UNIVERSITY OF CALIFORNIA SAN DIEGO

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# Characterizing Groupwise and Idiosyncratic Anomalies of Cortical Architecture and Links to Neuropsychological Function in Adults with Autism Spectrum Disorder

A dissertation submitted in partial satisfaction of the requirements for the degree Doctor of Philosophy

in

Clinical Psychology

by

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The Dissertation of Jiwandeep Kohli is approved, and it is acceptable in quality and form for publication on microfilm and electronically.

Chair

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# DEDICATION

Dedicated to my family, for instilling within me values for knowledge and service, and for their unwavering love and support through decades of formal education; and to my JDP friends, particularly the most cohesive cohort (CoCo), for sharing in the highs and lows of graduate school and learning with me, both in the lab and beyond.

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ABSTRACT OF DISSERTATION

Characterizing Groupwise and Idiosyncratic Anomalies of Cortical Architecture and Links to Neuropsychological Function in Adults with ASD

by

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Autism Spectrum Disorder (ASD) is a highly heterogeneous condition in terms of etiology, symptomatology, and severity. Our existing understanding of ASD derives mainly from research in children and young adults, with little known about neurobiological, cognitive, and behavioral changes later in life. This three-paper dissertation aimed to characterize changes in cortical architecture across middle to older age in ASD and determine how differences relate to cognition and behavior. Data were drawn from an ongoing study of adults with ASD and typical comparison (TC) participants, aged 40-70 years. Study 1 ($n_{ASD}$=20, $n_{TC}$=21; mean age=50.51 years, SD=6.35; Kohli et al., 2019) examined cortical morphology, including cortical thickness (CT), surface area (SA), and local gyrification index (LGI). LGI, but not CT or SA, was

regionally decreased bilaterally in the ASD group. LGI also showed several correlations with executive function scores in the ASD group. Study 2 ($n_{ASD}$=30, $n_{TC}$=36; mean age=51.50 years, SD=7.09) aimed to identify regionally varying differences in CT and gray-white contrast (GWC) using both group-wise and subject-specific analyses. CT did not differ significantly between groups using either approach. GWC did not differ in the group-wise analysis, but the ASD group showed a greater spatial extent of decreased GWC than controls in subject-specific analyses, along with associations between decreased GWC and ASD symptomatology and dysexecutive symptoms. In the same sample, Study 3 examined intracortical myelin content (MC). Groupwise analyses showed no group differences in average MC or its associations with age. In subject-specific analyses, neuropsychological function differed between subgroups classified by presence or absence of aberrant MC, with poorer performance in the ASD subgroup with atypically high MC in spatially heterogeneous regions. LGI was the only cortical feature demonstrating differences in ASD when examining group level averages, but subject-specific analyses revealed an additional decrease in GWC, along with broad associations between both GWC and MC and neuropsychological function. These complementary approaches demonstrate the importance of accounting for increasing sources of heterogeneity when studying adults with ASD and provide preliminary insights into links between brain structure and behavior in the second half of the lifespan in ASD.

# INTRODUCTION TO THE DISSERTATION

Autism Spectrum Disorder (ASD) is a highly heterogeneous condition in terms of etiology, symptomatology, and severity. Prevalence in the United States has recently been estimated at 1 in 54 (Maenner et al., 2020), based on a study of children aged 8 years old in the year 2016. While much has been learned about both etiology and outcomes in ASD, much remains unknown, and even our existing understanding is based predominantly on research in children and young adults. This has left a deficit of knowledge with regard to the neurobiological, cognitive, and behavioral changes that occur across the later portion of the lifespan, even though ASD are lifelong conditions (Robison, 2019). Given that the rate of autism has been shown to be age-independent (Brugha et al., 2011), the population of older adults with ASD in the U.S. can be projected to total over 1.3 million by the year 2030 (Vespa, Armstrong, & Medina, 2018), posing important economic and public health concerns (Ganz, 2007). Based on studies of adults ranging in age from 18 to 48 years, it is clear that many individuals with ASD continue to show some degree of cognitive impairment and require support beyond childhood (Billstedt, Gillberg, & Gillberg, 2005; Howlin, Goode, Hutton, & Rutter, 2004; Szatmari, Bartolucci, Bremner, Bond, & Rich, 1989; Wing & Shah, 2000). With a large literature in typical aging showing cognitive declines after age 50 years (Hedden & Gabrieli, 2004) added to the existing deficits well demonstrated in the first half of the ASD lifespan (Levy & Perry, 2011; Magiati, Tay, & Howlin, 2014; Steinhausen, Mohr Jensen, & Lauritsen, 2016), older individuals with ASD are particularly vulnerable. With developmental abnormalities resulting in less cognitive reserve, they may also demonstrate less resilience to neurodegenerative changes, and several major voices in the autism field have highlighted this as a high priority area of research (Pellicano, Dinsmore, & Charman, 2014; Warner, Parr, & Cusack, 2019). In fact, a few

preliminary studies in middle to older aged adults have found continuation and potential exacerbation of existing symptomatology along with accelerated neuroanatomical changes (Braden & Riecken, 2019; Hallahan et al., 2009; Kohli, Kinnear, Martindale, Carper, & Müller, 2019; Linke et al., 2020; Scheel et al., 2011).

Studying the neurobiology of autism in adulthood poses a number of unique challenges. Research in this area inherits the myriad potential complex interactions between genetic predisposition, early environmental influences, and dynamic developmental trajectories across prenatal and childhood maturation (Jeste & Geschwind, 2014; Mandy & Lai, 2016; Schreibman, Dufek, & Cunningham, 2011; Vorstman et al., 2017). Added to that is further complexity from diverse histories of pharmacological and psychosocial interventions with variable treatment response across the lifespan (Broadstock, Doughty, & Eggleston, 2007; Vivanti, Prior, Williams, & Dissanayake, 2014), and increasing age introduces greater sources of heterogeneity from these and other life experiences. Finally, with the onset of potential neurodegenerative processes in later life, it becomes difficult to parse group-wise developmental abnormalities from possible degenerative changes, especially without longitudinal designs. Previous studies from across the lifespan of ASD have already been limited by a necessity to average across individual participants (Marquand, Rezek, Buitelaar, & Beckmann, 2016), potentially washing out important and informative interindividual variability in a set of conditions that are acknowledged to be neurobiologically diverse. Against this backdrop, the three-paper dissertation aimed to characterize the evolution of cortical morphology and architecture across middle to older age in ASD and determine how any abnormalities, whether developmental or degenerative, relate to cognition and behavior. Given known heterogeneity in the disorder, the studies make use of both group-wise and subject-specific methodological approaches targeted toward a more

comprehensive characterization of cortical architecture in this largely understudied age range and a better understanding of links between brain structure and behaviors in autism.

**Neuropsychological Function and Brain Structure in Typical Aging and ASD**

Research on typical aging shows a decline in motor function beginning after the age of 50 years (Leversen, Haga, & Sigmundsson, 2012; Potvin, Syndulko, Tourtellotte, Lemmon, & Potvin, 1980), including declines in fine motor skills (Contreras-Vidal, Teulings, & Stelmach, 1998; Darling, Cooke, & Brown, 1989; Hoogendam et al., 2014; Smith et al., 1999), coordination (Seidler, Alberts, & Stelmach, 2002), and balance (Laughton et al., 2003; Woollacott & Tang, 1997). At the same time, research shows similar impairments in fine and gross motor function, coordination, and balance early in development in ASD, with deficits persisting into adolescence and even increasing with age (Freitag, Kleser, Schneider, & von Gontard, 2007; Lloyd, MacDonald, & Lord, 2013; McPhillips, Finlay, Bejerot, & Hanley, 2014). There is some evidence of motor abnormalities in young adults with ASD (Fukui et al., 2018; Glazebrook, Elliott, & Lyons, 2006), but little is known about motor function in adults with autism in later life (Hallett et al., 1993; Happé & Charlton, 2012; Mukaetova-Ladinska, Perry, Baron, Povey, & Group, 2011; Piven, Rabins, & Group, 2011), when we would expect decline even in typical aging. There have been reports of high rates of parkinsonism in adults with ASD (Starkstein, Gellar, Parlier, Payne, & Piven, 2015), along with research showing similar mechanisms of motor dysfunction involving the frontal lobes in both autism and Parkinson's Disease (Hollander, Wang, Braun, & Marsh, 2009). On top of existing developmental deficits in motor skills, these results suggest that motor function may be particularly vulnerable to accelerated decline with increasing age in some individuals with ASD (Croen et al., 2015).

Deficits in executive function (EF), a set of cognitive processes involved in controlling complex behavior, are among many cognitive symptoms associated with ASD, and may contribute to the more diagnostic behavioral deficits (Hill, 2004; Ozonoff, Pennington, & Rogers, 1991; Wilson et al., 2014). EF has been shown across a number of studies to decline in typical aging (Buckner, 2004; Kirova, Bays, & Lagalwar, 2015), and is also predictive of functional status, including independent activities of daily living in later life (Royall, Palmer, Chiodo, & Polk, 2004). A review of EF in ASD found an overall trend of delayed development of executive function across childhood in ASD (O'Hearn, Asato, Ordaz, & Luna, 2008), with improved performance in adolescence, but failure to reach developmentally typical levels of executive function by adulthood. A meta-analysis of executive function in ASD also reported moderately reduced EF that was relatively stable across development (Demetriou et al., 2018), but the sample disproportionately comprised studies of children and young adults. As with motor skills above, known EF deficits in ASD in the context of data supporting age-related decline in these abilities in the neurotypical population are alarming and support the need to understand the biological bases of this dysfunction to help predict which individuals are most at risk and to support their long-term needs.

Atrophy of cortical gray matter in typical aging has been shown to follow a roughly anterior-to-posterior gradient, with frontal and temporal association regions demonstrating earlier decline in both cross-sectional (Walhovd et al., 2011) and longitudinal studies of gray matter volume and cortical thickness (Driscoll et al., 2009; Galluzzi, Beltramello, Filippi, & Frisoni, 2008; Kalpouzos et al., 2009; Peelle, Cusack, & Henson, 2012; Pfefferbaum et al., 2013). This pattern overlaps anatomically with a confluence of ASD-related pathology in frontal and temporal cortices (Carper, Moses, Tigue, & Courchesne, 2002; Van Rooij et al., 2017; Wallace

et al., 2015), and suggests that middle-aged and older adults with ASD may be subject to aggravated age-related changes. This is highly concerning in light of the localization of executive functions in the frontal lobes (Alvarez & Emory, 2006; Stuss & Benson, 1984). Indeed, some preliminary research suggests accelerated rates of cortical thinning in adults with ASD, particularly in frontal and temporal regions, but this effect has only been demonstrated cross-sectionally in adults (Braden & Riecken, 2019; Libero, DeRamus, Deshpande, & Kana, 2014), and only one of these included adults over 40 years of age (n=25 in ASD group) (Braden & Riecken, 2019). Additionally, other studies have shown contradictory results, including an opposite pattern of decreased thinning with age in adults with ASD (ASD n=28; age 20-55 years) (Scheel et al., 2011), regionally varying increased and decreased thinning (ASD n=1571; age 2-64 years) (Van Rooij et al., 2017), and no difference as compared to typically aging individuals (ASD n =51; age 30-73 years) (Koolschijn & Geurts, 2016). These inconsistencies may simply relate to some small sample sizes, broad age ranges, or different methodologies used across studies, but they may also be attributable to substantial heterogeneity in ASD.

**Heterogeneity in ASD**

The ASD label is likely to encompass a group of conditions of diverse etiology, and heterogeneity within the disorder can be observed at multiple levels. A variety of clinical presentations are considered to fall within the spectrum, especially with changes in the diagnostic criteria over time (American Psychiatric Association, 2000, 2013). Behavioral symptomatology can vary widely along the two core diagnostic dimensions of (a) social communication and (b) restricted and repetitive patterns of behavior. The former includes deficits in social-emotional reciprocity, nonverbal communication, and ability to maintain relationships, and specific deficits can vary substantially between diagnosed individuals even within those categories. For example,

communication deficits can range from complete lack of verbal language ability to more subtle impairment in conversational turn-taking or misunderstanding of abstract forms of language (Frith & Happé, 1994; Pickles, Anderson, & Lord, 2014). Restricted, repetitive patterns of behavior, interests, and activities are similarly diverse, and can include stereotyped motor movements, use of objects, or speech, insistence on sameness and rigid adherence to patterns and routines, highly restricted interests that are abnormal in intensity or focus, and hyper or hypo-reactivity to sensory input. These symptoms can range from mild perseveration on certain topics to more severe self-injurious or compulsive behaviors (Esbensen, Seltzer, Lam, & Bodfish, 2009). The degree of impact on daily living can also range from requiring only mild assistance to being unable to function without substantial support, and is also related to variability in general cognitive abilities (Estes, Dawson, Sterling, & Munson, 2007) and frequency of co-occurring diagnoses in the disorder (Abdallah et al., 2011; Mazzone, Ruta, & Reale, 2012).

The risk and prognostic factors for such a clinically complex diagnosis are equally, if not more heterogenous than the symptoms, and the genetic landscape of ASD is vast. A number of genetic variants have been shown to confer increased risk of ASD (Pinto et al., 2010; Szatmari et al., 2007; Yuen et al., 2017), with different genetic abnormalities leading to varying levels of impairment (Freitag, 2007). Reviews of genetics research in ASD have reported hundreds of genetic variants and mutations that are related to autism (Jeste & Geschwind, 2014), also noting differences in the level of penetrance and variable gender ratios and comorbidities (e.g., epilepsy, schizophrenia, obsessive compulsive disorder, etc.) (Vorstman et al., 2017). Some studies have also shown differences in the mode of transmission between simplex autism and multiplex autism (Leppa et al., 2016; Sanders et al., 2015; Virkud, Todd, Abbacchi, Zhang, & Constantino,

2009). These data together suggest that diverse neurobiological mechanisms can give rise to the ASD phenotype, while it is still diagnosed using only behavioral symptoms.

In addition to genetic contributions toward the risk of ASD, environmental influences such as perinatal factors (Larsson et al., 2005), maternal immune response (Garay & McAllister, 2010; Patel et al., 2018), neuroinflammation (Vargas, Nascimbene, Krishnan, Zimmerman, & Pardo, 2005), and the interaction between genetic and environmental factors have also been found to contribute to increased autism risk (Mandy & Lai, 2016). Individuals with ASD also vary in experiential factors such as in the types and length of treatments they have received, a particularly important consideration when studying adults with half a lifetime or more of experience. Another factor contributing to this particular source of variability is the historical evolution of the procedures for the diagnosis and treatment of ASD since the inception of the diagnostic label in 1943 (Kanner, 1943). Just within the range of evidence-based therapies available today, the targeted symptoms can vary widely, along with the degree of efficacy for each intervention (Wong et al., 2015). For example, speech therapy may be employed to address specific articulation or structural language concerns in early childhood, while applied behavioral analysis may target the acquisition of more appropriate social behavior in adolescence, and social skills training may be employed for adults to practice more nuanced aspects of social communication. In addition, pharmacotherapies are often utilized in conjunction with behavioral interventions for the treatment of comorbid conditions such as hyperactivity or anxiety, or to address difficult behaviors such as self-harm (Broadstock et al., 2007; Howes et al., 2018). The type, age of intervention, and duration of each treatment, along with numerous combinations of multiple therapies, all have differing effects on symptoms and long-term outcomes for individuals with ASD (Helt et al., 2008; Klintwall, Eldevik, & Eikeseth, 2015). Taken together,

the evidence suggests highly heterogeneous etiologies in ASD that are further compounded by experiential variability, all of which have the potential to differentially impact brain structure and neural resilience later in life. Indeed, variability at the level of brain structure has been demonstrated across a number of studies spanning different features of cortical structure and different ages (Wallace, Dankner, Kenworthy, Giedd, & Martin, 2010; Zielinski et al., 2014). These results are likely to reflect, in part, the combined effects of neurodevelopmental and experiential heterogeneity, thus highlighting the need for subject-specific approaches and more advanced MRI measures, particularly in older subjects with ASD.

**New MRI Measures Targeting Cortical Microstructure**

While most neuroimaging studies examining atypical brain structure in adults with ASD have focused on volumetric (Ecker et al., 2012; Lange et al., 2015) and morphological features (Ecker et al., 2013; Ecker et al., 2014), attention has recently shifted toward measures of cortical microstructure to examine myelin content (discussed further below) and the gray-white matter boundary. The gray-white boundary is of interest in ASD as a result of evidence from histological studies that "blurring" of this margin relates to cortical microstructural differences (Hutsler & Avino, 2013). Post-mortem studies of autism report intra-individual heterogeneity in this type of pathophysiology, with abnormalities of cortical structure (e.g., indistinct lamination, cortical thickness changes, atypical neuronal density in deep cortical layers, etc.), that are described as "patchy" in that they are detected within restricted regions of cortex while adjacent regions are unaffected. These abnormalities are likely due to abnormal neural migration, are highly localized, and vary spatially between individuals (Avino & Hutsler, 2010; Bailey et al., 1998; Casanova et al., 2013).

Gray white contrast (GWC) has been proposed as an MRI-based index of in vivo cortical microstructure that can map onto these neuropathological aspects of development (Andrews et al., 2017) and has been examined in a few preliminary studies of ASD. A study in adults aged 18-42 years showed significantly reduced gray-white contrast in ASD in bilateral posterior-cingulate, medial frontal, entorhinal, and inferior and superior temporal cortices, left orbitofrontal cortex and temporo-parietal junction, and right dorsolateral prefrontal cortex (Andrews et al., 2017). A subsequent study in children and young adults ranging in age from 7-25 years also showed significantly reduced GWC in ASD, but in somewhat different regions, including bilateral prefrontal cortices, right inferior parietal cortex, postcentral gyrus, and precuneus and left supramarginal gyrus (Mann et al., 2018). The regional differences may be accounted for by the difference in age range but may also be attributable to other characteristics of the samples. While GWC has been shown to be a valuable measure in ASD, variability of intra- and inter-subject findings from post-mortem and MRI studies indicates that a subject-specific approach may be better suited toward its examination in autism. Additionally, it has become clear that it is vital to investigate MRI-based measures of cortical structure beyond morphology, including both GWC and intracortical myelin content.

**Cortical Myeloarchitectonics**

While inconsistencies in age related effects observed in previous studies of CT and GWC are likely to relate to the known heterogeneity of neuroanatomical abnormalities in ASD discussed above, an important additional factor should be considered. These features are important for studying neuroanatomical development and degeneration, but they are indirect measures usually derived from a single MR image. These measures typically use signal intensity differences from a T1-weighted scan to estimate the gray/white border and are likely influenced

by normal progressive myelination of intracortical fibers well into the fourth decade of life (Grydeland, Walhovd, Tamnes, Westlye, & Fjell, 2013), which can affect MRI signal in lower cortical layers (Ducharme et al., 2016). This could contribute to apparent development-related decline in MRI-based estimates of cortical thickness (Glasser & Van Essen, 2011), with one aspect of cortical structure (apparent thickness) confounded with another (myelin content). In addition, the location of the gray/white boundary is used in automated calculation of GWC, so that the measure is affected not only by signal intensity itself, but also by potential imprecise placement of the gray/white boundary. For this reason, one of the Study 3 of the dissertation focused specifically on measurement of intracortical myelin content, which may drive some of the previously observed age-related patterns of apparent cortical thinning in MRI studies and may provide a more robust gauge of neurobiological aging. Intracortical myelin content can be measured by combining information from T1 and T2-weighted MR images and does not depend on estimation of the gray/white boundary in the same manner, thus making it independent of the CT and GWC measures.

