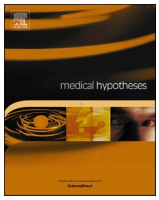
Medical Hypotheses 206 (2026) 111840

Contents lists available at ScienceDirect

Medical Hypotheses

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



Reducing hyper mirroring in misophonia: A proposal for cortico-cortical paired associative stimulation (ccPAS) as a potential intervention for treatment

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ARTICLE INFO

Keywords:
Misophonia
Treatment
TMS
ccPAS
Mirror-system

ABSTRACT

Misophonia, a condition characterized by intense emotional and physiological reactions to specific human-generated sounds, was recently proposed as a disorder of hyper mirroring, in which there is an over-representation of the actions of others. A recent study used rTMS to indirectly reduce the hyperactivity in the anterior insula of people with misophonia, leading to a modest reduction in misophonic distress. But further research is needed to optimize TMS for greater efficacy. Recent TMS studies using a paired associative approach have shown that it could be used to reduce automatic mirroring in healthy controls. We propose the use of ccPAS for reducing the aberrant "hyper" connectivity of the motor cortex, suggested to be associated with mirroring, found in misophonia which is directly accessible to TMS. We hope this theoretically driven neuromodulation approach can take advantage of recent advances in brain stimulation and address the need for developing an effective evidence-based treatment for misophonia.

Main

There is a pressing need to develop an effective treatment for misophonia, a condition in which people have extreme distress towards everyday sounds – particularly orofacial sounds generated by other people, like eating, chewing – known as trigger sounds [1]. This causes those affected to avoid social situations in which they could be triggered that occur at home, work, or in the community. Thus, they experience significant loneliness and isolation even within their home. Currently there is no consensus on an effective evidence-based treatment for misophonia. Based upon evidence from two recent non-invasive brain stimulation studies [2,3], as well as imaging and behavioural data in people with misophonia, we propose using cortico-cortical paired associative stimulation (ccPAS) as a potential therapeutic option for misophonia.

Using functional Magnetic Resonance Imaging (fMRI), we [1] reported stronger activation in misophonia subjects, specifically in response to trigger sounds, in an area of motor cortex that is known to be involved in representing orofacial muscles (e.g., lip, tongue, and jaw movement in chewing action). Secondly, this study also reported increased functional connectivity between this part of the motor cortex and planum temporale auditory cortex in misophonia subjects during perception of sound. Lastly, the study also found stronger resting state fMRI functional connectivity between the putative orofacial motor cortex and auditory and visual cortices in misophonia subjects. Recent evidence further confirms that motor cortex is activated during action observation in social contexts [4] in addition to further evidence for involvement of orofacial motor cortex in misophonia [5].

The above findings led to the development of a model of misophonia based on involuntary 'mirroring' of the action of others, where experiencing (e.g., hearing or seeing) trigger events activate the part of the brain in people with misophonia as if they are executing the movements themselves. In this model, people with misophonia experience involuntary overactivation of the 'mirror' system which can lead to either a sense of loss of control or interference in current goals and actions, resulting in extreme anger or irritation. A recent large-scale survey [6]

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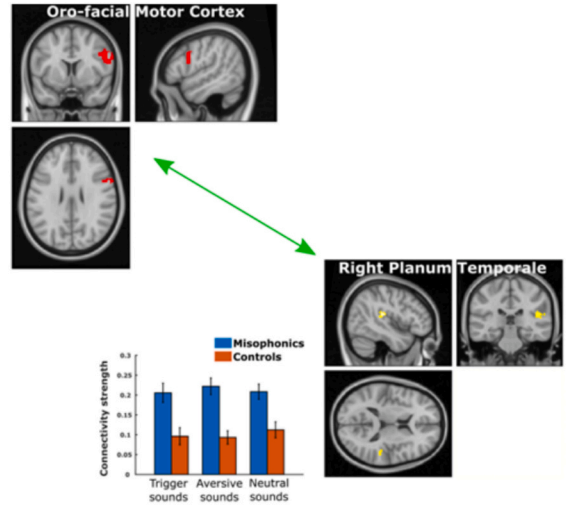
https://doi.org/10.1016/j.mehy.2025.111840
Received 8 August 2025; Received in revised form 22 November 2025; Accepted 23 November 2025
Available online 24 November 2025

established the role of mimicry in misophonia, in particular its high prevalence, correlation with misophonia severity, and the role of overt mimicry in providing relief. Viewed within the context of social cognition, mimicry can often facilitate liking between individuals, increase social cohesion, and may reflect increased motor empathy (i.e., increased representations of others' actions) [7]. This therefore lends support to the role of a motor mirroring system in misophonia and suggests that sensorimotor associative learning, which can involve pairing electrical or magnetic stimulation with motor movements and is known to reconfigure the mirror neuron system [8], may be a feasible basis for treatment of misophonia. There is an alternative model of misophonia which proposes that misophonia is a disorder of sound emotion processing, but it does not explain the urge to imitate the source of the trigger nor the involvement of brain regions responsible for motor movements. We therefore chose the hyper mirroring model for this proposal, based on the evidence that this system can be disrupted and may therefore reduce the negative affect and distress in people with misophonia (Fig. 1).

