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ORIGINAL RESEARCH

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Threshold sound conditioning in the treatment of sensorineural hearing loss

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Abstract

Objectives/hypothesis: Sensorineural hearing loss is one of the most common human disorders, with increasing incidence in elderly patients, severely restricting normal activities, and lowering quality of life. The introduction of sound conditioning has the potential to activate auditory pathway plasticity and improve basal frequency hearing. Our objective was to evaluate the safety and efficacy of threshold sound conditioning (TSC). The null hypothesis in this study was that TSC does not have a significant effect on auditory threshold amelioration.

Methods: Pure tone audiometry (PTA) was performed and hearing thresholds were measured once at baseline, and a second time following TSC intervention. Data were analyzed using an intention-to treat design.

Results: The TSC group (78%) significantly differed from the control group (44%) on auditory threshold amelioration; P = .008091 in DV1, P = .000546 in DV2 by Scheffe's post hoc test. Female subjects (77%) showed a significant difference in DV1 from male subjects (47%); P = .025468 in DV1 by Scheffe's post hoc test. Older subjects (75%) showed no significant difference from younger subjects (53%); P = .139149 in DV1, P = .082920 in DV2 by Scheffe's post hoc test.

Conclusions: We observed a significant improvement in a narrow band frequency threshold in this randomized controlled prospective clinical study in a broad range of subjects. These data have important clinical implications since there is no current long-term therapy for this widespread and growing disability. Additional physiologic, mechanistic, and molecular studies are necessary to fully elucidate the pathophysiology and mechanism of action of TSC.

Level of Evidence: 1a.

KEYWORDS

audiology, auditory physiology, sensorineural hearing loss

1 | INTRODUCTION

Sensorineural hearing loss is one of the most common human disorders. Despite efforts to prevent traumatic and occupational noise exposure, there is an increasing number of people affected by noise-induced hearing loss. In addition, the growing population of elderly patients has resulted in the increased prevalence of age-related hearing loss.

There are data showing that central neuronal plasticity with conditioned stimuli in young developing mammals is important for normal development of the physiological synapses within the central and peripheral auditory pathways. However, there is also growing evidence of residual capacity for plasticity in adults in both animal and human synaptic data.[1-3] 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 leads to tolerance and a protective effect against subsequent sound trauma.[4-6]

The authors presented pilot data confirming decreased hearing thresholds with backward sound conditioning in subjects with sensorineural hearing loss due to otoacoustic trauma.[7] 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 term for the investigational method of "threshold sound conditioning (TSC)". Previously published efficacious sound stimuli include octave band noise, broad-band noise, pure tones, and music.[4,8-12] These conditioning stimuli are known to protect against forward sensorineural acoustic trauma that is identical or within two to three octaves from the given stimuli.[4,9-11,13]

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 (2-3 weeks) with or without TSC delivered by a behind-the-ear digital hearing aid.

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.

2 | MATERIALS AND METHODS

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 consented and were screened through the single tertiary care University Neurology clinic. Based on medical history, physical examination, and screening PTA test, 52 people were excluded based on inclusion and exclusion criteria. The other 44 subjects consented to participate in the study. Two subjects dropped out for personal and logistic reasons unrelated to the study prior to randomization. Forty-two 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 the "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.

2.1 | Inclusion criteria

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

2.2 | Exclusion criteria

1. Subject who has three or more air bone gaps of over 10 to 15 dB.
2. Subject who has three 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.

2.3 | Hearing test

PTA (pure tone audiometry) was performed at eight to nine frequencies (0.25, 0.5, 1, 2, 3, 4, 6, 8, and 12 kHz) in both ears of each subject. The first PTA was the baseline hearing test prior to being randomized and wearing the assigned hearing aid. The second PTA was upon completion of the full intervention of using the assigned hearing aid for 2 to 3 weeks.

2.4 | Procedure

a. Subjects who meet inclusion/exclusion criteria visited the research site for the first PTA.
b. Based on the first PTA results, a single TSC region was selected at 3, 4, or 6 KHz for the TSC group. The TSC region was matched to the frequency that showed the poorest pure tone threshold.
c. 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 the TSC group underwent TSC for 1 hour per day at the lowest audible level (i.e., the hearing threshold level).
d. After undergoing 2 to 3 weeks of treatment, subjects visited the research site for the follow-up PTA.
e. The hearing threshold changes in the groups were statistically analyzed.

2.5 | Stimulus for TSC

The 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.

2.6 | Statistical plan

2.6.1 | 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.

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.

2.6.2 | Independent variables and dependent variables

There were three fixed factors in this study: TSC, sex, and age. TSC was 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: Dependent variable 1 (DV1) was expressed in a four-point scale by threshold change designating ameliorated change as "3," mixed change as "2," no change as "1," and deteriorated change as "0." Dependent variable 2 (DV2) was expressed in a two-point scale by threshold change designating ameliorated & mixed change as "1" and no change & deteriorated change as "0."