Myelin is formed by multiple layers of insulating glial cells, rich in lipids, that wrap around axons and facilitate the conduction of electrical impulses. It is vital for healthy brain function (Martenson, 1992), and while myelin is most abundant in white matter, a significant number of myelinated fibers are present in the lower layers of cortical gray matter (O. Vogt, 1910). Postmortem histological studies have shown substantial variability in the distribution of myelinated fibers between different cortical regions (Adolf Hopf, 1956; A Hopf, 1968; Nieuwenhuys, 2013; C. Vogt, 1919). The human brain is particularly high in myelin content (G Bartzokis & Lu, 2009) compared to other species, and is also unique in its protracted developmental processes (Yakovlev, Lecours, Minkowski, & Davis, 1967), with myelination

reaching its peak in the frontal lobes and association areas only in middle age (Flechsig, 1920; Sowell et al., 2003). These spatial and temporal patterns have been replicated using MRI derived myelin maps, which show that intracortical myelin maturation is ongoing into the fourth decade of life, followed by 20 relatively stable years before declining from the sixth decade (Grydeland, Westlye, Walhovd, & Fjell, 2015). Cortical myelin maturation and aging-related degradation have important implications for brain function and dysfunction, and prolonged myelination makes intracortical myelin content particularly interesting and important to study in developmental disorders and from a lifespan perspective (George Bartzokis, 2004a, 2004b). Variability in the distribution of myelin content across the cortex may be related to the density of neurons per unit cortical volume (Glasser, Goyal, Preuss, Raichle, & Van Essen, 2014), with high neuronal density in primary somatosensory, auditory, and visual areas (Collins, Airey, Young, Leitch, & Kaas, 2010) that also demonstrate higher myelin content (Glasser & Van Essen, 2011), and lower neuronal densities in more lightly myelinated areas that have larger neuronal cell bodies, and more complex intracortical circuitry, including larger dendritic field sizes and arbors with more dendritic spines (Elston, Benavides-Piccione, & DeFelipe, 2001; Elston et al., 2006). These correlations have important implications for cognitive processing. While myelination is likely to have evolved to speed axonal conduction in white matter (Hartline & Colman, 2007), it has been suggested that a primary function of *intracortical* myelination is actually insulation against the formation of aberrant synapses and superfluous connections (Braitenberg, 1962). This hypothesis is supported by a considerable amount of molecular evidence showing that myelin-related factors inhibit new axonal growth and synapse formation (Chen et al., 2000; Kapfhammer & Schwab, 1994; McGee & Strittmatter, 2003; McGee, Yang, Fischer, Daw, & Strittmatter, 2005; McKerracher et al., 1994). Therefore, regional deficits and

abnormal degeneration of intracortical myelin may be associated with aberrant connections, which might in turn underlie cognitive and behavioral problems such as those seen in ASD. Thus far, attempts to link trajectories of intracortical myelin content across the lifespan to even normal cognitive functioning have been limited, and relationships with neurological disorders have largely been based on post-mortem studies. One study showed that better performance stability on a speeded task was correlated with a greater degree of intracortical myelination, and the relationship was more prominent with advancing age, suggesting that age-related cortical demyelination contributes to dysfunctional increase in intraindividual variability in performance (Grydeland et al., 2013). Notably, aberrant intracortical myelination has been implicated in neuropsychiatric disorders such as schizophrenia and bipolar disorder, where postmortem myelin stains have shown reduced myelin localized to dorsolateral prefrontal cortex (Lake et al., 2017). There is also evidence of demyelination in mild cognitive impairment and dementia (Bouhrara et al., 2018). A study of myelin water fraction has shown reduced myelin content in the white matter in ASD (Deoni et al., 2015). The trajectory of intracortical myelination across the lifespan remains understudied, however, and there have yet to be in vivo investigations into abnormalities of cortical myeloarchitectonic developmental and degenerative processes in autism. MRI based intracortical myelin mapping shows promise for the identification of biomarkers of pathogenesis in clinical studies and may prove useful in identifying risk factors for accelerated decline in ASD (Lutti, Dick, Sereno, & Weiskopf, 2014).

**General Aims**

Spatially and directionally variable cortical anomalies in histological studies and the variation in group-wise neuroimaging findings discussed above highlight a need for more individualized approaches to the study of ASD. Such analytic designs would help account for

heterogeneity at multiple other levels of the disorders, including behavioral, genetic, and experiential variability. Indeed, neuropsychiatric research has begun to move beyond the traditional case-control study design to employ various types of normative models that allow better characterization of individual patterns of abnormality (Marquand et al., 2016), which also show strong links to behavioral symptoms (Blackmon et al., 2017; Zabihi et al., 2018). Results from these early studies support the need for continued research on inter-individual differences in cortical structure (Kanai & Rees, 2011). The dissertation employs specific methods for a more individualized approach to the study of cortical architecture in ASD in Studies 2 and 3.

The primary aims of the staple dissertation were to (1) examine cortical morphology, including cortical thickness, surface area, and local gyrification index at the group-wise level in middle to older adults with ASD, (2) identify regional abnormalities of cortical thickness and gray-white contrast that may vary between individuals along multiple dimensions using subject-specific approaches, and (3) quantify a novel variable of interest in ASD, intracortical myelin content, using both group-wise and subject specific analyses. Together, these aims contributed toward the overarching goals of achieving a comprehensive characterization of cortical architecture in this largely understudied age range, a better understanding of links between brain structure and behaviors, and detection of age-related brain changes that may identify risk factors for accelerated decline and predict long-term support needs for older adults with ASD.

Chapter 1. Study 1

**Regionally decreased gyrification in middle-aged adults with autism spectrum disorders.**

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## ABSTRACT

Objective: The present study examined changing features of cortical morphology in middle-aged adults with ASD versus typical comparison (TC) participants, hypothesizing regionally decreased Local Gyrification Index (LGI) given our previous findings of accelerated LGI decline during adolescence.

Methods: Following quality assurance, T1-weighted MRI sequences from 20 ASD and 21 TC participants (40-61 years) matched on age were analyzed. LGI, Cortical Thickness (CT), and Surface Area (SA) were measured using FreeSurfer v.5.3. Statistical analyses employed a general linear model including age, non-verbal IQ, and total brain volume as covariates. Clusters of significant group effects were used as regions of interest for behavioral analyses.

Results: Clusters of decreased LGI were observed bilaterally in the ASD group with large effect sizes in insular and anterior cingulate (ACC) regions, left postcentral and middle frontal, and right orbitofrontal and supramarginal regions. LGI was also shown to decline with age across groups in bilateral precentral and right supramarginal clusters. No significant group, age, or group by age interaction effects were observed for CT or SA in this age group. LGI showed a significant correlation with Social Responsiveness Scale total scores in a right caudal ACC cluster in the TC group only while several correlations were found in the ASD group between executive function scores and clusters in bilateral insula and right orbitofrontal cortex.

Conclusion: The pattern of regionally decreased LGI observed here in middle-aged adults with ASD is consistent with an abnormal trajectory of cortical folding changes across different stages of life in ASD as shown in previous studies.

## INTRODUCTION

Autism Spectrum Disorder (ASD) is a lifespan neurodevelopmental conditions associated with age-specific abnormalities in cortical morphology. Early cerebral overgrowth in the first years of life is reflected in various morphometric features (Redcay & Courchesne, 2005), but cortical thickness (CT) and surface area (SA) do not show definitive patterns of abnormality across later childhood and adulthood (Wallace et al., 2013; Yang et al., 2016). Our previous research showed regionally increased local gyrification index (LGI) in ASD in school-age children, potentially informative of earlier brain growth anomalies, but LGI declined rapidly from childhood to adolescence in ASD (Kohli et al., 2019). However, whether neuroanatomical trajectories remain atypical into adult life is not well understood.

Ecker and colleagues observed increased LGI in adults with ASD (18-43 years) in frontal and parietal regions (Ecker et al., 2016). No age effects were reported. Another study of 30-75 year old participants showed no group differences in LGI, but a subsample of older adults with ASD (mean age 62.35) showed atypical age-related decline of LGI in insular cortex (Koolschijn & Geurts, 2016). The present study further examined changing features of cortical morphology specifically in middle-aged adults with ASD versus typical comparison (TC) participants, with focus on cortical folding. Given our previous findings of accelerated decline in LGI during adolescence, we hypothesized that LGI would be regionally decreased in mature adults with ASD.

## METHODS

### Participants

53 adults (26 ASD, 27 TC; 40-61 years) were recruited. Participants with ASD were recruited through referrals from autism clinics, service providers (e.g., group homes, day

programs), contacts with the Autism Society San Diego, advertisement at local autism-related events (resource fairs, fund raisers, etc.), and community advertisement. A pre-existing diagnosis of ASD was not required for recruitment, but all diagnoses were confirmed as described below. Participants in the TC group were recruited through community advertisement. Participants with a history of neurological (e.g. epilepsy, tuberous sclerosis) or genetic (e.g. fragile X, Rett syndrome) conditions other than ASD were excluded. TC participants had no family history of autism nor personal history of other neurological conditions or serious mental illness. ASD diagnoses were made by a clinical psychologist based on Diagnostic and Statistical Manual of Mental Disorders 5$^{th}$ edition criteria (American Psychiatric Association, 2013) and supported by Module 4 of the Autism Diagnostic Observation Schedule, Second Edition (ADOS-2; Hus & Lord, 2014; Lord et al., 2012), along with developmental history when available. IQ was assessed using the Wechsler Abbreviated Scale of Intelligence, 2nd edition (WASI-II; Wechsler, 2011). Social skills were further assessed with the self-report version of the Social Responsiveness Scale, Second Edition (SRS-2; Constantino & Gruber, 2012). Executive functioning was assessed using the Trails, Verbal Fluency, and Color Word Interference subtests of the Delis-Kaplan Executive Function System (DKEFS; Delis et al., 2001).

**Standard protocol approvals, registrations, and patient consents**

The study was approved by the San Diego State University and University of California, San Diego institutional review boards. All participants (or their conservators) gave written informed consent prior to participation.

**Imaging Data**

Anatomical images were obtained using a 3 Tesla GE Discovery MR750 scanner with a 32-channel head coil and a T1-weighted magnetization prepared rapid gradient echo (MPRAGE)

sequence (TR=8.776 milliseconds, TE=3.656 milliseconds, flip angle=8°, matrix=320x320, 0.8mm$^3$ resolution). Two ASD participants with abnormal neuroanatomical findings (callosal dysgenesis; temporal lobe cyst) were excluded. Following visual assessment of MRI data and FreeSurfer output, 4 ASD and 6 TC participants were excluded due to insufficient quality of raw images or surface reconstruction. Individuals who were excluded were very similar to those who were included with regard to age, diagnostic, and cognitive characteristics with no significant differences between excluded and included participants for either the ASD or TC groups (Data available from Dryad; Supplemental Tables 1 and 2, doi:10.5061/dryad.tb971n0). Data from 20 ASD and 21 TC participants were subsequently analyzed, with groups matched on age, sex, race, and ethnicity (Table 1.1).

**Image Processing: Cortical Reconstruction & Quality Assessment**

FreeSurfer version 5.3.0 was employed to perform semi-automated cortical reconstruction (Dale et al., 1999; Fischl et al., 1999). In brief, individual scans were intensity normalized, skull stripped, and registered to a standard space. White matter and pial surfaces were then constructed using a polygonal tessellation. All images and surfaces were visually inspected on a slice-by-slice basis and images with inaccurate surfaces or excessive image artifacts, such as ghosting or ringing, were excluded. SA and CT were calculated at each FreeSurfer surface vertex and local gyrification index (LGI) was measured using an additional FreeSurfer processing stream (Schaer et al., 2008). LGI is a 3-D, surface-based method for calculating the ratio of cortical surface area buried within the sulcal folds relative to the amount of cortex on the outer visible cortex within a sphere of 25mm default radius surrounding each surface vertex.

**Statistical Analyses**

Statistical analyses were performed for each vertex using a two-step general linear model, with separate models for CT, SA, and LGI. All analyses were conducted with total brain volume (TBV) and non-verbal IQ as covariates, given group differences on these measures. A smoothing kernel of 15-mm full width half maximum was applied for CT and SA analyses, while no additional smoothing was implemented for LGI since the measure is inherently smoothed. Corrections for vertex-wise multiple comparisons were conducted using Monte Carlo null-z simulations, with a cluster forming threshold of $p<0.01$ and a cluster-wise significance threshold of $p<0.05$.

Main effects and group by age interactions were tested in separate models to ensure that the presence of main effects would not be confounded by interactions. Main effects of group and age were tested using the '*different offset, same slope*' (DOSS) matrix design as implemented in FreeSurfer with the model: $Outcome_i = \beta_0 + \beta_1 Age_i + \beta_2 Group_i + \beta_3 TBV_i + \beta_4 NVIQ_i + \varepsilon_i$. Group by age interactions were tested using the '*different offset, different slope*' (DODS) matrix design with the model: $Outcome_i = \beta_0 + \beta_1 Age_i + \beta_2 Group_i + \beta_3 Age_i * Group_i + \beta_4 TBV_i + \beta_5 NVIQ_i + \varepsilon_i$.

Clusters of significant group effects were used as regions of interest for behavioral analyses. Mean values were extracted and partial correlations controlling for age were run to examine the relationships between anatomy and scores on the SRS-2 (total score), ADOS-2 (Social Affect, Restricted and Repetitive Behavior, and Total scores), and subtests of the D-KEFS. Behavioral analyses were adjusted for multiple comparisons using False Discovery Rate (FDR; Benjamini & Hochberg, 1995).

**Data Availability**

Data included in these analyses will be available through the NIMH Data Archive (NDA; https://ndar.nih.gov/). Qualified researchers may request access through the NDA system.

## RESULTS

No significant group by age interactions were observed in the model for LGI, but the main effect model revealed several clusters of decreased LGI in the ASD group that reached large effect sizes (Figure 1, Table 1.2). These were observed bilaterally in perisylvian (G-4 & G-6) and anterior cingulate regions (G-2 & G-7), left postcentral (G-1) and middle frontal gyri (G-3), and right orbitofrontal (G-5) and supramarginal regions (G-8). Main effects of age were also observed (Figure), showing LGI declining with age in the right supramarginal (G-11) and bilateral precentral gyri (G-9 & G-10).

No main effects of group or group by age interactions were observed for CT or SA, but a significant negative main effect of age on CT was observed across the cortex. No main effects of age on SA were observed.

In the behavioral analyses (Table 1.3), no significant correlations were observed with ADOS scores in the ASD group. Greater gyrification bilaterally in insular regions in the ASD group (clusters G-4 and G-6) was associated with higher (better) verbal fluency scores, a neuropsychological measure of generativity on the D-KEFS (Table 1.4). Similarly, greater gyrification in the ASD group in the right orbitofrontal region (cluster G-5) was related to higher scores on a test of set shifting. This pattern of correlations is consistent with the main effect of regionally decreased gyrification in the ASD group, who showed lower performance on tests of executive function on average. In the TC group, greater gyrification in the right anterior cingulate (cluster G-7) was associated with higher SRS total scores, indicating poorer social

functioning, but this relationship was absent in the ASD group. Behavioral correlations did not remain statistically significant following FDR adjustment.

## DISCUSSION

The current study provides evidence of regionally decreased LGI in adults with ASD between 41 and 61 years of age. Decreased LGI may suggest accelerated tissue loss, possibly consistent with previous research reporting increased cortical thinning in early adulthood in ASD (Braden & Riecken, 2019). Two clusters of reduced LGI were located bilaterally in the insula, overlapping with areas of *increased* LGI found in a previous study (Kohli et al., 2019) of two independent samples of children and adolescents with ASD. This spatial overlap may indicate that regions most affected by early over-gyrification are also more susceptible to subsequent decline in ASD. However, given the lack of a statistically significant group by age interaction in the present study, this interpretation should be made with caution. Both the current and this previous study in adolescents showed group differences in LGI but not CT or SA, suggesting that LGI may be a more sensitive measure of abnormalities of cortical macrostructure in ASD. The observed correlations between LGI and executive function scores in the same insular clusters further supports the potential clinical relevance of these LGI differences.

While no group by age interactions were observed in the current study, the clusters of decreased LGI in the anterior cingulate are consistent with our previous report of a group by age interaction in an overlapping area, which showed greater decline in LGI across childhood and adolescence in individuals with ASD. This may indicate that LGI of the anterior cingulate cortex begins to decrease in adolescence leading to a measurable difference between groups in adulthood, again supporting an atypical trajectory of LGI change. The location of this effect is of particular interest given post-mortem reports of altered cellular density in anterior cingulate

cortex in ASD (Bailey et al., 1998) and the known importance of this brain region in social and emotional function (Mundy, 2003). Additionally, the presence of a correlation between gyrification in the right anterior cingulate and social function in the TC group but not in the ASD group may suggest a disruption of this region's typical function in the disorder.

In conclusion, the pattern of regionally decreased LGI observed here in middle-aged adults with ASD is consistent with an abnormal trajectory of cortical folding changes across different stages of life in ASD as shown in previous studies. Correlations between regional LGI and performance on tests of executive function suggests a potential functional impact of these brain changes.

**Limitations**

The present study examined a relatively small sample of adults with ASD. However, given the extremely limited literature on this age range, it provides valuable early insight into neuroanatomical differences that may present with older age in the disorder. The study included mostly high functioning individuals, which is necessary to ensure high quality MRI data but may limit the generalizability of findings. Finally, due to the cross-sectional nature of the data, we were unable to directly test for age-related changes. Follow-up longitudinal analyses will allow for better characterization of changes in brain structure that occur over the second half of the lifespan in ASD.

Chapter 1, in full, is a reprint of the material as it appears in the Journal *Neurology, 93,* e1900-e1905. **Kohli, J.S.,** Kinnear, M.K., Martindale, I.A., Carper, R.A. & Müller, R.A.**,** American Academy of Neurology, 2019. The dissertation author was the primary investigator and author of this paper.

