The Long-term Effectiveness of Tinnitus Multivariate Integrated Sound Therapy (T-MIST) in 148 Tinnitus Patients with Normal Hearing Thresholds: Our Initial Experience

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Running title: Long-term Effectiveness of Combined Sound Therapy

[Key Points]

1. This preliminary study provides a combined sound therapeutic strategy (called T-MIST) for the management of tinnitus patients with normal hearing thresholds. It takes into account individual tinnitus characteristics and personal choices of sounds to provide an efficient intervention.
2. High-resolution pure tone audiometry was used to measure precise tinnitus pitch and loudness. A Residual Inhibition Test (RIT) was performed using narrow band noise matched to tinnitus frequency at 10 dB above perceived tinnitus loudness for 60 seconds.
3. Effectiveness of long-term sound therapy was evaluated using the Tinnitus Handicap Inventory (THI) at the pre-sound therapy assessment as well as at follow-up visits held at 1, 3, 6, 9 and 12- months.
4. T-MIST had a positive long-term effect on tinnitus patients with normal hearing thresholds. The RIT appears to be a useful indicator for short-term effectiveness of sound therapy intervention. However, the audiometric tinnitus loudness measures may be insufficient in describing an individual's reaction to sound therapy intervention.
5. These results should be interpreted with caution due to the preliminary nature of this study. Further studies should be conducted to explore more convincing benefits derived from this intervention for chronic tinnitus and the associated influencing factors using systematic approaches, such as randomized controlled trials, and comparisons of tinnitus patients with varying degrees of hearing loss.

[Introduction]

Tinnitus can be highly problematic when symptoms persist and particularly where it causes health problems, such as loss of sleep, hearing difficulties and psychological problems.[1] In recent years, a number of sound-based therapeutic approaches have been developed and commonly used to manage tinnitus sufferers.[2] They involve exposing the patient to one or more types of sound at different levels, either for masking, sound enrichment or habituation, using hearing aids or sound generators. There are numerous rationales underlying sound therapy for tinnitus intervention, depending on the types of sound used in the practice.[3]

In tinnitus patients with a hearing loss hearing aids are primarily used to amplify sound to improve speech intelligibility and facilitate communication. Hearing aids however also have a masking effect on tinnitus because amplified environmental sound can be loud enough to mask the tinnitus and reduce the attention paid to the tinnitus.[3] Moreover, sound amplification matched to the hearing loss provides sufficient peripheral acoustic stimulation to compensate for deafferentation, and consequently reduce the sensory deprivation in the central auditory system.[3]

Alternatively, sound generators can be used to provide a variety of sounds such as; pure tone, narrow-band noise (NB noise), natural sounds (e.g., bird sounds, crickets, or thunderstorms) or music, for the purposes of inhibition, habituation, desensitization, or attention diversion.[4] It is widely accepted that narrow band noise can be used to suppress hyperactivity with decreases in cortical neural synchrony, or decreases in central gain [3] In contrast, because music is a form of art that combines sounds or sequences of notes in harmonious patterns pleasing to the ear and satisfying to the emotions, natural sounds and music provide positive effects on emotion and relaxation and can improve the patients acceptance of their tinnitus and intervention.[3]

Whilst there are a large number of studies investigating the benefits of sound therapy on tinnitus,

the results are inconsistent in terms of their effectiveness in reducing the intensity of tinnitus and distress caused. There remains considerable debate as to the effectiveness of sound therapy, because of the tinnitus condition and influencing factors.[3]

In this study, an innovative approach that combines multiple sound sources (Tinnitus Multivariate Integrated Sound Therapy, T-MIST) was used as a form of intervention for tinnitus patients with normal hearing thresholds. This approach introduced individually tailored management strategies using narrow band (NB) noise centered around the tinnitus frequency in combination with natural sound and relaxing music. The advantage of T-MIST is that it provides a combination of sounds that match the needs and preferences of the individual, which may enhance therapeutic effectiveness by engaging different levels of the auditory pathway, as each individual sound showed evidence of improving tinnitus measures.[5] It also appears more appropriate and feasible in terms of acceptance for tinnitus patients with normal hearing thresholds.[3]

