8-17-2021 1:00 PM

Does aberrant connectivity underlie the experience of misophonia?

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A thesis submitted in partial fulfillment of the requirements for the Master of Science degree in Neuroscience

Abstract

Misophonia is a condition characterized by an extreme aversion to certain ordinary sounds, such as chewing or breathing. These sounds are typically innocuous but elicit strong feelings of anger, anxiety, and disgust as well as physiological stress in people with misophonia. This misophonic reaction to “trigger” sounds is also marked by increased activity in regions of the brain that process sound, ascribe salience, and regulate emotion (Kumar et al., 2017; Schroder et al., 2019). It has therefore been theorized that aberrant connectivity between these brain regions (particularly the anterior insula, auditory cortex, amygdala, and hippocampus) may underlie the experience of misophonia. The current work addressed two hypotheses related to this overarching theory. In the first study, we examined resting-state connectivity in people with varying degrees of sound sensitivity and demonstrate that people with clinical misophonia show a trend toward reduced functional connectivity within this network in comparison to those with sub-clinical sensitivity to sound. In the second study, we show preliminary evidence of reduced phonemic perceptual narrowing in misophonics. Since perceptual narrowing is thought to be a behavioural correlate of synaptic pruning during development, this trending result provides indirect evidence for atypical neural connectivity in misophonia. Taken together, the studies implicate a potential developmental mechanism of abnormal salience attribution in misophonia and highlight the importance of studying individual differences in the misophonic experience. These findings also inform the neural and perceptual characterization of misophonia, and since misophonia is not yet listed as a psychological disorder in diagnostic manuals, such findings are an important step towards understanding and classifying misophonia.

Keywords: Misophonia, resting-state fMRI, perceptual narrowing, synesthesia, anterior insula, salience attribution

Summary for Lay Audience

People experience sound differently from one another. For instance, the sound of rainfall may be calming to one person while irritating to another. Misophonia is an extreme example of such individual differences in sound-emotion processing, where certain ordinary sounds (like chewing and breathing) elicit a stress response. When someone with misophonia hears their “trigger” sound, they experience feelings of intense anger, anxiety, and disgust as well as physiological symptoms such as increased heart rate and muscle contraction. This reaction to trigger sounds is reflected in differences in brain activity between misophonics and those without sensitivity to specific sounds. More specifically, in response to trigger sounds (but not other types of sounds), people with misophonia have heightened activity in brain regions that process sound, ascribe salience, and regulate emotion. However, it is unclear if these atypical patterns of brain activity reflect differences in *connectivity* between these regions. This thesis addressed this question through two separate studies. In the first study, we examined patterns of resting brain connectivity in people with varying degrees of sound sensitivity severity. Here, we demonstrated that, indeed, people with misophonia may have altered connectivity in a brain network associated with sound-salience processing, and that connectivity in this network may be distinct from those with sub-clinical irritation to sound. In the second study, we indirectly examined brain connectivity using a perceptual measure that is thought to be associated with the refinement and stabilization of neural connections. The results from this study are inconclusive, but trends in the data suggest that misophonia may be characterized by atypical brain connectivity that is shaped during development. Overall, these findings progress our understanding of the neural and perceptual components of misophonia. This is especially important because misophonia is currently under-researched, largely uncharacterized, and yet to be represented in clinical diagnostic manuals, so these findings inform how misophonia should be classified and motivate future research directions.

Acknowledgements

First and foremost, I want to thank my supervisor, Dr. Blake Butler, for his mentorship throughout my time as a master's student. I am extremely grateful for your advice, guidance, and support, which was integral to this thesis as well as my personal and academic growth over the past two years. Thank you for having confidence in my ideas and giving me the opportunity to study what I am truly passionate about. Joining your lab continues to be one of the best decisions I have made and I relish the opportunity to continue working alongside you for my next academic endeavor.

I would also like to extend my gratitude to the members of the NiSSL lab who helped me overcome many obstacles throughout my degree. A special thank you to Dr. Alexandra Levine, whose knowledge and mentorship was essential to the success of my neuroimaging study.

Thank you to my advisors, Dr. Ingrid Johnsrude and Dr. Derek Mitchell, for sharing thoughtful and encouraging feedback on my thesis. I greatly appreciate your expertise and support.

Many thanks to my relatives for believing I could follow in my grandmother's footsteps as the family academic. To my father Paul, thank you for raising me to be a curious person with questions about the world, my passion for science undoubtedly stems from you. To my mother Susan, thank you for being someone I look up to, you inspire me to make the world a better place.

To my beautiful and hilarious friends Dani, Pauli, Rebekah, Maria, and Connor – thank you for your unwavering love and kindness throughout this journey. Amidst the chaos of a global pandemic, breakups, and fainting spells, I would not have been able to achieve all that I have without your support.

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Chapter 1

Introduction

Sound is emotionally meaningful. However, people often experience dramatically different emotional responses to the same sound. For instance, the sound of rainfall may be calming to one person while irritating to another. An extreme example of these inter-individual differences occurs in misophonia – a condition where specific "trigger" sounds elicit feelings of intense anger, anxiety, and disgust as well as physiological symptoms such as increased heart rate and muscle contraction (Edelstein, Brang, Rouw, & Ramachandran, 2013; Schröder, Vulink, & Denys, 2013). Any sound can be a trigger for someone with misophonia, but more common triggers are human-produced repetitive sounds such as chewing and breathing (Edelstein et al., 2013; Rouw & Erfanian, 2018; M. S. Wu, Lewin, Murphy, & Storch, 2014). These types of sounds tend to be innocuous to the neurotypical population, but may elicit feelings of irritation and annoyance in some people. Although variation in emotional responses to sound is normal, the misophonic reaction is clinically distinct (Jager, de Koning, Bost, Denys, & Vulink, 2020; Schröder et al., 2013).

Misophonia can be psychologically debilitating. When exposed to trigger sounds, people with misophonia not only experience intense emotional and physiological reactions, but can also experience impaired attention and cognitive control (Frank, Roszyk, Hurley, Drejaj, & McKay, 2020; Seaborne & Fiorella, 2018; Silva & Sanchez, 2019). For example, one previous study demonstrated that in the presence of their trigger sounds, people with misophonia had higher anxiety and worse performance on a Stroop task than those without specific sound sensitivity (Daniels, Rodriguez, & Zabelina, 2020). Many individuals with misophonia rely on coping mechanisms to manage their symptoms. For example, someone with misophonia may confront or mimic people who are producing their trigger sound, escape the place where the trigger is being produced, or avoid environments where they encounter trigger sounds altogether (Edelstein et al., 2013; Rouw & Erfanian, 2018). Although these coping mechanisms provide short-term symptom relief, they can cause long-term distress, interference with academic and work functioning, and social isolation (Schröder et al.,

2013; Wu et al., 2014; Zhou, Wu, & Storch, 2017). Despite the growing body of evidence that misophonia is a psychological disorder characterized by distress and impairment, it is not listed in contemporary diagnostic manuals like the Diagnostic and Statistical Manual of Mental Disorders (DSM-5).

Misophonia is not yet represented in diagnostic manuals, primarily because its clinical presentation and underlying etiology remain poorly understood. Few peer-reviewed articles have been published that detail the experience of misophonia or its etiology, and a large portion of this literature comprises patient case studies (Potgieter et al., 2019; Siepsiak et al., 2019). As a result, misophonia remains largely uncharacterized, and it is unclear if it is a discrete disorder or a symptom of other comorbid psychological conditions such as attention-deficit hyperactivity disorder, obsessive-compulsive disorder, autism, and synesthesia (Rouw & Erfanian, 2018; Taylor, 2017). Moreover, academic and clinician awareness is low, so many people with misophonia go misdiagnosed and without treatment options (Brout et al., 2018; Claiborn, Dozier, Hart, & Lee, 2020; Porcaro & Danesh, 2019). This is particularly concerning because the prevalence of misophonia in young adults is estimated to be approximately 18% (Naylor, Caimino, Scutt, Hoare, & Baguley, 2021; Wu et al., 2014; Zhou et al., 2017). To address this problem, researchers have begun to characterize the psychological and physiological components of misophonia, including categorizing atypical patterns of neural activity, in an effort to understand this perceptual phenomenon.

1.1 Aberrant Neural Activity in Misophonia

While little is known about the neural basis of misophonia, two recent functional magnetic resonance imaging (fMRI) studies have shed light on a promising neural marker (Kumar et al., 2017; Schröder et al., 2019). These studies found that when compared to neurotypical controls, people with misophonia have heightened activity in auditory and limbic brain regions as well as the anterior insular cortex (AIC) in response to trigger sounds, but not other types of sound. The AIC is particularly responsive to highly salient stimuli (Phan et al., 2004; Uddin, Nomi, Hébert-Seropian, Ghaziri, & Boucher, 2017), so increased trigger-evoked AIC activity in those with misophonia

suggests they may assign abnormally high salience to these sounds. Since stimulus salience plays a modulatory role in attentional control (Kaya & Elhilali, 2017; Wiech et al., 2010; T. Wu et al., 2019), this may cause individuals with misophonia to reflexively attend to sounds that the general population ignores.

Patterns of activity in the AIC have also been shown to correlate with components of the misophonic reaction. Specifically, in response to trigger sounds, AIC activity has been shown to significantly mediate differences in heart rate and galvanic skin conductance between controls and misophonics (Kumar et al., 2017), suggesting that the AIC may play a role in the autonomic stress response. In addition, increased activity in the AIC in response to trigger sounds is associated with increased misophonia distress ratings (Kumar et al., 2017), indicating that this same brain area may also play an important role in the psychological experience of misophonia.

1.2 Aberrant Neural Connectivity in Misophonia

Misophonia is thought to be characterized by atypical functional and structural connectivity between brain regions that process sound and those that regulate emotion. Based on the available neuroimaging results, it has been suggested that the AIC may modulate the experience of misophonia by integrating auditory cues (arising from auditory cortical and subcortical structures) with information about internal bodily states and emotions (arising from structures of the limbic system) in an atypical fashion (Brout et al., 2018; Kumar et al., 2017; Palumbo, Alsalman, De Ridder, Song, & Vanneste, 2018). Indeed, one of the previously described neuroimaging studies also showed that the AIC had increased functional connectivity to regions of the limbic system, including the amygdala and hippocampus, in response to trigger sounds (Kumar et al., 2017). Thus, these patterns of atypical brain activity and subsequent physiological and psychological responses in those with misophonia may reflect aberrant functioning of a brain network that supports salience attribution and sound-emotion association.

The nature of the relationship between trigger and response that characterizes misophonia is highly similar to synesthesia–a condition characterized by hyperconnectivity between sensory regions in the brain that gives rise to atypical sensory perception (Hubbard & Ramachandran, 2005; Mattingley & Rich, 2004; Ward,

2013). Specifically, in synesthesia, the perception of a stimulus called the “inducer” automatically and consistently evokes an unrelated percept called the “concurrent”. There are many different types of synesthesia; for example, some synesthetes may perceive specific music notes (inducer) to be associated with specific colours (concurrent). This bears a striking similarity to misophonia, where specific sounds automatically and consistently evoke negative emotional responses. In addition, preliminary findings show that people with misophonia are more likely to experience synesthetic associations than people without misophonia (Rouw & Erfanian, 2018), suggesting these conditions may share a neural phenotype. Thus, it has been suggested that, while synesthesia is characterized by heightened connectivity between regions of the brain that modulate the perception of the inducer and concurrent, misophonia may be marked by heightened connectivity between brain regions involved in sound and emotion (Edelstein et al., 2013; McGeoch & Rouw, 2020; Palumbo et al., 2018).

In addition to atypical connectivity between sensory areas, synesthetes also exhibit atypical patterns of functional connectivity beyond brain regions directly involved in perception, including differences within and between frontal and parietal brain networks (Dovern et al., 2012; Rothen & Terhune, 2012; Tomson, Narayan, Allen, & Eagleman, 2013). This raises the question of whether atypical patterns of neural connectivity may be a more global phenomenon in individuals with misophonia. That atypical connectivity might exist beyond brain regions related to salience attribution and sound-emotion association is also directly supported by misophonic patient reports (Johnson et al., 2013; Webber, Johnson, & Storch, 2014). Indeed, in their 2013 study, Schröder and colleagues reported that in addition to sound sensitivity, many individuals with misophonia experience negative emotional responses to repetitive *movements* that may or may not involve the production of sound (e.g. a leg rocking back and forth). This phenomenon, termed misokinesia, suggests that while sound-evoked responses may present as the primary misophonia symptom, there is reason to believe that underlying patterns of aberrant brain activity extend beyond those directly involved in sound processing.

One method used to assess patterns of neural connectivity is resting-state functional connectivity analysis. In this approach, a participant's brain activity is observed in the absence of any task or overt stimulation, and brain regions in which blood-oxygenation level-dependent (BOLD) signal fluctuations are correlated over time are deemed to be functionally connected. Moreover, these patterns of resting connectivity are thought to reflect networks that are functionally coupled during stimulus perception and related behaviours (Sala-Llonch et al., 2012; Tavor et al., 2016), meaning that brain regions that show correlated resting-state activity may work together to support similar functions. Indeed many psychological disorders, including those comorbid with misophonia such as attention-deficit hyperactivity disorder, autism, and obsessive-compulsive disorder (Claiborn et al., 2020; Jager et al., 2020; Rouw & Erfanian, 2018), are characterized by atypical resting functional connectivity in brain networks responsible for psychological functioning (Peterson, Thome, Frewen, & Lanius, 2014; Woodward & Cascio, 2016). For instance, obsessive-compulsive disorder is marked by atypical connectivity within and between the frontal-parietal and default-mode networks (Stern, Fitzgerald, Welsh, Abelson, & Taylor, 2012), which play a role in disengaging from certain thoughts and attending to environmental stimuli. A recent study demonstrated that people with misophonia have abnormal resting functional connectivity between auditory, visual, and motor brain regions (Kumar et al., 2021). This atypical pattern of connectivity was suggested to reflect excessive motor mirroring, which in turn may result in hyper-responsiveness to auditory stimuli. While misophonia is marked by psychological impairments in salience attribution and sound-emotion relationships, it remains unclear whether brain networks responsible for these processes show atypical resting connectivity in those with misophonia.

1.3 The Current Studies

This thesis was designed to test hypotheses related to the overarching theory that misophonia is characterized by aberrant connectivity between regions of the brain that ascribe salience, process sound, and regulate emotion. Chapter 2 tests this directly by assessing resting-state functional connectivity in people with varying degrees of sound sensitivity to determine whether misophonia symptom severity scales with

connectivity differences in our network of interest. Chapter 3 indirectly tests the theory that misophonia is characterized by aberrant connectivity using a behavioural measure of perceptual narrowing that has been previously used to assess patterns of atypical sensory connectivity. Perceptual narrowing is a normal developmental process whereby sensory experiences during development shape adult perceptual abilities (Flom, 2014; Maurer & Werker, 2014). This process coincides with synaptic pruning of neural connections during development, and is considered a behavioural correlate of neural maturation (Grossmann, Missana, Friederici, & Ghazanfar, 2012; Lewkowicz, 2014). Thus, atypical perceptual narrowing in those with misophonia would provide indirect evidence of differences in neural connectivity. Taken together, these two experiments explore the role of aberrant connectivity in the experience of misophonia, and inform how neural phenotypes observed in misophonia give rise to atypical perception.

