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Original Article

Modulated Alpha Power as a Predictor of Tinnitus Alleviation

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BACKGROUND: Pain associated with subjective tinnitus is known to be alleviated by treatments using a repetitive transcranial magnetic stimulation (rTMS). However, the mechanisms underneath are still on debate. We investigated the mechanism of tinnitus alleviation using time–frequency analyses.

METHODS: Twenty-four patients were randomly assigned to the dual-site stimulation group (temporal and frontal stimulation, TF), single-site stimulation group (temporal stimulation, T), or sham stimulation group. An age-matched control group was also included (n = 12). Electroencephalography (EEG) was recorded and patient data were analyzed before and after treatment.

RESULTS: A frontal increase in EEG power was observed in the alpha (8-12 Hz) frequency band domain after treatment; this increase was most pronounced in the TF group, followed by the T group. The TF and T groups showed increased alpha power in the fronto-central channels only in the silent period between paired-pulse tones. The TF and T groups showed decreases in alpha power in the temporal region, particularly in the neural response to the first of the paired-pulse tones. The difference in tinnitus handicap index between pre- and post-treatment was positively correlated with the alpha power of the silent period in the frontal and fronto-central channels.

CONCLUSION: Dual-site stimulation showed the greatest alleviation of tinnitus-related discomfort, followed by single-site stimulation. Additionally, the modulation of alpha power was prominent in the active stimulation groups. Low frequency rTMS can alleviate tinnitus by increasing alpha band power and reducing hyperactivity.

KEYWORDS: Electroencephalography, predictor, tinnitus, treatment

INTRODUCTION

Subjective tinnitus is a phantom auditory perception that is not attributed to an existing external sound source. Because of its frequent occurrence, tinnitus has adverse effects on activities of daily living, quality of sleep, attention in the workplace, and mood. It is no longer presumed that tinnitus solely originates from a peripheral abnormality; the central nervous system is now acknowledged to sustain this activity of phantom perception that is initially induced by peripheral mechanisms.[1,2]

Tinnitus has been studied using various brain neuroimaging techniques, such as functional magnetic resonance imaging (MRI), electroencephalography (EEG), and magneto-encephalography. Multiple studies based on functional neuroimaging analyses have confirmed that tinnitus is associated with both non-auditory and auditory domains. Despite the superior spatial resolution of functional MRI, the main advantages of magneto-encephalography and EEG are that these signals directly measure the neural activity and reflect almost real-time firing of neurons.[3] Additionally, the lack of noise associated with EEG and MEG recordings is a significant advantage. Ear-drumming MRI is not recommended in patients with tinnitus. Because studies of tinnitus must measure subtle changes in the central auditory pathway, including the cortices, the presence of scanner noise (>80 dB nHL) can mask or contaminate target signals during scanning. Persistent tinnitus and hearing loss have occurred in otherwise healthy patients

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after MRI.[4] Multiple studies have used a sparse sampling strategy to reduce the effect of scanner noise;[5,6] however, this technique does not completely eliminate external noise.

Most functional MRI studies of tinnitus have examined resting-state responses (e.g., the default mode network or auditory network) or task-related responses.[7,8] True resting and true auditory networks may be affected by individual sensitivity to scanner noise. Studies using functional MRI have often targeted emotional differences in populations with tinnitus.[9,10] There is inevitably some concern regarding the extent of emotional disturbances caused by scanner noise because individuals exhibit different emotional mechanisms according to their level of tinnitus-related distress.[11]

One of the main models in current literature suggests that tinnitus is caused by disruption of activity between the thalamus and the cortex; initial neural deafferentation due to hearing loss leads to the inhibition of thalamic neurons. This inhibition leads to changes in oscillatory activity at the cortical level, as well as large-scale changes in slow-wave and gamma activity in the neighboring cortical regions.[12] Rauschecker et al[13] proposed a gating mechanism for the appearance of tinnitus depending on individual differences in the effectiveness of noise-cancelation systems mediated by structures within non-auditory regions.[13] Based on their hypothesis, we examined the gating mechanism using an auditory paired-pulse paradigm in patients with tinnitus, depending on responsiveness to treatment with repetitive transcranial magnetic stimulation (rTMS); our results confirmed that auditory sensory gating was modulated based on responsiveness to treatment.[14] Neural and sensory gating theories have focused on responses to conditioning and test stimuli, rather than the time course of responses to both stimuli. Because we were interested in the disturbance of the gating system in tinnitus and wished to examine specific time windows in the gating mechanism, we separated the whole response to a paired-pulse epoch into 3 time windows: t1, corresponding to the initial response to the first sound (conditioning) of paired pulses; t2, corresponding to a silent period between sounds; and t3, corresponding to the last sound (test) of the pair. We expected that the alleviation of tinnitus by rTMS treatment would be associated with neural changes in auditory temporal regions (t1 or t3) and the inhibitory control center (t2 or t3). Auditory stimulation as well as inhibition is expected to alleviate tinnitus perception.

