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Structural neuroimaging of the altered brain stemming from pediatric and adolescent hearing loss—Scientific and clinical challenges

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Abstract

There has been a spurt in structural neuroimaging studies of the effect of hearing loss on the brain. Specifically, magnetic resonance imaging (MRI) and diffusion tensor imaging (DTI) technologies provide an opportunity to quantify changes in gray and white matter structures at the macroscopic scale. To date, there have been 32 MRI and 23 DTI studies that have analyzed structural differences accruing from pre- or peri-lingual pediatric hearing loss with congenital or early onset etiology and postlingual hearing loss in pre-to-late adolescence. Additionally, there have been 15 prospective clinical structural neuroimaging studies of children and adolescents being evaluated for cochlear implants. The results of the 70 studies are summarized in two figures and three tables. Plastic changes in the brain are seen to be multifocal rather than diffuse, that is, differences are consistent across regions implicated in the hearing, speech and language networks regardless of modes of communication and amplification. Structures in that play an important role in cognition are affected to a lesser extent. A limitation of these studies is the emphasis on volumetric measures and on homogeneous groups of subjects with hearing loss. It is suggested that additional measures of morphometry and connectivity could contribute to a greater understanding of the effect of hearing loss on the brain. Then an interpretation of the observed macroscopic structural differences is given. This is followed by discussion of how structural imaging can be combined with functional imaging to provide biomarkers for longitudinal tracking of amplification.

This article is categorized under:

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CONFLICT OF INTEREST

The author has declared no conflicts of interest for this article.

Keywords

brain mapping; computational anatomy; deafened brain; morphometry

1 | INTRODUCTION

Sensorineural hearing loss is the most common type of deafness resulting in degraded transmission of acoustic information from the dysfunctional cochleae in the inner ears to the primary auditory cortex and secondary or association cortices in the brain (see Section 2). Such sensory deprivation results in a brain that is structurally different from one with normal hearing. This difference is likely to be related to the degree of hearing loss as well as plasticity induced by the brain adapting to auditory stimuli provided by a hearing aid or cochlear implant and/or visual stimuli provided by lipreading (or speechreading). Further differences can accrue from developing cognitive strategies to compensate for the hearing loss. Thus, the deafened brain has been both an attractive and challenging target of neuroimaging studies since the turn of the new millennium. These studies have been fueled by advances in technologies such as positron emission tomography (PET), magnetic resonance imaging (MRI), functional MRI (fMRI), diffusion tensor imaging (DTI), functional near-infrared spectroscopy (fNIRS), and cortical auditory evoked potential (CAEP) to name but a few.

Figure 1 illustrates the different structural and functional neuroimaging modalities used to examine the brain. At the macroscopic scale, three types of brain tissues can be discerned in a 3D volume of about 250 × 250 × 200 (12.5 M) voxels of 1 mm^3 resolution. These are gray matter, white matter, and cerebrospinal fluid. In general, gray matter is associated with cortical regions and subcortical structures while white matter is associated with connections between cortical regions and subcortical structures. The gray matter within the cortical region contains mostly neuronal cell bodies and unmyelinated fibers while subcortical regions contain deep gray nuclei and white matter contains axonal, usually myelinated, fibers.

The different tissue contrasts provided by MRI scans and the scalar images of fractional anisotropy, mean diffusivity, axial and radial diffusivity derived from DTI scans make it possible to parcellate the brain into hundreds of regions (or groups of regions called lobes) by mapping to atlases. The DTI scan can also generate a color map to indicate the 3D orientation of the white matter connections. Finally, structural images can be registered in common coordinates with functional ones such as fMRI, PET, CAEP, and fNIRS (described in Section 8) so that brain activity in different parts of the brain in response to acoustic and visual stimuli can be studied.

With respect to the three magnetic resonance modalities that exploit the magnetic properties of water molecules in the brain, fMRI has been by far the most popular imaging modality with about a hundred studies of brain activity in the deafened brain in response to visual and acoustic stimuli. In contrast, there have been fewer but an increasing number of MRI and DTI studies examining structural properties of the deafened brain.

The review begins with a brief description of the deafened auditory pathway from the two cochleae to the brain. This is followed by summaries of structural MRI, DTI, and clinical studies of people with hearing loss. The focus will be on populations of pre- or peri- lingual hearing loss with congenital or early onset etiology and postlingual hearing loss in pre-to-late adolescence whose pathologies are distinct from those who acquired hearing loss in adulthood. Next, a discussion on the limited focus on volumetric measures suggests how additional measures of morphometry and connectivity widely used in other structural neuroimaging studies could contribute to a greater understanding of the effect of hearing loss on the brain. Then, an interpretation of the observed macroscopic structural differences is given. This is followed by a summary of how structural imaging can be combined with functional imaging to provide potential biomarkers for longitudinal tracking of amplification. The review concludes with a discussion of future directions and opportunities for expanding neuroimaging studies beyond those done so far.

2 | THE DEAFENED AUDITORY PATHWAY

Figure 2 is a simplified schematic illustration of the transmission of acoustic information along the auditory pathway from the cochleae to the brain. Sensorineural hearing loss is attributed to missing or damaged hair cells in the cochlea in the inner ear (e.g., Ashmore et al., 2010; Fettiplace & Kim, 2014). The result is the diminished ability of the cochlear hair cells to transduce acoustic energy to electrical energy that is transmitted by nerves to the brain. Thus there is a cascade of atrophy resulting in degraded transmission of acoustic information (e.g., Kral, Hartmann, Tillein, Heid, & Klinke, 2000; Saada, Niparko, & Ryugo, 1996; Sanes & Kotak, 2011). Not even amplification provided by hearing aids is sufficient to provide neural activity levels for optimal transmission particularly at high frequencies (e.g., Takesian, Kotak, Sharma, & Sanes, 2013). However, it is clear that the high level stimulation rates provided by cochlear implants improve or restore integrity of neuroanatomical structures at different stages of the auditory pathway (e.g., Chen, Limb, & Ryugo, 2010; Muniak, Connelly, Tirko, O'Neil, & Ryugo, 2013; O'Neil, Connelly, Limb, & Ryugo, 2011; Ryugo & Limb, 2009). Thus, sensory deprivation causes plastic changes within the brain. These changes can be seen clearly at the microscopic scale albeit in post mortem human studies or animal models. There have been few post mortem studies of the auditory cortex and understandably none of babies with hearing loss (Huttenlocher & Dabholkar, 1997; Iyengar, 2012; Moore, 2002; Moore & Guan, 2001; Moore & Linthicum, 2007; Pundir et al., 2012). So, animal models have been used to understand the nature of atrophy at different stages of the auditory pathway (Butler & Lomber, 2013). Yet these microscopic studies have to be reconciled with structural neuroimaging studies at the macroscopic scale in humans which are reviewed in the next three sections.

3 | MRI ANALYSIS OF GRAY MATTER AND WHITE MATTER STRUCTURES IN PEOPLE WITH HEARING LOSS

MRI provides the opportunity to examine gray matter and white matter tissue in the brain at the macroscopic scale of 1 mm^3. Here gray matter characterizes cellular contents of cortical and subcortical structures, while white matter characterizes connections between cortical

and subcortical structures. The different biophysical properties of the water molecules in gray matter and white matter result in different responses to the magnetic field of the scanner. These differences provide the necessary contrasts between gray matter and white matter in 3D volumetric images of the brain (Figure 1). Thus it is possible to quantify morphometric properties of cortical and subcortical gray matter such as volume, surface area, and thickness.

Table 1 indicates there have been 32 structural MRI studies comparing populations of people with and without hearing loss. Figure 3 provides a visualization of the location of the structures implicated in many of these studies. A few observations can be made. First, there is a wide variation in the sample size with larger groups associated with large population centers (Shibata, 2007). Second, these groups are by design homogeneous, that is, the subjects are native users of sign language and generally have not been using hearing aids since infancy. Third, there is also a wide variation in the age in these groups and only one study focused on babies who were being evaluated for cochlear implants (K. M. Smith et al., 2011). Fourth, while morphometry analysis focused on mostly volumes of gray matter and white matter structures, nine measured cortical thickness (Hribar et al., 2014; Kumar & Mishra, 2018; W. Li et al., 2013; J. Li et al., 2012; Pereira-Jorge et al., 2018; Ratnanather et al., 2019; Shiell et al., 2016; Shiohama et al., 2019; Smittenaar et al., 2016) and one measured surface area (Kara et al., 2006). Fifth, weak differences were observed in several structures. Prominent among these are Heschl's gyrus and planum temporale considered as primary and secondary auditory cortices, respectively, which both lie on the dorsal (upper) surface of the superior temporal gyrus (see also Figure 1). Other affected structures included motor cortex; frontal cortex including Broca's area; occipital cortex including early visual areas; corpus callosum; insula; fusiform; cerebellum. Sixth, some reported unilateral differences; others reported that asymmetry was mainly preserved in the temporal lobe specifically Heschl's gyrus, planum temporale, and superior temporal gyrus. The two gray matter connectivity studies (E. Kim et al., 2014; W. Li et al., 2015) suggested increased connectivity between auditory and visual areas as well as weaker connectivity between regions such as temporal and parietal (motor) ones.

Thus, MRI is potentially useful in providing quantitative differences in volumes of cortical regions that play an important role in speech, language and hearing networks. But none of these studies have provided a deeper understanding of the biological effects of hearing loss.

4 | DTI ANALYSIS OF WHITE MATTER STRUCTURES IN PEOPLE WITH HEARING LOSS

DTI provides an opportunity to specifically examine white matter tissue in the brain at the resolution of 1 mm^3. Here, white matter tissue is characterized by the orientation of neural connections between the cortical and subcortical gray matter structures. DTI is a variant of MRI based on the diffusion of water molecules in white matter structures and provides another noninvasive way of analyzing connections between brain structures. The 3×3 matrix representing the tensor model of water diffusion at each voxel in the DTI scan yields an ellipsoid representing the orientation of the neural fibers within the voxel from which

eigenvalues are used to compute scalar quantities (Figure 1) such as fractional anisotropy, radial diffusivity, and mean diffusivity. These measures reflect the biophysical properties of the neurons passing through the voxel. For example, larger fractional anisotropy values indicate “dense axonal packing” (Feldman, Yeatman, Lee, Barde, & Gaman-Bean, 2010) while larger values of radial diffusivity indicate “axonal degeneration” and mean diffusivity is sensitive to “cellularity” (Tromp, 2016). The three corresponding eigenvectors are used to compute the color contrast map (Mori, Wakana, & Van Zijl, 2004).

