EXPLORING THE NEUROAUDIOLOGICAL PATHOPHYSIOLOGY OF MISOPHONIA: A SYSTEMATIC REVIEW

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CERTIFICATE

This is to certify that this dissertation entitled 'Exploring the Neuroaudiological Pathophysiology of Misophonia' is a bonafide work submitted as a part of the fulfillment for the degree of Master of Science (Audiology) of the student with Registration Number: 20AUD029. This has been carried out under the guidance of the 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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CERTIFICATE

This is to certify that this dissertation entitled "**Exploring the Neuroaudiological Pathophysiology of Misophonia: A Systematic Review**" has been prepared under my supervision and guidance. It is also being certified that this dissertation has not been submitted earlier to any other University for the award of any other Diploma or Degree.

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DECLARATION

This is to certify that this dissertation entitled "**Exploring the Neuroaudiological pathophysiology of Misophonia: A Systematic Review**" is the result of my study under the guidance of Dr. Prashanth Prabhu, Assistant Professor in Audiology, Department of Audiology, All India Institute of Speech and Hearing, Mysore and has not been submitted earlier to any other University for the award of any other Diploma or Degree.

Mysuru **Registration No: 20AUD029**

August 2022

Dedicated to मम्मी, बाबा

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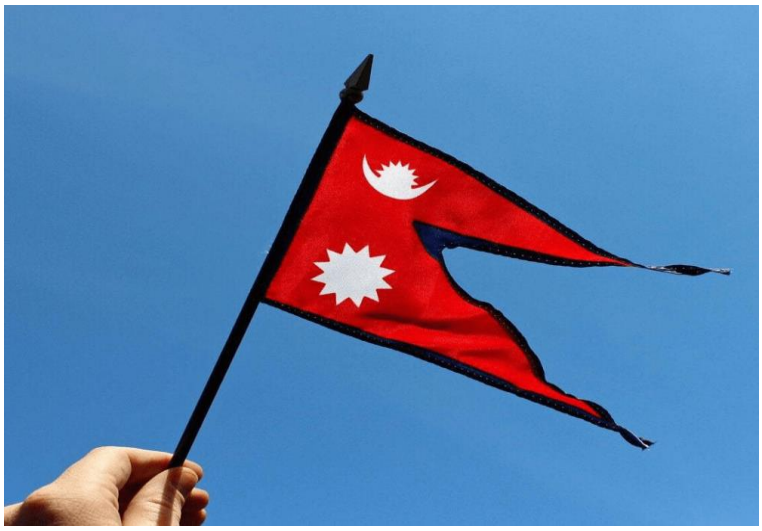
मेरो प्यारो देश नेपाल



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Abstract

Misophonia is a neurophysiological disorder in which certain sounds trigger an intensely emotional or physiological response caused by an increased autonomic nervous system reaction to the triggers. This is a relatively new condition, and the neurophysiological mechanism behind this condition is not known yet. The assessment and management of misophonia need a team approach. Audiologists are key members of the team. However, their roles in this condition are not well understood. Our study aims to review the neurophysiological mechanism of misophonia, highlighting the mechanism involved in the audiological pathway and direct the discussion towards applications of findings in the assessment and management of misophonia from the audiological perspective. A review of 12 articles from different databases was conducted to highlight neurophysiological mechanisms. Most of the studies selected were experimental designs involving individuals with misophonia. Assessment of study quality reported an overall low risk of bias. This review also highlights the need to include an audiologist as a team member in the assessment and management of misophonia.

Keywords: *Misophonia; Neurophysiology; Audiologist; Systematic Review; Assessment and management*

Chapter 1

Introduction

Misophonia is derived from the Greek word misos (hate) and phone (voice), which means hatred of sound. It is a new condition that is not clearly understood yet. Misophonia or sound selectivity syndrome is the sound tolerance disorder in which certain sounds trigger an intensely emotional or physiological response caused by increased autonomic nervous system reaction to certain triggers (Jastreboff & Jastreboff, 2014). Jastreboff first described this phenomenon in 2001 (Jastreboff & Jastreboff, 2001). Misophonia is not classified as a phobia because, unlike phonophobia, it is not characterized by a dread of occurring sounds. Jastreboff defined phonophobia as a kind of misophonia; hence the definitions and classification of these categories are debatable (Jastreboff, Margareth M.; Jastreboff, 2001)

Triggers are the sound that causes emotional outburst in a patient with misophonia. People with misophonia exhibit various physiological and emotional responses when exposed to certain auditory triggers, including an accelerated heart rate, sweating, anxiety, rage, irritability, and disgust (Jastreboff & Jastreboff, 2014). Since triggers are very much common in misophonic individuals, they can lead to social isolation and psychological problems. Jastreboff and Jastreboff (2002) reported that the triggers need not be only related to the human body. Misophonia can also be triggered by human-made sounds that are not directly related to the human body, such as pen clicking, rustling, tapping, etc.

The current knowledge level indicates that noises' acoustic properties have no impact on emotional arousals (Brout et al., 2018). The types of aversive triggers vary from individual to individual and depend on various factors, such as experience,

social context, and the psychological profile of the person (Jastreboff & Jastreboff, 2014). The sounds created by the human mouth or nose, such as chewing, breathing sounds, and sniffing are the most unpleasant of the many triggers that have been found. Few researchers have discovered that high-pitched sounds or baby crying can cause misophonia (Quek et al., 2018). However, a study by Kumar et al. (2017) found that compared to noises associated with eating, breathing, and sniffing, baby crying or high-pitched sounds produced significantly different responses on the psychophysiological and neurophysiological levels. According to their findings, these eating-related triggers in people with misophonia result in altered anterior insular cortex (AIC) activity and improper functional connectivity of these regions with the other brain regions in charge of processing and regulating emotions.

1.1 Prevalence of misophonia

Misophonia can occur on its own as a distinct disorder or in conjunction with other psychiatric disorders such as obsessive-compulsive disorders (OCD), attention deficit hyperactivity disorder (ADHD), and mood disorders. Additionally, misophonia often coexists with other similar conditions, such as tinnitus, hyperacusis, and phonophobia, which is necessary to differentiate (Jastreboff & Jastreboff, 2014). Tinnitus, typically linked to hearing loss, is the perception of sound without acoustic stimuli (Waechter, 2021). Contrarily, hyperacusis is an enhanced sensitivity to noises that causes discomfort or uncomfortable feelings in the sufferers and is correlated with the strength of the sounds (Tyler et al., 2014). Phonophobia is the fear of the occurrence of particular sounds.

The onset of the problem in misophonia patients has been reported variably across the literature. Few studies have mentioned that the onset is during adolescence

(Palumbo et al., 2018), few authors have mentioned during adulthood (Sanchez & Silva, 2018), and few have mentioned that there are no age criteria for the occurrence of misophonia as it can happen at any age (Potgieter et al., 2019). Very few studies have been reported regarding the prevalence of misophonia. Determining the prevalence of misophonia has been difficult due to a lack of diagnostic standards; however, estimates in the audiology literature suggest that the prevalence of decreased sound tolerance in the general population is roughly 3.5% (Jastreboff, 2015). Naylor et al. (2021) reported clinically significant misophonia in 49.1% of the study sample population among the UK undergraduate medical student population. Comparably, a study by Wu et al. (2014) involving a sample of 483 US college students using an online questionnaire revealed a prevalence of misophonia at 19.9%. The prevalence of misophonia was 20% in a study by Zhou et al. (2017), and there were no gender differences in the severity of misophonia. Hence, it can be stated that the prevalence of misophonia does not differ by age, gender, and ethnicity (Zhou et al., 2017; Wu et al., 2014)

1.2 Etiology

The exact cause of the misophonia is not known yet. Various researchers have given various hypotheses regarding the etiology of misophonia. According to Dozier (2015), misophonia is a conditioned behavior that becomes a bodily reflex as a result of Pavlovian conditioning. They hypothesized that misophonia is a two-step phenomenon in which the sound elicits an aversive conditioned physical reflex, and the adverse conditioned physical reflex generates aversion or disgust towards the sound. Due to a family history, they discovered in misophonic people, Edelstein et al. (2013) reported misophonia as a genetic condition. Psychiatric illnesses like OCD, anxiety disorders, and mood disorders are more prevalent in those with misophonia.

