Neurobiology of Disease 178 (2023) 106024

Contents lists available at ScienceDirect

Neurobiology of Disease

journal homepage: www.elsevier.com/locate/ynbdi

Noise-induced auditory damage affects hippocampus causing memory deficits in a model of early age-related hearing loss

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ARTICLE INFO

Keywords:
Neurodegeneration
Auditory cortex
Cognitive decline
Presbycusis
Inflammation
Oxidative stress

ABSTRACT

Several studies identified noise-induced hearing loss (NIHL) as a risk factor for sensory aging and cognitive decline processes, including neurodegenerative diseases, such as dementia and age-related hearing loss (ARHL). Although the association between noise- and age-induced hearing impairment has been widely documented by epidemiological and experimental studies, the molecular mechanisms underlying this association are not fully understood as it is not known how these risk factors (aging and noise) can interact, affecting memory processes. We recently found that early noise exposure in an established animal model of ARHL (C57BL/6 mice) accelerates the onset of age-related cochlear dysfunctions. Here, we extended our previous data by investigating what happens in central brain structures (auditory cortex and hippocampus), to assess the relationship between hearing and memory impairment and the possible combined effect of noise and sensory aging on the cognitive domain. To this aim, we exposed juvenile C57BL/6 mice of 2 months of age to repeated noise sessions (60 min/day, pure tone of 100 dB SPL, 10 kHz, 10 consecutive days) and we monitored auditory threshold by measuring auditory brainstem responses (ABR), spatial working memory, by using the Y-maze test, and basal synaptic transmission by using ex vivo electrophysiological recordings, at different time points (1, 4 and 7 months after the onset of noise exposure, corresponding to 3, 6 and 9 months of age). We found that hearing loss, along with accelerated presbycusis onset, can induce persistent synaptic alterations in the auditory cortex. This was associated with decreased memory performance and oxidative-inflammatory injury in the hippocampus, the extra-auditory structure involved in memory processes. Collectively, our data confirm the critical relationship between auditory and memory circuits, suggesting that the combined detrimental effect of noise and sensory aging on hearing function can be considered a high-risk factor for both sensory and cognitive degenerative processes, given that early noise exposure accelerates presbycusis phenotype and induces hippocampal-dependent memory dysfunctions.

1. Introduction

Age-related hearing loss (ARHL or presbycusis) refers to the age-dependent decline in hearing sensitivity, that can lead to increased auditory threshold in aged subjects. In the United States, >50% of people over 70 years show ARHL (Goman and Lin, 2016), and the prevalence of ARHL is expected to increase substantially in the worldwide population, due to population aging, increase in environmental risk factors (i.e., noise pollution), and wrong lifestyles (i.e., smoking and drinking alcohol, exposure to loud music, sedentary lifestyle) (Chang et al., 2019; Man et al., 2021). Presbycusis can be considered a multifactorial disease, and different types of the disorder has been identified accordingly to the Schuknecht description (sensory, neural, strial and mechanical), based on both the audiometric profile and on the localization of cochlear damage (Schuknecht, 1964). The audiometric pattern of sensory presbycusis is usually characterized by a progressive, bilateral and symmetrical hearing loss, involving first of all the high-frequency region of the hearing spectrum and progressing later in the low-

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https://doi.org/10.1016/j.nbd.2023.106024
Received 5 August 2022; Received in revised form 26 January 2023; Accepted 27 January 2023
Available online 29 January 2023

frequency range (Fetoni et al., 2011; Gates and Mills, 2005; Wang and Puel, 2020).

Of note, several epidemiological studies have underlined a link between auditory and cognitive decline in the elderly, showing a high prevalence of cognitive dysfunctions in presbycusis patients (Lin and Albert, 2014; Fortunato et al., 2016; Thomson et al., 2017). Recently, hearing impairment has been linked to accelerated cognitive decline (Lin et al., 2011; Loughrey et al., 2018; Bernabei et al., 2014; Amieva et al., 2015), incident cognitive impairment (Deal et al., 2017), and neurodegenerative pathologies, like Alzheimer's disease (AD) (Gallacher et al., 2012; Panza et al., 2015; Taljaard et al., 2016). Clinical studies reported that individuals with mild to moderate presbycusis show a decrease in memory and executive function ability (Lin et al., 2011; Anzivino et al., 2019) and that hearing loss is significantly related to global cognitive decline, social isolation, and depression (Lister et al., 2016; Panza et al., 2015). Moreover, we recently demonstrated that early noise-induced hearing loss (NIHL) can accelerate cognitive decline in a mouse model of AD (3×Tg-AD mice), accelerating memory dysfunctions with respect to the expected time course of the pathology and causing long-lasting functional, morphological, and molecular alterations not only in the auditory system but also in the hippocampus (HP), the brain structure most involved in memory functions (Scoville and Milner, 1957; Eichenbaum, 2001; Paciello et al., 2021). In line with this evidence, hearing loss has been considered by the Lancet consortium the major potentially modifiable risk factor for dementia (Livingston et al., 2020).

Among environmental risk factors leading to hearing impairment in midlife and increased susceptibility to ARHL, exposure to high-intensity noise is the most common. Indeed, NIHL accounts for about 16% of sensorineural hearing loss in the adult population worldwide (Gates and Mills, 2005; Nelson et al., 2005; Masterson et al., 2018). Increasing experimental evidence from animal models of presbycusis, including ours, highlights that exposure to loud noise may exacerbate aging mechanisms, making cochlear structures more susceptible to aging processes (Tanaka et al., 2009; Bielefeld et al., 2010; Fetoni et al., 2011; Wang and Puel, 2020; Fetoni et al., 2022). Recently, we evaluated the effect of repeated noise exposures early in life on age-related cochlear dysfunctions in an animal model of ARHL, the C57BL/6 mouse model. These animals show early onset of ARHL, with increased auditory thresholds spreading from high to low-frequency regions with advancing age (Willott et al., 1995; Parham, 1997; Fetoni et al., 2011; Möhrle et al., 2016). We found that noise exposure can accelerate the presbycusis phenotype, exacerbating cochlear damage induced by oxidative stress, inflammation, and vascular dysfunction (Fetoni et al., 2022).

Collectively, these findings suggest that aging and noise exposure can be considered common risk factors for both presbycusis and cognitive decline. Thus, it is of great importance to study the relationship between age- and noise-induced hearing impairment in determining dementia. Indeed, although the association among ARHL, NIHL, and cognitive impairment has been clinically widely documented (Lin and Albert, 2014; Wayne and Johnsrude, 2015; Panza et al., 2019; Johnson et al., 2021), the molecular mechanisms underlying this association are not fully understood, and it is not known how these risk factors (sensory aging and noise) can interact, affecting brain functions.

Here, we extended our previous data, by evaluating the impact of early noise exposure on the auditory cortex (ACx), and HP in the animal model of ARHL, the C57BL/6 mouse, to evaluate if and how ARHL and NIHL can interact as risk factors determining memory impairment. We found alterations in basal synaptic transmission in ACx, along with decreased working memory performance and increased hippocampal susceptibility to oxidative stress and inflammation, in presbycusis animals early exposed to noise.

To our knowledge, for the first time, we demonstrated that the combined interaction between noise- and age-induced hearing impairment can affect not only the auditory system but also the HP, causing memory dysfunctions.

2. Materials and methods

2.1. Animal model

As an animal model of presbycusis, we used male C57BL/6 mice (Charles River Laboratories, Lecco, Italy). These animals show a progressive age-related increase of auditory thresholds, early involving high frequencies and progressing toward lower frequencies with age (Willott et al., 1995; Parham, 1997; Fetoni et al., 2011; Möhrle et al., 2016). Experiments were performed on 75 animals, randomized as follows: control animals (Ctrl group; $n = 40$) of 3, 6, and 9 months of age (M); animals exposed to noise (pure tone of 100 dB, 10 kHz) for 60 min, 10 consecutive days at 2 M (Noise group, $n = 35$) and evaluated 1, 4 and 7 months after the onset of noise exposure (corresponding to 3, 6 and 9 M). The time schedule of protocols is shown in Fig. 1. Moreover, to evaluate the effect of noise exposure in an animal model that did not show presbycusis, $n = 23$ B6129SF2/J wild-type (WT) mice were used. For the whole experimental period, the animals were housed from 3 to 5 per cage at controlled temperature (22–23 °C) and constant humidity (60 ± 5%), under a 12-h light/dark cycle, with food (Mucedola 4RF21, Italy) and water *ad libitum*. All procedures were made to minimize animal suffering and to reduce their number, in accordance with the European Community Council Directive of 24 November 1986 (86/609/EEC). All procedures were performed in compliance with the Laboratory of Animal Care and Use Committee of the Catholic University, School of Medicine of Rome, and were approved by the Italian Department of Health (*Ministero della Salute*, Prot. No. 289/2018-PR).

2.2. Auditory brainstem responses (ABR)

To monitor auditory thresholds in control and noise-exposed animals, we measured ABRs at different time points (Fig. 1). Animals were mildly anesthetized (ketamine 35 mg/kg and medetomidine-domitor 0.25 mg/kg) and placed in the anechoic room. As described previously (Paciello et al., 2021; Fetoni et al., 2022) three stainless steel recording electrodes were subcutaneously inserted posterior to the tested pinna (active), vertex (reference), and contralateral pinna (ground). Tone bursts of pure tones from 6 to 32 kHz (1 ms rise/fall time, 10 ms total duration, 20/s repetition rate) were used. A PC-controlled TDT System 3 (Tucker Davis Technologies, Alachua, FL, United States) data acquisition system with real-time digital signal processing was used for ABRs recording and auditory stimulus generation. The responses were filtered (0.3–3 kHz), digitized, and averaged. The threshold value was defined as the lowest stimulus level that yielded a repeatable ABR wave I onset. Results are expressed in term of threshold shift (difference between noise and age-matched control threshold values).

2.3. Noise exposure

The acoustic trauma consisted of a 100 dB sound pressure level (SPL) exposure for 10 consecutive days for 60 min each day. The stimulus used was a continuous pure tone (10 kHz) generated by a waveform generator (LAG—120B, Leader, NY, USA) and amplified by an audio amplifier (A-307R, Pioneer, CA, USA), as previously described (Paciello et al., 2021; Fetoni et al., 2022). The sound was presented in an anechoic room in an open field by a dome tweeter (TW340X0; Audax) positioned at the center of the cage. The sound level was measured using a calibrated 1/4-in. microphone (model 7017; ACO Pacific) and using a sound level meter (LD-831 Larson Davis Technologies).

2.4. Behavioral analyses

All behavioral analyses were performed from 9:00 am to 4:00 pm using automated tracking software (ANY-maze™, Stoelting Co., IL).

