The Brain Basis for Misophonia

Highlights

- Trigger sounds elicit exaggerated response in anterior insula in misophonia
- In misophonia, there is abnormal functional connectivity of anterior insula
- Heightened autonomic responses are mediated by anterior insula in misophonia
- Misophonia is associated with altered interoception

Authors

Sukhbinder Kumar, Olana Tansley-Hancock, William Sedley, ..., Phillip E. Gander, Doris-Eva Bamiou, Timothy D. Griffiths

Correspondence

sukhbinder.kumar@ncl.ac.uk

In Brief

Kumar et al. show that misophonia is associated with abnormal activation, functional connectivity, and structural changes in the brain and heightened autonomic responses of the body.
The Brain Basis for Misophonia

Sukhbinder Kumar,1,2,7* Olan Tansley-Hancock,1 William Sedley,1 Joel S. Winston,2,3 Martina F. Callaghan,2 Micah Allen,2 Thomas E. Cope,1,4 Phillip E. Gander,5 Doris-Eva Bamiou,6 and Timothy D. Griffiths1,2

1Institute of Neuroscience, Medical School, Newcastle University, Newcastle upon Tyne NE2 4HH, UK
2Wellcome Trust Centre for Neuroimaging, 12 Queen Square, London WC1N 3BG, UK
3Institute of Cognitive Neuroscience, 17 Queen Square, London WC1N 3AR, UK
4Department of Clinical Neurosciences, University of Cambridge, Cambridge CB2 0SZ, UK
5Human Brain Research Laboratory, Department of Neurosurgery, The University of Iowa, Iowa City, IA 52242, USA
6UCL Ear Institute, 332 Grays Inn Road, London WC1X 8EE, UK
7Lead Contact
*Correspondence: sukhbinder.kumar@ncl.ac.uk
http://dx.doi.org/10.1016/j.cub.2016.12.048

SUMMARY

Misophonia is an affective sound-processing disorder characterized by the experience of strong negative emotions (anger and anxiety) in response to everyday sounds, such as those generated by other people eating, drinking, chewing, and breathing [1–8]. The commonplace nature of these sounds (often referred to as “trigger sounds”) makes misophonia a devastating disorder for sufferers and their families, and yet nothing is known about the underlying mechanism. Using functional and structural MRI coupled with physiological measurements, we demonstrate that misophonic subjects show specific trigger-sound-related responses in brain and body. Specifically, fMRI showed that in misophonic subjects, trigger sounds elicit greatly exaggerated blood-oxygen-level-dependent (BOLD) responses in the anterior insular cortex (AIC), a core hub of the “salience network” that is critical for perception of interoceptive signals and emotion processing. Trigger sounds in misophonics were associated with abnormal functional connectivity between AIC and a network of regions responsible for the processing and regulation of emotions, including ventromedial prefrontal cortex (vmPFC), postero-medial cortex (PMC), hippocampus, and amygdala. Trigger sounds elicited heightened heart rate (HR) and galvanic skin response (GSR) in misophonic subjects, which were mediated by AIC activity. Questionnaire analysis showed that misophonic subjects perceived their bodies differently: they scored higher on interoceptive sensibility than controls, consistent with abnormal functioning of AIC. Finally, brain structural measurements implied greater myelination within vmPFC in misophonic individuals. Overall, our results show that misophonia is a disorder in which abnormal salience is attributed to particular sounds based on the abnormal activation and functional connectivity of AIC.

RESULTS AND DISCUSSION

fMRI data were acquired in 20 misophonic and 22 age- and sex-matched controls while they listened to a set of three sounds: trigger sounds (which evoke a misophonic reaction in misophonic individuals; e.g., eating, breathing sounds), unpleasant sounds (which are perceived to be annoying by both groups but do not evoke misophonic distress; e.g., baby cry, a person screaming), and neutral sounds (e.g., rain). After listening to each sound, subjects rated (1) how annoying the sound was (both groups) and (2) how effectively the sound triggered a typical misophonic reaction (misophonic group only) or how anti-social (in the sense the subject would not like to be in the environment in which the sound is produced) the sounds were (control group only). Behavioral responses, galvanic skin response (GSR) and heart rate (HR), were acquired during the acquisition of fMRI data (see Figure 1A for a schematic of the paradigm). Whole-brain structural MRI data were acquired as multi-param-eter maps (MPMs) [9] to measure myelination content, water, and iron levels.

