Correlation Analysis of EEG Brain Network With Modulated Acoustic Stimulation for Chronic Tinnitus Patients

Xiabing Zhang, Yuanlin Jiang, Shu Zhang, Fali Li, Changfu Pei, Gang He, Min Ao, Dezhong Yao, *Senior Member, IEEE*, Yong Zhao, and Peng Xu

***Abstract*— The acoustic stimulation influences of the brain is still unveiled, especially from the brain network point, which can reveal how interaction is propagated and integrated between different brain zones for chronic tinnitus patients. We specifically designed a paradigm to record the electroencephalograms (EEGs) for tinnitus patients when they were treated with consecutive acoustic stimulation neuromodulation therapy for up to 75 days, using the tinnitus handicap inventory (THI) to evaluate the tinnitus severity or the acoustic stimulation treatment efficacy, and the EEG to record the brain activities every 2 weeks. Then, we used an EEG-based coherence analysis to investigate if the changes in brain network consistent with the clinical outcomes can be observed during 75-days acoustic treatment. Finally, correlation analysis was conducted to study potential relationships between network properties and tinnitus handicap inventory score change. The EEG network became significantly weaker after long-term periodic acoustic stimulation treatment, and tinnitus handicap inventory score changes or the acoustic stimulation treatment efficacy are strongly correlated with the varying brain network properties. Long-term acoustic stimulation neuromodulation intervention can improve the rehabilitation of chronic tinnitus patients, and the EEG network provides a relatively reliable and quantitative analysis approach for objective evaluation of tinnitus clinical diagnosis and treatment.**

***Index Terms*— Acoustic stimulation, EEG, coherent network, network properties, tinnitus.**

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I. Introduction

TINNITUS is an auditory phantom percept with a tone, hissing, or buzzing sound in the absence of any objective physical sound source [1]. Tinnitus is commonly observed in individuals above the age of 60 years and affects 8% to 20% of the elderly population; however, chronic tinnitus can occur at any age [2]. The comorbid factors of tinnitus, such as stress, attention deficit, insomnia, anxiety, depression, and even suicide, can be devastating to daily life [3], [4].

Most chronic tinnitus is triggered by central origin, and acoustic therapies can adequately stimulate the auditory pathway of tinnitus [5], [6]. Many studies have also shown aberrant neural activity within the central auditory pathway of tinnitus patients [7], [8]. Tinnitus is a frequent and heterogeneous disorder, resulting in most cases from neuronal changes occurring in the central nervous system as a reaction to auditory deprivation [9]. Since tinnitus severity is a composite of several behavioral measures or aspects of tinnitus perception, it is meant to divide tinnitus degree by the Tinnitus Handicap Inventory (THI), which classifies patients into 5 grades on a 100-point scale using a 25-item questionnaire, from slight (0-16), mild (18-36), moderate (38-56), severe (58-76) to catastrophic (78-100) [10]. Maudoux *et al.* examined a group of tinnitus patients with the THI scores ranging from 16 to 84 (mean 43.5) and noted the increased connectivity between the auditory resting-state network and right frontal and parietal areas, specifically higher-order prefrontal and parietal associative cortices [11]. Suppression of the tinnitus, which is the reduction or disappearance of the tinnitus perception and might last from a few seconds to days, maybe achieved if neuroplastic changes are produced [12], [13]. Acoustic stimulation is one of the most relevant tinnitus therapies and helps relieve the painful feeling of chronic tinnitus [14]. However, though the THI scale is widely used to evaluate the tinnitus degree of patients, it is largely influenced by the patient's subjective judgment, and the reliable metrics to objectively evaluate the tinnitus recovery degree is still lacked, which is mainly due

to the unclear rehabilitation neural mechanisms for tinnitus disorders.

