



Enriched Acoustic Environment as a customized treatment for tinnitus: A non-controlled longitudinal study

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ABSTRACT

Tinnitus is a heterogeneous hearing disorder with no cure at present, but some treatments, such as a combination of counselling and sound therapy, can alleviate the discomfort it causes. The sound therapy efficiency depends on both the type of sound stimulus and the time of exposure. This study describes the fundamentals of a personalized sound therapy that stimulates the auditory system with either continuous or sequential sounds whose spectra are adjusted to the hearing levels of the participants. This sound therapy is called Enriched Acoustic Environment and is assessed in a sample of 137 participants with tinnitus. Tinnitus-related distress relief was clinically relevant and statistically significant for 90% of these patients. This was quantified as a mean decrease of 24.3 points on the Tinnitus Handicap Inventory. 31% of participants were treated with sequential stimuli and achieved greater relief of distress (29.4 points on their Tinnitus Handicap Inventory score) compared to those treated with continuous sound (69%). According to these results, sequential sound seems to be optimal compared to continuous sound.

1. Introduction

Eggermont and Tass (2012) define tinnitus as the perception of a sound that has not been originated in any source external to the body. Tinnitus is said objective when it generates in some parts of the body. Subjective tinnitus is reserved for a sound arisen due to aberrant plastic compensation in the neural auditory system to peripheral deprivation. The focus of this study is subjective tinnitus. This auditory perception is rather heterogeneous in its risk factors as well as mechanisms (Cederroth et al., 2019), laterality, type of sound and frequency (Cobo and Cuesta, 2023), and the associated tinnitus-related distress (Brueggemann et al., 2016). Despite its prevalence (it affects around 10–15 % and impact severely on the life of roughly 0.5–2 % of adult people), there is no pharmacological cure for tinnitus (McFerran et al., 2019). However, many treatments are available to relief tinnitus distress, including psychological (e.g. Cognitive Behavioural Therapy (CBT)) and sound stimulation combined with counselling (e.g. Tinnitus Retraining Therapy (TRT)) (Cima et al., 2019).

Most cases of subjective tinnitus arise in the aberrant compensation response in the neural auditory pathway to deafferentation from the peripheral auditory system (Eggermont, 2012). This deafferentation

triggers plastic changes in the auditory pathway, including hyperactivity, hypersynchrony and/or reorganization of the tonotopic map, which lead to tinnitus (Eggermont, 2012). Deafferentation can be produced, for instance, by hearing loss (even hidden hearing loss (Liberman et al., 2016)).

Once the tinnitus is triggered, other neural systems, such as the amygdala and the hippocampus (parts of the limbic system), contribute to the reinforcement of the tinnitus-related distress (Jastreboff, 2015). The activation of the network between the auditory and limbic systems is especially relevant in the growing and worsening of tinnitus-related distress symptoms (stress, anxiety and depression, for instance) (Jastreboff, 2015). Therefore, an enhanced understanding of the auditory-limbic network should contribute to the design of new strategies for tinnitus treatment (Kraus and Canlon, 2012). TRT is an intervention that employs the neurophysiological model of tinnitus as it prioritizes reduction of auditory-limbic interactions (Jastreboff, 2015). The main goal of TRT is to achieve tinnitus habituation through counselling and sound therapy. Whilst counselling is intended to act on the limbic system thereby promoting habituation to the negative reactions, sound therapy works more on the auditory system to decrease the aberrant neural activity related to tinnitus (Jastreboff, 2015).

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Although standard TRT uses a broadband noise in the audible frequencies, many other sounds have been proposed for tinnitus treatment (Searchfield et al., 2017; Sereda et al., 2018; Pienkowski, 2019). According to Jastreboff and Jastreboff (2015), any type of sound that does not annoy, create discomfort, or damage hearing is better for tinnitus than silence. Moreover, customized sounds, personalized either to the tinnitus frequency (Vermeire et al., 2007; Herráiz et al., 2010; Adamchic et al., 2012; Pantev et al., 2012) or the hearing thresholds (Cobo, 2021; Cobo et al., 2021; Cuesta et al., 2022; Fernández et al., 2023), have been proposed for sound therapy of tinnitus.

Schaette and Kempter (2006, 2008) claimed that a customized wideband noise matched to the hearing curve of the participant could reverse tinnitus in some cases. Noreña and Eggermont (2003, 2005) established that a group of animals with altered cortical tonotopic maps (one of the mechanisms of tinnitus) due to a traumatizing noise, returned to their normal tonotopic map when they were exposed to an enriched acoustic environment (EAE) containing a random sequence of tone-pips. This sequence of tone-pips was applied mainly in animal models (Hermes et al., 1983; Eggermont, 2006). After that, Noreña and Chery-Croze (2007) used a sequence of tone-bursts, of random frequency and amplitude proportional to the hearing thresholds, as a sound therapy to decrease the hyperacusis suffered by a group of participants. Cobo (2021) adapted this EAE to tinnitus sound therapy, adding a new sequence of gammatones.

Therefore, EAE therapy of tinnitus can be implemented either as a sequence of tones or as a continuous broadband sound matched to the Hearing Level (HL) curves. This article is aimed to compare the efficiency of EAE therapy, using these sequential and continuous types of sound stimuli, on the relief of tinnitus-related distress on a sample of participants.

2. Materials and methods

2.1. Participants

The study was approved by the Institutional CSIC Ethics Committee (internal code 004/2022) and was conducted in accordance with the Declaration of Helsinki for experiments involving humans and the Spanish Law of Data Protection (RD1720/2007). A number of 230 volunteers with tinnitus (see Fig. 1), which gave their written informed consent, were recruited through a call in our institutional webpage (Estudio clínico sobre terapias sonoras del acúfeno | ITEFL.csic.es).