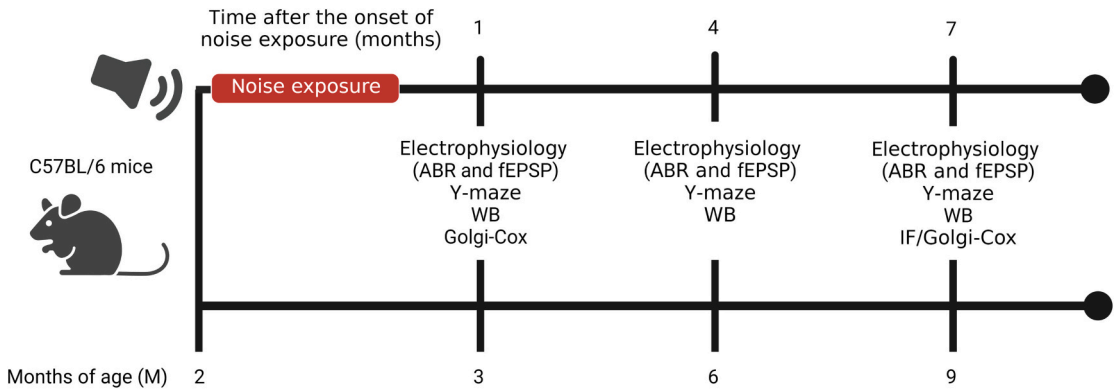

Fig. 1. Schematic representation of the experimental design and schedule of the protocols. C57BL/6 animals of 2 months of age at the beginning of the study were used. A cohort of animals underwent noise exposure sessions (pure tone, 10 kHz, 100 dB, 60 min/day for 10 consecutive days). After 1, 4, and 7 months from the onset of trauma sessions, when the mice aged 3, 6, and 9 months of age, electrophysiological (field excitatory post-synaptic potentials -fEPSP- and auditory brainstem response -ABR- measurements), behavioral (Y-maze test), Western blot (WB), immunofluorescence (IF) and Golgi-Cox evaluations were performed in auditory cortex and/or hippocampus. Created with BioRender.com.

Experimenters were blind to treatments. Animals underwent a daily 3-min handling session in the week before the tests to reduce stress arising from manipulation.

2.4.1. Y-maze and open field

The Y-maze was carried out as follows: animals were allowed to explore a Y-shaped arena for 8 min and the number and sequence of entrance into the three arms were recorded. A correct alternation sequence required the animals to enter the 3 different arms consecutively. Spontaneous alternations, a measure of spatial working memory, were calculated by dividing the number of correct alternations by the number of total entrances minus two and were expressed as a percentage. To avoid the confounding effect of deficits in locomotor activity, or stress/anxiety-related behavior, animals were further evaluated using the Open Field test. Briefly, the day after the Y-maze, animals were allowed to explore a square plexiglass arena (45 × 45 cm) for 10 min. Total distance traveled was recorded as a measure of locomotor activity, whereas time spent in the center of the arena was measured as an indirect stress/anxiety-related behavior, considering that the time spent in thigmotaxis is associated with anxiety. Both the Y-maze and Open Field apparatus were cleaned with a 70% ethanol solution between each animal, to avoid possible alterations due to odor cues.

2.5. Electrophysiology

Field recordings were performed on coronal slices, 400 μm-thick, collected from 2.18 mm to 3.4 mm posterior to bregma (Paxinos and Franklin, 2001) and containing the primary auditory field (Au1), which has been shown to functionally overlap with the primary auditory cortex (A1), ventral auditory field (VAF), anterior auditory field (AAF) and secondary auditory cortex (A2) (Narayanan et al., 2022). Slices were taken randomly from the tonotopic gradient representation. Briefly, mice were anesthetized by isoflurane inhalation (Esteve) and decapitated. The brain was rapidly removed and placed in an ice-cold cutting solution (in mM: 124 NaCl, 3.2 KCl, 1 NaH_2PO_4, 26 $NaHCO_3$, 2 $MgCl_2$, 1 $CaCl_2$, 10 glucose, 2 sodium pyruvate, and 0.6 ascorbic acid, bubbled with 95% O2–5% CO_2; pH 7.4). As previously described (Paciello et al., 2018; Paciello et al., 2021), slices were cut with a vibratome (VT1200S) and incubated in artificial cerebrospinal fluid (aCSF; in mM: 124 NaCl; 3.2 KCl; 1 NaH_2PO_4, 26 $NaHCO_3$, 1 $MgCl_2$, 2 $CaCl_2$, 10 glucose; 95% O_2–5% CO_2; pH 7.4) at 32 °C for 60 min and then at room temperature (RT) until use. Slices were transferred to a submerged recording chamber and continuously perfused with aCSF (flow rate: 1.5 ml/min). The bath temperature was maintained at 30–32 °C with an in-line solution heater and temperature controller (TC-344B, Warner Instruments). Identification of slice subfields and electrode positioning were performed with 4× and 40× water immersion objectives on an upright microscope (BX5IWI, Olympus) and video observation (C3077–71 CCD camera, Hamamatsu Photonics).

All recordings were made using MultiClamp 700B amplifier (Molecular Devices). Data acquisition and stimulation protocols were performed with the Digidata 1440A Series interface and pClamp 10 software (Molecular Devices). Data were filtered at 1 kHz, digitized at 10 kHz, and analyzed both online and offline. Field recordings were made using glass pipettes filled with aCSF (tip resistance 2–5 MΩ). Field excitatory post-synaptic potentials (fEPSPs) were evoked in pyramidal neurons of ACx layer II/III by stimulation of local connections using a concentric bipolar tungsten electrode (FHC Inc., Bowdoin, ME, USA) connected to a stimulator. Input/output (I/O) curves were obtained by afferent fiber stimulation at intensities ranging from 20 to 300 μA (in increments of 30 or 50 μA; stimulus rate of 1 pulse every 20 s).

2.6. Spine density analyses

To evaluate spine density, mouse brains were explanted and used for Golgi-Cox staining as previously described (Barbati et al., 2020; Paciello et al., 2021; Longo et al., 2022). Briefly, brains were immersed in a solution of 5% $Cr_2K_2O_7$, 5% Cl_2Hg, and 5% CrK_2O_4 (Sigma) in distilled water for 15 d, transferred to a 30% sucrose solution for 3–5 d, and then sectioned in 100 μm coronal sections and mounted on gelatinized slides. Slides were rinsed in distilled water for 1 min, placed in H_5NO (Sigma) for 30 min in the dark, rinsed in distilled water for 1 min, placed in Kodak Fix (Sigma) for the film for 30 min in the dark, rinsed in distilled water for 1 min, placed sequentially in 50%, 70%, and 95% alcohol for 1 min, twice in 100% alcohol for 5 min, in a solution of one-third chloroform, one-third xylene, and one-third 100% alcohol for 15 min, and then placed in xylene for 15 min. Finally, sections were coverslipped with Eukitt ® (Bio-Optica). Thus, pyramidal neurons of the CA1 region of the HP and pyramidal neurons of layer II/III of ACx were identified and selected only if the labeling was uniform and lacked any reaction precipitate, the dendritic arborizations were intact and spines were clearly marked. In a blinded manner, apical and basal dendritic trees were separately analyzed, and spine density was calculated along with ~25 μm length of dendritic segments. The stained sections were analyzed using Olympus BX63 microscope with a 100× oil-immersion objective lens.

2.7. Immunofluorescence analyses

Dihydroethidium (DHE) and 4-hydroxy-2-nonenal (4-HNE)

immunostaining were used to assess reactive oxygen species (ROS) and membrane lipid peroxidation, respectively. Brains from 3/animals/group were quickly removed after transcardial perfusion with PBS 4% and, subsequently, with paraformaldehyde (PFA) 4% in PBS and samples were then post-fixed in PFA 4% at 4 °C overnight. Immunofluorescence analyses were performed on 40-μm-thick coronal brain cryosections (Cryostat, SLEE Medical GmbH, Germany) containing the HP from Ctrl and Noise animals.

For DHE staining, slices were incubated with 1 μM DHE (Supplementary Table 1) in PBS for 30 min at 37 °C. For 4-HNE immunostaining, the slides were incubated in a blocking solution containing 1% fatty acid-free bovine serum albumin (BSA), 0.5% Triton X-100, and 10% normal goat serum in PBS for 1 h at room temperature (RT). The specimens were then incubated overnight at 4 °C with a solution containing anti-4-HNE primary antibody (Supplementary Table 1), 1:100 in PBS. At the end of the incubation, all slides were washed twice in PBS and incubated at RT for 2 h, light-protected, in labeled conjugated goat anti-rabbit secondary antibody (Supplementary Table 1) 1:400 in PBS. After another wash in PBS, samples were double-stained with 4′,6-Diamidino-2-Phenylindole, Dihydrochloride (DAPI, Supplementary Table 1) 1:1000 in PBS for 20 min in the dark at RT to identify cell nuclei. The slides were coverslipped with an antifade medium (Supplementary Table 1). Fluorescent images were obtained with a confocal laser microscope (Nikon Ti-E, Confocal Head A1 MP, Tokyo, Japan) with a 20× objective lens.

For all immunofluorescence analyses, control experiments were performed by omitting the primary antibody during the processing of tissues randomly selected across experimental groups; staining was absent in cochlear samples in which the primary antibody was omitted indicating a lack of non-specific background labeling (data not shown). The tissues from all groups were always processed together during the procedures to limit the variability related to antibody penetration, incubation time, post-sectioning age and condition of the tissue.

2.8. Western blot and dot blot analyses

Total proteins were extracted from ACx or HP of control and noise-exposed mice, using ice-cold RIPA buffer [Pierce; 50 mM Tris, 150 mM NaCl, 1 mM EDTA, 1% DOC, 1% Triton X-100, 1% SDS, and 1× protease, phosphatase-1, and phosphatase-2 inhibitor cocktails (Sigma)]. Tissues were incubated for 15 min on ice with occasional vortexing and the lysate was spun down at 22,000 ×*g* for 15 min, 4 °C, and 2 μl aliquot of the supernatant was assayed to determine the protein concentration (microBCA kit, Pierce). SDS-PAGE reducing sample buffer was added to the supernatant, and samples were heated to 95 °C for 5 min. Protein lysates (30 μg) were loaded onto 10% or 12% Tris-glycine polyacrylamide gels for electrophoretic separation. Precision Plus Protein Dual Color Standards (Bio-Rad) were used as molecular mass standards. Proteins were then transferred onto nitrocellulose membranes at 330 mA for 2 h at 4 °C in a transfer buffer containing 25 mM Tris, 192 mM glycine, and 20% methanol. Membranes were incubated for 1 h with blocking buffer (5% skim milk in TBST), and then incubated overnight at 4 °C with primary antibodies directed against one of the following proteins: pGluA1^{Ser845}, GluA1, PSD-95, Synaptophysin, CAMKII, GFAP, TNF-α, NF-κB, IL-1β, SOD2, GAPDH and α-tubulin (Supplementary Table 1). For dot blot, 5 μl of lysates were spotted in a TBST pre-wetted nitrocellulose membrane and processed as previously described (Paciello et al., 2021). After draining, equal loading of protein amounts was then verified by staining the membrane with Ponceau S. Protein tyrosine nitration (NT) and glutathionylated proteins (GSH) were detected using specific antibodies (Supplementary Table 1).

