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Atypical white-matter microstructure in congenitally deaf adults: A region of interest and tractography study using diffusion-tensor imaging

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ABSTRACT

Considerable research documents the cross-modal reorganization of auditory cortices as a consequence of congenital deafness, with remapped functions that include visual and somatosensory processing of both linguistic and nonlinguistic information. Structural changes accompany this cross-modal neuroplasticity, but precisely which specific structural changes accompany congenital and early deafness and whether there are group differences in hemispheric asymmetries remain to be established. Here, we used diffusion tensor imaging (DTI) to examine microstructural white matter changes accompanying cross-modal reorganization in 23 deaf adults who were genetically, profoundly, and congenitally deaf, having learned sign language from infancy with 26 hearing controls who participated in our previous fMRI studies of cross-modal neuroplasticity. In contrast to prior literature using a whole-brain approach, we introduce a semiautomatic method for demarcating auditory regions in which regions of interest (ROIs) are defined on the normalized white matter skeleton for all participants, projected into each participants native space, and manually constrained to anatomical boundaries. White-matter ROIs were left and right Heschl's gyrus (HG), left and right anterior superior temporal gyrus (aSTG), left and right posterior superior temporal gyrus (pSTG), as well as one tractography-defined region in the splenium of the corpus callosum connecting homologous left and right superior temporal regions (pCC). Within these regions, we measured fractional anisotropy (FA), radial diffusivity (RD), axial diffusivity (AD), and white-matter volume. Congenitally deaf adults had reduced FA and volume in white matter structures underlying bilateral HG, aSTG, pSTG, and reduced FA in pCC. In HG and pCC, this reduction in FA corresponded with increased RD, but differences in aSTG and pSTG could not be localized to alterations in RD or AD. Direct statistical tests of hemispheric asymmetries in these differences indicated the most prominent effects in pSTG, where the largest differences between groups occurred in the right hemisphere. Other regions did not show significant hemispheric asymmetries in group differences. Taken together, these results indicate that atypical white matter microstructure and reduced volume underlies regions of superior temporal primary and association auditory cortex and introduce a robust method for quantifying volumetric and white matter microstructural differences that can be applied to future studies of special populations.

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1. Introduction

Many systems within the developing brain respond to input from the environment through functional and structural changes (Johnson, 2001; Johnson and Munakata, 2005). In the case of profound congenital deafness, a developmental sensory experience that is highly atypical, these changes include cross-modal reorganization of auditory cortices, which become remapped to respond to visual, tactile, and signed language input (Auer et al., 2007; Bavelier et al., 2006; Bavelier and Neville, 2002; Finney et al., 2001; Johnson, 2001; Johnson and Munakata, 2005; Karns et al.,

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2012; Levänen et al., 1998; Neville and Lawson, 1987). Although functional neuroplasticity in primary auditory cortex has been controversial (Bavelier et al., 2006; Kral et al., 2003), recent findings in anatomically-defined primary auditory cortex, or Heschl's gyrus (HG), point to cross-modal functional reorganization (Karns et al., 2012; Scott et al., 2014). Together, these findings suggest widespread functional changes in auditory regions that extend to the cortical sites receiving the first afferent relay of auditory input.

1.1. Structural changes in auditory gray and white matter with deafness

The profound alteration in the functional role of auditory cortex observed following deafness is likely to co-occur with structural changes, and indeed, an emerging body of research suggests that one way this structural change manifests is via a decrease in the gross white matter volume of auditory regions in the early or congenitally deaf. Several studies investigating macro-structural volumetric change in HG or neighboring temporal lobe regions report reductions in white matter volume corresponding with preserved gray matter volume in deaf participants relative to their hearing counterparts (Emmorey et al., 2003; Hribar et al., 2014; Shibata, 2007; Smith et al., 2011). This finding suggests that early auditory deprivation impacts white matter volume more than gray matter. However, at least one study failed to find differences in either gray or white matter volume (Penhune et al., 2003), and other studies have reported decreases in auditory gray matter volume (Olulade et al., 2014) or volume differences that extend to non-auditory regions (Allen et al., 2013; Kim et al., 2009; Leporé et al., 2010; Li et al., 2012; Olulade et al., 2014). Yet the most consistent finding is reduced white matter in temporal lobe regions underlying auditory processing. One potential hypothesis is that volume differences reflect a different myelination profile in auditory cortex as has been previously suggested (Emmorey et al., 2003). A potential alternative or extension to this hypothesis is that remapped functions could change the microstructural profile of auditory cortical white matter, for example, by increasing the number of crossing fibers, but gross volumetric measures alone do not allow this to be tested directly.

1.2. Microstructural changes in white matter with deafness

As such, an important question is whether or how *micro*-structural changes in white matter underlie the cross-modal functional alterations in auditory cortices following congenital and/or early deafness. Microstructural change can be estimated with diffusion tensor imaging (DTI), an MRI imaging method that indexes the directionality of the diffusion of water in brain tissue. This diffusion is more directional in white matter and more diffuse in gray matter, and measures of estimated tensors can provide information about the microstructural profile of white matter. Five studies to date have addressed possible white matter microstructural differences between deaf and hearing following early or congenital deafness using DTI in humans (Hribar et al., 2014; Kim et al., 2009; Li et al., 2011; Lyness et al., 2014; Miao et al., 2013) with a sixth study relating microstructure to visual motion thresholds within a deaf sample (Shiell and Zatorre, 2016). These studies represent diverse characteristics of deaf populations, varied sample sizes, and different imaging, measurement, and statistical methods. They also represent a number of disparate findings. One study focused on subcortical thalamic tracts that project to large cortical regions of interest (ROIs) and found no difference between deaf and hearing groups in the thalamic projections to temporal lobes (Lyness et al., 2014). Another study found a small region of interest in the posterior superior temporal lobe is associated with visual motion detection in deaf participants while other measured regions were not (Shiell and Zatorre, 2016). The remaining four studies used a whole brain approach to DTI analyses and reported reductions in fractional anisotropy (FA: a measure of the amount of directional restriction of water in brain tissue using modeled tensors that reflects microstructural properties of white matter) in superior temporal white matter regions positioned beneath auditory cortices, though the anatomical specificity of these regions varies (Kim et al., 2009; Li et al., 2011; Miao et al., 2013). The reduced FA observed in these regions suggests reduced structural integrity of the axonal fibers and/or a greater number of crossing fibers in temporal lobe regions (Alexander et al., 2007; Assaf and Pasternak, 2007; Song et al., 2002). Two studies have also reported FA reductions in the splenium of the corpus callosum (Li et al., 2011; Miao et al., 2013), a finding which is compelling given that the left and right superior temporal lobes are connected via a tract that passes through the splenium (Hofer and Frahm, 2006) — but other studies have reported no change in the splenium (Hribar et al., 2014) or even *increased* FA in the forceps major, a tract connecting occipital lobes, which also crosses the midline at the splenium (Kim et al., 2009). Taken together, these prior DTI studies of early and/or congenitally deaf people have not yielded a specific profile of microstructural changes to the white matter in auditory brain regions, suggesting the need for further study on white matter microstructural changes following deafness. At the same time, the converging evidence and persuasive *a priori* justification for group differences in superior temporal lobe white matter regions beneath auditory cortices provides motivation for more detailed study focusing specifically on these regions.

