REVEALING THE EFFECTS OF DIFFERENT AUDITORY STIMULATIONS ON TINNITUS SUPPRESSION: AN AUDITORY BRAINSTEM RESPONSE (ABR) STUDY

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by

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LIST OF SYMBOLS

<	Less than
>	More than
%	Percentage
±	Plus-minus sign
μV	Microvolt
≤	Equal or less than
*	Asterisk
I	1
II	2
III	3
IV	4
V	5

LIST OF ABBREVIATIONS

A_I	Amplitude of wave I
A_V	Amplitude of wave V
$A_{V/I}$	Amplitude ratio of wave V/I
ABR	Auditory Brainstem Response
AEP	Auditory Evoked Potentials
AM	Amplitude Modulated
ANOVA	Analysis of Variance
ASHA	American Speech-Language Hearing Association
BAEP	Brainstem Auditory Evoked Potentials
BBN	Broadband Noise
BEST	Borang Evaluasi Soal-selidik Tinnitus
CBT	Cognitive Behavioral Therapy
d	Effect size
dB	Decibels
DPOAE	Distortion Product Otoacoustic Emissions
ENT	Ear Nose Throat
FM	Frequency Modulated
GSI	Grason-Stadler Inc.
HF	High frequency
HL	Hearing Level
hr	Hour
Hz	Hertz
H_0	Null Hypothesis
JASP	Jeffreys's Amazing Statistics Program
kg	Kilogram
kHz	Kilo Hertz
kΩ	Kilo Ohm
L_I	Latency of wave I

L_V	Latency of wave V
L_{I-V}	Interpeak latency of wave I-V
LTA	Left Temporoparietal Area
mg	Milligram
ms	Milliseconds
n	Sample Size
NBN	Narrowband Noise
NIHL	Noise-Induced Hearing Loss
NRS	Numeric Rating Scale
NSAIDs	Non-Steroidal Anti-Inflammatory Drugs
OAE	Otoacoustic Emissions
OEC	Outer Ear Canal
OW	Ocean Wave
p	*p* value
PICO	Participants, Interventions, Comparison and Outcomes
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analysis
PTA	Pure Tone Audiometer
PTS	Permanent threshold shift
r	correlation coefficient
RI	Residual Inhibition
sec/s	Second
SD	Standard Deviation
SL	Sensation Level
SNHL	Sensorineural Hearing Loss
SPL	Sound Pressure Level
TB	Tone Burts
tDCS	Transcranial Direct Current Stimulation
TEOAE	Transient Evoked Otoacoustic Emissions
TFI	Tinnitus Functional Index
THI	Tinnitus Handicap Inventory
THQ	Tinnitus History Questionnaire

TMS	Transcranial Magnetic Stimulation
TRQ	Tinnitus Reaction Questionnaire
TRT	Tinnitus Retraining Therapy
TSCHQ	Tinnitus Sample Case History Questionnaire
TTS	Temporary threshold shift
U. K	United Kingdom
USM	Universiti Sains Malaysia
VAS	Visual Analogue Scale
VAS-A	Visual Analogue Scale-Annoyance
VAS-L	Visual Analogue Scale-Loudness
vs	Versus
WHO	World Health Organization

LIST OF APPENDICES

PEMBUKTIAN KESAN DARIPADA PELBAGAI STIMULASI AUDITORI TERHADAP PENGURANGAN TINITUS: KAJIAN RESPONS AUDITORI BATANG OTAK

ABSTRAK

Tinitus, persepsi berdering di telinga memberi kesan kepada kira-kira 10-30% daripada populasi global, menjadikannya kebimbangan kesihatan yang lazim. Walau bagaimanapun, patofisiologi tinnitus yang tepat dan rawatan yang paling berkesan masih boleh dipertikaikan. Terapi bunyi yang menggunakan hingar jalur lebar (BBN) biasanya digunakan untuk pengurusan tinnitus, berdasarkan prinsip penindasan tinnitus. Namun, tidak semua pesakit bertindak balas positif terhadap terapi BBN. Memandangkan ini, adalah menarik untuk menyiasat mekanisme fisiologi penindasan tinitus apabila dirangsang dengan rangsangan pendengaran yang berbeza menggunakan ujian tindak balas batang otak auditori (ABR). Pada peringkat awal, kajian rintis melibatkan 5 orang dewasa yang sihat (10 telinga) dan 10 pesakit tinnitus (10 telinga) telah dijalankan untuk menentukan intensiti rangsangan optimum untuk penindasan tinitus apabila menggunakan rangsangan pendengaran yang berbeza. Rangsangan optimum daripada kajian rintis kemudiannya dibandingkan dengan rangsangan pendengaran yang berbeza dalam tindak balas ABR dalam eksperimen kawalan kes berikutnya. Untuk kajian utama, 28 peserta (56 telinga) daripada kumpulan kawalan (min umur: 37.39 ± 11.21 tahun) dan 31 peserta (45 telinga) daripada kumpulan tinitus (min umur: 40.74 ± 13.24) mengambil bahagian. Kajian rintis mendedahkan bahawa keamatan rangsangan pada 50dBSL menghasilkan amplitud yang lebih tinggi dan kependaman gelombang I dan V yang lebih pendek

berbanding dengan keamatan 30dBSL. 50dBSL telah dipilih untuk digunakan dalam kajian seterusnya. Keputusan untuk penemuan utama mendedahkan bahawa kependaman gelombang I dan V dan kependaman interpeak gelombang I-V adalah lebih pendek apabila dirangsang menggunakan rangsangan klik berbanding dengan rangsangan BBN dan NBN dalam kumpulan kawalan. Selain itu, amplitud gelombang I dan V dan nisbah amplitud gelombang V/I adalah lebih tinggi dengan rangsangan klik berbanding rangsangan BBN dan NBN dalam kumpulan kawalan. Keputusan ini adalah serupa dengan yang diperhatikan dalam kumpulan tinnitus. Untuk perbandingan antara kumpulan, kependaman gelombang I dan V adalah lebih pendek dalam kumpulan tinitus berbanding kumpulan kawalan apabila dirangsang menggunakan rangsangan klik dan BBN, tetapi lebih lama dengan rangsangan NBN pada 50dBSL. Terutama, hanya rangsangan klik menunjukkan perbezaan yang ketara dalam kependaman gelombang I dan V antara kumpulan. Mengenai amplitud gelombang I dan V, kumpulan tinitus menunjukkan amplitud yang lebih tinggi berbanding kumpulan kawalan apabila dirangsang menggunakan rangsangan klik, BBN dan NBN. Walau bagaimanapun, perbezaan ketara dalam amplitud gelombang I didapati hanya dengan rangsangan BBN, manakala amplitud gelombang V menunjukkan perbezaan yang signifikan hanya dengan rangsangan klik. Penemuan menunjukkan bahawa tinnitus membawa kepada perubahan dalam laluan pendengaran. Rangsangan BBN menunjukkan penindasan tinitus terbesar mungkin bermula pada tahap kolikulus inferior, yang menjana gelombang V ABR. Kajian ini memberikan pandangan yang berharga tentang mekanisme penindasan tinitus dan menyerlahkan potensi rangsangan pendengaran yang berbeza untuk campur tangan tinnitus yang disasarkan.