After three 10 min rinses in TBST, membranes were incubated for 2 h at RT with HRP-conjugated secondary antibodies (Supplementary Table 1). The membranes were then washed, and the bands were visualized with an enhanced chemiluminescence detection kit (GE Healthcare, United Kingdom). Protein expression was evaluated and documented using UVItec Cambridge Alliance.

2.9. Statistical analysis

Power analysis was performed to determine the sample size to provide a statistical power of 80% and an α level of 0.05. The results are presented as mean ± SEM. One- or two-way ANOVA and post-hoc comparison by Tukey's test were used to analyze the differences among group's means using SigmaPlot (version 14, Systat). For spine density and fEPSP analyses, the number of dendritic segments and the number of slices, respectively, have been considered independent factors. Statistical comparisons of means data from two experimental groups were made by Student's two-tailed *t*-test using a worksheet (Microsoft Office Excel 2017, Version 1.30). Mean values are quoted ± standard error of the mean (s.e.m.) where p values <0.05 indicate statistical significance.

3. Results

3.1. Age-related hearing loss induces functional and molecular alterations in the ACx

Considering that the effect of aging on hearing function in the mouse model of C57BL/6 is well known (Someya et al., 2009; Fetoni et al., 2011; Scimemi et al., 2014; Liu and Lee, 2019), we wondered if ARHL can induce functional alterations not only at the peripheral level but also in central auditory structures. To answer this question, we characterized synaptic function in neurons of the ACx in 3, 6, and 9 M animals. Thus, we studied fEPSPs in ACx layer II/III following stimulation of local connections. Interestingly, the comparison of the I/O curves, obtained by plotting fEPSP amplitude against stimulus intensities, showed a progressive decrease in recording amplitude during aging, with a significant reduction between 3 and 9 M (Fig. 2A; $n = 8$ slices from 4 mice of 3 M; $n = 10$ slices from 4 mice of 6 M and $n = 7$ slices from 3 mice of 9 M; two-way ANOVA, Tukey's post-hoc test, $F_{(2,154)} = 22.36$, $p < 0.001$).

In keeping with these data, western blot analysis showed significantly lower levels of the postsynaptic density protein 95 (PSD-95), a major scaffold protein that determines the structural and functional integrity of excitatory synapses (El-Husseini et al., 2002; Blanpied et al., 2008; Chen et al., 2008), in ACx of 9 M animals, compared with 3 M and, less severely, with 6 M mice (Fig. 2B; $n = 3$ animals/group; one-way ANOVA, 3 M vs. 9 M mice $p = 0.008$; 6 M *vs.* 9 M mice $p = 0.039$; 3 M *vs.* 6 M mice $p > 0.05$). To confirm western blot analyses indicating damage at postsynaptic terminals, we performed spine density evaluations in pyramidal neurons of layer II/III of the ACx in 3 and 9 M animals (Fig. 2C-D). By counting the number of dendritic spines in both apical and basal dendritic segments, we found in 9 M mice a significant decrease of spine density in both apical (Fig. 2c1,c3, D, Student's *t*-test, $p = 0.026$; 3 M $n = 39$ segments from $n = 3$ mice/group and 9 M $n = 38$ segments analyzed from $n = 3$ mice/group) and basal arborizations (Fig. 2c2,c4,D; Student's *t*-test, $p = 0.030$; 3 M $n = 37$ segments analyzed from $n = 3$ mice/group and 9 M $n = 37$ segments analyzed from $n = 3$ mice/group) compared to 3 M mice.

Moreover, considering that it is known that presbycusis processes can induce a redox imbalance and inflammatory processes in the cochlea (Fetoni et al., 2011; Wang and Puel, 2020; Fetoni et al., 2022), we also looked at oxidative stress and inflammation marker expression. We performed a dot blot to detect protein tyrosine nitration (NT), a marker of nitro-oxidative stress. Indeed, protein tyrosine nitration represents a prominent post-translational redox modification, and it is associated with different diseases (Ischiropoulos and Beckman, 2003). Dot blot analysis showed an increase of NT in ACx samples of 9 M mice, compared to younger mice of 3 and 6 M (Fig. 3A; $n = 4$ animals/group; one-way ANOVA, 3 M *vs.* 9 M mice $p = 0.010$; 6 M *vs.* 9 M mice $p = 0.034$; 3 M *vs.* 6 M mice $p = 0.704$).

We also analyzed the expression level of the superoxide dismutases-2 (SOD2), an important member of the antioxidant machinery, considering that it plays a crucial role in counteracting mitochondrial ROS

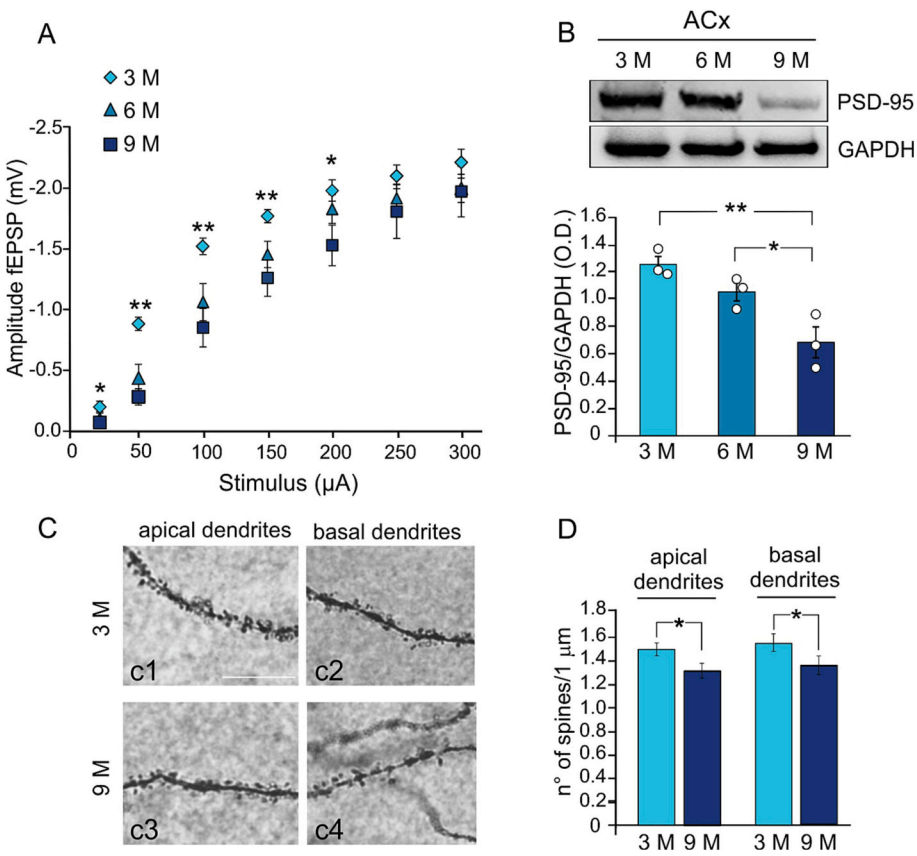

Fig. 2. C57BL/6 mice show auditory cortex synaptic alterations with advancing age.
A: Field excitatory post-synaptic potential (fEPSP) amplitude following stimulation of afferent fibers in auditory cortex (ACx) layer II/III at increasing intensities are shown for slices obtained from 3, 6, and 9 months of age (M) C57BL/6 mice. Statistical analysis by two-way ANOVA followed by Tukey's post-hoc revealed a significant decrease in basal synaptic transmission with aging, specifically between 3 and 9 M (3 M $n = 8$ slices from 4 mice; 6 M $n = 10$ slices from 4 mice; 9 M $n = 7$ slices from 3 mice). Asterisks indicate significant differences between 3 M and 9 M groups (**$p < 0{,}01$; *$p < 0{,}05$). B: Representative western blot images from ACx samples collected at 3, 6, and 9 M, showing significant molecular alterations in 9 M mice, with a decrease of the post-synaptic protein PSD-95. Histograms (means±SEM) show the results of densitometric analysis on all samples ($n = 3$ mice for each group; Student's *t*-test) normalized to total protein levels (GAPDH). C: Representative higher magnifications of dendritic segments of pyramidal neurons of layer II/III of ACx from apical and basal dendrites in 3 M (c1,c2) and 9 M (c3,c4) animals (100×, scale bar: 10 μm). D: Histograms show results of spine density analysis (Student's *t*-test) indicating a decreased spine number in both apical and basal arborization of 9 M animals compared to younger mice of 3 M. Asterisks indicate significant differences between groups (*$p < 0.05$; **$p < 0.01$).

during aging and in neurodegenerative diseases (Carvajal et al., 2018). Western blot analyses showed a significant decrease of SOD2 with advancing age (Fig. 3B; $n = 3$ animals/group; one-way ANOVA, 3 M *vs.* 9 M mice $p = 0.008$; 3 M *vs.* 6 M $p = 0.93$; 6 M *vs.* 9 M mice $p = 0.012$). Thus, together with increased NT expression level, the decreased expression of SOD2 suggests a redox imbalance in the ACx of early presbycusis mice. Finally, we evaluated neuroinflammation, focusing on two major inflammatory cytokines, such as TNF-α and IL-1β. An increase of both TNF-α and IL-1β was found in ACx lysates of 9 M animals, (Fig. 3C,D; TNF-α: $n = 3$ animals/group; one-way ANOVA, 3 M *vs.* 9 M mice $p = 0{,}009$; 6 M *vs.* 9 M mice $p = 0{,}026$; 3 M *vs.* 6 M $p > 0.05$; IL-1β: $n = 4$ animals/group; one-way ANOVA, 3 M *vs.* 9 M mice $p = 0.038$; 6 M *vs.* 9 M mice $p = 0.47$; 3 M *vs.* 6 M $p = 0.23$), suggesting inflammatory damage with advancing age in central auditory structures.

Of note, as shown in Supplementary Fig. 1, we did not find significant alterations in PSD-95, NT and TNF-α expression in another sensory cortex, such as the somatosensory cortex (Fig. S1), indicating a specific ACx dysfunction in C57BL/6 mice with advancing age, probably related to ARHL phenotype.

