Hearing loss is associated with gray matter differences in older adults at risk for and with Alzheimer's disease

Giroud, N. [1,2*], Pichora-Fuller, M. K. [3], Mick P. [4], Wittich, W. [5], Al-Yawer, F. [1], Rehan, S. [1], Orange, J.B., & Phillips, N. A. [1,2,7]

[1] *Department of Psychology, Centre for Research in Human Development, Concordia University, Montréal, Québec, Canada*

[2] *Centre for Research on Brain, Language, and Music, Montréal, Québec, Canada*

[3] *Department of Psychology, University of Toronto, Mississauga, Ontario, Canada*

[4] *Department of Surgery, College of Medicine, University of Saskatchewan, Saskatoon, Saskatchewan, Canada*

[5] *School of Optometry, Université de Montréal, Montreal, Quebec, Canada*

[6] *School of Communication Sciences and Disorders, Western University, London, Canada*

[7] *Lady Davis Institute for Medical Research, Jewish General Hospital, Montréal, Québec, Canada*

Contact information authors:

First author: Nathalie Giroud: nathalie.giroud@uzh.ch

Senior author: Natalie A. Phillips: natalie.phillips@concordia.ca

***Corresponding author**

Dr. Natalie Phillips, Concordia University, Cognition, Aging, and Psychophysiology Laboratory, 7141 Sherbrooke Street West, H4B 1R6 Montreal, Quebec, Canada, Phone: +1 (514) 848-2424 ext. 2218, Email: natalie.phillips@concordia.ca

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Abstract

Hearing loss in healthy older adults is associated with accelerated brain volume loss; however, little is known about this association in those with or at risk for dementia. Using data from the COMPASS-ND study we investigated associations between hearing loss and hippocampal volume as well as cortical thickness in older adults with subjective cognitive decline (SCD, N=35), mild cognitive impairment (MCI, N=79), and Alzheimer's dementia (AD, N=21). SCD participants with greater pure-tone hearing loss exhibited lower hippocampal volume, a biomarker of dementia. They also showed more cortical thickness in the left superior temporal gyrus and right pars opercularis, suggesting compensatory cortical changes. No significant associations were found in those with cognitive impairment (MCI or AD) who had greater brain atrophy, suggesting that dementia-related neuropathology may supercede any effects of pure-tone hearing loss on brain volume loss. In contrast, greater speech-in-noise reception thresholds were associated with lower cortical thickness bilaterally across much of the cortex in AD. The AD group also showed worse speech-in-noise thresholds compared to the SCD group, suggesting that strong brain atrophy driven by dementia-related neuropathology in AD is associated with hearing problems in noisy environments.

Words: 188

Key Words: subjective cognitive decline, mild cognitive impairment, Alzheimer's dementia, brain structure, hearing loss, CLSA

Highlights

- In older adults with subjective cognitive complaints, greater pure-tone hearing loss was associated with lower hippocampal volume.
- Pure-tone hearing loss was not associated with brain atrophy in older adults with cognitive impairment (i.e., MCI or AD).
- Older adults with Alzheimer's dementia exhibited higher speech-in-noise thresholds than older adults without cognitive impairment.
- In older adults with Alzheimer's dementia, greater brain atrophy across large portions of the cortex was associated with greater speech-in-noise thresholds.

1. Introduction

The global prevalence of Alzheimer's dementia (AD) is expected to triple by 2050, leading to immense personal, social, and health care costs[1]. Attention is now focused on behavioral and non-pharmacological interventions because of the low efficacy of pharmacological treatments (Livingston et al., 2017, 2020). Identifying and treating modifiable risk factors is being adopted as a strategy to delay the onset or progression of AD (Livingston et al., 2017, 2020). Indeed, it is estimated that delaying the onset of dementia by 5 years would lead to an approximate 50% reduction in prevalence after 10 years (Brookmeyer et al., 1998). In a meta-analysis by Livingston et al. (2017) examining risk factors for dementia, the population attributable fraction for hearing loss was estimated at 9%, which was higher than the value for all other modifiable risk factors in the study. In other words, hypothetically eliminating hearing loss from the population could lead to a 9% decline in the prevalence of AD, assuming a causal relationship. Currently, there is insufficient evidence regarding whether or not prevention of or treatments for hearing loss can modify dementia risk, but this is an active topic of research (Deal et al., 2018; Sanchez et al., in press).

Hearing loss is a chronic health issue among older adults and is considered to be one of the top three leading causes of disability in old age (Ciorba et al., 2012; Mathers et al., 2008). Typically, age-related hearing loss is characterized by elevated pure-tone audiometric thresholds for high-frequency sounds (International Organization for Standardization (ISO), 2017). Age-related hearing loss is multifactorial, with increased audiometric thresholds at high-frequencies often resulting from damage to cochlear outer hair cells or the stria vascularis in the auditory periphery (Dubno et al., 2013; Mills et al., 2006). In addition, there is evidence that degeneration in the synaptic connections between cochlear hair cells and nerve fibers may contribute to inaccurate coding of acoustic signals, leading to difficulties with speech understanding (Liberman & Kujawa, 2017). Notably, even older adults with normal or near-normal audiometric pure-tone thresholds can have difficulties understanding speech in noise in everyday situations because of age-related declines in auditory processing (Pichora-Fuller et al., 2017). In general, age-related hearing loss leads to difficulty participating in conversations and social interactions and is associated with reduced quality of life, social isolation, and higher rates of depressive symptoms (Arlinger, 2003; Ciorba et al., 2012; Pichora-Fuller et al., 2015; Vannson et al., 2015). Older adults often remark that they can hear but cannot discriminate or easily understand what is said in noisy environments.

There is a strong link between auditory and cognitive functioning (e.g. Lindenberger & Baltes, 1994). Hearing loss (defined by pure-tone thresholds or measures of auditory processing such as speech-in-noise or word recognition tests) is related to self-reported (Curhan et al., 2019) and behavioral measures of cognitive decline in aging (de la Fuente et al., 2019; Fischer et al., 2016; Fortunato et al., 2016; Merten et al., 2019). Hearing loss also is linked to incident all-cause dementia (Albers et al.,

[1] https://www.who.int/mental_health/neurology/dementia/guidelines_risk_reduction/en/

2015; Deal et al., 2015, 2019; Gates et al., 2011; Lin, Metter, et al., 2011; Lin & Albert, 2014; Osler et al., 2019). However, despite growing evidence for a link between auditory and cognitive decline, the underlying mechanisms are still unclear. Several hypotheses were proposed over 25 years ago to explain the relationship between hearing and cognitive decline (Lindenberger & Baltes, 1994 and versions of these hypotheses continue to motivate research); however, no single hypothesis can explain most of the effects reported in the literature (Pronk et al., 2019). Consistent with the common-cause hypothesis, associations between hearing and cognitive decline may be based on a common biological cause such as widespread age-related neural decline (Li & Lindenberger, 2002). According to the information degradation hypothesis, it is possible that older adults do not encode auditory information as well as those with normal hearing. When it is difficult to hear, such as in noisy environments, the listener may increase the allocation of cognitive resources to lower-level perceptual auditory processing, thereby diverting resources from higher-order cognitive processing and resulting in poorer cognitive performance on measures of memory for example (McCoy et al., 2005). In addition, according to the deprivation hypothesis, chronic reallocation of cognitive resources may bring about permanent changes in patterns of brain activation (Peelle & Wingfield, 2016).

