Sound-evoked pupil dilation quantifies misophonic symptoms

J.W. de Gee[1,2,@], L. Alonso-Marmelstein[3], K. Schwarz-Roman[3] & R. Rouw[2,3,@]

[1]Swammerdam Institute for Life Sciences, [2]Amsterdam Brain & Cognition, [3]Department of Psychology, University of Amsterdam, Amsterdam, NLD.

@ = Address correspondence to: j.w.degee@uva.nl and R.Rouw@uva.nl

ABSTRACT

Misophonia is a debilitating disorder where seemingly innocuous sounds (often human made, such as chewing or throat clearing) evoke intense negative cognitive, emotional and physical 'fight-or-flight' responses. Recent studies reported alarmingly high prevalence across different countries and population characteristics, revealing an urgent need for a better understanding of this condition as well as improved measurement and diagnostic tools. Firstly, current misophonia symptom measurements rely on (subjective) self-reports, and different studies employ various diagnostic approaches and cut-off scores. There is an urgent need for a complementary (objective) psychophysiological measurement tool. Secondly, the role of 'mild' or 'moderate' symptoms are currently topic of debate: are they still manifestations of the misophonic disorder? Here, we employ pupillometry to map out arousal responses to misophonia trigger sounds. We show that (i) pupil dilation can reliably differentiate misophonic responses from responses to generally unpleasant sounds (such as nails on chalk board), (ii) the 'milder cases' of misophonia still show arousal responses characteristic of misophonia, and (iii) pupillometry can even be used to aid diagnosis in a single individual. We conclude that even mild misophonic responses can reliably, objectively and cost-effectively be indexed by pupil-linked arousal.

INTRODUCTION

Individuals with misophonia experience strong negative emotions like rage or disgust in response to everyday, often human-made, sounds (e.g., chewing or throat clearing)[1–4]. The ubiquitous nature of the 'trigger' stimuli, and strength of the misophonic response can lead to severe distress and even suicide ideation[5–7]. Misophonia is a newly defined disorder, quickly gaining scientific attention across scientific disciplines (e.g., audiology, cognitive science, clinical psychology, occupational therapy, psychiatry, and neuroscience)[3,4,8–15]. Despite rapidly advancing research, much remains unknown about the etiology, course, or mechanisms of the condition, leaving open the question why seemingly innocuous daily sounds would evoke such strong aversive ('fight or flight') responses.

The need for a better understanding of misophonia extends beyond fundamental scientific interest. A recent series of studies revealed alarmingly high misophonia prevalence numbers of ~1 in 5 in general (non-clinical) population samples across different nations (Turkey[16], UK[17], India[18], China[19], USA[20]). Results furthermore showed a wide range of symptom severity; 'severe misophonia' was reported in 5% to 13 % of the population[16,20–22] while the same studies also report 'some' level of misophonic symptoms in as much as 79% of the population[16,20]. This reflects the current struggle on how to interpret 'mild' or 'moderate symptoms: are they still manifestations of a 'misophonic' response? Put differently, can 'mild' misophonic responses be discerned from normal annoyance to unpleasant sounds? The call for improved misophonia diagnostic and measurement tools thus entails a need for methodology that reliably distinguishes misophonic from non-misophonic complaints, while simultaneously being sensitive to variations in misophonic response severity.

To date, researchers have largely measured misophonic complaints using self-report measures. As the field is quickly expanding, assessment approaches include structured diagnostic interviews and standardized experimental designs[5,23–25]. Yet, misophonia researchers have pointed at the limitations of employing only self-report measurements[23,25]. Furthermore, while diagnostic psychiatric criteria have been formulated[3], different studies still employ various diagnostic approaches and different cut-off scores[5,8], complicating cross-study comparisons or conclusions. Misophonia research would benefit from a physiological tool to objectively characterize individual variation in misophonia symptom severity.

