ID: Pro00103863

Identifying the Optimal Neural Target for Misophonia Interventions

NCT04348591

Study protocol and statistical analysis plan

3/28/2023

Methods:

1. Participants and Procedures

This study was pre-registered under the Clinical Trials ID (NCT04348591) and ran between October 2020 and May 2022. The study was powered based on expected effect size derived from Kumar at al. [2], who compared misophonic participants (n = 20) with controls (n = 22) to find significant differences in AIC response, with an effect size of 1.27 (mean difference between groups = 2.7 a.u, SD = 2.11). For the proposed design, with planned comparisons across condition (downregulate, or listen), sound type (misophonic, aversive, or neutral) and group (misophonic vs. clinical control), and an expected effect size of 1.27, and alpha error rate set at .05, we expected adequate power (over 80%) with 29 participants in each group. Therefore, we aimed to recruit 30 participants in each condition.
Participants were recruited through online websites (e.g., Craigslist, Duklist), social media (Facebook, Reddit), flyers, and electronic medical record outreach. Participants reached the study predominantly by seeing advertisements on social media and research websites. Many participants who met the severity cutoff for misophonia also found the study via self-guided internet search (see Table 1 for how participants who met the cutoff for each group of interest for the study found the study information).

Table 1. Recruitment methods and success rate in identifying the groups of interest for the study

Recruitment material used	Misophonia participants	Emotion dysregulation participants
Social media (Facebook, Reddit, Instagram)	33.46%	36.42%
Websites (Dukelist, Dukescience, Duke Misophonia website, Dukehealth)	30.08%	28.90%
Word of mouth (friend or medical professional referral)	13.16%	9.83%
Self-guided internet search (including finding the study on clinicaltrials.gov)	12.78%	13.29%
Volunteer registries (BIAC, ResearchMatch, CMER)	6.39%	6.36%
Outreach using electronic medical record	3.38%	4.62%
Newspaper	0.75%	0.58%

Note. Participants were included in the misophonic group if they scored >= 2 on the MQ subscales and indicated a severity higher than 6 on the MQ severity scale; participants were included in the emotion dysregulation group if they scored above 89 on the DERS scale.

Interested participants completed an online and in-person screen before being invited for an imaging session. We received completed (n = 1120) or partially completed (n = 221) online screens from 1341 potential unique participants (79.6% female, 9.2% Hispanic, 79.7% Caucasian). Of those who completed, 40.4% identified themselves as being interested in the study because they suspect having misophonia (MMQ_Subscale_1 = 2.56, SD = 0.75; MMQ_Subscale_2 = 2.39, SD = 0.63; MMQ_Severity = 7.78, SD = 2.30; MDERS = 96.30, SD = 24.93), and 44.3% because they believed they had emotional dysregulation (MMQ_Subscale_1 = 1.67, SD = 0.84; MMQ_Subscale_2 = 1.43, SD = 0.73; MMQ_Severity = 4.57, SD = 2.62; MDERS = 111.22, SD = 21.84). Of those who self-identified as misophonic, 38.56% met our inclusion criteria for the misophonia group; 9.60% of those self-identified as having emotional dysregulation also met inclusion criteria for the misophonic group. In addition, 39.48% of those who self-

identified as having misophonia, and 72.39% of those who self-identified as high emotional dysregulation were above the inclusion cutoff for the emotion dysregulation clinical group.

Three hundred and thirteen potential participants who qualified at online screen and who could be reached, were screened by phone to further examine study inclusion/exclusion criteria. Of these, 177 qualified and were invited to an in person intake assessment. Participants were excluded from either online or phone screen primarily for not meeting the cutoffs for either group, for being unreachable after completing the online screen, or for being unable to travel to Duke for the study appointments. Furthermore, 183 participants were rejected at screen because the misophonia group enrollment was completed much faster than the control group and, as a result, we were no longer accepting misophonic participants. One hundred and forty four additional participants reported high emotional dysregulation, but were excluded from the control group because they were considered to have too many misophonic symptoms. Participants were allowed in the control group only if the second MQ subscale < 2 and MQ severity score was < 7. As a result, 23 potential controls were excluded because they had both subscale 2 and severity scale too high, 41 had the MQ severity score as too high, and 79 had subscale_2 score as too high.

One hundred and twelve unique adults signed consent and participated in an in person screen to establish diagnostic profile, and examine any remaining inclusion/exclusion criteria (See Figure 1 for a visual depiction of the study design). We repeated the MQ and DERS at the in person screen and only