One reason for the lack of consistency in prior studies may be the reliance on whole-brain analyses of normalized brains, typically using tract-based spatial statistics (TBSS) applied over the entire brain which requires cluster correction for multiple comparisons. While this approach provides a broad characterization of group differences, it requires more stringent statistical correction than region of interest (ROI) approaches and can lead to somewhat counterintuitive comparisons between studies. For example, in one whole brain analysis using threshold-free cluster correction (TFCE) with a relatively large sample of 60 congenitally deaf, 36 acquired deaf, and 38 hearing participants, Li and colleagues found FA group differences in just three regions (the right STG, the left HG, and the splenium of the corpus callosum) (Li et al., 2011), while counter intuitively, in a study with a much smaller sample size of 14 deaf participants and 14 hearing controls, a much more extensive set of regions met the TFCE criteria for significance, including many non-auditory regions (Hribar et al., 2014). For critical regions like HG, which show considerable inter-subject variability in morphology and for other auditory regions for which there is a strong *a priori* motivation for white matter differences between deaf and hearing, an anatomical region of interest approach may yield more reproducible results across studies with varying sample sizes.

1.3. Hemispheric asymmetries of white matter microstructure with deafness

Another important research question is whether white matter microstructural changes following deafness show hemispheric specificity, being different for left and right HG and/or STG; yet the prior DTI literature is inconsistent here as well (Hribar et al., 2014; Kim et al., 2009; Li et al., 2011; Miao et al., 2013). To date no study has included direct statistical tests for hemispheric specificity. For example, one study reported group differences in one left HG cluster and a second, more extensive, right STG cluster (Li et al., 2011), while another study reported bilateral superior temporal group differences that were described as more extensive on the

right (Hribar et al., 2014). However, neither study directly compared the measurements in structurally homologous left and right regions, which prevents strong conclusions of hemispheric specificity from being drawn. Indeed, no previous study has applied DTI to directly test for hemispheric differences despite the usefulness of this approach for volumetric measures of gross white and grey matter volume (e.g. Smith et al., 2011).

1.4. Fractional anisotropy, radial diffusivity, and axial diffusivity

Other methodological differences characterize the existing literature on microstructural white matter changes following deafness. Importantly, whereas all prior DTI studies of deaf humans include measures of fractional anisotropy (the general index of the structural integrity and directionality of axonal fibers within a voxel), not all studies additionally report radial diffusivity (RD, presumed to index levels of myelination) and/or axial diffusivity (AD, presumed to reflect integrity of microtubules along the axon) (Alexander et al., 2007; Song et al., 2002; but see Wheeler-Kingshott and Cercignani, 2009 for limitations). Another common measure, mean diffusivity (MD) is sometimes reported along with RD or AD, but as the mathematical combination of RD and AD ($MD = (2*RD + AD)/3$) it is less specific then RD and AD reported separately. Among the studies that measured both RD and AD, two have indicated that superior temporal reductions in fractional anisotropy following deafness can be attributed more to changes in radial than axial diffusivity (Li et al., 2011; Miao et al., 2013) while a third found group differences only for axial and not radial diffusivity (Hribar et al., 2014). Systematic test of AD, RD, and FA are needed to establish which measures are most pronounced in human congenital and early deafness.

1.5. Special considerations for studies of human deafness

A major challenge for the field of deaf neuroplasticity is unifying findings across studies with various samples representing diverse subpopulations. Inherent in the complex developmental profile of human deafness, even among congenitally- and early-deaf humans, is a diversity of etiologies, ages of onset, ages of language acquisition, and whether signed or spoken language is primary. Prior DTI studies of human deafness have included various subsets of these diverse populations due to different aims of the studies, such as assessing structural changes related to age of onset versus duration of deafness (Li et al., 2011) or controlling for age of sign language acquisition (Lyness et al., 2014; Miao et al., 2013). These findings, along with others (Olulade et al., 2014), indicate that not all structural changes with deafness generalize to a broad population of deaf individuals. A natural consequence of more specificity in a study of human deafness is a smaller sample size, and reproducible and statistically powerful approaches are needed for this situation. While there is certainly value in whole-brain approaches, we propose that using an ROI approach in auditory regions may allow the field to establish what is a typical profile of microstructural differences in deafness and the extent to which differences are consistent across varied subsamples of deaf populations that have been recruited for studies with different aims.

1.6. Aims and contributions of the current study

Here, we sought to extend prior research by examining microstructural white matter changes measured by DTI in specific temporal lobe regions that typically show cross-modal reorganization in deafness, specifically primary auditory cortex (HG), superior temporal lobe regions, and the splenium of the corpus callosum. In contrast to prior research, the present study used an anatomical region-of-interest rather than whole-brain approach. We demarcated left and right HG, as well as the left and right superior temporal gyrus, anterior and posterior to HG. These regions were anatomically defined on the mean FA white matter skeleton, back-projected to individual brains, and hand-corrected for stray voxels. This semiautomatic approach is reproducible, but the projection of the non-linear coregistration back to native space also allows researchers to assess the accuracy of spatial normalization in regions that are anatomically variable across individuals such as HG. An *a priori* ROI approach is also statistically powerful and allows for direct tests of left and right hemisphere differences. We also introduce a novel approach to generate a splenium ROI tract that connects homologous anterior STG regions across the midline. Finally, given the heterogeneity of deaf populations, there is a need for a study of auditory white matter microstructural changes in a sample of only congenitally, genetically deaf participants in which functional cross-modal plasticity has been demonstrated. As such, all participants in the present study were profoundly and congenitally deaf, who reported learning sign language from infancy, and all but one participated in one of our previous studies of cross-modal neuroplasticity in Heschl's gyrus (Karns et al., 2012; Scott et al., 2014).