Additionally, tinnitus, hyperacusis, and phonophobia frequently coexist with misophonia and other sound-related diseases. Ferreira et al. (2013) reported that misophonia is not an auditory disorder caused by neurological dysfunction reporting the psychological nature of misophonia. This is evidenced by many individuals with misophonia showing normal hearing thresholds (Schroder et al., 2013). However, misophonia is connected to more powerful limbic and sympathetic nervous system connections, which might result in aberrant processing of auditory inputs (Jastreboff & Jastreboff., 2014). Hence, it can be stated that there can be both audiological and psychiatric causes for misophonia as it borders the field of audiology and psychiatry.

1.3 Pathophysiology

The auditory system has two parallel channels, the classical and non-classical pathways, that carry information from the brainstem to the auditory cortex (Moller & Rollins., 2002). The primary location where the architecture of the non-classical pathway and the classical pathway diverge is in the thalamic relay nuclei. In the ventral region of the medial geniculate body, the conventional pathway is uneven. The medial and dorsomedial geniculate bodies' nuclei, however, block the non-classical pathway (Moller & Rollins., 2002). Misophonia is an adverse reaction to sounds driven on by enhanced limbic and autonomic responses without excessive auditory system amplification (Jastreboff., 2007). Due to the interaction between the limbic system and the classical and non-classical pathways, a breakdown in this process may increase the emotional and autonomic response to auditory inputs (Jastreboff., 2007). These concepts were developed in 1990 as the neurophysiological model. According to Jastreboff (1990) and Jastreboff & Jastreboff (2002)'s neurophysiological model, misophonia is a dislike or hatred of sound that is caused by abnormally strong reactions of the autonomic and limbic systems as a result of

enhanced connections between the auditory, limbic, and autonomic systems, or enhanced reactivity of the limbic and autonomic system to sound..

Compared to neutral video clips, the misophonic video clips caused the right insula, right anterior cingulate cortex, and right superior temporal cortex to become more active in neuroimaging studies employing functional magnetic resonance imaging (fMRI) (Schröder et al., 2019). According to a functional magnetic resonance imaging (fMRI) study by Kumar et al. (2017), misophonic trigger sounds caused the anterior insula to become more active and had abnormal functional connections to the hippocampus, amygdala, ventromedial prefrontal cortex, and posteromedial cortex, areas involved in the processing and regulating emotions. In misophonic patients, trigger sounds also increased heart rate (HR) and galvanic skin response (GSR), which were mediated by anterior insular cortex (AIC) activity (Kumar et al., 2017). Similarly, Schröder et al. (2014) revealed that the misophonic group's mean N1 peak amplitude was lower than the control group, suggesting that individual with misophonic may have low-level auditory information processing deficits. The right superior temporal cortex, right anterior insular cortex, and right anterior cingulate all showed greater activity in the misophonic group compared to the control group, according to Schröder et al. (2019). Giorgi (2015) found hyperactivation of the bilateral auditory cortex and left amygdala when exposed to the misophonic triggers compared to the control group.

Misophonia is commonly considered a condition of processing sound emotions in which specific sounds, such as eating or chewing, cause an unpleasant emotional response. However, sounds produced by other people can simulate the actions they represent. Therefore, it may be said that misophonia may just be the means via which the trigger person's action is reflected in the listeners. A study by

Kumar et al. (2021) explained the role of the mirror neuron system in misophonia and stated that the motor mechanism is responsible for misophonia. They discovered that trigger noises in misophonia lead the orofacial motor cortex to become hyperactive, suggesting that trigger sounds may excessively "mimic" orofacial activity. As a result of misophonic triggers, the primary auditory cortex won't become overactive, proving that misophonia isn't a problem with how sounds are processed but rather related to the orofacial motion that the sound signifies. This study supports the idea that misophonia is defined by the mirror neuron system's aberrant behaviour, which "mirrors" the trigger-actions person as represented by noises.

1.4 Diagnosis

Although misophonia has undergone substantial advancement, neither the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-V) nor the International Classification of Diseases, Eleventh Edition recognize misophonia as a distinct illness (ICD-11). However, misophonia is now recognized by Schröder et al. (2013) as a distinct psychiatric condition rather than a symptom of other disorders, and they have provided diagnostic criteria to support this claim. According to these criteria, misophonia is diagnosed when:

• An individual experiences a strong, immediate somatic reaction that begins with irritation or disgust, which quickly turns into anger in the presence or the expectation of aversive sounds. The anger makes a person feel out of control, sometimes leading to aggressive behaviour;

• The person assesses these reactions as disproportionate to the situation;

• Due to the consequences of unpleasant experiences caused by certain sounds, the person, if possible, avoids situations in which the trigger is expected or struggles with

high discomfort in its presence. Therefore, the condition has a significant, negative impact on the person's life;

- The avoidance and emotional reaction to certain triggers cannot be better explained by other disorders, such as post-traumatic stress disorder or obsessive-compulsive disorder.

As misophonia is studied in both audiology and psychiatry, audiologists classify misophonia as an audiological condition with other sound disorders including tinnitus, hyperacusis, and phonophobia. Despite significant symptom overlap and the possibility of having several conditions, misophonia is separate from these disorders (Jastreboff & Jastreboff, 2001; Jastreboff & Hazell, 2004).

Few questionnaires were developed to assess misophonia (Schröder et al., 2013; Wu et al., 2014). Amsterdam misophonia scale (A-MISO-S) is the checklist developed by Schröder et al. (2013) for assessing the severity of symptoms along the dimensions of the proposed criteria for misophonia. Six questions in the A-MISO-S are rated from 0 (none) to 4 (Extreme). The A-MISO-S lacks psychometric data as of yet. The misophonia questionnaire (MQ) developed by Wu et al. (2014) has two main dimensions: first one asks participants to self-rate [from 0 (not at all true) to 4 (always true)] their sensitivity to seven different types of sounds (such as eating, repetitive tapping, vocal expressions of consonants or vowels), and the other one consists of ten questions regarding reactions to the sounds rated at a 1 (rarely true) or higher for the prior seven. As the things are added together, the scale is graded. There isn't a defined cut-off point that identifies if someone has misophonia or not. The scale for a global severity rating is 1 (the lowest) to 15 (very severe). Other questionnaires, i.e., Duke Misophonia Questionnaire (Rosenthal et al., 2021) and the

Selective sound sensitivity syndrome scale (S-five) (Vitoratou et al., 2020), has also been developed and are in the validation phase for the assessment of the individuals with misophonia.

Even though few questionnaires were developed to determine the severity of misophonia symptoms, this scale's psychometric properties are unknown. To conduct a full assessment of misophonia, administering these questionnaires is insufficient. We have to rule out the other diagnostic condition that may account for sound sensitivity by administering primary diagnostic tools that may be necessary.

As misophonia borders audiology and psychiatry, audiological assessment is mandatory for misophonia patients. The audiological evaluation of misophonia is challenging, and there are no established techniques. As a result, there is a huge demand for research on misophonia from an audiological standpoint. Audiologists around the world use different protocols to evaluate misophonia. The pure tone threshold and loudness discomfort level (LDL) are part of the audiological evaluation. Individuals with misophonia may or may not have hearing loss. Loudness discomfort level (LDL) may be normal or at a reduced level (Jastreboff., 2013). In the literature, there is no accurate description of how to measure LDL in misophonia patients. Therefore, there is a greater chance of variability in the results due to the specific methods administered (Sherlock & Formby., 2005; Jastreboff., 2015).

Nonetheless, Jastreboff (2015) reported when misophonia is present with hyperacusis, the loudness discomfort level (LDL) value ranges from 30dBHL to 120dBHL. Therefore, LDL alone is not sufficient to correctly diagnose misophonia. Auditory evoked potentials have not been extensively studied in misophonia. According to Schroder et al. (2013), the misophonic individuals' reduced N1 peak in

response to the deviant tone during the oddball paradigm compared to the control group may reflect a problem with auditory information processing. In order to develop unbiased tools for misophonia assessment, research into auditory evoked potentials in the field of misophonia is necessary.

