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Original Article

Short-Term Effect of Adjunctive Transcranial Random Noise Stimulation on Idiopathic Sudden Sensorineural Hearing Loss and Tinnitus: A Preliminary Study

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BACKGROUND: Transcranial random noise stimulation has previously been used to manage tinnitus. This study assessed the feasibility of adjuvant transcranial random noise stimulation with conventional steroid treatment for idiopathic sudden sensorineural hearing loss with or without tinnitus.

METHODS: Prospective, randomized, single-blind study was conducted in Eulji University hospital. Twenty-four patients with idiopathic sudden sensorineural hearing loss were admitted for treatment between March 2019 and February 2020. The study group received 4 sessions of adjuvant transcranial random noise stimulation (frequency band: 0.1-100 Hz; target, T7/T8; duration: 20 minutes), while the control group received only conventional treatment. Hearing levels at admission, discharge day (day 7), and 4 weeks later and clinical characteristics were assessed. The primary outcome measure was hearing improvement at 4 weeks after neuromodulation. The secondary outcome measure was the presence of tinnitus at 4 weeks.

RESULTS: The mean hearing thresholds improved significantly over time ($P < .05$). Although initial hearing levels did not differ between the 2 groups, the study group had a significantly better hearing at 4 weeks after discharge ($P > .05$). A significant interaction was also observed between the mean hearing thresholds at various timepoints and transcranial random noise stimulation ($P = .001$). However, the persistence of tinnitus after treatment did not differ irrespective of the allocation groups.

CONCLUSION: Adjuvant transcranial random noise stimulation seems to be a potential treatment option for hearing restoration in patients with idiopathic sudden sensorineural hearing loss without serious complications. However, transcranial random noise stimulation does not seem to alleviate tinnitus.

KEYWORDS: Sudden hearing loss, neuromodulation, treatment, tinnitus

INTRODUCTION

Idiopathic sudden sensorineural hearing loss (ISSNHL) is defined as a sensorineural hearing loss of ≥30 dB at a minimum of 3 consecutive frequencies within 3 days without identifiable causes.[1] Contemporary treatments include corticosteroids, hyperbaric oxygen therapy either as initial combined therapy within 1 week or as salvage therapy within 4 weeks, and intratympanic steroid (ITS) injections within 2-6 weeks as salvage therapy. Among these treatments, all are options for ISSNHL except for ITS injections as salvage therapy.[1]

Approximately 70% of patients with unilateral ISSNHL complain of accompanying new-onset tinnitus, and auditory deafferentation is a possible cause of tinnitus.[2] Indeed, the generation of acute tinnitus is associated with hearing deterioration irrespective of tinnitus laterality.[3] Crucially, tinnitus has been diagnosed on the basis of contralateral hearing in patients with unilateral ISSNHL, that is, patients with ISSNHL tended to have tinnitus when they had better contralateral hearing irrespective of the severity of hearing loss.[2]

Prognostic factors for better recovery from ISSNHL include early response to treatment within 1 week and younger age, less severe initial hearing loss, and absence of vertigo.[4] Hearing level generally reaches a fixed level at 1 month after treatment.[5] However, eliciting the maximal treatment response as early as possible may be essential.

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Transcranial random noise stimulation (tRNS) is a noninvasive neuromodulation technique. It decreases hypersynchronicity and potentiates task-related neural activity via repeated subthreshold stimulation.[6] Unlike transcranial direct current stimulation (tDCS), which commonly poses a risk of burns on the electrode side, tRNS does not entail any serious complications.[6] Recently, multisite tRNS or a combination of tRNS and tDCS has also been used to treat chronic tinnitus.[7]

Since tinnitus is one of the most common accompanying symptoms in ISSNHL and tRNS has been used to control chronic tinnitus and since repetitive transcranial magnetic stimulation (rTMS) has been used as another neuromodulation technique to improve ISSNHL, we hypothesized that adjuvant tRNS might effectively treat both new-onset tinnitus and ISSNHL.[5-7] Accordingly, we performed this prospective, randomized, single-blind study to assess the feasibility of adjuvant tRNS with conventional steroid treatment for ISSNHL.