Previous studies have found that the resting-state functional connection network between auditory and non-auditory networks in tinnitus patients is abnormally changed, involving the edge network of auditory network, the default network of attention network, etc. [15]–[19]. This has led to the idea of a 'tinnitus network', typically characterized by altered auditory processing that generates the tinnitus sensation [20]. Carpenter-Thompson *et al.* [21] found the increased spontaneous brain activity in the middle temporal gyrus, inferior frontal gyrus, right superior frontal gyrus, parietal hippocampus, and posterior cerebellar lobe of tinnitus patients, and the changed connectivity observed in the default mode network. Kim *et al.* [22] found that patients with tinnitus had increased functional connections between the left amygdala and the prefrontal cortex, and also between the auditory cortex and attention networks, such as the dorsal prefrontal lobe. Schlee *et al.* used magnetoencephalogram (MEG) to provide evidence for the existence of a tinnitus network, and they found that abnormal functional connections were widely distributed in the brain [23]. When examining the anatomy of regions within the networks, we are more interested in the spatial information interactions between brain regions and nodes. In fact, neurophysiological measurements like electroencephalogram (EEG) serve as an objective outcome measure to quantify therapeutic benefit [24]. The brain functional network information may be a potential marker for EEG and its weighted adjacency matrix contains the fundamental spatial information. In complex network analysis, properties such as local information processing and global information efficiency can be quantitatively represented by statistical measurements such as clustering coefficients and the shortest path length [25]. Though those existing studies have evidenced the abnormal network changes in tinnitus patients, how the brain is dynamically changed during the long duration acoustic stimulation therapy is less probed in previously reported studies.

Functional interactions of networks among brain areas are not isolated but are instead governed by dynamic connectivity in the central nervous system that is shaped by the anatomical topology of the brain. The network analysis can provide a clear spatial pattern to reflect how the tinnitus information is exchanged among the whole brain. Traditional tinnitus treatment only focuses on the auditory region, while the non-auditory region also changes its function when tinnitus occurs. Brain network can analyze the influence of a certain tinnitus area on the whole brain area from a global perspective. Because of the large influence of subjects on the THI scale and the lack of objective indicators to evaluate the tinnitus recovery degree, we further put forward the method to evaluate the brain changes during acoustic stimulation from brain network aspects.

In this study, to reveal if the impaired brain networks can be gradually remodeled during a long duration acoustic stimulation therapy, and if the network information could be served as the potential biomarker to denote the tinnitus recovery degree, we used an EEG-based coherence analysis to investigate the network mechanism of tinnitus patients and the reconfigured changes of the network after treatment with periodic acoustic therapy. To realize this aim, we specifically designed a 75-day experiment with every 15 days as one session, during which the tinnitus patients will continuously receive the acoustic stimulation treatment with individually optimized stimulus parameters every day. In the experiment, every 15 days, patients will perform the THI test, and then participate in the EEG recording. Based on EEG, network analysis is performed to construct the functional networks for each session. Then, analysis is performed to investigate how the abnormal brain network is dynamically reshaped with the external acoustic stimulus, and also if the changes of the network properties are correlated with the THI score changes.

II. Materials and Methods

A. Participants

All experimental operations in this study were reviewed and approved by the ethics committee at the University of Electronic Science and Technology of China (UESTC). We recruited 30 subjects, 9 right-handed bilateral chronic tinnitus patients (54.4±10.8 years) finished the 75-day experiments, and the other 21 subjects withdrew from the experiments due to personal reasons. These subjects had tinnitus disorder for at least three months and were diagnosed by the Department of Otolaryngology, Sichuan Provincial People's Hospital. Before the experiment, subjects understood the purpose of the experiment and signed informed consent.