Collectively, these data demonstrate that, along with ARHL and cochlear alterations, presbycusis induces ACx dysfunction, with functional and molecular changes in auditory neurons, associated with oxidative/inflammatory damage.

3.2. Early noise exposure affects auditory thresholds and induces long-lasting alterations of synaptic transmission in the ACx of presbycusis mice

One month after noise exposure (at 3 M), a marked threshold shift was recorded in noise exposed animals (Fig. 4A), indicating, as expected, a detrimental effect of noise on hearing sensitivity. At 6 M (that corresponds to 4 months after noise exposure), the trend of threshold shift was still evident, especially between 6 and 20 kHz (Fig. 4B), considering that 6 M control mice show an increased auditory threshold at 24 and 32 kHz, due to an early ARHL onset (Fetoni et al., 2022). At 9 M, when control age-matched animals show an increase of auditory threshold (>70–80 dB, spanning in all frequencies) (Fetoni et al., 2022), a threshold shift (>15 dB) was still detectable in noise exposed animals (Fig. 4C).

Considering the long-lasting detrimental effect of noise exposure in hearing sensitivity, we monitored basal synaptic transmission in neurons of the ACx by recording fEPSPs in noise-exposed and age-matched not exposed (control) animals at different months of age, as specified in Fig. 1.

As expected, based on our previous findings obtained from different animal models that do not show presbycusis phenotype, such as Wistar rats or B6129SF2/J mice (Paciello et al., 2018; Paciello et al., 2021), 1 month after the onset of trauma sessions (3 M), fEPSPs were significantly smaller in animals subjected to noise compared to those not exposed (Fig. 4D; $n = 8$ slices from 4 Noise mice and $n = 8$ slices from 4 Ctrl mice; two-way ANOVA, Tukey's post-hoc test, $F = 80.28$, $p < 0.001$). Interestingly, in C57BL/6 mice this functional impairment persists over time, and noise-exposed animals of both 6 M and 9 M (corresponding to 4 and 7 months after noise exposure respectively) continued to show a significant decrease of fEPSP responses with respect to age-matched controls (Fig. 4E,F; $n = 9$ slices from 4 Noise mice of 6 M and $n = 10$ slices from 4 Ctrl mice of 6 M; two-way ANOVA, Tukey's post-hoc test, $F = 16.11$, $p=0.001$; $n = 11$ slices from 3 Noise mice of 9 M and $n = 7$ slices from 3 Ctrl mice of 9 M; two-way ANOVA, Tukey's post-hoc test, $F = 24.12$, $p < 0.001$).

These data suggest that, in this mouse model of ARHL, the ACx is severely affected by early noise exposure that can induce long-lasting alterations in basal synaptic transmission.

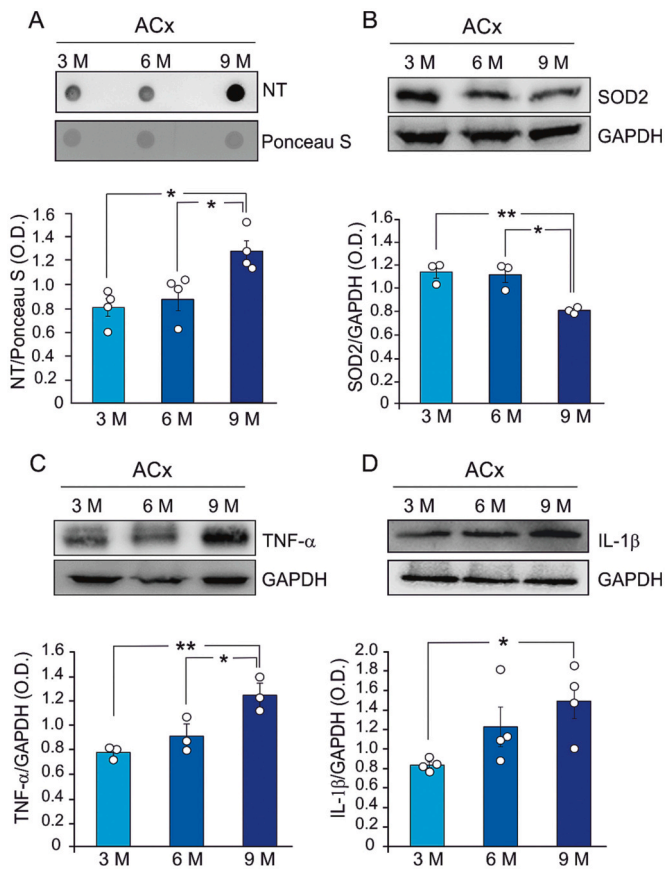

Fig. 3. Markers of redox imbalance and inflammation in the auditory cortex of 9 M mice.

A: Representative dot blot showing an increase of protein tyrosine nitration (NT, $n = 4$ mice for each group; Student's *t*-test) in the auditory cortex (ACx) of C57BL/6 mice with advancing months of age (M). Equal protein loading was checked by Ponceau S staining. B-D: Western blot representative bands showing decreased expression of SOD2 (B) and an increased expression of TNF-α (C) and IL-1β (D), indicating oxidative-inflammatory damage in the ACx of C57BL/6 mice with advancing age. Histograms (means±SEM) show results of densitometric analyses on all samples ($n = 3$ or 4 mice for each group; Student's *t*-test) normalized to total protein levels (GAPDH). Asterisks indicate significant differences between groups (*$p < 0.05$; **$p < 0.01$).

3.3. The association between early noise exposure and ARHL causes working memory impairment

Having established the long-lasting detrimental effects of early noise exposure on the ACx of C57BL/6 mice, we asked whether ACx damage could also be associated with hippocampal dysfunctions. Indeed, several pieces of evidence suggest a link between sensory and cognitive decline occurring during aging (Fortunato et al., 2016; Jafari et al., 2019; Slade et al., 2020; Nadhimi and Llano, 2021). To address this issue, we first analyzed the hippocampal-dependent memory performance in noise-exposed and control animals of different months of age, by using the Y-maze test. The Y-maze apparatus is a widely used behavioral paradigm for the assessment of spatial working memory which is quantified by the number of correct alternances performed by the animal during the 8 min of the test. The number of correct alternances is then computed as spontaneous alternations behavior. At 3 M, we did not observe differences in the performance of control and noise-exposed animals (68.1 ± 2.7% for Ctrl group, $n = 12$, 67.0 ± 3.6 for Noise group, $n = 11$, Student's *t*-test, $p = 0.804$; Fig. 5A). However, at 6 and 9 M, noise-exposed animals showed a significant reduction in their spontaneous alternation behavior (6 M: 68.1 ± 3.2% for Ctrl group, $n = 11$, 59.7 ± 1.6% for Noise group, $n = 9$, Student's *t*-test, $p = 0.036$; 9 M: 67.6 ± 2.6% for Ctrl animals, $n = 16$, 56.9 ± 2.9% for Noise animals, $n = 13$, Student's *t*-test, $p = 0.009$; Fig. 5B,C), thus suggesting working memory impairment. This effect was independent of total locomotor activity, as assessed by total distance traveled in the open field test (3 M: 36.9 ± 1.8 m for Ctrl animals, $n = 11$, 39.2 ± 3.5 m for Noise animals, $n = 11$, Kruskal Wallis ANOVA on Ranks, $p = 0.768$; 6 M: 35.4 ± 2.14 m for Ctrl group, $n = 12$, 37.8 ± 2.0 m for Noise group, $n = 11$, one-way ANOVA, F = 0.768, $p = 0.391$; 9 M: 41.3 ± 4.8 m for Ctrl animals, $n = 14$, 34.3 ± 3.1 m for Noise animals, $n = 13$, one-way ANOVA, F = 1.518, $p = 0.229$; Fig. 5D). Looking for a statistical correlation between hearing and memory impairment, we performed a correlation analysis (GraphPad, Prisma) by crossing mean ABR threshold values and Y-maze data at 6 and 9 M (when a memory alteration is observed in noise group). Results shown in Supplementary Fig. 2 indicate a significant statistical correlation between ABR and behavioral data (6 M: $R^2 = 0.597$, $p = 0.0002$; 9 M: $R^2 = 0.491$, $p = 0.0163$; Fig. S2), supporting our hypothesis.

Finally, considering that the noise exposure procedure can be stressful (Kraus and Canlon, 2012), to exclude stress as a confounding factor, we analyzed time spent by the animals in the center of the open field arena, and our results show no significant difference between Ctrl and Noise groups at 6 and 9 M, when memory impairment is manifested in the Noise group (Fig. 5E-F; 6 M: Ctrl *vs*. Noise group $p = 0.83$, Student's *t*-test.; Ctrl $n = 12$, Noise $n = 11$; 9 M: Ctrl *vs*. Noise group $p = 0.51$, Student's *t*- test.; Ctrl $n = 14$, Noise $n = 13$).

Moreover, to obtain more data supporting the hypothesis that the combined noise and age-related hearing loss could be responsible for memory impairment, we performed a behavioral analysis in a mouse strain with no ARHL phenotype, such as B6129SF2/J animals. In these mice, our noise exposure paradigm affects hearing sensitivity, inducing a long-lasting threshold shift (Paciello et al., 2021 and Fig. S3 A-C). Notably, the detrimental effect of early noise exposure on memory performance was not observed in B6129SF2/J animals (Fig. S3 D—F).

Thus, collectively, our findings support the hypothesis that it is the combined effect of noise and auditory sensory aging to impact memory function.

3.4. Early noise exposure affects spine density and synaptic protein expression in the HP of middle-aged animals with ARHL

Looking for molecular mechanisms underlying noise- and age-related hearing loss effect on memory alterations observed in C57BL/6 animals of 6 and 9 M, we performed immunofluorescence, western blot, and spine density analyses in the HP. Specifically, we focused on 9 M, the time point when memory impairment between noise-exposed and non-exposed animals was more evident. First, we studied the effect of noise exposure at the synaptic level, by evaluating the expression of both post-synaptic and pre-synaptic proteins in hippocampal lysates from noise-exposed mice of 9 M compared to age-matched controls. Among post-synaptic proteins, we evaluated the expression of PSD-95 and Ca^{2+}/calmodulin (CaM)-dependent protein kinase II (CAMKII).