METHODS

Patients and Ethics Statement

Between March 2019 and February 2020, patients admitted to a university hospital for the treatment of ISSNHL were screened for this prospective, randomized, single-blind study. The inclusion criteria were as follows: (1) willingness to participate in this study; (2) age $\geq$ 18 years; (3) sensorineural hearing loss on the affected side; (4) interval between the acute onset of symptoms to treatment of $\leq$7 days; and (5) mean pure-tone threshold at 500, 1000, 2000, and 3000 Hz of at least 30 dB on the affected side. The exclusion criteria were as follows: (1) previous history of ISSNHL; (2) previous history of neuromodulatory treatments, such as rTMS, tRNS, or tDCS; and (3) accompanying neuropsychiatric disorders, including Alzheimer's disease, epilepsy, schizophrenia, and intracranial malignancies. The following data were recorded at admission: age; sex; accompanying diseases (hypertension and diabetes mellitus); days from onset to treatment; affected side; accompanying symptoms, including tinnitus, dizziness, or aural fullness; and the results of questionnaires, such as the Tinnitus Handicap Inventory (THI) and Beck Depression Inventory. The Institutional Review Board of the Eulji University Hospital approved this study (IRB number: 2018-07-001-003). Written informed consent was obtained from all the patients.

Randomization

Simple randomization using Microsoft Excel (Microsoft Inc., Redmond, Wash, USA) was performed to allocate patients to the tRNS treatment or control group.

Treatment Regimens and Study Protocol

All patients were initially treated using 4 mg/kg oral methylprednisolone for 4 days, and the dose was tapered to 8 mg every 2 days. All patients also received 4 concomitant ITS injections starting from the second day of admission.

In addition, patients allocated to the study group underwent 4 consecutive sessions of tRNS (frequency band: 0.1-100 Hz; T7: anode; T8: cathode; duration: 20 minutes) using the DC-STIMULATOR PLUS (neuroConn GmbH, Ilmenau, Germany) before ITS injections from the second day of admission. Patients were asked to sit upright and received an education before treatment. Briefly, saline-soaked electrodes (35 cm^2) were placed at the target site according to the 10-20 system.

Calculation of Hearing Thresholds and Outcome Measures

Pure-tone audiometry and speech audiometry were performed every day from the initial visit to discharge from the hospital. The mean hearing thresholds were calculated using the arithmetic means of the hearing thresholds at 500 Hz, 1 kHz, 2 kHz, and 3 kHz. Hearing thresholds at admission (day 1), discharge day (day 7), and 4 weeks after discharge were documented. Complete recovery (CR) was defined if the mean hearing thresholds at 500 Hz, 1 kHz, 2 kHz, and 3 kHz were $\leq$25 dB. The primary outcome measure was hearing improvement at 4 weeks after neuromodulation. The secondary outcome measure was the presence of tinnitus at 4 weeks.

Adverse Events

The occurrence of headaches, tingling sensations, numbness, skin itching, and dizziness, as well as the aggravation of tinnitus and worsening of hearing loss, were documented.

Statistical Analysis

Data were analyzed according to the intention-to-treat principle. Repeated-measures analysis of variance (ANOVA) was performed to confirm the changes in hearing thresholds between and within the groups over time. Mauchly's test for the assumption of sphericity was also performed. Accompanying tinnitus was used as a covariate. tRNS was used for determining between-subject factors. The Kaplan–Meier survival analysis was performed to compare the presence of tinnitus loss in each group over time. For the testing index, the presence of tinnitus was used to determine the treatment effect. Binary logistic regression analysis with backward elimination was then performed using variables such as age, the onset of symptoms, pretreatment hearing thresholds on the affected and healthy sides, tinnitus, and dizziness to confirm the prognostic factors for CR. All analyses were performed using IBM SPSS Statistics for Macintosh, Version 27.0 (IBM SPSS Corp., Armonk, NY, USA). *P*-values $<$.05 were considered statistically significant.

