Poorer speech reception threshold in noise is associated with lower brain volume in auditory and cognitive processing regions

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Abstract

Purpose: Hearing loss is associated with changes in brain volume in regions supporting auditory and cognitive processing. The purpose of the present study was to determine whether there is a systematic association between hearing ability and brain volume in cross-sectional data from a large non-clinical cohort of middle-aged adults available from the UK Biobank Resource (www.ukbiobank.ac.uk).

Method: We performed a set of regression analyses to determine the association between speech reception threshold in noise (SRTn) and global brain volume as well as predefined regions of interest (ROI) based on T1-weighted structural images, controlling for hearing-related comorbidities and cognition as well as demographic factors. In a second set of analyses, we additionally controlled for hearing aid (HA) use. We predicted statistically significant associations globally and in ROI including auditory and cognitive processing regions, possibly modulated by hearing aid (HA) use.

Results: Whole brain grey matter volume was significantly lower for individuals with poorer SRTn. Further, the volume of nine predicted ROI including both auditory and cognitive processing regions was lower for individuals with poorer SRTn. The greatest percentage difference (-0.57%) in ROI volume relating to a 1 SD worsening of SRTn was found in the left superior temporal gyrus. HA use did not substantially modulate the pattern of association between brain volume and SRTn.

Conclusions: In a large middle-aged non-clinical population, poorer hearing ability is associated with lower brain volume globally as well as in cortical and subcortical regions involved in auditory and cognitive processing but there was no conclusive evidence that this effect is moderated by hearing aid use. This pattern of results

supports the notion that poor hearing leads to reduced volume in brain regions recruited during speech understanding under challenging conditions. These findings should be tested in future longitudinal, experimental studies.

Keywords

Brain volume; grey matter; speech reception threshold in noise; auditory; cognitive; hippocampus

Abbreviations

Digit Triplets Test (DTT)

FMRIB's Integrated Registration and Segmentation Tool (FIRST)

Harvard-Oxford cortical and subcortical atlases and the Diedrichsen cerebellar atlas (H-O-D)

Hearing Aid (HA)

Long-Term Memory (LTM)

Magnetic Resonance (MR)

Primary Auditory Cortex (PAC)

Region of Interest (ROI)

Signal-to-Noise Ratio (SNR)

Speech Reception Threshold in noise (SRTn)

Superior Temporal Gyrus (STG)

Townsend Deprivation Index (TDI)

Verbal Reasoning (VR)

1. Introduction

Differences in sensory input to the brain cause changes in its functional and structural organization (Merabet & Pascual-Leone, 2010). It is well-established that congenital deafness drives cross-modal plasticity in auditory processing regions (Cardin et al., 2013; Finney, Fine & Dobkins, 2001; Nishimura et al.,1999) and there is growing evidence that it influences the organization of cognition (Cardin et al., 2017; Ding et al., 2015; 2016). Recently there has been growing interest in neural changes associated with acquired hearing loss (for reviews see Cardin, 2016; Jayakody, Friedland, Martins & Sohrabi, 2018).

A number of cross-sectional studies have found that acquired hearing loss is associated with smaller volume in primary auditory cortex (PAC) in Heschl's gyrus (Eckert, Cute, Vaden, Kuchinsky & Dubno, 2012; Peelle, Troiani, Grossman & Wingfield, 2011) and supplementary auditory processing areas in superior temporal gyrus (STG, Husain et al., 2011; Yang et al., 2014). In the study by Eckert et al. (2012), T1-weighted anatomical MR images were obtained from 49 adults with a mean age of 70 years. Region of Interest (ROI) analysis showed that participants with more high frequency hearing loss had lower grey matter volume in the Te1.0 subregion of PAC bilaterally accompanied by greater volume of cerebrospinal fluid, while participants with more low frequency hearing loss had lower grey matter volume in the left Te1.2 subregion of PAC. These associations survived correction for age and gender. The results were interpreted as suggesting that auditory cortex atrophies with hearing loss.

The Peelle et al. (2011) study also used T1-weighted anatomical MR images, this time from 25 adults with a mean age of 66 years. ROI analysis showed poorer hearing (higher pure tone average threshold in the better ear across the frequencies

1, 2, and 4 kHz) was significantly associated with lower grey matter volume in right primary auditory cortex (areas TE1.0 and TE1.1), and there was a similar but nonsignificant trend in the contralateral region. These findings together with functional results were interpreted as evidence of age-related changes in hearing ability causing reduced grey matter in auditory cortex.

Husain et al. (2011) compared grey matter volume obtained from T1-weighted MR images in seven participants with hearing impairment (mean age 51 years) and 11 participants with normal hearing (mean age 48). Whole brain analysis showed that the hearing impairment group had lower grey matter volume in regions associated with cognitive control including the right anterior cingulate as well as the medial frontal gyrus bilaterally. ROI analysis showed that the hearing impairment group had lower grey matter volume in STG bilaterally than the group with normal hearing. The authors' interpretation was that hearing loss causes grey matter reduction in both auditory and higher cognitive processing regions.

Yang et al. (2014) collected T1-weighted MR images from 14 individuals with right-sided unilateral hearing loss and 19 healthy controls, both groups with a mean age of 54 years. The participants with hearing loss compared to the controls had lower grey matter volume in a number of both auditory and cognitive processing regions including the posterior cingulate gyrus bilaterally as well as the precuneus, left superior/middle/inferior temporal gyrus, right parahippocampal gyrus and lingual gyrus. The authors concluded that even unilateral hearing loss induces changes in brain morphology.

Thus, generally, the literature demonstates that acquired hearing loss is associated with smaller brain volume in both auditory and cognitive processing regions, and suggests that hearing loss probably causes neural atrophy in these regions.

However, one study, Boyen, Langers, de Kleine & van Dijk (2013) showed greater volume in STG and middle temporal gyrus (MTG) associated with hearing loss. Like the other cross-sectional studies reviewed here, this study was based on T1-weighted magnetic resonance (MR) images. Specifically, they were collected from 31 participants with hearing impairment and tinnitus (mean age 56 years), 16 participants with hearing impairment but no tinnitus (mean age 63 year) and 24 participants with normal hearing (mean age 58 years). Whole brain analysis showed that both hearing impairment groups compared to controls had larger grey matter volume in STG. The authors' interpretation of this finding was that brain volume increase associated with hearing impairment may be related to the role of the STG in semantic memory. In particular, they suggested that because individuals with hearing impairment miss part of the speech signal they may rely more heavily on semantic memory to maintain normal communication.

This explanation is in line with findings in the literature showing that cognitive training leads to increases in the volume of brain structures involved in cognitive processing (for a review see Lövdén, Wenger, Mårtensson, Lindenberger & Bäckman, 2013). On the other hand, it directly contradicts the results of Husain et al. (2011) and Yang et al. (2014) which both showed that hearing impairment was associated with, and probably caused, lower volume in the STG. Thus, review of the literature shows hearing impairment is consistently associated with lower brain volume in PAC and cognitive processing regions outside the STG, while there is controversy concerning whether hearing impairment is associated with higher or lower volume of the STG.

Hearing impairment is associated with aging (Roth, Hanebuth & Probst, 2011) and aging, like hearing impairment, is associated with functional and structural changes in regions of the brain supporting speech processing. Cross-sectional studies have

identified structural differences related to aging including smaller grey matter volume in STG and Heschl's gyrus in adults with a mean age of 70.5 years compared to those with a mean age of 29 years (Harris, Dubno, Keren, Ahlstrom & Eckert, 2009), smaller supratemporal cortex and ventral motor areas bilaterally in adults with a mean age of 68 years compared to those with a mean age of 26 years (Bilodeau-Mercure, Lortie, Sato, Guitton & Tremblay, 2015) as well as cortical thinning bilaterally in planum temporale, planum polare, STG, superior temporal sulcus, Heschl's gyrus, and Heschl's sulcus in adults with a mean age of 72 years compared to those with a mean age of 24 years (Giroud et al., 2018) . Age-related functional differences include modulation of speech intelligibility effects in regions showing structural differences including STG and Heschl's gyrus (Harris et al., 2009); sensorimotor cortex and left dorsal anterior insula (Bilodeau-Mercure et al., 2015) as well as left pars triangularis and left superior frontal gyrus (Wong, Ettlinger, Sheppard, Gunasekera, Dhar, 2010). Further, an association between thicker auditory cortex in the right hemisphere and better auditory performance in the older group in the study by Giroud et al. (2018) as well as more rightward intrinsic theta power lateralization, underlines the importance of right auditory cortex for speech processing in older adults.

