

For any issues with this document, please contact your library.

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

Source: LibKeyNomad

Copyright: CCG

NOTICE CONCERNING COPYRIGHT RESTRICTIONS:

The copyright law of the United States [[Title 17, United StatesCode](#)] governs the making of photocopies or other reproductions of copyrighted materials.

Under certain conditions specified in the law, libraries and archives are authorized to furnish a photocopy or other reproduction. One of these specific conditions is that the photocopy is not to be "used for any purpose other than private study, scholarship, or research." If a user makes a request for, or later uses, a photocopy or reproduction for purposes in excess of "fair use," that user may be liable for copyright infringement.

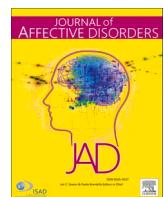
This institution reserves the right to refuse to accept a copying order if, in its judgment, fulfillment of that order would involve violation of copyright law.



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. Neacsu^{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, Bethesda, 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

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 psychophysiological measurements (e.g., skin conductance response [SCR] and level [SCL]) were collected.

Compared to controls, participants with misophonia reported higher distress ($\Delta_{SUDS} = 1.91\text{--}1.93$, $p < 0.001$) 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 $d_{SUDS} = 0.53$; $d_{SCL} = 0.14$). Excitatory rTMS also enhanced the regulation of emotions associated with misophonic sounds in both groups when measured by SUDS ($d_{Control} = 1.28$; $d_{Misophonia} = 0.94$), 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.

1. Introduction

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

definition was published only recently (Swedo et al., 2022). Current misophonia treatment approaches have limited existing evidence and include lifestyle modification, cognitive behavioral therapy, and audiological treatment (Potgieter et al., 2019). However, since the mechanisms underlying misophonia are unknown, the current treatments do not have clear targets for change; limited evidence exists 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 (Neacsu et al., 2022a), characterized by hyperactivity 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.neacsu@duke.edu (A.D. Neacsu), 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).

trigger stimuli (Kumar et al., 2017; Schröder 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. Qualitative 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 dysregulation 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; Neacsu 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 differences 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 processing, while the dlPFC is associated with conscious, effortful emotion regulation (Etkin et al., 2015). Therefore, low-frequency mPFC stimulation 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 neurostimulation 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 (Neacsu 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 strategies (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 interventions 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 presence of trigger sounds in misophonia (Neacsu et al., 2022a), we hypothesized 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). Therefore, we used connectivity analyses to find a node in the mPFC functionally 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 presentation and regulation of aversive sounds (H6). We planned to explore differences between the use of CR, LF-rTMS, HF-rTMS, and their combination (i.e., CR + HF-rTMS; CR + LF-rTMS) within and across groups, expecting combined interventions to lead to more reductions in arousal than 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 Institutional 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 intelligence 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

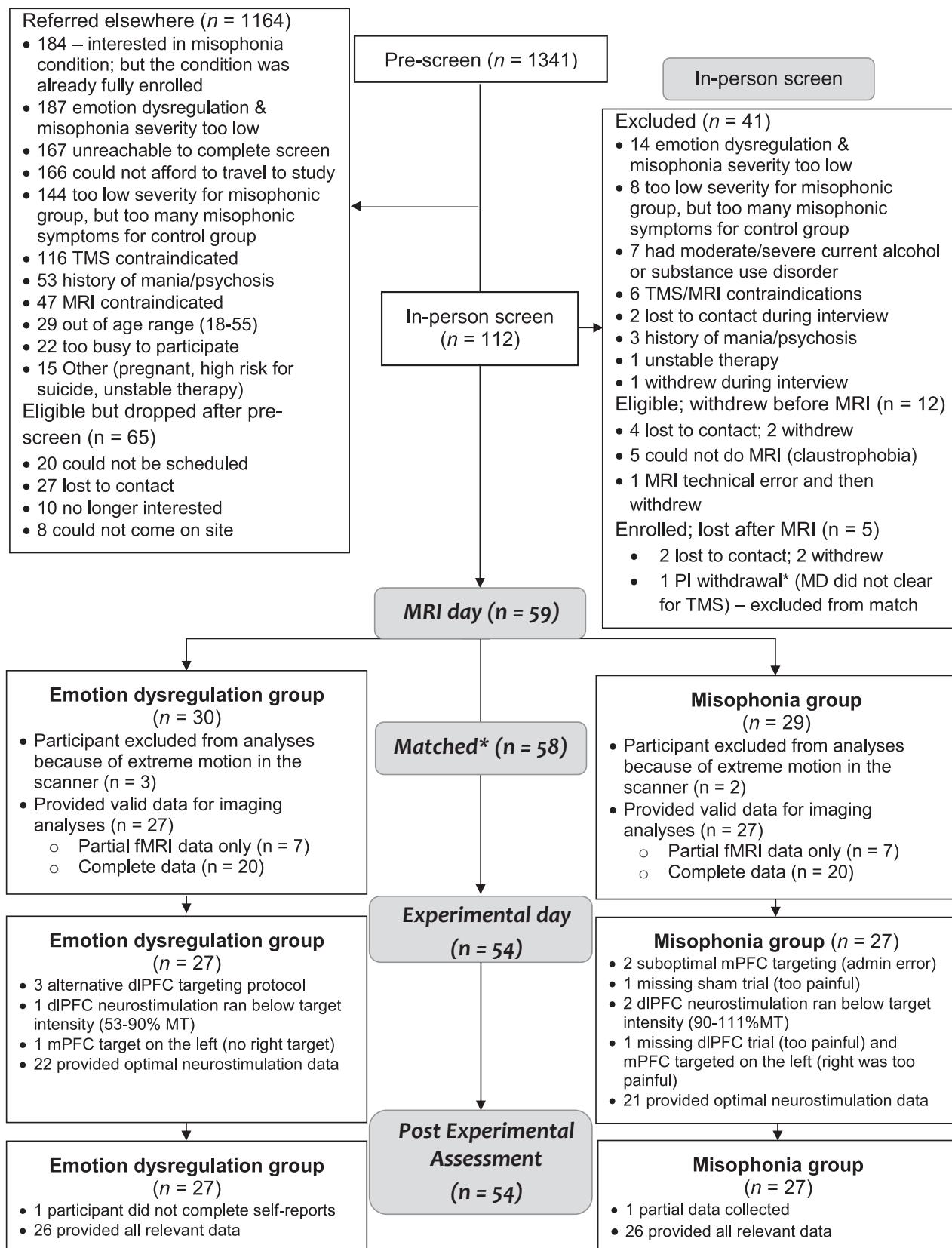


Fig. 1. CONSORT Diagram depicting study flow.