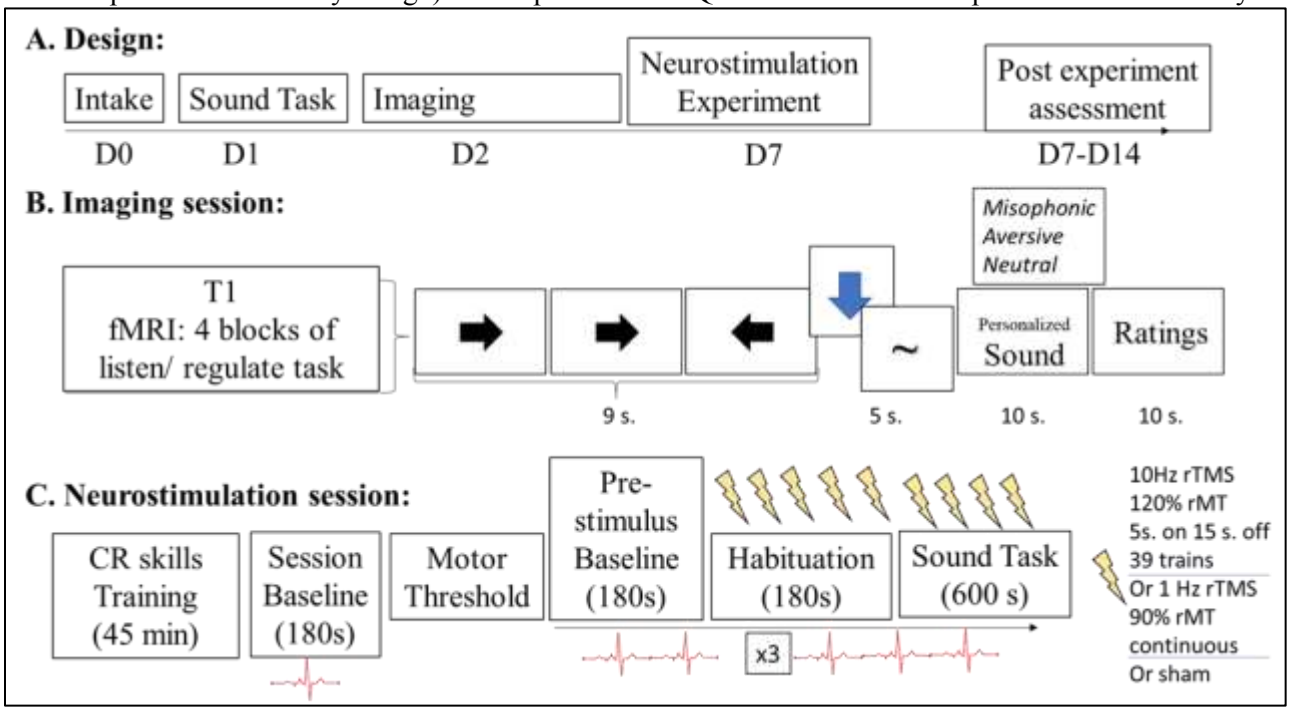

Figure 1. Experimental design

allowed participants in the study if the scales scores fit within our pre-determined parameters at the intake assessment. Twenty-two participants were no longer eligible at intake because their MQ and DERS scores changed sufficiently to be outside of the pre-determined cutoffs for the misophonic/clinical control groups. In addition, 19 participants were not eligible at the in person screen (see CONSORT) and 12 withdrew, were lost to contact before the experimental day, or couldn't do the MRI visit because of claustrophobia or technical difficulties. Thus, we had 59 enrolled participants for the study (enrolled group) of which 54 participants (completer group) were present for the neurostimulation experimental day (27 in each group).

Enrolled participants were 4 men and 52 women and 3 non-binary adults between the ages of 18 and 54 (M = 28.31; SD = 9.06 years old) who self-reported significant misophonic severity, or who met

criteria for any DSM-5 disorder (excluding active substance use, psychotic disorders, and Bipolar I) and self-reported above average emotional dysregulation. There was no significant difference between groups in age ($t[57] = -1.07$; $p = .30$) and gender ($\chi 2[4] = 2.98$, $p = .56$), suggesting that the matching was successful. Participants met criteria for an average of 1.75 (SD = 1.62) current diagnoses and 3.54 (SD = 2.26) lifetime diagnoses according to the structured interview for DSM-5 disorders (SCID-5) (28). The majority of participants (n = 45; 76.3%) met criteria for an anxiety disorder, 22% met criteria for a current depressive disorders (n = 13), 11.9% for a compulsive disorder (n = 7), 6.8% for an impulse control disorder, 1.7% for an eating disorder, and 10.2% for a stress disorder (n = 6). Twenty one participants (36.21%) met criteria for at least one personality disorder according to the SCID-5-PD (29). Ten percent of the control participants and 31% of the misophonia group participants did not have a current DSM-5 diagnosis. All control participants without an active diagnosis had a history of mental health disorders, and one (33%) had an active personality disorder diagnosis. Of those from the misophonia group without a current SCID-5 diagnosis, 44.44% had a history of mental health disorders; 17.24% of the entire misophonia group sample had no current and no history of mental health disorders.

2. Intake Session

After providing voluntary, written informed consent, participants completed diagnostic assessments (SCID-5, SCID-PD), a verbal intelligence test [46] and a questionnaire packet. Detailed results for the clinical interview and self-report differences will be presented elsewhere.

3. Measures

Diagnostic Assessment: The SCID-5 [43] and SCID-PD [44] have demonstrated high diagnostic accuracy (83%) and strong inter-rater reliability (.85 during training and .76 at a Quality Assurance check) [47]. Participants were led through both structured interviews by either the first author (65.5% of cases) or one of two trained diagnostic assessors under the supervision of the first author. In the cases where the first author did not conduct the interview, she reviewed in detail with the assessor the questions asked to confirm diagnostic profile. In case of disagreement, she reassessed the disorder at the next visit.

Difficulties in Emotion Regulation Scale (DERS): The DERS [45] is a 36-item instrument that assesses typical levels of emotion dysregulation across six domains (awareness, nonacceptance, strategies, goal oriented behaviors, impulsivity, and emotional clarity). Participants respond on a Likert scale ranging from 1 (almost never) to 5 (almost always). In the original measure development paper, the DERS was found to have high internal consistency ($\alpha = .93$), good test-retest reliability ($r = .88$, $p < .01$), and adequate construct and predictive validity. The total score is a sum of all items (some reversed). Higher scores indicate more dysregulation. In the present study, Cronbach's alpha at intake was .84, indicating acceptable internal consistency.

