이학박사 학위논문

Objective Assessments of the Transcranial Stimulations for Treatments of Tinnitus and Hyperacusis

이명과 청각과민증에서의 경두개 자극술 치료의 객관적 평가

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Ph.D. Dissertation

Objective Assessments of the Transcranial Stimulations for Treatments of Tinnitus and Hyperacusis

Bae, Eun Bit

February, 2019

Interdisciplimentary program in Brainscience
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Objective Assessments of the Transcranial Stimulations for Treatments of Tinnitus and Hyperacusis

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Abstract

Objective Assessments of the Transcranial Stimulations for Treatments of Tinnitus and Hyperacusis

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Tinnitus and hyperacusis are neuro-otological disorders, and both main symptoms are subjective. For example, tinnitus is a symptom of continuous hearing a sound without external sounds. Hyperacusis is a symptom of discomfort when people hear a loud sound, and sometimes hyperacusis accompanies headache or other physical symptoms. In addition, both disorders are not cured by medication and the severity of the symptoms can not be measured objectively so it is not diagnosed by objective examination method. From the 1950s onwards, the central mechanism of tinnitus has been mentioned by numerous studies, and the common brain state of tinnitus and hyperacusis has been revealed by various animal studies, such as recent central gain enhancement mechanisms.

The aim of this dissertation is to treat central hyperactivity of tinnitus and hyperacusis using transcranial electrical stimulation and transcranial magnetic stimulation, and to assess pathological status with an electro-physiological

method. In the previous tinnitus studies, the transcranial direct current stimulation and magnetic stimulation were used for the study of tinnitus treatment, and in this study, the transcranial random noise stimulation was used to treat hyperacusis. Questionnaire format is the most important measurement to assess the subjective symptoms of tinnitus, but the pathophysiologic status of the central mechanism of tinnitus can not be determined by questionnaires or audiometry. Therefore, in order to effectively evaluate the pathophysiological condition of tinnitus and hyperacusis and the therapeutic effects of the transcranial stimulations, we used an electroencephalography (EEG) as a neuroimaging technique. For objectively measuring pathologic status, verifiable standards of the EEG had to be established.

In the course of my doctoral degree, we conducted several studies to develop a treatment methods specific to tinnitus and hyperacusis using transcranial stimulations. As a result, we increased the therapeutic effect and the number of responders compared to the previous researches, and we also devised a specific treatment for hyperacusis. In addition, we focused on establishing the test methods that can confirm the therapeutic effects objectively through the EEG, questionnaires and a psychoacoustic measurement. In this doctoral dissertation, we used these three tests to complement each other's strengths and weaknesses to accurately evaluate the patho-physiologic status and therapeutic effects of tinnitus and hyperacusis.

Keywords : Tinnitus, Hyperacusis, Transcranial direct current stimulation, Transcranial magnetic stimulation, Transcranial random noise stimulation, Pure tone audiometry, Electroencephalography, Auditory cortex

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1. Introduction

1.1. Background of the study

Tinnitus and hyperacusis are not lethal to human life, but these are the auditory disorders with a high prevalence and high levels of depressive symptoms and suffering. Regardless of age and gender, tinnitus and hyperacusis can develop in anyone from children to adults to seniors (Kleinjung et al. 2011). With the development of technology, portable and electronic devices are becoming more popular, and the prevalence of the auditory and hearing disorders is rapidly increasing year by year. Furthermore, the number of teenage patients is increasing; thus, tinnitus and hyperacusis are becoming more critical in both social and clinical.

Tinnitus, except pulsatile tinnitus, and hyperacusis are primarily based on the subjective complaints of patients. Still, there are no test methods that can objectively measure the severity of tinnitus and hyperacusis or a specific treatment with a high therapeutic effect. Although drugs have been used primarily to treat symptoms of tinnitus and hyperacusis, most drugs are ineffective or have side effects. And to assess subjective symptoms of tinnitus, questionnaires are usually used. i.e. tinnitus questionnaire, tinnitus handicap inventory, visual analogue scale, etc. The only measurement for the

assessment of the pathophysiologic condition of tinnitus is the pitch matching test using pure-tone audiometry (PTA), which entirely depends on the subject's answer; therefore, the results usually vary depending on the health conditions of the patient. The measurements that objectively evaluate the neuronal hyperactivity resulting from central gain enhancement, the major cause of tinnitus and hyperacusis, are highly needed in these days.

1.2. Pathophysiological view of tinnitus and hyperacusis

Some people temporarily hear tinnitus depending on their health condition and body position in normal hearing while other hear tinnitus all the time after they lose their hearing (Shore, Zhou, and Koehler 2007). Hyperacusis is one of the symptoms accompany with tinnitus, and it also occurs when a person is exposed to repetitive or chronic high frequency noises. Hearing loss can cause hyperactivity in the middle of the bottom-up hearing pathway from the peripheral nerve of the cochlea to the cortex (Auerbach et al. 2014) in tinnitus and hyperacusis. Maladapted signals feed back to the cortex from the damaged hair cells or cochlea nerves, and this process causes central gain enhancement which can be detected as hyperactivity outside of the brain via neuroimaging techniques (Vanneste et al. 2014).

Previous studies have identified cortical circuits related to tinnitus and

hyperacusis associated with cognition, memory, and emotion (Vanneste et al. 2014, 2015, 2018). Sevral studies also discovered it via functional connectivity and neuroimaging showing that tinnitus and hyperacusis can develop these circuits into a strong maladapted connection (Chen et al. 2015; Chen et al. 2017; De Ridder et al. 2014). Symptoms of the central tinnitus and hyperacusis have been described in clinic from a century ago (Ear. 1893), and recent studies have more specifically identified these symptoms in central gain enhancement theory via animal experiments or human neuroimaging (Mantini et al. 2007). However, there are no specific and standardized measurements or therapies for tinnitus and hyperacusis in clinic.

The purpose of this doctoral dissertation is to maximize therapeutic effects of tinnitus and hyperacusis using the transcranial stimulations and evaluate pathologic status and therapeutic effects objectively through EEG with the studies described in the chapter 2 to the chapter 4.

1.3. Overview

This doctoral dissertation is consists of four parts:

The chapter 1 is introduction of the research background of the dissertation for social significances, necessity of the study and patho-physiological views about tinnitus and hyperacusis.

The details of the main studies were described in the chapter 2 to

chapter 4, and the contents were include as follows:

The studies evaluating effects of the single session of dual neuromodulation for the tinnitus treatments were presented in the chapter 2. We evaluated the therapeutic effects of transcranial direct current stimulation (tDCS) and transcranial magnetic stimulation (TMS) via questionnares and pure-tone audiometry.

The study on treatment specialized for hyperacusis using transcranial random noise stimulation (tRNS) was described in the chapter 3. The therapeutic effects of tRNS on hyperacusis were evaluated through visual analogue scale of the hyperacusis symptoms, uncomfortable hearing levels and electro-encephalography (EEG) of pre/ post treatment.

The research focusing on the comparison of the characteristics of EEG between workers who long-term exposed to occupational noise and other tinnitus/hyperacusis is described in the chapter 4. Through this study, occupational noise induced tinnitus/hyperacusis would be separated to other tinnitus/hyperacusis with/without hearing loss.

Finally, we gave the perspectives of the future works for transcranial stimulations and EEG validation on tinnitus and hyperacusis and suggested treatment and EEG methods for clinics in the chapter 5.

2. Stimulations for tinnitus treatment

2.1. Abstract

To treat motor disorders and psychiatric disorders, transcranial direct current stimulation (tDCS) and transcranial magnetic stimulations (TMS) are world-widely in use in clinics. For subjective tinnitus, we combined these two type of neuromodulation in this study, to evaluate how the effectiveness of single session of tDCS and TMS combined treatment is different to single treatment groups.

Eighty tinnitus subjects completed the clinical trial. Experimental groups were divided into four groups according to the combination of two types of stimulations, which are the tDCS group, tDCS with sham TMS group (tDCS-shTMS), tDCS with TMS combined group (tDCS-TMS) and TMS group. We used four types of questionnaires for self-assessments of subjective symptoms of tinnitus and audiometry results for evaluating auditory characteristics of respondents on the transcranial stimulations. To verify the correlation between hearing and responses of neuromodulation, each group was divided into respondents and non-respondents according to the pre-post treatment differences between VAS intensity and VAS distress and total eight groups were performed statistical analysis.

Using the paired t-test, we analyzed the differences of each group

between pre- and post-treatment score. In the tDCS-TMS group, THI, VAS intensity and distress were significantly decreased. The results of the four questionnaires of each of the four groups showed that VAS perception and intensity of tDCS-TMS group had made a significantly largest difference (tDCS-TMS group, $p=0.018$) while no significant difference in the group comparisons (Table 2-2, $P>0.05$). The p-value of VAS intensity between the tDCS-TMS and TMS groups was the lowest ($p=0.056$) compared to the other groups (Mann-Whitney U test, Table 2-2). Respondents of the tDCS-TMS group were the highest for VAS intensity, 70% of twenty subjects.

From the frequency based results of pure-tone audiometry (PTA), differences of the hearing thresholds of the right side for the respondents and non-respondents in tDCS-TMS group were decreased than other tDCS performed groups. The frequency range with statistically significant differences in hearing thresholds between responders and non-responders is wider in the tDCS-TMS group than in the other groups (ANOVA, post hoc, Fisher's, $P<0.05$). Also we confirmed tendency of the response following neuromoulation treatments via linear regression. Four group were clustered to single tDCS performed groups (TDCS group and TDCS-shTMS group) and TMS included groups (TDCS-TMS group and TMS group). In case of non-responders, single tDCS performed groups present more close to linear tendency than TMS included groups. It suggests that tDCS

respondents can be directly correlated to hearing frequencies and thresholds, and TMS does not related to hearing.

From the above results, we derived the following conclusions: The dual-neuromodulation could be consisted of the responders of frontal electric stimulation and the temporal magnetic stimulation. And the responders of the dual-neuromodulation were assumed that whose frontal area or temporal area were more abnormally activated than other brain areas (This assumption would be verified by assessing neuroimaging through EEG analysis in a subsequent study).

TMS could be helpful to make larger effect when using it with tDCS, but 200 pulses of TMS were not enough to statistically effective in group comparisons. From PTA results, we discovered that tDCS responders were depended on hearing loss and mainly related to 4kH frequency hearing thresholds while TMS does not correlated with hearing (frequency and thresholds).

2.2. Introduction

The usual treatment for tinnitus in clinics is medication. From the meta-analysis research, the clonazepam drug has been known to be effective for the treatment of tinnitus clinically, but in fact, more than half of the recipients of the drug have mild side effects. These drugs

are effective in tinnitus but cause side effects in more than half of the recipients. Drugs for blood circulation and depression have not been shown to be effective in tinnitus. Considering the development mechanism of tinnitus, recently, transcranial stimulations were used worldwide for tinnitus treatment in clinical trials.

Transcranial magnetic stimulation (TMS) was approved in depression and stroke by US Food and Drug Administration (FDA), and transcranial direct current stimulation (tDCS) was also approved for depression and peripheral motor disorders by Conformittee Europienne (CE) (Fregni et al. 2015). For non-invasive treatment, TMS and tDCS have been used worldwide for the treatment of psychiatric and neurological disorders via stimulation outside of the skull and modulating neuronal activity, and this neuronal modulation causes therapeutic effects (Lefebvre et al. 2015). Expecting similar therapeutic effects, TMS has begun to be used in clinical trials for tinnitus treatment (De ridder et al. 2004).

Previous studies on tDCS and TMS for the treatment of tinnitus have shown that the responders who reported positive outcomes were a maximum of around 50% of the total number of the subjects. There are no precedent studies in which all participants have experienced a treatment effect because of the variety of causes and types of tinnitus, and the standard method of neuromodulation of tinnitus has not yet

been established. Additionally, no previous studies have used two neuromodulation techniques in tinnitus patients.

We applied the frontal tDCS method, which has been reported to have statistically significant effects on depression (Brunoni, Ferrucci, et al. 2013, 2014), and the TMS method for the treatment of the temporal area (Fig.2-1). We combined these two prospective transcranial stimulations for the purpose of increasing the number of responders with positive outcomes and decreasing tinnitus symptoms. Another expected result from this study is to confirm that dual neuromodulation can dramatically change the cortical activity and significantly reduce tinnitus symptoms when compared to single treatment.

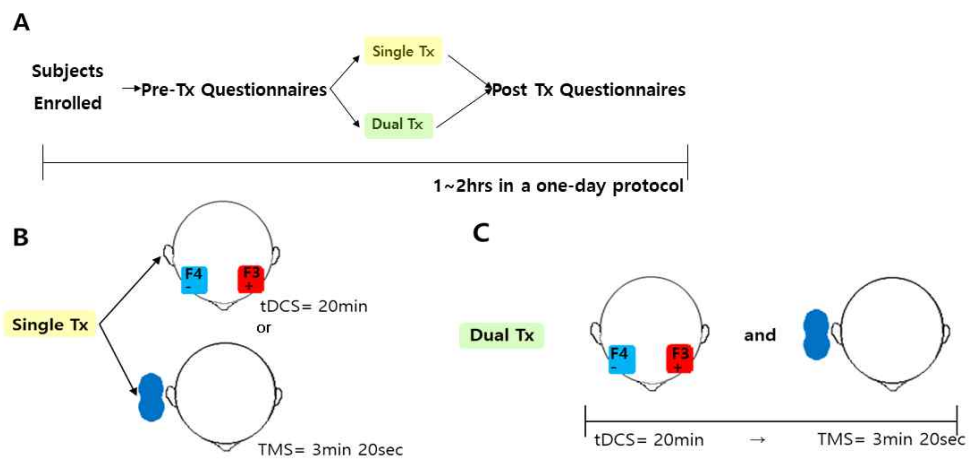

Fig.2-1 The procedure of the tDCS and TMS combined study for tinnitus treatment.

2.3. Methods and Materials

2.3.1. Randomize controlled trial.

Eighty-four subjects who had subjective tinnitus were enrolled and participated in the clinical trial, aged from 25 to 73 years. Four subjects who replied to the questionnaire on the other day of treatment were excluded. Patients who had serious neurological disorders, severe psychiatric disorders, or schizophrenia and patients whose main complication was not subjective tinnitus, such as pulsatile tinnitus and Meniere's disease, were excluded from the study.

The aim of the study was to evaluate that the effectiveness of a single session of tDCS and TMS combined treatment on subjective tinnitus compared to single treatment groups. The clinical trial and research were approved by the Institutional Review Board of the Seoul National University Bundang Hospital on August 29, 2016 (IRB No.: B-1607-355-004), and the clinical trial followed the guidelines of the Declaration of Helsinki. The tinnitus patients were primarily informed of the details of the clinical trial by the medical doctor, and an additional consultation was done with the researcher. All included patients gave their written informed consent. Research volunteers who agreed to participate in the clinical trial were gathered from the tinnitus clinic of the Department of Otorhinolaryngology -Head and Neck Surgery, Seoul National University Bun-dang Hospital.

2.3.2. Dual stimulation for tinnitus treatment

Subjects were randomly allocated to one of four types of treatments to participate a clinical trial, except for two subjects who underwent cardiovascular stenting surgical operation were excluded from the TMS group and TMS and tDCS group, and assigned to just only the tDCS group. Subjects in both the tDCS and TMS combined treatment group and tDCS with sham TMS treatment group were given the same information about the treatment stimulation procedures. The total number of subjects was eighty with four groups of twenty each, and the male and female ratio was nearly equal in all the experimental groups (Table 2-1). Each group and subject clinical characteristics correlations were not statistically significant (ANOVA, previous treatment questionnaire scores in THI ($p=0.838$), VAS intensity ($p=0.613$), VAS distress ($p=0.517$), VAS perception ($p=0.853$), age ($p=0.478$), tinnitus durations ($p=0.213$), and Cross tab, gender ratio ($p=0.849$)). Experimental groups consisted of four different combinations of dual modality of transcranial stimulations which were the tDCS group, tDCS with sham TMS group (tDCS-shTMS), tDCS-TMS group (tDCS-TMS), and TMS group. As shown in the previous research, bi-frontal tDCS decreased tinnitus annoyance, but the effects of temporal tDCS were reported to be less than that for

frontal tDCS(Joos et al. 2014). Using TMS, we stimulated the single side of temporal area where is contralateral side of the tinnitus. The tDCS device that was used is approved for depression and rehabilitation of motor disorders by the Korea Food and Drug Administration (Neuroconn, DC-stimulator Plus).

				Pre - treatment questionnaire score			
				THI	Intensity	Distress	Perception
Group	Age	Duration	M:F	Mean±SD	Mean±SD	Mean±SD	Mean±SD
tDCS	53.8 ± 13.8	3.4 ± 5.0	11:09	55.7 ± 21.0	6.5 ± 1.9	6.8 ± 2.2	77.3 ± 24.0
tDCS-shTMS	54.4 ± 12.9	3.4 ± 5.4	9:11	54.3 ± 19.5	6.7 ± 2.0	7.1 ± 1.7	75.0 ± 27.0
tDCS-TMS	57.5 ± 8.4	7.7 ± 11.1	9:11	58.6 ± 19.0	7.3 ± 2.0	7.6 ± 2.0	81.0 ± 22.7
TMS	51.5 ± 13.0	4.1 ± 6.8	11:09	53.0 ± 21.2	6.6 ± 2.2	6.6 ± 2.4	80.5 ± 25.0
P-value	0.604	0.316	0.849	0.799	0.439	0.485	0.876

Table 2-1. Clinical and demographic data of the tinnitus subjects. Tinnitus intensity, distress and perception were measured by Visual Analogue Scale and there were no significant differences among the groups.

