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Exploring the Relationship Between Misophonia Severity and Anterior Insular Cortex Activity

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Abstract

Misophonia is an under-recognized neuropsychological condition involving a severe sensitivity towards specific sounds called triggers. The aim of this study was to investigate how activity in the anterior insular cortex (AIC) differed with varying levels of sound sensitivity (SS); misophonia being the most severe. Data was collected from university undergraduates/young adults (N = 31). Participants completed an online survey to assess their misophonia severity and symptoms. A case study was conducted on some of the students (N = 4) to assess misophonia at a neurological level. In addition to experiencing a heightened sensitivity to sounds, the misophonia group reported having more primary triggers. Disgust, anger and anxiety were experienced more frequently in the misophonia group in response to a trigger. The participant with misophonia demonstrated heightened activity in the AIC in response to a trigger, but unexpectedly this activity did not exceed the activity elicited in the no SS participants. Differences in the misophonic reaction were found amongst varying levels of SS, but more participants are needed before conclusions can be made about whether or not these differences have a neurological basis.

Exploring the Relationship Between Misophonia Severity and Anterior Insular Cortex Activity

People naturally form powerful associations between sound and emotion. For example, the sound of rain can evoke feelings of relaxation up until it is accompanied with loud cracks of thunder which can quickly turn feelings of relaxation into unease in some people. Personal experiences and preferences can all play a role in what emotions get associated with different sounds. Misophonia is a neuropsychological condition where people attribute negative emotions to specific everyday sounds. For instance, the typically mundane sound of a person breathing could be enough to trigger an intense emotional reaction where feelings of anger and disgust come flooding in. This emotional reaction is frequently accompanied by an increase in autonomic arousal. The combination of these symptoms makes misophonia extremely debilitating. As a whole, misophonia remains relatively unexplored and as a consequence it has not been formally categorized as a psychological disorder and lacks diagnostic criteria. Uncovering the neural mechanisms behind misophonia would be an important step towards classification, and finding ways to help treat people living with the disorder. Researchers have begun using neuroimaging techniques to explore the differences in the brain between people with misophonia and neuro-typical individuals. A brain region known as the anterior insular cortex (AIC) has been found to be involved in the misophonic reaction. For this reason, the focus of the current study is to use functional magnetic resonance imaging (fMRI) to explore differences in AIC activity in people with varying misophonia symptom severity. Before going on to describe the current study, misophonia will be described in detail, and the findings from previous neuroimaging studies investigating the underlying neurological mechanisms of misophonia will be reviewed.

What is Misophonia?

Misophonia was first described by Jastreboff and Jastreboff (2001) to label a sound sensitivity associated with the hatred of very particular sounds. Prior to the existence of misophonia, the term phonophobia was used but widely rejected by patients as it implied a "phobia" or fear of sound, rather than a hatred or dislike (Jastreboff & Jastreboff, 2001). Although fear can be a symptom, having it as the central symptom failed to accurately represent this particular sound sensitivity – and so the term misophonia was developed. Misophonia is a condition that causes people to have intense emotional reactions and autonomic arousal in response to commonly occurring sounds (Kumar et al., 2014; Schröder, Vulink & Denys, 2013). It is important to note that people with misophonia are not sensitive to all sounds but rather only very particular auditory stimuli. The sounds that can induce a misophonic reaction are called "triggers" (Edelstein et al., 2013; Kumar et al., 2014), and they tend to be human-produced, repetitive sounds. Many common triggers originate orally or nasally, like chewing, breathing and sniffling but can also include sounds such as finger tapping, keyboard typing, and pen clicking (Kumar et al., 2014; Schröder et al., 2013; Wu, Lewin, Murphy & Storch, 2014). Trigger sounds automatically elicit emotional reactions, some of the most common being anger, disgust, anxiety and impulsivity (Cavanna & Seri, 2015; Schröder et al., 2013). Associated autonomic arousal is evidenced by "fight or flight" like symptoms including increased heart rate and galvanic skin response (Kumar et al., 2017). As research around misophonia continues to progress, so does the recognition that misophonia may represent a severe clinical problem (McKay, Kim, Mancusi, Storch & Spankovich, 2018). People with misophonia experience the condition as being out of their control (McKay et al., 2018), and can experience extreme distress in their day to day functioning as a result. People with misophonia constantly worry about when they might

encounter their trigger (McKay et al., 2018), leading them to avoid environments in which it would be most likely to occur (Wu et al., 2014). For example, people might avoid eating with others if they get triggered by the sound of people chewing (Wu et al., 2014). In addition to active avoidance, in an attempt to cope with symptoms, people can experience strong desires to escape their trigger. This can involve trying to cover up the sound or acting out impulsively against the source of the trigger in attempt to make it stop (Cavanna & Seri, 2015; Schröder et al., 2013). Although avoidance and escape can provide short-term relief, they often result in long-term distress and interference with daily activities. As some of the most common triggers are human-produced sounds, the relationships of people with misophonia tend to suffer as a result of the negative emotional reactions they experience (Neal & Cavanna, 2013; Schröder et al., 2013; Wu et al., 2014). Given that impairment in daily life of a person with misophonia is almost inevitable to some degree, working towards better understanding the condition is of considerable need.

Previous Studies of Misophonia

Attempts to estimate the prevalence of misophonia have typically involved self-report studies conducted with undergraduate students and young adults. Incidence rates of misophonia may be higher than initially expected as these studies find rates of significant misophonia symptoms in approximately 20% of their sample (Wu et al., 2014; Zhou, Wu, & Storch, 2017). Despite the fact that the majority of these survey data have been collected from undergraduate students, there has yet to be a neuroimaging study done using this same sample. Previous fMRI studies have only compared clinical samples of older individuals with misophonia to controls in order to investigate brain differences. To bridge the gap between neuroimaging studies conducted with older individuals and self-report studies estimating prevalence rates using

undergraduates/young adults, the current study will be the first to use neuroimaging techniques with a sample of undergraduates/young adults. It is important to investigate the brain differences amongst this population in order to investigate whether they differ from the clinical samples, and if so, how they differ. Additionally, previous studies have examined participants that have either extreme sound sensitivities or no sensitivities, thus sampling only the polar ends of the sound sensitivity spectrum. For this reason, it remains unclear how individuals experiencing milder sound sensitivity symptoms, falling somewhere in the middle on the sound sensitivity spectrum, differ in terms of their reaction to misophonic sounds. As the severity of their reaction differs, it is important to see how milder symptoms relate to differences in brain activity compared to people without symptoms as well as people with the most severe misophonic reactions. The current study will attempt to fill this gap in the literature by placing participants into one of three groups according to their symptom severity: severe sensitivity, mild sensitivity and symptom-free groups (as measured using a standardized test of symptom severity). Using three different severity groups will allow the current study to sample more successfully across a range of the sound sensitivity severity spectrum.

Previous Imaging Studies of Misophonia

The first published fMRI study to attempt to investigate brain differences in people with misophonia was conducted by Kumar and colleagues in 2017. They presented misophonic, aversive, and neutral auditory sounds to participants with and without misophonia. Misophonic sounds would have consisted of common triggers in attempt to induce a misophonic reaction (e.g. eating sounds). An aversive sound would consist of a generally annoying sound, but one that does not evoke a misophonic reaction (e.g. baby crying). Lastly, a neutral sound which would not elicit any heightened reaction (e.g. rain). Using fMRI, they found an exaggerated

Blood-oxygen-level-dependent (BOLD) response in the anterior insular cortex (AIC) among misophonic subjects in comparison to controls for the misophonic sounds, but no differences between groups in response to aversive or neutral sounds. More specifically, their study revealed that activity in both the left and right AIC increased as individual ratings of distress caused by misophonic triggers increased. The AIC is a key node in the salience network (Uddin, 2015), which responds to meaningful stimuli in the environment and functions to orient attention towards these stimuli. Atypical functioning within the salience network has been found to underlie many neuropsychiatric disorders (Uddin, 2015), which could also be the case with misophonia. Not only does the AIC serve a role in directing attention, it also has a critical role in emotional awareness (Gu, Hof, Friston, & Fan, 2013). Taking a closer look at the role of the AIC in emotional awareness could be helpful in attempting to explain some of the symptoms associated with misophonia. Neuroimaging studies have shown that AIC activity is associated with the feeling of disgust (Gu et al., 2013; Jabbi, Bastiaansen, & Keysers, 2008), one of the intense emotions that can result from hearing ones misophonic trigger.

Having identified the importance of the AIC, Kumar et al. (2017) sought to explore stimulus-dependent connectivity using the AIC as a seed region. Results revealed large amounts of functional connectivity between the AIC and the ventromedial prefrontal cortex (vmPFC) and the posteromedial cortex (PMC), but only among misophonic subjects responding to misophonic stimuli. Greater connectivity within this network of regions involved in processing and regulating emotions could be responsible for the abnormally high salience assigned towards specific sounds in individuals with misophonia (Kumar et al. 2017). Their study also found that activity in the AIC seemed to mediate symptoms of autonomic arousal, like increased heart rate and galvanic skin response, observed during a misophonic reaction. Other studies have also

linked AIC activity to cardiovascular functions (Gu et al., 2013), suggesting that the AIC could be involved in the increased autonomic arousal, including increased heart rate. This study significantly contributed towards the understanding of the neurological mechanisms governing misophonia.

The second study to use fMRI to investigate misophonia was conducted by Schröder and colleagues (2019). Schröder et al. (2019) expanded on the work of Kumar et al. (2017) by using auditory stimuli with simultaneous visual input. Although no studies have directly explored the difference between audio and audiovisual stimuli in triggering a misophonic reaction, the combination of audiovisual stimuli are likely necessary in order to evoke a true misophonic reaction. Using similar methods to Kumar et al. (2017), they presented misophonic, aversive and neutral stimuli to people with and without misophonia. Imaging results of their study revealed increased activity in the right AIC and right anterior cingulate cortex (ACC) in misophonic subjects in comparison to controls in response to misophonic stimuli. It is important to note that although AIC and ACC are functionally separable, they are commonly coactivated (Gu, Hof, Friston, & Fan, 2013), and both have important roles in the salience network (Uddin, 2015). The presence of an increased BOLD response in the ACC provides further support for a possible neural mechanism underlying this behavioral phenomenon (Kumar et al., 2017; Schröder et al., 2019). Together these two studies have highlighted a region of the brain, the AIC, that is involved in the misophonic reaction. This contribution provides future researchers with a starting point in terms of where to focus their efforts. Nevertheless, as with any emerging area of research there are many research gaps that need to be addressed.

The current study aims to build on two additional limitations present across both previous studies. First, previous studies used the same set of misophonic triggers for all participants. This

is problematic, as people with misophonia are triggered by different sounds. To combat this disparity and in order to elicit a genuine misophonic response, audiovisual stimuli will be tailored to each individual participant. Lastly, previous methodology compared activity elicited in response to aversive sounds to activity elicited by misophonia trigger sounds. The use of aversive stimuli is not ideal as they have little in comparison with misophonia trigger sounds. This is problematic because given that these two stimuli are different from each other they would be expected to elicit different levels of activity. In order to better understand these differences, aversive stimuli were replaced with disgust-evoking stimuli. The reason disgust-evoking stimuli were used in this study was because the AIC has been shown to be involved in the feeling of disgust (Gu et al., 2013; Jabbi, Bastiaansen, & Keysers, 2008). For this reason, disgust-evoking sounds would be expected to elicit AIC activity in all participants, regardless of the severity of their sound sensitivity. This would serve to ensure that all participants, and not just the ones in the misophonia group, are able to exhibit activity in the AIC. Additionally, this would allow for further insight into the nature of the relationship between disgust and misophonia. Overall, to expand upon the findings from Kumar et al. (2017) and Schröder et al. (2019), the current study will use the AIC as a region of interest to further explore how brain activity differs in people with various levels of sound sensitivities, leading up to misophonia as the most severe form.

The Present Study

In order to investigate how brain activity differs across people with different misophonia severity, changes in the BOLD response will be analyzed with a focus on the AIC. Changes in both the magnitude and duration of the BOLD signal will be recorded over the span of stimulus presentation to examine response dynamics. To compare across symptom severities, the current study will aim to sample participants from severe, mild and symptom-free groups. By sampling

across the spectrum, the study will provide insight into how AIC activity varies in accordance with symptom severity. In addition, a gap in the literature will be resolved pertaining to the use of older patients for imaging studies and undergraduates/young adults for studies estimating prevalence rates of misophonia. Lastly, tailoring the stimuli to each individual participant should allow for the most authentic misophonic response to be evoked and imaged in an experimental setting thus far. It is hypothesized that participants with the most severe misophonia symptoms will have the highest BOLD activity present in the AIC in response to a misophonia inducing trigger. If this hypothesis is supported, it would suggest that the AIC plays a particularly important role in maintaining salience of the trigger, and that this activity is quantitatively different for misophonic triggers than disgusting or generally aversive stimuli.