B. Experiment and Data Recording

1) Experimental Procedures: In this experiment, tinnitus patients were diagnosed by the doctor to determine who can participate in the experiment. During EEG collecting, the patients filled out a 5-minutes THI scale assessment as required by the physician. The Tinnilogic mobile tinnitus treatment device designed by BetterLife Medical, which was adaptively adjusted within 1000-3000Hz, was used to deliver the tinnitus acoustic stimulation therapy during the 75-days experiment. Then, patients were required to keep their eyes closed, head still, and body relaxed. They wore sound insulation earplugs and resting-state EEG was collected for 5 minutes, known as pre-stimulation of data collection (*Pre*). After *Pre* data collection, tinnitus patients wore earphones on the mobile tinnitus treatment device and performed physical acoustic intervention for 15 minutes. EEG signals were collected during acoustic stimulation, known as stimulation of data collection (*Stim*). Finally, EEG was collected for 5 minutes with the same requirements as that in the pre-data collection, known as post-stimulation of data collection (*Post*). Data collection of each patient were conducted for 6 sessions with 15-days interval between two sessions. During these 15-days intervals, the patients received the acoustic stimulation with the mobile tinnitus treatment device at home for 30 minutes every day, and doctors called or emailed each week to fill out the form and kept track of their tinnitus' treatment progress. When patients participated in our present experiment, they were only treated at home according to medical advice and did not take any medicine to alleviate tinnitus disorders. We marked the

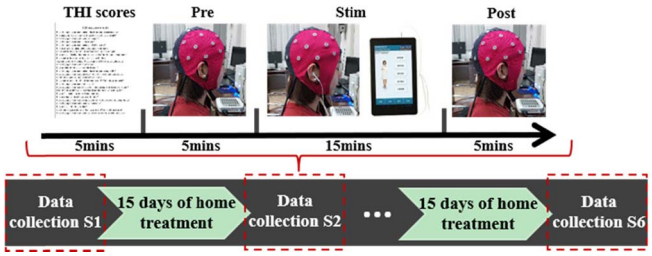

Fig. 1. The experiment procedure of acoustic stimulus and data collection.

data collection in the 6 times as S1, S2, S3, S4, S5, and S6, where S1 serves as the baseline without acoustic stimulation therapy. The detailed procedure of data collection and tinnitus treatment for each subject are shown in Fig. 1.

2) THI Test: Before the EEG data collection at each stage, doctors would diagnose the tinnitus status of each patient, and collect the patient's THI assessment scores. THI is a self-report measure that can be used in a business clinical practice to quantify the impact of tinnitus on daily life. All tinnitus patients completed the THI scale filling before the *Pre* stage in each data collection session, which aims to guarantee the consistency between the THI scores and the recorded EEG on the same day. In detail, during each data collection session, four stages were performed within half an hour, including filling out the THI scores based on the functional level, serious level, and emotional level of tinnitus, collecting tinnitus patients' EEG data in the *Pre* stage, *Stim* stage, and *Post* stage on the day.

3) EEG Recording: During the EEG acquisition, patients were seated in a quiet room with their eyes closed and relaxed as much as possible. The data included the eyes-closed resting EEG data with and without physical acoustic stimulation. We utilized the ASA-Lab amplifier (ANT Neuro) to acquire EEG signals with a sampling frequency of 500Hz. The EEG data sets were recorded with 64 Ag/AgCl electrodes that were positioned in compliance with the 10/20 international electrode placement system, including an external EOG lead to collect electrooculogram, and the built-in CPz and GND were used as the reference and ground respectively, and the contact impedance between the EEG electrode cap and the scalp was kept below 5KΩ.

C. Methods

In this study, resting-state EEG in *Pre* and *Post* stages of EEG collection were used to construct the corresponding EEG network. The pre-processing procedure and analysis procedure were depicted in Fig. 2, coherence network analysis was performed and the correlation between network properties and THI total scores were calculated.