Based on previous depression studies that published statistically significant results, we set the stimulation threshold at 1.5 mA. Subjects who were assigned to the tDCS group were given a 1.5 mA direct current stimulation on both frontal areas; the anode was placed on the left frontal area (F3), and the cathode was placed on the right

frontal area (F4) (Brunoni et al. 2013a, 2013b, 2014). The treatment time was 20 minutes of a simple single session on the treatment day. The first 3 to 5 minutes of tingling or stinging sensation is a common response, and none of the subjects complained of pain during the trial or requested to stop the stimulation.

Subjects who were assigned to the TMS groups (tDCS-TMS group and TMS group) had their resting motor thresholds (RMT) measured by the MagPro X100 (Tonica Elecktronik A/S, Denmark). The RMT is defined as the minimum stimulation intensity required to produce a motor response (Fizgerald & Daskalakis 2013). The response is defined as the minimum stimulus intensity, which is reproducible by about 3 times at about 50 μV. The subjects were given a stimulation at 80% intensity of the measured RMT, which ranged from 5% to a maximum 30% stimulator output(Schecklmann et al. 2015, Vanneste et al. 2012). Following the 10-20 EEG system, a single session of TMS applied to the contra-lateral single side of the temporoparietal cortex of the subject's tinnitus, between T3 or T4 and the P3 or P4, for 3 min. 20 sec. with 200 pulses at a low frequency of 1 Hz (Schecklmann et al. 2015, De Ridder et al. 2013, Vanneste et al. 2012, Langguth et al. 2006). The recording electrode was placed on the skin over the Abdoctor Pollicis Brevis muscle, and the reference electrodes were positioned to the interphalangeal joint. A ground electrode was applied around the flexor carpi radialis muscle.

2. Stimulations for tinnitus treatment

Considering the placebo effects of the tDCS-TMS group, we informed the tDCS-shTMS group and combined group the same way. The subjects included in the tDCS-shTMS group had their RMT measured, and a figure-eight-coil was placed on the temporal area of the contralateral side of tinnitus. The coil was erectly set up on the temporal area with the stimulus facing outward. The clinical trial was performed following the overall procedure (Fig. 2-2).

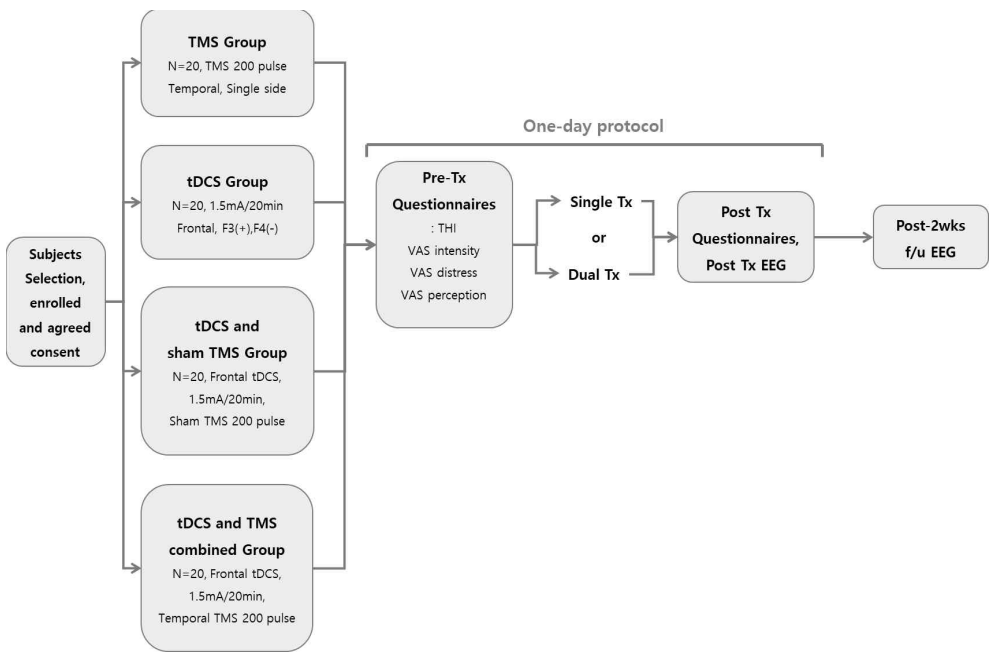

Figure 2-2. Procedures for the tDCS andTMS combined research. It is a maximum two hours in one-day protocol from filling in pre-treatment questionnaires to completing treatments and post-questionnaire. Two type of the single treatments are tDCS and TMS, Dual treatment is tDCS with TMS treatment and additional control group is tDCS with sham TMS for confirming placebo effects of the dual treatment.

On the second visit day, after the first day of treatment, two subjects complained of headache lasting 2 to 3 hours, one of the subjects had received tDCS, and the other had received tDCS with TMS. In the TMS group, two subjects temporarily perceived their tinnitus as being louder.

2.3.3. Measurements

The therapeutic effect of neuromodulation in tinnitus was assessed via four questionnaires. Tinnitus handicap inventory (THI) and Visual analogue scale (VAS) of tinnitus intensity (loudness), distress (annoyance) and perception (awareness) were used.

For the VAS intensity and distress, subjects checked the number or line with a number between 0 (not important or annoying) and 10 (very noisy or annoying) points. The numbered interval was one. THI questionnaire consisted of 25 questions, and the minimum interval was 2 points, and scores were measured between 0 and 100. The score range of the VAS perception was between 0% and 100%. Before and after the treatments, subjects completed the four questionnaires on the first trial day. We used the same questionnaires for the pre-treatment (pre-tx) and post treatment (post-tx) evaluations. Immediately before the start of the stimulation and shortly after the subjects were stimulated, subjects listened to their own tinnitus for about 5 minutes in the noise shielded room and filled in the questionnaire.

2.3.4. Analysis: Questionnaire

Each pre and post treatment score was analyzed within a treatment group via Wilcoxon signed ranks test analysis. The mean values of the pre-tx and post-tx scores of each group were obtained to confirm the difference, as shown in the box in Figure 2-4. Pre and post score differences were derived from each subject, and comparisons of the four questionnaire scores and treatment groups were performed via non-parametric, Kruskal-Wallis H test after multiplying the VAS intensity and distress by ten (Fig. 2-5). The criterion for defining whether a subject is a respondent of a questionnaire is set by the minimum response scores. We set a responder criterion at 5 or more in the THI and VAS perception, and the criterion for the VAS intensity and distress was set to 0.5. If a score is higher than the criterion, we categorized the subject as a responder. The percentage ratio of the responders were represented in a bar, and the ratio was not analyzed for statistical significance. Between and within group comparisons were also done for neuromodulation responders. Pre and post treatment scores were analyzed by two-related test for comparing within groups, and median test was done for between group comparisons. All the statistic results presented in the study were obtained by SPSS v.23, IBM.

2.3.5. Analysis: Pure-tone audiometry

We used pure-tone audiometry (PTA) to confirm hearing thresholds at 250Hz up to 8 kHz. The analysis group of PTA were divided into total 8 groups, divided into responders and non-responders in each of the four treatment groups. We analyzed the hearing thresholds of responders and non-responders in each group to identify correlations between response (therapeutic effects) of the treatments and hearing. ANOVA and post-hoc fishers were done for statistical analysis of hearing thresholds between responders and non-responders at each frequency. We obtained the difference of the thresholds between responders and non-responders, and performed the frequency analysis. And then, we performed linear regressions among four treatment groups. (Only tDCS-received groups: tDCS, tDCS-sham, TMS-received groups: tDCS-TMS, TMS). In the general case of hearing loss, conventional pure-tone audiometry showed a tendency to decrease from high-frequency hearing at 8 kHz. When the graph is plotted on the 8kHz hearing thresholds of y-axis and the average of hearing thresholds at 250Hz to 4kHz on the x-axis, the distribution of overall hearing loss subjects showed linear correlation (Fig. 2-3).

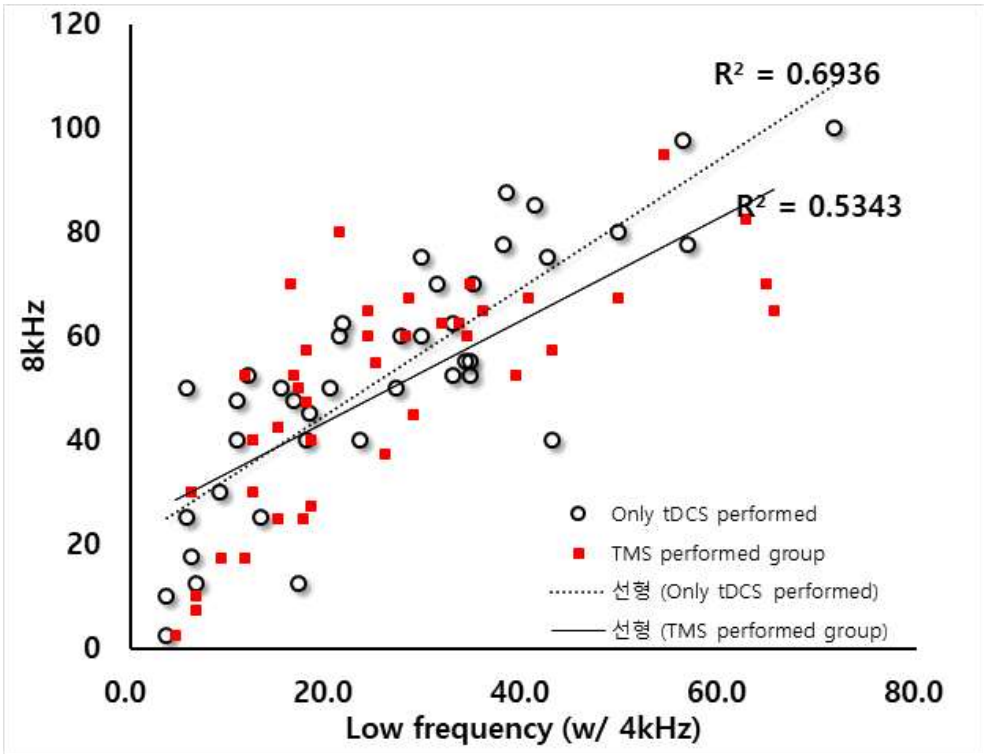

Figure 2-3. The hearing distribution of the overall subjects.

2.4. Results: Questionnaire

2.4.1. Questionnaire: Pre-post treatment score comparisons

Figure 2-4 shows the results of the pre and post treatment differences within each group. Only the tDCS treated groups showed statistically significant effects in the THI score (tDCS, p=0.030*; tDCS-shTMS, p=0.047* and tDCS-TMS, p=0.052). VAS intensity and distress were the most significantly decreased compared to the other questionnaires in all four treatment groups ($p<0.05$*). For the tinnitus perception, the tDCS, tDCS-shTMS and TMS groups showed significant results (p=0.004**, p=0.025*, p=0.026*) but not the tDCS-TMS combined group (p=0.186). In terms of each group, the tDCS and tDCS-shTMS groups had the most statistically significant results for all four questionnaires, and the tDCS-TMS group had significantly decreased scores for the THI, VAS intensity and distress except for the VAS perception. The TMS group results were significant for the VAS intensity, distress and perception (p=0.049*, p=0.022*, p=0.026*) and not significant for the THI (p=0.138). In the view of the pre and post score gap, the tDCS-TMS group had the highest differences when compared to the other groups for the intensity and distress (Fig. 2-4). Among the group comparison, there were no significant differences but the difference between tDCS-TMS group and TMS group was the largest than other group comparisons in the VAS

intensity ($p=0.056^{\dagger}$)

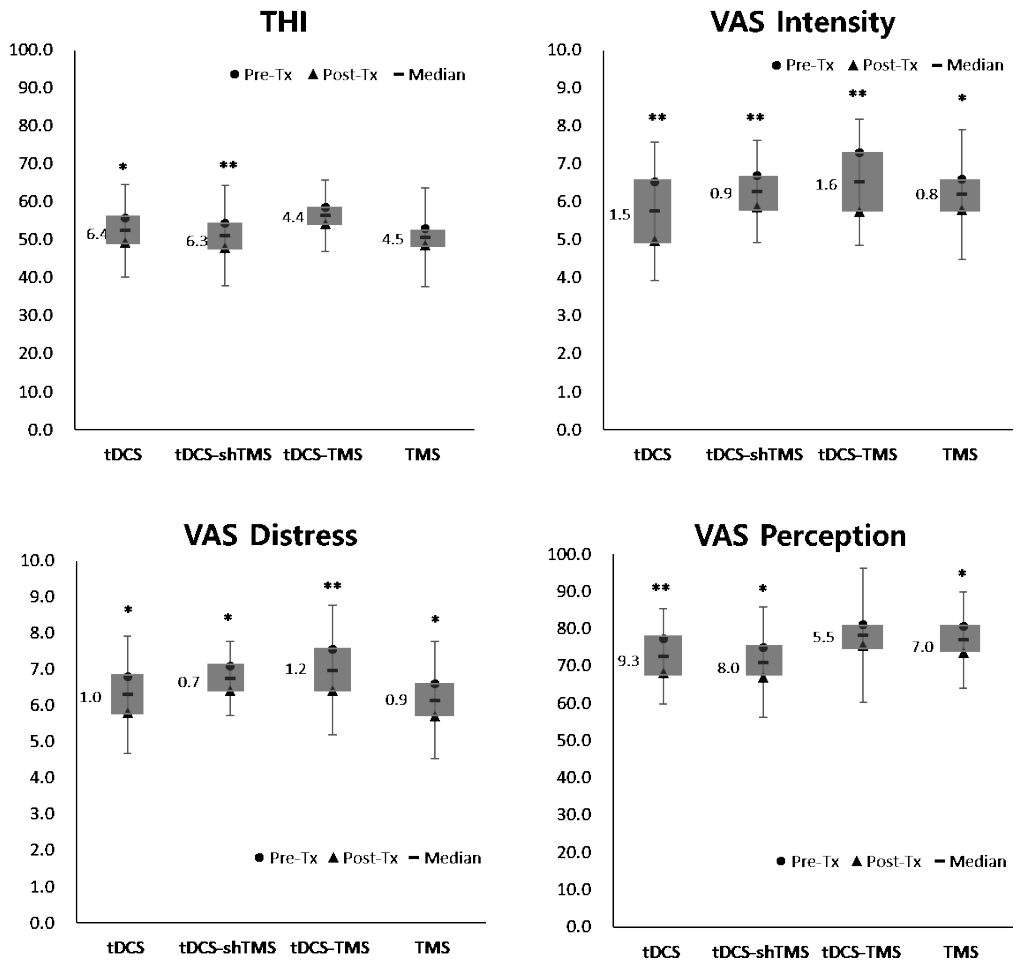

Figure 2-4. The effects of the treatments evaluated with the statistical analysis between pre and post treatment scores. Each group of the average of pre-tx represented filled circle, post-tx is filled triangle, and the difference range between pre- and post- treatment score was displayed as a box, median of the difference is represented as a hyphen inside the box. Presented error bar is standard deviations of the difference between pre-tx score and post-tx score. *p < 0.05, **p < 0.01

	THI		VAS Intensity		VAS Distress		VAS perception	
	z score	p value	*z score*	p value	*z score*	p value	*z score*	p value
tDCS/ tDCS-shTMS	-0.793	0.445	-0.768	0.495	-1.023	0.341	-0.629	0.565
tDCS/ tDCS-TMS	-0.014	0.989	-1.607	0.157	-0.336	0.758	-0.216	0.841
tDCS/ TMS	-0.452	0.659	-0.660	0.547	-1.609	0.134	-0.750	0.495
tDCS-shTMS/ tDCS-TMS	-0.736	0.478	-0.912	0.478	-1.501	0.157	-0.515	0.640
tDCS-TMS/ TMS	-0.424	0.678	-1.286	0.289	-2.002	0.056 †	-0.427	0.698

Table 2-2. The statistical results of the questionnaire comparison among the four groups.

2.4.2. Questionnaire: Multivariate comparisons

By classifying the variables into two types in this study, there were the four treatment groups and the four questionnaires for which eight variables were represented on the x-axis in the Fig 2-5. From the comparison results shown in the Fig 2-5 for the four questionnaires and the four groups, VAS perception and intensity had significantly the largest difference (in tDCS-TMS group, p=0.018) while no significant difference was observed among the group comparisons.

In the comparison among the groups, the p-value of the VAS intensity was the lowest between the tDCS-TMS group and TMS group compared to the other groups (Kruskal-Wallis H tests, p=0.152). In particular, THI and VAS perception in the tDCS-shTMS, tDCS-TMS and TMS groups had a higher standard deviation than that of the VAS intensity and distress. Considering that the THI and VAS perception had the highest variances as well as the results of the questionnaire comparisons, the THI and VAS perception do not seem to reflect the effect immediately after treatment.