Misophonia Questionnaire (MQ). The MQ is a three-part assessment of the types of misophonic sounds the participant is sensitive to and the symptoms experienced. Part one is an 8-item scale that assesses the participant's sensitivity in comparison to others of seven common misophonic triggers and one item for "other." The items use a 5-point Likert scale to identify to what degree the participant is sensitive to each, ranging from 0 (not at all true) to 4 (always true). Part two is completed only if the participant scores a 1 (rarely true) to any of the items in part one. Part two is an 11-item scale that assesses the frequency of ten reactions and one "other" reaction by the participant once they are aware of the misophonic sounds from part one. The items use a 5-point Likert scale to identify the frequency of each reaction, ranging from 0 (never) to 4 (always). Part three is a 15-point self-rating scale of sound sensitivity. There are 5 items with 3 points associated with each with responses ranging from 1-3 (minimal within range of normal or very mild sound sensitivities) to 13-15 (very severe sound sensitivities). Previous studies using the MQ have reported strong reliability and evidence of construct validity [1]. In the present study, Cronbach's alpha was .85 for part I and .92 for part II, indicating acceptable internal consistency.

Subjective Units of Distress Scale (SUDS). During the MRI sessions, neurostimulation session, at

follow-up, and during the ambulatory assessment, we asked participants to rate their current distress on a scale from 0 – no distress to 9 – extreme distress [48].

Manipulation Check: During the neurostimulation session we examined dissociation during each baseline and regulation period using a 4 item scale [49]. Participants were also asked to rate on a scale from 1 (I am certain I received sham stimulation) to 9 (I am certain I received active stimulation) their confidence in the assigned condition that they were kept blind to after each experimental trial. A rating of 5 indicated uncertainty. Before and after each experimental task (sounds, MRI, neurostimulation) we asked participants their current level of distress (rated on a scale from 1-7 [50]). After each experimental task, we also asked participants whether they were distracted or present and how successful they were in following the instructions.

Positive and Negative Affect Scale (PANAS). The PANAS [51] is a 28-item assessment of the degree to which the participant has felt a wide range of positive and negative emotions and feelings on the day of assessment. The items use a 5-point Likert scale ranging from 1 "Not at all or very slightly" to 5 "Extremely" with regard to the extent the participant has experienced each emotion. In this study, we examined changes in the PANAS negative affect scale before and after each experimental session in order to examine feasibility of proposed procedures. Cronbach's alpha at before the intake session was .88.

Tolerability Questionnaire: Before and after the intervention session, participants were asked to rate on a scale from 0–3 (absent, mild, moderate, severe) the intensity of their headache, neck pain, scalp pain, seizure (as observed by technician), hearing impairment and any other side effect that they might have experienced from the TMS treatment.

Exit Interview: An unpublished, previously developed interview [26] was used to examine feasibility and acceptability as directly relevant to the study. The interview included open-ended questions about the overall experience as well as Likert-type questions about feasibility of the intervention (e.g., difficulty with limiting movement, level of comfort, ability to concentrate given the TMS noise, distress about the procedures, ease to hear and understand clinician, connection with clinician, and session engagement), acceptability (of session length, skills training, TMS procedures, personalized stressors use, ambulatory phone assessment) and overall satisfaction (i.e., likelihood to recommend to someone else). Acceptability questions were rated on a scale from 0 (not at all) to 9 (extremely) and scores were reversed as needed and averaged in order to compute an overall acceptability score where 0 represented not feasible/acceptable at all and 9 represented very feasible/acceptable. Satisfaction was rated on a 0 (low) to 100 (high) continuous scale.

Amsterdam Misophonia Scale Revised (AMISOS-R): The AMISOS-R is a 10-item scale that assesses the severity of the participant's misophonia based on the participant's experience from hearing misophonic sounds in the last 3 days. The items use a 5-point Likert scale with responses ranging from 0 (*not*) to 4 (*extreme*) with total scores ranging from 0 to 40. Scores of 0-10 indicate normal to subclinical misophonia, 11-20 mild misophonia, 21-30 moderate to severe misophonia, and 31-40 severe to extreme misophonia.

Duke Misophonia Questionnaire (DMQ): The DMQ is a 10-part intake of the experience of the participant with exposure to certain sounds. Part one is a 16 item intake in which the participant indicates which misophonic sounds or sights bother them more than they do common people. Part two assesses the frequency in which the participant was bothered by all bothersome sounds on average in the past month. The item uses a 6-point Likert scale with responses ranging from *once per month or less* to *6 or more times per day*. The other eight parts assess the frequency of certain reactions or thoughts from the participant

when bothered by a misophonic sound or sounds on average throughout the past month. These items use a 5-point Likert scale with responses ranging from 0 (*never*) to 4 (*always/almost always*).

Disgust Propensity and Sensitivity Scale - Revised (DPSS-R): The DPSS-R is a 12-item questionnaire assessing the frequency of feeling disgust and related emotions in the participant. 6 items assess disgust propensity and 6 items assess disgust sensitivity based on the sum of the 6 items. The items use a 5-point Likert scale with responses ranging from 0 (*never*) to 4 (*always*).

