INTRODUCTION

Subjective tinnitus, one of the most prevalent symptoms of hearing disorders, is a perceived sensation of sound that occurs in the absence of external acoustic stimulation. Although subjective tinnitus may be associated with a wide variety of lesions of the external ear, middle ear, cochlea, auditory nerve, or central nervous system, it occurs most commonly as a result of cochlear dysfunction or damage to the auditory nerve. The cochlear dysfunction or damage to the auditory nerve can be caused by several factors, such as acoustic trauma, noise-induced hearing loss, or age-related hearing loss. The most common pattern of hearing loss in the general population, that is, age-related hearing loss, consists of elevated thresholds to high-frequency sounds of approximately 2000 Hz and greater. A consequence of high-frequency hearing loss, as revealed by animal models, is that cortical neurons in the hearing-loss region begin to respond preferentially to sound frequencies at the edge of normal hearing, such that the edge frequencies come to be overrepresented in the cortical tonotopic map in the auditory cortex. This “reorganization” of the tonotopic map, which is also known as brain plasticity, has been detected in human tinnitus patients.

Subjective tinnitus is perceived as continuous; therefore, it can become very bothersome and cause stress, such that connections among the auditory cortex, limbic systems, and autonomic nervous systems are strengthened, and tinnitus is perceived to be in-
There are various treatments to reduce the awareness of tinnitus; these include medication, cochlear implants, sound therapy (tinnitus masking [5] and hearing aids [6]), and psychological therapy.

Tinnitus retraining therapy (TRT), which has been used in many hospitals, [9-11] involves directive counseling and sound therapy. The aim of counseling is to explain the neurophysiologic source of tinnitus and the effect of sound therapy. The aim of sound therapy is to reduce the contrast between tinnitus and background neuronal activity, and to prompt adaptation to tinnitus by listening for a relatively long period. Patients are asked to avoid silent environments and listen to background noises, such as those generated by the use of hearing aids or sound generators (SGs). For patients with subjective hearing loss, the use of hearing aids is recommended, and patients without subjective hearing loss are recommended to use SGs. However, SGs are expensive and ineffective for patients in whom the tinnitus frequency includes the high-frequency bands of ≥6 kHz because of the SGs frequency characteristics. Furthermore, the background noise produced by SGs primarily comprises random “white” noise, and sound therapy with white noise may be more appropriate during TRT; however, previous studies have suggested that sound therapy using unstructured random noises should be avoided in tinnitus treatment [12]. Patients may abandon tinnitus treatment because of unpleasant white noise.

Instead of SGs, Fukuda et al. [14] evaluated the efficacy of TRT using a commercial portable audio player with a recorded environmental sound (murmur of a stream), which demonstrates constant energy over a wide frequency band. Their results showed that the Tinnitus Handicap Inventory score clearly decreased after 1 month; this effect continued over 12 months.

Furthermore, previous studies focused on brain plasticity, which may contribute to the generation of tinnitus. Okamoto et al. [15] attempted to reduce tinnitus roundness by exposing tinnitus patients to self-chosen, enjoyable music, which was modified so as to contain no energy in the frequency range surrounding the individual tinnitus frequency, so-called notched music. They showed significant reduction of subjective tinnitus loudness and revealed that reduction of tinnitus loudness can come from an enjoyable and custom-tailored notched music, potentially via reversing brain plasticity. However, it is unclear whether the lack of energy in the tinnitus frequency band was effective in reducing tinnitus loudness. In contrast, some studies that used a hearing aid reported that an amplification of the background sound was effective for the reduction of tinnitus loudness, based on the auditory cortex reorganization [16-18]. In summary, regarding tinnitus sounds in acoustic therapy for TRT, there are roughly two contrasting modification approaches, and they contain no energy (notched) or more energy (amplified) in the tinnitus frequency region.

