UNIVERSITY OF CALIFORNIA,
IRVINE

Perceptual Consequences of Tinnitus: Effects of Sensory Deficits and Top-Down Attention

DISSERTATION

submitted in partial satisfaction of the requirements
for the degree of

DOCTOR OF PHILOSOPHY

in Psychology

by

Matthew Lyle Richardson

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2018

DEDICATION

To

My mother and father for all their love and support, and to Stephanni for her abiding love and patience, and for always believing in me.

Life is like riding a bicycle, to keep your balance, you must keep moving forward.

Albert Einstein

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ABSTRACT OF THE DISSERTATION

Perceptual Consequences of Tinnitus: Effects of Sensory Deficits and Top-Down Attention

By

Matthew Richardson

Doctor of Philosophy in Psychology

University of California, Irvine, 2018

Professor Fan-Gang Zeng, Chair

Tinnitus is the phantom perception of sound without an external acoustic source. Although tinnitus affects 10-15% of adults, with symptoms from mildly bothersome to debilitating, current treatments are limited by an inadequate understanding of its underlying pathophysiology. Improved understanding must address perception at all levels, from a peripheral deficit (e.g. hearing loss), to central auditory plasticity generating the internal signal, to higher-order brain networks governing its conscious awareness. The first study examined top-down mechanisms of attention in modulating tinnitus and potentially its loudness, pitch, or distress. Subjects with and without chronic tinnitus monitored one of two tonal steams, one with similar frequency as tinnitus and the other well-outside this region. Cortical evoked-potentials showed enhanced attentional gain when tinnitus subjects focused to the tinnitus frequency, which related to increased tinnitus loudness. A later enhancement to the non-tinnitus frequency suggested tinnitus also impacts selective processing of other sounds. A discrimination analysis indicated that attention-derived variables could serve as a biomarker to detect tinnitus from control subjects with similar age and hearing. The second study employed psychophysical methods to uncover sensory deficits in tinnitus and improve its diagnosis. Tinnitus subjects showed normal temporal acuity for detecting silent gaps in pure-tones, including those matching the tinnitus pitch. Although gap detection is widely used to assess tinnitus in animal research, assuming tinnitus “fills-in” the gap, the procedure appears ill-suited for clinical diagnosis in humans. Tinnitus subjects also showed normal frequency discrimination. However, slightly improved intensity discrimination of low-level sounds indicated a mechanism of increased auditory gain in the central pathways. Together, these results suggest that “bottom-up” sensory deficits in tinnitus have subtle impacts on basic auditory processing, while top-down attention plays a central role in gating tinnitus perception and may be developed as an objective clinical biomarker

CHAPTER 1

Perceptual Consequences of Tinnitus on Auditory Temporal, Frequency, and Intensity Processing.

ABSTRACT

Tinnitus is characterized by the perception of sound in the absence of an external acoustic source. Although most cases of tinnitus are associated with cochlear hearing loss, less is known about relationship between tinnitus and suprathreshold hearing abilities. Here we systematically studied the perceptual consequences of tinnitus to better understand its pathophysiology and assess a potential diagnostic tool. Psychoacoustic measures of temporal gap detection, frequency discrimination, and intensity discrimination were administered to subjects with chronic tinnitus and subjects with normal hearing. Tinnitus subjects showed normal temporal acuity for detecting silent gaps in pure-tones, including those matching the tinnitus pitch. Although gap detection is widely used to screen tinnitus in animal research, assuming tinnitus "fills-in" the gap, the procedure appears ill-suited for clinical diagnosis in humans. Tinnitus subjects also showed normal frequency discrimination when accounting for hearing loss. However, tinnitus subjects with normal hearing showed slightly improved intensity discrimination for a mid-range frequency and low sound level. Together, these results suggest that standard psychoacoustic measures utilized in this study lacked sensitivity to detect tinnitus-specific peripheral deficits beyond expected effects of cochlear damage but may engage a tinnitus mechanism of central auditory gain in tasks that probe intensity resolution.

INTRODUCTION

The perceptual consequences of a sensory disorder can shed light on its underlying pathology leading to better diagnosis and management of the disease. In audition, perceptual consequences have helped delineate the mechanisms of peripheral and central auditory disorders and their effects on different neural codes. For example, while threshold elevation and abnormal intensity perception is related to cochlear hearing loss (e.g. Moore, 1996; Oxenham & Bacon, 2003; Ryan & Dallos, 1975), impaired temporal processing is a consequence of disrupted auditory nerve (AN) activity in auditory neuropathy (Zeng, 2005). Tinnitus is another hearing condition characterized by perception of sound in the absence of an external source. Tinnitus is thought to arise from altered neural coding following peripheral deafferentation (e.g. hearing loss) and subsequent plasticity in the central auditory pathways that generates the internal sound (Eggermont & Roberts, 2012; Noreña & Farley, 2013).

Surprisingly little behavioral data has been reported on the perceptual consequences of tinnitus in basic auditory discrimination tasks. While most people with tinnitus have a measurable hearing loss, ~15% of tinnitus sufferers show clinically normal hearing thresholds (Henry et al., 2005), and only 20-40% of individuals with hearing loss develop tinnitus (Hoffman & Reed, 2004). Therefore, suprathreshold auditory assessments may better elucidate specific cochlear or nerve dysfunctions that trigger central auditory changes underlying tinnitus. For instance, abnormal spectral processing suggested that loss of inner hair cells (IHC), rather than outer hair cells (OHC), is more important to tinnitus development (Tan et al., 2013; Weisz et al., 2006), while studies of temporal resolution implicated auditory nerve dysfunction as a source of tinnitus-related deafferentation (Paul et al., 2017; Jain & Dwarkanath, 2016; *but see* Moon et al., 2015; An et al., 2014). Here we focused on perceptual consequences of tinnitus related to basic auditory processing of time, frequency, and intensity in the same subjects.

The first experiment employed a temporal gap detection task requiring subjects to detect a brief silent interval in a sinusoidal stimulus. This experiment had two main objectives. The first objective was to test to feasibility of gap detection as a diagnostic tool for tinnitus. Currently, clinical assessments of tinnitus rely heavily on self-reports (e.g. questionnaires, rating scales, matching) as objective measures in humans have not been developed. In contrast, animal research has widely adopted a gap detection paradigm to screen for tinnitus in animal models who cannot report their tinnitus. Current versions of this task measure the acoustic startle reflex (ASR), an automatic response to sudden loud sounds, which is suppressed when the startle stimulus is preceded by a brief gap in an ongoing noise (i.e. a cue). (Basavaraj & Yan, 2012). This so-called pre-pulse inhibition is reduced in animals assumed to have drug- or noise-induced tinnitus, suggesting the internal sound "fills-in" the silent gap (Jastreboff et al., 1988). However, some researchers have questioned whether in fact tinnitus or other factors actually account for these results (Lobarinas et al., 2013; Salloum et al., 2016). In a translational study by Fournier & Hébert, (2013), human tinnitus subjects showed reduced pre-pulse inhibition of an eye-blink ASR when the startle stimulus was preceded by a gap. However, these effects were observed regardless of whether the stimulus had a similar pitch as the subjects' tinnitus, casting doubt on whether tinnitus actually filled in the gap.

Few studies have assessed the utility of behavioral gap detection in human tinnitus sufferers. While one study reported impaired detection of gaps in broadband noise (Sanches et al., 2010) other studies using narrow-band stimuli with varying center-frequency reported no difference in performance between tinnitus and control subjects (Campolo et al., 2013; An et al., 2014; Boyen et al., 2015). A potential limitation of these studies was that gap detection stimuli were not explicitly matched to the tinnitus pitch. Moreover, stimuli were typically presented at moderate sound levels, whereas tinnitus loudness estimates rarely exceed 15-20 dB SL (above threshold) when matched to an external sound (Hallam et al., 1985; Andersson et al., 2003). Therefore, we attempted to optimize a gap detection paradigm for detecting tinnitus by employing sinusoidal stimuli matched individually to subjects' tinnitus pitch and presented at very low levels (5 - 15 dB SL). Comparison stimuli were presented across a range of frequencies and the reliability of the procedure was assessed over several sessions.

Another objective of the gap detection experiment was to examine temporal acuity in tinnitus. Animal studies demonstrate that extended noise exposure produces significant degeneration of the auditory nerve synapse innervating the inner hair cells (IHC), while leaving thresholds and outer hair cells (OHCs) intact (Kujawa & Liberman, 2009; Lin et al., 2011). This synaptopathy is predominant among nerve fibers with high characteristic frequency and high-threshold fibers crucial for coding sounds at moderate to high levels (>40 dB SPL) (Furman et al., 2013). Moreover, synaptopathy is proposed to degrade the precise synaptic transmission and synchronized firing that supports phase-locked encoding of temporal sound information. (Bharadwaj et al., 2014). Hence, we hypothesize that synaptopathy as a potential source of deafferentation in tinnitus would produce deficits gap in detection, particularly at higher frequencies or the tinnitus-matched frequency.

In the second experiment we examined frequency and intensity discrimination in tinnitus subjects. Except for one intensity discrimination study (Epp et al., 2012) and several others using frequency discrimination as a means of training to treat tinnitus (e.g. Flor et al., 2004; Herraiz et al., 2007), we did not find any other studies that have systematically measured intensity or frequency discrimination. We hypothesized that peripheral damage underlying tinnitus would selectively impair different neural codes contributing to these tasks. For instance, impaired temporal processing due to synaptic degeneration may disrupt phase-locked encoding for discriminating pitch at low frequencies. Alternatively, given that noise-induced synaptopathy largely affects high-threshold/high-frequency nerve fibers, deficits would be expected at higher stimulus frequencies and sound levels. In both tasks, we tested whether any deficits in tinnitus were specific to subjects' individual tinnitus pitch.

GENERAL METHODS

Subjects

Upon enrollment in the study all subjects received a standard hearing test with a Grason Stadler GSI 61 audiometer to measure pure-tone thresholds from 0.125 to 8 kHz in octave steps as well as 6 and 12 kHz. The experiments were undertaken with written consent of each subject and were approved by the Institutional Review Board of the University of California Irvine (UCI). All subjects received monetary compensation upon completing the experiment.

Equipment

All acoustic stimuli and experimental procedures were designed and conducted in MATLAB (The Mathworks, Natick, MA). Digitally generated stimuli were delivered via an external sound card (Creative Labs E-MU 0404 USB, Creative Technology Ltd., Singapore, 24-bit, 44.1 kHz) and amplifier (Sound Blaster E1, Creative Technology Ltd., Singapore). Stimuli were presented monaurally through circumaural headphones (Sennheiser HDA-200, Wedemark, Germany) that were calibrated with a sound level meter in a 2cc artificial ear coupler (Bruel & Kjaer, Nærum, Denmark). Subjects sat in a in a double-walled, sound-attenuating booth and performed the tasks using a keyboard and a PC monitor.

Tinnitus Assessment

All tinnitus subjects completed an online questionnaire to assess their experience with tinnitus and its subjective characteristics (see details in **Table 1**). The Tinnitus Functional Survey (TFI) measures intrusiveness of tinnitus and its psychosocial impact, e.g.

sleep, distress (Meikle et al., 2012). The Khalfa Hyperacusis Quotient (KHQ) assesses the presence of hyperacusis (reduced tolerance to sound) that is frequently comorbid with tinnitus (Khalfa et al., 2002). The questionnaire also assessed tinnitus type, location, duration since onset, frequency of tinnitus occurrence, and subjective loudness rating. All subjects had tinnitus for 6 months or longer. If subjects reported multiple tinnitus sounds, they first described the loudest or most predominant component followed by the other components.

During the first experimental session subjects characterized the pitch of their dominant tinnitus sound using the tinnitus spectrum approach (Norena et al., 2002). Subjects were presented ten pure-tones (1-sec duration) from 0.25 to 8 kHz in octave steps as well as 6 and 12 kHz in random order. First, they adjusted the loudness of each tone to equal that of their tinnitus, then rated the similarity of the tone in pitch to their tinnitus with a 0-to-10 Visual Analogue Scale (VAS). For each tone, the procedure was repeated three times and the average similarity ratings defined the subject's tinnitus spectrum as a function of frequency.

Subjects also performed a tinnitus pitch matching procedure at the beginning of each session. A custom computer interface allowed subjects to adjust the frequency (0.25 – 20 kHz in logarithmic steps) and sound level (0 to 110 dB SPL) of a pure-tone stimulus (500-ms duration, 1 Hz repetition) along two separate axes. The stimulus was presented to the same ear for unilateral tinnitus or the ear with louder tinnitus in bilateral cases. Subjects adjusted the stimulus to match as closely as possible the pitch and loudness of their predominant tinnitus component. Once a match was selected, they rated the similarity to their actual tinnitus with a 0-to-10 Visual Analogue Scale (VAS). Finally, to account for potential octave confusion (Graham and Newby, 1962, Vernon et al., 1980), subjects matched the loudness of three tones (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.

EXPERIMENT 1: Gap Detection

Methods

Subjects

Eleven (7 female) tinnitus and ten (5 female) control subjects participated in the study (see details in **Table 1**). Control subjects were young individuals (Mean = 21 years old, Std = 2) with normal hearing pure-tone thresholds (≤25 dB HL) at all audiometric frequencies (**Fig. 1a**). Tinnitus subjects ranged in age from 22 to 70 (Mean = 48, Std = 18) with hearing that varied from normal in younger subjects (n = 5) to age-appropriate loss in older subject (n = 6). The severity of tinnitus indexed by TFI score ranged from "small problem" to "very big problem."

Figure 1b shows the mean tinnitus spectra (left y-axis) and a histogram of the tinnitus matched frequencies (right y-axis) for all tinnitus subjects and sessions (35 total matches). Following a typical tinnitus pattern (Norena et al., 2002; Roberts et al., 2008), similarity ratings and pitch matches increased with higher frequencies and reached maxima between 8 – 12kHz. This pattern of tinnitus pitch paralleled the high-frequency sloping hearing loss observed in tinnitus subject (**Fig. 1a**). However, several tinnitus frequencies (8/35) were matched at lower frequencies <2000 Hz.

Table 1. Subject demographics, Tinnitus Characteristics

	Group	
	Tinnitus	Control
Number (female)	7 (4)	5 (5)
Age (range)	48±18 (22-70)	21±2 (19-24)
Tinnitus Ear (bilateral/left/right)	9 / 2 / 0	
Tinnitus type (tonal/non-tonal/both)	9 / 1 / 1	
Tinnitus Duration (years)	13±14 (1-40)	
Loudness Rating (0-10)	5±2 (3-7)	
TFI (0-100)	36±18 (18-74)	
KHQ (0-42)	13±11 (0-36)	

Subject demographics and Tinnitus Characteristics. Tinnitus ear reports whether subjects at tinnitus percepts only in the left or right ear or both ears. Tinnitus types consisted of tonal (single or multi tone), non-tonal (noise-like), or a combination of tonal and non-tonal components. Tinnitus duration is the years since estimated onset of tinnitus. Loudness of tinnitus was rated on a 0-10 scale (10-As Loud as Possible, 9-Extremely Loud, 8-Very Loud, 7-Loud, 6-Medium Loud, 5-Medium, 4-Medium Soft, 3-Soft, 2-Very Soft, 1-Barely audible). Parentheses indicated 1 SD.

