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Tinnitus treatment with sound stimulation during sleep

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Abstract

A new strategy for idiopathic subjective tinnitus treatment – sound stimulation during sleep – has been applied. It was based on the knowledgement that the auditory system also works during sleep, processing the incoming information. Eleven patients were stimulated every night during 6 months. The stimulus was a sound that mimetized the tinnitus and was fixed at the same tinnitus intensity, applied through an iPod. All patients decreased their tinnitus intensity in the first month of treatment (statistically significant), most of them in the first week. Tinnitus intensity continued decreasing in the following weeks; three patients presented periods of total silence.

Keywords: Tinnitus, Treatment, Sleep.

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INTRODUCTION

Mechanisms that underlie tinnitus perception are still not well understood; nevertheless, nowadays it is accepted that interactions between altered cochlear inputs and distorted central auditory processing provoke tinnitus. The physiological abnormalities that cause subjective tinnitus perception arise in the central nervous system (CNS). It is now evident that most forms of subjective tinnitus are caused by changes in the function of the central auditory nervous system while these changes are not associated with any detectable anatomical lesion. The subjective tinnitus may be the result of the expression of neural plasticity and anomalies may develop because of decreased input from the ear, deprivation of sound stimulation, overstimulation or yet unknown factors[1]. Studies with brain imaging support the central correlates of tinnitus perception[2,3]. In a number of patients subjective tinnitus may be initiated by a discontinuity in the spontaneous or low-level stimulus inducing neural activity across auditory nerve fibers with different characteristic frequencies (CFs). This discontinuity may be caused by functional loss of outer hair cells in those regions where inner hair cells are preserved. The reduced spontaneous activity for nerve fibers with CFs in the hearing loss range may result in a reduction of inhibition, mediated by the auditory efferent system, at more central levels[4]. This reduced inhibition of neurons with CFs induces hypersensitivity and hyperactivity in these neurons, generating a "phantom sensation", that is a sensation referred in a different location on the body (in this case usually the ear) than the anatomical location of the abnormality that causes the symptoms[1]. Since most forms of severe tinnitus are caused by functional changes, it should be possible to reverse it with proper sound treatment, taking advantages of the neural plasticity properties of the CNS.

Auditory inputs during sleep. The sensory input represents the whole fan of information that the CNS receives, whose output responses, after complex processing, are elicited, e.g., motor, endocrine, neurovegetative, behavioral or changes in the CNS capacities such as memory, learning, and so on. Since the sensory information in general is continuously reaching the CNS, its processing will be differentiated according to the current physiological state of the brain: wakefulness, with different levels of motor activity and attention, and sleep[5]. Early in the twentieth century, the concept of sleep as the result of a blockage of the auditory inflow was introduced[6] while, later on, Bremer[7] proposed that it was the extensive deafferentation of ascending sensory impulses to the isolated brain that resulted in sleep. Nowadays, it is widely accepted the tenet that sleep is actively produced. Electrophysiological approaches as unitary recordings, immunoreactive staining techniques as well as functional magnetic resonance imaging in humans are some contributions to such concept[8-10]. Velluti and co-workers postulated the sensory systems as a main factor in active participation in sleep processes[11-14]. The processing of sensory information is definitely present during sleep, since profound modifications occur. All sensory systems reviewed, visual, auditory, somesthetic and olfactory, as well as temperature receptors, etc., demonstrate some influence on sleep and, at the same time, the sensory systems undergo changes that depend on the CNS sleep or waking condition. From several viewpoints, the auditory is a special system related to sleep neurophysiology, exhibiting a series of unique associated changes[12,15,16]. The auditory incoming signals to the CNS may change the sleep characteristics, while, conversely, the CNS can control by feedback mechanisms the auditory input in close correlation with the sleep-wakefulness cycle[11]. Receptor and auditory nerve action potentials exhibited amplitude changes when analyzed during quiet wakefulness, Slow Wave Sleep (SWS) and Paradoxical Sleep (PS) in guinea-pigs[16,17]. Auditory evoked potentials recorded from the primary cortical area in rats also exhibited amplitude shifts when the animal passed from wakefulness (W) to sleep. All evoked potentials components of the averaged waveform were larger during SWS than in W or PS[18]. The auditory system neuronal firing exhibits a variety of changes in all of its nuclei and primary cortical *loci* linked to the sleep-wakefulness cycle in many ways, i.e., increasing or decreasing their firing on passing to sleep, firing as during W, changing the discharge pattern, exhibiting theta rhythm phase-locking, while no auditory neuron stopped firing on passing to sleep[19-24]. Edeline et al. (2001)[25] also reported changes in the receptive field of cortical auditory neurons. Therefore, it can be concluded that when asleep many auditory units are active. Most relevant, reciprocally, auditory deprivation (experimental deaf guinea pigs and hamsters) produces changes in the sleep stages percentages[26,27]. Reports in humans showed marked changes on the evoked potentials later components during sleep[28-31]. A high amplitude complex waveform dominates in SWS stages 2, 3 and 4, which is the result of summed K-complexes evoked by sensory stimuli[32]. Semantic information is possible in SWS stage 2 and PS[33], whereas the presence of P3 seems to be essential for stimulus encoding, despite the question if W and sleep P3 could be considered equivalent remains to be answered[32]. Mismatch negativity shifts were reported in SWS[31] and during PS[34]. Moreover, this negativity has been reported also in newborns "quiet sleep" and linked to learning[35]. Intracochlear implanted humans changed their sleep characteristics when implant remained "on" during the night[36].

