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Longitudinal Heschl's gyrus growth during childhood and adolescence in typical development and autism

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Abstract

Heightened auditory sensitivity and atypical processing of sounds by the brain are common in autism. Functional studies that measure brain activity suggest abnormal neural response to sounds, yet the development underlying atypical sound processing in autism is unknown. We examined the growth of the first cortical area of the brain to process sound, the primary auditory cortex, also known as Heschl's gyrus. Volume of Heschl's gyrus gray and white matter was measured using structural MRI in 40 children and adolescents with autism and 17 typically developing

participants. Up to three time points of volumetric brain data, collected on average every 2.5 years, were examined from individuals 3-12 years of age at their first scan. Our study is the first to examine volumetric changes during childhood and adolescence in Heschl's gyrus longitudinally, or in the same individuals over time. Consistent with previous studies using only one time point of data, no differences between the participant groups were found in Heschl's gyrus gray matter volume. However, reduced longitudinal growth of Heschl's gyrus gray matter volume was found in the right hemisphere in autism. Reduced longitudinal white matter growth in the left hemisphere was found in the right-handed autism participants. Atypical growth of Heschl's gyrus white matter volume was found bilaterally in the autism individuals with a history of delayed onset of spoken language. Heightened reported sensitivity to sounds, obtained from the Sensory Profile, was associated with reduced gray matter volume growth in the right hemisphere. Our longitudinal analyses revealed dynamic gray and white matter changes in Heschl's gyrus throughout childhood and adolescence in both typical development and autism.

Keywords

autism; Heschl's gyrus; longitudinal development; MRI

Introduction

In his early description of autism, Dr. Leo Kanner noticed that affected children often had delayed onset of spoken language, abnormal language, and abnormal reactivity and sensitivity to sound (Kanner, 1943). Dr. Kanner's observations are consistent with a growing body of autism research, clinical experience, and parental report. Aberrant filtering of auditory information (Ashburner, et al., 2008; Kern, et al., 2007; Tomchek & Dunn, 2007; Wiggins, et al., 2009) and enhanced auditory discrimination may also occur (O'Riordan and Passetti, 2006). Abnormalities in hemispheric activation to auditory stimuli (Boddaert, et al., 2003; Bruneau, et al., 1999; Bruneau, et al., 2003; Flagg, et al., 2005; Gage, Siegel, Callen, et al., 2003; Kasai, et al., 2005; Muller, et al., 1999; Roberts, et al., 2008; Roberts, et al., 2010; Roberts, et al., 2011; Wilson, et al., 2007), auditory orienting to 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 been reported. In addition, many young children with autism are so unresponsive to sounds that deafness is queried.

In the face of evidence for atypical auditory function in autism, no study has directly examined longitudinal development of Heschl's gyrus. The transverse gyrus of Heschl (HG), the most anterior transverse gyrus on the superior temporal plane, contains the primary auditory cortex and serves a critical role in early auditory processing (Galaburda & Sanides, 1980; Galaburda, LeMay, et al., 1978; Galaburda, Sanides, et al., 1978). Early processing abnormalities of incoming auditory stimuli affect subsequent sensory perception and higher order processing, such as language perception and acquisition (Kuhl, 2004). Despite the importance of HG in early processing of incoming auditory stimuli, its structural development during childhood and adolescence in autism is unknown.

Cross-sectional studies of HG in children, adolescents and adults with autism have found mixed results. Case-control differences have been found in cortical thickness (Hyde, et al., 2010) but not gray matter (GM) volume or asymmetry (Knaus, et al., 2009; Rojas, et al., 2002; Rojas, et al., 2005). To date, a limited number of studies have examined HG volumes in autism and no studies have directly measured HG white matter (WM), even though WM reductions have been found in the absence of GM differences in deaf adults (Emmorey, et

al., 2003). No studies have longitudinally examined HG volume during childhood and adolescence in autism or even in typical development.

In this study, we test the hypothesis of abnormal volumetric growth of HG GM and WM during childhood and adolescence in autism. We use an accelerated longitudinal design with up to three time points of MRI data collected on average every 2.5 years. Because of previous studies showing structural and functional differences in autism subgroups, we also explore within-autism differences by classifying our autism sample based on language onset and by the presence of auditory sensitivity (Ashburner, et al., 2008; Kern, et al., 2006; Kern, et al., 2007; Tomchek & Dunn, 2007; Wiggins, et al., 2009; Yu, et al., 2011).