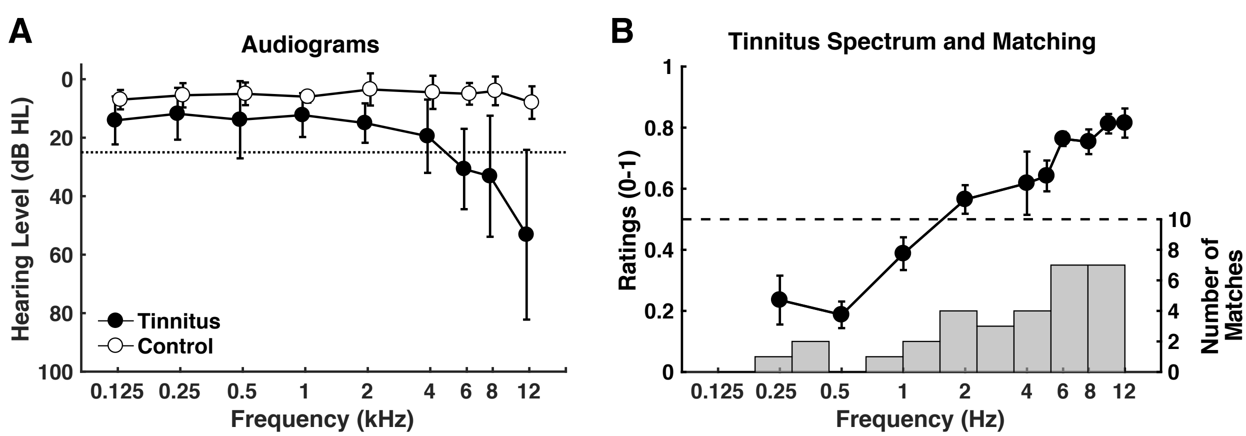

Figure 1. Audiogram, Tinnitus spectrum and pitch matches. **A.** Hearing thresholds as a function of frequency. Tinnitus subjects are indicated in solid circles and control subjects in open circles [change the grey filled circles to open circles because the histograms in panel B are also in grey]. Error bars indicate 1 SD. **B.** Tinnitus spectrum (black line) as a function of frequency and distribution of tinnitus pitch matches (histogram).

Stimuli

Stimuli to measure absolute hearing thresholds and gap detection thresholds consisted of sinusoids that were 400 ms in duration gated with 40 ms cosine-squared on/off ramps. The onset phase of the sinusoids was randomized on each presentation. All subjects were tested with three common frequencies: 500, 2000, 8000 Hz. In addition, tinnitus subjects were tested with frequencies obtained from the tinnitus matching procedure. In the gap detection task, sinusoids were either continuous (i.e. “standard”) or contained a temporal gap centered at 200-ms of the stimulus (i.e. “signal”). To produce the gap, the continuous sinusoid was modulated with a 2 ms cosine-squared offset/onset ramp, as previously described (Moore et al., 1992, 1993, Shailer and Moore, 1987). The gap duration was defined between the 6-dB down points of the offset/onset ramps. Gap detection stimuli were presented at three different sound levels: 5, 10, or 15 dB SL, defined as sensation level above the corresponding absolute hearing threshold. The use of low sound levels not only approximated the typical tinnitus level (Hallam et al., 1985, Andersson et al., 2003), but also reduced the potential use of spectral “splatter” in detecting the transient gap such that additional masking noise was not necessary (Moore et al., 1993, Formby and Forrest, 1991).

Procedures

At the beginning of each experimental session tinnitus subjects performed the tinnitus-matching procedure to estimate their tinnitus pitch and level. Subjects then performed an absolute threshold task for all task frequencies. Finally, they performed the gap detection task for all task frequencies in one or two of the sound level conditions. Control subjects followed the same testing sequence excluding the tinnitus matching procedure.

For both absolute threshold and gap detection tasks an adaptive three-alternative, forced-choice, 2-down and 1-up procedure was used to estimate the 70.7% percent correct performance (Levitt, 1971). Each trial consisted of three presentation intervals separated by 400 ms and marked visually by buttons on a computer interface. In the absolute threshold task, one interval randomly contained the sinusoidal signal while the other two were silent. The subject indicated via button click which of three contained the signal and feedback of "correct" or "incorrect" was provided after each response. Two consecutive correct responses would decrease the signal level and one incorrect response would increase the signal level. Each transition from an increment to a decrement or vice versa was recorded as a reversal point. The signal level began at 45 dB SL (or higher in cases of hearing loss) and varied first in steps of 10 dB SPL until the first reversal, 5 dB SPL until the fourth reversal, then 2 dB SPL for the remaining trials. After 10 reversal points, the threshold was calculated as the average dB SPL level over the last 6 reversals. Only one threshold run was completed for each frequency per session.

In the gap detection task, a signal stimulus containing the gap was randomly assigned to one interval while the other two contained the continuous standard. The subject indicated via button click which of three contained the signal and feedback of "correct" or "incorrect" was provided after each response. Two consecutive correct responses would decrease the gap duration and one incorrect response would increase the gap duration. The starting gap duration was always large enough to be easily detected (70-130 ms) and was subsequently varied by a constant factor of 1.4. Ten reversals were obtained for each run and a threshold was measured as the geometric mean of the last six reversals. 3-4 threshold runs were completed per subject for each frequency and level condition, except in some cases when a time-constraint only allowed for 2 threshold runs.

On the first session, subjects received 2-3 training blocks at the easier level conditions (10 or 15 dB SL), which always starting with the 500 Hz tone then moved to other frequencies. Thresholds from training were not included in the final analysis.

Table 2 details the number of sessions and level conditions performed by tinnitus subjects in the gap detection task. To complete data collection and assess the reliability of tinnitus-matched gap detection over multiple time-points, most subjects (except one) participated in two or more testing sessions. Five of the eleven subjects completed all three level conditions, five completed at least two levels, and one completed only the 5 dB SL condition. Likewise, control subjects completed the data collection over two to three sessions. Four of the ten control subject completed all three level conditions, while the remaining six completed two levels.

Statistical analysis

A 2-way mixed analysis of variance (ANOVA) was used to assess significant differences between groups or across stimulus frequencies. Gap thresholds were first log-transformed to achieve normality. Results were assessed for main effects (One between-subjects factor, Tinnitus vs. Control; One within-subjects factor, 500, 2000, 8000 Hz, tinnitus-match, and interactions, Group X Frequency). Should there be an overall significant main effect or interaction, posthoc *t*-tests were conducted to examine the conditions under which the difference occurred. Where appropriate the significance would be adjusted by

Bonferroni corrections to account for multiple testing. Statistics were conducted in MATLAB (The Mathworks, Natick, MA).

Results

Tinnitus Matches

Table 2 shows individual tinnitus match data recorded in each session, including frequency, likeness rating, level in dB SL, gap detection condition that was tested. In some cases, two matches were recorded when the subject indicated multiple tinnitus components or when octave confusion was highly ambiguous (e.g. T10 session 1). Tinnitus-matched frequencies typically showed good repeatability (e.g. < ¼ oct) across two or more sessions, but also showed some large deviations. For instance, T07 matched three out of four frequencies to ~2000 Hz but also one at 406 Hz. Tinnitus-matched similarity ratings were generally high with an average of 0.77 (SD = 0.14). Finally, tinnitus-matched sensation levels were generally low with an average of 13 dB SL (SD = 10 dB SL), replicating previous reports of tinnitus level (Hallam et al., 1985, Andersson, 2003).

Table 2. Tinnitus match information and session number

	Session 1				Session 2				Session 3				Session 4			
Subject	**Frequency**	**dB SL**	**Rating**	**Levels**	**Frequency**	**dB SL**	**Rating**	**Levels**	**Frequency**	**dB SL**	**Rating**	**Levels**	**Frequency**	**dB SL**	**Rating**	**Levels**
T07	2157	29	0.74	15/10	1918	24	0.7	15/10	406	32	0.67	15	2000	23.8	0.49	5
T09	1000/2000	18/3	.44/.67	15/10	2379	4	0.54	15	3148	7	0.51	15/10	3602	21	0.63	10/5
T10	827	13	0.77	15/10	827/1568	13/15	.77/.81	15/10	1302	20	0.76	15	1302	21	0.76	5
T06	5590/10kHz	27/16	0.73/0.86	15/10	10,314	30	0.83	15/10	8975	31	0.82	5				
T11	2727	-3	0.93	10	5373	10	0.92	10/5	3879	2	0.69	15				
T08	299	7	0.95	15	6016	20	0.98	15/10	5507/6736	5/4	0.95/.98	15/10				
T02	5686	1	16	15	5003	14	0.87	15/10								
T12	11774	8	0.93	5	9014	12	0.86	5								
T13	8000	4	0.85	10/5	8936	4	0.77	5								
T05	4000	3.2	0.63	10/5	250/5252	12/1.25	.7/.93	5								
T17	13131	1	0.83	10/5												

Individual tinnitus match data organized by sessions. Data includes that match frequency, sensation level, similarity rating, and the level conditions tested in the gap detection task.

Gap Detection Performance

Figure 2 shows that gap detection was similar as function of test frequency for each sensation level for both tinnitus and control groups. Indeed, 2-way ANOVA found no significant main effects of either group or frequency ($p > 0.09$) at any of the three sensation levels and no significant interaction effects ($p > 0.16$). In addition, gap detection at tinnitus-matched frequencies (TF) was not significantly different than control or tinnitus thresholds at any of the test frequencies ($p > 0.06$).

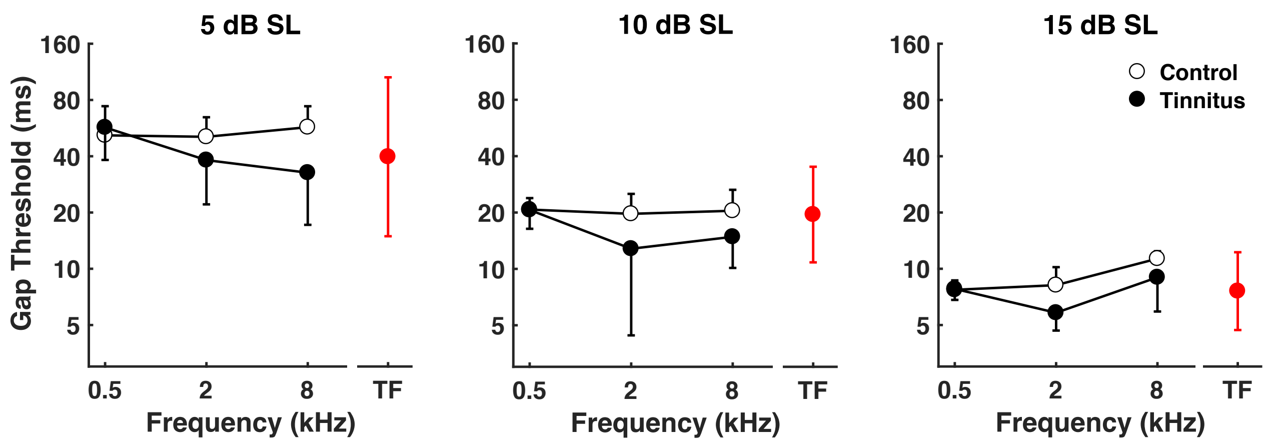

Figure 2. Gap detection thresholds. Each panel shows average gap detection thresholds as a function of frequency, including the tinnitus-matched frequency (TF). Error bars indicate 1 SE. Separate panels are the different sensation level conditions (5, 10, 15 dB SL).

Figure 3 shows that gap detection, averaged across the test frequencies, improved as a function of stimulus level in both control and tinnitus groups ($F(1,18) = 35.672$, $p < 0.001$). Gap detection showed the same pattern as a function of level at the tinnitus-matched frequencies in tinnitus subjects ($F(1,8) = 4.525$, $p = 0.048$). Overall, incrementing sensation level by 5 dB SL improved gap detection by a factor of ~2.5.

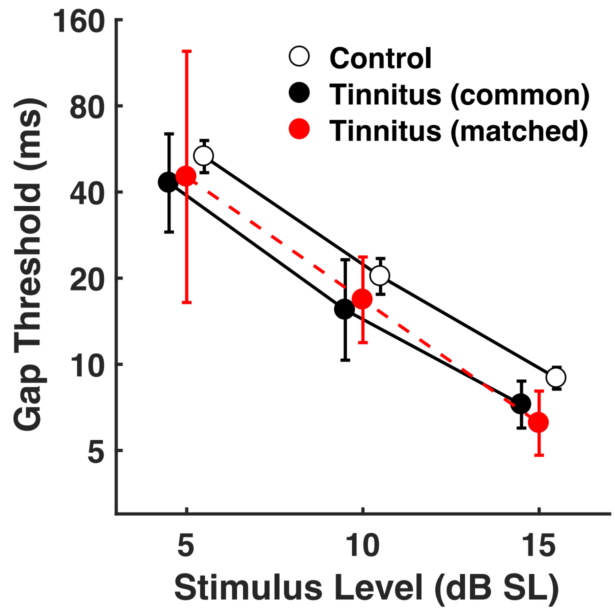

Figure 3. Gap detection thresholds as function of level. Gap thresholds were averaged over the common frequencies for Control (open) and Tinnitus "standard" (black) data. Tinnitus "matched" (red) data are averaged all tinnitus-matched stimuli. Error bars indicate 1 SE.

Tinnitus-matched gap detection by subject and session

Figure 4 shows gap detection thresholds for tinnitus-matches across sessions for each tinnitus subject. For each sensation level, individual data are compared to normative range of 2 standard deviations of the normal control thresholds (averaged across common frequencies). Tinnitus subjects are arranged (from left to right) by their average tinnitus-match frequency with individual tinnitus frequencies indicated by the symbol size.

Overall, tinnitus-matched gap detection performance was highly variable across individuals. Only one of eleven subjects (subject 3) consistently had one or more thresholds above the normative range. Performance was also highly variable between sessions, where tinnitus matches within a given subject could span the entire normative range (e.g. subject 3 and 5). There was no discernable pattern of frequency with respect to subject arrangement (e.g. left to right) or symbol size.

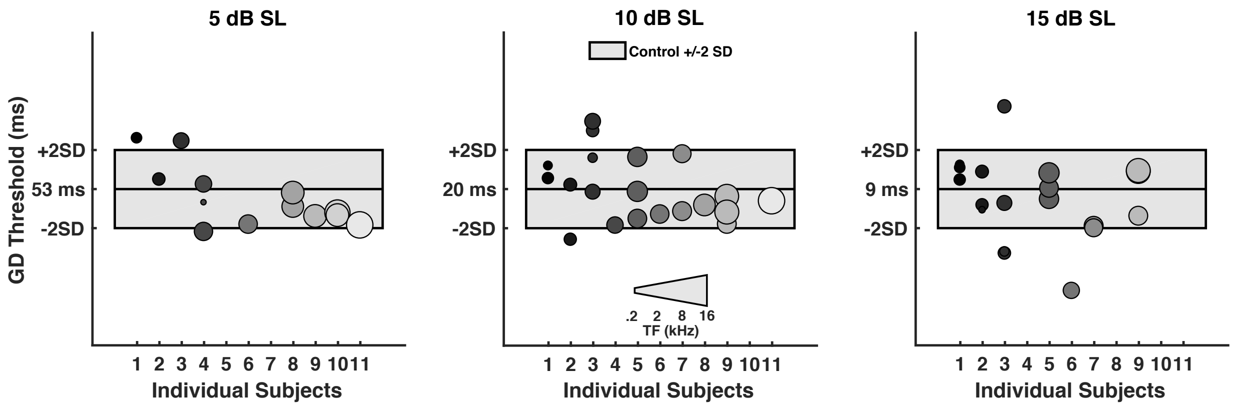

Figure 4. Gap detection thresholds for all individual tinnitus-matched stimuli. Separate panels show data for each sensation level condition (5, 10, 15 dB SL). Shaded boxes are the normative range (Mean +/- 2 SD) computed over the control subject data at all frequencies. Individual tinnitus subjects (x-axis) are different colors and arranged from left-to-right in order over their mean tinnitus match frequency. Larger marker sizes indicate higher matched frequency.

