

Auditory Notches in 134 Band Audiograms

Automated Micro Audiometer: AMA-PTA

Eunye Kwak¹, Sookjin Song¹, and Sangyeop Kwak¹

Abstract

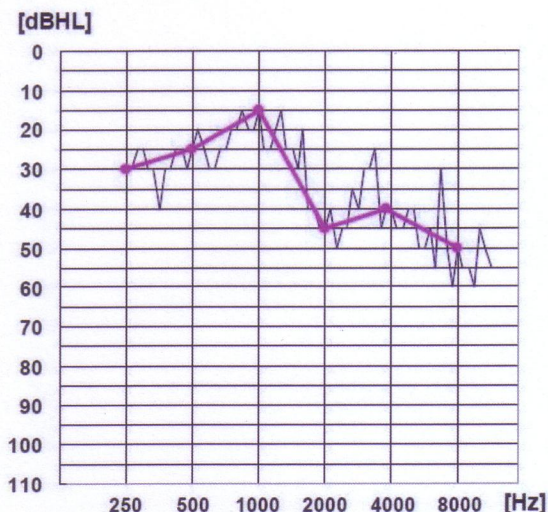
Several studies reported the prevalence of auditory notches. Auditory notches could be found in subjects with normal-hearing sensitivity as well as hearing-impaired subjects. To investigate the profile of threshold microstructure in human auditory system, frequency profiles of auditory notches were obtained from normal-hearing subjects. To identify the frequency of auditory notches, 134 band (1/24 Oct. resolution in 250~12,000 Hz) pure-tone audiometry was performed by using automated and randomized Bekesy audiometry (AMA-PTA).

AMA-PTA enabled to obtain 134 band audiogram within 35 ~ 45 minutes. The 134 band audiograms were compared with 6 band (1 Oct. resolution) audiograms. Auditory notches were observed in both ears of all subjects. However, the 6 band audiograms have missed most of the auditory notches observed in the 134 band audiograms. These auditory notches, which were not shown in conventional audiometry, were also observed in hearing-impaired subjects as well.

This study demonstrates that the conventional, 6 band audiometry has overlooked the microstructure of auditory thresholds.

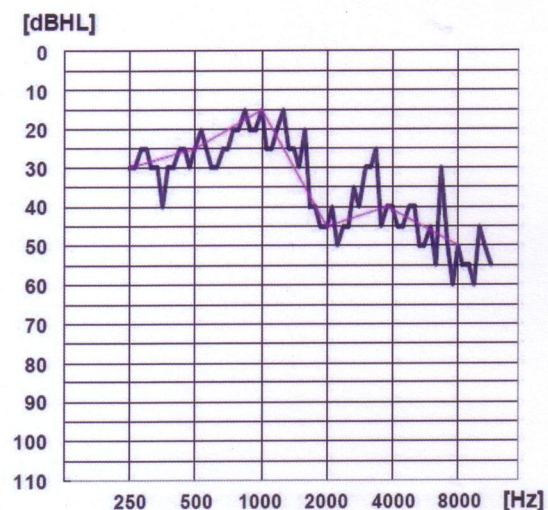
AMA-PTA

Automated Micro Audiometer - Pure Tone Audiometry
Which is your audiogram?



Conventional Audiometry

(6 Frequencies: 20 Minutes, 11 Frequencies: 35 Minutes)



AMA-PTA

(6 Frequencies: 2 Minutes, 67 Frequencies: 20 Minutes, 134 frequencies: 40 Minutes)

Randomized and Automated Quasi Bekesy Audiometry (RAQBA)

Conventional audiometry has underestimated the effect of auditory selective attention on the threshold results. The existing presentation method ordered in frequency produces spectral cue in subject's memory. Spectral cue induces efferent inhibition (or excitation) due to auditory selective attention. This may provide inconsistent results up to 30dB in the following repeated hearing test. The best way to exclude auditory selective attention is to randomize stimulus frequency to present.

Pulsed Pure Tone

Majority of hearing loss people suffer from tinnitus. Even normal hearing person may experience a number of "inner-ear sounds" (e.g. tinnitus, SOAE, etc.) when he/she is in a sound proof room. Most of inner-ear sounds are continuous, and

1. Earlogic Corporation, 3550 Wilshire Blvd. Suite 510, Los Angeles, U.S.A.

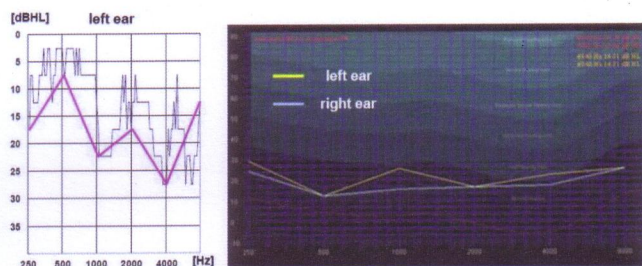
frequently confused with test tone (continuous pure tone) near the threshold levels. In this respect, pulsed pure tone would be more desirable than continuous pure tone as a stimulus.

3~4 Times Repeated Test

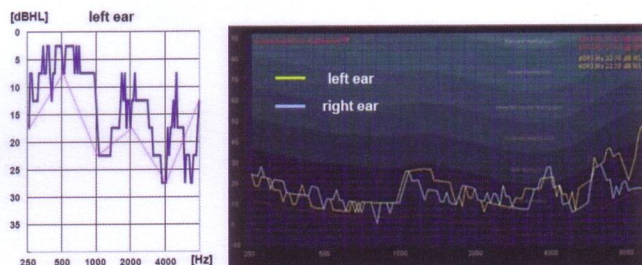
To provide more reliable threshold results, AMA-PTA executes 3~4 times repeated test in random order near the threshold levels.

Results

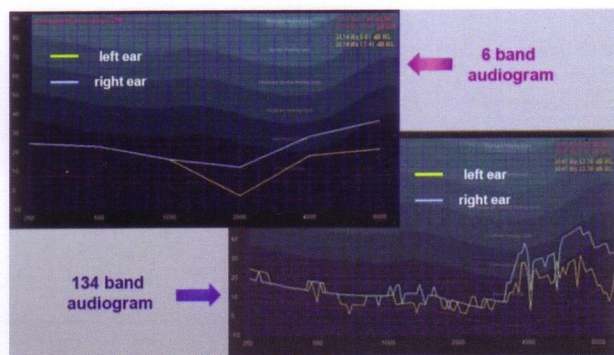
Subject A 6 band audiogram



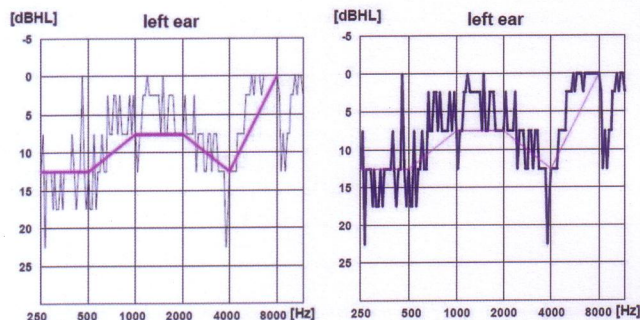
Subject A 134 band audiogram



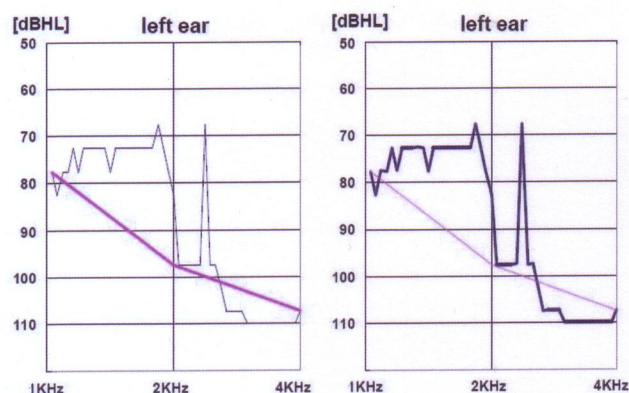
Subject B 6 & 134 band audiogram



Subject C 6 & 134 band audiogram (250~12000 Hz)



Subject D 6 & 134 band audiogram (1~4 KHz)



Conclusion

- AMA-PTA enables to obtain 134 band (1/24 Oct. resolution in 250 ~ 12,000 Hz) audiogram within 35 ~ 45 minutes.
- Auditory notches were observed in normal-hearing subjects as well as hearing-impaired subjects.
- Conventional, 6 band audiometry has missed most of the auditory notches observed in 134 band audiometry (AMA-PTA).

References

1. Oates P. & Stapells DR. (1997). Frequency specificity of the human auditory brainstem and middle latency responses to brief tones. I. High-pass noise masking. *J Acoust Soc Am* 102:3597-3608
2. McBride D. & Williams S. (2001). Characteristics of the audiometric notch as a clinical sign of noise exposure. *Scand Audiol* 30:106-111
3. Stapells DR. (2000). Frequency-specific evoked potential audiometry in infants. In R. C. Seewald (Ed.) *A Sound Foundation Through Early Amplification*. Basel: Phonak AG

Effects of Stimulus Duration on the Wave V and N1 Peak

Sangyeop Kwak¹ and Eunyee Kwak¹

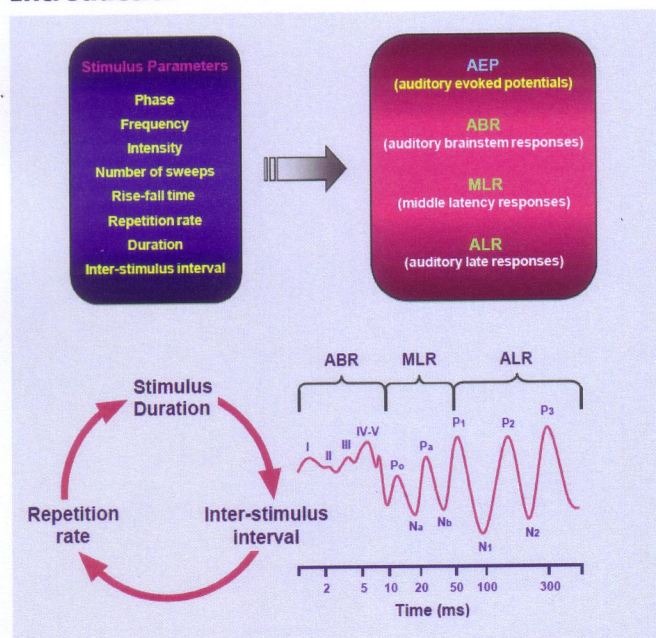
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Surgery Foundation (AAO-HNSF),
111th Annual Meeting & OTO
EXPO in Washington, DC from
September 16~19, 2007

Abstract

Various stimulus parameters affect on auditory evoked brainstem response (ABR) and long-latency cortical response. Among them are stimulus intensity, repetition rate, rise-fall time, duration, and interstimulus interval (ISI). To investigate the effects of stimulus duration on Wave V and N1 peak, two types of tone-bursts with different duration (2-1-2 vs. 2-46-2) were presented as stimuli. Since there is a controversy on the duration effects on Wave V amplitude, we intended to exclude both repetition rate and ISI effects. To this end, considerably long ISI (i.e. 250ms) was set for Wave V detection. Significant differences in the amplitudes of Wave V and N1 were observed between 2-1-2 and 2-46-2 tone-bursts.

Interestingly, increment of stimulus duration caused opposite effects on Wave V and N1 amplitude. While N1 amplitude increased with duration increment as previously reported, Wave V amplitude decreased when the longer stimulus was presented. These results demonstrate that stimulus duration may have opposite effects on ABR and auditory cortical responses.

Introduction



Method

A. Test Stimuli

Frequency: 1000 Hz tone-burst, Intensity: 80 dB HL, Duration: 2 ms rise/fall times, 1 ms or 46 ms plateau (i.e., 2-1-2 or 2-46-2), ISI: 250 ms (Wave V) or 500 ms (N1 peak)

B. Procedures

Number of sweeps: 1800 (wave V), 300 (N1 peak), 3 replications for each subject, Electrode location: (+) High forehead, (-) Ipsilateral mastoid

Results

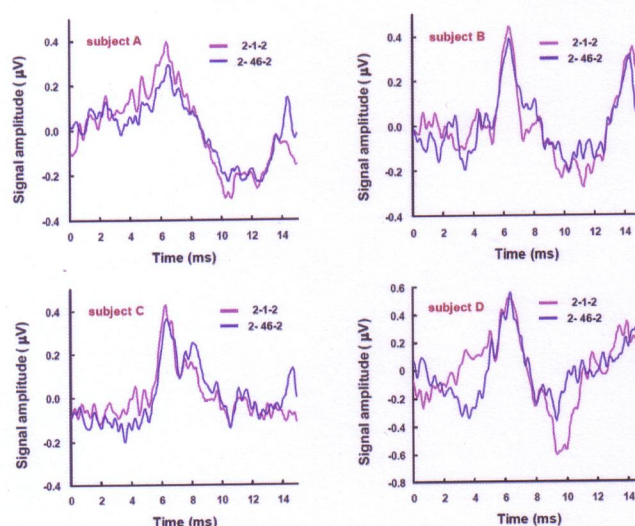


Fig.1. ABR waveforms of each subject. Each value is the mean of three replications (thus summed average waveforms of 5,400 stimulus presentations). Pink line: 2-1-2 stimulus; Blue line: 2-46-2 stimulus

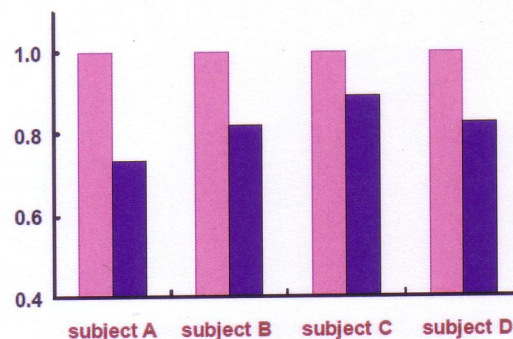


Fig.2. Relative amplitude of Wave V-SN10. Amplitudes of 2-1-2 stimulus were set to 1.0 in each subject. Pink Bar: 2-1-2 stimulus; Blue Bar: 2-46-2 stimulus

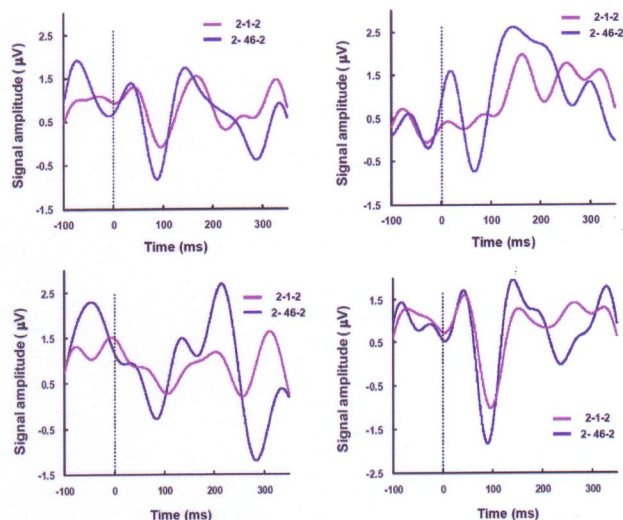


Fig.3. Late-latency responses of each subject. Each value is the mean of three replications. Pink line: 2-1-2 stimulus; Blue line: 2-46-2 stimulus

Conclusion

- Increment of stimulus duration had an opposite effect on Wave V and N1 amplitude.
- In contrast to the previous reports, Wave V amplitude decreased with increment of duration in the present experimental condition.
- N1 amplitude increased with increment of duration as previously reported.

