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Patterns of shared and differential neural activity in misophonia and non-misophonic clinical emotional dysregulation

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Abstract

Misophonia is a poorly understood clinical condition characterized by reduced tolerance to select trigger sounds. Whether misophonic distress and its regulation involve unique neural mechanisms compared to other forms of emotion dysregulation remains unclear. We used functional magnetic resonance imaging (fMRI) to identify putative neural signatures of misophonic reactivity and regulation compared to a transdiagnostic clinical control group. Twenty-nine adults with misophonia and 30 with high emotional dysregulation and a DSM-5 psychiatric disorder underwent an fMRI session. After the presentation of misophonic, aversive, or neutral sound cues, they either experienced emotions naturally or reduced negative affect through cognitive reappraisal. Compared to controls, participants with misophonia showed greater distress after listening to or downregulating misophonic sounds and lower distress when listening to non-misophonic aversive sounds. Listening to misophonic sounds elicited lower functional connectivity between the right insula and the left dorsomedial prefrontal cortex (dmPFC), and between the left insula and the right superior temporal sulcus, in the misophonia group compared with controls. During the regulation of misophonic sounds, the misophonia group showed increased left insula connectivity with the anterior cingulate cortex and increased right insula connectivity with the bilateral dmPFC and other sensorimotor regions compared to controls. In the misophonia group only, higher emotion dysregulation and lower habitual use of reappraisal were respectively associated with increased insula-dmPFC connectivity and with increased insula connectivity with the dorsolateral prefrontal cortex. Prefrontal cortex activation during regulation of misophonic distress was not significantly different between the two groups. Insula activity and connectivity may be key features that distinguish misophonia from other forms of emotional dysregulation. These novel findings identify candidate neural processes that may be selectively associated with misophonia, as well as processes that may be shared between misophonia and other forms of emotion dysregulation.

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Data from this paper were previously presented as part of several conference talks.

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Keywords Cognitive control, Emotional dysregulation, Misophonia, Functional magnetic resonance imaging, Insula, Neurostimulation

Introduction

Misophonia, characterized by extreme emotional reactions to specific auditory triggers [1], appears to be phenotypically similar to emotional dysregulation, a key feature of several psychiatric disorders [2–4]. Nevertheless, emerging research suggests that misophonia may be a distinct problem that does not fit within an existing DSM-5 disorder [1, 5–7]. Despite its hypothesized high prevalence (4.6% in a recent study [8]), misophonia is not yet recognized as a distinct psychiatric, hearing, or neurologic disorder, and comparisons of neurobiological function between participants with misophonia and clinical control samples are lacking [6]. Therefore, an essential next step in misophonia research is to identify whether misophonia involves unique neural processes relative to clinical conditions characterized by emotional dysregulation, which may help support its independence in a diagnostic classification scheme.

Brain regions implicated in prior normative imaging studies of emotion regulation

During normative emotion regulation, higher-order structures involved in cognitive control (i.e., lateral and medial prefrontal cortex [PFC]) and monitoring (i.e., dorsal anterior cingulate cortex [dACC]) are generally hypothesized to modulate emotional appraisals generated by the insular cortex and subcortical structures (i.e., amygdala) in a top-down fashion [9, 10]. In particular, cognitive reappraisal, an emotion regulation strategy involving the reinterpretation of emotionally-evoking situations, is associated with enhanced activity in the dorsolateral PFC (dlPFC), ventrolateral PFC (vlPFC), dorsomedial PFC (dmPFC), anterior cingulate cortex (ACC), and inferior parietal cortex (IPC) [11–13], reduced activity in the amygdala [9] and insula [14], and strengthened fronto-limbic connectivity [15]. By challenging and reframing maladaptive thoughts, individuals improve their ability to regulate attention and inhibit inappropriate affective responses. Cognitive reappraisal can also alter activity in the orbitofrontal cortex (OFC), which may help reduce negative biases and foster more balanced emotional evaluations [16].

The neurobiology of emotion dysregulation

The triple network theory of psychopathology proposes that common dysfunctional patterns in the central executive, salience, and default-mode brain networks underlie transdiagnostic impairments in cognitive control, accurate evaluation of the salience of environmental stimuli, and self-referential cognitive processes, respectively [17].

The essential nodes of the central executive (“cognitive control”) network include the dlPFC and IPC; the critical nodes of the salience network are the anterior insular cortex (AIC) and ACC; and the default-mode network includes the posterior cingulate cortex and ventromedial prefrontal cortex (vmPFC). Auditory components of psychiatric disorders, such as hallucinations in schizophrenia, have been associated with alterations in central executive and salience network connectivity [18], while primarily auditory phenomena, such as both acute and chronic tinnitus, have also been linked to triple network alterations [19]. Neurobiological evidence, therefore, points to disruptions within the triple network model as a foundational mechanism in disorders involving emotional dysregulation or auditory-perceptual abnormalities. See the Supplement for additional details on the neurobiology of emotion dysregulation.

Brain regions implicated in prior imaging studies of misophonia

It would be reasonable to expect a similar triple network dysfunction in misophonia. However, very few studies have used functional magnetic resonance imaging (fMRI) to evaluate brain regions implicated in misophonia, and all have compared misophonia to non-clinical controls. Adults with misophonia exposed to misophonic (or trigger) sounds show hyperactivity in the insula [20–22], ACC [21], midcingulate cortex (MCC) [22], amygdala [23], ventral premotor cortex (PMv) [22], supplementary motor area (SMA) [22], and superior temporal cortex (STC) [6, 21, 24]. In addition, these trigger sounds elicit hyperconnectivity in the following circuits: insula–vmPFC [20], insula – amygdala [20], insula – hippocampus [20], lateral OFC – SMA/ PMv [22], OFC–MCC [22], MCC– primary auditory cortex [22], and SMA/PMv–primary auditory cortex [22]. In non-clinical controls, these brain regions process emotions, integrate sensory information, and regulate emotion [14, 25–31]. See the Supplement for a more detailed discussion of brain regions and networks involved in misophonia. Given some commonalities between regions commonly implicated in triple network dysfunction and those involved in misophonia, it is essential to understand how patterns of neural activity in these regions in misophonia both converge with and diverge from those in non-misophonic individuals with transdiagnostic psychopathology characterized by difficulties regulating emotions.

The present study

To our knowledge, no studies to date have examined functional neural alterations in misophonia during effortful emotion regulation. To date, the vast majority of studies investigating neural processes in misophonia have limited comparisons to healthy control groups. Accordingly, there is a critical need for comparisons to non-misophonic clinical controls rather than healthy adults, in order to identify putative neural signatures that distinguish misophonia from other forms of psychopathology. The present study aims to fill a critical gap in the literature regarding the specificity of neural processing differences in misophonia versus non-misophonic emotional dysregulation during active attempts to downregulate negative affect. The insights gained from this mechanistic study could provide key evidence to determine whether misophonia has distinctive patterns of brain reactivity and regulation to trigger sounds.

