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REVIEW ARTICLE

Understanding misophonia from an audiological perspective: a systematic review

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Abstract

Purpose 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. Misophonia 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 vital members of the team. However, their roles in this condition are not well-understood. The study aims to review the neurophysiological mechanism of misophonia, highlighting the mechanism involved in the audiological pathway and directing the discussion toward applications of findings in the assessment and management of misophonia from the audiological perspective.

Methods We reviewed 12 articles from different databases to understand the neurophysiological mechanisms of misophonia. Most of the studies selected were experimental designs involving individuals with misophonia.

Results The result of the review revealed abnormal activation and connection among the different higher cortical structures in participants with misophonia. By signifying various neurophysiological and neuroradiological findings, the review confirms that misophonia is a neurophysiological disorder that may border between audiology, neurology, and psychiatry. Assessment of study quality reported an overall low risk of bias.

Conclusions This review highlights the need to include an audiologist as a team member in the evaluation and management of misophonia.

Keywords Misophonia · Neurophysiology · Audiologist · Systematic review · Assessment and management

Introduction

Misophonia or sound selectivity syndrome is a sound tolerance disorder in which certain sounds trigger an intensely emotional or physiological response caused by increased autonomic nervous system reaction to specific triggers [1]. Triggers are the sound that causes emotional outbursts in a patient with misophonia. When exposed to specific auditory triggers, people with misophonia exhibit various physiological and emotional responses, including an accelerated heart rate, sweating, anxiety, rage, irritability, and disgust [1]. Since triggers are very much common in misophonic individuals, they can lead to social isolation and psychological problems. 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 [1]. 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.

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. In addition, misophonia often coexists with other similar conditions, such as tinnitus, hyperacusis, and phonophobia, which is necessary to differentiate [1]. 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 [2], few authors have mentioned during adulthood [3], and few have mentioned that there are no age criteria for the occurrence of misophonia as it can happen at any age [4]. Determining the prevalence of misophonia has

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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% [5]. Similarly, Naylor et al. reported clinically significant misophonia in 49.1% of the study sample population among the U.K. undergraduate medical student population [6]

Misophonia is an adverse reaction to sounds driven by enhanced limbic and autonomic responses without excessive auditory system amplification [7]. 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 [7]. According to Jastreboff (1990) and Jastreboff and 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 [8, 9]

The neuroimaging studies employing functional magnetic resonance imaging (fMRI) showed hyperactivation of the right insula, right anterior cingulate cortex, and right superior temporal cortex with misophonic video clips compared to neutral video clips [10, 11]. In misophonic patients, trigger sounds also increased heart rate (H.R.) and galvanic skin response (GSR), which were mediated by anterior insular cortex (AIC) activity [11]. Similarly, Schröder et al. revealed that the misophonic group's mean N1 peak amplitude was lower than the control group, suggesting that misophonic people may have low-level auditory information processing deficits [12]. The right superior temporal cortex, right anterior insular cortex, and right anterior cingulate showed greater activity in the misophonic group than in the control group [10]. Similarly, Giorgi et al. found hyperactivation of the bilateral auditory cortex and left amygdala when exposed to the misophonic triggers compared to the control group [13].

Rationale and justification of the study

Although misophonia has undergone substantial advancement, neither the Diagnostic nor 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. as a specific psychiatric condition rather than a symptom of other disorders, and they have provided diagnostic criteria to support this claim [14]. Few questionnaires were developed to assess misophonia [15, 16]. Amsterdam misophonia scale (A-MISO-S) is the checklist developed by Schröder et al. for assessing the severity of symptoms along the dimensions of the proposed criteria for misophonia and has also been used widely across the literature [14].

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. Brout et al. had mentioned in their paper that there can be a central auditory processing disorder in individuals with misophonia, and there is a need for research from audiological perspectives [17]. The audiological evaluation of misophonia is challenging, and there is no established technique. As a result, there is a huge demand for research on misophonia from an audiological standpoint.