EXPERIMENT 2: Frequency and Intensity Discrimination

Methods

Subjects

Seventeen (8 female) tinnitus and ten (5 female) control subjects participated in this experiment (see details in **Table 3**). Control subjects were young individuals (Mean = 21, Std = 2) with normal hearing thresholds (≤25 dB HL) at all audiometric frequencies (**Fig. 5a**). Tinnitus subjects ranged in age from 20 to 70 (Mean = 42, Std = 17). Ten tinnitus subjects with ages 55 years or below had normal hearing thresholds (≤25 dB HL for 0.25-8 kHz). The remaining older subjects (n = 4, >60 years old) and two young subjects (20 and 33 years old) had mild high-frequency hearing loss (**Fig. 5a**). All control subjects and nine tinnitus subjects also participated in Experiment 1.

Tinnitus assessment including online questionnaire with surveys (THI, KHQ) and tinnitus characteristics are summarized in **Table 3**. Average tinnitus spectra and a histogram of pitch matching data are shown in **Figure 5b**.

Table 3. Subject demographics and Tinnitus Characteristics

	Group	
	Tinnitus	Control
Number (female)	8 (9)	5 (5)
Age (range)	42±17 (20-70)	21±2 (19-24)
Tinnitus Ear (bilateral/left/right)	14 / 3 / 0	
Tinnitus type (tonal/non-tonal/both)	14 / 2 / 1	
Tinnitus Duration (years)	9±12 (1-40)	
Loudness Rating (0-10)	5±2 (3-7)	
TFI (0-100)	45±20 (15-78)	
KHQ (0-42)	16±11 (0-40)	

Subject demographics and Tinnitus Characteristics. Same as **Table 1**.

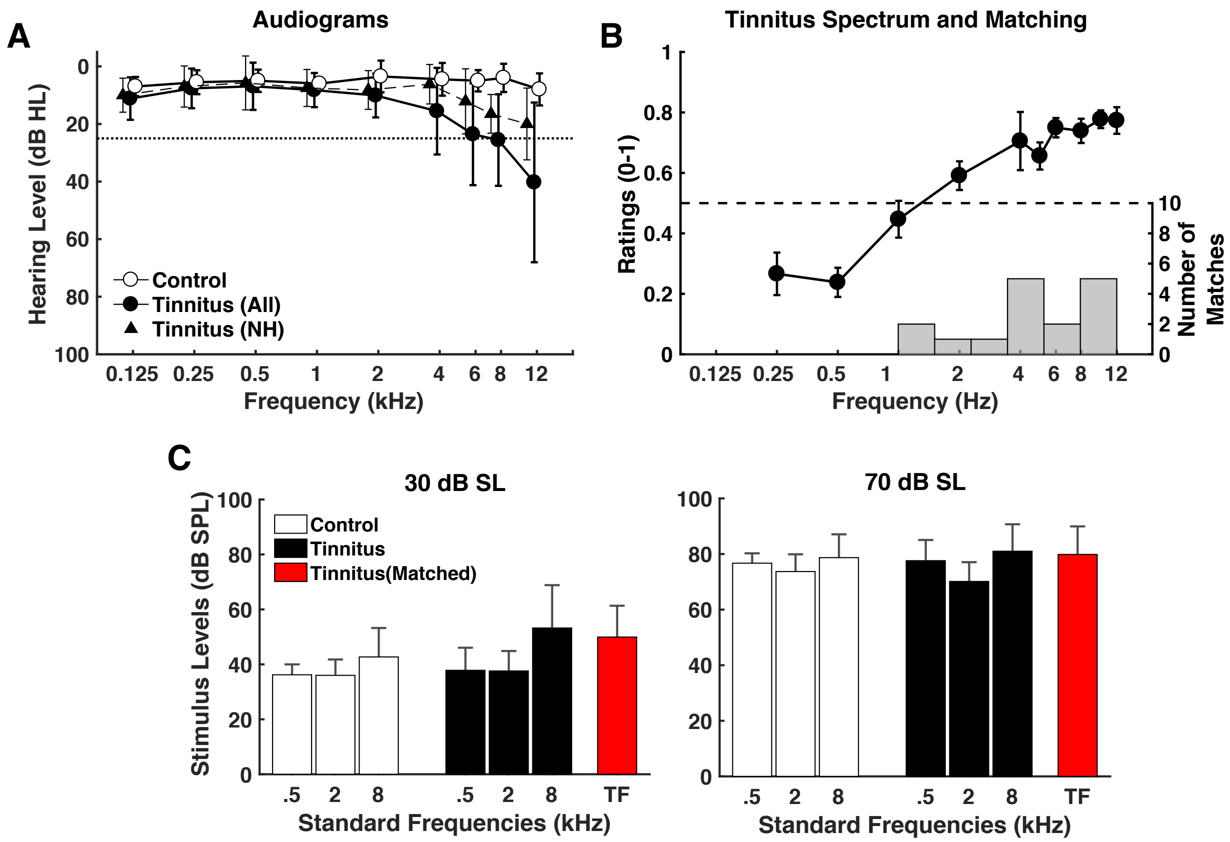

Figure 5. Audiogram, Tinnitus spectrum and pitch matches, and loudness balance. **A.** Hearing thresholds as a function of frequency. Tinnitus subjects are indicated in black circles, normal hearing tinnitus subjects in black triangles (dashed), control subjects in light gray. Error bars indicate 1 SD. **B.** Tinnitus spectrum (black line) as a function of frequency and distribution of tinnitus pitch matches (histogram). **C.** Average stimulus levels achieved in the loudness balancing procedures at 30 dB SL (left) and 70 dB SL (right).

Stimuli

Frequency discrimination (FD) and intensity discrimination (ID) consisted of identical sinusoidal stimuli that were 400 ms in duration gated with 40 ms cosine-squared on/off ramps. All subjects were tested with three common frequencies: 500, 2000, 8000 Hz. Tinnitus subjects were tested with one additional frequency obtained from the tinnitus matching procedure. In the FD task, the signal stimulus varied with a higher frequency than a fixed frequency standard and in the ID task the signal stimulus varied with a higher intensity than a fixed level standard.

The stimuli where presented in two level conditions, referred to as 30 dB SL ("soft") and 70 dB SL ("loud"). Specifically, subjects adjusted the level of each stimulus to match the loudness of a 500 Hz reference tone presented at 30 and 70 dB SL. A procedure equating loudness was chosen over equal sensation level because tinnitus subjects display steeper loudness growth (Hebert et al., 2013; Reavis et al., 2012) that might differentially influence performance across frequencies. In separate runs for the 30- and 70-dB SL conditions, the subject manually adjusted the level of each task frequency (in random order) until the loudness matched the reference as close as possible. This procedure was repeated three times for all frequencies and the averages were used as the stimulus levels in the task. **Figure 5c** shows the resulting stimulus levels in dB SPL. There were no significant group differences between corresponding frequencies ($p > 0.05$, two-sample *t*-tests). The levels of the tinnitus-matched frequencies closely resembled the 8000 Hz stimuli, likely reflecting the predominantly high-frequency tinnitus across subjects (**Fig 5b**).

Procedures

Discrimination in FD and ID experiments was measured using an adaptive three-alternative, forced-choice, 2-down and 1-up procedure, to obtain the point of 70.7% percent correct performance (Levitt 1971). On each trial, the standard was assigned randomly to two of three successive presentation intervals and the remaining interval contained the signal. Listeners were asked to select via buttons on a computer interface which of the three intervals was different than the other two, i.e. the signal interval. Feedback of "correct" or "incorrect" was provided after each response. Two consecutive correct responses would decrease the frequency/intensity of the target and one incorrect response would increase the frequency/intensity of the target. Each transition from an increment to a decrement of the target or vice versa was recorded as a reversal point. In the FD experiment, the target started 20% higher than the standard frequency and varied by a factor of 2 until the fourth reversal and a factor of 1.41 thereafter. In the ID experiment, the target intensity started 8 dB SPL higher than the standard and varied by 1 dB SPL for the first four reversals and .25 thereafter. As most subjects performed this experiment in tandem with other psychoacoustic tasks (Experiment 1), a time constraint limited the number of threshold runs to one per frequency/level condition. As a tradeoff, the total reversals in a run was increased to twelve and thresholds were calculated as the geometric mean (FD) or arithmetic mean (ID) over the last eight reversals. Thresholds are reported in Weber's fraction ($\Delta F/F$ or $\Delta I/I$).

Subjects completed all frequency and level conditions for either the FD or ID task before moving to the other tasks with the order balanced across subjects. Within each task, frequency and level conditions were presented in random order. Prior to each task, subjects completed at least 2 training blocks at the 70 dB SL level, always starting with 500 Hz then moving to other task frequencies. Additionally, to screen for noisy threshold runs showing large variance across trials, runs with standard deviation exceeding 4% of the standard frequency in the FD task and .75 dB SPL in the ID task were excluded from the analysis and the condition was repeated until the subject met these criteria.

Statistical analysis

A 2-way mixed analysis of variance (ANOVA) was used to assess significant differences between groups or across stimulus frequencies. Results were assessed for main effects (One between-subjects factor, Tinnitus vs. Control; One within-subjects factor, 500, 2000, 8000 Hz, tinnitus-match, and interactions, Group X Frequency). Should there be an overall significant main effect or interaction, posthoc *t*-tests were conducted to examine the conditions under which the difference occurred. Where appropriate the significance would be adjusted by Bonferroni corrections to account for multiple testing. Statistics were conducted in MATLAB (The Mathworks, Natick, MA).

Results

Frequency Discrimination

Figure 6 shows frequency discrimination as a function of standard frequency in tinnitus subjects and normal controls. On average, both groups required <1% to discriminate a pitch difference for 500 and 2000 Hz and <5% difference at 8000 Hz. Although tinnitus showed slightly poorer frequency discrimination than normal controls across conditions, the 2-way ANOVA showed no significant main effects of group for either level condition (30 dB SL: $p = 0.18$, 70 dB SL: $p = 0.23$) nor any interaction effects ($p > .7$).

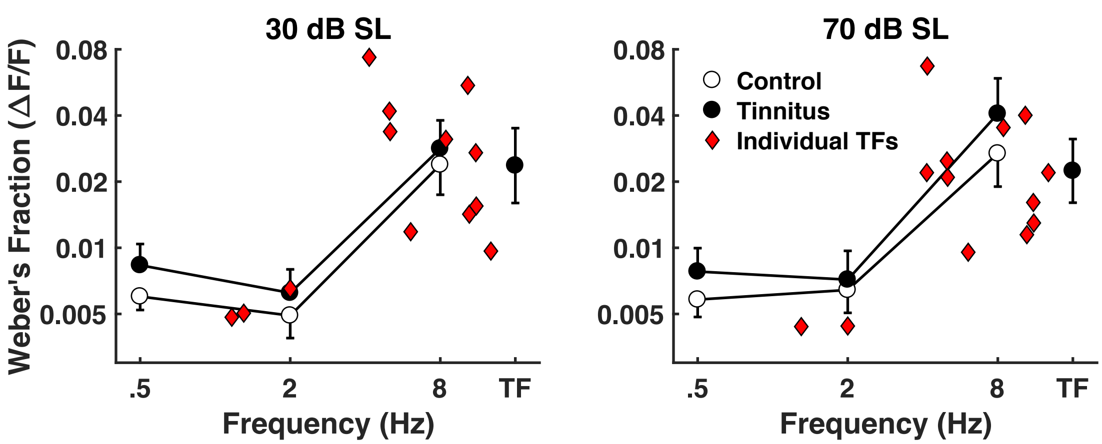

Figure 6. Frequency discrimination. Average frequency discrimination thresholds as a function of frequency, including the tinnitus-matched frequency (TF). Separate panels shows the level condition, 30 dB SL (left) and 70 dB SL (right). Control subjects are indicated in open circles, Tinnitus in black. Thresholds for the tinnitus-matched stimuli are indicated by red diamonds.

Figure 6 also shows frequency discrimination at the tinnitus-matched frequencies for tinnitus individuals (red diamonds). Similar to normal controls, the tinnitus subjects produced better frequency discrimination at lower frequencies (<=2k) than higher frequencies. When restricting tinnitus-matched frequencies to those within an octave of 8000 Hz, the average frequency discrimination in tinnitus subjects was not significantly different from the performance at 8 kHz in the same tinnitus subjects (paired sample *t*-test*:* 30 dB SL: p = 0.74; 70 dB SL: p = 0.064) or from that at 8 kHz in the control group (two-sample *t*-test: p > 0.5). However, there was a significant correlation in frequency discrimination between 30 and 70 dB SL (R = .88, p <.001), suggesting a level-independent common mechanism and good test reliability within subjects.

Intensity Discrimination

Figure 7 shows intensity discrimination as a function of standard frequency in tinnitus subjects and normal controls. Except for a significant level effect, or the well-known "near-miss to Weber's law" (F(1,22) = 251.532, p < .001), there was no significant main effect on stimulus frequency (p > 0.1) or tinnitus status (p > 0.064) nor was there any significant interactions at either level (p > 0.4)

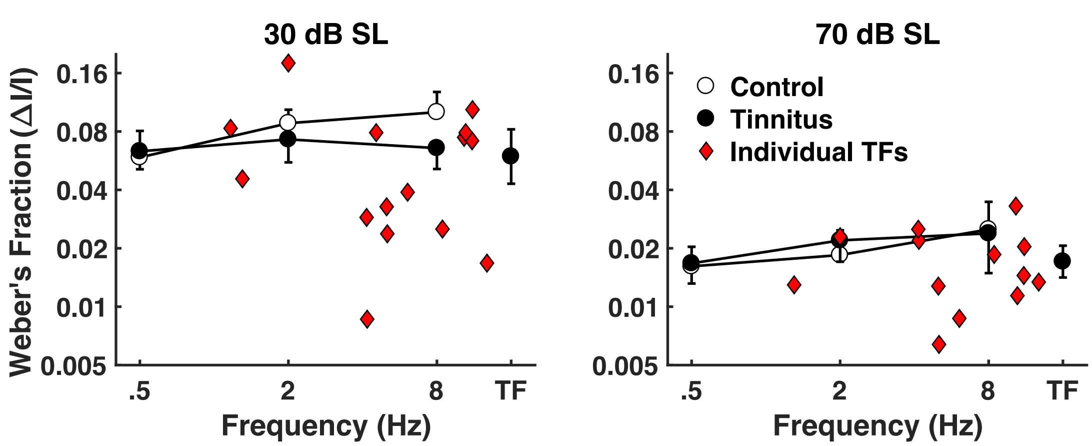

Figure 7. Intensity Discrimination. Average intensity discrimination thresholds as a function of frequency, including the tinnitus-matched frequency (TF). Separate panels shows the level condition, 30 dB SL (left) and 70 dB SL (right). Control subjects are indicated in open circles, Tinnitus in black. Thresholds for the tinnitus-matched stimuli are indicated by red diamonds.

F**igure 7** also shows intensity discrimination at the tinnitus-matched frequencies for tinnitus individuals (red diamonds). As with the FD results, tinnitus-matched ID was compared statistically to performance at 8000 Hz with tinnitus-matched data restricted to those within an octave of 8000 Hz. No significant differences were observed within the same tinnitus subjects at either sensation level (paired sample *t*-test*:* 30 dB SL: $p = 0.62$; 70 dB SL: $p = 0.18$). Tinnitus-matched Weber fractions were significantly lower than controls at 30 dB SL ($t(20) = -2.65$, $p = 0.0154$), but not 70 dB SL ($p = 0.45$).