Behavioral data (Figure 1B) showed that trigger sounds evoked misophonic distress in misophonic subjects, whereas the unpleasant sounds, although annoying, did not produce a misophonic reaction. There was no difference between the misophonic distress ratings of trigger sounds by the misophonic group and annoyance ratings of unpleasant sounds by the control group. It is likely, however, that the two groups used different subjective scales while rating the sounds. Random-effects analysis of fMRI data using the general linear model (GLM) [10] with group (two levels) and sound type (three categories) as factors demonstrated an interaction in the anterior insular cortex (AIC) bilaterally (Figure 2A; further regions are listed in Table S1). Further analysis showed that the interaction in AIC was driven by greater activation in misophonic subjects compared to control subjects in response to trigger sounds (see Figure 2B and Figure S1 for confirmatory plots; see also Figure S2). Significant activation differences between misophonic and control subjects did not occur to unpleasant or neutral sounds. Activity in both the left and right AIC varied linearly with the subjective rating of misophonic distress in the misophonic group, as shown in confirmatory plots in Figure 2C. A large body of evidence [11] implicates AIC in subjective feelings associated with emotions, including anger. Functionally, AIC is known to be a key node of...
the salience network \[12\], an intrinsic large-scale brain network for detecting and orienting attention toward stimuli that are behaviorally relevant and meaningful for an individual. Specific hyperactivity in AIC to trigger sounds supports the hypothesis that misophonic subjects assign aberrantly higher salience to these sounds.

Having identified AIC as a key region that differentiates trigger sounds in misophonic participants, we sought to explore its stimulus-dependent connectivity profile to establish whether there are alterations at the network level that are specific to misophonia. Using left AIC as a seed region, we analyzed its stimulus-dependent connectivity in the two groups. Greater functional connectivity of AIC for misophonic subjects was observed in a network of brain regions comprising the ventromedial prefrontal cortex (vmPFC), posteromedial cortex (PMC; posterior cingulate and retrosplenial cortex), hippocampus, and amygdala (Figure 3A). This increased functional connectivity was specific to trigger sounds: no significant differences in connectivity were observed for unpleasant sounds. Importantly, the functional connectivity pattern between the two groups for the same sounds was not only different quantitatively but also qualitatively: whereas the connectivity to vmPFC is positive (with respect to connectivity for neutral sounds) in misophonic subjects, the connectivity for controls for the same set of sounds is negative. Analysis of functional connectivity of right AIC also showed trigger-sound-specific increased connectivity to vmPFC and PMC (Figure 3A; functional connectivity to amygdala and hippocampus was also observed but at a slightly relaxed threshold). The vmPFC and PMC together form core parts of the default mode network (DMN) \[13\] (see Figure 3B for overlap between the DMN and the functional connectivity network of AIC), which is activated when subjects are engaged in internally directed thoughts and retrieval of memories \[14\] and is deactivated when attention is directed to external stimuli. Greater coupling of AIC with the DMN suggests that misophonic subjects, on hearing trigger sounds, are unable to “disengage” AIC from the DMN, which entails memories and contextual associations of trigger sounds to bear on the activation of AIC. This is also consistent with a recent study \[15\] using multivariate pattern classification, which showed that patterns of activity in vmPFC and PMC were most informative in distinguishing different types of emotions. Distinct functional connectivity of AIC to vmPFC and PMC in misophonics and controls for the same sounds suggests that these regions play a crucial role in instantiating different emotional responses for the trigger sounds in the two groups. This atypical functional connectivity could, therefore, underlie the abnormal activation of AIC and the aberrant salience assigned to trigger sounds by the misophonic group.

Because misophonia symptoms start early in life (mean age of onset is \(\sim\)12 years and can be as early as 5 years \[1\]), we also

---

**Figure 1. Experimental Paradigm and Subjective Ratings**

(A) fMRI paradigm: a standard block design was used in which sounds were presented for 15 s. After every sound, subjects gave two ratings on a scale from 1 to 4 with a button press for (1) how annoying the sound was and (2) how effective the sound was in triggering misophonic reaction (misophonia group) or how antisocial the sound was (control group). fMRI data were acquired continuously with a repetition time (TR) of 3.12 s. GSR and HR were also monitored throughout the experiment.

