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Editor-in-Chief
Prof. Henryk Skarzynski, M.D., Ph.D., Dr. h.c. multi

Special Issue: Misophonia and Hyperacusis

Guest Editor
Dr. Hashir Aazh

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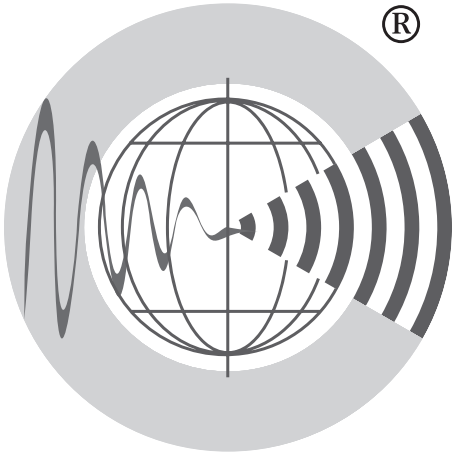

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Editorial

Articles

Following the success of the 7th International Conference on Hyperacusis and Misophonia (ICHM7), held in Warsaw, Poland, from 15 to 17 September 2024 – organised by the Institute of Physiology and Pathology of Hearing, the Institute of Sensory Organs, and the Hashir International Institute – it is my pleasure to introduce this special issue of the *Journal of Hearing Science* dedicated to hyperacusis and misophonia. The aims of this special issue are threefold: first, to present the most up-to-date research on the causes, mechanisms, diagnosis, and treatment of hyperacusis and misophonia; second, to promote worldwide awareness of these conditions in order to improve the lives of those affected; and third, to provide a foundation for further scientific dialogue and collaboration among clinicians, researchers, and policymakers.

This issue brings together contributions from leading experts across medical, surgical, audiological, psychological, and neuroscientific fields, along with invaluable perspectives from individuals with lived experience. Together, these articles demonstrate the increasing maturity of research into sound intolerance disorders and highlight the importance of interdisciplinary collaboration in shaping both scientific understanding and clinical practice.

This special issue opens with a fundamental contribution by **Brian Moore**, who examines the underlying mechanisms of loudness perception and provides an updated framework for understanding loudness hyperacusis. His discussion of cochlear activity, efferent modulation, and central adaptation offers a mechanistic foundation for the disorder and clarifies how abnormal loudness growth may occur even when standard audiograms are normal. This is followed by a comprehensive review by **Richard Salvi** and colleagues, who use animal models to explore the biological bases of hyperacusis in the context of stress, salicylate exposure, and Fragile X syndrome. Their findings reinforce the role of enhanced central gain and demonstrate how translational research can illuminate underlying neural mechanisms.

Clinical and psychosocial dimensions of hyperacusis are then explored in studies from the World Hearing Center and international collaborators. **Elżbieta Gos** and colleagues assess anxiety in adults with hyperacusis and tinnitus, highlighting important gender differences in psychological correlates and predictors of distress. **Fatima Branco-Barreiro, Talita Paulino** and co-authors extend the discussion into childhood by reporting on school-aged children, identifying associations between hyperacusis and sensory sensitivities such as light and odour intolerance. Together, these studies emphasise that hyperacusis affects individuals across the lifespan and may present with diverse sensory and emotional factors.

A transitional perspective is provided by **Ali Danesh** and colleagues, who examine decreased sound tolerance in the context of autism spectrum disorders (ASD) and consider how genetic or functional mechanisms may link ASD with both hyperacusis and misophonia. Building on this foundation, **Pawel and Margaret Jastreboff** present a neurophysiological model for hyperacusis and misophonia, clarifying the differences in subconscious auditory processing, central gain, and conditioned responses that make these conditions related but also clinically distinct. Their companion paper outlines diagnostic and treatment principles based on the same model, emphasising that appropriate counselling, sound therapy, and conditioning strategies must be tailored separately for hyperacusis and misophonia.

The final two papers focus on misophonia as a lived condition having complex emotional, developmental, and relational components. **Jaelline Jaffe** proposes a series of research priorities concerning the possible roots of misophonia, ranging from genetics and family factors to trauma, neural pruning, and personality traits. **Oleg Banyra** and colleagues conclude the issue with an important clinical study demonstrating that misophonia can have a significant negative impact on the quality of sexual life for both sufferers and their partners. These relational outcomes highlight the urgent need for improved diagnosis, treatment pathways, and social understanding.

The **International Conference on Hyperacusis and Misophonia (ICHM)**, which started in London in 2013, is a biennial scientific meeting designed to accelerate progress in understanding and treating sound intolerance disorders. The conference aims to advance discussion of the latest research findings regarding causes, mechanisms, diagnosis, and treatment; to facilitate the sharing of clinical experiences, case studies, and examples of effective clinical practice from around the world; to promote interdisciplinary dialogue by bringing together specialists in audiology, ENT, mental health, neuroscience, epidemiology, psychoacoustics, psychometrics, neurology, and other relevant fields; to encourage future developments and technological innovations in assessment and treatment; to increase awareness of the profound impact hyperacusis and misophonia can have on quality of life; and to support debates on how best to improve access to health, educational, and social services for those affected. Insights from previous conferences have been published in Noise & Health [1,2] and have helped shape the international research and clinical landscape.

Given this background, it is with great pleasure that I announce that the **8th International Conference on Hyperacusis and Misophonia (ICHM8)** will take place in **Hanover, Germany, from 14 to 16 October 2026**. We look forward to building on the momentum created by previous conferences and deepening our shared commitment to patients, research, and clinical excellence.

I hope you enjoy this special issue and that it inspires further innovation, collaboration, and progress in understanding and supporting individuals living with hyperacusis and misophonia

Dr. Hashir Aazh
Founder, International Conference on Hyperacusis and Misophonia (ICHM)
Guest Editor, Special Issue on Misophonia and Hyperacusis, Journal of Hearing Science

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D Data interpretation
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G Funds collection

HYPOTHESIS PAPER

LOUDNESS HYPERACUSIS: MECHANISMS OF LOUDNESS PERCEPTION AND THEIR BREAKDOWN

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Abstract

This paper is concerned with loudness hyperacusis, a condition where sounds of medium and high levels appear to be louder than normal. The "normal" perception of loudness can be understood using a model that takes into account the processing of sounds in the peripheral auditory system, including the outer ear, middle ear, and cochlea. This model has been modified to take into account the perception of loudness by people with cochlear hearing loss. The model predicts the loudness recruitment typically associated with cochlear hearing loss, and also predicts that hearing loss can sometimes be associated with "over-recruitment," so that some sounds appear louder than normal. However, the model does not account for the fact that loudness hyperacusis can occur for people with normal or near-normal audiograms. This suggests that factors associated with higher levels in the auditory system also need to be taken into account. Here, two such factors are considered: the functioning of the efferent system regulating the active mechanism in the cochlea, and effects of central plasticity and adaptation. Both may play a role in hyperacusis.

Keywords: brain plasticity • hyperacusis • loudness • efferent system • loudness recruitment

NADWRAŻLIWOŚĆ NA GŁOŚNE DŹWIĘKI: MECHANIZMY PERCEPCJI GŁOŚNOŚCI I ICH ROZKŁAD

Streszczenie

Niniejszy artykuł dotyczy nadwrażliwości słuchowej, czyli stanu, w którym dźwięki o średnim i wysokim poziomie wydają się głośniejsze niż normalnie. „Normalne" postrzeganie głośności można zrozumieć za pomocą modelu, który uwzględnia przetwarzanie dźwięków w obwodowym układzie słuchowym, w tym w uchu zewnętrznym, uchu środkowym i ślimaku. Model ten został zmodyfikowany w celu uwzględnienia percepcji głośności przez osoby z ubytkiem słuchu typu ślimakowego. Model przewiduje po pierwsze, rekrutację głośności charakterystyczną dla ślimakowego ubytku słuchu, a po drugie, że ubytek słuchu może czasami powodować „nadmierny efekt wyrównania głośności", tak że niektóre dźwięki wydają się głośniejsze niż normalnie. Model ten nie uwzględnia jednak faktu, że nadwrażliwość słuchowa może występować u osób z audiogramem w normie lub prawie w normie. Sugeruje to, że należy również wziąć pod uwagę czynniki związane z wyższymi poziomami układu słuchowego. Rozważane są tutaj dwa takie czynniki: funkcjonowanie układu eferentnego regulującego aktywny mechanizm w ślimaku oraz efekty plastyczności mózgu i jego zdolności adaptacji. Oba mogą odgrywać rolę w nadwrażliwości słuchowej.

Słowa kluczowe: plastyczność mózgu • nadwrażliwość słuchowa • głośność • układ eferentny • efekt wyrównania głośności

Key to abbreviations	
ART	acoustic reflex threshold
DPOAEs	distortion product otoacoustic emissions
ERB_N	equivalent rectangular bandwidth of the normal auditory filter
HCL	highest comfortable level
HL	hearing level
HQ	Hyperacusis Questionnaire
HTLs	hearing threshold levels
IHC	inner hair cell

Key to abbreviations	
IHS	Inventory of Hyperacusis Symptoms
LDL	loudness discomfort level
LS	loudness suppression
MAF	minimum audible field
MOC	medial olivocochlear
OHCs	outer hair cells
SLT	sound level tolerance
ULL	uncomfortable loudness level

Introduction

Loudness is defined as the intensive attribute of auditory sensation in terms of which sounds can be ordered on a scale extending from soft to loud [1]. Put more simply, loudness is the subjective impression of the strength of a sound. The unit of loudness is the sone. One sone is defined as the loudness of a 1000 Hz sinusoid at 40 dB SPL, presented binaurally from a frontal direction in a free-field as perceived by people with normal hearing. A sound with a loudness of 4 sones is 4 times as loud as a sound with a loudness of 1 sone. A loudness-related quantity that may be easier to interpret is the loudness level, which is decibel-like and has units of phons. The loudness level of any sound in phons is the level (in dB SPL) of the 1000 Hz sinusoid to which it sounds equal in loudness for listeners with normal hearing. For example, if a sound *S* appears to be as loud as a 1000 Hz sinusoid with a level of 45 dB SPL, then the sound *S* has a loudness level of 45 phons. For sounds with levels above about 40 dB SPL, the loudness in sones roughly doubles for each 10-phon increase in loudness level [2,3]. For example, if the loudness level is increased from 40 phons to 60 phons the loudness increases from 1 sone to 4 sones.

For most people with normal hearing, sounds are usually audible and comfortably loud over a wide range of sound levels, from about 0 to 90 dB SPL for mid-range frequencies. However, for some people, sounds become unpleasantly loud when their level is well below 90 dB SPL. This represents a form of hyperacusis. There is no universally agreed definition of hyperacusis, and there may be several varieties of hyperacusis [4]. Here, the focus is on *loudness hyperacusis*, a condition where sounds with moderate levels are perceived as uncomfortably or unpleasantly loud, even though those sounds would not be perceived as unpleasantly loud by most people.

Figure 1 illustrates various ways in which hyperacusis might occur. The figure plots the level of a 1-kHz tone against the loudness level of that tone in phons. For a person with normal hearing the loudness level of the tone is equal to its physical level, as indicated by the solid line in **Figure 1**. A function for a person who is hypersensitive at all levels is illustrated by the short-dashed line in **Figure 1**. This might occur if transmission through the middle ear was especially efficient or the active mechanism in the cochlea was especially efficient at the test frequency. Such cases are sometimes observed, but they are not common. A more common situation associated with loudness hyperacusis is where hearing sensitivity at low levels is normal (i.e., hearing threshold levels, HTLs, are normal) but moderately intense sounds are perceived as louder than normal, as illustrated by the medium-dashed line in **Figure 1**. For this example, a tone with a level of 70 dB SPL would have a loudness level of 90 phons. In other words, the 70 dB SPL tone appears as loud for the person with hyperacusis as a 90 dB SPL tone for a person with normal hearing. Finally, the long-dashed line in **Figure 1** illustrates a case of a person with hearing loss combined with loudness recruitment; the latter is an abnormally rapid growth of loudness once the level of a sound exceeds the detection threshold [5–7]. For levels above about 83 dB SPL, the loudness for the impaired ear is greater

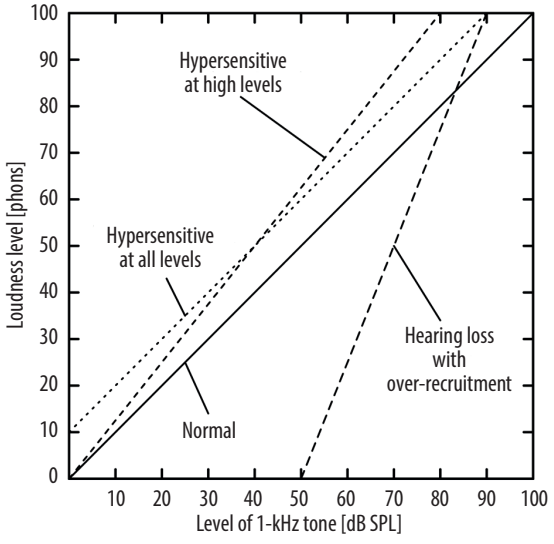

Figure 1. Illustration of various forms of loudness hyperacusis

than would be perceived by a person with normal hearing. This is sometimes called *over-recruitment*. Loudness recruitment is described in more detail in the next section.

Loudness hyperacusis can be diagnosed using a structured clinical interview, using questionnaires, such as the Hyperacusis Questionnaire (HQ) [8] or the Inventory of Hyperacusis Symptoms (IHS) [9,10], or by measurement of the level at which sounds first become uncomfortably loud [11]. Common measures of the last of these are the loudness discomfort level (LDL), the uncomfortable loudness level (ULL), and the highest comfortable level (HCL). Often, these terms are used interchangeably. The precise instructions to the person being tested are important. The British Society of Audiology [12] recommends the following instructions for determining the ULL: "I will gradually make the sound louder in your ear, and you must press the button (or raise your hand) as soon as the sound becomes uncomfortable (uncomfortably loud). This is not a test to find the loudest sound you can tolerate; it is a test to find what level of sound you find uncomfortable. You should press the button (or raise your hand) only when the sound becomes uncomfortable; but make sure you press (raise) it as soon as the sound reaches that level." In the clinic, ULLs are usually measured using sinusoidal tones presented via an audiometer, and the stimulus levels are calibrated in dB HL, rather than dB SPL.

For normal-hearing people without hyperacusis, the average ULL across the audiometric frequencies (usually from 0.5 to 4 kHz, but sometimes averaged over a wider range) usually lies between 86 and 100 dB HL [13–15]. The average ULLs reported for patients with hyperacusis vary widely across studies, from 66.3 dB HL ($SD = 15$) [16], to 77 dB HL [17], or to 83 dB HL ($SD = 17$) [15]. The differences across studies may reflect differences in the patient populations or in the exact instructions given to the patients. Aazh and Moore [18] proposed an overall measure to characterise ULLs for a given patient. ULL values were first averaged across all audiometric frequencies

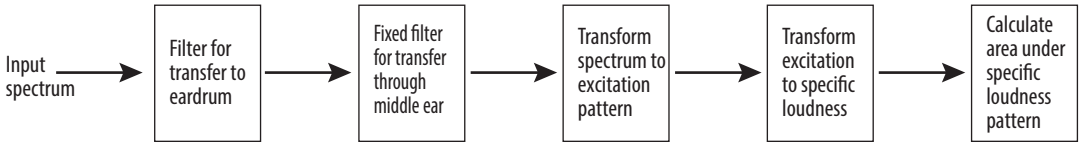

Figure 2. Block diagram of the stages of the model of loudness perception for normal hearing

(0.25, 0.5, 1, 2, 3, 4, 6, and 8 kHz), separately for each ear. The across-frequency average ULL for the ear with lower average ULL is denoted ULL_{min}; this provides an overall measure of loudness tolerance for the more sensitive ear.

The criteria for diagnosing hyperacusis handicap based on HQ scores are not generally agreed upon. Khalfa et al. [8] suggested a cutoff score of 28, Meeus et al. [19] suggested a cutoff score of 26, while Fackrell et al. [20] suggested that the cutoff score of 28 needs to be re-evaluated but did not propose a definite value. Aazh and Moore [18] showed that a diagnosis of hyperacusis handicap based on ULLs could be made consistent with a diagnosis based on HQ scores using the following cutoff values: $ULL_{min} \leq 77$ dB HL and HQ score ≥ 22. With these cutoff values, 95% of patients with ULL_{min} values meeting the criterion also met the criterion based on HQ scores, and vice versa.

Models of loudness perception

This section describes models of loudness that can predict the major features of loudness perception for people with normal hearing and people with hearing loss. The models are primarily based on simulations of the function of the peripheral auditory system. The model for normal hearing [21,22] is based on a modification of a model described by Zwicker and Scharf [23]. Its basic structure is illustrated in **Figure 2**. This version of the model is applicable only to steady sounds and uses the spectrum of the sound as its input. The model has been extended to deal with time-varying sounds [24–26], but that is beyond the scope of this paper.

The first stage of the model is a filter to account for the transfer of sound from the sound source to the eardrum (left-most box in **Figure 2**). The concha and ear canal together lead to a resonance centred near 3 kHz, which increases the level at the eardrum relative to that measured in the sound field by 12–15 dB [27,28]. This largely accounts for the fact that the absolute threshold, specified as the minimum audible field (MAF), is lowest for frequencies near 3 kHz [29].

The second stage of the model is a filter to account for the transfer of sound through the middle ear to the cochlea (second box in **Figure 2**). This transfer is most efficient for mid-range frequencies [30]. Transmission through the middle ear becomes progressively less efficient for frequencies below about 500 Hz, and this partly accounts for the fact that the MAF increases progressively as the frequency is decreased below 500 Hz. There is considerable individual variability in the efficiency of transfer of sound through the middle ear, especially at low frequencies, and this may partly account for the finding that some individuals are especially sensitive to and are bothered by low-frequency environmental sounds, such as those produced by wind generators [31].

The third stage of the model involves the transformation of the spectrum reaching the cochlea into an auditory excitation pattern (middle box in **Figure 3**). The cochlea is conceived of as containing an array of bandpass filters called the auditory filters, with centre frequencies ranging from about 50 Hz [32,33] to 17 kHz [34]. The excitation pattern is defined as the output of the auditory filters as a function of filter centre frequency [35,36], plotted with units of dB versus centre frequency, with the centre frequency transformed to the perceptually relevant ERB_N-number scale [37]. The excitation pattern can be conceived of as a smeared internal representation of the spectrum of the sound reaching the cochlea.

The fourth stage of the model involves transformation of the excitation level at each centre frequency into a quantity called *specific loudness*, which is a kind of loudness density (fourth box in **Figure 2**). Specific loudness has units sones/ERB_N, where ERB_N is the equivalent rectangular bandwidth of the auditory filter at that centre frequency for young listeners with normal hearing [36]. The transformation involves a compressive nonlinearity that simulates the compression that occurs in the cochlea and is mediated by the motor activity of the outer hair cells (OHCs) [38,39]. This is often referred to as the *active mechanism*. The active mechanism results in an amplification of the cochlear response by about 55 dB for low-level sounds, but the amplification decreases as the input level decreases [40]. As a result, when the input sound level increases from 0 to about 90 dB SPL, the response in the cochlea may increase by only 30–35 dB. It is assumed that the overall loudness of a sound is equal to the sum of the specific loudness values across centre frequencies, which is equivalent to the area under the specific loudness pattern (right-most box in **Figure 2**).

The loudness model described above has been modified so as to account for the perception of loudness for people with sensorineural hearing loss [41,42]. The models for impaired hearing are based on the assumption that the hearing loss at each frequency, HL_{TOTAL}, is the sum of the hearing loss due to reduced OHC function, HL_{OHC}, and the hearing loss due to reduced inner hair cell (IHC), synaptic and/or neural function, which for simplicity is denoted HL_{IHC}. This is expressed by the equation:

$$HL_{TOTAL} = HL_{OHC} + HL_{IHC}.$$

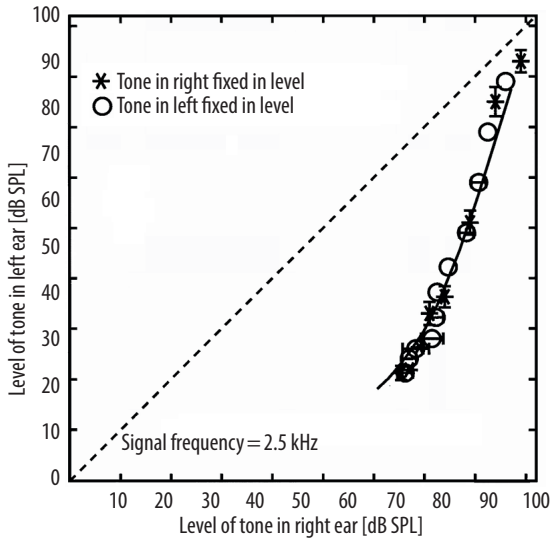

Figure 3. Results of loudness matching of tones presented in alternation to the two ears for a participant with near-normal hearing in the left ear and hearing loss in the right ear

For example, if the total hearing loss at a given frequency is 65 dB, 50 dB of that loss might be due to OHC damage and 15 dB to IHC damage. It is assumed that HL_{OHC} cannot be greater than about 55 dB. The effects of OHC damage are simulated by broadening of the auditory filters (and hence "smearing" of the excitation pattern) and by steepening the functions relating excitation level to specific loudness, both by an amount that increases with increasing HL_{OHC}. The latter mimics the effect of loss of cochlear compression produced by reduced functioning of the active mechanism [40,43]. The effects of IHC dysfunction are simulated by a simple attenuation of the excitation level.

The model can predict with good accuracy the typical effects of loudness recruitment. An example is given in **Figure 3**, which shows the results of loudness matching for tones presented alternately to the two ears via headphones for a participant with near-normal hearing in the left ear and a moderate-to-severe hearing loss in the right ear [7]. At the test frequency of 2.5 kHz the absolute threshold was 27.2 dB SPL for the left ear and 71.4 dB SPL for the right ear. Loudness matches were made with the level of the tone fixed in the right ear and the level in the left ear adjusted to achieve a loudness match (asterisks in **Figure 3**) or with the level fixed in the left ear and the level in the right ear adjusted (circles in **Figure 3**). The dashed line shows where the matches would lie if both ears were completely normal. The solid line shows the predictions of the loudness model [42]. It is clear that the model predicts the loudness matches with good accuracy. For this example, at the highest levels, equal loudness for the two ears occurred when the tones at the two ears were approximately equal in level. In other words, loudness recruitment was near "complete". If the value of HL_{OHC} for the impaired ear is set to its maximum value, the model predicts a small amount (about 5 dB) of over-recruitment; at equal high levels the sound would be louder for the impaired ear than for the normal ear. However, the magnitude of the predicted over-recruitment is small, probably too small to account for the loudness of moderate-level sounds experienced by hearing-impaired people with hyperacusis. Also, the model cannot account for the hyperacusis experienced by some people with normal audiometric thresholds. Hence, there must be factors influencing loudness perception that are not taken into account by the model. Two possible factors are next considered.

The role of the efferent system

The medial olivocochlear (MOC) efferent system is a system of projections from the superior olive to the cochlea [44]. The projections are mainly to the OHCs in the cochlea [44]. There is evidence that activation of the MOC system is driven by the responses of unmyelinated type II spiral ganglion cells in the cochlea, each of which innervates many OHCs [45]. The MOC system can be activated by a sound presented to either or both ears [46,47], and its main effect is to reduce the amplification provided by the cochlear active mechanism [48]. This reduced amplification occurs for both cochleae, even if the activating sound is presented to one ear only. The function of the efferent system is not clear [49]. It has been suggested that it reduces neural saturation effects and hence improves the ability to detect both non-speech and speech signals in the presence of background noise [50,51]. Another possibility is that the efferent system helps to protect the cochlea from the damaging effects of intense noise [52,53]. Whatever its function, it is clear that the efferent system influences the sound-evoked neural activity flowing from the cochlea to the brain, and this would be expected to influence loudness perception. The role of the efferent system is not taken into account in the loudness models described above.

To judge the loudness of sounds, the auditory system must "know" what regulatory signal is being sent to the cochlea from the MOC system at any moment. The neural activity flowing up the auditory nerve can be interpreted correctly only if the MOC signal is taken into account. Similar effects arise in other sensory systems and they are generally explained in terms of what is called *outflow theory* [54]. The idea behind outflow theory is that when a neural command/control signal is sent from the brain or brainstem to a more peripheral structure, a copy of the command/control signal is sent to the part of the brain that is concerned with interpreting signals from that peripheral structure. The copy is called a *corollary discharge* or *efference copy*. The copy is used by the brain to achieve an appropriate interpretation of the neural signals from the peripheral structure.

Outflow theory was proposed by Helmholtz [55] to explain the fact that the visual world appears stable when we move our eyes, despite movements of the image on the retina. He proposed that when the brain sends "instructions" to the eye muscles to move the eyes, an efference copy is sent to the part of the brain dealing with vision, and this copy is used to compensate for the change in retinal image produced by the eye movement. There are two key pieces of evidence supporting the outflow theory in the case of eye movements. Firstly, if the eye is moved by pressing on the eyelid with a finger and wobbling the finger, the world appears to move. This happens because

the retinal image moves, but there is no corresponding efference copy, because the brain did not instruct the eye muscles to move. The second piece of evidence is that if the eye muscles are temporarily paralysed, as is sometimes done during eye surgery, then if the person tries to move their eyes, the world appears to move, even though the retinal image stays stable. This happens because the efference copy is not matched by a corresponding change of the image on the retina.

A role for the efferent system in hyperacusis was suggested by Knudson et al. [56]. They assessed what they called *sound level tolerance* (SLT) for four groups of age-matched men, all with near-normal audiometric thresholds: (1) no tinnitus/high SLT; (2) no tinnitus/low SLT; (3) tinnitus/high SLT; (4) tinnitus/low SLT. SLT was assessed by measuring ULLs and also via three questions about sound tolerance in everyday life. MOC function was assessed using the change in magnitude of distortion product otoacoustic emissions (DPOAEs) measured in one ear canal and elicited by broadband noise presented to the contralateral ear. The noise reduced the magnitude of DPOAEs for all groups, as expected, but the reduction was significantly greater for the groups with tinnitus and/or low SLT, indicating hyperresponsiveness of the MOC system compared with the group with no tinnitus/high SLT. The authors concluded that for those with low SLT, "results suggest hyperresponsiveness of the interneurons of the MOC system residing in the cochlear nucleus and/or MOC neurons themselves".

Although these results appear to suggest a role of the efferent system in hyperacusis, they are actually in the opposite direction from what might have been expected if hyperactivity of the MOC system was the only factor affecting hyperacusis. Consider a situation where a moderately intense sound activates the efferent system, and this in turn sends control signals "instructing" the cochleae to reduce the gain provided by the active mechanism (together with an efference copy). If the efferent system is hyperactive in individuals with hyperacusis, as suggested by Knudson et al. [56], the reduction in gain will be greater than expected from the efference copy. In this case, the brain would be expected to interpret the sound as being softer than normal. However, Knudson et al. pointed out that, based on their own and previous data, neural pathways involving every major division of the cochlear nucleus show hyperactivity in humans or animals with tinnitus and/or low SLT. They suggested that top–down neuromodulation drives overactivation of the auditory brain stem generally. Consistent with this, Lauer et al. [49] suggested that MOC enhancement in those with reduced SLT may simply be a byproduct of decreased central inhibition. The roles of top–down influences and central inhibition are discussed in the next section of this paper.

Another possible way in which the efferent system may be linked to hyperacusis derives from the finding that the MOC reflex is driven by type II spiral ganglion cells [45]. Type II afferents are activated when OHCs are damaged [57], and this might lead to an increase in the MOC signal to the cochlea, together with an increase in the efference copy. However, the MOC signal might have only a small effect on the signals flowing from the cochlea because of the reduced ability of the damaged OHCs to alter cochlear gain. The mismatch between the efference copy and the effect of the MOC signal might result in an increased perception of loudness – i.e., hyperacusis.

An example that is consistent with changes in loudness perception resulting from a discrepancy between the control signal and the efference copy comes from a study of patients who had undergone surgery for vestibular schwannoma (also called acoustic neuroma) on one side only [58]. The surgery resulted in deafness on the operated side, because the auditory nerve was severed. All of the patients perceived tinnitus on the deaf side, as is common in such cases. Cope et al. [58] found that that presentation of a noise to the "good" (non-operated) ear resulted in an increase of the loudness of the tinnitus heard on the deaf side, and the higher the noise level the greater was the increase in loudness. Thus, rather than masking the tinnitus, the noise in the good ear increased its loudness. Cope et al. [58] explained this result in the following way. When noise was presented to the good ear, signals from the MOC system would have been sent to the cochleae on both sides, but the signals would not have reached the cochlea on the deaf side, as the MOC system was severed at the auditory nerve level as part of the surgery (and even if the cochlea did respond, there would be no resulting signal at higher levels in the auditory system, as the auditory nerve itself was severed). The efferent control signals would have carried "instructions" to decrease the gain of the active mechanism progressively as the level of the noise in the "good" ear was increased, and efference copies of the control signals would have been sent to the brain. However, the abnormal activity in the auditory pathway that gave rise to the tinnitus was presumably not affected by the signals from the MOC system. The unchanging tinnitus signal in combination with the efference copy of the "instructions" to decrease the gain, may have resulted in the increasing loudness of the tinnitus with increasing noise level in the good ear.

There are many studies of the role of the MOC system in animals using extreme manipulations, such as severing the efferent system surgically, but few if any studies of more graded changes in function of the MOC system [49]. There have been a few studies of patients who have had the MOC system severed during a surgical procedure called vestibular neurectomy, which was used to treat severe vertigo [59,60], but these studies did not assess loudness perception and the patients in the studies had hearing loss, which complicates the interpretation of the results. Hence, the role of the MOC system in loudness perception remains uncertain. Loudness hyperacusis may sometimes occur as a result of changes in the effectiveness of the MOC system, but research is needed to establish whether and how often this is the case.

Brain plasticity and central gain

There is considerable evidence that the perception of loudness can change as a result of auditory experience [61]. In other words, there is plasticity in loudness perception. Most studies of plasticity have assessed changes in loudness perception following changes in auditory input over relatively long time periods, typically weeks or months.

For example, when an earplug is placed in one ear only, say the left, the apparent locations of sound sources initially appear shifted to the right, presumably because sounds in the right ear appear louder than sounds in the left ear. However, with extended experience of using the unilateral earplug, the perceived spatial locations of sound sources shift back towards their veridical locations [62,63]. The effects of a unilateral earplug on loudness perception and other measures related to loudness were assessed by Hutchinson et al. [64]. They measured changes in the acoustic reflex threshold (ART) and loudness perception following two weeks of use of a unilateral earplug. A lower ART means that the sound level required to activate the acoustic reflex has decreased. The ART decreased on average by 8–10 dB, with modest increases in loudness perception after 1 week but no further increases after 2 weeks of earplug use. A similar study by Munro and Blount [65] showed decreases in the ART following 1 week of use of a unilateral earplug.

A complementary approach is to increase the sound level in one ear by fitting a unilateral hearing aid. Munro and Trotter [66] tested 12 participants with symmetrical age-related hearing loss. They measured ULLs for each ear prior to and 3 years after the fitting of unilateral hearing aids. Audiometric thresholds were symmetrical both pre- and post-fitting. Mean ULL values were symmetrical before fitting. The mean ULL values increased for both ears after fitting, but the mean increase was greater for the fitted ear (mean of 2 and 4 kHz = 14.5 dB) than for the non-fitted ear (mean of 7 dB). Several studies have shown that the preferred gain of hearing aids increases with increasing experience of the aids [67] and that the perceived loudness of sounds of a given level decreases with increasing experience of hearing aids [61].

The outcomes of these studies have usually been interpreted in terms of changes in *central gain* [68–71]. The idea is that following decreases (or increases) in the neural activity flowing from the cochlea, mechanisms in the brainstem or auditory cortex apply greater (or lower) "gain" to the signal coming from the auditory nerve to achieve a form of homeostasis. Auerbach et al. [69] described how increased central gain associated with cochlear dysfunction might occur in three ways: (1) via a decrease in inhibitory synaptic responses; (2) via an increase in excitatory synaptic responses; or (3) via alterations to intrinsic neuronal excitability. They presented evidence that all three of these occur. Sustained alterations in inhibitory input following cochlear dysfunction have been demonstrated at levels of the auditory system as peripheral as the cochlear nucleus, and also at more central levels, including the inferior colliculus and auditory cortex. These changes in inhibition often involve the neurotransmitter GABA. Increases in excitatory responses following cochlear dysfunction have been found in the auditory brainstem and midbrain, and often involve the neurotransmitter glutamate. Finally, changes in intrinsic excitability following cochlear dysfunction have been demonstrated in the dorsal cochlear nucleus and pyramidal cells of the auditory cortex. It seems plausible that all three types of change may be associated with hyperacusis following cochlear dysfunction. In addition, there can be plastic changes in the tononotopic mapping of frequency to place in the auditory cortex [72].

Plastic changes in the responses of the central auditory system in response to changes in peripheral input are often referred to as *maladaptive plasticity* when they result in undesired effects such as hyperacusis and tinnitus. It is beyond the scope of this paper to give details of the physiological mechanisms underlying adaptive plasticity. For reviews, see Auerbach et al. [69] and Roberts and Salvi [70].

Consider now how adaptive plasticity would apply to a person with hearing loss combined with loudness recruitment who does not use hearing aids. Such a person hears most sounds (with low and medium levels) as softer than normal. The person may adapt to this: the central auditory system increases the gain to compensate for the reduced signal coming from the cochlea. But this increased central gain may be applied to all sounds, regardless of their level. Hence, moderately intense sounds may be perceived as unpleasantly loud; the person has *loudness hyperacusis*.

It should be noted that the auditory cortex does not just relay or passively respond to information about sound coming from lower levels in the auditory system. Rather, it interprets and assigns meaning to sounds. Altered cortical processing may amplify the emotional or discomfort response to sounds that would otherwise be considered normal. Also, the auditory cortex and brainstem neural centres interact with the limbic system, which is concerned with emotional responses. There is considerable evidence that hyperacusis is associated with increased activity in the limbic system [73–75]. This may account for the distress that can be experienced by people with hyperacusis.

It is less clear how loudness hyperacusis might arise from changes in central gain for people whose audiometric thresholds are normal. One possibility is that that there is some underlying damage that reduces the signal coming from the cochlea but does not affect audiometric thresholds. There is evidence from both animal studies [76] and human studies [77,78] that noise exposure can lead to loss of the synapses that connect the IHCs to the neurons that make up the auditory nerve. This is called *cochlear synaptopathy*. It occurs very rapidly during or after the exposure. Subsequently, the neurons in the auditory nerve may degenerate, an effect called *neuropathy*. Both synaptopathy and neuropathy also occur with increasing age [79–81]. The audiogram can remain normal or near-normal even when there is quite substantial cochlear synaptopathy/neuropathy [82]. Consistent with this, noise exposure is associated with greater measured difficulty in understanding speech in noise [78,83–86] and greater self-reported hearing difficulty [87], even when the audiogram remains within normal limits. Hearing difficulty when audiometric thresholds are normal is often called *hidden hearing loss*, but the term *hidden hearing disorder* is preferable [88] because, by definition, hearing loss is what is measured using the audiogram. Cochlear synaptopathy/neuropathy would reduce the neural signals coming from the cochlea, and this might lead to increased central gain and hence loudness hyperacusis. There is considerable evidence that noise exposure is associated with an increased incidence of loudness hyperacusis [89,90], and that this may be mediated by cochlear synaptopathy/neuropathy [91–94]. It is worth noting that synaptopathy is thought primarily to affect the synapses between IHCs and neurons with

low spontaneous rates, which respond only at relatively high stimulus levels [95]. If this is the case for humans, it might explain why hyperacusis is associated with increased loudness for sounds presented at moderate and high levels, but not for sounds at low levels.

