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*	Clinical data provided by "Montevideo Tinnitus Center" personnel, who also co-supervised the essay.
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)	Work in Computational Neuroscience to analyze the clinical data with Matlab.
Data analysis	Thulasy analyzed the clinical results independently with Matlab after instructions provided. She interpreted the results in chats with supervisors.
Write-up	Thulasy wrote the text, which was corrected by the supervisors.
Production of submission including figures	Thulasy produced the figures independently with the Matlab codes provided by the supervisors.
Problems encountered if any	N/A
Any other comments/ contributions not listed	Thulasy showed initiative and critical thinking and took control of the final sequence of the essay.
Supervisor has seen the final draft of the dissertation – if no, please provide an explanation	Yes

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Supervisor Signature:  Date: 01/08/2024

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Evaluating the Impact of Tinnitus Treatment with Acoustic Stimulation During Sleep-on-Sleep Quality

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Abstract

Subjective idiopathic tinnitus (SIT) is a perception of sound present without physical noise or an apparent cause, making it challenging to diagnose and treat. SIT can vary in pitch and intensity, and its persistence can lead to significant distress, sleep problems, and impairment of daily functions. This study aimed to investigate the effectiveness of acoustic stimulation treatment administered during sleep regarding volume reduction and its correlation with sleep quality and psychometric variables. The study involved 23 subjective idiopathic tinnitus patients who underwent acoustic stimulation over a defined period. Pre- and post-treatment assessments were performed, including tinnitus volume change (dB) and several psychometric evaluations: Tinnitus Handicap Inventory (THI), Tinnitus Reaction Questionnaire (TRQ), Tinnitus Functional Index (TFI), and Insomnia Severity Index (ISI). We found a reduction in tinnitus volume, an improvement in sleep quality and an improvement in all psychometric evaluations after the treatment. Improvement of sleep maintenance and early morning awakening showed a significant correlation with tinnitus volume reduction. In a sub-population of patients who had insomnia at the start of the treatment, the magnitude of these linear dependences was increased in comparison with the total population. The correlations were non-significant in patients without insomnia. Our results showed that nocturnal acoustic stimulation improved tinnitus symptoms (volume reduction), sleep quality and general well-being of the patients. We found a significant correlation between sleep maintenance and volume reduction in insomniac patients.

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I would like to express my sincere gratitude to Dr. Alberto Capurro, Dr. Daniel Drexler and BSc. Verónica Méndez for their unwavering support and encouragement throughout this study. Their valuable insights and assistance were instrumental in shaping my ideas and overcoming challenges. I am also thankful to the Centro Montevideo Clinic team for providing access to the trail and data.

Contents

Abbreviations

SIT: Subjective Idiopathic Tinnitus

IC: The inferior colliculus

CF: Characteristic frequencies

OHC: Outer hair cells

DCN: Dorsal cochlear nucleus

THI: Tinnitus Handicap Inventory

AAS: Active Acoustic Stimulation

DPOAE: Distortion product otoacoustic emissions

TEOAEs: Transient evoked otoacoustic emissions

TRQ: Tinnitus Reaction Questionnaire

TFI: Tinnitus Functional Index

ISI: Insomnia Severity Index

SPL: Sound pressure level

TM: Tinnitus match

NS: Noise stimulus

BSG: Bedside sound generator

NRS: Numeric rating scale

Figures:

Tables:

1. Introduction

1.1 The Overview of the Auditory System

The auditory system is responsible for perceiving and interpreting sounds within the environment. This organ system comprises peripheral and central components, each playing a crucial role in detecting, transmitting and processing auditory information (Peterson et al., 2023).

1.1.1 Sound

Sound is the physical stimulus responsible for hearing. It includes mechanical disturbances in the medium, particularly pressure waves, in our environment from distant sources. Humans' auditory range at birth is within the 20 to 20,000 Hz range (Hester, 2005, Peterson et al., 2023).

1.1.2 The Peripheral Receptor

The peripheral receptor of the ear comprises three main structures:

a) The external ear includes the auricle and the external auditory canal (Fig 1), which funnel sound waves towards the eardrum. This structure selectively amplifies frequencies important for intraspecies communication.
b) The middle ear is situated between the eardrum and the oval window of the cochlea (Fig 1). It contains three ossicles, the malleus, incus, and stapes, that convert eardrum vibrations into waves in the inner ear's fluid and membranes (Fig 1). The tympanic cavity, enclosed by the tympanic part of the temporal bone, connects to the nasopharynx via the auditory (Eustachian) tube, which equalises pressure between the middle ear and throat. The primary role of the middle ear is to transfer and amplify sound energy from air to the fluid-membrane waves within the cochlea.
c) The inner ear, located deep within the temporal bone, is crucial for hearing and balance. It contains the bony labyrinth, which houses the cochlea (responsible for hearing) and the vestibular system (responsible for balance) (Fig 1) (Kandel et al., 2013).

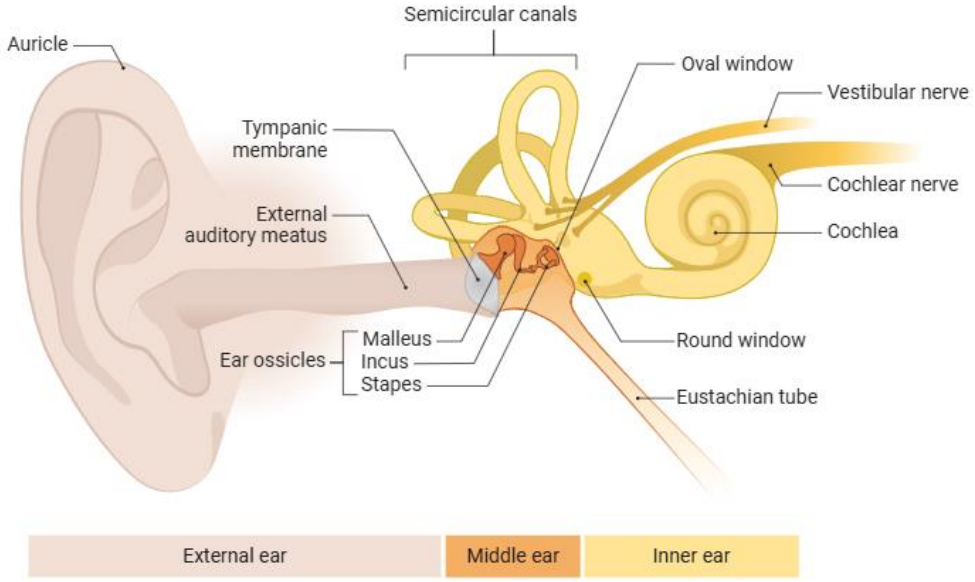

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Figure 1: Structural Anatomy of the Human Peripheral Auditory System. The outer ear comprises the pinna and the external ear canal, separated from the middle ear by the tympanic membrane. The middle ear contains the three ossicles: malleus, incus, and stapes. The inner ear includes the cochlea for hearing and the vestibular system for balance, connected to the brainstem by nerve fibers via the eighth cranial nerve. Ventilation of the middle ear is facilitated by the Eustachian tube.

1.1.3 The Cochlea

The cochlea is embedded in the temporal bone and is a fluid-filled, spiral-shaped structure located in the inner ear, essential for the process of auditory transduction. It is responsible for converting sound waves into electrical impulses that the brain can interpret as distinct sound frequencies. This process begins when sound waves enter the ear canal, causing vibrations in the tympanic membrane and in the ossicles of the middle ear. These vibrations are transferred to the oval window and into the fluid-filled cochlea. Within the cochlea, the vibrations travel through the scala vestibuli and scala tympani (Fig 2), creating waves in the perilymph. These waves then propagate through the endolymph in the cochlear duct, stimulating the hair cells in the organ of Corti (Fig 2). The mechanical stimulation of these hair cells results in the opening of potassium channels, leading to depolarization and the generation of electrical impulses that are transmitted to the brain via the vestibulocochlear nerve (CN VIII). This intricate process enables the perception of a wide range of sound frequencies, where different frequencies stimulate specific areas along its spiral (Casale et al., 2023). The cochlea exhibits

variability in both size and shape, with the length of the cochlear duct ranging from 30.8 to 43.2 mm and the number of turns also varying to a lesser extent (Koch et al., 2017).

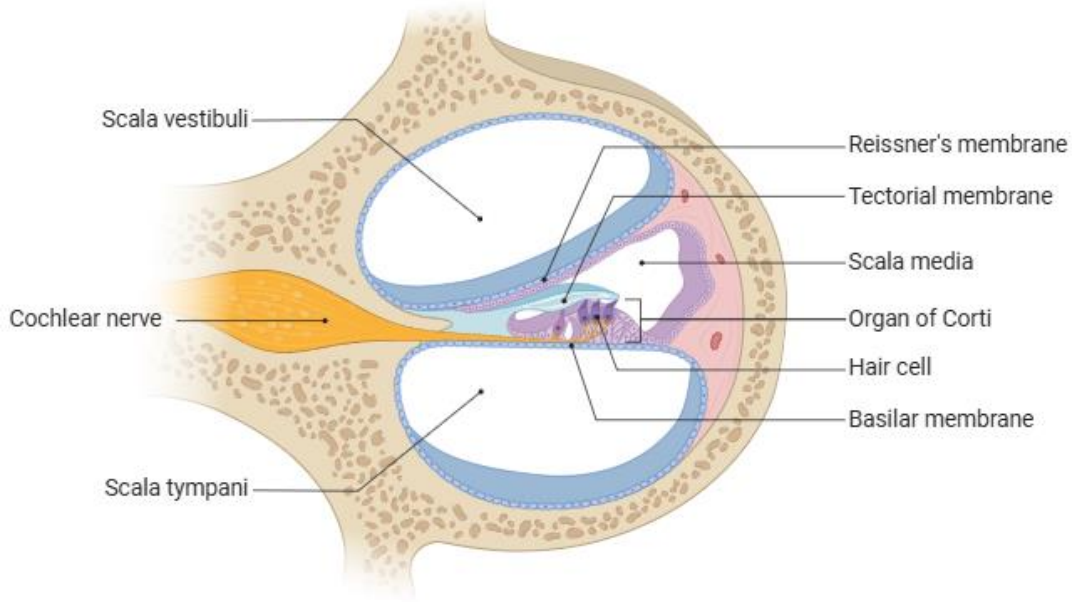

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Figure 2: Cross-Section of the Cochlea in the Inner Ear. Detailing the scala vestibuli, scala media, and scala tympani, each filled with fluid essential for transmitting sound waves. Key structures include Reissner's membrane, separating the scala vestibuli from the scala media, and the basilar membrane, which supports the Organ of Corti. The tectorial membrane overlays the hair cells within the Organ of Corti, the sensory receptors that transduce mechanical vibrations into electrical signals. These signals are relayed to the brain via the cochlear nerve, facilitating the process of hearing.

1.1.4 The Organ of Corti

The organ of the Corti is a vital structure within the cochlea of the inner ear, responsible for converting sound waves into neural signals. Positioned on the basilar membrane, it consists of mechanosensory hair cells surrounded by supporting cells. Inner hair cells, aligned in a single row, serve as the primary sensory receptors, transmitting auditory information to the brain through the auditory nerve. Outer hair cells, organised in three rows, amplify the movements of the basilar membrane through contractions of a protein called prestin, located in its cytoplasm. Prestin forms a network that shortens the length of the cell in response to changes in voltage generated by the entry of potassium ions. This mechanical feedback modulates the responsiveness and tuning of inner hair cells. Sound waves entering the

cochlea cause vibrations in the basilar membrane, which in turn move the hair cells' stereocilia, initiating a cascade of events involving potassium ion influx, depolarization, and neurotransmitter (glutamate) release. This process generates electrical signals that travel along the auditory nerve to the brain, where they are interpreted as sound. The organ of Corti's intricate architecture and functional specialisation enables precise frequency discrimination across the cochlear length, contributing to our ability to perceive a wide range of auditory frequencies (White et al., 2023).