A significantly decreased expression of PSD-95 was found in the HP of 9 M mice exposed to noise, compared with non-exposed age-matched animals (Fig. 6A; $n = 3$ animals/group; Student's *t*-test, $p = 0.008$). Moreover, consistently with the decreased expression of PSD-95, we found a significant decrease of CAMKII level in the HP of noise-exposed animals (Fig. 6B; $n = 3$ animals/group; Student's *t*-test, $p = 0.001$). Furthermore, to gain insight into the glutamatergic transmission, phosphorylation of AMPA receptor (AMPAR) GluA1 subunit at Ser845 ($pGluA1^{Ser845}$) was also evaluated in our experimental conditions, considering its role in AMPAR function, trafficking, and channel conductance (Derkach et al., 1999; Lee et al., 2000; Suzuki et al., 2005; Havekes et al., 2007; Man et al., 2007). Western immunoblot analyses revealed a significant decrease of $pGluA1^{Ser845}$ in the HP of the 9 M Noise group, compared with age-matched non-exposed animals (Fig. 6C; $n = 3$ animals/group; Student's *t*-test, $p = 0.007$). We also evaluated the expression of synaptophysin, a presynaptic membrane protein essential

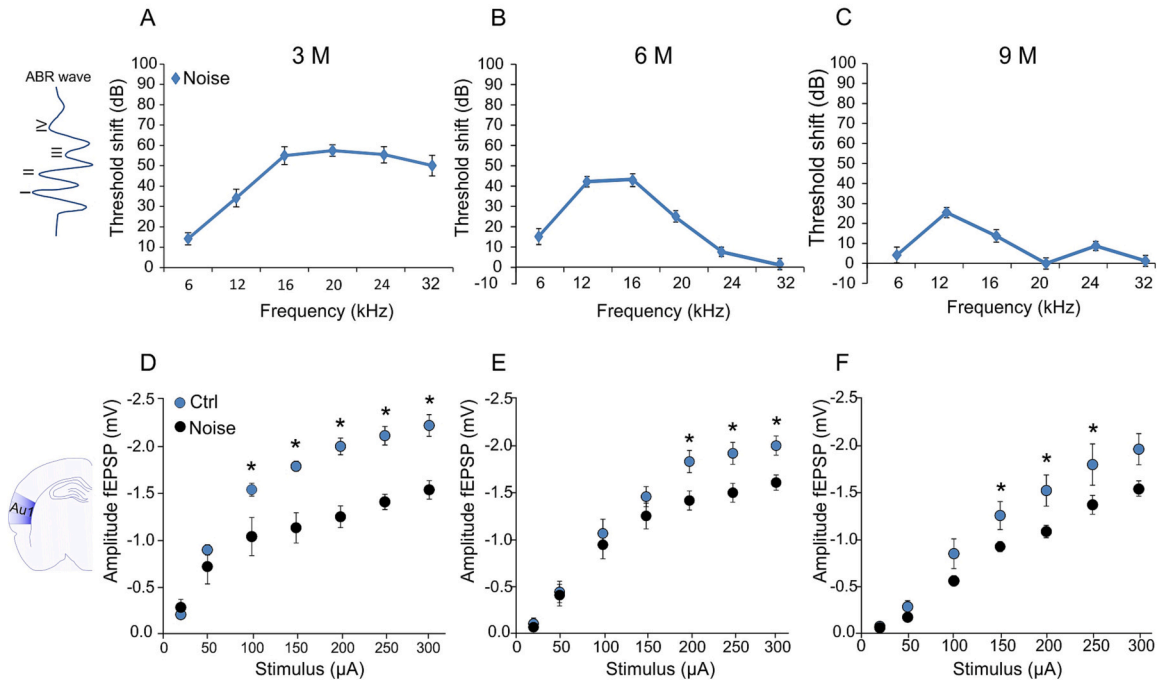

Fig. 4. Early noise-induced hearing loss affects basal synaptic transmission in the ACx.
A-C: Graphs show threshold shift (difference between noise and age-matched control auditory thresholds) obtained from ABR analyses (a representative ABR waveform containing waves I-IV is shown on the left) performed at 3, 6, and 9 months of age (M). At 3 M, noise causes a marked increase of auditory threshold, spanning at all frequencies (A). A high threshold shift was evident also at 6 M (B), and at 9 M (C) specifically in the middle frequency region. D-F: Field excitatory post-synaptic potential (fEPSP) amplitudes following stimulation of afferent fibers in auditory cortex (ACx) layer II/III (Au1 region from Paxinos and Franklin brain atlas) at increasing intensities in slices obtained from not-exposed (Ctrl group) and noise-exposed (Noise group) animals 1, 4 and 7 months after noise exposure, corresponding to 3, 6 and 9 M. Statistical analysis by two-way ANOVA followed by Tukey's post-hoc revealed a significant decrease of fEPSP between Ctrl and Noise groups at all time points analyzed (Ctrl 3 M $n = 8$ slices from 4 mice; Ctrl 6 M $n = 10$ slices from 4 mice; Ctrl 9 M $n = 7$ slices from 3 mice; Noise 3 M $n = 8$ slices from 4 mice; Noise 6 M $n = 9$ slices from 4 mice; Noise 9 M $n = 11$ slices from 3 mice). Data are expressed as mean ± SEM. Asterisks indicate significant differences between groups (*$p < 0.05$).

for neurotransmission and synaptic plasticity in the brain (Janz et al., 1999). Our results show a significant difference in synaptophysin expression levels between Noise and Ctrl animals (Fig. 6D, $n = 3$ animals/group; Student's t-test, $p = 0.001$), indicating dysfunctions not only at post-synaptic but also at the pre-synaptic level.

To confirm western blot analyses, we also performed spine density evaluations in pyramidal neurons of the hippocampal CA1 region (Fig. 6E). By counting the number of dendritic spines in both apical and basal dendritic segments, we found a significant decrease of spine density in both apical (Fig. 6e1,e2,F; two-way ANOVA, Tukey's post-hoc test, F = 12,932, p = 0,007; Ctrl $n = 30$ segments from n = 3 mice/group and Noise $n = 32$ segments analyzed from $n = 3$ mice/group) and basal arborizations (Fig. 6e3,e4,F; two-way ANOVA, Tukey's post hoc test, F = 12,932, $p = 0{,}022$; Ctrl $n = 28$ segments analyzed from $n = 3$ mice/group and Noise $n = 31$ segments analyzed from $n = 3$ mice/group) in Noise compared to Ctrl group.

Thus, these data indicate that early noise exposure alters dendritic spines, synaptic proteins, and glutamatergic transmission in HP neurons in middle-aged animals with a severe ARHL phenotype.

3.5. Hippocampal synaptic alterations in noise-exposed animals are associated with redox imbalance and neuroinflammation

To further characterize the molecular underpinnings of hippocampal dysfunctions, we investigated oxidative and inflammatory damage, considering that these are well-known consequences of both noise exposure, ARHL, and dementia (Fetoni et al., 2019; Wang and Puel, 2020; Alvarado et al., 2022) and that the HP is particularly prone to hearing loss-related oxidative stress (Stebbings et al., 2016; Nadhimi and Llano, 2021). Thus, to study redox status imbalance, we evaluated the expression level of ROS and lipid peroxidation in brain slices. Results of our immunofluorescence analyses shown in Fig. 7, demonstrated an increase of DHE red fluorescence (indicating an increase of ROS amount) in the HP (CA1 and DG regions) of noise-exposed animals, compared to age-matched controls (Fig. 7A). Consisting with these data, we also found an increased expression of 4-HNE, a marker of lipid peroxidation in the HP of noise-exposed animals, compared to controls (Fig. 7B).

The hippocampal oxidative stress was also confirmed by dot blot experiments, showing the significantly increased expression of NT (Fig. 7C, $n = 3$ animals/group; Student's t-test, $p < 0.0001$).

Furthermore, we investigated the endogenous antioxidant system. Among all antioxidant enzymes, we focused on SOD2, a key endogenous enzyme involved in clearing mitochondrial ROS, whose altered expression has been linked to cognitive impairment and hippocampal dysfunction during aging (Carvajal et al., 2018). Western blot analyses showed a significant reduction of SOD2 expression level in the HP of the 9 M Noise group, compared with age-matched non-exposed controls (Fig. 7D; $n = 3$ animals/group; Student's t-test, $p = 0.03$). Moreover, we evaluated total glutathionylated protein levels by using dot blot. Glutathionylation is a mechanism through which protein functions can be regulated by the redox status, and it can be considered an indicator of oxidized glutathione (GSSG)/reduced glutathione (GSH) ratio (Fratelli et al., 2002), reflexing tissue redox balance. Our results indicate a significant decrease of glutathionylated proteins in the HP of noise-exposed animals (Fig. 7E; $n = 4$ animals/group; Student's t-test, $p < 0.0001$).

To assess inflammatory processes, we studied NF-κB, TNF-α, and IL-1β, which are well-known inflammatory markers playing a key role in aging and neurodegenerative diseases (Tilstra et al., 2011; Babić Leko

