Cochlear Non-linearity and Efferent System Functioning in Individuals with Misophonia

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CERTIFICATE

This is to certify that this dissertation entitled **'Cochlear Non-linearity and Efferent System Functioning in Individuals with Misophonia'** is a bonafide work submitted in part fulfilment for degree of Master of Science (Audiology) of the student Registration Number: P01II21S0052. This has been carried out under the guidance of a faculty of this institute and has not been submitted earlier to any other University for the award of any other Diploma or Degree.

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This is to certify that this dissertation entitled **'Cochlear Non-linearity and Efferent System Functioning in Individuals with Misophonia'** is the result of my own study under the guidance a faculty at All India Institute of Speech and Hearing, Mysuru, and has not been submitted earlier to any other University for the award of any other Diploma or Degree.

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September, 2023

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ABSTRACT

Misophonia is a condition characterized by abnormally heightened sensitivity towards specific sound stimuli called triggers causing strong emotional and physiological reactions that can escalate to anger. The study aimed at understanding the cochlear (linear and non-linear) and auditory efferent system functioning in misophonics. 30 individuals each with misophonia and individuals without misophonia were included in the study. Transient evoked otoacoustic emission (TEOAE) and distortion product otoacoustic emission input-output (DPOAE I/O) function was obtained. TEOAEs were obtained in conditions with and without contralateral noise to assess the auditory efferent system.

Results showed no statistically significant difference (> 0.05) in the global amplitude of TEOAEs, suppression amplitude of TEOAEs and the slopes of the DPOAE I/O function between individuals with misophonia and without misophonia. Individuals with misophonia showed a statistically greater (<0.05) waveform shift upon contralateral noise presentation indicating hyperfunctioning of the auditory efferent system. Results suggest that the cochlear mechanisms are normally functional in individuals with misophonia whereas the auditory efferent system hyperactivity may indicate pathophysiological underpinnings in them, which needs to be further investigated. The findings of the study have clinical implications in terms of refining diagnostic criteria, developing targeted interventions, and enhancing our understanding of the mechanisms underlying misophonia.

Keywords: *Misophonia, TEOAE, DPOAE OAE, suppression and efferent system.*

Abbreviations: *Distortion product otoacoustic emission (DPOAE), distortion product otoacoustic emission input-output (DPOAE I/O), input-output (I/0), transient evoked otoacoustic emission (TEOAE), otoacoustic emission (OAE), misophonia assessment questionnaire (MAQ), misophonia questionnaire (MQ), general anxiety disorder-7 (GAD-7), Amsterdam misophonia questionnaire (A-MISO-S), magnetic resonance imaging (MRI), functional magnetic resonance imaging (fMRI), loudness discomfort level (LDL), auditory brainstem response (ABR), psychoacoustical tuning curves (PTCs) and root mean square (RMS).*

CHAPTER 1

INTRODUCTION

The term misophonia is derived from the Greek words misos and phónè, which means hate and voice, respectively. Previously, the terms used to describe misophonia were soft sound sensitivity syndrome or selective sound sensibility syndrome. however, from last two decades, the term misophonia is the most prevalent and accepted terminology (Potgieter et al., 2019). The prevalence of misophonia varies between 10% to 50% across various studies and populations.

According to Schröder et al., (2013) misophonia can be diagnosed when specific sounds made by humans (or anticipation of such sounds) immediately evoke feelings of irritation or disgust that escalate to anger. Swedo et al., (2022) defined misophonia as a disorder where the individual experiences reduced tolerance to specific auditory stimuli. These stimuli, known as "triggers" (sounds that create emotional reactions) are experienced as unpleasant or distressing sounds that evoke strong negative emotional, physiological, and behavioral responses that are not seen in most other people. The trigger stimulus can be of any auditory source (human, environmental, or animal origin) that varies across individuals. The most common ones are sounds produced by another individual, like lip smacking, chewing, loud breathing, tapping sounds (keyboard or pen clicking), etc. The most common triggers are related to eating (80%) (Schröder et al., 2013). The striking character of misophonia is the individual's adverse reaction to sound is devoid of the loudness of the trigger stimulus, and just audibility of the trigger

stimulus itself leads to a reflexive response (Schröder et al., 2019). Currently, misophonia is neither recognized by the Diagnostic nor Statistical Manual of Mental Disorders, Fifth Edition (DSM-V) nor in the International Classification of Diseases, Eleventh Edition (ICD-11) (Aryal & Prabhu, 2023b; Duddy & Oeding, 2014; Potgieter et al., 2019).

Wu et al.,(2014) reported a prevalence of 20% among undergraduate students in their study in the united U.S. In Turkey, the prevalence of misophonia was about 12.8% (Kılıç et al., 2021). Naylor et al., (2021) reported the prevalence among undergraduate students in the United Kingdom was reported to be 49.1%, while in the general population, about 18.4% reported having misophonia causing significant difficulty in life style (Vitoratou et al., 2023). The prevalence of individuals having moderate to severe degree of misophonia in college-going students in India was reported to be about 15.85% (Patel et al., 2023).

Misophonia, although it can occur as a standalone condition in an individual, many studies have reported association with both psychiatric (schizophrenia, mood disorders, depression, anxiety, obsessive-compulsive disorder, or post-traumatic stress disorder) (Rosenthal et al., 2022; Schröder, Vulink, et al., 2013; Wu et al., 2014) and audiological (Tinnitus and hyperacusis) (Jastreboff & Jastreboff, 2015) conditions. Misophonia and hyperacusis have shown similar characteristics, due to which Jastreboff & Jastreboff (2003) classified misophonia as a form of hyperacusis that also presented decreased sound tolerance, although there were vital differences between the two conditions. In hyperacusis, individuals presented with intolerance to moderate and loud sounds, whereas misophonics have reduced

tolerance towards soft, moderate, or loud “trigger” sounds. Previous findings have shown that individuals with tinnitus (60%) report having misophonia symptoms (Jastreboff & Hazell, 2008; Jastreboff & Jastreboff, 2003).

Misophonia has been hypothesized to have a genetical origin (Edelstein et al., 2013) and also be a result of pavlovian conditioning of reflexive response towards a trigger stimulus (Dozier, 2015), but the exact cause of misophonia is currently not well understood and its challenging to hypothesize the etiology of misophonia, requiring further research in the field to understand the etiology and pathophysiology involved (Duddy & Oeding, 2014; Jastreboff & Jastreboff, 2014; Schröder, Vulink, et al., 2013). While individuals with misophonia were reported to exhibit higher levels of activity in cortex including structures in the right anterior cingulate cortex, right insula, and right superior temporal cortex (Schröder et al., 2019), others have observed deviance in the anatomy and physiological connections between emotional centres, amygdala, cerebellum, auditory cortex, visual cortex and premotor cortex (Eijsker et al., 2021; Kumar et al., 2017, 2021; Schröder et al., 2015, 2019). Auditory underpinnings in the individuals with misophonia has also been postulated, with the studies showing diminished amplitudes of cortical evoked potentials (Schröder et al., 2014; Schröder, Mazaheri, et al., 2013). Although development of the neurophysiological model of misophonia (Jastreboff & Jastreboff, 2023) and neuro-audiological model of misophonia (Aryal & Prabhu, 2023b) show neurological basis and associate misophonia features to the cortical areas, the role of peripheral mechanism in misophonia generation is largely unexplored, highlighting the need for comprehensive

studies examining cochlear and auditory efferent processes to provide a holistic understanding of misophonia's neural underpinnings.

Misophonia is a condition that shows similarities and often coexists with auditory disorders like tinnitus and hyperacusis and is hypothesised to have pathophysiological similarities. Individuals with misophonia may present with similar physiological underpinnings with deviant mechanisms of linear and non-linear outer hair cell functioning (OHC) functioning that can be reflected in TEOAEs and DPOAEs, which are not yet explored. Individuals with tinnitus with normal hearing were reported to have absent or abnormal (80%) amplitudes of TEOAE (Thabet, 2009). Sarathy and Jaya, (2017) reported that there was a subtle difference in TEOAEs when contralateral noise was presented between individuals with and without tinnitus. On similar lines, studies using DPOAE measures found that individuals with tinnitus and normal hearing sensitivity had lower absolute amplitudes (Alshabory et al., 2022; Xiong et al., 2019) and a steeper input-output (I/O) function (Alshabory et al., 2022) when compared to the normal hearing controls without tinnitus. Compelling physiological evidence of reduced neural output from the cochlea in individuals with tinnitus and hidden hearing loss is also available in the literature (Schaette & McAlpine, 2011). Probing the role of atypical functioning of the medial olivocochlear bundle (MOCB) in in tinnitus sensation, Knudson et al. (2014) showed that those with tinnitus and hyperacusis had significantly higher DPOAE suppression when compared to other groups suggesting hyperresponsiveness of the MOCB in such individuals. Although misophonics may have similar underpinnings to that of Tinnitus individuals, there is a scarcity of literature on audiological findings in

the misophonic population as not many studies have not been conducted in the field. Considering the findings observed in individuals with tinnitus and hyperacusis, similar findings may be suspected in the misophonia population and further exploration in the domain is required. However, there have not been any studies that have been conducted to assess the role of cochlear linear and non-linear functioning and MOCB in generation of misophonia.

1.1 Need for the study

Misophonia is a condition that many researchers have been interested since the early 2000's and with increase in the number of publications since the last decade, most studies done have been in a neurological, psychology and psychiatry point of views and literature in a purely audiologist point of view have started to grow in recent years and a lot of areas remain unexplored and uncharted. Studies comparing the pure tone thresholds, temporal processing, auditory brainstem response, cortical auditory evoked potential and mismatch negativity (MMN) in individuals with and without misophonia have shown significant differences observed only in the cortical responses. There have been no studies targeted on the auditory end organ system functioning and the efferent system functioning.

In the present study, TEOAEs and DPOAE I/O function were used to assess the afferent and efferent system functioning in individuals with misophonia. TEOAEs are low level responses denoting the linear functioning and DPOAEs denote the non-linear functioning of the OHCs in the cochlea (Shera, 2004). Investigating otoacoustic emission (OAE) functioning will help contribute in understanding the pathophysiological underpinnings that is

involved in individuals with misophonia. Research has shown the OHCs are responsible for amplifying and fine tuning of the received auditory signal and disruptions in their functioning may lead to altered sound perception and emotional responses (Liberman, 2017). Investigating these processes can help provide valuable insights in the sensory processing in individuals with misophonia.

Additionally, understanding the auditory efferent system modulation on the cochlear mechanisms will provide important cues to the top-down processing (Asilador & Llano, 2021; Xiao & Suga, 2002) and the auditory efferent pathway is responsible for modulating the auditory system's sensitivity and filtering capabilities (Mammano & Nobilli, 2019). Dysfunction in the auditory efferent system can result in altered auditory processing and atypical reactions to specific sound stimuli (Wahab et al., 2016). Exploring the role of efferent functioning in misophonia may help uncover potential mechanisms underlying the enhanced sensitivity and emotional reactivity towards certain auditory stimuli observed in individuals with misophonia.

1.2 Aim of the study

The study aimed to understand the cochlear mechanisms (linear and non-linear) and olivocochlear efferent system functioning in individuals with misophonia.