1.5 Management

Individuals with misophonia display a broad range of emotional, physiological, and behavioural responses to their triggers depending on the context and environment (Dozier & Morrison., 2017). Avoidance and escape from the situation in which trigger sounds are present is the commonly employed coping strategy by the misophonic patient (Edelstein et al., 2013; Schröder et al., 2013). However, that is not an effective option. No studies have been done yet that looked into pharmacological options for treating misophonia. According to anecdotal evidence, anxiolytics and antidepressants may be used to treat misophonia-related reactions and co-morbid conditions. Despite the lack of pharmacological treatments, misophonia patients have tried various therapies that appear to be having some success.

The treatment program developed by Jastreboff, known as tinnitus retraining therapy (TRT), is primarily for those with tinnitus, with secondary benefits for hyperacusis and misophonia (Jastreboff & Jastreboff., 2006). The concept behind tinnitus retraining therapy (TRT) is that the relationship between the auditory system and the limbic and autonomic nervous systems can be reduced or even removed by altering conditioned reflexes at the subconscious level (Kiessling., 1980). Because misophonia involves an external trigger that may be altered to potentially eliminate the conditioned response, misophonia patients should react better to tinnitus

retraining therapy than tinnitus patients (Jastreboff & Jastreboff., 2002). When giving misophonic patients tinnitus retraining therapy, it is advised to avoid using a silent environment and wearing too much ear protection. The patient's response to their trigger sounds should be lessened by the introduction of soothing sounds. For people with misophonia, reclassifying the noises and intensive counseling are advised. The effectiveness of tinnitus retraining therapy in misophonia patients with and without hyperacusis was reported by Jastreboff (2015). In addition to tinnitus retraining therapy, additional neuropsychiatric therapies have been successfully used to treat misophonia in the literature (Schneider & Arch., 2015). Training in Cognitive-Relaxation, Coping Techniques, and Multicomponent In the literature, cognitive-behavioural therapy (CBT) has also successfully been used to treat misophonia (McGuire et al., 2015).

People with misophonia may benefit from neuromodulation methods such as transcranial magnetic stimulation, transcranial direct current stimulation, transcranial alternating current stimulation, transcranial random noise stimulation, neurofeedback, epidural and subdural cortical and deep brain stimulation, and vagus nerve stimulation to lessen hyperactivity in the non-classical auditory pathway (Umashankar & Prabhu., 2021). The individual with misophonia who is intolerant to specific sounds due to hyperactivity in the auditory and limbic system can be tried with vagus nerve stimulation as they have an auricular branch that inserts into the brainstem nucleus, thus reducing the hyperactivity (Yap et al., 2020).

1.6 Need for the study

Misophonia is the condition that borders between psychology and audiology. In psychology, researchers try to explain misophonia as a psychiatric disorder

(Schröder et al., 2013), and they try to assess and treat the patient with misophonia using the psychiatric approach. However, misophonia is less explored in audiology and a relatively new term. Nevertheless, the prevalence of misophonia is increasing with time, and many misophonia patients are seeking professional helps (Zhou et al., 2017; Wu et al., 2014). The neuroimaging data using functional magnetic resonance imaging (fMRI) has shown hyperactivation of the non-classical auditory pathway (Moller & Rollins., 2002). Similarly, the auditory evoked potentials (AEP) study using the oddball paradigm has shown a deficit in the misophonic group's auditory processing at the cortical level compared to the control group (Schröder et al., 2014).

These neurophysiological shreds of evidence suggest that misophonia should be treated using the audiological approach, which is lacking in the current scenario. Jastreboff (2015) has shown the efficacy of audiological approaches, such as tinnitus retraining therapy (TRT), in treating a patient with misophonia. However, it is not widely explored clinically. The complex nature of misophonia has made it a stressful disorder for sufferers and family members. Yet, little research has been done about underlying pathophysiological mechanisms, assessment, and management. To date, no specific protocols have been developed for misophonia assessment and management. Proper assessment and management of misophonia are impossible without understanding its core mechanism. Misophonia is still in its infancy stage and is not readily accepted in the scientific community as a valid disorder. Therefore, it can be hypothesized that highlighting more on the neurophysiological mechanism will help recognize misophonia as a separate and genuine disorder and provide a path for assessment and management using a team approach.

1.7 Aim of the study

This review aims to highlight the Neuroaudiological pathophysiology of misophonia and its implications in the assessment and management of misophonia from an audiological perspective.

1.8 Objectives of the study

- To explore the Neuroaudiological pathophysiology of misophonia.
- To investigate the methods and study design used in studying the Neuroaudiological pathophysiology of misophonia.
- To direct the discussion, particularly towards applications of findings of Neuroaudiological pathophysiology in assessment and management of misophonia from the audiological perspective.

Chapter 2

Methods

The study was carried out following ethical standards established by the institutional board of the All India Institute of Speech and Hearing (AIISH), Mysore. The procedures used for the study under the following headings are the main emphasis of this chapter.

2.1 Search Engines

2.2 Data extraction (Selection and Coding)

2.1 Search Engines

Studies were selected from various database searches such as African Journal Online (AJOL), Google Scholar, PubMed (National Center for Biotechnology Information), MEDLINE (US National Library of Medicine), Web of Science, Elsevier, Schematic Scholar, Cochrane library, and Comdisdome. The search was done with appropriate keywords to find articles related to this topic. These keywords included were "Misophonia," "Neuroaudiology," and "Pathophysiology" the derivatives of these words were used with the usage of appropriate Boolean operators. The inclusion criteria for the study were the article published in peer-reviewed journals till 2021 and articles published in English, including human participants. Duplicates were found and removed from the primary sample. Articles related to Neuroaudiological pathophysiology of tinnitus, hyperacusis, and phonophobia, articles based on animal models, and articles with insufficient data were excluded. Similarly, reviews, single case reports, histopathological studies, studies with duplicated data, studies with a

heterogeneous data group, and articles published in a language other than English were also excluded from this study.

2.2 Data Extraction (Selection and Coding)

The review was carried out using PRISMA guidelines (Moher et al., 2009). A comprehensive list of keywords was used to identify the relevant articles. The keywords used were 'Misophonia'; 'Selective sound sensitivity syndrome'; 'Sound rage'; 'Neuroaudiology'; 'Neurophysiology'; 'Pathophysiology'; and 'Mechanism .'The articles were selected based on the title and abstract screening using exclusion and inclusion criteria. All eligible articles' full texts were reviewed to assess eligibility as per the criteria. A manual search was also done to identify known articles, and a few articles were selected via hand picking. Disagreements at the screening stage between the reviewers were restored through discussion. A pre-piloted form was used to extract data from the included studies. The extracted information included the authors' names, type of research design, type of study population and the sample size, methodology, participant demographics, outcomes of the study, and the critical analysis of the findings.

Chapter 3

Results

This chapter deals with the results obtained from the review in terms of extraction of study, quality analysis of the selected articles, and a summary of the selected articles showing the Neuroaudiological pathophysiology using the various neuroimaging techniques in the participants suffering from misophonia.