To solve this problem, we propose amplifying energy in the frequency region corresponding to the tinnitus frequency of an individual patient, using environmental sound, as in the previous study by Fukuda et al. [14]. As the power of individual tinnitus frequency increases by amplification, the contrast between tinnitus and the background sound may decrease, relative to a notched sound. Furthermore, by amplifying only the tinnitus frequency band, the volume may be minimized when exposing tinnitus patients to a sound, relative to random noises. However, amplifying a sound may lead to increased unpleasantness, and the degree of unpleasantness may change depending on the modified frequency region. In this study, we conducted the following activities as a pilot experiment for the purpose of clinical TRT tests: 1) exploration of the unpleasantness of processed environmental sounds with amplified, attenuated, and removed (notched) modifications in seven different frequency regions; 2) comparison of the unpleasantness of processed sounds for older and younger participants; and 3) determining of an amplification level appropriate for a clinical test.

MATERIALS AND METHODS

Participants

Twenty-three elderly people (8 men and 15 women; average age 70.5 years) and 23 younger people (14 men and 9 women; average age 25.5 years) participated in the experiment. Written informed consent was obtained from all participants, and the experimental protocol was approved by the Ethics Committee of our institution (approval no. 30-003).

Stimuli and modification

As an environmental sound, we used the sound of a river, which was the most effective sound in a previous study [13]. The sampling frequency was 44.1 kHz. We processed the sound with three types of modification (amplified, attenuated, and notched) at a one-octave width of seven central frequencies (250, 500, 1000, 2000, 4000, 6000, and 8000 Hz). These seven central frequencies were assumed as tinnitus frequencies. For the amplification processing, we used five gain conditions, which comprised +6, +12, +15.6, +18, and +20 dB. For the attenuation, we used two conditions: -6 and -12 dB. For the notched condition, we processed to remove energy in the frequency range surrounding the tinnitus frequency. A total of 57 processed sounds, including the original sound (original), were used in the experiment. The long-term average spectrum of the processed sound with the amplification (+6 dB and +20 dB), attenuation (-6 dB and -12 dB), and notched at the center frequency (2000 Hz) is shown in Figure 1.

Procedure

The experiment was conducted in a quiet environment. Assuming a sound therapy at TRT, all participants adjusted the volume in the following manner. First, participants wore headphones (MDR-1RNC-MK2; Sony Marketing Inc., Tokyo, Japan), and we presented a 4000 Hz pure tone as pseudo tinnitus. Second, participants changed the sound volume of the pure tone such that the sound became annoying. Third, we presented the original sound (the sound of a river) to participants while presenting the adjusted pure tone. Participants changed the sound volume of the original sound so that the pure tone was not completely masked, and the sound of a river was not annoying. After changing the volume, we began the experiment. Each stimulus was presented to participants for 10 s, in random order. After presentation, participants evaluated the unpleasantness of the sound stimulus by adjusting the bar of a visual analog scale, displaying “0: unpleasantness–10: unpleasantness” on a tablet (Nexus 9; HTC Corporation, Taoyuan, Taiwan). The first three trials were practice trials, and the total number of trials was 60. The flow of the experimental procedure is shown in Figure 2. Further-
more, to investigate the hearing ability of each group (older and younger groups), the hearing threshold was measured by an audiometer (AA-75; RION Co., Ltd., Tokyo, Japan) for 11 participants of each group. The audiometric tests were conducted in a soundproof room (Silent Design, Tokyo, Japan).

Statistical Analysis
The obtained data were tabulated and entered in the R open source software, version 3.5.0 (R Development Core Team).