1.3 Objectives of the study

- To compare the absolute global TEOAE amplitude between individuals with and without misophonia

- To compare the magnitude of amplitude shift and waveform shift in contralateral suppression of TEOAE between individuals with and without misophonia
- To compare the slope of DPOAE I/O function between individuals with and without misophonia across frequencies

1.4 Null hypothesis

- There is no significant difference in the absolute global TEOAE amplitudes between individuals with and without misophonia
- There is no significant difference in the magnitude of amplitude shift and waveform shift in contralateral supersession of TEOAE between individuals with and without misophonia
- There is no significant difference in the slope of DPOAE I/O function between individuals with and without misophonia across frequencies

CHAPTER 2

REVIEW OF LITERATURE

2.1 Definition of misophonia

Misophonia was initially defined as an abnormally strong dislike/hatredness towards specific sound stimuli featuring distinct patterns or meanings, stemming from abnormal activation of the limbic and autonomic nervous systems in individuals with normal hearing. The physical characteristics of auditory stimuli such as intensity or pitch appeared to be less relevant in individuals with misophonia, as misophonia sufferers did not show any relation between the intensity of trigger stimulus and the generated reflexive responses (Jastreboff & Jastreboff, 2002, 2014, 2015).

There has been disagreement surrounding the usage of the term "misophonia," which is believed to derive from Greek and translates to "hatred towards sound." However, this label has been deemed inadequate due to the fact that individuals afflicted by this condition do not exhibit sensitivity to all sounds indiscriminately, rather their sensitivity is directed towards specific auditory triggers, defining misophonia as abnormal strong immediate and automatic reaction towards generally softer sounds those are usually associated with another person (or animal) (Duddy & Oeding, 2014). Although the trigger sounds in misophonics create discomfort and irritability, they are not related to tolerance issues. Misophonia has been categorized as a variant of hyperacusis or phonophobia, despite its distinct characteristics in terms of decreased sound tolerance (Jastreboff & Jastreboff, 2003). In cases of hyperacusis, individuals exhibit aversion to sounds of moderate and high

intensity. However, in the context of misophonia, individuals demonstrate diminished tolerance to sounds of various intensities - soft, moderate, or loud, particularly those sounds that evoke strong emotional reactions, commonly referred to as "trigger" sounds. What sets misophonia apart is that the distress caused by these trigger sounds is not solely dictated by their loudness level.

According to Swedo et al., (2022) in their pursuit for a consensus definition conveyed an expert committee meeting on misophonia. They defined misophonia a as a disorder wherein individuals experience reduced tolerance to specific auditory stimuli, independent of the stimuli's loudness. These stimuli, termed as “triggers” evoked an unpleasant or distressing experiences, associated with strong negative physiological (increased muscle tension, increased heart beat rate and sweating etc.,), emotional (anger, disgust, irritation and anxiety etc.,) and behavioural (avoidance/escaping and even aggression through verbal or physical outburst in extreme cases) responses, which are unexpected for such acoustic stimuli from a typically normal hearing individual without misophonia.

2.2 Prevalence of misophonia

Several prevalence studies across diverse global populations have reported prevalence rate of misophonia reporting rates ranging from 5% to about 50%. For eg., Sarigedik & Gulle, (2021) reported that 13.8% of students from Turkey high school and university college experienced misophonic symptoms. This report was based on online administration of Amsterdam Misophonia Questionnaire (A-MISO-S) on 1188 students. Similarly, Vitoratou et al., (2023) administered Selective Sound Sensitive

Syndrome Scale (S-Five), Misophonia Questionnaire (MQ), A-MISO-S, Patient Health Questionnaire-9 and General Anxiety Disorder-7 (GAD-7) on 772 United Kingdom residents (Mean age 46.4 years) and reported a misophonic prevalence of 18.4% who reported symptoms to cause significant burden in their life style. Notably, Naylor et al. (2021) found 49.1% of medical students with clinically significant misophonic symptoms using online administration of A-MISO-S. This study was conducted on 336 medical students (aged 18 to 24 years) studying at University of Nottingham (England). While the overall prevalence rate of misophonia was reported in 49.1% of the population sampled, 37% of students had mild misophonic symptoms, whereas 12% and 0.3% reported of moderate and severe symptoms, respectively.

Jakubovski et al., (2022) conducted a large-scale survey of sample size where 2519 individuals were visited at their homes in Germany (divided into 53,000 areas) and assessed misophonia prevalence through the A-MISO-S and MQ. Results indicated a prevalence rate of misophonia to be 5% and 5.9% in the surveyed population on MQ and A-MISO-S, respectively. Pfeiffer et al., (2023) administered A-MISO-S on 2522 participants in Germany aged 16 to 96 years and reported 33.3% prevalence rate. Upon analysing severity of symptoms, it was found that 21.3% displayed subthreshold symptoms, 9.9% exhibited mild symptoms, 2.1% reported moderate to severe symptoms, and 0.1% experienced symptoms classified as severe to extreme. In a study conducted in Ankara, the capital city of Turkey, researchers examined 541 individuals, all aged 15 years or older. They randomly selected 300 households within Ankara and conducted semi-structured interviews using the

misophonia Interview Scale. The findings of the study revealed that the prevalence of misophonia was reported to be 12.8% among the participants. Interestingly, a significant portion of the population (78.9%) mentioned being distressed by at least one specific sound (Kılıç et al., 2021). An online survey of administering questionnaires consisting of MQ, Adult Sensory Questionnaire, Sheehan Disability Scale, Obsessive Compulsive Inventory-Revised and Depression Anxiety Stress Scale-21 on 483 undergraduate students in University of South Florida in Tampa, Florida, reported prevalence of misophonia in 20% of the population (Wu et al., 2014).

Prevalence studies of misophonia in Indian population has shown prevenances 15% in college going students with moderate and above severity and to about 20% - 49% considering the younger adult population in the country across various questionnaires. The prevalence of misophonia assessed through A-MISO-S and MQ was found to be about 15.85% in 328 college-going undergraduate students in India, having a moderate to severe degree of the disorder. About 20% of the students presented with misophonia like symptoms (Patel et al., 2023). Aryal And Prabhu administered (2022) A-MISO-S and Misophonia Assessment Questionnaire (MAQ) on 172 college going students of University of Mysore aged between 18 to 30 years and reported 48.27% and 23.38% of the population having misophonic symptoms and clinically significant misophonia respectively, and also reported that misophonia could occur in isolation or along with other co-morbid conditions like tinnitus and hyperacusis.

2.3 Etiology and pathophysiology of misophonia

The precise cause of misophonia remains a mystery, and research in this area is still in its early stages. While several researchers have put forth hypotheses, a conclusive explanation has not yet been established. Initially, misophonia was associated with the neurophysiological model of tinnitus, suggesting that misophonia involves strengthened connections of the auditory, limbic, and autonomic nervous systems (Jastreboff, 1990; Jastreboff & Hazell, 2004; Jastreboff & Jastreboff, 2015). Literature shows researchers hypothesizing the etiology and pathophysiology of misophonia through conditioning reflex reactions, deviant brain functioning for trigger stimulus observed through imaging studies/event related auditory evoked potentials and models to explain the pathophysiological process.

2.3.1 Misophonia as a conditioned reflexive response

Dozier (2015) reported that misophonia is a result of pavlovian conditioning, hypothesizing that the bodily reflex response is a result of conditioned aversive reflexive response to sound stimulus. He postulated that the reflexive responses to the trigger sound stimuli were acquired due to life experiences explaining why different people are sensitive to different sounds presenting conditioned reflexive responses towards them. Later the reflexive responses become aversive and develop disgust towards the trigger sound stimulus.

2.3.2 Genetic links to misophonia

Edelstein et al., (2013) reported that misophonia mimics a genetic condition known as synesthesia, which is characterized by a particular sensory stimulus evoking consistent several other additional sensations. In their observations they reported increased autonomic responses in individuals with misophonia to auditory stimuli and not for visual stimuli, suggesting that there might be a genetic predisposition as a cause in developing misophonia leading to deviant autonomic nervous system functioning causing reactions towards the trigger sound stimulus.

2.3.3 Role of the cingulate, insular and temporal cortices in misophonia

Some researchers have reported misophonia to have an etiology related to abnormal neural anatomy and physiological interactions between neural structures. Schröder et al., (2019) did functional magnetic resonance imaging (fMRI) on 21 individuals with misophonia and 23 individuals without misophonia. The fMRI recordings were done with and without misophonic trigger and for neutral stimulus. Stimulus presented were videos of individuals performing an activity which resembles a misophonic trigger (eg. video of someone lip smacking or loud breathing), aversive (eg. violent and disgusting movie clips) and neutral stimuli (eg. a clip of someone meditating). Results showed that the right superior temporal cortex, right insula and right anterior cingulate cortex had increased activation for misophonic video clips than compared to the neutral video clips.

Kumar et al., (2017) conducted blood oxygen level dependent imaging on 20 individuals with misophonia and 22 individuals without misophonia and

found that individuals with misophonia had greater exaggerated activation in the anterior insular cortex when stimulated by trigger sounds. Trigger sounds elicited an abnormal connective functioning between the anterior insular cortex and other cortical areas responsible for processing and controlling emotions (ventromedial prefrontal cortex, posterior-medial cortex, hippocampus and amygdala). They also reported that on misophonic trigger sound stimulation the individuals presented with increase in heart rate and galvanic skin response. Kumar et al., (2021) conducted resting state fMRI for sound-evoked condition in 17 individuals with misophonia and 20 individuals without misophonia. They reported no significant difference in auditory cortex response while resting state fMRI showed strengthened connectivity between the auditory, visual and ventral premotor cortex which are responsible for orofacial motor activity. These connections showed enhanced functioning on stimulation of sound, more specifically for trigger stimuli. Schröder et al., (2015) conducted fMRI on 10 individuals with misophonia and 7 individuals without misophonia and reported that individuals with misophonia presented increased activity of left amygdala and right auditory cortex in presence of trigger stimuli.

These imaging evidences show that individuals with misophonia presented with enhanced activities with deviant connections between structures of the temporal, insular and cingulate cortices which were typically observed only for trigger stimulus. This response pattern observed in misophonics could be the possible neurological underpinning in individuals with misophonia causing hatred and aversive reflexive reactions.

2.3.4 Role of the amygdala in misophonia

Eijsker et al., (2021) conducted a study on 24 individuals with misophonia and 25 individuals without misophonia comparing the anatomical grey matter volumes and resting state function using magnetic resonance imaging (MRI) and fMRI and found that misophonics have a larger volume of right amygdala and showing a different pattern of connections with cerebellum with greater connectivity with left amygdala. The authors also found that the lateral occipital cortices and fusiform gyri of ventral attention network had greater connections. Authors hypothesised that the aversive emotional reactions are associated with the enlarged amygdala, whereas greater connectivity between amygdala and cerebellum are associated with the reflex like physical reactions to misophonic triggers. Schröder et al., (2015) also observed that the left amygdala presented with enhanced activity in fMRI following the presence of a trigger stimulus.

