Neural correlates of attention allocation versus sound habituation

in

Misophonia

by

Jeanpierre Tenesaca

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Committee Members

01-13-2023

Thesis Co-Advisor - Dr. Daniela Schiller   Date

01-13-2023

Thesis Co-Advisor - Dr. Jennifer Foss-Feig   Date

Dr. Muhammad Parvez

Dr. Nicolas Davidenko

Dean of Masters in Biomedical Sciences

01-13-2023

Dean - Dr. Marta Filizola   Date

Icahn School of Medicine at Mount Sinai

Abstract

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Jeanpierre Tenesaca

Advisors: Dr. Daniela Schiller & Dr. Jennifer Foss-Feig

Misophonia is characterized by a lowered tolerance coupled with a defensive reaction to socially-related auditory stimuli. Given the current gap in standardized diagnosis and treatment methods, there is a critical need to understand the processes underlying aversive auditory processing in misophonia. To address this, we used EEG to measure event-related potentials (ERPs), analyzing N1 (the registration of sensory input allocation of pre-attention) and P2 (the classification of stimuli of pre-attention) amplitudes. We examined whether misophonia triggers paired with either mechanical vs. social visual cues elicit attention allocation and/or habituation effects in comparison to autism spectrum disorder, and typically developing adults. Participants with misophonia displayed greater registration of sensory input (N1) and decreased classification of stimuli (P2) to first social cues. For the second cues, there was no significant display of context specific habituation to second cues despite source differences. These results suggest that adults with misophonia have an exaggerated tendency to focus on social cues, while reducing attention towards the social cues when firstly registering sensory inputs, possibly as a coping mechanism.

Preface

This thesis allowed me to get in touch with the humanity of what research is all about; learning what goes beyond the requirements of a master's degree. This opportunity allowed me to build relationships and lend a shoulder to lean on to those who had no one who believed in their truths. As part of my research, I had the privilege of meeting people who suffered from misophonia and allowed themselves to be open about their struggles to help others who had suffered the same way. Spending over a year listening to their stories motivated my efforts toward finding an answer for them. As a result of the present study, we can open more discussions and questions about how to help people with Misophonia. Hopefully, one day, misophonia will finally be understood enough to dismantle any hesitation in believing its beholder.

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Chapter 1: Introduction

Misophonia is a disorder that involves reduced tolerance to specific sounds made by other people, resulting in an aversive response that may be out of proportion to the presence of the irritant stimulus (Brout et al., 2018). Auditory stimuli may vary, including sniffing, chewing, nasal/accenting, and repetitive sounds not exclusively produced by the body (Erfanian, 2018). The affected individual's responses of disgust, irritation, rage, or anxiety are typically first observed in childhood or early adolescence (Schröder et al., 2013). An elevated physiological response and emotional reactivity in individuals with misophonia can lead to debilitating impairments to daily tasks. Avoidant and maladaptive behaviors can interfere with their everyday function, causing impairments to their well-being and interpersonal relationships as well (Brout et al., 2018).

Despite the rise in research toward understanding misophonia, there is still a lack of characterization of its causes, mechanisms, severity, and comorbidities (Brout et al., 2018). An estimated 20% of individuals may experience a form of misophonia (Wu et al., 2014), with 6% experiencing severe misophonia (Ferrer-Torres & Giménez-Llort., 2021). Misophonia research has been conducted for a little over 20 years, but the uptake has been slow, with the literature on misophonia-specific studies not surpassing 100 peer-reviewed papers as of 2022 (Ferrer-Torres & Giménez-Llort., 2022). Since misophonia lacks a classification and etiology, it might have comorbid hearing pathologies or mental disorders, resulting in alternative diagnoses in many misophonia patients (Potgieter et al., 2019). With no established DSM-5 or ICD criteria for misophonia, there is difficulty in providing clinically established diagnosis and treatment methods for this disorder. Standardized comparison between study cohorts is impossible without a fundamental consensus on evaluating misophonia. No psychometrically validated measurement tools can rigorously assess the effectiveness of varying treatment methods (Edelstein et al., 2013).

Through the Delphi process, a coalition of experts has redefined the concept of misophonia by assessing the etiology of reactions to misophonia triggers, influences on reactions, functional impairments, and their relationship to other disorders and conditions (Swedo et al., 2022). Current research has identified that misophonia is not a hearing disorder, since there is no relationship between reactivity and hearing thresholds prevalent among individuals with normal hearing, hard-of-hearing, or auditory pathologies (Taylor, 2017). Misophonia can develop without any peripheral or central auditory pathologies, and due to the specificity of the misophonia triggers, it is unlikely to arise from alterations in the auditory system (Møller., 2011). Furthermore, misophonia can present with neurological or psychiatric conditions or disorders, with high co-occurrence with anxiety, post-traumatic stress disorder, obsessive-compulsive disorders, and autism spectrum disorders (Taylor, 2017).

Due to the social nature of misophonia triggers, studies have suggested that social impairments play an essential role in aversive responses to misophonia triggers (Taylor et al., 2014). The levels of social dysfunction and sensory processing alterations might interact to affect the levels of misophonia severity. Understanding the fundamentals of social processing allows us to identify how neutral auditory cues are processed compared to misophonia triggers.

Within our everyday lives, the sounds of honking cars, someone chewing their gum next to us, or someone slurping their drink can firstly be noticed but eventually filtered out of our attention to focus on the task at hand. The process that allows the filtering of auditory stimuli is attention allocation. This essential cognitive processing mechanism allows individuals to face conflicting stimuli input by generating, maintaining, and adjusting a set of goal-directed processing tactics. Attention allocation reflects top-down processing and regulatory control, as they interact with various stimuli (Appelbaum et al., 2012). In misophonia, we suspect an impairment in attention allocation reduces the filtering of auditory cues, turning what would be considered a standard auditory stimulus into an aversive auditory cue that cannot be ignored.

Through first attention allocation, a habituation response developed a fundamental form of learning manifested by decreased neuronal responses to repeated sensory stimulations (Mutschler et al., 2010). Auditory habituation allows people to tune out non-essential, repetitive auditory stimuli and focus on sounds that demand attention. It can occur regularly in our everyday lives without our conscious awareness, like the clicking of a ticking clock. At the behavioral level, habituation can elicit reduced emotional reactions to repeated affective stimuli, a process that may be particularly impacted in misophonia.

This thesis examines attention allocation vs. auditory habituation in misophonia and whether these processes vary as a function of context (when the sound source is mechanical or social). We examined sensory processing using event-related potentials (ERP) recorded with electroencephalography (EEG) in participants with misophonia, compared to adults with autism spectrum disorder (ASD) as a clinical control and typically-developed (TD) adults as a comparative baseline representation of normative auditory processing.

Chapter 2: Misophonia Severity Assessments

Participant recruitment

Participants between the ages of 18 and 54 provided written informed consent, as approved by the Institutional Review Board at the Icahn School of Medicine at Mount Sinai. The author asserts that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008.

