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The neurobiological substrate of Misophonia - Recent Insights

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Abstract

Misophonia is a relatively new neurobehavioral condition in which specific human sounds (so-called trigger sounds) evoke a negative emotional response (primarily anger or disgust), together with an autonomic reaction. In the past ten years, the interest in misophonia and defining its underlying mechanism accelerated, as it is yet to be determined. So far, researchers have found an increased reactivity of the salience network, especially the anterior insular cortex (AIC) and the right anterior cingulate complex (ACC), upon exposure to a trigger sound, leading to hyper-focus on the sound. Other studies have shown hyperactivation of the amygdala and the hypothalamus, which both stand in close connectivity with the salience network, and are involved in pathways controlling aggression and fear, and the consolidating memories, leading to an association between the trigger sound and the immediate negative emotional response, followed by general arousal. So far, no medication has been approved yet to treat misophonic patients. However, therapy programs have shown to be beneficial for misophonic patients.

1. Introduction

Misophonia (literally meaning hatred of sound) refers to a condition in which there is a strong aversion to hearing specific human sounds (trigger sounds; e.g. chewing, breathing, swallowing, nose sniffing (Cavanna,A.E. 2015). In response to the trigger sound, the person reports unpleasant emotional experiences (mainly anger or disgust), muscle constriction and increased heart rate (Jastreboff,P.J. 2003; Schröder,A. 2019). Self-produced sounds do not elicit these responses, even though the sounds have the same spectrum and intensity (Cavanna,A.E. 2015), and trigger sounds produced by family members are more distressing than sounds produced by strangers (Taylor,S. 2017). Associative learning between the triggering sound and the negative emotions

occurs, as these emotions give salience to the triggering sounds, which then further intensifies the focus on the sound (Brout,J.J. 2018).

Based on the severeness of the symptoms, misophonia can be detrimental to a patient's life. Patients can suffer from a lenient form of misophonia, with mild discomfort or annoyance, or severe misophonia, with intense discomfort, disgust or even aggressive outbursts (Cavanna,A.E. 2015). Severe misophonia can lead to social isolation, as patients avoid social activities due to the concern that their behavior or aggression would be troubling for other people (Cavanna,A.E. 2015). Other coping strategies are wearing headphones and avoiding situations where the trigger might occur (Edelstein,M. 2013). Generally, patients recognize their anger or disgust as unnecessary and unreasonable. Still, misophonic patients find the other person's behavior or producing the sound inappropriate and inconsiderate (Edelstein,M. 2013; Taylor,S. 2017).

These strong reactions towards trigger sounds result from enhanced connections between the auditory and limbic system (Jastreboff,M.M. 2001). Components of the limbic system are, amongst others, the amygdala and the hypothalamus. It has long been known that the amygdala plays an essential role in supporting memories for emotionally arousing experiences, processing auditory signals, and is involved in pathways controlling aggression and fear (Derntl,B. 2009; Hermans,E.J. 2014). The lateral amygdala receives auditory information and transfers it to the central amygdala, which is responsible for the activation of the fight/flight response (Brout,J.J. 2018). It is thought, that upon exposure to a trigger sound, the fight/flight response is activated by the amygdala. Also, the activation of the amygdala leads to the consolidation of the memories that are formed during this event (McGaugh,J.L. 1996; Figure 1), making these memories similar to trauma memories. However, apart from the trigger sound, no traumatic event is associated with the memories in misophonic patients, indicating that there is another underlying mechanism to explain the misophonic response (Brout,J.J. 2018).

The hypothalamus is in control of the autonomic nervous system and will increase the heart rate when triggered by sound, in misophonic patients (Seoane-Collazo,P. 2015). Both the amygdala and the hypothalamus stand in close connectivity with the salience network, which is primarily composed of the anterior insula AIC and ACC. The salience network contributes to the detection and filtering of salient stimuli, for example, trigger sound. It is involved in social behavior, communication, and self-awareness by

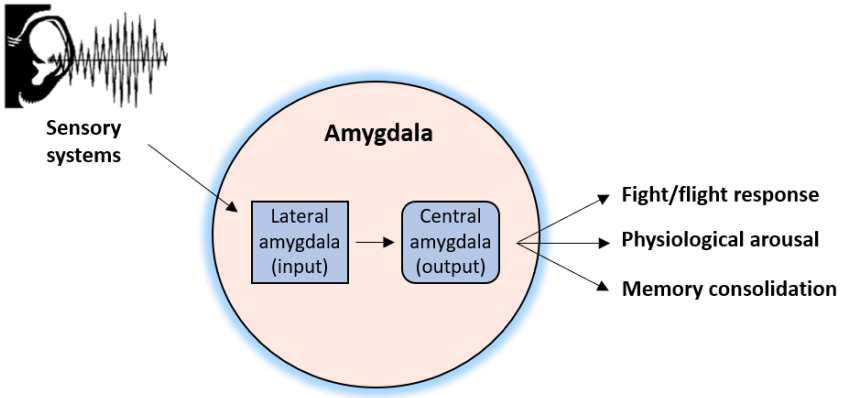

Figure 1: The amygdala's involvement in the processing of a misophonic trigger. Upon exposure to a trigger sound, sensory systems deliver the auditory information to the lateral amygdala, which transfers the information to the central amygdala. The central amygdala activates the fight/flight response together with physiological arousal. Besides, the amygdala consolidates the memories that are formed during the event. The exact mechanism is still unclear. Adapted from Brout et al, 2018.

processing sensory, emotional, and cognitive information (Steimke,R. 2017).

