**The Neurochemistry of Decreased Sound Tolerance:**

**A Magnetic Resonance Spectroscopy (MRS) study of Misophonia and Hyperacusis**

**Introduction**

Decreased sound tolerance is commonly thought to exist in several forms (e.g., misophonia, hyperacusis) and, in more severe cases, can cause disruption to daily living (e.g., avoidance of certain situations). It can occur without any known external cause, and it is not necessarily linked to hearing loss (Baguley & Hoare, 2018; Sheldrake et al., 2015). Misophonia is defined as a disorder of decreased tolerance to specific sounds (termed ‘triggers’) or their associated stimuli (Swedo et al., 2022). Common triggers are human oral/nasal sounds (e.g. lip-smacking, chewing) and common responses include body tension, rage, and anxiety, albeit with variability in the exact sound-response profile across individuals. It normally emerges in childhood or adolescence (Rouw & Erfanian, 2018). Hyperacusis has been defined as when “everyday sounds feel overwhelming, loud, intense, or painful that do not bother other people in the same way” (Fackrell et al., 2017). A postulated key difference is that misophonia is defined in terms of decreased tolerance to specific sounds, irrespective of loudness, whereas hyperacusis is regarded as broader in nature perhaps encompassing all sounds. Hyperacusis is more common in people with tinnitus but can occur in its absence (Aazh & Moore, 2017). Decreased sound tolerance is also a feature of certain neurodevelopmental disorders such as autism spectrum disorder (Williams et al., 2021). The extent to which autism resembles the misophonia of hyperacusis profile (or some third profile) is not well understood, and sound intolerances in autism likely reflect a broader pattern of sensory sensitivity encompassing all senses (Robertson & Simmons, 2013).

The present study will elucidate the neurochemistry of decreased sound tolerance using magnetic resonance spectroscopy (MRS) to measure individual differences in the excitatory and inhibitory neurotransmitters, glutamate and GABA respectively. Put simply, we hypothesise that decreased sound tolerance will be linked to a greater excitability of the relevant cortical regions, underpinned by an imbalance of excitatory and inhibitory neurotransmitters (either more glutamate or less GABA). This is related to theories that postulate enhanced ‘gain’ (amplification of neural activity in ascending neural pathways) in hyperacusis and misophonia (Auerbach et al., 2014; Rubenstein & Merzenich, 2003) and related theories that postulate that ascending sensory signals are more noisy (less sparse) due to increased excitation:inhibition (Rubenstein & Merzenich, 2003). The only genetic study to consider misophonia found a genotypic difference in a region near the gene coding for the GABA receptor (Smit et al., 2022).

Previous MRS investigations suggest that the balance between inhibitory and excitatory metabolites is associated with individual differences in perceptual experience in both the auditory and visual domains. For example, in the auditory condition tinnitus, where individuals experience a persistent tone (ringing) in the ears, Sedley et al. (2015) found that decreased concentrations of inhibitory neurotransmitter GABA in bilateral auditory cortices. A lack of inhibitory neural activity may lead to spontaneous sound-evoked auditory activity. In the visual modality, migraines with aura have also been connected to increased excitability of the visual cortex. For example, a number of studies have found elevate levels of glutamate in migraineurs with aura (Bridge et al., 2015). Individual differences in GABA concentrations in visual cortex in autism is also linked to differences in perceptual stability of ambiguous percepts (Robertson et al., 2016), and individual differences in glutamate in visual cortex are linked to phosphene thresholds induced by Transcranial Magnetic Stimulation (Terhune et al., 2015). GABA is harder to measure with standard MRS sequences (PRESS) because the signal is weaker and partially obscured by other molecules in the spectra, but the modified sequence of MEGA-PRESS improves GABA detection (Mullins et al., 2014).

