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Retinal Vascular Density on Optical Coherence Tomography Angiography and Age-related Central and Peripheral Hearing Loss in a Southern Italian Older Population

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ABSTRACT

Background: Age-related hearing loss (ARHL) and retinal vessel changes have both been associated to neurodegeneration/dementia, suggesting a possible link between these two conditions in older age. We aimed to determine whether superficial and deep vascular density (SVD and DVD) of the capillary plexi of macular vasculature can be associated with peripheral ARHL and age-related central auditory central processing (CAPD).

Methods: We analyzed data on 886 older participants (65 years+, age range:65-92 years) in the cross-sectional population-based Salus in Apulia Study. Optical coherence tomography angiography (OCT-A) was used to measure SVD and DVD of the capillary plexi of the macula at the 3-mm circle area centered on the fovea (whole retina), the parafoveal quadrant, and foveal quadrant. Disabling peripheral ARHL was defined as >40 dB HL of pure tone average on the frequencies from 0.5, 1, 2, and 4 KHz in the better ear, and age-related CAPD as <50% at the Synthetic Sentence Identification with Ipsilateral Competitive Message test in at least one ear.

Results: DVD at the whole retina and at the parafoveal quadrant were inversely associated only with age-related CAPD [odds ratio (OR):0.93; 95% confidence interval (CI): 0.88-0.96 and OR:0.94; 95 CI:0.90-0.99, respectively]. No further associations with peripheral ARHL were evident.

Conclusions: Retinal vasculature is associated with central auditory processing pathology, possibly playing an important role in early detection and intervention. The association of retinal vascular density with age-related CAPD may bring us a further step forward in understanding the biological mechanisms underlying the links between neurodegeneration/dementia and ARHL.

Keywords: Biomarkers; Sensory; Imaging; Age-related Central Auditory Processing Disorder

INTRODUCTION

Age-related hearing loss (ARHL), or presbycusis, is the most frequent sensory impairment among people aged 65+ years. In 2014, the estimated prevalence was 18% of the older population of high-income countries [1], with an exponential increase with aging, and some degree of hearing loss in 100% of centenarians [2]. The two main ARHL features are peripheral ARHL and age-related central auditory processing disorders (CAPD). Peripheral ARHL is mostly related to a progressive decline of cochlear function and is assessed by pure tone audiometry, while age-related CAPD refers to central auditory pathway disorders, assessed only in peripheral not disabling hearing loss subjects, who have difficulties in understanding speech against background noise or competitive speech [3].

In the last two decades, an important role of both central and peripheral ARHL in the development of age-related cognitive disorders and dementia has been suggested in several population-based studies [4-6]. Recently, ARHL has been defined as the most important modifiable risk factor for dementia development [7], also linked to other major adverse health-related outcomes such as different frailty phenotypes [8], late-life depression/disability [9], and low compliance to primary care in older age [10]. Despite its importance in the current public health scenario, only a minor proportion of people with ARHL are diagnosed and treated. ARHL prevention could minimize possible negative downstream consequences associated with hearing loss.

One of the most important risk factors and a pathophysiological determinant for ARHL is thought to be vascular disease [4-6]. This has well-structured prevention strategies and is thought to drive ARHL through a diminished cochlear blood supply. In particular, microvascular disease may share different features with ARHL, at both peripheral and central level, but this potential association has not been extensively investigated in epidemiological studies. It is also important to detect ARHL risk factors since the mechanism underlying the relationships between hearing loss and late-life cognitive disorders and dementia remains unclear [4-6]. Given that retinal microvasculature, which can act as a brain microvasculature index, is also associated with Alzheimer's disease (AD) [11] and dementia [12], the association between ARHL and cognitive deterioration may be partly clarified by

the assumption that both are pathophysiological consequences of an underlying microvascular etiology [13]. In addition, these shared mechanisms could raise some hypotheses on the role of retinal microvasculature as a determinant for the interaction between ARHL and cognitive function in older age.

Some studies have recently examined the association between peripheral ARHL and retinal vessel features, by measuring major vessel caliber through fundus oculi photography [14-16]. These findings supported the hypothesis of a link between inner ear and retinal abnormalities with a common underlying vascular-related pathophysiological mechanism. Despite these innovative ideas, measuring major vessel caliber through fundus oculi photography does not allow a direct quantification of the total vascular density of the retina. The retinal microcirculation is known to be composed of multiple vascular layers; the superficial and deep capillary plexi are those most commonly differentiated when exploring disease characteristics [17]. In particular, vessel density of the deeper layers has been shown to be associated with neurodegenerative phenomena, probably due to the close contiguity with the optic nerve neural tissue [18, 19]. Optical coherence tomography angiography (OCT-A) is an innovative, non-invasive clinical instrument which provides depth-resolved visualization of the retinal and choroidal microvasculature by using phase or amplitude decorrelation to identify the motion contrast of blood flow [20, 21]. OCT-A has been successfully used in several studies to explore the power of retinal vessel features for predicting neurodegenerative diseases [22-24], but to the best of our knowledge, no study has yet investigated the relationship of OCT-A findings with peripheral and central ARHL. In the present study, we aimed to determine whether superficial and deep vascular density (SVD and DVD) of the capillary plexi of macular vasculature was associated with peripheral ARHL and age-related CAPD in a large population of older adults in Southern Italy.