RESULTS

Patient Characteristics

A total of 24 patients (12 men and 12 women) were enrolled in this study. Their mean age was 51 years (SD: 10.827; range: 18-68 years), and the mean number of days from onset to treatment was 2.79 days (SD: 1.933; range: 1-7 days) (Table 1). Among them, 11 had right-sided hearing loss and 13 complained of left-sided hearing loss. The mean hearing thresholds of the affected side at 500 Hz, 1 kHz, 2 kHz, and 3 kHz were 71.77 dB (SD: 16.36; range: 33.75-105 dB). As accompanying symptoms, 22 (91.7%) had tinnitus and 9 (37.5%) had dizziness and aural fullness, and as accompanying diseases, 4 (16.7%) had diabetes and hypertension. With respect to tinnitus characteristics, 11 patients complained of pure tone, and 11 complained of narrow-band noise. The mean tinnitus frequency was 2.552 $\pm$ 2.957 kHz (range: 125-9 kHz). The mean tinnitus frequency was 2.552 $\pm$ 2.957 kHz (range: 125-9 kHz). Finally, 21 patients completed the study; 3 patients did not visit the outpatient clinic for the follow-up at 4 weeks after discharge (Figure 1). Patient characteristics of the study and control groups are shown in Table 1. No significant

Table 1. Baseline Clinical Characteristics

Variable	Total	Study Group	Control Group	*P*
Number	24	12	12	–
Age (years)	51.50 ± 10.83	50.17 ± 8.69	52.83 ± 12.88	.558
Sex (male/female)	12 (50)/12 (50)	8 (66.7)/4 (33.3)	4 (33.3)/8 (66.7)	.102
Diabetes mellitus	4 (16.7)	3 (25.0)	1 (8.3)	.590
Hypertension	4 (16.7)	1 (8.3)	3 (25.0)	.590
Days from onset to treatment	2.79 ± 1.933	3.33 ± 2.19	2.25 ± 1.55	.175
Affected side (right/left)	11 (45.8)/13 (54.2)	6 (50.0)/6 (50.0)	5 (41.7)/7 (58.3)	1.000
Dizziness	9 (37.5)	5 (41.7)	4 (33.3)	1.000
Tinnitus	22 (91.7)	12 (100.0)	10 (83.3)	.478
Aural fullness	9 (37.5)	3 (25.0)	6 (50.0)	.400
Tinnitus Handicap Inventory	43.22 ± 23.84 (n = 9)	44.00 ± 23.28 (n = 5)	42.25 ± 28.12 (n = 4)	.921
Beck Depression Inventory	8.88 ± 10.83 (n = 8)	10.60 ± 13.85 (n = 5)	6.00 ± 2.65 (n = 3)	.601
Initial SRT (dB HL)	67.08 ± 22.31	73.33 ± 26.57	60.83 ± 15.79	.175
Initial SDS (%)	35.17 ± 30.28	26.33 ± 34.34	44.00 ± 23.82	.157
Initial hearing (dB)	71.77 ± 16.36	78.54 ± 17.23	65.00 ± 12.77	.040
Initial contralateral hearing (dB)	14.11 ± 10.82	11.35 ± 6.96	16.88 ± 13.40	.219

Numerical data are expressed as means ± SDs and ranges. Nominal variables are expressed as numbers (percentages).
dB HL, decibel hearing loss; SDS, speech discrimination score; SRT, speech reception threshold.

differences were observed between the 2 groups except in the mean initial hearing thresholds.

Change in the Mean Hearing Thresholds and Tinnitus During the Follow-up Period

Mauchly's test indicated that the assumption of sphericity had been met ($P = .100$). Repeated-measures ANOVA demonstrated that the change in the mean hearing thresholds over time was significant ($P = .026$). In addition, a significant interaction was observed between the mean hearing threshold at each timepoint and tRNS ($P = .001$) (Figure 2). In addition, pairwise comparisons with Bonferroni correction demonstrated that hearing levels between the initial visit and week 4 ($P = .001$), and between week 1 and week 4 ($P = .012$) differed significantly. No significant difference in the hearing levels between the initial visit and the discharge day was observed. Additional analysis of the hearing thresholds at 4 kHz and 8 kHz showed similar results as Figure 2 (data not shown). For tinnitus, no significant interaction was shown between the hearing thresholds at each timepoint and tinnitus ($P = .696$). Changes in the numbers of patients with tinnitus in both groups over time are shown in Figure 3. The log-rank test also revealed no significant difference in the presence of tinnitus loss over time, irrespective of additional tRNS treatment ($P > .05$).