Chapter 2

Experiment 1: Resting-state functional connectivity and sound sensitivity severity

2.1 Introduction

Previous neuroimaging studies in individuals with misophonia have predominantly characterized the neural basis of the misophonic reaction by assessing sound-evoked neural activity. While few in number, these studies suggest misophonia is characterized by atypical activity in the anterior insular cortex (AIC) and structures commonly associated with the limbic system, in response to trigger sounds (Kumar et al., 2017; Schröder et al., 2019). However, it is unclear if there are neural characteristics of misophonia that can be observed at rest that may relate to these trigger-specific differences. Patterns of correlated neural activity during rest have been shown to be consistent across individuals, and predictive of disorder states when atypical (Mastrovito, 2013; Spisak et al., 2020). Moreover, a fulsome consideration of the interactions between neural activity across different functional states (e.g. task-evoked vs resting) is critical to understanding brain dynamics (Mastrovito, 2013). Thus, the current study was designed to provide one of the first quantifications of neural connectivity in the absence of overt stimulation using resting-state functional connectivity analysis in participants with misophonia.

What is known about the prevalence and clinical characteristics of misophonia (Naylor et al., 2021; Wu et al., 2014; Zhou et al., 2017) has largely been defined through self-report studies using surveys such as the Amsterdam Misophonia Survey (A-MISO-S; Schröder et al., 2013) and the Misophonia Questionnaire (Wu et al., 2014). These scales aim to determine whether specific sound sensitivity is present, to quantify the severity of the associated symptoms, and are designed to capture a broad range of severities (e.g. the A-MISO-S assigns a score ranging from 0 to 24, where 0 indicates no sensitivity and scores ≥10 are considered to represent clinical levels of sensitivity). In contrast, much of the work that has been done to characterize the neural basis of misophonia has treated individuals who meet the clinical criteria for misophonia as a homogenous group contrasted against controls without reported sound sensitivity

(Kumar et al., 2021, 2017; Schröder et al., 2019). However, emotional responses to sound vary greatly across neurotypical populations and among those with misophonia. For example, while the estimated prevalence of misophonia is approximately 18% (Naylor et al., 2021; M. S. Wu et al., 2014; Zhou et al., 2017), clinicians suggest that a smaller portion of this group has severe symptoms, such as an inability to disengage with trigger sounds, which result in severe clinical impairments, such as extreme interference with school and work functioning (Potgieter et al., 2019; Wiese, Wojcik, & Storch, 2021). In contrast, others with misophonia are able to disengage with trigger stimuli and attend to other stimuli in their environment, thereby allowing them to manage interference with occupational and social functioning. These differences indicate that misophonia is best characterized along a spectrum that ranges from mild specific sound sensitivity to severe misophonia; however, the neural correlates of these differences in symptom severity have yet to be studied. Moreover, studies investigating the neural correlates of misophonia have been conducted with older patient groups who are typically assessed by clinicians with diagnostic expertise rather than using self-report measures like the A-MISO-S, which have overwhelmingly been used to study the experiences of young adults. There therefore remains a substantial gap in the literature between descriptions of the experience of misophonia, and studies of the underlying patterns of brain activity.

Thus, the current study explored resting-state functional connectivity in individuals with varying degrees of sound sensitivity to address the following aims: 1) determine if individuals with misophonia show atypical neural connectivity at rest within a network hypothesized to play a role in sound salience attribution compared to participants with sub-clinical sound sensitivity and control participants; 2) determine if differences in resting functional connectivity within this network of areas scale with symptom severity; and 3) determine whether aberrant connectivity in misophonia extends beyond this network, with a focus on intermodal connectivity. The first two aims focus on a network that comprises regions previously demonstrated to show atypical patterns of stimulus-evoked activity in misophonics (bilateral anterior insular cortices, auditory cortices, amygdalae, and hippocampi), which are thought to play a role in attributing emotional salience to otherwise innocuous sounds. It was predicted that

individuals with higher misophonia severity scores would show greater resting-state connectivity within this sound-salience network. Finally, with respect to the third aim, it was hypothesized that individuals with misophonia might also show atypical connectivity between the auditory/anterior insular cortices and visual cortical areas (V1/V2 and V4), providing a potential neural substrate for the experience of misokinesia and/or synesthesia often reported in this population.

2.2 Methods

2.2.1 Participants

Fourteen participants between the ages of 20 and 30 with varying degrees of specific sound sensitivity were recruited through poster advertisements placed around the Western University campus (Table 1; a total sample size of 75 was determined appropriate according to previous studies. The current study represents a subset of this intended sample acquired prior to the onset of the COVID-19 pandemic). All participants were proficient in English, had normal or corrected-to-normal vision, and normal hearing thresholds (≤ 20dB HL between 250 and 8000 Hz). This study was approved by the Western University Health Sciences Research Ethics Board (HSREB; Appendix A).

Table 1: Characteristics of control, sub-clinical, and misophonia participants in experiment 1.

	Control (n=3)	**Sub-Clinical (n=5)**	**Misophonia (n=6)**
Age (M)	20-30 (24.3)	24-28 (26)	21-29 (23.3)
Sex	2 Females, 1 Male	3 Females, 2 Males	5 Females, 1 Male
A-MISO-S (M)	0	2-9 (6.2)	10-13 (11.3)
# Reporting Synesthesia	1	2	2
# Reporting Misokinesia	0	0	1

2.2.2 Procedure

Interested participants received a link to an online survey hosted on Qualtrics (Provo, UT). This survey included a screener to assess participant eligibility, following which implied consent to participate was collected from eligible participants. The remainder of the survey consisted of three sections: demographics, misophonia experience, and synesthesia experience. In the demographics section, participants provided information about their age, sex, race, and mental health history. In the misophonia section, participants completed the A-MISO-S, which assesses sound sensitivity severity and how it affects daily functioning. In the synesthesia section, participants completed the Synesthesia Questionnaire, which evaluates synesthetic associations by inquiring about specific inducer-concurrent relationships.

After completing the survey, an on-campus experimental session was scheduled. During this session, an audiometric assessment including otoscopic inspection and pure tone audiometry (GSI Pello; Grason-Stadler, Eden Prairie, MN) was completed to confirm normal hearing status (no threshold >20 dB HL between 0.25 and 8 kHz), and MR images were acquired at the Centre for Functional and Metabolic Mapping at Western University. During this session, anatomical and resting-state functional images were acquired using a Siemens MAGNETOM Prisma Fit 3 Tesla scanner (Siemens, Erlangen, Germany) and a 32-channel head coil. Prior to each resting-state scan, participants were asked to remain awake, not fixate on any one thought, and to fix their gaze on the cross presented on the screen above them. Participants were compensated $10 per hour for completing the online survey, and $30 per hour for the imaging session.

2.2.3 Psychological Measures

2.2.3.1 Amsterdam Misophonia Scale (A-MISO-S) (Appendix C)

The Amsterdam Misophonia Scale (A-MISO-S; Schröder et al., 2013) comprises a 6-item self-report measure that assesses a participant’s sensitivity to specific sounds, severity of misophonia symptoms, and the impact of these symptoms on daily functioning. Each item comprises a 5-point likert scale scored from 0-4. For each participant, scores on each item are summed to produce an overall A-MISO-S score: a

score of 0 indicates that the participant is not sensitive to specific sounds, scores between 1-9 indicate sub-clinical sensitivity to sound, and scores between 10-24 indicate clinical misophonia[1]. The A-MISO-S is an adaptation of the Yale-Brown Obsessive-Compulsive Scale (Y-BOCS) created by Goodman and Colleagues (1989).

2.2.3.2 Synesthesia Questionnaire (Appendix D)

The Synesthesia Questionnaire (Eagleman, Kagan, Nelson, Sagaram, & Sarma, 2007) comprises a standardized 7-item 'Yes' or 'No' self-report measure used to evaluate participants for synesthesia by asking questions about common synesthetic perceptions (colour-letter/number, time-colour, spatial sense-time, colour-auditory stimuli, language-, and smell-touch). A score of 1 or higher indicates that the participant may have synesthesia with higher scores suggesting multiple synesthetic associations. This questionnaire is typically used as a pre-test to the interactive Synesthesia Battery developed by David Eagleman (Eagleman, 2007; NB: the full battery was unavailable at the time of testing due to JAVA-related depreciation).

2.2.4 Magnetic Resonance Imaging Data Acquisition

2.2.4.1 Anatomical Data

High resolution, whole-brain structural T1-weighted MPRAGE images were obtained with the following imaging parameters: isotropic voxel size= 1.0 mm^3 isotropic voxels, TR= 2300 ms, TE= 2.38 ms, flip angle= 8°, field of view=176x256x256 mm, inversion time= 900 ms.

2.2.4.2 Functional Data

Functional data were obtained using a multiband (acceleration factor = 3) single-echo EPI sequence. Two 6:13 min resting-state scans were collected for each participant, with 310 whole-brain volumes run per scan. These data were acquired with the following imaging parameters: 2.5 mm^3 isotropic voxels, 51 slices (inter-leaved), TR= 1 s, TE= 30 ms, flip angle= 40, PE= A>>P, field of view= 208x208x128 mm.

[1] Participants described in Chapter 2 & 3 were not clinically evaluated for the presence of misophonia. Rather, group membership was determined according to A-MISO-S score alone. Throughout this thesis, individuals scoring 10 or greater on this measure will be referred to as misophonics.

2.2.5 Magnetic Resonance Imaging Preprocessing

The data were converted into Brain Imaging Data Structure (BIDS; Gorgolewski et al., 2016) format and preprocessed using fMRIprep 20.2.0 – a standardized open-source pipeline used to preprocess, fit, and register images to MNI space (Esteban et al., 2019). Anatomical preprocessing of T1-weighted images included brain extraction, tissue segmentation, spatial normalization to the MNI ICBM 152 template, and surface reconstruction. Functional preprocessing involved the following steps: first, a BOLD reference volume and its skull-stripped version were generated. Then, head-motion parameters were estimated with respect to this BOLD reference (transformation matrices, and six corresponding rotation and translation parameters) before any spatiotemporal filtering. BOLD runs were then slice-time corrected, and BOLD time-series were resampled to surfaces and onto their original, native space by applying a single, composite transform to correct for head-motion and susceptibility distortions. The BOLD time-series was then resampled into standard space. Following these fMRIprep preprocessing steps, additional effects of movement on the resting state BOLD signal were reduced by regressing out motion and physiological components using the PhysIO toolbox (Kasper et al., 2017).

2.2.6 Region of Interest (ROI) Generation

A total of seven regions of interest (ROIs; Figure 1) in each hemisphere were identified for the current study. The proposed sound-salience network comprised bilateral Heschl's gyri (auditory cortices), anterior insular cortices, hippocampi, and amygdalae. Additionally, two ROIs in the visual cortex of each hemisphere (V1/V2 and V4) were included to assess connectivity beyond this network, to regions potentially involved in the experience of misokinesia and/or synesthesia. Finally, Broca's area was included as an ROI to serve as a control region, to which group differences in functional coupling were not expected. Masks for the bilateral amygdalae, hippocampi, Heschl's gyri, and primary/secondary visual cortices (V1/V2) were collected from the Harvard-Oxford atlas (Desikan et al., 2006). Left and right anterior insular cortex (AIC) ROIs were created by producing 6 mm diameter mask around the MNI coordinates comprising the loci of peak trigger-evoked activity reported by Kumar & Colleagues

(2017), and then confining those spheres to lie within the bounds of the Harvard-Oxford atlas definition of the anterior insula (to avoid incorporating voxels from adjacent cortical regions). Finally, bilateral masks for V4 and Broca's area were retrieved from the Juelich Histological Atlas (Mohlberg, 1999; Rottschy et al., 2007). All ROI masks were resampled to functional resolution using FMRIB's Linear Image Registration Tool (Jenkinson, Bannister, Brady, & Smith, 2002; Jenkinson & Smith, 2001), then thresholded and binarized using *fslmaths.*

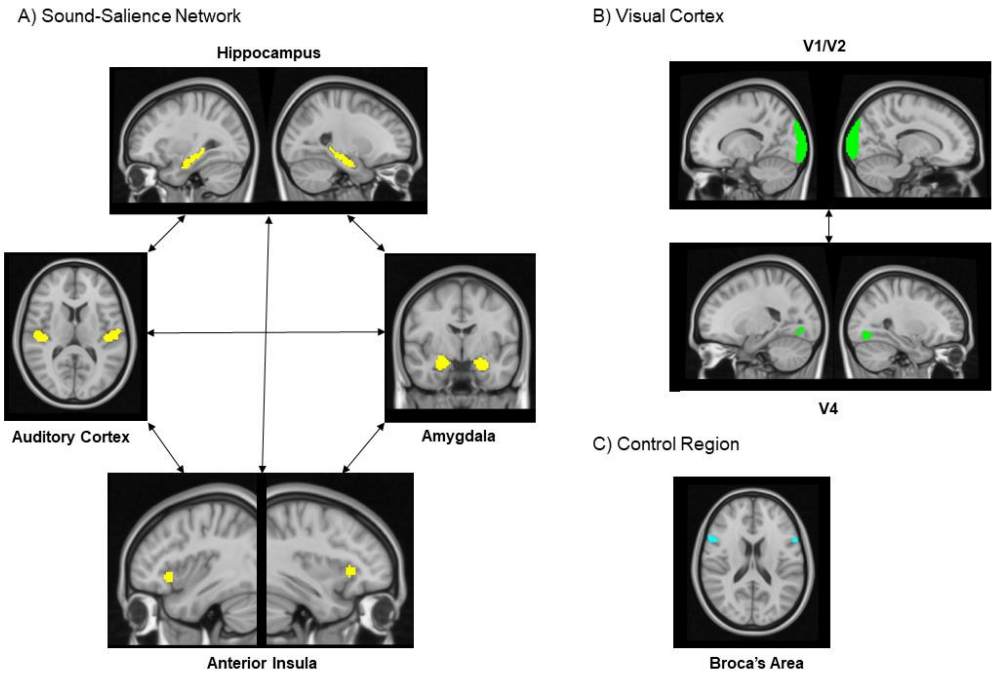


Figure 1: *Bilateral ROI masks.* ROIs in A) the sound-salience network, B) visual cortex, and C) control brain region.