Tinnitus and sleep disorders. Studies have demonstrated a strong relationship between sleep disorders and tinnitus. A large percentage of patients with tinnitus experiment disturbances/distortions of the normal sleep pattern; poor sleep and frequent waking are more common among subjects with tinnitus (60%). Sleep disturbances are a factor that strongly predicts decreased tolerance to tinnitus[37]. Furthermore, patients whose sleep was most disturbed rated significantly greater tinnitus annoyance in the evening underscoring the influence of tinnitus on sleep disorders[38]. On the other hand, daytime sleepiness is more common in subjects with tinnitus and it is even more frequent in patients with both tinnitus and poor sleep[39]. Insomnia is associated with greater perceived loudness and severity of tinnitus[40]. These facts underscore the importance of identification and successful treatment of sleep disorders in patients with tinnitus.

Tinnitus treatment with sound stimulation. There are several treatments for tinnitus based on sound stimulation at present, e.g., tinnitus masking, music, white noise, etc. Tinnitus Retraining Therapy (TRT) is a behavioral treatment that has roots in the hypothesis that tinnitus is caused by expression of the neural plasticity[41,42]. The aim of TRT is to psychologically disconnect the patient from dependence on the tinnitus while subjecting the patient to moderate levels of sounds to reverse the effect of sound deprivation on the function of the CNS[43]. Other tinnitus therapies based on sound are being applied as an special program of music therapy that strives to integrate the tinnitus sound into a musically controllable acoustic process[44], sequential sound therapy[45] and customized sounds[46,47]. Many of these therapies are still under investigation and only some of them have been objectively evaluated in clinical trials[48]. Up to date, no other therapies have shown to improve the tinnitus with certainty. Drugs have not demonstrated to provide replicable long-term reduction of tinnitus[49]; many of them are still at a research level, such as transcranial magnetic or cortical electric stimulation of the auditory cortex[50,51].

METHODS

This study was approached on a multidisciplinary basis: otolaryngology, psychology and sleep medicine.

