

## RESEARCH ARTICLE

# Reduced suprathreshold auditory nerve responses are associated with slower processing speed and thinner temporal and parietal cortex in presbycusis

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## Abstract

Epidemiological evidence shows an association between hearing loss and dementia in elderly people. However, the mechanisms that connect hearing impairments and cognitive decline are still unknown. Here we propose that a suprathreshold auditory-nerve impairment is associated with cognitive decline and brain atrophy. Methods: audiological, neuropsychological, and brain structural 3-Tesla MRI data were obtained from elders with different levels of hearing loss recruited in the ANDES cohort. The amplitude of waves I (auditory nerve) and V (midbrain) from auditory brainstem responses were measured at 80 dB nHL. We also calculated the ratio between wave V and I as a proxy of suprathreshold brainstem function. Results: we included a total of 101 subjects (age:  $73.5 \pm 5.2$  years (mean  $\pm$  SD), mean education:  $9.5 \pm 4.2$  years, and mean audiogram thresholds (0.5–4 kHz):  $25.5 \pm 12.0$  dB HL). We obtained reliable suprathreshold waves V in all subjects ( $n = 101$ ), while replicable waves I were obtained in 92 subjects (91.1%). Partial Spearman correlations (corrected by age, gender, education and hearing thresholds) showed that reduced suprathreshold wave I responses were associated with thinner temporal and parietal cortices, and with slower processing speed as evidenced by the Trail-Making Test-A and digit symbol performance. Non-significant correlations were obtained between wave I amplitudes and other cognitive domains. Conclusions: These results evidence that reduced suprathreshold auditory nerve responses in presbycusis are associated with slower processing speed and brain structural changes in temporal and parietal regions.

## Introduction

Epidemiological studies have associated hearing loss with cognitive decline in adults older than 55 years, showing that individuals with audiometric thresholds worse than 40 dB are more likely to develop dementia [1–4]. However, the mechanisms that connect this epidemiological association are still under research [5]. Age-related hearing loss or presbycusis is characterized by bilateral hearing loss, degraded speech understanding, and impaired music perception, especially in background noise conditions [6,7]. Presbycusis is also associated with executive dysfunction [8,9] and with brain atrophy in the temporal lobe [10,11]. Moreover, recent studies in presbycusis have shown cortical atrophy in regions beyond the auditory cortex, including the cingulate cortex and parietal regions [9,12,13].

In addition to audiogram threshold elevations, hearing impairments in presbycusis can also be due to an altered suprathreshold function [14]. In rodents, suprathreshold brainstem responses have been extensively studied in models of acoustic injury, in which after a transient acoustic trauma, there is a temporary auditory threshold elevation that recovers completely, but a permanent reduction in the amplitude of auditory nerve responses is observed at suprathreshold levels [15,16]. In humans, the reduction of the amplitude of wave I from auditory brainstem responses (ABR) without alterations in auditory thresholds and otoacoustic emissions levels has been termed as hidden hearing loss (HHL) [17]. The underlying structural abnormality found in animals with HHL is the loss of synapses between inner hair cells and auditory nerve neurons, a histologic feature that has been termed as cochlear synaptopathy [15,18,19]. Importantly, evidence in animals shows that cochlear synaptopathy is a contributor of the early pathophysiological process of presbycusis [20].

In humans, the suprathreshold amplitude of ABR wave I has been reported to be reduced in patients with tinnitus and normal audiograms [17], and in subjects exposed to noise [21], suggesting that HHL might be part of the pathophysiological mechanisms of these conditions. In addition, HHL has been proposed as one of the mechanisms that might degrade speech perception in noisy environments [22]. In this line, a reduction in the amplitude of suprathreshold auditory nerve responses could be considered as an early stage of hearing impairment, which can be detected before hearing loss becomes clinically evident. Whether these suprathreshold abnormalities are associated with cognitive impairment and structural brain changes in humans is unknown. Here, we hypothesize that a reduction in the amplitude of suprathreshold auditory-nerve responses (ABR wave I) is associated with brain atrophy and cognitive decline in the elderly.

## Methods

### Subjects

The ANDES (Auditory and Dementia study) project is a prospective cohort of non-demented Chilean elders ( $\geq 65$  years) with a Mini-Mental State Examination (MMSE)  $> 24$ , with different levels of age-related hearing impairment and no use of hearing aids at recruitment. Inclusion criteria were: preserved functionality measured by the Pfeffer activities questionnaire [23], auditory brainstem responses evaluated at 80 dB nHL, and magnetic resonance imaging (MRI) at 3 Tesla. Exclusion criteria for recruitment were: (i) other causes of hearing loss different from presbycusis; (ii) previous use of hearing aids (iii); stroke or other neurological disorders; (iv) dementia; and (v) major psychiatric disorders. All procedures were approved by the Ethics Committee of the Clinical Hospital of the University of Chile, protocol number: OAIC 752/15. All subjects gave written informed consent in accordance with the Declaration of Helsinki.

## Auditory evaluations

Hearing impairments were evaluated with threshold and supra-threshold tests. All auditory evaluations were assessed inside a sound attenuating room and were obtained by an experienced audiologist who was blind to cognitive and MRI evaluations. We obtained audiometric thresholds using a calibrated audiometer (AC40e, Interacoustics®) for each ear at 0.125, 0.250, 0.5, 1, 2, 3, 4, 6 and 8 kHz. Pure tone averages (PTA) were computed for each ear using 0.5, 1, 2 and 4 kHz thresholds. The better hearing ear was used for analyses. Distortion product otoacoustic emissions (DPOAE) ( $2f_1 - f_2$ ) were elicited using eight pairs of primary tones ( $f_1$  and  $f_2$ ) with  $f_2/f_1$  ratio = 1.22, and delivered at 65 and 55 dB SPL (ER10C, Etymotic Research®). DPOAE were measured at eight different frequencies per ear, between 707 and 3563 Hz. For subsequent analyses we counted the number of detected DPOAE, a value that considering both ears, goes from 0 to 16 (see [9,13] for more details on DPOAE analysis). ABR waveforms were averaged with alternating clicks presented at supra-thresholds levels (2000 repetitions, 80 dB nHL, bandpass 0.1–3 kHz, stimulus rate 21.1 Hz, EP25, Eclipse, Interacoustics®). The amplitudes of waves I and V were measured from peak to trough, and wave latencies from peaks. For computing wave V/I ratios, in those cases with no measurable wave I ( $n = 9$ , see results section), we used the minimum amplitude value that we obtained for wave I ( $0.02 \mu\text{V}$ ).

## Neuropsychological assessment

Subjects and their relatives were evaluated by a neurologist with a complete structured medical, functional and cognitive interview. Cognitive performance was assessed by an experienced psychologist in cognitive tests, including the MMSE adapted for the Chilean population for global cognition [23,24]; the Frontal Assessment Battery (FAB), perseverative errors from the Wisconsin Card Sorting (WCS) and Trail Making Test B (TMT-B) for measuring executive function [25]; the Trail Making Test A (TMT-A) and digit symbol for processing speed [26]; the Boston Nominating Test for Language [27]; the Fluency “P” for phonemic verbal fluency [28]; the Rey-Osterrieth Complex Figure Test for Visuospatial Abilities [29]; and the free recall of the Free and Cued Selective Reminding Test (FCSRT) to explore verbal episodic memory [30,31]. In order to ensure comprehension of cognitive tests, instructions were given verbally and visually using a presentation in a desktop computer.