2.2.7 Statistical Analyses

Average BOLD time-series for each ROI were extracted from functional scans using *fslmeants*. For each participant, Pearson correlation coefficients were computed for each ROI-ROI pair in each hemisphere for each 6:13 min scan. These coefficients were then averaged across scans and hemispheres for each participant. Finally, the mean network connectivity within the purported sound salience network (Figure 1A) was computed for each participant by averaging the correlation coefficients of all ROI-ROI pairs within the network.

2.2.7.1 Group Analysis of Sound Salience Network Connectivity

To examine group-level differences in resting-state connectivity between ROIs in our putative sound-salience network, average correlation coefficients for each group (control, sub-clinical sensitivity, and misophonia) were computed between ROIs in Heschl's gyrus, AIC, amygdala, and hippocampus. The resulting correlation matrices were compared using the Jennrich test of matrix equality. To determine if group differences existed within the sound-salience network as a whole, mean network connectivity values were averaged across individuals in each group and were compared using an ANCOVA with group as a between-subjects factor and average connectivity from regions of the sound-salience network to Broca's area as a covariate (to control for overall patterns of connectivity not specific to the sound-salience network).

2.2.7.2 Misophonia Symptom Correlation Analysis

To determine whether symptom severity is related to resting state functional connectivity within the sound-salience network, Spearman's rho correlation coefficients were calculated between each participant's A-MISO-S score and: 1) their mean sound-salience network connectivity value; and 2) the connectivity between each ROI-ROI pair within this network. Resulting correlations were tested for statistical significance ($p < 0.05$) and corrected for multiple comparisons using the Benjamini-Hochberg procedure.

2.2.7.3 Connectivity Between Sound Salience Network and Visual Cortex

Finally, to assess potential group differences in connectivity to regions outside of the sound-salience network that may be involved in the experience of misokinesia and/or synesthesia, average correlation coefficients for each group were computed between ROIs in Heschl's gyrus, AIC, V1/V2, and V4. The resulting correlation matrices were compared using the Jennrich test of matrix equality. To determine if group differences existed within auditory/AIC to visual cortex connectivity, mean network connectivity values were averaged across individuals in each group and were compared using an ANCOVA with group as a between-subjects factor and average connectivity from regions of the sound-salience network to Broca's area as a covariate.

2.3 Results

2.3.1 Planned Analyses

2.3.1.1 Group-wise Analyses

Average correlations between ROIs in the sound-salience network for each group (control, subclinical sensitivity, misophonia) are shown in Figure 2. Jennrich tests of matrix equality found no significant differences between the control and sub-clinical matrices (x^2=0.028, p=0.999), control and misophonia matrices (x^2=1.0, p=0.999), or sub-clinical and misophonia matrices (x^2=0.223, p=0.999).

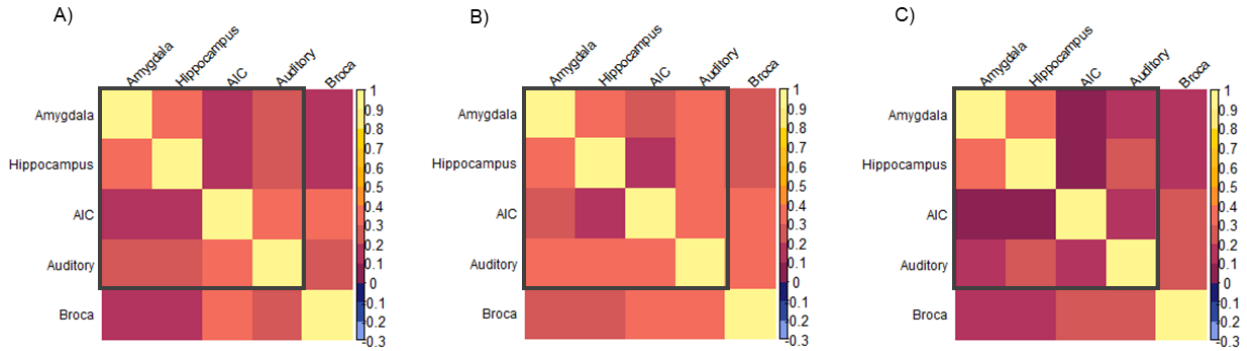


Figure 2: *Group averaged sound-salience network correlation matrices.* Correlation matrices for the A) control, B) sub-clinical sensitivity, and C) misophonia groups. Each square represents the group average Pearson's correlation coefficient between the mean timeseries for a given ROI-ROI pair. Note: connectivity from each sound-salience network ROI to Broca's area is also shown as a control.

Average connectivity across the sound-salience network for each group is shown in Figure 3. While the misophonia group was found to have lower mean network connectivity (M=0.143) than either the control (M=0.226) or sub-clinical groups (M=0.271), the main effect of group did not reach statistical significance ($F[2.0,10.0]=1.2$, $p=0.342$, $\eta^2=0.094$).

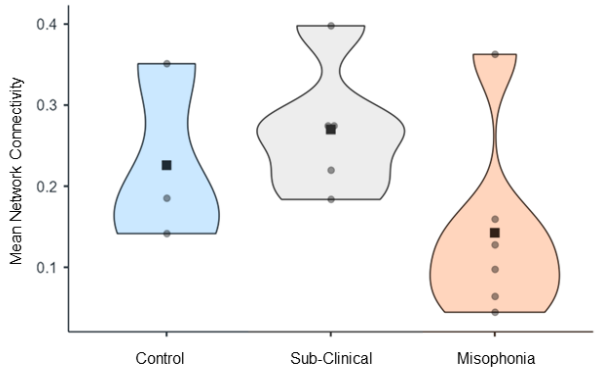
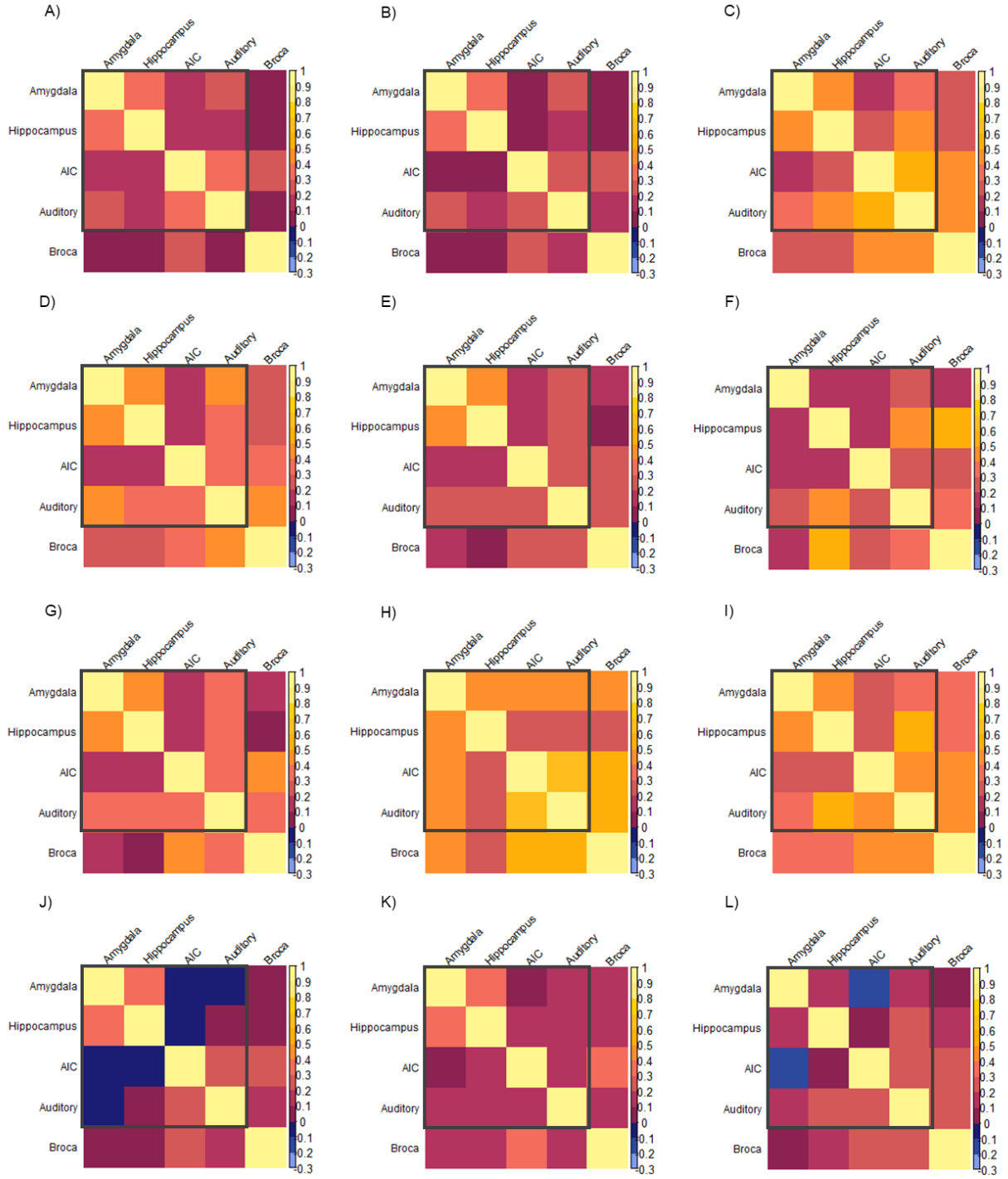


Figure 3: *Group differences in mean sound-salience network connectivity.* Violin plot outlining the distribution of mean network connectivity values for the control (blue), sub-clinical sensitivity (grey), and misophonia (orange) groups. Average mean network connectivity is denoted by a black square.

2.3.1.2 Misophonia Symptom Correlation Analyses

In addition to group-level analyses, individual participant data were analyzed to determine how resting-state connectivity within the sound-salience network relates to the severity of misophonia symptoms. Individual correlations between ROIs in the sound-salience network are illustrated in Figure 4.



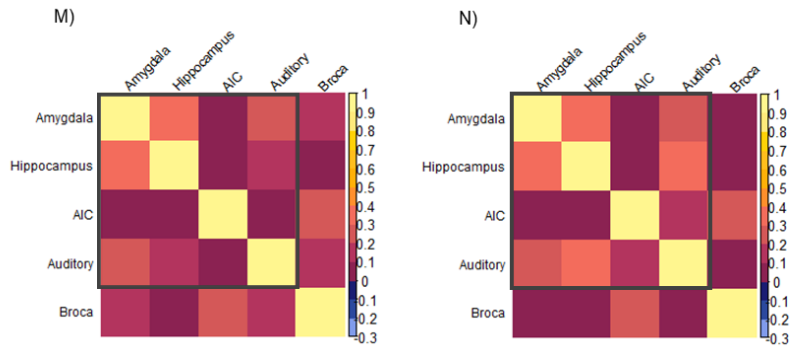


Figure 4: *Individual participant ROI-ROI correlation matrices.* Matrices A-N ordered by participant A-MISO-S scores (low to high): A-C) control, D-H) sub-clinical, I-N) misophonia. Each square represents the Pearson's correlation coefficient between the mean timeseries for a given ROI-ROI pair. Note: connectivity from each sound-salience network ROI to Broca's area is also shown as a control.

The relationship between the severity of sound sensitivity symptoms (A-MISO-S score) and mean network connectivity is shown in Figure 5A. A trend was observed whereby mean network connectivity decreased with increasing symptom severity; however, this relationship did not reach statistical significance (r=-0.548, p=0.052). Also shown are correlations between symptom severity and the resting state connectivity of each ROI-ROI pair (Figure 5 panels B-F). For each ROI-ROI pair, resting-state connectivity appears to decrease with increasing symptom severity, with a statistically significant correlation observed between A-MISO-S score and AIC-auditory cortex connectivity (r=-0.621, p=0.024). Correlations between severity of sound sensitivity and connectivity between the amygdala and hippocampus (r=-0.133, p=0.651), amygdala and AIC (r=-0.483, p=0.08), amygdala and auditory cortex (r=-0.303, p=0.292), hippocampus and AIC (r=-0.452, p=0.121), and hippocampus and auditory cortex (r=-0.24, p=0.43) were not statistically significant.

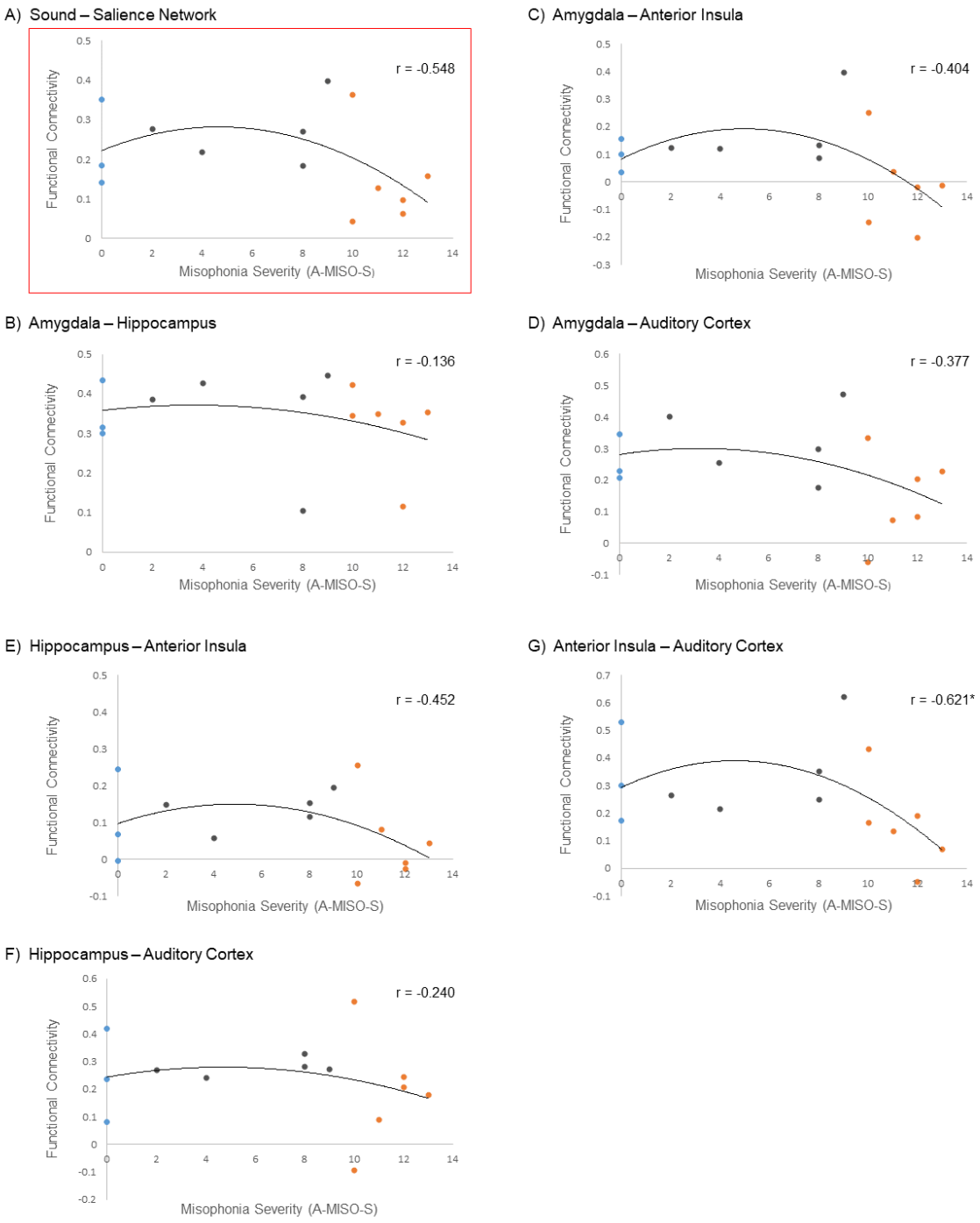


Figure 5: *Correlations between functional connectivity and sound sensitivity severity.* Spearman's correlation between participants' A-MISO-S scores and: A) mean connectivity in the sound sensitivity network; and B-F) functional connectivity between ROI-ROI pairs as labelled. Control participants (A-MISO-S =0) are shown in blue, participants with sub-clinical sensitivity (A-MISO-S = 1-9) are shown in grey, and participants with misophonia (A-MISO-S ≥ 10) are shown in orange, *$p < 0.05$.