References

1. Hecox K, Squires N, Galambos R. (1976). Brainstem auditory evoked responses in man. I. Effect of stimulus rise-fall time and duration. *J Acoust Soc Am* 60:1187-1192
2. Funasaka S. & Ito S. (1986). Stimulus duration and waves of auditory brainstem responses. *Audiology* 25:176-183
3. Gorga MP, Beauchaine KA, Reiland JK, Worthington DW, Javel E. (1984). The effects of stimulus duration on ABR and behavioral thresholds. *J Acoust Soc Am* 76:616-619
4. Barry SJ. & Barry EK. (1996). ABR slow wave and stimulus duration. *J AM Acad Audiol* 7:7-14
5. Alain C, Woods DL, Covarrubias D. (1997). Activation of duration-sensitive auditory cortical fields in humans. *Electroencephalogr Clin Neurophysiol* 104:531-539

1. Earlogic Corporation, 3550 Wilshire Blvd. Suite 510, Los Angeles, U.S.A.

New Method to Acquire Frequency-Specific Thresholds by BERA

Eunye Kwak¹, Sookjin Song¹, and Sangyeop Kwak¹

Abstract

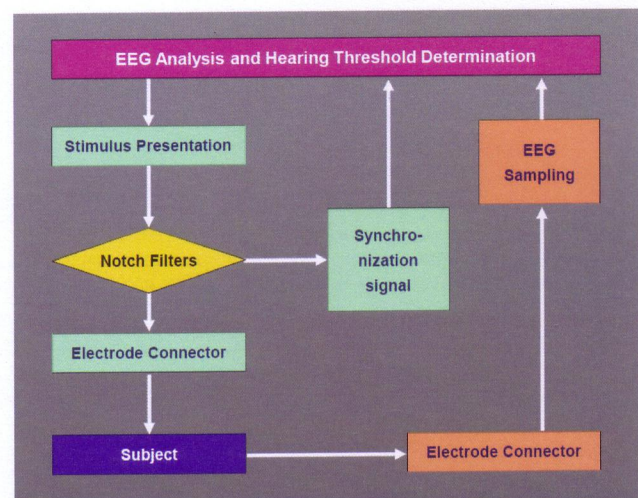
In the present study, we suggest a new automated method to acquire an objective frequency-specific audiogram by comparing the amplitude of Wave V with that of SN10. To increase signal to noise ratio in the automated ABR, the following three complementary controls called "triple artifact-rejection method" were adopted: (1) filtering periodic artifacts by real-time FFT monitoring, (2) randomization of ISI (interstimulus interval) to exclude periodic artifact influxed from the spontaneous potential, i.e., EEG, and (3) filtering fast component artifacts. To shorten test time without any deterioration of accuracy, "automated quasi Bekesy method" was adopted in the automated ABR. Hearing thresholds obtained from PTA (pure tone audiometry) were compared with those of the present automated ABR at 0.5, 1, 2, 4 KHz. The automated ABR predicted well the behavioral thresholds. Most importantly, there was a big time saving in the automated ABR proposed by the present study. That is, it took only 6~8 minutes which were only one-tenth of the testing time required for the conventional tone-pip ABR audiometry.

Background Information

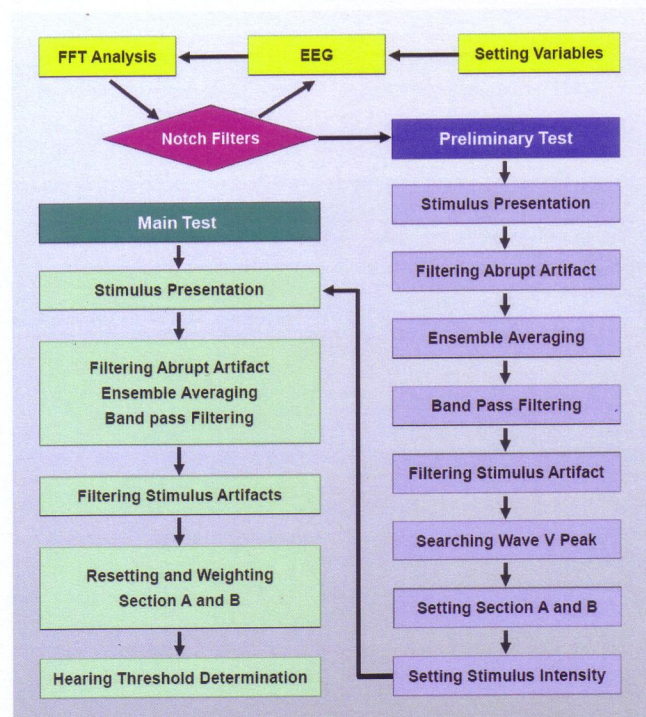
In the conventional tone-pip ABR audiometry, as each frequency-specific threshold should be estimated separately, it takes about 1.5~2 hours to test hearing thresholds. In addition, because clinician's determination of a subject's hearing threshold depends on visual discrimination of wave V peak of which amplitude decrease more and more when stimulus intensity gets closer to hearing threshold, it is difficult to avoid intervention of clinician's subjective judgment. It is the most serious problem of the conventional tone-pip ABR audiometry that very long time is required for the hearing test. It takes long time to set manually the test stimulus presented separately according to frequency and intensity. In addition, each test stimulus should be presented more than 1,500 times to obtain a significant signal-to-noise ratio. Most of all, because the more stimulus intensity gets closer to hearing threshold, the more amplitude of wave V decreases, it takes long time for a user to determine the presence or absence of wave V peak.

In order to solve above-mentioned problems of the conventional method, the present study provides a method for automation of tone-pip (or toneburst) ABR audiometry, which can exclude both manual operation and user's subjective judgment. In addition, the present study provides a method for shortening of testing time and for the minimization of

inaccuracy and errors which may be resulted from the automation and time shortening.

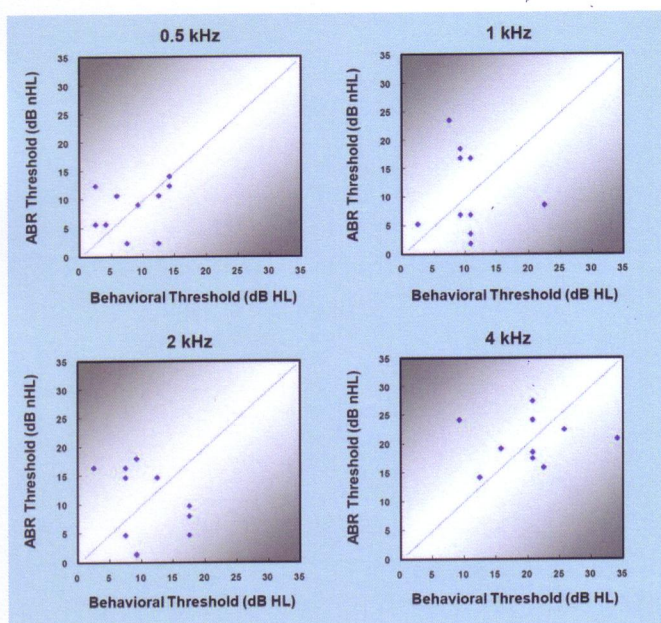


Configuration Chart of a Device for Performing Automated ABR Test



Flow Chart of Automated ABR Test

Results



Average Testing Time : 6~8 min.

Conclusion

According to the present study, clinicians can shorten testing time by automatically performing tone-pip (or tone-burst) ABR test without both manual operation and clinician's subjective judgment. Further, in spite of minimization of the averaging number, reliable hearing test data with excellent signal-to-noise ratio is obtained by applying a decision method of objective hearing thresholds based on the gap between wave V and SN10.

1. Earlogic Corporation, 3550 Wilshire Blvd. Suite 510, Los Angeles, U.S.A.

Hearing Improvement with Customized Sound Stimulation

Sangyeop Kwak, M.A.¹, Sookjin Song¹, Sung Hwa Hong, M.D.², and Eunyee Kwak, Ph.D.¹

Abstract

To investigate if hearing ability could be improved by sound stimulation, we applied customized sound stimuli to 9 patients with sensorineural hearing loss, and compared behavioral hearing thresholds before and after sound stimulation. The results of this study showed that acoustic stimuli could improve hearing ability. On overall average, the behavioral hearing threshold decreased by 8.91 dB after 2 weeks of sound stimulation followed by a 2 week break.

Objective

This study aimed to find out new methods for restoration of sensorineural hearing loss.

Background & Hypothesis

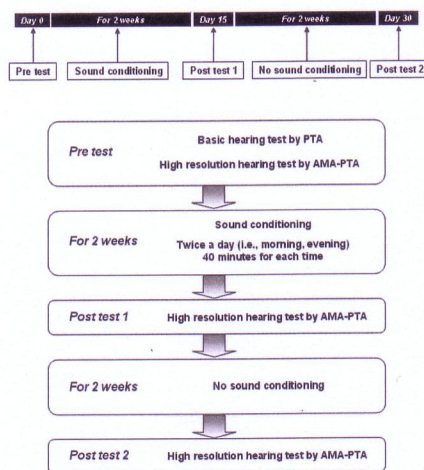
Several studies have been reported that sound conditioning (i.e., prior exposure to low-level sounds) could protect hearing ability against damage by traumatic noise in a number of mammalian species, including humans. Acoustic stimuli could also slow progressive sensorineural hearing loss. Thus, exposure to a moderately augmented acoustic environment could delay the loss of auditory function in mice. In addition to these protection and retardation effects, long-term sound conditioning could enhance cochlear sensitivity in normal hearing guinea pigs. Based on these results, we hypothesized that sound stimulation could also improve hearing ability in patients with sensorineural hearing loss.

Method

To investigate if sound stimulation could improve hearing loss, we applied customized sound stimuli to 9 patients with sensorineural hearing loss less than 70 dB HL.

Customized sound stimuli consisted of frequency-modulated tone and amplitude-modulated narrow band noise. The patients listened to the sound stimuli for 40 minutes twice a day (once in the morning and once in the evening) for 2 weeks. Behavioral hearing thresholds were compared before and after sound stimulation.

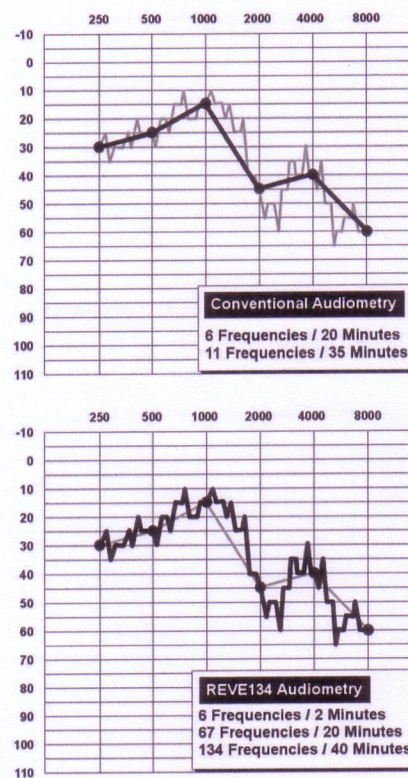
Study Protocol



To rule out the possibility of bias arising from test-retest variation, we repeated the behavioral hearing test (i.e., pure-tone audiometry) three times for each frequency and adopted the average value as a hearing threshold of the corresponding frequency. In this pilot study, we limited the frequency range for

sound stimulation to a 1/3 octave within the most hearing impaired region in each patient.

An Example of High-Resolution Hearing Test



Target Frequency Region of Each Patient

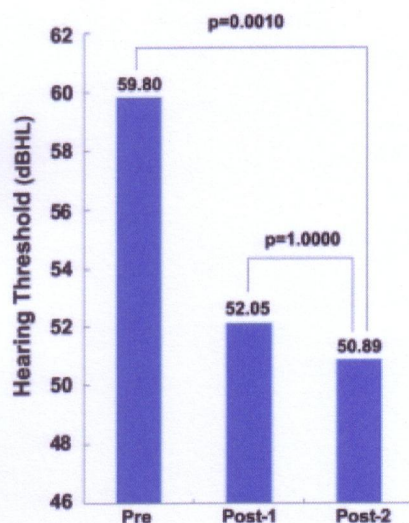
In this study, we decided the 1/3 Octave band showing the highest PTA hearing threshold (i.e., the worst hearing ability) as a target frequency region.

Patient	Target Frequency Region (Hz)
A	6093 – 7246
B	9956 – 11840
C	4186 – 4978
D	3328 – 3838
E	9956 – 11840
F	9956 – 11840
G	3322 – 3951
H	4186 – 4978
I	9956 – 11840

Result 1: Improvement of hearing ability

The average hearing threshold before sound stimulation was 59.80 dB HL, and this value decreased to 50.89 dB HL after 2 weeks of sound stimulation followed by a 2 week break. Thus, 8.91 dB of significant improvement in hearing ability was achieved.

Hearing Threshold of Target Frequency Region.



'Pre' refers to grand averages before modified sound conditioning. 'Post-1' refers to grand averages after 2 weeks of modified sound conditioning. 'Post-2' refers to grand averages 2 weeks after the conclusion of modified sound conditioning. Statistical analysis

was performed using *Wilcoxon's signed rank test with Bonferroni's correction*.

Result 2: Changes of Intra-Patient Hearing Thresholds

Significant improvements in hearing ability were observed in 7 of the 9 patients.

Patient	PreHearing Threshold (dB HL)	Post2 Hearing Threshold (dB HL)	P value**
A	56.55	50.83	0.0031
B	59.64	16.07	< 0.0001
C	72.50	67.50	< 0.0001
D	56.31	52.26	0.0013
E	57.02	46.79	0.0158
F	47.98	39.88	0.0156*
G	56.79	56.07	0.6286
H	70.36	64.40	0.0313*
I	61.07	64.17	0.3036

'Pre' refers to grand averages before modified sound conditioning. 'Post-2' refers to grand averages 2 weeks after the conclusion of modified sound conditioning. **Statistical analysis was performed using *the paired T-test or the Wilcoxon's signed-rank test (*)*.

Conclusion

In this study, we confirmed the possibility that customized sound stimulation could improve hearing ability in patients with sensorineural hearing loss.

References

1. Protection against noise trauma by pre-exposure to a low level acoustic stimulus. *Hear Res* 1988; 34: 197–200
2. Effect of low level acoustic stimulation on temporary threshold shift in young humans. *Hear Res* 1992; 60: 149–155
3. Protecting against noise trauma by sound conditioning. *J of Sound and Vibration* 2002; 250: 115–118

4. Exposure to an augmented acoustic environment alters auditory function in hearing-impaired DBA/2J mice. *Hear Res* 1998; 118: 101–113

5. Prolonged exposure to an augmented acoustic environment ameliorates age-related auditory changes in C57BL/6J and DBA/2J mice. *Hear Res* 1999; 78–88

6. Effects of prolonged exposure to an augmented acoustic environment on the auditory system of middle-aged C57BL/6J mice: cochlear and central histology and sex differences. *J Comp Neurol* 2004; 472: 358–370

7. Effects of exposure to an augmented acoustic environment on auditory function in mice: roles of hearing loss and age during treatment. *Hear Res* 2000; 142: 79–88

8. Henderson D. Increased resistance to free radical damage induced by low-level sound conditioning. *Hear Res* 2006; 213: 118–129

9. Changes in cochlear antioxidant enzyme activity after sound conditioning and noise exposure in the chinchilla. *Hear Res* 1998; 117: 31–38

10. COX-2 expression in the guinea pig cochlea is partly altered by moderate sound exposure. *Neurosci Lett* 2006; 394: 121–126

11. Long-term sound conditioning enhances cochlear sensitivity. *J Neurophysiol* 1999; 82: 863–873

12. Protection against acoustic trauma by forward and backward sound conditioning. *Audiol Neurotol* 2004; 9: 265–273

13. Enriched Acoustic environment after noise trauma reduces hearing loss and prevents cortical map reorganization. *J Neurosci* 2005; 25: 699–705

Further Studies

1. Stimulus condition for maximum effect; 1) Sound conditioning period, 2) Stimulus type (FM, AM, sound level)
2. Effects on different types of patients; 1) Different causes (aging, noise, abrupt..), 2) dependency on hearing loss severity (mild, moderate, severe hearing loss)
3. Mechanism underlying the hearing improvement effect of sound conditioning

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Tinnitus Spectrum and Its Realtime Visualization based on 134 band Cochlear Model



The Abstracts of the Association for Research in Otolaryngology is published annually and consists of abstracts presented at the Annual MidWinter Research Meeting.
[ISSN-0742-3152]

Sangyeop Kwak^{1,2}, Seoyoung Kim², Yunjeong Bae², and Eunye Kwak^{1,3}

Introduction

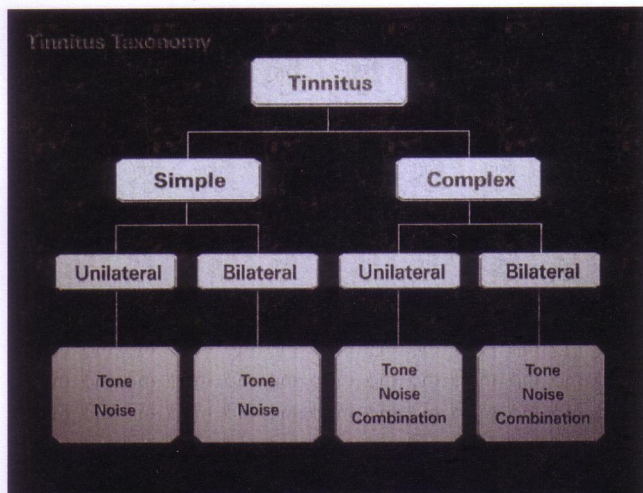
The existing method for matching tinnitus relies on the listening paradigm to a single pure tone or band pass filtered noise. There are many types of tinnitus spectrum in accordance with hearing loss regions; 1) single pure tone, 2) multiple pure tones (harmonic or non-harmonic complex tone), 3) single filtered noise, 4) multiple filtered noise, and 5) the combination of 1) ~ 4). In this respect, a new method has been designed to achieve accurate performance for finding various types of tinnitus spectrum.