3.1. Selection of the studies

Applying the initial search strategy and the inclusion and exclusion criteria provided 12 papers for quality analysis and synthesis. Among the 232 articles identified using database searches such as google scholar, PubMed, semantic scholar, Comdisdome, Research Gate, and Cochrane library, 15 were excluded due to duplicates, and a total of 217 articles were included for title screening. Among 217 articles for title screening, 165 were excluded by title screening and 42 by abstract screening. Ten articles met the inclusion criteria for complete reading, and two articles were selected through hand picking. Altogether 12 articles were finalized for review. All the studies included in the study were experimental. The selection process was further validated by inter-judge selection and discussion in case any ambiguity arises in finalizing the published manuscript. The detailed Preferred Reporting Items for Systematic Reviews (PRISMA) flow diagram for the selection of studies was used for the present systematic review, and the same is mentioned in figure 3.1

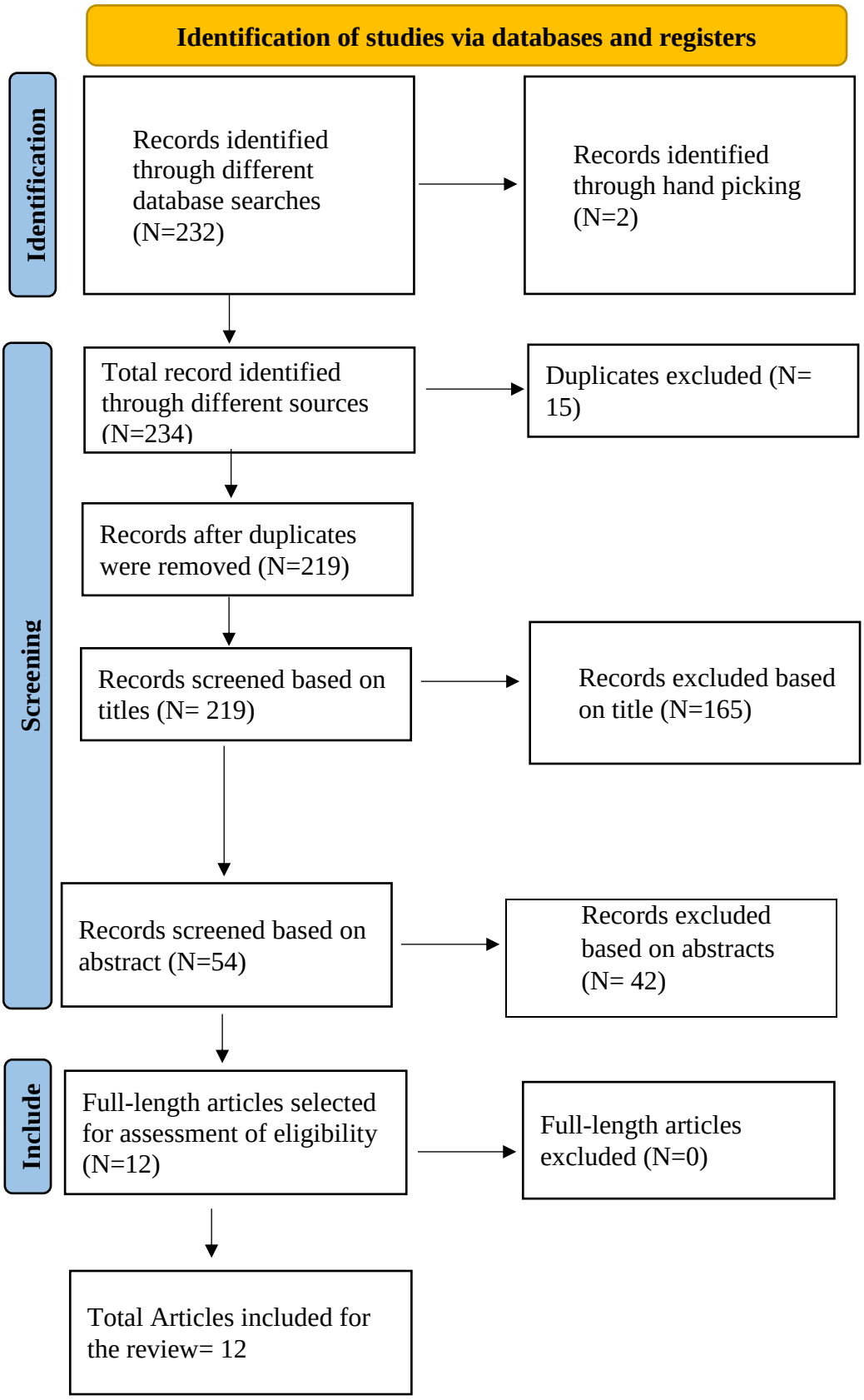

Figure 3.1: *Flowchart depicting the selection process of the articles in the systematic review*

3.2 Result of Quality Analysis after data extraction

Quality assessment is essential for the proper understanding of nonrandomized studies. QUADAS-2: A Revised Tool for the Quality Assessment of Diagnostic Accuracy Studies (Whiting et al., 2011) was used to determine the quality and strength of the study selected for the review. QUADAS-2 was developed for a systematic review to assess the quality and accuracy of diagnostic studies. Patient selection, index testing, reference standards, and flow and timing make up the four domains of this technology. Each domain is evaluated for bias risk, and the first three domains are evaluated for issues about applicability. Signalling inquiries are included to aid in assessing the likelihood of bias. This tool is suitable for a more transparent rating of the bias and applicability of diagnostic accuracy studies. Each item is rated as "high," "low," and "unclear" for assessing the risk of bias, source of variation, and quality.

All the studies were experimental design using calibrated instrumentation, standardized questionnaires, and proper methodology. Almost all the studies were well-controlled with proper selection and representativeness of cases and controls. There was good control of the study factors almost in all the studies with a low risk of bias. However, most of the studies lack the identification of the additional and confounding factors that might have deviated from the results and accounting for the same while analyzing the results. Misophonia is a complex neurological disorder and occurs with various co-morbid conditions; it is impossible to account for and remove all confounding factors. Most of the studies had shown a low risk of bias and source of variation in patient selection, flow, timing, and index test and had good implications for practice. The summary of the quality analysis of selected studies is shown in table 3.1.

Table 3.1

Tabular representation of quality analysis of the studies selected for the review using QUADAS-2

	Study Authors	Risk of Bias				Applicability concern		
SN		**Patient Selection**	**Index test**	**Reference standard**	**Flow and timing**	**Patient selection**	**Index test**	**Reference standard**
1.	Kumar et al., 2021	L	L	L	L	L	L	L
2.	Eijsker et al., 2021	L	L	L	L	L	L	L
3.	Libra et al., 2021	L	L	L	L	L	L	L
4.	Cerliani & Rouw., 2020	L	L	L	L	L	L	L
5	Schröder et al., 2019	L	L	L	L	L	L	L
6	Eijsker et al., 2019	L	L	L	L	L	L	L
7	Kumar et al., 2017	L	L	L	L	L	L	L

8	Eijsker et al., 2017	H	L	L	L	H	L	L
9.	Schröder et al., 2015	H	L	L	L	H	L	L
10.	Giorgi et.al., 2015	L	L	L	L	L	L	L
11.	Schröder et al., 2014	L	L	L	L	L	L	L
12.	Edelstein et al., 2013	H	L	L	L	U	L	L

L=Low risk	H=High risk	U=? Unclear risk

3.3 Summary of data extraction

Data were extracted from all the selected articles and classified using the following criteria-author, year of publication, research design, research question, type of population, method, outcome, and discussion. The data extraction sheet reveals that the studies included were published from 2013 to 2021. Selected studies mainly consisted of experimental studies. All the subjects included in the study were diagnosed with misophonia using standardized diagnostic protocols. Different standardized questionnaires, such as the misophonia Amsterdam questionnaire, the misophonia Questionnaire (MQ), misophonia symptoms severity questionnaire, and so on, have been used in most studies to differentiate the misophonia group from the control group.

Various modifications of the neuroimaging method such as functional magnetic resonance imaging (fMRI), structural fMRI, resting-state functional magnetic resonance imaging, sound-evoked fMRI, fMRI acquisition using BOLD during a stop-signal task (SST), fMRI acquisition during the performance of the visual stop-signal task and so on has been used in most of the studies to find the neurological pathophysiology of the misophonia (Kumar et al., 2021; Eijsker et al., 2021; Kumar et al., 2017). Along with that, evoked response potential (ERP) during the oddball task using electroencephalography (EEG) and comparison of Skin conductance response (SCR) among auditory and visual stimuli has also been used in a few studies to find the site of lesion in the misophonia participants (Edelstein et al., 2013; Schröder et al., 2014).