REVEALING THE EFFECTS OF DIFFERENT AUDITORY STIMULATIONS ON TINNITUS SUPPRESSION: AN AUDITORY BRAINSTEM RESPONSE (ABR) STUDY

ABSTRACT

Tinnitus, the perception of ringing in the ear affects approximately 10-30% of the global population, making it a prevalent health concern. However, the exact tinnitus pathophysiology and most effective treatment remain debatable. Sound therapy employing broadband noise (BBN) is commonly employed for tinnitus management, based on the principle of tinnitus suppression. Yet, not all patients respond positively to BBN therapy. In view of this, it is of interest to investigate the physiological mechanism of tinnitus suppression when stimulated with different auditory stimuli using an auditory brainstem response (ABR) test. In the initial stage, a pilot study involving 5 healthy adults (10 ears) and 10 tinnitus patients (10 ears) was conducted to determine the optimal stimulus intensity for tinnitus suppression when using different auditory stimulations. The optimal stimulus from the pilot studies was used to compare with click, BBN and narrowband noise (NBN) in the subsequent case control experiment. For main study, 28 participants (56 ears) from control group (mean age: 37.39 ± 11.21 years) and 31 participants (45 ears) from tinnitus group (mean age: 40.74 ± 13.24) participated. The pilot study revealed that stimulus intensity at 50dBSL produced higher amplitudes and shorter latencies of wave I and V compared to 30dBSL intensity. The 50dBSL was chosen to be used in the subsequent study. Results for the main findings revealed that the latency of wave I and V and interpeak latency of wave I-V were shorter when stimulated using click

stimulus compared to the BBN and NBN stimuli in the control group. Additionally, the amplitude of wave I and V and amplitude ratio of wave V/I were higher with click stimulus compared to the BBN and NBN stimuli in control group. These results were similar to those observed in the tinnitus group. For the comparison between groups, the latency of wave I and V was shorter in the tinnitus group compared to the control group when stimulated using click and BBN stimuli, but longer with NBN stimulus at 50dBSL. Notably, only click stimulus showed a significant difference in the latency of wave I and V between groups. Regarding the amplitude of waves I and V, the tinnitus group showed higher amplitudes compared to the control group when stimulated using click, BBN and NBN stimuli. However, a significant difference in the amplitude of wave I was found only with BBN stimuli, while the amplitude of wave V showed a significant difference only with click stimuli. The findings suggest that tinnitus leads to the changes in the auditory pathway. BBN stimulus showed the greatest tinnitus suppression likely starting at the level of the inferior colliculus, which generates wave V of the ABR. This study provides valuable insights into the mechanisms of tinnitus suppression and highlights the potential of different auditory stimuli for targeted tinnitus interventions.

CHAPTER 1

INTRODUCTION

This chapter describes an insightful overview of the study based on the research topic including its significance within the knowledge base. A brief on the tinnitus including its management, auditory brainstem response (ABR) and different auditory stimulations applicable in this study. In this chapter, the rationale for undertaking this study is thoroughly explained, aligning with research questions. From research questions, we elucidate both general and specific research objectives along with hypotheses to guide our findings.

1.1 Study Background

1.1.1 Introduction to Tinnitus

Tinnitus is generally defined as the perception of sound in the absence of a corresponding external stimulus. People often describe their tinnitus as buzzing, roaring, clicking and hissing. For clinical purposes, tinnitus is considered chronic when experienced for more than 12 months (Ahmadpour et al., 2021; Nemati et al., 2014; Said, 2012; Turner et al., 2022). Tinnitus is commonly divided into two categories namely objective and subjective tinnitus. Objective tinnitus is generated somewhere in the body and reaches the ear through conduction in body tissues. It can be heard by the observer and is caused by a mechanical sound in the body. Meanwhile, subjective tinnitus, as applied in this study, is more common compared to objective tinnitus. It is not associated with a physical noise and is only audible to the affected individual. There are several risk factors and causes that can trigger tinnitus such as noise exposure, ototoxic medication and presbycusis (Additional details are provided in Section 2.2.2).

The prevalence of tinnitus is significant, affecting approximately 10-30% of the global population, with 3-4% of patients seeking medical attention for this condition

(Davis & El Rafaie, 2000; Negrila-Mezei et al., 2011). According to the American Tinnitus Association, approximately 50 million people in the United States suffer from chronic tinnitus. The severity of tinnitus varies from person to person and from day to day. Studies have indicated an increase in prevalence with age (Ahmad & Seidman, 2004) and a slightly higher incidence in men than women (Holgers et al., 2005; Lockwood et al., 2002). However, some have described a slightly higher prevalence in women than in men (Axelsson & Ringdahl, 1989). A possible explanation for a higher prevalence in men maybe that they are more exposed to occupational noise (Pinto et al., 2010), while women often have more opportunities to seek medical care, potentially contributing to a higher prevalence among them (Pinto et al., 2010).

Tinnitus can also lead to psychological problems. It is frequently associated with depression as well as anxiety, annoyance, anger, frustration, and insomnia. Tyler & Baker (1983) highlighted the difficulties faced by tinnitus sufferers, sleep disturbances being the most commonly reported. Additionally, tinnitus has been associated with suicidal ideation and attempts. A study conducted by Seo et al. (2016) on 17,446 Korean individuals to investigate the prevalence of suicidal ideation and behavior in South Koreans with and without tinnitus found that 20.9% of the participants with tinnitus reported having thoughts of suicide and 1.2% reported actually and attempting suicide. Therefore, tinnitus is a serious yet common symptom of various comorbid conditions not only related to audiological problems but also behavioral health issues.

Until the early 1980s, it is believed that tinnitus was solely caused by cochlear phenomena. However, recent research has demonstrated that tinnitus occurs in the auditory pathways and auditory cortex. The mechanisms that contribute to the tinnitus perception include the impairment of hair cells in the cochlea, an increase spontaneous firing rate, neural synchronization and tonotopic reorganization (further details in Section 2.2.1).

