UNIVERSITY OF CALIFORNIA,
IRVINE

Investigations into Neural and Perceptual Correlates of Tinnitus

DISSERTATION

submitted in partial satisfaction of the requirements
for the degree of

DOCTOR OF PHILOSOPHY

in Cognitive Sciences

by

Katie Elizabeth Turner

Dissertation Committee:
Professor Fan-Gang Zeng, Chair
Professor Bruce G. Berg
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2021

DEDICATION

To

my parents and grandparents

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ACKNOWLEDGEMENTS

I would like to thank my committee chair, Professor Fan-Gang Zeng, my other committee members Professor Bruce G. Berg and Professor Michael D'Zmura, along with additional advancement committee members Karina Cramer and Raju Metherate, and present and past lab members Michelle Kapolowicz, Yasmeen Hamza, Ye Yang, Jason Luo, Matthew Suh, Phillip Tran, Matthew Richardson, Omid Moshtaghi, Neil Saez, Tom Lu, Jamal Alsamri, and Carol Pham.

I would also like to thank the Center for Hearing Research and the American Academy of Otolaryngology–Head & Neck Surgery Foundation for funding, and the Journal of Neuroscience for permission to include published work in Chapter 2. Thanks also to the many listeners who volunteered to participate in the studies.

Vita

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2021 **Ph.D. (expected) Cognitive Sciences**, Cognitive Neuroscience Concentration
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RESEARCH EXPERIENCE

2014-present Graduate Student Researcher, Hearing and Speech Lab
Principal Investigator: Dr. Fan-Gang Zeng
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Research topics: tinnitus, hyperacusis, hearing in noise, age-related hearing loss

2014 Graduate Research Assistant (rotating), Brain Circuits Laboratory
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2011-2013 Research Assistant / Study Coordinator, Stanford Cancer Center
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Zeng FG, Richardson M, **Turner K** (2020). Tinnitus Does Not Interfere with Auditory and Speech Perception. *Journal of Neuroscience* 40 (31) 6007-6017; DOI: https://doi.org/10.1523/JNEUROSCI.0396-20.2020.

UNDER REVIEW / IN PREPARATION

Turner K, Moshtaghi O, Saez N, Richardson M, Zeng FG, Lin HW. Effects of age, gender, hearing and tinnitus on auditory brainstem responses: Challenges in translating animal synaptopathy to human hidden hearing loss. *Completed*

POSTER PRESENTATIONS

Zeng FG, Richardson M, **Turner K**. (2020). Tinnitus does not impair auditory perception. Poster presented at the 43rd Annual MidWinter Meeting of the Association for Research in Otolaryngology, San Jose, CA.

Turner K, Moshtaghi O, Saez N, Richardson M, Zeng FG, Lin HW. (2019). Effects of age, hearing loss, and tinnitus on auditory brainstem and perceptual responses. Poster presented at the 42nd Annual MidWinter Meeting of the Association for Research in Otolaryngology, Baltimore, MD.

Turner K, Moshtaghi O, Saez N, Richardson M, Zeng FG, Lin HW. (2018). Effects of age, hearing loss, and tinnitus on auditory brainstem and perceptual responses. Poster presented at the annual SoCal Hearing Conference, University of Southern California, Los Angeles, CA

Turner K, Richardson M, Zeng FG. (2017). Investigating Suprathreshold Deficits in Listeners with Hyperacusis. Poster presented at the 40th Annual MidWinter Meeting of the Association for Research in Otolaryngology, Baltimore, MD.

Richardson M, Saromo S, **Turner K**, Zeng FG (2017). Event-related Potentials of Tinnitus Listeners in a Selective-attention Task. Poster presented at the 40th Annual MidWinter Meeting of the Association for Research in Otolaryngology, Baltimore, MD.

Turner K, Kunz P, Pitsiouni M, Cho-Phan C, Kaiser H, Fisher G. (2011). Testing a New Form of Irinotecan: Is it More Effective, Less Toxic, Both, or Neither? Poster presented at the New Successes in Colorectal Cancer Treatments and Outcomes patient symposium, Stanford University, Stanford, CA

TALKS

Turner, K. (2018). Objective and Subjective Measures of Auditory Function in Tinnitus. Presented at the Cognitive Sciences Graduate Student Presentation Bonanza, UCI Department of Neurobiology and Behavior, Irvine, CA

Turner, K. (2018). Objective and Subjective Measures of Auditory Function in Tinnitus. Presented at the Neuroblitz seminar series, UCI Department of Neurobiology and Behavior, Irvine, CA

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AWARDS AND HONORS

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INSTITUTIONAL AND ACADEMIC SERVICE

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2019 Journal of the Acoustical Society of America: review of application for journal article publication
2016 Hearing Research: review of application for journal article publication
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2014 Hearing Research: review of application for journal article publication

COMMUNITY OUTREACH

2016-2019 Lab workshop leader, UCI School of Medicine Summer Premed Program (pre-medical camp for high school students)
2019 Guest presenter, Orange County Tinnitus & Hyperacusis Self-Help Group
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2016 Guest presenter, Irvine Taiwanese Presbyterian Church Evergreen Class
2016 Lab workshop leader, COSMOS (science/math camp for high school students)
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TECHNICAL SKILLS

Computer Skills: MATLAB, SPSS, Excel
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ABSTRACT OF THE DISSERTATION

Investigations into Neural and Perceptual Correlates of Tinnitus

by

Katie Elizabeth Turner

Doctor of Philosophy in Cognitive Sciences

University of California, Irvine, 2021

Professor Fan-Gang Zeng, Chair

Tinnitus, commonly known as "ringing in the ears", is a perception of sound without physical sound stimulation. While anybody can experience tinnitus, it commonly co-occurs with hearing loss, noise exposure, and older age. The first chapter explores the auditory brainstem response (ABR) as a potential marker for human cochlear synaptopathy, a type of "hidden hearing loss" that has been hypothesized to underlie tinnitus in listeners with clinically normal hearing. Age and hearing loss produced the expected differences in ABR measurements, but tinnitus did not produce significant differences, suggesting the clinical utility of ABR as a human biomarker for tinnitus or cochlear synaptopathy is limited. The second chapter investigates the relationship between tinnitus and external sounds; while many individuals with tinnitus complain about hearing difficulty, these same individuals often have other conditions such as hearing loss, and the relationship between tinnitus itself and external sound perception has received limited study. After controlling for age and hearing loss, listeners with tinnitus performed similarly or in some cases even better than those without tinnitus. An attention-normalization model, where attention is shared between a top-down perceptual process for tinnitus and bottom-up perception of external

sounds, can both explain discrepancies between objective and subjective hearing experiences and account for the possibility that chronic tinnitus could increase auditory attention for certain low-level stimuli and actually lead to improved performance. The third chapter directly examines and models loudness perception of external sounds for listeners with and without tinnitus; at threshold, particularly, listeners with tinnitus report greater loudness perception. This is consistent with the idea that tinnitus reflects increased central noise as one aspect of overcompensation to hearing loss.

CHAPTER 1

Effects of sex, age, hearing, tinnitus and noise exposure on human auditory brainstem responses

Abstract

Cochlear synaptopathy is well established in animals, showing typically normal auditory brainstem responses (ABR) at thresholds but reduced ABR wave I amplitude at suprathreshold levels. In humans, cochlear synaptopathy has been conjectured to contribute to hearing difficulty and other auditory disorders such as tinnitus and hyperacusis that cannot be easily accounted for by threshold elevation. The present study measured ABR to clicks, 1000, 4000 and 8000-Hz tones at 30, 50 and 70 dB nHL in 43 human subjects with different sex, age, hearing, tinnitus and noise exposure status. Age and hearing loss were positively correlated, but neither was correlated with tinnitus severity. Statistical analysis of eight ABR parameters, including wave I and V amplitude and latency, V/I amplitude ratio, V-I latency difference, and I and V amplitude slopes, found a significant difference in six parameters between young and old and five between normal hearing and hearing impaired, but none for sex, tinnitus and noise factors. The ABR effect size, defined as the ratio between the mean difference and the standard deviation of two distributions, was medium for age (0.66) and hearing (0.65) but small for sex (0.15), tinnitus (0.18) and noise (0.17). The effect size analysis on individual ABR parameters showed that tinnitus affected ABR latency more than amplitude whereas noise exposure had the opposite effect. The overall small effect size implies that the ABR clinical utility is limited in detecting human hearing disorders such as tinnitus, hyperacusis or noise-induced cochlear synaptopathy.

Introduction

The auditory system consists of delicate sensory and neural organs that use mechanical, chemical and electrical processes to achieve exquisite functions from detecting nanometer acoustic vibrations to discriminating 1-Hz frequency or 10-μs timing differences (Hudspeth, 1997). These delicate structures or processes are susceptible to both biological and environmental factors from aging and genetics to noise and drugs, which may lead to various types of hearing deficits. Recent animal research has identified a new type of auditory disorder, termed cochlear synaptopathy, which may be caused by even moderate noise exposure (Kujawa and Liberman, 2009; Fernandez *et al.*, 2015). Cochlear synaptopathy typically does not involve outer hair cell damage, but rather is associated with swollen synapses between the inner hair cells and auditory nerve fibers, causing secondary nerve injury predominantly (but not solely) in the low-spontaneous-rate nerve fibers (Furman *et al.*, 2013). As a result, cochlear synaptopathy can be associated with normal otoacoustic emissions and auditory brainstem response (ABR) thresholds but reduced slope of the wave I input-output function (Kujawa and Liberman, 2009; Lin *et al.*, 2011; Lobarinas *et al.*, 2017; Johannesen *et al.*, 2019).

Cochlear synaptopathy can contribute to the so-called hidden hearing loss, which may not be detected by the conventional audiometric threshold test (Schaette and McAlpine, 2011). Cochlear synaptopathy may also be present when hearing thresholds are permanently elevated and contribute additionally to hearing difficulty in age- or noise-induced hearing loss (Fernandez *et al.*, 2015; Hesse *et al.*, 2016; Parthasarathy and Kujawa, 2018). At present, a clear relationship has not been convincingly demonstrated between reduced wave I amplitude and noise exposure in human subjects (Stamper and Johnson,

2015; Bramhall *et al.*, 2017; Grinn *et al.*, 2017; Grose *et al.*, 2017; Guest *et al.*, 2017; Guest *et al.*, 2018; Skoe and Tufts, 2018; Valderrama *et al.*, 2018; Bramhall *et al.*, 2019; Chen *et al.*, 2019; Johannesen *et al.*, 2019).

Cochlear synaptopathy has attracted much attention because it may underlie tinnitus and hyperacusis (e.g., Liberman and Kujawa, 2017; Bramhall *et al.*, 2019). The basic idea is that reduced peripheral input increases central noise, central gain, or both (Kaltenbach, 2011; Eggermont, 2012; Knipper *et al.*, 2013; Hickox and Liberman, 2014; Chambers *et al.*, 2016; Salvi *et al.*, 2016). The increased central activities do not necessarily elevate hearing thresholds, but may cause tinnitus and hyperacusis (Schaette and Kempter, 2006; Parra and Pearlmutter, 2007; Schaette and Kempter, 2008; Norena, 2011; Schaette and Kempter, 2012; Zeng, 2013). Recent human studies have provided some support for a cochlear synaptopathy link to tinnitus and hyperacusis. Compared with normal hearing controls, listeners with tinnitus showed reduced wave I but normal or even increased wave V amplitudes (Schaette and McAlpine, 2011; Gu *et al.*, 2012). In addition, reduced wave I amplitude also increased the risk of tinnitus in a group of young veterans and non-veterans with normal audiograms (Bramhall *et al.*, 2018). However, several studies found that tinnitus did not decrease wave I amplitude (Guest *et al.*, 2017; Shim *et al.*, 2017) but increased the V/I amplitude ratio (Valderrama *et al.*, 2018) or V-I latency difference (Omidvar *et al.*, 2018).

At present, a variety of non-invasive measures have been proposed to investigate whether noise-induced synaptopathy occurs in humans, but produce conflicting results (Liberman *et al.*, 2016; Mehraei *et al.*, 2016; Plack *et al.*, 2016; Grose *et al.*, 2017; Hickox *et al.*, 2017; Kobel *et al.*, 2017; Barbee *et al.*, 2018; Bramhall *et al.*, 2019; Guest *et al.*, 2019; Le

Prell, 2019). There are several hurdles in translating animal research into human clinical practice. First, ABRs obtained with invasive subdermal electrodes in animals have much higher signal-to-noise ratios than that with non-invasive skull electrodes in humans, making reliable estimates of wave I amplitude more difficult in humans than in animals. For comparison, Kujawa and Liberman (2009) needed only 512 averages to obtain ~3μV wave I amplitude for tone bursts presented at 90 dB SPL, whereas Schaette and McAlpine (2011) used more than 8000 averages to obtain ~0.1μV amplitude for clicks presented at 90 dB peak SPL. Second, there is a frequency-dependent tradeoff between the stimulus onset time and its spectral splatter. In high-frequency hearing in animals such as mice, tone bursts can have short onset time with relatively narrow spectral splatter, allowing for powerful within-subjects, place-specific comparisons, e.g., between the 12kHz control and the 32kHz place where cochlear synaptopathy was present (Kujawa and Liberman, 2009). Such place-specific ABRs are difficult to obtain in humans with relatively low-frequency hearing, requiring complicated stimulus design and signal processing to make meaningful comparisons, e.g., between 1kHz and 5kHz (Don and Eggermont, 1978; Gorga *et al.*, 2006). Third, animal studies minimized subject variables such as age, sex, genetics, hearing, noise exposure and even weight (e.g., Lin *et al.*, 2011), whereas human studies did not always carefully control for the effect of those variables. For example, tinnitus and hyperacusis are frequently comorbid, with approximately half of tinnitus patients also suffering from hyperacusis (Schecklmann *et al.*, 2014). Tinnitus is more common in men than women and increases in prevalence with age, noise exposure and hearing loss (Lockwood *et al.*, 2002). While it is important to control subject variables for research purposes, e.g., using only men or only women, or subjects with tinnitus but no hearing loss (Schaette and McAlpine, 2011;

Gu *et al.*, 2012), it is often difficult to avoid this great subject variability in the general population. In fact, these subject variables need to be taken into account in order to develop a sensitive yet specific clinical diagnosis for any auditory disorder.

The present study aimed to evaluate the effect of five independent subject variables including sex, age, hearing loss, tinnitus and noise exposure on human ABRs to click and tone stimuli presented at different levels. Eight ABR amplitude and latency parameters were measured as dependent variables. If cochlear synaptopathy played a major role in humans as conjectured by animal studies, then tinnitus or noise exposure would reduce wave I but not wave V amplitude slope, especially in those who had tinnitus or noise exposure but no hearing loss. In addition, the five subject variables were categorized into binary groups (i.e., female vs. male, young vs. old, normal vs. hearing loss, no tinnitus vs. tinnitus, and no noise exposure vs. noise exposure). The effect size of these variables, defined as the ratio between the mean difference and the standard deviation of the binary groups, was obtained for each of the eight ABR parameters. Finally, the ABR parameters were correlated with tinnitus and hyperacusis severity measures to investigate underlying mechanisms and potential biomarkers for these hearing disorders.

Methods

Subjects

The University of California Irvine Institutional Board approved the human subject protocol. A total of 43 human subjects, including 16 women and 27 men, participated in the present study. Written informed consent was obtained from all subjects. All subjects filled a general screening form, asking for personal and contact information, additionally

audiological and medical information including tinnitus ("ringing in the ears"), hyperacusis ("sensitivity to sound"), hearing loss, noise exposure history, existing medical conditions and medications. Those who reported tinnitus filled additional tinnitus and hyperacusis surveys and matched their tinnitus to external sounds (Newman *et al.*, 1996; Khalfa *et al.*, 2002; Folmer *et al.*, 2004; Reavis *et al.*, 2012; Henry *et al.*, 2016). Table 1 shows individual demographic and tinnitus related information for all tinnitus subjects as well as the group information between tinnitus and control subjects. These subjects were divided into the young group (n=22, 21-41 years old) or the old group (n=21, 47-77 years old), the normal-hearing group (n=24, thresholds≤20 dB HL at all audiometric frequencies between 125 and 8000Hz) or the hearing-impaired group (n=19, thresholds≥25 dB HL at any frequencies), and the tinnitus group (n=21) or the non-tinnitus group (n=22). Based on questionnaires asking whether a subject answered yes to any of the three questions: (1) Occupational Noise Exposure (ex. construction), (2) Recreational Noise Exposure (ex. concerts, shooting range), and (3) Military Noise Exposure (ex. tanks, aircraft, or weapons), the subject was then classified into a YES (n=22) or NO (n=16) noise exposure group; five subjects didn't answer these questions and were classified as Not Available (NA) and their data were not included in the noise vs. no noise analysis. Tinnitus index and hyperacusis index were normalized with 0 representing no symptom and 100 the maximal symptom. On average, the 21 tinnitus subjects had a tinnitus index of 35 (sd=19) and a hyperacusis index of 34 (sd=20). The likely tinnitus etiology was noise (n=13), trauma (n=1), sudden hearing loss (n=1), ear infection (n=1), or unknown (n=5). None of the tinnitus subjects reported Meniere's disease, otosclerosis, or acoustic neuroma.