There are no previous MRS studies of misophonia, although the study of Sedley et al. (2015) included the HQ (hyperacusis questionnaire) as a secondary measure in their tinnitus study. They did not find a correlation between GABA concentration and HQ in auditory cortices, but that study did not specifically recruit people with decreased sound tolerance. There are several studies of misophonia that have used other imaging modalities. The fMRI study of Kumar et al (2017) presented trigger and non-trigger sounds to misophonic and non-misophonic control participants and found bilateral activity in anterior insula cortex (AIC) linked specifically to trigger sounds. This AIC activity was correlated with psychophysiological arousal (heart rate, skin conductance). The anterior insula may normally function as an alerting mechanism (salience detection) (Uddin, 2015) but can be considered maladaptive in the case of misophonia given that most trigger sounds are not objectively threatening. A similar experimental design, using audio-visual stimuli, by Schröder et al. (2019) found activity in right anterior insula and right auditory (superior temporal) regions linked to misophonia. They interpreted this as “enhanced reactivity of the salience network in combination with hypervigilance, reflected by sensitization of the auditory cortex” (pg. 7). fMRI resting state differences were observed in misophonics between auditory and insular cortices and regions linked to orofacial movement (Kumar et al., 2021), and a more recent study pointed to greater right amygdala volume in misophonia (Eijsker et al., 2021). In sum, our focus on auditory and anterior insula regions is motivated both theoretically and in terms of prior literature. Our focus on right hemisphere is imposed by time limitations and motivated by the study of Schröder et al. (2019).

Our study design is optimised to detect group differences linked to misophonia by selecting participants from the two extremes of misophonia severity scores (Rinaldi et al., 2022). However, we also include standard measures of hyperacusis (Aazh & Moore, 2017; Khalfa et al., 2002) to determine whether misophonic group differences are better explained by hyperacusis as a co-morbid condition or, indeed, to establish whether hyperacusis has a different neurochemical signature to misophonia. We minimise differences linked to autism by matching groups on the AQ, autism-spectrum questionnaire (Baron-Cohen et al., 2001), and excluding anyone with a formal diagnosis of autism. We consider, as a secondary measure, multisensory sensory sensitivity by administering the GSQ (Robertson & Simmons, 2013). Based on the previous misophonia fMRI literature we focus on two regions of interest: auditory cortex and the anterior insular cortex. We hypothesise that misophonics will have more resting glutamate and/or less GABA in one or both of these regions, leading to greater stimulus-evoked excitability. A more specific (albeit speculative) hypothesis is that hyperacusis will be linked to neurochemical differences (more glutamate and/or less GABA) in the auditory cortex and misophonia to the insular cortex. This is motivated by the claim that hyperacusis is elicited by most sounds whereas misophonia is often accompanied by a bodily response. A third region, visual cortex, acts as a control in that we do not expect misophonia or hyperacusis to be linked to differences here. The GSQ, as a measure of multisensory sensory sensitivity, is hypothesised to correlate with both visual and auditory cortices independently from misophonia and hyperacusis status.

**Hypotheses**

Hypothesis 1. Misophonics will have greater cortical excitability (more glutamate and/or less GABA) in the auditory cortex and/or anterior insula cortex.

Hypothesis 2. Hyperacusis will be linked to greater cortical excitability (more glutamate and/or less GABA) in the auditory cortex.

Hypothesis 3. Neither misophonia or hyperacusis will be linked to greater cortical excitability (more glutamate and/or less GABA) in the visual cortex, although scores on the GSQ will be.

**Methods**

Participants

Thirty misophonics will be recruited from a database of participants at the University of Sussex, who have completed various screening measures (http://www.misophonia-hub.org/). Thirty non-misophonics will be recruited from a local opportunity sample including staff and students at the University. Participants will be assigned into groups based on their total score on the Sussex Misophonia Scale, SMS (Rinaldi et al., 2022). A score > 50.5 is indicative of misophonia (excellent AUC = 0.914 against self-report of misophonia) and this cut-off has excellent convergent validity against another commonly used measure (MQ severity item) where scores of 7 and above are indicative of moderate misophonia (excellent AUC = 0.891). Here we use a higher cut-off of > 75 on this measure which corresponds approximately to the ‘severe misophonia’ category used on other measures (Wu et al., 2014) and, to avoid recruiting controls just below the cut-off, we recruit only from scores of 35 and below. In this way, we maximise the likely effect size. Participants initially recruited as controls but found to have misophonia will be reassigned. Both groups (i.e., misophonic, control) will take part in the online self-report measures, complete the in-person behavioural assessment, and the MRS study.

