Journal of Otolaryngology and Neurotology Research
JONR, 1(1): 20-27
www.scitcentral.com

Original Research Article: Open Access

A Pre-Clinical Trial of a Novel Tinnitus Management Therapy: The Cochleural Alternating Acoustic Beam Therapy (CAABT)

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Received October 05, 2018; Accepted October 08, 2018; Published November 30, 2018

ABSTRACT

Purpose: A novel tinnitus treatment therapy, the Cochleural Alternating Acoustic Beam Therapy (CAABT), has received positive feedbacks from early clinical trials and studies. We intend to assess the effectiveness and safety of this new approach utilizing the psychoacoustic measures combined with rs-fMRI.

Materials and methods: This study enrolled 11 adult Chinese patients with unilateral chronic tinnitus of frequencies between 125-8000 Hz at an average loudness of 31 dB. The patients underwent a 12 week treatment with the CAABT method and the outcomes were evaluated with questionnaire scores, a set of psychoacoustic measures and rs-fMRI testing before treatment and at 3 months.

Results: Nearly all the patients reported reduced tinnitus annoyance after the three-month treatment. The THI and VAS scores showed decreased tinnitus severity. The rs-fMRI results indicated that the right middle frontal gyrus and the right superior temporal gyrus displayed noticeable decreases of the ReHo values for the subjects between the before and after treatments, supporting the clinical evidence of significant tinnitus reduction.

Conclusion: The therapy seemed effective in patients of varying severities, and no side effects were observed in this trial. The CAABT can be an alternative for those who are suitable for sound therapy once a large scale of and better controlled clinical studies have validated the findings of this experiment.

Keywords: rs-fMRI, CAABT method, Clinical trials, Psychoacoustic measures

INTRODUCTION

Tinnitus is a common health disorder affecting people of all ages around the world. Although the actual mechanism is still unclear, the latest functional imaging studies have revealed that tinnitus is possibly featured by alteration of the both regional neural activities and functional connectivity within and beyond the auditory network [1]. Among those, resting-state functional magnetic resonance imaging (rs-fMRI) has been recently used to analyze the abnormal regional neural activities, potentially being a parameter quantitatively measuring the severity of disease and objectively assessing the effects of tinnitus management.

For the last 40 years, sound treatment has been widely utilized at clinics to help tinnitus patients in desperate needs for medical intervention and reported to demonstrate identifiable effects with little side effects when used appropriately and assisted professionally. Nevertheless, the disadvantages of this approach have also been reported that a

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Citation: Liu C, Lv H, Jiang T, Xie J & He L, et al. (2018) A Pre-Clinical Trial of a Novel Tinnitus Management Therapy: The Cochleural Alternating Acoustic Beam Therapy (CAABT). J Otolaryngol Neurotol Res, 1(1): 20-27.

lack of the accuracy of targeting the pathological mechanism underlying the tinnitus has limited the potential benefits to a larger number of patients.

It is exactly in view of the limitations of the traditional methods that we have developed an innovative sound therapy: the Cochleural Alternating Acoustic Beam Therapy (CAABT), a novel tinnitus intervention, based on the latest neural science and cochlear plastic research, to neutralize the discordant responses of the dysfunctioning cochlea via acoustic beaming stimuli. This new approach attempts to treat each patient with a set of sound signals individually prescribed. This paper is to assess the effectiveness of the CAABT in a small group study before the formal clinical trial. The employment of the rs-fMRI evaluation will provide us with a different perspective to validate the standard tinnitus evaluation.

METHODS

Study participants

The research protocol was approved by the Beijing Friendship Hospital ethics committees (No. 2016-P2-012) prior to the experiment. The inclusion criteria applied to the patients with unilateral, chronic (longer than 6months) tinnitus, over 18 years old with normal communication abilities, the main tinnitus frequency between 125 and 8000 Hz and willing to participate in the study and commit to daily usage. We excluded those patients with conductive hearing loss, middle ear diseases, or retro cochlear auditory diseases, inability to read and write Chinese, healthy problems or ongoing tinnitus treatment, or any contraindications to MRI.

