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Title: Journal of affective disorders.

ArticleTitle: An experimental examination of neurostimulation and cognitive restructuring as potential components for Misophonia interventions

ArticleAuthor: Neacsiu

OCLC - 38911953; ISSN - 01650327; LCN - 2004233074;

Publisher: 2024-01-01

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Contents lists available at ScienceDirect 

Journal of Affective Disorders

journal homepage: www.elsevier.com/locate/jad

Research paper

An experimental examination of neurostimulation and cognitive restructuring as potential components for Misophonia interventions

Andrada D. Neacsiu c,e,f,\*, Lysianne Beynel b,c, Nimesha Gerlus a, Kevin S. LaBar a,d, Noreen Bukhari-Parlakturk a,c,d, M. Zachary Rosenthal a,c,e

a *Duke University, Durham, NC, USA* b *National Institute for Mental Health, Bethesta, DC, USA* c *Duke University School of Medicine, Durham, NC, USA* d *Duke Institute for Brain Sciences, Durham, NC, USA* e *Center for Misophonia and Emotional Dysregulation, Durham, NC, USA* f *Brain Stimulation Research Center, Durham, NC, USA*

ARTICLE INFO

*Keywords:*

Emotion dysregulation Intervention

Misophonia

Neuroscience

Neurostimulation

**1. Introduction**

ABSTRACT

Misophonia is a disorder of decreased tolerance to certain aversive, repetitive common sounds, or to stimuli associated with these sounds. Two matched groups of adults (29 participants with misophonia and 30 clinical controls with high emotion dysregulation) received inhibitory neurostimulation (1 Hz) over a personalized medial prefrontal cortex (mPFC) target functionally connected to the left insula; excitatory neurostimulation (10 Hz) over a personalized dorsolateral PFC (dlPFC) target; and sham stimulation over either target. Stimulations were applied while participants were either listening or cognitively downregulating emotions associated with personalized aversive, misophonic, or neutral sounds. Subjective units of distress (SUDS) and psychophysio logical measurements (e.g., skin conductance response [SCR] and level [SCL]) were collected.

Compared to controls, participants with misophonia reported higher distress (ΔSUDS = 1.91–1.93, *p*s *<* 0.001) when listening to and when downregulating misophonic distress. Both types of neurostimulation reduced distress significantly more than sham, with excitatory rTMS providing the most benefit (Cohen’s *dSUDS* = 0.53; *d*SCL = 0.14). Excitatory rTMS also enhanced the regulation of emotions associated with misophonic sounds in both groups when measured by SUDS (*dcontrol* = 1.28; *dMisophonia* = 0.94), and in the misophonia group alone when measured with SCL (*d* = 0.20). Both types of neurostimulation were well tolerated. Engaging in cognitive restructuring enhanced with high-frequency neurostimulation led to the lowest misophonic distress, highlighting the best path forward for misophonia interventions.

definition was published only recently (Swedo et al., 2022). Current

misophonia treatment approaches have limited existing evidence and

Misophonia is the decreased tolerance for certain aversive repetitive and common sounds such as chewing, swallowing, or keyboard tapping and for the stimuli associated with these sounds. When presented with those sounds, individuals with misophonia experience intense distress associated with heightened physiological reactions such as increased heart rate or skin conductance and have trouble disengaging from the trigger (Kumar et al., 2017). While the prevalence of misophonia is estimated at 5–12 % of the population (Wu et al., 2014), this condition is still not well understood, and the first consensus on a standardized

include lifestyle modification, cognitive behavioral therapy, and audi ological treatment (Potgieter et al., 2019). However, since the mecha nisms underlying misophonia are unknown, the current treatments do not have clear targets for change; limited evidence exits on the benefits of any interventions; and misophonic patients report limited satisfaction with many common approaches (Smith et al., 2022).

Emerging neuroscientific findings suggest that misophonia may be an independent disorder (Neacsiu et al., 2022a), characterized by hy peractivity of the anterior insular cortex (AIC) in response to misophonic

\* Corresponding author at: Duke University Medical Center (102505), Durham, NC 27710, USA.

*E-mail addresses:* andrada.neacsiu@duke.edu (A.D. Neacsiu), lysianne.beynel@nih.gov (L. Beynel), nimesha.gerlus@duke.edu (N. Gerlus), klabar@duke.edu (K.S. LaBar), noreen.bukhari@duke.edu (N. Bukhari-Parlakturk), mark.rosenthal@duke.edu (M.Z. Rosenthal).

https://doi.org/10.1016/j.jad.2024.01.120

Received 17 August 2023; Received in revised form 8 December 2023; Accepted 10 January 2024

Available online 14 January 2024

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trigger stimuli (Kumar et al., 2017; Schroder ¨ et al., 2019), and altered activity and connectivity of prefrontal structures. The anterior insula is central to subjective emotional experience, awareness of sensory perception, and higher-level integration of salient cues for emotional processing (Craig, 2009). Therefore, these findings suggest enhanced salience of and difficulty disengaging from misophonic sounds. Quali

tative studies report that the misophonic experience contains intense emotions of anxiety, anger, and disgust, among other emotions (Brout et al., 2018; Swedo et al., 2022; Remmert et al., 2022; Rosenthal et al., 2021), as well as difficulties with emotional regulation (Guetta et al., 2022; Rinaldi et al., 2022). Thus, examinations of emotional dysregu

lation and comparisons with clinical populations who have difficulty with their arousal and regulation are warranted. Although several candidate networks are at play in this complex disorder (e.g., sensory, auditory, or even motor (Kumar et al., 2021)), examining the similarities and differences of misophonia with other emotional disorders holds promise because of the wealth of existing interventions for emotional dysregulation across psychopathology (Mennin, 2006; Neacsiu et al., 2014; Gross, 2013).

In the present study, we compared transdiagnostic clinical adults who report high emotional dysregulation with adults with moderate to severe misophonia using multimethod assessment. We examined dif ferences in the response and regulation of aversive sounds to test broad emotional dysregulation in misophonia. Furthermore, we tested how clinical controls respond to and regulate emotions associated with trigger sounds to clarify the unique features of misophonia.