Table 2 indicates there have been 23 DTI studies comparing populations of people with and without hearing loss. Aside, Table 2 is similar to a summary table (Tarabichi et al., 2018). Figure 3 provides a visualization of the location of the white matter structures implicated in these studies. Again, a few observations can be made. First, with the exception of three studies all focused on homogeneous groups of hearing loss. One exceptional group consisted of adults who started using sign language in adolescence (Lyness et al., 2014), and two groups consisted of babies and young children prior to cochlear implantation (S. Wang et al., 2019; H. Wang et al., 2019). Second, there is again a wide variation in larger sample sizes from large population centers. Third, the analyses are mostly confirmatory in that differences in scalar measures, that is, fractional anisotropy (and sometimes radial diffusivity, mean diffusivity, and axial diffusivity) are seen in the temporal and occipital regions such as the acoustic radiation (or auditory tract), the optic radiation, superior temporal gyrus, corpus callosum, and with one exception (Cheng et al., 2019) the longitudinal fasisculi which connect the auditory and language cortical regions. Fourth, the two studies that focused on white matter connectivity were the ones at the scanner strength of 1.5 T, and one study not surprisingly revealed correlations in thalamo-cortical connections with temporal, parietal, motor, somatosensory, frontal and occipital lobes (Lyness et al., 2014).

Thus, DTI can be potentially useful in providing quantitative differences in connections between cortical and subcortical regions affected by hearing loss. Also combining MRI and DTI could be one way to uncover how people with hearing loss perform audio-visual integration tasks such as lipreading. To address this one would need to examine whether the long range white matter optic radiation tract connecting the occipital lobe and thalamus overlaps with the short range white matter tracts connecting the Heschl's gyrus and planum temporale (Figure 4).

5 | CLINICAL MRI AND DTI SCANS OF PEOPLE WITH HEARING LOSS

The advent of cochlear implants has dramatically changed the landscape of auditory habilitation and rehabilitation for more than 350,000 children and adults with hearing loss worldwide (Zeng & Canlon, 2015). This achievement was recognized by the 2013 Lasker-DeBakey Clinical Research Award (Hampton, 2013; Holmes, 2013; Niparko, 2013; Roland & Tobey, 2013; Williams, 2013), the 2015 National Academy of Engineering Russ Prize (Clark, 2014; Hochmair, Hochmair, Nopp, Waller, & Jolly, 2014; Merzenich, 2015; Wilson, 2014), and the 2018 Shambough Prize for the developers of the multichannel cochlear implant.

Prior to surgery, patients have computer tomography or MRI scans of the temporal bones encasing the cochleae (Schwartz & Chen, 2014; Sweeney et al., 2014; Teschner, Polite, Lenarz, & Lustig, 2013; Young, Ryan, & Young, 2014). With respect to whole brain scans, Table 3 lists 15 reports of structural MRI and DTI studies. These studies are prospective and thus the sample sizes are larger than those reported in research studies. Not surprisingly many studies involved pediatric subjects if only to exclude the possibility of abnormalities in the central nervous system. In general, the observed white matter changes are linked with immature myelination possibly due to abnormal neuronal processes that occur in the developing embryo (Long, Wan, Roberts, & Corfas, 2018). But two studies correlated structural differences mainly in the connections from thalamus to the frontal and temporal cortical lobes with positive outcomes. Due to the risk of device displacement, MRI and DTI are contraindicated for people with cochlear implants. So it is imperative that quantitative analysis such as connectivity and topography be considered at baseline in future studies if reasonable imaging biomarkers for predicting positive outcomes with cochlear implants are to be developed.

6 | MORPHOMETRY AND CONNECTIVITY OF STRUCTURES AFFECTED BY HEARING LOSS

A concern about MRI and DTI studies so far is the focus on volume. Volumes for closed structures such as subcortical ones can be interpreted. But that may be not the case for the cortical regions forming the highly folded ribbon that constitutes the cortex (Figure 1). This raises three points. First, the above studies were based on whole brain analyses which revealed inconclusive information about the effect of hearing loss on brain structures. In contrast, a region of interest approach based on networks of hypothesized structures maybe more meaningful and sensitive (e.g., Giuliani, Calhoun, Pearlson, Francis, & Buchanan, 2005) for generating biomarkers for positive outcomes for clinical procedures such as auditory training. This is where information from functional neuroimaging studies of language, speech and hearing may be helpful in focusing on structures hypothesized to be affected by hearing loss (see Section 8). Second, volume should be viewed as the product of two independent measures—surface area and thickness—to reflect the laminar structure of a cortical region (Dahnke & Gaser, 2018; Wagstyl & Lerch, 2018). This structure is brought about by the folding of the cortex to maximize cortical surface area in a confined space. Each cortical region is composed of fundamental units called cortical columns (Rakic, 1995, 1988) that traverse from the white matter to just beneath the skull. Also, each cortical region is composed of six layers which are stacked on top of each other such that thin layers in one part of the region are thicker in another part via the equivolumetric model of the cortex (Bok, 1929, 1959). Thus surface area and thickness may be associated with the distribution or density of cortical columns and the total thickness of the six layers, respectively. So, decreased or increased cortical volume may be misleading. In fact, decomposing volume into surface area and thickness was suggested for the primary auditory cortex in people with normal hearing by Meyer, Liem, Hirsiger, Jancke, and Hanggi (2014) who concluded that thickness and surface area should be quantified as separate measures. Also, given the possible effect of genetics on hearing loss (Dror & Avraham, 2009; R. J. H. Smith, Shearer, Hildebrand, & Van Camp, 1993) specifically in the development of cortical columns, it may

be best to analyze thickness and surface area separately (Panizzon et al., 2009; Winkler et al., 2010). A more recent study suggested that cortical thickness may be an useful biomarker for identifying shape and location of the primary auditory cortex (Zoellner et al., 2019). In addition, more realistic measures of cortical thickness can be developed via sophisticated equivolumetric models for the cortex (Ratnanather et al., 2019; Younes, Kutten, & Ratnanather, in press). Third, in particular for subcortical structures which have not been examined in great detail, it may be helpful to perform shape analysis (Faria et al., 2015; Miller et al., 2013, 2014; Mori et al., 2013; Ratnanather, Liu, & Miller, 2020) given the role the thalamus plays in the auditory pathway (Figure 2). Here, shape biomarkers are determined from computations of deformations of the structure relative to a template. This allows for determining atrophied subregions of the structure. Such data could be useful in determining specific pathways of degeneration between structures.

Furthermore, thickness may be correlated to brain activity in auditory cortical areas. First, acoustic fMRI studies have shown increased neural activity in the primary auditory cortex (Patel et al., 2007; Tan et al., 2013). Second, given the importance of CAEP biomarkers in assessing neural activity with amplification via hearing aids or cochlear implants (J. D. Campbell, Cardon, & Sharma, 2011; Sharma, Dorman, & Spahr, 2002), Liem, Zaehle, Burkhard, Jancke, and Meyer (2012) showed that the first negative amplitude (N1) of CAEP waveform responses strongly correlated with cortical thickness of the superior temporal gyrus which encompasses both the Heschl's gyrus and planum temporale (see Figure 1). Third, following PET studies gray matter density (Duncan, Gravel, Wiebking, Reader, & Northoff, 2013) and thickness (la Fougere et al., 2011) were found to correlate with gamma-aminobutyric acid (GABA) binding within cortical regions. As GABA is the primary inhibitory neurotransmitter in the brain and plays a crucial role in regulating neuronal activity, different rates of neural activity from the thalamus to the auditory cortex may be attributed to differences in GABA density distribution (Takesian et al., 2013) and possibly thickness.

To illustrate the possible benefits of analyzing cortical thickness, consider the Labeled Cortical Distance Mapping (LCDM) technique (Miller et al., 2003; Miller, Massie, Ratnanather, Botteron, & Csernansky, 2000; Ratnanather et al., 2013, 2014). LCDM generates histograms of distances of gray matter voxels relative to the gray/white surface of the cortical region. In turn this gives rise to laminar thickness derived as the 95th percentile and the corresponding volume (as the area under the histogram). The shape of an individual LCDM for a cortical region is influenced by the folding of the region. A flat region yields a “top-hat” LCDM while a folded region with variable thickness yields a “skewed” LCDM; similar profiles have been observed for whole brains (Hutton, De Vita, Ashburner, Deichmann, & Turner, 2008). Together with the corresponding surface areas, LCDMs can be analyzed in different ways via statistical tools (Ceyhan et al., 2011, 2013). Figure 5 shows individual LCDMs for the left and right Heschl's gyrus and planum temporale in a pilot study of five adults with hearing loss and matched controls (Ratnanather et al., 2019). This study was challenging because more subjects could not be recruited having acquired a cochlear implant by the time they were contacted. Nonetheless, the statistical power of pooled (grouped) analysis (Ceyhan et al., 2011) can provide useful information with significant p-values from one-sided Kolmogorov–Smirnov tests ($\leqslant .0001$) for the pooled

LCDM for the adults with hearing loss to be the left of that for the control subjects. As discussed in the next section, this suggests that in these auditory cortical areas there may be some similarities at smaller distances but differences at larger distances which have interesting interpretations at the microscopic level.

It is worth noting that after using hearing aids since infancy, four of the five subjects with hearing loss now have cochlear implants with excellent speech comprehension in quiet situations. This suggests the structural benefit of providing auditory stimulus to the brain via hearing aids as soon as hearing loss is diagnosed. The difference in the shape of the LCDMs may reflect the delayed maturation of synaptic activity (Huttenlocher & Dabholkar, 1997) followed by synaptic pruning (Selemon, 2013) in the developing brain. The pooled distributions suggest little differences in the left Heschl's gyrus which is associated with temporal processing (Marie, Maingault, Crivello, Mazoyer, & Tzourio-Mazoyer, 2016) and some differences on the right Heschl's gyrus which is associated with spectral processing (Marie et al., 2016). The former may be attributed to auditory training used in listening and spoken language after early detection and intervention with hearing aids as infants while the latter may be attributed to high frequency hearing loss. By comparison, thicker visual cortical areas have been observed in people blinded since infancy (J. Jiang et al., 2009).

As for DTI, two studies combined with functional studies of hearing loss have yielded interesting correlations. First, brain waveform activity correlated with increases in fractional anisotropy measures of the brainstem specifically the inferior colliculus (Reiman et al., 2009). Second, aerobic exercising by children with hearing loss resulted in improved executive function associated with reshaping white matter integrity in several structures (Xiong et al., 2018). DTI also offers the potential to visualize the topography of structures such as the acoustic radiation and optic radiation (Figure 4) as well as other long range white matter tracts that play different but important roles in processing of speech and language (Friederici, 2012). Recently, Dhir et al. (2020) showed that it was possible to generate the acoustic radiation in clinical scans as opposed to research scans which require long scan times. For the same deaf adults studied in Figure 5, they confirmed the findings of Maffei (2017) who suggested that lower fractional anisotropy values may be associated with poor myelination in the acoustic radiation which may account for weaker neural transmission.

