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## Research paper

## Does enriched acoustic environment in humans abolish chronic tinnitus clinically and electrophysiologically? A double blind placebo controlled study

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## ABSTRACT

Animal research has shown that loss of normal acoustic stimulation can increase spontaneous firing in the central auditory system and induce cortical map plasticity. Enriched acoustic environment after noise trauma prevents map plasticity and abolishes neural signs of tinnitus. In humans, the tinnitus spectrum overlaps with the area of hearing loss. Based on these findings it can be hypothesized that stimulating the auditory system by presenting music compensating specifically for the hearing loss might also suppress chronic tinnitus. To verify this hypothesis, a study was conducted in three groups of tinnitus patients. One group listened just to unmodified music (i.e. active control group), one group listened to music spectrally tailored to compensate for their hearing loss, and a third group received music tailored to overcompensate for their hearing loss, associated with one (in presbycusis) or two notches (in audiometric dip) at the edge of hearing loss. Our data indicate that applying overcompensation to the hearing loss worsens the patients' tinnitus loudness, the tinnitus annoyance and their depressive feelings. No significant effects were obtained for the control group or for the compensation group. These clinical findings were associated with an increase in current density within the left dorsal anterior cingulate cortex in the alpha2 frequency band and within the left pregenual anterior cingulate cortex in beta1 and beta2 frequency band. In addition, a region of interest analysis also demonstrated an associated increase in gamma band activity in the auditory cortex after overcompensation in comparison to baseline measurements. This was, however, not the case for the control or the compensation groups. In conclusion, music therapy compensating for hearing loss is not beneficial in suppressing tinnitus, and overcompensating hearing loss actually worsens tinnitus, both clinically and electrophysiologically.

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## 1. Introduction

In adults, 10–15% of the population perceive tinnitus chronically (Eggermont and Roberts, 2004) and about 6–25% of the affected people report interference with their daily living. Tinnitus can cause a considerable amount of distress, involving sleep deprivation (Alster et al., 1993; Cronlein et al., 2007), depression (Dobie, 2003), annoyance, cognitive problems (Hallam

et al., 2004), and work impairment (Baguley, 2002; Cronlein et al., 2007; Eggermont and Roberts, 2004; Heller, 2003; Langguth et al., 2007). To date, tinnitus treatment strategies predominantly aim at reducing the tinnitus associated distress. Hence, there is a great demand for causal treatment approaches targeting the tinnitus percept more directly.

The most frequent cause of tinnitus seems to be partial auditory deprivation, as most individuals with tinnitus also have hearing loss. Noise-induced hearing loss is known to induce tinnitus in many subjects (Norena and Eggermont, 2003; Seki and Eggermont, 2003). Importantly, cochlear damage causes a dramatic decrease of stimulus-induced and spontaneous activity in the cochlear nerve. Interestingly, a dramatic decrease of stimulus-induced and spontaneous activity in the cochlear nerve can result in

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neural hyperactivity (increase in stimulus-induced and spontaneous activity) at virtually all central stages of the auditory system (Eggermont and Roberts, 2004; Kaltenbach and Afman, 2000; Salvi et al., 2000) and reorganization of the auditory cortex (Eggermont and Komiya, 2000; Norena and Eggermont, 2003, 2005; Flor et al., 1995; Muhlnickel et al., 1998). Tinnitus has been proposed to result from thalamocortical dysrhythmia (Llinás et al., 1999): tinnitus may be caused by an abnormal, spontaneous and constant gamma band activity (>30 Hz) surrounding an area of slow wave (delta or theta) activity, generated as a consequence of hyperpolarization of specific thalamic nuclei induced by sensory deafferentation (De Ridder et al., 2011b; Llinás et al., 1999). In normal circumstances auditory stimuli increase thalamocortical alpha oscillations to gamma band activity (Crone et al., 2001; Joliot et al., 1994). In tinnitus, oscillatory alpha activity (8–12 Hz) decreases (Lorenz et al., 2009) and theta band activity increases (4–7 Hz). The key point of this model is that the increase of low frequency activity is accompanied by a reduction of GABA mediated lateral inhibition, which is supposed to cause a “halo” of gamma activity at the edge of the cortical region corresponding to the deafferented frequency region (De Ridder et al., 2011b; Llinás et al., 1999, 2005).

Recent animal research has shown that keeping animals after noise trauma in an acoustic environment enriched by high frequencies prevents tonotopic map reorganization in the auditory cortex (Norena and Eggermont, 2005), and the changes in the pattern of spontaneous firing after noise exposure (Norena and Eggermont, 2006). In addition, clinical research in humans demonstrated that a cochlear implant in patients with single-sided deafness and ipsilateral tinnitus has a tinnitus suppressing effect (Punte et al., 2011; Van de Heyning et al., 2008). Electrical stimulation of the