Participants included 16 individuals with moderate to severe misophonia symptoms (Mean age = 31.3 years, SD = 7.9), 18 with ASD (Mean = 25.6 years, SD = 6.4), and 14 TD controls (Mean = 28.2 years, SD = 8.4). A one-way ANOVA did not identify any significant differences among groups in terms of age [F(2, 45) = 2.36, p = 0.07], and a Chi-Square analysis confirmed no significant sex differences among groups [X 2 (2, N = 48) = 2.29, p = 0.32] (Table 1). Moderate symptoms of misophonia were defined as participants receiving the following minimum misophonia scores on at least two of four surveys: Misophonia Questionnaire (MQ): x>7 (MQ; Wu et al., 2014), Amsterdam Misophonia Scale (AMISOS): x>9 (Schröder et al., 2013), Amsterdam Misophonia Scale Revised (AMISOS -R): x>23 (AMISOS-R; Jager et al., 2020), and Misophonia Assessment Questionnaire (MAQ): x>21 (MAQ; Johnson, 2014). ASD and TD participants required a misophonia survey score below the threshold of moderate severity. ASD diagnoses were confirmed by the Autism Diagnostic Observation Schedule - 2 (ADOS-2, Lord et al., 2012), administered by a trained and research-reliable clinician, in conjunction with developmental history and clinical judgment applied to DSM-5 criteria. Neurotypical controls had no psychiatric disorders and no first-degree relatives with ASD.

We recruited misophonia participants through online advertisements on the misophonia support group pages (Reddit and Facebook) and online research participant recruitment sites. ASD and TD participants were recruited via recruitment websites, campus flyers, and online forums. Potential participants opted to participate in the study based on a brief description informing them that they would need to complete surveys assessing their mood, personality, and sensitivity to certain sounds, with a compensation of $20.00 per hour. Clinical staff and research specialists conducted psychological assessments and EEG sessions.

Misophonia and Psychiatric Measurements

Table 1: Participant population and surveys scores

Group Mean +/- SD

	Misophonia (n =16)	**ASD (n = 18)**	**TD (n = 14)**	**One-way ANOVA**	**p-Value**
Age (years)	31.3 +/- 7.9	25.6 +/- 6.4	28.2 +/- 8.4	F(2, 45) = 2.36	p = 0.11
Sex (M/F)	6M/10F	10M/8F	9M/5F	X^2 (2, N = 48) = 2.29 (Chi-Square Test)	p = 0.32
FSIQ-2	116.75 +/- 14.98	116.94 +/- 12.32 (16 out of 18)	121.71+/- 17.8	F(2, 38) = 0.59	p = 0.56
Misophonia Questionnaire (MQ)	8.36 +/- 1.89	5.56 +/- 2.0	2.07 +/- 1.3	F(2, 45) = 48.7	p = 5.6E-12
Amsterdam Misophonia Scale (AMISOS)	12.9 +/- 2.6	4.94 +/- 3.0	0.43 +/- 0.94	F(2, 45) = 13.3	p = 2.9E-5
Amsterdam Misophonia Scale Revised (AMISOS -R)	25.3 +/- 7.01	8.83 +/- 5.8	2.07 +/- 2.0	F(2, 45) = 72.5	p = 8.4E-15
Misophonia Assessment Questionnaire (MAQ)	40.7 +/- 10.4	9.44 +/- 11.6	0.50 +/- 1.2	F(2, 45) = 79.2	p = 1.8E-15

Broad Autism Phenotype Questionnaire (BAPQ)	3.11 +/- 0.7	3.70 +/- 0.7	2.54 +/- 0.43	F(2, 45) = 13.3	p = 2.9E-5
Fear of Negative Evaluation (FNE)	45.1 +/- 9.4	44.3 +/- 10.5	33.7 +/- 7.3	F(2, 45) = 6.89	p = 2.4E-3
Liebowitz Social Anxiety Scale Avoidance score (LSAS)	29.8 +/- 13.8	34.8 +/- 15.0	20.4 +/- 10.8	F(2, 45) = 4.60	p = 0.02
State-Trait Anxiety Inventory T-score (STAI)	51.1 +/- 12.6	54.4 +/- 8.6	36.5 +/- 10.4	F(2, 45) = 12.2	p = 5.9E-5
Zung Self-Rating Depression Scale Score (SDS)	44.1 +/- 10.6	45.2 +/- 7.8	32.2 +/- 8.5	F(2, 45) = 9.49	p = 3.6E-4
Obsessive Compulsive Inventory Score (OCI-R)	10.6 +/- 6.2	25.3 +/- 15.0	7.57 +/- 6.3	F(2, 45) = 13.6	p = 2.4E-5
Avoidant Personality Disorder Impairment Scale Score (AVPD-IS)	17.1 +/- 5.0	17.4 +/- 4.9	11.9 +/- 5.6	F(2, 45) = 5.32	p = 8.4E-3
Lehman Social Relations Objective: Social Contact Score (LSRO)	21.4 +/- 4.3	19.1 +/- 4.2	23.6 +/- 3.1	F(2, 45) = 5.10	p = 0.01
Lehman Social Relations Subjective: Satisfaction with Social Relations (LSRS)	28.4 +/- 7.4	32.5 +/- 5.9	35.6 +/- 4.2	F(2, 45) = 5.47	p = 7.4E-3

We administered four misophonia surveys to assess misophonia traits among the three subject groups. A commonly used method of measuring misophonia severity is the Misophonia Questionnaire (MQ; Wu et al., 2014), a self-report measurement consisting of three subscales in a Likert-type scale: (a) frequency of specific trigger sounds, (b) frequency of certain emotions and behavioral responses to trigger sounds, and (c) overall perception of the severity of sound sensitivities. A score above 6 has been proposed to indicate clinically significant symptoms (MQ; Wu et al., 2014). Within our study we only assessed one question of the MQ, severity of sound sensitivity from 1 (minimal) to 15 (very severe). Severity of misophonia symptoms was classified as follows: Minimal (1-3), Mild (4-6), Moderate (7-9), Severe sound sensitivities (10-12), Very severe sound sensitivities (13 -15).

Participants also completed the Amsterdam misophonia Scale (A-MISO-S), a 7-item self-report measure assessing the severity of misophonia symptoms, including preoccupation with trigger sounds, negative emotional responses to trigger sounds, lack of thought control, and interference with daily life (Schröder et al., 2013). The first six questions are scored on a 5-point Likert scale (0-4), whereas the last ask for free responses. The AMISOS is an adapted version of the Yale-Brown Obsessive-Compulsive Scale (Goodman et al., 1989). Total scores range from 0-24, with score categories of 0-4 (subclinical), 5-9 (mild), 10-14 (moderate), 15-19 (severe), and 20-24 (extreme; Schröder et al., 2013).

We also used an updated version of the AMISOS called the Amsterdam Misophonia Scale-Revised (AMISOS-R; Jager et al., 2020); it now incorporates physical movements of others as misophonia stimuli.

Lastly, the Misophonia Assessment Questionnaire (MAQ; Johnson, 2014), is a 21-item measure that assesses impact of misophonia. In one study (Dozier, 2015), the sum of the individual's score in the MAQ was used to rate the severity of symptoms as mild (1–21), moderate (22–42), or severe (43–63); a Likert-type scale of 0 (not at all/least) to 3 (all the time/most) is used to score the items.