Participants aged between 18 and 75 years, with non-pulsatile tinnitus, and with $\text{THI} \geq 20$ at baseline were included in this study. In a previous pilot non-controlled observational study, Cuesta and Cobo (2020) excluded patients with $\text{THI} \leq 32$. However, a THI score reduction of 20 points is considered to be clinically relevant (Jastreboff, 2015). Therefore, tinnitus participants with $\text{THI} \geq 20$ were included in this study. Patients with mental health condition, recent ear surgery, severe Ménière syndrome, and hydrocephaly were excluded. After applying these criteria, 207 patients were enrolled and 23 were excluded.

From 207 enrolled participants, 12 participants withdrew before treatment was started after learning more about the fundamentals and expectations of the study. An additional 58 participants did not complete monthly outcome measures and were counted as dropouts. This left 137 patients completing the treatment (see Fig. 1). Reductions in self-perceived tinnitus handicap were observed in 123 participants. 14 participants had a slight increase in self-perceived tinnitus handicap. Table 1 summarizes the average age and gender of the 123 successful participants. Female participants were, on average, 3 years younger.

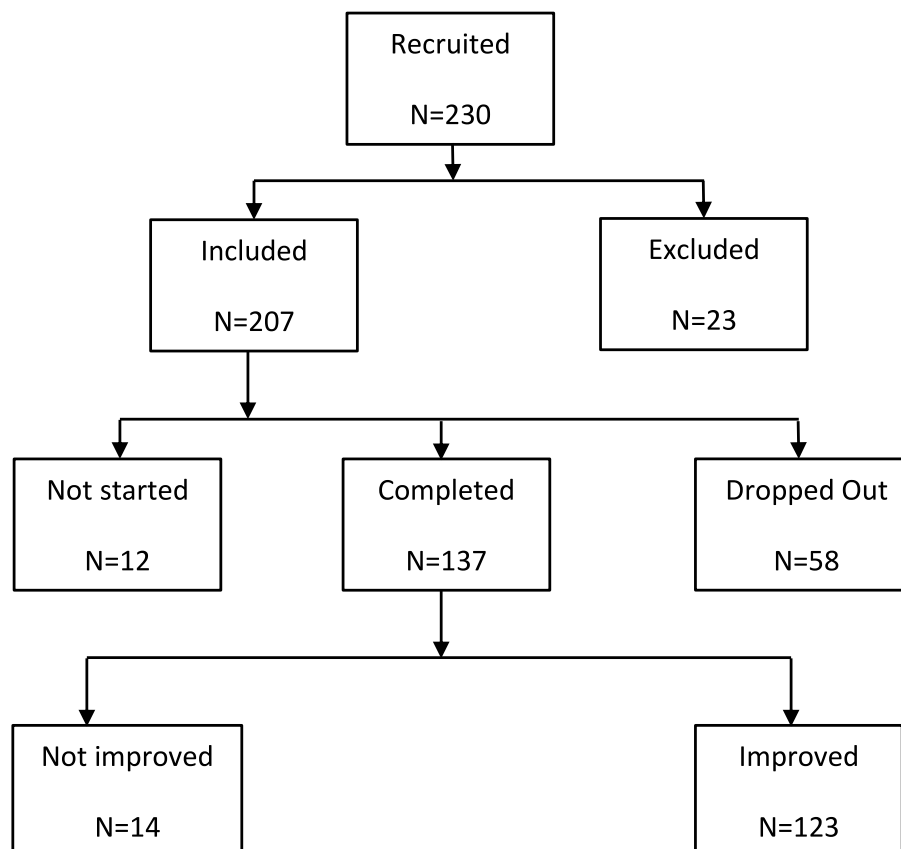


Fig. 1. Flow diagram of participants in this study.

Table 1
Gender and age of the 123 successful participants in this study.

	All	Male	Female
N	123	78	45
Age (mean) in years	52.7	53.8	50.6
Age (SD) in years	9.7	8.8	10.9

2.2. Hearing levels

Since this sound therapy stimulates selectively the auditory system of participants according to their HL, audiometry was conducted for each patient. Before the COVID19 lockdown (March 14, 2020), the HL of each participant were measured in our Audiology Room by pure-tone audiometry using pure tones at eleven pre-specified frequencies between 125 and 8000 Hz. After the COVID 19 lockdown, participants were required to afford their HL curves measured in any external clinic.

The average audiograms of all participants are shown in Fig. 2. Participants displayed poorer high-frequency hearing, a little larger at the left ear, and higher for male than female. Confidence intervals (± 1.96 SD/sqrt(N)), (SD = standard deviation, N = number of participants) are outlined by shaded areas around the HL curves.

2.3. Tinnitus characteristics

Case histories of participants were assessed just after they signed the informed consent using a tinnitus characteristics form. The gathered information of participants included tinnitus aspects such as temporal variability, frequency and type of sound, and lateralization (bilateral, left or right ear) as well as their tinnitus-related severity through a validated Spanish version of the THI (Herráiz et al., 2001) and anamnesis. Furthermore, participants were asked about the possible aetiology of their tinnitus, previous tinnitus treatments, and relevant comorbidities. Among the 123 participants, 56 (45.6%) had bilateral tinnitus, 42 (34.1%) had their tinnitus localized in the left ear and 25 (20.3%) heard their tinnitus in the right ear.