In clinics, some 10-15% of patients undergoing audiological assessment for a primary tinnitus complaint have hearing thresholds measured with pure tone audiometry within normal limits.[6] Because of the absence of abnormal audiometric findings when using conventional pure-tone audiometry, there are significant challenges to understand and manage this group of tinnitus patients when they attend the ENT/Audiology clinic.[6] Although various sound therapeutic approaches are clinically trialed as an effective intervention for tinnitus sufferers [4], to our best knowledge, specific intervention strategies (sound therapy protocols) applied to tinnitus patients with normal hearing thresholds and the long-term effectiveness of the sound therapy still remain to be investigated. This preliminary study aimed to explore the effectiveness of using T-MIST for tinnitus patients with normal hearing thresholds at 1-, 3-, 6-, 9- and 12 months.

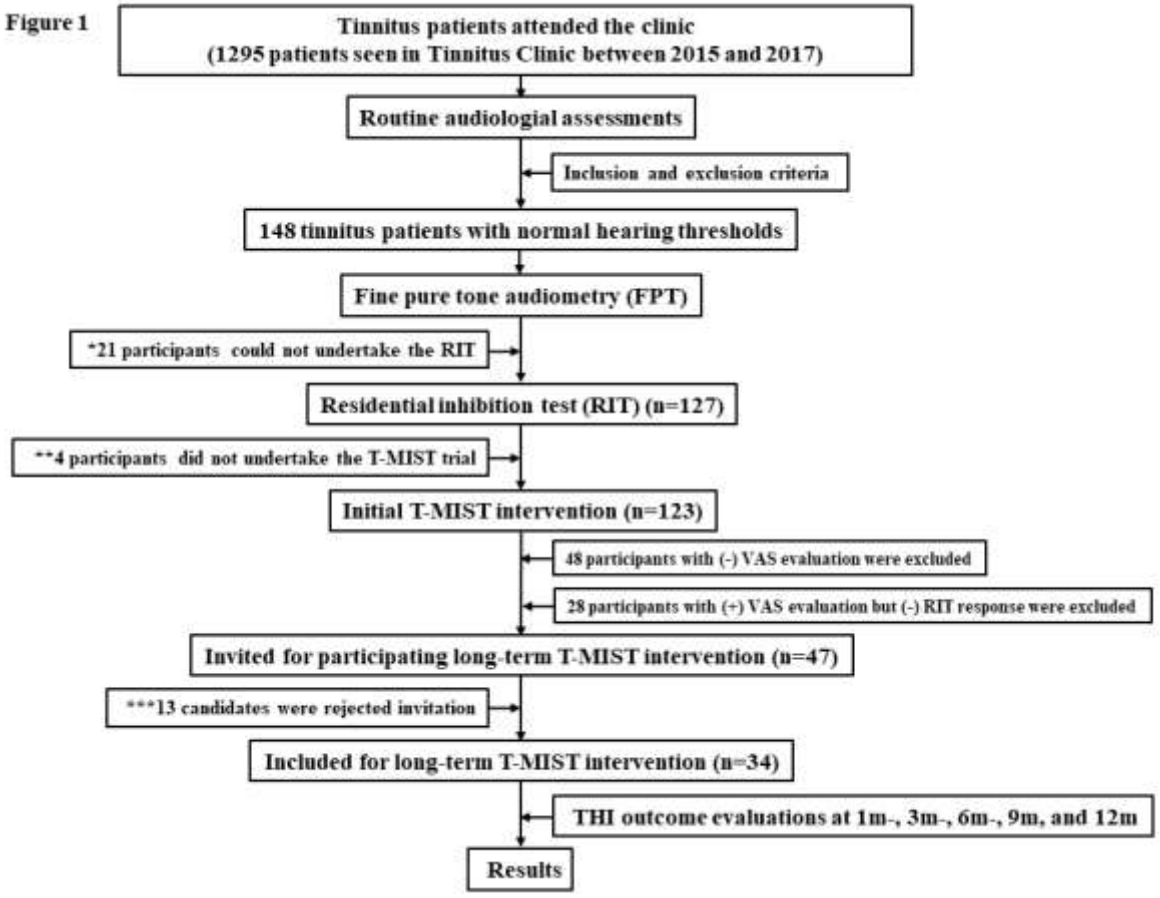
MATERIALS AND METHODS

Participants

148 patients with tinnitus but having hearing thresholds within normal limits were recruited from January 2015 to March 2017 in the First People's Hospital of Foshan, Guangdong, China. They had hearing thresholds audiometrically within 'normal limits', defined as ≤ 20 dB HL at each octave frequency from 500 to 4,000 Hz in the poorer ear, with no hearing level at any frequency between 250 and 8,000 Hz exceeding 30 dB HL.[6] The mean age of participants was 32.0 years (SD: 9.4), range 18 to 64 years. There were 72 males and 76 females.

Audiological investigation procedure

All participants followed a written clinical protocol (Figure 1), comprising otoscopic examination, pure tone audiometry, admittance test, and tinnitus match test.



