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OTOLOGY

Clinical characteristics of subjective idiopathic tinnitus and preliminarily analyses for the effect of tinnitus multielement integration sound therapy

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Abstract

Objective To study the psychoacoustic and audiological characteristics of patients with chronic subjective tinnitus and provide basis for the personalized diagnosis and treatment of tinnitus through a single tinnitus multielement integration sound therapy (T-MIST) and analysis of efficacy preliminarily.

Methods 145 patients with tinnitus were assessed by systematic medical history collection, professional examination of otolaryngology, audiology examination, full precision test (FPT), residual inhibition test (RIT), tinnitus handicap inventory (THI) and visual analog scale (VAS) annoyance. The correlation among factors was performed.

Results The frequency of tinnitus was correlated with the frequency of maximum hearing loss ($P < 0.05$). The loudness of tinnitus was correlated with the loudness of maximum hearing loss ($P < 0.05$). In this study, T-MIST was used to treat tinnitus. After treatment, tinnitus alleviated VAS annoyance ($P < 0.05$). The results of RIT were correlated with the effect of T-MIST ($P < 0.05$).

Conclusion There was a correlation between tinnitus and hearing loss. The RIT may indicate the effectiveness of acoustic therapy in patients. The FPT can find the hidden hearing loss without display on routine pure tone audiometry, so as to provide a clinical reference for the detection of early hearing loss in tinnitus patients.

Keywords Chronic subjective tinnitus · Tinnitus handicap inventory (THI) · Tinnitus multielement integration sound therapy (T-MIST) · Residual inhibition test (RIT) · Full precision test (FPT)

Introduction

Tinnitus refers to the sound perceived when there is no external voice or electrical stimulation [1]. Subjective tinnitus emphasizes that tinnitus is perceived by the patient, except for objective tinnitus such as abnormal eustachian tube opening, vascular pulsation, temporomandibular joint disorders and muscle contraction. Tinnitus affects between 5 and 42% of the world's population [2], approximately 3–9% of tinnitus patients report more than mild tinnitus-related disorders [3]. The incidence depends on the subject's age, hearing status and history of exposure to noise [4]. Tinnitus is a common but very serious global health problem that severely affects the quality of life of millions of people. From minor troubles to disastrous effects on quality of life, severe cases can lead to depression, anxiety and even suicidal tendencies [5].

Tinnitus is a debilitating condition associated with noise-related or age-related hearing loss which can destroy hair

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cells in Corti organs through damaging sensory receptor cells and neurons in the cochlea [6, 7]. Peripheral damage to the cochlea is thought to be due to the enlargement of the auditory cortex topography due to specific frequency of hearing deprivation [8]. The central auditory region compensates for the loss of input from the cochlea through a combination of nerve disinhibition and nerve sensitization, which is understood to produce hyperexcitability associated with phantom auditory event perception [9]. Therefore, chronic tinnitus has been extensively studied in humans using neuroimaging, electrophysiology, and invasive and non-invasive neuromodulation techniques [10, 11].

There are many treatments for tinnitus without gold standard. The American Academy of Otolaryngology Head and Neck Surgery recommends audiological assessment, counseling, education and the use of hearing AIDS for tinnitus patients. According to the Clinical Practice Guideline: Tinnitus in 2014 of American, acoustic therapy can be used as an option for tinnitus treatment. The resulting sound is set according to the characteristics of tinnitus including tinnitus pitch, loudness and minimum masking level, which promote habituation of tinnitus sensation, reduce the sensitivity of tinnitus and decrease the contrast between tinnitus and the environment [12]. Recently, with the development of tinnitus nerve synchronization and nerve remodeling mechanism, some studies have proposed individualized acoustic therapy to alleviate patients' tinnitus but not enough [13]. Currently, there is no effective treatment for tinnitus [14]. Therefore, tinnitus examination and treatment still have difficulties in life.

Thus, this study through full precision test (FPT) technology and tinnitus multielement integration sound therapy(T-MIST), research of chronic patients with subjective tinnitus, psychoacoustics and audiology characteristics explored its characteristics and the relationship between tinnitus and hearing loss in audiology and tried to give a single multivariate composite treatment, preliminary analysis of the curative effect, which can provide reference for further diagnosis and treatment of tinnitus.