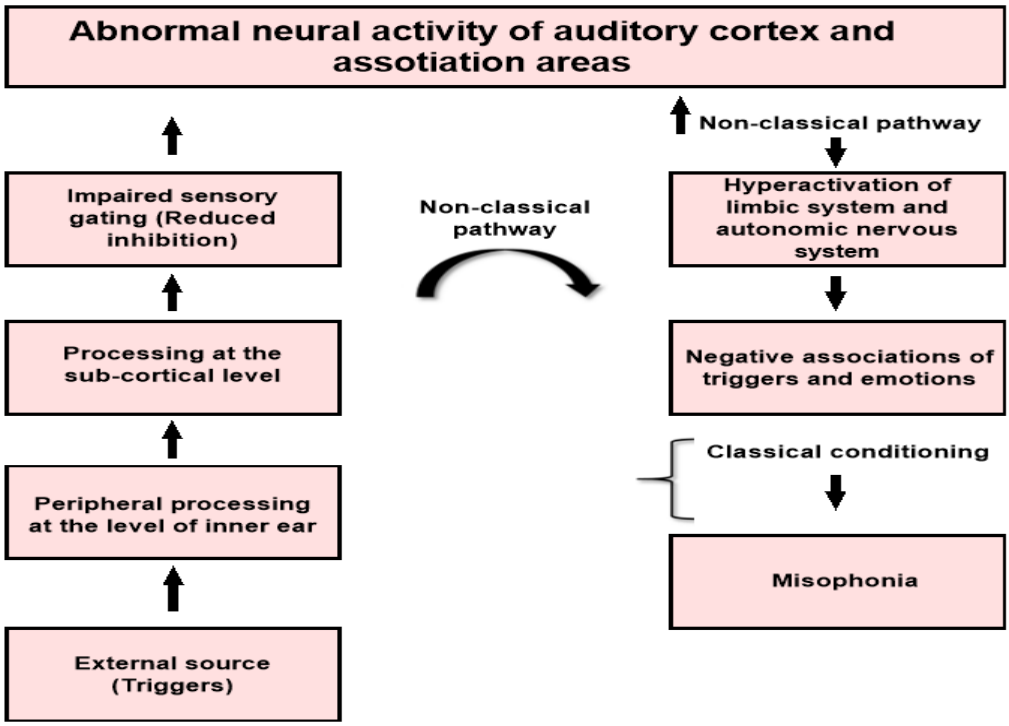
In summary, imaging studies showed that the right amygdala had anatomically larger volume and enhanced connectivity with the cerebellum in misophonics. In addition, individuals with misophonia also presented with enhanced neural activity in Amygdala to the trigger stimulus. Amygdala being the major center for processing and regulating emotions, these anatomical and physiological differences observed in misophonics could be the possible pathophysiology causing the heightened emotional associations towards few trigger sounds. The reflexive reactions to the triggers in misophonics can be traced to their higher connectivity with cerebellum.

2.3.5 Models to explain physiology of misophonia

2.3.5.1 Neuro-audiological model. Aryal & Prabhu (2023b) in their systematic review provided neuro-audiological model of misophonia that highlights the abnormal neural activity in auditory cortex and association areas. In addition, involvement of non-classical audiological pathway including hyperactivation of limbic system and autonomic nervous system leading to association of negative emotions to the trigger sounds in misophonics through classical conditioning is also postulated in the model as shown in Figure 2.1. The neuro-audiological model shows similarities with physiological models of tinnitus and hyperacusis. Based on similarities that misophonia shares with tinnitus, similarities in cochlear or efferent based activity can be postulated.

Figure 2.1

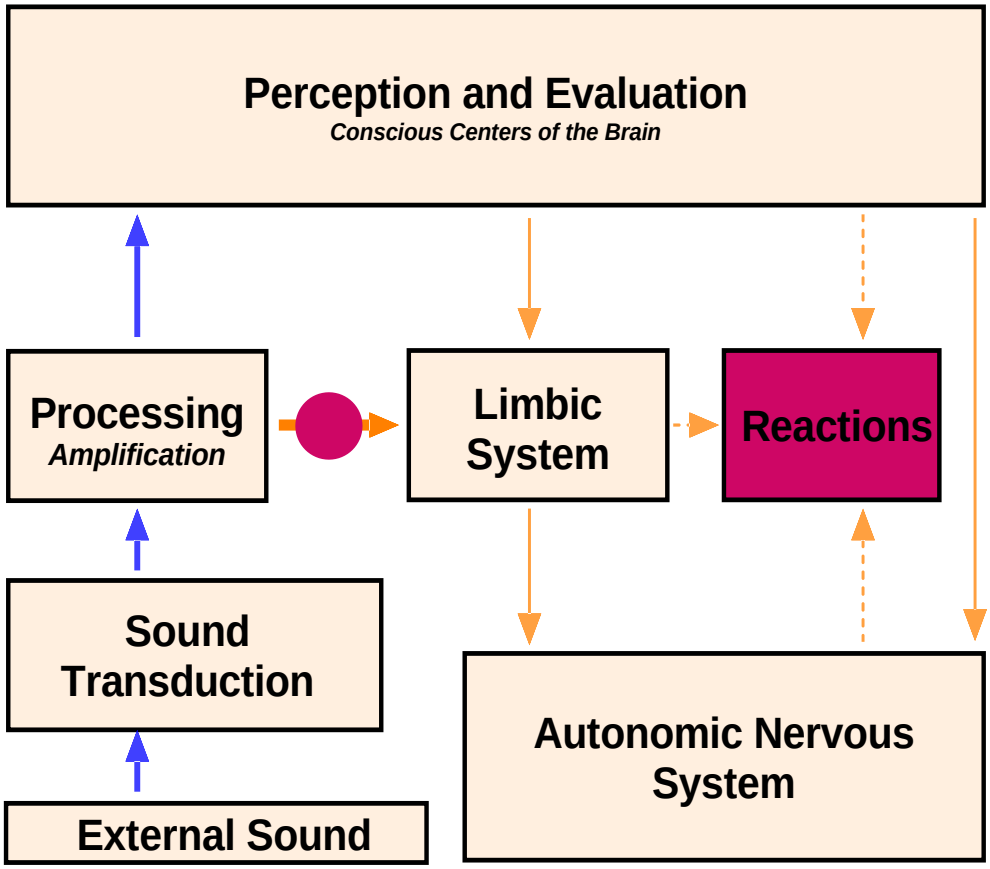
Neuro-audiological model of misophonia



2.3.5.2 Neurophysiological model. Jastreboff & Jastreboff (2023) proposed a neurophysiological model to explain the mechanism of misophonia. In misophonia the physical characteristics of trigger stimuli seldom plays a role indicating the auditory system plays a secondary role in misophonia generation. The model attributes misophonia to the reactions associated with the trigger sounds. The model highlights interactions of conscious, cognitive and subconscious with the auditory, limbic and the autonomic nervous system collectively play a significant role in the in conditioning the annoyance reactions triggered by specific stimuli, as shown in Figure 2.2. This association of meaning to the trigger sound or associating the trigger sound to past experiences leads to enhanced activity in the auditory, limbic and the autonomic nervous system that are inter linked to each other causing misophonic symptomatic reactions. The concept of complex conditioned stimuli explains why specific sounds are more likely to serve as misophonic triggers, even when their intensities are lower or equal to that of other non-trigger sounds. Additionally, it sheds light on why trigger sounds produced by close family members can evoke a more pronounced distressing reaction compared to those from other individuals. They postulated that using the neurophysiological model the treatment for misophonia can be primarily focused on the disconnection of the conditioned reflex associated with the auditory system and the cortical structures (Jastreboff & Jastreboff, 2023).

Figure 2.2

Neurophysiological model of misophonia



Note. The thick orange arrow in the red circle represents the functional connection between the auditory, limbic and autonomic nervous systems, which is theorized to be the cause of misophonia, with normal cortical functioning and the subconscious portion of the auditory system.

2.4 Diagnosis of misophonia

Despite progress in understanding of misophonia and increase in research over past two decades, neither the Diagnostic and Statistical Manuel of Mental Disorders, Fifth Edition (DSM-V) nor the International Classification of Diseases, Eleventh Edition (ICD-11) considers misophonia as

a distinct disorder/disease. Presently, there are no globally standardized diagnostic criteria available for misophonia, which raises concerns about potential misdiagnoses or, in more severe cases, the dismissal of patient's complaints based on the notion that no effective solutions are available to address their issues (Hadjipavlou et al., 2008).

Case history is the main tool that helps clinically diagnose misophonia and differentiate it with other similar conditions (hyperacusis and phonophobia) helping in understanding the onset, trigger acoustic stimuli, individual response and pattern of response (physiological, emotional and behavioural), coping mechanism they use and understanding its effect on relationships at home, school, college and work (Duddy & Oeding, 2014).

Schröder et al., (2013) recognising misophonia as a new and distinct psychiatric disorder proposed a diagnostic criterion to aid in the clinical diagnosis and encourage research. The suggested criteria state that a diagnosis of misophonia should be made when the all of the following conditions are met:

- The anticipation or presence of a misophonic trigger stimuli provokes an aversive physical reaction that initiates with a feel of disgust/irritation that instantaneously evolves into anger.
- Anger reaction towards specific sounds causes a sense of losing self-control with occasional instances of aggressive outbursts.
- Individual him/herself realizes the anger or disgust felt is excessive and unreasonable with disproportionate reactions to the circumstances.

- Individual makes efforts to avoid the misophonic situation, and if non avoidable the individual tends to tolerate/endure the misophonic sound with intense feel of anger, disgust and discomfort.
- The reactions towards misophonic triggers causes distress and impacts the life style of the individual.
- Individuals' reactions towards misophonic triggers should not be triggered by any other disorder.

Dozier et al., (2017) proposed a revised version of the diagnostic criteria proposed by Schröder et al., (2013). The revised criteria indicate diagnosis of misophonia when,

- Anticipation or presence of misophonic trigger as auditory, visual or any other sensory stimuli causing an intense reaction of irritation/disgust that further escalates into anger.
    a. Auditory and visual mode are the most common trigger stimuli than other sensory stimuli.
    b. The reaction towards triggers should be conditioned to a stimulus and not an unconditioned reaction towards a stimulus.
    c. Single instance of stimulus or small number of stimulus results in a conditioned reaction response.
    d. Stimuli to trigger should be of a lower intensity/low level and cannot be considered misophonia if reaction is only

towards loud stimulus that cause discomfort due to loudness increase or a startling response.

- An immediate physical reflexive response (muscle action, sexual response, heart rate and other physical reactions) towards the trigger stimuli. Preference given to immediacy of reflexive physical response over the type of response be used as an identification factor for misophonia.
- Moderate duration of stimuli of about 15 seconds triggering a physiological reaction.
- Disruption of thoughts and emotions with occasional aggressive outbursts, more commonly in children.
- Individual tries to evade the misophonic trigger but failing too results in enduring the situation with feelings of disgust/distress and discomfort.
- Individuals physical and emotional reactions causes interference in efficiently functioning in daily life situations.

Various misophonia assessment questionnaires have been developed and that are being used by researchers are shown in Table 2.1.