## Magnetic resonance imaging

Neuroimaging data were acquired by a MAGNETOM Skyra 3-Tesla whole-body MRI Scanner (Siemens Healthcare GmbH®, Erlangen, Germany) equipped with a head volume coil. T1-weighted magnetization-prepared rapid gradient echo (T1-MPRAGE) axial images were collected, and parameters were as follows: time repetition (TR) = 2300 ms, time echo (TE) = 232 ms, matrix =  $256 \times 256$ , flip angle =  $8^\circ$ , 26 slices, and voxel size =  $0.94 \times 0.94 \times 0.9 \text{ mm}^3$ . T2-weighted turbo spin echo (TSE) (4500 TR ms, 92 TE ms) and fluid attenuated inversion recovery (FLAIR) (8000 TR ms, 94 TE ms, 2500 TI ms) were also collected to inspect structural abnormalities. A total of 440 images were obtained during an acquisition time of 30 minutes per subject.

## Morphometric analyses

MRI data was used to determine the structural brain changes in all studied subjects ( $n = 101$ ), measuring the volume and thickness of bilateral cortical regions. FreeSurfer (version 6.0, <http://surfer.nmr.mgh.harvard.edu>) was used with a single Linux workstation using Centos 6.0

for T1-weighted images analysis of individual subjects. The FreeSurfer processing involved several stages, as follows: volume registration with the Talairach atlas, bias field correction, initial volumetric labeling, nonlinear alignment to the Talairach space, and final volume labeling. We used the “recon-all” function to generate automatic segmentations of cortical and subcortical regions. This command performs regional segmentation and processes gross regional volume in a conformed space (256×256×256 matrix, with coronal reslicing to 1 mm<sup>3</sup> voxels). The function “recon-all” creates gross brain volume extents for larger-scale regions (i.e., total number of voxels per region): total grey and white matter, subcortical grey matter, brain mask volume, and estimated total intracranial volume.

Additionally, we measured the cortical thickness in native space using FreeSurfer tools. We calculated the cortical thickness of each mesh of vertices by measuring the distance between the point on one surface and the closest conforming point on the opposite surface. Then we measured the average of the two values calculated from each side to the other [32]. Based on the brain regions that have been previously studied in presbycusis [10,33] our regions of interest (ROI) were bilateral frontal, inferior, middle, superior and transverse temporal gyri, and parietal cortex. We also included as regions of interest, cortical areas that have been implicated in the neural networks of degraded speech comprehension: bilateral anterior cingulate cortex, posterior cingulate cortex (PCC), and precentral and postcentral gyri [9,11,34].

## Data analyses

Possible correlations between cognitive tests and audiological functions were evaluated by means of partial Spearman associations adjusted by age, educational level, gender and audiogram thresholds. Gender comparisons were done using Mann-Whitney tests. Comparisons between subgroups were performed with ANCOVA adjusted by age, education, audiogram thresholds and gender. This approach was maintained for two group comparisons, as t-test do not allow covariates. Bonferroni corrections were performed for multiple comparisons when comparing more than two groups. Data are shown as mean ± standard deviation. Significant differences and correlations were considered for  $p < 0.05$ .

## Results

### Demographic and audiological variables

The mean age of the 101 studied subjects was  $73.5 \pm 5.2$  years with a mean education of  $9.5 \pm 4.2$  years, and mean PTA of the better hearing ear of  $25.5 \pm 12.0$  dB HL. A demographic description of the 101 subjects that completed the auditory, neuropsychological, and MRI evaluations is presented in Table 1. As one of our recruitment criteria was that subjects were not using hearing aids, the majority of the enrolled individuals had normal hearing thresholds (PTA < 25 dB HL,  $n = 55$ , 54.5%), while 46 subjects had some degree of hearing loss, including 33 (32.7%) with mild hearing loss (PTA  $\geq 25$  dB HL < 40 dB HL), and 13 individuals (12.8%) with moderate hearing loss (PTA  $\geq 40$  dB HL) according to audiogram thresholds of the better hearing ear. Age and audiogram thresholds were significantly correlated (Spearman,  $\rho = 0.326$ ,  $p = 0.001$ ), while the educational level was not correlated with PTA thresholds (Spearman,  $\rho = 0.0622$ ,  $p = 0.536$ ) (Fig 1A–1D).

Regarding supra-threshold ABR responses, we obtained measurable waves V at 80 dB nHL in the 101 subjects of this study, while wave I was obtained in 92 of these subjects (91.1%). The average amplitudes of wave I and V were  $0.120 \pm 0.070$   $\mu$ V and  $0.369 \pm 0.129$   $\mu$ V respectively, while mean latencies were  $5.71 \pm 0.39$  ms for wave V and  $1.56 \pm 0.14$  ms for wave I. We found a significant correlation between the amplitude of wave I and wave V (Fig 2A,  $\rho = 0.323$ ,  $p = 0.001$ ), while there were no correlations between the supra-threshold amplitudes of ABR

**Table 1. Summary of demographic data of the subjects considered in this report (obtained from ANDES cohort, n = 101).**

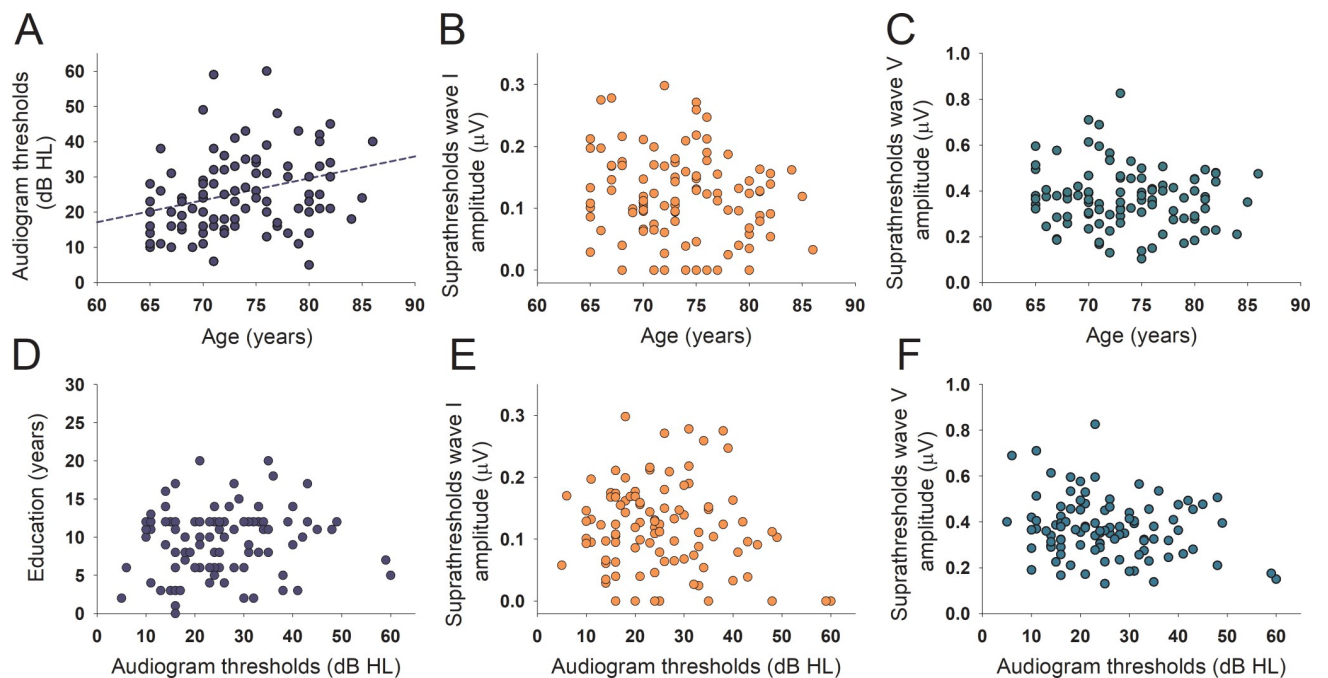
ANDES cohort	Female (n = 64)	Male (n = 37)	Total (n = 101)	p value
Age (years)	72.6 ± 5.2	75.1 ± 5.0	73.5 ± 5.2	p = 0.018
Education (years)	9.6 ± 4.5	9.3 ± 3.7	9.5 ± 4.2	n.s.
Hearing Thresholds (dB, better ear)	23.3 ± 11.5	29.1 ± 12.2	25.5 ± 12.0	p = 0.018
MMSE (score)	28.2 ± 0.9	27.8 ± 1.7	28.0 ± 1.3	n.s.
HHIE-S (score)	7.8 ± 8.5	6.6 ± 8.6	7.4 ± 8.6	n.s.

