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Electric hearing and tinnitus suppression by noninvasive ear stimulation

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ABSTRACT

While noninvasive brain stimulation is convenient and cost effective, its utility is limited by the substantial distance between scalp electrodes and their intended neural targets in the head. The tympanic membrane, or eardrum, is a thin flap of skin deep in an orifice of the head that may serve as a port for improved efficiency of noninvasive stimulation. Here we chose the cochlea as a target because it resides in the densest bone of the skull and is adjacent to many deep-brain-stimulation structures. We also tested the hypothesis that noninvasive electric stimulation of the cochlea may restore neural activities that are missing in acoustic stimulation. We placed an electrode in the ear canal or on the tympanic membrane in 25 human adults (10 females) and compared their stimulation efficiency by characterizing the electrically-evoked auditory sensation. Relative to ear canal stimulation, tympanic membrane stimulation was four times more likely to produce an auditory percept, required eight times lower electric current to reach the threshold and produced two-to-four times more linear suprathreshold responses. We further measured tinnitus suppression in 14 of the 25 subjects who had chronic tinnitus. Compared with ear canal stimulation, tympanic membrane stimulation doubled both the probability (22% vs. 55%) and the amount (−15% vs. −34%) of tinnitus suppression. These findings extended previous work comparing evoked perception and tinnitus suppression between electrodes placed in the ear canal and on the scalp. Together, the previous and present results suggest that the efficiency of conventional scalp-based noninvasive electric stimulation can be improved by at least one order of magnitude via tympanic membrane stimulation. This increased efficiency is most likely due to the shortened distance between the electrode placed on the tympanic membrane and the targeted cochlea. The present findings have implications for the management of tinnitus by offering a potential alternative to interventions using invasive electrical stimulation such as cochlear implantation, or other non-invasive transcranial electrical stimulation methods.

1. Introduction

Electric stimulation of the nervous system has generally taken two approaches for treating a variety of neurological disorders in humans. The invasive approach surgically places electrodes as closely as possible to a neural target, such as the thalamus for deep brain stimulation (Benabid et al., 2009) or the auditory nerve in cochlear implant stimulation (Zeng et al., 2008). A significant advantage of the invasive approach is that the proximity of the electrodes to the target minimizes electric current spread to nearby non-targeted structure, thus reducing undesired side-effects. A disadvantage of the invasive approach is that surgeries carry risks of complications and the device can be costly.

Alternatively, the noninvasive approach delivers electric current to a neural target via electrodes on the skin surface. Under normal operation, noninvasive stimulation has minimal risk of complications and is usually low cost. However, the noninvasive approach lacks focal stimulation, especially to deep neural targets, due to diffuse current flow from the electrodes to the target

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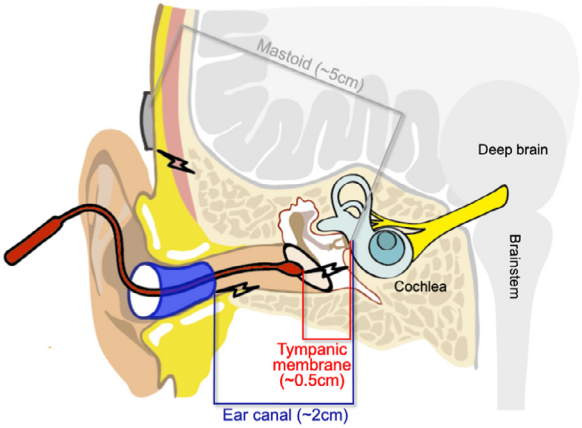

Fig. 1. Tympanic membrane or eardrum as a port for noninvasive electric stimulation of deep structures in the human skull. For a tympanic membrane electrode (red curve), the distance to the cochlea is the shortest or 0.5 cm (red line), followed by 2 cm for an ear canal electrode (blue line and blue earplug), and the furthest or 5 cm for a scalp electrode placed on the mastoid skin (gray line and gray plate behind the ear). The cochlea is close to the brainstem and other deep brain structures.

(Bortoletto et al., 2016). To improve the focality of noninvasive stimulation, recent research has manipulated either spatial or temporal patterns of multi-electrode stimulation, which may tune several broad electric fields into a relatively narrowly-focused field deep in the head (Dmochowski et al., 2011; Grossman et al., 2017; Minhas et al., 2010). However, these multi-electrode techniques are difficult to implement on the head of a living human with non-homogeneous electric properties (Cao et al., 2020; Rampersad et al., 2019). Focal and deep noninvasive electric stimulation remains a highly desirable yet challenging task in neuroengineering.