Table 1. Tinnitus subject demographics.
The 21 subjects had tinnitus for 5 months or longer. In addition to sex (F=women; M=men), they were classified as young (21-41 years old) or old (47-77), normal-hearing (thresholds≤20 dB HL at all audiometric frequencies) or hearing-impaired (thresholds≥25 dB HL at any frequencies), no noise exposure or yes to military, recreational, or occupational noise (NA=Not Available). TI=Tinnitus Index, which was the average of Tinnitus Functional Index, Tinnitus Severity Index and Tinnitus Handicap Index. HI=Hyperacusis Index, which was based on the Khalfa Hyperacusis Questionnaire. Both TI and HI scores were normalized to 100. Tinnitus etiology and description were gathered from questionnaire, interview, and tinnitus match if available. The bottom two rows show aggregated information for tinnitus (T) and control (C or non-tinnitus) subjects, respectively. The mean and one standard deviation values are also present for Years, TI and HI.

#	Sex	Age	Years	Hearing	Noise	TI	HI	Etiology	Description
1	F	Young	21	Normal	No	35	14	Vertigo	Bilateral (RE>LE), tonal pulsing
2	F	Young	21	Normal	NA	25	NA	Unknown	Bilateral, tonal (3602 Hz)
3	M	Young	22	Normal	Yes	86	48	Noise	Bilateral, tonal (17000Hz)
4	F	Young	25	Loss: Mild	Yes	37	36	Noise Trauma	L only, tonal (6736 Hz)
5	M	Young	25	Normal	Yes	25	29	Noise	R only, tonal (7035 Hz)
6	M	Young	27	Normal	Yes	16	2	Noise	Bilateral, tonal
7	M	Young	31	Normal	Yes	19	29	Noise	Bilateral, tonal
8	M	Young	35	Loss: Mild	Yes	41	79	Noise	Bilateral, tonal
9	M	Young	36	Normal	No	40	NA	Unknown	R only, tonal+pulsing+buzzing
10	M	Young	39	Normal	No	11	5	Unknown	L only, tonal
11	M	Young	41	Loss: Sloping	No	52	33	Sudden loss	Bilateral (L>R), tonal (5825 Hz)+nontonal
12	M	Old	47	Loss: Mild	Yes	35	45	Noise	Bilateral, tonal + nontonal
13	F	Old	52	Normal	No	29	31	Infection	Bilateral, tonal (527 Hz)+nontonal
14	F	Old	52	Normal	Yes	66	64	Noise	Bilateral, tonal
15	M	Old	56	Loss: Sloping	Yes	30	7	Noise	Bilateral, tonal (5400 Hz)
16	M	Old	57	Loss: Sloping	Yes	18	36	Noise	Bilateral, tonal+pulsing
17	M	Old	57	Loss: Sloping	Yes	35	26	Noise	Bilateral, nontonal
18	F	Old	60	Loss: Sloping	Yes	17	52	Noise	Bilateral, tonal
19	F	Old	60	Normal	Yes	55	48	Noise	Bilateral, tonal (6164 Hz in R)+nontonal
20	F	Old	65	Normal	No	15	29	Vertigo	Bilateral (RE>LE), tonal (5686 Hz)+nontonal
21	M	Old	70	Loss: Sloping	Yes	46	31	Noise	Bilateral (RE<LE), 9036-9845Hz noise

T	**8F**	**11Y**	**43±16**	**12Normal**	**6No**	**35 ±19**	**34 ±20**
21	**13 M**	**10O**		**9Loss**	**14Y**		
					1NA		
C	**8F**	**11Y**	**44±24**	**16Normal (11Y+5O)**	**10No**		
22	**14 M**	**11O**			**8Y**		
				6Loss (6O)	**4NA**		

Tests included pure-tone thresholds, uncomfortable loudness levels (ULLs), and auditory brainstem responses. All testing took place in a double-walled, sound-attenuated booth. For subjects without tinnitus, the ear with better thresholds was tested. For subjects with unilateral tinnitus, the tinnitus ear was tested. For subjects with bilateral tinnitus, the ear with more severe tinnitus was tested unless that ear had hyperacusis or hearing loss that prevented effective testing, in which case the other ear with less severe tinnitus was used.

Thresholds and Uncomfortable Loudness Levels (ULLs)

A GSI G1 clinical audiometer with TDH-50P headphones was used to obtain pure-tone (0.5-1 sec in duration) thresholds and ULLs in all 43 subjects at octave frequencies from 125 Hz to 8000 Hz, plus 12000 Hz. The threshold was defined as the pure-tone level in decibels Hearing Level (dB HL) at which the subject correctly detected the presence of the pure tone 2 of 3 times. ULLs were measured in 14 of the 22 non-tinnitus and 16 of 21 tinnitus subjects. The missing ULL data were due to non-inclusion of this test in the initial phase of the study. An ascending method of limits was used to increase the level in 5 dB steps of a pure-tone from threshold with the following instruction: “When you hear a tone, let me know by clicking a hand-held button if it's okay to get a little louder so that you will hear the next tone. When the tone reaches uncomfortably loud, do NOT click any button and let me know to stop.” The level at which the subject stopped was recorded as the ULL.

Auditory Brainstem Responses

Auditory brainstem responses were acquired using the Bio-logic AEP system (version 6.2.1.1(d)), with a 580-NAVPR2 Navigator Pro collection box. A Natus Jelly Tab Sensor electrode was placed on the high forehead and a tiptrode was placed in each ear canal (Bauch and Olsen, 1990; Bramhall *et al.*, 2015; Prendergast *et al.*, 2018). The skin area was prepared with alcohol and Nuprep gel such that impedance for all electrodes was ≤5 kOhms. The subject was seated in a recliner and instructed to remain still and relax as much as possible. Stimuli were presented via Bio-logic insert earphones and comprised 100-μs clicks and 3 tone bursts (1000 Hz, 4000 Hz, and 8000 Hz). Tone bursts had a rise and fall time of 0.5 ms (Blackman window) and a plateau of 4 ms. All stimuli were presented at a rate of 10.3/s, with alternating polarity, and at 30, 50, and 70 dB nHL presentation levels. These dB nHL values corresponded to 55, 75, and 95 dB peak SPL, respectively, for a continuous 1000-Hz tone calibrated by a sound level meter. For each stimulus, at each sound level, 8000 repetitions were obtained to an averaged ABR waveform. The recording epoch was 21.33 ms, beginning 5 ms prior to stimulus, with 512 sampling points recorded. Gain was set at 100,000 and the waveform was bandpass filtered between 3 and 5000 Hz. Any waveform with amplitude greater than 23.80 μV was rejected as artifacts. The numbers of accepted and rejected waveforms were monitored during collection. In case of excessive artifact occurrences, which were usually caused by the subject's movement, the subject was repositioned or given a break.

The recorded ABR waveform was imported into Matlab (version 2016b) for additional off-line processing. Direct current drift was removed by subtracting a linearly fitted line based on individual epochs (i.e., detrend.m in Matlab). A waveform baseline was defined as the average of the 4 ms prior to stimulus presentation. Following Gu et al.

(2012), wave I amplitude was defined as the difference between the wave I peak and following trough, while wave V amplitude was defined as the wave V peak (which was usually the largest peak) minus the baseline. Latency was defined as the duration between the onset of stimulus and the wave peak time. Two experienced observers visually identified the wave amplitudes and latencies. In cases of disagreement, a third observer was used to make the final determination.

Data Analysis

The following four direct ABR parameters were analyzed, including:

- wave I amplitude (μV – difference between the first peak and the following trough)
- wave I latency (ms – difference between the stimulus onset and the first peak)
- wave V amplitude (μV – difference between the largest peak and the baseline)
- wave V latency (ms– difference between the stimulus onset and the largest peak)

An additional four derived ABR parameters were analyzed, including:

- V-I latency (ms– difference between wave V and I latencies)
- V/I amplitude ratio (unitless– wave V amplitude over wave I amplitude with the ratio being logarithmically transformed to conform to normal distribution)
- wave I slope (μV /dB – obtained by a linear fit of wave I amplitude as a function of stimulus levels from 30 to 70 dB nHLs)
- wave V slope (μV /dB – obtained by a linear fit of wave V amplitude as a function of stimulus levels from 30 to 70 dB nHLs)

Both within-subjects and between-subjects analysis of variance (ANOVA) was performed for the above eight ABR parameters. The within-subjects factors included stimulus type (clicks and tone bursts) and stimulus levels (30, 50, and 70 dB nHL). The between-subjects factors included sex, age, hearing, tinnitus and noise exposure status. Should the main effect or interactions produce a significant difference, post-hoc two-tailed t-test assuming equal variance and without correction was used to identify the specific significant stimuli or variables.

The effect size of sex, age, hearing, tinnitus and noise status was calculated for each of the eight ABR parameters. The effect size was defined as the mean difference of two groups over their standard deviation:

$$\text{Effect size} = d' = \frac{m_1 - m_2}{\sigma}$$

Where m_1 was the mean of distribution 1 and m_2 the mean of distribution 2, whereas was the standard deviation of the distribution. In general, 0.2 was considered as a small effect size, 0.5 as medium, and 0.8 as large (Cohen, 1969). Finally, tinnitus severity, as well as hyperacusis severity, was correlated with all ABR parameters to investigate underlying mechanisms and potential biomarkers for tinnitus and hyperacusis.

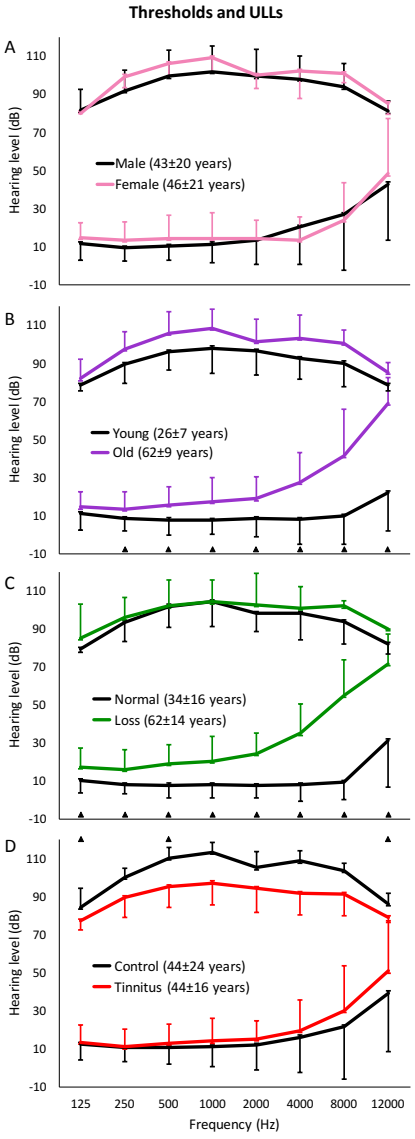
Results

Thresholds and Uncomfortable Loudness Levels (ULL)

Figure 1 shows average thresholds (bottom lines) and uncomfortable loudness levels (top lines) as a function of frequency, grouped by sex (A), age (B), hearing (C), tinnitus (D), and noise exposure (E). Fig. 1A shows that sex produced no significant difference for either thresholds [F(1,40)=0.49, p=0.49] or ULLs [F(1,16)=0.02, p=0.89]. Fig.

1B shows that the old group had overall 17-dB significantly higher thresholds than the young group [$F(1,40)=36.27$, $p<0.001$], at all frequencies [two-tailed t-test (df=41), $p<0.05$] except for 125 Hz, but there was no significant differences in ULLs between the young and old groups [$F(1,16)=1.04$, $p=0.32$]. Fig. 1C shows that the hearing-impaired group had 21-dB significantly higher thresholds than the normal-hearing group [$F(1,40)=79.80$, $p<0.001$] at all frequencies [two-tailed t-test (df=41), $p<0.05$], but there was no difference in ULLs between the normal and impaired groups [$F(1,16)=0.11$, $p=0.74$]. Opposite to the pattern of results for the age and hearing factors, Fig. 1D shows that tinnitus produced no significant difference in thresholds [$F(1,40)=1.26$, $p=0.27$], but a 8-dB significantly lower ULLs for the tinnitus group than the control group [$F(1,16)=6.50$, $p=0.02$] at 250, 500, 1000, 4000 and 8000 Hz [two-tailed t-test (df=41), $p<0.05$]. Fig. 1E shows that noise exposure produced no significant difference in either thresholds [$F(1,36)=0.03$, $p=0.87$] or ULLs [$F(1,15)=0.10$, $p=0.76$].

Figure 1. Average pure-tone thresholds (bottom lines in each panel) and uncomfortable loudness levels (ULLs: top lines in each panel) in dB HL as a function of frequency at octave frequencies from 125 Hz to 8000 Hz, plus 12000 Hz. Subjects were grouped by sex (A), age (B), hearing (C), tinnitus (D), and noise exposure (E), with the average age and standard deviation being noted in each panel. Error bars represented one standard deviation of the mean, with either an upward or downward bar showing for one group. Solid triangles indicated a significant difference at test frequencies.



Sex Effect

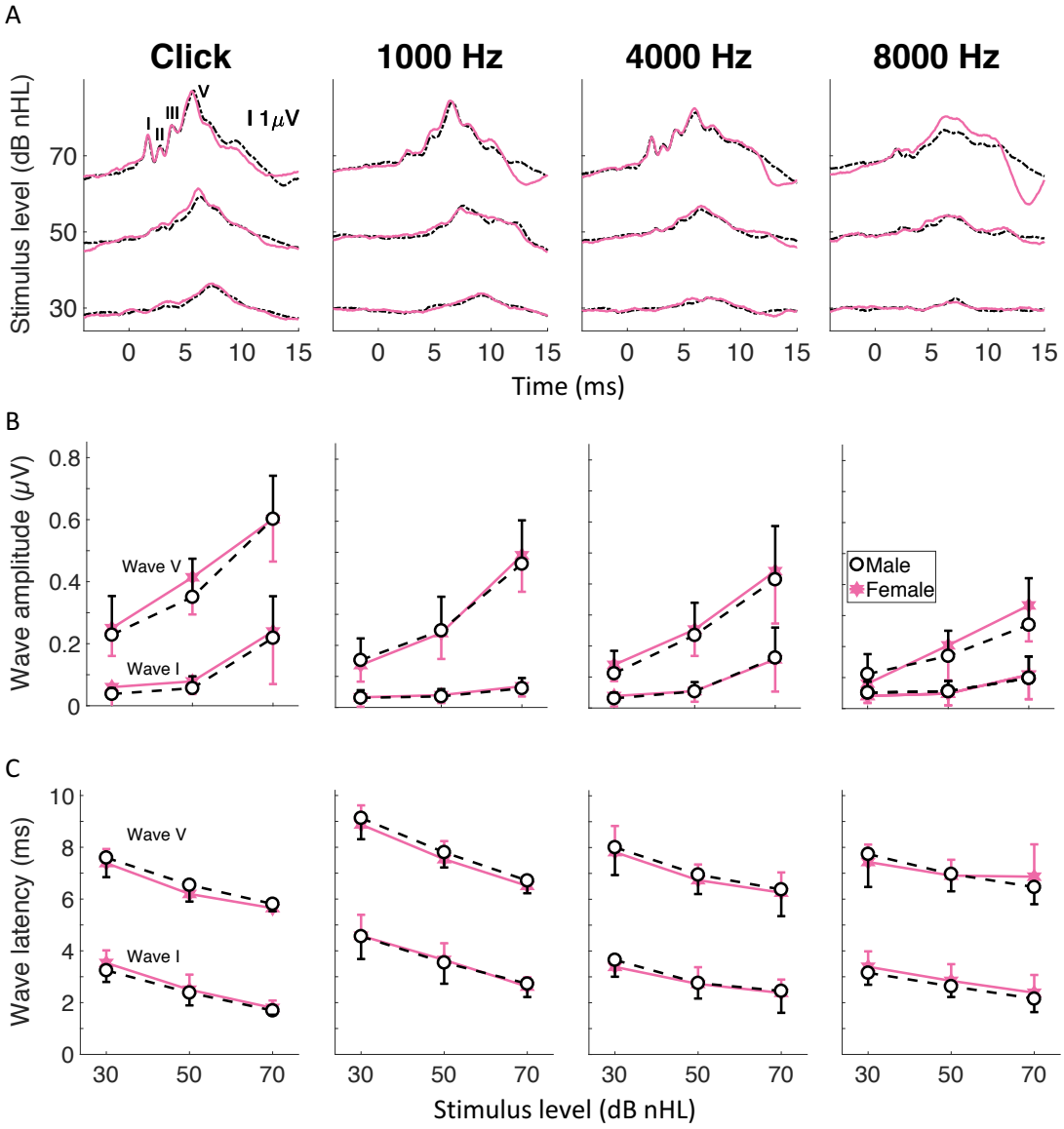
Figure 2 contrasts the ABR waveforms (A), wave amplitude (B), and latency (C) between men (black dashed lines or symbols) and women (pink solid lines or symbols) subjects. Figure 2A shows the averaged ABR waveforms as a function of time (x-axis) and stimulus level (individual traces representing 30, 50 and 70 dB nHL from bottom to top) for clicks, 1000-, 4000-, and 8000-Hz tone bursts (panels from left to right). Both men and

women produced well-identified waveforms in response to the 70-dB stimuli (see labeled waves on the top trace in the top-leftmost panel). Figure 2B shows the mean amplitude (lines) and one standard deviation (error bars) for wave I (bottom traces) and wave V (top traces) as a function of stimulus level between men and women. Figure 2C shows the same data for wave I and wave V latencies.

