Distinct disease mechanisms may underlie cognitive decline related to hearing loss in different age groups

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Abstract

Background: Hearing loss in older adults is associated with increased dementia risk. Underlying mechanisms that connect hearing loss with dementia remain largely unclear.

Methods: We studied the association of hearing loss and biomarkers for dementia risk in two age groups with normal cognition: 65 participants from the EMIF-AD 90+ study (oldest-old; mean age 92.7 years, 56.9% female) and 60 participants from the EMIF-AD PreclinAD study (younger-old; mean age 74.4, 43.3% female). Hearing function was tested by the 'digits-in-noise test' and cognition by repeated neuropsychological evaluation. Regressions and generalized estimating equations were used to test the association of hearing function and PET-derived amyloid burden, and linear mixed models were used to test the association of hearing function and cognitive decline. In the oldest-old group, mediation analyses were performed to study whether cognitive decline is mediated through regional brain atrophy.

Results: In oldest-old individuals hearing function was not associated with amyloid pathology (p = .7), whereas in the younger-old individuals hearing loss was associated with higher amyloid burden (p = .0034). In oldest-old individuals, poorer hearing was associated with a steeper decline in memory, global cognition and language, and in the younger-old with steeper decline in language only. The hippocampus and nucleus accumbens mediated the effects of hearing loss on memory and global cognition in the oldest-old individuals.

Conclusions: Hearing loss was associated with amyloid binding in younger-old individuals only, and with cognitive decline in both age groups. These results suggest that mechanisms linking hearing loss with risk for dementia depends on age.

Key messages

- What is already known on this topic

Hearing loss is associated with dementia risk, but underlying mechanisms remain largely unclear.

- What this study adds

Hearing loss was associated with cognitive decline in both age groups. In the younger-old it was also associated with amyloid burden, whereas this was not the case in the oldest-to-old, suggesting different mechanisms may be involved.

- How this study might affect research, practice or policy

Our results suggest that mechanisms linking hearing loss to cognitive decline depend on age. Future studies should investigate the separate underlying mechanisms for different age groups in more detail.

1. Introduction

Age related hearing loss has been associated with an increased incidence and prevalence of dementia[1-4]. It has been suggested that hearing loss is a modifiable risk factor for dementia that may have the largest effect on reducing dementia prevalence if modified in mid-age[5]. Whether hearing loss is associated with dementia at higher ages is unknown. Moreover, the biological mechanism that links hearing loss with the development of dementia remains largely unclear.

Multiple mechanisms linking hearing loss with dementia have been proposed (for a comprehensive review see Griffiths et al., 2020[6]). One mechanism could be that underlying pathology in the brain could result in both cognitive decline as well as hearing loss (i.e. the 'common pathology' mechanism). For Alzheimer's disease (AD), the most common cause of dementia, amyloid aggregation is one of the earliest pathological changes in the brain[7]. If amyloid aggregation would affect brain areas important for hearing functioning, then more amyloid burden should be related to worse hearing functioning. A few studies have investigated this hypothesis but showed conflicting results: One study found higher PET-derived amyloid and tau burden associated with hearing loss in 57 subjects of 67.1 years old[8]. Another study investigated 368 cognitively normal adults of approximately 70 years old, and found no relationship of hearing loss with amyloid status or typical patterns of Alzheimer's disease related neurodegeneration[9]. However, the group of amyloid positive individuals was relatively small, and it was not studied whether hearing functioning was associated with continuous measures for amyloid pathology. Another mechanism could be that auditory deprivation due to hearing loss may affect brain structures due to loss of activation, and subsequently affect that brain area's functioning, leading to cognitive decline. In this case it could be hypothesized that hearing loss is associated with cortical atrophy. Longitudinal studies that demonstrated an association of hearing loss with accelerated whole brain atrophy, and focal temporal lobe atrophy in midlife and later-life participants[10 11], including the hippocampus and entorhinal cortex[10]. However, those studies did not take into

account potential effects of amyloid aggregation, and so it remains unclear how hearing loss, atrophy and amyloid aggregation leads to dementia. Furthermore, as individuals grow older, hearing loss becomes more prevalent, and it remains unclear whether mechanisms that explain the relationship between hearing loss and cognitive decline would be similar for different age groups.