Currently, misophonia is not listed within the Diagnostic and Statistical Manual of Mental Disorders Fifth Edition (DSM-V) or the International Statistical Classification of Diseases and Related Health Problems 10th revision (ICD-10; Potgieter,I. 2019). Due to the condition being relatively new, it is still unclear whether misophonia can be defined as a mental disorder or as a symptom of some broader syndrome (Schröder,A. 2013; Taylor,S. 2017).

The aims of this review are to (a) give an overview of the already performed research on misophonia, (b) highlight the alterations between misophonic patients and control patients, and (c) discuss the pros and cons of misophonia getting registered as a disorder within the DSM-V or ICD-10.

2. Misophonia and its neurobiological substrate

Until 2001, patients experiencing discomfort or pain in the ears, associated with sound exposure, were diagnosed with "decreased sound tolerance". Decreased sound tolerance included the disorders hyperacusis (discomfort to sound, resulting from abnormally high activation of the auditory system), and phonophobia (being afraid of sound). However, Jastreboff and Jastreboff studied patients that didn't fit these disorders. Rather than fearing sounds, the patients felt anger or disgust towards sounds. In addition, no significant activation of the auditory system was observed in these patients. To describe the symptoms of these patients, Jastreboff and Jastreboff came up with the term "misophonia" (Jastreboff,M.M. 2001). In the following ten years, misophonia is only mentioned in one case study to describe the symptoms of two patients (Hadjipavlou,G. 2008).

In 2013, the interest in misophonia accelerated, when Schröder et al described the symptomatology of misophonia, based on patients with an extreme focus on specific sounds (smacking or breathing), to which they responded with aggression to make it stop. These symptoms did not fit the already known obsessive-compulsive or impulse control disorders. As misophonia is not officially classified as a disorder, they aimed to describe the symptomatology of misophonia. To measure the severity of the misophonia symptoms, they developed the Amsterdam Misophonia Scale (A-MISO-S), in which patients were asked about the time spent on misophonia, influence on social functioning, level of anger, impulse-resistance, the ability to control thoughts and anger, and time spent avoiding misophonic situations (Schröder,A. 2013). To rule out the fact that symptoms were caused by hearing problems, they randomly performed hearing tests on five patients, from which four did not show significant audiological distortion.

In all 42 patients, they found a similar pattern of symptoms. Based on these symptoms, they proposed the following five diagnostic criteria: 1) trigger sounds were all human-produced, self-produced sounds were not triggering. 2) Patients experience a feeling of loss of self-control due to the intensity of the anger. 3) Patients recognized their response towards the trigger sound as unreasonable, and losing self-control was morally unacceptable. 4) Patients' day-to-day life was affected, as they actively avoided social situations, wore headphones or produced anti-sound, to prevent being triggered. 5) Patients' personalities showed overlap with obsessive-compulsive personality disorder (OCDP) (Schröder,A. 2013). These diagnostic criteria were verified by a study of Edelstein et al. in which eleven misophonic patients were evaluated (Edelstein,M. 2013).

Both Schröder and Edelstein found that the misophonic symptom pattern overlaps with DSM-IV and ICD-10 classified disorders, like post-traumatic stress disorder (PTSD), obsessive-compulsive disorder (OCD) or OCPD. However, no disorder covers the whole pattern of misophonic symptoms. The driving emotion

of misophonia is aggression or anger, in contrast with the driving emotion of PTSD, which is fear, or OCD, which is anxiety. Therefore, they state that misophonia cannot be classified under already known disorders within DSM-IV and ICD-10, and should be classified as a separate psychiatric disorder (Edelstein,M. 2013; Schröder, A. 2013).

As mentioned before, Edelstein et al evaluated eleven misophonic patients. Most of their patients reported that their misophonia worsened over time, as their hatred increased alongside the number of triggering sounds. Prolonged and repeated exposure to a trigger sound might explain this phenomenon, but the exact mechanism behind this deterioration is not fully understood yet (Edelstein,M. 2013). Edelstein et al. were the first to assess the relationship between the emotional experience and the autonomic arousal, using the electrical skin conductance response (SCR), and thereby the amount of sweat produced They measured SCR, in response to aversive and triggering auditory and visual stimuli (Figure 2). They demonstrated that auditory stimuli were more aversive than the same visual stimuli for misophonic subjects (Figure 2A). In addition, they showed an increased SCR in misophonic patients, in response to auditory stimuli, but no significant difference to visual stimuli (Figure 2A and 2B). At last, the results showed a significant positive correlation between the level of mean aversiveness and mean SCR. These findings indicate that trigger sounds increase the autonomic response and that this response is related to the aversiveness of the stimuli.