3.4 Neuroaudiological pathophysiology found across studies

The functional magnetic resonance imaging (fMRI) paradigm with different modifications has been used as the preferred method in selected ten studies to determine the size of the lesion by comparing misophonia participants with the control group. The result of the fMRI acquisition showed hyperactivation of the various cortical areas, such as the medial premotor cortex, mid-cingulate, and ventrolateral premotor cortex, which are the region involved in planning and preparing motor movements and related to the urge to avoid or react to the trigger sounds in an individual with misophonia. In addition, fMRI analysis showed greater white matter volume in the left frontal cortex including the area inferior frontal-occipital fasciculus (IFOF), anterior thalamic radiation (ATR), and the body of the corpus callosum (BCC) in the misophonic participants compared to the control. The outcome of the ten-neuroimaging studies using fMRI with different modifications is shown in table 3.2

Table 3.2

The outcome of ten neuroimaging studies

Study	Research design	Characteristics/ Research question	Population type (n)	Testing parameters used	Outcome	Discussion
Kumar et al., 2021	Experimental design	Will there be stimulation of the motor system in the misophonic population? Could the mirror neuron system related to orofacial movements underlie misophonia?	17 participants with misophonia and 20 control participant**s** for RS-fMRI 20 misophonic participants and 22 control participants for SE-fMRI	1) The misophonia Amsterdam questionnaire 2) The misophonia Questionnaire 3) Resting-state fMRI (RS-fMRI) 4) Sound evoked fMRI	The result showed that misophonia is characterized by: 1) Increased functional connection between the auditory and visual cortex and the orofacial motor region during rest; 2) Increased functional connectivity of the orofacial motor regions and auditory cortex in	Misophonia is typically thought of as a condition of the processing of sound emotions in which specific sounds, such as eating, chewing, etc., cause a negative emotional response. However, sounds produced by other people can simulate the actions they represent. Therefore, misophonia may just be the conduit by which the trigger person's behaviour is reflected in the listeners. As a result, it can be said that trigger sounds in misophonia induce the orofacial motor cortex to become hyperactive, suggesting that trigger sounds may excessively "mimic" orofacial activity

		response to all kinds of sound; 3) Increased orofacial motor region activation primarily in response to trigger sounds; 4) As misophonic discomfort develops, an orofacial motor region becomes more active; 5) Enhanced functional connection between the insula and the orofacial motor region of the vPMC during rest.	Since the primary auditory cortex does not become hyperactive in response to misophonic triggers, it is clear that misophonia is related to the orofacial motion that the sound symbolizes rather than a disorder of sound processing. In misophonic people, mirroring of the action also underlies the activation of the anterior insula-based network. Authors have shed light on an alternative perspective on misophonia that emphasizes the trigger's activity more than the sounds that result from it.

Eijsker et al., 2021	Experimental design	Will there be structural and functional abnormalities in the brain in misophonic individuals?	24 participants with misophonia and 25 control participants	1)Structural magnetic resonance imaging 2) Resting-state functional magnetic resonance imaging	1) Misophonic individuals showed larger grey matter volume in the right Amygdala. 2) A multivariate functional connectivity analysis showed altered strong connections of the left Amygdala with the bilateral cerebellum, mainly the medial parts of crus 1 and 2, in patients with misophonia compared to the control group. 3) Misophonic patients showed greater connectivity of ventral attention network in the	The authors come to the conclusion that increased emotional reactivity is reflected by expanded grey matter volume in the right Amygdala in misophonia patients because the Amygdala is involved in detecting affective valence and associative unpleasant learning. The functional network involved in affective sound processing includes the amygdala and cerebellum. . The ventral attention network and left Amygdala can modulate activity in the auditory and visual areas to adequately process important information. In individuals with misophonia, triggers activate enhanced sensory processing because they have emotional value. Patients' sensitivity to sounds that are barely audible to most people may be described by this.

					bilateral superior lateral occipital extending to inferior lateral occipital cortices and fusiform gyri compared to the control group.	
Liebra et al., 2021	Experimental design	Will there be abnormalities of white matter in individuals with misophonia?	25 participants with misophonia and 25 control subject	Amsterdam misophonia scale Hamilton anxiety and depression rating scale fMRI acquisition	Misophonic participants were found to have a larger severity scale on the Amsterdam misophonia scale. Misophonic participants also showed higher anxiety, depression, hate, and general psychopathy scores than the control group.	The co-overactive brain function that was discovered to be impacted in misophonic participants involves social-emotional processing and attention to emotionally salient information. The participants with misophonia had microstructural and microstructural white matter changes, which supported the neurobiological theory of misophonia.

			fMRI analysis showed greater white matter volume in the left frontal cortex, including the area inferior fronto-occipital fasciculus (IFOF), anterior thalamic radiation (ATR), and the body of the corpus callosum (BCC) in the misophonic participants compared to the control. Misophonic participants also showed lower than average Radial and mean diffusivities with fractional anisotropy. Vowel-wise	

					comparison showed larger clusters of lower mean diffusivity for the misophonia group compared to the control. Similarly, macrostructural white matter differences were found in the tract connecting the frontopolar and basal orbitofrontal cortex to the occipital and superior parietal cortex and medial portion of superior frontal gyri bilaterally.	
Cerliani & Rouw., 2020	Experimental design	What will be the neural mechanism for an individual with misophonia?	19 participants with misophonia and 20 participants in the control group**.**	1) Misophonia symptoms severity questionnaire 2) fMRI paradigm	Results showed: 1) Increased anterior dorsal insular activity in the	The ventral anterior insula has a different functional connection than the dorsal anterior insula. The study supports the hypothesis that emotional reaction in

		Will there be a higher-order cognitive association of misophonia?	misophonia group in the right hemisphere, reporting that the left anterior insula and Right anterior insula proceed with different aspects of the audiovisual-linguistic association and emotional content, respectively. However, the result did not show any evidence for increased ventral anterior insular activity during the specific trigger. 2) Increased activation of the medial premotor cortex,	misophonia is mediated by a higher-order construct rather than by a direct auditory-limbic connection by revealing the limited effect of the trigger in the ventral insula compared to the dorsal insula. Instead of the primary emotional association, higher order brain mechanisms were implicated in the emotional and behavioral response to the trigger, as evidenced by the increased activity in the medial premotor cortex, mid-cingulate, and ventrolateral premotor cortex. The increased activity of the primary visual region may be because the stimuli used were audio-visual rather than visual only. Given the role of this brain region in the reappraisal of stimuli associated with negative emotions, increased trigger-specific functional

	mid-cingulate and ventrolateral premotor cortex which are the region involved in planning and preparing motor movements and related to the urge to avoid or react to the trigger sounds in an individual with misophonia. 3) Increased activity of the primary visual region. 4) Increased interaction between premotor and cingulate cortices with the orbitofrontal cortex in individuals with misophonia	connectivity of the lateral OFC in the misophonia patient may reflect an effort to downregulate the emotional response, which is automatically prompted by the trigger stimuli. Increased synchronization between the Mid-cingulate and primary auditory cortex is evidence for the abnormal auditory activity in the primary auditory region in misophonia, according to the proposed model of the disorder. Misophonia is linked to an altered connection between the auditory and limbic systems. With the help of all the available data, the authors proposed that high-order cognitive associations, which may be connected to previously established negative associations with the same stimuli, are a more likely explanation for the selectivity of misophonia for particular sounds and the emotional reaction they cause.

					during the trigger stimuli.	
Schröder et al., 2019	Experimental design	Will there be an alteration of the brain activity in an individual with misophonia?	25 misophonic participants and 25 healthy control group	Amsterdam misophonia scale Electrocardiogram (ECG) fMRI paradigm using misophonia trigger clip, neutral clip, and aversive audio-visual stimuli.	Behavioural analysis showed that misophonic participants showed greater anxiety symptoms, depression symptoms, and psychiatric symptoms than control participants. Physiological investigation using ECG showed misophonic participants showed significantly smaller inter-beat-interval (IBI) across the condition than the control subject.	In misophonia individuals, some audio-visual stimuli may trigger emotions like rage, grief, or disgust. These emotions are then followed by higher physiological arousal and increased activity in the right insula, right ACC, and right superior temporal cortex. Increased activity in the insula, ACC, and right temporal cortex indicate that the symptoms of misophonia may be caused by salience attribution to the misophonic signals. The salience network activity may be amplified by repeated exposure to the same misophonia trigger. Although participants with misophonia showed greater psychiatric symptoms following the misophonic clip, they were not angrier before being exposed to the misophonic clip.