Stratification by Hearing Loss

Both frequency and intensity discrimination are known to depend on age (He et al., 1998) and hearing loss (McDermott et al., 1998; Thai-Van et al., 2003). To better control for hearing ability in the present study, subjects were stratified by their pure-tone thresholds in the tinnitus ear (**Fig 8**). A normal hearing (NH) group consisted of 10 subjects with pure-tone threshold <25 dB HL from 125 – 12,000 Hz, except for 3 subjects with 30 dB HL (n=2) and 40 dB HL (n = 1) at 12,000 Hz (see **Fig 5b**). The remaining 7 subjects comprised the hearing loss (HL) group.

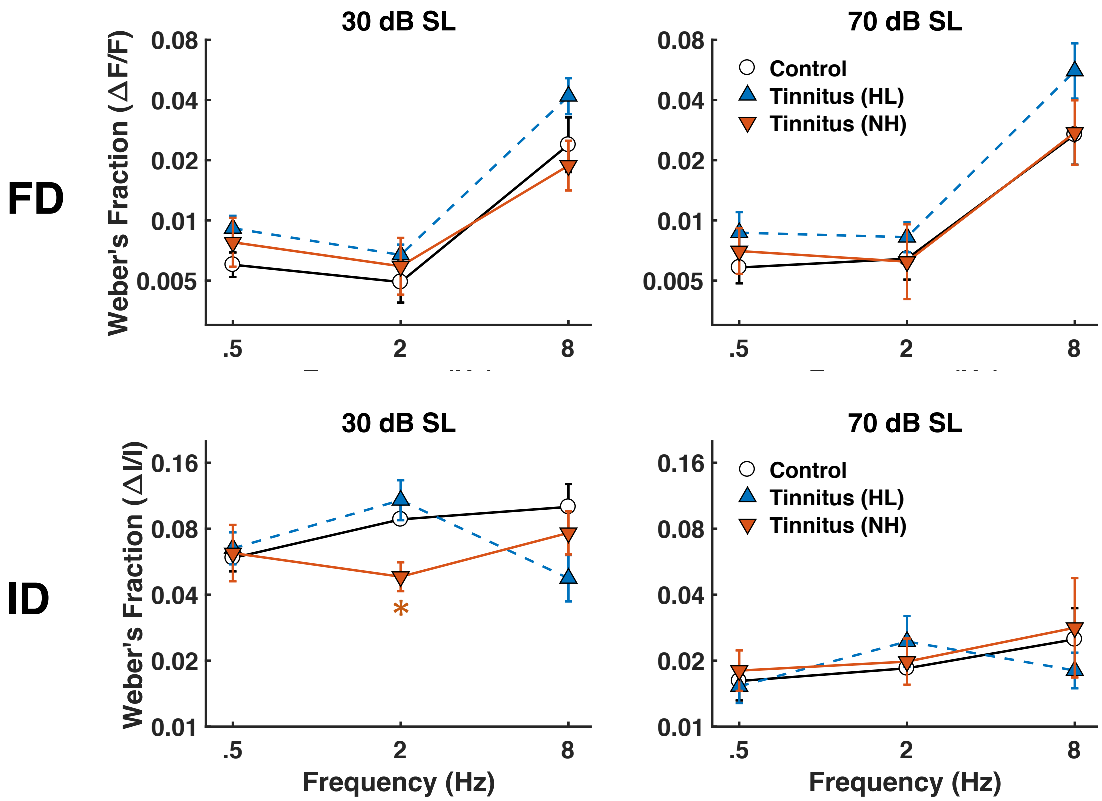

Figure 8. FD and ID by Hearing Loss. Average frequency and intensity discrimination thresholds as a function of frequency, including the tinnitus-matched frequency (TF). Control subjects are indicated with open circles, Tinnitus subjects with hearing loss with upward blue triangles, Tinnitus subjects with normal hearing with downward red triangles. Separate panels shows the level condition, 30 dB SL (left) and 70 dB SL (right). Thresholds are expressed as weber fractions relative to the standard frequency (ΔF/F).

As expected, frequency discrimination worsened for the group with hearing loss (dashed lines in **Fig 8**). ANOVA revealed a significant main effect between the HL tinnitus and normal controls in both level conditions (30 dB SL: $F(1,14) = 7.95$, $p = 0.014$; 70 dB SL: $F(1,14) = 6.66$, $p = 0.022$). NH tinnitus subjects showed no significant group differences from controls in frequency discrimination (ANOVA, $p > 0.4$).

Intensity discrimination showed group differences between normal controls and both tinnitus groups in the 30 dB SL condition (**Fig 8** bottom panels). ANOVA returned a significant Group X Frequency interaction for the HL group ($F(1,14) = 4.83$, $p = 0.016$), where

Weber's fraction was lower than controls at 8000 Hz (although post-hoc *t*-test did not reach Bonferroni correction of $p<0.004$, $\alpha = .05/12$). Group differences between NH tinnitus and normal controls were not significant in the ANOVA model (Main: $p = .088$, Int = 0.12). However, testing at individual frequencies revealed a significant effect of tinnitus at 2000 Hz ($t(18) = 3.7251$, $p = .0015$) such that intensity discrimination was ~4% (2-fold) better in NH tinnitus than controls (Bonferroni corrected, $p<004$). No significant group differences for either NH or HL were observed at 70 dB SL, suggesting that tinnitus or hearing loss affected intensity discrimination only at low sound levels.

DISCUSSION

This study investigated the perceptual consequences of tinnitus along three fundamental acoustic dimensions, time, frequency, and intensity. Compared to normal controls, tinnitus subjects showed no difference in temporal acuity for detecting silent gaps in pure-tone markers, including those marker frequencies matching the tinnitus pitch. Tinnitus subjects also showed normal frequency discrimination when accounting for hearing loss. Two subgroups of tinnitus sufferers with and without hearing loss showed evidence for improved intensity discrimination at high frequencies (2000 and 8000 Hz) and low sensation level (30 dB SL). Here we discuss these results with respect to previous findings and known pathologies in tinnitus.

Gap Detection

Sinusoidal gap detection in the present study replicated previous findings of normal performance in tinnitus subjects detecting gaps in narrow-band noise (Compolo et al., 2013;

Boyen et al., 2015). In contrast, one study reported poorer detection of gaps in broadband noise (Sanches et al., 2010), although this was not replicated in a study with a larger sample (An et al., 2014). A novel approach in the present study was the use of stimuli there were both matched to subject's tinnitus pitch and presented at sensation levels near or below their tinnitus loudness. If tinnitus is capable of filling-in the gap, we expected a deficit to be greatest at the lowest stimulus level of 5 dB SL. However, tinnitus-matched gap detection remained similar if not slightly better than controls at all levels (**Fig 3**). This and the previous results suggest that a behavioral gap detection, commonly used to screen tinnitus in animal research, may be ill-suited as a diagnostic tool in human patients

We observed large variations in tinnitus-matched gap detection both across subjects and between individuals' tinnitus matches (**Fig 4**). Using a correlational approach, we found this variability was unrelated to various tinnitus properties, including matched frequency, loudness, and similarity rating ($R = -0.35 – -0.05$, $p = .11 - .79$; except an effect of similarity at 5 dB SL, $R = -0.68$, $p = .0006$). On the other hand, lower gap thresholds were consistently related to higher hearing thresholds at the matched frequency (i.e. greater hearing loss) (**Fig. 9**: 5 – 15 dB SL, $R=-.59 – -.39$, $p=.004 – .049$). Thus, while input sensation levels were matched across subjects, gap detection remained sensitive to the overall stimulus level. This effect may be explained by changes in central auditory processing related to hearing loss and/or tinnitus. Both tinnitus and cochlear damage produces steeper than normal loudness growth (i.e. loudness recruitment) which is linked to increased neural gain measured within the auditory brainstem and cortex (Auerbach et al., 2014; Hebert et al., 2013; Noreña, 2011). Increased central gain may have compensated for the elevated auditory thresholds in subjects with more hearing loss, which in turn produced more audible gaps. This parallels the improved gap detection with increasing stimulus level shown in **Figure 3** and demonstrated by previous studies (Moore et al., 1993; Hall & Grose, 1997; Horwitz et al., 2011). This explanation can also account for the slightly reduced (although not significantly) gap thresholds observed in tinnitus at 2000 and 8000 Hz (**Fig 2**).

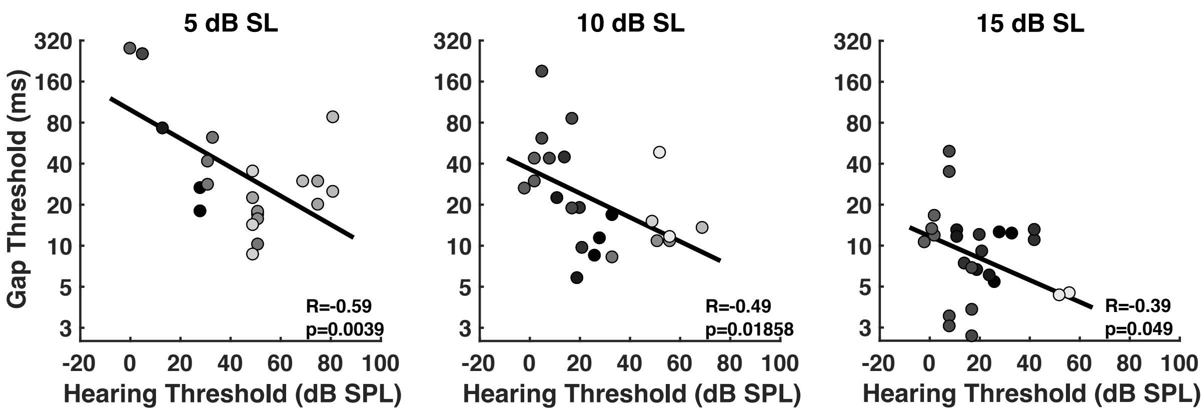

Figure 9. Pearson correlations and regression lines between tinnitus-matched gap detection threshold and the corresponding hearing threshold. Individual subjects are indicated by shades of gray. Correlations include all individual matched frequencies.

Normal sinusoidal gap detection further suggests that temporal acuity was unimpaired in tinnitus subjects. Consistent with previous studies in normal listeners, gap detection thresholds were similar across frequencies (**Fig 6**), providing no evidence of high-frequency synaptopathy (Green, 1973; Moore et al., 1993; Shailer & Moore, 1987). These results contradict reports of decreased amplitude modulation detection in tinnitus (Paul et al., 2017, Jain & Dwarkanath, 2015) as well as deficits in speech recognition (Gilles et al., 2016; Ivansic et al., 2017), which are interpreted as impaired temporal processing. This discrepancy may relate to differences in the nature of these tasks. While both gap and modulation detection are thought to probe temporal resolution their outcomes actually show no correlation (Formby & Muir, 1988; Shen & Richards, 2013). Importantly, gap detection is thought to probe low-rate temporal changes, which also rely on the intensity resolution of the auditory system (Strickland & Viemeister, 1997, Shen, 2014).

Frequency Discrimination

Although frequency discrimination has proved useful in probing different auditory neural codes (e.g. temporal vs. place-rate) (Zeng et al, 2005), we found no condition-specific deficits in our full tinnitus group. After stratifying by audiometric status, a non-specific deficit in the HL group could be attributed to cochlear damage, which uniformly impairs discrimination for all frequencies (Freyman & Nelson, 1991). Frequency discrimination remained unimpaired in the NH tinnitus subjects, which is broadly consistent normal spectral processing of tinnitus subjects in a spectral ripple test (Moon et al., 2015), and better frequency selectivity in a forward masking task (Tan et al., 2013). These results may suggest that significant OHC damage, which elevates hearing thresholds and reduces frequency selectivity, is not pertinent to tinnitus. However, subtle IHC dysfunction or disrupted nerve activity that is undetected by these tasks may still be an important source a of peripheral deafferentation. Lastly, the variability in tinnitus-matched frequency discrimination likely reflected the range of hearing ability across subjects as correlations with hearing threshold were highly significant (30 dB SL $R = 0.87$, $p < .001$; 70 dB SL: $R = 0.77$, $p = .002$).

Intensity Discrimination

Although intensity discrimination in the full tinnitus group was comparable to normal controls, a more complex pattern emerged among subgroups with normal and impaired hearing. Interestingly, both groups showed reduced weber fractions (i.e. better performance) only for the lower sensation level (30 dB SL). By comparison, Epp et al. 2012 found that tinnitus subjects with normal hearing had poorer than normal performance at a mid-level (50 dB SPL) but normal performance at low and high levels (30 and 70 dB SPL). They interpreted their results as reflecting a shallower input-output function, which is observed in deafferented AN fibers following noise-exposure and primarily affects levels around 40-60 dB SPL (Kujawa and Liberman 2009). Although mid-levels were not assessed in the present study, it is unclear what peripheral mechanism could account for the improve discrimination at low levels.

Instead, we suggest a mechanism of increased gain in the central pathway may have improved intensity discrimination. In the HL group, there was evidence for reduced weber fractions at 8000 Hz (i.e. Interaction effect, **Fig 8**), which coincided with a region of high-frequency hearing loss. Increased central gain measured in human and animal subjects with tinnitus is typically associated with the hearing loss frequency, whereby neural amplification compensates for the reduced cochlear input (Auerbach et al., 2014; Norena et al., 2011; Zeng, 2013). The present result suggests a different form of increased central gain, which is independent of hearing loss and is larger than normal at 30 dB SL but not 70 dB SL. Such nonlinear mechanism likely reflects central compensation to selective loss of high-threshold/low-spontaneous-rate auditory nerve fibers in tinnitus (Furman et al. 2013). Indeed, human electrophysiology studies provide evidence for gain enhancement at the brainstem level (Wave V of the ABR) in tinnitus subjects showing reduced nerve activity (Wave I of ABR) but normal hearing thresholds (i.e. synaptopathy) (Gu et al., 2012; Schaette & McAlpine, 2011). Thus, intensity discrimination may help delineate between different tinnitus etiologies, arising primarily from cochlear damage or more subtle damage to the auditory nerve.

CONCLUSIONS

The present result shows that standard psychoacoustic assessments using pure-tones may lack the sensitivity to detect tinnitus-specific deficits beyond the expected effects of cochlear hearing loss. However, tasks that probe intensity resolution of the auditory system may engage central tinnitus mechanisms of increased gain, which differ between tinnitus sufferers with and without clinical hearing loss. Future studies should expand the psychophysical investigation of tinnitus to further define its peripheral and central mechanisms and develop objective diagnostic tools to detect its presence and characterize its phenotypes.

CHAPTER 2

Tinnitus enhances attentional modulation: Evidence from cortical potentials recorded during selective auditory attention.

ABSTRACT

The phantom sensation of sound, known as tinnitus, is not only bothersome or even disabling in severe cases but may also compete for limited attention resources in the brain. In the present study we investigated the neurophysiological mechanisms of attention in modulating tinnitus and potentially its perceived loudness, pitch, or distress. Subjects performed a selective attention listening task in which they monitored one of two tonal sequences—one with similar frequency as tinnitus (5000 Hz) and one well-outside of this region (500 Hz). Electrocortical recordings showed enhanced neural signatures of selective attention in subjects with chronic tinnitus compared to control subjects of similar age and hearing. In particular, attention modulation of an early sensory response was 390% larger than controls when focusing to the tinnitus-relevant frequency. This result suggested that attention modified the frequency-specific representation of tinnitus within deafferented regions of auditory cortex, which correlated with increased tinnitus loudness. When focusing to the non-tinnitus frequency, tinnitus increased modulation of later a response by 300%, suggesting that attention-demanding phantom percepts also impact the selective processing of other ongoing sounds. The present results point to an attention-mediated gain mechanism that contributes to the neural and perceptual expression of tinnitus. Moreover, the observed signatures of attention modulation could provide objective biomarkers to detect the presence of tinnitus and monitor its psychophysiological impact in the brain.