Pure tone hearing thresholds were measured for both ears at frequencies between 125Hz and 8,000 Hz, using a calibrated GSI AudioStar Pro audiometer with TDH 39 headphones. The procedure used was that recommended by the British Society of Audiology.[7] High resolution

pure tone audiometry (TinniFit SFTest 330, Bluesound, China) was used to measure precise tinnitus pitch and loudness. The procedure for tinnitus pitch matching testing was that reported in Zhao et al.[6]

The Residual Inhibition Test (RIT) was conducted using narrow band (NB) noise matched to tinnitus frequency presented to the tinnitus ear at 10 dB above perceived tinnitus loudness for 60 seconds. The RIT results were categorized into the following conditions:[8]

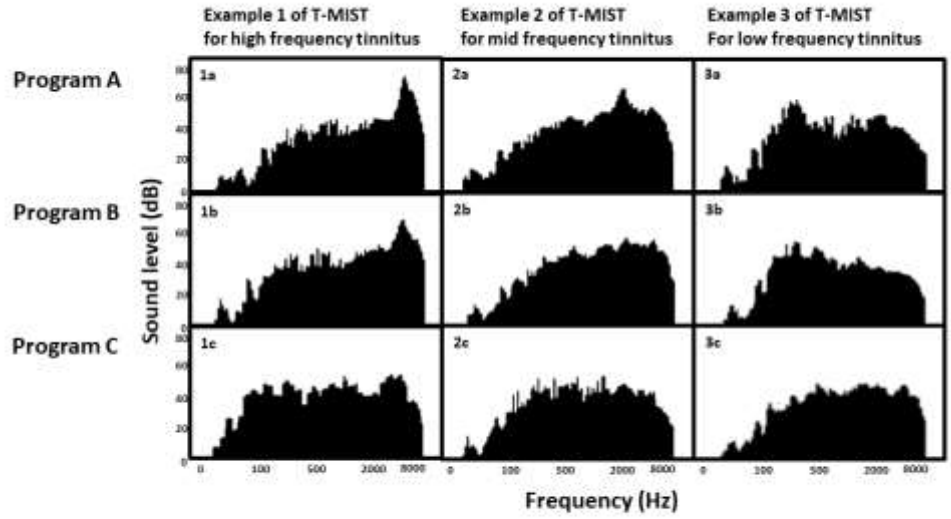
- *Positive*: tinnitus disappears completely (total residual inhibition);
- *Partially positive*: tinnitus loudness is reduced (partial residual inhibition);
- *Negative*: tinnitus is not changed;
- *Rebound*: tinnitus loudness is increased.

The protocol and procedure for combined sound therapy

Three sound therapy programs were prescribed on the basis of the combination of the sound sources as shown in Table 1. The patient's preference and frequency characteristics of n-Sounds and t-Sounds were considered when choosing the T-MIST programs. **Figures 2i, 2ii and 2iii** show frequency characteristics of three example T-MIST prescriptions.

The three prescribed T-MIST programs were then stored on a sound generator (TTBox). The tinnitus patients could choose one program, either A or B or C, or more programs e.g., A-B-C to play repeatedly.