Materials and methods

Participants

145 patients with chronic tinnitus receiving acoustic treatment in the outpatient department of otolaryngology head and neck surgery from June 2019 to January 2020 in The Second Affiliated Hospital of Anhui Medical University were collected. The inclusion criteria were as follows: subjective tinnitus, with or without sensorineural hearing loss, duration of disease at least 3 months, age ≥ 18 years. The exclusion criteria were as follows: (i) objective tinnitus, heart murmur, carotid artery murmur, temporomandibular joint disorder, tinnitus caused by vascular sound; (ii) history of chronic diseases, cardiovascular and cerebrovascular diseases, head and neck tumors and malignant tumors; (iii) systemic metabolic diseases and immune system diseases; (iv) otology-related diseases, otitis media, Meniere's disease, auditory neuropathy and conductive hearing loss; and (v) diagnosed mental illness. According to the age distribution in China, it was divided into three levels: youth (18–34 years), middle age (35–59 years) and old age (≥ 60 years). The duration was divided into four groups: 0.25–0.5 years, 0.5–1 years, 1–3 years, ≥ 3 years.

Study protocol

All of the patients undergo systematic physical examination, pure tone audiometry (PTA) (Madsen Itera, Denmark) and visual analog scale (VAS) annoyance which was divided into 0–10 grades (0 means no annoyance and 10 means extreme annoyance). The grade that patients judged annoyance on tinnitus before treatment was used as control data to compare with VAS after T-MIST. At the same time, patients received examination and treatment through TinniFit tinnitus rehabilitation treatment and matching platform (Foshan BOZY™ Medical Technology Co. LTD SFTest 330), which was used for consultation including clinical features and tinnitus handicap inventory (THI), FPT, tinnitus matching, residual inhibition test (RIT) and T-MIST in turn. After medical history collection on the TinniFit, patients completed THI scores on the platform. There were 25 items in the scale, including 11 score for function, 9 for emotion and 5 for disaster. The total score of THI is divided into five levels to evaluate the severity of tinnitus: 1–16 points (I), 18–36 points (II), 38–56 points (III), 58–76 points (IV) 78–100 points (V). The higher the score is, the greater the psychological impact on tinnitus patients [15].

Tinnitus matching

Then, the tinnitus site was matched through the Tinniest platform which was used to produce pure tone (narrow-band noise or white noise) for tinnitus according to the patient's routine PTA map. At 5 dB above the threshold of standard frequency or the maximum hearing loss frequency (if shown up on routine pure tone audiometry map), patients with headphone were given 3 adjacent test sounds, respectively, to enable the patient to distinguish whether the test sound is similar to the tinnitus sound. And then, the frequency range was narrowed with the test tone as the center, repeating with the three adjacent test sounds. Patients were asked to alternately listen and compare their own tinnitus. The audio that is most similar to tinnitus was selected and the frequency was set as the main tone of tinnitus. If the pure tone cannot

match the tinnitus of the patient, narrow-band noise or white noise was given for comparison to determine the tinnitus frequency. If the patient has unilateral tinnitus, the affected ear is the test ear. If bilateral tinnitus, the more serious side is the test ear; the severity of bilateral tinnitus was similar, and then the poor hearing side was selected as the test ear.

After setting main tone frequency of the tinnitus, on the basis of this frequency, with 2 dB as a unit, gradually increase the test sound intensity whose standard is just masking tinnitus. The loudness is tinnitus loudness.

FPT

FPT examination of the patient was accomplished subsequently with headphone on the platform. According to the method stipulated by GB7583-87, on the basis of routine pure tone audiometry at frequencies of 0.125 kHz, 0.250 kHz, 0.500 kHz, 1.000 kHz, 2.000 kHz,4.000 kHz and 8.000 kHz, the pure tone hearing threshold was finely measured in the 1/12 octave range before and after tinnitus frequency site. The frequency was subdivided into 10 levels according to FPT (Fig. 2) as well as loudness was classified into 5 levels according to WHO. FPT results were combined to diagnose whether the patient had hearing loss [16]. When the hearing threshold of any frequency was higher than 25 dB HL, hearing loss was considered.

RIT

The RIT [17] was based on tinnitus matching frequency. With headphone, narrow-band noise or white noise obtained according to tinnitus matching acoustic stimulation of 10 dB above masking threshold was given for 1 min at tinnitus matching frequency. If the tinnitus frequency is a pure tone, narrowband noise centered on the pure tone frequency was used; if white noise, the white noise was used. The change of tinnitus was recorded immediately after the acoustic stimulation. Positive means tinnitus completely disappeared, partial positive means loudness relief or change in frequency for a period of time and negative means no change.