In order to compare misophonia to other psychiatric conditions, participants also completed the Broad Autism Spectrum Questionnaire (BAPQ; Hurley et al., 2007), Fear of Negative Evaluation (Leary,1983), Liebowitz Social Anxiety Scale (LSAS Avoidance questions; Liebowitz, 1987), State-Trait Anxiety Inventory (STAI Trait questions; Skapinakis, 2014), Zung Self Rating Depression Scale (SDS; Zung, 1986), Obsessive-Compulsive Inventory-Revised

(OCI-R; Foa et al., 2002), Avoidant Personality Disorder Impairment Scale (AvPD-IS; Liggett et al., 2017), and Lehman's Social Relations Subjective & Objective Score (Lehman, A.F. 1983) (**Table 1**). Correlation analysis between all additional psychiatric surveys and misophonia surveys were assessed to identify the presence of comorbidities **(Table 2)**.

We conducted a series of IQ tests suitable for the age and developmental level of the misophonia and ASD and TD groups, including the Wechsler Abbreviated Scale of Intelligence – Second Edition (Wechsler, 2011). Only 16 out of 18 ASD participants were able to complete the IQ assessment.

Table 2: Misophonia Survey Correlations

	BAPQ	FNE	LSAS	STAI	SDS	AVPD-IS	LSRS
MQ	r(46) = .225 p = .124	r(46) = .420 p = .003 (+)	r(46) = .293 p = .043 (+)	r(46) = .432 p = .002 (+)	r(46) =.476 p < .001 (+)	r(46) = .361 p = .012 (+)	r(46) = .438 p = .002 (-)
AMISOS	r(46) = .913 p < .001 (+)	r(46) = .378 p = .008 (+)	r(46) = .326 p = .024 (+)	r(46) = .378 p = .008 (+)	r(46) = .402 p = .005 (+)	r(46) = .358 p = .013 (+)	(r(46) = .483 p < .001 (-)
AMISOS-R	r(46) = .913 p < .001 (+)	r(46) = .409 p = .004 (+)	r(46) = .227 p = .120	r(46) =.394 p = .006 (+)	r(46) =.425 p = .003 (+)	r(46) = .353 p = .014 (+)	r(46) = .443 p = .002 (-)
MAQ	r(46) = .867 p < .001 (+)	r(46) = .426 p = .003 (+)	r(46) = .237 p = .104	r(46) = .426 p = .003 (+)	r(46) = .42 p = .003 (+)	r(46) = .388 p = .006 (+)	r(46) = .451 p = .001 (-)

Table 2

Misophonia, ASD, & TD sum survey correlations versus personality surveys. (+) Positive Correlation & (-) Negative Correlation, shaded regions indicated no correlations.

Chapter 3: Attention Allocation & Auditory Habituation

A prior knowledge base of objects and events must be considered when deciding how to allocate sensory, motor, or mental resources. Additionally, auditory habituation refers to a gradual decline in neuronal response to successive auditory stimulations. Despite the success of EEG in measuring auditory ERPs, attention allocation and habituation properties remain unknown in participants with misophonia. A comparison of misophonia participants' attention allocation and auditory habituation enabled us to determine whether social vs. mechanical visual sources led to distinct ERP responses to misophonia triggers and whether source differences influence neuronal desensitization.

Previous studies of N1 and P2 assessments identified N1 as a potential filtering mechanism that triggers the activation of allocation of attention, while P2 sensory gating involves the early allocation of attention (Näätänen, 1992, pp. 113–135; Näätänen & Picton, 1987). Previous studies have identified a decrease in N1 magnitude with repeated auditory stimuli (Paiva et al., 2016). Similarly, P2 showed habituation, and sensory gating properties have been observed for consecutive stimuli with short and constant inter-stimulus intervals (Paiva et al., 2016). Therefore, we hypothesize misophonia participants to evince greater negative N1 and positive P2 peaks than participants with ASD or TD to the first sound stimuli, presumably due to increased registration of sensory input and pre-attentive classification of stimuli. Our studies should indicate a decreased habituation response to social cues in misophonia compared to ASD and TD.

MATERIALS AND METHODS

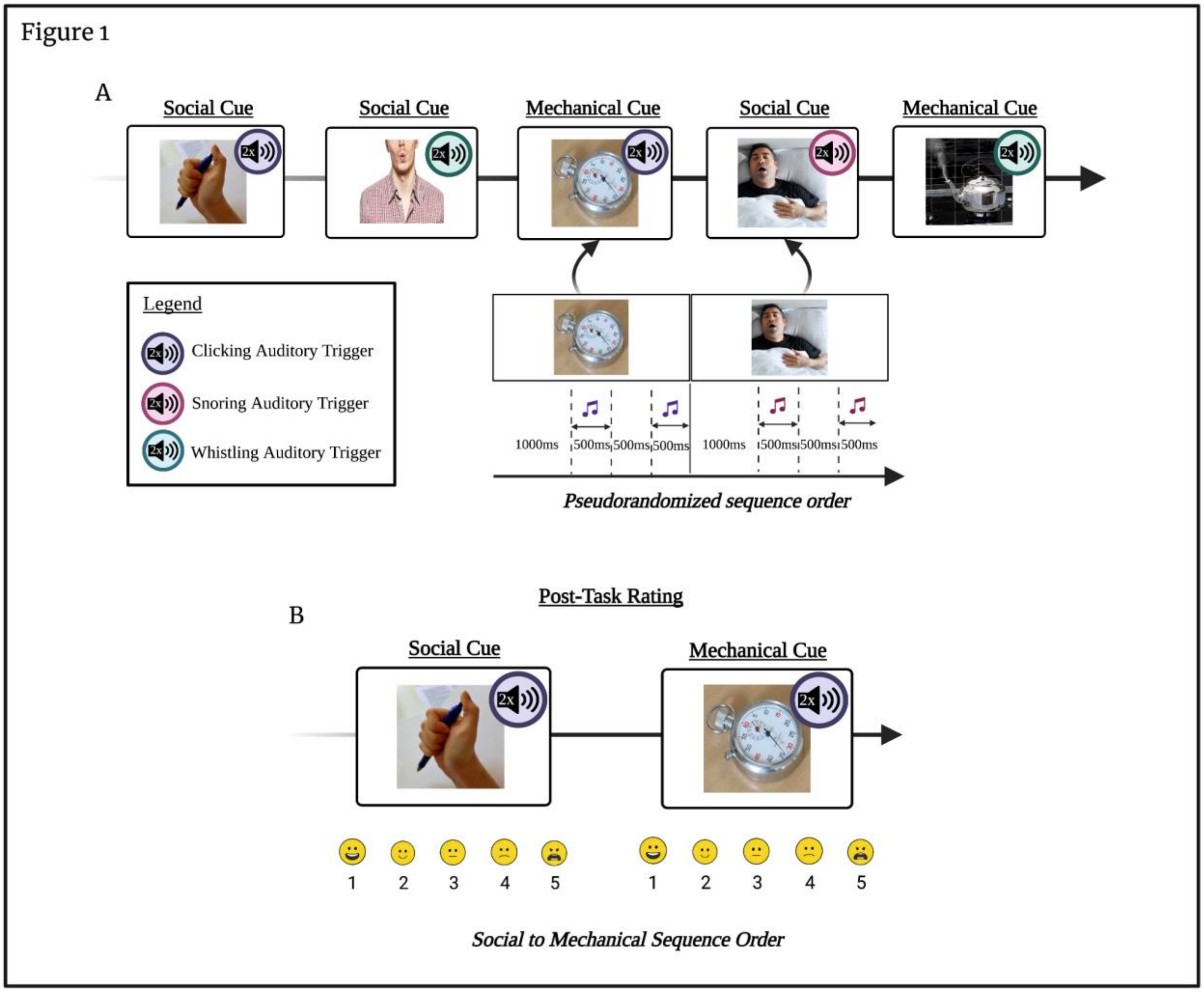

Figure 1. **Misophonia Visual-Auditory Cue habituation Task**

(A) *Source differentiation processing task* ***(B)*** *Post-task source differentiation ratings*