Treatment Outcome After 4 Weeks

Although 12 patients (50%) still complained of tinnitus after 4 weeks, none had new-onset tinnitus. Chi-square analysis demonstrated that accompanying tinnitus did not differ irrespective of tRNS treatment ($P > .05$). Moreover, 1 patient complained of a transient increase in tinnitus loudness as an adverse event, but none of the others had any discomfort. There was no significant difference in the presence of tinnitus according to the initial tinnitus characteristics on days 5-7 and days 28-32 ($P > .05$). Regarding final recovery, CR was achieved in 29.2% of patients (n = 7). While 60% of patients in the study group (n = 6) showed a CR, only 1 (9.1%) in the control group did. Chi-square analysis showed that this difference was significant ($P = .024$; 2-sided Fisher's exact test). Regression analysis with backward elimination revealed that tRNS treatment was an independent prognostic factor for CR ($B = -2.708$; EXP(B) = 0.067; 95% CI = 0.006-0.745). Other factors were not included in our regression model.

DISCUSSION

In this study, we found that adjuvant tRNS may have a beneficial effect on the treatment of ISSNHL. However, contrary to our expectations, it did not alleviate accompanying acute tinnitus. To our knowledge, this is a novel application of tRNS for the management of ISSNHL, and it could restore hearing in these patients.

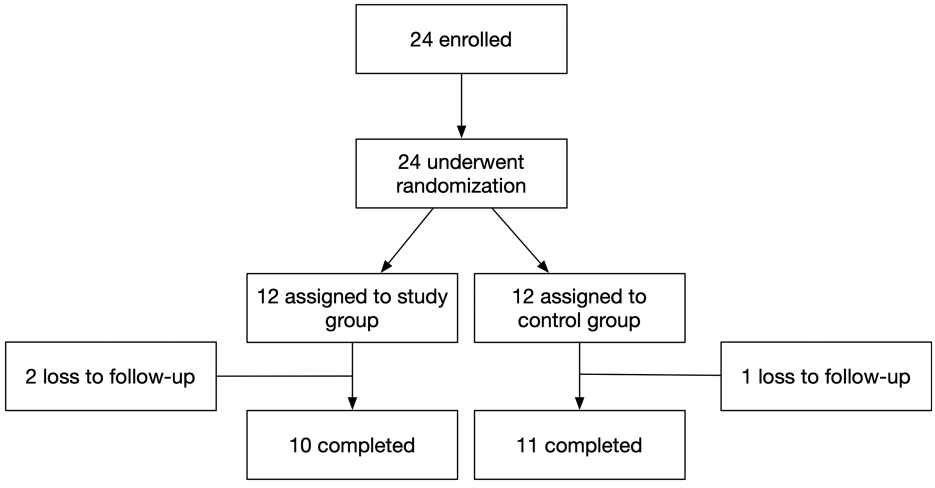

Figure 1. Flowchart of the study protocol.