In addition, we aimed to investigate whether a bottom-up versus a top-down approach is best suited for a misophonia intervention. Using repetitive transcranial stimulation (rTMS; see Supplement) (Hoogendam et al., 2010), we examined whether inhibiting insula activity with low

frequency mPFC stimulation or enhancing regulation with high frequency dlPFC stimulation during the presentation of misophonic sounds leads to larger reductions in misophonic distress when compared to listening to trigger sounds without any intervention. Diffusion tensor imaging data in humans have shown direct anatomical connections between the insula and both the mPFC and dlPFC (Ghaziri et al., 2017). The mPFC is thought to engage in automatic, implicit emotional pro cessing, while the dlPFC is associated with conscious, effortful emotion regulation (Etkin et al., 2015). Therefore, low-frequency mPFC stimu lation and high-frequency dlPFC stimulation allowed us to examine differential responses to inhibition of emotional reactivity versus augmentation of cognitive emotional control, respectively. We also wanted to compare the use of cognitive restructuring (an emotional regulation skill), with neurostimulation, and with skill use plus neuro stimulation as different avenues for treatment development using a within-subject design. Our goal was to answer several questions to

accelerate the development of treatments for misophonia. We trained all participants to use cognitive restructuring (CR) to understand whether skills training could be as effective for misophonic adults as it is for clinical emotional dysregulation (Neacsiu et al., 2014). Effective use of reappraisal during an emotion regulation task increases high-frequency heart rate variability (HF-HRV) (Denson et al., 2011), a marker of effective emotion regulation (Butler et al., 2006; Di Simplicio et al., 2012). HF-HRV has not yet been investigated in misophonia. Rather, changes in skin conductance level (SCL) and response (SCR) were identified as potential psychophysiological markers of misophonic distress (Kumar et al., 2017). There have been few examinations of the effect of emotion regulation tasks on SCL, with one study showing no differences in SCL between effective and maladaptive regulation stra tegies (Campbell-Sills et al., 2006). Therefore, one aim of this study was to test differences between adults with misophonia and clinical controls on HF-HRV, SCL, SCR, and self-reported distress (SUDS) during passive listening and regulation of aversive and misophonic sounds. The second aim was to examine whether potential misophonia in terventions should target reduction to sound reactivity or improvement in emotion regulation as the primary mechanism of change. To this aim,

we chose to apply excitatory neurostimulation over a node of the emotion regulation network (HF-rTMS over the right dlPFC) and inhibitory neurostimulation targeted towards the reactivity network (LF-rTMS over a prefrontal node functionally connected to the insula). Given the consistent finding that the insula is hyperactive in the pres

ence of trigger sounds in misophonia (Neacsiu et al., 2022a), we hy pothesized that one avenue towards intervention is to inhibit insula activity in the presence of sounds. Stimulation of the insula directly is difficult; nevertheless, connectivity based stimulation has been shown to successfully reach deeper brain structures (Beynel et al., 2021). There fore, we used connectivity analyses to find a node in the mPFC func tionally connected to the insula, and administered stimulation over this node with the aim of inhibiting activation in the entire network. Furthermore, we examined whether neurostimulation, cognitive restructuring, or their combination offers the most promise for a novel intervention.

We hypothesized that when compared to controls, participants with misophonia will exhibit (H1) higher distress (as measured with SUDS, SCL, and SCR) when listening to misophonic trigger sounds; (H2) lower distress when listening to aversive sounds; and (H3) lower HF-HRV during the regulation of misophonic sounds. We expected that both LF-rTMS (H4) and HF-rTMS (H5) stimulation will reduce distress significantly more than sham stimulation during the presentation of misophonic cues in the misophonia group. We expected HF-rTMS stimulation to lead to lower distress and higher regulation (HF-HRV) in both groups when compared to sham stimulation during the presen tation and regulation of aversive sounds (H6). We planned to explore differences between the use of CR, LF-rTMS, HF-rTMS, and their com

bination (i.e., CR + HF-rTMS; CR + LF-rTMS) within and across groups, expecting combined interventions to lead to more reductions in arousal that each component alone (H7).

**2. Methods**

*2.1. 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 sizes derived from Kumar et al. [2], The CONSORT diagram (Fig. 1) and the Supplement contain additional details regarding power analyses, participants, and study enrollment. Participants received a maximum compensation of $250. The study was approved by the Duke University Health System Institu

tional Review Board and it study conforms to the provisions of the Declaration of Helsinki. Fig. 2 depicts the study design.

*2.2. Intake session*

After providing voluntary, written informed consent, participants completed diagnostic assessments (SCID-5, SCID-PD), a verbal intelli gence test (Dunn, 1981), and a questionnaire packet [see Supplement].

*2.3. Sound task*

Qualifying participants completed an in-person task where they heard 101 pre-selected sounds: 31 aversive, 40 misophonic, and 30 neutral sounds. Each stimulus presentation was followed by valence and arousal ratings. Participants in the misophonia group alone were also asked whether the sound was a misophonic trigger for them (yes/no). Based on this task (see Supplement for details), for each participant, personalized sets of 12 aversive, 12 misophonic, and 12 neutral sounds were selected for the neurostimulation and neuroimaging sessions.

*2.4. Neuroimaging sessions*

Participants completed an imaging session (Fig. 2B) on average 9.83

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***MRI day (n = 59) Matched\* (n = 58)***

o oo

***Experimental day***

***(n = 54)***

***Post Experimental***

***Assessment***

***(n = 54)***

**Fig. 1.** CONSORT Diagram depicting study flow.

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**Fig. 2.** Experimental design. D represents the day in the study when these sessions were approximately scheduled. CR = Cognitive Restructuring; rTMS = repetitive transcranial magnetic stimulation; MT = motor threshold.

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days (SD = 9.97) after the eligibility intake session. Following stan dardized training, participants moved into a research-dedicated GE HD 3.0 T MRI scanner. The scan included an anatomical image and four runs of EPI functional images acquired while participants experienced and downregulated emotions related to personalized sounds (task-related acquisition: four runs). See Supplement for details.

FMRI analyses were performed immediately after the MRI session to define the individualized stimulation target. Structural and functional data were first examined with MRIQC and then preprocessed with fMRIprep v1.1.4 (Esteban et al., 2019). A psychophysiological interac

tion (PPI) analysis was also conducted to measure functional connec tivity with the left insula while listening to misophonic vs. neutral sounds. Connectivity with the left insula only was chosen because we aimed to find an mPFC target on the right hemisphere (to keep consis tent with the dlPFC targeting) and other research shows contralateral connectivity tends to be strongest between limbic and prefrontal regions (Banks et al., 2007), and, finally, when affective processing is lateralized to one side of the insula, it tends to be the left side (Duerden et al., 2013).

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 (Avants et al., 2011), and overlaid onto the anatomical image in neuronavigation software (BrainSight, Rogue Research, Canada). For each participant, the cluster within the right dlPFC showing the strongest positive z-statistic value for the “Downregulate” contrast was defined as the dlPFC target (average zdlPFC\_stimulation\_site = 2.74, SD = 0.73). The cluster within the right mPFC showing the strongest positive z-value above a threshold of z = 1.96 for the PPI-“Listen” contrast was defined as the AIC functional connectivity target(average zmPFC\_stimulation\_site = 3.03, SD = 1.50). See Fig. 3**A-B** for a visual depiction of the personalized targeting procedure and Supple ment for additional details.