All within-subjects effects were highly significant for the stimulus level and type factors. First, averaged across the four stimulus types, wave I amplitude increased monotonically from 0.037μV at 30 dB to 0.145μV at 70 dB nHL [$F(2,52)=63.68$, $p<0.001$], while wave V amplitude increased from 0.163μV at 30 dB to 0.483μV at 70 dB nHL [$F(2,46)=535.39$, $p<0.001$]. Second, averaged across the three stimulus levels, clicks produced the largest wave I amplitude (0.120μV), followed by the 4000-Hz (0.084μV), 8000-Hz (0.067μV), and 1000-Hz (0.045μV) tones [$F(3,78)=29.10$, $p<0.001$], while wave V amplitude was also the largest for the click (0.440μV), followed by the 1000-Hz (0.303μV), 4000-Hz (0.286μV), and 8000-Hz (0.212μV) tones [$F(3,69)=78.07$, $p<0.001$]. Third, averaged across stimulus types, wave I latency decreased monotonically from 3.76ms at 30 dB to 2.20ms at 70 dB nHL [$F(2,52)=277.19$, $p<0.001$], while wave V latency from 7.90ms at 30 dB to 6.18ms at 70 dB nHL [$F(2,50)=288.38$, $p<0.001$]. Fourth, averaged across stimulus levels, clicks produced the shortest wave I latency (2.49ms), followed by the 8000-Hz (2.75ms), 4000-Hz (2.84ms), and 1000-Hz (3.55ms) tones [$F(3,78)=34.71$, $p<0.001$], while wave V latency was also the shortest for the click (6.39ms), but followed by the 4000-Hz (6.83ms), 8000-Hz (6.98ms), and 1000-Hz (7.71ms) tones [$F(3,75)=35.88$, $p<0.001$]. Because these significant within-subjects effects were the same for other group comparisons, they would not be repeated in the remaining Results sections.

Between-subjects analysis showed that sex produced no significant effect on any of the four primary ABR wave parameters, namely the amplitude and latency for both wave I and wave V [$F(1,26) \leq 1.39$, $p \geq 0.25$]. Sex did not make any difference in any of the four derived parameters either, including the I-V latency difference [$F(1,25)=2.83$, $p=0.11$], V/I amplitude ratio [$F(1,22)=3.46$, $p=0.08$], wave I amplitude slope [$F(1,39)=0.000$, $p=0.996$], and wave V amplitude slope [$F(1,39)=1.33$, $p=0.26$].

Figure 2. Mean ABR waveforms (A), wave amplitude (B), and latency (C) functions in response to click, 1000-, 4000-, and 8000-Hz tone bursts (individual panels from left to right), in men (black lines and symbols) and women (pink lines and symbols) subjects. The ABR waveforms included three stimulus levels (*y*-axis) with a vertical black scale bar representing 1μV and labels representing wave I, II, III and V in the "Click" or top-leftmost panel. Error bars represented one standard deviation of the mean, with either an upward or downward bar showing for each group.

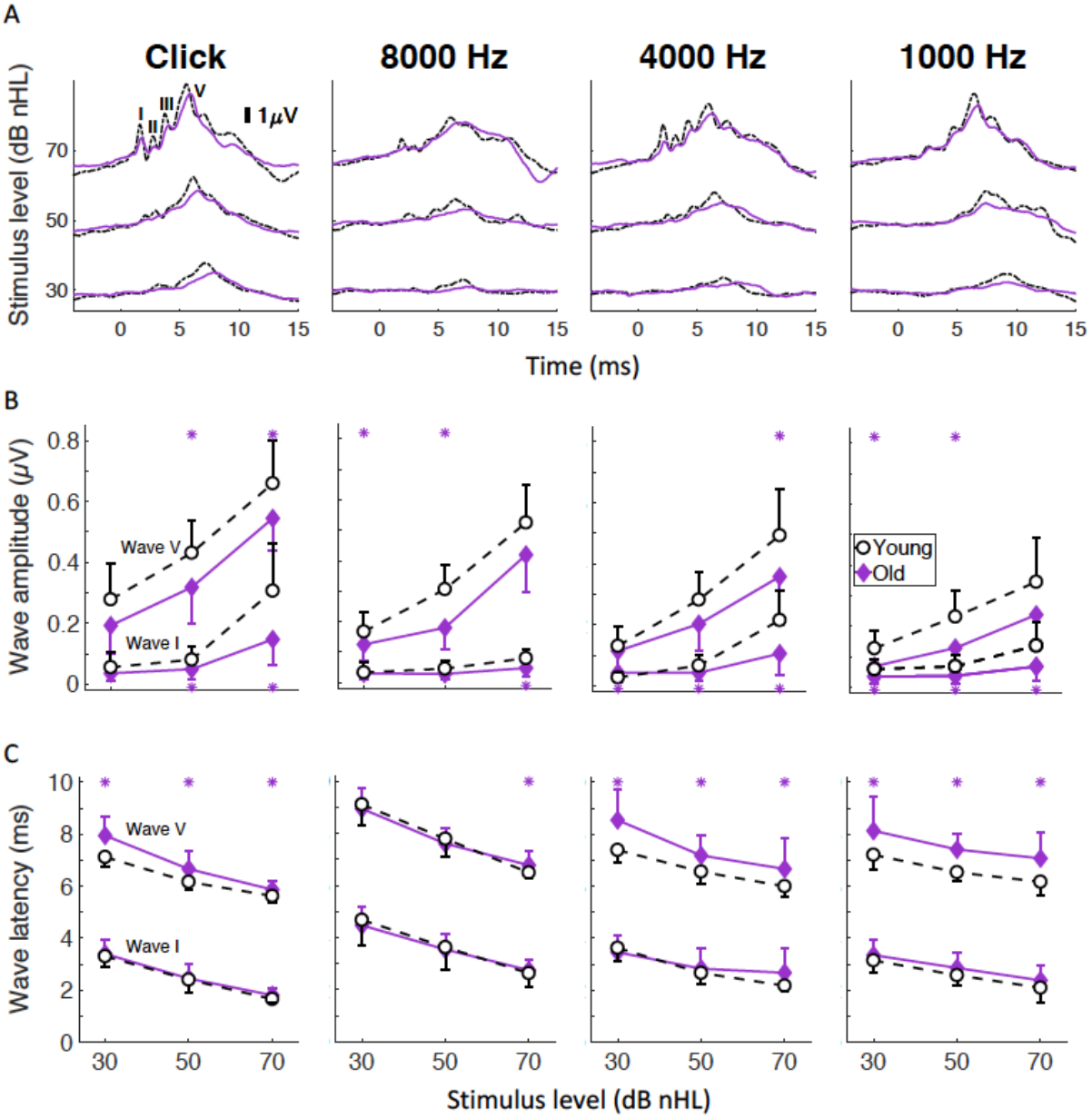


Age Effect

Figure 3 contrasts the ABR waveforms (A), wave amplitude (B), and latency (C) between the young (black dashed lines or symbols) and old (purple solid lines or symbols) subjects. Age produced a significant effect on three primary ABR wave parameters. Compared with the young group, the old group produced 50% smaller wave I amplitude [0.05 vs 0.10μV; $F(1,26)=31.86$, $p<0.001$], 17% smaller wave V amplitude [0.28 vs 0.33μV;

F(1,23)=5.64, p=0.03], and 6% longer wave V latency [7.24 vs 6.80ms; F(1,25)=8.7, p=0.007]. There was no significant difference in wave I latency between the old and young groups [2.98 vs 2.83ms; F(1,25)=2.51, p=0.13]. Age also produced a significant effect on three derived parameters: Compared with the young group, the old group had 26% larger V/I amplitude ratio [7.30 vs 5.78; F(1,22)=4.45, p=0.046], 7% longer V-I latency difference [4.27 vs 3.99ms; F(1,25)=5.48, p=0.03], and 67% shallower wave I amplitude slope [0.001 vs 0.003μV/dB; F(1,39)=16.44, p<0.001]. There was no significant difference in wave V amplitude slope between the young and old group [0.006 vs 0.008μV/dB; F(1,39)=3.92, p=0.06].

Figure 3. Mean ABR waveforms (A), wave amplitude (B), and latency (C) functions in response to click, 1000-, 4000-, and 8000-Hz tone bursts in young (black lines and symbols) and old (purple lines and symbols) subjects. The labels, lines and symbols are the same as Fig. 2, except for asterisks representing a significant difference between the two groups of subjects.

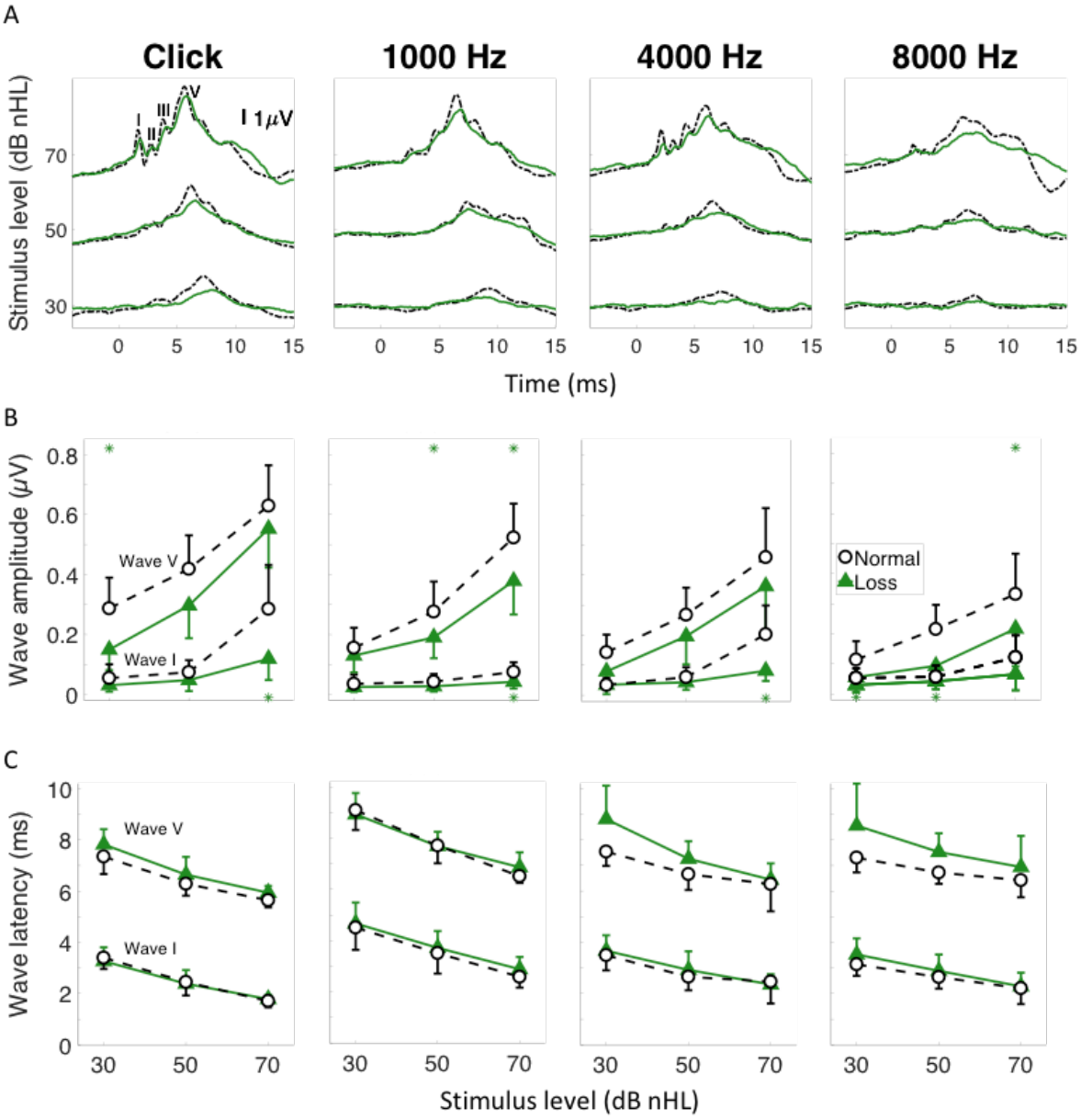


Hearing Effect

Figure 4 contrasts the ABR waveforms (A), wave amplitude (B), and latency (C) between normal-hearing (dashed black lines or symbols) and hearing-impaired subjects (solid green lines or symbols). The results were similar to those produced by the age factor, except for the V/I amplitude ratio. Compared with the normal-hearing group, the hearing-

impaired group produced 50% smaller wave I amplitude [0.05 vs 0.10μV; $F(1,25)=34.23$, $p<0.001$], 26% smaller wave V amplitude [0.26 vs 0.35μV; $F(1,24)=21.34$, $p<0.001$], and 6% longer wave V latency [6.89 vs 6.48ms; $F(1,24)=7.83$, $p=0.01$], but no significantly different wave I latency [2.96 vs 2.85ms; $F(1,25)=1.28$, $p=0.27$]. Second, different from the age factor, the impaired group did not produce a significant larger V/I amplitude ratio than the normal group [0.69 vs 0.68; $F(1,22)=0.03$, $p=0.86$]. Similar to the age factor, the impaired group had 8% longer V-I latency difference [4.31 vs 3.99ms; $F(1,24)=7.30$, $p=0.01$], 67% shallower wave I amplitude slope [0.001 vs 0.003μV/dB; $F(1,38)=19.21$, $p<0.001$], and no significant difference in wave V amplitude slope [0.007 vs 0.008 μV/dB; $F(1,38)=1.91$, $p=0.18$].

Figure 4. Mean ABR waveforms (A), wave amplitude (B), and latency (C) functions in response to click, 1000-, 4000-, and 8000-Hz tone bursts in normal-hearing (black lines and symbols) and hearing-impaired (green lines and symbols) subjects. The labels, lines and symbols are the same as Fig. 2, except for asterisks representing a significant difference between the two groups of subjects.

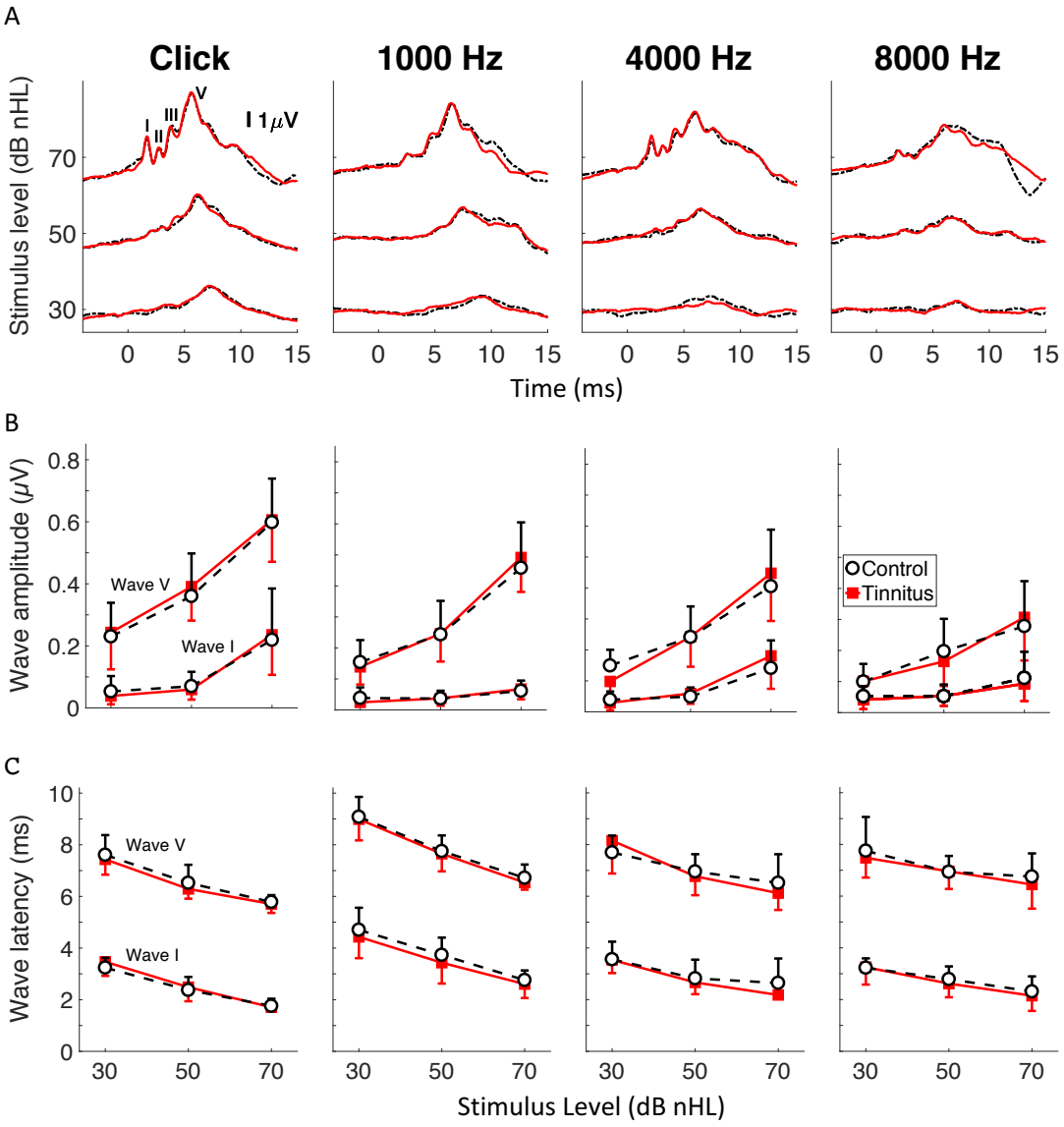


Tinnitus Effect

Figure 5 contrasts the ABR waveforms (A), wave amplitude (B), and latency (C) between the tinnitus (solid red lines or symbols) and control (dashed black lines or symbols) groups. Tinnitus did not produce any significant effect on the four primary ABR parameters, which were within 1-6% of each other between the tinnitus and control

groups [$F(1,26) \leq 0.76$, $p \geq 0.39$]. The four derived parameters were also virtually identical between the two groups, including V/I amplitude ratio [6.35 vs 6.44; $F(1,22)=0.42$, $p=0.53$], V-I latency difference [4.09 vs 4.13ms; $F(1,25)=0.08$, $p=0.78$], wave I amplitude slope [0.002 vs 0.002μV/dB; $F(1,39)=0.58$, $p=0.45$], and wave V amplitude slope [0.007 vs 0.008μV/dB; $F(1,39)=0.57$, $p=0.46$].

