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REVIEW PAPER

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

Richard Salvi[1EF], Yu-Chen Chen[2EF], Benjamin D. Auerbach[3EF]

[1] Department of Communication Disorders and Sciences, University of Central Florida, Orlando, USA
[2] Department of Radiology, Nanjing First Hospital, Nanjing Medical University, China
[3] School of Molecular and Cellular Biology, University of Illinois at Urbana-Champaign, USA

Corresponding author: Richard Salvi, Department of Communication Disorders and Sciences, University of Central Florida, 3280 Progress Drive Ste 500, 32826-3246, Orlando, USA; email: richard.salvi@ucf.edu

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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

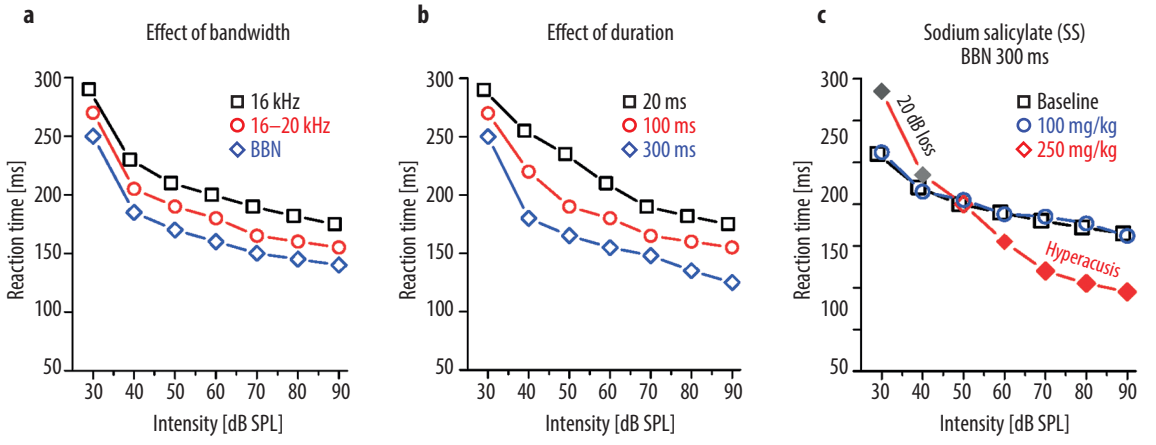

Figure 1. (**a**) RT-I functions for a 16 kHz tone (squares), 16–20 kHz narrow-band noise (circles), and broadband noise (diamonds). At each bandwidth, RT decreases with intensity. At each intensity, RT decreases as bandwidth increases, illustrating spectral integration of loudness. Schematics based 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

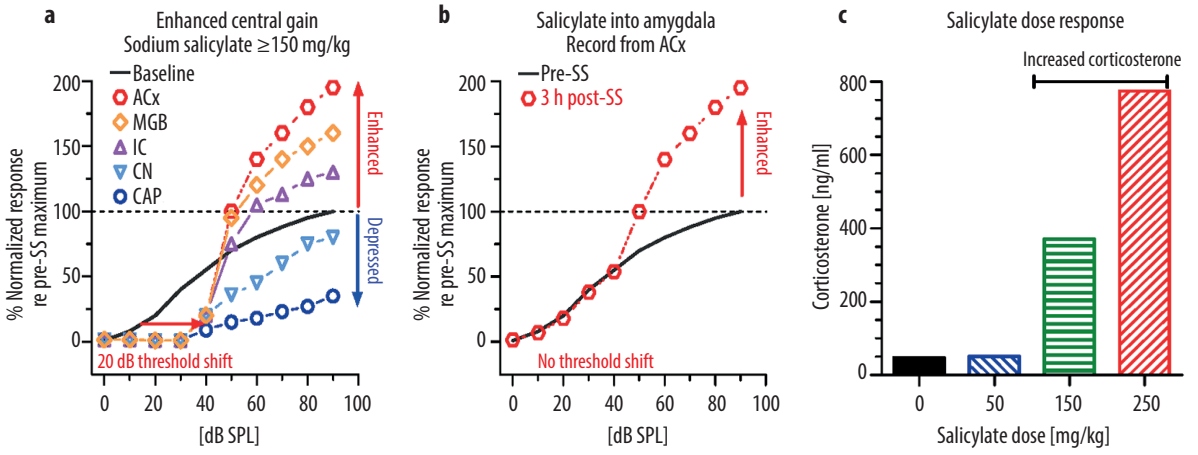

Figure 2. High dose sodium salicylate (150 mg/kg) causes ~20 dB cochlear threshold shift, but enhances sound-evoked neural activity in the central auditory pathway. (**a**) Normalized sound-evoked input/output functions (expressed as percentage of the maximum evoked response at baseline) for cochlear 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

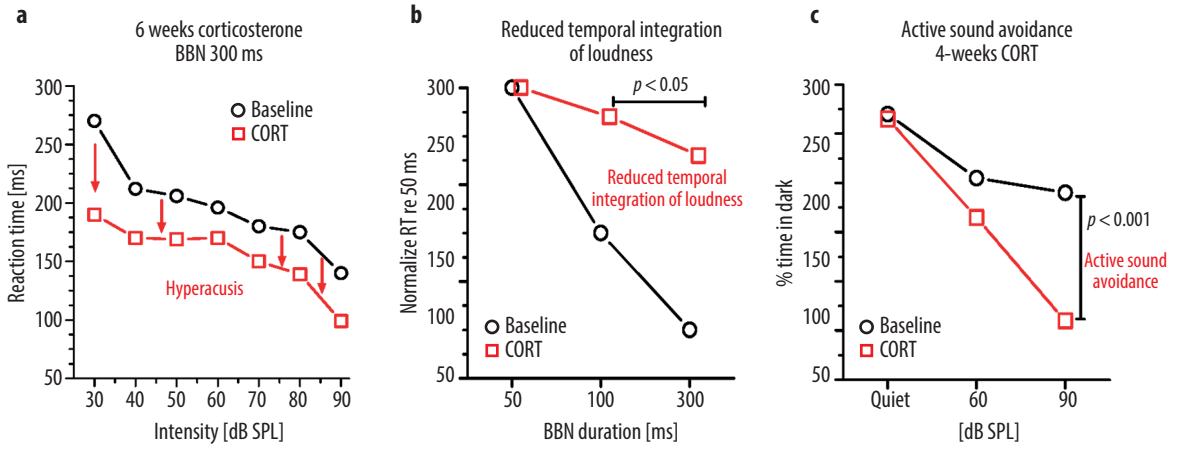

Figure 3. Chronic corticosterone treatment induces loudness hyperacusis, disrupts temporal integration of loudness, and induces sound avoidance hyperacusis. (**a**) Reaction time-intensity functions measured with 300 ms BBN noise bursts at baseline and following 6 weeks treatment with corticosterone 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,

