

The application of vagus nerve stimulation in individuals with misophonia

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ABSTRACT: Stimulating the Vagus nerve helps maintain the autonomic tone, indicating stabilising any hyperactivity in the nervous system. The vagus nerve stimulation is applied in individuals with seizures, depression, sepsis, pain, obesity, cardiovascular disease, lung disease, diabetes, stroke, and traumatic brain injury. Auditory neuroscience has been widely applied in individuals with tinnitus and has been demonstrated as a successful neuromodulation technique. Individuals with peripheral lesions of the hair cells induce a maladaptive change in the plasticity resulting in hyperactivity in the auditory and non-auditory structures. In order to reduce this hyperactivity, neuromodulation techniques 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. The vagus nerve stimulation is also one form of neuromodulation technique considered to reduce the symptoms of tinnitus. It is believed that the ramus Auricularis Nervi vagi, an afferent sensory branch of the vagus nerve, innervates the afferent sensory branch of the vagus nerve, the ramus auricularis nervi vagi also innervate the outer ear canal and parts of the auricle. This auricular branch of the vagus nerve also called Arnold's nerve, which gives a projection to the nucleus of the solitary tract. The vagus nerve stimulation in individuals with tinnitus works to activate the auricular branch of the vagus nerve to reduce its symptoms. A similar principle of vagus nerve stimulation can be tried upon in individuals with misophonia. Literatures states that individuals with misophonia have hyperactivity in their non-classical auditory pathway that can be suppressed with the help of vagus nerve stimulation. The article discusses the possible effects of vagus nerve stimulation in individuals with misophonia.

Keywords: misophonia; vagus nerve stimulation; tinnitus; non-classical auditory pathway; limbic system;

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1.0 INTRODUCTION

Vagus Nerve stimulation is generally any technique used that stimulates the vagus nerve (Howland, 2014). The vagus nerve is the largest cranial nerve that runs in the human body and is the X cranial nerve, and it plays an essential role in maintaining homeostasis. The nerve is a mixed cranial nerve with 20% efferent fibres and 80%

afferent fibres. It originates in the brainstem at the medulla oblongata. Its fibres bilaterally project from the brain stem along the neck and oesophagus before it branches to innervate the viscera. The full extent to which the vagus nerve innervates is still unknown. However, the branches that extend off the cervical vagus innervate the bronchi, lungs, heart, and

oesophagus. The vagus has five primary branches below the diaphragm, including the dorsal and ventral gastric branches that innervate the stomach, the dorsal and ventral celiac branches that innervate the proximal and descending colon. The hepatic branch of the vagus nerve is divided as the hepatic branch that innervates the liver and the gastroduodenal branch that innervates the duodenum and pancreas. Descending efferents are responsible for maintaining the cardiorespiratory and gastrointestinal autonomic tone as well as other autonomic functions. It performs other vocalisation and swallowing ([Butt et al., 2020](#); [Kaniusas et al., 2019](#)). Stimulating this nerve can help maintain the autonomic tone. The nerve is located at the neck region, easily accessible for a surgeon to place an Implant for acute stimulation ([Johnson & Wilson, 2018](#)). The Vagus nerve stimulation's initial purpose was to suppress the seizures as it provided an anticonvulsant effect and received FDA approval in 1997 ([Cristancho et al., 2011](#); [Noller et al., 2019](#)).

Surgically the electrodes are fitted at the level of the neck region, and the cervical region is selected as it contains a large number of unmyelinated fibres, thus giving the option for more development of computational models. It also reduces the risk of pain and complications while stimulating. Prior to the procedure, the neurosurgeon and other interdisciplinary team members must make sure that the nerve is intact. To assess the function of the vagus nerve, a complete voice and swallowing evaluation is carried out by the team to ensure the patient had no history or is currently not suffering a dysphonia or dysphagia. Ruling out the presence of abnormality of dysphonia and dysphagia indicates normal functioning of voice and swallowing. The left-sided vagus nerve is always preferred to place the electrode as there is reduced cardiac symptoms and bradycardia. Initially, an incision is made at the upper left side of the chest where a pulse generator that is 10-13 mm thick is placed, and later an incision of the neck region will be conducted. The surgeons would search for the nerve bundle with a thicker diameter, and a hypertrophic one would be avoided. A helical coil that connects the pulse generator and the vagus nerve would be wrapped around the nerve bundle. The stimulator is activated two to four weeks after the implantation, and the neurologist activates the device by programming the stimulator. The strength and duration of the electrical impulses are programmed. The device is programmed to switch on and off for specific periods continuously. The patients, too, can control the simulator with the help of a handheld magnet provided to them. An extra