Hypothesis-driven aims

In this study, we compared fMRI activity and connectivity between participants with misophonia and non-misophonic participants with transdiagnostic emotion dysregulation during reactivity to and regulation of misophonic, aversive, and neutral sound cues. Based on neurobiological models of psychopathology and prior findings in misophonia, we hypothesized that adults with misophonia would exhibit greater insular activity when exposed to misophonic sounds than to aversive sounds, relative to non-misophonic clinical controls (primary outcome: H1). We also hypothesized increased activity (H2) within the dlPFC and vmPFC during the regulation of misophonic versus aversive sounds and hyperconnectivity (H3) between these regions and the insula in misophonic adults versus controls (primary outcomes). We expected these neural differences to be positively correlated with self-reported distress collected during the neuroimaging task (secondary outcome).

Exploratory aims

We explored differences in emotion regulation networks across the dlPFC, vlPFC, mPFC, IPC, amygdala, ACC, and insula using whole-brain and region-of-interest (ROI) analyses. These exploratory analyses targeted five contrasts of interest: listening to misophonic vs. aversive sounds; listening to misophonic vs. neutral sounds; downregulating misophonic vs. aversive sounds; downregulating vs. listening to misophonic sounds; and downregulating vs. listening to aversive sounds. Within the misophonia group, we also explored correlations between misophonia and self-reports of emotion dysregulation, as well as neural activity and connectivity within brain regions of interest (ROIs) that showed significant

whole-brain activation and connectivity with the insula during contrasts of interest.

Experimental procedures

Recruitment procedures

This study was pre-registered at clinicaltrials.gov (Clinical Trials ID: NCT04348591; date of registration: 4/13/2020) and ran between October 2020 and May 2022 under the aegis of the Duke University Medical Center IRB. Participants received maximum compensation of \$250. The study was powered based on the expected effect size derived from Kumar et al. [20], who compared 22 adults with misophonia to 20 healthy controls and found significant differences in AIC response when listening to trigger sounds ($d = 1.27$). For the current study, with planned comparisons across condition, sound type, and group, we expected adequate power (over 80%, $d_{\text{expected}} = 1.29$, $\alpha = 0.05$) with 29 participants per group. The primary behavioral outcomes from the neurostimulation experiment, along with accompanying methodological details, including a CONSORT flow diagram, were reported in Neacsiu et al.¹ [32]. Here, we report data collected during the baseline fMRI session from the parent study.

Participants were recruited through online websites (e.g., Craigslist, Dukelist), social media (Facebook, Reddit), flyers, and electronic medical record outreach. Interested participants completed online and in-person screenings before attending an imaging session. One hundred and twelve adults signed written consent forms and participated in the in-person screening assessment designed to establish a diagnostic profile and to examine inclusion/exclusion criteria. Of these, 59 qualified participants were interested in continuing and provided neuroimaging data.

Inclusion criteria

Significant misophonic severity was operationally defined as a score of 2 or higher on both subscales of the Misophonia Questionnaire (MQ) [33] and a score of 7 or higher on the MQ severity scale. The MQ was used for inclusion/exclusion because it was the most used and well-studied self-report measure of misophonia at the time of the study. High emotional dysregulation was operationally defined as a total score of 89 or higher on the Difficulties in Emotion Regulation Scale (DERS) [34], as described previously [35]. Participants with misophonia were not excluded if they reported heightened emotional dysregulation.

¹While imaging data procedures collection were presented in this publication, in the 2024 study, participant-level imaging data during one contrast were used to guide targeting individual neurostimulation sessions and not analyzed at the group-level.

Participant characteristics

Enrolled participants were four men, 52 women, and three non-binary adults between the ages of 18 and 54 ($M = 28.31y$; $SD = 9.06$) who self-reported significant misophonic severity ($n = 29$) or who self-reported clinical levels of emotional dysregulation ($n = 30$) and met criteria for any DSM-5 disorder (excluding active substance use, psychotic disorders, and Bipolar I). High emotion dysregulation served as a transdiagnostic marker of psychopathology and provided a unifying phenotype, enabling comparison of misophonia to multiple psychiatric conditions rather than limiting analyses to a single disorder. Participants met criteria for an average of 1.75 ($SD = 1.62$) current diagnoses and 3.54 ($SD = 2.26$) lifetime diagnoses, as assessed by the Structured Clinical Interview for DSM-5 Disorders (SCID-5) [36]. Twenty-one participants (36.21%) met the criteria for at least one personality disorder, according to the SCID-5-PD [37]. Supplementary Table 1 lists the frequencies of observed DSM-5 diagnoses in both groups.

Of the 59 participants who completed the neuroimaging visit, 48 had all four functional runs collected, while 9 had three runs and 2 had only two runs. Functional runs with framewise displacement greater than 0.4 mm on more than 20% of TRs were excluded from analyses. Twenty-one runs exceeded this motion threshold, resulting in the complete exclusion of five participants with only one or no valid runs and partial exclusion for several others. One participant also showed extreme spatial distortions in two of four runs, leaving only the remaining two runs usable. Participants were excluded entirely if more than three of their runs were unusable. Overall, neuroimaging data from 54 participants were included in the final analysis, with data from 19 participants partially or fully missing.

Initial assessment

After providing voluntary, written informed consent, participants completed diagnostic assessments (SCID-5, SCID-PD), a verbal intelligence test [38], and a questionnaire packet. Participants also completed a sound task in the lab, during which they listened to 101 preselected 6-second sounds (31 aversive, 40 misophonic, and 30 neutral) and rated arousal and valence. Participants from the misophonia group were also asked whether the sound elicited a misophonic reaction. The top 10 most distressing misophonic sounds and the top 10 aversive sounds, along with a random selection of 4 neutral sounds, were selected as stimuli for the imaging sessions. We opted for this approach to stimulus selection, given the highly personalized nature of misophonic triggers [1] and evidence from the literature that exposure to trigger sounds is unlikely to lead to habituation [39]. Nevertheless, to mitigate the effects of repeated exposure, the sounds in

this sound task were shorter (6s) than those presented in the imaging session. See the Supplement for examples of sounds used and additional details relevant to the Sound Task.

Imaging session

Participants completed an imaging session as soon as possible after intake. During the first hour, participants were briefly trained in cognitive restructuring, an emotion regulation strategy, using standardized procedures [35] (See Supplement for additional details). Participants then moved into a research-dedicated GE HD 3.0 T MRI scanner and completed an anatomical image (3D MPRAGE pulse sequence; time repetition [TR] = 2300 ms; echo time [TE] = 3.2 ms; image matrix = 2562; flip angle = 12°; voxel size = 1-mm isotropic; 162 contiguous axial slices). Four functional runs (10 min each) were then acquired using a multi-band EPI sequence that optimizes temporal signal-to-noise following published specifications [40] (SENSE factor = 1; multi-band factor = 3; TR = 2000 ms; TE = 30 ms; image matrix = 1282; flip angle = 77°; voxel size = 2-mm isotropic; 68 contiguous axial slices). If time allowed, reverse-phase-encode direction echo-planar images (EPI) were collected to correct the functional images for spatial distortion due to magnetic field inhomogeneities (35 participants; 59.32%).

During the functional emotion regulation task, participants experienced and downregulated emotions related to personalized sounds (see Fig. 1). Each run consisted of five blocks, presented in a pseudo-random order (down-regulate aversive, downregulate misophonic, listen to neutral, listen to misophonic, listen to aversive), with three auditory stimuli per block. Following each sound, participants reported their current subjective level of distress (SUDS) on a scale from 0 (low) to 9 (high). Additional MRI task details can be found in the Supplement. Participants wore MRI-compatible earphones, and foam pads were placed on both sides of the head to attenuate scanner noise.