2.3.1.3 Sound Salience Network to Visual Cortex Analyses

Average correlations between ROIs in the visual cortex and sound-salience network (specially AIC and auditory cortex) for each group (control, sub-clinical sensitivity, misophonia) are shown in Figure 6. Jennrich tests of matrix equality found no significant differences between the control and sub-clinical matrices (x^2=0.055, p=0.999) control and misophonia matrices (x^2=0.155, p=0.999), or sub-clinical and misophonia matrices (x^2=0.205, p=0.999). Average connectivity between the sound-salience and visual network for each group is shown in Figure 7. The resulting ANCOVA found no significant main effect of group (F[2.0, 10.0]=0.383, p=0.691, η^2=0.039).

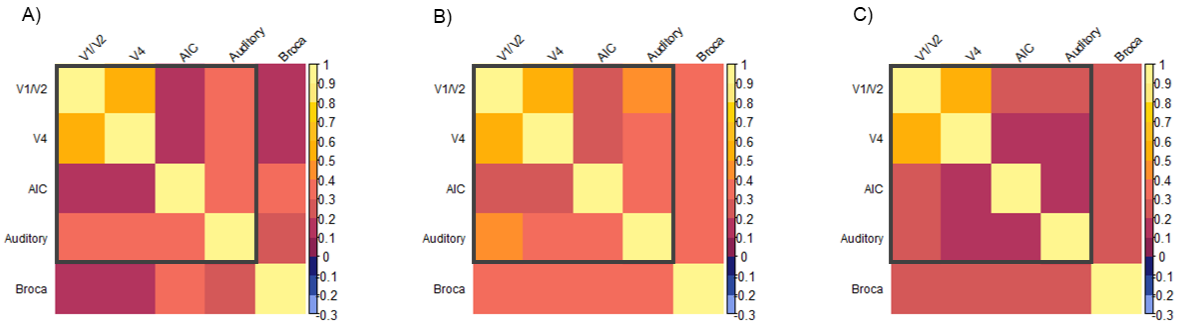


Figure 6: *Group averaged sound-salience to visual cortex correlation matrices***.** Correlation matrices for the A) control, B) sub-clinical sensitivity, and C) misophonia groups. Each square represents the group average Pearson's correlation coefficient between the mean timeseries for a given ROI-ROI pair. Note: connectivity from each sound-salience network ROI to Broca's area is also shown as a control.

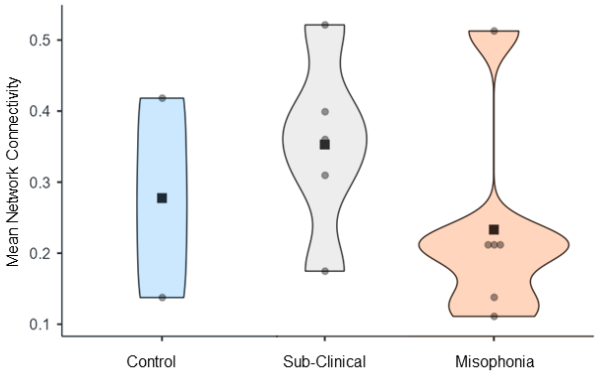


Figure 7: *Group differences in mean sound-salience to visual cortex connectivity.* Violin plot outlining the distribution of mean auditory/AIC to visual cortex connectivity values for the control (blue), sub-clinical sensitivity (grey), and misophonia (orange) groups. Average mean connectivity is denoted by a black square.

2.3.2 Exploratory Analyses

2.3.2.1 Groupwise Variability in Anterior Insula to Auditory Cortex Connectivity

Although functional connectivity between brain regions in the sound-salience network appeared to be negatively associated with misophonia symptom severity, connectivity between some ROI pairs in this network were better predictors of misophonia severity than others. In particular, since connectivity between the AIC and auditory cortex significantly correlated with misophonia symptom severity, group differences in functional connectivity between these regions was further explored. Mean functional connectivity between the anterior insula and auditory cortex for each of the three groups (control, sub-clinical, and misophonia; Figure 8) was compared using an ANCOVA with group as the between-subjects factor. Analysis revealed no significant main effect of group type ($F[2.0, 10.0]=2.26$, $p=0.155$, $\eta^2=0.177$) (Figure 8).

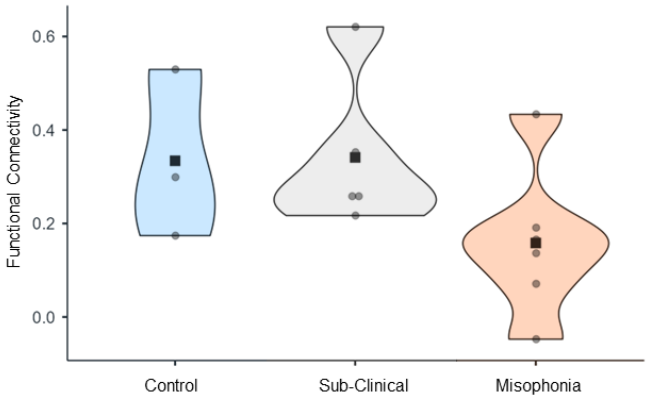


Figure 8: *Group differences in AIC-auditory connectivity.* Violin plot outlining the variation in connectivity between the AIC and auditory cortex for the control (blue), sub-clinical (grey), and misophonia (orange) groups. Mean connectivity is denoted by a black square.

2.3.2.2 Examining the Impact of Synesthetic Comorbidity

Five of the fourteen participants in this study reported having synesthestic associations (one in the control group, two in the sub-clinical group, and two in the misophonia group). Since individuals with synesthesia have been demonstrated to have atypical neural connectivity (Dovern et al., 2012; Rouw & Scholte, 2007; Zamm, Schlaug, Eagleman, & Loui, 2013), we explored the impact of synesthesia on functional connectivity in the sound-salience network. An independent samples t-test was conducted to analyze group differences in average functional connectivity in the sound-salience network between those with and without self-reported synesthetic associations. The resulting t-test was not statistically significant ($t[12.0]=1.63$, $p=0.129$, Cohen's $d=0.881$), but revealed a trend whereby those with synesthesia appeared to have greater functional connectivity than those without (Figure 9).

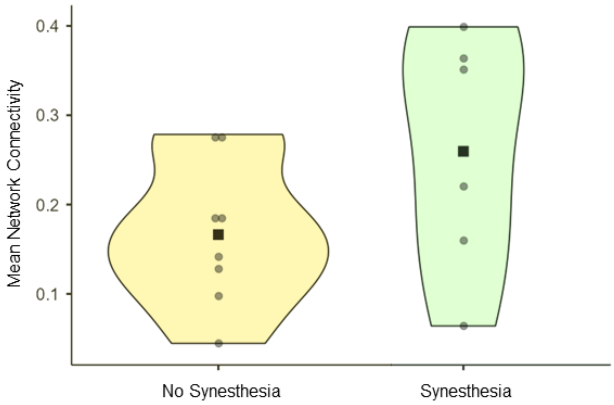


Figure 9: *Mean sound-salience network connectivity for participants with and without synesthesia.* Violin plot outlining the variation in average network connectivity for those with (green) and without (yellow) reported synesthetic associations. Mean average network connectivity is denoted by a black square.

To isolate the effects of misophonia from confounds related to comorbidity, participants with reported synesthetic associations were removed and analyses were re-conducted to explore the relationship between misophonia symptom severity and average sound-salience network connectivity, and group differences in average network connectivity respectively (Figure 10). The correlation analysis revealed a significant relationship between misophonia severity and average network connectivity ($r=-0.684$, $p=0.042$) and the ANCOVA revealed a significant main effect of group ($F[2.0, 5.0]=15.12$, $p=0.008$, $\eta^2 =0.728$). Subsequent t-tests demonstrated that those with misophonia have significantly lower resting state connectivity within the sound-salience network than those with sub-clinical sensitivity ($t[3.43]=4.54$, $p=0.031$, Cohen's $d=3.68$) but found no differences between the sub-clinical and control groups ($t[3.0]=2.18$, $p=0.221$, Cohen's $d=1.75$) or control and misophonia groups ($t[2.51]=2.80$, $p=0.155$, Cohen's $d=2.25$).

When the strength of connectivity within the network comprising the AIC, auditory cortex, V1/V2, and V4 was re-examined following the removal of individuals with synesthesia, an ANCOVA revealed no significant main effect of group ($F[2.0, 5.0]=1.69$, $p=0.276$, $\eta^2=0.345$).

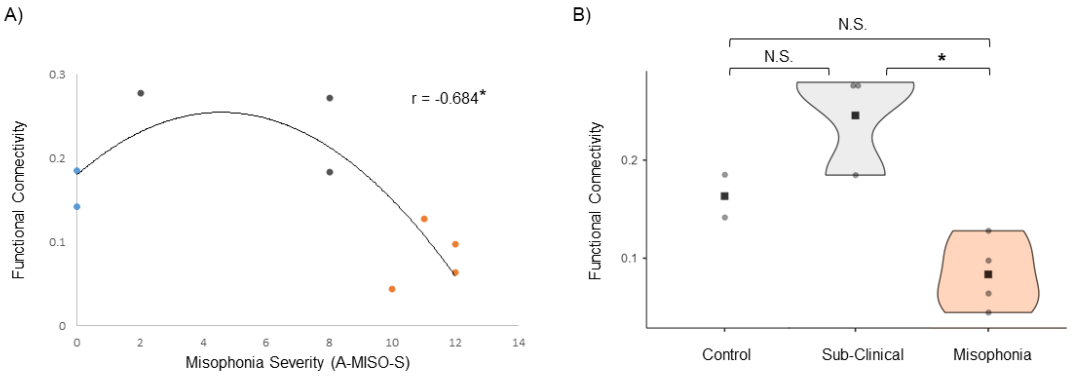


Figure 10: *Mean sound-salience network group differences and correlated severity scores after removing participants with synesthesia.* A) Spearman's correlation between participants' A-MISO-S scores and functional connectivity in the sound sensitivity network, *p < 0.05. Control participants are shown in blue, participants with sub-clinical sensitivity are shown in grey, and those with misophonia are shown in orange. B) Violin plot outlining the distribution in mean network connectivity for the control, sub-clinical (grey), and misophonia (orange) groups, *p < 0.05. Average mean network connectivity is denoted by a black square. Note: control group has n=2 and no observed variation.

2.4 Discussion

The current experiment was designed to examine how resting-state functional connectivity within a putative sound-salience network varies as a function of specific sound sensitivity severity. Restrictions on the extent of available data limited our ability to draw statistically significant conclusions in many cases; however, the data presented demonstrate interesting trends with respect to resting-state functional connectivity differences in people with misophonia. Specifically, we observed 1) reduced mean network connectivity in those with clinical misophonia symptoms, but not those with sub-clinical sound sensitivity; 2) that differences in connectivity were most apparent in the sound-salience network; and 3) that neural correlates of misophonia may be affected by synesthetic comorbidity. The following discussion focuses on these trends as the current study represents a subset of the total sample that will be acquired before more meaningful conclusions can be fully drawn.

2.4.1 Group Differences in Functional Connectivity

In the current experiment, participants with misophonia showed a trend toward reduced resting-state connectivity within our putative sound-salience network (but this failed to reach statistical significance). This apparent reduction in resting state connectivity was most clear in those with clinical misophonia (A-MISO-S ≥ 10). In fact, connectivity across this same network of areas appeared somewhat elevated in individuals with sub-clinical sound sensitivity (but this also failed to reach significance). If these patterns are consistent over the intended sample size, it may suggest that behavioural differences between these groups (which are captured by surveys like the A-MISO-S), are rooted in neurological differences. Interestingly, when individual participant data were plotted against both network connectivity and the correlations between individual ROI-ROI pairs, participants appear to cluster according to the previously described cutoff for clinical misophonia (Schröder et al., 2013). This suggests that the A-MISO-S is a valid measure with physiologically relevant cutoff scores.

One of the aims of this study was to determine whether atypical neural activity, previously observed in older participants with misophonia (Kumar et al., 2021, 2017; Schröder et al., 2019), is also present in younger individuals from whom the majority of survey data describing the experience of misophonia has been collected (Naylor et al., 2021; M. S. Wu et al., 2014; Zhou et al., 2017). Indeed, a trend toward atypical connectivity was observed in our sample of individuals with misophonia (mean age = 23.3 years), suggesting that neural correlates of misophonia may be present in young adults with self-reported symptoms. However, the observed *pattern* of atypical connectivity in this study is different from existing studies on connectivity in misophonia.

Contrary to our prediction, it appears that individuals with misophonia may have reduced resting-state connectivity in the purported sound-salience network. This network (comprising the anterior insula, auditory cortex, amygdala, and hippocampus) was proposed based on findings that individuals with misophonia have *increased* sound-evoked activity in, and evoked functional connectivity between, these regions in response to trigger sounds (Kumar et al., 2017; Schröder et al., 2019). The discordance between these previous findings and the trend observed in our data raise interesting questions about the relationship between resting and stimulus-evoked patterns of brain

activity. Although resting-state connectivity is often predictive of differences in evoked activity (Tavor et al., 2016), misophonia is unique in that atypical patterns of evoked activity are specific to trigger stimuli, and are not observed in response to neutral or universally aversive stimuli (Kumar et al., 2017; Schröder et al., 2019). In other words, the network appears to function atypically in response to trigger sounds, but typically in response to the vast majority of sounds. Thus, the relationship between resting activity and stimulus-evoked activity may be more complex in misophonia than in conditions with more homogenous patterns of evoked activity.