Procedures

The subjects were fitted with the sound generators embedded with the operating algorithm of the CAABT after completing all the necessary tests. They were fully instructed how to wear and adjust the devices by qualified audiologists. For a 12 week trial, the patients were advised to use the sound generators 15min each session, three times a day. The volume levels of the CAABT were set just audible to mix with the loudness of tinnitus as described by the TRT as “the mixing point”. The loudness was generally programmed to the most comfortable levels and the patients were advised to function naturally in their daily life, paying as less attention to the signals generated as possible. Each day they were followed up via the instant messaging apps on their phones by answering the questions like “How do you use your device today?”, “Please try to ignore the signals from your device”, “Please keep using the device as advised for the whole 12 weeks!”, “contact us if you have any questions”.

Outcome measurements

The outcome assessment protocol consists of the following:

- Tinnitus history for each patient as required
- The Chinese version of tinnitus handicap inventory (Thi)
- The visual analog scale (Vas) on numerical description of annoyance and tinnitus perception
- Pure tone audiometry
- Acoustic impedance
- Otoacoustic emissions (OAE)

The CAABT

The CAABT produced a set of synthesized sound consisting of the stimulus and carrier sounds. The stimulus sounds centered on the tinnitus frequency (Tf) as measured and covered the up and down of the Tf, marked as f1 and f2 in **Figure 1**. f1 equals to Tf (1-10%) Hz and f2 equals to Tf (1+10%) Hz. The 3 stimulus signals occurred at the exact interval of 500 ms each in the sequence of f1, Tf, f2 and f1+Tf+f2 in combination the three signals occurring simultaneously. The duration of f1, Tf, f2 and f1+Tf+f2 was 50 ms each, marked S1, S2, S3 and S4 in **Figure 1**. The carrier sounds were continuous and steady, such as ocean tides, running water or brook sound. The volumes of stimulus tone and carrier sounds were all prescribed by the individual MMLs of each patient. The stimulus tones were set at 5 dB below the MML with the carrier sounds at 10 dB below the MML. The audiologist would be responsible for setting up the stimulus levels and the patients would select the carrier sounds to his or her preference.

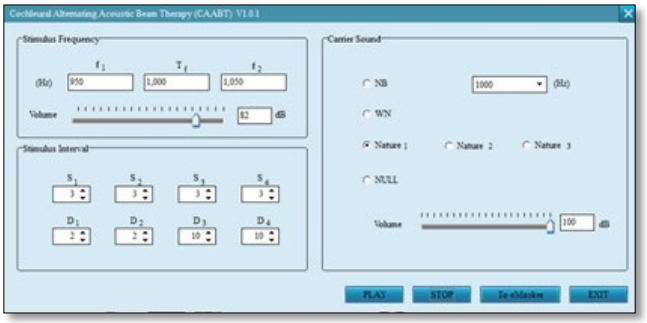

Figure 1. Test-run surface.

rs-fMRI

The MR data were acquired using a General Electric (GE) 3 Tesla scanner (Milwaukee, WI, USA). During the scan, the subjects were informed that they should keep their eyes closed, remain still and avoid mentally focusing on anything. Functional images were obtained using a GRE-EPI sequence: 28 slices; slice thickness/gap, 4 mm/1 mm; repetition time, 2000 ms; echo time, 35 ms; flip angle, 90°; field of view, 24 cm × 24 cm; matrix, 64 × 64. Each fMRI session lasted 400 s, containing 200 time points.

We also acquired structural images covering the whole brain by using a 3D-T1 sequence: 196 slices; slice thickness, 1.0

mm without gap; repetition time, 8.8 ms; echo time, 3.5 ms; inversion time, 450 ms; flip angle, 15°; field of view, 24 cm × 24 cm; matrix, 256 × 256. Data processing was performed with DPARSF (Data Processing Assistant for RS-fMRI; http://www.restfmri.net/based on SPM 8). Important steps of the data processing included removing first 10 time points, slice-timing, realign, normalization and re-sampling into 3 mm isotropic voxel, and regress out nuisance covariates. Those steps were collaborated described in previous studies. Structural images were applied in the normalization step to gain better results.

We used a rs-fMRI data analysis toolkit (REST; http://www.restfmri.net) to perform ReHo (regional homogeneity) assessment and a related statistical analysis of the rs-fMRI studies.

RESULTS

Tinnitus history

The detailed tinnitus history for all the subjects is listed in **Table 1**.

Table 1. Tinnitus history for each patient.