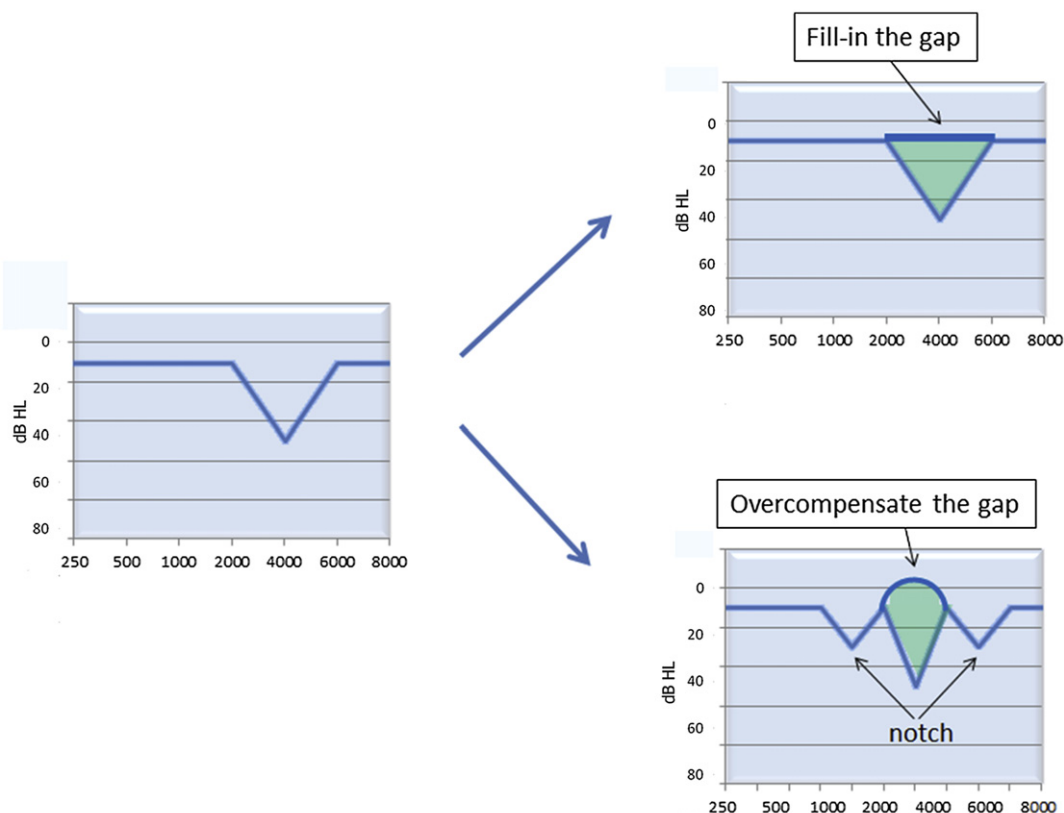
deafferented auditory nerve via a cochlear implant in animals furthermore reversed lesional down-modulations (Argence et al., 2008) by reafferenting the auditory system (De Ridder, 2011; Kleine Punte et al., 2011). Norena and Chery-Croze (2007) further showed that the reafferentation modulates both tinnitus and hyperacusis.

Based on the fact that a deprived acoustic environment can decrease spontaneous firing and cortical map plasticity and that stimulation of the deafferented auditory nerve can modulate long lasting tinnitus, it can be expected that stimulating the auditory system by presenting music compensating specifically for the hearing loss might also suppress chronic tinnitus. This latter option would be more acceptable for tinnitus patients than just presenting tones corresponding to the hearing loss frequencies (Norena and Chery-Croze, 2007). To verify this hypothesis, a study was conducted including three groups of tinnitus patients. One group listened to unprocessed music (i.e. active control group), one group listened to music individually tailored to compensate for their hearing loss (Fig. 1, upper right), and a third group received music overcompensated for their hearing loss, by adding notches at the lesion edge and increasing the spectral amplitudes for the hearing loss frequencies more than required to compensate (Fig. 1, lower right). In addition, source localized EEG was applied to verify any cortical changes associated with clinical changes.

## 2. Methods

### 2.1. Patients

Twenty-six tinnitus patients (17 males, 9 females) participated in this experiment at the multidisciplinary TRI tinnitus clinic of the



**Fig. 1.** Concept of the iPod music therapy. Participants were randomly assigned to one of the three groups: sham treatment (active control group, listening just to music), compensation treatment or overcompensation treatment. For the compensation treatment the audiometric dip, e.g. at 4000 Hz, is filled in (right upper image). This can be done by selectively increasing the amplitudes of the MP3 files of the original songs in those frequencies the patient doesn't hear well. For the overcompensation treatment the hearing loss is overcompensated (right lower panel): a notch is created at the edge of the hearing loss, and gap is overcompensated.