This invasive versus noninvasive dilemma is also exemplified by a lack of effective treatment for tinnitus. For example, cochlear implants have been known since their inception to be able to suppress tinnitus (Chang and Zeng, 2012; House, 1984; Yuen et al., 2021). Because most individuals with tinnitus have considerable residual or even normal hearing (Bainbridge et al., 2014; Nicolas-Puel et al., 2006), they are not candidates for invasive cochlear implantation. On the other hand, traditional noninvasive electric stimulation with scalp-based electrodes cannot provide targeted activation of cochlear structures such as detached auditory nerve fibers that may be needed for effective tinnitus suppression (Zeng et al., 2015). Ideally, safe and precise noninvasive electric stimulation of the cochlea can be developed for a large group of individuals who still have significant hearing but poor speech in noise understanding, ringing in the ears, or both. We hypothesized that electric stimulation of the cochlea may either enhance nerve responses in cases of preserved hair cells with impaired synaptic transmission or restore activities in auditory nerve fibers that are detached from the hair cells.

The overall goal of the present study was to find a location that allows targeted noninvasive electric stimulation of the cochlea for improved auditory perception and tinnitus suppression. The most efficient means of targeted stimulation is to decrease the distance between the electrode and the target (Huang et al., 2019). For stimulation of the cochlea and other deep brain structures (De Los Reyes et al., 2010), the closest location one can place an electrode noninvasively is the tympanic membrane at the medial end of the ear canal. For comparison, the distance to the cochlea is about 5 cm for the closest scalp electrode placed on the mastoid and 2 cm for a cartilaginous ear canal electrode, but only 0.5 cm for an electrode on the tympanic membrane (**Fig. 1**).

We already established that, compared to scalp electrodes, the ear canal electrode was six times more likely to evoke an auditory percept while requiring only half of the electric current (see Fig. 1d and Fig. 3a vs. 3b in F.G. Zeng et al., 2019a). Here we first characterized electric hearing evoked by an electrode placed on the tympanic membrane compared to the ear canal in 25 human adults. We then evaluated tinnitus suppression by the ear canal and tympanic membrane stimulation in 14 of these 25 subjects who had chronic tinnitus. If "the nearer the better" hypothesis holds, we would predict that the tympanic membrane stimulation produces a stronger auditory percept and more effective tinnitus suppression than the ear canal stimulation.

Insert Fig. 1 here

2. Methods

Subjects

Twenty-five human adults (10 females), aged between 20 and 82 years (mean=44 years), participated in the study. Fourteen subjects had normal hearing, four had mild-to-moderate hearing loss, and seven had high-frequency, sloping hearing loss (with five of them aged 58 and older). Fourteen of the 25 subjects reported having chronic tinnitus (mean duration=9 years; range=1 to 20 years) and participated in tinnitus suppression portion of the study. Six of the 14 tinnitus subjects had unilateral tinnitus and the remaining had bilateral tinnitus, with an average score of 24 (out of 100; range=2 to 38) measured by the tinnitus functional index (Meikle et al., 2012) and corresponding to relatively "a small problem" (Fackrell et al., 2018). The University of California Irvine Institutional Research Board approved the protocol and methods in accordance with principles set forth in the Belmont Report and Declaration of Helsinki. The present study has been registered in ClinicalTrials.gov (NCT03511807). All subjects gave written informed consent to participate in the study.