Significant gender differences were obtained for age and hearing thresholds, as men are older and have worse hearing thresholds than women ( $p < 0.05$ , Mann Whitney). MMSE: Mini Mental State Examination, HHIE-S: Hearing Handicap Inventory for the Elderly, ns: non-significant.

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waves I and V and age and audiogram thresholds (Fig 1B, 1C, 1E and 1F). In addition, there were non-significant differences in the amplitude of wave I when comparing subjects with hearing loss ( $n = 46$ ,  $0.113 \pm 0.79 \mu\text{V}$ ) with those with normal audiogram thresholds ( $n = 55$ ,  $0.124 \pm 0.62 \mu\text{V}$ ,  $F(1,96) = 0.82$ ,  $p = 0.775$ , ANCOVA controlled for age, education and gender). Regarding suprathreshold wave V amplitudes, we also obtained non-significant effects when comparing control and hearing loss subjects (controls:  $n = 55$ ,  $0.394 \pm 0.134 \mu\text{V}$ ; hearing loss;  $n = 46$ ,  $0.340 \pm 0.118 \mu\text{V}$ ,  $F(1,96) = 3.82$ ,  $p = 0.054$ , ANCOVA controlled for age, education and gender).

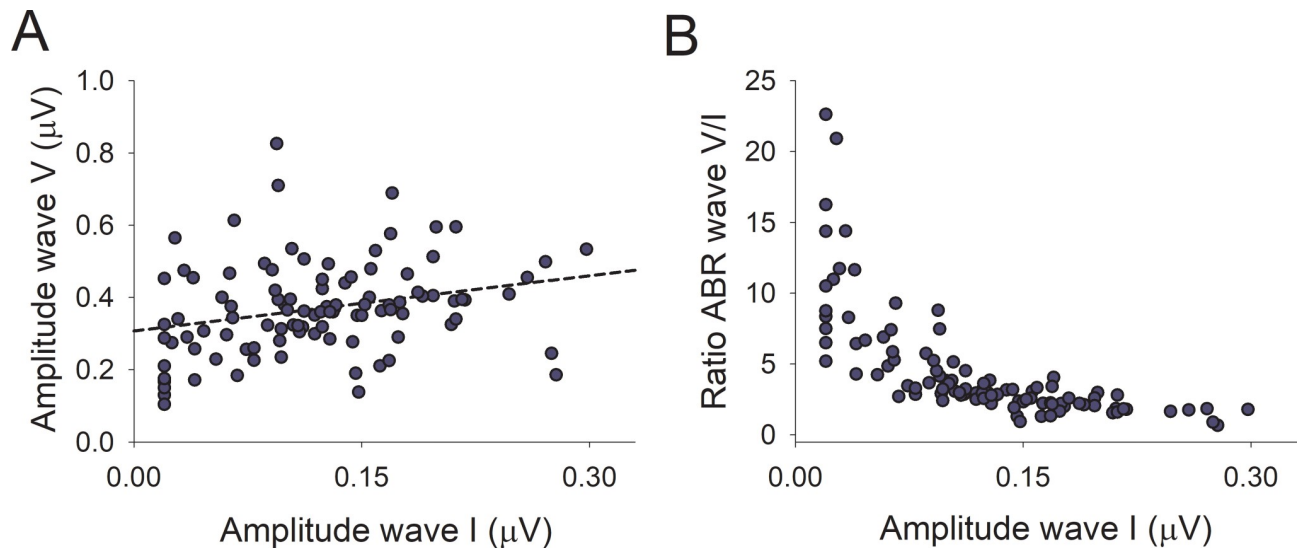
We also calculated the ratio between waves V and I which has been used as a measure of hidden hearing loss in previous studies [17,20]. The average wave V/I ratio was  $4.5 \pm 3.9$  (inter-quartile range 2.24–5.21). There was an asymmetric distribution of the wave V/I ratio as a function of wave I amplitude, denoting that wave V/I ratios for wave I amplitudes below



**Fig 1. Correlations between audiogram thresholds, age, education and supra-thresholds ABR responses.** A. Age and PTA were significantly correlated (Spearman,  $\rho = 0.326$ ,  $p = 0.001$ ). B. and E. Scatter plots showing no correlations between the amplitude of wave I with age (in the range between 65 and 85 years) and audiogram thresholds. C. and F. Scatter plots showing no correlations between the amplitude of wave V with age (in the range between 65 and 85 years) and audiogram thresholds. D. Audiogram thresholds were not correlated with the years of education.

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**Fig 2. Correlations between the amplitude and ratio of suprathreshold ABR responses.** A. The amplitude of wave I was significantly correlated with the amplitude of wave V ( $\rho = 0.323$ ,  $p = 0.001$ ). B. Wave ABR V/I amplitude ratio plotted as a function of wave I amplitude. It is important to show the ratio between waves V and I because it can be used as a proxy of hidden hearing loss. Notice an asymmetric distribution of wave V/I ratio as a function of wave I amplitude, showing larger wave V/I ratios for wave I amplitudes smaller than 0.15  $\mu\text{V}$ .

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0.15  $\mu\text{V}$  were significantly larger than for those above 0.15  $\mu\text{V}$  (Mann-Whitney,  $p < 0.001$ ) (Fig 2B, Table 2). Non-significant correlations were obtained between age and audiogram thresholds with the wave V/I ratio. In addition, there were non-significant differences in the wave V/I ratio when comparing subjects with hearing loss ( $n = 46$ ,  $4.7 \pm 4.2$ ) with those with normal audiogram thresholds ( $n = 55$ ,  $4.4 \pm 3.7$ ,  $F(1,96) = 0.42$ ,  $p = 0.519$ , ANCOVA controlled for age, education and gender).