Schröder et al were the first to publish electroencephalography (EEG) results to unravel the mechanisms involved in misophonia. To examine the early auditory processing systems in misophonic patients, they studied auditory event-related potentials (ERPs; P1, P2, and N1 components). They found a significant decrease in the mean amplitude of the auditory N1 in misophonic patients, compared to the control group (Figure 3). As the N1 is often associated with auditory attention and abrupt changes in the detection of sounds, their results indicate an auditory information processing deficiency in misophonic patients. Also, Schröder et al noted that misophonic patients had a significantly higher Total Mood Disturbance (TMD), compared to controls, which could indicate a general hyperarousal in misophonic patients, which would be in line with the previously described link between hyperarousal and misophonia by Edelstein et al (Edelstein,M. 2013). To conclude, they state that the N1 response is a potential neurophysiological marker for misophonia (Schröder,A. 2014). Their results indicate how misophonia can affect early auditory components.

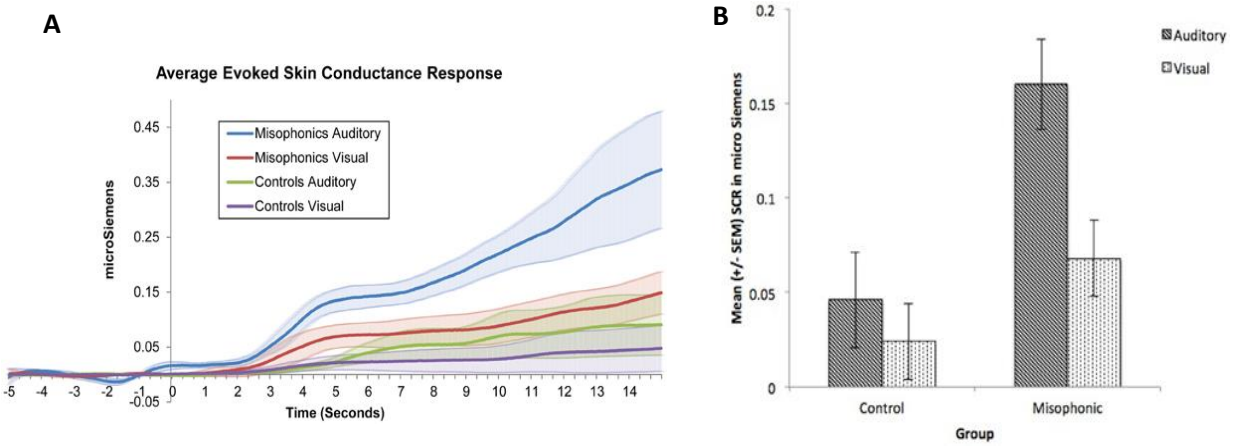

Figure 2: Average SCR response towards auditory and visual stimuli in misophonic and non-misophonic patients. (A) Misophonic and control subject' average SCR data in microSiemens towards auditory and visual conditions as a function of time. (B) Quantification of data shown in (A). ANOVAs with factor of Group (misophonic, controls) and Condition (auditory, visual) were performed. Adapted from Edelstein et al. 2013.

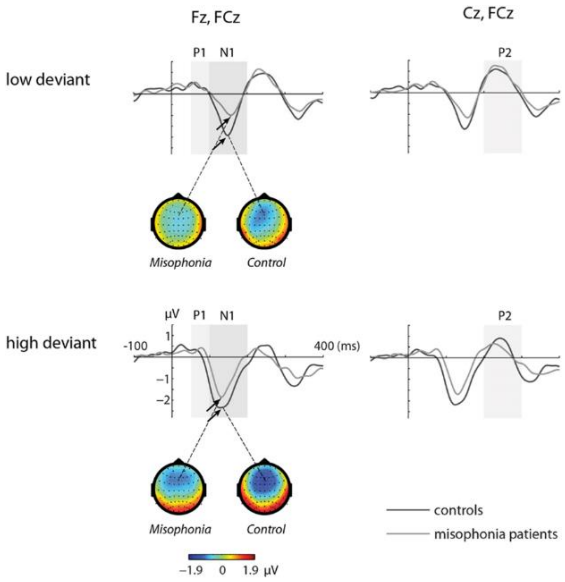

Figure 3: Average ERP wavelength of control and misophonic patients for deviant tones. P1: associated with pre-attentive orienting towards new sounds, N1: early attention, detection of abrupt changes in sensory input, P2: early allocation and initial conscious awareness. The misophonic group included 20 patients, and the control group 14 patients. Deviant tones represent tones higher (high deviant) or lower (low deviant) than standard tones (Schröder,A. 2014).