stimulation can be delivered by the patients when the magnet provided to them is swept over the pulse generator, and the generator can be turned off when the magnet is placed over the pulse generator. By removing it, the default stimulation cycle can be resumed. ([Whitehurst & McGivern, 2007](#); [Ben-Menachem et al., 2015](#)).

Apart from the surgically implanted device, vagus nerve stimulation can also be done in a transcutaneous way which is entirely non-invasive. It is placed in the ear canal as there are connections to the ear canal from the auricular branches of the vagus nerve and hence acts as a location to stimulate the vagus nerve. The cervical neck region also is used as a source for transcutaneous vagal nerve stimulation, where the implant is placed under the fascia of the neck region to stimulate the unmyelinated nerve fibres ([Ylikoski et al., 2020](#)). The application of this stimulation has been widely used to control seizures, depression, sepsis, pain management, obesity, cardiovascular disease, lung disease, diabetes, stroke and traumatic brain injury. The technique has been extensively used in tinnitus management ([Johnson & Wilson, 2018](#)).

The advantages of vagus nerve stimulation include treating seizures, depression and cardiovascular diseases by reducing their symptoms. Another classical advantage in tinnitus is that apart from reducing tinnitus symptoms, the vagal nerve stimulation also enables regulating depression and stress-related symptoms secondary to tinnitus, thereby improving the patients' quality of life. Regarding limitations, vagus nerve stimulation has side effects, including hoarseness, coughing, paresthesias, dysphagia, injury to the vagus nerve and nearby blood vessels, allergic reactions, bleeding, and even hematomas. However, researchers claim that the complication rate is only around 2% making it a relatively safe procedure ([Whitehurst & McGivern, 2007](#); [Ben-Menachem et al., 2015](#); [Johnson & Wilson, 2018](#); [Ylikoski et al., 2020](#)).

2.0 TINNITUS MANAGEMENT

Tinnitus is a medical condition that describes the conscious perception of an auditory sensation without a corresponding external stimulus. It is derived from the Latin verb *tinnire* (to ring). Tinnitus can be of a subjective kind or objective kind wherein subjective type, the individual alone perceives it, and objective type, the observer can hear it. The sensation of tinnitus can be of hissing, sizzling, and ringing types, although, in some cases, more complex sounds such as voices or music are perceived ([Baguley et al., 2013](#)).

There have been several models to explain the pathophysiology behind tinnitus. The models can be broadly classified as cochlear and non-cochlear models. The Cochlear models explain the cause of tinnitus to be due to the spontaneous otoacoustic emissions by outer hair cells in the tinnitus ear (Penner and Burns, 1987), the discordant damage of outer hair cells and inner hair cells, and the biochemical changes with an excess of neurotransmitters released by inner hair cells during outer hair cells damage. The non-cochlear model explains the change in neural activity at the central nervous system level, which includes the central gain mechanism. Many theories talk about the generation of tinnitus at the central level. Some of them include the shift in tonotopic resulting in over-representation of frequency near the edge frequency of the hearing loss. Another theory that explains tinnitus is the thalamocortical dysrhythmia due to hyperpolarisation of the thalamocortical pathway. Other theories for tinnitus include the involvement of the non-auditory areas (subgenual, anterior cingulate cortex, posterior cingulate cortex, precuneus, parietal cortex, and prefrontal cortex, anterior insula, parahippocampal area, amygdala, and hippocampus), and the dysfunctioning noise-cancelling mechanism by the limbic system (Baguley, 2002; Krauss et al., 2019; Knipper et al., 2020). **Figure 1** illustrates the change in the classical and non-classical auditory activities concerning the perception of an incoming trigger.