T-MIST

The T-MIST [18] was the combination of three sounds on Tinniest platform: i-tone, dual-sound and Transfocus. The i-tone: with fine frequency selection characteristics, it is mainly used to match the tinnitus frequency (narrowband noise or white noise) to realize the suppression and regulation of tinnitus, which contains various narrow-band noises. The loudness corresponds to the tinnitus loudness. The dual-sound: with specific frequency characteristics, dynamic range and psychological perception characteristics. It mainly uses its specific frequency to act on the tinnitus frequency, establishes new sound perception and covers the sound perception of tinnitus, which contains a variety of natural environment sounds. The Transfocus: with establishing pleasant and relaxing psychological perception, it has psychological perception characteristics and no frequency characteristics, which contains various types of music. They can choose pleased types of dual-sound and Transfocus and comfortable loudness. The compound sound of narrowband noise or white noise + natural sound + music sound by means of TinniFit platform acting on the inner ear, auditory cortex, and autonomic nervous system and limbic system was played with headphone for 15 min at a time. Once stopped, the patient's VAS annoyance and tinnitus changes were immediately assessed. The later VAS was compared with the first VAS annoyance to study if the therapy was effective in psychology and made patients self-evaluate whether the tinnitus was relieved, disappeared or unchanged. Through self-assessment, patients could initially understand whether sound therapy was effective for tinnitus in a short time.

Analyzing the relationship between tinnitus and refined hearing loss after completing tinnitus matching and FPT, exploring the potential relationship between RIT and sound T-MIST and studying the changes of VAS before and after sound therapy.

Statistical analysis

SPSS21.0 statistical software was used to analyze all the data. The characteristics distribution and correlation of each factor were analyzed with Spearman correlation analysis. At the same time, Rank-Sum Test was used to analyze whether there were differences in THI, tinnitus loudness and frequency between different genders. In addition, logistic regression analysis was used to study the influencing factors of acoustic therapy.

Results

Basic distribution

In this group, there were 86 males (50.31%) and 59 females (40.69%). The age of patients was 18–80 years, with mean age of 41.40 ± 14.37 years. The disease duration was 0.25–20 years, with mean of 3.15 ± 6.16 years. The average age was 42 for men and 40 for women, with no significant difference. In the frequency distribution of tinnitus, there were low frequency, medium frequency and high frequency. The highest frequency was 90 cases (62.07%) (Fig. 1).

By Rank-Sum test, tinnitus loudness was higher in males (mean 49.52 dB) than in females (mean 36.77 dB, $P < 0.05$). The loudness of middle (mean 48.90 dB) and old age (mean 51.78 dB) was higher than the young (mean 35.69 dB,