Method

Participants

This study comprised of 31 participants: 9 with misophonia symptoms, 14 with a sub-clinical sound sensitivity (SS), and 8 healthy controls with no SS (see Table 1). Participants were recruited from the University of Western Ontario using the Western SONA psychology research participation pool and through poster advertisements. All participants completed an online survey for which those recruited through SONA received .5 research credits, while all other participants received $5 compensation. Four participants went forward to complete an imaging session (see Table 2) for which those recruited through SONA received an additional 2 research credits, while all other participants received an additional $15 per 30 minutes.

Inclusion criteria for the study required that all participants be English-speaking individuals between the ages of 18-30 with normal or corrected-to-normal vision. Additionally, participants must have completed the online survey in order to proceed to the MRI session.

Exclusion criteria for all participants included any MRI contraindications or auditory impairments. An audiometric test was conducted on all participants to ensure hearing was in the normal range; normal has been classically defined as no pure tone threshold exceeding 20 dB normal hearing level. Any participant found to not have normal hearing was excluded from the study and referred to an audiologist.

The study was approved by Western University's Health Science Research Ethics Board (see Appendix A).

Table 1
Sample demographics with means and standard deviations.

	No SS/ control sample	**Subclinical SS sample**	**Misophonia sample**	**Combined sample**
Demographic items				
N	8	14	9	31
Age, Mean (SD)	22.13 (3.31)	24.29 (4.10)	21.78 (3.15)	23.00 (3.73)
(Range)	(18–29)	(18–30)	(18–29)	(18–30)
Gender				
Male	37.5%	35.7%	33.3%	35.5%
Female	62.5%	64.3%	66.7%	64.5%
Ethnic identity*				
African American/black	0.0%	0.0%	11.1%	3.2%
Asian/Pacific Islander	0.0%	14.3%	22.2%	12.9%
Latin/Hispanic	0.0%	14.3%	0.0%	6.5%
Middle Eastern	0.0%	0.0%	11.1%	3.2%
Native/indigenous	0.0%	7.1%	0.0%	3.2%
South Asian	0.0%	21.4%	0.0%	9.7%
White/Caucasian	87.5%	57.1%	70.0%	71.0%
Central Asian	12.5%	0.0%	0.0%	3.2%
Educational background				
High school	0.0%	7.1%	0.0%	3.2%
Some college/university	62.5%	42.9%	55.6%	51.6%
College/university graduate	0.0%	14.3%	11.1%	9.7%
Some post-graduate studies	12.5%	21.4%	33.3%	22.6%
Completed post-graduate studies	25.0%	14.3%	0.0%	12.6%
Mental health background				
Received mental health diagnosis	12.5%	21.4%	44.4%	25.8%
Received mental health treatment	12.5%	35.7%	33.3%	29.0%

Note: * Overall percent adds up to over 100 as some participants selected multiple ethnic identities.

Table 2
Imaging participant demographics with means and standard deviations.

	Participant one	Participant two	Participant three	Participant four
Misophonia Severity	No SS	Subclinical	Misophonia	No SS
A-MISO-S Score	0.00	3.00	13.00	0.00
Demographic items				
Age	22	21	22	21
Gender	Male	Female	Female	Male

Note. A-MISO-S = Amsterdam Misophonia Scale.

Materials

Amsterdam Misophonia Scale (A-MISO-S)

The A-MISO-S is a six item self-report questionnaire created by Schröder, Vulink, & Denys (2013), used to assess the amount of impairment experienced by an individual as a result of misophonia. Scores on the A-MISO-S were used to assign participants into groups according to their misophonia symptom severity. Participants were placed into one of three groups: no SS/control (A-MISO-S score of 0), sub-clinical SS (A-MISO-S score from 1-9), and misophonia (A-MISO-S score of 10 or greater).

Modified Misophonia Questionnaire (MQ)

The original MQ is a self-report questionnaire created by Wu et al. (2014), that consists of three parts: (1) The Misophonia Symptom Scale, (2) The Misophonia Emotions and Behaviors Scale, and (3) The Misophonia Severity Scale. The present study used modified versions of the first two scales. The Misophonia Symptom Scale was used to assess the frequency with which misophonia symptoms were experienced in response to a particular sound (see Appendix C, Question 13-13.18), and was modified to include a more extensive list of common misophonia triggers. The list consisted of 17 triggers, each of which was rated along the same scale ranging from 0 (not at all bothered) to 4 (always bothered). For any item that was rated as a three or four,

participants were asked 1) a follow up question which probed the severity of response to that particular trigger on a scale from not bothered more than most people to extremely bothered (I feel extremely uncomfortable, angry and experience a need to become aggressive/violent); and 2) a modified version of The Misophonia Emotions and Behaviors Scale (see Appendix C, Question 14) which assesses specifically which emotions are typically experienced. This scale was modified to ask how often each of 6 emotions (disgust, anxiety, anger, annoyance/irritation, sadness and fear) was evoked by each trigger sound with responses ranging from 0 (never) to 4 (always).

Imaging Stimuli

During the imaging session all participants were exposed to four examples from each of three audiovisual stimulus categories: misophonia trigger, disgust-evoking, and neutral (see Appendix B). A collection of common misophonic trigger sounds were obtained from the Misophonia Questionnaire (Schröder, Vulink, & Denys, 2013) and the Misophonia Institute website (Dozier, 2016), and included sounds such as person eating chips or typing on a keyboard. Disgust-evoking stimuli included sounds that have been shown to evoke a disgust reaction amongst humans (Cox, 2008), and are included in the International Affective Digitized Sound's (IADS) inventory (Stevenson & James, 2008). Examples of disgusting sounds included a person belching or blowing their nose. Neutral stimuli were also selected from the IADS (Stevenson & James, 2008), and included sounds with low arousal and positive valence such as background inaudible conversations or a person painting, which were not expected to evoke any particular emotion in participants. All stimuli were obtained from various YouTube channels. The misophonic trigger stimuli were tailored to each participant so that during the imaging

session each participant was presented with their specific trigger(s). Stimuli were randomly selected for any participant that did not have a sensitivity to any particular sound.

Procedure

Online Survey

In part one of the study participants completed an online survey prior to coming into the lab (see Appendix C). The purpose of the online survey was to determine (1) eligibility for the study, (2) participant demographic information, (3) what (if any) participant-specific sounds that serve as triggers or cause sensitivity, and (4) severity of the sensitivity. Prior to completing the survey participants were provided with a Letter of Information about the study and provided consent electronically (see Appendix D). Any participants that were found not eligible to participate in the MRI session did not complete the remainder of the survey but instead were given an electronic copy of the Debriefing Letter (see Appendix E).

The survey used items from the Amsterdam Misophonia Scale (A-MISO-S) (Schröder, Vulink, & Denys, 2013) as well as items derived from the Misophonia Questionnaire (MQ) (Wu et al., 2014), used to obtain information about misophonia symptoms and severity. The survey was conducted online through a secure administration (Qualtrics) and took approximately 30 minutes to complete. Following survey completion, participants were contacted to schedule the in-laboratory experimental session.

Imaging Session

Upon arrival, participants were provided with the Letter of Information (see Appendix D) again and were asked to provide ongoing consent before beginning the next session involving MRI imaging. All three groups of participants (misophonia, sub-clinical SS, and no SS/control) followed the same experimental procedure, starting with two tests to ensure inclusion criteria for

the study was met: 1) Participants had their audiometric thresholds tested and 2) were screened for any MRI contraindications using a standard questionnaire provided by the Centre for Functional and Metabolic Mapping. Any participants that were deemed ineligible for the study were excluded at this time and received their compensation in full.

All participants that met the inclusion criteria were put inside the Siemens 3 Tesla MRI scanner. While inside the scanner participants wore MRI-compatible noise cancelling headphones used to present the auditory stimuli. Due to the nature of this experiment, the stimuli vary in volume. However, computer volume was maintained at 75% so that all experimental stimuli had a dB level between 50-80, a range that is audible over the MRI but does not cause any hearing damage. The projection system inside the scanner was located at an average distance of 13.5cm from the participant and was used to present the accompanying visual stimuli. While inside the scanner, participants were instructed to fixate on the screen and to remain as still as possible. Participants were not required to respond to any of the stimuli while inside the scanner.

A block-design MRI paradigm was used to present the three different types of stimuli: misophonia trigger, disgust-evoking, and neutral. Stimuli were presented in four runs, each of which consisted of four blocks (see Figure 1). Each individual run was comprised of: a fixation cross (presented without sound) followed by each of the three conditions presented in random order. Between blocks there was a two second break which consisted of a black screen and no sound. The total experiment was repeated four times with a two-minute break in between repetitions. In total, each participant saw 12 different stimuli which repeated throughout the experiment.

After the imaging session was completed, participants were given the Debriefing Letter (see Appendix E) and received their compensation. The entire imaging session took approximately two hours.

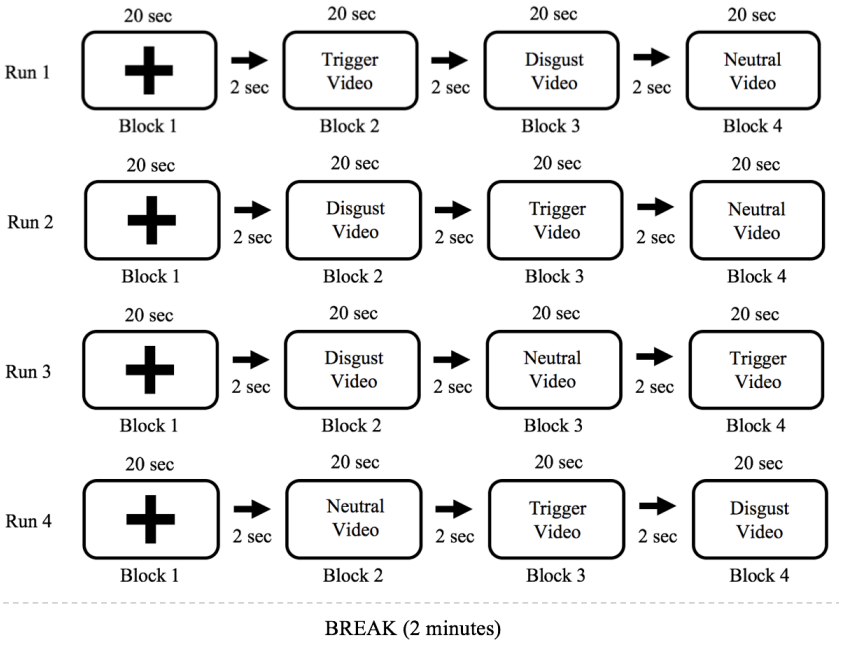

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Figure 1. Example of one experimental trial.

Scanning Parameters

Data was collected using a Siemens MAGNETOM Prisma Fit whole-body 3 Tesla MRI scanner located at the Centre for Functional and Metabolic Mapping at the Robarts Research Institute. Consent was obtained for scanning in accordance with Western University's Health Science Research Ethics Board (see Appendix A).

High-resolution structural T1-weighted MP2RAGE images were acquired prior to functional scanning with the following parameters: isotropic voxel size of $1mm^3$, 176 slices, FoV = 256mm, TE = 2.98ms, TR = 2300ms and a flip angle of 9.

Functional images were acquired over the whole brain in axial orientation with a single shot echo-planar imaging (EPI) acquisition with grappa acceleration and the following parameters: 2.5mm^3, 51 slices (interleaved), FoV = 208mm, TE = 30ms, TR = 1000ms and a flip angle of 40.

Image Acquisition

The present study used a region of interest (ROI) approach to analyze the fMRI data. Specifically, the AIC was the RIO, which was defined using the same NMI coordinates as Kumar et al. (2017) as their study indicated that this region showed a significant involvement in processing trigger sounds. The ROIs used in the current analysis were centered around cluster peaks in the left anterior insula (-41, 6, 0), right anterior insula (39, 23, 3), and second peak in the right anterior insula (35, 30, 0) derived from the above mentioned study (Kumar et al., 2017). Each region of interest was five voxels in size corresponding to 10mm^3 in diameter. BOLD activity elicited in response to misophonia trigger sounds was compared to activity elicited in response to neutral sounds, disgust evoking sounds, and a fixation cross (no sound). Activity elicited in response to disgust evoking sound was also compared to activity elicited in response to neutral sounds and a fixation cross (no sound). Lastly, BOLD activity elicited in response to neutral sounds was compared with activity elicited in response to a fixation cross (no sound).