MAIN POINTS

- Discomfort due to subjective tinnitus is known to be alleviated by rTMS but the mechanisms underneath are still on debate.
- In a radomized clinical trial using three rTMS treatments, we endeavored to explore which aspect of electrophysical characteristics may associate most with the outcomes, using a whole brain electroencephalography (EEG) spectral power analysis.
- Increase of EEG power was observed in the alpha (8–12 Hz) frequency band domain after treatment in the frontal lobe and the increase was most pronounced in the dual stimulation (frontal and temporal lobe) group, followed by the temporal stimulation group.
- The difference in tinnitus handicap index between pre- and post-treatments was positively correlated with the alpha power in the frontal and fronto-central channels.
- We speculate that the increase in alpha activity after an rTMS may associate with the underlying mechanism of tinnitus suppression.

Another possible biomarker for tinnitus alleviation is increased alpha power in the group responding to treatment. Using magnetoencephalography, Weisz et al[15] showed that the spontaneous neuronal activity in a group with tinnitus was characterized by a substantial reduction of activity in the alpha (8-12 Hz) domain. The oscillatory model of tinnitus was associated with characteristic changes in alpha (relative decrease) and gamma (relative increase) activities, compared with healthy controls. Alpha oscillation is presumed to reflect the degree of inter-neuronal synchronization in the auditory cortex; reduced alpha activity releases cortical inhibition, leading to an abnormal increase in gamma oscillatory synchrony and corresponding hyperactivity. These abnormal increases are responsible for the perception and exaggeration of tinnitus. The gamma oscillatory pattern in tinnitus is presumed to represent the conscious perception of tinnitus.[16,17] In addition to the auditory regions, frontal alpha activity is also associated with tinnitus. Based on the oscillatory characteristics of subjective tinnitus outlined above, suppressive therapies were suspected to alleviate tinnitus-related discomfort, particularly targeting frontal regions.[18] Malekshahi et al[19] recently reported regulation by auditory cortex alpha activity. This new method is based on the EEG-neurofeedback treatment approach that allows online auditory alpha self-regulation training in patients with chronic tinnitus. This approach detects the auditory alpha EEG activity that originates from the primary auditory cortices. Using pre-determined training, the investigators confirmed both the suppression of tinnitus and the reduction of alpha activity in the region of interest, demonstrating the feasibility of their algorithm and the procedure for auditory alpha neurofeedback. Thus far, these oscillatory modulation treatments in patients with tinnitus have been performed with the patient in a resting state. Due to new evidence that the online sensory gating mechanism is affected by treatment, there is a need for time-frequency analysis of event-related spectral perturbation in the separate response windows that are evoked by the paired-pulse.

MATERIAL AND METHODS

We used the data acquired in our previous study[14] and recruited an age-matched control group for comparison (n = 12). The study protocol was approved by the institutional review board of Seoul National University Hospital (IRB Approval No: H-1212-081-450) in accordance with the 1964 International Organization for Standardization criteria. All tests were conducted following the Declaration of Helsinki and the International Conference on Harmonisation Good Clinical Practice Guidelines. The study was registered as a clinical trial (ClinicalTrials.gov identifier: NCT02617953) before the initial patient enrollment. All participants provided written informed consent before conducting the experiment. All other procedures and outcome measures followed international standards. Because frontal activities related to oscillations are also related to depression, we excluded participants who had both tinnitus and depression to ensure clear separation of the 2 conditions. Beck's Depression Inventory was used to identify patients with clinically significant depression; patients with a score $\geq$14 were excluded from the study. Control participants ranged in age from 30 to 70 years; they did not have tinnitus or other neurological conditions. Normal hearing in each individual was defined as a mean hearing loss of <25 dB HL for 3 air-conduction thresholds (0.5, 1.0, and 2.0 kHz).

Repetitive Transcranial Magnetic Stimulation

Patients with tinnitus were assigned in a systematically randomized manner to 1 of 3 groups: dual-site stimulation (temporal and frontal

stimulation, TF; n = 8), single-site stimulation (temporal stimulation, T; n = 8), and sham stimulation (S; n = 8). The assignment was performed after confirmation of each patient's rTMS/EEG/MRI eligibility. The stimulation sites were as follows: T, the left auditory cortex (Langguth et al., 2006); and F, the left dorsolateral prefrontal cortex, which corresponded to F3 in the 10-20 EEG system.[20] The controls without tinnitus (n = 8) were not treated with rTMS.

Electroencephalography Recording

Two recording sessions were performed: one before and another at 2 weeks after rTMS (±3 days). Recordings were conducted in a dimly lit room shielded against sound, vibration, and stray electromagnetic fields. Electroencephalography signals were recorded via Quick-cap with sintered 64 Ag/AgCl surface electrodes and Neuroscan SynAmps2 amplifier using CURRY software version 7 (Compumedics, Charlotte, NC, USA) at a sampling rate of 1000 Hz in a sound-attenuated silent room. Electroencephalography was performed with the 64 electrodes in the standard 10-20 international placement with reference to the connected ears. The impedances at all electrodes were maintained <5 kΩ throughout the sessions. Patients sat in an upright position and received a series of auditory stimuli consisting of paired pulses through an insert earphone (ER2; Etymotic Research, Inc., Elk Grove Village, Ill, USA). Each stimulus consisted of two 1-kHz pure-tone beeps 20 ms in duration, with an inter-stimulus interval of 300 ms. A sound pressure level of 65 dB was intended, although a few participants listened to the tones at their own most comfortable level. Participants were discouraged from fully attending to the sound. Instead, they were instructed to rehearse any 2-syllable word sporadically presented and to stay awake. Each session consisted of 2 phases <16 minutes, separated by a break of ≥3 minutes. The paired-pulse suppression index was computed as the ratio of the amplitude of the second (test or A2) to the amplitude of the first test (conditioning or A1) response (A2/A1).[21]