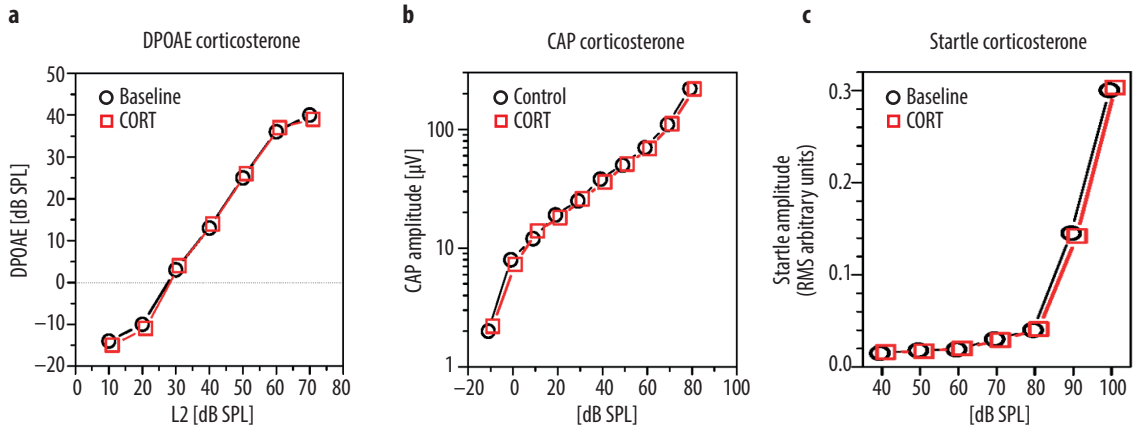

Figure 4. Chronic corticosterone fails to disrupt cochlear or brainstem responses. (**a**) 2f1–f2 DPOAE input/output functions at baseline and 1 week after 4 weeks of corticosterone treatment. Corticosterone treatment did not have a significant effect on DPOAE amplitudes. Schematics based on prior work [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

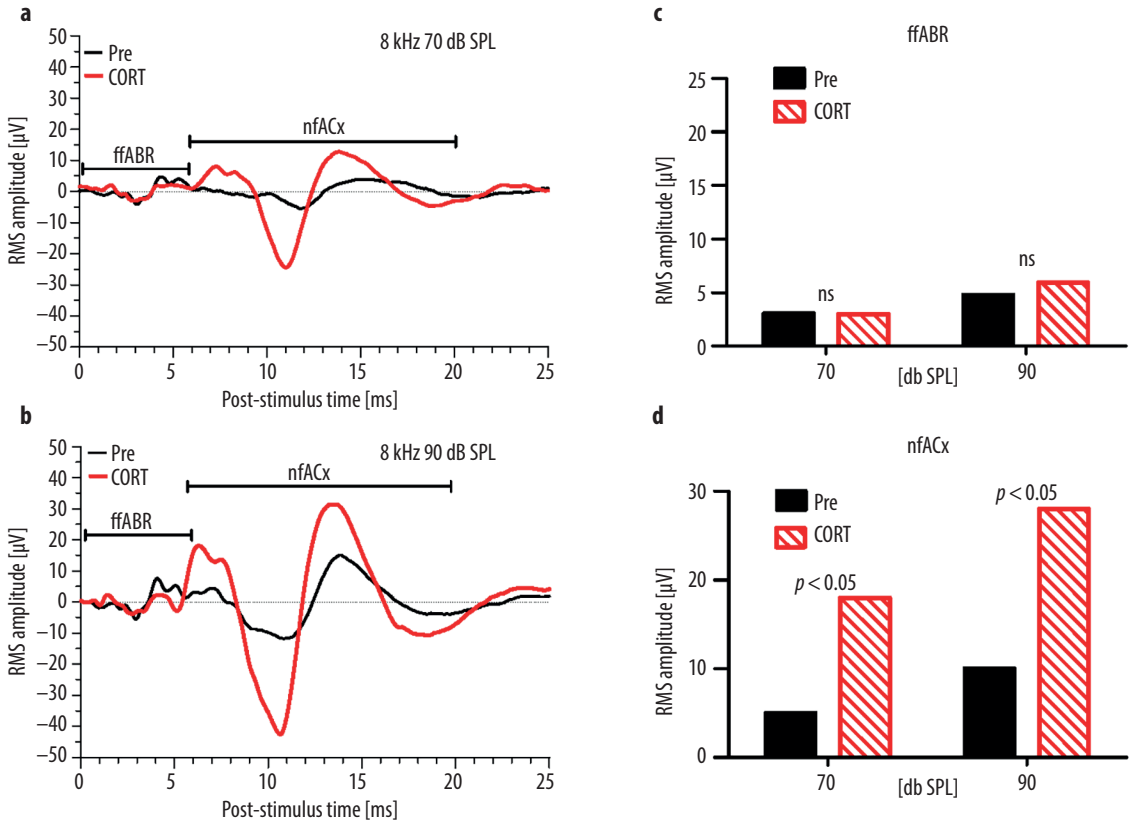

Figure 5. Chronic corticosterone treatment enhances the amplitude of near-field auditory evoked responses. (**a–b**) Auditory evoked responses recorded from a chronic electrode implanted over surface of the auditory cortex (ACx) before and 6 weeks after chronic corticosterone (CORT) treatment (25 mg/ml 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