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**Table 1.1 Participant demographics and group characteristics**

| | ASD (n=20) | | TC (n=21) | | |
|---|---|---|---|---|---|
| | mean (SD) | range | mean (SD) | range | *p-value* |
| Age | 50.2 (5.9) | 41.1-60.6 | 50.8 (6.9) | 40.4-60.9 | 0.77 |
| TBV ($cm^3$) | 1096 (103) | 876-1235 | 1165 (75) | 1031-1321 | 0.02 |
| SRS Total | 69.2 (12.0) | 54-90 | 44.5 (3.9) | 39-53 | <0.01 |
| WASI-II | | | | | |
| Verbal | 99.65 (29.05) | 44-160 | 118.38 (16.71) | 82-153 | 0.01 |
| Non-Verbal | 106.7 (22.91) | 56-142 | 117.43 (13.44) | 90-145 | 0.07 |
| Full Scale | 101.55 (27.76) | 48-154 | 120.90 (11.85) | 103-147 | 0.01 |
| ADOS-2 | | | | | |
| SA | 11.5 (3.9) | 6-19 | -- | -- | -- |
| RRB | 3.9 (1.9) | 1-8 | -- | -- | -- |
| Total | 15.4 (3.9) | 9-22 | -- | -- | -- |
| Female | n = 4 | | n = 1 | | 0.43 |
| Non-White | n = 2 | | n = 3 | | 0.42 |
| Hispanic | n = 2 | | n = 3 | | 0.43 |

ASD, Autism Spectrum Disorder; TC, Typical Comparison; TBV, Total Brain Volume; WASI-II, Wechsler Abbreviated Scale of Intelligence, Second Edition; ADOS-2, Autism Diagnostic Observation Schedule, Second Edition; SA, Social Affect; RRB, Restricted and Repetitive Behaviors

**Table 1.2 Clusters of significant effects on LGI**

| Cluster Number | Hemisphere | Location (Peak Vertex) | Direction | Size (mm2) | Cluster-Wise *p*-value | Effect Size (Cohen's *d*) |
|---|---|---|---|---|---|---|
| Main Effect of Group | | | | | | |
| G-1 | Left | Postcentral Gyrus | ASD<TD | 824.98 | 0.0002 | -1.23 |
| G-2 | Left | Caudal Anterior Cingulate Gyrus | ASD<TD | 1024.9 | 0.0002 | -1.46 |
| G-3 | Left | Caudal Middle Frontal Gyrus | ASD<TD | 501.71 | 0.0002 | -1.30 |
| G-4 | Left | Insula | ASD<TD | 362.1 | 0.0036 | -1.38 |
| G-5 | Right | Lateral Orbitofrontal Cortex | ASD<TD | 473.61 | 0.0002 | -1.40 |
| G-6 | Right | Insula | ASD<TD | 2033.66 | 0.0002 | -1.52 |
| G-7 | Right | Caudal Anterior Cingulate Gyrus | ASD<TD | 566.19 | 0.0002 | -1.44 |
| G-8 | Right | Supramarginal Gyrus | ASD<TD | 406.81 | 0.001 | -1.18 |
| Main Effect of Age | | | | | | |
| G-9 | Left | Precentral Gyrus | Decline | 1348.34 | 0.0002 | -- |
| G-10 | Right | Precentral Gyrus | Decline | 1337.72 | 0.0002 | -- |
| G-11 | Right | Supramarginal Gyrus | Decline | 1325.34 | 0.0002 | -- |

**Table 1.3 Pearson correlations with behavioral measures**

| Group | Cluster Number | SRS Total | DKEFS Trails Switching | DKEFS Letter Fluency | DKEFS Category Fluency | DKEFS Category Switching | DKEFS CWI Inhibition | DKEFS CWI Inhibition/Switching | ADOS SA | ADOS RRB | ADOS Total |
|---|---|---|---|---|---|---|---|---|---|---|---|
| ASD (n=20) | G-1 | 0.177 | -0.219 | -0.346 | -0.178 | -0.221 | -0.065 | -0.257 | 0.095 | 0.101 | 0.142 |
| | G-2 | 0.254 | 0.249 | 0.093 | 0.214 | 0.020 | 0.104 | 0.062 | 0.029 | -0.266 | -0.103 |
| | G-3 | -0.005 | -0.251 | -0.234 | -0.054 | -0.031 | -0.047 | -0.196 | 0.359 | -0.154 | 0.274 |
| | G-4 | -0.490 | 0.341 | 0.391 | .484* | 0.200 | 0.440 | 0.404 | -0.201 | 0.228 | -0.084 |
| | G-5 | 0.546 | .569* | 0.180 | 0.190 | 0.272 | 0.166 | 0.255 | 0.042 | -0.359 | -0.137 |
| | G-6 | 0.462 | 0.227 | .508* | 0.366 | .519* | 0.235 | 0.118 | -0.158 | -0.184 | -0.245 |
| | G-7 | -0.094 | 0.244 | 0.239 | 0.277 | 0.008 | 0.192 | 0.134 | 0.110 | -0.279 | -0.030 |
| | G-8 | 0.101 | -0.292 | -0.095 | -0.129 | 0.157 | -0.220 | -0.246 | -0.079 | -0.257 | -0.204 |
| TC (n=21) | G-1 | 0.131 | -0.341 | -0.396 | -0.474 | -0.456 | 0.030 | 0.080 | -- | -- | -- |
| | G-2 | 0.269 | -0.394 | -0.307 | -0.471 | -0.413 | -0.411 | -0.055 | -- | -- | -- |
| | G-3 | 0.059 | -0.278 | -0.406 | -0.307 | -0.224 | 0.094 | 0.224 | -- | -- | -- |
| | G-4 | 0.157 | -0.186 | 0.010 | -0.108 | -0.088 | 0.361 | 0.314 | -- | -- | -- |
| | G-5 | 0.356 | -0.471 | -0.232 | -0.421 | 0.087 | -0.184 | 0.105 | -- | -- | -- |
| | G-6 | 0.241 | 0.320 | 0.391 | 0.323 | -0.019 | 0.432 | .517* | -- | -- | -- |
| | G-7 | .662** | -0.196 | -0.285 | -0.412 | -0.306 | -0.049 | 0.218 | -- | -- | -- |
| | G-8 | 0.281 | -0.334 | -0.280 | -0.130 | -0.320 | 0.183 | 0.093 | -- | -- | -- |

ASD, Autism Spectrum Disorder; TC, Typical Control; SRS, Social Responsiveness Scale; DKEFS, Delis Kaplan Executive Function System; CWI, Color Word Interference; ADOS-2, Autism Diagnostic Observation Schedule, Second Edition; SA, Social Affect, RRB, Restricted and Repetitive Behaviors

*p < 0.05, **p < 0.01, uncorrected

All comparisons were non-significant following False Discovery Rate (FDR) adjustment

**Table 1.4 DKEFS scores**

| | ASD (n=20) | | TC (n=21) | | |
|---|---|---|---|---|---|
| | **mean (SD)** | **range** | **mean (SD)** | **range** | ***p-value*** |
| Trails: Switching | 9.9 (3.9) | 1-15 | 12.1 (2.4) | 6-15 | 0.05 |
| Verbal: Letter Fluency | 8.5 (4.5) | 1-19 | 13.3 (2.8) | 9-18 | <0.01 |
| Verbal: Category Fluency | 7.8 (3.9) | 1-14 | 13.4 (3.1) | 6-18 | <0.01 |
| Verbal: Category Switching | 9.0 (4.9) | 1-19 | 12.3 (4.2) | 1-17 | 0.04 |
| CWI: Inhibition | 8.4 (4.3) | 1-13 | 11.8 (2.8) | 5-16 | 0.01 |
| CWI: Inhibition/Switching | 9.3 (3.9) | 1-14 | 12.3 (1.8) | 5-16 | 0.01 |

CWI, Color Word Interference

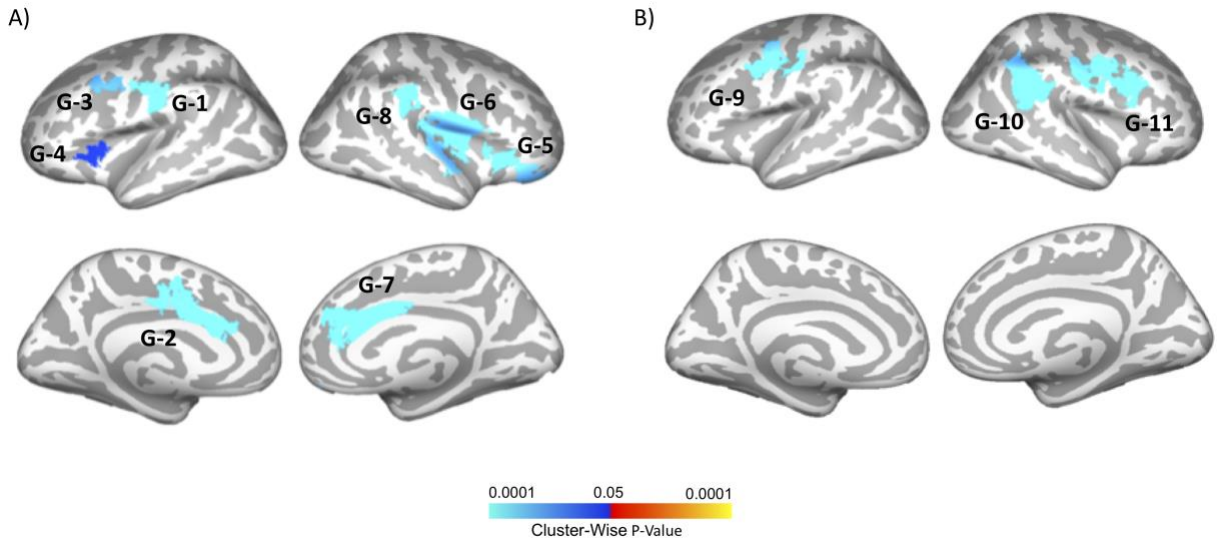


**Figure 1.1 Main effects of group and age on LGI**
A) LGI is significantly decreased bilaterally in anterior cingulate, insular, and perisylvian regions in the ASD group. B) LGI declines with age across groups in the right supramarginal and bilateral precentral gyri. Cluster forming threshold $p < 0.01$, cluster-wise significance threshold $p < 0.05$.

Chapter 2. Study 2

# Decreased gray-white contrast and links to symptomatology in middle to older aged adults with autism spectrum disorder

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## ABSTRACT

Autism Spectrum Disorder (ASD) is highly prevalent lifespan neurodevelopmental condition with substantial behavioral and neuroanatomical heterogeneity. Previous neuroimaging research from across the lifespan in ASD has been limited by approaches that compare group-level averages, potentially washing out important and informative interindividual variability in a set of conditions that are acknowledged to be neurobiologically diverse. The current study expands the use of a normative modeling approach to compare cortical thickness (CT) and gray-white contrast (GWC) between adults with ASD (n=30) and typical comparison (TC; n=36) participants aged 40-70 years. Group-wise analysis employed a general linear model approach, while subject-specific analyses were conducted using an outlier mapping method. Significant negative main effects of age were observed bilaterally for both CT and GWC in the group-wise analysis. Subject specific analyses showed a significantly greater extent of decreased GWC in ASD in spatially heterogenous regions, which was also associated with greater social affect symptoms and higher levels of dysexecutive symptoms in ASD. No significant group differences were observed in GWC in the group-wise analysis, highlighting the utility of the subject-specific approach in accounting for spatial heterogeneity in the localization of neuroanatomical differences. The classic case-control paradigm for studies attempting to link brain structure to diagnostic group or behavior in ASD is limited by the necessity to average across participants with heterogeneous symptoms, and ostensibly equally heterogenous neurobiological underpinnings. The subject-specific approach employed here contributes to a better understanding of how atypical structure of the cortex might relate to autism symptomatology and cognitive deficits in middle to older aged adults with ASD.

# INTRODUCTION

Autism Spectrum Disorder (ASD) is highly prevalent lifespan neurodevelopmental condition with substantial behavioral and neuroanatomical heterogeneity. While much is known about both etiology and outcomes in ASD, a large portion of our existing understanding is based predominantly on research in children and young adults. This has left a deficit of knowledge regarding the neurobiological, cognitive, and behavioral changes that occur across the later portion of the lifespan, even though ASD is a lifelong condition (Brugha et al., 2011; Robison, 2019). With a large literature in typical aging showing cognitive declines after age 50 years (Hedden & Gabrieli, 2004) added to the existing deficits well demonstrated in the first half of the ASD lifespan (Levy & Perry, 2011; Magiati et al., 2014; Steinhausen et al., 2016), older individuals with ASD may be particularly vulnerable. With developmental abnormalities potentially resulting in less cognitive reserve, they may also demonstrate less resilience to neurodegenerative changes.

## Neuropsychological Function in Typical Aging and ASD

Research in typical aging shows, among other changes, a decline in motor function beginning after the age of 50 years (Leversen et al., 2012; Potvin et al., 1980), including declines in fine motor skills (Contreras-Vidal et al., 1998; Darling et al., 1989; Hoogendam et al., 2014), coordination (Seidler et al., 2002), and balance (Laughton et al., 2003; Woollacott & Tang, 1997). Similar impairments in fine and gross motor function, coordination, and balance are seen early in development in ASD, with deficits persisting into adolescence and even increasing with age (Freitag et al., 2007; Lloyd et al., 2013; McPhillips et al., 2014). There is some evidence of motor abnormalities in young adults with ASD (Fukui et al., 2018; Glazebrook et al., 2006), but little is known about motor function in adults with autism in later life, when we would expect

decline even in typical aging. There have been reports of high rates of parkinsonism in adults with ASD (Starkstein et al., 2015), along with research showing similar mechanisms of motor dysfunction involving the frontal lobes in both autism and Parkinson's Disease (Hollander et al., 2009). On top of existing developmental deficits, these results suggest that motor function may be particularly vulnerable to accelerated decline with increasing age in at least some individuals with ASD.

Deficits in executive function, a set of cognitive processes involved in controlling complex behavior, are among many cognitive symptoms associated with ASD, and have been proposed to underly some of the diagnostic symptoms (Hill, 2004; Ozonoff, 1995; Wilson et al., 2014). Executive function has been shown across a number of studies to decline in typical aging (Buckner, 2004; Kirova et al., 2015), and is also predictive of functional status, including independent activities of daily living in later life (Royall et al., 2004). A review of executive function in ASD found an overall trend of delayed development across childhood in ASD (O'Hearn et al., 2008), with improved performance in adolescence, but failure to reach developmentally typical levels by adulthood. A meta-analysis of executive function in ASD reported moderately reduced EF that was relatively stable across development (Demetriou et al., 2018), but the sample disproportionately comprised studies of children and young adults. As with motor skills above, known executive function deficits in ASD –when viewed in the context of age-related decline in these abilities in the neurotypical population– are alarming and support the need to understand the biological correlates of this dysfunction in older adults with ASD, to help predict which individuals are most at risk and to support their long-term needs.

**Brain Structure in Typical Aging and ASD**

Atrophy of cortical gray matter in typical aging has been shown to follow a roughly anterior-to-posterior gradient, with frontal and temporal association regions demonstrating earlier decline in both cross-sectional (Walhovd et al., 2011) and longitudinal studies of gray matter volume and cortical thickness (Driscoll et al., 2009; Peelle et al., 2012; Pfefferbaum et al., 2013). This anatomical pattern overlaps broadly with a confluence of ASD-related differences in frontal and temporal cortices (Carper et al., 2002; van Rooij et al., 2018; Wallace et al., 2015), and again suggests that middle-aged and older adults with ASD may be at increased risk of aggravated age-related changes. This is highly concerning in light of the localization of executive functions in the frontal lobes (Alvarez & Emory, 2006; Stuss & Benson, 1984). Indeed, some preliminary research suggests accelerated rates of cortical thinning in adults with ASD, particularly in frontal and temporal regions, but this effect has only been demonstrated cross-sectionally in adults (Braden & Riecken, 2019; Libero et al., 2014), and only one of these included adults over 40 years of age (Braden & Riecken, 2019). Additionally, other studies have shown contradictory results, including an opposite pattern of decreased thinning with age in adults with ASD (Scheel et al., 2011), regionally varying increased and decreased thinning (van Rooij et al., 2018), and no difference as compared to typically aging individuals (Koolschijn & Geurts, 2016). In our own study of a sample partially overlapping with the current analyses, there were no significant differences in cortical thickness when comparing at the group level (18 ASD, 20 typical comparison; Kohli et al., 2019). These inconsistencies may simply relate to some small sample sizes, broad age ranges, or different methodologies used across studies, and they may be attributable to substantial heterogeneity in ASD.

**Heterogeneity at Multiple Levels in ASD**

The ASD diagnosis is likely to encompass a group of conditions of diverse etiology, and heterogeneity within the disorder can be observed at multiple levels. A variety of clinical presentations are considered to fall within the spectrum, especially with changes in the diagnostic criteria over time (American Psychiatric Association, 1952, 1968, 1980, 1994, 2000, 2013), with 5th edition of the Diagnostic and Statistical Manual of Mental Disorders specifically acknowledging heterogeneity within the diagnosis through a change in the nomenclature. Symptomatology can vary widely along the two core diagnostic dimensions of social communication and restricted and repetitive patterns of behavior (Esbensen et al., 2009; Frith et al., 1997; Pickles et al., 2014). The degree of impact on daily living can also range from requiring no assistance to being unable to function without substantial support, and is also related to variability in general cognitive abilities (Estes et al., 2007) and frequency of co-occurring diagnoses in the disorders (Abdallah et al., 2011; Mazzone et al., 2012). Variability in the autism phenotype can likely be attributed to both heterogeneity in the genotype – with a number of genetic variants linked to ASD (Freitag, 2007; Pinto et al., 2010; Yuen et al., 2017) – and experiential heterogeneity in environmental (Garay & McAllister, 2010; Larsson et al., 2005; Mandy & Lai, 2016; Patel et al., 2018; Vargas et al., 2005) and intervention related factors (Broadstock et al., 2007; Howes et al., 2018; Klintwall et al., 2015; Wong et al., 2015).

Interindividual variability at the level of brain structure has been demonstrated across a number of studies spanning different features of cortical structure and different ages (Wallace et al., 2010; Zielinski et al., 2014). These results are likely to reflect the combined effects of both neurodevelopmental and experiential heterogeneity, thus highlighting the need for analysis methods that account for such variability, particularly in older subjects with ASD. Additionally, post-mortem studies of autism report intra-individual heterogeneity in pathophysiology, with

abnormalities of cortical structure (e.g., indistinct lamination, altered cortical thickness, atypical neuronal density in deep cortical layers, etc.), that are described as "patchy" in that they are detected within restricted regions of cortex while adjacent regions are unaffected. These differences are likely due to abnormal neural migration, are highly localized, and vary spatially between individuals (Avino & Hutsler, 2010; Bailey et al., 1998; Casanova et al., 2013).

While most neuroimaging studies examining atypical brain structure in ASD have focused on macro-level differences such as volumetric (Ecker et al., 2012; Lange et al., 2015) and morphological features (Ecker et al., 2013, 2014), attention has recently shifted toward measures of cortical microstructure at the gray-white matter boundary. This zone is of interest in ASD as a result of evidence from histological studies that "blurring" of this margin relates to cortical microstructural differences (Hutsler & Avino, 2013). Gray-white contrast (GWC) has been proposed as an MRI-based index of in vivo cortical microstructure that can map onto these neuropathological aspects of development and has been examined in a few preliminary studies of ASD. A study in adults aged 18-42 years showed significantly reduced gray-white contrast in ASD in bilateral posterior-cingulate, medial frontal, entorhinal, and inferior and superior temporal cortices, left orbitofrontal cortex and temporo-parietal junction, and right dorsolateral prefrontal cortex (Andrews et al., 2017). A subsequent study in children and young adults ranging in age from 7-25 years also showed significantly reduced GWC in ASD, but in somewhat different regions, including bilateral prefrontal cortices, right inferior parietal cortex, postcentral gyrus, and precuneus and left supramarginal gyrus (Mann et al., 2018). The regional differences may be accounted for by the difference in age range but may also be attributable to other characteristics of the samples. While GWC has been shown to be a valuable measure in

ASD, variability of intra- and inter-subject findings from post-mortem and MRI studies indicates that a subject-specific approach may be better suited toward its examination in autism.