2. Material and methods

2.1. Participants

Participants were 23 deaf (17 females) and 26 hearing adults (14 females) who gave informed consent and all research procedures were approved by our institutional review board. Twelve of the deaf adults were included in our report on somatosensory and visual responses in primary auditory cortex (Karns et al., 2012). A non-overlapping 10 deaf adults participated in our study on peripheral visual responses in primary auditory cortex (Scott et al., 2014). The remaining deaf participant only completed a DTI and structural scan due to discomfort in the MRI scanner. Participants gave their informed and written consent and were paid for participation. The Institutional Review Board of the University of Oregon approved the procedures. Gender ratio did not differ between groups ($\chi^2(1) = 2.1$, $p > 0.05$), nor did age (deaf: 28 years ± 1.4 SEM; hearing: 25 years ± 1.0 SEM; $t(47) = 1.76$, $p > 0.05$). All participants were healthy, not taking psychoactive drugs or medications, and had no history of neurological or psychological disorders. Subjects were considered as congenitally deaf if they were profoundly deaf in both ears (>90 dB attenuation) since birth and had at least one closely related, congenitally deaf relative. As criteria for inclusion, deaf participants reported minimal past hearing aid use and learning American Sign Language (ASL) to fluency from infancy with ASL as their primary language. An English reading-comprehension and written-vocabulary assessment was given as a general screening for severe education deprivation (MacGinitie et al., 2000; level 4, Form S); due to time constraints, only 30 min were allotted for the test (compared to 55 min for standard test administration) and criterion for inclusion was a grade equivalent of at least 5 on completed items (3 deaf participants, not described in the sample of 23, did not meet this criterion and were excluded). Of the included deaf participants, 13 were at ceiling for this test (grade equivalent of at least 12). All hearing participants were at ceiling indicating likely group differences in English fluency, but due to nonstandard testing procedures between groups we determined that scores should not be directly compared. Non-verbal reasoning was assessed using a timed (30 min) 12 question short-form of Raven's Advanced Progressive Matrices (RPM) (Bors and Stokes, 1998) and differences between deaf and hearing participants were controlled using both a

statistical and subsample approach described in section 2.5.1.

2.2. Diffusion weighted imaging methods

Diffusion-weighted data were acquired on a 3.0 T Siemens Allegra scanner using echo planar imaging (32 × 2 mm thick axial slices, slice spacing of 2 mm, matrix size 128 × 128, field of view 256 × 256 mm), with interleaved acquisition. The diffusion weighting was isotropically distributed along 60 directions, an echo time of 118 ms and a repetition time of 11 s. For each set of diffusion-weighted data, 10 vol with no diffusion weighting ($b = 0$) were acquired at intervals throughout the acquisition. The b-value was 1000 s/mm^2 (or 700 s/mm^2 for 9 deaf and 16 hearing participants) and scan parameters were not significantly different by group, $\chi^2(1) = 2.5$, ($p > 0.05$).

The raw volume data were visually checked for artifacts by three raters. The largest artifacts were due to head motion, which were manifested by signal drop in extended regions and/or "zipper" artifacts in the z-direction due to the interaction of motion with interleaved acquisition. Volumes with artifacts were removed from the set of 60 vol per subject. Ten participants had at least one volume removed, all participants had fewer than nine of their total volumes removed (15%), and no subjects required exclusion for excessive motion. Other preprocessing was performed with FDT (FMRIB's Diffusion Toolbox http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/FDT) and other FMRIB Software Library (FSL) tools (Behrens et al., 2007, 2003a,b).

Eddy current correction was used to remove global stretching and shearing due to non-ideal gradient coil behavior, and non-brain voxels were removed using BET. In each data set, each scan was coregistered to a reference ($b = 0$) scan using affine registration with a maximization of mutual information algorithm (FLIRT). B0 images were coregistered to the first B0 image and averaged, and the 60 directional diffusion volumes were coregistered to B0 average. BEDPOSTX was used for local modeling of diffusion parameters and DTIFIT was used for tensor estimation. Fractional anisotropy (FA) maps of each subject were coregistered to an FA standard (FMRIB58_1mm), using the non-linear coregistration tool (FNIRT) with tract based spatial statistics (TBSS) default settings. The mean of coregistered and resampled FA maps was the basis for constructing a mean FA skeleton using iterated morphology operations. This mean FA skeleton was used to demarcate the superior temporal ROI definitions, and the nonlinear coregistration inverse transforms were used for individual ROI generation; see ROI methods (Section 2.3). A tractography analysis was conducted for each subject used PROBTRACKX, the FSL algorithm where tensors model crossing fibers (5000 samples, curvature threshold of 0.2 and a maximum number of steps of 2000, step length of 0.5). Tractography was used to estimate the location of tracts through the corpus callosum between homologous superior temporal regions in each hemisphere.

2.3. Semiautomatic anatomically-defined temporal regions of interest

Individual Heschl's gyrus (HG) and anterior and posterior superior temporal gyrus (aSTG/pSTG) ROIs were based on manual selection from the FA skeleton voxels in the normalized group mean image, guided by anatomical landmarks on a standard T1 structural image [FMRIB58_1mm] as described in section 2.2. After voxels on the standard skeleton were selected, the inverse nonlinear transform for each subject was applied. In other words, each ROI was drawn a single time on the skeleton for the standard brain and then back-projected to each participant's brain in native space. Surviving voxels in the subject's native space were then masked by each subject's FA values > 0.2 to eliminate voxels outside of white matter. Note that this is a low threshold approaching that of gray matter (Mamata et al., 2004) and gray-white boundaries were verified visually on individual brains to ensure that the threshold did not erode the boundaries of the ROI.

The HG ROIs were selected from the single ridge corresponding to white matter extending superior to the STG. All voxels of the ridge extending above the superior temporal sulcus were selected, on left and right hemispheres. The STG ROIs were selected in a similar manner. On the skeleton for the standard brain, the HG intersection with the STG skeleton was used as the boundary between anterior and posterior STG ROIs. The anterior extent of the aSTG was bounded anteriorly by MNI coordinate plane at $y = 2$. The posterior extent of the pSTG was constrained by the Harvard Oxford Planum Temporale atlas structure, thresholded above 10 percent. After backprojection to each participant's native space, these ROIs were checked on each participant's FA map to ensure that the projections spanned expected anatomical structures, the HG and STG white matter ridges. In cases of a doubled or partially doubled HG these single ridges projected primarily to the anterior gyrus, but voxels projected within the doubled gyrus were retained for analysis. Any projected voxels that were clearly posterior to the posterior STG or on the medial temporal gyrus were manually removed. Three raters examined each individual HG back-projection and determined whether it successfully encompassed HG white matter. All projections were rated as successful. The volume (mm^3) was calculated for all voxels in these white matter ROIs for each individual participant.

2.4. Corpus callosum tractography-derived ROIs

First, a liberal posterior corpus callosum ROI was drawn manually on the FMRIB58_FA_1mm standard. This region was defined as lying anterior to the posterior margin of the CC at midline, behind the plane 1/5 of the extent between the most anterior and posterior extent of the CC at midline, with the horns of the lateral ventricles as the lateral boundary (FA > 2000/8676). This region was then back-projected to individual brains as with the superior temporal ROIs. Note that we did not extract measures from this liberal ROI, but used it in conjunction with tractography to define a specific subregion of the posterior corpus callosum for further analysis. Within each subject, we used opposite hemisphere ROI that was anterior to HG (aSTG) as a waypoint and termination using the liberal pCC region as another waypoint resulting in a clear tract through the corpus callosum in individual brains. The same approach using the region posterior to HG (pSTG) was not successful in locating callosal tracts in individual brains. The number of tracts per voxel was divided by the maximum number of tracts per voxel for each subject (i.e., normalized to 1.0 for all subjects) which was then binarized at a threshold of 0.3 and back-projected to individual brains (from which volume was also measured). This constrained tractography-derived pCC ROI was used to extract FA, AD, and RD measures and volume from individual participants (reported as pCC measures).

