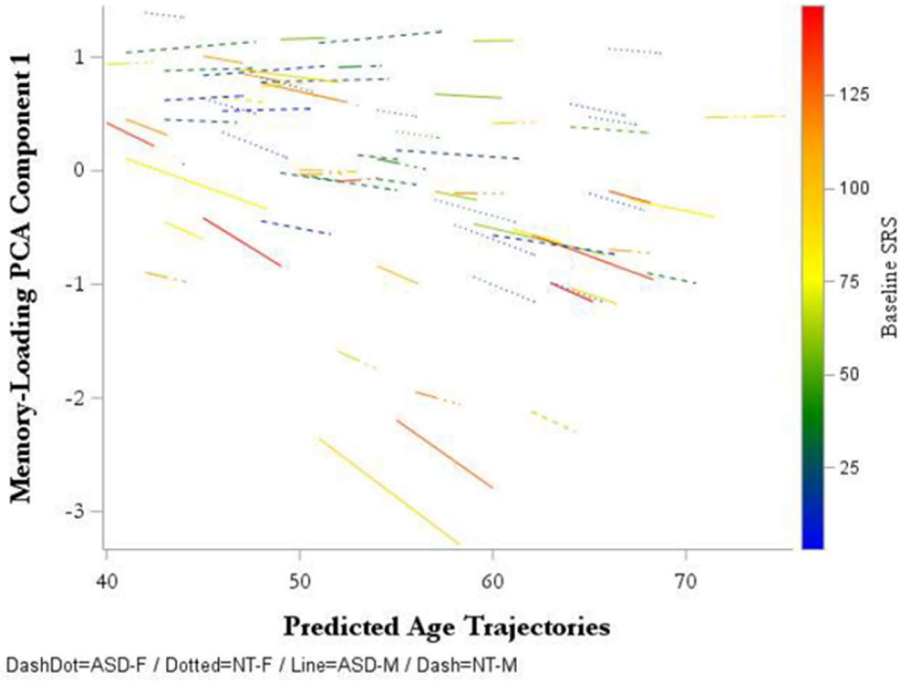

Fig. 2. Predicted age trajectories of the memory-loading PCA component 1 as a function of baseline scores on the Social Responsiveness Scale – 2 Adult Self Report (SRS).

Table 4: Cognitive control-loading PCA component

Solution for Fixed Effects					
Effect	Estimate	Standard Error	DF	t Value	Pr > |t|
Intercept	-0.053	0.16	78.7	-0.34	0.73
Age	-0.0060	0.018	80.3	-0.33	0.74
SRS Baseline	0.0022	0.0036	79.6	0.61	0.54
Age x SRS Baseline	-0.00037	0.00043	82.6	-0.86	0.39
Sex	0.019	0.19	72.2	0.10	0.92
Age by Sex	-0.011	0.022	76	-0.49	0.62
SRS Baseline by Sex	-0.0010	0.0044	71.8	-0.24	0.81
Age by SRS Baseline by Sex	0.00043	0.00051	74.6	0.85	0.40

Table 4: The solution for fixed effects analysis of the cognitive control-loading principal components analysis. There were no significant effects.

Graph Theory Functional Connectivity: Longitudinal Trajectories

There was a significant autistic traits-by-sex-by-age interaction for SIP trajectories (Table 5; Fig. 3). Post-hoc analysis of sex groups separately was conducted to investigate the group driving significance. This analysis revealed a significant autistic traits-by-age effect in men ($t_{39.8}$=2.78, p=.008), such that higher autistic traits predicted more positive SIP trajectories, indicating slower rates of information diffusion across aging. However, this effect was not significant in women ($t_{20.4}$=-0.33, p=.747). Furthermore, there was a significant main effect of sex (Table 5), such that women, on average, had lower SIP values than men, which may indicate faster rates of information diffusion. For traditional graph theory metrics, the BNP also showed a significant autistic traits-by-sex-by-age effect albeit weaker than the SIP (Table 6; Fig. 4). Given that the BNP is used to calculate the SIP, it is not unexpected that both measures may yield a significant effect. Post-hoc analyses separately in male and female groups showed that the autistic traits-by-age interaction was non-significant in men ($t_{43.1}$=1.35, p=.184) and women ($t_{19.5}$=-0.86, p=.402). However, the pattern of effects was generally similar to the SIP, such that higher autistic traits predicted more positive BNP trajectories in men and the inverse for women. Furthermore, ND showed a significant effect of sex, such that women had higher values than men. However, there were no other significant effects of autistic traits, sex, age, or their interaction for traditional graph theory measures. There were also no significant effects between diagnostic groups.