We hypothesized that pupillometry might be a (cost-effective and relatively easy to use) tool to reliably quantify misophonic responses to trigger sounds. Pupil size fluctuations at constant luminance reflect neuromodulatory activity and emotional arousal associated with increased sympathetic activity[26–30] and can synchronize to rapid

alterations in cognitive or emotional states: the pupil dilates transiently during challenging decisions[31], after surprising outcomes[32] and in response to emotional stimuli[29]; critically, pupil dilation also reflects positive emotional reactions to sounds in frisson[33], and the autonomous sensory meridian response[34]. Here, we test the predictions that pupillometry has: (i) the selectivity needed to differentiate misophonic responses from responses to generally unpleasant sounds, (ii) the sensitivity needed to examine whether 'mild' and 'moderate' cases show response characteristics of misophonia, and (iii) the reliability needed to add an objective measurement of misophonic complaints at the level of a single individual.

RESULTS

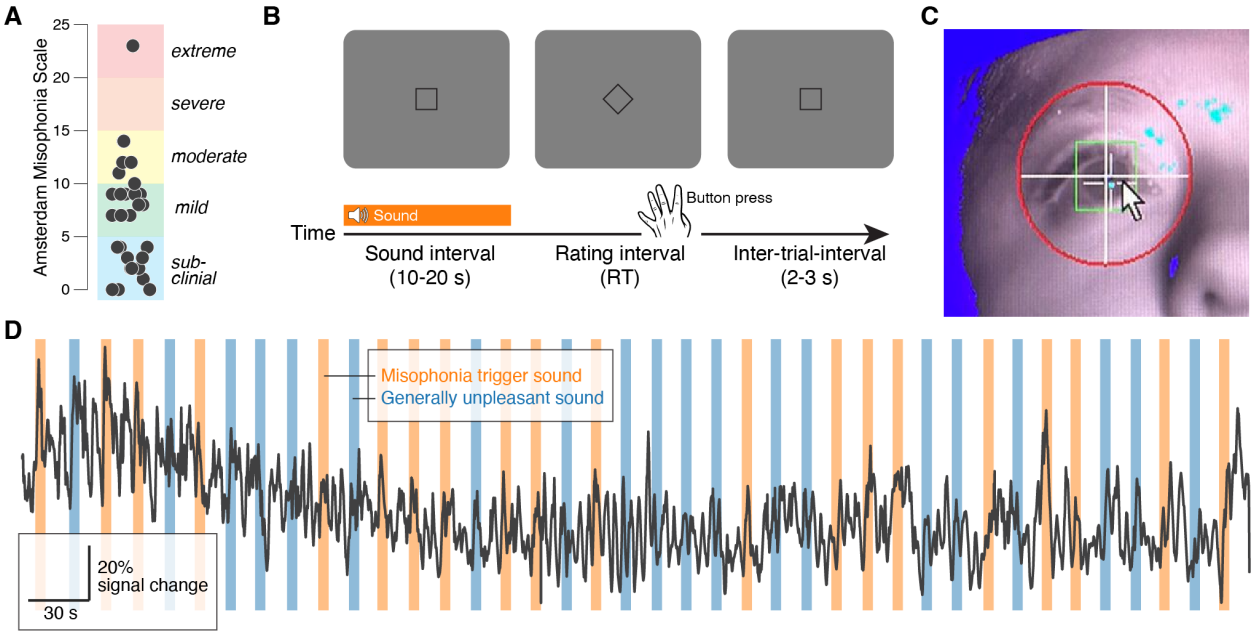

Figure 1. Misophonia protocol. (A) Amsterdam Misophonia Scale (AMS)[3] scores. Every data point is a participant (N=30). **(B)** Sequence of sound and rating interval during the misophonia protocol. **(C)** Image of pupil size recordings. **(D)** Example session. Black trace, pupil size time series; colored bars, sounds.