*2.5. Neurostimulation experimental session*

Participants returned for the 3.5-hour skills training/neuro stimulation session (Fig. 2C) on average 14.11 days after the MRI session (SD = 12.57). The first 45 min were spent on skills training, one-on-one with the first author, a clinical psychologist with expertise in cognitive

behavioral therapy. The session focused on in-depth learning and practice of CR (See Supplement). Next, the participant’s resting motor threshold (rMT) was established using standard procedures (Rossi et al., 2021).

Psychophysiological measurements were collected continuously during the experiment using the BIOPAC MP150 recording system (Goleta, CA) via GSR and HR electrodes. 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 per

formed using 5 s of stimulation and 15 s of an inter-train interval (ITI) at 120 % rMT. One Hz rTMS over the personalized mPFC-AIC-connectivity target (LF-rTMS) was performed using one pulse per second continu ously at 90 % rMT (Balconi and Bortolotti, 2012). Sham stimulation was applied using the same intensity setting but with the coil in placebo mode (Smith and Peterchev, 2018). Coil position and orientation were continually monitored through a stereotaxic neuro-navigation system (Brainsight, Rogue Research, Canada).

All participants received the three interventions. Each neuro stimulation 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 and decided on dose adjustments and course of action for any protocol de viations. The experimental session (Fig. 2C-D) is detailed in the Supplement.

High-frequency heart rate variability (HF-HRV), skin conductance response (SCR), and skin conductance level (SCL) were used as in dicators, respectively, of emotion regulation, peak emotional arousal, and average arousal. HF-HRV and SCL were extracted within each sound task block (120 s). SCR and change in SUDS were examine for each sound presentation (30s; see Fig. 2E for a visual depiction).

*2.6. Statistical analyses*

We conducted four analyses examining ΔSUDS, SCR, SCL, and HF HRV (see Fig. 2E). See Supplement for details. To account for multiple comparisons, we used a Bonferroni correction and reduced the alpha threshold to *<*0.0125. Planned covariates for all analyses included coil

**Fig. 3.** A. The top legend is the range for activation for the regulation contrast; regulation contrast is depicted with a blue-magenta map; the bottom legend is the range of activation for the reactivity contrast, depicted with the green-red map. The copper region is the structural mPFC mask used to constrain targets. It includes Brodmann Area (BA) 10 and the rostral portions of BA 9 and BA (Carl´en, 2017). The red region is the dlPFC mask used to constrain the regulation targets. It included the ventrolateral portion of BA6, and the superior border is the sulcus between the superior and middle frontal gyri. All images are in native space and are thresholded by a minimum z of 2.3. 1B: Coil position across all participants, with in dark blue the emotion dysregulation group, and light blue the misophonia group. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

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to-cortex distance (Lee et al., 2016; Stokes et al., 2005). Data-driven covariates such as the incidence of headaches post-stimulation were

**Table 1**

Demographics and clinical descriptive by group.

also examined and added as needed. Effect sizes were computed by using Feingold’s formula (Feingold, 2009) and interpreted using Cohen’s specifications (Cohen, 1977). The distribution of HF-HRV was trans

Emotion

dysregulation (*n* = 30)

Misophonia

(*n* = 29) Statistical difference

formed to normal using the function lg10 (HF-HRV\*1000000). All other data were normally distributed.

Mean age (SD) 27.07 (8.28) 29.59 (9.79) *t* (57) = − 1.07, *p* =

**3. Results**

Female gender identity (%)

.29

86.67 89.66 *χ2*[4] = 2.98, *p* = .56

*3.1. Feasibility, acceptability, tolerability, compliance, and blinding efficacy*

Latinx background (%) 23.33 3.45 *χ2*[1] = 4.98, *p* = .03

Racial background (%) *χ2*[5] =

Asian/Asian American 30.0 3.45

13.68, *p* = .02

Overall participants in both groups reported reduced stress at the end compared to the beginning of each experimental session (Δaverage\_intake\_change = − 0.56, SD = 1.53; Δaverage\_MRI\_change = − 0.31, SD = 1.22; Δaverage\_TMS\_change = − 0.48, SD = 0.89). These results suggest that the experimental tasks were feasible and acceptable to our partic

Black/African

American

Native American, American Indian, or Alaskan Native

3.33 0.00 3.33 0.00

ipants. Following the sham stimulation, 26 participants (48.15 %) re

White/Caucasian 56.67 96.55 Middle Eastern 6.66 0.00

ported some headache, compared to 40 participants (74.07 %) after the HF-rTMS trial, and 34 (62.96 %) after the LF-rTMS trial, a significant

On psychotropic medications:

40.00

difference (χ2[2] = 7.73, *p* = .02). Because of the higher incidence of

Recent psychotherapy: 50.00

headache in the active stimulation conditions, we included this variable as a data-driven covariate in analyses. There was no difference in guessing active versus sham assignments between types of neuro stimulation received (*Msham* = 5.72, *SD* = 2.27; *MHF-rTMS* = 6.74, *SD* =

Total # of diagnoses, current (SD)

Total # of diagnoses, lifetime (SD)

Current disorders (%)

1.97 (1.38) 1.52 (1.83) *t* (57)= 1.07, *p* = .29

4.07 (2.12) 3.00 (2.32) *t* (57) = 1.85, *p* = .07

2.07; *MLF-rTMS* = 6.43, *SD* = 2.18) or between groups (F [2, 151] =

Mood disorders 30.00 13.80 Anxiety disorders 83.30 69.00

11.05, *p* = .09), according to a multivariate ANOVA controlling for racial background (F [1, 151] = 0.06, *p* = .44). See Supplement for

Obsessive compulsive disorders

16.70 6.90

additional findings.

Stress disorders 10.00 10.30

Impulse control disorders

6.70 6.90

*3.2. Preliminary analyses examining confounds*

There were significantly more participants belonging to racial or ethnic minority groups in the emotional dysregulation condition

Eating disorders 0.00 3.40 Lifetime disorders (%)

Mood disorders 83.30 69.00 Anxiety disorders 93.30 75.90 Substance use disorders 26.70 27.60

(Table 1). Therefore, racial/ethnic background was recoded as 0 (non

Obsessive compulsive disorders

23.30 10.30

white) or 1 (white) and co-varied in subsequent analyses. A more nuanced covariate was not possible given that the misophonia group was 96.5 % white.