In addition to the auditory-cognitive link, an association between hearing loss and brain atrophy in gray and white matter has been reported. Greater hearing loss is significantly correlated with lower gray matter volume in brain regions associated with auditory perception (e.g., superior temporal lobe) as well as with cognition (e.g., hippocampus, parahippocampus) (Alfandari et al., 2018; Armstrong et al., 2019; Eckert et al., 2012; Ren et al., 2018; Rigters et al., 2018, 2017; Rudner et al., 2019; Tuwaig et al., 2017; Uchida et al., 2018; but see Profant et al., 2014). Moreover, longitudinal studies demonstrate that greater hearing loss is related to greater gray matter volume loss (Lin et al., 2014; Xu et al., 2019) and lateral ventricle expansion (Eckert et al., 2019) with aging. These findings are consistent with the sensory deprivation hypothesis, such that less and/or degraded sensory input into the brain may lead to long-term deprivation effects on the auditory pathways causing structural decline as well as neurofunctional changes (Lin et al., 2014; Peelle & Wingfield, 2016). For example, Lin et al. (2014) showed that cognitively normal older adults with greater hearing loss compared to those with normal hearing exhibit accelerated volume loss in several regions of the temporal lobe (i.e., right superior, middle, and inferior temporal gyri and the parahippocampus) that are important for auditory processing, semantic memory functioning, and cognitive processing. The associations between hearing loss and brain atrophy provide evidence for the sensory deprivation hypothesis because they suggest that long-term hearing loss is associated with structural loss in the brain.

Previous studies of the associations between hearing loss and brain atrophy have examined mainly healthy older adults with no clinically significant cognitive impairment. Studies of those who are particularly at risk for developing AD, as well as in those who have already been diagnosed with AD, could reveal whether hearing loss is independently associated with brain atrophy in those who typically have more vulnerable brains because of their neuropathology-related atrophy. AD

neuropathology typically causes accelerated gray and white matter declines which are also core biomarkers of AD (for a review see Pini et al., 2016). Furthermore, individual differences in cognitive performance correlate with brain structural measures in those with subjective cognitive decline (SCD) and mild cognitive impairment (MCI). For example, lower memory performance in a face-name recall test, which is sensitive to early stages of AD, correlated with smaller right hippocampal volume in SCD and MCI (Caillaud et al., 2019). SCD refers to those who have subjective complaints about their cognitive capacities, but who perform within normal limits on behavioral neuropsychological tests (Jessen et al., 2010, 2014). MCI refers to those who show clinically significant impairment in one or more cognitive domains, while their functional abilities in everyday life are judged to be intact (Chertkow et al., 2019, see section 2.1. for details about diagnostic criteria). There is longitudinal evidence that SCD is a risk factor for cognitive decline as well as for AD and occurs at the preclinical stage of AD and other dementias (Dufouil et al., 2005; Glodzik-Sobanska et al., 2007; Jessen et al., 2010; Reisberg et al., 2010; van Oijen et al., 2007). Similarly, MCI is a strong risk factor for AD and describes an intermediate stage between normal cognitive aging or preclinical AD and AD, although not all persons with MCI convert to AD with reported rates between 20-40% (Albert et al., 2011; Roberts & Knopman, 2013).

The extent to which hearing loss is independently associated with (sub)cortical gray matter loss in those with varying degrees of cognitive impairment and neuropathology has yet to be examined. There is little evidence that pathological features of AD, such as amyloid plaques or neurofibrillary tangles, are observed in the cochlea (Sinha et al., 1993; Wang & Wu, 2015, but see Omata et al., 2016). Thus, an independent association between hearing loss and brain atrophy in those at risk for or with AD would be evidence for the sensory deprivation hypothesis in these individuals.

In the current study, we analyzed data from the first wave of data released from the COMPASS-ND (Comprehensive Assessment of Neurodegeneration and Dementia) study (Chertkow et al., 2019). The COMPASS-ND sample includes participants with varying types and degrees of cognitive impairment (for more information about COMPASS-ND see: http://ccna-ccnv.ca/compass-nd-study/). We examined the extent to which hearing loss is related to gray matter atrophy in the hippocampus as well as in FreeSurfer-based whole-brain analysis on cortical thickness in those with SCD, MCI, and AD. We hypothesized that greater higher pure-tone thresholds and/or higher speech-in-noise thresholds would be associated with lower cortical thickness in all three groups. Specifically, we expected pure-tone thresholds to be negatively correlated with cortical thickness of primary and secondary auditory areas, the hippocampal volume, and possibly the prefrontal cortex (due to reallocation of resources) in individuals with hearing loss. Furthermore, we hypothesized speech-in-noise reception thresholds to be negatively associated with cortical thickness of primary and secondary auditory areas, the prefrontal cortex, and temporo-parietal areas involved in speech processing. Such associations would be evidence for the sensory deprivation hypothesis in those with or at high risk for developing dementia.

2. Material and Methods

2.1. Participants

Of the first and second wave of the COMPASS-ND data released in November 2018 and May 2019 respectively, we analyzed the data from individuals who met the criteria for SCD (N=35), MCI (N=85), or AD (N=25). Of those 145 participants, 10 were excluded because they did not have MRI data (3 MCI, 1 AD), did not have hearing data (1 MCI), or were outliers (+3 standard deviations (SD) above average) in cortical volume (2 MCI, 3 AD) skewing most of the correlations. This led to a final total of 135 included participants (N=35 SCD; N=79 MCI; N=21 AD). Table 1 provides an overview of the demographic and health variables for each group, as well as information about participants' vision. We found significant group differences in age, sex, as well as a group difference in education approaching significance (p=.1); thus, we included these variables as covariates in all analyses.

Table 1:
Summary statistics on demographic, vision, and health variables for COMPASS-ND participants as a function of diagnostic groups.

	SCD (N=35)		MCI (N=79)		AD (N=21)				
	N		N		N		F	*p*	Post-hoc
Female	20 (57 %)		29 (37%)		1 (5%)		8.48	**<.001**	SCD,MCI>AD
Hearing aid users	2 (6%)		13 (17%)		4 (19%)		1.48	.23	-
Right handedness	32 (91%)		76 (96%)		19 (91%)		1.41	.25	-
	M	SD	M	SD	M	SD			
Age, years	69.45	6.18	73.47	6.57	75.87	7.24	7.24	**.001**	SCD<MCI,AD
Education, years	16.79	3.19	15.52	3.07	15.31	2.96	2.36	.10	-
MoCA score	27.23	1.94	24.06	3.06	19.38	3.04	51.21	**<.001**	SCD>MCI>AD
Smoking (0=no, 1=yes)	.51	.51	.47	.50	.57	.51	.33	.72	-
Hypertension (0=no, 1=yes)	.23	.43	.35	.48	.33	.48	.89	.41	-
Contrast sensitivity (CS)* in log CS units**	1.70	.15	1.67	.15	1.48	.17	12.62	**<.001**	SCD,MCI>AD
Reading Acuity in logMAR units***	.28	.27	.30	.29	.20	.21	1.26	.29	-

SCD=subjective cognitive decline, MCI=mild cognitive impairment, and AD=Alzheimer's dementia groups.
*most of the study participants had normal CS (SCI: 87.5%, MCI: 93%, AD: 50%), while few had moderately impaired CS (SCI: 12.5%, MCI: 7%, AD: 50%); however, these levels of impairment are unlikely to interfere with test administration of visual stimuli
** < 1 log CS = severe impairment, 1-1.5 log CS = moderate impairment, > 1.5 log CS = normal for age 60+
*** logMAR = logarithm of the minimum angle of resolution; logMAR < .30 (equivalent of better than 20/40) = normal acuity. logMAR .30 to .50 (20/40 to 20/60) = moderate visual impairment

General COMPASS-ND inclusion criteria included: being between 50-90 years of age, having a study partner who sees the participant weekly and who can participate as required by the protocol, passing the safety requirements for the MRI scanning, and possessing sufficient proficiency in English or French (as judged by the examiner) to undertake self-report and neuropsychological testing. Exclusion criteria were as follows: presence of significant known chronic brain disease unrelated to AD, on-going alcohol or drug abuse which, in the opinion of the investigator, may have interfered with the person's ability to comply with the study procedures, severely cognitively impaired individuals with a score of $\leq$ 13/30 on the Montréal Cognitive Assessment (MoCA) (Nasreddine et al., 2005) or a symptomatic stroke within the previous year. Written informed consent was obtained from all participants. The COMPASS-ND study was approved by the Jewish General Hospital Research Ethics Board.