Table 5: SIP effects for autistic traits, age, and sex

Solution for Fixed Effects					
Effect	**Estimate**	**Standard Error**	**DF**	**t Value**	**Pr > |t|**
Intercept	-0.94	0.014	73.9	-69.04	**<0.01**
Age	-0.0022	0.0015	80.2	-1.50	0.14
SRS Baseline	0.00032	0.00032	72.2	1.02	0.31
Age x SRS Baseline	-0.000040	0.000036	83.2	-0.99	0.32
Sex	0.054	0.016	76.1	3.43	**<0.01**
Age by Sex	-0.00040	0.0018	69.3	-0.23	0.82
SRS Baseline by Sex	-0.00025	0.000368	77	-0.68	0.50
Age by SRS Baseline by Sex	0.000106	0.000043	80.6	2.47	**0.02**

Table 5. The solution for fixed effects analysis of the slope of the integrated persistent feature (SIP). There is a significant effect for the intercept, sex, and the interaction between age, autistic traits, and sex.

Figure 3: Age trajectories of the SIP as a function of autistic traits

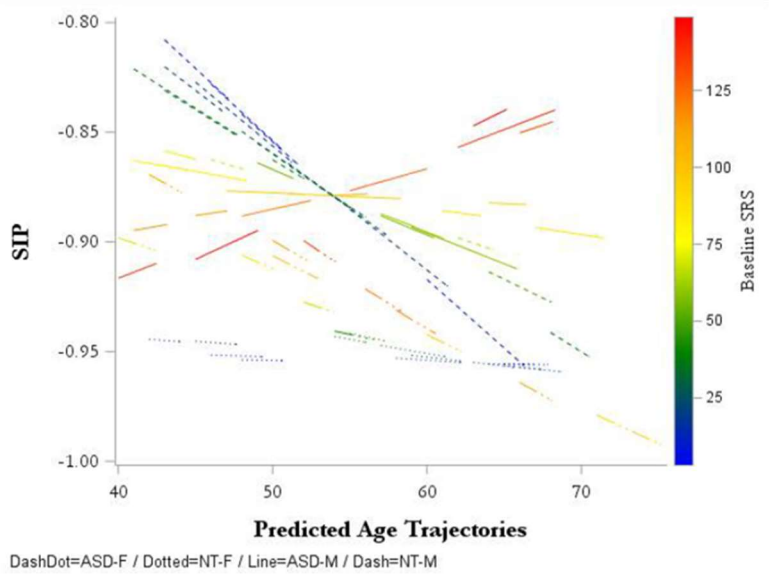

Fig. 3. Predicted age trajectories of the slope of the integrated persistent feature (SIP) as a function of baseline scores on the Social Responsiveness Scale – 2 Adult Self Report (SRS).

Table 6: BNP effects for autistic traits, age, and sex

Solution for Fixed Effects					
Effect	**Estimate**	**Standard Error**	**DF**	**t Value**	**Pr > |t|**
Intercept	-278.31	2.54	72.3	-109.51	**<0.01**
Age	-0.46	0.29	78.1	-1.58	0.12
SRS Baseline	0.068	0.059	71	1.16	0.25
Age x SRS Baseline	-0.0098	0.0069	79.7	-1.41	0.16
Sex	-0.83	3.10	74.2	-0.27	0.79
Age by Sex	0.20	0.36	72.2	0.55	0.59
SRS Baseline by Sex	-0.064	0.072	74.6	-0.89	0.38
Age by SRS Baseline by Sex	0.018	0.0086	78.4	2.05	**0.04**

Table 6. The solution for fixed effects analysis of the Betti number plot (BNP). There is a significant effect for the intercept and the interaction between age, autistic traits, and sex.