Figure 2



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120 **Tinnitus Handicap Inventory (THI) Questionnaire**

121 The effectiveness of the sound therapy was evaluated using the Tinnitus Handicap Inventory
122 (THI) at 1, 3, 6, 9 and 12- months [9] In addition, the effectiveness perceived by the participants
123 in terms of tinnitus loudness was assessed immediately after having the T-MIST intervention
124 using visual analog scales (VAS), which ranged from 0 to 10 (0 = tinnitus is absent, 10 = cannot
125 stand any more).

126 **Statistical design and analysis**

127 Statistical analysis was undertaken using the Mann-Whitney-Wilcoxon Rank sum test or
128 Kruskal–Wallis H test, a non-parametric alternative of analysis of variance (ANOVA) test.
129 Significance level was set at the conventional 5% for all tests.

130 **Ethical considerations**

131 This study was approved by the ethics committee of The First People's Hospital of Foshan and
132 Health Care and Food Ethics Panel, Cardiff School of Sport and Health Sciences, Cardiff
133 Metropolitan University.

Table 1. The T-MIST- Three sound therapy programs on the basis of the combination of various sound sources.

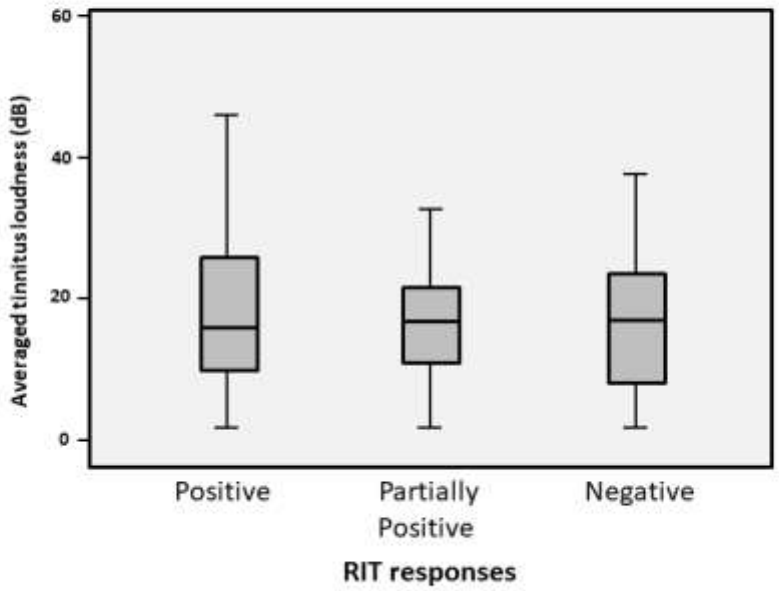
Sound Therapy Program		Frequency Characteristics	Sound level	Time length of each type of sound (seconds)	Recommended duration of sound therapy
Program A	***i-Tone***	Narrow-band noise centred around tinnitus frequency	Approximately 5dB above tinnitus loudness level	60 seconds	Minimum 2-3 repeat playbacks if it is used alone. (8-18 minutes)
	n-Sound	Natural sound chosen on the basis of tinnitus frequency	At the most comfortable level	120-150 seconds	
	t-Sound	Relaxing music chosen by individuals	At the most comfortable level	240-360 seconds	
Program B	***n-Sound***	Natural sound chosen on the basis of tinnitus frequency	At the most comfortable level	120-150 seconds	Minimum 2-3 repeat playbacks if it is used alone. (8-18 minutes)
	t-Sound	Relaxing music chosen by individuals	At the most comfortable level	240-360 seconds	
Program C	***t-Sound***	Relaxing music chosen by individuals	At the most comfortable level	240-360 seconds	Minimum 2-3 repeat playbacks if it is used alone. (8-18 minutes)

[Results]

1] Residual Inhibition Test (RIT) and the immediate effectiveness of T-MIST on tinnitus patients with normal hearing thresholds

According to the criteria described in the section on RIT measurement, out of 127 participants, 52 patients (52/127, 40.94%) had a positive or partially positive RIT response. Of these, 12 patients had tinnitus in the left ear, 12 had tinnitus of the right ear and 28 had bilateral tinnitus. However, 62 patients had a negative or rebound RIT response. Tinnitus loudness did not differ significantly between the groups with different RIT responses using the Kruskal-Wallis test (H=0.44, p=0.81) (Figure 3).