The majority of previous brain-mapping research from across the lifespan of ASD has been limited by approaches that essentially compare group-level averages, potentially washing out important and informative interindividual variability in a set of conditions that are acknowledged to be neurobiologically diverse. The current study employs a normative modeling approach (Marquand et al., 2016; Shan et al., 2022; Zabihi et al., 2019) to examine features of cortical structure (CT and GWC) that are hypothesized to vary spatially between individuals, in an effort to account for heterogeneity at multiple levels of the disorder. Participants with ASD were hypothesized to show local differences in cortical structure that deviate from the typical control (TC) mean in either direction for CT (i.e., increased or decreased CT as reported in previous studies), but primarily in the negative direction for GWC (i.e., decreased GWC, or "blurring"). Individual TC participants were also hypothesized to show local differences in either direction for both features, although to a lesser extent than in the ASD group. The degree of cortical atypicality was also hypothesized to be associated with cognitive and behavioral measures, including ASD symptomatology, dysexecutive symptoms, and motor skills.

## METHODS

### Participants

Potential participants for the ASD group were recruited through referrals from community advertisement, autism clinics and service organizations, and participation at local autism-related events (resource fairs, fund raisers, etc.). Given changes in the diagnostic criteria for ASD within the lifetimes of our target population, (American Psychiatric Association, 1952, 1968, 1980, 1994, 2000, 2013), a pre-existing diagnosis of ASD was not required for initial

recruitment, but all diagnoses were verified prior to inclusion in the study as described below. Participants in the TC group were recruited through community advertisement. Participants with a known history of neurological (e.g., epilepsy, tuberous sclerosis) or genetic (e.g., fragile X, Rett syndrome) conditions other than ASD were excluded. TC participants had no first-degree family history of autism nor personal history of other neurological conditions or serious mental illness. ASD diagnoses were confirmed by a clinical psychologist based on the DSM-5 criteria with support from module 4 of the Autism Diagnostic Observation Schedule, Second Edition (ADOS-2; Lord et al., 2012), along with developmental history when available. 110 adults (64 prospective ASD, 46 TC; 40-70 years old) were initially recruited. 27 individuals from the prospective ASD group did not meet these diagnostic criteria and were excluded from further study.

General cognitive abilities were assessed using the Wechsler Abbreviated Scale of Intelligence, 2nd edition (WASI-II; Wechsler, 2011). Motor skills and balance were assessed with the short form version of the Bruininks Motor Abilities Test (BMAT; Bruininks & Bruininks, 2013), with scores available for a subset of 45 participants (19 ASD, 26 TC). Dysexecutive symptoms were subjectively assessed with the Behavior Rating Inventory of Executive Function-Adult (BRIEF; Roth et al., 2000), an informant report measure. BRIEF data were available for a subset of 39 participants (21 ASD, 18 TC).

**MRI data acquisition, processing, and quality assessment**

T1-weighted (T1w) magnetization prepared rapid gradient echo (MPRAGE) (TR=8.776 milliseconds, TE=3.656 milliseconds, flip angle=8°, matrix=320x320, 0.8mm$^3$ resolution) anatomical MRI scans were collected using a 3 Tesla GE Discovery MR750 scanner with a 32-channel head coil with built-in PURE bias correction. The T1w images were processed using

FreeSurfer version 5.3.0-HCP to perform semi-automated cortical reconstruction (Dale et al., 1999; Fischl et al., 1999; Glasser et al., 2013). Briefly, this processing stream includes removal of non-brain tissue using a hybrid watershed/surface deformation procedure (Ségonne et al., 2004), automated Talairach transformation, intensity normalization (Sled et al., 1998), tessellation of the gray matter/white matter boundary, automated topology correction (Fischl et al., 2001; Segonne et al., 2007), and surface deformation following intensity gradients to optimally place the gray/white and gray/cerebrospinal fluid borders at the location where the greatest shift in intensity defines the transition to the other tissue class (Dale & Sereno, 1993; Fischl & Dale, 2000). All FreeSurfer output was examined on a slice-by-slice basis to identify any inaccuracies in surface placement. Scans with major artifacts, such as ghosting or ringing, or surface placement inaccuracies were excluded. Following visual assessment of anatomical MRI data and FreeSurfer output, 10 participants (4 ASD, 6 TC) were excluded from anatomical analyses due to insufficient quality of raw images or surface reconstruction. Two additional ASD participants with atypical neuroanatomical findings (callosal dysgenesis; temporal lobe cyst) were excluded.

Following quality assessment, anatomical MRI data for 66 participants (30 ASD, 36 TC) were included in subsequent statistical analyses. Cortical thickness was calculated as the closest distance from the gray-white boundary to the gray-CSF boundary at each vertex on the tessellated surface (Fischl & Dale, 2000). Gray-white contrast was calculated at each vertex as the ratio of gray matter intensity at a projection fraction of 30% into the cortex divided by the white matter intensity measured at 1.0 mm subjacent to the white matter surface. CT and GWC surface maps were smoothed at a 10mm full-width at half-maximum (FWHM) surface-based Gaussian kernel prior to group-wise statistical analyses.

**Statistical approach**

Group-wise statistical analyses were conducted using a general linear model (GLM) approach applied separately for each measure on a vertex-wise basis, testing for a group by age interaction on CT and GWC as well as main effects of group and age while controlling for perceptual reasoning index (PRI), total brain volume (TBV), and overall gray-white contrast to noise ratio (CNR) of the T1 images. Of note, we have previously reported findings from a similar GLM analysis of CT in a sample partially overlapping with the current study (18 ASD, 20 typical comparison; Kohli et al., 2019). Family wise error (FWE) correction for multiple comparisons using Permutation Analysis of Linear Models (PALM) software was implemented for the group-wise analyses (Winkler, Ridgway, Webster, Smith, & Nichols, 2014).

Subject specific analyses were conducted using an outlier mapping approach. For each individual with ASD, vertex-wise z-scores were calculated based on the mean and standard deviations of CT or GWC within the TC group (Marquand et al., 2016). Z-maps for TC participants were calculated using a leave-one-out procedure. Z-maps were smoothed at 10mm FWHM. A $|z| \geq 1$ threshold was applied, and maps were cluster thresholded to identify "outlier" clusters for each participant. Subsequently, the total surface area of outlier clusters was summed for positive clusters indicating high CT and GWC (HCT and HGWC, respectively) and for negative clusters representing low CT and low GWC (LCT and LGWC, respectively) separately, resulting in outlier "load" scores for each participant. Due to a non-normal distribution of load scores, overall group comparisons were made using non-parametric Mann-Whitney U tests. Behavioral associations were examined within each group using Spearman's correlations between load scores and ADOS, BRIEF, and BMAT scores. Behavioral analyses were adjusted for multiple comparisons with the false discovery rate (Benjamini & Hochberg, 1995).

## RESULTS

### Group-wise statistical analyses

The ASD and TC groups did not differ significantly in terms of age, PRI, gray-white CNR, sex, race, or ethnicity (Table 2.1). No significant group by age interaction effects or main effects of group were observed on either CT or GWC in the vertex-wise models. Significant negative main effects of age were observed bilaterally for both CT and GWC (Figure 2.1). Clusters of decreasing CT with age were located with peak values in right frontal, temporal, and parietal, as well as left frontal regions, while clusters of decreasing GWC with age were localized bilaterally in frontal and parietal regions (Table 2.2).

### Subject-specific statistical analyses

U-tests revealed no significant differences between the ASD and TC groups in the overall distribution of HCT ($p = 0.388$), LCT ($p = 0.487$), or HGWC ($p = 0.447$) outlier load scores, but ranked LGWC load scores ($p = 0.016$) were significantly greater in the ASD group (Figure 2.2). Further, LGWC scores were significantly associated with ADOS Social Affect and BRIEF Global Executive Composite (GEC) subscores in the ASD group (Table 2.3; Figure 2.3). Greater LGWC ranks were associated with greater Social Affect symptoms and higher levels of dysexecutive symptoms in ASD. Only the correlation between LGWC and BRIEF GEC scores remained significant after FDR adjustment of p-values. Load scores were not significantly associated with BMAT scores in the ASD group. No significant behavioral associations were demonstrated in the TC group, though this may have been partly due to floor effects for some measures.

## DISCUSSION

We examined T1w MRI derived CT and GWC measures in middle to older aged adults

compared to typical comparison participants using both group-wise and subject-specific approaches. The subject-specific approach showed a greater spatial extent of decreased GWC in the ASD group, as well as associations with ASD symptomatology and dysexecutive symptoms. No significant differences were observed between groups in GWC in the group-wise analysis, highlighting the utility of the subject specific approach in accounting for spatial heterogeneity in the localization of neuroanatomical differences in adults with ASD.

**Lower GWC in ASD in Spatially Heterogeneous Regions**

Previous studies of the gray-white matter boundary using both post-mortem (Avino & Hutsler, 2010) and in vivo MRI based approaches (Andrews et al., 2017) have proposed that structural abnormalities in this zone are related to disrupted neuronal migratory processes very early in development, with potential genetic underpinnings (Hoerder-Suabedissen et al., 2013; Pan et al., 2019; Reiner et al., 2016; Wegiel et al., 2010). It has also been suggested that GWC may be sensitive to changes in myelin integrity and other age dependent factors (Mann et al., 2018), rather than only atypical gray matter cytoarchitecture or ectopic cells in the white matter. The genetic risk and prognostic factors for ASD are equally, if not more, heterogenous than the symptoms. A number of genetic variants have been shown to confer increased risk of ASD (Pinto et al., 2010; Yuen et al., 2017), with different genetic abnormalities leading to varying levels of impairment (Freitag, 2007). Reviews of genetics research in ASD have reported hundreds of genetic variants and mutations that are related to autism (Jeste & Geschwind, 2014), also noting variability in the level of penetrance, gender ratios, and comorbidities (e.g., epilepsy, schizophrenia, obsessive compulsive disorder, etc.; Vorstman et al., 2017). These data together suggest that diverse neurobiological mechanisms can give rise to the ASD phenotype, which may

result in variable spatial patterns of atypical cortical structure related to early developmental differences between individuals with the diagnosis.

In addition to genetic contributions toward neurobiological differences in ASD, environmental influences such as perinatal factors (Larsson et al., 2005), maternal immune response (Garay & McAllister, 2010; Patel et al., 2018), neuroinflammation (Vargas et al., 2005), and the interaction between genetic and environmental factors have been found to contribute to the autism phenotype (Mandy & Lai, 2016). Individuals with ASD vary in experiential factors such as in the types and length of treatments they have received, a particularly important consideration when studying adults with half a lifetime or more of experience. Just within the range of evidence-based therapies available today, the targeted symptoms can vary widely, along with the degree of efficacy for each intervention (Wong et al., 2015). In addition, pharmacotherapies are often utilized in conjunction with behavioral interventions for the treatment of comorbid conditions such as hyperactivity or anxiety, or to address difficult behaviors such as self-harm (Broadstock et al., 2007; Howes et al., 2018). The type, age of intervention, and duration of each treatment, along with numerous combinations of multiple therapies, all have differing effects on symptoms and long-term outcomes for individuals with ASD (Helt et al., 2008; Klintwall et al., 2015). Taken together, the evidence suggests highly heterogeneous etiologies in ASD that are further compounded by experiential variability, all of which have the potential to differentially impact brain structure and neural resilience later in life. These impacts are likely to vary between individuals, and therefore might be expected to be reflected in heterogenous ways with regard to neuroanatomical organization as shown in our study. Such heterogeneity is also likely to impact the detection of associations with behavior.

## Behavioral Associations

Our results from the ASD group showed a positive association between the total load of decreased GWC and both social affect symptoms and dysexecutive symptoms. These correlations did not rely on a consistent localization of atypical brain structure across participants in the ASD group, but rather reflect the sum-total impact of diffusely located clusters of atypical GWC across the cortex. Although executive function relies heavily on the frontal lobes (Alvarez & Emory, 2006), the network of regions underlying this neuropsychological domain is much broader (Aron, 2008; Collette et al., 2006; Zink et al., 2021). For example, in an fMRI study of individuals with ASD ranging in age from 7-52 years old, executive dysfunction was related to under recruitment of parietal regions rather than differences in frontal lobe activity (May & Kana, 2020). Similarly, brain regions underlying social emotional behavior are distributed across the cortex (Barrett & Satpute, 2013; Blakemore, 2008), and growing evidence from neuroimaging research in ASD in particular suggests that the neural basis of symptomatology cannot be pinpointed to singular or specific regions of the brain, but rather differences in social neural networks comprising nodes throughout the lobes of the brain (Müller & Fishman, 2018). The normative modeling approach employed in the current study is advantageous for detection of brain behavior relationships in ASD in light of the distributed brain regions underlying the behavioral domains impacted in the condition.

## Age-Related Changes in CT and GWC

The trajectories of age effects in both CT and GWC from the vertex-wise analyses did not differ between groups in the current study. For CT, this is in part a recapitulation of our previous report of no group by age interaction effect in a partially overlapping sample including approximately 60% of the same participants (Kohli et al., 2019), and is consistent with another

study of adults aged 30-75 years (Koolschijn & Geurts, 2016). Previous reports of accelerated cortical thinning in adults with ASD have implicated an array of regions, including left temporal cortex (Braden & Riecken, 2019), right anterior cingulate cortex (Laidi et al., 2019), and the left hemisphere broadly (Khundrakpam et al., 2017). There has also been report of both accelerated and decelerated cortical thinning across the cortex in ASD varying based on region and developmental stage in a longitudinal study (Zielinski et al., 2014). It is important to note, however, that only the study by Braden et al. included participants over the age of 40 years. Although older adults with ASD may be vulnerable to accelerated neurodegenerative changes, the regions impacted may be distributed heterogeneously across participants, and differences may wash out when averaging across individuals. At the group level, the current study showed age-related decline in CT and GWC across both participants with ASD and typical controls, consistent with previous literature in typical aging for both structural features (Fjell et al., 2009; Salat et al., 2004, 2009; Thambisetty et al., 2010; Vidal-Piñeiro et al., 2016).

**Limitations and Future Directions**

The current study provides important insights into neuroanatomical differences and associations with cognition and behavior in adults with ASD in the second half of the lifespan, but results should be interpreted with several limitations in mind. The sample size was somewhat limited by difficulties recruiting from this unique, understudied, and underdiagnosed population (Brugha et al., 2011; O'Nions et al., 2023), along with the need for participants to be able to stay still for a long period of time for MRI scanning. Due to the latter, our results may not generalize to the full spectrum of cognitive and functional abilities of adults with ASD. Further, we employed a cross-sectional and linear approach to examine age-effects, which would benefit from follow up using longitudinal methods with consideration for non-linear trajectories of

change in cortical structure. Finally, while we examined CT and GWC as independent indices of cortical anatomy, it should be noted that contrast differences can impact the placement of the gray-white boundary in FreeSurfer, subsequently impacting thickness estimates. Blurring of the boundary as suggested by decreased GWC may lead to inconsistencies in CT measurements.

Despite these limitations, the current study benefits from complementary group-wise and subject-specific analysis approaches for a more comprehensive characterization of cortical anatomy in middle to older aged adults with autism, which may inform future directions for research in this population. The classic case-control paradigm for studies attempting to link brain structure to diagnostic group or behavior in ASD is limited by the necessity to average across participants with heterogeneous symptoms, and ostensibly equally heterogenous neurobiological underpinnings. The subject-specific approach employed here contributes to a better understanding of how atypical structure of the cortex might relate to autism symptomatology and cognitive deficits, as it does not rely on consistent localization or direction of effects across individuals. Continued use of such methods is well suited toward expanding our understanding of how the links between brain structure and behavior evolve as individuals with ASD age, and in future research, may aid in the detection of accelerated degenerative brain changes.

Chapter 2, in full, is currently being prepared for submission for publication. **Kohli, J.S.**, Linke, A.C., Wilinson, M., Alemu, K., Fishman, I., Müller, R.-A., & Carper, R.A. The dissertation author was the primary investigator and author of this paper.

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**Table 2.1** Overall participant characteristics and group matching

| | ASD (n=30) | | | TC (n=36) | | | |
|---|---|---|---|---|---|---|---|
| | Mean | SD | Range | Mean | SD | Range | *p*-value |
| Age (years) | 50.42 | 6.56 | [40.22-67.17] | 51.76 | 7.54 | [40.05-69.89] | 0.452 |
| WASI-II | | | | | | | |
| VCI | 103.83 | 22.43 | [45-160] | 112.47 | 14.20 | [85-144] | 0.062 |
| PRI | 106.74 | 19.65 | [56-138] | 109.64 | 13.27 | [75-138] | 0.768 |
| FSIQ-4 | 104.97 | 20.48 | [51-143] | 112.56 | 12.53 | [90-138] | 0.163 |
| Total Brain Volume | 1100.57 | 105.52 | [876-1397] | 1131.32 | 95.95 | [886-1309] | 0.332 |
| Gray-White CNR | 1.39 | 0.33 | [0.57-1.81] | 1.57 | 0.32 | [0.46-1.89] | 0.786 |
| ADOS-2 | | | | 51.76 | 7.54 | [40.05-69.89] | 0.452 |
| Total Score | 14.03 | 4.18 | [7-23] | -- | -- | -- | -- |
| SA | 10.47 | 3.78 | [5-19] | -- | -- | -- | -- |
| RRB | 3.57 | 1.77 | [1-8] | -- | -- | -- | -- |
| Gender (Male/Female) | 23/7 | | | 28/8 | | | 0.758 |
| Race (White/Non-White) | 24/4 | | | 32/3 | | | 0.485 |
| Ethnicity (Not Hispanic/Hispanic) | 24/3 | | | 29/3 | | | 0.866 |

ASD, Autism Spectrum Disorder; TC, Typical Control; WASI-II, Wechsler Abbreviated Scale of Intelligence, Second Edition; VCI, Verbal Comprehension Index; PRI, Perceptual Reasoning Index; FSIQ, Full-Scale IQ; CNR, Contrast to Noise Ratio; ADOS-2, Autism Diagnostic Observation Schedule, Second Edition; SA, Social Affect; RRB, Restricted and Repetitive Behavior

*p*-value corresponds to t-test or chi square test

**Table 2.2 Main effects of age**

| Measure | Hemisphere | Location (Peak Value) | Cluster-Wise p-value | Size (mm2) | TalX | TalY | TalZ |
|---|---|---|---|---|---|---|---|
| Cortical Thickness | Left | rostral middle frontal | 0.0078 | 520.95 | -31.2 | 47.1 | 4.8 |
| | | pars orbitalis | 0.0005 | 745.64 | -34.2 | 43.5 | 10.8 |
| | | rostral anterior cingulate | 0.0001 | 838.1 | -10.4 | 42.4 | 0.6 |
| | Right | postcentral | 0.0001 | 1674.81 | 61.6 | -6.4 | 25.4 |
| | | supramarginal | 0.0002 | 780.53 | 35.3 | -22.5 | 20.5 |
| | | rostral middle frontal | 0.0058 | 554.38 | 30.5 | 38.7 | 17.6 |
| | | superior frontal | 0.0001 | 1013.81 | 13.9 | 33.3 | 15.7 |
| | | lateral orbitofrontal | 0.0001 | 935.17 | 32.5 | 38.3 | -8.6 |
| Gray-White Contrast | Left | precentral | 0.0001 | 3425.01 | -47 | 3 | 26.5 |
| | | pars triangularis | 0.0001 | 2310.13 | -48.4 | 32.5 | -1.3 |
| | | superior frontal | 0.0001 | 1509.46 | -19.2 | 13 | 47.6 |
| | Right | pars opercularis | 0.0001 | 2715.02 | 37.7 | 21.3 | 9.1 |
| | | paracentral | 0.0001 | 2616.81 | 7.2 | -19.1 | 48.9 |
| | | precentral | 0.0001 | 2916.86 | 39.3 | -15.1 | 31.4 |