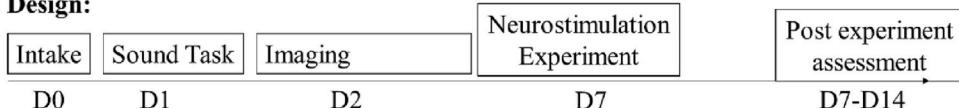
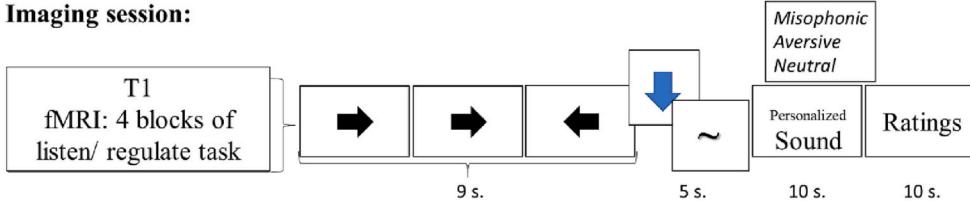
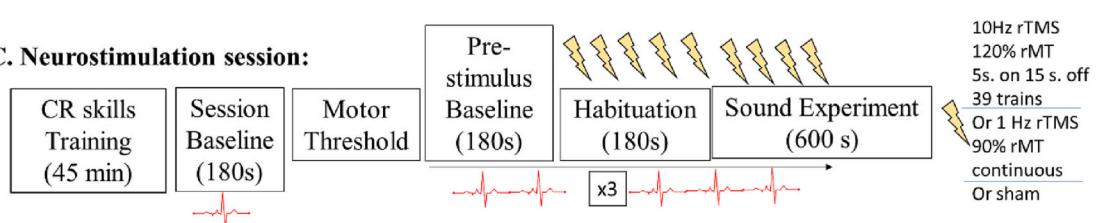
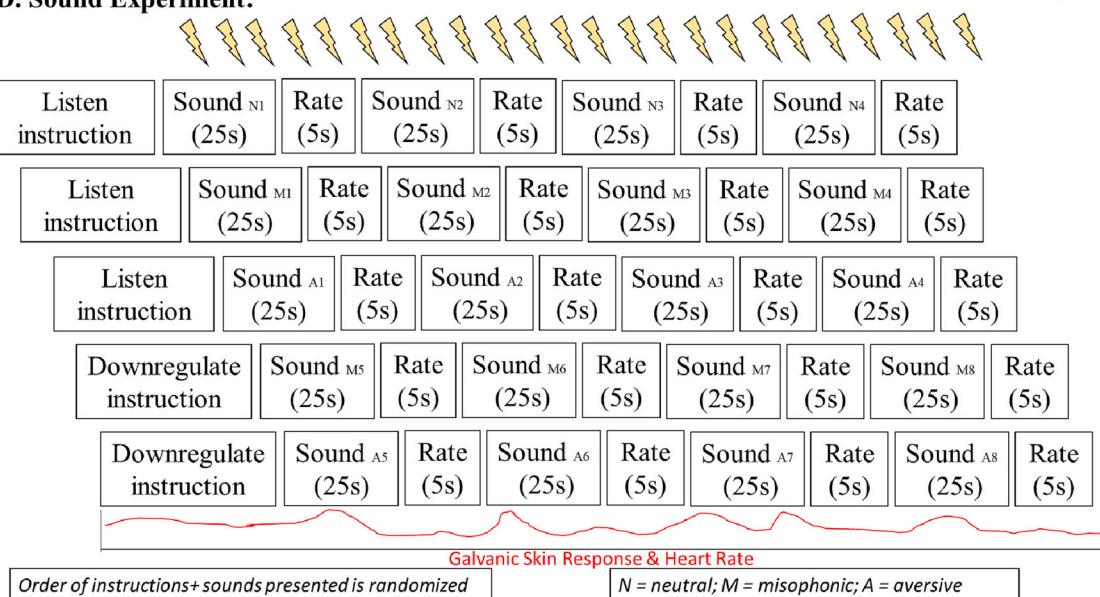
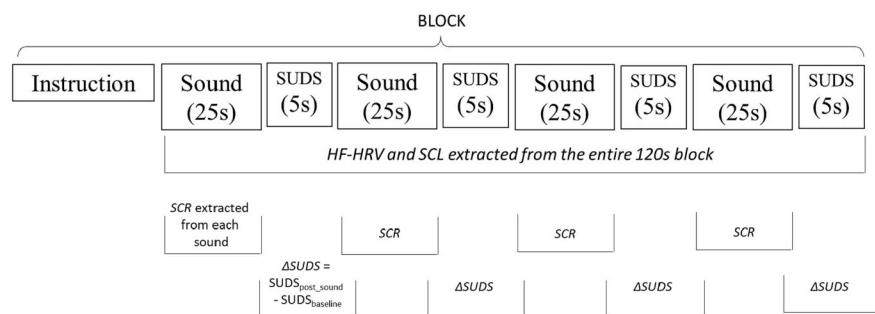
A. Design:**B. Imaging session:****C. Neurostimulation session:****D. Sound Experiment:****E. Outcome variables extracted:**

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.

days ($SD = 9.97$) after the eligibility intake session. Following standardized 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 interaction (PPI) analysis was also conducted to measure functional connectivity 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 consistent 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 $z_{dlPFC_stimulation_site} = 2.74$, $SD = 0.73$). 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 $z_{mPFC_stimulation_site} = 3.03$, $SD = 1.50$). See Fig. 3A-B for a visual depiction of the personalized targeting procedure and Supplement 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 performed 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 continuously 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 deviations. 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 indicators, 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 Δ SUDS, 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