A small amount of data has already been collected (~10 participants) to check the protocol and for quality control purposes. No data has been analysed with respect to the hypotheses.

*Inclusion criteria*:

* Scores above 75 (severe misophonia) or below 35 (controls with no misophonia) on the SMS
* Within 18-65 years of age and groups matched by mean age (non-significant difference and Cohen’s d effect size < .5), mean AQ score (non-significant difference and Cohen’s d effect size < .5), and gender (non-significant difference established by chi-square)
* Availability to travel to the University of Sussex

*Exclusion criteria (prior to scanning)*:

* Hearing loss (self-reported) or tinnitus (by selecting ‘Definitely does apply to me’ in the hearing questionnaire)
* Uncorrected visual impairment (wearing glasses or contact lenses is acceptable)
* Neurological condition (e.g., epilepsy, stroke, dementia)
* History of migraine
* A diagnosis of autism
* Standard exclusion criteria for MRI including pacemakers, permanent piercings, or claustrophobia.

*Exclusion criteria (after scanning; outliers and quality control)*:

* Missing/incomplete metabolite concentrations due to scan termination or failure to detect a peak
* Data that are more than 2 SDs away from the mean across groups (within each voxel) for linewidth of NAA (given by the FWHM)
* Data that are more than 2 SDs away from the mean across groups (within each voxel) for signal-noise ratio (SNR)

Note: the application of the post-scanning exclusion criteria could result in different Ns in different analyses

*Sample size justification*

A sensitivity analysis was run using G\*Power (alpha = 0.05, power = 0.8, N1 & N2 = 30) which shows that a medium effect size (Cohens d) of 0.65 would be required for analyses of group differences. We find that behavioural measures related to misophonia (e.g., sensory hyper-sensitivity on the GSQ questionnaire) are at least this order of magnitude (Andermane et al., 2023), and we maximise power by recruiting from the two ends of the scale.

# Similarly, a sensitivity analysis was run using G\*Power (alpha = 0.05, power = 0.8, N = 60) which shows that a medium effect size (Cohen’s *f*2) of 0.19 would be required for the variance explained within the model by the predictors to be different than zero.

# Bayes factors will be computed to determine whether the observed effects (whether significant or null) are sensitive, as outlined below.

Materials: Behavioural Measures

A summary of the list of behavioural measures is given in Table 1 and this corresponds to the order in which they are completed by participants. Each measure is described in turn below, and the stimuli and questionnaires are included in a separate folder in this OSF.

*Table 1: Questionnaires and behavioural measures*

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Completed online prior to being invited to the scanning session** | | | | | |
| **Construct** | **Measure** | **Type** | **Items** | **Time (mins)** | **Reference** |
| Hearing questionnaire: screener | Questions related to hearing issues, eg tinnitus, misophonia, hyperacusis | Questionnaire | 6 | 5 | Andermane et al. (2023) |
| Misophonia | Sussex Misophonia Scale (SMS) | Questionnaire | 39 | 12 | Rinaldi et al. (2022) |
| Sensory sensitivity | Glasgow Sensory Questionnaire (GSQ) | Questionnaire | 42 | 7 | Robertson & Simmons (2013) |
| Autistic traits | Autism Quotient | Questionnaire | 50 | 8 | Baron-Cohen et al. (2001) |
| Hyperacusis | Hyperacusis Questionnaire (HQ) | Questionnaire | 14 | 3 | Khalfa et al. (2002) |
|  |  |  | Total | 41 |  |
| **Completed in-person whilst attending the scanning session** | | | | | |
| Hyperacusis | Uncomfortable loudness levels Test (ULL) | Psychophysical | 6 tones per ear, varying in loudness | 10 | British Society of Audiology (2011) |
|  |  |  | Total | 10 |  |

*Hearing questionnaire.* This asks about tinnitus, migraine phonophobia, phonophobia, misophonia, hyperacusis, and hearing difficulties (speech in noise). These are not used as independent variables in the analysis but are included for information and (for tinnitus, migraine) as exclusion criteria if participants select “Definitely applies to me”.