1) EEG Data pre-Processing: Aiming to acquire artifact-free data trials, the raw EEG data sets were pre-processed with zero reference by the reference electrode standardization technique (REST) referencing [26], [27], 8-13 Hz bandpass offline filtering aiming to extract the alpha information in the data collection state, 5s data segmentation, and artifact trials removal ($\pm 75\mu$V as the threshold). After REST reference, in order to reduce the influence of the volume conduction between network nodes, 21 electrodes ('Fp1', 'Fpz', 'Fp2', 'F7', 'F3', 'Fz', 'F4', 'F8', 'T7', 'C3', 'Cz', 'C4', 'T8', 'P7', 'P3', 'Pz', 'P4', 'P8', 'O1', 'O2', and 'Oz') of the 64 channels were selected for the subsequent processing [28].

Previous studies found that the alpha band was significant increased after electrical stimulation in tinnitus patients while beta and theta bands were not significant [22]. Alpha oscillations, reflecting excitatory-inhibitory balance with decreased levels of alpha in excitatory conditions and increased inhibition, are the dominant rhythm at rest in the sensory regions [29]. Given the fact that changes in the alpha band reflect shifts between excitatory-inhibitory processes and the view that tinnitus is a result of excitatory-inhibitory imbalance, we mainly focus on the analysis in the alpha EEG band (8-13Hz).

2) EEG Network: The brain network can be used to describe the connectivity among multiple regions. Coherence is one of the most commonly used to measure the interaction strength between different nodes [30]. Coherence (COH) represents the linear relationship between two different channel signals $x(t)$ and $y(t)$ in a specific frequency domain of f. The coherence coefficients of the two-time processes $x(t)$ and $y(t)$ are defined as:

$$C_{xy}(f) = (|P_{xy}(f)|^2)/(P_{xx}(f)P_{yy}(f)), \quad x \neq y \tag{1}$$

where $P_{xy}(f)$ is the cross-spectrum of $x(t)$ and $y(t)$, and $P_{xx}(f)$ and $P_{yy}(f)$ are the power spectrum for $x(t)$ and $y(t)$, respectively.

After coherence calculation in (1), the coherence is further averaged within 8-13Hz to get the final linkage strength between two nodes. The value range of the coherence coefficient is 0-1. The closer the coherence coefficient is to 1, the stronger the coherence of the two signals in this frequency band will be. Since the EEG data for each trial includes 21 channels, which means that the networks have 21 nodes, the EEG network was constructed with a 21×21 weighted adjacency matrix.

3) Network Properties: Based on the final adjacent matrix, the network properties of each subject were calculated. The EEG network is quantitatively measured by network properties, namely the clustering coefficient (Clu), global efficiency (Ge), local efficiency (Le), and characteristic path length (L) [31]. These four network properties are calculated as below:

$$Clu = \frac{1}{T}\sum_{i\in N}\frac{\sum_{j,l\in N}(C_{ij}C_{il}C_{jj})^{1/3}}{\sum_{j\in N}(\sum_{j\in N}C_{ij}-1)} \tag{2}$$

$$L = \frac{1}{T}\sum_{i\in N}L_i = \frac{1}{T}\sum_{i\in N}\frac{\sum_{j\in N, j\neq i}d_{ij}}{T-1} \tag{3}$$

$$Ge = \frac{1}{T}\sum_{i\in N}\frac{\sum_{j\in N, j\neq i}d_{jl}^{-1}}{T-1} \tag{4}$$

$$Le = \frac{1}{T}\sum_{i\in N}\frac{\sum_{j,l\in N, j\neq i}(C_{ij}C_{il}[d_{jl}(N_i)]^{-1})^{1/3}}{\sum_{j\in N}C_{ij}(\sum_{j\in N}C_{ij}-1)} \tag{5}$$