INTRODUCTION

Tinnitus is the phantom perception of sound without an external acoustic source. Tinnitus affects 10-15% of the general population, with 1-2% having debilitating symptoms that require medical attention (Shargorodsky et al., 2010). Analogous to phantom limb pain, tinnitus involves plastic reorganization of sensory cortex following peripheral deafferentation as a result of noise exposure, aging, or other causes (De Ridder et al., 2011; Eggermont & Roberts, 2004, 2012). Because deafferentation does not always produce phantom percepts, top-down, attention-like mechanisms likely play a significant role in the conscious processing, including the awareness of the internal signals (De Ridder et al., 2011; Rauschecker et al., 2010, 2015; Roberts et al., 2013; Vanneste & De Ridder, 2012). Indeed, many tinnitus sufferers report difficulties with neurocognitive tasks requiring attention and memory (Tyler & Baker, 1983; Andersson et al., 1999; Mohamad et al., 2016; Tegg-Quinn et al., 2016). It is possible that tinnitus acts as a competing stimulus that attracts central resources while reducing information processing capacity in other tasks (Hallam et al., 2004; Rossiter et al., 2006; Stevens et al., 2007; Desimone & Duncan, 1995).

A perceptual consequence of attention is modulation of neural gain, which potentially augments tinnitus expression including its loudness and quality (Hillyard et al., 1973, 1998; Rauschecker et al., 2010; Roberts et al., 2013; Sedley et al., 2016, Kauramäki et al., 2007, Okamoto et al., 2007). However, most previous studies used either a passive, no-task paradigm, or a simple subtraction paradigm that contrasts active performance to a passive baseline. Reduced attention modulation in these latter studies was suggested to reflect a persisting activation of attention in the passive tinnitus brain (Delb et al., 2008; Paul et al., 2014). However, other studies showed normal or even reduced passive responding in tinnitus, indicating that effects of “bottom-up” attention, or arousal, are not well-controlled with the passive listening approach (Jacobson et al., 1991; Jacobson & McCaslin, 2003; Diesch et al., 2012; Sereda et al., 2013). One exception was the Jacobson et al., 1996 study, which found an early physiological index of selective attention was increased when tinnitus subjects actively attended or ignored the same sounds. Although the Jacobson study provided evidence for tinnitus competing against other sounds, it did not address the influence of selective attention to tinnitus itself.

The present study first replicated the Jacobson et al., 1996 study in a stimulus paradigm where a subject monitored one of two tone steams, with one stream within the typical tinnitus frequency region and the other one well below this region. We then derived physiological variables responsible for attention modulation in both the non-tinnitus and tinnitus-relevant frequencies. Finally, we examined whether the physiologically measured attention effects would correlate with tinnitus loudness and pitch, not only elucidating top-down mechanisms underlying phantom sounds but also serving as a biomarker that would distinguish tinnitus from control subjects of similar age and hearing.

METHODS

Ethics Statement

The experiments were undertaken with the understanding and written consent of each subject, following the Code of Ethics of the World Medical Association (Declaration of Helsinki), and were approved by the Institutional Review Board of the University of California Irvine (UCI).

Subjects

Nineteen tinnitus and fourteen control subjects participated in this study. Subjects were recruited from a laboratory archive and the UCI Institute for Memory Impairments and Neurological Disorders Consent to Contact Participant Registry. Subjects were screened by self-report for neurological disease or history of significant brain injury. All subjects signed informed consent and received monetary compensation upon completing the experiment. One tinnitus subject was excluded due excessively noisy electroencephalography (EEG) even after data cleaning procedures. One control subject was excluded due inability to properly follow task instructions. Thus 18 tinnitus (7 females) and 13 control (8 females) subjects were included in the final analysis.

Tinnitus and Control subjects were matched in age (Tinnitus: Mean = 60.9, Std = 13.1; Control: Mean = 67.1, Std = 12.9; see **Table 1**). Subjects were also matched in hearing as assessed by pure-tone thresholds at frequencies from 125 Hz to 8000Hz in 1 octave steps as well as 6 and 12 kHz (see **Figure 1A**). On average, the subjects had age-appropriate high-frequency sloping hearing loss. Four relatively young subjects (ages 29, 56 for the control group and 29, 51 for the tinnitus group) had relatively normal thresholds (≤25 dB HL) from 125 to 8000 Hz.

Tinnitus Assessment

All tinnitus subjects completed an online questionnaire consisting of the Tinnitus Handicap Quotient (THQ) and Tinnitus Severity Index (TSI) which appraises the negative impacts of tinnitus including its intrusiveness and associated distress (Kuk et al., 1990; Folmer et al., 1999). The questionnaire also consisted of the following items to characterize subjects' subjective tinnitus: tinnitus type, location, duration since onset, frequency of tinnitus occurrence, loudness rating. All subjects had tinnitus for 6 months or longer. If subjects reported multiple tinnitus sounds, they first described the loudest or most predominant then other components. These data are summarized in **Table 1**.

The subjects characterized their tinnitus pitch using a custom adjustment program. The program consisted of a graphical interface with a marker that moves along a horizontal axis to vary stimulus frequency from 250 to 20,000 Hz along a logarithmic scale and a separate marker that moves along a vertical axis to vary stimulus intensity from 0 to 100 dB SPL in 1 dB steps. The stimulus was a 500-ms sinusoid that repeated once every second continuously. 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 loudest tinnitus for bilateral tinnitus. Once a match was selected, they rated the similarity to their actual tinnitus with a 0-to-10 Visual Analogue Scale (VAS). Finally, to account for possible octave confusion (Graham & Newby, 1962; Vernon et al., 1980), subjects matched the loudness of three tones (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.

Figure 1B shows subjects tinnitus matches weighted by their corresponding similarity rating. The type of tinnitus is indicated by different symbols as tonal (circles; single- and multi-tone), non-tonal (triangle), or a combination of tonal and non-tonal (diamond). Two thirds of the subjects (12/18) matched their tinnitus pitch >4000 Hz (median = 5962 Hz, 25th and 75th percentiles = 3040 and 7608 Hz). Similarity ratings were generally high >.7 (median = 0.8) with the exception of 3 subjects who were <0.4, two of which had non-tonal components and the other had multi-tonal tinnitus. Two subjects had markedly lower frequency matches, near or below 1000Hz, both of which were the subjects with relatively normal hearing thresholds.

Table 1. Subject demographics, Stimulus thresholds and levels, Tinnitus characteristics.

	Group	
	Tinnitus	Control
Number (female)	18 (7)	13 (8)
Age	67 (13)	61 (13)
Threshold at 500 Hz (dB SPL)	25 (8)	26 (7)
Threshold at 5000 Hz (dB SPL)	51 (16)	49 (16)
Stimulus Level at 500 Hz (dB SPL)	86 (8)	87 (6)
Stimulus Level at 5000 Hz (dB SPL)	86 (10)	89 (8)
Tinnitus Ear (bilateral/left/right)	13 / 3 / 2	
Tinnitus type (tonal/non-tonal/both)	12 / 3 / 3	
Tinnitus Duration (years)	26 (23)	
Loudness Rating (0-10)	6 (2)	
TSI (0-60)	30 (14)	
THI (0-100)	28 (22)	

Table 1. Subject count and age for control and tinnitus groups. Auditory thresholds determined with a 2-down, 1-up procedure and stimulus levels determined with loudness match procedure are reported in dB SPL. Tinnitus ear reports whether subjects at tinnitus percepts only in the left or right ear or both ears. Tinnitus types consisted of tonal (single or multi tone), non-tonal (noise-like), or a combination of tonal and non-tonal components. Tinnitus duration is the years since estimated onset of tinnitus. Loudness of tinnitus was rated on a 0-10 scale (10-As Loud as Possible, 9-Extremely Loud, 8-Very Loud, 7-Loud, 6-Medium Loud, 5-Medium, 4-Medium Soft, 3-Soft, 2-Very Soft, 1-Barely audible). Parentheses indicated 1 SD.

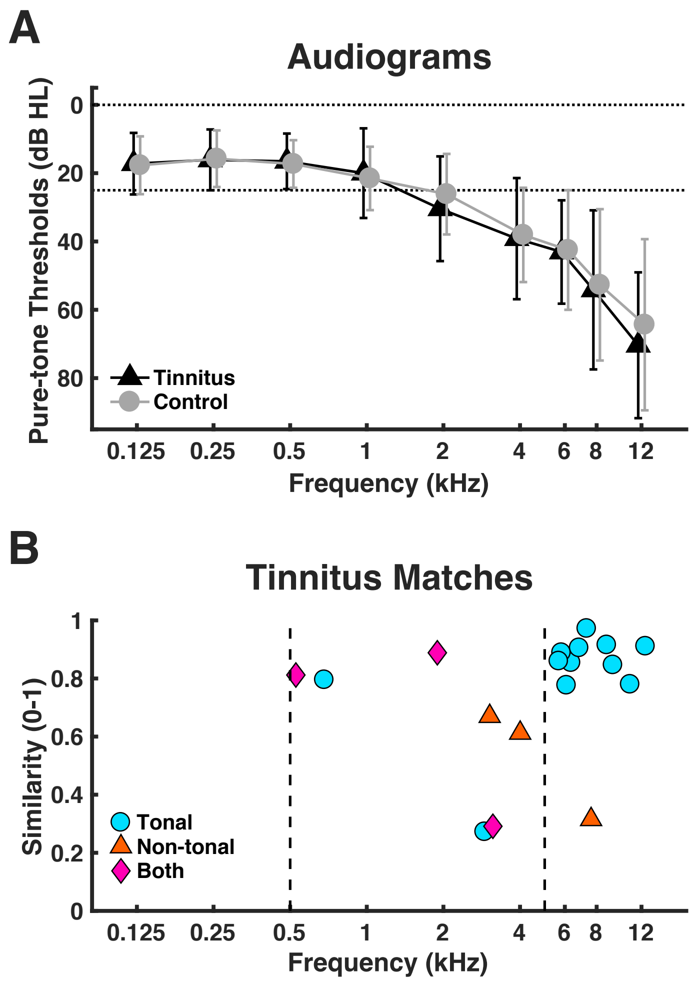

Figure 1 A: Audiograms: Hearing thresholds as a function of frequency. Tinnitus subjects are indicated in black and control subjects in light gray. Error bars indicate 1 SD. **B:** Tinnitus Match Frequencies: The x-axis represents the selected tinnitus match frequency (kHz) and the y-axis represents the corresponding similarity between the match and actual tinnitus rated on a Visual Analog Scale (VAS). Different symbols correspond to the described tinnitus type as tonal (blue circles), non-tonal (red triangles), or multi-component tinnitus containing both tonal and non-tonal types (magenta diamond). Dashed lines indicate the frequencies of the task stimuli, 500 and 5000 Hz.

Equipment

Stimulus generation, experimental procedures, and offline behavioral and EEG data analyses were designed and conducted in MATLAB (The Mathworks, Natick, MA). Digital auditory stimuli were converted with an external sound card (Creative Labs E-MU 0404 USB digital audio system, Creative Technology Ltd., Singapore, 24-bit, 44.1 kHz) and amplified via a headphone buffer (Tucker-Davis-Technologies, HB7, Alachua, FL). Stimuli in the tinnitus matching procedure were delivered through circumaural headphones (HDA-200, Sennheiser electronic GmbH & co. KG, Wedemark, Germany) and stimuli in the selective attention task were delivered through ER-2 insert earphones (Etymotic Research, Inc., Elk Grove, IL). Transducers were calibrated using a sound level meter with C-frequency weighting in a 2cc artificial ear coupler (Bruel & Kjaer, Nærum, Denmark).

Selective Attention Task

Auditory Stimuli

In the selective attention task, subjects were presented with two sequences of pure tone bursts, consisting of a 500 Hz stream and a 5000 Hz stream (see **Fig 2A**). The choice of these frequencies followed Roberts et al. (2012), where 5000 Hz fell within the tinnitus region, which was typically associated with high-frequency hearing loss, whereas 500Hz had normal hearing and was well below the tinnitus region. Each stream consisted of standard tones that were 60-ms in duration and occurred on 83.33% of presentations, and deviant tones, which were slightly longer in duration and occurred on 16.67% of presentations. During an experimental run, subjects monitored one of the two streams in order to detect the infrequent deviant tones. Deviants within the task-relevant stream were called "targets". Deviant durations were adjusted per subject and frequency (see Task Design) to achieve similar performance of 80-90% correct detection during the task. The duration adjustment helped ensure that potential ERP differences between groups and frequencies were driven by relevant intrinsic neural properties, rather than by task difficulty. All tones were shaped with a 5-ms squared-cosine onset and offset ramps and presented monaurally. For tinnitus subjects with unilateral tinnitus the same ear was chosen and for bilateral tinnitus the ear with the louder tinnitus was chosen. Ear selection was balanced across control subjects to match the tinnitus group.

The inter-stimulus intervals (ISI) between all tones were between 200 and 400ms, drawn randomly from a uniform distribution with 10 ms steps. The use of this fairly rapid presentation rate minimized attention switching between streams by requiring continuous focus to the task-relevant frequency to perform the task. Moreover, previous studies have shown that faster ISIs (<400ms) induced attentional modulation at earlier latencies, commencing before or around 100 ms (Hansen & Hillyard, 1984; Teder et al., 1993). Tone presentations were pseudo-randomized so that no more than three standard tones of the same frequency occurred consecutively, and two deviants did not occur consecutively.

Sound levels were also adjusted for each listener to approximately equate the subjective loudness between the two tones. Equal loudness was chosen over equal sensation level because tinnitus subjects displayed steeper loudness growth (Hebert et al., 2013; Reavis et al., 2012) that might create a salience imbalance between streams. First, thresholds were measured for the 500 and 5000 Hz tone bursts with a 2-down, 1-up procedure (5dB step size). Next, the subject manually adjusted the level of the 5000 Hz tone to match its loudness to a 500 Hz tone presented at 65 dB SL. This loudness matching procedure was repeated three times, with the average being used as the stimulus level for the task.

Task Design

The experiment consisted of two active conditions and one passive condition. For the active conditions, labelled "Attending," and "Ignoring," subjects were instructed to focus attention either to the 500 Hz or 5000 Hz stream, respectively, and ignore the other stream to the best of their ability. They were asked to press a button as quickly and accurately as possible when they detected a target within the attended stream. Performance was measured by percent of correct responses and reaction times within a window of 450-1200ms post-target onset. False alarms were counted as any responses outside of this time window. Additionally, each active condition was preceded by a train of 10 tones only at the attended frequency to orient the subject's attention toward the correct stream. At the end of each run, the monitor displayed the subject's percent correct and false alarms. For the passive condition subjects were asked to ignore all sounds while reading from a choice of magazines. Throughout each run, a computer monitor displayed the current condition with a visual cue (see **Fig 2A**).