1.1.2 Tinnitus Management

There are various strategies have been developed for tinnitus management. It was managed by multidisciplinary such as ENT doctors and audiologists. In audiology perspective, hearing aids and sound therapy are commonly used for tinnitus management. Hearing aids are used to amplify sounds and suppress tinnitus in individuals with hearing loss and tinnitus. Jacquemin et al. (2022) conducted a systematic review on 28 studies to investigate the effectiveness of hearing aid in helping tinnitus with significant hearing loss. The outcomes show that approximately 68% of the studies showed a significant improvement in tinnitus when utilized hearing aids.

Nevertheless, individuals with tinnitus who do not have hearing loss might be beneficial by sound therapy. Sound therapy utilizing broadband noise (BBN) is frequently used for tinnitus management. It is designed mainly based on the tinnitus suppression principle or masking. Tinnitus suppression is defined as a percent reduction in tinnitus loudness. However, the efficacy of sound therapy varies. BBN is a noise that has continuous spectrum and present over a wide range of frequencies (see Figure 1.1). Apart from that, narrowband noise (NBN) is another type of auditory masking that has been used for tinnitus suppression. It is a noise that only occupy narrow range of frequencies from BBN. For example, narrowband noise of 1/3 octave with amplitude spectrum cover more at area A as illustrated in Figure 1.2. Further details will be discussed in section 2.3.3.

The effectiveness of tinnitus suppression is commonly evaluated using subjective assessment such as behavioral test and questionnaires. Meanwhile, the evaluation of the tinnitus suppression using objective test is limited. Due to the limited studies, the aim of this study to utilize auditory brainstem response (ABR) as an alternative objective measurement to assess the effectiveness of auditory stimulations in suppressing tinnitus.

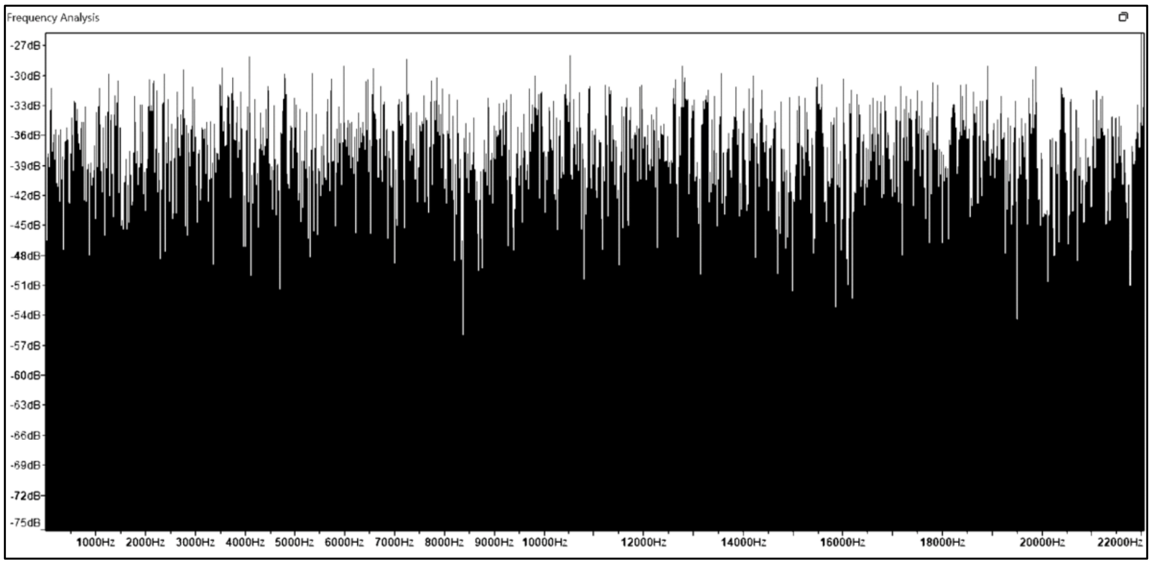

Figure 1.1 The spectrum of broadband noise stimulus (adapted from Audacity 3.4.2 www.audacityteam.org)

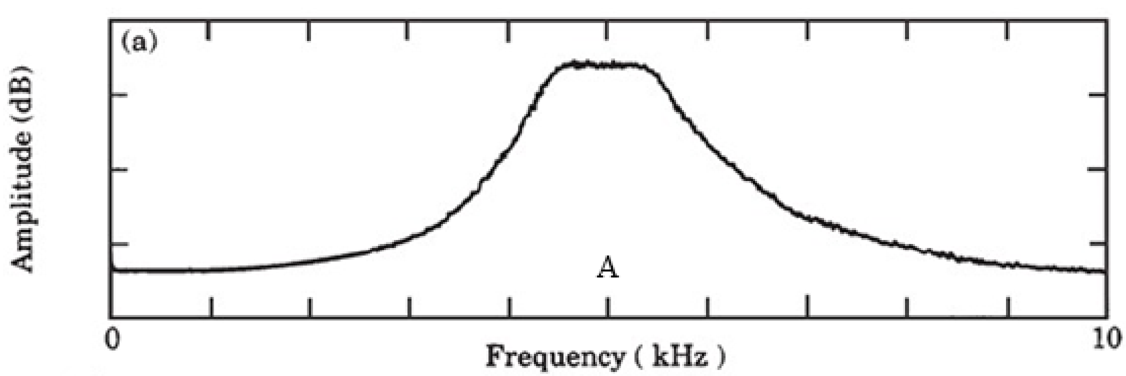

Figure 1.2 Narrowband noise of 1/3 octave with amplitude spectrum (by American Speech-Language-Hearing Association www.asha.org)

1.1.3 Auditory Brainstem Response (ABR)

Auditory brainstem response (ABR) also known as brainstem auditory evoked potentials, is an objective measurement of auditory pathway function from the auditory nerve to the inferior colliculus. ABR consists of five to seven positive waves with waves I to V are commonly evaluated: wave I (generated by the eighth cranial nerve), wave II (generated by cochlear nucleus), wave III (generated by superior olivary complex), wave IV (generated by lateral lemniscus) and wave V (generated by inferior colliculus) (Hall, 2007). These waves generally occur in the first 10 ms after the stimulation and the generators of ABR waves are illustrated in Figure 1.3.