The complex nature of misophonia has made it a stressful disorder for sufferers and family members. However, little research is 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 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. Hence, this review aims to highlight the Neuroaudiological pathophysiology of misophonia and its implications in the assessment and management of misophonia from an audiological perspective.

Methods

The study was conducted after registration in the PROSPERO (Regd ID: CRD42021279965). The review was carried out using Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines in various databases for literature search [18]. These databases included African Journal Online (AJOL), Google Scholar, PubMed (National Centre for Biotechnology Information), MEDLINE (U.S. 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’; ‘Selective sound sensitivity syndrome’; ‘Sound rage’; ‘Neuroaudiology’; ‘Neurophysiology’; ‘Pathophysiology’; and ‘Mechanism and the

derivatives of these words 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 on the 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. 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. 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.

Results

Records/article selection

Applying the initial search strategy and the inclusion and exclusion criteria provided 12 papers for quality analysis and synthesis. Among the 234 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. Twelve articles meeting the inclusion criteria for complete reading 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 arose 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 which is mentioned in Fig. 1

Result of quality analysis after data extraction

QUADAS-2: A Revised Tool for the Quality Assessment of Diagnostic Accuracy Studies [19] was used to determine the quality and strength of the study selected for the review. All the studies were experimental designs 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. The summary of the quality analysis of selected studies is shown in Table 1.

Summary of data extraction

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 Amsterdam Misophonia Questionnaire [20] and the Misophonia Questionnaire (MQ) [15] 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 [11, 15, 20, 21]. 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 [22, 23].

Neuroaudiological pathophysiology found across studies

The functional magnetic resonance imaging (fMRI) paradigm with different modifications has been used as the preferred method in ten selected 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 of 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. Various neurophysiological studies have shown