This study suggests two inventions; 1) tinnitus taxonomy based on 10 types of tinnitus spectrum and 2) a method for visualization of tinnitus spectrum using 3D cochlear model with 134 bands (1/24 Oct) frequency resolution.

Methods

Acoustic properties of all types of tinnitus were classified in the 4 spectral categories; simple tone (pure tone), complex tone, noise, and a combination of tone and noise. Their spectra are named as follows.

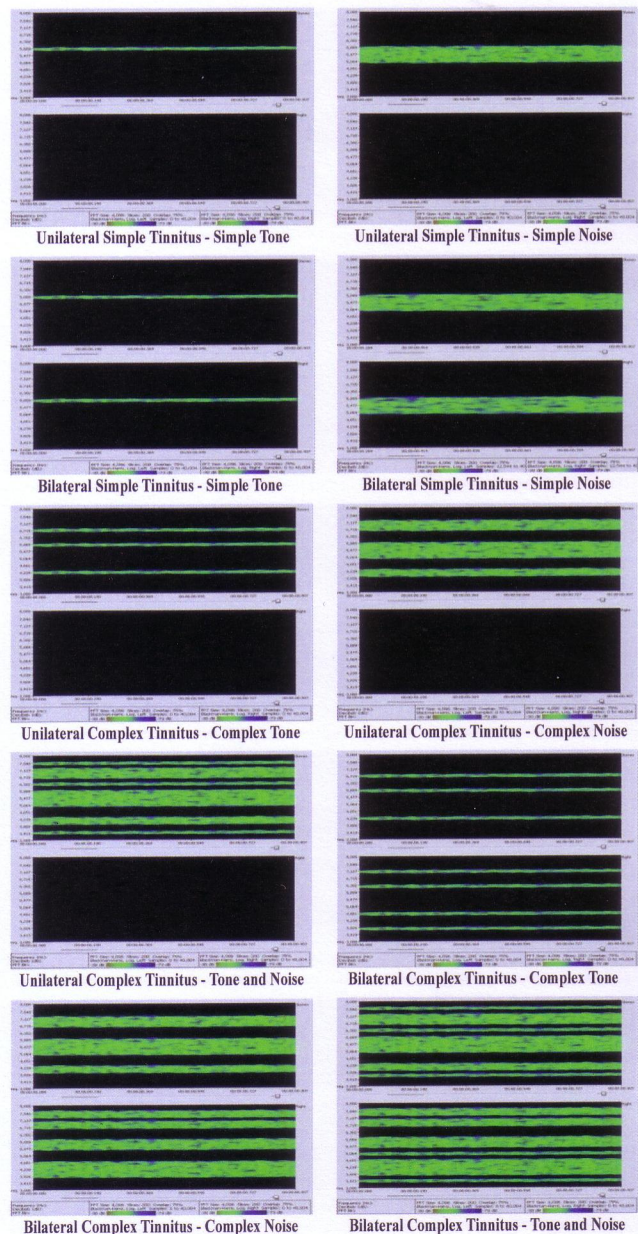
Tinnitus Taxonomy



Tinnitus Spectrum

- Unilateral Simple Tinnitus - Simple Tone
- Unilateral Simple Tinnitus - Simple Noise
- Bilateral Simple Tinnitus - Simple Tone
- Bilateral Simple Tinnitus - Simple Noise
- Unilateral Complex Tinnitus - Complex Tone

- Unilateral Complex Tinnitus - Complex Noise
- Unilateral Complex Tinnitus - Tone and Noise
- Bilateral Complex Tinnitus - Complex Tone
- Bilateral Complex Tinnitus - Complex Noise
- Bilateral Complex Tinnitus - Tone and Noise



Results

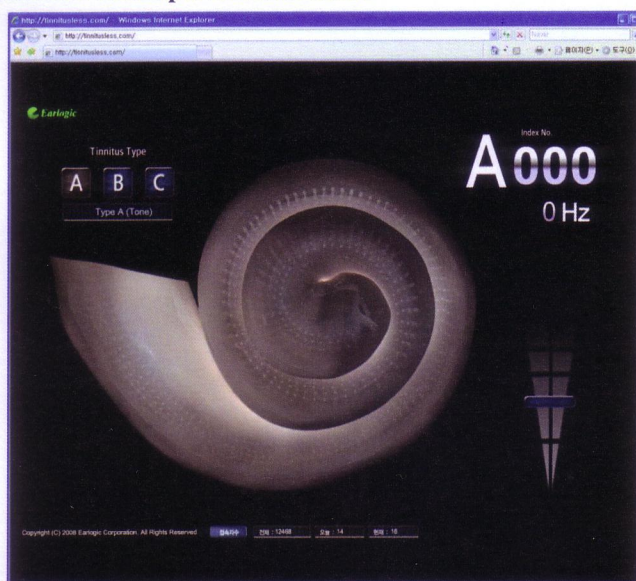
Simple Tinnitus Tester

Simple tinnitus tester was linked to the internet site, www.tinnitusless.com. Tinnitusless.com provides 402 simple tinnitus samples (134 tones, 134 noises, and 134 combinations of tone and noise).

Complex Tinnitus Tester

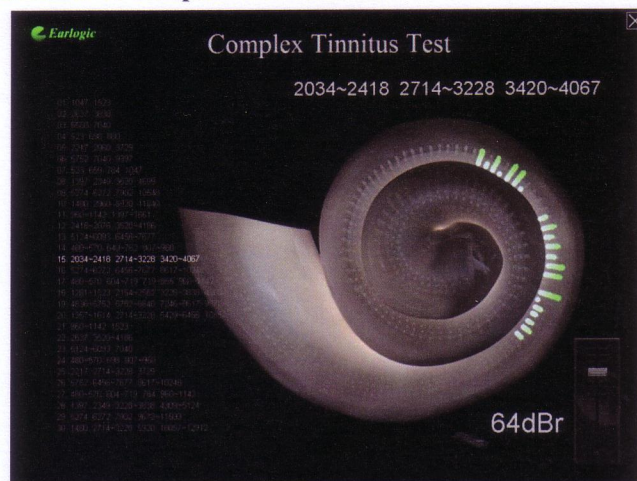
Complex tinnitus tester (Version 1.0) was designed to distribute as freeware application. It provides 30 complex tinnitus samples (10 tones, 10 noises, and 10 combinations of tone and noise).

Interface of Simple Tinnitus Tester



Simple tinnitus tester provides 3 types (A, B, C) of tinnitus sound. A is for pure tone, B is for 1 bark filtered noise, and C is for the combination of A and B. Each sample of tinnitus can be easily compared with real tinnitus of human.

Interface of Complex Tinnitus Tester



Complex tinnitus tester provides 30 different tinnitus spectra as tinnitus samples. No. 1~10 are non-harmonic complex tones, 11~20 are complex noises, and 21~30 are the combination of non-harmonic complex tones and noises.

Conclusion

3D cochlear graphic model in this study is designed based on the frequency resolution with 0.2 Bark (approx. 1/24 Oct.). It is useful for advanced tinnitus matching task with high frequency resolution. Tinnitus taxonomy proposed by this study is based on the acoustic spectrum of 10 types of physical sound.

Reference

<http://www.google.com/patents/US20110263926>

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Ameliorative Effect of Customized Sound Stimulation on Sensorineural Hearing Loss

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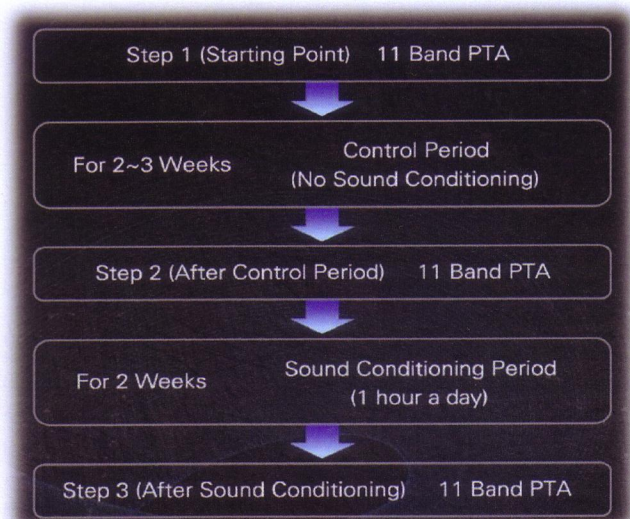
Introduction

Several studies have been reported that sound conditioning (i.e., prior exposure to low-level sounds) could protect hearing ability against damage by traumatic noise in a number of mammalian species, including humans.¹⁻³ Acoustic stimuli could also slow progressive sensorineural hearing loss. Thus, exposure to a moderately augmented acoustic environment could delay the loss of auditory function in mice.⁴⁻⁷

In addition to these protection and retardation effects, long-term sound conditioning could enhance cochlear sensitivity in normal hearing guinea pigs.⁸

Based on these results, we hypothesized that sound stimulation could also improve hearing ability in patients with sensorineural hearing loss.

Methods



To investigate if sound conditioning could improve hearing loss, we applied customized sound stimuli to 12 subjects with sensorineural hearing loss.

Customized sound stimuli consisted of frequency-modulated tone and amplitude-modulated narrow band noise. The frequency band of a customized sound stimulus was designed to cover mostly the frequency regions in which a subject showed deteriorated hearing ability. During the sound conditioning period, the subjects listened to the sound stimuli at a barely audible level.

To examine the effect of sound conditioning, Pure-tone

audiometry (PTA) hearing threshold changes were compared. To rule out the possibility of bias arising from test-retest variation, we repeated the behavioral hearing test (i.e., pure-tone audiometry) 2~4 times for each frequency at each step and adopted the average value as a hearing threshold of the corresponding frequency.

Controls of hearing threshold changes were obtained by subtracting step 2 (after control period) hearing threshold from step 1 (starting point) hearing threshold.

Ameliorative effects of sound conditioning were obtained by subtracting step 3 hearing threshold (after sound conditioning) from step 2 hearing threshold.

Results

1. Hearing Thresholds at Each Step

Hearing Thresholds at Starting Point (Step 1) (dBHL)													
		Subject (Age)											
		YH (63)	LGH (9)	HHB (51)	LSY (41)	JDS (59)	KDG (43)	KMS (66)	SIW (22)	BMS (28)	CDS (49)	JDG (77)	BJW (28)
Left Ear	250 Hz	12.5	32.5	7.5	47.5	40.0	50.8	50.0	2.5	10.0	0.0	60.0	72.5
	500 Hz	20.0	39.2	12.5	57.5	32.5	47.5	50.0	2.5	10.0	-2.5	42.5	72.5
	750 Hz	32.5	45.8	7.5	67.5	37.5	49.2	55.0	7.5	42.5	0.0	42.5	72.5
	1000 Hz	32.5	42.5	2.5	67.5	47.5	52.5	67.5	5.0	62.5	-2.5	52.5	67.5
	1500 Hz	37.5	47.5	2.5	62.5	65.0	55.8	62.5	2.5	67.5	7.5	47.5	67.5
	2000 Hz	52.5	54.2	9.2	67.5	75.0	62.5	67.5	12.5	65.0	12.5	55.0	67.5
	3000 Hz	62.5	57.5	15.8	72.5	87.5	67.5	82.5	32.5	75.0	25.0	67.5	62.5
	4000 Hz	90.0	60.8	24.2	75.8	100.0	57.5	107.5	40.0	77.5	22.5	80.0	50.0
	6000 Hz	98.8	47.5	12.5	59.2	92.5	40.8	92.5	62.5	57.5	17.5	75.0	15.0
	8000 Hz	87.5	40.8	9.2	45.8	90.0	25.8	90.0	52.5	52.5	12.5	75.0	22.5
12000 Hz	90.0	60.8	37.5	65.8	90.0	44.2	90.0	52.5	42.5	42.5	90.0	50.0	
Right Ear	250 Hz	17.5	32.5	9.2	47.5	25.0	47.5	10.0	2.5	12.5	-2.5	57.5	77.5
	500 Hz	22.5	37.5	12.5	67.5	32.5	47.5	5.0	2.5	35.0	2.5	47.5	77.5
	750 Hz	30.0	45.8	10.8	67.5	37.5	47.5	15.0	2.5	52.5	2.5	42.5	70.0
	1000 Hz	30.0	42.5	12.5	67.5	47.5	47.5	27.5	0.0	67.5	0.0	47.5	70.0
	1500 Hz	32.5	47.5	5.8	62.5	57.5	57.5	42.5	5.0	72.5	2.5	50.0	67.5
	2000 Hz	42.5	54.2	12.5	72.5	75.0	57.5	47.5	7.5	75.0	10.0	52.5	72.5
	3000 Hz	40.0	65.8	14.2	77.5	105.0	67.5	75.0	27.5	82.5	22.5	70.0	70.0
	4000 Hz	60.0	72.5	37.5	84.2	107.5	64.2	80.0	47.5	82.5	37.5	72.5	62.5
	6000 Hz	72.5	50.8	4.2	52.5	95.0	49.2	50.0	62.5	65.0	12.5	62.5	37.5
	8000 Hz	55.0	42.5	2.5	49.2	85.0	30.8	72.5	52.5	57.5	7.5	62.5	40.0
12000 Hz	88.8	62.5	45.8	74.2	73.8	45.8	90.0	52.5	57.5	50.0	90.0	67.5	

Hearing Thresholds after Control Period (Step 2) (dBHL)													
		Subject (Age)											
		YH (63)	LGH (9)	HHS (51)	LSY (41)	JDS (59)	KDG (43)	KMS (66)	SIW (22)	BMS (28)	CDS (49)	JDG (77)	BJW (28)
Left Ear	250 Hz	15.0	32.5	7.5	47.5	32.5	49.2	52.5	5.0	15.8	5.0	57.5	72.5
	500 Hz	22.5	37.5	12.5	57.5	40.0	44.2	47.5	5.0	20.8	-2.5	42.5	72.5
	750 Hz	27.5	45.0	7.5	67.5	42.5	47.5	57.5	5.0	49.2	-2.5	42.5	70.0
	1000 Hz	27.5	45.0	2.5	67.5	50.0	50.8	67.5	2.5	67.5	2.5	50.0	67.5
	1500 Hz	37.5	47.5	2.5	62.5	67.5	57.5	62.5	-2.5	65.8	5.0	47.5	67.5
	2000 Hz	52.5	57.5	7.5	67.5	72.5	62.5	67.5	12.5	72.5	10.0	55.0	67.5
	3000 Hz	57.5	65.0	20.0	72.5	92.5	64.2	80.0	27.5	79.2	27.5	67.5	62.5
	4000 Hz	87.5	65.0	27.5	80.0	97.5	59.2	107.5	37.5	70.8	30.0	82.5	47.5
	6000 Hz	100.0	55.0	12.5	52.5	95.0	37.5	97.5	67.5	59.2	15.0	75.0	20.0
	8000 Hz	87.5	37.5	12.5	47.5	90.0	22.5	90.0	55.0	60.8	10.0	72.5	15.0
12000 Hz	90.0	65.0	37.5	62.5	90.0	42.5	90.0	57.5	57.5	50.0	90.0	52.5	
Right Ear	250 Hz	17.5	30.0	7.5	47.5	37.5	40.8	10.0	5.0	12.5	0.0	57.5	77.5
	500 Hz	20.0	37.5	10.0	67.5	37.5	47.5	7.5	2.5	32.5	2.5	47.5	77.5
	750 Hz	27.5	45.0	10.0	67.5	42.5	45.8	12.5	7.5	50.8	0.0	42.5	72.5
	1000 Hz	27.5	42.5	12.5	67.5	52.5	42.5	27.5	2.5	67.5	2.5	50.0	67.5
	1500 Hz	35.0	47.5	5.0	62.5	57.5	55.8	45.0	7.5	77.5	2.5	60.0	67.5
	2000 Hz	47.5	57.5	12.5	72.5	75.0	57.5	47.5	7.5	77.5	12.5	67.5	67.5
	3000 Hz	42.5	60.0	15.0	77.5	102.5	59.2	72.5	22.5	77.5	22.5	82.5	65.0
	4000 Hz	60.0	67.5	50.0	80.0	107.5	62.5	75.0	42.5	75.8	42.5	70.0	62.5
	6000 Hz	70.0	52.5	2.5	52.5	97.5	49.2	52.5	60.0	67.5	12.5	60.0	37.5
	8000 Hz	55.0	37.5	2.5	47.5	90.0	30.8	72.5	57.5	70.8	27.5	57.5	37.5
12000 Hz	82.5	60.0	47.5	75.0	88.8	42.5	90.0	52.5	55.8	60.0	87.5	67.5	