Significant differences were found between experimental conditions (sham vs. active rTMS) during the habituation period (i.e., when neu rostimulation alone was administered at rest). At rest, HF-rTMS administered over the right dlPFC enhanced HF-HRV (*F* [2, 90.49] = 6.63, *p* = .002), SCR (*F* [2, 90.76] = 14.27, *p <* .001), and SCL (*F* [2, 96.22] = 27.17, *p <* .001) significantly more than sham neuro stimulation (ΔHF-HRV = 0.12, SE = 0.03; ΔSCR = 2.84, SE = 0.54; ΔSCL = 1.76, SE = 0.24). LF-rTMS over the right mPFC did not significantly affect HF-HRV, but significantly increased SCR (ΔSCR = 1.72, SE = 0.52) and SCL (ΔSCL = 0.72, SE = 0.23) when compared to sham. Participants experienced significantly higher tonic arousal (SCL) during HF-rTMS than during LF-rTMS (ΔSCL = 1.05; SE = 0.24, *p <* .001). As planned, because of these observed differences, habituation values for outcomes variables replaced task baseline values as co-variates in main analyses.

Effect sizes were computed by using Feingold’s formula (Feingold, 2009) and interpreted using Cohen’s specifications (Cohen, 1977). The SD for HF-HRV (0.59), SCR (4.26), and SCL (3.60) during the session baseline, and for ΔSUDS post-pre session baseline (0.58) were used to compute the effect sizes.

*3.3. The effect of neurostimulation and cognitive restructuring on reactivity and regulation*

Table 2 includes EMMs for main and interaction effects across all outcome analyses.

Stress disorders 31.00 20.70

Eating disorders 13.30 13.80

Any pd. (%) 48.27 24.14 *χ2*[1] = 3.66, *p* = .06

Note: SD = Standard Deviation; PD = personality disorder.

*3.3.1. Self-report results (SUDS)*

The MMANOVA analysis of SUDS used a Toeplitz covariance struc ture (see the syntax in Supplement) and found a significant main effect of experimental neurostimulation (*F*[2, 373.52] = 19.50, *p <* .000000001). Pairwise comparisons between the three neurostimulation conditions demonstrated that SUDS ratings were significantly lower when HF-rTMS over the dlPFC was administered than when either LF rTMS over the mPFC (*p <* .00001, Cohen’s *d* = 1.0) or sham (*p <* .000000001, *d* = 1.58) were administered. See supplement for addi tional results for main effects.

A significant interaction was found between experimental neuro stimulation, experimental instruction, and group (*F*[22, 705.00] = 18.36, *p <* .000000001). The interaction revealed that participants in the misophonia group experienced significantly more distress than controls when listening (Δ = 1.91, *SE* = 0.32, *p <* .001, *d* = 3.34) and when downregulating (Δ = 1.93, *SE* = 0.32, *p <* .001, *d* = 3.34) miso phonic sounds across all experimental conditions, a finding that sup ports H1. In addition, participants in the misophonia group reported significantly less distress than participants with emotion dysregulation when listening to aversive sounds (Δ = 1.76, SE = 0.32, *p <* .001, *d* = 3.04), a finding that supports H2. In the sham condition alone, partici pants with emotional dysregulation reported more distress when downregulating aversive sounds than participants with misophonia (Δ

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**Table 2**

Estimated marginal means (and standard errors) from mixed models analyses by experimental condition and group.

A. Main Effects

ΔSUDS SCL SCR HF-HRV

(ΔSHAM-HF-tTMS = 1.15, *p <* .001, *d* = 1.99) and misophonic (ΔSHAM-HF rTMS = 1.51, *p <* .001, *d* = 2.59) sounds, which supports H6. LF-rTMS did not outperform sham stimulation in this group (Fig. 4).

For participants with misophonia, unlike patients with emotion dysregulation, the rTMS effect was specific for the misophonic sounds.

Sham rTMS 1.67 (0.16) 9.33 (0.15)

HF-rTMS 0.76 (0.17) 8.84 (0.16)

10.03 (0.59) 10.27 (0.60)

1.98

(0.02) 1.92

(0.02)

Contrary to H6, there were no differences between both active and sham neurostimulation when participants listened to neutral or aversive sounds or when they downregulated aversive sounds. This is likely because participants with misophonia reported relatively low distress

Lf –rTMS 1.34 (0.16) 8.86

9.68 (0.59) 1.91

when listening to aversive sounds (*EMM* = 1.55, *SE* = 0.34). Never

Listen to neutral − 0.01 (0.19)

(0.15) 8.99

(0.13)

(0.02)

9.90 (0.59) 1.93 (0.02)

theless, the distress produced by a misophonic sound was significantly lower in the HF-rTMS condition when compared to sham when partic ipants were instructed to listen (ΔSHAM-HF-rTMS = 0.92, *p* = .001, *d* =

Listen to aversive 2.43 (0.29) 8.96 (0.15)

10.08 (0.61)

1.92

(0.03)

1.59) or to downregulate (ΔSHAM-HF-rTMS = 1.02, *p <* .001, *d* = 1.76),

Listen to misophonic 2.72 (0.19) 9.09 (0.13)

9.96 (0.59) 1.94 (0.02)

which supports H5. LF-rTMS was marginally superior to sham during listening (ΔSHAM-LF-tTMS = 0.58, *d* = 1.00, Bonferroni corrected *p* = .16),

Downregulate aversive 0.53 (0.20) 9.06

10.04

1.95

or downregulation of misophonic sounds (ΔSHAM-LF-rTMS = 0.64, *d* =

Downregulate

(0.14)

(0.60)

(0.02)

1.11, Bonferroni corrected *p* = .12). Thus, H4 was not supported. There

misophonic

B. Interaction effects

0.62 (0.26) 8.95

(0.15)

Emotion

dysregulation group

9.97 (0.61) 1.92 (0.03)

Misophonia group

was no difference between the two active rTMS conditions (*p >* .05). To examine the effects of implementing a behavioral skill alone, we examined differences within the sham condition only. Instructions to downregulate led to significantly less distress than instructions to listen

ΔSUDS SCL ΔSUDS SCL

to aversive (Δ = 1.88, *SE* = 0.39, *p <* .001, *d* = 3.25) and misophonic (Δ

Listen to neutral Sham rTMS

HF

rTMS

0.53

(0.29) − 0.39 (0.30)

9.54

(0.20) 8.91

(0.20)

0.06

(0.31) − 0.48 (0.32)

9.08

(0.23) 8.70

(0.23)

= 2.12, *SE* = 0.33, *p <* .001, *d* = 3.66) sounds across groups. Thus, in both conditions, excitatory neurostimulation as well as implementation of an emotion regulation skill individually reduced emotional distress, and therefore are promising interventions for both emotional dysregu

LF rTMS 0.30

8.87

− 0.06

8.84

lation and misophonia.