Inventory of Depression and Anxiety Symptoms (IDAS) ill temper subscale.: The IDAS is a 64-item scale that assesses the frequency of a variety of emotions in the participant in the past two weeks. The ill temper subscale refers particularly to items 25, 28, 30, 31, 33. These items use a 5-point Likert scale with responses ranging from 1 (*not at all*) to 5 (*extremely*).

Anxiety Sensitivity Index (AIS): The AIS is a 16-item measure of the degree to which anxious emotions affect the participant. The items include assessments of the emotions and thoughts of the participant in regard to their anxiety. The items use a 5-point Likert scale with responses ranging from 0 (*very little*) to 4 (*very much*).

Acute Stress Disorder Scale-Adapted for COVID (ASDS): The ASDS is a 20-item measure of the ongoing COVID-19 pandemic's impact on the participant's stress. The scale includes items measuring the degree of emotional and physiological impact of the pandemic on the participant. The items use a 5-point Likert scale with responses ranging from 1 (*not at all*) to 5 (*very much*). The original measure from 2000 was adapted in March 2020 for use in the COVID pandemic.

Distress Tolerance Scale (DTS): The DTS is a 15-item measure of how well the participant is able to cope and tolerate feelings of distress. The items also measure the participant's self-acceptance with their feelings of distress and how they compare with others. The items use a 5-point Likert scale with responses ranging from 1 (*strongly agree*) to 5 (*strongly disagree*). The scale includes four subscales, tolerance, absorption, the scores of which are the mean of their contained items. The higher-order DTS score is formed from the mean of the four subscale scores. A higher DTS score represents a greater tolerance for feelings of distress.

PROMIS Self-Efficacy for Managing Emotions Scale (SEMES): The SEMES is a 26-item assessment of the participant's confidence in managing their emotions and ability to employ coping mechanisms. The items use a 5-point Likert scale with responses ranging from 1 (*I am not at all confident*) to 5 (*I am very confident*).

Vividness Questionnaire (VVIQ): The VVIQ is a 16-item instrument that assesses how well the participant is able to visualize certain prompts. The VVIQ demonstrates adequate test-retest reliability (ρ_I=0.74) and acceptable internal consistency (r_{II}=0.85). The questionnaire is split into four scenarios each with four items of visualization prompts. The participants self-rate their ability to visualize each item on a 5-point Likert scale with responses ranging from 1 (*Perfectly clear and as vivid as normal vision*) to 5 (*No image at all, you only 'know' that you are thinking of the object*).

Body Awareness Questionnaire (BAQ): The BAQ is an 18-item scale measuring the participant's self-reported attentiveness to their body's physiological processes, specifically body cycles and rhythms, deviations from normal functions, and ability to anticipate future bodily reactions. The items use a 7-point Likert scale with responses ranging from 1 (*Very untrue of me*) to 7 (*Very true of me*) and item 10 is reverse scored.

PROMIS-43 Profile: The PROMIS-43 is a 43-item scale measuring the participant's self-reported physical, emotional, and social health. The items assess the frequency at which the participant is able to conduct daily tasks or experiences symptoms relating to mental health or physical pain in the past 7 days. The items use different responses depending on section but generally employ a 5-point Likert scale with responses ranging from 1 (*Never*) to 5 (*Always*) or 5 (*Without any difficulty*) to 1 (*Unable to do*). The last item rates pain from 0 (*No pain*) to 10 (*Worst pain imaginable*).

Hyperacusis Questionnaire (HQ): The HQ is a 14-item measure of the participant's self-reported sensitivity to noise in everyday life. The questionnaire includes items on the frequency of the impact of sound and noise on aspects of the participant's daily and social life. The items use a 4-point Likert scale with responses ranging from *No* to *Yes, a lot*.

University of Washington Risk Assessment and Management Protocol (UWRAMP): The UWRAMP is a series of assessments and protocols for the management of risk for potentially depressed participants before, during, and after assessment. This begins with a Face Sheet of 6 items assessing the participant's stress and urges before assessment begins. The items use a 7-point numeric scale to identify the likelihood of certain urges and behaviors, ranging from 1 (Low) to 7 (High). To be next completed on first meeting with the participant is the Mood Improvement Protocol, which begins with a pair of questions posed by the assessor to the participant about methods in which to address stress or negative emotions that may arise during the interview. The second part of the Mood Improvement Protocol involves the assessor recording the mood induction activity that was offered to the participant after debrief and evaluating the effect on their mood. At the end of each session, the assessor administers the Debriefing Form, evaluating the participant's current stress and urges, mirroring the items from the Face Sheet. The Debriefing Form also evaluates suicidality in the participant and provides resources to manage any potential harmful thoughts or behaviors. Additional forms are provided to the assessor to describe if and why assessment was stopped at any point, describe participant behavior, and record methods used to handle the crisis.

Four Item Dissociative Symptom Scale (DSS-4): The DSS-4 is a 4 item questionnaire that assesses the participant's perception of themselves and their senses at the moment of assessment. The items use a 10-point numeric rating scale ranging from 0 for no experience of a certain perception to 9 for a very strong experience of a certain perception.