In thirty participants, recruited from a general population, we replicated the substantial variation in misophonia severity, as measured with the *'Amsterdam Misophonia Scale'* (AMS)[3] (Methods): 40% was sub-clinical (scores 1-4), 36% experienced mild misophonia (scores 5-9), 20% experienced moderate misophonia, and 4% experienced extreme misophonia (**Figure 1A**). The same thirty participants listened to a sequence of sounds and rated their aversiveness on a four-point scale (**Figure 1B**; Methods): half were generally unpleasant (e.g., nails on chalkboard) and half were

common misophonia triggers (e.g., clearing throat). See Methods for full list of sounds and **Figure S1** for their spectrograms. We simultaneously recorded pupil size (**Figure 1C,D**).

On average, subjective aversiveness ratings were higher for misophonia trigger versus generally unpleasant sounds (**Figure 2A**) and, likewise, sound-evoked pupil responses were larger (**Figure 2B**). This is in line with the average AMS score of our sample being 7 (classified as mild clinical misophonia[3]; **Figure 1A**). Importantly, sound-evoked pupil responses were also larger for misophonia trigger sounds when matched for subjective aversiveness rating (**Figure 2C**; mixed linear model: main effects for aversiveness rating [$z = 5.159$, $p < 0.001$] and sound type [$z = 6.247$, $p < 0.001$]). We verified that these results were not due to differences in eye blinks or saccades. Thus, for the same subjective aversiveness rating, the pupil dilated more in response to misophonia trigger sounds, than generally unpleasant sounds.

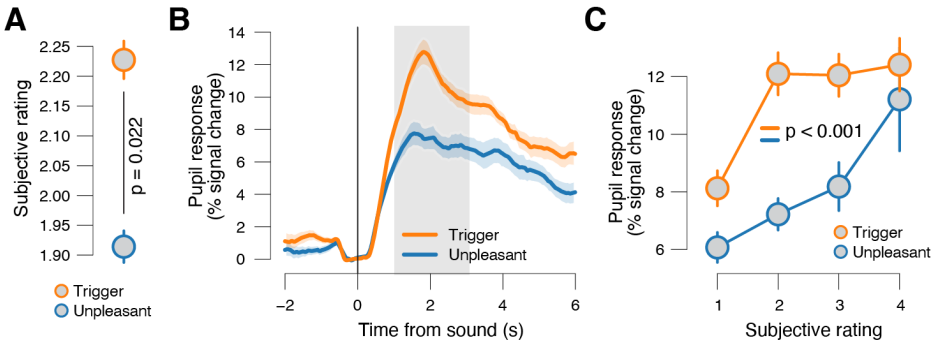

Figure 2. More pupil dilation in response to misophonia trigger sounds than generally aversive sounds. (A) Mean rating, separately for misophonic triggers and generally unpleasant sounds. Stats, paired samples t-test. **(B)** Pupil response time courses separately for sound category (misophonia trigger and generally unpleasant; collapsed across rating), time-locked to sound onset. Grey shading, interval used for quantifying task-evoked pupil responses (Methods) **(C)** Sound-evoked pupil response magnitude, separately per rating and sound category (see **Figure S2A** for pupil response time courses split by aversiveness ratings). Stats, mixed linear model (see main text and Methods). All panels: shading or error bars, S.E.M across participants (N=30).

We observed that, across subjects, the difference in pupil response magnitude (trigger vs unpleasant) was positively correlated to the difference in aversiveness rating (trigger vs unpleasant) (**Figure S3A**). In other words, those participants who rated the misophonia trigger sounds as more aversive than the generally unpleasant sounds also had bigger pupil responses during trigger versus unpleasant sounds. This relationship was robust but not perfect ($r = 0.43$, $p = 0.018$), which means that aversiveness ratings and pupil responses could, in principle, predict unique parts of the across-subjects variance in misophonia severity.