2.4.2 Specific or Global Connectivity Differences?

The current study presents preliminary evidence in support of reduced functional connectivity in individuals with misophonia between regions involved in the attribution of sound salience and the regulation of emotion. However, this pattern of decreased connectivity does not appear to reflect a global reduction in synchronous neural activity. For example, connectivity between nodes of the sound-salience network and Broca's area (a control region expected to be functionally coupled to this network, but not expected to play a role in the experience of misophonia) was similar between the control and misophonia groups (Figures 2 & 6). Moreover, a recent study by Kumar & colleagues (2021) demonstrated that misophonics show *increased* resting-state connectivity between the motor cortex and both the auditory and visual (V1/V2) cortices. Thus, misophonia may be characterized by a complex pattern of changes in resting-state connectivity that extend beyond the sound-salience network, and the directionality of these changes appears to vary by region of focus. Indeed, a data-driven, whole-brain approach to quantifying group differences in resting-state connectivity is necessary to get a more complete picture. Due to our limited sample size, the current study focused on hypothesis-driven analyses with pre-determined ROIs, but in the future we plan to examine both intra- and inter-network connectivity using independent component analysis (these analyses have been pre-registered on the Open Science Framework, https://osf.io/p6qrm/).

2.4.3 The Relationship between Sound Sensitivity Severity and Functional Connectivity

Similar to the trends observed at the group level, we observed an association between misophonia symptom severity and functional connectivity in the sound-salience network that was opposite to what we predicted (but which failed to reach statistical significance): individuals with the highest A-MISO-S scores had the lowest connectivity in the sound-salience network. However, because individual data are clustered by group, with a very small sample in each (Figure 4) this relationship is likely currently being driven by the observed group differences. In order to draw conclusions on how functional connectivity differences scale with symptom severity, it is necessary to acquire larger samples with a greater range of A-MISO-S scores in each group. This is particularly important to observe differences in the misophonia group, where we have currently sampled A-MISO-S scores between 10-13 on a scale that extends to 24.

2.4.4 The Role of Synesthesia in Individual Differences Among those with Misophonia

Previous studies have reported that the incidence of synesthesia is greater in individuals with misophonia (9-17%; [Rouw & Erfanian, 2018]) than in the neurotypical population (2-4%; [Simner et al., 2006]). The sample sizes presented here are insufficient to quantify relative incidence rates; however, 35.7% of our overall sample reported having synesthetic associations. Because individuals with synesthesia have been shown to have atypical neural connectivity (Hubbard & Ramachandran, 2005; Rothen & Terhune, 2012), and because we were interested in patterns of connectivity specific to the experience of misophonia, we examined data from the current study after removing participants with self-identified synesthetic associations. After doing so, within-group variability decreased and between-group differences in average sound-salience network connectivity were found to be statistically significant (Figure 10). This suggests that the already complex pattern of changes to resting-state connectivity associated with misophonia may be further complicated by the presence of synesthesia. Given the current sample size, we were unable to investigate this question statistically. However, our data suggest that future studies should continue to assess those with misophonia for the presence of synesthesia and explore these individual differences rather than treating misophonia as a homogenous phenomenon.

Chapter 3

Experiment: Perceptual narrowing in misophonia

3.1 Introduction

Similar to the neuroimaging studies described in Chapter 2, previous behavioural studies have largely focused on measuring perceptual and cognitive functions of those with misophonia in the presence of trigger sounds (Daniels et al., 2020; Frank et al., 2020; Seaborne et al., 2018; Silva et al., 2019). These studies have shown that people with misophonia have impaired attention, decreased cognitive control, and poorer perceptual performance in the presence of their trigger sounds. However, it is unclear how the perceptual abilities of those with misophonia may differ from typically-developed controls at baseline, in the absence of triggers. Just as we might expect neural differences at rest to reflect differences in brain activity in response to trigger sounds, we might expect baseline perceptual abilities of those with misophonia to shape their cognitive and perceptual experience when exposed to trigger sounds.

As described above, misophonia is similar in nature to synesthesia (i.e. both are phenomena in which a sensory stimulus automatically elicits an atypical response), and these similarities have led to the suggestion that misophonia and synesthesia may have a common underlying neural mechanism (Edelstein et al., 2013; McGeoch et al., 2020; Palumbo et al., 2018). Synesthesia is characterized by functional and structural hyperconnectivity between sensory brain regions (Dovern et al., 2012; Rouw & Scholte, 2007; Zamm, Schlaug, Eagleman, & Loui, 2013), which is hypothesized to develop as a result of reduced synaptic pruning (Carmichael & Simner, 2013; Hubbard & Ramachandran, 2005; Spector & Maurer, 2009). Early in development, the brain enters a phase of neuronal exuberance, during which many more neurons and synapses are produced than are required by the mature brain (Innocenti & Price, 2005). Over time, the selective deletion of axons, axonal branches and/or synapses leads to maintenance of some of these juvenile structures, while others are eliminated, leaving a more mature and efficient pattern of neuronal circuitry (Innocenti & Price, 2005). This synaptic pruning co-occurs with perceptual narrowing – a normal developmental process where children learn to perceive stimuli to which they are regularly exposed (native stimuli;

Grossmann, Missana, Friederici, & Ghazanfar, 2012; Lewkowicz, 2014). As a result of narrowing, perceptual abilities are fine-tuned such that the mature brain processes native stimuli with greater efficiency and accuracy than non-native stimuli. For example, while English-speaking adults have difficulty discriminating between Hindi phonemes that are distinct to Hindi-speaking adults, English-learning infants aged 6–8 months old perceive the distinction (Werker, Gilbert, Humphrey, & Tees, 1981). Subsequent work has shown that the decline in discrimination of these non-native speech sounds (i.e. perceptual narrowing) occurs between 6 and 10 months of age (Werker & Tees, 1984). Indeed, similar results have been demonstrated for infant perception of native vs. non-native faces, with the process of perceptual narrowing becoming evident between 4 and 9 months of age (Maurer & Werker, 2014). Interestingly, infants in this sensitive period also show evidence of synesthetic perception. For example, infants have been shown to demonstrate associations between specific colours and shapes (Wagner & Dobkins, 2009). Researchers have theorized that these early atypical sensory associations are a consequence of neuronal exuberance and immature synaptic pruning, and suggest that since synesthetes have these atypical sensory associations into adulthood, this phenotype may co-occur with reduced perceptual narrowing.

Indeed, Maurer & Colleagues (2020) demonstrated that synesthetes have better discrimination accuracy for non-native phonemes and faces than typically-developed controls. However, synesthetes and controls performed similarly on native phoneme and native face discrimination tasks, suggesting that reduced perceptual narrowing does not diminish participants' perceptual abilities for native stimuli. If synesthesia and misophonia have a common neural mechanism (i.e. aberrant neural connectivity resulting from atypical synaptic pruning), those with misophonia may also demonstrate evidence of reduced perceptual narrowing. Thus, the current study adapted the experimental approach described by Maurer and colleagues (2020) to test the hypothesis that individuals with misophonia show reduced perceptual narrowing compared to typically-developed controls in support of the following aims: 1) to characterize the perceptual abilities of those with misophonia in the absence of trigger sounds, and 2) to use the results of these behavioural tests to make inferences about neural connectivity in misophonia.

3.2 Methods

3.2.1 Participants

Eighteen participants with misophonia and eighteen participants without misophonia[2] were recruited through online advertisements, including postings circulated to misophonia support groups on social media and the OurBrainsCAN registry (Table 2). All participants had English as their first language, normal or corrected-to-normal vision, and no known hearing impairments. Participants who had knowledge of Hindi were excluded from this study, as Hindi phonemes were used as non-native auditory stimuli. This study was approved by the Western University Non-Medical Research Ethics Board (NMREB; Appendix B). All experimental methods and data analyses for this study were pre-registered on the Open Science Framework (https://osf.io/auenm)**.**

Table 2: Characteristics of control and misophonia participants in experiment 2.

	Control (n=18)	**Misophonia (n=18)**
Age (M)	19-40 (26)	18-49 (26.8)
Sex	12 Females, 6 Males	16 Females, 2 Males
# Reporting Synesthesia	1	3

3.2.2 Procedure

Testing was completed entirely online using personal computers or laptops. Interested participants received a link to an online survey hosted on Qualtrics (Provo, UT). This survey included a screener to assess participant eligibility, after which implied consent was collected from eligible participants. The remainder of the survey consisted of three sections: demographics, misophonia experience, and synesthesia experience.

[2] Based on replicating the findings of Maurer and colleagues (2020) we aimed to recuit a total sample size of 90 (45 misophonics, 45 controls) for the current study. Enrollment for this study is currently ongoing.

In the demographics section, information was collected about the participant's age, sex, race, and mental health history. In the misophonia section, participants were first asked if they "have strong emotional reactions to specific sounds": those who answered "no" comprised the control group, while those who answered "yes" completed the Amsterdam Misophonia Scale (A-MISO-S; Schröder et al., 2013). Participants who scored at or above the cutoff for clinical misophonia (A-MISO-S score ≥10) comprised the misophonia group (A-MISO-S scores ranged from 10-20, mean A-MISO-S = 13.9). In the synesthesia section, all participants were provided with a brief description of synesthesia and asked if they "suspect that they have synesthesia": those who answered "yes" proceeded to the Synesthesia Questionnaire (Eagleman et al., 2007), which evaluated synesthetic associations by inquiring about inducer-concurrent relationships.

Participants then completed a series of behavioural tasks written in PsychoPy/PsychoJS (Peirce et al., 2019) and hosted on Pavlovia (Nottingham, UK), which consisted of auditory, visual, and control tasks adapted from Maurer & colleagues (2020), and which were presented in random order. To minimize environmental variability, participants were asked to dim the lights, turn up the brightness on their computer screen, minimize distractions, adjust the computer volume to a level that was loud but not uncomfortable, and sit squarely in front of their computer 50 cm away from the screen. In addition, participants were instructed to measure the height of their screen in centimeters and enter it along with their participant ID at the beginning of each behavioural task so that stimulus size was consistent across participants (and the same as that used by Maurer et al., 2020).

In the auditory task (Figure 11), participants were presented with a phoneme pair in either English (native) or Hindi (non-native) and asked to indicate whether the two phonemes were the same or different using their keyboard arrow keys. The first phoneme was presented, followed by silence for 1000ms, and then by the second phoneme. A text prompt then appeared to cue participants to respond with their arrow keys to indicate whether they believed the phonemes were the same or different. Participants completed 40 test trials, which consisted of 24 native/English phoneme pairings (8 same/16 different) and 16 non-naitve/Hindi phoneme pairings (8 same/8

different) presented in random order without feedback (Appendix E). In order to minimize the effect of response bias, perceptual accuracy was computed using d' or the discriminability sensitivity of the 'different' trials (signal) relative to the 'same' trials (noise).

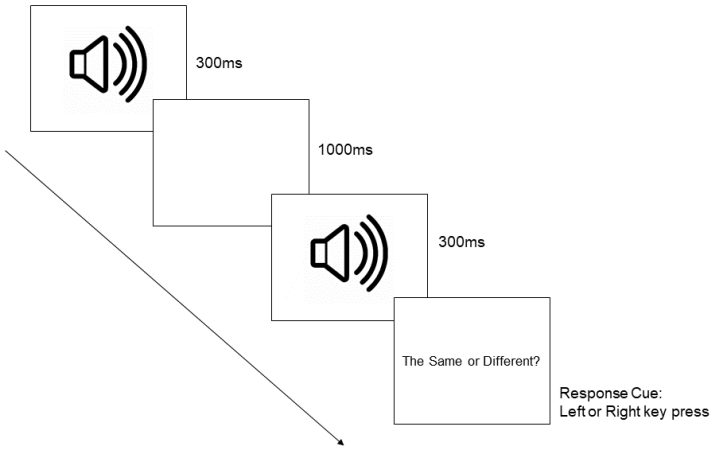


Figure 11: *Auditory phoneme discrimination task.*

In the visual task (Figure 12), participants were presented with a target face at the top half of their screen and two test faces at the bottom half of their screen. One of the test faces was identical to the target face and the other contained slight facial alterations (described below). Participants were instructed to determine which of the two test faces matched the target face. Participants completed three versions of this task: human faces presented in upright orientation (native), human faces presented in inverted orientation (native species/non-native orientation), and chimpanzee faces (non-native species). During each of these tasks, the three faces were presented simultaneously (the upright human and chimpanzee faces were presented for 1000ms and the inverted human faces were presented for 1500ms), followed by a 250ms visual noise mask to obscure any potential afterimage effects. A question mark then appeared to cue participants to indicate whether the face on the bottom left or right matched the target image using their left and right arrow keys. For each face type, participants completed four practice trials before beginning the test block, wherein each of the nine faces was presented as the target image four times for a total of 36 trials per stimulus type. The order of presentation of target faces was randomized in each task and the

position of the correct matching image (left/right) was counterbalanced. Perceptual accuracy was measured as the percentage of correctly matched faces of each type (upright human, inverted human, chimpanzee).

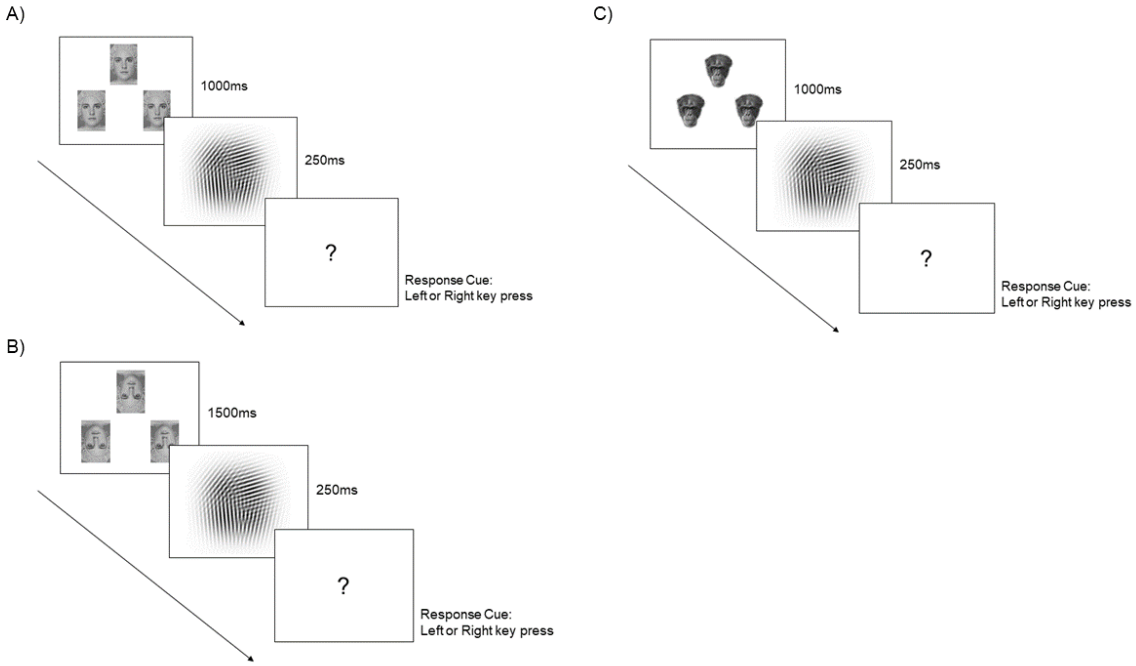


Figure 12: *Visual face matching tasks:* A) upright human faces, B) inverted human faces, C) chimpanzee faces.