Antwerp University Hospital, Belgium. The mean age was 48.18 years ( $Sd = 8.22$ ; range: 31–61 years). Fourteen patients had narrow band noise and 12 patients presented with pure tone tinnitus. Twelve patients perceived bilateral tinnitus and 14 patients unilateral tinnitus. The mean tinnitus duration was 3.45 years ( $Sd = 2.81$ ; range: 1–9 years). All participants underwent a complete audiological, ENT and neurological investigation to rule out possible treatable causes for their tinnitus. Tinnitus matching was performed by presenting sounds to the ear in which the tinnitus is not perceived in unilateral tinnitus, bilaterally in bilateral tinnitus patients. Technical investigations included MRI of the brain and posterior fossa, pure tone and speech audiometry and tympanometry. Individuals with pulsatile tinnitus, Ménière disease, otosclerosis, chronic headache, neurological disorders such as brain tumors, and individuals being treated for mental disorders were excluded from the study. The study was approved by the Antwerp University Hospital IRB ('Comité voor medische ethiek').

## 2.2. Audiometry and tinnitus matching

Pure tone audiometry was carried out before and after 4 weeks of treatment using the "up 5–down 10" method at 0.125, 0.25, 0.5, 1, 2, 3, 4, 6 and 8 kHz (Audiology, 2008). Tinnitus patients were tested for the tinnitus pitch by tinnitus matching analysis. In unilateral tinnitus patients, the tinnitus analysis was performed contralaterally to the tinnitus ear. In bilateral tinnitus patients, tinnitus analysis was performed contralaterally to the worse tinnitus ear. The tinnitus matching analysis consisted of the assessment of the tinnitus pitch and loudness. First, a 1 kHz pure tone or a narrow band noise around 1 kHz (depending whether the patient perceived a pure tone or narrow band noise) was presented contralateral to the (worse) tinnitus ear at 10 dB above the patient's hearing threshold in that ear. The pitch was adjusted until the patient judged the sound to resemble his/her tinnitus most correctly. The loudness of this tone was then adjusted in a similar way until it corresponded to the patient's specific tinnitus loudness as well. The tinnitus loudness (dB SL) was computed by subtracting the absolute tinnitus loudness with the auditory threshold at that frequency (dB HL). This method has previously been used and published in several other research papers (Meeus et al., 2011, 2009). Only patients are selected if the tinnitus pitch fell within the area of hearing loss.

## 2.3. MP3 player

Based on the audiogram of the patient, a linearly spaced spectrum was obtained using piecewise cubic hermite interpolation in Matlab (MathWorks, Natick, MA). If the audiogram showed a clear local minimum (an audiometric 'dip') either this dip was filled in, i.e. the hearing loss was compensated by increasing the amplitude of those frequencies with increased hearing thresholds (Fig. 1, upper right), or a double-sided notch with overcompensation was applied. In other words, for the compensation condition we set the stimulus at the sound level that compensates for the amount of hearing loss in dB (e.g. if the maximal hearing loss was 40 dB, we then set the sound level at 40 dB higher than the level of the sound outside the region of hearing loss). Overcompensation means that the amplitudes of the hearing loss frequencies were increased more than necessary to fill in the gap (Fig. 1, lower right). If the spectrum showed a clear 'roll-off' single-sided notching with overcompensation was applied. In both cases of overcompensation (one sided or two sided notch) the minimum of the spectrum was attenuated with an additional –6 dB notch. The span of the lobes was chosen to be 1/3 octave. The spectrum is subsequently converted from log-scale to linear scale, normalized and inverted to make it suitable for filtering the audio

signal. Filtering was achieved by using a sliding window technique with a Hann-window of 4001 samples (90.7 ms) and an overlap factor of 0.5. For each step the data was converted to the frequency domain using a Fast Fourier transform, multiplied with the previously obtained spectrum and then transformed back to the time domain using the inverse Fast Fourier transform. Finally automatic gain control was used to give the filtered signal the same level as the original signal. For both signals the time average of the power was determined from which the autogain can be determined using  $G = \sqrt{P_{in}/P_{out}}$  in which  $G$  is the gain and  $P_{in}$  and  $P_{out}$  are the average power of the original and filtered signal respectively. To illustrate the working principle of the filtering, the concept is presented in Fig. 1. Participants were randomly assigned to one of the three groups: sham treatment (active control group, listening just to music), compensation treatment or overcompensation treatment. Patients received an MP3 player (iPOD shuffle, Apple) each with the same 200 songs (mixture of pop, rock and classical music) and individually tailored to their audiogram (Fig. 1A) depending on the group they were assigned to. Both the patient and the researcher who had contact with the patient were blinded to the three treatment methods and were not informed about the different treatment methods. Patients were told to try to listen to their MP3 player at least 3 hours a day, 7 days per week for one month. Patients controlled the volume on their MP3 player. Ten patients were assigned to the compensation group, 8 patients to the sham group and 8 patients to the overcompensation group.

## 2.4. Clinical measures

A Dutch translation of the Hospital Anxiety and Depression Scale (HADS), Visual Analog Scale (VAS) for tinnitus loudness and annoyance was used for a baseline measure and after one month of treatment.

### 2.4.1. VAS

A visual analog scale for loudness ('How loud is your tinnitus?') and annoyance ('How stressful is your tinnitus?') was assessed on a scale from 0 (no tinnitus/no stress) to 10 (extremely loud/extremely stressful).