ABR commonly employs click stimulus to estimate the individual's hearing sensitivity thresholds and identify retrocochlear pathologies. Click stimulus is a broad frequency spectrum as illustrated in Figure 1.4 and there is a well-known normative data for ABR evoked by click stimulus mentioned by Hall (2007). The details will be discussed further in Section 2.3.3.

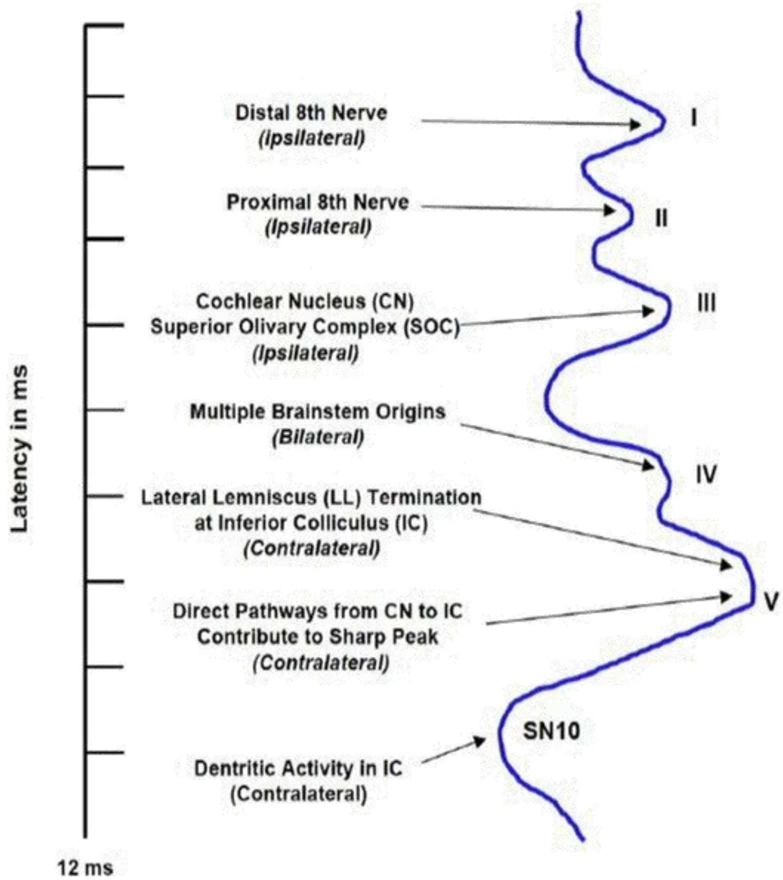

Figure 1.3 ABR waves from wave I to V represent each generator of ABR waves based on research findings (taken from handbook of auditory evoked responses by Hall, 1992)

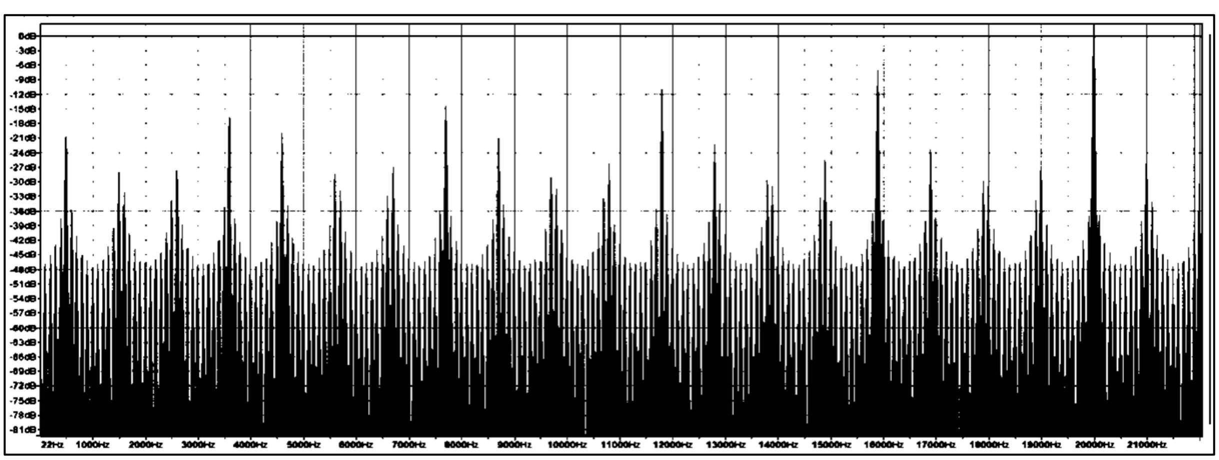

Figure 1.4 The spectrum of click stimulus (adapted from Audacity 3.4.2 www.audacityteam.org)

1.2 Problem Statement

Tinnitus, a ringing sound in the ear, is estimated to affect approximately 10-15% of people in the UK (Hoare et al., 2012). Meanwhile, in Malaysia, a comprehensive study in prevalence of tinnitus is yet to be conducted. However, Laporan Tahunan Perkhidmatan Pemulihan Perubatan Audiologi 2021 does provide valuable insights. According to the report, there are 278 new patients with tinnitus registrations in a year. Although this number may not fully reflect the actual count of patients with tinnitus in Malaysia, it serves as evidence that tinnitus is a prevalent issue among Malaysians.

Human imaging methods and animal model studies have suggested that the site of tinnitus generation may arise from the central auditory system in response to decreased peripheral input (Valderrama et al., 2018). It results in the increment of the spontaneous firing, neural synchrony and tonotopic reorganization (Eggermont & Roberts, 2004).

Even though there are many uncertainties due to the poor understanding of tinnitus pathophysiology, different types of tinnitus management options are now available. Sound therapy is one of the most common approaches for tinnitus management. It is designed based on the tinnitus suppression principle which is to ‘cover up’ and divert the tinnitus sound.

ABR, a short latency of auditory evoked potential, is widely used to evaluate the neural activity along the auditory pathway in response to auditory stimuli, yet its potential in elucidating tinnitus suppression mechanism remains largely unexplored. Previous studies using ABR have shown promising results particularly regarding the utility of click stimulus on tinnitus mechanism. However, the literature is limited and inconclusive when considering confounding factors such as gender, age and hearing status.

So far, no study has been performed to investigate the potential usefulness of ABR in understanding the tinnitus suppression mechanism. It is of interest to study the fundamental aspect of tinnitus suppression at a physiological level when stimulated by different auditory stimuli such as BBN, NBN and click using ABR testing. While BBN has been recognized for its efficacy in tinnitus suppression, the inclusion of NBN allows for a comparative analysis to determine the optimal stimulus for tinnitus suppression, particularly targeting the dominant pitch matching and potentially guiding future research and inspiring innovative approaches to tinnitus management.