4. Sound Task

Participants who qualified at the intake assessment were invited to an in-person baseline task where they were sat in a sound-attenuated room with noise canceling headphones on in front of a computer. The task was programmed in MATLAB. All participants heard 101 pre-selected sounds: 31 aversive, 40 misophonic, and 30 neutral sounds. Sounds were selected from the International Affective Digitized Sound

System (IADS [20]; n = 64 sounds), from freely available sound databases (https://www.fesliyanstudios.com/royalty-free-sound-effects-download; n = 12 sounds), as well as from published literature [5] (n = 25 sounds). The IADS is a standardized set of .wav files that have been normed for arousal and valence levels. Non-misophonic aversive and neutral stimuli for this task were selected using the standardized values of valence and arousal from the IADS. Misophonic sounds were selected using the literature, to include sounds that have been previously described as being particularly triggering for misophonic individuals. To make sounds from various sources consistent, each sound was cut or repeated so that the amount of time the sound would play was 6 s. Each sound was followed by rating screens and a 6 s return to baseline period. All participants were asked to rate after each sound whether it was a positive, neutral, or negative sound and the intensity of their (positive/negative) arousal when listening to the sound. In addition, participants in the misophonia group alone were asked whether the aversive sound was a misophonic trigger for them (yes/no).

Based on this task, for each participant, a personalized set of sounds was selected for the neurostimulation and for the neuroimaging sessions. For the misophonia group, the highest negative arousal sounds that were flagged as misophonic triggers were included in the misophonic sounds condition. The highest negative arousal sounds that were not marked as misophonic triggers were included in the aversive condition. Sounds marked as neutral were randomly sampled for the neutral condition. For the control group, highest negative arousal sounds that were initially labeled as potentially misophonia related created the misophonic sounds, the highest negative arousal sounds that were from either the original aversive or neutral groups were selected for the aversive condition, and a random sampling of neutral sounds was selected for the neutral stimuli condition.

If there were too many high arousal sounds, a randomizer was employed to select the stimuli. If there were too few sounds, the stimulus set could have the same sound repeating twice (repeating sounds being selected at random). For the experimental sessions, 12 of each misophonic, aversive, and neutral sounds were selected. These sounds were shuffled so they would play in different orders during the imaging and during the neurostimulation sessions. Sounds repeated during the neurostimulation session, once for each run (i.e., the same sounds were played during different neurostimulation conditions, but in different order). One participant did the task twice because their answers failed to record the first time. Another participant came too late to do their sound task, could not be rescheduled, and as a result, another participant's personalized stimulus set (from the same group) was used to run them through the experimental sessions.

5. Neuroimaging sessions

MRI training:

Participants completed an imaging session as soon as possible after the eligibility intake. During the first hour of this session, participants were introduced to the task stimuli and were trained in how to respond accordingly: simply look at the screen when a cross was presented (passive baseline); indicate with a button press the direction of an arrow showed on the screen (active baseline); prepare to downregulate emotions associated with the sounds they hear when seeing a downward arrow; and prepare to throw themselves into listening and allowing any experience that arises during a sound file when seeing a wave symbol on the screen (~).

Participants were then introduced to CR as a strategy to use when instructed to downregulate emotions. Participants were taught to think that sounds were not real (e.g., a movie sound effect), or that the context meant something less negative (e.g., someone is about to pick up a baby that is crying). Participants practiced these strategies on two standardized sounds. Strategies were briefly covered for the participant to be able to engage in the targeted behavior during the scan, but not such that the participant learned new ways to downregulate emotions.

MRI acquisition:

After training, participants moved into a research-dedicated GE HD 3.0 T MRI scanner. The scan started with an anatomical image (3D MPRAGE pulse sequence; time repetition [TR] = 2300 ms; echo time [TE] = 3.2 ms; image matrix = 2562; flip angle = 12°; voxel size = 1-mm isotropic; 162 contiguous axial

slices). Field maps were collected for half of the sample (depending on time available during the scan) to correct for offline distortion of BOLD images. Four runs of EPI functional images were then acquired utilizing in-plane and multi-band acceleration, allowing the collection of high-resolution functional data while minimizing spatial distortion and signal dropout related to magnetic susceptibility (SENSE acceleration factor = 1; multi-band factor = 3; TR = 2000 ms; TE = 30 ms; image matrix = 1282; flip angle = 77°; voxel size = 2-mm isotropic; 68 contiguous axial slices).

Functional runs were acquired while participants experienced and downregulated emotions related to personalized sounds (task-related acquisition: four runs with 15 trials: 40 minutes). On each trial, participants first observed a fixation cross (jittered time interval from 3 to 7s) followed by the active baseline task. Then, participants saw the type of strategy to use (downregulate or hear). Next, they were presented with a misophonic, aversive, or neutral sound (3 trials/block). Each run had five blocks in a pseudo-random order (downregulate aversive, downregulate misophonic, hear neutral, hear misophonic, hear aversive). Participants rated their subjective distress after each trial. Participants viewed the screen via a mirror system located on the head coil and the start of each run was electronically synchronized with the MRI acquisition computer. Behavioral responses were recorded with a 4-key fiber-optic response box (Resonance Technology, Inc.). Participants wore earphones to hear the sounds and to attenuate scanner noise. Head motion and further outside sound exposure was minimized with foam pads placed on both sides of the participants' head. When necessary, vision was corrected using MRI-compatible lenses that matched the distance prescription used by the participant. Data from this imaging session were used to develop the neurostimulation targets.

Randomization:

Following the MRI visit, participants who still qualified were assigned a randomized sequence of targets to be used during the neurostimulation session. Each participant received active neurostimulation over the right dlPFC, active over the right mPFC, and sham over either the right dlPFC or the mPFC (random). The order of these targets was randomized (using excel random number generator) in such a way in which the subject and the PI who conducted the neurostimulation session did not know if any specific trial was active or sham. The technician who assisted with the session and prepared the equipment was not blind to the target order, and was responsible for following the randomization protocol during the neurostimulation visit. The technician did not influence in any way the course of the neurostimulation experiment and had minimal interaction with the participant.