METHODS

Study population and design

Data used in the present study are drawn from a population-based study of a representative population of residents in Castellana Grotte (Puglia Region, Southern Italy) aged 65 years or older at the time of baseline recruitment. The design of Salus in Apulia Study and data collection method has been described in detail elsewhere [25, 26]. Briefly, the sampling frame was the 19,675 residents listed in the health registry office on December 31, 2014, of which 4,021 were aged 65 years or older. From 31st December of 2015 to 1st December 2019, of 4,021 invited subjects only 2038 agreed to enrollment in the study (response rate: 50.6%). From the 6th January of 2017 to the 1st December of 2019, a subpopulation of 1021 new participants of the Salus in Apulia Study was invited to undergo ophthalmological assessment, only 889 of whom consented to the examination; their data are used in this cross-sectional analysis. All participants signed an informed consent form and the study was approved in 2014 and again in 2019 by the IRB of the National Institute of Gastroenterology "S. De Bellis", where all the examinations described in this study were performed.

Ophthalmological assessment

Each participant underwent manual refraction and best-corrected visual acuity (BCVA) determination of each eye. BCVA was recorded as Snellen visual acuity and converted to the logarithm of minimal angle of resolution (LogMar) units for statistical analysis. Patients underwent slit lamp biomicroscopy and intraocular pressure (IOP) measurement using a Goldmann-type applanation tonometer (Perkins MK2 Handheld Tonometer, Clement-Clarke Haag-Streit, Essex, UK). After pupil dilation using tropicamide 1% ophthalmic solution, funduscopy and OCT-A were performed using the AngioVue OCT-Angiography (Optovue RTVue XR 100 AVANTI, Optovue, Inc.). The OCT-A machine captures two consecutive B-scans (M-B frame) each containing 304 A-scans with an A-scan rate of 70,000 scans per second using a lightsource with a bandwidth of 45 nm centered on 840 nm. The split-spectrum amplitude-decorrelation angiography (SSADA) then extracts blood flow information

by quantifying the decorrelation value, which represents differences in signal intensity between consecutive B-scans of the same location on the retina. OCT-A also analyzes retinal structure, so multiple retinal layers can be identified and the vasculature in the corresponding layers can be segmented. OCT segmentation was performed using the AngioVue module with Optovue RTVue XR 100 AVANTI software (version 2014.2.0.13). The RTvue software provided the signal strength index (SSI), which represents the scan's reflectance signal strength, and a quality index (Q-score), which represents the overall quality of the image, taking into account factors like SSI and motion artifacts [27, 28]. In the present study, we only included images with a Q-score of 6 or above, a SSI above 70, and without motion or shadow artifacts. We obtained 3.0x3.0 mm OCT angiograms centered on the fovea, which were automatically segmented to define the superficial capillary plexus from 3 μm below the internal limiting membrane to 15 μm below the inner plexiform layer and the deep capillary plexus from 15 to 70 μm below the inner plexiform layer (Figure 1a). Both capillary plexi were analyzed using the vessel density (VD) parameter. VD was defined as the percentage of the sample area occupied by vessel lumens following binary reconstruction of the image. The VD at each capillary plexus (SVD and DVD) was calculated for the whole 3-mm circle area centered on the fovea (whole retina), for the area between the outer 3-mm circle and the inner 1-mm circle (parafoveal quadrant), and for the area inside the central 1-mm circle (foveal quadrant) (Figure 1b). SVD and DVD were expressed as percentages (%) and, in order to explore the minimal detectable changes among ARHL and retinal vasculature, only the eye with the lowest SVD and DVD was included in both the models and descriptive analysis. All OCT-A scans were reviewed for retinal disease by a board-certified group of 5 ophthalmologists (G.S., A.N., G.G., A.P. and P.P.). Exclusion criteria for all study participants included a recent history of vitreoretinal surgery, diabetic retinopathy, demyelinating disorders, glaucoma, macular edema or other vitreoretinal pathologic features that could interfere with the OCT-A analysis.

Peripheral age-related hearing loss assessment

Peripheral ARHL was assessed with pure tone audiometry, following the Hughson-Westlake method, in a soundproof booth with HDR 39 headphones (Sennheiser electronic GmbH & Co. KG, Wedemark, Germany) and the PIANO Audiometer (Inventis SRL, Padua, Italy), calibrated and executed according to international standards for audiometric testing. Pure tone average (PTA) was calculated at the middle-low frequencies of 0.5, 1, 2 and 4 KHz, just using the label PTA [29]. Peripheral ARHL was defined as a PTA threshold greater than 40 dB hearing level (HL) in the better ear according to the World Health Organization (WHO) definition of disabling peripheral ARHL [30].