### 2.4.2. HADS

The Hospital Anxiety and Depression Scale is designed as a simple yet reliable tool for use in medical practice (Zigmond and Snaith, 1983) and considered to be a measure of general distress (Grulke et al., 2005; McCue et al., 2006; Robjant et al., 2009). This scale consists of 14 questions, seven measuring anxiety (score from 0 to 21) and seven measuring depression (score from 0 to 21). A total score can also be calculated, ranging from 0 to 42. Each question was rated on a 4-point scale.

## 2.5. EEG recording

EEG recordings were obtained in a fully lighted room with each participant sitting upright on a small but comfortable chair. The actual recording lasted approximately 5 min. The EEG was sampled with 19 electrodes (Fp1, Fp2, F7, F3, Fz, F4, F8, T7, C3, Cz, C4, T8, P7, P3, Pz, P4, P8, O1, O2) in the standard 10–20 International placement referenced to linked ears and impedances were checked to remain below 5 k $\Omega$ . Data were collected eyes-closed (sampling rate = 1024 Hz, band passed 0.15–200 Hz). Data were resampled to 128 Hz, band-pass filtered (fast Fourier transform filter) to 2–44 Hz and subsequently transposed into Eureka! Software (Congedo, 2002), plotted and carefully inspected for manual artifact-rejection. All episodic artifacts including eye blinks, eye movements, teeth clenching, body movement, or ECG artifact were removed from the stream of the EEG.

In addition, an independent component analysis (ICA) was conducted to further verify if all artifacts were excluded. It was however rare that after visual inspection an artifact was still found. To investigate the effect of possible ICA component rejection we compared the power spectra in two approaches: (1) after visual artifact rejection only (before ICA) and (2) after additional ICA component rejection (after ICA). Average Fourier cross-spectral matrices were computed for bands delta (2–3.5 Hz), theta (4–7.5 Hz), alpha1 (8–10 Hz), alpha2 (10–12 Hz), beta1 (13–18 Hz), beta2 (18.5–21 Hz), beta3 (21.5–30 Hz) and gamma (30.5–44 Hz).

Standardized low-resolution brain electromagnetic tomography (sLORETA) was used to estimate the intracerebral electrical sources that generated the scalp-recorded activity in each of the eight frequency bands (Pascual-Marqui, 2002). To calculate the source localization we used average reference, which is the standard procedure with sLORETA (Bertrand et al., 1985; Pascual-Marqui, 2002; Pascual-Marqui et al., 2002). sLORETA computes electric neuronal activity as current density ( $A/m^2$ ) without assuming a predefined number of active sources. The sLORETA solution space consists of 6239 voxels (voxel size:  $5 \times 5 \times 5$  mm) and is restricted to cortical gray matter and hippocampi, as defined by digitized MNI152 template (Fuchs et al., 2002). Scalp electrode coordinates on the MNI brain are derived from the international 5% system (Jurcak et al., 2007). The tomography sLORETA has received considerable validation from studies combining LORETA with other more established localization methods, such as functional Magnetic Resonance Imaging (fMRI) (Mulert et al., 2004; Vitacco et al., 2002), structural MRI (Worrell et al., 2000) and Positron Emission Tomography (PET) (Dierks et al., 2000; Pizzagalli et al., 2004; Zumsteg et al., 2005). Further sLORETA validation has been based on the localization findings obtained from invasive, implanted depth electrodes, in which case there are several studies in epilepsy (Zumsteg et al., 2006a,c) and cognitive ERPs (Volpe et al., 2007). It is worth emphasizing that deep structures such as the anterior cingulate cortex (Pizzagalli et al., 2001), and mesial temporal lobes (Zumsteg et al., 2006b) can be correctly localized with this method.

In addition, the log-transformed electrical current density was averaged across all voxels belonging to the region of interest of, respectively, the left and right primary auditory cortex (BA 41) separately for frequency bands delta (2–3.5 Hz), theta (4–7.5 Hz), alpha1 (8–10 Hz), alpha2 (10.5–12.5 Hz), beta1 (13–18 Hz), beta2 (18.5–21 Hz), beta3 (21.5–30 Hz) and gamma (30.5–45 Hz).

To verify whether the reference using the ears might affect the results, we included an additional analysis on one tinnitus patient in the supplementary materials. This patient received EEGs before and after transcranial direct current stimulation (tDCS). An EEG was obtained twice before the treatment, once placing the reference at the ears and once placing the reference at the hands. A similar method was used after treatment. Source localization was applied on the different conditions and compared. In addition, the subtraction was calculated between the pre- and post-treatment for, respectively, the condition with the reference at the ears and at the hands. A comparison between the EEG with the reference at the ears and hands for the pre-treatment (see Fig. 1S) and post-treatment (see Fig. 2S) revealed almost no differences. A comparison between the subtractions (post-treatment – pre-treatment) revealed no differences at all (see Fig. 3S). Based on this additional analysis we can conclude that the obtained method is reliable when we use the ears as references.

## 2.6. Statistical analyses

### 2.6.1. Clinical measurements

A comparison was made among baseline measures and post-treatment measures in sham and compensation treatment groups

for VAS loudness, VAS annoyance, depression and anxiety as measured with the HADS using a Wilcoxon Signed Rank test.