					fMRI data showed larger activation around the occipital, parietal and superior temporal cortex for both misophonic and aversive clips compared to the neutral clip. Also, reduced activity in the right inferior temporal gyrus was found in the misophonic group compared to the control group.	The increased heart rate in response to the misophonic clip and aversive clip suggested that the participant with misophonia experienced extreme aversive reactions in general.
Eijsker et al., 2019	Experimental design	What is the neural basis of response bias on the stop-signal task in misophonia?	22 misophonic participants and 21 healthy control group	The symptom checklist, Hamilton anxiety rating scale, Hamilton depression rating scale, and	Misophonic participants scored higher on the anxiety, depression, and anger scale than the control subjects. The severity score	The participants with misophonia show a marginal response bias on the stop-signal task (SST), favouring speed over accuracy. Additionally, misophonic participants tended to activate the left dorsolateral prefrontal cortex more during

		Amsterdam misophonia scale. Behavioural analysis of stop-signal delay (SSD) and stop-signal reaction time (SSRT) fMRI acquisition using BOLD during a stop-signal task (SST)	was higher for the misophonic subject on the Amsterdam misophonia scale. Behavioural analysis showed more extended SSD for the misophonic participants than for the control. However, misophonic participants and control did not differ in the SSRT and Reaction time. The participants with misophonia showed a lack of inhibition success related activation of the left dorsolateral premotor frontal cortex that the	responding than successful inhibition, similar to the control. Therefore, author concluded that misophonia participants did not show impaired response inhibition even though they tend to show response bias on the stop-signal task.

				control showed. Also, they tended to activate this region more during correct going than during successful inhibition. Misophonic participants showed less superior mid frontal gyri (SMFG) activation during the inhibition success compared to the failure. Whereas control showed inhibition success-related activity in the posterior cingulate cortices (PCC)

Kumar et al., 2017	Experimental design	What is the brain basis of misophonia?	20 misophonic participants and 22 control subject	fMRI using blood oxygen level-dependent (BOLD) Subjective rating Behavioural response, galvanic response (GSR), and heart rate (HR) were also acquired during the fMRI data acquisition.	When participants listened to three different types of sounds trigger, unpleasant, and neutral sounds, fMRI data and behavioural responses were acquired. Behavioural data showed that trigger sounds evoked misophonic distress in misophonic participants, whereas unpleasant sounds, although annoying, did not produce misophonic stress. There was no significant	AIC is the brain network that is functionally responsible for detecting and directing attention toward the stimuli which are behaviourally meaningful and relevant to the individuals. Hyperactivity in the AIC in response to the trigger sounds supports the hypothesis that misophonic participants assign aberrantly higher silence to these sounds. Atypical functional connectivity of AIC to vmPFC and PMC in microphonic and controls for the same sounds suggests that these regions play a crucial role in different emotional responses to the trigger sounds in the two groups and could, therefore, underlie the abnormal activation of AIC and the aberrant salience assigned to trigger sounds by the misophonic group.

					difference between the misophonia distress rating of trigger sounds by misophonic participants and the annoyance rating of unpleasant sounds by the control group. Analysis showed greater activation of the Anterior Insular Cortex (AIC) in response to the trigger sounds in the misophonic group compared to the control group. Activation difference does not occur between the misophonic and control groups for unpleasant

			and neural stimuli. Greater functional connectivity of AIC was observed in the ventromedial prefrontal cortex (vmPFC), posteromedial cortex (PMC; posterior cingulate and retrosplenial cortex), hippocampus, and amygdala regions of the brain for the misophonic participants. Activity in both right and left AIC varied linearly with subjective rating of misophonic distress in the

					misophonia group. Physiological response measurement showed greater HR and GSR response evoked by the trigger sounds in the misophonic group compared to the control group throughout the sound presentation. No difference was observed between the unpleasant and neutral sounds.	
Eijsker et al., 2017	Experimental design	Will there be impaired response inhibition in an individual with misophonia?	20 participants with misophonia and 20 control subject	fMRI acquisition during the performance of the visual stop-signal task.	According to the horse-race model, stop signal reaction time (SSRT) is a good indicator of how strong an inhibitory	Participants with misophonia exhibited reaction inhibition as a behavioural outcome. The misophonic individuals may have focused more on stopping appropriately than reducing their reaction times, as evidenced by the group

		response is. The difference between the start of the go and stop stimuli on stop trials is known as the stop-signal delay (SSD). Using two-sample t-tests to analyse group differences in the fMRI data, it was discovered that misophonic participants had shorter SSRT and longer SSDs than the control group. Misophonic participants displayed slower reaction times on both successful and unsuccessful inhibition attempts than	difference for the going stimulus, which could reflect group differences in task strategies. Although the visual cortex and IFG, which are crucial for stopping a task, were similarly activated in both groups, misophonic subjects displayed hypoactivation of the mid-cingulate cortex, which is the region that performs improperly during the cognitive task in several diseases. The left caudate was less active in the misophonic participants during the successful inhibition than during the unsuccessful inhibition.

			the control group. Whole-brain analysis showed that during the successful stopping compared to the going task, both patient and controls showed similar activation of the bilateral occipital cortex, angular cortex, and right inferior frontal cortex. In addition, controls showed activation of the bilateral insula, extending into the striatum. A between-group investigation revealed that controls had	

					higher midcingulate brain activity during successful versus unsuccessful inhibition than patients. ROI studies showed that the left caudate head was more activated in controls than in patients, although there were no group differences in the right IFG or STN.	
Schröder et al., 2015	Experimental design	What is the neuroanatomical correlate of impulsive aggression is misophonia?	10 participants with misophonia and 7 participants in control group	1) Amsterdam misophonia scale 2) fMRI symptom provocation paradigm using three conditions, i.e., common	In the misophonia group, neural activity was increased in the visual and auditory cortex and weak areas of the brain, i.e., the Amygdala during	The increased activity in the auditory cortex and left Amygdala in the misophonic participants might be associated with increased vigilance towards specific misophonic sounds. .

				aversive cues (violent or repulsive movie clips), misophonia-related cues (such as lip-smacking and noisy breathing), and neutral cues.	misophonia and aversive videos, compared to the control group. The group interaction with the neutral condition showed increased activity in the misophonic participants' auditory cortex in the right superior temporal cortex. Additionally, misophonic participants increased activity in the left Amygdala during group engagement with the unpleasant condition.	
Giorgi et al., 2015	Experimental design	Will there be hyperactivity in the brain	10 participants with	fMRI paradigm using the	Participants with misophonia and	The current investigation results demonstrated that misophonia participants

	areas in misophonia?	misophonia and 10 healthy control participants	audio-visual stimulus of misophonia trigger clip, aversive stimulus, and neutral stimulus	the healthy control group employing the misophonia condition had similar BOLD responses, indicating no discernible difference between the two groups. When contrasting misophonia participants with the misophonia stimulus and the neutral stimulus condition, a significant difference in BOLD response was discovered. According to the analysis, the misophonic subjects' right and left superior temporal cortex were hyperactive.	experienced a number of functional impairments when exposed to misophonia triggers. In contrast to neutral settings, the BOLD response was shown to be greater in the affective, auditory, and visual processing areas under non-neutral situations. Since misophonia and aversive situations are more salient and involve more sounds and movement than neutral recordings, these findings can be explained. Increased attention to auditory stimuli, which has been associated with hyperactivation of the auditory cortex, may be the cause of hyperactivation of the bilateral auditory cortex. The misophonic participants' left Amygdala hyperactivity has been associated with attentional processing and vigilance. As misophonic sufferers are intensely focused on the trigger noises, increased alertness during the

		ROI analyses displayed greater activity in the left Amygdala in the misophonic participants than in the healthy control subject when comparing the misophonia condition with the aversive condition. When comparing misophonia and aversive conditions, ROI analyses of the Amygdala showed no significant difference in the misophonic participants. However, the hearing control subject did not	misophonia condition may cause the amygdala's hyperactivity.

			significantly affect the left Amygdala when comparing the aversive condition with the misophonia condition.

Electrophysiological tests (ERP) and Skin conductance response (SCR) have been used as the preferred method in two studies ((Edelstein et al., 2013; Schröder et al., 2014). The evoked response potential (ERP) result showed a smaller N1 component in response to the deviant tone in the misophonia participants than in the control group. The skin conductance response (SCR) result showed a higher skin conductance response in the misophonic group than in the control group. The detailed outcome of these studies is shown in table 3.3.