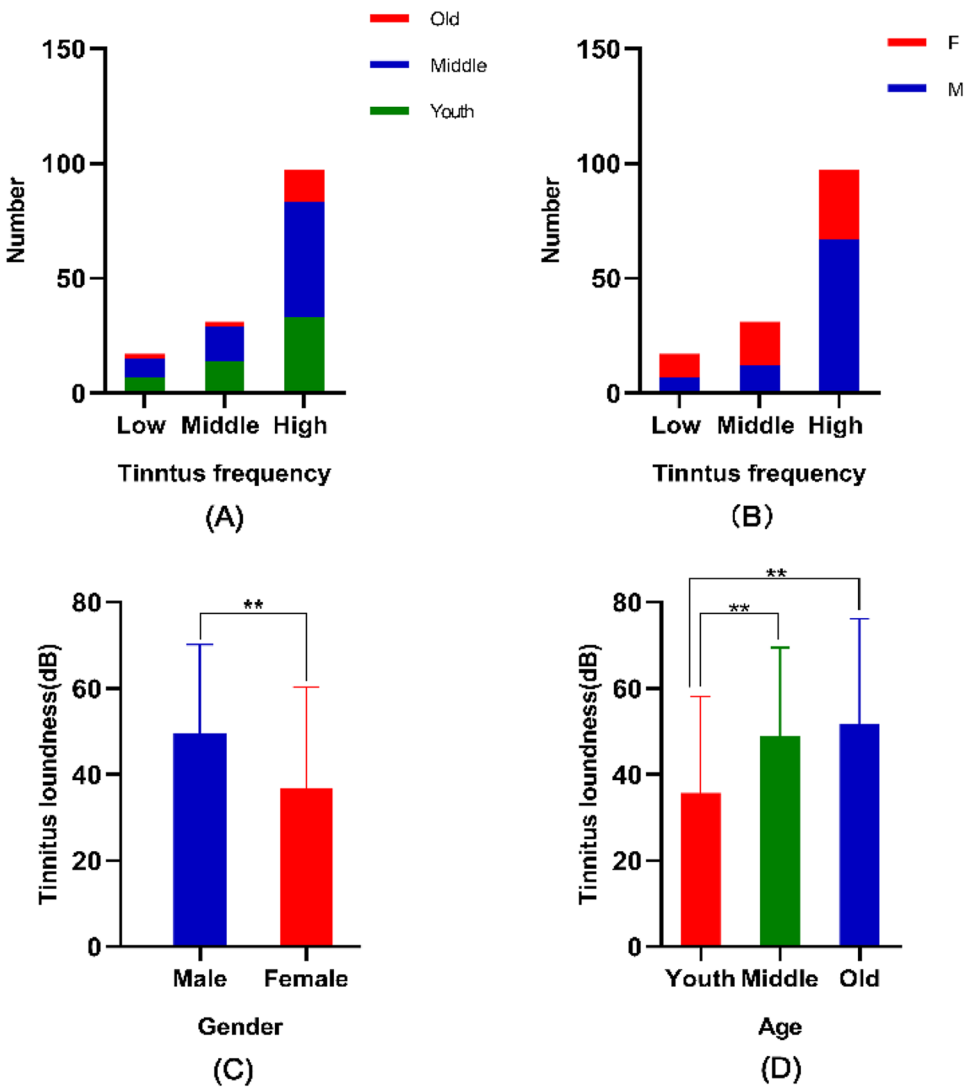

Fig. 1 **a** The distribution of tinnitus frequency in different age groups. **b** Represents the distribution of tinnitus frequency in different genders. Both **a** and **b** suggest that there are more high-frequency patients. **c** Indicates that there is a difference in tinnitus loudness in gender, with males greater than females ($P<0.05$). **d** Tinnitus loudness among different age groups. Middle-aged and elderly patients are greater than young patients ($P<0.05$)

$P<0.05$). And there was no difference in the frequency as well as loudness of tinnitus in gender and age ($P>0.05$) (Fig. 1).

Relationship between tinnitus and hearing loss

According to the results of conventional pure tone audiometry, 45 cases (31.03%) had normal hearing and 100 cases (68.97%) had impaired hearing.

In addition to the FPT, 22 cases (15.17%) were found to have normal hearing and 123 cases (84.83%) have hearing loss. Among the 45 pure tone audiometry patients with "normal hearing", some patients were found to have hearing loss at certain frequencies during the accurate hearing examination (Fig. 2). Furthermore, some patients with hearing loss had more severe hearing loss notch. Among the 145 patients with tinnitus, we found 88 (60.69%) whose tinnitus site frequency was completely consistent with the frequency of maximum hearing loss. There were 25 cases of tinnitus site frequency within first or last half octave range of the frequency of maximum hearing loss on the hearing curve. The sum of the two was 113 cases (77.93%). Therefore, FPT results showed that there was a high consistency between hearing loss frequency and tinnitus frequency.

Spearman correlation analysis showed that the frequency of tinnitus is related to the frequency of hearing loss. ($r=0.662$, $P<0.05$) (Fig. 3).

After accurate hearing examination, tinnitus loudness was correlated with the degree of maximum hearing loss. Spearman correlation analysis showed that the correlation ($r=0.860$, $P<0.05$) (Fig. 3).

RIT and the effect of T-MIST

After statistical analysis, the overall effective rate after treatment was 70.4% (Table 1). Spearman correlation analysis showed that the correlation between RIT and the effect of T-MIST ($r=0.498$, $P<0.05$).