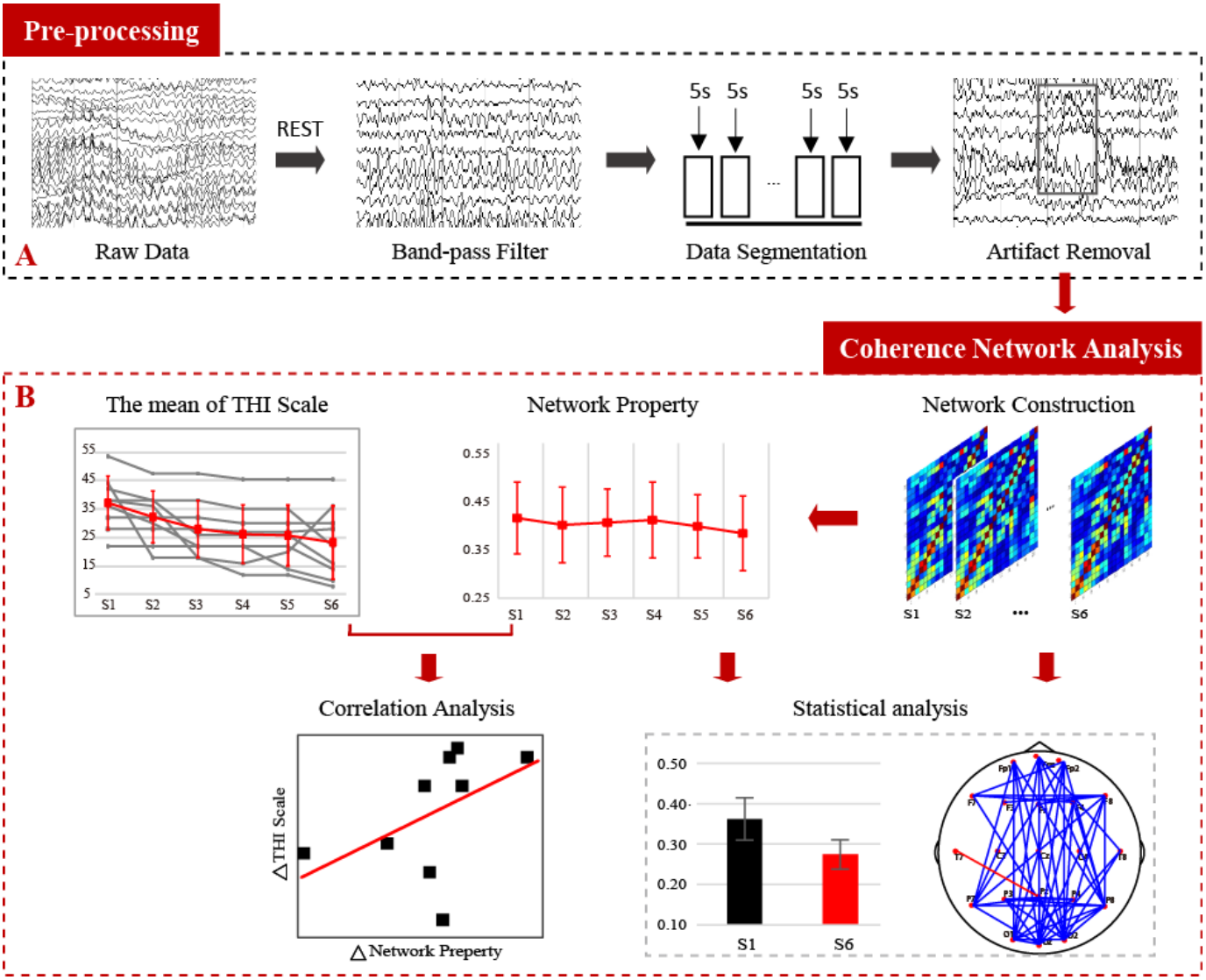

Fig. 2. The procedure for EEG data analysis.

where d_{ij} is the shortest weighted path length between i and j, C_{ij} is the coherence coefficient between channel i and channel j, where coherence represents the linear relationship between two different channel signals in a specific frequency domain, T is the node number, and N is the set of all nodes in a single-trial network. Specifically, *Clu* is defined as the fraction of triangles around an individual network node. *Le* is the average efficiency of the local subgraphs. *Clu* and *Le* are related to the estimation for functional segregation between brain regions. *Ge* is the average efficiency of the related brain network, and L is the mean value of the shortest path length between all pairs of network nodes. For each session, the network properties were averaged across all subjects.