Outcome measures

Misophonic distress was measured using the (MQ) [33] and the Duke Misophonia Questionnaire (DMQ) [41]. The (DERS) [34] was used to assess levels of emotion dysregulation across different domains. The cognitive reappraisal subscale of the Emotion Regulation Questionnaire (ERQ) was used to measure the tendency to use cognitive reappraisal to regulate emotions [42]. For additional description and psychometric details of these measures, see the Supplement.

Neuroimaging data processing

Structural and functional data were first examined with MRIQC and then preprocessed with fMRIPrep [43].

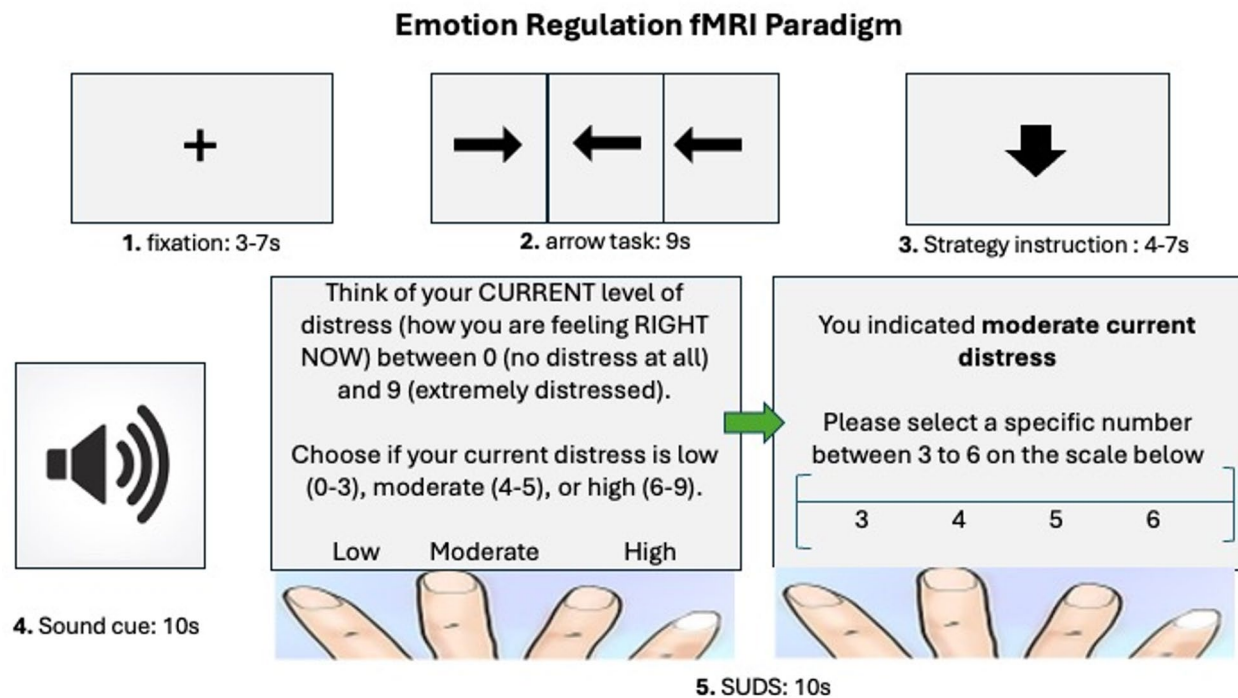


Fig. 1 Affective sound fMRI paradigm. Example of a task trial. Participants first fixated on a cross (3–7 s, jittered); indicated the direction (left or right) of an arrow in an active baseline task (9 s); were cued (4–7 s, jittered) to either downregulate (downward arrow) emotional distress or passively listen (~symbol) to a sound stimuli; presented with an auditory stimulus (misophonic, aversive, or neutral); and indicated their level of distress (10 s) using the SUDS to select a rating between 0 (not distressed at all) and 9 (extremely distressed)

When reverse-phase-encode-direction EPI data were available, they were used to correct for spatial distortions. Susceptibility distortion correction (SDC) using displacement field estimation via nonlinear registration [44] was used when these data were unavailable (52% of participants in the control group, 30% in misophonia group, $z_{\text{proportion difference}} = 1.66, p = .097$). At the first level, functional data were analyzed as individual runs using a general linear model (GLM) implemented in FSL's FEAT [45]. The results for each subject were then concatenated into second-level fixed-effects models. Activation contrasts were compared with each group (misophonic, clinical control) and between the two groups in whole-brain analyses. Participant-level z-statistic maps underwent threshold-free cluster enhancement (TFCE) [46] and permutation testing [FSL's randomize [47], 10,000 permutations] to correct for multiple comparisons, with a threshold of $p = .01$ for resulting TFCE T-statistic images. Generalized psychophysiological interaction (PPI) analyses were also conducted, using the time courses of the left insula and the right insula as the anatomical seeds (Supplementary Fig. 1), given prior evidence for insula involvement in misophonia [6]. This method was used for all subjects and each run. Run-level PPI maps were then combined into second-level (participant). These participant-level results were combined into a third (group-level) analysis, in which contrasts were compared

within and between the two groups (misophonic, clinical control). Whole-brain analyses used mixed-effects (FSL's FLAME 1; Oxford Univ., UK) modeling with cluster-wise FWE correction [48] at $p = .05$ for multiple comparisons following a voxel-wise Z-score threshold of 2.3. A more thorough description of neuroimaging data pre-processing can be found in the Supplement.

Exploratory ROI analyses

ROI analyses were conducted in the misophonia group using participant-wise 6-mm spherical ROIs placed within anatomically defined region masks (additional details available in the Supplement). For both functional activation and connectivity analyses, the contrasts of interest were as follows: listen to misophonic vs. aversive sounds, listen to misophonic vs. neutral sounds, downregulate misophonic vs. aversive sounds, downregulate vs. listen to misophonic sounds, and downregulate vs. listen to aversive sounds. If functional activation differences in emotion regulation brain regions (insula, amygdala, lateral PFC, medial/orbital PFC, ACC, and IPC) were found between groups or in the misophonia group only during contrasts of interest, then functional activity in the specific brain region(s) was correlated with misophonic distress and emotion dysregulation (average MQ score, DMQ subscale scores, DERS, and ERQ-R). If differences in functional connectivity were found between

these brain regions with either a left or right insula, either between groups or in the misophonia group only during contrasts of interest, then we examined correlations in functional connectivity between the insula and the brain region associated with misophonic distress and emotion dysregulation. When significant associations between neural data and total DERS score were found, we also explored correlations between neural changes and DERS subscales, including non-acceptance of emotional responses, difficulties with impulse control, lack of emotional awareness, limited access to regulation strategies, lack of emotional clarity, and difficulties engaging in goal-directed behavior. Exploration of post-hoc associations between neural patterns and behavior were therefore constrained to a priori regions of interest and were not corrected for multiple comparisons.

