ATYPICAL NEURODEVELOPMENT IN AUDITORY AND LANGUAGE CORTEX AND THE CORPUS CALLOSUM IN AUTISM

by

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ABSTRACT

Abnormalities in language and communication, auditory sensitivity, and complex information processing are associated with autism, yet the neural underpinnings are unknown. The studies in this dissertation examine neurodevelopment of several brain regions implicated in these abnormalities. We first examine age-related changes in midsagittal corpus callosum area in a large cross-sectional cohort from early childhood to adulthood. Increased variability in total corpus callosum area and atypical regional development in the rostrum and isthmus are found in autism compared with typical controls. In autism, larger areas are associated with reduced severity of autism behaviors, higher intelligence, and faster speed of processing, providing support to theories of underconnectivity in the autism brain. Longitudinal maturation of Heschl's gyrus gray matter and white matter and planum temporale during childhood and adolescence in autism and a typically developing sample are then described. Despite previous cross-sectional studies reporting typical Heschl's gyrus structure in autism, reduced developmental trajectories in the right gray matter and atypical white matter maturation are identified. Our longitudinal findings also expand on previous reports of reduced planum temporale asymmetry in autism by showing that the reduced asymmetry develops during later childhood and adolescence. In addition to the case-control comparisons, different developmental trajectories in those individuals with autism with delayed versus early language onset in Heschl's gyrus white matter and planum temporale asymmetry

are apparent. Finally, individuals with autism exhibit associations between smaller Heschl's gyrus volumes and reduced auditory sensitivity and higher language function, and smaller planum temporale volumes associated with increased vocabulary aptitude. Our findings highlight the importance of longitudinal studies of brain development and examining behavioral profiles of individuals to identify functional and maladaptive pathological neurodevelopment.

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CHAPTER 1

INTRODUCTION

The ultimate goals of autism neuroscience imaging research are to understand pathological changes in brain development that are shared by all who are affected and also identify pathological brain structure that explains interindividual differences in severity, course and outcome associated with the disorder. An understanding of the biological basis of autism will lead to the discovery of genes and other factors involved and ultimately drive the development of specific treatment based on the biology of the disorder (Lainhart and Lange, 2010).

Many individuals with autism have impairments in language and IQ in addition to the behavioral symptoms that diagnostically define the disorder. These impairments often persist into adulthood and can have a greater impact on functional outcome than autistic symptomatology (Howlin et al., 2004). The purpose of this dissertation research is to begin to understand the neural basis of persistent impairments in language and IQ in autism. We examine three brain structures: a major white matter track essential for interhemispheric communication, the corpus callosum, and two cortical regions involved in language, Heschl's gyrus (location of the primary auditory cortex) and the planum temporale (secondary auditory cortex containing Wernicke's area) (Geschwind and Levitsky, 1968; Galaburda et al., 1978). Three critical questions were asked. First, is there evidence of pathology in the corpus callosum, Heschl's gyrus and the planum

temporale in autism? Second, if persistent pathology is present, is it static or dynamic? Third, are the structure-function relationships in autism similar to typical development?

The remainder of Chapter 1 provides a brief overview of the literature that led to these dissertation questions. A review of the public health relevance of autism research and a current understanding of the neurobiology of autism is presented. This is followed by a summary of typical neurodevelopment of the corpus callosum, Heschl's gyrus, and the planum temporale and evidence in autism for the involvement of these structures. This dissertation addresses critical gaps in knowledge of the neurodevelopment of these regions in autism.

1.1 Autism spectrum disorders

Dr. Leo Kanner, in 1943, described a group of 11 unique children seen in the Phipps Clinic at Johns Hopkins. He noted "individual differences in the degree of their disturbance" but summarized characteristics common in all the children that formed a unique "syndrome" not previously reported: autism (Kanner, 1943). Since this initial description, autism has become a common developmental disorder. The most recent prevalence rates from the Centers for Disease Control and Prevention estimate that in 2008, about 1 in 88 children were classified as having an autism spectrum disorder (commonly known as autism or ASD; CDC 2012). The diagnosis of autism is based on qualitative impairments in communication and social interaction, and restricted, repetitive and stereotyped patterns of behaviors and interests (APA, 1994). In addition, prior to 3 years of age, all individuals exhibit delays or abnormal functioning in social interaction, communicative language, or symbolic play (APA, 1994). It costs an estimated $3.2 million dollars to care for an individual with autism across the lifetime (Ganz, 2007),

creating a financial burden not only on the families of affected individuals but also on the public health system.

For the majority of individuals, autism is a condition that is present from birth. Although its genetic origins have been known for many years (Folstein and Rutter, 1977), the specific etiology is unknown in almost 90% of cases. Despite early identification of the disorder in many individuals, significant functional deficits almost always persist into adulthood (Farley et al., 2009; Howlin et al., 2004). Thus, there is a critical need to identify underlying neural causes of persistent, impairing manifestations of the disorder. This understanding, at the biological level, will lead to targeted interventions and treatments for older children, adolescents, and young adults that optimize functional outcomes.

Convergent evidence shows that autism is a disorder of brain connectivity. The underconnectivity theory, first described by Just and colleagues, proposes that underfunctioning circuitry results in difficulties integrating information and the behavioral profiles seen in autism (Just et al., 2004). It is now known that abnormal connectivity in the brain in autism involves underconnectivity between many regions and overconnectivity between other regions. Many studies have suggested that structural pathology involving cortical gray and white matter and white matter tracks contribute to abnormalities of connectivity in the autism brain (Casanova and Trippe, 2009; Courchesne and Pierce, 2005; Geschwind and Levitt, 2007).

1.2 The role of the corpus callosum in autism

Multiple lines of evidence suggest that one of the brain structures most commonly affected in autism is the corpus callosum, the major white matter fiber system connecting the cerebral hemispheres, and an index of structural interhemispheric connectivity.

1.2.1 Corpus callosum development

Corpus callosum (CC) development begins in utero and continues into young adulthood (Giedd et al., 1996; Giedd, 2004; Keshavan et al., 2002; LaMantia & Rakic, 1990; Pujol et al., 1993). In utero, callosal projection neurons, or interhemispheric commissural pyramidal neurons, are born throughout corticogenesis. These neurons migrate to layers in the developing cortex, and send out projection axons that cross the midline, forming the CC, that migrate in the contralateral hemisphere predominantly to homotopic targets (Fame et al., 2011). The CC is evident by 17 weeks of human gestation with diffusion tensor imaging (DTI; Takahashi et al., 2011). Interhemispheric connections established before birth are refined soon after birth by activity-dependent mechanisms (Fame et al., 2011). In humans, myelination of the CC begins in posterior regions at 3-4 postnatal months and in anterior regions at 6-8 postnatal months (Deoni et al., 2011). Subsequently, in typical development, growth of midsagittal CC area proceeds from an anterior to posterior direction, which is in contrast to the posterior to anterior directionality of cortical maturation (Giedd, 2004; Jancke et al., 1999). Longitudinal MRI studies confirm this anterior-posterior development and show that the greatest callosal changes during childhood and adolescence occur in the posterior regions (Giedd et al., 1999; Thompson et al., 2000). The integrity of CC microstructure, indexed by fractional

anisotropy measured by DTI, sharply increases between birth and two years of age and then slowly increases up to about 21 years (Trivedi et al., 2009).

1.2.2 Corpus callosum abnormalities in autism

In autism, studies of CC structure report reduced mean area, volume, and white matter (WM) density compared to typical development (Alexander et al., 2007; Casanova et al., 2011, 2009; Chung et al., 2004; Frazier and Hardan, 2009; Freitag et al., 2009; Hardan et al., 2009; He et al., 2008; Hong et al., 2011; Keary et al., 2009; Kilian et al., 2008; Waiter et al., 2005) with a few exceptions (Elia et al., 2000; Kilian et al., 2008; McAlonan et al., 2002; Rice et al., 2005; Tepest et al., 2010). Work by Casanova and colleagues shows a reduced "gyral window", or space for afferent and efferent fibers to enter and exit cortex, in autism (Casanova et al., 2009). The reduced "gyral window" suggests a reduction in long-range cortico-cortical connections in the brain of individuals with autism (Casanova et al., 2009), and is consistent with decreased CC area and underconnectivity.

Further support for involvement of the CC in autism is based on impaired performance on neuropsychological tasks requiring more complex processing and interhemispheric information transfer (Minshew et al., 1997; Nyden et al., 2004). Clinico-pathological studies using structural MRI have suggested a relationship between CC size and clinical features of autism (Hardan et al., 2009; Keary et al., 2009). In addition, functional magnetic resonance imaging (fMRI) studies have shown correlations between the size of callosal subregions and functional connectivity measured during tasks that tap cognitive skills frequently impaired or relatively preserved in the disorder (Damarla et al.,

2010; Just et al., 2007, 2004; Kana et al., 2009, 2006; Keary et al., 2009; Mason et al., 2008; Schipul et al., 2011).

1.2.2.1 Research questions to be addressed

Despite strong evidence for CC abnormalities in autism, there are several important unanswered questions about callosal development. Many studies report decreased size of the CC in individual samples of young children, older children, adolescents, or adults with autism, but information about age-related changes is limited (Chung et al., 2004) and the issue of static versus dynamic pathology of the CC in autism has not been addressed. Although decreased mean CC size has been repeatedly found, the *distribution* of CC size has not yet been examined; the proportion of affected individuals with abnormally small CC is not known. Finally, little is known about how CC size is related to intelligence (IQ) in autism. IQ can vary widely and independently of severity of autistic symptomatology, and as mentioned above, impacts functional outcome. These research questions are addressed in Chapter 2.

1.3 Auditory and language cortex and autism

Difficulties in language acquisition, communication, and language impairments persisting into adulthood are common in autism. Thus, we investigated the structure and development of two key areas in the language neural network: auditory and language cortex in the temporal lobe.

1.3.1 Typical development of temporal lobe auditory and language cortex

Two notable structures of the superior temporal gyrus (STG) are the first transverse temporal gyrus, known as primary auditory cortex or Heschl's gyrus, and the auditory association cortex, the planum temporale, also known as Wernicke's area (Geschwind and Levitsky, 1968).

During fetal development, although the right gyral homologue appears a few weeks prior to Heschl's gyrus in the left hemisphere, a leftward volumetric asymmetry of the transverse temporal gyrus (or Heschl's gyrus) is evident as early as 31 weeks gestation (Chi et al., 1977). Postnally, MRI studies show leftward asymmetry of Heschl's gyrus thickness and planum temporale length as early as 1-4 months of age (Glasel et al., 2011). The auditory cortex continues to undergo dynamic growth during the first decade of life. Early childhood postmortem research describes an overproduction of synapses between 1-4 years of age and further maturation of thalamocortical afferents innervating the auditory cortex in typical development (Huttenlocher & Dabholkar, 1997; Moore, 2002). Myelination reaches adult levels around 5 years of age and a stable neuronal population is established by 7 years, making the auditory cortex the latest developing sensory cortex (Devous et al., 2006; Moore & Linthicum, 2007).

The maturation of commissural and association axons during later childhood, with synapse elimination and mature axonal density reached by around 12 years of age, allows for more complex auditory and language processing (Huttenlocher and Dabholkar, 1997; Moore, 2002; Moore and Linthicum, 2007). Neural signals obtained during MEG studies show age-related changes in both the latency and amplitude of auditory response

generated from sources in the primary auditory cortex during childhood and adolescence (Kotecha et al., 2009). Prolonged development of complexity and maturation of the planum temporale is evident in a SPECT study that shows decreasing resting rCBF between 7 and 19 years of age, suggesting that higher order language areas continue to mature, with synaptic and neuronal pruning and refinement of neuronal interconnections, into later adolescence (Devous et al., 2006). The age-range of the individuals in the studies described in Chapters 3 and 4 was chosen to capture gray and white matter development of language maturation during childhood and adolescence.

1.3.1.1 Asymmetry of language cortex in typical development

In typical development, there is a shifting of functional language lateralization from rightward and bilateral to leftward hemispheric asymmetry (Flagg et al., 2005; Saugstad, 1999). Studies of the planum temporale note leftward volumetric asymmetry (e.g., Anderson et al., 1999; Luders et al., 2006; Geschwind and Levitsky, 1968; Herve et al., 2006; Shapleske et al., 1999) and a functional correlation between planum temporale asymmetry and verbal ability (Eckert et al., 2008). Hemispheric dominance in Heschl's gyrus has also been suggested. An fMRI study found leftward asymmetry in Heschl's gyrus activation during auditory tones presented to either ear (Devlin et al., 2003). Another fMRI study reports effective connectivity (the functional activity in one region predicting another region) between Heschl's gyrus and planum temporale in the left but not right hemisphere during language processing (Upadhyay et al., 2008). Higher myelin content in the left Heschl's gyrus and planum temporale, compared to their right hemisphere homologues, is also suggested from MRI (Sigalovsky et al., 2006). These

results demonstrate structural and functional asymmetry associated with language development in typically developing individuals.

1.3.2 Auditory and language processing in autism

In his early description of autism, Dr. Kanner noticed that in addition to delayed onset and abnormal language, his patients exhibited abnormal reactivity and sensitivity to sound (Kanner, 1943). Hyperacusis, or increased loudness perception, has been found in some affected individuals (Khalfa et al., 2004; Rosenhall et al., 1999). Parents also report that their children with autism show abnormal auditory sensitivity and response to auditory stimuli, noting aberrant auditory filtering in particular (Ashburner et al., 2008; Kern et al., 2006, 2007; Tomchek and Dunn, 2007; Wiggins et al., 2009). Enhanced auditory discrimination has also been shown in children with autism compared to typically developing children (O'Riordan and Passetti, 2006). Early processing abnormalities of incoming auditory stimuli may have a great effect on subsequent sensory perception and higher order processing, such as language perception and acquisition (Kuhl, 2004).

1.3.2.1 Functional studies

Studies of neural activation during auditory processing show abnormal patterns of brainstem and cortical processing in some individuals. Prolonged latencies of bilateral auditory brainstem responses have been found in children and adolescents with autism (Kwon et al., 2007; Rosenhall et al., 2003; Roth et al., 2012). Abnormalities in hemispheric activation to auditory stimuli (Boddaert et al., 2003; Bruneau er al., 2003; Bruneau et al., 1999; Flagg et al., 2005; Gage et al., 2003; Kasai, et al., 2005; Muller et

al., 1999; Roberts et al., 2011; Roberts et al., 2010; Roberts et al., 2008; Wilson et al., 2007), auditory orienting for speech stimuli (Ceponiene et al., 2003; Lepisto et al., 2005; Lepisto et al., 2007), and detection of auditory change (Oram Cardy et al., 2005; Roberts et al., 2011; Samson et al., 2011) have all been reported. Abnormal hypoperfusion in the bilateral STG and sulcus has also been found (Ohnishi, et al., 2000; Zilbovicius, et al., 2000). A reduced synchronization between temporal and frontal language activation obtained during functional magnetic resonance imaging (fMRI) supports abnormal connectivity between language-related cortices in the autism brain (Just et al., 2004).

1.3.2.2 Age-related changes

Functional studies have also shown abnormal age-related activation in response to auditory stimuli. Bilateral to right lateralization of auditory activation with age was found in autism in contrast to bilateral to left lateralization of auditory activation with age in typically developing children (Flagg et al., 2005). Abnormal age-related decline and a right lateralized reduction in transiently evoked otoacoustic emissions have been reported in adolescents with autism (Khalfa et al., 2001). Additionally, MEG studies have shown delayed auditory evoked responses in the right hemisphere in autism and an absence of typical age-related changes (Gage et al., 2003; Roberts et al., 2010). Atypical development in auditory cortex may greatly contribute to a lack of typical left hemisphere dominance found during speech and auditory processing during functional studies (e.g., Boddaert et al., 2003; Bruneau et al., 1999; Bruneau et al., 2003; Dawson et al., 1989; Flagg et al., 2005; Muller et al., 1999; reviewed in Roberts et al., 2008).

1.3.3 Auditory and language cortex structure in autism

Evidence for structural abnormalities in the auditory and language pathways in autism can be found as early as the brainstem. A postmortem study found atypical morphology in the medial superior olive, a brainstem nucleus that detects timing differences between the ears (Kulesza and Mangunay, 2008). Structural findings at such an early level of processing raises the hypothesis that subsequent auditory structures may also be affected.

1.3.3.1 Heschl's gyrus development in autism

Previous volumetric studies of small samples of children, adolescents and adults have found no group differences in Heschl's gyrus GM volume or typical leftward asymmetry (Knaus et al., 2009; Rojas et al., 2002, 2005). A more recent study found increased cortical thickness in Heschl's gyrus bilaterally 15 older adolescents and young adults with autism compared to 15 typically developing controls, suggesting structural cortical differences may exist (Hyde et al., 2010). A study of an autism only sample showed greater Heschl's gyrus GM asymmetry in older (12-19 years) versus younger (7-11 years) individuals, suggesting increasing asymmetry with age (Knaus et al., 2009). Thus, to date, a limited number of studies have examined Heschl's gyrus volumes in autism and no studies have directly measured Heschl's gyrus WM. No studies of typical development or autism have examined development of Heschl's gyrus morphology longitudinally during childhood and adolescence. Appendix A provides a summary table of studies examining Heschl's gyrus or planum temporale structure in autism to date.

1.3.3.2 Planum temporale in autism

Studies investigating planum temporale structure in autism have provided inconsistent results. In some samples of children and adults with manually segmented regions of interest, reduced left hemisphere planum temporale volume and reduced leftward asymmetry are reported (Rojas et al., 2002, 2005). In other samples, with volumes acquired from manual and automatic segmentation, no case-control differences in volume or asymmetry are found (Knaus et al., 2009, 2010). The investigation of an autism only sample of children found an absence of planum temporale asymmetry measured with cortical parcellation units, with a trend toward rightward asymmetry in right-handed males (Gage et al., 2009). Another group found more extreme leftward planum temporale asymmetry in boys with high-functioning autism compared to control boys (Herbert et al., 2002). Finally, in another cortical parcellation study, the autism group was divided into those with current language impairment and normal language. The language-impaired autism group showed significant leftward planum temporale asymmetry, a finding that was absent in the language-normal autism group (De Fosse et al., 2004). In summary, most but not all studies find reduced asymmetry of the planum temporale in autism, and, importantly, that variations in language functioning are associated with variations in planum temporale structural asymmetry.

Investigations of planum temporale development have involved age and region correlations in cross-sectional samples or comparisons between samples of different ages. One study shows a rightward planum temporale asymmetry increase during childhood and adolescence (Gage et al., 2009), but another study shows a leftward planum temporale increase during this same period due to a decrease in right volume (Knaus et

al., 2009). Clearly lacking from the literature is a longitudinal investigation of planum temporale development in a well-characterized sample of individuals with autism compared to a typically developing sample.

1.4 Research objectives

The studies presented in this dissertation will contribute to the understanding of the biological brain basis of variations in language functioning and IQ in autism. Chapter 2 focuses on morphology of the corpus callosum, which continues to change in size into adulthood (Pujol et al., 1993) and has high heritability (Holshoff Pol et al., 2006; Tramo et al., 1998). Chapter 3 describes longitudinal development of Heschl's gyrus and the planum temporale in typical development and autism. Chapter 4 reports on the relationships between language functioning, auditory sensitivity, and longitudinal development of Heschl's gyrus and planum temporale in autism.

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CHAPTER 2

CORPUS CALLOSUM SIZE AND RELATION TO FUNCTION IN CHILDREN AND ADULTS WITH AUTISM

2.1 Introduction

Decreased mean corpus callosum (CC) size is one of the most replicated findings in autism research (Casanova et al., 2009; Frazier and Hardan, 2009 for meta-analysis; Freitag et al., 2009). Neuropsychological profiles of autism suggest functional correlates of CC abnormalities, shown by impaired performance on tasks requiring complex processing and interhemispheric information transfer (Minshew et al., 1997; Nyden et al., 2004). Additionally, deficits in social communication and interaction, language and self-awareness have all been found in non-autistic populations with abnormal CC, such as callosal agenesis (Badaruddin et al., 2007; Paul et al., 2007; Symington et al., 2010), traumatic brain injury (Beauchamp et al., 2009; Mathias et al.. 2004; Gale & Prigatano, 2010), and preterm birth (Lawrence et al., 2010). Nonetheless, the relation between severity of core diagnostic features of autism, intelligence, and processing speed in relation to CC area are unknown.

As with many structural correlates of the disorder, such as larger head circumference and increased prefrontal neurons (Courchesne et al., 2011; Lainhart and Lange, 2011) or atypical fractional anisotropy and mean diffusivity in the CC (Alexander et al., 2007), abnormalities are not present in all affected individuals; such is likely the

case for small callosal size. The size distribution of the CC has not been examined in detail and the proportion of affected individuals with abnormally small CC not yet reported. In addition, decreased CC size appears most evident when it is considered relative to total brain volume (TBV; Boger-Megiddo et al., 2006; Just et al., 2007), though an exception has been found in a high-functioning adult sample (Tepest et al., 2010). However, scaling of CC size to TBV in autism and the age-invariance of such scaling has not yet been examined.

In this study we examine CC size from a developmental perspective across a 30-year age range in a large cross-sectional sample of individuals with autism. We find increased variability in total area in autism and a trend toward developmental differences in the rostrum and isthmus. We also find that increased midsagittal areas are associated with reduced severity of autism behaviors, higher intelligence and faster speed of processing. Thus, these results suggest potential maturational abnormalities in autism and that individuals with autism functionally benefit from increased CC area.

2.2 Materials and methods

2.2.1 Participants

Sixty-eight (68) individuals with autism spectrum disorder (lifetime diagnosis autistic disorder in 62, pervasive developmental disorder not otherwise specified PDD-NOS in 6) and 47 typically developing controls were selected from a large, ongoing neuroimaging study. Participants were selected if they met the following inclusion criteria: male; age between 3 and 36 years; performance IQ ≥70; quantitative handedness score, which ranges from completely left-handed (-100) to completely right-handed (+100), ≥ 0; and very good quality of scan at the 1st wave of data collection. The

inclusion criteria were chosen to decrease heterogeneity other than age in the autism sample and potential associated neuroanatomic heterogeneity, and, as a result, increase statistical power. Handedness in particular may be associated with CC morphology in both typical and atypical development (Gilliam et al., 2011; Witelson, 1989).

Diagnoses of autism were based on the Autism Diagnostic Interview-Revised [ADI-R; (Lord et al., 1994)], Autism Diagnostic Observation Schedule-Generic [ADOS-G; (Lord et al., 2000)], and DSM-IV (American Psychiatric Association, 1994). Participants were excluded if history, Fragile-X gene testing, karyotype, or examination identified medical causes of autism or other medical conditions that could affect brain morphometry, such as history of severe head injury, hypoxia-ischemia, seizures, and other neurologic disorders. Forty-one percent of the autism participants were taking psychotropic medication (28% serotonin reuptake inhibitor, 13% stimulant, 9% neuroleptics, 1.5% atypical agents, 16% multiple medications). Possible effect of psychotropic use on CC size was explored in the data analysis.

Control participants underwent neuropsychological testing, standardized psychiatric assessments (Leyfer et al., 2006), and were assessed with the ADOS-G (Lord et al., 2000) to confirm typical development. Controls with any history of developmental, learning, cognitive, neurological, or neuropsychiatric conditions were excluded. All autism and control participants were recruited, assessed, and scanned at the University of Utah.