Age-related central auditory processing disorder assessment

Age-related CAPD was assessed only in those participants with no disabling hearing loss, i.e., PTA < 40 dB HL in the better ear and a speech recognition threshold at 30 dB over the PTA greater than 70% in the better ear. Age-related CAPD was diagnosed using the Italian version of the Synthetic Sentence Identification with Ipsilateral Competitive Message (SSI-ICM) test [31, 32], that measures central auditory dichotic processing. The test consists of administering, for each ear, a primary signal of ten short sentences against a background competition signal (a male talker reading a passage). The rate of identification of sentences is expressed as a proportion (0-100%) at various message/competition ratios (0, +5, +10 dB Sound Pressure Level) [32]. In accordance with Gates and colleagues [31], age-related CAPD was considered present when the patient scored <50% in the better ear with a 0-dB message/competition ratio.

Other covariates

A blood sample was collected in the morning after overnight fasting to measure the levels of the following covariates, selected as confounding factors, related to retinal vessel disorders and different subtypes of ARHL: fasting blood glucose (FBG), total cholesterol, high-density lipoprotein (HDL) cholesterol, and low-density lipoprotein (LDL) cholesterol, using standard automated enzymatic

colorimetric methods (AutoMate 2550, Beckmann Coulter, Brea, Ca, US), under strict quality control. Plasma glucose was determined using the glucose oxidase method (Sclavus, Siena, Italy), while the concentrations of plasma lipids (triglycerides, total cholesterol, HDL cholesterol) were quantified with an automated colorimetric device (Hitachi; Boehringer Mannheim, Mannheim, Germany). LDL cholesterol was calculated using the Friedewald equation. Cognitive mental status was assessed with the Mini Mental State Examination (MMSE) which includes eleven questions and concentrates only on the global cognitive aspects of mental functions [34]. The clinical evaluation included extemporaneous ambulatory systolic blood pressure (SBP) and diastolic blood pressure (DBP), determined in a sitting position after at least a 10-min rest, and at least three different times, using the OMRON M6 automatic blood pressure monitor. Body mass index (BMI) was calculated as kg/m^2. Finally, work-related noise exposure was recorded as positive when a subject referred exposure to noise exceeding the Italian legal limits, during his\her career. Diabetes mellitus and hypertension were categorized based on the subject self-report confirmed by his\her general practitioner and in addition using the international standard diagnostic cut-offs: FBG higher than 125 g\dl and SBP\DBP greater than or equal to 130\80 mmHg, respectively.

Statistical analyses

Continuous variables were expressed as mean ± standard deviation (SD) and categorical variables as proportion (%). Statistical significance was set at a p-value less than or equal to 0.05, with 95% confidence intervals (CI). The whole sample was subdivided according to the ARHL phenotypes. Peripheral ARHL was compared to the not disabling hearing loss group and then age-related CAPD was compared to the not disabling hearing loss group after excluding peripheral ARHL subjects. Wilcoxon rank sum test for means, and Chi squared test were performed to assess differences between groups, for continuous and categorical variables, respectively. Logistic regression models were employed to assess associations, using SVD and DVD unit increases (expressed as percentage) at different sites as independent variable and peripheral ARHL and age-related CAPD as outcomes. We

built two different hierarchical models: a partially-adjusted model, corrected for age class (65-70, 71-75, 81-85, >85 years) and sex and a fully-adjusted model corrected for age class, sex, education, diabetes mellitus, hypertension, noise exposure, BMI, total cholesterol, smoking status, and MMSE. In the models used to estimate associations, peripheral ARHL and age-related CAPD subjects were excluded from the bases of logistic regression analyses. All analyses were performed using StataCorp 2019 Stata (Release 16 statistical software, College Station, TX, StataCorp LLC). Graphical output were created using Software RStudio v1.2.5042.

RESULTS

Descriptive Analysis

From 2016 to 2019, of the 2038 participants in the Salus in Apulia Study, 892 underwent ophthalmological and audiological examinations. This was due to the fact that ophthalmological evaluations were introduced later than the other research parameters. Furthermore, 8 were excluded due to severe cognitive impairment, 6 to middle ear acute\chronic diseases. Overall, 886 participants were eligible for the analysis presented in this study, 407 (46%) of them men. The mean age of the whole sample was 73.6±6.3 years, with a mean education level of 6.9±3.8 years, an average BMI of 28.3±4.3. The peripheral ARHL prevalence was 18% (N 160), higher in women (22.17%) than in men (20.01%). Age-related CAPD was present in 10.33% (N 75) of subjects without disabling peripheral ARHL (N 726) and significantly more prevalent (p< 00.1) in men (25.16%) than in women (16.21%). Table 1 shows the differences between subjects with and without disabling peripheral ARHL. Subjects with disabling peripheral ARHL were significantly older and less educated than individuals without disabling peripheral ARHL (p <0.01); moreover, the group with disabling peripheral ARHL showed a lower average MMSE score than the group without (p <0.01). There were no significant differences among metabolic profile biomarkers between these two groups (Table 1). Subjects with disabling peripheral ARHL also showed significantly poorer visual acuity in both eyes compared to individuals without (<0.05). Table 2 shows the differences between age-related CAPD subjects and individuals without age-related CAPD and disabling peripheral ARHL (i.e., normal hearing subjects). The age-related CAPD subjects were older, less educated and with lower MMSE scores than normal hearing subjects (p< 00.1). There were significant statistical differences as regards metabolic profile biomarkers between these groups: the age-related CAPD subjects were significantly more likely to have diabetes mellitus and on average lower values of total cholesterol, LDL cholesterol, and triglycerides than normal hearing subjects. Moreover, subjects with age-related CAPD had significantly worse visual acuity than normal hearing subjects in both eyes (p<0.01). DVD, measured at the whole retina and the parafoveal quadrant of the worse eye, was significantly lower in

age-related CAPD subjects ($p < 0.01$). On the contrary, the SVD and DVD of the foveal quadrant were generally higher in the age-related CAPD subjects compared to normal hearing subjects.