In the current study we investigated the relationship between hearing function, amyloid aggregation, and cognitive decline in two cohorts of younger-old and oldest-old with normal cognition at baseline. For the oldest-old individuals, brain atrophy data was available at the time of hearing testing, and in this cohort we investigated whether cognitive decline due to hearing loss is mediated through regional brain atrophy.

2. Methods

2.1 Participants

We selected individuals from two cohorts with different ages from two studies at the Alzheimer center at the Amsterdam UMC: Cognitively normal individuals with audiometry, amyloid-PET and repeated neuropsychological testing were selected from the EMIF-AD 90+ study aged between 88-102 years[12] representing the oldest-to-old population, and from the Amsterdam EMIF-AD PreclinAD study with monozygotic twins aged between 64-95 years representing the younger-old population[13]. Both cohorts were part of the European Medical Information Framework for AD (EMIF-AD) project, which is designed to discover diagnostic markers, prognostic markers and risk factors for AD in nondemented adults (http://www.emif.eu/about/emif-ad). Cognitively normal subjects were recruited via advertisements and general practitioners in the EMIF-AD 90+ study, and via the Netherlands Twin Register[14] in the EMIF-AD PreclinAD study. The studies had the same design for hearing assessment and amyloid-PET scanning. Differences in neuropsychological assessment and definitions for normal cognition are described below. Unlike the younger-old individuals, the oldest-old individuals had MRI data available at the time of auditory testing. At baseline, normal cognition was defined as Clinical

Dementia Rating (CDR) = 0 and MMSE ≥ 26 in the EMIF-AD 90+ study, and CDR = 0 and a delayed recall score above -1.5 SD of demographically adjusted normative data on the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) 10-word list in the EMIF-AD PreclinAD study[13]. Repeated neuropsychological test data were collected during home visits and hospital visits with yearly intervals in the oldest-old individuals, and bi-yearly in the younger-old individuals. Individuals were excluded from the cohort if they were physically unable to undergo the procedures, had visual impairment or hearing impairment that made neuropsychological testing impossible, severe depression (Geriatric Depression Scale score ≥ 11 points), medication or comorbidity that could influence cognition at the discretion of the investigator. Both studies were approved by the Medical ethics committee of the Amsterdam UMC. Participants gave informed consent in accordance with the Declaration of Helsinki.

2.2 Hearing function

Hearing function was assessed at baseline using the digits-in-noise test, which tests the ability to recognize digit triplets in a background of masking noise. The test determines a speech reception threshold (SRT), i.e., the speech-to-noise ratio (SNR) at which participants are able to recognize 50% of the digit triplets[15]. Normal hearing was defined as SRT < -5.5 dB SNR, insufficient hearing ability as −5.5 ≤ SRT ≤ −2.8 dB SNR and poor hearing ability as SRT > -2.8 dB SNR[16]. Participants were provided with over-ear headphones (Sennheiser HD 202) during the test and were not allowed to use hearing aids.

2.3 Neuropsychological assessment

All participants underwent a standardized neuropsychological test battery[12][13], which assessed the following cognitive domains: memory, language, attention, and executive functioning. Memory functioning was assessed using the CERAD 10 words test (delayed recall)[17] and the Wechsler Logical Memory test (delayed recall)[18] in the EMIF-AD 90+ study, and the Dutch version of the Rey Auditory Verbal Learning Test[19] and the Face-

name associative memory exam (FNAME)[20] in the EMIF-AD PreclinAD study, and the Rey Complex Figure Test[21], and the Visual Association Test A[22] in both cohorts. Language functioning was assessed with the 2 min Animal Fluency score[23] and the Graded Naming Test[24]. Attention was assessed with the Trail Making Test part A (TMT-A)[25], the WAIS-III Digit Span forward subtest[26], and the Digit Symbol Substitution Test[27]. Executive functioning was assessed with the Trail Making Test part B (TMT-B)[25] corrected for TMT part A, the WAIS-III Digit Span backward subtest[26], Letter Fluency (the Dutch version of the Controlled Oral Word Association Test with letters D,A,T, one minute per letter)[23], and Clock drawing test (in oldest-old individuals only)[28]. Global cognition was assessed by combining all the neuropsychological tests with the MMSE. All cognitive tests were Z-transformed using the mean and standard deviation of the baseline scores as reference. The TMT-A and TMT-B were inverted such that lower scores reflected worse performance. Tests of each cognitive domain were averaged into composite scores.