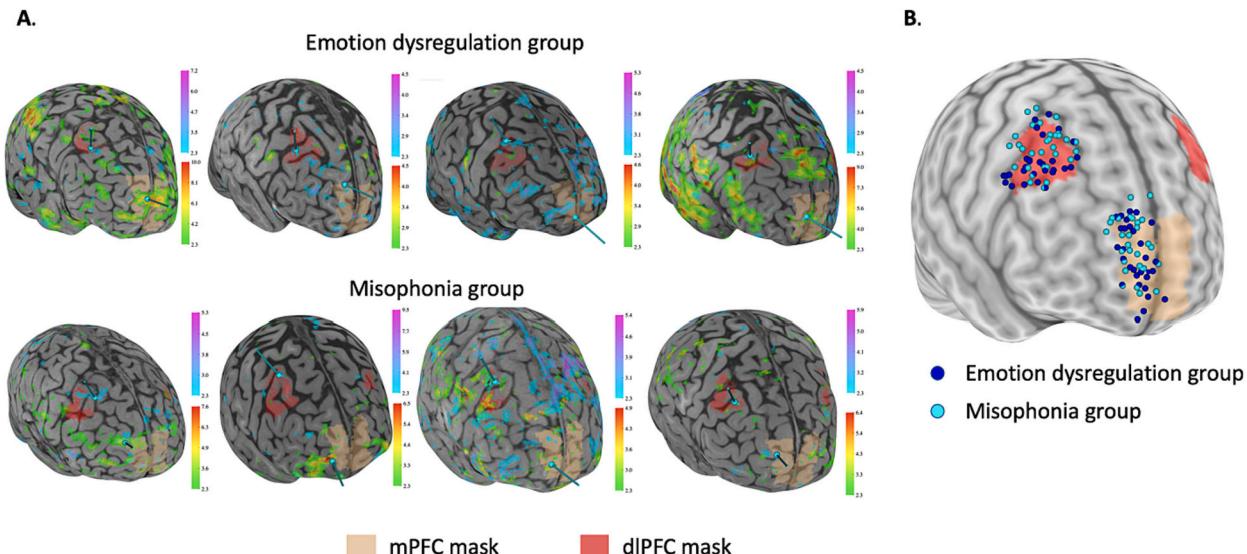


Fig. 3. A. The top legend is the range for activation for the regulation contrast; regulation contrast is depicted with a blue-magenta map; the bottom legend is the range of activation for the reactivity contrast, depicted with the green-red map. The copper region is the structural mPFC mask used to constrain targets. It includes Brodmann Area (BA) 10 and the rostral portions of BA 9 and BA (Carlén, 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.)

to-cortex distance (Lee et al., 2016; Stokes et al., 2005). Data-driven covariates such as the incidence of headaches post-stimulation were 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 transformed to normal using the function $\lg 10(\text{HF-HRV}^*1000000)$. All other data were normally distributed.

3. Results

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

Overall participants in both groups reported reduced stress at the end compared to the beginning of each experimental session ($\Delta_{\text{average_intake_change}} = -0.56$, SD = 1.53; $\Delta_{\text{average_MRI_change}} = -0.31$, SD = 1.22; $\Delta_{\text{average_TMS_change}} = -0.48$, SD = 0.89). These results suggest that the experimental tasks were feasible and acceptable to our participants. Following the sham stimulation, 26 participants (48.15 %) reported some headache, compared to 40 participants (74.07 %) after the HF-rTMS trial, and 34 (62.96 %) after the LF-rTMS trial, a significant difference ($\chi^2[2] = 7.73$, $p = .02$). Because of the higher incidence of 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 neurostimulation received ($M_{\text{sham}} = 5.72$, SD = 2.27; $M_{\text{HF-rTMS}} = 6.74$, SD = 2.07; $M_{\text{LF-rTMS}} = 6.43$, SD = 2.18) or between groups ($F[2, 151] = 11.05$, $p = .09$), according to a multivariate ANOVA controlling for racial background ($F[1, 151] = 0.06$, $p = .44$). See Supplement for additional findings.

3.2. Preliminary analyses examining confounds

There were significantly more participants belonging to racial or ethnic minority groups in the emotional dysregulation condition (Table 1). Therefore, racial/ethnic background was recoded as 0 (non-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 neurostimulation 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 neurostimulation ($\Delta_{\text{HF-HRV}} = 0.12$, SE = 0.03; $\Delta_{\text{SCR}} = 2.84$, SE = 0.54; $\Delta_{\text{SCL}} = 1.76$, SE = 0.24). LF-rTMS over the right mPFC did not significantly affect HF-HRV, but significantly increased SCR ($\Delta_{\text{SCR}} = 1.72$, SE = 0.52) and SCL ($\Delta_{\text{SCL}} = 0.72$, SE = 0.23) when compared to sham. Participants experienced significantly higher tonic arousal (SCL) during HF-rTMS than during LF-rTMS ($\Delta_{\text{SCL}} = 1.05$; 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 Δ_{SUDS} 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.

Table 1
Demographics and clinical descriptive by group.

	Emotion dysregulation (n = 30)	Misophonia (n = 29)	Statistical difference
Mean age (SD)	27.07 (8.28)	29.59 (9.79)	$t(57) = -1.07$, $p = .29$
Female gender identity (%)	86.67	89.66	$\chi^2[4] = 2.98$, $p = .56$
Latinx background (%)	23.33	3.45	$\chi^2[1] = 4.98$, $p = .03$
Racial background (%)			$\chi^2[5] = 13.68$, $p = .02$
Asian/Asian American	30.0	3.45	
Black/African American	3.33	0.00	
American Native American, American Indian, or Alaskan Native	3.33	0.00	
White/Caucasian	56.67	96.55	
Middle Eastern	6.66	0.00	
On psychotropic medications:			
Recent psychotherapy:	50.00		
Total # of diagnoses, current (SD)	1.97 (1.38)	1.52 (1.83)	$t(57) = 1.07$, $p = .29$
Total # of diagnoses, lifetime (SD)	4.07 (2.12)	3.00 (2.32)	$t(57) = 1.85$, $p = .07$
Current disorders (%)			
Mood disorders	30.00	13.80	
Anxiety disorders	83.30	69.00	
Obsessive compulsive disorders	16.70	6.90	
Stress disorders	10.00	10.30	
Impulse control disorders	6.70	6.90	
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	
Obsessive compulsive disorders	23.30	10.30	
Stress disorders	31.00	20.70	
Eating disorders	13.30	13.80	
Any pd. (%)	48.27	24.14	$\chi^2[1] = 3.66$, $p = .06$

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

3.3.1. Self-report results (SUDS)

The MMANOVA analysis of SUDS used a Toeplitz covariance structure (see the syntax in Supplement) and found a significant main effect of experimental neurostimulation ($F[2, 373.52] = 19.50$, $p < .00000001$). 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 ($p < .00000001$, $d = 1.58$) were administered. See supplement for additional results for main effects.