The association between hearing ability and cognition is well established in behavioural studies showing associations between speech recognition in noise and cognitive skills (Akeroyd, 2008; Besser, Koelewijn, Zekveld, Kramer & Festen, 2013) as well as in experimental studies demonstrating the effect of cognitive load on speech processing under challenging conditions (Hunter & Pisoni, 2018; Obleser, Wöstmann, Hellbernd, Wilsch & Maess, 2012; Zekveld, Kramer, Rönnberg & Rudner, 2018). This association is described by the Ease of Language

Understanding model (ELU, Rönnberg et al., Rönnberg, Holmer & Rudner, 2018). Speech processing proceeds relatively effortlessly under optimal conditions (Mattys, Davis, Bradlow & Scott, 2012). However, when listening conditions are challenging, for example in background noise and/or when the listener has a hearing impairment, explicit cognitive functions need to be recruited for successful speech understanding (Rönnberg et al., 2013; Rudner, Rönnberg & Lunner, 2011). Thus, listening under challenging conditions increases cognitive load (Zekveld, Rudner Kramer, Lyzenga & Rönnberg, 2014) and is perceived as effortful (Rudner, Lunner, Behrens, Thorén, Rönnberg, 2012).

In addition to auditory processing regions in the STG and language processing regions in the left inferior frontal gyrus and at the temporoparietal junction, speech understanding in noise engages prefrontal and superior parietal regions (Scott & McGettigan, 2013; Wong et al., 2009) supporting working memory, as well as the hippocampus (Zekveld, Rudner, Johnsrude, Heslenfeld, Rönnberg, 2012) supporting long-term memory (LTM). Cerebral regions that are functionally involved in speech understanding in noise largely coincide with regions whose volume covaries with hearing ability. Because long-term changes in the functional recruitment of brain regions lead to long-term changes in structure (Merabet & Pascual-Leone, 2010), it is likely that the long-term functional recruitment of brain regions by speech understanding under challenging conditions also leads to changes in their structure (Peelle & Wingfield, 2016). These changes could either reflect negative effects due to disuse (c.f. Rönnberg et al., 2013) or positive effects consonant with those brain training (c.f. Lövdén et al., 2013) and in either direction are likely to be greater for individuals with poorer hearing ability, for whom listening is even more challenging.

The most common treatment for hearing impairment is hearing aids (HA) which amplify weak sounds, making them more audibile. It seems reasonable to assume that this may lead to enhanced neural representation of speech and consequently preservation of neural integrity in PAC and other auditory processing regions. Indeed, it has been shown that HA intervention leads to enhanced cortical (Karawani, Jenkins & Anderson 2018b) and subcortical (Jenkins, Fodor, Presacco & Anderson, 2018; Karawani, Jenkins & Anderson 2018a) processing of speech. In everyday challenging conditions, HA are not able to separate target speech from background noise. However, they can improve the speech-to-noise ratio when speech and noise are spatially seperated by at least 45 degrees, with the use of directional microphones. This means that HA can in some circumstances ameliorate challenging listening conditions for the listener with hearing impairment. Indeed, there is evidence that HA may reduce listening effort after a period of familiarization (Giroud, Lemke, Reich, Matthes, & Meyer, 2017; Rudner, Foo, Rönnberg & Lunner, 2009) and improve working memory (Karawani et al., 2018b). Changes in neural recruitment caused by HA use may in the long term result in changes in brain volume.

Using data from 126 individuals aged 56-86 years included in a neuroimaging substudy of the Baltimore Longitudinal Study of Aging, Lin et al. (2014) found no effect of hearing loss on brain volume at baseline measurement. However, decline in brain volume over time was greater globally and in the temporal lobes for the group with hearing impairment (n = 51) than the group without. Because of the small number of HA users (n = 13) in the study, Lin et al. (2014) were unable to study the effect of HA use.

In the present study, we investigated the relationship between hearing ability and brain volume in a much larger set of data from a non-clinical cohort of middle-aged adults available from the UK Biobank Resource. The hearing measure in this data set is speech reception threshold in noise (SRTn) indexed by the Digit Triplets Test (DTT, Dawes, Fortnum, et al., 2014; Smits, Kapteyn & Houtgast, 2004). DTT scores and pure tone average hearing thresholds (PTA) are highly correlated (*r* = .77, Dillon, Beach, Seymour, Carter & Golding, 2016). We predicted that poorer SRTn would be associated with lower brain volume globally as well as in PAC and cognitive processing regions outside STG involved in the processing of speech in noise. We also predicted an association in STG although we did not specify its direction owing to contradictory results reported in the literature. We also expected that these predicted associations would be modulated by HA use.

2. Methods

The present study is based on cross-sectional data available from the UK Biobank Resource, a prospective study including lifestyle, physical and cognitive measures for over 500 000 participants who were aged 40–69 years when they were recruited in 2006–2010 (Sudlow et al., 2015), 100 000 of whom are being called back for MRI-scanning (Miller et al., 2016).

2.1 Participants

The participants in the present study (N=8701, 47.4 % male) included the total number of participants in the UK Biobank for whom T1-weighted structural images and relevant variables were available. This approach means that there are no missing data in any of the analyses. Mean age at time of scanning was 62.3 years (SD = 7.4 years) and mean socioeconomic status was -1.97 (SD = 2.63) on the

Townsend Depriviation Index (TDI, Townsend, Phillimore & Beattie, 1988). TDI is based on the participant's postal code according to the national census preceding inclusion in the UK Biobank and a higher score indicates lower socioeconomic status. According to the UK Data Service (www.ukdataservice.ac.uk), the overall population mean is 0 and SD = 3.44. All participants provided informed consent prior to testing and other ethical procedures are described in Miller et al. (2016) for imaging and Sudlow et al. (2015) for behavioural measures.

2.2 T1 data acquisition

According to UK Biobank Brain Imaging Documentation (Smith, Almagro & Miller, 2017), the T1 data were collected using a dedicated standard Siemens Skyra 3T running VD13A SP4, with a standard Siemens 32-channel RF receive head coil. The field-of-view was automatically determined based on Siemens' auto-align software or failing that, set by the radiographer. The T1 structurals were acquired using straight sagittal orientation and a 3D MPRAGE sequence. T1 scanning lasted 5 minutes and was part of a longer series of scans lasting 35 minutes. Resolution is 1x1x1 mm and field-of-view is a 208x256x256 matrix. Standard Siemens on-scanner conversion of complex multi-coil data was carried out for the T1 data.

2.3 T1 data processing

T1 data processing took place as follows (Smith, Almagro & Miller, 2017). The full field of view was cut down to reduce the amount of non-brain tissue and gradient distortion correction was applied in conjunction with a standard-space T1 template. This was achieved using Brain Extraction Tool (Smith, 2002) and the Linear Image Registration Tool developed at the Oxford Centre for Functional MRI of the Brain (Jenkinson & Smith, 2001, Jenkinson, Bannister, Brady, & Smith, 2002), in

conjunction with the 1 mm resolution version of MNI152 “nonlinear 6th generation” standard-space T1 template http://www.bic.mni.mcgill.ca/ServicesAtlases/ICBM152NLin6.

The data were then nonlinearly warped to MNI152 space. As Alfaro-Almagro et al., (2018) have pointed out, this is a critical processing step in the pipeline, and because T1 images in UK Biobank had brighter internal carotid arteries than those in the MNI152 template a custom reference brain mask was applied to exclude this part of the image when estimating the transformation. A standard-space brain mask was then back-transformed into the space of the T1 and applied to the T1 image to generate a brain-extracted T1. Next, tissue-type segmentation was applied to generate a fully bias-field-corrected version of the brain-extracted T1. The external surface of the skull was estimated from the T1, and used to normalise brain tissue volumes for head size.