Figure 5. Mean ABR waveforms (A), wave amplitude (B), and latency (C) functions in response to click, 1000-, 4000-, and 8000-Hz tone bursts in control or non-tinnitus (black lines and symbols) and tinnitus (red lines and symbols) subjects. The labels, lines and symbols are the same as Fig. 2.



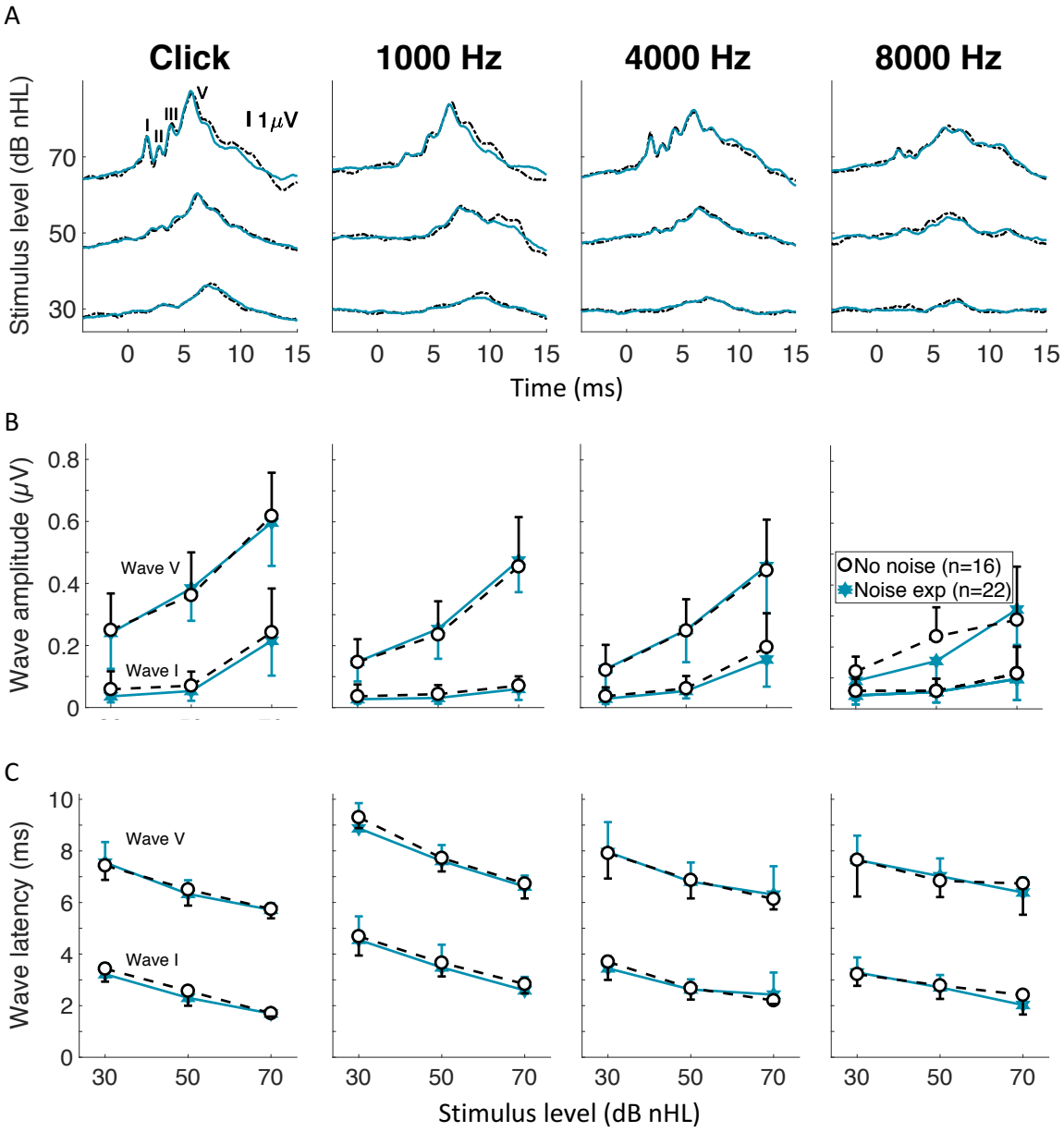
Additional statistical analysis was performed to strengthen the test of our working hypothesis, namely, tinnitus reduces wave I but not wave V amplitude slope. First, ABR wave amplitude did not grow linearly as a function of stimulus level. For example, in the click condition (Fig. 5B), wave I amplitude increased more steeply from 50 to 70 dB than from 30 to 50 dB. Therefore, the slope over the 50-70 dB range was specifically analyzed

but did not show any significant difference between the control and tinnitus groups: wave I slope [0.005 vs. 0.005μV/dB; F(1,31)=0.01, p=0.91] and wave V slope [0.009 vs. 0.010μV/dB; F(1,31)=0.87, p=0.36]. Second, to remove the age and hearing loss factors, analysis was performed on a subset of 11 no-tinnitus and nine tinnitus subjects who were young and had normal hearing. Under this stringent condition, no significant difference was observed between the no-tinnitus and tinnitus groups: wave I slope [0.007 vs 0.006μV/dB; F(1,16)=0.36, p=0.56] and wave V slope [0.010 vs 0.010μV/dB; F(1,16)=0.01, p=0.92].

Noise Effect

Figure 6 contrasts the ABR waveforms (A), wave amplitude (B), and latency (C) between the noise exposure (solid blue lines or symbols) and control (dashed black lines or symbols) groups. Noise exposure did not produce any significant effect on the four primary ABR parameters, which were within 2-17% of each other between the noise and control groups [$F(1,24) \leq 1.54$, $p \geq 0.23$]. Similarly, noise exposure did not produce any significant effect on the four derived parameters: wave V/I amplitude ratio [6.66 vs 5.77; F(1,21)=0.28, p=0.60], wave V-I latency difference [4.122 vs 4.119ms; F(1,23)=0.000, p=0.98], wave I amplitude slope [0.002 vs 0.002μV /dB; F(1,34)=0.01, p=0.92], and wave V amplitude slope [0.007 vs 0.007μV /dB; F(1,34)=0.07, p=0.79].

Figure 6. Mean ABR waveforms (A), wave amplitude (B), and latency (C) functions in response to click, 1000-, 4000-, and 8000-Hz tone bursts in control or non-noise-exposure (black lines and symbols) and noise exposure (blue lines and symbols) subjects. The labels, lines and symbols are the same as Fig. 2.



The same additional analysis as in the tinnitus effect was performed for the noise exposure factor. First, the slope over the 50-70 dB range was specifically analyzed in all subjects and was found to be not significantly different between the no-noise and noise groups: wave I slope [0.006 vs. 0.004μV/dB; $F(1,28)=1.62$, $p=0.21$] and wave V slope

[0.010 vs. 0.010μV/dB; F(1,28)=0.00, p=0.99]. Second, the same analysis was performed on 10 no-noise-exposure and eight noise-exposure subjects who were young and had normal hearing. Again, no significant difference was observed between the no-noise and noise groups: wave I amplitude slope [0.006 vs 0.007μV/dB; F(1,14)=0.12, p=0.74] and wave V amplitude slope [0.011 vs 0.010μV/dB; F(1,14)=0.10, p=0.76].

Effect size

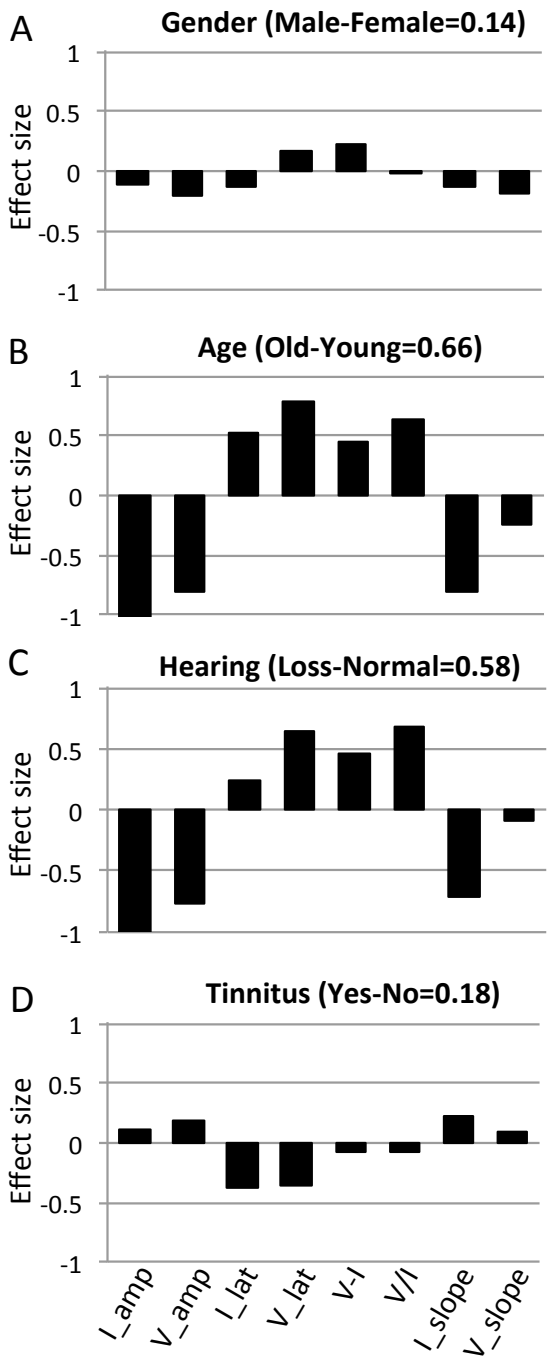
The effect size was separately calculated for wave I amplitude, V amplitude, I latency, V latency, V-I difference and V/I ratio at 70 dB nHL, as well as for wave I slope and V slope over the 30-70 dB nHL range. Figure 7 shows the average effect size (y-axis) of these eight ABR parameters (x-axis), averaged over the four stimuli, on five subject-related factors: Sex (A), Age (B), Hearing (C), tinnitus (D), and noise exposure (E). The panel title describes the subject variable, the contrast, and the averaged effect size (mean of the absolute value of the eight parameters). The effect size for sex was small (0.15). Overall, men produced smaller wave V amplitudes than women (effect size= −0.20) but longer wave V latency (0.18) and V-I latency difference (0.22), consistent with a larger head and longer cochlea in men (e.g., Mitchell *et al.*, 1989; Don *et al.*, 1993).

The pattern of results was similar between age and hearing status. The effect size for age (0.66) and for hearing status (0.65) was 4 times greater than the effect size for sex (0.15). Wave I and V amplitudes were much reduced in both the old and hearing-impaired subjects (=large effect size: −0.8 to −1.2). Wave I and V latencies, as well as V-I difference, were longer in the old and hearing-impaired subjects (~medium effect size of 0.5). Previous studies reported similar effects of age and hearing loss on smaller wave amplitude

and longer latency (e.g., Jerger and Hall, 1980; Watson, 1996; Verhulst *et al.*, 2016). The three derived ABR amplitude parameters, V/I ratio, I slope and V slope, showed an interesting pattern of results that was consistent with the central gain hypothesis. Both age and hearing loss factors reduced the amplitude of both wave I and V, but their amplitude ratio, V/I, was actually enhanced (effect size=0.6 and 0.7, respectively). This pattern of results meant that the V/I ratio was enhanced because age and hearing loss reduced the wave I slope (effect size~ –0.8) more than the wave V slope (effect size~–0.2). Indeed, this difference in slope patterns can be seen in Fig. 3B and Fig. 4B.

The effect size was overall small for tinnitus (=0.18) and noise exposure (=0.17), but there seemed to be an opposite pattern of results between the two factors. In the tinnitus case (7D), the largest effect size (~0.4) was reduced wave I and V latencies, whereas in the noise case (7E), the largest effect size (~0.3) was reduced wave I amplitude (=0.30) and enhanced V/I ratio. This different pattern of results suggests that tinnitus and noise exposure may have different effects on ABR measures with tinnitus affecting latency and noise exposure affecting amplitude.

Figure 7. Effect size (y-axis), averaged over the four stimuli, for eight ABR parameters (x-axis) on five subject-related factors: Sex (A), Age (B), Hearing (C), tinnitus (D), and noise exposure (E). The panel title describes the subject variable, the contrast, and the averaged effect size (=mean of the absolute value of the 8 parameters).



Discussion

Correlation between behavioral variables

Linear correlations were performed between subjects' behavioral variables, revealing several interesting findings (Table 2). First, age was significantly correlated with hearing thresholds (r=0.82), but not with uncomfortable loudness levels, tinnitus index or hyperacusis index, suggesting that age may predict conventional hearing loss but not hidden hearing loss. Second, uncomfortable loudness levels were negatively correlated with hyperacusis severity (r=-0.47), but not with tinnitus severity, suggesting that lower sound tolerance is an indicator for hyperacusis but not necessarily for tinnitus. Third, the moderately significant correlation between tinnitus and hyperacusis (r=0.51) further suggests that they are co-morbid but not totally overlapping disorders.

Table 2. Correlation of subjective variables.
Cross correlation coefficients of five subjective variables between Age (years), Threshold (dB averaged from 125 to 12000 Hz), Uncomfortable loudness level or ULL (dB averaged from 125 to 12000 Hz), Tinnitus index (0-100) and Hyperacusis index (0-100). Bold font with ** represents significant correlation at the 0.01 level while bold font with * represents at the 0.05 level (2-tailed).