Stimuli

The stimuli were based on a previous study (F.G. Zeng et al., 2019a), which are briefly described here. All stimuli were charge-balanced, alternating-current sinusoids to avoid skin irritation (Anderson et al., 1951), hearing loss (Early et al., 2018), or other adverse effects (Bikson et al., 2016). The stimulus duration was 500 ms for the electric hearing characterization experiment. The stimulus duration was 3 min or longer for the tinnitus suppression experiment. All stimuli included a 100-ms linear onset and offset ramp. The inter-stimulus interval was at least 1 s, depending on the subject's response time. Six stimulus frequencies were tested: 0.01, 0.1, 0.5, 1, 2, and 10 kHz. The stimulus level was systematically increased from 0 mA until either the upper limit of 2 mA was reached or the subject reported any intolerable sensation. The default stimulus level step size was 0.1 mA for ear canal stimulation and 0.002 mA for tympanic membrane stimulation. The stimuli were digitally generated using Matlab on a personal computer. A constant-current source (STMISOLA, Biopac Systems, Inc., Goleta, CA, USA) converted the voltage stimulus to a current stimulus. An oscilloscope (TDS 2014, Tektronix, Beaverton, OR, USA) was used to calibrate the equipment and to monitor the input voltage between the two stimulating electrodes during the experiment. Prior to testing a subject, a 1-kOhm resistor was connected to the output of the constant-current source to calibrate the maximum current output to be 2 mA in peak amplitude. The resistor was disconnected during the test session. For safety, an isolation transformer power supply (IS500, Tripp Lite, Chicago, IL, USA) was used to isolate the subject and equipment from the mains.

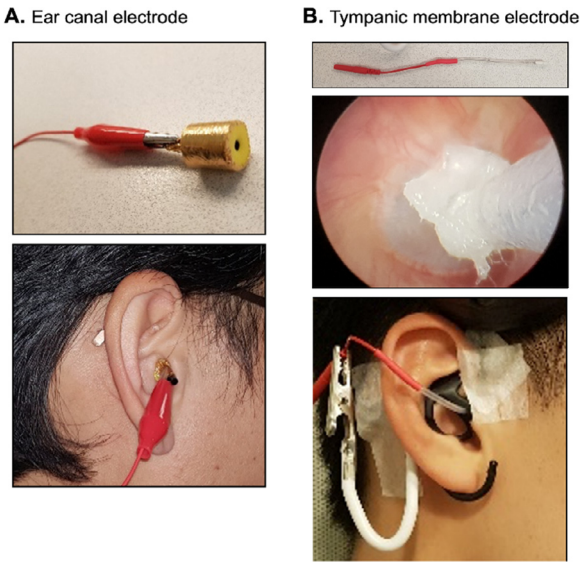

Fig. 2. Ear canal and tympanic membrane stimulation. **A.** Top panel: A gold-plated foam tiptrode connected by an alligator clamp connector (red). Bottom panel: The gold-plated tiptrode inserted in a subject's ear canal. **B.** Top panel: A cotton wick electrode (white tip at the right end). Middle panel: The wick electrode attached to the tympanic membrane. Bottom panel: The wick electrode fixed by an ear hook and mold (black) and an alligator clamp (white).

2.1. Ear electrode placement

A stimulating electrode was placed either in the ear canal or on the tympanic membrane. Prior to the experiment, an ear surgeon examined the ear canal and tympanic membrane to ensure both were free of infection or excessive cerumen, which would be removed to avoid blockage of the electrode (Schwartz et al., 2017). The ear canal electrode was a gold-plated foam tiptrode (top panel in **Fig. 2A**, radius=0.65 cm, length=1.30 cm, Etymotic ER3–26A, Elk Grove Village, IL, USA). The tiptrode was covered in conductive gel (SignaGel, Parker Laboratories, Inc., Fairfield, NJ, USA) and squeezed for easy insertion into the ear canal. The tiptrode was pushed gently to reach an insertion depth of about 1.5 cm. The foam expanded to seal the ear canal and the gold foil was connected electrically to the current source by an alligator clamp connector (bottom panel in **Fig. 2A**). The tympanic membrane electrode was a cotton wick electrode (top panel in **Fig. 2B**, wick tip area≈0.13 cm^2, Lilly TM-Wick Electrode, Intelligent Hearing Systems, Miami, FL, USA). Two hours before testing, the cotton wick was soaked in a conductive gel (Parker Laboratories, Fairfield, NJ, USA) mixed with saline in a 1:2 vol ratio (Simpson et al., 2020). While inserting the wick electrode, the depth was monitored with an endoscope to ensure gentle attachment of the cotton wick to the tympanic membrane (mid panel in **Fig. 2B**). The wick electrode was held in place by a silicon radio ear mold placed in the concha, an earpiece behind the auricle, and an alligator clamp attached to the earpiece (bottom panel in **Fig. 2B**). Such a setup minimized electrode movement that may cause uncomfortable sensation during experiment. Direct current impedance <200 kOhms usually indicated reliable and stable contact between the wick electrode and the tympanic membrane. The return electrode was a rectangular plate electrode (2.2 × 3.0 cm, Jelly Tab Sensors, Natus, Seattle, WA, USA) adhered to the subject's forehead. The forehead skin was cleaned using an electrode skin prep pad and gel (Dynarex Corp., Orangeburg, NY, USA and Nuprep, Weaver and Company, Aurora, CO, USA).