In contrast with the findings of Schröder et al, Renéé San Giorgi found a hyperactivation in the bilateral auditory cortex. He was the first to publish data of a functional magnetic resonance imaging (fMRI) study of the blood-oxygen-level-dependent (BOLD) responses in misophonic patients. Next to the bilateral auditory cortex, he also found hyperactivation of the left amygdala in misophonic patients in response to triggering sounds (San Giorgi,R. 2015).

The finding of abnormal functioning of the amygdala was later supported by a study of Kumar et al in 2017. Using the same technique, they found that trigger sounds elicited a great BOLD response in the anterior insular cortex (AIC), in misophonic patients (Figure 4). In addition, they observed increased functional connectivity between the left and right AIC with the amygdala, hippocampus, posteromedial cortex (PMC) and the ventromedial prefrontal cortex (vmPFC), all regions responsible for processing and regulating emotions (Figure 5). This response was trigger sound specific, as no significant difference was observed for unpleasant sounds. PMC and vmPFC are components of the default mode network (DMN), which is activated when a person is awake, but not actively engaged in an attention-demanding task (Raichle,M.E. 2001). In this state, a person is retrieving memories and engaged in thoughts. DMN is deactivated when external stimuli require attention. Kumar et al. suggest the possibility that AIC is stronger connected to DMN in misophonic patients. When exposed to a trigger sound, patients are less able to disconnect AIC from DMN. This results in memories and contextual associations of trigger sounds, which are projected to AIC (Kumar,S. 2017).

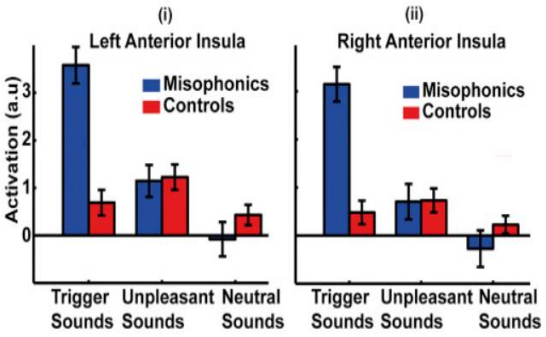

Figure 4: Activation of the left (i) and right (ii) anterior insula in misophonic and control patients. Activation of the left and right anterior insula, in response to trigger sounds, unpleasant sounds or neutral sounds. The misophonic group includes 22 patients, and the control group 22 patients.

Another structural change in the brain, reported by Kumar et al is increased myelination in the gray matter of vmPFC in misophonic patients, which could be a possible explanation for the altered functional connectivity of AIC to vmPFC (Kumar,S. 2017).

At last, they demonstrated a trigger sound specific autonomic response (increased heart rate and increased SCR) in misophonic patients, compared to controls. These findings support the already described link between misophonia and the activated fight/flight response. Using mediation analysis, they found that AIC activity plays a key role in the autonomic response towards a trigger sound (Kumar,S. 2017).

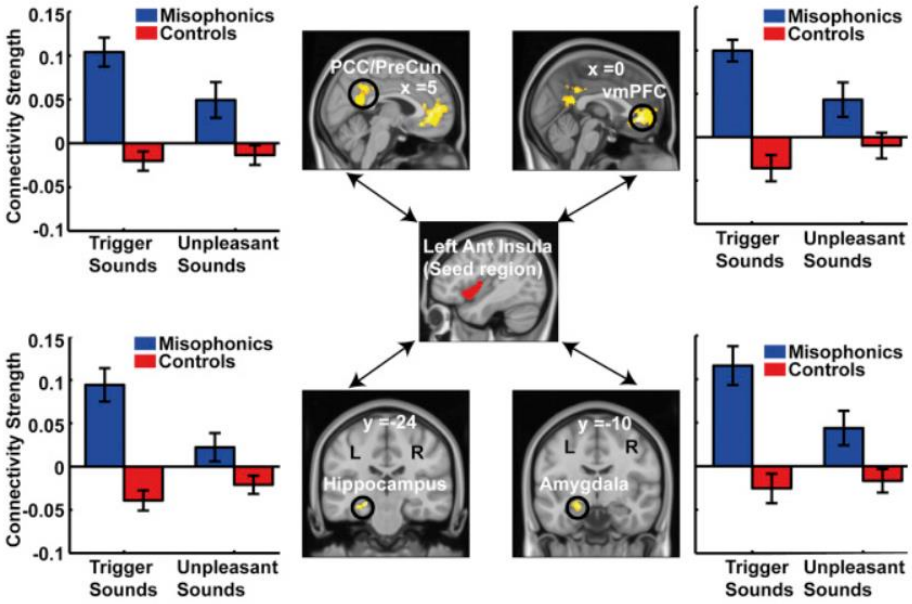

Figure 5: Data analysis of functional connectivity. Brain regions with increased connectivity with the left AIC, upon exposure to trigger sounds, in misophonic patients. Greater connectivity was observed in PMC (upper left), vmPFC (upper right), hippocampus (lower left) and amygdala (lower right).