**Table 2. Demographic and neuropsychological variables compared according to the two groups with different amplitude of auditory nerve responses.**

ANDES cohort (n = 101)	Auditory nerve less than 0.15 $\mu\text{V}$ ABR wave I (n = 68)	Auditory nerve more than 0.15 $\mu\text{V}$ ABR wave I (n = 33)	p value ANCOVA
Age	74.0 $\pm$ 5.3	72.6 $\pm$ 4.9	n.s.
Years of education	9.7 $\pm$ 4.3	9.0 $\pm$ 4.1	n.s.
PTA 0.5–4 kHz (dB)	26.8 $\pm$ 13.3	23.1 $\pm$ 8.5	n.s.
DPOAE (n, both ears)	7.0 $\pm$ 5.8	7.8 $\pm$ 5.1	n.s.
ABR wave V amplitude ( $\mu\text{V}$ )	0.349 $\pm$ 0.132	0.410 $\pm$ 0.115	n.s.
Wave V/I ratio	5.64 $\pm$ 4.32	2.15 $\pm$ 0.73	$p < 0.001^*$
MMSE	27.82 $\pm$ 1.40	28.42 $\pm$ 1.30	n.s.
Digit symbol	36.3 $\pm$ 14.7	40.5 $\pm$ 13.1	n.s.
TMT-A (s)	66.3 $\pm$ 31.5	51.9 $\pm$ 23.0	$p = 0.005^*$
TMT-B (s)	172.4 $\pm$ 84.0	176.8 $\pm$ 91.1	n.s.
Perseverative errors (WCS)	11.1 $\pm$ 9.1	10.2 $\pm$ 6.3	n.s.
FAB	13.3 $\pm$ 2.5	14.0 $\pm$ 2.0	n.s.
Fluency P	10.0 $\pm$ 4.8	10.1 $\pm$ 4.3	n.s.
Boston nomination	24.4 $\pm$ 3.2	25.0 $\pm$ 3.4	n.s.
Rey Figure	30.0 $\pm$ 5.4	29.4 $\pm$ 5.1	n.s.
FCRST free recall	25.9 $\pm$ 7.9	26.2 $\pm$ 7.0	n.s.

ANCOVA was corrected by age, gender, education and audiogram thresholds. Note that TMT-A time is the only significant difference in cognitive performance between the groups ( $p < 0.05^*$ , adjusted by Bonferroni for multiple comparisons).

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As the increased wave V/I ratio might be reflecting a compensatory midbrain gain increase of wave V responses in the group with wave I < 0.15  $\mu$ V, we divided data according to the amplitude of wave I into two groups: (i) those with wave I responses smaller than 0.15  $\mu$ V ( $n = 68$ ) and (ii) those with wave I responses larger than 0.15  $\mu$ V ( $n = 33$ ). [Table 2](#) shows demographic, audiological and neuropsychological data comparing these two groups with different wave I amplitudes. There were no differences in age, education and hearing thresholds (assessed by audiogram and DPOAEs) between these two groups.

### Suprathreshold ABRs and cognitive assessments

Regarding cognitive tests, and after adjusting by age, education, gender, audiogram thresholds, and Bonferroni correction for multiple comparisons (10 cognitive tests), the only significant difference was obtained in the TMT-A speed, showing that the group with smaller wave I responses had slower processing speed ( $66.3 \pm 31.5$  s) than the group with larger wave I responses ( $51.9 \pm 23.0$  s,  $p = 0.005$ ).

Next, we performed partial Spearman correlations in the whole sample ( $n = 101$ ) between ABR and cognitive tests, corrected by age, education, gender and audiogram thresholds. The only cognitive tests that showed significant correlations with the amplitude of supra-threshold wave I were those that measure processing speed: the TMT-A time ([Fig 3A](#),  $\rho = -0.27$ ,  $p = 0.007$ ), and the digit symbol ( $\rho = 0.199$ ;  $p = 0.049$ ). On the other hand, we there was no correlation between the supra-threshold amplitude of wave V and TMT-A time ([Fig 3B](#)) ([Table 3](#)).

### Suprathreshold ABRs and cortical volume and thickness

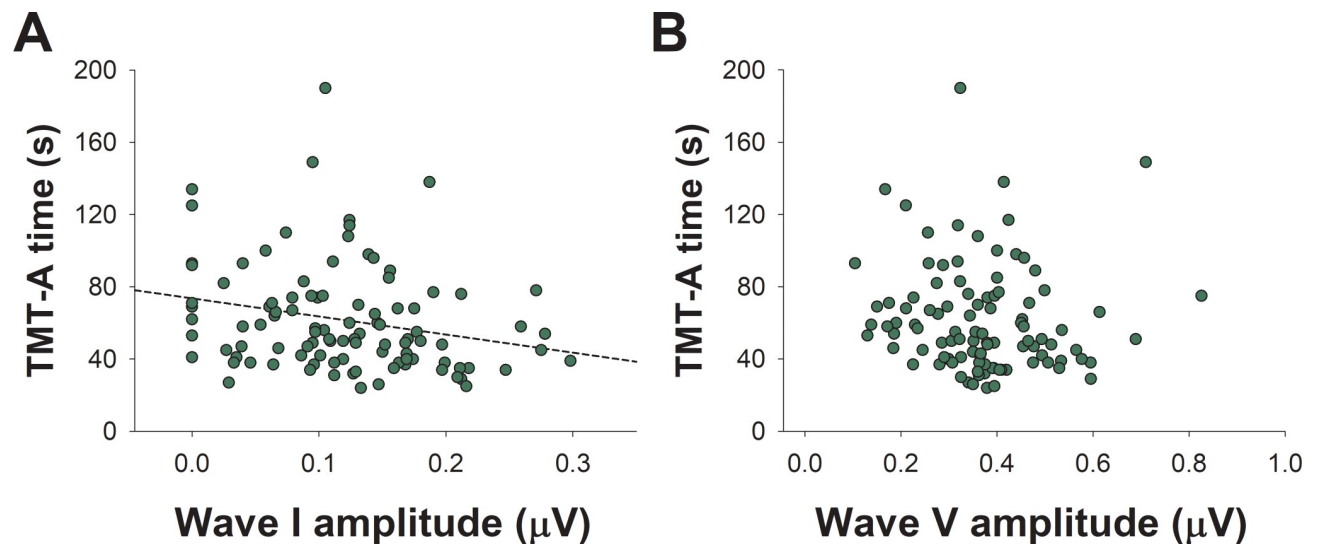
We performed partial Spearman correlations between the suprathreshold amplitudes of wave I and V responses with all the cortical volumes and thickness of the ROIs in the brain (corrected by age, education, gender and audiogram thresholds). Non-significant differences were found when analyzing cortical volumes in all the ROIs between the two groups with different supra-threshold ABR amplitudes. We found significant Spearman correlations between the amplitude of wave I and the thickness of bilateral middle and inferior temporal cortex, and bilateral inferior parietal cortex ([Fig 4](#), [Table 4](#)). We also found significant correlations between wave I amplitude and the cortical thickness of: right posterior cingulate, right medial orbitofrontal, left superior parietal, and for left inferior and transverse temporal cortices ([Table 4](#)). Regarding wave V amplitude, we only found a significant correlation with left inferior and transverse temporal cortices.

## Discussion

Here we give evidence that a reduced amplitude of suprathreshold auditory nerve responses (wave I) is associated with slower processing speed (TMT-A, digit symbol) and with thinner bilateral temporal and parietal cortices in non-demented elderly humans. In addition, we show that the wave V/I ratio as a function of wave I amplitude yielded an asymmetric distribution, suggesting a midbrain compensatory gain increase for reduced suprathreshold auditory nerve responses.

### Aging, audiogram thresholds and suprathreshold ABRs

Although, in our data we did not find any significant correlation between the suprathreshold amplitudes of waves I and V with age ([Fig 1](#)), these results should be taken carefully, as the range of age of our subjects was between 65 and 85 years, and probably if we extend the range



**Fig 3. Correlations between TMT-A performance and supra-threshold ABR responses.** (A) Trail-Making Test A speed is associated with the suprathreshold amplitude of wave I amplitude, but not with (B) the suprathreshold amplitude of wave V.