The mean and SD of the tinnitus duration, tinnitus pitch and THI at baseline of all participants, as well as for male/female, are summarized in Table 2. Females had significantly lesser tinnitus duration (2.8 years), lower tinnitus pitch (1905 Hz) and higher tinnitus severity (THI) at baseline (4.6). These differences were statistically significant at $p < 0.05$.

Table 2
Mean and SD of tinnitus duration, tinnitus pitch and baseline tinnitus severity. Data for the participants who withdrew are included in brackets for comparison.

		All	Male	Female
N		123 (56)	78 (41)	45 (15)
Tinnitus duration (years)	Mean	6.8 (5.9)	7.8 (5.52)	5.0 (7.1)
	SD	9.7 (8.0)	10.3 (7.42)	8.5 (9.7)
Tinnitus pitch (Hz)	Mean	4987 (5014)	5684 (5017)	3779 (5007)
	SD	3013 (2655)	2870 (2701)	2899 (2620)
THI _{baseline}	Mean	53.4 (57.0)	51.7 (56.4)	56.3 (58.8)
	SD	22.3 (22.6)	22.1 (23.4)	22.7 (18.9)

Data for the dropped out participants are included in brackets for comparison. As it can be seen, tinnitus duration was lesser (0.9 years), tinnitus pitch was roughly the same, and THI score was greater (2.6 points) for dropped out participants. For the withdrawn participants, tinnitus duration was lesser for males and greater for females, tinnitus pitch was lower for males and higher for females, and THI was larger for males and females.

To match the tinnitus pitch and sound type a custom-designed Graphical User Interface (GUI) was used (Cuesta et al., 2022). A band-pass filtered noise was generated using this GUI, where the central frequency (CF) and bandwidth (BW) could be tuned. These parameters are varied to generate tonal ($BW < 0.01$ CF), ringing (0.02 CF $< BW < 0.1$ CF), or hissing ($BW > 0.1$ CF) sound types.

The GUI to match the tinnitus pitch was controlled by the experimenter. During counselling session, the participant was requested to pay attention to the sound type generated by the GUI. For the tinnitus pitch, participants might to match the CF of the sound type to their own tinnitus sound. Firstly, they were familiarized to the sound type (tonal, ringing and hissing) and the effect of the BW. Then they identified roughly the sound type more similar to their tinnitus. Finally, the sound generated by the GUI was tuned to their own tinnitus.

2.4. Counselling

Participants completed a virtual counselling session of roughly 60 minutes just after they accepted to be enrolled in the study. A Power-Point presentation was used to explain the participants the fundamentals of the auditory system functioning, as well as the mechanisms, aetiology, epidemiology, and possible treatments of tinnitus. After that, the

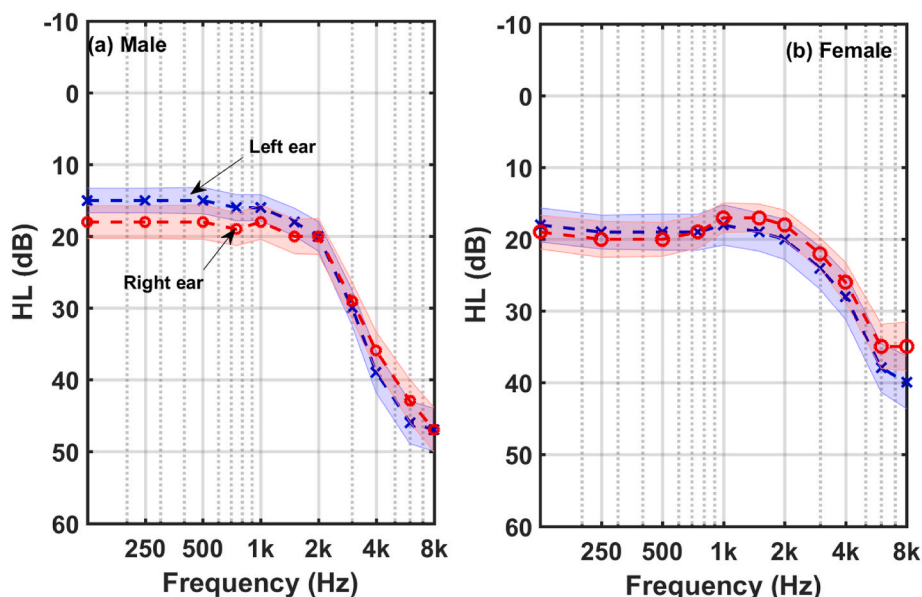


Fig. 2. Average HL of the 78 males and 45 females who finished the treatment. Shaded areas display the 95% confidence intervals.

bases of EAE were presented. Finally, the participants chose the EAE stimulus (either sequential or continuous) and they were instructed in its listening protocol (volume of sound, type of headphones, time of hearing, etc.). All this process was conducted virtually.

2.5. Sound therapy

Participants were exposed to the EAE sound therapy 1 h a day for four months. The stimulus consisted of a stereo audio file customized to the HL curves of the participant. This stimulus could be sequential or continuous. The bases of both stimuli are presented in the following.