The post-treatment scores were subtracted from the baseline scores for the three conditions. A positive score indicates an improvement, while a negative score reveals a worsening. A comparison was made between the sham, compensation and overcompensation group using a Kruskal–Wallis test. When a significant effect was obtained a Mann–Whitney *U*-test was conducted to perform a mutual comparison between overcompensation and sham group, overcompensation and compensation group and compensation and sham group.

### 2.6.2. EEG measurements

In order to identify potential differences in brain electrical activity between groups, sLORETA was then used to perform voxel-by-voxel between-condition comparisons of the current density distribution. Nonparametric statistical analyses of functional sLORETA images (statistical non-parametric mapping; SnPM) were performed for each contrast employing a *t*-statistic for paired groups (baseline versus post-treatment) and a corrected ( $p < 0.05$ ). As explained by Nichols and Holmes (2002), the SnPM methodology does not require any assumption of Gaussianity and corrects for all multiple comparisons. We performed one voxel-by-voxel test (comprising 6239 voxels each) for the different frequency bands.

For the region of interest analysis a comparison was made on the log-transformed current density for respectively the left and right primary auditory cortex between pre- versus post-treatment using a Wilcoxon Signed Rank test.

## 3. Results

### 3.1. A comparison between the specific treatment options

The mean pretreatment score for VAS tinnitus loudness across the three groups was 5.97 (Sd = 2.35). For the sham group the mean baseline score for VAS loudness was 6.28 (Sd = 2.08), for the compensation group 6.75 (Sd = 2.12) and the overcompensation group 4.60 (Sd = 2.53). For VAS annoyance the mean baseline scores across the three groups was 6.25 (Sd = 2.70). That was respectively 6.77 (Sd = 2.39) for the sham group, 7.06 (Sd = 2.55) for the compensation group and 4.71 (Sd = 2.81) for the overcompensation group. For depression and anxiety, as measured with the HADS, a mean baseline score of respectively 7.19 (Sd = 4.46) and 7.04 (Sd = 2.72) was obtained. The sham group had a mean baseline score of 7.42 (Sd = 3.31) on depression and 6.43 (Sd = 1.51) on anxiety, while the compensation group had a mean baseline score of 9.63 (Sd = 4.52) on depression and 8.00 (Sd = 3.19) on anxiety. The overcompensation group had a mean baseline score of 3.62 (Sd = 2.92) on depression and 6.25 (Sd = 2.71) on anxiety. A comparison among the different conditions on the VAS loudness, VAS annoyance, depression and anxiety as measured with the HADS revealed no significant differences.

All patients confirmed they had listened to the music at least 3 hours per day, 7 days per week for one month. No patient dictated that the music they received was annoying or felt artificial or distorted due to the adjustments made.

A detailed comparison among the baseline measures and post-treatment measures in sham and compensation treatment groups revealed no significant effects for VAS loudness, VAS annoyance or depression and anxiety as measured with the HADS. Significant effects were however obtained for the pre- and post-treatment comparison in the overcompensation treatment group for VAS loudness ( $Z = -2.37$ ,  $p < 0.05$ ), VAS annoyance ( $Z = -2.12$ ,  $p < 0.05$ ) and depression ( $Z = -2.04$ ,  $p < 0.05$ ) as measured with the HADS. It

was shown that after overcompensation the patients scored worse on VAS loudness ( $M = 5.63$ ,  $Sd = 2.18$ ), VAS annoyance ( $M = 5.51$ ,  $Sd = 2.55$ ), and depression ( $M = 5.00$ ,  $Sd = 2.56$ ) in comparison to the baseline VAS loudness ( $M = 4.60$ ,  $Sd = 2.53$ ), VAS annoyance ( $M = 4.71$ ,  $Sd = 2.81$ ), and depression ( $M = 3.64$ ,  $Sd = 2.92$ ). No significant effect was obtained for anxiety as measured with the HADS.

A comparison between the different treatment options obtained a significant difference for respectively VAS loudness, VAS annoyance and depression measured with the HADS (see Table 1). No significant effect was obtained for anxiety measured with the HADS. Further analysis for VAS loudness revealed that the patients who were assigned to the overcompensation treatment had a significant worsening of their tinnitus in comparison to the sham group ( $U = 9$ ,  $p < 0.05$ ) and the compensation group ( $U = 19.5$ ,  $p < 0.05$ ). No significant effect was observed for the comparison between the sham group and the compensation group ( $U = 33$ ,  $p = 0.66$ ). A similar analysis was conducted for VAS annoyance revealing that in comparison to the sham treatment, patients in the overcompensation group had a significant increase in annoyance ( $U = 10$ ,  $p < 0.05$ ). In addition a comparison between the compensation treatment and overcompensation group showed that this latter group had a worsening of their annoyance ( $U = 11.5$ ,  $p < 0.05$ ). No significant effect was observed between the sham and compensation treatment.