Figure 3



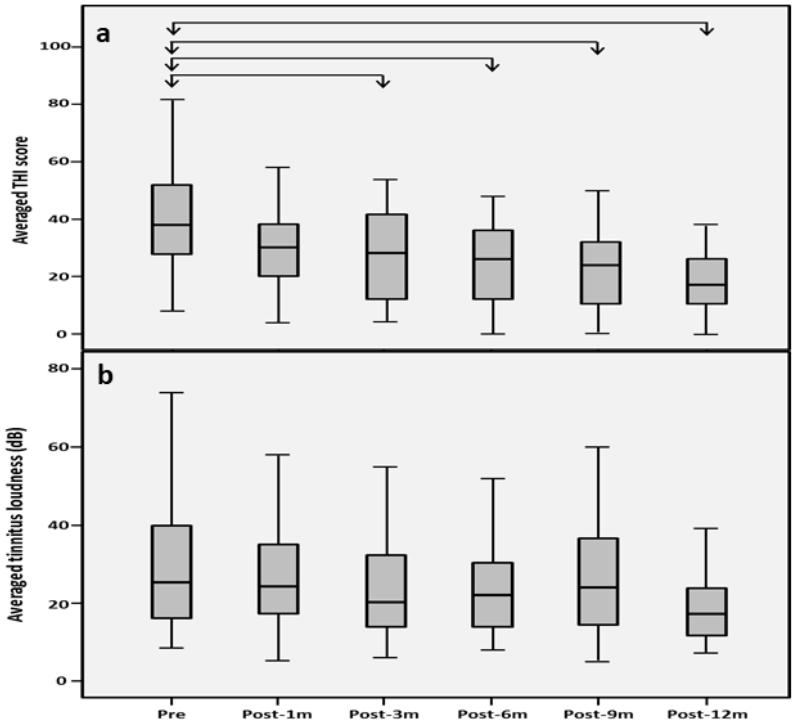
According to the study protocol (Figure 1), a trial of the T-MIST intervention was provided to the participants after the RIT, no matter whether they had positive or negative RIT responses, followed by an immediate assessing of the effectiveness of the T-MIST intervention using visual analog scales (VAS). 75 (75/123, 61.0%) participants showed a decreased VAS score,

whereas 48 (48/123, 39.0%) reported that their experience with tinnitus was unchanged. Further analysis showed that a significantly higher proportion of tinnitus patients with positive or partially positive responses found benefit from the T-MIST intervention when compared to those with a negative experience of the RIT (x^2=20.67, *df*=2, p<0.0005).

2] Effectiveness of T-MIST: a long-term follow up of tinnitus patients with normal hearing thresholds

As shown in Figure 1, 34 participants with positive or partially positive RIT and showing immediate positive effectiveness of T-MIST intervention (34/47, 72.3%) were included in the longitudinal study to evaluate changes of THI and tinnitus loudness in order to determine the long-term effectiveness of T-MIST intervention. Figure 4a shows the averaged THI scores obtained at *pre*-and *post*-T-MIST interventions. A Kruskal-Wallis test was performed to analyze the changes in the THI scores at different follow-up stages. Significant decreases in the THI scores were found between *pre*-and *post*-sound T-MIST intervention at all follow-up stages except 1 month after the T-MIST intervention (*pre*- vs. *post-1m:* p=0.13; *pre*- vs. *post-3m:* p=0.048; *pre*- vs. *post-6m:* p=0.003; *pre*- vs. *post-9m:* p=0.001; *pre*- vs. *post-12m:* p<0.0005). However, THI scores did not differ significantly between the different follow-up steps. Furthermore, as shown in Figure 4b, tinnitus loudness was not significantly different when measured at *pre*-and *post*-T-MIST intervention using the Kruskal-Wallis test (H=5.12, p=0.40).

