Agreed student contribution to the MSc project

It is important that the examiners are aware of exactly how much the student contributed to the project in order to judge the complexity and demands of the project and to which aspects attention should be paid for marking. The supervisor and the student should agree on the contribution to be reported in the table below.

NO PROJECT WILL BE MARKED WITHOUT THIS DECLARATION

Contribution to:	Student's contribution
Collection of specimens/material/patient recruitment*	Tinnitus data was provided by the Tinnitus Center of Montevideo (CTM) where patients were recruited and treated.
Experimental work- please briefly outline what was/was not done by the student (if help was given with any aspect by others, please note this here)	The experimental work consisted of the Matlab coding learning and data analysis sessions, which were proficiently carried out and completed by the student.
Data analysis	The student independently analysed the data with provided Matlab scripts, gaining a sound understanding of Matlab coding. She attended summer boot camp in computational neuroscience.
Write-up	The student wrote the text independently with feedback from supervisors is several instances.
Production of submission including figures	The student produced the figures independently with the initial Matlab code lines provided by the supervisors during the summer bootcamp.
Problems encountered if any	N/A
Any other comments/ contributions not listed	Very proactive student, evidencing strong critical thinking and very good effort throughout the research project.
Supervisor has seen the final draft of the dissertation – if no, please provide an explanation	Yes

Student Name and Student Number: Maryam Zuhair Aziz Waheed. 250202124.....
Student Signature:……..Date: …28/07/2025.....
Supervisor Name: Alberto Capurro, Veronica Mendez, Daniel Drexler

Supervisor Signature:... ..... Date: .....28/07/2025.....

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Treatment of Tinnitus with Acoustic Stimulation During Sleep; Analysis of Patient Responses to a Sound that Mimics the Characteristics of Tinnitus.

Author: Maryam Zuhair Aziz Waheed

Student ID: 250202124

Course: MSc Neuroscience

Supervisor: Dr. Alberto Capurro

Co-supervisor: BSc. Verónica Méndez and Dr. Daniel Drexler

Blizard Institute,

Barts and The London School of Medicine and Dentistry,

Queen Mary University of London

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Abstract

Tinnitus, the perception of sound in the absence of external stimuli, is often associated with cochlear damage and maladaptive neuroplasticity, remaining a therapeutic challenge. This study investigates the tolerability and response to an Individualized Acoustic Recipe (IAR) used in tinnitus treatment through Acoustic Stimulation during Sleep (SAS). Twenty-one adult patients with subjective tinnitus from the Montevideo Tinnitus Center received SAS treatment via the SONUS4 digital platform over 8-12 months. The IAR, customized to match each patient's tinnitus frequency and loudness, was delivered nightly. Subjective tolerability and emotional response to the IAR were quantified using the CLP IAR Response Index (CLPi IAR) at the treatment start and completion.

Histograms of CLPi scores before and after treatment revealed no aversive responses in most patients. An increased mean CLPi indicated a shift from neutral to positive IAR perception over time. Paired statistical analysis (Wilcoxon test) confirmed significant CLPi improvement. Patients were separated into two groups based on initial IAR response, showing that improvement was primarily driven by those with initial aversive risk —supporting the involvement of habituation and desensitization mechanisms. No significant associations emerged between IAR response and patient age or tinnitus duration, suggesting broad applicability.

Customizable IAR delivery during sleep likely promotes auditory neuroplasticity without disrupting sleep architecture. Our findings challenge historic assumptions about aversive responses to tinnitus-like stimuli, demonstrating that targeted nocturnal sound therapy is well tolerated from treatment onset, with significant improvement in patients with poorer initial scores.

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Abbreviations

Vestibulocochlear nerve (CN VIII)

Inner hair cells (IHC)

Outer hair cells (OHC)

Superior olivary complex (SOC)

Inferior colliculus (ICc)

Medial geniculate body (MGB)

Medial olivocochlear (MOC)

Lateral olivocochlear (LOC)

Ventral cochlear nucleus (VCN)

Dorsal cochlear nucleus (DCN)

Lateral nucleus (LN)

External nucleus (ICx) of the inferior colliculus

The secondary auditory cortex (AII)

Noise induced hearing loss (NIHL)

Olivocochlear bundle (OCB)

Cognitive Behavioural Therapy (CBT)

Sound Therapy (ST)

Tinnitus retraining therapy (TRT)

Individualised Acoustic Receipt (IAR)

Acoustic Stimulation during Sleep (SAS)

Montevideo Tinnitus Clinic (CTM)

Product otoacoustic emissions (DPOAEs)

Transient evoked otoacoustic emissions (TEOAEs)

Continuo Learning Platform (CLP)

CLP IAR Response Index (CLPi IAR)

Slow-wave sleep (SWS)

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1 Introduction

The mammalian auditory system is an extraordinary product of evolution, capable of perceiving and interpreting sounds across a broad spectrum of frequencies and intensities. (Robles & Ruggero, 2001)

1.1 Sound

Waves of energy across a medium are the source of sound. The altering of air pressure is a result of back-and-forth particle's movement in the same direction the wave is travelling. Humans can hear sounds within 20Hz to 20,000 kHz, although the upper limit usually deceases with age. (Peterson et al., n.d.)

1.2 The Peripheral Auditory System

1.2.1 Peripheral Auditory Anatomy and Function:

The human auditory system includes three anatomically and functionally distinct divisions (Fig. 1).

1.2.1.1 Outer Ear

The pinna collects and focusses sound waves through the external acoustic meatus to the tympanic membrane (Fig 1), contributing to sound amplification in the 2–5 kHz range and providing directional cues via spectral filtering (Pickles, J. O., 2008).

1.2.1.2 Middle Ear

The tympanic membrane's vibrations are transmitted via the ossiclar chain which is three bones (malleus, incus, and stapes) (Fig 1). These three bones act like a bridge between the tympanic membrane and the inner ear through the oval window, efficiently coupling airborne sound to the fluid-filled cochlea (Pickles, J. O., 2008). The ear and the rhinopharynx are connected through the Eustachian tube (Fig 1), which equalises the pressure on either side of the eardrum, allowing the optimal transmission of the vibration in the inner ear (Casale et al., 2025).

1.2.1.3 Inner Ear

Resides within the petrous portion of the temporal bone, consists of two interconnected components. The bony labyrinth and the membranous labyrinth, which together maintain the ionic environments essential for signal transduction and spatial orientation (Bruss & Shohet, 2025). The bony labyrinth forms a rigid, osseous enclosure filled with perilymph, a fluid characterized by with high sodium and low potassium concentration. Its composition closely mimics that of extracellular fluid, making it suitable for propagating mechanical signals generated by sound waves and head movements (Pickles, J. O., 2008). Suspended within the bony labyrinth is the membranous labyrinth, a flexible, epithelial-lined structure containing endolymph. This fluid has a very high concentration of potassium and low concentration to sodium, alike the intracellular fluid, thereby creating an electrochemical environment optimized for sensory transduction (Bruss & Shohet, 2025).

Functionally, the membranous labyrinth has two parts: an auditory (cochlea) and a vestibular (semicircular canals, utricle, and saccule) (Fig 1). (Bruss & Shohet, 2025). Importantly, the separation of these compartments by perilymph allows for localized regulation of ionic gradients, thereby enabling precise activation of hair cells in response to mechanical stimuli (Pickles, J. O., 2008).

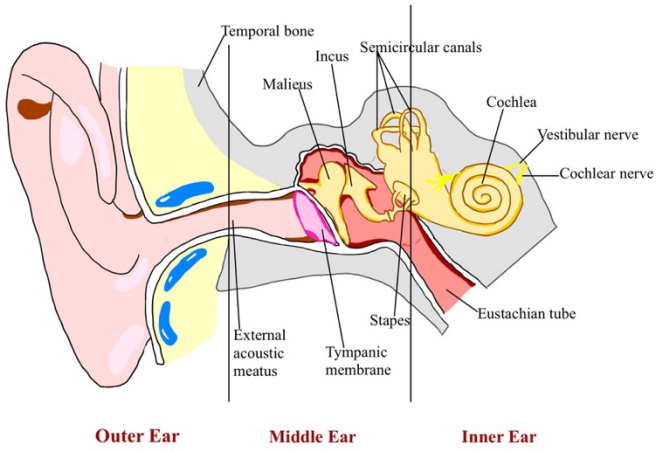


Figure 1. Anatomy of the human ear. The outer ear consists of the pinna, ear canal, and eardrum (which divides the outer and middle ear). The middle ear houses the three small bones: malleus, incus, and stapes. The inner ear contains the cochlea and semicircular canals and connects to the brainstem via the vestibulocochlear nerve (CN VIII). Additionally, the Eustachian tube links the middle ear to the nasopharynx.

1.2.2 Cochlear Transduction Mechanisms

1.2.2.1 Cochlear Architecture and Fluid Compartments

This spiral-shaped organ, the cochlea, consists of three chambers filled with fluid (scalae) (Fig 2). Scala vestibuli located in the inner part, filled with perilymph and begins at the oval window (Bruss & Shohet, 2025). Scala media, also known as cochlear duct, is filled with endolymph. It houses key structures including the basilar membrane which provides structural support for the Organ of Corti, the principal site of auditory transduction (Pickles, J. O., 2008). Above it lies the tectorial membrane, in which the stereocilia of hair cells are embedded (Hudspeth, 2014). Scala tympani is located in the outer part, containing perilymph, and ending at the round window (Bruss & Shohet, 2025). The helicotrema—a small opening—at the apex of the cochlea, connects the scala vestibuli and scala tympani, enabling low-frequency pressure waves to bypass the cochlear partition and dissipate efficiently (Pickles, J. O., 2008).

1.2.2.2 Mechanoelectrical Transduction in the Organ of Corti

The basilar membrane supports the organ of Corti, which contains two specialized hair cells types: inner hair cells (IHC) serve as primary sensory receptors transmitting auditory information to the brain, while outer hair cells (OHC) provide mechanical amplification through voltage-dependent length changes (electromotility), enhancing frequency selectivity (Fettiplace & Hackney, 2006).