Participants completed a 9-min visual-auditory habituation task during a high-density EEG while seated in a chair facing a desktop computer, with an approximate 2-4 min post-rating task with a Chronos Response Box. We used E-Prime 2.0 to implement the experiment. The experiment consisted of a total of 4 blocks containing 32 trials per block, with eight distinct social visual cues (e.g., whistling man) and eight distinct mechanical visual cues (e.g., whistling teapot). All visual cues were validated in a prior study with Misophonia participants rating the unpleasantness plausibility of the auditory cues paired with the visual stimuli (Banker, 2022). Each distinct visual cue was presented twice per block in a randomized order for 2000 ms; the

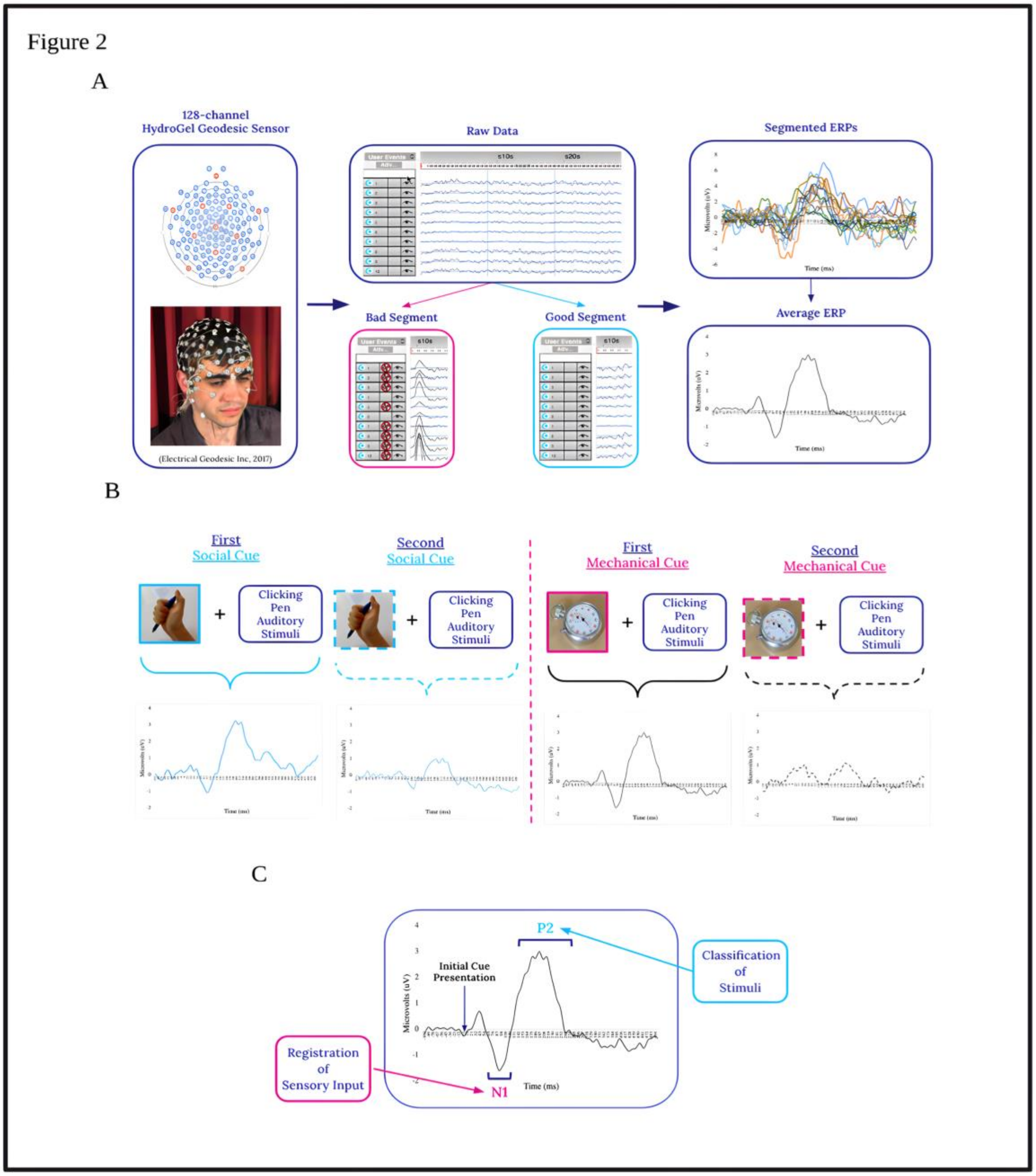

***Figure 2*. ERP Acquisition and Segmentation**

(A) *EEG processing and ERP collection,* ***(B)*** *ERP Segmentation,* ***(C)*** *ERP components* misophonia auditory stimuli were identical for pairs of social and mechanical images and matched both visual cues (e.g., whistling sound) in a pseudorandomized order. Auditory cues were presented twice per distinct visual cue. The auditory cues were presented 1000ms after the visual cues for 500ms each with a 500ms buffer in between each auditory presentation (Figure 1A). After completing the task, participants rated the image paired with the same auditory stimuli from the task on a 1-5 scale (1 = Pleasant to 5 = Unpleasant) (Figure 1B).

We acquired EEG data using NetStation Software Version 5.4.2 and a Philips HydroGel Geodesic sensor with 128 channels (Figure 2A). Original EEG files were processed in a 0.50 - 55.00 Hz Bandpass filter and then segmented into the four distinct cue segments (M1: First mechanical visual cue, M2: Second mechanical visual cue, S1: First social visual cue, and S2: Second social visual cue) of 600 ms epochs from -100ms to 500ms and time-locked to the onset of each tone during pre-processing (Figure 2B). Each recorded segment was manually inspected for the removal of motor movement (eyeblinks, eyebrow shifts, head tilt). The processing steps involve classifying and replacing outlier channels with interpolated values in the continuous data, removing outlier epochs from single participant data, and removing outlier components. Data were averaged separately for each auditory cue in the trial's sequence, and the baseline was corrected using a 100 ms pre-stimulus interval. Recordings were included in final analyses if they included a minimum of 10 viable segments per cue, with viability meaning a maximum of 25 electrode channels that were removed per segment for >80% viability (Figure 2A). We performed repeated measures ANOVAs and t-tests to compare component amplitude by the group across social and mechanical stimuli and repetitions. RStudio was used for ERP analysis and statistical significance.