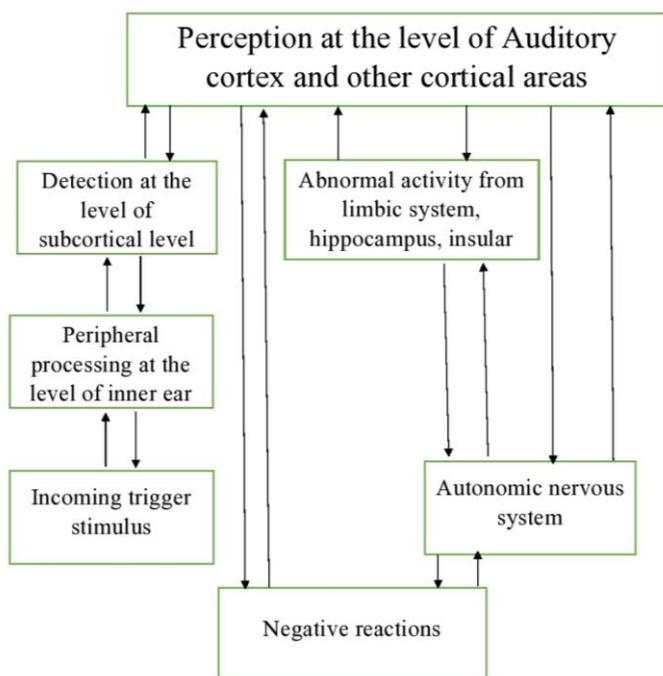


Figure 1: A flow chart that represents the perception of an incoming trigger with interconnections between the direct auditory pathway and non-classical auditory pathway.

Tinnitus treatment has been sparse as the actual cause and treatment have not been established yet due to varied treatment techniques that have been tried, ranging from tinnitus retraining therapy (Scherer et al., 2020), fitting of hearing aids (Haines et al., 2020), the utility of cognitive behavioural therapy (Landry et al., 2020), counselling (Searchfield et al., 2020), pharmacotherapy drugs such as tricyclic antidepressants, Alprazolam (Xanax), lifestyle managements, ear wax removal, treating blood vessel conditions like hypertension (Asnis, 2020), fitting of Cochlear Implants (Perreau et al., 2020), and even surgical disconnection of the auditory nerve bundle in extreme cases.

Another approach towards tinnitus treatment is the usage of neuromodulation techniques. Animal models demonstrate both the auditory and non-auditory areas that involve in individuals with chronic tinnitus. In individuals with a peripheral lesion of the hair, cells induce a maladaptive change in the plasticity resulting in hyperactivity in the auditory and non-auditory structures. Neuromodulation techniques such as transcranial magnetic stimulation, transcranial direct current stimulation, transcranial alternating current stimulation, transcranial random noise stimulation, neurofeedback, epidural and subdural cortical stimulation, and deep brain stimulation can be utilised to reduce hyperactivity (Peter & Kleinjung, 2019).

The vagus nerve stimulation is also one form of neuromodulation technique considered to reduce the symptoms of tinnitus. It is believed that the ramus auricularis nervi vagi, an afferent sensory branch of the vagus nerve, innervates the afferent sensory branch of the vagus nerve, the ramus auricularis nervi vagi also innervate the outer ear canal and parts of the auricle. This auricular branch of the vagus nerve also called Arnold's nerve, which gives a projection to nucleus of the solitary tract. The vagus nerve stimulation in individuals with tinnitus works to activate the auricular branch of the vagus nerve to reduce its symptoms. The vagal nerve stimulation can be given in two forms: an implanted vagal nerve stimulation or a transcutaneous vagal nerve stimulation (Peter & Kleinjung, 2019). **Figure 2** depicts the activation of the vagus nerve and its projection to the cortex. Individuals with tinnitus, hyperacusis and misophonia all have excitation in their non-classical auditory pathway, but the utilisation of the vagus nerve stimulation has only been widely documented for tinnitus management and not for tinnitus misophonia management. Tinnitus, hyperacusis, phonophobia, and misophonia are the

auditory symptoms with neuropsychological impact. There is a need to carry out literature concerning vagal nerve stimulation in misophonic individuals. This review discusses the possible application of the effectiveness of vagal nerve stimulation in individuals with misophonia regarding the application of vagal nerve stimulation in tinnitus management.