2.5. Statistical approach

Our main dependent measures included FA (Standard Deviation($\lambda_1, \lambda_2, \lambda_3$)/Mean($\lambda_1, \lambda_2, \lambda_3$)) and volume. We examined these dependent measures within three regions of interest within the superior temporal lobe: Heschl's Gyrus (HG), posterior superior temporal gyrus (pSTG), and anterior superior temporal gyrus (aSTG). A fourth ROI in the splenium of the corpus callosum was determined via tractography (pCC) between the left and right aSTG. For the three temporal lobe ROIs, left and right hemisphere was included as a factor in all analyses to test for hemispheric effects:

left and right Heschl's gyrus (HGL, HGR), left and right anterior superior temporal gyrus (aSTGL, aSTGR), left and right posterior superior temporal gyrus (pSTGL, pSTGR). In any region showing significant group differences in FA, additional analyses compared RD (mean(λ_2, λ_3)) and AD (λ_1) between groups to further clarify the underlying nature of group differences in FA.

Separate ANOVAs were used to examine each of the four ROIs. Analysis of the three temporal lobe ROIs was conducted using mixed-design ANOVAs including Group (Hearing, Deaf) as a between subjects factor and Hemisphere (Left, Right) as a within subjects factor. Analysis of the pCC included Group (Hearing, Deaf) as the only between subjects factor.

2.5.1. Treatment of group behavioral differences

Our sample of congenitally deaf adults scored lower than our sample of hearing adults on a 12-item short timed measure of nonverbal reasoning – published means in a university sample of 99 hearing participants was 7.5 (Bors and Stokes, 1998). Previous large studies and meta-analyses using other measures indicate mean nonverbal IQ performance deaf children is equivalent to that of the hearing population (Braden, 1991; Vernon, 2005) but in our sample we did find a systematic group difference (RPM deaf: 5.8 ± 0.5 SEM, range 2–11; RPM hearing: 9.0 ± 0.45 SEM, range 3–12; $t(47) = 4.7$, $p < 0.001$). We took two approaches to control for these group differences in RPM to directly assess whether differences in RPM affected our white matter measurements: In Analysis 1, we included group-mean normalized RPM scores as covariates in the repeated measures ANOVA using the full sample; the z-scores were normalized to the mean separately for the deaf and hearing groups and these adjusted scores were added as an RPM covariate in the ANOVA (Delaney and Maxwell, 2010). The RPM covariate, though retained for Analysis 1, was not statistically significant and did not significantly interact with any variables, all $p > 0.05$. In Analysis 2, for any significant group differences observed in Analysis 1, we also analyzed a subsample of 11 hearing (6 female) and 10 deaf adults (7 female) matching these participants for RPM scores. The deaf and hearing groups in the subsample did not differ by gender ($\chi^2(1) = 0.53$, $p > 0.05$) or age (deaf: 26 years ± 1.4 SEM; hearing: 25 years ± 1.2; $t(19) = 0.38$, $p > 0.5$). The covariate analysis of the full sample has the advantage of a larger number of participants with a statistical control for potential RPM differences, while the second subgroup analysis represents a more direct control for RPM differences but has a smaller number of participants and therefore less statistical power.

2.5.2. Treatment of group behavioral differences

In addition to the results reported below, in an exploratory step, we also performed a standard whole-brain voxel-wise tract-based spatial statistics (TBSS) analysis with permutation based cluster correction in FSL using TFCE. Although we visually confirmed that the clusters with the smallest corrected TFCE p-values were in HG, the superior temporal lobe, and the posterior corpus callosum, these clusters did not reach statistical significance and so whole-brain results are not reported further.

3. Results

3.1. White matter microstructure: temporal lobe ROIs and corpus callosum

As detailed in the methods (Section 2.5), the statistics reported represent the full sample and when significant ($p < 0.05$) or approaching significance ($p < 0.10$), we also performed the same test in the subsample matched for RPM scores. As shown in Fig. 1 and detailed below, across all four temporal lobe ROIs, we found