Figure 4: Age trajectories of the BNP as a function of autistic traits

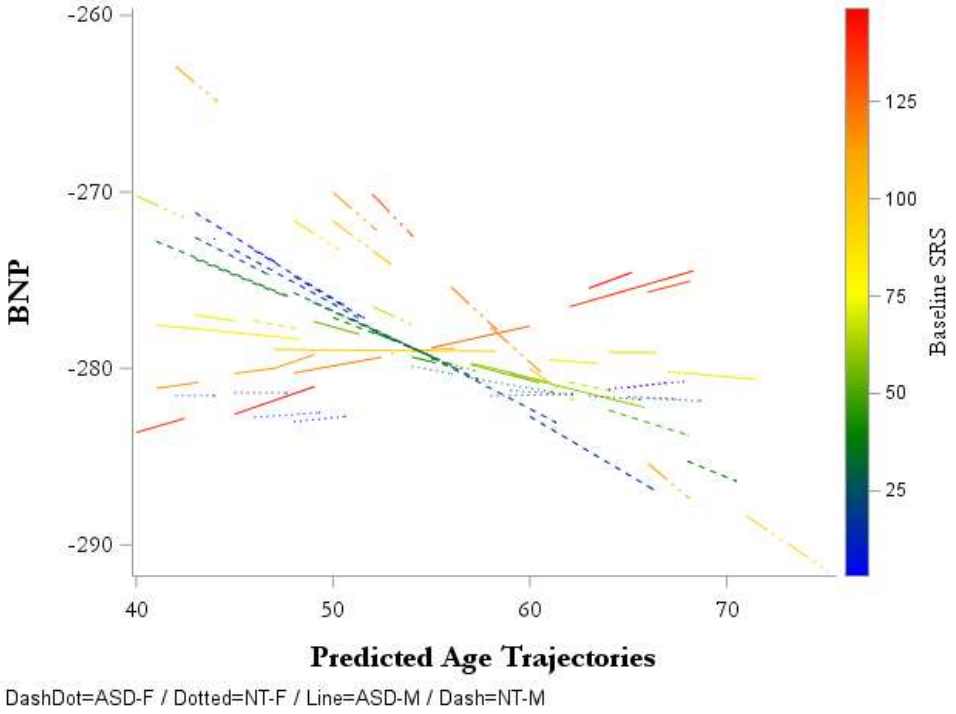

Fig. 4. Predicted age trajectories of the Betti number plot (BNP) as a function of baseline scores on the Social Responsiveness Scale – 2 Adult Self Report (SRS).

Cognitive-Brain Associations

We explored whether SIP trajectories predict poorer cognitive aging trajectories in the group that showed the most positive SIP trajectories (men with ASD). We found that variability in subject-level SIP values at each time point approached significance for predicting the memory-loading PCA component (p=.065; Table 7; Fig. 5). Specifically, when a participant's SIP values were relatively more positive, the "memory" growth curve was pushed down, indicating a lower "memory" score at the time point. In contrast, when a participant's SIP values were relatively more negative, the "memory" growth curve was pushed up, indicating higher "memory" scores at that time point. However, trait-level SIP values (e.g., the participant's mean SIP value across time points) was not a significant predictor of the memory-loading PCA component.

Table 7: Interactions between the SIP and memory-loading PCA component in males with ASD

Solution for Fixed Effects					
Effect	**Estimate**	**Standard Error**	**DF**	**t Value**	**Pr > |t|**
Intercept	-0.31	0.25	16.3	-1.24	0.23
Age	-0.06	0.021	29.2	-2.95	**0.01**
Mean SIP	-0.12	3.41	14.8	-0.03	0.97
SIP Residuals	-1.19	0.62	25.4	-1.93	**0.07**

Table 7. The solution for fixed effects analysis of the SIP in predicting the memory-loading PCA component in males with ASD. There is a significant effect for age and a near-significant effect for SIP residuals.