Table 2.1

Severity assessment questionnaires for misophonia

Sl. No.	Questionnaires
1	Amsterdam Misophonia Scale (Schröder et al., 2013)
2	Misophonia Questionnaire (Wu et al., 2014)
3	Misophonia Assessment Questionnaire (Johnson et al., 2013)
4	Duke Misophonia Questionnaire (Rosenthal et al., 2021)
5	Selective Sound Sensitivity Syndrome Scale (S-Five) (Vitoratou et al., 2021)
6	Misophonia Response Scale (Dibb et al., 2021)
7	MisoQuest (Siepsiak et al., 2020)
8	Sussex Misophonia Scale for Adoloscents (Rinaldi et al., 2022)
9	Berlin Misophonia Questionnaire – Revised (Remmert et al., 2022)

2.5 Misophonia and auditory processing

Along with case history and use of questionnaires, the use of pure tone audiometry and loudness discomfort level assessment (LDL) are included in the audiological evaluation for misophonia. Aazh et al., (2022) reported that there was no correlation between pure tone thresholds in individuals with misophonia, except that the frequency of misophonic symptoms reduced in individuals with steeply sloping pattern audiogram. There is general agreement that LDL values in misophonics are low, ranging between 30 to 120 dB HL Individuals who present with more frequent misophonic symptoms had lower LDL levels than those who exhibit lesser frequency of misophonic

symptoms (Aazh et al., 2022). In addition to LDL and PTA, literature on temporal processing in individuals with misophonia are also available (Ila et al., 2023). Investigating temporal processing abilities in a sample size of 30 each of individuals with and without misophonia using duration pattern test, pitch pattern test and gap detection test, Ila et al (2023) reported no significant group differences.

Audiological testing in misophonics was not only confined to subjective tests, but few investigations on the objective testing using auditory evoked potentials are also available. Aryal & Prabhu., (2023a) administered auditory brainstem response (ABR) in 30 individuals with misophonia and 15 individuals without misophonia and reported no statistically significant difference in the ABR between the two groups. Schröder et al., (2014) recorded auditory cortical evoked potentials on 14 individuals without misophonia and 20 individuals with misophonia and analyzed the P1-N1-P2 complex and reported a significantly diminished N1 in individuals with misophonia and speculated there may be an impairment in the auditory processing abilities in individuals with misophonia. Schroder et al., (2014; 2013) investigated MMN using 64 channel recording in 20 individuals with misophonia and 14 individuals without misophonia and found that misophonic individuals presented with significantly reduced peak amplitudes as compared to individuals without misophonia, though the peak amplitude latencies were similar between the groups while standard audiological testing showed no difference between the groups.

Misophonia is a considered to linger between the field of audiology and psychiatry, with no well-established diagnostic criteria nor established

assessment techniques in both the fields. Behavioural audiological evaluation has not shown any conclusive evidence of altered auditory processing in misophonics and extensive research has not been conducted in the field of auditory evoked potentials in individuals with misophonia, with the existing literature showing that there seems to be a deviance in the auditory processing at the cortical level. Only a handful of studies are available on misophonia in an audiological perspective covering only a few audiological areas and extensive research is required in the field to understand the condition and how auditory processing is affected at various levels.

From the comprehension of existing literature, it is evident that individuals with misophonia may present with deviance in the auditory processing which needs to be further investigated to understand the condition. misophonia is known to be similar to/ co-exist with other co-morbid audiological conditions (example like tinnitus and hyperacusis) that have shown deviant functioning of the peripheral and central level system in response to an auditory stimulus in various audiological tests that may also be expected in individuals with misophonia. There have not been any research studies conducted in evaluating the OAE characteristics and the efferent system functioning in individuals with misophonia. The OAEs are known to be affected in individuals with tinnitus and hyperacusis which have been closely been associated with misophonia, where individuals with tinnitus have shown absent/abnormal amplitudes of TEOAEs with subtle differences present with contralateral stimulation (Sarathy & Jaya, 2017; Thabet, 2009). DPOAEs were observed to have lower amplitudes in individuals with tinnitus having normal hearing sensitivity and having a steeper I/O function when compared

to controls (Alshabory et al., 2022; Xiong et al., 2019) and individuals with tinnitus presented with absence of suppression effects (Fávero et al., 2006) while studies have also shown hyper responsiveness of the auditory efferent system functioning in both individuals with tinnitus and hyperacusis (Knudson et al., 2014). As misophonia is a condition similar to tinnitus and hyperacusis and also known to co-exist with them, similar findings in OAEs maybe expected and need to be explored to help understand the cochlear and the auditory efferent system functioning in individuals with misophonia.

CHAPTER 3

METHODS

3.1 Study Design and ethical guidelines

A convenience sampling procedure was used to select the participants for the study. A standard group comparison method (Orlikoff et al., 2014) involving two groups (with and without misophonia) was carried out. The study is quasi-experimental descriptive research where the OAE characteristics of misophonics is compared with those without misophonia. Consent was obtained from the participants of the study and adhered to the ethical guidelines of the institute.

3.2 Participants

A total of 60 participants were divided into two groups of 30 participants each, namely individuals with misophonia (Group I) and individuals without misophonia (Group II). Table 3.1 shows the demographic details and the audiological fundings in the participants.

3.3 Selection Criteria

3.3.1. Individuals with misophonia

To fulfil the objectives of the study, a minimum of 30 participants diagnosed to have misophonia aged between 18 to 35 years were considered for the study (Group I). Participants were selected based on the diagnostic criteria provided by Schröder et al., (2013). Severity of misophonia was assessed by administering MAQ (Johnson et al., 2013). Only participants who satisfied the diagnostic criteria only were included for the study.

All the participants with pure tone thresholds within the normal limits (15 dB HL) and having 'A' type tympanogram with present acoustic reflexes were included in the study. Both the ears of the participants were tested.

3.3.2. Individuals without misophonia

A group of 30 normal-hearing individuals age matched to the former group experiencing no misophonic symptoms and no otological complaints having hearing sensitivity within normal limits (15 dB HL) having 'A' type tympanogram with present acoustic reflexes were considered for Group II.

Table 3.1

Demographic and basic audiological findings of the participants

	Individuals with misophonia (Group I)	**Individuals without misophonia (Group II)**
Mean age of participants (in years)	23.33 ± 0.22	21.86 ± 0.18
No. of participants	30	30
No. of ears	60	60
Tympanogram type	'A' Type	'A' Type
Average PTA	9.81 ± 2.42	10.03 ± 2.21
Average SIS scores	100 % ± 0	100 % ± 0
Average ipsilateral reflex thresholds	87.63 ± 0.86	89.18 ± 0.73
Average contralateral reflex thresholds	98.42 ± 0.81	99.07 ± 0.91

3.3.3. Exclusion criteria for individuals with and without misophonia

The individuals who had the complaints of the following conditions were excluded from the study:

- Individuals with anxiety disorder
- Individuals with depression
- Individuals with hearing loss
- Individuals with tinnitus
- Individuals with hyperacusis
- Individuals who use/used of hearing aids
- Individuals with history of ear related surgery
- Individuals with ear-related pathology
- Individuals with migraine

All these Conditions were screened using an informal screening checklist.

3.4 Procedure

Informed consent was obtained through google forms from all the participants included in the study. Institutional ethical guidelines for bio-behavioral research (Venkatesan & Basavaraj, 2009) studies were followed. The study involved three phases of data collection, Phase I involved recruiting participants and assessment of their misophonia severity, phase II involved routine audiological evaluation and phase III involving the OAE testing and contralateral suppression.

3.4.1 Recruiting participants and Assessment of misophonia severity

The participants in the study were recruited using a survey based on Google forms, E-mail or through social media such as WhatsApp, Instagram and Facebook. A questionnaire containing details such as consent for participation, demographic and contact details, MAQ questionnaire, tinnitus handicap inventory questionnaire (Newman et al., 1996), GAD-7 questionnaire (Williams, 2014), Khalfa hyperacusis questionnaire (Khalfa et al., 2002) were distributed through above mentioned digital platforms. The questionnaires used in the study is shown in appendix 1-4.

The assessment of severity of misophonia was done for individuals who fit the diagnostic criteria provided by Schröder at al., (2013) and severity was assessed through the administration of MAQ. The MAQ consists of 21 items that are evaluated using a 4-point rating scale from 0 to 3 points depending on the frequency of the occurrence of the problem/issue (0 = not at all, 1 = occasionally, 2 = frequently, and 3 = nearly always). Using the total score, misophonia severity is determined. Scores ranging from 0–21 was mild; 22–42 moderate; 43–63 was severe. Only participants with definite misophonia diagnosis (those who have symptoms as listed in the diagnostic criteria) were considered in Group I.

3.4.2 Routine audiological evaluation

All audiological testing were conducted for both ears of each participant in an electrically and acoustically insulated chamber with noise levels that are within the permissible limits of ANSI standards (ANSI S3.1-1991, R2018). Otoscopic examination was carried out as a routine procedure to visually assess the integrity of external auditory canal and tympanic

membrane. Behavioral pure tone audiometry for both ears was administered using the modified version of the Hughson-Westlake procedure (Carhart & Jerger, 1959), using a calibrated 2 channel Grason-Stadler Incorporation Audio Star Pro audiometer (Grason Stadler, Inc, MN, USA).

For air conduction, pure tone thresholds of 0.5 to 8 kHz were established using TDH 39 supra-aural headphones (Telephonics, Farmingdale, NY, USA), and for bone conduction from 0.5 to 4 kHz using a Radioear B-81 bone vibrator (RadioEar, Middelfart, Denmark). Evaluation of immittance with a 226 Hz probe tone and testing acoustic reflex thresholds were carried out using a calibrated Grason-Stadler Incorporation Tympstar Pro immittance audiometer (Grason Stadler, Inc, MN, USA) was done to ensure normal middle ear functioning.

3.4.3 OAE Testing and Contralateral Suppression

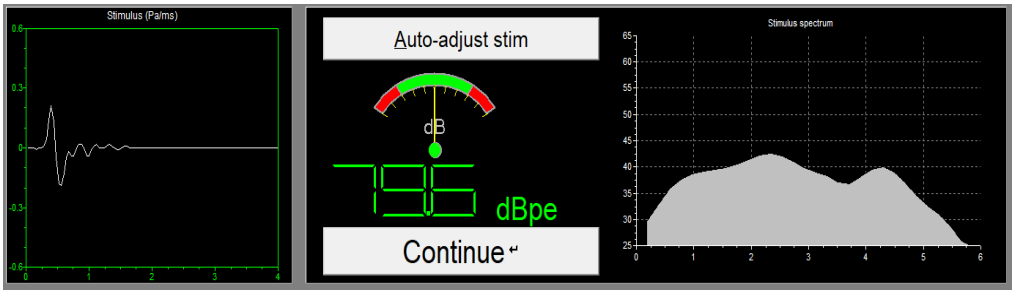
OAEs were obtained using a calibrated ILOv6 (Otodynamics Ltd, Hatfield, United Kingdom) OAE equipment. Efferent system functioning in both the groups of participants was tested using contralateral noise for TEOAE suppression. The rationale for using contralateral suppression measures of TEOAE over DPOAE suppression is due to its high test-retest reliability and contralateral suppression of DPOAE showed less than satisfactory results across frequencies in both single and multiple probe fit (Kalaiah et al., 2018; Kumar et al., 2013).

TEOAE measurement: TEOAEs were recorded in both ears of the participants using non-linear pulse trains click stimuli at intensity level of approximately 80 dB peak SPL of 80 μs stimulus duration with recording time

window of 20 ms having a flat frequency spectrum, as shown in Figure 3.1. Global amplitudes of TEOAE and global noise floor were noted, as depicted in Figure 3.2. Recordings were only accepted if the reproducibility of recordings were greater than or 80%.