2.5.1. Sequential EAE

The equation for a sequential EAE is

$$eae_{seq}(t) = \sum_m A_m(f_m) env_m(t - \tau_m) \cos[2\pi f_m(t - \tau_m)], \quad (1)$$

where f_m is a random frequency within the audio frequency range (125 Hz-8 kHz), A_m is an amplitude factor given by

$$A_m(f_m) = 10^{\frac{HL(f_m)}{20}}, \quad (2)$$

which contains the customization of the stimulus to the HL curves, τ_m is the repetition time of tones (inverse of number of tones per second), env_m is the envelope of the tone

$$env_m(t - \tau_m) = \begin{cases} t^{\gamma-1} e^{-\alpha(t-\tau_m)} & \text{for tone - pips} \\ w(t - \tau_m) & \text{for tone - burts} \\ \left(\frac{b_m}{6}\right)^3 t^3 e^{-b_m(t-\tau_m)} & \text{for gammatones} \end{cases}, \quad (3)$$

being (α, γ) two parameters controlling the envelope of the tone-pips, w a time-window function (e.g., Hanning, Hamming, Blackman-Harris, etc. (Nuttall, 1981)), and b_m is the Equivalent Rectangular Band (ERB), given by (Glasberg and Moore, 1990; Katsiamis et al., 2007)

$$ERB = b_m = 0.108f_m + 24.7. \quad (4)$$

Fig. 3 shows a tone-burst with Blackman-Harris window (Nuttall,

1981), a tone-pip with $(\alpha, \gamma)=(3,300)$ and a gammatone at 1000 Hz. Fig. 4 shows the corresponding log-spectra. The tone-burst has a symmetric envelope. Since this pulse is larger in the time domain, its main lobe in the frequency domain is shorter and has the typical side-lobes. The EAE with tone-burst is the same that the EAE proposed by Noreña and Chery-Croze (2007). The tone-pip and gammatone are asymmetric and have also asymmetric log-spectra. The gammatone is shorter in the time domain and has a wider main-lobe. The EAE with tone-pips was already used by Noreña and Eggermont (2003, 2005) in animal models.

Let us illustrate the sequential EAE stimulus with an example. Fig. 5 shows the HL curves of a tinnitus participant, consisting of high frequency hearing losses in both ears. Furthermore, a slight scotoma at 6 kHz is observed in the left ear. Fig. 6(a) and (b) show the first 2 s of a sequence of tone-pips with parameters $(\alpha, \gamma)=(3,300)$ and $\tau = 0.25$ s. Since the HL is different in the right and left ears, the corresponding tone-pips have also distinct amplitudes. The random nature of the tone frequencies is better seen in the spectrograms of the sequences, Fig. 6(c) and (d). Note also that the sequence of tone-pip is a diotic stimulus (the left and right tone-pips at each instant have the same pitch). Sequential stimuli sound as a sequence of tones with random frequency, within the hearing frequency band, and amplitude proportional to the hearing loss at this frequency.

2.5.2. Continuous EAE

The equation for a continuous EAE is

$$eae_{cont}(t) = \mathcal{F}^{-1}\{A(f)RAND(f)\}, \quad (5)$$

where f is the frequency (in the audio frequency range 125 Hz-8 kHz), $A(f)$ is an amplitude factor given by the interpolation of Eq. (2) in the full frequency range, $RAND(f)$ is a random function, and \mathcal{F}^{-1} stands for inverse Fourier transform. The continuous EAE is the implementation of the broadband stimulus matched to the hearing loss curve proposed by Schaette and Kempter (2006, 2008). The log-spectra of a continuous EAE stimulus adjusted to the HL curves of Fig. 5 are shown in Fig. 7. The HL curves are superimposed for comparison. As expected, the log-spectra of the continuous EAE match exactly the HL curves. Continuous stimuli are heard as broadband sounds filtered by the hearing loss of the participants.

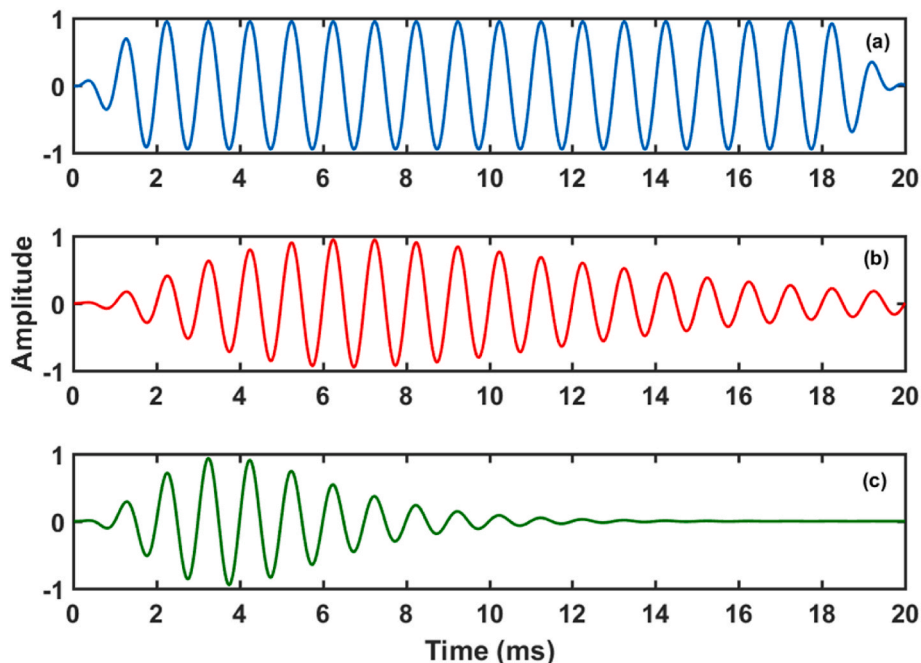


Fig. 3. (a) A tone-burst of 20 ms and $f = 1000$ Hz, (b) a tone-pip with $(\alpha, \gamma)=(3,300)$, and (c) a gammatone at $f = 1000$ Hz.