Hearing Thresholds after Sound Conditioning (Step 3) (dBHL)												
	Subject (Age)											
	YH (63)	LGH (9)	HHS (51)	LSY (41)	JDS (59)	KDG (43)	KMS (66)	SNW (22)	BMS (28)	CDS (49)	JDG (77)	BNW (28)
Left Ear	250 Hz	10.0	27.5	7.5	47.5	32.5	47.5	52.5	-2.5	12.5	5.0	57.5
	500 Hz	15.0	37.5	12.5	57.5	40.0	45.0	50.0	2.5	14.2	5.0	42.5
	750 Hz	25.0	45.0	7.5	67.5	45.0	52.5	47.5	0.0	44.2	0.0	42.5
	1000 Hz	27.5	47.5	2.5	67.5	52.5	52.5	62.5	-2.5	62.5	0.0	47.5
	1500 Hz	37.5	47.5	0.0	62.5	70.0	57.5	57.5	-2.5	65.8	7.5	47.5
	2000 Hz	47.5	57.5	7.5	67.5	77.5	62.5	62.5	7.5	72.5	12.5	55.0
	3000 Hz	55.0	67.5	22.5	75.0	87.5	67.5	80.0	22.5	84.2	32.5	65.0
	4000 Hz	92.5	57.5	22.5	75.0	102.5	57.5	105.0	22.5	75.8	30.0	82.5
	6000 Hz	100.0	50.0	10.0	52.5	90.0	45.0	98.8	45.0	59.2	22.5	72.5
	8000 Hz	88.8	37.5	12.5	47.5	90.0	25.0	90.0	42.5	45.8	10.0	72.5
	10000 Hz	90.0	60.0	42.5	67.5	90.0	42.5	90.0	30.0	49.2	57.5	90.0
	12000 Hz	22.5	30.0	10.0	50.0	37.5	47.5	10.0	-2.5	12.5	10.0	57.5
Right Ear	250 Hz	27.5	37.5	15.0	67.5	40.0	47.5	7.5	-2.5	37.5	2.5	52.5
	500 Hz	35.0	42.5	10.0	72.5	42.5	47.5	10.0	0.0	52.5	5.0	42.5
	750 Hz	35.0	42.5	15.0	67.5	47.5	47.5	25.0	-2.5	65.8	2.5	47.5
	1000 Hz	32.5	47.5	7.5	62.5	55.0	57.5	42.5	2.5	70.8	7.5	60.0
	1500 Hz	37.5	62.5	17.5	72.5	77.5	55.0	45.0	2.5	69.2	15.0	67.5
	2000 Hz	37.5	65.0	22.5	77.5	107.5	67.5	70.0	12.5	89.2	27.5	72.5
	3000 Hz	50.0	65.0	37.5	95.0	107.5	67.5	72.5	35.0	79.2	37.5	65.0
	4000 Hz	72.5	50.0	2.5	52.5	97.5	50.0	60.0	55.8	17.5	60.0	37.5
	6000 Hz	45.0	40.0	17.5	47.5	88.8	32.5	65.0	52.5	55.8	15.0	57.5
	8000 Hz	88.8	57.5	47.5	72.5	90.0	37.5	90.0	45.0	57.5	75.0	67.5
	10000 Hz	22.5	30.0	10.0	50.0	37.5	47.5	10.0	-2.5	12.5	10.0	57.5
	12000 Hz	27.5	37.5	15.0	67.5	40.0	47.5	7.5	-2.5	37.5	2.5	52.5

We repeated the behavioral hearing test (i.e., pure-tone audiometry) 2~4 times for each frequency at each step and adopted the average value as a hearing threshold of the corresponding frequency.

2. Hearing Threshold Changes

Hearing Changes after Control Period (dB) = Step 1 Threshold - Step 2 Threshold												
	Subject (Age)											
	YH (63)	LGH (9)	HHS (51)	LSY (41)	JDS (59)	KDG (43)	KMS (66)	SNW (22)	BMS (28)	CDS (49)	JDG (77)	BNW (28)
Left Ear	250 Hz	-2.5	0.0	0.0	0.0	7.5	1.7	-2.5	-2.5	-5.8	-5.0	2.5
	500 Hz	-2.5	1.7	0.0	0.0	-7.5	3.3	2.5	-2.5	-10.8	0.0	0.0
	750 Hz	5.0	0.8	0.0	0.0	-5.0	1.7	-2.5	2.5	-6.7	2.5	0.0
	1000 Hz	5.0	-2.5	0.0	0.0	-2.5	1.7	0.0	2.5	-5.0	-5.0	2.5
	1500 Hz	0.0	0.0	0.0	0.0	-2.5	-1.7	0.0	5.0	1.7	2.5	0.0
	2000 Hz	0.0	-3.3	1.7	0.0	2.5	0.0	0.0	0.0	-7.5	2.5	0.0
	3000 Hz	5.0	-7.5	-4.2	0.0	-5.0	3.3	2.5	5.0	-4.2	-2.5	0.0
	4000 Hz	2.5	-4.2	-3.3	-4.2	2.5	-1.7	0.0	2.5	6.7	-7.5	-2.5
	6000 Hz	-1.3	-7.5	0.0	6.7	-2.5	3.3	-5.0	-5.0	-1.7	2.5	0.0
	8000 Hz	0.0	3.3	-3.3	-1.7	0.0	3.3	0.0	-2.5	-8.3	2.5	7.5
	10000 Hz	0.0	-4.2	0.0	3.3	0.0	1.7	0.0	-5.0	-15.0	-7.5	0.0
	12000 Hz	0.0	2.5	1.7	0.0	-12.5	6.7	0.0	-2.5	0.0	-2.5	0.0
Right Ear	250 Hz	2.5	0.0	2.5	0.0	-5.0	0.0	-2.5	0.0	2.5	0.0	0.0
	500 Hz	2.5	0.8	0.0	0.0	-5.0	1.7	2.5	-5.0	1.7	2.5	0.0
	750 Hz	2.5	0.0	0.0	0.0	-5.0	5.0	0.0	-2.5	0.0	-2.5	2.5
	1000 Hz	2.5	0.0	0.0	0.0	-5.0	5.0	0.0	-2.5	0.0	-2.5	2.5
	1500 Hz	-2.5	0.0	0.0	0.0	-1.7	-2.5	-2.5	-5.0	0.0	-10.0	0.0
	2000 Hz	-5.0	-3.3	0.0	0.0	0.0	0.0	0.0	0.0	-2.5	-2.5	-15.0
	3000 Hz	-2.5	5.8	-0.8	0.0	2.5	8.3	2.5	5.0	5.0	0.0	-12.5
	4000 Hz	0.0	5.0	-12.5	4.2	0.0	1.7	5.0	5.0	6.7	-5.0	2.5
	6000 Hz	2.5	-1.7	1.7	0.0	-2.5	0.0	-2.5	2.5	-2.5	0.0	2.5
	8000 Hz	0.0	5.0	0.0	1.7	-5.0	0.0	-5.0	-5.0	-13.3	-30.0	5.0
	10000 Hz	6.3	2.5	-1.7	-0.8	-15.0	3.3	0.0	0.0	1.7	-10.0	2.5
	12000 Hz	0.0	2.5	1.7	0.0	-12.5	6.7	0.0	-2.5	0.0	-2.5	0.0

Hearing Changes after Sound Conditioning (dB) = Step 2 Threshold - Step 3 Threshold												
	Subject (Age)											
	YH (63)	LGH (9)	HHS (51)	LSY (41)	JDS (59)	KDG (43)	KMS (66)	SNW (22)	BMS (28)	CDS (49)	JDG (77)	BNW (28)
Left Ear	250 Hz	5.0	5.0	0.0	0.0	1.7	0.0	7.5	3.3	0.0	0.0	0.0
	500 Hz	7.5	0.0	0.0	0.0	0.0	-0.8	-2.5	2.5	6.7	-7.5	0.0
	750 Hz	2.5	0.0	0.0	0.0	-2.5	-6.0	10.0	5.0	5.0	-2.5	0.0
	1000 Hz	0.0	-2.5	0.0	0.0	-2.5	-1.7	5.0	5.0	5.0	2.5	0.0
	1500 Hz	0.0	0.0	0.0	0.0	-2.5	0.0	5.0	0.0	0.0	-2.5	0.0
	2000 Hz	5.0	0.0	0.0	0.0	-5.0	0.0	5.0	0.0	-2.5	0.0	0.0
	3000 Hz	2.5	-2.5	-2.5	-2.5	5.0	-3.3	0.0	5.0	-5.0	0.0	2.5
	4000 Hz	-5.0	7.5	5.0	5.0	-5.0	1.7	2.5	15.0	-5.0	0.0	0.0
	6000 Hz	0.0	5.0	2.5	0.0	5.0	-7.5	-1.3	22.5	0.0	-7.5	2.5
	8000 Hz	-1.3	0.0	0.0	0.0	-2.5	0.0	12.5	15.0	0.0	0.0	0.0
	10000 Hz	0.0	5.0	-5.0	-5.0	0.0	0.0	27.5	8.3	-7.5	0.0	2.5
	12000 Hz	-5.0	0.0	-2.5	-2.5	0.0	-6.7	0.0	7.5	0.0	-10.0	0.0
Right Ear	250 Hz	-7.5	0.0	-5.0	0.0	-2.5	0.0	5.0	-5.0	0.0	-5.0	0.0
	500 Hz	-7.5	2.5	0.0	-5.0	0.0	-1.7	2.5	7.5	-1.7	-5.0	0.0
	750 Hz	-7.5	0.0	-5.0	0.0	-1.7	2.5	7.5	7.5	-1.7	-5.0	0.0
	1000 Hz	-7.5	0.0	-2.5	0.0	5.0	-6.0	2.5	5.0	1.7	0.0	2.5
	1500 Hz	2.5	0.0	-2.5	0.0	2.5	-1.7	2.5	5.0	6.7	-5.0	0.0
	2000 Hz	10.0	-5.0	-5.0	0.0	-2.5	2.5	2.5	5.0	8.3	-2.5	0.0
	3000 Hz	5.0	-5.0	-7.5	0.0	-5.0	-6.3	2.5	10.0	-11.7	-5.0	-2.5
	4000 Hz	10.0	2.5	12.5	-15.0	0.0	-5.0	2.5	7.5	-3.3	5.0	5.0
	6000 Hz	-2.5	2.5	0.0	0.0	0.0	-0.8	-7.5	10.0	1.7	-5.0	0.0
	8000 Hz	10.0	-2.5	-15.0	0.0	1.3	-1.7	12.5	5.0	15.0	12.5	0.0
	10000 Hz	-6.3	2.5	0.0	2.5	-1.3	5.0	0.0	7.5	-1.7	2.5	12.5
	12000 Hz	0.0	2.5	1.7	0.0	-12.5	6.7	0.0	-2.5	0.0	-2.5	0.0

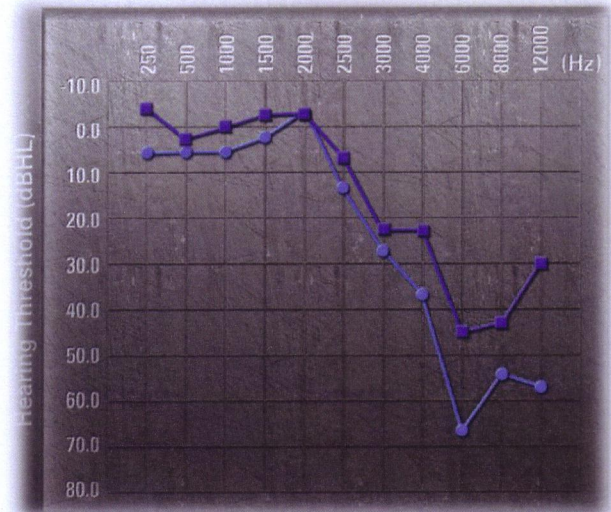
Hearing Improvement & Hearing Decline				
Hearing Improvement (HI)	Number of Subject*		Number of Samples**	
	Control	Sound Conditioning	Control	Sound Conditioning
10 dB ≤ HI < 20 dB	0	7	0	14
20 dB ≤ HI	0	1	0	2
Hearing Decline (HD)	Number of Subjects*		Number of Samples**	
	Control	Sound Conditioning	Control	Sound Conditioning
10 dB ≤ HD < 20 dB	5	4	10	4
20 dB ≤ HD	1	0	1	0

* Number of subjects who showed the corresponding amount of hearing changes at least one frequency region.

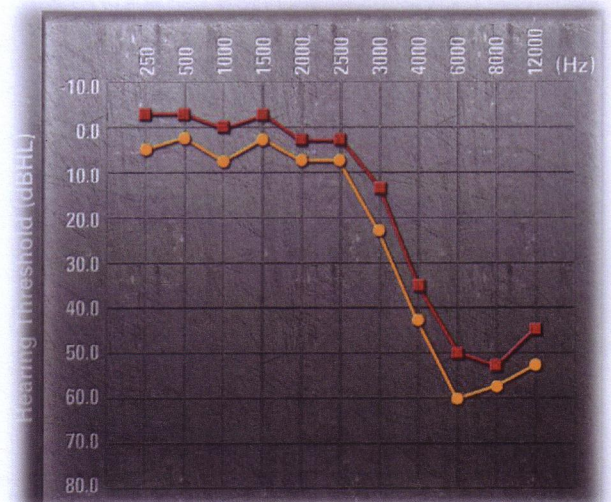
** Each frequency of each subject was considered as an individual sample.

3. Examples of Audiogram: Before and After Sound Conditioning (i.e., step 2 & 3)

ID: SJW (left ear)



ID: SJW (right ear)

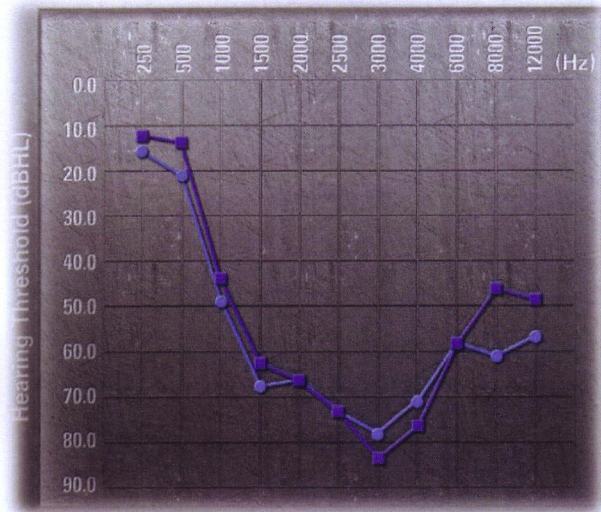


¹Earlogic Corporation, Los Angeles, CA, U.S.A.

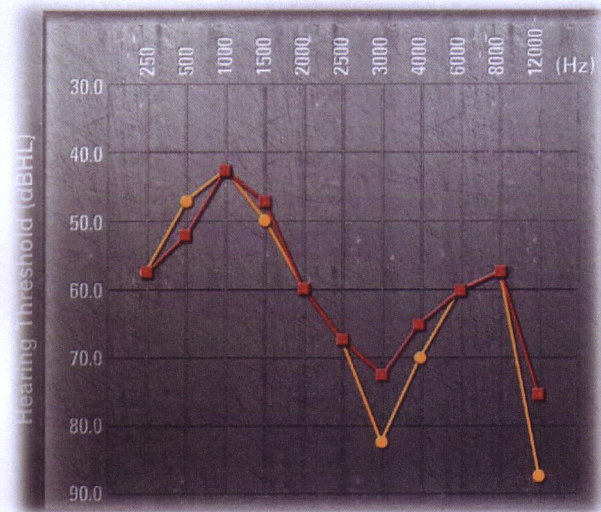
²Earlogic Clinic, Seoul, Korea

³Earlogic Auditory Research Institute, Seoul, Korea

ID: BMS (left ear)



ID: JDG (right ear)



Conclusion

1. Customized sound conditioning showed ameliorative effect on sensorineural hearing loss.
2. Hearing improvement at least one frequency region was observed in 7 subjects out of 12 subjects.
3. Customized sound conditioning may reduce hearing declining.