Association models

Logistic regression models of SVD and DVD are shown in Tables 3 and 4, with peripheral ARHL and age-related CAPD as dependent variables, respectively. Only DVD at the parafoveal quadrant [odds ratio (OR): 0.94; 95% CI: 0.90-0.99] and the whole retina (OR: 0.93; 95% CI: 0.88-0.96) was significantly associated with age-related CAPD in the fully-adjusted models. The dose-response effect of the DVD quartiles categorization for age-related CAPD revealed a linear decrease of ORs in the deep capillary plexus at the parafoveal and whole retina areas (Supplementary Figure 1). An increasing trend of ORs in the DVD at the foveal site was also observed (Supplementary Figure 1).

DISCUSSION

In the present population-based cross-sectional study, the loss of vascular density of the inner retinal layers, measured with OCT-A scans of the central retina including the foveal and parafoveal areas, was associated only with age-related CAPD, also after confounder adjustment. However, the effect size of the association is small (OR:0.93) and there is a risk of unmeasured confounding variables. To the best of our knowledge, this is the first report supporting the association between deep retinal microcirculation and age-related CAPD. On the contrary, peripheral ARHL was not associated with any quantitative parameter of the retinal vasculature.

In previous epidemiological studies, age-related CAPD was found to be strongly associated with late-life cognitive disorders and neurodegeneration at different stages, i.e. mild cognitive impairment (MCI), AD, and dementia in cross-sectional [4, 6] and longitudinal studies [4, 33,35]. However, despite this increasing body of epidemiological evidence suggesting a link between central auditory dysfunction and cognitive decline, the causal mechanisms underlying this association are still unknown [3,6]. A seminal neuropathological study supported the hypothesis that age-related CAPD may result from a degenerative pathway other than cognitive decline observed in AD, showing that brain amyloid-β, believed to be the initial event characterizing AD, was uncommon in central auditory pathways early in the clinical course of the disease [36]. By contrast, there was early formation of neurofibrillary tangles (NFTs), mainly consisting of hyperphosphorylated tau protein, suggesting that neurodegeneration in the auditory cortex may be an ongoing process throughout the AD course [36]. These seminal findings and the neurobiological plausibility of this relationship have recently been confirmed by suggestive neuropathological results showing an association of clinician-reported ARHL with the highest Braak stage, suggesting an increased NFT burden in cognitively unimpaired/hearing impaired subjects [37, 38]. In particular, the most severe Braak stage involves central auditory processing core areas, i.e., the superior temporal gyrus and the primary auditory cortex [37, 38]. These findings increase the attention on age-related CAPD as a cognitive-hearing impairment. Furthermore, the relationship between age-related CAPD and NFT-based

neurodegenerative phenomena could lay in a shared underlying microvascular etiology. Given that the diagnosis of age-related CAPD is much simpler than clinical diagnosis of dementia - that needs comprehensive neuropsychological and imaging features - central auditory dysfunction could be an important element to be monitored by clinicians, particularly geriatricians. However, a limitation of monitoring age-related CAPD is that its diagnosis is based only on subjective indicators of speech perception, and therefore may require accessory objective biomarkers able to confirm its presence. Given the neurovascular implications of central auditory dysfunction, one of the methods could be the use of retinal vascular biomarkers, which have been found cross-sectionally associated with age-related CAPD in the present study.

Furthermore, retinal vascular biomarkers have been found associated also with cognitive impairment in older age and dementia. In fact, although OCT-A is a relatively young procedure, several reports have explored its fundamental role in the *in vivo* study of retinal vascular changes and their connection with AD and MCI [22-24, 39-44]. In particular, three OCT-A studies have reported decreased retinal vascular density in the whole retina, foveal and parafoveal quadrants of AD patients [22], the parafoveal quadrant only in MCI subjects and early AD patients [24], and whole retina regions of AD patients [43] compared with cognitively healthy and/or MCI subjects. Furthermore, Jiang and colleagues found that the deep capillary plexus had the strongest association, also in the early stages of AD, i.e., MCI [39]. Therefore, we can speculate that since age-related CAPD was also strongly associated with prodromal forms of dementia and dementia itself [3, 4], its association with the deep vessel density of the retina may indicate that the deep capillary plexus could be a good indicator for neurodegenerative phenomena. Of course, longitudinal findings will be needed to confirm this hypothesis currently tainted from reverse causality bias.