It is possible that cochlear synaptopathy/neuropathy occurs to some extent even for people with normal audiometric thresholds who have not been noise exposed. This could be the case for some people who have difficulties understanding speech in noise but have normal audiometric thresholds [96,97]. This might account for the existence of loudness hyperacusis among people with normal audiometric thresholds and no history of excessive noise exposure.

The evidence for plasticity in loudness perception has led to proposals for treatments that might reverse maladaptive plasticity, and hence might alleviate loudness hyperacusis [61]. In a recent study, Formby et al. [98] described the results of a 6-month field trial of an intervention for debilitating hyperacusis. The intervention included structured counselling, promotion of safe sound exposure, and exposure to broadband sound from sound generators. The authors stated that "This intervention is designed to overcome barriers to successful delivery of therapeutic sound as a tool to downregulate neural hyperactivity in the central auditory pathways (i.e., the maladaptive mechanism believed to account for primary hyperacusis) and, together with the counselling, reduce the associated negative emotional and physiological reactions to debilitating hyperacusis." The 12 participants had normal or near-normal audiometric thresholds and ULLs ≤ 75 dB HL at several frequencies. The low-level broadband therapeutic sound was delivered by ear-mounted devices fitted bilaterally with either occluding earpieces and output limiting (with adjustable limiting threshold called *loudness suppression*, LS) or open domes. The LS thresholds were incrementally adjusted across visits based on changes in loudness judgments for running speech. Secondary outcomes included categorical loudness judgments, speech understanding, and questionnaires to assess hyperacusis problems, quality of life, and depression. At the end of the trial there was a large mean change in LS (35 dB), indicating greater tolerance for high-level sounds. Most (11 of the 12) participants achieved a change in LS ≥ 16 dB, consistent with improvements in sound-based questionnaire scores.

While the results of this study are encouraging, the complicated nature of the intervention makes it hard to assess the relative importance of the different components, e.g., counselling versus sound generators. Also, the study did not include a control group, so some of the improvements may reflect a treatment/placebo effect.

Other studies of the use of therapeutic sounds for treatment of hyperacusis have also yielded promising but inconclusive results; for a review see Henry [99]. Clearly, further research is needed to clarify whether controlled sound exposure is effective in the treatment of hyperacusis.

Conclusions

Models of loudness perception for "typical" individuals with normal or impaired hearing, based primarily on peripheral auditory processing, can predict several aspects of loudness perception, including the loudness recruitment associated with cochlear hearing loss. However, these models do not predict the existence of loudness hyperacusis among people with normal audiometric thresholds, and they do not account for the low ULLs that can occur for some people with hearing loss. These limitations probably reflect the failure of the models to take into account central processes that may influence loudness perception. Two such processes are the operation of the efferent (MOC) system and changes in central gain following altered signals from the cochlea.

Loudness hyperacusis may occur when the MOC system fails to result in changes in cochlear gain, perhaps because of damage to the active mechanism in the cochlea. However, there is evidence that hyperacusis is associated with hyperactivity of the auditory system at many levels. The role of the efferent system in loudness perception is not fully understood. More research on this role is clearly needed.

Loudness hyperacusis may also be a result of plasticity in the brainstem or auditory cortex following a reduction of the output from the cochlea. The output from the cochlea may be reduced as a consequence of hearing loss (primarily damage to the OHCs and IHCs). It may also be reduced as a consequence of synaptopathy/neuropathy, which reduces the output of the cochlea without markedly affecting audiometric thresholds. The brain appears to adapt to the reduced signal from the cochlea by increasing the central gain, and this may lead to loudness hyperacusis.

In principle, central gain might be reduced by the use of therapeutic sounds, providing an avenue for the treatment of hyperacusis. While the results of clinical trials evaluating the effectiveness of sound therapies for hyperacusis have been encouraging, there is a dearth of well-controlled clinical trials, so the effectiveness of sound therapy requires further evaluation.

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REVIEW PAPER

REVIEW: HYPERACUSIS, ANIMAL MODELS, CHRONIC STRESS, AND AUTISM IN FRAGILE X

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Contributions:
A Study design/planning
B Data collection/entry
C Data analysis/statistics
D Data interpretation
E Preparation of manuscript
F Literature analysis/search
G Funds collection

Abstract

Hyperacusis is a loudness intolerance disorder associated with many medical conditions. To investigate the biological bases of hyperacusis in animals, we developed an auditory reaction time-intensity (RT-I) paradigm to assess the growth of loudness in rats treated with sodium salicylate, a drug suspected to cause hyperacusis. Loudness growth was unaffected by low-dose salicylate; however, high doses significantly reduced reaction times at high intensities, resulting in behavioral evidence of hyperacusis. To identify the neural correlates of salicylate-induced hyperacusis, neural activity was monitored along the auditory pathway. Salicylate significantly reduced the neural output of the cochlea. Paradoxically, neural responses were progressively amplified when relayed towards the central auditory pathway resulting in responses 2x larger than normal in auditory cortex (ACx), evidence of enhanced central gain. Because salicylate dose-dependently increased corticosterone stress hormone levels, rats were chronically fed corticosterone stress hormone to determine its behavioral and electrophysiological effects. This led to enhanced sound-evoked neural response in ACx without altering the neural responses from the cochlea and auditory brainstem. Patients with autism often suffer from sound tolerance issues (i.e., hyperacusis). Fragile X (FX) syndrome is a leading genetic cause of autism. To determine if rats with the FX mutation suffered from hyperacusis, we compared loudness growth functions in FX rats with littermate controls. FX rats had normal hearing thresholds but exhibited behavioral evidence of loudness hyperacusis and abnormal temporal and spectral integration of loudness. These behavioral models of hyperacusis can guide the search for biological bases of hyperacusis.

Keywords: corticosterone • animal models • autism spectrum disorder • hyperacusis • enhanced central gain • Fragile X syndrome

PRZEGLĄD: NADWRAŻLIWOŚĆ SŁUCHOWA, MODELE ZWIERZĘCE, PRZEWLEKŁY STRES I AUTYZM W ZESPOLE ŁAMLIWEGO CHROMOSOMU X

Streszczenie

Nadwrażliwość słuchowa jest zaburzeniem polegającym na obniżonej tolerancji na głośne dźwięki, powiązane z wieloma stanami chorobowymi. Aby zbadać biologiczne podłoże nadwrażliwości słuchowej u zwierząt, opracowaliśmy paradygmat czasu i intensywności reakcji słuchowej (RT-I) u szczurów leczonych salicylanem sodu – lekiem podejrzewanym o wywoływanie nadwrażliwości słuchowej. Niskie dawki salicylanu nie powodowały zmiany w zachowaniu szczurów; jednak wysokie dawki znacznie skróciły czas ich reakcji na głośne dźwięki, powodując zachowania świadczące o nadwrażliwości słuchowej. W celu zidentyfikowanych neuronalne korelatów nadwrażliwości słuchowej wywołanej salicylanem, monitorowano aktywność neuronalną drogi słuchowej. Aktywność neuronalna ślimaka pod wpływem salicylanu znacznie się zmniejszyła. Paradoksalnie odpowiedzi neuronalne w trakcie przechodzenia w kierunku ośrodkowej drogi słuchowej były stopniowo wzmacniane, przez co na poziomie kory słuchowej były dwukrotnie większe niż normalnie, co świadczy o zwiększonym wzmocnieniu ośrodkowym. Ponieważ salicylan zależnie od dawki zwiększał poziom kortykosteronu (hormonu stresu), szczurom przez dłuższy czas podawano ten hormon w celu określenia skutków behawioralnych i elektrofizjologicznych. Zwiększenie poziomu kortykosteronu doprowadziło do podwyższonych odpowiedzi neuronalnych na dźwięki w korze słuchowej przy niezmienionych odpowiedziach neuronalnych ślimaka i pnia mózgu. Pacjenci z autyzmem często cierpią na problemy związane z obniżoną tolerancją na dźwięki (np. nadwrażliwość słuchową). Zespół łamliwego chromosomu X (FX) jest główną genetyczną przyczyną autyzmu. Aby ustalić, czy szczury z mutacją FX mają nadwrażliwość słuchową, porównaliśmy funkcje wzrostu głośności u szczurów FX z grupą kontrolną z tego samego miotu. Szczury FX miały progi słyszenia w normie, ale wykazywały zachowania świadczące o nadwrażliwości na dźwięki oraz nieprawidłowej integracji głośności w odniesieniu do czasu i zakresu dźwięków. Behawioralne modele nadwrażliwości słuchowej mogą pomóc w poszukiwaniu biologicznych podstaw nadwrażliwości słuchowej.

Słowa kluczowe: kortykosteron • modele zwierzęce • zaburzenia ze spektrum autyzmu • nadwrażliwość słuchowa • zwiększone wzmocnienie ośrodkowe • zespół łamliwego chromosomu X

Key to abbreviations	
ACx	auditory cortex
ASAP	active sound avoidance paradigm
ASD	autism spectrum disorder
ASR	acoustic startle reflex
BBN	broadband noise
CAP	compound action potential
CN	cochlear nucleus
CORT	corticosterone
COX	cyclooxygenase
DPOAE	distortion product otoacoustic emissions
FDA	Federal Drug Administration
ffABR	far-field auditory brainstem response
FX	Fragile X syndrome
HPA	hypothalamic–pituitary–adrenal axis
IC	inferior colliculus
IHC	inner hair cells
KO	knock-out
MGB	medial geniculate body
mGlu5	metabotropic glutamate receptor 5
NBN	narrow-band noise
nfACx	near-field evoked response from the ACx
ns	not significant
Oct	octave
OHC	outer hair cell
re	referenced to
RMS	root-mean-square
RT	reaction time
RT-D	reaction time–duration functions
RT-I	reaction time–intensity functions
SS	sodium salicylate
ULL	uncomfortable loudness level
WT	wild-type

Introduction

Hyperacusis is a potentially debilitating disorder in which everyday sounds are perceived as intolerably loud, annoying, and sometimes painful [1,2]. The prevalence of hyperacusis among adults ranges from 8 to 15%; however, the exact number varies with age, gender, and other factors, including the criteria used to define hyperacusis [3,4]. Much of what is known about hyperacusis comes from clinical studies in which patients report mild or debilitating hyperacusis linked to a long list of medical disorders such as noise-induced hearing loss, fibromyalgia, Williams syndrome, autism spectrum disorder (ASD), superior canal dehiscence, head trauma, migraine, Lyme disease, Bell's palsy, anxiety, and chronic stress [5–11]. Some patients also develop hyperacusis after taking certain Federal Drug Administration (FDA) approved drugs [12–14]. These clinical reports have provided important clues regarding biological factors that may be involved in triggering hyperacusis; however, in many cases the results of these clinical associations with hyperacusis are variable and not compelling [15].

Identifying the biological conditions responsible for inducing hyperacusis in patients is especially difficult because of the lack of control over endogenous and exogenous factors. Consequently, some researchers have begun to investigate the biological bases of hyperacusis in animal models where it is possible to precisely control specific genetic and experimental variables that give rise to hyperacusis and then precisely measure the behavioral, neurophysiological, and biological consequences. This approach has required the development of valid behavioral methods to determine if an experimental manipulation results in hyperacusis (i.e., "the sound is too loud or annoying"). Here we describe several behavioral techniques that have been developed to assess loudness, hyperacusis, and sound avoidance in laboratory rats – a widely used species for studying the behavioral and neurophysiological bases of hyperacusis [16–21]. The behavioral techniques developed in rats have been used to identify drugs and genetic mutations that give rise to loudness hyperacusis, associated neurophysiological changes in the central nervous system, and neuropharmacological approaches to suppressing hyperacusis.

Materials and methods

The methodology for this review focuses on the use of behavioral techniques to assess hyperacusis in rats and the associated neurophysiological changes that occur along the rat auditory pathway during the induction, maintenance, and resolution of hyperacusis. The criteria for selecting articles for this review are peer-reviewed publications that have focused on behavioral measurements of hyperacusis in rats and the associated neurophysiological changes. The changes that occurred in rats before, during, and after hyperacusis were induced by: (1) administering high doses of the ototoxic drug sodium salicylate (the active ingredient in aspirin), which also induces temporary hearing loss and tinnitus; (2) giving chronic oral doses of corticosterone stress hormone; and (3) deletion of the *Fmr1* gene that creates a Fragile X (FX) model of autism. The material in this review was selected from database searches of peer-reviewed publications that appeared on PubMed and Google Scholar up to May 2024. Searches for relevant publications employed the following keywords: rats, behavioral, hyperacusis, loudness hyperacusis, temporal integration, spectral integration, corticosterone, annoyance hyperacusis, Fragile X, autism, *Fmr1*, sodium salicylate, corticosterone, and chronic stress.

Results

Behavioral reaction time measure of loudness growth

The loudness of a pure tone increases with intensity, but as the level approaches 100 dB HL, normal hearing listeners perceive the sound as uncomfortably loud, defined as the

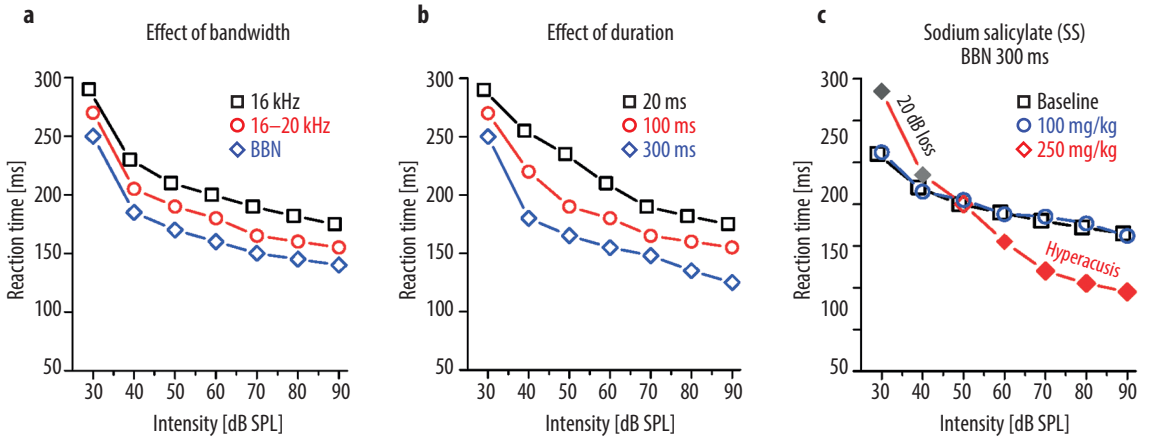

Figure 1. (**a**) RT-I functions for a 16 kHz tone (squares), 16–20 kHz narrow-band noise (circles), and broadband noise (diamonds). At each bandwidth, RT decreases with intensity. At each intensity, RT decreases as bandwidth increases, illustrating spectral integration of loudness. Schematics based on investigator's prior work [32]. (**b**) Graph of RT-I functions for broadband noise bursts of 20, 100, and 300 ms. RT decreases with intensity. At each intensity, RT, a measure of loudness, decreases as bandwidth increases, illustrating the spectral integration of loudness. Schematics based on investigator's prior work [32]. (**c**) RT-I functions using 300 ms BBN bursts in the same animals at baseline and after intraperitoneal injection of 100 or 300 mg/kg of sodium salicylate. RT-I functions following 100 mg/kg sodium salicylate are not significantly different from baseline. RTs after 250 mg/kg sodium salicylate are longer than baseline at 30 dB SPL because salicylate induces approximately 20 dB hearing loss. RTs at intensities from 60 to 90 dB are significantly shorter than baseline, evidence of salicylate-induced hyperacusis. Schematics based on investigator's prior work [32]

uncomfortable loudness level (ULL) [22–24]. However, many other factors affect perceived loudness. For example, the perceived loudness of a tone increases with duration up to approximately 300 ms, after which it plateaus, which is evidence of the temporal integration of loudness [25,26]. Broadband noise is also perceived as louder than a tone of the same overall intensity, which points to the spectral integration of loudness [27]. Psychoacoustic studies in humans have shown that reaction time (RT) decreases as sound intensity increases; thus, reaction time-intensity (RT-I) functions can be used to assess the growth of loudness under different experimental conditions [28].

Neuroscientists have used RT-I functions to assess the growth of loudness in different species [29–31]. **Figure 1a** illustrates the orderly decrease in RT as a function of sound intensity. This relationship is representative of data obtained from rats trained on a "go/no-go" operant conditioning paradigm [32]. To illustrate the spectral summation of loudness, RT-I functions are shown for 16 kHz tone bursts, 16–20 kHz noise bursts, and broadband noise bursts presented at the same intensity. RTs are longest for the 16 kHz tone, slightly shorter for the 16–20 kHz narrow band noise, and shortest for broadband noise – results that are qualitatively consistent with those from humans [27]. **Figure 1b** illustrates RT-I functions obtained from rats using 20, 100, and 300 ms broadband noise bursts. Note that the RTs for 20 ms noise bursts are longer and lie above those for 100 ms, and the RTs for 100 ms are consistently longer and lie above those for 300 ms. Both these results are consistent with human data on the temporal summation of loudness [33,34].

Drug-induced hyperacusis

High doses of sodium salicylate results in sound-evoked hyperactivity in the central auditory pathway [35,36], which is electrophysiological evidence suggestive of hyperacusis. To determine if high doses of salicylate could induce behavioral evidence of hyperacusis, RT-I functions have been measured before and after administering different doses of sodium salicylate, as shown schematically in **Figure 1c** [37]. The open squares in **Figure 1c** show the baseline RT-I function. When rats were treated with 100 mg/kg of salicylate, the RT-I function measured a few hours after treatment was not significantly different from baseline. Similar results were obtained with lower doses of salicylate. In contrast, RT-I functions measured 2–3 h after administering 250 mg/kg of salicylate were shorter than baseline at high intensities, but longer than normal at low intensities (**Figure 1c**). RTs at 30 and 40 dB SPL were longer than baseline because salicylate induced a hearing loss of 20–25 dB. Consequently, low intensity sounds were just above the threshold of hearing, making them less audible (**Figure 1c**, gray filled diamonds). However, RTs at suprathreshold intensities equal to or greater than 60 dB SPL were much shorter than baseline (**Figure 1c**, red filled diamonds), clear evidence of salicylate-induced hyperacusis. Some 1–2 days after discontinuing salicylate treatment, RT-I functions returned to normal (not shown).

Sound-evoked hyperactivity and enhanced central gain

High doses of salicylate have different effects on sound-evoked neural responses measured in the peripheral and central auditory pathway. High doses of salicylate are ototoxic and produce a cochlear hearing loss of about 20–25 dB [38], caused primarily by a reduction in outer hair cell (OHC) electromotility, which disrupts the cochlear amplifier and leads to elevated hearing thresholds [36,39,40]. However, as illustrated in **Figure 2a**, salicylate exerts different effects on sound-evoked neural responses from the peripheral and central nervous systems. The solid black

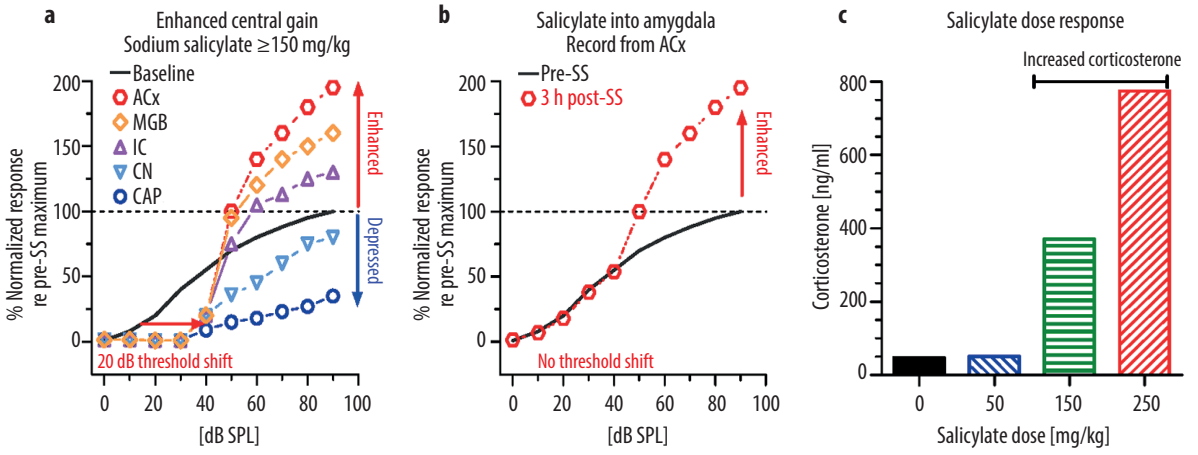

Figure 2. High dose sodium salicylate (150 mg/kg) causes ~20 dB cochlear threshold shift, but enhances sound-evoked neural activity in the central auditory pathway. (**a**) Normalized sound-evoked input/output functions (expressed as percentage of the maximum evoked response at baseline) for cochlear compound action potential (CAP), cochlear nucleus (CN), inferior colliculus (IC), medial geniculate body (MGB), and auditory cortex (ACx). Baseline normalized input/output function has a maximum value of 100% at the highest intensity, 90 dB SPL. High dose salicylate causes ~20 dB cochlear threshold shift that is reflected at all recording locations. Salicylate causes the largest amplitude reductions in the CAP; smaller reductions occur in the CN (decreased CAP and CN). Salicylate causes suprathreshold amplitudes to become progressively larger (enhanced responses above 50 dB SPL) in IC, MGB, and ACx. Schematics based on investigator's prior work [46,120]. (**b**) Normalized sound-evoked input/output function in the ACx before and after infusion of sodium salicylate into the amygdala. Normalized evoked response input/output functions expressed as percentage of maximum evoked response at baseline (100% at 90 dB SPL). Infusion of salicylate into amygdala does not cause cochlear threshold shift, but enhances evoked response in ACx above baseline. Schematics based on investigator's prior work [45,121]. (**c**) Graph illustrating the rise in serum corticosterone versus salicylate dose. Intraperitoneal dose of 50 mg/kg salicylate fails to cause an increase in serum corticosterone above baseline, whereas corticosterone levels increase significantly as salicylate dose increases from 150 to 250 mg/kg. Schematics based on investigator's prior work [44,120]

line in the figure represents the normalized neural response at each intensity relative to the maximum neural response evoked by a 90 dB SPL stimulus (which is defined as 100%). This curve represents the normalized input/output function at different sites along the auditory pathway before administering high doses of sodium salicylate. Before salicylate treatment, neural response amplitudes are at 100% of the maximum amplitude at 90 dB SPL; the normalized response amplitudes gradually decline as stimulus intensity declines. High dose salicylate treatments (≥ 150 mg/kg, i.p.) cause a 20 dB rightward threshold shift of all the normalized input/output functions as illustrated in **Figure 2a**. This 20 dB rightward shift of all the input/output functions is largely due to loss of OHC electromotility and is reflected in a 20 dB rightward shift of the compound action potential (CAP) threshold, an electrophysiological measure reflecting the synchronized sound-evoked neural responses of the cochlear auditory nerve fibers. This peripheral CAP threshold shift is also reflected in all the other input/output functions (rightward shift of 20 dB) at higher levels of the auditory pathway. The CAP input/output function is not only shifted to the right, but the maximum amplitude is depressed by more than 60%, indicating that the neural output of the cochlea has been reduced. The input/output function from the cochlear nucleus (CN) in the auditory brainstem is also shifted to the right 20 dB, reflecting the cochlear threshold shift. The amplitude of the CN response is also depressed compared to its baseline; however, the maximum CN amplitude is only reduced to about 80% of its pre-treatment maximum, indicating that the CAP signal relayed from the auditory nerve to the CN has been amplified to partially compensate for the large amplitude reduction of the CAP response. The input/output function measured at the inferior colliculus (IC) is also shifted to the right by 20 dB, again reflecting a threshold shift at the level of the cochlea. However, the maximum sound-evoked responses from the IC increase rapidly with intensity, and become noticeably larger than baseline values at intensities > 60 dB SPL – evidence of enhanced central gain (amplification) of neural activity received from lower levels of the auditory pathway. Input/output functions measured at the medial geniculate body (MGB) and primary auditory cortex (ACx) show the same rightward threshold shift, but even greater enhanced central gain as the response is relayed rostrally. The maximum neural response in the ACx is nearly twice as large as that measured before high dose salicylate treatment. While there is no improvement in threshold as the signal is relayed from cochlea to cortex, the data in **Figure 2a** indicate that the suprathreshold neural responses leaving the cochlea (i.e., the CAP) are progressively enhanced (amplified) as the neural response is relayed from the cochlea to the brainstem, midbrain, and cortex, evidence of enhanced central gain.

High dose salicylate increases corticosterone (CORT) stress hormone

High doses of salicylate, which are potentially toxic, could elicit a systemic stress response, leading to the release of hormones from the hypothalamic–pituitary–adrenal (HPA) axis [41–43]. To test this hypothesis, the levels of CORT stress hormone in serum were measured before and after treating rats with escalating doses of sodium salicylate [44]. CORT levels were extremely low 2 h after

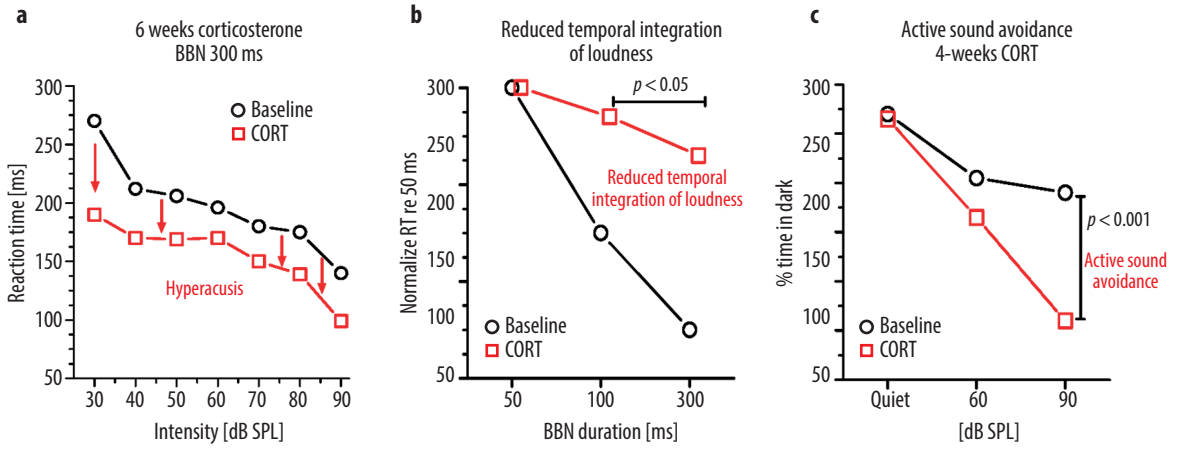

Figure 3. Chronic corticosterone treatment induces loudness hyperacusis, disrupts temporal integration of loudness, and induces sound avoidance hyperacusis. (**a**) Reaction time-intensity functions measured with 300 ms BBN noise bursts at baseline and following 6 weeks treatment with corticosterone in drinking water (25 mg/mL). Chronic corticosterone treatment caused a significant decrease in RTs, evidence of loudness hyperacusis. Schematics based on investigator's prior work [18,122]. (**b**) Normalized RT-D functions measured with BBN bursts of 50, 100, and 300 ms; mean data between 30 and 90 dB SPL and normalized to values obtained with 50 ms BBN bursts. Baseline values declined from 1.0 for 50 ms noise bursts to approximately 0.75 for 300 ms bursts, a 25% reduction. RTs measured after 6 weeks of chronic corticosterone treatment decreased from a normalized value of 1.0 for 50 ms noise burst to 0.93 for 300 ms noise bursts, a 7% reduction. Schematics based on investigator's prior work [18,122]. (**c**) Effects of 4 weeks chronic corticosterone treatment (25 mg/ml drinking water) on active sound avoidance. During baseline testing, rats spent approximately 94% of time in a dark enclosure on quiet trials (no sound), but time in the dark enclosure declined to 82% and 78% during presentation of BBN at 60 and 90 dB SPL respectively. One week after 4-week corticosterone treatment, time in the dark enclosure remained similar to baseline (~93%), but declined to 73% and 52% respectively during presentation of 60 and 90 dB SPL BBN. Schematics based on investigator's prior work [18,122]

treatment with vehicle control (0) or 50 mg/kg of sodium salicylate as illustrated in **Figure 2c**. However, intraperitoneal injections of 150 or 250 mg/kg of sodium salicylate caused a significant, dose-dependent increase in serum CORT levels. Serum CORT levels returned to normal 1–2 days post-treatment (not shown) [45,46].

Chronic CORT stress induces hyperacusis

The preceding results suggest that high levels of CORT stress hormone can act as a powerful trigger for inducing hyperacusis, as suggested by clinical studies [47–50]. To test this hypothesis, rats were administered drinking water containing 25 mg/ml of CORT for 4–6 weeks. RT-I functions were measured with 300 ms broadband noise (BBN) bursts before and after treatment to determine if chronic CORT stress hormone would induce hyperacusis. The RT-I function measured after 6 weeks of CORT treatment fell significantly below baseline values at all intensities from 30–90 dB SPL (**Figure 3a**) [18], behavioral evidence of CORT-induced hyperacusis.

Under conditions of normal hearing, the loudness of a sound increases with stimulus duration up to approximately 300 ms, but it is unclear if CORT treatment would affect temporal integration of loudness. To answer this question, RT-I functions were measured with 50, 100, and 300 ms broadband noise bursts before and after a 6-week treatment of CORT administered in drinking water [18]. To quantify the effect that CORT had on the temporal integration of loudness, RTs measured at 50, 100, and 300 ms were normalized to the RT at 50 ms (value of 1.0) at each intensity between 30 and 90 dB SPL. Then the normalized RT versus duration functions (RT-D) were averaged across all intensities from 30 to 90 dB SPL to obtain the mean normalized RT-D function (**Figure 3b**). The mean normalized RT-D functions measured before treatment (baseline) declined from a normalized value of 1.0 at 50 ms to ~0.85 for 100 ms and then to ~0.75 for 300 ms. The 25% decrease in RT between 50 and 300 ms noise bursts provides clear evidence of temporal integration of loudness. The mean normalized RT-D function measured after CORT treatment decreased from 1.0 at 50 ms to approximately 0.93 at 300 ms, representing just a 7% decline in RT between 50 and 300 ms, substantially less than the 25% decline measured at baseline. Thus, chronic treatment with CORT stress hormone not only induced hyperacusis, but also substantially reduced the temporal integration of loudness.

Chronic CORT stress causes active sound avoidance hyperacusis

To determine if rats would actively avoid moderate or intense sounds, an active sound avoidance paradigm (ASAP) was developed that took advantage of the preference of rats to stay in a dark enclosure while avoiding brightly illuminated open areas, a behavioral preference likely aimed at avoiding capture by natural predators such as hawks. The ASAP apparatus consists of a darkly illuminated enclosure with an opening leading to a brightly illuminated runway connected to a large open arena [18]. On Quiet trials (no sound presented), rats naturally spend about 95% of their time in the dark enclosure. To test for sound avoidance behaviors,

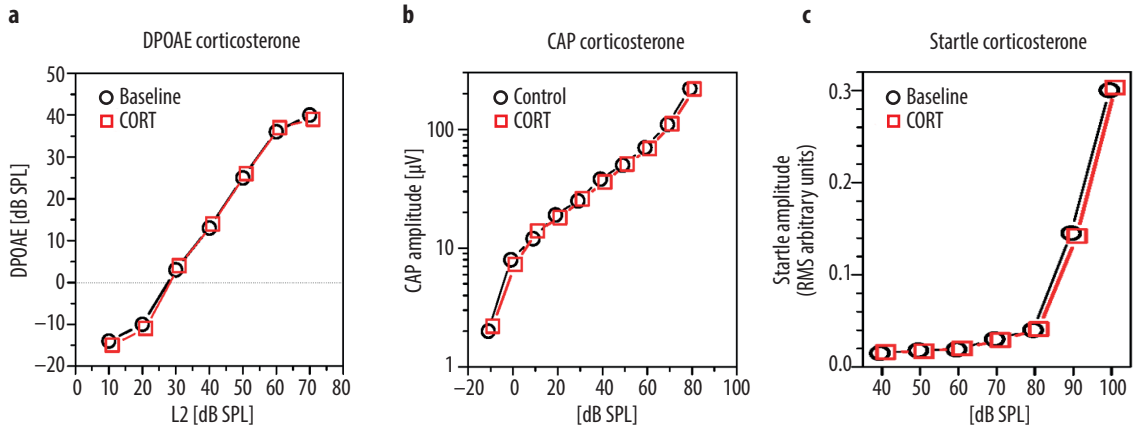

Figure 4. Chronic corticosterone fails to disrupt cochlear or brainstem responses. (**a**) 2f1–f2 DPOAE input/output functions at baseline and 1 week after 4 weeks of corticosterone treatment. Corticosterone treatment did not have a significant effect on DPOAE amplitudes. Schematics based on prior work [122,18]. (**b**) Toneburst-evoked CAP input/output functions at baseline and 1 week after 4 weeks of corticosterone treatment. Corticosterone treatment did not have a significant effect on CAP amplitudes. Schematics based on investigator's prior work [18,122]. (**c**) Amplitude of acoustic startle reflex input/output functions evoked by BBN bursts measured at baseline and 1 week after 6 weeks of corticosterone treatment. Corticosterone treatment did not have a significant effect on the amplitude of the acoustic startle reflex. Schematics based on investigator's prior work [18,122]

60 or 90 dB SPL BBN is presented through a loudspeaker mounted on the roof of the dark enclosure during sound trials. If the sounds are perceived as annoying or aversive, the rats should spend less time in the noisy, dark enclosure and more time in the bright open arena [18]. **Figure 3c** shows the ASAP results obtained from a group of rats before (baseline) and 1 week after 4 weeks of corticosterone treatment (25 mg/ml drinking water). During baseline testing, rats spent about 95% of the time in the dark enclosure on Quiet trials (no sound); however, on trials in which 60 or 90 dB SPL BBN was presented, the percent time in the dark enclosure declined to 82% and 78% respectively, behavioral evidence for active avoidance of the BBN. After the 4-week corticosterone treatment, the percent time spent in the dark enclosure during Quiet trials was nearly identical to baseline values. However, when the 60 and 90 dB SPL BBN was presented, the percent time spent in the dark enclosure decreased below baseline values to ~73% and ~52% respectively. The corticosterone-induced decrease in sound avoidance at 90 dB SPL was significantly less than baseline ($p < 0.001$) [18]. These results suggest that chronic corticosterone treatment had induced avoidance hyperacusis.

Normal distortion product otoacoustic emissions (DPOAE) post-CORT

Circulating CORT, which binds to glucocorticoid receptors in the central nervous system, could conceivably enhance sound-evoked neural activity at one or more sites along the auditory pathway [51–54]. CORT could bind to glucocorticoid receptors expressed on OHCs [55,56] and potentially alter DPOAE amplitudes. To test this hypothesis, DPOAE input/output functions were measured with two primary tones, f1 and f2 ($f2 = 1.2 \times f1$) with the intensity of L2 set 10 dB lower than that of L1 [18]. DPOAE input/output functions were measured across a broad range of 2f1–f2 distortion product frequencies before and 1 week after discontinuing a 4-week treatment with 25 mg/ml of CORT in drinking water. **Figure 4a** shows the DPOAE input/output functions measured at an f2 frequency of 16 kHz before and after the 4-week CORT treatment. CORT treatment did not significantly alter DPOAE input/output functions at any frequency [18]. It is therefore unlikely that CORT-induced hyperacusis was mediated by a change in OHC function.

CAP normal post-CORT

Because glucocorticoid receptors are expressed on inner hair cells (IHC) and auditory nerve fibers [55–57], chronic CORT treatment could conceivably enhance the neural output of the cochlea as reflected in the cochlear CAP. To test this hypothesis, CAP input/output functions were measured over a range of frequencies 1 week after discontinuing the 4 weeks of CORT treatment (25 mg/ml drinking water) and the results compared to similar data collected from an untreated group of control rats. **Figure 4b** compares the CAP input/output function at 16 kHz from the control group and the CORT group. No significant differences were observed either at 16 kHz or at other test frequencies. Thus, chronic CORT treatment did not significantly alter the gross neural output of the cochlea at 16 kHz or at other test frequencies [18].