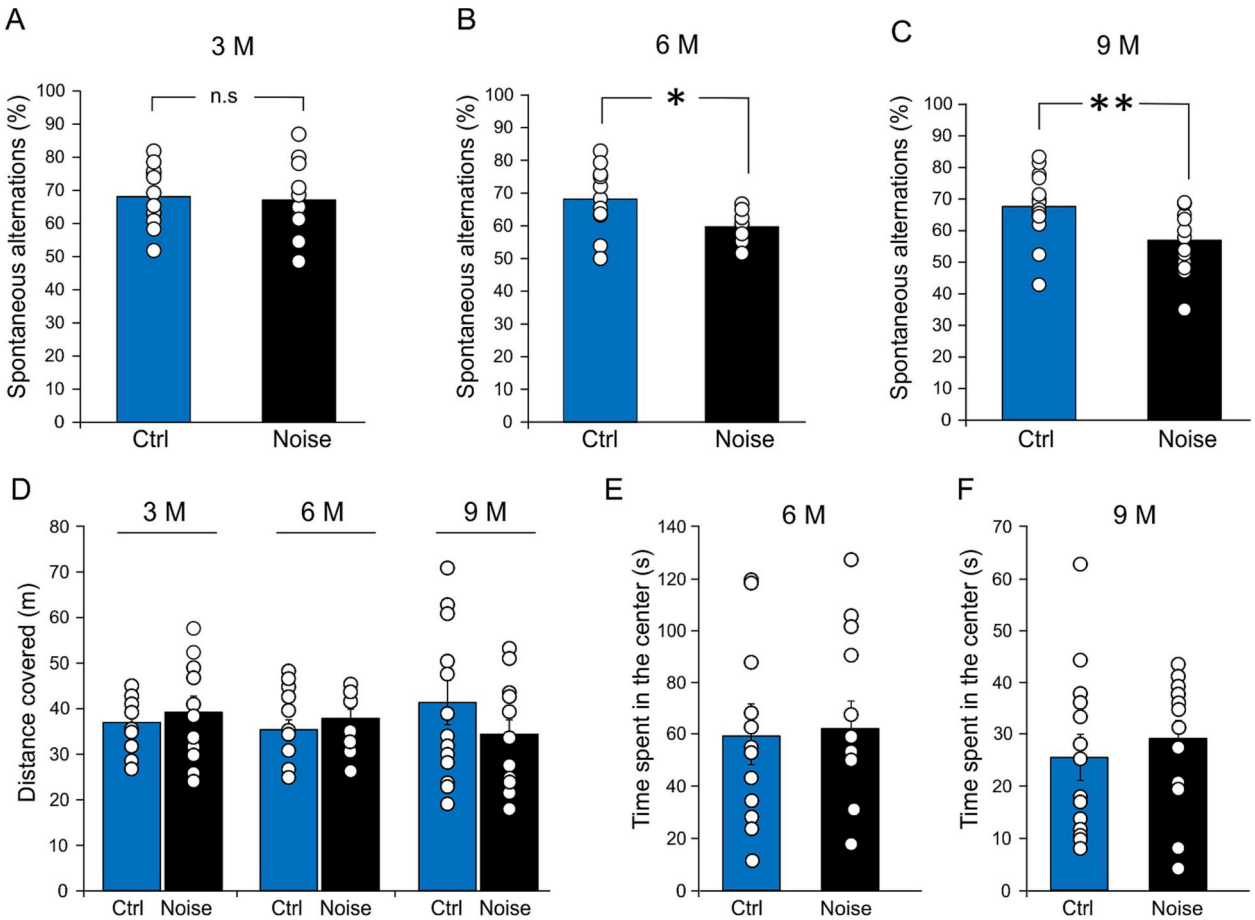

Fig. 5. Memory dysfunctions in mice exposed to noise with early presbycusis phenotype.
A-C: Spontaneous alternation behavior in the Y-maze of not-exposed (Ctrl group) and noise-exposed (Noise group) animals 1, 4, and 7 months after noise exposure, corresponding to 3, 6, and 9 months of age (M). Statistical analyses performed by Student's *t*-test revealed a significant difference between control and noise-exposed animals at 6 and 9 M (6 M: Ctrl $n = 11$, Noise $n = 9$, $p = 0.036$; 9 M: Ctrl $n = 16$, Noise $n = 13$, $p = 0.009$). This effect was independent of alterations in locomotor activity, evaluated by analyzing total distance covered in the open field arena (D) or from anxiety behavior, evaluated by analyzing time spent in the center of the open field arena (E-F). Data are expressed as mean ± SEM. Asterisks indicate significant differences between groups (*$p < 0.05$; **$p < 0.01$).

et al., 2020) and which activation is strongly related to oxidative stress (Blaser et al., 2016; Gloire et al., 2006; Fabisiak and Patel, 2022). Data of Western blot showed significant increases of NF-κB, TNF-α, and IL-1β in the HP of C57BL/6 mice exposed to noise compared with age-matched controls (Fig. 8A-C; NF-κB, $n = 3$ animals/group; Student's *t*-test, $p = 0.004$; TNF-α, $n = 4$ animals/group; Student's *t*-test, $p = 0.03$; IL-1β, $n = 3$ animals/group; Student's *t*-test, $p = 0.026$). Moreover, we studied molecular markers of glial cell activation. Indeed, microglia and astrocytes are critical to neuronal health and are capable of modulating inflammatory events in the central nervous system (Saijo et al., 2009; Muzio et al., 2021). Thus, we found a significant increase of glial fibrillary acidic protein (GFAP) expression levels in hippocampal samples of noise-exposed animals, indicating astroglia activation (Fig. 8D, $n = 3$ animals/group; Student's *t*-test, $p = 0.002$).

4. Discussion

Epidemiological and experimental studies suggest a strong association between loss of function in the auditory system induced by noise or aging processes and the onset and development of cognitive decline. Indeed, people with ARHL or hearing impairment show high susceptibility to developing dementia. However, the nature of this relationship is still poorly understood.

In this study, we explored the effect of the interaction between two main risk factors, such as ARHL and NIHL, on brain structures involved in auditory and memory functions, the ACx and the HP. Specifically, we wondered what is the effect of the accelerated presbycusis induced by noise exposure on memory function.

First, we characterized ACx synaptic damage in C57BL/6 mice of different months of age, to monitor how the onset and progression of ARHL can affect auditory brain structures. Indeed, the C57BL/6 mouse, used in this study, is the most frequently used mouse model of human ARHL (Fetoni et al., 2011), due to the genetic defect of the *Ahl* gene that codes for the hair cell-specific cadherin (Johnson et al., 1997; Noben-Trauth et al., 2003). Interestingly, at 9 M, when these animals show severe hearing loss (>70 dB), involving all frequency regions (Fetoni et al., 2022), the basal synaptic transmission measured in horizontal connections of the ACx was significantly decreased compared to what was observed in younger mice (of 3 and 6 M). Moreover, a decreased expression of PSD-95, together with a significant decrease in spine density, indicates damage of postsynaptic terminals, leading to synaptic destruction and dysfunction. According to experimental evidence, our findings support the hypothesis that ARHL can affect the central nervous system, causing a dramatic change in activity, tuning, and coding strategies of auditory cortical neurons as a function of age and, presumably, in response to the decreased drive from the cochlea (Ouda et al., 2015; Gray and Recanzone, 2017; Recanzone, 2018; Bishop et al., 2022). Our results are also consistent with clinical evidence, indicating decreased central hearing ability (i.e., central auditory processing, speech-in-noise performance) in ARHL patients (Keithley, 2020; Powell et al., 2022).

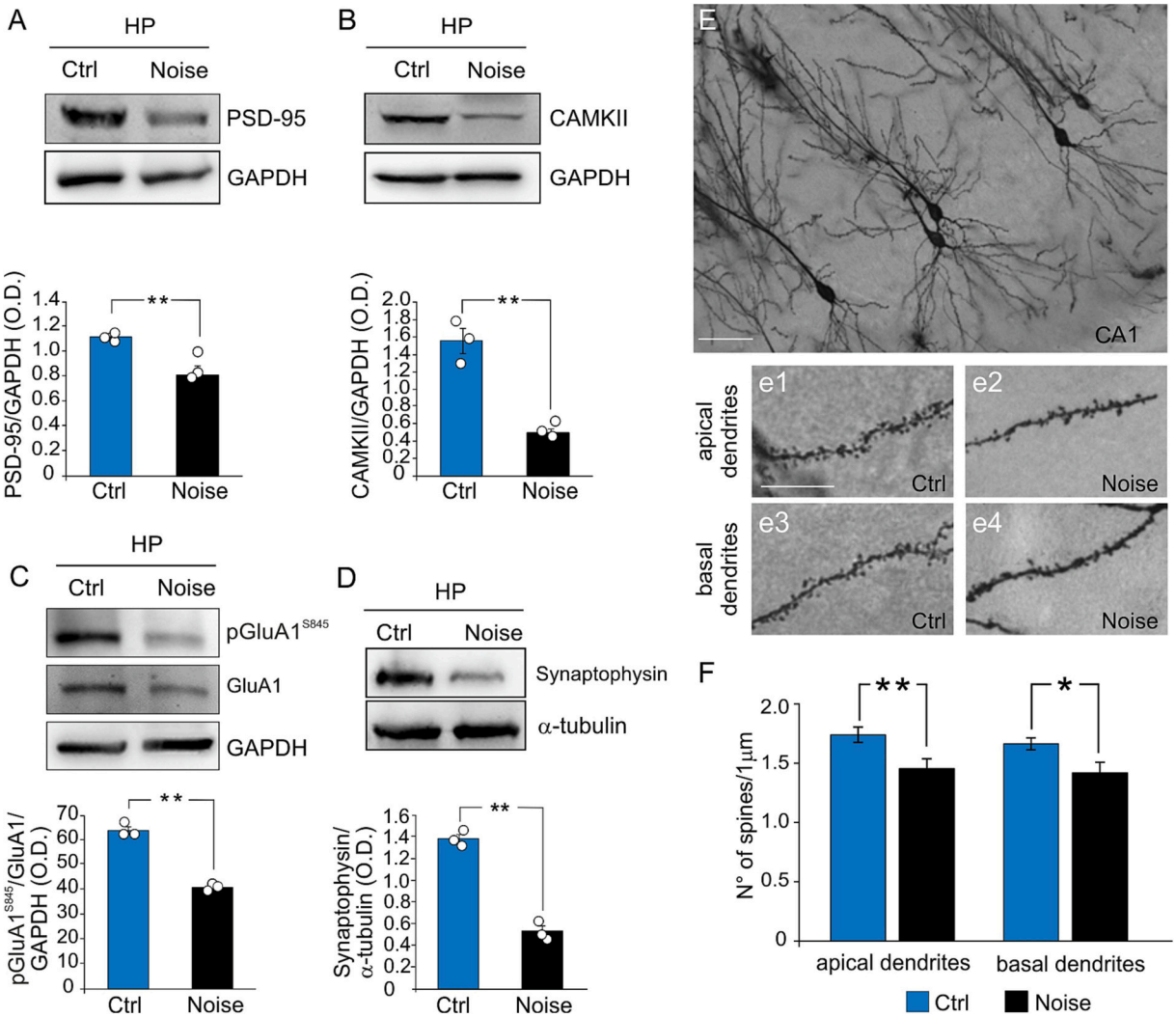

Fig. 6. Early noise exposure affects synaptic proteins and spine density in the hippocampus C57BL/6 mice of 9 M.
A-D: Representative western blot showing decreased PSD-95 (A) and CAMKII (B) expression levels, decreased GLUA1 phosphorylation at serine 845 (C), and decreased synaptophysin expression level (D) in the hippocampus (HP) of C57BL/6 mice of 9 months of age (M) exposed to noise at 2 M (Noise group) or not (Ctrl group). Bar graphs show the results of densitometric analyses on all samples ($n = 3$ mice for each group; Student's *t*-test) normalized to the corresponding total protein levels (GluA1, GAPDH, or α-tubulin). E: Representative image of pyramidal neurons of CA1 region of the hippocampus (20×, scale bar: 50 μm). e1-e4: Representative higher magnifications of dendritic segments from apical and basal dendrites in Ctrl (e1,e3) and Noise (e2,e4) groups (100×, scale bar: 10 μm). F: Histograms show results of spine density analysis (two-way ANOVA, n = at least 30 neurons/group; Tukey's post-hoc test) indicating a decreased spine number in both apical and basal arborization of noise-exposed animals compared to age-matched controls. Data are expressed as mean ± SEM. Asterisks indicate significant differences between groups (*$p < 0.05$; **$p < 0.01$).