N1 & P2 amplitudes were extracted over electrode Cz at the vertex of the head, where auditory event-related potentials are easily detected (Rosburg et al., 2010). Each participant's N1 component reflects minimum voltage within a window from 70 to 120ms; the P2 component has the maximum voltage within a latency range of 120-210 ms post-stimulus. Latency was defined as the time-to-peak amplitude for each component (Figure 2C).

RESULTS

Figure 3

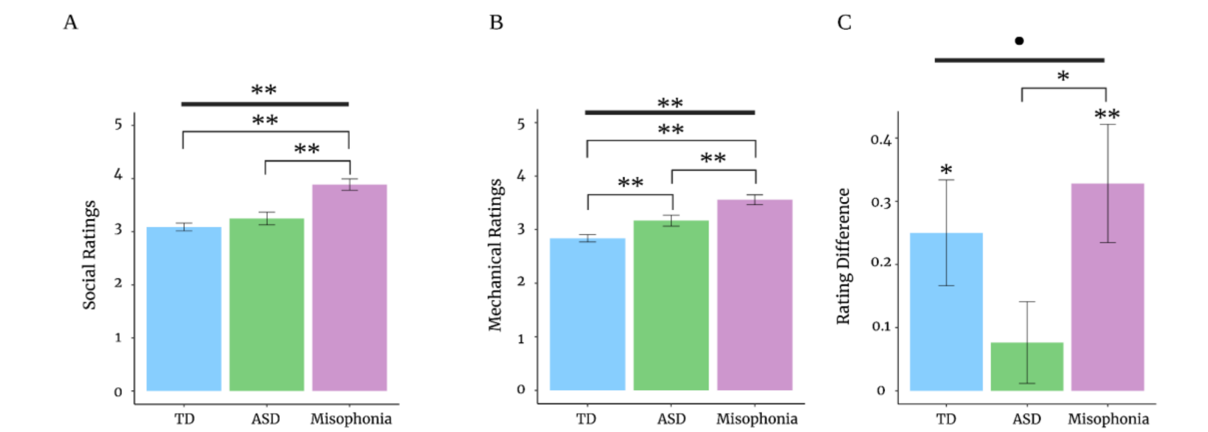

***Figure 3*. Post-Task Ratings**

*Misophonia, ASD, and TD, **(A)** Social rating and **(B)** Mechanical Rating (1 = Pleasant to 5 =Unpleasantness); **(C)** Rating differences (Social-Mechanical) between social and mechanical visual cues for all three groups. ● : $p < 0.1$; * : $p < 0.05$; ** : $p < 0.01$*

Post-Task Visual Cue Association Ratings

A one-way ANOVA was performed to compare groups (Misophonia, ASD, and TD) on mechanical ratings, there is a statistically significant difference in mechanical ratings (MR) between the three groups [F(2, 43) = 14.22, p = 0.00002]. Another ANOVA was also performed to compare groups (Misophonia, ASD, and TD) on social ratings, there is a statistically significant difference in social ratings (SR) between the three groups [$F(2, 43) = 15.31$, $p = 0.00001$] (**Figure 3A & 3B**). Between-group MR analysis using post-hoc t-tests assuming unequal variances, identified differences between misophonia vs TD ($t(26) = 6.2$, $p < 0.01$), misophonia vs ASD ($t(32) = 2.8$, $p < 0.01$), and TD vs ASD ($t(26) = 2.7$, $p < 0.05$), with unpleasantness ratings highest in misophonia, followed by ASD, then TD . While SR analysis indicated significant differences between misophonia vs TD ($t(26) = 6.1$, $p < 0.01$) and misophonia vs ASD ($t(32) = 4.0$, $p < 0.01$), again with unpleasantness ratings highest in the misophonia group, there were no differences in SR unpleasantness rating for ASD vs TD ($t(27) = 1.1$, $p = 0.27$) (**Figure 3A & 3B**).

These data indicate that participants with misophonia responded more severely to social and mechanical visual cues than other groups, while maintaining a statistically significant elevated rating towards social visual cues compared to mechanical cues within group (**Figure 3C**). Misophonia participants found the social cue more unpleasant while ASD participants experienced an equivalent dislike to the auditory cue regardless of the visual pairing. The increase in unpleasantness ratings corresponded to an increase in misophonia severity (**Table 3**).

Table 3: Misophonia Surveys & Post-Task Ratings Correlations

Correlation Analysis	AMISOS-R	MQ	MAQ	AMISOS
Social Rating	$r(46) = .556$, $p < .001$ (+)	$r(46) = .565$, $p < .001$ (+)	$r(46) = .62$, $p < .001$ (+)	$r(46) = .648$, $p < .001$ (+)
Mechanical Rating	$r(46) = .586$, $p < .001$ (+)	$r(46) = .566$, $p < .001$ (+)	$r(46) = .601$, $p < .001$ (+)	$r(46) = .611$, $p < .001$ (+)