Neuroimaging Data Analysis:

FMRI analyses were performed right after the MRI session to define the individualized stimulation target. Structural and functional data were first examined with MRIQC and preprocessed with fMRIprep v1.1.4 [52] right after each subject for identification of the target. The section below describes the steps required to define the stimulation target; The complete fMRI analyses will be presented elsewhere (Neacsiu et al., in prep). Preprocessing of the high-resolution, T1-weighted anatomical images included intensity correction using N4BiasFieldCorrection [53], skull-stripping, and spatial normalization to the ICBM 152 Nonlinear Asymmetrical template v2009c [54]. Initial preprocessing of the functional image data included slice time correction, calculation of motion correction transforms, and calculation of the transform for spatial registration to the high-resolution T1-weighted image. The fMRI data were then moved to standard space by applying the concatenated motion-correction transforms, fMRI-to-T1 transform, and T1-to-ICBM transform. The non-aggressive variant of ICA-based automatic removal of motion artifacts (AROMA) [55] was also applied to the fMRI data. After this preprocessing by fMRIprep, the fMRI data were skull-stripped (FSL's Brain Extraction Tool) [56], underwent high-pass temporal filtering with a 100-second cutoff (FSL's fslmaths), and was masked to exclude erroneous signal outside the brain. At the first level, functional data were analyzed as individual runs, using a general linear model (GLM) as implemented in FSL's FEAT procedure [57]. Model regressors were created for the fixation cross (3-7s), arrow task (9s), seeing the "listen" instruction (5s), seeing the "downregulate" instruction (5s), "listen" strategy during a neutral sound ("Hear Neutral", 10s), "listen" strategy during an aversive sound ("Hear Aversive", 10s),

"listen" strategy during a misophonic sound ("Hear misophonic", 10s), "downregulate" strategy during an aversive sound ("Downregulate Aversive"; 10s), "downregulate" strategy during a misophonic sound ("Downregulate Misophonia"; 10s), and distress ratings (10 s). A weight of 1 was attributed to each task regressor in the general linear model (GLM). Trial "on" times were convolved with a double-gamma hemodynamic response function to create the final GLM regressors.

The "downregulate vs. listen to a misophonic sound" contrast used for dlPFC targeting was defined as part of a second-level analysis, in which the first-level results for each of the four runs were combined using a fixed-effect model. A psychophysiological interaction (PPI) analysis was also conducted, using the time course of the left insula as the seed and the "listen to misophonic vs. neutral sound" contrast as the psychological regressor. First, the time series of the left insula [defined by the anatomical mask available as part of the FSL Harvard-Oxford sub-cortical structural segmentations] was extracted using "fslmeants", and was used as the physiological regressor. For the targeting analysis, activation in the insula was thresholded using a z score of 1.96 to allow a higher probability of finding a target. Statistical PPI maps from each of the four runs were then combined into a second level analysis using a fixed-effect model for each person.

Target identification:

The statistical maps for the contrasts of interest ("downregulate vs. listen to a misophonic sound", and "PPI-listen to misophonic vs. neutral sound") were transferred to native space back from standard space using the inverse ANTS transformation [58], and overlaid onto the anatomical image in a neuronavigation software (BrainSight, Rogue Research, Canada). The cluster within the right dlPFC showing the strongest positive z-value for the "Downregulate" contrast was defined as the dlPFC target. The cluster within the right mPFC showing the strongest positive z-value for the PPI-"Listen" contrast was defined as the anterior insular cortex (AIC) connectivity target. The coil orientation was visually set up so that the induced E-field was perpendicular to the closest sulcal wall. When this orientation was not feasible (e.g., coil handle in front of participant's face), the symmetric orientation was used, and the current was reversed. Scalp-to-cortex distance in mm at each site of stimulation was measured using the tape tool in BrainSight. Hair thickness in mm was measured using a digital depth gauge (Audew, HK, resolution: 0.01 mm) installed on a custom-made plastic base placed over the target (89). Brain to coil distance was computed as the sum of the hair thickness and the distance from the scalp to each target and was included as a co-variate in the analyses given previous results that it may impact outcomes [25]. See **Figure 3** for a visual depiction of all personalized targets.

6. Neurostimulation Experimental Session

Participants returned for the 3.5-hour neurostimulation session as soon as possible after the targets were identified and no later than a month since intake (Figure 2B).

Skills training:

The first 45 minutes were spent on skills training, one-on-one with the first author, a clinical psychologist with expertise in cognitive behavioral therapy, and was focused on in-depth learning of CR and practicing on standardized and personal examples. Skills training used standardized procedures blending psychotherapeutic approaches [59,60] with instructions in CR that matched prior neuroimaging studies [61]. Participants were told that thoughts and emotions are interconnected and one validated way to change emotional experiences is to think less unhelpful thoughts in situations that prompt the emotions [60,62-64].

In teaching *distancing*, adopting a detached and unemotional attitude was introduced as objective distancing [65]. Distancing by using time and space were also discussed and practiced on standardized examples [22]. For the misophonia group, distancing was further refined as thinking about what else could be making that sound (to have a different visual in mind), thinking that the sound is time limited, or thinking that, in the context of one's day, the misophonic experience is but a small percentage of time. We also

discussed space distancing, trying to focus one's attention on another element of the situation that is not as upsetting (i.e., not the visual stimulus that produces the trigger sound).