Including a self-report questionnaire on tinnitus severity is valuable for understanding the subjective experience of tinnitus and its relationship to the physiological data being collected. Given that the Borang Evaluasi Soal-Selidik Tinnitus (BEST) questionnaire is newly developed in Malaysia, this study also aims to compare with the existing questionnaires.

1.3 Research Questions

1. Are there differences in the mean latencies and amplitudes of wave I and V between control and tinnitus groups when stimulated by different auditory stimuli in 50dBSL and 30dBSL? (Pilot Study).
2. Are there differences in the mean latencies, amplitudes of wave I and V and interpeak latencies of wave I-V between click, broadband noise, and narrowband noise in the control group?
3. Do the mean latencies, amplitudes of wave I and V and interpeak latencies of wave I-V differ between click, broadband noise, and narrowband noise in the tinnitus group?

4. Are there differences in the mean latencies and amplitudes of wave I and V, interpeak latencies of wave I-V and amplitude ratio of V/I between control and tinnitus groups when stimulated by different auditory stimuli?
5. Are there any correlation observed between tinnitus measurement methods, specifically the Visual Analogue Scale (VAS), Borang Evaluasi Soal-Selidik Tinnitus (BEST) questionnaire and loudness matching?

1.4 Research Objective

1.4.1 Main Objective

This study aims to investigate the effects of different auditory stimulations on tinnitus suppression using ABR in adults.

1.4.2 Specific Objectives

STEP 1 (PILOT STUDY)

1. To conduct a pilot study comparing the ABR parameters (latencies and amplitudes of wave I and V) between control and tinnitus groups at 50dBSL and 30dBSL (between-group comparisons).

STEP 2 (MAIN STUDY)

2. To compare the ABR parameters (latencies, amplitudes of wave I and V and interpeak latencies of wave I-V) between click, broadband noise, and narrowband noise in control group (within-group comparisons).

3. To compare the ABR parameters (latencies, amplitudes of wave I and V and interpeak latencies of wave I-V) between click, broadband noise, and narrowband noise centred at

the individual's tinnitus dominant frequency in tinnitus group (within-group comparisons).

4. To compare the ABR parameters (latencies, amplitudes of wave I and V, interpeak latencies of wave I-V and amplitude ratio of V/I) between control and tinnitus groups (between-group comparisons).

5. To identify the correlation between tinnitus measurement methods: visual analogue scale (VAS), BEST and loudness matching in assessing tinnitus severity.

1.5 Research Hypothesis

1.5.1 Null Hypothesis

1. There is no significance difference of ABR parameters (latencies and amplitudes of wave I and V) between control and tinnitus groups at 50dBSL and 30dBSL (between-group comparisons) (Pilot Study).

2. There is no significance difference of ABR parameters (latencies, amplitudes of wave I and V and interpeak latencies of wave I-V) between click, broadband noise, and narrowband noise in control group (within-group comparisons).

3. There is no significance difference of ABR parameters (latencies, amplitudes of wave I and V and interpeak latencies of wave I-V) between click, broadband noise, and narrowband noise centred at the individual's tinnitus dominant frequency in tinnitus group (within-group comparisons).

4. There is no significance difference of ABR parameters (latencies, amplitudes of wave I and V, interpeak latencies of wave I-V and amplitude ratio of V/I) between control and tinnitus groups (between-group comparisons).

5. There is no correlation between tinnitus measurement methods: visual analogue scale (VAS), BEST and loudness matching.

CHAPTER 2

LITERATURE REVIEW

This chapter explains broadly about the study in the context of previous research, presents a critical synthesis of empirical literature according to the relevant variables. In this chapter, we also justify on how the studies addresses a gap or problem in the literature and outlines the theoretical or conceptual framework of the study. We also include the theoretical argument and demonstrate our ideas and findings that pertain to our topic.

2.1 Introduction

This chapter presents the literature search for the current follow-up study. An initial study, conducted by an undergraduate student in 2023 as an unpublished thesis, found no significant differences in latencies and amplitudes of ABR wave I and wave V across all stimuli and intensities between patients with hearing loss with and without tinnitus. This suggests that the increase in wave V amplitude firing rate is influenced more by the presence of tinnitus than by recruitment. In our current study, we are also using dBSL (decibel sensation level) instead of a standard fixed intensity. Further details about the methodology will be discussed in Chapter 3.

At the beginning of this chapter, important literature is offered to learn about the pathophysiology and mechanism of tinnitus which is also involved the type, causes and management of tinnitus.

Then, the discussion continues with a literature search about the objective evaluation of tinnitus suppression which serves the main reason of this study. This section investigates the objective evaluations of tinnitus suppression that have been initiated by previous researchers. From this literature review, research gaps were identified what is lacking in previous studies.

Next, we discussed further about ABR and the most suitable research tools used in this study. Then, the discussion continues with a literature search about ABR in tinnitus. It will explain and review the basic concepts of how the framework is built.

2.2 Tinnitus

2.2.1 The Pathophysiology & Mechanism of Tinnitus

2.2.1(a) Neurophysiological Model

Tinnitus is a ringing in the ear and originating within the head. Various theories have been proposed to elucidate the unclear pathophysiology of tinnitus, with considerable attention initially focused on cochlear mechanisms. However, recent advancements in human neuroimaging methods and animal models highlight the central auditory system as the main site of tinnitus generation.

Studies suggested that **increase spontaneous firing rate** and **neural synchronization** along the central auditory pathway may be implicated in tinnitus generation (Henry et al., 2014; Kaltenbach et al., 2002). Studies on animals have found that when the central auditory system is not receiving input due to cochlear damage, it increases its spontaneous firing rates in order to restore the normal activity in the central auditory pathway. Nevertheless, some disadvantages of using animals for tinnitus research exist, the main one being the lack of a standardized animal model of tinnitus.

One theory has proposed that the generation of tinnitus is due to the **reorganization of cortical tonotopic map** in auditory structures (Eggermont & Roberts, 2004). For example, if the auditory cortex is not receiving stimulation from the cochlea such as in the high frequency regions due to high frequencies loss, the neurons are responsible for processing the high frequencies in auditory cortex are still intact since the damage is in the cochlea. In order to restore the normal activity in the auditory cortex, these neurons will begin to respond to the frequencies close to the impairment region such as the mid-frequencies. As a result, the edge of the impairment area becomes overrepresented. Figure 2.1 demonstrates the changes in tonotopy after exposed to a 4kHz tone at 123dB for 7 hours in the mice. The reorganisation of the tonotopic map in the auditory cortex has been suggested as a possible contributor to the tinnitus perception.