2.4 MRI acquisitions and preprocessing

In EMIF-AD 90+, 3D-T1 weighted images were acquired at baseline on a Philips 3T Achieva scanner using an 8-channel head coil and a sagittal turbo gradient-echo sequence (T1: 1.00 mm^3 isotropic voxels, repetition time (TR) = 7.9 msec, echo time (TE) = 4.5 msec, flip angle (FA) = 8 degrees;). An experienced radiologist inspected the structural T1-weigted MRI scans for pathology other than neurodegeneration. Cortical thickness was estimated from 3D T1 MRI using FreeSurfer (v5.3; https://surfer.nmr. mgh.harvard.edu). Non-brain tissue was removed, followed by transformation to Talairach space, segmentation and creation of cortical surface meshes[29]. Cortical thickness values were summarized in anatomical regions according to the Desikan–Killiany atlas implemented in FreeSurfer[30]. Subcortical and total intracranial volumes were obtained using the FIRST tool (v5.0.1) of the FSL package[31]. We averaged cortical thickness and subcortical volumes across left and right hemispheres to reduce the

number of variables for testing.

2.5 Amyloid PET

Dynamic amyloid PET scanning was performed on a Philips Ingenuity PET-MRI scanner in both cohorts. The first part of the scan consisted of a 30-minute dynamic emission scan together with an intravenous injection of 185 MBq [^{18}F]flutemetamol. The second part of the scan was performed 90 - 110 minutes after the injection[32]. Prior to each part a dedicated MRI scan was performed for attenuation correction. The head was immobilized to reduce movement artifacts The co-registration of the images was performed with VINCI Software 2.56 (https://vinci.sf.mpg.de), and the regions were defined using PVELab[33]. Parametric nondisplaceable binding potential images (BP$_{ND}$) were estimated based on SRTM2 (noise reduction in the simplified reference tissue model for neuroreceptor functional imaging using inhouse build software (PPET))[34], with cerebellar gray matter as a reference tissue[35]. Global cortical BPnd was calculated from an average of 22 brain regions[36]. Amyloid positivity was visually assessed by consensus of three readers (nuclear physician or radiologist).

2.6 Statistical analysis

Statistical analyses were performed with R (version 4.1.0). We compared the two cohorts on demographical characteristics with T-tests, Kruskal-Wallis tests and Chi^2-tests when appropriate. Next, we tested relationships between hearing function and continuous amyloid BP$_{ND}$ binding potential values, using linear regression in the EMIF-AD 90+ cohort and generalized estimating equation (GEE) in the PreclinAD cohort to take into account family dependencies. Next, we studied the association between hearing function and cognitive decline over time with linear mixed models, including a fixed effect for time, hearing function and their interaction, and we modelled random intercepts and fixed slopes. Finally, for the EMIF-AD 90+ cohort only, because they had both hearing tests and MRI available at the same time point, we tested whether hearing function was

related to regional cortical thickness and subcortical volumes using linear regressions. For brain regions related with hearing function, we also determined whether they were associated with cognitive decline, as a prerequisite for further mediation analyses to identify whether cognitive decline in patients with hearing loss is mediated by regional cortical thickness or subcortical volumes. When these brain regions were associated with cognitive decline in the same domains that were associated with hearing loss, we investigated whether this brain region mediated the effects of hearing on cognitive decline. Mediation analyses were performed using the "mediation" package (v4.5)[37]. Age, sex, and amyloid status were included as covariates in all models when they were not explicit fixed effects; all the EMIF-AD PreclinAD analyses were additionally corrected for twin-status; subcortical volumes were additionally corrected for total intracranial volume; random intercepts and fixed slopes were modelled in the linear mixed models on cognitive decline, and education was added in the association of hearing and cognitive decline. Results with p< .05 were considered to be statistically significant.

3. Results

3.1 Sample description

Table 1 shows the patient characteristics of both groups, comprising in total 125 individuals. From the EMIF-AD 90+ 65 participants were included (mean ± SD age = 92.7± 2.9, range 88-102 years, 56.9% female). Eleven participants had normal hearing (16.9%), 20 participants had insufficient hearing (30.8%), and 34 participants had poor hearing (52.3%). Over half of the participants used hearing aids (n=38; 58.5%). Amyloid status was abnormal in 29.5% of the participants (n=18; 4 missing). From the EMIF-AD PreclinAD 60 participants were included (mean ± SD age = 74.4 ± 6.5, range 65-95 years, 43.3% female). Forty participants had normal hearing (66.7%), 16 participants had insufficient hearing (26.7%%), and 4 participants had poor hearing (6.7%). Twelve participants used hearing aids. Amyloid status was abnormal in 15.3% of the participants (n= 9; 1 missing). Compared to EMIF-AD PreclinAD, participants in the EMIF-AD 90+

study were older (p< .001), had a higher amyloid binding potential (p = .0012), performed

worse on the hearing task (p< .00001), and used hearing aids more often (p = .00001).