Insert Fig. 2 here -

2.2. Characterization of electric hearing

There were typically two test sessions with each session lasting about 4 h. The subject sat in a double-walled, sound-proof booth. The subject could terminate the test at any time. Electrically evoked thresholds were determined by increasing the stimulus level until the subject heard an auditory percept. Loudness growth function was measured as a function of the stimulus level by asking the subject to estimate its magnitude on a 0–10 scale, with 0 representing inaudible and 10 uncomfortably loud. The trial ended when the subjective magnitude reached the maximum tolerable loudness or the 2-mA maximum stimulation level. The method of adjustment was used to match the frequency of a pure tone to the electrically evoked pitch. The subject listened to the electrically evoked sound for as long and as often as needed, then adjusted the frequency of the pure tone, via an insert earphone, to first make its pitch noticeably higher than the electric pitch, then noticeably lower than the electric pitch, and finally arrive at a frequency that best matched the electric pitch (Zeng, 2002).

2.3. Tinnitus suppression

The effect of electric stimulation on tinnitus was characterized similarly to a previous study (Zeng et al., 2019). The stimulus frequency varied from 0.01 to 10 kHz. The stimulus current was set individually to evoke the maximum comfortable loudness or the 2-mA level even if it did not reach the maximum comfortable loudness. Three-minute stimulation was delivered to the tinnitus ear in unilateral cases, or the ear with more severe tinnitus in bilateral cases. Prior to stimulation, the subject reported the baseline tinnitus loudness on the same 0–10 loudness scale. During stimulation, the subject reported their tinnitus loudness every 30 s. The subject continued to report tinnitus loudness at the offset of stimulation and every 30 s after that until the tinnitus returned to the baseline level. Tinnitus loudness typically returned to the baseline, in 3–5 min but occasionally much longer (10 min to hours) after the stimulation offset.

2.4. Sham electric stimulation

Sham stimulation was delivered to estimate the degree of a placebo effect on tinnitus suppression. The participant was not told about the sham stimulation, in which either no electric stimulation (passive sham) or 10-second (active sham) electric stimulation was delivered at the onset of the trial. Because of rapid adaptation of the tactile sensation, the 10-second stimulation could simulate tactile sensation produced by its three-minute counterpart at least in the transient portion. However, the 10-second simulation could not simulate the audible percept of the three-minute counterpart. All other aspects of the sham stimulation followed the actual tinnitus suppression procedure.

2.5. Quantifying tinnitus suppression

To average across subjects, a relative change in tinnitus loudness was calculated by removing the individual difference in its pre-stimulation baseline (Tang et al., 2006)

$$Tinnituschange(\%) = \frac{Tinnitusloudnessestimate - Baseline}{Baseline} * 100$$

where 0% indicates no effect of electric stimulation on tinnitus baseline, a negative value indicates a decrease in tinnitus loudness, and a positive value indicates an increase in tinnitus loudness.

The maximum amount and time course of tinnitus suppression was described by an exponential decay function:

$$Tinnitus\,change(\%) = s(1 - e^{-\frac{t}{\tau}})$$

where s is the maximum amount of tinnitus suppression and τ is time constant in minutes.

2.6. Adverse events

Subjects were instructed to report any adverse or unexpected events, including but not limited to electric shocks, hearing loss, skin irritation or infection, during and after the experiment. However, concurrent tactile sensation and occasionally visual sensation, which could be sometimes annoying (Fertonani et al., 2015; F.G. Zeng et al., 2019a), were not reported as adverse events in the present study.

2.7. Statistical analysis

The Chi-square test was used to determine significant difference in the probability and frequency of evoked electric hearing. The student *t*-test was used to compare hearing threshold between electrode locations. In tinnitus suppression, the normality of the tinnitus change histograms was evaluated using the Kolmogorov-Smirnov test. Tinnitus change between the three treatment groups (sham, ear canal and tympanic stimulation) was compared using the student *t*-test for normal distribution or the Mann-Whitney U test for non-normal distribution. Bonferroni correction was applied for the three group comparisons with a difference being considered significant for $p<0.017$. The effect size was calculated as either the relative risk, RR (Citrome, 2010) or the Cohen's *d'* (Sullivan et al., 2012).