A significant interaction was found between experimental neurostimulation, experimental instruction, and group ($F[22, 705.00] = 18.36$, $p < .00000001$). The interaction revealed that participants in the misophonia group experienced significantly more distress than controls when listening ($\Delta = 1.91$, SE = 0.32, $p < .001$, $d = 3.34$) and when downregulating ($\Delta = 1.93$, SE = 0.32, $p < .001$, $d = 3.34$) misophonic sounds across all experimental conditions, a finding that supports H1. In addition, participants in the misophonia group reported significantly less distress than participants with emotion dysregulation when listening to aversive sounds ($\Delta = 1.76$, SE = 0.32, $p < .001$, $d = 3.04$), a finding that supports H2. In the sham condition alone, participants with emotional dysregulation reported more distress when downregulating aversive sounds than participants with misophonia (Δ

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
Sham rTMS		1.67 (0.16)	9.33 (0.15)	10.03 (0.59)	1.98 (0.02)
HF-rTMS		0.76 (0.17)	8.84 (0.16)	10.27 (0.60)	1.92 (0.02)
Lf-rTMS		1.34 (0.16)	8.86 (0.15)	9.68 (0.59)	1.91 (0.02)
Listen to neutral		-0.01 (0.19)	8.99 (0.13)	9.90 (0.59)	1.93 (0.02)
Listen to aversive		2.43 (0.29)	8.96 (0.15)	10.08 (0.61)	1.92 (0.03)
Listen to misophonic		2.72 (0.19)	9.09 (0.13)	9.96 (0.59)	1.94 (0.02)
Downregulate aversive		0.53 (0.20)	9.06 (0.14)	10.04 (0.60)	1.95 (0.02)
Downregulate misophonic		0.62 (0.26)	8.95 (0.15)	9.97 (0.61)	1.92 (0.03)
B. Interaction effects		Emotion dysregulation group		Misophonia group	
		ΔSUDS	SCL	ΔSUDS	SCL
Listen to neutral	Sham	0.53 (0.29)	9.54 (0.20)	0.06 (0.31)	9.08 (0.23)
	rTMS	-0.39 (0.30)	8.91 (0.20)	-0.48 (0.32)	8.70 (0.23)
	HF	0.30 (0.30)	8.87 (0.21)	-0.06 (0.32)	8.84 (0.23)
	LF rTMS	0.30 (0.30)	8.87 (0.21)	-0.06 (0.32)	8.84 (0.23)
Listen to aversive	Sham	3.78 (0.37)	9.33 (0.22)	1.63 (0.37)	9.14 (0.25)
	rTMS	2.81 (0.37)	9.20 (0.22)	1.50 (0.38)	8.51 (0.25)
	HF	3.33 (0.37)	8.64 (0.22)	1.52 (0.31)	8.92 (0.25)
	LF rTMS	2.48 (0.29)	9.66 (0.20)	4.17 (0.30)	9.21 (0.22)
Listen to misophonic	Sham	0.98 (0.29)	9.07 (0.20)	3.25 (0.32)	8.65 (0.23)
	rTMS	1.83 (0.29)	8.85 (0.20)	3.59 (0.31)	9.09 (0.22)
Downregulate aversive	Sham	1.36 (0.30)	9.54 (0.21)	0.28 (0.32)	9.16 (0.24)
	rTMS	0.22 (0.31)	9.12 (0.21)	-0.15 (0.33)	8.75 (0.25)
	HF	1.22 (0.30)	8.99 (0.22)	0.28 (0.33)	8.80 (0.24)
	LF rTMS	0.28 (0.35)	9.32 (0.23)	2.13 (0.34)	9.31 (0.24)
Downregulate misophonic	Sham	-1.23 (0.35)	8.87 (0.24)	1.11 (0.37)	8.57 (0.27)
	rTMS	-0.11 (0.35)	8.88 (0.24)	1.50 (0.34)	8.72 (0.25)

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

= 1.08, SE = 0.40, $p < .008$, $d = 1.87$). During dlPFC and mPFC stimulation, this difference between groups was no longer significant, suggesting 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 ($\Delta_{\text{SHAM-HF-rTMS}} = 0.92$, $p = .004$, $d = 1.59$), aversive sounds ($\Delta_{\text{SHAM-HF-rTMS}} = 0.97$, $p < .001$, $d = 1.68$), or misophonic sounds ($\Delta_{\text{SHAM-HF-rTMS}} = 1.50$, $p < .001$, $d = 2.59$). HF-rTMS also enhanced the downregulation of aversive

($\Delta_{\text{SHAM-HF-rTMS}} = 1.15$, $p < .001$, $d = 1.99$) and misophonic ($\Delta_{\text{SHAM-HF-rTMS}} = 1.51$, $p < .001$, $d = 2.59$) 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. 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 when listening to aversive sounds ($EMM = 1.55$, $SE = 0.34$). Nevertheless, the distress produced by a misophonic sound was significantly lower in the HF-rTMS condition when compared to sham when participants were instructed to listen ($\Delta_{\text{SHAM-HF-rTMS}} = 0.92$, $p = .001$, $d = 1.59$) or to downregulate ($\Delta_{\text{SHAM-HF-rTMS}} = 1.02$, $p < .001$, $d = 1.76$), which supports H5. LF-rTMS was marginally superior to sham during listening ($\Delta_{\text{SHAM-LF-rTMS}} = 0.58$, $d = 1.00$, Bonferroni corrected $p = .16$), or downregulation of misophonic sounds ($\Delta_{\text{SHAM-LF-rTMS}} = 0.64$, $d = 1.11$, Bonferroni corrected $p = .12$). Thus, H4 was not supported. There 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 to aversive ($\Delta = 1.88$, $SE = 0.39$, $p < .001$, $d = 3.25$) and misophonic ($\Delta = 2.12$, $SE = 0.33$, $p < .001$, $d = 3.66$) 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 dysregulation and misophonia.

To examine across groups whether neurostimulation alone was superior 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 CR. We also compared the combination of neurostimulation with CR with either intervention alone. Utilizing a behavioral skill was superior to neurostimulation alone ($p_{\text{aversive}} = 0.001$, $d = 2.31$; $p_{\text{misophonic}} = 0.012$, $d = 1.57$) in reducing distress induced by aversive sounds. The combination of neurostimulation and skill use led to significantly lower distress at the end of the sound presentation for both misophonic and aversive sounds when compared to either intervention modality alone ($ps < 0.001$, $ds > 2.90$). Therefore, in line with H7, the combined intervention leads to the highest reduction in distress, followed by utilizing only behavioral skills, followed by neurostimulation alone.