Finally, to control for motivation and attention as potential confounds, participants completed a digit-span task to assess working memory. In the digit span task, participants were instructed to remember and reproduce a string of digits that appeared at the centre of their screen. During the task, the digits appeared one by one for 500ms each. In the first block, participants were asked to recall the string of digits in the order they appeared (forward digit span), while in the second they were asked to recall the digits in the reverse order that they appeared (backward digit span). The sequence to be recalled began with 3 digits, and increased in length over the course of the task until a participant made errors on two consecutive trials of a given sequence length. Working memory performance was quantified as total digit span (the sum of the numbers recalled in the forward and backward digit span tasks).

3.2.3 Measures & Materials

3.2.3.1 Psychological Measures

The presence and severity of misophonia and/or synesthesia were captured using the A-MISO-S (Appendix C) and Synesthesia Questionnaire (Appendix D), respectively (detailed descriptions of each are provided in section 2.2.1).

3.2.3.2 Auditory Stimuli

The auditory stimuli (Appendix E), provided by Maurer and colleagues (2020), were sets of synthesized English (native) and Hindi (non-native) phonemes, each with a duration of 300 ms. Discrete phonemes were generated at each point along an 8-point continuum from /ra/ to /la/ (English/native), or from the retroflex /ɖa/ to dental /ɖa/ (Hindi/non-native), and were presented in white noise at a signal-to-noise ratio of 25 dB. Trials consisted either of a pair of identical phonemes (3-3 or 6-6 phonemes), or a pair of different phonemes (1-2, 1-8, 8-1, 2-1 for native phonemes; 1-8 or 8-1 for non-native phonemes), with each pairing presented four times. Highly similar native phonemes (1-2, 2-1) were included to increase task difficulty in the native condition.

3.2.3.3 Visual Stimuli

The visual stimuli, provided by Maurer and Colleagues (2020), were faces presented in sets of three. The native visual stimuli comprised nine Caucasian female human faces that were each presented at a size of 7.5 cm high and 5.0 cm wide (participant screen measurements were used to normalize stimulus size across participants). The set included one original face and 8 faces with slight facial alterations to the location of the eyes and mouth. These alterations included moving the eyes upwards (EU)/downwards (ED) or towards (EI)/away (EO) from the nose by 4mm, and moving the mouth upwards (MU)/downwards (MD) by 2mm (Figure 13A). The non-native visual stimuli comprised inverted human faces (native species/non-native orientation; Figure 13B) and chimpanzee faces (non-native species Figure 13C). The inverted human faces were presented at the same size and comprised the same alterations as the upright stimuli, except they were inverted by 180 degrees. The array of chimpanzee faces was created using the same facial transformations described for

the native stimulus set, and were presented at a size of 5.0 cm high and 4.61 cm wide.

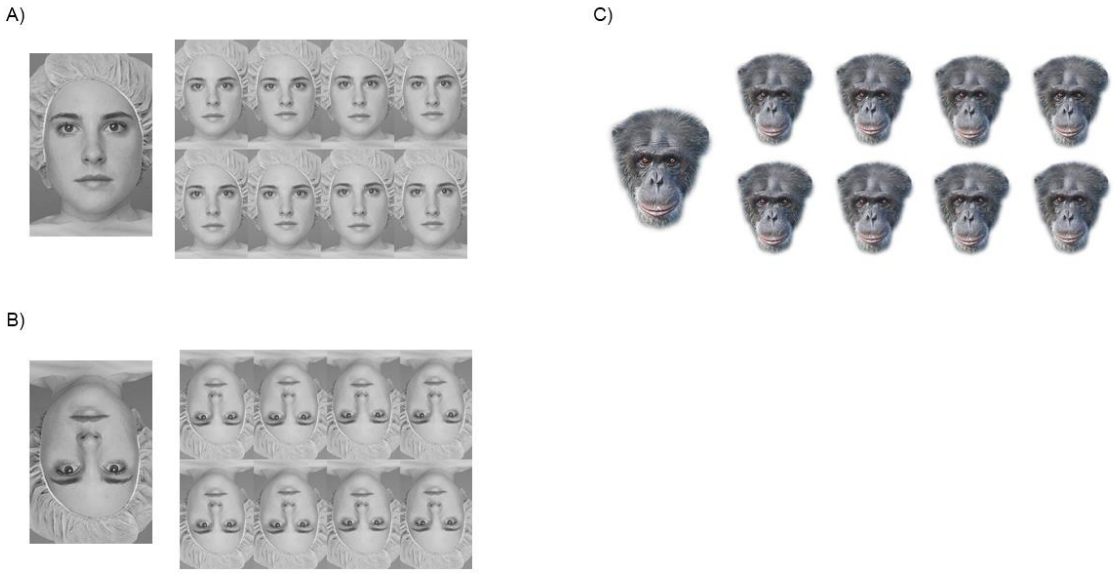


Figure 13: *Visual stimulus sets*: A) upright, B) inverted, and C) chimpanzee. For each stimulus set, the original image is presented at left, and the facial modifications are as follows: top row (EDMD, EDMU, EIMD, EIMU), bottom row (EOMD, EOMU, EUMD, EUMU).

3.2.4 Statistical Analyses

For the auditory task, we computed a two-way ANOVA with group (misophonia, control) as a between-subjects factor and stimulus type (English/native, Hindi/non-native) as a within-subject factor. Perceptual accuracy (d') for each stimulus type was the dependent variable. The standard $p<0.05$ criterion was used to determine the presence of a significant main effect or interaction.

For the visual task, we computed a two-way ANOVA with group type (misophonia, control) as a between-subjects factor and stimulus type (human upright, human inverted, chimpanzee) as a within-subject factor. Percent correct for each stimulus type was the dependent variable. Again, $p<0.05$ was used to determine the presence of a significant main effect or interaction, and t-tests were performed to interpret significant effects where applicable.

Finally, for the digit span task, an independent samples t-test was conducted to analyze group differences.

3.3 Results

3.3.1 Group Differences in Auditory and Visual Discrimination Performance

For the auditory task, the ANOVA conducted on d' values revealed no significant main effect of group (F[1.0, 68.0]=0.249, p=0.619, η^2=*0.004*), no significant main effect of stimulus type (F[1.0, 68.0]=0.01, p=0.919, η^2=*0.0*), and no significant interaction (F[1.0, 68.0]=0.383, p=0.538, η^2=*0.008*) (Figure 14). Therefore, there were no observed group differences in phoneme discrimination accuracy between misophonics and controls for either stimulus type (native/non-native).

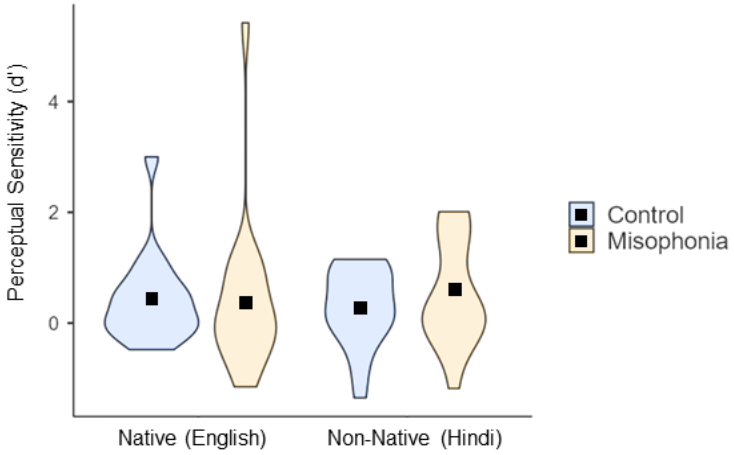


Figure 14: *Group differences in phonemic perceptual sensitivity.* Violin plot outlining the variation in perceptual sensitivity (d') of native and non-native phonemes for controls (blue) and misophonics (orange). Mean d' for each group is denoted by a black square.

For the visual task, the ANOVA revealed a significant main effect of stimulus type (F[2.0, 102.0]=15.985, p<0.001, η^2=*0.231*), but no significant main effect of group (F[1.0, 102.0]=0.238, p=0.627, η^2=*0.002*), and no significant interaction (F[2.0, 102.0]=1.98, p= 0.144, η^2=*0.029*) (Figure 15). Follow-up related samples t-tests demonstrated that across groups, participants were significantly better at matching upright faces than either inverted faces (t[102.0]=3.47, p=0.002) or chimpanzee faces (t[102.0]=5.6, p=<0.001). Therefore, participants had better visual perceptual accuracy for native than non-native stimuli (both non-native orientation or species), but there were no group differences in accuracy between controls and misophonics.

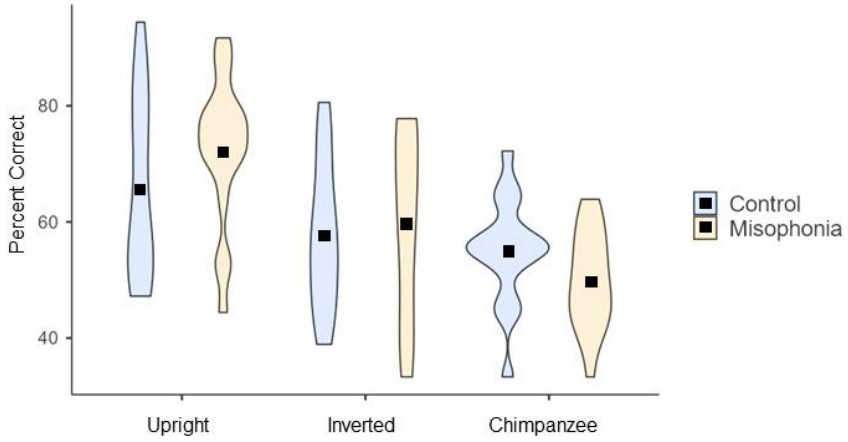


Figure 15: *Group differences in visual perceptual accuracy.* Violin plot outlining the variation in perceptual accuracy (percent correct) of upright/inverted/chimpanzee face matching for controls (blue) and misophonics (orange). Mean proportion correct for each group is denoted by a black square.

For the control task, the independent samples t-test revealed no significant difference between the misophonia and control groups on total digit span performance (t[34.0]=0.725, p=0.473, M_{ctrl} = 14.9, M_{miso} = 14.3).

3.3.2 Relationship Between Symptom Severity and Perceptual Behaviours

In the current study, participants with misophonia were better than chance ($t(17.0)=2.48$, $p=0.024$), and slightly better than control participants at discriminating non-native phonemes ($d'_{miso}=0.55$; $d'_{ctrl}=0.29$), although this group difference did not reach statistical significance. If differences in perceptual performance are related to the experience of misophonia, then variability in perceptual sensitivity among individuals with misophonia may correlate with misophonia symptom severity. Thus, a planned analysis of the relationship between misophonia severity and phoneme discrimination accuracy was conducted whereby the Pearson's correlation between A-MISO-S score and sensitivity to non-native phonemes (d' score) was computed for participants with misophonia. Figure 16 suggests that there may be a trend toward a positive association between symptom severity and perceptual sensitivity; however, this correlation was not statistically significant (Pearson's $r=0.112$, $p=0.659$). As there was no trend toward a group difference in visual discrimination performance, a similar analysis was not undertaken for face matching data.

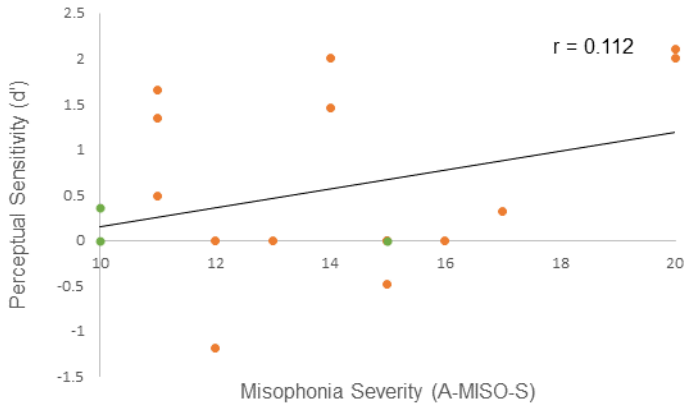


Figure 16: *Correlation between phonemic perceptual sensitivity and sound sensitivity severity.* Spearman's correlation between misophonia symptom severity (A-MISO-S) and perceptual accuracy (d') on non-native phoneme discriminations. Participants with synesthesia are marked in green.

3.4 Discussion

The current study sought to adapt the experimental approach of Maurer and colleagues (2020) to determine whether individuals with misophonia show evidence of reduced perceptual narrowing for phonemes and faces. In our examination of native/non-native phoneme discrimination, both misophonics and control participants struggled to discriminate native (M_{miso} d'=0.38; M_{ctrl} d'=0.41) and non-native phonemes (M_{miso} d'=0.55; M_{ctrl} d'=0.29). Poor overall performance may be related to moving the study online, where there is little control over the testing environment and stimulus presentation hardware; however, it should be noted that the in-lab study of Maurer & colleagues (2020) reported similarly poor performance for their control participants (M_{ctrl} d'=0.39 for non-native stimuli).

It is also worth noting that, due to features of the experimental design, the absence of an effect of stimulus type (native/non-native) in the phoneme discrimination task should not be interpreted as evidence of equal performance across conditions; the native condition included trials in which participants were asked to discriminate between pairs of highly similar phonemes (e.g. those generated at steps 1 and 2 along an 8 step continuum) that were not included in the non-native condition. Rather, the experimental approach was designed to determine whether individuals with misophonia are better able to discriminate non-native phonemes than controls while showing similar performance for native sounds (i.e. a group x stimulus type interaction).