A total of 139 regional grey matter volumes were generated by summing the grey matter partial volume estimates within 139 regions of interest (ROIs) defined in MNI152 space using the Harvard-Oxford cortical and subcortical atlases https://fsl.fmrib.ox.ac.uk/fsl/fslwiki/Atlases and the Diedrichsen cerebellar atlas http://www.diedrichsenlab.org/imaging/propatlas.htm.

Subcortical structures were modelled using FIRST (FMRIB’s Integrated Registration and Segmentation Tool). For more details see Smith, Almagro and Miller (2017). There are 15 such regions and these are also shown in Appendix A. It should be noted that the hippocampus is defined by both procedures, the difference being that the atlas-based procedure defines grey matter while FIRST does not distinguish tissue type.

Out of the total of 154 defined regions, we selected a subset of 48 as directly relevant to our predictions, see Appendix A. Of these, 22 are defined as auditory processing regions and 26 as cognitive processing regions. However, it should be noted that several of these regions are large and may encompass a range of functions.

2.4 Speech reception threshold in noise (SRTn)

The Speech Reception Threshold in noise (SRTn, Plomp, 1978) is a measure of the ability to recognize speech in noise. In the present study, SRTn was determined on the basis of performance on the Digit Triplets Test (DTT, Dawes, Fortnum et al., 2014; Smits et al., 2004). The DTT data were collected in connection with the imaging visit and obtained under headphones using a self-administered program running on a computer with a touch screen. Before testing commenced, the participant was instructed to remove any hearing aids and to set a comfortable volume. Then, the participant listened to 15 sets of three digits presented in steady state speech-shaped background noise. The task was to enter each triplet into an onscreen keypad after the set of digits had been presented. If the triplet was entered correctly, the next set of digits was presented at a higher noise level, otherwise the noise was lowered. For more details of DTT and its development see Smits et al. (2004) and Dawes, Fortnum et al. (2014). In the present study, SRTn was defined as the signal-to-noise ratio (SNR; ranging between -12 and +8 dB) at which half of the presented digits could be recognized correctly in the better ear (ears were tested separately). The better ear largely determines auditory function in daily life, and indicates occupational hearing loss for insurance purposes (Rönnberg, Hygge, Keidser & Rudner, 2014). When the DTT score was only available for one ear, we assumed that it was the better one.

Mean SRTn among the participants in the present study was -6 dB, SD = 1.6 dB. A higher SRTn indicates poorer hearing and normal hearing is considered to be represented by SRTn < -5.5 dB (Dawes, Fortnum et al., 2014). Thus, 61% of the participants in the present study had an SRTn in the normal range.

2.5 Cognitive ability

The cognitive abilities such as reasoning and memory that are engaged to achieve comprehension during listening under adverse conditions (Peelle & Wingfield, 2016), display a natural variation within the population. Furthermore, better speech recognition in noise is related to better cognitive ability, especially for individuals with hearing impairment (Akeroyd, 2008; Besser et al., 2013; Rudner et al., 2011). Further, hearing impairment is associated with increased risk of incident dementia, ie. a pathological reduction in cognitive ability (Deal et al., 2017), which in turn is related to reduced brain volume (Henneman et al., 2009). Thus, both SRTn and brain volume are likely to be related to cognitive ability, making it important to control for cognitive ability when investigating the association between SRTn and brain volume. The UK Biobank includes data from a test of Verbal Reasoning (VR) which taps into the cognitive functions that support speech processing under challenging conditions. We have previously shown an association between worse VR score and worse SRTn (Keidser, Rudner, Seeto, Hygge & Rönnberg, 2016).

The VR data were collected during a separate visit to a regional assessment center using a self-administered program running on a touch screen computer. VR was measured using 13 multiple choice questions of which as many as possible were to be answered in two minutes. Examples of questions are: 1) ”Bud is to flower as child is to?” with the answer to be selected from: Grow, Develop, Improve, Adult and Old;

and 2) ”If sixty is more than half of seventy-five, multiply twenty-three by three. If not subtract 15 from eighty-five. Is the answer?” with the answer to be selected from: 68, 69, 70, 71, 72 and with the additional options of ”Do not know” and ”Prefer not to answer” in both cases. These questions tap into semantic LTM and at the same time require logical reasoning. For more details see Keidser et al. (2016). The mean VR score of participants in the present study was 6.9, SD = 2.1.

2.6 Vascular and vision problems

Poor hearing is associated with vascular and vision problems. Vascular problems are assumed to lead to poor hearing due to a reduced blood supply to the cochlea, which results in a disruption of the chemical balance of the inner ear that affects the electrical activity of the hair cells. The relation between vascular problems and poor hearing has been demonstrated in several epidemiological studies (e.g. Helzner et al., 2011; Liew et al., 2007; Torre, Cruickshanks, Klein, Klein & Nondahl, 2005). In the present study, 28.5 % participants had vascular problems indicated by self-report of having a diagnosis of at least one (ever) of heart attack, angina, stroke or high blood pressure.

Older adults with poor hearing sometimes have poor vision too (Saunders & Echt, 2007). For example, Jee et al. (2005) found that among persons aged 65-99 years being evaluated for aged care services at a geriatric assessment center, west of Sydney, Australia, 22.5% had dual sensory problems. A study based on data from the UK Biobank, and thus tapping into the same population as the present study, showed a prevalence of dual sensory impairment of 3 % among adults aged 40-69 (Dawes, Dickinson et al. 2014). In the present study, with an older sample (Mean age 62.3 years, SD = 7.4), 15 % of the participants had vision problems indicated by

at least one of the following self-reported conditions diabetes-related eye disease, glaucoma, injury or trauma resulting in loss of vision, cataract, macular degeneration, or other serious eye condition.

2.7 Hearing aid use

Hearing aids (HA) are one means of providing better audibility for individuals with poor hearing and regular use may influence hearing-related brain plasticity (Giroud et al., 2017). HAs also seem to influence the cognitive load associated with recognition of degraded speech (Lunner, Rudner & Rönnberg, 2009; Ng, Rudner, Lunner, Rönnberg, 2015), depending on the type of HA setting (Souza, Arehart, Neher, 2015) and length of use (Rudner et al., 2009). Data from the UK Biobank showed that prevalence of HA use was 2 % among adults aged 40-69 (Dawes, Fortnum et al., 2014). In the present study, with a sample drawn several years later from the same population, 6 % of the participants reported that they used HAs most of the time. Surprisingly, 204 (41%) of the individuals who reported using HA most of the time produced an SRTn on their better ear within the normal range (SNR < -5.5 dB, Dawes et al., 2014). However, of those 204, with the worse ear, 42 met the criterion for poor hearing (SRTn > -3.5 dB SNR, Dawes, Fortnum et al., 2014), and a further 96 were in the intermediate range between poor and normal hearing, while 9 more had SRTn for one ear only. Thus, the majority of HA users did have behavioural hearing difficulties in at least one ear, and some may have had hearing difficulties that were not apparent from the data available, or used HAs to alleviate tinnitus.

2.8 Statistical analysis

The data were analysed using two sets of regression models for whole brain and each of the 154 predefined brain regions. In model sets 1 and 2, the dependent variable was the normalized volume (in mm^3) of one of the predefined brain regions and the independent variables included: age, age^2, gender, TDI, VR, vascular problems, vision problems and SRTn. In model set 1, these were the only independent variables, see appendix A. In model set 2, HA use was also entered as an independent variable, see appendix B.

Examination of intercorrelations among independent variables revealed the expected association between SRTn and age (r = .26, p < .001) and SRTn and HA use (r = .18, p < .001) as well as between age and HA use (r = .18, p < .001). There were also associations between age and vascular problems (r = .23, p < .001) and age and vision problems (r = .25, p < .001). Further, there was an association between vascular problems and gender (r = .13, p < .001) indicating that vascular problems were more prevalent in men than women. None of the other intercorrelations had a coefficient exceeding .1.