Recently, Schröder et al published a study to unravel the neural, physiological and behavioral responses of misophonic patients, towards trigger sounds. In their study, they found increased physiological arousal, and increased activity of the right AIC, right anterior cingulate (ACC) and right superior temporal cortex, in misophonic patients, in response to trigger sounds. These findings are in line with results Kumar et al. obtained. The salience attribution to misophonic sounds, caused by hyperactivation of the salience network, can explain the symptoms observed in misophonia (Schröder,S. 2019). They suggest a two-step process in which the misophonic sound will first initiate physiological arousal and aversive emotions, followed by amplification of the salience network activity when exposure to the trigger sound is repeated. The originally neutral sound is then more and more associated with greatly aversive emotions (Schröder,S. 2019).

Next, they explained that the hyperactivation of the right superior temporal cortex in misophonic patients may increase the response to the specific stimulus, as this region plays a central role in selective auditory attention (Schröder,S. 2019). In contrast with Kumar et al did not find significant differences in the activity of the amygdala itself in misophonic patients, upon hearing trigger sounds (Schröder,S. 2019).

From all the provided data, it was not possible yet to determine whether misophonia is a disorder itself, or a symptom caused by another condition. To clarify this uncertainty, a recent study from Erfanian and Rouw showed that misophonia is not a consequence of another psychiatric condition, but can also occur as a separate disorder. In their study, the demonstrated the co-morbidity of psychiatric disorders and misophonia. They demonstrated that 21 out of 52 participants reported an absence of psychiatric symptoms, which indicates that misophonia can develop without comorbidity with other disorders. These results are a promising step in the recognition of misophonia as a disorder itself (Erfanian,M. 2019). Besides, they observed a correlation between the amount of overlapping symptoms wit

h other psychiatric disorders and the severity of the misophonia.

To conclude this section, misophonia is an auditory disorder, independent of auditory thresholds or impairment or hyperactivation of the auditory pathways (Wu,M.S. 2014). Studies have shown that misophonia is associated with increased connectivity in the neural system of the auditory, limbic and autonomic system. Several studies have verified the autonomic response, towards trigger sounds (increased heart rate and increased SCR) (Schröder,S. 2013; Edeleistein,M. 2013; Kumar,S. 2017; Schröder,S. 2019). Two studies have shown an increased reactivity of the salience network in misophonic patients, particularly in the regions AIC (Kumar,S. 2017; Schröder,S. 2019), and the ACC (Schröder,S. 2019), giving more salience to a trigger sound. Whether the amygdala itself is also hyperactivated, is yet to be verified, as contradictory results were found in various studies. Nevertheless, as the AIC and ACC stand in close connectivity with the amygdala, and the amygdala consolidates formed memories, it is assumed that associative learning occurs between the trigger sound and the negative emotional response.

3. Coping with misophonia: treatment

Until 2013, treating misophonic patients consisted of tinnitus retraining therapy (TRT). The goal of TRT was to reclassify the annoying sound (in tinnitus patients: ringing, buzzing, or hissing noise), to a neutral stage. This could allow patients to cope with the triggering sounds, however, no evidence is provided yet that TRT reduces or eliminates misophonia (Jastreboff,P.J. 1993; Bernstein,R.E. 2013).

3.1. Cognitive behavioral therapy

Bernstein et al suggested cognitive behavioral therapy (CBT) as an alternative treatment for the underlying mechanisms of misophonia. The CBT treatment included (1) a cognitive component to confront automatic negative thoughts, (2) a behavioral component to put an end to the avoidance of social activities and practicing helpful coping strategies, and (3) a physiological component to reset the autonomic response (Bernstein,R.E. 2013). The therapy strategy is depicted in figure 6. In their study they applied CBT on a 19-year-old college student, with misophonic symptoms (immense aversion to the sounds of people chewing, swallowing, and slurping). The goal of the treatment was to 1) ensure a significant increase of her threshold for triggering sounds, causing highly aversive sounds to become "only" unpleasant, and 2) increase the number of social activities in which she anticipated (Bernstein,R.E. 2013).

Through several therapy sessions, the student was able to better cope with trigger sound. Cognitively, she changed her immediate assumptions upon hearing trigger sounds, which were the urge to leave the room or to loathe the person making the sound. On behavioral level, they stated that regular exercise, and redirecting attention towards ambient or self-produced sounds are beneficial in coping with misophonia. In addition, directly focusing on the person making the triggering sound, instead of focusing on the sound itself, turned out to be helpful. It was also necessary to stop glaring, or eye-rolling. Instead of being misophonic, the student rated the chewing noises as only unpleasant, but they were no longer affecting here social functioning. For four months, she did not report symptoms of relapse (Bernstein,R.E. 2013).