This speculative hypothesis could also be supported by anatomical reasons. Embryologically, there is a close anatomical correlation between the macrovascular and the microvascular blood supply to the brain and the retina, and both vascular networks share similar vascular regulatory processes [45]. Unlike the brain vessels, the retina endpoint arterioles are unable to create anastomoses. This

constitutional factor decreases the autoregulation of the flow, making it more susceptible to ischemic processes, and decreasing perfusion and blood-retinal barrier performance [46]. Moreover, it causes a slower blood flow in the deeper retina layer, with a clear disadvantage from the hemodynamic point of view, both owing to the greater predisposition to ischemic insults, and to a greater difficulty in achieving substances clearance, which can cause an accumulation of molecules, especially of inflammatory origin [20]. These unfavorable anatomical features should make retinal vascular alterations, particularly in the deepest layers, good grounds for exploring early vascular-related neurodegeneration phenomena, such as age-related CAPD.

An interesting secondary finding of the present study was that the vessel density at the foveal site, which is normally lower than at other retinal sites in physiological conditions, being defined as the foveal avascular zone (FAZ), showed a greater mean value in subjects with age-related CAPD compared to individuals without disabling peripheral ARHL. This positive association was also confirmed by the dose-response effect, demonstrating that higher vessel density at the foveal area, especially the deep layer, increased the probability of age-related CAPD. A number of high-quality studies showed that FAZs are more likely to be larger in both predementia and AD subjects [24], also when AD is confirmed by neuroimaging and cerebrospinal fluid biomarkers [47]. This finding seems to be in contrast with the higher DVD in the foveal quadrant of the age-related CAPD group compared to the subjects without disabling peripheral ARHL and without age-related CAPD in our population, although we had not measured the true size (mm^2) of the FAZ but only the proportion of vascular densities. Higher values of foveal DVD in the age-related CAPD group could depend mostly on the age effect; in fact, when the models were adjusted for age the association was attenuated. Some studies have suggested that the foveal circumference at OCT-A imaging may be more sensitive to artifacts because it is farther from the transducer [48]. Some optical parameters, such as the axial length of the eye, and particularly myopic conditions, could induce noise in the image, making the vascular network appear artificially denser because of the larger area being scanned under less magnification [48, 49]. The increase in axial length with age [50] could be the reason explaining why

in our models the association disappeared when adjusted for age. Thus, the axial length should be implemented as a confounding factor in models involving OCT-A imaging.

Contrary to our expectations, we did not find any type of association between quantitative parameters of retinal vasculature and peripheral ARHL. Although this could seem controversial, the studies supporting this relationship did not present a comparable retinal vessel density measure. In fact, both the Blue Mountains Study [15] and the ARIC-NCS [16] showed low estimates of an association between fundus oculi-diagnosed retinopathy and peripheral ARHL, but without directly quantifying the density of the retinal vessels.

The strengths of the present study included a rigorous and standardized diagnosis of peripheral ARHL and age-related CAPD and high technology OCT-A scanning combined with a complete ophthalmological clinical examination, in order to avoid optical interferences due to ocular media abnormalities. Moreover, this was a population-based study, so increasing the generalizability and external validity of the findings, further supported by the consistency of our prevalence estimates of peripheral ARHL and age-related CAPD with other similar studies. Furthermore, we also performed an accurate adjustment for known confounders to reduce overestimation bias. Among limitations, we must acknowledge that it was impossible to define the direction of the association due to the cross-sectional nature of the findings, yielding a high risk of reverse causality bias. Moreover, despite adjustment for global cognition, the measures of peripheral ARHL, both with pure tone and speech audiometry, could be affected by impaired cognition and the related inability to execute the commands needed for responses in those examinations. A limitation of the present study could be considered the lack of substantial OCT-A measures such as retinal nerve fiber layer (RNFL) thickness and ganglion cell-inner plexiform layer (GC-IPL) thickness. Those measures could have a fundamental role in distinguishing effects of neurodegeneration from microvascular changes. Another important limitation is the absence of axial length of the eye measurement. This factor could have an important effect on the quality of both OCT-A images and analysis interpretation and should be used as a major confounder in the association models. Finally, we had no measures of the true size of the

retinal microvasculature (i.e., FAZ , vessel length, and calibers), to compare with other studies that found these measures to be associated with peripheral ARHL and dementia [14,22,40].

In the present population-based cross-sectional study, we identified a consistent association between age-related CAPD and deep retinal vessel density. Given that ARHL, both at peripheral and central level, and retinal vessel changes have both been associated to neurodegeneration/dementia, exploration of the retina by OCT-A imaging may help to better understand the complex neurobiological relationship between age-related CAPD and dementia. Early deep retinal vessel changes in older subjects without hearing disorders may be predictive of the subsequent development of age-related CAPD. However, to confirm the present suggestive findings and the possible preclinical detection of central auditory pathway disorders through OCT-A imaging, larger, longitudinal high-quality studies are needed, adopting the same methodology.

Author Contributions

Conceptualization: R.S. and F.P.; Methodology, R.S, F.P., and N.Q.; Formal Analysis, V.G., R.D.; Investigation: R.S, L.L., I.B., R.Z., I.B.,G.S., A.N., G.G., F.P.; Data Curation, F.C., I.B, G.L.; Writing—Original Draft Preparation, R.S. and A.N.,G.G. ; Writing—Review & Editing, R.S., F.P., M.L., L.L..; Supervision: G.S.,F.B.,G.A. and N.Q.; Project Administration, R.S. and G.G.; Funding Acquisition, G.G. All authors have read and agreed to the published version of the manuscript.