2.2. Criteria for SCD participants

One core criterion for SCD is a self-experienced persistent decline in cognitive capacities in comparison to previous normal status, which is unrelated to an acute event. This criterion was operationalized by two questions 1) "Do you feel like your memory or thinking is becoming worse?" and, if so, 2) "Does this concern you?". Only individuals who answered the two questions with "yes" were assigned to the SCD group (following Jessen et al., 2014). Further inclusion criteria for SCD were normal age- and education-adjusted performance on standardized cognitive tests (Chertkow et al., 2019) including a) a score of $\geq$ 26/30 on the MoCA (Nasreddine et al., 2005), b) a word list recall score of > 5 on the Consortium to Establish a Registry for Alzheimer's Disease (CERAD), c) 2 above ADNI education-adjusted cut-offs on the WMS-III Logical Memory test the Logical Memory Subtest of the Wechsler Memory Scale-3rd ed. (WMS-III) (Tulsky et al., 2003), and d) no symptoms (i.e., a zero) in the Clinical Dementia Rating (CDR) (Hughes et al., 1982).

2.3. Criteria for MCI participants

Participants and/or informants who reported a concern regarding a change in the participant's cognition were included in the MCI group if they also met at least one of the following four criteria representing impairment in one or more cognitive domains (Albert et al., 2011): a) WMS-III Logical Memory score < ADNI education-adjusted cut-offs, b) CERAD word list recall < 6, c) MoCA score 13-24/30, d) assigned a CDR of $\leq$ 0.5 and determined to be able to follow daily life routines independently (Chertkow et al., 2019).

2.4. Criteria for AD participants

Participants who were diagnosed with AD were selected based on the following criteria (following McKhann et al., 2011): a) A gradual progressive change in memory and/or other cognitive functions over more than six months based on the participant's and/or informant's report; b) Objective evidence of a significant decline in at least two domains of cognition (i.e., episodic memory, reasoning, problem

195 solving, visuospatial abilities, language, personality/behavior) as defined by fulfilling at least two of
196 the following criteria: Logical Memory score below ADNI cutoffs, CERAD word list recall < 7,
197 MoCA score 13-24/30 (with at least one point lost in a non-memory task), or positive response to the
198 question: "Has the participant had any changes in personality or behaviour?"; c) The presence of
199 impairment in functional abilities was operationalized by a positive response to the statement, "The
200 cognitive deficits interfere with independence in everyday activities such as paying bills or managing
201 medications" (Chertkow et al., 2019).

202 ## 2.5. Hearing loss

203 ### 2.5.1. Pure-tone audiometry

204 Pure-tone audiometry was assessed in an abbreviated screening protocol using a GSI 18 audiometer in
205 a quiet clinical examination room at each site. The screening protocol assessed if participants were
206 able to detect at least one of two pure tones presented in each ear at each of 3 pre-selected frequencies
207 at fixed dB HL levels. First, there were two trials where a 2-kHz pure tone was presented at 40 dB HL.
208 If the participant successfully detected that, then 2 kHz, 1 kHz, and 4 kHz were tested with two trials
209 each at 25 dB HL. Participants who failed to hear a 2 kHz pure tone at 40 dB HL were provided with a
210 pocket talker assistive listening device throughout the neuropsychological and clinical assessment if
211 they did not have their own hearing aid.

212 For the present analyses, participants were assigned to one of six hearing loss categories based on their
213 ability to detect at least one of the two 2-kHz pure tones as described in Table 2[2]. In order to validate
214 these categories, based on the detection of 2-kHz at 25 and 40 dB HL, we applied the same
215 classification method to two large databases in which participants had comprehensive audiometric
216 thresholds measured using standard procedures. First, we applied it to a community-based sample of
217 healthy Canadians who were participants in the comprehensive cohort of the Canadian Longitudinal
218 Study on Aging (CLSA) (Raina et al., 2009), and had undergone a comprehensive bilateral 7-
219 frequency air-conduction pure-tone audiometry as part of their baseline assessment in the study
220 (CLSA data release 3.2; see https://www.clsa-elcv.ca/doc/529 for CLSA audiometry protocol).
221 Audiometric data were analyzed for 27,444 of 30,097 members of the comprehensive cohort who had
222 audiometry data. Table 2 shows the 1000, 2000, and 4000 Hz pure-tone average (PTA) of members of
223 the CLSA comprehensive cohort based on the COMPASS-ND classification scheme described above.
224 There was a monotonic worsening in PTA from Category 1 (better hearing) to Category 6 (worse
225 hearing), confirming that the COMPASS-ND method properly distinguishes people according to their
226 hearing abilities.

227

[2] Based on an ANOVA, there were no differences between males and females in HL category in SCI, MCI, or AD.

Table 2:
Validation of the 6-level hearing classification system used in the current study. Table 2 demonstrates the pure tone averages (1000, 2000, and 4000 Hz) of participants in the Canadian Longitudinal Study on Aging when the classification system was applied to them.

Hearing loss categorization			PTA for 1, 2, 3, 4 kHz (dB HL)		ASHA grade (dB HL)	
	Better ear	Worse ear	Left	Right	Left	Right
Category 1: 'Normal Hearing' both ears detected tone at 25 dB HL	<=25 dB	<=25 dB	16.4	15.0	Slight (16-25)	Normal (<=15)
Category 2: 'Mild 1' better ear detected tone at 25 dB HL, worse ear at 40 dB HL	<=25 dB	26-40 dB	29.9	31.5	Mild (26-40)	Mild
Category 3: 'Mild 2' both ears detected tone at 40 dB HL	26-40 dB	26-40 dB	39.1	36.7	Mild	Mild
Category 4: 'Moderate 1' better ear detected tone at 25 dB HL, worse ear failed at 40 dB HL	<=25 dB	>40 dB	41.0	45.4	Moderate (41-55)	Moderate
Category 5: 'Moderate 2' better ear detected tone at 40 dB HL, worse ear failed at 40 dB HL	26-40 dB	>40 dB	50.9	50.7	Moderate	Moderate
Category 6: 'Moderate 3' both ears failed to detect tone at 40 dB HL	>40 dB	>40 dB	59.9	57.7	Moderate-severe (56-70)	Moderate-severe

PTA= pure-tone average, ASHA = American Speech-Language-Hearing Association.

Second, we used data from the another project (N=242, mean age = 70.67 (SD = 5.94), mean years of education = 15.25 (SD = 2.31), 69.4% women), to investigate stigma related to aging and hearing loss in Canada, to correlate our hearing loss categorization variable with the PTA of full audiograms (1000, 2000, 4000 Hz) of the better ear (r=.84, p<.001) and the worse ear (r=.85, p<.001). Overall, these two additional datasets show that our hearing loss categorization based on the more restricted COMPASS-ND hearing protocol was valid.

For the statistical analyses we treated the six hearing loss categories as scaled data, because Categories 1-6 reflect the degree of hearing loss.

2.5.2. Canadian digit triplet test (CDTT)

The Canadian Digit Triplet Test (CDTT) was used to assess participants' speech perception abilities in an adverse listening condition. The CDTT application was run on a Dell XPS laptop using a USB audio card (Creative Sound Blaster X-Fi Go! Pro). The CDTT computes a speech reception threshold (SRT) which corresponds to the signal-to-noise ratio at which triplets of digits are recognized 50% of the time. Participants were instructed to listen to three digits presented in speech-shaped background

noise and to repeat them. The CDTT uses an adaptive 1-up-1-down procedure registering a correct response if all three digits were repeated correctly by the participant (Ellaham et al., 2016; Giguère et al., 2020). The standard deviation (SD) of the responses by each participant and the number of her/his reversals were used to identify erratic runs. Based on this procedure, SRTs from all participants were shown to be valid with the exception of 2 participants (1 AD, 1 MCI) who had SDs higher than +3 above the mean SD. Their results were coded as missing. Furthermore, the SRT of 1 additional participant (SCD) was coded as missing because this individual's SRT was higher than +4 dB SNR which is atypical for persons with mild hearing loss in this sample (this participant was categorized as "Mild 1" based on our categories for hearing loss)[3].

2.6. MRI data acquisition and analyses

T1-weighted images were obtained from each participant using 3T scanners from different COMPASS-ND sites across Canada following the Canadian Dementia Imaging Protocol (CDIP) (Duchesne et al., 2019). The CDIP is a validated, harmonized protocol for MRI data acquisition in neurodegeneration and is available for GE, Phillips, and Siemens scanners. The parameters for the acquisition of the 3D T1-weighted images can be found here https://www.cdip-pcid.ca/. Parameters varied depending on the scanner type and version allowing for the images to be as comparable as possible.