Table 1. Summary of patient characteristics

Demographics	EMIF-AD 90+ Study	EMIF-AD PreclinAD Study
No. (male/female)	65 (28/37)	60 (34/26)
Age	92.7 (2.9)	74.4 (6.5)***
Education in years	12 (10-15)	13 (10-13)
MMSE	29 (28-30)	29 (28-30)
Amyloid positive/negative PET scan (n missing)	18/43 (4)	9/50 (1)
Amyloid Binding Potential	0.27 (0.22)	0.16 (0.13)**
Speech Reception Threshold	-2.0dB (3.8)	-5.9dB (1.8)***
Normal/insufficient/poor hearing[a]	11/20/34	40/16/4***
Hearing aids yes/no	38/27	12/48***
Follow-up 1 available (%)[b]	49 (75.4%)	37 (61.7%)
Follow-up 2 available (%)[b]	18 (27.7%)	0 (0%)[c]

Data are presented as N, mean (SD), or median (IQR). MMSE, mini mental state examination; dB, decibels.
[a] Normal hearing was defined as < -5.5 dB SRT, insufficient hearing ability was defined as −5.5 ≤ SRT ≤ −2.8 dB poor hearing ability as > -2.8 dB
[b] FU every year in the oldest-old and every two years in the younger-old
[c] No FU performed after 4 years

* p <0.05
** p < 0.01
*** p < 0.001

3.2. Relationship between hearing function and amyloid burden

In the younger-old cohort we found that poorer hearing function was associated with

higher amyloid binding potential values (β ± SE = 3.5 ± 1.2, p = .0034, Figure 1). In the

oldest-old we found no association between hearing function and the amyloid binding

potential values (β ± SE = -0.26 ± 2.1, p = .9).

3.3 Relationship between hearing function and cognitive decline

Next, we tested associations of hearing function and changes in cognition over time

(Figure 2, with group lines for groups stratified into normal, insufficient and poor hearing).

In the oldest-old poorer hearing function was associated with steeper decline in memory

(β ± SE = -0.0176 ± 0.0071; p = .0153), global cognition (β ± SE = -0.0167 ± 0.0069; p =

.0178) and language (β ± SE = -0.0143 ± 0.0069; p = .0427; Table S1). In the younger-old cohort, worse hearing function was associated with a steeper decline in language (β ± SE = -0.087 ± 0.02; p = .000082; Table S2).

3.4 Relationship between hearing function and cortical and subcortical brain structures in the oldest-old participants

We then studied the relationship between hearing function and regional cortical thickness and subcortical volumes in the oldest-old individuals. We found that, irrespective of amyloid status, hearing loss was associated with thinner cortex of the medial orbitofrontal cortex (β ± SE = -0.07 ± 0.034; p = .045; p(FDR-corrected) = .98), smaller hippocampal volume (β ± SE = -0.096 ± 0.034; p = .0058; p(FDR-corrected) = .047) and smaller nucleus accumbens volume (β ± SE = -0.081 ± 0.036; p = .029; p(FDR-corrected) = .12) (Figure 3).

3.5 Mediation analyses hearing function, brain structures, and cognitive decline in the oldest-old participants

Mediation analyses were performed to determine if hearing loss resulted in cognitive decline (direct effect) or if it was mediated by regional atrophy (mediation effect). To this end, we first tested whether the brain regions that were associated with hearing function (i.e. medial orbitofrontal cortex, hippocampus, and nucleus accumbens) were also associated with cognitive decline. Thinner medial orbitofrontal cortex was associated with steeper decline in language (β ± SE = 0.063 ± 0.025; p = .013; p(FDR-corrected) = .17); lower hippocampal volume was associated with steeper decline in global cognition (β ± SE = 2×10^{-4} ± 0; p = .00026; p(FDR-corrected) = .0013) and memory composite scores (β ± SE = 2×10^{-4} ± 0; p = .00002; p(FDR-corrected) = .0002). Lower nucleus accumbens volume was associated with steeper decline in global cognition (β ± SE = 6×10^{-4} ± 1×10^{-4}; p = .00001; p(FDR-corrected) = .00009), memory (β ± SE = 6×10^{-4} ± 1×10^{-4}; p< .00001; p(FDR-corrected) = .00008), language (β ± SE = 4×10^{-4} ± 1×10^{-4}; p = .0029; p(FDR-corrected) = .01), and executive functioning (β ± SE = 3×10^{-4} ± 1×10^{-4}; p = .023; p(FDR-