Descriptive Analysis of Sample

Mean Number of Primary and Secondary Misophonia Triggers

Literature has shown that people with misophonia are more sensitive to sound than people with sub-clinical SS. The present study wanted to investigate if people with misophonia were also sensitive to a greater number of sounds. During the online survey participants were asked to indicate the sounds they were sensitive to and the degree to which the sound(s) bother

them. If participants indicated that they were ‘often’ or ‘always’ sensitive to a particular sound (see Appendix C, Item 13) in comparison to other people, the sound was defined as a sensitivity causing sound. If participants then proceeded to indicate that they were ‘a little bothered’ or ‘bothered’ by the sound (see Appendix C, Item 13.1 – 13.18), it was defined as a secondary trigger. If participants indicated that they were ‘very bothered’ or ‘extremely bothered’ by that sound (see Appendix C, Item 13.1 – 13.18), then it was defined as a primary trigger. To investigate whether significant differences in the mean number of reported sensitivity causing sounds were present between groups, a one-way between-subjects ANOVA was conducted. The ANOVA revealed a significant main effect of group ($F(2, 28) = 14.43$, $p < .001$, $\eta^2 = .508$, power = 1.00) (see Figure 2A). To further analyze these results, Tukey’s HSD post-hoc tests were conducted and revealed that participants in the misophonia group reported having significantly more sensitivity causing sounds than the subclinical SS group ($q(3, 28) = 4.13$, $p = .018$), and the no SS group ($q(3, 28) = 7.60$, $p < .001$) (see Table 3). Additionally, participants in the subclinical SS group reported having significantly more sensitivity causing sounds compared to the no SS group ($q(3, 28) = 4.35$, $p = .013$). Levene’s test for homogeneity of variances was significant ($F(2, 28) = 6.76$, $p = .004$), indicating that the assumption of homogeneity of variances has been violated and that results be interpreted with caution.

Another one-way between-subjects ANOVA was conducted to investigate whether there were significant differences in the number of secondary misophonia triggers reported between groups. The ANOVA revealed a significant main effect of group ($F(2, 28) = 7.96$, $p = .002$, $\eta^2 = .362$, power = .93) (see Figure 1B). To further analyze these results, Tukey’s HSD post-hoc tests were conducted and revealed that participants in the misophonia group did not report having significantly more secondary misophonia triggers than the subclinical SS group ($q(3, 28) = 0.74$,

p = .860), but did report having significantly more secondary misophonia triggers than the no SS group (q(3, 28) = 5.12, p = .003). Additionally, participants in the subclinical SS group reported having significantly more secondary misophonia triggers compared to the no SS group (q(3, 28) = 4.90, p = .005). Levene's test for homogeneity of variances was significant (F(2, 28) = 5.45, p = .010), indicating that the assumption of homogeneity of variances has been violated and that results be interpreted with caution.

To investigate whether there were significant differences in the number of primary misophonia triggers reported between groups, another one-way between-subjects ANOVA was conducted. The ANOVA revealed a significant main effect of group (F(2, 28) = 11.59, p < .001, η^2 = .453, power = .99) (see Figure 1C). To further analyze these results, Tukey's HSD post-hoc tests were conducted and revealed that participants in the misophonia group reported having significantly more primary misophonia triggers than the subclinical SS group (q(3, 28) = 5.71, p = .001) and the no SS group (q(3, 28) = 6.19, p < .001). Additionally, participants in the subclinical SS group did not reported having significantly more primary misophonia triggers compared to the no SS group (q(3, 28) = 1.29, p = .637). Levene's test for homogeneity of variances was significant (F(2, 28) = 14.93, p < .001), indicating that the assumption of homogeneity of variances has been violated and that results be interpreted with caution. Taking the results from these three analyses together, participants in the misophonia group reported significantly more sensitivity causing sounds and primary misophonia triggers than participants in the subclinical SS group, but they did not report significantly more secondary misophonia triggers.

Table 3
Means and Standard Deviations for Number of Self-Reported Sensitivity Causing Sounds and Triggers

	No SS Mean *(SD)*	Subclinical SS Mean *(SD)*	Misophonia Mean *(SD)*
Sensitivity causing sounds	0.25 *(0.71)*	5.57 *(4.45)*	10.44 *(4.56)*
Secondary triggers	0.00 *(0.00)*	4.07 *(3.29)*	4.67 *(2.65)*
Primary triggers	0.00 *(0.00)*	0.93 *(1.27)*	4.89 *(3.98)*

Note. $N = 31$; SD = standard deviation.

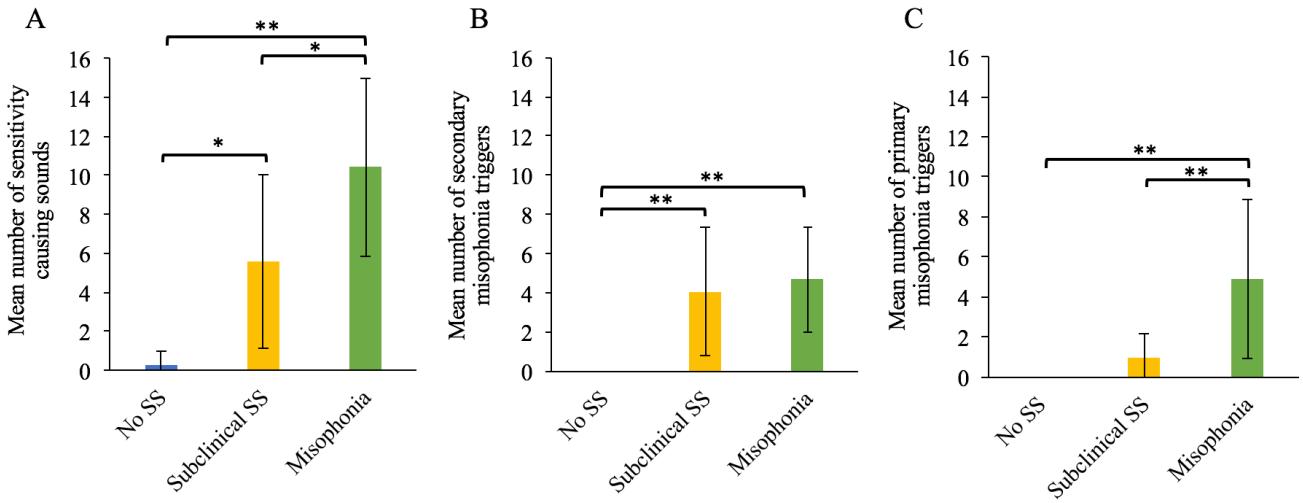


Figure 2. (A) Mean number of sensitivity causing sounds reported by participants in each group. (B) Mean number of secondary misophonia triggers reported by participants in each group. (C) Mean number of primary misophonia triggers reported by participants in each group. *Note.* * $p < .05$, ** $p < .01$.

Relation Between MQ and A-MISO-S

Two scales have been developed that assess misophonia severity; the Misophonia Questionnaire (MQ) created by Wu et al. (2014) and the Amsterdam Misophonia Scale (A-MISO-S) created by Schröder et al. (2013). Previous online studies have mostly measured misophonia severity using the MQ, whereas the Schröder et al. (2019) neuroimaging study used the A-MISO-S to measure misophonia severity. Likewise, this study used the A-MISO-S to

measure misophonia severity and group participants into groups accordingly, as this measure is the closest thing available to diagnostic criteria. Given that the focus of the current study is to bridge the gap between the online and neuroimaging studies, it was necessarily to ensure that these two scales were measuring misophonia severity similarly. The present study obtained scores for both the MQ and the A-MISO-S, but only used scores from the A-MISO-S to group participants. In order to check that scores on the two scales were related, a Pearson correlation was conducted and showed that scores on the MQ (M = 4.45, SD = 3.55) were significantly positively correlated with scores on the A-MISO-S (M = 6.23, SD = 4.98) (r = .88, p < .001) (Figure 3). Therefore, it can be concluded that the two scales are highly related in their measurements of misophonia.

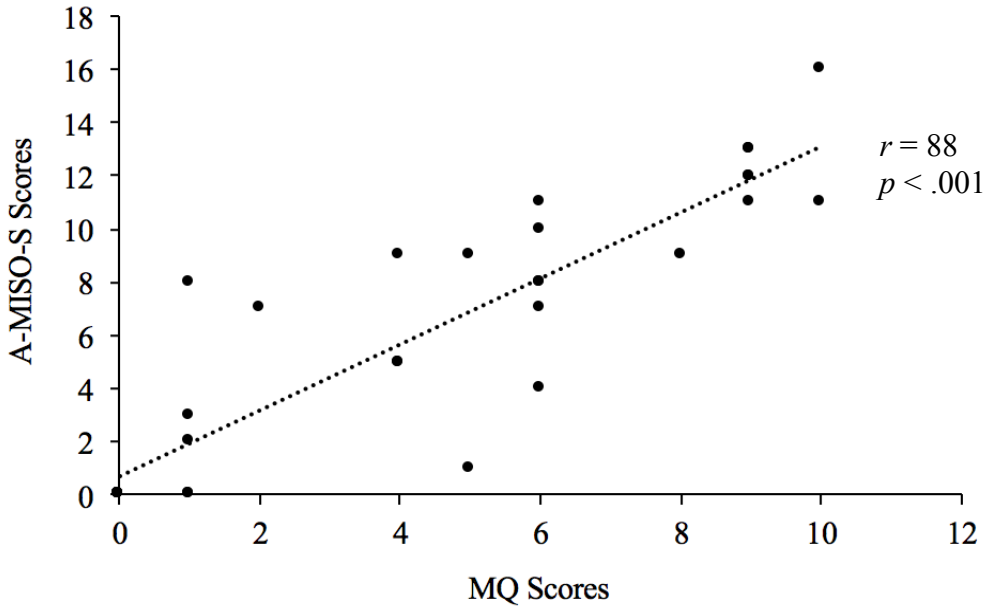


Figure 3. Pearson correlation between MQ scores and A-MISO-S.
Note. MQ = Misophonia Questionnaire; A-MISO-S = Amsterdam Misophonia Scale; Some participants had the same scores which explains why 31 markers are not visible in this figure.

Results

Online Survey Results

Participants were asked how frequently they experience disgust, anxiety, anger, irritation, sadness and fear in response to the sound(s) they are sensitive to (see Appendix C, Item 14). To investigate the differences in emotions elicited in response to trigger sounds between groups, a three (Misophonia Severity: No SS, Subclinical SS, and Misophonia) × six (Emotion: Disgust, Anxiety, Anger, Irritation, Sadness and Fear) mixed-model factorial ANOVA was conducted.

The ANOVA revealed that there was a significant interaction between emotion and group ($F(5.35, 74.83) = 4.98$, $p < .001$, $\eta^2 = .262$, power = .98). More specifically, it was found that there were significant group differences in mean frequency scores for disgust ($F(2, 100.39) = 12.05$), anxiety ($F(2, 100.39) = 15.60$), anger ($F(2, 100.39) = 12.20$), and irritation ($F(2, 100.39) = 22.54$), at $p < .01$ ($F_{obt} = 4.82$), but not for sadness ($F(2, 100.39) = 1.36$), or fear ($F(2, 100.39) = 1.44$), at $p < .05$ ($F_{obt} = 3.09$) (see Figure 4). To further investigate this significant interaction, Tukey-HSD post-hoc tests were conducted for disgust, anxiety, anger and irritation but not for sadness and fear as no significant group differences existed for those two emotions (see Table 4).

Disgust. Results for the experience of disgust revealed that participants in the misophonia group experienced significantly more frequent disgust than participants in the subclinical SS group ($q(2, 100.39) = 3.92$, $p = .01$), and participants in the no SS group ($q(2, 100.39) = 6.94$, $p = .01$) (Figure 5). Additionally, participants in the subclinical SS group experienced significantly more frequent disgust than participants in the no SS group ($q(2, 100.39) = 3.83$, $p = .01$).

Anxiety. Results for the experience of anxiety revealed that participants in the misophonia group experienced significantly more frequent anxiety than participants in the subclinical SS group ($q(2, 100.39) = 3.41$, $p = .05$), and participants in the no SS group ($q(2,$

100.39) = 7.84, p = .01) (Figure 5). Additionally, participants in the subclinical SS group experienced significantly more frequent anxiety than participants in the no SS group (q(2, 100.39) = 5.32, p = .01).

Anger. Results for the experience of anger revealed that participants in the misophonia group experienced significantly more frequent anger than participants in the subclinical SS group (q(2, 100.39) = 3.04, p = .05), and participants in the no SS group (q(2, 100.39) = 6.94, p = .01) (Figure 5). Additionally, participants in the subclinical SS group experienced significantly more frequent anger than participants in the no SS group (q(2, 100.39) = 4.68, p = .01).

Irritation. Results for the experience of irritation revealed that participants in the misophonia group did not experience significantly more frequent irritation than participants in the subclinical SS group (q(2, 100.39) = 1.47 p > .05), but participants in the misophonia group did experience significantly more frequent irritation than participants in the no SS group (q(2, 100.39) = 8.71, p = .01) (Figure 5). Additionally, participants in the subclinical SS group experienced significantly more frequent irritation than participants in the no SS group (q(2, 100.39) = 8.13, p = .01).

In terms of the mixed-model factorial ANOVA, Mauchly's test of sphericity was significant, W = 0.14, $\chi^2(14) = 51.86$, $p < .001$, $\varepsilon_{G\text{-}G} = .534$, suggesting that the assumption of circularity has been violated; to correct for the violation a Greenhouse-Geisser correction was applied to all further analyses involving within-subjects effects. Levene's test for homogeneity of variance was significant for each of the six emotions, suggesting that group variances differ significantly and results should be interpreted with caution (disgust F(2, 28) = 10.17, p < .001, anxiety F(2, 28) = 9.65, p = .001, anger F(2, 28) = 10.11, p < .001, irritation F(2, 28) = 4.55, p = .020, sadness F(2, 28) = 14.06, p < .001, and fear F(2, 28) = 7.27, p = .003).