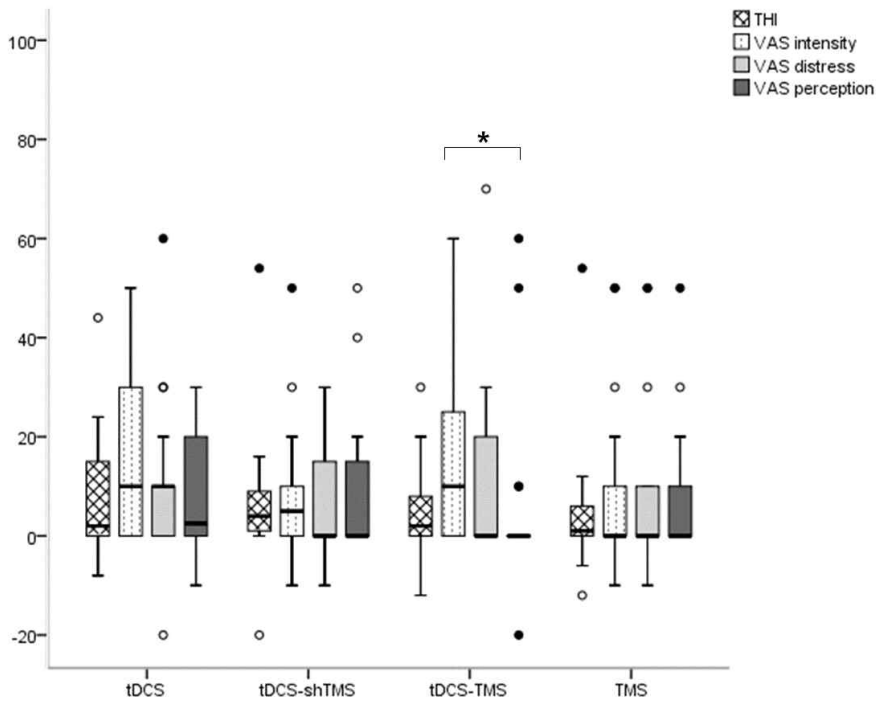

Figure 2-5. The multivariate comparison results. Four questionnaire scores were normalized to a score range of 0-100 and each of the comparison analysis among four questionnaires/ four treatment groups was done via Kruskal-Wallis H test. (p = 0.018*).

2.4.3. Questionnaire: Percentage ratio by responders

In order to accurately determine responders to the transcranial neuromodulation, we excluded the THI and VAS perception questionnaires, and we used the VAS intensity and distress which can reflect the immediate effect of a single session of neuromodulation.

For the VAS intensity, figure 2-6 shows that the TMS responders were 35% of the 20 subjects, the lowest among the four groups, and 70% of the highest responders were observed in the combined group. The highest ratio of responders to VAS distress, 60%, were in the tDCS group, and the other 45% were in the other three treatment groups (tDCS-shTMS, combined and TMS group).

The criteria for responders who have experienced immediate tinnitus changes was set as neuromodulation responders who showed effective change in either of two questionnaires, the VAS intensity and distress. Figure 2-6 shows that the combined group had the highest responders in response to the VAS intensity and one of the two questionnaires.

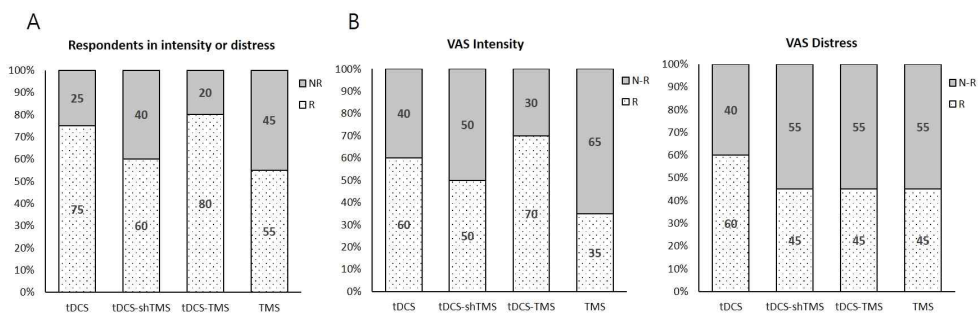

Figure 2-6. The percentage ratio of neuromodulation responders and non-responders. A number of participants in each group is twenty. Following the criteria as we set for responders of each questionnaire, each group of subjects was divided into responders and non-responders, and both were represented in a bar. The responders were presented in a bottom of a bar filled with a dot and non-responders were colored with grey.

A. The responders in one of the VAS intensity or VAS distress. B. Th e responders of each of the VAS intensity and the VAS distress

2.4.4. Questionnaire: Comparisons of responders

As a final step, to determine if there was a difference in the treatment effect between the groups in the responders, statistical analysis was performed only on the responders and not the non-responders. Because the VAS intensity and distress were more reliable to evaluate immediate tinnitus effects, we used those two questionnaires as a baseline for the neuromodulation responders. We compared the pre and post treatment scores through two-related tests and compared them among the four groups with median tests in the responders. Before the group comparison, difference values were obtained by subtracting the post-tx score from the pre-tx scores and then performed the median test. The results show all four questionnaires scores were significantly reduced in the tDCS and tDCS-shTMS groups (Fig 2-7).

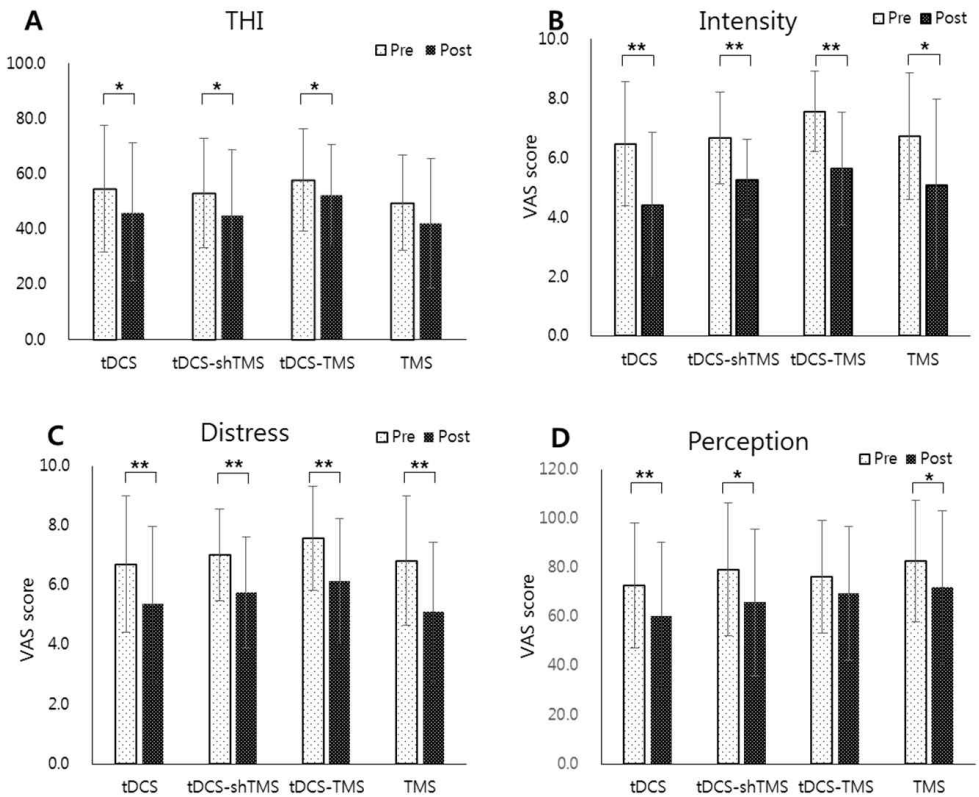

Figure 2-7. Between and within group comparisons in responders. We analyzed for only responders of the neuromodulation. Pre-tx score and post-tx score were analyzed by two-related test for comparison within groups. Median test was done between group comparisons ($p < 0.05$*, $p < 0.01$).**

The tDCS group was the most statistically significant for all questionnaires followed by the tDCS with sham TMS group, the combined group and then the TMS group who were significant in responders (Table 2-3). The TMS group showed no statistical significance in THI, and the tDCS-TMS group had no effects on VAS

perception (Table 2-3). The tDCS, tDCS-shTMS and combined groups had a highly significant effect in the VAS intensity and distress (P<0.01**). However, still, there was no significant result shown in the comparison between the treatment groups

	Respondents					
	THI	Intensity	Distress	Perception	Intensity or Distress	
Group	P-value	P-value	P-value	P-value	R	NR
tDCS	0.027	0.002	0.01	0.008	15	5
tDCS-shTMS	0.028	0.008	0.007	0.026	12	8
tDCS-TMS	0.032	0.001	0.007	0.223	16	4
TMS	0.109	0.017	0.006	0.027	11	9
Total N	80	80	80	80	54	26

Table 2-3. The statistical results of the responders in one of the VAS intensity or the VAS distress. P-values are represented on the left side and numbers of the responder and non-responder are on the right side.

2.5. Results: Pure-tone audiometry

2.5.1. Frequency analysis

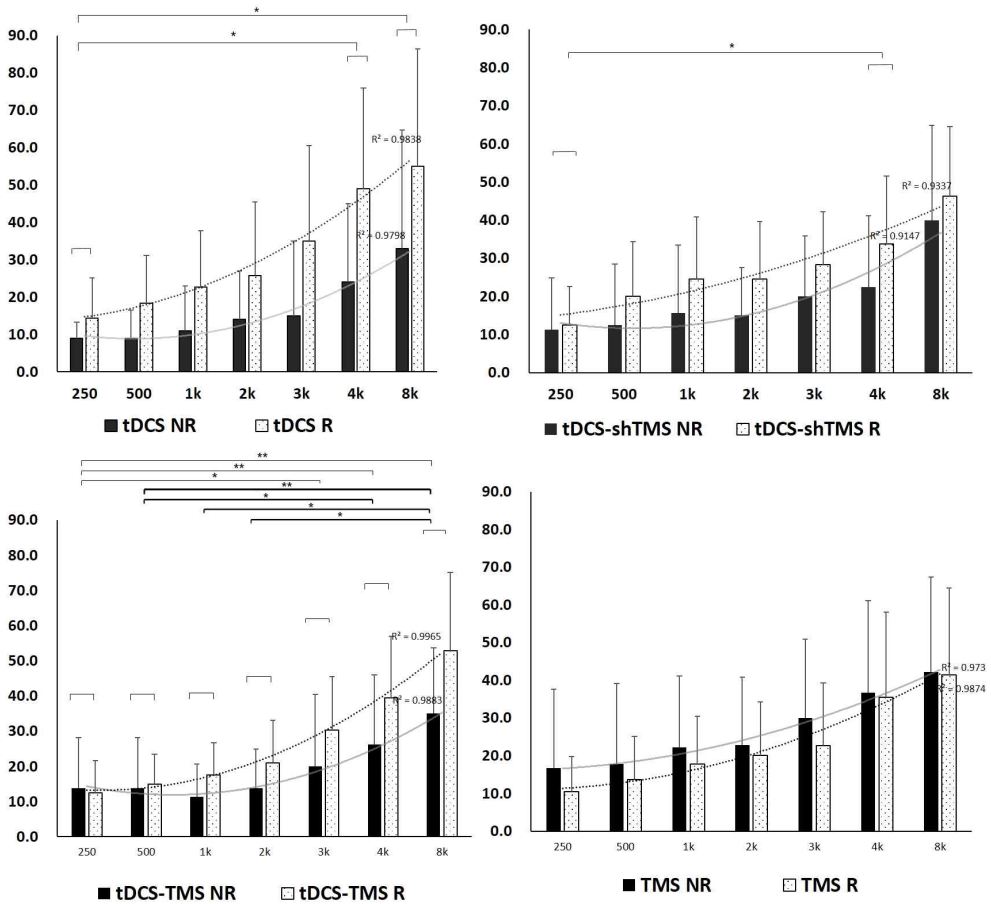

Figure 2-8. The results of the seven frequency analysis using ANOVA.

The results of the tDCS group showed the statistically significant

differences between 250Hz and 4kHz and between 250Hz and 8kHz (Fig. 2-8, Left, upside). Given that the white bars are relatively high compared to black, the hearing of the responders is relatively poor at all frequencies than non-responders. In the tDCS-TMS group, the frequency band showed significant differences were from 3kHz to 8 kHz (Fig. 2-8, Left, Down side). The frequency domain, which is statistically different, is wider than that of the single trial groups. TMS showed no difference in thresholds between responders and non-responders, and no significant difference was found in the frequency analysis (Fig. 2-8, Right, Down side).

2.5.2. Hearing thresholds analysis

To statistically determine whether thresholds differ between responder and non-responder, three groups of non-responders were grouped together (total 17 of non-responders in the three groups) and compared to the responders (tDCS;15, tDCS-TMS;12, tDCS-TMS;16, see fig.2-9). In the combined group, the difference between the non-responders of gray and the responders of light blue was found to be very significant at 3, 4 kHz (Fig. 2-9, $P<0.01$). In all three groups of tDCS received groups (tDCS, tDCS-shTMS, tDCS-TMS), responders (light blue coloured region) have higher hearing thresholds than non-responders (grey coloured region) overall. In the TMS group,

There is little difference in hearing between responders (light blue line) and non-responders (black dotted line), and the results show that the p-value is close to 1 at most frequencies.

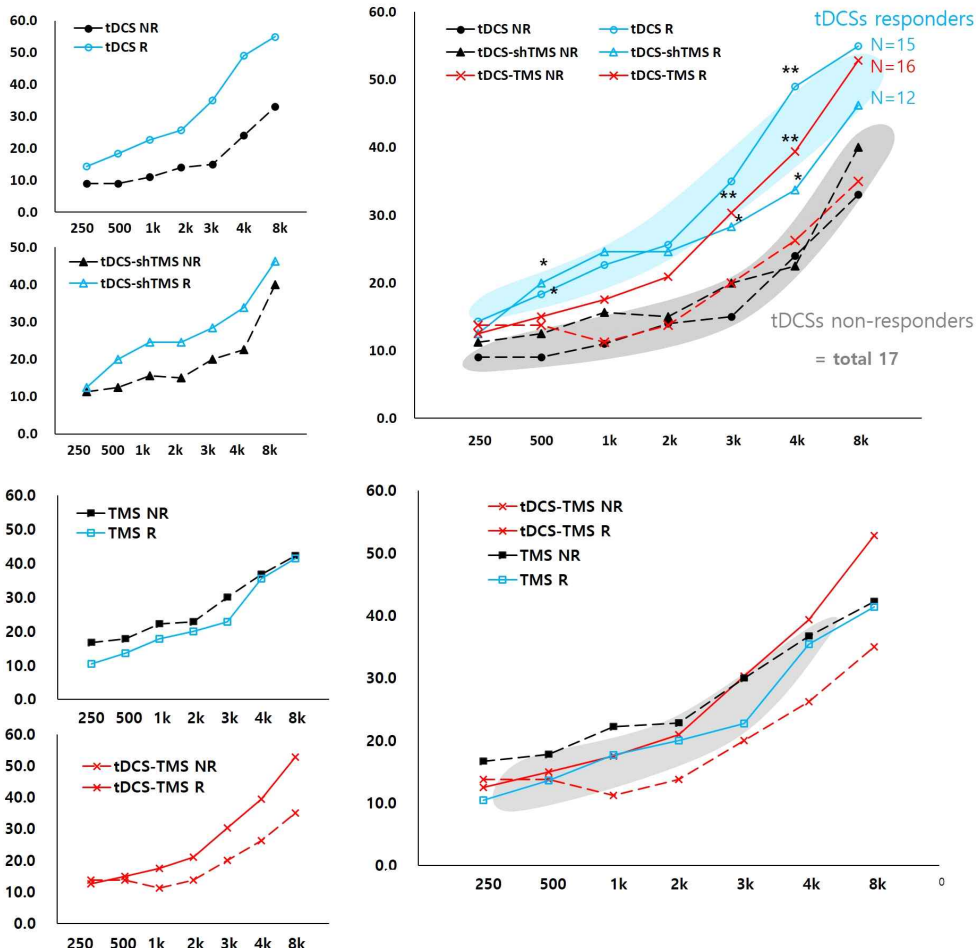

Figure 2-9. Thresholds comparison between responders and non-responders. Mann-whitney U test.

2.5.3. Group analysis

The comparison of each frequency of hearing thresholds between the 8 groups (four groups of responders/ non-responders) showed a significant difference in the tDCS group at 3 and 4 kHz (Fig. 2-10). The average values of the tDCS, tDCS-shTMS, tDCS-TMS groups were different between responders and non-responders, but does not statistically significant in the tDCS-shTMS and tDCS-TMS groups. The average values of the TMS group were no differences between the responders and non-responders.

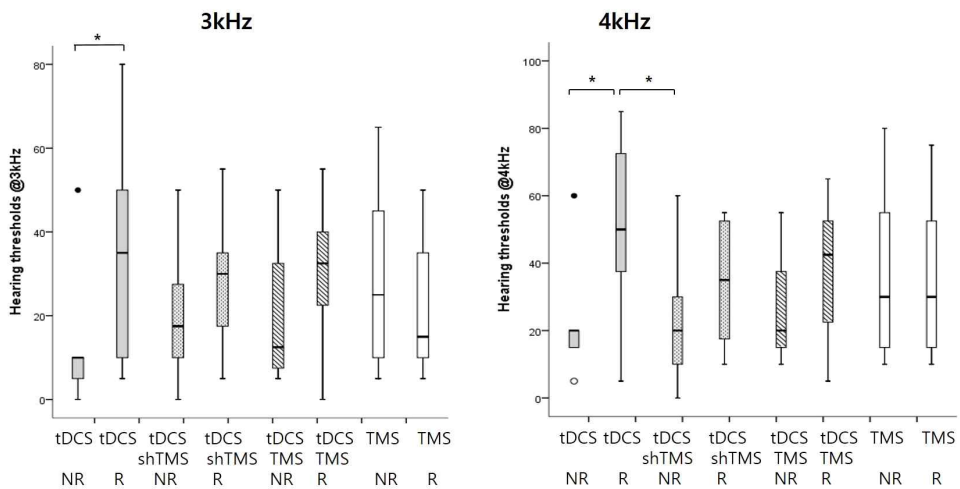

Figure 2-10. Eight group comparisons. ANOVA, Fisher test (post-hoc).

