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Advances in electrical stimulation-based therapy for tinnitus

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Abstract: Tinnitus is a phantom percept of noise heard only by the affected person. The principal problem of persons suffering from tinnitus is the inability to deflect their attention from the phantom sound, resulting in insomnia and problems with concentration, followed by significant health issues. To date, no therapy would relieve patients from the phantom sound. Instead, commonly used therapeutic approaches for tinnitus aim primarily at the reduction of tinnitus-induced distress and are based on various tinnitus habituation methods. Our project aims to quench the tinnitus percept using an implant. To develop such an implant, this research group joined the INTAKT network initiated by the German Federal Ministry of Education and Research and dedicated to the development of smart implants. During this still ongoing, prospective clinical study, the efficacy of two protocols using electrical stimulation is assessed for tinnitus silencing. The electrical stimulation used in the presented study is non-invasive and applied on three consecutive days in the form of short sessions. In a sample of 48 subjects, following three stimulation sessions, 48% of patients reported a significant reduction of tinnitus loudness; 10% reported a brief increase of tinnitus loudness, and 42% stated no change. In one case, the first course of stimulation led to the total distinguishing of tinnitus. On average, the stimulation did not affect the grade of tinnitus-induced distress during the time of measurement. Our current results prompt us to broaden our investigations, expand the subject sample, and further optimize the stimulation conditions.

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Introduction

Tinnitus is an auditory symptom accompanying various health conditions such as hearing loss, diabetes, hypertension, intracranial hypertension, and some types of tumors, e.g., vestibular schwannoma, meningioma, head and neck injuries, and many others [1]. Persons perceiving tinnitus report hearing a sound without semantic meaning (e.g., ringing, hissing, static, crickets, screeching, whooshing, roaring). The tinnitus percept has no external source and shares many physiological and neurological similarities with the phantom pain occurring in persons with amputated limbs.

The incidence rate of clinically meaningful tinnitus rises as the population ages [2]. Unfortunately, to date, no successful therapy for tinnitus, which would quench the phantom sound, has been developed. Instead, numerous psychotherapeutic approaches, such as cognitive-behavioral therapy, are used to reduce the psychological burden induced by tinnitus. These approaches help the sufferers to cope better with the problem but do not solve the problem itself.

The present study was prompted by earlier reports primarily dealing with cochlear implantation and pre-implantation diagnostics. Cochlear implantation is an acknowledged method of auditory rehabilitation for people with severe hearing loss. The majority of the patients who qualify for cochlear implantation have tinnitus, which accompanies hearing loss [3]. Interestingly, cochlear implantation significantly reduces tinnitus [4–7], which can be explained not only by the restored auditory abilities but also by the process of electrical stimulation of the hearing nerve occurring *via* cochlea [8]. An additional piece of evidence suggesting an essential role of the electrical stimulation for the extinguishing of tinnitus was delivered by a promontory stimulation test, a part of pre-implantation diagnostics that assesses the functionality of the hearing nerve. A significant proportion of the patients reported improvement of their tinnitus during the promontory stimulation test [9]. We, therefore, hypothesized that in subjects with tinnitus and no or only mild hearing loss, the electrical stimulation applied *via* cochlea (e.g., an implant placed on the round window) might suppress the activity of

auditory system leading to the perception of tinnitus and that the degree of suppression could depend on varying stimulation parameters.

The main aim of our ongoing project is to determine the effect of electrostimulation on tinnitus loudness and tinnitus-induced distress. In addition, we aimed to test the parameters that could modulate the influence of stimulation on tinnitus, and that be used for the construction of an anti-tinnitus implant.

Patients and methods

Forty-eight adult subjects with chronic tinnitus (29 men and 19 women) were included in this prospective interventional study that was granted by the local ethics committee (permit number EA1_125_18). Each of the subjects was scheduled to be stimulated on three consecutive days.

Measuring tinnitus

For the measurement of the subjective loudness of tinnitus as well as tinnitus-induced distress, a visual analog scale (VAS) was used. The first VAS measured tinnitus loudness where “1” signifies that tinnitus was very quiet and “10” that tinnitus is very loud. The second VAS measured tinnitus-induced distress (1 – no distress and 10 – great distress). The measurement was performed shortly before and immediately after each electrical stimulation session.

Electrical stimulation

The non-invasive electrical stimulation was conducted with an external, golden ball-shaped electrode that was placed in the external ear canal of each subject.

Two stimulation protocols were applied to address the following research questions: 1. Is tinnitus suppression primarily dependent on the frequency of stimulation used? 2. Does the suppression effect depend on the ratio of tinnitus frequency/stimulation frequency?