2.2.2 Assessments

2.2.2.1 Severity of core features of autism

ADOS-G Algorithm scores were used as estimates of autism severity (Lord et al., 2000). Because all participants were cognitively high-functioning and standardized methods are not yet available to calculate severity scores across all 4 modules (Gotham et al., 2009), raw Social scores were used and Communication and Total algorithm scores across modules were equated by prorating.

2.2.2.2 Intelligence (IQ)

Verbal (VIQ) and performance IQ/nonverbal ability (PIQ) were ascertained with the Differential Abilities Scale (DAS) or WISC-III in children, and the WAIS-III in adults (Elliott, 1990; Wechsler, 1997, 1991). For the DAS, VIQ was estimated from the Verbal Cluster, and PIQ estimated from the Nonverbal Cluster (preschool) and Special Nonverbal Composite (school-age) Standard Scores.

2.2.2.3 Processing speed

A difference score from the Trail Making Test (Trails B – Trails A) was used as a measure of processing speed (Lezak et al., 2004). This score removes the common motor component, providing an estimate in processing time to complete attention set shifting, working memory, and executive functioning required by the more complex Trails B (Sanchez-Cubillo et al., 2009). Both the child (age <15 years) and adult (age ≥15 years) Trail Making Test versions were administered and results examined separately.

2.2.2.4 Head circumference

Maximal occipital frontal head circumference was measured on participants.

2.2.2.5 Handedness

The Edinburgh Handedness Inventory (Oldfield, 1971) was used as a measure of handedness. This provides a quantitative measure of handedness ranging from -100, or completely left-handed to +100 or completely right handed.

2.2.3 Image acquisition and processing

Magnetic resonance images were acquired on a single Siemens Trio 3.0 Tesla Scanner. An 8-channel, receive-only RF head coil was used to acquire 3D T1-weighted image volumes with 1mm isotropic resolution using an MP-RAGE sequence (TI=1100msec, TR=1800msec, TE=2.93msec, flip angle=12degrees, sagittal, field of view=25.6cm, matrix=256x256x160).

2.2.3.1 Corpus callosum measurement

DICOM images were converted to ANALYZE® format (Robb, 2001, 1995) and re-sampled to a $1mm^3$ volume. The midsagittal slice was selected in MRIcro (Rorden and Brett, 2000). Images were imported into ImageJ (Rasband, 1997-2011) and the midsagittal image was rotated (pitch-adjusted) such that a horizontal line was fit from the most anterior to the most posterior CC. Manual thresholding classified white matter voxels. The CC was subdivided into 7 Witelson regions using an automated macro (see Figure 2.1; Witelson, 1989). The CC was measured 4 times per individual. Two independent raters blind to diagnosis and age measured each brain twice and intra-rater areas were averaged. Final areas were calculated by averaging interrater areas. Intrarater reliability was ICC > 0.95 and interrater reliability ICC > 0.90.

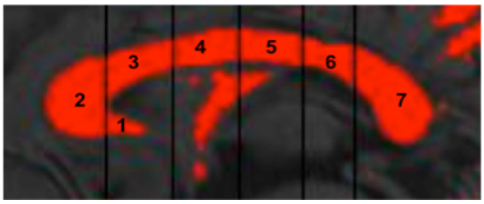

Figure 2.1 Sample image of midsagittal corpus callosum area and Witelson regions. Subregions are labeled as follows: (1) rostrum, (2) genu, (3) rostral body, (4) anterior midbody, (5) posterior midbody, (6) isthmus, (7) splenium

2.2.3.2 Brain and total intracranial size measurement

Total brain volume (TBV) and total intracranial volume (TICV) were generated using Freesurfer version 4.3.1. TBV included GM and WM of the forebrain and hindbrain (cerebellum and brainstem). Although only the forebrain is directly connected by the CC, 95% of the variance in TBV as measured is explained by forebrain volume (Jancke et al., 1997).

2.2.4 Statistical analyses

Linear regression models and smooth nonparametric curves (Cleveland, 1979) were used to assess group differences in demographics and brain measures. Models examining group differences in total CC area and the seven subregions included the following:

$$\text{CC area} = \text{Intercept} + \beta_1*\text{group} + \beta_2*\text{age} + \beta_3*\text{age}^2 + \beta_4*\text{group by age} + \beta_5*\text{group by age}^2 + \varepsilon$$

Age was centered and quadratic age was included to allow for nonlinear growth with age (Giedd et al., 1999). Models with the lowest AIC criterion were selected. The inclusion of

handedness did not improve the model fit. Analyses were repeated including TBV as a covariate because evidence suggests the CC is smaller than expected for TBV in autism (Boger-Megiddo et al., 2006). IQ, and group by IQ interaction effects were also examined. The relationship between area and age was further shown in the autism and control groups separately using bivariate correlations and partial correlations controlling for TBV. The relationships between area and autism severity and processing speed measures were examined using linear regressions controlling for age and TBV. A Bonferroni correction of $p=0.05/7=0.007$ was employed to calculate a significance value that controlled for multiple comparisons of the seven subregions.

Within group linear regressions were also used to examine the relationship between CC area and TBV. Total area and a ratio of total area/TBV were examined. Centered age, age^2, TBV, TBV^2 and TBV by age interactions were included as potential covariates. In accordance with the study by Jancke et al. (1999), our descriptive correlations between TBV and area and ratio of total CC area/TBV were performed in our groups split into child (age $\leq$14) and adult (age $\geq$18) samples.

To estimate the distributions of CC size in the autism group relative to our control sample, we calculated age-normalized z-scores for total area and the ratio of total CC/TBV, using our control data as the reference data in four age-bins (3-5yr, 6-11yr, 12-18yr, 19+yr). Participants were classified as having an abnormally large or small CC ("macroCC" and "microCC", respectively) using standard clinical criteria for abnormality of size of a structure: z-scores > 1.88 standard deviations from the control mean (Lainhart et al., 2006). Group differences in rates of macroCC and microCC were

tested with independent samples t-tests. Analyses were performed in PASW Statistics18.0.

2.3 Results

As indicated in Table 2.1, the sample groups do not significantly differ in age or handedness, and IQ is decreased in the autism group. After controlling for age, no group differences are found in mean head circumference, TBV, or total intracranial volume (TICV).

2.3.1 Typically developing sample

Because the generalization of the results of our case-control comparisons depends on the representativeness of our control group, we compared our control sample to published findings in other typically developing samples. Age-related changes in CC size in our control group are similar to changes in two very large mixed cross-sectional and longitudinal typically developing samples from other studies (Giedd et al., 1999; Gilliam et al., 2011). Similar to these larger samples, our control group shows an anterior-posterior gradient of age-related increase in area from early childhood to the early twenties. In addition, the rostrum and genu have negligible growth, posterior subregions robust growth, and the total area increases in size (see Section 2.3.3). Compared to other typically developing samples, our control group shows similar scaling of CC area to TBV (see Section 2.3.5; Jancke et al., 1999, 1997), a roughly symmetric distribution of age-standardized area particularly when adjusted for TBV (see Section 2.3.6), and negative correlations between CC area and intelligence quotient (IQ) (Ganjavi et al., 2011; Luders et al., 2011) and processing speed (Jancke and Steinmetz, 1994; see Section 2.3.7).

Table 2.1 Participant Demographics

	Autism n=68		Control n=47		Group difference	
	Mean (sd)	Range	Mean (sd)	Range	t	p
Age years	14.1 (7.5)	3-36	15.3 (6.5)	4-29	0.9	ns*
Handedness[a]	79.8 (22)	0-100	76.7 (26)	0-100	0.6	ns
VIQ[b]	99.8 (23)	51-145	116.7 (14)	91-151	5.1	<0.001
PIQ[c]	101.2 (16)	70-135	117.8 (15)	90-155	5.2	<0.001
HC[d]	55.2 (2.7)	49-60.7	55.4 (2.2)	51.6-59.3	0.1	ns
TBV[e]	1442 (143)	1049-1735	1469 (122)	1242-1889	1.1	ns
TICV[f]	1669 (149)	1311-1991	1713 (168)	1399-2171	1.2	ns

*ns indicates p-values >0.2; [a]Edinburgh Handedness Inventory (Oldfield 1971); [b]Verbal IQ; control N=47, ASD N=67; [c]Performance IQ/Nonverbal Ability; [d]Head Circumference in cm; [e]Total Brain Volume in cm^3; [f]Total Intracranial Volume in cm^3

2.3.2 Mean corpus callosum areas in autism

Table 2.2 provides group means and group effects from linear models controlling for linear and nonlinear age. Results adjusted for TBV follow unadjusted findings. Total area, isthmus, and splenium are significantly smaller in the autism group than in the control group. When adjusted for TBV, only isthmus area remains significantly smaller in cases, suggesting that case-control differences in this area are unique to the isthmus and not due to global TBV effects. TBV appears to explain some case-control differences in total area and splenium, although none survive Bonferroni correction.

2.3.3 Cross-sectional age-related changes in corpus callosum area in autism

A tendency toward smaller CC area in autism could be due to abnormal development by early childhood (hypoplasia), abnormal growth during later childhood and adolescence, loss of area over time (atrophy), or a combination of these factors. We

Table 2.2 Corpus callosum midsagittal areas in the autism and control groups

	Group means				Group Difference[a]			
	Autism		Control		Unadjusted for TBV		Adjusted for TBV	
	Mean (sd)	Range	Mean (sd)	Range	t	p	t	p
Total CC	5.74 (0.91)	3.71-8.49	6.25 (0.88)	4.43-7.71	2.2	0.030	2.0	0.050
Rostrum (1)[b]	0.18 (0.08)	0.05-0.43	0.19 (0.07)	0.05-0.36	0.2	ns[c]	0.02	ns
Genu (2)	1.30 (0.29)	0.66-2.27	1.42 (0.28)	0.91-2.22	1.9	0.055	1.7	0.092
Rostral body (3)	0.81 (0.15)	0.54-1.14	0.88 (0.15)	0.63-1.26	1.5	0.128	1.3	ns
Ant midbody (4)	0.68 (0.13)	0.38-1.12	0.74 (0.12)	0.51-0.97	1.5	0.134	1.2	ns
Post midbody (5)	0.64 (0.12)	0.40-1.02	0.68 (0.12)	0.40-0.90	1.1	ns	0.7	ns
Isthmus (6)	0.48 (0.11)	0.26-0.70	0.52 (0.11)	0.23-0.83	2.4	0.016	2.3	0.021
Splenium (7)	1.65 (0.30)	1.07-2.50	1.81 (0.30)	1.19-2.61	2.1	0.039	1.9	0.062

[a]Group effect from linear regressions controlling for linear and quadratic age effects (when present), unadjusted and adjusted for TBV; [b](Corresponding Witelson subdivision); [c]ns indicates p-values > 0.2

examined our data for evidence of these potential mechanisms. Age-related changes in CC area were investigated in three ways: correlational analysis, visual inspection of scatterplots with smooth curves, and regression analysis that included a group by age interaction term. Table 2.3 shows the patterns of correlations between age and area in the autism sample and the typically developing group. Figure 2.2 shows the scatterplots and smooth curves between CC area development and age.

2.3.3.1 Total corpus callosum

Age-related changes in total area were similar to typical controls. Figure 2.2, panel A suggests that the trend toward decreased mean total area in the case-control analysis appears due to slower-than-typical age-related increase during late childhood and adolescence.

2.3.3.2 Anterior corpus callosum: rostrum and genu

Although case-control differences in mean area were not observed in the rostrum or genu, age-related correlations indicate abnormal increasing area with age in autism in

Table 2.3 Pearson correlations between corpus callosum area and age

	Autism				Controls			
	Unadjusted for TBV		Adjusted for TBV[a]		Unadjusted for TBV		Adjusted for TBV	
	r	p	r	p	r	p	r	p
Total Corpus Callosum	0.28	0.018	**0.38**	**0.001**[c]	**0.46**	**0.001**	**0.48**	**0.001**
Rostrum (1)[b]	0.29	0.015	**0.35**	**0.004**	0.11	ns	0.08	ns
Genu (2)	0.05	ns[d]	0.11	ns	0.17	ns	0.10	ns
Rostral body (3)	0.13	ns	0.20	0.098	**0.38**	**0.007**	**0.41**	**0.005**
Anterior midbody (4)	0.14	ns	0.22	0.068	0.28	0.053	0.31	0.039
Posterior midbody (5)	**0.32**	**0.007**	**0.42**	**<0.001**	**0.39**	**0.007**	**0.41**	**0.005**
Isthmus (6)	0.27	0.0.28	0.29	0.015	**0.42**	**0.003**	**0.42**	**0.004**
Splenium (7)	**0.37**	**0.002**	**0.43**	**<0.001**	**0.55**	**<0.001**	**0.55**	**<0.001**

[a]Partial correlation adjusted for total brain volume (TBV) in cm^3; [b](Corresponding Witelson subdivision); [c]**Bold** correlations indicate $p \leq 0.007$, significant after Bonferroni correction; [d]ns indicates p-values > 0.2

the rostrum but typical lack of this relation in the genu. Visual inspections of the smooth curves in Figure 2.2 panel B suggest that the rostrum may increase in size abnormally during adulthood. The significant correlation between age and rostral area adjusted for TBV could have been due to abnormal age-related changes in TBV or a combination of abnormally increasing rostral area and decreasing TBV during young adulthood in the autism group. We therefore examined age-related changes in TBV in our autism and control samples (see Section 2.3.4).

2.3.3.3 Body of the corpus callosum

The rostral body and anterior midbody have different correlations between area and age in the autism and control samples, despite no differences in mean areas. The posterior midbody shows a significant linear increase with age, similar across groups. Visual inspection of the smooth curves suggests possible case-control differences in age-related changes in young adulthood in areas of the three parts of the body (see Figure 2.2, panels D-F).

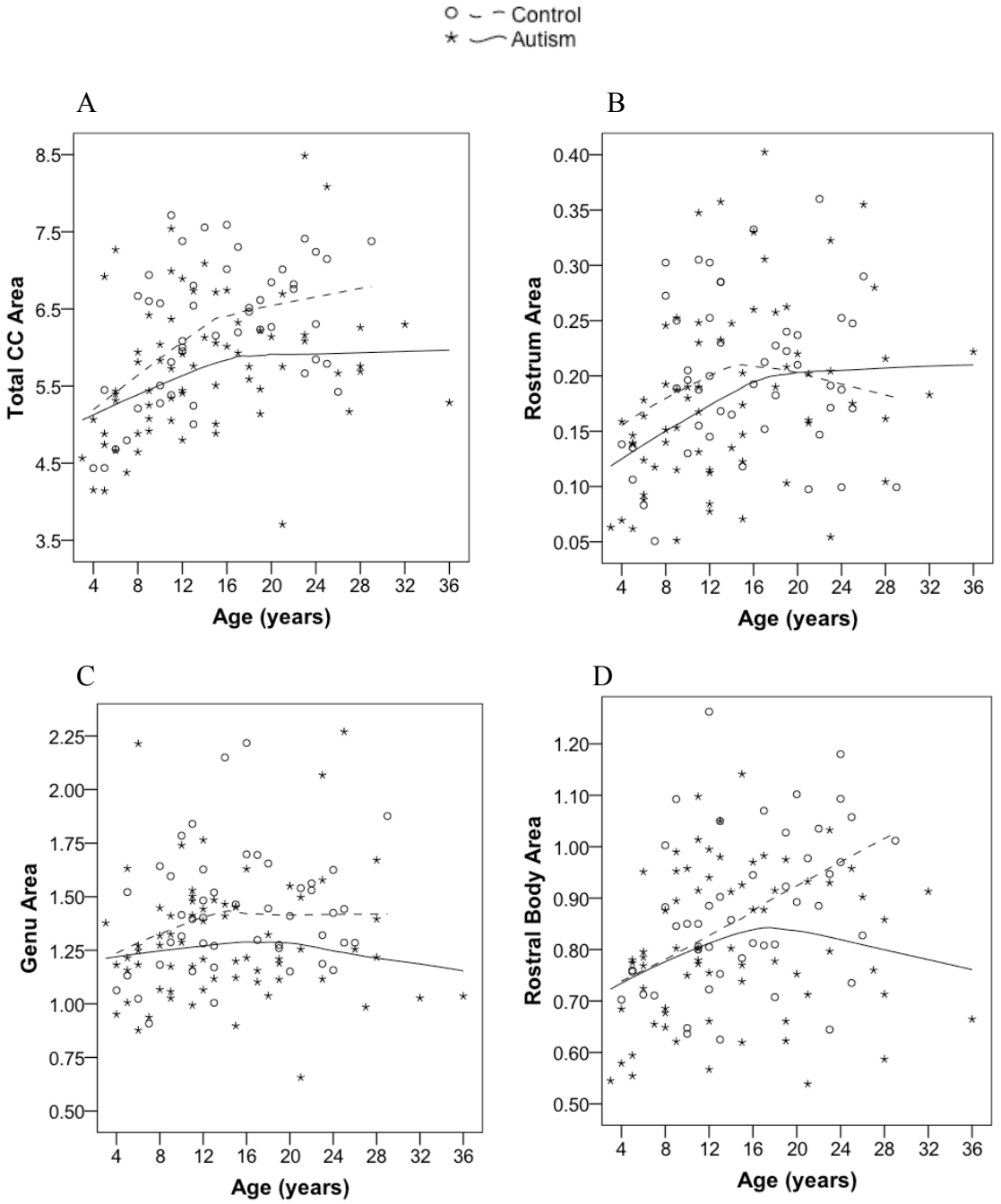

Figure 2.2 Cross-sectional age-related changes in total corpus callosum (A), rostrum (B), genu (C), rostral body (D) area unadjusted for TBV. Smooth lines show development in autism participants (solid line and stars) versus typically developing controls (dashed line and open circles).

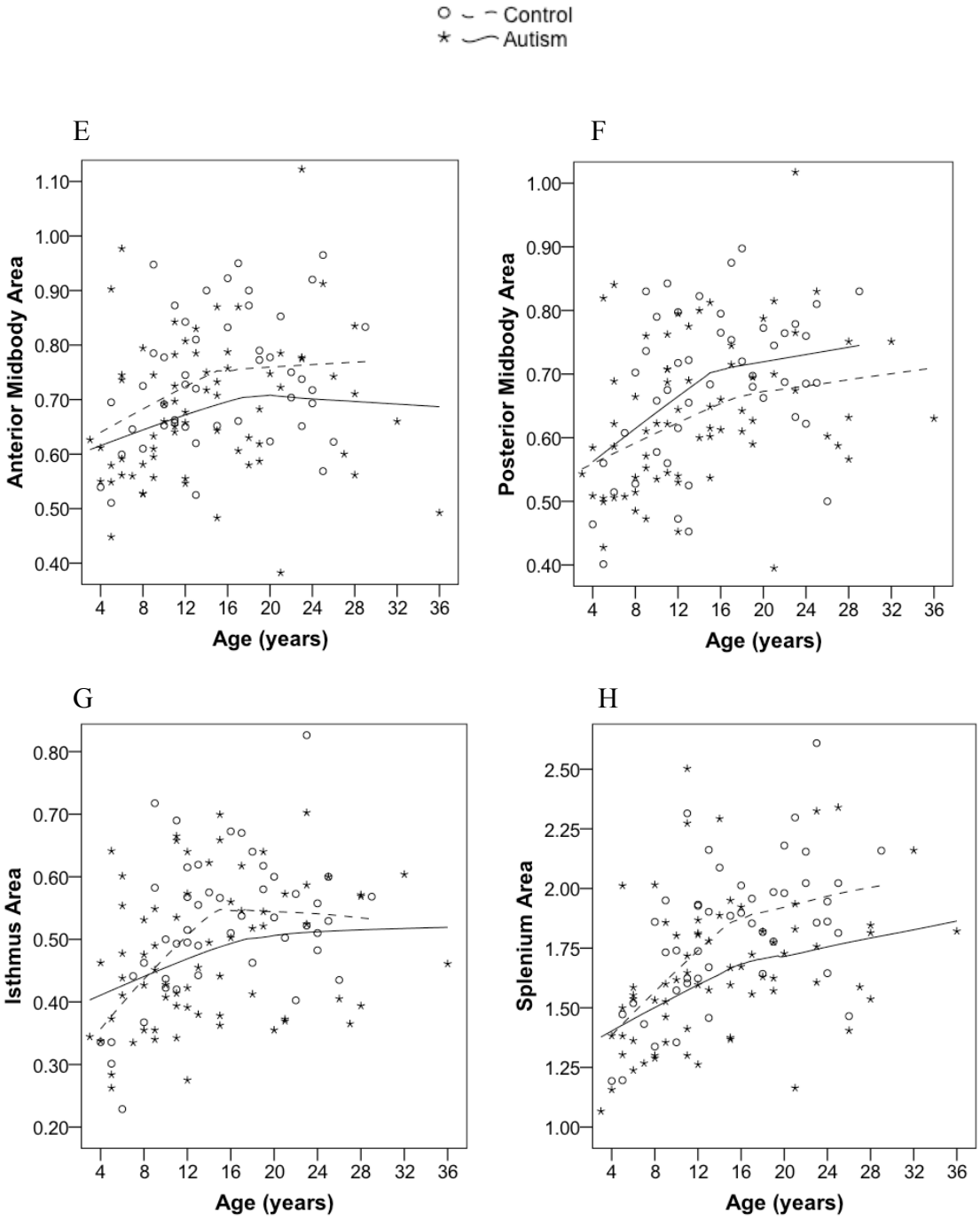

Figure 2.2 (continued) Anterior body (E), posterior midbody (F), isthmus (G), and splenium (H) area unadjusted for TBV.

2.3.3.4 Posterior corpus callosum: isthmus and splenium

The posterior areas of the CC, the isthmus and splenium, show different age-related changes. Age by area correlations suggest lack of expected increase in the isthmus but normal age-related changes in the splenium. In the isthmus, a group by age interaction (group by age squared $t=2.2$, $p=0.029$, uncorrected) confirms the visual impression of the scatterplot: isthmus area appears to be atypically larger during early childhood and not to increase with age (see Figure 2.2, panel G). Visual inspection of age-related changes in the splenium suggests that the trend toward decreased mean area of the splenium is possibly related to lack of normal growth during childhood (see Figure 2.2, panel H).

2.3.4 Age-related changes in total brain volume

Our findings are similar to results reported previously in published cross-sectional analysis of TBV in autism: a tendency toward larger mean TBV in younger children with autism, followed by an atypically low rate of subsequent growth in later childhood and resulting in similar or decreased mean TBV compared to typically developing controls by young adulthood (Figure 2.3).

2.3.5 Relationship of corpus callosum area to total brain volume

Figure 2.4 is a scatterplot of total area and TBV in the autism and control samples with smooth regression lines. Total area is related to TBV in a strongly linear manner in the typically developing control sample ($t=3.8$, $p<0.001$). Lack of significant age by TBV interactions suggested that TBV predicted CC area similarly across groups and a broad age range.