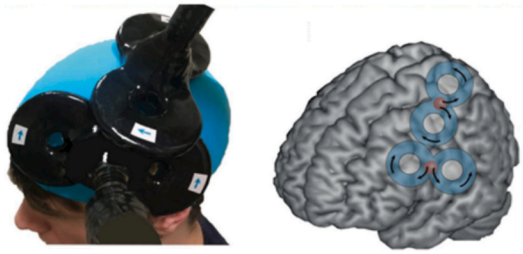
Recently, Neacsiu, Beynel [2] demonstrated that TMS may be an effective treatment approach for misophonia. Here, the authors targeted repetitive transcranial magnetic stimulation (rTMS) to the prefrontal cortex to indirectly reduce hyperactivity in the anterior insula of people with misophonia, leading to a reduction in misophonic distress. This was particularly evident when combined with cognitive restructuring through emotion regulation, though further research is needed to determine how TMS may be optimised for greater efficacy.

The above imaging data, behavioural data and stimulation study in misophonia support the idea of attempting a different stimulation study to develop a treatment approach. A recent social cognition study showed that imitative behaviour could be reduced using ccPAS by decreasing effective connectivity of the mirroring system [3]. PAS is a network-based TMS protocol based on Hebbian spike-timing dependent plasticity that offers spatiotemporal specificity to modulate brain networks, which can be used to alter a patient's pathological network [10,11]. Recently visuo-motor PAS studies [12–15] have shown their utility to alter network connectivity in the action observation network. Turrini, Fiori [3] used ccPAS to alter effective connectivity between regions of motor cortex involved in representing action observation. They showed that enhancing (or weakening) the connectivity between the ventral premotor cortical area (PMv) and the primary motor cortex (M1) increases (or decreases) the tendency to automatically imitate the behaviour of others. They also showed that enhancing supplementary motor area (SMA) connectivity with M1 induces a greater ability to reduce imitation when it is inappropriate to the context. This provides us with a promising avenue to treat misophonia when considered as a disorder of "hyper" mirroring.

Given the imaging and behavioural data implicating the important involvement of the motor cortex in misophonia, we propose to employ ccPAS network-based TMS to efficiently manipulate brain connectivity [3] in people with misophonia. This approach would involve decreasing effective connectivity between orofacial motor cortex (PMv) and M1, achieved by activating the post-synaptic area (M1) before a pre-synaptic one (PMv), which is known to produce long term depression [16]. The approach used in [3] targets alteration of overall connectivity without reference to any particular stimulus. In the context of misophonia, an alternative would involve using ccPAS stimulation while people with misophonia listen to their triggering sounds. This approach may enable sufferers to be less sensitive to interference in their everyday tasks and current goals and consequently reduce distress resulting in some relief. Here, the proposal involves reducing the "hyper" connectivity of the mirroring system which is directly accessible to TMS compared to anterior insula, as targeted indirectly by [2].



(A) The "hyper-mirroring" model (The Problem)



(B) The ccPAS intervention (The Solution)

(C) Experimental design and treatment groups (The Study)

Step 1: Baseline Assessment (Pre-Intervention)

- fMRI (resting-state connectivity)
- Questionnaires (misophonia severity)
- Cortico-spinal excitability during action observation (motor evoked potentials)
- Clinical rating (urge to mimic)
- Distress to triggers

Step 2: Randomization

- Group 1 (main treatment): ccPAS targeting PMv (pre-synaptic) → M1 (post-synaptic)
- Group 2 (alternative treatment): ccPAS targeting sensory cortex (auditory / visual – pre-synaptic) → mirror system (post-synaptic)
- Control group: delayed treatment

Step 3: Intervention

- ccPAS treatment Sessions (consecutive weekdays for a week)
- Reduce connectivity – stimulate post synaptic region before pre-synaptic region

Step 4: Evaluation (Post-Intervention)

- Repeat all baseline assessments

Hypothesized Outcomes:

- Reduced hyper-connectivity
- Reduced motor resonance
- Reduced misophonic distress

Fig. 1. ccPAS based treatment for misophonia. (A) The "hyper-mirroring" model (The Problem) panel showing results published in [1]. (B) The ccPAS intervention (The Solution) panel showing TMS coil configuration from [9]. (C) Experiment design and treatment groups (The Study) consisting of step 1 – Baseline assessments (pre-intervention), step 2 – Randomization, step 3 – Intervention, step 4 – Evaluation (post-Intervention), Hypothesized outcomes.