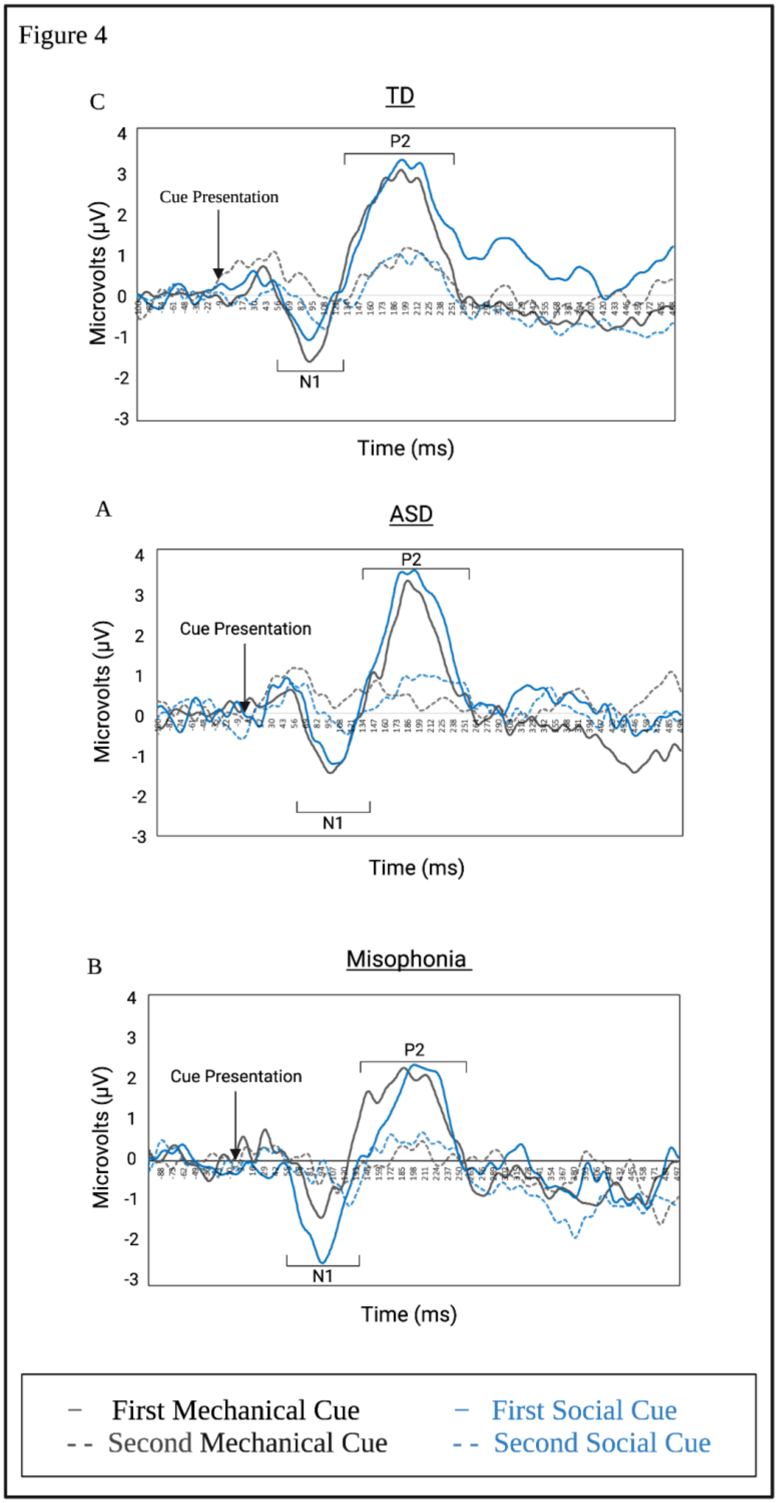

***Figure 4*. First and Second ERPs to social vs mechanical sources**

(A-C) *ASD, Misophonia, and TD ERPs, respectively*

First ERP Responses to Misophonia triggers paired with Social vs Mechanical Cue

ERPs were collected for the first and second auditory stimuli presentations paired with both mechanical and social cues (**Figure 4**). A one-way ANOVA was conducted to determine the effect of group (Misophonia, ASD, TD) on first N1 responses to social cues; the results indicate a significant effect [$F(2, 43) = 3.46$, $p = 0.04$] (**Figure 5A2**). In particular, post-hoc comparisons using between-group t-tests indicated a significantly larger N1 response to the first presentation of sounds paired with social images for misophonia participants compared to TD ($t(26) = -2.31$, $p < 0.05$), as well as a trending significance between misophonia and ASD ($t(32) = -1.99$, $p = 0.06$) participants. There were no differences in N1 response to the first presentation of sounds paired with social images between ASD and TD participants ($t(27) = -0.33$, $p = 0.73$). There were no significant differences in N1 for first presentation of the sounds when paired with mechanical images among groups (**Figure 5A1**).

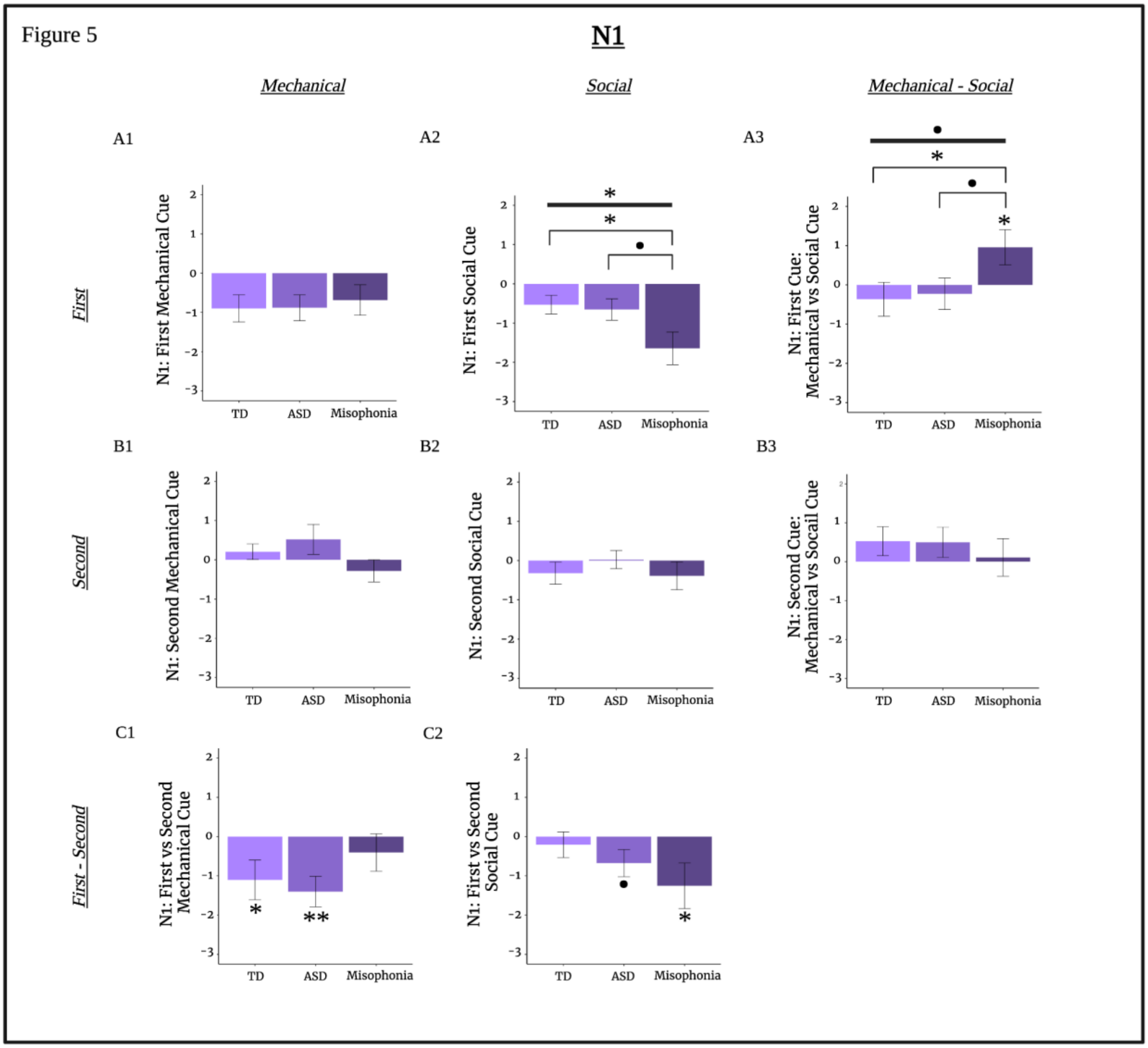

***Figure 5*. N1: First and Second ERP Source Difference Analysis**

(A1-A3) *Misophonia, TD, & ASD first ERP's responses for N1: Mechanical, Social, & Mechanical - Social, respectively.* ***(B1-B3)*** *Misophonia, TD, & ASD second ERP's responses for N1: Mechanical, Social, & Mechanical - Social, respectively. ● : p < 0.1; * : p < 0.05)*

A one-way ANOVA was conducted to determine the effect of group (Misophonia, ASD, TD) on the differences between first N1 mechanic vs first N1 social responses; the results indicate a leaning significant effect [$F(2, 43) = 2.93$, $p = 0.064$] (**Figure 5A3**). In particular, t-tests comparing misophonia and ASD ($t(32) = -1.99$, $p = 0.057$) showed a marginally significant difference, while t-tests comparing misophonia and TD showed a statistically significant difference ($t(26) = -2.13$, $p < 0.05$). A within group analysis indicated a significant difference between N1 first mechanical and N1 first social in misophonia($t(15) = 2.1$, $p = .050$), all other groups did not show significant within group differences. These tests suggest that only in misophonia was the N1 larger within the social than the mechanical context.