**Table 2.3 Behavioral associations (spearman rank order correlations)**

| | | Load Score | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | HCT | | LCT | | HGWC | | LGWC | |
| Group | Behavioral Measure | *rho* | *p*-value | *rho* | *p*-value | *rho* | *p*-value | *rho* | *p*-value |
| ASD | ADOS SA | 0.062 | 0.744 | 0.032 | 0.866 | -0.239 | 0.204 | **0.433** | **0.017** |
| | ADOS RRB | 0.16 | 0.399 | 0.11 | 0.564 | 0.229 | 0.224 | 0.158 | 0.404 |
| | BMAT | 0.04 | 0.87 | -0.027 | 0.912 | 0.121 | 0.621 | -0.108 | 0.660 |
| | BRIEF GEC | 0.205 | 0.385 | -0.29 | 0.215 | -0.242 | 0.303 | **0.590** | **0.006** |
| TC | BMAT | -0.119 | 0.562 | -0.166 | 0.419 | -0.17 | 0.406 | 0.104 | 0.612 |
| | BRIEF GEC | 0.005 | 0.984 | 0.15 | 0.553 | -0.118 | 0.642 | 0.126 | 0.619 |

ASD, Autism Spectrum Disorder; TC, Typical Control; HCT, High Cortical Thickness; LCT, Low Cortical Thickness; HGWC, High Gray White Contrast; LGWC, Low Gray White Contrast; ADOS, Autism Diagnostic Observation Schedule; SA, Social Affect; RRB, Restricted and Repetitive Behaviors; BMAT, Bruininks Motor Abilities Test; BRIEF, Behavior Rating Inventory of Executive Function; GEC, Global Executive Composite

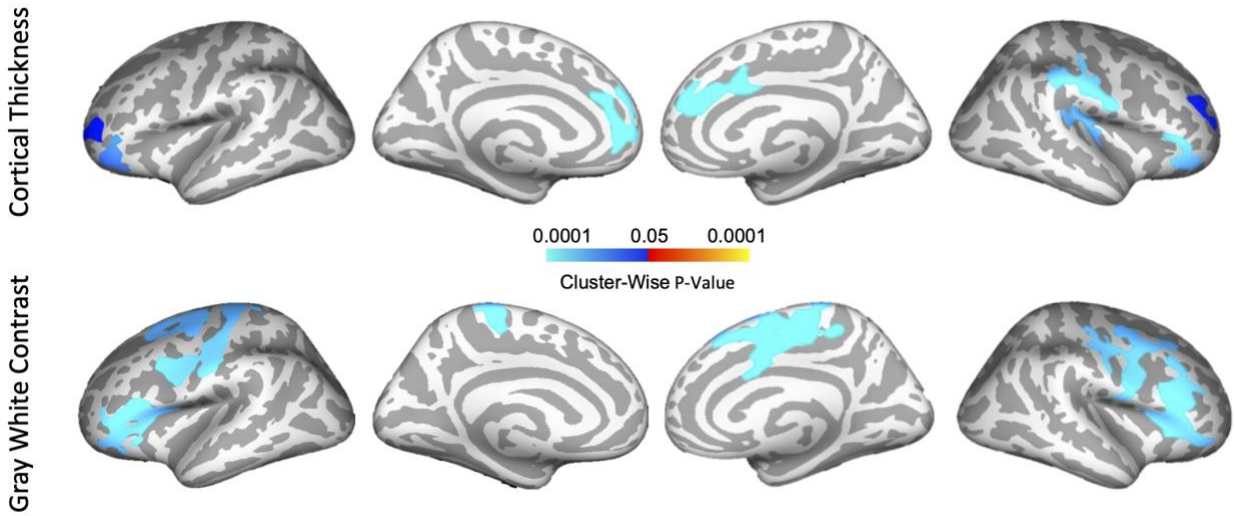


**Figure 2.1 Main effects of age on CT and GWC**
Significant negative main effects of age were observed bilaterally for both CT and GWC. Clusters of decreasing CT with age were located with peak values in right frontal, temporal, and parietal, as well as left frontal regions, while clusters of decreasing GWC with age were localized bilaterally in frontal and parietal regions.
CT, Cortical Thickness; GWC, Gray White Contrast

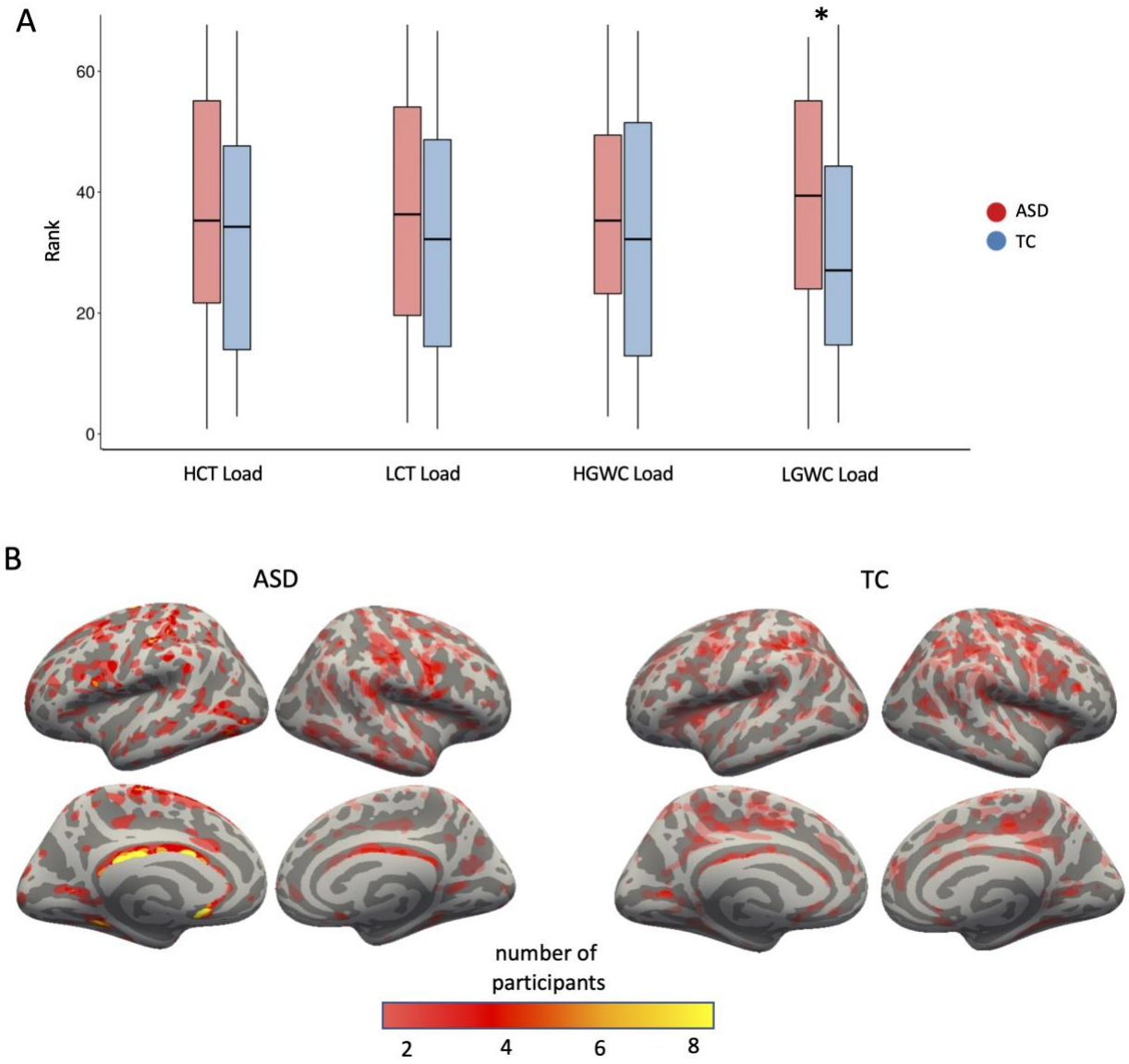


**Figure 2.2 Load score ranks and overlap map of LGWC outlier clusters by group**
(A) U-tests showed higher mean load scores in the ASD group across all load score types, although the difference between groups was only statistically significant for LGWC load (*p = 0.016). (B) Overlap maps of LGWC outlier clusters displayed separately for each group. Clusters were localized diffusely across the bilateral cortex in both groups.
ASD, Autism Spectrum Disorder; TC, Typical Control; HCT, High Cortical Thickness; LCT, Low Cortical Thickness; HGWC, High Gray White Contrast; LGWC, Low Gray White Contrast

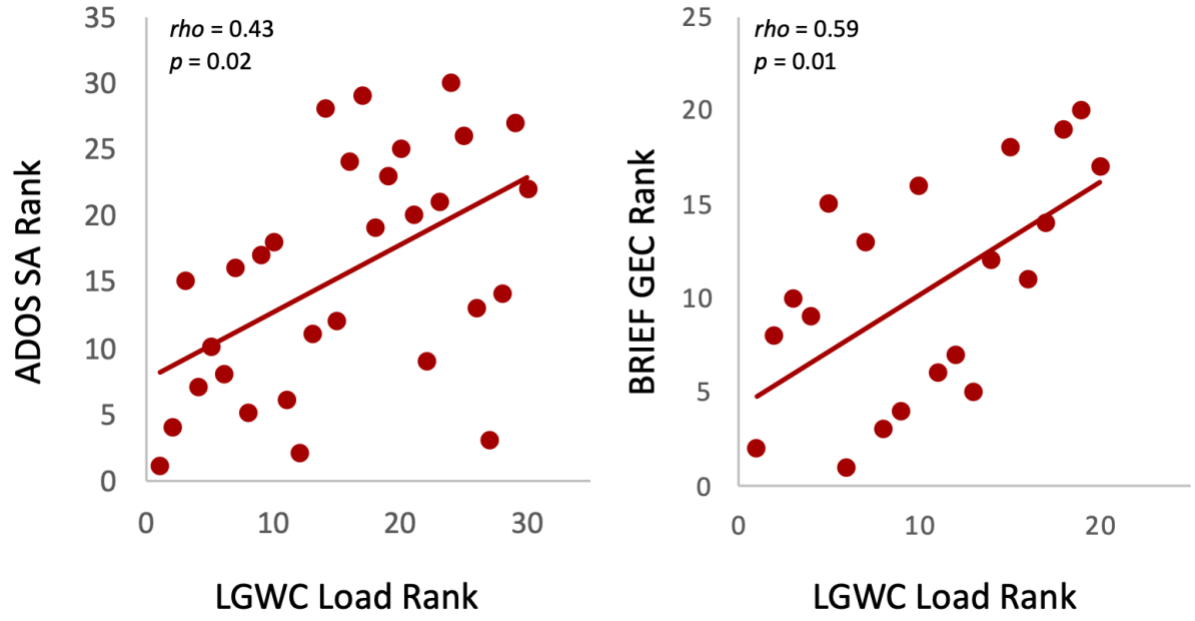


**Figure 2.3 Behavioral associations**
Higher LGWC load ranks were associated with greater SA symptom severity (*rho* = 0.43, *p* = 0.02) and greater dysexecutive symptoms in ASD (*rho* = 0.58, *p* = 0.01). Only the correlation between LGWC load and BRIEF GEC scores remained significant after FDR adjustment of p-values.
LGWC, Low Gray White Contrast; ADOS, Autism Diagnostic Observation Schedule; SA, Social Affect; BRIEF, Behavior Rating Inventory of Executive Function; GEC, Global Executive Composite

Chapter 3. Study 3

# Associations Between Atypical Intracortical Myelin Content and Neuropsychological Functions in Middle to Older Aged Adults with ASD

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## ABSTRACT

In vivo myeloarchitectonic mapping based on MRI provides a unique view of gray matter myelin content and provides information complementary to other morphological indices commonly employed in studies of autism spectrum disorder (ASD). The current study sought to determine if intracortical myelin content (MC) and its age-related trajectories differ between individuals with ASD (n=30) and age-matched typical control (TC; n=36) participants aged 40-70 years. Given substantial heterogeneity demonstrated in both etiology and outcomes in ASD, we utilized both group-wise and subject-specific approaches to test for signs of atypical intracortical MC. Groupwise analyses showed no significant differences between groups in average MC or its associations with age, but revealed significant positive age effects bilaterally, with MC increasing with age across much of the cortex. In subject-specific analyses, neuropsychological function differed between subgroups classified within diagnostic groups by presence or absence of clusters of aberrant MC, with poorer performance on average in the ASD subgroup with atypically high MC compared to all other subgroups in spatially heterogeneous cortical regions. Differences were noted across several domains, including overall intellectual functioning, processing speed, and aspects of executive function. The groupwise and subject-specific approaches employed here demonstrate the value of examining inter-interindividual variability and provide important preliminary insights into potential links between brain structure and behavior in the second half of the lifespan in ASD.

# INTRODUCTION

*In vivo* myeloarchitectonic mapping based on MRI provides a unique view of gray matter content and offers complementary information to the morphological indices that have been commonly employed in many studies of brain-behavior relationships (e.g., cortical thickness, surface area, etc.). Intracortical myelin development and remodeling are protracted across the typical lifespan, and there is evidence of atypical cortical myelination in some neuropsychiatric disorders (Lake et al., 2017), as well as in age-related mild cognitive impairment and dementia (Bouhrara et al., 2018). Autism spectrum disorder (ASD) is a neurodevelopmental disorder characterized by social communication deficits and restricted and repetitive behaviors (American Psychiatric Association, 2013) and is a lifelong condition (Robison, 2019), but there is a deficit of knowledge about the neurobiological, cognitive, and behavioral changes that may occur across the later portion of the lifespan in ASD. In young adults with ASD, myelin content (MC) has been shown to be reduced in white matter (Deoni et al., 2015), but patterns of intracortical myelination specifically have not yet been examined in older adults with ASD. With the added risk of demyelination associated with aging, middle- to older-aged adults with ASD are an important population to examine, as they may be doubly at risk for alterations in cortical myelination.

## Ongoing Intracortical Myelin Development and Changes in Adulthood

Myelin is formed by multiple layers of insulating glial cells, rich in lipids, that wrap around axons and facilitate the conduction of electrical impulses. It is vital for healthy brain function (Martenson, 1992) and while myelin is most abundant in white matter, a significant number of myelinated fibers are present in some layers of cortical gray matter (Fracasso et al., 2016; O. Vogt, 1910). Postmortem histological studies have shown substantial variability in the

regional distribution of myelinated fibers between different cortical areas (Hopf, 1956, 1968; Nieuwenhuys, 2013; C. Vogt & Vogt, 1919). Compared to other species, the human brain is particularly high in myelin content (Bartzokis & Lu, 2009) and is also unique in its protracted development (Yakovlev et al., 1967) with myelination reaching its peak in multimodal association areas of the prefrontal cortex only in middle age (Flechsig, 1920; Sowell et al., 2003). These spatial and temporal patterns have been replicated using MRI-derived myelin maps, which further confirm that intracortical myelin maturation is ongoing at least into the fourth decade of life, followed by 20 relatively stable years before declining from the sixth decade (Grydeland et al., 2013).

Myelin content varies across the cortex in conjunction with the density of neurons per unit cortical volume (Glasser et al., 2014), with high neuronal density in primary somatosensory, auditory, and visual areas (Collins et al., 2010) that also demonstrate higher myelin content (Glasser & Van Essen, 2011). In contrast, lightly myelinated areas that have larger neuronal cell bodies demonstrate lower neuronal densities and more complex intracortical circuitry, including larger dendritic field sizes and arbors with more dendritic spines (Elston et al., 2001, 2006). This regional variability has important implications for cognitive processing. While myelination is likely to have evolved to speed axonal conduction in white matter beneath the cortex (Hartline & Colman, 2007), it has been suggested that a major function of *intracortical* myelination is to inhibit formation of aberrant or superfluous connections (Braitenberg, 1962). This hypothesis is supported by a considerable amount of molecular evidence showing that myelin-related factors inhibit new axonal growth and synapse formation (M. S. Chen et al., 2000; Kapfhammer & Schwab, 1994; McGee et al., 2005; McGee & Strittmatter, 2003; McKerracher et al., 1994). Therefore, regional deficits and atypical degeneration of intracortical myelin may increase

susceptibility to aberrant connections, which might in turn underlie some cognitive and behavioral problems like those seen in developmental conditions such as autism spectrum disorder (ASD).

**Cognitive and Neuroanatomical Changes in Middle to Older Aged Adults with Autism**

Based on studies of adults ranging in age from 18 to 48 years, it is clear that a large portion of individuals with ASD continue to show some degree of cognitive impairment and require support beyond childhood (Billstedt, Gillberg, & Gillberg, 2005; Howlin, Goode, Hutton, & Rutter, 2004; Szatmari, Bartolucci, Bremner, Bond, & Rich, 1989; Wing & Shah, 2000). A large literature in typical aging shows cognitive declines after age 50 years (Hedden & Gabrieli, 2004). Added to the existing deficits well demonstrated in the first half of the ASD lifespan (Levy & Perry, 2011; Magiati, Tay, & Howlin, 2014; Steinhausen, Mohr Jensen, & Lauritsen, 2016), older individuals with ASD may be doubly at risk of deficits. With developmental differences resulting in less cognitive reserve, they may experience less resilience to neurodegenerative changes. A few preliminary studies in middle- to older-aged adults have indeed found continuation and potential exacerbation of existing symptomatology along with accelerated neuroanatomical changes. For example, cortical thickness has been found to be reduced in ASD in brain areas related to social cognition in adults aged 20-55 (Scheel et al., 2011), as has cerebellar volume in adults aged 18-58 (Hallahan et al., 2009). Other anatomical studies examining age related effects have indicated differential rates of morphological change across adulthood compared to typical controls both in our own sample (Kohli et al., 2019) and others (Braden & Riecken, 2019). Our own connectivity studies have suggested both functional and anatomical differences underlying motor dysfunction in adults with ASD, with results indicating reduced and more variable sensorimotor cortex functional connectivity (Linke et al.,

2020) and diminished morphological laterality and u-fiber connectivity based on diffusion MRI analyses (Hau et al., 2022).

**Intracortical Myelin Content is Associated with Cognition and Neuropsychiatric Disorders**

Thus far, attempts to link lifespan trajectories of intracortical myelin content to cognitive functioning have been limited, even in typical populations, and associations in neurological disorders have largely been based on post-mortem studies. One study of adults aged 20-83 years showed that better performance stability on a speeded task was correlated with a greater degree of intracortical myelination, and the relationship was more prominent with advancing age, suggesting that age-related cortical demyelination contributes to dysfunctional increase in intraindividual variability in performance (Grydeland et al., 2013). There is also evidence of demyelination in mild cognitive impairment and dementia (Bouhrara et al., 2018).