1.1.5 Tonotopic Coding Through Labelled Lines at the Basilar Membrane

The cochlea's outer and inner hair cells are arranged tonotopically, each responding to specific sound frequencies based on their position in the cochlear spiral. This organisation activates particular auditory nerve fibers, creating a labelled line code. Thus, distinct frequencies trigger action potentials in specific nerve fibers, enabling precise sound frequency detection and neural coding (Kandel et al, 2013).

1.1.6 Central Auditory System

The auditory system consists of integrated afferent and efferent pathways that work together to process and modulate sound signals from the environment to the brain and back to the peripheral hearing structures (Burguetti et al., 2008).

Afferent Pathway

The afferent auditory pathway begins with auditory information from the cochlea travelling via the auditory nerve to the cochlear nucleus. From there, signals mostly cross to the contralateral superior olivary complex, then ascend through the lateral lemniscus to the inferior colliculus and the medial geniculate nucleus. Finally, the information reaches the auditory cortex in the temporal lobe for perception. This pathway processes sound properties such as pitch, loudness, and localisation, utilising both ipsilateral and contralateral information at each relay point. Parallel descending pathways from the cortex modulate and refine auditory processing through feedback mechanisms (Peterson et al., 2023; Hawkins, 2024).

Efferent Pathway

The efferent system in the auditory pathway comprises neuronal pathways from the central nervous system to the peripheral hearing system, influencing auditory processing.

Structurally, it includes the rostral part (corticothalamic and corticocollicular pathways) and the caudal part (olivocochlear system). The primary function of the auditory efferent system is to modulate sensory input by inhibiting signals at lower levels, thus enhancing auditory processing, particularly in challenging listening conditions. This system improves hearing accuracy, helps in auditory attention, and modulates auditory signals based on relevance, learned behaviours, and emotional state. It achieves this through interconnected descending circuits involving the auditory cortex and other brain regions (Lotfi et al., 2019).

1.2 Tinnitus

Tinnitus is the perception of persistent or intermittent auditory sensations without external acoustic stimuli (Marker, 2021). Approximately 7.1 million adults in the UK, which accounts for around 13% of the adult population, suffer from persistent tinnitus. While tinnitus is more common as people age, it can also affect individuals of any age, including children, and does not show a significant difference in occurrence between men and women (NICE, 2022). Estimating the entire EU28 population, around 65 million adults are affected by tinnitus, with 26 million finding it bothersome and 4 million experiencing severe symptoms (Biswas et al., 2021). About 10% of US adults, totalling over 25 million, experience tinnitus, with 5 million facing chronic challenges and 2 million experiencing significant debilitation (American Tinnitus Association, 2024).

1.2.1 Objective Tinnitus Vs Subjective Tinnitus

Objective tinnitus is an uncommon condition where the tinnitus is caused by mechanical sounds produced within the body (Lockwood et al., 2002). Subjective tinnitus is the perception of sound without any auditory stimulus and is audible to the patient only (Cesarani et al., 2002). Subjective tinnitus has many potential causes, but only 3-4% of cases are linked to identifiable pathologies such as multiple sclerosis, brain tumours, high blood pressure, metabolic disorders, neurovascular conflicts, ear wax plugs and middle ear pathology. The remaining 96-97% of cases, where no specific cause is found, are classified as SIT (Atik 2014).

1.2.3 Characteristics of SIT

The sounds associated with most cases are often described as ringing, hissing, water running, humming, crickets, cicadas, whistling, the wind blowing, neon lights buzzing, and engines running (Stouffer et al., 1990). These sounds are often high-pitched over 3000Hz (Chan,

2009). The sound can vary in duration, starting suddenly or gradually building up. It is most perceived in quiet environments, undisturbed by background noises. Researchers from “Centro of Tinnitus Montevideo Uruguay” conducted a comprehensive categorisation of tinnitus based on its acoustic profiles. They identified five primary types: single pure tones, combinations of pure tones, broadband noise, combinations of broadband noise with single pure tones, and white noise. Notably, patients frequently reported a specific type resembling the sound of a 'cricket' (Drexler et al., 2016).

1.2.4 Etiopathology of SIT

Tinnitus pathogenesis is triggered by dysregulation of central auditory processing due to altered cochlear inputs (Jastreboff, 1990). Damage to outer hair cells in specific cochlear regions reduces spontaneous activity in associated nerve fibers, disrupting the balance of excitatory and inhibitory networks causes neuronal hypersensitivity and hyperactivity (Eggermont & Roberts, 2004). This hyperactivity may result from cortical tonotopic map reorganisation following cochlear damage, leading to a release from efferent inhibition at frequencies that lose cortical representation. Increased spontaneous firing rates have been observed at various auditory pathway levels: the dorsal cochlear nucleus, inferior colliculus, and auditory cortex because the brain is not able to discern if this abnormal incoming flux of information is related to real environmental sound resulting in the phantom sensation of tinnitus (Drexler et al., 2016). Moreover, PET and fMRI imaging studies indicate that loss of cochlear input to central auditory neurons leads to abnormal neural activity in the auditory cortex, which triggers tinnitus (Cai et al., 2019). Furthermore, inhibition in the neural feedback circuits crucial for regulating auditory memory can diminish in the auditory pathways and cortex. This disruption can create alternate synaptic pathways, resulting in the abnormal processing of information that underlies tinnitus (Artik, 2014). Therefore, tinnitus arises from complex neuroplastic changes in the central auditory system due to cochlear damage, leading to persistent phantom auditory perceptions.

1.3 Causes of Tinnitus

1.3.1 Hearing Loss

Noise-induced hearing loss is a common tinnitus trigger, primarily due to damage to the cochlea's inner and outer hair cells. Inner hair cells convert sound vibrations into neural signals, while outer hair cells amplify these vibrations (Davis et al., 2019). Noise exposure can cause temporary or permanent hearing threshold shifts, with temporary shifts potentially

leading to cochlear synaptopathy, marked by the loss of "ribbon" synapses. This damage distorts auditory signals, potentially causing tinnitus through central auditory network plasticity (Henton & Tzounopoulos. 2021).

1.3.2 Ototoxic Cause

Ototoxic medications or substances such as chemotherapeutic and antimicrobial drugs can cause bilateral tinnitus by damaging hair cells, the eighth cranial nerve, or their central nervous connections (Dille et al., 2010). This damage can manifest as hearing loss, vertigo, or tinnitus, often indicating cochlear impairment (Crummer & Hassan., 2004).

1.3.3 Tonotopic Cortical Maps Reorganisation

Tinnitus could arise from the expansion of the tonotopic map at the periphery of hearing impairment. Increased representation of frequencies near the edge of hearing loss may lead to increased neural activity, generating the perception of tinnitus (Henry et al., 2014). The disruptions to the peripheral auditory system, such as through noise exposure or cochlear damage after these, alterations in inner hair cell activation thresholds lead to shifts in the tonotopic organisation within the cochlea resulting in each inner hair cell having tonotopic connections, through its associated ganglion cells, to cells in the cochlear nucleus (Mann et al., 2011). This results in altered frequency topographic maps in central auditory structures such as the inferior colliculus (IC) and auditory cortex, characterised by abnormal neural firing patterns and increased spontaneous activity, underlying the perception of phantom sounds like tinnitus. These changes manifest as shifts in characteristic frequencies (CFs) and expanded frequency-response areas at the IC level, with multi-peaked or distorted representations. This plasticity observed in CF mapping correlates with increased spontaneous neural firing rates, a hallmark of tinnitus. This phenomenon is hypothesised to arise from reduced inhibition and increased excitation within affected neural circuits, perpetuating aberrant neural activity associated with phantom auditory sensations. Moreover, the temporal progression of CF threshold shifts post-exposure supports a dynamic relationship between tonotopic map alterations and tinnitus development. Thus, tonotopic cortical map reorganisation is a crucial mechanism linking peripheral auditory damage to the perceptual phenomena of tinnitus (Wang et al., 2013).

1.3.4 The Edge Theory

Edge theory, also known as contrast theory, posits that tinnitus arises from increased spontaneous activity at the boundary between healthy and damaged Outer Hair Cells (OHCs) in the cochlea. This edge area, typically between the intact apical region (low-frequency) and the damaged basal region (high-frequency), experiences increased activity due to the discordance between functional and dysfunctional OHCs (Haider et al., 2018). Ototoxic drugs or intense noise primarily damage the basal OHCs, leading to this disparity (Dubey., 2022). The theory suggests that this abnormal activity shift from the apical to the basal side triggers tinnitus, as the auditory pathway responds to the irregular signals generated at this transition zone (Han et al., 2009).

1.3.5 Discordant theory

The discordant dysfunction theory posits that cochlear damage caused by noise, drugs, or viral infections initially affects the outer hair cells, which amplify sound, before affecting the inner hair cells, which transduce sound. This differential damage alters the spontaneous firing rates of neurons in the dorsal cochlear nucleus (DCN), leading to hyperactivity. The DCN, a key site for integrating acoustic and sensory inputs, becomes crucial in tinnitus generation. The theory suggests that normal auditory activity turns pathologically persistent due to synaptic changes in the DCN. Specifically, excitation from functioning inner hair cells, unopposed by damaged outer hair cells, may lead to abnormal neural activity perceived as tinnitus (Fioretti et al., 2011).

Table 1: Diagnosing Tinnitus

Stages of diagnosis	Explanations
1: Clinical History	Identify causes like acoustic trauma, occupational noise, or ototoxic drugs. Note if tinnitus is unilateral or bilateral, its pitch and if it is pulsatile. Assess if it is bothersome and look for associated symptoms like hearing loss, vertigo, or neurologic deficits.
2: Physical Examination	Focus on cranial nerve assessment and otoscopic examination to detect infection, eardrum perforation, or middle ear tumours. Auscultate for bruits in pulsatile tinnitus to identify vascular anomalies.
3: Audiologic Evaluation	Assess auditory function and quantify tinnitus characteristics such as pitch and loudness.
4: Imaging Studies	Magnetic resonance angiography and venography for pulsatile tinnitus to rule out vascular abnormalities. Non-contrast MRI for non-pulsatile unilateral tinnitus or asymmetrical sensorineural hearing loss.
5: Referral	Refer to an otolaryngologist for pulsatile tinnitus, unilateral tinnitus, or abnormal otoscopic findings for further investigation (Wu et al., 2018).

1.4 The Impact of Tinnitus on Quality of Life

1.4.1 Stress

Tinnitus patients are significantly affected by stress, which may be a predisposing risk factor and contribute to the transition from mild to severe tinnitus. Stress can trigger maladaptive coping strategies and elevate neuroticism, worsening symptoms. Tinnitus itself can act as a stressor, increasing physiological arousal and psychological distress. Dysfunctional autonomic nervous system processes, particularly in the sympathetic branch, and alterations in limbic structures such as the amygdala contribute to persistent distress and hinder habituation to tinnitus, often exacerbating insomnia and depression (Betz et al., 2017).