Patient evaluation. Twenty two patients were evaluated; thirteen of them complied with inclusion criteria and were studied, two abandoned the treatment, remaining eleven within the protocol. Every patient was evaluated by an otolaryngologist with a clinical interview and specific tests: impedanciometry, tonal liminal audiometry, high frequency audiometry, logoaudiometry, otoacustic emissions (spontaneous, transients and distortion product) and magnetic resonance imaging (MRI). Also general evaluation was done through routine tests (blood lipids, serum thyroid hormones, glucose test, urea and electrolytes, creatinine, complete blood test, urine test). The inclusion criteria were adult patients with idiopathic subjective tinnitus, with normal imagenology and without any organic causes. Objective tinnitus secondary to organic causes was excluded.

Psychological evaluation. Patients were evaluated by a psychologist at the beginning of the treatment and also in the middle and at the end of it. Personal interview to evaluate anxiety and depression, and a specific test for tinnitus repercussion (Tinnitus Handicap Inventory, THI) were done.

Sleep evaluation. Patients' sleep conditions were clinically evaluated, exploring possible insomnia related to tinnitus or other sleep disturbances (i.e. apneas, restless legs syndrome). Conventional Polysomnography was recorded in two patients, during two nights each one (first night without sound stimulation and the second one during the stimulation with their specific sound) in order to analyze potential hypnograms changes due to the sound. Conventional Polysomnography consisted in six electroencephalographic recordings, eye movements, electromyogram, respiration, oximetry and electrocardiogram.

Tinnitus characterization and sound stimulation. Sound generation and stimulation were programmed to reproduce a sound with the same characteristics as that of each patient's tinnitus. Audio stimulation was performed using commercial iPod Shuffles (Apple, USA) with their own ear buds. All sounds were created with custom software developed in Matlab, creating complex sounds by combining pure tones, white and pink noise and filtered white noise (peak filter, Q) at 44100 samples per second. These sounds could be created selecting their frequency, power (relative to full scale), Q and duration. Once the sound was created, it could be independently saved to left or right ear. After the sound mimicked the perceived tinnitus, it was saved as a .wav file (16 bit, PCM) and consequently loaded to the iPod Shuffle. In order to equal the output of the computer where the sound was created and the iPod shuffle, both computer and iPods linearity and flat frequency response were measured with RightMark Audio Analyzer 6.0.5 and an M Audio 66 sound card. The custom software was programmed to adjust the power of the sound signal in order to have equal full scale voltage output. The same ear buds were used to mimic and deliver the stimulus, thus ensuring that equal voltage would be transduced into equal sound pressure. Figure 1 shows the frequency response (in A) and output @1Khz at several signal powers (in B).

Treatment Protocol. After concluding the otolaryngology evaluation, eleven patients began the treatment and they were followed up and evaluated during 24