Participants were also taught *reframing* using an adapted version of existing paradigms [61,66,67]. Specifically, we emphasized with pictures and examples the relationship between thoughts and emotions in ambiguous situations, identified effectiveness as the objective in an emotional situation, and instructed participants to find interpretations that are less toxic in order to be effective rather than right when upset. Participants learned to think about elements of the situation that they did not pay attention to or information that was missing, and to reframe their cognitions based on the full picture with an eye towards effectiveness. Participants were also taught to examine the worst-case scenario, the probability of it occurring, and the likelihood of survival if it occurred.

For the misophonia group, we worked on reframing thoughts related to the person producing the sound ("they're hungry rather than they're rude"; "they're anxious rather than they're annoying me on purpose"). We also discussed using the three questions (worst case scenario, likelihood it will happen and likelihood of survival) during an experience where misophonic triggers are present. The CR training ended with a quiz that included definitions as well as fake scenarios to practice in order for the clinician to ensure that the skills were understood and could be applied appropriately.

TMS experiment

Following successful completion of the behavioral training, resting motor threshold (rMT) was established and GSR Ag/AgCl electrodes filled with an isotonic gel were placed on the distal phalanges of the index and ring fingers. HR electrodes were placed on the ankle and wrist. Amplified analog data were converted to digital recording and filtered using BIOPAC's AcqKnowledge 4.1 software. Psychophysiological measurements were collected continuously during the experiment using the BIOPAC MP150 recording system (Goleta, CA).

Active and sham rTMS were performed with a figure-8 coil (A/P Cool-B65) and a MagPro X100 stimulator (MagVenture, Denmark) set up to deliver biphasic pulses. Ten Hz rTMS over the personalized right dlPFC target (HF-rTMS) was performed using 5s of stimulation and 15s of an inter-train interval (ITI) at 120% rMT. After careful consideration, we decided to stimulate with 10 Hz because this frequency has been successfully used in affective disorders [68-71], and an ITI of 15 s was chosen based on evidence suggesting superiority of 15s over 26s [72].

One Hz rTMS over the personalized mPFC-AIC-connectivity target (LF-rTMS) was performed using one pulse per second continuously at 90% rMT [73]. Sham stimulation was applied using the same intensity setting but with the coil in placebo mode, which produced similar clicking sounds and somatosensory sensations (via electrical stimulation with scalp electrodes) without a significant magnetic field reaching the brain [74]. This type of sham stimulation allowed participants and the experimenter to stay blinded to the type of stimulation they received.

Coil position and orientation were continually monitored through a stereotaxic neuronavigation system (Brainsight, Rogue Research, Canada). Each participant received the three interventions. Each neurostimulation experimental session was conducted by the first author (AN), with the assistance of a TMS technician. AN, who was blinded to the stimulation condition, led the participant through the session, decided on dose adjustments and course of action for any protocol deviations. For example, if a participant could not tolerate rTMS, the first author could decide to drop the intensity to rMT and slowly ramp it back up during habituation. The TMS technician was not blinded to the condition and prepared the coil but did not influence the course of the session or interact with the participant.

For each participant, we extracted a personalized target related to emotion regulation in the right dlPFC (average $z_{dlPFC\_stimulation\_site} = 2.74$, SD = .73; 87% of z scores were above significance [>1.96]), and one related to reactivity to misophonia triggers in the right mPFC (average $z_{dlPFC\_stimulation\_site} = 3.03$, SD = 1.50; 87% of z scores were above significance > 1.96). Examples of how targets were extracted for five individuals in each group are included in Figure 3A. DlPFC targets were on average 14.23 mm away from the skull (SD = 1.89mm, range 9.8 mm – 18.4 mm), similar to mPFC targets (M = 14.94 mm, SD = 1.93,

range = 10.4 – 18.8 mm). Stimulation intensity ranged from 38 to 97% from maximum stimulator output (MSO) for the dlPFC target (M = 56.19, SD = 10.75), and from 29 to 73% MSO for the mPFC target (M = 42.19, SD = 8.10). The coil position across all participants is illustrated in Figure 3B.

The experimental session (Figure 2C) included a 180s pre- session baseline, followed by three experimental runs, one using HF-rTMS over the right DLPFC (39 trains), one using continuous LF-rTMS over the right mPFC, and one using sham rTMS applied over one of those two targets, in a randomized order. Each run included a pre-task baseline (180s), a habituation period (180s) where neurostimulation was administered while the participant was not given any instruction, a sound task, including 5 blocks (600s), and a 600s break. Neurostimulation was administered throughout the sound task. Each block (120s long) started with an instruction (downregulate or listen) and was followed by four sounds played on repeat for 25 seconds (either misophonic, neutral, or aversive depending on the block). Sound and block order was randomized within each run. During the sound presentation a downward arrow (for downregulate), or wave symbol (~, for listen) was present on the screen to guide participants on what to do, neurostimulation and psychophysiological data collection was ongoing.

Psychophysiological Data

HR and GSR were recorded during the whole duration of the sound task and the neurostimulation session. AcqKnowledge software was used to collect and pre-process raw ECG data by using a built in automated heart rate variability (HRV) analysis tool that follows established frequency domain algorithm guidelines [75]. For each baseline, habituation, and 120s listen or down-regulate block, high frequency HRV (HF-HRV) was extracted to capture emotion regulation. Reactivity to emotional cues was captured through GSR. For each baseline, habituation period, and for each sound presentation we extracted the maximum GSR value as a measure of peak emotional arousal. We then removed from the GSR signal, with the help of a MATLAB program, skin conductance responses (SCRs) by leveling the signal when clear spikes were identified [76]. In this way, the tonic signal, or skin conductance level (SCL), was also extracted from each baseline, habituation to rTMS, and 120s listen/regulate block. SCL values represent average arousal during these distinct time periods.