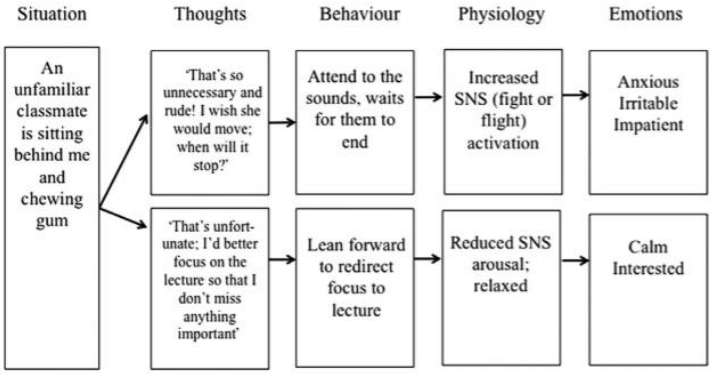

Figure 6: CBT model to treat a misophonic patient. The interconnectivity between physiology, behavior, and cognition, in which behavior of focusing on the trigger sound increases anxiety and irritation, whereas leaning forward and shifting attention to something else will reduce the salience to the noise and decrease the fight/flight response. SNS, sympathetic nervous system.

Important to note, they were not able to make any conclusion on the physiological changes, as they did not perform any measurements before, during, or after the treatment to determine these changes. In addition, the improvement of the misophonic symptoms was only measured by rating scales, but unfortunately, they did not include these ratings in the paper. Nevertheless, although it was only one study case, a reduction in misophonic symptoms was reported after treatment.

The finding of CBT being helpful in coping with misophonia was two years later supported by McGuire et al. They published a report describing two misophonic patients who were treated with CBT. During their therapy, the patients were habituated to the stress by repeated, and prolonged exposures, but at the same time preventing the response. Unfortunately, in this study, they do not clarify how they prevent the response from occurring. After habituation, the frequency, intensity, and proximity of the sound would be increased, which would increase the threshold of the patient for the trigger sound. Besides, cognitive restructuring was used to change the assumptions connected to the sound, comparable to the approach of Bernstein et al. Just like Bernstein et al, they also did not include measurements to make any conclusions on the physiological changes after treatment. In the end, both patients experienced a decrease in misophonic patients after the treatment, but they still experience some symptoms.

Another treatment method was described by Thomas H. Dozier. He treated a misophonic patient with a technique called 'counterconditioning', in which a positive repetitive positive stimulus was paired with an intermittently delivered trigger sound. By doing so, the trigger sounds would no longer elicit an immediate aversive misophonic response, but a positive emotional response instead (Dozier,H.T. 2015). During treatment, the patient answered three questionnaires, the Misophonia Assessment Questionnaire (MAQ), the Misophonia Coping Responses (MCR), and the Misophonia Trigger Severity scale (MTS). After treatment, the patient's MAQ dropped from 41 to 17, meaning that she went from being classified as severe misophonic to being mildly misophonic (figure 7). At second, her MTS score dropped from 8 to 2, indicating a great decrease of physical and emotional response to a trigger sound. They did not clarify differences in coping response (MCR), before and after treatment. Dozier performed follow-up assessments after 4 and 10 months, in which the patients concluded that some trigger sounds had been eliminated.

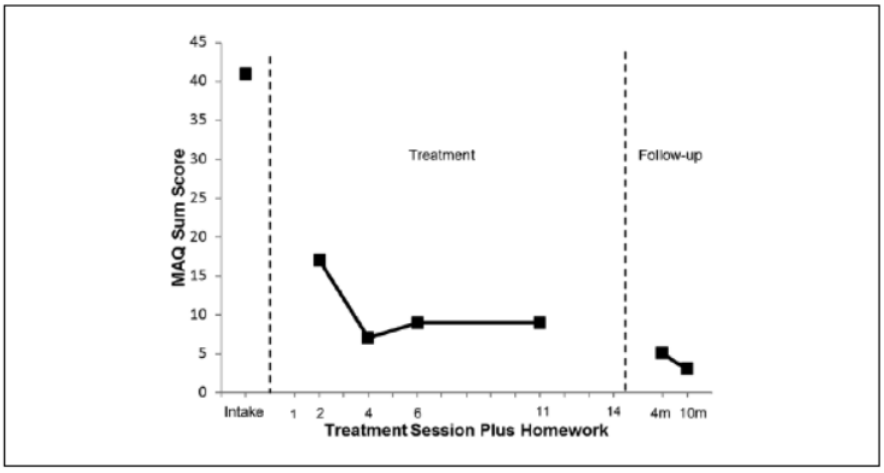

Figure 7: MAQ Sum Score to measure the severeness of misophonia. Before, during and after (follow-up) treatment MAQ scores were obtained to measure the efficiency of the treatment. Treatment was performed on one patient, who participated in eleven therapy sessions.

Other triggers still evoked a misophonic response, but to a lesser extent (Dozier,H.T. 2015).

Even though the treatment was beneficial for the patient, the stimuli were produced by one source in one particular context, making it uncertain whether the treatment is also helpful in variable contexts. Therefore, Dozier suggests that the treatment needs to be further validated. At last, he states that clinicians should test their patients for their individual physical responses, towards a personal list of trigger sounds (Dozier,H.T. 2015).