Signal Pre-Processing and Time-Frequency Analysis

Electrophysiological data were analyzed using MATLAB R2019b (MathWorks, Natick, Mass, USA), along with Fieldtrip and the EEGLAB toolbox. Data were filtered offline using 0.1-50 Hz fourth-order Butterworth band-pass filters. Bad channels (<10 channels total) were corrected using automated spherical spline interpolation. The window of analysis was 1000 ms, including a 200 ms pre-stimulus baseline. Epochs that contained amplitudes exceeding ± 100 μV were excluded using a built-in automatic rejection algorithm in EEGLAB software (version 2021.0). Eye blinks and muscle movement-related artifacts were corrected by independent component analysis based on the Infomax algorithm[22] and subsequent visual inspection. Data were then re-referenced to a common mean reference and baseline-corrected separately for each channel, according to the mean amplitude of the EEG during the 200-ms period preceding stimulus onset. The final number of epochs for each session was 155-217. The grand means for each group were then computed for analysis and visualization purposes.

Spectral Power

To detect transient event-related shifts in the power spectrum, event-related spectral perturbation and inter-trial phase coherence images of 999 frames sampled at 1000 Hz were computed from 60 scalp electrodes. Each trial included samples from −200 ms before to 799 ms after the time-locking event. A wavelet was generated in each successive and overlapping time window (Makeig, 1993). The time values for time/frequency decomposition in these data may not be entirely uniformly distributed. The mean baseline spectrum was computed by estimating 69 linearly spaced frequencies from 7.5 Hz to 50.0 Hz and processing time from 1 to 40 points (out of 200 points).

Three time windows (t1: 0-150 ms, t2: 151-300 ms, and t3: 301-450 ms) were compared. The first time window (t1) corresponded approximately to the first stimulus of the paired-pulse, whereas the second time window (t2) corresponded to the silent period between the pulses. Finally, the third time window (t3) corresponded to the second tone of the paired pulses. Because we did not perform data down-sampling, the time resolution was not straightforward (t1: 1-148 ms; t2: 151-299 ms; t3: 301-450 ms). The following 3 frequency ranges were used: alpha: 8.125-12.5 Hz, beta: 14.375-24.375 Hz, and gamma: 30-50 Hz.

Determination of Responders

A clinically meaningful difference was defined as an improvement in the tinnitus handicap index (ΔTHI) of ≥ 7 points.[23] Patients who had a meaningful improvement in the THI score following active rTMS were classified as responders. The remaining patients were considered as non-responders.

Statistical Analysis

Because the data exhibited a normal distribution, paired *t*-tests were used to compare the various time-frequency data of individuals before and after treatment. *P*-values < .05 were considered indicative of statistical significance. Bonferroni correction was applied as necessary. Statistical Package for the Social Sciences (SPSS) Statistics for Windows, version 24.0 (IBM SPSS Corp.; Armonk, NY, USA) and MATLAB software (2014a and 2019b) were used for the statistical analyses.

RESULTS

In total, 24 patients and 8 age-matched control volunteers participated in the study. Each treatment group consisted of 8 patients. The demographic characteristics of the patients have been reported previously.[14] Participants in the control group had a mean age of 55 years (range: 47-58 years); the group included six women (50%), and all control volunteers had a hearing level within the normal range.

Paired-Pulse Evoked Grand Mean

Figure 1 shows the grand mean potential evoked by auditory paired-pulse stimulation compared between all patients with tinnitus (n = 24) and all age-matched controls (n = 12). The 3-time windows analyzed in the study were t1, t2, and t3. Patients with tinnitus had a smaller paired-pulse suppression index (A2/A1) than age-matched controls, suggesting that patients with tinnitus had less natural suppression due to disruption of the sensory gating mechanism.

Whole-Epoch Spectral Analysis

The pre- and post-treatment whole-epoch spectral power was computed for each subject. Sample event-related spectral perturbations (ERSPs) of responders and non-responders in pre- and post-treatment sessions are presented in Figure 2.