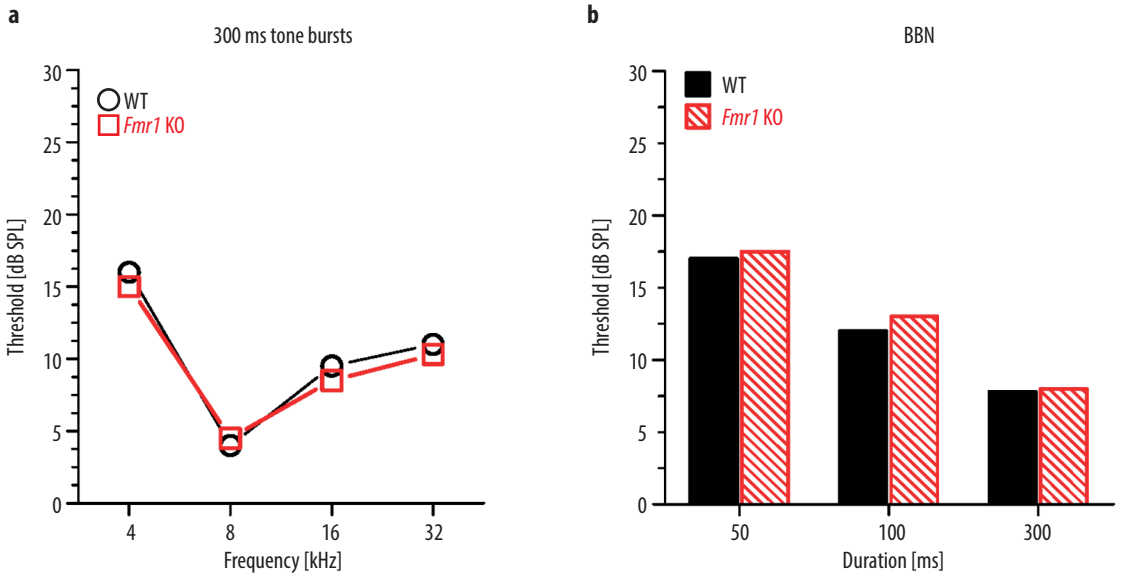

Figure 6. *Fmr1* KO rats have normal behavioral thresholds in quiet and exhibit normal temporal integration at the threshold of audibility. (**a**) WT rats and *Fmr1* KO rats have similar behavioral thresholds to 300 ms tone bursts presented at 4, 8, 16, and 32 kHz. Schematics based on investigator's 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.

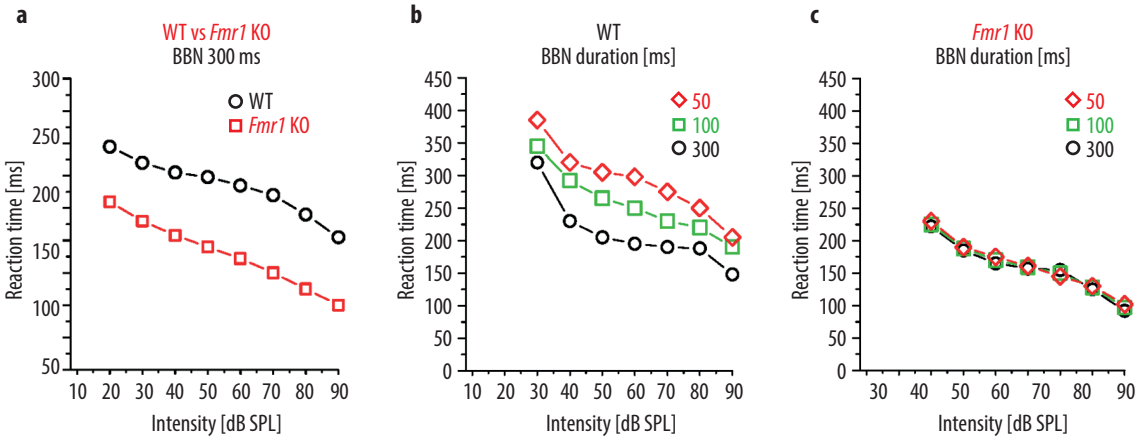

Figure 7. *Fmr1* KO rats show evidence of loudness hyperacusis and absence of temporal integration of loudness at suprathreshold intensities. (**a**) RT-I function to 300 ms BBN bursts for male *Fmr1* KO rats and WT rats. RTs at all suprathreshold intensities are significantly shorter in *Fmr1* KO rats 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

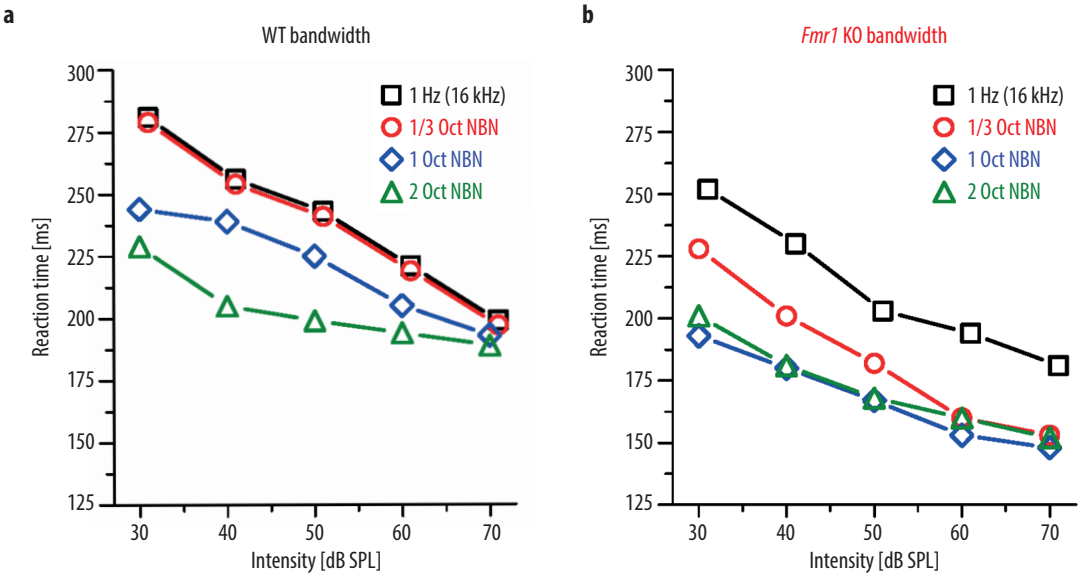

Figure 8. Critical band for loudness is disrupted in *Fmr1* KO rats. (**a**) WT rat RT-I functions for bandwidths of 1 Hz and 1/3, 1, and 2 octaves. (**b**) *Fmr1* KO rat RT-I functions for bandwidths of 1 Hz and 1/3, 1, and 2 octaves. See text for details. Schematics based on investigator's prior work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