corrected) = .05; Table S5). Then, for the cognitive domains that were associated with hearing loss (i.e., memory, global cognition and language) and brain regions associated with decline in these cognitive domains (medial orbitofrontal cortex, hippocampus and nucleus accumbens) we performed mediation analyses. Hippocampal volume mediated the association between hearing function and decline in memory function ($p < .00001$; p(FDR-corrected) = $p < .00001$; 54.5%); and global cognition ($p = .002$; p(FDR-corrected) = .006; 40.9%). Nucleus accumbens volume mediated decline in memory function ($p = .01$; p(FDR-corrected) = .015; 44.9%), and global cognition ($p = .008$; p(FDR-corrected) = .015; 37.2%; Figure 4). The direct effect of hearing loss on memory and global cognition lost significance after adding hippocampal or nucleus accumbens volume as mediator. The nucleus accumbens did not mediate the association of hearing function and decline in language function ($p = .068$) (Figure 4). The mediation analyses of the medial orbitofrontal cortex demonstrated no mediation effect ($p = .22$) or direct effect ($p = .082$) of the association of hearing function with language decline.

4. Discussion

This study has several main findings: first, worse hearing function was associated with higher amyloid burden in younger-old individuals, and no associations were found in the oldest-old individuals. We further found that hearing loss was associated with steeper cognitive decline in both cohorts, even when controlling for amyloid status. Finally, mediation analyses in the oldest-old suggested that the volume of the hippocampus and nucleus accumbens mediated the effects of hearing loss on decline in memory and global cognition, but not on decline in language.

We observed that hearing loss was associated with amyloid binding potential in individuals with a mean age of 74.4 years. This is in line with a recent study that found higher PET-derived amyloid burden in 57 subjects of 67.1 years old[8]. Another study looked at amyloid status in relation to hearing function in healthy adults aged approximately 70 years and found no association[9]. That study did however not

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investigate the association of hearing loss with continuous measures of amyloid burden. In our oldest-old individuals with a mean age of 92.7 years, we did not find an association between amyloid binding potential and hearing loss. This suggests that the mechanism through which hearing loss is associated with dementia, might be different depending on age. Our results in younger-old individuals support the 'common pathology' hypothesis, which proposes that loss of hearing function may be associated with accumulation of AD pathology in brain structures important for both auditory processing as well as in other brain areas that are related to cognitive decline[6]. Further longitudinal studies in even younger populations are needed to further investigate whether hearing impairment follows amyloid aggregation. In the oldest-to-old we did not observe an association between hearing function and amyloid burden, but instead we observed a relationship with cortical atrophy. Those results support the idea that perhaps sensory deprivation mechanisms may play a role in the association of hearing loss and cognitive decline in the oldest-to-old. In addition to hearing loss, other factors that are associated with hearing loss such as social isolation, depression, and frailty may contribute to sensory deprivation in this group[38], and future research should aim to study the influence of such additional factors.

We further found that hearing impairment was associated with subsequent steeper cognitive decline over time in both cohorts, even when controlling for amyloid status. In both cohorts worse hearing function was associated with steeper decline in language functioning, and in the oldest-old participants it was additionally associated with decline in global cognition and memory. Our mediation analyses in the oldest-old further suggested that language performance was not mediated by brain atrophy, which suggests that hearing loss is directly related to decline in language functioning. An alternative possibility is that our result reflects the notion that language tasks tend to involve processing of acoustic signals. It would be of interest for future studies whether such sensory deprivation would lead to future atrophy in brain areas important for language.