	Age	Threshold	ULL	Tinnitus	Hyperacusis
Age	1	**0.82****	0.28	-0.07	0.06
Threshold		1	0.24	-0.23	0.10
ULL			1	0.28	**-0.47***
Tinnitus				1	**0.51***
Hyperacusis					1

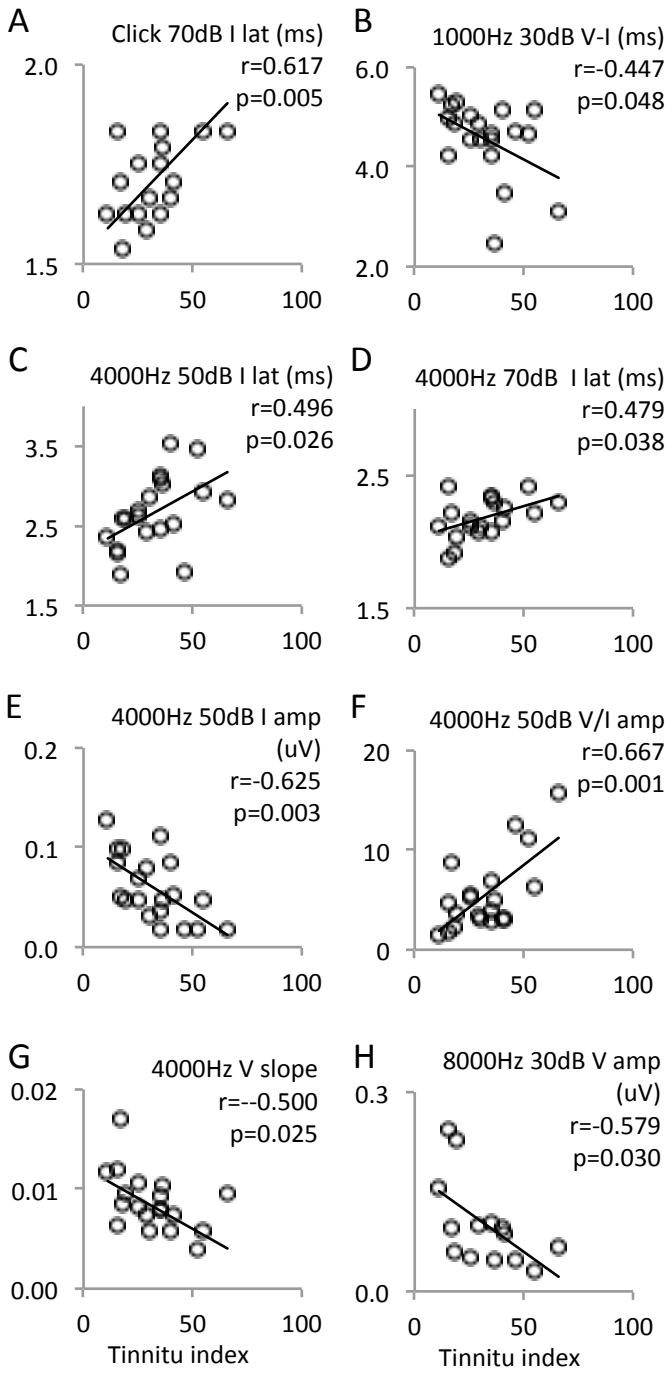
Correlation could not be performed between tinnitus and noise exposure, because the latter in the present study was a binary variable (i.e., either yes or no to noise exposure questions; see Subjects in the Methods section). However, Table 1 shows that two-thirds of the tinnitus subjects (14/21) had prior noise exposure, but one-third of them (6/21) did not report any noise exposure history. Conversely, eight of 18 subjects without tinnitus reported prior noise exposure. This intertwined relationship suggested that, like age and

hearing loss, noise exposure increases the risk of tinnitus but is neither necessary nor sufficient to cause tinnitus.

Correlation with ABR

Tinnitus index was correlated with all 80 ABR parameters (6 non-slope parameters x 4 stimuli x 3 levels + 2 slope parameters x 4 stimuli). The analysis revealed five significant correlations ($p<0.05$) without Bonferroni correction for multiple comparisons. Had the correction been applied (i.e., $p<0.05/80=0.000625$), none of the five significant correlations would remain significant. Nevertheless, these significant correlations are reported for two reasons. First, Bonferroni correction is known to minimize the type-I error (non-significant becomes significant) by assuming the null hypothesis for all comparisons simultaneously (Perneger, 1998). Second, given the lack of a biomarker for tinnitus, it seems reasonable to aggressively seek for any correlation that may confirm an existing mechanism or predict an unknown one. Figure 8 shows that more severe tinnitus was positively correlated with longer wave I latency (70-dB click in 8A and 30-dB 1000-Hz tone in 8B), while negatively with wave I amplitude (30-dB click in 8C and 50-dB 4000-Hz tone in 8D). Figure 8E shows positive correlation between tinnitus severity and V/I amplitude ratio for the 4000-Hz tone. The longer wave I latency was likely related to a selective loss of high-spontaneous-rate auditory nerve fibers (Meddis, 2006), while smaller wave I amplitude related to loss of both high- and low-spontaneous-rate auditory nerve fibers (Furman *et al.*, 2013; Makar *et al.*, 2017; Mohrle *et al.*, 2018). The positive correlation between tinnitus severity and the V/I amplitude ratio likely reflected increased central gain in tinnitus (Schaette and McAlpine, 2011; Gu *et al.*, 2012).

Figure 8. Correlations (A-E) between a significant ABR parameter (panel title) and tinnitus severity index (x-axis). The legend shows corresponding correlation coefficient (r) and p value.



Hyperacusis index was also significantly correlated with five of the 80 ABR parameters. Four of these correlations were similar to that found in tinnitus, including negative correlation with wave I amplitude (70-dB 1000-Hz and 50-dB 4000-Hz), positive correlation with wave I latency (30-dB 8000-Hz) and with V/I amplitude ratio (50-dB 1000-Hz). The different pattern was the negative correlation between hyperacusis severity and 30-dB 8000-Hz wave V amplitude, suggesting that the location of increased central gain may not be in the cochlear nuclei, but in the inferior colliculus or even the auditory cortex (Chambers *et al.*, 2016; Salvi *et al.*, 2016).

Implications

To translate research into practice, it is important to evaluate the effect size because research may show significant group differences but this difference cannot help diagnosis in practice if the corresponding effect size is small. In animal studies using subdermal penetrating electrodes, reduced place-specific ABR wave I amplitude at suprathreshold levels was the most sensitive measure in detecting cochlear synaptopathy (Kujawa and Liberman, 2009; Lin *et al.*, 2011). Under carefully controlled subject and stimulus conditions and with a relatively large sample size, human tinnitus subjects had significantly reduced wave I amplitude (Schaette and McAlpine, 2011; Gu *et al.*, 2012). However, the wave I amplitude effect size was generally small (0.2-0.4) using non-invasively recording techniques in humans. In addition, cochlear synaptopathy may co-exist with conventional hearing loss (Fernandez *et al.*, 2015; Hesse *et al.*, 2016; Parthasarathy and Kujawa, 2018), requiring comparison of wave I amplitude at equal sensation levels to differentiate between cochlear, synaptic and neural loss. The small effect size and the technical

complexity will likely limit wave I's clinical utility in sensitively and specifically diagnosing cochlear synaptopathy in humans at least in the near term.

Wave V is much a greater signal than wave I, and can produce a relatively large effect size in humans. However, the absolute wave V amplitude is heavily influenced by age, sex, hearing loss and other subject variables (e.g., Jerger and Hall, 1980; Watson, 1996). Indeed, the present and previous studies have found that wave V amplitude may decrease, increase, or remain unchanged in human tinnitus subjects (Schaette and McAlpine, 2011; Gu *et al.*, 2012; Mohrle *et al.*, 2018). The V/I amplitude ratio is potentially an effective measure in diagnosing tinnitus and hyperacusis in humans, because it is a relative, within-subjects measure allowing cancellation or at least reduction of the subject-related variability. The present study showed not only positive correlation between the V/I ratio and tinnitus or hyperacusis severity (Fig. 8E), but also a possible use of V/I ratio to separate the tinnitus and noise exposure factors (Fig. 7D and 7E).

ABR latency is presently underexplored in diagnosing tinnitus and hyperacusis in humans. One reason for studying latency effects is that human cochlea and head are larger than commonly used laboratory animals such as mice, rats and cats, which will likely accentuate latency differences in humans. Another reason is that latency parameters may be more appropriate than amplitude parameters because behavioral studies have shown that temporal processing is impaired in human subjects with tinnitus or exposed to noise (Moon *et al.*, 2015; Paul *et al.*, 2017; Bakay *et al.*, 2018). Previous studies have implicated the utility of latency parameter, e.g., V latency as a marker of cochlear synaptopathy (Mehraei *et al.*, 2016). Future investigation needs to explore latency as a potential biomarker for tinnitus and hyperacusis.

Summary and Conclusions

The present study systematically measured auditory brainstem responses (ABR) to clicks, 1000, 4000 and 8000Hz tones at 30, 50 and 70 dB nHLs in 43 human subjects including both sexes, young and old, normal-hearing and hearing-impaired, tinnitus and non-tinnitus, or prior noise exposure and no prior noise exposure history. Eight ABR parameters were calculated, including four direct measures (wave I and V amplitudes and latencies) and four derived measures (V-I latency difference, V/I amplitude ratio, I and V amplitude slopes). Statistical analysis was performed to relate the subject and stimulus variables to the eight ABR parameters.

- Age and hearing loss were positively correlated, and so were tinnitus severity and hyperacusis severity; but neither age nor hearing loss was significantly correlated with tinnitus or hyperacusis severity.
- Some tinnitus and some non-tinnitus subjects both reported prior noise exposure while other tinnitus subjects reported no prior noise experience, suggesting that, like age and hearing loss, noise exposure increases the risk of tinnitus but is neither necessary nor sufficient to cause tinnitus.
- Sex was not a significant factor for any ABR parameters; Age was a significant factor for six ABR parameters but not for wave I latency and V slope; Hearing loss was similar to age except for an additional insignificant effect on V/I ratio.
- Tinnitus or noise exposure was not a significant factor for any of the eight ABR parameters; in particular, tinnitus or noise exposure did not decrease the wave I

amplitude slope nor did it change the wave V amplitude slope, even under the condition when both the age and hearing loss factors were removed.

- Averaged over the four stimuli, the ABR effect size was medium for age (0.66) and hearing loss (0.65) but small for sex (0.15), tinnitus (0.18) and noise exposure (0.17), suggesting that the ABR clinical utility is limited in detecting non-conventional human hearing disorders such as tinnitus, hyperacusis or noise-induced cochlear synaptopathy.

CHAPTER 2

Consequences of tinnitus for auditory and speech perception

Abstract

Tinnitus is sound heard by 20% of the general population in the absence of any external sound. Because external sounds can sometimes mask tinnitus, tinnitus is widely assumed to affect the perception of external sounds, leading to hypotheses such as "tinnitus filling in the temporal gap" in animal models and "tinnitus inducing hearing difficulty" in human patients. Here we compared performance in temporal, spectral, intensive, masking and speech-in-noise perception tasks between 45 human listeners with chronic tinnitus (18 females and 27 males with a range of ages and degrees of hearing loss) and 27 young, normal-hearing listeners without tinnitus (11 females and 16 males). After controlling for age, hearing loss and stimulus variables, we discovered that not only does tinnitus not impair perception of external sounds in general, but it slightly improves intensity discrimination and speech in noise perception under specific stimulus and subject conditions. We interpret the present result to reflect a bottom-up pathway for the external sound and a top-down pathway for the internal tinnitus. We also propose that these two perceptual pathways can be independently modulated by attention, which leads to both the asymmetrical interaction between external and internal sounds and several other tinnitus phenomena such as discrepancy in loudness between tinnitus rating and matching. The present results suggest not only a need for new theories involving attention and central noise in animal tinnitus

models but also a shift in focus from treating tinnitus itself to managing its co-morbid conditions when addressing tinnitus sufferers' complaints about hearing difficulty.

Introduction

Subjective tinnitus, or "ringing of the ears", is a phantom sound that can be heard by a person in the absence of any physical sound stimulation (Roberts et al., 2010). Tinnitus affects about 20% of the population, especially those with hearing loss, older age, noise exposure and head injury (Baguley et al., 2013; McCormack et al., 2016). Different from auditory hallucinations that are often associated with meaningful linguistic and musical content, tinnitus typically contains meaningless steady or fluctuating sounds with the quality being tonal, noisy, or a combination of multiple tones and noises (Meikle and Taylor-Walsh, 1984; Stouffer and Tyler, 1990). Previous studies on perceptual aspects of tinnitus focused on two areas. One area was characterizing the perceptual quality of tinnitus via subjective description or matching tinnitus loudness, pitch and spectrum (Reed, 1960; Goodwin and Johnson, 1980; Penner, 1995; Norena et al., 2002; Patuzzi et al., 2004; Moore, 2012). The other area was using various external sounds, from pure tones and noises to modulated sounds and even music, to attempt to mask tinnitus for treatment purposes (Feldmann, 1971; Penner, 1987; Okamoto et al., 2010; Reavis et al., 2012). Surprisingly much less has been done to answer the reverse question: Does tinnitus affect the perception of external sounds? While many tinnitus sufferers complain about hearing difficulty, especially poor speech perception in noise, this hearing difficulty was mostly based on self-reports from subjects who had not only tinnitus but also other co-morbid conditions such as hearing loss and older age (Tyler and Baker, 1983; Andersson et al., 2000; Soalheiro et al., 2012;

Vielsmeier et al., 2016; Ivansic et al., 2017). The effect of tinnitus on auditory perception remains understudied, contributing to a lack of effective clinical management of tinnitus at present.

This knowledge gap has also hampered the understanding of mechanisms underlying tinnitus. Recent animal studies have suggested several neural correlates of tinnitus, ranging from central hyperactivity and maladaptive plasticity to abnormal homeostasis and network connectivity (Muhlnickel et al., 1998; Kaltenbach, 2006; Yang et al., 2011; Chen et al., 2015; Shore and Wu, 2019). To better understand the relationship between tinnitus and external sounds, we characterized the effect of tinnitus on temporal modulation detection and speech in noise perception. We compared performance for a heterogeneous group of tinnitus subjects with that for a homogeneous control group of young, normal-hearing, non-tinnitus subjects. Our hypothesis was that tinnitus subjects would perform more poorly than the control group. We controlled for the hearing loss factor by presenting stimuli at a frequency where hearing threshold was normal or using either an equal sensation level (SL) or comfortable level for frequencies where the threshold was elevated. We also controlled for the age factor by dividing the tinnitus subjects into young and old groups and comparing their performance as well as comparing performance between young tinnitus subjects and the controls.

Methods

Subjects

The University of California, Irvine Institutional Research Board approved the experimental protocol. All subjects gave a written informed consent to participating in the

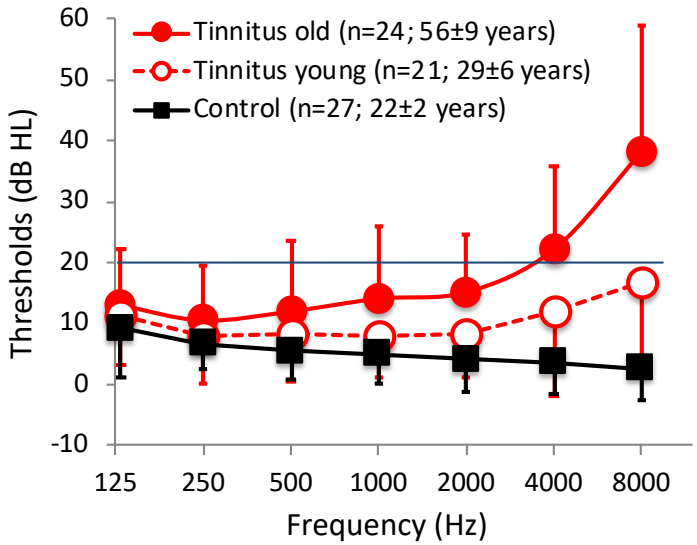
study. A homogeneous group of 27 young adults (mean±std=22±2 years old) served as control subjects. These subjects consisted of 11 females and 16 males, were free of tinnitus, and had normal hearing thresholds (≤20 dB HL) at audiometric frequencies from 125 to 8000 Hz (solid black squares in **Fig. 1a**). A heterogeneous group of 45 adults (44±15 years old, 18 females and 27 males) who had chronic tinnitus (>6 months) served as experimental subjects. These consisted of 24 older (>42 years old; solid red circles in **Fig. 1a**) and 21 younger (<39 years old; open red circles in **Fig. 1a**) subjects. On average, the old tinnitus subjects had hearing loss (>20 dB HL) at 4000 and 8000 Hz, while the young tinnitus subjects had normal hearing at all frequencies. On an individual level, seven of the 21 young subjects had mild hearing loss (25-40 dB HL) at one or more frequencies, one had moderate hearing loss (45-50 dB HL) at two frequencies, while the remaining 13 had normal hearing at all frequencies (≤20 dB HL). The individual tinnitus demographic information can be found in the Extended Data (**Extended Data Table 1**).

All tinnitus subjects, except for two, completed an online questionnaire consisting of the Tinnitus Functional Index (Meikle et al., 2012) and Tinnitus Handicap Inventory (Newman et al., 1996). They had a mean tinnitus index score of 38±22 out of 100. There was no significant difference in tinnitus severity between the old and young tinnitus subjects (34±17 vs. 42±27; two-tailed, two-sample t-test, p=0.28). Additionally, 19 of the 45 tinnitus subjects characterized their tinnitus loudness and pitch using a custom adjustment program with a graphical interface. The subjects moved a marker along a horizontal axis to vary the stimulus frequency from 250 to 20,000 Hz on a logarithmic scale and a separate marker that moved along a vertical axis to vary the stimulus level from 0 to 100 dB SPL in 1-dB steps. The stimulus was a 500-ms sinusoid that repeated once every second. The subjects adjusted the

stimulus to match as closely as possible the pitch and loudness of their predominant tinnitus component. The stimulus was presented to the ipsilateral ear for unilateral tinnitus or the ear with the louder tinnitus for bilateral tinnitus. Once a match was selected, they rated the similarity to their actual tinnitus using a 0-to-10 visual analogue scale. Finally, to allow for possible octave confusion (Moore et al., 2010), subjects matched the loudness of three tones (the original match, 1-octave below, 1-octave above) to their tinnitus, then selected the one most similar in pitch to their tinnitus. If the selection differed from their original match, a new similarity rating was recorded, and this stimulus was taken as their tinnitus match. The subjects rated the matched stimulus to be highly similar to their tinnitus (mean similarity=8 out of 10). On average, the matched stimulus had a low level of 10 dB SL but a relatively high frequency (arithmetic mean=6675 Hz; geometric mean=3964 Hz). There was no significant difference in tinnitus level between the old and young subjects (11.4±5.4 vs. 9.1±8.4 dB SL; two-tailed, two-sample t-test, p=0.46; solid vs. open red circles in **Fig. 1b**).