4) Statistical Analysis: In this study, considering the smaller sample of chronic tinnitus data, the Wilcoxon signal-rank test of non-parametric paired samples was used to investigate the differences between S1 and S6 for network topology and network properties [32]. Besides, to assess the possible relationship between tinnitus improvement and cortical activity in patients, we calculated the Spearman correlation between network properties and THI scores [33], [34].

III. Results

A. The Network Changes During Long-Term Acoustic Stimulation

Based on the EEG networks in each time of data collection, the network properties are calculated as shown in Fig. 3, where the red and green line represents the network properties of *Pre* and *Post*, respectively. On the whole, *Clu*/*Ge*/*Le* shows a decreasing trend with the continuous progress of tinnitus treatments, and L shows a rising trend.

To further reveal network changes after the long-term acoustic stimulation neuromodulation treatment, Fig. 4 shows the statistical differences of network topology and properties between S1 and S6, respectively. Fig. 4(top) shows the network topology difference between S1 and S6 for the *Pre* and *Post* stages, where the blue line indicates enhancement (S1 > S6) and while the red line indicates reduction.

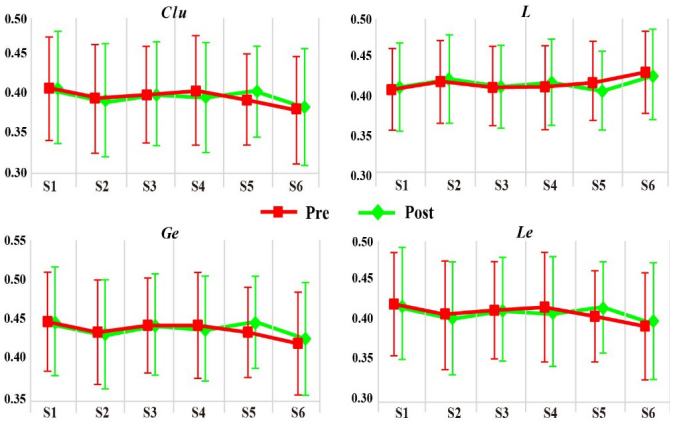

Fig. 3. The network properties during long-term acoustic stimulation treatment.

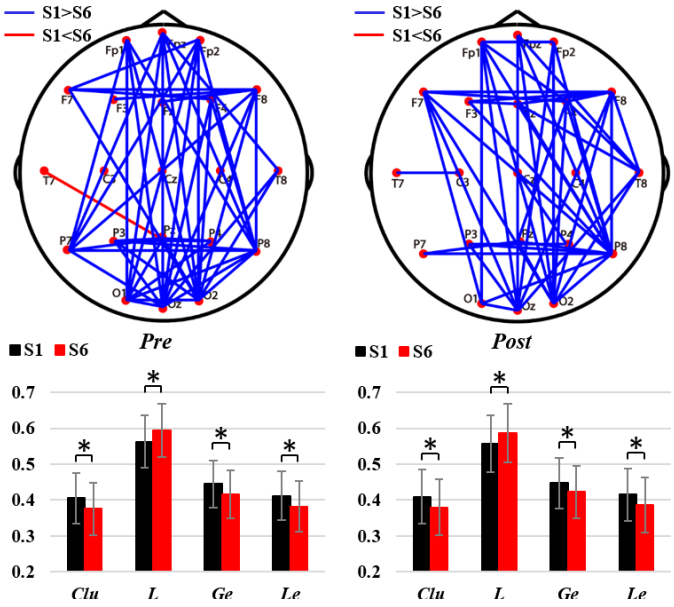

Fig. 4. The statistical differences of network topology and properties between S1 and S6 for the *Pre* and *Post* stages.