Two groups of tDCS-only performed groups (tDCS, tDCS-shTMS) were grouped according to origin of the stimulusand the two groups

with TMS were grouped together (tDCS-TMS, TMS) and compared by tDCS versus TMS groups. There was a significant difference in hearing thresholds between non-responders and responders in the tDCS-only group ($p < 0.01$). At the 8 kHz, the hearing of the tDCS responders was greater and statistically significant with all non-responders including TMS performed groups (Fig. 2-11).

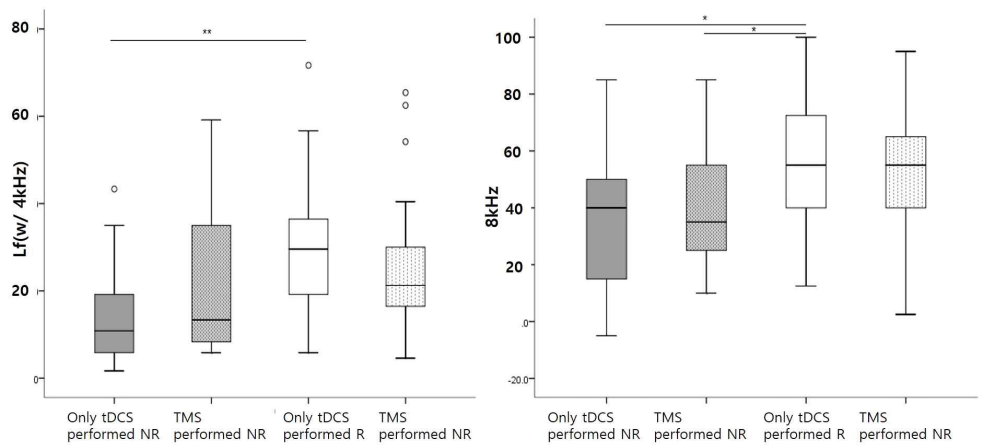

Figure 2-11. Comparison between direct current stimulation and magnetic stimulation. Mann-Whitney U test.

We compared the hearing thresholds of responders and non-responders according to treatment modalities and clinical differences between transcranial direct current stimulation and transcranial magnetic stimulation were confirmed. The hearing distribution of the total tinnitus subjects is linearly correlated with average thresholds at low

frequency to 4kHz of x-axis and hearing thresholds at 8kHz of y-axis. Non-responders were also relatively linear in the tDCS group, but non-responders of the TMS group had no linear correlation with hearing. (Fig. 2-12)

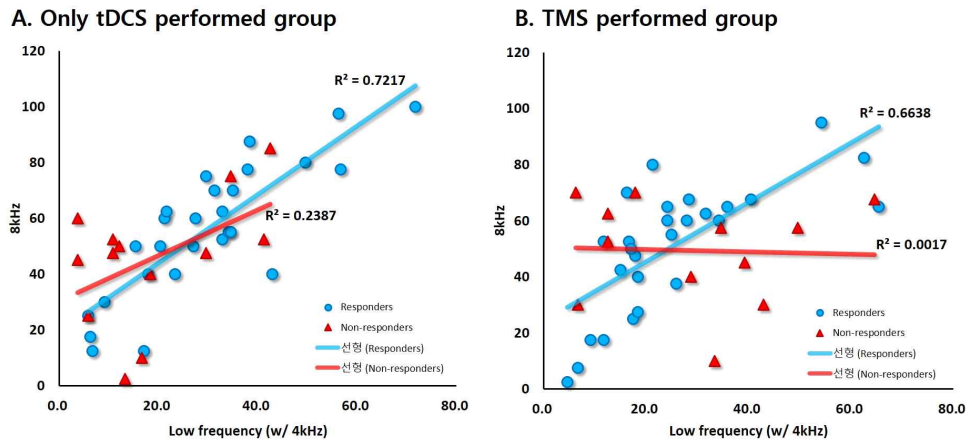

Figure 2-12. The linear correlations represented between tDCS respondents and hearing thresholds and between TMS respondents and hearing thresholds.

Left: only tDCS performed group. Right: TMS performed group.

Circle: responders Filled triangle: non-responders

2.6. Discussion

2.6.1. Discussion of the questionnaire results

In this study, differences in the pre and post treatment scores were

significantly decreased generally in all groups; thus, the four treatments, frontal tDCS, ipsi-temporal 200 pulses TMS, tDCS with sham TMS and combined dual treatments were considered to be statistically effective on tinnitus. Because there are some extremely high responders in each group, including the 200 pulses TMS group, the pre-post treatment scores of all four groups were significantly decreased statistically, and we suggest that this is the reason why there is no significant difference among the groups, even though the largest difference is in the combined group (Fig. 2-5).

Twenty-five of the THI questions were mostly about daily social lives, for example, ‘Does your tinnitus make it difficult for you to enjoy life?’ and the question on VAS perception asked for the average percentage of time while hearing tinnitus during waking hours on a routine day. Because it was a single session and the review time was as short as 5 minutes, it was difficult to reflect the immediate treatment effect. As such, the THI question reflects the therapeutic effects of long-term daily life after treatment. Subjects answered that their tinnitus was not gone and was still heard. It means that the tinnitus decreased but did not disappear, so the perception was also inadequate to effectively reflect the treatment effect. Plus, in the comparison among the questionnaires, the tDCS-TMS combined group showed statistically significant results between intensity and perceptions. Especially, the VAS perception in

the tDCS-TMS group had the largest standard deviation among the 16 variables (Fig 2-5. variables were equal to the multiplied four treatments groups and four questionnaires).

Considering that the tDCS-TMS group and TMS group were not significant in THI and VAS perception, we indirectly deduce that the THI and perception questions were not exactly suitable for assessing tinnitus changes just before and after treatments in this study.

Although there wereno significant differences among the treatment groups, the ratio of responders was the largest; 70% were responders in the tDCS and TMS combined group, who answered lower scores to the post questionnaire than the pre questionnaire for VAS intensity. This means that subjects who experienced the effects of neuromodulations were more than the other groups. To summarize the responders' feelings of changes in tinnitus sounds, they generally expressed one of three common opinions: 'decreased tinnitus loudness', 'it was moved far behind the head' and 'sharp sounds changed to softened ones'.

For the reasons already mentioned, we had defined the VAS intensity and distress as a questionnaire that best reflects the immediate effects of neuromodulation evaluating responders. We analyzed multivariate comparisons in the neuromodulation responders, but there were still no differences compared the among groups in statistics (Fig. 2-7). The

results from the 80 subjects and the results of the responder comparison showed almost the same pattern (Fig. 2-4, Fig. 2-7).

The common areas reported in most tinnitus imaging studies are the dorsal lateral prefrontal cortex, tempo-parietal areas and amygdala (Sh ore et al. 2007, 2016, Vanneste et al. 2018, Dehmel et al. 2012). The relative activity of tinnitus was higher than that of the control group, which was confirmed by the various imaging techniques such as fMRI, PET, and EEG[v].(Vanneste et al. 2014, 2015, Chen et al. 2015, 2017, 2018).

Because of the above reason, most of the frontal tDCS studies on tinnitus were conducted and stimulated on theright anodal and left cathodal. One of the previous studies reported no therapeutic effect was found for tDCS with the left anode and right cathode unless the right anodal and left cathodal tDCS suppressed tinnitus in perception (Vanneste et al. 2010). Considering the 29% VAS perception in tinnitus in the right anodal group, the number of subjects in the left anodal group was 16 times lower than that in the right cathodal group, suggesting that there was no statistically significant difference (Vanneste et al. 2010).

Our results have shown that left anodal stimulation, which is effective for depression, has the effect of reducing the size of tinnitus and suffering from tinnitus (Brunoni et al. 2013a, 2013b, 2014). Based on

several previous studies of tDCS fortinnitus, it seems more important to stimulate the abnormal tinnitus circuit more effectively than in the left and right directions of the positive and negative electrodes in the same area (Lefaucheur et al. 2017).

If the subject responds to temporal magnetic stimulation or frontal electric stimulation, it may also be effective in combined treatment. Despite single-session stimulation, the pre-post mean difference was the largest in the combined treatment. The mean value of the combined group tended to be the highest overall, but the difference between the groups was not large enough to be statistically significant, because there was a high number of responders in each group. Even though the differences were not significant among thetreatment groups, it seems that a large number of tDCS-TMS responders were included as much as the total number of the frontal tDCS responders and the temporal TMS responders.

The cause for the differences between the tDCS and tDCS-shTMS groups could not be revealed by the questionnaire analysis and will be confirmed in subsequent analyses of audiometry and neuroimaging. In fact, neuroimaging studies can confirm whether subjects with abnormal hyperactivity in the frontal or temporal lobe are effective in the combined treatment group. We have also found that tDCS-TMS has the potential to have a greater effect on the reduction of tinnitus,

and TMS is considered to be performed over 200 pulses for statistically significant effects.

2.6.2. Discussion of the Pure-tone audiometry results

Through analysis for hearing thresholds of respondents and non-respondents in the four treatment groups, we newly observed the several scientific facts regarding the clinical characteristics of the tDCS and TMS.

Statistical analysis of the non-responders in the three groups receiving tDCS and the responders of each group showed statistically significant differences between the responders and non-responders at 500 Hz and 3, 4 kHz in all three groups (Fig. 2-9). In the tDCS-received groups, the hearing of the responders were poor than non-responders overall, which is interpreted as a better recognition of tDCS effects when hearing loss is greater. This suggests that tDCS in patients with good hearing may make it difficult to know whether the tinnitus has improved. And hearing may be irrelevant in recognizing the TMS modulation effects through the results.

Comparison of hearing thresholds between responders and non-responders were analyzed with raw data of the PTA and the frequency analysis was done with difference values between hearing

thresholds of the responders and non-responders. Through frequency analysis, we could observed the change in frequency domain which was statistically significant following treatments groups. The gap of the significant differences in combined group between responders and non-responders were observed at 3, 4 and 8kHz, and this can be interpreted as more regions of the frequency that can distinguish between responders and non-responders in a combined treatment group than in a single treatment group (Fig. 2-8).

Additional analysis was performed to observe the correlation between hearing and therapeutic effectiveness. There were statistically significant differences between responders and non-responders in the tDCS group at 3, 4kHz. The tDCS group showed statistically significant difference between the responders and non-responders over the frequency range of 250- 4kHz and 8kHz, and there was no statistically significant difference in the TMS group.

Overall hearing distribution of the subjects was following general hearing distribution which is higher hearing loss at high frequency (Fig. 2-3). According to the results of the linear regressions, we clarified that the worse the hearing, the more greater the therapeutic effect in tDCS. However, also we re-confirmed that the effectiveness of the TMS is totally independent of hearing thresholds from the results of the distribution of the non-responders.

In sum, our findings can be interpreted as follows: For the tDCS, the greater the loss of hearing, the higher the probability of recognizing the effect. The response of the tDCS can be determined by 4kHz hearing threshold, but TMS is assumed as not being affected by hearing thresholds and frequency. The combination of hearing-dependent tDCS and hearing-independent TMS tended to lower the mean hearing of responders and increase the number of responders.

Because the hearing differences between the responders and the non-responders are statistically quite certain, we though that perhaps a little more effort here would be able to establish a baseline for distinguishing the responders in further works.

3. Stimulation on hyperacusis

3.1. Abstract

Hyperacusis is assumed to be caused by hyperactivity of the central pathway by noise. To evaluate and develop specific treatment modality in hyperacusis, we used transcranial random noise stimulation (tRNS), a recently introduced non-invasive neuromodulation method in research fields.

Ten subjects (5 males and 5 females, mean age 31.5±11.4 years) with hyperacusis symptoms were enrolled for the clinical trial of this study. Nine subjects had normal hearing thresholds and the other one subject had severe hearing loss in the left ear. Median of the uncomfortable loudness level (UCL) of nine subjects are 69.8 (±8.24) dB on the right side and 84 (±6.92) dB on the left side. Total 8 sessions of tRNS were applied to each patient on the bi-temporal area, during 4 weeks. Subjective symptoms such as loudness and distress of hyperacusis subjectively assessed by visual analogue scale (VAS) befor e and after treatment, and the resting-state of cortical activity changes were evaluated by 31-channel of the electroencephalography (EEG).

All ten patients reported significant improvement with regard to VAS intensity and distress after treatment. After 8 sessions of the tRNS, median VAS intensity decreased from 6.9(±1.58) to 3.4(±2.07) (P

=0.017, by Wilcoxon signed rank test), and median VAS distress improved from 7.2(±1.10) to 4.0 (±2.70) (P = 0.017, by Wilcoxon signed rank test). Also, UCL of the sound was evaluated by PTA, improved about 21.5(±11.0)dB on the right side at 250 and 8000Hz ($p<0.05$), and 20(±9.11)dB on left side at 250, 500, 1000, 2000 and 8000Hz after 8 sessions of tRNS. On the other hand, when we performed twice of sham stimulations on the same patients, VAS scores had no differences between the sham treatment score and the prior session of the sham treatments ($p=0.317$). Moreoever, qEEG revealed that resting-state of cortical activity decreased at alpha and beta frequency after 8 sessions of tRNS and we performed follow-up qEEG after 4weeks from last the 8th session.

Taken together, our preliminary results corroborated that tRNS may be a good treatment option in hyperacusis patients. Future studies with a larger number of subjects should be performed to further validate treatment effects of tRNS in hyperacusis patients.

3.2. Methods: Procedure, stimulation

3.2.1. Subjects

This study was designed as a sham-controlled study and approved by both the Institute of Research Board of the Seoul National University Bundang Hospital (April 14th, 2017, No. B1612-373-001) and the Korea Ministry of Food and Drug Safety (November 6th, 2017, No. 807). We followed the regulations of the good clinical practice (GCP) and conducted the clinical trial of medical device in accordance with the Declaration of Helsinki. After consultation with the physician and the researcher, all the subjects gave informed written consent. Total ten diagnosed hyperacusis patients (mean age 31.5±11.4, M:F=5.5) were enrolled in the Tinnitus clinic at the Otorhinolaryngology department (Table 3-1).

Patients who had the hyperacusis symptoms for minimum 3 months were applied to the inclusion criteria; subjective symptoms were discomforts that can be felt when exposed to noise and the noise intensity which provoked hyperacusis symptoms were vary; residential noise to loud noise. Physical symptoms including pain and migraine are physical reactions to muscle contraction after exposed to uncomfortable sounds. We did not set a baseline for hearing in our subject inclusion criteria, nine out of ten were within standard (normal) hearing and one subject has severe hearing loss on his left

side (Table 3-1). The exclusion criteria was applied to the following cases: 1) Having a history of prescription for a psychiatric disorders or a seizure. 2) Implantation of an in vivo stent or artificial organ. 3) A woman who is pregnant or scheduled to be pregnant. All of the participants in this study did not have any of the exclusion criteria. Unlike tDCS, subjects receiving tRNS did not experience side effects such as stinging and stabbing sense or headache during 8 real sessions.

						Pre Tx (Mean of Frequency)				Pre-Tx (VAS score)	
Patient No.	Age	Sex	Side	(yr) Duration	Hearing loss	UCL ®	UCL ①	PTA ®	PTA ①	Intensity	Distress
1610-RN-01	41	F	B L<R	2	N	84.3	94.3	7.9	9.3	6	6
1610-RN-02	34	F	B	3	N	37.1	42.9	5.0	8.6	8	8
1610-RN-03	22	M	B L<R	0.25	N	72.1	81.4	5.7	6.4	7	8
1610-RN-04	20	M	B L<R	2.3	N	61.4	75.0	1.4	6.4	5	9
1610-RN-05	31	F	B L<R	4	N	65.7	71.4	3.6	3.6	9	7.5
1610-RN-06	19	M	L	3	N	111.4	107.1	2.1	3.6	6	6
1610-RN-07	38	M	B L<R	0.5	N	61.4	81.4	7.1	7.1	7	6
1610-RN-08	26	F	B L<R	10	N	84.3	84.3	5.7	4.3	7	7
1610-RN-09	56	M	R	0.5	L deaf	77.1	-	18.6	-	9	9
1610-RN-10	28	F	B L<R	3.5	N	79.3	74.3	5.7	5.0	10	10
Mean ±SD or Ratio	31.5 ±11.4	5:5	1:8	2.9 ±2.8	1:9	73.4 ±19.4	79.1 ±17.6	6.3 ±4.8	6.0 ±2.1	7.4 ±1.6	7.65 ±1.4

Table 3-1. The clinical characteristics of the hyperacusis subjects

3.2.2. Procedure

All ten subjects were received 8 sessions of tRNS and seven of ten were given additional two times of sham stimulation. Sham stimulation was treated with built-in sham protocol of the DC-stimulator made by the Neuroconn. The real stimulations were performed consecutively from the first session to the eighth session of tRNS twice in a week, and the sham treatments were performed two consecutive times after the pre-treatment EEG or after the 4 weeks post-treatment EEG. There were no previously reported adverse reaction of tRNS and no adverse effect occurred in this study.