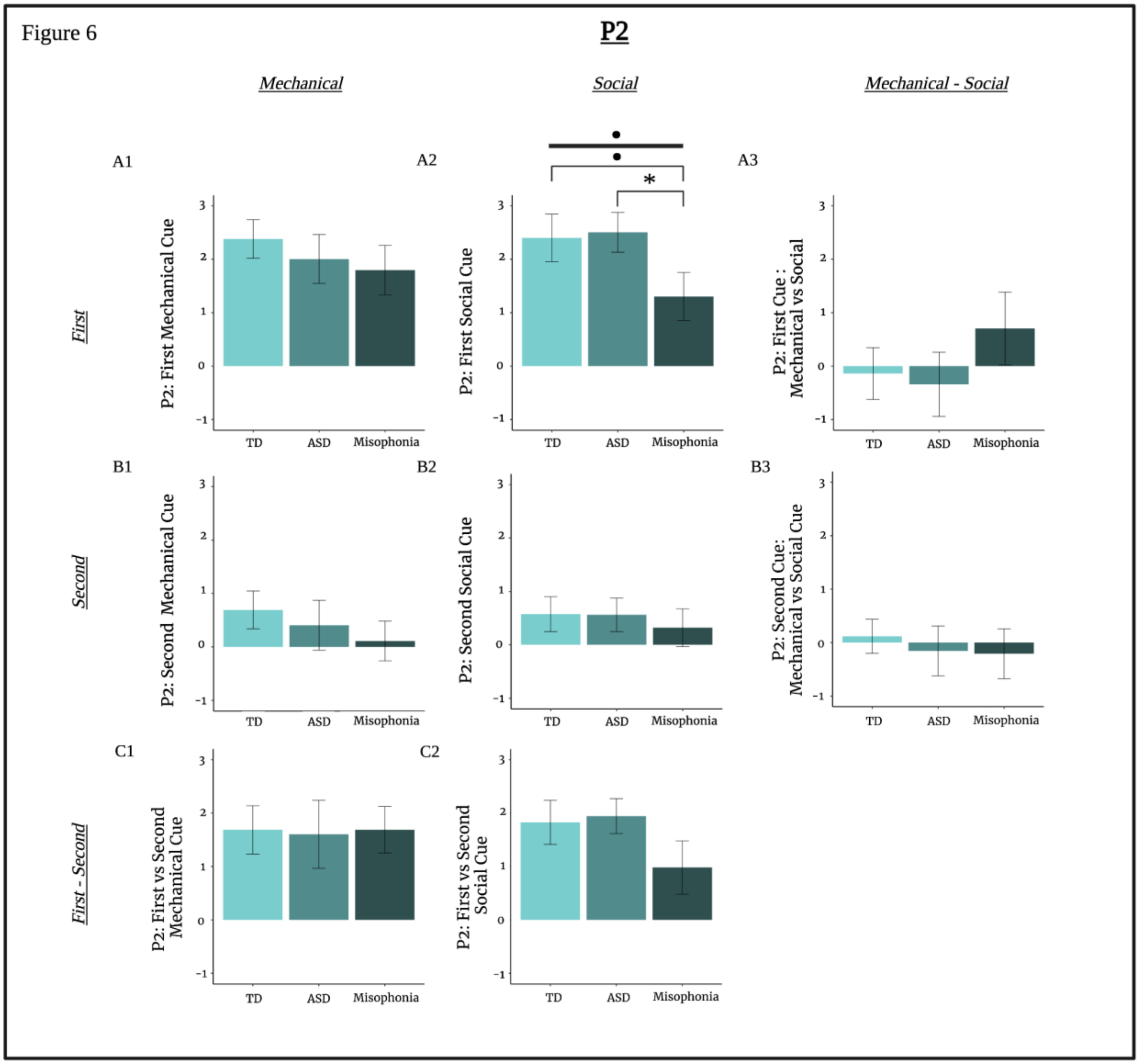

***Figure 6*. P2: First and Second ERP Source Difference Analysis**

(A1-A3) *Misophonia, TD, & ASD first ERP's responses for P2: Mechanical, Social, & Mechanical - Social, respectively.* ***(B1-B3)*** *Misophonia, TD, & ASD second ERP's responses for P2: Mechanical, Social, & Mechanical - Social, respectively. ((● : $p < 0.1$) & (* : $p < 0.05$))*

Regarding the P2 response to the first presentation of the auditory cue paired with mechanical/social visual cue, there was a trend toward significant differences among groups for the social contexts. A one-way ANOVA was conducted to determine the effect of group (Misophonia, ASD, TD) on first P2 responses. The results indicate a marginally significant effect, [$F(2, 43) = 2.52$, $p = 0.09195$] (**Figure 6A2**). Between group t-test were conducted for P2 responses to sounds paired with social cues: no difference was detected between ASD and TD participants ($t(27) = -0.18019$, $p = 0.9$); a significant difference between misophonia and ASD participants ($t(32) = -2.06$, $p = 0.047$) and marginally significant difference between misophonia and TD participants ($t(26) = -0.17$, $p = 0.09$) was identified. No statistically significant group differences were observed in the differences between P2 response amplitude to social vs mechanical cues.

Altogether, only misophonia participants showed within group differences between first social N1 and first mechanical N1, for all other groups, analysis of first mechanical vs first social exposure did not reveal any significant differences in N1 or P2 within groups between social and mechanical cues. However, analysis of the first presentation of auditory cues paired to social image N1 and P2 components showed distinct *between* group differences. According to our results, misophonia participants, compared to the other groups, displayed larger N1 responses, , as well as a decreased P2 to social visual cues, when misophonia auditory cues are paired with social visual cues.

Habituation from First to Second sound presentation with ERP analysis

Given that there were no differences between groups in first presentations of the sounds paired with the mechanical cue, we examined differences in habituation–the degree of difference between the first and second presentation of the sounds paired with the mechanical cue and for the social cue via a ratio between the first and second auditory cue ERP (**Figure 7**). A two-way repeated measures ANOVA was performed to analyze the effect of group (Misophonia, ASD, and TD) and presentation order (First and Second) on N1 responses or P2 responses to mechanical cues. The results indicated that there was no statistically significant interaction between the effects of group and presentation order in N1 ($F(2,90) = 1.21$, $p = 0.30$) and P2 ($F(2,90) = 0.07$, $p = 0.93$) for mechanical cues (**Figure 6C1**).

For the sounds paired with social cues, given the significant group differences in first sound attention processing in N1 [$F(2, 43) = 3.46$, $p = 0.04031$] (**Figure 5A2**) and a trending significant difference in P2 [$F(2, 43) = 2.52$, $p = 0.09195$] (**Figure 6A2**), we could not examine habituation per se without considering the significant ERP component differences for the first stimulus. We therefore examined the overall ERP response difference between first social cue and second social cue processing through ratio differences for the mechanical cue and social cue.