In all models, gender, vascular and vision problems as well as HA use were entered as dichotomous variables while the remaining variables were continuous. Preliminary analyses conducted on the full set of data included squared terms for all independent variables as linearity was not assumed. The only squared term that significantly improved model fit across many regions was the age-squared term. Thus, the age-squared term was retained in the reported regression models, while the squared terms relating to the other variables were excluded to simplify the models.

There were 48 regions that we predicted would have an association with SRTn. With a significance level of 0.05, applying a Bonferroni correction for this set of regions would give a critical p-value of 0.05/48 ≈ 0.001. However, it is well-known that the Bonferroni correction is too conservative when there is a large number of non-independent tests (e.g. Bland & Altman, 1995), so its use is likely to result in real effects being missed. For these 48 regions, to ensure that we had some protection against an increased false rejection rate due to multiple comparisons without being too conservative, we chose a critical p-value of 0.01 as a compromise between the nominal value of 0.05 and the Bonferroni value of 0.001. For the other 106 regions, we used a critical p-value of 0.001.

3. Results

Significant associations between SRTn and global and regional brain volume are shown in Table 1 (model set 1) and Table 2 (model set 2).

Tables 1 and 2 here

3.1 Whole brain

According to model set 1, poorer SRTn was significantly associated with lower whole brain grey matter volume (but not white matter volume, see Appendix A). In particular, a worsening of SRTn by 1 SD, i.e. an increase in SRTn of 1.6 dB, was associated with a predicted decrease of 1.1 cm^3 or 0.14 % in whole brain grey matter volume, if other predictor values are constant. This effect size can be compared to the mean difference of 1.2 cm^3 in annual rate of change in whole brain volume between individuals with normal and impaired hearing reported by Lin et al. (2014). However, when HA use was controlled for in model set 2, the association no longer reached significance, $p = .0114$, volume change = -1.0 cm3 or 0.13%.

We predicted an association between SRTn and brain volume in 48 regions. We found a significant association in nine of those regions with model 1 (see Table 1) and in all but one (right insular cortex) of these nine regions in model 2. All significant associations indicated that poorer SRTn was related to smaller regional brain volume. No significant associations were found in any of the other defined regions with either model sets 1 or 2.

3.2 Auditory processing regions

In accordance with our prediction, model set 1 showed that greater SRTn (i.e. poorer hearing) was associated with smaller grey matter volume in auditory processing regions including the left STG within both anterior and posterior divisions (see Figure 1) as well as right STG within the posterior division, see Table 1. The decrease in STG volume relating to 1 SD worsening of SRTn in the left anterior (10.89 mm3) and posterior (19.18 mm3) divisions represent similar percentage decreases in mean volume (0.57 %). The equivalent decrease in the right posterior division (17.53 mm3) can be compared to the difference in annual rate of decrease in rSTG volume relating to hearing impairment reported by Lin et al. (2014) of 0.10 cm3 or 100 mm3.

Figure 1 about here.

When HA use was controlled for in model set 2, associations between SRTn and grey matter volume in these three regions all remained significant, and in addition, we found that HA use was associated with smaller grey matter volume in the left thalamus (p = .0084, volume change = -42.41 mm3 or 1.22 % of mean volume 3476 mm3).

Contrary to previous studies, we did not find any significant association between regional brain volume and SRTn in primary auditory cortex (PAC, Eckert et al., 2012; Peelle et al., 2011) or the subcortical auditory pathway, see Appendix A.

3.3 Cognitive processing regions

We predicted that greater SRTn (poorer hearing) was related to lower brain volume in a number of regions known to be engaged during comprehension of degraded speech. In particular, we predicted lower brain volume in frontal, superior parietal and medial temporal regions.

3.3.1 Frontal regions

Lower grey matter volume in the right insular cortex, right middle frontal gyrus, the left precentral gyrus, right frontal medial cortex and the left paracingulate gyrus was associated with poorer SRTn with model set 1. In model set 2 (controlling for HA use), the association between right insular cortex volume and SRTn was no longer significant while the effects of age and gender remained significant.

3.3.2 Superior parietal regions

There were no significant associations between SRTn and the volume of superior parietal regions.

3.3.3 Medial temporal region

Poorer SRTn was associated with lower regional brain volume in the right hippocampus with both models. There was no significant effect of SRTn in the left hippocampus but it is worth noting that here the effect of vascular disorder was significant along with the effects of age and gender. This region was defined according to both extraction methods, a significant association was found in the right

hemisphere region only with the FIRST extraction method which does not distinguish tissue type. There was no significant association with SRTn in this region in either hemisphere defined according to the atlas based extraction method that isolates grey matter. However, there were significant effects of age and gender on hippocampus grey matter volume bilaterally as well as a significant effect of vascular disorder in the left hemisphere. Importantly, there was an effect of VR on hippocampus grey matter volume bilaterally such that poorer VR was associated with lower volume. Together these findings suggest that the association with SRTn in the right hippocampus relates to white rather than grey matter. This is in contrast to the other regional associations as well as the whole brain association with SRTn. The change in right hippocampal volume of 19.7 mm^3 per SD SRTn with model 1 can be compared to the difference in annual rate of decrease in right hippocampal volume of 0.01 cm^3 (10 mm^3) relating to hearing impairment reported by Lin et al. (2014).

Figure 2 about here.

Other regions included in the medial temporal region are the anterior and posterior divisions of the parahippocampal gyrus. There was no significant association with SRTn in any of these regions but all of them showed effects of age and gender, the left anterior region showed a significant effect of vascular disorder, while the right anterior and the left posterior regions showed significant effects of VR.

4. Discussion

The present study is the first, to our knowledge, to show an association between smaller regional brain volume and functional hearing in a non-clinical cohort of middle-aged adults. Building on data from 8701 particiants in the UK Biobank, It

shows that lower grey matter volume in both auditory processing regions in temporal cortex and cognitive processing regions in frontal cortex, as well as lower hippocampal volume are associated with poorer ability to recognize speech in noise. This is an extension of previous experimental studies showing an association between brain volume and pure tone thresholds in clinical populations (Boyen et al., 2013; Husain et al., 2011; Yang et al., 2014) and older adults with hearing loss (Eckert et al., 2012; Pelle et al., 2011). The present study also extends another recent population study (N = 2562) which showed an association between white matter volume in association tracts and poorer hearing (Rigters et al., 2018). In the study by Rigters et al. (2018), a breakdown into older and younger age groups showed that white matter volume was associated with functional hearing (but not pure tone thresholds) in the older segment of the sample (age range 70 – 100 years) but that in the younger segment of the sample, with an age-range (51 – 69 years) more comparable to the middle-aged participants in the present study, the opposite pattern was found, i.e. an association between white matter volume and pure tone thresholds (but not functional hearing). The lack of an association between functional hearing and regional brain volume in middle-aged adults in the study by Rigters et al. (2018) may be due to the substantially lower number of participants in the corresponding age group compared to the present study.

4.1 Whole brain

Results of the present study showed that poorer SRTn was associated with lower grey (but not white) matter volume globally. Because grey matter consists largely of synaptically dense neuropil while white matter consists largely of myelinated axons, this finding suggests that the lower volume is due to fewer synapses rather than fewer axons. The size of the effect was comparable to the reported increment in

annual rate of change in whole brain volume associated with hearing impairment as measured with pure tone thresholds (Lin et al., 2014) and apparent despite significant effects of age, gender, socioeconomic status and vascular disorder. It did not change substantially when HA use was controlled for.

4.2 Auditory processing regions

Results showed that poorer SRTn was associated with smaller grey matter volume in STG comparable with the annual hearing-related reduction in STG volume reported by Lin et al. (2014) but of a lower order of magnitude in terms of volume difference compared to the effects of age. These results replicate the findings of Husain et al. (2011) and Yang et al. (2014) who showed that hearing impairment is associated with smaller STG volume, and extends them to a non-clinical population in which speech perception in noise is linked with STG volume (c.f. Giroud et al., 2018; Harris et al., 2009). Conversely, it provides no support for results reported by Boyen et al. (2013) showing that hearing impairment was related to greater STG volume, or for the notion that increased long-term engagement of semantic LTM due to poorer hearing (Boyen et al., 2013) leads to enlargement of the underlying neural structure. Thus, the association between hearing ability and STG volume in the present study suggests that poorer hearing ability in a non-clinical population is associated with smaller grey matter volume in STG and that this decrement is not compensated by corresponding long-term engagement of semantic long-term memory. This notion should be tested in a longitudinal study.