Studies on the auditory system reported an age-related imbalance between excitatory and inhibitory neurotransmission in the auditory pathway. Indeed, it has been shown a down-regulation of inhibition, with loss of pre-and postsynaptic GABAergic and glycinergic inhibitory neurotransmission, across the afferent auditory pathway, including cochlear nuclei, inferior colliculus, and primary auditory cortex (Willott et al., 1993; Caspary et al., 1995; Ling et al., 2005; Caspary et al., 2008; Burianova et al., 2009; Richardson et al., 2013; Ouda et al., 2015). In line with this evidence presbycusis in C57BL/6 mice, observed as early as 6–7 months of age, is associated with the functional reorganization of the auditory cortex (Trujillo and Razak, 2013) and of the inferior colliculus. Decreased temporal coding and minimal gap threshold increases are also observed (Walton et al., 2008) and neurons in the high-frequency region start responding better to the middle frequencies (Willott et al., 1988). Similarly, Barsz et al. (2007) reported that inferior colliculus units from hearing-impaired mice displayed broader frequency receptive fields (Barsz et al., 2007). On the other hand, a significant reduction of the vesicular glutamate transporters and the vesicular GABA transporter has been reported in the cochlear nucleus of Wistar rats with aging (Alvarado et al., 2014), suggesting that the concomitant reduction in both excitatory and inhibitory markers might reflect a common central alteration in animal models of ARHL. Consistent with this hypothesis, our results showed a decreased excitatory synaptic response of ACx neurons of 9 M animals, together with a decrease in spine number and PSD-95 expression in the same region. These results are consistent with the age-dependent decrease of dendritic spines, the core site of glutamatergic transmission (Dickstein et al., 2013). Our hypothesis is that the impairment of the excitatory transmission we observed could be a compensatory activity-dependent mechanism, whereby a diminished input from the cochlea cannot sustain a large number of excitatory connections. Indeed, neurons undergo compensatory changes in synaptic activity after damage to the peripheral sensory systems, to restore original levels of activity (Turrigiano, 1999, 2007; Rich and Wenner, 2007; Fetoni et al., 2015). Thus, we can speculate that the decrease of excitatory post-synaptic responses observed in early presbycusis mice could be the result of functional

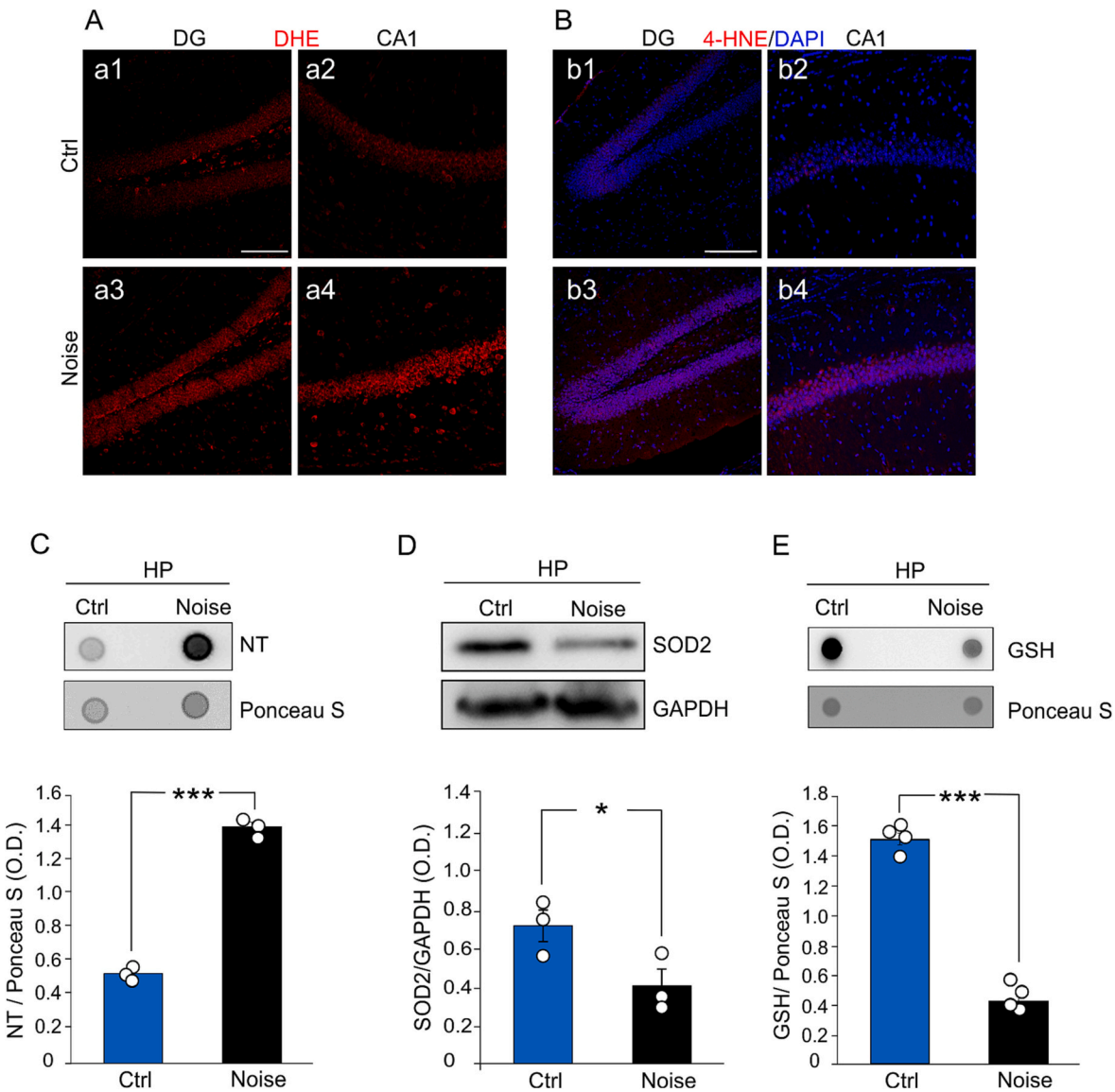

Fig. 7. Noise induces redox imbalance in the hippocampus of mice with early presbycusis onset.
A: Representative images of brain coronal sections stained with DHE, showing dentate gyrus (DG, a1,a3) and CA1 (a2,a4) hippocampal regions of C57BL/6 mice of 9 months of age (M) exposed to noise (Noise group) compared to age-matched not-exposed animals (Ctrl group). B: Representative images of brain coronal sections stained with 4-HNE as a marker of lipid peroxidation (red fluorescence) and DAPI (blue fluorescence) to label cell nuclei in DG (b1, b3) and CA1 (b2,b4) hippocampal regions. Scale bar: 100 μm. C: Representative dot blot and densitometric analysis showing the increase of protein tyrosine nitration ($n = 3$ mice for each group; Student's *t*-test) in the hippocampus (HP) of noise-exposed animals. Equal protein loading was checked by Ponceau S staining of the membrane. D: Representative western blot showing decreased expression of the endogenous antioxidant enzyme SOD2 in Noise group compared to Ctrl group. Bar graphs show the results of densitometric analyses on all samples ($n = 3$ mice for each group; Student's *t*-test) normalized to the corresponding total protein levels (GAPDH). E: Representative dot blot and densitometric analysis showing decreased protein glutathionylation ($n = 4$ mice for each group; Student's *t*-test) in HP of noise-exposed animals. Equal protein loading was checked by Ponceau S staining of the membrane. Asterisks indicate significant differences between groups (*$p < 0.05$; ***$p < 0.001$). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

disorganization induced by aging in the ACx, probably involving both reduction in glutamatergic function and a decline in inhibitory neurotransmission.

Of note, we did not find increased expression of oxidative/inflammatory markers in other sensory cortices (i.e., SCx), which could suggest an up-spread damage from the cochlea to the ACx, along with the progressive early onset of presbycusis in C57BL/6 mice. Of course, to establish the age-induced damage in ACx by evaluating longer life span, as well as, to study the impact of aging in different sensory domains could be interesting to learn more about the link between sensory and cognitive neurodegeneration and it needs further investigations.

Considering that aging is a shared factor between presbycusis and dementia-related diseases, and that noise exposure can be considered a risk factor for both sensory and cognitive decline (Johnson et al., 2021; Nadhimi and Llano, 2021; Paciello et al., 2021; Fetoni et al., 2022) our next step was to evaluate the effect of early noise exposure on memory function in ARHL mice. Our data, demonstrating a decreased performance in spatial working memory, measured by the Y-maze test, starting from 6 M and still detectable at 9 M in mice exposed to noise at 2 M, indicate that the detrimental effect of early noise exposure can contribute not only to accelerating cochlear age-dependent dysfunctions (Fetoni et al., 2022), but can also affect cognitive domain, causing memory impairment. Indeed, it has been shown that old C57BL/6 mice with profound hearing loss show spatial memory alterations, as

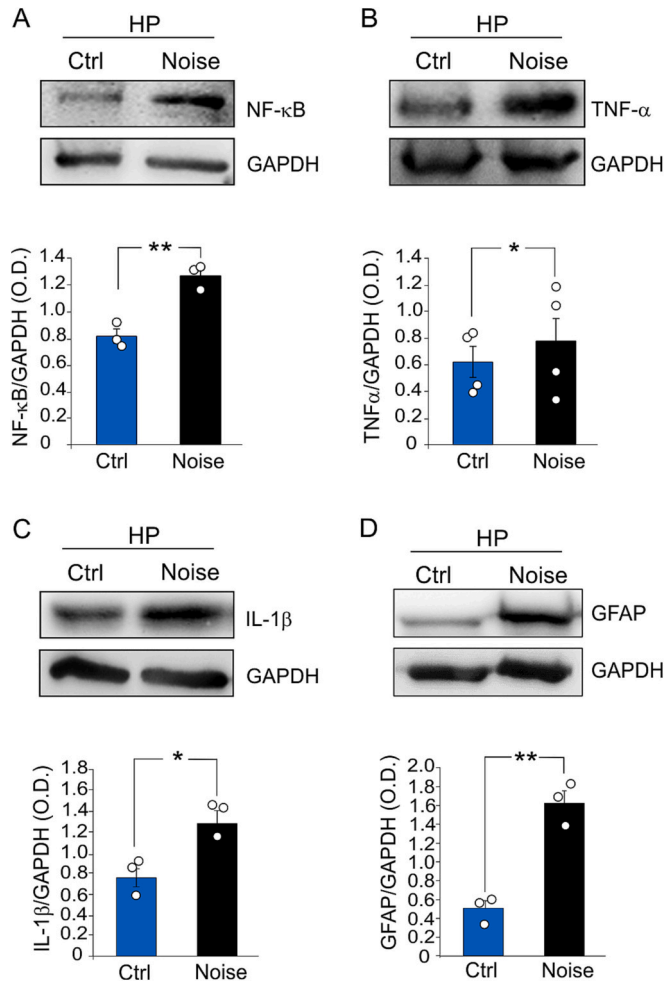

Fig. 8. Noise induces neuroinflammation in the hippocampus of middle age mice.