These hair cells are arranged tonotopically along the basilar membrane from base to apex. This spatial organization reflects frequency selectivity, as the membrane's graded stiffness and mass distribution create maximal vibrations at specific locations: high-frequency sounds peak near the base (close to the oval window), while low-frequency sounds propagate to the apex (Robles & Ruggero, 2001). The basilar membrane exhibits a structural gradient where the basal region is stiffer, narrower, and bears shorter stereocilia, optimizing it for high-frequency sound detection. In contrast, the apical region has a wider, more compliant membrane with taller stereocilia, suited for low-frequency transduction (Robles & Ruggero, 2001). This tonotopic map enables frequency-specific neural encoding, a process sharpened by the non-linear activity of the cochlear amplifier created by OHC motility (Tani et al., 2021).

The mechanical transduction process begins when vibrations from the middle ear are transmitted through the oval window, inducing vertical displacements of the basilar membrane. This movement bends the stereocilia of hair cells embedded in the overlying tectorial membrane (Bruss

& Shohet, 2025). Directional bending toward the tallest cilium (kinocilium) opens mechanically-gated K^+ channels, depolarizing the hair cell through K^+ influx from the endolymph, while bending away causes hyperpolarization by channel closer (Hudspeth, 2014). At their basal poles, hair cells form glutamatergic synapses with spiral ganglion neurons, regulating action potential firing in the vestibulocochlear nerve (CN VIII) for transmission to the cochlear nucleus and ultimately the auditory cortex. (Purves & Williams, 2004)

The ionic environment supporting this transduction consists of perilymph filling scala tympani and vestibuli, while hair cells maintain an apical pole in contact with K^+-rich endolymph and a basal pole facing Na^+-rich perilymph. This polarity ensures proper mechanoelectrical transduction when stereocilia bend toward the kinocilium, allowing K^+ influx to depolarize the cell (Pickles, J. O., 2008).

The cochlea's tonotopic organization establishes place coding ("labelled lines"), where specific frequencies activate distinct auditory nerve fibers according to their characteristic tuning. This frequency map is preserved throughout the central auditory pathway, from cochlear nuclei to auditory cortex, enabling the brain to precisely decode frequency information (Ehret & Romand, 1997).

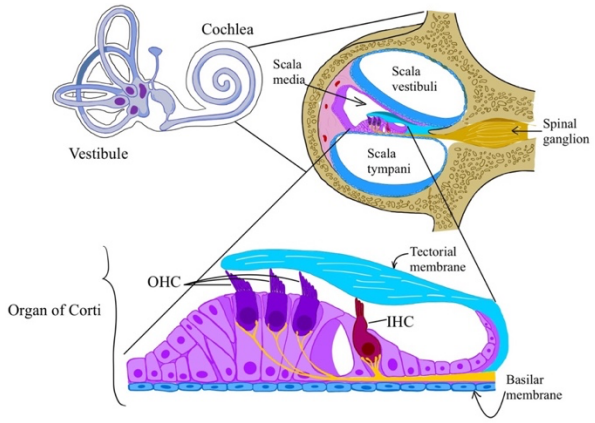


Figure 2. A cross-sectional view of the cochlea. The cochlea comprises three fluid-filled chambers: the scala vestibuli, scala media, and scala tympani. Key anatomical structures include the basilar membrane, which holds the Organ of Corti, and the tectorial membrane, which interacts with the hair cells inside the Organ of Corti. These sensory hair cells consist of two types: IHCs and OHCs.

1.3 Central Auditory System

The central auditory system represents a sophisticated neural network responsible for processing and interpreting auditory information from the periphery reaching the brainstem through the auditory nerve (Peterson et al., n.d.).

1.3.1 Ascending Auditory Pathway

The pathway begins with the transmission of neural impulses from the cochlear hair cells via spiral ganglion neurons that form the auditory component of CN VIII (cochlear nerve) (Peterson et al., n.d.). These afferent fibers project to the cochlear nuclei at the pontomedullary junction, representing the first synaptic relay station in the central auditory pathway (Burkard, 2008). From the cochlear nuclei, second-order neurons project along three main routes: ipsilaterally and contralaterally to the superior olivary complex (SOC), and to the inferior colliculus (ICc). These projections continue in an orderly progression, from ICc to medial geniculate body (MGB) of the thalamus, and to the primary auditory cortex in the temporal lobe (Burkard, 2008). The cochlear nucleus is monoaural, as it receives information only from the ipsilateral ear. On the other hand, the binaural term is used for the pathways starting from the SOC to the cortex, where the inputs are received from both ears. The later organisation permits a more precise localisation of auditory stimuli, for instance, when a sound originates from directly in front of or behind the head, it reaches both ears concurrently. On the contrary, if the sound comes from one side, it creates a temporal delay in the sensory input reaching the opposite ear, which is then processed by the SOC (Fig 3). In addition the tonotopic organization is preserved along the entire signalling cascade (Peterson et al., n.d.).

1.3.2 Descending Auditory Pathway

The central nervous system modulates peripheral auditory function through the efferent pathway that modulates peripheral function and refines auditory perception in real time (Peterson et al., n.d.). This descending control initiates in the auditory cortex and integrates signals from higher-order brain regions. The pathway projects from the auditory cortex, travelling to the ICc, SOC, and cochlear nucleus though its direct projections. These modulatory signals incorporate information about learned behaviours, emotional state. Such higher-order functions arise in a variety of brain regions, including the prefrontal cortex, hippocampus, nucleus basalis of Meynert, and limbic circuits. The pathway terminates at the cochlea through two olivo-cochlear systems, the medial olivocochlear (MOC) fibers that innervate the OHCs to control cochlear amplification, and the lateral olivocochlear (LOC) fibers that innervate the IHCs to adjust dynamic range of cochlear responsiveness (Peterson et al., n.d.).

The auditory system maintains continuous feedback loops between peripheral and central structures, where ascending signals are constantly modulated by descending cortical and subcortical outputs (Peterson et al., n.d.). This reciprocal connectivity enables adaptive processing of auditory information, allowing the system to optimize sound perception in challenging acoustic environments, enhance frequency discrimination, and prioritize behaviourally relevant stimuli (Burkard, 2008).

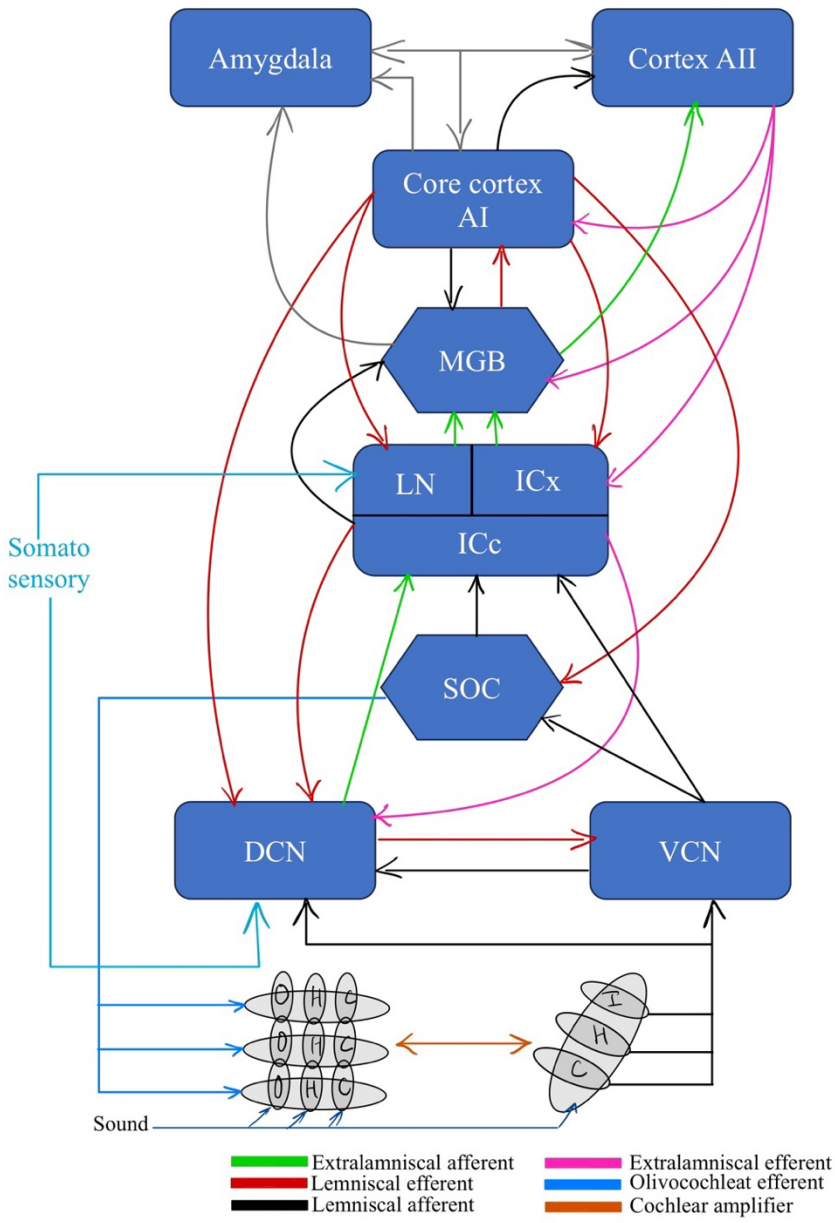


Figure 3. The auditory neural pathway. This diagram illustrates both afferent and efferent pathways, beginning with sound stimulation of the OHCs and IHCs in the cochlea. Auditory nerve fibers bifurcate, sending signals to the ventral (VCN) and dorsal cochlear nuclei (DCN), which then relay information to the SOC. The extralemniscal pathway includes the lateral nucleus (LN) and external nucleus (ICx) of ICc, along with MGB thalamic regions and the secondary auditory cortex (AII). Changes in cortical activity—especially due to diminished inhibition—can directly modulate subcortical structures like the ICc's central nucleus and DCN, while indirectly affecting the cochlea via the olivocochlear bundle.

1.4 Tinnitus

Tinnitus is an auditory sense of illusion felt in the lack of external stimuli (Eggermont & Roberts, 2004). Epidemiological studies indicate a prevalence ranging from 10% to 15%, establishing it as a significant auditory disorder (Langguth et al., 2013). While many individuals occasionally experience transient ringing due to reversible factors like loud noise exposure or medication, persistent tinnitus is of growing interest in auditory neuroscience. It bridges clinical and neurological domains, particularly as research reveals its association with hearing loss and explores emerging avenues for treatment and prevention (Eggermont & Roberts, 2004).