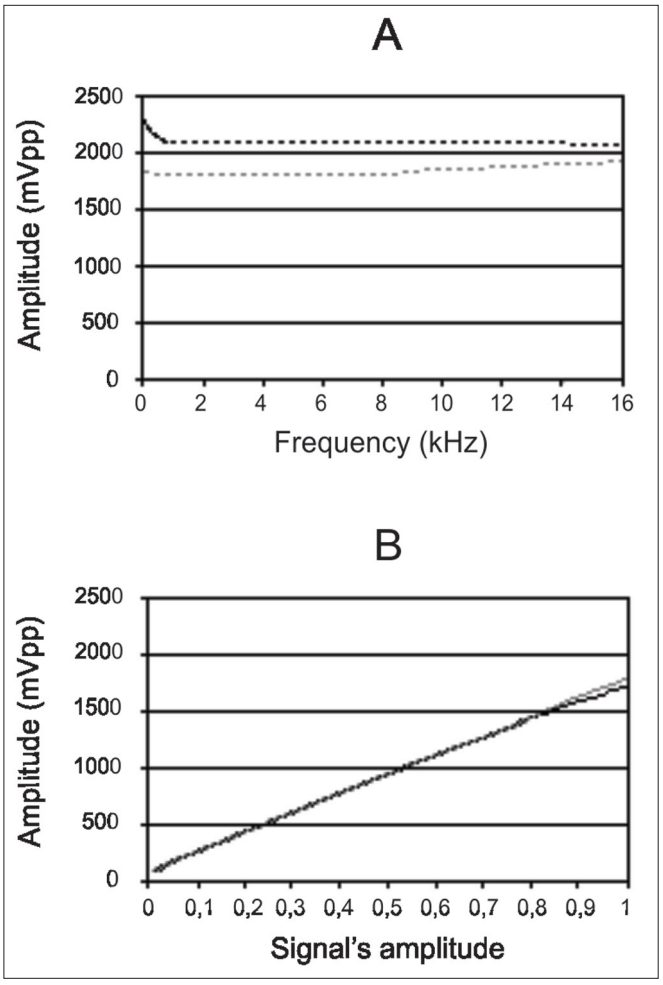

Figure 1. A, amplitude of the response at different frequencies of the iPod (gray trace) and the notebook (black trace) showing flat response along the working bandwidth. B, iPod and notebook output at 1 KHz for several signal amplitudes. Applying linearity of the created sounds, we assume that all sounds show the same response and power both in the notebook and iPods output (voltage).

weeks. Sound stimulation was applied through an *ipod*, to the same side that patients perceived the tinnitus (unilateral or binaural). Each night, patients fixed the sound stimulation intensity at the tinnitus masking level, selecting among the 25 *ipods* steps. Patients wrote down each night the stimulation intensity and the hours stimulated, together with other observations that they considered important (illnesses, relevant stress situations, etc.).

This research has been approved by the Ethical Committee of the Faculty of Medicine CLAEH University, according to the International Ethic Guidelines for human research. Patients were informed and signed a conformed letter.

RESULTS

Eleven patients with idiopathic subjective tinnitus (10 males and one female, from 31 to 71 years old) were studied during 24 weeks. All of them showed normal imagenology, impedanciometry, otoscopy and blood tests. Table 1 shows tinnitus evaluation (side, years of evolution, and acuphenometry). Between 1 and 6 years of tinnitus evolution were considered, with no differences in the results presented. Tinnitus was binaural in 6 patients while it was perceived monaurally in the other 5. Table 2 shows audiological evaluation; while all patients showed alteration in at least one of the parameters explored, no one needed to be equipped with audiphones. In 8 patients greater alterations in the tonal liminal audiometry (TLA), logoaudiometry, and/or high frequency audiometry (HFA) were coincident with the tinnitus perception side (8 out of 11, 72%), although L.C., E.G. and J.N. showed asymmetries no coincident with the tinnitus side. Otoacoustic Emissions (OAE) -spontaneous, transient and distortion product- were recorded in each patient. All of them showed some asymmetry in the responses; in Ma.F. an increment of the spontaneous otoacustic emission appeared at the affected side.

Sound stimulation during sleep improved the tinnitus intensity in all patients; most of them (8 out of 11) exhibited the greatest decrement in the first week of treatment, while in the remaining 3 patients the tinnitus intensity took 2 or 3 weeks to decrease. Figure 2 shows the tinnitus intensity average evolution week by week (in A), being statistically significant the differences of tinnitus