First, we compared the degree of global atrophy between diagnostic groups as lower gray matter volume (i.e., greater atrophy) is often used as a biomarker for Alzheimer's disease. Therefore, cortical volumes of all lobes were extracted from the T1-weighted images by submitting them to the Civet pipeline (version 1.1.11; http://wiki.bic.mni.mcgill.ca/index.php/Civet) developed at the Montreal Neurological Institute (MNI) at McGill University for fully automated structural image analysis (Ad-Dab'bagh et al., 2006; Zijdenbos et al., 2002). Gray matter volumes of left and right frontal, temporal, occipital, and parietal lobes were extracted.

Second, in order to analyze the associations between hearing loss and brain structural measures, hippocampal volume was extracted and a FreeSurfer analysis performed as described in the following. Hippocampal volumes were extracted from the T1-weighted images by submitted them to the ANIMAL (automatic non-linear image matching and anatomical labeling) segmentation method which is an atlas-based segmentation method that uses non-linear registration to a pre-labeled template (Collins et al., 1995; Collins & Pruessner, 2010). We then performed a FreeSurfer analysis (version 4.2, http://freesurfer.net/) on the T1-weighted images of the same participants. The FreeSurfer pipeline performs surface-based morphometry (SBM) which involves several processing steps that have been described in detail in previous publications (Dale et al., 1999; Dale & Sereno, 1993; Fischl et al.,

[3] Running an ANOVA, we did not find any differences between males and females in the CDTT thresholds in SCI, MCI, or AD.

2001, 2002; Fischl, Salat, et al., 2004; Fischl, Sereno, & Dale, 1999; Fischl, Sereno, Tootell, et al., 1999; Fischl, Van Der Kouwe, et al., 2004; Fischl & Dale, 2000; Reuter et al., 2010; Ségonne et al., 2004). The fully automated pipeline was run on CBRAIN (Sherif et al., 2014), a web-based software for computing intensive analyses that generates individual cortical surface models with high spatial precision. Five MCI participants were excluded due to errors during preprocessing. All other brain scans were manually checked for the segmentation precision and 3 MCI participants were further removed from the analysis due to severe segmentation errors.

For cortical thickness, the minimal distance between the gray-white matter border and the pial surface, statistical analyses were calculated across the whole brain using the FreeSurfer built-in general linear model (GLM) toolbox to identify thickness of brain regions associated with hearing loss category (GLM 1) and CDTT (GLM 2). Cortical thickness has previously been validated against manual measurements as well as histological analysis (Cardinale et al., 2014; Kuperberg et al., 2003; Rosas et al., 2002; Salat et al., 2004) and has been shown to be reliable in healthy OA (Liem et al., 2015). In order to compute the GLMs, each participant's segmented brain was morphed to an average spherical surface and smoothed using a FWHM kernel of 15 mm. A significance threshold of p=.001 was applied.

2.7. Statistical analyses and covariates

We used age, sex, and education as covariates in all statistical analyses (see Table 1). Comparing the gray matter volume of the cortical lobes between the diagnostic groups, we included the intracranial cavity (ICC) as a covariate in order to control for potential differences in premorbid brain volume between groups (Voevodskaya et al., 2014). When exploring the relationship between CDTT performance and brain structure, we controlled for hearing loss category in order to examine the relationship with CDTT and other measures independent of pure-tone thresholds.

Three families of statistical analyses were conducted as follows: First, the three diagnostic groups were compared in regard to their degree of hearing loss and (sub)cortical volumes using one-way ANOVAs (Section 3.1.). Second, the association between the two different measures of hearing loss (i.e., hearing loss category and CDTT) was explored within each diagnostic group using partial correlations (Section 3.2.). Third, in order to evaluate the associations between hearing loss and brain structure, hippocampal volumes were correlated with hearing loss measures using partial correlations and FreeSurfer analyses on cortical data were computed as described above (Section 3.3.). Unless otherwise indicated, an alpha level of $\alpha = 0.05$ was accepted and effect sizes were indicated by partial eta squares (η_p^2).

3. Results

3.1. Diagnostic group comparisons

3.1.1. Hearing loss

Figure 1 shows the diagnostic group differences in hearing loss measures. The diagnostic groups did not differ significantly in their hearing loss categories ($F(2,126)=.33$, $p=.72$, $\eta_p^2=.005$; Figure 1, left panel). Most participants were normal hearing or had mild hearing loss, although a notable minority had moderate or greater hearing loss. Diagnostic groups differed in CDTT performance ($F(2,109)=2.73$, $p=.07$, $\eta_p^2=.05$), see Figure 1 right-hand side. Post-hoc t-tests showed that there were higher speech reception thresholds (i.e., poorer performance on the CDTT) in the AD compared to the SCD group ($p=.08$), with this difference between groups approaching but not reaching significance.

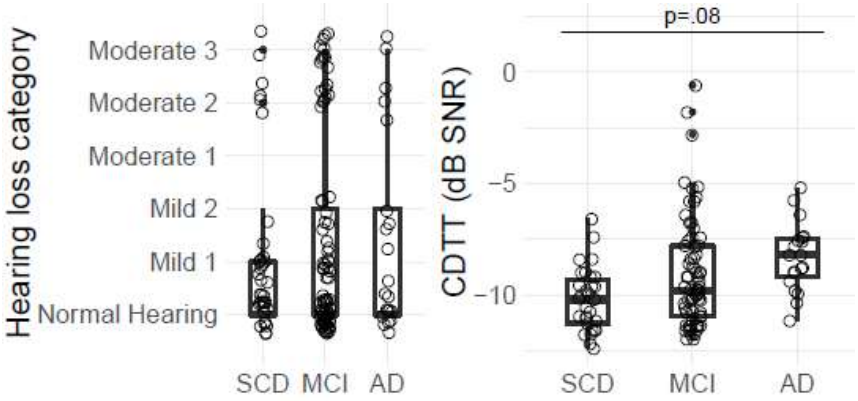

Figure 1: Figure 1 depicts the diagnostic group comparisons in pure-tone hearing loss categories and in speech-in-noise thresholds (dB SNR) on the Canadian Digit Triplet Test (CDTT). There was no significant difference in pure-tone hearing loss category between cognitive diagnostic groups, but the ANOVA indicated differences in speech-in-noise thresholds between groups which were higher (worse performance) in the AD compared to the SCD group (controlling for age, sex, education, and HL category). The boxplot lines represent the group median (thick line) and the 25th and 75th percentiles (outer lines). SCD: subjective cognitive decline, MCI: mild cognitive impairment, AD: Alzheimer's dementia.

3.1.2. Cortical and hippocampal volume

The F-statistics and the box plots of the results of the one-way ANOVAs comparing diagnostic groups in cortical volume of the extracted lobes and hippocampal volume can be found in Table 3 and Figure 2. All lobes, but not the hippocampus, showed significant group differences mostly revealing that the AD group had lower cortical volume than the SCD and the MCI groups, while the SCD and the MCI groups did not differ from each other.