Materials and Methods

Participants

This study examined 40 males with a lifetime diagnosis of autism spectrum disorder (34 autism, 6 pervasive developmental disorder, not otherwise specified), hereafter referred to as autism, and 17 typically developing males. 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. 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 3 years of age and postmortem studies suggest that by 12 years of age, neuroanatomical maturation of the auditory cortex is adult-like (Huttenlocher & Dabholkar, 1997; Moore, 2002). Thus, the focus on our study is HG GM and WM volumes during the final stages of auditory cortex development (Moore, 2002).

Autism diagnosis was based on the Autism Diagnostic Interview-Revised (ADI-R; Lord et al., 2004), the Autism Diagnostic Observation Schedule-Generic (ADOS-G; Lord et al., 2000) and DSM-IV (American Psychiatric Association, 1994) criteria. Individuals with autism were excluded if there was a history of premature birth (prior to 36 weeks gestation), intubation or ventilator after birth, hypoxia-ischemia, head injury, seizures, or if medical history of karyotype or Fragile X testing identified medical causes of autism. Fifty-two percent 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 psychotropic medications). Typically developing participants with any history of cognitive, behavioral, neurological or neuropsychiatric conditions were excluded.

Behavioral measures

Autism severity—The ADOS-G was used to assess diagnostic communication and social behaviors at the time of initial evaluation (Lord, et al., 2000). A calibrated severity score based on ADOS module and participant age was calculated for each participant with autism (Gotham, et al., 2009).

Intellectual (IQ) functioning—At the time of the first scan, the Differential Abilities Scale (DAS; Elliott, 1990) was utilized to assess 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 individuals with autism received the Mullen Scales of Early Learning (Mullen, 1995). The Wechsler Intelligence Scales for Children (WISC-III; Wechsler, 1991) was administered to 1 control and 3 autism participants.

Handedness—Handedness was collected using the Edinburgh Handedness Inventory (Oldfield, 1971). It results in a quantitative score ranging from –100, completely left-handed, to +100, completely right handed.

Language onset—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. Verification was made through early childhood record review when available (75% of the sample).

Auditory sensitivity—At time point 3, the Sensory Profile (Dunn, 1999) was administered. This caregiver questionnaire assesses the frequency with which the child exhibits certain behaviors related to sensory processing. Previous studies of autism report auditory sensory processing abnormalities using this measure (Kern, et al., 2007; Rogers, et al., 2003; Tomchek & Dunn, 2007). 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.

Brain measures

Imaging protocol—Magnetic resonance images were acquired on a Siemens Trio 3.0 Tesla scanner at the University of Utah. At time point 1, an 8-channel, receive-only RF head coil was used to acquire 3D T1-weighted image volumes with 1×1×1mm isotropic resolution using an MP-RAGE sequence (TI=1100msec, TR=1800msec, TE=2.93msec, flip angle=12degrees, sagittal, field of view=25.6cm, matrix=256×256×160). At time points 2 and 3, a 12-channel, receive-only RF head coil was used to obtain 3D T1-weighted image volumes with 1×1×1.2mm resolution using an MP-RAGE sequence (TI=900msec, TR=2300msec, TE=2.91msec, flip angle=9degrees, sagittal, field of view=25.6cm, matrix=256×256×160).

Image processing—At the time of each 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 in-house automated tissue segmentation program available at the Scientific Computing and Imaging Institute (SCI) at the University of Utah (Prastawa, et al., 2004; Van Leemput, et al., 1999).

Heschl's gyrus ROI identification

HG was defined as the most anterior transverse gyrus on the superior surface of the superior temporal gyrus (STG). HG 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 coronal MRI images. The anterior boundary was the first transverse sulcus of the temporal lobe, with the most anterior slice where HG is first distinguished from the STG in the coronal plane. The lateral boundary was Heschl's sulcus. When duplicate transverse gyri were present, only the most medial gyrus was included. HG is often bifurcated by an intermediate sulcus. In cases where a second transverse gyrus merged with HG prior to the insula (partial bifurcation), the entire HG stem posterior from the merge was included in the ROI.