1.4.2 Depression

Depression has a direct impact on tinnitus. Patients with positive depression screenings have a significantly higher impact on the quality of life measured through the psychological test for tinnitus assessment. Depression substantially worsens the quality of life in tinnitus patients (Dall et al., 2004).

1.4.3 Poor Speech Perception Performance

Tinnitus can adversely affect speech performance through various biological mechanisms. For example, increased neural activity in auditory pathways can interfere with the processing of speech signals. This increased neural activity and potential structural changes in the auditory cortex due to prolonged auditory input alterations may reduce the brain's ability to accurately decode speech in noisy environments. Thus, tinnitus can impair speech perception by disrupting neural coding and cortical processing of auditory information (Gilles et al., 2016).

1.4.4 Poor Cognitive Function

Tinnitus significantly affects cognitive functions, as evidenced by a study showing a strong correlation between cognitive processing speed, measured by the Brain Speed Test, and self-reported tinnitus severity in individuals with bothersome tinnitus. This suggests that tinnitus leads to maladaptive cortical processes that impair cognitive functions such as processing speed. The study found that the brain speed test score was an independent predictor of tinnitus severity, highlighting the importance of cognitive impairment in the condition. Therefore, there is a critical need to address cognitive deficits effectively (Das et al., 2012).

The impact of sleep quality will be addressed in a separate subsection in this introduction since it is a directly relevant topic of this study.

1.5 Introduction to Sleep Quality and Its Importance

Sleep is a fundamental physiological process essential for human survival, encompassing both the quantity and quality of sleep (Irwin., 2015). Restoring sleep is crucial for physical, cognitive, and psychological well-being. Conversely, poor or disordered sleep can impair cognitive and psychological functions and deteriorate general physical health (Brand & Kirov, 2011). Sleep plays a key role in the circadian rhythm, stages linked to the autonomic nervous system, and it is essential for repairing circulatory, respiratory, musculoskeletal, and

central nervous systems during sleep. It constitutes about one-third of a person's life and is vital for memory consolidation, learning, physical growth, emotion regulation, and overall quality of life. Prolonged sleep deprivation weakens the immune system and increases the risk of cardiovascular diseases, hypertension, obesity, metabolic deregulation, and diabetes (Mendonca et al., 2019). Therefore, prolonged sleep deprivation in tinnitus patients further impairs cognitive function and psychological health and intensifies the existing symptoms.

1.5.1 How Tinnitus Affects Sleep Quality

Recent research on tinnitus has revealed increased neural excitability and spontaneous activity in the auditory pathway, which may spread to broader brain regions across different vigilance states. This overlap could create a conflict between pathological tinnitus-related activity and natural brain processes. Persistent pathological activity, akin to conditions like insomnia, might induce hyperarousal, disrupting normal sleep patterns. However, natural brain state shifts can also influence tinnitus perception, potentially modulating the phantom sounds throughout the sleep-wake cycle (Milinski et al., 2022). This dynamic interaction suggests that homeostatic and circadian influences play crucial roles in the fluctuation of tinnitus perception over time

1.5.2 Acoustic Stimulation for the Treatment of Tinnitus

Since most forms of severe tinnitus are caused by functional changes, it should be possible to reverse it with sound treatment, taking advantage of the plastic properties of the brain (Pedemonte et al., 2010). Acoustic stimulation emerged as a treatment option in the late 1970s, initially employing white noise generators to mask tinnitus and enhance patient quality of life (Vernon, 1977). Known as "Passive Function," this method offers temporary relief only during sound exposure, lacking enduring effects on information processing once the stimulus ceases. Consequently, tinnitus typically resumes its original characteristics post-stimulation withdrawal.

1.5.3 Active Acoustic Stimulation (AAS)

In the early 21st century, AAS protocols aimed to induce persistent changes in auditory processing through neuroplasticity. This reorganisation of neural networks sought to restore the balance between inhibition and excitation in involved neural groups. Various mechanisms have been proposed to explain the changes observed with AAS treatment, the most accepted being:

a) Increasing the inhibitory tone of the efferent auditory system to reduce spontaneous discharge patterns.

b) Preventing synchronisation of spontaneous discharges in the auditory nerve.

c) Preventing cortical reorganisation to restore the representation of affected frequencies in the primary auditory cortex and, therefore, their efferent projection on the neurons involved in the genesis of tinnitus (Eggermont & Komiya, 2000).

d) Reducing abnormal activity at the “edges” of cochlear damage by increasing the inhibitory tone of cholinergic synapse activity between the olivocochlear system and external hair cells (Roberts et al., 2013).

Over the past two decades, effective therapeutic results have been achieved when sound stimulation is tailored to the spectral and intensity characteristics of tinnitus (Schaette et al., 2010). Various protocols have been developed, including sounds or melodies with altered frequencies, white noise, phase-displaced pure tones, amplitude and frequency modulation, and combinations of pure tones. These approaches aim to mitigate tinnitus symptoms by addressing the specific auditory features of the condition (Schaette et al., 2010; Vermeire et al., 2007; Davis et al., 2008).

1.5.4 Acoustic Stimulation During Sleep

With the premise that there is a direct correlation between the spectral characteristics of the sound the patient hears and the frequency range in which there is a deficit in the provision of information that triggers tinnitus, an Uruguayan team of clinicians and researchers introduced two decades ago a novel approach to customising sound to match each patient's tinnitus frequency and intensity. This method aims to restore auditory balance by addressing specific deficits in acoustic information linked to tinnitus triggers. By precisely replicating these features, the therapy provides targeted instructions to the auditory system and encourages the brain to self-regulate the balance between excitation and inhibition, potentially alleviating tinnitus symptoms (Drexler et al., 2016).

The strategy was founded on an understanding of the auditory system's great capacity for discriminating; this skill evolved over hundreds of thousands of years, during which hearing was fine-tuned as an alert system against predators and as the primary channel of intra-species communication. The human ear possesses a great ability to discern both dynamic range and frequency range. The therapeutic approach was created to interact with the brain by

using specific acoustic patterns that targeted the appropriate frequencies and intensities. The team developed hardware and software that, combined with an advanced sound synthesis method, allowed them to create personalised acoustic designs to replicate each patient's tinnitus. This is defined as an Individualised Acoustic Receipt. The treatment seeks to compensate for tinnitus by retraining the auditory system through neuroplasticity. The therapy program spans one year and includes at least 12 consultations, either in-person or online, with different members of the clinician's team. In this process, they facilitate auditory stimulation and psycho-emotional desensitisation processes intended to alleviate tinnitus and minimise related symptoms (Drexler et al, 2016).

1.5.5 Why During Sleep?

The protocol is used during nighttime sleep, in contrast to all acoustic stimulation protocols created in recent years, which apply sound stimulation during the day. Research indicates that auditory processing persists during sleep, influencing learning and memory across sleep stages (Velluti, 2018). Treating tinnitus during sleep leverages these processes, offering significant benefits. Tinnitus sufferers often experience a detrimental cycle between their condition and sleep quality: worsening tinnitus intensifies, and reducing sleep quality at nighttime exacerbates this as reduced ambient noise increases tinnitus perception, particularly during sleep consolidation (Hurtuk et al., 2011). Administering treatment during sleep addresses these challenges by providing relief without disrupting daytime activities also approach to proven to be beneficial because during sleep the patient is not aware of acoustic stimulation while it is taking place, which reduces the treatment-related anxiety. In addition, during sleep, there is less input sensory competition of the information with acoustic stimulation provided by the therapy. Finally, the nighttime provides a wider window of stimulation and does not interfere with daily activities.

1.6 Study Aims, Hypothesis, and Objectives

Study Aims

The main aim of this study is to investigate the effectiveness of acoustic stimulation treatment performed during sleep in improving sleep quality and to determine if changes in sleep quality are correlated with tinnitus volume. Additionally, we aim to assess the patient's reaction to the customised acoustic stimulation through a targeted questionnaire, correlating the scores with sleep quality and tinnitus volume. Looking into the future, we aim to confirm the clinical impression in the sense that the reaction to the acoustic stimulus is generally

positive or neutral in most patients, challenging the widespread idea that it can be aversive. This aspect is crucial in understanding the complex relationship between tinnitus and sleep and its impact on the overall quality of life for patients.

Study Hypotheses

Primary Hypothesis: The decrease in tinnitus volume will have an impact on patient well-being through the improvement of sleep quality.

Secondary Hypothesis: The impact on sleep quality will be especially marked in the patients that had insomnia (score equal to or larger than 8) at the start of the treatment.

Objectives of the Study

Primary Objective: Investigate the effectiveness of acoustic stimulation treatment during sleep-on-sleep quality.

Secondary Objectives: Determine if changes in sleep quality correlate with tinnitus volume and evaluate patients' reactions to the customised acoustic stimulation.

2. Methods and Materials

2.1 Recruitment and Screening

This study was recruited among patients at the Montevideo Tinnitus Clinic without a specific call for a research project. Patients underwent a diagnostic process and medical analysis. Those who met the predefined inclusion criteria signed a consent permitting the use of their data for research purposes. The patients in this study received treatment with the LEVO system for acoustic stimulation during sleep from 2015 to 2021. Only patients with complete data were selected for the study to ensure data integrity and reliability.

2.2 Inclusion Criteria

The study includes patients aged 18 to 70 with subjective idiopathic tinnitus, whether unilateral or bilateral. Eligible participants must have experienced tinnitus for more than six months. Additionally, they should have undergone sleep acoustic stimulation treatment for a minimum of three months. To qualify, patients must also have a THI score above 16.

2.3 Exclusion Criteria

In this study, we implemented stringent exclusion criteria to maintain the integrity and specificity of our findings. patients with incomplete data were not considered. Additionally, it excluded those with secondary tinnitus, whether objective or subjective. Patients experiencing hearing loss of 50 dB or worse in more than three audiogram frequencies were also excluded. Patients who had received alternative treatments for tinnitus within the preceding year were not included, nor were those currently using hearing aids. The use of psychoactive drugs was another criterion for exclusion. Furthermore, we excluded individuals diagnosed with sleep disorders not directly attributable to tinnitus, such as sleep apnea, restless legs syndrome, narcolepsy, parasomnia, and insomnia of aetiologies other than tinnitus.

To assess these criteria, each patient was interviewed and examined by an otolaryngologist, an audiologist, and a psychologist. The laboratory assessment included MRI and blood tests to measure lipids, thyroid hormones, glucose levels, urea, electrolytes, and creatinine.

The audiology evaluation included impedanciometry, audiometry for thresholds at 0.125, 0.25, 1, 2, 3, 4, 6, and 8 kHz, loudness discomfort level, speech audiometry, and high-frequency audiometry (8, 10, 12, 14, and 16 kHz). Otoacoustic emissions were assessed using

distortion product otoacoustic emissions (DPOAEs) and transient evoked otoacoustic emissions (TEOAEs). DPOAEs involved three pairs of pure tones per octave from 1-6 kHz, while TEOAEs were measured using broadband clicks from 1-5 kHz.