The order of experimental conditions is described in the **Figure 2B**. The first run was always the passive condition, followed by a set of one Attending Low and Attending High condition. After a short break (5-10 minutes) there was another set of the Attending Low and Attending High conditions, concluding with a second run of the passive condition. The order of the active conditions was counter-balanced across subjects, alternating low-to-high or high-to-low. For each condition an experimental run consisted of 360 tones, including 180 tones for each stream (150 standards, 30 deviants). Nine early subjects (4 Control, 5 Tinnitus) performed a slightly longer version of the task that included 540 tones, with 270 per stream (225 standards, 45 deviants). As data analysis including unequal trial number or equal number of trials (i.e. random selection) yielded essentially the same outcome, the present results include all original trial counts after preprocessing.

Prior to the main experiment, all subjects completed a training procedure to familiarize them with the task and determine individual target durations. The training procedure consisted of consecutive blocks of 60 tones per stream (50 standards, 10 deviants). Initial target durations were 150-200ms and reduced on each block by 20ms until correct detections fell below 80%. On subsequent blocks target durations were adjusted up or down by 10ms until performance between 80-90% was achieved three times for a given duration. Listeners first completed this procedure for the 500 and 5000 Hz streams in isolation. Next both streams were presented together, as in the main task, and the procedure was completed for the "Attending High" and "Attending Low" conditions. The resulting target durations were used in the main task.

Table 2 displays the behavioral results from the main experiment. These results showed that the degree of difficulty was well balanced across groups and attention conditions, with average percent correct scores falling within the target range of 80-90% correct and no significant differences between groups ($p>.05$). False Alarms were limited (<3) and were also balanced between groups and attention conditions. Average reaction times were not significantly different between groups ($p>.05$), however, there was a main effect of stimulus frequency in which reaction times were 24-ms faster for the 500 Hz target than the 5000 Hz target ($F(1,29)=5.621$, $p=0.025$).

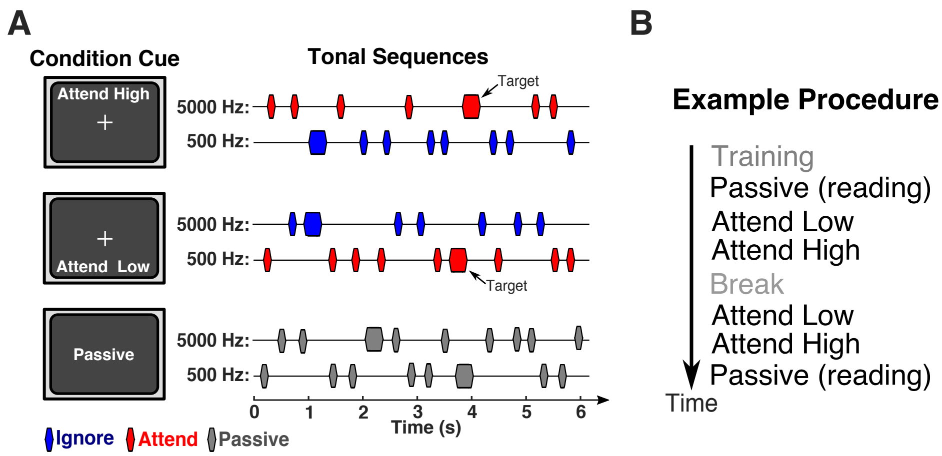

Figure 2. A: Illustration of the task stimuli consisting of tonal sequences at 500 and 5000 Hz presented in three task conditions, Attending 5000 Hz (top), Attending 500 Hz (middle), Passive (bottom). Standard tones are the more short-duration markers and deviant/target tones are the less frequent long-duration tones. **B:** Example of the order of task conditions. Following training, passive conditions were always the first and last conditions. Attending Low and High were counter-balanced alternating Low to High as in the example of High to Low.

Table 2. Behavioral Results

	500 Hz		5000 Hz	
	Control	Tinnitus	Control	Tinnitus
Percent Correct (%)	85.5 (2.1)	83.3 (2.6)	85.8 (1.8)	84.0 (2.5)
False Alarms	1.3 (0.2)	2.3 (1.1)	1.3 (0.3)	1.5 (0.7)
Reaction time (ms)	721 (18)	704 (13)	755 (16)	717 (15)

Table 2. Behavioral results averaged across subjects for each group and stimulus frequency including percent correct of target detections, number of false alarms, and reaction time in milliseconds. For each subject, scores were average across corresponding task conditions. Parentheses are 1 SD.

EEG acquisition

Electroencephalography (EEG) data were collected during all experimental runs. EEG signals were recorded with a Neuroscan SynAmp2 system using Scan 4.5 software and a QuikCap 64-channel cap following the standard 10/20 configuration (Compumedics, Victoria, Australia). A vertex reference channel was located between Cz and CPz and all impedances were monitored to be near 10kΩ or below. Continuous online data were digitalized at 2000 Hz, filtered between DC-500 Hz,and stored for offline analysis. During the EEG recordings, subjects were seated upright facing a computer monitor that displayed the task instruction. During the passive runs, subjects were asked to minimize body movement while reading. In the active conditions, subjects looked forward at a fixation cross on the monitor, restricting movements to finger presses on a keyboard.

Data analysis

Preprocessing

The continuous data were first down sampled to 250Hz and bandpass filtered between 0.1 and 50 Hz (Second-order Butterworth) then re-referenced to the average mastoid channels. Channels showing continuous amplifier artifact during a recording were replaced by spline interpolation of the neighboring electrodes. The data were segmented into epochs of 400ms pre- to 1000ms post-stimulus onset. The data were then submitted to independent component analysis using a standalone version of Infomax ICA algorithm from the EEGLAB toolbox (Delorme & Makeig, 2004). Components were reviewed to identify those containing activity attributable to blinks or horizontal eye movements. On average 2.6 (SD = 1.6) components per subject were removed. Finally, the data were transformed back to channel space and screened for excessively noisy trials related to body movements or other transient artifacts. For each channel, a normalized variance was calculated by dividing the variance of each trial by the average variance across trials. This emphasizes deviant trials relative to the channel’s standard noise level. A threshold was set for the maximum normed variance allowed and trials were rejected if this was exceeded on 20% or more electrodes. Thresholds were determined for each subject so that no more than 10% of trials were rejected per data set. Note, both before and after artifact rejection, the excluded subject showed small waveform amplitudes (< ±1 uV) with indiscriminate ERP peaks deemed unusable in the main analysis.

Lastly, trials were sorted with respect to their stimulus frequency (500 or 5000 Hz) and attentional condition (attending, ignoring, passive). For the active conditions this yields four sets of responses: Attending 500 Hz, Ignoring 500 Hz, Attending 5000 Hz, Ignoring 5000 Hz. For the passive condition there are two sets of responses: Passive 500 Hz, Passive 5000 Hz.

Event-related potentials

Trial data were lowpass filtered at 20 Hz and averaged to form event-related potentials (ERPs). A baseline correction was applied by subtracting the mean voltages from a 200 ms pre-stimulus window from each time point. Only ERPs to standard stimuli were analyzed in full as deviant ERPs contained too few trials to obtain reliable waveforms. The analysis was focused on an "Average Channel" derived as the grand mean voltage waveform across all electrodes. All ERP waveforms in both groups contained the obligatory P1-N1-P2 auditory responses as well as a slow negativity (SN), characterized by a pronounced negative response following the P2 that spanned approximately 300-600ms in the attending conditions. Ignored and passive responses typically showed a similar negatively with slightly narrower time course and reduced amplitude. Hence, four component responses were identified for analysis as follows: The P1, N1, P2 were selected as the maxima/minima voltages within 30-80, 60-150, and 150-250 ms, respectively, whereas the SN was measured as the mean amplitude across 300-600ms. For each condition (passive, attending, ignoring) the individual component amplitudes and latencies were assessed for differences involving group and/or frequency. Due to experimenter error, EEG data during the passive condition of two subjects (both tinnitus) were not properly stored and are therefore omitted from the analysis.

The effect of top-down attention on ERP amplitudes during the active conditions was analyzed by computing the difference in ERP between Attending and Ignoring to the same probe frequency, e.g. Attending-500 Hz – Ignoring-500 Hz. The resulting waveform produces the "negative difference" (Nd) wave, a negative-going response indexing neurophysiological operations of selective attention including modulation of neural gain (Hansen & Hillyard, 1980, 1984; Giard, 2000; Näätänen et al., 2002). Here, the amplitudes of the Nd waveforms were initially quantified by averaging over successive 28-ms time windows for each group and frequency. For clarity, latencies will be reported as the nearest fifth (i.e. 30-ms). Additional methods for comparing the Nd within and between subject groups are described in the corresponding results sections.

Statistical Analysis

The primary group analyses, including behavior, individual component amplitudes and latencies, and Nd measures, were performed with a 2-way mixed analysis of variance (ANOVA, IBM SPSS Statistics, Version 25.0). Results were tested for main effects (One between-subjects factor, Tinnitus vs. Control; One within-subjects factor, 500Hz vs. 5000 Hz) and Interactions (Group X Frequency). Significance was assessed at the level of $p < 0.05$, except for individual component measures which received a Bonferroni correction for testing over three conditions ($\alpha = 0.05/3 = 0.017$). Greenhouse-Geisser epsilons (ε) were used for non-sphericity correction when necessary, although the original degrees of freedom are reported. When a significant main effect or interaction was found, follow-up analyses assessed group differences at each individual frequency (one-way ANOVA) as well as differences between frequencies within each group (repeated-measures ANOVA). Additionally, an initial analysis of the Nd was performed separately for each group and condition. As the Nd wave is defined by a characteristic negativity, statistical significance was assessed by comparing the Nd amplitudes with one-tailed *t*-tests to 0 mV in successive 30 ms time windows. A false discovery rate (FDR) correction was applied to account for false positive dues to multiple comparisons over time (Benjamini et al., 1995; Genovese et al., 2002).

Pearson correlations were carried out to determine the relationship of ERP attentional effects to subjects' tinnitus perceptual characteristics and severity. Perceptual characteristics consisted of tinnitus loudness ratings (0-10 VAS scale) and a relative tinnitus frequency. It was hypothesized that the degree of attention gain would depend on how closely the subject's tinnitus match coincided with the task probes. Hence, the relative tinnitus frequency (*rTF*) was computed as the absolute distance in octaves between each subjects' match and task frequency (*tf*). See **Equations 1 and 2**. Tinnitus severity was assessed using by the TSI score only, as both severity measures, TSI and THI, were highly correlated (r = 0.92, p<.0001).

$$Equation\ 1: \quad rTF_{500Hz} = \left|\log_2\left(\frac{tf}{500}\right)\right|$$

$$Equation\ 2: \quad rTF_{5000Hz} = \left|\log_2\left(\frac{tf}{5000}\right)\right|$$

RESULTS

Passive Evoked Responses: Effects of Group and Stimulus Frequency

Figure 3 shows grand average ERP waveforms for the Passive condition as recorded from the Average channel. All subjects exhibited visible a P1-N1-P2 complex (labeled in the top panel only), with corresponding characteristic latencies of approximately, 50, 100, and 200-ms, respectively. Additionally, the waveforms contained a slow negativity (SN) from 300-600-ms. Although the tinnitus subjects exhibited similar overall waveform characteristics to controls, tinnitus appeared to reduce the P1 as well as increase the N1 and SN amplitudes. To quantify these potential differences between tinnitus and control subjects, P1, N1, P2 and SN were obtained in each individual and submitted to statistical analysis.

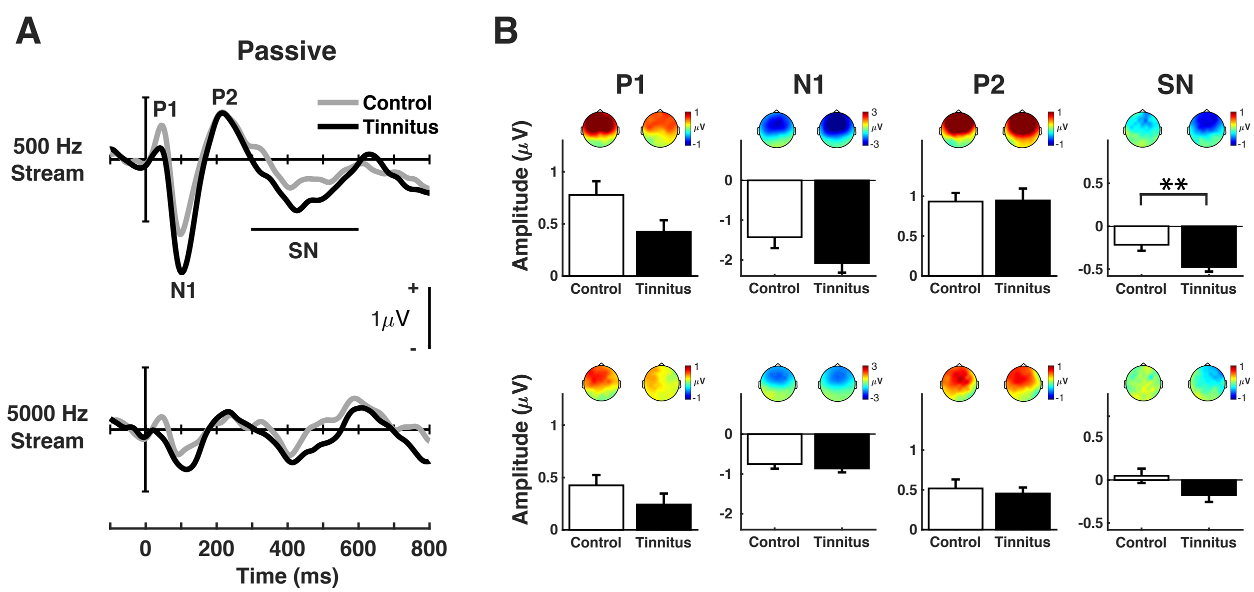

Figure 3. Passive condition. A. Evoked-response waveforms averaged over 64 electrode sites. X-axes indicate time in milliseconds relative to stimulus onset (0 ms) and y-axes are response amplitudes in microvolts. Each panel contains waveform response for tinnitus (black) and control (gray) subjects overlaid. The top panels show responses to the 500 Hz tone bursts and bottom panels shows responses to the 5000 Hz tone bursts. **B.** P1, N1, P2, and SN component amplitudes averaged across control (open) and tinnitus (black) subjects. Error bars indicate standard error of the mean. Each panel shows the respective scalp voltage topographies averaged across subjects for each group and frequency (*p<.05, **p<.01).

Figure 3b depicts mean ERP amplitudes in the Passive condition for all components and their corresponding topographic representations. Topographies typically showed maximal amplitudes typically occurring within a frontocentral region. Of the four measures, only the Passive SN showed a significant main effect of group in which tinnitus increased the slow negativity ($F(1,27) = 14.23$, $p = .00081$). Group comparisons at individual frequencies show that this group effect was driven by significant differences at 500 Hz ($F(1,27) = 8.78$, $p = .0063$), whereas differences at 5000 Hz were in the same direction but not significant ($p = .066$). Although no other effects involving group reached significance, the P1 and N1 tended to be larger in tinnitus (Main Group Effect; P1: $F(1,27)=4.26$, $p=0.049$; N1: $F(1,17) = 3.41$ $p = 0.06$). Regardless of tinnitus or condition, there was a significant main effect of frequency across all components, with the 500 Hz eliciting larger responses than the 5000 Hz stimulus ($F(1,27) = 8.25 – 26.37$, $p = .008 – .00002$). Latency values recorded for the P1, N1, and P2 were submitted to the same analysis but showed no significant main effects nor interactions.