Interface of Customized Sound Stimulus Generator



References

1. Protection against noise trauma by pre-exposure to a low level acoustic stimulus. *Hear Res* 1988; 34: 197–200
2. Effect of low level acoustic stimulation on temporary threshold shift in young humans. *Hear Res* 1992; 60: 149–155
3. Protecting against noise trauma by sound conditioning. *Journal of Sound and Vibration* 2002; 250: 115–118
4. Exposure to an augmented acoustic environment alters auditory function in hearing-impaired DBA/2J mice. *Hear Res* 1998; 118: 101–113
5. Prolonged exposure to an augmented acoustic environment ameliorates age-related auditory changes in C57BL/6J and DBA/2J mice. *Hear Res* 1999; 78–88
6. Effects of prolonged exposure to an augmented acoustic environment on the auditory system of middle-aged C57BL/6J mice: cochlear and central histology and sex differences. *J Comp Neurol* 2004; 472: 358–370
7. Effects of exposure to an augmented acoustic environment on auditory function in mice: roles of hearing loss and age during treatment. *Hear Res* 2000; 142: 79–88
8. Long-term sound conditioning enhances cochlear sensitivity. *J Neurophysiol* 1999; 82: 863–873

Customized Sound Stimulation Improves Pure-Tone Hearing Threshold

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Introduction

Several studies have been reported that sound conditioning (i.e., prior exposure to low-level sounds) could protect hearing ability against damage by traumatic noise in a number of mammalian species, including humans.¹⁻³

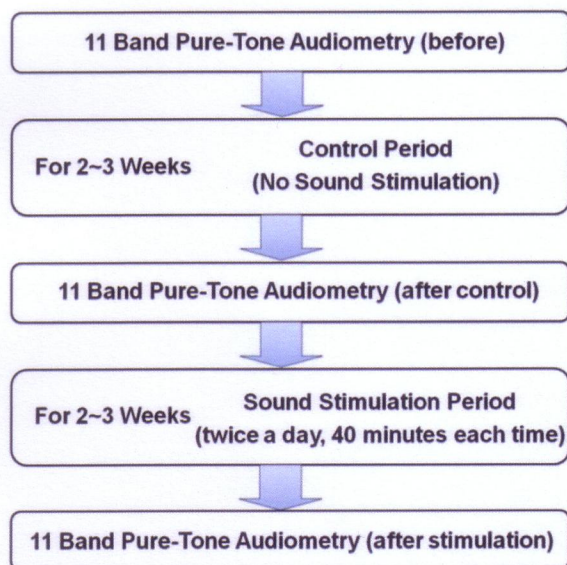
The hearing protective effect was shown even when the sound stimulation was provided after noise trauma.⁴⁻⁵ Acoustic stimuli could also slow progressive sensorineural hearing loss. Thus, exposure to a moderately augmented acoustic environment delayed the loss of auditory function.⁶⁻⁹ In addition to these protection and retardation effects, long-term sound conditioning enhanced cochlear sensitivity in normal hearing guinea pigs.¹⁰

Based on these results, we hypothesized that sound stimulation could improve hearing ability in people with sensorineural hearing loss.

Methods

To investigate if sound stimulation could improve pure-tone hearing threshold, we applied customized sound stimulation to 17 participants with sensorineural hearing loss.

Study Protocol



One or two frequencies between 2~8 kHz at which a participant showed the worst hearing ability were determined

as a target frequency. Customized sound stimulus consisted of frequency-modulated tone and amplitude-modulated narrow band noise. The frequency range of a sound stimulus was 1/3 octave and centered at a target frequency. During the sound conditioning period, participants listened to the sound stimuli with one ear (target ear) at a minimum audible level.

To examine the effect of sound stimulation, pure-tone hearing thresholds before, after control period, and after sound stimulation period were compared. The hearing test (pure-tone audiometry) was conducted 3 times for each frequency at each step. In the case that a participant had two target frequencies, the averaged hearing threshold of the two frequencies was used for data analysis.

Target ears, target frequencies, and demographic aspects of participants

Participant	Age (years)	Sex	Target ear ^a	Target frequency ^b
1	53	M	Left	4 kHz
2	41	F	Left	4 kHz
3	34	F	Left	4 kHz
4	29	M	Right	6 kHz
5	56	M	Right	3 and 4 kHz
6	52	F	Right	4 kHz
7	33	F	Left	4 kHz
8	29	M	Left	4 kHz
9	52	M	Right	3 and 4 kHz
10	60	F	Right	4 kHz
11	22	M	Right	3 and 4 kHz
12	25	M	Right	3 and 4 kHz
13	44	M	Left	4 kHz
14	49	F	Right	4 kHz
15	43	F	Right	4 kHz
16	46	M	Left	4 kHz
17	57	F	Right	4 kHz

F, female; M, male

a Ear stimulated with customized sound.

b Center frequency of sound stimulation region

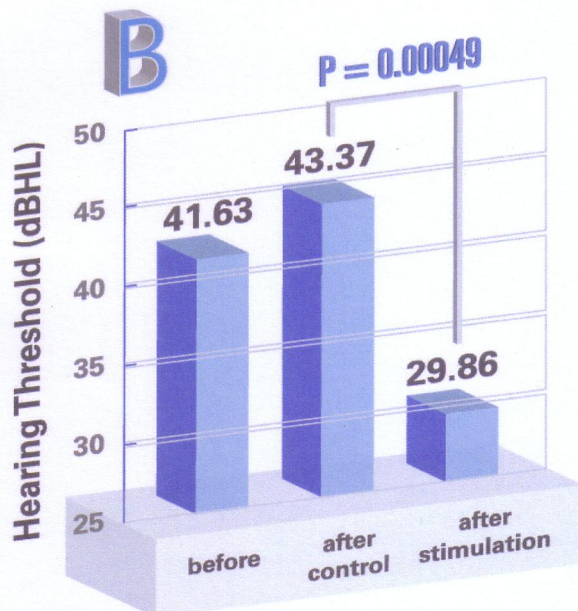
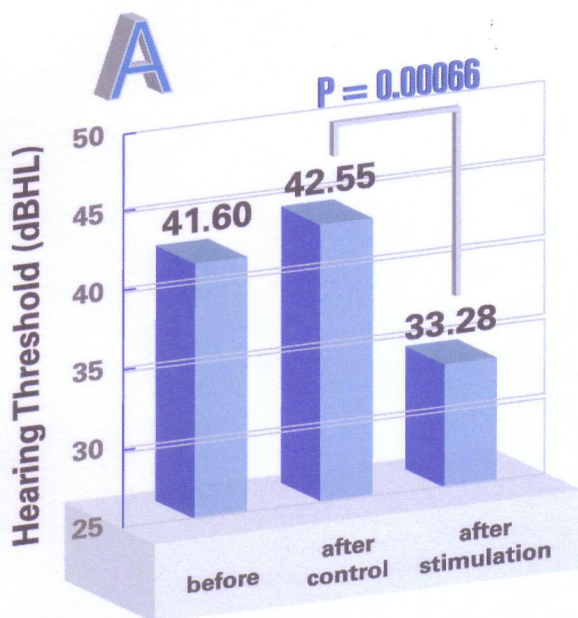
Results

More than 6 dB of hearing threshold decreases were observed in 12 Participants' target ears after sound stimulation period. The hearing threshold decrease was more dominant at the target ears than the opposite ears.

Decrease of pure-tone hearing threshold at target frequency

Amount of Threshold Decrease (D)	Number of Participants			
	After Control Period		After Sound Stimulation Period	
	Target ear	Opposite ear	Target ear	Opposite ear
18 dB < D	0	0	2	0
12 dB < D ≤ 18 dB	0	0	2	1
6 dB < D ≤ 12 dB	0	1	8	2
D ≤ 6 dB	17	16	5	14
Total	17	17	17	17

Change of averaged pure-tone hearing threshold



Averaged hearing thresholds at target frequency of target ear before, after control period, and after sound stimulation period. A. Averaged hearing thresholds of all participants. B. Averaged hearing thresholds of 12 participants who showed more than 6 dB of hearing threshold decrease. Wilcoxon's signed rank test was used to test the differences in hearing thresholds.

Conclusion

1. Customized sound stimulation decreased pure-tone hearing threshold.
2. More than 6 dB of hearing threshold decrease was observed in 12 participants' target ears after the sound stimulation period.
3. After the sound stimulation period, the average of hearing threshold decrease of the 12 participants was 13.51 dB ($P=0.00049$).

Reference

1. Protection against noise trauma by pre-exposure to a low level acoustic stimulus. *Hear Res* 1988; 34: 197–200
2. Effect of low level acoustic stimulation on temporary threshold shift in young humans. *Hear Res* 1992; 60: 149–155
3. Protecting against noise trauma by sound conditioning. *Journal of Sound and Vibration* 2002; 250: 115–118
4. Enriched Acoustic Environment after Noise Trauma Reduces Hearing Loss and Prevents Cortical Map Reorganization. *J Neurosci* 2005; 25: 699–705
5. The effects of acoustic environment after traumatic noise exposure on hearing and outer hair cells. *Hear Res* 2009; 250: 10–18
6. Exposure to an augmented acoustic environment alters auditory function in hearing-impaired DBA/2J mice. *Hear Res* 1998; 118: 101–113
7. Prolonged exposure to an augmented acoustic environment ameliorates age-related auditory changes in C57BL/6J and DBA/2J mice. *Hear Res* 1999; 78–88
8. Effects of exposure to an augmented acoustic environment on auditory function in mice: roles of hearing loss and age during treatment. *Hear Res* 2000; 142: 79–88
9. Ameliorative effects of an augmented acoustic environment on age-related hearing Loss in middle-aged Fischer 344/NHsd rats. *Laryngoscope* 2009; 119: 1374–1379
10. Long-term sound conditioning enhances cochlear sensitivity. *J Neurophysiol* 1999; 82: 863–873

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Ameliorative Effect of 1/3 Octave Sound Stimulation on Pure-Tone Hearing Thresholds in the People with Sensorineural Hearing Loss

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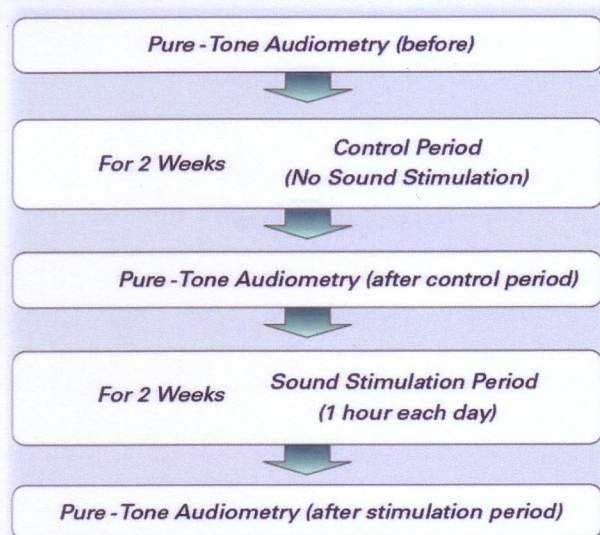


The Abstracts of the Association for Research in Otolaryngology is published annually and consists of abstracts presented at the Annual MidWinter Research Meeting.
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Abstract

Sound stimulation using a non-traumatic, moderate-level acoustic signal is a well-known method to protect from age-related or noise-induced hearing loss in animals. Several studies reported that sound stimulation can delay hearing loss in DBA/2J and C57BL/6J mice and Fischer 344/NHsd rats, which exhibit progressive sensorineural hearing loss. Pre-sound stimulation (i.e., exposure to a non-traumatic level sound before traumatic noise exposure) reduces noise-induced hearing loss. This protective effect of the sound stimulation has been observed in a number of different species including humans. Post-sound stimulation (i.e., exposure to a non-traumatic level sound after traumatic noise exposure) was also reported to reduce noise-induced hearing loss in animals. In this study, we investigated the effect of sound stimulation on sensorineural hearing loss in 22 participants who had various types of audiogram. Pure-tone hearing threshold changes with or without 2 weeks of sound stimulation were compared. Of 22 participants, 14 participants showed a ≥ 10 of hearing threshold decrease at least at one frequency. Two participants showed a ≥ 10 of hearing threshold decrease at 5 frequencies. Totally, 26 samples showed a ≥ 10 of hearing threshold decrease after the sound stimulation period.

Method



Results

Table 1. Demographic aspects of participants, listening ears, center frequencies, pure-tone hearing thresholds before sound stimulation

Participant	Age (years)	Sex	Listening ear ^a	Center Frequency ^b	Hearing Thresholds (dB HL) 0.5, 1, 1.5, 2, 3, 4, 6, 8 (kHz)
1	50	F	Right	3 kHz	(L) 20, 30, 35, 40, 50, 55, 45, 35 (R) 25, 35, 55, 70, 60, 55, 60, 50
2	57	M	Left	4 kHz	(L) 10, 15, 15, 15, 15, 35, 35, 35 (R) 15, 10, 10, 10, 10, 10, 30, 15
3	30	M	Right	6 kHz	(L) 20, 20, 20, 20, 20, 25, 30, 25 (R) 15, 15, 15, 15, 25, 40, 65, 60
4	60	M	Left	6 kHz	(L) 10, 10, 10, 10, 25, 30, 65, 45 (R) 10, 10, 10, 30, 30, 50, 35
5	23	M	Left	6 kHz	(L) 10, 10, 10, 10, 10, 15, 50, 55 (R) 10, 10, 10, 10, 10, 10, 15, 30
6	28	F	Right	3 kHz	(L) 30, 50, 60, 65, 75, 75, 90, 85 (R) 30, 50, 65, 60, 65, 70, 90, 95
7	28	M	Right	4 kHz	(L) 10, 10, 15, 10, 10, 20, 75, 70 (R) 10, 10, 15, 10, 15, 45, 80, 80
8	25	F	Right	6 kHz	(L) 10, 10, 10, 10, 5, 10, 15, 15 (R) 5, 5, 5, 5, 5, 10, 25, 20
9	24	M	Left	4 kHz	(L) 10, 15, 25, 15, 20, 45, 55, 50 (R) 10, 15, 15, 10, 10, 25, 95, 90
10	41	M	Right	3 kHz	(L) 15, 10, 10, 15, 15, 15, 15, 15 (R) 15, 15, 15, 15, 55, 55, 55, 45
11	49	M	Right	6 kHz	(L) 40, 40, 35, 40, 35, 40, 85, 95 (R) 30, 30, 20, 25, 25, 30, 45, 75
12	39	M	Right	4 kHz	(L) 10, 15, 10, 10, 20, 55, 55, 30 (R) 10, 15, 15, 10, 10, 65, 75, 80
13	52	F	Right	6 kHz	(L) 15, 10, 20, 10, 15, 15, 20, 25 (R) 35, 30, 30, 20, 25, 35, 40, 35
14	44	F	Right	6 kHz	(L) 45, 55, 55, 55, 55, 50, 60, 60 (R) 45, 55, 55, 60, 55, 50, 65, 60
15	25	M	Right	4 kHz	(L) 10, 10, 10, 10, 10, 75, 65, 25 (R) 10, 10, 10, 10, 10, 60, 55, 40
16	46	M	Left	6 kHz	(L) 25, 15, 20, 20, 30, 30, 40, 40 (R) 25, 15, 15, 10, 20, 20, 25, 25
17	42	M	Left	3 kHz	(L) 25, 25, 20, 15, 55, 75, 80, 70 (R) 20, 20, 20, 30, 85, 100, 95
18	38	M	Left	6 kHz	(L) 35, 30, 35, 35, 40, 45, 60, 75 (R) 40, 45, 40, 45, 35, 40, 55, 90
19	48	M	Right	6 kHz	(L) 45, 30, 30, 40, 45, 50, 60, 55 (R) 40, 30, 30, 40, 35, 40, 50, 60
20	28	M	Left	3 kHz	(L) 15, 25, 25, 30, 70, 65, 70, 50 (R) 10, 20, 25, 15, 20, 15, 25, 15
21	41	M	Right	3 kHz	(L) 15, 30, 25, 20, 65, 60, 75, 70 (R) 15, 15, 30, 50, 60, 75, 75, 65
22	28	M	Left	8 kHz	(L) 15, 15, 15, 15, 15, 15, 20, 25 (R) 15, 10, 20, 15, 15, 15, 25, 20

F, female; M, male

a. Ear that was stimulated with the acoustic stimulus.

b. Center frequency of the 1/3 octave acoustic signal for sound stimulation.

Table 2. Participants with clinically significant threshold decreases after sound stimulation

Frequency	Participants with clinically Significant TD (n)	
	Left ear	Right ear
0.5 kHz	0	0
1 kHz	0	0
1.5 kHz	0	0
2 kHz	2	1
3 kHz	2	3
4 kHz	2	3
6 kHz	3	2
8 kHz	2	6

TD: Threshold decrease

Clinically significant: 10dB or more

Table 3. Participants with clinically significant threshold decreases after sound stimulation: details

Participant	Listening ear	TD frequency	
		Left ear	Right ear
1	Right		2 kHz
4	Left		3 kHz
5	Left		8 kHz
6	Right		6 kHz
8	Right		6 kHz
9	Left		8 kHz
11	Right	2 kHz	
		3 kHz	
		6 kHz	
		8 kHz	8 kHz
12	Right		8 kHz
13	Right		4 kHz
16	Left	6 kHz	
			8 kHz
17	Left	4 kHz	
		6 kHz	
18	Left	2 kHz	
		3 kHz	
		4 kHz	4 kHz
			8 kHz
20	Left		3 kHz
22	Left	8 kHz	

TD: Threshold decrease

Figure 1. Change of averaged pure-tone hearing threshold

Average hearing thresholds of the 26 frequencies that showed threshold decrease of 10 dB or more after the sound stimulation.; * $P < 0.0001$.