Results

Behavioral responses to misophonic sounds

As expected, sounds from the misophonia stimulus set included in the MRI session emotion regulation task were moderately-to-highly distressing to both groups (as rated during the intake sound task), with misophonic participants indicating higher distress to them ($M=3.01$, $SD=0.91$) than participants with non-misophonic emotional dysregulation ($M=2.19$, $SD=0.94$; $t[422] = -8.42$, $p < .001$). Pairwise comparisons of a significant group by strategy by sound type interaction ($F[4, 2404.87] = 43.814$, $p < .001$) showed that, as hypothesized, participants in the control group had significantly lower distress than misophonic participants after passively listening to ($\Delta = -1.02$, $SE = 0.36$, $p = .006$) or downregulating ($\Delta = -1.13$, $SE = 0.36$, $p = .002$) misophonic sounds during the MRI scan. Participants with misophonia experienced significantly lower distress than control participants when passively listening to aversive sounds ($\Delta = -1.32$, $SE = 0.36$, $p < .001$). A complete set of analyses of feasibility, acceptability, and behavioral responses to sounds is reported in the Supplement as are procedures for assessing and addressing normal distribution in the outcome data.

Hypothesis-driven fMRI analyses

Response to misophonic sounds (H1)

We found significant differences between groups in the contrast comparing passively listening to misophonic vs. aversive sounds (see Table 1; Fig. 2A). Participants with misophonia showed more activation in the left SMA during presentation of misophonic sounds ($t=6.06$, $p = .0012$) than clinical controls.

In partial support of our first hypothesis (H1), participants in the misophonia group alone showed more activation in the bilateral insula ($ts=7.19-7.62$; $ps < 0.001$) during exposure to misophonic versus non-misophonic

unpleasant sounds; however, the difference between groups was not significant (Table 1).

Regulation of distress induced by misophonic sounds (H2)

Participants in the misophonia group showed significant differences in functional activation in the right insula and bilateral inferior parietal cortex ($ts=5.93-7.51$; $ps < 0.05$) when downregulating misophonic versus aversive sounds (Table 1). Contrary to our hypothesis (H2), whole-brain analyses did not reveal significant functional activation differences in lateral or medial PFC activity between the misophonic versus control group in the contrast comparing downregulating misophonic versus downregulating aversive sounds (Fig. 3C). Additionally, we found no significant between-group differences in brain activation when downregulating versus passively listening to misophonic sounds.

Whole-brain functional connectivity (H3)

In line with our third hypothesis (H3), whole brain analyses showed greater connectivity between the right insula and both the left ($z=4.25$, $p = .000030$) and right ($z=4.30$, $p < .000001$) dmPFC in participants with misophonia compared to clinical controls during the downregulation of trigger sounds versus aversive sounds (Fig. 3B). In misophonic participants compared to controls, we also found significantly greater right insula connectivity with the left planum temporale ($z=4.02$, $p = .00678$), left inferior temporal gyrus ($z=4.16$, $p = .0124$), right paracentral lobule ($z=3.64$, $p = .0176$), left thalamus ($z=4.57$, $p = .0232$), right middle temporal gyrus ($z=3.86$, $p = .0314$), and right cuneus gyrus ($z=4.61$, $p < .000001$) during regulation versus listening to sounds. Whole brain analyses using the anatomical left insula as seed found significantly greater left insula connectivity with the left anterior MCC ($z=3.69$, $p = .0241$) in the misophonia group compared to the control group during the contrast that compared downregulating versus passively listening to misophonic sounds (Fig. 3A). Results suggest that aberrant insula connectivity may be associated with both distress reactivity and regulation.

Misophonic participants alone also showed increased functional connectivity between the right insula with both left and right dlPFC ($ts=3.58-3.97$, $ps < 0.05$) as well as with the left and right inferior parietal lobule ($ts=4.09$, $ps < 0.0001$) when downregulating versus passively listening to misophonic sounds (Table 2).

Activation differences when passively listening to misophonic sounds versus neutral sounds, as well as brain changes during regulation versus passively listening to aversive sounds, are reported in the Supplement.

Table 1 Areas of activation following whole brain analyses

whole brain activation								
Contrast	Group	Cluster index	voxels	P	T-max	T-max x (mm)	T-max y (mm)	T-max z (mm)
Downregulate aversive > Listen aversive	Misophonia	Left vlPFC	251	0.001300	5.72	-56	24	20
	Misophonia	Left inferior frontal gyrus, pars triangularis	21	0.005700	5.74	-54	20	-4
	Control	Left vlPFC	292	0.001000	5.47	-48	34	14
	Control	Left dlPFC	169	0.000600	6.15	-44	10	44
	Control	Left inferior parietal lobule	40	0.004900	5.27	-48	-58	22
	Control	Right vlPFC	28	0.006200	5.21	44	18	24
	Control	Right vlPFC	25	0.006400	5.40	56	22	18
	Control	Left vlPFC	10	0.007200	5.52	-52	24	-6
	Control	Right dlPFC	8	0.007500	5.35	38	10	30
	Control	Right vlPFC	6	0.008400	4.95	50	32	12
	Control	Right vlPFC	6	0.008400	4.95	50	32	12
Listen misophonic > Listen aversive	Misophonia	Left SMA	433	0.001200	6.06	0	0	60
	Misophonia	Right SMA	770	0.000100	7.99	2	4	54
	Misophonia	Right anterior insula	656	0.000300	7.19	40	16	0
	Misophonia	Left anterior insula	322	0.000300	7.62	-34	20	6
	Misophonia	Left precentral gyrus	8	0.007300	6.53	-60	8	24
	Control	Right dlPFC	161	0.000800	6.41	48	20	30
	Control	Right inferior parietal lobule	38	0.006900	5.22	38	-60	48
	Control	Right frontal opercular cortex	7	0.008500	5.64	34	26	4
	Misophonia	Right SMA	1697	0.000100	8.61	2	2	56
	Misophonia	Right inferior parietal lobule	935	0.000600	6.93	62	-30	22
	Misophonia	Left middle insula	896	0.000200	7.10	-38	4	2
Listen misophonic > Listen neutral	Misophonia	Right frontal opercular cortex	248	0.000130	6.37	46	10	0
	Misophonia	Left precentral gyrus	90	0.003300	6.24	48	0	42
	Misophonia	Right precentral gyrus	66	0.002000	7.28	60	6	18
	Misophonia	White matter	2	0.010000	4.18	-54	0	20
	Control	Right anterior superior temporal sulcus	1090	0.000100	7.00	48	-28	-4
	Control	Left posterior superior temporal sulcus	143	0.002300	6.35	-58	-52	12
	Control	Left dmPFC	1	0.010000	6.55	-4	20	54
	Control	Left dmPFC	1	0.010000	6.55	-4	20	54
	Control	Left dmPFC	1	0.010000	6.55	-4	20	54
	Control	Left dmPFC	1	0.010000	6.55	-4	20	54
	Control	Left dmPFC	1	0.010000	6.55	-4	20	54
	Control	Left dmPFC	1	0.010000	6.55	-4	20	54
Downregulate misophonic > Downregulate aversive	Misophonia	Left SMA	149	0.002600	5.69	-8	2	52
	Misophonia	Right inferior parietal lobule	136	0.000300	7.51	64	-22	26
	Misophonia	Right posterior insula	89	0.001300	7.18	38	-2	2
	Misophonia	Right frontal opercular cortex	19	0.004400	6.48	36	26	10
	Misophonia	Left inferior parietal lobule	18	0.011010	5.76	-62	-20	24
	Misophonia	Left inferior parietal lobule	2	0.008700	5.93	-64	-22	36
	Control	Left postcentral gyrus (tongue/larynx area)	326	0.000800	6.07	-60	-16	20
	Misophonia	Right superior temporal gyrus (Heschl's)	1048	0.000100	11.9	52	-8	2
	Misophonia	Left superior temporal gyrus (Heschl's)	761	0.000100	9.94	-52	-16	6
	Control	Right superior temporal gyrus (Heschl's)	281	0.000100	6.46	54	-6	2
	Control	Left superior temporal gyrus (Heschl's)	44	0.000100	6.09	-52	-10	4

vlPFC = ventrolateral prefrontal cortex. dlPFC = dorsolateral prefrontal cortex. SMA = supplementary motor area. dmPFC = dorsomedial prefrontal cortex