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 ($F[1, 668.90] = 15.22$, $p < .001$). There was also a marginally significant main effect for coil-to-cortex distance ($F[1, 717.11] = 5.06$, $p = .03$). Higher 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 ($ps < 0.03$). A significant main effect of experimental 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 ($\Delta = 0.35$, $SE = 0.16$, $p = .03$). There was no significant main effect for group, instructions provided, or racial background ($ps > 0.05$). 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

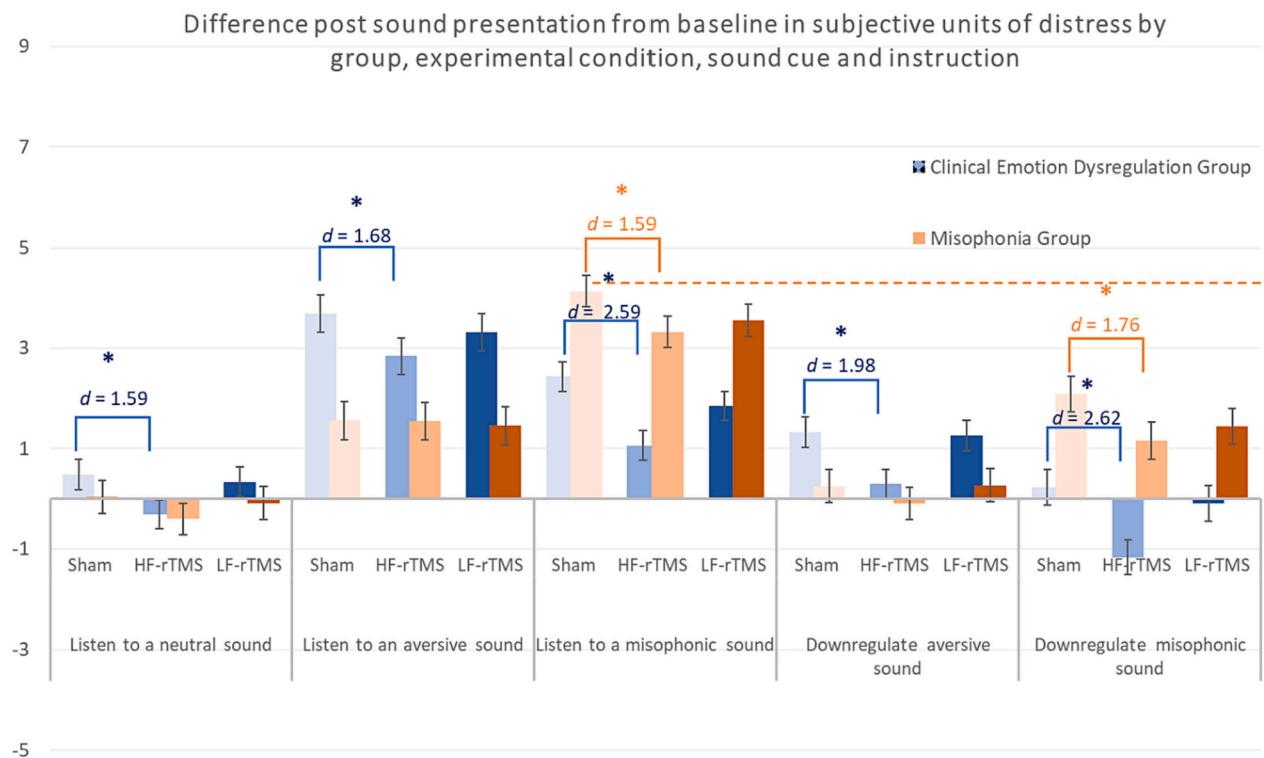


Fig. 4. Self-report units of distress by instruction provided, experimental group, and experimental neurostimulation. Values represent estimated marginal means from the mixed models analysis of variance, adjusted for covariates and main effects. The Orange dotted line represents our closest approximation 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).

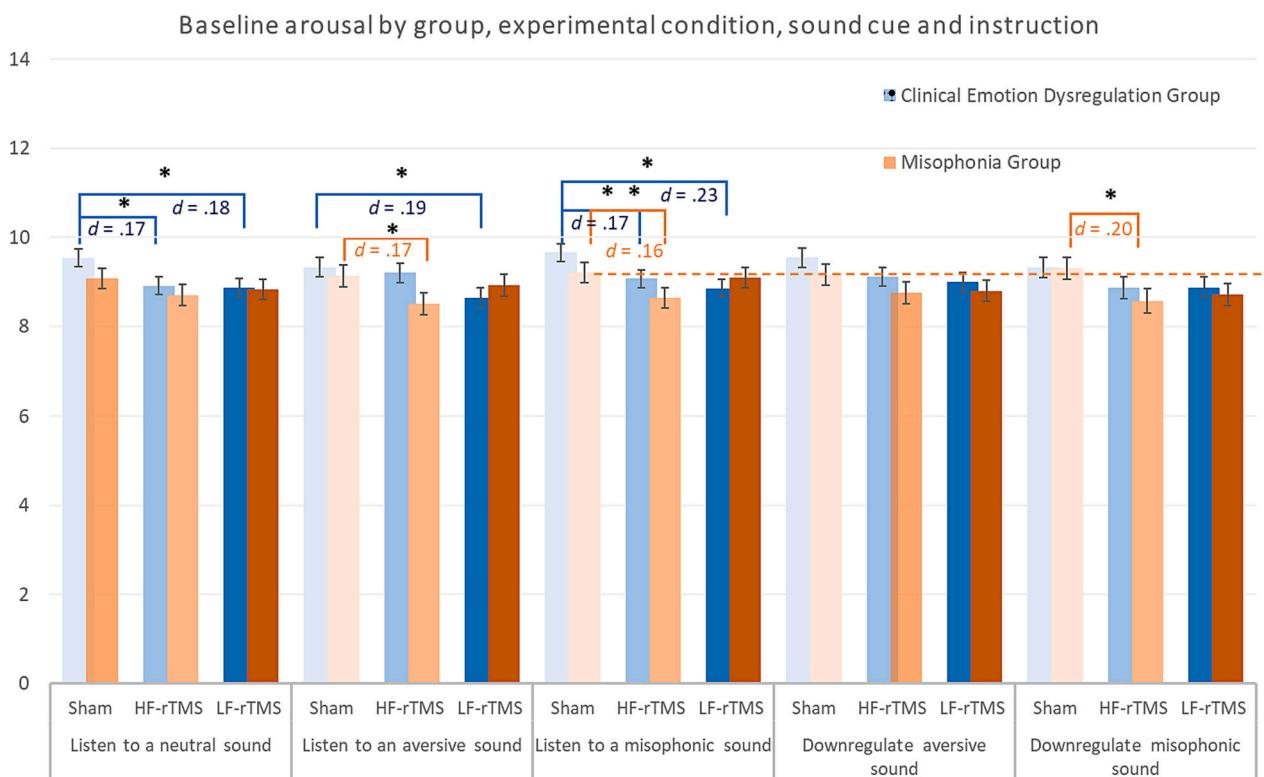


Fig. 5. Average skin conductance level in micro siemens depending on experimental group, instruction provided, and experimental neurostimulation. Values represent estimated marginal means from the mixed model analysis of variance, adjusted for covariates and main effects. D values refer to Cohen's d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

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 ($p_{HF_rTMS} = 0.001; p_{LF_rTMS} = 0.002; ds = 0.14$), with no difference between active conditions ($p > .05$) suggesting that both types of neurostimulation 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 ($ps < 0.001$). Thus, SCL decreased over time during the run independent of the experimental condition. There was no significant main effect for the experimental group, instructions provided, headache, racial background, or coil-to-cortex distance ($ps > 0.05$). Therefore, the SCL results did not support H1 and H2.