Across subjects, AMS scores were positively related to the difference in aversiveness rating (**Figure S3B**) as well as to the difference in pupil response magnitude (trigger vs unpleasant) (**Figure 3A**). We used multiple linear regression to assess the unique contribution of aversive ratings and pupil responses in predicting AMS scores. In this multiple regression model, aversiveness ratings did no longer significantly predict misophonia severity (t = 1.126, p = 0.218) whereas pupil response magnitude did (t = 4.233, $p < 0.001$). In other words, pupillometry explained more variation in the AMS than aversiveness ratings of the trials. We observed the same qualitative result when excluding one participant with severe misophonia (score > 20) from the analysis, who could be considered an outlier in our sample: aversiveness ratings did not significantly predict misophonia severity (t = 1.696, p = 0.102) whereas pupil response magnitude did (t = 2.805, p = 0.009).

Finally, we used leave-one-out cross-validation to quantify the error between pupil-predicted misophonia severity and actual misophonia severity. Specifically, we computed the linear relationship between the AMS scores and the difference in pupil response magnitude (trigger vs unpleasant) based on the data from all participants minus one, and then predicted the AMS score for the left-out participant based on his/her pupil data. This analysis showed that AMS score could be reliably predicted, based on only pupil dilation, at the level of a single individual (**Figure 3B**): the median absolute error was 2.80, which is below the granularity of severeness categories of the AMS (**Figure 1A**). This suggests that if group performance on the questionnaire is reliable, a single individual with unrealistic questionnaire scores (e.g., due to misinterpretation) might be detectable by adding pupillometry as an objective tool.

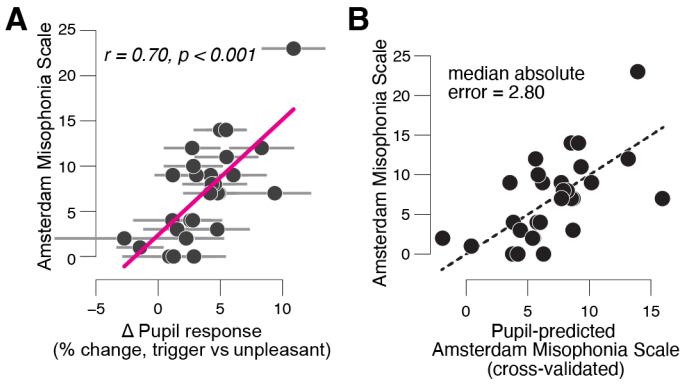

Figure 3. Sound-evoked pupil dilation reliably predicts individual misophonia severity. (A) AMS score plotted against individual mean difference in pupil response magnitude (trigger vs unpleasant sounds). Each data point is a participant. Error bars, bootstrapped 67% confidence intervals. **(B)** AMS score plotted against pupil-predicted AMS score (cross-validated). Each data point is a participant; dashed line, identity line.

DISCUSSION

Our study demonstrates for the first time that pupillometry is a sensitive method for measuring misophonic responses, even in milder cases. Pupil response discerned misophonic responses to 'trigger' sounds from normal aversive responses to generally unpleasant sounds. Furthermore, pupillometry proved sensitive to variations in the intensity of the misophonic response across different individuals and may therefore be used to aid diagnosis of the condition.

The findings suggest that pupillometry is a valuable addition to self-report paradigms. While self-report is an important tool to measure phenomenological and emotional experiences, it has some intrinsic weaknesses including unintentional (e.g., misunderstandings or biases) and intentional (malingering) measurement errors. Furthermore, our results show how the (continuous) pupillometry variance can explain additional variance over the (categorical) ratings for misophonic sounds. Thus, adding pupillometry to the misophonia diagnostic toolbox could greatly help deciphering out the different types and severities within a group of individuals reporting misophonic complaints.

Previous studies measured increased autonomic nervous system response in galvanic skin response and heart rate variability[1,4,9,10,23,35] and shown how the involuntary emotional and physiological response is an essential characteristic of misophonia[8]. In these previous studies, only the autonomic nervous system response to misophonic sounds in misophonic versus non-misophonic participants was obtained. Our current goal was to add an objective measurement that would provide a more sensitive measurement of across-subject variations in autonomic nervous system response. Pupil size fluctuations at constant luminance have previously been shown to reflect neuromodulatory activity and emotional arousal associated with increased sympathetic activity[26–30]. The signal-to-noise ratio of pupil responses is higher compared to galvanic skin heart rate (variability) responses[36]. Furthermore, the temporal resolution of pupillometry is higher compared to functional MRI and physiological measures like the galvanic skin response. Together, this allowed us to take previous findings a step further and use pupillometry measurements to reflect variations in the strength of misophonic responses (between participants, or between trials). Indeed, our results reflected such response variation, even in moderate and mild cases of misophonia.