2.4 Psychological Evaluation

A psychological evaluation was conducted at the beginning and end of treatment, focusing on anxiety, depression, and the impact of tinnitus on quality of life. Three questionnaires were used: the THI, TRQ, and TFI. Patients completed these questionnaires independently before each interview. The THI, comprising 25 items, is designed to diagnose the severity of tinnitus, with a total score ranging from 0 to 100. It includes functional, emotional, and catastrophic subscales, but the global score is recommended due to questions about the subscales' use. Higher scores indicate greater impairment or distress. The TFI, also with 25 items, assesses the functional effects of tinnitus and tracks changes during treatment. It includes 8 subscales: intrusiveness, sense of control, cognition, sleep, auditory, relaxation, quality of life, and emotional distress. Scores range from 0 to 100, with responses scaled between 1 and 10, providing higher resolution in detecting changes (Fernandez et al., 2022). The TRQ, a 26-item measure, evaluates psychological distress associated with tinnitus. It consists of four subscales: General Distress, Interference, Severity, and Avoidance. Each item is rated on a Likert scale from 1 (Totally Disagree) to 5 (Totally Agree), yielding a total score range of 26 to 130, where higher scores denote greater distress (Morning et al., 2016).

2.5 Sleep Evaluation

Sleep quality was assessed using the ISI scale at the start and end of the treatment. ISI is a 7-item scale that assesses the severity of nighttime and daytime insomnia symptoms, including sleep onset, maintenance, and daytime functioning, using a 5-point Likert scale, with scores ranging from 0 to 28. The highest scores indicate severe insomnia (Ceri et al., 2023). Therefore, subjective perceptions related to sleep onset, sleep maintenance, and early morning wakening were examined. The effects of sleep disturbances on daytime wakefulness, including memory issues, irritability, and excessive drowsiness, were also evaluated. Additionally, the impact of tinnitus on sleep quality was measured using the TFI sleep subscale.

2.6 Tinnitus Characterisation and Sound Stimulation

To address the complex nature of tinnitus, characterised by combinations of pure tones, harmonics, white noise, and band noises, we developed a specialised software system. This system featured two components: software installed on the physician's iPad and another on the patient's iPod Touch. The iPad application allowed the physician to tailor sound profiles to each patient's specific tinnitus characteristics, while the iPod Touch app enabled patients to adjust the intensity of sound stimulation nightly and store daily sound-intensity data. These devices communicated via Wi-Fi, facilitating the transfer of data from the patient's iPod to the physician's iPad during appointments. This data was then graphically displayed, enabling real-time adjustments and monitoring of the sound therapy.

Custom in-ear earbuds were designed to complement this system. Medical-grade silicon molds were made based on ear canal impressions for each patient. These molds ensured maximum occlusion to prevent air leaks and were designed to avoid protrusion from the ear's pinna, thus enhancing comfort during sleep and minimising sound leakage. The earbuds housed Etymotic ER4 series drivers with an impedance of 20 ohms at 1 kHz and a sensitivity of 103.5 dB SPL for 0.1V at 1 kHz. They were connected to the iPod via a 52-inch supple cable with a silver clear jacket. Calibration involved using an artificial ear (Ear Simulator 43AC by GRAS Sound and Vibration), a Bruel & Kjaer type 2250 microphone, and a Bruel & Kjaer type 4231 sound calibration system set at 1 kHz and 94 dB SPL. The frequency response of all customised earbuds was measured, covering a range from 0.125 to 16 kHz, with the average deviation from the mean response curve being less than 3 dB SPL. This precise calibration was crucial for ensuring accurate and consistent sound pressure levels in the customised sound therapy.

2.7 Participants Safeguard

To minimise the risk of excessive noise exposure, several safeguards were integrated into the Levo System device. The software design restricts treatment durations to a maximum of 8 hours, and further guidelines suggest limiting exposure based on sound intensity levels: at 65 dB SPL or higher, the duration should be under 8 hours; at 80 dB SPL, it should be limited to 4 hours; and at the maximum output of 84.9 dB SPL, the duration is capped at 2 hours. The device is pre-programmed in the clinic to adhere to these limits, and it automatically ceases sound therapy once the designated hours are reached. Data-logging features enable monitoring of compliance with these guidelines during follow-up visits. To avoid additional

risk, individuals exposed to loud noise in their occupation or leisure activities were excluded from the study. Regular audiometric tests were conducted to confirm stable hearing thresholds, while otoscopic evaluations at each visit checked for any ear irritation caused by the custom-fit earbuds. If irritation was found or reported, adjustments to the earbuds were made to alleviate discomfort.

2.8 Tinnitus Perception Match

Patients underwent a customised process where physicians created sound combinations tailored to their tinnitus characteristics using specialised software and a calibrated sound system. This system offered five types of sounds: pure tones, bandpass noise, a ‘cricket’ sound, white noise, and pink noise. For pure tones, frequencies could be adjusted between 0.125 and 16 kHz. Bandpass noise allowed for center frequency adjustments within the same range, with a variable Q factor to set bandwidth. The cricket sound was generated by selecting a center frequency and adjacent pairs of pure tones at higher and lower pitches. This center frequency was also adjustable within the 0.125 to 16 kHz range, and the adjacent tones were set relative to it. All sound types could have their intensity adjusted from 0 to 85 dB SPL. These sounds could be played individually or combined, with the system calibrated to ensure accurate overall sound pressure level output. The goal was to match the patient's perceived tinnitus sound as closely as possible, facilitating more effective treatment and precise intensity follow-up measurements.

2.9 Treatment Protocol

Tinnitus intensity was recorded before going to sleep each night, and patients were instructed not to perform sound stimulation during this period to establish a 'control week' of tinnitus progression without intervention. Following this control phase, patients underwent nightly customised sound stimulation during sleep for three months, followed by an additional three months of follow-up. During follow-up, patients could use the stimulation as needed. Patients were directed to use the stimulation every night, setting the intensity just above their perceived tinnitus sound. Data regarding intensity of the stimulation in dB SPL and daily usage was stored on each device. Based on these data, an intensity follow-up was performed providing information about the evolution of the treatment. Appointments were held every fifteen days to assess stimulation, sleep quality, and psychological well-being. Data from the devices were downloaded, stored, and presented graphically and as logs on the physician’s

iPad during these sessions. If patients reported changes in their tinnitus's spectral characteristics, the customised sound was adjusted to match these changes.

2.10 Volume Time Series and Statistical Considerations

Every night, the patient sets the volume of the device playing the acoustic stimuli to be slightly higher than the perceived intensity of their tinnitus. This volume level is recorded in the mobile app, which transmits the data to the doctor's computer for monitoring and analysis. After adjusting the volume, the patient proceeds to sleep, with the acoustic stimulation being continuously administered through the app.

To evaluate the effects of the treatment, the tinnitus volume, sleep quality and psychological scores were compared between the start and the end of the treatment (800 hrs of stimulation) with a Wilcoxon paired test (the null hypothesis is that the two compared samples came from continuous distributions with equal medians, against the alternative that they do not). In addition, sleep quality and psychological scores were correlated with the reduction in volume using Spearman correlation. A linear function was fitted, and the slope was determined. In this manner, the slope indicates the size of the effect, and the p-value of the Spearman correlation evaluates its significance. This non-parametric evaluation can indicate whether the dependent variable increases as the independent variable increases, even if the relationship is non-linear. The null hypothesis of no correlation is against the alternative hypothesis of a nonzero correlation. All analyses were performed using MATLAB.

3. Results

3.1 Overall Population Analysis

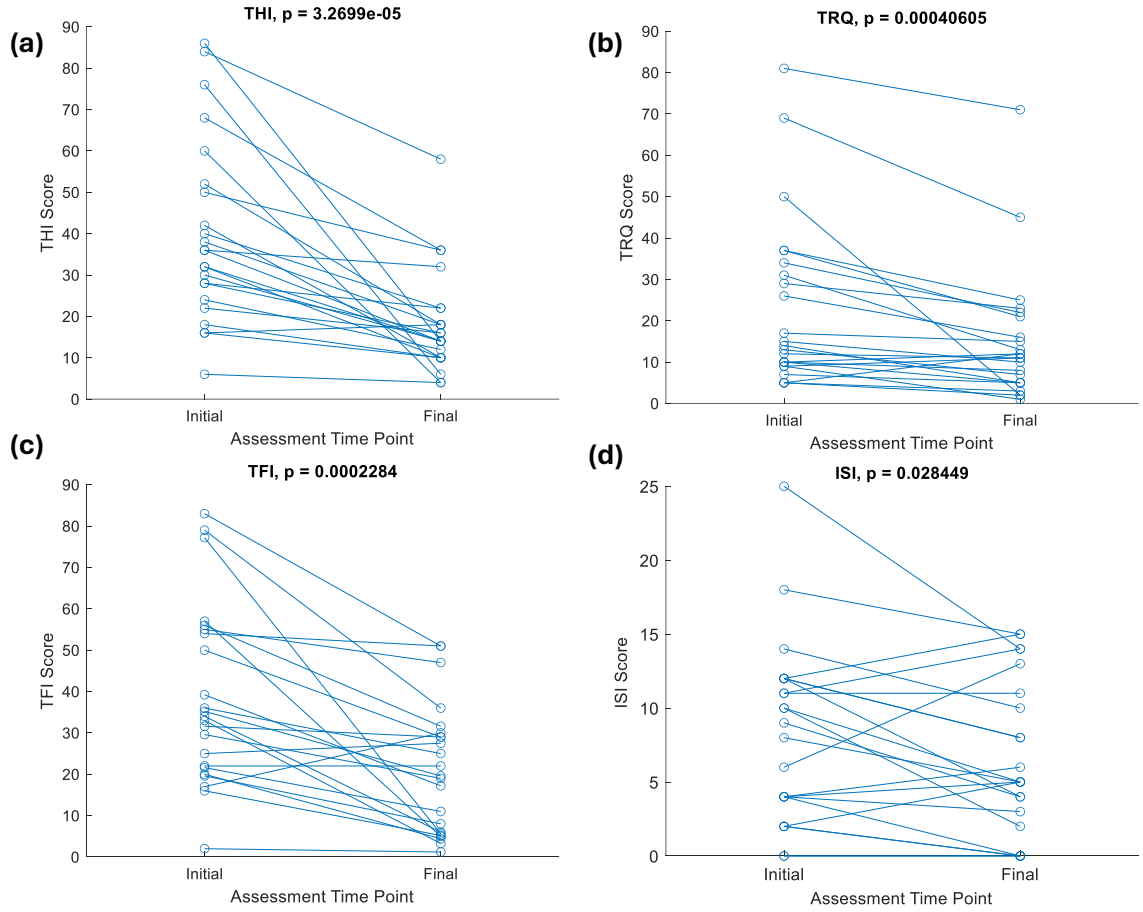

Figure 3: Decrease in Psychological Measures after Treatment. Significant reductions in THI (p = 0.0005), TRQ (p = 0.0004), TFI (p = 0.00022), and ISI (p = 0.028) scores after acoustic stimulation, indicating improved tinnitus severity and sleep quality.

The presented graphs depict the results of Wilcoxon signed-rank tests assessing the changes in THI, TRQ, TFI, and ISI scores from the initial to the final assessment time points for tinnitus patients undergoing acoustic stimulation during sleep. The plots show a significant reduction in scores across all four measures (Fig 3), indicating an improvement in sleep quality and general well-being. Specifically, the THI scores show a marked decrease, demonstrating substantial alleviation in the perceived handicap due to tinnitus. Similarly, the TRQ scores decline, highlighting a reduction in the psychological distress caused by tinnitus. The TFI scores, which evaluate the functional impact of tinnitus, also exhibit a notable

downward trend, reflecting improved daily functioning and reduced interference from tinnitus. Lastly, the ISI scores decrease significantly, indicating an enhancement in sleep quality among the participants. The statistical analysis reveals that all these improvements are significant, with p-values less than 0.001 across all measures (Fig 3).