Table 3.3

The outcome of the physiological tests used across the studies

Author/year	Research design	Characteristics / Research question	Population type (n)	Testing parameters used	Outcome	Discussion
Schröder et al., 2014	Experimental design	Will there be a deficit in auditory processing in misophonic individuals?	20 participants diagnosed with misophonia and 14 participants in the healthy control group.	Hearing tests (tone and speech audiogram and loudness discomfort levels) Recorded auditory event-related potentials (ERPs) during the oddball task using EEG Standard tones (80%) had a frequency of 1000 Hz, and the deviant	All the participants with misophonia reported normal hearing. Compared to the control group, the deviant tones elicited the misophonia with a reduced N1 component. There was no discernible difference in the N1 component's peak latency between the misophonic group	The lower mean N1 peak amplitude in the misophonic group compared to the control group suggests a little auditory information processing disadvantage in misophonic people. The difference in clinical characteristics between the two groups, according to the author, is what accounts for the lower N1 peak amplitude in the misophonic group. The misophonic group reported higher TMD

		tone was lower than the standard tone (250 Hz). A tone higher than the standard (4000 Hz) was added to the sequence. Both deviants were presented in 10% of trials. Profile of mood states (POMS) scale Total mood disturbances (TMD) scale	and the control group. Additionally, there were no changes between the control group and the misophonic people regarding the P1, P2 average amplitude, or peak latencies. Effect of deviant tone was found for P1, N1, and P2 averages amplitude. For P1 and P2, low deviant tone elicited larger amplitude, whereas for N1 low deviant tone elicited smaller amplitude. Peak latency of N1 was also found to be different for high deviant tone and low tone. The high tone showed an earlier peak compared to the low peak. No significant differences were reported in the	scores than the control group, which reflects the general hyperarousal in misophonic individuals. And because of hyperarousal or general irritability, misophonia patients might not have attended to the sounds as much as the controls group. The authors also suggest that the misophonia patients' usage of psychotropic medications or some other psychiatric co-morbidity may be to blame for the difference in N1 peak amplitude between the misophonia group and the control group.

					average amplitude and peak latency of the P1, N1, or P2 responses elicited by the standard stimuli between the misophonic group and the control group.	
Edelstein et al., 2013	Experimental Design	Will the misophonic subjective experiences evoke an anomalous physiological response to certain auditory stimuli?	Six participants with misophonia and five control subjects.	Comparison of Skin conductance response (SCR) among auditory and visual stimuli. Subjective aversiveness rating.	Misophonic individuals showed a higher skin conductance response than the control group. Also, misophonic individuals showed higher SCR in response to the auditory stimuli but not visual stimuli. In the subjective aversiveness rating, misophonic individuals rate the auditory stimuli more aversive than visual stimuli. The result showed a positive correlation between subjective	The authors concluded that the individual with misophonia reports physiological distress to the specific sounds with a high level of knowledge demonstrating prolonged and specific physiological reactions. The significant positive correlation between the misophonic aversiveness rating and the control aversiveness rating suggest that misophonia may experience an extreme form of discomfort

		aversiveness rating and the SCR measurement.	that the normal individual experience to normally aversive or irritating stimuli. This raises the important hypothesis that there is nothing intrinsically different about misophonic individuals from those in the normal population, and the misophonic individual falls at the tail end of the distribution.

Chapter 4

Discussion

The present systematic review aimed to study the Neuroaudiological pathophysiology of misophonia. The result of the review revealed abnormal activation and connection among the different higher cortical structures in participants with misophonia. Highlighting the misophonia pathophysiology helps identify misophonia as a separate disorder and provides the pathway for assessment and management of misophonia from different perspectives.

4.1 Different self-report measures used for diagnosing misophonia across studies

Across the studies, various self-report questionnaires have been used along with the interview to characterize the psychological correlates of misophonia**.** Many studies aim to characterize 1) Subjective response to triggers and experiences 2.) Physiological correlates of the different triggers 3) Correlation of the psychiatric symptoms with the neurophysiological findings. Out of 12 articles selected for the review, five studies have used Amsterdam Misophonia Scale Questionnaire to characterize the subjective response of the individual with misophonia (Liebrand et al., 2021; Kumar et al., 2021; Eijsker et al., 2019). Few studies have used Misophonia Questionnaire (MQ) (Kumar et al., 2021), and others have used the Hamilton anxiety rating scale and Hamilton depression rating scale (Liebrand et al., 2021).

This result shows Amsterdam misophonia scale questionnaire is the most widely used questionnaire to diagnose misophonia. Amsterdam misophonia scale questionnaire developed by Schröder et al. (2013) has been validated in different languages. It is one of the most reliable and valid questionnaires with good sensitivity

and specificity across languages (Naylor et al., 2021). The use of the Amsterdam Misophonia questionnaire across most of the studies selected for the review reflects the reliability of the findings.

4.2 Different physiological measures used for studying the brain basis of misophonia

Different methods used for studying the brain basis of misophonia have been explored. Across the studies, various neurophysiological, neurobiological, neuroimaging, and autonomic measures have been explored to find the brain functioning of the individual with misophonia. Across the studies, the subjective response to the misophonics is correlated with the physiological measurement of increased autonomic arousal in response to the misophonic triggers, which validates the experience of sufferers. These findings demonstrate misophonic trigger atypical sympathetic arousal and negative conditioning. Similarly, across the neuroimaging studies, it was found that misophonics showed an atypical neuronal and physical response, which again validates the condition is real and special attention is needed to develop the assessment and management strategies. Neurobiological studies showed central auditory processing impairment in individuals with misophonia. However, the findings of these studies using various methods are inconclusive, and further research is needed in the future, focusing on both the peripheral and central nervous systems.

4.2.1 Neuroimaging findings in misophonia

The neurophysiological correlates of misophonia have been studied, and most research found abnormalities in the auditory cortex, limbic system, and non-classical pathway (Schröder et al., 2019; Eijsker et al., 2019). The Anterior Insular Cortex (AIC) showed increased neural activity in the fMRI study by Kumar et al. (2017),

employing the unpleasant trigger sounds, which is regarded as the strongest evidence supporting the neurological etiology of misophonia. Since the AIC is the main region in charge of emotional awareness, we might anticipate that this region will respond more strongly when exposed to trigger sounds.

Another fMRI study by Giorgi (2015) discovered that when an individual with misophonia is exposed to auditory triggers, the left Amygdala and bilateral auditory cortex become hyperactive. Schröder et al (2015) reported similar findings as well. The ventromedial prefrontal cortex (vmPFC), a node of the default mode network, has more gray matter demyelination in misophonics, according to Kumar et al. structural analysis of the brain data (DMN). This anatomical discrepancy may explain the aberrant functional connection of AIC to DMN in misophonics compared to controls. Overall, Kumar et al. findings' indicate aberrant AIC activity and functional connectivity, suggesting potential areas and systems that could represent the neurological process underlying misophonia. Ultimately, these discoveries may be clinically significant since they give clinical scientists important information about potential biological systems that might be changed when creating treatment plans for people with misophonia.

However, there is several limitations to the study by Kumar et al. (2017). The first limitation is a lack of a clinical control group, without which we can not conclude that findings from the study are unique and specific to misophonia. Another drawback is that establishing correlations and connections between behavioral activity and brain patterns does not support causal interpretations.

Further evidence of the misophonia's neurophysiological basis has been given by Schroder et al.(2014). Schroder and colleagues studied the N1 component of the

late evoked auditory potentials. They reported reduced amplitude of the N1 component in the oddball stimuli, the marker linked to early attention and detection of abrupt sensory changes. Their findings showed a neurobiological deficit in individuals with misophonia, which could impair auditory processing of the incoming stimuli, although there is no direct causal link. Similary, Schroder et al. (2013) used mismatch negativity response as the objective test of central auditory processing and reported reduced MMN response in individuals with misophonia compared to the control group.