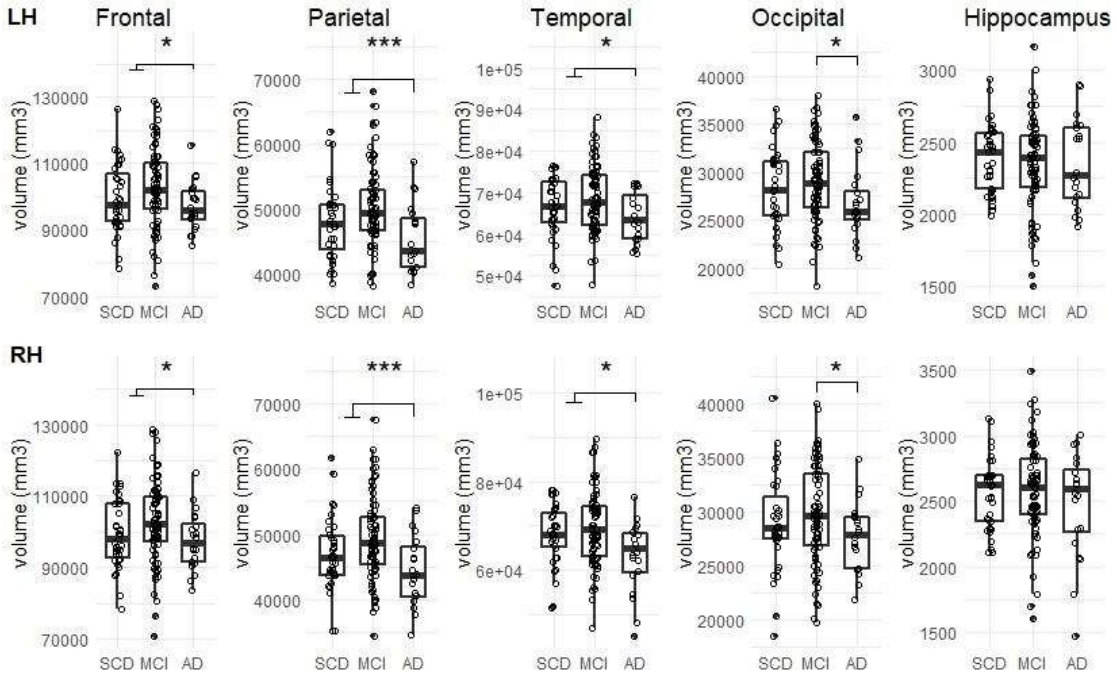

Figure 2: Figure 2 shows the diagnostic group comparisons in gray matter volume (mm^3) in lobes of the left (LH) and right (RH) hemisphere and the hippocampus. Controlling for age, sex, education, and intracranial cavity (ICC), the Alzheimer's dementia (AD) group had more atrophy than the subjective cognitive decline (SCD) and the mild cognitive impairment (MCI) group in all cortical brain areas, with the exception of the hippocampus (*$p < .05$, ***$p < .001$). The boxplot lines represent the group median (thick line) and the 25th and 75th percentiles (outer lines).

Table 3: Table 3 shows the diagnostic group differences in cortical and hippocampal volume with $F(2,124)$-values, p-values, η_p^2 as a measure for the effect size, as well as post-hoc t-tests for diagnostic group comparisons in gray matter volume.

	F	p	η_p^2	Post-hoc
LH				
Frontal lobe	5.34	**.006**	.08	SCD,MCI>AD
Parietal lobe	9.47	**<.001**	.32	SCD,MCI>AD
Temporal lobe	6.04	**.003**	.09	SCD,MCI>AD
Occipital lobe	2.97	.06	.05	MCI>AD
Hippocampus	.69	.50	.01	-
RH				
Frontal lobe	5.27	**.006**	.08	SCD,MCI>AD
Parietal lobe	9.94	**<.001**	.14	SCD,MCI>AD
Temporal lobe	7.62	**.001**	.11	SCD,MCI>AD
Occipital lobe	3.22	**.043**	.05	MCI>AD
Hippocampus	1.55	.22	.02	-

LH=left hemisphere, RH=right hemisphere, SCD=subjective cognitive decline, MCI=mild cognitive impairment, AD=Alzheimer's dementia.

3.2. Associations between hearing loss category and speech-in-noise thresholds

Partial correlations between hearing loss category and CDTT thresholds (see Figure 3) revealed significant positive associations in the SCD group ($r(24)=.64$, $p<.001$, $R^2=.41$), the MCI group

(r(63)=.70, p<.001, R^2=.49), and approaching significance in the AD group (r(14)=.43, p=.07, R^2=.18), suggesting that the more pure-tone hearing loss our participants exhibited, the greater (worse) their speech-in-noise thresholds were on the CDTT. Furthermore, even though the association was only trending in the AD group, the Fisher r-to-z transformation of the correlation coefficients suggested that the strengths of the associations were not different between the diagnostic groups (SCD vs. MCI p=.56, SCD vs. AD p=.36, MCI vs. AD p=.58).

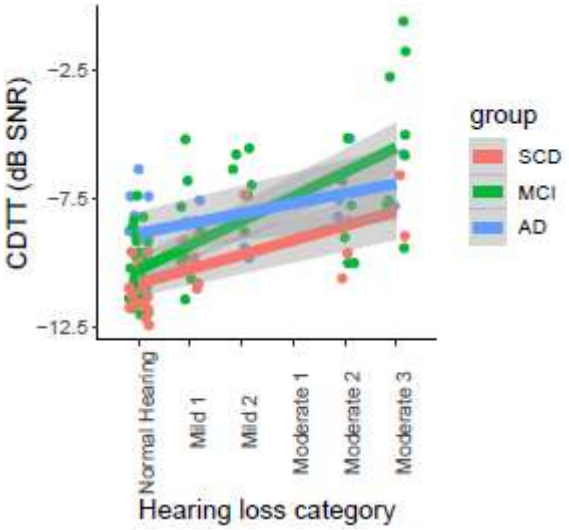

Figure 3: Figure 3 shows the associations between pure-tone hearing loss category and the speech-in-noise thresholds (dB SNR) on the Canadian Digit Triplet Test (CDTT) for the subjective cognitive decline (SCD), mild cognitive impairment (MCI), and Alzheimer's dementia (AD) groups: Significant positive associations were found in the SCD group (R^2=.41) and the MCI group (R^2=.49 or .30 when outliers were excluded), and approaching significance (p < .1) in the AD group (R^2=.18). Grey areas indicate 95% confidence intervals.

3.3. Associations between hearing measures and brain structural measures

3.3.1. Hearing loss and hippocampal volume

Table 4 and Figure 4 show the associations between the two hearing loss measures and hippocampal volumes. SCD participants who had greater pure-tone hearing loss had lower gray matter volume in the right hippocampus (R^2=.17). No effects were found in the MCI and AD groups, suggesting that for those with stronger cognitive impairment, the association between pure-tone hearing loss and brain structure was weaker.

Table 4:
Partial correlations controlled for age, sex, and education between pure-tone hearing loss category as well as CDTT performance (controlled also for hearing loss category) and hippocampal volume are shown for each cognitive diagnostic group separately.

	SCD		MCI		AD	
	Left HC	Right HC	Left HC	Right HC	Left HC	Right HC
Hearing loss category	-.14	**-.41**	.09	-.07	-.30	-.38
CDTT	.02	-.02	.08	.00	-.52	.01

Bold indicates p < .05. HC=hippocampus. SCD=subjective cognitive decline, MCI=mild cognitive impairment, AD=Alzheimer's dementia.