We further found in the oldest-old individuals, where we had combined hearing function and brain imaging data available, that hearing impairment was associated with smaller volumes of the hippocampus and nucleus accumbens and thinner medial orbitofrontal cortex. Smaller hippocampal volume has previously been associated with hearing impairment[10]. Our mediation analyses further suggests that the association between hearing function and memory decline was mediated by hippocampus volume and the nucleus accumbens. An association between hearing loss and the nucleus accumbens volume has previously been reported to be associated with tinnitus[39]. Possibly, alterations in (auditory) sensory input may influence brain structural integrity. This effect on brain integrity might be modifiable, since hearing functioning can be improved through hearing aids. However, the majority of individuals with poor hearing functioning wore hearing aids, and still showed cognitive decline, suggesting that this may not be sufficient. More longitudinal studies in younger people are needed to test whether wearing hearing aids may slow brain atrophy, and/or amyloid aggregation.

A potential limitation of our study is the relatively small sample size and short duration of follow-up. This may have reduced the statistical power to detect associations, and replication of our findings in in larger samples is needed. Furthermore, in the oldest-old cohort there is a possibility of selection bias of participants who had such severe hearing impairment that neuropsychological testing was impossible. Although this might have resulted in less variability, there where many participants with poor hearing in this cohort. On the other hand, few participants in the younger-old cohort had poor hearing. Another potential selection bias is that findings in our participants who were required to have normal cognition may not apply to older individuals in general. A strength of this study was that we were able to investigate the association of hearing function and biomarkers for dementia in two cohorts of different age groups that were extensively phenotyped.

5. Summary

In conclusion, our study demonstrated that age related hearing loss was associated with amyloid binding potential in younger-old individuals only, and with cognitive decline in both younger-old and oldest-old. The hippocampus and nucleus accumbens mediated hearing loss related decline in memory and global cognition. These results suggest that different mechanisms link hearing loss with cognitive decline in different age groups.

Ethics approval

Both studies were approved by the medical ethics committee of the Amsterdam UMC, location VUmc, reference number 2015.374 (EMIF-AD 90+) and 2014.210 (EMIF-AD PreclinAD).

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Figure 1. Associations between amyloid burden and performance on hearing test

Older participants are displayed in panel A, and younger-old participants are displayed in panel B. Amyloid burden (BP_{ND}) is displayed on the x-axis, and performance on the hearing test is displayed on the y-axis. A higher speech reception threshold (SRT) depicts a worse performance on the hearing test. The blue dots depict negative amyloid status, and the red dots depict positive amyloid status.

Figure 2. Cognitive decline stratified for hearing function

In the EMIF-AD 90+ cohort (upper panel) we found a steeper decline in decline in memory (Normal – Poor); global cognition (Insufficient – Poor); language (Normal – Insufficient; Insufficient – Poor); and executive functioning (Insufficient – Poor) with hearing loss. For more details see Table S3. In the EMIF-AD PreclinAD cohort (B) we found a steeper decline in language (Normal – Poor), and memory (Normal – Insufficient)

with hearing loss. The results were corrected for age, sex, education and amyloid status and genetic relatedness in the EMIF-AD PreclinAD cohort. For details on precise statistical values for stratified results see Table S4. The EMIF-AD 90+ cohort consisted of 11 participants with normal hearing, 20 with insufficient hearing and 34 with poor hearing; the EMIF-AD PreclinAD cohort consisted of 40 participants with normal hearing, 16 with insufficient hearing and 4 with poor hearing.

Figure 3. Brain regions associated with hearing loss EMIF-AD 90+

The subcortical (panel A) and cortical structures (panel B) are displayed. Worse Hearing function was associated with thinner medial orbitofrontal cortex, and lower volumes of hippocampus, and nucleus accumbens. The displayed scores are Z-transformed. Cortical thickness was corrected for age, sex and amyloid status, subcortical volumes were additionally corrected for total intracranial brain volume.

Figure 4. Mediation analysis showing how regional brain volumes mediate the effect of hearing loss on cognitive decline EMIF-AD 90+

Illustrated are the total effects of hearing function on decline in global cognition, memory and language (A); the mediation effects of the hippocampus (B); the mediation effects of the nucleus accumbens on (C); and the mediation effects of the medial orbitofrontal cortex (OFC) (D). The figure shows regression coefficients with 95% confidence intervals or Standard Errors. a = the effect of hearing loss on regional brain volume; b = the effect of regional brain volumes on cognitive decline; c = the total effect; c' = the direct effect of hearing loss on cognitive decline; c-c' = the mediation effect of regional brain volumes; *p≤ .05; **p≤ .01; ***p≤ .001.; N.E. = Not Estimated because we found no association between the brain region and cognitive domain.