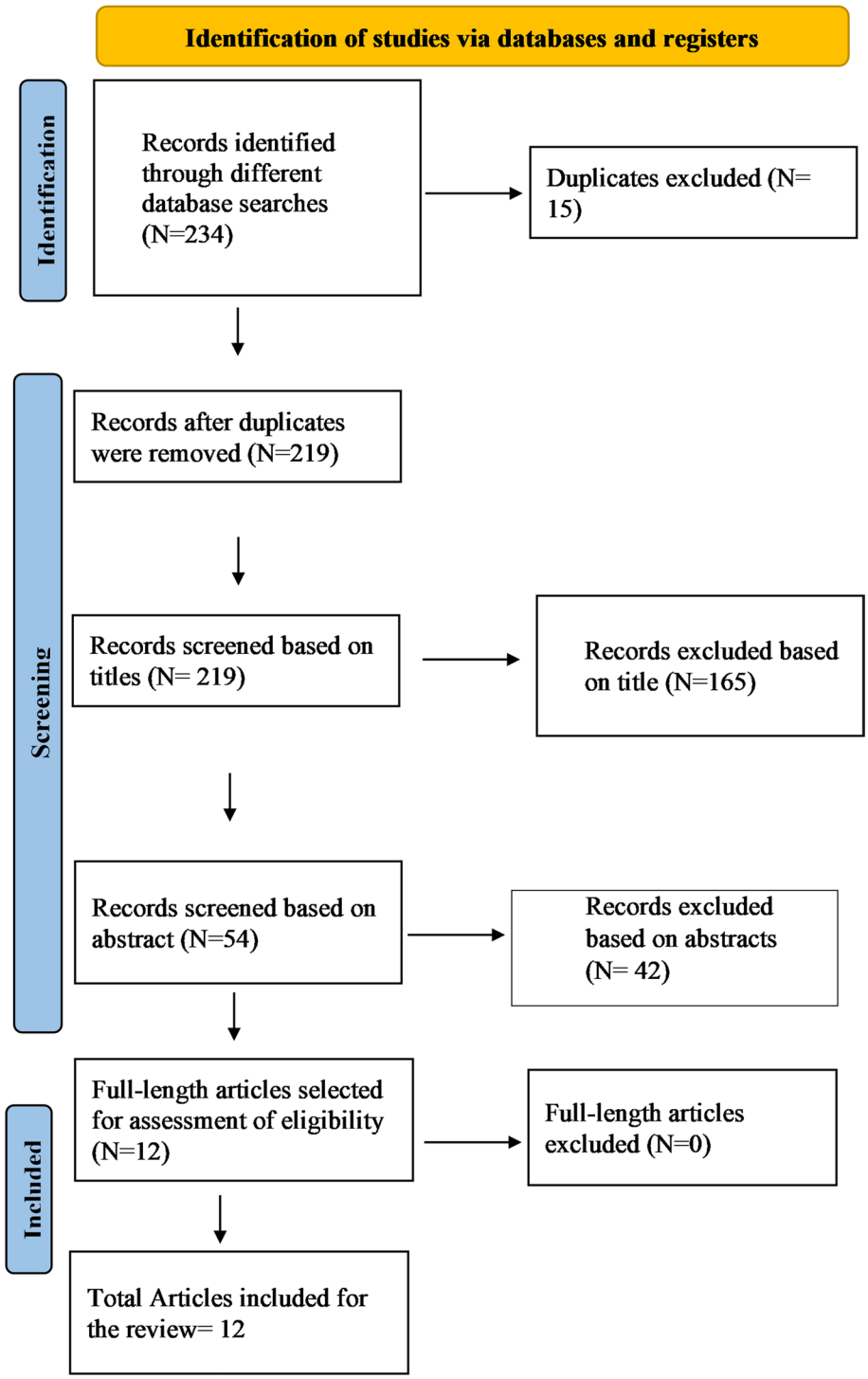

Fig. 1 Flowchart depicting the selection process of the articles

hyperactivation of the non-classical auditory pathway in an individual with misophonia [11]. The outcome of the ten-neuroimaging studies using fMRI with different modifications is shown in Table 2.

Electrophysiological tests (ERP) and Skin conductance response (SCR) have been used as the preferred method in two studies [23, 24]. 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 suggesting impaired sensory gating in individuals with misophonia. 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.

The results from the review show problem in the audiological pathway, which highlights the need to explore

Table 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

misophonia from an audiological perspective. From the literature review and the author's understanding, the neuroaudiological model has been formulated to understand misophonia from the audiological perspective, as illustrated in Fig. 2.

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. 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 that the condition is real and special attention is needed to develop the assessment and management strategies. Neurobiological studies showed central auditory processing impairment in misophonics. 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.

The neurophysiological correlates of misophonia have been explored, and most research found abnormalities in

Table 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 participants 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 and in response to all kinds of trigger sounds 2) Enhanced functional connection between the insula and the orofacial motor region of the vPMC during rest	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 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
Eijsker et al., 2021	Experimental design	Will there be structural and functional abnormalities in the brain in misophonic individuals?	24 misophonic participants 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, altered connections of the left amygdala with the bilateral cerebellum, and Greater connectivity of ventral attention network in the bilateral superior lateral occipital extending to inferior lateral occipital cortices and fusiform gyri compared to the control group	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 unpleasant associative learning

Table 2 (continued)

Study	Research design	Characteristics/research question	Population type (*n*)	Testing parameters used	Outcome	Discussion
Liebra et al., 2021	Experimental design	Will there be abnormalities of white matter in misophonia?	25 participants with misophonia and 25 control subject	Amsterdam misophonia scale Hamilton anxiety and depression rating scale fMRI acquisition	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), and lower than average Radial and mean diffusivities with fractional anisotropy in the misophonic participants 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	The co-overactive brain function that was discovered to be impacted in misophonic participants involves social–emotional processing and attention to emotionally salient information Microstructural and microstructural white matter changes in individuals with misophonia supported the neurobiological theory of misophonia

Table 2 (continued)