Figure 5: Age trajectories of the memory-loading PCA component as a function of the SIP

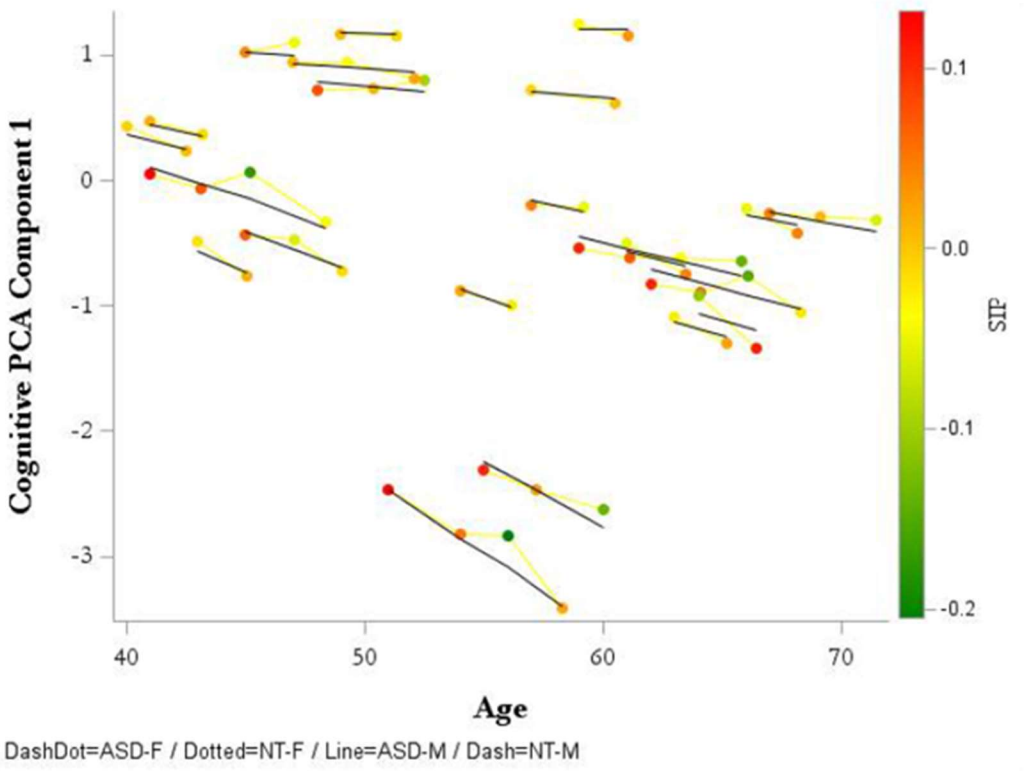

Fig. 5. Predicted age trajectories of the memory-loading PCA component as a function of the slope of the integrated persistent feature (SIP).

CHAPTER 4

DISCUSSION

Summary

The results supported our hypothesis that autistic trait severity is a more sensitive metric than diagnostic group. In terms of cognitive aging trajectories, there were sex-by-autistic traits differences for the PCA memory-loading component, but not the cognitive control-loading component. Higher autistic traits predicted a steeper decline in cognitive ability over time, but this effect was only significant in males. The results supported our hypothesis that the SIP is more sensitive to differences in functional connectivity than other graph theory metrics including CPL, ND, and EC. In terms of SIP aging trajectories, there was a significant effect for sex-by-autistic traits where in males, higher autistic traits predicted a more positive SIP over time. We also found that in males with ASD, SIP trajectories trended towards predicting the memory-loading PCA component. This finding supports the hypothesis that positive SIP values reflect slower, less efficient information processing with age (Kuang et al. 2019).