1.4.1 Classification of Tinnitus

Objective tinnitus is the hearing of a real sound. It is thought that this sound originates occurs outside the cochlea such as in the middle ear's muscles or vessels. (Pickles, J. O., 2008)

On the other hand, subjective tinnitus is the sensation of sound with no outer stimulus, typically referred to one or both ears, or perceived within the head. It varies in form -from ringing and pure tones to more complex noises- and in severity. Patients' information is the only basis for the diagnosis, and patients can report it as mild, moderate, or severe (Gudwani et al., 2013). It is believed that most subjective tinnitus are secondary to alterations or lesions in the cochlea (Pickles, J. O., 2008).

1.4.2 Etiological Factors of Tinnitus

Tinnitus can result from pathological changes in any part of the auditory pathway. In most cases it is due to maladaptive plasticity secondary to cochlear lesion (Langguth et al., 2013).

1.4.2.1 Hearing loss

Chronic noise exposure may result in noise-induced hearing loss (NIHL), a form of sensorineural deafness characterized by progressive hair cell apoptosis and spiral ganglion neuron degeneration. This results in elevated hearing thresholds and diminished speech recognition. While NIHL is a common cause of tinnitus and is associated with alterations in central auditory pathways, the precise neural loci of these alterations remain vague (T.-C. Wang et al., 2020).

1.4.2.2 Ototoxicity

While noise exposure is the leading cause of tinnitus and hearing loss, over 130 medications are recognized as ototoxic, including antibiotics, anti-inflammatories, antimalarials, loop diuretics, and antineoplastics. These drugs primarily damage OHCs, mainly by oxidative stress, leading to peripheral hearing loss and triggering maladaptive neuroplastic modifications in the central auditory system that may result in tinnitus. Additionally, their neurotoxic effects may directly impact central auditory pathways, potentially intensifying tinnitus perception (Baguley, 2015).

1.4.3 Neural Mechanisms of Tinnitus: From Cochlear Damage to Cortical Reorganization

The pathophysiology of tinnitus is fundamentally rooted in maladaptive neuroplasticity following cochlear damage. When auditory input is diminished due to noise trauma, ototoxicity, or age-related degeneration, central auditory pathways undergo compensatory hyperactivity, primarily through reduced inhibitory control (Vasilkov et al., 2023). This phenomenon persists even in cases without overt hair cell loss, suggesting that subtle cochlear nerve dysfunction can trigger widespread neural changes. Animal models demonstrate that cochlear injury leads to tonotopic remapping in the primary auditory cortex, characterized by exaggerated representation of frequencies bordering areas of hearing impairment. These cortical changes correlate strongly with emergence of tinnitus perception (Henry et al., 2014). This mechanism suggests tinnitus originates from central gain changes secondary to focal cochlear damage (Noreña & Farley, 2013).

Two complementary theories explain this process at the cellular level:

1 Edge theory, also referred to as contrast theory, proposes that tinnitus arises from elevated spontaneous neural activity at the boundary between damaged and intact cochlear regions. OHCs in basal cochlear regions are particularly vulnerable to acoustic trauma, creating a sharp transition zone where residual OHC function meets dysfunction (Han et al., 2009). This discontinuity generates abnormal spontaneous activity that is misinterpreted as sound.

2 Discordant theory extends this concept by emphasizing the imbalance between OHC and IHC damage. While OHCs typically degenerate first, relatively preserved IHCs continue transmitting aberrant signals to a disinhibited DCN, creating a phantom auditory percept (Han et al., 2009).

The efferent auditory pathway, olivocochlear bundle (OCB)—particularly the medial olivocochlear (MOC) fibers—plays a modulatory role in cochlear sensitivity. Normally, MOC

activation suppresses OHC output and alters otoacoustic emissions. Disruption within this network may impair auditory filtering and facilitate tinnitus-related excitation, especially given its contralateral organization and interplay with subcortical structures (Tayade & Tucker, 2022). However, in tinnitus, this regulatory mechanism fails, permitting the establishment of pathological neural synchrony. Cortical neurons in affected frequency bands show three hallmark changes: increased spontaneous firing rates, decreased GABAergic inhibition, and enhanced cortical synchronization (Eggermont & Roberts, 2004). Critically, this maladaptive plasticity initiates with peripheral hearing loss but rapidly involve the entire neuroaxis. From DCN hyperactivity to thalamocortical dysregulation, the pathological gain increases compensation for reduced peripheral input. Reduced intracortical inhibition permits pathological synchronization, where co-active neurons strengthen their connections via Hebbian plasticity, the resulting networks become self-sustaining circuits that generate phantom perceptions (Eggermont & Roberts, 2004). The process is exacerbated by age-related declines in central inhibition, explaining why tinnitus prevalence rises with age despite similar cochlear damage across ages (Henry et al., 2014) (Fig 4).

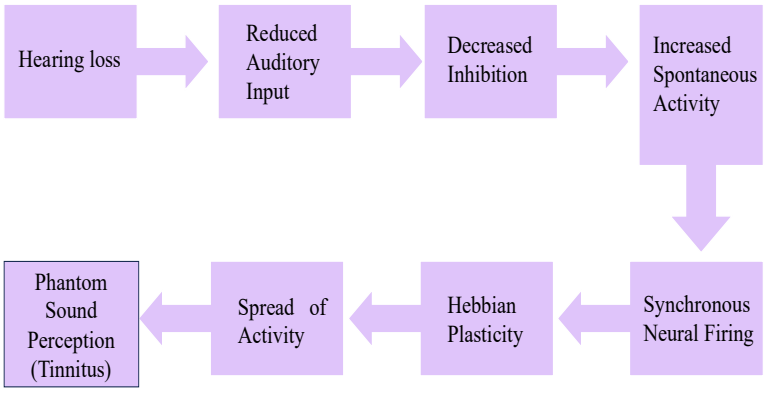


Figure 4. Maladaptive Plasticity Leading to Tinnitus. This flowchart shows the process of neural changes related to maladaptive plasticity in tinnitus. Starting with hearing loss, leading to reduced auditory input to central auditory pathways. Decreasing in intracortical inhibition, resulting in increased spontaneous neural activity. These changes encourage synchronous neural firing, which is further reinforced through Hebbian plasticity. As a result, this synchronous activity spreads across cortical areas, ending in the sensation of phantom sounds (tinnitus).

1.4.4 The Impact of Tinnitus on Quality of Life

Tinnitus can significantly impair physical, psychological, and social well-being. Common consequences include heightened anxiety, depression, insomnia, headaches, and concentration difficulties. The severity of distress varies among individuals and is influenced by cognitive patterns like catastrophic thinking, which are closely linked to personality traits (Swain, 2021). Gabr et al., emphasize the reciprocal relationship between tinnitus and psychological conditions - anxiety and depression can exacerbate tinnitus symptoms while tinnitus can worsen these conditions. Therefore, cognitive and psychological factors are essential considerations in the assessment and management of tinnitus (Gabr et al., 2011).

1.4.5 Evaluation of Tinnitus

Assessment of tinnitus begins with a detailed patient history and otologic examination, which can be performed in a general practice setting. The external auditory canal and tympanic membrane should be inspected for cerumen impaction, perforation, or infection. A cranial nerve exam is essential to identify signs of brainstem pathology or auditory deficits. Auscultation for vascular causes over the neck, mastoid, orbits, and periauricular regions, such as venous tinnitus, which can sometimes be suppressed by ipsilateral jugular vein compression. Audiometric testing is critical, as subjective tinnitus does not reliably correlate with objective sound characteristics. Standard assessments include pure-tone audiometry, speech discrimination, and tympanometry. Imaging is reserved for specific cases: contrast-enhanced CT or MRI is recommended for pulsatile tinnitus to evaluate vascular abnormalities, while gadolinium-enhanced MRI is preferred for non-pulsatile tinnitus. In some cases, both modalities may be necessary to fully assess auditory and adjacent structures (Crummer & Hassan, 2004).

1.4.6 Tinnitus Treatment Over the Years

The clinical management of tinnitus requires first and foremost an accurate differentiation between its subjective and objective forms, as this distinction fundamentally guides subsequent treatment decisions. This diagnostic precision is critical because these two tinnitus types involve distinct pathophysiological mechanisms and therefore demand different therapeutic strategies (Lockwood et al., 2002). Contemporary tinnitus management incorporates a range of evidence-based interventions, each targeting specific aspects of the condition. These includes cognitive

behavioural Therapy (CBT) addresses maladaptive thought patterns and emotional responses to tinnitus. Sound therapy (ST), hearing aids for patients with comorbid hearing loss, music therapy, physical therapies (massage and cervical extension), electrical cochlear stimulation and tinnitus retraining therapy (TRT). TRT is a type of adaptation treatment that operates on the neurophysiological model of tinnitus (Han et al., 2009). It focuses on nonauditory systems, notably the limbic (emotional processing) and autonomic nervous systems (stress response), and is predicated on the premise that tinnitus is an adverse effect of the brain's natural compensating processes (Han et al., 2009).

1.4.6.1 Historical Overview of the Use of Sound in the Treatment of Tinnitus

As the majority of severe tinnitus develop from functional alterations, it should be feasible to correct it with sound therapy, taking into account the plasticity of the brain (Drexler, López-Paullier, et al., 2016). The application of sound-based interventions for tinnitus has undergone substantial transformation throughout the past hundred years. What began as incidental clinical findings and temporary masking techniques has progressed into advanced therapeutic methods designed to induce enduring neurological adaptations (Hoare et al., 2014; Searchfield et al., 2017). This review systematically examines pivotal developments in tinnitus sound therapy, categorizing treatment approaches into passive, active, and intermediate modalities according to their capacity to promote neuroplastic changes, facilitate learning processes, and maintain therapeutic benefits post-treatment.

> *Early 20th Century – Ambient Sounds and Spontaneous Relief*

Early reports revealed that individuals with tinnitus experienced relief when immersed in ambient sounds like wind, flowing water, or rainfall. Though not developed as formal therapeutic interventions, these natural acoustic inputs provided short-term masking effects by diminishing the perceptual disparity between tinnitus and complete silence. In modern terms, such approaches are categorized as passive sound stimulation, as their benefits dissipate once the auditory input stops and they do not facilitate neuroplastic adaptation or perceptual learning mechanisms (Searchfield et al., 2017).