Table 4

Means and Standard Deviations for Self-Reported Frequencies of Emotions in Response to Hearing Trigger Sound

	No SS *n = 8* Mean *(SD)*	Subclinical SS *n = 14* Mean *(SD)*	Misophonia *n = 9* Mean *(SD)*
Disgust	0.00 *(0.00)*	1.29 *(0.91)*	2.56 *(0.88)*
Anxiety	0.00 *(0.00)*	1.79 *(1.37)*	2.89 *(0.78)*
Anger	0.00 *(0.00)*	1.57 *(1.02)*	2.56 *(0.88)*
Irritation	0.13 *(0.35)*	2.86 *(1.23)*	3.33 *(0.50)*
Sadness	0.00 *(0.00)*	0.14 *(0.36)*	0.78 *(0.83)*
Fear	0.00 *(0.00)*	0.79 *(1.18)*	0.67 *(0.71)*

Note. $N = 31$; SD = standard deviation.

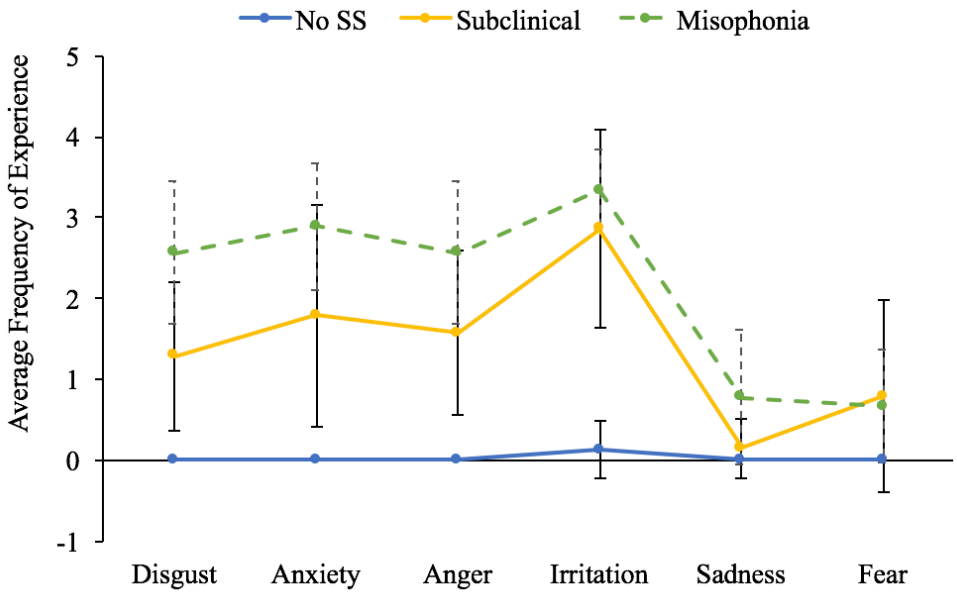
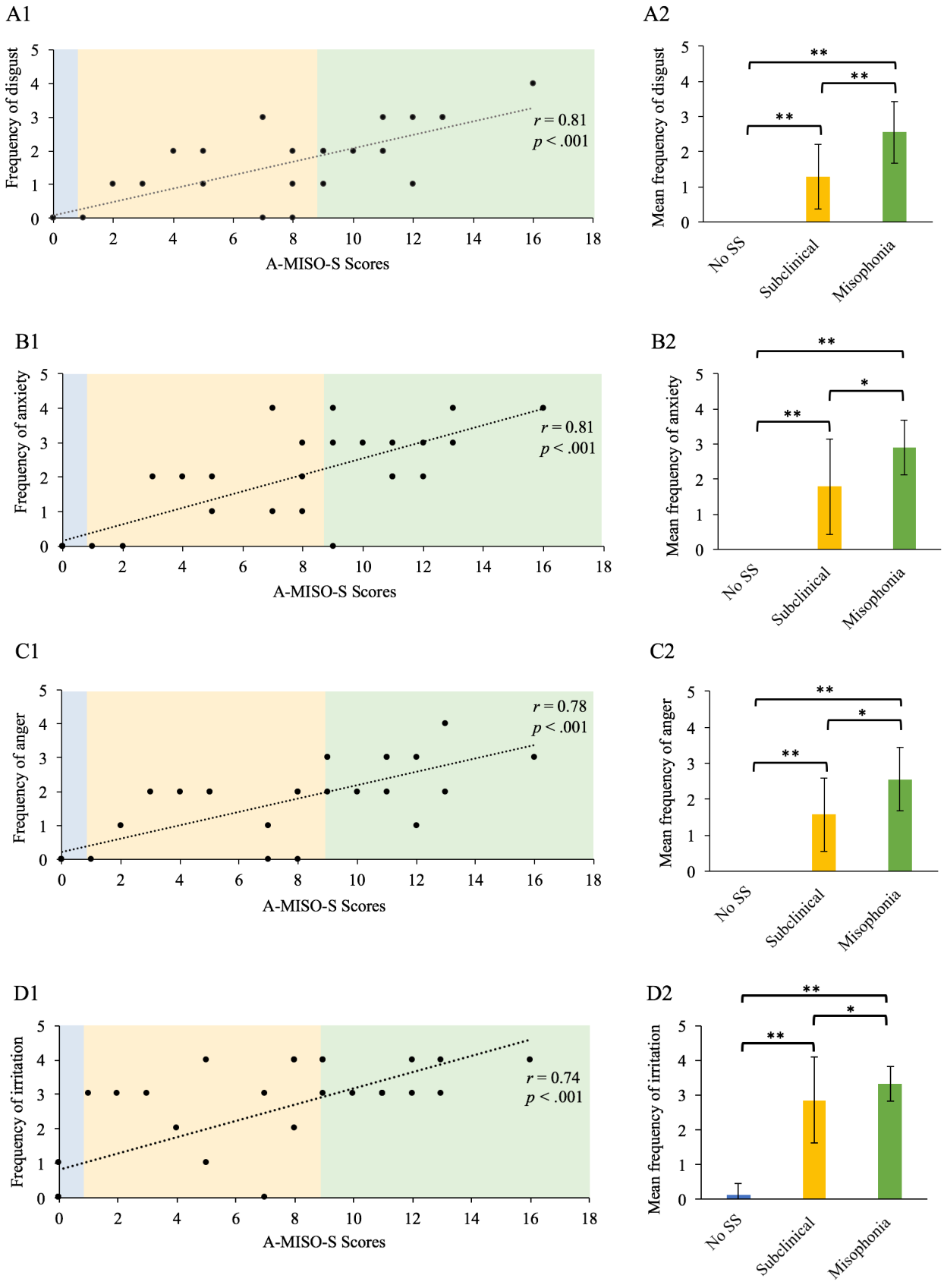


Figure 4. Comparison of mean emotion frequency scores elicited in response to misophonia trigger sounds.


A1
Frequency of disgust
A-MISO-S Scores
r = 0.81
p < .001
A2
Mean frequency of disgust
No SS
Subclinical
Misophonia
B1
Frequency of anxiety
A-MISO-S Scores
r = 0.81
p < .001
B2
Mean frequency of anxiety
No SS
Subclinical
Misophonia
C1
Frequency of anger
A-MISO-S Scores
r = 0.78
p < .001
C2
Mean frequency of anger
No SS
Subclinical
Misophonia
D1
Frequency of irritation
A-MISO-S Scores
r = 0.74
p < .001
D2
Mean frequency of irritation
No SS
Subclinical
Misophonia

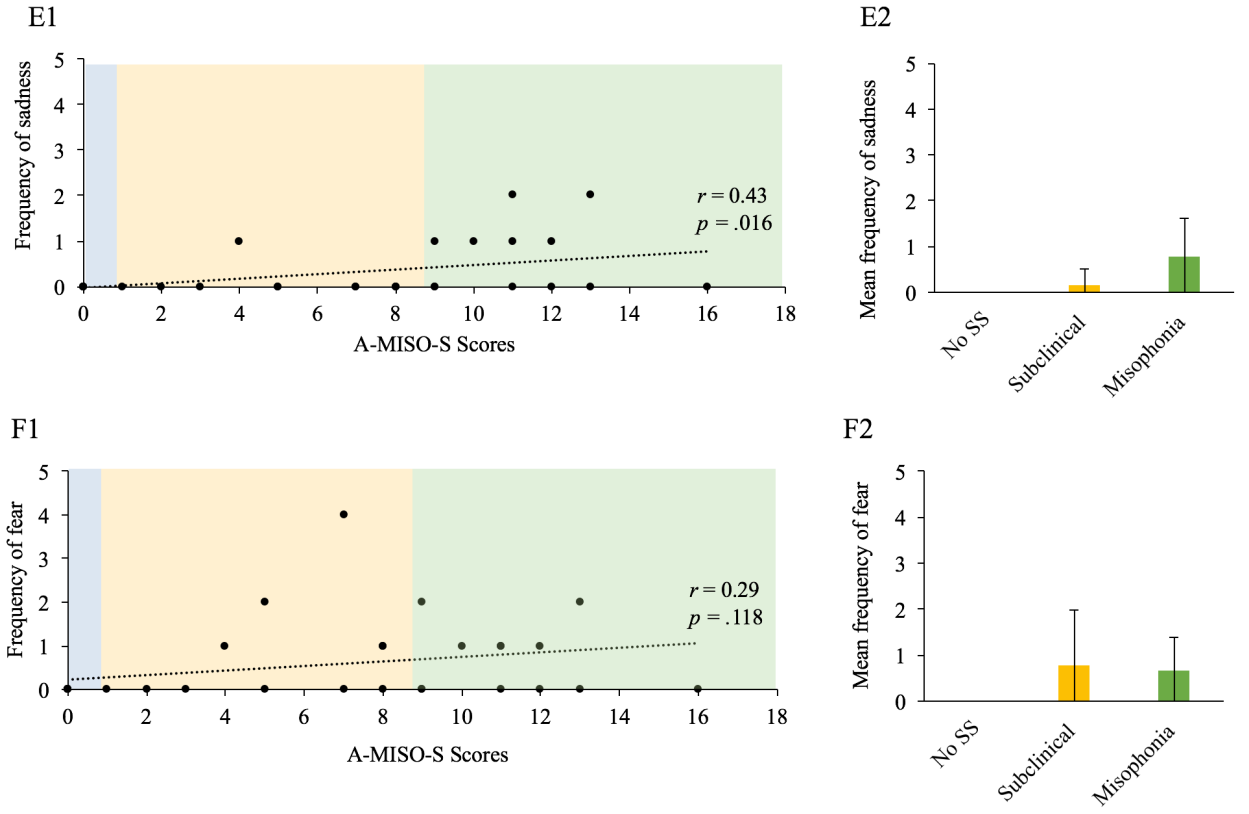


Figure 5. (A1-F1) Correlation between A-MISO-S score and frequency of disgust, anxiety, anger, irritation, sadness and fear, respectively. (A2-F2) Mean frequency of emotional experience between conditions for disgust, anxiety, anger, irritation, sadness and fear respectively. *Note.* * $p = .05$, ** $p = .01$.

Correlations Between A-MISO-S Scores and Emotions

Pearson correlation analysis was conducted between A-MISO-S scores (misophonia severity) and mean frequency of emotional experience scores for disgust, anxiety, anger, irritation, sadness and fear (see Figure 5). There were significant positive correlations between A-MISO-S scores and frequency of disgust ($r = 0.81$, $p < .001$), anxiety ($r = 0.81$, $p < .001$), anger ($r = 0.78$, $p < .001$), irritation ($r = 0.74$, $p < .001$) and sadness ($r = 0.43$, $p = .016$), and no significant correlation between A-MISO-S scores and frequency of fear ($r = 0.29$, $p < .118$). These results are in line with the categorical analysis that was conducted with participants divided into groups for all emotions besides sadness. Results of the categorical analysis found no

significant differences between groups on the mean frequency of sadness, but a significant correlation exists between individual A-MISO-S scores and frequency of sadness. It is likely that no significant differences were found with the categorical analysis because the correlation between A-MISO-S scores and frequency of sadness was only moderate, whereas correlations for disgust, anger, anxiety and irritation were strong. The present study having found no significant differences between groups and frequency of sadness would be in line with previous literature as sadness is not one of the hallmark emotions associated with misophonia, while disgust, anger, and anxiety are.

Imaging Results

Data using fMRI was collected for four participants, two of which were from the No SS group, one from the Subclinical SS group and one from the Misophonia group (Table 2). First-level statistical analysis of each participant's functional data was carried out using FEAT (FMRI Expert Analysis Tool) Version 6.00, part of a toolbox available in FSL (FMRIB's Software Library). Registration to high resolution structural and/or standard space images was carried out using FLIRT (Jenkinson 2001, 2002). Registration from high resolution structural to standard space was then further refined using FNIRT nonlinear registration (Andersson 2007a, 2007b).