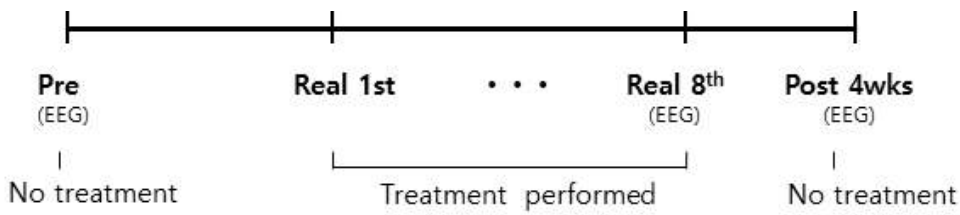

Figure 3-1. The clinical trial procedure for hyperacusis treatment.

3.2.3. Measurements

We assessed the subjective effectiveness by the visual analogue scale for hyperacusis intensity and distress. The degree of symptom was rated from 0 to 10 points. If the hyperacusis symptoms are too small to be felt the score is set to 0, and 10 points that are too large to

withstand symptoms. Total ten subjects were checked the VAS questionnaires from pre-treatment scores to 8th post-treatment scores, nine subjects for post-4wks scores and seven subjects for the sham treatments.

The hearing thresholds and uncomfortable level of sounds of the subjects were measured by the pure-tone audiometry. The hearing test was measured at seven frequencies from 250Hz to 8kHz.

To investigate changes of neuronal activity, 31 electrodes were performed on the day of pre-treatment, 8th session and 4weeks of post-treatment. EEG data were deriven using Mitsar EEG device and EEG were conducted in eye-closed states and recorded for 5 minutes in an electrical noise and sound shielding booth.

3.2.4. Data analysis

The VAS scores were statistically analyzed between pre and each of the session score via paired sample test. e.g. pre and 8th session treatment, pre and sham treatment, pre and post- 4 weeks scores.

Each left and right side of the uncomfortable level was analyzed between pre and 8th session of the post-treatment via paired sample test. The percentage improvement of the frequency analysis was done with differences of the pre and 8th post-treatment via non-parametric, Kruskal-wallis test.

The changes of brain activity caused by stimulations were analyzed via comparing EEG data of pre, 8th and 4wks post treatment. Brain activity were assessed with amplitude and frequency rate of the EEG data, and preparation of the raw EEG data was done using the Mitsar software. Seven spectrum (delta, theta, alpha 1, 2, beta 1~3, gamma) analysis and connectivity were performed via sLORETA. The brodmann areas were represented with sLoreta density and statistically analyzed via Kruskal-Wallis test. All the statistical results presented in this study were obtained by SPSS v.23, IBM.

3.3. Results

3.3.1. Questionnaire score comparisons

The average score of the hyperacusis severity (intensity) was 7.4(±1.6) and distress was 7.65(±1.4) before tRNS treatment. After 8th session of the treatment, the average scores were decreased to 4.4(±2.2) in the intensity and 4.8(±2.4) in the distress. However, after the sham treatments, there was no difference from the pre-treatment score. (Fig. 3-2)

3. Stimulation on hyperacusis

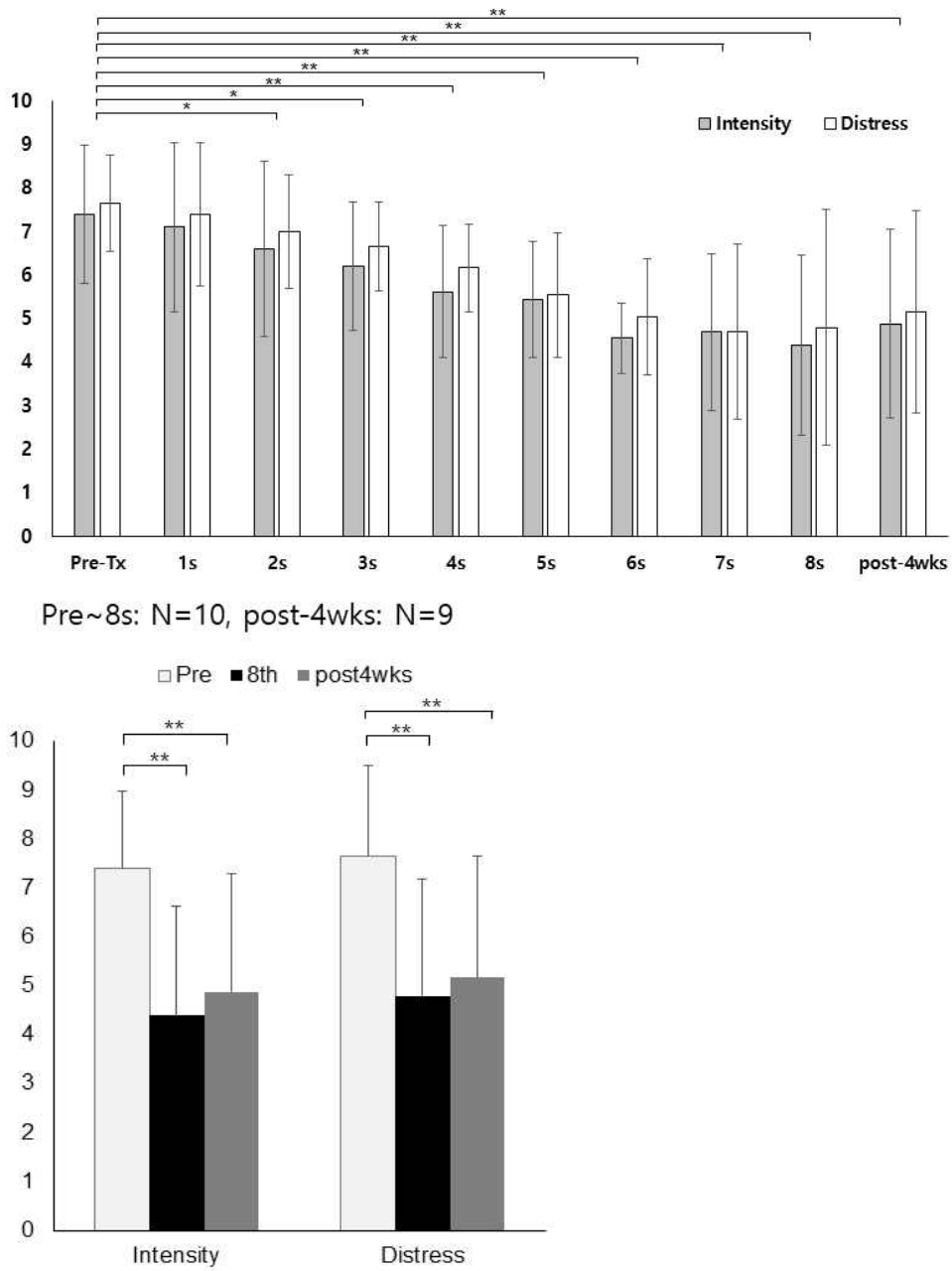

Figure 3-2. This is the graph showing the changes of the hyperacusis symptoms on the visual analogue scale according to the number of tRNS treatment.

3.3.2. Psychoacoustic level comparisons

The uncomfortable level of pre-treatment was 73.43(±20.12) dB on the right side and 79.13(±18.02) dB on the left side, and UCL of the 8th session of treatment was 86.51(±57.88) dB on the right side and 92.5 (±17.32) dB on the left side.

The tRNS effectiveness had no correlation with hearing side and the hearing thresholds of the pre and post treatment have been no differences founded.

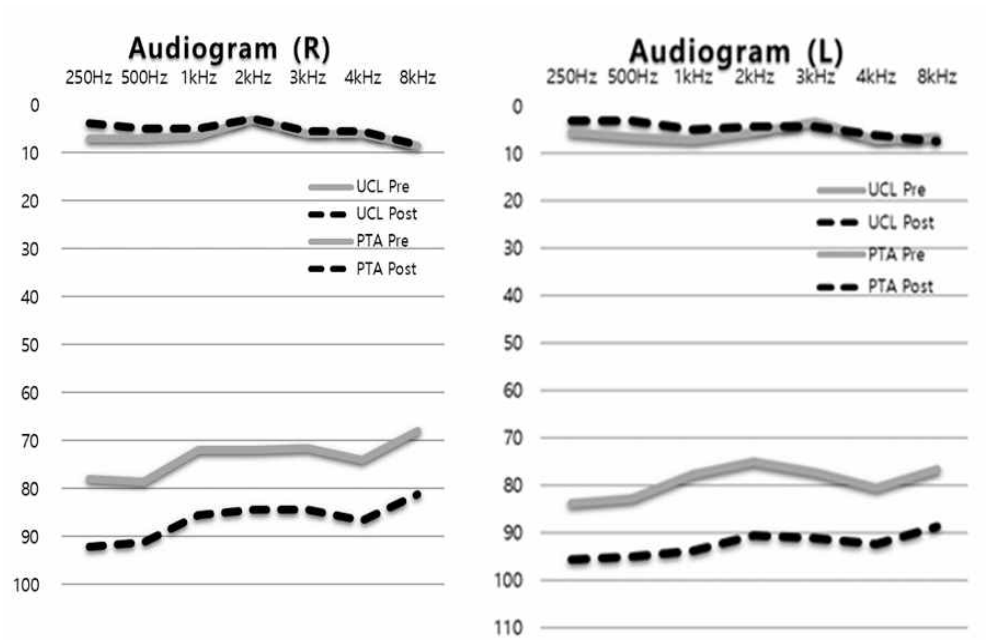

Figure 3-3. The audiogram presented the hearing threshold of pre and post treatment and UCL. Post audiogram was examined within a month after 8th treatment.

The results of the percentage improvement of UCL showed that the 8th session of tRNS was highly effective on the left side at 1kHz. However, there was no significant difference observed in the hearing thresholds. Because there was no difference between left and right side in the statistical results, tRNS seems to affect the hearing side irrelevantly.

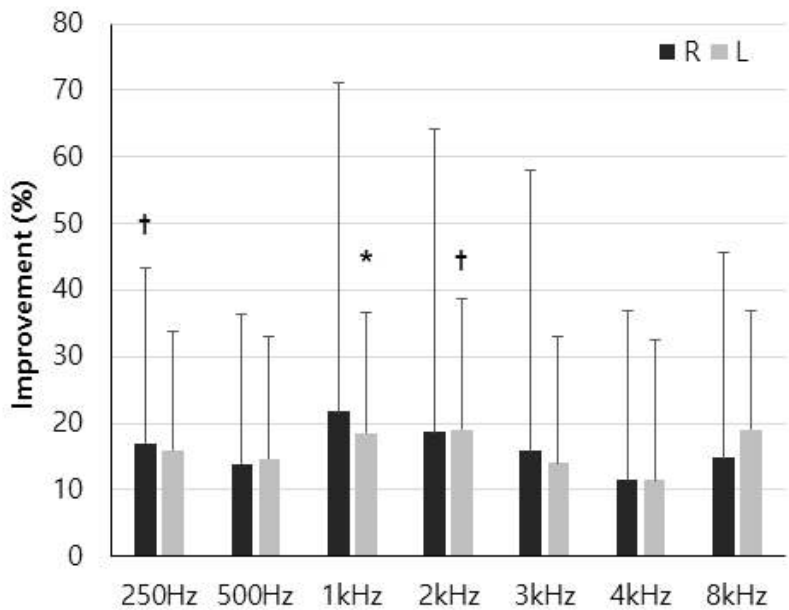

Fig 3-4. The improvement of UCL displayed as decreased UCL decibel and improvement percentage. The frequency comparison analysis was done by Kruskal Wallis Test.

3.3.3. Neuroimaging

The brain topography with power ratios of beta2+gamma/ delta+theta

is normalized to a maximum of 50 (Fig. 3-5, upper) and the gamma power is normalized to a maximum 2% (Fig. 3-5, down). In the pre-treatment scalp map, The gamma-beta/ theta-delta ratio of the bilateral central to parietal cortices and the right temporal cortex were highly activated than the post-treatment brain states. The gamma-beta/ theta-delta ratio was decreased after the 8th treatment and decreased brain activity was maintained until after 4weeks of the 8th treatment. Gamma frequency was still high in right after the 8th session of treatment but the gamma power of the bilateral auditory cortices was decreased after 4weeks of the 8th treatment.

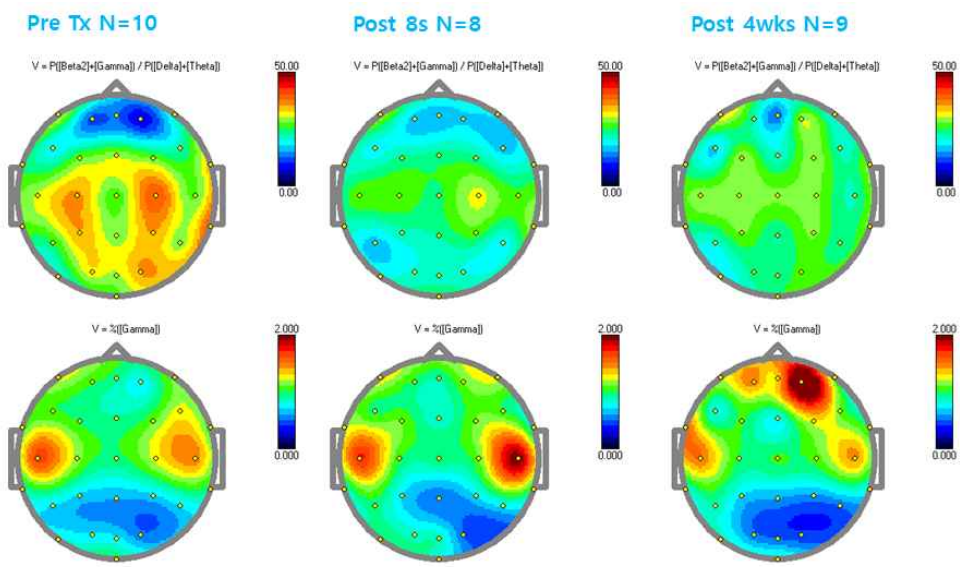

Figure 3-5. The scalp map was colored following the amplitude of the brain activity. Three states of the subject's brain were on the Pre-treatment, post 8th session and post 4weeks

The spectrum analysis results were also similar to scalp map results. Spectrum analysis was performed a paired group analysis with 8th treatment and pre-treatment using sLORETA. The brain activities after the 8th session of tRNS of the bilateral temporal cortices were slightly higher in all frequencies, the delta to gamma, and the central to parietal cortices were lower than the pre-treatment status (Fig. 3-6).

The brain connectivity results showed that the brodmann area 46 and temporal area (BA 37) was simulateously decreased right after 8th session of tRNS compared than pre-treatment states in the alpha 2 (post-8th < pre, $p = 0.0108$) (Fig. 3-7). The theta activity of the right side of temporo-parietal area was decreased but correlated or synchronized areas was not found in the results.

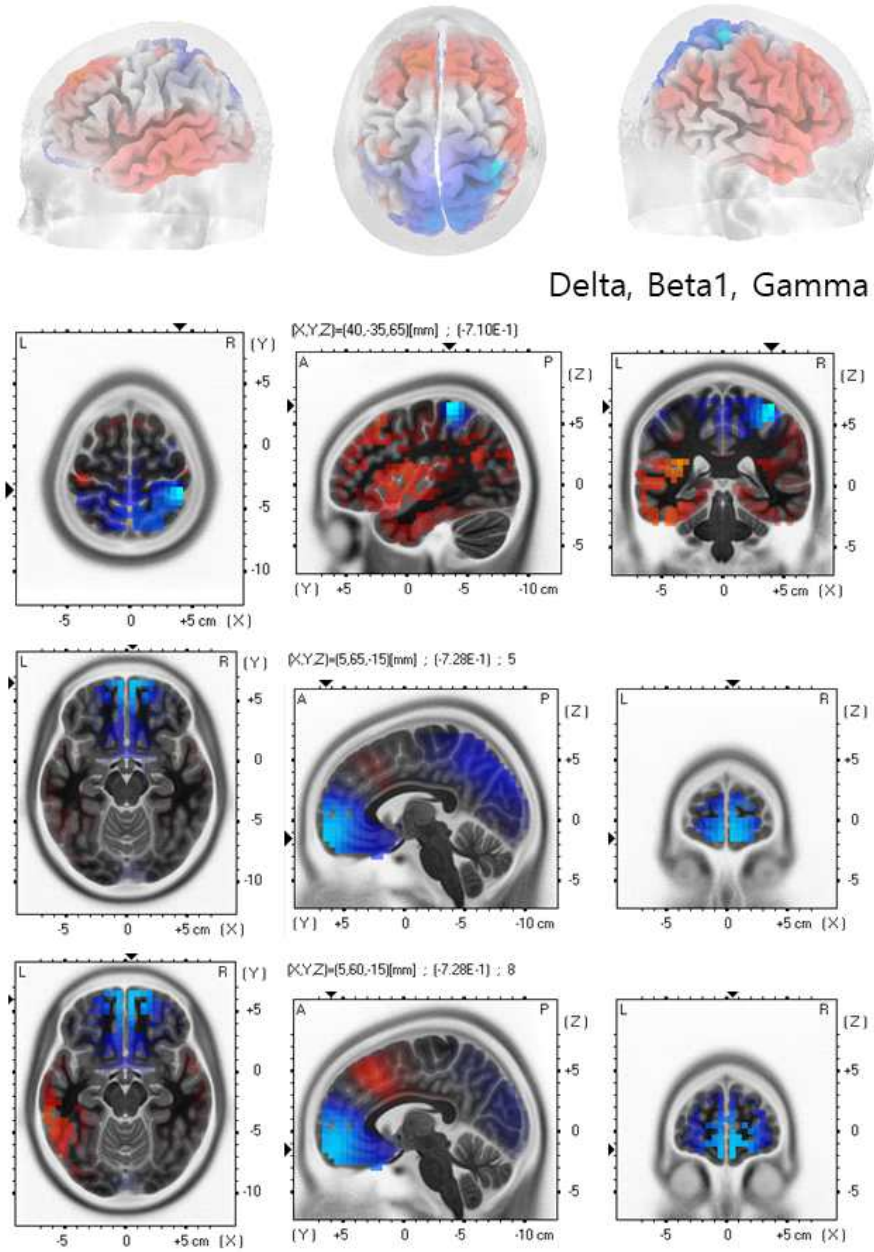

Figure 3-6. The result of spectrum analysis between 8th treatment and pre treatment via sLORETA. Above: delta Below: delta, beta1, gamma