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of age to younger subjects, it is very likely that we would find significant age effects. Indeed, previous studies performed in animals [35,36] as well as in humans [37–39] found significant reductions in wave I amplitudes with age.

In our study we also found that the amplitudes of suprathreshold ABR responses were not associated with audiogram thresholds (PTA calculated between 0.5 and 4 kHz), suggesting that auditory thresholds and suprathreshold functions are independent measures of auditory processing. In this line, we previously showed that a deteriorated hearing threshold function as evidenced by a reduced number of DPOAE is associated with atrophy of the anterior cingulate cortex and executive dysfunction in presbycusis [9]. In contrast, here we show that a reduced amplitude of suprathreshold auditory nerve responses is not associated with deteriorated executive function, but with slower processing speed (longer TMT-A latencies and worse digit symbol scores) and with thinner temporal and parietal cortex. These findings suggest that the impairment of different auditory functions (threshold and suprathreshold) could affect different brain structures and cognitive domains.

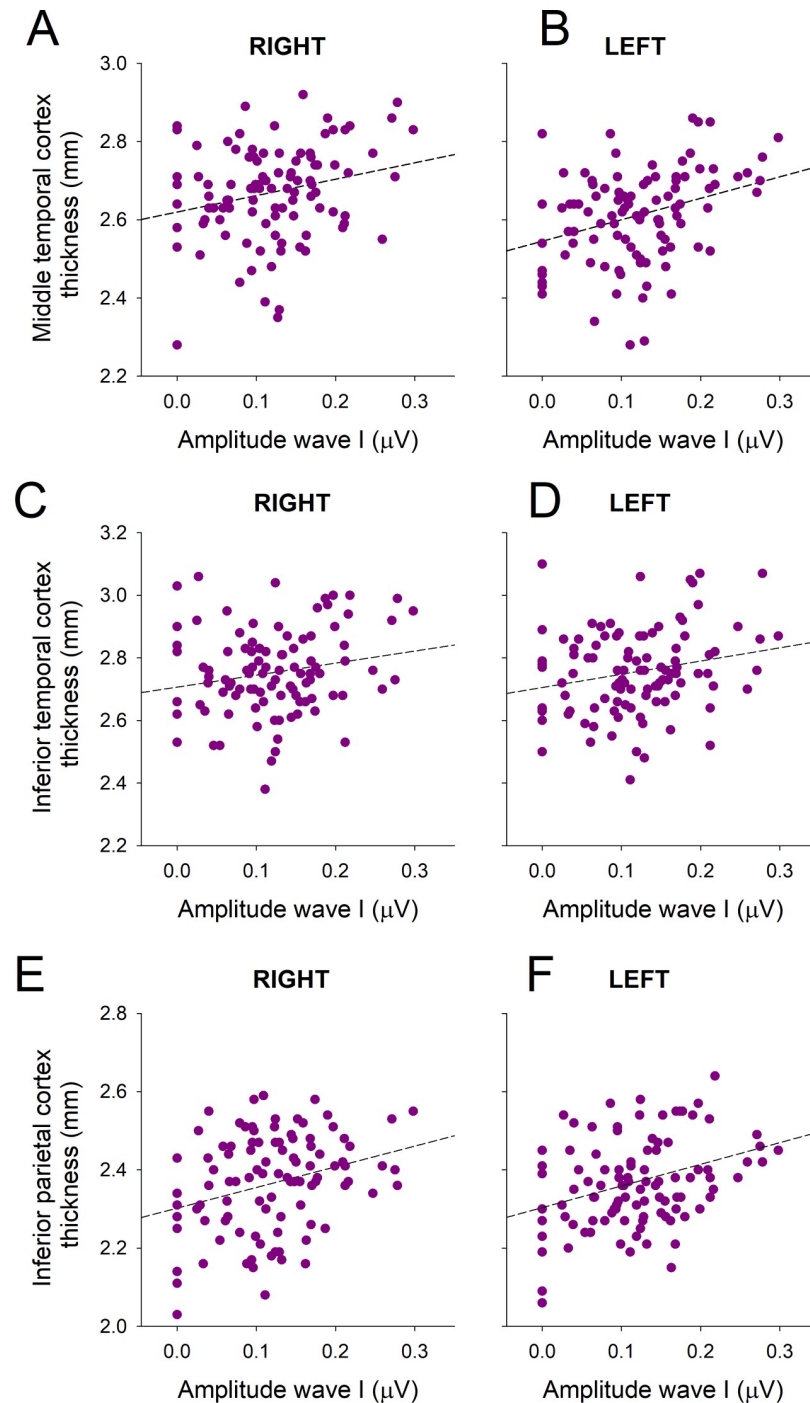
**Table 3. Partial correlations between ABR amplitudes and latencies and neuropsychological tests in the ANDES cohort (n = 101).**

ANDES cohort (n = 101)	ABR wave I amplitude	ABR wave V amplitude	ABR wave I latency	ABR wave V latency
Digit symbol	<b>rho = 0.199 p = 0.049</b>	rho = 0.178 p = 0.079	rho = -0.079 p = 0.461	rho = -0.121 p = 0.234
TMT-A	<b>rho = -0.272 p = 0.007</b>	rho = -0.065 p = 0.524	rho = 0.065 p = 0.544	rho = 0.119 p = 0.243
TMT-B	rho = 0.136 p = 0.208	rho = 0.044 p = 0.683	rho = 0.067 p = 0.536	<b>rho = 0.243 p = 0.023</b>
Perseverative errors	rho = -0.024 p = 0.817	rho = -0.066 p = 0.516	rho = -0.051 p = 0.634	rho = 0.135 p = 0.186
FAB	rho = 0.041 p = 0.692	rho = 0.015 p = 0.882	rho = 0.084 p = 0.436	rho = -0.062 p = 0.542
Fluency P	rho = -0.071 p = 0.485	rho = -0.072 p = 0.479	rho = 0.045 p = 0.677	rho = -0.119 p = 0.243
Boston nomination	rho = 0.068 p = 0.504	rho = 0.161 p = 0.114	rho = -0.097 p = 0.363	<b>rho = -0.208 p = 0.039</b>
Rey Figure	rho = -0.009 p = 0.929	rho = -0.110 p = 0.285	rho = 0.038 p = 0.724	rho = -0.117 p = 0.256
FCSRT free recall	rho = -0.10 p = 0.327	rho = -0.120 p = 0.238	rho = -0.094 p = 0.382	rho = 0.160 p = 0.876

All correlations were adjusted by age, education, gender and audiogram thresholds. Notice significant correlations (shown in bold) between TMT-A time and digit symbol with the amplitude of ABR wave I. In addition, Boston and TMT-B time were significantly correlated with the latency of wave V.

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**Fig 4. The thickness of bilateral middle and inferior temporal cortex and inferior parietal cortex are correlated with the amplitude of ABR wave I responses.** (A) Right and (B) left middle temporal thickness correlated with wave I amplitude. (C) Right and (D) left inferior temporal cortex thickness correlated with wave I amplitude. (E) Right and (F) left inferior parietal cortex thickness correlated with wave I amplitude.