HG ROIs were manually segmented on contiguous coronal slices in native space using itk-SNAP (www.itksnap.org; Yushkevich, et al., 2006), allowing simultaneous viewing on the coronal, sagittal, and axial planes. The left and right hemisphere were traced and segmented separately. GM and WM volumes within HG were calculated for each hemisphere in itk-SNAP (see Figure 1). In addition to total GM and WM volumes, an asymmetry index ($[(L - R)/(L + R)/2]$) was calculated for HG GM and WM separately and HG GM/WM ratios were calculated for each hemisphere.

Manual segmentation of HG ROIs was performed by the first author as the primary rater (MDP) and two other trained raters (EP, KM). Intra-rater and inter-rater reliabilities were assessed by intraclass correlation (ICC). Both intra and inter-rater 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 rater, with average measurements as the final volumes. The final intra-rater reliabilities were: HG GM ICC > 0.91, HG WM ICC > 0.88. The final inter-rater reliabilities were: HG GM and WM ICC > 0.96.

Hemispheric and total brain volume

Hemispheric GM and WM volumes were obtained using Freesurfer v5.1.0 (<http://surfer.nmr.mgh.harvard.edu>).

Statistical Analysis

Between-group differences in age, inter-scan interval, handedness and IQ were examined with independent samples t-tests. Group differences in HG ROIs were examined in two ways: cross-sectionally and longitudinally. To compare our participants to previously published cross-sectional samples, ROIs from the first time point were examined for between-group mean differences and cross-sectional age-related changes. Regressions with an age covariate, squared age (age²) term, to allow for nonlinear age-related changes, group by age interactions, hemispheric GM or WM volume, and group by hemispheric volume interactions were examined as possible covariates, with the best model selected according to the lowest Akaike Information Criterion (AIC; Akaike, 1974).

Longitudinal changes in HG volume, asymmetry and GM/WM ratios were examined using linear mixed-effects models. This analysis allows us to model multiple observations per participant, which contain dependence between measurements, obtained over non-uniform 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:

$$\text{ROIrepeat} = \beta_0 \text{Intercept} + \beta_1 \text{Group} + \beta_2 \text{Age} + \beta_3 \text{Group} * \text{Age} + \beta_4 \text{Age}^2 + \beta_5 \text{Group} * \text{Age}^2 + \beta_6 \text{Hemispheric Volume} + \beta_{0i} + e$$

Hemispheric GM or WM 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).

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

Results

Imaging data

Imaging data suitable for analysis were three scans from 26 of 40 autism and 12 of 17 typically developing control participants (TDC), two scans from 12 autism and 5 TDC, and one scan from 2 autism participants (see Figure 2). Scan data were not available from all participants at all three time points for the following reasons: scan quality/motion (4 autism scans), inability to be scanned due to motion (7 autism participants), no contact for family (1 TDC, 3 autism), and not able to participate (3 TDC, 2 autism). The autism participants with only 1 or 2 time points were younger than those with 3 time points at the initial scan ($p<0.001$) and had significantly lower full-scale IQ ($p=0.016$). There were no differences in age at initial scan or IQ between the TDC participants with three versus two scans.

Participants and demographics

Characteristics of the autism and TDC samples are presented in Table 1. There were no group differences in mean age at time point 1 or average inter-scan interval. Mean quantitative handedness score was similar in the two groups but the range was greater in autism. Mean PIQ, VIQ, and FSIQ were lower in the autism group.

Volume of Heschl's gyrus

Cross-sectional analysis—We examined time point 1 volumes and effect of cross-sectional age to compare our sample to previous cross-sectional studies. Mean volumes at the first time point are provided in Table 2. No significant effects of group, age, or group by age interactions were found for HG GM or WM. Accordingly, there was no evidence of change in HG GM or WM volume with age between 3 and 12 years of age in either group. Hemispheric GM volume was significantly related to HG volumes (left $t=2.5$, $p=0.017$; right $t=2.4$, $p=0.018$) similarly for both groups.

Longitudinal analysis—Table 3 depicts results of the best-fitting mixed effects models for HG GM and WM. Estimated growth trajectories are displayed in Figure 3.