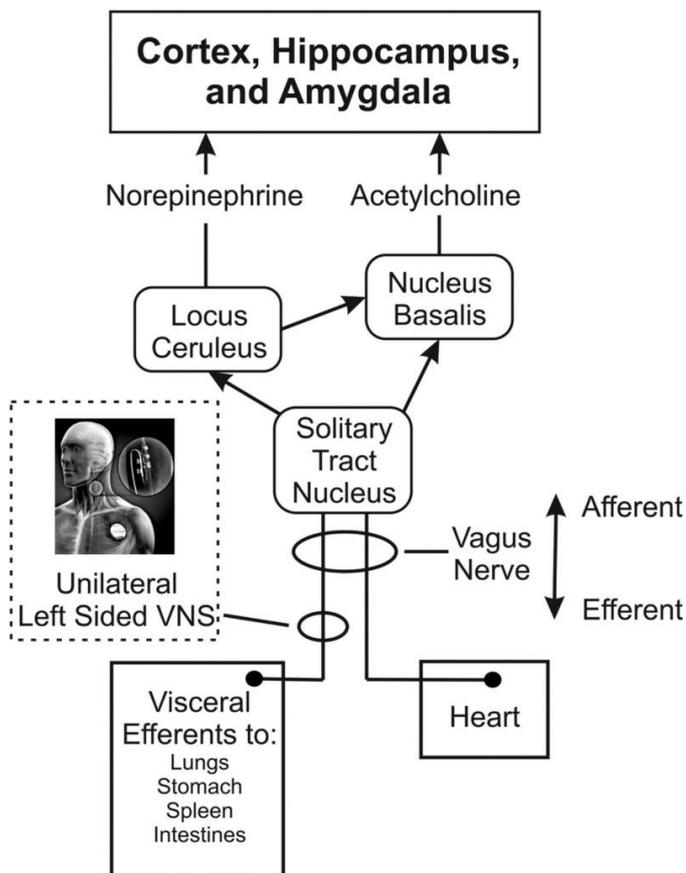


Figure 2: A block diagram of the activation of the vagus nerve (vagus nerve stimulation). The figure is taken from Kochilas et al. (2020) published as an open access article under the terms of the Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International (CC BY-NC-ND 4.0).

3.0 MISOPHONIA

The phenomenon of misophonia was brought into the lime of light in 2002 by Pawel Jastreboff, which indicates the hatred towards the sound. The traditional definition for misophonia is "an abnormally strong reaction occurring to a sound with a specific pattern and/or meaning to an individual" (Jastreboff & Jastreboff, 2014). The disorder is classified both as an auditory disorder and tinnitus, hyperacusis, phonophobia and as a psychiatric disorder classified under the DSM V under a form of obsessive-compulsive disorder. However, it is

proven not to be a hearing disorder as hearing loss does not lead to misophonia or effect. Instead, it results from the strength of the connection between the limbic and sympathetic nervous systems, which causes abnormal processing of sound stimuli. With tinnitus being the abnormal perception of a ringing or buzzing sound, hyperacusis being unusual tolerance to environmental noise and a broad range of noises, phonophobia being extreme fear towards specific trigger sounds, misophonia on the other hand, is a selective sound aversion syndrome where they tend to have negative reactions towards specific sounds such as eating/chewing, lip-smacking, pen clicking, clock ticking and scratching.

Misophonia occurred with comorbid conditions such as OCD, attention deficit hyperactivity disorder, asthma, Tourette, dysthymic disorder, eating disorders, posttraumatic stress disorder, social phobia, body dysmorphic disorder, and panic disorder. Individual cases were also reported with borderline personality disorder, tinnitus and hearing loss, specific phobia, agoraphobia, generalised anxiety disorder, Kawasaki disease, hypochondria, skin picking, and bipolar disorder. However, these conditions were present alongside Misophonia, and no association between them has been established yet (Potgieter et al., 2019).

The onset of this problem has been reportedly varied across the literature. Few studies quote the onset to be during adolescence (within 18 years), few studies quote the onset to be during adulthood (above 18 years), and some say it can occur at any age (Potgieter et al., 2019).