Listen to aversive Sham rTMS

HF

rTMS

(0.30) 3.78

(0.37) 2.81

(0.37)

(0.21) 9.33

(0.22) 9.20

(0.22)

(0.32) 1.63

(0.37) 1.50

(0.38)

(0.23) 9.14

(0.25) 8.51

(0.25)

To examine across groups whether neurostimulation alone was su perior to behavioral skill implementation, we compared the change in distress when listening to aversive or misophonic sounds while receiving HF-rTMS with changes during sham while participants were engaged in

LF rTMS 3.33

8.64

1.52

8.92

CR. We also compared the combination of neurostimulation with CR

Listen to

misophonic

Sham rTMS HF

rTMS

(0.37) 2.48

(0.29) 0.98

(0.30)

(0.22) 9.66

(0.20) 9.07

(0.20)

(0.31) 4.17

(0.30) 3.25

(0.32)

(0.25) 9.21

(0.22) 8.65

(0.23)

with either intervention alone. Utilizing a behavioral skill was superior to neurostimulation alone (*paversive* = 0.001, *d* = 2.31; *pmisophonic* = 0.012, *d* = 1.57) in reducing distress induced by aversive sounds. The combi nation of neurostimulation and skill use led to significantly lower

LF rTMS 1.83

8.85

3.59

9.09

distress at the end of the sound presentation for both misophonic and

Downregulate aversive

Sham rTMS HF

rTMS

(0.29) 1.36

(0.30) 0.22

(0.31)

(0.20) 9.54

(0.21) 9.12

(0.21)

(0.31) 0.28

(0.32) − 0.15 (0.33)

(0.22) 9.16

(0.24) 8.75

(0.25)

aversive sounds when compared to either intervention modality alone (*p*s *<* 0.001, *d*s *>* 2.90). Therefore, in line with H7, the combined intervention leads to the highest reduction in distress, followed by uti lizing only behavioral skills, followed by neurostimulation alone.

LF rTMS 1.22

8.99

0.28

8.80

Downregulate misophonic

Sham rTMS HF

rTMS

(0.30) 0.28

(0.35) − 1.23 (0.35)

(0.22) 9.32

(0.23) 8.87

(0.24)

(0.33) 2.13

(0.34) 1.11

(0.37)

(0.24) 9.31

(0.24) 8.57

(0.27)

*3.3.2. Peak arousal (SCR) results*

A MMANOVA analysis using a Toeplitz covariance structure found a main effect of baseline (*F*[1, 674.27] = 33.99, *p <* .00000001), the time during the block (*F*[3, 99.85] = 48.86, *p <* .001), and headache (*F*[1,

LF rTMS − 0.11 (0.35)

8.88

(0.24)

1.50

(0.34)

8.72

(0.25)

668.90] = 15.22, *p <* .001). There was also a marginally significant main effect for coil-to-cortex distance (*F*[1, 717.11] = 5.06, *p* = .03). Higher

*Note.* rTMS = repetitive transcranial magnetic stimulation; HF-rTMS = high frequency rTMS; LF rTMS = low frequency rTMS; SUDS = change in subjective units of distress from baseline; SCL = skin conductance level; SCR = Skin conductance response; HF-HRV = high frequency heart rate variability. EMMs = estimated marginal means computed controlling for baseline and for cova

riates (coil to cortex distance, headache, racial background).

= 1.08, SE = 0.40, *p <* .008, *d* = 1.87). During dlPFC and mPFC stim ulation, this difference between groups was no longer significant, sug gesting that neurostimulation normalized the regulation of aversive sounds for controls.

Group-specific results were as follows: for participants with emotion dysregulation, confirming H6, HF-rTMS decreased SUDS more than sham when participants were asked to listen to neutral (ΔSHAM-HF-rTMS = 0.92, *p* = .004, *d* = 1.59), aversive sounds (ΔSHAM-HF-rTMS = 0.97, *p <* .001, *d* = 1.68), or misophonic sounds (ΔSHAM-HF-rTMS = 1.50, *p <* .001, *d* = 2.59). HF-rTMS also enhanced the downregulation of aversive

baseline SCR (i.e., during habituation; parameter estimate [PE] = 0.17, *SE* = 0.03), lower coil-to-cortex distance (*PE* = − 0.12, *SE* = 0.03), and presence of head discomfort (*PE* = − 0.82, *SE* = 0.21) led to higher SCR during individual sound presentations. SCR decreased significantly over time within each block (*p*s *<* 0.03). A significant main effect of experi

mental neurostimulation was also found (*F*[2, 587.82] = 6.98, *p* = .001), but pairwise comparisons only found a marginally significant difference between sham and the LF-rTMS conditions (Δ = 0.35, *SE* = 0.16, *p* = .03). There was no significant main effect for group, instructions pro vided, or racial background (*p*s *>* 0.05). The interaction effect between experimental neurostimulation, instruction provided and experimental group was marginally significant, and as a result, was not investigated further (*F*[22, 1262.55] = 1.65, *p* = .03). Therefore, the SCR results did not support any of our hypotheses.

*3.3.3. Average arousal (SCL) results*

A MMANOVA analysis using an unstructured covariance structure

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**Fig. 4.** Self-report units of distress by instruction provided, experimental group, and experimental neurostimulation. Values represent estimated marginal means from the mixed models analysis of variance, adjusted for covariates and main effects. The Orange dotted line represents our closest approximation of the misophonic experience. Higher positive values represent more distress when compared to baseline (accounting for covariates and other factors). D values refer to Cohen’s d effect sizes for significant differences marked by an \*. Orange line depicts typical distress in misophonia when encountering a trigger sound (listen to a misophonic trigger +

sham stimulation condition).

**Fig. 5.** Average skin conductance level in micro siemens depending on experimental group, instruction provided, and experimental neurostimulation. Values represent estimated marginal means from the mixed model analysis of variance, adjusted for covariates and main effects. D values refer to Cohen’s d effect sizes for significant differences, marked by an \*.