RESULTS
First, a two-way analysis of variance (ANOVA) was conducted with the three processing methods and seven frequencies (250, 500, 1000, 2000, 4000, 6000, and 8000 Hz). The analysis revealed a significant interaction between the processing method and frequency ($F[12,630]=3.98, p<0.001$). A simple effect analysis for the processing and frequency interaction revealed the effect of processing at six frequencies, except for 8000 Hz (250 Hz: $F[2,90]=15.0, p<0.001$; 500 Hz: $F[2,90]=6.71, p<0.01$; 1000 Hz: $F[2,90]=14.8, p<0.001$; 2000 Hz: $F[2,90]=7.32, p<0.01$; 4000 Hz: $F[2,90]=5.46, p<0.01$; 6000 Hz: $F[2,90]=3.63, p<0.05$). The analysis showed a significant primary effect of processing ($F[2,630]=29.1, p<0.001$). Multiple comparison tests were performed between the amplified and attenuated conditions ($p<0.05$), as well as between the attenuated and notched conditions ($p<0.05$). We determined the mean unpleasantness values of each processing condition for older and younger groups; these are depicted in Figure 3. The mean unpleasantness value of the original sound was 2.37.

Second, a two-way ANOVA with age (older and younger groups) and the three processing methods (amplified, attenuated, and notched) was conducted. The analysis revealed a significant interaction between the processing and age ($F[2,88]=6.37, p<0.01$). A simple effect analysis for the interaction between the processing and age revealed the effect of processing at younger age ($F[2,88]=16.3, p<0.001$). Multiple comparison tests showed significant differences between the amplified and attenuated conditions ($p<0.05$), as well as between the attenuated and notched conditions ($p<0.05$). We determined the mean unpleasantness values of each processing condition for older and younger groups; these are depicted in Figure 4.
Third, we focused on the amplified condition and investigated the effects of frequency and the power level of the amplifier on unpleasantness ratings for older and younger groups. A three-way ANOVA with age, frequency, and the amplified level (+6, +12, +15.6, +18, and +20 dB) was conducted. The analysis revealed a significant interaction between age and frequency ($F_{(6,264)}=4.04, p<0.001$). A simple effect analysis for the interaction of age and frequency revealed the effect of frequency at older age ($F_{(6,132)}=5.65, p<0.001$). Multiple comparison tests showed significant differences between 250 and 6000 Hz ($p<0.05$), as well as between 250 and 8000 Hz ($p<0.05$). We determined the mean unpleasantness values of each frequency condition for older and younger groups; these are depicted in Figure 5. The analysis revealed a significant interaction between the amplified level and frequency ($F_{(24,1056)}=2.40, p<0.001$). A simple effect analysis regarding the interaction of the amplification level and frequency revealed the effect of the amplified level at the following frequencies: 250 Hz: $F_{(4,176)}=7.74, p<0.001$; 500 Hz: $F_{(4,176)}=6.86, p<0.001$; 1000 Hz: $F_{(4,176)}=4.52, p<0.01$; 2000 Hz: $F_{(4,176)}=4.07, p<0.01$. Furthermore, the analysis showed a significant primary effect of the amplified level ($F_{(4,176)}=6.63, p<0.001$). Multiple comparison tests showed significant differences between +6 and +12 dB ($p<0.05$), between +6 and +18 dB ($p<0.05$), between +6 and +20 dB ($p<0.05$), and between +15.6 and +20 dB ($p<0.05$). We determined the mean unpleasantness values of each amplification level for each age group; these are depicted in Figure 6.

**DISCUSSION**

Differences in unpleasantness among processed sounds with three modifications

The analysis showed significant differences among the processing methods at six frequencies, except for 8000 Hz. The amplified sound unpleasantness ratings were higher than those of attenuated sounds at the central frequencies of 250, 1000, 2000, 4000, and 6000 Hz; they were higher than that of the notched sound at the central frequency of 250 Hz. For 8000 Hz, there was no difference in unpleasantness between the processing methods. This may be because the sound of the river used in the experiment had less energy in the high-frequency region than in the low-frequency region, as shown in the long-term average spectrum of sound stimuli (Figure 2). In particular, the notched sounds with the center frequencies of 500, 1000, and 2000 Hz had high unpleasantness values, as shown in Figure 4; thus, we suspect that these frequencies are important for recognizing a water sound. These results indicated that processing the energy of high-frequency regions gave no effect on the processed sound, compared with processing for low frequencies.