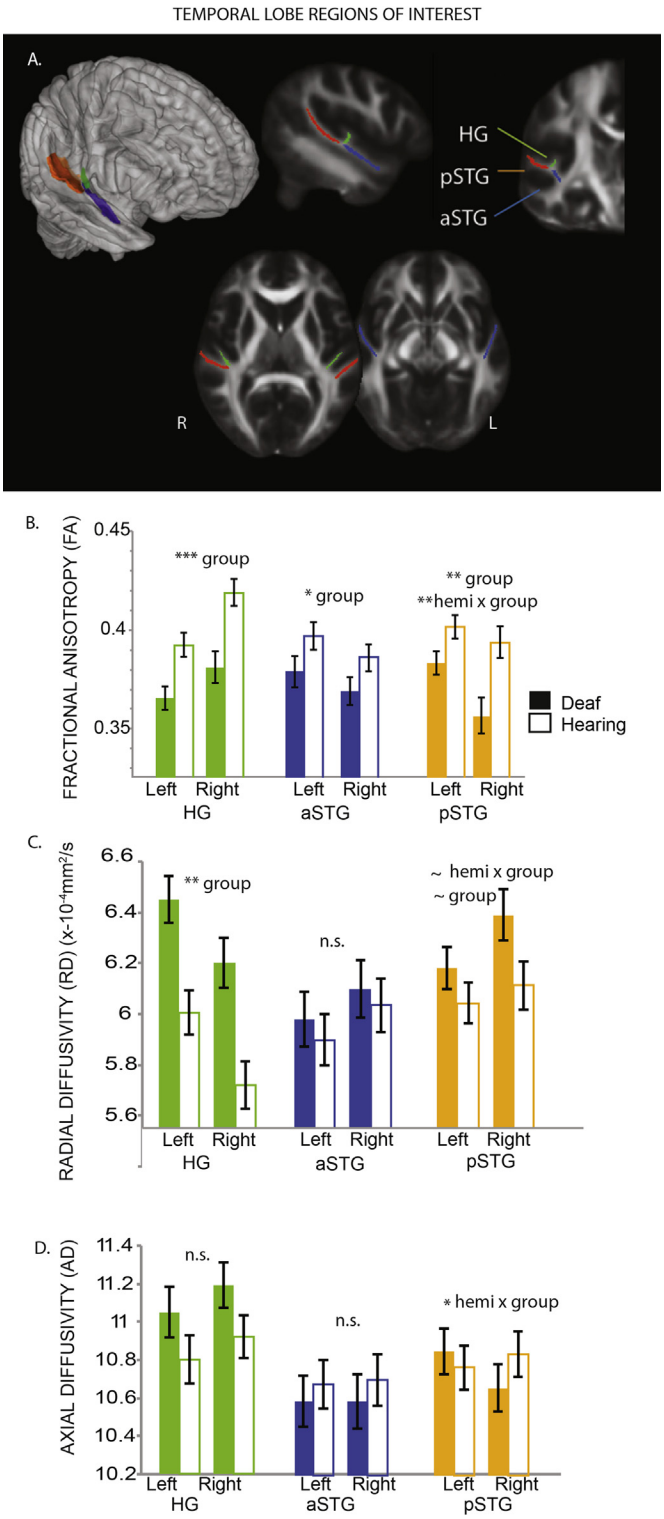

Fig. 1. A) Temporal ROIs (HG: Heschl's gyrus [Green], aSTG: anterior superior temporal gyrus [Blue], and posterior superior temporal gyrus [Orange]) were drawn on the coregistered mean FA skeleton as shown and back-projected to the brains of individual subjects. We measured fractional anisotropy (FA) as well as axial diffusivity (AD) and radial diffusivity (RD). Solid bars represent the means for the deaf participants, with white bars representing the man for hearing participants. Error bars represent ±1 S.E.M. B) FA was reduced in deaf participants and differences between deaf and hearing were larger for the right pSTG. C) RD was higher for the deaf in HG. D) Group differences in AD manifested as a Hemisphere × Group interaction in pSTG. *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$, n.s. not significant.

evidence for reduced FA in deaf adults that appeared to be driven primarily but not entirely by differences in RD. Within HG, deaf adults showed significantly reduced FA ($F(1, 46) = 20.9$, $p < 0.001$; subsample analysis: $F(1,19) = 4.25$, $p = 0.05$). Differences in HG FA were due primarily to increased RD in the deaf group ($F(1,26) = 15.0$, $p < 0.001$; subsample analysis: $F(1,19) = 6.19$, $p < 0.03$) rather than AD ($F(1,46) = 2.67$, $p > 0.10$). Similar results were observed in the pSTG, where deaf adults showed lower overall FA values ($F(1, 46) = 7.12$, $p = 0.01$; subsample analysis: $F(1,19) = 7.38$, $p < 0.03$). Overall the group differences in FA in the pSTG corresponded primarily with increased RD in the deaf participants ($F(1,46) = 2.9$, $p < 0.10$; subsample: $F(1,19) = 6.33$, $p < 0.03$) but not AD where the main effect of group was not significant ($F(1,46) = 0.1$, $p > 0.10$). In addition to these main effects, in the pSTG there was some evidence that group differences in FA were larger on the right than left hemisphere (Hemi x Group, $F(1,46) = 10.1$, $p = 0.003$), but this result was not statistically significant in the matched subsample (Hemi x Group, $F(1,19) = 1.2$, $p > 0.10$). In the aSTG, deaf adults also showed reduced overall FA ($F(1,46) = 4.64$, $p < 0.04$), though this effect was not statistically significant in the smaller matched subsample ($F(1,19) = 1.23$, $p > 0.10$). Follow up analyses to the FA reduction in deaf participants in the aSTG were unable to localize group differences to either RD or AD group differences were not significant for both comparisons (RD: $F(1,46) = 0.24$, $p > 0.10$; AD: $F(1,46) = 0.007$, $p > 0.10$).

Finally, in the tractography-derived pCC ROI (Fig. 2), deaf adults also showed reduced FA ($F(1,46) = 5.24$, $p < 0.03$; subsample analysis: $F(1,19) = 6.1$, $p < 0.03$). Within the pCC, group differences in FA corresponded with increased RD in deaf adults ($F(1,46) = 4.49$, $p < 0.05$; subsample analysis: $F(1,19) = 4.63$, $p < 0.05$) but not AD ($F(1,46) = 1.28$, $p > 0.10$).

In summary, group differences in FA were robust in HG, pSTG, and pCC with these overall group differences corresponding with increased RD rather than AD. There was also evidence for reduced FA in aSTG, but differences in RD and AD were not significant. Evidence for hemispheric differences in FA, RD, and AD manifested only for the pSTG with larger group differences in the right hemisphere, corresponding with increased AD on the left compared to right for deaf participants.

3.2. Volume: temporal lobe ROIs and corpus callosum

Fig. 3 shows white matter volume measures for all four ROI categories. In HG, deaf adults showed overall reductions in volume ($F(1,46) = 30.4$, $p < 0.001$; subsample analysis: $F(1,19) = 11.4$, $p = 0.003$) with a significant interaction between group and hemisphere indicating a reduced hemispheric asymmetry in white matter in the deaf participants – but only in the full sample ($F(1,46) = 6.56$, $p < 0.02$; subsample analysis $F(1,19) = 2.0$, $p > 0.10$). In the aSTG, deaf adults also had reduced volume, though these effects were greater and, in the subsample only apparent in, the right hemisphere (full sample analysis: Group, $F(1,46) = 8.63$, $p = 0.005$, Group x Hemi, $F(1,46) = 12.5$, $p = 0.001$; subsample analysis: Group, $F(1,19) = 1.76$, $p > 0.10$, Group x Hemi, $F(1,19) = 6.51$, $p < 0.01$). In the pSTG, overall reductions in white matter volume were only apparent in the full sample analysis (full sample: $F(1,46) = 6.25$, $p < 0.02$; subsample analysis: $F(1,19) = 1.86$, $p > 0.10$) with no hemispheric differences between groups ($p > 0.10$). Analysis of the tractography-derived pCC ROI did not reveal group differences in volume ($F(1,46) < 1$, $p > 0.10$).

3.3. Heschl's gyrus comparison to the literature

Our temporal lobe volume measures were determined by drawing an anatomical region of interest on a template brain and