Exploratory analyses

Response to misophonic sounds

Given that the misophonia group showed increased activation in the bilateral insula during listening to misophonic versus aversive sounds (see Table 1), we conducted correlation analyses to assess the relationships between clinical measures and changes in peak insular

activation. Within the misophonia group, the peak activation difference while passively listening to misophonic versus aversive sounds was significantly correlated with the average MQ score in the left insula ($r = .60$, $p = .001$), but not the right insula. Because these analyses were not

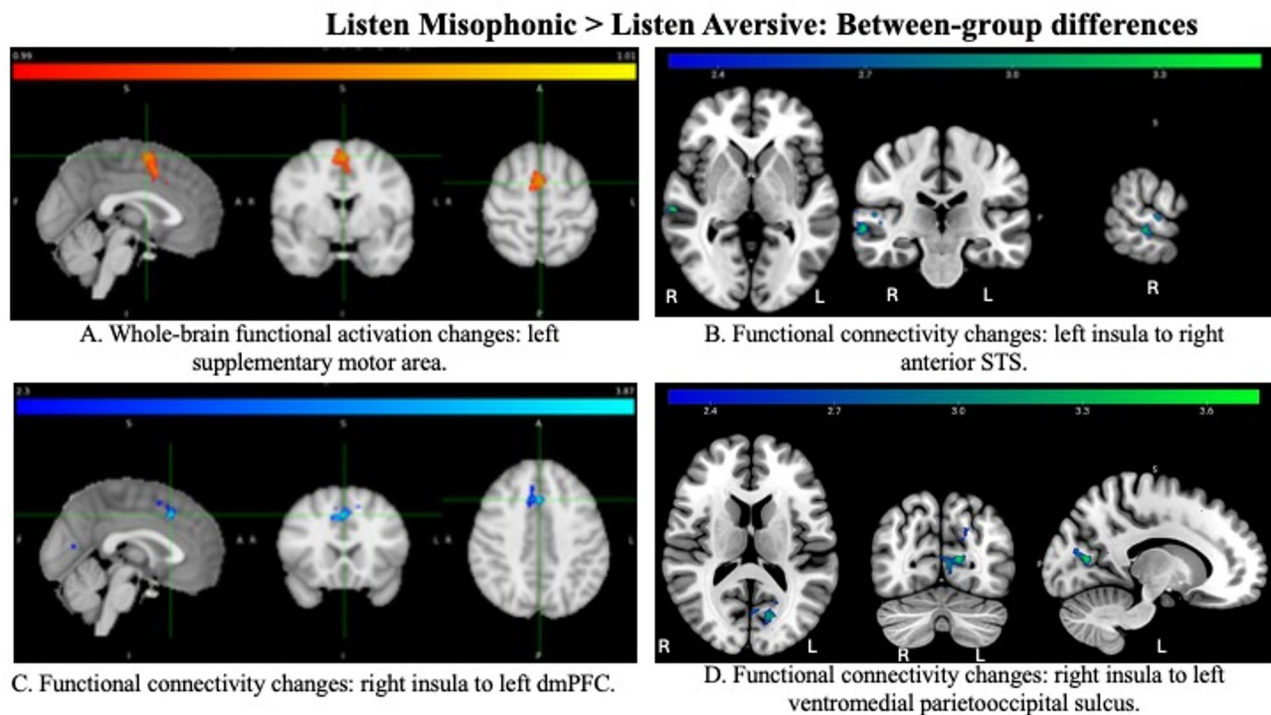


Fig. 2 Between-group differences in brain activation and functional connectivity when listening to misophonic versus aversive sounds. Blue-green scale indicates brain regions where participants with misophonia ($n = 27$) displayed less activation than control participants ($n = 27$), and red-yellow scale indicates brain regions where participants with misophonia displayed increased activation compared to control participants. For 2 A, color-bar scale = $1-p$. For 2B, 2 C, 2D, color bar = z statistic. **(A)** Participants with misophonia show increased left supplementary motor area activation compared to clinical controls. **(B)** Participants with misophonia show decreased functional connectivity between right insula and right anterior superior temporal sulcus (aSTS) compared to clinical controls. **(C)** Participants with misophonia show decreased functional connectivity between right insula and left dorsomedial prefrontal cortex (dmPFC) compared to clinical controls. **(D)** Participants with misophonia show decreased functional connectivity between right insula and left ventromedial parietooccipital sulcus compared to clinical controls

conducted in independent samples, replication is needed to confirm these findings.

Whole-brain functional connectivity Compared to control participants, misophonic participants showed significantly lower coupling between activity in the left insula and activity in the right anterior superior temporal sulcus ($z = 3.53$, $p = .0223$) when listening to misophonic versus aversive sounds (Fig. 2B). Compared to clinical controls, misophonic participants also showed decreased functional connectivity between the right insula and the left dmPFC ($z = 3.84$, $p = .00347$) as well as between the right insula and the left ventromedial parietooccipital sulcus ($z = 3.65$, $p = .000155$) when listening to misophonic versus aversive sounds (Fig. 2C and D).

Insula functional connectivity with a-priori ROIs Given that we found significant functional connectivity differences between the left insula and the left dmPFC using an a priori ROI (Table 2), we used correlation analyses to determine whether the strength of functional connectivity between these regions was associated with clinical measures. We did not find any significant

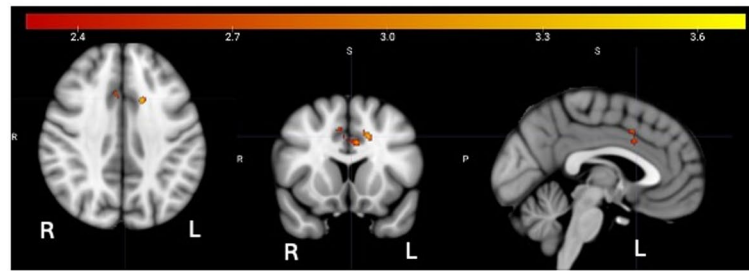
relationships between differences in left insula-dmPFC connectivity during listening to misophonic versus aversive sounds and misophonia or emotion dysregulation severity.

Regulation of distress induced by misophonic sounds

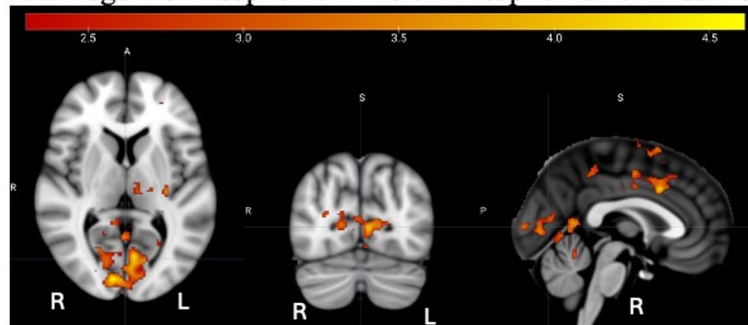
Although the misophonia group displayed increased peak activation in the right insula and bilateral inferior parietal cortex during downregulation of distress associated with misophonic versus non-misophonic unpleasant stimuli, none of these functional changes were significantly correlated with clinical measures.