Notably, aberrant intracortical myelination has been implicated in neuropsychiatric disorders such as schizophrenia and bipolar disorder, where postmortem myelin stains have shown reduced myelin localized to dorsolateral prefrontal cortex compared to controls (Lake et al., 2017). An MRI study of myelin water fraction in young adults with ASD showed widespread reduction of myelin content in cerebral white matter (Deoni et al., 2015). Another MRI study found differential age-related trajectories of estimated intracortical myelin content between typically developing (TD) toddlers and pre-school aged children and those with ASD, where TD children showed increases that were absent in the ASD group in early myelinating regions such as visual, posterior cingulate, and precuneus cortices (B. Chen et al., 2022). The trajectory of intracortical myelination across the lifespan remains understudied, however, and there have yet to be in vivo investigations into cortical myeloarchitectonic developmental and degenerative processes across adulthood in autism.

**In Vivo Study of Myelin Content and Associations with Cognition in Adults with Autism**

MRI based intracortical myelin mapping has shown promise as an in vivo index of myelin content and may prove useful in testing for altered rates of change in ASD. Non-invasive MRI measures of myelin have been directly validated using myelin stains in marmoset monkeys (Bock et al., 2009), as well as against histological stains in post-mortem human brain samples showing correspondence between cyto- and myeloarchitecture (Geyer et al., 2011). The T1w/T2w ratio method used in the current study in particular has been demonstrated to be informative across the full range of myelination densities in the cortex, from highly myelinated primary auditory and visual cortices to the more lightly myelinated higher order areas such as anterior insula and cingulate cortex (Glasser et al., 2014). The current study sought to determine if intracortical myelin content (MC) and its age-related change trajectories differ between individuals with ASD and age-matched typical control (TC) participants aged 40-70 years. Given substantial heterogeneity demonstrated in both etiology and outcomes in ASD (Jeste & Geschwind, 2014; Lenroot & Yeung, 2013), the current study also employed subject-specific analyses to reveal potential directional and spatial variability across individuals in the regions demonstrating atypical intracortical MC. MC was hypothesized to be decreased due to neurodegenerative effects, as in other disorders (Bouhrara et al., 2018; Davis et al., 2003). However, analyses allowed for the detection of increased MC as well, given evidence that disruption of myelin-related molecular factors that inhibit new axonal growth and synapse formation (Chen et al., 2000; Kapfhammer & Schwab, 1994) may relate to differences in cortical connectivity (Glasser et al., 2014). Analyses of age-effects were hypothesized to show a pattern of cortical demyelination across both groups based on research in typical aging (Peters, 2002; Safaiyan et al., 2016), but with potential accelerated decline with increasing age in ASD. Finally,

the current study related MC measures to cognitive abilities at risk of decline during typical aging, hypothesizing associations between atypical MC and poorer neuropsychological performance in ASD.

## METHODS

### Participants

110 adults (64 prospective ASD, 46 TC; 40-70 years old) were initially recruited as part of an ongoing longitudinal study. Potential participants for the ASD group were recruited through referrals from autism clinics and service organizations, advertisement at local autism-related events (resource fairs, fund raisers, etc.), and community advertisement. Adults in the target age range were born between 1945 and 1975. Our understanding of the symptomology of autism has changed substantially over the course of their lifetimes with a steady broadening of diagnostic criteria (American Psychiatric Association, 1952, 1968, 1980, 1994, 2000, 2013). We therefore cast a broad net for recruitment of prospective participants for the ASD group, and a pre-existing diagnosis of ASD was not required for initial recruitment, but all diagnoses were confirmed as described below before full study inclusion. Participants in the TC group were recruited through community advertisement. Participants with a history of neurological (e.g., epilepsy, tuberous sclerosis) or genetic (e.g., fragile X, Rett syndrome) conditions other than ASD were excluded. TC participants had no family history of autism nor personal history of other neurological conditions or serious mental illness. ASD diagnoses were verified by a clinical psychologist based on the Diagnostic and Statistical Manual of Mental Disorders, 5$^{th}$ edition criteria and supported by module 4 of the Autism Diagnostic Observation Schedule, Second Edition (ADOS-2; Lord et al., 2012), along with developmental history when available.

27 individuals from the prospective ASD group did not meet these diagnostic criteria and were excluded from further study.

General cognitive abilities were assessed for both ASD and TC groups using the Wechsler Abbreviated Scale of Intelligence, 2nd edition (WASI-II; Wechsler, 2011). Aspects of processing speed and executive function were objectively assessed using the Trail Making and Verbal Fluency Tests from the Delis-Kaplan Executive Function System (DKEFS; Delis et al., 2001). Specifically, the Number Sequencing and Letter Sequencing conditions from the Trail Making Test were interpreted as processing speed indices, while the Number Letter Sequencing condition reflected set shifting ability. Dysexecutive symptoms were subjectively assessed with the Behavior Rating Inventory of Executive Function-Adult (BRIEF; Roth et al., 2000), an informant report measure. BRIEF data were available for a subset of 39 participants (21 ASD, 18 TC).

**MRI data acquisition**

Anatomical MRI scans were obtained using a 3 Tesla GE Discovery MR750 scanner with a 32-channel head coil with built-in PURE bias correction, and included a T1-weighted (T1w) magnetization prepared rapid gradient echo (MPRAGE) sequence (TR=8.776 milliseconds, TE=3.656 milliseconds, flip angle=8°, matrix=320x320, 0.8mm$^3$ resolution) and T2-weighted (T2w) CUBE sequence (TR=61.803 milliseconds, TE=3200 milliseconds, flip angle=8°, matrix=320x320, 0.8mm$^3$ resolution). Data included in this study will be available through the National Institute of Mental Health Data Archive (nda.nih.gov). Qualified researchers may request access through this system.

**MRI data processing and quality assessment**

Anatomical images were registered in preprocessing using affine boundary based cross-modal registration (Jenkinson et al., 2012). The T1w images were then processed using FreeSurfer version 5.3.0-HCP to perform semi-automated cortical reconstruction (Dale et al., 1999; Fischl et al., 1999). Briefly, this processing stream includes removal of non-brain tissue using a hybrid watershed/surface deformation procedure (Ségonne et al., 2004), automated Talairach transformation, intensity normalization (Sled et al., 1998), tessellation of the gray matter/white matter boundary, automated topology correction (Fischl et al., 2001; Segonne et al., 2007), and surface deformation following intensity gradients to optimally place the gray/white and gray/cerebrospinal fluid borders at the location where the greatest shift in intensity defines the transition to the other tissue class (Dale & Sereno, 1993; Fischl & Dale, 2000). All FreeSurfer output was examined on a slice-by-slice basis to identify any inaccuracies in surface placement. Scans with major artifacts, such as ghosting or ringing, or surface placement inaccuracies were excluded. Following visual assessment of anatomical MRI data and FreeSurfer output, 10 participants (4 ASD, 6 TC) were excluded from anatomical analyses due to insufficient quality of raw images or surface reconstruction. Two additional ASD participants with atypical neuroanatomical findings (callosal dysgenesis; temporal lobe cyst) were excluded.

Intracortical MC was estimated in postprocessing by dividing the T1w image by the T2w image and mapping values onto the FreeSurfer-generated cortical surface in order to facilitate surface-based analyses (Glasser et al., 2014; Glasser et al., 2013; Glasser & Van Essen, 2011). Myelin maps were further quality assessed by visual inspection to ensure proper translation from the cortical ribbon into surface space. After completion of quality control steps, anatomical MRI data for 66 participants (30 ASD, 36 TC) were included in subsequent statistical analyses.

**Statistical approach**

Group-wise statistical analyses were conducted using a general linear model approach applied on a vertex-wise basis, testing for a group by age interaction on MC as well as main effects of group and age while controlling for perceptual reasoning index (PRI), total brain volume (TBV), and gray-white contrast to noise ratio (CNR) of the T1 images. Family wise error (FWE) correction for multiple comparisons using Permutation Analysis of Linear Models (PALM) software was implemented (Winkler, Ridgway, Webster, Smith, & Nichols, 2014).

Subject-specific analyses were conducted using an outlier mapping approach. For each individual with ASD, vertex-wise z-scores were calculated based on the mean and standard deviations of MC within the TC group (Marquand et al., 2016). Z-maps for TC participants were calculated using a leave-one-out procedure. Maps were smoothed at FWHM 10mm. A $|z| \geq 2$ threshold was applied, and maps were cluster thresholded to identify "outlier" clusters for each participant. Subsequently, the total surface area of outlier clusters was summed for high MC (greater than TC average) and low MC (less than TC average) clusters separately, resulting in outlier "load" scores (HMC-load and LMC-load, respectively). Overall group comparisons for MC load scores were made using non-parametric Mann-Whitney U tests to account for non-normal distribution of load scores. Load scores were observed to be zero-inflated across groups, so participants in both diagnostic groups were divided into subgroups based on outlier status. When categorized based on HMC-load, the groups were those with elevated MC (ASD-HMC+, n=20; TC-HMC+, n=22) and those without (ASD-HMC-, n=10; TC-HMC-, n=14) and when derived from LMC-load they were those with reduced MC (ASD-LMC+, n=9; TC-LMC+, n=13) and those without (ASD-LMC-, n=21; TC-LMC-, n=23).

Behavioral associations were tested two ways. First, t-tests between subgroups based on diagnostic and outlier status were run to examine whether the presence of outliers was associated with behavioral differences. The following subgroups were compared: (i) ASD-HMC+ vs ASD-HMC- to examine the impact of outlier status within ASD, (ii) ASD-HMC+ vs TC-HMC- to examine the impact of both ASD and outlier status, (iii) ASD-HMC+ to TC-HMC+ to examine the impact of diagnostic status within outlier groups, and (iv) TC-HMC+ vs TC-HMC- to examine the impact of positive outlier status independent of ASD diagnosis. Corresponding comparisons were performed for LMC derived subgroups. Second, Spearman correlations probed the magnitude of associations between load scores and behavioral variables within the HMC+ and LMC+ groups specifically. Behavioral analyses were adjusted for multiple comparisons with the false discovery rate (Benjamini & Hochberg, 1995).

## RESULTS

### Group-wise statistical analyses

Participants in the ASD and TC groups did not differ significantly overall in terms of age, PRI, gray-white CNR, sex, race, or ethnicity (Table 3.1). No significant group by age interaction effects were observed on MC in the vertex-wise models. Significant positive main effects of age were observed bilaterally (Figure 3.1), reflecting increasing MC with age broadly across much of the cortex, with peak values and largest clusters located in left superior frontal, middle frontal, paracentral, and right precentral, superior frontal, and postcentral regions (Table 3.2). Additional smaller clusters were found in frontal, parietal, and temporal lobes as well as the insula, in both hemispheres. There were no significant main effects of group in either direction.

### Subject specific analyses

Non-parametric U-tests revealed no significant differences between the ASD and TC groups in the distribution of whole-brain HMC or LMC outlier load scores. Diagnostic groups were then split by outlier status to account for zero-inflated data. Subgroups did not differ significantly in terms of age, TBV, or gray-white CNR (Tables 3.3 and 3.4), with the exception of a significant difference in TBV between the ASD-LMC+ and TC-LMC+ groups. Qualitatively, HMC outliers were more abundant than LMC outliers in both groups (Figure 3.2). Both types of outliers were diffuse across the cortex and only partially overlapping across participants.

Results of subgroup comparisons for behavioral measures are summarized in Table 3.5 and Figure 3.3. The following comparisons were significant following FDR adjustment of *p*-values. When groups were split by HMC outlier status, the ASD-HMC+ group demonstrated significantly lower FSIQ scores than both the ASD-HMC- and TC-HMC+ groups. The ASD-HMC+ group showed significantly higher BRIEF GEC scores than the TC-HMC+ group, and within the ASD-HMC+ group, BRIEF GEC scores were strongly positively correlated with HMC-load scores ($\rho$=0.610; $p$=0.016), although this association did not remain significant after FDR adjustment of p-values. The ASD-HMC+ group showed significantly lower DKEFS Trail Making Number and Letter Sequencing scores than all other subgroups, and lower Number-Letter Sequencing scores and both ASD-HMC- and TC-HMC- subgroups. The ASD-HMC+ group showed significantly lower DKEFS Verbal Fluency Letter Fluency and Category Fluency scores than both the TC-HMC- and TC-HMC+ subgroups, along with lower Category Switching scores than all other subgroups. The ASD-HMC+ and ASD-HMC- groups showed no significant differences in ADOS scores. All other Spearman correlations within the outlier positive subgroups were non-significant.

When groups were split by LMC outlier status, t-test comparisons revealed no significant differences between subgroups after FDR adjustment of p-values. Similarly, Spearman correlations within the LMC+ subgroups were non-significant.

## DISCUSSION

The present study used group-wise and subject-specific approaches to examine intracortical MC and its associations with age and neuropsychological function in middle- to older-aged adults with ASD compared to typical control participants. Vertex-wise analyses at the group level revealed a positive main effect of age on MC, by which greater age was associated with higher MC in clusters across bilateral frontal, parietal, and temporal lobes. In subject-specific analyses, diagnostic groups did not differ in terms of overall outlier load, but after accounting for zero-inflation of load scores by subgrouping participants based on load status, associations between elevated outlier load and various aspects of neuropsychological function were detected. The presence of atypically high MC at the subject-specific level was associated with a number of differences in neuropsychological function between subgroups, with poorer performance on average in the ASD subgroup with atypically high MC in spatially heterogeneous cortical regions. Differences were noted across several cognitive domains, including in overall intellectual functioning, processing speed, and various aspects of executive function.

### Clusters of Atypically High MC in Both Groups

Our subject-specific approach revealed outlier clusters of high MC in many participants in both the ASD and TC groups, which varied in their exact regional localization from person to person. High regional MC could reflect developmental differences (local or diffuse) in the rate of ongoing myelination into adulthood. However, it should be noted that the total area of outlier

clusters did not differ between diagnostic groups, indicating that patches of HMC are not specific to individuals with ASD. Given evidence to suggest that an important role of intracortical myelin is to insulate against formation of aberrant connections (Braitenberg, 1962), these clusters could underly individual differences in cortical connectivity (Hensch, 2005; Hill et al., 2018; McGee et al., 2005; Nave & Werner, 2014). The specific circuits and networks impacted by MC differences could potentially be associated with different cognitive phenotypes. Although comparison of overall outlier load scores did not reveal differences between the ASD and TC groups as hypothesized, subgrouping participants based on HMC load status revealed associations with neuropsychological functions, indicating a potential link between altered MC and behavioral or cognitive differences in ASD. The individual level spatial distributions of HMC+ clusters could reflect genetic or early neurodevelopmental differences, and although not directly related to diagnostic status, may be associated with neuropsychological dysfunction present earlier in life (Ecker et al., 2022). Alternatively, HMC clusters could reflect a compensatory response to aging-related functional decline, with added myelin forming to guide the development of new connections given what has been shown about myelin's role in nervous system plasticity (Bonetto et al., 2021; Fields, 2015; Forbes & Gallo, 2017).

Within both diagnostic groups, the spatial distribution of both HMC and LMC clusters was highly variable between subjects. Although our sample size was not sufficient to quantitatively test for areas of high susceptibility (Bethlehem et al., 2020), visual inspection of the overlap of HMC clusters in our sample suggested a more anterior (frontal and parietal) distribution of HMC in the ASD group than in the TC group (Supplementary Figure 2). It is likely that spatial variability in atypical myelin content reflects another aspect of the heterogeneity that characterizes ASD at multiple levels. Along with heterogeneity in the

symptom profile and severity (Esbensen et al., 2009; Estes et al., 2007; Pickles et al., 2014), risk and prognostic factors are variable and complex, and the genetic landscape of ASD is vast. A number of genetic variants have been shown to confer increased risk of ASD (Pinto et al., 2010; Yuen et al., 2017), with different genetic abnormalities leading to varying levels of impairment (Freitag, 2007). Additionally, older aged adults with ASD are subject to a lifetime of environmental (Garay & McAllister, 2010; Larsson et al., 2005; Mandy & Lai, 2016; Patel et al., 2018; Vargas et al., 2005), experiential, interventional (Helt et al., 2008; Klintwall et al., 2015; Wong et al., 2015), and pharmacological (Broadstock et al., 2007; Howes et al., 2018) contributions to their behavioral and neurodevelopmental outcomes. Co-occurring physical and mental health conditions are also common across the lifespan in ASD (Dhanasekara et al., 2023; Hand et al., 2020), with certain conditions becoming more prevalent with increasing age (Fortuna et al., 2016). Together, highly heterogeneous etiologies in ASD that are further compounded by other sources of variability across the lifespan have the potential to differentially impact brain structure and neural resilience later in life.

**Relationships Between Atypical MC and Neuropsychological functions in ASD**

After splitting each diagnostic group based on HMC load status, the ASD-HMC+ group showed several significant differences from all other groups, with different implications based on the subgroups being compared. When compared to the ASD-HMC- group, the ASD-HMC+ group showed lower IQ and poorer processing speed and set-shifting ability, along with a positive association between load scores and overall dysexecutive symptoms. This is notable considering inconsistency in previous studies of neuropsychological profiles of ASD across the adult lifespan, with some studies reporting deficits in intellectual, executive, and attentional functioning (Brighenti et al., 2018; Fried et al., 2016), among other cognitive domains (Lever &

Geurts, 2016; Torenvliet et al., n.d.), and others demonstrating no significant differences compared to typical comparison groups (Brighenti et al., 2018; Geurts et al., 2020; Torenvliet et al., 2023; Wilson et al., 2014). Subgrouping or clustering of individuals with ASD based on a variety of features, including neuroimaging characteristics (Hong et al., 2020; Katuwal et al., 2016) and other medical or genetic factors (Ousley & Cermak, 2014), has been broadly utilized as a means of parsing heterogeneity in the disorder (Ousley & Cermak, 2014). The present results suggest that subgrouping by HMC load status may have utility in exploring links between brain structure and behavior despite inter-subject variability.

When comparing the ASD-HMC+ group to the TC subgroups, ASD-HMC+ participants showed lower performance on all tests included. In contrast, performance in the ASD-HMC- group was similar to that in both the TC-HMC- and TC-HMC+ groups across most tests, and the TC subgroups did not show differences from one another based on HMC outlier status. This suggests that elevated MC may have a broader effect on function in individuals with ASD than those without. However, the distribution of scores in the TC group was narrow, potentially limiting our ability to detect similar effects. LMC clusters appeared to have less of an impact in terms of cognition. While this may reflect a true difference in the functional impact of high versus low myelin content, it is also possible that the relatively small number of participants in the ASD-LMC+ (n=9) and TC-LMC+ (n=13) groups limited the statistical power to detect associations with neuropsychological function.