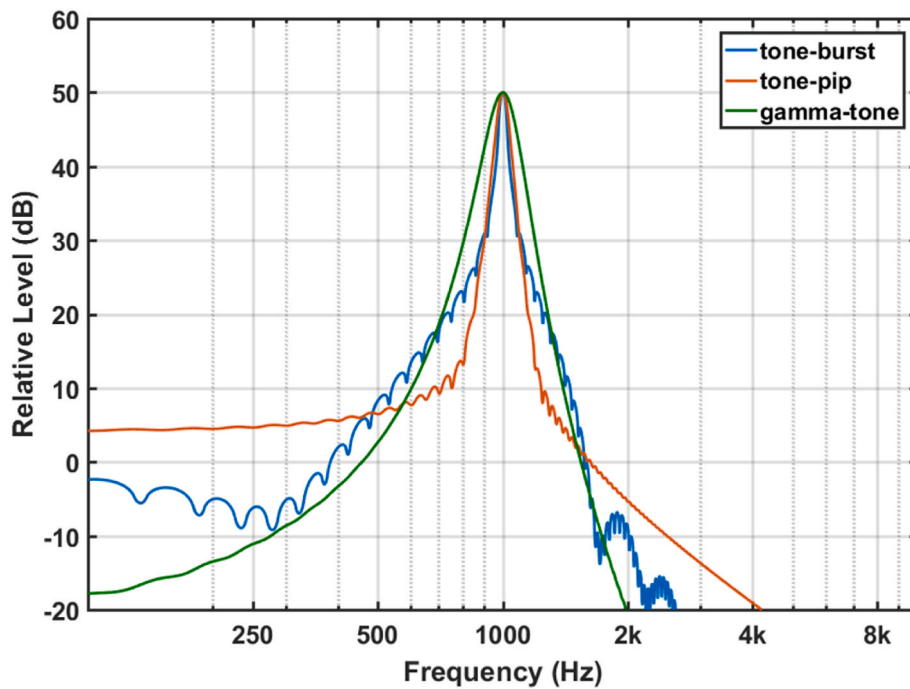


Fig. 4. Log-spectra of the tone-burst, tone-pip and gammatone of Fig. 3.

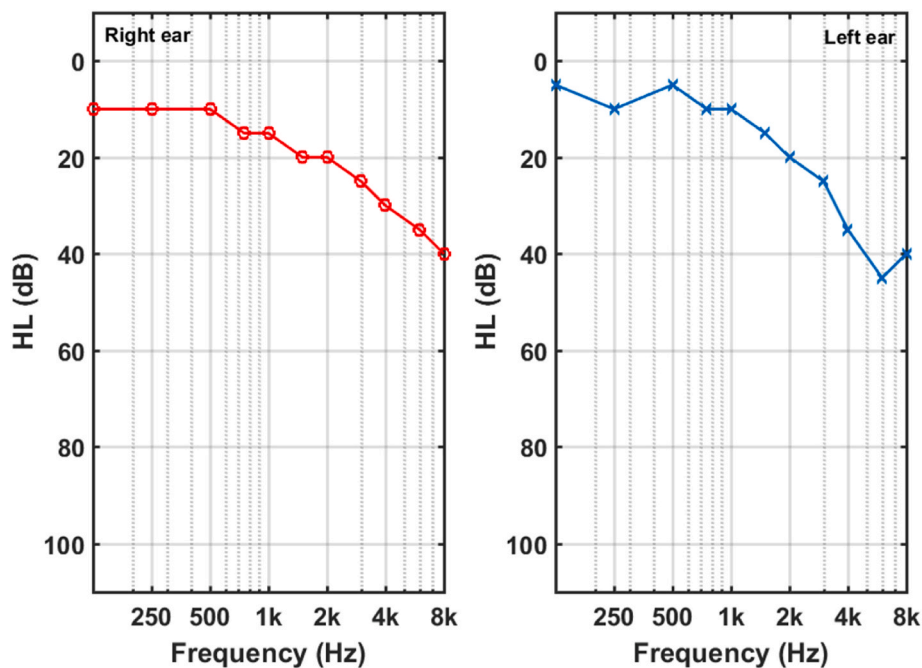


Fig. 5. Right and left HL curves.

2.5.3. Implementation of EAE

Another GUI (distinct to the GUI for tinnitus pitch matching) was used to calculate the EAE stimulus for sound therapy. Since comfort is crucial for this sound therapy, the four types of stimuli (sequences of tone-pips, tone-bursts or gammatones, and continuous EAE) were played to the participant so that he/her could choose the more comfortable one. After that, the chosen EAE stimulus was generated and saved as a stereo audio file (mp3 format). This EAE stimulus was given to the participant with the recommendation of listening it with any audio playing device with circumaural headphones at a volume just below its own tinnitus sound volume (the mixing point (Jastreboff, 2015)).

2.6. Tinnitus outcome

The tinnitus-related severity was assessed using a validated Spanish version of the THI (Herráiz et al., 2001). According to the severity scale of THI (McCombe et al., 1999), 40/123 (33%) of participants had mild handicap ($18 \leq \text{THI} \leq 36$), 31/123 (25%) were concerned by moderate handicap ($38 \leq \text{THI} \leq 56$), 24/123 (20%) had severe handicap ($58 \leq \text{THI} \leq 76$), and 28/123 (23%) had catastrophic handicap ($\text{THI} \geq 78$).