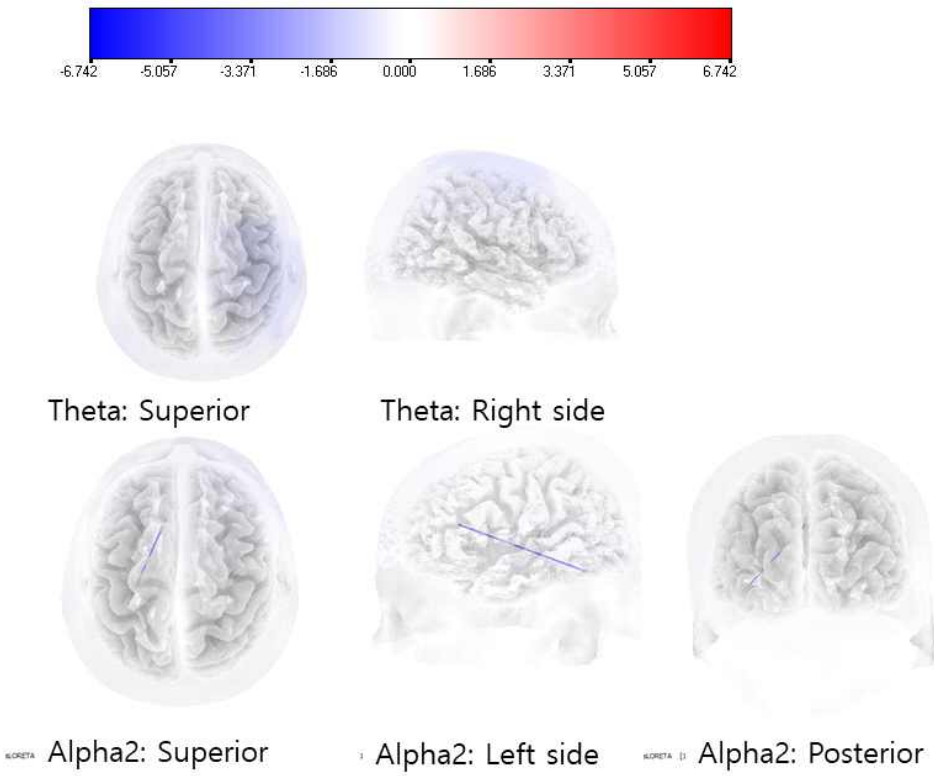

Figure 3-7. The connectivities between post 8th session of treatment and pre-treatment.

	t (0.01)	t (0.05)	Extreme P
post-8th > preTx	9.140	6.742	0.60040
post-8th < preTx	-8.287	-6.742	0.01080
Two-tailed	9.656	7.853	0.02320

Table 3-2. The statistical significances of the LORETA connectivity. t (p-value); scalp or wire thresholds, Wire thresholds=8.287

3.4. Discussion

In the results of the VAS questionnaires, tRNS was statistically effective from the 2nd treatment, and gradually reduced the severity of the symptoms (Fig. 3-2). When we checked the hearing test results within one month after the 8th tRNS, both right and left UCL were increased, which enabled tRNS to withstand noise in hyperacusis patients (Fig. 3-3, 3-4).

Analysis of the EEG revealed that the brain state of the subjects before treatment had a decreased inhibitory function of delta and theta (Fig. 3-5). Considering the questionnaires, the hyperacusis symptoms were gradually improved during eight sessions of the treatment, and the activity of auditory cortex, the stimulation site of tRNS, was similar to that before the treatment. However, the inhibitory function of delta and theta band was enhanced and the hyperactivity of the central-parietal cortices (C3, C4, CP3, CP4, P4) were significantly reduced. These central and parietal regions were represented by brodmann area (BA) 1~4, BA 21 and BA 40 which are sensory-motor cortices. After the 8th session of treatment, the temporal activity of the auditory cortices seem to higher but it was not statistically significant (Fig. 3-6, $p=0.1204$).

The connectivity between the two domains can be explained by coherence and phase synchronization. The lagged phase coherence of

sLORETA confirmed by brain connectivity. As a result, we found that the strong brain connectivity between the right brodmann area 37 and the right brodmanna rea 46, which are the temporal area and the dorsal lateral prefrontal cortex, was simultaneously decreased by the eighth tRNS ($p = 0.0108$). In the VAS questionnaire, the hyperacusis symptom was increased 4 weeks later after the 8^{th} treatment, and the brain activity increased in the temporal area on the 4th weeks of the post-treatments. The temporal tRNS reduced the abnormality and activity of the central to parietal cortices in the sensory-motor cortices and increased both inhibition function and hyperactivity in the temporal areas.

The results of applying 8 times of tRNS to hyperacusis patients are summarized as follows. Throughout the questionnaire, 10 out of 10 patients had symptomatic improvement, with an average improvement of 68% from pre-treatment score. EEG was performed to confirm the objective therapeutic effect. As a result, the sites were directly stimulated by tRNS, and it did not lower activity but augmented both inhibition function and hyperactivity, therefore, decreased abnormal hyper-activity in the central to parietal and temporal to parietal cortices. This makes it possible to maintain normal activity by being able to withstand or uncomfortable sound and not be abnormally activated by environmental noise.

Limitation

3. Stimulation on hyperacusis

When the EEG is performed immediately after the 8th session, the activity of the right side of anode attached region is increased due to the influence of the temporal stimulation. In order to obtain more accurate validation of the efficacy after the 8th treatment, EEG should be performed one or two days later after the 8th treatment.

4. Tinnitus and Hyperacusis Caused by Occupational Noise Exposure

4.1. Abstract

Noise pollution has been called an invisible killer. It has been a critical issue for the people working in the noisy environments especially in industry and education. This study was conducted to evaluate the differences in neuronal activity between groups who are professions in occupational noise environments and a control group who did not, all of whom had either tinnitus or hyperacusis. We used the electroencephalography data of 17 patients. The two experimental subjects (one tinnitus case and one hyperacusis case) had normal hearing. The fifteen control subjects had normal hearing with either tinnitus (N=7) or hyperacusis (N=8). We compared the brain activity for three states among the groups: after noise-induced state, no sound exposure state for the two experimental subjects and no sound exposure state for the control group. The neuronal output and frequency rates of the auditory cortex in the experimental group after noise exposure were significantly increased in the gamma band ($p = 0.002$) and decreased in the delta and theta band. In other brain areas, the rates of the delta, theta, beta 1~3 and gamma bands for the control group were higher than the experimental subjects for both with or without noise exposure states. Through this study, it was

suggested that the professions of tinnitus and hyperacusis with normal hearing in occupational noise environment could be maintain their pathological states by abnormal hyper-activation of the primary and secondary auditory cortex alone.

Keywords: Noise, Occupational noise exposure, Tinnitus, Hyperacusis, Auditory cortex, Electroencephalography

4.2. Introduction

Tinnitus, perception of hearing ringing, buzzing or hissing sound without external sounds, is a typical chronic symptom of permanent hearing loss (Baguley, McFerran, and Hall 2013; Levine 2013). Sometimes when people are exposed to a loud noise like noise from public transportation, transient threshold shift (TTS) of hearing can occur in normal condition of healthy people and subjective tinnitus may also possible to develop temporarily (Ryan et al. 2016; Clark and Bohne 1999). Loud noise and chronic noise exposure such as occupational noise exposure are develop to permanent threshold shift (PTS) which is belong to causative factors of permanent hearing loss and it is classified and so called as noise-induced hearing loss which can develop chronic subjective tinnitus (Ryan et al. 2016; Ryan and Bone 1978; Lonsbury-Martin, Martin, and Bohne 1987). In these unexpected and unpreventable situations from noise, transient or permanent tinnitus is well-known as a major symptom of noise exposure.

In the symptoms of hyperacusis, when hyperacusis patients are exposed to general living noise whose intensity is lower than that of healthy adults, they suffered from an uncomfortable feeling and physical symptoms such as migraine and pain and these sensations are the main symptoms of hyperacusis (Klein et al. 1990; Baguley 2003;

Møller et al. 2010; Vernon 1987). Because noise is an invisible, unpredictable and so powerful energy source, these subjective hearing disorders, tinnitus and hyperacusis, are becoming worse and a crucial issue in an occupational noise environment (Basner et al. 2014).

Also, there have recently been studied with a large number of subjects, of hundreds to thousands, regarding effects of the occupational noise exposure, e.g., construction workers (Leensen, van Duivenbooden, and Dreschler 2011; Seixas et al. 2005; Seixas et al. 2012), industry (Frederiksen et al. 2017), comparisons of the four occupations (cf. education, music, industry and other occupational noise environment (Lindblad et al. 2014), staffs working in obstetric wards (Fredriksson et al. 2015). In usual circumstances of these working environments, occupational noise exposure is usually long-term and higher than 80dB of noise intensity, continuously generated from the working environments in every day and whole time of the working hours (Leensen, van Duivenbooden, and Dreschler 2011). Consequently, chronic noise exposure in the occupational noise environment physically affects hearing of the workers and critically affects their susceptibility of the noise-induced stress and their quality of life (Chiovenda et al. 2007; Corso 1952). Audiometry results, especially in the industry and education, were represented that the workers who suffered from inner ear disorders were significantly higher than other occupational groups (Lindblad et al. 2014).

Since 1970's, several research group have attempted to study evaluating the hearing and clinical pathology status of the central nervous system via audiometry and electro-encephalography (EEG) of the professions of the certain occupations in chronic noise environments, e.g., tractor operator (Kozlov and Kiseleva 1971), industry professions (Brattico et al. 2005; Strel'nikova 1991; Chkannikov 1993; Khaimovich and Sokolova 1978; Angeleri, Granati, and Lenzi 1972), traffic police officer (Chiovenda et al. 2007), veteran (Bressler, Goldberg, and Shinn-Cunningham 2017), aviation pilot (Kuleshova et al. 2017), and other occupational noise environments (Shidlovskaia et al. 1988; Sagalovich et al. 1987; Novotny et al. 1984).

The subjects participated above the studies had been undergoing low ability performing attention task (Chiovenda et al. 2007; Bressler, Goldberg, and Shinn-Cunningham 2017), enhancement of (auditory) sensory processing in silent condition (Chiovenda et al. 2007), and a disorder of central auditory processing in non-speech condition of the noise-exposed and normal hearing subjects (Brattico et al. 2005).

Central pathologic status of tinnitus and hyperacusis has been studied via neuroimaging. Among of them, research related to auditory resting state of tinnitus represented pathological brain states of the patients and resting state of EEG was assessed through spectrum analysis and connectivity (Maudoux et al. 2012b; Song et al. 2014; Song,

Vanneste, and De Ridder 2015; Maudoux et al. 2012a; Neff et al. 2018; Ahn, Hong, and Min 2017; Chen et al. 2015; Eggermont and Tass 2015). Along with above the EEG study and results, resting state of quantitative EEG was used and evaluated activity of the auditory/ non-auditory brain area which location were designated based on 10-20 montage and anatomical location (see, Fig.1).

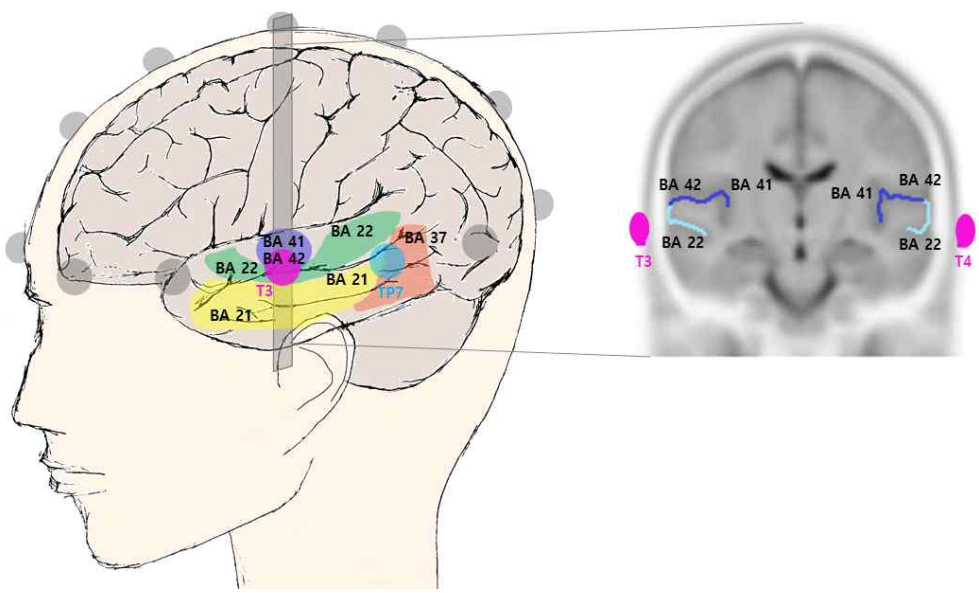

Figure 4-1. The anatomical and functional location around the temporal cortex. Left: The location of the electrodes on the auditory cortex and the brodman areas in the temporal cortex. Right: The anatomical location of the primary and secondary auditory cortex with EEG electrodes.

Because most of these central problems of tinnitus and hyperacusis patients were developed by peripheral hearing loss, hearing researches also have been conducted in certain environments in which otologic disorders frequently occurs.

According to previous reports, in over twenty different construction industry professions, hearing was statistically significantly worse (Leensen, van Duivenbooden, and Dreschler 2011), and condition of chronic occupational noise exposure and that of duration were also significantly associated with subject hearing (Seixas et al. 2005; Seixas et al. 2012). Also, in the study of normal hearing workers, the occupational noise index of the workers in obstetric wards was significantly related to tinnitus and auditory fatigue induced by sound (Fredriksson et al. 2015).

In the previous reports regarding cellular level of noise-induced condition, neuronal activity was showed the fast gamma pattern with spiky in the temporal and auditory cortex in animal models (Eggermont and Tass 2015; Kaltenbach and McCaslin 1996; Vianney-Rodrigues, Iancu, and Welsh 2011; Hickox and Liberman 2014; Jenison et al. 2015).

Comprehensively, above the cohort and/or clinical trials in human and the in-vivo researches in the animal models, we carried out this study with hope that the study could evaluate the pathophysiologic differences previously reported (e.g. high gamma pattern), and the

relation of these differences of neuronal activity and the clinical pathology symptoms (e.g. tinnitus and hyperacusis) caused by occupational noise exposure in normal hearing workers. Also, we intended to suggest that how their default mode is different from those who do not expose occupational noise to tinnitus and hyperacusis.

4.3. Materials and methods

4.3.1. Participants

The EEG data from two experimental subjects from a previous study were included in this study. We compared the EEG data between the experimental group (N=2) and the control group (N=15). Of the two experimental subjects, one had tinnitus and the other hyperacusis; thus, we selected patients with the same disorders as a control group from a previous research database. EEG data from 17 subjects in total were used who completed a clinical trial in previous studies. The tinnitus research was approved by the Institutional Review Board of the Seoul National University Bundang Hospital on August 29, 2016 (IRB No.: B-1607-355-004), and the hyperacusis research was approved in April 2017 (IRB No.: B-1612-373-001).

Because the two subjects had normal hearing, we selected EEG data from patients who had the same normal hearing from these approved research databases. In the first study, 7 out of 80 subjects had normal hearing; the mean score for right ear hearing was 8 (±4) dB and 8.9 (±4.9) dB for left ear hearing. In the second study, the control EEG data were from 8 out of 9 subjects who had normal hearing; the mean score for right ear hearing was 5 (±3.6) dB and 6.1 (±3.9) dB for left ear hearing (Table S1). Thus, the EEG data from a total of 17 subjects, 2 in the test group and 15 in the control group, all with

an otologic disorder, were used in this study. In total, the EEG data from eight tinnitus cases were used. One case was for the test group and seven cases were for the control group. From the hyperacusis database, one case was used for the test group, and eight cases were used for the disorder control group (Table 1).

Patients Initial	Age	Age	Side	Duration (yr)	VAS intensity	VAS distress	Noise exposure environments	Noise induced symptoms
JK	M	54	B	4.5	6	10	Laboring at construction sites	Louder tinnitus
JS	F	26	R	10	7	7	High school teacher	Hearing sounds of ear muscle contraction Hearing noises in the ear

Control N=	M:F	Age	Duration	VAS intensity	VAS distress	C.C
7	6:1	45.7±15	4.96± 7.91	7.3± 0.8	7.1± 1.3	Tinnitus
8	4:4	31.5± 11.4	2.9± 2.8	7.4± 1.6	7.7± 1.4	Hyperacusis
Total control						
15	10:5					Otologic disorder

Table 4-1. Demographic data of the subjects and 15 control of the two otologic disorders.