Despite the poor overall performance, misophonics appeared to have higher discrimination accuracy for non-native phonemes than control participants (Figure 14). However, the magnitude of this group difference was much smaller than what was previously observed in a sample of individuals with synesthesia (M_{miso} d' = 0.55 vs M_{ctrl} d' = 0.29; M_{syn} d' = 1.59 vs M_{ctrl} d' = 0.39 [Maurer et al., 2020]). This group x stimulus type interaction failed to reach statistical significance in the current study; however, the sample included here (n=36) is only a portion of the total sample we aim to recruit. Regardless, while a group difference in non-native phoneme discrimination may exist between misophonics and controls, the current effect size (η^2=0.004) is very small, indicating that the effect of group differences on phonemic sensitivity is marginal and unlikely to be comparable to that observed in synesthetes (η^2=0.055).

The current study also examined the relationship between misophonia symptom severity and perceptual accuracy for non-native phoneme discriminations, revealing a trend whereby participants with the greatest symptom severity appeared to also have the highest perceptual accuracy (Figure 16). Additional data points, particularly from individuals with more severe misophonia symptoms, are necessary to determine whether this relationship is meaningful. Finally, it is interesting to note that the three individuals who self-identified as experiencing both misophonia and synesthesia (Figure 16, green circles), did not outperform those participants experiencing misophonia alone on the phoneme discrimination task. While one cannot draw meaningful conclusions from this small sample, it is possible that the presence of misophonia affects the relationship between synesthesia and auditory perceptual narrowing.

The current study found no evidence of group differences in perceptual accuracy on the face-matching task. This suggests that unlike the synesthetes tested by Maurer and colleagues (2020), if atypical perceptual narrowing *is* present in misophonics, it may be restricted to the auditory domain. Given that misophonia primarily involves sensitivity to sound, this result is somewhat intuitive. Indeed, synesthetes have also been shown to have enhanced perception that is specific to their sensory modality. For instance, Banissy & colleagues (2009) found that tactile synesthetes show superior tactile, but not colour discrimination, while colour synesthetes show superior colour, but not tactile discrimination. The sample tested by Maurer & colleagues (2020) included a large number of individuals with visual (41/41) *and* auditory (27/41) synesthetic associations; thus, that they observed superior non-native face *and* phoneme discrimination aligns with this pattern of results. Expanding the current sample to include participants who report experiencing misokinesia (aversive reactions to small, repetitive movements) would allow us to explore the modality-specific nature of perceptual enhancement in misophonics.

Overall, trends in the data shown here suggest that if misophonics show any evidence of reduced perceptual narrowing, it is likely restricted to the auditory domain and that group differences are lesser in magnitude than those with synesthesia.

Chapter 4

Discussion

In this work, two distinct studies were conducted to test the theory that misophonia is characterized by aberrant connectivity between regions of the brain that ascribe salience, process sound, and regulate emotion. In the first experiment (Chapter 2), we provide support for this theory by demonstrating that misophonia may be characterized by reduced resting connectivity in a network of brain regions related to these functions. In the second experiment (Chapter 3), we present preliminary data that suggest people with misophonia may have reduced phonemic perceptual narrowing. Since reduced perceptual narrowing is thought to be a behavioural correlate of altered synaptic pruning during development, resulting in atypical connectivity in adults, confirmation of this result would provide indirect evidence for the overarching theory of aberrant connectivity in misophonia.

4.1 Proposed Mechanism of Abnormal Salience Attribution in Misophonia

To date, the majority of misophonia studies have focused on characterizing the neural and behavioural components of the trigger response. This body of work has demonstrated that people with misophonia have strong psychological and physiological reactions to specific sounds (Edelstein et al., 2013; Schröder et al., 2013) and while these otherwise innocuous sounds are easily ignored by the general population, individuals with misophonia reflexively attend to them (Dozier & Morrison, 2017). Moreover, previous neuroimaging studies have shown that the misophonic reaction to trigger sounds is marked by heightened activity in the anterior insula (Kumar et al., 2017; Schröder et al., 2019), a region of the brain that responds to highly salient sounds and plays a role in determining which environmental stimuli to focus on, and which to ignore (Uddin et al., 2017; Wiech et al., 2010; T. Wu et al., 2019). Aberrant activity in this brain region therefore suggests that individuals with misophonia may assign high salience to their trigger sounds, but it is unclear how this atypical process of salience attribution develops.

The current studies are some of the first to investigate baseline neural activity and perceptual abilities in people with misophonia. These experiments separately demonstrate that differences between misophonics and typically-developed controls may be detectable in the absence of trigger sounds. If the trends observed in the current studies are evident in larger samples, this would shed light on a potential mechanism that may give rise to abnormal salience attribution in misophonia. Specifically, if misophonics are determined to show evidence of reduced auditory perceptual narrowing, this may present indirect evidence of atypical synpatic pruning during development. This synaptopathy would be expected to give rise to atypical patterns of connectivity in the brain. We therefore propose the following theoretical mechanism: misophonia is characterized by atypical refinement of neural circuity during development that gives rise to atypical functional connectivity in the sound-salience network and subsequent salience attribution impairments.

4.1.1 Circuit Refinement, Development, and Misophonia

There is some evidence to support the idea that atypical development of neural projections underlies the experience of misophonia; a genetic investigation conducted by Fayzullina et al. (2015) indicated that a single nucleotide polymorphism (SNP or “snip”) at a locus near the TENM2 gene (encoding the Teneurin-2 protein) is associated with sensitivity to chewing sounds. Teneurin proteins have been shown to play a role in synapse induction, regulation of neuronal morphology, and the spatial organization of neuronal projections (Mosca, 2015); thus, genetic variation in the encoding and subsequent expression of this protein may underlie atypical synapse formation and elimination in the misophonic brain.

If atypical synaptic pruning, perhaps related to abnormal Teneurin-2 expression, gives rise to the experience of misophonia, then one might expect the onset of related symptoms to occur relatively early in life. Indeed, the misophonic reaction to specific sounds has often been described as a conditioned response that typically develops in the preteen years (Edelstein et al., 2013; Wu et al., 2014). In his 2015 collection of case reports, Dozier describes how young misophonia patients developed their first trigger, often describing situations wherein individuals struggle to ignore repetitive sounds,

experience distress, and subsequently develop a misophonic response. This suggests that individuals with misophonia experience deficits in sound-salience processing prior to developing the characteristic pattern of aversive psychological and physiological responses to trigger sounds. This sequence of events and early age of onset support the idea that misophonia may arise subsequent to atypical early circuit development.

4.1.2 Atypical Resting-state Connectivity & The Misophonic Experience

It stands to reason that atypical circuit refinement throughout early periods of development would manifest as atypical patterns of structural and functional brain connectivity in adulthood. As discussed in Chapter 2, those with misophonia showed a trend toward reduced functional connectivity in our putative sound-salience network at rest. A key node of this network, the anterior insula, has been implicated in a vast array of functions, including directing behavioural responses to salient sounds (Uddin, 2015; Wiech et al., 2010). While part of this role may involve coordinating the auditory and limbic systems to produce sound-evoked autonomic responses and associated motor behaviours, it is likely that an equally important function of the anterior insula is to ensure these behaviours are suppressed in response to innocuous sounds. This type of ‘sensory gating’ is essential for filtering out the myriad of behaviourally-irrelevant sounds to which we are exposed in order to retain the capacity to respond appropriately to appetitive or aversive stimuli. That the anterior insula has been shown to process emotional salience pre-attentively (Chen et al., 2014), suggests it is well positioned to play a role in sensory gating. Indeed, atypical insular function has been demonstrated to result in impaired salience processing, cognitive control, and attention (Uddin, 2015; T. Wu et al., 2019). This includes conditions characterized by deficits in sensory gating such as attention-deficit hyperactivity disorder and autism, which are similarly marked by reduced connectivity between the insula and other brain regions at rest (Francis et al., 2019; Zhao et al., 2017). Thus, a reduction in sound-salience connectivity in misophonics may underlie difficulty ignoring typically innocuous sounds. Specifically, decreased coordinated activity between the anterior insula, auditory cortex, and limbic structures may impair the ability of the anterior insula to make accurate judgements about sound salience, leading to impaired sensory gating. This may, in turn, lead to

reduced ability to ignore repetitive sounds that are normally suppressed, and the formation of atypical responses to otherwise innocuous sounds (such as those previously observed in trigger-evoked patterns of BOLD activity [Kumar et al., 2017; Schröder et al., 2019]).

In summary, we propose that reduced connectivity between regions of the sound-salience network may modulate aberrant salience attribution in misophonia, and that this deficit may arise subsequent to synaptopathy in early development. However, to test these hypotheses, it would be necessary to conduct a longitudinal study of misophonia development.

4.2 Implications & Future Directions

4.2.1 Differences between Sub-Clinical Sound Sensitivity and Misophonia

The theoretical mechanism proposed above is supported by the apparent trends in group differences in sound-salience network connectivity discussed in Chapter 2. In that experiment, participants with misophonia showed a consistent, yet not statistically significant *reduction* in connectivity within the sound-salience network compared to control participants – a pattern that was distinct from what was observed in participants with sub-clinical sound sensitivity. In fact, the mean sound-salience network connectivity among participants with sub-clinical sound sensitivity appeared to be somewhat *increased* relative to controls (Figures 2 & 3). If this pattern of results is reproduced in the larger samples, both groups may indeed show evidence of atypical connectivity within this network of areas; however, differences in the direction of change relative to controls appears to be related to symptom severity. One of the defining characteristics of clinical misophonia is severe difficulty disengaging from thoughts about trigger sounds (McKay, Kim, Mancusi, Storch, & Spankovich, 2018; Schröder et al., 2013). In contrast, while those with sub-clinical sound sensitivity may be irritated by specific sounds, they are typically able to control and redirect their thoughts and emotions. As described above, we believe that reduced connectivity within the sound-salience network and subsequent impairments to sensory gating may underlie differences in cognitive control that have been observed between clinical and sub-clinical sensitivity.

Importantly, the trending group differences observed in the current study suggest that resting state measures of neural connectivity may have diagnostic potential and that future studies should continue to investigate differences between those with sub-clinical sound sensitivity and misophonia. In addition, since neural differences can be observed at rest, this suggests it is possible to study the misophonic brain without subjecting participants to trigger sounds.

4.2.2 Individual Differences in Misophonia

The current study highlights the importance of studying individual differences in misophonia. Misophonia is a heterogeneous phenomenon with vast variation in triggering stimuli, emotions involved in the misophonic reaction, symptom severity, and the presentation of comorbid conditions including (but not limited to) misokinesia and synesthesia. Historically, attempts have been made to control for this variability (e.g. by using comorbid conditions as an exclusion criteria) in order to begin characterizing misophonia as a discrete neuropsychological condition (Jager et al., 2020; Potgieter et al., 2019; Rouw & Erfanian, 2018; M. S. Wu et al., 2014). However, misophonia is not yet categorized as a disorder in diagnostic manuals, and understanding these individual differences is critical to achieving a nuanced and accurate categorization of the disorder. Although the current studies were underpowered to statistically investigate individual differences, tracking and exploring the impact of these variables on neural connectivity and perceptual abilities revealed some interesting trends.

4.2.3 How Similar are Misophonia and Synesthesia?

Misophonia is commonly compared to synesthesia, and the two phenomena are suggested to share similar perceptual and neural phenotypes. Previously, some researchers have speculated that misophonia may be a type of synesthesia where sound is the inducer and emotion is the concurrent (Edelstein et al., 2013; Palumbo et al., 2018). However, trends apparent in the current study indicate that misophonia may be perceptually and neurologically distinct from synesthesia. Synesthesia is typically characterized by hyperconnectivity within and between brain networks (Dovern et al., 2012; Rothen & Terhune, 2012), and while misophonia may be similarly characterized

by atypical connectivity, the nature of aberrant connectivity in misophonia appears distinct. Particularly, misophonia may be characterized by atypical connectivity that is reduced in some networks (i.e. sound-salience) and enhanced in others (i.e. the sensory-motor networks discussed by Kumar & colleagues [2021]). Moreover, in the current study, misophonics with reported synesthetic associations appeared to be outliers with different patterns of sound-salience network connectivity (however, small sample sizes precluded a group wise comparison). We therefore suggest that researchers and clinicians refrain from classifying misophonia as a form of synesthesia until the neural and perceptual differences between these groups are further investigated. To accomplish this, future studies may opt to: 1) use whole-brain connectivity analyses to explore atypical functional connectivity more broadly; and 2) robustly explore differences between misophonic participants with and without comorbid synesthesia, and where possible, recruit a group of synesthetes without comorbid misophonia for comparison.

4.3 Limitations

As mentioned throughout this thesis, both the neuroimaging (Chapter 2) and perceptual narrowing (Chapter 3) studies had small samples. As a result, the majority of our findings did not reach statistical significance and the analyses for the neuroimaging study were restricted to hypothesized networks rather than whole-brain, data driven approaches. However, both of these studies are ongoing, so once full samples are acquired the statistical significance and effect sizes of trends discussed here can be fully interpreted, allowing us to make more meaningful conclusions.

In addition, both studies also relied on self-reported measures of symptom presence and severity in order to group participants rather than a clinical evaluation or more comprehensive diagnostic battery. Although this design choice allowed us to bridge a critical gap between existing self-report and neuroimaging studies of misophonia, we cannot be sure of the validity of participants' reported experiences of misophonia or synesthesia. Both samples were also predominantly female, and since it is unknown if misophonia and synesthesia are characterized by sex differences, the generalizability of these findings may be limited.

4.4 Conclusions

Misophonia is a psychologically debilitating and prevalent, yet understudied, condition. Although this research area has gained traction over the last few years, misophonia remains largely uncharacterized and there are a number of pertinent questions that need to be addressed before it can be classified in diagnostic manuals. The current work sought to address some of these etiological gaps by investigating neural connectivity and perceptual abilities in people with misophonia.

This work importantly demonstrated that those with misophonia may show differences in neural activity observed at rest when compared to both people with sub-clinical sensitivity to specific sounds and control participants. Specifically, misophonia may be distinctly characterized by reduced connectivity in a brain network that we hypothesize to play a role in assigning salience to sound (comprised of the anterior insula, auditory cortex, amygdala, and hippocampus). Given that people with misophonia assign high salience to their trigger sounds, reflexively attend to such sounds, and have great difficulty redirecting focus away from them, this result aligns with differences in symptomology between people with misophonia and sub-clinical sound sensitivity.

Throughout this work we also highlighted individual differences in perception and neural connectivity as a function of sound sensitivity severity and comorbid synesthesia. These findings further implicate misophonia as a heterogeneous phenomenon; and since understanding these individual differences is pertinent to achieving a nuanced classification of misophonia, we suggest that researchers incorporate these differences into their study designs whenever possible.

In a world that comprises a cacophony of sound, people with misophonia struggle with extremely aversive reactions to ordinary sounds. This experience is not only psychologically distressing, but can have detrimental cognitive and social impacts. The results of this work are a step towards understanding and legitimizing this experience. In addition, this work informs the neural and perceptual characterization of misophonia, and since misophonia is not yet classified as a psychological disorder, this will play an important role in progressing and shaping the classification process.