These findings are also partially in line with Eckert et al. (2012) who reported an association between high frequency hearing loss and reduced grey matter volume in bilateral temporal lobe regions, predominantly in left PAC, and Peelle et al. (2011)

who reported that hearing loss was related to lower grey matter volume in STG, albeit predominantly in the right hemisphere. However, while we found associations with SRTn in anterior and posterior portions of left STG and the posterior portion of right STG, we found no significant associations in PAC (Heschl's gyrus). It should be noted here that both Eckert et al. (2012) and Peelle et al. (2011) investigated the association between frequency-specific audiometric thresholds and smaller more specific ROI, neither of which were available to us in the present study. Further, they used more targeted methods focusing specifically on PAC.

Similarly, we found no associations with SRTn in the subcortical portion of the auditory pathway. There were, however, significant effects of age on grey matter volume in all these regions as well as a significant effect of VR in PAC. The effect of VR in PAC is particularly interesting as this is the first cortical station along the auditory pathway and not specifically attuned to language and cognition (Cardin et al., 2016; Scott & McGettigan, 2013). One interpretation of this finding is that individuals with better cognitive abilities make better use of the auditory signal, maintaining PAC volume. Such an interpretation implies that cognitive skills may counteract atrophy of PAC driven the degraded auditory input caused by poor hearing. This should be investigated in longitudinal, experimental studies.

4.3 Cognitive processing regions

The predicted cognitive processing regions included frontal, superior parietal and medial temporal regions.

4.3.1 Frontal regions

Results showed that poorer SRTn was associated with reduced grey matter volume in five frontal regions, namely the right middle frontal gyrus, left precentral gyrus,

right frontal medial cortex, left paracingulate gyrus and right insular cortex. The middle frontal gyrus, frontal medial cortex and the precentral gyrus are associated with explicit working memory processing which is engaged during speech processing under challenging conditions (Rönnberg et al., 2013). Interestingly, both the paracingulate gyrus and the insular cortex are cingulo-opercular regions involved in performance monitoring that appear to optimize performance during challenging tasks (Eckert, Teubner-Rhodes, Vaden, 2016). Thus, decreased volume in these regions may be caused by reduced functional recruitment during comprehension of degraded speech, not only as a result of poor hearing as such, but also poorer performance monitoring. In the present study, findings of lower grey matter volume in areas of the prefrontal cortex associated with poorer ability to perceive speech in noise are in line with Bilodeau-Mercure et al. (2015) and Wong et al. (2010).

When HA use was controlled for, the association between SRTn and volume of right insular cortex was no longer significant. Because insular cortex is functionally associated with arousal, the modulation of the association with SRTn may indicate lowering of the high arousal levels associated with poor hearing through HA use (Kramer, Teunissen & Zekveld, 2016). This notion should be tested in a longitudinal, experimental study.

4.3.2 Superior parietal regions

The lack of association between SRTn and the volume of superior parietal regions implicated in speech recognition in noise (Scott & McGettigan, 2013; Zekveld et al., 2014) and working memory storage suggests that this is one region of the brain that does not atrophy as a result of poor hearing despite its functional role in listening under challenging conditions.

4.3.3 Medial temporal region

The hippocampus underpins LTM encoding (Rolls, 2010) and previous work has shown that its size is associated positively with cognitive abilities (Henneman et al., 2009; Maguire et al., 2000) and increases with training (Erickson et al., 2011) but is negatively associated with hearing thresholds (Lin et al., 2014). Greater activation of the hippocampus is found during speech recognition in noise (Zekveld et al., 2012). Further, poor hearing is related to poorer episodic LTM despite HA use (Rönnberg et al., 2011; 2014) as well as to incident dementia (Deal et al., 2017). The results of the present study are well in line with these findings, showing that poorer SRTn is associated with lower regional brain volume in the right hippocampus even when HA use is corrected for. Further, poorer VR was associated with lower grey matter volume in the hippocampus bilaterally and in the right parahippocampal gyrus bilaterally.

This pattern of findings supports previous evidence of a crucial role for the hippocampus in recognition of degraded speech. It is also in line with findings of a relation between smaller white matter association tracts, including the superior longitudinal fasciculus and uncinate fasciculus, and poorer hearing (Rigters et al., 2018). While the superior longitudinal fasciculus is known to be involved in cognitive control, the uncinate fasciculus is connected to the medial temporal region and its volume has been shown to be positively related to memory performance (Wendelken et al., 2015).

We propose that a bidirectional mechanism is likely to be in force. In one direction, mental agility keeps the episodic LTM encoding mechanism (supported by the hippocampus and other medial temporal structures) in trim, boosting hippocampal

volume (Maguire et al., 2000). In the other direction, poorer hearing leads to less activation of the episodic LTM mechanism during communication and consequent disuse (Rönnberg et al., 2011; 2014), with reduced hippocampal volume and possibly also smaller association tracts as a consequence.

4.4 Hearing aid use

Model set 2 controlled for HA use whereas model set 1 did not. Apparent differences between the models should be interpreted cautiously as only a small proportion of participants reported using HAs regularly, some of whom had SRTn on the better ear in the normal range. In sum, the analyses provide no conclusive evidence that HA use moderates the effect of SRTn on brain volume.

HA use increases with age and socioeconomic status (Dawes, Fortnum et al., 2014). Both these factors are controlled for in our analyses. However, efficacy of hearing rehabilitation is also affected by e.g. type of HA, how long the HA has been worn relative to when the hearing loss was first detected, and whether HA are fitted on one side or both; these data were not available from the UK Biobank and should be carefully controlled in future studies.

HA use was significantly associated with smaller volume in one of the predicted regions, namely the left thalamus. This region is extensive and multifunctional. It forms part of the subcortical auditory pathway but also plays a key role in cognition (Schmitt et al., 2017). It has extensive feedforward and feedback connections with cognitive processing regions in the frontal cortex (Lee, 2015; Peelle et al., 2011) and regulates functional connectivity within and between cortical regions (Nakajima & Halassa, 2017). Importantly, we found a significant effect of VR in this region in addition to significant effects of age and gender. Although we found no hearing-

related volume reduction in this region in the present study, such an association has been demonstrated in animal models (Basta, Tzschentke, Ernst, 2005), and Peelle et al., (2011) observed reduced neural activation during language processing relating to hearing loss. One interpretation of our findings is that HA use modulates the cognitive function of the thalamus during comprehension of degraded speech, leading to volume reduction. This should be investigated in further studies.

4.6 Limitations

The great advantage of the current study is that it includes data from a large cohort, allowing us to include only participants for whom complete data sets were available. However, it also has a number of related limitations. In particular, the authors of the present study had no control over many aspects of the design including the choice of cognitive and audiometric tests or preprocessing of the imaging data. As regards cognitive and audiometric testing, availabilitity of standard tests of specific cognitive functions such as working memory and executive function as well as pure tone audiometry whould have allowed more analytical analysis of the imaging data. On the other hand, we believe that the VR task provides a good functional measure of everyday cognition in the present study while the DTT provides a well-established measure of functional hearing ability, lending the results of our study good validity. ROIs were determined automatically based on established atlases in the present study and were thus not designed to test hypotheses specific to the study. However, the automaticity of the preprocessing pipeline does ensure good reliability. Unfortunately, data on volume of cerebrospinal fluid within ROIs was not available to confirm the specificity of SRTn effects (c.f. Eckert et al., 2012).

Further, the information available about hearing rehabilitation was minimal. Participants reported current HA use most of the time but there was no information on whether they used one or two aids or how long they had been using them. Also, among those who reported HA use, many performed well on the DTT, suggesting that their functional hearing ability was good. This makes it hard to interpret results relating to HA use.