A comparison between the patients in the overcompensation group with the compensation group and the sham group showed that the overcompensation group scored significantly worse for depression ( $U = 19.5$ ,  $p < 0.05$  in comparison to compensation;  $U = 6$ ,  $p < 0.01$  in comparison to sham). No significant effect was obtained between the sham and compensation group.

### 3.2. Audiometry and tinnitus matching

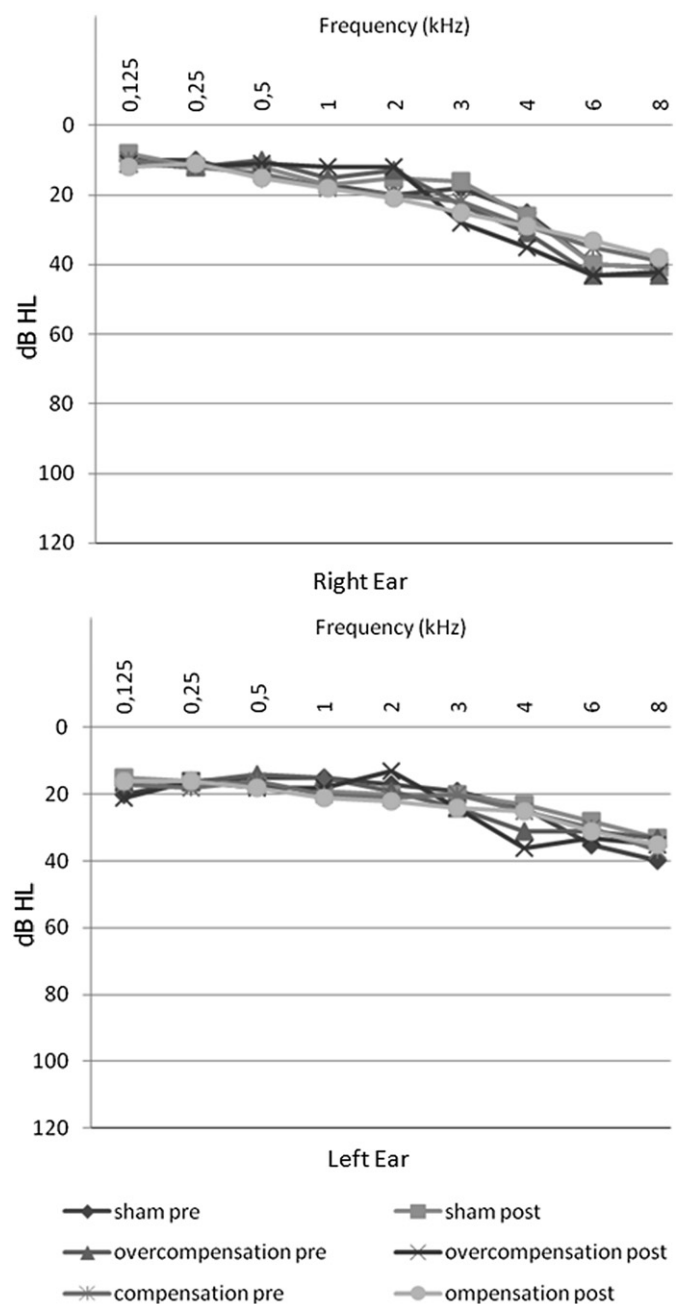
Mean auditory thresholds for left and right ear are shown in Fig. 2. No significant differences were obtained after treatment in comparison to pre-treatment for the sham, compensation or overcompensation group. Also no significant differences were demonstrated between the different groups for pre- and post-treatment. In general, tinnitus patients had a hearing loss of 20 dB at 3000 Hz trending to a 40 dB loss at 8000 Hz.

The tinnitus matching analysis revealed that the mean tinnitus pitch for the sham group was 4750 ( $Sd = 3344.77$ ), for the compensation group 5272.72 Hz ( $Sd = 3157.24$ ) and for the overcompensation group 5281.25 Hz ( $Sd = 3867.07$ ). The tinnitus loudness for the sham group was 5.71 dB SL ( $Sd = 4.50$ ), for the compensation group 8.09 dB SL ( $Sd = 7.56$ ) and for the overcompensation group 11.25 dB SL ( $Sd = 9.54$ ). A comparison between the different conditions on the tinnitus pitch and tinnitus loudness revealed no significant differences.

**Table 1**  
Mean difference between baseline and respectively sham, compensation and overcompensation group.

	Sham		Compensation		Overcompensation		H-value
	M	%	M	%	M	%	
VAS loudness	-0.10 <sup>a</sup>	-1.17%	-0.06 <sup>a</sup>	-1.31%	-1.03 <sup>b</sup>	-17.25%	5.94*
VAS annoyance	0.06 <sup>a</sup>	1.14%	0.10 <sup>a</sup>	.01	-0.80 <sup>b</sup>	-34.67%	6.21*
Anxiety	-0.57	-7.65%	0.64	7.50%	0.88	8.75%	1.52
Depression	1.43 <sup>a</sup>	23.56%	0.36 <sup>a</sup>	1.58%	-1.38 <sup>b</sup>	-53.49%	7.72*

\* $p < 0.05$ ; Superscript letter indicates significant differences between the different stimulation parameters. Numbers with a different superscript letter represent significant differences for each other.