Typically developing participants: In the typically developing group, HG GM volume significantly increased with age in both hemispheres (both $p<0.001$, see Table 3 and Figure 3). HG WM volume also significantly changed with age. Age-related WM changes were more linear in the left hemisphere (age effect $p=0.005$) and quadratic in the right hemisphere (age² effect $p=0.009$). Some of the variance in HG GM was due to global hemispheric GM effects (left $p=0.059$; right $p=0.010$). Variance in left HG WM was not significantly related to global hemispheric WM.

Autism participants compared to typically developing participants: There was no main effect of group, i.e., mean GM and WM volumes in HG did not significantly differ in the autism and typically developing groups. Longitudinal change in left HG GM volume did not differ between groups. In the right HG, longitudinal change in GM volume was significantly different in the autism group (group by age interaction $p=0.007$). Estimated growth of right HG GM was only 0.46% per year in the autism group compared to 2.0% per year in the typically developing control group (see Figure 3, Panel B). Statistical trends were found in autism-control differences in the trajectories of HG WM bilaterally. Compared to the typical group, the autism group exhibited a trend toward reduced linear growth in the left WM (group by age interaction $p=0.069$) and reduced quadratic age effects in the right hemisphere (group by age² interaction $p=0.063$). Due to potential handedness effects on brain structure, our analyses were repeated excluding the four non-right handed autism participants. Findings in the right HG WM and bilateral GM did not change. In the left WM, the group by

age interaction was significant ($t=2.09$, $p=0.0402$), suggesting the right handed autism participants may be driving the trend toward group differences in left WM growth.

Heschl's gyrus asymmetry

Typically developing participants—Significant leftward asymmetry in HG GM volume (GM intercept=0.27, $t=4.0$, $p<0.001$), invariant across the age range examined, was present in the typical group. HG WM volume was also leftward asymmetric and increased with age (WM intercept=0.23, $t=2.7$, $p=0.009$; age effect $\beta=0.018$, $t=2.5$, $p=0.002$).

Autism participants compared to typically developing controls—Leftward asymmetry characterized HG GM and WM volumes in the autism group with no significant differences from the TDC group (group effect: GM $\beta=0.017$, $t=0.2$, ns; WM $\beta=0.011$, $t=0.1$, ns). Age effects on GM and WM asymmetry in the autism group were similar to effects in the TDC group; GM asymmetry did not change across the age-range studied, whereas leftward asymmetry of WM volume increased with age. These results did not change when only right-handed autism participants were included in the analysis.

Heschl's gyrus GM/WM ratio

Typically developing participants—Over three times more GM than WM was present in both the left and right HG (GM/WM ratio: left=3.40; right=3.27). In the right HG, GM/WM ratio increased with age (right HG: age $\beta=0.07$, $t=3.6$, $p<0.001$; age² $\beta=0.010$, $t=2.6$, $p=0.003$; left HG: age $\beta=0.01$, $t=0.6$, ns; age² $\beta=0.009$, $t=1.9$, $p=0.095$). Figure 3 (panels B and D) suggests this is due to increasing GM and decreasing WM during adolescence.

Autism participants compared to typically developing controls—HG GM/WM ratios in both hemispheres in the autism group were similar to the control group (GM/WM ratios: left=3.52; right=3.31). Also similar to controls, the GM/WM ratio increased with age in the right but not left HG (left HG: group by age $\beta=0.01$, $t=0.5$, ns; group by age² $\beta=-0.009$, $t=1.8$, $p=0.078$; right HG: group by age $\beta=-0.03$, $t=1.3$, $p=0.19$; group by age² $\beta=-0.007$, $t=1.6$, $p=0.11$). In both hemispheres, the marginally significant group by age² interactions were significant when only including the right-handed autism participants (left HG: group by age² $\beta=-0.011$, $t=2.2$, $p=0.029$; right HG: group by age² $\beta=-0.009$, $t=2.1$, $p=0.038$).

Heschl's gyrus volume and onset of spoken language

Twelve of the autism participants had typical, or nondelayed, onset of both words and phrases and 18 participants had delayed language onset. There were no differences between the autism subgroups in age at scan or inter-scan intervals but there was a greater degree of left-handedness in the nondelayed language group relative to both the delayed and typically developing groups (see Supplementary Table 1 for demographic information).