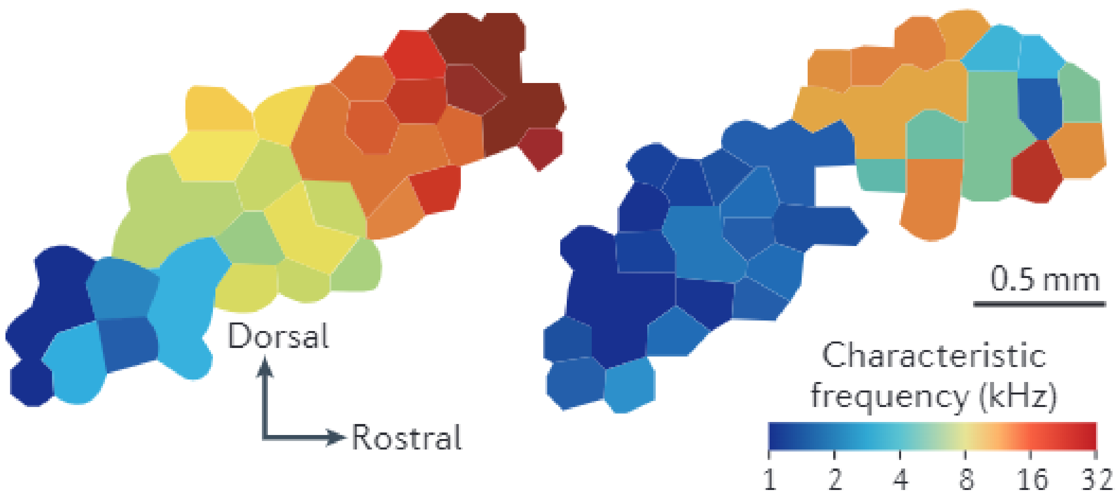

Figure 2.1 Changes in tonotopy after hearing loss. Taken from Elgoyhen et al. (2015)

2.2.1(b) Neuropsychological Model

In addition to the physiological model for tinnitus generation, the neuropsychological model Jastreboff (1990) proposes that fear is a conditioned response that is responsible for generating a bothersome tinnitus. There are some stages for behavioral psychology which are generation of the tinnitus-initiating signal in the peripheric auditory system, detection of the neuronal activity induced by tinnitus and perceptional evaluation of tinnitus. Haider et al. (2018) mentioned that the frontal cortex become more engaged in subjects with mild, habituation tinnitus and this may facilitate bypassing the emotional processing from the amygdala and the use of alternate limbic pathways involving the insula and parahippocampus gyrus. An accumulation of knowledge of fundamental mechanism might help to develop novel treatments and prevention modalities for tinnitus.

2.2.2 Tinnitus Causes

Tinnitus is always associated with hearing loss and the prevalence showed approximately 90% of people with tinnitus also have hearing loss and most of them do not realize that they have both conditions (Henry, 2022).

The primary causes of tinnitus linked with hearing loss often include noise induced hearing loss, presbycusis, and ototoxic drugs. Further details will be discussed further in the following section.

2.2.2(a) Noise Induced Hearing Loss

Noise induced hearing loss (NIHL) is the most prevalent cause of tinnitus (McCormack et al., 2016) and study from Henry et al. (2014) stated that, excessive noise exposure is the second most common cause of tinnitus for about 19.6% followed by ototoxicity about 16.8% and presbycusis about 16.3%. Tinnitus that results from noise exposure can occur suddenly or gradually and patients may perceive an increase in loudness and a change in pitch. There are about 1.1 billion teenagers and young adults worldwide who have suffered from NIHL and mostly because of the use of headphones and music players or other recreational noise (Chadha & Cieza, 2017).

Occupational noise also can cause NIHL and probably cause more cases of tinnitus than all other etiologies combined. There are many people who have a long history of noise exposure complaint of tinnitus that is high pitched (above 3000 Hz) and tonal in quality. Small temporary changes in the outer hair cells following noise exposure can trigger tinnitus by increasing the gain of the central auditory system (Jastreboff & Hazell, 2004). There are many factors that can cause tinnitus and mostly related to the effect of noise on the auditory system and subsequent damage to the microstructures in the cochlea.

Exposed to loud noise for a long time can lead to permanent threshold shift (PTS) However, tinnitus also can occur even a person expose to a single noise exposure. It also can cause a temporary threshold shift (TTS). TTS is a change in hearing sensitivity which recovers to baseline levels in minutes, hours, days or weeks with up to 30 days post exposure (Ryan et al., 2016).

2.2.2(b) Ototoxic Drugs

Ototoxicity is inner ear damage that arises as a side effect of specific medications. It can result in issues concerning hearing and balance, as well as lead to symptoms of tinnitus. There are some oral medications that can cause bilateral tinnitus such as salicylates, nonsteroidal anti-inflammatory drugs and chemotherapy agents. The mechanism causing drug-induced ototoxicity is still unclear but it may involve biochemical and electrophysiological changes in the inner ear and eighth cranial nerve impulse transmission.

The severity of tinnitus depends on the drug, dosage and how long a person take the medicines. The tinnitus symptoms can be permanent or temporary and usually if the patients stop taking the medications, the symptoms typically receded. However, based on American Tinnitus Association, ototoxic drugs such as non-Steroidal Anti-Inflammatory

Drugs (NSAIDs), cancer medications and Quinine-based medications will cause permanent tinnitus symptoms.

Ototoxic drugs cause damage to the inner ear and the effects from ototoxic may progress up to 6 months after stopping the injectable drug (Duggal & Sarkar, 2007). The American Speech-Language-Hearing Association recommended to screen at 3 and 6 months after terminating ototoxic drugs to allow delayed hearing loss to be detected.

2.2.2(c) Presbycusis

Presbycusis is hearing loss that develops gradually as a person get older. It is a type of sensorineural hearing loss resulting from damage to the inner ear. Presbycusis can also result in the symptom of tinnitus. Nuttall et al. (2004) stated that any pathologic lesion in the auditory pathway or any reduction in auditory nerve function due to aging has the potential to produce tinnitus. Tinnitus in elderly can be stressful and might disturb daily activities. It also causes emotional and sleep alterations as it is a complex symptom that can be dramatically compromise the individual's quality of life. The age-related hearing loss showed why tinnitus is so prevalent among seniors.