Figure 1. **(a)** Pure-tone audiograms showing hearing thresholds as a function of tone frequency for 27 young, normal-hearing control (solid black squares), 21 young tinnitus (open red circles) and 24 old tinnitus (solid red circles) subjects. The solid black horizontal line represents normal hearing threshold (=20 dB HL). Error bars are one standard deviation of the mean. **(b)** Tinnitus matching levels (y-axis) and frequencies (x-axis) for 19 tinnitus subjects. The 19 subjects included 9 old (small solid red circles) and 10 young subjects (small open red circles). The average tinnitus matching values are represented by the large circles (solid=old subjects; open=young subjects).

a



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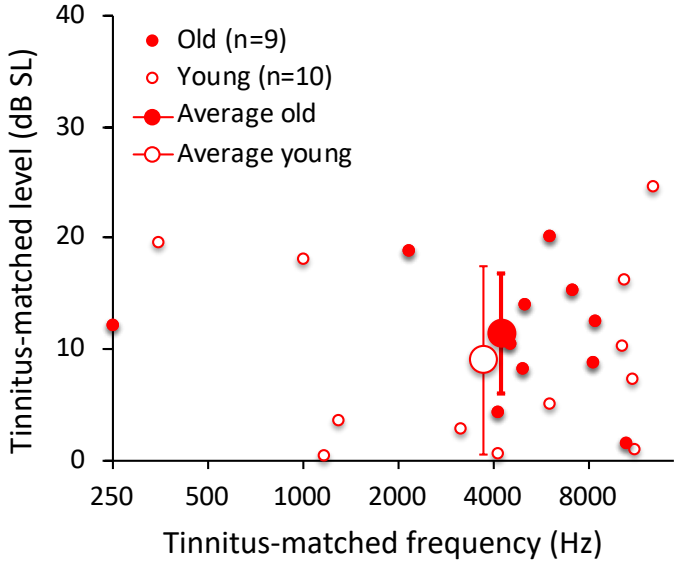


Experimental Design

Due to time constraint, only a subset of the 45 tinnitus subjects participated in each individual experiment, ranging from 23 in the TMTF experiment to 31 in the speech in noise

perception experiment. The information regarding the individual subject's participation can be found in the Extended Data (**Extended Data Table 1**).

The temporal modulation experiment used the following psychophysical procedure (e.g., Zeng et al., 2005b). Briefly, an adaptive three-alternative, forced-choice, 2-down and 1-up procedure was used to estimate 70.7% percent correct performance. Each trial consisted of three intervals separated by 400 ms and marked visually by buttons on a computer interface. The subject had to choose which of the three intervals contained the target signal – i.e., the stimulus that was different from the other two intervals. Pilot experiments established the initial signal strength, making the task easy for the subject at the beginning, and also the step size for adjusting the signal strength afterwards, making the experiment efficient. Visual feedback of "correct" or "incorrect" after each trial further facilitated learning the task. Before formal data collection, all subjects received 1-3 training blocks to become familiar with the procedure.

The temporal modulation experiment employed three carrier frequencies, 250, 2000 and 8000 Hz, each serving as either an unmodulated standard or the signal that was amplitude modulated by a sinusoid at 4, 41 or 80 Hz. The level of the modulated signal was dynamically adjusted according to the modulation depth (m) to have the same root-mean-square level as the unmodulated standard (Viemeister, 1979). The modulation detection threshold was measured in dB (=$20log m$). Both the modulated signal and the unmodulated standard were 500 ms in duration including 40-ms cosine-squared onset and offset ramps, and presented at 60 dB SPL or the most comfortable loudness level adjusted by the individual subject.

The speech in noise perception experiment followed a previously described protocol (Zeng et al., 2005c). Briefly, the target speech stimuli were sentences with each containing 4-5 keywords, spoken by a male talker. The three backgrounds were a steady noise with a spectrum matched to the male talker's long-term spectral shape, a competing female talker, and a competing male talker (different from the male target talker). An adaptive 1-down and 1-up procedure was used to estimate the speech-to-background ratio, or speech reception threshold (SRT), that produced the 50% percent correct performance. A correct response required all keywords in the sentence to be correctly identified. No feedback was provided.

Statistics

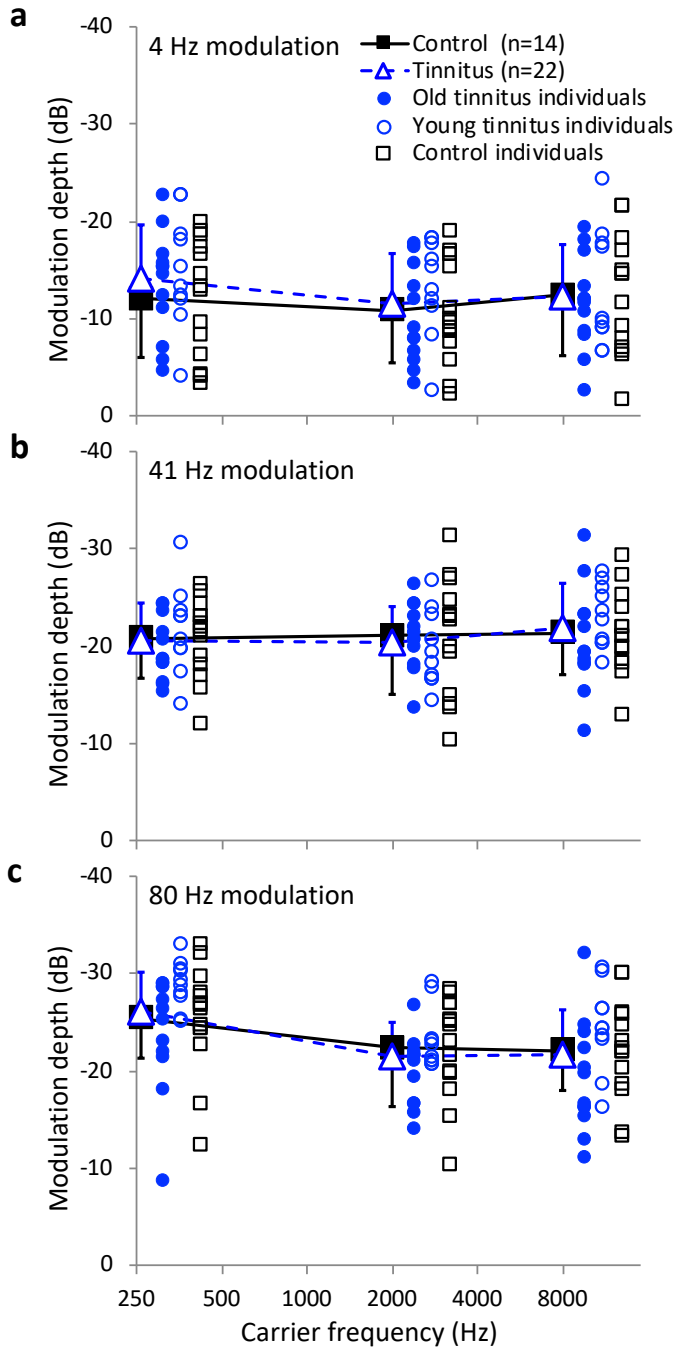
We used within-subjects ANOVA to assess stimulus effects and between-subjects ANOVA to assess effects of age, hearing and tinnitus as categorical variables. The age category was either young (<39 years old) or old (>42). The hearing category was either normal hearing (≤20 dB HL at all audiometric frequencies between 125 and 8000 Hz) or hearing loss (≥25 dB HL at any audiometric frequencies). Because the binary definition of both the age and hearing factors was arbitrary, which also broadly applies to the typically-used 20 dB HL "normal" hearing criterion (Leger et al., 2012; Bernstein and Trahiotis, 2016), we also used years of age and average threshold (over 125-8000 Hz) as continuous or scale variables to perform linear correlation and regression. Two-tailed t-tests was used to assess significant differences, with Bonferroni correction for multiple comparisons. For results meeting the criterion for significance ($p<0.05$), effect size was calculated as the difference in mean between two distributions divided by their joint standard deviation, with 0.2, 0.5, and 0.8 representing small, medium and large effect (Cohen, 1969).

Results

No effect of tinnitus on temporal modulation detection

We measured temporal modulation detection as a function of carrier frequency (250, 2000 and 8000 Hz) for modulation frequencies of 4 Hz (**Fig. 2a**), 41 Hz (**Fig. 2b**) and 80 Hz (**Fig. 2c**). There was no significant effect for age [$F(1,34)=1.01$, $p=0.32$], hearing loss [$F(1,34)=0.71$, $p=0.41$], or tinnitus [$F(1,34)=0.25$, $p=0.62$]. There were significant effects for the modulator [effect size=0.75, $F(2,68)=103.05$, $p<0.001$] and the carrier [effect size=0.15, $F(2,68)=5.71$, $p=0.005$], but no significant interactions with any subject variables ($p>0.45$).

Figure 2. Temporal modulation detection. **(a)** Detection threshold of 4-Hz sinusoidal amplitude modulation as a function of carrier frequency (250, 2000 and 8000 Hz). The open blue triangles show the average threshold for 22 tinnitus subjects and the solid black squares show the average threshold for 14 control subjects. The solid blue circles represent individual data for the 12 old tinnitus subjects, open blue circles for the 10 young tinnitus subjects, and black open squares for the 14 control subjects. Error bars show one standard deviation of the mean. **(b)** The same as **(a)** except for detecting 41-Hz modulation. **(c)** The same as **(a)** except for detecting 80-Hz modulation.



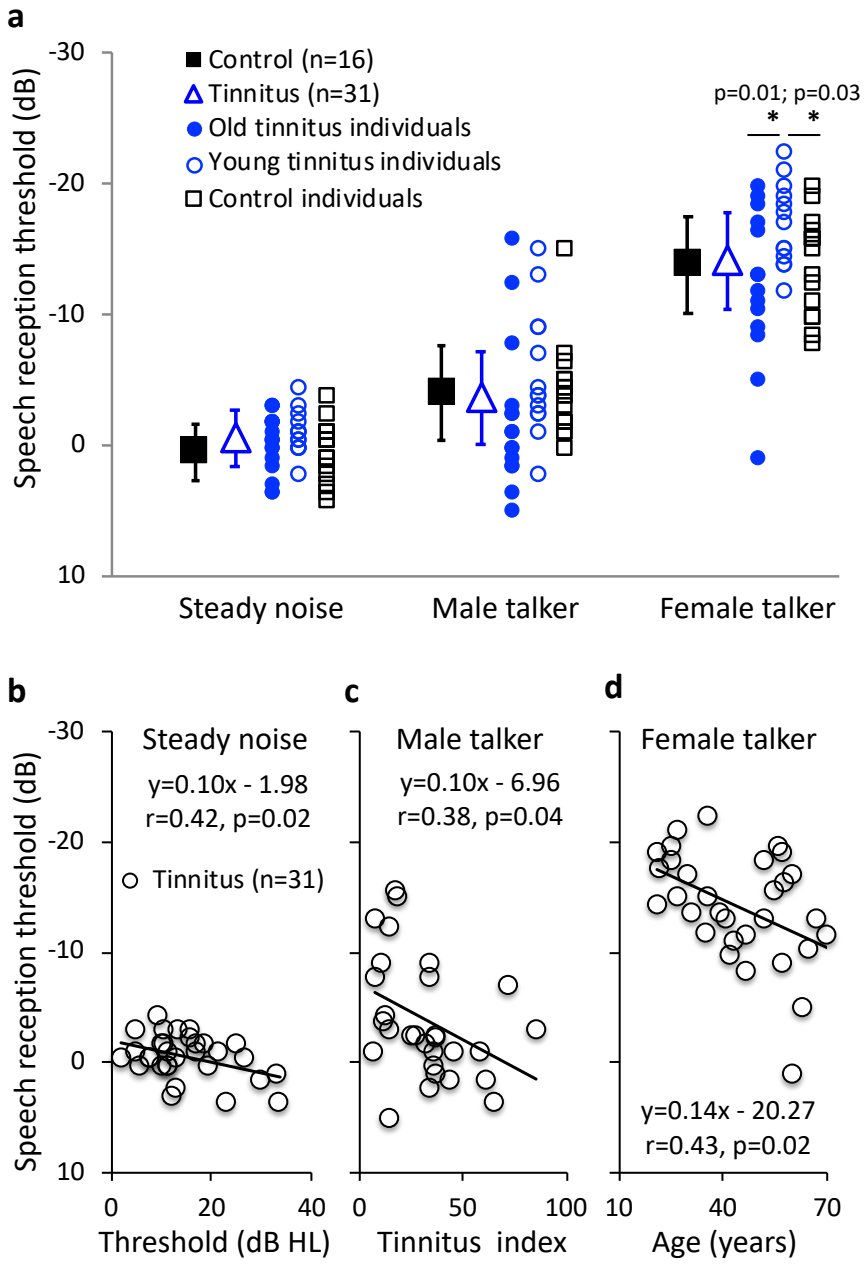
Interactive effects of tinnitus, age and hearing loss on speech perception in noise

We estimated the speech-to-background ratio or speech reception threshold (SRT in dB) at which 50% of keywords in spoken sentences were correctly recognized in three backgrounds: a steady noise, a male talker and a female talker (**Fig. 3a**). There was no

significant effect for tinnitus [F(1,45)=0.10, p=0.75], hearing loss [F(1,45)=0.55, p=0.46], or age [F(1,45)=3.47, p=0.07]. There was a significant effect of background type [effect size=0.83, F(2,90)=235.55, p<0.001], with the steady noise producing the highest speech threshold at -0.1 dB, followed by the male talker at -3.8 dB and the female talker at -14.0 dB. Interaction analysis showed a significant age effect for the female talker background [F(2,90)=3.4, p=0.04]: the young tinnitus subjects outperformed not only the old tinnitus subjects by 4.5 dB (effect size=1.08, p=0.01) but also the young control subjects by 3.0 dB (effect size=0.86, p=0.03).

We correlated SRTs from 31 tinnitus subjects with their age, average audiometric thresholds and tinnitus severity index. First, the steady noise SRT was significantly correlated with only the average threshold (r=0.42, p=0.018, **Fig. 3b**). Second, the male talker SRT was significantly correlated with only the tinnitus severity index (r=0.38, p=0.046, **Fig. 3c**). Third, the female talker SRT was significantly correlated with both the age (r=0.43, p=0.015, **Fig. 3d**) and the average threshold (r=0.51, p=0.003). Multiple regression analysis showed that the age accounted for 19% of the variance in the female SRT data while the average thresholds accounted for an additional 12%, with a total of 31% variance accounted for by both factors. These observations are likely related to the role of tinnitus in energetic and informational masking, to be discussed later.

Figure 3. Speech reception thresholds (SRTs). **(a)** SRTs for three backgrounds. The solid black squares represent the average SRTs for 16 control subjects and the open blue triangles represent the average SRTs for 31 tinnitus subjects. The blue solid circles represent individual data for 18 old tinnitus subjects, blue open circles for 13 young tinnitus subjects, and black open squares for 16 control subjects. Error bars show one standard deviation of the mean. The asterisks and the lines below represent significant differences between the groups. **(b)** Correlation between the SRT and average audiometric threshold for the steady noise background in 31 tinnitus subjects. Circles represent individual data. The equation and line show the linear regression. **(c)** Same as (**b**) except for correlation between the SRT and tinnitus severity index for the male background. **(d)** Same as (**b**) except for correlation between the SRT and age for the female background.



Attention normalization model

We propose an attention-normalization model to account for the perceptual relationship between tinnitus and stimulus (**Fig. 4a**). Different from the traditional bottom-up pathway for perception of external sounds (*Ps* in the bottom box), tinnitus has an internal

origin, e.g., cental neural noise (Zeng, 2013; Mohrle et al., 2019), reflecting a top-down perceptual process or *Pt* in the top box (Jastreboff, 1990; Sedley et al., 2016). These two pathways do not overlap, but influence each other through an attention-normalization mechanism (Reynolds and Heeger, 2009), in which the total perception is determined by the sum of attention-weighted tinnitus percept and external sound percepts (a_tP_t+a_sP_s) over the total level of attention (a_t+a_s):

$$P = \frac{a_tP_t+a_sP_s}{a_t+a_s} \quad (1)$$

Both the total percept (P) and individual percepts (P_t, P_s) are multi-dimensional, including loudness, pitch, time and other components, but we focus on loudness here for simplicity. We illustrate the dynamic role of selective attention in tinnitus and stimulus perception by fixing the baseline tinnitus loudness and attention level (e.g., assuming P_t =50 and a_t =0.5 in **Fig. 4b**). The resulting tinnitus loudness ($\frac{a_tP_t}{a_t+a_s}$) decreases with increased attention to the stimulus (the red dashed line), whereas the stimulus loudness ($\frac{a_sP_s}{a_t+a_s}$) increases with increasing stimulus attention (the four black lines represent four stimulus loudness baseline levels at 100, 50, 25 and 10 from top to bottom, respectively). The model predicts a strong role of attention, which can make a given tinnitus equally loud to a stimulus of different levels (the blue circles at the intersection of the tinnitus and stimulus loudness curves).