There is also a practical reason to add pupillometry to the misophonia toolbox. As compared with neuroimaging or electrophysiological techniques, pupillometry is cheap, mobile, and non-invasive. This is not only relevant to misophonia research, as a similar quest for objective measurements exist in the pluriform and extensive research on sound sensitivity in related research areas (e.g., autism, tinnitus, hyperacusis, or PTSD[37–39]. A

recent preprint showed that emotionally evocative sounds elicited abnormally large pupil dilations in a 'disordered hearing' (tinnitus and hyperacusis) group[40]. This invites further research of employing pupillometry in sound sensitivity in other conditions. We propose that pupillometry could be employed as a non-invasive, relatively easy-to-use and cost-effective manner to map out and compare responses both within and across the different conditions. An additional advantage is that this methodology can even be used in cases where self-report is limited (e.g., due to age effects or language impairments of the participant group).

There are several limitations to our study. First, follow-up studies can elucidate whether particular choices in experimental design may increase or decrease obtained effects. In particular, a different set of misophonic/aversive sound stimuli may affect the size of the autonomic nervous system (and therefore pupil) response. For example, we choose to use the same standard stimuli for all participants, but using participants' individual misophonic trigger sounds may lead to different results. However, we expect that such a change in design would only enhance our current results. Second, analyzing which trigger sound most strongly drives pupil responses in an individual, or a more in-depth analysis of individual differences in misophonia was not feasible in the current design, due to limitations in the number of trials and participants. This remains a topic for future research. Finally, because of the recruitment method and limited number of participants, our results cannot be used to estimate misophonia prevenance in the general population.

The current results reflect how even milder misophonic cases can experience emotional disturbances related to 'triggers' in their normal daily life. There are practical implications to these findings, as for sufferers from misophonia the relatively unknown and ill-understood status of the condition impedes explaining misophonia to others, or even understanding their misophonic responses themselves[1,3,5,7]. Adding pupillometry as an objective misophonia measurement tool can improve this situation. Pupil dilation can clearly display the physical response of the sufferers to the triggers. Such objective validation can bring relief to sufferers and improve understanding from their environment. Furthermore, the current lack of objective diagnostic tools hinders rigorous assessment of the efficacy of different treatment approaches of misophonia[6,8]. Our findings suggest that pupillometry can help assess strategies and evaluate new treatments and thus help build effective treatments for this debilitating condition.

METHODS

Participants

Thirty-five healthy participants (28 females; 18-52 y) participated in the experiment. All participants had normal or corrected-to-normal hearing and vision. Participants gave written informed consent and were remunerated by the hour or received credit points. The experiment was approved by the ethics committee of the Department of Psychology at the University of Amsterdam. Five participants were excluded due to technical issues.

Procedure

The experiment lasted for 1.5 hours and consisted of the following parts (explained in detail below): (i) misophonia protocol (block 1), (ii) breathwork/distraction intervention, (iii) misophonia protocol (block 2), (iv) frisson protocol (two blocks), and (v) post-experiment questionnaires. We collected eye and heart rate data during all sound presentations (steps i, iii and iv).