Evoked Responses During Selective Attention

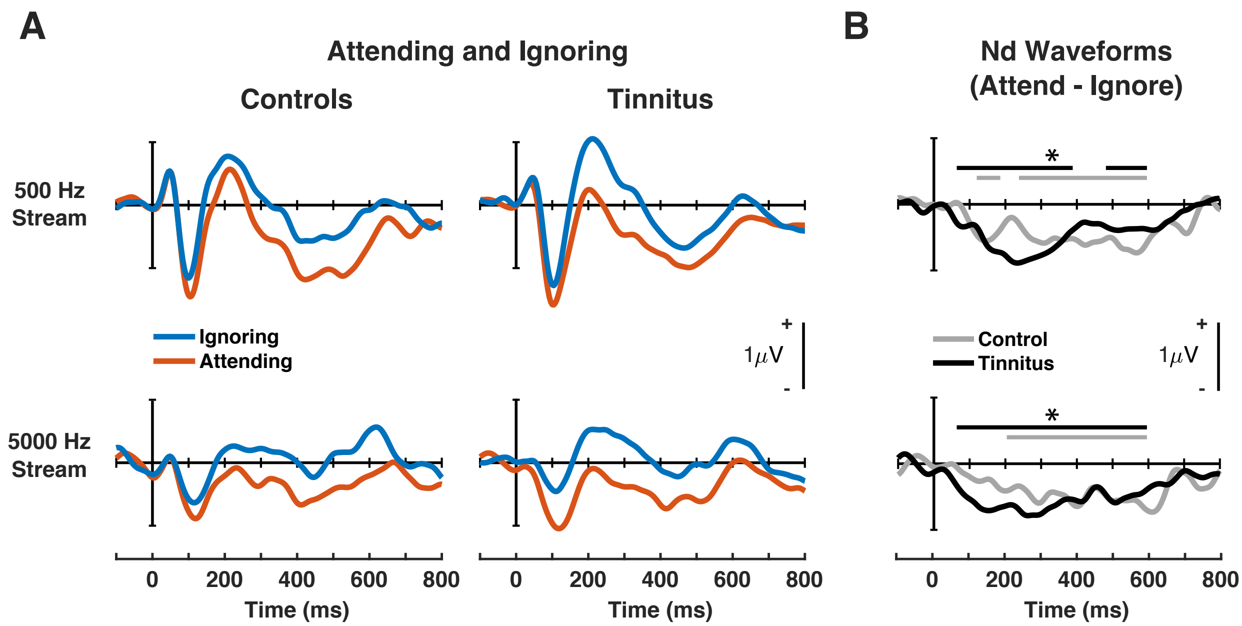

Figure 4. Active conditions. A. Evoked-response waveforms from the Attending and Ignoring conditions averaged over 64 electrode sites. Each panel contains two overlapping waveforms that correspond to Attending (red) and Ignoring (blue) conditions. Left panels show responses of control subjects and right panels show responses of tinnitus subjects. The top panels show responses to the 500 Hz tone bursts and bottom panels shows responses to the 5000 Hz tone bursts. **B.** Nd waveforms derived by subtracting Attending and Ignoring responses to the same stimuli. For each panel, control (gray) and tinnitus (black) are overlaid. Horizontal bars above the Nd waveform express the time-points at which the Nd amplitude were significant with respect to zero (*p<.05; FDR corrected).

Individual Components: Attending and Ignoring conditions

Figure 4a shows grand average ERP waveforms for the Attending (red traces) and Ignoring (blue traces) conditions separated for tinnitus (left panels) and control subjects (middle panels). Across subject groups and conditions, there were visible peak components corresponding to a P1-N1-P2 complex as well as the SN, which was highly reduced in the ignoring 5000 Hz condition. For individual components obtained separately for the attending and ignoring conditions, no significant group differences in amplitude or latency were observed. However, there was a significant main effect of frequency for all components, with the 500 Hz eliciting larger responses than the 5000 Hz stimulus ($F(1,29) = 10.63 – 30.74$, $p = .0028 – .00001$).

Effects of Attention: Nd Waveforms

A comparison between conditions shows that attention induced a pronounced negative displacement relative to the ignoring response. To quantify this attention effect, the Nd waveform was obtained by subtracting ERPs to ignored stimuli from the same stimuli when attended. The Nds are depicted in **Figure 4b** and consisted of negativity that commenced before 100ms and continued until approximately 700ms. An early portion of the Nd was more pronounce in tinnitus subjects, with maximal amplitudes over the P2 latency (200 – 250ms), consistent with previous descriptions of the Nd under similar task conditions (e.g. ISI) (Alho et al., 1994; Fujiwara et al., 1998; Hansen & Hillyard, 1980, 1984). Additionally, the Nd at 5000 Hz showed an earlier peak in tinnitus subjects near the N1 latency (100-120ms). These greater attention effects in tinnitus corresponding to N1 and P2 latency can be seen in the original ERP waveforms (**Fig 4a**) for 5000 Hz and 500 Hz, respectively. A late portion of the Nd (>300ms) was similar in magnitude between groups and possibly reduced in tinnitus at 500 Hz.

The amplitudes of the individual Nds were initially assessed over successive 30-ms time segments (FRD corrected). The significance of the Nd began earlier in tinnitus subjects, starting at 65 ms and continued to 600 ms for both frequencies, except a brief interval near ~400-500 ms at 500 Hz. By contrast, significant Nd values began later in controls, at 120 ms (500Hz) and 200 ms (5000 Hz) but also continued to 600ms at both frequencies, including a discontinuity near ~200 ms at 500 Hz. Significant portions of the individual Nds are indicated in **Figure 4B** (bars above the Nd waveforms).

To examine Nd amplitude differences between tinnitus and control groups, a global Nd waveform was defined by averaging across frequencies over 60-600ms, the time window in which significant Nd amplitudes were observed. An ANOVA assessed group differences over the successive 30 ms time segments and revealed a significant Group X Time interaction ($F(1,29) = 2.6$, $p = .036$; Greenhouse-Geisser correction) that reflected a greater Nd in tinnitus circumscribed to the early portion of the response.

Temporal Dynamics of Attention: P1, N1, P2, SN

To examine the temporal dynamics of the Nd amplitudes more closely, including their dependence on task frequency, an analysis utilized the difference between attending and ignoring measured for the P1, N1, P2, and SN separately at 500 and 5000 Hz. Importantly, the latency of these components corresponded closely with the relevant time-course of the Nd waveforms; moreover, this approach enabled the results during active listening to be related to group differences measured in passive listening.

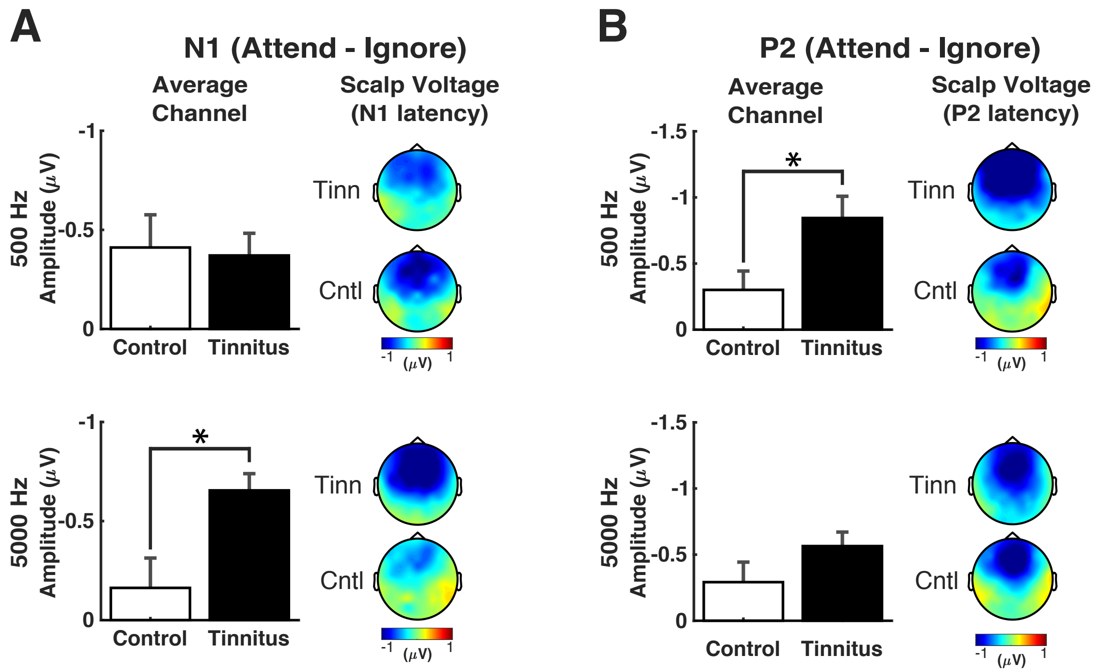

Figure 5. Attentional modulation of the N1 and P2. Difference between Attend and Ignore responses for the average channel for **A.** N1 and **B.** P2 response. Negative values are inverted in the upward direction. Left panels show averages across subjects for control subjects (open) and tinnitus subjects (black). Error bars indicate standard error of the mean. Right panels are the corresponding scalp voltage topographies averaged across subjects at all electrode sites (*p<.05, **p<.01).

Tinnitus showed no significant differences from controls for the P1 or SN but produced frequency-specific effects attention on the N1 and P2. **Figure 5** (left panels) shows the average Attending-Ignoring differences for N1 and P2 between control and tinnitus. For the N1 (**Fig 5A**), the ANOVA returned a significant Frequency X Group interaction ($F(1,29)=6.96$, $p=.0132$). On average, tinnitus produced a 3.9-times greater attentional effect on the N1 at 5000 Hz relative to the control subjects (Tinnitus Mean = 0.66, Control Mean = 0.17, $F(1,29) = 8.88$, $p = .006$). There was no difference between groups at 500 Hz ($p > .3$). Moreover, only tinnitus showed a significant within-subjects difference between frequencies with greater attention effect at 5000 Hz than 500 Hz ($F(1,17) = 5.75$, $p =.028$). This significant frequency-specific attention effect is also evident in the scalp topographies (insets of **Fig 5a**), where the darkest and broadest distribution occurred for the tinnitus scalp at 5000 Hz.

By comparison, the P2 difference (**Fig. 5B**) showed a significant main effect of group where tinnitus produced larger attention effects across frequencies ($F(1,29)=5.882$, $p=.0218$). Within task frequency, tinnitus produced a 3-times greater attentional effect on the P2 at 500 Hz relative to control subjects ($F(1,29) = 6.29$, $p = 0.018$), but the group difference was not significant at 5000 Hz ($F(1,29) = 2.50$, $p = 0.125$). The larger attention effect at 500 Hz in tinnitus is evident as the darkest and broadest scalp voltage distribution (inset of **Fig 5b**). Altogether, tinnitus produced larger overall Nd attention effects than controls, which occurred earlier for 5000 Hz, corresponding to the N1, and later for 500 Hz, corresponding to the P2.

Relationship Between Attention Effects and Tinnitus Characteristics

Table 3: Correlations with attention modulation and tinnitus variables

Attention Difference; n = 18				
	N1 500-Hz	N1 5000-Hz	P2 500-Hz	P2 5000-Hz
Loudness	-0.38	-0.36	-0.25	-0.41
rTF	0.18	0.02	0.10	0.46
TSI	-0.62***	-0.38	-0.31	-0.47
Attention Gain (dB); n = 17				
Loudness	-0.38	0.69***		
rTF	-0.13	-0.46		
TSI	0.53*	0.40		

Table 3. Pearson correlations between attention modulation (N1, P2) and tinnitus variables: Loudness, relative tinnitus frequency (rTF), and Tinnitus Severity Index (TSI). Asterisks indicate significant correlations (*p<.05, **p<.01, ***p<.005, uncorrected).

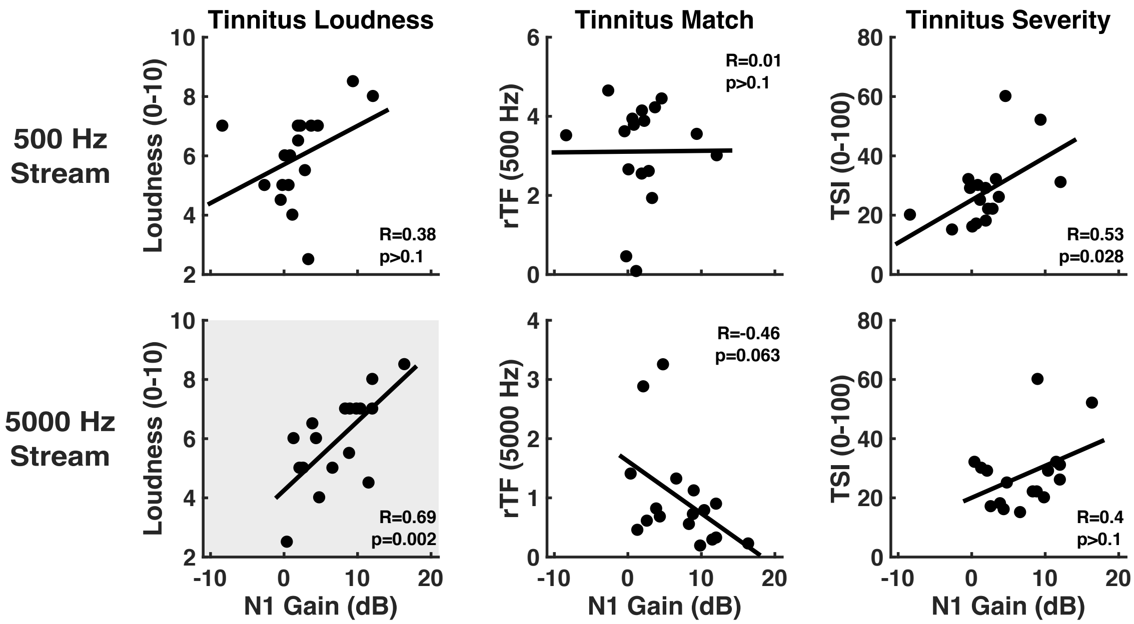

Figure 6. Correlation analysis. Linear regressions performed for attention measures ($N1_{dB}$) and tinnitus variables: Loudness, relative tinnitus frequency (rTF), and Tinnitus Severity Index (TSI). Correlations were performed separately for attention measures 500 Hz (top panels) and 5000 Hz (bottom panels). Shaded panels indicated significant correlations ($p < .05$).

Table 3 shows correlational outcomes between attention effects and tinnitus variables: loudness, relative tinnitus frequency (rTF) , TSI. Correlations were limited to the N1 and P2 attention effects showing significant group effects. Correlations carried out with the standard difference measure of attention (Attending—Ignoring) were generally non-significant. Greater N1 modulation at 500 Hz related to greater tinnitus severity ($r = -0.62$, $p = .008$) but not need reach a Bonferroni correction ($p < .0028$, $\alpha = 0.05/18$) and was likely influenced by two outliers with high TSI (>40).