Acoustic startle reflex normal post-CORT

Glucocorticoid receptors are expressed in the hindbrain, raising the possibility that CORT treatment could enhance sound-evoked neural activity in the brainstem [58,59]. To test this hypothesis, the acoustic startle reflex (ASR), an abrupt sudden motor reflex movement of the head, neck, and hind limbs was measured using moderately intense (> 70 dB SPL) sounds to activate auditory-motor reflex circuits in the brainstem [60,61]. The ASR was measured before and after a 6-week treatment with CORT (25 mg/ml of water) [18]. **Figure 4c** shows the acoustic reflex input/output functions elicited by BBN bursts. ASR amplitude increased rapidly as BBN intensity increased between 70 and

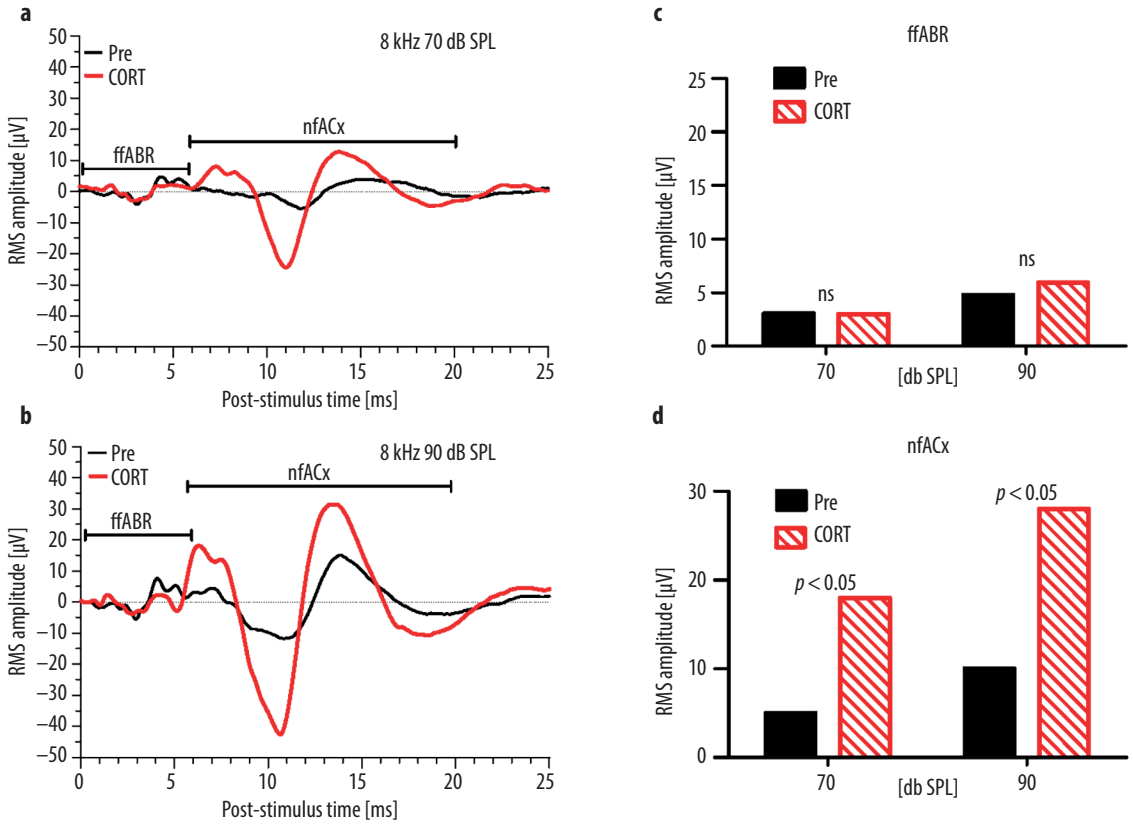

Figure 5. Chronic corticosterone treatment enhances the amplitude of near-field auditory evoked responses. (**a–b**) Auditory evoked responses recorded from a chronic electrode implanted over surface of the auditory cortex (ACx) before and 6 weeks after chronic corticosterone (CORT) treatment (25 mg/ml drinking water). Auditory evoked responses elicited by 8 kHz tone bursts presented at 70 dB (panel **a**) and 90 dB (panel **b**) before (baseline) and after CORT treatment. Small amplitude evoked response waveform occurring between 0 and 6 ms reflects early, far-field evoked response from auditory brainstem (ffABR). Large amplitude evoked response occurring between 6 and 20 ms reflects near-field response from ACx (nfACx). CORT treatment had little effect on ffABR amplitude, but significantly enhanced negative–positive–negative peaks in the nfACx response. Schematics based on investigator's prior work [18,122]. (**c–d**) Root-mean-square (RMS) amplitude of ffABR (0–6 ms) and nfACx (6–20 ms) measured before (Pre) and after CORT treatment. CORT did not significantly (ns) alter ffABR amplitude at 60 and 90 dB SPL, results consistent with the findings in **a–c**. Chronic CORT treatment significantly ($p < 0.05$) enhanced the amplitude of the nfACx response, evidence of enhanced central gain. Schematics based on investigator's prior work [18,122]

90 dB SPL. However, there was little difference between the ASR input/output functions measured at baseline and 6 weeks after CORT treatment. The lack of change in ASR amplitudes following treatment suggests that CORT-induced hyperacusis is unlikely to be due to neural hyperactivity originating in the brainstem.

CORT-induced ACx hyperactivity

As shown above, high doses of salicylate result in progressively greater hyperactivity from the IC to the ACx. These results suggest that CORT might give rise to hyperactivity at higher levels of the auditory pathway (**Figure 2a**). To test this hypothesis, a chronic electrode was implanted on the surface of the ACx in order to record the near-field evoked response from the ACx (nfACx) along with the far-field auditory brainstem response (ffABR) to tone bursts presented once every 800 ms at 70 and 90 dB SPL [18]. Electrophysiological measurements were obtained from awake rats before (Pre) and 1 week following 4 weeks of CORT treatment (25 mg/ml drinking water). **Figure 5a–b** shows the early (0–6 ms) small amplitude ffABR and the late large amplitude nfACx response (6–20 ms) measured pre- and post-CORT; data are shown for 8 kHz tone bursts presented at 70 and 90 dB SPL. CORT significantly enhanced the nfACx response, particularly the large negative peak around 11 ms, whereas the amplitude of the much smaller ffABR was largely unchanged after CORT treatment. To quantify the treatment effect, the root-mean-square (RMS) amplitudes of the early ffABR (0–6 ms) response and late nfACx (6–25 ms) response were computed pre- and post-CORT. The mean RMS amplitude of the ffABR response showed little or no change following CORT treatment as shown schematically in **Figure 5c**. In contrast, CORT significantly increased the RMS amplitude of the nfACx response (**Figure 5d**). These results are consistent with the increase in amplitude of the human N1–P2 and P300 auditory evoked responses following subchronic hydrocortisone treatment [62]. In contrast to salicylate, chronic CORT treatment induced hyperacusis and neural hyperactivity in the central auditory pathway without causing a cochlear hearing loss. These experimental results

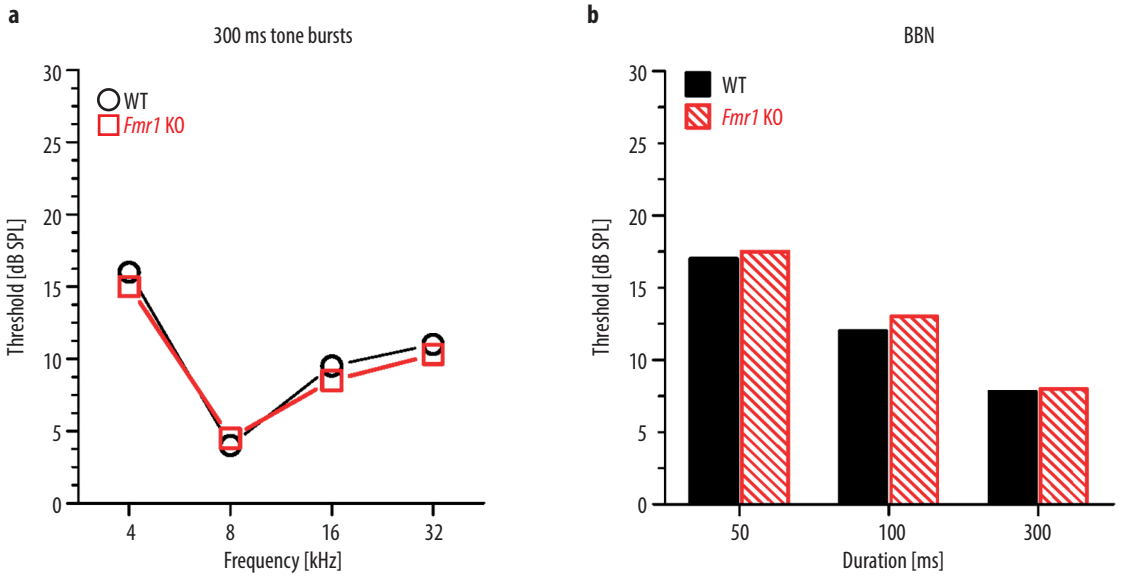

Figure 6. *Fmr1* KO rats have normal behavioral thresholds in quiet and exhibit normal temporal integration at the threshold of audibility. (**a**) WT rats and *Fmr1* KO rats have similar behavioral thresholds to 300 ms tone bursts presented at 4, 8, 16, and 32 kHz. Schematics based on investigator's prior work [75]. (**b**) Behavioral thresholds of *Fmr1* KO rats and WT rats have similar thresholds to 50, 100, and 300 ms BBN bursts; both groups show a similar increase in thresholds as BBN duration decreases from 300 to 50 ms, evidence of normal temporal integration of loudness at the threshold of audibility. Schematics based on investigator's prior work [75]

are relevant to clinical reports of hyperacusis in some patients with normal hearing [63,64] as well as rodent genetic models of hyperacusis.

Sensory hypersensitivity in FX and ASD

Patients with Fragile X (FX) syndrome, the leading genetic cause of ASD [65], often present with sensory hypersensitivity disorders often resulting in hyperacusis [66]. FX is caused by a genetic mutation resulting in a CGG expansion around the *FMR1* gene. This results in transcriptional silencing of the gene, loss of the FMRP protein product [67] and, according to some reports, excessive metabotropic glutamate receptor 5 (mGlu5) signaling [68,69]. Knowledge of the genetic mutations responsible for FX have led to the development of rodent models of FX that have been used to study the neural and molecular mechanisms of sensory hypersensitivity disorders [70,71]. A critical step in assessing the validity of such models is whether these *Fmr1* knock-out (KO) models of FX syndrome have normal or impaired hearing and whether they show behavioral evidence of hyperacusis. To address these issues, measures of auditory sensitivity and loudness perception were obtained from male FX rats in which a 122 bp deletion in exon 8 of the *Fmr1* gene [72] had led to key cellular pathophysiologies associated with FX, such as abnormal mGlu5 signaling and excessive protein synthesis [73,74].

Normal threshold in *Fmr1* KO

To determine if male *Fmr1* KO rats had normal auditory sensitivity, their hearing thresholds were measured in quiet to 300 ms tone bursts presented at 4, 8, 16, and 32 kHz and the results compared to normal hearing wild-type (WT) littermates [75]. The behavioral thresholds for *Fmr1* KO and WT rats were nearly identical across all four frequencies, as illustrated in **Figure 6a** [75]. Tone burst thresholds were lowest around 5 dB SPL at 8 kHz and increased to roughly 15 dB SPL at 4 kHz and 10 dB SPL at 32 kHz.

To test for temporal integration of acoustic energy at the threshold of audibility, behavioral thresholds were measured with BBN bursts with stimulus durations of 50, 100, and 300 ms, as shown schematically in **Figure 6b** [75]. BBN behavioral thresholds for male *Fmr1* KO and WT rats were lowest, approximately 7 dB SPL, for 300 ms noise bursts. As BBN duration decreased, threshold gradually increased to roughly 17 dB SPL at 50 ms [75]. These results are consistent with the degree of temporal integration of acoustic energy observed near the threshold of audibility in normal listeners [76–78]. These results indicate that *Fmr1* KO rats have normal hearing thresholds for tones and BBN and they exhibit normal temporal integration of acoustic energy at the threshold of audibility.

Loudness hyperacusis and impaired temporal integration of loudness in *Fmr1* KO

To determine if *Fmr1* KO rats demonstrate signs of loudness hyperacusis, RT-I functions were measured in WT and male *Fmr1* KO rats using 300 ms BBN bursts. As shown schematically in **Figure 7a**, RTs in both *Fmr1* KO and WT rats both decreased as the intensity of the BBN increased; however, RTs were significantly shorter in *Fmr1* KO rats than WT rats at all suprathreshold intensities [75]. These results indicate that *Fmr1* KO rats perceived the 300 ms BBN bursts as much louder than normal WT rats across a broad range of intensities.

To determine if temporal integration of loudness was disrupted in *Fmr1* KO rats, BBN burst RT-I functions in WT rats were compared to those measured in KO rats.

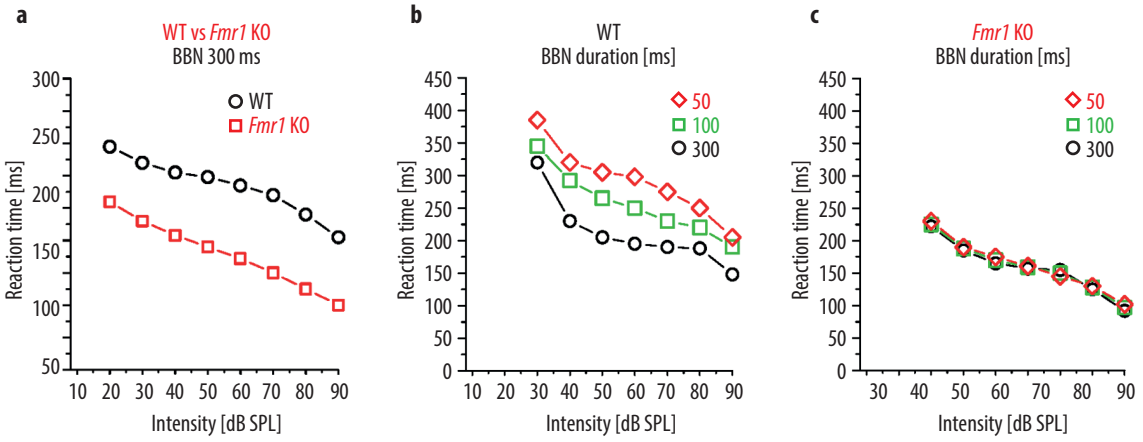

Figure 7. *Fmr1* KO rats show evidence of loudness hyperacusis and absence of temporal integration of loudness at suprathreshold intensities. (**a**) RT-I function to 300 ms BBN bursts for male *Fmr1* KO rats and WT rats. RTs at all suprathreshold intensities are significantly shorter in *Fmr1* KO rats than WT rats, behavioral evidence of loudness hyperacusis. Schematics based on investigator's prior work [75]. (**b**) RT-I functions in WT rats measured with 50, 100, and 300 ms BBN bursts. WT rat RTs show an orderly decrease with intensity at each burst duration. At each intensity, RTs decrease as BBN burst duration increases from 50 to 300 ms, evidence of temporal integration of loudness at suprathreshold intensities. Schematics based on investigator's prior work [75]. (**c**) RT-I functions in *Fmr1* KO rats measured with 50, 100, and 300 ms duration BBN bursts. RTs show an orderly decrease with intensity; however, RTs of *Fmr1* KO rats show little effect of increase in burst duration, evidence of a lack of temporal integration of loudness at suprathreshold intensities in *Fmr1* KO rats. Schematics based on investigator's prior work [75]

Figure 7b shows WT RT-I functions for 50, 100, and 300 ms BBN bursts [75]. At each duration, WT RTs show the expected orderly decrease with increasing intensity. Importantly, at each intensity, RT decreased as stimulus duration increased, clear evidence of temporal integration of loudness in WT rats. **Figure 7c** shows BBN RT-I functions for 50, 100, and 300 ms BBN bursts in *Fmr1* KO rats. RTs show an orderly decrease with increasing intensity; however, functions for 50, 100, and 300 ms lie largely on top of one another. Thus, the 300 ms BBN bursts are apparently perceived to be as loud as the much shorter 50 ms BBN bursts, indicating a total lack of temporal integration of loudness at suprathreshold intensities.

Aberrant spectral integration of loudness in *Fmr1* KO

The loudness of a suprathreshold sound initially stays constant as the bandwidth of a stimulus increases; however, further increases beyond the critical band lead to an increase in loudness even though the overall intensity remains constant [79,80]. To determine whether the critical band for loudness summation was disrupted by FX, RT-I functions were measured at four bandwidths centered at 16 kHz: 1 Hz, 1/3 octave, 1 octave, and 2 octaves as shown schematically in **Figure 8a** [75]. RTs for bandwidths of 1 Hz and 1/3 octave were virtually identical, indicating that a signal 1/3 octave wide was perceived as having the same loudness as a 1 Hz wide 16 kHz tone burst. However, RTs at each intensity became progressively shorter, and therefore perceived as louder, as signal bandwidth increased from 1/3 to 1 and then 2 octaves. The growth in loudness with increasing bandwidth, reflected as a decrease in RT, was most pronounced at moderate intensities (30–50 dB SPL), consistent with human psychophysical studies [79]. The *Fmr1* KO rat RT-I functions for different bandwidth are shown schematically in **Figure 8b**. RTs only decrease for bandwidths from 1 Hz to 1 octave. Importantly, the RTs for the 1/3-octave band noise lies well below that for 16 kHz (1 Hz). These results suggest that the critical band for loudness summation in *Fmr1* KO rats (< 1/3 octave) is much less than for WT rats (> 1/3 octave). Loudness increases over a much narrow frequency range in *Fmr1* KO rats than in WT littermates [75]. These results indicate that the critical band for loudness summation is disrupted in *Fmr1* KO rats. The much smaller critical band means that loudness grows more rapidly as bandwidth increases in *Fmr1* KO rats compared to WT rats.

mGlu5 inhibition suppresses hyperacusis in *Fmr1* KO

Some of the neurological symptoms associated with FX are believed to result from overactivation of the mGlu5 glutamate receptors [73]. Support for this hypothesis comes from preclinical studies in *Fmr1* mutant mice in which many FX neurological symptoms were pharmacologically suppressed by treatment with MTEP, an mGlu5 receptor negative allosteric modulator [69,81]. On the basis of these encouraging results, *Fmr1* KO rats were treated with escalating doses of MTEP to determine if it would suppress RT-I measures of hyperacusis behavior [75]. As a control, WT rats were treated with 1, 3, or 10 mg/kg MTEP (i.p.). RT-I functions from WT rats were not significantly altered by any dose of MTEP as shown schematically in **Figure 9a**. Baseline RT-I functions in *Fmr1* KO rats were characterized by much shorter RTs than in WT rats as schematized in **Figure 9b**. Treatment of *Fmr1* KO rats with 1, 3, and 10 mg/kg of MTEP resulted in a dose-dependent rise in the RT-I functions such that the RT-I function in those treated with 10 mg/kg was nearly the same as the baseline RT-I function in WT controls. These results suggest that MTEP can suppress loudness hyperacusis in *Fmr1* KO rats, providing novel insights

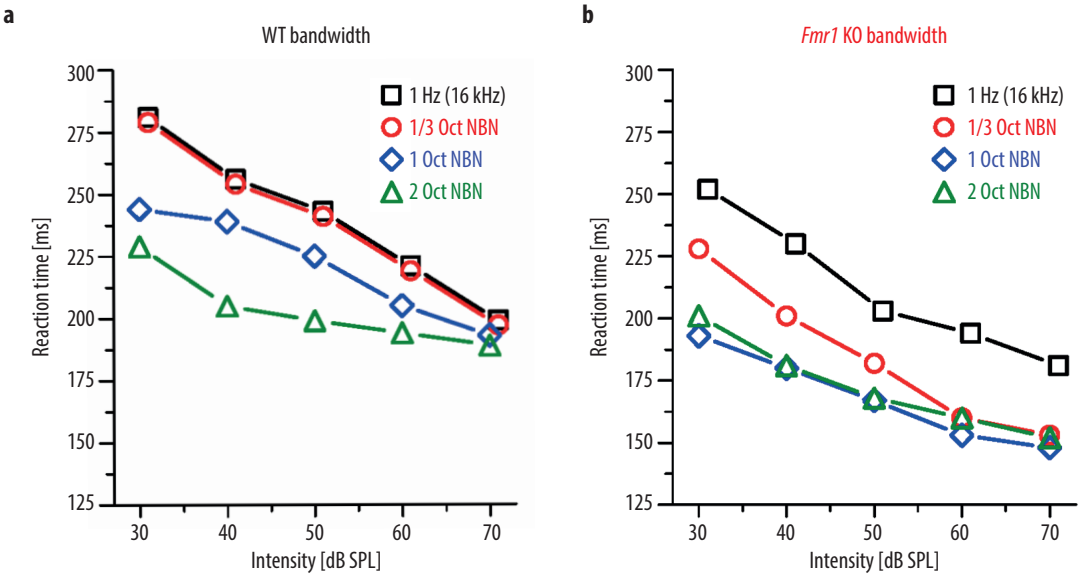

Figure 8. Critical band for loudness is disrupted in *Fmr1* KO rats. (**a**) WT rat RT-I functions for bandwidths of 1 Hz and 1/3, 1, and 2 octaves. (**b**) *Fmr1* KO rat RT-I functions for bandwidths of 1 Hz and 1/3, 1, and 2 octaves. See text for details. Schematics based on investigator's prior work [75]

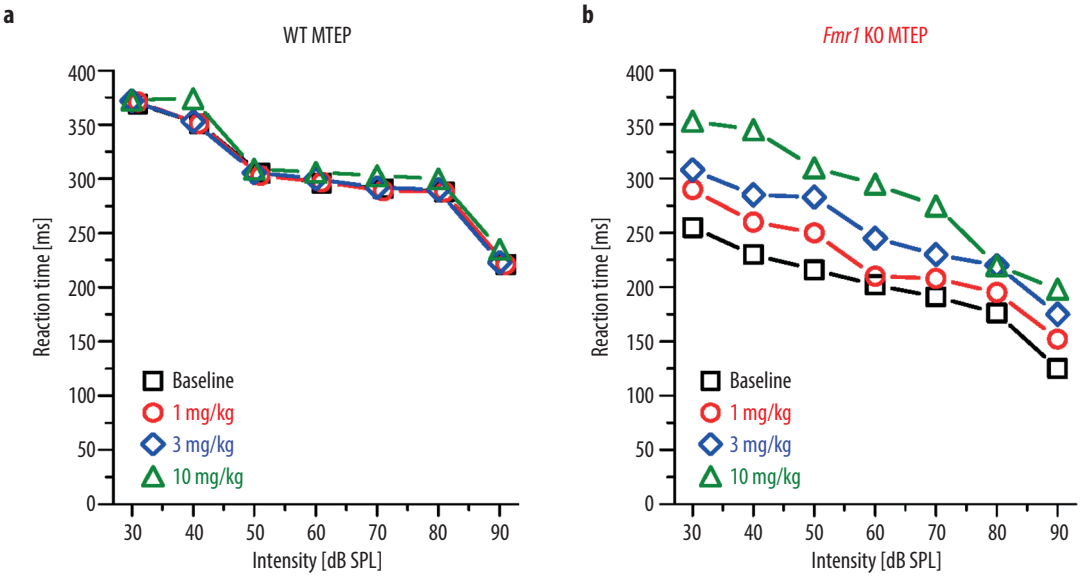

Figure 9. MTEP can normalize RT-I functions, eliminating hyperacusis behavior in a dose-dependent manner. (**a**) RT-I functions from WT rats at baseline and following treatment with 1, 3, and 10 mg/kg of MTEP. RT-I functions largely unaffected by MTEP. (**b**) As for (**a**), but for *Fmr1* KO rats. MTEP increases RTs across all intensities in a dose-dependent way. RT-I function after 10 mg/kg MTEP is similar to baseline RT-I function in WT rats, suggesting that MTEP has largely eliminated hyperacusis in *Fmr1* KO rats. Schematics based on investigator's prior work [75]

into underlying mechanisms and potential pharmacologic treatment for hyperacusis and other hypersensitivity caused by aberrant mGlu5 signaling [82].

Discussion

Drug-induced hyperacusis

Because loudness is a graded, subjective phenomenon, most individuals with moderate loudness intolerance are often unaware that they have hyperacusis [83]. Consequently, the number of studies of drug-induced hyperacusis is extremely limited. Much of what is known comes from reports listing hyperacusis as a possible side effect of taking or discontinuing a small number of medications such as phenytoin, risperidone, or monoamine oxidase inhibitors [15,84–87]. A study that searched for genes and proteins linked to hyperacusis and tinnitus on the basis of drug side effects in the SIDER database listed 36 drugs associated

with hyperacusis (some mentioned above) and 102 drugs associated with tinnitus [12].

The ASAP and RT-I behavioral techniques could be used to assess the frequency and severity of the 36 hyperacusis drugs listed in the database. High doses of salicylate, a cyclooxygenase (COX) inhibitor, have long been known to cause tinnitus. COX inhibitors are listed as the most frequent target of drugs that cause tinnitus [12]; however, they are not listed as targets among the 36 drugs that cause hyperacusis. Nevertheless, RT-I measurements clearly demonstrate that sodium salicylate, a COX inhibitor, dose-dependently induces hyperacusis. These RT-I measures of hyperacusis are consistent with data buried in a clinical study that attributed salicylate intoxication as the cause of hyperacusis in 2% of the patient sample [88]. These results suggest that other drugs with a pharmacologic profile similar to salicylate (e.g. COX inhibitor AKR1C1) might be tested with these procedures to determine if they induce hyperacusis [89,90].

An unexpected finding was that the high doses of salicylate needed to induce hyperacusis significantly increased corticosterone stress hormone levels. These results compare well with a study in which acute stress-induced hyperacusis among women with high levels of emotional exhaustion [48] and another report in which individuals with hearing loss, tinnitus, and hyperacusis exhibited greater stress to noise [91]. Rats exposed to high level noise for 30 days manifested a significant increase in plasma CORT, evidence of chronic noise-induced CORT stress [92] that might lead to hyperacusis. Indeed, when rats were chronically exposed to intense high frequency noise, they developed hyperacusis at low frequencies where thresholds were normal [93]. This may explain why hyperacusis is common among military personnel exposed to the emotional stress of combat combined with the stress of chronic noise exposure [94]. Evidence of stress associated with hyperacusis combined with evidence that hyperacusis is associated with stress leads to a feedback model that can generate dire consequences.

Genes and hyperacusis

Genetic factors combined with one's environment and lifestyle likely play major roles in the development of hyperacusis, as illustrated by results obtained with chronic CORT stress and *Fmr1* KO rats. Many medical conditions are associated with hyperacusis, such as William's syndrome [95], fibromyalgia [96], and migraine [97]. An analysis of the genetic mutations, gene products, and neural disorders common to several of these hyperacusis-linked disorders might shed light on new treatments for hyperacusis, as illustrated from the MTEP studies with *Fmr1* KO rats. Another approach involves performing a network pharmacology analysis of drugs that list hyperacusis as one of its side effects and the genes and protein products associated with these drugs [12].

Hyperacusis therapies

Hyperacusis is associated with a myriad of medical conditions, suggesting it may arise through diverse mechanisms. Consequently, finding a drug to treat hyperacusis may prove difficult unless one has a clear understanding of the mechanisms responsible for hyperacusis in a particular individual or specific condition such as FX. The MTEP studies suggest that mGlu5 antagonists might be effective in treating hyperacusis in some patients with FX syndrome. However, MTEP is not an FDA approved drug; therefore, extensive and expensive clinical trials would need to be carried out to determine its efficacy and potential side effects. No FDA-approved drug is available to treat hyperacusis. However, if an individual's hyperacusis is associated with excessive anxiety, fear, or stress, clinicians might consider treating these individuals with drugs approved for these symptoms [98,99] provided they do not exacerbate hyperacusis.

Currently, the most widely used therapies to treat individuals with troubling hyperacusis and tinnitus involve sound therapy combined with some form of counseling or specific counseling approaches, such as cognitive behavioral therapy [100,101]. The rationale for using sound therapy to treat a loudness intolerance disorder is based in part on studies showing that depriving the auditory system of sound stimulation (e.g., cochlear hearing loss or ear plugs) can enhance sound-evoked responses in the central auditory pathway, and that the enhanced central gain can be reversed by chronic exposure to moderate level sound [102–105]. One obstacle to employing sound therapy for individuals with severe hyperacusis is fear of inadvertently being exposed to an unexpected intense sound (e.g., firecracker noise). To deal with this problem, a transitional treatment has been developed that combines counseling, progressive sound management, and low-level sound as a therapeutic agent [106–108]. Counseling educates the hyperacusis patient about the nature of the disorder, the risks of sound avoidance behaviors, and the bases for the various treatment components. Earplugs prevent the hyperacusis patient from being exposed to excessively loud sound. An ear-level device connected to an earplug provides unity gain over the range of sound levels up to those judged to be loud but okay. This maximizes exposure to healthy, comfortable sound levels. For sound levels above the 'loud but okay' judgment, the hearing device uses multi-stage output-limiting to prevent exposure to high level sounds. This provides both protection and healthy sound exposure and comfortable communication. The device also delivers continuous, low-level therapeutic sound that gradually brings about neuroplastic changes in the central auditory pathway and, over time, can reverse the excessive neural gain responsible for hyperacusis. Severe hyperacusis is often accompanied by cognitive issues such as anxiety, fear, and depression, possibly driven in part by a disrupted stress responses mediated by the hypothalamic–pituitary–adrenal axis [49,109,110]. In some cases, cognitive behavioral therapy or other counseling approaches are sufficient to reduce or alleviate the emotional reaction to certain annoying or disturbing sounds [1,2,111–113].

Limitations

Because rats and other animal models are unable to verbally report on their subjective perception of the loudness of a sound and indicate when a sound is too loud or annoying, it is difficult to know if the nonverbal responses and behaviors of the rats described in this review accurately

reflect the perception of loudness and hyperacusis experienced by a human listener. However, reaction time measures have been found to correlate closely with the growth of loudness in human studies [28,114,115] – results supporting the use of reaction time to measure the normal and abnormal growth of loudness in rats and other animal models [30,32]. One trend that has emerged from numerous neurophysiological studies is that hyperacusis is associated with enhancement of sound-evoked neural activity at higher levels of the auditory pathway. Enhanced central gain in the central auditory pathway has been proposed as a neural correlate of hyperacusis in many animal studies, as well as some human brain imaging studies [83,116]. However, other reports in the literature have failed to observe a correlation between enhanced central gain and hyperacusis [117]. One older study in humans showed that the P300 long latency auditory evoked response was smaller in FX patients than in normal controls; these results suggest that central gain is reduced in FX patients, a result contradicting the enhanced central gain model [118]. However, a more recent study showed that the sound-evoked N1 response (50–150 ms) was greatly enhanced in FX patients compared to normal controls; moreover, enhanced central gain was associated with heighted sensory sensitivities in these FX patients [119]. While *Fmr1* KO rats showed clear behavioral evidence of hyperacusis, further electrophysiological studies are needed to determine if loudness hyperacusis in *Fmr1* KO rats is associated with enhanced central gain in the auditory pathway and, if so, where along the auditory pathway the enhanced gain occurs.

Conclusions

Considerable progress has been made in the past decade to develop powerful animal models to investigate loudness hyperacusis and sound avoidance hyperacusis. These behavioral techniques can also be used to determine if temporal summation and spectral summation of loudness are disrupted in animals with hyperacusis. With the appropriate dose of salicylate, CORT, and noise, researchers can now reliably induce hyperacusis and begin to explore the neurophysiological and biochemical mechanisms associated with the onset and recovery of hyperacusis. These behavioral techniques can also be used to determine which genetic mutations are likely to give rise to hyperacusis and to assess the effectiveness of new drugs or therapeutic interventions to suppress or prevent hyperacusis.

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ORIGINAL ARTICLE

ANXIETY IN PATIENTS WITH HYPERACUSIS AND TINNITUS: DIFFERENCES BETWEEN WOMEN AND MEN

Contributions:
A Study design/planning
B Data collection/entry
C Data analysis/statistics
D Data interpretation
E Preparation of manuscript
F Literature analysis/search
G Funds collection

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Abstract

Introduction: Hyperacusis is a specific auditory disorder characterized by an increased sensitivity to sounds, which is often accompanied by a significant psychological component. Some studies suggest that individuals with hyperacusis exhibit greater anxiety compared to the general population. However, it remains unclear whether gender affects the relationship between hyperacusis and anxiety. The aim of this study was therefore to investigate the role of gender in the interplay between hyperacusis, tinnitus, and anxiety.

Material and methods: The study group consisted of 106 patients with hyperacusis and tinnitus. There were 55 women and 51 men. The women were aged between 20 and 72 years ($M = 44.9$; $SD = 12.8$); the men were aged between 19 and 72 years ($M = 45.4$; $SD = 12.0$). A clinical interview, an audiological examination, and three questionnaires – State-Trait Anxiety Inventory (STAI), Hyperacusis Assessment Questionnaire (HAQ), and Tinnitus Handicap Inventory (THI) – were applied.

Results: The levels of anxiety in women and men were similar, but exceeded normative values established for the general population. In women, hyperacusis was not a significant predictor of anxiety ($\beta = 0.13$, $p = 0.34$), whereas tinnitus severity was ($\beta = 0.47$, $p = 0.002$). In men, both hyperacusis ($\beta = 0.36$, $p = 0.004$) and tinnitus severity ($\beta = 0.48$, $p < 0.001$) significantly predicted anxiety.

Conclusions: This study highlights the complex interplay between gender, hyperacusis, tinnitus, and anxiety. The findings suggest that interventions for subjects with hyperacusis and tinnitus should be gender-specific.

Keywords: anxiety • hyperacusis • tinnitus • gender

LĘK U PACJENTÓW Z NADWRAŻLIWOŚCIĄ SŁUCHOWĄ I SZUMAMI USZNYMI: RÓŻNICE MIĘDZY KOBIETAMI A MĘŻCZYZNAMI

Streszczenie

Wprowadzenie: Nadwrażliwość słuchowa jest specyficznym zaburzeniem słuchu, charakteryzującym się zwiększoną wrażliwością na dźwięki, któremu często towarzyszą problemy psychologiczne. Niektóre badania sugerują, że osoby z nadwrażliwością słuchową wykazują wyższy poziom lęku w porównaniu z populacją ogólną. Jednak nadal nie jest jasne, czy płeć ma wpływ na związek między nadwrażliwością słuchową a lękiem. Celem badania było zbadanie roli płci w interakcji między nadwrażliwością słuchową, szumami usznymi i lękiem.

Materiał i metody: Grupa badana składała się ze 106 pacjentów z nadwrażliwością słuchową i szumami usznymi. Było wśród nich 55 kobiet i 51 mężczyzn. Kobiety były w wieku od 20 do 72 lat ($M = 44,9$; $SD = 12,8$), mężczyźni – w wieku od 19 do 72 lat ($M = 45,4$; $SD = 12,0$). Przeprowadzono wywiad kliniczny, badanie audiologiczne oraz zastosowano trzy kwestionariusze: *State-Trait Anxiety Inventory* (STAI), *Kwestionariusz nadwrażliwości słuchowej* (KNS), oraz *Tinnitus Handicap Inventory* (THI).

Wyniki: Poziom lęku u kobiet i mężczyzn był podobny, ale przekraczał wartości normatywne ustalone dla populacji ogólnej. U kobiet nadwrażliwość słuchowa nie była istotnym czynnikiem prognostycznym lęku ($\beta = 0,13$, $p = 0,340$), natomiast istotnym czynnikiem prognostycznym było nasilenie szumów usznych ($\beta = 0,47$, $p = 0,002$). U mężczyzn zarówno nadwrażliwość słuchowa ($\beta = 0,36$, $p = 0,004$), jak i nasilenie szumów usznych ($\beta = 0,48$, $p < 0,001$) były istotnymi czynnikami prognostycznymi lęku.