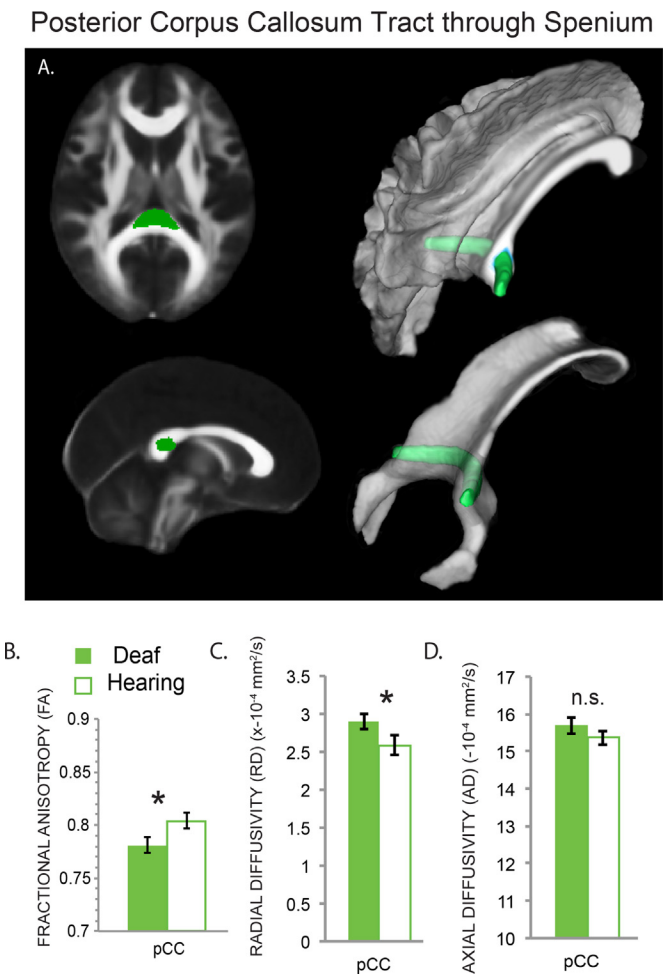

Fig. 2. A) Tractography derived corpus callosum ROI in the splenium (posterior corpus callosum tract: pCC) [Green]. The pCC ROI was determined using tractography to locate tracts connecting the homologous left and right superior temporal gyri. B) FA was reduced in the deaf participants (solid bars) relative to hearing (white bars). C) RD was increased in the deaf participants in the pCC. D) AD was not different between the deaf participants and hearing participants. Error bars represent ±1 S.E.M. *$p < 0.05$, n.s. not significant.

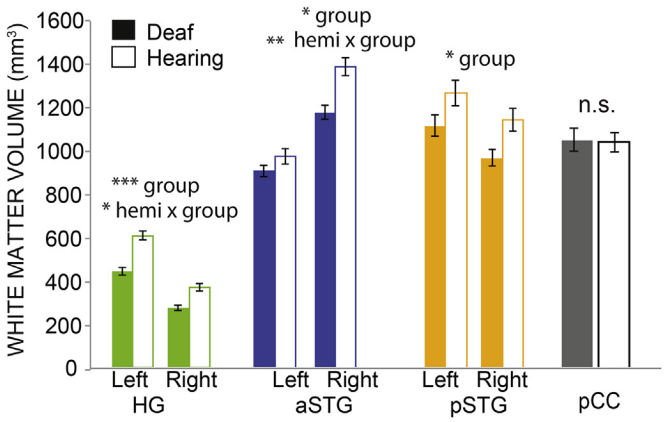

Fig. 3. White matter volumes were derived from our ROIs projected into individual participant native space (HG: Green; aSTG, blue; pSTG orange; pCC tract, black). Deaf participants had smaller white matter volumes in all ROIs. In the aSTG ROI, group differences were larger on the right, but in the HG ROI, group differences were larger on the left. There was no group difference in volume for the pCC tract.

using non-linear transformations based on the FA skeleton to back-project this ROI onto each individual's FA map. This method of ROI demarcation has the advantage of being a semiautomatic approach that does not depend primarily upon rater decisions in individual brains, however its comparability to previously published volumetric analyses has not been established. We compared our HG volumes to those of previous studies that used various HG ROI demarcation methods and also published their mean or individual volume measures for deaf and/or hearing participants. Fig. 4 plots the volume of HG for the left and right hemispheres for the participants in our study relative to published values (Supplementary Fig. 1 also plots the relationship of left to right volume measurements for our study and published studies). None of our white matter volume measures fall outside of the range of published values for left or right HG suggesting that our semi-automated method of WM measurement from DTI, at least in HG, is comparable to other methods of volumetric WM measurements.

4. Discussion

The present study introduced a semi-automatic ROI-based approach in auditory cortex to measure microstructural differences in white matter between deaf and hearing adults. Deaf participants were congenitally, genetically deaf adults who had learned sign language from infancy. Consistent with previous studies using whole-brain approaches, we found reductions in FA in superior temporal lobe regions underlying auditory processing. More specifically, FA reductions observed in the present study included the white matter ridge beneath primary auditory cortex (HG), as well as the superior temporal gyrus anterior and posterior to HG (aSTG and pSTG). FA reductions were also observed in a tractography-defined posterior corpus callosum ROI that connects the left and right anterior superior temporal gyri (pCC). Importantly, this novel tractography-defined approach constrained potential white matter differences in the splenium to those likely to support cortical processing in the superior temporal lobes. As detailed below, these findings also extend prior research in three ways: (Section 4.1) establishing a semiautomatic anatomical methodology for quantifying microstructural differences in auditory cortices, which may be useful to determine the degree to which future studies in special populations drawing on smaller sample sizes reproduce prior results, (Section 4.2) including a systematic characterization of additional measures of radial and axial diffusivity, (Section 4.3) incorporating direct tests of hemispheric asymmetry in white matter microstructure along with volumetric measures.

4.1. A semiautomatic region of interest approach to quantify FA differences in deafness

Whole brain approaches are important for broad characterization of group differences, but this approach has yielded inconsistent findings across previous DTI studies of human deafness. This may be because of constraints of threshold-free cluster correction (TFCE) applied to whole brain analyses (for example the dissimilar results of Li et al., 2011; Hribar et al., 2014). Without discounting the potential utility of a whole-brain approach, we suggest that focusing more strategically on auditory regions to determine the reproducibility of white matter microstructure changes in deafness is important for the field broadly, and will be important for future studies with special populations of deaf participants more particularly.

In the current study, we examine microstructural white matter changes in specific temporal lobe regions that typically show cross-modal reorganization in deafness, specifically primary auditory cortex (HG) and superior temporal lobe regions, and include a tract through the splenium of the corpus callosum, following previous reports that found general FA reductions within the splenium with a whole-brain approach. Our region-of-interest approach (anatomically-defined regions projected back to native space with manual correction) is an approach that we suggest could be implemented by other groups to provide consistency and assess reproducibility across studies. This ROI approach also allowed us to directly test for hemispheric asymmetries, which we discuss further in section 4.3. However, the overall pattern of group FA differences observed in the present study indicate that congenitally, genetically deaf adults show reductions in FA relative to hearing participants in all four temporal lobe regions of interest, which included HG, pSTG, aSTG, and pCC. These findings add to the growing body of literature indicating that atypical auditory white matter occurs in congenital deafness.