7 | INTERPRETING STRUCTURAL MRI AND DTI CHANGES CAUSED BY HEARING LOSS

It would appear from MRI and DTI studies so far that subtle structural changes occur in the Heschl's gyrus and planum temporale. These two structures are the primary and secondary auditory cortical regions, respectively. Granted that other structures particularly association cortical regions in the speech and language network are also affected, an interpretation of these macroscopic changes with respect to the microscopic observations from animal models of hearing loss is now given.

One of the most advanced and well developed animal model of cortical activity stemming from cochlear implants has been the cat (Kral, 2013; Raggio & Schreiner, 1994, 1999, 2003; Ryugo & Menotti-Raymond, 2012; Schreiner & Raggio, 1996). Specifically,

electrophysiological measurements across the six layers of the primary and secondary auditory cortices have revealed the effect of the absence of neural activity in the sensitive period of development (Eggermont & Ponton, 2003; Kral, 2013; Kral & Tillein, 2006; Kral & Eggermont, 2007; Kral, Tillein, Heid, Hartmann, & Klinke, 2005; Kral, Tillein, Heid, Klinke, & Hartmann, 2006). Specifically, there is a delay in the synaptic activation of the upper (supragranular) layers and virtual absence of activity in the lower/deep (infragranular) layers. The absence of activity in the lower/deep layers may be attributed to incomplete development and alteration of information flow to and within the primary auditory cortex. While neurons project from the upper layers of the primary area to the secondary areas, some project back to lower/deep layers of the primary area. Thus the absence of activity in the lower/deep layers suggests that the primary auditory area is decoupled from the secondary area, and the feedback loop is weakened. In this decoupling hypothesis (Kral et al., 2005) illustrated in Figure 6, the secondary area is no longer able to provide “top-down” cognitive processing which is helpful for comprehension of spoken language (Kral & Eggermont, 2007). At the same time, the upper layers are unable to perform “bottom-up” processing which is helpful for discerning phonemes that are the basic elements of spoken language.

The LCDMs of adults with hearing loss (Figure 5) who had been using listening and spoken language via hearing aids since infancy suggest that the decoupling mechanism can be averted with consistent use of amplification. Indeed, the similarities (with small variance) at smaller LCDM distances corresponding to the lower/deep layers suggest that sufficiently aided adults with hearing loss can develop linguistic understanding and the larger differences (with larger variances) at LCDM distances corresponding to the upper layers suggest that these adults may be able to understand speech only in quiet. Thus the shapes of LCDMs may reveal a little more information about the upper and lower layers than just the overall laminar thickness that is computed from the distance between the gray/white and gray/inner surfaces. But for morphometry of the layers one may need to consider equivolumetric models of cortical folding (Ratnanather et al., 2019; Younes et al., in press).

However, the weaker input from the thalamus to the auditory cortex may manifest in diverted inputs to other cortical areas such as the parietal (motor) cortex as observed in 3D reconstruction of CAEP activity in late implanted children (lower right panel in Figure 6 [fig. 3 of Gilley et al., 2008]). This suggests that hearing loss results in two-speed thalamic transmission (Takesian et al., 2013). One conjectures that the demyelinated thalamo-parietal pathway cannot tolerate the high activity levels stemming almost immediately after activation of the cochlear implant, thus enforcing the neural transmission along the acoustic radiation to the Heschl's gyrus (top and middle right panels in Figure 6 [fig. 2 of Gilley et al., 2008]).

However, more substantial quantitative analysis of morphometry and connectivity is needed to provide a more complete model of the structure and functional relationship between cortical and subcortical structures in the deafened brain.

8 | COMBINING STRUCTURAL AND FUNCTIONAL IMAGING FOR LONGITUDINAL TRACKING OF AMPLIFICATION

It is constructive to see how recent functional neuroimaging technologies could be combined with structural imaging to shed light on the benefits of amplification on the deafened brain. The importance of functional changes accruing from amplification cannot be understated (J. D. Campbell et al., 2011; Cardin et al., 2013; Shiell, Champoux, & Zatorre, 2015). So changes in the brain due to amplification should correlate morphometric and connectivity measures with data derived from CAEP (Gilley et al., 2008; Liem et al., 2012), PET (Barone, Lacassagne, & Kral, 2013; Lazard, Lee, Truy, & Giraud, 2013; Liem, Hurschler, Jancke, & Meyer, 2014; Strelnikov et al., 2014), fMRI (Patel et al., 2007; Tan et al., 2013), and fNIRS (Lawler, Wiggins, Dewey, & Hartley, 2015; Sevy et al., 2010).

In particular, functional neuroimaging should be combined with structural neuroimaging in longitudinal studies of amplification or auditory training (Boothroyd, 2010). This could be achieved via MRI (Teschner et al., 2013) as well as DTI and resting state fMRI (Z. Li et al., 2015; B. Liu et al., 2015; Zhang et al., 2015) followed by one of PET, CAEP, or fNIRS. In the case of cochlear implants, MRI, DTI and fMRI can only be done at baseline prior to surgery. A possible translational study would be to find regional or subregional biomarkers in the superior temporal gyrus that correlate with phonetic processing of speech with amplification (Boatman, 2004; Crinion, Lambon-Ralph, Warburton, Howard, & Wise, 2003; Mesgarani, David, Fritz, & Shamma, 2014; Nourski & Howard 3rd, 2015).

The notion of a “sensitive” period in sensory neurodevelopment (Knudsen, 2004) alluded to in the previous section is supported by CAEPs which are noninvasive electroencephalography measurements that track the maturation of the central auditory system via changes in latency and amplitude (Steinschneider, Nourski, & Fishman, 2013). The first positive peak (P1), which is a summation of synaptic activities and neuronal conduction times as the signal travels from the ear to the primary auditory cortex, decreases with age in children with normal hearing (Eggermont & Ponton, 2003). Prompted by the seminal work by Ponton et al. (1996), Sharma et al. (2002) performed what is now a landmark study of children with cochlear implants. They observed that children with shortest period of deprivation (i.e., absence of auditory stimuli) of 3.5 years or less had P1 latencies fall into the normal range about 6 months after implantation while those with deprivation periods of 7 years or more had abnormal CAEPs. Similar observations were seen in children who used hearing aids consistently even before getting a CI (J. D. Campbell et al., 2011). Also, the first negative peak (N1) which manifests itself post-adolescence in normal hearing also occurs in people who had been using amplification since infancy (Sharma, Campbell, & Cardon, 2015).

Evidence suggests that P1 and N1 latencies reflect neural generators from thalamo-cortical projections to the primary auditory cortex in the Heschl's gyrus and the secondary auditory cortex in the planum temporale, respectively (Liegeois-Chauvel, Musolino, Badier, Marquis, & Chauvel, 1994) together with second order processing via a feedback loop between the primary and secondary auditory cortices mentioned earlier (Kral & Eggermont, 2007). Gilley et al. (2008) observed bilateral activation of the auditory cortical areas (superior

temporal gyrus and inferior temporal gyrus) in normal hearing children. Children who received cochlear implants at an early age showed activation in the auditory cortical areas (contralateral to the implant) which were similar to those in normal hearing children while activation in late-implanted children was severely compromised. This led to the decoupling hypothesis (Kral et al., 2005) which may be the basis of cross-modal plasticity via increased activity in occipital and motor lobes. This notion of visual dominance in audio-visual integration and/or takeover of the auditory areas by visual stimuli was suggested by Bavelier and Neville (2002). It is worth noting that Shiell et al. (2015) observed that consistent use of hearing aids (i.e., amplification) resulted in reduced visual fMRI activity in contrast with those who did not use hearing aids. These differences have also been observed in a recent fMRI study of different groups of people using hearing aids or sign language (Cardin et al., 2013).

For people with hearing loss, fMRI is challenging because it is uncertain whether the subject would be able to comprehend speech especially if the degree of hearing loss is profound given the noisy environment of the scanner. fMRI measures brain activity detecting changes associated with increased blood flow into a cortical region that is responding to stimuli such as speech. A few laboratories have been able to provide acoustic stimuli through tubephones and headphones customized to deliver sound levels up to 130 db with low distortion, flat frequency response, reliable phase and noise cancellation (Hall & Paltoglou, 2009). While there have been no reported studies of people with hearing loss with these customized devices, another group has examined the use of fMRI in sedated babies prior to cochlear implantation (DiFrancesco, Robertson, Karunanayaka, & Holland, 2013; Patel et al., 2007; Schmithorst et al., 2005). They demonstrated that levels of brain activity as a reflection of hearing levels in the primary auditory cortex correlated strongly with the improvement in hearing after getting a cochlear implant. More recently, the same group applied pattern classification methods to results of MRI and fMRI data to make some predictions about speech and language outcomes in babies who then received a cochlear implant (Deshpande, Tan, Lu, Altaye, & Holland, 2016; Tan et al., 2013). Others have observed brain activity at low frequencies in the auditory cortex of people with partial hearing loss (Skarzynski et al., 2013) and positive changes in activation of the auditory cortex after a period of using hearing aids (Hwang, Wu, Chen, & Liu, 2006). So it ought to be possible to adapt tubephones or headphones to create a hearing aid-like transfer function rather than a flat one (e.g., Palmer, Bullock, & Chambers, 1998) to examine how the brain functions with hearing aids.

Given the contraindication of ferromagnetic properties of cochlear implants with MRI scanners, PET has emerged as a tool for longitudinal tracking of cochlear implants. PET measures metabolic processes in the brain so cortical regions that are actively responding to stimuli such as speech have increased metabolism (D. S. Lee et al., 2001). Significant brain reorganization in the first few months after cochlear implantation has been observed mainly in the left superior temporal gyrus and Broca's area in the frontal cortex of subjects with postlingual hearing loss but not those with prelingual hearing loss (Petersen, Gjedde, Wallentin, & Vuust, 2013). This suggests that prior experience of language which is the case in the former group is a good indicator of positive outcomes. Further, visual cues may have a positive effect on auditory perception (Strelnikov et al., 2014) which suggests audio-visual

integration plays an important role in brain plasticity (R. Campbell, MacSweeney, & Woll, 2014). Earlier studies reviewed by Giraud and Lee (2007) suggested that resting metabolism can be a good measure of speech performance after cochlear implantation and changes in PET activity reflect adaptation in higher order cognitive processes.