As shown in Figure 3, the alpha power in the frontal region (channel Fz) was significantly lower (*P* = .0081) in patients with tinnitus before

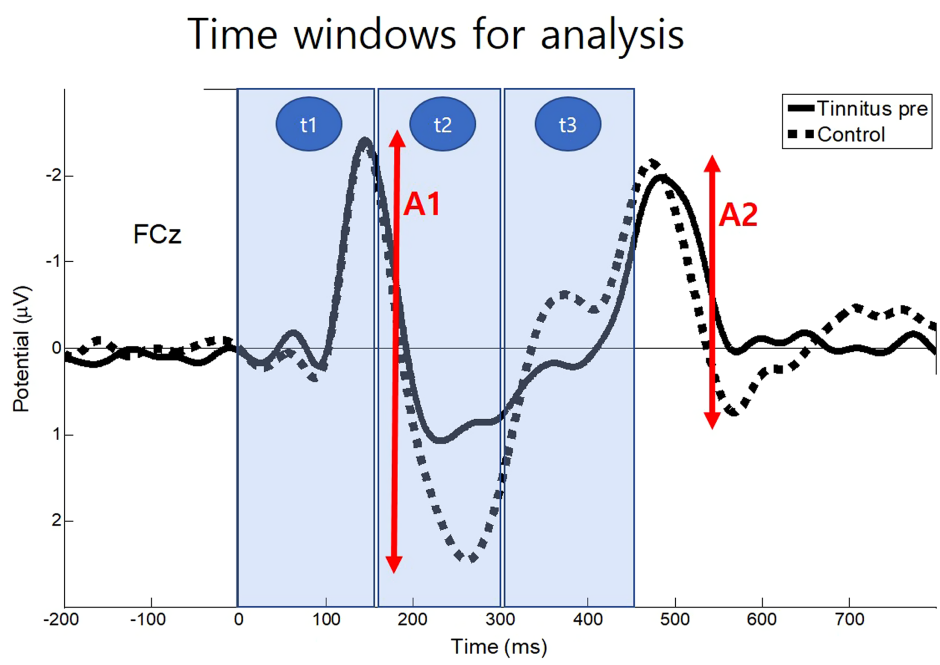

Figure 1. Grand mean waveforms evoked by paired-pulse stimulation in the tinnitus (thick line) and control groups (dotted line) collected at the FCz electrode and 3 time windows: t1, t2, and t3. t1 corresponds to the first (conditioning) sound of the paired-pulse, t2 corresponds to silent period between paired pulses, and t3 corresponds to the second (test) sound of the paired-pulse. FCz, fronto-central midline. Tinnitus, n = 24; control, n = 12.

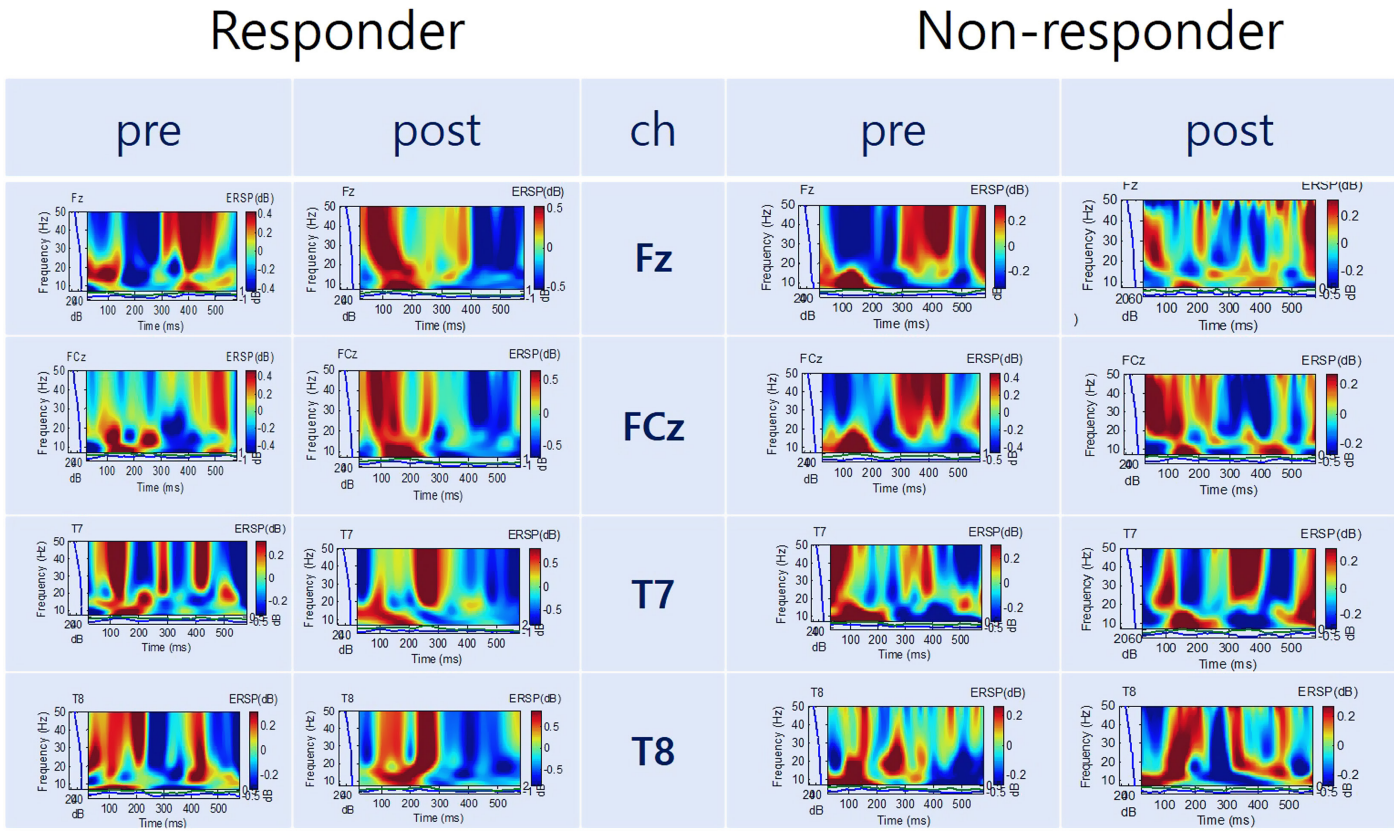

Figure 2. Sample ERSPs of a responder and a non-responder in pre- and post-treatment sessions at channels Fz, FCz, T7, and T8. ch, channel; FCz, fronto-central midline; Fz, frontal channel.