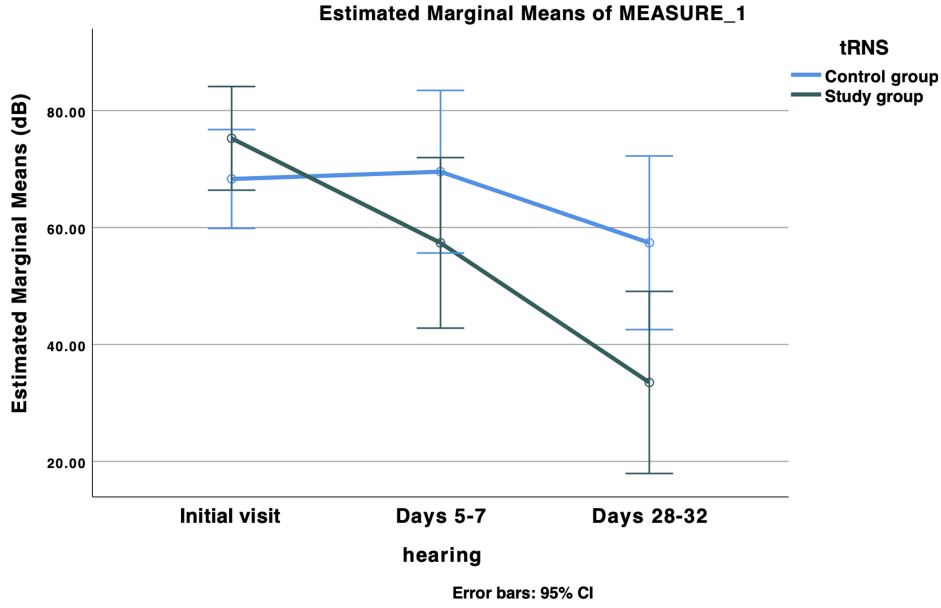

Figure 2. Changes in the hearing thresholds over time according to the allocation groups. Error bars represent SDs. Post hoc Bonferroni correction reveals that the hearing level between the initial visit and week 4 ($P = .001$) and between day 7 and week 4 ($P = .012$) differs significantly. tRNS, transcranial random noise stimulation.

A previous study showed that the addition of 20 sessions of rTMS to conventional steroid treatment plus hyperbaric oxygen therapy resulted in better treatment outcomes in the treatment group than in the control group.[5] This study also reported that abrupt, unilateral hearing loss may lead to asymmetric activation of the central auditory pathway.[5] Further, it demonstrated that rTMS on the temporoparietal area increased regional cerebral brain flow (rCBF) in multiple brain lesions, including those in the temporal, parietal, and occipital lobes and thalamus, as observed using single-photon emission computed tomography.[5] These effects are similar to those of anodal tDCS, wherein a similar increase in rCBF was observed during anodal stimulation and was retained after anodal stimulation.[8] These findings suggested that rTMS may improve auditory processing in ISSNHL.[5]

Similarly, another group reported an improvement in speech reception threshold in noise after rTMS.[9] However, they assumed this improvement might be caused by the training effect, and not by brain stimulation itself. In their case series, 1 patient's hearing was aggravated suddenly and necessitated conventional steroid treatment.[9]

The mechanism of tRNS remains unclear; it usually increases neuronal excitability via stochastic resonance.[6,10,11] Long-term potentiation is induced by repeated subthreshold stimulation. However, it disrupts synchrony in tinnitus patients who already have increased spontaneous firing.[10] As far as the authors know, the mechanism of action of tRNS on hearing has never been studied. Similar to rTMS, increased rCBF in the temporoparietal area and increased auditory processing