Concerning the tinnitus volume measured with the phone app by the patient (Figure 4), we also found a significant reduction (p=0.0014), in line with previous studies (Drexler et al., 2016). The tinnitus volume is very important because it quantifies the intensity of the main symptom that constituted the reason for consultation of these patients. We must consider that, given the logarithmic scale used to calculate decibels, the observed mean reduction of 4.5 dB is equivalent to reducing to half the volume of an acoustic device.

Overall, these findings suggest that the acoustic stimulation treatment administered during sleep effectively mitigates tinnitus symptoms, improves psychological well-being, and enhances sleep quality in patients.

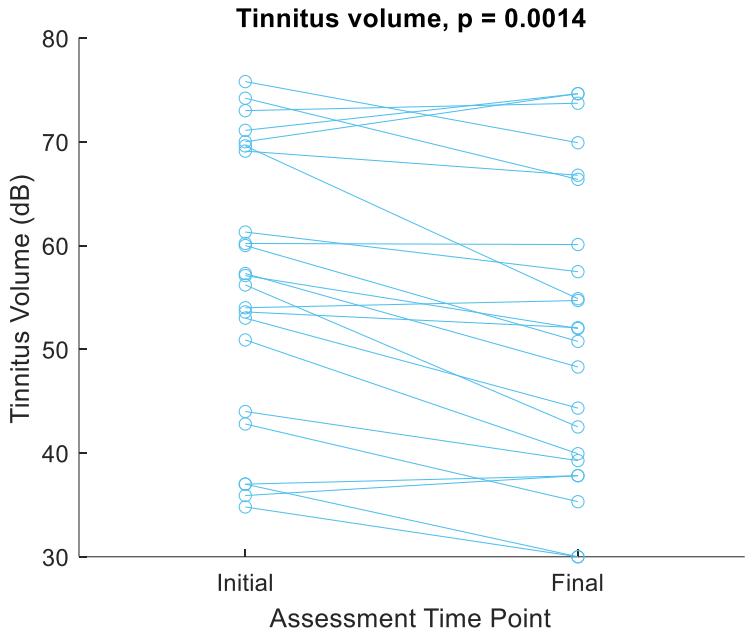

Figure 4: Tinnitus Volume Reduction after Treatment. tinnitus volume decreased after treatment, with statistical significance (p = 0.0014) determined by the Wilcoxon signed-rank test.

The treatment resulted in a notable reduction in tinnitus volume from the initial to the final assessment. Most participants experienced a decrease in tinnitus loudness, with the initial values ranging from 30 dB to 80 dB, with a mean reduction of 4.55 dB (Fig 4). This

consistent downward trend indicates that the treatment was effective for most of the participants.

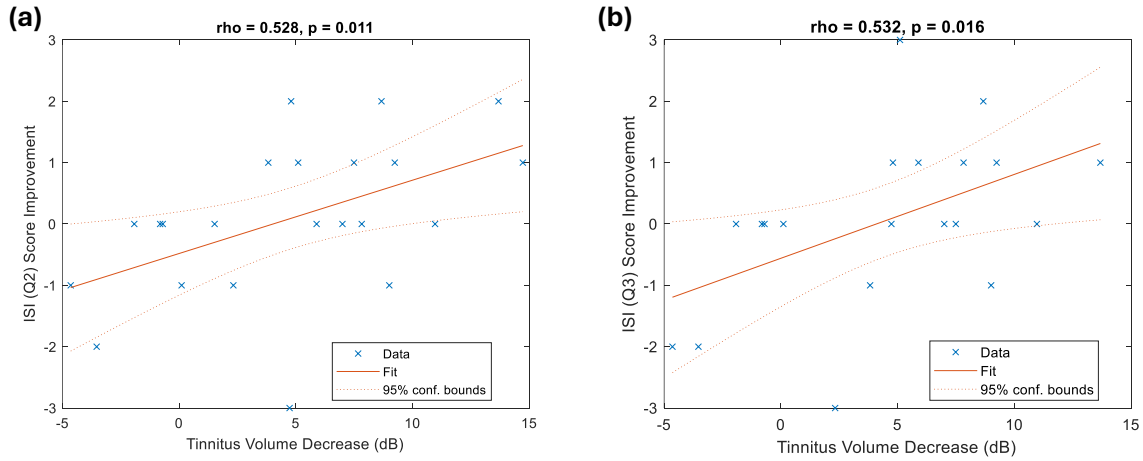

Figure 5: Correlation Between Tinnitus Volume Decrease and Sleep Maintenance Score Improvements. Significant correlations ($p < 0.05$) exist between tinnitus volume decrease and improvements in ISI Question 2 ($p = 0.011$) and Question 3 ($p = 0.016$) sleep maintenance scores.

A positive correlation exists between tinnitus volume decrease and improvements in ISI Q2 and Q3 scores, which are directly linked to sleep maintenance. The p-values from the Spearman correlations are significant ($p<0.05$) indicating a reliable increasing relationship, with slopes (rho) larger than 0.5 (Fig 5). This suggests that greater reductions in tinnitus volume are associated with better sleep maintenance. The significant Spearman correlation supports the hypothesis that acoustic stimulation during sleep can improve sleep quality in tinnitus patients.

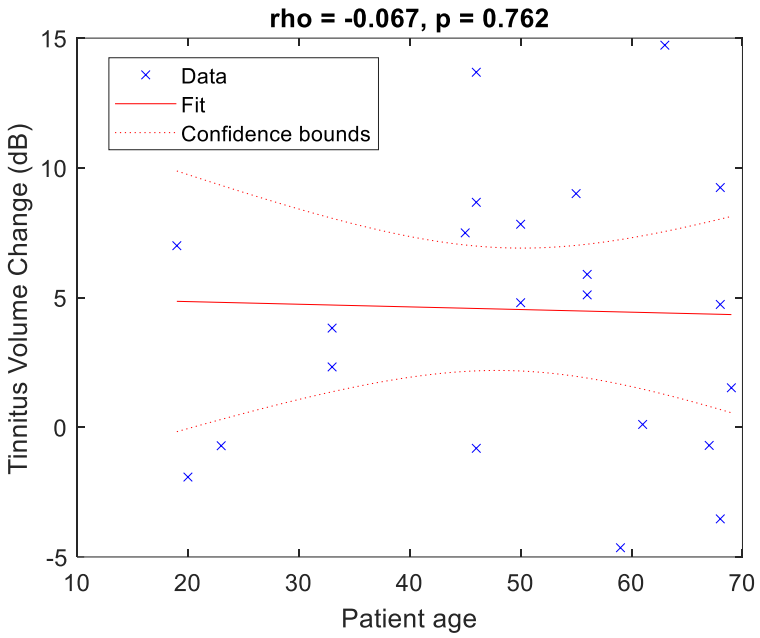

Figure 6: Age effect on Customised Sound Stimulation Treatment. Correlation between patient age and tinnitus volume decrease. The fitted line is not significantly different than the horizontal (p = 0.808), implying no effect of age.

The analysis of tinnitus volume changes revealed that neither age nor sex significantly influenced the extent of reduction. Specifically, the Spearman test shows a non-significant (p = 0.76) relationship between the patient's age and tinnitus volume change, indicating that age did not affect the reduction in tinnitus volume (Fig 6). Additionally, analysis of sex differences showed no significant difference in tinnitus volume change between males and females, with Spearman p = 0.808 and U test p = 0.826. This suggests that the intervention's effectiveness in reducing tinnitus volume was consistent across sexes.

3.2 Sub-groups Analysis

From the patient population included in this study, some individuals started the treatment having insomnia symptoms, while others did not. To enquiry if our results could be affected by this difference, we separated the patients into two groups according to the score in the ISI. The patients who started the treatment with a score ≥ 8 were considered to have insomnia (N=13) while the ones with a score < 8 were considered non-insomniacs (N=10). Although this separation decreased the N values from the original number of 23 to 13 and 10, we repeated the analysis in the two separate groups because of the importance of insomnia in the context of tinnitus.

3.2.1 Insomniacs Patients' Analysis

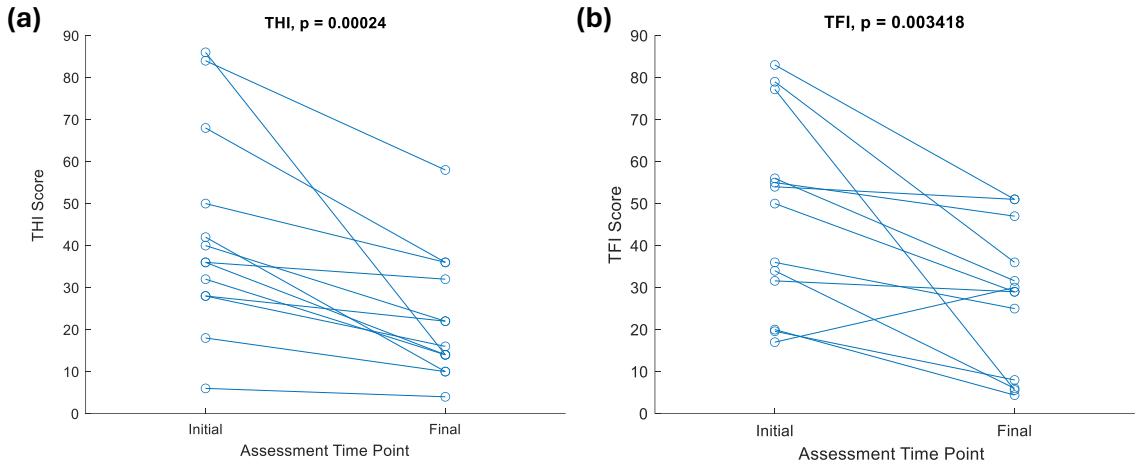

Figure 7: THI and TFI Scores Post-Treatment for Insomniacs. Comparison of initial and final THI and TFI scores showing significant reductions post-acoustic stimulation treatment, highlighting improved tinnitus severity and functional impact among insomnia patients.

The Wilcoxon signed-rank test results demonstrate a statistically significant reduction in THI and TFI scores among insomnia patients undergoing acoustic stimulation treatment during sleep. The observed p-values (THI, p=0.00024 and TFI, p= 0.0034) (Fig 7) underscore the robustness of these findings, despite the reduction in the N number.

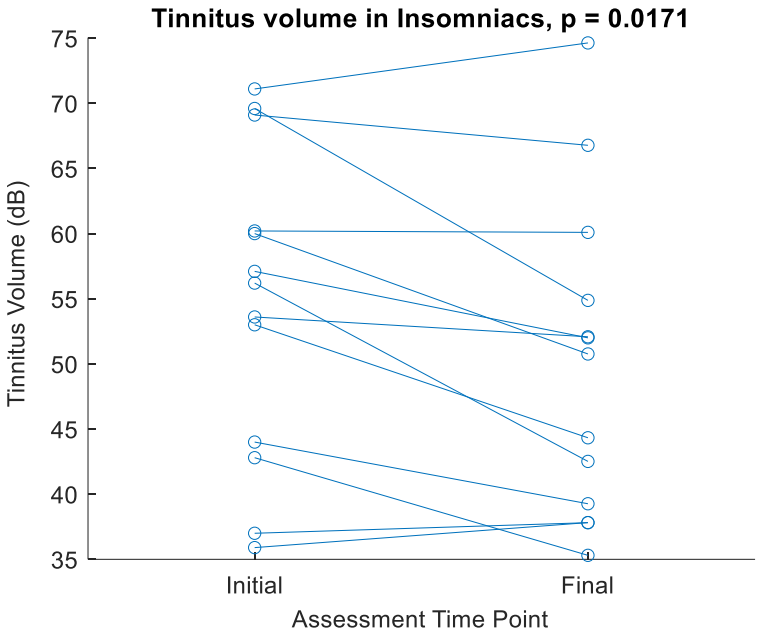

Figure 8: Reduction in Tinnitus Volume in Insomniacs. Tinnitus volume before and after acoustic stimulation treatment in insomnia patients, showing significant reduction.