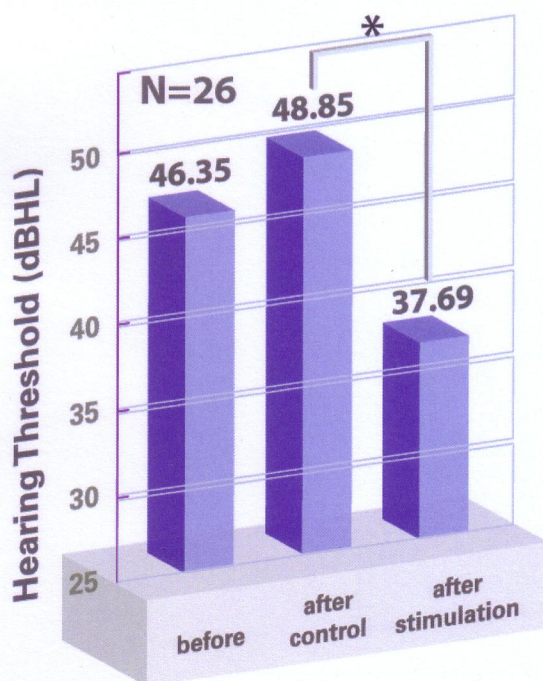
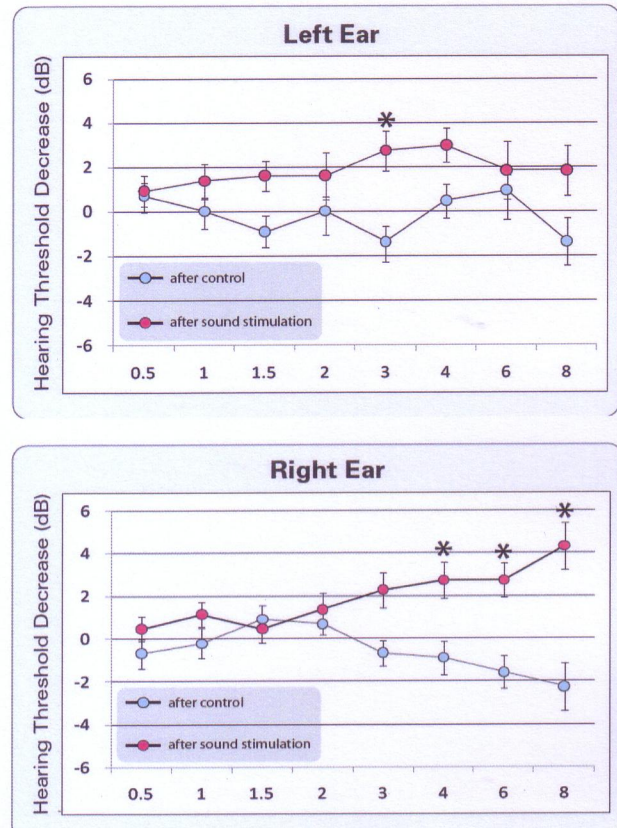


Figure 2. Average hearing threshold decrease at each frequency

Average hearing threshold decrease at each frequency ($\pm$ SEM). Each value was obtained from all 22 participants' data; * $P < 0.05$.



Conclusion

1. Sound stimulation decreased pure-tone hearing thresholds.
2. Fourteen out of 22 participants (63.6 %) had at least a single frequency threshold decrease of 10 dB or more.
3. Totally, 26 frequencies showed threshold decrease of 10 dB or more.
4. A significant, 11.16 dB of hearing threshold decrease was observed after the sound stimulation in the 26 frequencies.

References

- [1] Willott JF, Turner JG (1999) Prolonged exposure to an augmented acoustic environment ameliorates age-related auditory changes in C57BL/6J and DBA/2J mice. *Hear Res* 135: 78-88.
- [2] Tanaka C, Bielefeld EC, Chen GD, Li M, Henderson D (2009) Ameliorative effects of an augmented acoustic environment on age-related hearing loss in middle-aged Fischer 344/NHsd rats. *Laryngoscope* 119: 1374-1379.
- [3] Canlon B, Borg E, Flock A (1988) Protection against noise trauma by pre-exposure to a low level acoustic stimulus. *Hear Res* 34: 197-200.

- [4] Miyakita T, Hellström PA, Frimanson E, Axelsson A (1992) Effect of low level acoustic stimulation on temporary threshold shift in young humans. *Hear Res* 60: 149-155.
- [5] Noreña AJ, Eggermont JJ (2005) Enriched acoustic environment after noise trauma reduces hearing loss and prevents cortical map reorganization. *J Neurosci* 25: 699-705.
- [6] Niu X, Tahera Y, Canlon B (2004) Protection against acoustic trauma by forward and backward sound conditioning. *Audiology and Neurotology* 9: 265-273.
- [7] Tanaka C, Chen GD, Hu BH, Chi LH, Li M, et al. (2009) The effects of acoustic environment after traumatic noise exposure on hearing and outer hair cells. *Hear Res* 250: 10-18.
- [8] Noreña AJ, Chery-Croze S (2007) Enriched acoustic environment rescales auditory sensitivity. *Neuroreport* 18: 1251-1255.
- [9] Kujawa SG, Liberman MC (1999) Long-term sound conditioning enhances cochlear sensitivity. *J Neurophysiol* 82: 863-873.
- [10] Engineer ND, Percaccio CR, Pandya PK, Moucha R, Rathbun DL, et al. (2004) Environmental Enrichment Improves Response Strength, Threshold, Selectivity, and Latency of Auditory Cortex Neurons. *J Neurophysiol* 92: 73-82.

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Effect of Threshold Sound Conditioning on Pure-Tone Hearing Thresholds in Human Subjects with Sensorineural Hearing Loss

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Abstract

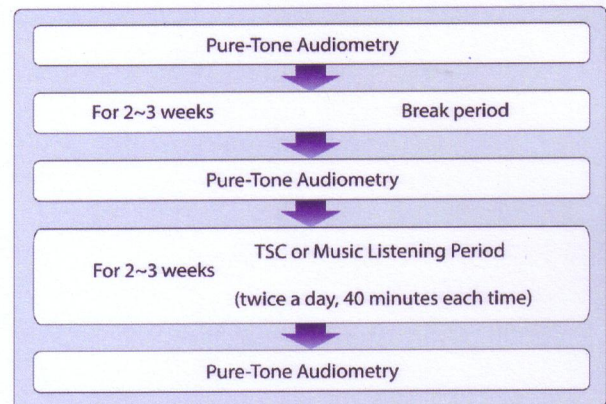
Sensorineural hearing loss has long been considered to be an irreversible phenomenon. Most likely for this reason, there has been little or no attempt to investigate the effect of sound conditioning on the hearing threshold in people with sensorineural hearing loss. Because we have observed the same phenomenon (i.e., a hearing threshold decrease due to sound conditioning) during research on tinnitus treatment, we decided to investigate the effect of sound conditioning on pure-tone hearing threshold in people with sensorineural hearing loss. Sound conditioning using a non-traumatic, moderate-level acoustic signal is a well-studied method to protect against age-related or noise-induced hearing loss in animals. In humans, acoustic signals provided at the hearing threshold level or slightly higher than the hearing threshold level have been studied for the treatment of hyperacusis and tinnitus and have been found to have positive effects. In this study, we adopted the term “sound conditioning” instead of “sound training” because the subjects were not asked to pay attention to the acoustic signals. In addition, because the subjects in the experimental group were instructed to listen to the acoustic signals at their hearing threshold levels (i.e., a barely audible level), we named the experimental method “threshold sound conditioning (TSC)”.

We examined the changes in the pure-tone hearing threshold after 2~3 weeks of TSC (i.e., sound conditioning with a frequency-specific acoustic signal at the hearing threshold level) or music listening (i.e., listening to music at a comfortable listening level). In addition, we examined hearing threshold changes without TSC or music listening in both groups.

After the music listening period in the control group, the only change observed was a hearing threshold increase at one frequency. In contrast, statistically significant decreases in the hearing threshold were observed at several frequencies after the TSC period. Clinically significant threshold decreases of 10 dB or more were observed at 9 subjects in the experimental group. In total, clinically significant threshold decreases were observed for 33 frequencies. The average hearing threshold of the 20 TSC frequencies before the break period, after the break period, and after the TSC period was analyzed. A hearing threshold decrease of 12.6 dB $\pm$ 2.8 dB (mean $\pm$ SEM) was observed for the TSC frequencies of the TSC ear ($P < 0.001$).

Threshold sound conditioning can decrease pure-tone hearing thresholds in people with sensorineural hearing loss.

Study Protocol



Subjects

TSC ears, TSC frequencies, frequency ranges of the acoustic signals, and demographic aspects of subjects in the experimental group

Subject ID	Age (years)	Sex	TSC ear ^a	TSC frequency ^b	Frequency range ^c
TSC-1	53	M	Left	4 kHz	3623 - 4309 Hz
TSC-2	41	F	Left	4 kHz	3623 - 4309 Hz
TSC-3	34	F	Left	4 kHz	3623 - 4309 Hz
TSC-4	56	M	Right	3 and 4 kHz	2714 - 3228 Hz 3623 - 4309 Hz
TSC-5	52	F	Right	4 kHz	3623 - 4309 Hz
TSC-6	33	F	Left	4 kHz	3623 - 4309 Hz
TSC-7	29	M	Left	4 kHz	3623 - 4309 Hz
TSC-8	52	M	Right	3 and 4 kHz	2714 - 3228 Hz 3623 - 4309 Hz
TSC-9	60	F	Right	4 kHz	3623 - 4309 Hz
TSC-10	22	M	Right	3 and 4 kHz	2714 - 3228 Hz 3623 - 4309 Hz
TSC-11	25	M	Right	3 and 4 kHz	2714 - 3228 Hz 3623 - 4309 Hz
TSC-12	44	M	Left	4 kHz	3623 - 4309 Hz
TSC-13	49	F	Right	4 kHz	3623 - 4309 Hz
TSC-14	43	F	Right	4 kHz	3623 - 4309 Hz
TSC-15	46	M	Left	4 kHz	3623 - 4309 Hz
TSC-16	57	F	Right	4 kHz	3623 - 4309 Hz

TSC, threshold sound conditioning; F, female; M, male

^a Ear that was stimulated with the acoustic stimulus.

^b Frequency at which a subject showed the worst hearing and is the approximate center frequency of the corresponding acoustic signal

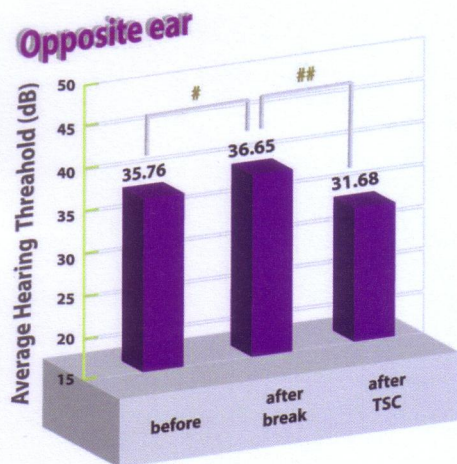
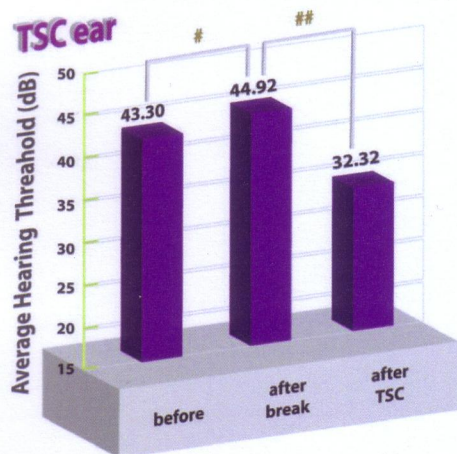
^c Frequency range of the acoustic signal for TSC

Types of the music and demographic aspects of subjects in the control group

Subject ID	Age (years)	Sex	Type of music
Con-1	51	M	Popular music
Con-2	29	F	Popular music
Con-3	30	F	Popular music
Con-4	31	M	Piano music
Con-5	61	F	Piano music
Con-6	58	F	Piano music
Con-7	45	M	Piano music
Con-8	47	M	Piano music
Con-9	57	F	Piano music
Con-10	51	F	Piano music
Con-11	29	F	Piano music
Con-12	63	F	Piano music
Con-13	41	M	Piano music

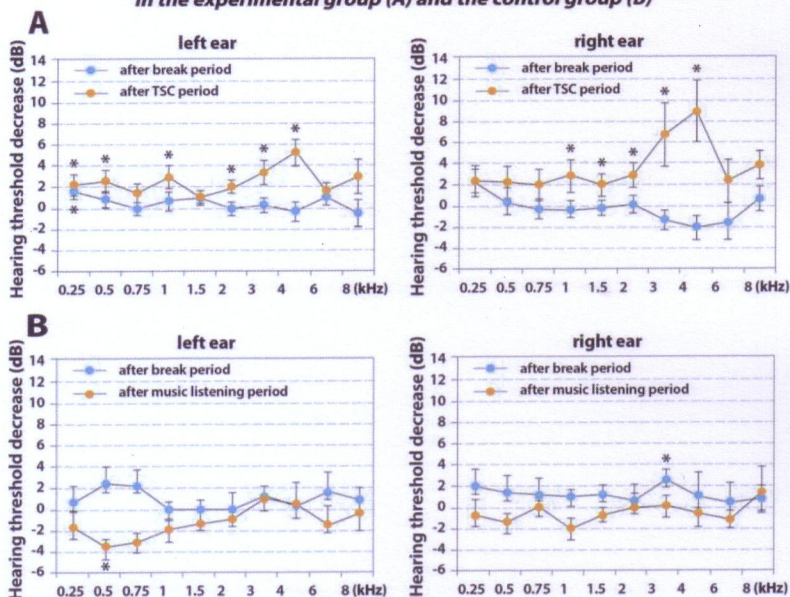
Results

Average hearing thresholds of 20 target frequencies before the break period, after the break period, and after the TSC period



A significant hearing threshold decrease was observed after the TSC period. There were no significant changes in the hearing threshold after the break period (i.e., without TSC). # $P > 0.05$ ## $P < 0.001$

Average hearing threshold decrease at each frequency ($\pm$ SEM) in the experimental group (A) and the control group (B)



Hearing threshold decreases at each frequency were assessed after the break period, the TSC period, and the music listening period. In the absence of sound stimulation (after the break period), a statistically significant hearing threshold decrease was shown only at one frequency in each group. After the music listening period in the control group, the only change observed was a hearing threshold increase at one frequency in the left ear. Statistically significant decreases in the hearing threshold were observed at several frequencies after the TSC period. * $P < 0.05$

Subjects with clinically significant threshold decreases in the experimental group after TSC

Subject ID	TD frequency		Subject ID	TD frequency	
	Left ear	Right ear		Left ear	Right ear
TSC-3	0.5 kHz	0.25 kHz	TSC-11	8 kHz	4 kHz
TSC-5	8 kHz		TSC-13		0.25 kHz
TSC-7	4 kHz		TSC-13		0.75 kHz
TSC-8	3 kHz	3 kHz	TSC-13		1 kHz
TSC-8	4 kHz	4 kHz	TSC-13	0.25 kHz	0.25 kHz
TSC-10		2 kHz	TSC-13	0.5 kHz	0.5 kHz
TSC-10		3 kHz	TSC-13	0.75 kHz	0.75 kHz
TSC-10	4 kHz	4 kHz	TSC-13	1 kHz	1 kHz
TSC-10		6 kHz	TSC-13		4 kHz
TSC-11		0.25 kHz	TSC-15	6 kHz	
TSC-11	3 kHz	3 kHz	TSC-15		8 kHz

TD: Threshold decrease

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References

- [1] Willott JF, Turner JG (1999) Prolonged exposure to an augmented acoustic environment ameliorates age-related auditory changes in C57BL/6J and DBA/2J mice. *Hear Res* 135: 78-88.
- [2] Tanaka C, Bielefeld EC, Chen GD, Li M, Henderson D (2009) Ameliorative effects of an augmented acoustic environment on age-related hearing loss in middle-aged Fischer 344/NHsd rats. *Laryngoscope* 119: 1374-1379.
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- [4] Miyakita T, Hellström PA, Frimanson E, Axelsson A (1992) Effect of low level acoustic stimulation on temporary threshold shift in young humans. *Hear Res* 60: 149-155.
- [5] Noreña AJ, Eggermont JJ (2005) Enriched acoustic environment after noise trauma reduces hearing loss and prevents cortical map reorganization. *J Neurosci* 25: 699-705.
- [6] Niu X, Tahera Y, Canlon B (2004) Protection against acoustic trauma by forward and backward sound conditioning. *Audiology and Neurotology* 9: 265-273.
- [7] Tanaka C, Chen GD, Hu BH, Chi LH, Li M, et al. (2009) The effects of acoustic environment after traumatic noise exposure on hearing and outer hair cells. *Hear Res* 250: 10-18.
- [8] Noreña AJ, Chery-Croze S (2007) Enriched acoustic environment rescales auditory sensitivity. *Neuroreport* 18: 1251-1255.
- [9] Kujawa SG, Liberman MC (1999) Long-term sound conditioning enhances cochlear sensitivity. *J Neurophysiol* 82: 863-873.
- [10] Engineer ND, Percaccio CR, Pandya PK, Moucha R, Rathbun DL, et al. (2004) Environmental Enrichment Improves Response Strength, Threshold, Selectivity, and Latency of Auditory Cortex Neurons. *J Neurophysiol* 92: 73-82.