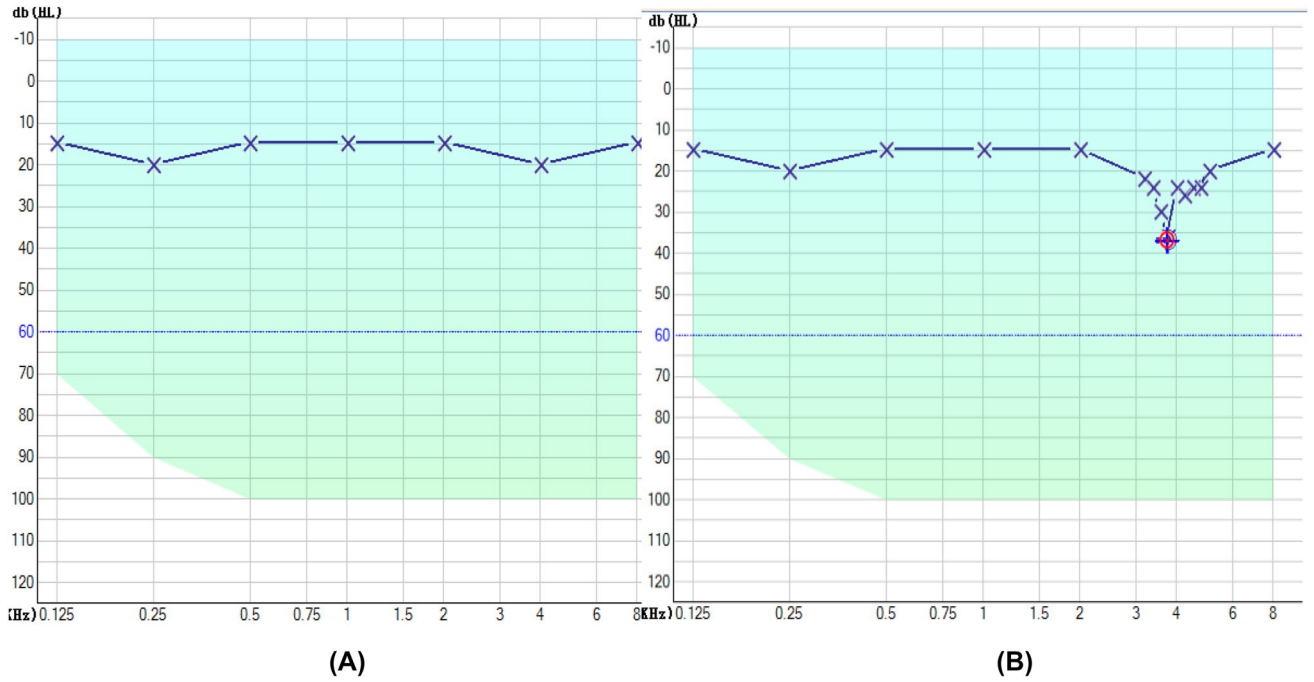

Fig.2 **a** Pure tone audiometry with normal hearing. **b** Accurate examination of hearing loss between 3 and 4KHZ in FPT

VAS and THI

The patients were rated before treatment on VAS annoyance. Spearman correlation analysis showed that VAS was correlated with THI ($r = 0.628$, $P < 0.05$). After acoustic treatment, the annoyance difference before (mean 5.18) and after (mean 3.37) the comparison is statistically significant ($P < 0.05$), suggesting that acoustic treatment can reduce the patients' annoyance (Fig. 4). THI was independent of tinnitus frequency, loudness, disease duration, and RIT but age related, ($r = 0.204$, $P < 0.05$) (Table 2). The Rank-Sum test between gender and THI showed that there was no difference in THI between men and women ($z = -0.663$, $P > 0.05$). THI is correlated with age and VAS annoyance ($P < 0.05$).

Analysis of T-MIST

Logistic regression analysis was performed between the effect of acoustic therapy and factors including patients' gender, age, duration, VAS, tinnitus frequency and loudness, THI. The therapeutic effect was independent of the of duration and other factors ($P > 0.05$).