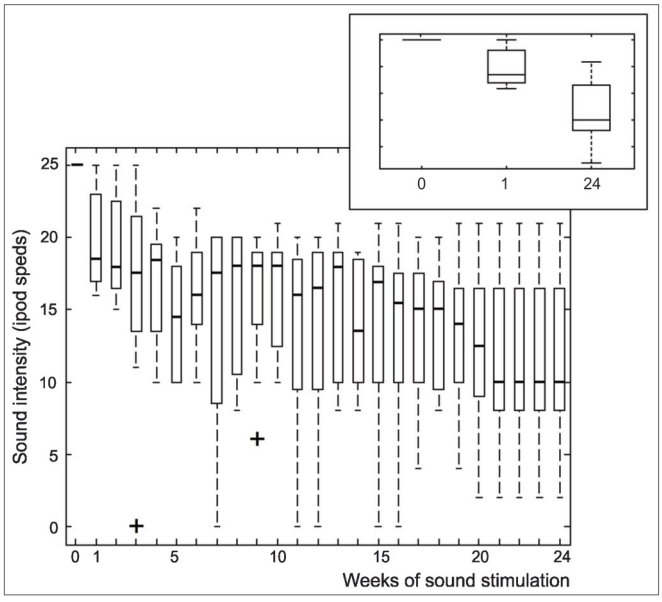

Figure 2. Box plot showing tinnitus intensity evolution during 24 weeks of treatment. Tinnitus intensity for each patient was considered by averaging the values along the week. Each bar is the average of sound intensity of all patients, week by week. Tinnitus intensities were normalized as steps in the *ipod*, being 25 the highest for each patient before beginning the treatment (week 0). Decrement in tinnitus intensity was statistically significant ($p<0.001$) comparing values between week 0 and 1, and week 1 and 24 (Wilcoxon test). Crosses, out lie values not considered in the averaging.

Table 1. Patient's tinnitus evaluation.

Patient male (m) female (f) years old	Tinnitus topography and evolution Right (R), Left (L)	Acufenometry Frequency (kHz) Attenuation from 100 dB SPL
E.A, m, 53	R, L, 3 years	9,50 kHz, -53
N.B., m, 31	L, 2 years	8,40 kHz, -65
A.B., m, 61	R, 6 years	5,80 kHz, -43
L.C., m. 48	R, L, 3 years	8,34 kHz, -55
J.D., m, 44	L, 2 years	8,00 kHz, -48
Ma.F., f, 45	L, 1 year	Broadband noise 1,70 kHz, Q 20 -70
E.G., m, 40	R, L, 2 year	3,88 kHz, -62
J.N., m, 61	R, 3 years	13,00 kHz, -25
J.R., m, 18	R, L, 3 years	7,50 kHz, -35
M.F., m, 43	R, L, 3 years	11,30 kHz, -45
R.P., m, 71	R, L, 2 years	6,85 kHz, -30 dB(L) -40(R)

Table 2. Patient's audiology evaluation

Patient	TLA (dB HTL)	Logo (dB HTL)	HFA (dB SPL)
E.A.	R,L, ↓ 5 dB (4, 6, 8 kHz)	R, L, SRT 10 dB	R, ↓10 dB (8, 10, 12, 14, 16 kHz)
N.B.	R,L, Normal	R,L, SRT 8 dB	L, ↓40 dB (8, 10, 12, 14, 16 kHz)
A.B.	R, ↓30 dB (4 kHz), ↓60 dB (6, 8 kHz) L, ↓30 dB (4, 6, 8 kHz)	R, L, SRT 12 dB	R,L, bilateral symmetric draw
L.C.	R, ↓20 dB (4 kHz) L, ↓30 dB (4 kHz), ↓40 dB (8 kHz)	R, SRT 10 dB L, SRT 12 dB	L, ↓50 dB (12 KHz), ↓35 db (14 kHz)
J.D.	R, ↓10 dB (3 kHz), ↓20 dB (6 kHz) L, ↓ 30 dB (4 kHz), ↓60 dB (6, 8 kHz)	R, SRT 12 dB L, SRT 37 dB, *	L, ↓20 dB (8, 10, 12, 14, 16 kHz)
Ma.F.	R , Normal L, ↓25 dB (1 kHz), ↓15 dB (6 kHz)	R, SRT 15 dB L, SRT 18 dB	L, ↓25 dB (8, 10, 12, 14, 16 kHz)
E.G.	R, ↓35 dB (4 kHz),↓15 dB (6 kHz) L, ↓55 dB (4 kHz), ↓10 dB (6 kHz)	R, L, SRT 7 dB	R, ↓20 dB (8, 10, 12, 14, 16 kHz)
J.N.	R,L, Normal	R, L, SRT 5 dB	L, ↓15 dB (8, 10, 12, 14, 16 kHz)
J.R.	R, ↓5 dB (0,250 kHz),↓5 dB (2 kHz) L , ↓5 dB (0,250 kHz), ↓15 dB (6 kHz)	R, SRT 5 dB L, SRT 7 dB	R, ↓15 dB (8, 10, 12, 14, 16 kHz)
M.F.	R, ↓15 dB (4 kHz), ↓ 25 dB (8 kHz) L, ↓15 dB (4 kHz), ↓30 dB (8 kHz)	R, L, SRT 8 dB *	R,L, ↓40 dB bilateral symmetric draw
R.P.	R, ↓15 dB (2 kHz), ↓35dB (4), ↓60 (8 kHz) L, ↓10 (2), ↓35 (4), ↓70 (8)	R, L, SRT 20 dB *	R,L, ↓50 dB bilateral symmetric draw