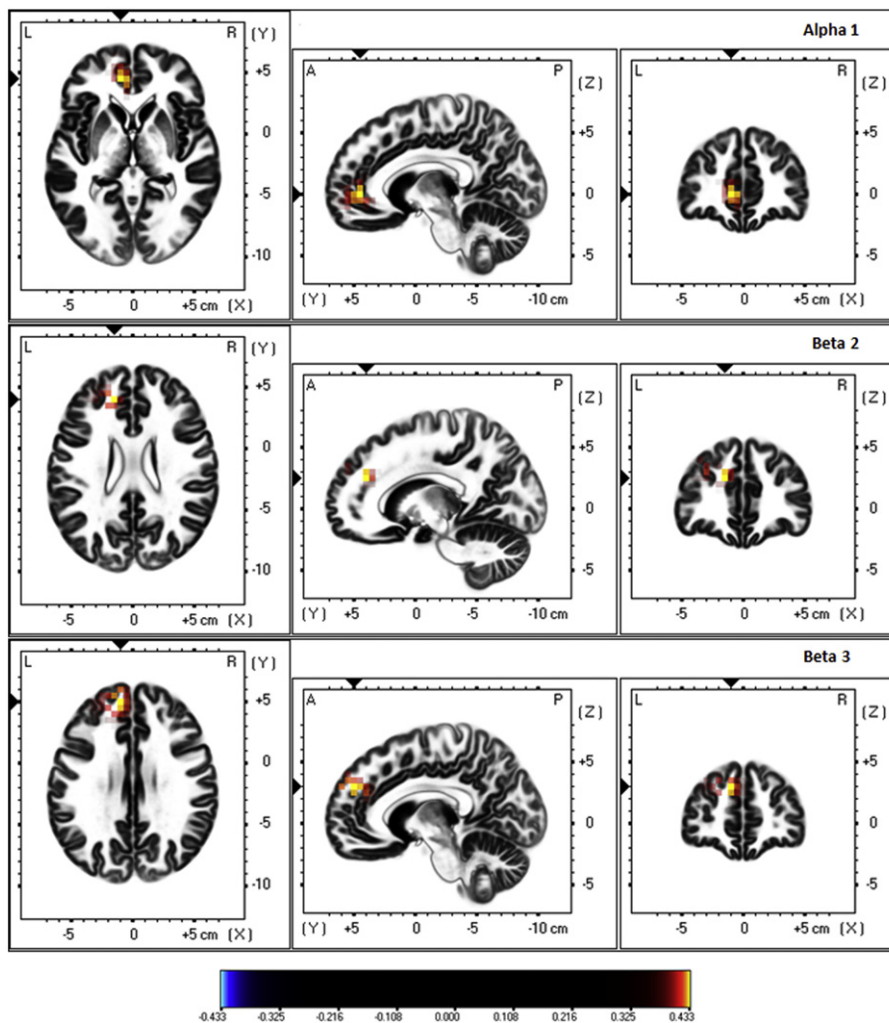


**Fig. 2.** Audiogram for the left and right ear during baseline and post-treatment for respectively sham, compensation and overcompensation group.

### 3.2.1. EEG measurements

**3.2.1.1. Pre- versus post-treatment.** A comparison between pre- and post-treatment measures revealed a significant effect ( $p < 0.05$ ) for the overcompensation group, indicating that after one month of treatment an increase was demonstrated for alpha2 activity within the left dorsal anterior cingulate cortex as well as for beta1 and beta2 band in the left pregenual anterior cingulate cortex (see Fig. 3). No significant effect was demonstrated for delta, theta, alpha1, beta1 and gamma bands.

A comparison between baseline and post-treatment for the control group as well as for compensation group obtained no significant effect on delta, theta, alpha1, alpha2, beta1, beta2, beta3 and gamma.



**Fig. 3.** Increased alpha2, beta2 and beta3 activity in respectively the pregenual and dorsal anterior cingulate cortex for the overcompensation group after one month of treatment in comparison to baseline measurement.

**3.2.1.2. Region of interest analysis.** When making a comparison between pre-treatment ( $M$  left = 3.08;  $Sd$  = 0.53 and  $M$  right = 3.25;  $Sd$  = 0.59) and post-treatment measures ( $M$  left = 3.53;  $Sd$  = 0.45 and  $M$  right = 3.50;  $Sd$  = 0.46) we found a significant difference for the gamma frequency for the overcompensation treatment group for the left ( $Z = -2.20$ ,  $p < 0.05$ ) and the right primary auditory cortex ( $Z = -2.20$ ,  $p < 0.05$ ). As demonstrated in Fig. 4 after treatment the current density increased for the left and right primary auditory cortex. No significant effects were found for the left and right primary cortex for delta, theta, alpha1, alpha2, beta1, beta2 and beta3. No significant effect was demonstrated for the left and right secondary auditory cortex for delta, theta, alpha1, alpha2, beta1, beta2, beta3 and gamma frequency.