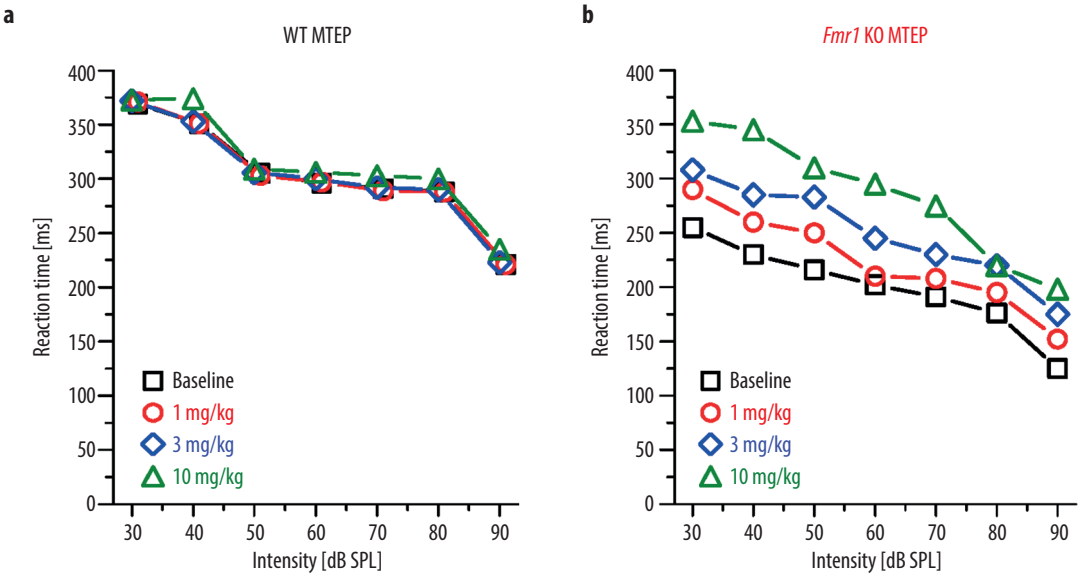

Figure 9. MTEP can normalize RT-I functions, eliminating hyperacusis behavior in a dose-dependent manner. (**a**) RT-I functions from WT rats at baseline and following treatment with 1, 3, and 10 mg/kg of MTEP. RT-I functions largely unaffected by MTEP. (**b**) As for (**a**), but for *Fmr1* KO rats. 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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References

1. Pienkowski M, Tyler RS, Roncancio ER, Jun HJ, Brozoski T, Dauman N, et al. A review of hyperacusis and future directions: part II. Measurement, mechanisms, and treatment. Am J Audiol, 2014; 23(4): 420–36. https://doi.org/10.1044/2014_AJA-13-0037
2. Tyler RS, Pienkowski M, Roncancio ER, Jun HJ, Brozoski T, Dauman N, et al. A review of hyperacusis and future directions: part I. Definitions and manifestations. Am J Audiol, 2014; 23(4): 402–19. https://doi.org/10.1044/2014_AJA-14-0010
3. Coey JG, De Jesus O, 2024. Hyperacusis, StatPearls [Internet]. Treasure Island, FL: StatPearls Publishing; 2025.
4. Smit AL, Stegeman I, Eikelboom RH, Baguley DM, Bennett RJ, Tegg-Quinn S, et al. Prevalence of hyperacusis and its relation to health: the Busselton Healthy Ageing Study. Laryngoscope, 2021; 131(12): E2887–E2896. https://doi.org/10.1002/lary.29768
5. Assi H, Moore RD, Ellemberg D, Hebert S. Sensitivity to sounds in sport-related concussed athletes: a new clinical presentation of hyperacusis. Sci Rep, 2018; 8(1): 9921. https://doi.org/10.1038/s41598-018-28312-1
6. Blomberg S, Rosander M, Andersson G. Fears, hyperacusis and musicality in Williams syndrome. Res Dev Disabil, 2006; 27(6): 668–80. https://doi.org/10.1016/j.ridd.2005.09.002
7. Gomes E, Pedroso FS, Wagner MB. Auditory hypersensitivity in the autistic spectrum disorder. Pro Fono, 2008; 20(4): 279–84. https://doi.org/10.1590/s0104-56872008000400013
8. Johns DR. Assessment of hyperacusis in Bell's palsy. Ann Intern Med, 1986; 105(6): 973. https://doi.org/10.7326/0003-4819-105-6-973_1
9. Juris L, Andersson G, Larsen HC, Ekselius L. Psychiatric comorbidity and personality traits in patients with hyperacusis. Int J Audiol, 2013; 52(4): 230–5. https://doi.org/10.3109/14992027.2012.743043
10. Nields JA, Fallon BA, Jastreboff PJ. Carbamazepine in the treatment of Lyme disease-induced hyperacusis. J Neuropsychiatry Clin Neurosci, 1999; 11(1): 97–9. https://doi.org/10.1176/jnp.11.1.97
11. Williams ZJ, Suzman E, Woynaroski TG. A phenotypic comparison of loudness and pain hyperacusis: symptoms, comorbidity, and associated features in a multinational patient registry. Am J Audiol, 2021; 30(2): 341–58. https://doi.org/10.1044/2021_AJA-20-00209
12. Elgoyhen AB, Langguth B, Nowak W, Schecklmann M, De Ridder D, Vanneste S. Identifying tinnitus-related genes based on a side-effect network analysis. CPT Pharmacometrics Syst Pharmacol, 2014; 3(1): e97. https://doi.org/10.1038/psp.2013.75
13. Wen H, Ding Y, Chen F. A real-world pharmacovigilance study of FDA adverse event reporting system events for atogepant. Expert Opin Drug Saf, 2024; 1–8. https://doi.org/10.1080/14740338.2024.2377347
14. Zhang S, Wang Y, Qi Z, Tong S, Zhu D. Data mining and analysis of adverse event signals associated with teprotumumab using the Food and Drug Administration adverse event reporting system database. Int J Clin Pharm, 2024; 46(2): 471–9. https://doi.org/10.1007/s11096-023-01676-9
15. McFerran D. Hyperacusis: Medical diagnoses and associated syndromes. In: Hyperacusis and disorders of sound intolerance: clinical and research Perspectives. Fagelson M, Bahuley DM, Editors. San Diego, CA: Plural Publishing; 2018, 107–31.
16. Alkharabsheh A, Xiong F, Xiong B, Manohar S, Chen G, Salvi R, et al. Early age noise exposure increases loudness perception: a novel animal model of hyperacusis. Hear Res, 2017; 347: 11–7. https://doi.org/10.1016/j.heares.2016.06.018