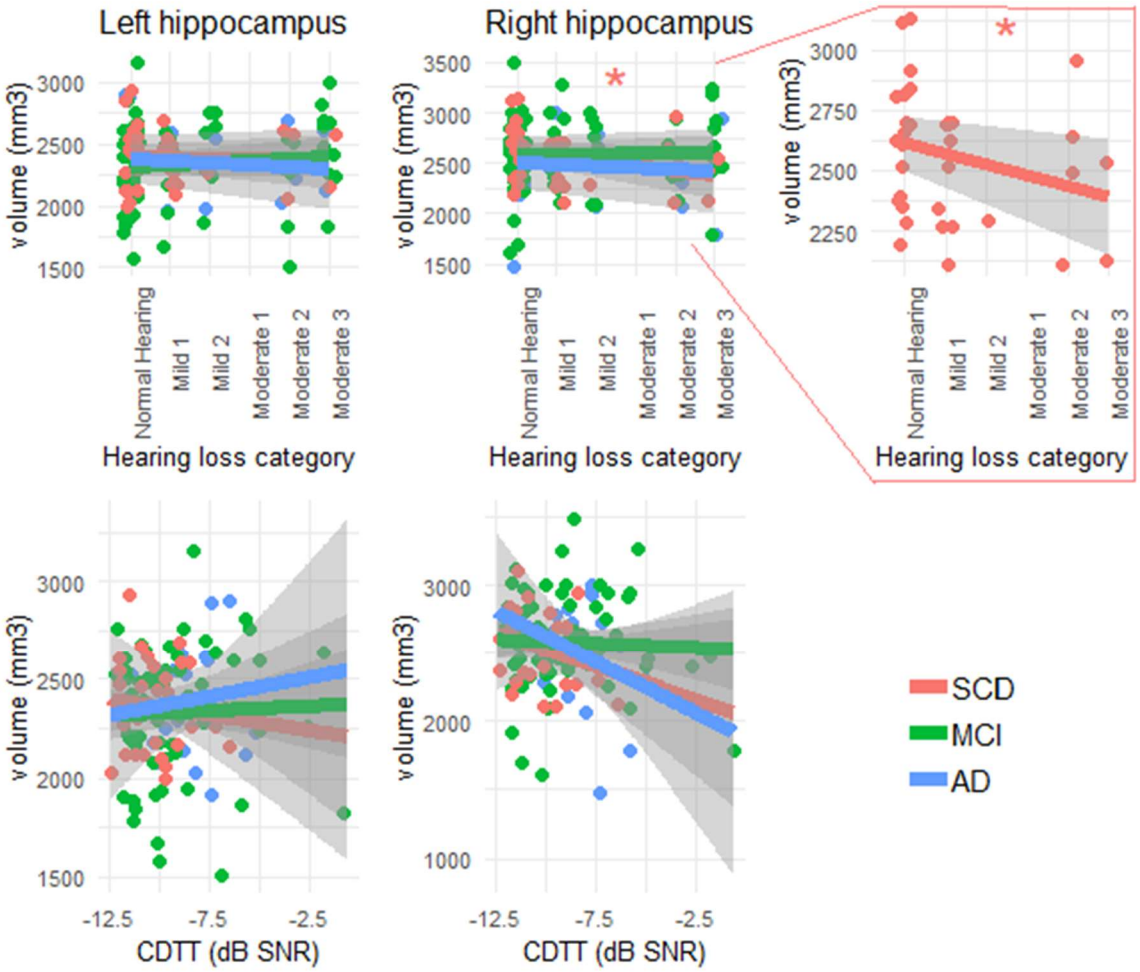

Figure 4: Figure 4 shows the correlations between pure-tone hearing loss category as well as the speech-in-noise thresholds (dB SNR) on the Canadian Digit Triplet Test (CDTT) and hippocampal volume (mm^3). In the subjective cognitive decline (SCD) group, there was a significant association, with greater hearing loss associated with lower right hippocampal volume, marked with colored square (*$p < .05$). Grey areas indicate 95% confidence intervals. MCI: mild cognitive impairment, AD: Alzheimer's dementia.

3.3.2. Hearing loss and cortical thickness

The whole-brain GLM model showed that there were two significant positive associations between hearing loss category and cortical thickness in the left superior temporal gyrus and the right pars opercularis ($p<.001$) as shown in Figure 5 and Table 5. Both of these significant associations were observed in the SCD group, suggesting that those who had more pure-tone hearing loss had more cortical thickness in those brain regions. No significant associations were found in the MCI or AD groups once we controlled for multiple comparisons.

Table 5: Table 5 shows the signifcant effects of the assocations between pure-tone hearing loss category as well as the speech-in-noise thresholds (dB SNR) on the Canadian Digit Triplet Test (CDTT) and cortical thickness in the subjective cognitive decline (SCD), mild cognitive impairment (MCI), and Alzheimer's dementia (AD) groups. The log10(p) at each vertex was set to 3 (values > 3 correspond to $p < .001$).

			Correlation	Max	MNI		
SCD					x	y	z
Hearing loss category							
	LH	Superior temporal gyrus	positive	3.06	-39.88	-20.29	-20.40
	RH	Pars opercularis	positive	3.75	21.98	39.72	-10.32
CDTT							
	LH	Posterior cingulate cortex	positive	3.98	37.97	-8.41	13.51
	RH	Superior temporal gyrus	positive	3.08	37.77	-28.2	-25.35
MCI							
Hearing loss category		-	-	-	-	-	-
CDTT	LH	Supramarginal gyrus	positive	3.10	-32.09	-47.51	24.74
	RH	Superior frontal gyrus	positive	3.45	-31.23	79.16	9.91
		Lateral orbitofrontal gyrus	positive	3.52	0.92	72.74	-45.23
		Anterior cingulate gyrus	positive	3.25	-33.03	61.90	14.18
AD							
Hearing loss category		-	-	-	-	-	-
CDTT	LH	Superior temporal gyrus	negative	-3.30	-39.88	-20.29	-20.40
	RH	Superior parietal gyrus	negative	-3.50	-18.38	-95.97	9.31
		Superior temporal sulcus	negative	-3.34	37.77	-28.2	-25.35
		Lateral occipital gyrus	negative	-3.32	10.43	-92.77	-20.07
		Inferior temporal gyrus	negative	-3.05	18.67	-11.54	-64.7

LH: Left hemisphere, RH: Right hemisphere, Max: log10(p) at peak, Montreal Neurological Institute (MNI) coordinates.

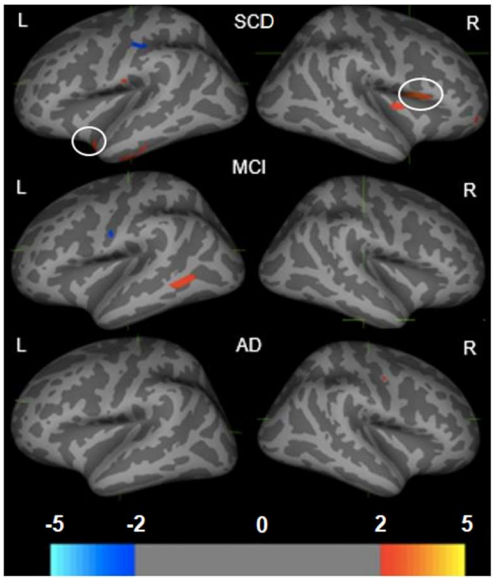

Figure 5: Figure 5 depicts the signifcant assocations between pure-tone hearing loss category and cortical thickness in the subjective cognitive decline (SCD), the mild cognitive impairment (MCI), and the Alzheimer's dementia (AD) group (red = positive association, blue = negative association). For graphical purposes, the log10(p) at each vertex was set to 2 (values > 2 correspond to $p < .01$), while the p-value was lowered to $p < .001$ to control for multiple comparisons in Table 5 where the significant brain clusters are listed. Significant ($p < .001$) positive correlations (i.e., greater pure-tone hearing loss – greater CT) were found in the SCD group for the left superior temporal gyrus and the right pars opercularis (indicated with circles).

The whole-brain GLM model for CDTT resulted in several significant clusters across the brain as shown in Figure 6 and Table 5. In the SCD and MCI groups, there were a few positive correlations found. In the AD group, there were only negative correlations in temporal, parietal, and occipital brain regions suggesting that those who have greater hearing loss, as measured by speech-in-noise reception thresholds, have lower cortical thickness in a number of brain regions across the cortex.

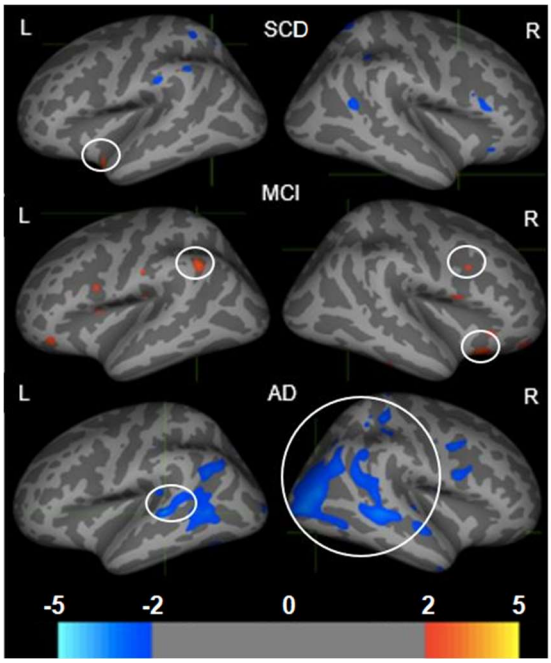

Figure 6: Figure 6 shows the signifcant assocations between speech-in-noise thresholds (dB SNR) on the Canadian Digit Triplet Test (CDTT) and cortical thickness in subjective cognitive decline (SCD), mild cognitive impairment (MCI), and Alzheimer's dementia (AD) groups (red = positive association, blue = negative association). The log10(p) at each vertex was set to 2 for the figure (values > 2 correspond to $p < .01$), while the p-value was lowered to $p < .001$ to control for multiple comparisons in Table 5 where the significant brain clusters are listed. Significant associations at $p < .001$ were found as indicated with circles.