Wnioski: Wyniki badania wskazują na złożoną wzajemną zależność między płcią, nadwrażliwością słuchową, szumami usznymi i lękiem. Interwencje wobec osób cierpiących na nadwrażliwość słuchową i szumy uszne powinny uwzględniać płeć pacjenta.

Słowa kluczowe: lęk • nadwrażliwość słuchowa • szumy uszne • płeć

Key to abbreviations	
AC	air conduction
BC	bone conduction
HAQ	Hyperacusis Assessment Questionnaire
STAI	State-Trait Anxiety Inventory
THI	Tinnitus Handicap Inventory
ULL	uncomfortable loudness level

Introduction

Some studies suggest that people with hyperacusis are more likely to suffer from psychiatric disorders, particularly those related to anxiety [1,2]. According to the American Psychological Association, anxiety is an emotion marked by feeling of tension, worried thoughts, and physical changes (e.g. in blood pressure). It is an inappropriate, future-oriented, prolonged response broadly focused on a diffuse and not clearly identifiable threat [3]. There also other characteristic features of anxiety discussed in the scientific literature, including uncomfortable feelings, a state of apprehension and uncertainty, and persistent feelings of worry that can impair daily functioning [4]. The uncertainty about the future triggers worry, which manifests as obsessive thoughts about possible negative events that are hard to dismiss and persist in the person's mind [5].

Another feature of anxiety is non-adaptive physical and mental reactions, e.g. sleep disturbance, loss of appetite, and avoidance behaviors which disturb people's normal lives [6]. The most common anxiety disorders are: i) generalized anxiety disorder (free-floating anxiety without a specific cause); ii) panic disorder with recurrent attacks of severe anxiety; iii) obsessive-compulsive disorder with obsessional thoughts or compulsive acts; iv) phobic anxiety disorders (e.g. social phobia, agoraphobia) with anxiety evoked in well-defined situation. The global prevalence of anxiety disorders is estimated at 7.3% and women are twice as likely as men to have an anxiety disorder [7].

Aaazh and Allot [8] in their review showed results of eight studies on the relationship between anxiety and hyperacusis. Nearly all of them indicated that subjects with hyperacusis exhibited significantly more anxiety symptoms. This raises the question of whether these two phenomena are simply co-occurring or share common underlying mechanisms, e.g. overactivation of some brain regions responsible for attention and heightened sensitivity to potential threats, which can lead to an excessive focus on minor stimuli or perceived dangers [9,10].

Hyperacusis is a specific auditory disorder which is highly subjective and has a significant psychological component. Unlike many other medical conditions, it is not subject to objective measurement, and its diagnosis relies almost entirely on the patient's self-reported experience. This can readily be seen when it comes to defining these phenomena. In the Delphi study conducted by Adams and colleagues among hearing healthcare professionals, they developed the following definition of hyperacusis: "A reduced tolerance to sound(s) that are perceived as normal to the majority of the population or were perceived as normal to the person before their onset of hyperacusis" [11]. Of course, this definition carries a great deal of subjectivity (which must be the case, since the phenomenon itself is eminently subjective). The prevalence of hyperacusis is estimated to be from 8.5% [12] to 15–17% [13,14], but it is much higher in some special populations, e.g. musicians, individuals with William syndrome, autism, and hearing disorders [15].

Hyperacusis is often comorbid with tinnitus. Jastreboff and Jastreboff [16] reported that approximately 60% of tinnitus patients have decreased sound tolerance, with about 30% requiring treatment for hyperacusis. Anari reported that 86% of adults with hyperacusis suffer from tinnitus as well [17]. Tinnitus is accompanied by a broad range of negative emotional symptoms, cognitive dysfunction, and significantly impacts on quality of life [18,19]. It has been shown that subjects with tinnitus are more likely to suffer from depression and anxiety [20].

Juris et al. [1] studied the relationship between psychiatric disorders and hyperacusis in a group of Swedish patients. There were 62 subjects with hyperacusis and 79% of them had comorbid tinnitus. It was found that 47% of subjects fulfilled the criteria for an anxiety disorder. The most common was social phobia (23%), generalized anxiety disorder (16%), agoraphobia (15%), and obsessive-compulsive disorder (10%). The researchers also showed that anxiety as a personality trait was significantly higher in patients with hyperacusis than in the general Swedish population.

Similar conclusions are drawn from the study of Sachetto and al. [2]. It was found that subjects with hyperacusis exhibited a higher anxiety level than controls (without hyperacusis); they were also more depressed, had high levels of somatic attention, and were more hypervigilant to bodily sensation. Blaesing and Kroener-Herwig [21] showed that tinnitus severity was similar in subjects who had hyperacusis and tinnitus as in subjects with tinnitus alone. But anxiety was significantly higher in subjects who had both tinnitus and hyperacusis than in those with tinnitus alone. This suggests that hyperacusis may be a factor exacerbating anxiety.

Studies to date do not indicate whether gender plays any role in the relationship between hyperacusis and anxiety. A systematic review published in 2023 suggests there are no gender-specific differences in hyperacusis (i.e. men and women exhibit a similar level of hyperacusis) [22]. On the other hand, it is known that women report greater anxiety than men and the prevalence of anxiety disorders is significantly higher in women than in men [23,24].

Given these gender differences in anxiety, it becomes important to explore whether this factor causes men and women to experience hyperacusis differently. The aim of our study was to assess the role of gender in the relationship between hyperacusis, tinnitus, and anxiety.

Material and methods

Setting

This study involved patients who were referred to the tertiary ENT center in Poland. Prior to the study, all subjects were informed about its nature, and informed consent was obtained from them. The study was conducted in compliance with the principles outlined in the Declaration of Helsinki. The research protocol was approved by the local Ethics Committee (KB.IFPS: 9/2020). Patient data were anonymised to ensure participant confidentiality. Personal information was removed and the dataset was stored in the database using only medical record numbers.

Participants

There were 106 adult patients who were admitted to our tertiary referral center due to hyperacusis and/or tinnitus. All of them reported having both hyperacusis and tinnitus. There were 55 women and 51 men. The women were aged between 20 and 72 years and their mean age was 44.9 years ($SD = 12.8$). Men were aged between 19 and 72 years; their mean age was 45.4 years ($SD = 12.0$). The age difference between women and men was not statistically significant ($t = 0.22$; $p = 0.829$).

Interview

An interview was carried out by an ENT doctor and focused on different aspects of hyperacusis and tinnitus. Patients were asked about the onset and duration of their symptoms. They were also questioned about which sounds triggered their hyperacusis, whether they experienced fear of certain sounds, or avoided specific noisy environments. Additionally, patients were asked if noise worsened their tinnitus and which issue they found most troublesome – tinnitus, hyperacusis, or hearing loss.

Audiological examination

Audiological assessment comprised pure-tone audiometry, impedance audiometry, and measurement of uncomfortable loudness level (ULL). Hearing thresholds for each patient were evaluated in both ears. Air conduction (AC) thresholds were measured at frequencies of 0.125, 0.25, 0.5, 1, 2, 4, and 8 kHz, while bone conduction (BC) thresholds were assessed at 0.25, 0.5, 1, 2, and 4 kHz. Impedance audiometry included measurement of the tympanometric curve and stapedial reflex testing. Middle ear function was confirmed as normal using 226 Hz tympanometry, with tympanometric peak pressures ranging from –100 to +100 daPa and peak compensated static acoustic admittance between 0.2 and 1.0 mmhos. Ipsilateral and contralateral acoustic reflex thresholds were also recorded for tones at 0.5–4 kHz. The ULL test aimed to determine the minimum sound level that the patient perceived as uncomfortably loud. This test was conducted at frequencies of 1, 2, and 4 kHz using pure-tone stimuli. During the test, the intensity of the sound was gradually increased, and patients were instructed to signal as soon as they found the sound to be uncomfortably loud.

Questionnaires

Three questionnaires – State-Trait Anxiety Inventory, Hyperacusis Assessment Questionnaire, and Tinnitus Handicap Inventory – were self-administered by the patients. They were provided with a quiet clinical setting to ensure minimal distraction, and the assessments took approximately 20 minutes to complete.

State-Trait Anxiety Inventory

The STAI is a psychological questionnaire designed to measure anxiety captured as state (temporary condition) and trait (stable predisposition) [25]. In this study only trait anxiety was assessed, because it reflects a stable predisposition to perceive situations as threatening and experience anxiety over time, making it a good indicator of an individual's general anxiety level. The trait anxiety scale consists of 20 self-report items, rated on a 4-point Likert scale ranging from "almost never" (1 point) to "almost always" (4 points). The total score is calculated by summing up the responses, with higher scores indicating greater levels of trait anxiety. In the study, the Polish version of the STAI was utilized, adapted and validated by Wrzesniewski et al. [26].

Hyperacusis Assessment Questionnaire

The HAQ is a questionnaire developed by Raj-Koziak et al. [27]. It assesses the severity of hyperacusis in terms of loudness, fear, and pain. It consists of 14 items scored on 5-point Likert scale from "definitely not" (0 points) to "definitely yes" (4 points). It has three subscales: the Loudness Hyperacusis subscale (comprising 7 items), the Fear Hyperacusis subscale (4 items), and the Pain Hyperacusis subscale (3 items). The scores are obtained by summing up the answers from appropriate items. The tool has been validated in a clinical group of patients with hyperacusis and tinnitus [27].

Tinnitus Handicap Inventory

The THI comprises 25 items. For each item the patient can respond with a "yes" (scored 4 points), "sometimes" (2 points), or "no" (0 points). The total score is obtained by summing the points from all responses, with higher scores indicating greater tinnitus severity [28]. In this study, the Polish version of THI adapted and validated by Skarzynski and colleagues was utilised [29].

Statistical analysis

The assumption of normality was checked with a Kolmogorov–Smirnov test, which confirmed that anxiety, overall hyperacusis, and tinnitus severity followed a normal distribution. A Student *t*-test for independent samples was conducted to compare the level of measured variables between women and men. Cohen's *d* was also calculated to check how meaningful the differences were in practical

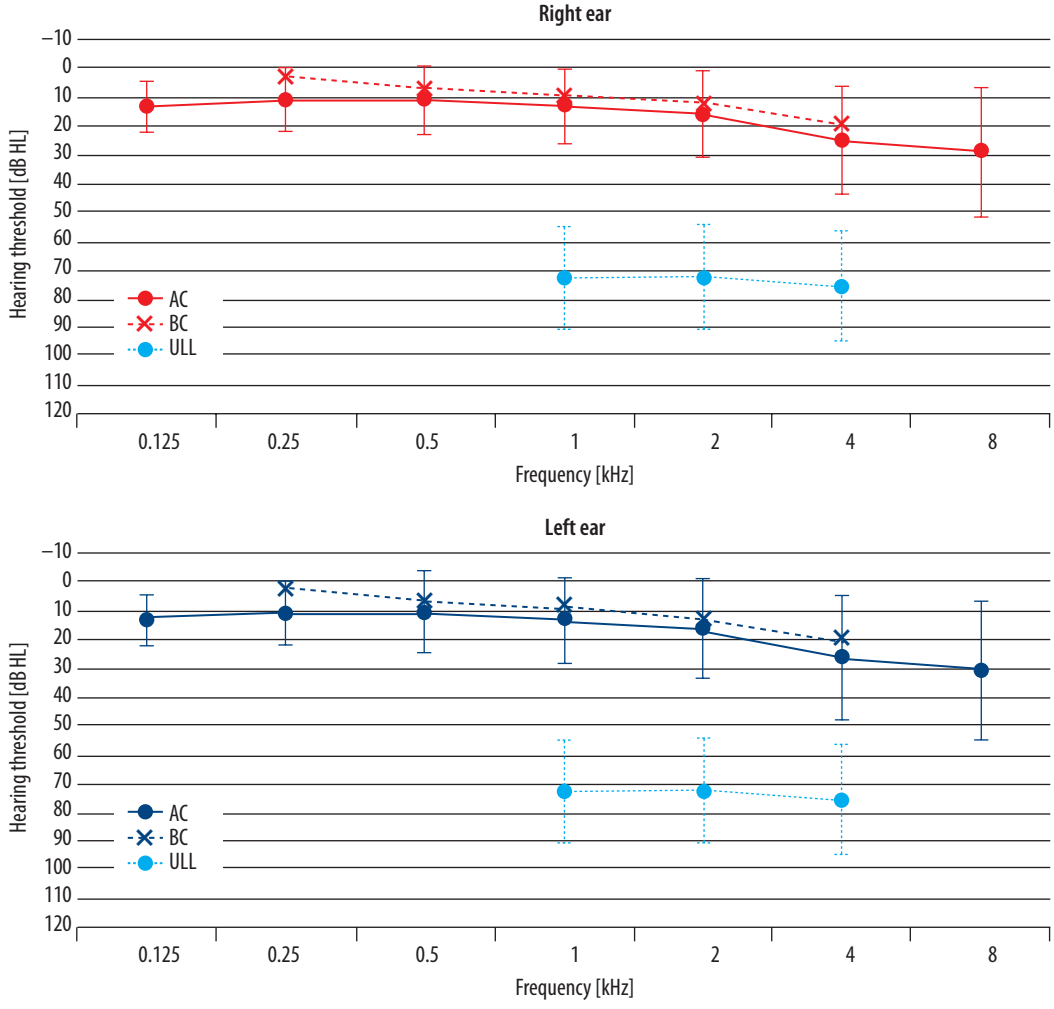

Figure 1. Hearing thresholds and uncomfortable loudness levels for the right and left ears. Note: AC, air conduction; BC, bone conduction; ULL, uncomfortable loudness level

terms. Pearson's correlation coefficient was applied to examine the relationship between the variables. Linear multiple regression models were built to evaluate the impact of hyperacusis and tinnitus severity (as potential predictors) on anxiety (the dependent variable). Statistical significance was set at $p < 0.05$. All analyses were performed using SPSS software (v.24).

Results

Audiological characteristics of patients

Mean AC threshold averaged for all frequencies from 0.125 to 8 kHz was 16.9 dB HL ($SD = 11.8$) for the right ear and 17.7 dB HL ($SD = 14.1$) for the left. Mean BC threshold averaged for all frequencies from 0.25 to 4 kHz was 9.8 dB HL ($SD = 9.3$) for the right ear and 10.5 dB HL ($SD = 10.8$) for the left. The difference between women and men was not statistically significant for either the right ear ($t = 0.15$; $p = 0.885$) or the left ear ($t = 0.30$; $p = 0.766$). Similarly, there was no significant difference in hyperacusis duration ($t = 0.47$; $p = 0.640$). There were 62 patients (58.5%) with normal hearing (i.e. an average hearing threshold better than 20 dB in both ears) and 44 patients (41.5%) with hearing loss (i.e. with an average hearing threshold worse than 20 dB HL in at least one ear). Mean ULL averaged for 1, 2, and 4 kHz was 73.4 dB HL ($SD = 17.8$) for the right ear and 73.5 dB HL ($SD = 18.1$) for the left. **Figure 1** shows hearing thresholds for air conduction and bone conduction in the right and left ears, as well as ULLs in both ears.

Levels of anxiety in women and men

The level of anxiety measured with STAI in all patients was between 28 and 72 points, with a mean score of 47.5 ($SD = 9.3$). In women the mean level of anxiety was 48.6 ($SD = 9.0$); in men it was 46.4 ($SD = 9.6$), and the difference was not statistically significant ($t = 1.18$; $p = 0.241$).

Normative values for anxiety measured with STAI were established for Polish population by Wrześniewski et al. [26]. They were drawn up separately for women and men and the mean normative anxiety score for women is 46.8, while for men it is 42.2. In our study, the mean anxiety scores were slightly higher, exceeding the normative values by 1.8 points for women ($M = 46.8$) and 4.2 points for men ($M = 42.2$). Normative values were also provided for women and men of different ages: 21–40 years, 41–54 years,

Table 1. The level of anxiety: comparison of normative values vs. own study results

Anxiety (STAI)	Polish normative study		This study	
	M	*SD*	*M*	*SD*
Women				
21–40 years	43.27	8.06	47.45	10.27
41–54 years	47.80	9.78	50.09	8.19
55–69 years	48.12	8.40	48.91	9.02
Men				
21–40 years	39.46	7.06	47.37	10.22
41–54 years	42.20	7.62	46.43	9.18
55–69 years	44.42	9.12	44.10	10.07

Note: Data for 70–79 years are not given, since there were only 2 women and 1 man above 70 in this study

Table 2. Comparison of hyperacusis and tinnitus severity in women and men

	Women ($n = 55$)		Men ($n = 51$)		*t*; *p*
	M	*SD*	*M*	*SD*	
Anxiety	48.6	9.0	46.4	9.6	1.18; 0.241
Loudness hyperacusis	21.9	5.1	20.5	5.5	1.62; 0.109
Fear hyperacusis	7.8	5.0	7.9	4.8	0.01; 0.991
Pain hyperacusis	7.6	3.6	7.8	3.6	0.37; 0.715
Overall hyperacusis	37.3	11.1	36.3	11.7	0.66; 0.511
Tinnitus severity	56.9	24.7	55.3	28.2	0.08; 0.904

Note: Minimum and maximum possible scores: anxiety (measured by STAI), 20–80 points; hyperacusis (overall, measured by HAQ), 0–56 points; tinnitus severity (measured by THI), 0–100 points

Table 3. Correlations (*r*-Pearson coefficients) between anxiety, hyperacusis, and tinnitus severity

	All ($n = 106$)		Women ($n = 55$)		Men ($n = 51$)	
	Anxiety	Tinnitus severity	Anxiety	Tinnitus severity	Anxiety	Tinnitus severity
Loudness hyperacusis	0.33**	0.28**	0.27*	0.45**	0.38**	0.15
Fear hyperacusis	0.46**	0.36**	0.43**	0.33*	0.51**	0.39**
Pain hyperacusis	0.11	0.08	0.01	0.03	0.23	0.13
Overall hyperacusis	0.39**	0.31**	0.32*	0.36*	0.46**	0.27
Tinnitus severity	0.55**	–	0.52**	–	0.58**	–

Note: ** $p < 0.01$; * $p < 0.05$

55–69 years, and 70–79 years. Our participants were similarly categorized into these age groups to facilitate comparisons with the normative data. The comparison is shown in **Table 1**.

The comparison of anxiety levels (STAI scores) between the Polish normative study and the findings from the present research revealed a consistent pattern of elevated anxiety among younger individuals with hyperacusis and tinnitus. It was found both in women and men; however among men this tendency was stronger.

Levels of hyperacusis and tinnitus severity

Table 2 shows the differences between women and men for both hyperacusis and tinnitus severity. As can be seen,

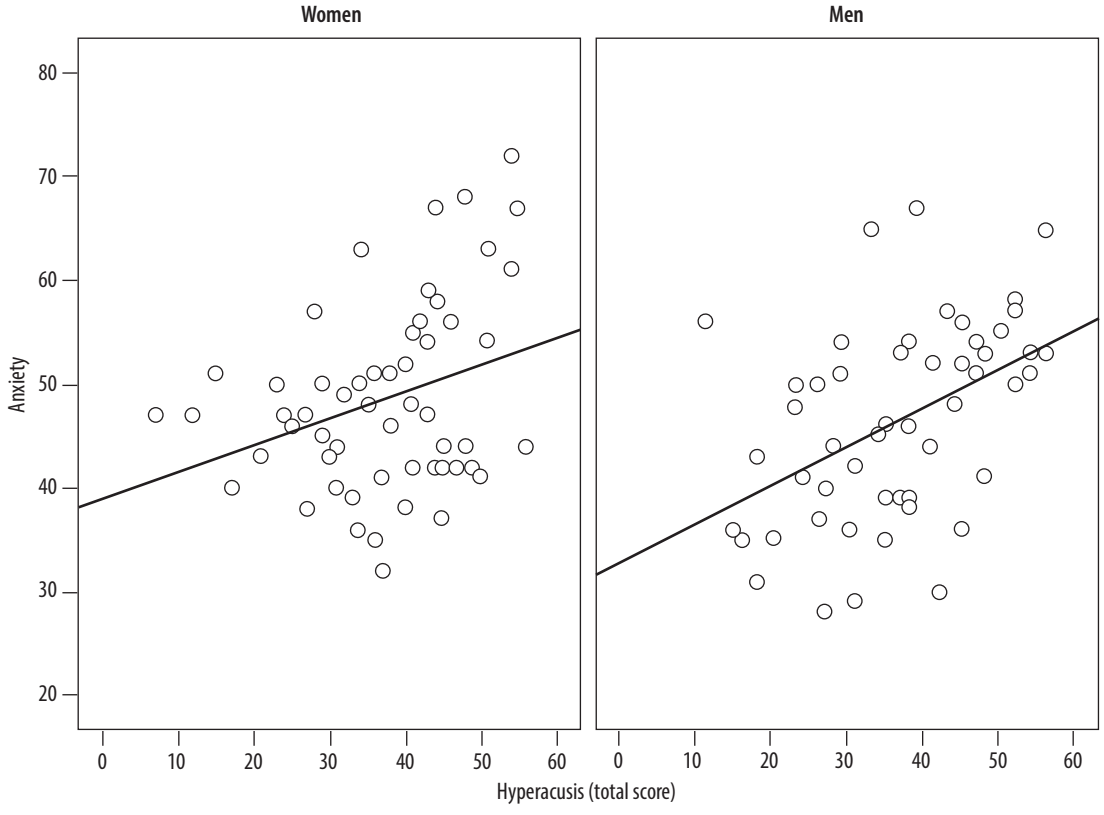

Figure 2. Relationships between anxiety and hyperacusis in men and women

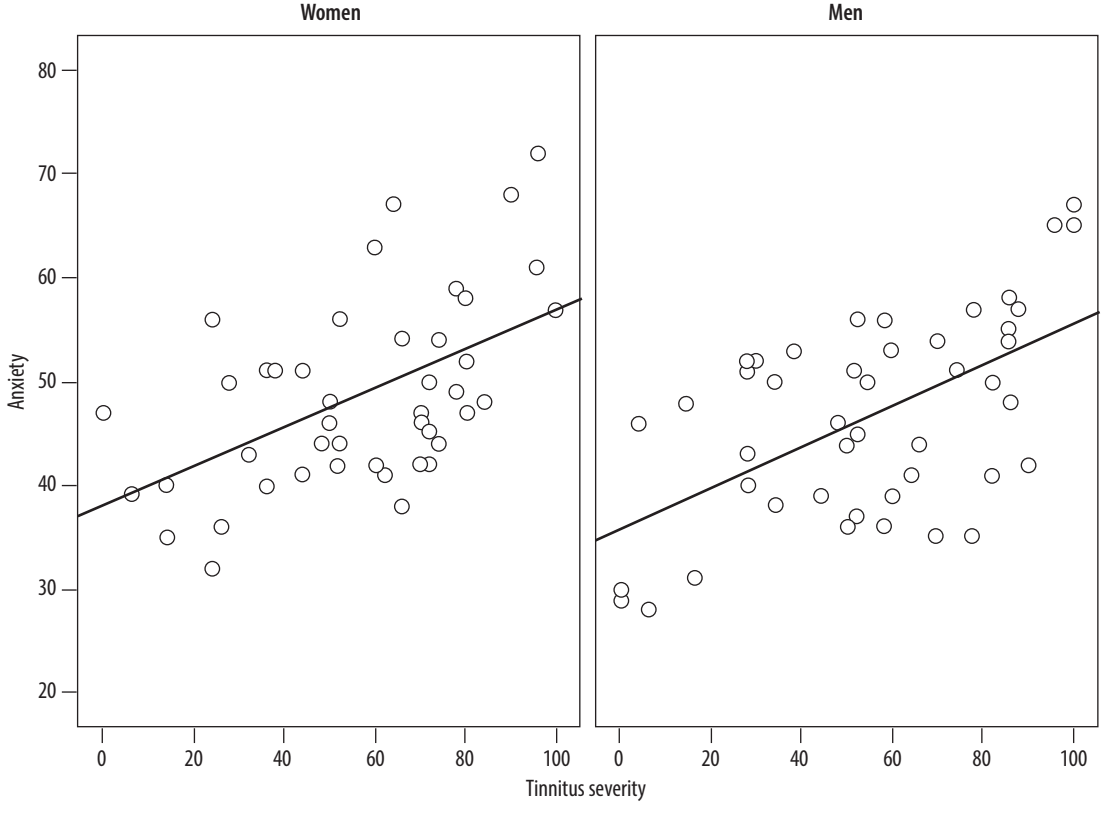

Figure 3. Relationships between anxiety and tinnitus severity in men and women

Table 4. Results of regression analysis predicting anxiety based on hyperacusis and tinnitus severity

	All ($n = 106$)		Women ($n = 55$)		Men ($n = 51$)	
	$R^2 = 0.35$; $F = 25.10$; $p < 0.001$		$R^2 = 0.25$; $F = 8.41$; $p = 0.001$		$R^2 = 0.42$; $F = 17.49$; $p < 0.001$	
	β	*p*	β	*p*	β	*p*
Overall hyperacusis	0.26	0.005	0.13	0.340	0.36	0.004
Tinnitus severity	0.47	< 0.001	0.47	0.002	0.48	< 0.001

the level of hyperacusis was similar in both women and men. Additionally, there was no significant difference in the severity of tinnitus between the two groups.

Relationships between anxiety, hyperacusis, and tinnitus severity

Table 3 presents correlation coefficients between anxiety, hyperacusis, and tinnitus severity for the entire sample, and for women and men separately.

Correlations between anxiety and hyperacusis (loudness, fear, and overall score) were statistically significant and positive for both women and men. However, these correlations were generally moderate in men but mostly weak in women. Higher levels of hyperacusis were associated with higher anxiety, with this relationship being more pronounced in men than in women. The strongest correlations, as expected, were found between anxiety and fear hyperacusis. Correlations between anxiety and tinnitus severity were also statistically significant, positive, and moderate for both women and men. The higher the tinnitus severity, the higher the anxiety in both groups. **Figure 2** and **Figure 3** show the relationships between anxiety, hyperacusis, and tinnitus severity in both men and women.

Table 4 shows the results of regression analysis predicting anxiety based on hyperacusis and tinnitus severity. The assumptions for homoscedasticity and the absence of multicollinearity were met (the plot of standardized residuals versus predicted values was inspected visually; variance inflation factors (VIF) were 1.10 and 1.11). In women only did tinnitus severity significantly predict anxiety ($\beta = 0.47$, $p = 0.002$), whereas hyperacusis as a predictor was not statistically significant ($\beta = 0.13$, $p = 0.340$). For men, both tinnitus severity ($\beta = 0.48$, $p < 0.001$) and hyperacusis ($\beta = 0.36$, $p = 0.004$) significantly predicted anxiety, with tinnitus severity having a slightly stronger effect.

Discussion

The aim of this study was to examine the role of gender in the relationship between hyperacusis, tinnitus, and anxiety. Specifically, we sought to determine whether gender influences the severity of anxiety associated with these auditory conditions.

The results of this study revealed no statistically significant differences between women and men in their levels of hyperacusis, which is consistent with findings of Musumano et al. [22]. In their systematic review, which included 282 subjects with hyperacusis (125 women and 157 men) it was concluded that women and men exhibited a similar level of hyperacusis. In our study we found that the level of loudness hyperacusis and overall hyperacusis were slightly higher in women than in men, but the differences were not statistically significant. Also tinnitus severity was similar in both genders.

The levels of anxiety observed in men and women with hyperacusis were found to be similar. This lack of difference is rather intriguing, as in the general population women exhibit higher levels of anxiety than men. It is also worth mentioning the study by Blomberg et al. [30] on individuals with Williams syndrome, which revealed gender differences in fear and hyperacusis, with female participants reporting higher levels of both compared to male participants. The absence of this expected gender difference in individuals with hyperacusis raises a question regarding the interplay between hyperacusis and anxiety, suggesting that hyperacusis may be a factor that overrides or mitigates the typical gender-related pattern of anxiety observed in the general population. One systematic review [23] indicates that greater anxiety in women compared to men may be explained by a combination of biological, genetic, and psychosocial factors.

Anxiety levels in both women and men with hyperacusis exceeded Polish normative values, indicating heightened psychological burden among affected individuals. In the 21–40 age group, anxiety levels were higher in the present study compared to normative data, with a similar trend in the 41–54 age group. These results suggest heightened anxiety in younger women and men relative to standardized benchmarks.

The elevated anxiety levels in our participants compared to normative values echo findings by Jüris et al. [1] and Sacchetto et al. [2]. The former reported a high prevalence of anxiety disorders, such as social phobia and generalized anxiety disorder in patients with hyperacusis; similarly, the latter noted heightened anxiety levels in hyperacusis patients compared to controls, emphasizing the psychological burden of this condition. Our results contribute further evidence by confirming that this heightened anxiety persists regardless of gender, but manifests differently in its predictors, particularly when hyperacusis and tinnitus coexist.

Our findings also corroborate the conclusions of Blaesing and Kroener-Herwig [21] who demonstrated that individuals with both tinnitus and hyperacusis experience higher anxiety levels compared to those with tinnitus alone. This suggests that hyperacusis may act as a significant aggravator

of psychological distress. Interestingly, while [21] did not examine gender-specific effects, our study identifies a stronger influence of hyperacusis on anxiety among men. This distinction underscores the necessity of considering gender as a moderating factor in clinical assessments and interventions.

The significant positive correlations between hyperacusis (loudness, fear, and overall score) and anxiety, as well as between tinnitus severity and anxiety, reinforce the notion that these auditory conditions substantially affect emotional well-being. These relationships were slightly stronger among men, indicating potential gender differences in vulnerability to anxiety related to hyperacusis and tinnitus.

The key finding of our study is that while hyperacusis severity itself does not differ by gender, its role in predicting anxiety varies between men and women, which is a novel contribution to the field. The gender differences in predictors of anxiety observed in our study raise important questions about underlying mechanisms. Women have consistently been reported to exhibit higher baseline levels of anxiety [23], which might explain why tinnitus severity alone significantly predicts anxiety in this group. Conversely, men, who typically report lower baseline anxiety levels, may require the additive stressor of hyperacusis for significant psychological impact. This distinction is supported by our findings of generally stronger correlations between anxiety and auditory conditions in men compared to women. Regression results also suggest that hyperacusis may play a greater role in male anxiety responses.

Aazh and Allott [8] emphasized the necessity of integrating psychological care into the management of hyperacusis, particularly due to its strong link with anxiety. Our findings extend this recommendation by highlighting the importance of tailoring psychological interventions to gender-specific needs. For instance, interventions focusing on hyperacusis management may yield greater benefits for men, while tinnitus-specific therapies could be prioritized for women.

Our study has some limitations. First, the study group consisted of individuals with both hyperacusis and tinnitus. A more comprehensive design would involve separate groups: individuals with hyperacusis alone, those with both hyperacusis and tinnitus, those with tinnitus alone, and a control group without either condition. This approach would allow for a clearer understanding of the relationship between hyperacusis, tinnitus, and anxiety. Second, the sample consisted of patients from a tertiary referral center, which may limit the generalizability of findings to broader populations with hyperacusis and tinnitus. Lastly, the study's cross-sectional design does not allow for causal inferences about the relationship between anxiety and auditory disorders (hyperacusis and tinnitus may contribute to increased anxiety, but also anxious individuals may be more sensitive to sound). Longitudinal studies would be better suited to determine the directionality of these relationships.

Conclusions

This study highlights the complex interplay between gender, hyperacusis, tinnitus, and anxiety. The finding that both tinnitus severity and hyperacusis are stronger predictors of anxiety in men has important clinical implications, suggesting the need for gender-tailored interventions. For women, management of tinnitus severity may yield significant psychological benefits, while for men, addressing both tinnitus and hyperacusis should be prioritized.

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ORIGINAL ARTICLE

HYPERACUSIS AND ASSOCIATED FACTORS IN SCHOOLCHILDREN: AN INTERNET SURVEY BASED ON REPORTS FROM BOTH PARENTS AND CHILDREN

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Contributions:
A Study design/planning
B Data collection/entry
C Data analysis/statistics
D Data interpretation
E Preparation of manuscript
F Literature analysis/search
G Funds collection

Abstract

Introduction: The aim was to investigate sound tolerance in schoolchildren aged 9–14 years, examine differences across age groups, and identify possible associated factors.

Material and methods: This was a cross-sectional exploratory study. An internet-based survey was conducted with children aged 9 to 14 years and their parents/guardians, recruited via social media. Parents/guardians and children completed separate questionnaires; the one developed for children has not been formally validated although it has been applied in prior pediatric studies. Hyperacusis was classified as present when both parent and child report were positive. Associated factors were analyzed using Fisher's exact test to compare individuals with auditory hypersensitivity in terms of whether they were also sensitive to lights, odors, or motion sickness. Inter-rater agreement between parents and children was evaluated with the kappa coefficient (κ).

Results: From the 75 parents recruited, there were just 60 questionnaires that had been completed by their children (age range 9–14 years; mean 12 years; 61.7% male). Listening difficulties were more frequently reported in children aged 9–10 years ($p = 0.010$), while earphone use was significantly higher among adolescents aged 13–14 years ($p = 0.010$). Motion sickness was more prevalent in children aged 11–12 years ($p = 0.033$). Tinnitus was reported by 20% of children, and hyperacusis by 10.3%, with no significant differences across age groups. Sensitivity to light and odors was significantly associated with hyperacusis according to parents' reports ($p = 0.007$) and to children's reports ($p = 0.020$). No association was observed between motion sickness and hyperacusis.

Conclusions: Although the prevalence of hyperacusis among schoolchildren was relatively low, the occurrence of sound-related discomfort was notable. Sound tolerance should be considered in clinical evaluations. The findings should be interpreted with caution due to the small sample size and the use of non-validated questionnaires.

Keywords: children • hearing • hypersensitivity to sounds

NADWRAŻLIWOŚĆ SŁUCHOWA I CZYNNIKI Z NIĄ ZWIĄZANE U DZIECI W WIEKU SZKOLNYM: INTERNETOWE BADANIE ANKIETOWE OPARTE NA ODPOWIEDZIACH RODZICÓW I DZIECI

Streszczenie

Wprowadzenie: Celem badania była analiza dotycząca tolerancji na dźwięki u dzieci w wieku szkolnym 9–14 lat, przeanalizowanie różnic między grupami wiekowymi i zidentyfikowanie potencjalnych zależności.

Materiał i metody: Przeprowadzono badanie eksploracyjne o charakterze przekrojowym. Zastosowano metodę ankiety internetowej z udziałem dzieci w wieku od 9 do 14 lat oraz ich rodziców/opiekunów, zrekrutowanych za pośrednictwem mediów społecznościowych. Rodzice/opiekunowie i dzieci wypełnili oddzielne kwestionariusze; kwestionariusz opracowany dla dzieci nie został formalnie walidowany, ale stosowano go we wcześniejszych badaniach pediatrycznych. Nadwrażliwość słuchową kwalifikowano jako występującą, gdy zarówno rodzic, jak i dziecko zgłosili jej obecność. Korelacje przeanalizowano za pomocą testu Fishera, porównując osoby z nadwrażliwością słuchową pod kątem tego, czy były one również wrażliwe na światło, zapachy lub chorobę lokomocyjną. Zgodność pomiędzy ocenami rodziców i dzieci zweryfikowano z wykorzystaniem współczynnika kappa (κ).

Wyniki: Zrekrutowano 75 rodziców, jednak ostatecznie 60 dzieci wypełniło kwestionariusz (przedział wiekowy 9–14 lat; średnia 12 lat; 61,7% chłopców). Trudności ze słuchem były częściej zgłaszane u dzieci w wieku 9–10 lat ($p = 0{,}010$), podczas gdy dzieci w wieku 13–14 lat ($p = 0{,}010$) istotnie częściej korzystały ze słuchawek. Choroba lokomocyjna występowała częściej u dzieci w wieku 11–12 lat ($p = 0{,}033$). Szumy uszne zgłosiło 20% dzieci, a nadwrażliwość słuchową – 10,3%, przy czym nie wystąpiły istotne różnice między grupami wiekowymi. Wrażliwość na światło i zapachy była istotnie powiązana z nadwrażliwością słuchową według relacji rodziców ($p = 0{,}007$) i relacji dzieci ($p = 0{,}020$). Nie zaobserwowano związku między chorobą lokomocyjną a nadwrażliwością słuchową.