Participants	Gender	Age (Years)	Laterality	Tinnitus Perception	Treatments	Treatment Duration
1	Female	59	L	Rumbling	TCM	6
2	Male	76	L	Birds chirping	none	
3	Female	47	R	Buzzing	HO+VD+M+A	6
4	Male	39	R	Unable to describe	TCM+A	5
5	Female	28	L	Buzzing	TCM+VD	2
6	Male	64	L	Cicadas chirping	TCM+PT+A+VD	12
7	Female	59	L	Mixed sound	TCM+HO+VD	6
8	Male	33	L	Metal or whistle	TCM+VD	0.5
9	Female	39	R	Buzzing	TCM	0.5
10	Female	52	L	Unable to describe	TCM+VD	6
11	Female	49	R	Mosquito sounds	TCM+VD	24

Abbreviations: L: Left Sided; R: Right Sided; TCM: Traditional Chinese Medicine; HO: Hyperbaric Oxygen; VD: Vasodilator Drugs; M: Massage; A: Acupuncture; PT: Physical Therapy

Hearing thresholds in the ears with tinnitus

The pure tone hearing thresholds for each patient in his or her tinnitus ear are summarized in **Figures 2 and 3**.

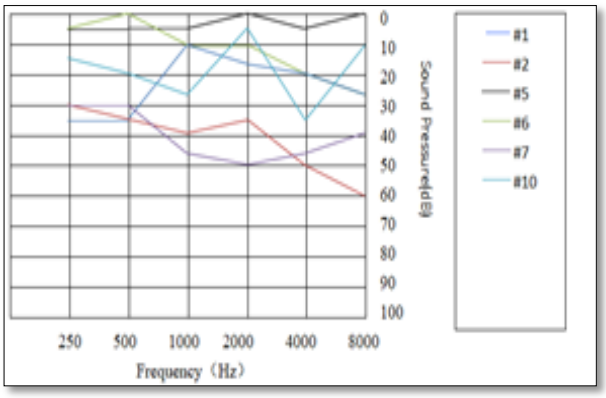

Figure 2. The hearing thresholds of the left ear for the patient with tinnitus on the same side.

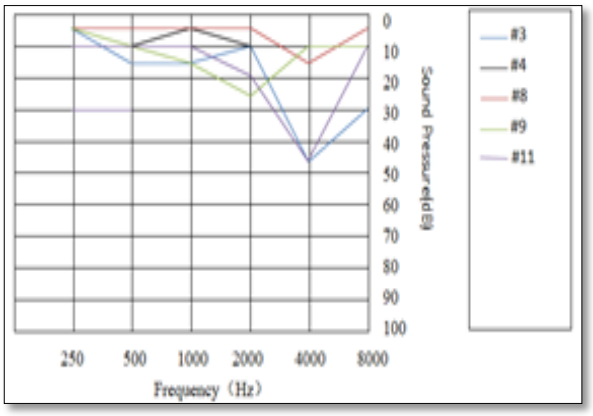

Figure 3. The hearing thresholds of the right ear for the patient with tinnitus on the same side.

The tinnitus evaluation

The tinnitus evaluation results from a set of psychoacoustic measures were summarized in **Table 2**.

Table 2. A set of psychoacoustic measures for each patient (loudness matching in **Table 4**).

Participants	Types	Pitch-match (Hz)	RI	Feldmann Types	First Loudness	Final Loudness	Tone Change
1	Pure tone	125	Partial positive	Overlapping type	48	25	
2	Pure tone	4000	Total positive	Divergence type	65	65	
3	Pure tone	3750	Partial positive	Convergence type	35	37	
4	Pure tone	4000	Total positive	Convergence type	18	10	
5	Pure tone	3975	Total positive	Convergence type	10	8	
6	Pure tone	7900	Total positive	Convergence type	45	32	7300
7	Pure tone	8000	Total positive	Convergence type	50	51	
8	Pure tone	3800	Total positive	Convergence type	15	11	3700
9	Pure tone	7500	Partial positive	Convergence type	10	8	
10	Pure tone	4000	Negative	Convergence type	40	20	Twitter tone
11	Pure tone	4000	Total positive	Convergence type	45	0	