Memory

We found that elevated autistic trait severity was associated with a reduction in cognitive ability over time and that this effect was more pronounced in males than in females. In men, higher autistic traits were associated with lower intercepts and more negative slopes of the memory-loading PCA component. These results extend cross-sectional research suggesting that older adults with ASD have less desirable cognitive aging outcomes than NT adults (Geurts and Vissers, 2012; Davids et al., 2016; Geurts et al., 2020). One prior study found that increasing age in adults with ASD is associated

with greater deficits in free recall and processing speeds than NT adults (Powell, Klinger, and Klinger, 2017). However, other cross-sectional age research in ASD finds evidence for equivalent or protective aging trajectories (Abbott, Happé, and Charlton, 2018; Lever and Geurts, 2016; Lever et al., 2015). Our results suggest that contradictory findings on how ASD impacts memory through the aging process may be a result of analyzing males and females together without modeling sex interactions. We found sex differences in how memory changes over time in males and females, so it may be more appropriate to analyze the sexes separately and/or investigate interactions.

Brain Aging in Autism

Our results support existing research suggesting that older adults with ASD have less desirable brain aging trajectories than the general population. We found that higher autistic traits correlated with more positive SIPs and thus less efficient information processing. The results also indicated that the SIP trends towards predicting the memory-loading PCA component in men with ASD, such that variability in SIP scores from one timepoint to the next predicts "memory trajectories." Specifically, more positive SIP values are linked to lower scores on the memory-loading PCA component. This evidence supports the hypothesis that more positive SIPs are associated with less efficient brain information diffusion (Kuang et al., 2019). The results support cross-sectional research on brain aging in ASD, including studies that found reduced age-related white matter integrity (Koolschijn et al., 2017), increased age-related cortical thinning (Braden and Riecken, 2019), and reduced age-related functional connectivity in adults with ASD (Walsh et al. 2019). Our results combined with existing research support the hypothesis

that men with ASD with high autistic traits have steeper age-related declines in functional connectivity than those with lower autistic traits and NT men.

Categorical vs. Dimensional Measures of Autism

Our results also support the hypothesis that autistic traits show greater sensitivity to differences in brain aging than diagnostic group. Based on our results and findings from previous studies, quantifying ASD based on trait severity may be more sensitive than categorical group difference analyses. In a study involving the general population, higher autistic traits were associated with accelerated aging processes including a variety of biomarkers, facial age, and poorer health outcomes (Mason et al., 2021). There are few studies that use a dimensional analysis of autistic traits in older adults, and no studies were identified that directly compare categorical and dimensional analyses (Mason et al., 2022). However, there is consensus that autistic traits are distributed throughout the population in individuals with and without an ASD diagnosis (Hoekstra et al., 2007; Colvert et al., 2015; Tick et al., 2016). Among the general population, individuals who endorse higher autistic traits have similar social and cognitive difficulties as adults with ASD (Stewart et al., 2020; Stewart, Charlton, and Wallace, 2018; Wallace, Budgett, and Charlton, 2016), and they also demonstrate similar mental health patterns (Stewart et al., 2021). Another study found that individuals with elevated autistic traits have accelerated age-related subjective cognitive impairment (Caselli et al., 2018). There is also evidence that autistic trait severity is associated with differences in brain development and functional connectivity (Gibbard et al., 2013; Pua et al., 2021; Di Martino et al., 2009). Several of these studies found stronger correlations between symptom severity and differences in brain features in female participants (Cauvet et al., 2019; Kozhemiako et

al., 2020). Dimensional analyses may be more appropriate given the heterogenous nature of ASD and changes in diagnostic criteria over time.

Graph Theory in Autism

These results also support previous research studying graph theory in ASD. There are no existing studies measuring the IPF or SIP in ASD, but other graph theory metrics have been used to compare group differences in functional connectivity and to develop screening tools for ASD (Sadeghi et al., 2017). Most existing research in this field focuses on children and adolescents with ASD, and there are few graph theory-based studies examining aging trajectories in ASD. Several studies involving children and younger adults found that ASD is associated with abnormal network organization and reduced network efficiency and density (Keown et al., 2017; Alaerts et al., 2015). Another study on adolescents in ASD found that posterior overconnectivity was associated with higher ASD trait severity and frontal underconnectivity was associated with lower ASD trait severity, which supports our hypothesis that trait severity may be a more sensitive metric than diagnostic group (Keown et al., 2013). Similarly, a study of adults with ASD found decreased degree centrality in areas related to speech comprehension and that degree centrality was negatively correlated with ADOS scores (Lee at al., 2017). These findings are supported by graph theoretical analyses of behavioral data. A study that mapped networks involved in social cognition found decreased connectedness between nodes in young adults with ASD compared with NT adults (Vagnetti et al., 2020). One study used principal components analysis to derive a rs-fMRI based graph theory metric that predicts aging trajectories in ASD throughout the lifespan. They found that a quadratic model best predicted aging trajectories and that