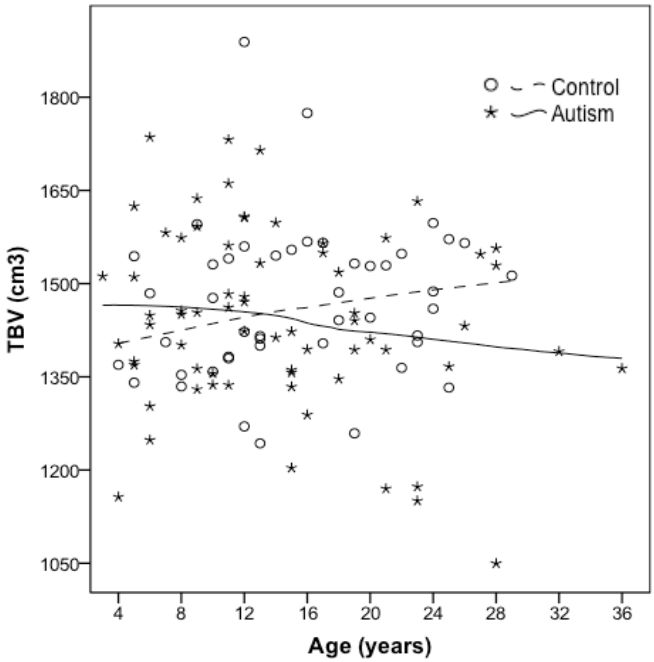

Figure 2.3 Cross-sectional age-related changes in TBV in the autism and typically developing participants.

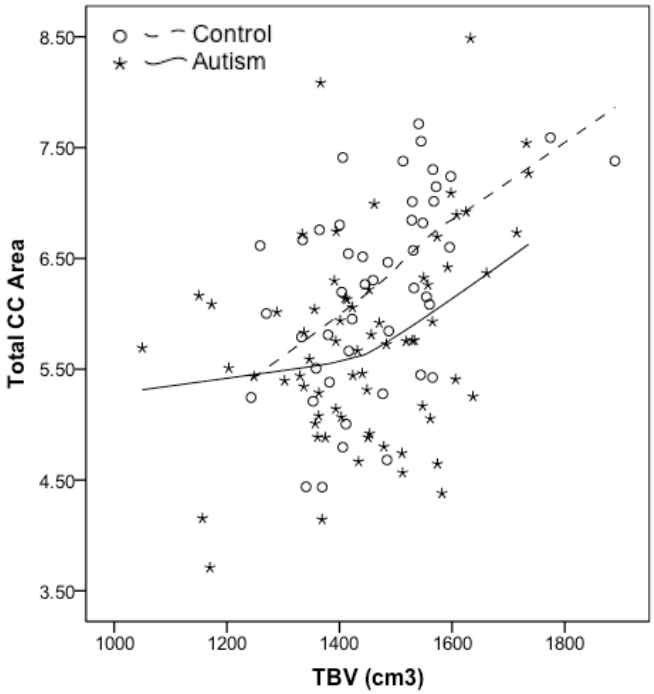

Figure 2.4 Scatterplot demonstrating the relationship between total corpus callosum area and TBV in the autism and typically developing participants.

In both autism and control samples, bivariate correlations between total area and TBV are higher during childhood, as expected when both total area and TBV increase (typical children age <15 years, n=23, r=0.52, p=0.010; typical adults age ≥18 years, n=18, r=0.20, p=0.431; autism children, n=39, r=0.53, p<0.001; autism adults, n=20, r=0.36, p=0.113).

To examine scaling of CC and TBV across the broad age range, we examined the relationship between the ratio of total area to TBV and age in the autism and control groups (Figure 2.5). A significant and common nonlinear quadratic age effect (t=3.0, p=0.003) is found in both groups; there is no significant group effect or group by age interaction. These findings suggest scaling of CC and TBV is similar in autism and typical development.

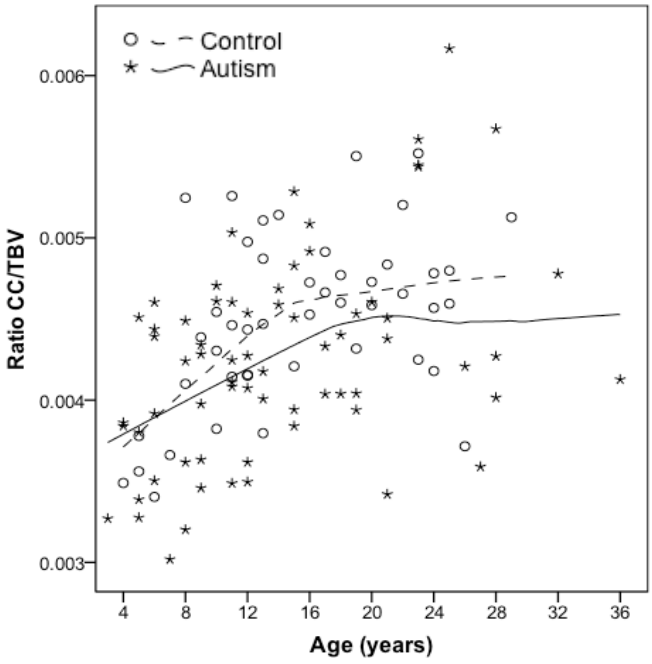

Figure 2.5. Scatterplot of cross-sectional age-related changes in the ratio of total corpus callosum area to TBV in the autism and typically developing groups.

We then studied the relationship between CC area and TBV in small vs. large brains (Jancke et al., 1999, 1997) by first examining the relationship between total CC area/TBV and TBV. In regression analysis, TBV does not significantly predict CC/TBV in the typical controls ($p=0.55$) and there is no age by TBV interaction. When correlations between CC/TBV and TBV are examined in typical children and adults separately, there is a trend for a significant negative correlation in adults ($\geq$ 18 years, $r=-0.462$, $p=0.054$) but not in children ($\leq$ 14 years, $r=-0.052$, $p=0.81$). In the autism group, the relationship is more clear-cut with larger TBVs predicting a lower CC/TBV ratio than smaller TBVs. There are significant linear ($t=2.2$, $p=0.020$) and quadratic TBV ($t=2.2$, $p=0.030$) effects on CC area/TBV in the autism group, but the results do not survive Bonferroni correction.

2.3.6 Distribution of corpus callosum area across the autism sample

Figure 2.6 shows the distributions of age-standardized total CC areas (zCC, defined in Section 2.2.4). The estimated distributions of total standardized area in autism, in both the unadjusted and adjusted for TBV conditions, show a mean shift to the left and increased variance relative to the typical control sample particularly after TBV adjustment. Figure 2.7 shows the rates of abnormally small and large callosal areas. The rates of abnormally small area are increased for several subregions in the autism group compared to the control group. Surprisingly, several individuals with autism show abnormally large areas of two subregions, the anterior and posterior midbody, relative to TBV.

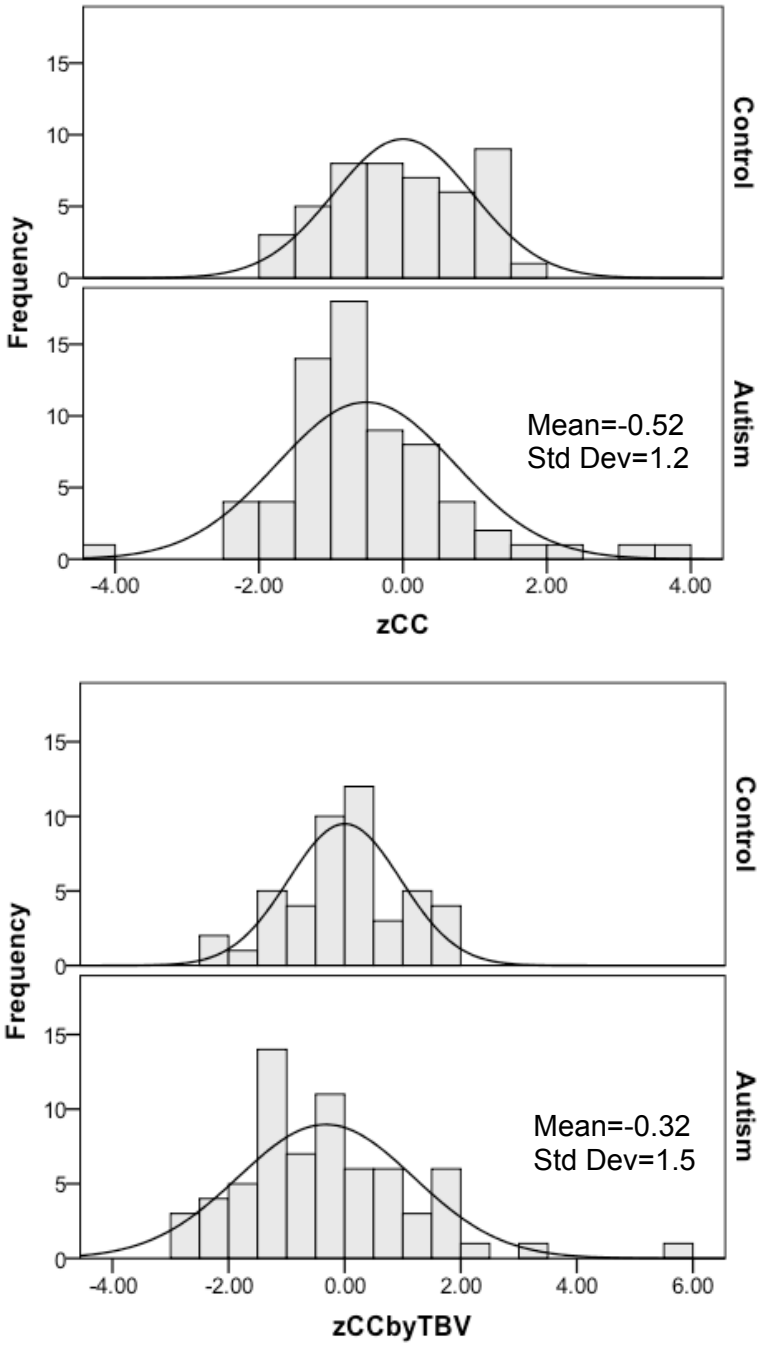

Figure 2.6 Distribution of age-standardized corpus callosum area in the control and autism samples unadjusted (zCC, top panel) and adjusted for TBV (zCCbyTBV, bottom panel).

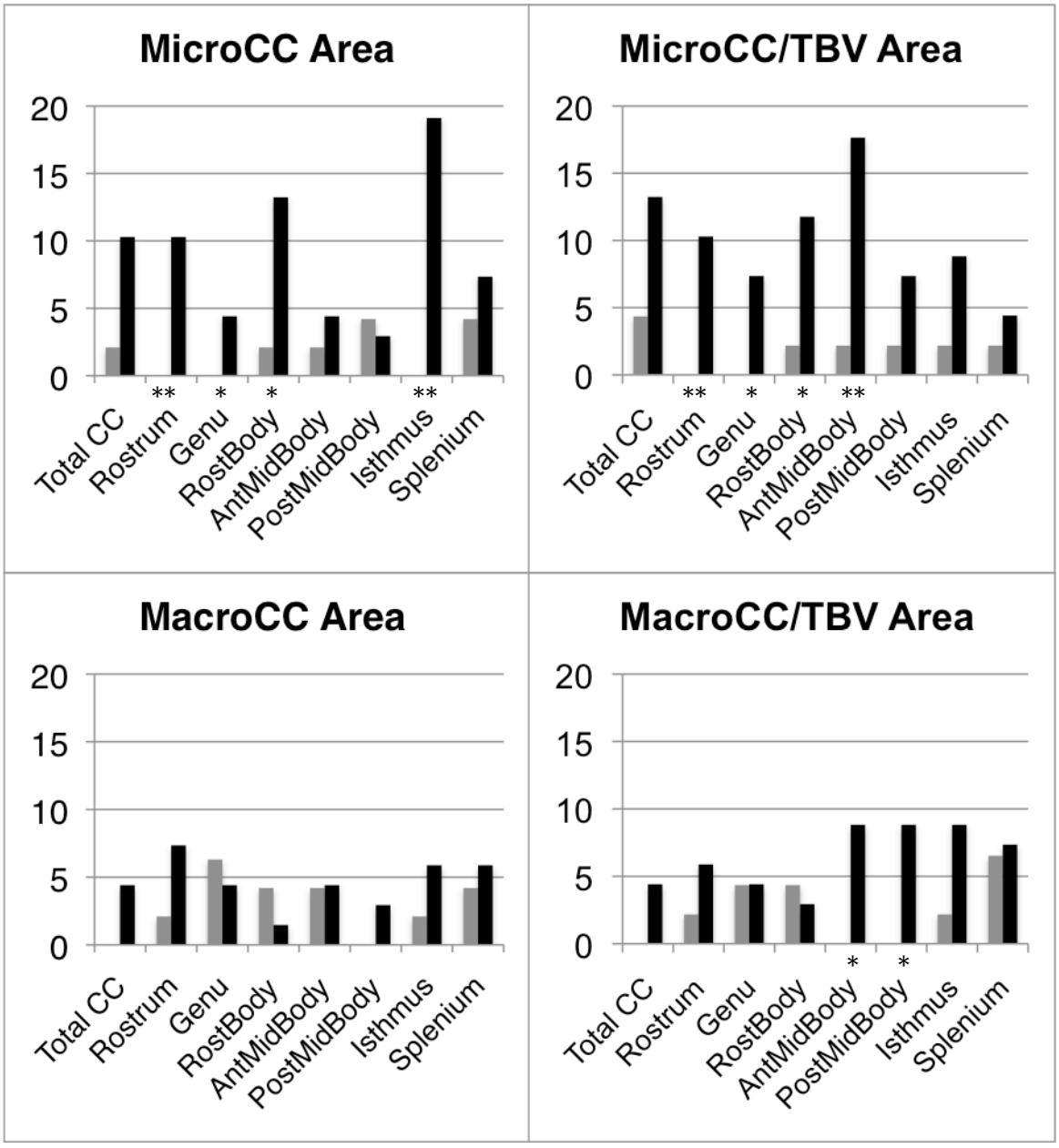

Figure 2.7 The percentage of individuals with microCC or macroCC. Bar charts display the percentage of autism (black) and control (gray) individuals with microCC (> 1.88SD below control CC areas normalized by age) or macroCC (> 1.88SD above control CC areas normalized by age). CC area unadjusted for TBV (left panels) and ratio of CC/TBV (right panels) are shown. Significant differences between group percentages are indicated: *significant difference between groups at $p<0.05$, **significant at $p\leq0.007$.

2.3.7 Corpus callosum area in relation to autism severity, IQ, and processing speed

2.3.7.1 Autism severity

In the autism group, we examined the relationship between areas of total CC and the seven subregions and ADOS social and communications algorithm scores. ADOS social scores are related significantly to anterior midbody ($t=-3.1$, $p=0.003$) and genu area ($t=-2.1$, $p=0.040$); the former survived Bonferroni correction. Figure 2.8, panel A provides evidence that higher (more severe) ADOS social algorithm scores are associated with smaller midsagittal anterior midbody area (correlation controlling for age $r=-0.36$, $p=0.003$).

2.3.7.2 IQ

We first determined if differences in VIQ and PIQ in the autism and control groups may have affected the case-control comparison of mean CC areas. Including VIQ and PIQ separately in our regression analysis results in an improved model fit for the rostrum only, where a group effect emerges (VIQ: group effect $t=2.5$, $p=0.011$; PIQ: group effect $t=2.1$, $p=0.031$). VIQ or PIQ by itself does not predict midsagittal area in the combined autism and control group. Group by VIQ and group by PIQ interactions in analysis of the rostrum suggest the relationship between IQ and rostral area is different in the autism and control groups (VIQ: group by VIQ $t=2.7$, $p=0.007$; PIQ: group by PIQ $t=2.3$, $p=0.022$). The group by VIQ interaction survives multiple comparisons. Results are similar when only participants with autism and VIQ > 90, in the range of the typically developing group, are included in the analysis. Figure 2.8, panel B shows increased rostral area associated with decreased VIQ in the typically developing group but

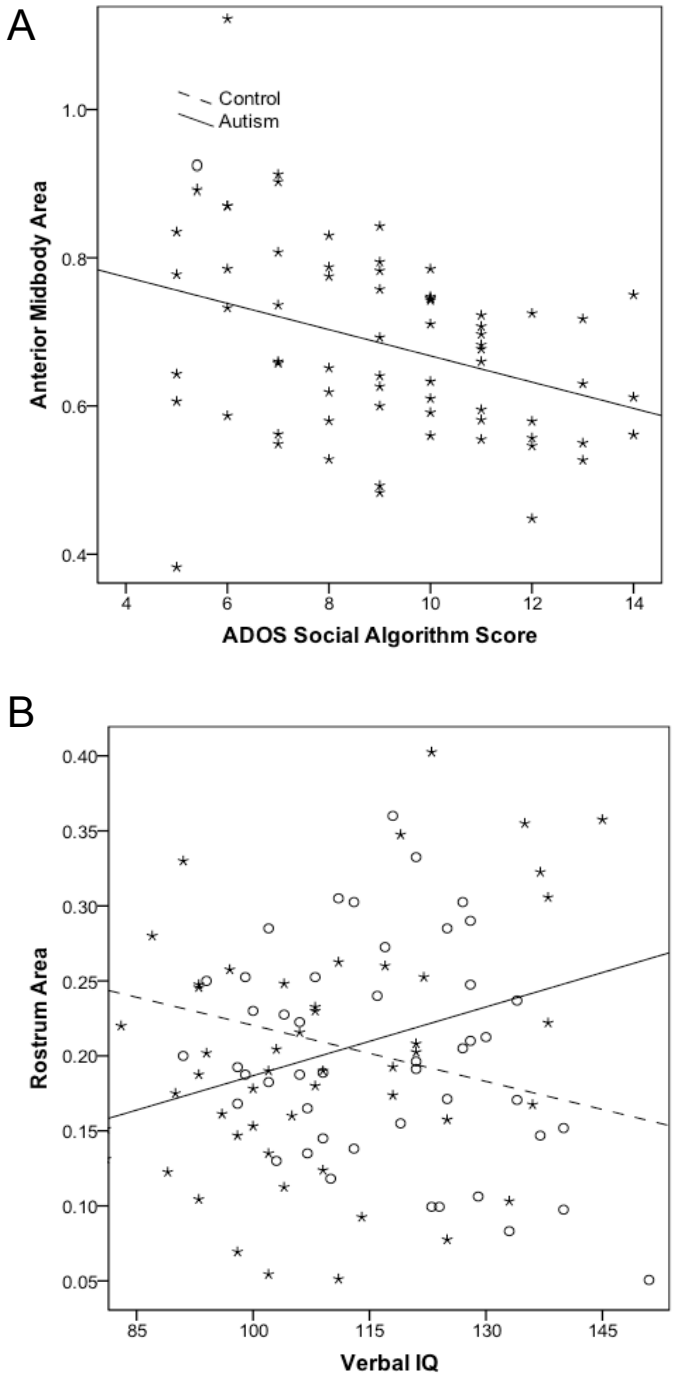

Figure 2.8 Scatterplots demonstrating the relationship between corpus callosum area and level of functioning. Panel A shows that larger midbody areas are associated with lower Social algorithm scores in autism. Panel B shows the relationship between larger rostrum area and higher VIQ in autism and lower VIQ in controls.

increased VIQ in the autism (partial correlations controlling for age and TBV: autism r= 0.314, p=0.011; control r=-0.292, p=0.054). The lack of an age by rostrum interaction suggests age-invariance of the relationship between VIQ and rostrum area.

2.3.7.3 Processing speed

There are case-control differences in participants tested with the adult version of the Trail Making Test (age ≥15 years; autism n=27, control n=22) but not the child version (autism n=18, control n=17). Significantly slower processing speed is found in autism (t=3.7, p=0.001). Processing speed improves with age from mid-adolescence into adulthood in the control group but not in the autism group (control r=-0.48, p=0.025; autism r=-0.18, p=0.37). In the linear models, increased isthmus area predicts faster processing speed (t=2.6, p=0.013) in the autism sample only (correlations: autism r=-0.40, p=0.041; control r=-0.33, p=0.147). Processing speed is significantly correlated with total area and posterior midbody area in controls but not the autism group (total CC: controls r=-0.57 p=0.007, autism r=-0.03 p=0.86; posterior midbody: controls r=-0.50 p=0.021, autism r=0.06, p=0.78).

2.3.8 Effect of psychotropic medication on corpus callosum area

Because 41% of the individuals in the autism sample had a history of psychotropic medication use, we felt it was important to test if medication use had an effect on the significant case-control differences found in isthmus area. Examination of the medicated versus unmedicated autism participants shows no significant differences in area or development. Based on visual impressions of smooth curves, we observe that although isthmus area in individuals with autism tend to be smaller than in typical

controls during late childhood and adolescence, growth rates appeared better in the medication subgroup than in the subgroup not taking medication, but this observation lacks statistical significance at present. By adulthood, case-control differences in isthmus area are no longer present in the medication subgroup.

2.4 Discussion

This study has presented a collection of new findings regarding atypical and typical age-related changes in CC areas, increased rates of abnormally small subregions even in the absence of case-control differences in mean area, an association between anterior midbody area and severity of impairment in the social domain, and atypical relationships between area and verbal IQ and processing speed in individuals with autism. Overall, we found evidence of pathology involving CC area in autism to be more complex than previously described. Most importantly, we found evidence of multiple functional implications of atypical changes in CC area in autism.

2.4.1 Age-related changes

Similar to longitudinal MRI studies of typical development (Giedd et al., 2004, 1999; Gilliam et al., 2011), our cross-sectional sample of typically developing individuals had an anterior-to-posterior gradient of age-related increase in midsagittal CC area. During later childhood, adolescence, and young adulthood, area increased mainly in posterior regions. Although our autism sample showed typical age-related change in the posterior midbody, splenium, and the CC as a whole, these changes were atypical in the rostrum and isthmus. The autism group showed an increase in rostrum area with age and different age-related changes in isthmus area relative to the typical group. A previous

study utilizing 2-D voxel-based morphometry found decreased white matter density in the rostrum/genu and splenium and abnormal age-related density increases in the rostrum/genu in autism (Chung et al., 2004). The tendency toward decreased total area and most subregions, present by late childhood and persisting into adulthood in our autism sample, is consistent with results of a previous 2-year follow-up study of callosal volume in autism (Frazier et al., 2012).

Age-related increase in rostrum area in the autism sample was most significant when adjusted for total brain volume (TBV). The atypical increase appeared to occur in adulthood, when the rostrum size is typically static, along with some atypical decrease in TBV. A similar finding in ADHD has been reported by a recent longitudinal study of children and adolescents with ADHD; compared to typically developing controls, the size of anterior CC in young people with ADHD was found to increase (Gilliam et al., 2011).

The rostrum contains interhemispheric fibers connecting homotopic orbitofrontal cortex and the subgenual part of the ventromedial prefrontal cortex (Hofer and Frahm, 2006; Huang et al., 2005; Pannek et al., 2010; Peltier et al., 2010a; Witelson, 1989; Zarei et al., 2006). Volumetric abnormalities have been found in the orbitofrontal cortex in autism (Girgis et al., 2007; Hardan et al., 2006). The rostrum also contains heterotopic fibers connecting orbitofrontal cortex with contralateral temporal pole and running through the temporal stem, the "callosal radiations of Peltier" (Peltier et al., 2010a, 2010b). Temporal pole and orbitofrontal cortex are both important in social cognition, particularly inferring the mental state of others (Kringelbach, 2005; Vollm et al., 2006), a cognitive process involved in Theory of Mind and empathy, impaired in many children and adults with autism (Baron-Cohen and Belmonte, 2005).

Atypical age-related isthmus changes in the autism sample were complex. As expected for posterior CC regions in typical development, a strong linear relationship between age and isthmus area was observed in our control sample during childhood and adolescence. In the autism sample, the isthmus appeared to be atypically larger during early childhood and late childhood and adolescence, and to increase at a much slower rate than typically observed during the latter epoch. Fibers traversing the isthmus connect superior temporal and parietal regions in the two hemispheres (Pannek et al., 2010; Park et al., 2008; Witelson, 1989; Zarei et al., 2006), regions strongly implicated in idiopathic autism (Bigler et al., 2007, 2003; Boddaert et al., 2004; Hoeft et al., 2011; Lange et al., 2010; Lee et al., 2009, 2007).