3. Results

3.1. Electric hearing

The 25 adults responded to a total of 257 conditions for stimulus frequencies from 0.01 to 10 kHz and levels from 0.001 to 2 mA. No adverse events were observed within this stimulus parametric space. Compared with the ear canal stimulation, the tympanic membrane stimulation was four times more likely to produce an auditory percept (48% vs. 12%, $X^2(1, n = 200) = 31.28$, $p<0.001$, $RR=3.88$; **Fig. 3A**), while requiring eight-fold lower current level to reach the hearing threshold (0.1 vs. 0.8 mA; $t(51)= -9.81$, $p<0.001$, $d = 1.72$; **Fig. 3B**). The tympanic membrane stimulation also produced more linear loudness and pitch responses than the ear canal stimulation. The loudness of electric hearing increases as a power function of electric level for both stimulation types, but the slope of the power function was nearly twice as steep for the ear canal stimulation (1.38 vs. 2.39; **Fig. 3C**). Nevertheless, the slope of loudness growth in both types of stimulation is steeper than the 0.3 slope of loudness growth in normal acoustic hearing (Stevens, 1961). In matching the frequency of a pure tone to the pitch of a corresponding electric stimulus, the tympanic membrane stimulation produced four times more linear or 1:1 match in frequency than the ear canal stimulation (75% vs. 17%, $X^2(1, n = 44) = 12.29$, $p<0.001$, $RR=4.50$; **Fig. 3D**). Conversely, doubling acoustic frequency was required to match the electric frequency 25% of the times for the tympanic membrane stimulation, but 75% for the ear canal stimulation. In one condition of the ear canal stimulation (the filled triangle in **Fig. 3D**), a much lower 0.1-kHz acoustic frequency was matched to an electric stimulus of 0.6 kHz.

-Insert Fig. 3 here -

3.2. Tinnitus suppression

Fourteen subjects with chronic tinnitus participated in 96 trials, which measured changes in tinnitus loudness in response to either tympanic membrane or ear canal stimulation (see four representative examples in **Fig. 4A**). Subject #19 (first panel) reported that ear canal stimulation (0.5-kHz, 2-mA and 3-minute sinusoid, shaded area) produced no change in tinnitus (or 0%), which remained at the baseline level (blue triangles) before, during and after the stimulation. Subject #18 experienced a reduction in tinnitus loudness from 3.5 at baseline to 3 immediately after the onset of ear canal stimulation and a further reduction to 2.5 two minutes into the stimulation, resulting in −29% decrease in tinnitus loudness (see arrowed line in the second panel). Similarly, subject #22 perceived a − 40% decrease in tinnitus loudness (red circles) in response to tympanic membrane stimulation, except for a small rebound at the offset of the stimulation. Subject #07 had the most desirable outcome, namely complete suppression of tinnitus (−100%) two minutes into tympanic membrane stimulation, and even 10 min after the stimulation was turned off (only two data points were shown here).

Fig. 4B shows histograms of tinnitus change in response to sham (top panel), ear canal (middle) and tympanic membrane (bottom) stimulation. The sham stimulation produced a 7 ± 37% increase in tinnitus loudness (dashed vertical line), which was not significantly different from no change or 0% ($t(10)=0.59$, $p = 0.567$). Compared with the sham stimulation, the ear canal stimulation did not produce significantly different tinnitus suppression (−5 ± 11%; Mann Whitney $U = 226$, $p = 0.242$) but tympanic membrane stimulation did (−22±27%; $U = 93.5$, $p = 0.015$). Note that only 22% subjects reported tinnitus suppression (a negative value) using the ear canal stimulation, compared to 55%