The participants interacted with the experimenter virtually (by videoconference) just during the counselling session (see Section 2.4). After that, the experimenter sent each month the questionnaires to the

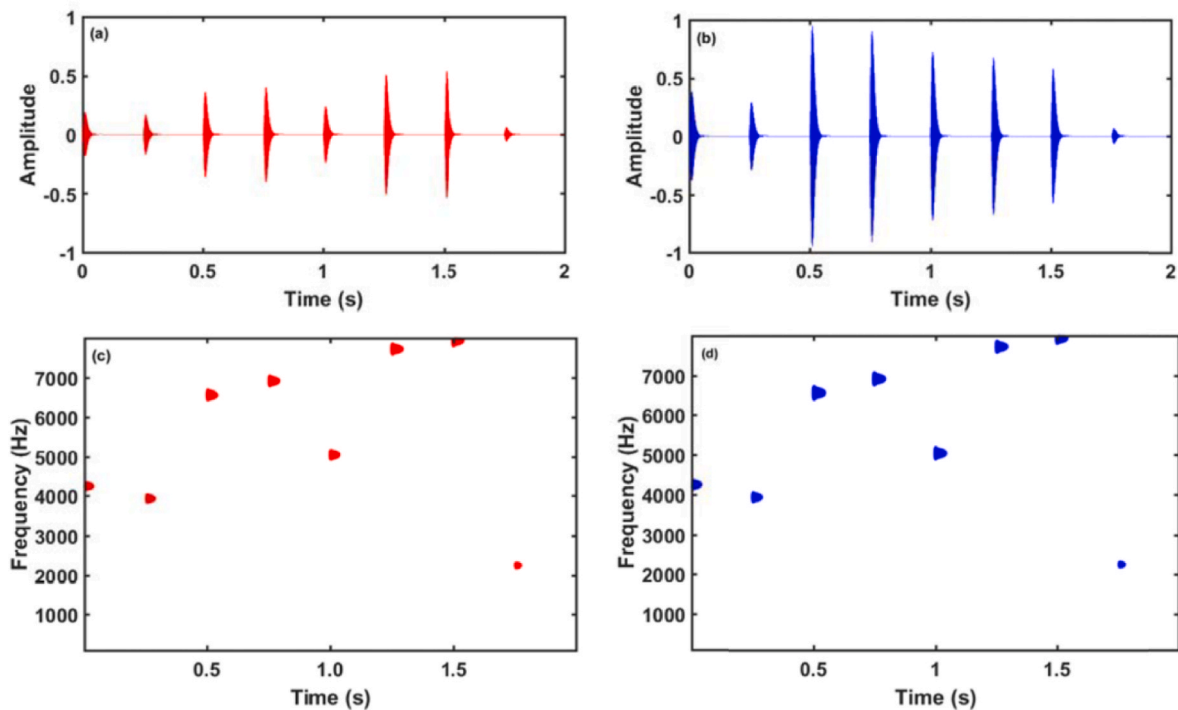


Fig. 6. (a) Right and (b) left sequences of tone-pips. Spectrograms of (c) left and (d) right sequences of tone-pips.

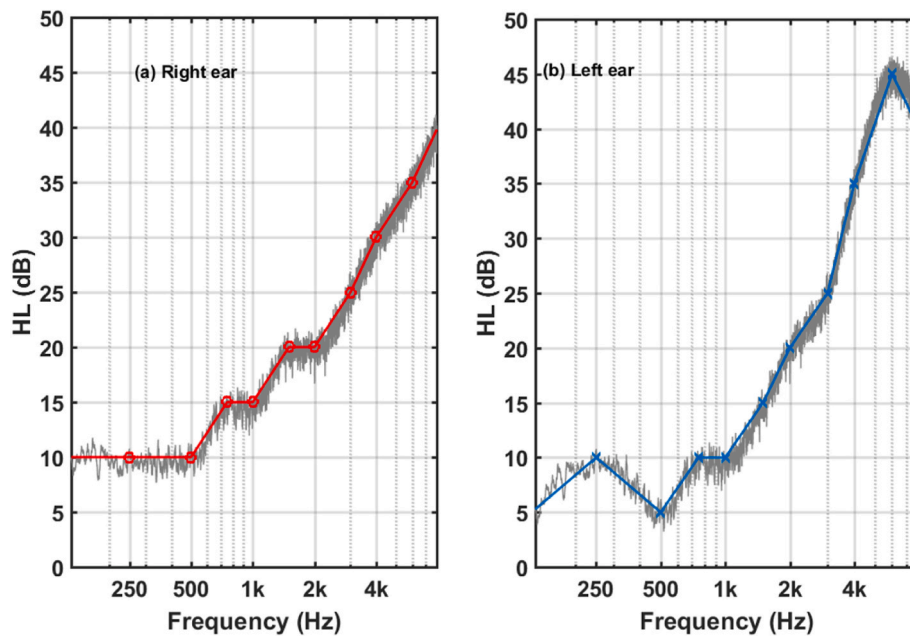


Fig. 7. (a) Right and (b) left log-spectra of the continuous EAE stimulus. The HL curves are superimposed for comparison.

participants, who completed them, and sent them back to the experimenter.

3. Results

As explained above, tinnitus relief was assessed by the THI questionnaire. Since this questionnaire evaluates the tinnitus-related distress, the success of the therapy was calculated through the change in scores across the study’s four-month duration. As reported in Section 2.1, 137 of 230 participants (59.6%) completed the 4 months of sound therapy. From these, 123 (90%) achieved some tinnitus relief and 14

(10%) did not (see Fig. 1).