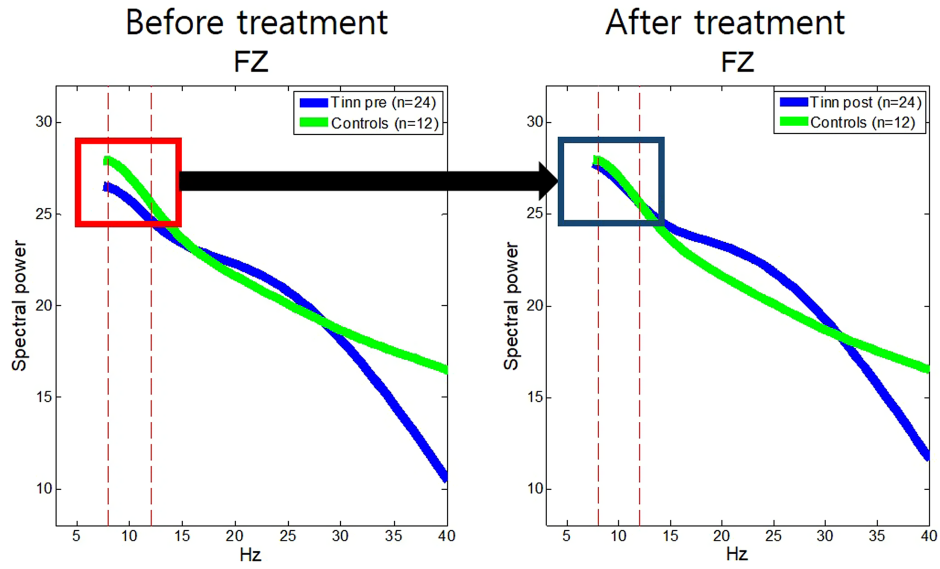

Figure 3. Spectral power analysis. Patients (blue line) with tinnitus before and after active repetitive transcranial magnetic stimulation treatment at channel frontal channel; compared with age-matched controls (green line). Before treatment, there was a substantial difference in alpha power (red square) between the tinnitus patients and age-matched controls, but there were no differences after treatment (blue square). Dotted red lines indicate the alpha frequency range (8-12 Hz). Fz, frontal channel.

treatment (blue line in red square) than in the control group (green line in red square). After active rTMS treatment, no significant differences ($P = .4890$) were observed between the 2 groups (blue square).

Pre- vs. Post-Treatment

An overall significant increase in alpha power was observed at the frontal channel (Fz) after T or TF rTMS treatment ($P = .038$).

Sequential Responses to Paired-Pulse Stimulation

As shown in Figure 4, the changes in spectral power during t1, t2, and t3 according to the type of treatment were characterized by a substantial increase in alpha power in t2 at the frontal region in the responders, compared with the non-responders; this pattern was also found in the active stimulation groups (T and TF). In particular, among the 3-time windows, the t2 and t3 time windows in channel Fz showed a significant increase in alpha power after T or TF rTMS treatment (t2: $P = .006$, t3: $P = .041$).

Compared to controls, patients with tinnitus showed a significantly lower alpha power in all time windows (t1: $P = .001$, t2: $P = .0002$, t3: $P = .0228$) (left panel; Figure 5). This difference in alpha power between tinnitus patients and controls disappeared after treatment at t2 and t3 (right panel; Figure 5).

Changes in Alpha Power According to Repetitive Transcranial Magnetic Stimulation Type

The TF group consistently showed a significant increase in the frontal alpha power compared to the T and S groups. Figure 6 shows the spectral power in the significant channel Fz between responders and non-responders (A), between S and TF groups (B), and between T and TF groups (C). The TF group showed a substantial increase in alpha power compared to the S and T groups.

Correlations between Alpha Power and Tinnitus Handicap Index

The changes in t2 alpha power at Fz ($r = 0.4041$, $P = .05$) and FCz ($r = 0.3994$, $P = .05$) were positively correlated with ΔTHI (Figure 7). A greater difference in THI between pre- and post-stimulation was correlated with larger increases in alpha power in Fz and FCz. The changes in alpha power at t1 and t3 were not correlated with ΔTHI in any channel.