TLA, tonal liminal audiometry; SRT speech recognition threshold; HFA, high frequency audiometry; Logo, logoaudiometry; R, right ear; L, left ear; * recruitment.

intensity prior to the treatment compared with the tinnitus intensity one week after the stimulation onset and with the last week of stimulation) (Wilcoxon test, $p < 0.001$).

Psychological evaluation. Each patient was seen by a psychologist three times, at the beginning, the middle and the end of the treatment. All patients reported to suffer a stressful situation related to the tinnitus. Everyone has a particular lifestyle, with demanding jobs and no vacation time by own initiative. Three of them have obsessive personality and one was depressive and rejected psychotherapy. Personal interviews with the psychologist showed the patients' evolution much better than the THI scale, which did not appear as a precise technique to evaluate evolution, at least when the degree of tinnitus repercussions were not severe. There

was no close correlation between the tinnitus intensity and psychological impact.

Sleep evaluation. Five out of eleven patients had sleep disorders at the beginning of the treatment, four of them suffered insomnia characterized by difficulty to fall asleep with the corresponding daytime consequences such as tiredness, lack of energy, concentration difficulty, irritability. Everyone improved their insomnia with the tinnitus treatment, two of them – treated chronically with benzodiazepines- abandoned successfully their chronic treatment. One patient –N.B., a rock musician- had periods with circadian rhythm distortion, closely related to the tinnitus increment. Nobody suffered sleep changes caused by the sound stimulation during the night. Patients were continuously clinically evaluated and two of them were also studied by polysomnography. Changes neither in the sleep stages percentages nor in the sleep architecture (hypnogram) were exhibited when comparing two completed nights (with and without sound stimulation) in each patient.

DISCUSSION

In this pilot study we show the positive result –significant decrement in the tinnitus intensity - of the sound stimulation applied during sleep. The present protocol was based on the tenet that most forms of tinnitus are caused by functional changes; thus, it should be possible to reverse them by proper sound treatment taking advantages of the neural plasticity properties of the CNS. Since we found changes in the auditory tests (TLA, HFA, logo and OAE) in tinnitus patients, we proposed the sound stimulation with the same characteristics in frequencies and intensity as the tinnitus as a way of reinstalling the normal balance in the central level processing of information, hypothesizing that tinnitus emerges to replace an input deficit.

On the other hand, it is well accepted that mechanisms of learning and memory occur during sleep, organizing sensory inputs and consolidating memories, in a different way than during wakefulness, and even better since less sensory inputs disturb processing, consequently, our protocol is based on stimulation during sleep. Furthermore, the method here suggested is in many ways advantageous since: 1) sleep provides a long period of time for daily treatment without interfering with the patient daytime activity; 2) sound stimulation during sleep decreases tinnitus perception, thus improving sleep disorders caused by tinnitus; 3) improvement of sleep quality increases tinnitus tolerance; 4) improvement of sleep quality with sound stimulation during sleep may also improve patient adherence to the treatment and 5) as a consequence of improving sleep and tinnitus perception, the incidence of depression and anxiety, common in these patients, exhibits a decrease.

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