2.6.3 | Statistical samples for ANOVA

Statistical samples for ANOVA were shown in Table 1.

3 | RESULTS

Table 2 shows the results of hearing threshold changes in terms of the number of subjects in total subjects. In this study, hearing threshold change means 10 dB or more change.

"Ameliorated Subject" means the subject who showed only a threshold decrease of 10 dB or more in at least one frequency band without any threshold increase. "Deteriorated Subject" means the subject who showed only a threshold increase of 10 dB or more in at least one frequency band. "Mixed subject" means the subject who showed both of the threshold decrease and increase of 10 dB or more. "No change" means the subject who showed neither threshold decrease nor increase of 10 dB or more.

Table 3 shows the results of hearing threshold changes in terms of the number of the frequency bands that showed a threshold change of 10 dB or more in total subjects. "Ameliorated band" means the frequency band that showed a threshold decrease of 10 dB or more. "Deteriorated band" means the frequency band that showed a threshold increase of 10 dB or more.

Table 4 shows 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.

Table 5 shows 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.

Table 6 shows the number of the frequency bands that showed a threshold change of 10 dB or more in TSC group.

Table 7 shows the number of the frequency bands that showed a threshold change of 10 dB or more in control group.

The numbers expressed in percentages indicate 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 confirmed by Scheffe's post hoc test or Tukey's HSD post hoc test.

The TSC group (78%) significantly differed from the control group (44%) on auditory threshold amelioration; $P = .008091$ in DV1, $P = .000546$ in DV2 by Scheffe's post hoc test. Female subjects (77%) showed a significant difference in DV1 from male subjects (47%); $P = .025468$ in DV1 by Scheffe's post hoc test. Older subjects (75%) showed no significant difference from younger subjects (53%); $P = .139149$ in DV1, $P = .082920$ in DV2 by Scheffe's post hoc test.

The other statistical results were as follows:

Female in TSC vs. male in control: $P = .004504$ in DV1, $P = .001537$ in DV2 by Scheffe's post hoc test.

Male in TSC vs. male in control: $P = .134098$ in DV1, $P = .016449$ in DV2 by Scheffe's post hoc test.

Older in TSC vs. younger in control: $P = .046568$ in DV1, $P = .003339$ in DV2 by Scheffe's post hoc test.

Older in TSC vs. older in control: $P = .026420$ in DV1, $P = .003339$ in DV2 by Scheffe's post hoc test.

TABLE 1 Statistical samples for ANOVA

TSC group (1)																							
ID	**02**	**04**	**20**	**22**	**29**	**44**	**52**	**55**	**58**	**59**	**60**	**65**	**67**	**71**	**72**	**73**	**76**	**78**	**80**	**81**	**84**	**89**	**93**
Sex	F	F	F	M	M	F	F	M	F	F	M	F	F	F	M	M	M	M	F	M	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	21
DV1	3	0	2	2	3	3	2	2	3	3	3	1	3	3	2	2	1	2	2	0	3	3	0
DV2	1	0	1	1	1	1	1	1	1	1	1	0	1	1	1	1	0	1	1	0	1	1	0
Control group (0)																							
ID	**03**		**06**		**30**		**53**		**56**		**57**		**64**		**66**		**74**		**79**		**85**		**87**
Sex	F		M		F		M		F		M		F		M		F		M		F		F
Age	78		77		65		69		80		78		45		46		57		82		54		71
DV1	0		0		3		0		0		1		0		1		3		0		1		1
DV2	0		0		1		0		0		0		0		0		1		0		0		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**	**23**
IV2	1	1	1	0	0	1	1	0	1	1	0	1	1	1	0	0	0	0	1	0	1	1	0
IV3	0	0	1	1	1	0	0	0	0	1	1	0	1	1	0	1	0	0	1	0	1	1	0
DV1	3	0	2	2	3	3	2	2	3	3	3	1	3	3	2	2	1	2	2	0	3	3	0
DV2	1	0	1	1	1	1	1	1	1	1	1	0	1	1	1	1	0	1	1	0	1	1	0
IV1: Control group (0)																							
N	**24**		**25**		**26**		**27**		**28**		**29**		**30**		**31**		**32**		**33**		**34**		**35**
IV2	1		0		1		0		1		0		1		0		1		0		1		1
IV3	1		1		0		0		1		1		0		0		0		1		0		1
DV1	0		0		3		0		0		1		0		1		3		0		1		1
DV2	0		0		1		0		0		0		0		0		1		0		0		0

Note: 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).