(B) Subjective ratings: (i) misophonic distress rating of three types of sounds by misophonic group; (ii) antisocialness rating of sounds (control subjects); and (iii) annoyance rating of sounds by both groups. Misophonic subjects rated the trigger sounds as evoking greater misophonic reaction compared to unpleasant (\(p < 0.001\)) and neutral sounds (\(p < 0.001\)). Unpleasant sounds were still perceived to be annoying (\(p < 0.001\) compared to neutral sounds) by the misophonic subjects, demonstrating a dissociation between general annoyance and misophonic reaction. See also Figure S4 for subjective scores on body perception. Data are represented as mean (±SEM).
Figure 2. Group-Level, Random-Effects GLM Analysis of fMRI Data

The GLM was modeled as a factorial design with group (two levels) and sound types (three levels) as factors.

(A) Statistical parameter maps (SPMs) overlaid on a standard MNI-152 template brain for the critical interaction between the two factors (group and sound type) thresholded at \( p = 0.05 \) family-wise error (FWE) corrected for whole-brain volume. The effect is maximal in AIC (bilateral) with maxima at MNI coordinates \((-41, 6, 0)\).

(B) Confirmatory plots of activity averaged over clusters in AIC (see also Figures S1 and S2 and Table S1) show that the interaction effect was driven by higher activity for trigger sounds in misophonic subjects compared to controls.

(C) Confirmatory plots of activity in AIC with misophonic ratings in misophonic subjects. Data in (B) and (C) show mean (± SEM).
Figure 3. Functional Connectivity and Structural Data Analysis

(A) Left AIC was taken as a seed region and its functional connectivity to all voxels of the brain was analyzed. The figure illustrates those brain areas that show greater connectivity for trigger sounds (compared to neutral sounds) in misophonic subjects (compared to controls). The four areas that survive the threshold are (1) PMC (posterior cingulate cortex [PCC]/precuneus), (2) vmPFC, (3) hippocampus, and (4) amygdala. The bar chart for each region shows confirmatory plots of connectivity for trigger and unpleasant sounds with respect to neutral sounds. Displayed connectivity strengths are cluster thresholded at p < 0.05 with cluster-forming threshold at p < 0.001 (see Figure S3 for functional connectivity of right AIC and overlap of the connectivity network with the default mode network).

(B) (i) indicates TMaps at x = 3, y = 44, and z = 2 for left and right lateral views. (ii) indicates MT Saturation (p,u) for misophonic controls.
predicted that there would be brain structural differences in misophonic subjects compared to controls. We created whole-brain structural maps of magnetization transfer (MT) saturation that reflects myelination in brain gray matter. For significance testing, we limited our search to brain areas that showed higher MT saturation, which reflects higher myelination, compared to controls in vmPFC. This change suggests a possible structural basis for the altered functional connectivity to vmPFC observed in misophonic subjects.

After identification of functional and structural changes in the brain, we next determined physiological responses of the body (B) Brain structural changes in misophonia. Misophonic subjects show higher MT saturation, which reflects higher myelination, compared to controls in vmPFC. When corrected for multiple comparisons (p < 0.05 FWE corrected for brain areas that show higher functional connectivity in misophonic to trigger sounds; i.e., the functional network shown in (A) along with the seed region AIC), 15 voxels of vmPFC with maxima at (−3, 44, −2) survive the correction. For display purposes in the figure, a threshold of p < 0.001 uncorrected is used. p.u., percent units. Data in bar charts show mean (± SEM).
and their driving sources in the brain. We measured GSR and HR while subjects listened to three sets of sounds in the MRI scanner. Trigger sounds evoked greater GSR and HR responses in misophonic subjects than control subjects (Figure 4A). Physiological responses were sustained throughout the duration of sound presentation and were specific to trigger sounds, with no difference in GSR or HR response between the two groups for unpleasant and neutral sounds. The heightened trigger-specific autonomic responses we observed are consistent with the strong tendency of misophonic subjects to escape from the environment of trigger sounds [1, 2] or experience strong anxiety and anger if unable to escape (fight/flight response).