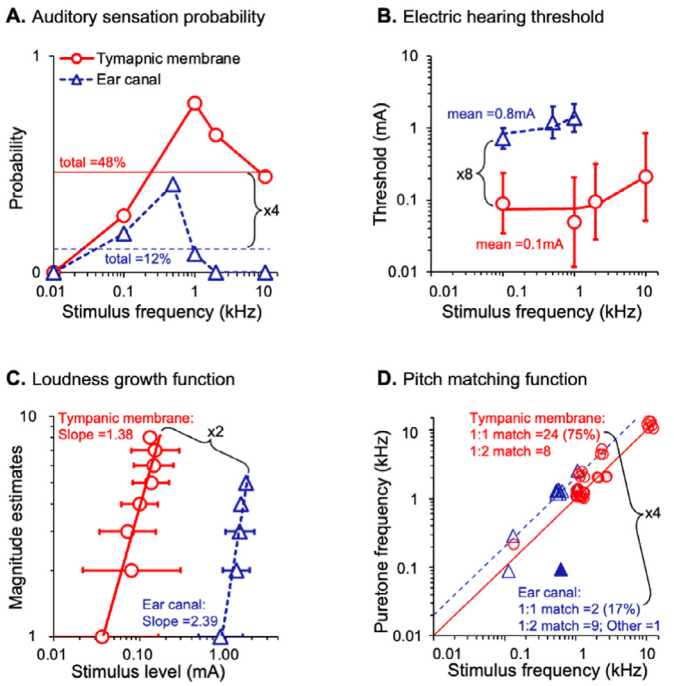

Fig. 3. Characteristics of electric hearing evoked by tympanic membrane (red) and ear canal (blue) stimulation. **A.** Probability of auditory sensation as a function of electric stimulus frequency. Solid and dashed horizontal lines represent the probability of auditory sensation from the total number of conditions across subjects in the tympanic membrane and ear canal stimulation, respectively. **B.** Hearing threshold as a function of stimulus frequency. Solid and dashed lines represent a first-order Butterworth low-pass filter best fit to the data. **C.** Loudness growth as a function of stimulus level. Solid and dashed lines represent a best-fit power function with its exponent, or slope on a log-log scale being displayed next to the data. **D.** Pitch matches between acoustic and electric hearing. The solid red diagonal line represents 1:1 match between electric stimulus frequency and acoustic puretone frequency whereas the dashed blue line represents 1:2 match. Error bars represent ±one standard deviation.