An additional correlational analysis incorporated a measure of N1 attention modulation computed in decibels ($N1_{dB}$) between attending and ignoring. See **Equation 3**. Only N1 was computed in this manner as P2 frequently contained negative-valued ratios ill-defined in the logarithmic transform (due to negative P2 during attending). One tinnitus subject's N1 ratio was also negative and omitted from the correlations. **Figure 6** shows correlations and regressions fits between $N1_{dB}$ at 500 Hz and 5000 Hz and the tinnitus variables. Shaded panels indicate significant correlations. Among the tinnitus variables, $N1_{dB}$ most strongly related to tinnitus loudness. Specifically, greater $N1_{dB}$ at 5000 Hz correlated positively with louder tinnitus ($R = 0.69$, $p = .002$, Bonferonni corrected $p < 0.0028$). It may be noted that while $N1_{dB}$ did not correlate significantly with rTF at either frequency, $N1_{dB}$ at 5000 Hz tended to be greater for tinnitus matches nearer to the 5000 Hz probe ($R = .0.46$, $p = .063$); also, two subjects matched furthest away (~500 Hz) showed relatively small $N1_{dB}$ magnitudes at 5000 Hz.

$$Equation\ 3{:}\ N1_{dB} = 20\log_{10}\left(\frac{N1\ Attending}{N1\ Ignoring}\right)$$

The significant loudness correlation observed with $N1_{dB}$ but not for N1 difference may be attributed to an improved comparison across individual subjects. ERPs are known to vary widely in overall magnitude between individuals due to “nuisance” factors including electrode impedance and head and brain geometry. As suggested by previous studies, computing ERP modulation on a logarithmic scale (as opposed to linear scale) better compensates for these inter-subject variations (e.g. Dai & Shinn-Cunningham, 2016) and theoretically can be aligned with an effect of attention that is modelled as a change in multiplicative gain (Choi et al., 2014; Hillyard et al., 1998). Notably, $N1_{dB}$ maintained the same frequency-specific group effect as the N1 difference, with ≥3-fold larger attention effect in tinnitus at 5000 Hz than other within- or between-group comparisons (Group X Frequency Interaction: $F(1,29) = 9.11$, $p = .0054$).

Multiple linear regression was applied to further investigate the predictive relationship between ERP attentional effects and tinnitus characteristics. A full model including all relevant attention measures [500 Hz and 5000 Hz; $N1_{dB}$ and $P2_{difference}$ significantly predicted Tinnitus Loudness ($F(4,16) = 3.332$, $p = .047$, $R^2 = .526$, Adjusted $R^2 = .368$). Only $N1_{dB}$ at 5000 Hz added significantly to the prediction ($p = .032$). Regression coefficients and standard errors can be found in **Table 4**. This full model accounted for slightly greater variance (unadjusted R^2) than found with simple Pearson correlations. However, a model that removed the dependence on the 500 Hz (by dropping N1 and P2 measures at 500 Hz) resulted in a significantly better fit to the results, having smaller AIC ($F(2,16) = 7.012$, $p = 0.008$, $R2 = .500$, $R2$ adjusted = .429). Only the contribution from $N1_{dB}$ at 5000 Hz was significant ($p = .009$). This suggests that tinnitus loudness can better be predicted by attention measures corresponding to the TFR region (i.e. 5000 Hz), and specifically for effects related to the sensory N1. Models of rTF and TSI failed to reach significance when all attention measures were included (rTF $p = .25$; TSI $p = .076$) and for the limited model with only 5000 Hz measures (rTF $p = .076$; TSI $p = .059$).

Table 4: Tinnitus Loudness Multiple Regression Coefficients

Full Model (all variables)					
	Intercept	N1 500-Hz	N1 5000-Hz	P2 500-Hz	P2 5000-Hz
B	4.188	0.060	0.193*	0.141	-0.602
SE_B	0.629	0.075	0.079	0.473	0.675
β		-0.174	0.571	0.067	-0.203
Reduced Model (5000 Hz variables)					
B	4.111		0.211*		-0.495
SE_B	0.574		0.069		0.606
β			0.626		-0.816

See text for details. * $p < .05$; B = unstandardized regression coefficient; SE_B = Standard error of the coefficient; β = standardized coefficient

DISCUSSION

The present study investigated top-down modulation of cortical potentials in tinnitus sufferers selectively attending to one of two stimulus steams: one within the typical tinnitus frequency region (TFR: 5000 Hz) and one well-below this region (500 Hz). Except for an enhanced passive SN in tinnitus, individual responses (P1, N1, P2, SN) were comparable for all task conditions between tinnitus and control groups. However, the attention modulation, defined as the difference in individual responses between the Attending and Ignoring conditions, was 3.9 times larger in tinnitus than control for the N1 response at 5000 Hz and was 3 times larger for the P2 response at 500 Hz.

Comparison with previous studies

The attention-related Nd wave in the present study resembled that of previous electro- and magnetencephalography studies requiring subjects to focus to a particular stimulus stream (i.e. channel) among ongoing distractors. When sound sources are highly distinctive (e.g. frequency and/or location) and presented at fast rates, Nd waves begin as early as 50ms and consist of an early portion (Nd_{Early}) peaking over the N1 and P2 latency and a late sustained portion (Nd_{Late}, >300 ms) (Hansen & Hillyard, 1980; R. Näätänen et al., 1981, Alho et al., 1994).

Compared to age and hearing-matched controls, tinnitus subjects showed evidence of enhanced attention modulation whereby the Nd_{Early} occurred earlier and with greater magnitude. This result replicated the Jacobson et al., 1996 study, showing larger Nd_{Early} amplitudes (110-140ms) in tinnitus subjects attending to 500 or 1000 Hz streams. Although the previous study test subjects within their range of normal hearing, tinnitus sufferers tend to localize tinnitus percepts at higher-frequencies corresponding closely to the region affected by hearing loss (see **Fig 1**; Norena et al., 2002; Roberts et al., 2008). A novel finding in the present study was that abnormal attention modulation in tinnitus acted earlier, on the N1, when focused to the tinnitus region, and later on the P2 when focused away from this region. By contrast, the late SN at both frequencies showed similar sensitivity to attention in tinnitus and control groups.

Group differences in attention modulation could not be attributed to neural changes in tinnitus alone as N1 and P2 amplitudes during a baseline passive were comparable between groups. However, tinnitus did enhance the passive SN response at 500 Hz. Interestingly, this effect resembled a late attention-induced negativity (i.e. Nd_{late}) during active listening. In this respect we note, the passive P1 and N1 at 500 Hz also tended to be more negative in tinnitus. These observations accord with previous studies suggesting persistent activation of attention in the passive tinnitus state. For example, Delb et al. (2008) reported reduced modulation of the N1 in high-distress tinnitus subjects when comparing attended to passive listening. Similarly, Paul et al., (2014) found no N1 effect at either 500 or 5000 Hz. Heightened arousal or "bottom-up" attention to tinnitus may have mitigated attentional effects in these studies. By contrast, selective attention may reveal a genuine neuromodulation by comparing responses under similar states of engagement (e.g. attend vs. ignore) and contrasting highly focal attention to the target frequency against actively diverted attention, or even suppression, for the ignored frequency.

Potential mechanisms of attention in tinnitus

A pattern of abnormal attention in tinnitus may reflect both lesion-induced neuroplasticity generating tinnitus within auditory pathways (Eggermont et al., 2004) as well as changes observed among executive control networks associated with attention in tinnitus sufferers (including dorsolateral prefrontal, parietal, and anterior cingulate cortices) (Adjamian et al., 2009; Lanting et al., 2009; Rauschecker et al., 2015; Vanneste & De Ridder, 2012). Indeed, source analyses of the Nd_{Early} localize its effects to regions of supratemporal auditory cortex with contributions in high-order brain areas including frontal and parietal cortices (Hari et al., 1989; Rif et al., 1991; Woldorff et al., 1993, Degerman et al., 2008, Ross et al., 2010). Here, we consider neurophysiological mechanisms associated with the Nd_{Early} that may explain the differential modulation at 5000 Hz (N1) and 500 (P2) in tinnitus

First, attention may produce a true modulation of the exogenous sensory responses via top-down gain control. Attentional gain accords well with modulation of the N1, although it is unclear how it can explain the reduced P2 amplitude during attention. Converging evidence suggests attention directly modulates the N1 generators localized to auditory cortex, including discrete tonotopically organized fields in primary auditory cortex (A1) (Alcaini et al., 1995; Fujiwara et al., 1998; Neelon et al., 2006; Okamoto et al., 2007; Woldorff et al., 1993). Hence, it is possible that tinnitus-related neuroplasticity within deafferented portions of A1 (such as tonotopic remapping, reduced intracortical inhibition, increased neural synchrony) modified the normal expression of attention gain for the 5000 Hz stimulus, i.e. facilitating N1 modulation. This interpretation aligns with previous evidence for abnormal evoked responses initiated in tinnitus-frequency regions of A1 (Flor, Diesch, et al., 2004; Roberts et al., 2012, 2015; Wienbruch et al., 2006), including an enlarged mismatch negativity reflecting bottom-up auditory attention (Näätänen et al., 2001; Weisz et al., 2004*).* Alternatively, recent tinnitus models propose that focused attention, acting via the basal forebrain cholinergic system, increases postsynaptic gain afforded to cortical neurons coding tinnitus (Roberts et al., 2013, Sedley et al., 2015). In turn, attention gain within the TFR would potentially alter the neural expression of tinnitus and its perceptual attributes. Indeed, we found a significant correlation between $N1_{dB}$ attention gain at 5000 Hz and tinnitus loudness, suggesting frequency-specific attention influences salience and possibly awareness of the phantom sound.

Second, an endogenous selective attention process may explain the observed attention effects. In particular, the $Nd_{Ear;ly}$ peaking over the P2 is associated with an attention-specific neural system separable from the obligatory sensory response (Näätänen, 1992, Alho et al., 1994; Michie et al., 1990; Rif et al., 1991). This Nd_{Early} component has received different interpretations (Alain & Arnott, 2000), but it widely believed to index an early selection process for gating stimuli within an attended channel for further perceptual processing separate from irrelevant events (Näätänen 1992; Alho, 1992; Woods, 1990). For example, according to an "attentional trace" model, the Nd_{Early} reflects a comparative operation between incoming stimuli and an actively formed neural representation of attended stimulus features (Näätänen, 1982, 2002). In the present study, severe tinnitus may have acted similarly to chronic pain in representing a salient, emotionally aversive, internal signal that can subsume available attentional resources (Eccleston & Crombez, 1999). Hence, given task difficultly was matched between groups, the presence of attention-demanding tinnitus may have required greater neural processing (i.e. effort) to perform the same channel-specific operations. A similar hypothesis was invoked by Jacobson et al., 1996, as well as studies reporting reduced and delayed P300 responses during attention to non-standard stimuli (Gabr et al., 2011; Mannarelli et al., 2017). This supposition is also consistent the common complaint by tinnitus sufferers of difficulty concentrating (i.e. cognitive load) and a general impairment in tasks requiring top-down attention in both auditory and visual domains (Andersson et al., 2000; Araneda et al., 2015; Hallam et al., 2004; Ivansic et al., 2017; Rossiter et al., 2006; Stevens et al., 2007).

Clinical implications

Currently, tinnitus lacks a distinguishing neural correlate separate from neural changes related to hearing loss alone (Adjamian et al., 2012). As such, an objective biomarker to aid the diagnosis and treatment of tinnitus has not been developed, and clinical evaluations presently rely on self-reports measures (questionnaires, surveys, ratings). While neuroplasticity of the auditory pathways following deafferentation may be necessary to tinnitus, a successful biomarker may reflect top-down brain mechanisms that mediate its conscious awareness. Here, we ascertained the ability of attention modulation to detect tinnitus from control subjects using a logistic regression analysis (see **Figure 7**). Attention modulation (Attend – Ignored) for N1 5000 Hz and P2 500 Hz were used as predictors. The logistic regression model was significant ($\chi 2(2) = 10.093$, p =.006) with an area under the ROC curve of 0.816 (95% CI: 0.638-0.995, p = .003), indicating a relatively strong level of discrimination (Hosmer et al. 2013). A criterion with the lowest bias yielded a sensitivity of 83.3% and a specificity of 76.9%. Although not sensitive enough to adopt for clinical diagnosis, this result suggests that measures of auditory selective attention could be optimized as an objective tool for detecting of tinnitus, independent of factors relating to hearing loss alone.

Furthermore, an attention-related biomarker may be useful for predicting or monitoring the symptoms of tinnitus. In particular, our correlational results indicate that attention gain ($N1_{dB}$ 5000Hz) can potentially convey the loudness of tinnitus. It may be noted that tinnitus awareness can fluctuate based on a person's psychophysiological state (stress, fatigue) and engagement in other tasks. As such, future studies may explore whether attentional gain dynamically reflects these changes in awareness overtime. Currently a number of clinical interventions, including cognitive behavioral therapies (Jastreboff & Jastreboff, 2006; Cima et al., 2014; Searchfield et al., 2011; R. Tyler & Noble, 2004), acoustic or electromagnetic stimulation (Henry et al., 2002, De Ridder et al., 2012; Tass et al., 2012; Vanneste & De Ridder, 2011), and perceptual training paradigms (Flor et al., 2004; Searchfield et al., 2007, Krick et al., 2017), attempt to explicitly or implicitly manipulate attention away (i.e. ignoring) from the tinnitus percept to facilitate its habituation. The present selective attention biomarker can be combined with these approaches for monitoring and personalizing the intervention to reduce tinnitus loudness. The frequency-specificity of attention gain in this study suggests it may also be a useful marker in treatments aimed at reversing pathological neuroplasticity of the underlying tonotopic representation (Tass et al., 2012, Flor et al., 2004, Herraiz et al., 2007).

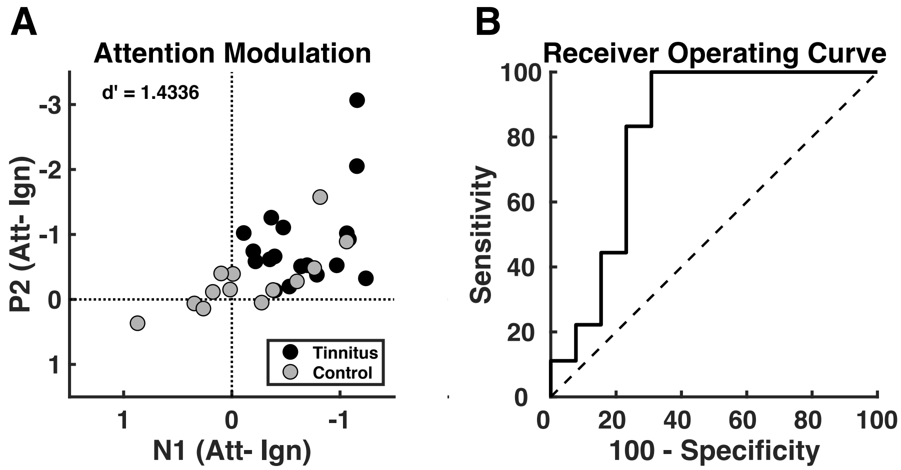

Figure 7. Discrimination Analysis. A. Scatterplot of the attention modulation variables: Attend – Ignore N1 5000 Hz (x-axis) and Attend – Ignore P2 500 Hz (y-axis), including the combined d' score. **B.** Receiver operating characteristic (ROC) curve measuring the ability of a logistic regression model to discriminate tinnitus and control subjects based on the attention modulation variables. ROC curve is derived from the predicted probabilities for individuals obtained in the logistic regression model.

CONCLUSIONS

The present study investigated electrophysiological signatures of selective attention in tinnitus sufferers focusing toward or away from a tinnitus-relevant frequency. Compared to age and hearing-matched controls, tinnitus subjects showed enhanced early attention modulation. These results suggest: 1) that focused attention to tinnitus modifies its frequency-specific sensory representation and may contribute to its loudness; and 2) attention-demanding tinnitus reduces efficiency in the selective processing of other ongoing sounds. Moreover, these results indicate a selective attention biomarker can be used to detect tinnitus and monitor the treatment impact.

Author Contributions

Conceived and designed the experiment: MR, FGZ. Performed the experiment and analyzed the data: MR. Wrote the paper: MR, FGZ.

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