Regarding tinnitus volume in insomniacs, the Wilcoxon signed-rank test indicates a significant reduction in tinnitus volume post-treatment, with a p= 0.017 (Fig 8). The results presented in Figures 7 and 8 suggest that acoustic stimulation effectively reduces tinnitus perception in insomnia patients, improving their sleep quality and overall well-being.

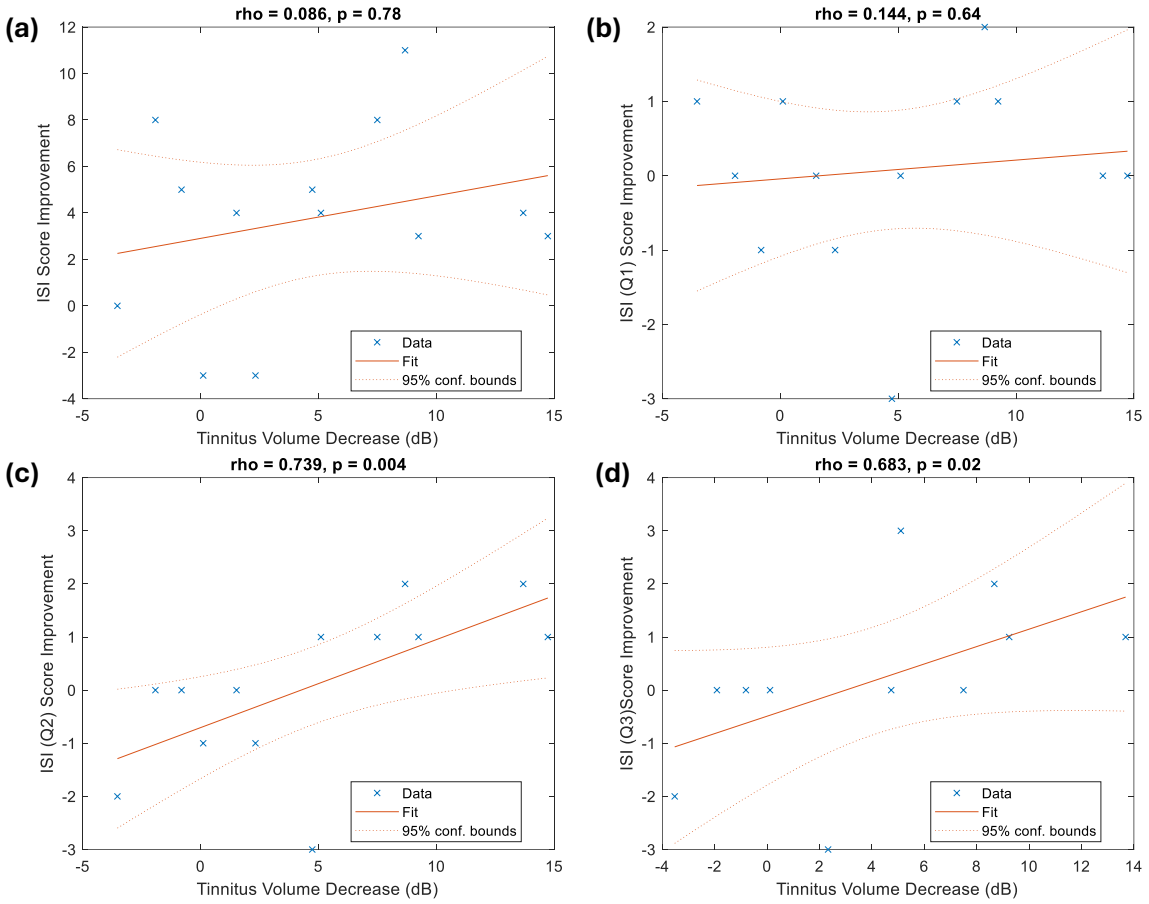

Figure 9: ISI Score Improvement in Insomniac Patients. Correlation between tinnitus volume decrease (dB) and ISI score improvement for overall ISI score and specific questions (Q1, Q2 and Q3). Data points, fit lines, and 95% confidence bounds are depicted.

Concerning the correlation between tinnitus volume and the sleep quality in insomniacs we found a positive correlation between tinnitus volume decrease and the Q2 and Q3 subsets of the ISI score. The overall ISI score ($p = 0.78$) and ISI Q1 ($p = 0.64$) showed non-significant correlations, while ISI Q2 ($p = 0.004$) and ISI Q3 ($p = 0.02$) exhibited statistically significant correlations (Fig 9) with larger slopes in the linear regression than the ones observed in the total population of patients (Table 2).

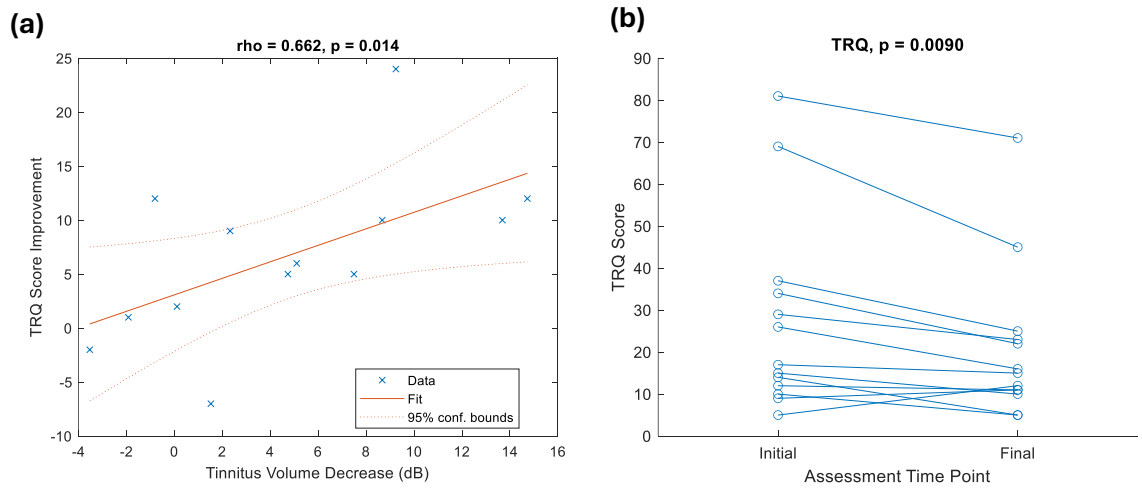

Figure 10: TRQ Score Improvement in Insomniac. Fig10a: Correlation between tinnitus volume decrease (dB) and TRQ score improvement with fit line and 95% confidence bounds. Fig 10b: TRQ scores at initial and final assessment time points for individual subjects.

In insomniac patients, the TRQ score improvement correlates positively with tinnitus volume decrease (Fig 10a), indicating a statistically significant association observed in the insomniac patients (p= 0.014). Also, the Wilcoxon signed-rank test showed significant improvement in the TRQ (p = 0.0090). The line plot (Fig 10b) demonstrates a reduction in TRQ scores from the initial to the final assessment, suggesting improvement over time.

3.2.2 Non-insomniacs Patients Analysis

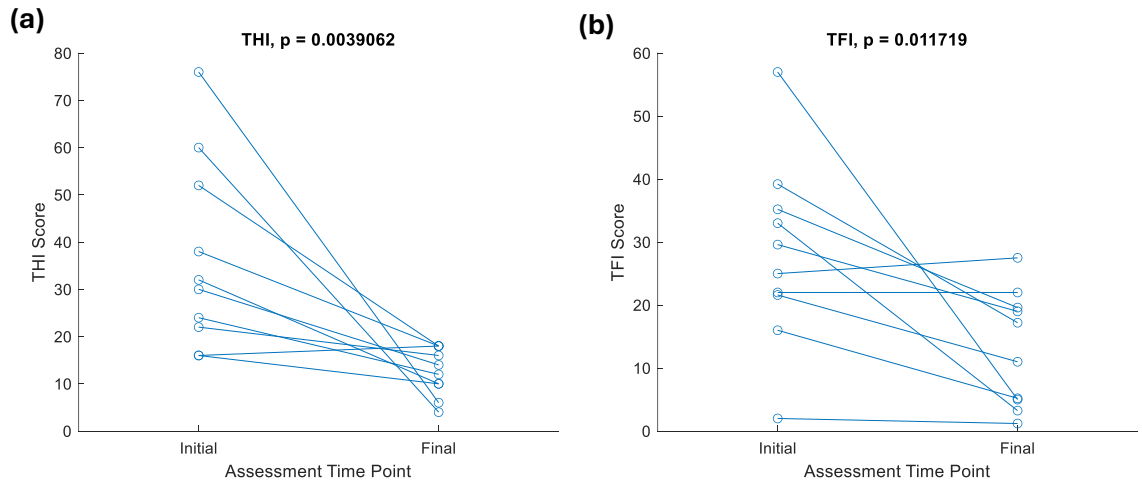

Figure 11: Non-Insomniacs' THI and TFI Score Changes. Fig11a: THI scores pre- and post-treatment for non-insomniac patients. Fig 11b TFI scores pre- and post-assessment for non-insomniac patients.

The THI (Fig 11a) and TFI (Fig 11b) scores both show a noticeable reduction from initial to final assessment time points. The Wilcoxon signed-rank test indicates a statistically significant decrease in THI and TFI scores ($p < 0.05$). This reduction suggests a marked improvement in tinnitus-related distress and functional impairment among non-insomniac subjects throughout the intervention. The parallel line plots further illustrate this consistent improvement across individual subjects.

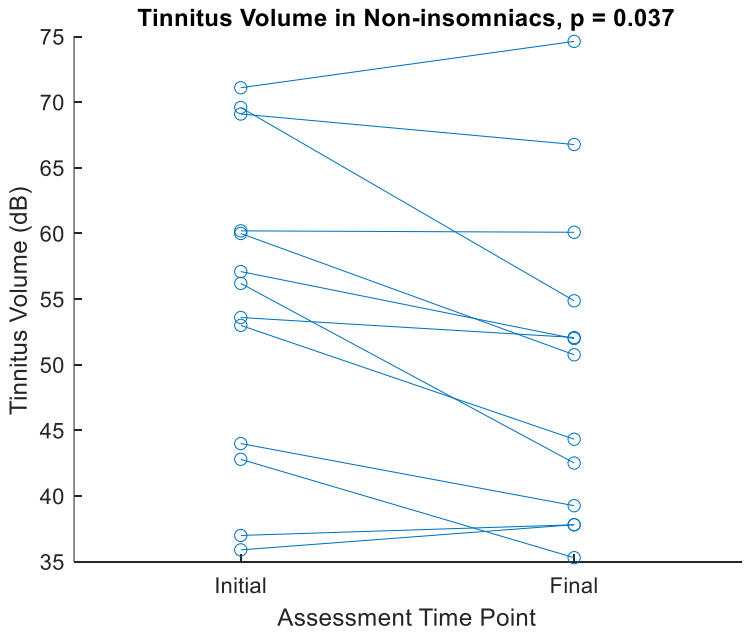

Figure 12: Tinnitus Volume Change in Non-Insomniac Patients. Initial and final tinnitus volumes for non-insomniac patients, showing individual changes over the treatment period. Most patients exhibit reduced tinnitus volume post-treatment.