> *1970s–1990s – Structured Masking and Sound Generators*

In 1977, Jack Vernon introduced the concept of therapeutic masking, which utilized white or broadband noise to mask the perception of tinnitus (Vernon, 1977; Vernon et al., 1990). This approach, aimed at providing short-term symptom relief, spurred the development of portable masking devices. As clinical audiology progressed, hearing aids equipped with integrated sound generators became available for patients with hearing loss (Hanley & Davis, 2008). These strategies are considered passive, as their efficacy is contingent upon continuous acoustic stimulation, lacking the capacity to induce long-term neuroplastic changes or sustained auditory learning.

> *1990s –TRT*

Jastreboff and Hazell established a ground-breaking neurophysiological framework for understanding tinnitus, which formed the basis for developing TRT, which integrates auditory stimulation with targeted psychological counselling (Jastreboff & Hazell, 1993, 2004). While the auditory component remains passive, the therapeutic process facilitates habituation through implicit mechanisms, encouraging the gradual reorganization of emotional and perceptual associations. In this context, TRT can be characterized as a hybrid intervention: although sound therapy provides non-interactive input, counselling guides patients toward perceiving tinnitus as a neutral stimulus, fostering adaptive neuroplasticity and sustaining therapeutic gains beyond the cessation of external input.

In the initial formulation of TRT, Jastreboff suggested adjusting the sound stimulus to the "mixing point"—the subtle threshold where external sound starts to blend with tinnitus perception without complete masking (Jastreboff, 1990). In this method, the sound employed is usually is a neutral, nonspecific, broadband noise designed to homogeneously activates the auditory pathways without triggering adverse emotional responses. It is not customized to match the specific acoustic features of the patient’s tinnitus but is instead delivered as a standardized auditory input, making it straightforward to apply in standardized clinical settings.

In subsequent refinements to the therapeutic protocol, Jastreboff introduced a critical adjustment by recommending that the auditory stimulus be set marginally below the mixing point. This approach preserves the perceptibility of tinnitus while diminishing its salience by attenuating the contrast between the internal perception and ambient auditory input (Jastreboff & Hazell, 2004).

This modification is consistent with the conceptual principles underlying CBT, which posit that effective desensitization necessitates prolonged, intentional, and benign exposure to the maladaptive stimulus (Andersson, 2002).

> *2000–2010 – Personalized Interventions and Filtered Music*

With the rise of digital technologies, individualized auditory therapies like notched music have been developed. This method involves selectively removing sound frequencies near the tinnitus pitch from an enjoyable musical composition (Okamoto et al., 2010). Its therapeutic goal is to reshape cortical processing through lateral inhibition, thereby contributing to a more consistent reduction in tinnitus perception. Similarly, interventions such as Neuromonics utilize music embedded with targeted auditory cues to influence emotional states (Searchfield et al., 2017). These approaches are considered active treatments, as they aim to facilitate long-term neuroplastic changes through repeated exposure to tailored auditory input, though the extent of attentional engagement may differ across modalities.

> *2010s and Beyond – Digital Platforms and Stimulation During Sleep*

During the last decade, advancements in mobile and digital technologies have enabled the implementation of customized acoustic treatments during sleep. One such technique involves the use of Individualized Acoustic Recipes (IAR), which replicate the spectral properties of each patient's tinnitus (Pedemonte et al., 2010; Mekanathan, 2024). This modality represents an active intervention strategy targeting synaptic reorganisation and auditory learning processes, with the aim of eliciting objective neuroplastic adaptations that continue beyond the cessation of the stimulation. Concurrently, it employs neuronal remodelling to design therapeutic alterations in pathologically elevated neural synchrony (Desyncra Operating GmbH, Hauptstrasse & Hauptmann, 2018).

Our study falls into the latter group of active interventions. It analyses the responses of patients treated with the Levo digital platform, which provides customized acoustic stimulation during sleep using IAR that mimics each individual's unique tinnitus frequency and loudness profile.

1.4.6.2 Acoustic Stimulation During Sleep Using an IAR

A Uruguayan research group discovered that acoustic stimulation delivered during sleeping, tailored to the individual's frequency and severity experienced by each tinnitus patient, successfully reduced the tinnitus intensity. Acoustic Stimulation during Sleep (SAS) using IAR originated in 1999 and has since developed into a comprehensive tinnitus treatment protocol combining active acoustic stimulation with psychoeducational desensitization. Table 1 contrasts SAS using with traditional STs like TRT.

Table 1. Comparison between SAS (IAR) and traditional ST (TRT)

	ST (TRT)	**IAR (SAS)**
Type of sound	Neutral broadband noise, without customization.	Highly customized sound that mimics the tonal characteristics of the patient's tinnitus.
Stimulation intensity	Below the mixing point: blends with the tinnitus without masking it, reducing contrast.	Just above the tinnitus: aims to activate neuroplastic mechanisms without causing masking.
Sleep/ Wakefulness	Indicated during the day, in a wakeful state, for several hours.	Mainly applied during sleep, allowing prolonged exposure without interfering with daily life.

Advantages of SAS with IAR:

1. Precision Matching through IAR

This innovative approach aims to restore auditory homeostasis by targeting specific impairments in sound processing related to tinnitus. By precisely replicating each patient's unique tinnitus perception, the therapy delivers focused directions to the auditory system and enables the brain to maintain the steadiness of excitation and inhibition, possibly decreasing symptoms of tinnitus. The researchers used a mix of specialized hardware and software, as well as a new sound synthesis technique, to create unique acoustic profiles that precisely replicate every individual's tinnitus perception, that is known as IAR (Drexler, López-Paullier, et al., 2016).

The IAR is generated in the audiologic clinic by a specialized technician through a feedback process four sound templates: pure tones, band noise, white noise, and cricket sound. The last one enables to synthesize a vast type of sounds through the modulation of two parameters that control their wave shapes (Baker et al., 2016; Drexler, Baker, et al., 2016). All the templates can be combined to reach a sound that reproduces frequency and volume qualities of the patient's tinnitus perception. This personalized sound results more effective to undo the maladaptive plasticity than white noise or a masking sound.

2. Optimal Delivery During Sleep

Sound stimulation during sleep is useful as it maximizes treatment duration without disrupting daily activities, takes advantage of reduced sensory competition during sleep and operates below conscious awareness. These benefits may be essential when contrasted to different therapies that use tailored auditory stimulation during the day for less time (Drexler, López-Paullier, et al., 2016). Recent advances in neuroscience have demonstrated that non-invasive acoustic stimulation during slow-wave sleep provides an ideal window for neuroplastic interventions (Ngo et al., 2013). This has opened new avenues for therapeutic applications, including tinnitus, where maladaptive plasticity plays a central role (Shore et al., 2016). The therapy aid in enhancing memory consolidation and synaptic downscaling without disrupting sleep quality, facilitating the reorganization of maladaptive tinnitus-related networks (Pedemonte et al., 2014, 2018; Milinski et al., 2022).

Initial concerns about SAS using an IAR were related to the fear of disrupting sleep architecture, inducing auditory fatigue, exacerbating symptoms, or even causing panic attacks. Theodoroff et al. (2017) showed an example of the avoidance of aggressive acoustic interventions during sleep, stemming from concerns about sleep disruption and potential exacerbation of tinnitus. However, previous studies have shown that nocturnal stimulation with correctly calibrated IAR does not interfere with sleep quality (Pedemonte et al., 2010; Mekanathan, 2024).

3. Precision Stimulation Intensity

Though platforms like Sonus and Levo, patients can precisely adjust their IAR volume to maintain optimal stimulation levels slightly above their tinnitus perception threshold (Drexler, López-Paullier, et al., 2016). This innovative methodology marks a departure from conventional sound

therapy approaches, offering several distinct advantages that align with current neurophysiological understanding.

Unlike traditional sound therapies that often rely on louder masking sounds, the SAS approach employs a more nuanced strategy. By avoiding excessive volume levels that can cause signal compression, the treatment maintains precise frequency targeting tailored to each patient's unique tinnitus profile. This precision promotes gradual desensitization while simultaneously reducing the emotional distress frequently associated with tinnitus perception. The clinical effectiveness of this approach stems from its firm grounding in established neurophysiological principles (Drexler, López-Paullier, et al., 2016). The rationale behind this stimulation protocol involves keeping stimulation near tinnitus threshold enhances neuroplasticity. The use of mild, tinnitus-like sounds promotes signal redundancy without overwhelming the auditory pathways. This careful balance prevents the triggering of defensive auditory system responses while simultaneously facilitating emotional disassociation from the tinnitus percept. As a result, the auditory cortex receives precise sensory input at precisely those frequencies where deprivation-related abnormalities exist (Drexler, López-Paullier, et al., 2016).

Furthermore, for successful therapeutic outcomes, patient’s engagement is essential, as voluntary exposure to the tinnitus-matched sounds forms the foundation of the desensitization process. The maintenance of non-invasive stimulation levels ensures patient comfort and prevents emotional rejection of the therapy. If the sound is too loud, the auditory system—particularly at the level of the cochlear amplifier—tends to compress the signal, ultimately reducing its effectiveness as a neuroplastic modulator. By contrast, the SAS approach’s mild, carefully matched acoustic stimuli allow the brain to naturally recognize redundant neural signals, thereby helping to disassociate tinnitus from threat perception and promote gradual attenuation (Drexler, López-Paullier, et al., 2016).

1.4 Study Aim

The central goal of this investigation is to characterize and evaluate patients' reactions to the sound used in the acoustic stimulation protocol during sleep for the treatment of tinnitus. Looking ahead, our goal is to validate the clinical observation that most patients respond to acoustic stimuli in a positive or neutral manner, thereby challenging the prevailing belief that such stimuli are typically aversive.

Hypothesis 1: (Tolerability Hypothesis)

It is hypothesized that the exposure to the IAR will not elicit a negative or aversive reaction in patients, and that the majority will report a neutral or positive subjective response, indicating tolerability and potential therapeutic acceptability.

Hypothesis 2: (Positive Response Evolution Hypothesis)

It is hypothesized that patients who initially present with a negative response to the IAR sound (displeasure or annoyance) may evolve toward a neutral or relieved response over the course of treatment, as a result of a process of habituation or redefinition of the stimulus. Likewise, it is expected that those who initially respond more negatively (low scores) will show greater improvement over the course of treatment, while those who initially respond positively tend to maintain their favourable perception, with minimal variations. This positive evolution is clinically relevant, as it may promote therapeutic adherence.