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found a significant main effect for experimental neurostimulation (*F*[2, 79.70] = 7.18, *p* = .001). Tonic arousal was significantly higher in the sham condition when compared to either active stimulation condition (*p* HF\_rTMS = 0*.*001; *p*LF\_rTMS = 0.002; *d*s = 0.14), with no difference between active conditions (*p >* .05) suggesting that both types of neuro

stimulation reduced tonic arousal. Higher SCL at baseline (i.e., during habituation) led to higher SCL during the experimental runs (*F*[1, 57.77] = 2488.10, *p <* .001). There was also a significant effect of time during the experimental run, with earlier blocks having significantly higher SCL than later blocks (*p*s *<* 0.001). Thus, SCL decreased over time during the run independent of the experimental condition. There was no significant main effect for the experimental group, instructions pro

vided, headache, racial background, or coil-to-cortex distance (*p*s *>* 0.05). Therefore, the SCL results did not support H1 and H2. A significant interaction was found between experimental neuro stimulation, instruction provided, and group (*F*[22, 111.50] = 2.69, *p <* .0005, Fig. 5). There were no significant differences between groups, and therefore we examined this interaction within each group. For clinical control patients with emotion dysregulation, when listening to neutral (ΔSHAM-HF-rTMS = 0.63, *p* = .004; ΔSHAM-LF-rTMS = 0.67, *p* = .002) or misophonic sounds (ΔSHAM-LF-tTMS = 0.811, *p <* .001, *d* = 0.23; ΔSHAM-HF-rTMS = 0.59, *SE* = 0.203, *p* = .004, *d* = 0.16), both HF-rTMS and LF-rTMS decreased tonic arousal when compared to sham stimulation, with no difference between the two stimulation conditions. Therefore, SCL results support H6. LF-rTMS alone reduced SCL signifi cantly more when listening to an aversive sound when compared to sham (ΔSHAM-LF-rTMS = 0.69, *p* = .002, *d* = 0.19). There were no sig nificant differences between experimental neurostimulation conditions during the regulation blocks.

For patients with misophonia, and supporting H5 and H6, HF-rTMS reduced SCL significantly more than sham when listening to either aversive (ΔSHAM-HF-tTMS = 0.63, *p* = .009, *d* = 0.18) or misophonic sounds (ΔSHAM-HF-tTMS = 0.56, *p* = .009, *d* = 0.16) and when down

regulating misophonic sounds (ΔSHAM-HF-tTMS = 0.73, *p* = .006, *d* = 0.20). The lowest SCL when exposed to misophonic sounds in the misophonia group was during the combination of behavioral skill uti

lization and HF-rTMS stimulation. H4 was not supported. To investigate the effects of using only behavioral skills, we exam ined differences within the sham condition and found no significant reduction in SCL when implementing CR alone (i.e., sham stimulation during listening was not significantly different from sham stimulation during downregulation; *p*s *>* 0.35). Thus, in both groups, excitatory neurostimulation alone reduced emotional distress.

We also aimed to examine differences across groups in SCL after receiving different intervention approaches while listening to and downregulating aversive and misophonic sounds. Therefore, we compared tonic arousal across three conditions: when participants were downregulating sounds in the sham condition; when participants were listening to sounds and receiving HF-rTMS; when participants were downregulating emotions associated with sounds while receiving HF

rTMS. For both aversive and misophonic sounds, neurostimulation alone (*paversive* = 0.014; *pmisophonic* = 0.014) or in combination with cognitive restructuring (*paversive* = 0.017; *pmisophonic* = 0.001) led to less arousal than CR alone. There was no significant difference between neurostimulation alone and the combined approach (*p*s *>* 0.10). Therefore, H7 was partially supported. There was also no difference between groups in response to these different interventions. This sug

gests that a neurostimulation-based treatment might be optimal for intervention for misophonia as well as emotional dysregulation.

*3.3.4. High-Frequency Heart Rate Variability (HF-HRV) results* A MMANOVA analysis using an unstructured covariance structure did not reveal any main effect of group, instruction provided, headache, or racial background (*p*s *>* 0.05). Therefore, H3 was not supported. However, we found significant main effects of experimental neuro stimulation type (*F*[2, 86.03] = 6.37, *p* = .003). Contrary to our

expectations in H6, across both groups and all trials, HF-HRV was significantly higher in the sham condition when compared to either active stimulation condition (*p*HF\_rTMS = 0*.*008; *p* LF\_rTMS = 0.001, *d*s = 0.10). In the same analysis, there was a significant main effect of HF HRV value during habituation (*F*[1, 67.58] = 1088.48, *p <* .00000001) and of coil-to-cortex distance (*F*[1, 121.62] = 11.71, *p <* .0009), with lower coil-to-cortex distance (*PE* = − 0.02, *SE* = 0.01) and higher HF-HRV values during habituation (*PE* = 0.82, *SE* = 0.03) leading to higher HF-HRV values during experimental trials. Finally, only a marginally significant interaction was found between experi mental neurostimulation, instruction, and experimental group (*F*[22, 130.82] = 1.84, Bonferroni corrected *p* = .076), and therefore the interaction was not investigated further.

In sum, when controlling for the increase in HF-HRV induced by neurostimulation or sham alone, participants have higher HF-HRV during the sham experimental trials than during the active stimulation trials. Raw means of HF-HRV across groups are higher for active than for sham neurostimulation (*MHF-rTMS* = 0.000186; *MLF-rTMS* = 0.000166; *Msham* = 0.000153), which is aligned with H6.

*3.4. Exit interview*

Participants perceived response to neurostimulation varied; some commented that neurostimulation either made them more numb to their feelings while others commented that neurostimulation led them to feel things more deeply. Participants with misophonia also described a sense of overwhelming hope, as well as wanting to laugh during the presen

tation of misophonic triggers because they were much less aversive than when experiencing these stimuli in the absence of neurostimulation. All participants indicated an above-average willingness to engage in neurostimulation enhanced behavioral treatment to help reduce mental health distress (*M* = 6.13, *SD* = 2.64, range 0 –unwilling – 9 – extremely willing; *pgroup\_difference* = 0.39). All participants found CR training very helpful (*M* = 7.59, *SD* = 1.83, Range: 0–9; *pgroup\_difference* = 0.56), the combined procedures highly acceptable *Macceptability* = 8.13, *SD* = 1.03, Range 0–9; *pgroup\_difference* = 0.68) and reported high likelihood to recommend this treatment to a friend (*M* = 74.98 %, *SD* = 19.89, range 0–100 %; *pgroup\_difference* = 0.88).

**4. Discussion**

Emerging research highlights that misophonia is a serious disorder that significantly impairs the quality of life and functioning (Swedo et al., 2022). Several studies have characterized misophonia across behavioral and biological domains (Neacsiu et al., 2022a; Brout et al., 2018; Siepsiak et al., 2022); nevertheless, given the intense emotional reaction to specific sounds, it is yet unclear whether misophonia should be considered a unique disorder under the purview of any particular clinical discipline. Furthermore, how to best intervene for those who meet criteria for this disorder continues to be unclear (Palumbo et al., 2018). Therefore, in this study, we compared adults with moderate and severe misophonia severity to a transdiagnostic sample of adults who meet criteria for a DSM-5 disorder and who self-report clinically high difficulties with regulating emotions. We also examined whether in terventions should aim to reduce sound reactivity or improve emotion regulation and whether neurostimulation, cognitive restructuring, or their combination offers the most promise to intervene on this disorder.