Age-related differences in unpleasantness for processed sounds

With regard to the differences in unpleasantness ratings between the age groups, the younger group showed higher unpleasantness ratings for the amplified and notched sounds than for the attenuated sound. In contrast, there were no differences in unpleasantness ratings among processing conditions for the older group. Younger participants tended to report the notched sound as unpleasant, compared with the attenuated sound. This may be due to the lack of power in the important frequency region for recognizing the river sound, as previously mentioned.

Age-related differences in the unpleasantness of the amplified sound

The most salient finding was that the unpleasantness of the amplified sound was significantly different between the processed sounds at the central frequency of 250 Hz and those at a high central frequency (6000 Hz).
or 8000 Hz) only for the older group. Figure 5 presents the mean unpleasantness values of amplified sounds for each frequency and hearing threshold for 11 participants from each group. Older participants rated unpleasantness lower than younger participants for amplified sounds at a high central frequency. In contrast, younger participants reported that these processed sounds had higher unpleasantness. Considering the auditory thresholds for older and younger participants, it is reasonable that the hearing thresholds of older participants decreased as the frequency increased. Due to the sensory loss of a high-frequency sound, older participants might have not noticed the changes in the processed sound. Therefore, the hypothesis that the amplified sound provided unpleasantness was confirmed only for younger participants.

Sound stimuli for a clinical test
Finally, we determined sound stimuli for our next clinical test. As a TRT clinical test, we are going to confirm the effects of a processed sound with the amplification in the frequency width corresponding to the tinnitus frequency of individual patients, using environmental sounds. Based on the experimental results of the present study, we determined the amplification level for the next clinical test as follows. We will target tinnitus patients with a frequency of 4000 Hz in a clinical test, because tinnitus is a symptom highly prevalent in elderly patients, and they often have sensory loss of a high-frequency sound over 4000 Hz. Thus, the unpleasantness of processed sound may be low if the sound is amplified at a high-frequency width. Furthermore, with regard to the amplification level, because there were no marked differences among the amplification levels in the older group (as in Figure 6), we will amplify power with a 20 dB gain in the frequency corresponding to the tinnitus frequencies of each individual patient.

CONCLUSION
In this study, we focused on sound therapy for TRT and proposed to amplify the sound energy in the frequency region corresponding to the tinnitus frequencies of individual patients using environmental sounds. To confirm this concept in a clinical test, we aimed to 1) investigate the unpleasantness of processed environmental sounds with the amplified, attenuated, and removed (notched) modifications in seven different frequency regions, 2) compare the unpleasantness of processed sounds for older and younger participants, and 3) determine the amplification level that is appropriate for a clinical test. Our results showed there were no differences in the unpleasantness ratings among three different modifications for older participants. Furthermore, older participants rated unpleasantness lower than younger participants for processed sound in the high-frequency region. Additionally, with regard to the amplification level, marked differences were not observed among the amplification levels for older participants. In a future clinical test, we are going to target older patients who have a tinnitus frequency over 4000 Hz and compare the effect of an amplified environmental sound with a 20 dB gain in the frequencies corresponding to individual patients’ tinnitus to notched sound. Further, we will design a smartphone application of sound therapy for TRT, which may be available for use easily and conveniently in medical settings.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Department of Engineering and Design, Kagawa University (approval no. 30-003).

Informed Consent: Written informed consent was obtained from the patient who participated in this study.

Peer-review: Externally peer-reviewed.


Acknowledgements: The authors would like to thank the Director, Department of Engineering and Design, Kagawa University, for granting permission to carry out our study and the participants for their cooperation.

Conflict of Interest: The authors have no conflict of interest to declare.

Financial Disclosure: This work was supported by Kagawa University Research Promotion Program (KURPP).

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