5. Conclusion

We have extended previous work by showing in a large non-clinical cohort of middle-aged adults that poorer SRTn - a measure of functional hearing - is related to lower grey matter volume in the whole brain as well as in predicted functional networks including the STG and frontal regions. SRTn is also related to reduced white matter volume in the hippocampus. This supports previous work indicating that poor hearing leads to reduced volume in PAC and suggests that a similar mechanism may apply to other auditory and cognitive regions recruited during speech understanding under challenging conditions. There was no conclusive evidence that HA moderates the effect of poor hearing on brain volume in the population studied. The findings of this study should be evaluated in future longitudinal, experimental studies.

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References

Akeroyd, M.A. (2008). Are individual differences in speech reception related to Individual differences in cognitive ability? A survey of twenty experimental studies with normal and hearing-impaired adults. *International Journal of Audiology, 47* Suppl 2, S53-71.

Alfaro-Almagro, F., Jenkinson, M., Bangerter, N.K., Andersson, J.L.R., Griffanti, L., Douaud, G., … Smith, S.M. (2018). Image processing and Quality Control for the first 10,000 brain imaging datasets from UK Biobank. *Neuroimage, 166*, 400-424. https://doi.org/10.1016/j.neuroimage.2017.10.034.

Basta, D., Tzschentke, B. & Ernst, A. (2005). Noise-induced cell death in the mouse medial geniculate body and primary auditory cortex. *Neuroscience Letters, 381*(1-2), 199-204.

Besser, J., Koelewijn, T., Zekveld, A.A., Kramer, S.E. & Festen, J.M. (2013). How linguistic closure and verbal working memory relate to speech recognition in noise—a review. *Trends in Amplification, 17*(2), 75-93.

Bilodeau-Mercure, M., Lortie, C.L., Sato, M., Guitton, M.J. & Tremblay, P. (2015). The neurobiology of speech perception decline in aging. *Brain Structure and Function, 220*(2), 979-97. https://doi.org/10.1007/s00429-013-0695-3.

Bland, J.M. & Altman, D.G. (1995). Multiple significance tests: the Bonferroni method. *British Medical Journal, 310*, 170.

Boyen, K., Langers, D.R.M., de Kleine, E. & van Dijk, P. (2013). Gray matter in the brain: differences associated with tinnitus and hearing loss. *Hearing Research, 295,* 67e78.

Cardin, V. (2016). Effects of aging and adult-onset hearing loss on cortical auditory regions. *Frontiers in Neuroscience, 10*:199. https://doi.org/10.3389/fnins.2016.00199

Cardin, V., Orfanidou, E., Rönnberg, J., Capek, C.M., Rudner, M. & Woll, B. (2013). Dissociating cognitive and sensory neural plasticity in human superior temporal cortex. *Nature Communications, 4*, 1473. https://doi.org/10.1038/ncomms2463.

Cardin, V., Rudner, M., De Oliveira, R.F, Andin J, Su M.T., Beese, L., et al… Rönnberg, J. (2017). The organization of working memory networks is shaped by early sensory experience. *Cerebral Cortex, 30*, 1-15. https://doi.org/10.1093/cercor/bhx222.

Cardin, V., Smittenaar, R.C., Orfanidou, E., Rönnberg, J., Capek, C.M., Rudner, M. & Woll, B. (2016). Differential activity in Heschl's gyrus between deaf and hearing individuals is due to auditory deprivation rather than language modality. *Neuroimage, 124*(Pt A):96-106.

Dawes, P., Dickinson, C., Emsley, R., Bishop, P.N., Cruickshanks, K.J., Edmondson-Jones, M., … Munro, K. (2014). Vision impairment and dual sensory problems in middle age. *Ophthalmic and Physiological Optics 34*(4):479-88

Dawes, P., Fortnum, H., Moore, D.R., Emsley, R., Norman, P., Cruickshanks, K., et al… Munro, K. (2014). Hearing in middle age: a population snapshot of 40- to 69-year olds in the United Kingdom. *Ear and Hearing, 35*(3), e44-51.

Deal, J.A., Betz, J., Yaffe, K., Harris, T., Purchase-Helzner, E., Satterfield, S., et al… Lin, F.R. for the Health ABC Study Group (2017). Hearing impairment and incident dementia and cognitive decline in older adults: The Health ABC Study. *The Journals of Gerontology. Series A, Biological Sciences and Medical Sciences, 72*(5), 703-709. https://doi.org/10.1093/gerona/glw069.

Ding, H., Ming, D., Wan, B., Li, Q., Qin, W. & Yu, C. (2016). Enhanced spontaneous functional connectivity of the superior temporal gyrus in early deafness. *Scientific Reports, 6*:23239. https://doi.org/10.1038/srep23239.

Ding, H., Qin, W., Liang, M., Ming, D., Wan, B., Li, Q. & Yu, C. (2015). Cross-modal activation of auditory regions during visuo-spatial working memory in early deafness. *Brain, 138*(Pt 9), 2750-65. https://doi.org/10.1093/brain/awv165.

Eckert, M.A., Cute, S.L., Vaden, K.I. Jr, Kuchinsky, S.E. & Dubno, J.R. (2012). Auditory cortex signs of age-related hearing loss. *Journal of the Association for Research in Otolaryngology, 13*, 703–713.

Eckert, M.A., Kuchinsky, S.E., Vaden, K.I., Cute, S.L., Spampinato, M.V. & Dubno, J.R. (2013). White matter hyperintensities predict low frequency hearing in older adults. *Journal of the Association for Research in Otolaryngology, 14*(3), 425–433.

Eckert, M.A., Teubner-Rhodes, S., Vaden, K.I. Jr. (2016). Is listening in noise worth it? The neurobiology of speech recognition in challenging listening conditions. *Ear and Hearing, 37* Suppl 1:101S-10S. https://doi.org/10.1097/AUD.0000000000000300.

Erickson, K.I., Voss, M.W., Prakash, R.S., Basak, C., Szabo, A., Chaddock, L., … Kramer, A.F. (2011). Exercise training increases size of hippocampus and improves memory. *Proceedings of the National Academy of Sciences of the United States of America 108*, 3017–3022.

Finney, E. M., Fine, I. & Dobkins, K. R. (2001). Visual stimuli activate auditory cortex in the deaf. *Nature Neuroscience, 4*, 1171–1173.

Giroud, N., Hirsiger, S., Muri, R., Kegel, A., Dillier, N. & Meyer, M. (2018). Neuroanatomical and resting state EEG power correlates of central hearing loss in older adults. *Brain Structure and Function, 223*(1), 145-163. https://doi.org/10.1007/s00429-017-1477-0.

Giroud, N., Lemke, U., Reich, P., Matthes, K., Meyer, M. (2017). The impact of hearing aids and age-related hearing loss on auditory plasticity across three months – An electrical neuroimaging study, *Hearing Research, 353*,162-175. https://doi.org/10.1016/j.heares.2017.06.012.

Harris, K.C., Dubno, J.R., Keren, N.I., Ahlstrom, J.B. & Eckert, M.A. (2009). Speech recognition in younger and older adults: a dependency on low-level auditory cortex. *Journal of Neuroscience, 29*(19), 6078-87. https://doi.org/10.1523/JNEUROSCI.0412-09.2009.

Good, C. D., Johnsrude, I. S., Ashburner, J., Henson, R. N. A., Friston, K.J., & Frackowiak, R. S. J. (2001). A voxel-based morphometric studyof ageing in 465 normal adult human brains. *NeuroImage, 14*, 21–36.

Helzner, E.P., Patel, A.S., Pratt, S., Sutton-Tyrrell, K., Cauley, J.A., Talbott, E., … Newman, A.B. (2011). Hearing sensitivity in older adults: associations with cardiovascular risk factors in the health, aging and body composition study. *Journal of the American Geriatrics Society*, 59(6), 972-976.

Henneman, W.J., Sluimer, J.D., Barnes, J., van der Flier, W.M., Sluimer I.C., Fox, N.C., … Barkhof, F. (2009). Hippocampal atrophy rates in Alzheimer disease: added value over whole brain volume measures. *Neurology, 17;72*(11), 999-1007. https://doi.org/10.1212/01.wnl.0000344568.09360.31.