The present model can be used to predict the effects of tinnitus on the loudness growth function for an external stimulus. At present we do not know how attention varies as a function of loudness. For simplicity, we assume attention is a linear function of loudness,

namely, a_t=P_t and a_s=P_s =$I^{0.3}$ (Stevens's power law), where is constant and I is stimulus intensity. The total loudness of tinnitus and stimulus is obtained by rewriting Eq. (1) as:

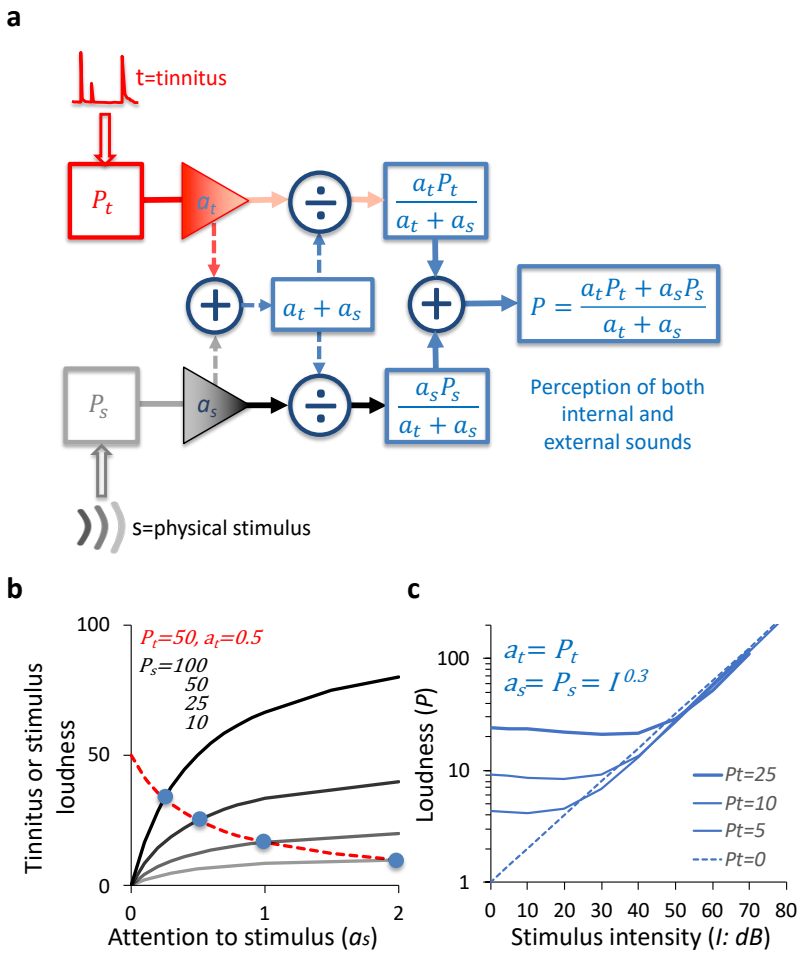
$$P = \frac{\alpha P_t^2 + \alpha P_s^2}{\alpha P_t + \alpha P_s} = \frac{P_t^2 + I^{0.6}}{P_t + I^{0.3}} \qquad (2)$$

At low stimulus levels, $I << P_t$, so the total loudness $P \approx P_t$, which serves as a floor due to tinnitus. At high stimulus levels, $I >> P_t$, so the total loudness $P \approx I^{0.3}$, following normal loudness growth (**Fig. 4c**). This prediction is consistent with the idea conceptualizing tinnitus as internal noise, which increases the loudness estimates at low stimulus levels but not the slope of the loudness function (Zeng, 2013).

The present model can also account for both previous and the present results. First, there is a well-known discrepancy between loudness rating and matching, in which tinnitus sufferers often rate their tinnitus as subjectively loud but match it to a surprisingly low-level sound (Reed, 1960; Pan et al., 2009; Fig. 1b). In a subjective rating task where external stimuli are absent (a_s=0), tinnitus loudness is the greatest (=50 in **Fig. 4b** for example**)**. However, in a matching task, the presence of external stimuli increases attention to the stimulus, reducing tinnitus from the 50-loud tinnitus in the rating task to a 10-loud external stimulus in the matching task (a_s=2 or the rightmost circle in **Fig. 4b**). This factor of five change in loudness due to attention is not impossible considering a factor of four attention effect on loudness for a level-decreasing sound from 90 to 50 dB SPL (Schlauch, 1992). Second, the present model can explain puzzling tinnitus masking phenomena, in which loud, high-pitched and steady tinnitus could be masked by softer, low-frequency, or dynamic external sounds (Vernon and Meikle, 1981; Zeng et al., 2011; Reavis et al., 2012) or not masked by any external sounds (Penner, 1987). These puzzling phenomena are opposite the predictions of a traditional energy-based masking model but can be simply explained by

relative changes in attention to stimulus and tinnitus. Third, it would be difficult if not impossible for the traditional model to explain how tinnitus could enhance auditory performance, e.g., perception of male speech in the presence of a female talker (**Fig. 3a**). We note that the tinnitus-enhanced performance occurred at relatively low stimulus levels (-14 dB SRT for the female background). We speculate that chronic tinnitus selectively increases attentional gain for low-level stimuli so that a "spotlight" strategy cab be used to enhance auditory performance at these low levels (Luce and Green, 1978; Leek et al., 1991).

Figure 4. Attention normalization tinnitus model and predictions. **(a)** Independent top-down and bottom-up pathways for perception of internal (tinnitus) and external sounds. Tinnitus (t) is of an internal origin, reflecting increased internal noise, and produces a percept P_t. An external sound (s=physical stimulus) produces a percept P_s. Both percepts are modified by attention (a_t=attention to tinnitus and = a_s to stimulus), then influence each other via an attention-normalization mechanism (i.e., divided by a_s+a_t). The total percept is the sum of the attention-weighted individual percepts ($a_sP_t+a_tP_s$) over the total attention level (a_s+a_t). **(b)** Prediction of the role of attention in perception of tinnitus and stimulus. Tinnitus baseline loudness is set at 50 and tinnitus attention level at 0.5. Tinnitus loudness (red dashed line) decreases with attention to stimulus (x-axis). Stimulus loudness increases with attention to stimulus, with four black lines representing four stimulus loudness baseline levels at 100, 50, 25 and 10 from top to bottom, respectively. The blue circles represent equal loudness of tinnitus and stimulus at four stimulus baseline levels. **(C)** Prediction of the effect of tinnitus on loudness growth. Loudness growth for three tinnitus loudness baseline levels (25, 10 and 5) is represented as blue lines and contrasted against the non-tinnitus loudness growth baseline (the dotted diagonal line, representing the power law $P=I^{0.3}$, where I is stimulus intensity and plotted in a logarithmic form $10\log I$ or dB here).



Discussion

Comparison with previous studies

There are few previous studies on the perceptual consequences of tinnitus. In seven previous gap-detection studies using human tinnitus subjects, four observed a small gap-detection deficit (1-4 ms worse than the normal) for tinnitus subjects (Sanches et al., 2010; Mehdizade Gilani et al., 2013; Jain and Dwarkanath, 2016; Ibraheem and Hassaan, 2017), but the other three did not find any deficit (An et al., 2014; Boyen et al., 2015; Morse and Vander Werff, 2019). One study on frequency discrimination of a 1000-Hz tone at 80 dB SPL

reported a 20 Hz threshold for the normal controls and 30-40 Hz for the tinnitus subjects (Jain and Sahoo, 2014). We consider the result of this study to be unreliable because both the 20-40 Hz thresholds themselves and their large variability were much greater than the ~10 Hz threshold and ~6 Hz standard deviation for a 2000-Hz tone at 70 dB SL in the present study (**Fig. 3b**). Two studies found little or no effect of tinnitus on intensity discrimination (1 dB or less, Epp et al., 2012; Jain and Sahoo, 2014). Two studies found significant but small (<10 dB) increase in thresholds for detecting a tone in noise (Weisz et al., 2006; Buzo and Carvallo, 2014).

One of the two studies on temporal modulation detection found no tinnitus effect except for improved detection (~2 dB) of 10-Hz sinusoidal modulation in the tinnitus ear relative to the non-tinnitus ear for a group of unilateral tinnitus subjects with normal audiograms (Moon et al., 2015). The other study found no tinnitus effect on detection of 19-Hz modulation of a 500-Hz carrier but worse performance (2 dB) for a 5000-Hz carrier in tinnitus subjects (Paul et al., 2017). The present study is largely consistent with the non-significant or small tinnitus effect found in these previous studies.

Despite widespread self-reports of poor speech perception, especially in noise, by tinnitus subjects (Ivansic et al., 2017), previous studies actually found little or no deficits when age and hearing loss were carefully controlled (0-2 dB differences in speech reception thresholds, Moon et al., 2015; Gilles et al., 2016; Tai and Husain, 2018). Indeed, tinnitus can be subjectively loud and annoying, but most often its matched level is low at 10-20 dB SL and its matched frequency high at >4000 Hz (Reed, 1960; Pan et al., 2009; Fig. 1b). In contrast, speech sounds have a conversational level at or above 50 dB SL and main frequencies lower than 4000 Hz (Studebaker et al., 1987; Cox et al., 1988). The lack of an energetic overlap

between speech and tinnitus would predict the lack of an effect of tinnitus on speech perception. The present results surrounding speech perception in steady noise (the average 0-dB SRT and its only significant correlation with the individual's audibility, **Fig. 3a, b**) support this energy-based mechanism. Other mechanisms are needed to explain the seemingly contradictory tinnitus effects on two-talker speech perception. First, we use the "spotlight" strategy (Luce and Green, 1978; Leek et al., 1991) or enhanced auditory attention to explain how the young tinnitus subjects performed better than the young normal controls in the male target and female background condition (**Fig. 3a**). Because the male and female talkers represent two relatively distant auditory objects, the tinnitus-enhanced "spotlight" improves the male talker's perception while ignoring the female background. Second, we use impaired selective attention to explain why more severe tinnitus gave poorer speech reception threshold for the male target and male background condition (**Fig. 3C**). Because two male talkers represent two closely located objects, not even the tinnitus-enhanced attention filter can produce sufficient separation to perform the "spotlight" strategy on one of them. In this case, tinnitus, instead, becomes a burden or distractor, with more severe tinnitus taking more attention away from performing the speech perception task. There is evidence for tinnitus impairing selective attention when performing complex and demanding cognitive tasks (Andersson et al., 2000; Hallam et al., 2004; Dornhoffer et al., 2006; Rossiter et al., 2006; Stevens et al., 2007; Husain et al., 2015; Li et al., 2018). Future studies are needed to delineate the relative contribution of enhanced auditory attention versus impaired selective attention to auditory and speech perception in tinnitus subjects.

Comparison with other hearing disorders

It is interesting to compare the perceptual consequences of tinnitus and other common hearing disorders. Cochlear hearing loss is the most common hearing disorder that produces higher thresholds, broader frequency tuning and poorer speech performance in noise than for normal controls (Moore, 1996). The perceptual consequences are different between tinnitus and cochlear hearing loss. First, while elevated thresholds are highly correlated with tinnitus, 15% of tinnitus sufferers have normal thresholds (Axelsson and Ringdahl, 1989; Henry et al., 2005). Second, tinnitus sufferers have similar or even sharper tuning than the non-tinnitus controls depending on degrees of hearing loss (Tan et al., 2013; Buzo and Carvallo, 2014). These perceptual differences likely reflect the different pathophysiologies between cochlear hearing loss (damage to hair cells and other cochlear structure) and tinnitus (e.g., selective loss of low-spontaneous-rate neurons) (Furman et al., 2013).

Tinnitus is similar to, yet different from, auditory neuropathy, a hearing disorder that is characterized by normal cochlear amplification function but abnormal neural activitiy (Starr et al., 1996). People with both tinnitus and auditory neuropathy may present with normal audiometric thresholds, but their suprathreshold processing deficits are different. Auditory neuropathy produces impaired temporal processing mostly at low frequencies (Zeng et al., 2005b), while tinnitus produces minimal perceptual impairment, and if any, mostly at high frequencies (Weisz et al., 2006; Paul et al., 2017). Auditory neuropathy is characterized by speech recognition that is poorer than expected from reduced audibility (Zeng and Liu, 2006). In contrast, tinnitus rarely impairs speech perception in quiet (Tai and Husain, 2019) and its effect on speech perception in noise is minimal (the present results).

Tinnitus shares some attributes associated with central auditory processing disorder. For example, the "right-ear advantage" for speech in noise perception in tinnitus (Tai and Husain, 2019) is similar to the "left-ear deficit" in central auditory processing disorder (Bellis et al., 2008; Westerhausen et al., 2015). Additionally, 52% of tinnitus subjects with normal audiograms showed abnormal performance in central auditory processing tests such as low-pass filtered speech and dichotic competing speech perception (Goldstein and Shulman, 1999). Tinnitus is associated with impaired selective attention, working memory, cognitive processing and cross-modality processing (Hallam et al., 2004; Rossiter et al., 2006; Araneda et al., 2015; Li et al., 2018). Although these perceptual and cognitive consequences of tinnitus have been suggested to reflect central changes in excitability, homeostasis, reorganization, or network connectivity (Muhlnickel et al., 1998; Kaltenbach, 2006; Yang et al., 2011; Chen et al., 2015), the exact amount of contribution from tinnitus remains unclear because the co-morbid hearing loss factor may also contribute to cognitive impairment (Dupuis et al., 2015; Mohamad et al., 2016).

Significance

Theorectically, the present study suggests that tinnitus, as central noise, travels through an independent top-down pathway and can only affect perception of external sounds indirectly via an attention mechanism. Future tinnitus animal models may consider two possibilities for tinnitus experiments. First, the presence of tinnitus in animals increases the level of central noise, which can be measured directly (Mohrle et al., 2019) or indirectly (Jones et al., 2013). Second, the presence of tinnitus in animals increases the level of attention (Roberts et al., 2013), with one recent study showing increased vigilance but impaired attention in rats with tinnitus (Brozoski et al., 2019). Ideally, such tinnitus animal models

would use an easily accessible biomarker to detect not only the presence of tinnitus but also the specific affected frequency region (e.g., Jacobson et al., 1996).

If tinnitus does not impair perception of external sounds, why then do many tinnitus sufferers complain about hearing difficulty? We believe this hearing difficulty is due to tinnitus co-morbid conditions and secondary effects. First, 80-90% of tinnitus sufferers have some degree of hearing loss, which impairs both audibility and suprathreshold processing to directly contribute to the hearing difficulty (Moore, 1996). Second, as many as 40% of tinnitus sufferers have co-morbid hyperacusis (Jastreboff and Jastreboff, 2000), which reduces their dynamic range and forces them to listen to abnormally soft sounds, resulting in increased listening difficulty. Third, although tinnitus increases auditory attention (Jacobson et al., 1996), which could improve auditory performance under specific stimulus conditions (the present study), it may increase cognitive load, and induce stress, fatigue or even fear to result in subjective complaints about hearing difficulty under realistic listening situations (Jagoda et al., 2018; Zhang et al., 2018). Our results suggest that, because tinnitus does not affect auditory performance including speech perception in noise, clinicians need to shift the focus from treating tinnitus to treating its co-morbid conditions and secondary effects in dealing with the tinnitus subjects' complaint about hearing difficulty.

Extended Data Table 1. Tinnitus subject demographic and audiological information.

A total of 45 tinnitus subjects participated in the study, indicated by the subject code from 1 to 45, followed by age (years), C (category: Y=Young; O=Old), S (Sex: F=Female; M=Male), audiometric thresholds (dB HL) from 125 Hz to 8000 Hz, and self-reported tinnitus type, tinnitus laterality, etiology. TSI (tinnitus severity index) is the average of Tinnitus Functional Index (Meikle et al., 2012) and Tinnitus Handicap Inventory (Newman et al., 1996), with both being normalized to a scale from 0 to 100. Tinnitus match measures include tinnitus frequency (Hz), level (dB SL) and similarity rating (0-1, with 0 indicating not at all similar to the perceived tinnitus and 1 being identical to the tinnitus).