4. Discussion

The findings of the present study indicate that hearing loss status is differently associated with brain anatomical traits in our diagnostic groups. In persons at risk for dementia (i.e., SCD), pure-tone hearing loss category was associated with reduced right hippocampal volume and increased cortical thickness in the left superior temporal gyrus and the right pars opercularis. For participants with diagnosed AD, the CDTT speech-in-noise thresholds are associated with wide-spread loss in cortical thickness. These findings are consistent with the sensory deprivation hypothesis. Importantly, we demonstrate that diagnostic group moderates the relationship between both hearing measures and brain structure. Our results also provide new insights into the differential relationship between pure-tone threshold measures of hearing loss (i.e., categories based on pure-tone thresholds) and measures of auditory processing (i.e., CDTT) with brain structure. The significance and implications of the findings are discussed in detail in the next sections.

4.1. The diagnostic group moderates the relationship between pure-tone hearing loss and brain structure

We found that our diagnostic groups did not differ in hearing loss category based on detection of pure tones when controlling for age, sex, and education. Yet, the diagnostic groups differed in the associations between pure-tone hearing loss and neuroanatomical traits. Importantly, this suggests that associations between pure-tone hearing loss and brain structure are not confounded by group differences in their pure-tone hearing. A previous study reported that there was a higher prevalence of hearing loss (> 35 dB HL based on PTA of 500, 1000, 2000, and 4000 Hz in the better ear) in MCI compared to healthy older adults and in AD compared to MCI and healthy older adults (Quaranta et al., 2014); however, most studies do not have such data because they examine the association between pure-tone hearing loss and cognitive decline in healthy older adults or in a group who were initially healthy and at risk of developing dementia (de la Fuente et al., 2019; Deal et al., 2015, 2016, 2019; Okely et al., 2019; Osler et al., 2019).

Furthermore, our data indicate that, as expected, those with a higher degree of cognitive impairment also had more brain atrophy. Mostly, the AD group had lower lobe-level gray matter volume compared to the SCD and MCI group, except for the occipital lobe for which the AD group only had smaller volume than the MCI group. This is consistent with the well-known finding that dementia-related neuropathology is related to brain atrophy (for a review see Pini et al., 2016). However, we did not find a difference between the diagnostic groups in the hippocampal volume, which is somewhat unexpected. We note that hippocampal volume was highly variable in our MCI group. There is literature suggesting that those with MCI may be very heterogenous, even when controlling for various underlying neurophysiological causes, likely because some (approximately > 40%) of these individuals will progress to AD or other forms of dementia (Roberts & Knopman, 2013), while others will not (Nordlund et al., 2005).

We assessed the association between hearing loss categories, based on the detection of pure tones, and hippocampal volume. We found that more severe pure-tone hearing loss was related to more cortical atrophy in the right hippocampus, but only in the SCD group. Notably, our results indicate that SCD participants with moderate hearing loss (those in hearing loss categories 5 or 6) have 4% lower volume in the right hippocampus than SCD participants with normal hearing or mild hearing loss (those in hearing loss categories 1, 2, or 3),even after controlling for age, sex, and education. In other words, the right hippocampus of these individuals with moderate to severe hearing loss “looks” approximately 8 years older given that the normal shrinkage is approximately 0.5% annually for people above 60 years of age (Fjell et al., 2009). Previous cross-sectional research has found similar associations between pure-tone hearing loss and hippocampal volume in healthy older adults (Uchida et al., 2018). There have been similar findings in longitudinal studies showing accelerated decline in the hippocampus (Xu

et al., 2019) and in the right parahippocampus (Lin et al., 2014) across time in healthy older adults with pure-tone hearing loss. Our results therefore extend previous findings showing that the association between hearing loss and hippocampal volume is also evident in older adults who subjectively believe that their cognition has declined and who are at risk of developing Alzheimer's disease. Future research should investigate a possible link between hearing loss, cognition, and hippocampal volume, given that cognitively healthy older adults with greater pure-tone hearing loss perform worse on memory tasks such as in (delayed) word recall (Colsher & Wallace, 1990; Deal et al., 2015; Ray et al., 2018) and in the free and cued selective reminding test (FCSRT) (Lin, Ferrucci, et al., 2011)) and performance in such tasks is mediated by the hippocampus (e.g. word recall (Fernández et al., 1999) and FCSRT (Slachevsky et al., 2018)), while there are also sex differences to be considered (Al-Yawer et al., submitted).

In contrast, the FreeSurfer-based cortical thickness analyses revealed positive associations between pure-tone hearing loss and cortical thickness in the SCD group (corrected for multiple comparisons), but not in the MCI and the AD group. The results suggest that the associations between pure-tone hearing loss and gray matter loss are undetectable or not significant in groups with greater cognitive impairment (i.e., MCI and particularly AD), even though they exhibited strong reductions in gray matter as compared to the SCD group. This is consistent with Xu et al. (2019) who found that more rapid decline in the hippocampus in those with greater pure-tone hearing loss in the preclinical stage (i.e., when AD is clinically asymptomatic but biomarkers suggest the presence of amyloid pathology) and in MCI, but not in individuals already diagnosed with dementia. Nevertheless, it remains an open question as to whether persons with either MCI or AD who have pure-tone hearing loss show greater cognitive decline than those without pure-tone hearing loss.

Interestingly, the associations between pure-tone hearing loss and cortical thickness in the SCD group were mostly positive, meaning that those with greater pure-tone hearing loss had more cortical thickness in the left superior temporal gyrus (STG) and the right pars opercularis. Previous studies also have found positive relationships between degree of pure-tone hearing loss and gray matter volume which were interpreted using a compensation framework (Alfandari et al., 2018). The left STG, belonging to the auditory association cortex, is involved in the spectro-temporal analysis of speech (Hickok & Poeppel, 2007) and multisensory integration of auditory and visual speech cues (Callan et al., 2001; Möttönen et al., 2002). The structural integrity of the left STG is a predictor of auditory working memory (Leff et al., 2009). It is possible therefore that those who have greater pure-tone hearing loss rely more on multisensory cues (e.g., visual speech cues) and on working memory during speech understanding such that they show alterations in the structure of the STG as a function of pure-tone hearing loss. Similarly, the right pars opercularis is involved in speech processing (Vigneau et al., 2011), particularly in speech perception tasks involving vowel tone pitch discrimination (Joanisse & Gati, 2003), syllable discrimination (Poeppel et al., 2004), and in sentence pitch and linguistic prosody processing (Meyer et al., 2002). Thus, it is possible that those with greater pure-tone hearing loss

might rely more on prosodic speech cues (Giroud et al., 2018, 2019), leading to structural plasticity in the right pars opercularis.

In sum, our cross-sectional analysis indicates that moderate pure-tone hearing loss in those who are otherwise cognitively healthy, but who have subjective cognitive complaints, is associated with lower volume in the right hippocampus, a biomarker of dementia. We note that we did not find lower hippocampal volume as a function of pure-tone hearing loss in the MCI or AD group in our sample. Furthermore, those with greater pure-tone hearing loss in the SCD group also exhibited more cortical thickness in the left STG and the right pars opercularis. This finding suggests potentially compensatory structural plasticity insofar as those with greater pure-tone hearing loss may rely more on multisensory and prosodic speech cues as well as the phonological loop component in their working memory during speech understanding compared to those with less severe pure-tone hearing loss. The fact that these hearing-brain structure associations were found only in individuals with SCD, but not MCI or AD, suggests that dementia-related neuropathology, which is reflected in brain atrophy among other biomarkers, overshadows the potential effects of pure-tone hearing loss on brain structure.