Figure 4



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170 **[Discussion]**

171 In this preliminary study, a combined sound therapy approach was used as a tool to facilitate
172 the effective intervention of tinnitus patients with normal hearing thresholds. This intervention
173 consisted of an inhibition-tone, e.g., a NB noise, with specific frequency characteristics
174 matched to their tinnitus, embedded within personalized natural sound and soothing music. It
175 appears effective, showing significant decreases in THI scores. The natural sounds and
176 soothing music produce an enriched sound background and consequently the neuronal
177 activities towards background sounds in the auditory system are increased through interactions
178 of the auditory, emotional, and cognitive systems in the cortex.[5] Music therapy currently also
179 shows great potential for positive outcomes in alleviating tinnitus perception. Okamoto et
180 al.[10] showed significantly reduced subjective tinnitus loudness compared to a control group
181 who were exposed to different forms of background noise after 12 months of music intervention.

This is likely to work through the limbic system and adjustment of the auditory cortex response. A significant difference was found between participants with various Residual Inhibition Test (RIT) results and outcomes of the sound therapy. This result is in keeping with several previous studies.[11] These studies have shown that residual inhibition is a temporary quieting of tinnitus and a source of relief for tinnitus sufferers. Furthermore, evidence shows that the function of inhibition sound is associated with hearing deficits measured using pure tone audiometry. Roberts et al.[11] suggest that tinnitus frequency specific inhibition sound presented at supra threshold levels provides sufficient suppression over the tinnitus signals by decreasing tinnitus-related spontaneous neuronal activity within the auditory system. Therefore, RIT appears to be a useful indicator for short-term effectiveness of the sound therapy intervention.

Although this preliminary study provides a useful intervention protocol for an effective management strategy for tinnitus, the limitations of the current study should be noted. For example, a randomized control group was not recruited and measured. There was a high drop-out rate, mainly due to patient compliance and unclear expectations. The long-term nature of the study required a number of hospital visits over a long period, this combined with the various assessments caused inconvenience to the patient. In addition, the patients may perceive uncertainty of intervention efficacy in this clinical trial, and thus dropout to seek alternative intervention elsewhere. Therefore, further studies are in the process of preparation to explore the potential benefits derived from this intervention for chronic tinnitus and the associated influencing factors, using systematic approaches such as randomized controlled trials, and comparisons of tinnitus patients with various degrees of hearing loss. In the meantime, appropriate strategies need to be carefully considered in terms of the unique characteristics of tinnitus patients with normal hearing thresholds, in order to reduce the drop-out rate for the long-term follow-up studies.

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Contributors

YXZ and FZ contributed equally to this work in terms of study design, data analysis and writing up the paper. AER and TXL provided suggestion and comment on study design, result interpretation and discussion. In addition, BCW, DPC, and KGC contributed to data collection.

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None

Competing interests

None declared.

Data sharing statements

No additional data are available. However, the original data that support the findings derived from this study can be requested by emailing fzhao@cardiffmet.ac.uk

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[Captions of Figures]

Figure 1. A flow chart of study protocol and procedures

** 21 patients attended the Tinnitus Clinic, but did not present measurable symptoms of tinnitus so could not undertake the RIT.*

*** Two patients with positive RIT responses dropped out from the study, and two other patients with rebound RIT responses were not included.*

**** 13 participants with positive or partially positive Residual Inhibition Test (RIT) and showing immediate effectiveness of T-MIST intervention dropped out the longitudinal study*

Figures 2a, 2b and 2c. Frequency characteristics of three example T-MIST programs.

Figure legend:

1a, 2a and 3a: the frequency spectrum of a combined sound by integrating three types of sound (i.e., i-Tone, n-Sound and t-Sound) used in Program A.

1b, 2b and 3b: the frequency spectrum of a combined sound by integrating two types of sound (i.e., n-Sound and t-Sound) used in Program B.

1c, 2c and 3c: the frequency spectrum of a t-Sound only used in Program C.

Figure 3. Comparison of tinnitus loudness among patients with different RIT responses using tinnitus frequency-matched stimulus

Figures 4a and 4b. A long-term effectiveness of T-MIST in tinnitus patients with normal hearing thresholds.