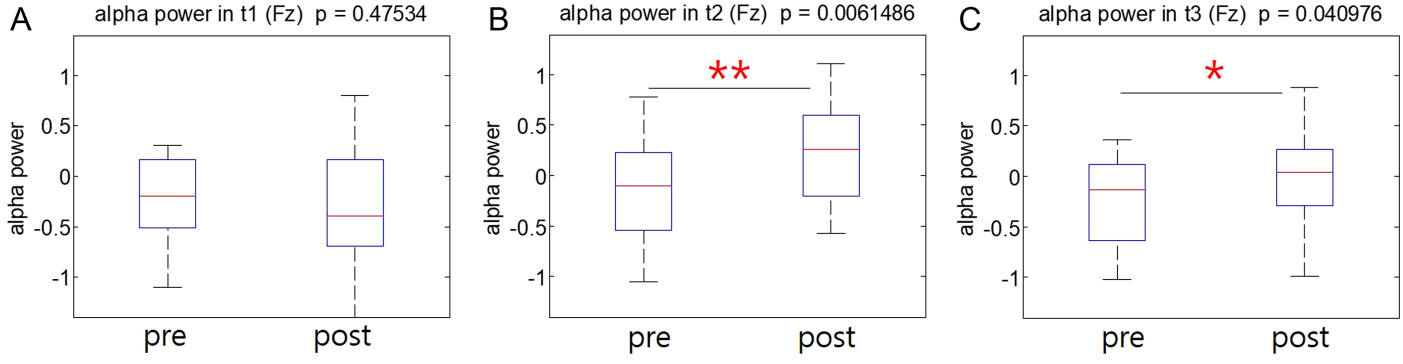

Figure 4. Comparison of alpha power at channel frontal channel between pre- and post-treatment in patients with tinnitus (T, TF rTMS, or sham, n = 24) according to elapsed time: t1 (A), t2 (B), and t3 (C). *$P < .05$, **$P < .01$. Fz, frontal channel; TF, temporal and frontal stimulation; rTMS, repetitive transcranial magnetic stimulation; T, temporal stimulation.

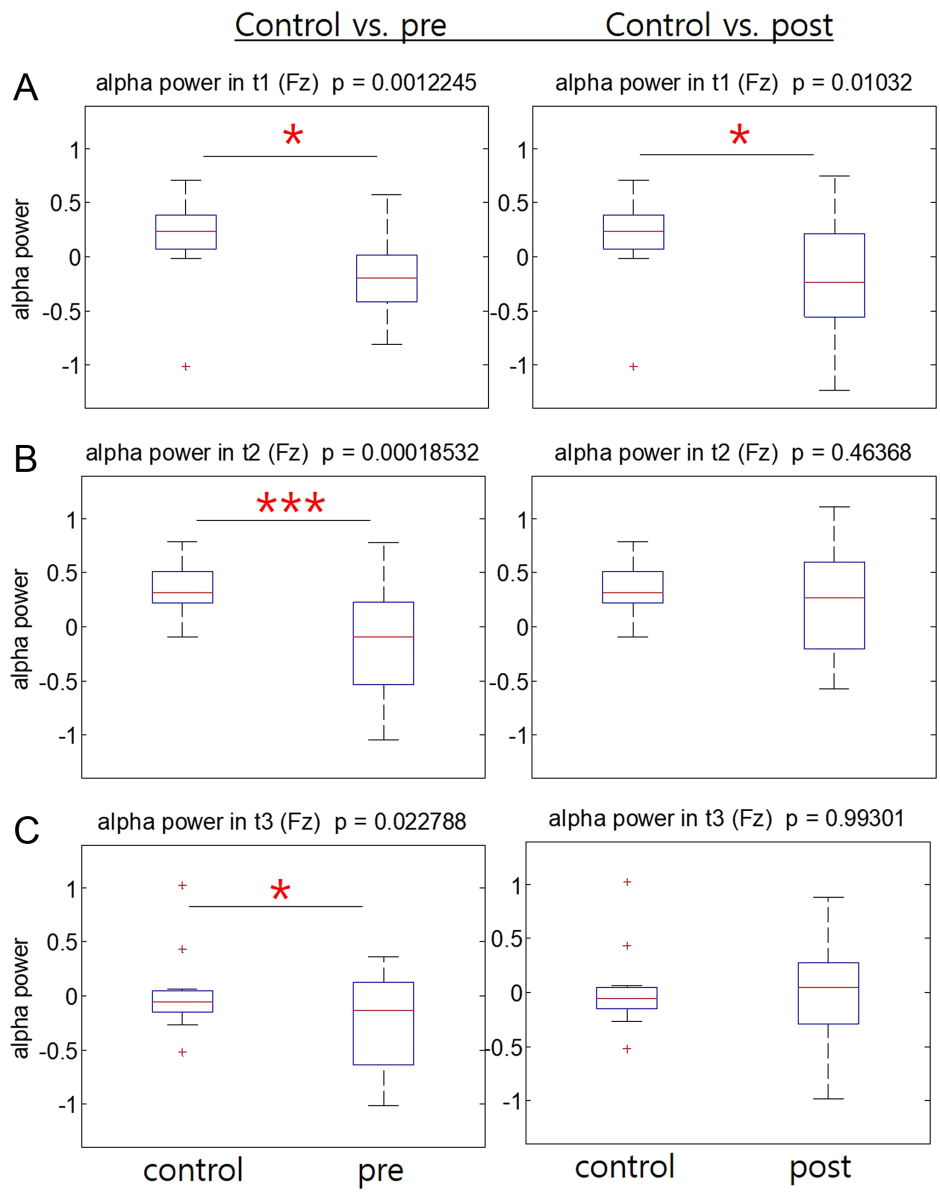

Figure 5. Comparison of alpha power at channel frontal channel between controls and patients pre- and post-treatment according to the elapsed time: t1 (A), t2 (B), and t3 (C). Red+: outlier **P* < .05, ***P* < .01, ****P* < .001. Fz, frontal channel.