Figure 3.1

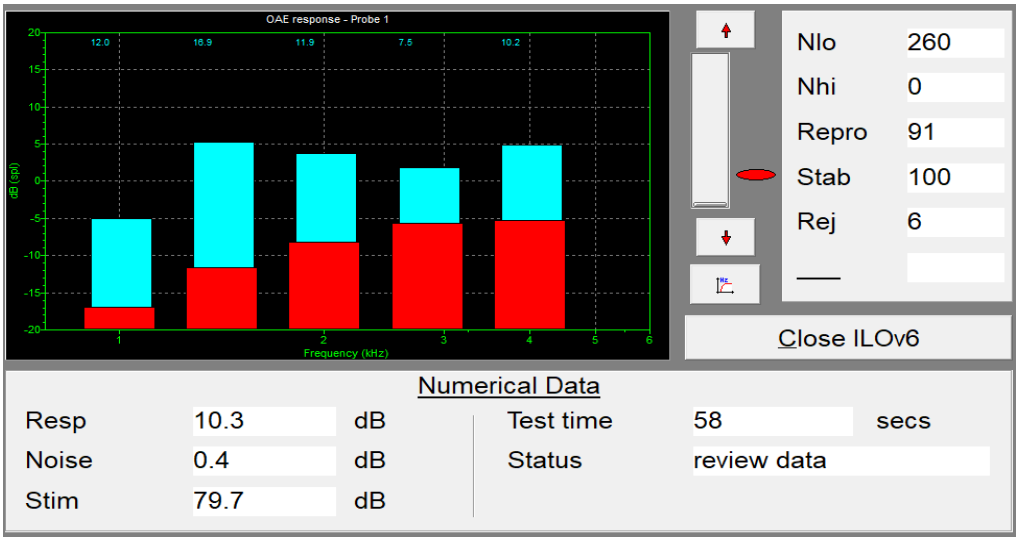
Stimulus parameters set for TEOAE recording in the ILOv6 software



Note. stimulus waveform (left), stimulus intensity (middle) and stimulus spectrum in the ear canal (right).

Figure 3.2

Recording of TEOAE response in ILOv6 software



Note. Blue bars represent the TEOAE response amplitude while the red bars represent the noise floor amplitude at each frequency along with information of

stimulus stability, high/low noise recordings, response reproducibility, stimulus level, global response and noise amplitudes.

Analyses. Global amplitude was noted and considered present if the emission reproducibility was greater than 80%.

Contralateral suppression of TEOAE: For contralateral suppression testing, a 50 dB SPL continuous white noise was presented to the opposite ear while the TEOAE recording was being conducted. A calibrated double-channel diagnostic audiometer, Grason-Stadler Incorporation 61 (Grason Stadler, Inc, MN, USA) with ER-3A insert earphones (Etymotic Research, Inc, IL, USA) was used to present contralateral noise while testing suppression on TEOAE. The global amplitudes of TEOAE and global noise level were noted.

Analyses.

a*) Magnitude of amplitude suppression:* The difference between the baseline Global TEOAE amplitude (SNR) and the global TEOAE amplitude (SNR) measured in the presence of contralateral noise was used to quantify the magnitude of contralateral suppression (suppression amplitude).

b) *Percentage of waveform shift*: The percentage of waveform shift was calculated using the root mean square (RMS) pressure differences of OAE in time domain between the suppressed and unsuppressed waveform using the formula given below (Jedrzejczak et al., 2022; Lewis, 2019).

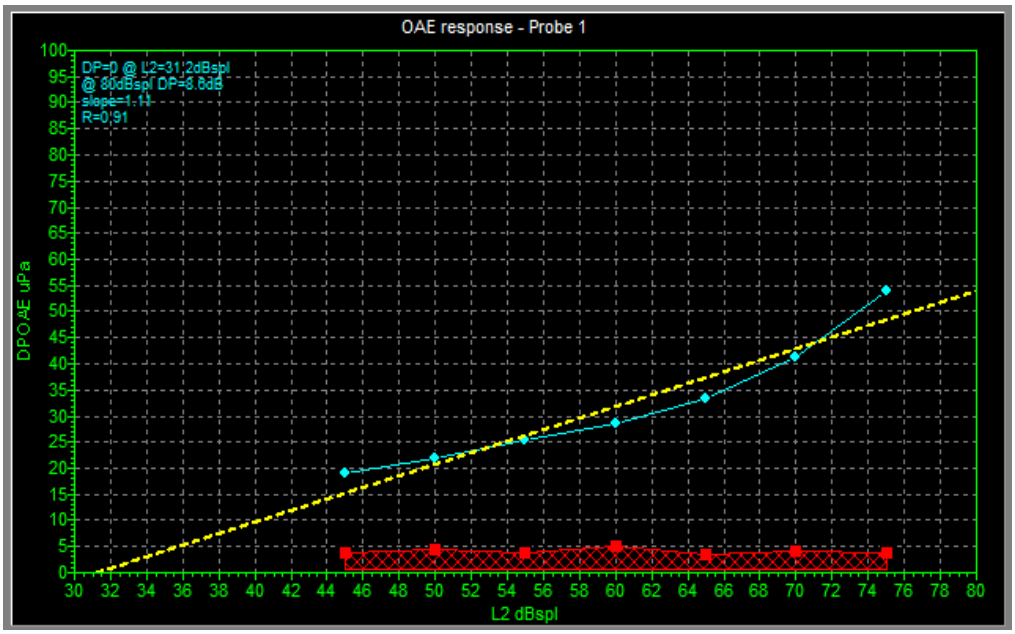
$$\Delta_{MOC} = 100 \times \sqrt{\frac{1}{N}\sum_{n=1}^{N}\left(a_{quiet}[n] - a_{noise}[n]\right)^2} \Big/ \sqrt{\frac{1}{N}\sum_{n=1}^{N}\left(a_{quiet}[n]\right)^2}$$

This formula not only accounts for amplitude shifts in the overall waveform but also takes into account the phase changes between the waveforms. The output of the TEOAEs stored as '.DTA file' format for the with and without noise conditions and were analysed using the Jedrzejczak et al. (2022) formula using a custom script running on MATLAB platform (Mathworks Inc, Chicago, USA).

DPOAE I/O function measurement: DPOAEs were obtained for two tones, F_1 and F_2 (primaries), their ratio being 1.22, with intensities of 65 dB SPL and 55 dB SPL (L_1 and L_2) respectively. The I/O function was obtained for tones of frequencies 1 kHz, 1.5 kHz, 2 kHz, 3 kHz, 4 kHz and 6 kHz, holding the frequency ratio between the test tones constant at 1.22, for different intensities. The intensities were set according to the stimulus paradigm found to be optimal for clinical testing (Janssen et al., 2006; Kummer et al., 2000) where primary tone stimulus is $L_1=(0.4*L_2)$ +39 dB SPL, as the L_2 decreases in 5 dB steps. The output corresponding to the DPOAE I/O measurement is shown in Figure 3.3.

Figure 3.3

DPOAE I/O function (6 kHz) in ILOv6 software



Note. Blue line represents the DPOAE response at different input levels, yellow line represents the slope of the I/O function as calculated by the software, red shaded region represents the noise floor in the ILOv6 software.

Analyses. The comparison of DPOAE I/O function was done using the slope, which was calculated using a linear trend model. The DPOAE I/O data were fitted with linear functions for the stimulus range from 75 to 45 dB SPL. Once a linear fit was obtained, the slope was estimated at 2 points of the x coordinate equal with x_2=75 dB SPL and x_1=45 dB SPL. Given the corresponding points of the DPOAE amplitude as y_2 and y_1, the slope of the fitted linear function was defined as: $b = (y_2–y_1)/(x_2–x_1)$. This analysis was done for separately for each of the six DPOAE frequencies (f_2 = 1 kHz, 1.5 kHz, 2 kHz, 3 kHz, 4 kHz, and 6 kHz).

3.5. Statistical analyses

The recorded data was tabulated in Statistical Package for the Social Sciences 26.0 (IBM Corp.; Armonk, NY, USA) and subjected to statistical analysis. Shaprio-wilk test was used to determine whether the data is normally distributed or not. Depending on whether the data is normally or non-normally distributed appropriate parametric (independent-samples t-test, paired samples t test) and non-parametric tests (Mann-Whitney U test, Wilcoxon sign ranked test) were administered respectively. Effect size was calculated using Cohen's d (Cohen, 1988) for the t-test, while for the Mann-Whitney U test and Wilcoxson sign rank test, Rosenthals effect size (Rosenthal, 1994) was calculated.

CHAPTER 4

RESULTS

The results of the present study are discussed under the following sub headings.

4.1 Descriptive statistics and testing of normality

4.2 Ear effect on TEOAEs and DPOAEs

4.3 Comparison of absolute amplitude of TEOAEs between the groups

4.4 Determination of presence of suppression effect in TEOAEs in the two groups

4.5 Comparison of suppression amplitude between the groups

4.6 Compression of percentage of RMS amplitude shift between the groups

4.7 Comparison of slope of DPOAE I/O function at across frequencies between the groups

4.1 Descriptive statistics and tests of normality

The study included 60 participants divided into two groups of 30 each with and without misophonia. Data of TEOAEs and DEOAEs were obtained from both ears from each subject. Among whom 14 participants were male and 46 participants were females. The mean MAQ scores was 23.80 ± 1.77 with 15 Mild, 14 Moderate and 1 severe misophonic. The descriptive data containing details of demographic data are tabulated in table 4.1.

Table 4.1

Descriptive statistics

	Individuals with misophonia (Group I)	**Individuals without misophonia (Group II)**
Number of males (count/30)	2 / 30	12 / 30
Number of females (count/30)	28 / 30	18 / 30
Age of participants (in years) (Mean ± SD)	23.33 ± 0.22	21.86 ± 0.18
Ears with present TEOAEs (count/60)	56 / 60 (29 right and 27 left)	59 / 60 (30 right and 29 left)
Ears with present DPOAE I/O function (1, 1.5, 2, 3, 4 and 6 kHz) (count/30)	60 / 60 (30 right and 30 left)	60 / 60 (30 right and 30 left)

The results of Shapiro-wilks test for normality on both the groups showed that the data was normally distributed ($p > 0.05$) for the global amplitude of TEOAE, this was observed in both groups in both with and without noise conditions. The data on percentage shift in RMS amplitude of waveforms also adhered to normality distributed ($p > 0.05$) in both individuals with and without misophonia. The slopes of DPOAE I/O function across the six frequencies and the suppression amplitude of TEOAEs were non-normally distributed ($p < 0.05$).

4.2 Ear effect on TEOAEs and DPOAEs

Results of independent samples t test comparing the absolute global amplitudes of TEOAEs and percentage shift in waveforms between the right and left ear showed no statistically significant differences ($p > 0.05$) between the two ears. This was seen in both individuals with and without misophonia as represented in table 4.2.