Misophonia protocol

See main text. Additionally: all participants were asked to sit in a dimly lit room and to rest their head on a chin rest, which was placed at 50cm distance in front of the screen. Each trial consisted of a sound interval, a rating interval and an inter-trial interval. The sound interval showed a blank grey screen and a fixation square, and a sound was presented (duration, 10-20 s; loudness, 30-70 dB). In the rating interval, the fixation square rotated 45° (into a diamond) and participants were prompted to rate how aversive the sound was, on a scale from 1 to 4, with a left-handed button press on the keyboard in front of them: “G” for neutral, “H” for mild dislike, “J” for disgust or anger”, and “space bar” for full misophonic reaction. Participants had received instructions on using the sound rating scale (including an explanation of what entails 'full misophonic reaction') prior to starting the experiment. The trial ended with an inter-trial interval (2-3 s, uniformly distributed). Visual stimuli were displayed on a gamma-corrected monitor (spatial resolution of 2560 by 1440 pixels) with a vertical refresh rate of 100 Hz, and sound stimuli were presented using IMG Stageline MD-5000DR headphones.

The generally unpleasant sounds were chosen based on refs. [1,41]: baby crying, bicycle breaks, clarinet squeaks, construction drilling, dog barking, fire alarm, glass on metal, modem dialup, nails on a chalkboard, and Styrofoam squeak. Misophonia trigger sounds were chosen based on ref. [1]: apple eating, chip bag crinkling and eating (Cheetos), chip eating, clearing throat, dog eating, gum chewing, keyboard typing, pen clicking, runny nose, and slurping. Participants rated how aversive the sound was on a four-point scale. All sounds were acquired copyright free from https://freesound.org/, except for the clarinet squeak which was recorded by K. Schwarz (one of the authors).

Breathwork/distraction intervention

Participants were randomly allocated into one of two experimental conditions: breathwork or distraction. Each intervention lasted 30 minutes. The breathwork interventions did not affect any of the reported pupillometry results (**Figure S2B**).

The breathwork intervention was scripted and recorded by L. Alonso-Marmelstein (a certified breath coach and registered yoga teacher) and included multiple breathing techniques used in previous studies[42]. The specific breathing techniques were belly breathing, 4:4 breathing, 4:4:4:4 box breathing and 4:7:8 breathing. Each technique is presented for an average of 7.5 minutes. Participants were allowed to sit on a chair, cushion or lay down on a yoga mat for the duration of the intervention. We played the training video on a laptop that they could appropriately position.

The distraction intervention consisted of continuously playing the game "Snake" from Google.com. The participant used the arrow keys to move a digital snake around the board and the objective was to not crash into one's own tail, which kept growing. They were encouraged to beat the highest score set by other participants.

Frisson protocol

Participants were asked to provide a song they felt gave them chills, tingles down the spine, welling in the chest, or provided strong physiological sensations during listening. To control for effects of length, loudness, and musical features, the second song was the previous participant's chosen song[33]. Participants were asked to report the start (z button) and end (m button) of any physical feeling while listening. Frisson data were collected after the experimental conditions reported in this manuscript, and thus do not relate to current results. Frisson data will be the focus of another report.

Post-experiment questionnaires

Participants filled out the Body Consciousness Scale to measure the degree to which people view their bodies as an object that can be changed after internalizing societal expectations, the Amsterdam Misophonia Scale to measure misophonia severity[3], and the STAI-S questionnaire to measure current state of mood.

Eye data acquisition

Eye data were obtained with Eyelink 1000 devices (SR Research, Osgoode, Ontario, Canada) at 1000 Hz with an average spatial resolution of 15 to 30 min arc. See *Extended Methods* for more information about analyses and statistical comparisons.

Heart rate acquisition

Heart rate and heart rate variability were measured with an Electrocardiogram (ECG) device. Three electrodes are placed on the participant's body: one on either side of their chest, and one on the lower left torso. Heart rate data will be the focus of another report.

Analysis of pupil responses

Preprocessing

Periods of blinks and saccades were detected using the manufacturer's standard algorithms with default settings. The remaining data analyses were performed using custom-made Python software. We applied to each pupil recording (i) linear interpolation of values measured just before and after each identified blink (interpolation time window,

from 150 ms before until 150 ms after blink), (ii) band-pass filtering (third-order Butterworth, passband: 0.01–6 Hz), (iii) removal of pupil responses to blinks and to saccades, by first estimating these responses by means of deconvolution and then removing them from the pupil time series by means of multiple linear regression[43], and (iv) conversion to units of modulation (percent signal change) around the mean of the pupil time series from each block.