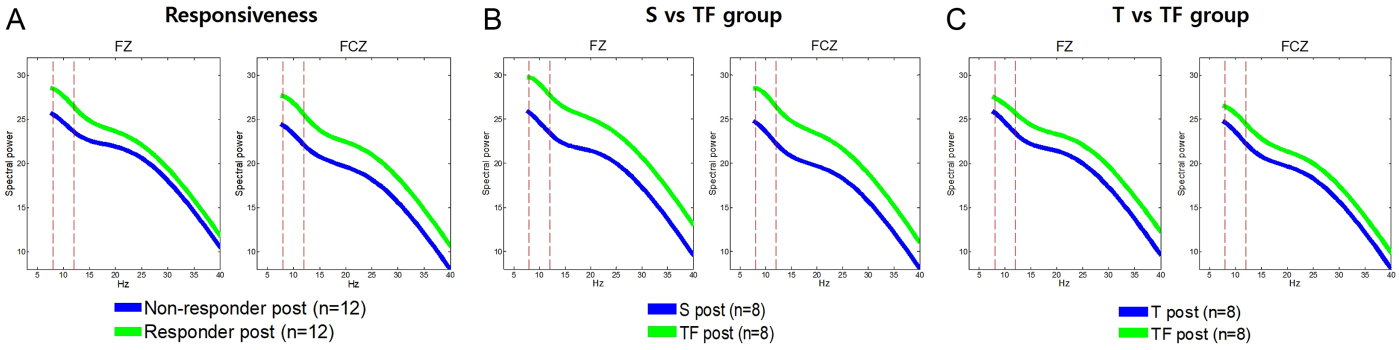

Figure 6. Comparison of spectral power in frontal channel and fronto-central midline channels according to responsiveness (A) between the S and TF groups (B) and T and TF groups before (solid blue lines) and after (solid green lines) treatment. Dotted red vertical lines indicate the alpha frequency range (8-12 Hz). FCz, fronto-central midline; Fz, frontal channel; T, T, temporal stimulation; TF, temporal and frontal stimulation.

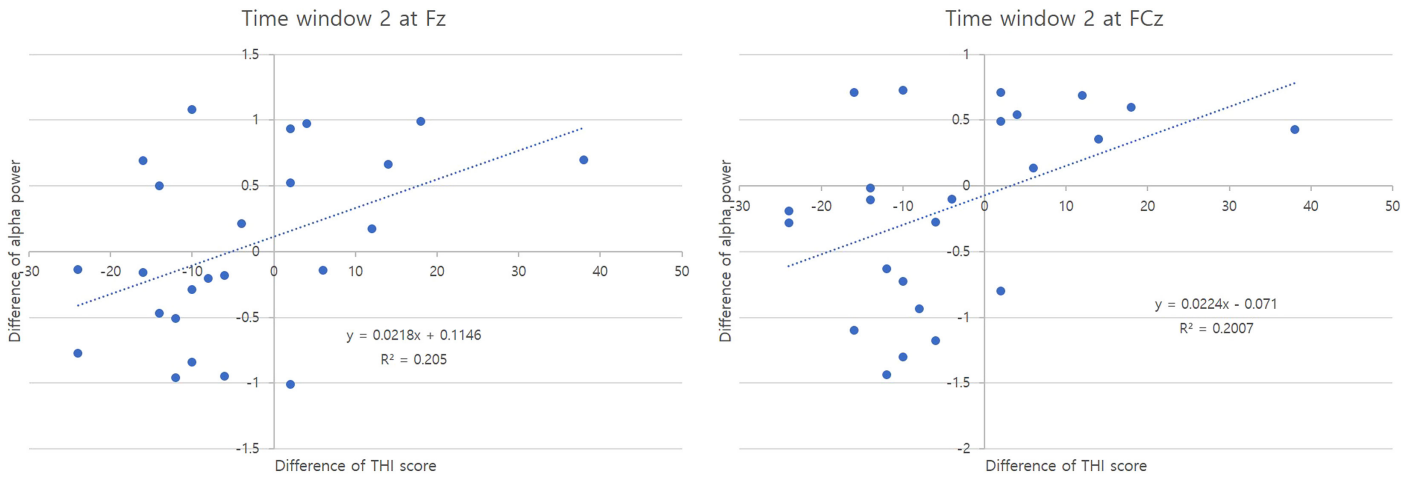

Figure 7. Correlations between alpha power and tinnitus handicap index in t2 at channels Fz (A) and FCz (B). FCz, fronto-central midline; Fz, frontal channel; THI, tinnitus handicap index.