17. Auerbach BD, Radziwon K, Salvi R. Testing the central gain model: loudness growth correlates with central auditory gain enhancement in a rodent model of hyperacusis. Neurosci, 2019; 407: 93–107. https://doi.org/10.1016/j.neuroscience.2018.09.036
18. Manohar S, Chen GD, Li L, Liu X, Salvi R. Chronic stress induced loudness hyperacusis, sound avoidance and auditory cortex hyperactivity. Hear Res, 2023; 431: 108726. https://doi.org/10.1016/j.heares.2023.108726
19. Pace E, Zhang J. Noise-induced tinnitus using individualized gap detection analysis and its relationship with hyperacusis, anxiety, and spatial cognition. PLoS One, 2013; 8(9): e75011. https://doi.org/10.1371/journal.pone.0075011
20. Turner JG, Parrish J. Gap detection methods for assessing salicylate-induced tinnitus and hyperacusis in rats. Am J Audiol, 2008; 17(2): S185–192. https://doi.org/10.1044/1059-0889(2008/08-0006)
21. Zhang C, Flowers E, Li JX, Wang Q, Sun W. Loudness perception affected by high doses of salicylate: a behavioral model of hyperacusis. Behav Brain Res, 2014; 271: 16–22. https://doi.org/10.1016/j.bbr.2014.05.045
22. Domico WD. Bekesy-tracked aural harmonic distortion thresholds and uncomfortable loudness levels. Ear Hear, 1985; 6(5): 260–5. https://doi.org/10.1097/00003446-198509000-00007
23. Pascoe DP. Clinical measurements of the auditory dynamic range and their relation to formulas for hearing aid gain. In: Hearing Aid Fitting: Theoretical and Practical Views. Jensen HH, Editor. Copenhagen: Stouggaard Jensen; 1988, pp. 129–54.
24. Sherlock LP, Formby C. Estimates of loudness, loudness discomfort, and the auditory dynamic range: normative estimates, comparison of procedures, and test–retest reliability. J Am Acad Audiol, 2005; 16(2): 85–100. https://doi.org/10.3766/jaaa.16.2.4
25. Buus S, Florentine M, Poulsen T. Temporal integration of loudness, loudness discrimination, and the form of the loudness function. J Acoust Soc Am, 1997; 101(2): 669–80. https://doi.org/10.1121/1.417959
26. Florentine M, Buus S, Robinson M. Temporal integration of loudness under partial masking. J Acoust Soc Am, 1998; 104(2 Pt 1): 999–1007. https://doi.org/10.1121/1.423314
27. Scharf B. Loudness of complex sounds as a function of the number of components. J Acoust Soc Am, 1959; 31: 783–5.
28. Marshall L, Brandt JF. The relationship between loudness and reaction time in normal hearing listeners. Acta Otolaryngol, 1980; 90(3–4), 244–9. https://doi.org/10.3109/00016488009131721
29. Lauer AM, Dooling RJ. Evidence of hyperacusis in canaries with permanent hereditary high-frequency hearing loss. Semin Hear, 2007; 28(4): 319–26.
30. May BJ, Little N, Saylor S. Loudness perception in the domestic cat: reaction time estimates of equal loudness contours and recruitment effects. J Assoc Res Otolaryngol, 2009; 10(2): 295–308. https://doi.org/10.1007/s10162-009-0157-z
31. Moody DB. Behavioral studies of noise-induced hearing loss in primates: loudness recruitment. Adv Otorhinolaryngol, 1973; 20: 82–101. https://doi.org/10.1159/000393090
32. Radziwon K, Salvi R. Using auditory reaction time to measure loudness growth in rats. Hear Res, 2020; 395: 108026. https://doi.org/10.1016/j.heares.2020.108026
33. Algom D, Rubin A, Cohen-Raz L. Binaural and temporal integration of the loudness of tones and noises. Percept Psychophys, 1989; 46(2): 155–66. https://doi.org/10.3758/bf03204975
34. Pedersen CB, Salomon G. Temporal integration of acoustic energy. Acta Otolaryngol, 1977; 83(5–6): 417–23. https://doi.org/10.3109/00016487709128866
35. Chen YC, Li X, Liu L, Wang J, Lu CQ, Yang M, et al. Tinnitus and hyperacusis involve hyperactivity and enhanced connectivity in auditory-limbic-arousal-cerebellar network. eLife, 2015; 4: e06576. https://doi.org/10.7554/eLife.06576
36. Sheppard A, Hayes SH, Chen GD, Ralli M, Salvi R. Review of salicylate-induced hearing loss, neurotoxicity, tinnitus and neuropathophysiology. Acta Otorhinolaryngol Ital, 2014; 34(2): 79–93.
37. Radziwon K, Holfoth D, Lindner J, Kaier-Green Z, Bowler R, Urban M, et al. Salicylate-induced hyperacusis in rats: dose- and frequency-dependent effects. Hear Res, 2017; 350: 133–8. https://doi.org/10.1016/j.heares.2017.04.004
38. Day RO, Graham GG, Bieri D, Brown M, Cairns D, Harris G, et al. Concentration-response relationships for salicylate-induced ototoxicity in normal volunteers. Br J Clin Pharmacol, 1989; 28(6): 695–702. https://doi.org/10.1111/j.1365-2125.1989.tb03562.x
39. Oghalai JS. Chlorpromazine inhibits cochlear function in guinea pigs. Hear Res, 2004; 198(1-2): 59–68. https://doi.org/10.1016/j.heares.2004.03.013
40. Pienkowski M, Ulfendahl M. Differential effects of salicylate, quinine, and furosemide on guinea pig inner and outer hair cell function revealed by the input–output relation of the auditory brainstem response. J Am Acad Audiol, 2011; 22(2): 104–12. https://doi.org/10.3766/jaaa.22.2.5
41. Cronheim G, King JS Jr, Hyder N. Effect of salicylic acid and similar compounds on the adrenal–pituitary system. Proc Soc Exp Biol Med, 1952; 80(1): 51–5. https://doi.org/10.3181/00379727-80-19519
42. Done AK, Ely RS, Kelley VC. Studies on 17-hydroxycorticosteroids. III. Blood levels in salicylate intoxication. J Pediatr, 1954; 44(2): 153–8. https://doi.org/10.1016/s0022-3476(54)80234-4
43. Eades CH Jr, King JS. Detectable amounts of ACTH in blood following salicylate administration. Endocrinology, 1953; 52(5): 594–6. https://doi.org/10.1210/endo-52-5-594
44. Chen YC, Chen GD, Auerbach BD, Manohar S, Radziwon K, Salvi R. Tinnitus and hyperacusis: contributions of paraflocculus, reticular formation and stress. Hear Res, 2017; 349: 208–22. https://doi.org/10.1016/j.heares.2017.03.005
45. Chen GD, Manohar S, Salvi R. Amygdala hyperactivity and tonotopic shift after salicylate exposure. Brain Res, 2012; 1485: 63–76. https://doi.org/10.1016/j.brainres.2012.03.016
46. Salvi R, Auerbach BD, Lau C, Chen YC, Manohar S, Liu X, et al. Functional neuroanatomy of salicylate- and noise-induced tinnitus and hyperacusis. Curr Top Behav Neurosci, 2021; 51: 133–60. https://doi.org/10.1007/7854_2020_156
47. Fransen E, Cassiers LLM, Chubar V, Gilles A, Van Rompaey V, van der Werf I, et al. Differential effect of panic on the DNA methylation of the glucocorticoid receptor gene exon 1F in chronic subjective tinnitus with distress. Psychiatr Genet, 2023; 33(4): 134–44. https://doi.org/10.1097/YPG.0000000000000339
48. Hasson D, Theorell T, Bergquist J, Canlon B. Acute stress induces hyperacusis in women with high levels of emotional exhaustion. PLoS One, 2013; 8(1): e52945. https://doi.org/10.1371/journal.pone.0052945
49. Hebert S, Lupien SJ. The sound of stress: blunted cortisol reactivity to psychosocial stress in tinnitus sufferers. Neurosci Lett, 2007; 411(2): 138–42. https://doi.org/10.1016/j.neulet.2006.10.028