Quantification of task-evoked pupil responses

We computed task-evoked pupil response measures for each trial as the mean of the pupil diameter modulation values in the window 1 s to 3 s from sound onset, minus the mean pupil size during the 0.5 s before sound onset. We additionally removed (via linear regression) sound-to-sound variation in the pupil response amplitude that was related to the pre-sound baseline pupil size (through reversion to the mean[44]).

Statistical comparisons

We used a mixed linear regression model to quantify the dependence of pupil response magnitude on aversiveness rating (values 1-4) and sound category (0, unpleasant; 1, trigger). The fixed effects were specified as:

$$P \sim \beta_0 1 + \beta_1 R + \beta_2 C$$

with P as trial-wise pupil response magnitudes, R as the sound-wise aversiveness ratings, C as sound-wise sound category and β as the regression coefficients. We included the maximal random effects structure justified by the design[45], which meant that intercepts and rating and category coefficients could vary with participant.

We quantified across-participant correlations using Pearson's correlation coefficient.

Data, Materials and Software availability

Data and analysis scripts will be made publicly available upon publication.

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SUPPLEMENTARY FIGURES (SEPARATE)

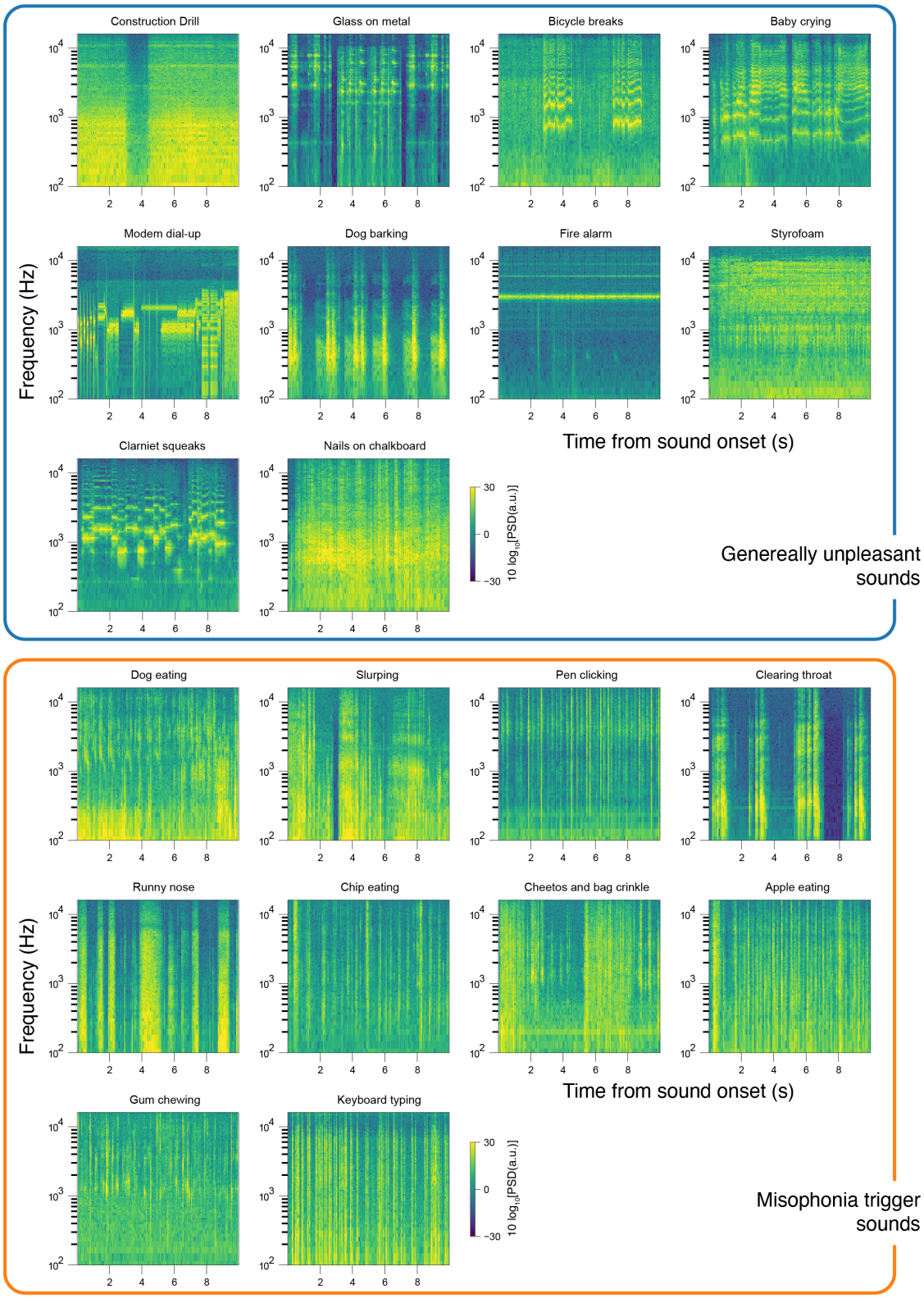
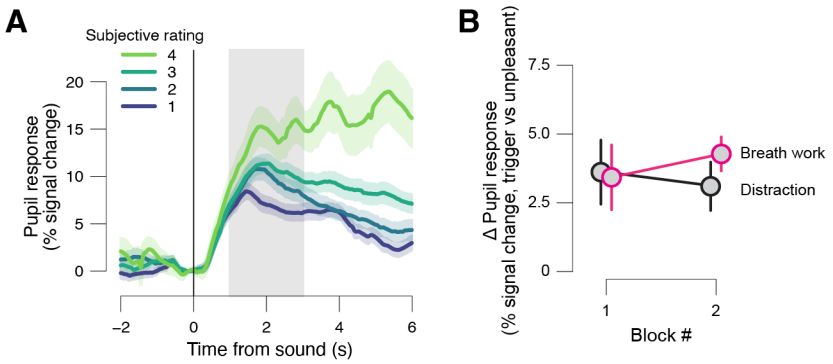