2.2.3 Tinnitus Management

Tinnitus is a heterogenous condition with many possible etiologies and often associated with significant psychological states. Even though there are many treatments applied for tinnitus patients in Malaysia but still there are no tinnitus treatment is singularly effective. Tinnitus management strategies are diverse and dependent on the clinical specialty involved. Approaches to managing tinnitus aim either to reduce or eliminate the physical perception of tinnitus or to change the patient's reaction to it. This section discusses key management strategies.

2.2.3(a) Tinnitus Suppression Mechanism

Research has identified several mechanisms through which tinnitus may be suppressed, ranging from neural plasticity to the modulation of neural activity within the auditory pathways. For example, studies suggest that repeated auditory stimulation can lead to neural plasticity, resulting in the habituation of the tinnitus perception (Henry et al., 2014; Noreña, 2015; Wang et al., 2020).

2.2.3(b) Management Approaches

2.2.3(b)(i) Tinnitus Retraining Therapy (TRT)

Tinnitus retraining therapy (TRT) is a well-documented treatment approach that leverages the principles of neural plasticity and habituation to manage tinnitus. TRT combines sound therapy with directive counselling to help patients habituate to the tinnitus signal, thereby reducing its impact on their daily lives. To facilitate habituation by providing continuous low-level sound that reduces the contrast between tinnitus and background noise. Continuous exposure to sound helps in remodelling the auditory pathways and encourages the brain to reclassify tinnitus as an unimportant sound, thereby reducing its perceptual prominence. Meanwhile directive counselling is to alter the patient's negative associations with tinnitus and provide strategies to cope with the emotional and psychological impact. There is a study from Cuesta & Cobo (2020) found 22 participants out of 25 benefited from a tinnitus treatment combined with counselling and BBN. It proposed that this treatment was effective in reducing patients with tinnitus.

2.2.3(b)(ii) Sound Therapy

Sound therapy, including white noise, narrowband noise and notched music at dominant tinnitus pitch matching, has been shown to reduce tinnitus severity by promoting auditory masking and neural reorganization. Evidence indicates that specific types of acoustic stimulation such as auditory masking and habituation can lead to a decrease in hyperactivity within the central auditory system, contributing to tinnitus suppression.

For example, white noise therapy is a widely-used treatment approach for tinnitus that leverages continuous sound to mask tinnitus and promote habituation. White noise is a type of sound that contains all frequencies at equal intensity, providing a consistent auditory signal that can help to reduce the perception of tinnitus. White noise masks the tinnitus sound, making it less perceptible. This masking effect helps to reduce the immediate awareness and annoyance of tinnitus. Over time, the consistent auditory input from white noise encourages the brain to reclassify the tinnitus sound as less important. This process involves neural plasticity, where the brain's auditory pathways adjust to prioritize the external white noise over the tinnitus signal.

The effectiveness of sound therapy in reducing tinnitus severity has been demonstrated in other studies (M. Zakaria, 2020; M. Zakaria et al., 2020). Henry et al. (2008) found that white noise significantly reduced the perception and distress associated with tinnitus in many patients. The study highlighted that continuous exposure to white noise could lead to substantial improvements in tinnitus symptoms.

2.2.3(b)(iii) Neuromodulation Techniques

Techniques such as transcranial magnetic stimulation (TMS) and transcutaneous electrical nerve stimulation (TENS) target specific brain regions to alter neural activity associated with tinnitus. These methods have demonstrated efficacy in reducing tinnitus symptoms by modulating the excitability of the auditory cortex and brainstem.

2.2.3(b)(iv) Cognitive Behavioral Therapy (CBT)

CBT has been used widely to treat tinnitus patient and it has been studied by many researchers and was originally developed by Beck (1979). CBT is a concept of counselling which is a combination of numerous psychological interventions that have been developed and evolved from cognitive and behavioral therapies. Beck (1979) first applied CBT for those who have depression, anxiety or insomnia which is the main concept is to allow patient to have more positive and realistic thoughts which is referred to as cognitive restructuring. It plays an important role on tinnitus treatment as it can reduce the impact of tinnitus on quality of life rather than directly change the perceived loudness.

CBT for tinnitus is focused on reducing the distress and handicap induced by tinnitus. It separates the tinnitus from the patient's reaction to it and they will prepare to learn different ways of reacting it. Study from Jun & Park (2013) stated that CBT is effective for alleviating the annoyance caused by tinnitus and give positive effect to the patient's emotion. Even though it does not give any effect on improving acoustic characteristics of tinnitus, but it improves response to tinnitus. Thus, still CBT is one of the good options for tinnitus treatment.

2.2.3(c) Residual inhibition (RI) of tinnitus and its underlying mechanism

Residual inhibition (RI) is defined as a temporary decrease of tinnitus after a prolonged acoustic stimulation. It is often applied as a rapid management strategy in tinnitus clinic to provide relief for individuals experiencing tinnitus. Zakaria et al. (2020) studied the residual inhibition outcomes which is another method to measure tinnitus suppression psychophysically in patients with tinnitus in response to various auditory stimuli.

There is a study from Folmer et al. (2005) stated sound generators that delivered broadband sound frequencies which is typically 100-8000Hz give immediate benefits for tinnitus patients. They experience residual inhibition and usually brief for about 30-60 seconds and for several patients, residual inhibition can last hours, days or weeks. In Feldman's (1971) study, a considerable number of participants reported a temporary decrease in their tinnitus following the cessation of the masker.

Sound-evoked suppression of spontaneous activity has frequently been observed in neurons within the auditory system (Smith, 1977; Harris and Dallos, 1979; Relkin and Turner, 1988; Ebert and Ostwald, 1995; Galazyuk et al., 2005; Wehr and Zador, 2005; Portfors and Roberts, 2007; Nelson et al., 2009). This reduction, which can last for hundreds of milliseconds, has been observed in auditory nerve fibers (Smith, 1977; Harris and Dallos, 1979; Relkin and Turner, 1988), cochlear nucleus (Ebert and Ostwald, 1995; Portfors and Roberts, 2007), inferior colliculus (Galazyuk et al., 2005; Nelson et al., 2009) and auditory cortex (Wehr and Zador, 2005; Bender et al., 2016). Figure 2.2 below illustrates an example of the sound evoked suppression of spontaneous firing in an inferior colliculus neuron in a mouse.

The suppression of spontaneous firing induced by sound has been extensively investigated in echolocating bats (Voytenko and Galazyuk, 2010, 2011) and mice (Galazyuk et al., 2017). Despite the widespread occurrence of this phenomenon, little was known about the cellular mechanism responsible for this long-lasting suppression of spontaneous firing.