TABLE 2 Hearing threshold changes in total subjects

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)						
	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)

TABLE 3 The number of frequency bands that showed threshold changes

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

Older female subjects in TSC group vs. younger male subjects in control group: $P = .039637$ in DV1, $P = .005917$ in DV2 by Tukey's HSD post hoc test.

Older female subjects in TSC group vs. older male subjects in control group: $P = .047998$ in DV1, $P = .016162$ in DV2 by Tukey's HSD post hoc test.

TABLE 4 Hearing threshold changes after 2 to 3 weeks of TSC 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)				
	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)

TABLE 5 Hearing threshold changes 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)				
	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)

TABLE 6 The number of frequency bands that showed threshold changes in TSC group

The number of the frequency bands that showed a threshold change of 10 dB or more (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)

TABLE 7 The number of frequency bands that showed threshold changes in control group

The number of the frequency bands that showed a threshold change of 10 dB or more (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)

Older male subjects in TSC group vs. younger male subjects in control group: P = .152064 in DV1, P = .023918 in DV2 by Tukey's HSD post hoc test.

4 | DISCUSSION

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 for protecting against age-related or noise-induced hearing loss in animals.[4,14,15] 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.[14,16-21] 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.

Forward sound conditioning (i.e., exposure to a non-traumatic-level sound before traumatic noise exposure) reduces the extent of noise-induced permanent hearing threshold shift (PTS), and this PTS reduction can be as large as 30 to 40 dB. This protective effect of sound conditioning has been documented in a number of different species of animals, including guinea pigs,[4] chinchillas,[22] gerbils,[5] rats,[23] and mice.[6] These studies have employed 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.[6,24]

In an early human study, the effect of low-level training acoustic stimulation (70 dB for 6 hr/day for 9 days) on the susceptibility to noise was first assessed in teenage subjects by comparing noise-induced temporal hearing threshold shifts.[11] During the training period, the subjects listened to music at the 70 dBA prespecified levels, and this acoustic intervention significantly reduced noise susceptibility compared with the level of susceptibility in the pretraining

period, particularly in the 3 to 3.5 kHz on and after D9. The experiment continued past the 5 days, and showed a further reduction of TTS which expanded to 2 to 5 kHz. In addition, the training effect diminished 4 days after stimulation cessation, clearly implying that the reported stimulation parameters have reversible effects. In animal models, Canlon et al[4] showed that guinea pigs maintained some level of protective effect for several weeks to a month after forward stimulation. These differences may be partially explainable by natural differences in species, length of training, intensity and frequency of stimulation. In addition, there is mounting evidence that suggests that periodic stimulation interspersed with quiet rest also may add to the forward protective effects.[25,26] 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, as well as their ability to condition to repetitive environmental stimulation, and post-stimulation fatigue have been described. This allows the hair cells to not only function as mechano-electrical transducers, but also to 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[27] 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 was shown to have 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[28] 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 has been further evidence that sound conditioning releases adrenocorticotrophin hormone and glucocorticoid release and alteration of the hypothalamic-pituitary-adreal (HPA) axis. There has also been secondary evidence, such as the fact that adrenalectomy resulting in HPA disruption negates the efficacy of sound conditioning. In addition, subsequent corticosterone replacement of these same adrenalectomized mice also shows 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.[24] It is hypothesized that sound conditioning may prevent the trauma-induced downregulation of glucocorticoid receptors at the level of the hair cells in the cochlea, and eventually the central components of the hypothalamic-pituitary axis.

Backward sound conditioning (ie, exposure to a nontraumatic level sound after traumatic noise exposure) has also been reported to reduce noise-induced hearing loss.[15,29,30] Compared with the control group that was exposed only to acoustic trauma, guinea pigs conditioned with non-traumatic level sound after the traumatic noise exposure exhibited a reduced ABR and distortion product otoacoustic emissions threshold shift.[29] In addition to the ABR threshold shift reduction, the level of outer hair cell loss was also decreased in sound-conditioned chinchillas.[30] The ameliorative effect on hair cell damage was induced even with an ambient level of sound conditioning.[31] Cochlear damage is known to be followed by the reorganization of the cortical tonotopic map in cats,[32] 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 in the peripheral region.[15]

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.[33,34] 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 any corresponding external sound. Both symptoms are known to be closely related to sensorineural hearing loss. Noreña and Chery-Croze[33] reported that hyperacusis could be improved through hearing-threshold-level acoustic stimulation. 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.[34]

In recent years, there has been mixed data regarding the ameliorating backward effects of threshold sound conditioning in sensorineural hearing loss.[7,15,29,30] 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 Meniére's disease. Furthermore, with the growing broader understanding of TSC with the 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 toward 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 are necessary to fully elucidate the pathophysiology and mechanism of action of TSC.

CONFLICT OF INTEREST

No potential conflict of interest was reported by the authors.

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