4.2. Radial and axial diffusivity measures in auditory white matter

One advantage of DTI over volumetric measures alone is its ability to compare microstructural measures of diffusivity along the

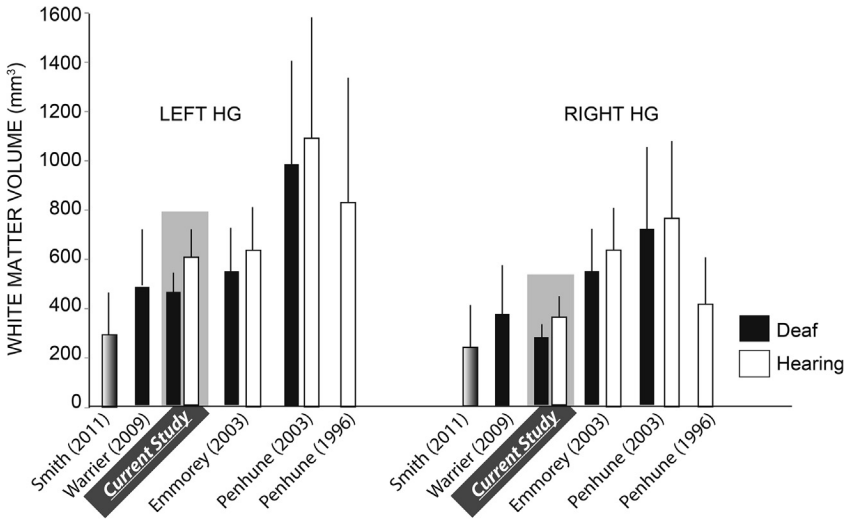

Fig. 4. Heschl's gyrus white matter asymmetry volume: comparison to five published volumetric studies. Our measured volumes from semiautomatic HG ROIs using DTI-based methods are well within the range of volume measures published using other methods. The means from the current study are plotted as means and error bars represent ±1 S.D.

principle directional axis of tensor diffusion versus the non-principle axis, which can elucidate the nature of white matter change within regions that may or may not have different white matter volumes (Hribar et al., 2014). However, not all prior DTI studies of deaf humans have taken advantage of this potential benefit by including analyses of radial diffusivity and axial diffusivity alongside the FA measurements. Yet these additional measures, which are related to white matter pathology reduced myelination with RD and microtubule deficits with AD (Alexander et al., 2007; Song et al., 2002), can aid in the interpretation of overall FA differences, and may also index more complex cytoarchitecture such as increased crossing fibers since tensors model diffusion within several millimeters of white matter tissue (Wheeler-Kingshott and Cercignani, 2009).

Here, we analyzed both RD and AD in any region displaying group differences in overall fractional anisotropy values. In both left and right HG and in pCC, we found deafness was associated with increased RD, but no significant differences in AD. This is consistent with two reports that indicated that superior temporal reductions in FA following deafness can be attributed more to changes in radial than axial diffusivity (e.g. Li et al., 2011; Miao et al., 2013), however a third study reported group differences only for axial and not radial diffusivity (Hribar et al., 2014).

There are at least two accounts consistent with our finding of increased RD in HG and pCC; the increased RD could reflect decreased myelination or it could reflect an increased number of crossing fibers. We cannot definitively adjudicate between these two possibilities. An increased number of crossing fibers would be consistent with increased cross-modal processing in HG and neighboring superior temporal cortex, such as the visual and/or somatosensory processing that we demonstrated in our previous cross-modal functional MRI studies in these participants. In these fMRI studies, there were group differences in cross-modal BOLD signal in anatomically defined HG ROIs as well as superior temporal cortex both anterior and posterior to HG, regions which overlap extensively with those we focused on in the current report (Karns et al., 2012; Scott et al., 2014). Another approach that could relate microstructure to cross-modal plasticity would be a correlational approach which has been useful in some studies (Shiell et al., 2016; Shiell and Zatorre, 2016). We did not perform correlational analyses in the present report because our main purpose in the present study is to clarify microstructural differences between deaf and hearing in auditory cortices using an anatomical ROI approach that does not depend on the idiosyncrasies of different functional imaging studies, an approach we think is an important step for the field. Still, correlational analyses in larger sample sizes will be important in future studies to clarify the potential role of crossing fibers in supporting cross-modal neuroplasticity.

While cross-modal plasticity in auditory cortex in the congenitally deaf can explain some of our results, a second possibility is that higher RD in deaf participants is indexing reduced myelination, either from atrophy or a failure of myelination during development, or perhaps owing to reduced demands for the fast-processing required for auditory perception. This interpretation would also be consistent with the smaller volumes in white matter underlying auditory cortices. Overall, these speculations remain untested, and would be most practical to address in animal studies that can include a thorough post-mortem analysis, providing more conclusive evidence on the reason higher radial diffusivity with lower FA is observed in auditory cortices with congenital deafness.

Overall, our results do not support a simple explanation of group differences. For example, while increased radial diffusivity in deafness (without altered axial diffusivity) was most robust in HG and pCC, this pattern did not generalize across the remaining ROIs. In aSTG, the region where FA differences were smallest, neither RD nor AD group differences reached significance. Based on our results taken together with these other studies, it seems likely that neither AD nor RD alone account for FA group differences in auditory regions. Important for future study is the question of whether there is consistency within specific regions: for example, a consistent pattern of robust RD increases in well-defined HG and pCC with deafness, with less distinct differences between AD and RD in other regions.

4.3. Hemispheric asymmetry in volume and microstructure

A question that has been alluded to, but not directly tested, in prior DTI research on deafness is whether white matter microstructural changes following deafness show hemispheric specificity. In the present study, we directly compared microstructure and volume of structurally homologous anatomically defined regions in the left and right hemisphere. This provided an important statistical test of whether asymmetries suggested but not tested in prior studies are significant.

4.3.1. Group differences in white matter volume asymmetries

Using a DTI-derived approach to extracting the volume of white matter within our semi-automatically demarcated ROIs, we observed gross volumetric asymmetries in the effects of deafness on white matter in HG and the superior temporal gyrus, which is consistent with several previous reports (Emmorey et al., 2003; Hribar et al., 2014; Olulade et al., 2014; Shibata, 2007; Smith et al., 2011). More specifically, we observed decreased HG and aSTG white matter volume in deaf participants, but not pSTG volume suggesting that gross volumetric differences in white matter are not uniform across different auditory processing areas. In contrast to several previous studies (Emmorey et al., 2003; Smith et al., 2011), we observed WM asymmetry in HG via a hemisphere by group interaction. This disparity could be attributed to methodological differences between our DTI based approach and VBM approaches. For example, intuitively it would seem that the FA threshold (anisotropy > 0.2) to classify tissue as white matter used might reduce the volumes in the deaf if they have lower FA, but counter to this explanation is that a threshold anisotropy of 0.2 approaches the diffusion anisotropy of gray matter (Mamata et al., 2004), and is over 3 standard deviations below our lowest mean FA indicating that it is unlikely to account for our results. Furthermore, the group differences in volume we observed do not mirror the FA effects – pSTG hemispheric differences in FA did not translate to hemispheric differences in volume and volume differences in HG did not translate to hemispheric differences in FA. Each projection was inspected in native space to ensure boundaries of the ROI were appropriate and finally, as shown in Fig. 4, the overall magnitude of our DTI-derived volumetric measures in HG are consistent with previously published volumetric measures using various methods suggesting that our approach is valid (Emmorey et al., 2003; Penhune et al., 2003, 1996; Smith et al., 2011; Warrier et al., 2009).