Patient's feedbacks on the treatment

Patient #1 reported reduced annoyance after being treated with the CAABT. While Patient #2 felt his tinnitus was intermittent, he did report that he sometimes felt comfortable in his conditions. Patient #4 reported that his tinnitus was reduced in loudness and only noticed it before or shortly after sleeping. Patient #7 mentioned that his tinnitus had "moved out "from his ear. He felt that the CAABT treatment was quite effective to help him cope with increasing loudness in tinnitus which happened once when one of his family members suddenly became ill during the time of the treatment. Patient #10 reported his tinnitus was nearly absent and occurred only for very short durations. Patient #11 felt she had reduced the loudness and particularly alleviated the impact on herself which was quite severe before the treatment. This improvement could be seen in the decreased perception of the intensity levels at which the CAABT was delivered even at the same control. During the session, the patient reported the perception of her tinnitus had become diminished in both the loudness levels and occurrence intervals. More noticeably she felt quite relieved because of reduced annoyance by her tinnitus after a four week treatment.

Subjective scores (THI and VAS)

The THI and VAS scores in **Table 3** noticeably depicted a decreasing tendency of tinnitus annoyance for all the patients after the CAABT treatment. It is worth mentioning that the measured tinnitus loudness and subjective perception of tinnitus were well matched with the clinical validation findings.

Table 3. THI, VAS scores and loudness matching before and after treatment.

Patients	THI		VAS		Tinnitus Loudness	
	Baseline (F+E+C)	12 weeks (F+E+C)	Base line	12 weeks	Baseline	12 weeks
1	82 (30+32+20)	22 (8+8+6)	10	4	38	15
2	92 (44+32+16)	8 (0+0+8)	9	2	45	45
3	54 (26+16+12)	20 (10+4+6)	5	2	35	37
4	46 (16+18+12)	4 (4+0+0)	4	1	18	10
5	42 (16+16+10)	2 (2+0+0)	3	2	10	8
6	46 (14+16+16)	10 (4+0+6)	6	5	45	32
7	20 (10+4+6)	6 (6+0+0)	4	3	39	40
8	12 (8+0+4)	4 (4+0+0)	3	1	15	11
9	26 (12+6+8)	8 (4+2+2)	4	1	9	8
10	42 (18+14+10)	6 (6+0+0)	4	3	40	20
11	50 (26+10+14)	0 (0+0+0)	7	0	45	0

Side effect

During the experiment, none of the subjects experienced any side effects.

rs-fMRI

The subjects of the both groups were matched in ages, genders and left-right handedness except for the tinnitus complained by the study group which had subsequently received the treatment by the CAABT. Further comparative analyses were conducted to examine the differences of the tinnitus group based on the data obtained before and after the tinnitus treatment in month 1 (Group 1) and month 4 (Group 2), respectively, and the normal control group in month 1 (Group 3) and month 4 (Group 4). The rs-fMRI findings were displayed in **Figure 4**. The brain regions showed significant differences in ReHo values among the groups **(Figure 4 and Table 4)**. A closer look at the data shows that in the R-MFG (right middle frontal gyrus), the R-STG (right superior temporal gyrus), the cerebellar tonsil, the pons, and the fusiform gyrus, the ReHo values from the study group increased from yellow to red. Among the 5 brain regions, a noticeable decrease in the two regions of the R-MFG and the R-STG for the tinnitus patients before and after treatment, which clearly indicated in **Figures 5 and 6**. At this time no reduction was found in the other 3 regions.

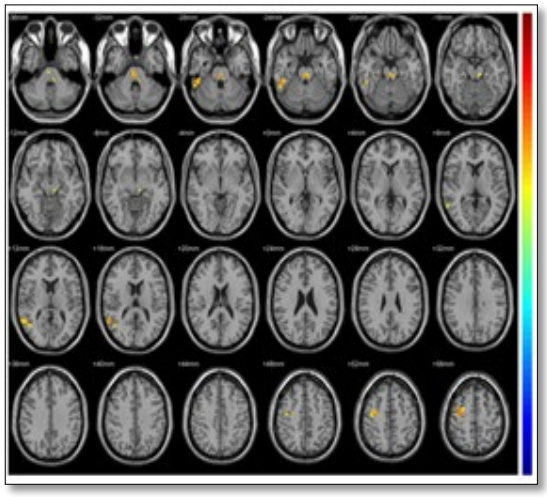

Figure 4. Results of 11 patients compared with healthy controls (two sample t-test).