Discussion

Hair cells (HCs) and spiral ganglion neurons (SGNs) are two main cell types responsible for hearing function in the inner ear of humans. HC's function is converting the mechanical sound waves into the electrical neural signals, while these signals are transmitted by SGN into the auditory cortex to have the hearing [19]. HCs and SGNs are sensitive and vulnerable for multiple stress and damages, including inflammation, noise, aging, ototoxic drugs or other stress [20, 21]. However, in mammals, there are only very little regeneration ability remaining after the HCs and SGNs are damaged [22], which lead to the irreversible loss of the HCs and SGNs. Tinnitus is usually accompanied by hearing loss. In this study, the 1/12-octave FPT was more detailed than routine PTA. FPT can find hidden hearing loss that cannot be detected by routine PTA. Hearing loss notch appeared at 4 kHz in FPT, while routine PTA showed normal hearing (Fig. 2). This situation is called hidden hearing loss (HHL) [23]. Studies have been proposed that HHL was related to the pathology of the cochlear afferent pathway caused by noise exposure, drug damage, aging and other factors [24]. The pathology failed to affect absolute auditory acuity, which indicated that the routine PTA was normal but the speech recognition rate under the noise environment was reduced. Therefore, FPT improved the detection rate of hearing loss by refining the hearing frequency, which made up for the limitations of PTA to a certain extent.

FPT was not only a refined test for PTA, but also a refined test for tinnitus frequency. Through refined tinnitus matching, the detection rate and accuracy of tinnitus frequency were improved. Through FPT, the percentage of frequency in tinnitus coincided with that of hearing loss went from 60.69% to 77.93%, which showed that the