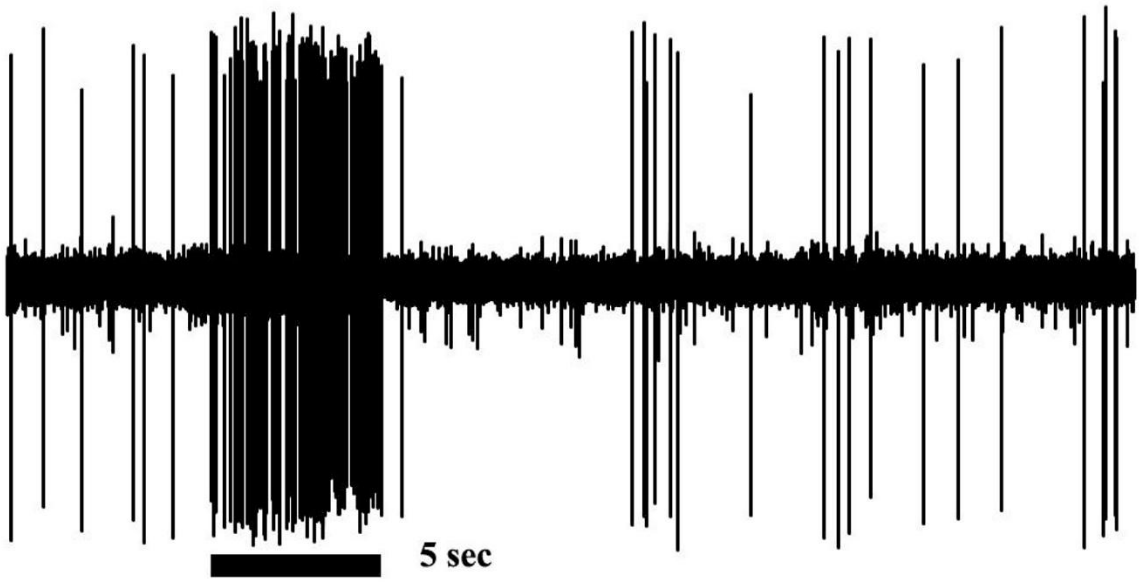

Figure 2.2 Sound-evoked suppression of spontaneous firing after stimulus presentation. A recording trace of an inferior colliculus neuron exhibiting spontaneous activity which was recorded extracellularly in awake restrained mouse. Vertical lines show action potentials of this neuron recorded before, during, and after a 5 second sound stimulus. Note the suppression of spontaneous firing in this neuron following the response to a sound

2.2.4 The Effectiveness of Tinnitus Suppression

Despite the high prevalence of tinnitus and its significant impact on quality of life, there is currently no cure for it. The effectiveness of tinnitus suppression also can be measured using subjective and objective tests. Further details will be discussed in the following section below.

2.2.4(a) Subjective Test

The effectiveness of tinnitus suppression can be measured using subjective test such as behavioral assessments and questionnaires. Study by Kim et al. (2014) compared the effectiveness of three band filtered noises in 38 tinnitus participants for about 9 weeks using BBN, narrowband noise and mixed band noise using psychometric questionnaires including Tinnitus Handicap Inventory (THI), visual analogue scale (VAS) on annoyance and numerical description of hours of tinnitus perception. The study revealed all noises can be beneficial and BBN offers the highest reduction.

Another study conducted by Durai & Searchfield (2017) investigated the effectiveness of the BBN and nature sounds on 18 participants. The study found that the BBN resulted significantly higher reduction of Tinnitus Functional Index (TFI) after 8 weeks of treatment.

Study from Vernon & Meikle (2003) also reported 88% of individuals with tinnitus reported some degree of tinnitus suppression. This study found the duration of tinnitus suppression varied among individuals with tinnitus, ranging from several seconds to more than 10 minutes. The tinnitus suppression is also dependent on the intensity, duration and type of stimulus used.

Research conducted by De Ridder et al. (2005) utilized TMS to suppress tinnitus, revealing that TMS could transiently suppress tinnitus either partially or completely in approximately 53% of patients with subjective tinnitus. De Ridder et al. (2005) also mentioned in their study that animal studies conducted by He et al. (2002), demonstrated that low-frequency (1 Hz) electrical stimulation of the auditory cortex in bats led to a decreased firing rate in the thalamus.

2.2.4(b) Objective Test

Indeed, objective test have been used in numerous studies to evaluate the effectiveness of tinnitus suppression. Among these tests, electrical current has been utilized, including transcranial direct-current stimulation (tDCS) and TMS for tinnitus suppression (De Ridder et al., 2005; Joos et al., 2014; Konopka et al., 2001; Shekhawat &

Vanneste, 2018; Vanneste et al., 2013; Paffi et al., 2018; House, 1989; Ito & Sakakihara, 1994; Balkany et al., 1987; Okusa et al., 1993; Hazell et al., 1989).

Study by Joos et al. (2014) also used objective test which is **tDCS** to suppress the tinnitus and they found a significant suppressive effect of tDCS when applied over the auditory cortex, particularly in reducing tinnitus loudness and annoyance. However, this effect was observed only when tDCS was applied with an intensity of 2mA. They suggested that the reduction in tinnitus intensity might be attributed to a disruptive effect on ongoing hyperactivity within the auditory cortex and functionality related brain areas, independent of polarity. Additionally, they proposed that auditory cortex stimulation could influence the tinnitus related distress network.

Konopka et al. (2001) used **electrical promontory stimulation (EPS)** for tinnitus suppression and they found that tinnitus was reduced in 41.9% of patients with NIHL and in 50% of patients with non-noise induced hearing loss. They suggested that electrical stimulation by using positive direct current can change the spontaneous activity of cochlear nerve fibres. Then, it is suggested that the mechanism of beneficial effect can be due to increased microcirculation in part of the auditory pathways as a reflex effect. The mechanism by which EPS suppressed tinnitus may be related by synchronising discharges of the auditory nerve fibres (Waternabe et al., 2001).

There is one study from Riga et al. (2016) conducted a study on the objective assessment of subjective tinnitus through contralateral suppression of **otoacoustic emissions (OAE)** by white noise. Their findings indicated that tinnitus could be suppressed by the application of contralateral white noise at a level of 50dBSL. Many researchers have sought to uncover any correlation between tinnitus and the amplitudes of OAEs (Granjeiro et al., 2008; Dejonckere et al., 2009; Fabijan´ska et al., 2012; Modh