Hunter, C.R., Pisoni, D.B. (2018). Extrinsic cognitive load impairs spoken word recognition in high- and low-predictability sentences. *Ear and Hearing, 39*(2), 378-389. https://doi.org/10.1097/AUD.0000000000000493.

Husain, F.T., Medina, R.E., Davis, C.W., Szymko-Bennett, Y., Simonyan, K., Pajor, N.M., Horwitz, B. (2011). Neuroanatomical changes due to hearing loss and chronic tinnitus: a combined VBM and DTI study. *Brain Research, 1369*: 74–88.

Jayakody, D.M.P., Friedland, P.L, Martins, R.N. & Sohrabi, H.R. (2018). Impact of aging on the auditory system and related cognitive functions: A narrative review. *Frontiers in Neuroscience, 12*, 125. https://doi.org/10.3389/fnins.2018.00125

Jee, J., Wang, J.J., Rose, K.A., Lindley, R., Landau, P. & Mitchell, P. (2005). Vision and hearing impairment in aged care clients. *Ophthalmic Epidemiology, 12*(3), 199-205.

Jenkins, K.A., Fodor, C., Presacco, A. & Anderson, S. (2018). Effects of amplification on neural phase locking, amplitude, and latency to a speech syllable. *Ear and Hearing, 39*(4), 810-824. https://doi.org/10.1097/AUD.0000000000000538.

Jenkinson, M., Bannister, P., Brady, J., & Smith, S. (2002). Improved optimisation for the robust and accurate linear registration and motion correction of brain images. *NeuroImage, 17*(2), 825–841.

Jenkinson, M. & Smith, S. (2001). A global optimisation method for robust affine registration of brain images. *Medical Image Analysis, 5*(2), 143–156.

Karawani, H., Jenkins, K.A., Anderson, S. (2018a). Neural and behavioral changes after the use of hearing aids. *Clinical Neurophysiology, 129*(6), 1254-1267. https://doi.org/10.1016/j.clinph.2018.03.024.

Karawani, H., Jenkins, K. & Anderson, S. (2018b). Restoration of sensory input may improve cognitive and neural function. *Neuropsychologia, 114*, 203-213. https://doi.org/10.1016/j.neuropsychologia.2018.04.041.

Keidser, G., Rudner, M., Seeto, M., Hygge, S. & Rönnberg, J. (2016). The effect of functional hearing and hearing aid usage on verbal reasoning in a large community-dwelling population. *Ear and Hearing, 37*:e26–e36.

Kramer, S. E., Teunissen, C., Zekveld, A. A. (2016). Cortisol, chromogranin A, and pupillary responses evoked by speech recognition tasks in normally hearing and hard-of-hearing listeners: a pilot study. *Ear and Hearing, 37*, 126S–135S.

Lee, C.C. (2015). Exploring functions for the non-lemniscal auditory thalamus. *Frontiers in Neural Circuits, 9*, 69. https://doi.org/10.3389/fncir.2015.00069

Liew, G., Wong, T.Y., Mitchell, P., Newall, P., Smith, W. & Wang, J.J. (2007). Retinal microvascular abnormalities and age-related hearing loss: The Blue Mountains Hearing Study. *Ear and Hearing, 28*: 394–401.

Lin, F.R., Ferrucci, L., An, Y., Goh, J.O., Doshi, J., Metter, E.J., … Resnick, S.M. (2014). Association of hearing impairment with brain volume changes in older adults. *Neuroimage 90*: 84–92.

Lövdén, M., Wenger, E., Mårtensson, J., Lindenberger, U., Bäckman, L. (2013). Structural brain plasticity in adult learning and development. *Neuroscience and Biobehavioral Reviews, 37*(9 Pt B):2296-310. https://doi.org/10.1016/j.neubiorev.2013.02.014.

Lunner, T., Rudner, M., Rönnberg, J. (2009). Cognition and hearing aids. *Scandinavian Journal of Psychology, 50*(5):395-403.

Maguire, E. A., Gadian, D. G., Johnsrude, I. S., Good, C. D., Ashburner, J., Frackowiak, R. S. F., & Frith, C.D. (2000). Navigation-related structural change in the hippocampi of taxi drivers. *Proceedings of the National Academy of Sciences of the United States of America, 97*, 4398–4403.

Mattys, S.L., Davis, M.H., Bradlow, A.R. & Scott, S.K. (2012) Speech recognition in adverse conditions: A review, *Language and Cognitive Processes, 27*, 7-8, 953-978, https://doi.org/10.1080/01690965.2012.705006

Merabet, L.B, & Pascual-Leone, A. (2010). Neural reorganization following sensory loss: the opportunity of change. *Nature Reviews Neuroscience, 11*:44–52.

Miller, K.L., Alfaro-Almagro, F., Bangerter, N.K., Thomas, D.L., Yacoub, E., Xu, J., … Smith, S.M. (2016) Multimodal population brain imaging in the UK Biobank prospective epidemiological study. *Nature Neuroscience, 19*(11):1523–1536.

Nakajima, M. & Halassa, M.M. (2017). Thalamic control of functional cortical connectivity. *Current Opinion in Neurobiology, 44*, 127-131. https://doi.org/10.1016/j.conb.2017.04.001.

Nishimura, H., Hashikawa, K., Doi, K., Iwaki, T., Watanabe, Y., Kusuoka, H., … Kubo, T. (1999). Sign language 'heard' in the auditory cortex. *Nature 397*, 116.

Ng, E.H., Rudner, M., Lunner, T., Rönnberg, J. (2015). Noise reduction improves memory for target language speech in competing native but not foreign language speech. *Ear and Hearing, 36*(1), 82-91.

Obleser, J., Wöstmann, M., Hellbernd, N., Wilsch, A. & Maess, B. (2012). Adverse listening conditions and memory load drive a common α oscillatory network. *Journal*

of Neuroscience, 32(36), 12376-83. https://doi.org/10.1523/JNEUROSCI.4908-11.2012.

Peelle, J.E., Troiani, V., Grossman, M. & Wingfield, A. (2011). Hearing loss in older adults affects neural systems supporting speech comprehension. *Journal of Neuroscience, 31*, 12638–12643.

Peelle, J.E, & Wingfield, A. (2016). The neural consequences of age-related hearing loss. *Trends in Neurosciences, 39*(7), 487-497.

Plomp, R. (1978). Auditory handicap of hearing impairment and the limited benefit of hearing aids. *Journal of the Acoustical Society of America, 63*(2), 533-49.

Rauschecker, J.P. & Scott, S.K. (2009). Maps and streams in the auditory cortex: nonhuman primates illuminate human speech processing, *Nature Neuroscience, 12*(6), 718-724

Rigters, S.C., Cremers, L.G.M., Ikram, M.A., van der Schroeff, M.P., de Groot, M., Roshchupkin,… Vernooij, M.W. (2018). White-matter microstructure and hearing acuity in older adults: a population-based cross-sectional DTI study. *Neurobiology of Aging, 61*, 124-131. https://doi.org/10.1016/j.neurobiolaging.2017.09.018.

Rolls, E.T. (2010). A computational theory of episodic memory formation in the hippocampus. *Behavioral Brain Research, 215*, 180–196

Rönnberg, J., Hygge, S., Keidser, G. & Rudner, M. (2014). The effect of functional hearing loss and age on long- and short-term visuospatial memory: evidence from the UK biobank resource. *Frontiers in Aging Neuroscience, 6*:326.

Rönnberg J, Holmer, E., Rudner M (2018). The ease of language understanding (ELU) model: Predictive and postdictive aspects. Under 2nd review.

Rönnberg, J., Lunner, T., Zekveld, A., Sörqvist, P., Danielsson, H., Lyxell, B., … Rudner, M. (2013). The ease of language understanding (ELU) model: Theoretical, empirical, and clinical advances. *Frontiers in Systems Neuroscience, 7*, 31. https://doi.org/10.3389/fnsys.2013.00031.

Roth, T.N., Hanebuth, D. & Probst, R. (2011). Prevalence of age-related hearing loss in Europe: a review. *European Archives of Otorhinolaryngology, 268*, 1101–1107.