A significant interaction was found between experimental neurostimulation, 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 ($\Delta_{SHAM-HF_rTMS} = 0.63, p = .004$; $\Delta_{SHAM-LF_rTMS} = 0.67, p = .002$) or misophonic sounds ($\Delta_{SHAM-LF_rTMS} = 0.811, p < .001, d = 0.23$; $\Delta_{SHAM-HF_rTMS} = 0.59, SE = 0.203, p = .004, d = 0.16$), 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 significantly more when listening to an aversive sound when compared to sham ($\Delta_{SHAM-LF_rTMS} = 0.69, p = .002, d = 0.19$). There were no significant 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 ($\Delta_{SHAM-HF_rTMS} = 0.63, p = .009, d = 0.18$) or misophonic sounds ($\Delta_{SHAM-HF_rTMS} = 0.56, p = .009, d = 0.16$) and when downregulating misophonic sounds ($\Delta_{SHAM-HF_rTMS} = 0.73, p = .006, d = 0.20$). The lowest SCL when exposed to misophonic sounds in the misophonia group was during the combination of behavioral skill utilization and HF-rTMS stimulation. H4 was not supported.

To investigate the effects of using only behavioral skills, we examined 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; $ps > 0.35$). 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 ($p_{aversive} = 0.014; p_{misophonic} = 0.014$) or in combination with cognitive restructuring ($p_{aversive} = 0.017; p_{misophonic} = 0.001$) led to less arousal than CR alone. There was no significant difference between neurostimulation alone and the combined approach ($ps > 0.10$). Therefore, H7 was partially supported. There was also no difference between groups in response to these different interventions. This suggests 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 MANOVA analysis using an unstructured covariance structure did not reveal any main effect of group, instruction provided, headache, or racial background ($ps > 0.05$). Therefore, H3 was not supported. However, we found significant main effects of experimental neurostimulation 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 ($p_{HF_rTMS} = 0.008; p_{LF_rTMS} = 0.001, ds = 0.10$). 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 experimental 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 ($M_{HF_rTMS} = 0.000186; M_{LF_rTMS} = 0.000166; M_{sham} = 0.000153$), 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 presentation 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; $p_{group_difference} = 0.39$). All participants found CR training very helpful ($M = 7.59, SD = 1.83$, Range: 0–9; $p_{group_difference} = 0.56$), the combined procedures highly acceptable $M_{acceptability} = 8.13, SD = 1.03$, Range 0–9; $p_{group_difference} = 0.68$) and reported high likelihood to recommend this treatment to a friend ($M = 74.98 \%, SD = 19.89$, range 0–100 %; $p_{group_difference} = 0.88$).

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 (Neacsu 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 interventions 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 preliminary 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 significant difficulties regulating emotions with a range of DSM-5 disorders in physiological reactivity and arousal. Thus, existing evidence-based

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 (Neacsu 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 (Neacsu et al., 2022b; Neacsu et al., 2021; Neacsu 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 bothered 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 experiences. An alternative interpretation could be that SCL/SCR/HF-HRV are not appropriate measures to capture the difference in response between groups and other objective measures should be tested to differentiate 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 processes. 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 measures for the top-down approach. Participants with misophonia experienced 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 (Neacsu 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 success (Eijsser 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 (Neacsu 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 cognitive 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 interventions. 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 outperforms 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 (Neacsu et al., 2022b; Neacsu 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 experimental 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 (Neacsu et al., 2022b).

As in other studies (Stokes et al., 2005; Neacsu et al., 2022b), we found that coil-to-cortex distance was a significant covariate; a larger distance predicted less efficacy of neurostimulation for several outcomes. 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 decreases. 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 regulation interventions in people without misophonia. First, adults with

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 neurostimulation 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 (Neacsu 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 dysregulation. 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 results. We included all data available and described our study deviations because the problems we encounter mimic real-world issues and solutions 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 transcranial 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 combination 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. Neacsu: 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. **Nimesha Gerlus:** Data curation, Formal analysis, Writing – original draft, Writing – review & editing. **Kevin S. LaBar:** Conceptualization, Resources, 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): Neacsu, A., LaBar, K., Rosenthal, 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 participants 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>.

References

- Avants, B.B., Tustison, N.J., Song, G., Cook, P.A., Klein, A., Gee, J.C., 2011. A reproducible evaluation of ANTs similarity metric performance in brain image registration. *NeuroImage* 54 (3), 2033–2044.
- Balconi, M., Bortolotti, A., 2012. Detection of the facial expression of emotion and self-report measures in empathic situations are influenced by sensorimotor circuit inhibition by low-frequency rTMS. *Brain Stimul.* 5 (3), 330–336.