Insula functional connectivity with a-priori ROIs Given that we found right insula hyperconnectivity with the bilateral dlPFC, left dmPFC, and left inferior parietal cortex when downregulating versus passively listening to misophonic sounds, we examined whether the degree of functional coupling in these five connections with the right insula was significantly correlated with clinical measures in the misophonia group. Increased functional connectivity between the right insula and the left dmPFC was associated with significantly higher total

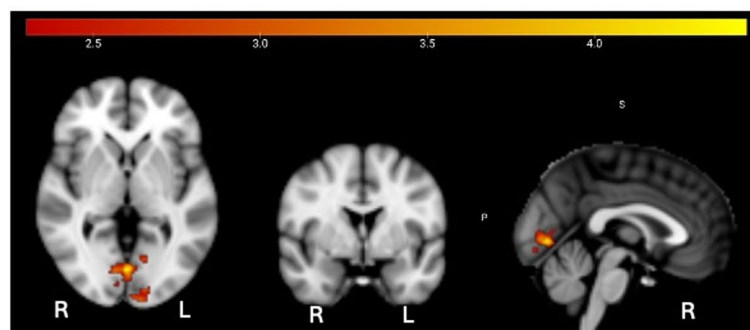
Downregulation of misophonic sounds: Misophonia > Control



A. Downregulate Misophonic > Listen Misophonic: left insula seed.



B. Downregulate Misophonic > Listen Misophonic: right insula seed.



C. Downregulate Misophonic > Downregulate Aversive: right insula seed.

Misophonia group: Higher emotion dysregulation is associated with increased right insula-PFC coupling during downregulation of misophonic sounds

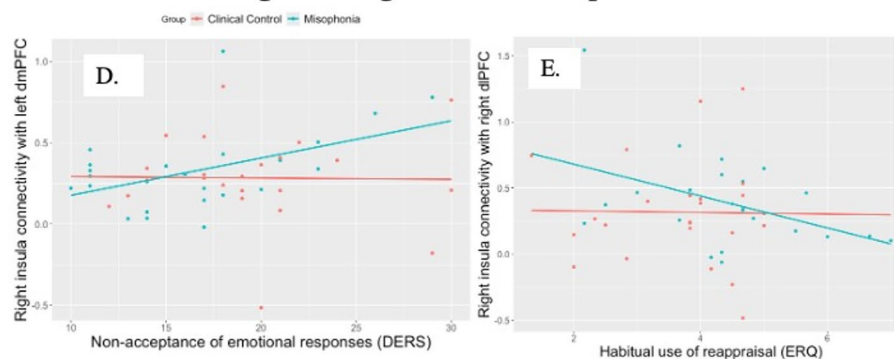


Fig. 3 (See legend on next page.)

(See figure on previous page.)

Fig. 3 Downregulating versus listening to misophonic sounds: functional connectivity and associations between connectivity and emotion regulation. Red-yellow scale indicates brain regions where participants with misophonia displayed increased functional coupling compared to control participants. **(A)** Between-group differences in whole-brain functional connectivity with the left insula when downregulating versus listening to misophonic sounds. **(B)** Between-group differences in whole-brain functional connectivity with the right insula when downregulating versus listening to misophonic sounds. **(C)** Between-group differences in whole-brain functional connectivity with the right insula when downregulating misophonic versus aversive sounds. **(D)** Participants with misophonia show a positive correlation between non-acceptance of emotional responses (DERS) and right insula functional connectivity with the right dmPFC ($r = .48, p = .010$). **(E)** Participants with misophonia show a negative correlation between habitual use of cognitive reappraisal (ERQ) and right insula functional connectivity with the right dlPFC ($r = -.437, p = .026$)

DERS score ($r = .426, p = .027$). Specifically, greater right insula/left dmPFC connectivity during downregulation, compared with listening to misophonic sounds, was significantly associated with increased non-acceptance of emotional responses ($r = .488, p = .010$; Fig. 3D). We also found that increased functional connectivity between the right insula and the right dlPFC was negatively correlated with ERQ ($r = -.437, p = .026$), indicating that low habitual use of cognitive reappraisal emotion regulation strategies may be associated with greater strength of right insula/right dlPFC functional connectivity during downregulating versus listening to misophonic sounds (Fig. 3E). There were no significant correlations between clinical measures and functional coupling between right insula with left dlPFC, right insula with right dmPFC, or right insula with either left or right inferior parietal lobule.

Discussion

This study investigated the neural correlates of emotional reactivity and regulation in adults with misophonia compared to a transdiagnostic sample of adults with heightened emotion dysregulation. This is the first study to rigorously compare neural processes in misophonia with those of a clinical control group. Importantly, we first demonstrated that participants with misophonia experienced significantly higher distress both when listening to misophonic sounds and downregulating emotions associated with these sounds compared to clinical controls. They also experienced significantly less distress when listening to aversive sounds and downregulating emotions associated with these sounds (see Supplement). Therefore, behavioral responses between the two groups differed, lending validity to the premise that misophonic trigger sounds are cognitively processed via mechanisms distinct from other aversive sounds.

Our hypotheses were partially supported. We found evidence of hyperactivity in the bilateral AIC when listening to misophonic versus aversive triggers in the misophonia group, although functional insula activation changes did not differ significantly between groups (H1). We did not find between-group differences in activity (H2) and connectivity (H3) with the dlPFC/vmPFC during the regulation of misophonic sounds. However, during the regulation of misophonic sounds, post-hoc analyses revealed increased right insula functional connectivity with both left and right dmPFC in misophonic

participants compared to controls. In the misophonia group only, the strength of functional connectivity between right insula and left dmPFC during regulation was positively correlated with higher emotion dysregulation in exploratory analyses. Finally, participants in the misophonia group showed increased right insula functional connectivity with both left and right dlPFC during the regulation of misophonic distress. Additionally, exploratory analyses showed that the strength of right insula/right dlPFC functional coupling was negatively correlated with the tendency to use cognitive reappraisal skills in the misophonia group.

Our data provide additional support to prior studies that found increased bilateral AIC activation when listening to misophonic sounds in participants with misophonia versus non-clinical controls [20]. Given that the anterior insula has been shown to respond to the emotional component of auditory stimuli [49, 50], our findings suggest that misophonia may interfere with the neurobiological processes underlying the integration of emotion and auditory function in a way that is independent of other disorders. In light of prior literature [6], these findings suggest that changes in the insular cortex reflect a unique disturbance in misophonia. Interestingly, nearly all between-group differences in functional connectivity were observed in the right insula. The right insula is central to attention to bodily states that contribute to perceived emotional experience [51, 52], perhaps due to a greater density of functional connections with frontal regions than in the left insula [53, 54]. Further research is needed to examine the efficacy of decreasing right insula activation during cue exposure.