Wnioski: Częstość występowania nadwrażliwości słuchowej wśród dzieci w wieku szkolnym była stosunkowo niska, jednak występowanie dyskomfortu związanego nadwrażliwością słuchową było znaczące. W ocenie klinicznej pacjenta należy uwzględnić jego tolerancję na dźwięk. Wyniki niniejszego badania należy interpretować ostrożnie ze względu na małą liczebność próby i wykorzystanie niewalidowanych kwestionariuszy.

Słowa kluczowe: dzieci • słuch • nadwrażliwość słuchowa

Introduction

Auditory hypersensitivity can be understood as an abnormal perception of sound that negatively impacts daily life, including social and leisure activities [1]. Also referred to as sound intolerance or reduced sound tolerance, it describes discomfort when exposed to everyday sounds that are usually tolerable for most people. Three subtypes are described in the literature: hyperacusis, defined as increased sensitivity to environmental and everyday sounds [2,3]; misophonia, a negative reaction to specific patterned sounds such as chewing or tapping [4]; and phonophobia, a persistent fear of particular sounds [5].

The pathophysiology of hyperacusis remains under debate. Proposed mechanisms include altered amplification in cochlear outer hair cells [3] and dysfunction in the medial olivocochlear efferent system, leading to abnormal auditory gain and exaggerated behavioral responses to sound [7]. Hyperacusis often co-occurs with other conditions such as Williams syndrome and autism spectrum disorder [2], and it shows strong associations with tinnitus [8–11], suggesting shared neurophysiological mechanisms and broader sensory vulnerabilities [12–14].

Although more frequently described in adults, hyperacusis also occurs in children and can be distressing, with reactions ranging from mild avoidance to extreme behavioral or physiological responses [15,16]. Prevalence estimates in pediatric populations range from 3.2% to 17.1% [15], but results remain inconsistent due to heterogeneous definitions, study designs, and the absence of validated child-specific assessment tools [2]. This contrasts with tinnitus, for which more prevalence studies exist, though estimates are variable (7.5–60%) [16].

The lack of standardized pediatric protocols makes diagnosing hyperacusis particularly challenging, as it is inherently subjective and younger children may have difficulty articulating their experiences [15]. Hyperacusis in children remains underexplored, and most available protocols are adapted from adult populations, limiting their applicability. Currently, there is no validated tool for assessing hyperacusis in children, since most questionnaires are designed for adults. Although audiological measures such as loudness discomfort levels are used in adults, no standardized pediatric protocol currently exists.

Moreover, hyperacusis is inherently subjective, only understood through the individual's own perception of everyday sounds. For this reason, self-report is considered the most valid method for capturing sound intolerance in children. Because children may under- or overreport their difficulties, and parents may misinterpret or overlook symptoms, a dual-report strategy allows for a more comprehensive assessment. Furthermore, previous studies have primarily examined clinical populations; little is known about sound tolerance in community-based samples. The internet-based survey design used here enables the recruitment of a broader sample of school-aged

subjects and provides valuable epidemiological data to help fill the existing knowledge gap.

Given the multiple challenges, self-report remains the best method for assessing hyperacusis. Nevertheless, children's accounts may differ from perceptions of their parents, with potential under- or overestimation by either party. Combining both perspectives provides a more comprehensive understanding of sound intolerance in children. Moreover, most existing research has focused on clinical populations, whereas little is known about hyperacusis and associated factors in community-based samples.

This study aims to investigate sound tolerance in schoolchildren aged 9–14 years, examine differences across age groups, and identify possible associated factors. By using an internet-based dual-report approach, this study seeks to address the current lack of population-based data on pediatric hyperacusis and provide evidence to support early identification strategies. Given the lack of validated pediatric instruments for hyperacusis, this study was an exploratory investigation to try to characterize sound intolerance using reports from both caregivers and their children.

Material and methods

This cross-sectional study followed the STROBE statement for observational studies [17]. The study was approved by the local ethics committee of our university department (protocol no. 5.037.928) and conducted in accordance with the Declaration of Helsinki and its amendments. Informed consent was obtained from both children and their parents. Data collection occurred during the COVID-19 pandemic, and all recruitment and assessments were conducted online.

Participants

Children aged 9–14 years, regardless of gender, were eligible if they had functional auditory, visual, and cognitive capacities, access to the internet via mobile network or wi-fi, had an electronic device (notebook or smartphone), and provided informed assent. Participants were recruited through invitations distributed on social media platforms (Instagram and Facebook) addressed to parents. Children were then recruited by their parents. Questionaires which indicated that the child had auditory hypersensitivity but where the child did not complete the specific question about triggering sounds were excluded.

Measurement tools

The two questionnaires developed by Coelho (2007) [18] – a demographic questionnaire and a two-part questionnaire used by two other studies [19,20] – were adopted. It is one of the few instruments designed to explore hyperacusis in children, although it has not been formally validated. This choice was motivated by the absence of validated pediatric measures and the need for a developmentally appropriate approach.

Parents first completed the demographic questionnaire, which included questions about sensitivity to light, odors, and motion, as well as a modified two-part questionnaire.

Table 1. Sociodemographics of the study sample ($n = 60$) by gender and education level

		n	%
Gender	Female	23	38
	Male	37	62
Education Level	Elementary School I	17	28
	Middle School	43	72
Age group [years]	9 to 10	14	23
	11 to 12	18	30
	13 to 14	28	47
Study sample	*n*	60	
	Mean	12.0	
	Median	12.0	
	Minimum	9.0	
	Maximum	14.0	
	Standard deviation	1.5	

Part one of the latter assessed hypersensitivity to everyday sounds using four multiple-choice questions (yes = 4, don't know = 2, no = 0). A child scoring > 8 points was classified as hypersensitive. Part two included 6 questions assessing common behavioral reactions to sounds. See the **Supplementary questionnaire**.

In turn, children completed three main questions investigating hearing loss, the presence of tinnitus, and subjective hypersensitivity to sounds. Children also had to indicate which sounds annoyed them, chosen from a list of 20 sounds. If positive answers were given to the question "Are you bothered by any kind of sound or noise?" and the child indicated 5 or more from the list of 20 annoying sounds, the child was classified as "hypersensitive to sound" [19]. All surveys were administered via Google Forms, with participants accessing them through an electronic link.

Data analysis

Statistical analyses were performed using SPSS Statistics version 28.0 (IBM Corp., Armonk, NY, USA), with a significance level of 5% ($p \leq 0.05$). Associations between categorical variables were analyzed using a Pearson's chi-square test or Fisher's exact test (including the Fisher–Freeman–Halton extension for tables larger than 2×2, when appropriate). Inter-rater agreement between parent and child reports was assessed using the kappa coefficient (κ) [20], with interpretation based on McHugh (2012) [21]. The analytical framework followed Field (2017) [22]. Given the exploratory nature of this study, multiple statistical tests were performed without correction for multiple comparisons (it is therefore acknowledged that the overall Type I error rate could exceed the nominal 5% significance level for individual tests, so some results with $p < 0.05$ may have occurred by chance). Nevertheless, only a few findings reached statistical significance. Thus, the results should

Table 2. Health of the study sample (general and auditory) based on the report of parent or guardian and stratified by age of child (9–10, 11–12, and 13–14 years)

		Age group [years]						Total		*p*-value
		9 to 10		11 to 12		13 to 14				
		n	%	*n*	%	*n*	%	*n*	%	
Does your child have any health problem?	No	12	86	15	83	21	75	48	80	0.767[a]
	Yes	2	14	3	17	7	25	12	20	
Do you think your child has listening difficulties?	No	10	71	18	100	27	96	55	92	0.010[a]
	Yes	4	29	–	–	1	4	5	8	
Has your child already had audiometry?	No	6	43	6	33	13	46	25	42	0.676[b]
	Yes	8	57	12	67	15	54	35	58	
If he/she did, was the result normal?	No	1	12	–	–	–	–	1	3	0.222[a]
	Yes	7	87	12	100	16	100	35	97	
Has your child ever had an ear infection?	No	5	35	12	67	12	43	29	48	0.116[b]
	Yes	9	64	6	33	16	57	31	52	
Does your child use headphones a lot?	No	8	57	8	44	4	14	20	33	0.010[b]
	Yes	6	43	10	56	24	86	40	67	
Does your child have difficulties understanding conversations in a noisy environment?	No	9	64	14	78	20	71	43	72	0.702[b]
	Yes	5	36	4	22	8	29	17	28	
Does your child consume a lot of sugar?	No	9	64	10	56	11	39	30	50	0.266[b]
	Yes	5	36	8	44	17	61	30	50	
Does your child do physical exercise?	No	5	36	8	44	8	29	21	35	0.544[b]
	Yes	9	64	10	56	20	71	39	65	
Does your child sleep well?	No	1	7	1	6	5	18	7	12	0.512[a]
	Yes	13	93	17	94	23	82	53	88	
Does your child have learning difficulties at school?	No	13	93	15	83	23	82	51	85	0.727[a]
	Yes	1	7	3	17	5	18	9	15	
Is your child bothered by smells and/or lights?	No	12	86	14	78	20	71	46	77	0.628[a]
	Yes	2	14	4	22	8	29	14	23	
Does your child feel sick in the car, on the bus, or on the subway?	No	11	79	10	56	25	89	46	77	0.033[a]
	Yes	3	21	8	44	3	11	14	23	

Note: [a] Extended Fisher's exact test, [b] Pearson's chi-square test

be interpreted with caution and considered exploratory, providing a basis for future confirmatory analyses using appropriate corrections.

Results

A total of 75 parents were recruited for the study. However, 15 were excluded because their children did not meet the eligibility criteria, resulting in a final sample of 60 schoolchildren aged 9 to 14 years (mean age 12.0 years). Of these, 37 (62%) were male and 23 (38%) were female. Regarding educational level, 28% were in elementary school and 72% in middle school (**Table 1**).

Most parents reported no health problems in their children (80%). Similarly, the majority reported no listening difficulties (92%), no difficulty understanding conversations in noisy environments (72%), no sleep problems (88%), no learning difficulties (85%), no sensitivity to smells and/or lights (77%), and no motion sickness (77%), independent of age. Overall, two-thirds of the children (67%) used headphones, particularly adolescents aged 13–14 years ($p = 0.010$) (**Table 2**).

Table 3. Hyperacusis in the study sample, based on the reports of parents or guardians and stratified by age group (9–10, 11–12, and 13–14 years)

		Age group [years]						Total		*p*-value
		9 to 10		11 to 12		13 to 14				
		n	%	*n*	%	*n*	%	*n*	%	
Do you think your son or daughter is very sensitive to everyday sounds?	No	12	86	14	78	20	71	46	77	0.235[a]
	Yes	1	7	4	22	8	29	13	22	
	I don't know	1	7	–	–	–	–	1	2	
Is there a sound that your son or daughter doesn't like?	No	7	50	12	67	16	57	35	58	0.342[a]
	Yes	4	29	4	22	11	39	19	32	
	I don't know	3	21	2	11	1	4	6	10	
Is there a sound that your son or daughter finds painful?	No	13	93	16	89	21	75	50	83	0.413[a]
	Yes	1	7	2	11	3	11	6	10	
	I don't know	0	0	0	0	4	14	4	7	
Is there a sound that scares your child?	No	12	86	15	83	21	75	48	80	0.767[a]
	Yes	2	14	3	17	7	25	12	20	
	I don't know	0	0	0	0	0	0	0	0	

Note: [a] Extended Fisher's exact test

Table 4. Auditory health and hyperacusis in the study sample, based on children's reports, stratified by age group (9–10, 11–12, and 13–14 years)

		Age group [years]						Total		*p*-value
		9 to 10		11 to 12		13 to 14				
		n	%	*n*	%	*n*	%	*n*	%	
Do you hear well?	No	–	–	–	–	–	–	–	–	0.315[a]
	Yes	14	100	18	100	25	89	57	95	
	I don't know	–	–	–	–	3	11	3	5	
Do you hear a noise in your ears or head?	No	9	64	14	78	23	82	46	77	0.490[a]
	Yes	5	36	3	17	4	14	12	20	
	I don't know	–	–	1	6	1	4	2	3	
Are you bothered by any kind of sound?	No	8	57	8	44	15	54	31	52	0.718[a]
	Yes	6	43	10	56	11	39	27	45	
	I don't know	–	–	–	–	2	7	2	3	

Note: [a] Extended Fisher's exact test

Listening difficulties were reported significantly more often by parents of children aged 9–10 years compared with older children ($p = 0.010$). Motion sickness was more prevalent among children aged 11–12 years ($p = 0.033$).

No significant differences were observed among age groups regarding parents' perception of their children's sensitivity to everyday sounds ($p = 0.235$), dislike of specific sounds ($p = 0.342$), sounds perceived as painful ($p = 0.413$), or frightening sounds ($p = 0.767$) (**Table 3**).

Tinnitus was reported by 20% of children, although no significant differences were observed among age groups in relation to hearing ($p = 0.315$), tinnitus ($p = 0.490$), or being bothered by sound ($p = 0.718$) (**Table 4**).

Hyperacusis was reported by both parents and children in 10.3% of participants. No significant differences were found among age groups, either based on parents' perception ($p = 0.851$) or children's self-report ($p = 0.267$) (**Table 5**).

Table 5. Hyperacusis in the study sample, based on parents/guardians and children's reports, stratified by age group (9–10, 11–12, and 13–14 years)

		Age group [years]						Total		*p*-value
		9 to 10		11 to 12		13 to 14				
		n	%	*n*	%	*n*	%	*n*	%	
Hyperacusis (parents/guardians' report)	No	12	86	14	78	21	75	47	78	0.851[a]
	Yes	2	14	4	22	7	25	13	22	
Hyperacusis (children's report)	No	13	93	13	72	23	88	49	84	0.267[a]
	Yes	1	7	5	28	3	11	9	15	
Hyperacusis	No	14	100	15	83	23	88	52	90	0.351[a]
	Yes	–	–	3	17	3	11	6	10	

Note: [a] Extended Fisher's exact test

Table 6. Comparison of sensitivity to lights and odors and hyperacusis occurrences in the study sample, stratified by age group (9–10, 11–12, and 13–14 years)

			Sensitivity to light and odors				Total		*p*-value
			No		Yes				
9 to 10 years	Hyperacusis (parents/guardians' report)	No	11	92%	1	50%	12	86%	0.275[a]
		Yes	1	8%	1	50%	2	14%	
	Hyperacusis (children's report)	No	11	92%	2	100%	13	93%	> 0.999[a]
		Yes	1	8%	–	–	1	7%	
11 to 12 years	Hyperacusis (parents/guardians' report)	No	11	79%	3	75%	14	78%	> 0.999[a]
		Yes	3	21%	1	25%	4	22%	
	Hyperacusis (children's report)	No	12	86%	1	25%	13	72%	0.044[a]
		Yes	2	14%	3	75%	5	28%	
13 to 14 years	Hyperacusis (parents/guardians' report)	No	18	90%	3	38%	21	75%	0.009v
		Yes	2	10%	5	62%	7	25%	
	Hyperacusis (children's report)	No	18	95%	5	71%	23	88%	0.167[a]
		Yes	1	5%	2	29%	3	12%	
Total	Hyperacusis (parents/guardians' report)	No	40	87%	7	50%	47	78%	0.007[a]
		Yes	6	13%	7	50%	13	22%	
	Hyperacusis (children's report)	No	41	91%	8	62%	49	85%	0.020[a]
		Yes	4	9%	5	38%	9	15%	

Note: [a] Extended Fisher's exact test

To further illustrate the comparison between parent- and child-reported hypersensitivity, we provide a **Supplementary table 1** that presents individual-level data. Each participant is represented by a unique identifier, with corresponding information on parental and child reports of hypersensitivity, agreement status, specific sounds identified as bothersome, and the child's behavioral reactions to these sounds (e.g., covering ears, recoiling, or fleeing). This table one to see the discrepancies and concordances between informants, as well as the variety of sound triggers and coping responses reported by children.

An association was observed between sensitivity to light and odors and the presence of hyperacusis, based on both parents' reports ($p = 0.007$) and children's self-perception ($p = 0.020$). This association was particularly evident among adolescents aged 13–14 years ($p = 0.009$) (**Table 6**). No significant association was found between motion sickness and hyperacusis, either according to parents' perception ($p = 0.478$) or children's reports ($p > 0.999$) (**Table 7**).

Table 7. Comparison of motion sickness and hyperacusis occurrences in the study sample, stratified by age group (9–10, 11–12, and 13–14 years)

			Motion sickness				Total		*p*-value
			No		Yes				
9 to 10 years	Hyperacusis (parents/guardians' report)	No	9	82%	3	100%	12	86%	> 0.999[a]
		Yes	2	18%	–	–	2	14%	
	Hyperacusis (children's report)	No	10	91%	3	100%	13	93%	> 0.999[a]
		Yes	1	9%	–	–	1	7%	
11 to 12 years	Hyperacusis (parents/guardians' report)	No	8	80%	6	75%	14	78%	> 0.999[a]
		Yes	2	20%	2	25%	4	22%	
	Hyperacusis (children's report)	No	6	60%	7	88%	13	72%	0.314[a]
		Yes	4	40%	1	12%	5	28%	
13 to 14 years	Hyperacusis (parents/guardians' report)	No	20	80%	1	33%	21	75%	0.145[a]
		Yes	5	20%	2	67%	7	25%	
	Hyperacusis (children's report)	No	21	91%	2	67%	23	89%	0.319[a]
		Yes	2	9%	1	33%	3	11%	
Total	Hyperacusis (parents/guardians' report)	No	37	80%	10	71%	47	78%	0.478[a]
		Yes	9	20%	4	29%	13	22%	
	Hyperacusis (children's report)	No	37	84%	12	86%	49	85%	> 0.999[a]
		Yes	7	16%	2	14%	9	15%	

Note: [a] Extended Fisher's exact test

Discussion

This study aimed to investigate hyperacusis in school-aged children (9–14 years) using both parental perception and children's self-assessment, and to examine whether auditory health-related factors, such as motion sickness or tinnitus, as well as hypersensitivity to light and odors, were associated with hyperacusis. Importantly, we stratified results by age, as suggested during peer review, which allowed more precise detection of age-specific patterns and eliminated previous borderline statistical associations.

At present, there is no universally accepted gold standard for the diagnosis of hyperacusis in children. Most validated questionnaires, such as Khalfa's Hyperacusis Questionnaire, were developed for adults and may not be developmentally appropriate for children. The instrument we used in this study [18] has not undergone formal psychometric validation; however, it was selected because it is one of the few tools specifically designed to explore sound intolerance in children and has been applied in previous research. Objective measures such as Loudness Discomfort Levels (LDL/ULL) are often recommended in combination with questionnaires in adults to provide supportive information, but they are difficult to administer reliably in children and are not validated as diagnostic tools for this age group. Consistent with current recommendations, we prioritized caregiver and child self-report to capture the subjective nature of hyperacusis, while acknowledging that future studies should aim to combine structured questionnaires with behavioral or psychoacoustic measures, and to further validate instruments for use in pediatric populations.

Considering the parental questionnaire, most children were reported to be in good health (**Table 2**), with 80% having no health problems, 65% engaging in regular physical activity, and 88% reporting adequate sleep. The high prevalence of physical activity is notable, as habits formed in this period often persist into adulthood and may reduce long-term health risks.

Regarding auditory health, 92% of parents reported that their children heard well; however, 67% of children frequently used headphones, particularly in the 13–14-year-old group ($p = 0.010$). While headphone use is increasingly common, prolonged or high-volume exposure can pose auditory health risks.

Previous studies have reported an association between tinnitus in children and a history of motion sickness, suggesting a possible overlap between vestibular and auditory pathways. For instance, Coelho et al. (2007) [18] identified motion sickness as one of the significant risk factors for tinnitus in school-aged children, alongside noise exposure and hyperacusis. In our study, however, we did not find a significant association between auditory hypersensitivity and motion sickness. Instead, we observed that hypersensitivity to light and odors was more strongly related to sound intolerance, which may point

toward a broader multisensory processing vulnerability rather than a vestibular-specific contribution.

Our findings of an association between sound intolerance and sensitivity to light and odors are in line with previous studies in adults reporting co-occurrence of multisensory hypersensitivity. For instance, Nordin et al. (2013) [24] observed that individuals with noise sensitivity also showed increased odor sensitivity, and that stress played a mediating role in this relationship. This suggests that a common vulnerability across sensory systems may underlie decreased tolerance to everyday stimuli. Extending these findings to a pediatric population, our results indicate that auditory hypersensitivity in children may also be embedded in a broader sensory profile, potentially influenced by stress-related mechanisms.

Hyperacusis prevalence was 17% according to parental perception and 15% by children's self-report. Combining both criteria, 5 children were classified as hyperacusis-positive, consistent with prior pediatric prevalence studies (3–17%) [15]. Notably, 20% of children reported tinnitus, and hyperacusis and tinnitus appeared to co-occur, supporting findings in both pediatric and adult populations [8,18,20]. Age-stratified analysis revealed that younger children (9–10 years) more frequently exhibited listening difficulties, while older children (13–14 years) reported higher headphone usage. No significant differences were found between age groups regarding parents' perception of sensitivity to everyday sounds, highlighting that hyperacusis may manifest independently of age within this range.

Our results complement clinical data from Rosing et al. (2016) [25], who described referral patterns and interventions for Danish children with tinnitus and hyperacusis. While their study reflects children already referred to specialized services, our community-based findings indicate that hypersensitivity to everyday sounds and tinnitus are also reported by school-aged children outside clinical contexts. Taken together, these studies highlight two critical issues: first, parental perception plays a major role in whether children access care; second, the absence of validated pediatric assessment tools contributes to variability in both referral and management. This convergence underscores the need for standardized screening approaches that can be applied both in clinical and community settings.

Some discrepancies between parent and child reports were observed, reflecting the complexity of assessing sound sensitivity in children. Parents may interpret their child's reactions through their own expectations, whereas children may have difficulty articulating discomfort, potentially leading to underreporting. Social desirability bias may further reduce self-reported prevalence. These findings underscore the need for dual-report approaches, as parental perception alone may overestimate or underestimate actual hypersensitivity, and highlight the challenges of defining clear cutoff criteria for hyperacusis in pediatric populations.

Our findings are also in line with those of Coelho et al. (2007) [18], who investigated tinnitus in children and associated risk factors. Similar to their results, we observed that tinnitus and sound sensitivity are present in school-aged children, highlighting the importance of considering these symptoms beyond clinical populations. Whereas their study identified potential audiological and environmental risk factors, our contribution emphasizes the value of integrating child self-reports and parental perspectives in early recognition. Together, these results suggest that systematic inquiry into tinnitus and sound hypersensitivity may facilitate timely detection and prevention strategies in pediatric populations.

The absence of misophonia or phonophobia assessment is a limitation, since these subtypes of auditory hypersensitivity were not evaluated.

Methodological considerations include reliance on self-report questionnaires without audiological confirmation and use of adapted tools that are not validated for children. The small, convenience-based, online sample limits generalizability and may introduce selection bias, though it allowed safe data collection during the COVID-19 pandemic. Also, as this study was exploratory and multiple statistical tests were conducted without correction for multiple comparisons, some statistically significant findings may have arisen by chance. These results should therefore be interpreted with caution and considered preliminary, highlighting the need for future studies with confirmatory analyses and appropriate adjustments for multiple testing.

Future research should incorporate objective auditory evaluation, including determination of uncomfortable loudness levels, and aim to develop validated pediatric hyperacusis questionnaires. Further studies should explore discrepancies between parent and child reports, the influence of social desirability, and the broader sensory environment, which may inform targeted interventions and clinical assessment strategies.

Conclusions

This study indicates that sound tolerance problems, including hyperacusis and tinnitus, occur in school-aged children, with prevalence rates of approximately 10% and 20%, respectively. No age-related differences were observed, although listening difficulties were more common in younger children and headphone use more common in adolescents. Importantly, sensitivity to light and odors was associated with hyperacusis, suggesting that auditory hypersensitivity may be part of a broader sensory vulnerability rather than an isolated phenomenon.

Although these findings provide new insights, they should be interpreted cautiously, since this is an exploratory study using a non-validated questionnaire. Future research should aim to validate pediatric-specific assessment tools and incorporate objective measures.

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Supplementary questionnaires

Sociodemographic Questionnaire for Parents

1. **Gender**
   a. Male
   b. Female

2. **Age**

3. **Does your child have any health problems?**
   a. Yes
   b. No

If yes, which of the following?
   a. Diabetes
   b. High blood pressure
   c. Asthma
   d. Migraine
   e. Attention deficit
   f. Epilepsy
   g. Auditory processing disorder
   h. Autism
   i. Other (please specify): _____

4. **Do you believe your child has difficulty hearing?**
   a. Yes
   b. No

Has your child ever undergone an audiometry test?
   a. Yes
   b. No

If yes, were the results normal?
   a. Yes
   b. No

6. **Has your child ever had an ear infection?**
   a. Yes
   b. No

If yes, how many times? _____

7. **Does your child frequently use headphones?**
   a. Yes
   b. No

If yes, for how many hours per day? _____

8. **Does your child have difficulty understanding speech in noisy environments?**
   a. Yes
   b. No

9. **Does your child consume a lot of sugar?**
   a. Yes
   b. No

10. **Does your child engage in physical exercise?**
    a. Yes
    b. No

11. **Does your child sleep well?**
    a. Yes
    b. No

12. **Does your child have learning difficulties at school?**
    a. Yes
    b. No

13. **Is your child sensitive to smells and/or lights?**
    a. Yes
    b. No

14. **Does your child experience motion sickness in cars, buses, or subways?**
    a. Yes
    b. No

Questionnaire for Parents

1. **Do you think your child is very sensitive to everyday sounds?**
   a. Yes
   b. No
   c. I don't know

2. **Is there any sound your child dislikes?**
   a. Yes
   b. No
   c. I don't know

3. **Is there any sound your child finds painful?**
   a. Yes
   b. No
   c. I don't know

4. **Is there any sound that scares your child?**
   a. Yes
   b. No
   c. I don't know

5. **Indicate your child's most frequent reaction to sounds:**
   a. Covers their ears
   b. Cries
   c. Runs away from the sound
   d. Pulls back to avoid the sound
   e. Says "I don't like this sound" or "This sound hurts"
   f. Other (please specify): _____

Children's Questionnaire

1. Do you hear well?
a. Yes
b. No
c. I don't know

2. Do you hear a noise in your ears or in your head?
a. Yes
b. No
c. I don't know

3. Does any kind of sound bother you?
a. Yes
b. No
c. I don't know

4. Do any of these sounds bother you?

a. Recess
b. Classroom noise
c. Screaming
d. School bell
e. TV
f. Radio
g. Blender
h. Telephone
i. Car
j. Motorcycle
k. Truck
l. Ambulance
m. Toy
n. Balloon
o. Whistling
p. Musical instruments
q. Fireworks
r. Firecrackers
s. Thunder
t. Dog barking

Supplementary table 1. Individual-level data on hypersensitivity: parental and child reports, agreement status, bothersome sounds, and children's behavioral reactions

Child ID	Age	Parent-reported hypersensitivity	Child self-reported hypersensitivity	Agreement	Annoying sounds reported	Reactions to sounds
1	13–14	No	Yes	No	F, L	01
2	11–12	No	Yes	No	C	None
3	11–12	No	Yes	No	C, G, I, J, L	02
4	9–10	No	Yes	No	None	05
5	13–14	No	Yes	No	N	02
6	11–12	No	Yes	No	C	None
7	13–14	No	No	No	C	None
8	11–12	No	Yes	No	C	None
9	13–14	No	No	No	None	02
10	11–12	Yes	Yes	Yes	B, C, D, G, J, N, Q, R, S	02
11	9–10	Yes	Yes	Yes	J, K	02
12	9–10	No	No	No	None	None
13	11–12	Yes	Yes	Yes	C, D, F	02
14	13–14	Yes	No	No	None	02
15	9–10	No	No	No	None	01
16	9–10	No	No	No	None	05
17	13–14	No	Yes	No	None	03
18	13–14	No	Yes	No	C, H, J, T	01
19	9–10	No	Yes	No	C, J	05
20	13–14	No	No	No	S	None
21	9–10	No	Yes	No	B, C, D, F, J, K, L, Q, T,	None
22	13–14	No	No	No	H, S	05
23	9–10	No	No	No	F	02
24	9–10	No	Yes	No	None	05
25	13–14	Yes	Yes	Yes	B, C, F, J, O, R	01
26	13–14	No	No	No	None	None
27	13–14	Yes	No	No	None	02
28	11–12	No	No	No	G	05

Supplementary table 1 continued. Individual-level data on hypersensitivity: parental and child reports, agreement status, bothersome sounds, and children's behavioral reactions

Child ID	Age	Parent-reported hypersensitivity	Child self-reported hypersensitivity	Agreement	Annoying sounds reported	Reactions to sounds
29	11–12	No	Yes	No	None	05
30	13–14	No	No	No	C, T	03
31	13–14	No	No	No	None	None
32	11–12	No	No	No	None	None
33	13–14	No	No	No	C, F, R	None
34	13–14	Yes	No	No	None	04
35	11–12	Yes	Yes	Yes	C, J, L, N, R, S	05
36	11–12	No	Yes	No	C, H, I, J, K,, L, M	02
37	11–12	No	No	No	None	None
38	13–14	No	Yes	No	None	05
39	13–14	No	No	No	None	None
40	13–14	No	Yes	No	C, J	None
41	9–10	No	No	No	G, L, S	01
42	13–14	Yes	Yes	Yes	J, K, N	02
43	13–14	No	No	No	None	04
44	13–14	No	No	No	R	02
45	9–10	No	No	No	None	None
46	13–14	No	No	No	None	None
47	13–14	Yes	Yes	Yes	None	02
48	11–12	Yes	Yes	Yes	C, F, L, M, S, T	02
49	11–12	No	No	No	None	01
50	9–10	No	Yes	No	S	None
51	11–12	No	No	No	None	05
52	9–10	No	No	No	C, F, K, T	02
53	13–14	No	No	No	G	05
54	11–12	No	No	No	K, L, R, S	None
55	9–10	No	No	No	N	02
56	13–14	Yes	Yes	Yes	B, C, D, G, J, K, S	02
57	13–14	No	No	No	None	02
58	11–12	No	No	No	None	05
59	11–12	No	No	No	B, K	01
60	13–14	Yes	Yes	Yes	B, G, J, L, T	02

Note: Numbers 1 to 60 indicate ID of child. Types of annoying sounds: A – Recess; B – Classroom noise; C – Screaming; D – School bell; E – TV; F – Radio; G – Blender; H – Telephone; I – Car; J – Motorcycle; K – Truck; L – Ambulance; M – Toy; N – Balloon; O – Whistling; P – Musical instruments; Q – Fireworks; R – Firecrackers; S – Thunder; T – Dog barking. Reactions to sound: 01 – Move away to avoid the sound; 02 – Covers the ears; 03 – Says "I don't like that sound"; 04 – Runs away from the sound; 05 – Others

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REVIEW PAPER

OUTLOOK ON HYPERACUSIS AND MISOPHONIA IN AUTISM SPECTRUM DISORDERS (ASD)

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Abstract

Individuals with autism spectrum disorder (ASD) frequently experience decreased sound tolerance (DST), which reduces their social interaction and engagement. The purpose of this perspective piece is to look at the gap in the literature concerning the possible genetic and functional bases for the comorbidity of ASD and two distinct types of DST, hyperacusis and misophonia.

Keywords: autism spectrum disorders • hyperacusis • misophonia • decreased sound tolerance

NADWRAŻLIWOŚĆ SŁUCHOWA I MIZOFONIA W ZABURZENIACH ZE SPEKTRUM AUTYZMU (ASD)

Streszczenie

Osoby z zaburzeniami ze spektrum autyzmu (ASD) często doświadczają obniżonej tolerancji na dźwięki (DST), co ogranicza ich interakcje społeczne i zaangażowanie. Celem niniejszego artykułu jest przyjrzenie się lukom w literaturze na temat możliwych genetycznych i funkcjonalnych podstaw współwystępowania ASD i dwóch odrębnych typów DST – nadwrażliwości słuchowej i mizofonii.

Słowa kluczowe: zaburzenia ze spektrum autyzmu • nadwrażliwość słuchowa • mizofonia • obniżona tolerancja na dźwięki

Key to abbreviations	
ABR	auditory brainstem response
ASD	autism spectrum disorders
CBT	cognitive behavioral therapy
DBS	dysregulated behavioral symptoms
DPOAEs	distortion product otoacoustic emissions
DST	decreased sound tolerance
GAD	generalized anxiety disorder
MDD	major depression disorder
PTSD	post-traumatic stress disorder
SNP	single nucleotide polymorphisms
SPD	sensory processing disorders

Autism spectrum disorders (ASD) is a neurodevelopmental disorder affecting communication and social skills and is often characterized by repetitive and restrictive behaviors [1]. Individuals with ASD frequently experience sensory processing disorders (SPD), with decreased sound tolerance (DST) being the most common [1–3]. Everyday sounds and noises considered tolerable to the general population, such as crowds, construction, and yelling, are reported as significantly heightened in individuals with autism spectrum disorder [2]. When exposed to such sounds, individuals with the condition may exhibit adverse reactions such as distress, irritation, and anger [4]. Two distinct types of DST include hyperacusis and misophonia. Both conditions are present in individuals with normal hearing thresholds [5], suggesting that peripheral hearing loss may not be a potential cause [2].

Misophonia is represented by an over-responsiveness to specific "triggering" sounds often produced by humans, such as sniffing, chewing, and coughing [6], or repetitive sounds like pen clicking or tapping [7]. On the other hand, individuals with hyperacusis have a reduced threshold for loudness discomfort, which increases their sensitivity to general everyday sounds and results in a decreased tolerance of them [8]. The sounds are often described as painfully loud and uncomfortable by those with hyperacusis, although they do not cause problems for most neurotypical individuals [4]. Individuals with hyperacusis may also have a higher prevalence of tinnitus, suggesting a possible relationship between the two conditions [9].

It is essential to understand the types of DST, considering they are highly prevalent in the ASD population. Scheerer et al. [2] found that DST leads to fewer opportunities for

Table 1. Prevalence of hyperacusis in the ASD population based on five studies

Study	Participants	Age [years]	ASD category	Prevalence of hyperacusis [%]
Williams et al. (2021) [8]	metanalysis	NA	autism	41–60
Demopoulos & Lewine (2016) [10]	60 (48 males, 12 females)	5–18	high–low functioning	37
Danesh et al. (2015) [9]	55 (46 males, 9 females)	4–42	high-functioning (Asperger)	69
Rosenhall et al. (1999) [11]	199 (153 males, 46 females)	children adolescents	autism	18
Rimland & Edelson (1995) [12]	17 (11 males, 6 females)	4–21	unspecified	mild – 53 moderate – 24 strong – 18

autistic children and young adults to engage at home, at school, and in the community. In a meta-analysis, Williams et al. [8] reported the current and lifetime prevalence of hyperacusis in ASD to be 41–60%. **Table 1** summarizes a few studies of the prevalence of hyperacusis in the ASD population.

Despite the high prevalence, the etiology of both hyperacusis and misophonia is unclear. Various theories have been proposed to understand the reasoning behind the relationship of DST in this population. The theories extend to anatomical and physiological disruption, efferent pathways of the auditory system, genetic factors, and pharmacological causes [4].