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Conflict of Interest

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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LEGENDS TO THE FIGURES

Figure 1. Panel A. Retinal segmentation at optical coherence tomography (OCT) angiography. The colored lines in horizontal and vertical OCT B-scans show segmentation lines that define the different depth in the retinal tissue of the superficial capillary plexus (1A) and deep capillary plexus (2A). **Panel B. Graphic representation of retinal area evaluated at OCT angiography.** The software automatically selected the 3x3-mm image with 2 rings of 3.0- and 1.0-mm diameter centered on the fovea. The vessel density was calculated for the whole 3-mm circle area centered on the fovea (whole retina) (1B), for the area between the outer 3-mm circle and the inner 1-mm circle (parafoveal quadrant) (2B), and for the area inside the central 1-mm circle (foveal quadrant) (3B).

Supplementary Data

Supplementary Figure 1 Dose-response graphs showing the fully adjusted odds ratio for age-related central auditory processing disorder estimated from logistic regressions for incremental increases of both deep vessel density and superficial vessel density, stratified in quartiles (Q1 to Q4).

Table 1 Sociodemographic and clinical variables in subjects with and without disabling peripheral age-related hearing loss (ARHL). The Salus in Apulia Study (n=886).

	Without disabling peripheral ARHL (726)	With disabling peripheral ARHL (160)	p value
General Features			
Men	313 (43.11)	66 (41.25)	0.74 χ^2
Women	413 (56.88)	94 (58.75)	0.74 χ^2
Age (years)	74.37 ± 5.89	78.28 ± 6.14	<0.01
Age ranges (min-max, years)	65-92	65-92	-
Education (years)	7.08 ± 3.9	5.49 ± 3.53	<0.01
Smoking status (yes)	31 (4.42)	5 (3.12)	0.55 χ^2
MMSE Raw Score	26.44 ± 3.99	24.03 ± 5.35	<0.01
Noise Exposure (yes)	44 (6.06)	62 (38.12)	<0.01 χ^2
Hearing Measures			
PTA worse ear (dB HL)	26.14 ± 9.68	52.11 ± 15.6	<0.01
PTA better ear (dB HL)	25.64 ± 10.69	51.95 ± 16.6	<0.01
SSI-ICM worst ear	74.19 ± 30.02	-	-
Metabolic Profile			
SBP (mmHg)	134.61 ± 14.50	134.69 ± 16.00	0.82
DBP (mmHg)	77.87 ± 7.52	76.39 ± 8.77	0.09
BMI (mmHg)	27.82 ± 4.54	28.32 ± 4.9	0.44
FBG (mg/dl)	104.00 ± 26.38	105.64 ± 27.41	0.35
Total cholesterol (mg/dl)	184.04 ± 38.16	184.05 ± 31.81	0.99
HDL cholesterol (mg/dl)	49.59 ± 13.34	49.29 ± 13.37	0.68
LDL cholesterol (mg/dl)	114.20 ± 32.16	114.47 ± 29.78	0.88
Triglycerides (mg/dl)	99.70 ± 49.27	96.22 ± 50.17	0.26
Diabetes mellitus (yes)	75 (10.33)	18 (11.25)	0.11 χ^2
Hypertension (yes)	91 (12.53)	20 (12.5)	0.99 χ^2
Eye features			
BCVA right eye	0.14 ± 0.32	0.20 ± 0.41	0.01
BCVA left eye	0.15 ± 0.36	0.19 ± 0.33	0.04
SVD Whole Retina (%)	49.68 ± 4.57	48.87 ± 4.22	0.09
SVD Parafoveal Quadrant (%)	51.73 ± 4.94	50.90 ± 4.85	0.14
SVD Foveal Quadrant (%)	24.12± 3.96	25.33± 3.12	0.09
DVD Whole Retina	53.74 ± 5.01	53.06 ± 5.58	0.23
DVD Parafoveal Quadrant	56.65 ± 5.34	55.91 ± 5.89	0.17
DVD Foveal Quadrant	21.32±4.12	22.36±5.01	0.10

Data are shown as mean ± SD for continuous variables and as percentage (%) for proportions

Wilcoxon rank sum test was used for continuous and $\chi 2$ for categorical variables

MMSE: Mini-Mental State Examination; PTA: pure tone average; SSI-ICM: Synthetic Sentence Identification with Ipsilateral Competitive Message; SBP: systolic blood pressure; DBP diastolic blood pressure; BMI: body mass index; FBG: fasting blood glucose; HDL: high-density lipoprotein; LDL: low-density lipoprotein; BCVA: best-corrected visual acuity; SVD: superficial vessel density; DVD: deep vessel density

Table 2 Sociodemographic and clinical variables in subjects with age-related central auditory processing disorders (CAPD) and without age-related CAPD and disabling peripheral age-related hearing loss (normal hearing individuals). The Salus in Apulia Study (n=726).