Additionally, while we expected to find between-group differences in vmPFC and dlPFC functional activation as well as insula connectivity with the vmPFC and dlPFC, we instead found between-group differences in insula-dmPFC connectivity. The appraisal-by-content model of prefrontal cortex functional specialization proposes that, while all prefrontal subregions contribute to appraisal during emotion regulation, they differ in the content being appraised [55]. The dmPFC is thought to contribute to the evaluation of others' mental states and traits, while the vmPFC appraises self-referential information, and the lateral PFC appraises emotional states and context-dependent strategies. Given the growing body of evidence highlighting the importance of social context

Table 2 Areas functionally connected with the insula following whole-brain gPPI analyses

Functional connectivity									
Contrast	Group	Seed	Cluster index	voxels	P	Z-max	Z-max x (mm)	Z-max y (mm)	Z-max z (mm)
Downregulate aversive > Listen aversive	Misophonia > Control	Left insula	Right SMA	354	0.00135	4.35	6	0	62
	Misophonia > Control	Left insula	Right dlPFC	339	0.00189	4.23	30	16	56
	Misophonia > Control	Right insula	Right precuneus	209	0.0434	3.99	4	-46	68
	Misophonia	Left insula	Right dlPFC	545	0.0000274	4.29	42	12	30
Listen miso- phonic > Listen aversive	Control > Misophonia	Left insula	Right anterior superior tempo- ral sulcus	234	0.0223	3.53	62	-26	-2
	Control > Misophonia	Right insula	Left ventromedial parietooc- cipital sulcus	446	0.000155	3.65	-6	-68	4
	Control > Misophonia	Right insula	Left dmPFC	305	0.00347	3.84	0	20	42
	Misophonia	Right insula	White matter	334	0.00177	4.60	38	-46	0
Listen miso- phonic > Listen neutral	Control > Misophonia	Right insula	Right frontal pole	732	0.000001	4.44	32	38	46
	Control > Misophonia	Right insula	Left dorsomedial parietooc- cipital sulcus	288	0.005	3.76	-18	-56	22
	Control > Misophonia	Right insula	Left precentral gyrus	271	0.00756	3.76	-12	-8	56
	Control > Misophonia	Right insula	Left subgenual ACC	249	0.0131	3.98	0	46	4
Downregu- late miso- phonic > Listen misophonic	Misophonia	Right insula	White matter	252	0.0121	3.64	30	-40	20
	Misophonia > Control	Left insula	Left anterior mid-cingulate cortex (dACC)	241	0.0241	3.69	-14	12	38
	Misophonia > Control	Right insula	Right cuneus gyrus	2540	<0.000001	4.61	12	-88	8
	Misophonia > Control	Right insula	Right dmPFC	1026	<0.000001	4.30	12	10	40
	Misophonia > Control	Right insula	Left dmPFC	536	0.000030	4.25	-26	50	30
	Misophonia > Control	Right insula	Left planum temporale	281	0.00678	4.02	-32	-30	14
	Misophonia > Control	Right insula	Left inferior temporal gyrus	256	0.0124	4.16	-44	-64	0
	Misophonia > Control	Right insula	Right paracentral lobule	242	0.0176	3.64	8	-34	50
	Misophonia > Control	Right insula	Left thalamus	231	0.0232	4.57	-10	-22	10
	Misophonia > Control	Right insula	Right middle temporal gyrus	219	0.0314	3.86	50	2	-28
	Misophonia	Right insula	Right cuneus gyrus	3037	<0.000001	5.10	10	-88	6
	Misophonia	Right insula	Left dmPFC	1124	<0.000001	4.31	0	40	40
	Misophonia	Right insula	Right inferior parietal lobule	1123	<0.000001	4.09	52	-44	44
	Misophonia	Right insula	Left inferior parietal lobule	590	0.000011	4.09	-28	-70	50
	Misophonia	Right insula	Left dlPFC	450	0.000164	3.97	-26	50	32
	Misophonia	Right insula	Left paracentral lobule	278	0.00728	3.75	-2	-34	50
	Misophonia	Right insula	Right thalamus	271	0.00862	4.46	6	-20	10
	Misophonia	Right insula	Right dlPFC	258	0.0118	3.58	46	20	44
	Misophonia	Right insula	Right dorsomedial parietooc- cipital sulcus	254	0.013	4.11	22	-68	28
	Misophonia	Right insula	Left thalamus	220	0.0306	4.12	-10	-8	-2
	Misophonia	Right insula	Right caudate	220	0.0306	4.62	14	8	18
	Misophonia	Right insula	Left dlPFC	217	0.0331	3.92	-44	6	38
	Misophonia > Control	Right insula	Right cuneus gyrus	644	0.000007	4.46	2	-76	0
	Misophonia	Right insula	Right thalamus	406	0.000627	4.27	10	-20	12

in misophonic distress [56–58], the increased involvement of the dmPFC in the misophonia group may reflect greater externalized appraisal of misophonic reactions than in the clinical control group.

Conversely, the absence of vmPFC and dlPFC differences in our sample, despite prior reports of altered activity and connectivity in these regions when

comparing individuals with misophonia to non-clinical controls, suggests that vmPFC/dlPFC function and their connectivity with the insula may reflect transdiagnostic mechanisms of emotion dysregulation (which are likely to be at play in misophonia) rather than processes unique to misophonia. Given our finding that increased insula-PFC connectivity is associated with both greater emotion

dysregulation and reduced use of cognitive reappraisal in misophonia, interventions that develop cognitive reappraisal skills to reduce misophonic distress appear to be a promising next step in intervention development. Additional research is needed to better understand how adults with misophonia appraise misophonic distress and how different PFC subregions contribute to appraisal in this population.

Our secondary goal was to explore neural differences between groups during the downregulation of emotional distress in response to misophonic trigger sounds. In the misophonic group, compared with clinical controls, we found increased connectivity between the left insula and the left dACC when downregulating, versus listening to misophonic trigger sounds, highlighting a possible increased involvement of the salience network in misophonia during regulation. The dACC is critical for motivating emotion regulation by monitoring contexts that influence action choice [53] and, along with the mPFC, contributes to the appraisal of negative emotion [59]. Dysfunction in this circuit during regulation may reflect hyperactive monitoring of auditory stimuli perceived as distressing, leading to ineffective selection of regulatory strategies. Increased activation of regions that function to process basic and higher-order visual features (right cuneus, right middle temporal gyrus, left inferior temporal gyrus), auditory comprehension (left planum temporale), sensory perception (right paracentral lobule and left thalamus) during regulation in the misophonia group compared to clinical controls may indicate that multimodal sensory integration requires greater cognitive resources for adults with misophonia versus clinical controls. When downregulating aversive stimuli, we found, as expected, activation in the emotion regulation network with no differences between groups.

Taken together, our results suggest that misophonia may display triple network instability, as evidenced by insula hyperactivation in response to misophonic trigger sounds and insula-PFC hyperconnectivity associated with the downregulation of misophonic distress in the misophonia group. These findings suggest that misophonia represents a distinct clinical condition warranting formal classification and targeted intervention. Components of these large-scale networks, such as the dmPFC and/or dlPFC, would therefore be candidate targets for future research aimed at developing and optimizing neurostimulation interventions to treat misophonia. We did not find evidence supporting differential prefrontal cortex nor insula activation between groups, suggesting that engagement of neural networks via connectivity between the prefrontal cortex and other emotion regulation regions (i.e., insula) may underlie between-group differences in neural patterns. The uniquely dysfunctional insula functional connectivity patterns in misophonia

relative to clinical controls supports the view that misophonia is an independent disorder. Given that our functional connectivity analyses identify task-related coupling but not directionality, future longitudinal studies are needed to clarify whether aberrant insula functional connectivity is a causal mechanism of misophonia pathophysiology.