50. Simoens VL, Hebert S. Cortisol suppression and hearing thresholds in tinnitus after low-dose dexamethasone challenge. BMC Ear Nose Throat Disord, 2012; 12: 4. https://doi.org/10.1186/1472-6815-12-4
51. Herman JP, Dolgas CM, Marcinek R, Langub MC Jr. Expression and glucocorticoid regulation of natriuretic peptide clearance receptor (NPR-C) mRNA in rat brain and choroid plexus. J Chem Neuroanat, 1996; 11(4): 257–65. https://doi.org/10.1016/s0891-0618(96)00170-6
52. Lee SH, Lyu AR, Shin SA, Jeong SH, Lee SA, Park MJ, et al. Cochlear glucocorticoid receptor and serum corticosterone expression in a rodent model of noise-induced hearing loss: comparison of timing of dexamethasone administration. Sci Rep, 2019; 9(1), 12646. https://doi.org/10.1038/s41598-019-49133-w
53. Patel PD, Lopez JF, Lyons DM, Burke S, Wallace M, Schatzberg AF. Glucocorticoid and mineralocorticoid receptor mRNA expression in squirrel monkey brain. J Psychiatr Res, 2000; 34(6): 383–92. https://doi.org/10.1016/s0022-3956(00)00035-2
54. Rarey KE, Gerhardt KJ, Curtis LM, ten Cate WJ. Effect of stress on cochlear glucocorticoid protein: acoustic stress. Hear Res, 1995; 82(2): 135–8. https://doi.org/10.1016/0378-5955(94)00171-l
55. Kil SH, Kalinec F. Expression and dexamethasone-induced nuclear translocation of glucocorticoid and mineralocorticoid receptors in guinea pig cochlear cells. Hear Res, 2013; 299: 63–78. https://doi.org/10.1016/j.heares.2013.01.020
56. Terakado M, Kumagami H, Takahashi H. Distribution of glucocorticoid receptors and 11 beta-hydroxysteroid dehydrogenase isoforms in the rat inner ear. Hear Res, 2011; 280(1–2): 148–56. https://doi.org/10.1016/j.heares.2011.05.006
57. ten Cate WJ, Curtis LM, Rarey KE. Immunochemical detection of glucocorticoid receptors within rat cochlear and vestibular tissues. Hear Res, 1992; 60(2): 199–204. https://doi.org/10.1016/0378-5955(92)90021-e
58. Aronsson M, Fuxe K, Dong Y, Agnati LF, Okret S, Gustafsson JA. Localization of glucocorticoid receptor mRNA in the male rat brain by in situ hybridization. Proc Natl Acad Sci USA, 1988; 85(23): 9331–5. https://doi.org/10.1073/pnas.85.23.9331
59. Joels M, Karst H, Sarabdjitsingh RA. The stressed brain of humans and rodents. Acta Physiol (Oxf), 2018; 223(2): e13066. https://doi.org/10.1111/apha.13066
60. Fendt M, Li L, Yeomans JS. Brain stem circuits mediating prepulse inhibition of the startle reflex. Psychopharmacology, 2001; 156(2-3): 216–24. https://doi.org/10.1007/s002130100794
61. Yeomans JS, Frankland PW. The acoustic startle reflex: neurons and connections. Brain Res Brain Res Rev, 1995; 21(3): 301–14. https://doi.org/10.1016/0165-0173(96)00004-5
62. Ashton CH, Lunn B, Marsh VR, Young AH. Subchronic hydrocortisone treatment alters auditory evoked potentials in normal subjects. Psychopharmacol, 2000; 152(1): 87–92. https://doi.org/10.1007/s002130000528
63. Jahn KN, Wiegand-Shahani BM, Lobarinas E. Audiometric profiles across a clinical population of children with hyperacusis. Am J Audiol, 2024; 33(4): 1155–63. https://doi.org/10.1044/2024_AJA-24-00090
64. Sheldrake J, Diehl PU, Schaette R. Audiometric characteristics of hyperacusis patients. Front Neurol, 2015; 6: 105. https://doi.org/10.3389/fneur.2015.00105
65. Hagerman RJ, Berry-Kravis E, Hazlett HC, Bailey DB Jr, Moine H, Kooy RF, et al. Fragile X syndrome. Nat Rev Dis Primers, 2017; 3: 17065. https://doi.org/10.1038/nrdp.2017.65
66. Rotschafer SE, Razak KA. Auditory processing in fragile X syndrome. Front Cell Neurosci, 2014; 8: 19. https://doi.org/10.3389/fncel.2014.00019
67. Verkerk AJ, Pieretti M, Sutcliffe JS, Fu YH, Kuhl DP, Pizzuti A, et al. Identification of a gene (FMR-1) containing a CGG repeat coincident with a breakpoint cluster region exhibiting length variation in fragile X syndrome. Cell, 1991; 65(5): 905–14. https://doi.org/10.1016/0092-8674(91)90397-h
68. Dolen G, Osterweil E, Rao BS, Smith GB, Auerbach BD, Chattarji S, et al. Correction of fragile X syndrome in mice. Neuron, 2007; 56(6): 955–62. https://doi.org/10.1016/j.neuron.2007.12.001
69. Pop AS, Gomez-Mancilla B, Neri G, Willemsen R, Gasparini F. Fragile X syndrome: a preclinical review on metabotropic glutamate receptor 5 (mGluR5) antagonists and drug development. Psychopharmacol, 2014; 231(6): 1217–26. https://doi.org/10.1007/s00213-013-3330-3
70. Ferraguto C, Bouleau Y, Peineau T, Dulon D, Pietropaolo S. Hyperacusis in the adult *Fmr1*-KO mouse model of fragile X syndrome: the therapeutic relevance of cochlear alterations and BKCa channels. Int J Mol Sci, 2023; 24(14): 11863. https://doi.org/10.3390/ijms241411863
71. McCullagh EA, Poleg S, Greene NT, Huntsman MM, Tollin DJ, Klug A. Characterization of auditory and binaural spatial hearing in a fragile X syndrome mouse model. eNeuro, 2020; 7(1): eneuro.0300-19.2019. https://doi.org/10.1523/eneuro.0300-19.2019
72. Hamilton SM, Green JR, Veeraragavan S, Yuva L, McCoy A, Wu Y, et al. *Fmr1* and *Nlgn3* knockout rats: novel tools for investigating autism spectrum disorders. Behav Neurosci, 2014; 128(2): 103–9. https://doi.org/10.1037/a0035988
73. Bear MF, Huber KM, Warren ST. The mGluR theory of fragile X mental retardation. Trends Neurosci, 2004; 27(7): 370–7. https://doi.org/10.1016/j.tins.2004.04.009
74. Till SM, Asiminas A, Jackson AD, Katsanevaki D, Barnes SA, Osterweil EK, et al. Conserved hippocampal cellular pathophysiology but distinct behavioural deficits in a new rat model of FXS. Hum Mol Genet, 2015; 24(21): 5977–84. https://doi.org/10.1093/hmg/ddv299
75. Auerbach BD, Manohar S, Radziwon K, Salvi R. Auditory hypersensitivity and processing deficits in a rat model of fragile X syndrome. Neurobiol Dis, 2021; 161: 105541. https://doi.org/10.1016/j.nbd.2021.105541
76. Gleich O, Kittel MC, Klump GM, Strutz J. Temporal integration in the gerbil: the effects of age, hearing loss and temporally unmodulated and modulated speech-like masker noises. Hear Res, 2007; 224(1–2): 101–14. https://doi.org/10.1016/j.heares.2006.12.002
77. Hall J W, Fernandes MA. Temporal integration, frequency resolution, and off-frequency listening in normal-hearing and cochlear-impaired listeners. J Acoust Soc Am, 1983; 74(4): 1172–7. https://doi.org/10.1121/1.390040
78. Oxenham AJ, Moore BC, Vickers DA. Short-term temporal integration: evidence for the influence of peripheral compression. J Acoust Soc Am, 1997; 101(6): 3676–87. https://doi.org/10.1121/1.418328
79. Scharf B. Critical Bands. In: Foundations of modern auditory theory. Tobias JV, Editor. New York: Academic Press; 1970, pp. 157–202.
80. Zwicker A, Flottorp G, Stevens S. Critical bandwidth in loudness summation. J Acoust Soc Am, 1957; 29(5): 548–57.
81. Nickols HH, Conn PJ. Development of allosteric modulators of GPCRs for treatment of CNS disorders. Neurobiol Dis, 2014; 61: 55–71. https://doi.org/10.1016/j.nbd.2013.09.013