Figure S1. Spectrograms of all sounds.



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452 **Figure S2. (A)** Pupil response time courses separately for subjective rating (of physical and emotional
453 discomfort on a 4-point scale; collapsed across sound category), time-locked to sound onset. Grey shading,
454 interval used for quantifying task-evoked pupil responses (Methods). **(B)** Difference in pupil response
455 magnitude (trigger vs unpleasant sounds), separately per experimental manipulation (distraction versus
456 breathwork) and block number. All panels: shading or error bars, S.E.M across participants (N=30).

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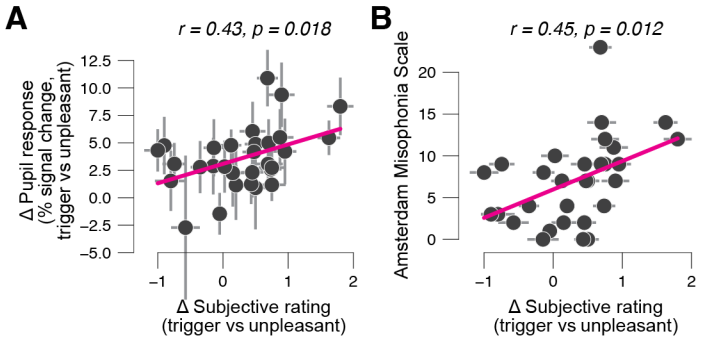

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461
462 **Figure S3. (A)** Individual mean difference in pupil response magnitude (trigger vs unpleasant sounds)
463 plotted against individual mean difference in subjective rating (trigger vs unpleasant sounds). **(B)**
464 Amsterdam Misophonia Scale score plotted against individual mean difference in pupil response
465 magnitude (trigger vs unpleasant sounds). All panels: data points are individual participants; stats,
466 Pearson's correlation coefficient.