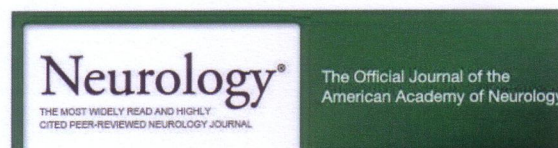
Threshold Sound Conditioning

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1. INTRODUCTION: BACKGROUND OF THE STUDY

Sensorineural hearing loss is one of the most common human disorders, severely restricting normal activities of daily living and lowering quality of life. More than 278 million people suffered from moderate to profound hearing loss in 2005 according to global estimates by the World Health Organization (WHO). And, despite efforts to prevent traumatic and occupational noise exposure, there are increasing number of people affected by noise-induced hearing loss, partially due to excessive exposure to loud noise with personal audio equipment and inadequate workplace precautions. In addition, the growing demographics of elderly patients has resulted in increasing prevalence of age-related hearing loss.



Sensorineural hearing loss is considered an irreversible phenomenon. There are data for central neuronal plasticity with conditioned stimuli in young developing mammals, important for normal development of physiological synapses within the central and peripheral auditory pathways. However, there is also growing evidence of residual capacity for plasticity in adults, both animal and human synaptic data (Rees, Guldner, Aitkin 1985; Snyder, Rebesch, Cao et al 1990; Snyder, Rebesch, Leake,

et al 1991). The introduction of sound conditioning with the use of hearing aids has the potential to activate auditory pathway plasticity and improve basal frequency hearing as measured by pure tone audiometry. Additional supportive data of forward sound conditioning (pre-conditioning) with exposure to non-damaging sound stimulation creates a tolerance and protective effect to subsequent sound trauma (Canlon et al. 1988, Ryan et al. 1994, Yoshida and Liberman 2000).

The authors presented pilot data confirming decreased hearing threshold with backward sound conditioning in subjects with sensorineural hearing loss due to otoacoustic trauma[22]. As the subjects in the experimental group were treated with acoustic signals at their hearing threshold levels (i.e., just below audible levels), we coined the investigational method "threshold sound conditioning (TSC)". The primary endpoint was change in the pure-tone audiometry measured hearing threshold, specifically in the basal frequency loss prior to TSC, after 2~3 weeks of treatment (i.e., sound conditioning with a frequency-specific acoustic signal) or music listening volume (i.e., listening to music at a comfortable listening level). Previously published efficacious sound stimuli include octave band noise, broad-band noise, pure tones or music (Henselman et al., 1994; McFadden et al., 1997; Kujawa and Liberman, 1997; Miyakita et al., 1992; Canlon et al., 1988; Canlon and Fransson, 1998). These conditioning stimuli are known to protect against forward sensorineural acoustic trauma that are identical or within 2-3 octave span from the given stimuli (McFadden et al., 1997; Kujawa and Liberman, 1997; Canlon et al., 1988; Franklin et al., 1991; Miyakita et al., 1992). After the music listening period in

the control group, the only change observed was a hearing threshold increase at one frequency. In contrast, the presented data and analysis demonstrates statistically significant decreases in the hearing threshold at several frequencies after the TSC period.

The focus of the present study is to confirm the previously presented pilot data in a large double blinded randomized controlled study comparing the specific frequency hearing threshold changes after short term treatment (4 weeks) with or without TSC delivered by an behind-the-ear digital hearing aid.

2. PURPOSE OF THE STUDY

This study provides class 1 evidence through a double blind randomized placebo controlled trial of threshold sound conditioning (TSC) and its safety and efficacy in ameliorating increased threshold of hearing frequency as measured by pure tone audiometry. Null hypothesis in this study was that TSC doesn't have a significant effect on auditory threshold amelioration. Alternative hypothesis was that TSC has a significant effect on auditory threshold amelioration.

3. METHOD

The study protocol and consent forms were approved through the Stanford University Medical Center Human Subjects Research and Institutional Review Board of the Research Compliance Office. Ninety six subjects were consented and screened through the single tertiary care University Neurology clinic. Based on history, physical examination, and screening PTA test, 52 people were excluded based on inclusion and exclusion criteria. The other 44

subjects were consented to participate in the study. Two subjects dropped out for personal and logistic reasons unrelated to the study prior to randomization. 42 subjects were randomized and all completed the study. Data from three subjects were excluded in the data analysis for pre-specified reasons outlined in the statistical plan (frequent false response, ear wax, test fallacy, etc.). Data from the final 39 subjects were used to analyze “safety and efficacy of threshold sound conditioning by conditioning-enhanced hearing aid (TSC hearing aid)” using an intention-to-treat design. Of the 39 subjects, 23 were in the TSC group, and 16 were in the control group.

Inclusion Criteria:

- 1) Subject with 1 or more frequency threshold value over 40 dB HL
- 2) Subject who can operate the TSC volume of the test hearing aid

Exclusion Criteria:

- 1) Subject who has 3 or more air bone gaps of over 10~15 dB
- 2) Subject who has 3 or more frequency regions with profound hearing loss of over 90 dB
- 3) Subject who cannot comply with or violates protocol instructions
- 4) Subject who is currently participating in another study protocol

3.1. Hearing Test

PTA (Pure Tone Audiometry) was performed at 8~9 frequencies (0.25, 0.5, 1, 2, 3, 4, 6, 8, and 12 KHz) in both ears of each subject. The 1st PTA was the baseline hearing test prior to being randomized and wearing the assigned hearing aid. The 2nd PTA was after completing the full intervention of using the assigned hearing aid for 2~3 weeks.

3.2. Procedure

- 1) Subjects who meet inclusion/exclusion criteria visited the research site for the 1st PTA. Hearing thresholds were obtained at 8~9 frequencies (0.25, 0.5, 1, 2, 3, 4, 6, 8, and 12 KHz).
- 2) Based on 1st PTA results, a single TSC region was selected at 3, 4, or 6 KHz for the TSC group.
- 3) Subjects used a TSC conditioning-enhanced hearing aid for 2~3 weeks, or an identical hearing aid without TSC for

the control group. Subjects in TSC group underwent TSC for 1 hour per day at the lowest audible level (i.e., the hearing threshold level).

- 4) After undergoing 2~3 weeks of treatment, subjects visited the research site for the follow-up PTA.
- 5) The hearing threshold changes in the groups were statistically analyzed.

3.3. Stimulus for TSC

TSC target was to stimulate one Bark region in the cochlea (Approx. 1 mm i.e., a single auditory filter in a cochlear length of total 25 mm). The TSC signal type was the amplitude and frequency modulated sinusoidal stimulus presented at the lowest audible level. The center frequency of the stimulus was 3, 4, or 6 KHz.

4. STATISTICAL PLAN

4.1. Statistical Methods

Chi Square Test and One-Way, Two-Way, and Three-Way ANOVA were used as statistical tools to evaluate the clinical test results in this study.

4.2. Subject (N=39)

Older group: ≥ 70 years old, $n=20$

Younger group: < 70 years old, $n=19$

Female group: $n=22$

Male group: $n=17$

TSC group: $n=23$

Control group: $n=16$

Ameliorated Subject: Subject who showed a threshold decrease of 10 dB or more in at least one frequency band without any threshold increase

Mixed Subject: Subject who showed both a threshold decrease and threshold increase of 10 dB or more

No Change: Subject who showed neither threshold decrease nor increase of 10 dB or more

Deteriorated Subject: Subject who showed a threshold increase of 10 dB or more in at least one frequency band without any threshold decrease

Ameliorated Band: Frequency band that showed a threshold decrease of 10 dB or more

Deteriorated Band: Frequency band that showed a threshold increase of 10 dB or more

4.3. Independent Variables and Dependent Variables

There were three fixed factors in this study; TSC, sex, and age. TSC was an independent variable 1 (IV1) designating TSC group as ‘1’ and non-TSC (control) group as ‘0’. Sex was independent variable 2 (IV2) designating the female group as ‘1’ and male group as ‘0’. Age was independent variable 3 (IV3) designating older group (≥ 70 years old) as ‘1’ and younger group (< 70 years old) as ‘0’. There were two dependent variables. A dependent variable 1 (DV1) was expressed in four-point scale by threshold change designating ameliorated change as ‘3’, mixed change as ‘2’, no change as ‘1’, and deteriorated change as ‘0’. A dependent variable 2 (DV2) was expressed in two-point scale by threshold change designating ameliorated & mixed change as ‘1’ and no change & deteriorated change as ‘0’.

Dependent Variable 1 (DV1):

Threshold Change (Ameliorated=3, Mixed=2, No Change=1, Deteriorated=0)

Dependent Variable 2 (DV2):

Threshold Change (Ameliorated & Mixed=1, No Change & Deteriorated=0)

Independent Variable 1 (IV1):

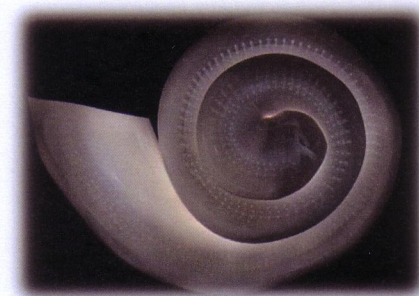
TSC (TSC=1, Control=0)

Independent Variable 2 (IV2):

Sex (Female=1, Male=0)

Independent Variable 3 (IV3):

Age (Older=1, Younger=0)



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4.4. Statistical Samples for ANOVA

IV1: TSC (1), Control (0) / IV2: Female (1), Male (0) / IV3: Older (1), Younger (0)
 DV1: Ameliorated (3), Mixed (2), No Change (1), Deteriorated (0)
 DV2: Ameliorated & Mixed (1), No Change & Deteriorated (0)

TSC Group (1)																						
ID	02	04	20	22	29	44	52	58	59	60	65	67	71	72	73	76	78	80	81	84	89	93
Sex	F	F	F	M	M	F	F	F	F	M	F	F	F	M	M	M	F	M	F	F	F	M
Age	68	64	70	71	70	52	72	53	55	77	79	45	72	80	67	72	69	64	76	66	74	71
DV1	3	0	2	2	3	3	2	2	3	3	3	1	3	3	2	2	1	2	2	0	3	3
DV2	1	0	1	1	1	1	1	1	1	1	1	0	1	1	1	1	0	1	1	0	1	1

Control Group (0)																						
ID	03	06	30	53	56	57	64	66	74	79	85	87	88	90	95	96						
Sex	F	M	F	M	F	M	F	M	F	M	F	F	M	F	F	M						
Age	78	77	65	69	80	78	45	46	57	82	54	71	54	76	76	32						
DV1	0	0	3	0	0	1	0	1	3	0	1	1	0	3	3	1						
DV2	0	0	1	0	0	0	0	0	1	0	0	0	0	1	1	0						

IV1: TSC Group (1)																						
N	01	02	03	04	05	06	07	08	09	10	11	12	13	14	15	16	17	18	19	20	21	22
IV2	1	1	1	0	0	1	1	0	1	1	0	1	1	1	0	0	0	0	1	0	1	1
IV3	0	0	1	1	1	0	0	0	0	1	1	0	1	1	0	1	0	0	1	0	1	1
DV1	3	0	2	2	3	3	2	2	3	3	3	1	3	3	2	2	1	2	2	0	3	3
DV2	1	0	1	1	1	1	1	1	1	1	1	0	1	1	1	1	0	1	1	0	1	1

The Number of Subjects Who Showed Either a Threshold Change of 10 dB or More in at Least One Frequency Or No Threshold Change (in Total Subjects)						
in Total Subject	Older (N=20)	Younger (N=19)	Female (N=22)	Male (N=17)	TSC (N=23)	Control (N=16)
Ameliorated Subject	45% (N=9)	26% (N=5)	55% (N=12)	12% (N=2)	43% (N=10)	25% (N=4)
Deteriorated Subject	20% (N=4)	32% (N=6)	18% (N=4)	35% (N=6)	13% (N=3)	44% (N=7)
Mixed Subject	30% (N=6)	26% (N=5)	23% (N=5)	35% (N=6)	35% (N=8)	19% (N=3)
No Threshold Change	5% (N=1)	16% (N=3)	4% (N=1)	18% (N=3)	9% (N=2)	12% (N=2)

Ameliorated Subject: Subject who showed a threshold decrease of 10 dB or more in at least one frequency band without any threshold increase / **Mixed Subject:** Subject who showed both of the threshold decrease and increase of 10 dB or more / **No Change:** Subject who showed neither threshold decrease nor increase of 10 dB or more / **Deteriorated Subject:** Subject who showed a threshold increase of 10 dB or more in at least one frequency band

The number of the frequency bands that showed a threshold change of 10 dB or more in total subjects

The Number of the Frequency Bands That Showed a Threshold Change of 10 dB or More (in Total Subjects)						
in Total Subject	Older (N=49)	Younger (N=40)	Female (N=54)	Male (N=35)	TSC (N=52)	Control (N=37)
Ameliorated Band	57% (N=28)	55% (N=22)	72% (N=39)	31% (N=11)	60% (N=31)	51% (N=19)
Deteriorated Band	43% (N=21)	45% (N=18)	28% (N=15)	69% (N=24)	40% (N=21)	49% (N=18)

Ameliorated Band: Frequency band that showed a threshold decrease of 10 dB or more / **Deteriorated Band:** Frequency band that showed a threshold increase of 10 dB or more

The number of subjects who showed either a threshold change of 10 dB or more in at least one frequency or no threshold change in TSC group

The Number of Subjects Who Showed Either a Threshold Change of 10 dB or More in at Least One Frequency Or No Threshold Change (in TSC Group)				
in TSC Group	Older (N=12)	Younger (N=11)	Female (N=13)	Male (N=10)
Ameliorated Subject	58% (N=7)	27% (N=3)	62% (N=8)	20% (N=2)
Deteriorated Subject	0% (N=0)	27% (N=3)	8% (N=1)	20% (N=2)
Mixed Subject	42% (N=5)	27% (N=3)	23% (N=3)	50% (N=5)
No Threshold Change	0% (N=0)	18% (N=2)	7% (N=1)	10% (N=1)

The number of subjects who showed either a threshold change of 10 dB or more in at least one frequency or no threshold change in control group

The Number of Subjects Who Showed Either a Threshold Change of 10 dB or More in at Least One Frequency Or No Threshold Change (in Control Group)				
in Control Group	Older (N=8)	Younger (N=8)	Female (N=9)	Male (N=7)
Ameliorated Subject	25% (N=2)	25% (N=2)	44.4% (N=4)	0% (N=0)
Deteriorated Subject	50% (N=4)	37.5% (N=3)	33.3% (N=3)	57% (N=4)
Mixed Subject	12.5% (N=1)	25% (N=2)	22.2% (N=2)	14% (N=1)
No Threshold Change	12.5% (N=1)	12.5% (N=1)	0% (N=0)	29% (N=2)

The number of the frequency bands that showed a threshold change of 10 dB or more in TSC group

The Number of the Frequency Bands That Showed a Threshold Change of 10 dB or More (in TSC Group)				
in TSC Group	Older (N=28)	Younger (N=24)	Female (N=28)	Male (N=24)
Ameliorated Band	68% (N=19)	50% (N=12)	79% (N=22)	37% (N=9)
Deteriorated Band	32% (N=9)	50% (N=12)	21% (N=6)	63% (N=15)

The number of the frequency bands that showed a threshold change of 10 dB or more in control group

The Number of the Frequency Bands That Showed a Threshold Change of 10 dB or More (in Control Group)				
in Control Group	Older (N=21)	Younger (N=16)	Female (N=26)	Male (N=11)
Ameliorated Band	43% (N=9)	62.5% (N=10)	65% (N=17)	18% (N=2)
Deteriorated Band	57% (N=12)	37.5% (N=6)	35% (N=9)	82% (N=9)

5. RESULT

5.1. Basic Results

The number of subjects who showed either a threshold improvement of 10 dB or more in at least one frequency versus increase of 10 dB or no threshold change in total subjects

5.2. Statistical Results (See the Appendix 1: ANOVA RESULTS)

The number expressed in percentages indicates the ratio of the number of subjects who showed a threshold amelioration of 10 dB or more in at least one frequency band. All P values were proved by *Scheffe's post hoc test* or *Tukey's HSD post hoc test*.