Hypothesis 3: (Hypothesis of Worsening Reaction Throughout the Treatment)

It is hypothesized that the subjective experience of the IAR sound may not be stable throughout treatment. Given the long-term nature of the treatment (approximately one year), it is possible that some patients who initially report a positive response may, over time, develop feelings of boredom, lack of motivation, or fatigue, leading to a negative reaction or irritation toward the stimulus. This phenomenon highlights the importance of ongoing clinical monitoring to identify changes in sound perception and adjust therapeutic support accordingly.

2. Methods and Materials

2.1 Recruitment and Screening

Patients were recruited from the Montevideo Tinnitus Center (CTM) following comprehensive diagnostic evaluation and medical assessment. Eligible participants who satisfied the study's requirements signed informed consent documents permitting research use of their data. Only patients who completed the full SAS therapy protocol with complete datasets were included to ensure the integrity and reliability of the analysis.

2.2 Inclusion Criteria

The study included 21 white Uruguayan patients aged 22 to 81years with either unilateral or bilateral subjective idiopathic tinnitus. All participants should have experienced tinnitus for more than 3 months with no upper time limit and competed 8-12 months of SAS therapy.

2.3 Exclusion Criteria

Patients with incomplete data were not considered. Also, patients with either objective or secondary subjective tinnitus were excluded. Patients presenting with profound hearing loss (≥80 dB at ≥3 audiometric frequencies) were excluded from participation. Additionally, individuals who had undergone other forms of tinnitus treatment within the previous 12 months were not considered for inclusion.

For safety reasons, avoiding the generation of auditory damage due to high intensity exposure, patients with tinnitus intensity measure (with SONUS4 device) > 85 dB HTL were excluded.

Moreover, exclusion of individuals who have a diagnosis of sleep disorders not directly related to tinnitus, like sleep apnoea, restless legs syndrome, narcolepsy, parasomnia, and insomnia of causes other than tinnitus. Patients with any psychological disorders were excluded.

2.4 Participants Evaluation

To evaluate eligibility, all participants underwent interviews and clinical assessments conducted by a multidisciplinary team consists of an otolaryngologist, an audiologist, and a psychologist. Diagnostic tests included magnetic resonance imaging (MRI) and blood analyses to determine levels of lipids, thyroid hormones, glucose, urea, electrolytes, and creatinine. Audiological assessments comprised pure-tone audiometry at frequencies of 0.125, 0.25, 1, 2, 3, 4, 6, and 8 kHz, measurements of loudness discomfort levels, speech audiometry, and extended high-frequency audiometry at (8, 10, 12, 14, and 16 kHz). Assessment of otoacoustic emissions using 24 distortion product otoacoustic emissions (DPOAEs) and transient evoked otoacoustic emissions (TEOAEs). The DPOAE protocol utilized three pairs of pure tones per octave spanning the frequency range of 1–6 kHz, whereas TEOAEs were elicited using broadband click stimuli covering frequencies from 1–5 kHz.

2.5 Sound Stimulation

CTM introduces two novel elements the use of an IAR that mimics the patient's tinnitus in the frequency content, and the indication to apply stimulation a threshold slightly above the one of the perceived tinnitus.

Continuo Learning Platform (CLP) IAR, administered at two moments of the therapeutic process (at day 4 and in the end of treatment). The CLP IAR has four sub-indices reaction, control, comprehension and trust.

The CLP IAR Response Index (CLPi IAR) was designed to systematically record this subjective response. It is used to evaluate the patient's emotional reaction when exposed to a therapeutic sound that imitates their own tinnitus by calculating the total score using the formula: (Sub1 x 0.9) + ((Sub2 + Sub3 + Sub4) / 3 x 1) – penalty. CLPi IAR score was normalized from 0-10, where 5 means neutral response to SAS and above 5 indicates a good/ positive response.

SONUS4 is a two-part system developed to treat subjective tinnitus using IAR. It includes:

-Clinician Interface (Back Office): A desktop tool that allows healthcare providers to create personalized IARs tailored to each patient's tinnitus characteristics. It also gathers nightly data on stimulation levels, duration, and usage issues to track treatment progress.

- Patient App (SONUS Player): A mobile app that provides IAR through headphones during sleep. Patients manually adjust the volume each night to slightly surpass their tinnitus loudness, while the frequency settings remain constant

The system supports remote monitoring and long-term tracking of patient engagement and treatment outcomes, in line with evidence-based sound therapy approaches for tinnitus.

2.6 Statistical Analysis

ALL analyses used MATLAB software. Non-parametric tests were selected due to non-normal data distribution. A paired Wilcoxon test (left-tailed) was conducted to evaluate differences between initial and final CLPi IAR scores, with the null hypothesis stating both measurements came from distributions with identical medians, and the alternative suggesting a decrease in scores. (Signrank - Wilcoxon Signed Rank Test - MATLAB, n.d.). The Spearman correlation was selected over Pearson correlation as it evaluates monotonic rather than strictly linear relationships and does not assume normally distributed data, making it more appropriate for our dataset. (Rovetta, n.d.). The correlation measured the relationship between the initial and final reaction and CLPi score of

the 21 patients, between age and the difference between initial and final CLPi score and between the evolution time of tinnitus and the difference between initial and final CLPi score were measured. (Corr - Linear or Rank Correlation - MATLAB, n.d.).

The visualization methods included, a histogram illustrating both the initial and final CLPi scores was generated for all 21 patients (Histogram - Histogram Plot - MATLAB, n.d.). This non-parametric analysis provides insight into potential trends, indicating whether changes in the dependent variable correspond to variations in the independent variable—even when the relationship is not strictly linear. A parallel plot was used to visualize all patient's scores of reactions and CLPi in a single panel. A parallel coordinates plot displays multivariate data from the matrix x, where each data point is shown as a line connecting its values across multiple axes, each representing a different variable (Parallelcoords - Parallel Coordinates Plot - MATLAB, n.d.). Lastly, to have a detailed view of each patient's scores the function of subplot was used (Subplot - Create Axes in Tiled Positions - MATLAB, n.d.).

Power calculations were performed in our comparison with the Wilcoxon test. This allows to determine the statistical power of the actual compares (n=21) as well as the number of patients that would be required to reach a power of 0.8. This approach prioritizes avoiding false positives (5% risk) than missing true differences. The probability of avoiding missing a true difference is the power and the probability of false positives is the p-value. The power = 1-β, where β is the false negative (Sampsizepwr - Sample Size and Power of Test - MATLAB, n.d.).

3. Results

3.1 Hypothesis Testing and Clinical Outcome

The combined analysis of Table 1 and the mean CLPi scores supports our first hypothesis regarding treatment tolerability (patient reaction to the IAR exposure will not be a negative or aversive reaction, but the majority of patients will react neutrally or positively, showing tolerability and potential therapeutic acceptability). The mean initial CLPi is 5.16 indicates predominantly neutral or ambivalent patient reactions to the IAR exposure, while the final mean score of 6.34 demonstrates significant improvement to good response levels (Fig 5). These findings confirm that the majority of patients tolerated the therapy well, with some showing very positive responses.

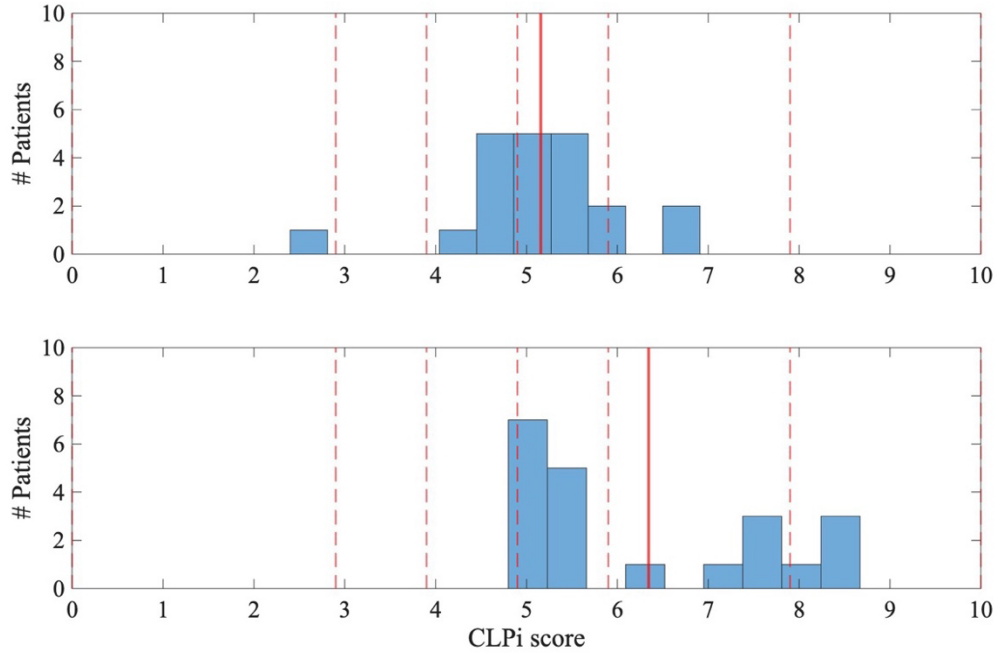


Figure 5. Histogram of the initial and final CLPi scores for all patients. The red continuous line represents the mean of the initial CLPi score (upper panel), and the mean of the final CLPi score (bottom panel). The areas between every two dashed red lines indicate the levels of interpretation of the CLPi score (Table 1).

Table 2. Interpretation of the CLPi score

Total CLPi Score	Level of Interpretation
0.0 – 2.9	Intense resistance to IAR
3.0 – 3.9	Moderate resistance or mild acceptance to IAR
4.0 – 4.9	Risk of negative response
5.0 – 5.9	Neutral or ambivalent response
6.0 – 7.9	Good response to IAR
8.0 – 10.0	Very positive response to IAR

3.2 Differential Treatment Responses

Our second hypothesis, predicting that patients with initial negative responses would show improvement over time, patients were grouped based on their baseline scores either >4.9 or <4.9. Among the 7 patients who started with poor CLPi scores (<4.9), we observed statistically

significant improvement ($p < 0.05$) as illustrated in Figure 6b. Power calculations revealed high statistical power (0.94) for both reaction and CLPi scores, with sample size indicating 32-33 patients needed for 0.99 power.