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Appendix A

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

Dear Dr. Blake Butler

The Western University Health Science Research Ethics Board (HSREB) has reviewed and approved the above mentioned study as described in the WREM application form, as of the HSREB Initial Approval Date noted above. This research study is to be conducted by the investigator noted above. All other required institutional approvals must also be obtained prior to the conduct of the study.

Documents Approved:

Document Name	Document Type	Document Date	Document Version
Clip Survey	Paper Survey	31/Oct/2019	2.0
Email Script for Recruitment	Email Script	31/Oct/2019	2.0
Info_letter_consent_Nov19	Written Consent/Assent	21/Nov/2019	3.0
Misophonia_DebriefingLetter	Debriefing Script	31/Oct/2019	2.0
MisophoniaStudy_Protocol	Protocol	31/Oct/2019	2.0
Poster_Controls	Recruitment Materials	31/Oct/2019	1.0
Posters_Miso	Recruitment Materials	31/Oct/2019	2.0
Qualtrics Survey_Nov19	Online Survey	21/Nov/2019	3.0
SONA Ad_Nov19	Recruitment Materials	21/Nov/2019	2.0

Documents Acknowledged:

Document Name	Document Type	Document Date	Document Version
Misophonia_CitationList	References	26/Sep/2019	1

No deviations from, or changes to, the protocol or WREM application should be initiated without prior written approval of an appropriate amendment from Western HSREB , except when necessary to eliminate immediate hazard(s) to study participants or when the change(s) involves only administrative or logistical aspects of the trial.

REB members involved in the research project do not participate in the review, discussion or decision.

The Western University HSREB operates in compliance with, and is constituted in accordance with, the requirements of the TriCouncil Policy Statement: Ethical Conduct for Research Involving Humans (TCPS 2); the International Conference on Harmonisation Good Clinical Practice Consolidated Guideline (ICH GCP); Part C, Division 5 of the Food and Drug Regulations; Part 4 of the Natural Health Products Regulations; Part 3 of the Medical Devices Regulations and the provisions of the Ontario Personal Health Information Protection Act (PHIPA 2004) and its applicable regulations. The HSREB is registered with the U.S. Department of Health & Human Services under the IRB registration number IRB 00000940.

Please do not hesitate to contact us if you have any questions.

Appendix B

Date: 12 November 2020

To: Dr. Blake Butler

Project ID: 116080

Study Title: Assessing perceptual abilities in misophonia

Short Title: Misophonia Perceptual Narrowing

Application Type: NMREB Initial Application

Review Type: Delegated

Full Board Reporting Date: December 4 2020

Date Approval Issued: 12/Nov/2020

REB Approval Expiry Date: 12/Nov/2021

Dear Dr. Blake Butler

The Western University Non-Medical Research Ethics Board (NMREB) has reviewed and approved the WREM application form for the above mentioned study, as of the date noted above. NMREB approval for this study remains valid until the expiry date noted above, conditional to timely submission and acceptance of NMREB Continuing Ethics Review.

This research study is to be conducted by the investigator noted above. All other required institutional approvals must also be obtained prior to the conduct of the study.

Documents Approved:

Document Name	Document Type	Document Date	Document Version
Protocol_misosyn	Protocol	05/Oct/2020	1.0
DefiefingStatement_misosyn	Debriefing document	05/Oct/2020	1.0
Notice of Ineligibility	Debriefing document	05/Oct/2020	1.0
RecruitmentEmail_misosyn	Recruitment Materials	05/Oct/2020	1.0
Database Posting	Recruitment Materials	05/Oct/2020	1.0
QualtricsSurvey_misosyn	Online Survey	05/Oct/2020	1.0
Chimpanzee Face Discrim	Online Survey	02/Nov/2020	1.0
Human Face Discrim	Online Survey	02/Nov/2020	1.0
Phoneme Example	Online Survey	02/Nov/2020	1.0
Indentifying information_Revised	Protocol	06/Nov/2020	2.0
OurBrainsCAN Posting	Recruitment Materials	05/Nov/2020	1.0
LOI_misosyn_Revised	Implied Consent/Assent	05/Nov/2020	2.0
RecruitmentPosters_misosyn_Revised	Recruitment Materials	05/Nov/2020	2.0

Documents Acknowledged:

Document Name	Document Type	Document Date	Document Version
Screener_misosyn	Screening Form/Questionnaire	05/Oct/2020	1.0

No deviations from, or changes to the protocol should be initiated without prior written approval from the NMREB, except when necessary to eliminate immediate hazard(s) to study participants or when the change(s) involves only administrative or logistical aspects of the trial.

The Western University NMREB operates in compliance with the Tri-Council Policy Statement Ethical Conduct for Research Involving Humans (TCPS2), the Ontario

Appendix C

Amsterdam Misophonia Scale (A-MISO-S)*

1. How much of your time is occupied by misophonic sounds? (How frequently do the (thoughts about the) misophonic sounds occur?)

None	◯	0
Mild, less than 1 hr/day,or occasionally (thoughts about) sounds (no more than 5 times a day)	◯	1
Moderate, 1 to 3 hrs/day, or frequent (thoughts about) sounds (no more than 8 times a day, most of the hours are unaffected).	◯	2
Severe, greater than 3 hrs and up to 8 hrs/day or very frequent (thoughts about) sounds.	◯	3
Extreme, greater than 8 hrs/day or near constant (thoughts about) sounds.	◯	4

2. How much do these misophonic sounds interfere with your social, work or role functioning? (Is there anything that you don't do because of them? If currently not working determine how much performance would be affected if you were employed.)

None	◯	0
Mild, slight interference withi social or occupational/school activities, but overall performance not impaired.	◯	1
Moderate, definite interference with social or occupational performance, but still manageable.	◯	2
Severe, causes substantial impairment in social or occupational performance.	◯	3
Extreme, incapacitating.	◯	4

3. How much distress do the misophonic sounds cause you? (In most cases, distress is equated with irritation, anger, or disgust. Only rate the emotion that seems triggered by misophonic sounds, not generalized irritation or irritation associated with other conditions.)

None	◯	0
Mild, occasional irritation/distress.	◯	1
Moderate, disturbing irritation/anger/disgust, but still manageable.	◯	2
Severe, very disturbing irritation/anger/disgust.	◯	3
Extreme, near constant and disturbing anger/disgust.	◯	4

*Amsterstam Misophonia Scale (A-MISO-S) from Schröder, A., Vulink, N., & Denys, S. (2013). Misophonia: Diagnostic criteria for a new psychiatric disorder. *PLoS ONE*, *8*(1), e54706. doi:10.1371/journal.pone.0054706

4. How much effort do you make to resist the (thoughts about the) misophonic sounds? (How often do you try to disregard or turn your attention away from these sounds? Only rate effort made to resist, not success or failure in actually controlling the thought or sound.)

Makes an effort to always resist, or symptoms so minimal, doesn't need to actively resist.	◯	0
Tries to resist most of the time.	◯	1
Makes some effort to resist.	◯	2
Yields to all (thoughts about) misophonic sounds without attempting to control them, but does so with some reluctance.	◯	3
Completely and willing yields to all obsessions.	◯	4

5. How much control do you you have over your thoughts about the misophonic sounds? How successful are you in stopping or diverting your thinking about the misophonic sounds? Can you dismiss them?

Complete control.	◯	0
Much control, usually able to stop or divert thoughts about misophonic sounds.	◯	1
Moderate control, sometimes able to stop or divert thoughts about misophonic sounds.	◯	2
Little control, rarely successful in stopping or dismissing thoughts about misophonic sounds, can only divert attention with difficulty.	◯	3
No control, experience thoughts as completely involuntary, rarely able to alter thinking about misophonic sounds.	◯	4

6. Have you been avoiding doing anything, going any place, or being with anyone because of your misophonia? (How much do you avoid, for example, by using other loud sounds, such as music?)

No deliberate avoidance.	◯	0
Mild, minimal avoidance, Less than an hr/day or occasional avoidance.	◯	1
Moderate, some avoidance. 1 to 3 hr/day or frequent avoidance	◯	2
Severe, much avoidance. Greater than 3 up to 8 hr/day. Very frequent avoidance.	◯	3
Extreme very extensive avoidance. Greater than 8 hr/day. Doing almost everything you can to avoid triggering symptoms.	◯	4

Total Score:
0 = No specific sound sensitivity
1-9 = Sub-clinical sound sensitivity
10-24 = Misophonia

Appendix D

The Synesthesia Questionnaire
Developed by the authors of the Synesthesia Battery

Please indicate your responses to the questions below

1. Do numbers or letters cause you to have a colour experience? Example: does the letter J “mean” yellow to you? Or does “5” make you perceive purple?

   Yes, I have had similar experiences

   No, I have not had such experiences

2. Do weekdays and months have specific colors? Example: does July always mean Navy Blue to you? Is Wednesday always orange?

   Yes, I have similar associations

   No, I do not have such associations

3. Do you imagine or visualize weekdays, months, and/or years as having a particular location in space around you? Example: is September always located two feet in front of you to the left?

   Yes, I have always felt these specific spatial locations

   No, I have never felt this kind of association

4. Does hearing a sound make you perceive a colour? Example: does a shrill car horn cause you to see the colour green? Does C sharp make you see pink?

   Yes, I do have such experiences

   No, I have not had such experiences

5. Do certain words trigger a taste in your mouth? Example: does the name ‘Derek’ taste like earwax?

   Yes, this is familiar to me

   No, I have never felt like this

6. Do you feel a sense of touch when you smell things? Example: does the smell of coffee make you feel as though you are touching a cold glass surface?

   Yes, I have had such experiences

   No, this doesn't happen with me

7. Many other unusual blendings of the senses have been reported. Do you suspect that you experience an unusual blending that other people do not have (other than the ones listed above)? These could include automatically hearing a sound when you see movement, or the sense of a shape being triggered by a taste, or experiencing a colour when feeling pain.

   Yes, I believe I may have other forms of unusual sensory experiences

   Not that I know of

Appendix E

Phoneme Pair Information
Created by Maurer et al., (2020)

- Based on an eight-point continuum that was used by Werker and Lalonde (1988) and Yoshida, Pons, Maye, and Werker (2010)
- Artificially synthesized sounds (see Werker & Lalonde, 1988)
- The stimulus files were created by re-saving the original sound files from Yoshida et al. (2010) in AIFF format using Praat
- Each condition was used four times in the experiment

ED = Experimental-Different = [d̪a] and [ɖa] pairs

SYN07_noise25.aiff	vs.	SYN14_noise25.aiff	×2
SYN14_noise25.aiff	vs.	SYN07_noise25.aiff	×2

ES = Experimental-Same = [d̪a] and [d̪a] pairs or [ɖa] and [ɖa] pairs

SYN09_noise25.aiff	vs.	SYN09_noise25.aiff	×2
SYN12_noise25.aiff	vs.	SYN12_noise25.aiff	×2

FD = Filler-Different = [ra] and [la] pairs

RLA1_noise25.aiff	vs.	RLA8_noise25.aiff	×2
RLA8_noise25.aiff	vs.	RLA1_noise25.aiff	×2

FS = Filler-Same = nonidentical exemplars of [ra] and [ra] pairs or [la] and [la] pairs

RLA1_noise25.aiff	vs.	RLA2_noise25.aiff	×1
RLA2_noise25.aiff	vs.	RLA1_noise25.aiff	×1
RLA7_noise25.aiff	vs.	RLA8_noise25.aiff	×1
RLA8_noise25.aiff	vs.	RLA7_noise25.aiff	×1

FI = Filler-Identical = identical exemplars of [ra] and [ra] pairs or [la] and [la] pairs

RLA1_noise25.aiff	vs.	RLA1_noise25.aiff	×2
RLA8_noise25.aiff	vs.	RLA8_noise25.aiff	×2

About the file names

- SYN07_noise25.aiff presents the token at the extreme dental end of the dental/retroflex continuum
- SYN14_noise25.aiff presents the token at the extreme retroflex end of the dental/retroflex continuum
- RLA1_noise25.aiff presents the token that sounds most like “ra” of the ra-la continuum
- RLA8_noise25.aiff presents the token that sounds most like “la” of the ra-la continuum
- See below for details about the recent changes to the stimuli for this task

Adding white noise

- White noise, generated by a mathematical function, was mixed into the speech sounds, using MATLAB, to reduce the participants' phonetic discrimination capabilities while wearing headphones
- The function was created following the work of Narayan (2008)

$$s + \sqrt{\frac{1}{10^{snr/10}}} \cdot s \cdot (\pm 1)$$

- *s* is the signal (i.e., the speech sound)
- The signal-to-noise ratio (snr) was chosen to be 25dB

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Curriculum Vitae

Kate Raymond

Education

2019-Present	MSc – Neuroscience Western University, London, ON
2014-2018	BSc – Psychology, Neuroscience, and Behaviour McMaster University, Hamilton, ON

Scholarships & Awards

2021	Neuroscience Travel Award • Value: $300; accepted
2020-2021	CGS-M NSERC • Value: $17,500; accepted
2020-2021	Ontario Graduate Scholarship • Value: $15,000; declined
2020-2021	Psychology Graduate Research Award • Value: $750; accepted
2019-2020	Ontario Graduate Scholarship • Value: $15,000; accepted

Related Work Experience

2019-2021	Teaching Assistant Western University, London, ON
2018-2019	Research Assistant SickKids Research Institute, Toronto, ON

Volunteer & Mentorship Experience

2019-Present	Support Line Volunteer Canadian Mental Health Association, London, ON
2019-2021	Undergraduate Thesis Advisor Western University, London, ON

Publications & Presentations

Raymond, K., Levine, A., & Butler., B. (2021). Connectivity between auditory and limbic systems in people with specific sound sensitivites (Poster presentation). Cognitive Neuroscience Society Conference.

Merovitch, M., **Raymond, K.**, & Zhengping, J. (2019). Do we know each other? Regulation of social memory by the actin-binding protein cofilin (Poster presentation). Canadian Physiological Society Conference, Toronto, ON.

Bose, A. P., McCallum, E. S., **Raymond, K**., Marentette, J. R., & Balshine, S. (2018). Growth and otolith morphology vary with alternative reproductive tactics and contaminant exposure in the round goby Neogobius melanostomus. Journal of fish biology, 93(4), 674-684.

Raymond, K. Patterson, B., & Van Ameringen, M. (2017). The prevalence and clinical characteristics of misophonia in an undergraduate sample (Poster presentation). NeuroXchange, McMaster University, Hamilton, ON.

Raymond, K. (2017). Breaking the stigma of addiction through neuroscience (Public talk). PNB talks, McMaster University, Hamilton, ON. Available at: http://macintropsych.ca/index.php/pnbtalks.