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**Table 4. Partial correlations between ABR amplitudes and cortical thickness in presbycusis patients from the ANDES cohort (n = 101).**

Right hemisphere	Wave I	Wave V
Inferior temporal	<b>rho = 0.240; p = 0.018*</b>	rho = 0.064; p = 0.536
Middle temporal	<b>rho = 0.221; p = 0.029*</b>	rho = 0.107; p = 0.298
Superior temporal	rho = 0.157; p = 0.124	rho = 0.195; p = 0.056
Transverse temporal	rho = 0.129; p = 0.207	rho = 0.193; p = 0.058
Superior parietal	rho = 0.132; p = 0.198	rho = 0.130; p = 0.203
Inferior parietal	<b>rho = 0.212; p = 0.037*</b>	rho = 0.052; p = 0.610
Lateral orbitofrontal	rho = 0.093; p = .366	rho = -0.014; p = 0.894
Medial orbitofrontal	<b>rho = 0.232; p = 0.022*</b>	rho = 0.053; p = 0.603
Caudal middle frontal	rho = 0.155; p = 0.130	rho = -0.028; p = 0.786
Rostral middle frontal	rho = 0.071; p = 0.486	rho = 0.052; p = 0.616
Superior frontal	rho = 0.109; p = 0.290	rho = -0.001; p = 0.994
Anterior cingulate	rho = -0.027; p = 0.793	rho = -0.036; p = 0.730
Posterior cingulate	<b>rho = 0.214; p = 0.036*</b>	rho = -0.034; p = 0.743
Precentral thickness	rho = 0.154; p = 0.133	rho = -0.009; p = 0.930
Postcentral thickness	rho = 0.047; p = 0.648	rho = 0.052; p = 0.610
<b>Left hemisphere</b>	<b>Wave I</b>	<b>Wave V</b>
Inferior temporal	<b>rho = 0.216; p = 0.034*</b>	<b>rho = 0.232; p = 0.022*</b>
Middle temporal	<b>rho = 0.263; p = 0.009**</b>	rho = 0.111; p = 0.280
Superior temporal	rho = 0.198; p = 0.052	rho = 0.066; p = 0.524
Transverse temporal	<b>rho = 0.215; p = 0.034*</b>	<b>rho = 0.214; p = 0.035*</b>
Superior parietal	<b>rho = 0.265; p = 0.009**</b>	rho = 0.136; p = 0.183
Inferior parietal	<b>rho = 0.235; p = 0.020*</b>	rho = 0.102; p = 0.322
Lateral orbitofrontal	rho = 0.170; p = 0.097	rho = 0.021; p = 0.835
Medial orbitofrontal	rho = .099; p = 0.337	rho = -0.059; p = 0.568
Caudal middle frontal	rho = 0.141; p = 0.168	rho = 0.038; p = 0.709
Rostral middle frontal	rho = 0.066; p = 0.519	rho = -0.094; p = 0.362
Superior frontal	rho = 0.124; p = 0.226	rho = -0.104; p = 0.310
Anterior cingulate	rho = 0.068; p = 0.507	rho = 0.199; p = 0.051
Posterior cingulate	rho = 0.006; p = 0.954	rho = -0.007; p = 0.945
Precentral thickness	rho = 0.161; p = 0.116	rho = -0.007; p = 0.946
Postcentral thickness	rho = 0.053; p = 0.604	rho = -0.009; p = 0.928

All correlations were controlled by age, education, gender and audiogram thresholds. Significant correlations are highlighted in bold (\* $p < 0.05$  \*\* $p < 0.01$ ).

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### Midbrain gain increase

We found an increased wave V/I ratio in the group with reduced suprathreshold auditory nerve responses ( $< 0.15 \mu\text{V}$ ), which was independent of age and hearing thresholds. The gain increase of midbrain responses is also supported by the fact that the amplitudes of wave V responses were similar between the two groups with different wave I amplitudes (Table 2). Thus, the preserved amplitude of suprathreshold wave V responses in the group with reduced wave I could be reflecting a compensatory gain increase in the midbrain. A similar mechanism has been proposed for peripheral de-afferentation [17,40]. Moreover, animal models have shown that cochlear de-afferentation is sufficient for inducing an increase in the spontaneous activity of auditory cortex neurons [41], showing that the effects of peripheral de-afferentation can also affect cortical processing. Here we show in humans, that the group with reduced

auditory nerve amplitudes has structural brain changes that were located bilaterally in the temporal and inferior parietal cortices, and in the posterior cingulate cortex of the right hemisphere.

### Brain atrophy in presbycusis

Previous studies have related audiogram threshold loss with right temporal and cingulate cortex atrophy [9–12,42,43]. Here we extended these results, showing that in addition to audiogram threshold elevation, reduced suprathreshold amplitudes of auditory nerve responses are associated to significant reductions in the cortical thickness of temporal and inferior parietal regions, but not to the cortical volume of these regions. These results suggest that the cortical thickness is a more sensitive measure than cortical volume loss for evidencing brain atrophy related to suprathreshold auditory impairments. In addition, our data show that these structural brain changes can be detected in earlier stages of presbycusis, or even in subjects with normal hearing (at least as evaluated by audiogram thresholds between 0.5 and 4 kHz).

In a previous work [9], we demonstrated that reduced PCC thickness was correlated with worse auditory thresholds in patients with presbycusis and cochlear dysfunction, suggesting that the atrophy of the right PCC is related to hearing loss. Here, we showed that a reduction in the cortical thickness of the right PCC is also associated with suprathreshold hearing impairments, suggesting that PCC atrophy is related to hearing threshold and suprathreshold impairments. The right posterior cingulate cortex is important for visuospatial abilities like orientation and spatial navigation. Interestingly the PCC is among the earliest regions that get atrophied in prodromal and preclinical Alzheimer's disease [44]. In this line, the right PCC might be an important brain region linking hearing impairments with cognitive decline in presbycusis. In addition to the PCC, we also found that reduced suprathreshold auditory-nerve responses are associated to thinner bilateral inferior parietal cortex (Table 4). The inferior parietal cortex is considered a multimodal area involved in several neural networks including speech, voice production, and visual attention [45]. Importantly, visual attention is necessary for the execution of the TMT-A and digit symbol tests. In this line, a speculative explanation for our results is that impaired visual attention due to the bilateral reduction of cortical thickness in the inferior parietal cortex could affect TMT-A and digit symbol performance.

### Processing speed and suprathreshold auditory-nerve function

Previous evidence has shown that worse audiogram thresholds [10,46] or an alteration of the cochlear function as evidenced by loss of DPOAE [9] are associated with executive dysfunction, memory loss and global cognitive decline. In addition to these associations, here we show that reduced suprathreshold auditory-nerve responses are associated to slower processing speed, as evidenced by TMT-A responses (Fig 3, Table 3) and digit symbol performance (Table 3), cognitive tests which do not rely on auditory inputs. Processing speed tests are usually categorized as “fluid cognition” and are influenced by the aging process, but also by sensory impairments and visual attention [45,47]. One speculative explanation for the association between reduced amplitude of auditory-nerve responses and slower processing speed could be related to the physiological aging process, resulting in loss of synapses at different levels of the nervous system [48]. In this sense, we can propose that due to the aging process, the loss of synapses between the inner hair cells and auditory nerve neurons would result in reduced amplitude of suprathreshold wave I responses [20], while reduced synapses at the central nervous system would lead to slower processing speed [48]. Although cochlear synaptopathy has been associated to loss of synapses due to acoustic trauma, it could also be an indirect measure

of a general loss of synapses in the central nervous system, and therefore the greater the loss of synapses in different circuits of the nervous system, the slower is the processing speed. In this sense, it would be important to estimate the loss of auditory nerve synapses due to acoustic injury for adding this variable to our models. Unfortunately, in the present study we did not collect data about occupational or recreational noise exposure. Another speculative explanation is that processing speed could be related to white matter microstructural changes in the peripheral and central auditory pathways, including the auditory nerve, as a reduced fractional anisotropy in diffusion tensor imaging has been demonstrated in diverse white matter tracts of patients with hearing loss [49].