DISCUSSION

We found that perceived tinnitus, measured using THI questionnaire, was alleviated after repetitive TMS treatment. Treatment success was associated with changes in frontal alpha band activity. Our time-frequency analysis revealed that the active stimulation group showed an increased spectral power density amplitude in the alpha band, primarily over the frontal sites (Fz and FCz). The increase was most pronounced in the dual-site stimulation group (TF), followed by the single-site stimulation group (T). In the silent period between the pair of sounds presented (t2), the difference in THI was positively correlated with the changes in alpha power at the frontal and fronto-central channels. These results are in line with the hypothesis that low-frequency (1 Hz) rTMS inhibits cortical function.[24] Furthermore, rTMS enhances the cortical sensory gating mechanism, particularly at t2. The t2 strengthening of the inhibitory alpha power reduces tinnitus. On the other hand, t1 and t3, which reflect the auditory-evoked response rather than sensory gating, were not affected by rTMS. This is the first study to elucidate the effects of rTMS on sensory gating at sequential time points.

Our results are consistent with a recent report that high alpha entrainment alleviates tinnitus discomfort by suppressing the cortical processing of pain.[25] The correlation between the difference in THI and t2 alpha power may also support the gating hypothesis. Because information is gated when task irrelevancy is inhibited and this functional inhibition is reflected by alpha power, the increase in alpha power in our respondent group suggests clinical restoration of inhibitory function via rTMS treatment.[26] The increase in alpha activity may be an underlying mechanism of tinnitus suppression after rTMS. The increase in alpha activity in our study was most pronounced in the temporal channels in the dual-site stimulation group; this finding is consistent with a previous report that rTMS can cause inhibition in normal hearing participants, although this functional inhibition is not accompanied by auditory cortex-specific increases in alpha activity.[27]

Despite the small sample size of our study, statistical analysis can be used to determine the expected treatment outcomes. Successful treatment is associated with a temporal decrease in alpha activity in the t2 time window. Notably, a decrease in alpha power was observed at the temporal channel (T8) in the dual- and single-site stimulation groups (but not in the sham group), specifically in the response duration to the first of the paired stimuli (t1). However, an increase in alpha power was observed in the dual- and single-site stimulation groups (but not in the sham group), specifically in the interval that corresponded to the silent period (t2). Further studies with larger samples are needed.

In our study, hyperactivity in tinnitus patients may have been inhibited by low-frequency rTMS, which is in line with previous studies. Many studies have suggested that spontaneous neural activity in the temporal cortex is a biomarker of tinnitus. A previous fluoro-deoxyglucose positron emission tomography study identified hypermetabolism in the auditory cortices of tinnitus patients.[28] Temporal cortex synchrony and excitability have also been reported in tinnitus patients.[29,30] The decrease in alpha power at T8 observed in the present study may have been related to inhibition of the auditory cortex, which is pathologically upregulated in tinnitus patients.

The time point of post-treatment EEG is critical: the effect of rTMS on alpha spectral power and sensory gating depends on the time of administration. In the present study, post-treatment EEG was performed during the second week, which may explain the large effect of rTMS. Based on the long follow-up of the present study, we found that the treatment outcomes were more discrete among groups at 2 weeks after treatment.[20] Because we evaluated patients 14 days after rTMS, the maximum change in alpha spectral power may not have been recorded. Based on behavioral observations, we predict more readily distinguishable treatment outcomes among groups with an appropriate interval between pre- and post-treatment EEG. Future studies should evaluate the long-term modulation in alpha spectral power and sensory gating after rTMS.

This study had some limitations; however, first, the sample size was insufficient to generalize rTMS effects. Within the current data, the slowest waves (e.g., delta and theta) could not be observed because our epoch length was 1 seconds; thus, the frequency resolution was <6.9 Hz and we filtered the signal offline 0.1-50 Hz. Further studies are needed to examine whether rTMS can modulate higher frequency activity depending on treatment outcome, specifically in

terms of the time course response to the paired-pulse tone, because high-frequency activity in the temporal lobe is a characteristic of intractable tinnitus.[29]

In summary, alpha modulation in patients with tinnitus may be related to disruptive effects on the salient and emotional networks, most frequently in the frontal and temporal brain regions.[9] In the present study, the degree of tinnitus alleviation by rTMS, measured by change in THI difference, was positively correlated with an increase in alpha activity in the frontal channels, particularly during the silent period. Our results will contribute to the treatment of tinnitus by cortical neuromodulation of alpha power using rTMS.

Ethics Committee Approval: This study was approved by the Ethics Committee of Seoul National University Hospital (Approval No: H-1212-081-450; Date: January 4, 2016).

Informed Consent: Informed consent was obtained from the participants who agreed to take part in the study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – J.S.K., M.W.S.; Design – J.S.K., M.W.S.; Supervision – M.W.S.; Resources – M.W.S., J.S.K.; Materials – M.K., J.L., S.H.O., M.W.S.; Data Collection and/or Processing – J.S.K., T.N.; Analysis and/or Interpretation – J.S.K.; Literature Search – J.S.K., M.W.S.; Writing – J.S.K.; Critical Review – J.S.K., M.W.S.

Declaration of Interests: The authors have no conflicts of interest to declare.

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