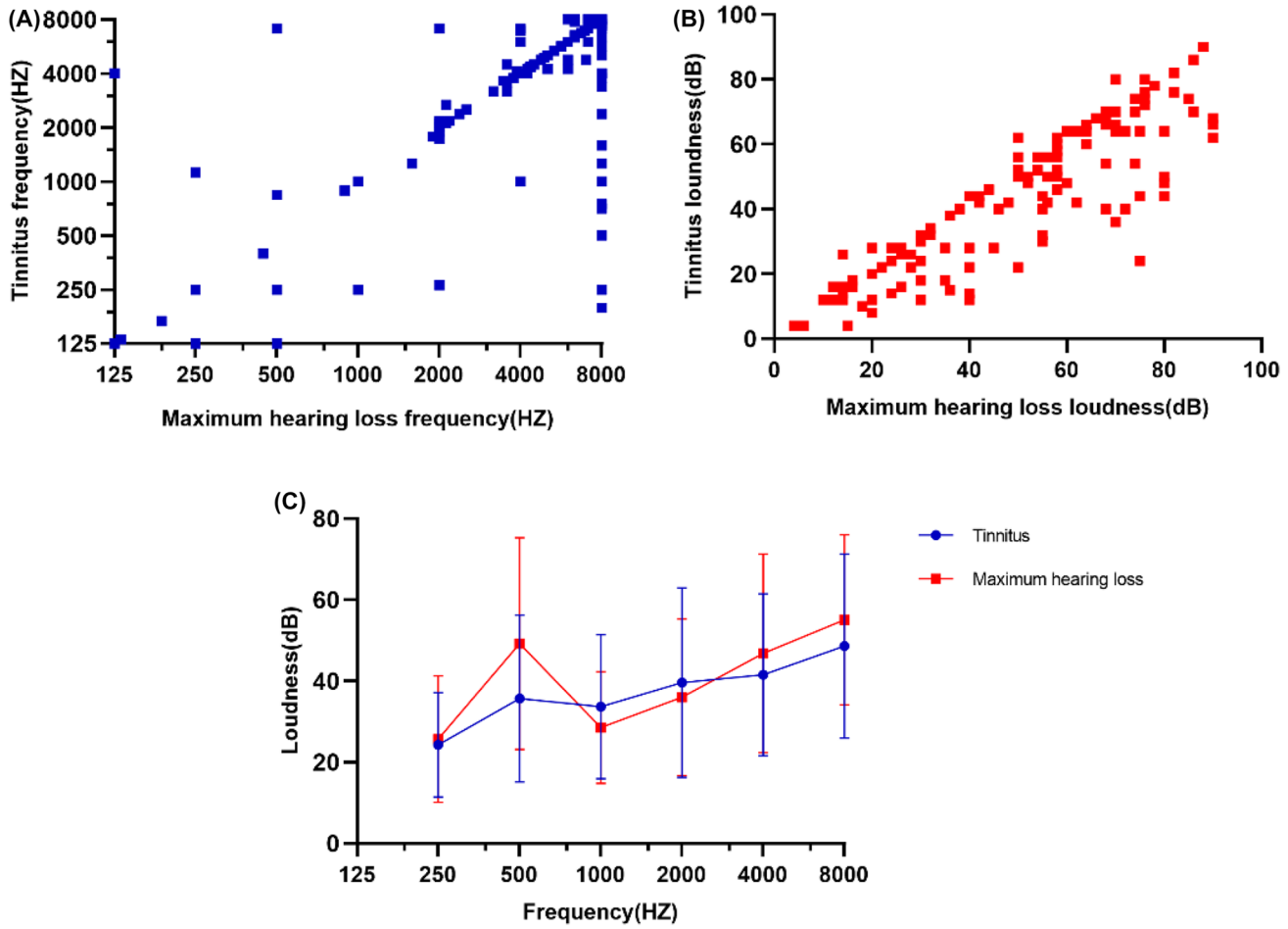

Fig.3 Suggesting the relationship between tinnitus and hearing loss. **a** indicates that tinnitus frequency is correlated with maximum hearing loss ($P<0.05$). **b** Indicates that tinnitus loudness is correlated with maximum hearing loss ($P<0.05$). **c** Indicates that tinnitus is correlated with maximum hearing loss

Table 1 RIT and TMIST distribution

T-MIST	RIT			Sum (%)
	Negative	Partial positive	Positive	
No change	26	15	2	43 (29.66)
Relief	21	48	12	81 (55.86)
Disappear	1	6	14	21 (14.48)
Sum (%)	48 (33.1)	69 (47.59)	28 (19.31)	145

frequency of hearing loss may be consistent with the frequency of tinnitus and implied that hearing loss could be the initiating factor of tinnitus. Studies proposes that when the inner ear is damaged, the change in sound information causes the brain to alert which increased excitability of the auditory center and hair cell sensitivity. Compensation is active around the damaged frequency area, while the function is normal and the transmitted acoustic signal is undistorted. However, the spontaneous activity of the hair cells in the damaged area is enhanced to produce aberrant signals under the adjustment of the auditory system. These aberrant signals are sensed and produced tinnitus. Therefore, the frequency of tinnitus is mostly consistent with the frequency of hearing loss [25]. As the degree of refinement increased, the consistency of the two also improved. However, due to the small sample size in this study, a large sample size clinical study is still needed. It is necessary to study the relationship between tinnitus frequency and hearing loss frequency by comparing with other finer octave bands.

Study confirms that the most active hearing compensation happened in the thalamus level [26]. If the compensation system functions properly, the tinnitus signal will terminate at the thalamus level, which will not be uploaded and sensed. However, chronic tinnitus can be caused when the compensation system is affected by age, external head injury, peripheral hearing, sleep and emotional system regulated by dopamine and 5-HT [27]. Neuronal overactivity and plasticity

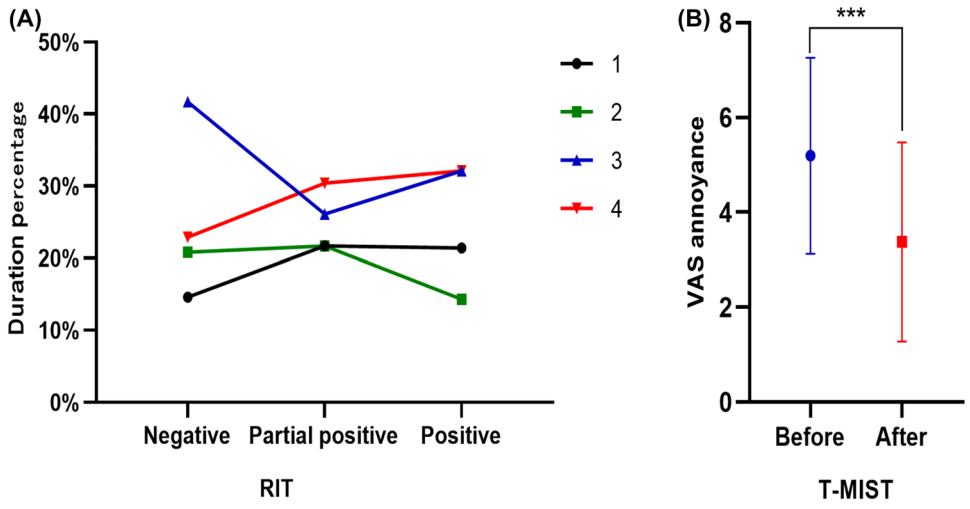

Fig. 4 **a** RIT is independent of the duration of the disease, (1) 0.25–0.5 years, (2) 0.5–1 years. (3) 1–3 years; (4) ≥ 3 years. **b** represents the significant difference of VAS dysphasia before and after acoustic treatment ($P < 0.05$)