Table 4.2

Comparison of the absolute global amplitude of TEOAEs between the right and left ear separately for individuals with and without misophonia

	Global amplitudes of TEOAE (Mean ± SD)				
	Right ear	**Left ear**	**df**	**t(df)**	***p***
Individual with misophonia (Group I)	11.83 ± 4.07	11.17 ± 4.23	54	0.60	0.55
Individuals without misophonia (Group II)	12.01 ± 3.90	11.50 ± 4.71	57	0.45	0.66

Similarly, the results of Mann-Whitney U test on the suppression amplitude of TEOAEs and slope of DPOAE I/O between the right and left ears revealed that there was no statistically significant difference ($p > 0.05$)

between the right and left ears for both groups as shown in table 4.3 and 4.4 respectively.

Table 4.3

Comparison of suppression amplitude of TEOAE between the right and left ear separately between individuals with and without misophonia

		Suppression amplitude (Mean ± SD)		
	Ear	**Median with interquartile range**	**/Z/**	***p***
Individual with misophonia (Group I)	**Right**	1.78 ± 1.80	1.68	0.09
	Left	1.18 ± 1.96		
Individuals without misophonia (Group II)	**Right**	2.29 ± 0.02	1.30	0.19
	Left	1.32 ± 1.89		

Table 4.4

Comparison of the slope of DPOAE I/O function between the right and left ears separately for individuals with and without misophonia

	Individuals with misophonia (Group I)				**Individuals without misophonia (Group II)**			
	Ear	**Median with interquartile range**	**/Z/**	***p***	**Ear**	**Median with interquartile range**	**/Z/**	***p***
1 kHz	**Right**	0.25 ± 0.30	0.15	0.88	**Right**	0.17 ± 0.20	0.68	0.50
	Left	0.24 ± 0.31			**Left**	0.13 ± 0.24		
1.5 kHz	**Right**	0.22 ± 0.21	0.33	0.74	**Right**	0.16 ± 0.23	0.39	0.69
	Left	0.20 ± 0.14			**Left**	0.21 ± 0.30		
2 kHz	**Right**	0.28 ± 0.33	0.94	0.35	**Right**	0.21 ± 0.26	0.38	0.70
	Left	0.25 ± 0.29			**Left**	0.27 ± 0.20		
3 kHz	**Right**	0.18 ± 0.19	0.30	0.76	**Right**	0.15 ± 0.22	0.47	0.64
	Left	0.19 ± 0.17			**Left**	0.20 ± 0.24		
4 kHz	**Right**	0.14 ± 0.17	0.48	0.63	**Right**	0.15 ± 0.15	0.04	0.96
	Left	0.19 ± 0.21			**Left**	0.17 ± 0.14		
6 kHz	**Right**	0.31 ± 0.19	0.47	0.64	**Right**	0.26 ± 0.26	0.10	0.92
	Left	0.27 ± 0.29			**Left**	0.28 ± 0.25		

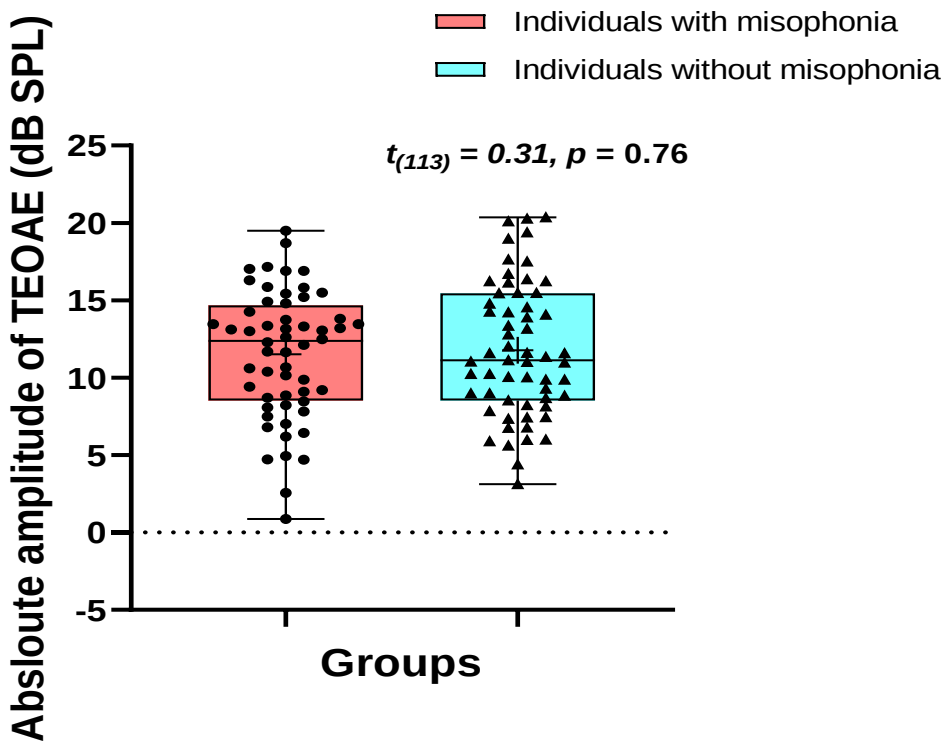
As the independent samples t-test, paired samples t-test, and Mann-Whitney U test failed to reveal any statistically significant differences between the right and left ears, all the data was combined without distinguishing between the right and left ears. This resulted in a total of 60 ears for individuals in both the groups, making them eligible for further statistical analysis. All 120 ears were included in the analysis of DPOAE I/O functions. For TEOAE analysis, we considered 59 ears from individuals without misophonia and 56 ears from individuals with misophonia.

4.3 Comparison of absolute global amplitude of TEOAEs between the groups

Results of independent samples t test showed that absolute global amplitude of TEOAEs did not differ significantly ($p > 0.05$) between the two groups. The absolute global amplitudes of TEOAEs along with the test statistic for the groups are represented as box plots in figure 4.1.

Figure 4.1

Comparison of absolute global amplitudes of TEOAEs between individuals with and without misophonia



Note. Circles and triangles represent the individual ears values in individuals with and without misophonia respectively and '+' symbol represents the mean.

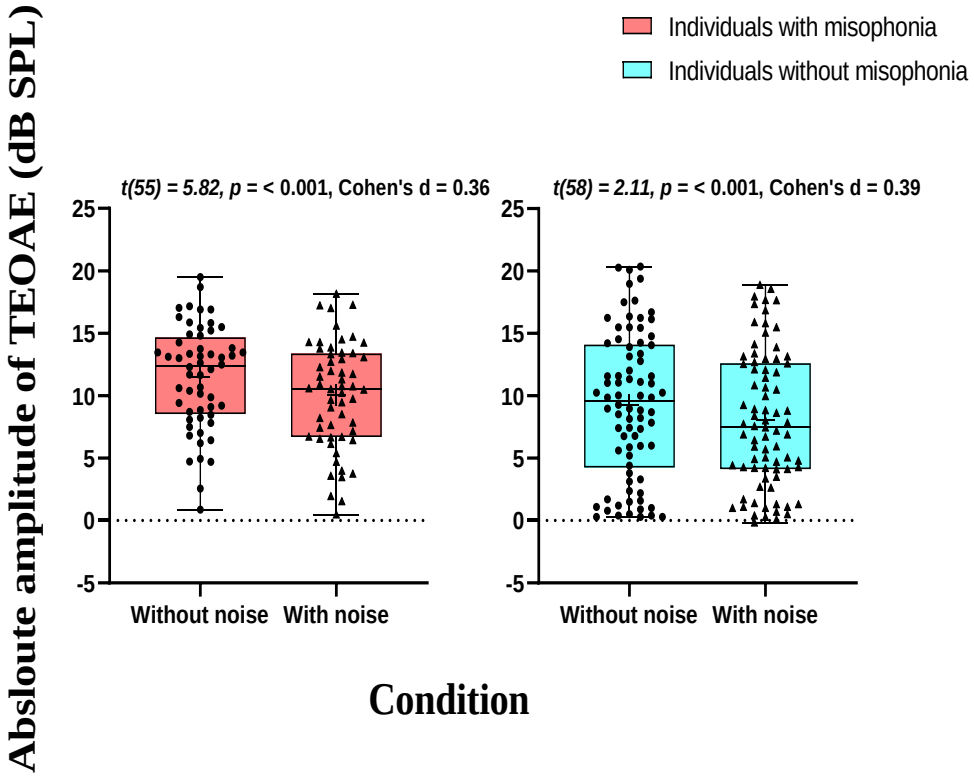
4.4 Determination of presence of suppression effect in TEOAEs in the two groups

Paired samples t test was administered to check for difference between the global amplitudes of TEOAEs obtained with and without noise between individuals with misophonia and individuals without misophonia. The results of paired samples t test showed that statistically significant ($p < 0.01$) suppression effect was present (i.e., the amplitude of TEOAEs with noise was significantly lower than without noise) in both individuals with and without

misophonia. Figure 4.2 represents a box plot the comparison suppression amplitudes of TEOAEs which shows both the individuals with and without misophonia had significant suppression of TEOAE amplitudes post noise exposure.

Figure 4.2

Comparison of absolute global amplitudes of TEOAEs between conditions with noise and without noise in individuals with and without misophonia



Note. Circles and triangles represent the individual ears values without noise and with noise respectively and '+' symbol represents the mean.

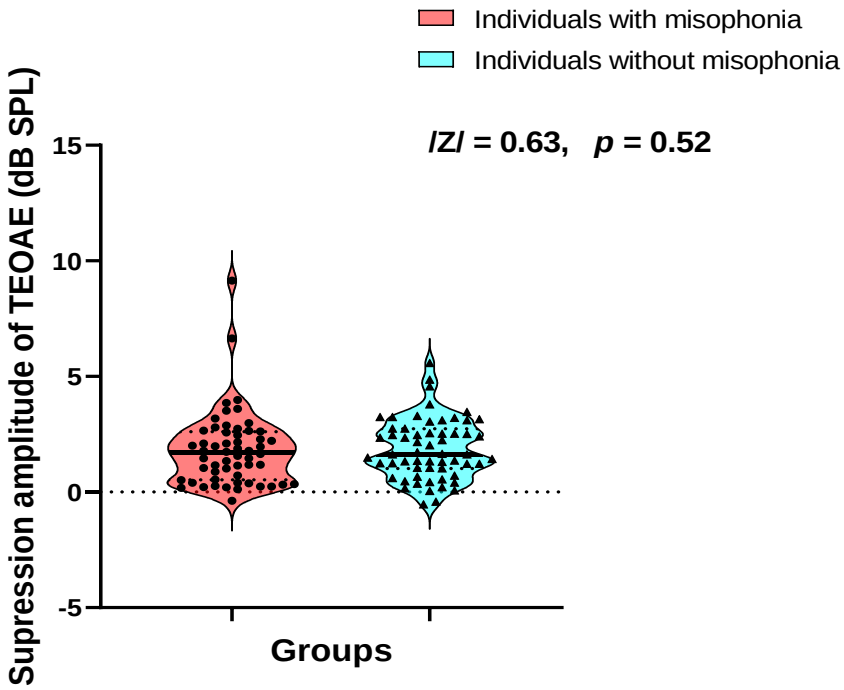
4.5 Comparison of suppression amplitude between the groups

Results of Mann-Whitney U test showed that suppression amplitude of TEOAEs did not differ significantly ($p > 0.05$) between individuals with and

without misophonia. The suppression amplitude of TEOAEs along with the test statistic (/Z/ and *p* values) for the groups (with and without misophonia) are shown in violin plots in figure 4.3 showing no group differences.