Study	Research design	Characteristics/research question	Population type (*n*)	Testing parameters used	Outcome	Discussion
Cerliani & Rouw., 2020	Experimental design	What will be the neural mechanism for an individual with misophonia? Will there be a higher order cognitive association of 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 misophonia group in the right hemisphere, reporting that the left anterior insula and Right anterior insula proceed with different aspects of the audio–visual–linguistic association and emotional content, respectively 2) Increased activation of the medial premotor cortex, Mid-cingulate and ventro-lateral premotor cortex are the region involved in planning and preparing motor movements and are related to the urge to avoid or react to the trigger sounds in an individual with misophonia	The study supports the hypothesis that emotional reaction in 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 The increased activity of the primary visual region may be, because the stimuli used were audio–visual rather than visual only Increased synchronization between the mid-cingulate and primary auditory cortex is evidence of 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 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

Table 2 (continued)

Study	Research design	Characteristics/research question	Population type (*n*)	Testing parameters used	Outcome	Discussion
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	Physiological investigation using ECG showed misophonic participants showed significantly smaller inter-beat-interval (IBI) across the condition than the control subject 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	Some audio–visual stimuli may trigger emotions, such as rage, grief, or disgust in misophonia individuals. These emotions are then followed by higher physiological arousal and increased activity in the right insula, right ACC, and right superior temporal cortex. This 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
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, and Amsterdam misophonia scale Behavioral analysis of stop-signal delay (SSD) and stop-signal reaction time (SSRT) fMRI acquisition using BOLD during a stop-signal task (SST)	Behavioral 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 to activation of the left dorsolateral premotor frontal cortex that the control showed. In addition, they tended to activate this region more during correct going than during successful inhibition	The participants with misophonia show a marginal response bias on the stop-signal task (SST), favoring speed over accuracy. In addition, misophonic participants tended to activate the left dorsolateral prefrontal cortex more during 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

Table 2 (continued)

Study	Research design	Characteristics/research question	Population type (*n*)	Testing parameters used	Outcome	Discussion
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) Behavioral 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—fMRI data and behavioral responses were acquired Behavioral data showed that trigger sounds evoked misophonic distress in misophonic participants, whereas unpleasant sounds, although annoying, did not produce misophonic stress Analysis showed greater activation of the Anterior Insular Cortex (AIC), including the ventromedial prefrontal cortex (vmPFC), posteromedial cortex (PMC; posterior cingulate and retrosplenial cortex), hippocampus, and amygdala region of the brain in response to the trigger sounds in the misophonic group compared to the control group Physiological response measurement showed greater HR and GSR response evoked by the trigger sounds in the misophonic group compared to the control group	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

Table 2 (continued)

Study	Research design	Characteristics/research question	Population type (*n*)	Testing parameters used	Outcome	Discussion
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	Using two-sample *t* tests to analyze 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 successful and unsuccessful inhibition attempts than 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	Participants with misophonia exhibited reaction inhibition as a behavioral outcome. The misophonic individuals may have focused more on stopping appropriately than reducing their reaction times, as evidenced by the group 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

Table 2 (continued)

Study	Research design	Characteristics/research question	Population type (*n*)	Testing parameters used	Outcome	Discussion
Schröder et al., 2015	Experimental design	What is the neuroanatomical correlate of impulsive aggression is misophonia?	10 participants with misophonia and seven healthy control group	Amsterdam misophonia scale fMRI symptom provocation paradigm uses three conditions, i.e., common aversive cues (violent or repulsive movie clips), misophonia-related cues (such as lip-smacking and noisy breathing), and neutral cues	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 misophonia and aversive videos, compared to the control group Increased activity was observed in the auditory cortex in the right superior temporal cortex and left amygdala during group engagement with the unpleasant condition	The increased activity in the auditory cortex and left amygdala in the misophonic participants might be associated with increased vigilance toward specific misophonic sounds
Giorgi et al., 2015	Experimental design	Will there be hyperactivity in the brain areas in misophonia?	10 participants with misophonia and ten healthy control participants	fMRI paradigm using the audio–visual stimulus of misophonia trigger clip, aversive stimulus, and neutral stimulus	Results showed the misophonic subjects' right and left superior temporal cortex to be hyperactive 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	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 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 may cause the amygdala's hyperactivity during the misophonia condition