The multiple sounds that can trigger a misophonic condition include oral sounds, especially those made by people eating, such as chewing, lip-smacking, swallowing noises, and throat noises, nasal sounds, such as breathing, blowing nose, sniffing, sneezing, consonants and/or vowels and specific voices were also reported as triggers. A context that includes a family, friends, and occupational or educational setting, is more likely to cause a stronger misophonia reaction. Other common trigger sounds include repetitive clicking and tapping or sounds produced by using utensils, keys, or ice in a glass. Individual cases also describe bird chirps, dog barking, rustling, and other movement-related triggers such as rubbing of hands, swinging arms/legs, and jiggling, which can be classified under misokinesia (Cavanna & Seri, 2015; Potgieter et al., 2019; Jastreboff & Jastreboff, 2014).

The reaction towards a misophonia can differ from individual to individual. Some can be combinations of discomfort, distress, anxiety, annoyance, disgust, panic, extreme irritation, anger, hate, or sometimes rage with aggressive outbursts or involuntary violence. A physical reaction to trigger sounds included contraction, tension, or sensation in specific muscles, heavy breathing, pressure in the chest, arms or head, muscle tension. Recent study documents post mental trauma to commit suicide or near defying death post misophonia ([Cavanna & Seri, 2015](#); [Edelstein et al., 2013](#); [Kluckow et al., 2014](#); [Bernstein et al., 2013](#)).

The neurophysiology behind Misophonia has been documented extensively in the literature. Schroder et al. ([2014](#)) documented the event-related potential findings in individuals with Misophonia. Results indicated a reduced N2 response indicating auditory information processing deficits. The same authors commented on significantly higher mood disturbances when compared to the normals. Functional imaging studies have been documented, and an fMRI study of the blood oxygen level-dependent (BOLD) on individuals with misophonia reveals hyperactivation of the bilateral Auditory Cortex and hyperactivation of the left Amygdala ([Eijsker et al., 2019](#)). Schroder et al. ([2020](#)) found increased physiological arousal, increased activity of the right Anterior Insular Cortex, right anterior cingulate and right superior temporal cortex. Kumar et al. ([2017](#)) conducted similar fMRI studies of the blood oxygen level-dependent and found increased activity in all regions responsible for regulating emotions, including the amygdala, hippocampus and posteromedial cortex (PMC), and the ventromedial prefrontal cortex (vmPFC). They observed increased hyperactivity in the right and left anterior insular cortex. Giorgi ([2015](#)) found hyperactivation in the bilateral auditory cortex and the left amygdala in patients with misophonia only with a misophonia trigger stimulus but not a neutral stimulus. Concerning the neuropsychological basis of Misophonia, very little literature has discussed the complex neuropsychological task. According to Frank et al. ([2020](#)), individuals with Misophonia have a long-standing neuropsychological weakness as in their task involving attention, individuals with misophonia had difficulty maintaining alertness. Silva & Sanches ([2019](#)) administered the dichotic sentence test in individuals with misophonia, tinnitus, and controls and found out that individuals with misophonia possess poor selective attention with a misophonic trigger as noise compared to individuals with tinnitus and normal. Eijsker et al., ([2018](#)) performed a stop-signal task and found intact

response inhibition favouring accuracy over speed and hyperactivity of superior medial frontal gyrus in inhibition and hypoactivity of the posterior cingulate cortex during the success in a BOLD technique of fMRI.

The diagnosis of Misophonic individuals comes up with a detailed case history in an interview mode, documenting the history of possible comorbid issues and administration of questionnaires. The most commonly used questionnaire is the Amsterdam Misophonia scale ([Schröder et al., 2013](#)) based on the Yale-Brown Obsessive-compulsive scale. Other scales include Misophonia Assessment Questionnaire (MAQ), Misophonia Coping Responses Survey (MCR), Misophonia Trigger Severity Scale (MTS), Misophonia Activation Scale. The Misophonia Physiological Scale (MPS), Misophonia Emotional Response, Misophonia Questionnaire, and Misophonia Severity Scale (MSS) ([Potgieter et al., 2019](#)).