Danesh et al. [4] described a variety of potential correlates of hyperacusis in the ASD population, such as anatomical differences in the inner ear. They indicated that 29% of autistic individuals had superior semicircular canal dehiscence (as reported in [13]). Superior semicircular canal dehiscence involves a window between the cranial cavity and the inner ear, causing those with the condition to perceive sounds extremely loudly. They cited another study [14] which examined the correlation between the stapedial acoustic reflex and loudness tolerance which showed significantly lower stapedial reflex thresholds and significantly delayed responses in young participants with autism. The contralateral suppression of distortion product otoacoustic emissions (DPOAEs) has also been studied in individuals with hyperacusis. A study by Ohmura et al. [15] analyzed stapedial reflex threshold with contralateral suppression of DPOAEs and found that the stapedial reflex was decreased in the ASD population. In addition, Kaf and Danesh [16] noted that sound hypersensitivity in high-functioning autistic children could result from abnormal neural connections at proximal structures to the medial olivary complex, such as the temporal lobe, limbic system, and autonomic nervous system. In a related study of autism [17], the same researchers studied 14 children with ASD and 28 age-matched controls, and noticed that the DPOAEs had smaller amplitude and insufficient contralateral suppression in the ASD group, a finding which tends to support the involvement of the efferent auditory pathways in hyperacusis.

Genetics may also play a significant role in the development of hyperacusis in the ASD population [4]. Mertcati et al. [18] reported that extra copies of the contactin five gene (*CNTN 5*) and deletions and mutations of the contactin six gene (*CNTN 6*) have been found in autistic individuals with hyperacusis. The expression of these gene variants may result in changes in their auditory brainstem response (ABR) waveforms within the auditory pathway, presenting as sound hypersensitivity [4].

Misophonia has been observed to be comorbid with a variety of psychiatric and developmental disorders but cannot be applied exclusively to one specific disorder [8,19]. Triggered by specific sounds, misophonia elicits a negative emotional response (e.g., anger, rage, and irritation) and a fight or flight reaction [1]. As this disorder typically develops during childhood or adolescence, it is important to further investigate misophonia within specific populations to gain a greater understanding of its development and progression, as well as effective therapeutic interventions for it [6]. The current literature considers misophonia as an unclassified disorder, and its nature remains unclear [7]. Siepsiak et al. [6] found that over 50% of their misophonia cases had at least one family member with the condition. In a genome-wide association study, Smit et al. [20] further investigated the genetic etiology of misophonia by focusing on the most reported related symptom, rage. They reported specific single nucleotide polymorphisms (SNP) linked to misophonia, including *TENM2*, *TMEM256*, *NEGR1*, *TFB1M*, and GABA-related genes. They considered that misophonia was not just a sensory disorder as it shares genetic etiology with conditions such as major depression disorder (MDD), post-traumatic stress disorder (PTSD), and generalized anxiety disorder (GAD) [20]. Rinaldi and al. [21] tested 142 children and 379 adults for traits associated with autism and found that autistic traits were more prevalent in those with misophonia compared to controls.

Despite the growing relevance of decreased sound tolerance disorders such as hyperacusis and tinnitus, there is a lack of knowledge and evidence of effective treatment for this disorder [1]. However, as knowledge of the causes, diagnostic criteria, and management of hyperacusis and misophonia improves, potential treatment options have increased. These include cognitive behavioral therapy (CBT), habituation training [4], exposure therapy, mindfulness, and drugs [1]. Pan et al. [1] presented a case of a 32-year-old male with ASD, multiple psychiatric comorbidities, and misophonia. They found that an increase in his risperidone dosage resulted in an unexpected improvement in his misophonia. Naguy et al. [7] reported similar success using a low dose of risperidone in a 4-year-old child with ASD. Despite the positive findings, further research is needed to confirm the efficacy of such pharmacological agents.

In an effort to describe the role of auditory training in the management of hyperacusis in the ASD population, Danesh et al. [4] examined the impact of habituation training as a treatment method for ASD individuals. Habituation training utilizes retraining to desensitize the emotional and non-classical auditory pathways to reduce the fear response to sound. The authors indicated that this specific intervention was effective in reducing the adverse reaction to sounds in ASD individuals.

In a systematic review, Stephanelli et al. [22] looked at various questionnaires used by professionals and highlighted the lack of standardized tools used to determine dysregulated behavioral symptoms (DBS) due to the heterogeneity of ASD manifestations. Although the researchers did not find any evidence-based tools for treatment regarding hyperacusis, they did suggest that the auditory behavior tests showed involvement of the afferent and efferent auditory pathways.

Conclusions

In this brief piece, we have looked specifically at DST in the ASD population, focusing on hyperacusis and misophonia. There appears to be a gap in the literature regarding hyperacusis and misophonia in individuals with autism. At present information is still lacking about etiology, diagnosis, and effective management. Future research should address therapeutic strategies such as auditory habituation, user-friendly AI-based CBT, and explore low-level electrical stimulation (as currently used for managing tinnitus). Effective treatments will decrease social isolation and increase the quality of life of affected individuals.

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HYPOTHESIS PAPER

THE NEUROPHYSIOLOGICAL MODEL FOR HYPERACUSIS AND MISOPHONIA

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D Data interpretation
E Preparation of manuscript
F Literature analysis/search
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Abstract

Tinnitus patients frequently complain about Decreased Sound Tolerance (DST) as well. Based on the observations of several hundred patients with Decreased Sound Tolerance the existence of unrecognized earlier auditory disorder with distinctive and different from hyperacusis characteristics has been identified. Patients with this disorder exhibited negative emotional and autonomic reactions evoked by a specific for a given patient patterns of sound. Consequently, the name *misophonia* for this previously not described disorder and its definition based on data gathered from our patients was proposed in 2001. It is possible to have tinnitus, hyperacusis, and misophonia in combination or as isolated conditions.

On the basis of analysis of characteristic features of patients with DST, and general neuroscience, the neurophysiological model for both misophonia and hyperacusis has been proposed. The key characteristic of misophonia is the formation of inappropriate, pattern-specific, subconscious connections, between the auditory system and other systems of the brain, governed by the principles of conditioned reflexes. Notably, the brain systems and connections involved in misophonia are the same as in the case of tinnitus.

The mechanism of hyperacusis is based on abnormally increased gain within the subconscious part of the auditory pathways. This yields a high level of neuronal activity, equivalent to activity evoked by a much stronger sound in normal subjects. The activation of the other systems in the brain is a consequence of spreading this abnormally enhanced sound-evoked activity by normally functioning neuronal connections from the auditory to other systems in the brain. In misophonia, sound-evoked signals within the auditory pathways are normal, but development of incorrect pattern-specific connections yield abnormally strong activations of various systems in the brain. In hyperacusis and misophonia reactions evoked by bothersome sound are very similar, even identical and cannot be used to differentiate these two disorders. Importantly, both clinical observations and predictions of the model point out that misophonia requires a different approach for diagnosis and treatment than hyperacusis.

Keywords: The Neurophysiological Model of Tinnitus and Decreased Sound Tolerance • DST • hyperacusis • misophonia • tinnitus

NEUROFIZJOLOGICZNY MODEL SZUMÓW USZNYCH I OBNIŻONEJ TOLERANCJI NA DŹWIĘKI

Streszczenie

Pacjenci cierpiący na szumy uszne często skarżą się również na obniżoną tolerancję na dźwięki (DST). Na podstawie obserwacji kilkuset pacjentów z DST zostało zidentyfikowane nieznane dotąd zaburzenie słuchu, wyraźnie różniące się od nadwrażliwości słuchowej (hyperakuzji). Pacjenci cierpiący na to zaburzenie wykazują negatywne reakcje emocjonalne i odpowiedzi z autonomicznego układu nerwowego wywołane przez specyficzne dla danego pacjenta wzorce dźwiękowe. W 2001 roku została zaproponowana nazwa *mizofonia* dla tego nieznanego dotąd zaburzenia, a jego definicję oparliśmy na danych zebranych od naszych pacjentów. Szumy uszne, nadwrażliwość słuchowa i mizofonia mogą występować łącznie lub jako oddzielne schorzenia.

Na podstawie charakterystycznych cech pacjentów z DST zaproponowano neurofizjologiczny model zarówno hyperakuzji, jak i mizofonii. Niniejszy artykuł rozszerza aspekty modelu przedstawionego podczas 7th International Conference on Hyperacusis and Misophonia (ICHM), która odbyła się w dniach 15–17 września 2024 r. w Warszawie. Kluczową cechą mizofonii jest rozwój – regulowany przez odruchy warunkowe – nieodpowiednich, specyficznych dla danego wzorca, podświadomych połączeń między układem słuchowym a innymi częściami mózgu. Co istotne, zarówno w przypadku mizofonii, jak i szumów usznych aktywne są te same układy i połączenia mózgowe.

Mechanizm nadwrażliwości słuchowej opiera się na nieprawidłowo zwiększonej czułości w podświadomej części ścieżek słuchowych. Powoduje to wysoki poziom aktywności neuronalnej odpowiadający aktywności wywołanej przez znacznie silniejszy dźwięk u osoby zdrowej. Aktywacja tych innych układów nerwowych wynika z rozprzestrzeniania się nadmiernie wzmocnionej aktywności wywołanej dźwiękiem z układu słuchowego do innych układów w mózgu poprzez prawidłowe połączenia neuronowe. W przypadku mizofonii sygnały wywołane dźwiękiem w ścieżkach słuchowych są prawidłowe, ale rozwój nieprawidłowych połączeń specyficznych dla danego wzorca powoduje nieadekwatnie silną

aktywację różnych innych układów w mózgu. W przypadku nadwrażliwości słuchowej i mizofonii reakcje wywołane przez uciążliwy dźwięk są bardzo podobne, a nawet identyczne, i nie można ich wykorzystać do rozróżnienia tych dwóch zaburzeń. Zarówno obserwacje kliniczne, jak i prognozy modelowe sugerują, że mizofonia wymaga innego podejścia do diagnozy i leczenia niż nadwrażliwość słuchowa.

Słowa kluczowe: neurofizjologiczny model powstawania szumów usznych i obniżonej tolerancji na dźwięki • DST • nadwrażliwość słuchowa • mizofonia • szumy uszne

Key to abbreviations	
DST	Decreased Sound Tolerance
GAD	Generalized Anxiety Disorder
GAD-7	General Anxiety Disorder-7 (questionnaire)
ICD-10-CM	International Classification of Diseases, 10th Revision, Clinical Modification
ICD-11	International Classification of Diseases, 11th Revision
PHQ-9	Patient Health Questionnaire-9
TRT	Tinnitus Retraining Therapy

The aim of this paper is to expand description of the model described recently in *Frontiers in Neuroscience* publication [1], which we presented during the 7th International Conference on Hyperacusis and Misophonia, 15–17 September 2024, Warsaw, Poland. As such, we do not attempt to describe the model in detail, but only to delineate it, stressing specific issues which were not sufficiently described in previous publications [1,2].

Most of our tinnitus patients treated since 1990 reported having problems when exposed to external sound. Based on the literature, interactions with professionals from the field of auditory disorders, and our accumulated knowledge from clinical practice, we proposed to define Decreased Sound Tolerance (DST) as present when a person exhibits negative reactions following exposure to sound that would not evoke the same response in an average listener. DST is listed as a syndrome in many medical conditions (e.g., acoustic trauma, migraines, William's syndrome, Lyme Disease, and some mental health conditions, e.g., autism). For years, two terms, hyperacusis and phonophobia, have been used in literature to describe abnormal reactions to sound. These two conditions were not carefully defined and still are frequently used interchangeably, resulting in confusion. Clinical observations revealed that a certain category of DST cannot be classified as either hyperacusis or phonophobia. Therefore, in 2001 we proposed a new term – misophonia – for this type of DST [3].

First, based on clinical observation, behavioral definitions for hyperacusis and misophonia have been proposed, which are independent of etiology or potential theoretical mechanisms [1,2].

- *Hyperacusis* is defined as a condition when negative reactions to a sound depend only on its physical characteristics (i.e., spectrum, intensity). Time course (coded in the phase of spectrum) and meaning of the sound are irrelevant.

- *Misophonia* defined as condition when negative reactions occur to sounds with specific patterns and/or meaning to a given patient; physical characteristics are secondary (for detailed definitions see [1,2,4]).

Considering these behavioral definitions and general knowledge of neuroscience, the following mechanisms-based definition have been proposed [1,2].

- *Hyperacusis* – reflects abnormally strong reactivity of the auditory pathways to sound, which only in turn yields activation of the limbic and autonomic nervous systems (**Figure 1**).

- *Misophonia* – reflects abnormally strong reactions of the autonomic and limbic systems resulting from enhanced functional connections between the auditory, limbic, and autonomic systems for specific for a given patient pattern of sound (**Figure 2**).

There is a discussion regarding definitions of DST and furthermore misophonia. Proposed definitions are based on neurophysiology and should not be considered to be audiological, or psychological. Fundamental postulate of the neurophysiological model of tinnitus and DST is that in these disorders the auditory system plays a secondary role and other systems in the brain are dominant. We have never postulated that misophonia is a purely auditory condition! It is clearly stated in our definition of misophonia: Misophonia – reflects abnormally strong reactions of the autonomic and limbic systems resulting from enhanced functional connections between the auditory, limbic and autonomic systems for specific for a given patient pattern of sound (**Figure 2**) [1,2]. The basic postulate of the neurophysiological model of tinnitus and DST is that the auditory system plays a secondary role in clinically-significant (i.e., problem impacting subjects to such extent that they search for help and frequently become patients) tinnitus, hyperacusis and misophonia.

In 2022 Swedo at al. [4] published paper presenting attempt to create a consensus definition of misophonia, using Delphi method. However, the definition presented in Swedo's paper should not be treated as final one, but as first step in creating misophonia definition. This is clearly stated in Swedo's paper: "This definition represents an important first step for researchers and clinicians to progressively build-upon and revise as the body of knowledge in the published scientific literature grows over time" [4]. This point is presented in Brout's [5] paper as well: "The consensus definition is fluid and will change over time, and we should read it with that in mind".

The Delphi method defines consensus as 80% of committee members agreeing on an issue, acknowledging that some disagreement is expected. This highlights that the "consensus definition" within the Delphi framework is different from unanimity, as certain points will always have dissenting opinions among committee members. While a definition may be widely accepted, individuals are free to propose their own interpretations, and it is up to the readers to decide whether to accept them.

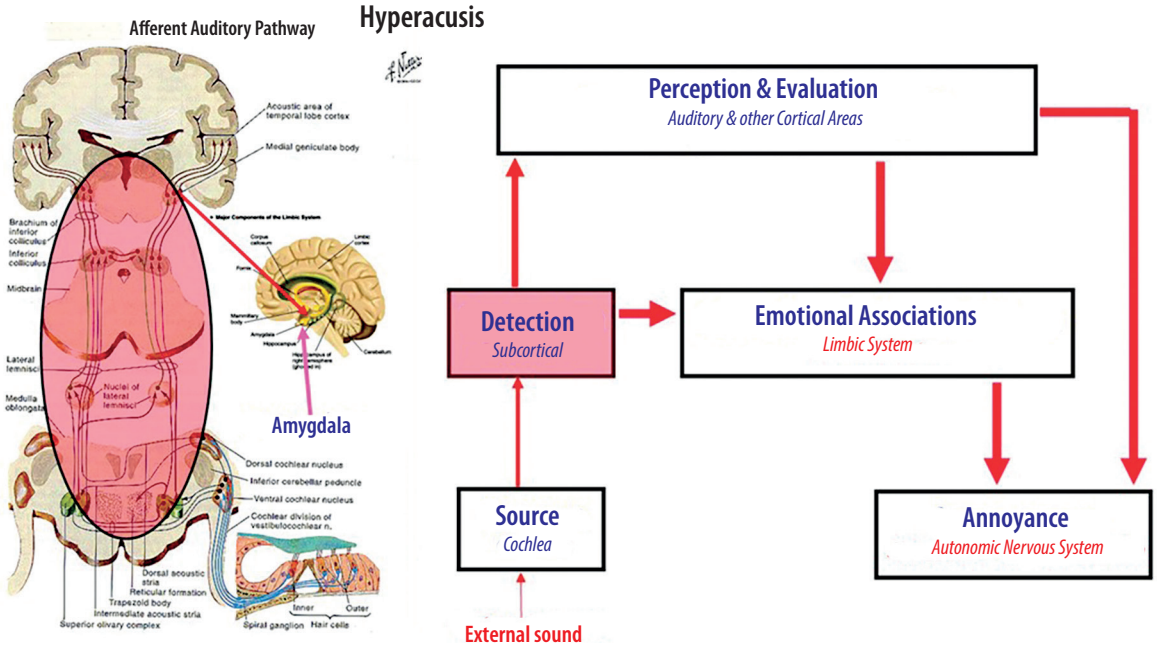

Figure 1. Proposed neurophysiological mechanism of hyperacusis. Hyperacusis reflects abnormally strong reactivity (abnormally high gain) of the auditory pathways to sound, which only in turn yields activation of the limbic and autonomic nervous systems

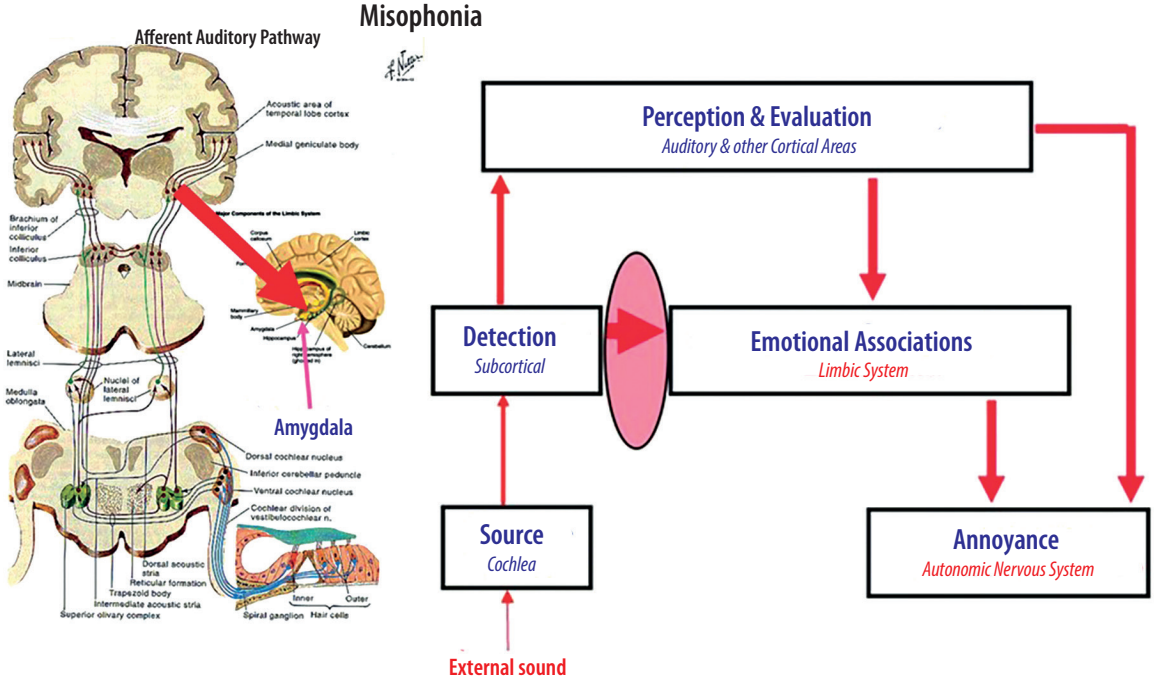

Figure 2. Proposed neurophysiological mechanism of misophonia. Misophonia reflects abnormally strong reactions of the autonomic and limbic systems resulting from enhanced functional connections between the auditory, limbic, and autonomic systems specific to a given patient and patterns of sound

In our opinion misophonia is a specific case of a category of disorders manifested by negative reactions to a sensory stimulus from variety of modalities, which develops when a sensory stimulus is paired with negative reinforcement, e.g., *misoángigma* (touch), *misoórasi* (vision), *misokinisi* (movement), *misoosmi* (smell), *misogefsi* (taste), etc. In our population of patients, we have cases where negative reaction occurs only to olfactory, or only visual stimuli without any involvement of sound. This points out the possibility of the existence of other disorders in which negative

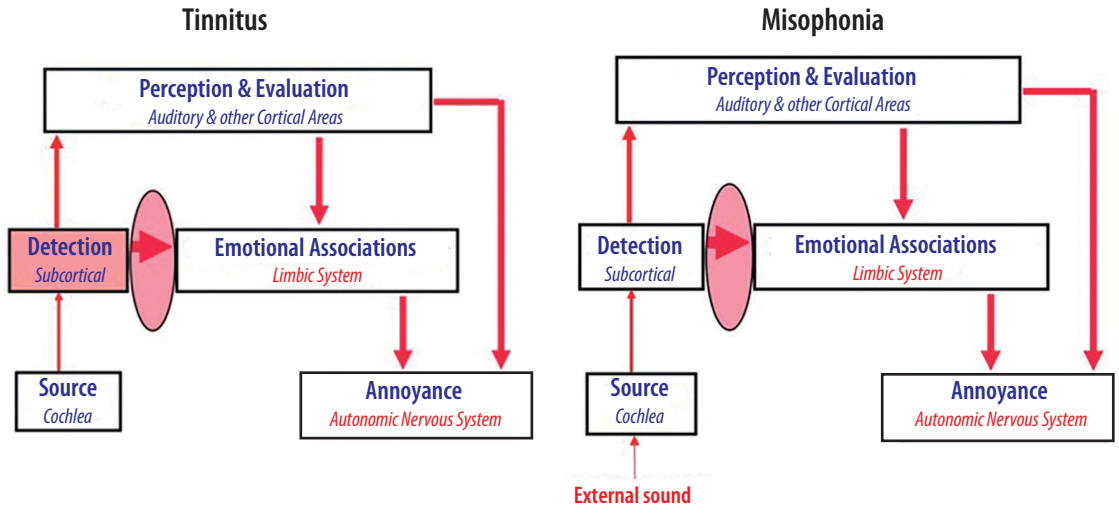

Figure 3. Similarity of mechanisms of tinnitus and misophonia. Tinnitus and misophonia differ by the origin of the sound – internal for tinnitus (phantom auditory perception) and external for misophonia, but otherwise the same systems and connections in the brain are involved

reactions are evoked by the stimuli of various modalities without sound being involved. Of course, reactions may be evoked by complex conditioned stimuli consisting of stimuli of different modalities and stimuli generalization may occur as well, which seems to be predominant situation in misophonia, e.g., presence of trigger sound while its source is visible (e.g., lawnmower, somebody eating) causes association of this visual stimulus with discomfort and consequently create secondary conditioned reflex causing that this specific visual stimulus alone evokes negative reaction. Again, similarly with smell, possibly with taste, as well as with repetitive movements.

There are some similarities, and crucial differences between mechanisms of tinnitus, hyperacusis and misophonia. All these phenomena reflect abnormal (i.e., different that for general population) reactions to sound. In all of them subconscious conditioned reflexes, connecting the auditory system with other systems in the brain are crucial, with conscious part playing secondary role, particularly in the acute phase of these disorders. None of them require dysfunction of other systems in the brain.

Psychological profile of a patient as well as potentially coexisting mental disorders may facilitate development of tinnitus, hyperacusis, and misophonia and they may influence the extent of reactions; note however, that mental disorders are not necessary for existence of tinnitus, hyperacusis or misophonia. Both tinnitus and hyperacusis (but not misophonia) involve some dysfunction within the auditory system.

Notably, reactions to external sound observed in hyperacusis and misophonia are remarkably similar, frequently identical, and cannot be used to differentiate these two phenomena. Tinnitus and misophonia differ by the origin of the neuronal activity perceived as sound – internal for tinnitus (phantom auditory perception) and external (sound-evoked) for misophonia, but otherwise the same systems and connections in the brain are involved (**Figure 3**). In misophonia the important postulate is that it may exist with all the systems of the brain functioning in the normal manner - problems arise from creating subconscious, functional connections between the auditory system and other systems in the brain governed by principles of conditioned reflexes. In hyperacusis, the underlying problem is an abnormal increase of the gain within the subconscious part of the auditory system, consequently resulting in activation of other systems in the brain, as it would occur in the person without DST, stimulated with high level of sound.

The crucial point which we are postulating is that tinnitus and misophonia do not require abnormal activity of any system in the brain (except abnormal neuronal activity in the auditory system perceived as tinnitus), but their mechanisms are based at misjudgment of the significance of perceived sound, treating these sounds as something linked to unpleasant or dangerous situation, threatening. Consequently, the brain forms automatic reactions at a subconscious level which are governed by the principles of conditioning reflexes. These reactions link the perception of tinnitus or misophonic triggers to activation of the limbic system (which deals with emotions, memory, and motivation) and the autonomic nervous system (which controls involuntary bodily functions like heart rate, breathing, and digestion). As a result, exposure to these triggers can automatically lead to emotional distress, anxiety, or physical symptoms. Reactions are correct, but to incorrect stimuli. This happens because misophonic triggers or tinnitus are misclassified (subconsciously, and sometimes consciously) as having a negative meaning [1].

Dysfunctions of some brain systems may facilitate emergence of tinnitus or misophonia and then may enhance negative reactions evoked by these disorders. However, they are not necessary for the emergence of tinnitus or misophonia! This issue may explain why imaging studies performed for many years in the field of tinnitus [6], and recently in misophonia failed to provide coherent results [7].

Kumar's [8] and Neasciu's [7] data support our model but push attention into direction which is in our opinion secondary. We hypothesize that all brain systems and their connections in misophonia patients may function entirely normally. Any observed alterations in the functionality of various brain centers are likely a consequence of already developed misophonia, rather than the primary cause. Furthermore, it is not even necessary for these functional modifications to be present in all misophonic individuals. While such modifications might contribute to the development of misophonia or intensify the reactions to triggers, they are not considered fundamental or essential for the condition to exist.

Neasciu's [7] observation of lack of consistency in imaging data further supports our postulate. The situation seems to be the same as in the case of tinnitus, where after many years and extensive researcher efforts, existing data are inconsistent, and the only common observation is involvement of limbic system. In 2023 Husain and Khan [6] published a review paper on neurophysiological basis of tinnitus, concluding "Currently, the most consistent findings of neural patterns associated with tinnitus have been observed when using the tool of resting-state fMRI. Results in structural imaging literature appear to be inconsistent". While research on misophonia is much shorter the conclusion is similar "The rapid advancements in understanding the neuroscience behind misophonia are promising. One drawback of the current literature is the little overlap in findings, despite similar paradigms" [7].

Described neurophysiological model provided guidance in creating a treatment approach, known as Tinnitus Retraining Therapy (TRT). Note that since a very beginning when TRT was introduced in 1990, hyperacusis and its treatment were a crucial element and part of classification of patients with tinnitus and DST into 5 categories. Just for brevity it was not included in the name of TRT. Once we noticed existence of phenomenon which we labeled "misophonia" the model has been expanded to include it and specific treatment has been developed, with protocol level (1) published in 2002 [9]. Treatment of misophonia is different from treatment for hyperacusis and applying hyperacusis treatment for misophonia is not effective. Description of misophonic treatment has been provided already [1,2,10], with published success rate of 83%. Interestingly, in many cases it was possible to achieve a cure, i.e., total disappearance of negative reaction to previously highly bothersome misophonic triggers [1,10,11].

Conclusions and recommendations

Misophonia is not a disease but a disorder resulting from development of conditioned reflexes linking the auditory system with other systems in the brain, particularly limbic and autonomic nervous systems, created for specific for a given patient patterns of sound. Misophonia can develop in anyone, triggered by any sound, when that sound is paired with a strong negative emotional or physiological experience. This pairing is sufficient and necessary conditions to create conditioned reflex, where the previously neutral sound becomes associated with the unpleasant state, ultimately triggering similar negative reactions on its own.

As such it should not be categorized as a mental disorder as is frequently postulated [7]. The confusion started in 2013 when Schroeder on the basis of results obtained in population of patients form psychiatric clinic proposed different definitions of misophonia and claimed that it is a mental disorder [12]. We strongly disagree with his definition and presented detail critique in our paper [1]. As with all medical disorders there is a comorbidity of misophonia with mental disorders. Recent literature suggests that it is not as common as initially thought resulting in a postulate that is a separate unique disorder [7]. Moreover, it was reported "that up to 50% of those who describe misophonic distress do not have any other mental health disorders" [13]. On the basis of our experience and literature we postulate that misophonia is not a mental disorder.

The issue of categorizing misophonia as a mental disorder is exacerbated by an insufficient distinction, in research, publications, and proposed treatments, between depression and anxiety that arise from specific situations and those that have a primarily physiological basis. The ICD-10-CM (the International Classification of Diseases, Tenth Revision, Clinical Modification, used to code and classify medical diagnoses) which differentiate between the Situational-Evoked (Reactive) Depression, ICD-10 codes F43.21 (Adjustment Disorder with Depressed Mood) or F43.23 (Adjustment Disorder with Mixed Anxiety and Depressed Mood) are versus Chronic Depression, codes F32.0 (Major Depressive Disorder, Single Episode, Mild), F32.1 (Moderate), F32.2 (Severe without psychotic features), or F32.3 (Severe with psychotic features), Generalized Anxiety Disorder (GAD) (F41.1): this code is intended to be used for anxiety that is ongoing and pervasive, not merely a reaction to specific circumstances. It should only be applied to situation-specific anxiety if the individual's symptoms meet the established diagnostic criteria for Generalized Anxiety Disorder [14,15]. Corresponding codes in ICD-11 are 6B41 (Adjustment disorder with depressed mood), 6B43.Z (Adjustment disorder, with mixed emotional and conduct symptoms), 6A70.3 represents (Single episode depressive disorder, severe, without psychotic symptoms) and 6A71.3 (Recurrent depressive disorder, current episode severe, without psychotic symptoms) and 6B00 (Generalized Anxiety Disorder) [16].

Commonly used questionnaires for depression (PHQ-9) and for anxiety (GAD-7) do not differentiate between situation-evoked problems versus chronic, medical problems. In published results on misophonia there is not information whether this distinction was taken into account and presence of depression or anxiety is treated as a proof that patient have "mental disorder". Applying this reasoning, e.g., cancer or other medical problems evoking depression or anxiety should be classified as a mental disorders. While psychologists and psychiatrists acknowledge the difference between situation-induced and physiologically-based anxiety, there is a lack of clear evidence that this distinction is consistently applied in their misophonia research, clinical treatments, and published works. In our experience practically all patients with significant misophonia exhibit depression and anxiety, but detailed interviews reveal that the vast majority of them got these problems after the start of misophonia and that depression and anxiety are situation-evoked.

Importantly, the differences in postulated mechanisms between hyperacusis and misophonia necessitate different treatments. Specifically, treatment as for hyperacusis is not effective for misophonia while treatment as for misophonia has limited effectiveness for hyperacusis. According to proposed model and our clinical observations focusing on the psychoacoustical parameters of misophonic triggers as well as on psychological or psychiatric categorization of patients are counterproductive. Analysis of social and environmental factors is important for understanding, treatment, and prevention of misophonia to occur and may play a significant role in the development of misophonia.

Noteworthy, patients' accommodation should be kept to a bare minimum as it enhances the severity of misophonia and hinders its treatment. Our observation for over 30 years suggested that the extent of accommodation correlates with misophonia severity and that gradually decreasing accommodation improves severity while increasing accommodation yields worsening of the problem. While some accommodation is needed, particularly at the beginning of the treatment, it should be kept to a minimum and for limited time only.

Recent publication support concerns regarding accommodation pointing out that "Excessive and maladaptive accommodation may be one potential candidate to target in interventions when considered within a broader treatment plan. Importantly, adaptive accommodations should also be considered in day-to-day management if they improve functioning and quality of life" [17].

Misophonia can be induced by social norms imposed in society, e.g., Prof. Norena's postulate "misophonia can be caused by a failure in the organization of the perceived world" and "In this context, the role of social rules acquired throughout life is considerable. Table manners, for example, are a set of deeply regulated and controlled behaviors (it's considered impolite to eat with the mouth open and to make noise while eating), which contribute to shape the way the perceived world is organized. So, it's not surprising to find sounds from the mouth (chewing etc.) among the most common misophonic sound triggers" [18].

Discussed ideas are presented in more detail in Jastreboff PJ and Jastreboff MM (2023) "The neurophysiological approach to misophonia: theory and treatment" [1].

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HYPOTHESIS PAPER

DIAGNOSIS AND TREATMENT OF MISOPHONIA AND HYPERACUSIS BASED ON THE NEUROPHYSIOLOGICAL MODEL

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Contributions:
A Study design/planning
B Data collection/entry
C Data analysis/statistics
D Data interpretation
E Preparation of manuscript
F Literature analysis/search
G Funds collection

Abstract

The complaints of patients with hyperacusis and misophonia are very similar, and frequently identical. However, there are distinctive differences between these conditions. The recognition of these differences is crucial to properly diagnose and treat hyperacusis and misophonia. Audiological evaluation, while helpful, is not sufficient for differential diagnosis. Specific patient interview is critical. The treatment for hyperacusis is based on the desensitization of auditory subconscious pathways and it is aimed at decreasing abnormally increased gain within the auditory system. For misophonia the treatment involves utilization of passive and active extinction of subconscious conditioned reflexes as well as purposefully creating and modifying complex conditioning stimuli. The treatments for both conditions include counseling and sound therapy but they are distinctively different. The treatment effective for hyperacusis is not successful for misophonia and the treatment for misophonia has limited effectiveness for hyperacusis. The treatment of Decreased Sound Tolerance (DST), based on the Neurophysiological Model of Tinnitus and Decreased Sound Tolerance, showed over 80% success rate of clinically significant improvement and can even provide a cure for hyperacusis and misophonia.

Keywords: hyperacusis • misophonia • tinnitus • diagnosis • treatment • results

DIAGNOSTYKA I LECZENIE MIZOFONII I NADWRAŻLIWOŚCI SŁUCHOWEJ Z WYKORZYSTANIEM MODELU NEUROFIZJOLOGICZNEGO

Streszczenie

Dolegliwości pacjentów z nadwrażliwością słuchową i mizofonią są bardzo podobne, a często wręcz identyczne. Istnieją jednak wyraźne różnice między tymi schorzeniami, a ich rozpoznanie jest kluczowe dla postawienia prawidłowej diagnozy i leczenia. Ocena audiologiczna, choć pomocna, nie jest wystarczająca do postawienia diagnozy różnicowej. Podstawą jest wywiad z pacjentem. Leczenie nadwrażliwości słuchowej opiera się na desensytyzacji podświadomych dróg słuchowych i ma na celu zmniejszenie nieprawidłowo zwiększonego wzmocnienia w obrębie narządu słuchu. W przypadku mizofonii leczenie obejmuje bierne i czynne wygaszanie podświadomych odruchów warunkowych, a także celowe tworzenie i modyfikowanie złożonych bodźców warunkowych. Leczenie obu schorzeń obejmuje poradnictwo i terapię dźwiękiem, ale różni się diametralnie. Leczenie skuteczne w przypadku nadwrażliwości słuchowej nie jest skuteczne w przypadku mizofonii, a leczenie mizofonii ma ograniczoną skuteczność w przypadku nadwrażliwości słuchowej. Leczenie obniżonej tolerancji na dźwięki (DST) oparte na neurofizjologicznym modelu powstawania szumów usznych i obniżonej tolerancji na dźwięki wykazało skuteczność wynoszącą ponad 80% w odniesieniu do klinicznie istotnej poprawy, a nawet może zapewnić całkowite wyleczenie nadwrażliwości słuchowej i mizofonii.

Słowa kluczowe: nadwrażliwość słuchowa • mizofonia • szumy uszne • diagnoza • leczenie • wyniki

Key to abbreviations	
DST	Decreased Sound Tolerance
LDLs	Loudness Discomfort Levels
THI	Tinnitus Handicap Inventory
TRT	Tinnitus Retraining Therapy
TTS	Tensor Tympani Syndrome
VAS	Visual Analog Scales

Introduction

We proposed to define Decreased Sound Tolerance (DST) as present when a subject exhibits negative reactions following exposure to a sound that would not evoke the same response in an average listener [1–3], and that DST consists of two components: hyperacusis and misophonia [2].