### Clinical relevance

Importantly, structural brain changes and auditory-nerve responses described in the present manuscript were obtained by MRI and ABR techniques, which are non-invasive examinations that can be used in a clinical setting. Future longitudinal studies should examine whether patients with reduced suprathreshold wave I amplitude and morphological changes in the temporal and parietal regions are at a higher risk of developing dementia.

### Conclusion

We conclude that a reduction of the suprathreshold amplitude of auditory nerve responses is related to slower processing speed and reduced cortical thickness in bilateral middle and inferior temporal cortices, bilateral inferior parietal, and in the right posterior cingulate cortex. Taken together, the present and our previous findings [9] suggest that thresholds and suprathreshold hearing impairments are associated with different types of cognitive functions and brain structural changes.

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## References

1. Deal JA, Betz J, Yaffe K, Harris T, Purchase-Helzner E, Satterfield S, et al. Hearing Impairment and Incident Dementia and Cognitive Decline in Older Adults: The Health ABC Study. *The Journals of Gerontology Series A: Biological Sciences and Medical Sciences*. 2016; 72: glw069. <https://doi.org/10.1093/gerona/glw069>
2. Livingston G, Sommerlad A, Orgeta V, Costafreda SG, Huntley J, Ames D, et al. Dementia prevention, intervention, and care. *Lancet*. 2017; 390:2673–2734. [https://doi.org/10.1016/S0140-6736\(17\)31363-6](https://doi.org/10.1016/S0140-6736(17)31363-6) PMID: 28735855
3. Wei J, Hu Y, Zhang L, Hao Q, Yang R, Lu H, et al. Hearing Impairment, Mild Cognitive Impairment, and Dementia: A Meta-Analysis of Cohort Studies. *Dement Geriatr Cogn Dis Extra*. 2017; 7:440–452. <https://doi.org/10.1159/000485178> PMID: 29430246
4. Yuan J, Sun Y, Sang S, Pham JH, Kong WJ. The risk of cognitive impairment associated with hearing function in older adults: a pooled analysis of data from eleven studies. *Sci Rep*. 2018; 8:2137. <https://doi.org/10.1038/s41598-018-20496-w> PMID: 29391476
5. Lin FR, Albert M. Hearing loss and dementia—who is listening? *Aging Ment Health*. 2014; 18:671–3. <https://doi.org/10.1080/13607863.2014.915924> PMID: 24875093
6. Gates GA, Mills JH. Presbycusis. *The Lancet*. 2005; 366: 1111–1120.
7. Moreno-Gómez FN, Véliz G, Rojas M, Martínez C, Olmedo R, Panussis F, et al. Music Training and Education Slow the Deterioration of Music Perception Produced by Presbycusis in the Elderly. *Front Aging Neurosci*. 2017; 9:149. <https://doi.org/10.3389/fnagi.2017.00149> PMID: 28579956
8. Lin FR, Ferrucci L, Metter EJ, An Y, Zonderman AB, Resnick SM. Hearing loss and cognition in the Baltimore Longitudinal Study of Aging. *Neuropsychology*. 2011; 25:763–70. <https://doi.org/10.1037/a0024238> PMID: 21728425
9. Belkhiria C, Vergara RC, San Martín S, Leiva A, Marcenaro B, Martínez M, et al. Cingulate Cortex Atrophy Is Associated With Hearing Loss in Presbycusis With Cochlear Amplifier Dysfunction. *Front Aging Neurosci*. 2019; 11:97. <https://doi.org/10.3389/fnagi.2019.00097> PMID: 31080411
10. Lin FR, Ferrucci L, An Y, Goh JO, Doshi J, Metter EJ, et al. Association of hearing impairment with brain volume changes in older adults. *Neuroimage*. 2014; 90:84–92. <https://doi.org/10.1016/j.neuroimage.2013.12.059> PMID: 24412398
11. Peelle JE, Wingfield A. The Neural Consequences of Age-Related Hearing Loss. *Trends Neurosci*. 2016; 39: 486–497. <https://doi.org/10.1016/j.tins.2016.05.001> PMID: 27262177
12. Ren F, Ma W, Li M, Sun H, Xin Q, Zong W, et al. Gray Matter Atrophy Is Associated With Cognitive Impairment in Patients With Presbycusis: A Comprehensive Morphometric Study. *Front Neurosci*. 2018; 12:744. <https://doi.org/10.3389/fnins.2018.00744> PMID: 30405333
13. Belkhiria C, Vergara R, San Martín S, Leiva A, Martínez M, Marcenaro B, et al. Insula and Amygdala Atrophy Are Associated with Functional Impairment in Subjects with Presbycusis. *Front Aging Neurosci*. 2020. <https://doi.org/10.3389/fnagi.2020.00102>
14. Frisina DR, Frisina RD. Speech recognition in noise and presbycusis: relations to possible neural mechanisms. *Hear Res*. 1997; 106:95–104. [https://doi.org/10.1016/s0378-5955\(97\)00006-3](https://doi.org/10.1016/s0378-5955(97)00006-3) PMID: 9112109
15. Kujawa SG, Liberman MC. Adding insult to injury: cochlear nerve degeneration after "temporary" noise-induced hearing loss. *J Neurosci*. 2009; 29:14077–85. <https://doi.org/10.1523/JNEUROSCI.2845-09.2009> PMID: 19906956
16. Liberman MC. HIDDEN HEARING LOSS. *Scientific American*. 2015; 313:48–53.
17. Schaette R, McAlpine D. Tinnitus with a normal audiogram: physiological evidence for hidden hearing loss and computational model. *J Neurosci*. 2011; 31:13452–7. <https://doi.org/10.1523/JNEUROSCI.2156-11.2011> PMID: 21940438
18. Bharadwaj HM, Verhulst S, Shaheen L, Liberman MC, Shinn-Cunningham BG. Cochlear neuropathy and the coding of supra-threshold sound. *Front Syst Neurosci*. 2014; 8:26. <https://doi.org/10.3389/fnsys.2014.00026> PMID: 24600357