4.2. Hearing loss - brain structure associations depend on hearing loss measurement

In addition to the association between measures of brain structure and hearing loss category based on the detection of pure tones, we conducted the same analyses using the CDTT measure of speech-in-noise threshold. Independent of hearing loss category, CDTT speech-in-noise thresholds were lower (better) for the SCD group compared to the AD group. This result suggests that those with AD have difficulty recognizing even very simple speech stimuli in noise, which was also shown in previous research which found strong dysfunctions of auditory processing in individuals with AD and partially also in those with MCI (Idrizbegovic et al., 2011).

We also investigated the associations between the CDTT results and cortical thickness in all three diagnostic groups. For the AD group only, we found negative correlations between the CDTT speech-in-noise thresholds and brain structure across the whole brain, such that those with poorer performance on the CDTT had lower gray matter volume in bilateral frontal, parietal, and temporal lobes, as well as in the right occipital lobe and lower cortical thickness in bilateral superior temporal gyri, right inferior temporal gyrus, right lateral occipital gyrus, and the right superior parietal gyrus. Previous research has found similar associations between speech-in-noise perception performance and macro-anatomical measures of the cortex in healthy older adults, which were more focal in nature (Giroud et al., submitted, 2018; Rudner et al., 2019). Cortical volume and cortical thickness change as a function of experience, training, pathology, and lifespan changes and are therefore subject to plasticity (Bermudez et al., 2009; Engvig et al., 2010; Fjell et al., 2009). It is possible that poorer CDTT speech-in-noise thresholds in the AD group might correspond to a lower number, packing density, and size of cells within neural columns (Rakic, 1988, 1995) in multiple brain regions. Thus, these results may support

the sensory deprivation hypothesis insofar as continued impoverished auditory input may have wide-spread effects across the cortex that manifests as gray matter atrophy.

An alternative, and equally likely an explanation, derives from the fact that a large (sub)cortical brain network supporting auditory-cognitive functioning is involved in speech-in-noise processing from the auditory brainstem (Anderson et al., 2011, 2013) up to higher areas such as the right inferior frontal gyrus and the right insula (Bidelman & Howell, 2016), including parietal brain regions such as the precuneus (Wong et al., 2009). These brain regions involved in speech-in-noise processing are similar to the brain structures we show to correlate with CDTT speech-in-noise reception in the present study. Thus, it also is possible that the association found in the present study between the CDTT measure of speech-in-noise processing and brain structures reflect the neural sources involved in performing the complex task of speech discrimination in noise. In other words, it is possible that individuals with reduced gray matter volume and cortical thickness (more atrophy, i.e., those with AD) in those brain regions perform worse on the speech-in-noise task due to less available neural resources. However, longitudinal research and functional imaging is needed to clarify the direction of the results since it is also possible that increasing difficulties understanding speech-in-noise perception could lead to a structural decline in those brain regions, as suggested by a recent cross-sectional study in healthy older adults (Rudner et al., 2019). The study found that lower performance on a speech-in-noise task was related to lower gray matter volume in brain regions associated with hearing and cognition.

Similar to Giroud et al. (2018), we found associations between speech-in-noise perception performances and brain structures in visual brain areas (i.e., volume in the right occipital lobe and cortical thickness in the right lateral occipital gyrus). Visual activation is present during hearing tasks (Giraud & Truy, 2002), especially in individuals with severe hearing loss such as those using cochlear implants (Giraud et al., 2001). It is possible that individuals with greater hearing loss rely more on visual speech cues and therefore co-activate visual areas during speech understanding, potentially even when there are no visual speech cues available. We speculate that this interpretation could be valid in the present study because most participants had good visual acuity (Table 1). Nevertheless, we recognize that there is a distinction between structure and function and that the association between neural activation and cortical thickness is not straightforward.

As mentioned above, we only found very wide-spread and negative associations between CDTT speech-in-noise reception thresholds and brain structure in the AD group who had most pronounced brain atrophy. In the other two groups, we found few and only very focal positive associations between speech-in-noise reception thresholds and cortical thickness (SCD: left posterior cingulum, right superior temporal gyrus; MCI: right superior frontal gyrus, right lateral orbitofrontal gyrus, and anterior cingulum). Given that these groups have less brain atrophy than the AD group, our findings suggest that individuals who have better brain structural integrity in regions involved in cognitive processes (Metzler-Baddeley et al., 2012; Schermuly et al., 2010) during speech-in-noise perception

(Bidelman & Howell, 2016; Du et al., 2016) might be able to use these regions to compensate for difficulties understanding speech-in-noise (Rönnberg et al., 2008, 2013).

Overall, our data provide evidence that speech-in-noise recognition may be disproportionately impaired in older adults with AD. Our results further show that persons with AD who have more structural decline in the frontal, temporal, and parietal lobes perform worse on the CDTT. It is possible, that dementia-related neuropathology, which leads to accelerated decline of brain structures, may exacerbate or lead to a decline in speech processing in adverse listening conditions. Alternatively, declines in auditory processing may have wide-spread effects on brain atrophy in older adults with AD. Longitudinal studies are needed to clarify the direction of these effects.

4.3. Limitations

One limitation of the present study is that we do not have standard pure-tone audiograms for our participants because of the audiometric screening approach that was used. However, we were able to validate our hearing loss categorization method by mapping it to grades of hearing determined based on audiograms in two independent samples of older adults. Moreover, we have shown that there is a significant positive correlation between our hearing loss categorization and the speech-in-noise reception thresholds in the CDTT (R^2 ranging from .18 - .41 depending on diagnostic group), indicating that our hearing loss categorization meaningfully reflects losses in hearing that affect speech-in-noise perception as shown previously in the literature (Dubno et al., 1984; Giroud et al., 2017; Gordon-Salant & Fitzgibbons, 2001; Zekveld et al., 2011).

Another shortcoming is the cross-sectional nature of the study. In order to clarify the direction of the hearing loss - brain volume/thickness associations, longitudinal data are needed. In the COMPASS-ND study, longitudinal data are currently being collected from the same participants. Thus, the current report is a first step toward understanding the possible effects of hearing loss on brain structures in those diagnostic groups.

Furthermore, it remains an open question as to what degree our sample is representative of others with SCD, MCI, and AD in the general population. First, we did not find differences in hippocampal volume between the diagnostic groups, even though this is a well-reported finding in the literature. Second, our diagnostic groups have skewed sex ratios, which may not be representative of each of the diagnostic groups. Finally, our participants were self-selected volunteers from clinical research sites who agreed to be in a research study involving the administration of an extensive test battery.

4.4. Conclusion

Our study investigated the association between hearing loss and brain structure in older adults at risk of and with dementia, extending previous research on healthy older adults. As compared to previous research, we not only tested pure-tone thresholds to assess hearing loss, but also included a measure of

auditory perception, namely speech-in-noise reception thresholds. Older adults with near-normal pure-tone thresholds often report to have difficulties understanding speech in noisy environments.

Our results are consistent with the sensory deprivation hypothesis. In those with greater pure-tone hearing loss in the SCD group we found lower hippocampal volume, which is a biomarker of dementia, as well as more cortical thickness in auditory and higher-order language-related areas potentially reflecting compensatory effects. No such associations between pure-tone hearing loss and brain structure were found in MCI or AD suggesting that pathology-related atrophy dominates potential neuroanatomical effects of pure-tone hearing loss. Nevertheless, in the MCI and AD group only, we found that those with greater speech-in-noise reception thresholds exhibited lower cortical thickness globally in both hemispheres. It is therefore possible that an age-related decline in speech-in-noise understanding may result in brain structural decline in older adults who have (mild) cognitive impairment. Alternatively, and because the AD group performed slightly worse in the speech-in-noise task compared to the SCD group, it is also possible that dementia-related atrophy in brain regions supporting auditory processing leads to a decline in speech-in-noise understanding. Longitudinal research is needed to clarify the potential causal mechanisms. Our work extends the research on hearing-brain associations to include those who have subjective or objective cognitive complaints and suggests that these relationships evolve as disease progresses.

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