The behavioral and mechanisms-based definitions of hyperacusis and misophonia are presented in an accompanying paper [4].

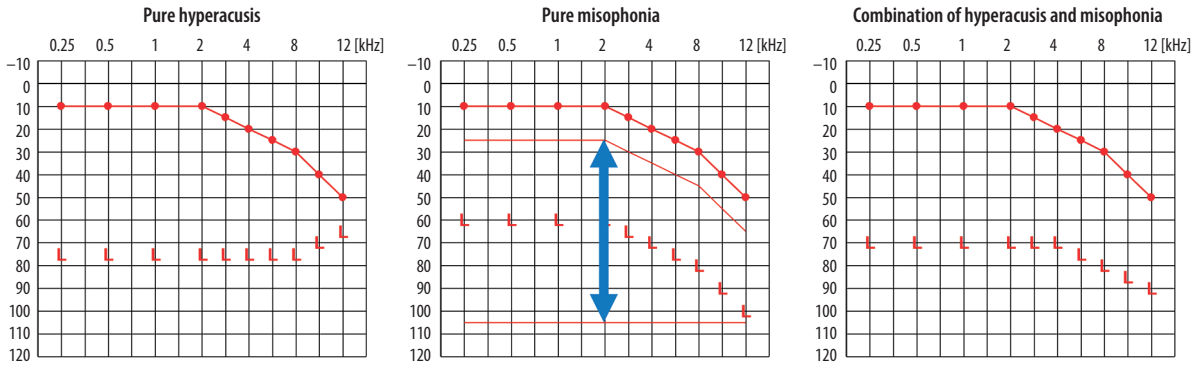

Figure 1. Comparison of shapes of audiogram and LDLs in patients with DST. For pure hyperacusis LDLs are flat with tendency of lower values for higher frequency (left panel). In case of pure misophonia LDLs follow the shape of audiogram (center panel). Note that they may have any values from very low to very high. Frequently both hyperacusis and misophonia are present together resulting in combination of these two graphs (right panel)

Note, that the proposed behavioral definitions, based on observation of patients with DST, are independent of etiology or potential theoretical mechanisms: Hyperacusis – negative reactions to a sound which depend only on its physical characteristics (i.e., spectrum, intensity). Time course (coded in the phase of spectrum) and meaning of the sound are irrelevant. Misophonia – negative reactions to sounds with specific patterns and/or meaning to a patient with physical characteristics being secondary. The reaction to a misophonic trigger can also vary significantly based on the specific person making the sound or the location where the sound occurs. Notably, reactions to bothersome sounds are remarkably similar, even identical on hyperacusis and misophonic patients, and cannot be used to distinguish between these disorders. Furthermore, audiological evaluation alone is not enough, as misophonia triggers negative reactions to sounds with specific patterns and/or meaning to a given patient.

Methods

To assess the presence of hyperacusis most commonly Loudness Discomfort Levels (LDLs) are used [5]. LDL testing aims to identify the maximum sound intensity a person can tolerate before it becomes uncomfortably loud. A series of pure tones are presented at increasing intensities, and the individual indicates when the sound becomes uncomfortably loud. LDLs reflect the combination of effects of hyperacusis and misophonia.

In case of pure hyperacusis the LDLs will always have lower values as in hyperacusis the *level* of any sound is the determining factor. Therefore, normal values of LDLs preclude the presence of hyperacusis. Comparing Loudness Discomfort Levels (LDLs) to speech uncomfortable levels can offer some insight into misophonia for patients whose misophonic triggers are voices. These patients might exhibit normal LDLs when tested with pure tones, yet still experience a reduced uncomfortable level specifically for speech. This highlights that misophonia is sound-specific, even if general loudness tolerance (measured by pure tones) remains unaffected.

In case of pure misophonia, if the sound of pure tones (resembling sounds of flute) is not within range of patient's misophonic triggers, the LDLs will be normal (around 100 dB HL), even if patients have very strong reactions to other even soft sounds of, e.g., eating or speech. In this case the contribution of misophonia to LDLs values, even strong, is not existing, and since there is no hyperacusis the LDLs have normal values. However, if pure tones are within the range of misophonic triggers, then LDLs values will be lower than normal.

Nevertheless, certain audiological indicators are useful in detecting misophonia and distinguishing it from hyperacusis. Our clinical observation pointed out that in the majority of cases there is a relation between shape of audiogram and LDLs in pure misophonia which is absent in case of pure hyperacusis (**Figure 1**). In cases where there is pure hyperacusis the LDLs are flat, with values typically below 80 dB HL, with some tendency to decrease for high frequency (**Figure 1**, left panel). For pure misophonia LDLs follow the shape of audiogram keeping approximately the same distance between audiogram and LDLs and all values, form very low (e.g., 25 dB HL) to over 100 dB HL, are observed (**Figure 1**, center). This phenomenon exists not only for high frequency hearing loss, but also for any other types of hearing loss (e.g., "cookie-bite audiogram" or low frequency hearing loss).

For majority of DST cases both hyperacusis and misophonia are present, yielding LDLs which are initially flat and only when there is larger hearing loss, they start to increase in value (**Figure 1**, right panel). As the majority of misophonic patients have normal hearing up to 8 kHz, it is recommended to do audiogram and LDLs evaluation for frequency range at least up to 12 kHz where majority of patients have some hearing loss. Preferably, the measurements should be done up to 20 kHz as many misophonic patients, particularly children, have excellent hearing even up to 12 kHz. Evaluating audiogram and pure tone Loudness Discomfort Levels assessed for all frequencies measured at audiogram is helpful.

Therefore, to accurately diagnose and distinguish between hyperacusis and misophonia, a specific and detailed

SOUND TOLERANCE

DST Y / N First noticed_____ Physical discomfort
Description of troublesome sounds
Are you bothered by: all loud sounds Y / N e.g.,
specific sounds Y / N e.g.,
only in specific situations Y / N e.g.,
only prodcuced by specific person(s) Y / N e.g.,
Reactions to bothersome sounds
Favorite sounds
Effect of short loud snd: No / Bt / Wrs Persists for: m / h / d
Ear overprotection Y / N ___ % of time In quiet Y / N
Changes of DST with time: None / Better / Worse
Why is DST a problem
Activities prevented or affected by DST:

0 1 2 3 4 - *High pitch sounds*	0 1 2 3 4 - *Work*
0 1 2 3 4 - *Loud events*	0 1 2 3 4 - *Social*
0 1 2 3 4 - *Restaurants*	0 1 2 3 4 - *Childcare*
0 1 2 3 4 - *Housekeeping*	0 1 2 3 4 - *Shopping*
0 1 2 3 4 - *Kitchen sounds*	0 1 2 3 4 - *Church*
0 1 2 3 4 - *Movie theater*	0 1 2 3 4 - *Other*

0 1 2 3 4 5 6 7 8 9 10 *Loudness*
0 1 2 3 4 5 6 7 8 9 10 *Annoyance*
0 1 2 3 4 5 6 7 8 9 10 *Effect of life*
Past & current treatments for DST

Figure 2. Part of the Structured Interview Form related to hyperacusis and misophonia [19,21]

interview is essential. During this interview, an assessment of the relation of severity of sound-evoked reactions on physical parameters of the sound is crucial (**Figure 2**) as in the case of hyperacusis the level of a sound is dominant factor, while in the case of misophonia the meaning and association of a sound are crucial. For example, if for a patient the sound of person voice, or the sound of eating are evoking negative reactions then, performing spectral analysis of these sound (e.g., by Fast Fourier Transform, FFT) provides detailed information about spectrum and phase relation of its components and allows for full reconstruction of the original sound. If, however, reconstruction is performed but with removing all phase information, these sound will have exactly the same spectrum but will be perceived as meaningless noise.

Hyperacusis patient will be responding to both, the original sounds and reconstructed from them noise in the same manner as in hyperacusis the crucial factor is physical characteristics of the sound (i.e., level, spectrum, total energy) and meaning is irrelevant. On the other hand, a misophonic patient who had negative reactions to the original sounds will not react to reconstructed sounds, in spite that this sound has the same physical characteristics as original, but reconstructed sounds have no meaning. This method may serve as a diagnostic approach for identifying the presence of misophonia.

During the interview, the goal is the assessment whether physical characteristics or meaning of bothersome sounds are crucial and to which extent the loudness of these sound affects their severity. In hyperacusis all sound "louder than" will evoke negative reaction and increase of the level of these sounds will results in proportional increase of their severity. In misophonia the level of the sound inducing reactions will be different for different misophonic triggers, e.g., a very soft sound (e.g., chewing) can evoke strong reaction, while it will be necessary to present a less bothersome trigger, e.g., voice, at a higher level to evoke similar reactions). Furthermore, the extent of reaction will be only weakly dependent on the level of a given trigger.

The important question, from the perspective of patients, is what should be considered an effective treatment? For patients, effective treatment means that negative reactions evoked by sound are eliminated or they are decreased to such an extent that they have a low-level impact on their lives. If pain induced by sound is one of the reactions it has to be significantly attenuated, preferably totally removed as pain has a special meaning, warning about problems and is difficult to habituate. To determine if a treatment has led to a clinically significant improvement, it is essential to look at the patient's final severity score. A change that is statistically significant – or a drop by a certain number of points – is not enough on its own and can be misleading. The key is whether the treatment brings the patient's condition to a low level of severity. Note that reactions to sounds cannot be used to differentiate hyperacusis and misophonia as for both phenomena they are very similar, and even identical.

Both our clinical experiences as well the predictions from the neurophysiological model show that treatments for hyperacusis and misophonia are different (**Figure 3**) [3,6]. Treatment for hyperacusis is aimed at a decrease of abnormally increased gain in the auditory system. Counseling aims at describing to a patient the mechanisms of hyperacusis, particularly the decrease of abnormally increased gain in subconscious parts of the auditory system; it is not aimed at habituation of reactions evoked by sound. Sound therapy is based on desensitization of the auditory system by consistent, day and night exposure to neutral external sounds. This treatment is not effective for misophonia.

Treatment for misophonia involves passive and active extinction of subconscious conditioned reflexes, furthermore, purposefully creating complex conditioned stimuli (which includes misophonic triggers and other positive, multisensory components), and principle of generalization [3,6] and description of protocol [4] explained below. Counseling is extensive and involves an explanation of all mentioned mechanisms and teaching patient's basis of using complex conditioned stimuli in treatment.

Sound therapy for misophonia involves four protocols, which are applied depending on the stage of treatment and specifics of a given patient. The first three protocols aim at increasing the 'likability' of sounds. In protocol (1) the type of sound, its level and duration are totally under patient's control, therefore this protocol can be used by all patients with DST, even in patients with high severity of hyperacusis or misophonia. Typically, music, most liked at the given moment, is used.

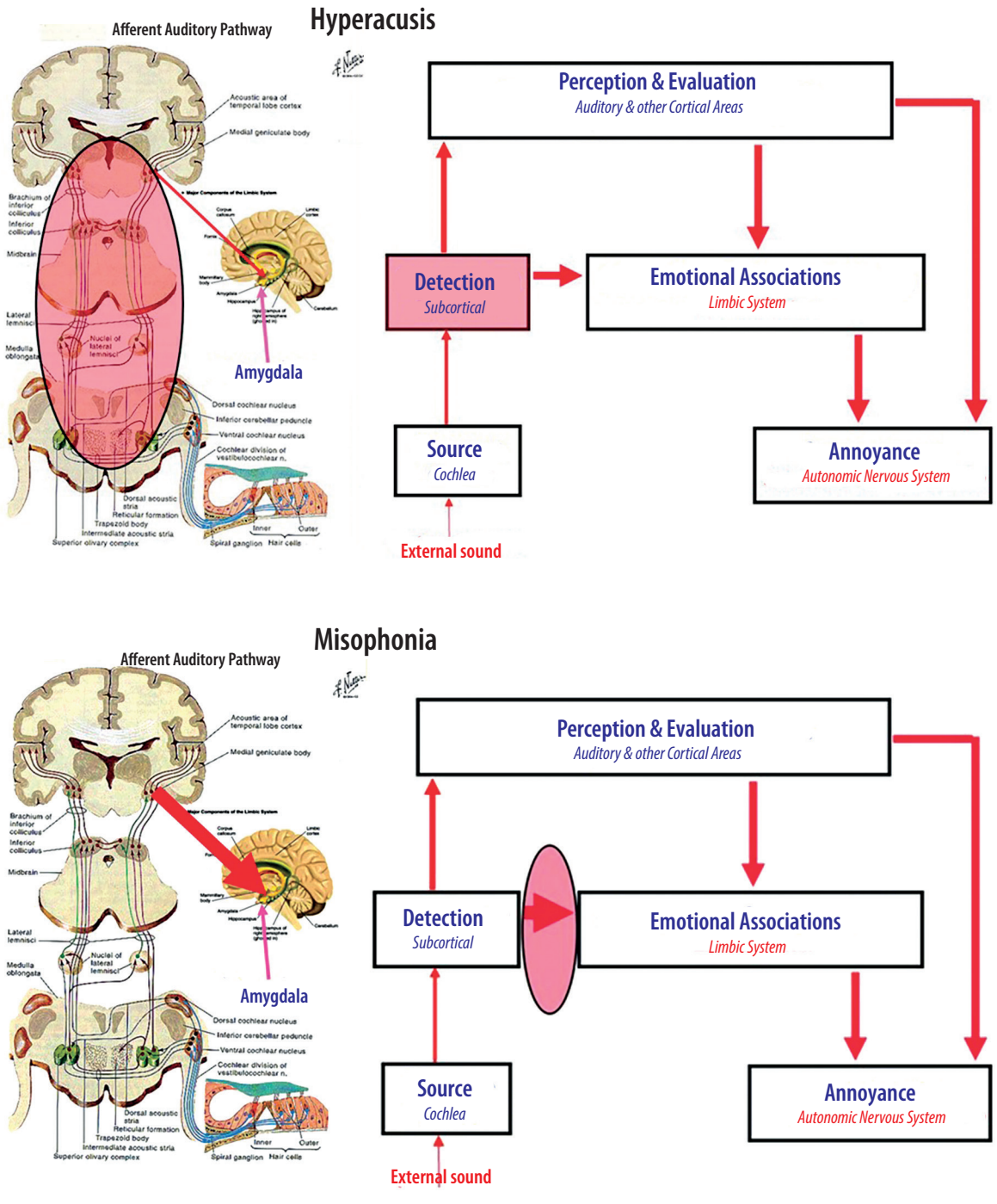

Figure 3. Comparison of postulated mechanisms for hyperacusis and for misophonia

In protocol (2), the sound level is set by someone familiar with the patient and her/his preferences. This person adjusts the sound to what they believe is optimal, then fine-tunes it for subsequent sessions based on the patient's feedback. Thus, a patient has indirect control of the sound level while she/he has full control of its type. This protocol combines auditory and visual stimuli with aim that achieved combination is pleasant to patients, e.g., watching a favorite movie at home.

In the protocol (3) patients have no control over sound level but have full control of its type; level fluctuates in an unpredictable manner (e.g., going to a movie theater to watch their favorite movie).

Protocol (4) is based on the concept of complex conditioned stimulus – creating such stimulus by combining misophonic trigger with positive sounds and other positive elements from different sensory modalities

(e.g., visual, smell, taste, surrounding), combination of which have a positive connotation [6]. Then, over a period of time the level of positive components gradually decreased. This protocol is typically used together with protocols (1) and/or (3).

Tensor Tympani Syndrome (i.e., fullness in the ear, ear pain, dysacusis consisting of various abnormal acoustic sensations, e.g., murmurs, clicks, tickling sensations, sound distortion) is often observed in patients with DST [7–9]. It is especially troubling when pain is involved, whether it is triggered by a sound or appears without an obvious cause. It has been proposed that it is facilitated by hyperacusis [8]. In our experience it is rather linked to the presence of misophonia. The treatment is focused on removing DST combined with exercises aimed at activation of Eustachian tube (tensor tympani muscle is part of network cleaning middle ear and is contracting when Eustachian tube is opening). Once this is achieved, in the majority of cases the Tensor Tympani Syndrome disappears.

Results

To assess the severity of DST and evaluation of results of the treatment patients were asked to judge the severity of their DST, the annoyance induced by it, the effect of DST on their lives, and to rate DST as a problem on a scale from 0 to 10 (where 0 corresponded to an absence of DST and 10 indicated that DST was as big of a problem as they could imagine). Patients were asked to consider an average over the last month in their responses. The levels of "Annoyance" and "Effect on Life" "DST as a problem" are main parameters to determine severity of DST (**Figure 2**). Treatment has been considered to be clinically effective when all these measures decreased by at least two and final scores were not greater than 2. Furthermore, for patients diagnosed with hyperacusis it was requested that their average LDLs were in normal range (around 100 dB HL). Our results indicate 83% effectiveness in treating DST to a clinically significant extent. In many cases it is possible to achieve a cure [3].

Ongoing discussion on how to evaluate severity of hyperacusis and misophonia have not produced consensus. There is lack of randomized clinical trials, with the exception of one trial on misophonia which shows 48% of success rate of significantly improving misophonia [10]. A number of reviews delineate situation with determining severity of hyperacusis and misophonia describing wide variety of approaches and results, without presenting consensus [11–18].

Conclusions

There is fundamental difference in mechanisms of hyperacusis and misophonia, which necessitates careful differential diagnosis and different treatment approaches to these disorders. Analysis of sound induced reactions cannot be used to differentiate hyperacusis and misophonia. Audiological evaluation (audiogram, LDLs, speech discomfort level), while needed and providing useful information in diagnosis, offers only a partial indication and alone cannot be used for diagnosis. Normal values of LDLs, however, preclude the presence of hyperacusis. Therefore, a detailed interview is crucial, with audiological evaluation providing only some help in diagnosis (**Figure 2**) [19]. Proper criteria allowing to determine achieving clinically significant improvement are essential.

We argue that the extent of decrease in severity measured by Visual Analog Scales (VAS) or specific questionnaires is not sufficient as well as achieving statistically significant decrease of severity on these measures. For example, in the field of tinnitus, Tinnitus Handicap Inventory (THI) is a validated questionnaire for tinnitus and specific studies determined that decrease of total score by 20 points document clinically significant improvement [20]. The maximal score in THI is 100 and the range from 80 to 100 is considered Catastrophic; the level below 18 is considered non-significant tinnitus. If a patient has an initial score e.g., 90 the decrease by 20 points means that the score is now 70 (i.e., in the range of severe tinnitus 58–76). From a practical standpoint, this patient will continue to experience significant suffering and may not even notice any improvement. Even if the initial score is 50 or 60 (frequently observed in clinical practice), decrease of these scores by 20 will not remove tinnitus as a problem and life of a patient will still be negatively affected by tinnitus. Therefore, we are postulating that to declare clinically significant improvement, in addition to decrease of the initial score, there is a requirement that THI score is below 20.

Given the lack of consensus on a standardized questionnaire for DST and even less agreement on how to distinguish misophonia from hyperacusis, we opted to use our own forms for Structural Initial and Follow-up interviews [19,21] to evaluate the severity of both tinnitus and DST in our study and require that all scores of "Annoyance" and "Effect on Life" and "DST as a problem" decrease by at least 2 points, and that their final scores are not larger than 2. Use of proper criteria for declaring improvement is essential and we are concerned that currently used approaches may provide misleading results.

The TRT (Tinnitus Retraining Therapy) approach, based on the neurophysiological model of tinnitus, hyperacusis and misophonia, which we have been using for over 25 years, is very effective, even providing cure in many cases [3]. Diagnosis and treatments are presented in more detail in Jastreboff PJ and Jastreboff MM (2023) [6].

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ORIGINAL ARTICLE

THE ROOT CAUSES OF MISOPHONIA: TEN TOPICS FOR FORMAL STUDY

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Contributions:
A Study design/planning
B Data collection/entry
C Data analysis/statistics
D Data interpretation
E Preparation of manuscript
F Literature analysis/search
G Funds collection

Abstract

Introduction: This article presents the results of some of my informal surveys and speculations from my private clinical psychotherapy practice regarding causes of misophonia and its possible relationship to family dynamics and other non-auditory factors. My hope is that researchers might take these as a starting point and conduct formal studies to verify or dismiss my informal results. My observations and relevant surveys address ten key questions and speculations about the root causes of misophonia. Understanding the causes of this complex disorder will lead to better treatments and possibly even prevent its development.

Material and methods: Following a brief section on context and background of existing research, ten proposed topics are presented for possible future research: Ancient brain; Genetics/ twins; Epigenetics/ family; Religion; Personality type; Trauma; Intelligence/ neural pruning; Gender expectations; Perinatal factors; Other considerations.

Results: The background for each of the ten topics is followed by a rationale for further exploration.

Conclusions: In the short number of years since misophonia was first identified as a distinct disorder, there has been increasing interest into more clearly defining the condition, and many studies have looked for potential causes. There is now ample evidence that it *exists*, but it is not yet clear *why*. So as to better understand this complex condition, this article proposes fertile avenues for future research.

Keywords: misophonia • causes • genetics • family factors • epigenetics

KORZENIE MIZOFONII: DZIESIĘĆ ZAGADNIEŃ DO NAUKOWEJ EKSPLORACJI

Streszczenie

Wprowadzenie: W niniejszym artykule przedstawiam wyniki szeregu nieformalnych badań własnych i rozważań przeprowadzonych w ramach mojej prywatnej praktyki psychoterapii klinicznej, dotyczących przyczyn mizofonii i jej możliwego związku z dynamiką rodziny oraz innymi czynnikami pozasłuchowymi. Mam nadzieję, że naukowcy potraktują je jako punkt wyjścia do przeprowadzenia formalnych badań w celu ich zweryfikowania lub odrzucenia. Moje obserwacje i badania dotyczą kluczowych pytań i spekulacji na temat możliwych źródeł mizofonii, których dokładne rozpoznanie i zrozumienie doprowadzi do opracowania lepszych metod leczenia tego złożonego zaburzenia, a być może nawet do opracowania sposobów zapobiegania jego rozwojowi.

Materiał i metody: W artykule zwięźle omówiono kontekst i podstawy dotychczasowych badań oraz zaproponowano dziesięć potencjalnych kierunków przyszłych badań, a mianowicie: mózg pierwotny, genetyka/ bliźnięta, epigenetyka/ rodzina, religia, osobowość, trauma, inteligencja/ przycinanie synaptyczne (ang. *neural pruning*), oczekiwania dotyczące płci, czynniki okołoporodowe, pozostałe kwestie.

Wyniki: Po omówieniu każdego z dziesięciu tematów podano uzasadnienie dalszych badań.

Wnioski: W ciągu kilku lat od momentu, gdy mizofonia została po raz pierwszy zidentyfikowana jako odrębne zaburzenie, wzrosło zainteresowanie bardziej precyzyjnym zdefiniowaniem tego schorzenia, a wiele badań skupiało się na poszukiwaniu jego potencjalnych przyczyn. Obecnie wiele jest dowodów na to, że zaburzenie to *istnieje*, ale nie określono jeszcze w sposób jednoznaczny *dlaczego*. W niniejszym artykule zaproponowano obiecujące kierunki przyszłych badań, których wyniki pomogłyby lepiej zrozumieć tę złożoną chorobę.

Słowa kluczowe: mizofonia • przyczyny • genetyka • czynniki rodzinne • epigenetyka

Introduction

Even though misophonia was initially identified by audiologists, there is no scientific evidence that the auditory system is the source of the disorder. An early fMRI study [1] found a connection between the auditory cortex and misophonic reactions related to the amygdala. This led to further investigation, resulting in the well-received paper entitled *The brain basis for misophonia* [2]. Numerous other studies [3] come mainly from neuroscience, psychiatry, psychology, and behavioral sciences. One wide-ranging review in 2024 [4] reported that the most frequently cited factors associated with misophonia were mental disorders and female gender. While there is some research on the relationship of misophonia and mental health disorders, including OCD/OCPD [5], most of the topics I set out below do not yet appear in the literature. It is these topics that I hope will spark further exploration.

As a solo practice clinician, over the past dozen years I have treated many hundreds of individuals and families affected by misophonia. I have taken their stories to heart and have conducted several informal surveys to consider whether their experiences are shared by others dealing with this complex condition. As I am not in a university or medical setting, I do not have the equipment or staff to conduct formal studies to test my observations, questions, and conclusions. It is my hope that researchers who are in such settings will find some of these speculations worthy of further investigation.

Topics for Investigation

Ancient brain

Is there a larger proportion of Neanderthal DNA in people with misophonia than those without?

Misophonia appears to be a fight or flight phenomenon, in which the brain acts like it is in danger and goes into survival mode. Do people with misophonia have more activation in the amygdala and/or the reptilian brain? Could this reflect more Neanderthal DNA?

Since the popularity of genetic analysis platforms such as 23andMe, there is more speculation about possible traits related to a variety of medical conditions, including misophonia. One reported factor is the percentage of Neanderthal DNA. The 23andMe reports include a section that includes:

- I have more Neanderthal DNA than __% of other 23andMe customers.
- All together, my Neanderthal ancestry accounts for less than __% of my DNA.
- ___ of ____ variations were tested.

I could find no research relating misophonia to Neanderthal DNA. There is one study [6] reporting that individuals with schizophrenia have less Neanderthal-derived genetic variation than unaffected individuals. Further imaging suggested a neurobiological mechanism underlying the associations with schizophrenia risk. A larger study [7] investigated Neanderthal genetics related to the shape of the modern cranium, but neither of these studies refer to misophonia.

I began to conduct an informal survey of people with and without misophonia who had results from their 23andMe genetic tests, asking them to provide their reports in the above format. I was unable to acquire a large enough sample to gather meaningful information. It seems that virtually everyone taking the test has less than 2% Neanderthal DNA. If that is accurate, then that piece of information is probably not useful. However, for unexplained reasons, respondents reported anywhere from 200 of 2872 variations tested to 313 of 7462 variations tested. It would be helpful to communicate with the 23andMe company for an explanation of their reports, allowing better comparisons between misophonia and non-misophonia respondents to be made.

If research could confirm any connection between Neanderthal DNA and people with misophonia, there could be a case for calming the adrenaline reaction to certain sounds through cognitive and/or somatic psychotherapy.

Genetics/ twins

Are people with misophonia more likely to have a family lineage including this or other neurological disorders, compared to families without misophonia?

There are many speculations about the possibility of genetics as a source of misophonia. The only article [8] that I could locate on genetics related to misophonia is one discussing a particular aspect of misophonia – rage – found in 23andMe reports. That leaves a wide-open field of possibilities to explore whether misophonia might be genetically based.

In my clinical approach, I always create a genogram (family tree), in which I ask if there are other family members on either parental side who have any known neurological condition. There always seems to be someone in three generations of the extended family with ADHD, dementia, autism, or other neurological diagnosis. In some cases, there are reports of close family members with misophonia.

I have seen a number of clients who have a twin, sometimes with a different kind of issue (such as ADHD), but very few where both twins have misophonia, even in identical twins. I think it would be useful to research whether identical twins, fraternal twins, or other siblings are also more likely to have misophonia. In my experience, very few do, but I have no solid data about it, and could find no research addressing that issue.

Epigenetics/ family

What role do epigenetics and family factors play in the development of misophonia?

We could think of genetics as the "nature" axis and epigenetics as the "nurture" axis. As defined by medlineplus.gov, "Epigenetics is the study of how cells control gene activity without changing the DNA sequence. 'Epi-' means on or above in Greek, and 'epigenetic' describes factors beyond the genetic code. Epigenetic changes are modifications to DNA that regulate whether genes are turned on or off" [9].

There does not seem to be much research addressing epigenetic factors in misophonia. The most obvious factor that could affect the genetic aspect of misophonia would be things that occur within the family environment. It is commonly observed that people with misophonia react much more strongly to sounds made by other family members or close contacts. A few studies [e.g. 10] have looked at whether the context of a sound source was a factor in misophonia.

Another study [11] of factors such as age, psychiatric disorders, and maternal psychological states reported that "Children with misophonia did not differ from their peers in terms of ADHD, ODD, ASD, dyslexia, social and emotional competencies, head injuries, epilepsy, tinnitus, being prematurely born, or delivered via cesarean sections. However, they had significantly higher symptoms of anxiety and depression, more frequent occurrences of OCD, migraines, and psychosomatic complaints. *Their mothers self-reported postpartum depression significantly more frequently than mothers in the control group*" (emphasis added).

In one study [12] addressing tinnitus and hyperacusis, it was reported that patients seeking treatment for those conditions and who were screened for suicidal ideation were more likely to have a parent suffering from a mental illness in the patient's childhood. By extrapolation, it could be speculated that those with misophonia might also have had a parent dealing with mental illness. More study could be done to explore the relationship between these factors.

Epigenetics may also account for transgenerational trauma, a repository of past traumas and emotional overwhelm that affects future generations. One book [13] discussing this in depth refers to several studies of descendants of the Holocaust. These studies looked at whether symptoms of the deceased's trauma could be seen in their children, even two or three generations later. One study [14] conducted by the Max Planck Institute in Munich found that:

- Descendants of Holocaust survivors had higher than average PTSD symptoms compared to the general population, and
- The makeup of their *FKBP5* gene – the gene that regulates stress – was fundamentally altered.

If misophonia is possibly genetic, that may account for it developing with age, usually showing up in late childhood or around puberty. But then why does that hard-wired switch suddenly turn on? Did something happen to cause it? I believe a significant contribution to understanding possible causes of misophonia would be research into family dynamics, to determine whether some environmental factors are contributing epigenetically to that switch being unwittingly turned on by parental actions. The next section addresses one potentially significant family factor affecting the development of misophonia.

Religion

Is there a larger percentage of people with misophonia in the US who were raised in families of origin which adhered to more structured religions compared to less structured religions?

Two themes I often hear in therapy sessions with misophonia clients are guilt and shame. Although sometimes used interchangeably, the distinctions are:

Guilt – a focus on *behavior*:
- I *did* something bad or wrong
- I'm sorry – I *made* a mistake
- If only I hadn't…
- Linked to empathy and understanding other perspectives
- Can be motivating to work toward change.

Shame – a focus on the *self*:
- I *am* bad for what I did or just for being who I am
- I'm sorry – I *am* a mistake
- If only I weren't…
- Highly correlated with addiction, depression, aggression, eating disorders, violence, bullying, suicide.

Although initially I did not consider the connection, these two themes could easily be seen as related to religious upbringing. As has often been the case, clients raise questions about the source of misophonia, and sometimes their thoughts have led me in a new direction. One such situation involved a man in his 30s from a Hispanic background. He told me his mother went to Catholic church daily, and that he was also expected to go regularly. He recounted being instructed in concepts of guilt, shame, sin, evil, right and wrong – concepts fairly basic to his religion. He wondered if there might be some connection with his development of misophonia. I had never considered this factor, so I decided to do a very informal survey of people on a Yahoo list group called Sound Sensitivity. Without explanation, I tossed out a question: what was the religion of your family of origin? (Because my interest was in factors affecting their own upbringing, I specified "family of origin" as distinguished from their current family.) The results were surprising:

- Of about 100 random respondents, more than 40% had been raised Catholic;
- Adding in other highly structured religions, the number was closer to 66%;
- The US population of Catholics at that time was about 22%.

Why the disproportionate amount? Could it be related to guilt/shame? I wonder if more highly structured, more rigid belief systems with stricter rules about acceptable behavior, and more black-and-white or all-or-nothing thinking could relate to the development of misophonia. One respondent to the survey commented:

"I think many people with religious upbringing are taught to not confront, disrespect, or question those who are looked at as leaders or elders which include parents. We were expected to sit at the dinner table while the adults chew, smack, crunch but tell the children to eat with their mouth closed. When it's pointed out to us as kids and then we see adults doing it (mainly mom and dad) we can't say anything about it. It grows and festers… You see it more and more. It becomes louder and more apparent. You start to focus in on their noises and why can't you tell them to stop. Because it's disrespectful… Guilt and shame of the feelings, and also resentment, build and build."

Table 1. Responses of 195 people on the Sound Sensitivity Yahoo group to what is your 4-letter type on the Myers–Briggs Inventory?

	Introvert	Extrovert	Total
Judging	92 (49.5%)	22 (61.3%)	114 (61.3%)
Perceiving	43 (23.1%)	29 (15.6%)	72 (38.7%)
Total	135 (72.6%)	51 (27.4%)	186 (100%)

Note: Results exclude 9 mixed types [17]

This was a very informal survey [15], not a scientific study. Formal research is lacking. An internet search for "misophonia and religion" finds very few mentions, other than comments on sites such as Reddit, where individuals express opinions and concerns. I would be very interested to see what a larger, more structured study would reveal, and how that information might be utilized to help families coping with this condition.

Personality type

Is personality type a factor in misophonia?

Are people with misophonia more likely to have Myers–Briggs types IJ (Introversion/ Judgment) than the average percentages of those types in the general population? This was a question raised by a client whose psychology class administered the MBTI to students. This inventory, developed in the 1940s with a long-standing record for workplace application, has four paired polarities, giving 16 possible combination of letters. Details of each type can be found on the Myers–Briggs website [16]. Their definition of INTJ sounds like it could easily describe many people with misophonia: "Have original minds and great drive for implementing their ideas and achieving their goals. Quickly see patterns in external events and develop long-range explanatory perspectives. When committed, organize a job and carry it through. Skeptical and independent, have high standards of competence and performance – for themselves and others" [16].

There are many online articles and studies related to the MBTI, but I could find none specifically regarding its relationship to misophonia. My curiosity to answering this student's question led me back to the Sound Sensitivity Yahoo group where I asked, "If you have taken the Myers–Briggs Inventory, what was your 4-letter type?" 195 people with misophonia responded to my request for MBTI types [17]. The results are shown in **Table 1.**

The results show that:
- Almost two-thirds of respondents are judging (J);
- Almost three-fourths of respondents are introverts (I), while only about one-fourth are extraverts (E);
- Half of respondents are introvert/judging (I/J), while the other half are split among the other three cells;
- Of the 114 total Js, almost 81% (92) are introverts (I).

Again, this is not a scientific study, just a survey of those who self-selected to answer my query about their type. Because I was answering my client's question about the I/J components, I disregarded the two other dichotomies. It would be interesting to see what a more complete study of personality types would yield. A further question would be whether people with misophonia were already I/Js or if their misophonia experiences led to their more introverted and judgmental behaviors.

Trauma

Is there a correlation between onset of misophonia symptoms with stressful life circumstances? Do people with misophonia have higher ACEs (Adverse Childhood Experiences) scores than comparison groups?

The ACE study was conducted in 1998 by the US government Center for Disease Control (CDC) in conjunction with Kaiser Permanente (one of the largest Health Maintenance Organizations in the country) [18]. Participants were mostly white middle-class and upper middle-class people in San Diego, CA. The study measured 10 types of childhood trauma. Five were personal (physical, verbal, or sexual abuse, and physical or emotional neglect), and five related to family (alcoholism, domestic violence, incarceration, mental illness, or abandonment). The study found that two-thirds of the 17,000 people had at least one of these ten traumas in their history. And of those two-thirds, 87% had more than one of these traumas. These were people with good jobs and good health care, not impoverished or poorly educated people.

Another study [19] also found that there was a strong correlation between high ACEs scores and outcomes of serious health issues in adults: chronic adult diseases, heart disease, lung cancer, diabetes, autoimmune diseases, social and emotional problems, depression, alcohol/drug addiction, violence, being a victim of violence, or suicide. In a study [20] of over 300 people with misophonia, only posttraumatic stress disorder (PTSD) was related to the severity of the misophonic symptoms. I could find no studies of ACEs scores related to misophonia. This could be a valuable area of research in understanding the possible connection between early life traumatic events and development of the condition.

Intelligence/ neural pruning

Do people with misophonia have less neural pruning than others?