*Sussex Misophonia Scale (SMS).* This consists of a checklist of possible misophonia trigger sounds followed by 39 questions answered on a 0-4 Likert scale such as “The sound made by some people makes me feel the need to avoid them”. These are summed to give a total score and this determines group membership. Group status (coded as 1 and 0) is an independent variable in the analysis, noting that the data is effectively binarized by selecting from high and low ends of the possible range of scores.

*Sensory sensitivity (GSQ).* Thisconsists of 42 questions, half relating to hyper-sensitivity and half to hypo-sensitivity, and relating to seven modalities (vision, hearing, smell, taste, touch, vestibular, proprioception). Example items include “Do you cut the labels out of your clothes?” with responses given on a 5-point scale coded from 0-4 (never, rarely, sometimes, often, always). For our primary analyses, we will use the total hyper-sensitivity score as an independent variable noting that this (more so than hypo-sensitivity) has also been linked to misophonia (Andermane et al., 2023).

*Autism quotient (AQ)*. The AQ is 50-item quotient including five subscales (Baron-Cohen et al., 2001). Example items include “I would rather go to a library than a party” and responses are given on a four-point scale (Definitely disagree, Slightly disagree, Slightly agree, Definitely agree) and recoded as 1 or 0 depending on whether the trait resembles an autistic behaviour or not. We shall compute the total score (/50) for the purposes of matching mean scores between the groups. It is not entered as an independent variable in the planned analyses.

*Hyperacusis questionnaire (HQ)*. This measure was developed before the designation of misophonia as a separate entity (Jastreboff & Jastreboff, 2001) and, hence, is a broad measure of decreased sound tolerance. We have recently conducted an analysis that shows some items are sensitive to misophonia and some to hyperacusis (the latter being items 3, 4, 5, 7 and 8), e.g. HQ4 “Do you have trouble concentrating in noisy surroundings?”. As such we will use the summed score of the five hyperacusis-specific items as an independent variable (although we administer the whole questionnaire for completeness and to permit secondary analyses by others).

*Uncomfortable Loudness Levels (ULL) test.* Participants are asked to listen to sound clips of pure tones (each lasting approximately 1s) that get successively louder, ranging from 60dB to 90dB (in 5dB intervals). Participants are presented with pure tones at six different frequencies (250Hz, 500Hz, 1000Hz, 2000Hz, 4000Hz, 8000Hz), separately via headphones for their left and right ears. Participants are instructed to raise their hand when the sound becomes uncomfortable to listen to. The instructions are adapted from the BSA protocol and are as follows “I now want to measure the level at which sounds become uncomfortable for you, so I am going to slowly and steadily increase the level of sounds that I present to you. Please raise your hand as soon as the sound reaches a level of loudness that you feel is so loud that it has become uncomfortable. This is not an endurance test; please don’t wait until you can’t cope with the sound any further before raising your hand”. (British Society of Audiology, 2022). Pure tones were created in Audacity and edited in Waveform Free. Following Aaazh and Moore (2017), we will calculate the across-frequency average ULL for the ear with the lowest ULLs (ULLmin) as an independent variable. The individual ULLs separated by frequency and ear will be reported for descriptive purposes.

MRI Hardware and Scanning Sequences

The MRI hardware consists of a Siemens 3T Prisma scanner with a 32-channel head coil.

A structural scan was first obtained to guide voxel placement and to calculate GM/WM/CSF fractions in the analysis pipeline. This consisted of a T1w MPRAGE scan (TR = 2300, TE = 2.19, slices per slab = 192, phase encoding A > P) with 1 mm resolution, lasting 5 mins 30 seconds, during which time the participant could watch a video.