Table 2 THI is related to VAS and Age

Related factors	*r*	*P*
VAS	0.628	0.000
Tinnitus frequency	0.126	0.132
Tinnitus loudness	0.148	0.076
Disease duration	-0.029	0.728
Age	0.204	0.014
RIT	0.112	0.181

changes on the central auditory pathway are involved in the pathophysiological process of long-term tinnitus [28].

Therefore, the purpose of acoustic therapy is to reduce the relative intensity of tinnitus-related nerve activities so as to weaken nerve signals reaching the subconscious level of auditory system, stimulation of the lateral system and the cognitive level of the auditory dermal layer to accelerate the habituation of tinnitus reaction [29].In conclusion, the T-MIST based on the biological-psycho-social theory not only promote the changes of neural remodeling in the auditory pathway but also reduce the negative perception of the brain's higher circuit, which benefits the majority of tinnitus patients. Although numerous studies have investigated the benefits of sound therapy for tinnitus, results have been inconsistent in reducing tensity and pain caused by tinnitus. Thus, there is still considerable controversy about the efficacy of sound therapy [30].

In recent years, cognitive behavioral therapy (CBT) has played an important role in tinnitus. CBT can alter the negative plasticity of tinnitus and significantly relieve subjective tinnitus symptoms with eliminating mood disorders and reducing stress [31]. Some studies proposed that cochlear implants could alleviate tinnitus by stimulating auditory nerves. However, due to its invasiveness and the risk of permanent auditory damage, it is not suitable for tinnitus patients with residual, even normal hearing [32]. The application of individualized repetitive transcranial electrical stimulation (rTMS) in tinnitus treatment has been reported to reduce tinnitus with poor experience [33]. In addition, there is no sufficient evidence to show that percutaneous lidocaine, indoor injection of lidocaine and traditional Chinese acupuncture are safe and effective for tinnitus [34–36].

RIT was associated with the efficacy of T-MIST, suggesting that RIT could predict the short-term efficacy of acoustic therapy and explore the underlying neural tinnitus network in this way [37]. It is effective to treat tinnitus with T-MIST whose sound prescription is close to the tinnitus and makes patients comfortable. We also found that RIT was not affected by duration. The RIT is to mask the affected ear according to the patient's tinnitus matching. After the masking sound, the masking effect continues for a short period of time. If the patient's perception of tinnitus can be reduced or eliminated during this period, the RIT is positive. Studies believe that the mechanism is to weaken the neural activity of one's own tinnitus through the given masking sound [38] whose purpose is to adapt to tinnitus rather than eliminate it [39]. This study found that the results of RIT have nothing to do with the duration of tinnitus. That is to say, the duration of the disease failed to affect the effect of tinnitus masking, which was similar to the viewpoint of Yuexin Cai [14]. This may also indicate that the RIT can be performed regardless of the length of the disease, which was unable to affect the test results. However, this study only conducted a single treatment without following up the patients with long-term acoustic therapy. Thus, the effect of treatment duration could not be compared and the long-term effect could not be confirmed.

Besides, by analyzing the results of VAS annoyance, acoustic therapy could decrease annoyance. In this study, it was found that the elderly patients whose THI and tinnitus loudness were greater than that in the young which

meant that hair cell damage and compensation mechanism in elderly patients were inferior to that in young patients. As this study is affected by the sample size and region, multi-center, large-sample and long-term follow-up are still needed in the future. So that more accurate research results can be obtained.

In summary, the psychological effect of tinnitus on patients can be alleviated by T-MIST and RIT can predict the efficacy of acoustic therapy. Therefore, T-MIST is the development trend of tinnitus. FPT can detect hidden hearing loss and there is a correlation between tinnitus and hearing loss which provide conditions for understanding the mechanism of tinnitus.

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Data availability The data used to support the findings of this study are available on request to the corresponding author: Jianming Yang, Email: Jmingyang88@163.com.

Compliance with ethical standards

Conflicts of interest The authors declare that they have no conflicts of interest.

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