Variables	Normal hearing (651)	Age-related CAPD (75)	p value
General Features			
Men	269 (41.22)	39 (52.0)	0.08 χ^2
Women	382 (58.78)	36 (48.0)	0.08 χ^2
Age (years)	73.69 ± 5.65	77.78 ± 5.94	<0.01
Age Ranges (min to max)	65 to 90	67 to 92	-
Education (years)	7.35 ± 3.87	5.73 ± 3.80	<0.01
Smoking status (yes)	28 (4.44)	3 (3.09)	0.84 χ^2
MMSE	27.04 ± 3.26	23.40 ± 5.63	<0.01
Noise exposure (yes)	36 (5.52)	8 (10.66)	0.03 χ^2
Hearing Measures			
PTA worse ear (dB HL)	25.78 ± 6.48	35.42 ± 20.69	<0.01
PTA better ear (dB HL)	24.66 ± 7.28	35.13 ± 21.35	<0.01
SSI-ICM worst ear (%)	85.10 ± 15.78	19.44 ± 27.86	<0.01
Metabolic Profile			
SBP (mmHg)	135.05 ± 14.21	132.04 ± 15.81	0.16
DBP (mmHg)	78.11 ± 7.43	76.66 ± 7.94	0.18
BMI (mmHg)	27.62 ± 4.33	28.82 ± 5.41	0.10
FBG (mg/dl)	101.89 ± 20.70	114.6 ± 43.89	0.14
Total cholesterol (mg/dl)	185.53 ± 37.71	176.54 ± 39.75	0.05
HDL cholesterol (mg/dl)	49.71 ± 13.40	49.0 ± 13.09	0.75
LDL cholesterol (mg/dl)	115.34 ± 32.06	108.48 ± 32.26	0.07
Triglycerides (mg/dl)	100.80 ± 48.95	94.24 ± 50.85	0.06
Diabetes mellitus (yes)	52 (7.91)	16 (21.33)	<0.01 χ^2
Hypertension (yes)	85 (13.05)	7 (9.33)	0.54 χ^2
Eye Features			
BCVA right eye	0.12 ± 0.25	0.25 ± 0.53	<0.01
BCVA left eye	0.12 ± 0.31	0.28 ± 0.52	<0.01
SVD Whole Retina	49.83 ± 4.60	48.76 ± 4.29	0.05
SVD Parafoveal Quadrant	51.91 ± 4.98	50.66 ± 4.55	0.02
SVD Foveal Quadrant	23.48±3.62	24.09±4.12	0.06
DVD Whole Retina	54.06 ± 4.67	51.81 ± 6.45	<0.01
DVD Parafoveal Quadrant	56.97 ± 6.88	54.72 ± 6.88	0.01
DVD Foveal Quadrant	21.53±4.22	23.49±3.01	0.02

Data are shown as mean ± SD for continuous variables and as percentage (%) for proportions

Wilcoxon rank sum test was used for continuous and $\chi 2$ for categorical variables

MMSE: Mini-Mental State Examination; PTA: pure tone average; SSI-ICM: Synthetic Sentence Identification with Ipsilateral Competitive Message; SBP: systolic blood pressure; DBP diastolic blood pressure; BMI: body mass index; FBG: fasting blood glucose; HDL: high-density lipoprotein; LDL: low-density lipoprotein; BCVA: best-corrected visual acuity; SVD: superficial vessel density; DVD: deep vessel density

Table 3 Logistic regression models with peripheral age-related hearing loss as dependent variable and regressors. The Salus in Apulia Study (n=886).

	Partially-adjusted model*		**Fully-adjusted model****	
	OR	**CI 95%**	**OR**	**CI 95%**
Superficial vessel density (1%)				
Parafoveal quadrant	0.96	0.92-1.01	0.98	0.93-1.03
Foveal quadrant	1.00	0.97-1.04	1.00	0.97-1.03
Whole retina	0.97	0.91-1.01	0.98	0.92-1.03
Deep vessel density (1%)				
Parafoveal quadrant	0.96	0.92-1.01	1	0.94-1.03
Foveal quadrant	1.01	0.98-1.04	1.01	0.98-1.05
Whole retina	0.97	0.94-1.01	1	0.95-1.05

OR: odds ratio; CI; confidence interval

* Adjusted for age class (65-70, 71-75, 76-80, 81-85, >85 years) and sex

** Adjusted for age class, sex, education, hypertension, diabetes mellitus, noise exposure, body mass index, total cholesterol, smoking status, and Mini Mental State Examination

Table 4 Logistic regression models with age-related central auditory processing disorder as dependent variable and regressors. The Salus in Apulia Study (n=886).

	Partially-adjusted model*		**Fully-adjusted model****	
	OR	**CI 95%**	**OR**	**CI 95%**
Superficial vessel density (1%)				
Parafoveal quadrant	0.95	0.90-1.00	0.97	0.91-1.03
Foveal quadrant	1.01	0.97-1.04	1.01	0.97-1.05
Whole retina	0.95	0.89-1.01	0.97	0.91-1.04
Deep vessel density (1%)				
Parafoveal quadrant	0.92	0.91-0.95	0.94	0.90-0.99
Foveal quadrant	1.00	0.97-1.06	1.00	0.97-1.04
Whole retina	0.91	0.88-0.96	0.93	0.88-0.96

OR: odds ratio; CI; confidence interval

* Adjusted for age class (65-70, 71-75, 76-80, 81-85, >85 years) and sex

** Adjusted for age class, sex, education, hypertension, diabetes mellitus, body mass index, noise exposure, total cholesterol, smoking status, and Mini Mental State Examination