2.4.2 Mean area and the distribution of corpus callosum in autism

Smaller mean area in autism was found in the total CC, isthmus, and splenium, although case-control differences were modest and did not survive correction for multiple comparisons. Although a meta-analysis of CC size in autism found case-control mean difference effect sizes largest in the anterior regions (Frazier and Harden, 2009), studies using voxel based morphometry (VBM), which are not restricted to predefined ROIs, have shown strong effects both anteriorly and in the splenium (Chung et al., 2004; Vidal et al., 2006).

Examination of the distribution of CC areas provided additional information. Increased variance was observed in the autism distribution, the mean was shifted to the left, and increased rates of abnormally small areas were found even in subregions not showing group differences in mean area. The proportions of individuals with abnormally

small areas in the anterior third of the CC and the isthmus were increased in the autism group. Surprisingly, increased variation in the autism sample was not only due to a tendency toward small areas. The middle third of the CC areas were larger than expected given TBV. Similar to the distribution of head circumference in autism (Lainhart et al., 2006), the distribution of CC area in autism is abnormally wide.

A number of reasons for discrepant results in past studies of CC area in autism were apparent, in addition to known effects of gender and handedness. Our data support past reports suggesting clinical heterogeneity in IQ and severity of autism may affect results (Boger-Megiddo et al., 2006; Elia et al., 2000; McAlonan et al., 2002), and strongly implicate the effect of age and stage of development (Frazier and Hardan, 2009; Tepest et al., 2010). The wide distribution of callosal area in autism suggests studies using small samples will, by chance alone, differ in the proportion of subjects with small CC area. Given the known variability of CC area in normative samples (Giedd et al., 1999), representativeness of control groups can also affect the results of case-control studies particularly when sample sizes are small. Our data provide additional evidence of a complex interaction between CC area and TBV. Scaling of CC area to TBV differs in individuals with autism who have larger versus smaller brains (Kilian et al., 2008; Rice et al., 2005), a finding consistent with those of Jancke et al. (1997), who found that CC area increased proportionately less in typical individuals with larger total brain volumes.

2.4.3 Clinical correlations

CC pathology, manifested by atypical changes in cross-sectional area, was related to clinically important types of interindividual variation in the autism sample. Variations in social impairment, IQ, and processing speed were related to variations in the area of

CC subregions. Age-invariance of the relationships between CC area and social impairment and IQ suggests that a biological link between CC area and these clinical features is established early in childhood and persists into adulthood.

2.4.3.1 Smaller CC area and greater social impairment in autism

Interindividual variation in severity of social impairment, as measured by the ADOS social algorithm score, was associated with variation in area of the anterior midbody. Smaller anterior midbody area was associated with more severe social impairment. These results are in agreement with other studies suggesting a relationship between smaller CC volume and more severe impairment of core diagnostic features of autism (Hardan et al., 2009), worse performance on related neuropsychological tasks (Keary et al., 2009), lower fMRI functional connectivity while performing tasks (Mason et al., 2008; Schipul et al., 2011), and decreased interhemispheric transfer of information (Hardan et al., 2009). A study of traumatic brain injury found that children with increased CC volume loss had greater difficulties with social reintegration following injury (Gale & Prigatano 2010).

The anterior midbody contains fibers connecting the premotor and supplementary motor cortices and part of the pars opercularis of the inferior frontal gyrus (Hofer and Frahm, 2006; Pannek et al., 2010; Witelson, 1989; Zarei et al., 2006). Anterior midbody connections are thus involved in guidance, planning, coordination of motor movements, and in language. Reduced gray matter in the pars opercularis in individuals with autism or Asperger's disorder has been associated with more impairment in a social communication factor that included imitation and verbal and nonverbal communication (Yamasaki et al., 2010).

2.4.3.2 Smaller CC area and lower IQ in autism

Area of the rostrum was associated with verbal IQ in our typically developing and autism samples but in different directions: smaller rostrum area was associated with higher verbal IQ in controls but with lower verbal IQ in autism. This opposing structure-function relationship between the groups suggests that CC subregions may be similar in size but have very different functional correlates and neurodevelopmental mechanisms. Similar group differences between structure and function has been found in cortical thickness and IQ in individuals with autism and typically developing controls, interestingly in the orbitofrontal cortex, a region connected by the rostrum (Hofer and Frahm, 2006; Huang et al., 2005; Pannek et al., 2010; Witelson, 1989; Zarei et al., 2006). Thinning of the cortex with age was previously associated with increased IQ in typical controls but not autism spectrum disorder subjects (Misaki et al., 2012). Our data suggest that smaller rostrum area may be functionally adaptive in typically developing controls and functionally maladaptive in autism.

2.4.3.3 Smaller CC area and slower processing speed

We found slower processing speed in autism during adolescence and adulthood, as in previous studies (Kleinhans et al., 2005; Minshew et al., 2002; Rumsey and Hamburger, 1988). Case-control differences in processing speed, as measured by the Trail Making Test, were not evident in young individuals in our study. Processing speed improved between mid-adolescence and adulthood in the typically developing group but not in the autism group. In the typical group, processing speed had a strong linear relationship with total CC area, apparently driven by posterior midbody area. In adolescents and adults with autism, smaller isthmus area was associated with slower

processing speed. A previous study by our group found a strong relationship between processing speed and CC diffusion tensor imaging (DTI) measures (radial diffusivity in particular; Alexander et al., 2007). Although microstructural properties of the CC cannot be identified by area alone, future studies linking multimodal imaging will help identify properties of the CC that may be developing abnormally in autism.

2.4.4 Limitations

The most important limitation of this study is the cross-sectional nature of the dataset, the results require verification by longitudinal data. In addition, only males with autism with general cognitive normality were studied; findings may not apply to females, individuals with low-functioning autism, or very young or old individuals with the disorder. Future research will benefit from the use multimodal imaging measures of CC growth, development, pathology, and function beyond CC area. Postmortem studies of the CC are needed to determine the microscopic histological basis of abnormalities identified using in vivo neuroimaging. Finally, demonstrating specificity of our findings to autism will require comparison to groups of individuals with other neurodevelopmental disorders.

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CHAPTER 3

LONGITUDINAL DEVELOPMENT OF HESCHL'S GYRUS AND PLANUM TEMPORALE VOLUME IN AUTISM AND TYPICALLY DEVELOPING CONTROLS

3.1 Introduction

Language impairments are found in the majority of individuals with autism and impact functional outcome into adulthood (Howlin et al., 2004; Szatmari et al., 2009). Functional studies repeatedly show atypical auditory and language activation in the brains of individuals with autism, but the underlying causes remain unknown.

Few studies to date have investigated the structure of temporal lobe auditory and language cortex in autism. Autism-control differences have not been found in Heschl's gyrus gray matter (GM) volume or leftward asymmetry in cross-sectional samples (Rojas et al., 2002, 2005; Gage et al., 2009; Knaus et al., 2009; Herbert et al., 2005). Recently, increased Heschl's gyrus cortical thickness has been found in older adolescents and adults with autism compared to typically developing controls (Hyde et al., 2010), suggesting that developmental differences may exist. No studies to date have examined Heschl's gyrus white matter (WM) in autism. Given that WM reductions have been found in the absence of GM differences in deaf adults (Emmorey et al., 2003), and many individuals with autism are so unresponsive to sounds that deafness is often queried in

early childhood, investigation into WM development is important. As mentioned in Section 1.3.3.2, reported structural case-control differences in the planum temporale in autism are inconsistent but suggest atypical age-related changes (Gage et al., 2009; Knaus et al., 2009). Nothing is known about how Heschl's gyrus and planum temporale change in volume longitudinally within individuals with autism or even in typically developing individuals from childhood to adulthood.

In this chapter, we test the hypothesis of abnormal development of Heschl's gyrus GM and WM and planum temporale volumes in autism. We used an accelerated longitudinal design to examine changes from age 3 to 17. Up to three timepoints of longitudinal MRI data, collected on average 2.5 years apart, are compared in individuals with autism and typically developing controls. The results show evidence of abnormal development of Heschl's gyrus in autism: an atypical trajectory of right hemisphere GM volume and a trend toward atypical volumetric change in WM bilaterally. The results also show evidence of abnormal changes in planum temporale volume and asymmetry with age in autism: left volume and leftward asymmetry increase during adolescence in typical development but not in autism.

3.2 Materials and methods

3.2.1 Participants

The individuals in this study were chosen from a larger sample of males participating in a longitudinal study of brain development at the University of Utah. Autism diagnosis and inclusion/exclusion criteria for the autism and typically developing participants are described in Chapter 2.

All participants between the ages of 3-12 years at the time of their first scan were included. This age range was chosen because the youngest autism participants were age 3 at the time of their first scan, and postmortem studies suggest that most development of the auditory cortex is complete by age 12 (Huttenlocher and Dabholkar, 1997; Moore, 2002). Of the original cohort, 18 typically developing controls and 44 individuals with autism met the age criteria for inclusion. Further review of medical records and recent medical questionnaires resulted in 17 typically developing males and 40 individuals with a lifetime diagnosis of an autism spectrum disorder (34 individuals met criteria for full autism), hereafter referred to as autism. 52% of the autism group was taking psychotropic medications at some point during the study (47.5% SSRIs or tricyclic antidepressant, 27.5% stimulants, 2.5% valproic acid, 25% multiple types of medications). Effects of medications were explored.

3.2.2 Behavioral assessments

3.2.2.1 Intellectual functioning

At the time of the first scan, the Differential Abilities Scale (DAS; Elliott, 1990) was utilized to assess intelligence (IQ) for the majority of participants. Verbal IQ (VIQ) was estimated from the Verbal Cluster and performance IQ/nonverbal ability (PIQ) estimated from the Nonverbal Cluster (preschool) and Special Nonverbal Composite (school-age) standard scores. Two young individuals with autism received the Mullen Scales of Early Learning (Mullen, 1995) and the Wechsler Intelligence Scales for Children (WISC-III; Wechsler, 1991) was administered to 1 control and 3 autism participants. At the second and third timepoints, IQ was assessed with the Wechsler Abbreviated Scales of Intelligence (WASI; Wechsler, 1997). Due to differing subtests of

the WASI administered, VIQ, PIQ and FSIQ were available at timepoint 2, and FSIQ at timepoint 3.

3.2.2.2 Handedness

Handedness was collected using the Edinburgh Handedness Inventory (Oldfield, 1971), providing a quantitative measure of handedness ranging from -100, or completely left-handed to +100 or completely right handed.

3.2.3 Brain measures

3.2.3.1 Imaging protocol

Magnetic resonance images were acquired on a Siemens Trio 3.0 Tesla Scanner. At timepoint 1, an 8-channel, receive-only RF head coil was used to acquire 3D T1-weighted image volumes with 1x1x1mm isotropic resolution using an MP-RAGE sequence (TI=1100msec, TR=1800msec, TE=2.93msec, flip angle=12degrees, sagittal, field of view=25.6cm, matrix=256x256x160). At timepoints 2 and 3, a 12-channel, receive-only RF head coil was used to obtain 3D T1-weighted image volumes with 1x1x1.2mm resolution using an MP-RAGE sequence (TI=900msec, TR=2300msec, TE=2.91msec, flip angle=9degrees, sagittal, field of view=25.6cm, matrix=256x256x160).

3.2.3.2 Image processing

At the time of the scan, datasets were assigned a random number, allowing image processing and regions of interest (ROI) identification to be performed blind to participant age and diagnosis. Images were realigned along the anterior-posterior commissure in the axial, coronal, and sagittal planes to eliminate head rotation using

Analyze® Version 10.0 (Mayo Clinic, Rochester, MN). GM, WM, and cerebrospinal fluid (CSF) were classified using an automated tissue segmentation program (Prastawa et al., 2004; Van Leemput et al., 1999).

3.2.3.3 ROI identification

3.2.3.3.1 Heschl's gyrus. Heschl's gyrus was defined as the most anterior transverse gyrus on the superior surface of the superior temporal gyrus (STG). Heschl's gyrus ROI identification was performed according to methods described previously (Emmorey et al., 2003; Knaus et al., 2009; Penhune et al. 1996; Rademacher et al., 2001; Rojas et al., 1997). Located in the Sylvian fissure, the posterior boundary of Heschl's sulcus and medial boundary of the meeting of the gyrus with the insular junction were easily identified on MRI images. The anterior boundary was the first transverse sulcus of the temporal lobe, with the most anterior slice where Heschl's gyrus is first distinguished from the STG. The lateral boundary was Heschl's sulcus (see Figure 3.1 for Heschl's gyrus sample segmentation). When duplicate transverse gyri were present, only the most medial gyrus was included and duplicate transverse gyri were included in the planum temporale measurements. Heschl's gyrus is often bifurcated by an intermediate sulcus. In cases where a second transverse gyrus merged with Heschl's gyrus prior to the insula (partial bifurcation), the entire Heschl's gyrus stem posterior from the merge was included in the ROI. The second transverse gyrus prior to the merge was included in the planum temporale.

3.2.3.3.2. Planum temporale. In order to compare our study to previous reports in typically developing and autism samples, the classic definition of the planum temporale was adopted (Geschwind and Levitsky, 1968; Witelson and Kigar, 1992). The planum

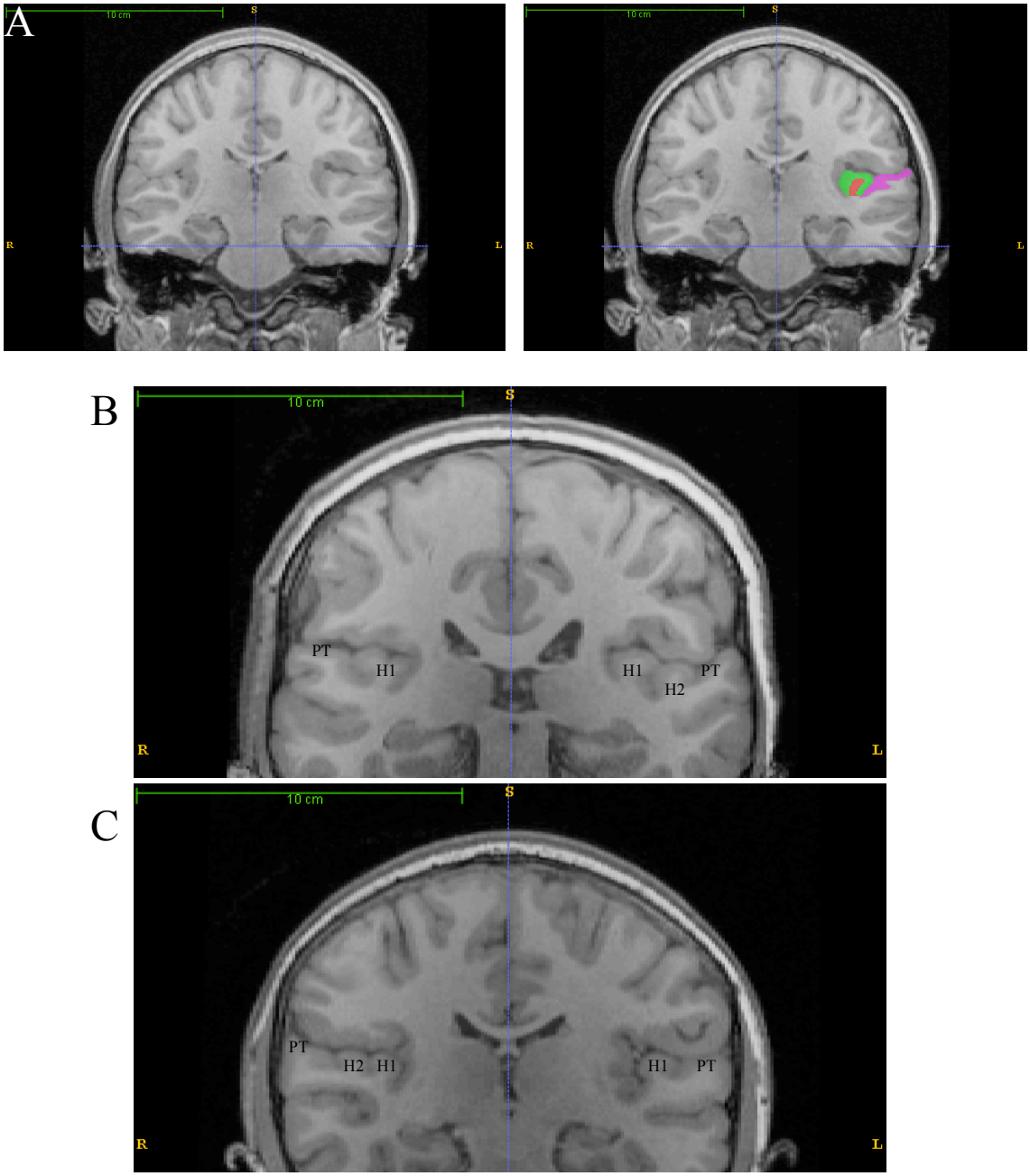


Figure 3.1. Sample images of Heschl's gyrus (HG) and planum temporale (PT) on coronal sections. A. Sample brain showing before and after segmentation of left Heschl's gyrus gray matter (green), white matter (red) and planum temporale (pink). B. Example of single right (H1) and duplicate left Heschl's gyrus, (H2). C. Example of duplicate right and single left Heschl's gyrus. H2 gray matter was included in planum temporale volumes.

temporale was defined as the section of cortex posterior to Heschl's gyrus, located on the superior surface of the STG and extending along the horizontal segment of the Sylvian fissure (Emmorey et al., 2003; Foundas et al., 2001; Geschwind and Levitsky, 1968; Knaus et al., 2009; Penhune et al., 2003; Rojas et al., 2002; Westbury et al., 1999; Witelson and Kigar, 1992). In cases where the endpoint of the horizontal ramus was not clearly identifiable on sagittal views due to an ascending sloping of the Sylvian fissure, a knife-cut method was used to determine the endpoint of the planum temporale (Foundas et al., 2001; Geschwind and Levitsky, 1968). The anterior boundary was Heschl's sulcus (or the first gyrus if a duplicate gyrus), the lateral boundary was the edge of the Sylvian fissure, and the medial boundary was Heschl's gyrus on anterior sections and the circular sulcus and insula on posterior sections.

3.2.3.4 ROI volume calculation

Heschl's gyrus and planum temporale ROIs were manually segmented on contiguous coronal slices in native space using itk-SNAP (Yushkevich et al., 2006), allowing simultaneous viewing on the coronal, sagittal, and axial planes. The left and right hemisphere were traced and segmented separately. ROIs were combined with the GM, WM, CSF voxel classification using brainseg version 1.8b, an inhouse segmentation program available at the Scientific Computing and Imaging Institute (SCI), resulting in separately labeled GM and WM voxels (see Figure 3.1). GM and WM volumes within Heschl's gyrus and GM of the planum temporale were calculated for each hemisphere in itk-SNAP.

3.2.3.5 Reliability

ROIs were performed by the primary rater (MDP) and two other trained raters. Intrarater and interrater reliabilities were assessed by intraclass correlation (ICC). Both intra and interrater reliabilities > 0.90 were first established on a subset of 10 brains (20 hemispheres). All subsequent ROIs were traced twice by the primary rater and at least once by another trained rater, with average measurements as the final volumes. The final intrarater reliabilities were Heschl's gyrus GM ICC > 0.91, Heschl's gyrus WM ICC > 0.88, planum temporale ICC > 0.92. The final interrater reliabilities were Heschl's gyrus GM and WM ICC > 0.96, planum temporale ICC > 0.95.

3.2.3.6 Asymmetry and ratios

In addition to total GM and WM volumes, an asymmetry index ([L-R]/[(L+R)/2]) was calculated for Heschl's gyrus GM and WM separately and Heschl's gyrus GM/WM ratios were calculated for each hemisphere.

3.2.3.7 Global brain volumes

Total brain volume (TBV), hemispheric GM and WM, temporal lobe, and superior temporal gyrus volumes for each timepoint were obtained through the imaging resources at the Brain Imaging and Behavior Lab at Brigham Young University using Freesurfer v5.1.0 (http://surfer.nmr.mgh.harvard.edu).

3.2.4 Statistical analysis

Between-group differences in age, interscan interval, handedness and IQ were examined with independent samples t-tests. Group differences in Heschl's gyrus and planum temporale ROIs were examined in two ways. We first examined between-group

mean differences and cross-sectional age-related changes from data obtained at the first timepoint using regressions with an age covariate. Squared age (age^2), to allow for nonlinear age-related changes, group by age interactions, TBV, and group by TBV interactions were examined as possible covariates, with the best model selected according to the lowest AIC criteria.

Longitudinal changes in Heschl's gyrus and planum temporale volume and asymmetry and Heschl's gyrus GM/WM ratio were examined using linear mixed-effects models. This analysis allows us to model multiple observations per participant, which contain dependence between measurements, obtained over nonuniform intervals. Mixed models also allow us to model our participants as random effects, so that each person has their own intercept that will vary by individual. The following model was used:

$$\text{ROI repeat} = \beta_0\text{Intercept} + \beta_1\text{Group} + \beta_2\text{Age} + \beta_3\text{Group*Age} + \beta_4\text{Age}^2 +$$

$$\beta_5\text{Group*Age}^2 + \beta_6\text{Hemispheric Volume} + \beta_{0i} + e$$

Hemispheric GM, WM or total volume was included to control for more global brain changes. The following additional variables were considered for inclusion in the models, using the lowest AIC criterion to determine the best-fitting model: group by hemispheric volume interaction, handedness, and PIQ. All ages and predictor variables were centered on the grand mean to allow for interpretation of the regression coefficients (Cohen et al., 2003). The effect of psychotropic medication use on brain development was examined using mixed models. We first compared longitudinal changes in the autism medicated to the nonmedicated group while controlling for severity of autism. We then compared both groups to typical development.

To analyze the relationship between auditory and language regional volumes in relation to larger brain changes, volumes were transformed by the natural logarithm. Mixed effects models described above were used to examine the relationship between changes in the natural logarithm of Heschl's gyrus and planum temporale and changes in the natural logarithm of larger brain regions as covariates (log TBV, log temporal lobe, log STG), allowing for additional tests of group by log brain region interactions. In the absence of group by log region interactions, mixed models were run for the autism and control groups separately to estimate the relationship between log brain changes and log Heschl's gyrus and log planum temporale.

All analyses were performed in SAS® software, version 9.2 (SAS Institute, 2008) or PASW Statistics 18.0.

3.3 Results

Imaging data suitable for analysis were three scans from 26 autism and 12 control participants, at least two scans from 12 autism and 5 control participants, and 1 scan from 2 autism participants. Scan data were not available from all participants at all three time point for the following reasons: scan quality/motion (4 autism scans), inability to be scanned due to previous sedation scanning (7 autism participants), no contact for family (1 control, 3 autism), and declined participation (3 control, 2 autism).

3.3.1 Participants and demographics

Characteristics of the autism and typically developing control samples at the three timepoints are presented in Table 3.1. There are no group differences in mean age at Time 1; at Time 3 the autism group is on average 1.5 years older than the control group.

The average interval between scans is 2.65 years. Quantitative handedness is similar in the two groups. As expected, mean PIQ, VIQ, and FSIQ are significantly lower in the autism group than in typical controls.