Initial and final tinnitus volumes in non-insomniac patients show significant improvement post-treatment (Fig 12). Each line represents an individual's tinnitus volume change, with most lines sloping downwards, indicating a reduction in volume. The Wilcoxon signed rank test yields a p-value < 0.05, confirming a statistically significant decrease in tinnitus volume (Fig 12). This consistent downward trend across patients highlights the treatment's effectiveness in reducing tinnitus symptoms for non-insomniac patients. The results suggest that the treatment positively impacts tinnitus volume, improving patient outcomes.

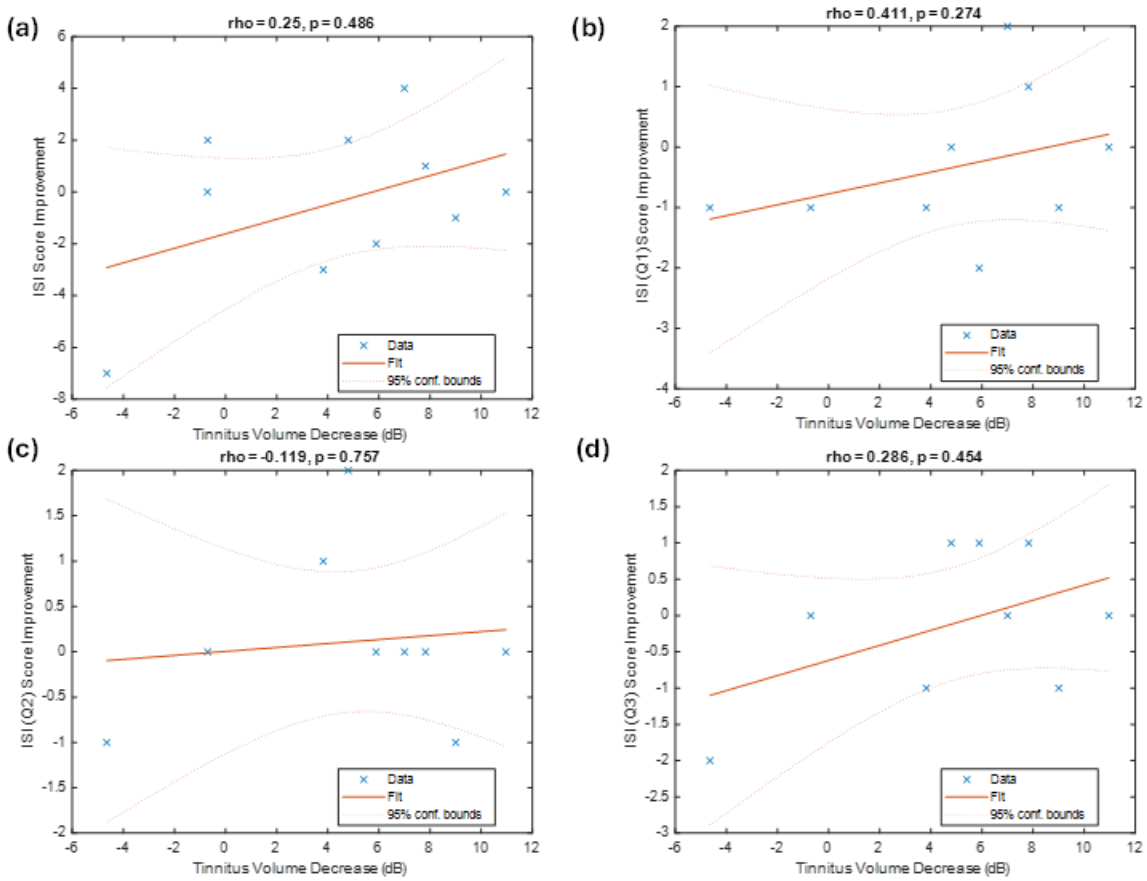

Figure 13: Sleep Quality Improvements in Non-Insomniac Tinnitus Patients. ISI score improvements versus tinnitus volume decrease in non-insomniac patients. Each subplot represents a different sleep quality aspect, with fit lines and 95% confidence bounds.

The Spearman correlation tests revealed no significant results, with p-values (ISI total, p =0.486, ISI 1, p = 0.274, ISI 2 p = 0.757 and ISI 3, p = 0.454) (Fig 13) indicating a lack of statistical significance in all aspects of sleep quality examined. These findings suggest that the observed changes in tinnitus volume do not have a significant impact on sleep quality improvements in non-insomniac patients.

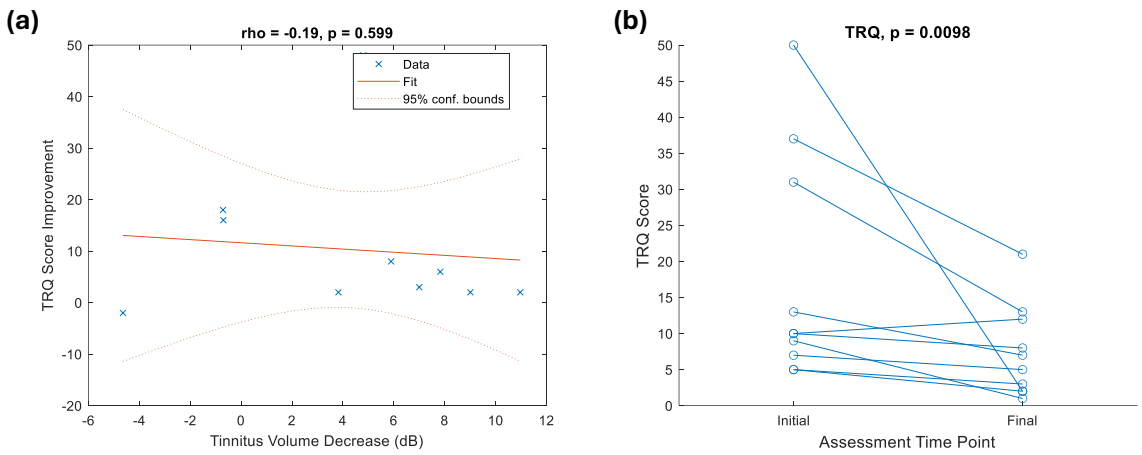

Figure 14: TRQ Results for Non-Insomniacs Patients. Fig 14a: scatter plot depicts TRQ score improvements Vs tinnitus volume decreases, including a fit line with 95% confidence bounds. Fig 14b: line plot shows TRQ scores for non-insomniac patients at initial and final assessment time points, indicating individual changes over time.

The Spearman correlation reveals no significant results between tinnitus volume decrease and TRQ score improvement, as indicated by the non-significant p-value (Fig 14a, p = 0.599). The trend line is nearly flat, and the confidence bounds are wide, further confirming the lack of a significant statistical relationship. These results indicate that tinnitus volume reduction does not significantly affect TRQ score improvements in non-insomniac patients.

Despite this lack of correlation with the tinnitus volume, the TRQ score improved significantly in non-insomniac patients (Fig. 14 b, p=0.0098).

Table 2: Correlation Coefficients of ISI with Subsets of ISI Comparison.

	Overall Population	**Insomniacs**	**Non-Insomniacs**
ISI total rho value	Rho= 0.203, p = 0.352	Rho= 0.086, p = 0.78	Rho= 0.25, p = 0.486
ISI (Q1) rho value	Rho= 0.276, p = 0.214	Rho= 0.144, p = 0.64	Rho= 0.411, p = 0.274
ISI (Q2) rho value	Rho= 0.528, p = 0.011	Rho= 0.739, p = 0.004	Rho= -0.119, p = 0.757
ISI (Q3) rho value	Rho= 0.532, p = 0.016	Rho= 0.683, p = 0.02	Rho= 0.286, p = 0.454

The data shows correlation coefficients of ISI scores with subsets for the overall population, insomniacs, and non-insomniacs. Significant positive correlations are found for Q2 and Q3 in the overall population and insomniacs, but not for non-insomniacs (Table 2).

Table 3: Reduction in the Percentage of the Psychometric and Sleep Evaluation

	Overall Population (%)	Insomniacs (%)	Non-Insomniacs (%)
THI	55	48.01	65.57
TRQ	35.51	24.30	58.19
TFI	46.42	42.26	53.33
ISI	23.44	29.88	14.29

The data indicates that non-insomniacs experienced the highest reductions in THI, TRQ, and TFI percentages compared to insomniacs and the overall population. Insomniacs showed the greatest reduction in ISI scores (Table 3).

4. Discussion

4.1 Treatment Efficacy

The findings of this study indicate that the administration of acoustic stimulation during sleep does cause a significant decrease in the tinnitus volume when compared before and after treatment. Also, the statistical test demonstrated significant improvements across all the psychological and sleep evaluations from the initial to final assessment points. Notably, tinnitus volume decreased significantly, and substantial reductions were observed in THI, TRQ, TFI and ISI scores (all $p < 0.01$), indicating overall treatment improvement and reduction in tinnitus intensity improved quality of life and sleep.

4.1.1 Correlation Analysis

The main aim of using the correlation analysis was to check how the different variables correlate with the decrease in tinnitus volume, in order to understand how the intensity of the symptom impacts both on sleep and overall quality of life.

No significant correlation between patient age and sex on tinnitus improvement was found. This demonstrates that the treatment effectiveness in reducing tinnitus volume is consistent across different age groups and sexes, highlighting its broad applicability and potential benefit for a diverse patient population.

Regarding the correlation between the different variables (psychological and sleep evaluation) and the tinnitus intensity reduction, we found that score improvements in sleep questions related to sleep maintenance were significantly correlated with volume reductions (TFI 11, ISI 2, ISI 3).

4.1.2 Comparison Between Insomniacs and Non- insomniacs

Patients having an ISI score ≥ 8 at the beginning of the treatment were classified as insomniacs. Reduction of tinnitus volume and improvement in the psychological and sleep tests were observed in both sub-populations of patients (insomniacs and non-insomniacs).

When we analysed the sub-population that had insomnia at the beginning of the treatment, we found that the effect size of the correlations (rho value) that were significant in the total population substantially increased (TFI 11, ISI 2 and ISI 3). Moreover, the effects were non-

significant among the population that had no insomnia (Table 2). This is expected because their sleep quality was already normal.

Regarding the TRQ test, which showed no significant correlation in the total population, we found that it became significant in the sub-population of insomnia patients and not significant in the non-insomniac patients. This means that the improvement in their well-being pointed out by the tests is related to the improvement of their sleep quality.

4.2 Percentage Improvement

A previous study provides valuable insights into the potential therapeutic effects of customised acoustic stimulation during sleep by examining the tinnitus intensity and its consequent positive impact on the quality of life for patients with subjective idiopathic tinnitus (Drexler et al., 2016). The results showed a 62% reduction in perceived tinnitus sound, with a significant average decrease of 14.1 dB. Psychometric tests indicated substantial improvements for example, THI by 65%, TRQ by 78%, and TFI by 77%. The findings suggest that the intensity reduction protocol significantly enhances patients' quality of life. This demonstrated that customised acoustic stimulation during sleep is an effective treatment for reducing tinnitus intensity. In this study, we confirmed a reduction in tinnitus volume and improvement in all three psychometric test scores (Table 3). While the reductions are highly significant, they reach less magnitude than the previous study (Drexler et al., 2016). This may be due to differences in the inclusion criteria.