19. Boero LE, Castagna VC, Di Guilmi MN, Goutman JD, Elgoyhen AB, Gómez-Casati ME. Enhancement of the Medial Olivocochlear System Prevents Hidden Hearing Loss. *J Neurosci*. 2018; 38:7440–7451. <https://doi.org/10.1523/JNEUROSCI.0363-18.2018> PMID: 30030403
20. Sergeyenko Y, Lall K, Liberman MC, Kujawa SG. Age-Related Cochlear Synaptopathy: An Early-Onset Contributor to Auditory Functional Decline. *J Neurosci*. 2013; 33:13686–94. <https://doi.org/10.1523/JNEUROSCI.1783-13.2013> PMID: 23966690
21. Stamper GC, Johnson TA. Auditory function in normal-hearing, noise-exposed human ears. *Ear Hear*. 2015; 36:172–84. <https://doi.org/10.1097/AUD.000000000000107> PMID: 25350405
22. Parthasarathy A, Kujawa SG. Synaptopathy in the Aging Cochlea: Characterizing Early-Neural Deficits in Auditory Temporal Envelope Processing. *J Neurosci*. 2018; 38:7108–7119. <https://doi.org/10.1523/JNEUROSCI.3240-17.2018> PMID: 29976623
23. Quiroga P, Albala C, Klaasen G. Validation of a screening test for age associated cognitive impairment in Chile. *Rev Med Chile*. 2014; 132:467–478.
24. Folstein MF, Folstein SE, McHugh PR. Mini-mental state. A practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res*. 1975; 12: 189–98. [https://doi.org/10.1016/0022-3956\(75\)90026-6](https://doi.org/10.1016/0022-3956(75)90026-6) PMID: 1202204
25. Dubois B, Slachevsky A, Litvan I, Pillon B. The FAB: a Frontal Assessment Battery at bedside. *Neurology*. 2000; 55:1621–1626. <https://doi.org/10.1212/wnl.55.11.1621> PMID: 11113214
26. Army Individual Test Battery. Manual of Directions and Scoring. 1944. Washington.
27. Kaplan E. The Boston Naming Test. 1978. Philadelphia: Lea & Febiger.
28. Canning SJ, Leach L, Stuss D, Ngo L, Black SE. Diagnostic utility of abbreviated fluency measures in Alzheimer disease and vascular dementia. *Neurology*. 2004; 62:556–562. <https://doi.org/10.1212/wnl.62.4.556> PMID: 14981170
29. Rey A. Test de copie d'une figure complexe. 1959. Paris: Centre de Psychologie Appliquée.
30. Grober E, Buschke H, Crystal H, Bang S, Dresner R. Screening for dementia by memory testing. *Neurology*. 1988; 38: 900–900. <https://doi.org/10.1212/wnl.38.6.900> PMID: 3368071
31. Delgado C, Muñoz-Neira C, Soto A, Martínez M, Henríquez F, Flores P, et al. Comparison of the Psychometric Properties of the “Word” and “Picture” Versions of the Free and Cued Selective Reminding Test in a Spanish-Speaking Cohort of Patients with Mild Alzheimer’s Disease and Cognitively Healthy Controls. *Archives of Clinical Neuropsychology*. 2016; 31:165–75. <https://doi.org/10.1093/arclin/acv107> PMID: 26758367
32. Fischl B, Dale AM. Measuring the thickness of the human cerebral cortex from magnetic resonance images. *Proc Natl Acad Sci U S A*. 2000; 97: 11050–5. <https://doi.org/10.1073/pnas.200033797> PMID: 10984517
33. Rigters SC, Bos D, Metselaar M, Roshchupkin GV, Baatenburg de Jong RJ, Ikram MA, et al. Hearing Impairment Is Associated with Smaller Brain Volume in Aging. *Front Aging Neurosci*. 2017; 9: 2. <https://doi.org/10.3389/fnagi.2017.00002> PMID: 28163683
34. Peelle JE. Listening Effort: How the Cognitive Consequences of Acoustic Challenge Are Reflected in Brain and Behavior. *Ear Hear*. 2018; 39:204–214. <https://doi.org/10.1097/AUD.0000000000000494> PMID: 28938250
35. Boettcher FA, Mills JH, Norton BL. Age-related changes in auditory evoked potentials of gerbils. I. Response amplitudes. *Hear Res*. 1993; 71:137–145. [https://doi.org/10.1016/0378-5955\(93\)90029-z](https://doi.org/10.1016/0378-5955(93)90029-z) PMID: 8113132
36. Torre P, Fowler CG. Age-related changes in auditory function of rhesus monkeys (*Macaca mulatta*). *Hear Res*. 2000; 142:131–140. [https://doi.org/10.1016/s0378-5955\(00\)00025-3](https://doi.org/10.1016/s0378-5955(00)00025-3) PMID: 10748335
37. Oku T, Hasegawa M. The influence of aging on auditory brainstem response and electrocochleography in the elderly. *ORL J Otorhinolaryngol Relat Spec*. 1997; 59:141–6. <https://doi.org/10.1159/000276927> PMID: 9186968
38. Konrad-Martin D, Dille MF, McMillan G, Griest S, McDermott D, Fausti SA, et al. Age-related changes in the auditory brainstem response. *J Am Acad Audiol*. 2012; 23:18–75. <https://doi.org/10.3766/jaaa.23.1.3> PMID: 22284838
39. Johannesen PT, Buzo BC, Lopez-Poveda EA. Evidence for age-related cochlear synaptopathy in humans unconnected to speech-in-noise intelligibility deficits. *Hear Res*. 2019; 374:35–48. <https://doi.org/10.1016/j.heares.2019.01.017> PMID: 30710791
40. Hesse LL, Bakay W, Ong HC, Anderson L, Ashmore J, McAlpine D, et al. Non-Monotonic Relation between Noise Exposure Severity and Neuronal Hyperactivity in the Auditory Midbrain. *Front Neurol*. 2016; 7:133. <https://doi.org/10.3389/fneur.2016.00133> PMID: 27625631



41. Eggermont JJ, Kral A. Somatic memory and gain increase as preconditions for tinnitus: Insights from congenital deafness. *Hear Res.* 2016; 333:37–48. <https://doi.org/10.1016/j.heares.2015.12.018> PMID: 26719143
42. Cardin V. Effects of Aging and Adult-Onset Hearing Loss on Cortical Auditory Regions. *Front Neurosci.* 2016; 10:199. <https://doi.org/10.3389/fnins.2016.00199> PMID: 27242405
43. Mudar RA, Husain FT. Neural Alterations in Acquired Age-Related Hearing Loss. *Front Psychol.* 2016; 7:828. <https://doi.org/10.3389/fpsyg.2016.00828> PMID: 27313556
44. Coughlan G, Laczó J, Hort J, Minihane AM, Hornberger M. Spatial navigation deficits—overlooked cognitive marker for preclinical Alzheimer disease? *Nat Rev Neurol.* 2018; 14:496–506. <https://doi.org/10.1038/s41582-018-0031-x> PMID: 29980763
45. Binkofski FC, Klann J, Caspers S. On the Neuroanatomy and Functional Role of the Inferior Parietal Lobule and Intraparietal Sulcus. Ed: Hickok G, Small SL. *Neurobiology of Language*, Chapter 4. Academic Press, 2016, pp: 35–47.
46. Lin FR. Hearing loss and cognition among older adults in the United States. *J Gerontol A Biol Sci Med Sci.* 2011; 66:1131–6. <https://doi.org/10.1093/gerona/glr115> PMID: 21768501
47. Humes LE, Busey TA, Craig J, Kewley-Port D. Are age-related changes in cognitive function driven by age-related changes in sensory processing? *Atten Percept Psychophys.* 2013; 75:508–24. <https://doi.org/10.3758/s13414-012-0406-9> PMID: 23254452
48. Murman DL. The Impact of Age on Cognition. *Semin Hear.* 2015; 36:111–21. <https://doi.org/10.1055/s-0035-1555115> PMID: 27516712
49. Husain FT, Medina RE, Davis CW, Szymko-Bennett Y, Simonyan K, Pajor NM, et al. Neuroanatomical changes due to hearing loss and chronic tinnitus: a combined VBM and DTI study. *Brain Res.* 2011; 1369:74–88. <https://doi.org/10.1016/j.brainres.2010.10.095> PMID: 21047501