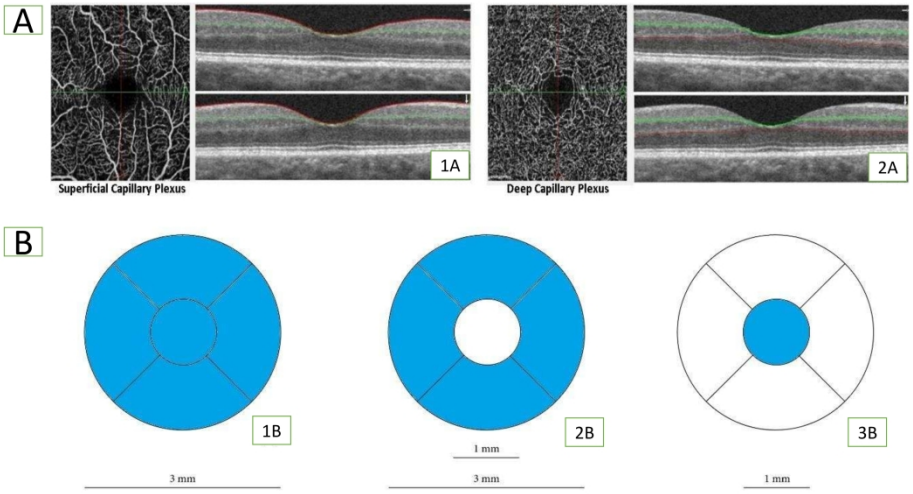
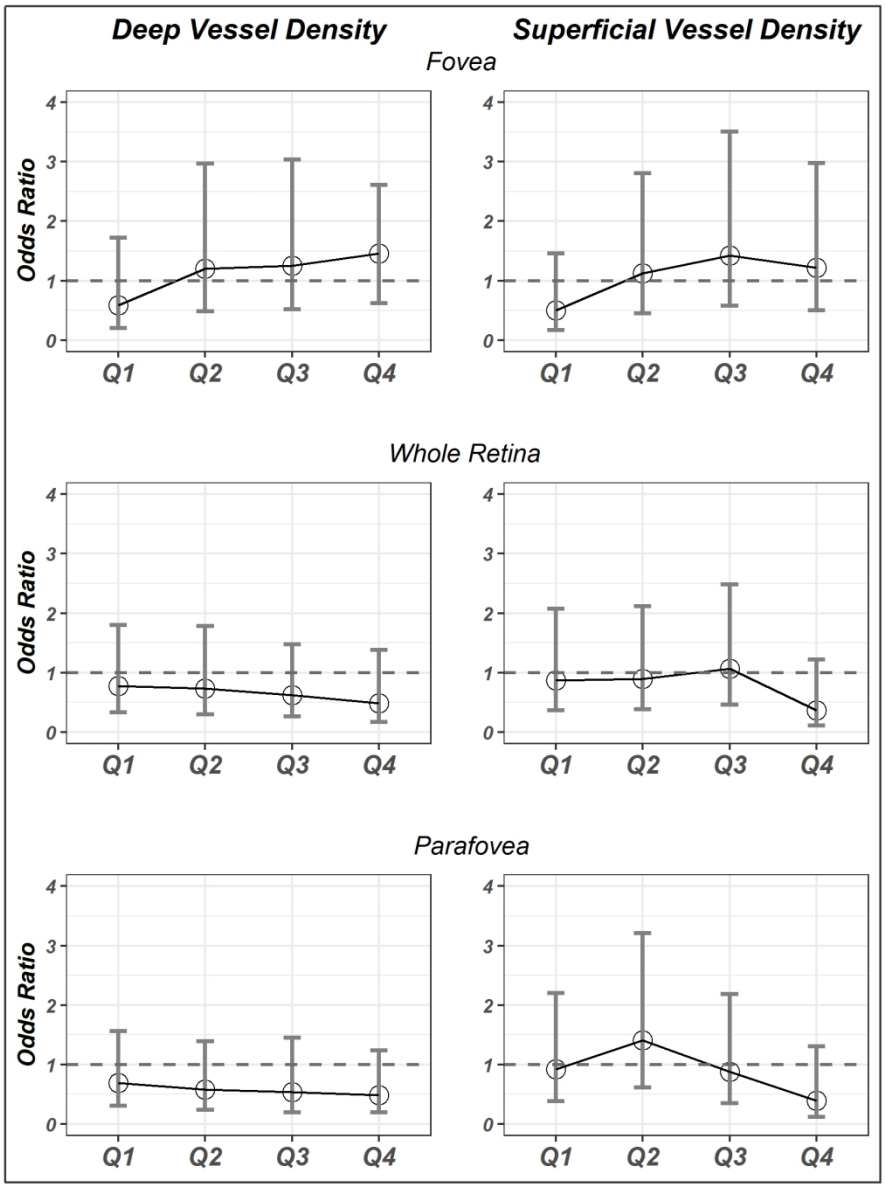


Figure 1

338x190mm (300 x 300 DPI)



149x199mm (300 x 300 DPI)