Neural or synaptic pruning has been confirmed in many brain scan studies [21]. Scans done at birth show that there are few neurological connections in the brain. Within a few years, scans show increased density of connections that makes the image appear darker. By early adolescence, there are so many neural connections, there is almost no white

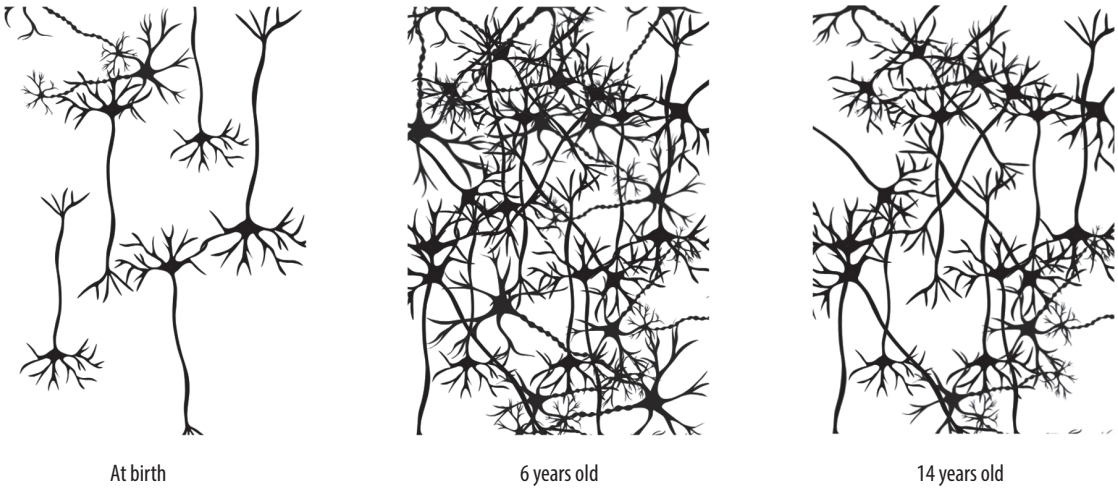

Figure 1. Graphical representation of neural scans

space. The brain then "prunes" out neural pathways that are not being used to allow more efficient functioning (see **Figure 1**).

In my clinical experience, people with misophonia have above average intelligence. I have worked with many hundreds of people with this condition and have yet to find anyone who is not very bright. Despite their challenges in the classroom with sounds and visual distractions, almost all misophones I have seen get excellent grades in school. They often seem to have hyper-auditory acuity and sometimes also hyper-visual acuity. These observations lead me to wonder about their brain activity. Do they have more active connectivity in the brain leading to higher intelligence and also to higher sensitivity?

I would welcome fMRI or other research comparing misophonia and non-misophonia brains in terms of neural density, or indications of less synaptic pruning.

Gender expectations

Are girls more often affected by misophonia in part because they are acculturated to be less assertive and to have weaker boundaries around other people?

I have seen many hundreds of young adolescents with misophonia. In my practice, at least 75% are female, or AFAB (assigned female at birth). Although there is some disagreement, most research regarding gender and misophonia indicates that females account for a larger percentage of patients with this condition [22], and more severity of symptoms [23]. While hormones in females might play a part (especially considering that symptoms often manifest around puberty), that would not explain the presence of symptoms in males. In my clinical observations, there may be a different explanation for the disparity between females and males with misophonia.

Females in our culture are generally expected to be nice, good, quiet, take care of others, suppress their needs, more passive, and definitely not aggressive. They may be discouraged or punished for expressing emotions. It becomes very difficult for girls to speak up for themselves, to ask for what they want. My teen female clients often exhibit features of the "parentified child." They might assume responsibility for matters generally presumed to be parental tasks, and frequently say they do not want to tell their parents what is happening because they don't want to upset the parents. They may develop ways of coping that turn their difficult feelings onto themselves (eating disorders, self-injury, compulsive behaviors, or suicidal thoughts).

In his book, *When the Body Says No: The Cost of Hidden Stress* [24], physician and author Gabor Maté discusses both the research and his clinical observations on a variety of medical conditions, such as autoimmune disorders, ALS (Lou Gehrig's disease), MS (multiple sclerosis), and various kinds of cancer. He found surprising correlations between illness and repression of emotions, especially anger. Research and observations such as these have led me to wonder whether unexpressed emotions and lack of assertiveness might be factors in there being more females struggling with misophonia.

I believe it would be useful for parents to allow and even encourage their daughters' expression of feelings, even "negative" ones, so their anger does not continue to build, and so that perhaps they will not develop symptoms of misophonia or other illnesses. Assertiveness training for both parents and their children would be an interesting research project, and could potentially reduce the appearance of misophonia.

Perinatal factors

Is there any correlation between misophonia and an issue in any particular part of a pregnancy or delivery, or related to infant or early childhood illnesses?

There has been extensive research [25,26] on the effects of prenatal stress on fetal development. Some outcomes noted are low birth weight, premature birth, heart defects, cleft lip, other birth defects, and other physiological issues such

as pre-eclampsia [27] or gestational diabetes. Significant health issues have been found in adults who are the products of such stress in their birth mothers [28]. Other research has found that early childhood illnesses have led to such disorders as PANS (pediatric acute-onset neuropsychiatric syndrome), PANDAS (pediatric autoimmune neuropsychiatric disorders associated with Streptococcal infections), or sudden onset of OCD [29]. I have found no research addressing the potential relationship of such conditions with misophonia.

There is also a process called fetal microchimerism (FMc) [30], in which cells pass through the placenta from mother to fetus throughout pregnancy and shape conditions for brain function later in life; cells also pass from fetus to mother and can stay in her organs for many years. When I do an initial intake with a family and ask about pregnancy history, I often hear of miscarriages, abortions, difficult births, or premature deliveries via C-section. It does not appear that any research has been done to see if there is any connection with misophonia. I am curious about whether an incomplete pregnancy might have left behind vestiges of the earlier fetus that somehow might impact a later pregnancy, and maybe contribute to a disorder such as misophonia.

Other considerations

Is there a relationship between eating disorders and misophonia?

I have seen several adolescents with misophonia and eating disorders. This does seem a logical connection, but other than anecdotal reports on sites such as Reddit, I could only find one study [31] with three cases.

Is there a relationship between allergies and misophonia?

People with misophonia usually have sensitivities to more than one sound, and are often very selective about what they eat, which could have to do with sounds or maybe for other reasons. It is sometimes said that they are "allergic to sound." Are people with misophonia also dealing with food allergies, sensitivity to scents, and having more reactivity to environmental chemicals and toxins? The only references I found were anecdotal, on Reddit.

Is there a relationship between self-injury and misophonia?

Several of my adolescent misophonia clients, especially females, eventually disclose they have engaged in self-injury. Sometimes they report hitting their head, but usually it involves cutting themselves in areas that are hidden from parental view. This is not generally related to suicidal ideation, but more of a stress or pressure release.

I found only one study [32] addressing self-harm and misophonia. More research in this area would be a significant contribution to the literature on misophonia.

Conclusions

In the short number of years since misophonia was first identified as a distinct disorder, there has been increasing interest and research to more clearly define the condition, and many studies looking for potential causal factors. There is now ample evidence that it *exists*, but it is not yet clear *why*. This article proposes some additional directions that I hope future research might take in bringing more understanding to this complex condition, so that more targeted treatment and possibly prevention can occur.

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ORIGINAL ARTICLE

MISOPHONIA AND THE QUALITY OF SEXUAL LIFE IN COUPLES

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Contributions:
A Study design/planning
B Data collection/entry
C Data analysis/statistics
D Data interpretation
E Preparation of manuscript
F Literature analysis/search
G Funds collection

Abstract

Introduction: Misophonia or selective 'hatred of sound' is a newly recognized mental disorder characterised by negative emotional reactions, feelings, and thoughts with or without impulsive behavior to specific irritating triggering sounds. The term *misophonics* has been used to refer to misophonia sufferers. A major effect reported by misophonics is a negative, or even ruinous, impact on close romantic relationships. The aim of our study was to evaluate the quality of sexual life (QoSL) in misophonics of both sexes and their close partners.

Material and methods: We enrolled 91 misophonics aged 25.1 ± 5.4 years old (24 males and 67 females) and 91 opposite-sex partners aged 27.3 ± 4.9 years old. Their misophonia was confirmed by use of the Amsterdam Misophonia Scale (A-Miso-S) questionnaire. For evaluation of the QoSL in male misophonics, we used the International Index of Erectile Function (IIEF) and the Sexual Quality of Life–Male (SQoL-M) self-report questionnaires. For female misophonics we used the self-report questionnaire Sexual Quality of Life–Female (SQoL-F) and the Female Sexual Function Index (FSFI). For comparison, the total scores from the misophonics were compared with scores from controls, who were healthy peers (91 males and 91 females who were loving couples) without misophonia.

Results: We found that the total SQoL-F scores in female misophonics were statistically lower than in controls (62.7 ± 3.5 vs 89.4 ± 4.7 in controls, $p = 0.004$). In males with misophonia, the SQoL-M total score was 38.3 ± 4.2 vs 60.7 ± 4.6 in controls ($p = 0.002$), while IIEF total scores were correspondingly 40.6 ± 5.8 and 68.1 ± 6.3 ($p = 0.001$). Erectile function score in males with misophonia was 16.3 ± 2.4 vs 27.2 ± 2.8 in controls ($p = 0.003$). Partners of misophonics of both sexes also demonstrated decreased scores in total IIEF, SQoL-M, SQoL-F, and FSFI. In female partners of misophonic males, SQoL-F total score was 71.4 ± 4.6 vs 89.4 ± 4.7 in controls ($p = 0.007$). Erectile function score in male partners of misophonic females was 20.1 ± 3.2 vs 27.2 ± 2.8 in controls ($p = 0.015$). In misophonics of both sexes who had comorbid mental disorders, the scores that characterized QoSL were even lower.

Conclusions: Misophonia decreases the quality of sexual life in sufferers of both sexes as well as their partners.

Keywords: relationships • misophonia • hyperacusis • sexual life • erectile function

MIZOFONIA A JAKOŚĆ ŻYCIA SEKSUALNEGO W PARACH MAŁŻEŃSKICH

Streszczenie

Wprowadzenie: Mizofonia lub wybiórcza „nienawiść do dźwięków" to nowo rozpoznane zaburzenie psychiczne charakteryzujące się negatywnymi reakcjami emocjonalnymi, uczuciami i myślami, z impulsywnymi zachowaniami lub bez nich, wywołanymi przez określone irytujące dźwięki. Termin „mizofonicy" jest używany w odniesieniu do osób cierpiących na mizofonię. Osoby te jako główny skutek mizofonii

zgłaszają jej negatywny, a nawet destrukcyjny wpływ na relacje romantyczne z partnerami. Celem naszego badania była ocena jakości życia seksualnego (QoSL) osób cierpiących na mizofonię obu płci oraz ich partnerów.

Materiał i metody: Do badania włączyliśmy 91 osób cierpiących na mizofonię w wieku 25,1 ± 5,4 lat (24 mężczyzn i 67 kobiet) oraz ich 91 partnerów płci przeciwnej w wieku 27,3 ± 4,9 lat. Mizofonię potwierdzono za pomocą kwestionariusza *Amsterdam Misophonia Scale* (A-Miso-S). Do oceny jakości życia mężczyzn cierpiących na mizofonię wykorzystaliśmy kwestionariusze samooceny *International Index of Erectile Function* (IIEF) oraz *Sexual Quality of Life–Male* (SQoL-M). W przypadku kobiet cierpiących na mizofonię wykorzystaliśmy kwestionariusz samooceny *Sexual Quality of Life–Female* (SQoL-F) oraz *Female Sexual Function Index* (FSFI). Łączne wyniki osób cierpiących na mizofonię porównano z wynikami osób z grupy kontrolnej, które były zdrowymi osobami w podobnym wieku (91 mężczyzn i 91 kobiet pozostających w związkach partnerskich) niecierpiących na mizofonię.

Wniki: Całkowite wyniki SQoL-F u kobiet cierpiących na mizofonię były statystycznie niższe niż w grupie kontrolnej (62,7 ± 3,5 w porównaniu z 89,4 ± 4,7 w grupie kontrolnej, $p = 0{,}004$). W przypadku mężczyzn z mizofonią łączny wynik SQoL-M wyniósł 38,3 ± 4,2 w porównaniu z 60,7 ± 4,6 w grupie kontrolnej ($p = 0{,}002$), natomiast łączne wyniki IIEF wyniosły odpowiednio 40,6 ± 5,8 i 68,1 ± 6,3 ($p = 0{,}001$). Wynik funkcji erekcji u mężczyzn z mizofonią wyniósł 16,3 ± 2,4 w porównaniu z 27,2 ± 2,8 w grupie kontrolnej ($p = 0{,}003$). Wyniki partnerów i partnerek osób cierpiących na mizofonię obu płci również były obniżone wyniki w skalach IIEF, SQoL-M, SQoL-F i FSFI. W przypadku kobiet będących partnerkami mężczyzn cierpiących na mizofonię całkowity wynik w skali SQoL-F wyniósł 71,4 ± 4,6 w porównaniu z 89,4 ± 4,7 w grupie kontrolnej ($p = 0{,}007$). Wyniki funkcji erekcji u partnerów kobiet cierpiących na mizofonię wyniosły 20,1 ± 3,2 w porównaniu z 27,2 ± 2,8 w grupie kontrolnej ($p = 0{,}015$). U osób cierpiących na mizofonię obu płci, które miały współistniejące zaburzenia psychiczne, wyniki charakteryzujące jakość życia były jeszcze niższe.

Wnioski: Mizofonia obniża jakość życia seksualnego zarówno u osób cierpiących na tę dolegliwość, jak i ich partnerów.

Słowa kluczowe: relacje • mizofonia • nadwrażliwość słuchowa • życie seksualne • erekcja

Key to abbreviations	
A-Miso-S	Amsterdam Misophonia Scale
DD	depressive disorder
FM	female misophonics
FP	female partners of misophonic males
FSFI	Female Sexual Function Index
GAD	generalized anxiety disorder
IIEF	International Index of Erectile Function
MM	male misophonics

Key to abbreviations	
MP	male partners of misophonic females
OCD	obsessive-compulsive disorder
PD	panic disorder
QoSL	quality of sexual life
ROCD	relationship obsessive-compulsive disorder/ relationship OCD
SQoL-F	Sexual Quality of Life–Female
SQoL-M	Sexual Quality of Life–Male

Introduction

Misophonia or selective 'hatred of sound' is a mental disorder characterised by intense negative emotional reactions, feelings, and thoughts (with or without impulsive behavior) to specific irritating sounds [1,2]. The term *misophonics* has been used to refer to people living with misophonia [3]. The annoying sounds, or triggers, are typically produced by the human mouth, throat, or nose and include chewing, crunching, slurping, breathing, sniffing, and so on. The sounds of cutlery and environmental or machine sounds can also be triggers [4]. Unfortunately, misophonia can negatively impact relationships in complex ways [5]. A major effect reported by misophonics is a destructive impact on close partner marked by aggression, 'fight or flight' responses, and a worsening, or even ruinous, effect on the romantic relationship [6–8].

It is known that various neurological or psychiatric diseases have a negative impact on the sexual function and behavior of patients. For example, multiple sclerosis can affect the sexuality of sufferers [9]. Depression and use of antidepressants can significantly worsen sexual function [10]. Reduced sexual desire is associated with many personality disorders: schizoid personality disorder, character schizoid accentuation, accentuations of the cycloid, asthenoneurotic, hysteroid, unstable, psychasthenic, sensitive and infantile-dependent types. Similar effects are seen in mood (affective) disorders such as dysthymia (depressive neurosis), bipolar disorder, schizophrenia, mental retardation, dementia, epilepsy, and organic brain damage [11].

Recently misophonia has been recognised as a mental disorder and its incidence in the population may reach 33% [12]. More specifically, there can be sound triggers from their sexual partners so that the misophonic becomes dissatisfied with their intimate relationship, sometimes expressed at a visit to their doctor. This problem requires further study and systematization. Although the nosology is novel, there are a considerable number of cases of misophonics presenting with sexological complaints to sexologists, urologists, and gynecologists, with the result that we were prompted to plan and conduct this study.

The aim of our study was to evaluate the quality of sexual life (QoSL) in misophonics of both sexes and their close partners.

Material and methods

We enrolled 91 misophonics aged 25.1 ± 5.4 years old with a male-to-female ratio of 1: 2.8 (24 males and 67 females). We also enrolled their opposite-sex partners without misophonia, this time with a male-to-female ratio of 2.8 : 1 (67/24) aged 27.3 ± 4.9 years old. Only couples in loving relationships that had lasted more than 6 months were included in the study to avoid honeymoon euphoria.

Individuals with misophonia were recruited during their visits to psychiatrists/ psychotherapists ($n = 42$, 46%), otorhinolaryngologists ($n = 20$, 22%), gynecologists ($n = 17$, 19%), and urologists ($n = 12$, 13%).

Their misophonia was confirmed by use of the Amsterdam Misophonia Scale (A-Miso-S) questionnaire developed by Schröder et al. [13]. We used 1 point as cut-off on the A-MISO-S scale. Participants with confirmed misophonia were divided, as recommended, into the following subgroups according to their A-Miso-S total score: scores from 1 to 4 were considered subclinical misophonic symptoms ($n = 22$), 5–9 mild ($n = 46$), 10–14 moderate ($n = 18$), 15–19 severe ($n = 3$), and 20–24 extreme ($n = 2$) [14,15].

For evaluation of the quality of sexual life in males, we used the International Index of Erectile Function (IIEF) and Sexual Quality of Life–Male (SQoL-M) self-report questionnaires [16,17]. In females, we used the self-report questionnaire Sexual Quality of Life–Female (SQoL-F) and the Female Sexual Function Index (FSFI) [18–20].

To evaluate the scores of misophonics we compared them with the survey results of controls without misophonia, 91 males and 91 females who were couples in love (aged 26.5 ± 5.1 years old) and did not have any distinct mental/ urological/ gynecological pathology.

All the patients with complaints of selective sound hypersensitivity and elevated A-Miso-S total scores were referred to a psychiatrist/ psychotherapist for deeper examination in order to confirm misophonia and to detect or exclude concomitant mental illnesses.

To exclude hyperacusis and tinnitus, otorhinolaryngologists performed routine audiological testing; relevant questionnaires were also retrospectively gathered from the records of the patients. Measures included pure tone audiometry and uncomfortable loudness levels; questionnaires included the tinnitus impact questionnaire, the hyperacusis impact questionnaire, and the screening for anxiety and depression in tinnitus questionnaire (as recommended in [21]).

Mann–Whitney *U*-tests to compare the two groups were used. Statistical significance was judged at $p < 0.05$ [22].

Results

Among the 91 persons with confirmed misophonia, there were 32 (35%) who had misophonia only (without concomitant mental disorders) comprised of 21 (64%) females and 11 (36%) males. Comorbid mental disorders in misophonics were registered in 59 (64%) patients: 46 (78%) females and 13 (22%) males, and included generalized anxiety disorder (GAD), $n = 21$ (36%), 16 females, 5 males; depressive disorder (DD), $n = 12$ (21%), 9 females, 3 males; panic disorder (PD), $n = 11$ (19%), 8 females, 3 males; obsessive-compulsive disorder (OCD), $n = 8$ (14%), 6 females, 2 males; and relationship obsessive-compulsive disorder (ROCD), $n = 7$ (10%), 7 females, 0 males.

Taking into account the presence of mental comorbidities, we analysed misophonics with each comorbid mental disorder separately from those who have misophonia only. Survey data in female misophonics, female partners of misophonic males, and female controls are presented in **Table 1**. Total FSFI and SQoL-F scores in examined females are presented graphically in **Figure 1**.

As shown in **Figure 1**, the quality of sexual life in female misophonics (FM) and female partners of men with misophonia (FP) is worse than in the control group. Total SQo-F score in females with misophonia only was 62.7 ± 3.5 vs 89.4 ± 4.7 in controls ($p = 0.004$). In females, partners of misophonic males SQoL-F total score was 71.4 ± 4.6 vs 89.4 ± 4.7 in controls ($p = 0.007$). Concomitant mental disorders further impair QoSL, with accompanying depressive disorders, generalised anxiety disorder, and panic disorder having the worst impact in females with misophonia.

Survey data in male misophonics, male partners of misophonic females, and male controls are presented in **Table 2**, while total IIEF and SQoL-M scores in examined males are presented graphically in **Figure 2**.

As shown in **Figure 2**, the quality of sexual life in male misophonics (MM) and male partners of women with misophonia (MP) is lower than in the control group. In males with misophonia only the SQoL-M total score was 38.3 ± 4.2 vs 60.7 ± 4.6 in controls ($p = 0.002$), while IIEF total scores were 40.6 ± 5.8 vs 68.1 ± 6.3 correspondingly ($p = 0.001$). Comorbid mental disorders further impair QoSL, with accompanying depressive disorders having the worst impact in males with misophonia.

In males with depressive disorder and misophonia (MM+DD), the SQoL-M total score was 18.3 ± 5.1 vs 60.7 ± 4.6 in controls ($p = 0.0001$), while IIEF total scores were 24.9 ± 2.4 vs 68.1 ± 6.3 correspondingly ($p = 0.0005$). Erectile function score in males with misophonia only (MM) was 16.3 ± 2.4 vs 27.2 ± 2.8 in controls ($p = 0.003$), while in male partners of misophonic females (MP), that score was 20.1 ± 3.2 vs 27.2 ± 2.8 in controls ($p = 0.015$) as presented in **Table 2** in the domain "Erectile function".

In general, as presented in **Table 1** and **Table 2**, the quality of sexual life in males and female partners of misophonics was statistically lower than in their controls. Female partners of misophonic males (FP) reported lower orgasm and less sexual satisfaction after intercourse with preserved arousal and sexual desire. Decreased orgasmic feelings, sexual desire, intercourse, and overall satisfaction with preserved erectile function were registered in male partners of misophonic females (MP).

Table 1. Results of surveys of 67 female misophonics, 24 female partners of misophonic males, and 91 female controls using three tools: A-Miso-S, SQoL-F, and FSFI

Scales		FM+DD (*n* = 9)	FM+GAD (*n* = 16)	FM+PD (*n* = 8)	FM+OCD (*n* = 6)	FM+ROCD (*n* = 7)	FM (*n* = 21)	FP (*n* = 24)	Controls (*n* = 91)
A-Miso-S	Total score	8.6 ± 3.7*	11.3 ± 4.1*	9.5 ± 6.3*	11.8 ± 3.7*	8.4 ± 6.2*	9.4±4.2*	0	0
SQoL-F	Psycho-sexual feelings	16.2 ± 3.6*	18.7 ± 3.1*	20.8 ± 5.7*	21.4 ± 6.4*	20.7 ± 6.3*	26.8 ± 4.1*	30.5 ± 3.7*	37.2 ± 4.1
	Sexual and relationship satisfaction	10.3 ± 2.8*	12.4 ± 2.4*	11.6 ± 4.1*	16.2 ± 2.1*	16.3 ± 3.2*	17.6 ± 3.2*	19.4 ± 4.3*	22.9 ± 4.7
	Self-worthlessness	5.6 ± 1.6*	6.7 ± 1.9*	6.3 ± 2.4*	8.7 ± 3.1*	7.2 ± 2.8*	10.4 ± 2.6*	11.3 ± 1.9*	14.7 ± 2.8
	Sexual repression	4.5 ± 1.2*	5.4 ± 2.7*	7.6 ± 2.3*	7.2 ± 2.1*	6.4 ± 0.8*	8.4 ± 1.9*	10.2 ± 0.7*	15.6 ± 2.9
	Total score	37.2 ± 3.3*	43.2 ± 3.8*	48.3 ± 2.6*	53.5 ± 3.2*	50.6 ± 3.8*	62.7 ± 3.5*	71.4 ± 4.6*	89.4 ± 4.7
FSFI	**Total score**	15.2 ± 1.9*	14.3 ± 2.6*	15.7 ± 2.3*	17.1 ± 2.4*	16.5 ± 1.8*	17.8 ± 1.4*	22.4 ± 1.8*	32.2 ± 3.1

Note: FM, female misophonics without mental comorbidities; FM+DD, female misophonics with depressive disorder; FM+GAD, female misophonics with generalized anxiety disorder; FM+PD, female misophonics with panic disorder; FM+OCD, female misophonics with obsessive compulsive disorder; FM+ROCD, female misophonics with relationships obsessive compulsive disorder; FP, female partners of misophonic males; * $p < 0.05$ compared with female controls

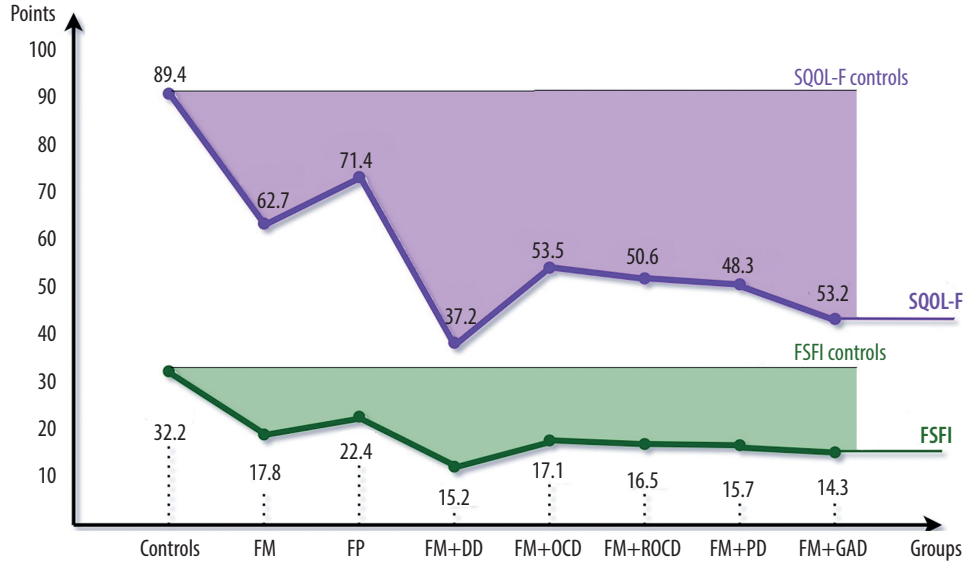

Figure 1. Total FSFI and SQoL-F scores in examined females. Legend: FM, female misophonics; FP, female partners of misophonic males; FM+DD, female misophonics with depressive disorder; FM+OCD, female misophonics with obsessive-compulsive disorder; FM+ROCD, female misophonics with relationships obsessive-compulsive disorder; FM+PD, female misophonics with panic disorder; FM+GAD, female misophonics with generalised anxiety disorder

Discussion

Intimacy is a special, tender part of being human. According to literature data and our own more than three decades of medical experience, several factors have a negative impact on the quality of sexual life. Among them there are somatic, mental disorders, stress, and psychological interpersonal conflicts [23–26]. Based on the results of our previous studies, we have continued to evaluate the QoSL in misophonics [6,27,28].

It has been previously found that persons with misophonia cannot maintain a constant close relationship with loved ones. Sound triggers produced by partners were the cause of breakup. Moreover, when misophonics were asked: "Would the relationship with each abandoned partner last longer if he did not produce trigger sounds?" they answered: "Most likely so", "Probably yes", and "Yes". Taking into account frequent changing of sex partners in examined misophonics, we asked them: "Would you so often terminate the relationships if you did not have the misophonia?". The answers were "Probably not", "Unambiguously not", "I think not", and "It seems to me

Table 2. Results of surveys of 24 male misophonics, as well as of 67 male partners of misophonic females and 91 male controls, using three tools: A-Miso-S, IIEF, and SQoL-M

Scales		MM+DD ($n = 3$)	MM+GAD ($n = 5$)	MM+PD ($n = 3$)	MM+OCD ($n = 2$)	MM ($n = 11$)	MP ($n = 67$)	Controls ($n = 91$)
A-Miso-S	Total score	9.8 ± 3.4*	10.3 ± 3.5*	8.7 ± 3.4*	9.5 ± 4.5*	8.9 ± 5.7*	0	0
IIEF	Erectile function	8.1 ± 0.7*	9.6 ± 0.7*	10.8±1.6*	10.9 ± 1.5*	16.3 ± 2.4*	20.1 ± 3.2*	27.2 ± 2.8
	Orgasmic function	4.2 ± 1.3*	4.1 ± 1.2*	5.1 ± 2.7*	6.5 ± 2.0*	7.4 ± 2.6*	8.8 ± 1.6*	13.6 ± 2.9
	Sexual desire	4.6 ± 2.5*	5.3 ± 0.8*	6.4 ± 1.8*	5.0 ± 2.5*	4.9 ± 1.6*	6.4 ± 2.7*	8.1 ± 1.7
	Intercourse satisfaction	4.8 ± 1.6*	5.8 ± 3.7*	6.1 ± 3.2*	7.5 ± 1.5*	7.8 ± 2.1*	8.3 ± 3.3*	11.5 ± 2.4
	Overall satisfaction	3.2 ± 1.1*	3.5 ± 1.6*	4.3 ± 0.7*	5.5 ± 1.5*	4.5 ± 2.3*	5.7 ± 2.1*	7.7 ± 1.6
	Total score	24.9 ± 2.4*	28.3 ± 3.6*	32.7 ± 2.8*	35.4 ± 2.2*	40.6 ± 5.8*	49.3 ± 5.2*	68.1 ± 6.3
SQOL-M	**Total score**	18.3 ± 5.1*	22.6 ± 4.3*	26.5 ± 5.5*	32.1 ± 3.6*	38.3 ± 4.2*	44.2 ± 5.5*	60.7 ± 4.6

Note: MM, male misophonics without mental comorbidities; MM+DD, male misophonics with depressive disorder; MM+GAD, male misophonics with generalized anxiety disorder; MM+PD, male misophonics with panic disorder; MM+OCD, male misophonics with obsessive compulsive disorder; MP, male partners of misophonic females; * $p < 0.05$ compared with male controls

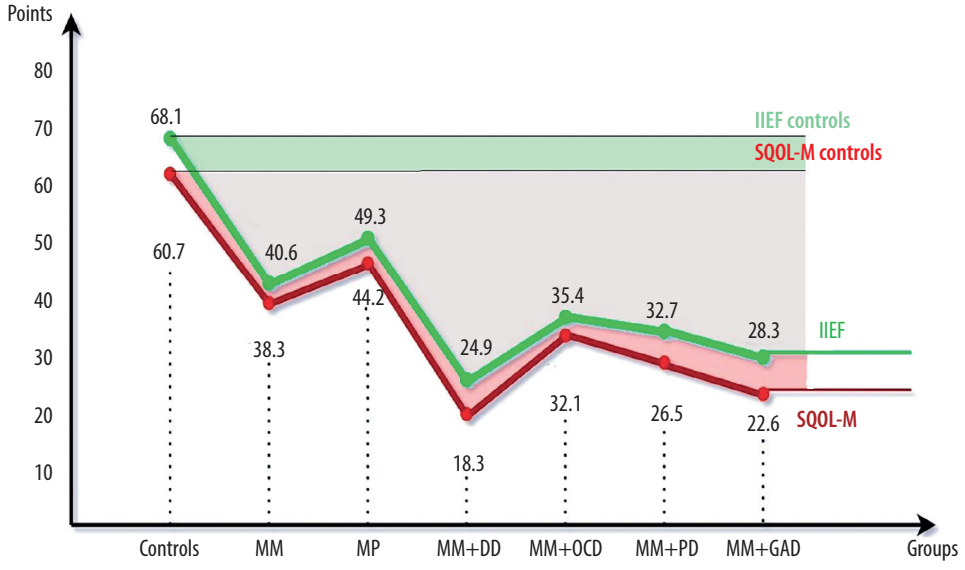

Figure 2. Total IIEF and SQoL-M scores in examined males. Legend: MM, male misophonics; MP, male partners of misophonic females; MM+DD, male misophonics with depressive disorder; MM+OCD, male misophonics with obsessive-compulsive disorder; MM+PD, male misophonics with panic disorder; MM+GAD, male misophonics with generalised anxiety disorder.

that no". Obviously, although they had a desire to live longer with a stable partner, misophonia sufferers were aware that their selective sound sensitivity and induced negative emotions deprived them of that opportunity [6].

The presented study addresses the intimate topic of QoSL in persons with misophonia. Using approved standard questionnaires, we have shown that individual total scores characterising the quality of sexual life in misophonics of both sexes and their partners differed greatly from the same indicators among their peers without misophonia (the controls). According to our results, the presence of concomitant mental disorders makes QoSL even lower.

Interestingly, the QoSL scores of females with misophonia but without mental comorbidities were statistically lower that in controls but higher than in individuals with other comorbidities (**Figure 1**). Similarly, misophonic males with misophonia only had lower total QoSL scores than controls, but had higher scores than comorbid cases (**Figure 2**).

We appear to be the first to study aspects of the sexuality in misophonics and their partners. The present research confirms our previous findings about the negative impact of misophonia on the quality of life in patients of both sexes and their partners [27,28].

Our observations show that misophonia often prevents patients from maintaining long-term and stable intimate relationships. The condition might be considered a major cause of inadequate intimacy and broken close relationships. According to our survey, misophonics are not the only initiators of the relationship breakup. Some case reports reveal that the partners of misophonic women left them because the partners were annoyed by the need to limit their behavior and restrain natural physiological sounds during communication, meals, or sex. The constant claims of misophonics about their partner's eating behavior "did not suit them [the partner]" and therefore the healthy partner was the first to take steps towards ending the relationship [6].

The effect of misophonia on close relationships and QoSL indicates the need to bring together sexologists, urologists, and gynecologists into multidisciplinary teams for complete misophonia management [28].

More studies on this issue have yet to be conducted, so we invite our colleagues with larger patient databases for cooperation. In our opinion, it would be appropriate to use the questions proposed by us ("Would the relationship with each abandoned partner last longer if he did not produce trigger sounds?" and "Would you so often terminate the relationships if you did not have the misophonia?") during surveys of misophonics. We consider it reasonable to use the SQoL-F, SQoL-M, IIEF, and FSFI questionnaires among misophonics to analyse their sexual function and satisfaction, although some modifications may be appropriate.

Our results may induce clinical researchers to focus on assessing the sexuality of misophonia sufferers and their partners. New therapeutic strategies need to be developed with the aim of improving the QoSL in couples where one has misophonia. If needed, a sexologist may be included into a multidisciplinary team for misophonia management.

Limitations

The small sample of enrolled males with misophonia might be considered the main limitation of our study. Statistically, the small number of misophonics with mental comorbidities is also a limitation.

Conclusions

Misophonia diminishes the quality of sexual life in sufferers of both sexes and their partners. Male misophonics may suffer erectile dysfunction, as may healthy males who are the partners of female misophonics. These aspects should be taken into account by psychiatrists, psychotherapists, and psychologists during the management of couples where one has misophonia.

Ethical standards

The authors assert 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.

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Statement of interests

The authors declare no competing interests.

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World Hearing Center

OF THE INSTITUTE OF PHYSIOLOGY AND PATHOLOGY OF HEARING

The World Hearing Center is a modern specialized hospital providing medical care at the highest quality level in the fields of otolaryngology, audiology, phoniatrics, rehabilitation and biomedical engineering. It is superbly equipped for research and education, and includes modern conference facilities. The Center conducts a wide range of research and educational activities addressed to specialists from Poland and other countries. The Center is one of the leading medical institutions in the field of hearing disorders treatment, running, among others, one of the largest hearing implant programs in the world and performing 15,000 to 21,000 surgical procedures yearly.

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- congenital and acquired malformations of the external, middle and inner ear,
- hearing, speech and balance disorders of different etiologies,
- disorders of the mouth cavity, throat and larynx,
- disorders of the nose and paranasal sinuses,
- sleep disorders.

World Hearing Center:

- is a global leader in terms of the number of performed otorhinolaryngological surgeries and the number of outpatient consultations (more than 200,000 consultations per year),
- is the place where unique and highly specialized medical procedures are performed, including reconstruction surgeries of congenital defects of the outer ear, treatment of profound and partial deafness with various hearing implants, phonosurgeries, endoscopic sinus surgeries under image guidance, and many others,
- employs a team of highly qualified and experienced specialists,
- has state-of-the-art medical equipment and instrumentation,
- offers comfortable conditions for hospital stays,
- uses the most modern telemedical solutions providing remote consultations via the world-first National Network of Teleaudiology.

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