4.3.2. Group differences in white matter microstructure asymmetries

As mentioned above in Section 4.3.1, groups differed in the degree of hemispheric asymmetries in microstructure, but these asymmetries did not occur in the same regions where we observed volume asymmetries, highlighting the utility of DTI as a complementary methodology for understanding structural differences in deafness. The only region where groups differed in microstructure asymmetry was the pSTG. In the pSTG, FA reductions with deafness were larger on the right, and this same asymmetry was observed in the analysis showing corresponding reductions in AD in the deaf sample. AD represents diffusion along the primary axis of the

estimated tensor, and is typically interpreted as integrity of axonal microtubules but as previously noted, this relationship may not hold in regions with complex architecture and more crossing fibers (Wheeler-Kingshott and Cercignani, 2009). As we previously noted, one earlier report found no differences in RD between deaf and hearing, but significant *decreases* in AD in left hemisphere superior temporal and HG regions but not on the right (Hribar et al., 2014) a finding that our direct test of hemispheric asymmetries does not replicate. Future study is needed to resolve this discrepancy before strong conclusions can be drawn and systematic tests of hemispheric asymmetries, as have been useful in volumetric studies (e.g. Smith et al., 2011), will be important to shed light on this critical question.

Although group differences in white-matter asymmetries may not be entirely consistent across studies, it would be unwise to completely discount these findings. Although to our knowledge ours is the first study to directly compare left and right DTI measures, four previous reports with different special populations of deaf participants have suggested that decreases in superior-temporal FA are either more pronounced on the right or correlate more strongly with demographic measures of interest on the right (Hribar et al., 2014; Kim et al., 2009; Li et al., 2011; Miao et al., 2013). Our results indicate that hemispheric and overall group differences in microstructure may be anatomically specific, most pronounced in the portion of the STG *posterior* to HG (pSTG). One potential explanation is that aspects of sign language processing, which generally rely on a similar language network as that of speech (MacSweeney et al., 2008), may recruit the right hemisphere to a greater degree (Newman et al., 2010). As suggested in previous DTI studies (e.g. Hribar et al., 2014) if microstructural differences are larger on the right, this may reflect the demands of sign language. Here, all of our participants were native, fluent signers so we cannot assess this possibility but future studies such as that of Olulade et al. (2014) could include deaf non-signers or hearing native signers to examine the degree to which these differences can be attributed to sign language use per se.

4.4. Limitations

Deafness in humans is developmentally complex and developmental heterogeneity can arise from or co-occur with a variety of factors. Studies of human deafness often vary in the sample of study, and care must be taken when generalizing findings from samples with different etiologies and developmental histories. Our deaf sample included only congenitally-deaf individuals with at least one deaf relative, limited hearing aid use, and who self-reported learning sign language from birth, a population we consider important for our functional studies on cross-modal neuroplasticity (for example by avoiding potential widespread atrophy or brain-damage due to meningitis, premature birth, or drug toxicity). Although our population was not severely educationally deprived – all met a reading screening criterion and the range and mean of non-verbal reasoning was within normal limits – our population did exhibit lower levels of non-verbal reasoning (assessed by a short Ravens measure; Bors and Stokes, 1998) than hearing controls, suggesting additional differences were present in our sample. Previous research indicates that deaf and hearing children have similar IQ (Braden, 1991; Vernon, 2005), though direct comparisons of deaf and hearing adults are not typically reported in studies of human deafness (Vernon, 2005). Thus, it is unknown whether the overall group difference in IQ found here is a sampling artifact, or might be explained by a third factor, such as socioeconomic status or reduced educational opportunity, which are known to correlate with matrices IQ scores (Raven, 2000) but were not collected here.

We took two statistical approaches to address the potential limitation of group differences in non-verbal reasoning, and importantly the main findings were robust using both methods. For example, our first analysis including group mean-centered non-verbal reasoning scores as a covariate did not reveal any significant relationship between the IQ covariate and our microstructure measurements, though we retained the covariate in all analyses. We also performed a second follow-up analysis with a subset of deaf and hearing participants matched for non-verbal reasoning, and almost all findings with the covariate-adjusted full sample were confirmed even in this smaller subsample. The exceptions were the hemispheric asymmetries in FA in the pSTG, the smaller FA difference in aSTG, and group differences in pSTG volume and HG volume asymmetry. Additional research is needed to confirm whether this is due to a smaller sample size in the subsample analysis or whether it meaningfully reflects some effect of non-verbal reasoning on auditory cortex asymmetries in white matter microstructure.

Another potential limitation is that with the specificity of an ROI analysis comes a trade-off in terms of breadth. The ROI approach was valuable as we were guided by prior findings, but we did not test any regions outside of HG and the superior temporal regions. However, we note that the application of an exploratory whole-brain approach with threshold-free cluster correction was not successful in our study. Previous studies indicate that sample size alone does not predict the number of clusters that will survive a cluster-based correction procedure (Hribar et al., 2014; Li et al., 2011). This underscores the tradeoff: In the present study robust group differences were observed with the ROI approach, but a whole-brain analysis would have missed these differences. An *a priori* focus on auditory regions is certainly justified in the case of deafness and an anatomical ROI approach allows specificity of where changes are observed. A further limitation is the assumption that the anatomically defined white-matter regions reflect primarily the functions supported by the cortical regions that enfold them. This assumption is most justified in the case of HG, but tracts in pSTG likely ferry information from various multimodal cortical regions in addition to the auditory cortices (which also have multisensory properties) that they lie beneath. A multimodal imaging approach incorporating functional imaging and DTI such as that employed by Sammler and colleagues could be useful in this regard (Sammler et al., 2015) and there is much opportunity for future research to determine how structure supports functional neuroplasticity in human deafness.

5. Conclusions

In the present study we introduce a method for investigating microstructural and volumetric differences in white matter between congenitally deaf and hearing adults using diffusion-tensor imaging, focusing on auditory regions of interest in the HG, superior temporal gyrus, and splenium of corpus callosum, with direct hemispheric comparisons of both volume and microstructure. Bilateral reductions in FA across all regions of interest indicate that cross-modal plasticity in auditory cortex co-occurs with distinct changes in white-matter microstructure. Neither radial nor axial diffusivity alone accounted for all differences between deaf and hearing suggesting a complex profile of white matter changes that could indicate increased crossing fibers supporting cross-modal neuroplasticity, or reduced demands for myelination in deaf auditory cortex. In contrast to volumetric measures, which showed reductions across HG, aSTG, and pSRG, group differences in hemispheric asymmetry of microstructure were apparent only in one ROI, the pSTG, suggesting that more pronounced microstructural differences in the right-hemisphere may be anatomically and perhaps functionally specific. We suggest that the complex profile

of human deafness requires that studies focus on *a priori* methods such as ROI analyses and the reporting of means and variability statistics rather than only whole-brain statistical maps to ensure reproducibility across studies, to determine which effects generalize to other deaf populations, and to facilitate future meta-analyses. Overall we are optimistic that a more complete understanding of structural and functional neural changes with deafness will not only elucidate basic mechanisms of neuroplasticity, but allow for more advanced interventions to improve the quality of life for deaf individuals.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.heares.2016.07.008.

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