Figure 4.3

Comparison of suppression amplitudes of TEOAEs between individuals with and without misophonia



Note. Circles and triangles represent the individual ears values in individuals with and without misophonia respectively, horizontal line represents the median and dotted line represents the quartiles.

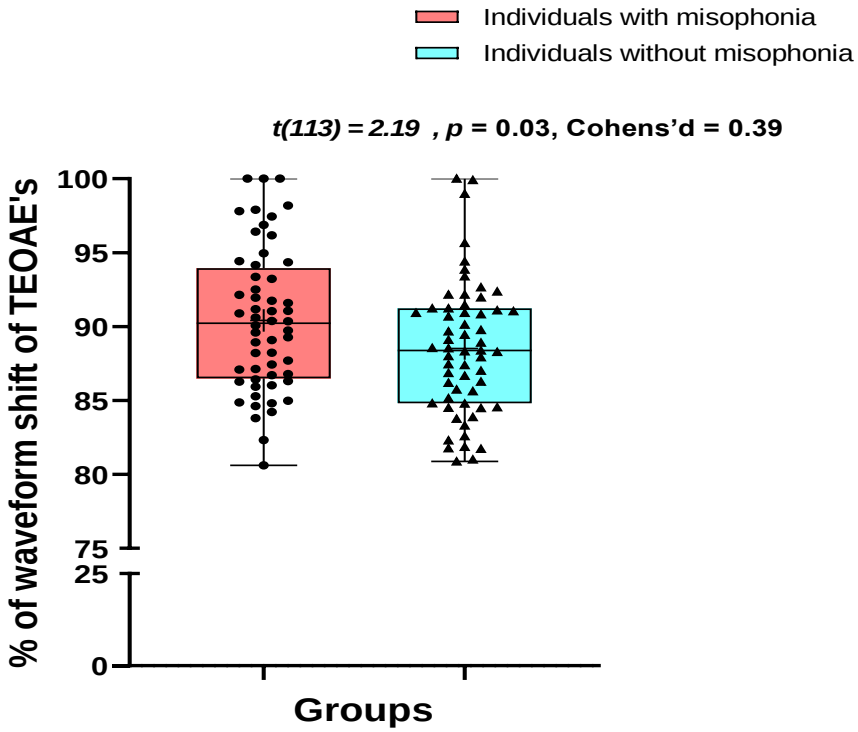
4.6 Comparison of percentage of RMS amplitude shift between the groups

Results of independent samples t test showed that the percentage of RMS shift was statistically lesser in individuals with misophonia ($t(113)$=

2.19, $p = 0.03$, Cohens'd = 0.39) between the two groups as shown in figure 4.4, with those having misophonia showing greater waveform shifts compared those without misophonia.

Figure 4.4

Comparison of percentage of waveform shift in TEOAE waveforms between individuals with and without misophonia



Note. Circles and triangles represent the individual ears values in individuals with and without misophonia respectively, '+' symbol represents the mean.

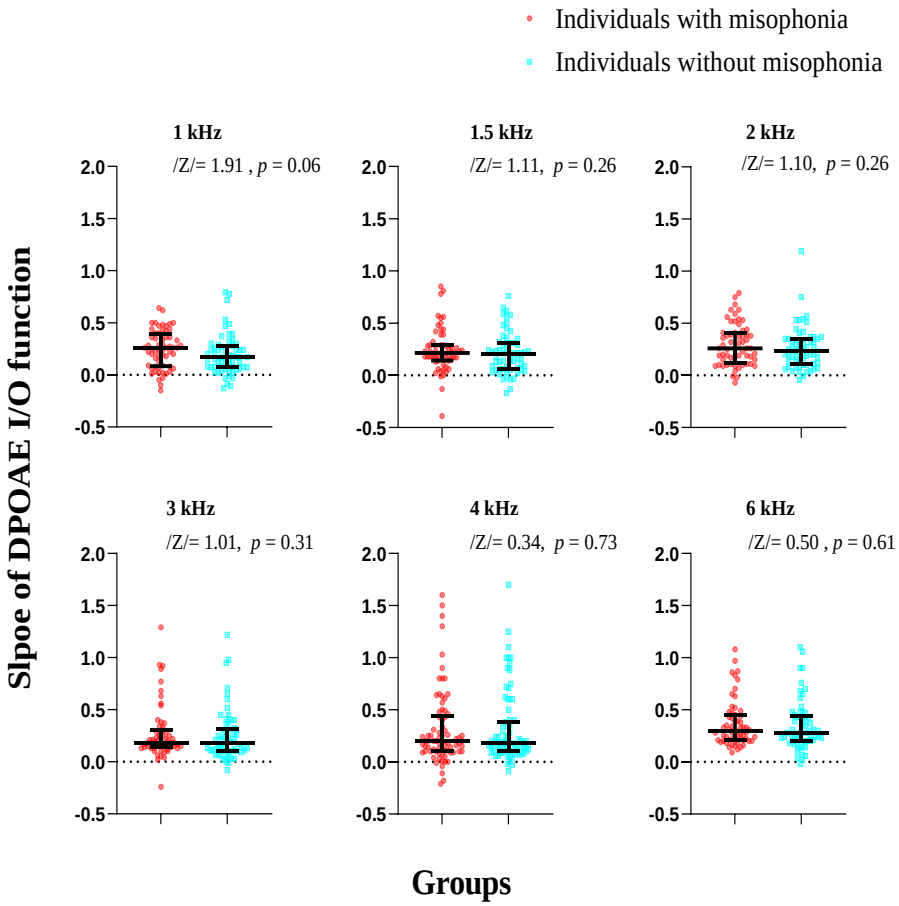
4.7 Comparison of slope of DPOAE I/O function at across frequencies between the groups

Results of Mann-Whitney U test showed that there was no statistically significant difference ($p > 0.05$) in slope of DPOAE I/O function at all six frequencies assessed between individuals with misophonia and individuals

without misophonia. Figure 4.5 shows the results of Mann-Whitney U test across the 6 frequencies assessed along with the /Z/ and p values representing no group differences.

Figure 4.5

Comparison of slope of DPOAE I/O function between individuals with and without misophonia across frequencies



Note. The horizontal bars represent the median and interquartile range.

In summary, results of the statistical analysis showed there was no statistically significant difference in the absolute global TEOAEs amplitudes, suppression TEOAE amplitude nor the slopes of DPOAE (1, 1.5, 2, 3, 4 and 6 kHz) between individuals with and without misophonia. Statistically

significant difference was observed in the percentage of RMS shift (waveform shift) of TEOAEs after contralateral suppression in individuals with misophonia, who showed greater percentage of phase shift when compared with individuals without misophonia.

CHAPTER 5

DISCUSSION

The present study is preliminary research which aimed at understanding the role of linear and non-linear cochlear mechanisms and auditory efferent system functioning in individuals with misophonia.

5.1 Cochlear linear and non-linear mechanisms in misophonics

In the study, the linear cochlear emissions measured using TEOAEs and the non-linear emissions recorded using DPOAEs I/O functions. Results of the present study revealed that there were no statistically significant differences in amplitude of both the TEOAE & DPOAE amplitudes between the right and left ears, for both the groups (individuals with and without misophonia) (tables 4.2, 4.3 and 4.4). The amplitudes of TEOAE were slightly higher in right ear than the left ear, although this finding was not statistically significant. The findings are in accordance with previous research findings (Keefe et al., 2008; Khalfa et al., 1998). These findings are indicative of no ear differences observed in individuals with misophonia, which could be expected as both the participants in both the groups were matched on their hearing thresholds. All the participants in the study had no complaints of ear related issues and had normal hearing sensitivity in both ears.

TEOAE absolute global amplitude showed no statistically significant differences between individuals with and without misophonia indicating that the linear cochlear mechanisms are functioning normally in individuals with misophonia (figure 4.1). DPOAE I/O function measured as slope of DPOAE across all the frequencies (1, 1.5, 2, 3, 4 and 6 kHz) also showed no

statistically significant differences between individuals with misophonia and without misophonia (figure 4.5), indicating that the non-linear mechanisms of cochlear functioning in individuals with misophonia were also comparable to those without misophonia. This finding is in contrast to those reported in the literature in individuals with tinnitus, where the absolute amplitudes of TEOAEs were lesser in the tinnitus suffers compared to those without tinnitus (Emadi et al., 2018; Fernandes & Santos, 2009; Thabet, 2009; Urnau & Tochetto, 2012). Similarly, individuals with tinnitus showed steeper DPOAE I/O function (Alshabory et al., 2022; Zhou et al., 2011) than individuals without tinnitus, indicating a potential correlation between tinnitus presence and altered cochlear function.

Although it was hypothesised that individuals with misophonia might have altered cochlear mechanisms (similar to those with tinnitus), the findings of the study did not present any abnormalities in OAEs in misophonia group. This finding is attributed to the distinct nature of the underlying pathophysiological mechanisms between the two conditions (tinnitus and misophonia). tinnitus and misophonia are both auditory-related conditions, but they manifest differently in terms of their core symptoms and triggers. Individuals with tinnitus present with symptoms of ringing or buzzing sounds that may be continuous or intermittent (Koops et al., 2019), while those suffering with misophonia do not present with continuous symptoms rather their auditory issues are confined towards single/multiple specific trigger stimuli such as chewing, tapping, or breathing. These triggers often differ from the stimuli that induce OAEs, minimizing cochlear mechanism changes in misophonics (if any). As misophonia triggers operate within a separate realm

from the auditory stimuli traditionally used in such assessments, lack of group differences can be explained.

Moreover, the severity of misophonia among individuals could also account for the lack of discernible group differences. In the present study individuals with mild, moderate, and severe misophonia were grouped together, and OAE responses in them are compared with those without misophonia. Individuals with varying degrees of misophonia severity may exhibit different physiological response and possibly display distinct patterns of cochlear and efferent system activity. This variability in response might lead to a lack of significant differences when misophonia individuals are grouped together.

5.2 Auditory efferent system and misophonia

Magnitude of amplitude suppression was obtained by calculating the difference between the TEOAE global amplitudes without and with contralateral acoustic (noise) stimulation to assess the auditory efferent system functioning. Amplitude suppression effect of TEOAE upon contralateral acoustic (noise) stimulation was present in individuals with and without misophonia (figure 4.2). On comparison of the magnitude of amplitude suppression, individuals with misophonia showed no deviance in the auditory efferent system functioning compared to those without misophonia (figure 4.3). On comparison of the percentage of RMS shift in TEOAE waveforms after suppression, individuals with misophonia showed a significantly greater percentage of waveform shifts than individuals without misophonia. The presence of group differences in the RMS shifts and not suppression amplitude

(dB) can be attributed to sensitivity of the measurement tool. While RMS shifts account for the phase differences (Jedrzejczak et al., 2022) the amplitude shifts measured conventionally do not consider phase differences brought about by suppression. Jedrzejczak et al. (2022) reported that phase changes could better quantify medial olivocochlear reflex functioning than the conventional measure of suppression amplitude (dB). Deeter et al., (2009) reported that contralateral acoustic stimulation affected both the amplitude and phase of the OAE waveforms to a greater extent towards the characteristic frequency than the neighbouring frequency regions.