3.3.2 Heschl's gyrus

3.3.2.1 Qualitative Analysis

Heschl's gyrus gross morphology was similar in the autism and control groups. In the left hemisphere, a single Heschl's gyrus is found in 35% of the autism group and Table 3.1. Demographic summary of participant age at scan, interscan interval, and behavioral assessments 38% of controls, complete duplication in 6.2% of autism and controls, and partial duplication in 8.7% of autism and 9.3% of controls. In the right hemisphere, a single Heschl's gyrus is found in 40% autism and 34% controls, complete duplication in 7.5% autism and 6.2% controls, and partial duplication in 2.5% autism and controls. These percentages fall in the range reported in typical populations (Leonard et al., 1998).

3.3.2.2 Cross-sectional volumetric analysis

We examine Time 1 volumes and the effects of cross-sectional age and age by group interactions to compare the results from our samples to previous cross-sectional studies. Heschl's gyrus total, GM and WM mean volumes by group, presented in Table 3.2, are in the range of previous reports of typically developing children and children with autism (Gage et al., 2009; Knaus et al., 2009; Rojas et al., 2005). Nonsignificantly larger mean GM and WM volumes are found in autism. No significant effects of age or group by age interactions are found. The inclusion of TBV improves the model fit for Heschl's gyrus GM and WM comparisons: TBV is significantly related to right GM and

Table 3.1 Demographic summary of participant age at scan, interscan interval, and behavioral assessments.

	Autism		**Control**		
	mean (sd)	**range**	**mean (sd)**	**range**	**t (p-value)**
Time 1	n=40		n=17		
Age (years)	8.5 (3.1)	3.5-12.9	9.0 (2.6)	4.0-12.3	0.5 ns[b]
Handedness[a]	73 (39)	-67-+100	79 (13)	+20-+100	0.4 ns
PIQ[c]	90 (20)	50-128	120 (15)	96-145	5.5 (<0.001)
VIQ	90 (22)	51-136	114 (15)	91-151	4.0 (<0.001)
FSIQ	86 (21)	49-127	120 (16)	95-153	5.9 (<0.001)
Time 2	n=38		n=17		
Age (years)	11.3 (3.0)	5.9-15.5	11.6 (2.7)	6.0-15.2	0.3 ns
Time 1 to 2 (years)	2.7 (0.7)	2.0-6.5	2.6 (0.6)	1.8-3.7	0.5 ns
PIQ[d]	101 (16)	74-138	120 (12)	102-138	3.5 (0.001)
VIQ	90 (18)	55-118	110 (20)	74-140	3.1 (0.003)
FSIQ	95 (16)	70-121	117 (17)	87-144	3.8 (<0.001)
Time 3	n=26		n=12		
Age (years)	15.1 (2.3)	10.7-17.8	13.6 (2.6)	8.8-17.1	1.7 (0.08)
Time 2 to 3 (years)	2.7 (0.5)	2.0-4.2	2.6 (0.5)	1.9-3.5	0.7 ns
FSIQ[e]	103 (17)	76-128	119 (10)	105-138	3.3 (0.002)

[a]based on Edinburgh Handedness Inventory (Oldfield, 1971), ranging from -100, or completely left handed, to +100, completely right handed; [b]ns indicates *p*-value > 0.2; [c]Time 1 autism: PIQ n=38, VIQ n=32, FIQ n=39; [d]Time 2 PIQ, VIQ, FSIQ: autism n=29, control n=12; [e]Time 3 FSIQ: autism n=24, control n=12.

Table 3.2. Heschl's gyrus (HG) mean volumes (mm^3) at Time 1

	Autism n=40		Control n=17		Group Difference
	mean (sd)	range	mean (sd)	range	t (p-value)
Left Hemisphere					
HG GM	1630 (499)	838-2596	1492 (455)	897-2271	0.9 ns[a]
HG WM	493 (199)	188-908	443 (169)	225-736	0.7 ns
HG Total	2124 (682)	1026-3505	1936 (614)	1128-3007	0.8 ns
Right Hemisphere					
HG GM	1203 (306)	549-1869	1124 (349)	511-1747	1.4 (0.157)
HG WM	384 (130)	179-758	354 (111)	160-528	0.9 ns
HG Total	1587 (426)	769-2627	1477 (450)	671-2242	0.9 ns

[a]ns indicates significance *p*-values >0.20

WM volumes (t=2.0, p=0.046; t=2.4, p=0.020, respectively) similarly in both groups.

3.3.2.3 Longitudinal Age-Related Volumetric Changes

Table 3.3 depicts the results of the final best-fitting mixed effects models for Heschl's gyrus total, GM, and WM. The typically developing group is the reference group and any differences between typical development and autism are modeled in the group effect and interactions.

3.3.2.3.1 Typically developing participants. In contrast to the absence of cross-sectional age effects, significant age-related changes are found in the longitudinal analysis. Heschl's gyrus total volume and GM volume significantly increase with age in both hemispheres (total volume age effect: left $p<0.001$, right $p=0.001$, age^2 effect: left $p=0.055$, right $p=0.067$; GM volume age effect: $p<0.001$, see Table 3.3 and Figure 3.2 and 3.3). Some of the variance in Heschl's gyrus GM volume is due to global hemispheric GM effects (left $p=0.059$, right $p=0.010$).

Heschl's gyrus WM volume is also increasing with age in the left hemisphere (age effect $p=0.005$). Figure 3.4 shows WM increase in Heschl's gyrus bilaterally during early childhood followed by subsequent volumetric decline particularly in the right hemisphere (age^2 effect: left $p=0.076$, right $p=0.009$).

3.3.2.3.2. Autism participants. Similar to the cross-sectional analyses, no significant group effects are found in mean Heschl's gyrus volumes. In contrast to the cross-sectional findings, the autism and controls groups significantly differ in longitudinal change in Heschl's gyrus volume with age (see Table 3.3). The significant group by age interaction in the right total Heschl's gyrus ($p=0.014$) is driven by group differences in GM development ($p=0.007$; estimated percent growth per year: control

Table 3.3 Results for Heschl's gyrus (HG) best-fit mixed-effects model analysis between the typically developing and autism groups. The typically developing group is the reference group and the autism group is modeled in the group effects and interactions. For each effect, significance levels are provided below parameter estimates.

	Intercept	Group	Age	Group* Age	Age^2	Group* Age^2	Hemis Vol[a]
Left Hemisphere							
HG Total	2029	187	31.7	-11.3	-1.5	-0.77	0.001
		ns[b]	<0.001	0.254	0.055	ns	ns
HG GM	1642	92	23.9	-5.9	-0.35	-1.5	0.005
		ns	<0.001	ns	0.131	ns	0.059
HG WM	481	27.4	8.7	-6.8	-1.0	0.74	---[c]
		ns	0.005	0.069	0.076	ns	
Right Hemisphere							
HG Total	1478	66.7	25.1	-21.5	-2.5	1.97	0.003
		ns	0.001	0.014	0.067	ns	0.013
HG GM	1205	39.6	24.3	-18.5	---	---	0.003
		ns	<0.001	0.007			0.010
HG WM	371	22.1	1.1	-2.5	-1.4	1.2	0.001
		ns	ns	ns	0.009	0.063	0.062

[a]Hemispheric GM or WM volume; [b]ns indicates $p>0.2$; [c]covariate did not improve model fit and was excluded from the analysis.

2.0%, autism 0.46%; Figure 3.3 Panel B). No differences in longitudinal left GM growth are found.

Trends toward developmental WM differences are found (left hemisphere: group by age p=0.069; right: group by age^2 p=0.063). Figure 3.4 shows reduced WM increase in autism during later childhood in the left hemisphere and a greater right WM decline during adolescence in the typically developing group.

3.3.2.4 Asymmetry

3.3.2.4.1 Cross-sectional analysis. Figure 3.5 shows similar leftward asymmetry in Heschl's gyrus GM and WM in both groups. The mean asymmetry estimates are: GM control=0.27, range -0.51 to 1.25; GM autism=0.28, range -0.3 to 0.79; WM control=0.18, range -0.6 to 1.23; WM autism=0.21, range -0.4 to 0.73. The absence of

A. Heschl's gyrus total volume: Left hemisphere

B. Heschl's gyrus total volume: Right hemisphere

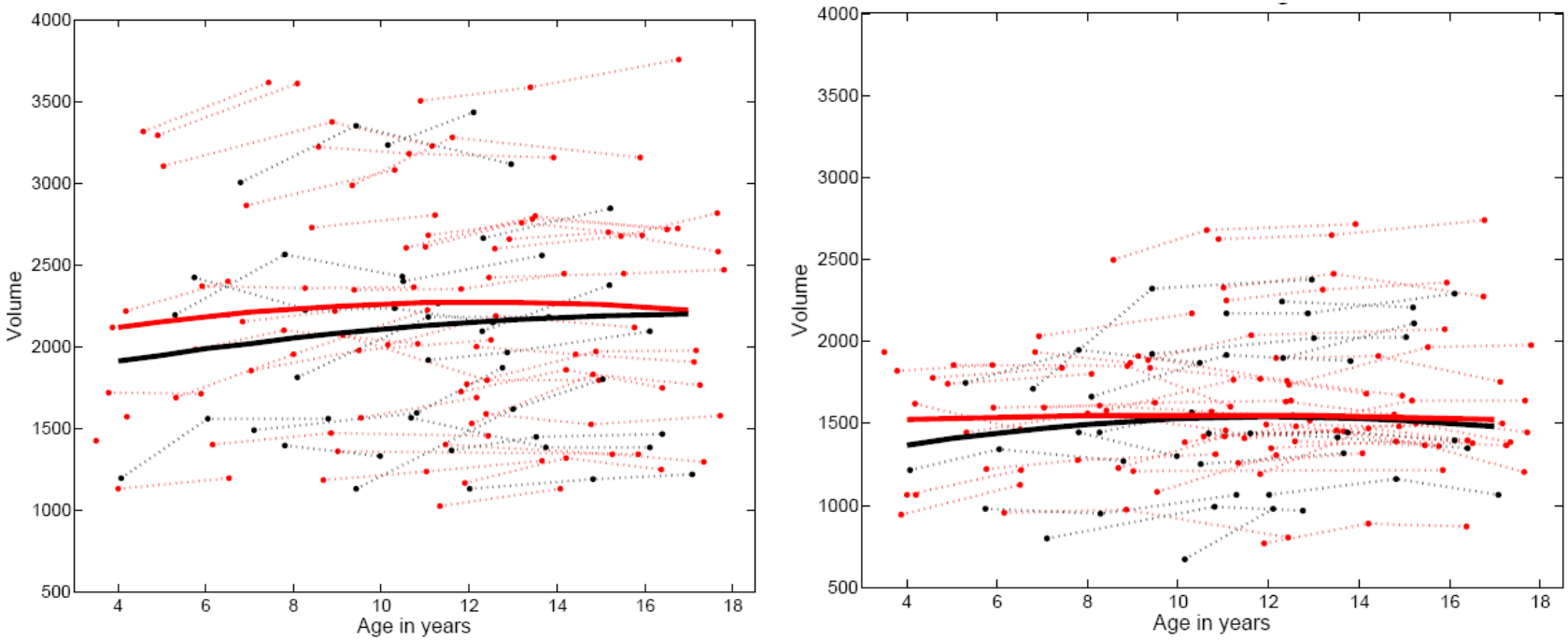


Figure 3.2 Longitudinal Heschl's gyrus total volume development in the left (A) and right (B) hemisphere. Individual scans for each participant are depicted by black (typical development) or red (autism) dots. Dotted lines connect multiple scans for each participant. Solid lines represent longitudinal development for each group obtained from the mixed models.

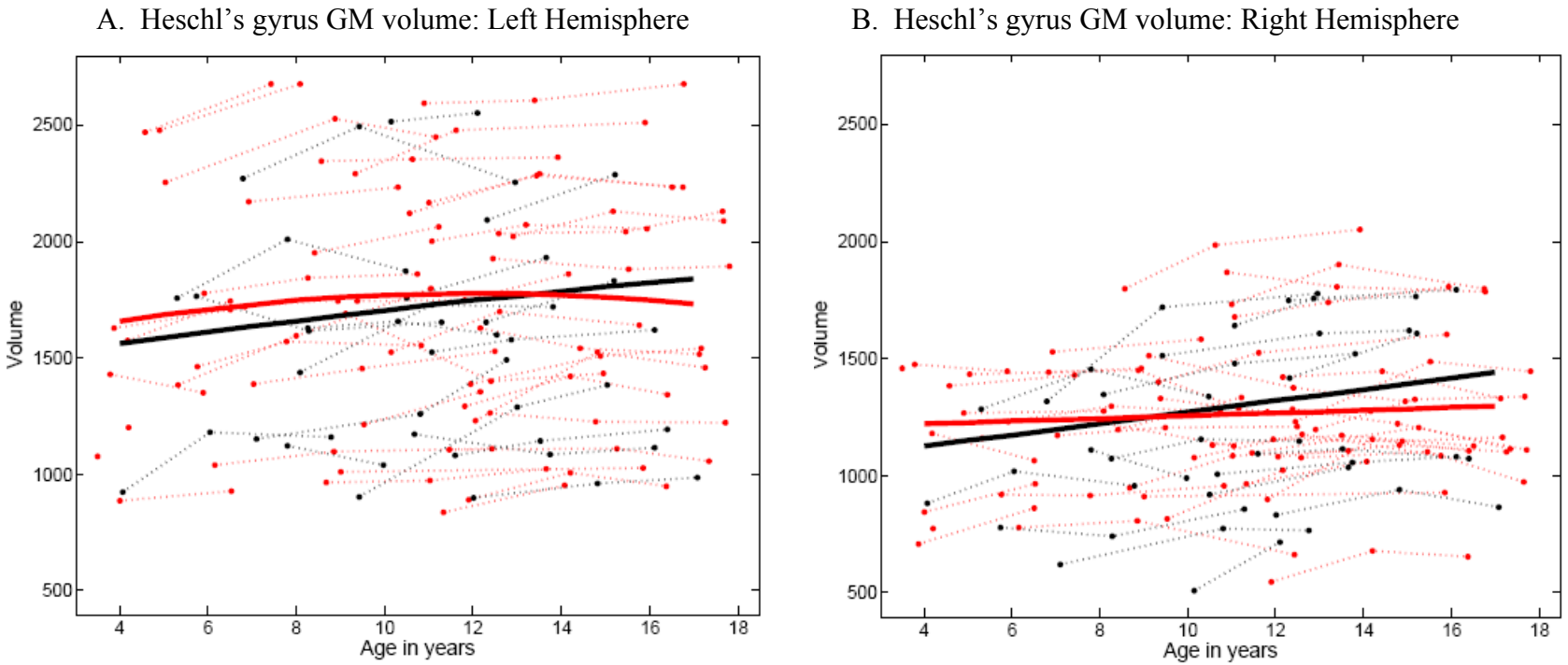
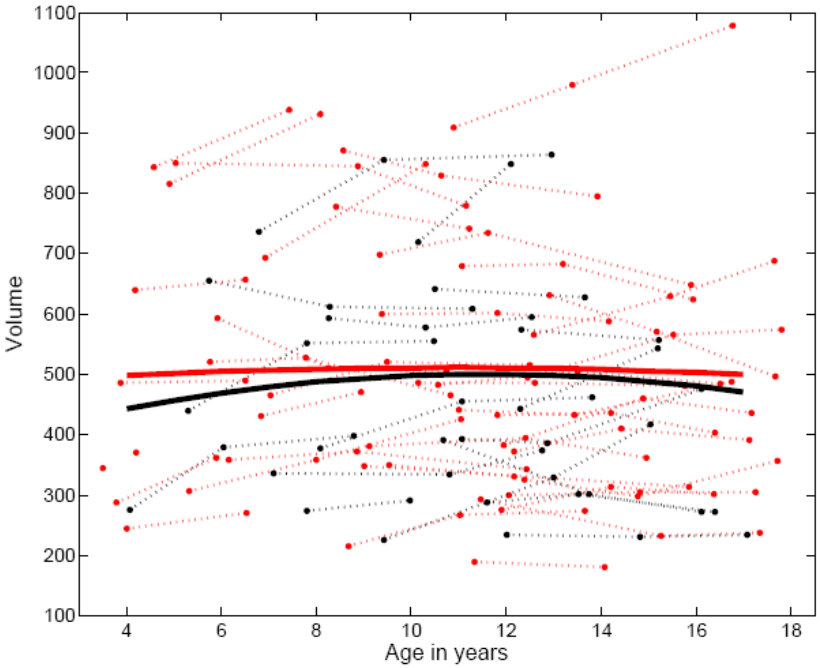


Figure 3.3 Longitudinal Heschl's gyrus GM volume development in the left (A) and right (B) hemisphere. Individual scans for each participant are represented for typical development (black dots and lines) and autism (red dots and lines). Solid lines represent group longitudinal fit lines from the mixed effects models. Individual scans are represented by dots and dotted lines connect multiple scans for the same participant.

A. Heschl's gyrus WM volume: Left Hemisphere



B. Heschl's gyrus WM volume: Right Hemisphere

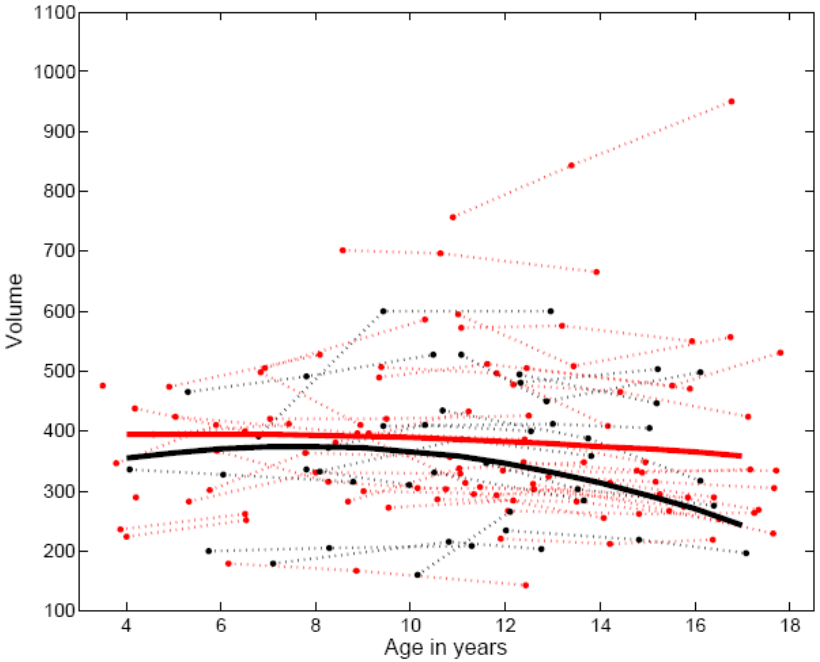


Figure 3.4 Longitudinal Heschl's gyrus WM development in the left (A) and right (B) hemisphere. Individual scans for each participant are represented for typical development (black dots and lines) and autism (red dots and lines). Solid lines represent longitudinal WM fit lines from the mixed models.

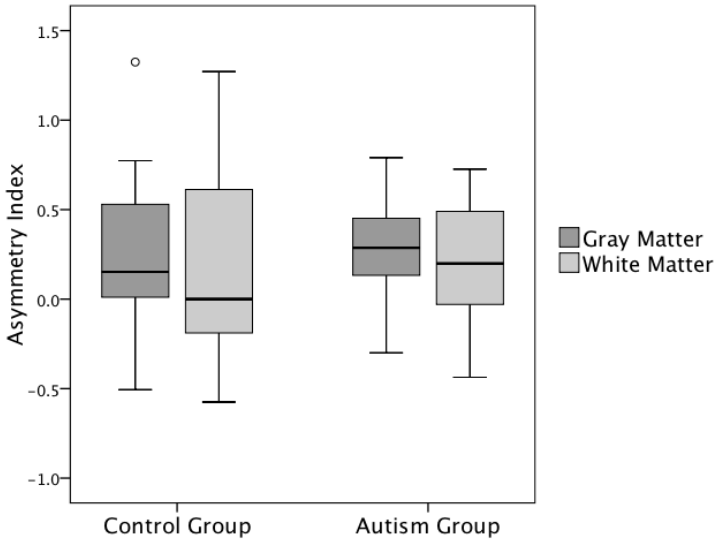


Figure 3.5 Heschl's gyrus GM and WM asymmetry from Time 1 scans in the typically developing and autism groups. Positive asymmetry index [(L-R)/((L+R)/2)] indicates leftward asymmetry and negative index rightward asymmetry.

significant age or group by age interactions replicates previous cross-sectional studies of GM volume in autism (Rojas et al., 2002, Herbert et al., 2005, Rojas et al., 2005, Gage et al 2009, Knaus et al., 2009).

3.3.2.4.2 Longitudinal changes in asymmetry. Significant leftward asymmetry in both GM and WM (GM Intercept=0.27, $p<0.001$, group effect ß=0.016, ns; WM Intercept=0.23, $p=0.009$, group effect ß=0.011, ns) is also found in the longitudinal analysis. Figure 3.6 shows the absence of age-related GM asymmetry changes in either group. In contrast to the cross-sectional findings, Heschl's gyrus WM becomes more leftward asymmetric over time in both typical development and autism (age effect ß=0.018, $p=0.002$; group by age interaction ß=-0.009, ns; Figure 3.6). The age-related asymmetry changes are due to a greater decrease in right WM volume during adolescence (Figure 3.4, Panel B).

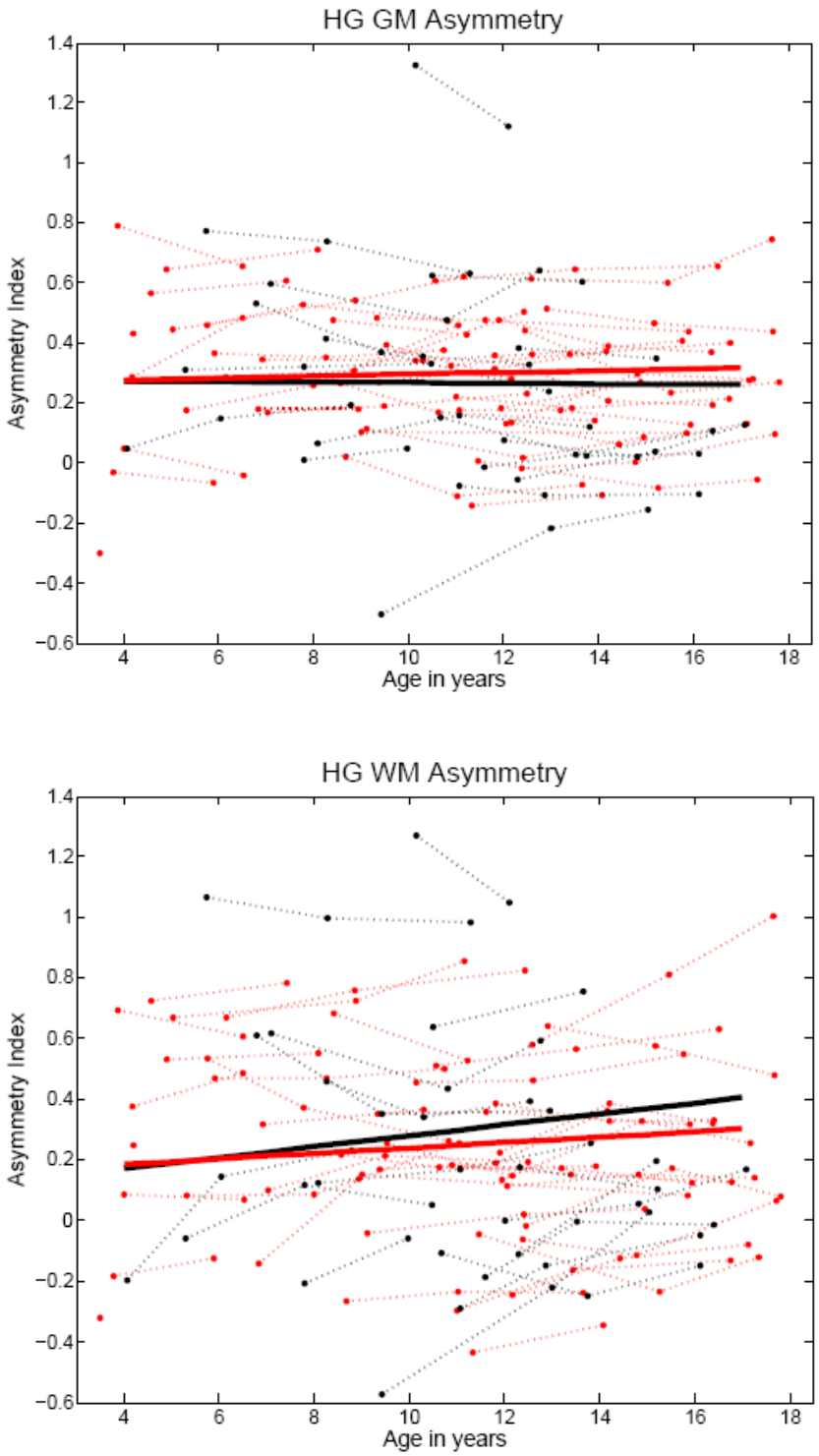


Figure 3.6 Longitudinal development of Heschl's gyrus asymmetry. HG GM (top panel) and WM (lower panel) asymmetry are shown in autism (red dots and lines) and typical development (black dots and lines).