- Banks, S.J., Eddy, K.T., Angstadt, M., Nathan, P.J., Phan, K.L., 2007. Amygdala-frontal connectivity during emotion regulation. *Soc. Cogn. Affect. Neurosci.* 2 (4), 303–312.
- Beynel, L., Campbell, E., Nacario, M., Galla, J.T., Ghosal, A., Michael, A.M., Davis, S.W., Appelbaum, L.G., 2021. The effects of functionally guided, connectivity-based rTMS on amygdala activation. *Brain Sci.* 11 (4), 494.
- Brout, J.J., Edelstein, M., Erfanian, M., Mannino, M., Miller, L.J., Rouw, R., et al., 2018. Investigating misophonia: a review of the empirical literature, clinical implications, and a research agenda. *Front. Neurosci.* 12, 36.
- Butler, E.A., Wilhelm, F.H., Gross, J.J., 2006. Respiratory sinus arrhythmia, emotion, and emotion regulation during social interaction. *Psychophysiology* 43 (6), 612–622.
- Campbell-Sills, L., Barlow, D.H., Brown, T.A., Hofmann, S.G., 2006. Effects of suppression and acceptance on emotional responses of individuals with anxiety and mood disorders. *Behav. Res. Ther.* 44 (9), 1251–1263.
- Carlén, M., 2017. What constitutes the prefrontal cortex? *Science* 358 (6362), 478–482.
- Cecilione, J.L., Hitti, S.A., Vrana, S.R., 2022. Treating adolescent misophonia with cognitive behavioral therapy: considerations for including exposure. *Clin. Case Stud.* 21 (3), 175–191.
- Cohen, J., 1977. Statistical Power Analysis for the Behavioral Sciences Rev. ed. ed. Academic Press, New York, NY.
- Cohen, S.L., Bikson, M., Badran, B.W., George, M.S., 2022. A visual and narrative timeline of US FDA milestones for Transcranial Magnetic Stimulation (TMS) devices. *Brain Stimul. Basic Transl. Clin. Res. Neuromodul.* 15 (1), 73–75.
- Craig, A.D., 2009. How do you feel — now? The anterior insula and human awareness. *Nat. Rev. Neurosci.* 10 (1), 59–70.
- Denson, T.F., Grisham, J.R., Moulds, M.L., 2011. Cognitive reappraisal increases heart rate variability in response to an anger provocation. *Motiv. Emot.* 35 (1), 14–22.
- Di Simplicio, M., Costoloni, G., Western, D., Hanson, B., Taggart, P., Harmer, C.J., 2012. Decreased heart rate variability during emotion regulation in subjects at risk for psychopathology. *Psychol. Med.* 42 (08), 1775–1783.
- Duerden, E.G., Arsalidou, M., Lee, M., Taylor, M.J., 2013. Lateralization of affective processing in the insula. *NeuroImage* 78, 159–175.
- Dunn, L.M., 1981. PPVT-revised Manual. American Guidance Service, Circle Pines, MN, p. 1981.
- Eijker, N., Schröder, A., Smit, D.J., van Wingen, G., Denys, D., 2019. Neural basis of response bias on the Stop Signal Task in misophonia. *Front. Psychol.* 10, 765.
- Esteban, O., Markiewicz, C.J., Blair, R.W., Moodie, C.A., Isik, A.I., Erramuzpe, A., et al., 2019. fMRIprep: a robust preprocessing pipeline for functional MRI. *Nat. Methods* 16 (1), 111.
- Etkin, A., Büchel, C., Gross, J.J., 2015. The neural bases of emotion regulation. *Nat. Rev. Neurosci.* 16 (11), 693–700.
- Feingold, A., 2009. Effect sizes for growth-modeling analysis for controlled clinical trials in the same metric as for classical analysis. *Psychol. Methods* 14 (1), 43.
- Ghaziri, J., Tucholka, A., Girard, G., Houde, J.-C., Boucher, O., Gilbert, G., et al., 2017. The corticocortical structural connectivity of the human insula. *Cereb. Cortex* 27 (2), 1216–1228.
- Gross, J.J., 2013. Handbook of Emotion Regulation, Second Edition. Second Edition ed. The Guilford Press, New York. (2013/12/05/. 669 p).
- Guetta, R.E., Cassiello-Robbins, C., Trumbull, J., Anand, D., Rosenthal, M.Z., 2022. Examining emotional functioning in misophonia: the role of affective instability and difficulties with emotion regulation. *PLoS One* 17 (2), e0263230.
- Hoogendam, J.M., Ramakers, G.M., Di Lazzaro, V., 2010. Physiology of repetitive transcranial magnetic stimulation of the human brain. *Brain Stimul.* 3 (2), 95–118.
- Jager, J.J., Vulink, N.C., Bergfeld, I.O., van Loon, A.J., Denys, D.A., 2021. Cognitive behavioral therapy for misophonia: a randomized clinical trial. *Depress. Anxiety* 38 (7), 708–718.
- Kozel, F.A., Motes, M.A., Didehbani, N., DeLaRosa, B., Bass, C., Schraufnagel, C.D., et al., 2018. Repetitive TMS to augment cognitive processing therapy in combat veterans of recent conflicts with PTSD: a randomized clinical trial. *J. Affect. Disord.* 229, 506–514.
- Kumar, S., Tansley-Hancock, O., Sedley, W., Winston, J.S., Callaghan, M.F., Allen, M., et al., 2017. The brain basis for misophonia. *Curr. Biol.* 27 (4), 527–533.
- Kumar, S., Dheerendra, P., Erfanian, M., Benzaquén, E., Sedley, W., Gander, P.E., et al., 2021. The motor basis for misophonia. *J. Neurosci.* 41 (26), 5762–5770. <https://doi.org/10.1523/JNEUROSCI.0261-21.2021>.
- Kumar, K., Charan, M., Anand, A., 2022. Current Status of Transcranial Magnetic Stimulation in Mental and Behavioral Health Treatment. SAGE Publications Sage India, New Delhi, India, pp. 197–198.
- Lee, E., Duffy, W., Hadimani, R., Waris, M., Siddiqui, W., Islam, F., et al., 2016. Investigational effect of brain-scalp distance on the efficacy of transcranial magnetic stimulation treatment in depression. *IEEE Trans. Magn.* 52 (7), 1–4.
- Lee, A., Yau, C.E., Mai, A.S., Tan, W.A., Ong, B.S.Y., Yam, N.E., et al., 2022. Transcranial alternating current stimulation and its effects on cognition and the treatment of psychiatric disorders: a systematic review and meta-analysis. *Ther. Adv. Chronic Dis.* 13, 20406223221140390.
- Lepping, P., Schonfeldt-Lecuona, C., Sambhi, R.S., Lanka, S.V., Lane, S., Whittington, R., et al., 2014. A systematic review of the clinical relevance of repetitive transcranial magnetic stimulation. *Acta Psychiatr. Scand.* 130 (5), 326–341.
- Lewin, A.B., Dickinson, S., Kudryk, K., Karlovich, A.R., Harmon, S.L., Phillips, D.A., et al., 2021. Transdiagnostic cognitive behavioral therapy for misophonia in youth: methods for a clinical trial and four pilot cases. *J. Affect. Disord.* 291, 400–408.