The observation regarding higher RMS shifts in individuals with misophonia and its potential link to efferent suppression mechanisms is intriguing. The contralateral suppression of OAE's not only leads to reduction of the cochlear amplification processes but also broadens the auditory filters (Francis & Guinan, 2010). This results in reduced the latencies of the OAE responses in supressed waveforms, thus accounting for phase differences (Francis & Guinan, 2010). Therefore, higher phase shifts in misophonics can hint at already broadened auditory filters in them, even before suppression. The contralateral noise in addition to the existing wide auditory filters in misophonics could have further broadened them, leading to higher phase shifts compared to individuals without misophonia where only suppression caused widening of auditory filters is seen. Test results from conventional amplitude analyses (dB) of the raw TEOAEs and DPOAEs do not provide information of the broadening of auditory filters in the misophonics. However, the measure of RMS change in the supressed TEOAEs might be postulated to be indirectly sensitive to these auditory filter changes, as it takes into account the phase

related variations in the supressed and unsuppressed waveforms. To further advance our understanding of auditory filter changes in misophonics, it remains to be explored if the auditory filter shapes are deviant in misophonics using specific tests such as psychoacoustical tuning curves (PTCs). PTCs can assess the sharpness or broadness of frequency tuning in the auditory system, helping to pinpoint the specific regions where auditory filters have been affected (Lin et al., 2001). In addition, by combining the results of tuning curve measurements with temporal modulation transfer functions and temporal summation tests, researchers can gain a comprehensive understanding of how the auditory system in misophonics integrates information over time.

The finding that phase accounted RMS change shifts are largely evident in misophonics (Figure 4.4), and the associated latency shifts in the supressed waveforms postulates the role of auditory efferents in misophonia generation. The medial olivocochlear actions on contralateral stimulation cause latency shifts as high as 0.5 milliseconds which could cause profound effects on interaural timing delays which could lead to binaural localization difficulties (Francis & Guinan, 2010) in misophonics. Although this hypothesis is yet to be tested, investigating localization deficits during noisy environments in individuals with misophonia might help disentangle the underlying mechanisms in misophonia generation. Also, the phase shifts can result in interferences of different phases on the basilar membrane leads to complex physiological processes that may affect the pitch perception and timbre perception (Moore, 2002), which can also be further explored.

While, both individuals with tinnitus and hyperacusis have shown hyper functional auditory efferent functioning presenting with greater

amplitude suppression of TEOAEs with contralateral acoustic stimulation (Knudson et al., 2014), individuals with misophonia seem to show no such differences in the amplitude suppression. On other hand, individuals with misophonia showed significantly increased RMS shift compared to those without misophonia, suggesting differences in the auditory efferent system functioning in the misophonics. Imaging evidences showing that there are cortical differences seen in individuals with misophonia, wherein changes in the descending auditory efferent pathways from the cortical structures can also be a possibility in misophonics (Delano & Elgoyhen, 2016).

5.3 Limitations of the study and future directions

The study grouped individuals with mild, moderate, and severe misophonia together, comparing them with those without misophonia. This mix may explain the lack of significant differences found. A better approach would have separate groups for each misophonia level, allowing a more comprehensive understanding of auditory function. In addition, the study predominantly included females and minimal male (two) participants; a gender-matched study is needed to explore potential gender-related differences in misophonia-related characteristics.

The study only analyzed overall amplitudes of TEOAEs, limiting insights into role of frequency specific regions in cochlea in Misophonia generation. Including individual frequencies and DPOAE suppression measurements would enhance comprehension. A comprehensive study encompassing various OAEs (SOAEs, SFOAEs) in addition to their contralateral suppression is needed for broader insights.

The study found normal cochlear function but abnormal auditory efferent system in misophonia individuals, as shown by increased RMS shift in Misophonics. In the present study the entire waveform phase (global phase) was compared although studies have shown that phase characteristics can vary across the frequencies upon contralateral stimulation during OAE recording, it would be interesting to further investigate focusing on specific frequency bands while quantifying and comparing phase differences. Further investigation in this area with a larger sample size is warranted to solidify the findings of this present study indicating deviant auditory efferent system functioning that could be a neurological underpinning in the pathophysiology of misophonia.

Investigation on misophonia from an audiological perspective has shown no differences in the peripheral auditory functioning (Aazh et al., 2022), auditory brainstem processing (Aryal & Prabhu, 2023a) and temporal processing (Ila et al., 2023). whereas cortical potentials such as auditory late latency response and MMN (Schröder et al., 2013, 2014) have shown significant differences. More audiological studies in the lines of physiological measures (tympanometry, acoustic reflexes, and OAEs), auditory evoked potentials and higher auditory cortical potentials correlating with the behavioral measures of auditory functioning might prove to be promising in identifying the pathophysiological bearings of misophonia on auditory processing. In addition, inclusion of individuals with a more severe degree along with milder degrees might help profile the spectrum of auditory deficits in misophonia, which when done in conjunction with neuro-imaging studies will help pin point possible neurological underpinnings causing the condition.

CHAPTER 6

SUMMARY AND CONCLUSIONS

Misophonia is a complex neurophysiological and behavioural condition characterized by disproportionate reactions (emotional or physiological) towards specific sound stimuli like chewing, loud breathing, metal sound and tapping noise and many more (mostly sounds made by humans). The lack of objective measure to identify misophonia characteristics lead to the present study. It aimed to understand the cochlear (linear and non-linear) and auditory efferent system functioning in 30 normal hearing individuals with misophonia and 30 normal hearing individuals without misophonia. The study used OAE testing (TEOAE and DPOAE I/O function) to assess the cochlear linear and non-linearities respectively. Contralateral suppression of TEOAEs was used to assess the auditory efferent system functioning. The results of the study revealed no statistically significant differences in the either the cochlear linear and non-linear mechanisms in individuals with misophonia compared with those without misophonia. However, in the efferent suppression of TEOAE, there individuals with misophonia had a significantly higher RMS shift in supressed waveforms than their non-misophonic counterparts, representing either hyperfunctioning auditory efferent system or a widened cochlear filter in them.

6.1 Advantages of the study

- The study is the first of its kind investigating the OAE characteristics in misophonics

- The study contributes to understand the cochlear and auditory efferent system functioning in misophonics
- The study contributes to understanding the possible etiology and pathophysiological processes in misophonics

6.2 Limitations of the study

- Global amplitude was the only parameter assessed in TEOAEs.
- Misophonia group consisted of all severities (Mild, moderate and severe), although no sub-classification based on misophonia severity was done.
- Global waveform was considered while comparing waveform shifts with suppression, although it needs to be explored if frequency specific bands would have provided valuable insights.

6.3 Future directions

- To study the OAE characteristics in a larger population to generalize the findings.
- To study the auditory processing in misophonics using various audiological behavioral and physiological measures.
- Imaging studies to understand and pin point the neurological underpinnings involved in misophonia.

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APPENDIX 1

Questions in MAQ

Question number	Question
1	My sound issues currently make me unhappy.
2	My sound issues currently create problems for me.
3	My sound issues have recently made me feel angry.
4	I feel that no one understands my problems with certain sounds.
5	My sound issues do not seem to have a known cause.
6	My sound issues currently make me feel helpless.
7	My sound issues currently interfere with my social life.
8	My sound issues currently make me feel isolated.
9	My sound issues have recently created problems for me in groups.
10	My sound issues negatively affect my work/school life (currently or recently).
11	My sound issues currently make me feel frustrated.
12	My sound issues currently impact my entire life negatively.
13	My sound issues have recently made me feel guilty.
14	My sound issues are classified as ‘crazy’.
15	I feel that no one can help me with my sound issues.
16	My sound issues currently make me feel hopeless.
17	I feel that my sound issues will only get worse with time.
18	My sound issues currently impact my family relationships.
19	My sound issues have recently affected my ability to be with other people.
20	My sound issues have not been recognized as legitimate.
21	I am worried that my whole life will be affected by sound issues.

APPENDIX 2

Questions in THI

Question number	Question
1	Because of your tinnitus, is it difficult for you to concentrate?
2	Does the loudness of your tinnitus make it difficult for you to hear people?
3	Does your tinnitus make you angry?
4	Does your tinnitus make you feel confused?
5	Because of your tinnitus, do you feel desperate?
6	Do you complain a great deal about your tinnitus?
7	Because of your tinnitus, do you have trouble falling to sleep at night?
8	Do you feel as though you cannot escape your tinnitus?
9	Does your tinnitus interfere with your ability to enjoy your social activities (such as going out to dinner, to the movies)?
10	Because of your tinnitus, do you feel frustrated?
11	Because of your tinnitus, do you feel that you have a terrible disease?
12	Does your tinnitus make it difficult for you to enjoy life?
13	Does your tinnitus interfere with your job or household responsibilities?
14	Because of your tinnitus, do you find that you are often irritable?
15	Because of your tinnitus, is it difficult for you to read?
16	Does your tinnitus make you upset?
17	Do you feel that your tinnitus problem has placed stress on your relationships with members of your family and friends?

18	Do you find it difficult to focus your attention away from your tinnitus and on other things?
19	Do you feel that you have no control over your tinnitus?
20	Because of your tinnitus, do you often feel tired?
21	Because of your tinnitus, do you feel depressed?
22	Does your tinnitus make you feel anxious?
23	Do you feel that you can no longer cope with your tinnitus?
24	Does your tinnitus get worse when you are under stress?
25	Does your tinnitus make you feel insecure?

APPENDIX 3

Questions in GAD-7

Question number	Question
1	Feeling nervous, anxious, or on edge
2	Not being able to stop or control worrying
3	Worrying too much about different things
4	Trouble relaxing
5	Being so restless that it is hard to sit still
6	Becoming easily annoyed or irritable
7	Feeling afraid, as if something awful might happen

APPENDIX 4

Questions in khalfa hyperacusis questionnaire

Question number	Question
1	Do you have trouble concentrating in a noisy or loud environment?
2	Do you have trouble reading in a noisy or loud environment?
3	Do you ever use earplugs or earmuffs to reduce your noise perception? (Do not consider the use of hearing protection during abnormally high exposure situations.)
4	Do you find it harder to ignore sounds around you in everyday situations?
5	Do you find it difficult to listen to speaker announcements (such as airport, airplanes, trains, etc.)?
6	Are you particularly sensitive to or bothered by street noise?
7	Do you “automatically” cover your ears in the presence of somewhat louder sounds?
8	When someone suggests doing something (going out, to the cinema, to a concert, etc.), do you immediately think about the noise you are going to have to put up with?
9	Do you ever turn down an invitation or not go out because of the noise you would have to face?
10	Do you find the noise unpleasant in certain social situations (e.g., nightclubs, pubs or bars, concerts, firework displays, cocktail receptions)?
11	Has anyone you know ever told you that you tolerate noise or certain kinds of sounds badly?
12	Are you particularly bothered by sounds others are not?
13	Are you afraid of sounds that others are not?
14	Do noise and certain sounds cause you stress and irritation?
15	Are you less able to concentrate in noise toward the end of the day?

16	Do stress and tiredness reduce your ability to concentrate in noise?
17	Do you find sounds annoy you and not others?
18	Are you emotionally drained by having to put up with all daily sounds?
19	Do you find daily sounds having an emotional impact on you?
20	Are you irritated by sounds others are not?