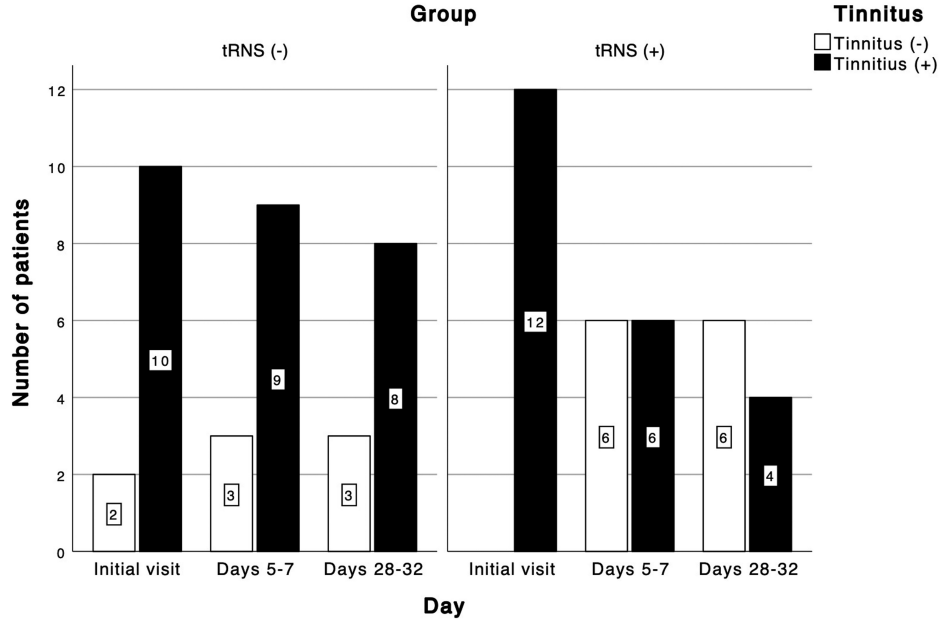

Figure 3. Changes in the numbers of patients with tinnitus in both groups over time.

may be a possible explanation for the hearing improvement.[5,8,9] In addition, we assumed that alterations in the auditory pathway through the top-down mechanism might be possible. However, this hypothesis should be verified by electroencephalographic or functional magnetic resonance imaging (fMRI) studies. Clinicians may overlook that cortical reorganization can also occur in ISSNHL. A healthy-side dominance has been detected using auditory evoked magnetoencephalography, and patients with poor recovery after ISSNHL have been shown to have a higher degree of reorganization.[12] Thus, there is some scope for the application of neuromodulation for the treatment of ISSNHL. However, to our knowledge, the effect of tRNS on hearing improvement has never been studied in ISSNHL.

Tinnitus is one of the most common and debilitating symptoms in ISSNHL. However, the clinical significance of tinnitus has been a subject of debate. In this study, the presence of tinnitus on days 5-7 and days 28-32 did not differ in accordance with the initial tinnitus characteristics. A previous study showed that tinnitus was not a prognostic factor. Instead, the contralateral hearing level was a significant predictor of recovery.[13] In contrast, other studies reported that the occurrence of tinnitus and milder hearing impairment were predictors of better recovery.[14] The presence of tinnitus may indicate better recovery because it indicates that hair cells have remained viable after cochlear injury.[15]

Nevertheless, tinnitus usually persists for a long time after ISSNHL. A previous study reported that tinnitus was alleviated in only 26% of the included patients after treatment.[16] Younger patients with good recovery experienced an improvement in tinnitus between 6 and 24 months after treatment.[17] In tinnitus, the severity of initial hearing impairment in ISSNHL was not associated with the tinnitus distress level, and the median recovery time was approximately 2 years.[18] The increased emotional stress also tends to reduce slowly after hearing improvement is achieved. However, patients may have persistent tinnitus in case of no improvement.[19] Taken together, these studies suggest that restoring normal hearing after ISSNHL may be a prerequisite for the recovery of tinnitus. However, the generation of tinnitus percept has no association with the degree of hearing impairment in the affected ear.

Unlike in ISSNHL, the applicability of tRNS in chronic tinnitus has been tested in many studies. The neuromodulatory effect may produce different treatment outcomes depending on the frequency used. When the frequency band is divided into 3 groups, low-frequency tRNS (lf-tRNS) ranges from 0.1 to 100 Hz, and high-frequency tRNS (hf-tRNS) ranges from 101 to 640 Hz; the full frequency range is also applicable (wf-tRNS). Both tinnitus loudness and distress were reduced after a single session of lf-tRNS or hf-tRNS, but not after wf-tRNS.[11] In addition, hf-tRNS showed a significant decrease in both loudness and distress in tone-like tinnitus. Considering that tone-like tinnitus was about 2 times more common than noise-like tinnitus, the application of hf-tRNS may be more reasonable.[20] However, in a study using hf-tRNS for the treatment of chronic tinnitus, only 27% of patients responded to 10 sessions of hf-tRNS treatment (2 mA; target: T7/T8; duration: 20 minutes).[6] Moreover, 20% of patients complained of worsening tinnitus after or during treatment.[6] Those researchers assumed that a transient increase in tinnitus after hf-tRNS might be caused by the stimulation of more medial areas, such as the posterior insula or hippocampus.[6]