82. McCullagh EA, Rotschafer SE, Auerbach BD, Klug A, Kaczmarek LK, Cramer KS, et al. Mechanisms underlying auditory processing deficits in fragile X syndrome. FASEB J, 2020; 34(3): 3501–18. https://doi.org/10.1096/fj.201902435R
83. Gu JW, Halpin CF, Nam EC, Levine RA, Melcher JR. Tinnitus, diminished sound-level tolerance, and elevated auditory activity in humans with clinically normal hearing sensitivity. J Neurophysiol, 2010; 104(6): 3361–70. https://doi.org/10.1152/jn.00226.2010
84. Soyka M. Treatment of benzodiazepine dependence. N Engl J Med, 2017; 376(12): 1147–57. https://doi.org/10.1056/NEJMra1611832
85. Surer Adanir A, Gizli Coban O, Ozatalay E. Increased hyperacusis with risperidone in an autistic child. Noro Psikiyatr Ars, 2017; 54(2): 187–8. https://doi.org/10.5152/npa.2017.18062
86. Tyrer P. Clinical effects of abrupt withdrawal from tri-cyclic antidepressants and monoamine oxidase inhibitors after long-term treatment. J Affect Disord, 1984; 6(1): 1–7. https://doi.org/10.1016/0165-0327(84)90002-8
87. Yang L, Agarwal P. Systematic drug repositioning based on clinical side-effects. PLoS One, 2011; 6(12): e28025. https://doi.org/10.1371/journal.pone.0028025
88. Anari M, Axelsson A, Eliasson A, Magnusson L. Hypersensitivity to sound: questionnaire data, audiometry and classification. Scand Audiol, 1999; 28(4): 219–30. https://doi.org/10.1080/010503999424653
89. Curhan SG, Glicksman J, Wang M, Eavey RD, Curhan GC. Longitudinal study of analgesic use and risk of incident persistent tinnitus. J Gen Intern Med, 2022; 37(14): 3653–62. https://doi.org/10.1007/s11606-021-07349-5
90. Hinz B, Cheremina O, Brune K. Acetaminophen (paracetamol) is a selective cyclooxygenase-2 inhibitor in man. FASEB J, 2008; 22(2): 383–90. https://doi.org/10.1096/fj.07-8506com
91. Hebert S, Lupien SJ. Salivary cortisol levels, subjective stress, and tinnitus intensity in tinnitus sufferers during noise exposure in the laboratory. Int J Hyg Environ Health, 2009; 212(1): 37–44. https://doi.org/10.1016/j.ijheh.2007.11.005
92. Monsefi M, Bahoddini A, Nazemi S, Dehghani GA. Effects of noise exposure on the volume of adrenal gland and serum levels of cortisol in rat. Iran J Med Sci, 2006; 31(1): 5–8.
93. Radziwon K, Auerbach BD, Ding D, Liu X, Chen GD, Salvi R. Noise-induced loudness recruitment and hyperacusis: insufficient central gain in auditory cortex and amygdala. Neurosci, 2019; 422: 212–27. https://doi.org/10.1016/j.neuroscience.2019.09.010
94. Karch SJ, Capo-Aponte JE, McIlwain DS, Lo M, Krishnamurti S, Staton RN, et al. Hearing loss and tinnitus in military personnel with deployment-related mild traumatic brain injury. US Army Med Dep J, 2016; (3–16): 52–63.
95. Nikitina E A, Medvedeva AV, Zakharov GA, Savvateeva-Popova EV. Williams syndrome as a model for elucidation of the pathway genes – the brain – cognitive functions: genetics and epigenetics. Acta Naturae, 2014; 6(1): 9–22.
96. Buskila D, Sarzi-Puttini P, Ablin J N. The genetics of fibromyalgia syndrome. Pharmacogenomics, 2007; 8(1): 67–74. https://doi.org/10.2217/14622416.8.1.67
97. Sutherland HG, Albury CL, Griffiths LR. Advances in genetics of migraine. J Headache Pain, 2019; 20(1): 72. https://doi.org/10.1186/s10194-019-1017-9
98. Bandelow B. Current and novel psychopharmacological drugs for anxiety disorders. In: Anxiety Disorders: Rethinking and understanding recent discoveries. Kim Y-K, Editor. Singapore: Springer Singapore; 2020, pp. 347–65.
99. Jovanovic T, Phifer J E, Sicking K, Weiss T, Norrholm SD, Bradley B, et al. Cortisol suppression by dexamethasone reduces exaggerated fear responses in posttraumatic stress disorder. Psychoneuroendocrinol, 2011; 36(10): 1540–52. https://doi.org/10.1016/j.psyneuen.2011.04.008
100. Aazh H, Landgrebe M, Danesh AA, Moore BC. Cognitive behavioral therapy for alleviating the distress caused by tinnitus, hyperacusis and misophonia: current perspectives. Psychol Res Behav Manag, 2019; 12: 991–1002. https://doi.org/10.2147/PRBM.S179138
101. Aazh H, Moore BC, Lammaing K, Cropley M. Tinnitus and hyperacusis therapy in a UK National Health Service audiology department: patients' evaluations of the effectiveness of treatments. Int J Audiol, 2016; 55(9): 514–22. https://doi.org/10.1080/14992027.2016.1178400
102. Cherri D, Formby C, Secor CA, Eddins DA. Counseling protocol for a transitional intervention for debilitating hyperacusis. J Speech Lang Hear Res, 2024; 67(6): 1886–1902. https://doi.org/10.1044/2023_JSLHR-23-00353
103. Hutchison P, Maeda H, Formby C, Small BJ, Eddins DA, Eddins AC. Acoustic deprivation modulates central gain in human auditory brainstem and cortex. Hear Res, 2023; 428: 108683. https://doi.org/10.1016/j.heares.2022.108683
104. Parry LV, Maslin MRD, Schaette R, Moore DR, Munro KJ. Increased auditory cortex neural response amplitude in adults with chronic unilateral conductive hearing impairment. Hear Res, 2019; 372: 10–16. https://doi.org/10.1016/j.heares.2018.01.016
105. Sheppard A, Stocking C, Ralli M, Salvi R. A review of auditory gain, low-level noise and sound therapy for tinnitus and hyperacusis. Int J Audiol, 2020; 59(1): 5–15. https://doi.org/10.1080/14992027.2019.1660812
106. Eddins DA, Armstrong S, Juneau R, Hutchison P, Cherri D, Secor CA, et al. Device and fitting protocol for a transitional intervention for debilitating hyperacusis. J Speech Lang Hear Res, 2024; 67(6): 1868–85. https://doi.org/10.1044/2024_JSLHR-23-00359
107. Formby C, Cherri D, Secor CA, Armstrong S, Juneau R, Hutchison P, et al. Results of a 6-month field trial of a transitional intervention for debilitating hyperacusis. J Speech Lang Hear Res, 2024; 67(6): 1903–31. https://doi.org/10.1044/2024_JSLHR-23-00360
108. Formby C, Secor CA, Cherri D, Eddins DA. Background and rationale for a transitional intervention for debilitating hyperacusis. J Speech Lang Hear Res, 2024; 67(6): 1984–93. https://doi.org/10.1044/2023_JSLHR-23-00352
109. Hebert S, Canlon B, Hasson D. Emotional exhaustion as a predictor of tinnitus. Psychother Psychosom, 2012; 81(5): 324–6. https://doi.org/10.1159/000335043
110. Hebert S, Paiement P, Lupien SJ. A physiological correlate for the intolerance to both internal and external sounds. Hear Res, 2004; 190(1–2): 1–9. https://doi.org/10.1016/S0378-5955(04)00021-8
111. Aazh H, McFerran D, Salvi R, Prasher D, Jastreboff M, Jastreboff P. Insights from the first international conference on hyperacusis: causes, evaluation, diagnosis and treatment. Noise Health, 2014; 16(69): 123–6. https://doi.org/10.4103/1463-1741.132100
112. Henry JA, Theodoroff SM, Edmonds C, Martinez I, Myers PJ, Zaugg TL, et al. Sound tolerance conditions (hyperacusis, misophonia, noise sensitivity, and phonophobia): definitions and clinical management. Am J Audiol, 2022; 31(3): 513–27. https://doi.org/10.1044/2022_AJA-22-00035
113. Jastreboff PJ. 25 years of tinnitus retraining therapy. HNO, 2015; 63(4): 307–11. https://doi.org/10.1007/s00106-014-2979-1