3.3.2.5 Age-related changes in GM/WM Ratio

Figure 3.7 shows similar Heschl's gyrus GM/WM ratios between the autism and typically developing groups in both hemispheres (left ratios: control=3.49, autism=3.47; right ratios: control=3.22, autism=3.23). The longitudinal analysis demonstrates increasing GM/WM ratio with age in the right hemisphere (age ß=0.07, $p<0.001$; group by age ß=-0.02, p=0.19; age^2 ß=0.010, p=0.010; group by age^2 ß=-0.007, p=0.11) and trend in the left (age^2 ß=0.009, p=0.052; group by age^2 ß=-0.009, p=0.078). The trends toward group differences in age-related changes in GM/WM ratio are due to the combination of reduced GM increase and reduced WM decrease during later adolescence in autism relative to the typical group.

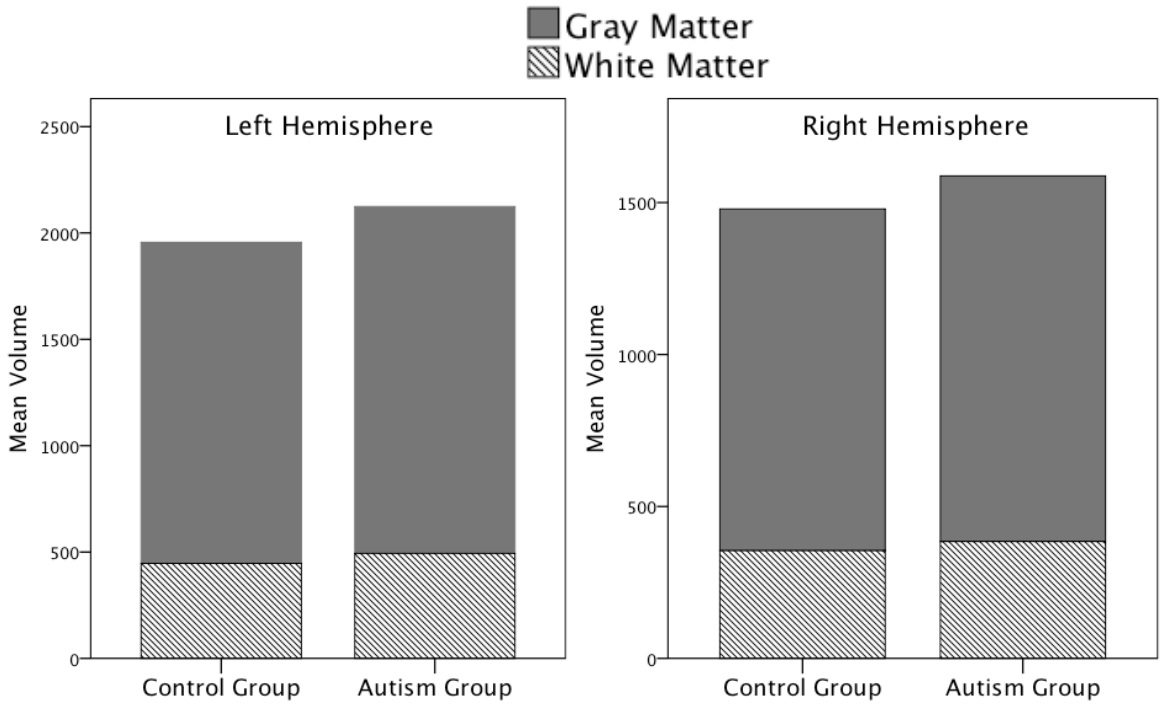


Figure 3.7 Heschl's gyrus GM/WM ratio obtained from Time 1 scans in the left and right hemispheres.

3.3.2.6 Psychotropic medication use in autism

Exploratory analyses reveal a possible effect of psychotropic medication use on left Heschl's gyrus WM development. A slight volumetric decline with age in the nonmedicated autism group (ß=-3.4, t=1.2, ns) differs significantly from WM increase found in the medicated group (group by age interaction ß=9.6, t=2.5, p=0.013). The nonmedicated autism group also differs significantly from typical development (group by age interaction ß=-11.4, t=2.6, p=0.008). In the right WM, medication did not differentially affect autism compared to typical development. The nonmedicated group shows a slight volumetric decline with age (ß=-4.2, t=1.8, p=0.078) and a marginally significant group by age interaction is found (ß=5.8, t=1.8, p=0.070). These preliminary findings suggest history of psychotropic medication use may affect WM development.

3.3.3 Planum temporale

3.3.3.1 Cross-sectional volumetric age-related changes

Mean planum temporale volumes at Time 1 for the typically developing [left: 2343 (sd 632), range 1396-3428; right: 2037 (sd 406), range 1360-2710] and autism [left: 2319 (sd 688), range 1213-4663; right: 2086 (sd 652), range 622-4029] groups are in the ranges of previous studies (Gage et al., 2009; Rojas et al., 2003). In both hemispheres, no group differences in volume, effects of age or group by age interactions are present in the cross-sectional analysis.

3.3.3.2 Longitudinal volumetric development

3.3.3.2.1 Typically developing controls. Similar to the Heschl's gyrus GM effects, significant longitudinal age-related changes are found bilaterally in the planum temporale (left $p<0.001$, right $p<0.001$; see Table 3.4 and Figure 3.8).

3.3.3.2.2 Autism participants. Table 3.4 summarizes the results from the best fitting mixed effects models. Significant group by linear and quadratic interactions ($p=0.031$, $p=0.012$, respectively) show greater volumetric increase with age in the typically developing group in the left hemisphere only (see Figure 3.8, Panel A).

3.3.3.3 Planum temporale asymmetry

Planum temporale asymmetry is marginally leftward asymmetric in controls (Intercept=0.12, $p=0.086$). In the absence of between-group differences in planum temporale asymmetry (group effect ß=-0.004, ns), the increase in leftward asymmetry during later childhood and adolescence in typical development is not found in autism (group by age $p=0.053$, group by age^2 $p=0.039$; See Figure 3.9).

Table 3.4 Results from the planum temporale (PT) best-fit mixed-effects model analysis. The typically developing group is the reference group and effects due to autism diagnosis are captured in the group effect and interactions.

	Intercept	Group	Age	Group* Age	Age^2	Group* Age^2	Hemis Vol[a]
Left PT	2574	-141 ns[b]	51.5 <0.001	-21.2 0.031	2.8 0.679	-4.8 0.012	0.010 0.003
Right PT	2196	-26.5 ns	32.4 <0.001	-7.2 ns	---[c]	---	0.009 0.004

[a]Hemispheric GM volume; [b]ns indicates $p>0.2$; [c]covariate did not improve model fit and was excluded from the analysis.

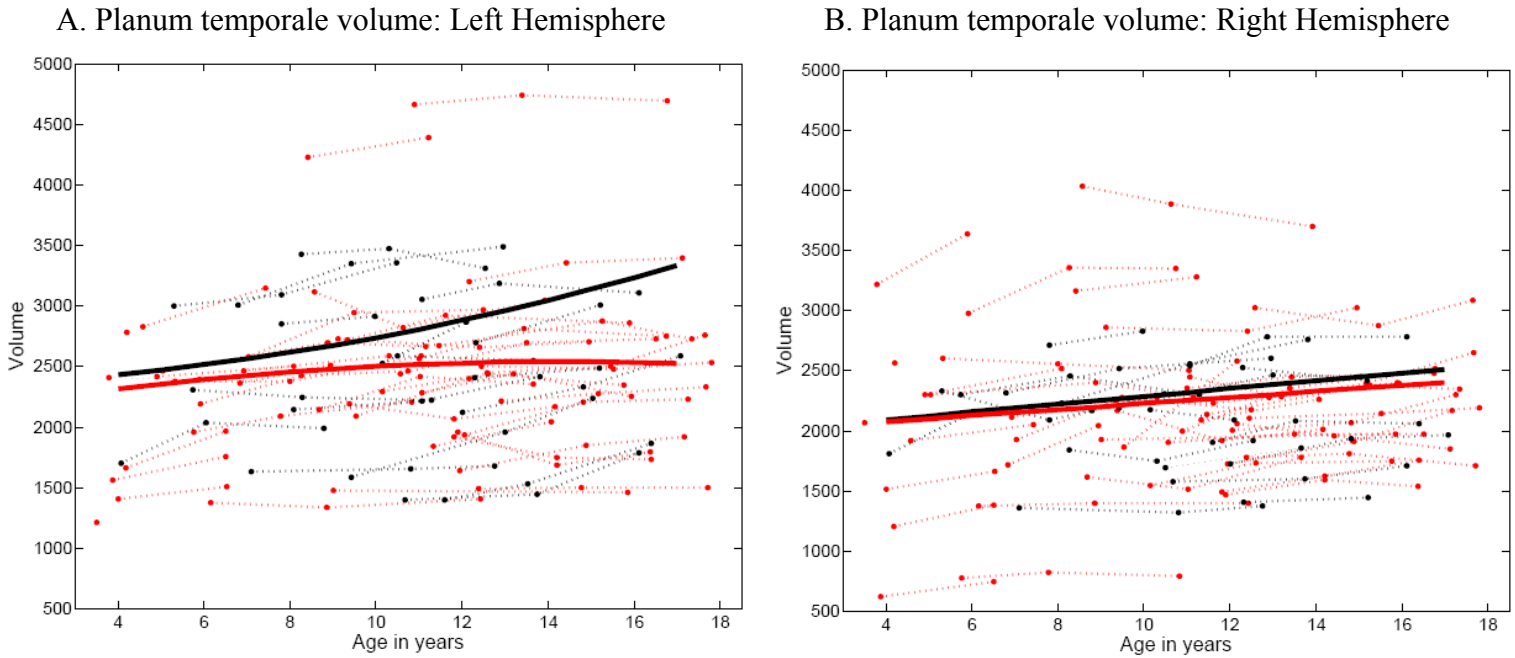


Figure 3.8 Longitudinal development of planum temporale volume in the left (A) and right (B) hemispheres. Black dots and lines indicate typically developing controls, red dots and lines indicate individuals with autism. Solid lines represent longitudinal growth estimated from the mixed models.

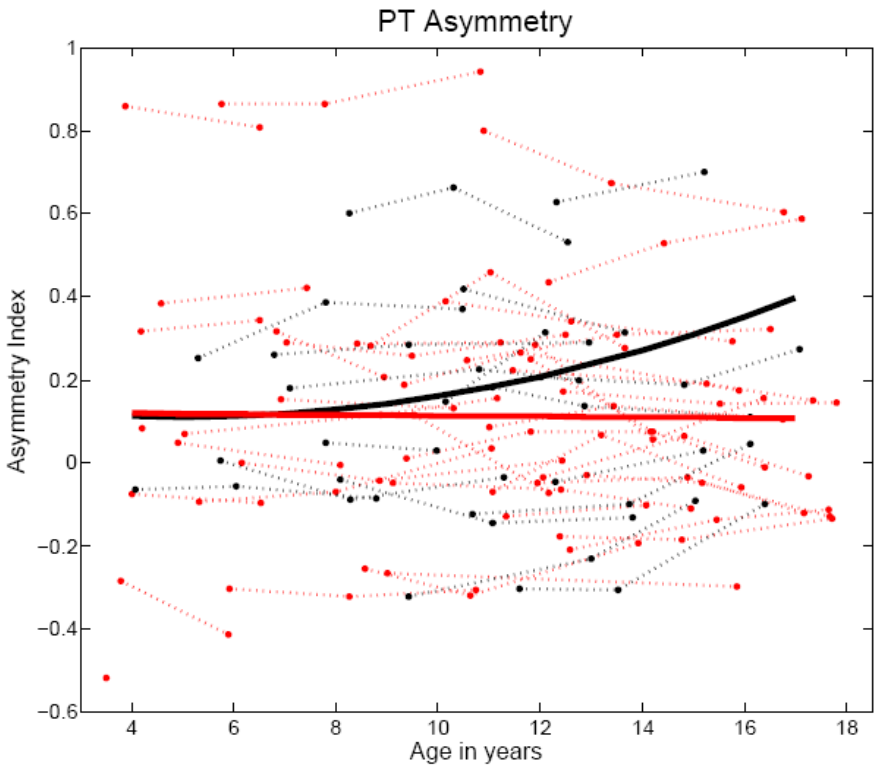


Figure 3.9 Longitudinal changes in planum temporale asymmetry. Individual and group changes in asymmetry are shown in typical development (black) and autism (red). Positive asymmetry indices indicate leftward asymmetry and negative indices rightward asymmetry.

3.3.4 Regional growth in relation to larger brain regions

3.3.4.1 log Heschl's gyrus growth

At Time 1, no group differences are found in TBV (mean cm^3: control=1305, autism=1348, t=1.1 ns), temporal lobe (mean left: control=102.6, autism=100.1, t=0.7 ns; mean right: control=100, autism=102, t=0.6 ns), or STG volumes (mean left: control=22.4, autism=23.1, t=0.7 ns; mean right: control=21.5, autism=22.2, t=0.8 ns). Table 3.5 shows the separate regression estimates for the autism and control groups

between log Heschl's gyrus development and log regional brain development. Although there are no significant group interactions, log TBV and log STG are related to log left

Table 3.5 Summary of the age adjusted regression coefficients from log Heschl's gyrus (HG) and log planum temporale (PT) volume on log TBV, log temporal lobe, and log STG

	Left Hemisphere		**Right Hemisphere**	
	Autism	Control	Autism	Control
log Total HG				
log TBV	0.28	0.66	0.95***	0.43
log temporal lobe	0.01	0.32	0.32*	0.26
log STG	0.16	0.25	0.39**	-0.02
log HG GM				
log TBV	0.49*	0.54	0.73**	0.09
log temporal lobe	0.12	0.26	0.40**	0.07
log STG	0.27*	0.21	0.44**	-0.14
log HG WM				
log TBV	-0.25	0.85	0.61	1.3
log temporal lobe	-0.26	0.27	-0.14	0.64
log STG	-0.20	0.26	0.11	0.15
log PT				
log TBV	0.65**	0.75	1.3***	0.44
log temporal lobe	0.20*	0.12	0.33*	0.23
log STG	0.38***	0.31	0.46**	0.44*

***p<0.001, **p<0.01, *p<0.05

Heschl's gyrus GM in autism. In addition, significant effects of log TBV, log temporal lobe and log STG on log right GM is found in autism. No significant effects are found for typically developing controls.

3.3.4.2 log planum temporale growth

In the typical group, developmental changes in log STG are related to log planum temporale. In autism, log TBV, log temporal lobe and log STG are related to left and right log planum temporale. In the right planum temporale, a marginally significant group by log TBV interaction is found (p=0.055). Regression coefficients presented in Table

3.5 demonstrate a trend toward a greater change in right log planum temporale than would be expected based on log TBV in autism compared with typical development.

3.4 Discussion

In this study we modeled, for the first time, longitudinal volumetric development of Heschl's gyrus GM and WM and the planum temporale in autism. In comparison to the typical group, participants with autism demonstrated abnormal GM development in right Heschl's gyrus and left planum temporale. In addition, atypical WM changes in the auditory cortex in autism are suggested. The longitudinal design allowed us to capture brain growth not previously identified using cross-sectional samples.

3.4.1 Typical development of auditory and language cortex

Longitudinal age-related increase in bilateral Heschl's gyrus and planum temporale GM volume during childhood and adolescence was found (Figure 3.3). Longitudinal studies of lobar development suggest that the temporal lobe is the last to mature, with estimated peak GM volume and STG thickness occurring around 14-16 years of age (Giedd et al., 2004; Gogtay et al., 2004; Shaw et al., 2008). In our sample, the left hemisphere planum temporale volume increased during early adolescence, resulting in an increase in leftward asymmetry with age. Our findings support perisylvian maturation work by Sowell and colleagues. The authors compared child (7-11 years), adolescent (12-16 years) and adult (23-30 years) samples and found increased leftward asymmetry, in the order of a 40-100% increase, from childhood to adulthood (Sowell et al., 2002). These findings also show structural support for longitudinal fMRI studies of language processing reporting strengthening of functional asymmetries during later childhood (Szaflarski et al., 2006).

The Heschl's gyrus WM trajectories in our typical group, shown in Figure 3.4, estimate the peak in left WM occurring around age 12, and the right hemisphere prior to the left. Postmortem studies suggest that adult myelination is reached in the primary auditory cortex around 5 years of age, and up until age 12, connections are forming with adjacent cortex and the opposite hemisphere (Moore and Linthicum, 2007). Previous studies of temporal lobe development show WM increase continuing into adolescence (Carper et al., 2002; Giedd et al., 2004), but no studies have directly examined Heschl's gyri. It may be that continued temporal lobe WM development in adolescence is capturing development outside of the primary auditory cortex, for instance, myelination and higher-order association fibers contributing to more complex social, language, and other temporal lobe processing.

3.4.2 Atypical auditory and language cortex development in autism

Although our cross-sectional findings replicated previous studies of Heschl's gyrus volume in children and adolescents with autism, showing no abnormalities in autism (Herbert et al., 2005; Knaus et al., 2009; Rojas et al., 2005), the longitudinal analysis revealed developmental differences. Decreased GM development in the right hemisphere was found in autism (Figure 3.3). This finding provides structural support for previous MEG studies reporting delayed auditory evoked responses and atypical age-related responses in the right hemisphere in autism (Gage et al., 2003; Roberts et al., 2010).

The results presented in Figure 3.4 suggest a trend toward atypical WM development in autism because the age-related volumetric increase during childhood and decrease during adolescence in the control group is reduced in autism. Atypical auditory

WM growth might greatly contribute to the aberrant activation reported in many functional studies of autism (e.g., Oram Cardy et al., 2005; Roberts et al., 2011). Our finding of more typical Heschl's gyrus WM development in the left hemisphere in the autism participants with a history of psychotropic medication use is preliminary but suggests further research is warranted.

Our study expands on previous cross-sectional studies of planum temporale structure in autism and provides novel information about development during adolescence. The most striking planum temporale difference, shown in Figure 3.8, is the absence of left hemisphere volumetric increase during adolescence in autism exhibited by the typically developing group. This finding results in the lack of an increase in leftward asymmetry with age in autism. Two previous research groups, using similar methodology to the current study, report on planum temporale asymmetry in autism. Studies by Rojas and colleagues (2002, 2005), found reduced asymmetry in autism due to smaller left planum temporale compared to controls in one study with a sample ages 5-16 and another study in adults. Work by Knaus and colleagues (2009) found evidence for increasing asymmetry with age by comparing younger adolescents (age 7-11 years) to a group of older adolescents (age 12-19 years). They report no effect of diagnosis, but an examination of the means between their older and younger samples reveals that right planum temporale volumes decreased in both autism and controls and left planum temporale volumes actually increased in controls but decreased in autism. Our longitudinal investigation shows that reduced planum temporale asymmetry in autism might not be present from early childhood but actually develops during later childhood and early adolescence. This structural finding supports the absence of a developmental

increase in leftward activation found in functional autism studies (Flagg et al., 2005) and may explain the lack of typical left hemisphere dominance during speech processing found in typical development (reviewed in Roberts et al., 2008).

The relationship between early behavioral profiles and current level of functioning in autism may impact structural development, thus, this research question is addressed in Chapter 4.

3.5 References

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CHAPTER 4

AN EXAMINATION OF STRUCTURAL CHANGES IN HESCHL'S GYRUS AND PLANUM TEMPORALE IN RELATION TO LANGUAGE FUNCTION AND AUDITORY SENSITIVITY IN AUTISM

4.1 Introduction

Autism is a heterogeneous disorder. In order for autism imaging research to understanding the trajectory of brain development underlying atypical function, an examination of interindividual differences that contribute to this heterogeneity is necessary.

Many individuals with autism exhibit abnormal reactivity and sensitivity to sound (Kanner, 1943; Khalfa et al., 2004; Rosenhall et al., 1999), but the neural underpinnings are unknown. Functional studies showing prolonged auditory brainstem responses (Kwon et al., 2007; Rosenhall et al., 2003; Roth et al., 2012), and abnormal hemispheric activation to auditory stimuli (e.g., Roberts et al., 2008) suggest aberrant neural function.

Differing structure-function relationships depending on language ability and current functioning have been found in autism. Individuals with autism plus language impairment show reversed asymmetry of evoked responses to linguistic stimuli (Dawson et al., 1986) and delayed auditory mismatch field latency (Roberts et al., 2011) compared

to autism without language impairment. Current language function in autism has also been related to differences in WM microstructure of the temporal segment of the superior longitudinal fasciculus (Nagae et al., 2012). In addition, reduced P50 (Orekhova et al., 2008) and atypical planum temporale volumetric asymmetry in low functioning children have all been reported (Gage et al., 2009). These cross-sectional studies support within autism differences in structure and function, but none examine how development may differ between the autism subgroups. A behavioral study showing that early language delay predicts lower language function in younger children (< 6 years) but not language ability in older individuals (Eisenmajer et al., 1998) suggests that different developmental trajectories may exist within the disorder.

This chapter will test the hypothesis that brain development differs between individuals with autism based on behavioral characteristics. Delayed onset of communication and spoken language are common in many, but not all, individuals diagnosed with the disorder, thus we examine how onset of language is related to Heschl's gyrus and planum temporale development. In addition, current reported auditory sensitivity and level of performance on standardized tests of language and communication are examined. We find evidence for developmental differences in Heschl's gyrus WM and planum temporale asymmetry based on language onset and that increased right Heschl's gyrus WM and atypical GM development are associated with heightened auditory sensitivity. Finally, smaller volumes in auditory and language regions are associated with better performance on tests of language and communication in autism.