The overall mean THI drop, $\Delta\text{THI} = \text{THI}_{\text{baseline}} - \text{THI}_{\text{final}}$, was 24.3. According to Jastreboff (2015), this THI reduction was clinically relevant. Furthermore, the potential of THI reduction is proportional to the THI score at baseline, i.e., the higher the THI score is at baseline, the more THI score reduction can be achieved (Cuesta et al., 2022). This is observed in Fig. 8, which shows the mean THI score decreases for each tinnitus severity grade. The tinnitus-related severity of participants descended two (catastrophic) or one (severe, moderate and mild) degrees.

Table 3 summarizes the number of participants within each severity

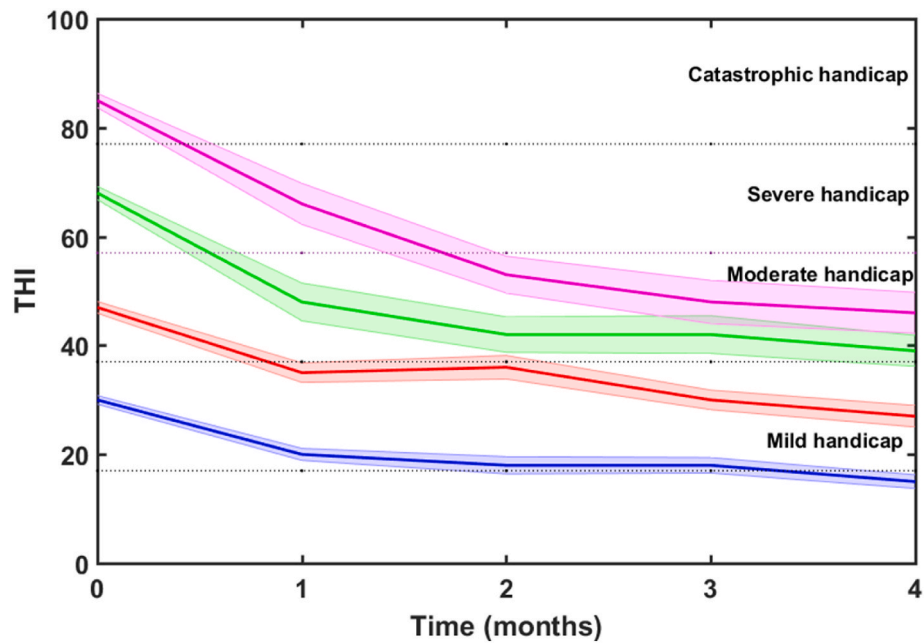


Fig. 8. Average THI score change over time for the different severity grade subgroups. Shaded areas display the 95% confidence interval.

Table 3

Mean and SD of THI scores at the beginning and final of treatment, and THI score drop for each tinnitus-related severity grade.

Severity scale	Number of participants	$THI_{baseline}$		THI_{final}		ΔTHI	p	Cohen's d
		Mean	SD	Mean	SD			
Mild	40	29.5	5.2	15.4	7.8	14.1	<0.001	2.2
Moderate	31	47.0	5.9	27.2	11.5	9.8	<0.001	2.3
Severe	24	68.3	6.1	38.8	14.4	29.5	<0.001	2.9
Catastrophic	28	84.8	6.6	45.6	20.3	41.2	<0.001	2.9
Overall	123	54.1	22.4	29.8	18.0	24.3	<0.001	1.2

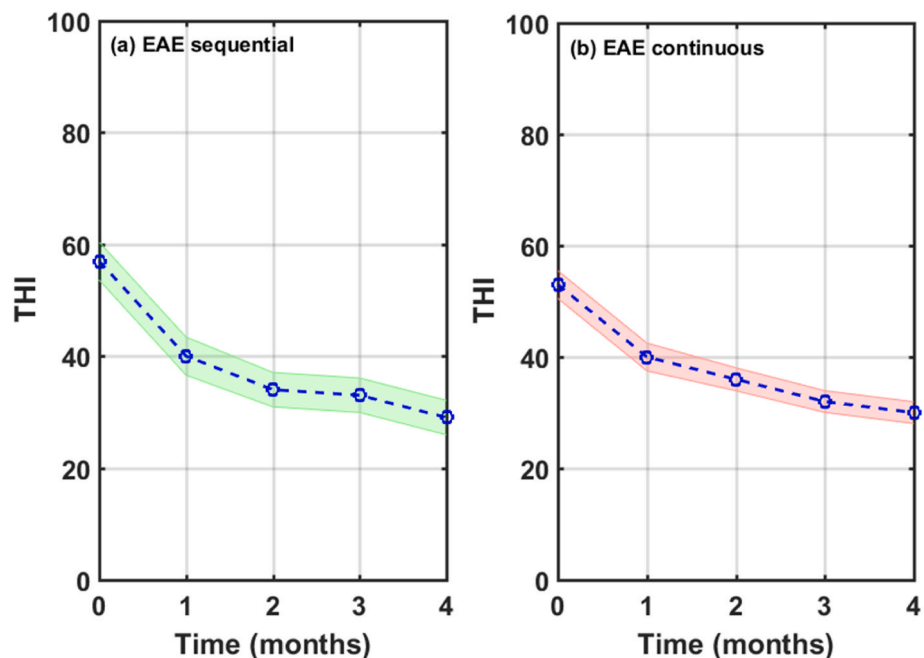


Fig. 9. Average THI score change for (a) sequential and (b) continuous EAE stimulus types.

scale, their mean and standard deviation (SD) THI scores at baseline and final (after the four months of EAE therapy), and the THI reduction (Δ THI). The last two columns display the significance levels (p), estimated applying an ANOVA test, and the Cohen's d of these score reductions. Results show that the THI score decrease for each severity grade was statistically significant at $p < 0.001$, and that the corresponding effect sizes were very large.