A major limitation of PET is the use of radioactive tracers which limits the ability to perform longitudinal analysis over a short period especially when plasticity changes are significant. This could be overcome by fNIRS which has just emerged in the past decade as a potentially useful tool (Sevy et al., 2010). Here as in fMRI, neuronal activity results in changes in levels of oxygen in blood but with near-infrared light passing through brain tissue. It is now possible to assess activity in the auditory cortex in response to speech (Lawler et al., 2015), differentiate from scrambled speech as a measure of outcome with amplification (Pollonini et al., 2014), lipreading before and after cochlear implantation (Anderson, Lazard, & Hartley, 2017; Anderson, Wiggins, Kitterick, & Hartley, 2017) and speech and language processing (Bortfeld, 2019; McKay et al., 2016; Zhou et al., 2018). Limitations such as sensitivity and accuracy of quantification of brain activity in deeper cortical regions (e.g., the Heschl's Gyrus) may be resolved by newer optical measurements (Hasnain, Mehta, Zhou, Li, & Chen, 2018; Mehta et al., 2017).

9 | FUTURE DIRECTIONS AND OPPORTUNITIES

This review has revealed limitations that make it difficult to make inferences about plastic changes in the brain caused by hearing loss regardless of whether amplification was used or not. Several suggestions are offered that could increase the impact of structural neuroimaging as a biomarker to aid the development of speech, language, and hearing.

Future studies should extend beyond homogeneous groups that in fact represent a very small segment of the spectrum of people with hearing loss. In fact, the World Health Organization estimated that 15% of the world's population has a hearing loss of which a third, that is, 360 million, have a disabling hearing loss (World Health Organization, 2013) ranging from partial to profound. Further, the World Federation of the Deaf estimates that 70 million use sign language (http://wfdeaf.org/faq). This means that these homogeneous groups characterize just 6% of people with hearing loss. Only one neuroimaging study considered this limitation and attempted to provide new answers (Olulade et al., 2014).

Studies should go beyond the structures other than the ones known to play an important role in speech, language, and hearing. Granted that hearing loss has broad consequences for the developing and maturing brain, it is important to discern the different forms of plasticity in the brain. Use of more quantitative and sophisticated analyses of morphometry and connectivity measures could go a long way to deepen understanding of the biological substrates of plasticity. Further, these methods could be useful for analysis of structural neuroimaging of other types of hearing loss such as aged-induced hearing loss (Eckert et al., 2013; Eckert, Cute, Vaden, Kuchinsky, & Dubno, 2012; F. R. Lin et al., 2014; Peelle, Troiani, Grossman, & Wingfield, 2011; Vaden, Kuchinsky, Ahlstrom, Dubno, & Eckert, 2015), unilateral hearing loss (Rachakonda, Shimony, Coalson, & Lieu, 2014; C. M. Wu, Ng, & Liu, 2009; Yang et al., 2014) and tinnitus (Husain et al., 2011).

Studies should also consider federating neuroimaging datasets by archiving data from all over the world. The sample sizes given in Tables 1 and 2 are relatively small compared to those in recorded in other structural neuroimaging studies. On the other hand, the wider spectrum of people with hearing loss calls for alternative and more sophisticated statistical tests to deal with sizes and heterogeneity of these samples; for example, snowball sampling (Cardin et al., 2013) or pooling (Ceyhan et al., 2011). Federation is becoming common in neuroimaging projects such as schizophrenia (Alpert, Kogan, Parrish, Marcus, & Wang, 2015) and the ENIGMA project for many neurodegeneration and neurodevelopmental diseases (Thompson et al., 2014). This is where “Big Data” analytical tools such as data mining (Ramos-Miguel, Perez-Zaballos, Perez, Falconb, & Ramosb, 2014; Tan et al., 2013) could be used to uncover potential biomarkers for positive outcomes for amplification. Combining such data will require techniques such as diffeomorphometry (Miller et al., 2014; Ratnanather et al., 2020) to map imaging data to common coordinates for analysis and comparison. Personalized inference of clinical and behavioral data could then be achieved (Faria et al., 2015; Miller et al., 2013; Mori et al., 2013). A significant step in that direction was taken by Feng et al. (2018) who used machine learning methods to find that neural structures unaffected by auditory deprivation were best predictors for outcomes with cochlear implants in young children.

10 | CONCLUSION

Plastic changes in the brain due to pre- or peri-lingual pediatric hearing loss with congenital or early onset etiology and post-lingual hearing loss in pre-to-late adolescence are seen to be multifocal rather than diffuse. Differences are consistent across most of the regions implicated in the hearing, speech and language networks in the brain (Friederici, 2012) regardless of modes of communication and amplification, be these via listening and spoken language or sign language. To a lesser extent, structures in networks that play an important role in cognition are affected (X. M. Xu et al., 2019b). Quantitatively differences are subtle for some structures and variable for other structures. That said, it is remarkable that the asymmetry properties of the structures in the hearing, speech and language pathways are mostly preserved. Yet, little is known about the deeper underlying biological effects of hearing loss on the brain. For example, one asks what are the structural consequences of limited acoustic stimuli that belies demyelination (Long et al., 2018) and increasing fatigue and effort associated with listening (Willis, 2018). If the classic tensegrity model of brain connectivity by Van Essen (1997) holds, then one may expect to see weaker tension in the white matter fibers connecting cortical regions responsible for auditory function. In turn, the weaker tension could result in abnormal cortical folding with weaker mechanical forces upon the thicker and shallower sulcal fundi (cortical folds or valleys). This will have mechanical and morphological effect on the deep layers that have been observed to be inactive in animal models of auditory deprivation. Such an interpretation remains to be tested at the macroscopic level. However, new methods that are capable of analyzing properties of the acoustic radiation, optic radiation, thalamo-cortical, and cortico-cortical connections may contribute to a greater understanding of the anatomical pathologies of hearing loss in the brain. Thus there is a need for clinical neuroimaging to uncover

biomarkers for longitudinal tracking and monitoring of progress with amplification provided by either cochlear implants or hearing aids.

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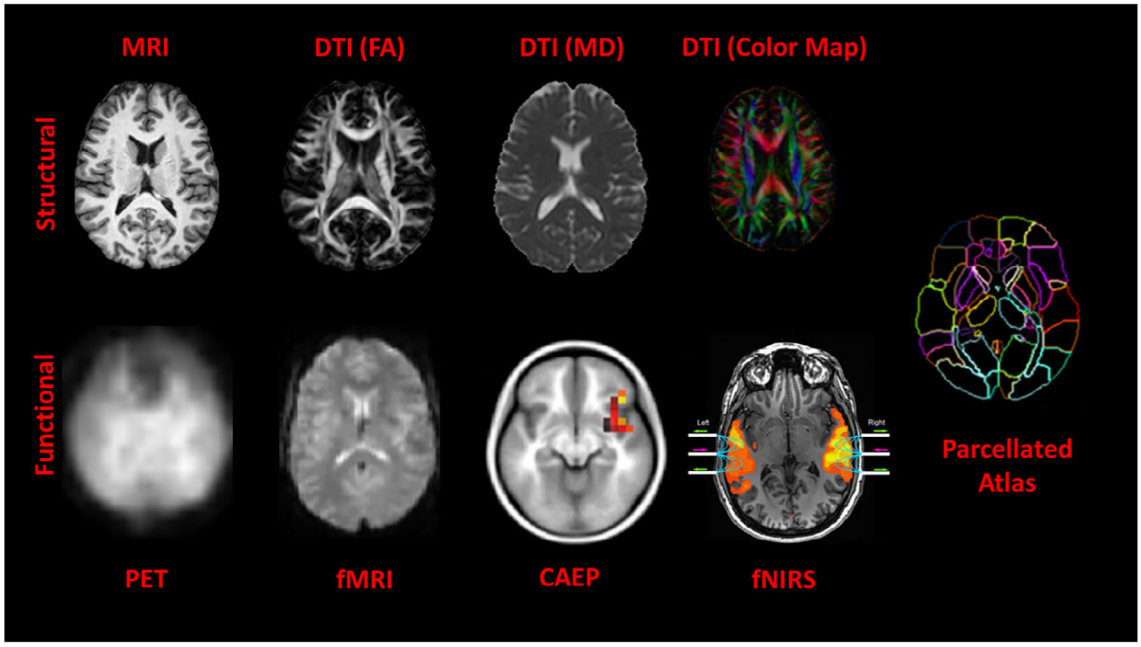

FIGURE 1.

Different image modalities stratified into structural (top row) and functional (bottom row) imaging. The different contrasts at the macroscopic level of 1 mm^3 provide information about three types of tissues: gray matter, white matter, and cerebrospinal fluid. An MRI scan provides a view of the highly folded cortex (shown in light grayscale) and the underlying white matter (shown in bright grayscale). The scalar modalities (FA, MD, and color map) derived from DTI scans provide different ways of looking at white matter structures. The red, green, and blue colors in the color map indicate orientation in the left–right, anterior–posterior, and superior–inferior directions, respectively. The PET and fMRI scans provide a view of responses to brain activity. CAEP and fNIRS brain activity are overlaid on MR scans for reference. Activity associated with the first positive peak in the CAEP waveform (i.e., P1) is located in the primary auditory cortex contained within the Heschl's gyrus. (Reprinted with permission from Sharma et al. (2016, fig. 2). Copyright 2016, Wolters Kluwer Health) Activity associated with speech is located in the superior temporal gyrus containing Heschl's gyrus and planum temporale (often called the primary and secondary auditory cortex) on both sides (Reprinted with permission from Figure 2b in Sevy et al. (2010). Copyright 2010, Elsevier). Mapping these scans to parcellated atlases provides an opportunity to perform quantitative analysis of structural and functional data in common coordinates (Miller, Faria, Oishi, & Mori, 2013; Miller, Younes, & Trouvé, 2014; Mori, Oishi, Faria, & Miller, 2013)

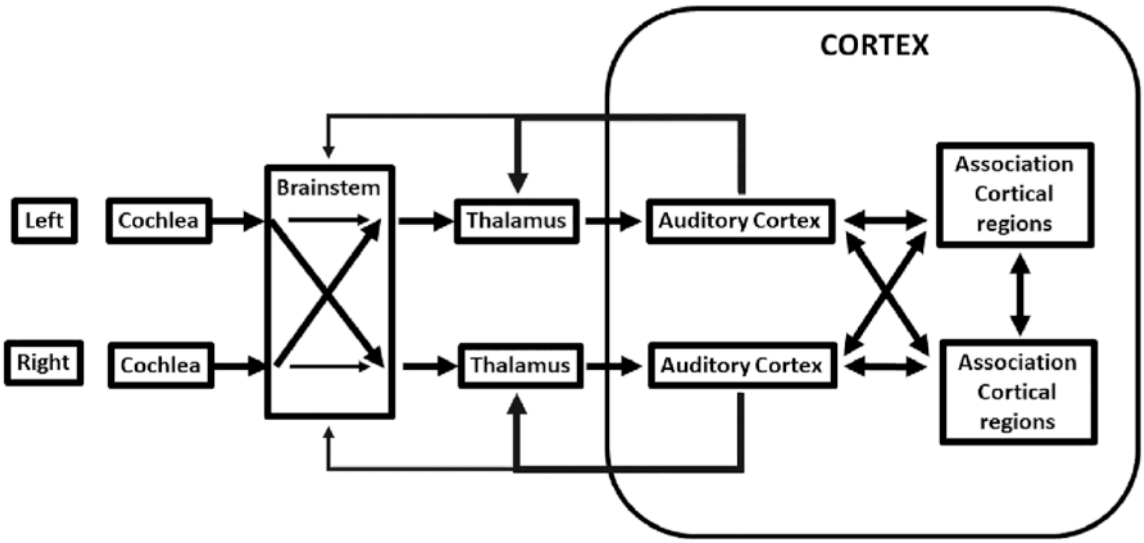

FIGURE 2.