What is the brain source(s) of these heightened autonomic responses in misophonia? To answer this, we used mediation analysis [16], which aims to test whether a relation from variable X (group membership; i.e., misophonic or control) to Y (GSR or HR) could be explained (mediated) by a third variable, M (brain activation). A significant mediation implies that there is an indirect path from X to M to Y and that what is explained by group membership is what is explained by brain activity [21, 22]. Over the last decade, there has been a growing recognition that interoception (perception of internal bodily states) can influence the salience and experience of emotions associated with a stimulus [17–20]. Interestingly, AIC is the key brain structure that integrates ascending visceral inputs from the body with external sensory inputs. In accordance with this, atypical interoception and activation in AIC have been shown to underlie a number of social-emotional disorders [21, 22].

Conclusions

Overall, our data show that for misophonic subjects, trigger sounds cause hyperactivity of AIC and an abnormal functional connectivity of this region with medial frontal, medial parietal, and temporal regions; that there is abnormal myelination in medial frontal cortex that shows abnormal functional connectivity to AIC; and that the aberrant neural response mediates the emotional coloring and physiological arousal that accompany misophonic experiences. Together, our data suggest that abnormal salience attributed to otherwise innocuous sounds, coupled with atypical perception of internal body states, underlies misophonia. With the available data, it is not possible to decide whether misophonia is a cause or consequence of atypical interoception, and further work is needed to delineate the relation between the two.

Misophonia does not feature in any neurological or psychiatric classification of disorders; sufferers do not report it for fear of the stigma that this might cause, and clinicians are commonly unaware of the disorder. This study defines a clear phenotype based on changes in behavior, autonomic responses, and brain activity and structure that will guide ongoing efforts to classify and treat this peculiar disorder.

SUPPLEMENTAL INFORMATION

Supplemental Information includes Supplemental Experimental Procedures, four figures, one table, and one questionnaire and can be found with this article online at http://dx.doi.org/10.1016/j.cub.2016.12.048.

AUTHOR CONTRIBUTIONS

T.D.G. would like to thank the Wellcome Trust for the financial support of this project (grants WT091681MA and WT106964). J.S.W. holds a Wellcome Trust Postdoctoral Training Fellowship for MB/PhD Graduates (grant 095939). The Wellcome Trust Centre for Neuroimaging is supported by core funding from the Wellcome Trust (grant 091593). This study was approved by the UCL ethics committee.

Received: September 20, 2016
Revised: November 21, 2016
Accepted: December 22, 2016
Published: February 2, 2017

REFERENCES

1. Kumar, S., Hancock, O., Cope, T., Sedley, W., Winston, J., and Griffiths, T.D. (2014). Misophonia: a disorder of emotion processing of sounds. J. Neurol. Neurosurg. Psychiatry 85, e3.
2. Edelstein, M., Brang, D., Rouw, R., and Ramachandran, V.S. (2013). Misophonia: physiological investigations and case descriptions. Front. Hum. Neurosci. 7, 296.
3. Schröder, A., Vulink, N., and Denys, D. (2013). Misophonia: diagnostic criteria for a new psychiatric disorder. PLoS ONE 8, e54706.
4. Schröder, A., van Diepen, R., Mazaheri, A., Petropoulos-Petalas, D., Soto de Amesti, V., Vulink, N., and Denys, D. (2014). Diminished N1 auditory evoked potentials to oddball stimuli in misophonia patients. Front. Behav. Neurosci. 8, 123.
5. Jastreboff, M.M., and Jastreboff, P.J. (2001). Components of decreased sound tolerance: hyperacusis, misophonia, phonophobia. J. Speech, Language, and Hearing Research 44, 189–199.
6. Krauthamer, J.T. (2013). Sound-Rage: A Primer of the Neurobiology and Psychology of a Little Known Anger Disorder (Chalcedony Press).
7. Hadjipavlou, G., Baer, S., Lau, A., and Howard, A. (2008). Selective sound intolerance and emotional distress: what every clinician should hear. Psychosom. Med. 70, 739–740.
8. Ferreira, G.M., Harrison, B.J., and Fontenelle, L.F. (2013). Hatred of sounds: misophonic disorder or just an underreported psychiatric symptom? Ann. Clin. Psychiatry 25, 271–274.
9. Weiskopf, N., Suckling, J., Williams, G., Correa, M.M., Inkster, B., Tat, R., Ooi, C., Bullmore, E.T., and Lutti, A. (2013). Quantitative multi-parameter
mapping of R1, PD(*), MT, and R2(*) at 3T: a multi-center validation. Front. Neurosci. 7, 95.