The following pre-statistics processing was applied: motion correction using MCFLIRT (Jenkinson 2002), slice-timing correction using Fourier-space time-series phase-shifting, non-brain removal using BET (Smith 2002), spatial smoothing using a Gaussian kernel of FWHM 5mm, grand-mean intensity normalization of the entire 4D dataset by a single multiplicative factor, high pass temporal filtering (Gaussian-weighted least-squares straight line fitting with sigma = 45.0s). Time-series statistical analysis was carried out using FILM with local autocorrelation correction (Woolrich 2001).

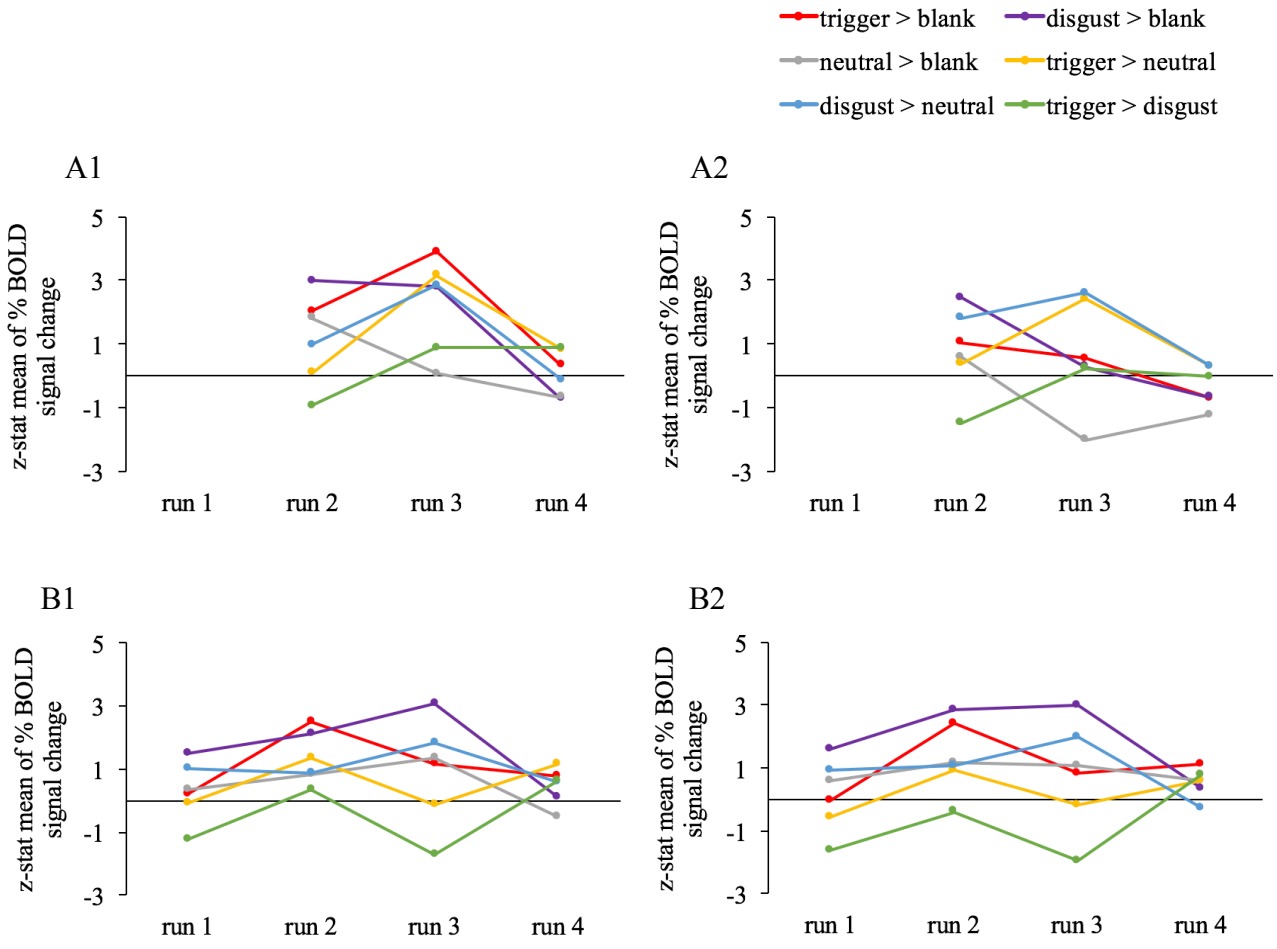
FEATquery (FMRIB toolbox in FSL) was used to extract mean z-statistics for neural activity differences (percent of BOLD signal change) for each contrast outlined in the methods section. Data from participant one, run one, was excluded from analysis due to inadequate sound during stimuli presentation. Activity differences were plotted across the four experimental runs for each participant (see Figure 6). Participants displayed some variability in activity across the four runs so an average of the mean z-statistic scores was taken (see Figure 7). Scores from the two participants with no SS were combined to allow for easier comparison between the three groups. No statistical tests to determine significance of results were conducted on the fMRI data due to the small sample size used in the imaging portion of this study. However, through visual examination three main patterns emerge.

Left and Right AIC. Through visual examination there appear to be differences in activity between the left and right AIC (see Figure 7). After averaging activity across the four runs, participants in the misophonia condition and no SS condition demonstrated greater activity in the left AIC in response to the misophonia trigger condition when compared to the neutral condition (see Figure 7).

Trigger, Neutral and Blank Contrasts. The participant in the misophonia group showed greater activity in the AIC in response to the misophonia trigger condition, compared to the neutral condition and blank condition (fixation cross) (Figure 7). This increased activity was more apparent in the left AIC than the right AIC. Unexpectedly, participants in the no SS group also demonstrated greater activity in the AIC in response to the misophonia trigger condition, compared to the neutral condition and blank condition (see Figure 7). In contrast, participants in the subclinical SS group showed activity that was quite different from both the misophonia group and no SS group. The activity elicited in response to the misophonia trigger condition was often

lower than the activity elicited in response to the neutral sound condition and blank condition (see Figure 7).

Trigger and Disgust Contrasts. Activity was relatively equal between the three groups in response to the misophonia trigger condition compared to the disgust-evoking condition (see Figure 7). Generally, the contrasts between the misophonia trigger condition and the disgust-evoking condition were smaller than the contrasts between the misophonia trigger condition and the neutral condition (see Figure 7).



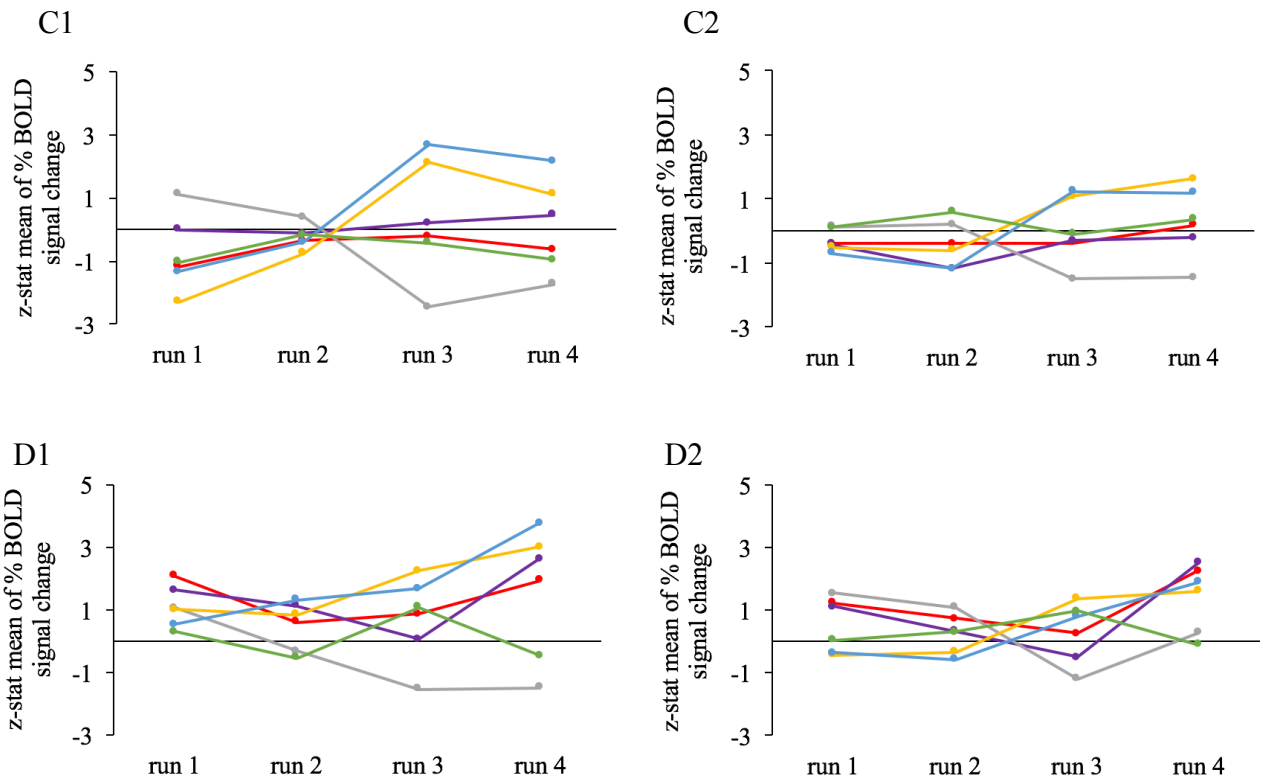


Figure 6. AIC elicited BOLD activity in response to different experimental stimuli (A1 and A2) Participant with no SS in the left AIC and right AIC, respectively. (B1 and B2) Participant with no SS in the left AIC and right AIC, respectively. (C1 and C2) Participant with subclinical SS in the left AIC and right AIC, respectively. (D1 and D2) Participant with misophonia in the left AIC and right AIC, respectively.

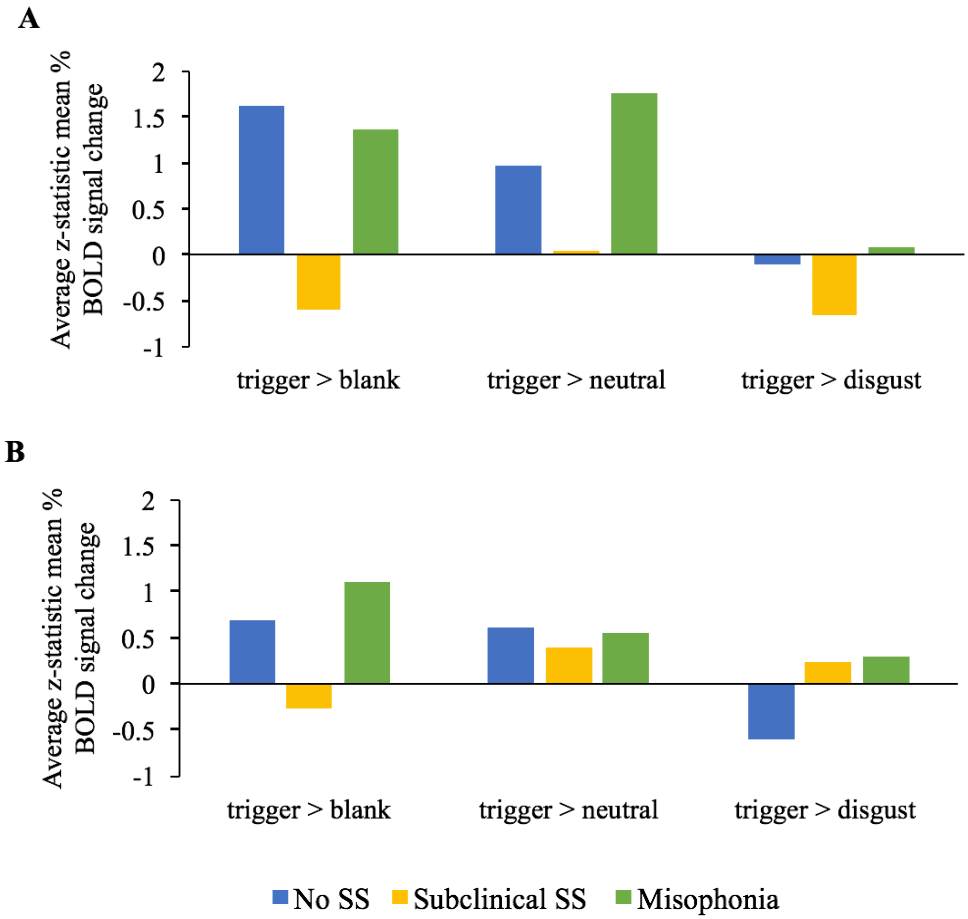


Figure 7. Average change in AIC activity according to experimental contrast. (A) Left AIC. (B) Right AIC.

Statistical maps were generated for one participant with misophonia and one participant with no SS (Figure 8). These maps highlight the AIC as the RIO and show the activity change contrasts between the misophonia trigger condition and the neutral condition during a single run. The participant with misophonia exhibited increased activity in the AIC in comparison to the participant with no SS. The participant with misophonia also shows increased activity in the left AIC (RIO highlighted in yellow) in comparison to the right AIC (RIO highlighted in green).