A single session of lf-tRNS was also shown to be superior to a single session of tDCS or transcranial alternating current stimulation (tACS) in reducing tinnitus loudness and distress.[10] The same group also showed that 8 sessions of lf-tRNS (2 mA; target: T3/T4; duration, 20 minutes; frequency: twice per week) reduced both tinnitus loudness and distress significantly, but tACS did not produce such an effect.[21]

Recently, multisite stimulation has also been tried, such as a combination of different neuromodulations at 2 sites for tinnitus. For example, lf-tRNS was used after 20 minutes of tDCS (1.5 mA; anode: F4; cathode: F3), and 8 sessions of this treatment produced a significant reduction in tinnitus loudness and distress.[22] Although tDCS without any additional lf-tRNS also showed similar results, tDCS alone did not produce a significant reduction in the THI after treatment.[22] Another group used multisite tRNS comprising hf-tRNS (2 mA; duration: 10 minutes) of the prefrontal cortex and lf-tRNS (2 mA; duration: 10 minutes) of the auditory cortex and showed that it was effective in reducing tinnitus loudness without serious adverse events.[7] The frequency of adverse events, including headache, tingling, nervousness, and pain were similar irrespective of single or multiple sessions. A network meta-analysis of various noninvasive neuromodulation techniques also revealed that the best efficacy in terms of the severity of tinnitus changes was achieved using tDCS (anode: F4; cathode: F3) plus tRNS (T3).[23]

Other studies have focused on the electroencephalographic changes in ISSNHL, especially those before and after neuromodulation. One such study compared the resting-state quantitative electroencephalographic (qEEG) findings in ISSNHL with and without tinnitus.[24] Those researchers presumed that tinnitus accompanied by ISSNHL may be linked to the default mode network (DMN); thus, tinnitus was regarded as normal and was perceived when the pregenual anterior cingulate cortex-based top-down gatekeeper system (between emotion and cognition) was involved. However, another study observed an inhibition of brain activity and decreased functional connectivity between the auditory system and dorsal attention network in patients with ISSNHL and tinnitus.[25] A weakened left frontal lobe activity implies the inhibition of the DMN. Therefore, these patients may have decreased attention to auditory information or emotional behavior. Taken together, these findings suggest that ISSNHL with tinnitus accompanies changes in the nonauditory area associated with emotion or attention. That is, a comprehensive approach targeting brain regions from the periphery, through the central auditory system, to the nonauditory areas will be necessary instead of conventional treatments such as ITS injections or the administration of systemic steroids.

Our study has several limitations. First, a more objective assessment, such as qEEG, was not performed. A previous study reported the changes in oscillatory power after multisite tRNS in patients with chronic tinnitus, including decreased beta2 activity at the prefrontal cortex, anterior cingulate cortex, and parahippocampus and decreased functional connectivity of the alpha wave between the right prefrontal cortex and left auditory cortex.[26] We aim to perform a qEEG analysis in an upcoming study to validate our findings more objectively. Second, 4 weeks of follow-up after treatment in a small sample population may be too short a time to make a firm conclusion that lf-tRNS on the auditory cortex may be effective for treating ISSNHL. Because hearing restoration is rather slow after 1 month,

we focused on the early stage of ISSNHL. However, this might have resulted in us overlooking the potential late complications after tRNS, and we could not evaluate the long-term prognosis after treatment. Further studies are warranted to confirm these novel findings. Third, we did not classify or analyze the enrolled patients following their audiometric configuration, which may be associated with the prognosis. This might affect the treatment outcomes in this preliminary study. Lastly, we analyzed the data from only 24 patients in this preliminary study. Further research focusing on the effect of tRNS on ISSNHL patients using a larger sample size divided according to the occurrence of tinnitus is required.

In conclusion, adjuvant lf-tRNS seems a potential treatment option for hearing restoration in patients with ISSNHL without serious complications. However, it does not alleviate accompanying acute tinnitus. This suggests that additional multisite neuromodulation may be necessary to reduce tinnitus.

Ethics Committee Approval: The Institutional Review Board of the Eulji University Hospital approved this study (IRB number: 2018-07-001-003).

Informed Consent: Written informed consent was obtained from all the patients who participated to this study.

Peer-review: Externally peer-reviewed.

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Declaration of Interests: The authors declare that they have no competing interests.

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