Counterconditioning has also been used in another case study, which was performed by Schröder and colleagues in 2017. In this study, 90 misophonic patients were treated with CBT. They suggested that the increased focus on misophonic sounds could be explained by impaired attention control, together with increased irritability levels (Schröder,A.E. 2017). To maximize the CBT treatment effects, they used four different techniques to treat the patients: task concentration exercises, counterconditioning, stimulus manipulation, and relaxation exercises. Task concentration exercises were used to improve the capability of the patient to focus on different sensory input, than the salient stimulus. As this technique has already been shown to help treat patients with erythrophobia (Mulken,S. 2001), they suggested that it could also be useful for misophonic patients. Comparable to Thomas Dozier, Schröder et al believed that counterconditioning could ensure positive associations with misophonia trigger, rather than eliciting an aversive reaction (Schröder,A.E. 2017). Using stimulus manipulation, they gave patients the possibility to change the misophonic triggers. By doing so, the feeling of uncontrollability of patients over the trigger sounds would decrease, which created a feeling of control over the trigger sound. At last, the relaxation techniques, which are already found to be helpful in PTSD patients (Blanaru,M. 2012), and anger management (Brondolo,E.R. 1997), were used to lower the irritability of the misophonic sound. The goal of their study was to learn patients to mentally and physically tranquilize themselves in a misophonic situation (Schröder,A.E. 2017). Treatment response was determined by scoring the A-MISO-S before and after treatment. After treatment, which consisted of eight sessions, the combination of techniques was reported to be beneficial for 42 patients (Figure 8), as seen by a 30% decrease in the A-MISO-S. Still, half of the participants did not improve (data not shown; Schröder,A.E. 2017). They did not clarify which trigger sound they used to provoke a misophonic response. In addition, they did not determine the trigger sound per participant. As each patient reacts to a different variety of trigger sounds, this could be a possible explanation of why half of the participants did not respond to the treatment. Also, the average duration of misophonic symptoms of their patients was 21 years. It is possible that a longer duration of symptoms also requires alternative treatment.

In conclusion, the study of Schröder et al is the first study with a bigger group of patients, which demonstrated that CBT can reduce misophonic symptoms. To determine lasting treatment effects, a follow-up study would be needed to be performed.

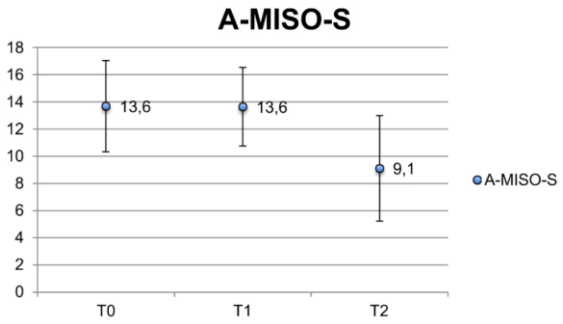

Figure 8: Change of A-MISO-S in misophonic patients. Indicates the severity of the misophonia: 0-4 are subclinical misophonic symptoms, 5-9 is mild, 10-14 is moderate, 15-19 severe and 20-24 extreme misophonia. T0 represents the interview to determine whether the patient is suitable for the study, T1 represents the start of the treatment, and T2 represents the end of the treatment.

3.2. Dialectical behavior therapy

As mentioned before, CBT has been demonstrated by several researchers to be beneficial in the reduction of misophonic symptoms (McGuire,J.F. 2015; Bernstein,R.E. 2013; Schröder,A.E. 2017). However, Kamody et al published a case study in which a misophonic patient did not benefit from CBT. The patient reported that CBT treatment intensified her anger towards a trigger sound, instead of diminishing it. Through individual DBT sessions, the patient altered her relationship to negative emotions. Also, the therapy ensured awareness of her being able to respond differently (Kamody,R.C. 2017). To determine the severity of the misophonia, the patient completed the A-MISO-S and the MAQ. A reduction of misophonic severeness was observed, indicating that the treatment was helpful. These results suggest that, next to CBT, CBD may also be a promising approach to treat misophonic patients (Kamody,R.C. 2017).

3.3. Pharmacological treatment

To date, no studies have been published reporting the effect of pharmacological treatments. Even though therapy can be sufficient enough for some misophonic patients to decrease the impact of misophonia on their lives, patients with more severe misophonia might only benefit from a combination of therapy, with psychotropic medication.

There are reports in which patients have indicated that caffeine intensified the misophonic response (Edeleistein,M. 2013). It has been known that caffeine is a substance that reduces auditory sensory gating, which could result in hyper-focus on the trigger sound. On the other hand, alcohol has been described to soothe the intensity of the misophonic reaction (Edeleistein,M. 2013). Important to note, these reports are solely based on patients' self-reported experiences. No specific studies were performed to elucidate the exact influence of these substances on misophonic responses.