HG GM mean volume and longitudinal change did not differ between the autism subgroups based on language onset. Figure 4 shows atypical longitudinal changes in HG WM in the delayed language group compared to both the nondelayed language group (left WM: group by age $\beta=-8.4$, $t=2.1$, $p=0.042$; right WM: group by age $\beta=-9.7$, $t=2.5$, $p=0.013$) and typically developing controls (left WM: group by age $\beta=-9.4$, $t=2.2$, $p=0.035$, group by age² $\beta=1.1$, $t=1.3$, $p=0.178$; right WM: group by age $\beta=-8.3$, $t=2.2$, $p=0.029$, group by age² $\beta=1.7$, $t=2.4$, $p=0.017$).

Heschl's gyrus volume and auditory sensitivity

According to the Sensory Profile auditory sensitivity index, auditory sensitivity was atypical in 19 participants with autism (a “definite difference” from typical development) and normal in 8 participants. These autism groups did not differ in age at scan or inter-scan interval; VIQ was lower in the autism subgroup with atypical sensitivity only compared to the control group (see Supplementary Table 2 for demographic comparison).

In the left hemisphere, mean HG GM volume and longitudinal change did not differ between the autism participants with atypical versus nonatypical auditory sensitivity. In the right hemisphere, mean HG GM volume was non-significantly smaller in the atypical group ($\beta=-207$, $t=1.9$, $p=0.075$) and no group differences in longitudinal change were found. Compared to the control group, the trajectory of GM volumetric age-related changes in the right hemisphere significantly differed in the atypical auditory autism subgroup (group by age interaction: autism atypical $\beta=-21$, $t=2.5$, $p=0.012$; autism non-atypical $\beta=-16$, $t=1.8$, $p=0.072$). Figure 5 displays the graded volumetric increase in GM for the control group (2%), non-atypical autism (0.56%) and atypical autism (0.26%).

In the left hemisphere, individuals with non-atypical auditory sensitivity showed deviations in left WM age-related changes compared to both the atypical autism group (group by age² $\beta=2.9$, $t=3.1$, $p=0.003$) and controls (group by age $\beta=-10$, $t=1.9$, $p=0.05$, group by age² $\beta=2.6$, $t=2.6$, $p=0.011$; see Figure 6). In the right hemisphere, although there were no longitudinal growth differences, the non-atypical autism group had larger WM volumes compared to the atypical auditory ($\beta=124$, $t=2.0$, $p=0.052$) and typically developing ($\beta=128$, $t=2.2$, $p=0.028$) participants.

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

Discussion

In this study we modeled, for the first time, longitudinal volumetric growth of HG GM and WM during childhood and adolescence. The longitudinal design allowed us to capture brain growth in autism and typical development not previously identified using cross-sectional samples. The main findings are abnormal GM volumetric growth in the right HG in the autism sample compared to typically developing controls and evidence of dynamic age-related change in GM and WM volumes in HG in typical development continuing past the age when maturation of the auditory cortex is thought to be complete. We show evidence that the abnormality in the trajectory of right HG GM volume in the autism group may be driven by the subgroup of children with autism who have abnormal auditory sensitivity.

Heschl's gyrus growth in typical development

The longitudinal data showed evidence of dynamic change of HG GM and WM volumes in the typically developing group. The longitudinal age-related linear increase in bilateral HG GM volume during childhood and adolescence in our typically developing sample is consistent with longitudinal studies of temporal lobe volume development. The temporal lobe is the last lobe to complete its growth and maturation, with estimated peak GM volume and STG thickness occurring around 14-16 years of age (Giedd, 2004; Gogtay, et al., 2004; Shaw, et al., 2008). The combination of linear and nonlinear WM volumetric changes in the typically developing controls estimate the peak in left HG 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 that by age 12, axonal density reaches adult levels (Moore & Guan, 2001). During childhood and adolescence, primary auditory connections are forming with adjacent cortex and the contralateral hemisphere (Moore & Linthicum, 2007). Previous studies of temporal lobe development show WM increase continuing into adolescence (Carper, et al., 2002; Giedd, 2004), which is consistent with our findings in HG.