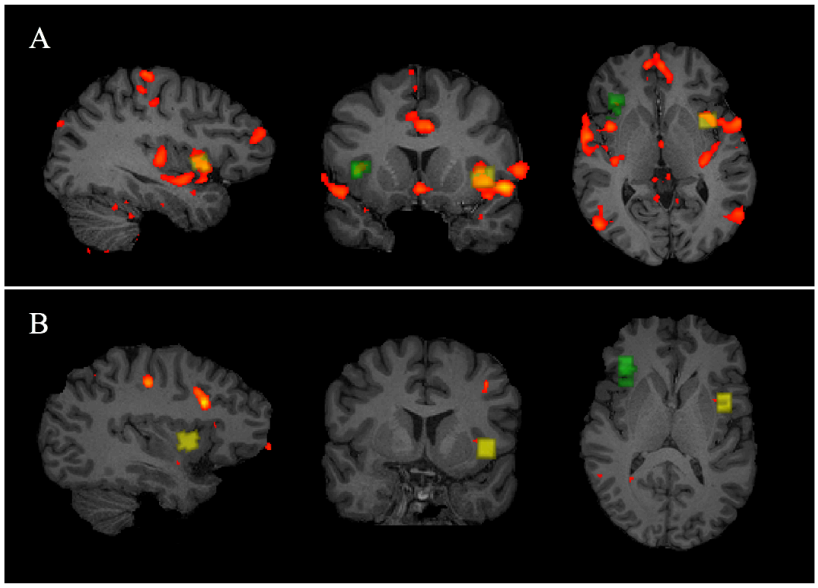


Figure 8. Statistical maps displaying BOLD activity in the AIC for the trigger > neutral contrast. (A) Participant with misophonia (B) Participant with no SS. *Note.* Yellow = left AIC; Green = right AIC; (Gaussianised T/F) statistic images were thresholded using GRF-theory-based maximum height thresholding with a (corrected) significance threshold of $p = 0.05$ (Worsley, 2001).

Discussion

Misophonia is a chronic neuropsychological condition which causes clinical level symptoms leading to significant impairment in daily functioning. Some of the previous research on misophonia has used samples of young adults to study the clinical characteristics and prevalence of the condition. While other research has used clinical misophonia patients to study the neural correlates of misophonia. More specifically, this study was interested in how brain activity differs in people with varying levels of misophonia severity, with the AIC being the region of interest for a variety of reasons. First, the AIC has been shown in past studies to exhibit increased activity in response to a misophonia trigger in participants with misophonia when compared to controls (Kumar et al. 2017; Schröder et al., 2019). Furthermore, the AIC is also a key node of the salience network (Uddin, 2015), playing a role in directing attention towards

relevant stimuli in the environment. Lastly, the AIC has also been shown to have a role in the experience of disgust (Gu et al., 2013; Jabbi, Bastiaansen, & Keysers, 2008), which is a common emotion experienced by people with misophonia. It was predicted that individuals with the most severe misophonia symptoms would have the highest BOLD activity present in the AIC in response to a misophonia trigger stimuli.

Primary and Secondary Triggers

Secondary misophonia triggers were defined as sounds that were bothersome, while primary misophonia triggers were defined as sounds that were 'very' or 'extremely' bothersome. People in the misophonia group reported on average having significantly more primary misophonia triggers than both the subclinical SS and no SS groups. This is a novel finding in the misophonia literature and it has important implications relevant to the level of impairment individuals with misophonia face on a regular basis. It suggests that in addition to having a heightened sensitivity to sounds, individuals with misophonia are sensitive to a larger number of sounds and that these sounds are significantly bothersome. Having more primary misophonia triggers makes it more likely that an individual with misophonia will come across one of these triggers on any given day, making impairment as a result of misophonia more likely to occur in addition to already being more severe.

The Emotional Reaction and Misophonia

Misophonia elicits intense emotional reactions that most commonly take on the form of anger, disgust, anxiety and impulsivity (Cavanna & Seri, 2015; Schröder et al., 2013), although the emotional response can differ across people. Not all people with misophonia experience the same emotional reaction. For some individuals' anger might make up the primary emotional experience, while for others it might be anxiety. It was found that individuals in the misophonia

group experienced significantly more frequent disgust, anger and anxiety in response to trigger sounds than both the subclinical SS and no SS groups. It was further found that individuals in the misophonia group did not experience significantly more frequent irritation than the subclinical SS group. These findings replicate previous research which has found disgust, anger and anxiety to be at the forefront of the misophonic reaction. Although individuals with subclinical SS experience irritation when hearing a particular sound, they do not become overwhelmed by the same level of functional impairment that an individual with misophonia would experience. The main point here is that symptoms of subclinical SS differ from symptoms of misophonia in terms of the impairment they cause. Misophonia symptoms cause severe emotional and physiological symptoms to emerge in addition to irritation causing a great deal of impairment. Not only do misophonia symptoms cause increased impairment, but this impairment is also more likely to occur as individuals with misophonia have more primary misophonia triggers. This means that when engaging in customary tasks like going to school or work and even socializing, an individual with misophonia is much more likely to hear one of their trigger sounds and experience a severe reaction. The increased number of primary misophonia triggers combined with the heightened severity of symptoms, causes simple tasks to become unbearable for individuals with misophonia. Presence of significant impairment in daily functioning is a key factor distinguishing individuals with misophonia from individuals with subclinical SS. These results suggest that clinical-level differences exist between misophonia and subclinical sound SS, opening up for the possibility that these differences are further rooted in neurological differences.

Misophonia and Subclinical Sound Sensitivities

The participant with misophonia showed heightened AIC activity in response to their specific trigger sound in the misophonia trigger condition and this activity was greater than the

activity elicited in response to the neutral condition and the blank condition. What was unexpected was that participants in the no SS group exhibited very similar activity patterns in response to the misophonia trigger condition as the participant in the misophonia group. When considering the participant with misophonia alone, these results replicate those found in previous literature, showing that individuals with misophonia experience greater AIC activity in response to a trigger sound. However, when comparing the activity elicited in response to a trigger sound between conditions, these findings do not appear to replicate results of previous literature. The current study found participants in the no SS group to have similar activity levels as the participant in the misophonia group, while previous studies have shown that individuals with misophonia exhibit increased activity in comparison to controls when hearing a trigger sound (Kumar et al., 2017; Schröder et al., 2019). It is possible that as this part of the study was a case study, differences between groups did not have a chance to fully emerge.

This was the first study to incorporate a group with subclinical SS. The participant in the subclinical SS group displayed lower activity in response to a trigger sound when compared to the participant in the misophonia condition and the participants in the no SS condition. If these lower levels of AIC activity emerge again in a larger sample, then these results would suggest that subclinical SS are not defined by heightened AIC activity but rather heightened activity in other brain regions. Some brain regions that have been found to contribute to the misophonic reaction are the posterior cingulate cortex, superior temporal cortex, hippocampus and amygdala (Kumar et al., 2017; Schröder et al., 2019), which might be displaying heightened activity in comparison to the AIC in individuals with subclinical SS. Additionally, the AIC is a key node of the salience network making it responsible for orienting attention towards salient stimuli in the environment. In this case, decreased AIC activity would suggest that for people with subclinical

SS, misophonia triggers are not particularly salient, resulting in a less specific sensitivity no sounds. Whereas individuals with misophonia are sensitive to very specific sounds and experience extreme difficulty diverting attention away from the sound once it has been brought into focus. It is also possible that sensitivity to certain sounds in people with subclinical SS is a result of something more than simply AIC activity. People with subclinical SS may have a more variable sensitivity for which contextual or personal factors play a greater role in determining the severity of the reaction at a given time. For example, an individual with subclinical SS may experience a heightened sensitivity to certain sounds when they are experiencing a depletion in cognitive resources, like being overly tired or hungry. These depleted cognitive resources might make them temporarily more sensitive to sounds. This would be supported by the finding that irritation was a common emotional response in people with subclinical SS, providing an overlap with irritation also being experienced as a result of cognitive resource depletion.

Misophonia and Disgust

Knowing that the AIC plays a role in the experience of disgust, this study was interested in how activity elicited in response to the misophonia trigger condition compared to activity elicited in response to the disgust-evoking condition. The participant with misophonia displayed similar levels of activity when responding to the misophonia trigger condition and the disgust-evoking condition. This suggests that misophonia trigger stimuli and disgust-evoking stimuli elicited a similar reaction in the participant with misophonia. However, it remains unclear how much of the activity in the AIC is attributable to the experience of disgust. Given that differences exist in the experience of disgust between the subclinical SS group and the misophonia group, it is expected that these differences have a neurological basis. Everyone experiences disgust but not everyone experiences misophonia. Even if misophonia is primarily a disgust reaction, there still

exist differences in how people with misophonia experience disgust compared to people with no SS. Individuals with misophonia experience intense disgust towards a sound that individuals with no SS would consider to be neutral or not disgusting. Additionally, people with misophonia experience increased physiological symptoms similar to a fight-or-flight reaction in response to hearing this sound. They might feel an overwhelming urge to escape the sound, cover it up, or make it stop, while people with no SS do not experience these same aversive reactions when they experience disgust. A more detailed analysis on the nature of this relationship is needed to conclude how disgust is experienced differently in individuals with misophonia and individuals with no SS.

Left and Right AIC

Previous literature does not agree on whether the left or right AIC are particularly more active when a trigger sound is presented. Kumar et al. (2017) found fairly similar levels of activation between the left AIC and the right AIC; whereas Schröder et al. (2019) found greater activity in the right AIC than the left AIC. The results from the present study do not appear to replicate either of these previous findings; as it was the left AIC that appeared to show greater activity than the right AIC when the participant in the misophonia condition was presented with a trigger sound. More research is needed in order to disentangle these activity differences between the left and right AIC in individuals with misophonia.

Limitations and Future Directions

Overall the results from this study are only somewhat in line with the previous literature, but not entirely. The biggest limitation of this study is the small sample size that was used in the imaging portion of the study. More participants are needed before conclusions can be made about how activity in the AIC differs with varying levels of misophonia severity.

A secondary limitation was that each of the participants used in the imaging portion of the study had a lower A-MISO-S score, and therefore a lower severity of sound sensitivity within their respective groups. This is likely to have the strongest impact on the results from the imaging analysis as differences between the groups may have been missed as a result of not being significant enough on their own. Through increasing the sample size, we would achieve a greater variation of A-MISO-S scores in the subclinical SS and misophonia groups allowing these samples to become more representative of these groups.

An additional limitation was that the present study used self-report questionnaires that were administered through an online survey to determine if participants had clinically significant symptoms of misophonia or not. The previous studies which used fMRI to investigate misophonia conducted thorough in-person interviews to see if participants had misophonia. The self-report questionnaires may have been less reliable in comparison to conducting in-person interviews with a trained professional. This may have inflated the rate of participants in the misophonia group, as participants were essentially providing a self-diagnosis of their misophonia severity. However, given that no official clinical diagnostic criteria currently exists for misophonia, the self-report questionnaires were the next best available tool and have shown to be fairly reliable in their ability to measure misophonia severity.

One final limitation that will be mentioned is how the experience of a misophonia trigger sounds in the lab might be different from the experience of these sounds in an uncontrolled environment. For example, participants were presented with pre-recorded audiovisual stimuli which are not the same as a real person making the sound. Additionally, the MRI environment being noisy and limiting movement may have caused additional irritation for participants. Overall, the experience of a misophonia trigger in the experiment is not entirely same as the

experience of a misophonic trigger out in the real world, an issue that provides some potential challenges towards ecological validity.

A notable future direction for this study would be to include a comparison between self-report ratings of disgust and the activity contrasts of the misophonia trigger condition against the disgust-evoking condition. This would allow more insight into the nature of the relationship between misophonia and disgust. As for example, one participant might report disgust being their primary emotional response when hearing a trigger sound, while another participant might report anger as their primary emotional response. These two participants might differ in the amount activity elicited in the AIC in response to the disgust-evoking condition. This would mean that the activity contrasts between the misophonia trigger condition and the disgust-evoking condition would also differ between these two participants. However, this difference would not account for how much of the activity in the AIC can be attributed to the experience of disgust in some participants over others. Looking more closely at the differences in disgust elicited in response to the misophonia trigger condition and disgust-evoking condition would allow for a more detailed understanding of the relationship between misophonia and disgust.

The current study was able to contribute to the present literature around misophonia by beginning to shed more light onto how misophonia differs at varying levels of severity. Although the imaging portion of this study was a case study consisting of only four participants, patterns emerged regarding activity differences in the AIC in people with varying levels of misophonia severity. This study found results that suggest clinical-level differences exist between misophonia and subclinical sound sensitivities, but would further benefit from implementing a larger sample size so that conclusions can be made about whether or not differences in clinical-level symptoms of misophonia are also rooted in differences in anterior insular cortex activity.