Though hearing is the dominant form of triggering, any modality can act as a trigger. Thus, this indicates that a fundamental pathological mechanism might not be in the sensory cortex per se but rather in the communication with its motor representation – as is supported by a general lack of difference in fundamental sound processing in the auditory cortices of people with misophonia (e.g. [1,5]). We therefore plan to first test the therapeutic effect of reducing effective connectivity between PMv and M1 for providing distress reduction in people with misophonia. In another treatment group, we plan to determine the outcome of reducing effective connectivity between primary auditory cortex and/or primary visual cortices (depending on the dominant trigger stimulus in each individual) with the mirror neuron system, to reduce motor resonance in the first place instead of reducing its after effect i.e., the urge to imitate.

Operationalising and Testing Motor Resonance: In this proposal, motor resonance is defined as the automatic activation of the observer's motor system during perception of others' actions, reflected in motor-cortical dynamics. Consistent with established literature on the mirror neuron system and PAS-based modulation of action observation networks, we will quantify motor resonance using three converging measures.

(i) Neuroimaging index: Resting-state fMRI will be used to quantify functional connectivity between PMv → M1 or sensory cortices (auditory/visual) → orofacial motor cortex. Reduced connectivity after ccPAS will indicate reduced motor resonance.
(ii) Neurophysiological index: We will measure corticospinal excitability during action observation using single-pulse TMS over M1, assessing whether observed actions modulate motor-evoked potentials (MEPs), following protocols used in visuo-motor PAS research [14,15].
(iii) Clinical/phenomenological index: Participants will rate their urge to imitate or mimic the trigger source (e.g., chewing motion), which has been shown to correlate with misophonia severity and mimicry prevalence [6].

Together, these measures allow us to directly test whether ccPAS produces a measurable reduction in motor resonance, thereby linking changes in mirror-system connectivity to behavioural and clinical outcomes.

Hypothesis: We hypothesize that performing ccPAS on people with misophonia, by activating post-synaptic area (M1) before a pre-synaptic one orofacial motor cortex (PMv), would decrease the pathological hyper connectivity in this action observation network reported in people with misophonia previously [1] due to Hebbian spike timing dependent plasticity mechanisms between M1 and PMv. This would in turn decrease misophonic distress based on disrupting a hyperactive mirroring circuit.

The stimulation parameters of our study will be similar to existing ccPAS studies in motor cortex [2,3]. Based on the effect size seen in [3], we plan to have 20 subjects in treatment and control/sham groups (including participants with misophonia in a delayed treatment protocol for ethical considerations). The effectiveness of the proposed therapeutic intervention will be evaluated after each ccPAS session using resting state fMRI, to assess if the pathological hyper connectivity in the action observation network has reduced. Furthermore, the functional outcomes will be evaluated by self-reported distress in response to a standardized trigger sound paradigm, measured pre- and post-intervention. Finally, misophonia symptom severity will be evaluated using misophonia questionnaires before the start and at the end of treatment. The outcomes of the two treatment groups will also be compared directly against each other to assess the efficacy of the ccPAS protocols in providing therapeutic relief. We expect that the second treatment group, because of the involvement of the sensory system identified specific to their misophonia, may have a misophonia-specific reduction in mirroring whereas the first treatment group will have a more generic reduction in automatic mirroring. While the main hypothesis of the current proposal is that there will be a reduction in connectivity of the mirror neuron system (PMv) during rest in misophonia participants relative to their pre-treatment baseline, it is possible that we might need to further adapt the ccPAS method for increased efficacy or trigger-sound specificity through concurrent presentation of subject-specific misophonia trigger sounds during neurostimulation.

Network-based TMS is used to treat a variety of psychiatric [10] and neurological disorders. TMS is usually well tolerated, with minimal side effects, and does not require sedation or surgery. Patients are fully awake during the stimulation, which typically takes 10–30 min and is given over consecutive weekdays for a week. Given these features of TMS, one can be hopeful of the potential for ccPAS [16] for treating misophonia.

Declaration for consent/ethics approval statement

This paper presents a theoretical framework and does not involve human participants or data collection. Therefore, formal ethics approval will be obtained from the relevant institutional review board before data collection. The study adheres to ethical principles of research integrity and transparency.

CRediT authorship contribution statement

Pradeep Dheerendra: Writing – review & editing, Writing – original draft, Visualization, Conceptualization. **Sukhbinder Kumar:** Writing – review & editing. **Phillip E. Gander:** Writing – review & editing. **Joel I. Berger:** Writing – review & editing. **Lars F. Muckli:** Writing – review & editing.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Sukhbinder Kumar, Phillip E Gander, Joel I Berger reports financial support was provided by Misophonia Research Fund. Lars F Muckli reports financial support was provided by Biotechnology and Biological Sciences Research Council. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgement

S.K, P.E.G., and J.I.B. are funded by the Misophonia Research Fund (REAM Foundation). L.F.M. is funded by Biotechnology and Biological Sciences Research Council (BB/V010956/1).

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