(a)

(b)

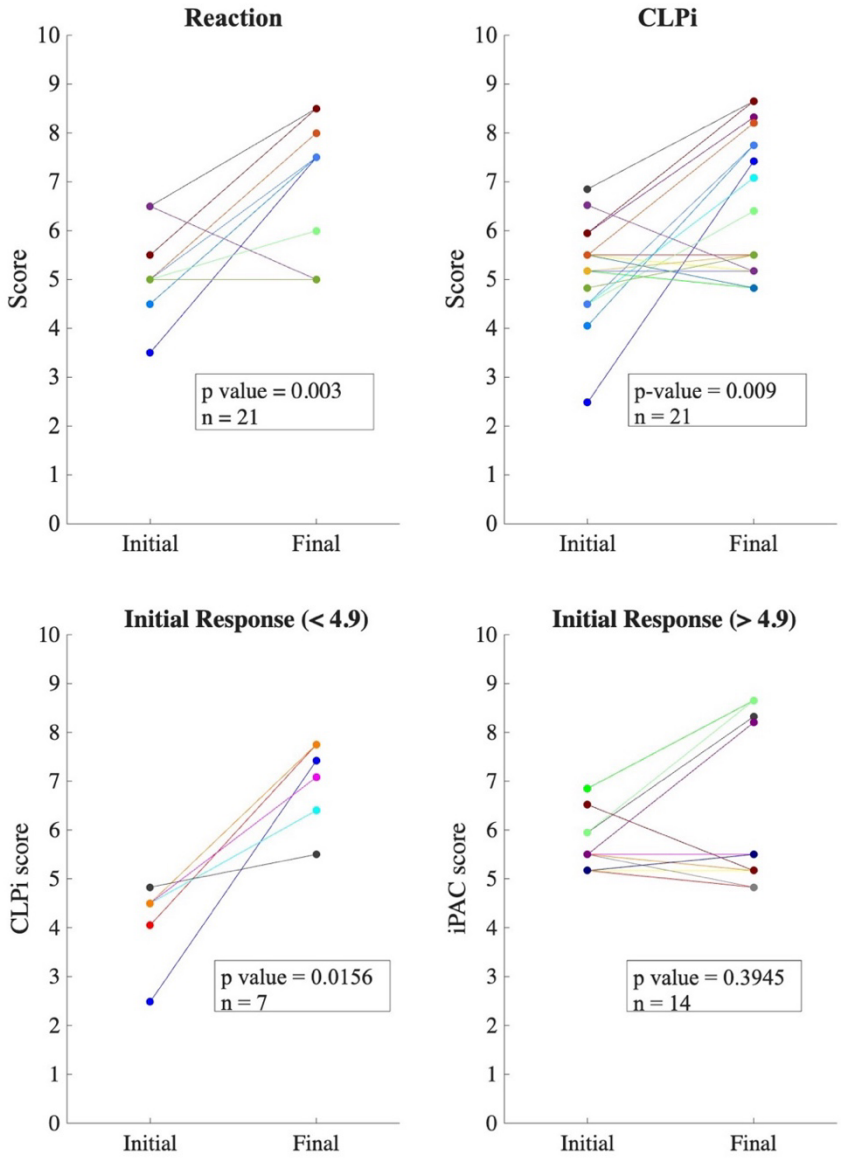
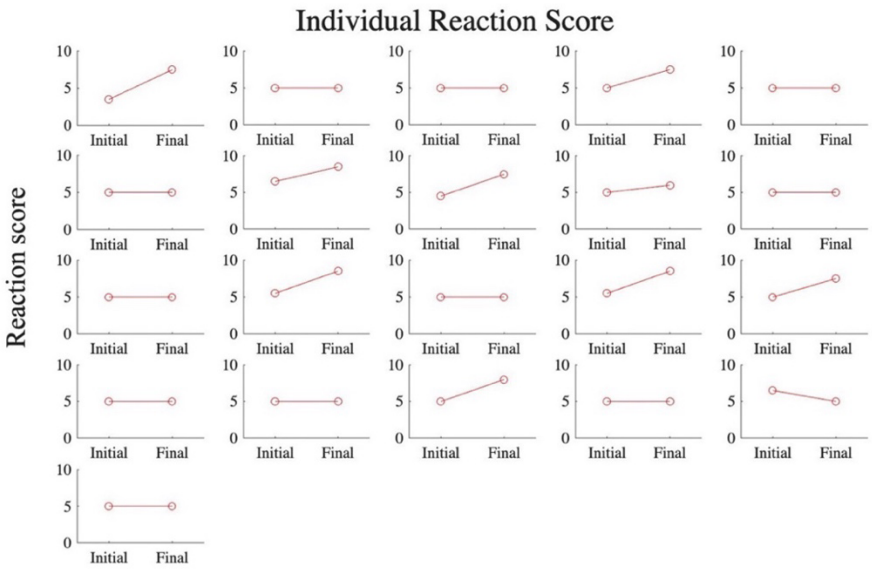


Figure 6. Parallel plot showing patient's scores at the beginning and ending of the treatment with SAS IAR. 6a. Shows patient's reaction (left panel) and CLPi scores (right panel) at the start and end of the treatment. Each pair of dots linked with a line represents a patient. 6b. Initial and final CLPi scores separated into cases based on initial score, with CLPi < 4.9 (left panel) and CLPi > 4.9 (right panel). Each pair of dots linked with a line represents a patient. The calculated p-values are found in the corresponding panels.

The parallel plots allow for a rapid and accurate visual representation of all patients looking at a single panel. However, in some cases the dots can superimpose because there can be two or more patients with the same initial and final values. To overcome this issue, we appealed to an alternative representation using a multi-panel figure in which each patient is plotted in a single panel (Fig 7). This type of representation avoids the problem mentioned above at the cost of increasing complexity.

(a)



(b)

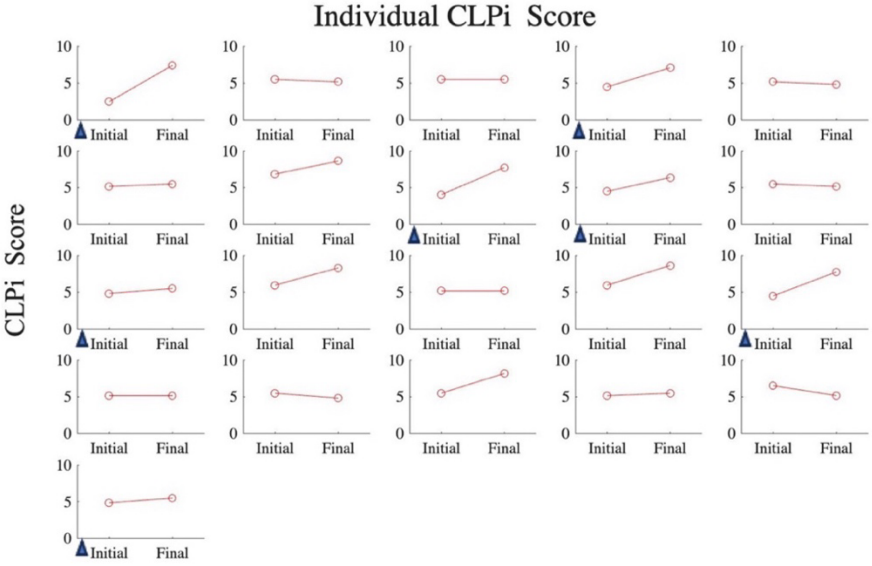


Figure 7. Individual parallel plots for reaction scores (a) and CLPi scores (b). 7a shows each patient's reaction scores both initially and finally (p-value = 0.003). 7b shows the CLPi scores in each patient (p-value = 0.009). patients that started initially with < 4.9 score are marked with (▲).

The parallel plot (Fig 6b) and individual patient subplots (Fig 7) reveal significant improvement in patients with initial CLPi score < 4.9, despite the fact only 7 patients fell in this category. In the remaining 14 patients with initial CLPi > 4.9 no significant differences were found. Moreover, no patient exhibited worsening scores regardless of baseline status. These findings confirm the second part of our hypothesis (those who had low initial response will show greater improvement, meanwhile those who started positively tend to maintain their response, with minimal variations) regarding differential improvement patterns while rejecting the possibility of treatment-related worsening. It also reveals that the significant differences found in Fig 6a were created mainly by the patients with poorer initial score. Furthermore, these findings are clinically relevant, as it may help patients adhere better to therapies.

A Spearman correlation between the initial CLPi and the difference between the final and initial CLPi was calculated. (Fig 8)

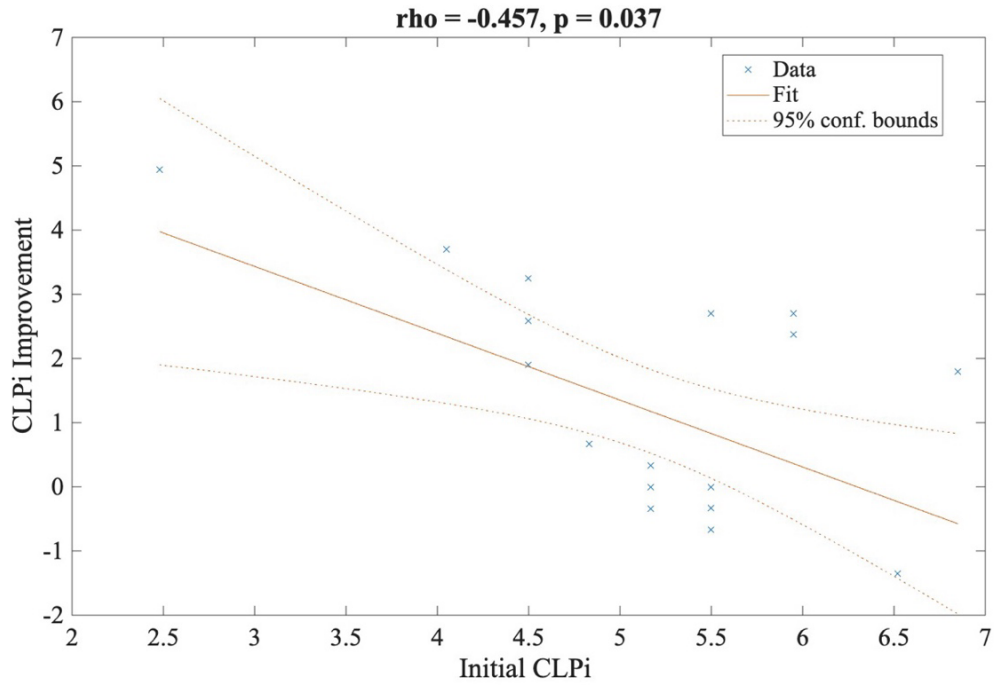


Figure 8. Correlation between initial CLPi scores and the CLPi improvement (difference between final and initial CLPi scores). The scatter plot (crosses) shows the relationship between patients' initial and difference of CLPi scores. A linear fitting to the points is represented with a red line with 95% confidence intervals (dotted lines). The vertical dashed line indicates the score of 4.9 (upper boundary of the risk of negative response category).