7. Statistical Analyses

Preliminary analyses, including *t*-tests and chi-squares, were conducted to assess demographic differences between experimental groups. We also examined any differences on matching variable (sex at birth, age) and other potential confounding variables like demographic characteristics, use of medication, dissociation during the experimental task, sleepiness during the experimental day, discomfort during neurostimulation, or psychophysiological effects induced by rTMS alone.

Primary outcomes set *a priori* were BOLD signal differences within the dlPFC and vmPFC during regulation of misophonic versus aversive sounds, BOLD signal differences within the AIC when listening to misophonic versus aversive sounds, change in HF-HRV and GSR during experimental blocks from baseline, acceptability of procedures as measured by percent of participants who complete the sessions. Secondary outcomes included self-reports (SUDS during the neurostimulation experiment, DERS, PROMIS-43), whole-brain BOLD changes when comparing aversive with neutral sound presentation and regulation, and when comparing misophonic with neutral sounds presentation and regulation.

To examine differences in functional activation between groups during the neuroimaging experiment, a group analysis was performed. Each functional and PPI FSL Level 2 analysis for each participant was entered into a third level FSL FEAT analysis assessing the differences between participants who in either the misophonia or the clinical control group.

To compare groups on functional connectivity during contrasts that were not included for targeting, four additional whole brain PPI analyses were performed using the same left insula seed, thresholded at 2.3, and then using the time series from this anatomical mask as the physiological regressor. In addition to the functional task regressors, each additional PPI analysis included one of the contrasts of interest as

regressors: [listen to misophonic vs. aversive sounds], [downregulate vs. listen to misophonic sounds], [listen to aversive vs. neutral sounds], and [downregulate vs. listen to aversive sounds]. For all, the PPI was defined as the interaction between this event and the physiological regressor (66, 67). This method was performed for each subject and for each run. A third level analysis was then performed to assess the differences between groups. PPI analyses probe the synchronization of brain activity between two brain regions allowing us to differentiate regions which interact with each other versus work independently during experimental tasks (68). Whole brain Z image statistics (from both functional and PPI analyses) were thresholded using clusters determined by $Z > 2.3$ and a corrected cluster significance of $p = .05$ (69). Mixed-effects hierarchical linear models (MMANOVA) with analytically determined covariance structures were used to analyze the repeated measures data (70). All MMANOVA models used a restricted estimated maximum likelihood model to account for missing data (71) (i.e., cases with missing data were not discarded, but slopes for each participant were computed with the data available). Estimated marginal means (EMMs) were compared using LSD corrections for significant main and interaction effects, and are presented in the results section. For data that was not repeated, independent sample *t*-tests or non-parametric equivalents were employed. To test the neurobiological basis of misophonia, correlation analyses with neuroimaging data extracted from regions of interest (ROIs) and baseline behavioral measures were employed.

To compare the effects our neurostimulation conditions, we conducted four analyses examining SUDS, peak GSR (SCR; peak arousal), SCL (tonic arousal), and HF-HRV. For the SUDS analyses, we examined the difference between SUDS at the end of each sound and the baseline SUDS collected after the task baseline. If task baseline SUDS were missing, session baseline SUDS were utilized instead. For the SCR analysis, the maximum value of the GSR during the presentation of each sound was used as outcome. For those two variables, the experimental group was used as a between-subject variable (misophonic or emotion dysregulation), and the experimental neurostimulation condition (active HF-rTMS over the right DLPFC, active LF-rTMS over the mPFC- insula, sham rTMS), the block instruction (downregulate misophonic, downregulate aversive, hear misophonic, hear aversive, hear neutral), the order effect of the 3 neurostimulation condition time within the task (0-2, corresponding with the runs employed), within the run (0-4, corresponding to each block), and within the block (0-3, corresponding to each of the sounds played),were used a within-subject variable. The experimental group by neurostimulation condition by block instruction interactions were entered as effects in the SUDS and SCR analyses. For SCR, the maximum GSR value during the habituation period was also controlled for. For the SCL and HF-HRV analyses, the experimental group and neurostimulation condition, and block instruction were also used but only the average within each block was used as outcome, time within block was excluded because HF-HRV requires at least 120s to be accurately assessed, and baseline values were added as main effects, time was considered a categorical variable. To account for multiple comparisons, we used a Bonferroni correction, and dropped the significance threshold to .0125. Differences between LF and HF rTMS were not hypothesized, but explored where both stimulation conditions were different than sham.

Planned covariates for all analyses included coil-to-cortex distance- given evidence that higher distance may impede the effectiveness of neurostimulation interventions for emotion regulation that are not designed to account for this parameter [77,78] - and data-driven covariates were also examined and added to these analyses as needed. Effect sizes were computed by using Feingold's formula [79] and interpreted using Cohen's specifications [80].

Normality Assumption: All variables were tested to examine whether they violated the normality of distribution assumption using Shapiro-Wilk normality tests ($W < .90$). HF-HRV was transformed to normal using the function lg10 (HF-HRV*1000000). All other data were normally distributed.

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