Heat map (upper, right) shows increased ReHo values areas (values -11.2 to 11.2; blue to red, respectively).

Table 4. Brain regions which showed significant differences between different groups.

Brain region	Peak MNI, mm			Peak *Z* score	Voxels
	x	*y*	*z*		
R Superior Temporal Gyrus	57	-54	15	7.5074	36
R Middle Frontal Gyrus	33	-3	66	8.9249	48
R Fusiform Gyrus	54	-39	-24	8.4982	19
Pons	3	-27	-30	9.2049	50
L Cerebellar Tonsil	-45	-66	-51	9.6696	75

R: Right Sided; L: Left Sided; MNI: Montreal Neurological Institute. Thresholds were set at P<0.05, corrected for FDR corrections

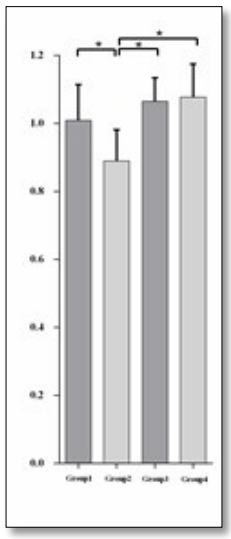

Figure 5: R-MFG.

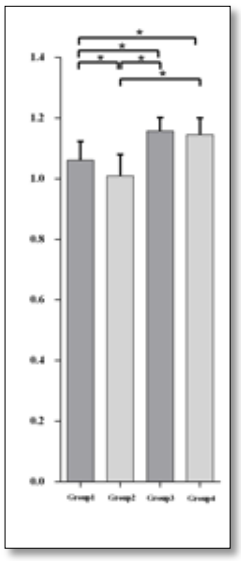

Figure 6. R-STG.

DISCUSSION

The findings of the study indicate that out of 11 patients who have received the CAABT treatment for three months have shown noticeable reductions in the THI and VAS scores as compared to the pretreatment. The subjects reported various decreases in the tinnitus loudness. A close look at the scores of the THI subscales yields an overall reduction of scores in F, E and C, more noticeable in E and C in that several the patients (#4, #5, #7, #8 and #11) scored zero. The interpretation of the zero in the scores of E subscales suggests little catastrophic impact on the patients with tinnitus, thus reducing effects on the scores in F subscales. A further analysis of the psychoacoustic results obtained from those patients displays a wide range of characteristics of tinnitus in pitch perception, loudness and masking. It should be stressed that among all the psychoacoustic assessments described above, the key was to obtain all results as accurately as possible so that the prescription of the CAABT can be achieved to precisely adjust the parameters to achieve the maximum effects on an individual basis. The 12 week sessions with the CAABT have been proved effective to reduce tinnitus annoyance on the patients and can be credited for the thorough, comprehensive and precise measure of their tinnitus.

rs-fMRI change

We have adopted the regional homogeneity approach (ReHo) to analyzing the changing characteristics of the local nerve activities. In general, the increase in ReHo represents an increase in synchrony in regional brain activity and vice versa, which may be considered to explain the central mechanism for the occurrence of tinnitus.

The results obtained by rs-fMRI showed that the changes in the brain activities occurred under the condition that the patients' hearing was normal with no communicative impairment. This was a strong implication that the neural alterations in the brain were related to tinnitus instead of auditory integrity of sensitivity. The rs-fMRI findings have

disclosed the noticeable differences between the tinnitus patients and control subjects. What we have found indicate that for the tinnitus patients, there are abnormal neural activities in the R-MFG and the R-STG and at the same time changes are observed in non-auditory systems such as the pons, the fusiform gyrus and the cerebellar tonsil. The positive findings associated with the CAABT treatment can be viewed as the strong evidence of the effects of the brain plasticity relating to the specially structured acoustic stimuli. Further studies and applications are possible to provide hopes for new treatment in the long battle of the management of chronic tinnitus.