This figure indicates that the patients that started with poorer CLPi score improved more. The Spearman test is significant ($p = 0.037$), with an effect size that can be classified as medium in the context of biological studies ($\rho = 0.457$). This result is in line with the results shown in Fig. 6b, in the sense that significant improvement occurred only in patients with initial CLPi < 4.9. In this case no threshold was needed to separate the groups because the correlation analysis provides a continuous evaluation of the existing decreasing trend. This is another evidence that the patients with poor initial CLPi improved better, supporting the second hypothesis.

3.3 Demographic and Temporal Factors

3.3.1 Age Effect

A correlation analysis was conducted to examine the relationship between patient age and the difference in CLPi scores (final CLPi - initial CLPi). No significant correlation was found ($p = 0.393$), despite a negative trend in the slope value (-0.197). There exists the possibility that treatment effectiveness could decrease with age, and indeed a sight decreasing trend was found, but far from the significance level. We can conclude that age is not a predictor of the treatment effect.

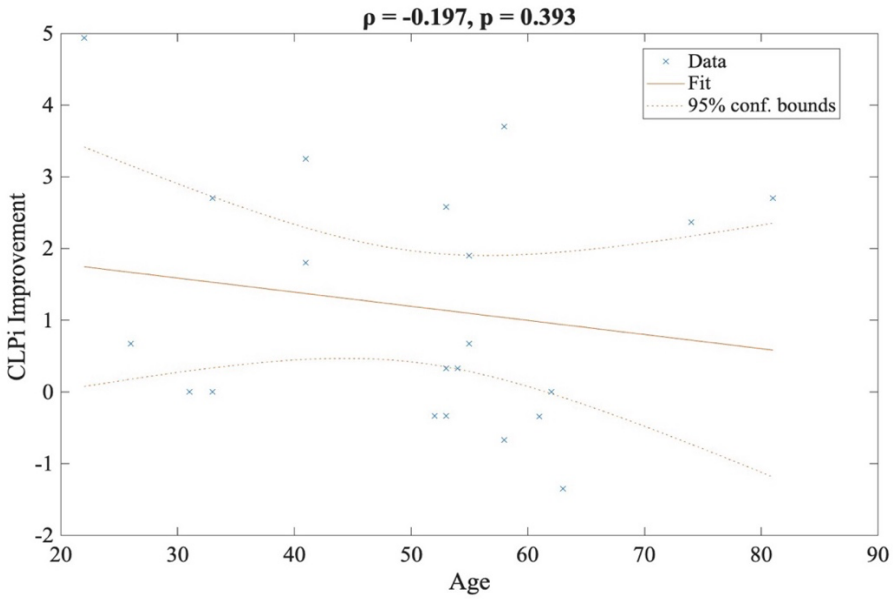
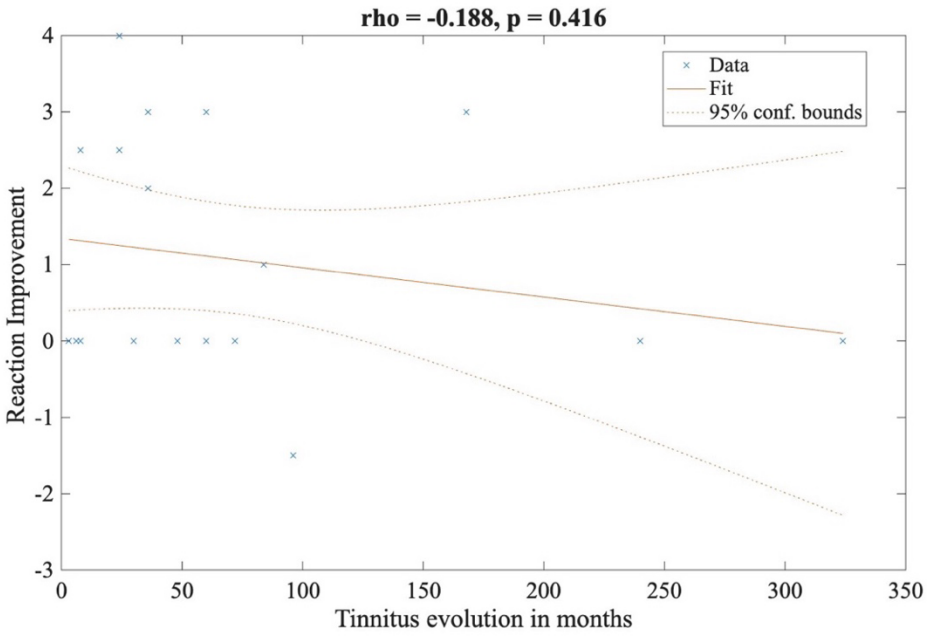


Figure 9. Correlation between age and CLPi improvement following SAS treatment with IAR. The scatter plot illustrates the relationship between patient age and the difference in CLPi scores (final - initial). The correlation coefficient was ρ = –0.2 with a p-value of 0.393, showing a weak negative association that was not statistically significant.

3.3.2 Tinnitus Duration

At last, testing if the the tinnitus evolution time affect the effectiveness of the treatment, a correlation analysis between the evolution time (in months) and the difference of the reaction scores and the CLPi scores were performed. The result shows that the duration of tinnitus does not significantly affect changes in reaction or CLPi scores after treatment.

(a)



(b)

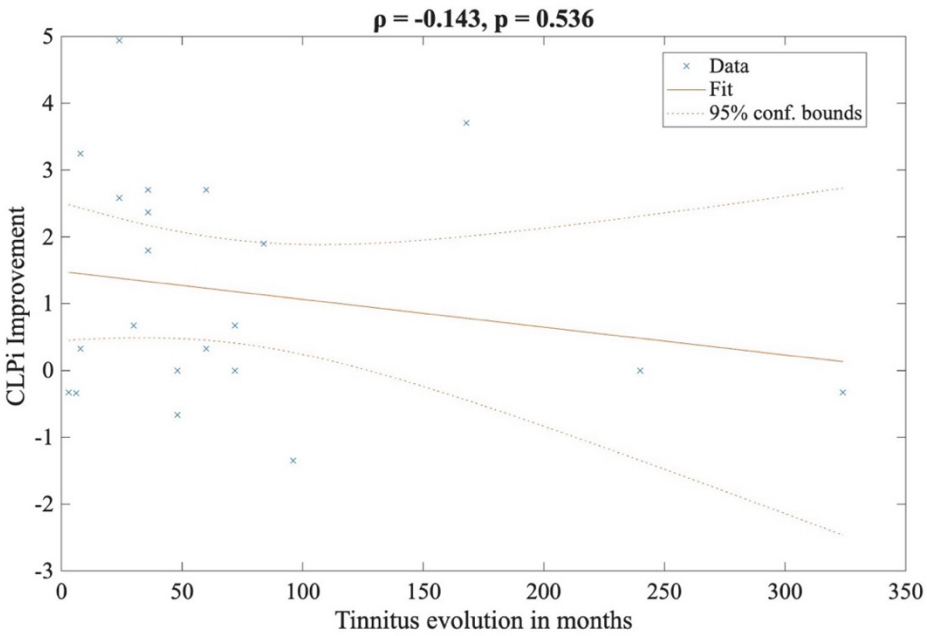


Figure 10. Correlation between tinnitus duration and CLPi improvement following SAS IAR treatment. 10a. shows the relationship between tinnitus evolution time (in months) and the reaction improvement (final reaction score – initial reaction score). A weak negative correlation (ρ -0.19) with a p-value of 0.42, indicate no significant association. 10b. illustrates the correlation between tinnitus evolution time and CLPi improvment (final CLPi score – initial CLPi score), with a weak negative correlation (ρ -0.14) and a p-value of 0.54, also showing no significant relationship.

4. Discussion

The development of SAS IAR represents a significant advancement in tinnitus treatment, addressing long-standing concerns about tolerability and efficacy of sound-based therapies. In this study we investigated the patient's response to acoustic stimulation protocol during sleep as a treatment for tinnitus. Our findings demonstrate that SAS IAR not only well-tolerated but also show the effectiveness of this novel intervention, while providing new insights into the neurophysiological mechanisms underlying tinnitus desensitisation and its modulation through targeted acoustic therapy.

4.1 Historical Context and Neurophysiological Rationale for SAS IAR

Early reservations about SAS using IAR stemmed from concerns about disrupting sleep architecture, exacerbating tinnitus symptoms, or inducing auditory fatigue or panic attacks. These concerns were compounded by the limitations of traditional sound therapies, which often relied on generic noise generators or standardized sound protocols (H. Wang et al., 2020) -approaches that lacked personalisation and demonstrated inconsistent results. Together with the absence of robust clinical trials, these factors fostered cautious clinical adoption.

The emergence of precision medicine in tinnitus treatment marked a pivotal shift from "one size fits all" approaches to individualised strategies (Pedemonte et al., 2010; Searchfield et al., 2017). This evolution is embodied in SAS IAR, which integrates two key innovations: sleep-stage focused stimulation (capitalizing on enhanced neuroplasticity during slow-wave sleep (SWS)) and personalized acoustic recipes tailored to each patient's tinnitus features (Searchfield et al., 2017). The individualized component builds on evidence that effective tinnitus compensation requires stimulus parameters matched to the patient's unique characteristics (Schaette et al., 2010; H. Wang et al., 2020).

Clinical evidence strongly supports this personalised approach. A randomized crossover trial by Mahboubi et al. (2017) demonstrated that customized ST led to significant reduction in tinnitus loudness and anxiety, while non-customised approaches showed only marginal benefits. These clinical outcomes reflect underlying neurophysiological mechanisms: personalisation enhances cortical reorganization and disrupts maladaptive neural synchrony (H. Wang et al., 2020). Moreover, customized therapy improves patient engagement and adherence, as individuals

perceive greater relevance in treatments tailored to their specific tinnitus profile (Searchfield et al., 2017).