Simplified schematic illustration of transmission of acoustic information from the left and right cochleae to the brain. Note information crosses over in the brainstem as well as in the cortex. Please refer to Figures 3 and 4 for association cortical regions such as planum temporale. The white matter connections include those between primary and associated cortical regions and those that project back to other structures via the thalamus and brainstem

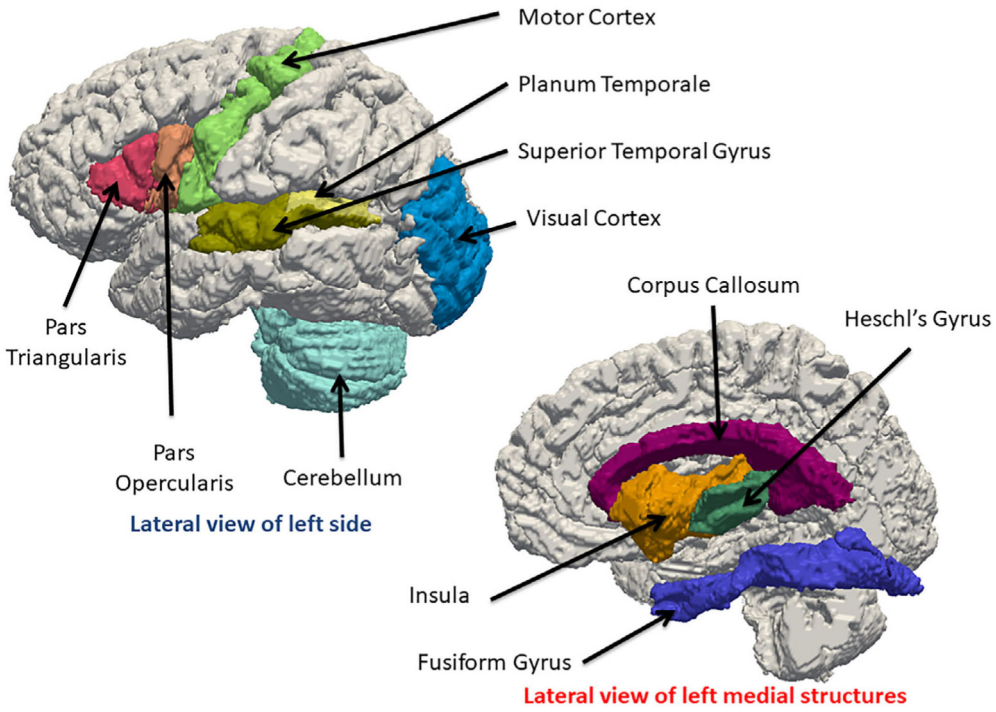

FIGURE 3.

3D visualization of gray matter and white matter structures found to be different in people with hearing loss based on Table 1. Please refer to Figure 2 for the possible roles these structures play in the auditory pathway. Upper left shows the lateral view of the left side of the JHU-MNI-SS brain (Oishi et al., 2009); lower right shows the lateral view of the left medial structures adjacent to the mid-sagittal plane of the right hemi-brain. The cortical structures (Pars Triangularis, Pars Opercularis, Motor Cortex, Superior Temporal Gyrus, Planum Temporale, Visual Cortex and Cerebellum, Heschl's Gyrus, Insula, Fusiform Gyrus) and one white matter structure (corpus callosum) were obtained from the JHU-MNI-SS labels and triangulated. CAWorks (www.cis.jhu.edu/software/caworks) was used for visualization

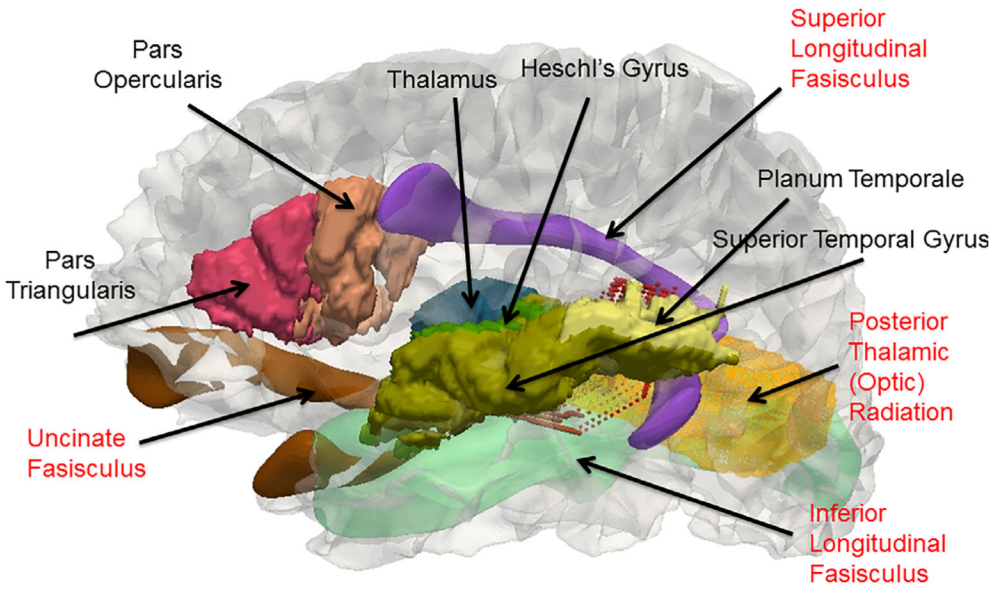

FIGURE 4.

3D visualization of connectivity between cortical and subcortical structures found to be different in people with hearing loss based on Tables 2 and 3. Please refer to Figure 2 for the possible roles these structures play in the auditory pathway. The lateral view of the left side of the gray/white surface of the JHU-MNI-SS template (Oishi et al., 2009) generated by FreeSurfer and transferred to native space (Fischl, 2012) is shown. The cortical structures (Pars Triangularis, Pars Opercularis, Superior Temporal Gyrus, Planum Temporale, Heschl's Gyrus), one subcortical structure (Thalamus), and the white matter Posterior Thalamic Radiation tract which contains the optic radiation were obtained from the JHU-MNI-SS labels and triangulated. The other white matter fasisculi structures were obtained from the IXI template (Yushkevich, Zhang, Simon, & Gee, 2008) and transferred via diffeomorphic mapping (Ceritoglu et al., 2009) of the IXI fractional anisotropy image to the corresponding JHU-MNI-SS image. Short range fiber tracts from the Heschl's Gyrus to Planum Temporale generated by dynamic programming (M. Li, Ratnanather, Miller, & Mori, 2014; Ratnanather et al., 2013) are partially hidden. CAWorks (www.cis.jhu.edu/software/caworks) was used for visualization

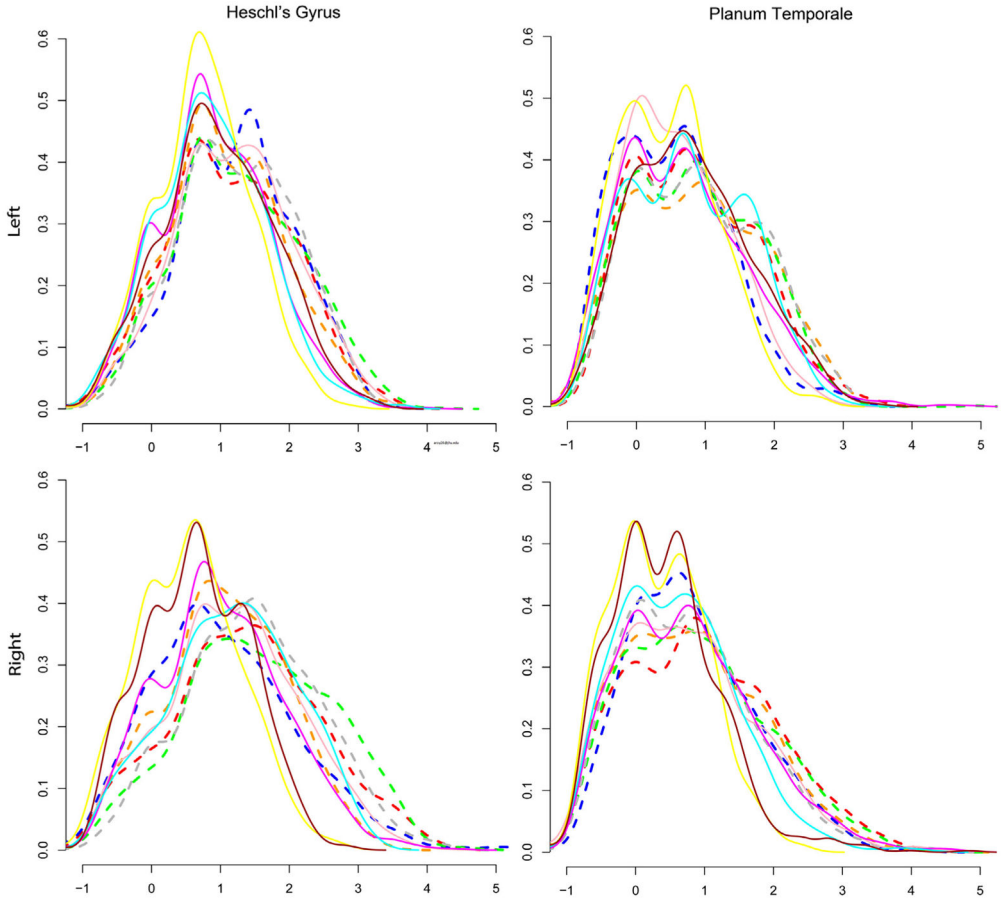

FIGURE 5.