4.2.2.Psychophysiological findings in misophonia

The first study to examine misophonia utilizing psychophysiological testing was conducted by Edelstein et al. (2013). They measure the sympathetic nervous system response utilizing unisensory and multisensory stimuli in people with misophonia and control subjects using the skin conductance response (SCR). When compared to controls, misophonia patients responded more strongly to auditory-only stimuli in SCR data, but there was no discernible difference for visual-only stimuli. The average level of aversiveness and mean SCR across all participants and unisensory and multisensory trials were found to be significantly positively correlated**.** Similarly, Kumar et al. (2017) reported triggers eliciting increased heart rate and galvanic skin response in individuals with misophonia compared to the control group. From these findings, we can report that misophonic responses can be measured in the autonomic nervous system.

However, there are several limitations in the study by Edelstein et al. (2013)**.** The few limitations to be noted are lack of adequate sample size, lack of clinical comparison group, and lack of proper screening measures for psychiatric and

psychological measures. There is a need to carry out research in the future using this method by improving these limitations.

4.3 Auditory gating and processing in individuals with misophonia

Sensory gating is the brain's capacity to selectively regulate sensitivity to a sensory stimulus (Yadon et al., 2009). Auditory gating is when the brain shows a reduced response to repeated stimuli. There is a role of inhibition in the gating function to filter out the non-novel input leaving adequate resources for the brain to process relevant information. The auditory gating function has been investigated across various disorders such as Autism spectrum disorder (ASD), Schizophrenia, Sensory processing disorder (SPD), hearing loss, and Tinnitus. However, as misophonia is a new condition and is in the developing phase, there are not enough studies investigating auditory gating in misophonia.

In the study by Brett-Green et al. (2010), early evoked response potentials (ERP) have been documented in the sensory cortex suggesting abnormal information processing in sensory over-responsive children. Similarly, the study by Schröder et al.(2014) also supports the previous findings reporting a reduction in the mean amplitude of the N1 peak in individuals with misophonic. These results suggest that atypical sensory processing might be present in adults and children with misophonia and sensory processing disorders (SPD). The reduction in the amplitude of the N1 peak might be suggestive of sound encoding deficits in misophonia. However, there is a need to carry out collaborative studies in the future with different field researchers to gain deep insight into the gating function in an individual with misophonia.

4.4. Implications of Neuroaudiological findings in Assessment of Misophonia

Assessment of misophonia is not known yet. There is no standardized recommended protocol for the assessment of misophonia. The misophonia assessment needs an interdisciplinary approach involving psychologists, audiologists, neurologists, and occupational therapists. Many researchers are trying to show a path for the assessment in different ways using different models and hypotheses.

In the literature, assessment of misophonia has been done subjectively using different questionnaires. However, assessment using subjective questionnaires only is not sufficient, as it is challenging to come to a valid diagnosis using subjective measures only. We need to assess using different objective procedures, including electrophysiological measures and neuroimaging methods. The result from the review showed hyperactivation in the auditory and limbic systems. Hence, there is a need to develop an assessment protocol using a different electrophysiological measure like an auditory long-latency response (ALLR), Mismatch negativity (MMN), and P300. However, the assessment of misophonia from the audiological perspective is not well explored, and there is a need to develop a better assessment protocol using different electrophysiological measures from the audiological perspective.

4.5 Implications of Neuroaudiological findings in the management of misophonia

There is no standardized protocol developed for the management of misophonia. Various medical and non-medical approaches have been tried in literature to manage misophonia. However, success with the different approaches is limited. The result from the review states that using neuromodulation techniques like transcranial magnetic stimulation, transcranial direct current stimulation, transcranial alternating current stimulation, transcranial random noise stimulation, neurofeedback,

epidural and subdural cortical and deep brain stimulation, and vagus nerve stimulation, hyperactivity in the auditory and limbic systems of a person with misophonia can be suppressed (Umashankar & Prabhu., 2021). However, these approaches have not been tried clinically.

Various neurophysiological studies have shown hyperactivation of the non-classical auditory pathway in an individual with misophonia (Kumar et al., 2017). Hence, treatment approaches from audiological perspectives, such as Tinnitus Retraining Therapy (TRT) and Cognitive Behavioural Therapy (CBT), must be explored clinically to properly manage misophonia. Hence, understanding detailed Neuroaudiological pathophysiology will help the clinician to develop the proper management program for the individual suffering from misophonia.

Chapter 5

Summary and Conclusion

Misophonia is a new neurophysiological condition that is relatively less explored. The exact neurophysiology of misophonia is not known yet, and this is the topic of debate between psychology, audiology, and neurology. The proper assessment and management of the individual with misophonia are impossible without understanding the core mechanism behind it. Therefore, to gain detailed insight into the neurophysiology of misophonia, we reviewed all the research articles about the physiology of misophonia published till 2021 using proper inclusion and exclusion criteria.

The main purpose of our study was to see the brain basis of an individual with misophonia highlighting more the auditory neurophysiology. We reviewed 12 research articles that were related to the pathophysiology of misophonia. Most studies have used various neuroimaging methods, such as the functional Magnetic Resonance Imaging (fMRI) paradigm with different modifications to see the neurophysiology of the misophonic brain. Few studies have used electrophysiological measures such as Mismatch negativity (MMN) and P300. In summary, we found that the brain functioning of an individual with misophonia differs from that of a control subject. Most studies have shown hyperactivation of the cortical areas, including the auditory and limbic areas, in individuals with misophonia. In addition, few studies have noted hyperactivation in the non-classical auditory pathway and impaired sensory gating in an individual with misophonia. Even though the aim of the studies and methodology are the same across the studies, there is variation in the findings. This may be due to variation in descriptive characteristics of the individual with

misophonia recruited in the study. Also, none of the studies tries to see neurophysiological mechanisms according to the severity of misophonia. This can also be a confounding variable to result in different findings across studies.

This review will act as the baseline for the researchers interested in researching misophonia from audiological and neurological perspectives. This review highlights the need to develop more advanced objective physiological measures from audiological and neurological perspectives to gain detailed insight into the physiological mechanism of misophonia. Also, there is a need to develop precise subjective tools to categorize the types and severity of misophonia and compare the physiological mechanism accordingly.

5.1. Implications of the study

Misophonia is considered a psychological disorder. By signifying various neurophysiological and neuroradiological findings, the review confirms misophonia is a neurophysiological disorder that may border between audiology, neurology, and psychology. The review also highlights the need to include neurophysiological and audiological measures for diagnosing misophonia as only subjective measures from psychological perspectives are insufficient for properly assessing the misophonia.

As misophonia is the topic of debate in the literature, this review will help to confirm misophonia is a real disorder as there are various neurophysiological alterations in the brains of individuals with misophonia and also may show the significance of including misophonia in the International Classification of Diseases (ICD) classification and Diagnostic and Statistical Manual of Mental Disorders (DSM).

The present systematic review helped to understand the gap in the literature classification of misophonia. The present systematic review will shed light on understanding the Neuroaudiological pathophysiology of misophonia and provide the compiled information on the pathophysiology of misophonia. The findings of this review can be used further in the assessment and management of misophonia from audiological and neurological perspectives. In addition, this review's findings help differentiate the pathophysiology of misophonia from other sound disorders like tinnitus and hyperacusis and provide the path for assessment and management strategies.

5.2. Limitation of the study

The present review has a few limitations. Few articles included for the review have an inadequate sample size, which could have biased the results. Misophonia can occur in isolation or as a co-morbid condition. However, most studies did not discuss co-morbidity and exclusion of the participants based on the co-morbidities. Hence, the results obtained may also be due to co-morbidities. In addition, none of the studies tries to see the physiological mechanism based on the severity of the misophonia. Although a salient concern, this review only included studies published in English.

5.3. Future directions

- With the advancement in technology, there is a need to discover various neurophysiological and neuroaudiological tools for assessment protocol which may provide detailed insight into the physiological mechanism of the mechanism
- In the future, we must conduct the research using an adequate sample size and methodology.

- There is a need to develop a reliable and valid tool with good sensitivity and specificity to categorize misophonia according to the degree of severity. There is a need to compare physiological mechanisms across the degree of misophonia.
- There is a need to develop proper management strategies for helping an individual with misophonia, focusing on the neurophysiological mechanism behind it.

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