**Age related increases in MC**

The present study showed a main effect of linearly increasing MC with age in group-wise analyses, with no evidence for any group difference in the age-related trajectory of intracortical MC. Linear increases in cortical MC have been shown at younger ages extending into at least the

4th decade of life (Shafee et al., 2015). More recently, a significant linear increase with age was found across most of the frontal lobe and in temporo-parietal regions in the same age range as the current study (Parent et al., 2023). Correlations with gene expression data in the same study suggest that this increase may be related to oligodendrocyte and oligodendrocyte precursor cell density (Seidlitz et al., 2020). Other studies employing different MC estimation methods and non-linear models suggest that a linear model may not provide the best fit. MC indexed by myelin water fraction (MWF) showed an inverted U-shaped relationship across most cerebral white and gray matter (Dvorak et al., 2021), although this approach was limited by the use of a single mask averaged across all gray matter, potentially failing to account for regional variability in the age-related trajectory of cortical MC. The same pattern has also been demonstrated in a study looking specifically at MWF in individual subcortical gray matter structures (Khattar et al., 2021). It was also noted that these quadratic relationships were driven largely by study participants <25 years of age, and a study spanning young adulthood has shown similar patterns with earlier peak ages (Rowley et al., 2017). It is likely that cortical gray matter myelination follows a different temporal pattern, depending heavily on the age range sampled. Sample size limited our ability to test a quadratic relationship, and further investigation in larger sample sizes and with longitudinal methods will be necessary to establish these trajectories.

**Limitations and Conclusions**

Although this is one of few studies examining brain structure in middle to older aged adults with ASD, and to our knowledge the first to examine MC in such groups, some limitations must be acknowledged when interpreting these results. First, the T1w/T2w ratio method employed here provides a proxy index of myelin content, and may be subject to influence from other aspects of cortical brain anatomy, including iron content (Fukunaga et al., 2010), or to

errors in surface reconstruction impacting the precision of its estimate. However, this method also has important advantages when compared to similar MRI based metrics of MC, including elimination of the MR-related image intensity bias and enhancement of the contrast to noise ratio for myelin. The method is informative across the full range of cortical myelin densities and demonstrates good correspondence with myeloarchitectonic maps from animal and post-mortem studies (Glasser & Van Essen, 2011). Second, the relatively modest sample size and highly exploratory nature of the subject-specific analyses likely limit the generalizability of these results. In particular, our sample size did not allow for inquiries into differences in the specific spatial localization of outlier clusters between groups on a lobar or region wise level, and this research question would benefit from follow up with a larger sample. Finally, the cross-sectional approach limits interpretation of the findings with regard to differentiating between effects arising early in development, compensatory changes occurring across the lifespan, and neurodegenerative changes in later life. Longitudinal studies will be necessary to elucidate these factors and are currently underway.

The protracted nature of myelination in humans makes it unique as an index of brain development and degeneration, making it vital to study in developmental disorders from a lifespan perspective. The multifaceted groupwise and subject-specific approaches employed herein demonstrate the importance of accounting for increasing sources of heterogeneity when studying older adults with ASD. Despite its limitations, the current study provides important preliminary insights into potential links between brain structure and behavior in the second half of the lifespan in ASD.

Chapter 3, in full, is currently being prepared for submission for publication. **Kohli, J.S.**, Linke, A.C., Wilkinson, M., Alemu, K., Hau, J., Fishman, I., Müller, R.-A., & Carper, R.A. The

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**Table 3.1** Overall participant characteristics and group matching

| | ASD (n=30) | | | TC (n=36) | | | |
|---|---|---|---|---|---|---|---|
| | Mean | SD | Range | Mean | SD | Range | *p*-value |
| Age (years) | 50.42 | 6.56 | [40.22-67.17] | 51.76 | 7.54 | [40.05-69.89] | 0.452 |
| WASI-II | | | | | | | |
| VCI | 103.83 | 22.43 | [45-160] | 112.47 | 14.20 | [85-144] | 0.062 |
| PRI | 106.74 | 19.65 | [56-138] | 109.64 | 13.27 | [75-138] | 0.768 |
| FSIQ-4 | 104.97 | 20.48 | [51-143] | 112.56 | 12.53 | [90-138] | 0.163 |
| Total Brain Volume | 1100.57 | 105.52 | [876-1397] | 1131.32 | 95.95 | [886-1309] | 0.332 |
| Gray-White CNR | 1.39 | 0.33 | [0.57-1.81] | 1.57 | 0.32 | [0.46-1.89] | 0.786 |
| ADOS-2 | | | | 51.76 | 7.54 | [40.05-69.89] | 0.452 |
| Total Score | 14.03 | 4.18 | [7-23] | -- | -- | -- | -- |
| SA | 10.47 | 3.78 | [5-19] | -- | -- | -- | -- |
| RRB | 3.57 | 1.77 | [1-8] | -- | -- | -- | -- |
| Gender (Male/Female) | 23/7 | | | 28/8 | | | 0.758 |
| Race (White/Non-White) | 24/4 | | | 32/3 | | | 0.485 |
| Ethnicity (Not Hispanic/Hispanic) | 24/3 | | | 29/3 | | | 0.866 |

ASD, Autism Spectrum Disorder; TC, Typical Control; WASI-II, Wechsler Abbreviated Scale of Intelligence, Second Edition; VCI, Verbal Comprehension Index; PRI, Perceptual Reasoning Index; FSIQ, Full-Scale IQ; CNR, Contrast to Noise Ratio; ADOS-2, Autism Diagnostic Observation Schedule, Second Edition; SA, Social Affect; RRB, Restricted and Repetitive Behavior

*p*-value corresponds to t-test or chi square test

**Table 3.2 Clusters of increasing MC with age**

| Hemisphere | Location | Cluster-Wise p-value | Size (mm2) | MNI-X | MNI-Y | MNI-Z |
|---|---|---|---|---|---|---|
| Left | superiorfrontal | 0.0002 | 900.76 | -9.8 | 1.2 | 49.5 |
| | rostralmiddlefrontal | 0.0002 | 825.55 | -18.4 | 58.3 | -13.7 |
| | paracentral | 0.0002 | 438.05 | -7.9 | -26.5 | 51.5 |
| | parsopercularis | 0.0002 | 421.05 | -46.9 | 12.7 | 3 |
| | lateralorbitofrontal | 0.0002 | 367.95 | -26.7 | 23.7 | -4.4 |
| | precentral | 0.0002 | 267.79 | -40 | 1 | 27.1 |
| | insula | 0.0002 | 264.74 | -37.7 | -16.5 | 20.9 |
| | transversetemporal | 0.0002 | 245 | -44.8 | -22.8 | 7.6 |
| | superiortemporal | 0.0002 | 226.21 | -49.6 | -36.5 | 9.1 |
| | precentral | 0.0002 | 223.88 | -32.4 | -8.4 | 45 |
| | postcentral | 0.0008 | 177.94 | -48.8 | -17.9 | 35 |
| | superiorfrontal | 0.00519 | 145.92 | -19.4 | 9.1 | 55.9 |
| | precentral | 0.00619 | 141.69 | -52.3 | 3.7 | 10.7 |
| | insula | 0.01097 | 133.21 | -35.5 | -3.5 | 10.1 |
| | lateralorbitofrontal | 0.01475 | 125.93 | -29.8 | 30.3 | -14.2 |
| | parsorbitalis | 0.01613 | 124.08 | -38.1 | 42.7 | -11.7 |
| Right | precentral | 0.0002 | 3163.67 | 59.6 | 5.6 | 23.9 |
| | superiorfrontal | 0.0002 | 1407.81 | 10.2 | 7.1 | 46.9 |
| | postcentral | 0.0002 | 1088.82 | 60.6 | -11.8 | 31.7 |
| | middletemporal | 0.0002 | 520.92 | 61 | -10.7 | -23.9 |
| | superiortemporal | 0.0002 | 466.54 | 66.1 | -25.4 | 4.3 |
| | superiortemporal | 0.0002 | 369.65 | 52 | -11.1 | -1.3 |
| | inferiorparietal | 0.0002 | 363.46 | 54 | -52.8 | 35.4 |
| | superiorparietal | 0.0002 | 342.66 | 29.6 | -48.9 | 46.2 |
| | caudalmiddlefrontal | 0.0002 | 217.85 | 38.3 | 19.8 | 35.4 |
| | precentral | 0.0002 | 208.29 | 32 | -17.7 | 44.4 |
| | superiorfrontal | 0.0008 | 185.69 | 20.7 | -4.9 | 57.9 |
| | insula | 0.002 | 167.31 | 36 | 9 | -9.3 |
| | precuneus | 0.002 | 166.32 | 7.1 | -71.4 | 48 |
| | middletemporal | 0.0022 | 165.28 | 62.1 | -49.8 | 1.6 |
| | rostralmiddlefrontal | 0.0022 | 164.8 | 29.9 | 49.1 | 2.2 |
| | inferiorparietal | 0.0022 | 160.07 | 42.7 | -72.4 | 16.4 |
| | precuneus | 0.00579 | 141.23 | 8.6 | -52.5 | 56 |
| | superiorparietal | 0.00659 | 136.75 | 20.5 | -86.7 | 29.2 |
| | supramarginal | 0.03194 | 110.77 | 57.9 | -41 | 27.8 |
| | caudalmiddlefrontal | 0.04058 | 107.25 | 36.3 | 8.7 | 38 |

**Table 3.3 Subgroup characteristics**

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | High Myelin Content (HMC) | | | | | |
| | | | ASD-HMC- (n=10) | | | ASD-HMC+ (n=20) | | | TC-HMC- (n=14) | | | TC-HMC+ (n=22) |
| | Mean | SD | Range | Mean | SD | Range | Mean | SD | Range | Mean | SD | Range |
| Age (years) | 53.13 | 6.65 | [41.92-67.17] | 49.06 | 6.24 | [40.22-63.66] | 51.63 | 8.53 | [40.54-69.89] | 51.84 | 7.05 | [40.05-64.81] |
| Total Brain Volume | 1101.42 | 71.03 | [1013-1190] | 1109.84 | 120.75 | [876-1397] | 1103.71 | 112.39 | [886-1309] | 1148.88 | 81.80 | [1005-1309] |
| Gray-White CNR | 1.32 | 0.40 | [0.65-1.75] | 1.41 | 0.30 | [0.57-1.81] | 1.52 | 0.14 | [1.36-1.89] | 1.33 | 0.37 | [0.45-1.67] |
| | | | | | | | Low Myelin Content (LMC) | | | | | |
| | | | ASD-LMC- (n=21) | | | ASD-LMC+ (n=9) | | | TC-LMC- (n=23) | | | TC-LMC+ (n=13) |
| | Mean | SD | Range | Mean | SD | Range | Mean | SD | Range | Mean | SD | Range |
| Age (years) | 51.62 | 6.67 | [403.16-67.17] | 49.29 | 6.30 | [40.22-63.66] | 53.28 | 7.57 | [41.05-69.89] | 49.08 | 6.97 | [40.05-57.94] |
| Total Brain Volume | 1125.85 | 102.76 | [955-1397] | 1110.56 | 114.50 | [876-1397] | 1120.83 | 103.39 | [886-1309] | 1149.87 | 81.67 | [1031-1309] |
| Gray-White CNR | 1.38 | 0.34 | [0.62-1.81] | 1.43 | 0.29 | [0.57-1.81] | 1.43 | 0.24 | [0.71-1.67] | 1.37 | 0.43 | [0.45-1.89] |

ASD, Autism Spectrum Disorder; TC, Typical Control; HMC, High Myelin Content; LMC, Low Myelin Content; WASI-II, Wechsler Abbreviated Scale of Intelligence, Second Edition; VCI, Verbal Comprehension Index; PRI, Perceptual Reasoning Index; FSIQ, Full-Scale IQ; CNR, Contrast to Noise Ratio; ADOS-2, Autism Diagnostic Observation Schedule, Second Edition; SA, Social Affect; RRB, Restricted and Repetitive Behavior

**Table 3.4 Subgroup matching (p-values)**

| High Myelin Content (HMC) | | | | |
|---|---|---|---|---|
| | Subgroup | ASD-HMC+ | TC-HMC- | TC-HMC+ |
| **Age (years)** | ASD-HMC- | 0.082 | 0.649 | 0.631 |
| | ASD-HMC+ | -- | 0.316 | 0.184 |
| | TC-HMC- | -- | -- | 0.611 |
| | TC-HMC+ | -- | -- | -- |
| **Total Brain Volume** | ASD-HMC- | 0.812 | 0.955 | 0.124 |
| | ASD-HMC+ | -- | 0.882 | 0.223 |
| | TC-HMC- | -- | -- | 0.114 |
| | TC-HMC+ | -- | -- | -- |
| **Gray-White CNR** | ASD-HMC- | 0.188 | 0.103 | 0.969 |
| | ASD-HMC+ | -- | 0.219 | 0.453 |
| | TC-HMC- | -- | -- | 0.067 |
| | TC-HMC+ | -- | -- | -- |
| **Low Myelin Content (LMC)** | | | | |
| | Subgroup | ASD-HMC+ | TC-HMC- | TC-HMC+ |
| **Age (years)** | ASD-HMC- | 0.186 | 0.446 | 0.297 |
| | ASD-HMC+ | -- | 0.517 | 0.607 |
| | TC-HMC- | -- | -- | 0.110 |
| | TC-HMC+ | -- | -- | -- |
| **Total Brain Volume** | ASD-HMC- | 0.807 | 0.873 | 0.481 |
| | ASD-HMC+ | -- | 0.167 | **0.041** |
| | TC-HMC- | -- | -- | 0.391 |
| | TC-HMC+ | -- | -- | -- |
| **Gray-White CNR** | ASD-HMC- | 0.092 | 0.647 | 0.888 |
| | ASD-HMC+ | -- | 0.634 | 0.955 |
| | TC-HMC- | -- | -- | 0.594 |
| | TC-HMC+ | -- | -- | -- |

ASD, Autism Spectrum Disorder; TC, Typical Control; HMC, High Myelin Content; LMC, Low Myelin Content; Contrast to Noise Ratio

**Table 3.5 Subgroup behavioral comparisons (t-test results, p-values)**

| | High Myelin Content (HMC) | | | |
|---|---|---|---|---|
| | ASD-HMC+ vs ASD-HMC- | ASD-HMC+ vs TC-HMC- | ASD-HMC+ vs TC-HMC+ | TC-HMC+ vs TC-HMC- |
| WASI-II FSIQ | **0.0014** | 0.033 | **0.013** | 0.71 |
| BRIEF GEC | 0.62 | 0.0039 | **0.0000012** | 0.27 |
| DKEFS TM NS | **0.00014** | **0.000099** | **0.003** | **0.023** |
| DKEFS TM LS | **0.01** | **0.006** | **0.009** | 0.48 |
| DKEFS TM NLS | **0.008** | **0.012** | 0.035 | 0.35 |
| DKEFS VF LF | 0.042 | **0.00089** | **0.00023** | 0.84 |
| DKEFS VF CF | 0.3 | **0.0067** | **0.000038** | 0.52 |
| DKEFS VF CS | **0.000055** | **0.000072** | **0.00099** | 0.37 |
| | **Low Myelin Content (LMC)** | | | |
| | ASD-LMC+ vs ASD-LMC- | ASD-LMC+ vs TC-LMC- | ASD-LMC+ vs TC-LMC+ | TC-LMC+ vs TC-LMC- |
| WASI-II FSIQ | 0.35 | 0.72 | 0.41 | 0.07 |
| BRIEF GEC | 0.94 | 0.014 | 0.048 | 0.55 |
| DKEFS TM NS | 0.6 | 0.3 | 0.24 | 0.72 |
| DKEFS TM LS | 0.98 | 0.26 | 0.34 | 0.54 |
| DKEFS TM NLS | 0.72 | 0.47 | 0.41 | 0.79 |
| DKEFS VF LF | 0.67 | 0.11 | 0.015 | 0.18 |
| DKEFS VF CF | 0.49 | 0.0066 | 0.0037 | 0.37 |
| DKEFS VF CS | 0.26 | 0.2 | 0.45 | 0.49 |

Bold p-values remain significant after FDR adjustment
WASI-II, Wechsler Abbreviated Scale of Intelligence, Second Edition; FSIQ, Full Scale IQ; BRIEF, Behavior Rating Inventory or Executive Function; GEC, Global Executive Composite; DKEFS, Delis Kaplan Executive Function System; TM, Trail Making; NS, Number Sequencing; LS, Letter Sequencing; NLS, Number Letter Sequencing; VF, Verbal Fluency; LF, Letter Fluency; CF, Category Fluency; CS, Category Switching

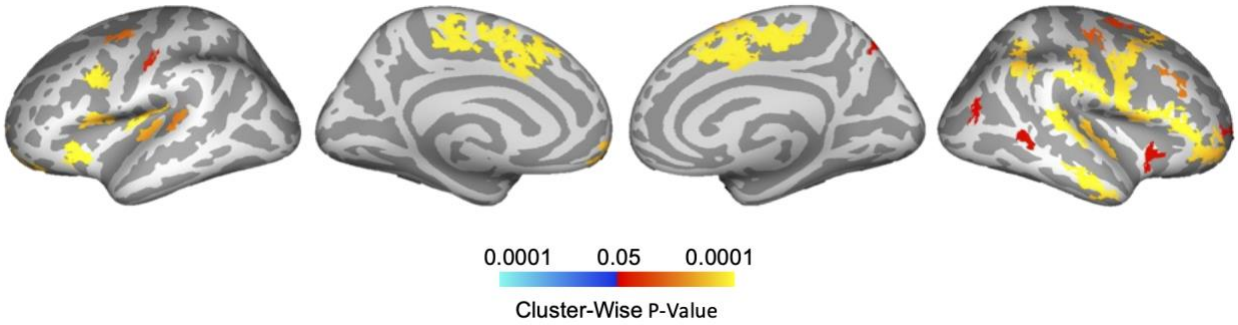


**Figure 3.1 Main effect of age on myelin content**
Significant positive main effects of age were observed bilaterally, reflecting increasing MC with age broadly across much of the cortex, with peak values and largest clusters located in left superior frontal, middle frontal, paracentral, and right precentral, superior frontal, and postcentral regions. Additional smaller clusters were found in frontal, parietal, and temporal lobes as well as the insula, in both hemispheres.