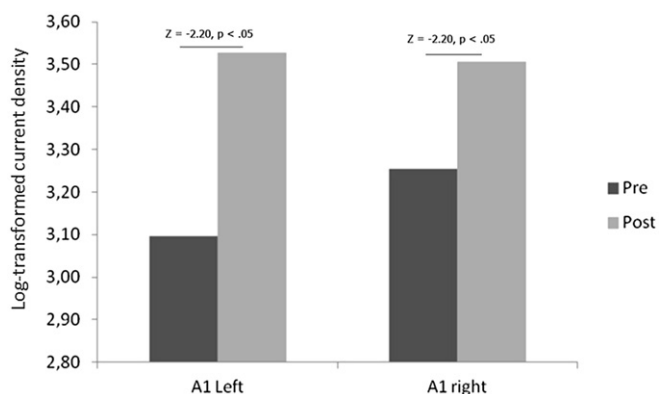
For the sham and compensation groups no significant effects were obtained for the left and right primary and secondary auditory cortex for delta, theta, alpha1, alpha2, beta1, beta2, beta3 and gamma frequency.

#### 4. Discussion

The present data directly indicate that applying overcompensation to the hearing loss worsens the tinnitus loudness, the tinnitus annoyance and their depressive feelings. This is associated with an increase in alpha2 current density within the dorsal

anterior cingulate cortex and beta1 and beta2 current density in the pregenual anterior cingulate cortex. This most likely reflects worsening of the annoyance and distress, as previous EEG studies have shown that alpha and beta activities in the anterior cingulate cortex are markers of increased tinnitus distress (De Ridder et al., 2011a; Vanneste et al., 2010). A region of interest analysis also demonstrated an associated increase in gamma activity in the primary auditory cortex after overcompensation in comparison to baseline measurements. This was however not the case for patients in the sham or a compensation treatment group. As gamma band activity correlates with the perceived tinnitus intensity (van der Loo et al., 2009) the worsening of the tinnitus loudness is very likely related to this increase of gamma band activity.

As patients in all treatment groups did not differ in hearing level after treatment in comparison to baseline measurement, this suggests that the worsening in the overcompensation is not related to a change in hearing loss levels before and after the iPod treatment. In contrast to studies previously published and showing that compensating for the deprived sensory inputs improved tinnitus (Jastreboff, 2007; Moffat et al., 2009; Trotter and Donaldson, 2008; Hanley and Davis, 2008; Schiette et al., 2010), it is shown here that music individually tailored by amplifying frequencies with increased thresholds did not improve tinnitus and that overcompensation even worsened it.



**Fig. 4.** Increased gamma activity in the left and right primary auditory cortex after overcompensation treatment in comparison to baseline.

Many explanations can be put forward to account for the lack of effect of amplified music in the present study. First, it is possible that the tinnitus in subjects who took part in the study was not always the result of cochlear trauma, but might be related to temporo-mandibular dysfunction or whiplash. In this context, compensating for the decrease in sensory inputs is understandably ineffective. The fact that patients were only selected if the tinnitus pitch fell within an area of hearing loss makes this explanation less likely.

Second, assuming that tinnitus is indeed caused by auditory deprivation, it is possible that amplified music did not restore adequately the “normal” auditory inputs. The presence of dead regions may prevent the amplified music from stimulating the frequency regions of severe hearing loss. Finally, amplified music may be annoying for subjects who also have some hyperacusis.

In addition, recent research in animals revealed that after sound exposure resulting in tinnitus, the tinnitus was mainly driven by cochlear processes, but that after 8 weeks the hyperactivity becomes less dependent on cochlear input, suggesting that central neurons transition from a state of hyperexcitability to a state in which they generate their own endogenous firing (Robertson et al., 2012). It is possible that the present treatment might only exert an effect in a short time window after developing tinnitus.

Another possibility is that the treatment of 3 hours a day for 4 weeks was too short to obtain any improvement. Previous studies reported only a 10% improvement after 6 weeks (Surr et al., 1999). However this latter hypothesis cannot explain why after 4 weeks of stimulation, patients had a worsening of their tinnitus for the overcompensation treatment group. The fact that our study had a relatively small sample is one of the limitations of the study. There were some differences in the baseline scores between the three groups, namely control, compensation and overcompensation group, but these differences were not significant, and patients were randomly assigned to one of the three conditions, suggesting that differences between groups at the start of the iPOD treatment cannot account for the worsening of the overcompensation group.

In sum, this research shows that patients who perceive music for 3 hours a day for one month compensating for their hearing loss do not benefit from tailor made music, and that overcompensating the hearing loss actually worsens the subjective feeling of the tinnitus loudness, the tinnitus annoyance and their depressive feelings, associated with oscillatory activity which has been linked to tinnitus distress and tinnitus loudness.

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#### Appendix A. Supplementary material

Supplementary material associated with this article can be found, in the online version, at <http://dx.doi.org/10.1016/j.heares.2012.10.003>.

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