A-C: Representative western blot showing increased expression of inflammatory markers (NF-κB, TNF-α, and IL-1β) in the hippocampus (HP) of C57BL/6 mice of 9 months of age (M) exposed to noise (Noise group) compared to age-matched not-exposed animals (Ctrl group). Bar graphs show the results of densitometric analyses on all samples ($n = 3$ mice for each group; Student's *t*-test) normalized to the corresponding total protein levels (GAPDH). D: Increased expression of active astrocyte markers (GFAP) in the hippocampus of noise-exposed animals (Noise group) compared to age-matched not-exposed group (Ctrl group). Bar graphs show the results of densitometric analyses on all samples ($n = 3$ animals/group; Student's *t*-test) normalized to the corresponding total protein levels (GAPDH). Asterisks indicate significant differences between groups (*$p < 0.05$; **$p < 0.01$).

evaluated by the Morris water maze, in association with synapse alterations in the CA3 hippocampal region (Yu et al., 2011; Dong et al., 2018). Consistently, we found fewer dendritic spines in CA1 hippocampal neurons, in association with the altered expression levels of post-synaptic and pre-synaptic proteins in hippocampal lysates of 9 M animals.

It has been reported that ARHL in C57BL/6 mice is accompanied by extensive reorganization of plasticity-related neurotransmitter expression in ACx and HP, and it is associated with altered hippocampal synaptic plasticity, memory impairments (Beckmann et al., 2020), as well as with changes in the response properties of ACx neurons in old mice (Bishop et al., 2022). In parallel, clinical evidence shows an increased incidence of cognitive dysfunctions in presbycusis patients (Panza et al., 2015; Fortunato et al., 2016; Su et al., 2017; Panza et al., 2019) with decreased functional connectivity between inferior parietal lobule, insula, right supplementary motor area, middle temporal gyrus, and HP (Chen et al., 2020), supporting the strong relationship between cognitive decline and sensory aging.

Like age-related hearing impairment, noise exposure has been widely associated with cognitive decline and dementia (Manukyan, 2022; Meng et al., 2022). Moreover, it has been suggested that both noise- and age-related hearing loss share common pathogenic pathways, involving the excess of free radicals, due to increased metabolic demands after noise overstimulation and metabolism dysregulation (Le Prell et al., 2007; Bielefeld et al., 2010; Huang and Tang, 2010; Fetoni et al., 2011; Shi, 2011; Yamasoba et al., 2013; Tavanai and Mohammadkhani, 2017; Fuentes-Santamaría et al., 2022). At the same time, noise exposure positively correlated with mild cognitive impairment (Tzivian et al., 2016; Weuve et al., 2021). Noise-exposed mice exhibit higher levels of p-Tau and lipofuscin in the HP (Cui et al., 2012; Li et al., 2014; Park et al., 2018), decreased neurogenesis (Kraus et al., 2010; Liu et al., 2016; Manohar et al., 2020) and brain alterations at the level of synapses, dendrites, and vascularization (Fetoni et al., 2013; Paciello et al., 2018; Fetoni et al., 2022). We previously demonstrated that exposure to noise in a pre-symptomatic phase can accelerate AD pathology with respect to the expected time-course of the disease, in the 3×Tg-AD mice, an established animal model of AD. We found that the noise exposure affected hippocampal functions, by increasing oxidative stress, inflammation, and molecular hallmarks of AD, such as Tau phosphorylation (Paciello et al., 2021). Of note, dementia-related pathological changes, such as brain increase in amyloid precursor protein and phosphorylated Tau protein levels, have been detected both in ARHL and NIHL (Park et al., 2018; Zheng et al., 2022).

Thus, taken together, literature data suggest a strong association between memory impairment and auditory damage induced by both noise and presbycusis insults. In this study, for the first time, we demonstrated that hearing loss induced by the association between NIHL and ARHL can affect a brain structure involved in memory functions, such as HP. Notably, we found a significant statistical correlation between auditory thresholds and Y-maze behavior in 6 and 9 M animals (Fig. S2), suggesting a link between hearing loss and memory impairment.

Looking for a molecular mechanism linking hearing and memory loss, we analyzed molecular changes in the HP of middle-aged (9 M) animals with severe memory impairment (Fig. 5). It is known that the HP participates in the processing of auditory information conveyed by the lemniscal and non-lemniscal paths (Steward, 1976; Germroth et al., 1989; Moxon et al., 1999; Budinger and Scheich, 2009; Munoz-Lopez et al., 2010; Zhang et al., 2018). Both pathways convey information from the cochlear nuclei to the HP, which is critically involved in spatial learning tasks (Adams et al., 2008). On the other hand, the HP can respond to acoustic stimuli as well as to visual and olfactory stimuli, as it processes such information to create spatial memories (Kemp and Manahan-Vaughan, 2008; André and Manahan-Vaughan, 2013; Dietz and Manahan-Vaughan, 2017). In this study, we found a decreased $pGluA1^{Ser845}$ in the HP of aged mice, indicating a decreased AMPAR stabilization at the plasma membrane and, potentially, a decreased channel conductance in the HP of mice exposed to noise at a young age compared to non-exposed age-matched animals. Such post-translational modification of GluA1 is known to stabilize glutamate receptors at dendrites (Kessels et al., 2009) and it is considered critical for sensory deprivation-induced homeostatic synaptic response and experience-dependent synaptic plasticity (He et al., 2009; Goel et al., 2011). The morphological and molecular synaptic alterations in the HP observed in the same animals, support this hypothesis. Indeed, we found a decreased spine density in CA1, the hippocampal region sending direct projection to the ACx (Cenquizca and Swanson, 2007). We also found decreased expression levels of crucial post-synaptic proteins involved in synaptic transmission and long-term potentiation, such as PSD-95 and CAMKII (Petersen et al., 2003), along with decreased levels of synaptophysin, a presynaptic membrane protein essential for neurotransmission and synaptic plasticity in the brain (Janz et al., 1999) that we previously

found to be affected in the ACx after chronic noise exposure (Paciello et al., 2018). Collectively, these data reflect a down-regulation of synaptic function and plasticity in the HP of noise-exposed animals.

It has been recently demonstrated that hearing loss induced by ototoxic drug administration increased inflammatory cytokine levels in the HP and induces neuronal death, in conjunction with an up-regulation of dementia-related protein expression (Shen et al., 2021). Similarly, we found oxidative/inflammatory damage in the HP of presbycusis noise-exposed animals, confirming a high vulnerability of this brain structure to neuroinflammatory insult caused by hearing loss. Neurons are seen as a crucial target of oxidative attacks (Di Domenico et al., 2017), and HP is particularly susceptible to oxidative stress damage (Venkateshappa et al., 2012; Shen et al., 2015). In line with these considerations, literature data allows us to hypothesize a key role of oxidative stress in determining hippocampal dysfunctions in our experimental model, considering that the alterations in redox balance are shared pathological features in age-related neurodegenerative diseases (Alvarado et al., 2022). Our data, showing a significant increase of ROS amount and lipid peroxidation, in conjunction with decreased expression of the endogenous antioxidant enzyme SOD2 and decreased level of glutathionylated proteins, indicate hippocampal redox imbalance. Moreover, the increased expression of neuroinflammatory markers, as well as astrocyte activation in the HP of noise-exposed animals, indicate a possible interplay between oxidative and inflammatory damage in the hippocampal injury induced by hearing loss, with an increase of oxidative stress that, in turn, can induce an inflammatory status, in a vicious cycle loop.

However, understanding the role of activated glial cells in mediating the crossroad between oxidative stress and neuroinflammatory processes needs further investigation. Indeed, the feedback loop between oxidative stress and neuroinflammation, probably mediated by glial cell activation, is a common feature of neurodegenerative pathology, including dementia and AD (González-Reyes et al., 2017; Ganguly et al., 2021; Bai et al., 2022), and the production of oxidizing free radicals, including ROS and reactive nitrogen species, can be induced by increased cytokine production (Naik and Dixit, 2011). Considering that, as discussed above, hearing loss is associated with a functional reorganization in all steps of the auditory pathway, such as the inferior colliculus (Willott, 1986; Caspary et al., 2008; Ouda and Syka, 2012), we cannot exclude that functional, morphological, and molecular changes observed here in ACx and HP are associated also with maladaptive modifications in the brainstem and midbrain nuclei of the auditory system. It could be interesting to address this issue in further studies, to better understand the impact of synaptic alterations across the auditory pathway, caused by early NIHL and ARHL, on memory function.

5. Conclusions

In conclusion, our data support the hypothesis that noise exposure and aging, by acting as risk factors, can cause memory impairment, showing a combined detrimental effect on central nervous system structures more vulnerable to both sensory and cognitive degeneration. At the molecular level, this involves the common pathological markers shared among noise, presbycusis, and memory dysfunction, such as oxidative stress and inflammation, targeting the HP, the brain structure involved in memory processes, and particularly vulnerable to oxidative/inflammatory insult induced by both noise and sensory aging. Considering that memory dysfunction is usually the first cognitive symptom of dementia (like AD) onset, from a translational point of view, our results support the hypothesis that associating auditory and memory screenings could represent a powerful non-invasive tool to potentially identify subjects with a high risk to develop dementia, allowing early diagnosis and treatment.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.nbd.2023.106024.

Funding

This work was supported by BRiC INAIL 2016-DiMEILA17 and INAIL Bando BRIC 09. Università Cattolica del Sacro Cuore contributed to the funding of this research project and its publication (D1, D3.1 intramural funds). Financial support of “Ricerca Corrente 2023” from Fondazione Policlinico Universitario “A. Gemelli” IRCCS to C.G. We would like to acknowledge the contribution of "Microscopy" Core Facilty G-STeP and the contribution of the Core Facility G-STeP "Electrophysiology",Fondazione Policlinico Universitario “A. Gemelli” IRCCS.

CRediT authorship contribution statement

Fabiola Paciello: Conceptualization, Data curation, Formal analysis, Investigation, Writing – original draft, Writing – review & editing. **Anna Pisani:** Formal analysis, Investigation, Methodology. **Marco Rinaudo:** Investigation, Methodology. **Sara Cocco:** Investigation. **Gaetano Paludetti:** Supervision, Funding acquisition. **Anna Rita Fetoni:** Conceptualization, Supervision, Validation, Writing - review & editing. **Claudio Grassi:** Conceptualization, Funding acquisition, Project administration, Supervision, Validation, Writing – review & editing.

Declaration of Competing Interest

The authors declare that no commercial or financial relationships that could be construed as a potential conflict of interest.

Data availability

The data included in the article are available from the corresponding authors.

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