4.3.2. Experimental subjects

The experimental subject with tinnitus has been working at a noisy construction site with an extremely loud booming sound that could cause hearing loss in healthy people, such as a metal banging sound or sound from heavy equipment. Even if his bilateral hearing thresholds were within normal range, see Table 1, tinnitus can develop because of chronic exposure to an extremely noisy working environment during working hours for a long duration (Dobie and Clark 2014; Lindblad et al. 2014).

Although the noise level of the working environment was not enough to cause hearing loss in the subject, it is thought that tinnitus, which is commonly found in hearing loss patients, is caused by chronic exposure to loud noises (Leensen, van Duivenbooden, and Dreschler 2011). The tinnitus got louder on the days he worked, and he also complained that his tinnitus remained even on his off days. During much of his working hours, he was exposed to high random frequencies and high intensity noise; thus, he was defenseless to the sound and could not help but hear the noise. As a result, he experienced auditory trauma from the noise in his working environment (Minen et al. 2014; Buchler, Kompis, and Hotz 2012; Bressler, Goldberg, and Shinn-Cunningham 2017; Chen et al. 2007; Ryan et al. 2016).

Another otologic disorder is chronic hyperacusis. Hyperacusis has different symptoms than those of tinnitus in that the condition cannot be recognized without an external noise (Baguley 2003). Tinnitus is a ringing sound in the ear that occurs all the time without any external noise regardless of hearing loss (Schecklmann et al. 2014; Møller et al. 2010; Baguley, McFerran, and Hall 2013). However, hyperacusis symptoms in normal hearing usually occur only when patient heard a sound in a noisy environment. Sound or noise is a necessary condition to provoke hyperacusis with normal hearing. In the second experimental case, the female patient was aware of her physical symptoms herself when she was exposed to only a noise louder than her uncomfortable level (UCL).

She was an art teacher in a girl's high school. Most of her unpleasant sounds came from the working environment. The sounds that provoked her symptoms were piano, food plate scraping, stereo sound, and speaker sound in the (school) playground, and she also got symptoms when high school girls would suddenly shout loudly. These sounds that were unpredicted, high frequency and loud noises caused physical symptoms. The UCL was measured by pure-tone audiometry, and the mean threshold was 84.3 (±5.0) dB, and she had the same UCL on the right and left ear. This UCL was a higher intensity than that of the other hyperacusis controls whose average thresholds were 76.3 (±19.5) dB (detailed values in Table S1.).

4.3.3. Noise condition

Tinnitus is the perception of noise or ringing in the ears which is heard all the time, and tinnitus is louder after exposure to loud noise. For the experimental tinnitus subject, we used two pre-treatment EEG datasets for different conditions. One dataset was recorded on his working day when his condition was in severe temporal hyper-activated tinnitus state (STHS) and the other dataset was for his mild temporal hyper-activated tinnitus state (MTHS) recorded on his day-off.

For the experimental hyperacusis subject, a speech sound was given. The procedure for the speech stimulation was the same as described in a previous study (EBB&JHL JAO). Two or three seconds of a speech sound under 20 dB of a female voice evoked temporal hyper-activated states which is similar with the tinnitus EEG.

4.3.4. Electroencephalography test

The same procedure was used as in a previous study (prev. ref). EEG data were recorded from the two experimental subjects and 15 controls. Two reference electrodes were located each on the right and left ear, and we used the average reference montage. EEG was recorded in a sound- and electrically-shielded booth. While recording the EEG for 5 minutes, no sound was induced except for case 2 with hyperacusis. Post-processing of the EEG data included baseline

correction, eye movement and other artifact rejection, interpolation of bad channels, and averaging using Independent Component Analysis methods. The recorded EEG data of the 15 controls were analyzed from a minimum epoch of 192.4 seconds to an epoch of 595.6 seconds.

4.3.5. Analysis

Comparisons were done among the two noise conditions in the experimental subjects and the control group. A total of three groups were used: the no sound exposed state (NS) group, the after Noise Induced condition (aNI) group, and the tinnitus and hyperacusis control group (see Fig.2).

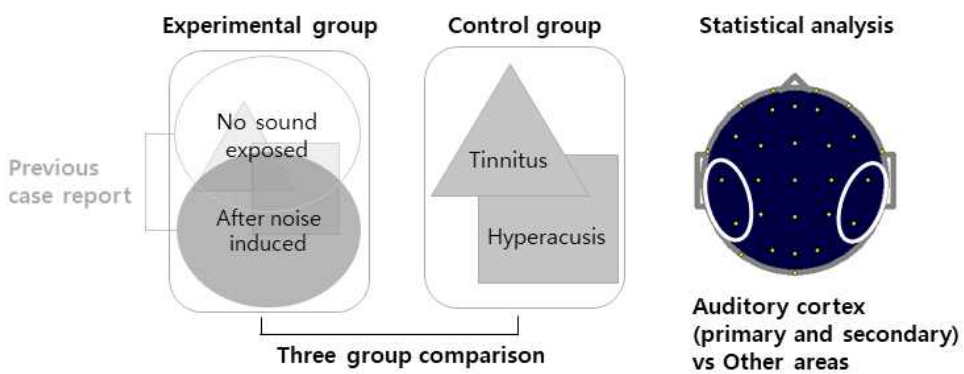

Figure 4-2. The diagram for analyzing procedure.

The neuronal power density of each group was represented by brain topography. The color scale bar of the gamma band was normalized to 20% of the maximum thresholds, and the gamma-theta ratio was normalized to 300%.

Neuronal activity was evaluated by the amplitude and frequency rates. Brain areas were grouped by bilateral auditory and non-auditory cortex; statistically, a minimum of four channels were used for auditory cortex (see, Fig1, 2). Non-parametric analysis was done by two-independent test. Moreover, Kruskal Wallis test was done among the three groups. All the statistically results presented in this study were obtained by SPSS v.23, IBM.

Using LORETA, we compared the activity of the whole brain area among the noise induced states of the two experimental subjects, the no sound exposed state, and the tinnitus and hyperacusis control group.

4.4. Results

4.4.1. Brain Topography

Figure 3-A, B shows the neuronal power density results of the experimental subjects. Figure 3-A shows the neuronal power density for the mild temporal hyper-activated states (MTHS) for the no sound exposed state (NS). Figure 3-B shows the neuronal power density for the severe temporal hyper-activated state (STHS) for the after noise induced condition (aNI). In Figure 3-A, the bilateral auditory cortices had a weaker hyperactivity evident by the absence of pointed waveforms when there was no speech stimulation and noise exposure. The gamma wave intensity of the neurons was dramatically increased after noise exposure. In the tinnitus and hyperacusis control group, abnormally high oscillations were observed in general, while in the two experimental subjects, the gamma band was observed only in the auditory cortices before and after noise exposure.

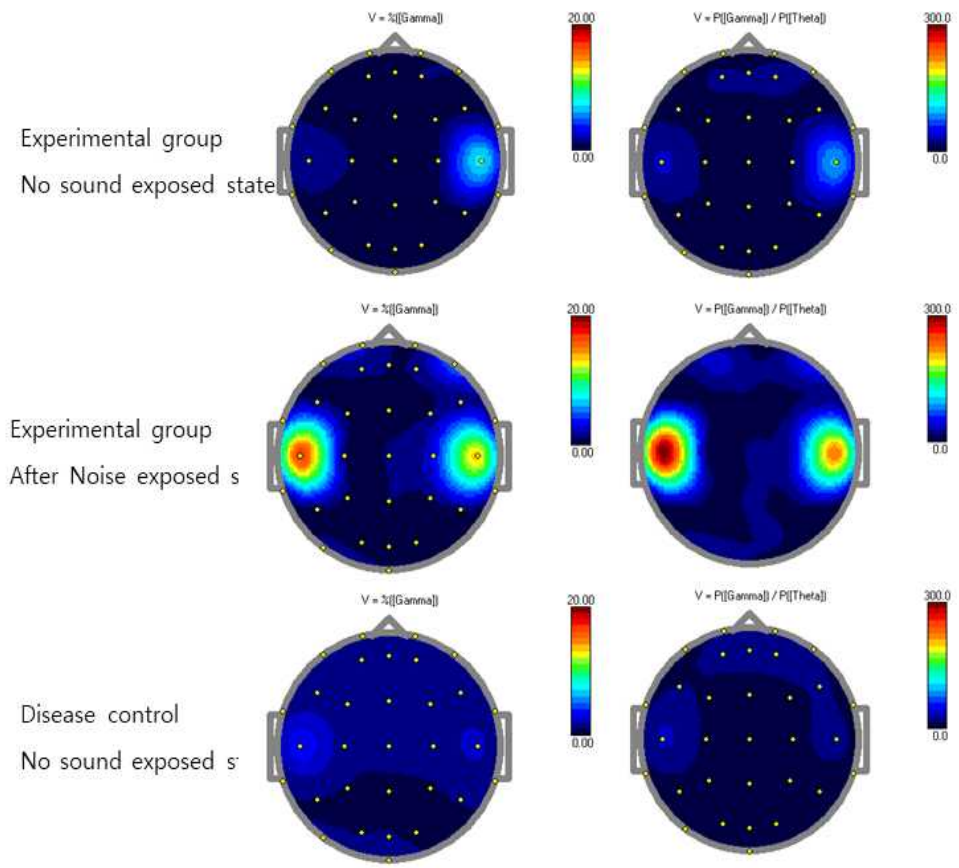

Figure 4-3. The brain activity of the two subjects and the control represented on the brain topography. A: resting state, no sound exposed condition in the two subjects. B: resting state after speech sound induced, (no listening) condition. C: Otologic disorder control (tinnitus and hyperacusis, n=16).

4.4.2. Neuronal activity comparisons

Neuronal activity was evaluated comparing the neuronal power density and the rates of the neuronal frequency between the three groups. In Figure 4-A, in the bilateral auditory cortex, the neuronal power of alpha 2, beta3 and gamma bands for the aNI group was significantly higher than the tinnitus and hyperacusis control group. The percentage of delta and theta bands was significantly different between the tinnitus and hyperacusis control group and the aNI group. In Figure 4-B, in other brain areas, the neuronal power was significantly reduced between the NS group and the tinnitus and hyperacusis control group in the delta, theta, alpha, beta2, and beta3 bands. In contrast to the power, the percentage rates for seven frequency bands except for the alpha2 band were significantly higher in the control group than in the experimental groups.

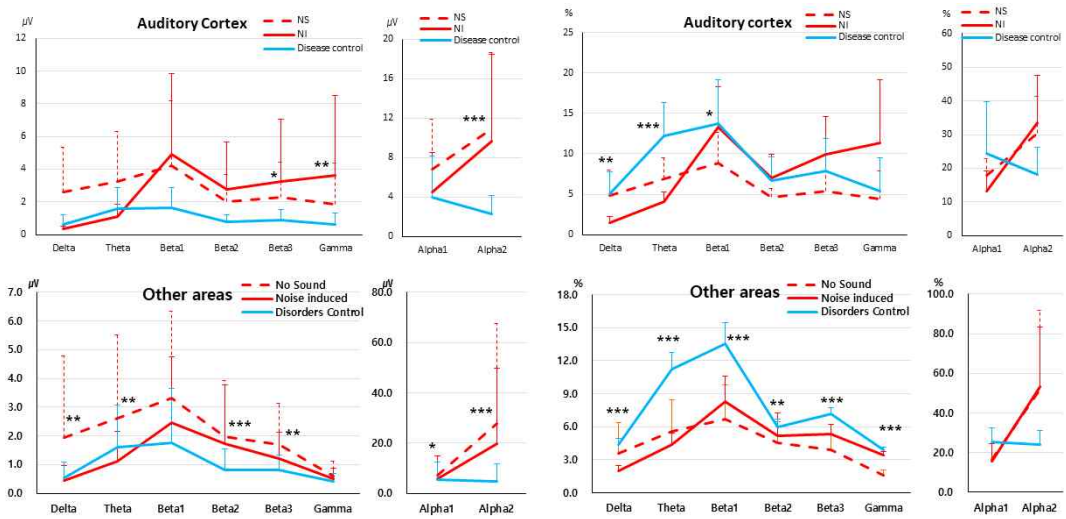

Figure 4. Neuronal activity was presented by the power and frequency rate. NS: no sound exposed condition, aNI: after noise induced state, Disorders control: normal hearing tinnitus and hyperacusis (n=16). A: auditory cortex (T3, T4, TP7, TP8) B: Other brain areas (27 channels). Significance: p<0.05*,p<0.01,p<0.001*****

4.4.3. LORETA analysis

Frequency analysis was done between the aNI group and the control group and between the aNI group and the NS group. As a result of subtracting the NS from the aNI using sLORETA in the Figure 5, the left auditory cortex had a positive score (red to yellow), and all other areas were minus (skyblue to blue). When the control was subtracted from the aNI, the result was positive on the left side and little difference on the right side.

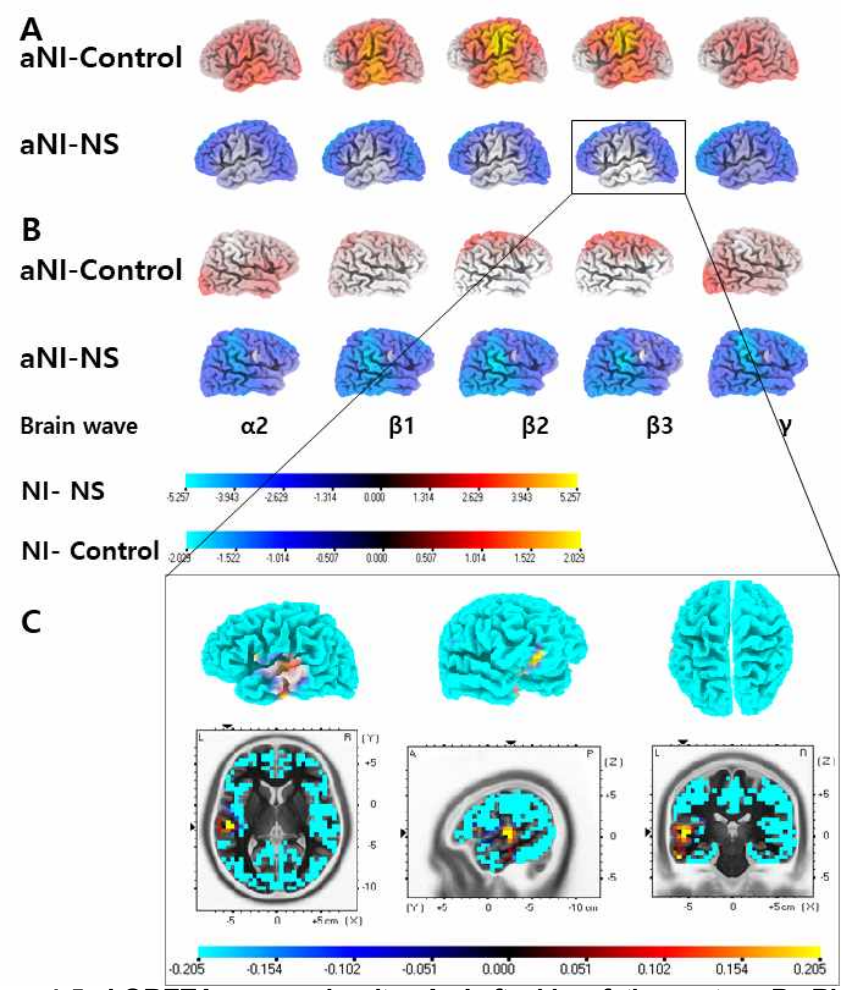

Figure 4-5. LORETA power density. A: Left side of the cortex. B: Right side of the cortex. C: Threshold of the right side of the cortex modulated focusing on BA22, 41 in the beta 3 band.

aNI-NS: (after noise-induced condition) – (No sound exposed state), $p<0.000$

aNI-Control: (after noise induced condition) – (Disorder control), $p=0.00020$

4.5. Discussion

Considering that neuronal power dramatically changed in only the bilateral auditory cortex, after noise-exposed in silent state, and did not change in other brain areas (see, Fig.3-A and B), the auditory cortex of the experimental subjects seems to be separate from the surrounding areas and acts differently in the subjects. Abnormal spiky signals were only observed in the primary and secondary auditory cortex areas (see, Fig.1, EBB&JHL JAO), and the original signals were assumed to come from cochlear nerve (Schaette and McAlpine 2011; Auerbach, Rodrigues, and Salvi 2014).

In Fig.4-A, the percentage rates of delta and theta band in the aNI condition of these noise industry professions were significantly decreased compared to the NS and control groups. It means that the inhibitor function of delta and theta were not properly working when exposed to noise. Gamma, beta3 and the phase coupling ratio of delta and theta also increase at the same time due to noise. This suggests that the main and original functions of the auditory brain area might be sensitized to chronic and occupational noise exposure, and that auditory cortex separately and hysterically act by auditory stimulation and eventually could be develop into physical symptoms and disorders, see Fig.1, e.g. tinnitus and hyperacusis. If auditory stimulus causes abnormal neuronal activity, this physical condition may be

classified as a wide range of auditory trauma and in this respect, this results are similar with (Chen, Sheppard, and Salvi 2016) that minor damage could developed hyperactivity of the auditory cortex in tinnitus and/or hyperacusis. According to calculation of recovery time curve, if someone exposed to 100dB of noise to 17minutes, more than 8 hours of recovery time was expected and in case of occupational chronic exposure, 2 hours of 105dB of noise exposure may lead to 40-50dB of TTS, it would need about one and a half day (33.3 hours) of recovery time (Ward 1960, 1970) it is known that the recovery time needs to be more than 15 minutes after noise exposure, and the recovery time can be different based on the noise intensity and exposure time (Chen et al. 2007; Ward 1960, 1970). For long-term auditory fatigue by noise trauma, auditory recovery was thought to take a long time (Miller 1974).