TSC group (78%) showed a significant difference from **control group (44%)** on auditory threshold amelioration; $P=0.008091$ in DV1, $P=0.000546$ in DV2 by *Scheffe's post hoc test*. **Female subjects (77%)** showed a significant difference in DV1 from **male subjects (47%)**; $P=0.025468$ in DV1 by *Scheffe's post hoc test*. **Older subjects (75%)** showed no significant difference from **younger subjects (53%)**; $P=0.139149$ in DV1, $P=0.082920$ in DV2 by *Scheffe's post hoc test*. The other statistical results were as follows;

Female in TSC vs. Male in Control: $P=0.004504$ in DV1, $P=0.001537$ in DV2 by *Scheffe's post hoc test*

Male in TSC vs. Male in Control: $P=0.134098$ in DV1, $P=0.016449$ in DV2 by *Scheffe's post hoc test*

Older in TSC vs. Younger in Control: $P=0.046568$ in DV1, $P=0.003339$ in DV2 by *Scheffe's post hoc test*

Older in TSC vs. Older in Control: $P=0.026420$ in DV1, $P=0.003339$ in DV2 by *Scheffe's post hoc test*

Older Female Subjects in TSC Group vs. Younger Male Subjects in Control Group: $P=0.039637$ in DV1, $P=0.005917$ in DV2 by *Tukey's HSD post hoc test*

Older Female Subjects in TSC Group vs. Older Male Subjects in Control Group: $P=0.047998$ in DV1, $P=0.016162$ in DV2 by *Tukey's HSD post hoc test*

Older Male Subjects in TSC Group vs. Younger Male Subjects in Control Group: $P=0.152064$ in DV1, $P=0.023918$ in DV2 by *Tukey's HSD post hoc test*

6. DISCUSSION

Utilizing the Pure Tone Audiometry method of providing an acoustic signal corresponding to a frequency band to subjects, and subsequently measuring the hearing ability at the frequency band through user responses, the sensorineural hearing loss and specific bands were documented (compared to age/sex-matched reference hearing thresholds). The user's response information on the volume adjustment was stored as the hearing threshold corresponding to the acoustic signal of the selected frequency band – corresponding to the threshold of the hair cell region having frequency specificity on the selected frequency band. Based on the comparison results, the algorithm could determine a target frequency band requiring treatment. In addition, these algorithm comparisons can also determine adjacent hair cell region limitations and high hearing thresholds as added targets. The data were used to ascertain a stimulation region of each frequency band, detecting hair cell regions to which the TSC was provided. Particularly, the detection of the stimulation region determined the frequency band corresponding to a damaged hair cell region.

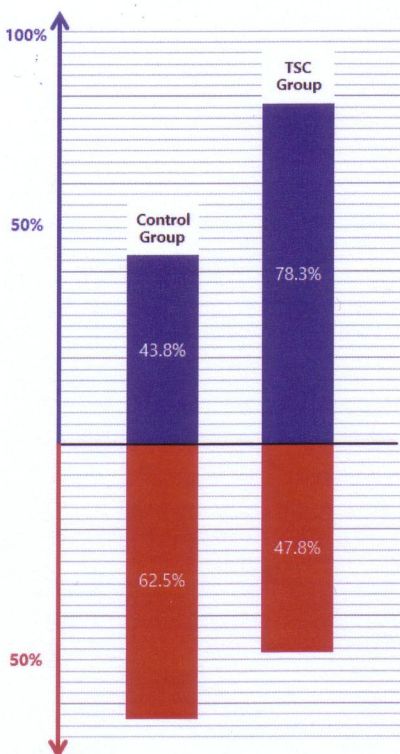
The TSC output the acoustic signal with a preset intensity to the frequency band of the damaged hair cell. The treatment algorithm allowed for an intensity higher by predetermined level than the hearing threshold of corresponding band. In addition, the acoustic signal corresponded to at least one of the amplitude modulated tone, frequency modulated tone, pulse tone and amplitude modulated narrow band noise, or combination of the tones and the noise. Although the exclusion criteria attempted to reject those with too extensive or diffuse sensorineural loss, such as those with several damaged hair cell regions, the acoustic signal could be provided to the damaged hair cell regions in an order of damage severity, randomly or simultaneously. The proprietary algorithm allowed for TSC signal delivery at various intensities, types or orders.

After the target frequency band was confirmed, the behind-the-ear hearing aid was fitted for the individual's ear, set with the algorithm determined intensity,

type, and outputs of the acoustic signal set.

TSC showed a significant effect on auditory threshold amelioration. There was no safety issue with the hearing aid, the TSC algorithm, or the overall study. The efficacy of TSC was statistically significant ($P=0.0271$ by *Chi Square Test*, $P=0.008091$ in DV1 by *Scheffe's post hoc test*, $P=0.000546$ in DV2 by *Scheffe's post hoc test*).

Ratio of the number of subjects who showed one or more frequency regions with threshold amelioration above 10 dB



Ratio of the number of subjects who showed one or more frequency regions with threshold deterioration above 10 dB

Sound conditioning using a non-traumatic, moderate-level acoustic signal, a technique that is also known as "augmented acoustic environment (AAE)" or "enriched acoustic environment," is a well-established forward method to protect against age-related or noise-induced hearing loss in animals [1],[2],[3]. A series of studies reported that AAE can delay hearing loss in C57BL/6J and DBA/2J mice and Fischer 344/NHsd rats that exhibit progressive sensorineural hearing loss [1],[4-9]. The

AAE-exposed animals showed lower auditory brainstem response (ABR) thresholds than the control group. In an alternative study with Fischer 344/NHsd rats, the backward ameliorative effect was induced even when the AAE was applied several months after the onset of hearing loss, and interestingly, some improvement in the ABR thresholds (i.e., a decrease in the ABR thresholds) was observed in one AAE-exposed rat [9].

Forward sound conditioning (i.e., exposure to a non-traumatic-level sound before traumatic noise exposure) reduces the extent of the noise-induced permanent hearing threshold shift (PTS), and the PTS reduction can be as large as 30~40 dB. This protective effect of sound conditioning has been documented in a number of different species of animals, including guinea pigs [2], chinchillas [10], gerbils [11], rats [12], and mice [13]. These studies have used a variety of pre-exposure sounds and traumatic noises that vary with respect to the acoustic signal type (i.e., noise or pure-tone), frequency, intensity, and duration. Surprisingly, hearing protection was induced even with sound conditioning as short as 15 minutes in mice [13],[14].

In an early human study, the effect of low-level training acoustic stimulation (70 dB for 6 hours/day for 9 days) on the susceptibility to noise was first assessed in teenage subjects by comparing noise-induced temporal hearing threshold shifts [15]. During the training period, the subjects listened to music at the 70 dBA pre-specified levels, and this acoustic intervention significantly reduced noise susceptibility compared with the level of susceptibility in the pre-training period, particularly in the 3-3.5 kHz on and after D9. The experiment continued past the 5 days, and showed further reduction of TTS which expanded to 2-5 kHz. In addition, the training effect diminished four days after stimulation cessation clearly implying the reported stimulation parameters have reversible effects. In animal models, Canlon et al. (1991) showed that rabbits maintained some level of "protective effect for several weeks to a month after forward stimulation. These differences may be

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partially explained by natural differences in species, length of training, intensity and frequency of stimulation. In addition, there is mounting evidence that suggests periodic stimulation interspersed with quiet rest also may add to the forward protective effects (Clark et al. 1987, Anderson et al. 1991, Subramanian et al. 1991). These factors were included in the design of the current methodology and treatment algorithm.

There are potentially many underlying physiologic adaptive responses, although the exact mechanism(s) are not fully delineated. For example the motor capacity of the outer hair cells, and their ability to condition to repetitive environmental stimulation, and post-stimulation fatigue have been described. This allows the hair cells, not only function as mechano-electrical transducers, but also have active capacity to dampen or screen the persistent auditory stimulations as a protective mechanism at the ipsilateral cochlea and basilar membrane level.

An alternative set of data that suggests more proximal or central involvement came from Cody et al. (1982) demonstrating improvement of monaural hearing sensitivity loss from contralateral ear stimulation. In the same experiment, contralateral same frequency activation reduced the monaural deficiency; however, alternative frequency contralateral stimulation had no ameliorating effect. Finally, the administration of strychnine to the hair cells in the basilar membrane of cochlea, an auditory efferent activity blocker, also eliminated the ameliorating effects suggesting the efferent effects of both ipsilateral and contralateral auditory pathways play a role in threshold sound conditioning. Klinke and Galley (1974) proposed how the contralateral efferent pathways reduce the ipsilateral afferent potentials, essentially downgrading the amplitude of the compound action potentials, thereby dampening the central signaling pathways.

More recently, there is further evidence that sound conditioning releases adrenocorticotrophin hormone and glucocorticoid release and alteration of the hypothalamic-pituitary-adrenal (HPA) axis. Secondary evidence such as adrenalectomy resulting in HPA disruption negates the efficacy of sound

conditioning. And, subsequent corticosterone replacement of these same adrenalectomized mice also show the normalized protective threshold effects. Similarly, disrupting those same glucocorticoids in a non-adrenalectomized mouse (using metyrapone + RU486) again removes the protective effects of sound conditioning (Tahera et al. 2007). It is hypothesized that sound conditioning may prevent the glucocorticoid blocking effects at the level of the hair cells in the cochlea, and eventually the central components of the hypothalamic-pituitary axis. And while the forward conditioning does not elevate glucocorticoid levels a measurable amount, the outer hair cells may gain an increased sensitivity to baseline glucocorticoid levels through rapid GR receptor upregulation or and stabilization, and decrease GR degradation (Conway-Campbell et al. 2007, Schaff and Cidlowski 2002).

Backward sound conditioning (i.e., exposure to a non-traumatic level sound after traumatic noise exposure) has also been reported to reduce noise-induced hearing loss [3],[16],[17]. Compared with the control group exposed only to acoustic trauma, guinea pigs conditioned with non-traumatic level sound after the traumatic noise exposure exhibited a reduced ABR and DPOAE (Distortion Product Otoacoustic Emissions) threshold shift [16]. In addition to the ABR threshold shift reduction, the level of outer hair cell loss was also decreased in sound-conditioned chinchillas [17]. The ameliorative effect on hair cell damage was induced even with an ambient level of sound conditioning [18]. Cochlear damage is known to be followed by the reorganization of the cortical tonotopic map in cats [19], and backward sound conditioning prevented this reorganization, indicating that the ameliorative effect of sound conditioning can be induced in the central auditory system as well as the peripheral region [3].

In humans, acoustic signals that are provided at the hearing threshold level or slightly higher than the hearing threshold level have been studied for the treatment of hyperacusis and tinnitus [20],[21]. Hyperacusis is a disorder involving loudness perception, and people with hyperacusis complain of bothersome loudness at moderate levels. Tinnitus is

the perception of sound in the absence of corresponding external sound. Both symptoms are known to be closely related to sensorineural hearing loss. Noreña and Chery-Croze reported that hyperacusis could be improved by hearing-threshold-level acoustic stimulation [20]. The ameliorative effect was observed as soon as 2 weeks after the initiation of acoustic stimulation. Tass et al. used acoustic signals slightly higher than hearing threshold levels for tinnitus treatment, and these acoustic signals induced a significant decrease in tinnitus loudness and symptoms [21].

Over recent years, there is mixed data regarding the ameliorating backward effects of threshold sound conditioning in sensorineural hearing loss. The pilot human data, and this randomized controlled robustly powered prospective clinical study in a broad range of subjects demonstrates a significant improvement in a narrow band frequency threshold. These data have important clinical implications since there is no current long term therapy for this widespread and growing disability. In addition, this may have far-reaching implications for acute-chronic associated disorders such as tinnitus and Menière's disease. Furthermore, with the growing broader understanding of TSC with triggered downstream activation of the central and peripheral glucocorticoid pathways, algorithmic therapies, including adjunct combination of sound conditioning with steroids can be further tested. These data are the latter steps of gaining regulatory review of this technology to potentially make it widely available in a systematic and controlled standardized fashion to patients. Additional physiologic, mechanistic, and molecular studies may be necessary to fully elucidate the pathophysiology and mechanism of action of TSC.

7. REFERENCES

- [1] Turner JG, Willott JF (1998) Exposure to an augmented acoustic environment alters auditory function in hearing-impaired DBA/2J mice. *Hear Res* 118: 101-113.
- [2] Canlon B, Borg E, Flock A (1988) Protection against noise trauma by pre-exposure to a low level acoustic stimulus. *Hear Res* 34: 197-200.
- [3] Noreña AJ, Eggermont JJ (2005) Enriched acoustic environment after noise trauma reduces hearing loss and prevents cortical map

reorganization. *J Neurosci* 25: 699-705.

[4] Willott JF, Turner JG (1999) Prolonged exposure to an augmented acoustic environment ameliorates age-related auditory changes in C57BL/6J and DBA/2J mice. *Hear Res* 135: 78-88.

[5] Willott JF, Bross L (2004) Effects of prolonged exposure to an augmented acoustic environment on the auditory system of middle-aged C57BL/6J mice: cochlear and central histology and sex differences. *J Comp Neurol* 472: 358-370.

[6] Willott JF, Bross LS, McFadden S (2005) Ameliorative effects of exposing DBA/2J mice to an augmented acoustic environment on histological changes in the cochlea and anteroventral cochlear nucleus. *J Assoc Res Otolaryngol* 6: 234-243.

[7] Willott JF, VandenBosche J, Shimizu T, Ding DL, Salvi R (2006) Effects of exposing gonadectomized and intact C57BL/6J mice to a high-frequency augmented acoustic environment: Auditory brainstem response thresholds and cytochrome c oxidase. *Hear Res* 221: 73-81.

[8] Willott JF, VandenBosche J, Shimizu T, Ding DL, Salvi R (2008) Effects of exposing C57BL/6J mice to high- and low-frequency augmented acoustic environments: auditory brainstem response thresholds, cytochrome c oxidase, anterior cochlear nucleus morphology and the role of gonadal hormones.

Hear Res 235: 60-71.

[9] Tanaka C, Bielefeld EC, Chen GD, Li M, Henderson D (2009) Ameliorative effects of an augmented acoustic environment on age-related hearing loss in middle-aged Fischer 344/NHsd rats. *Laryngoscope* 119: 1374-1379.

[10] Campo P, Subramaniam M, Henderson D (1991) The effect of 'conditioning' exposures on hearing loss from traumatic exposure. *Hear Res* 55: 195-200.

[11] Ryan AF, Bennett TM, Woolf NK, Axelsson A (1994) Protection from noise induced hearing loss by prior exposure to a non-traumatic stimulus: role of the middle ear muscles. *Hear Res* 72: 23-28.

[12] Pukkila M, Zhai S, Virkkala J, Pirvola U, Ylikoski J (1997) The 'toughening' phenomenon in rat's auditory organ. *Acta Otolaryngol Suppl* 529: 59-62.

[13] Yoshida N, Liberman MC (2000) Sound conditioning reduces noise-induced permanent threshold shift in mice. *Hear Res* 148: 213-219.

[14] Tahera Y, Meltser I, Johansson P, Salman H, Canlon B (2007) Sound conditioning protects hearing by activating the hypothalamic-pituitary-adrenal axis. *Neurobiol Dis* 25: 189-197.

[15] Miyakita T, Hellström PA, Frimanson E, Axelsson A (1992) Effect of low level acoustic stimulation on temporary threshold shift in young humans. *Hear Res* 60: 149-155.

[16] Niu X, Tahera Y, Canlon B (2004)

Protection against acoustic trauma by forward and backward sound conditioning. *Audiol Neurotol* 9: 265-273.

[17] Tanaka C, Chen GD, Hu BH, Chi LH, Li M, et al. (2009) The effects of acoustic environment after traumatic noise exposure on hearing and outer hair cells. *Hear Res* 250: 10-18.

[18] Fukushima N, White P, Harrison RV (1990) Influence of acoustic deprivation on recovery of hair cells after acoustic trauma. *Hear Res* 50: 107-118.

[19] Eggermont JJ, Komiya H (2000) Moderate noise trauma in juvenile cats results in profound cortical topographic map changes in adulthood. *Hear Res* 142: 89-101.

[20] Noreña AJ, Chery-Croze S (2007) Enriched acoustic environment rescales auditory sensitivity. *Neuroreport* 18: 1251-1255.

[21] Tass PA, Adamchic I, Freund HJ, von Stackelberg T, Hauptmann C (2012) Counteracting tinnitus by acoustic coordinated reset neuromodulation. *Restor Neurol Neurosci* 30: 137-159.

[22] Kwak E, Kwak S, Kang Y (2013) Effect of threshold sound conditioning on pure-tone hearing thresholds in human subjects with sensorineural hearing loss. 36th ARO MidWinter meeting.