10. Friston, K.J., Holmes, A.P., Worsley, K.J., Poline, J.P., Frith, C.D., and Frackowiak, R.S.J. (1994). Statistical parametric maps in functional imaging: a general linear approach. Hum. Brain Mapp. 2, 189–210.

11. Craig, A.D. (2009). How do you feel—now? The anterior insula and human awareness. Nat. Rev. Neurosci. 10, 59–70.

12. Seeley, W.W., Menon, V., Schatzberg, A.F., Keller, J., Glover, G.H., Kenna, H., Reiss, A.L., and Greicius, M.D. (2007). Dissociable intrinsic connectivity networks for salience processing and executive control. J. Neurosci. 27, 2349–2356.

13. Raichle, M.E., MacLeod, A.M., Snyder, A.Z., Powers, W.J., Gusnard, D.A., and Shulman, G.L. (2001). A default mode of brain function. Proc. Natl. Acad. Sci. USA 98, 676–682.

14. Huijbers, W., Pennartz, C.M., Cabeza, R., and Daselaar, S.M. (2011). The hippocampus is coupled with the default network during memory retrieval but not during memory encoding. PLoS ONE 6, e17463.

15. Saarimaki, H., Gotoupolous, A., Jäääskeläinen, I.P., Lampinen, J., Vuilleumier, P., Hari, R., Sams, M., and Nummenmaa, L. (2016). Discrete neural signatures of basic emotions. Cereb. Cortex 26, 2563–2573.

16. Wager, T.D., Waugh, C.E., Lindquist, M., Noll, D.C., Fredrickson, B.L., and Taylor, S.F. (2009). Brain mediators of cardiovascular responses to social threat: part I: reciprocal dorsal and ventral sub-regions of the medial prefrontal cortex and heart-rate reactivity. Neuroimage 47, 821–835.

17. Craig, A.D. (2007). Interception and emotion: a neuroanatomical perspective. In Handbook of Emotions, M. Lewis, J.M. Haviland-Jones, and L.F. Barret, eds. (Guilford Press), pp. 272–290.

18. Wiens, S. (2005). Intercognition in emotional experience.Curr. Opin. Neurol. 18, 442–447.

19. Seth, A.K. (2013). Intercognitive inference, emotion, and the embodied self. Trends Cogn. Sci. 77, 565–573.

20. Garfinkel, S.N., and Critchley, H.D. (2013). Intercognition, emotion and brain: new insights link internal physiology to social behaviour. Commentary on: “Anterior insular cortex mediates bodily sensibility and social anxiety” by Terasawa et al. (2012). Soc. Cogn. Affect. Neurosci. 8, 231–234.

21. Paulus, M.P., and Stein, M.B. (2010). Intercognition in anxiety and depression. Brain Struct. Funct. 214, 451–463.

22. Garfinkel, S.N., Tiley, C., O’Keefe, S., Harrison, N.A., Seth, A.K., and Critchley, H.D. (2016). Discrepancies between dimensions of intercognition in autism: implications for emotion and anxiety. Biol. Psychiat. 114, 117–126.

23. Seth, A.K., and Friston, K.J. (2016). Active intercognitive inference and the emotional brain. Philos. Trans. R. Soc. Lond. B Biol. Sci. 371, 20160007.

24. Smith, R., and Lane, R.D. (2015). The neural basis of one’s own conscious and unconscious emotional states. Neurosci. Biobehav. Rev. 57, 1–29.

25. Miller, L.C., Murphy, R., and Buss, A.H. (1981). Consciousness of body: private and public. J. Pers. Soc. Psychol. 47, 397–406.