Labeled cortical distance map (LCDM) histograms are normalized frequencies of distances of gray matter 1 mm^3 voxels relative to gray/white cortical surfaces. Shown are individual LCDMs for the Heschl's gyrus and planum temporale in five adults with hearing loss (dashed) and five matched controls (solid lines). Horizontal and vertical scales are from −1 to 5 mm and 0.0 to 0.6, respectively. *p*-Values from one-sided Kolmogorov–Smirnov tests for the pooled cummulative distribution function (cdf) for the control subjects to be left of the pooled cdf for the subjects with hearing loss were significant for all four structures ($\ll$.0001). For pooled LCDMs, see Ratnanather et al. (2019)

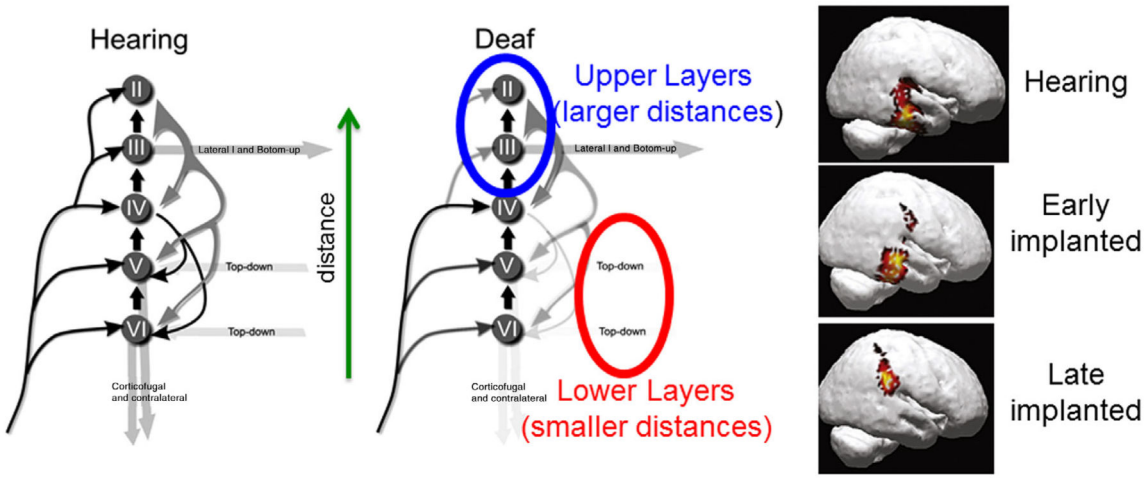

FIGURE 6.

Interpretation of Kral's decoupling hypothesis (Adapted from Kral and Eggermont (2007, fig. 3). Copyright 2007 Elsevier) based on LCDM analysis in Figure 5. Similarities at smaller distances, that is, lower cortical layers may facilitate top-down processing, that is, contextual or linguistic comprehension. This may be due to priming of the auditory pathway in childhood via amplification with hearing aids albeit at a lower rate than with cochlear implants. However, this might be compromised by larger differences at larger distances, that is, upper cortical layers which may be attributed to weaker thalamic inputs and make bottom-down processing, that is, comprehension of phonemes comprehension difficult and complex. In turn, the inputs to the lower layers and thence the other cortical areas are weakened. Additional evidence of weaker thalamic connections may manifest in those to other cortical areas such as the parietal cortex as might be in the case in the visualization of current density reconstruction in late implanted children (lower right panel from fig. 3 in Gilley, Sharma, & Dorman (2008). Copyright 2008, Elsevier). This suggests that hearing loss results in two-speed thalamic inputs (Takesian et al., 2013). One conjectures that amplification provided by hearing aids is weaker than that provided by cochlear implants and further that the thalamo-parietal pathway cannot tolerate the high activity levels stemming almost immediately after activation of the cochlear implant, thus forcing the neural activity to traverse along the acoustic radiation to the Heschl's gyrus (top and middle right panels from fig. 2 in Gilley et al. (2008))

TABLE 1

Summary of magnetic resonance imaging studies of gray and white matter structures in people with hearing loss

Studies	Groups	Age	Communication	Scanner strength	Structure	Tissue	Measure	Analysis	Main result	Other results
Penhune, Cismaru, Dorsaint-Pierre, Petitto, and Zatorre (2003)	12 DS vs. 10	29	ASL or LSQ	1.5 T	HG	GM and WM	Volume	ROI manual	No difference	Asymmetry preserved
					PT	GM	Volume	ROI manual	No difference	Asymmetry preserved
					Left motor hand area	GM	Whole brain	VBM (SPM)	Larger density	Asymmetry preserved
Emmorey, Allen, Bruss, Schenker, and Damasio (2003)	25 DS vs. 25	23.8 ± 4.1	ASL	1.5 T	Temporal lobe	GM and WM	Volume	ROI manual	No difference in GM/WM ratio	
					STG	GM and WM	Volume	ROI manual	Larger GM/WM ratio	
					HG	GM and WM	Volume	ROI manual	Larger GM/WM ratio	Asymmetry preserved
					PT	GM and WM	Volume	ROI manual	Left PT larger (GM)	
Fine, Finney, Boynton, and Dobkins (2005)	6 DS vs. 6 HS vs. 6	27 ± 5.7	ASL	1.5 T	Early visual areas	GM	Volume	Retinotopic fMRI	No difference	Only auditory area affected
Kara et al. (2006)	18 DS vs. 18	41.2 ± 7.5	TSL	1.5 T	CC	WM	Length	ROI manual	No difference	
							Width	ROI manual	No difference	
							Area	ROI manual	No difference	
Shibata (2007)	53 DS vs. 51	21	ASL	1.5 T	Left posterior STG	WM	Whole brain	VBM (SPM)	Focal deficit	
					Posterior STG	WM	Whole brain	VBM (SPM)	Focal deficit in asymmetry	
					Frontal/temporal perisylvian	GM	Whole brain	VBM (SPM)	Asymmetry preserved	
Meyer et al. (2007)	6 DS vs. 6	NR	DGS	3 T	Left post-long uncinate fasisculus	WM	Whole brain	VBM (SPM)	Less	
					Left post-inferior uncinate fasisculus	WM	Whole brain	VBM (SPM)	Less	
					Posterior Sylvian fissure	WM	Whole brain	VBM (SPM)	Steeper	

Studies	Groups	Age	Communication	Scanner strength	Structure	Tissue	Measure	Analysis	Main result	Other results
Allen, Emmorey, Bruss, and Damasio (2008)	25 DS vs 16 HS vs. 25	23.8 ± 4.1	ASL	1.5 T	Left posterior insula lobule	GM	Volume	ROI manual	Larger in DS	
					Right insula	WM	Volume	ROI manual	Larger in DS and HS	
Xia, Qi, and Li (2008)	20 DS vs. 20	9–12	CSL	1.5 T	Left HG, right HG	GM/WM	Ratio	ROI manual	Larger in DS	
	20 DS vs. 20	19–22	CSL	1.5 T	Left HG and left STG	GM	Volume	ROI manual	Larger in DS	
D. J. Kim, Park, Kim, Lee, and Park (2009)	13 DS vs. 29	29.3 ± 6.8	KSL	3 T	STG	WM	Volume	VBM (SPM)	Smaller bilaterally	
					Temporal sub-gyral	WM	Volume	VBM (SPM)	Smaller bilaterally	
					Left parietal	WM	Volume	VBM (SPM)	Smaller	
					Left superior frontal	WM	Volume	VBM (SPM)	Smaller	
					Left medial frontal	WM	Volume	VBM (SPM)	Smaller	
Lepore et al. (2010)	14 DS vs. 16	29.5	LSQ	1.5 T	Frontal lobe (Broca's)	WM	Volume	TBM (voxel-wise Jacobian)	Larger	
					Adjacent: Motor	WM	Whole brain	TBM (voxel-wise Jacobian)	Larger	
					Adjacent: Language	WM	Volume	TBM (voxel-wise Jacobian)	Larger	
					CC (splenium: temporal/occipital)	WM	Manual	ROI manual	Difference	
K. M. Smith et al., 2011	16 D vs. 26	12 ± 2.8 mo	NR	3 T	HG	GM	Whole brain	VBM (SPM)	Increased	Asymmetry not preserved
						WM	Whole brain	VBM (SPM)	Decreased	
J. Li et al. (2012)	16 DS vs. 16	14.56 ± 2.1	CSL	3 T	Left precentral gyrus	GM	Thickness	CIVET	Smaller	
					Right postcentral gyrus	GM	Thickness	CIVET	Smaller	
					Left superior occipital gyrus	GM	Thickness	CIVET	Smaller	
					Left fusiform gyrus	GM	Thickness	CIVET	Smaller	
					Whole brain	GM	Thickness	CIVET	Smaller	
					Left middle frontal gyrus	WM	Volume	VBM (SPM)	Focal decrease	
					Right inferior occipital gyrus	WM	Volume	VBM (SPM)	Focal decrease	

Studies	Groups	Age	Communication	Scanner strength	Structure	Tissue	Measure	Analysis	Main result	Other results
Allen, Emmorey, Bruss, and Damasio (2013)	25 DS vs. 16 HS vs. 25	23.8 ± 4.1	ASL	1.5 T	Calcarine sulcus (VI)	GM	Volume	ROI manual	Larger in DS	Asymmetry in DS and HS
					Pars Triangularis (Broca's)	GM	Volume	ROI manual	Larger in DS	
					Handknob (precentral gyrus)	GM	Volume	ROI manual	No difference	Asymmetry in DS and HS
Boyen, Langers, de Kleine, and van Dijk (2013)	16 HI vs. 24	63 ± 10	Tinnitus stud	3 T	STG, MTG	GM	Volume	VBM (SPM)	Increase	
					SFG, occipital, hypothalamus	GM	Volume	VBM (SPM)	Decrease	
					Frontal	GM	Volume	ROI	Decrease	
					Limbic	GM	Volume	ROI	Increase	
W. Li et al., 2013	16 DS vs. 16	14.56 ± 2.10	CSL	3 T	Cerebellum	GM	Volume	VBM (SPM)	Rightward asymmetrj	
					Posterior cingulate gyrus	GM	Thickness	CIVET	Leftward asymmetry	
					Gyrus rectus	GM	Thickness	CIVET	Leftward asymmetry	Negatively correlated with HA
					Auditory cortex (HG)	GM	Thickness	CIVET	Asymmetry preserved	
Penicaud et al. (2013).	9 DS (birth) vs. 8 DS (early) vs. 6 DS (late) vs. 43	39.2 ± 12.3	ASL	1.5 T	Early visual areas	GM	Volume	VBM (SPM)	Later ASL: lower	Deaf not different from hearing
F. R. Lin et al. (2014)	51 DS vs. 75	73.8 ± 7.3	NR	1.5 T	Right STG, right MTG, right ITG, right PHG	GM	Volume	RAVENS	Accelerated loss over time	
Hribar, Suput, Carvalho, Battelino, and Vovk (2014)	14 DS vs. 14	35.4 ± 6	SSL	3 T	Left HG	WM	Volume	ROI manual	Less	
					Middle medial left superior frontal gyrus	GM	Volume	FreeSurfer	Focal decrease	
					Left supramarginal gyrus	GM	Thickness	FreeSurfer	Focal decrease	
					Cerebellum	GM	Whole brain	VBM (FSL)	Increased volume	