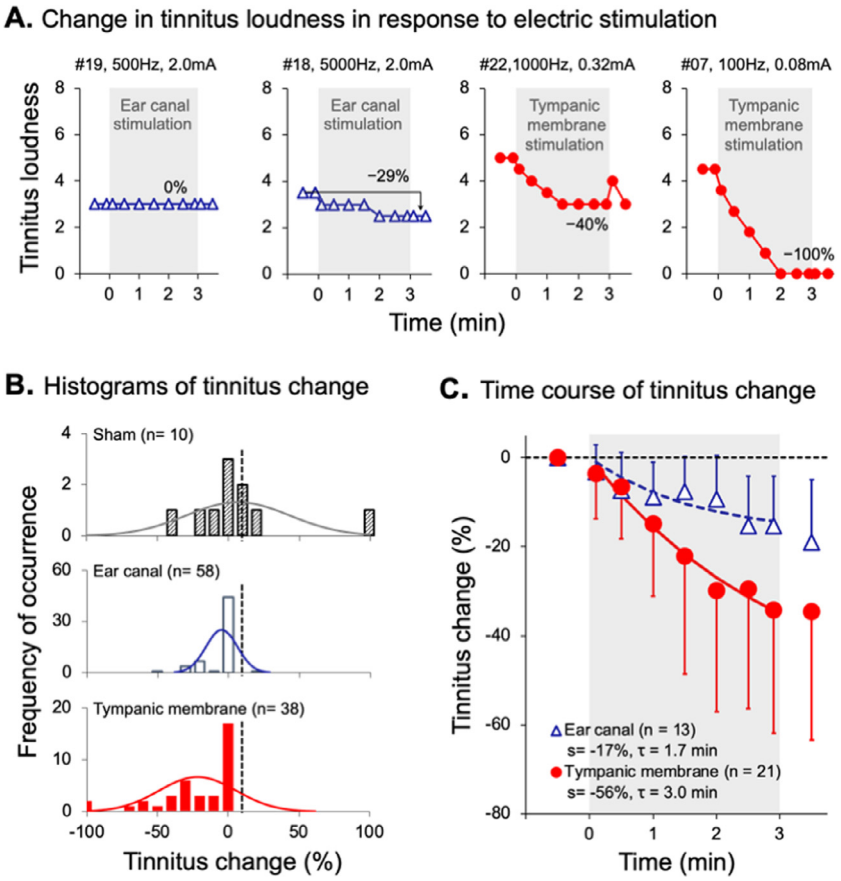

Fig. 4. Tinnitus suppression in response to electric stimulation. **A.** Representative examples of tinnitus loudness estimates (y-axis) in response to three-minute electric stimulation (shaded area). The first two examples are tinnitus loudness measures in response to ear canal stimulation (blue triangles), while the last two examples are the same measures in response to tympanic membrane stimulation (red circles). The stimulus parameters are displayed on top of each panel. The maximum percentage of change in tinnitus loudness is displayed near the end of the three-minute stimulation. **B.** Histograms of tinnitus change for all 96 trials, including 10 for sham stimulation (top), 58 for ear canal stimulation (mid) and 38 for tympanic membrane stimulation (bottom). The vertical dashed line represents the mean value from the sham stimulation. The solid bell-shaped lines represent the best-fit normal distribution. **C.** Average tinnitus loudness change for ear canal (blue triangles) and tympanic membrane stimulation (red circles) in those who showed suppression in response to three-minute electric stimulation (shaded area). Error bars represent standard deviation. Curved lines represent a best-fit exponential function with two free parameters, maximum suppression or saturation (s) and a time constant (τ, see Methods).

of subjects using the tympanic membrane stimulation (2.5 times more likely, $z(97)= -3.3$, $p<0.001$).

Fig. 4**C** shows average changes in tinnitus as a function of stimulus duration from the subjects who reported tinnitus suppression (i.e., 22% subjects using ear canal stimulation and 55% using tympanic membrane stimulation). At the end of 3-minute stimulation, on average, tympanic membrane stimulation produced two times more tinnitus suppression than ear canal stimulation ($-34\pm28\%$ vs. $-15\pm11\%$; $t(32)= -2.36$, $p = 0.025$, $d = 0.90$). An exponential decay model was fitted to the present data (blue and red lines), showing that tympanic membrane stimulation took about half time (1 min) to reach the maximum suppression level produced by ear canal stimulation (-15%).

-Insert Fig. 4 here -

4. Discussion

We have placed a noninvasive electrode in either the ear canal or on the tympanic membrane to deliver electric stimulation to the cochlea, where the auditory nerve is attached and has close proximity to other cranial nerves and deep brain structures. The present result confirmed the “the nearer the better” hypothesis that stimulation of the tympanic membrane, which is four times closer to the cochlea than the ear canal (**Fig. 1**), was also four times more likely to evoke an auditory percept. In addition, the tympanic membrane stimulation produced eight times lower hearing thresholds and two-to-four times more linear loudness growth and pitch matches (**Fig. 3**). As a result, the tympanic membrane stimulation was twice more likely than the ear canal stimulation to suppress tinnitus and if suppressed, doubled the amount of tinnitus suppression (**Fig. 4**).

Using the same experimental protocol, we previously showed that ear canal stimulation was six times more likely than scalp electrodes to evoke an auditory percept and if evoked, required half of the current level to reach the threshold (F.G. Zeng et al., 2019a). Therefore, we could infer from the previous and present results that comparing with electric stimulation on the scalp, the tympanic membrane stimulation not only requires 16 times lower current level to reach the hearing threshold, but also is 24 times more likely to evoke an auditory percept. Lower current levels are generally preferred in both invasive and noninvasive electric stimulation because they save power and improve safety. More importantly, lower thresholds are indicative of more targeted stimulation as in the case of intraneural stimulation against the standard cochlear implant stimulation (Middlebrooks et al., 2007).

5. Mechanisms of electric hearing

Earlier studies applied electric signals to a metal plate electrode on dry skin, which serves as a microphone that converts electric signals into mechanical vibrations to evoke hearing through the usual auditory pathway (Flottorp, 1953; Mallinckrodt et al., 1953).

This direct electrical-to-mechanical conversion is unlikely to occur in the present study because we placed the electrode on a wet surface (see Methods). Furthermore, had such direct conversion occurred, one would expect similar sensation to that caused by normal acoustic stimulation. Instead, we observed abnormally steep loudness growth and pitch distortion, suggesting alternative mechanisms.

The first mechanism is via activation of the cochlear outer hair cells, which in turn move the inner hair cells to produce an auditory percept. The outer hair cells are highly nonlinear mechanical amplifiers that provide as much as 1000-fold gain for low-level sounds but no gain for high-level sounds (Ruggero, 1992). The outer hair cells can respond to electric stimulation (Le Prell et al., 2006; Ren et al., 1995) and their nonlinearity is likely responsible for the pitch distortion, especially by the ear canal stimulation in the present study.