including sex differences improved the accuracy of their model (Ball, Beare, and Seal, 2017). Our findings agree with the existing body of research that ASD may be associated with functional underconnectivity and less efficient information processing.

Sex Differences in ASD Aging

We found sex differences in how autistic trait severity predicts changes in memory ability over time. We found that elevated autistic traits were associated with a greater reduction in cognitive ability over time, but this effect was less pronounced in females. We also found that higher autistic traits predicted a more positive SIP in males but not females, and overall, females had more negative SIPs than males. Although no prior studies have examined sex differences in aging processes from the perspective of autistic trait severity, these results support the conclusions of the few other studies examining age-by-sex-by-diagnosis interactions in ASD. One group reported that females with ASD have more distinct developmental trajectories than males with ASD, and they found similar developmental patterns between males and females with ASD and NT males (Kozhemiako et al., 2019; Kozhemiako et al., 2020). They hypothesized that more changes in local connectivity patterns are needed to create symptoms that reach a diagnostic threshold for females with ASD, and the female brain may be protective against autistic traits. Our results support this hypothesis, as we found that autistic traits predicted less of a reduction in cognitive ability over time in females compared to males. Another study also reported age-by-sex-by-diagnosis differences in network communication, as both males and females with ASD had negative quadratic trajectories while NT males had flatter trajectories and NT females had quadratic trajectories (Henry et al., 2018). These findings also suggest that aging in ASD for both males and females

may follow a path that is more similar to typical male aging patterns. Our results coupled with prior research suggest that there are sex differences in brain aging patterns in ASD and that this field warrants further study.

Limitations

Sex is an important factor to consider in ASD research because historically, men have been diagnosed nearly four times as frequently as women (Giarelli et al., 2010). Our sample size of female participants was smaller compared to male participants, which influences the statistical power for within sex analyses. Specifically, for longitudinal data the study first recruited exclusively men for three years before securing funding to recruit women. Additional research investigating sex differences in functional connectivity with a larger sample is warranted. The present study also addressed relationships between cognitive abilities and functional connectivity metrics, which is a first step in exploring the brain mechanisms of cognitive changes. However, further research is required to determine the clinical significance of the SIP. A final limitation of this study is that approximately one third of all individuals who are diagnosed with ASD have comorbid intellectual disability (ID). We excluded individuals with ID, which limits generalizability of findings to the larger ASD population. Further research is required to determine how functional connectivity differs in those with ASD and comorbid ID.

Conclusions

In this study, we found that the SIP, a novel threshold-free graph theory metric, is more sensitive to age-related changes in functional connectivity in ASD than other graph theory metrics (BNP, CPL, ND, or EC). We also found that quantifying ASD trait severity continuously rather than categorically based on diagnosis may be more sensitive

for understanding cognitive and brain aging in ASD. We found that higher autistic traits are associated with declining functional connectivity and less efficient information processing in men. We explored the association between the SIP and cognitive ability in males with ASD, and found that variability in the SIP over time predicted cognitive performance on the memory component of the PCA. In the future, we plan to further study how physiological biomarkers such as the SIP are associated with cognitive outcomes. Future studies examining sex differences in brain aging patterns are also warranted. Our study includes a longitudinal sample up to six years in length, but continuing this research for a longer period of time will increase the power of the study and allow us to determine how the aging process in ASD differs over extended periods of time. This research has clinical applications because understanding the unique challenges faced by an aging population of older adults with ASD is necessary to develop effective interventions for improved quality of life and maintaining independence.

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