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Appendix A

Western University's Health Science Research Ethics Board Ethics Approval Letter

Western Research

Date: 25 November 2019

To: Dr. Blake Butler

Project ID: 114700

Study Title: Imaging Neural Structure and Function in Individuals with Specific Sound Sensitivities (Misophonia)

Application Type: HSREB Initial Application

Review Type: Delegated

Meeting Date / Full Board Reporting Date: 03/Dec/2019

Date Approval Issued: 25/Nov/2019

REB Approval Expiry Date: 25/Nov/2020

Appendix B

Still Images of Audiovisual Stimuli Presented During Experimental Session

Common Misophonia Trigger	Disgust-evoking	Neutral
 Actor eating chips	 Actor belching	 Background conversation
 Actor typing	 Actor blowing nose	 Actor painting

Appendix C

Online Survey

Checking the box below indicates that you have read the letter of information, have had the nature of the study explained to you, and agree to take part in the study. You acknowledge that you can leave the study at any time.

○ Yes, I have read the above description and agree to participate

Section 1 of 6: Inclusion/Exclusion

Q1. Do you have any auditory impairments? (Do not consider your sound sensitivity when answering this question).
- □ No
- □ Yes

Q2. Do you have normal or corrected to normal vision?
- □ No
- □ Yes

Q3. Do you suffer from claustrophobia or intense fear in tight spaces?
- □ No
- □ Yes

Q4. Do you have a cardiac pacemaker?
- □ No
- □ Yes

Q5. Do you have any metal implants in your body?
- □ No
- □ Yes

If inclusion criteria are not met: Debriefing Statement will be presented and study will end.

Thank your interest in this study.

However, your answers to the previous questions indicate that you are not eligible to participate in the imaging experiment. Please view the debriefing statement below.

Section 2 of 6: Demographics

Q6. What is your first name? Please use the textbox below to answer.

_____

Q7. What gender do you identify with?
- Male
- Female
- Transgender
- Non-binary
- Other _____

Q8. What is your full date of birth?
Month _____
Day _____
Year _____

Q9. What is your race/ethnicity? Select all that apply.
- Black/African American
- Native/Indigenous
- Asian/Pacific Islander
- Latin/ Hispanic
- Middle Eastern
- White/Caucasian
- South Asian
- Other _____

Q10. What is the highest level of education you have obtained?
- Less than high school
- High school
- Some college/university
- College/university graduate
- Some post-graduate studies
- Completed post-graduate studies

Q11. Have you previously received treatment for any mental health problems?
- No
- Yes

Q11.1 Please specify the treatments you have used in the past. Select all that apply.
- Talk therapy
- Cognitive behavioural therapy
- Mindfulness
- Medication
- Herbal remedies
- Meditation/yoga
- Other _____

Q12. What is your phone number? Please use the textbox below to answer.
_____

Section 3 of 6: Misophonia Symptoms

Q13. Please rate how much the following statements describe you on a scale from **0-4**.

0 = Not at all True
1 = Rarely True
2 = Sometimes True
3 = Often True
4 = Always True

In comparison to other people, I am sensitive to the sound of:

	0	**1**	**2**	**3**	**4**
People eating (e.g. crunching, lip smacking, jaw clicking)	○	○	○	○	○
People drinking (e.g. slurping, gulping, swallowing)	○	○	○	○	○
Table-related noises (e.g. fork scraping plate, glasses clinking)	○	○	○	○	○
Gum chewing/gum popping	○	○	○	○	○
Pen clicking	○	○	○	○	○
Typing on a keyboard	○	○	○	○	○
Repetitive foot or finger tapping	○	○	○	○	○
Rustling (e.g. opening plastic wrappers, crinkling garbage)	○	○	○	○	○
Breathing (e.g. people snoring, inhaling and exhaling heavily)	○	○	○	○	○
People sniffling	○	○	○	○	○
Throat-related noises (e.g. coughing, throat clearing)	○	○	○	○	○

People yelling/screaming	○	○	○	○	○
Baby crying	○	○	○	○	○
Animal related noises (e.g. barking, meowing, whimpering)	○	○	○	○	○
Home equipment (e.g. refrigerator humming, clock ticking)	○	○	○	○	○
Nail clipping or biting	○	○	○	○	○
Singing, whistling, humming	○	○	○	○	○
Other (use the text box to list any sounds you are sensitive to that are not listed above)	○	○	○	○	○

*Q13.1. When I hear the sound of people eating I am

- **Not bothered** much more than most people
- **A little bothered** - I experience some discomfort, but I can easily distract myself and divert my thoughts away
- **Bothered** - I experience a good deal of discomfort and have difficulty diverting my thoughts away, but I can tolerate it without taking action
- **Very bothered** - I feel very uncomfortable and experience a need to escape the sound (e.g. by using ear plugs/headphones or leaving the room)
- **Extremely bothered** - I feel extremely uncomfortable, angry, and experience a need to become aggressive/violent

*Q13.2. When I hear the sound of people drinking I am:

- **Not bothered** much more than most people
- **A little bothered** - I experience some discomfort, but I can easily distract myself and divert my thoughts away
- **Bothered** - I experience a good deal of discomfort and have difficulty diverting my thoughts away, but I can tolerate it without taking action
- **Very bothered** - I feel very uncomfortable and experience a need to escape the sound (e.g. by using ear plugs/headphones or leaving the room)
- **Extremely bothered** - I feel extremely uncomfortable, angry, and experience a need to become aggressive/violent

*Q13.3. When I hear table-related noises I am:

- **Not bothered** much more than most people
- **A little bothered** - I experience some discomfort, but I can easily distract myself and divert my thoughts away
- **Bothered** - I experience a good deal of discomfort and have difficulty diverting my thoughts away, but I can tolerate it without taking action
- **Very bothered** - I feel very uncomfortable and experience a need to escape the sound (e.g. by using ear plugs/headphones or leaving the room)
- **Extremely bothered** - I feel extremely uncomfortable, angry, and experience a need to become aggressive/violent

*Q13.4. When I hear the sound of gum chewing/popping gum I am:

- **Not bothered** much more than most people
- **A little bothered** - I experience some discomfort, but I can easily distract myself and divert my thoughts away
- **Bothered** - I experience a good deal of discomfort and have difficulty diverting my thoughts away, but I can tolerate it without taking action
- **Very bothered** - I feel very uncomfortable and experience a need to escape the sound (e.g. by using ear plugs/headphones or leaving the room)
- **Extremely bothered** - I feel extremely uncomfortable, angry, and experience a need to become aggressive/violent

*Q13.5. When I hear the sound of pen clicking I am:

- **Not bothered** much more than most people
- **A little bothered** - I experience some discomfort, but I can easily distract myself and divert my thoughts away
- **Bothered** - I experience a good deal of discomfort and have difficulty diverting my thoughts away, but I can tolerate it without taking action
- **Very bothered** - I feel very uncomfortable and experience a need to escape the sound (e.g. by using ear plugs/headphones or leaving the room)
- **Extremely bothered** - I feel extremely uncomfortable, angry, and experience a need to become aggressive/violent

*Q13.6. When I hear the sound of typing on a keyboard I am:

- **Not bothered** much more than most people
- **A little bothered** - I experience some discomfort, but I can easily distract myself and divert my thoughts away
- **Bothered** - I experience a good deal of discomfort and have difficulty diverting my thoughts away, but I can tolerate it without taking action
- **Very bothered** - I feel very uncomfortable and experience a need to escape the sound (e.g. by using ear plugs/headphones or leaving the room)
- **Extremely bothered** - I feel extremely uncomfortable, angry, and experience a need to become aggressive/violent

*Q13.7. When I hear the sound of repetitive foot or finger tapping I am:

- **Not bothered** much more than most people
- **A little bothered** - I experience some discomfort, but I can easily distract myself and divert my thoughts away
- **Bothered** - I experience a good deal of discomfort and have difficulty diverting my thoughts away, but I can tolerate it without taking action
- **Very bothered** - I feel very uncomfortable and experience a need to escape the sound (e.g. by using ear plugs/headphones or leaving the room)
- **Extremely bothered** - I feel extremely uncomfortable, angry, and experience a need to become aggressive/violent

*Q13.8. When I hear the sound of rustling I am:

- **Not bothered** much more than most people
- **A little bothered** - I experience some discomfort, but I can easily distract myself and divert my thoughts away
- **Bothered** - I experience a good deal of discomfort and have difficulty diverting my thoughts away, but I can tolerate it without taking action
- **Very bothered** - I feel very uncomfortable and experience a need to escape the sound (e.g. by using ear plugs/headphones or leaving the room)
- **Extremely bothered** - I feel extremely uncomfortable, angry, and experience a need to become aggressive/violent

*Q13.9. When I hear the sound of people breathing I am:

- **Not bothered** much more than most people
- **A little bothered** - I experience some discomfort, but I can easily distract myself and divert my thoughts away
- **Bothered** - I experience a good deal of discomfort and have difficulty diverting my thoughts away, but I can tolerate it without taking action
- **Very bothered** - I feel very uncomfortable and experience a need to escape the sound (e.g. by using ear plugs/headphones or leaving the room)
- **Extremely bothered** - I feel extremely uncomfortable, angry, and experience a need to become aggressive/violent

*Q13.10. When I hear the sound of people sniffling I am:

- **Not bothered** much more than most people
- **A little bothered** - I experience some discomfort, but I can easily distract myself and divert my thoughts away
- **Bothered** - I experience a good deal of discomfort and have difficulty diverting my thoughts away, but I can tolerate it without taking action
- **Very bothered** - I feel very uncomfortable and experience a need to escape the sound (e.g. by using ear plugs/headphones or leaving the room)
- **Extremely bothered** - I feel extremely uncomfortable, angry, and experience a need to become aggressive/violent

*Q13.11. When I hear throat related noises I am:

- **Not bothered** much more than most people
- **A little bothered** - I experience some discomfort, but I can easily distract myself and divert my thoughts away
- **Bothered** - I experience a good deal of discomfort and have difficulty diverting my thoughts away, but I can tolerate it without taking action
- **Very bothered** - I feel very uncomfortable and experience a need to escape the sound (e.g. by using ear plugs/headphones or leaving the room)
- **Extremely bothered** - I feel extremely uncomfortable, angry, and experience a need to become aggressive/violent

*Q13.12. When I hear the sound of people yelling/screaming I am:

- **Not bothered** much more than most people
- **A little bothered** - I experience some discomfort, but I can easily distract myself and divert my thoughts away
- **Bothered** - I experience a good deal of discomfort and have difficulty diverting my thoughts away, but I can tolerate it without taking action
- **Very bothered** - I feel very uncomfortable and experience a need to escape the sound (e.g. by using ear plugs/headphones or leaving the room)
- **Extremely bothered** - I feel extremely uncomfortable, angry, and experience a need to become aggressive/violent

*Q13.13. When I hear the sound of a baby crying I am:

- **Not bothered** much more than most people
- **A little bothered** - I experience some discomfort, but I can easily distract myself and divert my thoughts away
- **Bothered** - I experience a good deal of discomfort and have difficulty diverting my thoughts away, but I can tolerate it without taking action
- **Very bothered** - I feel very uncomfortable and experience a need to escape the sound (e.g. by using ear plugs/headphones or leaving the room)
- **Extremely bothered** - I feel extremely uncomfortable, angry, and experience a need to become aggressive/violent

*Q13.14. When I hear animal related noises I am:

- **Not bothered** much more than most people
- **A little bothered** - I experience some discomfort, but I can easily distract myself and divert my thoughts away
- **Bothered** - I experience a good deal of discomfort and have difficulty diverting my thoughts away, but I can tolerate it without taking action
- **Very bothered** - I feel very uncomfortable and experience a need to escape the sound (e.g. by using ear plugs/headphones or leaving the room)
- **Extremely bothered** - I feel extremely uncomfortable, angry, and experience a need to become aggressive/violent

*Q13.15. When I hear the sound of home equipment (e.g. refrigerator humming or clock ticking) I am:

- **Not bothered** much more than most people
- **A little bothered** - I experience some discomfort, but I can easily distract myself and divert my thoughts away
- **Bothered** - I experience a good deal of discomfort and have difficulty diverting my thoughts away, but I can tolerate it without taking action
- **Very bothered** - I feel very uncomfortable and experience a need to escape the sound (e.g. by using ear plugs/headphones or leaving the room)
- **Extremely bothered** - I feel extremely uncomfortable, angry, and experience a need to become aggressive/violent

*Q13.16. When I hear the sound of nail clipping or biting I am:

- **Not bothered** much more than most people
- **A little bothered** - I experience some discomfort, but I can easily distract myself and divert my thoughts away
- **Bothered** - I experience a good deal of discomfort and have difficulty diverting my thoughts away, but I can tolerate it without taking action
- **Very bothered** - I feel very uncomfortable and experience a need to escape the sound (e.g. by using ear plugs/headphones or leaving the room)

- **Extremely bothered** - I feel extremely uncomfortable, angry, and experience a need to become aggressive/violent

*Q13.17. When I hear the sound of singing, whistling, or humming I am:

- **Not bothered** much more than most people
- **A little bothered** - I experience some discomfort, but I can easily distract myself and divert my thoughts away
- **Bothered** - I experience a good deal of discomfort and have difficulty diverting my thoughts away, but I can tolerate it without taking action
- **Very bothered** - I feel very uncomfortable and experience a need to escape the sound (e.g. by using ear plugs/headphones or leaving the room)
- **Extremely bothered** - I feel extremely uncomfortable, angry, and experience a need to become aggressive/violent

*Q13.18. When you hear the other sounds you described as being sensitive to (that were not listed in question 12), you feel:

- **Not bothered** much more than most people
- **A little bothered** - I experience some discomfort, but I can easily distract myself and divert my thoughts away
- **Bothered** - I experience a good deal of discomfort and have difficulty diverting my thoughts away, but I can tolerate it without taking action
- **Very bothered** - I feel very uncomfortable and experience a need to escape the sound (e.g. by using ear plugs/headphones or leaving the room)
- **Extremely bothered** - I feel extremely uncomfortable, angry, and experience a need to become aggressive/violent

	0 Never	1 Rarely	2 Sometimes	3 Often	4 Always
Disgusted	○	○	○	○	○
Anxious or distressed	○	○	○	○	○
Angry	○	○	○	○	○
Annoyed or irritated	○	○	○	○	○
Sad	○	○	○	○	○
Fearful	○	○	○	○	○

**Q14. Once you are aware of the sound(s) you are sensitive to, because of the sound(s) how often do you become:

Note: * indicates items that will only be seen by participants if any of the corresponding items from question 12 were rated at a level of three or four (i.e. participant rates having a sensitivity to drinking sounds at three or four, they will be presented with question 12.2, asking specifically about their sensitivity to drinking sounds). ** indicates items that will only be seen by participants if at least one of the 18 items from question 12 were rated at a three or a four.