Rudner, M., Foo, C., Rönnberg, J., & Lunner, T. (2009). Cognition and aided speech recognition in noise: specific role for cognitive factors following nine-week experience with adjusted compression settings in hearing aids. *Scandinavian Journal of Psychology, 50*, 405–418.

Rudner, M., Lunner, T., Behrens, T., Thorén, E.S., Rönnberg, J. (2012). Working memory capacity may influence perceived effort during aided speech recognition in noise. *Journal of the American Academy of Audiology, 23*(8), 577-89.

Rudner, M., Rönnberg, J. & Lunner, T. (2011). Working memory supports listening in noise for persons with hearing impairment. *Journal of the American Academy of Audiology, 22*(3), 156-67.

Saunders, G.H. & Echt, K.V. (2007). An overview of dual sensory impairment in older adults: Perspectives for rehabilitation. *Trends in Amplification 11*(4): 243–258.

Schmitt, L.I., Wimmer, R.D., Nakajima, M., Happ, M., Mofakham, S. & Halassa, M.M. (2017). Thalamic amplification of cortical connectivity sustains attentional control. *Nature, 545*(7653), 219-223. https://doi.org/10.1038/nature22073.

Scott, S.K. & McGettigan, C. (2013). The neural processing of masked speech. *Hearing Research, 303*, 58-66. https://doi.org/10.1016/j.heares.2013.05.001.

Scott, S.K., Rosen, S., Lang, H. & Wise, R.J.S. (2006). Neural correlates of intelligibility in speech investigated with noise vocoded speech—A positron emission tomography study. *Journal of the Acoustical Society of America, 120*(2), 1075–1083. HTTPS://DOI.ORG/10.1121/1.2216725

Smith, S. (2002). Fast robust automated brain extraction. *Human Brain Mapping, 17*(3), 143–155.

Smith, S., Almagro, F.A., & Miller, K. (2017). *UK Biobank Brain Imaging Documentation, Version 1.3*. http://www.ukbiobank.ac.uk

Smits, C., Kapteyn, T.S. & Houtgast, T. (2004). Development and validation of an automatic speech-in-noise screening test by telephone. *International Journal of Audiology, 43*, 15–28.

Souza, P., Arehart, K., & Neher, T. (2015). Working memory and hearing aid processing: Literature findings, future directions, and clinical applications. *Frontiers in Psychology, 6,* 1894.

Sudlow, C., Gallacher, J., Allen, N., Beral, V., Burton, P., Danesh, J., … Collins, R. (2015) UK biobank: An open access resource for identifying the causes of a wide range of complex diseases of middle and old age. *PLoS Med 12*(3), e1001779.

Torre III, P., Cruickshanks, K.J., Klein, B.E.K., Klein, R., Nondahl, D.M. (2005). The association between cardiovascular disease and cochlear function in older adults. *Journal of Speech, Language, and Hearing Reseacrh*, 48, 473–481.

Townsend, P., Phillimore, P., & Beattie, A. (1988). *Health and Deprivation: Inequality and the North*. London: Routledge.

Wendelken, C., Lee, J. K., Pospisil, J., Sastre, M., Ross, J. M., Bunge, S. A., & Ghetti, S. (2015). White Matter Tracts Connected to the Medial Temporal Lobe Support the Development of Mnemonic Control. *Cerebral Cortex*, *25*(9), 2574–2583. http://doi.org/10.1093/cercor/bhu059

Wong, P.C., Ettlinger, M., Sheppard, J.P., Gunasekera, G.M., Dhar, S. (2010). Neuroanatomical characteristics and speech perception in noise in older adults. *Ear and Hearing, 31*(4):471-9. https://doi.org/10.1097/AUD.0b013e3181d709c2.

Wong, P.C., Jin, J.X., Gunasekera, G.M., Abel, R., Lee, E.R. & Dhar, S. (2009). Aging and cortical mechanisms of speech perception in noise. *Neuropsychologia, 47*(3), 693-703. https://doi.org/10.1016/j.neuropsychologia.2008.11.032.

Yang, M., Chen, H.-J., Liu,B., Huang, Z.-C., Feng,Y., Li, J., … Teng, G.-J. (2014). Brain structural and functional alterations in patients with unilateral hearing loss. *Hearing Research, 316*, 37–43.doi:10.1016/j.heares.2014.07.006

Zekveld, A.A., Kramer, S.E., Rönnberg, J. & Rudner, M. (2018). In a concurrent memory and auditory perception task, the pupil dilation response is more sensitive to memory load than to auditory stimulus characteristics. *Ear and Hearing*, Publish Ahead of Print - https://doi.org/10.1097/AUD.0000000000000612

Zekveld, A.A., Rudner, M., Johnsrude, I.S., Heslenfeld, D., Rönnberg, J. (2012). Behavioural and fMRI evidence that cognitive ability modulates the effect of semantic context on speech intelligibility. *Brain and Language, 122*(2), 103-113. HTTPS://DOI.ORG/10.1016/j.bandl.2012.05.006

Zekveld AA, Rudner M, Kramer SE, Lyzenga J, Rönnberg J. (2014). Cognitive processing load during listening is reduced more by decreasing voice similarity than

by increasing spatial separation between target and masker speech. *Frontiers in Neuroscience, 8*:88. https://doi.org/10.3389/fnins.2014.00088.

Figure, table and appendix legends.

Figure 1. Significant association with correction for age, age2, gender, TDI, VR, vascular problems and vision problems between greater SRTn (poorer hearing ability) and lower adjusted normalized grey matter volume (mm3) in superior temporal gyrus, posterior division (left).

Figure 2. Significant association with correction for age, age2, gender, TDI, VR, vascular problems and vision problems between greater SRTn (poorer hearing ability) and lower adjusted normalized volume (mm3) of right hippocampus.

Table 1. Significant effects of SRTn on global and regional brain volume according to model set 1. Effects on these regions of the other independent variables are also shown.

Table 2. Significant effects of SRTn on global and regional brain volume according to model set 2 including correction for HA use. Effects on these regions of the other independent variables are also shown.

Note for Tables 1 and 2

Note. All regions are shown for which a significant change in brain volume was obtained in either model. H-O-D indicates that the region was extracted using the Harvard-Oxford cortical and subcortical atlases and the Diedrichsen cerebellar atlas and refers to grey matter. FIRST indicates that the region was modelled according to FMRIB's Integrated Registration and Segmentation Tool and does not differentiate between grey and white matter. Models are based on normalized brain volume and correction was made for age, age^2, gender, TDI (Townsend Deprivation Index which is a measure of socioeconomic status), VR (Verbal reasoning), vascular and vision problems. The volume decrease in mm^3 and % of mean volume is for 1 SD (1.6 dB)

worsening of SRTn. SES (Standardized Effect Size) is the volume change expressed as a fraction of the SD of the volume. STG, Superior Temporal Gyrus; L, left; R, right.

Note for Appendices A and B

Note. H-O-D indicates that the region was extracted using the Harvard-Oxford cortical and subcortical atlases and the Diedrichsen cerebellar atlas and refers to grey matter. FIRST indicates that the region was modelled according to FMRIB's Integrated Registration and Segmentation Tool and does not differentiate between grey and white matter. All regions are shown. The volume decrease in mm^3 and % of mean volume is for 1 SD (1.6 dB) worsening of SRTn. SES (Standardized Effect Size) is the volume change expressed as a fraction of the SD of the volume. Models are based on normalized brain volume and correction was made for age, age^2, gender, TDI (Townsend Deprivation Index which is a measure of socioeconomic status), VR (Verbal reasoning), vascular and vision problems. L, left; R, right; vent., ventricle; Cx, Cortex; IFG, Inferior Frontal Gyrus; triang., triangularis; operc., opercularis; Temp., Temporal; STG, Superior Temporal Gyrus; ant., anterior division; post., posterior division; MiTG, Middle Temporal Gyrus; temporooccip., temporooccipital; ITG, Inferior Temporal Gyrus; SMG, Supramarginal Gyrus; Parahipp, Parahippocampal. Heschl's gyrus includes H1 and H2.