This study demonstrates that there are few psychophysiological differences in the response and regulation of distress related to sounds between clinical emotional dysregulation and misophonia. Prior pre liminary studies did show psychophysiological differences (especially in SCR) between adults with misophonia and non-clinical controls (Kumar et al., 2017). Our findings highlight that when confronted with trigger sounds, adults with misophonia are similar to adults who have signifi cant difficulties regulating emotions with a range of DSM-5 disorders in physiological reactivity and arousal. Thus, existing evidence-based

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interventions that successfully address arousal and emotion regulation developed for other clinical problems also may provide some benefit to misophonia sufferers. Dialectical behavior therapy skills training (Neacsiu et al., 2014), adaptations of the unified protocol (Lewin et al., 2021), or neurostimulation-augmented emotion regulation training may reduce emotion dysregulation across clinical samples (Neacsiu et al., 2022b; Neacsiu et al., 2021; Neacsiu et al., 2021) and, therefore, may be promising approaches for new interventions for misophonia.

Significant differences were found in participants’ self-report of distress and regulation. Specifically, clinical controls were more both ered by aversive sounds than those with misophonia; misophonic adults were more upset when compared to controls following triggers and while trying to downregulate emotions induced by trigger sounds. In light of the physiological findings, we interpret this as sensitization: the sounds that one finds most aversive (misophonic for participants with misophonia and aversive for participants with emotional dysregulation) lead to heightened subjective experience of distress which doesn’t necessarily mirror the psychophysiological response. In other words, if one is bothered by a specific sound (i.e., is sensitized to it), hearing it may lead to higher perception of distress than the body actually expe

riences. An alternative interpretation could be that SCL/SCR/HF-HRV are not appropriate measures to capture the difference in response be tween groups and other objective measures should be tested to differ entiate misophonia from clinical distress. Nevertheless, until a different measure is identified, interventions intended to change misophonic distress should focus on self-reported distress as a unique differentiator from other clinical conditions.

We also examined whether the best way to approach intervention for misophonic distress was to change top-down versus bottom-up pro cesses. Using a functional imaging paradigm, we identified specific functionally connected regions in the anterior insular cortex and medial prefrontal cortex that were more engaged during the presentation of misophonic versus neutral sounds. We examined whether intervening using a bottom-up process, by inhibiting reactivity with the use of neurostimulation, was a potential intervention for misophonia. We also identified the region in the right dorsolateral prefrontal cortex that was most active during regulation when compared to just listening to misophonic sounds. We examined whether a top-down intervention, simulated in the study by enhancing regulation with neurostimulation and/or the use of an emotion regulation skill, could be beneficial for misophonia. Our design allowed us to compare both approaches. We found clear superiority across both self-report and tonic arousal mea

sures for the top-down approach. Participants with misophonia experi enced significantly less distress in the presence of misophonic triggers when their regulation network was engaged via either excitatory rTMS over the right dlPFC or the use of an emotion regulation skill. This finding strongly suggests that interventions aimed towards emotion regulation have promise for misophonia.

There have been few neuroimaging findings for misophonia that highlight dlPFC dysfunction (Neacsiu et al., 2022a). In one study, healthy controls alone evidenced increased activity in the dlPFC when successfully inhibiting behavior during a stop signal task. Participants with misophonia did not display dlPFC changes during inhibition suc

cess (Eijsker et al., 2019). Our findings align with this study, given that inhibition during a stop signal task involves regulation. The lack of activation in the dlPFC during regulation suggests that participants with misophonia recruit other brain regions for regulation, which may lead to a less efficient process. Promoting dlPFC activity during regulation, may, therefore, restore a faulty process. It is important to highlight that the majority of imaging studies with misophonia thus far have not included regulation paradigms (Neacsiu et al., 2022a). Therefore, the role of the dlPFC in misophonia needs additional exploration.

In the last two decades, neurostimulation has accumulated exciting new evidence that supports its potential for intervention (Lepping et al., 2014). There are currently five neurostimulation-based protocols that are FDA approved for the treatment of depression, obsessive-compulsive

disorder, and smoking (Cohen et al., 2022), although research continues to be needed to validate these treatments and clarify long- and short term effects (Kumar et al., 2022). While initially neurostimulation was reserved for treatment-resistant cases, the evidence suggests that non treatment-resistant adults can benefit from this treatment (Voigt et al., 2019), which opens up this approach to any condition as a candidate novel intervention. In the case of misophonia, no clear pathway for intervention exists yet. Nevertheless, some findings suggest that cogni tive behavioral therapy (Jager et al., 2021; Cecilione et al., 2022) and the use of emotion regulation skills (Lewin et al., 2021; Tonarely-Busto et al., 2022) can offer promise for misophonia. We, therefore, wanted to compare whether neurostimulation alone, emotion regulation alone, or

their combination lead to the biggest decrease in distress. First, it is important to highlight that engaging in either cognitive regulation or neurostimulation alone reduced distress when compared to no intervention for both misophonic and emotionally dysregulated adults. Thus, both neurostimulation and emotion regulation training should be considered important options for future misophonia in terventions. Second, the combined intervention on both misophonic and aversive sounds led to significantly less self-reported distress and lower tonic arousal when compared to implementing the emotion regulation skill alone. Self-report results showed the superiority of the behavioral intervention alone versus the neurostimulation alone, while the finding was reversed for the tonic arousal measure. Therefore, if the intended outcome is a reduction in physiological arousal, neurostimulation out performs behavioral skills. Nevertheless, when it comes to perceived distress, behavioral intervention reduces this perception more so than neurostimulation alone. Given that we found differences primarily in self-reported distress, these findings suggest that a combination of neurostimulation and emotion regulation training is a promising avenue for a misophonia intervention. If a combined treatment is not possible, a behavioral intervention focused on emotion regulation holds more promise than exposing participants to sounds alone.

There were some key differences between our study and prior studies. First, in our prior examination of psychophysiology during neurostimulation, we found no difference between active and sham rTMS in heart rate variability and indices of arousal (Neacsiu et al., 2022b; Neacsiu et al., 2021). In this study, HF-rTMS increased HF-HRV significantly more than sham during the habituation period, and both types of stimulation increased arousal more than sham. This difference may be due to the procedures employed. This study employed an enhanced stimulation regimen with shorter ITT (15 vs. 26 s) and more pulses administered in a shorter amount of time (3 vs 10 min). More intensive excitatory neurostimulation may lead to more effect on HF HRV, and the shorter duration may not allow sufficient time for behavioral regulation alone to happen. Furthermore, across all experi

mental conditions, HF-HRV ended up being higher in sham than in active neurostimulation conditions when controlling for the enhanced effect of neurostimulation alone on this measure during habituation. This would suggest that rTMS does not enhance regulation, but rather it facilitates a faster regulation process. Indeed, in our prior trial, where participants regulated for 10 min, the sham condition “caught up” and showed similar HF-HRV towards the end of the regulation period, but was significantly different at the beginning of the regulation period (Neacsiu et al., 2022b).