114. Kohfeld DL, Santee JL, Wallace ND. Loudness and reaction time: II. Identification of detection components at different intensities and frequencies. Percept Psychophys, 1981; 29(6): 550–62. https://doi.org/10.3758/bf03207371
115. Seitz PF, Rakerd B. Auditory stimulus intensity and reaction time in listeners with longstanding sensorineural hearing loss. Ear Hear, 1997; 18(6): 502–12. https://doi.org/10.1097/00003446-199712000-00008
116. Knipper M, Van Dijk P, Nunes I, Ruttiger L, Zimmermann U. Advances in the neurobiology of hearing disorders: recent developments regarding the basis of tinnitus and hyperacusis. Prog Neurobiol, 2013; 111: 17–33. https://doi.org/10.1016/j.pneurobio.2013.08.002
117. Mohrle D, Hofmeier B, Amend M, Wolpert S, Ni K, Bing D, et al. Enhanced central neural gain compensates acoustic trauma-induced cochlear impairment, but unlikely correlates with tinnitus and hyperacusis. Neurosci, 2019; 407: 146–69. https://doi.org/10.1016/j.neuroscience.2018.12.038
118. St Clair DM, Blackwood DH, Oliver CJ, Dickens P. P3 abnormality in fragile X syndrome. Biol Psychiatry, 1987; 22(3): 303–12. https://doi.org/10.1016/0006-3223(87)90148-x
119. Ethridge LE, White SP, Mosconi MW, Wang J, Byerly MJ, Sweeney JA. Reduced habituation of auditory evoked potentials indicate cortical hyper-excitability in Fragile X syndrome. Transl Psychiatry, 2016; 6(4): e787. https://doi.org/10.1038/tp.2016.48
120. Salvi R, Radziwon K, Manohar S, Auerbach B, Ding D, Liu X, et al. Review: neural mechanisms of tinnitus and hyperacusis in acute drug-induced ototoxicity. Am J Audiol, 2021; 30(3S): 901–15. https://doi.org/10.1044/2020_AJA-20-00023
121. Chen GD, Radziwon KE, Kashanian N, Manohar S, Salvi R. Salicylate-induced auditory perceptual disorders and plastic changes in nonclassical auditory centers in rats. Neural Plast, 2014; 2014: 658741. https://doi.org/10.1155/2014/658741
122. Manohar S, Chen GD, Ding D, Liu L, Wang J, Chen YC, et al. Unexpected consequences of noise-induced hearing loss: impaired hippocampal neurogenesis, memory, and stress. Front Integr Neurosci, 2022; 16: 871223. https://doi.org/10.3389/fnint.2022.871223

Richard Salvi, email: richard.salvi@ucf.edu • 0000-0001-9061-8602
Yu-Chen Chen, email: chenyuchen1989@126.com • 0000-0002-8539-7224
Benjamin D. Auerbach, email: bda5@illinois.edu • 0000-0001-6253-2246