Therapy induced changes

In the study, the treatment outcomes of the patient #11 were most noticeable. As a senior high-school teacher, the patient had a history of asthma for 22 years and for the last two years, she complained of tinnitus mimicking mosquito sounds on her right ear. She had normal hearing thresholds at all frequencies except for 4000 Hz where a notch of 45 dB HL was noted, a pattern similar to noise-induced hearing loss. However, all the testing results had excluded noise exposure. She had tried to seek treatment for the tinnitus, including taking oral vasodilator medicines. Before the course of the CAABT treatment, she disappointed and had stopped the medication for about 3 months. While, shortly after the session began, she reported the immediate disappearance of tinnitus. This “disappearance effects” had remained throughout the whole study and our follow-up indicates she has still maintained the tinnitus free status at the time of writing this article. What really happened to her tinnitus remains as a challenge until further studies are carried out to examine all aspects of this case. Despite this was an individual case, the potential interactions and effects from this case may shed light on the mechanism of the CAABT treatment approach as well as the possible application to patients like her.

The mechanisms of the CAABT

The CAABT is an innovative management approach to simultaneously presenting a two-set sound specifically targeting at the patient with a just audible steady signal along with a series of alternating tone bursts to desensitize the auditory response towards the tinnitus. This therapy is based on several key principles which fully reflect the latest progress of the research on the psychoacoustics, psychophysiology and neurophysiology. First, from the stand of points of psychoacoustics, the two-tier sound treatment creates a low level sound background below the tinnitus loudness which as the sound therapy involved in TRT to induce a steady habituation on the patient method frequently adopted in the traditional sound therapy, studies have shown that broadband noise can achieve the maximum effects [2], at the same time, the alternating burst programmed to match the tinnitus pitch and loudness of the patient work their way to desensitize the annoying tinnitus. The purpose of the well-structured sound system is to maximize the habituation through minimizing the discomfort of the masking sounds with this below-and-at the tinnitus sound therapy.

Second, from the standpoint of neurophysiology, the CAABT intends to reduce the strength of the tinnitus related neural activities. At or near the frequencies of the tinnitus, the alternative bursts of the CAABT directly produce a positive hearing sensation like the tinnitus but at a very fast time. As a result, this sensation will be interpreted not as a negative tinnitus associated with stress and annoyance, merely as “hearing dots” which can be gradually reduced at levels as the neural responses to tinnitus is decreased. During this process, the role of the steady background sound accompanying the alternating bursts is equally important in that sounds below the tinnitus intensity thresholds contribute to habituation [3], quite different from other sound treatment philosophies like masking therapy. At the just audible level, it acts like acoustic distraction away from the uncontrollable focus on tinnitus as reported by many patients and verified by studies. The subconscious intervention contributes to the holistic effects of the CAABT on the reduction of tinnitus related neural activities; therefore, the decoding of tinnitus by the auditory cortex can be gradually reprogrammed to be disassociated with the past unpleasant experience.

Third, the CAABT therapy is delivered at stages to help the patient have a gradual process of hearing and perceive sound. As closely related to the above mentioned neurophysiological explanation, the auditory processing will begin with hearing the treatment signals at the peripheral level as any other new sounds, but gradually move to the stage where tinnitus like sound along with proper counseling will be decoded or interpreted positively at the brain level. Through counseling, patients can better understand its potential negative impact on the perception and reaction towards this disorder, thus interrupting the vicious cycle between the non-auditory system and the auditory system; ultimately a “revised” or “changed” perception of the tinnitus like sounds will occur thanks to the auditory plasticity. It is believed that this process will have a significant impact on the auditory memory of the patient in association with specific acoustic signals, whether negative or positive. This memory alternation can be also because of auditory reprogramming by the brain in perceiving neutrally edited acoustics.

In short, the CAABT is designed in such a way to integrate all the above three functions into one system to achieve the goals of helping patients cope with tinnitus simultaneously at peripheral, neural and brain levels.

CONCLUSION

In conclusion, the clinical study on the efficacy of the CAABT has shown positive outcomes for the treatment of tinnitus. Nearly all the patients in the study reported

different degrees of tinnitus reduction which have ultimately improved the quality of their life. In short, the outcomes of this study do show positive therapeutic effects both on severe and slight tinnitus patients, but more importantly this has further confirmed the possibility of employing acoustics to achieve a more effective intervention through continuing improvement and innovation.

ACKNOWLEDGEMENT

This work was supported by Grant No. TJSHG201510025004 from Ministry of Science and Technology of the People's Republic of China and we specially thanks to the Micro-DSP Technology Co., Ltd. for providing the personal sound devices.

DECLARATION OF INTEREST STATEMENT

The authors declare that there are no competing interests in third trial.

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