A voxel, size 30 (AP) x 27 (RL) x 20 (FH), was placed on the right auditory cortex (Heschl’s gyrus) to be horizontally aligned with the lower bank of the supra-temporal plane, in coronal section, and angles/positioned to minimise CSF in the volume. Automated Bo shimming sequences (FastestMap TR = 2000, TE = 49.2) reduce the background variation in the magnetic field. There were four such sequences, in order: 3 linear directions (TA = 6.1s), 6 full directions (TA = 12s), 6 linear directions (TA = 24s), and 6 linear directions with TAU10 (TA = 24s). Water suppression used the VAPOR (the VAriable Power and Optimized Relaxations delays) method. Manual calibration of the VAPOR parameters for flip angle (FA) and inter-pulse delays (D7) were obtained in two scans (TAs of 1:06 and 51s respectively) with scan parameters: TR/TE = 3000/68, editing pulse frequency/bandwidth = 9ppm/60Hz. This was followed by the Mega-PRESS sequence lasting 13 minutes 21 seconds (vector size = 2048, averages = 128, TR/TE = 3000/68 ms, editing pulse frequencies of 9ppm [EDIT-OFF] and 1.9ppm [EDIT-ON], editing pulse bandwidth 70Hz, acquisition bandwidth 2000Hz, water suppression bandwidth 135Hz). Finally, an unsuppressed water scan was obtained to provide an absolute concentration reference (TA = 33s, same parameters as Mega-PRESS).

The insula and visual cortices used a shorter automated sequence (semi-laser MRS). The right anterior insula region was based on a voxel size of 30 (AP) x 15 (RL) x 20 (FH), and the visual cortex was based on a voxel of 30 (AP) x 20 (RL) x 15 (FH) centered on the bilateral calcarine sulcus, tilted to the angle of the sulcus. Automated shimming consisted of three sequences FM, LW, and 90deg\_calib lasting 1:30, 15s, and 39s respectively (TR = 3000, TE = 8/10/12, bandwidth = 6000Hz [FM] and 2500Hz [LW and 90deg]). A VAPOR scan of 45s was used for water suppression (TR = 3000, TE = 8/10/12, bandwidth = 2500Hz). This was followed by the MRS scan lasting 3:39 (vector size = 2048, averages = 64) with the same scan parameters as for the VAPOR.

MRS Pre-Processing and Quality Control Measures

*MRS data*

The metabolite data will be processed prior to analysis using LCModel software in Matlab, with bespoke scripts.

Finally, data will be referenced to the separately collected unsuppressed water concentration and corrected for contamination of CSF fractions (metabolite concentration \* 1/1-CSF fraction).

Data quality will be reported (and compared across groups for each voxel) for the following variables: Signal-noise ratio (SNR); NAA/Water; Creatine/Water; NAA/Creatine; NAA line width; Water line width; % CRLB values for GABA, Glu, Glx, and NAA; and Absolute CRLB values for GABA, Glu, Glx, and NAA.

**Analyses**

The main experimental hypotheses relate to Glu and GABA concentrations, as dependent variables, as described in the hypotheses below:

Hypothesis 1: Group differences related to misophonia

4 x independent samples t-tests (2 regions- auditory cortex/anterior insula cortex; 2 chemicals: glutamate/GABA) with concentration as the dependent variable, and group (misophonia status: misophonic/control) as the independent variable.

Bayes Factors will also be calculated, using the room-to-move heuristic (Dienes, 2019) in which the effect size of the behavioural difference between groups (Cohen’s d based on total SMS score) acts as a ceiling on the expected effect size for differences in neurotransmitter concentrations (this is used to model H1 as 2SDs of a normal distribution). Rather than postulating a minimally interesting effect size, this approach involves specifying a rough scale of effect (Dienes, 2021).

Hypotheses 2 and 3: Regression models to consider all variables

6 linear models (3 regions, 2 chemicals) with concentration as the dependent variable, and independent variables of misophonia (total SMS score), hyperacusis (ULLmin, a subset of HQ questions, see above), and GSQ score (Hyper-sensitivity scale, collapsed across 7 sense modalities).

Bayes factors will be computed using the ratio-of-scales heuristic in which H1 is modelled as a slope given by the rough scale of the dependent variable (maximum minus minimum neurotransmitter concentration) and the rough scale of the independent variable (maximum minus minimum obtained values), where the magnitude of the slope is 2SDs of the H1 normal distribution.

The following exploratory analyses are noted:

* Substituting Glx (glutamate + glutamine) as a dependent variable instead of glutamate
* Using choline concentration as a dependent variable, noting that a previous study linked this to subjective tinnitus loudness and hearing loss in right auditory cortex (Sedley et al., 2015).
* One-way ANOVAs (by group) on each voxel comparing structural brain changes, namely differences in GM, WM, and CSF fractions.

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