As in other studies (Stokes et al., 2005; Neacsiu et al., 2022b), we found that coil-to-cortex distance was a significant covariate; a larger distance predicted less efficacy of neurostimulation for several out comes. Greater distance means that the strength of the electric field induced by neurostimulation is reduced by the time it reaches the cortical target, and, therefore, the efficacy of neuromodulation de creases. Furthermore, the presence of headaches increased skin response during experimental trials. Therefore, future research should control for these variables when interpreting outcomes.

Our findings also are relevant to the development of emotion regu lation interventions in people without misophonia. First, adults with

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clinical emotional dysregulation had more difficulty in using an emotion regulation skill successfully when compared to misophonic adults. Nevertheless, this difference was no longer significant when neuro stimulation was added, suggesting that the addition of TMS can help normalize a dysfunctional process in this clinical sample. In other words, adults with emotion dysregulation may need additional support to implement emotion regulation skills successfully. Furthermore, as with misophonia, the combination of behavioral skills and neuromodulation led to the least distress, suggesting that future interventions should focus on this combined approach for maximum benefit. This finding aligns well with research that highlights the superiority of behavioral therapy in tandem with neurostimulation when compared to behavioral therapy alone (Neacsiu et al., 2022b; Kozel et al., 2018). The hypothesized mechanism is that neurostimulation facilitates neural processing in localized cortical regions via inducing Hebbian-like plasticity (Stefan et al., 2000) which may have therapeutic effects and may remediate deficits in affected neural networks (Luber et al., 2008).

These results should be considered in light of several key limitations. While the study was adequately powered, the sample size was small and lacked racial and ethnic diversity across groups. Results should be replicated with a larger sample size and better representation of minoritized populations. A full factorial design could have clarified whether the stimulation intensity or brain region stimulated was the active ingredient for the results we found. Future replications should consider executing a complete stimulation by region and by group experimental design (HF vs. LF, insula vs. dlPFC, misophonia vs control). LF-rTMS was applied at 90 % MT and HF-rTMS was applied at 120 % MT per existing protocols at the time when the study was designed. The superiority of HF-rTMS may be due to the higher stimulation intensity. Higher LF-rTMS intensity and alternative ways to target the anterior insula should be investigated before completely discounting the viability of targeting with neurostimulation the anterior insula via its functional connectivity with the mPFC to treat misophonia or emotional dysregu lation. Despite our efforts to control for cumulative effects, lingering rTMS effects may have also influenced the results. A between-subjects design would be ideal for a replication study to rule out the influence of cumulative effects, although here we controlled for task order and presented experimental conditions in a randomized order. Lastly, there were several protocol deviations engaged that may confound study re sults. We included all data available and described our study deviations because the problems we encounter mimic real-world issues and solu

tions that would need to be implemented in a community practice should an intervention emerge from our protocol.

Alternative neurostimulation techniques, such as the use of trans cranial electrical stimulation, may also be important lines of research for future intervention development. For example, tinnitus symptoms were shown to be modulated by transcranial direct current stimulation (tDCS) (Vanneste et al., 2013; Yuan et al., 2018). Transcranial alternating current stimulation (tACS) may facilitate improvement in cognition as well as in depressive symptoms, with mixed results associated with amelioration of schizophrenia symptoms (Lee et al., 2022). Both non invasive electrical neurostimulation modalities are safe and well tolerated (Matsumoto and Ugawa, 2016). The precision of targeting is reduced with these alternative methods when compared to rTMS although these methods are less costly and may lead to more scalable interventions. Therefore, conduction of blinded, randomized placebo controlled trials would be needed to evaluate its clinical application and efficacy.

Taken together, these findings highlight that neurostimulation and cognitive restructuring are promising avenues of intervention for misophonia, with their combination showing the most promise. Engaging in regulation may lead to more reduction in misophonic distress than attempting to inhibit reactivity to sounds. Adults with misophonia have similar psychophysiological responses to stress and triggers as adults with clinical emotional dysregulation, although self

reported distress differentiates groups. This highlights the conclusion

that misophonia may be a disorder comparable to other DSM disorders and that additional biomarkers that capture the unique misophonic distress are still needed. It is important to highlight that our study sampled different approaches for intervention, but did not test an intervention per se. Future studies should examine the short and long

term effects of neurostimulation, emotion regulation, or their combi nation for misophonia.

**Funding sources**

This research and the completion of the manuscript were supported by a Misophonia Fund award granted to the first author by the REAM Foundation.

**CRediT authorship contribution statement**

**Andrada D. Neacsiu:** Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Supervision, Validation, Writing – original draft, Writing – review & editing. **Lysianne Beynel:** Conceptualization, Investigation, Software, Visualization, Writing – original draft. **Nime**

**sha Gerlus:** Data curation, Formal analysis, Writing – original draft, Writing – review & editing. **Kevin S. LaBar:** Conceptualization, Re sources, Supervision. **Noreen Bukhari-Parlakturk:** Conceptualization, Investigation, Supervision, Writing – original draft, Writing – review & editing. **M. Zachary Rosenthal:** Conceptualization, Supervision, Writing – review & editing.

**Declaration of competing interest**

The authors reported no biomedical financial interests or potential conflicts of interest.

**Data availability**

Data in SPSS and .csv format along with the data dictionary was submitted and accepted on 10/27/2022. It is available currently at the Duke Research Data Repository (RDR): Neacsiu, A., LaBar, K., Rosen thal, M. Z., Bukhari-Parlakturk, N., Kelley, L. (2022). Identifying the optimal neural target for misophonia interventions. Duke Research Data Repository. https://doi.org/10.7924/r4ww7jg4k. Imaging data is available upon request.

**Acknowledgments**

The authors would like to thank the REAM foundation and the Milken Institute for their generous grant (through the Misophonia Research Fund). Data from the present paper were presented as part of several conference talks. The authors would like to thank the partici

pants who took part in this study and acknowledge Lisalynn Kelley, Victoria Szymkiewicz, Judith Wright, Brenden Li, Jessica Choi, John Powers, Ph.D., Simon Davis, Ph.D., and our research assistants and the DUMC, BIAC, and BSRC staff for their contributions.

**Appendix A. Supplementary data**

Supplementary data to this article can be found online at https://doi. org/10.1016/j.jad.2024.01.120.

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