Table 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 were diagnosed with misophonia, and 14 were 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	The deviant tones elicited misophonia with a reduced N1 amplitude component than the control group There was no discernible difference in the N1 component's peak latency between the misophonic and control groups In addition, there were no changes between the control group and the misophonic people regarding the P1, P2 average amplitude, or peak latencies	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
Edelstein et al., 2013	Experimental design	Will the misophonic subjective experiences evoke an abnormal 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. In addition, misophonic individuals showed higher SCR in response to the auditory stimuli but not visual stimuli Misophonic individuals rate the auditory stimuli more aversive than visual stimuli. The result showed a positive correlation between subjective aversiveness rating and the SCR measurement	An 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 that the typical individual experience to normally aversive or irritating stimuli. This raises the critical hypothesis that there is nothing intrinsically different about misophonic individuals from those in the average population, and the misophonic individual falls at the tail end of the distribution

the auditory cortex, limbic system, and non-classical pathway [25, 26]. The Anterior Insular Cortex (AIC) showed increased neural activity in the fMRI study by Kumar et al., employing the unpleasant trigger sounds, which are regarded as the most substantial evidence supporting the neurological etiology of misophonia [27]. Since the AIC is the central 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 discovered that when an individual with misophonia is exposed to auditory triggers, the left amygdala and bilateral auditory cortex become hyperactive [13]. Schröder et al. reported similar findings as well [28]. The ventromedial prefrontal cortex (vmPFC), a node of the default mode network, has more gray matter demyelination in misophonics, according to Kumar et al.'s structural analysis of brain data (DMN) [11]. This anatomical discrepancy may explain the aberrant functional connection of AIC to DMN in misophonics compared to controls. Overall, Kumar et al. findings.'s indicate aberrant AIC activity and functional connectivity, suggesting potential areas and systems that could represent the neurological process underlying misophonia [11]. Ultimately, these discoveries may be clinically significant, since they give important information about potential biological systems that might be changed when creating treatment plans for people with misophonia.

Further evidence of the misophonia's neurophysiological basis has been given by Schroder et al. [23]. 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. Similarly, Schroder et al. 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 [29].

Edelstein et al. conducted the first study to examine misophonia utilizing psychophysiological testing [20]. 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 the unisensory and multisensory trials were positively correlated**.** Similarly, Kumar et al. reported triggers eliciting increased heart rate and galvanic skin response in individuals with misophonia compared to the control group [11]. 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. [20]. 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 [20]. There is a need to carry out research in the future using this method by improving these limitations.

In the study by Brett-Green et al., early evoked response potentials (ERP) have been documented in the sensory cortex suggesting abnormal information processing in sensory over-responsive children [30]. Similarly, the study by Schröder et al. also supports the previous findings reporting a reduction in the mean amplitude of the N1 peak in individuals with misophonic and reported impaired sensory gating in individuals with misophonia [23]. 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.

Implications of the study

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

As misophonia is the topic of debate in the literature, this review will help to confirm that 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.

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. This review highlights the need to develop assessment protocols using both behavioural and electrophysiological measures from