Participants could choose which EAE stimulus, either sequential or continuous, use for their four-month therapy, based uniquely on their hearing comfort feeling. 85 of 123 (69%) chose the continuous while 38 of 123 (31%) selected the sequential EAE stimuli. From these last 38 participants, 31 chose the sequence of gammatones, 6 selected the sequence of tone-pips, and 1 picked the sequence of tone-bursts. Fig. 9 shows the average THI score drop of each subgroup.

Baseline and final mean values of THI score, as well as the Δ THI after the four-month therapy, are summarized in Table 4. Participants in the sequential EAE subgroup had a greater mean THI score at baseline. It is seen that the THI score drop of participants in the sequential EAE subgroup was, on average, 5.1 points greater than that those of the continuous EAE subgroup. Again, two columns are added with the significance levels provided by ANOVA tests and the Cohen's d effect sizes. Thus, THI score drops for each subgroup were statistically significant at $p < 0.001$. Furthermore, the Cohen's d effect sizes were very large. Since the difference of both THI score drops was 5.1, we conclude that the sequential EAE stimulus provided slightly more tinnitus-related distress relief than the continuous EAE.

4. Discussion

TRT combines counselling with sound therapy. The sound therapy of the TRT applies usually a broadband noise, although other sound types have been proposed, such as coloured broadband noises (white, red and pink) (Barozzi et al., 2017), custom sounds (Henry et al., 2004), and band-filtered noise (Kim et al., 2014). Our proposal combines also our own counselling session with sound therapy but differs in the use of EAE as a personalized sound stimulus. Since hearing loss is considered as one of the major risks of deafferentation to the auditory system, and hence, one of the potential tinnitus trigger, we proposed to compensate the EAE sound stimulus with an amplitude function (see Eq. (2)) proportional to this hearing loss. Note that some participants could suffer of tinnitus with an apparent normal audiometry (McFerran et al., 2019; Cuesta et al., 2022, 2023). In this case, the continuous EAE proposed here becomes just the broadband noise used in TRT.

The TRT applied in most clinics requires listening the broadband sound stimulus for 4–8 h/day during 12–18 months, affording reduced tinnitus-related distress in a high percentage of participants (80% according to Jastreboff, 2015). One of our aims was to demonstrate that it is possible to achieve similar (or even better) results with lower exposure time. Specifically, 90% of our participants reached some tinnitus-related distress being the average THI score drop of 24.3 points in just four months. When compared with other TRT results, only those of Jastreboff (2015) and Barozzi et al. (2016) achieved a comparable THI score drop of 23 and 20 points, respectively, but with higher exposure time. Lower THI reductions of 7 (Henry et al., 2006), 13 (Bauer et al., 2017) and 10 points (Oishi et al., 2013) were reported by others in four months.

Our results, as well as the results in the articles above referred, provided the mean THI score change in the four-month treatment. This means not that all (90%) of participants achieved a THI score drop of 24.3 points. Some of them reduced 10 points (for instance) of their THI score and some others decreased it on 40 points (for example). Another analysis procedure reporting the percentage of patients who achieved clinically-relevant improvement in their self-assessed tinnitus handicap should be very interesting but was not applied to these data.

The 10% of participants who did not achieve tinnitus relief deserve some mention. In general, they are refractory participants unable to change their thoughts regarding their tinnitus (even though this issue

Table 4

THI scores pre- (baseline) and post-treatment for the different severity grade subgroups.

	N	THI			p	Cohen's d
		Baseline	Final	Δ THI		
All	123	54.1	29.8	24.3	<0.001	1.2
Sequential EAE	38 (31%)	57.3	29.5	27.8	<0.001	1.4
Continuous EAE	85 (69%)	52.6	29.9	22.7	<0.001	1.1

was emphasized during the counselling session) along the therapy time. Their monthly THI slightly fluctuated around their baseline score but, at the end of treatment, they failed to reach any progress. Finding a treatment able to alleviate the suffering of these participants is the target of our future research.

4.1. Limitations

This is a non-controlled non-randomized quasi-experimental longitudinal study. Because the study lacks control conditions for the sound (ie. counselling only condition) and the counselling (ie. sound only conditions) or a control group that received neither intervention, it cannot be stated with any certainty that the study results were due separately to the sound or to the counselling. Similarly to TRT, we did not discriminate between the separate effects of counselling and sound therapy. Therefore, we claimed the success of the combined counselling + EAE sound therapy treatment.

5. Conclusions

This study aimed to optimize a tinnitus sound therapy regarding its duration as well as the sound stimulus type. The sound stimulus consisted of a continuous or sequential customized Enriched Acoustic Environment, matched to the HL curves of the participant.

A total of 137 tinnitus participants were treated with this type of stimuli. From these, 90% of participants reached some tinnitus-related distress relief being their average Tinnitus Handicap Inventory (THI) score drop 24.3 points. This mean tinnitus-related distress relief was clinically relevant and statistically significant. Participants exposed with sequential stimuli (31%) achieved slightly greater distress relief (5.1 points more in their mean THI score) than those stimulated with continuous sound (69%). Therefore, although both type of stimuli provided tinnitus-related distress reduction, sequential Enriched Acoustic Environment should be recommended in the future in this type of sound therapy.

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Institutional review board statement

The study was conducted in accordance with the Declaration of Helsinki, and approved by the Institutional Ethics Committee of the CSIC (protocol code 004/2022).

Informed consent statement

Informed consent was obtained from all participants involved in the study.

Declaration of competing interest

The authors declare no conflict of interest.

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