We opted to personalize the stimuli included in the imaging experiment to enhance ecological validity. It is possible that, while more closely mimicking the misophonic and aversive sound experience, this design decision could have introduced heterogeneity that, in principle, could reduce internal validity and obscure mechanistic inferences. Nevertheless, misophonia is highly context-dependent [57], and standardized sound sets may fail to elicit the core phenomenon. Personalization, therefore, represents a necessary design choice rather than a methodological weakness. Importantly, several factors mitigate the concern that between-group differences reflect variability in stimulus content rather than underlying neural mechanisms. First, participants explicitly identified the selected sounds as misophonic triggers during the sound task, ensuring that stimuli were valid exemplars of each participant's trigger profile. Second, both groups exhibited comparable variability in the types of sounds chosen (see Supplement), making it unlikely that systematic group differences in the acoustic or semantic properties of the selected sounds drove the observed neural effects. Third, despite the additional variability introduced by personalization, our findings replicate core patterns reported in prior misophonia neuroimaging studies that prioritized standardization [20], further supporting the interpretation that these effects reflect genuine diagnostic differences rather than idiosyncratic stimulus features. In this light, the fact that robust group differences emerged despite increased stimulus variability strengthens, rather than weakens, our confidence that the results capture meaningful neural signatures of misophonia.

One limitation of the current study is that misophonic trigger sounds were drawn from standard sound databases and the prior literature. Although sound sets were personalized based on the level of distress specific to each participant, current misophonia research highlights the importance of social context in sound processing [57]; it is, therefore, unclear whether neural correlates of misophonic sound processing may differ based on additional contextual factors, such as the presence of visual stimuli that accompany common auditory triggers (i.e., visualizing mouth movement in addition to hearing chewing sounds) or the closeness of the relationship to the person producing the trigger sound. A second limitation is the low racial and gender diversity in our sample, which constrains the generalizability of our findings. Third, missing

fMRI data from a subset of the sample may have reduced statistical power in detecting neuroimaging effects; along this line, while the study was adequately powered based on expected effect sizes derived from previous neuroimaging comparisons between adults with misophonia ($n = 22$) and a non-clinical control group ($n = 20$), it is possible that comparing adults with misophonia ($n = 27$) to another clinical group ($n = 27$) may require a larger sample size for adequate detection power given the clinical overlap in emotion dysregulation. Future studies should therefore replicate our findings in larger samples. Fourth, the clinical group had higher emotion dysregulation than the misophonia group, and, as a result, the observed differences could also reflect differences in emotion dysregulation between groups. Additional research should match clinical and misophonic participants on emotion dysregulation severity and replicate these analyses. Fifth, participants with misophonia rated sounds marked as misophonic as more aversive than participants in the control group. While this validates our experimental paradigm, the observed differences may stem from differences in affect intensity in response to these sounds. Future studies should better match sounds for control samples. Sixth, exploratory post-hoc tests examining the relationships between clinical measures and neural changes in a-priori ROIs during contrasts of interests were uncorrected and should therefore be interpreted as preliminary. Finally, although this study was designed to examine differences between two clinical groups (misophonia and transdiagnostic emotion dysregulation), the absence of a group without a psychiatric history limits our ability to replicate previously reported between-group differences in brain activation in adults with misophonia and in non-clinical adults [20, 21].

This study has provided essential insights into misophonia by highlighting brain regions and circuitry that may be effective targets for neuroscience-based therapeutic interventions, using behavioral, device-based, pharmacological, brain stimulation, or other treatment modalities. We have demonstrated that while some neural patterns during reactivity and regulation overlap across groups, other patterns exhibit differential neural activation and functional connectivity patterns in participants with misophonia compared to non-misophonic controls characterized by transdiagnostic emotion dysregulation. These differences are observed particularly in brain regions and circuits involved in reappraisal when participants are asked to downregulate the emotional distress elicited by misophonic cues. We have also shown that these altered activation and connectivity patterns are associated with emotion dysregulation in adults with misophonia. Our results suggest that aberrant activation and connectivity in the insula may lead to imbalances in the cognitive control network, which may contribute to

dysfunctional emotional and sensorimotor processing of trigger sounds in participants with misophonia. Research using non-invasive neuromodulatory interventions to target the frontoparietal network to boost its cognitive control function is ongoing; critical future directions of this line of work include characterizing how brain activation and brain connectivity in misophonia change after therapeutic interventions, as well as whether any post-intervention neurobiological changes are associated with reduced emotional distress and/or improved regulation.

Abbreviations

fMRI	functional magnetic resonance imaging
DSM-V	Diagnostic and Statistical Manual of Mental Disorders, 5th Edition
dmPFC	dorsomedial prefrontal cortex
dACC	dorsal anterior cingulate cortex
vlPFC	ventrolateral prefrontal cortex
dlPFC	dorsolateral prefrontal cortex
ACC	Anterior cingulate cortex
IPC	Inferior parietal cortex
OFC	Orbitofrontal cortex
AIC	Anterior insular cortex
vmPFC	ventromedial prefrontal cortex
MCC	Midcingulate cortex
PMv	Ventral premotor cortex
SMA	Supplementary motor area
STC	Superior temporal cortex
ROI	Region of interest
DEERS	Difficulties in Emotion Regulation Scale
SUDS	Subjective units of distress
SCID-5	Structured Interview for DSM-5 Disorders
rMT	resting motor threshold
rTMS	repetitive transcranial magnetic stimulation
MQ	Misophonia Questionnaire
DMQ	Duke Misophonia Questionnaire
ERQ	Emotion Regulation Questionnaire
GLM	General linear model
TFCE	Threshold-free cluster enhancement
PPI	Psychophysiological interaction
MMANOVA	Mixed-effects hierarchical linear model

Supplementary Information

The online version contains supplementary material available at <https://doi.org/10.1186/s12888-026-08331-3>.

Supplementary Material 1

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Author contributions

ADN contributed to funding acquisition, study conceptualization, project administration, methodology, formal analysis, data curation, supervision, writing of the original draft, and review and editing of the final draft. NG contributed to formal analysis, data curation, writing of the original draft, and review and editing of the final draft. JLG contributed to study conceptualization, formal analysis, methodology, writing of the original draft, and review and editing of the final draft. NBP contributed to the methodology, review, and editing of the final draft. JYC contributed to the methodology, review, and editing of the final draft. MZR contributed to funding acquisition,

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Data availability

The datasets supporting the conclusions of this article are available from the corresponding author upon reasonable request.

Declarations

Human ethics and consent to participate

This study was pre-registered at clinicaltrials.gov (Clinical Trials ID: NCT04348591; date of registration: 4/13/2020) and ran between October 2020 and May 2022. The study was submitted to and approved by the Duke University Health System Institutional Review Board (Reference ID: Pro00103863-INIT-1.0). Informed consent to participate was obtained from all the participants in the study. This study adhered to the Declaration of Helsinki.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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