A variety of treatment options have been explored in these individuals to reduce the symptoms of their behaviour as the cause of misophonia still is challenging to investigate. These individuals develop coping strategies through avoidance behaviour, like wearing earphones and avoiding situations during an incoming trigger sound. Some have also quit their work if their work environment has trigger stimulus. Some strategies included telling the offender or confronting the offender to stop producing the trigger sound. Some also mimic the offensive or trigger sound for adaptation. Some try to engage with positive internal dialogue, distracting their mindset by producing anti sounds to the incoming trigger sounds. or diverting their thoughts ([Schröder et al., 2014](#)). A few rare cases report muscle-relaxing exercises as a coping strategy for misophonia. The most widely used treatment option is cognitive behavioural therapy. The main goal of cognitive behavioural therapy is to incorporate psychoeducation that helps in achieving habituation. The therapy incorporates a cognitive task by asking the patient to; practice diverting their attention to neutral stimulus, counter condition to break the association between the trigger sounds and negative emotions, and stimulus manipulation to achieve habituation ([Roushani & Mehrabizadeh Honarmand, 2021](#)). Few pieces of literatures have used mindfulness and acceptance methods using dialectal behavioural therapy, which aids a patient with misophonia transition from predisposed anger to an alternate solution ([Schneider & Arch, 2017](#)).

Another discussed treatment is the usage of desensitisation therapy (DST) in misophonics.

Desensitisation therapy is used in individuals with tinnitus and hyperacusis; however, the approach must be different for misophonics because their auditory system works within the norms. A DST must be incorporated with regular counselling. If possible cognitive behavioural therapy to remove the negative effects of the trigger sound, in misophonics the principle is to weaken the enhanced connection between the auditory system and the limbic system. This can be done based on four different protocols. Protocol one involves the patient having complete access to the sound type and controlling the type and volume sound. Protocol two involving the patient having partial access to the type of sound with the family member setting the appropriate volume control. Protocol three involves the patient knowing the type of sound but the clinician manipulating the sound types to give the patient different sounds. Protocol four involves combining the unpleasant sound with a normal sound enabling the patient to adapt ([Jastreboff & Jastreboff, 2014](#)).

There has been literature attempting to prescribe pharmacotherapy drugs, including escitalopram and alprazolam, to reduce their obsessive-compulsive behaviours. The alprazolam belonging in a class of benzodiazepines does have antianxiety effects, thus reducing obsessive-compulsive behaviours. However, it can also have adverse effects such as memory loss, drowsiness, talkativeness, tremor, low blood pressure, blurred vision, weight gain, nausea, and difficulty in speech ([O'Sullivan et al., 1994](#); [Potgieter et al., 2019](#)).

Although these treatment options have been discussed, vagus nerve stimulation has not been discussed in the literature and can also be used as an additional option. The vagus nerve stimulation improves symptoms of psychogenic related disorders like stress and depression, along with controlling the hyperactivity of the brain. Individuals with misophonics who have an intolerance to specific sounds due to the hyperactivation in the auditory cortex, limbic system, amygdala, hippocampus, posterior medial cortex, the insular cortex can be tried with vagal nerve stimulators as they have an auricular branch that inserts in the nucleus of the brainstem, hence reducing the hyperactivity ([Yap et al., 2020](#)).

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Even though the VNS has shown progress in a variety of individuals from epileptic to tinnitus when it comes to its clinical utility, the possible side effects must be considered. The limitations of implanting a vagus nerve stimulator include the possible general side effects, which are hoarseness, coughing, dysphonia, pain, throat and neck pain, headache, insomnia, indigestion, muscle twitch, nausea or vomiting, impaired sense of touch, tingling sensation in the skin ([Yap et al., 2020](#)). Another possible limitation of vagus nerve stimulation in misophonia is that there have been no known articles published related to it, and hence the efficacy of misophonics cannot be hypothesised or assumed unless related articles are published.

4.0 CONCLUSIONS

VNS has shown progress in individuals with auditory related disorders and psychogenic disorders, misophonia being a combination of both, can also improve VNS. In these misophonics it is advisable to start with a minimally invasive transcutaneous VNS then go for other implantable neuromodulation techniques to reduce the complications as the pathophysiology has still not been clearly understood. Even though there hasn't been any documentation for VNS in misophonia, a reference with the application of VNS in tinnitus can be considered. Hence the vagus nerve stimulation can be applied in individuals with misophonia by considering the similar mechanism of VNS in tinnitus as both tinnitus and misophonia have a similar neurophysiological basis. With adequate literature published in the future and if there is good efficacy of VNS in misophonia, the VNS can be used as a treatment option for individuals in misophonia and other options of drugs and psychotherapy, an enhanced treatment can be seen, and a test battery can be formulated.

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