Studies	Groups	Age	Communication	Scanner strength	Structure	Tissue	Measure	Analysis	Main result	Other results
Olulade, Koo, LaSasso, and Eden (2014)	15 DS vs. 15 HS vs. 15 DO	23.4 ± 3.3	ASL (DS/HS), oral/cued (DO)	3 T	Early visual areas	GM	Volume	VBM (SPM)	Less in both DS and DO	
	vs 15				Left early auditory areas	GM	Volume	VBM (SPM)	Less in both DS and DO	
					Left STG	WM	Volume	VBM (SPM)	Differences in DS	
					Left inferior frontal gyrus	WM	Volume	VBM (SPM)	Differences in DS	
					General	GM and WM	Volume	VBM (SPM)	DO less different than DS from controls	
E. Kim et al. (2014)	8 DS vs. 11 DO vs. 11	50.4 ± 6.1	NR	3 T	Primary auditory cortex	GM	Density	VBM (SPM)	No difference in DS	Decrease in DO
					Primary auditory cortex	GM	Connectivity	Voxel-wise correlation	Correlated in DS	Increased bilateral temporal connectivity in DO
					Whole brain	GM	Connectivity	Brain connectivity toolbox	Connectivity measures increased in DS	Fronto-limbic and left temporal correlated and temporo-parietal weakly coupled in DS
Tae (2015)	8 DS vs. 9	15.6	KSL	1.5 T	Left anterior HG	GM	Volume	VBM	Decreased	
					Left and right inferior colliculus	GM	Volume	VBM	Decreased	
					Lingual gyri, nucleus accumbens, thalamic reticular nucleus	GM	Volume	VBM	Decreased	
Amaral et al. (2016)	15 DS vs. 16	20.4	CSL	3 T	Thalamus	GM	Volume	Manual	Right > left	
					Left geniculate nucleus	GM	Volume	Manual	Right > left	
					Inferior colliculus	GM	Volume	Manual	Right > left	
Shiell, Champoux, and Zatorre (2016)	11 DS vs. 11	28.2	LSQ/ASL	3 T	Right PT	GM	Thickness	FreeSurfer	Increased	
Smittenaar, MacSweeney, Sereno, and	15 DS vs. 15	39	BSL	1.5 T	VI	GM	Thickness	FreeSurfer	Decreased	

Studies	Groups	Age	Communication	Scanner strength	Structure	Tissue	Measure	Analysis	Main result	Other results
Schwarzkopf (2016)										
Kumar and Mishra (2018)	50 vs. 50	19.5	Acquired ISL at age 10.8 years	3 T	Bilateral STG, bilateral ITG, bilateral fusiform, bilateral MFG	WM/GM, GM, GM	Volume	VBM, SBM and PBCT	Decreased, increased, increased, increased	Increased thickness
Feng et al. (2018)	37 vs. 40	17.9 mo	HA before CI	3 T	Bilateral AC (middle part of STG)	GM/WM	Density	VBM and MVPS	Most significant, less significant—IFG, CG, occipital, hippocampus, precuneus	Regions unaffected by auditory deprivation provided good outcomes for CI
X. M. Xu et al. (2019a)	35 vs. 54	56	Postlingual	3 T	Insula	GM	Density and connectivity	VBM	Insignificant differences	Reduced connectivity with other regions
X. M. Xu et al. (2019b)	37 vs. 38	55.6	Postlingual	3 T	Thalamic subfield connectivity	GM	Relative volume	VBM	Decrease in right motor thalamus and somatosensory thalamus	
Pereira-Jorge et al. (2018)	14 vs. 11	51.3	Postlingual (before HA)	1.5 T	PFC. precuneus. fusiform gyrus, and MTG; insula, supramarginal gyrus, medial temporal gyrus, occipital, posterior cingulate cortex, and claustrum		Thickness	FreeSurfer	Increase, decrease	After 1 year of HA, increase in multimodal integration regions
Shiohama, McDavid, Levman, and Takahashi (2019)	30 vs. 90	5.3–6.7	NR	3 T	Left middle occipital and left inferior occipital	GM	Thickness	CIVET	Smaller	
	35 vs. 23	39 ± 1.8	NR	3 T		GM	Volume	VBM (SPM)	Smaller	
Qi, Su, Zou, Yang, and Zheng (2019)					Right fusiform and right middle occipital gyrus					
Ratnanather et al. (2019)	5 DO vs. 5	31	LSL and HA	1.5 T	HG and PT	GM	Thickness	LCDM	Thicker	See also Dhir, Kutten, Li, Faria, and Ratnanather (2020)

Note: Structures observed to be affected by hearing loss are shown in Figures 3 and 4. Gender information can be obtained from original papers and is not recorded here due to lack of correlation. Age is given as mean ± SD or mean.

Abbreviations: ACC, anterior cingulate cortex; ASL, American sign language; BSL, British sign language; CC, corpus callosum; CG, cingulate gyrus; CI, cochlear implant; CIVET, combined interoperability validation evaluation tool; CSL, Chinese sign language; D, deaf; DO, deaf oral; DS, deaf signing; DGS, German sign language; fMRI, functional MRI; FSL, FMRIB software library; GM, gray matter; HA, hearing aids; HG, Heschl's gyrus; HI, hearing impaired; HS, hearing signing; ISL, Indian sign language; ITG, inferior temporal gyrus; KSL, Korean sign language; LCDM, labeled cortical distance mapping; LSL, listening and spoken language; LSQ, langue signe quebecois; MFG, middle frontal gyrus; mo, month; MTG, middle temporal gyrus; MVPS, multivoxel pattern similarity; NR, not recorded; PBCT, projection-based cortical thickness; PFC, prefrontal cortex; PHG, parahippocampal gyrus; PT, planum temporale; RAVENS, regional analysis of volume examined in normal space; ROI, region of interest; SSL, Slovenian sign language; STG, superior temporal gyrus; SFG, superior frontal gyrus; SPM, statistical parametric mapping; TSL, Turkish sign language; TBM, tensor-based morphometry; VBM, voxel-based morphometry; WM, white matter.

TABLE 2

Summary of diffusion tensor imaging studies of white matter structures in people with hearing loss

Studies	Group	Age	Communication	Scanner strength	Structure	Tissue	Measure	Analysis	Main result	Other results
Chang et al. (2004)	10 D vs. 10	33.7	NR but mild-to-severe HL	3 T	SON, IC, TB, LL. AR	FA	Single brain analysis	Voxel-Wise	Abnormal	See also S. H. Lee, 2004
Nath et al. (2007)	14 D vs. 8	30	NR	1.5 T	LL	FA	Whole brain	ROI	Less	
					IC	FA	Whole brain	ROI	Less	
					PCT	FA	Whole brain	ROI	Less	
Y. Lin et al. (2008)	37 D vs. 10	32.4 ± 11.9	NR	3 T	LL	FA and RD	Whole brain	DTIStudio	Less FA and more RD	
					IC	FA and RD	Whole brain	DTIStudio	Less FA and more RD	
Xia and Qi (2008)	20 DS vs. 20	9–12	CSL	1.5 T	Right HG	ADC	Whole brain	ROI manual	Different	
	20 DS vs. 20	19–22	CSL	1.5 T	Bilateral HG	ADC	Whole brain	ROI manual	Different	
S. Wang et al. (2009)	6 CD vs. 6	20.8	CSL (3 after HA usage at 4 years)	3 T	Right STG	FA	Whole brain	Voxel-based analysis	Less	Asymmetry preserved
D. J. Kim et al. (2009)	13 D vs. 29	29.3 ± 6.8	No HA	3 T	Superior temporal	FA	Whole brain	TBSS	Less	
					Right internal capsule	FA	Whole brain	TBSS	Less	
					SLF	FA	Whole brain	TBSS	Less	
					Left inferior FOF	FA	Whole brain	TBSS	Less	
					Right forceps major	FA	Whole brain	TBSS	More	
					Left forceps major	FA	Whole brain	TBSS	More	
					Left STG	Volume	Whole brain	TBSS	Less WM	
					Right STG	Volume	Whole brain	TBSS	Less WM	
					Left parietal	Volume	Whole brain	TBSS	Less	
					Superior frontal	Volume	Whole brain	TBSS	Less	
					Medial frontal	Volume	Whole brain	TBSS	Less	
Z.-H. Liu et al. (2010)	15 D vs. 28	16	CSL for more than 6 years and HA usage since 2 years old	1.5 T	Left STG	FA	Whole brain	TBSS	Less	
					Right STG	FA	Whole brain	TBSS	Less	