The second mechanism is via activation of the cochlear inner hair cells, which are sensory transducers that convert mechanical vibrations into action potentials in the auditory nerve fibers (Glowatzki et al., 2002). Electric currents may activate the inner hair cells via an electric tuning mechanism, particularly in the case of tympanic membrane stimulation (Crawford et al., 1981; Lewis et al., 1983). To differentiate between the outer and inner hair cell activation mechanisms, future studies may need to measure the masking pattern between acoustic and electric stimulation, with a linear and single-peak pattern favoring the inner hair cell activation (Le Prell et al., 2006; Lin et al., 2011).

The third mechanism is direct activation of the auditory nerve. In subjects with severe-to-profound hearing loss, broad-band or noise-like auditory percepts had been observed with noninvasive electric stimulation (F.G. Zeng et al., 2019a). However, in subjects with normal or sufficient residual hearing, direct activation of the auditory nerve may be mixed with both the inner and outer hair cell activation (Sato et al., 2016). Human perception for such mixed activation is unknown.

5.1. Limitations and applications

The present study has several limitations, including a small size for tinnitus subjects, their relatively mild symptoms that may not be representative of those who look for relief, and a lack of true sham stimulation. Furthermore, the present study does not explicitly address the hearing mechanisms of electric stimulation. Future studies need to test at least totally deafened individuals so that the auditory nerve activation hypothesis can be tested. It is not clear how to differentiate activation between hair cells and auditory nerve fibers or between the inner and outer hair cells. Finally, several technical advances need to be made to translate the present study into a safe and effective product. First, the whole system needs to be miniaturized to fit inside the ear canal. Second, new electrodes need to be developed for easy and long-term attachment to the tympanic membrane. The electrode development should not be technically challenging as transtympanic tubes are routinely used for treatment of middle ear disease (Aazh et al., 2017). Third, the presence of concurrent tactile sensation, and occasionally visual sensation, can sometimes be annoying in essentially all forms of noninvasive transcranial electric stimulation (Fertonani et al., 2015; F.G. Zeng et al., 2019a). Electrode and stimulus control may be used to minimize tactile sensation (Voroslakos et al., 2018).

5.2. Broader implications for neuromodulation

As a deep orifice in the head, the ear canal or tympanic membrane may serve as a port for general-purpose, noninvasive electric stimulation of other cranial nerves and deep brain structures (Adair et al., 2020). Using the tympanic membrane as either a stimulation or reference location, we can manipulate other electrode positions and stimulating waveforms to potentially improve the depth and focality of noninvasive deep brain stimulation (Foutz et al., 2010; Grossman et al., 2017; McIntyre et al., 2000; Mehta et al., 2015; Tran et al., 2019). The closest target is the vestibule, with its stimulation being able to not only potentially treat Meniere's disease, vestibular migraine, or vestibulopathy (Beh, 2020; Helmchen et al., 2019), but also potentially prevent falls in the elderly (Serrador et al., 2018) or even enhance immersive experience in augmented and virtual realities (Byrne et al., 2016). Other potential targets include vagus nerve, trigeminal nerve, thalamus, the limbic system and other brain structures. Such an integrated system may lead to cost-effective alternatives to the current invasive and expensive neural stimulation for not only treating depression, epilepsy or tremor (George et al., 2000; Lee et al., 2019) but enhancing normal perceptual and cognitive performance (Keshavarzi et al., 2020; Ketz et al., 2018; Riecke et al., 2018).

6. Author contributions

MS and PT contributed to experimental design, data collection and analysis, and writing manuscript. MR, SS, YX, HD and HL contributed to experimental design and data collection. FGZ oversaw the study from experimental conception to manuscript preparation. All authors commented and approved the final version of the manuscript.

Declaration of Competing Interest

FGZ owns stock in Axonics, DiaNavi, Nurotron, Syntiant, Velox and Xense. HRD has equity interest in Cactus Medical, Mind:Set Technologies, and is a consultant to NXT Biomedical and Alcon. The other authors declare no competing interests.

Data availability

Although only representative examples of individual results and the average data were presented in the paper, full data are available upon request by contacting the corresponding author.

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