4.2 Materials and methods

4.2.1 Participants

Participants included 17 typically developing males and 40 males with autism described in Chapter 3, section 3.2.1 and shown in Table 3.1.

4.2.2 Behavioral assessments

4.2.2.1 Autism severity

As described in Chapter 2, Section 2.2.1, the ADOS-G was used to assess autism severity (Lord et al., 2000). An ADOS calibrated severity score based on ADOS module and participant age was calculated for each participant with autism (Gotham et al., 2009). The ADOS severity scores range from 1 to 10, with higher numbers indicating greater autism related behaviors.

4.2.2.2 Language onset: delayed vs. nondelayed

Onset of spoken language was obtained from parent report on the ADI-R (Lord et al., 1994). Delayed language onset was defined as first spoken words after 24 months and onset of spoken phrases after 33 months. Autism participants were classified as delayed language (delayed words and phrases) or nondelayed language onset. Verification was made through early childhood record review when available (75% of the autism sample).

4.2.2.3 Auditory sensitivity: atypical vs. nonatypical

At Time 3, the Sensory Profile (Dunn, 1999) was administered. Previous studies of autism report auditory sensory processing abnormalities using this measure (Kern et al., 2007; Rogers et al., 2003; Tomchek and Dunn, 2007). This caregiver-completed questionnaire measures sensory processing and contains a section on auditory processing

and sensitivity. Raw scores classified participants based on established norms of children without developmental disabilities: typical performance (scores within 1 standard deviation from norms), probable difference (scores between 1 to 2 standard deviations from norms), or definite difference (scores below 2 standard deviations). All of our typically developing participants scored in the typical range. At Time 3, an audiometer was used to confirm normal hearing.

4.2.2.4. Intellectual functioning

As mentioned in Chapter 3, Section 3.2.2.1, intelligence was assessed at each timepoint.

4.2.2.5 Language function

4.2.2.5.1 CELF-Receptive Language. The Clinical Evaluation of Language Fundamentals (CELF; Semel et al., 1995) was used to assess receptive language function. The CELF measures development of structural language, is widely used in language studies of autism and different structure-function relationships in autism and controls have been found using this measure (Bigler et al., 2007). CELF scores were obtained at timepoints 1 and 3. At timepoint 1, participants received the CELF-preschool, CELF-3 or CELF-4, and the CELF-3 was administered at timepoint 3. Although multiple versions of the CELF were administered, age-standardized scores are available for each test with mean 100 and standard deviation of 15 for typically developing participants, allowing for between-version comparison of language function.

4.2.2.5.2 Vineland Communication. The Vineland Adaptive Behavior Scales – Communication domain score was an additional test of functional use of language at

timepoint 1 (Sparrow et al., 2005). The Vineland is a parent interview measuring aspects of communication, socialization, daily living, and maladaptive behavior. The Communication domain score assesses receptive, expressive, and written language function and is standardized across the age-range of participants.

4.2.2.5.3 PPVT. Peabody Picture Vocabulary Test (PPVT; Dunn and Dunn 1997) Third Edition was used to test receptive vocabulary at timepoint 3. This test presents participants with 4 pictures at a time, and the tester vocalizes the name of one of the images or activities pictured. Participants are to indicate, by pointing or vocalizing, the correct image. This test has an advantage over other vocabulary tests because no reading, writing, or vocalizations are required of participants.

4.2.2.5.4 CTOPP nonword repetition. Phonological short-term memory was examined with the Comprehensive Test of Phonological Processing (CTOPP) nonword repetition subtest at timepoints 1 and 3 (Wagner et al., 1999). This subtest requires participants to verbally repeat phoneme combinations of audibly presented made-up words. Phonological short-term memory is thought to be a cognitive phenotype in autism and other language disorders with genetic underpinnings (Newbury et al., 2005).

4.2.3 Brain measures

Heschl's gyrus GM and WM and planum temporale volumes and asymmetry indices were examined in both hemispheres. The study imaging protocol and ROI identification are described in Chapter 3, Section 3.2.3.

4.2.4 Statistical analysis

Between-group differences in age, interscan interval, handedness, IQ, and language function were measured between the autism subgroups (delayed vs. nondelayed language; atypical vs. nonatypical auditory sensitivity) and typically developing participants with univariate analysis of variance (ANOVA) tests, allowing for post-hoc tests of between group differences. Similar to analysis described in Chapter 3, mixed-effects models were used to test for group differences in longitudinal ROI development. The following model was used:

$$\text{ROI repeat} = \beta_0\text{Intercept} + \beta_1\text{Group} + \beta_2\text{Age} + \beta_3\text{Group*Age} +$$

$$\beta_6\text{Hemispheric Volume} + \beta_{0i} + e$$

As described in Chapter 3, Section 3.2.4, age^2, a group by age^2 interaction, PIQ, and group by hemispheric volume interactions were also examined and the lowest AIC criterion was used to determine the best-fitting model. We first examined models with just the autism participants divided into delayed versus nondelayed language onset or atypical versus nonatypical auditory sensitivity. The analyses of the autism only group also examined ADOS severity score and group by ADOS severity score interactions as potential covariates. Mixed effects models including the typically developing controls as the reference group provided direct comparisons of each autism group to typical development.

Further examination of structure-function relationships in autism was carried out with exploratory Pearson correlations controlling for participant age. Time 1 ROIs were correlated with Time 1 VIQ, CELF, raw CTOPP, Vineland Communication and autism severity scores. Time 2 ROIs were correlated with Time 2 VIQ and Time 3 ROIs were

correlated with Time 3 raw Sensory Profile auditory sensitivity scores, raw CTOPP scores and PPVT and CELF scores. To further test the relationship between language performance and brain development, significant behavioral measures identified with the cross-sectional correlations above were tested as predictor variables in mixed models that included all three timepoints of brain data as outcome measures.

4.3 Results

4.3.1 Delayed versus nondelayed onset of spoken language

4.3.1.1 Participants and demographics

Eighteen of the autism participants have delayed onset of both spoken words and phrases and 12 autism participants have typical language onset, hereafter referred to as nondelayed language onset. Within the autism participants, there are no subgroup differences at Time 1 in age or interscan intervals (see Table 4.1). CELF-Receptive language is lower in the autism delayed compared to autism nondelayed group at Time 1 ($p=0.034$), but this difference is not significant at Time 3 ($p=0.297$). There is a greater degree of left-handedness in the nondelayed language group relative to both the delayed group and typical development.

4.3.1.2. Longitudinal development of Heschl's gyrus

We do not find evidence for any effects of language onset on Heschl's gyrus GM volume or development in either hemisphere.

Atypical longitudinal development of Heschl's gyrus WM is found in the autism group with delayed language onset. Figure 4.1, Panel A shows that in the left WM, the delayed language group lacks the developmental WM increase during childhood found in

Table 4.1 Participant demographics and behavioral measures: Delayed and nondelayed onset of spoken language and typically developing controls

	Nondelayed Language Onset (ND)		**Delayed Language Onset (D)**		**Typically Developing Controls (TDC)**		**Group Differences at p<0.05**
	Mean (sd)	Range	Mean (sd)	Range	Mean (sd)	Range	
Time 1	n=12		n=18		n=17		
Age in Years	9.0 (3.1)	3.7-12.6	8.5 (3.3)	3.5-12.9	9.0 (2.6)	4-12.3	ns[*]
PIQ[a]	87 (16)	64-120	87 (19)	64-123	120 (15)	96-145	TDC > ASD[b]
VIQ[c]	95 (22)	64-136	89 (23)	51-125	114 (15)	91-151	TDC > ASD
FSIQ[d]	88 (19)	62-123	81 (22)	49-127	120 (16)	95-153	TDC > ASD
CELF[e]	86 (25)	50-135	68 (21)	50-118	114 (15)	83-147	TDC > ASD, ND > D
CTOPP[f]	8.3 (2.1)	5-11	7.5 (2.3)	2-11	10.1 (2.3)	7-16	TDC > D
Vineland[c]	71 (9)	54-86	69 (15)	51-109	112 (15)	97-138	TDC > ASD
Handedness	57 (53)	-100-+100	87 (9)	+14-+100	79 (13)	+20-+100	TDC, D > ND
ADOS Severity Score	8.2 (1.2)	6-10	7.5 (1.6)	4-10	----	----	ns
Time 2	n=12		n=17		n=17		
Age in Years	11.7 (3)	5.9-15.5	11.3 (3.1)	6.5-15.2	11.6 (2.7)	6-15.2	ns
Interval Time 1 to 2	2.7 (.47)	2.1-3.8	2.6 (.43)	2.0-3.8	2.6 (0.5)	1.8-3.7	ns
PIQ[g]	97 (11)	82-116	102 (16)	80-138	120 (12)	102-138	TDC > ASD
VIQ	93 (19)	63-118	88 (17)	55-113	110 (20)	74-140	TDC > ASD
FSIQ	95 (15)	70-115	94 (14)	76-118	117 (17)	87-144	TDC > ASD
Time 3	n=9		n=11		n=12		
Age in Years	15.6 (2)	11-17.7	15.1 (2.7)	10.7-17.7	13.6 (2.6)	8.8-17.1	TDC < ND (p=0.08)
Interval Time 2 to 3	2.6 (.46)	2.1-3.4	2.7 (.38)	2.3-3.3	2.6 (0.5)	1.9-3.5	ns
FSIQ[h]	100 (14)	81-124	97 (16)	76-127	119 (10)	105-138	TDC > ASD
CELF[i]	84 (24)	50-112	74 (19)	50-108	117 (14)	94-139	TDC > ASD
CTOPP[j]	7.7 (3.5)	1-12	7.5 (2.7)	1-12	8.7 (1.7)	6-11	ns
PPVT[i]	98 (19)	75-128	85 (24)	40-131	122 (7)	111-137	TDC > ASD, ND > D (p=0.09)
Vineland[k]	70 (7)	60-79	61 (12)	42-82	113 (6)	109-120	TDC > ASD

[*]no significant between group difference at $p>0.2$; [a]participant numbers that differ from available scan data are indicated by footnotes: D n=16; [b]ASD= both nondelayed and delayed groups; [c]ND n=11, D n=12; [d]D=17; [e]ND n=11, D n=16, TDC n=15; [f]ND n=11, D n=14; [g]Time 2 PIQ, VIQ, FSIQ: ND n=10, D n=12, TDC n=12; [h]behavioral data was collected on some individuals that were unable to be scanned at Time 3: ND n=11, D n=12; [i]ND n=11, D=14, TDC n=15; [j]ND n=11, D n=13, TDC n=13; [k]ND n=5, D n=9, TDC n=3.

the nondelayed group (group by age interaction p=0.023) and typical controls (group by age interaction p=0.023). In the right WM, the delayed group exhibits a maturational decline in childhood, which is in contrast to the volumetric increase in the nondelayed and typical group (group by age interactions p=0.013, p=0.029, respectively; Figure 4.1, Panel B).

4.3.1.3 Longitudinal planum temporale development

The language delayed and nondelayed groups show similar differences from typical development in the left planum temporale (left hemisphere: group by age interaction: delayed autism t=1.1, p=0.02; nondelayed autism t=2.1, p=0.05; group by age^2 interaction: delayed autism t=2.2, p=0.03; nondelayed autism t=1.8, p=0.07). There are no significant group effects or interactions between the autism subgroups. Figure 4.2 Panel A shows that neither autism group exhibits the increase in left planum temporale volume during adolescence found in the control group. We do not find group differences in right planum temporale development.

4.3.1.4 Asymmetry

No effects of language onset were found in measures of Heschl's gyrus GM or WM asymmetry.

The delayed language autism group has reduced planum temporale asymmetry (t=2.1, p=0.046) compared to the nondelayed autism group and shows a trend toward developmental differences (group by age: t=1.7, p=0.089; Figure 4.3). The decline in leftward asymmetry with age in the nondelayed language group differs significantly from typical development (nondelayed group vs. controls: group by age t=2.3, p=0.024; group

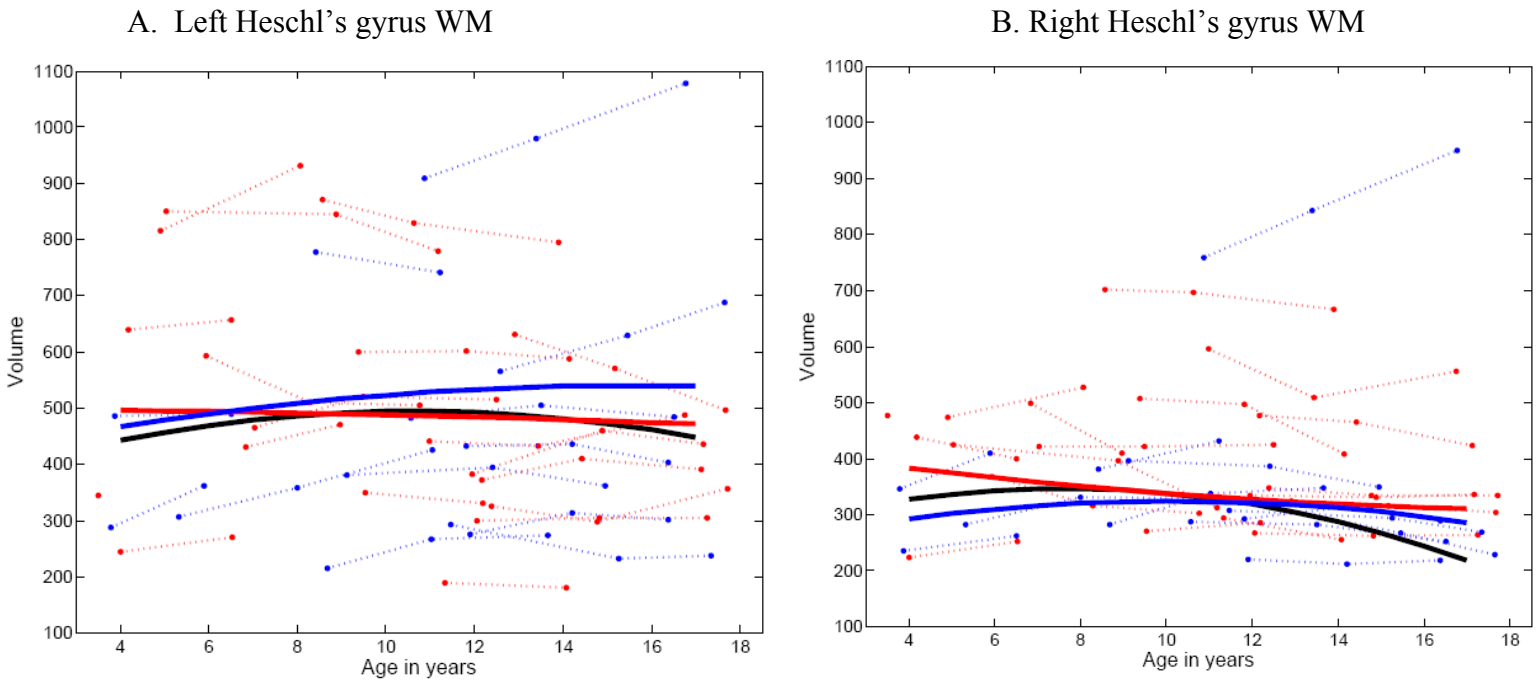

Figure 4.1 Longitudinal Heschl's gyrus WM development in autism according to language onset. Delayed language onset (red) versus nondelayed language onset (blue) are shown in the left (A) and right (B) hemispheres. Solid lines represent estimated longitudinal trajectories for the delayed language (red), nondelayed language (blue), and typically developing (black) participants according to the mixed models. Individual data points for the typically developing participants were presented in Figure 3.4.

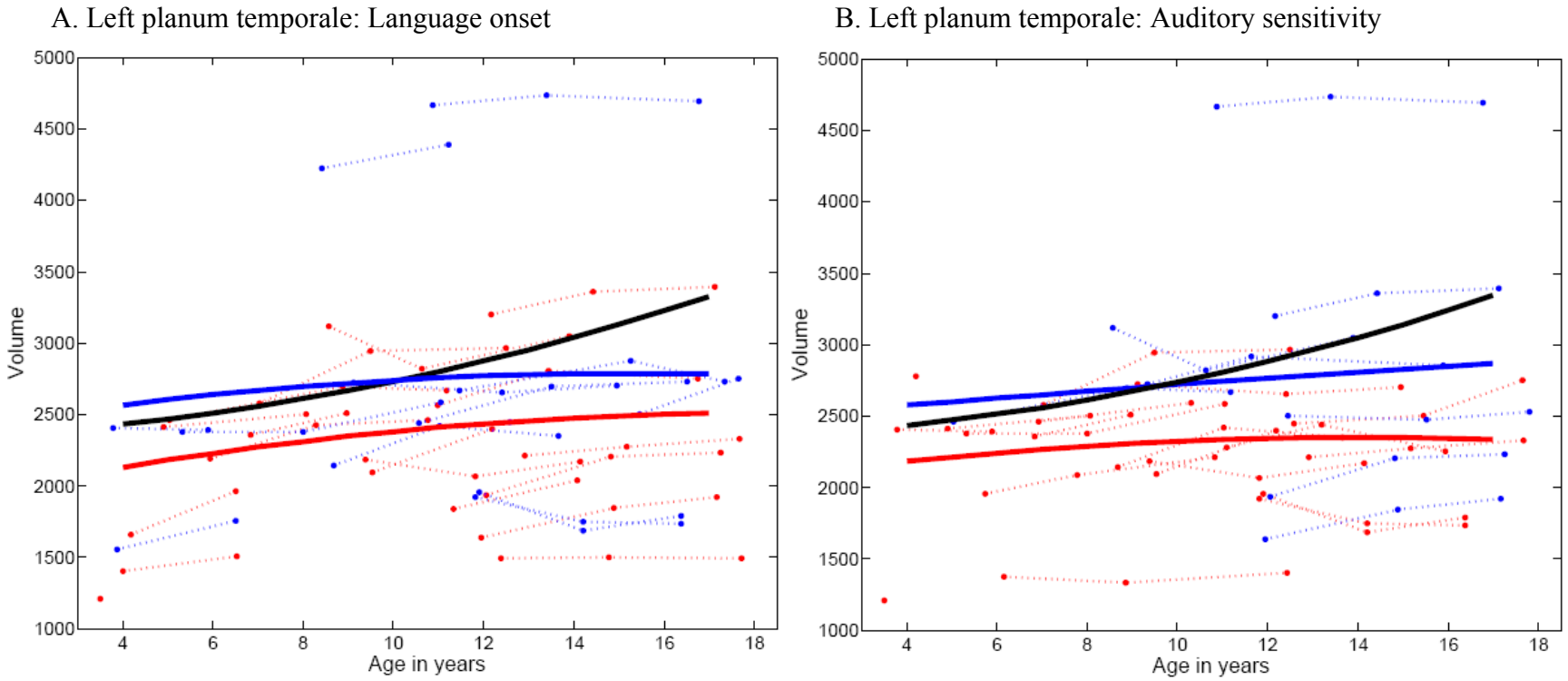

Figure 4.2 Longitudinal left planum temporale development in autism according to language onset and auditory sensitivity. Delayed (red) versus typical (blue) language onset are shown in Panel A. Atypical (red) versus nonatypical (blue) reported auditory sensitivity are shown in Panel B. Solid lines represent developmental trajectories estimated from the mixed effects models. The typically developing group trajectories are presented in black.

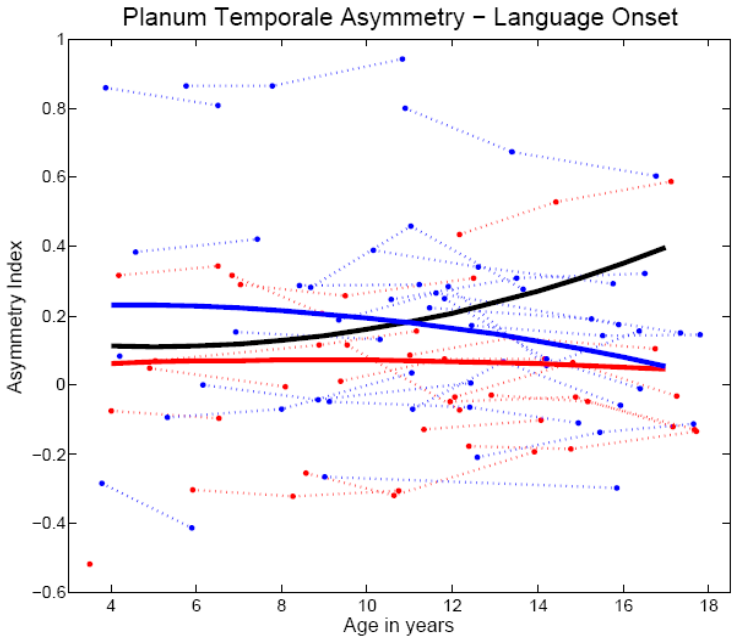

Figure 4.3 Longitudinal changes in planum temporale asymmetry in autism based on language onset. Solid lines represent estimates of longitudinal change from the mixed effects models for the autism participants with delayed language (red), nondelayed language (blue), and typical development (black).

by age^2 t=2.0, p=0.049; delayed group vs. controls: group by age t=1.3, p=0.18; group by age^2 t=1.8, p=0.078).

4.3.2 Auditory sensitivity

4.3.2.1 Participant Demographics

According to the Sensory Profile auditory sensitivity index, 19 participants with autism fall in the range of "definite difference" from typical development, or atypical auditory sensitivity, and 8 participants fall in the "typical" range, hereafter referred to as nonatypical autism. There are no group differences in age at scan or interscan interval

(see Table 4.2). At Time 1 VIQ and CTOPP nonword repetition are lower in the atypical group only compared to controls.

4.3.2.2 Heschl's Gyrus Development

In the right GM, there are no significant group by age interactions between the atypical versus nonatypical auditory group, but a greater difference from control development is found in the atypical group (group by age interaction: autism atypical t=2.5, p=0.012; autism nonatypical t=1.8, p=0.072). Figure 4.4 demonstrates the reduced volumetric GM increase for either autism group (estimated volumetric increase per year: control group 2%, nonatypical autism 0.56%, atypical autism 0.26%). No group effects or developmental differences are found in the left GM.

Figure 4.5 demonstrates that volumetric changes in the left WM differ significantly in individuals with nonatypical auditory sensitivity from atypical autism (group by age^2 p=0.003) and controls (group by age p=0.05, group by age^2 p=0.011). In the right hemisphere, although there are no age-related differences, the autism typical group has larger WM volumes compared to both controls (p=0.028) and the nonatypical group (p=0.052).

4.3.2.3 Planum Temporale Development

Similar to the findings in the delayed language group, the atypical auditory sensitivity group has marginally significantly smaller volumes from both the nonatypical (t=1.8, p=0.072) and control (t=1.8, p=0.072) groups (see Figure 4.2, Panel B). There are no autism subgroup differences in development, or between group differences in the right planum temporale.