4.2.1 Insomnia Components

Insomnia manifests in various forms, including sleep onset or conciliation insomnia (difficulty falling asleep), sleep maintenance insomnia (difficulty staying asleep), and early morning awakening (Fiorentino & Martin, 2010). This last category refers to individuals who do not struggle with initiating or maintaining sleep during the night but wake earlier than desired and cannot resume sleep (Lack et al., 2023). This study assessed components of insomnia using the THI, TRQ, TFI, and ISI measures. Key questions from these psychological tests specifically target insomnia components. For instance, (TFI 11, ISI 1 AND ISI 2) demonstrated a significant correlation between p-values with volume reduction, pointing to improvements in sleep maintenance and morning awakening. A comparative analysis between insomniac and non-insomniac patients revealed notable differences in psychological measures. The magnitude of this correlation (rho value) was larger in

insomniacs and non-significant in non-insomniac patients. Therefore, non-insomniacs' sleep quality remained unchanged post-treatment despite improvements in their psychological scores. These findings indicate that tinnitus volume, which was reduced in both groups, was related to sleep quality only in the insomniacs. The efficacy of sound stimulation to reduce tinnitus volume is mediated by neuroplastic mechanisms and does not directly depend on sleep, although in insomniac patients it improves the quality of sleep.

4.3 Treatment Comparison

Lenire and Neuromonics

The Lenire device treats tinnitus using bimodal neuromodulation with sound stimulation via wireless headphones and electrical stimulation on the tongue. This dual approach targets auditory and somatosensory pathways, aiming to reduce symptoms by activating related brain regions. Lenire involves two 30-minute sessions daily and is FDA and EU-approved (Conlon et al., 2022).

Neuromonics customises broadband frequency sounds embedded in relaxing music to treat tinnitus. This FDA-approved method stimulates auditory pathways to promote habituation and improve quality of life, requiring over 2 hours of daily use for six months (Wang et al., 2020).

Lenire or Neuromonics does not report data about tinnitus intensity measurement or reduction. In contrast, the LEVO system, which is also FDA-approved, provides comprehensive data on tinnitus intensity measurement and reduction. LEVO reports improvements in sleep quality, a parameter not addressed by Lenire and Neuromonics. The LEVO system is distinguished by its highly customised individual sound design, whereas Lenire does not offer customised sound design, and Neuromonics provides a less individualized sound design in comparison to LEVO. Additionally, LEVO is unique in offering daily information about tinnitus intensity and adhering to a highly intensive monitoring protocol. Psychological test results from the three systems vary significantly, with Lenire showing THI score reduction of 7-29, TFI score reduction of 24.2, and no available ISI scores; Neuromonics presenting no available scores for THI, TFI, or ISI; and LEVO demonstrating THI score reduction of 27.3, TFI score reduction of 55.2, and ISI score reduction ranging from 3-5. LEVO's significant benefits are attributed to its customised approach and comprehensive monitoring.

Pharmacological Treatment

A network meta-analysis of 36 RCTs with 2,761 participants found that pharmacologic treatments with brain-acting (e.g., amitriptyline) and anti-inflammatory/antioxidant effects improved tinnitus severity better than placebo (Chen et al., 2021). However, these treatments often have side effects such as dizziness, nausea, dry mouth, fatigue, and potential drug dependence. It may also impact habituation, resulting in temporary or permanent changes in tinnitus perception (Kim et al., 2021). Customised sound stimulation, with fewer side effects, is generally more effective and safer than pharmacologic options.

Neuroplasticity and Sound Stimulation Treatment

Neuroplasticity plays a crucial role in the development and adaptation of an organism's sensory systems. While it is most prominent during childhood, the brain retains the ability to regenerate and recover in adulthood following an injury (Markham and Greenough, 2004). Changes in auditory inputs can significantly alter the auditory pathways, potentially leading to an imbalance between excitatory and inhibitory mechanisms and resulting in abnormal sound perception. Since severe tinnitus is often due to these functional changes, it is feasible to reverse them through sound stimulation treatments that leverage the brain's plasticity (Pedemonte et al., 2010). Supporting this, research has indicated that patients with hearing aids or cochlear implants for hearing loss also experience improvements in their tinnitus symptoms (Kleinjung et al., 2009; Servais et al., 2017). Since the late 1980s, various acoustic stimulation protocols have been developed to reverse the neuroplastic changes underlying tinnitus (Davis et al., 2008). These treatments aim to counteract pathological neuroplastic changes by promoting further neuroplastic reorganisation of neural networks.

Extensive evidence suggests that acoustic stimulation can remodel neural networks at all levels of the auditory pathway (Rojas et al., 2018). Tonotopic maps, especially in the auditory cortex, can be modified with appropriate acoustic stimulation (Langers and Dijk, 2012). Similar to hearing aids or cochlear implants, customised sound stimulation treatments, such as those used in this study, are designed to induce beneficial neuroplastic changes. This treatment protocol involves nightly customised sound stimulation during sleep, using a system that tailors sound profiles to each patient's specific tinnitus characteristics. By leveraging the plastic properties of the brain, this method aims to reduce tinnitus volume and improve sleep quality, thereby enhancing overall patient well-being. However, hearing aids,

cochlear implants and sound stimulation treatments require external devices potentially be costly and require ongoing maintenance. Furthermore, some external devices that can cause discomfort and may not always be effective in addressing the underlying neuroplastic changes associated with tinnitus.

Comparative Efficacy of Tinnitus Therapies

The Otoharmonics Levo System's customised sound therapy was tested on sixty participants with bothersome tinnitus, randomised into three groups such as tinnitus-matched (TM), noise stimulus (NS), and bedside sound generator (BSG) to assess its effectiveness in reducing tinnitus perceptions and reactions during sleep. Outcome measures included the TFI, a numeric rating scale (NRS) of tinnitus loudness, and tinnitus loudness match. Results showed improvements across all groups, with an 87% certainty that TM or NS therapies led to a greater reduction in mean TFI compared to BSG, with an efficacy of 4.5–5 points. Additionally, TM therapy showed a significant reduction in tinnitus loudness, with a 95% certainty and a 0.75-point greater reduction in the NRS compared to other groups (Theodoroff et al., 2017). This supports our study findings that customised acoustic stimuli, particularly tinnitus-matched are more effective in lowering tinnitus loudness and reactions. However, this study directly assesses the tinnitus intensity decrease but the previous study investigated the efficacy of the sound therapy devices for tinnitus. This would be a limitation because the previous study's focus on the efficacy of sound therapy devices may not have comprehensively captured the specific mechanisms by which customised stimuli, such as the tinnitus-matched stimulus, influence tinnitus perceptions and reactions. Differences in study design, outcome measures, and participant characteristics could impact the comparability of results and limit the generalisability of the findings.

4.4 Benefits of the Study

The use of customised sound stimulation is a key advantage of this study, as it tailors the treatment to each patient's specific tinnitus characteristics. By closely matching the acoustic properties of the perceived tinnitus, the therapy is more likely to reduce the tinnitus perception effectively. This individualised approach enhances patient comfort and compliance, potentially leading to better treatment outcomes. Moreover, it allows for precise monitoring and adjustment of the therapy over time, ensuring that any changes in the tinnitus

characteristics are addressed promptly, thereby maintaining the efficacy of the treatment throughout the study period.

Safety measures and risk minimisation were implemented to prevent excessive noise exposure, such as limiting treatment duration based on sound intensity and monitoring compliance, and prioritising patient safety. Regular audiometric and otoscopic evaluations were conducted to further protect against potential adverse effects.

Moreover, the clinic created a method to estimate the tinnitus intensity with the intervention of the patient. The patient levels the device volume (playing the acoustic receipt) with he/her own tinnitus internal perception, every night before going to sleep.

Finally, acoustic sound stimulation treatment was approved by the FDA ensuring rigorous safety and efficacy standards. Its approval signifies that the treatment has undergone thorough evaluation and leading to reliable, safe outcomes.

4.5 Study Limitations

Reliance on self-reported measures in assessing tinnitus impact, sleep quality, and psychological state can introduce significant bias. Such data heavily relies on individuals' subjective perceptions and interpretations, which may not always align with objective measures or clinical assessments. Factors like individual mood, cognitive biases, and social desirability can influence how respondents report their symptoms, potentially leading to overestimation or underestimation of their true experiences. Therefore, while self-reported measures provide valuable insights, their inherent subjectivity underscores the importance of triangulating findings with objective measures to ensure a comprehensive understanding of the conditions being studied.

Focusing exclusively on patients treated with the LEVO system who have a THI score above 16 poses limitations on the generalisability of the study's findings to a broader tinnitus population. By excluding patients with lower THI scores or those who have undergone different treatments, the study may not capture the variability in tinnitus severity and responsiveness to various therapies. This narrow focus could restrict the applicability of results beyond specific subsets of patients with more severe tinnitus or those specifically responsive to the LEVO system. To enhance generalizability, future studies could include a more diverse range of patients with varying tinnitus characteristics and treatment histories.

Incorporating comparative groups receiving different therapies or stratifying analyses by THI scores could provide insights into the broader efficacy and suitability of the LEVO system across different patient profiles.

The study's reliance on technological devices, such as portable devices, software, and custom earbuds, presents a potential limitation. Technical malfunctions, such as hardware failures, software bugs, or connectivity issues, could disrupt data collection and limit the study's validity. Additionally, variations in device performance or user familiarity with the technology might introduce inconsistencies. Ensuring all equipment functions correctly and participants are adequately trained is crucial, but unforeseen technical problems remain a risk that could impact results. To mitigate this, having technical support readily available during the study can address issues promptly, ensuring smooth operation.

4.6 Future Directions

Future research should address the limitations of this study by incorporating a broader patient population with varying tinnitus severities and treatment histories to enhance generalizability. Expanding the study to include different sound therapy devices and comparative treatment approaches, such as CBT or pharmacotherapy, could provide a more comprehensive understanding of their relative effectiveness. Long-term follow-up studies are needed to assess the durability of treatment benefits and potential relapse rates. Additionally, integrating objective measures of tinnitus and sleep disturbances, such as physiological recordings or actigraphy, could complement self-reported data and reduce bias. Future studies should also explore the underlying neuroplastic mechanisms of acoustic stimulation through neuroimaging techniques, which could reveal more about how these treatments affect auditory pathways and brain function. Addressing these areas could refine treatment protocols and improve patient outcomes across diverse tinnitus populations.

4.7 Conclusion

In conclusion, this study demonstrates that customised acoustic stimulation during sleep effectively reduces tinnitus volume and significantly improves related psychological and sleep outcomes, as evidenced by substantial decreases in THI, TRQ, TFI, and ISI scores. Tinnitus volume reductions correlate with sleep maintenance. The treatment's efficacy appears consistent across variations in age and sex, with particularly pronounced benefits observed in individuals with insomnia. Compared to existing tinnitus therapies, such as those

offered by Lenire, Neuromonics, and pharmacological treatments, the acoustic stimulation approach not only shows promise in modulating tinnitus perception through neuroplasticity but also offers a safer, more personalised alternative with fewer side effects. Despite the study's limitations, including reliance on self-reported measures and potential technical challenges, the findings underscore the potential of customised sound therapy to enhance patient quality of life and sleep. Future research should aim to broaden participant diversity, incorporate various treatment modalities, and utilise objective measures to further validate and optimise tinnitus management strategies.

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