This was supported by a one way measure ANOVA with factors of group on habituation ratio differential (|*First Cue*| - |*Second Cue*|*)/(*|*First Cue*| - |*Second Cue*|) for N1 Social [$F(2, 45) = 0.45$, $p = 0.65$], N1 Mechanical [$F(2, 45) = 0.13$, $p = 0.88$], P2 Social [$F(2, 45) = 0.34$, $p = 0.71$], P2 Mechanical [$F(2, 45) = 0.29$, $p = 0.75$], exhibiting no significant differences in habituation between social contexts and groups. **(Figure 7)**. These data suggest that, overall, misophonia participants exhibited similar habituation processing (in first to second presentation) to social and mechanical cues; as well as in the other groups (ASD and TD).

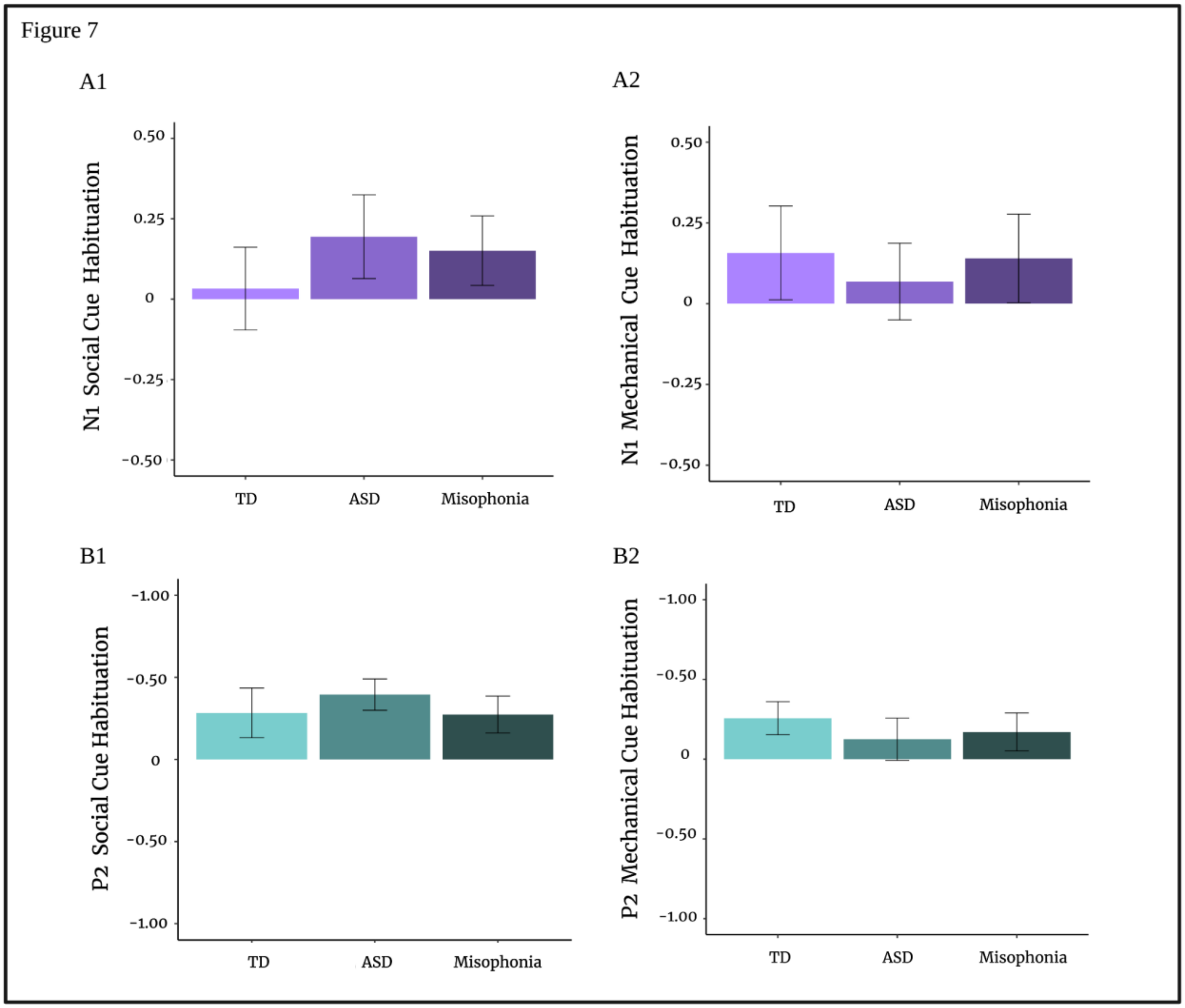

***Figure 7*. N1 and P2: Habituation Ratio Differentials**

(A) *N1 Social Habituation* ***(B)*** *N1 Mechanical Habituation* ***(C)*** *P2 Social Habituation* ***(D)*** *P2 Mechanical Habituation. Habituation Ratio Differential = (|First Cue| - |Second Cue|)/(|First Cue| - |Second Cue|).*

Discussion

Our main finding was that, compared to typically developing individuals and clinical ASD controls, participants with misophonia showed increased registration of sensory input to trigger sounds presented in social contexts even before classification of stimuli of the source of the sound. Unknowingly allocating enhanced attention to sounds paired with social visual cues supports the idea that misophonia involves exaggerated first registration of sensory input classification of stimuli to socially-relevant auditory stimuli, which may underlie the severe aversion to these triggers.

In addition, misophonia participants' attention to sounds paired with social images decreased when they were classifying social stimuli, perhaps as a coping mechanism. A recent clinical study indicated that individuals with misophonia have developed several coping strategies in response to their aversive reactions to trigger sounds. These coping mechanisms include avoiding or removing themselves from certain situations, mimicking trigger sounds or the action producing them, "canceling out" or "retaliating," using earplugs, headsets or listening to music, distracting oneself, reciting positive internal dialog to help calm themselves, asking others to stop making the sounds, and being mindful of their sounds. (Edelstein et al., 2013). In most of these coping mechanisms, participants deliberately remove themselves from the stressor. Our finding of reduced P2 responses could be used as a biological marker to assess and develop new treatments for coping.

Finally, the habituation hypothesis was not supported by our findings: we found intact habituation to misophonia triggers in N1 and P2 responses regardless of the sound source, whether mechanical or social. These findings question the idea that impaired sensory habituation underlies misophonia symptoms. From an interventional standpoint, our initial findings suggest that misophonia treatment should perhaps focus on decreasing first N1 responses rather than habituating to the aversive stimuli over time.

As part of future research, we will examine the preceding responses to visual clues before sound presentation with the goal of assessing the overall effect of arousal and high-level responses to social context and its impact on sound processing. We will also examine whether differences in habituation may be more apparent on larger timescales, by examining responses to the sounds paired with social cues early versus later in the task.

Conclusion

As far as the auditory processing mechanism of misophonia is concerned, this study allows a view into the differentiation of the visual and auditory aspects of this illness. This project is a part of a larger initiative designed to address the needs of people with misophonia that are severely limited in their daily lives because of this disorder. It is important to have a solid understanding of both pre-attentive registration of sensory input and pre-attentive classification of sensory stimuli in order to be able to make sense of why misophonia is a socially-oriented disorder. Future research into auditory and visual processing mechanisms across social and non-social contexts in misophonia is on the horizon in an attempt to create a standardized method for diagnosing and treating the condition.

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