Leftward volumetric asymmetry of HG GM was present throughout the age-range studied, whereas HG WM volume became more leftward asymmetric with age. In typical development, higher myelin content has been found in the left compared to the right HG using MRI (Sigalovsky, et al., 2006). Leftward functional HG asymmetry has been found in an fMRI study during auditory tones presented to either ear (Devlin, et al., 2003). Another fMRI study reported effective connectivity (the functional activity in one region predicting another region) between HG and planum temporale in the left but not right hemisphere during language processing in typically developing individuals (Upadhyay, et al., 2008).

We found continued HG growth past 12 years of age into adolescence. Our findings suggest that HG GM volume increases during this later period of development and non-parallel and more complex changes occur in WM volume. 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). The maturation of association and commissural axons during later childhood allows for more complex auditory and language processing during development (Huttenlocher & Dabholkar, 1997; Moore, 2002; Moore & Linthicum, 2007).

Heschl's gyrus growth in autism

Our results show evidence of abnormal volumetric development of HG in autism: an atypical trajectory of right HG GM volume was found along with a trend toward atypical change in WM volumes bilaterally. The decreased longitudinal GM volumetric development in the right hemisphere is consistent with MEG studies reporting delayed and atypical age-related auditory evoked responses in the right hemisphere in autism (Gage, Siegel, & Roberts, 2003; Roberts, et al., 2010). The trend toward group differences in left WM growth was driven by the right-handed autism participants. Atypical auditory GM and WM growth might contribute to the aberrant activation reported in many functional studies of autism (e.g., Oram Cardy, et al., 2005; Roberts, et al., 2011).

The group differences in right HG GM growth appeared to be driven by the subgroup of autism participants with reported auditory sensitivity. Although our auditory measure was a caregiver questionnaire, a recent auditory evoked fields study demonstrated delayed peak latency and enlarged dipole moments in autism with hypersensitivity relative to non-hypersensitive autism and controls (Matsuzaki, et al., 2012). Interestingly, our autism participants without auditory sensitivity had larger right WM volumes and different left WM longitudinal growth compared to autism with atypical sensitivity and control participants. Variation in WM volumes and age-related changes could represent a number of structural differences, such as increased thalamocortical connections or U-fibers, the balance of excitatory and inhibitory connections, or WM microstructural differences affecting volume. We also found different WM growth trajectories in the autism participants with delayed language onset compared to the nondelayed autism and control groups. Previous studies show behavioral language improvement over time in those with delayed language onset (Eisenmajer et al., 1998). Thus, our WM findings may represent pathologic development that is functionally beneficial in the disorder. Clearly, further research into structural phenotypes that may underlie behavioral heterogeneity within the disorder is needed.

Longitudinal compared to cross-sectional studies of Heschl's gyrus volume

The cross-sectional findings presented replicated previous cross-sectional studies of HG volume in children and adolescents with autism: no abnormalities in autism were found (Gage, et al., 2009; Herbert, et al., 2005; Knaus, et al., 2009; Rojas, et al., 2005). Our longitudinal analysis revealed significant case-control age-related differences in the trajectory of right HG GM volume. Different findings in our longitudinal study compared to past cross-sectional volumetric studies may be related to the power of modeling longitudinal changes within individuals compared to estimating developmental changes by using cross-sectional data from different individuals of different ages. Longitudinal inferences about development from cross-sectional studies can be seriously misleading (Kraemer, et al., 2000). Some critical questions about development can only be answered by longitudinal studies.

Limitations

This study has a number of limitations. We consider the findings preliminary because this is the first study to longitudinally examine HG volumes in children from age 3 to 17 years, the sample size of the typically developing children was relatively small, and only up to 3 time points of data over a 6 year period were available for individual participants. Although accelerated longitudinal designs are a significant advancement over cross-sectional studies, they can still be affected by cohort effects. If replicated, the findings will suggest that the window of HG volumetric development is more protracted than postmortem studies of auditory cortex maturation have found.