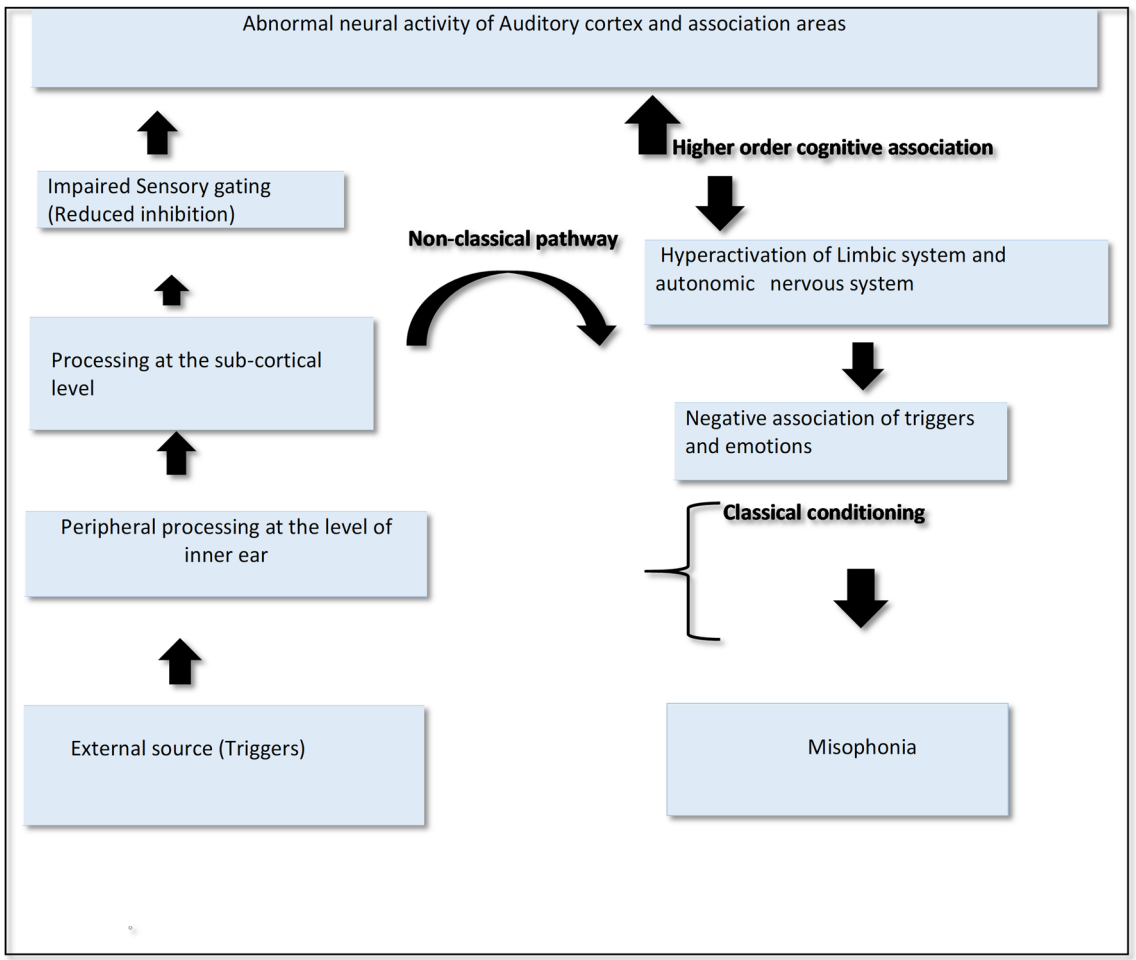

Fig. 2 Neuroaudiological model of misophonia

audiological perspectives. In addition, this review's findings help differentiate the pathophysiology of misophonia from other sound disorders such as tinnitus and hyperacusis and provide the path for assessment and management strategies.

Limitations of the study

The present review has a few limitations. Few articles included in 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 the exclusion of the participants based on co-morbidities. Hence, the results obtained may also be due to co-morbidities. Although a salient concern, this review only included studies published in English.

Conclusions

Misophonia is a new neurophysiological condition that is relatively less explored. The exact neurophysiology of misophonia is not known yet, and this is still the topic of debate between psychiatry, 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 primary 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. 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 problems 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. In addition, 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. In addition, the review highlights the need of assessment protocols for misophonia using various subjective and objectives tests, such as pure tone audiometry, speech audiometry, Loudness discomfort level (LDL) tests, otoacoustic emissions (OAE) with and without contralateral supression, Auditory Brainstem response (ABR), Auditory Late Latency Response (ALLR), P300, and Mismatch negativity (MMN) from the audiological perspectives. In addition, there is a need to develop precise subjective tools to categorize the types and severity of misophonia and compare the physiological mechanism accordingly.

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Availability of data and materials The datasets analyzed during the current study are available from the corresponding author upon reasonable request.

Declarations

Conflict of interest There is no conflict of interest to disclose.

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