The stimulation signal consisted of a biphasic square wave, presented in the form of bursts:

- 100 Hz signal: carrier frequency 100 Hz, modulation frequency 1 Hz, interstimulus interval 10 ms, pulse width 1 ms.
- 1000 Hz signal: carrier frequency 1000 Hz, modulation frequency 5 Hz, interstimulus interval 1 ms, pulse width 400 μ s.

The first group of patients was stimulated on day one with 1000 Hz, on day two with 1000 Hz and day three with 100 Hz.

The second group of patients was stimulated on day one with 100 Hz, on day two with 100 Hz and day three with 1000 Hz. The stimulation current used was between 0.4 and 3.0 mA.

The patients were randomly assigned to a given stimulation group. There were no differences between the groups regarding VAS scores before the first stimulation.

Results

Immediately after the electrical stimulation, tinnitus loudness was reduced in 21 of 48 subjects (Figure 1). Two persons reported a reduction of tinnitus loudness after the second or third stimulation sessions. In five persons, tinnitus became *temporarily* louder after stimulation, and in 20, there was no change in tinnitus loudness.

We observed changes in the tinnitus loudness. In the first stimulation group (25 subjects), 12 patients reported a reduction in tinnitus loudness during the first stimulation; one subject reduction in tinnitus loudness on the second day and two subjects reported their tinnitus as louder than before stimulation. In the second group (23 subjects), nine subjects reported a reduction of tinnitus loudness directly after first stimulation; one subject reported tinnitus loudness reduction on the second day, and three subjects reported a brief increase in the loudness of their tinnitus. One patient from the second group described total distinguishing of tinnitus loudness and tinnitus-induced distress after the first session.

Overall, patients tolerated the stimulation well. Few patients had a perception of having water in the ear canal; in a few other cases, the clamping electrode was perceived as unpleasant. However, none of this has led to the interruption of stimulation.

Changes in tinnitus loudness after electrical stimulation

Figure 1: Influence of electrical stimulation on tinnitus in the subject sample tested.

No statistically significant differences were determined between the two stimulation groups regarding the tinnitus loudness and the degree of tinnitus-induced distress before stimulation (t-test, $p=0.565$ and $p=0.868$, respectively).

No significant changes in the scores indicating tinnitus-induced distress were noted following electrical stimulation.

We compared the VAS values indicating tinnitus loudness before the first stimulation with those obtained after the third stimulation (Figure 2). One-way analysis of variance (ANOVA) with pairwise multiple comparison procedures (Dunn's method) indicated a significant decrease in the tinnitus loudness ($p<0.05$) in each stimulation group.

We found no significant differences in the outcome measured between the two stimulation groups, suggesting a lack of influence of chosen stimulation parameters on the outcome.

In addition to the two groups of patients who underwent various stimulation protocols, we included a sham control group. The idea of sham control was based on a strong notion in the field about the critical role of the placebo effect in tinnitus therapy [10]. Therefore, our sham control subjects were subjected to the same physical maneuvers as the treated group, with one difference: no electrical stimulation was applied. All the operations –

setting up the wires, placing the electrode in the ear canal – were identical for all groups. All patients were informed identically by the physician who performed the tests: “Please prepare, we are starting now.” Because of the pandemic, we were able to recruit only three subjects to the sham control group. None of the three persons reported changes in tinnitus loudness or the tinnitus-induced distress following sham stimulation. Presently, more patients are being recruited.

Conclusion

The main aim of the presented project was to determine the effect of electrostimulation on tinnitus loudness and tinnitus-induced distress. We conclude that electrical stimulation reduces tinnitus loudness in about 50% of the treated patients and, therefore, seems to be a promising method to treat idiopathic tinnitus. However, electrical stimulation did not influence tinnitus-induced distress, at least not within the time window of measurements. We also aimed to test the parameters that could modulate the influence of stimulation on tinnitus, and be used for the construction of an anti-tinnitus implant. We found that the stimulation parameters we have chosen to modulate (signal frequency 100 vs. 1000 Hz, carrier frequency 100 vs. 1000 Hz, modulation frequency 1 vs. 5 Hz, interstimulus interval 1 vs. 10 ms, and the pulse width 1 ms vs. 400 μ s) have not influenced the outcome of stimulation, measured by VAS-tinnitus loudness. It remains to be determined if the duration of stimulation and a various number of sessions for patients with a first positive response may further tune-up this form of non-invasive tinnitus treatment and pave the way for setting the anti-tinnitus implant parameters.

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Figure 2: The mean values of subjective tinnitus loudness decrease after electrical stimulation. Tinnitus loudness was measured with VAS (*significance $p<0.05$).

Ethical approval: Forty-eight adult subjects with chronic tinnitus (29 men and 19 women) were included in this prospective interventional study that was granted by the local ethics committee (permit number EA1_125_18).

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