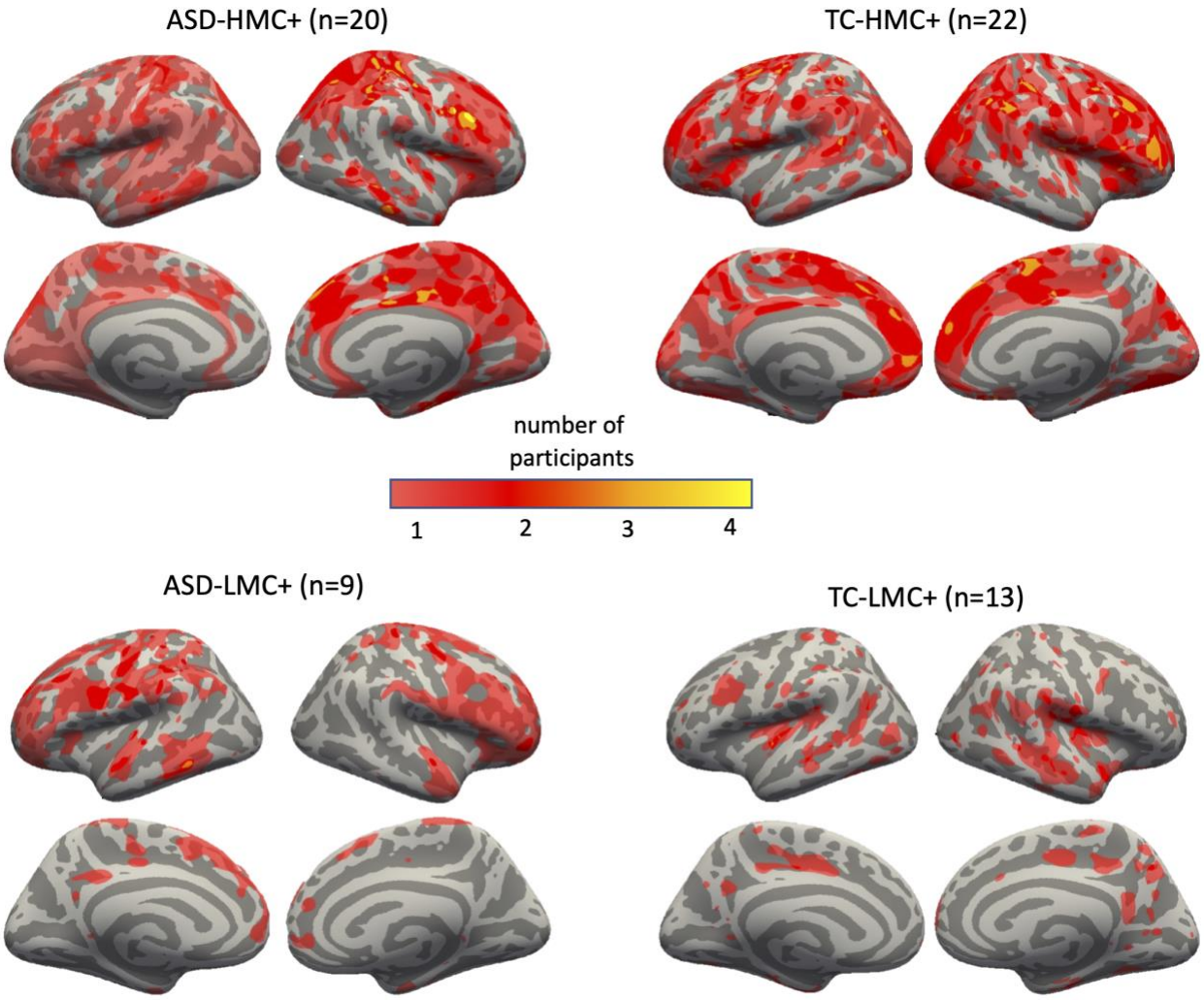


**Figure 3.2 Spatial overlap map across HMC+ and LMC+ participants by group**
Qualitatively, HMC outliers were more abundant than LMC outliers in both groups. Both types of outliers were diffuse across the cortex and only partially overlapping across participants.

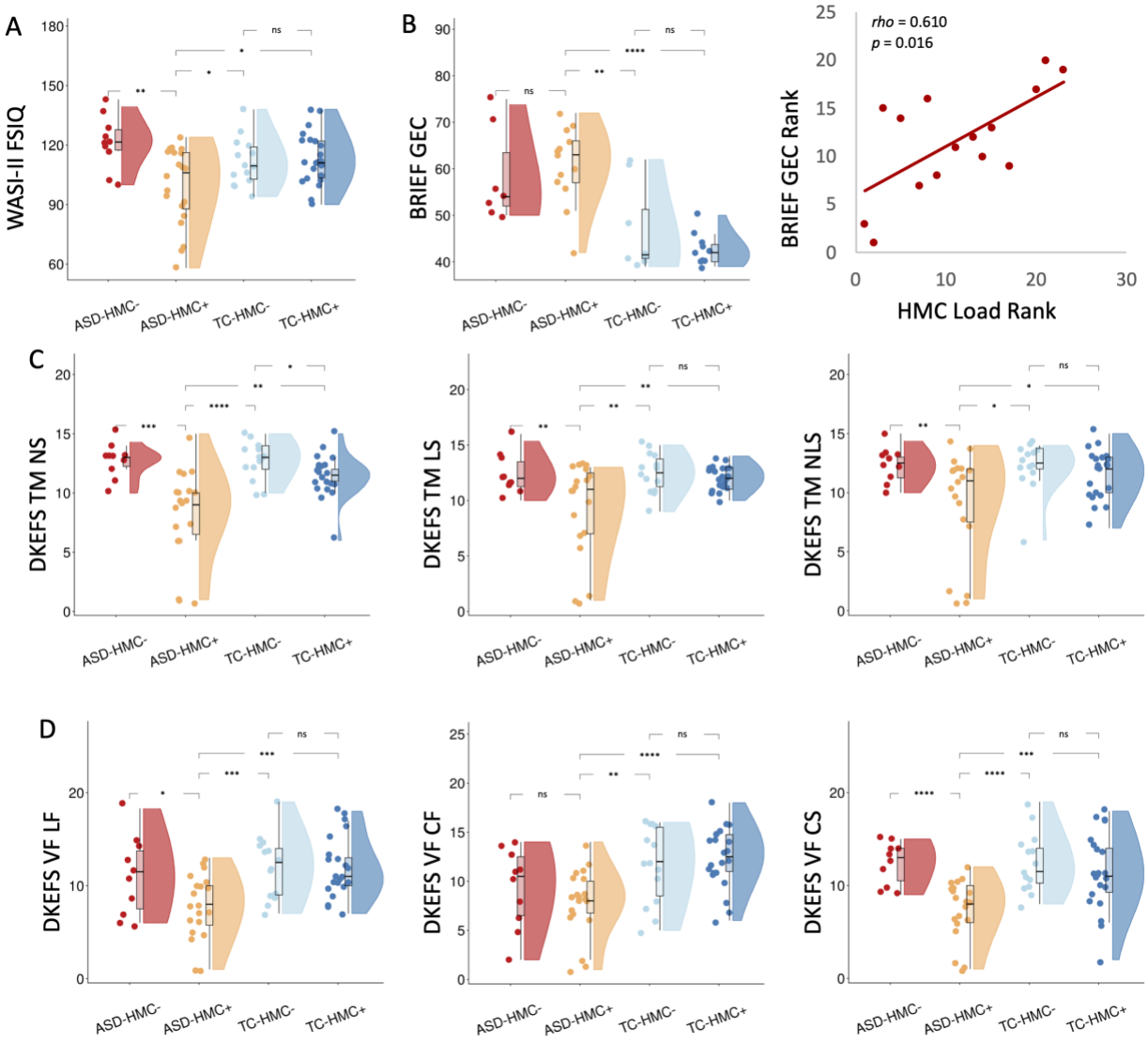


**Figure 3.3 Subgroup comparisons based on HMC status**
(A) When groups were split by HMC outlier status, the ASD-HMC+ group demonstrated significantly lower FSIQ scores than both the ASD-HMC- and TC-HMC+ groups. (B) The ASD-HMC+ group showed significantly higher BRIEF GEC scores than the TC-HMC+ group, and within the ASD-HMC+ group, BRIEF GEC scores were strongly positively correlated with HMC-load scores, although this association did not remain significant after FDR adjustment of p-values. (C) The ASD-HMC+ group showed significantly lower DKEFS Trail Making Number and Letter Sequencing scores than all other subgroups, and lower Number-Letter Sequencing scores and both ASD-HMC- and TC-HMC- subgroups. (D) The ASD-HMC+ group showed significantly lower DKEFS Verbal Fluency Letter Fluency and Category Fluency scores than both the TC-HMC- and TC-HMC+ subgroups, along with lower Category Switching scores than all other subgroups.
ns, non-significant; *p<0.05; **p<0.01; ***p<0.001; ****p<0.0001

# CONCLUSION OF THE DISSERTATION

The overarching goal of this three-paper dissertation was to characterize the evolution of cortical morphology and architecture across middle to older age in ASD and determine how any abnormalities, whether developmental or degenerative, relate to cognition and behavior. To address this goal, the primary aims were to (1) examine cortical morphology, including cortical thickness (CT), surface area (SA), and local gyrification index (LGI) at the group-wise level, (2) identify regionally varying differences in CT and gray-white contrast (GWC) using subject-specific approaches, and (3), investigate intracortical myelin content (MC) in ASD using both group-wise and subject specific analyses. Across the three studies, associations between features of cortical structure, age, and behavioral and cognitive measures were also examined, with a particular focus on neuropsychological domains thought to be vulnerable to early or accelerated decline in ASD. Differences were observed at the group-wise and/or subject-specific level for several, but not all, features examined, and behavioral analyses revealed associations with executive function and ASD symptomatology, but not motor skills. The studies did not provide evidence of group-by-age interaction effects on any of the cortical features examined, though main effects of age consistent with existing literature in typical aging were observed. LGI was the only cortical feature demonstrating differences in ASD when examining group level averages, but subject-specific analyses revealed an additional but spatially heterogeneous decrease in GWC, along with broad associations between both GWC and MC and aspects of neuropsychological function.

## Group-Wise Differences

Study 1 provided evidence of regionally decreased LGI in adults with ASD between 41 and 61 years of age in bilateral insular and anterior cingulate (ACC), left postcentral, and middle

frontal, and right orbitofrontal and supramarginal regions. Although we did not find group by age interaction effects in this n=41 (20 ASD, 21 TC) sample (main effects of age discussed under Age-Related Changes below), lower LGI may suggest accelerated tissue loss in ASD when viewed in the context of previous research from our group showing greater gyrification in similar bilateral insular regions in children and adolescents with autism (Kohli et al., 2019). Across the three studies of the dissertation, no other cortical features examined (SA, CT, GWC, MC) demonstrated significant group differences when examined using a vertex-wise approach at the group level. In other words, results of these analyses did not provide evidence of group differences in any consistent spatial location. Some have suggested that LGI may be a more sensitive measure of atypical cortical macrostructure than other morphological features (Schaer et al., 2008; Shimony et al., 2016), and our finding of LGI differences in the absence of spatially-consistent group differences in other aspects of cortical architecture may be consistent with this. Higher sensitivity of LGI to group differences may be related to its method of calculation, which employs a sphere of 25mm radius to quantify cortical folding in the area surrounding each vertex. This approach, though "localized," may allow for detection of slightly spatially varying differences in gyrification across individual participants because values at each vertex reflect information from the surrounding area in a manner different from the calculation of other structural features. Differences in those features may be washed out by variance in the precise localization of anomalies when using traditional group-wise analyses, highlighting a need for analytic approaches that account for anatomical heterogeneity, such as normative modeling (Marquand et al., 2016, 2019).

**Subject-Specific Differences and Heterogeneity in ASD**

Given the lack of significant group differences in vertex-wise group level analyses for most of the cortical features examined, Studies 2 and 3 employed a subject-specific normative modeling approach to examine CT, GWC, and MC, all measures that were calculated at individual vertices across the cortical surface. Subject specific analyses relied on a z-score mapping approach for each feature of interest, whereby the average surface map of the TC group was subtracted from each individual participant's map and divided by the standard deviation map of the TC group (using a leave-one-out procedure for the TC group). This resulted in individual z-maps for each participant, which were subsequently thresholded to identify "outlier" clusters where the feature of interest deviated most from the TC mean, specific to each individual. For all features, outlier clusters were located in spatially heterogeneous regions of the cortical surface. To facilitate comparisons between groups, overall "load" scores were calculated to summarize the total surface area of cortex demonstrating outlier clusters in each individual subject.

There were no significant differences between the ASD and TC groups in CT outlier load scores in Study 2, neither in terms of increased nor decreased thickness. Similarly, there was no difference in the load scores reflecting increased GWC, but load scores for decreased GWC were significantly greater in the ASD group. Decreased GWC, often described as "blurring" of the gray-white boundary, has been linked to disrupted neuronal migratory processes in early development (Andrews et al., 2017; Avino & Hutsler, 2010) with genetic underpinnings (Hoerder-Suabedissen et al., 2013), as well as to changes in myelin integrity and other age dependent factors (Mann et al., 2018; Vidal-Piñeiro et al., 2016). Our analysis of MC using the same subject specific approach in Study 3 did not reveal any differences in overall load scores reflecting either increased or decreased myelin content in ASD. These data were observed to be zero-inflated, however, with many participants in both groups displaying no outlier clusters at

the threshold employed. Groups were therefore split by outlier status and subsequently compared on behavioral measures, revealing several differences in the ASD group that showed clusters of high MC, discussed under Behavioral Associations below.

GWC and MC in middle to older aged adults with ASD are likely impacted by heterogeneity at multiple levels in the disorder, as discussed in Studies 2 and 3. Heterogeneity can be observed in terms of the symptom profile and severity of the disorder (Esbensen et al., 2009; Estes et al., 2007; Pickles et al., 2014), as well as in the genotype –with a number of genetic variants linked to ASD ( Freitag, 2007; Pinto et al., 2010; Yuen et al., 2017). Further, adults with ASD are subject to a lifetime of environmental (Garay & McAllister, 2010; Larsson et al., 2005; Mandy & Lai, 2016; Patel et al., 2018; Vargas et al., 2005), possible pharmacological (Broadstock et al., 2007; Howes et al., 2018), and experiential or interventional (Helt et al., 2008; Klintwall et al., 2015; Wong et al., 2015) contributions to their behavioral and neurocognitive outcomes, compounding the developmental and early life factors that contribute to variability. Taken together, heterogeneous etiologies in ASD interacting with a lifetime of other variable influences have the potential to differentially impact brain structure and neural resilience later in life. These are dynamic processes, and as such, the neuroanatomical correlates of ASD are also impacted heavily by the stage of development being examined.

**Age-Related Changes**

In addition to probing for group differences in cortical architecture, the studies presented here examined linear age-related effects in all the structural features of interest to investigate whether trajectories differ across middle to older age in ASD. Results provided no evidence of a group by age interaction effect on CT, though there has been previous report of increased cortical thinning in early adulthood in ASD (Braden & Riecken, 2019). This was the case for all features

examined across studies, with no statistically significant differential age effects observed for LGI, SA, GWC, or MC. However, LGI, CT, GWC, and MC showed significant main effects of age when examining across groups. Study 1 showed age related decline in LGI in combined groups, and Study 2 showed similar effects for CT and GWC, largely in frontal and parietal regions for all three features. These results are consistent with a large body of evidence demonstrating age-related declines in these structural indices in aging populations without autism (Fjell et al., 2009; Hogstrom et al., 2013; Lamballais et al., 2020; Madan, 2021; Salat et al., 2004, 2009; Thambisetty et al., 2010; Vidal-Piñeiro et al., 2016). Conversely, in Study 2 a positive linear main effect of age was observed, with areas of increasing MC in frontal, temporal, and parietal regions. This age-related increase is in line with a recent study on the same age range, in which a significant linear increase with age was found across most of the frontal lobe and in temporo-parietal regions (Parent et al., 2023). Correlations with gene expression data in the same study suggest that this increase may be related to oligodendrocyte and oligodendrocyte precursor cell density (Seidlitz et al., 2020).

Various studies examining these anatomical features in typical development and aging have suggested that age-related trajectories differ regionally across the cortex and may exhibit non-linear patterns of change in some areas. CT, for example, has demonstrated greater rates of decline in frontal and parietal regions than temporal and occipital (Thambisetty et al., 2010). The same study found significant non-linear changes in the postcentral, precentral, and orbitofrontal gyri on the left and inferior parietal, cingulate, and orbitofrontal gyri on the right, although other research has suggested that CT follows a largely monotonic linear decline across the cortex (Ducharme et al., 2016; Parent et al., 2023). GWC has similarly been modeled using both linear and non-linear approaches, with both showing significant effects varying across the cortex (Salat

et al., 2009; Vidal-Piñeiro et al., 2016). MC, estimated using a few different methods, has repeatedly been shown to follow non-linear trajectories (Dvorak et al., 2021; Grydeland et al., 2013; Khattar et al., 2021). Sample size limited our ability to test a quadratic relationship in the current study, and further investigation in larger sample sizes and with longitudinal methods will be necessary to establish these trajectories in ASD with greater confidence, particularly in the understudied older adult age range.

**Behavioral Associations**

The dissertation studies employed a number of behavioral measures to quantify ASD symptomatology (ADOS-2, SRS-2), general cognitive abilities (WASI-II), executive function (DKEFS subtests, BRIEF), and motor skills (BMAT). Motor skills as measured by the BMAT did not show significant differences between groups, nor significant associations with the structural features of interest across studies. Several aspects of executive function were shown to correlate with brain structure in ASD, however. In study 1, within bilateral insular and left orbitofrontal regions of decreased LGI compared to TC participants, those with lower LGI showed poorer performance on verbal fluency and set shifting tasks. Similarly, the ASD subgroup that had clusters of high myelin content in Study 3 exhibited poorer letter fluency and category switching abilities (DKEFS verbal fluency subtest) than all other subgroups. This subgroup also showed poorer processing speed and set shifting abilities as indexed by the DKEFS trail making subtest. Global dysexecutive symptoms as measured by the BRIEF GEC score also correlated with low GWC load scores in ASD in Study 2, as well as with high MC load scores in ASD in Study 3. These executive function correlations suggest important clinical relevance of several of the structural indices examined across studies, with significant associations in ASD in both the group-wise and subject-specific analyses. In the latter, low GWC

load scores also correlated positively with ADOS Social Affect subscores, with greater symptom severity associated with a greater extent of atypical GWC in the ASD group.

The networks of regions underlying both executive (Aron, 2008; Collette et al., 2006; Zink et al., 2021) and social-emotional functions (Barrett & Satpute, 2013; Blakemore, 2008) involve brain regions that are dispersed, though widely interconnected. Alterations in any of the nodes of these networks or in the integrity of their connections could impact cognition and behavior in ASD (Müller & Fishman, 2018), and the spatially independent load-score approach employed in Studies 2 and 3 is particularly well suited for addressing potentially highly heterogeneous impacts on these types of broad networks.

**General Conclusions**

The dissertation studies presented herein demonstrated differences in aspects of cortical anatomy in middle aged to older adults with ASD, including decreased LGI in frontal and temporal areas at the group level and decreased GWC diffusely across the cortex using a subject-specific approach. Results also showed several notable correlations between executive function and LGI, GWC, and MC in the ASD group. In this population, the differences and associations observed could be related to either or both early neurodevelopmental changes and differences in aging across later life. The cross-sectional approaches employed in these studies do not allow for disentangling such developmental, degenerative, or compensatory effects on brain structure in relation to cognition and symptomatology, supporting a need for follow up with longitudinal designs. The behavioral associations observed, however, provide valuable preliminary insight into links between brain structure and behavior in the second half of the lifespan in ASD.

The classic case-control paradigm for attempting to link brain structure to diagnostic group or behavior in ASD is limited by the necessity to average across participants with

heterogeneous symptoms, and ostensibly equally heterogenous neurobiological underpinnings, including topographic variability in cortical anatomy. The complementary group-wise and subject-specific normative modeling approaches employed in these dissertation studies allow for a better understanding of how atypical anatomy of the cortex relates to autism symptomatology and associated cognitive abilities, as it does not rely on consistent localization across subjects, nor a consistent direction of effects. This method has recently gained favor in the clinical neuroimaging field and has generated compelling results in a few studies of adolescents and young adults with ASD (Shan et al., 2022; Zabihi et al., 2019), but this is its first application to a cohort of middle to older age adults with ASD. The findings outlined here contribute to a more comprehensive characterization of neuroanatomy in adults with ASD. Examining differences in cortical architecture and age-related trajectories at both the group and subject-specific level in this population expands our understanding of how the links between brain structure and behavior evolve as individuals with ASD age and highlights the importance of accounting for heterogeneity at multiple levels in trying to identify risk factors for early or accelerated decline in autism.

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