Another limitation is that only cognitively high-functioning individuals with autism were examined. Thus, the generalizability of the results will need to be tested with larger and more diverse samples and specificity of the results to autism will require comparison to other patient groups. Our measure of auditory sensitivity was obtained through a caregiver report. Future studies that directly measure physiological auditory response in relation to longitudinal auditory development are needed. Finally, only HG volume was examined. A report of increased HG cortical thickness in autism during later adolescence and adulthood (Hyde, et al., 2010) highlights the need for further examination of longitudinal cortical thickness and WM microstructural changes in the disorder.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Clinical Relevance

It will be important to determine causal relationships between HG volumetric development, auditory sensitivity, subsequent auditory and language outcomes, and mechanisms involved.

Figure 1.
Sample coronal image of a Heschl's gyrus ROI segmented into GM (green) and WM (red)

Figure 2.

Scan ages for all participants. Each control (black) and autism (red) participant is on a different row. Each scan is represented by a circle, with subsequent scans for each participant connected by a line.

Figure 3. Longitudinal volumetric (mm^3) growth of Heschl's gyrus left GM (A), right GM (B), left WM (C), and right WM (D) in typical development (black) and autism (red). 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.

Figure 4.

Longitudinal HG WM volumetric (mm^3) changes in autism according to language onset: non-delayed language (blue) versus delayed language (red). Solid lines represent estimated longitudinal trajectories for the non-delayed (blue), delayed (red) and typically developing (black) participants. Individual data points for the typically developing controls are presented in Figure 3.

Figure 5. Right HG GM volumetric (mm^3) growth according to reported auditory sensitivity: atypical auditory sensitivity (red) and non-atypical sensitivity (blue). Estimated longitudinal change in typical development is represented by the black regression line.

Figure 6. Left HG WM volumetric (mm^3) changes in atypical (red) versus non-atypical (blue) reported auditory sensitivity. Estimated longitudinal change in typical development is represented by the black regression line.

Table 1

Demographic summary of the autism and typically developing control groups

	Autism n=40		Typically Developing n=17		
	Mean (sd)	Range	Mean (sd)	Range	t (p-value)
Time 1 age (years)	8.5 (3.1)	3.5-12.9	9.0 (2.6)	4.0-12.3	0.5 ns ^a
PIQ ^b	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)
Handedness ^c	73 (39)	-67-+100	79 (13)	+20-+100	0.4 ns
ADOS Severity Score	7.9 (1.5)	4-10	---	---	---
Interscan interval:					
Time 1 to 2 (years) ^d	2.7 (0.7)	2.0-6.5	2.6 (0.6)	1.8-3.7	0.5 ns
Time 2 to 3 (years) ^e	2.7 (0.5)	2.0-4.2	2.6 (0.5)	1.9-3.5	0.7 ns

^a ns indicates p-value > 0.2;

^b autism: PIQ n=38, VIQ n=32, FSIQ n=39;

^c Edinburgh Handedness Inventory (Oldfield, 1971), ranging from -100, completely left handed, to +100, completely right handed;

^d autism n=38, control n=17;

^e autism n=26, control n=12.

Table 2

Heschl's gyrus (HG) mean volumes (mm³) at timepoint 1

	Autism n=40		Typically Developing n=17		Group Difference
	Mean (sd)	Range	Mean (sd)	Range	t (p-value)
Left Hemisphere					
HG GM	1630 (499)	838-2596	1509 (488)	897-2515	0.9 ns ^a
HG WM	493 (199)	188-908	446 (173)	225-736	0.8 ns
HG Total	2124 (682)	1026-3505	1956 (651)	1128-3234	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 > 0.2

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.

Table 3

	Intercept	Group	Age	Group by Age	Age ²	Group by Age ²	Hemis Vol ^a
Left Hemisphere							
HG GM	1642	92	23.9	-5.9	-0.35	-1.5	0.005
		<i>ns</i> ^b	<0.001	<i>ns</i>	0.131	<i>ns</i>	0.059
HG WM	481	27.4	8.7	-6.8	-1.0	0.74	--- ^c
		<i>ns</i>	0.005	0.069	0.076	<i>ns</i>	
Right Hemisphere							
HG GM	1205	39.6	24.3	-18.5	---	---	0.003
		<i>ns</i>	<0.001	0.007			0.010
HG WM	371	22.1	1.1	-2.5	-1.4	1.2	0.001
		<i>ns</i>	<i>ns</i>	<i>ns</i>	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.