Comparing the intensity of the overall brain area activation, the firing strength of the inhibition band in the noise industry professions tends to decrease (Fig. 4-B, NS-NI), and the alpha2, beta, and gamma bands show a statistically significant increase (Fig. 4-A). It is interpreted that the theta and delta bands that inhibit the gamma and beta3 activity are decreased and that the spiky abnormal beta and gamma activity due to sound stimulation persist for a long time (Hickox and Liberman 2014; Jenison et al. 2015; Kaltenbach and McCaslin 1996; Vianney-Rodrigues, Iancu, and Welsh 2011). However,

power strength of the gamma band has not changed, whether noise exposed or not. Contrary to other brain areas, the gamma band in the auditory cortex was significantly increased between the aNI status and the NS condition and between the aNI status and the control of disorders.

In contrast to the experimental subjects, the intensity of the brain activity in the control group was generally weak overall brain area (Fig. 4-A left, B left), and the inhibition activity of the delta and theta bands were significantly higher proportion in the control auditory cortex while gamma band was lowered than noise induced state of the experiment subjects. It suggests that the results of our control group, tinnitus and hyperacusis patients who are non-occupational noise exposed, supported previously reported results. The results is that the auditory cortex of hyperacusis patients with tinnitus did not show hyperactivity in auditory resting state (Song et al. 2014). Unlike other tinnitus and hyperacusis subjects (control group), occupational chronic noise exposed subjects showed highly activated solely auditory cortex (see, Fig3,5). Applying neural plasticity theory to our results, auditory hyperactivity (temporal hyperactivity) could increase the hyperactivity of other brain areas if the subject is exposed to work environment noise from months to decades during working hours every day (Chen, Sheppard, and Salvi 2016; Chen et al. 2015; Kraus and Canlon 2012).

Our results also provide following clinical view same with previous reported in (Chiovenda et al. 2007; Brattico et al. 2005; Fredriksson et al. 2015); 1. The results showed that still strong and enhanced gain in the auditory cortex even in the silent condition. 2. Our subjects who have been long-term exposed to occupational noise with normal hearing has persisted symptoms of tinnitus and hyperacusis in no-sound condition. 3. The workers, our subjects, in the occupational noise environments had tinnitus and hyperacusis caused by chronic sound exposure.

From above the results, it is recommended that treatment may be approached differently in general cases of tinnitus and hyperacusis and in noise industry professions because central neural processing and clinical neuro-pathologic symptoms might be different. Previously reported studies, (Norena and Eggermont 2005) showed that sound enriched environments reduced effects of hearing loss in the case of noise-induced hearing loss. However, in the case of the normal hearing experimental subjects in this study, sound using therapy may temporarily worsen the symptoms. Considering recovery time of TTS, recovery time is related to noise exposure duration and noise intensity, however it is determined directly by TTS thresholds rather than exposure time or noise intensity (Ward 1970). To sum it all up, we suggest routine check-up for hearing through hearing conservation program during working period in noise environments, and we

recommend that noise industry professions work as far away from noise sources as possible, or minimize the period they are exposed to noise. By further minimizing noise exposure, it is thought that there will be improvement (Ryan et al. 2016; Clark and Bohne 1999; Department of Labor 2018).

4.5.1. Limitation and Future work

This study, which analyzed resting EEG, shows that the EEG changes at the time of sound stimulation are unknown. This is a study on abnormal and active states in the absence of sound stimuli after noise exposure. Despite the differences in sex, age, noise working environment, and symptoms, these common pattern identified in this study by tinnitus and hyperacusis seem to be an impact of clinical significance and should not be underestimated. According to the results of this study, even though the noise environment causing the tinnitus is different from the noise environment in which hyperacusis occurs, it is difficult to confirm the common mechanism of these two disease groups when the same conditions are applied to one noise environment.

Furthermore, it is difficult to confirm this common mechanism in separate clinical trials in an occupation group. In order to identify the implications of this study as a prospective study, it is recommended that patients be screened as a group of workers in several different

noise work environment or occupations and be selected who has tinnitus and hyperacusis symptoms with normal hearing.

4.5.2. Conclusion

The results of this study are clinically meaningful in the following two perspectives: The first is the finding of the first affected area in the central region of the tinnitus and hyperacusis caused by noise through simple EEG. Second, for noise environmental professionals, it is important that they differ from normal neural activity patterns seen in normal hearing tinnitus and hyperacusis. In general, for tinnitus and hyperacusis patients, the activity of various parts of the brain including the auditory cortex is high, whereas in the two subjects who worked in noise environment professions, abnormal cortical beta3 and gamma bands occurred in only the auditory cortex and lasted for a long time. This is interpreted to be due to the fact that the delta and theta bands are rapidly reduced at the same time with noise exposure, and inhibition of the beta and gamma bands is not achieved. This is the first attempt to distinguish subtypes of tinnitus and/or hyperacusis according to an onset mechanism using EEG. And also our results may help to prevent permanent hearing loss or chronic tinnitus and hyperacusis (Ahlf et al. 2012) for the professions in the occupational noise environment by a regular inspection of simple EEG. If a more research with large number of subjects is

done in the future, the results that we reported may be useful for establishing a marker that distinguish the tinnitus and hyperacusis of occupational noise exposure in normal hearing from general tinnitus and hyperacusis.

5. Conclusion and Perspective

5.1. How do we treat tinnitus and hyperacusis using the transcranial stimulation?

A review paper has reported that frontal tDCS was observed statistically effective for tinnitus, but temporal tDCS has not been statistically revealed to be effective. Although transcranial random noise stimulation has recently been studied and confirmed effects of the pain related disorders, and lots of TMS studies for tinnitus treatment have been continuously published, there is still no evidence for a detail mechanism of tinnitus and hyperacusis on the effect or response criteria.

Important findings to maximize the effectiveness of tinnitus treatment include the following scientific results:

- The scientific facts confirmed through previous studies:

① Frontal tDCS has an effect on tinnitus

② Temporal tDCS has not been revealed an effect of tinnitus

- The scientific facts confirmed through this study (Chapter 2, 3):

① Single session of frontal (DLPFC) tDCS has an effect on tinnitus

② The lower the hearing level of tDCS group, the greater the degree of improvement than non-responders in tinnitus.

③ TMS is expected to have a great effect when the number of stimulation is increased more than 200 pulses.

④ TMS would be effective regardless of hearing, but duration of disorder could be the factor affecting TMS response (P=0.092).

According to source of stimulations, the in vivo mechanism of the treatment effect in humans differs, therefore, in order to see the therapeutic effect of tinnitus using transcranial stimulation, the treatment efficiency can be improved by differentiating the screening criteria according to the stimulation method. According to the above results, in order to see the effects of DC stimulation applied to the tinnitus, it is necessary to select the treatment subjects considering hearing. TMS is considered to be effective when the stimulation of 200 pulses or more should be conducted and the subjects are selected considering the duration of tinnitus.

In hyperacusis patients, tRNS could be a strong and specific treatment because 8 times of tRNS have a big effect on all subjects. If other neurological symptoms are combined, we actively encourage a shorter interval between treatment sessions or increase session of the treatment.

5.2. What can we do via EEG on tinnitus and hyperacusis?

Questionnaires and audiometry are commonly used methods in the otorhinolaryngology department and these measurements can not be use to assess the central nervous system and cerebral activity.

5. Conclusion

Quantitative EEG can be used easily and accurately to confirm the reproducibility by using recent various analysis programs. (Ch 3, Methods). Considering results of the Ch 4, EEG also can be used to identify patients before the onset of tinnitus and hyperacusis, and to use it to prevent tinnitus and hyperacusis.

EEG has been used in various fields (Brain-computer interface, biofeedback, cognitive science, medical research, diagnosis, etc.) and in various disciplines (social science, psychology, language, information and communications engineering, etc.). Nevertheless, in clinics, it is only used for epilepsy diagnosis, and for depression in mental health department as supplementary test, or it is used mostly for research purpose. Since the device is very sensitive due to the amplifier for detecting small brain waves electronic noise contamination is common, and the spatial resolution is lower than that of imaging tests because it confirms the brain area as many as the number of electrodes. Currently, epilepsy is the only disease diagnosed by EEG. EEG can be diagnosed not only by the presence of epilepsy but also by the detailed type of epilepsy.

To more accurately and objectively evaluate therapeutic effects of our multimodal neuromodulation, we suggest using more than three measurements: One is for subjective symptoms, hearing test for clinical pathological states and objective measurement (EEG or other neuroimaging exam). It is the final step and the final goal of chapter

2 to identify the subjective symptom improvement of the tinnitus patients through the objective measurement (neuroimaging) via three measurement methods that can explain the causal relationship of each other.

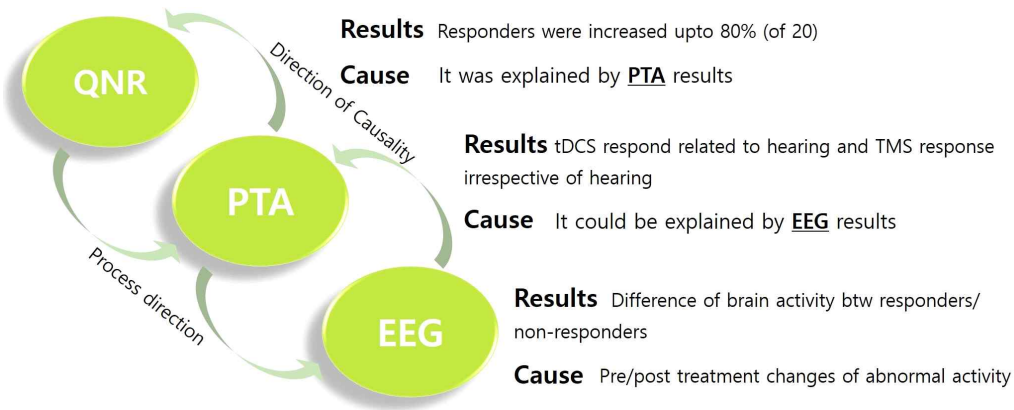

Figure 5-1. Diagram of further study process for treatment effects of dual-neuromodulation in tinnitus and hyperacusis.

Through multimodal measurements, we optimistically anticipate that the scientific key questions, figure 5-2, will be reveal soon.

If above the study is successfully conducted, we assume that tinnitus and hyperacusis can also be diagnosed or prevented by applying EEG to the disorders if the neuropathologic mechanism, such as epilepsy was, is known precisely according to the mechanism of onset and cause. In order to do this, the ongoing EEG studies in tinnitus and hyperacusis should be confirmed, and the common neuropathic

mechanisms of various types of the tinnitus and hyperacusis also should be confirmed.

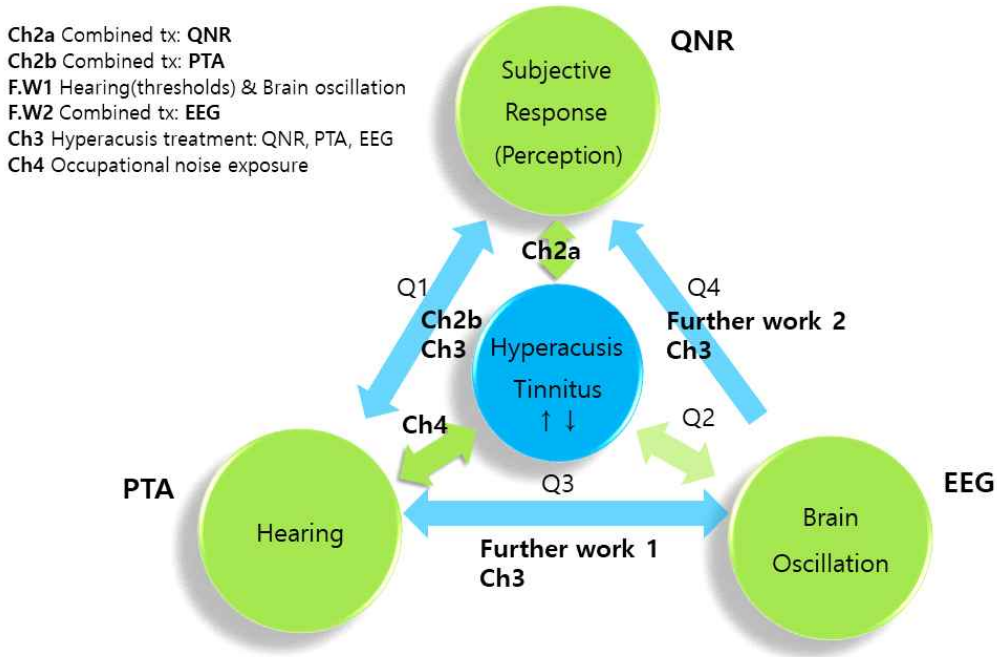

Figure 5-2. The researches diagram of this thesis.

Q1. Can the greater the tinnitus intensity (the greater the hearing loss), the greater the degree of perception of tinnitus modulation?

Q2. If the tinnitus intensity is high, is the abnormal oscillation relatively modulated to the effect?

Q3. If the hearing threholds are large in the PTA that indirectly represents the tinnitus intensity, it is likely to be the same as or similar to the result of Q2.

→ Correlation between Hearing and Brain oscillation (assuming that

hearing reflects tinnitus intensity)

Q4. Does it recognize the effect of changes in oscillation due to neuromodulation?

According to the Figure 5-2, EEG can be used to improve treatment efficiency by identifying the hearing loss affected region for intensive treatment of lesion in further study. The correlation between brain activity in hearing loss and tinnitus and/or hyperacusis also can be assess via multimodal neuroimaging including EEG.

In this regard, EEG and neuroimaging play an important role to evaluate certain status of brain activity. Besides, to determining the criteria for the detailed type of brain activity of tinnitus and hyperacusis patients, depending on the location of the cerebral lesion or on the cause of development of the disorders, hearing test and survey of the subjective symptoms are also should be considered altogether, and then, it will help to fully understand physiological mechanism of the disorders.

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국문 초록

이명과 청각과민증은 신경이과 질환이며 두 질환 모두 주관적인 증상 (예. 울리는 소리, 고주파 소음을 들었을 때 불편한 느낌) 을 주호소로 합니다. 또한 두 질환은 모두 약물 치료가 불가능하며 아직은 검사로 진단 할 수 없어, 객관적으로 증상의 심각성을 측정 할 수가 없습니다. 1950 년대 이후부터 여러 연구들에 의해, 이명의 중추 기전이 지속적으로 언급되어 왔으며, 최근 중추 기능 항진 기전과 같이, 이명과 청각과민증의 공통된 뇌신경 상태가 다양한 동물 연구에 의해 밝혀진바 있습니다.

본 박사학위 논문에서 우리는 경두개 전기 자극과 경두개 자기 자극을 사용하여 이명과 청각과민증의 중추 기능 항진을 치료하는 것과 병리적 상태를 전기생리학적 방법으로 평가하는 것을 목표로 삼았습니다. 본 연구에서는 이명 치료를 위해 경두개 직류 자극술과 경두개 자기장 자극술을 사용하였고, 청각과민증 치료를 위해 경두개의 무작위 잡음 자극술을 사용 했습니다.

설문지 형식은 이명의 주관적 증상을 평가하는 가장 중요한 측정이지만, 이명의 대뇌 관련 기전의 병태 생리학적 상태는 설문지 및 청력 검사로 확인할 수 없습니다. 따라서 경두개 자극의 치료 효과를 효과적으로 평가하기 위해, 뇌파를 이용한 뇌영상 기술을 사용하였고 객관적 측정을 위해서는 검증 가능한 기준을 수립해야 했습니다.

0. 국문초록

박사 학위 과정에서 저는 경두개 자극술을 사용하여 이명과 청각과민증에 특이적인 치료방법을 개발하기 위해 몇 가지 연구를 시행한 결과, 기존 선행 연구들에 비해 치료효과, 반응자 수를 증가시켰으며 청각과민증에 특이적 치료법을 고안 해냈습니다. 또한 뇌파, 설문지 및 순음청력검사를 통해 치료 효과를 객관적으로 확인할 수 있는 검사방법을 수립하는 데 중점을 두었습니다. 이 세 가지 검사를 이용해 서로 장단점을 보완하여 이명 및 청각과민증의 병태생리적 상태와 치료효과를 객관적이고 정확하게 평가 하고자 몇가지 연구를 진행하면서 학위를 했습니다.

주요어 : 이명, 청각과민증, 경두개 직류자극술, 경두개 자기자극술, 경두개 무작위 소리 자극술, 순음청력검사, 뇌파, 청각 피질

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짧지 않은 학위 기간 중에 크고 작은 어려움과 힘든 일에 부닥칠 때 마다 외면하지 않고 들어주시고, 아무것도 없는 저를 믿어주시고, 또 힘써 해결해 주신 이준호 교수님과 여러 심포지움, 학회, 세미나, 연구회 등에 참가하여 이비인후과, 이과, 청각 연구를 배우며, 또 연구를 지속 할 수 있도록 도와주시고 크고 작은 조언을 아끼지 않고 해주신 오승하 교수님께 감사의 말씀 올립니다.

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