Studies	Group	Age	Communication	Scanner strength	Structure	Tissue	Measure	Analysis	Main result	Other results
					Left IFG	FA	Whole brain	TBSS	Less	
					Right IFG	FA	Whole brain	TBSS	Less	
					Left post-medial MTG	FA	Whole brain	TBSS	Less	Reduction less in L than R
					Right post-medial MTG	FA	Whole brain	TBSS	Less	
					Right Int Cap	FA	Whole brain	TBSS	Less	
					Left Int Cap	FA	Whole brain	TBSS	Less	
					Right Ext Cap	FA	Whole brain	TBSS	Less	
					Left Ext Cap	FA	Whole brain	TBSS	Less	
					Left OR	FA	Whole brain	TBSS	Less	Reduction less in L than R
					Right OR	FA	Whole brain	TBSS	Less	
Y. Li et al. (2012)	60 CD vs. 36 AD vs. 38	21.1 ± 2.26 (CD), 21.5 ± 1.54 (AD)	CSL only	3 T	Right STG	FA	Whole brain	TBSS	Less	Correlated with onset age
					Left STG	FA	Whole brain	TBSS	Less	
					SCC	FA	Whole brain	TBSS	Less	
Chang, Lee, Paik, Lee, and Lee (2012)	18 D	5.9	NR	3 T	Broca's	FA	Whole brain	Voxel-wise	Higher	Correlated with auditory scores after CI
					Genu of CC	FA	Whole brain	Voxel-wise	Higher	Correlated with auditory scores after CI
					AR	FA	Whole brain	Voxel-wise	Higher	Correlated with auditory scores after CI
					MGN	FA	Whole brain	Voxel-wise	Correlated with auditory scores after CI	
Miao et al. (2013)	16 D vs. 16	14.56 ± 2.1	CSL after late HA usage	3 T	Left STG	FA and RD	Whole brain	TBSS	FA lower and RD higher	
					Right STG	FA and RD	Whole brain	TBSS	FA lower and RD higher	RD correlated with CSL usage
					HG	FA and RD	Whole brain	TBSS	FA lower and RD higher	

Studies	Group	Age	Communication	Scanner strength	Structure	Tissue	Measure	Analysis	Main result	Other results
					PP	FA and RD	Whole brain	TBSS	FA lower and RD higher	
					SCC	FA and RD	Whole brain	TBSS	FA lower and RD higher	
Lyness, Alvarez, Sereno, and MacSweeney (2014)	13 DS vs. 13	39.08 ± 11.08	BSL after 10 years (11 used spoken language)	1.5 T	Frontal and occipital	MD and RD	Thalamic Parcellation	FreeSurfer and FSL	Increased MD and RD	
					Frontal	FA	Thalamo-cortical	FreeSurfer and FSL	Reduced FA	
					Motor	FA, MD and RD	Thalamo-cortical	FreeSurfer and FSL	Increased MD and RD	Reduced FA
					Somatosensory	FA and RD	Thalamo-cortical	FreeSurfer and FSL	Increased RD	Reduced FA
					Parietal	FA	Thalamo-cortical	FreeSurfer and FSL	Reduced FA	
					Occipital	FA	Thalamo-cortical	FreeSurfer and FSL	Reduced FA	
C. X. Wu et al. (2014)	92 (three groups)	4.9	31 had CI	1.5 T	STG	FA	Whole brain	DTIStudio	Less	
					AR	FA	Whole brain	DTIStudio	Less	Correlated with CAP score in the 31 with CI
Karns, Stevens, Dow, Schorr, and Neville (2017)	23 DS vs. 26	28 ± 1.4	ASL	3 T	Bilateral HG, anterior STG, posterior STG	FA and volume	Whole brain	FSL	Less	More RD in bilateral HG; right posterior STG had larger differences between groups
					Posterior CC	FA	Whole brain	FSL	Less	More RD
J. Kim, Choi, Eo, and Park (2017)	18 (10 postlingual) vs. 29		KSL and HA	3 T	Right Int Cap, right thalamus, SCC, right STG and left STG, right temporal lobe WM	Diffusion anisotropy	Whole brain	TBSS	Less	Prelingual less in R STG, bilateral WM, genu and anterior CC
Maffei (2017)	10 DS vs. 10	34 ± 6	LIS	4 T	Acoustic radiation	FA, RD and MD	Whole brain	FSL	Less, more	Atlas-based analysis, subset of Benetti et al. (2018)
Benetti et al. (2018)	14 DS vs. 15 HS vs. 15	34 ± 6	LIS	4 T	Occipito-temporal, fusiform-temporal	FA and RD	Connectivity	FSL	Less FA and more RD	
Zou et al. (2018)	80 vs. 78	41.7	CSL for 10+ years	3 T	Bilateral STG	GM and WM	Diffusion kurtosis	VBM (SPM)	Decreased	"Hypomyelination" of WM

Studies	Group	Age	Communication	Scanner strength	Structure	Tissue	Measure	Analysis	Main result	Other results
Qi et al. (2019)	35 vs. 23	39 ± 1.8	NR	3 T	Multiple WM structures	GM	FA	TBSS	Decreased	RD increased
M. Jiang et al. (2019)	23 vs. 18	7.21 ± 2.67	No HA usage	3 T	Left ATR, right CST, CC	AD	Whole brain	TBSS	Increased	RD increased in several WM tracts
H. Wang et al. (2019)	52 vs. 19	0.9–6	Prior to CI	3 T	Bilateral IC	FA	ROI	FSL, PickAtlas, SPM	Lower	Correlated with postop CAP scores
S. Wang et al. (2019)	46 vs. 33	17.59 mo	Prior to CI	3 T	Bilateral SLF, IFOF, ILF; right CST, PTR; left UF	FA	Whole brain	TBSS	Lower	Increased resting state functional connectivity between bilateral auditory cortices and right insula and STG
Cheng, Roth, Halgren, and Mayberry (2019)	12 vs. 12	33.33	ASL	1.5 T	IFOF, AF, ILF, UF	FA	ROI	DTIStdio	No difference	
Dhir et al. (2020)	5 DO vs. 10	31 ± 11	LSL and HA	1.5 T	AR	FA	Whole brain	MRICloud and DTIStudio	Less	

Note: Structures observed to be affected by hearing loss are shown in Figures 3 and 4. Gender information can be obtained from original papers and is not recorded here due to lack of correlation. Age is given as mean ± SD or mean.

Abbreviations: AD, acquired deaf; ADC, apparent diffusivity coefficient; AR/OR, acoustic/optic radiation; AF, arcuate fasciculus; ASL, American sign language; ATR, anterior thalamic radiation; BSL, British sign language; CAP, categories of auditory performance; CC, corpus callosum; CD, congenitally deaf; CI, cochlear implant; CSL, Chinese sign language; CST, corticospinal tract; D, deaf; DS, deaf signing; FA, fractional anisotropy; FOF, fronto-occiptal fasciculus; FOT, fronto-occipital tract; FSL, FMRIB software library; GM, gray matter; HA, hearing aid; HG, Heschl's gyrus; HL, hearing loss; HS, hearing signing; IC, inferior colliculus; IFG, inferior frontal gyrus; IFOF, inferior fronto-occiptal fasciculus; ILF, inferior longitudinal fasciculus; Int/Ext Cap, internal/external capsule; LL, lateral leminscus; LSL, listening and spoken language; LIS, lingua italiana dei segni; MD, mean diffusivity; MGN, medial geniculate nucleus; MTG, middle temporal gyrus; NR, not recorded; PCT, pontine crossing tract; PP, planum polare; PTR, posterior thalamic radiation; RD, radial diffusivity; ROI, region of interest; SCC, splenium of CC; SOF, superior occipial fasciculus; SLF, superior longitudinal fasciculus; SON, superior oliviary nucleus; SPM, statistical parametric mapping; STG, superior temporal gyrus; TB, trapezoid body; TBSS, tract-based spatial statistics; UF, uncinate fasciculus; WM, white matter.

TABLE 3

Preclinical MRI and DTI whole brain imaging studies

Studies	Size	Group	Age	Modality	Results
Lapointe, Viamonte, Morriss, and Manolidis (2006)	40	SNHL	Pediatric	T1 and T2	Some changes in T2 but eight had abnormalities from myelination delays to migrational anomalies
Trimble, Blaser, James, and Papsin (2007)	92	Preop CI	Pediatric	FLAIR	32% abnormalities in TB; some subcortical signal intensities discrepancies
Roche et al. (2010)	118	ANSD	Pediatric	MR	40% had brain abnormalities; 28% had CN deficiencies
				CT	16% had cochlear dysplasia
Hong, Jurkowski, and Carvalho (2010)	57	Preop CI	Pediatric	MR	18% with white matter abnormalities (two had postop delays in performance), no serious CNS diseases
Chilosi et al. (2010)	80	SNHL	Pediatric	MR	48% with additional disabilities (cognitive, behavioral–emotional and motor). 37 signal abnormalities—brain malformations (46%) and white matter abnormalities (54%)
Chang et al. (2012)	18	Preop CI	Pediatric	DT	FA in Broca's, genu CC, auditory tract and MGN correlated with auditory scores after CI
Mackeith, Joy, Robinson, and Hajioff (2012)	158	Preop CI	Pediatric and adults	MR	Detected abnormalities (n = 27.9%, missed by CT in 6.3%) of which only 12.7% considered significant
				CT	6.3% only noncritical abnormalities in CT
Moon et al. (2012)	177	Preop CI	Pediatric	MR	Children with no lesions (n = 150) performed better than those with lesions
Proctor, Gawne-Cain, Eyles, Mitchell, and Batty (2013)	51	Preop CI	Pediatric and adults	MR	Five adults and 16 children—whole brain abnormalities; 36 had at least one CI. Of 15 who did not have CI, eight positive findings in whole brain MRI
Jonas et al. (2012)	162	Preop CI	Pediatric	MR	30% had abnormalities mostly white matter changes related to pre-existing medical conditions
Z. Y. Jiang, Odiase, Isaacson, Roland, and Kutz (2014)	188	Preop CI	Adult	MR	9% had cochlear pathway and white matter abnormalities; in others, 65% had normal MRI scans
X.-Q. Xu, Wu, Hu, Su, and Shen (2015)	157	Preop CI	Pediatric	MR and CT	White matter changes most common but effect on CI minimal
Huang et al. (2015)	24	Preop CI	Pediatric	DT	Lesser FA in TB, SON, IC, MGB, AR and WMHG in 16 with CAP <6
Park, Chung, Kwon, and Lee (2018)	1	Preop CI	Pediatric	DT	Less FA in WMHG, IFOF, UF, SLF and forceps major only in age <4 years
Feng et al. (2018)	37	Preop CI	Pediatric	MR	Auditory association and cognitive brain regions which are unaffected by auditory deprivation provide positive outcomes

Abbreviations: ANSD, auditory neuropathy spectrum disorder; AR, acoustic radiation; CAP, category of auditory performance; CC, corpus callosum; CI, cochlear implant; CN, cochlear nerve; CNS, central nervous system; CT, computed tomography; DT, diffusion tensor; FA, fractional anisotropy; FLAIR, fluid-attenuated inversion recovery; IC, inferior colliculus; IFOF, inferior fronto-occiptal fasciculus; MGB, medial geniculate body; MGN, medial geniculate nucleus; MR, magnetic resonance; Preop, pre-operative; SLF, superior longitudinal fasciculus; SNHL, sensorineural hearing loss; SON, superior oliviary nucleus; T1/T2, MR-weighted image; TB, temporal bone; UF, uncinate fasciculus; WMHG, white matter Heschl's gyrus.