Subject info				Audiogram (Hz/dB HL)							Tinnitus information						
Sub #	Age	C	S	125	250	500	1000	2000	4000	8000	Type	Laterality	Etiology	TSI	Freq (Hz)	Level (dB SL)	Similarity (0-1)
1	20	Y	F	5	5	10	10	15	50	45	Tonal	Bilateral	Recreational noise	15	4150	0.6	0.9
2	21	Y	F	5	5	0	10	20	0	15	Multi-tonal	Bilateral	Unknown	25	1000 /3148	18.0/2.8	0.44/0.51
3	21	Y	F	20	15	20	15	10	15	15	Tonal +pulsing	Bilateral	Vertigo	36			
4	22	Y	M	5	5	5	0	0	0	0	Tonal	Bilateral	Recreational noise	86			
5	23	Y	M	5	0	0	5	0	0	5	Tonal	Bilateral	Recreational noise	77	10462	16.1	0.8
6	25	Y	F	25	25	30	25	15	10	20	Multi-tonal	Left	Occu/Rec noise/Trauma	37	348 /6016	19.5/5.0	0.81/0.98
7	25	Y	M	20	15	15	5	10	10	5	Tonal	Right	Recreational noise	19			
8	27	Y	M	15	0	5	10	5	5	-5	Tonal	Bilateral	Occu/Rec noise	13			
9	27	Y	M	25	25	15	5	5	0	-10	Tonal	Bilateral	Recreational noise	8			
10	30	Y	M	15	10	10	0	0	25	20	Tonal	Bilateral	Occu/Rec noise	82			
11	31	Y	M	0	5	5	5	5	0	20	Tonal	Bilateral	Recreational noise	12			
12	31	Y	F	15	10	15	15	10	10	25	Tonal	Bilateral	Recreational noise	78	1166	9.9	0.53
13	32	Y	M	5	5	0	0	7	0	25	Nontonal	Head	Rec noise/Medication	55	12765	24.6	0.65
14	32	Y	M	10	0	0	0	-5	0	20	Tonal	Bilateral	Recreational noise	37	11154	0.9	0.8
15	33	Y	M	5	5	10	10	10	30	30	Tonal	Bilateral	Recreational noise		10314	10.3	0.83
16	35	Y	M	0	0	5	20	25	25	15	Tonal	Bilateral	Occu/Rec/Military noise	34			
17	35	Y	M	25	20	15	10	10	10	25	Tonal	Left	Unknown (stress)	27	1302	3.5	0.76
18	36	Y	M	10	10	0	5	0	-5	15	Tonal	Right	Unknown (pain)	34			
19	36	Y	M	5	5	10	15	15	30	40	Tonal	Bilateral	Occu/Rec noise	72			
20	36	Y	M	10	0	0	0	10	20	15	Tonal	Bilateral	Unknown (cold)	74	11105	7.3	0.71
21	39	Y	M	15	5	5	5	10	20	10	Tonal	Left	Unknown (ear pain)	10			
22	41	O	M	30	20	15	10	35	55	65	Tonal +noise	Bilateral	Sudden hearing loss	37			
23	42	O	F	0	0	5	30	30	10	18	Tonal +noise	Bilateral	Rec noise/Medication	32			
24	43	O	M	15	15	15	15	15	10	45	Tonal	Left	Recreational noise	34			
25	44	O	M	5	5	0	5	10	5	10	Tonal	Left	Occu/Rec noise	52	4538	10.5	0.88
26	47	O	M	10	15	25	20	20	25	20	Tonal	Bilateral	Military noise	38			
27	47	O	M	15	5	10	15	5	15	25	Tonal	Bilateral	Recreational noise	8			
28	52	O	F	15	10	10	10	10	15	10	Tonal +noise	Bilat +Head	Ear infection/Vertigo	27	2157 /6016	18.8/20	0.74/0.98
29	52	O	F	10	10	10	5	5	5	10	Tonal	Bilateral	Occu/Rec/Military noise	61			
30	54	O	F	10	5	0	10	5	15	15	Tonal +noise	Right +Head	Medication	43	8424	12.5	0.86

31	55	O	M	5	5	5	15	20	10	15	Tonal +noise	Bilateral	Unknown (Medication)	46			
32	56	O	M	10	0	5	0	5	35	55	Tonal	Bilateral	Occupational noise	18			
33	57	O	M	10	5	15	20	30	30	50	Nontonal	Bilateral	Occu/Rec noise	36			
34	57	O	M	10	10	15	20	20	30	70	Tonal +pulsing	Bilateral	Recreational noise	14			
35	57	O	F	20	20	20	20	20	25	55	Tonal +pulsing	Bilateral	Occu/Rec noise/Medication	18	250 /10504	12.0/1.4	0.70/0.90
36	58	O	F	5	5	5	5	5	15	30	Nontonal	Bilateral	Recreational noise	7			
37	60	O	F	25	35	40	55	20	10	50	Tonal	Bilateral	Occu/Rec noise	14			
38	60	O	F	-5	0	5	5	15	20	35	Tonal +noise	Bilateral	Occu/Rec noise	58			
39	62	O	M	20	5	0	5	15	42.5	40	Tonal	Bilateral	Rec/Military noise	35	4173	4.2	0.84
40	63	O	F	15	10	5	5	5	25	20	Tonal	Bilateral	Meniere's				
41	65	O	F	20	20	20	20	30	35	65	Tonal	Right +Head	Vertigo	15	5003	8.1	0.87
42	67	O	M	25	15	5	5	5	15	50	Tonal	Bilateral	Recreational noise	66	7145	15.2	0.74
43	68	O	F	25	25	45	25	20	20	70	Tonal	Bilateral	Recreational noise	49	8263	8.7	0.85
44	70	O	M	20	15	10	15	15	50	60	Tonal +noise	Bilateral	Occu/Rec noise	44			
45	70	O	F	0	0	5	5	5	15	30	Tonal	Bilateral	Noise/Migraine	33	5034	13.9	0.9

CHAPTER 3

Loudness perception in listeners with and without tinnitus

Introduction

Loudness, like other sensations such as brightness, increases as a function of stimulus intensity (Stevens 1960, Zwislocki 1965). However, loudness perception can be affected by conditions such as hearing loss and tinnitus. Hearing loss has been shown to increase perception of loudness at threshold but does not change the slope of loudness growth near the threshold (Buus and Florentine 2002). Based on the active loudness model in Zeng (2013) and the idea that increased central noise is associated with tinnitus, we predict that tinnitus also increases loudness at threshold. In this study, we sought to characterize loudness growth curves for listeners with tinnitus and control listeners without tinnitus.

Methods

Subjects

The University of California, Irvine Institutional Research Board approved the experimental protocol. A total of 22 human subjects aged 16-74, including 13 females and 9 males, participated in the study. Informed consent was obtained for all participants; for the one minor participant, assent was obtained and parental consent was obtained. Of the group, 11 subjects reported chronic tinnitus and 11 did not. Ten of the subjects with tinnitus completed the Tinnitus Functional Index (TFI) questionnaire; mean tinnitus index score was 45 +- 27.

Experimental Design

Each subject performed the experiment with anywhere from 1-14 different stimuli, depending on time and hearing status. Most subjects performed the experiment with all 14 stimuli. Stimuli varied on 3 dimensions: frequency (250, 1000, 4000 Hz), tone vs noise, and modulated vs unmodulated. In addition, modulated and unmodulated white noise was tested. Because there were not clear differences in loudness growth curve between the stimulus types, all stimulus types were analyzed together for the final analysis. Stimuli were 300 ms in duration with cosine-squared onset and offset ramps of 20 ms, calibrated and played over Sennheiser HDA200 headphones. Bandpass noise (centered on 250, 1000, and 4000 Hz) was ½ octave around the center frequency. White noise contained frequencies 1000-16000. Modulation was 100% at 41 Hz. For modulated stimuli, RMS was normalized to the unmodulated stimulus.

For each separate stimulus tested, the threshold, upper loudness limit (ULL), and loudness growth curve was measured according to the following procedure. Threshold was measured using an adaptive three-alternative two-down-one-up forced choice procedure estimating 70.7% correct performance. The subject was given three possible intervals and had to determine which interval contained the sound. Initial sound level was 45 dB SPL, adjusting by 10 db until the first reversal and then by 5 dB until 10 reversals had been achieved; threshold was determined to be the average of the reversals. ULL was then determined by asking the subjects, starting sounds just above threshold or 50 dB SPL, whichever was greater: "Was this the loudest sound you can tolerate?" Sound level increased by 5 dB until the subject answered "yes" or the sound level reached 120 dB SPL. Having established the threshold and ULL, we then presented the subjects with the stimulus varying in level, starting at threshold and increasing in 5-dB increments, not to

exceed the ULL. For each stimulus presented, subjects were asked to specify how loud each sound by assigning numbers, using any positive numbers that seem appropriate (whole numbers or decimals). The set of level varying stimuli were presented in random order, and this was repeated three times. For each tested sound level, the average of the three trials was used for loudness growth analysis.

Analysis

For each subject with each stimulus, a loudness growth curve was fit to the loudness estimates using the equation $L = k[(I + cI_0)^{\theta} - (cI_0)^{\theta}]$. Best-fit values for k, c, and theta were estimated. Threshold, loudness at threshold, and theta (as a representation of slope) were compared between tinnitus and control subjects; additionally, hearing status (normal hearing or hearing loss) was considered. For a given stimulus, the subject was considered to have normal hearing if their threshold was 20 dB SPL or below, and hearing loss if the stimulus was over 20 dB SPL. Two-tailed t-tests were used to assess significant differences, with Bonferroni correction for multiple comparisons. Separately, we fit curves to the entire set of estimates for tinnitus and control subjects, together and split into normal hearing and hearing loss.

Results

Loudness estimates at threshold were significantly greater for tinnitus subjects than nontinnitus controls subjects when looking at both the whole group of subjects/conditions ($p = 3.5E-8$, Bonferroni-corrected p-value was .00833) and normal-hearing conditions ($p = 2.4E-05$). The difference was not significant when looking at hearing loss conditions ($p = .016$); the sample size for hearing loss conditions was also smaller. Predicted loudness

based on the fitted curve follows a similar pattern. Threshold was not quite significantly different when looking at the whole group ($p = .0087$), only normal-hearing conditions ($p = .018$), or only hearing loss conditions ($p = .22$). Theta was also not significantly different for the whole group ($p = .14$), normal-hearing conditions ($p = .08$), or hearing loss conditions ($p = .78$). These results can be seen in Figure 1.

These patterns are reflected in Figure 2, which shows curves fitted to the entire set of estimates for tinnitus and control listeners, separated into normal hearing and hearing loss as well as all together. All together, the estimated loudness near 0dB SPL was .23 for tinnitus compared with .063 for control. Theta was .069 for tinnitus and .054 for control. For normal hearing, the estimated loudness near 0dB SPL was .27 for tinnitus compared with.056 for control. Theta was .067 for tinnitus and .045 for control. For hearing loss, the estimated loudness near 20 dB SPL was .39 for tinnitus compared with .17 for control. Theta was .036 for tinnitus and .17 for control.

Figure 1. Comparisons between tinnitus and control values for (a), (b), (c) loudness estimates at thresholds, (d), (e), (f) thresholds, and (g), (h), (i). (a), (d), (g) represent comparisons within the normal hearing (NH) conditions, (b), (e), (h) represent comparisons within the hearing loss (HL)conditions, and (c), (f), (i) represent comparisons with all measurements together.

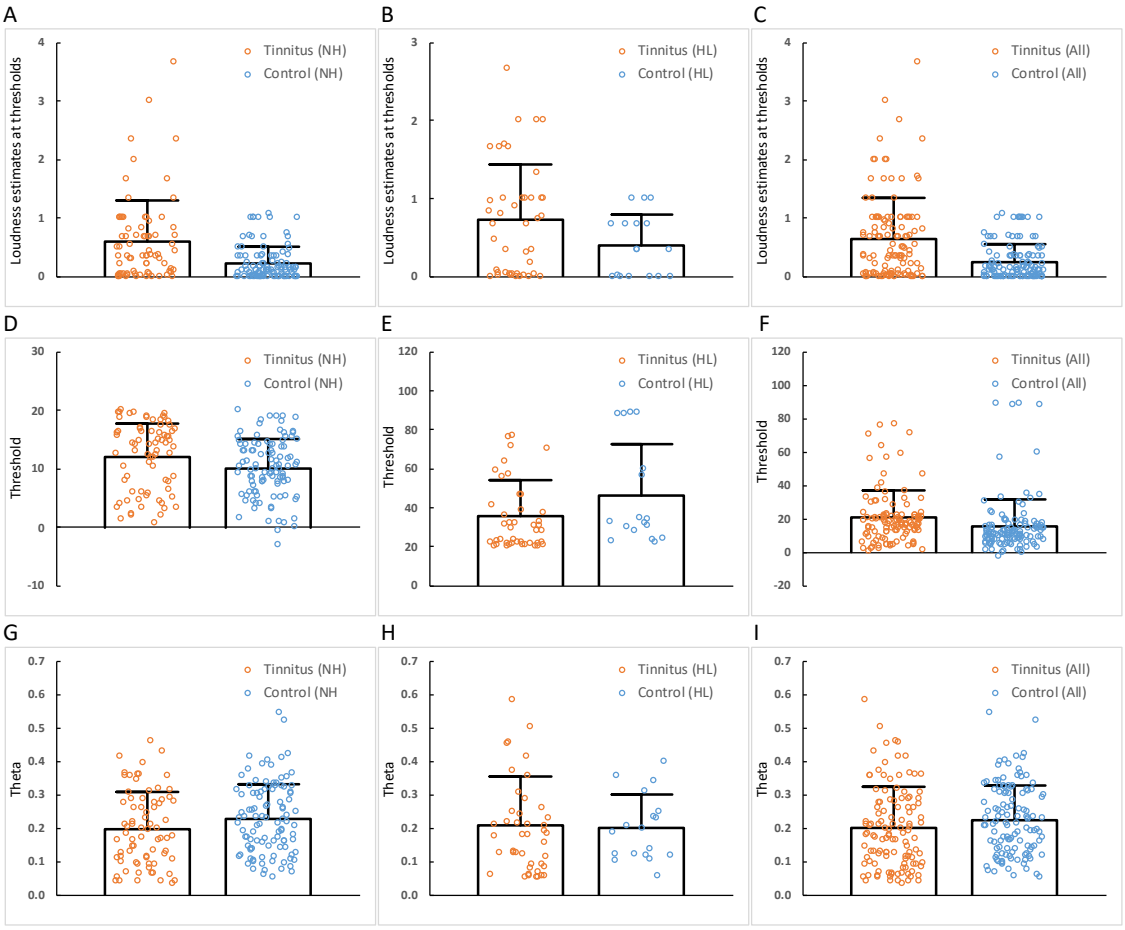
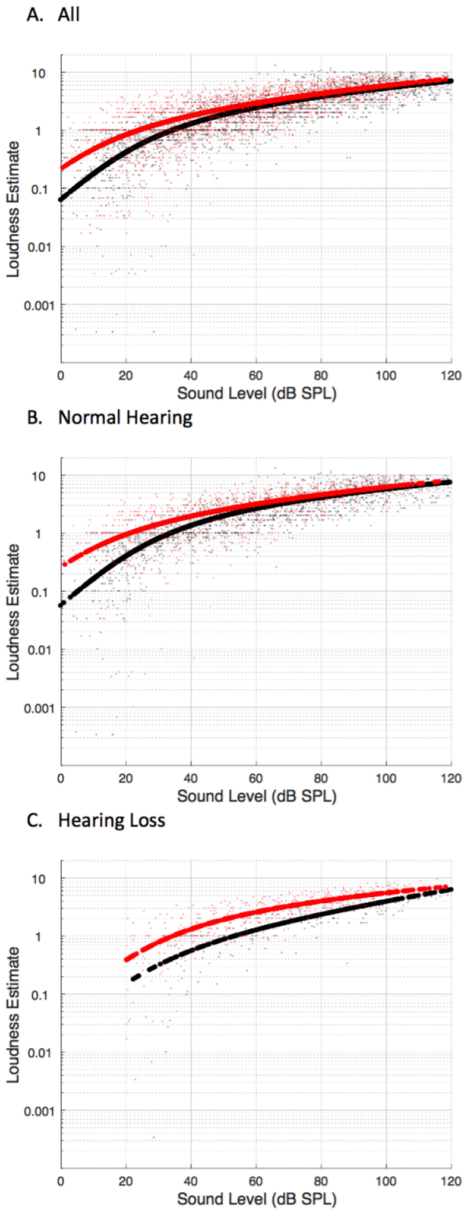


Figure 2. Fitted loudness growth curves for tinnitus (red) and control (black) listeners, showing (a) normal hearing and hearing loss combined, (b) normal hearing conditions, and (c) hearing loss conditions



Discussion

Loudness estimates at threshold were higher for subjects with tinnitus. Subjects in this group with hearing loss also had significantly higher thresholds and loudness at threshold than subjects with normal hearing, but the loudness effect was bigger for tinnitus than hearing loss (.7 and .7 vs .4 and .5 collected and estimated). There was no slope

difference for either hearing loss or tinnitus. The results of this study are consistent with predictions that both hearing loss and tinnitus increase loudness at threshold. Further, the hearing loss and tinnitus effects appeared to be additive. The effect of hyperacusis was not considered in this study, but a recent model (Zeng 2021) suggests that hyperacusis would increase the slope of the loudness growth function but not loudness at threshold.

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