Table 4.2 Participant demographics and behavioral measures: Atypical versus nonatypical auditory sensitivity

	Nonatypical Auditory Sensitivity (NA)		**Atypical Auditory Sensitivity (AA)**		**Group Differences at p<0.05**
	Mean (sd)	Range	Mean (sd)	Range	
Time 1	n=8		n=19		
Age in years	10.3 (2.5)	5.0-12.4	7.9 (3.0)	3.5-12.9	NA > AA (p=0.06)
PIQ	93 (21)	64-123	84 (20)	50-128	TDC[a] > ASD
VIQ[b]	94 (26)	65-125	87 (24)	51-136	TDC > AA
FSIQ[c]	93 (25)	58-127	83 (20)	49-123	TDC > ASD
CELF[d]	75 (25)	50-118	72 (21)	50-125	TDC > ASD
CTOPP[e]	8.6 (1.3)	7-11	7.8 (2.6)	2-11	TDC > AA
Vineland[d]	72 (17)	54-104	73 (13)	51-109	TDC > ASD
Handedness	64 (55)	-67-+110	65 (39)	-43-+100	ns*
ADOS Severity Score	8 (1.3)	6-10	8.35 (1.2)	6-10	ns
Time 2	n=8		n=17		
Age in years	13 (2.3)	8.9-15.5	11 (2.9)	5.9-15.5	NA > AA (p=0.09)
Interval Time 1 to 2	2.7 (.57)	2.1-3.8	2.5 (.42)	2.0-3.4	ns
VIQ[f]	97 (18)	71-113	82 (17)	55-112	TDC > AA
PIQ	111 (13)	95-131	98 (16)	74-138	TDC > AA NA > AA (p=0.14)
FSIQ	104 (16)	86-121	89 (15)	70-121	TDC > AA NA > AA (p=0.15)
Time 3	n=8		n=12		
Age in years	15.8 (2.2)	11.1-17.8	14.5 (2.4)	10.8-17.7	ns
Interval Time 2 to 3	2.8 (.71)	2.3-4.2	2.6 (.43)	2.2-3.6	ns
FSIQ[g]	102 (21)	76-127	97 (15)	76-128	TDC > ASD
CELF[d]	84 (19)	50-110	74 (22)	50-112	TDC > ASD
CTOPP[h]	7.1 (2.4)	5-12	6.7 (3.1)	1-10	ns
PPVT[d]	94 (21)	58-124	92 (22)	50-131	TDC > ASD
Vineland[i]	62 (7)	55-71	64 (12)	49-85	TDC > ASD

[*]ns=no significant difference between groups at p>0.2; [a]ASD=both nonatypical and atypical groups, TDC means and ranges provided in Table 4.1; [b]NA n=6, AA n=17; [c]NA n=7; [d]AA=17; [e] AA=16; [f] Time 2 VIQ, PIQ, FSIQ NA n=5; [g]NA n=7, AA n=14; [h]NA n=7, AA n=17; [i]NA n=4, AA n=10

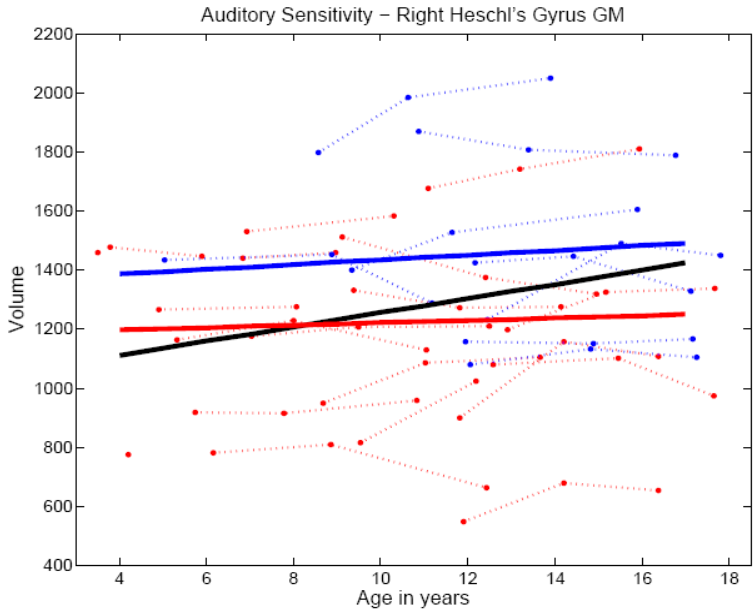

Figure 4.4 Right Heschl's gyrus GM development according to auditory sensitivity. Red indicates atypical auditory sensitivity and blue indicates nonatypical sensitivity. Estimated longitudinal change in typical development is represented by the black regression line.

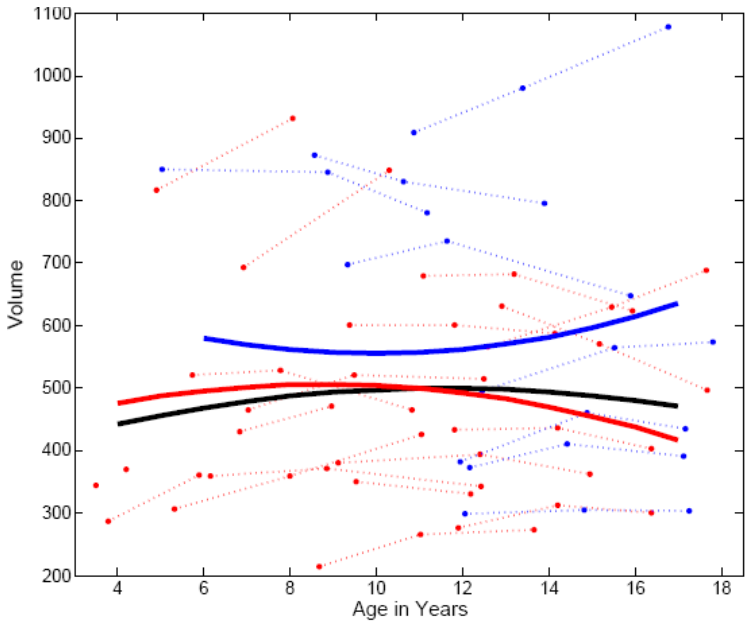

Figure 4.5 Left Heschl's gyrus WM development according to auditory sensitivity. Red indicates atypical auditory sensitivity, blue nonatypical auditory sensitivity and estimated longitudinal development in control participants is also shown (black).

4.3.2.4 Asymmetry

No developmental asymmetry differences are found in Heschl's gyrus GM or WM or planum temporale based on auditory sensitivity classification.

Compared to controls, the atypical auditory sensitivity group shows marginally significant linear and significant quadratic differences (group by age: ß=-0.01, t=1.8, p=0.064, group by age^2: ß=-0.003, t=2.2, p=0.029), whereas a trend toward differences in quadratic growth in the nonatypical group is found (ß=-0.003, t=1.9, p=0.054).

4.3.2.5 Auditory sensitivity raw scores

An examination of raw Sensory Profile scores shows no significant correlations between scores and Heschl's gyrus or planum temporale volumes at Time 3.

4.3.2.6 Overlap between auditory sensitivity and language onset

The participant overlap between the auditory sensitivity classification and language onset are the following: nonatypical auditory + nondelayed language n=1; nonatypical auditory + delayed language n=5; atypical auditory + nondelayed language n=7; atypical auditory + delayed language n=7. Further analysis between participants atypical/delayed in both language and auditory versus nonatypical/nondelayed was prevented due to the small numbers of nonatypical/nondelayed participants.

4.3.3 Functional correlations

Exploratory correlations at each timepoint suggest that smaller left Heschl's gyrus and right planum temporale volumes are associated with higher performance on language tests in autism. Table 4.3 presents a summary of the Pearson correlations controlling for age. At Time 1, smaller left Heschl's gyrus GM is associated with higher CELF-receptive

language and higher overall communication measured with the Vineland (see Figure 4.6, Panel A). Smaller left Heschl's gyrus WM is correlated with higher CELF-receptive language and better phonological memory measured by the CTOPP. Vocabulary ability measured by the PPVT is related to right planum temporale volume at Time 3 (Figure 4.6, Panel B).

An examination of structure-function using mixed models reveals significant case-control differences in the relationship between Heschl's gyrus GM development and Vineland Communication scores (estimates: autism Vineland effect ß=-12.7, p=0.028; group by Vineland interaction ß=24, p=0.042) and trend toward significance in CELF-receptive score and Heschl's gyrus WM development (estimates: autism CELF effect ß=-4.3, p=0.009; group by CELF interaction ß=7.3, p=0.053). These interactions suggest that a developmental increase in Heschl's gyrus volume is associated with a decrease in language scores in autism but an increase in typical development.

Table 4.3 Summary of Pearson correlations between behavioral measures and brain volumes in autism controlling for age.

	Left Hemisphere			Right Hemisphere		
	HG GM	**HG WM**	**PT**	**HG GM**	**HG WM**	**PT**
Time 1						
Autism Severity	0.11 ns[a]	-0.19 ns	0.15 ns	0.09 ns	0.06 ns	0.25 (0.14)
CELF-Receptive	**-0.36***	**-0.35***	-0.13 ns	-0.31 (0.06)	-0.32 (0.05)	-0.23 (0.17)
CTOPP	-0.31 (0.08)	**-0.36***	-0.06 ns	-0.20 ns	-0.20 ns	-0.19 ns
Vineland	**-0.35***	-0.32 (0.06)	-0.10 ns	-0.21 ns	-0.25 (0.14)	-0.04 ns
VIQ	-0.35 (0.05)	-0.29 (0.11)	-0.25 (0.18)	-0.34 (0.06)	-0.36 (0.05)	-0.32 (0.07)
Time 2						
VIQ	-0.12 ns	-0.15 ns	0.08 ns	-0.15 ns	-0.20 ns	-0.20 ns
Time 3						
CELF-Receptive	-0.17 ns	-0.21 ns	-0.16 ns	-0.36 (0.08)	-0.35 (0.08)	-0.28 (0.17)
CTOPP	-0.01 ns	-0.05 ns	0.16 ns	0.28 (0.18)	0.17 ns	0.19 ns
PPVT	-0.30 (0.14)	-0.37 (0.06)	-0.26 ns	-0.34 (0.10)	-0.35 (0.08)	**-0.41***

* indicates $p<0.05$, p-values > 0.05 are indicated in parentheses; [a] ns indicates p-values > 0.2

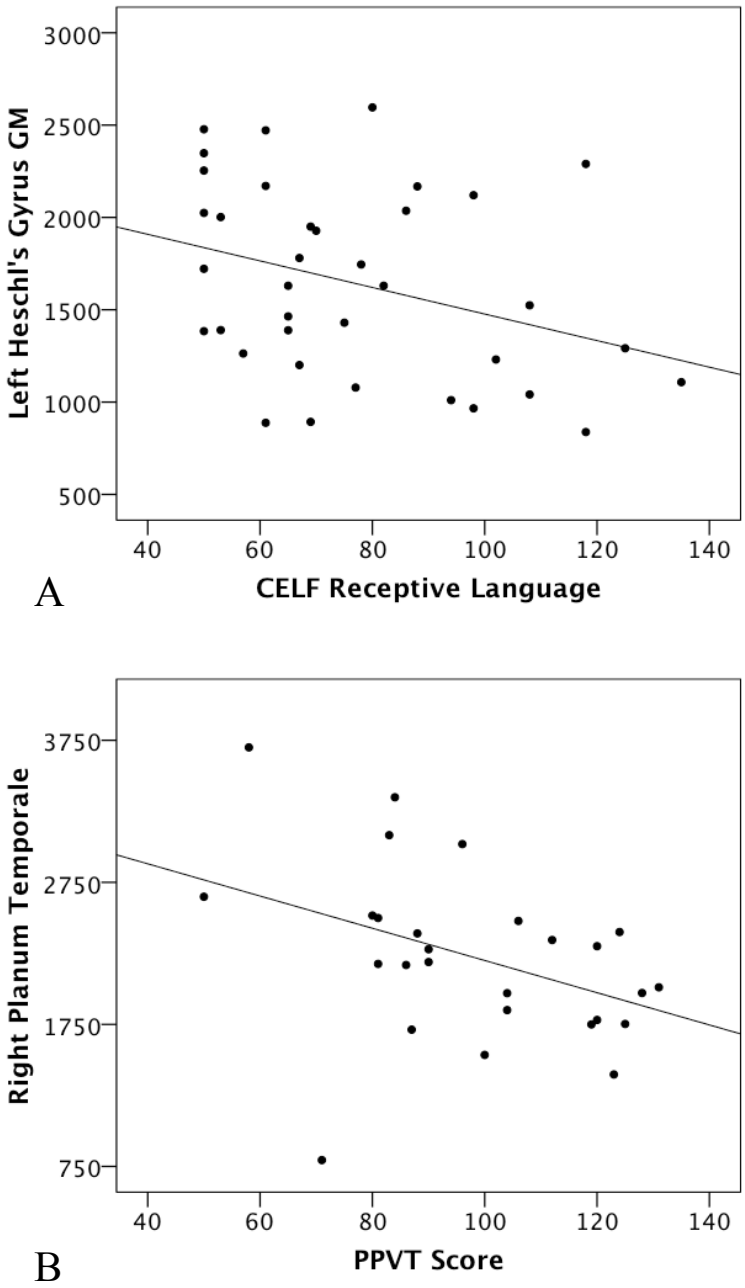

Figure 4.6 Scatterplots demonstrating the relationship between language function and brain structure in autism. (A) Time 1 CELF receptive language score and left Heschl's gyrus GM volume and (B) Time 3 PPVT score and right planum temporale volume. In both figures, improved performance is associated with smaller volumes.

4.4 Discussion

In this study, we identified developmental differences in participants with autism based on language onset and current level of functioning. Our findings highlight the impact that the heterogeneity of autism may have in studying the disorder and suggest that early behavioral profiles, such as onset of spoken language, should be considered as a useful measure to subgroup individuals.

Atypical Heschl's gyrus WM development was found in the autism group with delayed language onset in comparison to the nondelayed language and control groups. Specifically, a slight volumetric increase during childhood was absent, suggesting a different trajectory of auditory cortex maturation than typical (Moore and Linthicum, 2007). Reduced planum temporale asymmetry and a trend toward atypical development were also found in the delayed group compared to the nondelayed group. Despite the atypical trajectories and asymmetry, language scores of the delayed language group improved during the course of the study. Previous studies also show behavioral language improvement over time in those with delayed language onset (Eisenmajer et al., 1998). Thus, the atypical trajectories identified in some individuals might be functionally beneficial.

A previous study of handedness and disordered early language in autism found reduced degree of right or left-handedness, or laterality, in the nondisordered language group (Escalante-Mead et al., 2003). We also found reduced right-handedness in our nondelayed group relative to delayed autism and controls and a reduction in planum temporale asymmetry over time in the nondelayed group. Although we do not have functional imaging data to examine language laterality, we can hypothesize that the

nondelayed language group might rely more on bilateral language regions for early language development. Future studies utilizing both functional and structural MRI may be able to determine if this is the case.

Relative to the control group, the autism subgroup with heightened auditory sensitivity was lower functioning and showed reduced GM development. Previous studies show that delayed auditory processing in the right hemisphere is related to language ability (Oram Cardy et al., 2008). The comparison of the autism subgroups based on reported auditory sensitivity reveals increased WM volumes in the right hemisphere and different age-related changes in the left in the autism typical group. Although our auditory measure was a caregiver questionnaire, functional correlates for atypical structure and volume of auditory cortex are found in a recent auditory evoked fields study demonstrating delayed peak latency and enlarged dipole moments in autism with hypersensitivity relative to nonhypersensitive autism and controls (Matsuzaki et al., 2012). Increased WM volumes in the typical group could represent a number of structural differences between the groups, such as increased thalamocortical connections or U-fibers, the balance of excitatory and inhibitory connections or aberrant WM microstructure. Future studies utilizing multimodal imaging methods will help identify what comprises the structural differences found in those individuals reporting heightened or typical sensitivity.

Interestingly, the examination of the autism group as a whole suggests that smaller Heschl's gyrus GM and WM volumes are associated with better performance on tests of language function and overall communication. This is in contrast to the positive association between left Heschl's gyrus volume and language and communication found

in typical development. We also found that decreased right planum temporale volume was associated with improved performance on vocabulary comprehension in autism. Our study suggests that previous reports of atypical auditory response (Oram Cardy et al., 2005; Roberts et al., 2011; Samson et al., 2011) or absence of left hemisphere dominance during speech processing (Roberts et al., 2008) might reflect neural development in autism that is functionally adaptive in the disorder.

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CHAPTER 5

CONCLUSION

The purpose of this dissertation was to examine the development of brain regions in autism that are important for language and intelligence, which are frequently impaired in autism and impact long-term outcome. We examined Heschl's gyri, planum temporale and the corpus callosum and found evidence of persistent pathology, dynamic in nature, in all three structures examined during this final stage of development of language and intelligence. The dynamic nature of changes in late neurodevelopment and the fact that the size of the structures are related to clinical features that impact long-term outcome in autism, suggests a prolonged developmental window for secondary and tertiary preventive interventions in autism. Our results also highlight the heterogeneity of the disorder and show the importance of examining early behavioral profiles and current levels of functioning when interpreting structural brain development.

The studies in Chapter 2 described the development of CC area from early childhood to adulthood in a large cross-sectional sample. We hypothesized decreased area and abnormal age-related changes in autism and found evidence for atypical development in the rostrum and isthmus. Decreased CC size is one of the most replicated findings in the autism literature (Frazier and Hardan, 2009 for a meta-analysis), but our results demonstrated several novel findings. We found a wide distribution of CC areas and reported the proportion of individuals with abnormally small and large CC relative to

the typical group. In both the autism and control groups, larger subregional areas were associated with faster speed of processing, but opposing structure-function relationships were also found. Atypical relationships between IQ and midsagittal rostrum area, linking prefrontal and temporal regions (Hofer and Frahm 2006; Huang et al., 2005; Pannek et al., 2010; Peltier et al., 2010; Witelson 1989; Zarei et al., 2006;), suggests that smaller rostrum may be functionally adaptive in typically developing controls but functionally maladaptive in autism. Smaller CC subregions were also associated with greater degree of social impairment in autism, which is in line with previous studies of CC volume (Hardan et al., 2009).

Assuming the CC is an index of structural connectivity in autism, our findings imply that young people with the disorder may benefit from interventions that normalize interhemispheric communication and CC growth and development. In some regions of the CC, the greatest opportunity for change may continue into the late twenties (Pujol et al., 1993). Given complex excitatory and inhibitory effects of CC fibers on cortical neurons (Innocenti, 2009) and the interaction of interhemispheric connectivity and cerebral lateralization, it is not known if increasing or decreasing interhemispheric connectivity in autism will provide the most benefit.

Chapter 3 described the first results of longitudinal growth trajectories of Heschl's gyrus and the planum temporale in childhood and adolescence in typical development and in autism. Prior to the 2010 Hyde et al. report on cortical thickness, all previous cross-sectional autism studies reported typical Heschl's gyrus structure in autism (Herbert et al., 2005; Knaus et al., 2009; Rojas et al., 2005), but our longitudinal examination found evidence for atypical developmental trajectories. The autism group showed

reduced right GM development and lacked the typical WM decline in adolescence found in the control group. These structural findings suggest that atypical Heschl's gyrus development may contribute to previous autism studies reporting abnormal auditory activation and age-related changes (e.g., Gage et al., 2003; Roberts et al., 2008, 2010). Although volumetric measures do not allow the identification of how axonal maturation, synapse elimination, or other factors during this period contribute to the atypical trajectories (Moore and Linthicum, 2007), our results strongly suggest that further investigations into primary auditory cortex development in autism is warranted.

Our findings also contribute to previous work on planum temporale structure in autism (Knaus et al., 2009, 2010; Rojas et al., 2002, 2005) by demonstrating that reduced leftward asymmetry might not be present from early childhood but develops during later childhood and adolescence. This result expands on previous functional studies showing atypical age-related changes in language lateralization in autism (Flagg et al., 2005) and previous cross-sectional DTI studies showing decreased leftward asymmetry of arcuate WM microstructure in adolescence (Fletcher et al., 2010; Lo et al., 2011). Our study does not allow further examination into how experience-driven plasticity and development of complex language contributes to left planum temporale growth during adolescence but suggests that dynamic changes in this region during late neurodevelopment provides a developmental window for potential interventions.

In Chapter 4, we identified onset of spoken language as a useful measure to compare individuals within the disorder. Different developmental trajectories in Heschl's gyrus WM and planum temporale asymmetry between individuals with autism with delayed versus typical language onset were found, which supports previous functional

results (Dawson et al., 1986). We also identified a static association between larger Heschl's gyrus WM volumes and typical auditory sensitivity, suggesting structural heterogeneity within the autism group.

The structure-function relationships found in autism suggest that individuals functionally benefit from increased hemispheric communication, whereas smaller Heschl's gyrus and planum temporale cortical volumes were associated with greater language function. Both of these results are opposite structure-function relationships from that found in typical development. In addition, the autism group with delayed language onset and "atypical" structural development actually showed improved language performance during the course of the study. Our results highlight the importance of longitudinal studies and suggest that investigations into regional brain development in autism, and other developmental disorders, should not assume that trajectories that differ from typical are functionally maladaptive.

The main limitation of our studies is that microstructural properties or neural organization cannot be identified by area or volumetric measures alone. The work of this dissertation provides the groundwork for future, more detailed, longitudinal multimodal imaging research to determine how development of Heschl's gyrus, the planum temporale, and interhemispheric fibers, are related to abnormal late neurodevelopment and clinical functioning in autism.

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APPENDIX. Summary of studies reporting Heschl's gyrus and planum temporale structure in autism

Authors	Year	Autism sample size	Control sample size	Autism Age Yrs Mean± SD Range	Control Age Yrs Mean± SD Range	Type of Measure	Structural Findings
Rojas et al Neurosc Lett	2002	15	15 TD[a]	30±9 9-47	30±9 17-47	GM Volume Asy Manual	HG: no group diff L>R PT: ASD ↓ L TD: L>R ASD no asy
Herbert et al Ann Neurol	2002	16	15 TD	9±1 7-11	8.3±2 7-11	GM Asy CPU[b]	PT: ASD greater asy TD 5% L>R ASD 25% L>R
DeFosse et al Ann Neurol	2004	6 ALN[c] 16 ALI	11 TD 9 SLI[d]	8±1 6-13 10±2 6-13	10±2 6-13 10±2 6-13	GM Asy CPU	PT: L>R in ALI, SLI only
Herbert et al Brain	2005	16	15 TD 15 DL	5.7-11.3	5.7-11.3 5.7-11.3	GM Asy CPU	HG: no group diff L>R all groups (nonsignificant)
Rojas et al JADD	2005	12	12 TD	12±3 5-16	12±2	GM Volume Asy Manual	HG: no group diff L>R PT: no group diff TD: L>R ASD no asy
Gage et al J Neurodev Disord	2009	50 (9 F) (30 R hand)	---	7±2.7 2-14	---	GM Asy CPU	HG: L>R PT: no asymmetry Trend R>L R hand Males only: PT: R>L PT asy ↑ w/ age
Knaus et al Brain Imag Beh	2009	20 7-11yr 20 12-19yr (4 F)	20 TD 7-11yr 20 TD 12-19yr (4 F)	9±1.3 7-11 14.9±2.2 12-19	9±1.3 7-11 14.9±2.1 12-19	GM Volume Asy Manual	HG: no group diff L>R PT: no group diff L>R PT age changes: TD: L ↑ Young ASD: R ↓
Knaus et al Brain & Language	2010	14	20 TD	16±2 11-19	14±2 11-19	GM Volume Asy Freesurfer	PT: no group diff L>R
Hyde et al Hum Brain Map	2010	15	13 TD	22 14-33	29 14-34	VBM Cortical thickness	HG: ↑ cortical thickness in ASD

[a]TD: Typical development; [b]CPU: Cortical parcellation units; [c]ALN, ALI: Autism Lang Normal or Impairment; [d]SLI: Specific Lang Impairment; [e]DLD: Developmental Lang Disorder