- Luber, B., Stanford, A.D., Bulow, P., Nguyen, T., Rakitin, B.C., Habeck, C., et al., 2008. Remediation of sleep-deprivation-induced working memory impairment with fMRI-guided transcranial magnetic stimulation. *Cereb. Cortex* 18 (9), 2077–2085.
- Matsumoto, H., Ugawa, Y., 2016. Adverse events of tDCS and tACS: a review. *Clin. Neurophysiol. Pract.* 2, 19–25.
- Mennin, D.S., 2006. Emotion regulation therapy: an integrative approach to treatment-resistant anxiety disorders. *J. Contemp. Psychother.* 36 (2), 95–105.
- Neacsu, A.D., Eberle, J.W., Kramer, R., Wiesmann, T., Linehan, M.M., 2014. Dialectical behavior therapy skills for transdiagnostic emotion dysregulation: a pilot randomized controlled trial. *Behav. Res. Ther.* 59, 40–51.
- Neacsu, A.D., Beynel, L., Powers, J.P., Szabo, S.T., Appelbaum, L.G., Lisanby, S.H., et al., 2021. Enhancing cognitive restructuring with concurrent repetitive transcranial magnetic stimulation for transdiagnostic psychopathology: a proof of concept randomized controlled trial. *Psychother. Psychosom.* 91 (2), 94–106.
- Neacsu, A.D., Szymkiewicz, V., Galla, J.T., Li, B., Kulkarni, Y., Spector, C.W., 2022a. The neurobiology of misophonia and implications for novel, neuroscience-driven interventions. *Front. Neurosci.* 16, 893903 <https://doi.org/10.3389/fnins.2022.893903>.
- Neacsu, A.D., Beynel, L., Graner, J.L., Szabo, S.T., Appelbaum, L.G., Smoski, M.J., et al., 2022b. Enhancing cognitive restructuring with concurrent fMRI-guided neurostimulation for emotional dysregulation: a randomized controlled trial. *J. Affect. Disord.* 301, 378–389.
- Palumbo, D.B., Alsalam, O., De Ridder, D., Song, J.-J., Vanneste, S., 2018. Misophonia and potential underlying mechanisms: a perspective. *Front. Psychol.* 9, 953.
- Potgieter, I., MacDonald, C., Partridge, L., Cima, R., Sheldrake, J., Hoare, D.J., 2019. Misophonia: a scoping review of research. *J. Clin. Psychol.* 75 (7), 1203–1218.
- Remmert, N., Jebens, A., Gruzman, R., Gregory, J., Vitoratou, S., 2022. A nomological network for misophonia in two German samples using the S-Five model for misophonia. *Front. Psychol.* 13, 902807.
- Rinaldi, L., Simner, J., Koursarou, S., Ward, J., 2022. Autistic traits, emotion regulation, and sensory sensitivities in children and adults with Misophonia. *J. Autism. Dev. Disord.* 1–13.
- Rosenthal, M.Z., Anand, D., Cassiello-Robbins, C., Williams, Z.J., Guetta, R.E., Trumbull, J., et al., 2021. Development and initial validation of the duke misophonia questionnaire. *Front. Psychol.* 12, 709928.
- Rossi, S., Antal, A., Bestmann, S., Bikson, M., Brewer, C., Brockmöller, J., Hallett, M., 2021. Safety and recommendations for TMS use in healthy subjects and patient populations, with updates on training, ethical and regulatory issues: Expert Guidelines. *Clin. Neurophysiol.* 132 (1), 269–306.
- Schröder, A., van Wingen, G., Eijker, N., San Giorgi, R., Vulink, N.C., Turbyne, C., et al., 2019. Misophonia is associated with altered brain activity in the auditory cortex and salience network. *Sci. Rep.* 9 (1), 1–9.
- Siempsik, M., Rosenthal, M., Raj-Kozia, D., Dragan, W., 2022. Psychiatric and audiologic features of misophonia: use of a clinical control group with auditory over-responsivity. *J. Psychosom. Res.* 156, 110777.
- Smith, J.E., Peterchev, A.V., 2018. Electric field measurement of two commercial active/sham coils for transcranial magnetic stimulation. *J. Neural Eng.* 15 (5), 054001.
- Smith, E.E., Guzick, A.G., Draper, I.A., Clinger, J., Schneider, S.C., Goodman, W.K., et al., 2022. Perceptions of various treatment approaches for adults and children with misophonia. *J. Affect. Disord.* 316, 76–82.
- Stefan, K., Kunesch, E., Cohen, L.G., Benecke, R., Classen, J., 2000. Induction of plasticity in the human motor cortex by paired associative stimulation. *Brain* 123 (3), 572–584.
- Stokes, M.G., Chambers, C.D., Gould, I.C., Henderson, T.R., Janko, N.E., Allen, N.B., et al., 2005. Simple metric for scaling motor threshold based on scalp-cortex distance: application to studies using transcranial magnetic stimulation. *J. Neurophysiol.* 94 (6), 4520–4527.
- Swedo, S.E., Baguley, D.M., Denys, D., Dixon, L.J., Erfanian, M., Fioretti, A., Raver, S.M., 2022. Consensus definition of misophonia: a delphi study. *Front. Neurosci.* 16, 841816.
- Swedo, S.E., Baguley, D.M., Denys, D., Dixon, L.J., Erfanian, M., Fioretti, A., et al., 2022. Consensus definition of misophonia: a delphi study. *Front. Neurosci.* 224.
- Tonarely-Busto, N.A., Phillips, D.A., Saez-Clarke, E., Karlovich, A., Kudryk, K., Lewin, A.B., et al., 2022. Applying the unified protocol for transdiagnostic treatment of emotional disorders in children and adolescents to misophonia: a case example. *Evid.-Based Pract. Child Adoles. Ment. Health* 1–15.
- Vanneste, S., Walsh, V., Van De Heyning, P., De Ridder, D., 2013. Comparing immediate transient tinnitus suppression using tACS and tDCS: a placebo-controlled study. *Exp. Brain Res.* 226 (1), 25–31.
- Voigt, J., Carpenter, L., Leuchter, A., 2019. A systematic literature review of the clinical efficacy of repetitive transcranial magnetic stimulation (rTMS) in non-treatment resistant patients with major depressive disorder. *BMC Psychiatry* 19, 1–11.
- Wu, M.S., Lewin, A.B., Murphy, T.K., Storch, E.A., 2014. Misophonia: incidence, phenomenology, and clinical correlates in an undergraduate student sample. *J. Clin. Psychol.* 70 (10), 994–1007.
- Yuan, T., Yadollahpour, A., Salgado-Ramírez, J., Robles-Camarillo, D., Ortega-Palacios, R., 2018. Transcranial direct current stimulation for the treatment of tinnitus: a review of clinical trials and mechanisms of action. *BMC Neurosci.* 19 (1).