Section 4 of 6: Misophonia Severity 1

Q15-20. Amsterdam Misophonia Scale (A-MISO-S) (Schröder, Vulink, & Denys, 2013).

Section 5 of 6: Misophonia Severity 1

Q21. MQ Symptom Severity Scale (Wu et al., 2014).

Section 6 of 6: Visual Symptoms

Q22. In comparison to other people, are you sensitive to repetitive visual stimuli? (For example: jaw movements, leg jiggling, pen tapping, nail biting)

- Not at all
- Rarely
- Sometimes
- Often
- Always

Q23. When I see these types of repetitive visual stimuli I am:

- **Not bothered** more than most people
- **A little bothered** - I experience some discomfort, but I can easily distract myself and divert my thoughts away
- **Bothered** - I experience a good deal of discomfort and have difficulty diverting my thoughts, but I can tolerate it without taking action
- **Very bothered** - I feel very uncomfortable and experience a need to escape it (e.g. by leaving the room)
- **Extremely bothered** - I feel extremely uncomfortable, angry, and experience a need to become aggressive/violent

End Message

Thank you for completing this survey.

We will contact you within 3 business days to schedule your experimental session.

Appendix D

Letter of Information and Consent Form

Project Title: Imaging Neural Structure and Function in Individuals with Specific Sound Sensitivities

Principal Investigator: Blake Butler, Ph.D.,
Department of Psychology | Brain and Mind Institute
The University of Western Ontario, WIRB 5150
(519) 661-2111 extension 85831
Email: bbutler9@uwo.ca

Introduction: Why are you here.
Dr. Blake Butler and his research team would like to invite you to participate in a study titled: "Imaging Neural Structure and Function in Individuals with Specific Sound Sensitivities". You are being invited to participate in this study because you are either a) an individual reporting sensitivities to particular sounds, or b) an individual reporting no such sensitivity. This study is voluntary, and participation involves completing an online survey and attending an experimental session on campus at Western University.

Background: What is the purpose of this study?
Dr. Butler and his team want to understand how the structure and function of the brain may differ between people who report sensitivities to particular sounds (sometimes referred to as misophonia) from those who report no such sensitivity. Previous findings suggest that misophonic stimuli evoke additional neural activity in regions of the brain commonly associated with emotions.

This study aims to investigate how the extent to which these differing brain response reflect differences in structural and functional connectivity between brain regions that normally process sound and those that regulate emotion. It is anticipated that 60-75 participants will be enrolled.

Participate – If you want to take part in the study, you will first be asked to complete an online survey that will confirm your eligibility to participate in this study; in order to be eligible, you must be between 18 and 30 years old, have normal hearing and normal/corrected to normal vision, and be able to safely take part in an fMRI experiment. If you are eligible to continue, the survey will also collect basic demographic data, and will ask a series of questions about your perceptions of sensory stimuli and the degree to which you feel particular emotions. Upon completing the survey, a member of the research team will contact you within 3 business days to schedule a subsequent visit to the lab.

During this visit, you hearing will be assessed and you will have an opportunity to review this document. You will then participate in a MRI brain imaging session, during which you will be presented with audiovisual stimuli (e.g. video of a person speaking, chewing, whistling, or singing) while lying in a research-dedicated 7 Tesla MRI scanner (for reference, clinical MRI scanners typically have a field strength of 1.5-3 Tesla). This part of the study will take place at the Robarts Research Institute at Western. You will be asked to lie comfortably within the scanner, remaining as still as possible, and to attend to the stimuli. During their presentation, your brain activity will be recorded using Magnetic Resonance imaging, a non-invasive technique that does

not involve injections, x-rays, or radiation. The MRI scanner will also be used to take structural images of your brain; during these scans you will not be required to perform a task.

The scanning session will proceed as follows:

- We will begin by completing a checklist to make sure that you can safely enter an MRI scanner.
- We will insert earplugs to play sounds and to protect your ears from the noise of the magnet.
- You will lie on your back on the scanner bed. Pillows will be placed under your legs for comfort and we will provide a blanket if you like. When ready, the bed will slide into the scanner.
- You will be asked to remain as still as possible while several images are taken, each lasting several minutes. We will place foam around your head to help minimize movement.
- You will be asked to attend to a variety of auditory and visual stimuli, but no response will be required. Periodically, you may be asked to complete a brief survey of your emotional state.
- At some point during the session, additional brain images will be acquired of your brain anatomy. During these scans, you will be asked to lie as still as possible, but will not have to perform any tasks.

Thorough out the whole session, we will ask you to lie as still as possible, and speak to the MR technician from time to time. The total actual scanning will take approximately 60 minutes, while the entire visit may last approximately 1.5-2 hours from the time you arrive until the time you leave.

Voluntary Participation & Withdrawal
Your participation in this study is voluntary. You may elect not to participate at any time, including after the study has begun. You may leave the study at any time without affecting your compensation. If you no longer want to participate, or you do not want your data to be used in this research, you should tell either the experimenter that is with you in the room, or contact Dr. Butler (see contact information at the first page). They will ensure that your data as well as your personal information will be permanently deleted. If the data have already been analyzed as part of a group, it will no longer be possible to withdraw those results. However, your data will not be used future analyses. You can request withdrawal of your data until 7 years from data collection. After that time, it won't be possible to delete your data, as we will no longer know which data are yours.

Risks
This study involves a Magnetic Resonance Imaging (MRI) system, a common medical diagnostic tool that uses a strong magnetic field, a low frequency magnetic field, and a radio frequency field to take images of the brain. There are no known biological risks associated with MR imaging. Some people cannot have an MRI because they have some type of metal in their body. For instance,

if you have a heart pacemaker, artificial heart valves, metal implants such as metal ear implants, bullet pieces, chemotherapy or insulin pumps or any other metal such as metal clips or rings, they cannot have an MRI. During this test, you will lie in a small closed area inside a large magnetic tube. Some people may get scared or anxious in small places (claustrophobic). An MRI may also cause possible anxiety for people due to the loud banging made by the machine and the confined space of the testing area. You will be given either ear plugs or specially designed headphones to help reduce the noise. Finally, some stimuli may elicit an emotional response. You may pause or abort the experiment at any time if you are unable to continue.

Incidental Findings

As indicated above, the current study will involve a hearing-screening test. This is not a clinical measure, and the experimenters are not qualified to make a clinical diagnosis based upon these findings. Should a potential hearing deficit be suspected, you will be referred for audiological assessment by a trained professional.

The MRI scans carried out for this study are performed solely for scientific purposes. The data collected are not optimized to make clinical diagnoses and the research team involved in this experiment is not trained to make medical evaluations. By participating, you agree that the experimenters are not expected to arrive at a clinical interpretation of the data collected.

Nevertheless, there is a small possibility that a potential abnormality might be observed – otherwise known as an incidental finding. If this occurs, you will be notified of the issue by the principal investigator of the study who will assist you with your options for follow-up. Investigators are not responsible for the outcome of medical follow-up or for any incurred costs during medical follow-up. By participating, you agree to the possibility of being informed about a potential incidental finding, according to the above-described procedure. If you do not agree to the potential risk of an incidental finding, you should not participate in this study.

Benefits

There will be no direct benefit to you by participating in this study.

Confidentiality

As part of our data collection, the online survey you are about to complete will ask you to provide your phone number, email address, and full date of birth. These identifying data are securely stored behind a high-end firewall system, and access is restricted to only those on the research team* and will be kept for a minimum of 7 years (for more information regarding Qualtrics survey data security, please visit qualtrics.com/security-statement/). De-identified data from this study will be shared on the Open Science Framework and Open fMRI, which allow other researchers access to the de-identified data indefinitely. The shared data **will not** contain any information that could identify you.

If you choose to withdraw from this study, your data will be removed and destroyed from all databases. If you would like to be contacted about future research studies for which you may be eligible, you can choose to have your identifiable information entered into "OurBrainsCAN: University of Western Ontario's Cognitive Neuroscience Research Registry" by the researchers of this study OR alternatively you can be given the web address of OurBrainsCAN where you are able to enter your (or your child's) information. This is a secure database of potential participants for research at Western University, which aims to enrol 50,000 volunteers over a period of 5 years. The information in this database will be stored indefinitely. The records are

used only for the purpose of recruiting research participants and will not be released to any third party. When you are invited to participate future research studies, you will be given a full description of what your involvement would entail. You are, of course, free to turn down any invitation. If, at any time, you decide that you do not want your contact information to be a part of this database, please contact ourbrains@uwo.ca to remove your information.

*Representatives of the University of Western Ontario Health Sciences Research Ethics Board may look at your study records at the site where these records are held, for quality assurance (to check that the information collected for the study is correct and follows proper laws and guidelines).

Costs & Compensation
You will not have to pay for any part of the study. Free parking will be provided. As a token of our appreciation for your participation in this study, you will receive $5 or 0.5 SONA credits for completing the initial survey and $15 per 30 minutes, or 2.0 SONA credits for completing the imaging experiment.

Rights as a Participant
If you are harmed as a direct result of taking part in this study, all necessary medical treatment will be made available to you at no cost. You do not waive any legal rights by signing the consent form.

Questions about the Study
If you have any questions about the study, please contact:

Blake Butler, PhD
Department of Psychology | Brain and Mind Institute
The University of Western Ontario, WIRB 6126
(519) 661-2111 extension 85831
Email: bbutler9@uwo.ca

If you have any questions about your rights as a research participant or the conduct of this study, you may contact The Office of Research Ethics (519) 661-3036, email: ethics@uwo.ca.

This letter is yours to keep

Consent form

Your signature on this form indicates that you have read the letter of information, have had the nature of the study explained to you, and agree to take part in the study. You acknowledge that you can leave the study at any time.

_____	_____	_____
Print Name of Participant	Signature	Date
_____	_____	_____
Print Name of Person Obtaining Consent	Signature of Person Obtaining Consent	Date

I consent to being added to the OurBrainsCAN: University of Western Ontario's Cognitive Neuroscience Research Registry to be contacted about future research studies for which I may be eligible:

Please initial:

___ Yes, I already signed-up.
___ Yes, the researcher can enter my information into the database on my behalf.
___ Yes, please provide me the link to join the database myself.

Participant's Name (Please print):

Participant's Signature:

Date:

Appendix E

Debriefing Letter

Project Title: The Neural Basis of Misophonia

Principal Investigator: Dr. Blake Butler

Thank you for taking part in this study. The purpose of these experiments is to see if people with specific sound sensitivities (misophonia) have different brain activity in response to misophonic stimuli than people without sound sensitivities. In this manner, we aim to determine which brain regions are associated with the emotional/physiological reaction seen in people with misophonia and assess how these brain regions might be functionally connected.

We predicted that people with specific sound sensitivities would have increased brain activity in regions of the salience network, auditory cortex, and limbic system in response to misophonic stimuli (but not other types of stimuli) in comparison to people without sound sensitivities. In addition, we expected that greater activity in these regions would correlate with increased aversive emotion ratings and heart rate in response to misophonic stimuli.

Here are some references if you would like to read more on the topic:

Edelstein, M., Brang, D., Rouw, R., & Ramachandran, V. S. (2013). Misophonia: physiological investigations and case descriptions. *Frontiers in Human Neuroscience*, *7*, 296.

Kumar, S., Tansley-Hancock, O., Sedley, W., Winston, J. S., Callaghan, M. F., Allen, M., ... & Griffiths, T. D. (2017). The brain basis for misophonia. *Current Biology*, *27*(4), 527-533.

Schröder, A., van Wingen, G., Eijsker, N., San Giorgi, R., Vulink, N. C., Turbyne, C., & Denys, D. (2019). Misophonia is associated with altered brain activity in the auditory cortex and salience network. *Scientific reports*, *9*(1), 7542.

Thank you,

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