In summary, misophonia is a phenomenon in which cognitive, emotional, memory, social aspects, together with associative learning and environmental factors are all involved in the biological process. So far, CBT has been shown by several studies to be beneficial as a treatment for patients (McGuire,J.F. 2015; Bernstein,R.E. 2013; Schröder,A.E. 2017). Besides, DBT was described to be sufficient (Kamody,R.C. 2017), and no pharmacological treatment has been approved yet, to treat misophonic patients. To maximize the improvement of all patients, they should be treated individually, based on their severity, and the hierarchy of trigger sounds.

3.4 Classifying misophonia

As stated before, misophonia is not listed within the Diagnostic and Statistical Manual of Mental Disorders Fifth Edition (DSM-V) or the International Statistical Classification of Diseases and Related Health Problems 10th revision (ICD-10; Potgieter,I. 2019). Erfarian and Rouw already proposed promising data, which indicated misophonia being a discrete mental disorder (Erfarian,M. 2019). In this section, the pros and cons of misophonia being classified as a discrete disorder will be discussed.

It has been proposed by several studies to recognize misophonia as a distinct mental disorder, for various reasons (Schröder,A. 2014; Taylor,S. 2017; Kumar,S. 2017). First, it will raise public awareness. As a consequence, sufferers will be provided with information and validation. Secondly, misophonia being recognized as a disorder could decrease the prejudgment of non-sufferers. Another consequence would be that interest in unraveling the underlying mechanism of misophonia would further accelerate, increasing the ability to provide more and more patients with treatment.

A reason to not classify misophonia as a DSM-V or ICD-10 disorder is the fear of misdiagnosis or over-diagnosis. People with behavior that does not fit the current "ideal", are labeled as

having a disorder more easily. For example, the number of children labeled with attention deficit and hyperactivity disorder (ADHD) increased massively as the diagnostic criteria changed the last few years, resulting in a great increase in the number of Ritalin-using children (Nemeroff,C.B. 2013). Another example, a child who is suffering from a tantrum, is more quickly diagnosed with disruptive mood dysregulation disorder.

As DSM-6 will be released around 2030, there are ten years left to determine the exact mechanism underlying misophonia. To prevent people to get misdiagnosed or over-diagnosed, it is important that misophonia gets further researched.

4. Conclusion

Since 2013, when Schröder et al described the symptomatology of misophonia, the interest in misophonia accelerated. Even though these diagnostic criteria are later widely used in case studies to determine the severity of misophonia, these diagnostic criteria are not yet validated. Several studies have now been conducted, using fMRI, EEG, and SCR, to elucidate the neurological correlates of misophonia. Although these findings are only preliminary, various studies have verified the link between autonomic arousal and the trigger sound. The most recent studies reported that AIC and ACC, components of the salience network, are hyperactivated. Both components stand in close connectivity with the amygdala, which was found in two studies to be hyperactivated. In another study, no significant differences in the activation of the amygdala was observed. In addition, one study described a deficiency in the auditory information process, which could serve as a potential neurophysiological marker for misophonic patients. However, these findings need to be further validated. Based on the current findings, misophonia involves a mechanism in which specific human sounds evoke a conditioned response with anger and physical arousal. It seems that misophonia involves a hyperactivation of the salience network, giving more salience to a trigger sound. In addition, increased connectivity between the salience network and the amygdala results in activation of the fight/flight response, and consequently a negative emotional association with the trigger sound. At last, the activation of the fight/flight response leads to general arousal. As the amygdala is also involved in supporting memory consolidation, an association occurs between the negative emotional response and a trigger sound.

As these findings are preliminary and are yet to be confirmed, there is still a lot unclear about the mechanism underlying misophonia. For example, it is still not clear whether hyperactivity of components of the salience network is causing the misophonia or a consequence of the disorder. Besides, further research is required to validate malfunctioning of the auditory system and to determine whether the amygdala itself is hyperactivated in misophonic patients.

Interestingly, almost all misophonic patients reported that at least one close relative also suffers from the disorder. Research should be performed to elucidate a possible hereditary etiology.

CBT and CBD are beneficial as treatment on a large proportion of patients. Studies have demonstrated promising results, using these therapies. The severity of these patients was determined using A-MISO-S and MAQ. Even though these measuring tools are not validated yet, both tools are widely used. Still, there are a lot of patients who do not respond to the therapies. It has already been suggested by various studies that treatment should be individually based, as patients have their own hierarchy of triggering sounds. In addition, counterconditioning is based on linking the trigger sound to positive emotions, which are different for every patient, supporting the suggestion of individualized treatment. Patients with prolonged suffering of

misophonia may need a variable or longer therapy, or even in combination with pharmaceuticals. Unfortunately, to date, no studies have been published reporting the effect of pharmacological treatments.

Classifying misophonia within the DSM or ICD could further increase the interest in the disorder, resulting in a better understanding of the underlying mechanism, and improve the treatment. Also, acknowledging misophonia as a disorder can increase the number of participants in the following studies, resulting in more reliable results.

5. Literature

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