The effectiveness of personalized approaches aligns with the predominant model of tinnitus as a disorder of central auditory processing, characterized by increased spontaneous activation, reduced inhibition, and pathological neuronal synchrony in the auditory cortex (Henry et al., 2014). The IAR approach addresses these mechanisms directly: by delivering sounds that closely resemble the patient's tinnitus perception, it facilitates tonotopic reorganization and restores the balance between excitation and inhibition (Drexler, López-Paullier, et al., 2016). This process also promotes progressive habituation by guiding the brain to reclassify the tinnitus percept from a threatening stimulus to a neutral one (Jastreboff & Hazell, 2004). Unlike conventional masking therapies that aim to obscure the tinnitus signal, this approach fosters enduring neuroplastic changes through targeted auditory engagement.

The integration of sleep-stage stimulation adds another therapeutic dimension. The brain's enhanced plasticity during unconscious states, particularly SWS, creates unique opportunities for intervention (Ngo et al., 2013). By delivering IAR during SWS – a phase critical for synaptic refinement and memory consolidation– the therapy enables the brain to process stimuli without the conscious interference, fostering more profound and efficient neural reorganization (Pedemonte et al., 2010). This nocturnal approach offers several advantages: it ensures consistent delivery without requiring active patient participation (Mekanathan, 2024), reduces the likelihood of auditory fatigue or annoyance (Searchfield et al., 2017), and minimizes interference with daytime activities.

The scientific rationale for sleep-based stimulation is robust. Research shows that auditory cues presented during sleep can influence cortical excitability and drive neuroplastic adaptations (Milinski et al., 2022). These findings align with the framework of targeted memory reactivation (TMR), where sensory stimuli reinforce specific neural pathways during sleep cycles (Shore et al., 2016). Together, these mechanisms explain why applying the IAR during sleep represents not just a convenient delivery method, but a biologically optimized approach to tinnitus therapy.

4.1.1 Clinical Considerations on the Use of Tinnitus Mimics

The clinical use of sounds that replicate the acoustic profile of a patient's tinnitus has garnered significant attention, primarily due to concerns surrounding treatment acceptability, emotional

impact, and the potential for aversive reactions. During the initial medical consultation or preliminary informational sessions, patients often express well-reasoned concerns about this therapeutic approach. These are typically framed in questions such as: “If my tinnitus already causes significant discomfort, why would I intentionally listen to a sound that imitates it?”, “Will I be able to endure it nightly without experiencing increased discomfort?”, or “Given the prolonged nature of the treatment, is there a possibility that, even if it’s tolerable at first, it may become increasingly irritating over time?”

Although these concerns are not based on direct exposure to acoustic stimulation, they reflect a rational and clinically relevant patient perspective. This rationale prompted the need for a systematic investigation into the subjective experience of IAR sounds and their potential progression throughout the treatment course. To address this, the CLPi “Response to IAR” index was developed as an integrated, automated data collection tool within the treatment software.

Compounding the issue is a notable epidemiological observation: multiple studies have identified a substantial incidence of hyperacusis, misophonia, and algiacusis among individuals with tinnitus—disorders characterized by markedly reduced auditory tolerance thresholds. Estimates suggest that up to 40% of tinnitus patients experience hyperacusis (Pienkowski, 2021), underscoring the imperative to develop meticulously tailored acoustic stimuli that minimize the risk of aggravating sensory or emotional discomfort.

Nonetheless, such objections appear incongruent with clinical observations from SAS protocols that utilize personalized tinnitus-mimicking sounds, particularly within platforms like Sonus and Levo. Contrary to anticipated rejection, many patients report experiences of relief or neutrality, even when the auditory stimulus closely reflects their tinnitus features. These consistent clinical patterns highlighted the necessity of quantifying the prevalence and evolution of discomfort and/or aversion responses to IAR, ultimately leading to the development of an automated metric within the Sonus platform—namely, the CLPi “IAR Response.”

4.2 Result Analysis

The results demonstrate:

a. The increase in the mean CLPi scores from 5.16 initially to 6.34 post treatment, proves that patient’s response shifted from a neutral or ambivalent response to IAR to a good or sometimes a very positive response.

b. A statistically significant improvement in patient CLPi scores over the course of SAS IAR treatment (p-value < 0.05). Combining with the increased mean, the tolerability hypothesis can be validated, suggesting that IAR is not only well-tolerated but also tends to show improvement throughout the treatment.
c. Clinical data show that the length of exposure to the treatment does not negatively impact how patients react to the therapeutic sound that mimics their tinnitus. This finding is particularly relevant, as one could hypothesize that, given the prolonged stimulation protocol—lasting up to a year—some patients might develop fatigue, boredom, or even irritation when faced with the repeated stimulus. However, the evidence collected does not support this concern: most patients do not worsen their tolerance to the sound over the course of the process, suggesting that familiarity with the stimulus does not increase aversion.

The parallel plots (Fig 6 and 7) visually confirm these improvements across all patients, regardless of baseline severity. Figure 8 proves that patients who started with low initial score (< 4.9) improved more than those who started with high score (> 4.9). This is due the process of desensitization that provides patients with poor initial reaction with more room to improve. The subpopulation of patients with a good start did not show statistical difference.

Desensitisation refers to the process of gradually reducing the maladaptive neuroplasticity of tinnitus signals through repeated, controlled exposure to IAR. This process leverages habituation mechanisms (diminished response to a persistent stimulus) and promotes reorganization of auditory and limbic pathways to reduce tinnitus-related distress (Roberts, 2018). Sleep-based acoustic stimulation with IAR enhances desensitization by targeting the brain's natural neuroplasticity mainly during slow-wave sleep, facilitating subconscious adaptation without conscious frustration.

Based on the results the power calculation was 0.94, meaning that our data has 94% chance of avoiding false negatives, in other words it has 6% chance of missing a real effect (false negative of beta error). This risk of false positives, represented by the p value, is much lower (see panels in Figures 6,7 and 8).

The results show that most patients perceive the therapeutic sound that mimics their tinnitus as neutral or even soothing, contradicting the preconception that such a stimulus would be inherently annoying. In cases where a response of displeasure or annoyance is initially observed, it tends to diminish over the course of treatment, suggesting a process of progressive habituation.

Furthermore, patients who initially show a positive subjective response to the sound do not show any deterioration in their tolerance over the course of the year of treatment.

4.3 Age, Tinnitus Evolution Time and Treatment Outcome

We found an absence of significant correlations between patient's response to IAR and either patient age ($\rho = -0.2$, $p = 0.393$) or tinnitus evolution time ($\rho = -0.14$, $p = 0.54$). While it is well-established that neuroplasticity tends to decline with age (Marzola et al., 2023) and that longer tinnitus duration can be associated with more entrenched maladaptive changes, these factors did not predict the patient's response to IAR in this study. This suggests that maladaptive plasticity is not a limiting factor for the patient's response to IAR.

Similarly, the lack of association with tinnitus duration implies that even long-established maladaptive patterns remain positively responsive to IAR. This finding has important clinical implications, suggesting that patients should not be excluded from treatment based on symptom chronicity.

These findings have several important usages in clinical practice. The lack of age or evolution time-related effects suggests that SAS IAR can be used in a wide range of patients, including those with chronic or age-related tinnitus. The success of the therapy hinges on the precise replication of the patient's tinnitus percept, highlighting the importance of individualised treatment. Clinicians can reassure patients that initial scepticism or neutral reactions do not preclude therapeutic benefit. In addition, the use of mobile technology and remote monitoring makes this type of therapy more accessible and easier to integrate into daily life.

4.4 Limitations

While the results are promising, several limitations must be acknowledged. The sample size was relatively small (n=21). Also, all of the 21 patients were from the same ethnicity (Uruguay), limiting the generalizability. Future research should include randomized controlled trials with larger, more diverse populations to confirm these findings. Additionally, objective neurophysiological measures (e.g., EEG, evoked auditory potentials, fMRI) should be incorporated to directly assess changes in cortical activity and validate the proposed mechanisms.

4.5 Clinical Implications and Future Directions

The results of this study affirm SAS-IAR as a promising and well-tolerated therapeutic approach for individuals with chronic tinnitus across varied demographics. Specifically:

- High tolerability of the auditory stimulus promotes sustained engagement, which is essential for the success of prolonged therapeutic regimens.
- The observed shift from neutral or negative perceptions toward positive responses points to a robust habituation process with potential for long-term maintenance.
- Broad Applicability, the absence of significant associations between IAR response and factors such as patient age or tinnitus duration expands the applicability of SAS-IAR treatment, even among those with long-standing or late-onset symptoms.
- Personalisation, the IAR is customized to each patient's tinnitus features, ensuring precise targeting of maladaptive neural activity.
- Convenience, administration during sleep minimizes disruption to daily life and enhances adherence.

Looking ahead, several key directions are proposed to enhance the evidence base and optimize therapeutic efficacy:

- Implementing controlled trials with expanded participant cohorts drawn from diverse sociocultural populations to strengthen generalizability.
- Integrating neurophysiological tools such as EEG or fMRI to elucidate the underlying mechanisms of auditory neuroplasticity with greater precision.
- Assessing the durability of therapeutic outcomes following the cessation of treatment to determine long-term efficacy.
- Developing and embedding adaptive algorithms capable of dynamically modulating IAR parameters in real time, complemented by objective biomarkers to monitor and personalize treatment response.

5. Conclusion

This study demonstrates the tolerability and positive subjective effects of sleep-based administration of an Individualized Acoustic Recipe (IAR) designed to match patients' tinnitus profiles. Contrary to initial concerns, most participants perceived the auditory stimulus as neutral or even calming from the outset, while those who experienced initial discomfort tended to improve over time. Notably, individuals who responded favourably early in treatment maintained this positive perception throughout the intervention.

These findings highlight the importance of neutral or positive auditory perception in promoting adherence—patients are more likely to continue treatment when the stimulus is not aversive. Given the year-long therapeutic protocol, sustained motivation and compliance are critical for success. The observed improvement among initially non-tolerant patients further supports IAR's viability across different perceptual thresholds.

Importantly, this positive response was consistent across age groups and tinnitus duration, suggesting that subjective perception of IAR does not limit its therapeutic application. No clinical subgroups were identified in which the intervention was contraindicated, reinforcing its suitability even for older patients and those with long-term tinnitus.

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