Fig. 4(bottom) gives the corresponding network properties difference between S1 and S6 for the *Pre* and *Post* stages with the black bars and red bars representing network properties of S1 and S6, respectively ($^*p < 0.05$).

Based on Fig. 4, we further calculated the relative change rate (RCR, RCR=(S6-S1)/S1) of the network properties between S1 and S6 in Table I, where we can see that the network properties have approximately over 5% improvement after the long-term stimulation treatment.

B. Correlation of Network Properties and THI Scores

As shown in Fig. 3, the network properties overall exhibit a decreasing trend. Clinically, the lower THI score represents a less severe disorder. Fig. 5(a) shows the THI scores during the six sessions and Fig. 5(b) gives the scatter plots of network properties and THI for the six stimulation sessions, where a decreasing THI trend and a strong correlation are revealed ($r = 0.77,\ p = 0.10$).

TABLE I
THE RELATIVE CHANGE RATE OF NETWORK PROPERTIES OF S1 AND S6

RCR	*Pre*	*Post*
Clu(%)	-7.34	-7.08
L(%)	5.54	5.23
Ge(%)	-6.39	-5.65
Le(%)	-7.07	-6.72

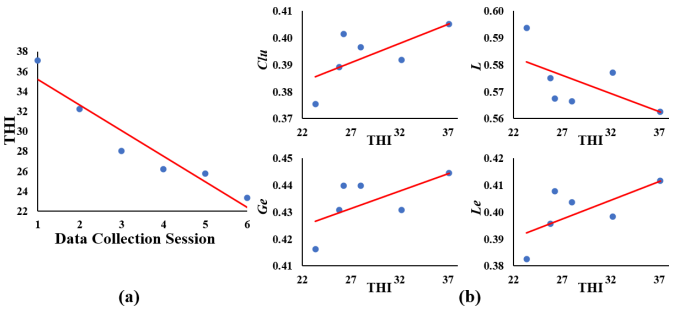

Fig. 5. The THI during the six stimulation sessions (a) and the correlation between the network properties and THI during the six stimulation sessions (b).

To further reveal that after the long-term stimulation, if the changes of THI scores could be reflected by the corresponding changes of network properties, correlation analysis was adopted to investigate the relationship of network property changes and THI variations ($\Delta THIs$) between S1 and S6 for the *Pre* and *Post* stages, respectively. Network property changes including ΔClu, ΔL, ΔGe, and $\Delta\ Le$ are calculated by subtracting the network properties in S1 from that in S6, and the THI variations ($\Delta THIs$) is measured by the THI score difference between S1 and S6 for each subject. Then the correlation analysis is performed for the paired network properties and scores changes for the nine subjects, which is shown in Fig. 6. The upper part of Fig. 6 represents correlation of *Pre* (correlation coefficients of *Clu*/*L*/*Ge*/*Le* are as follows: $r = 0.61,\ p = 0.06$; $r = -0.57,\ p = 0.09$; $r = 0.57,\ p = 0.09$; $r = 0.52,\ p = 0.13$), and the lower part of Fig. 6 represents correlation of *Post* (correlation coefficients of *Clu*/*L*/*Ge*/*Le* are as follows: $r = 0.46,\ p = 0.18$; $r = -0.45,\ p = 0.20$; $r = 0.52,\ p = 0.12$; $r = 0.46,\ p = 0.18$). Correlations in Fig. 6 show that the changes of THI (i.e., the improvement of chronic tinnitus degree) could be reflected from the corresponding changes of brain networks.

IV. DISCUSSION

In this work, considering that tinnitus involves multiple brain zones and the disorder may be reflected from the connectivity patterns of the brain, we used the weighted EEG function networks that can reflect the couplings among brain zones to investigate if the acoustic stimulation neuromodulation could improve the impaired brain networks during a relatively long-term stimulation.

Fig. 3 overall shows an upward trend for L while decreased trend for *Clu*, *Ge*, and *Le* with the ongoing of the stim-

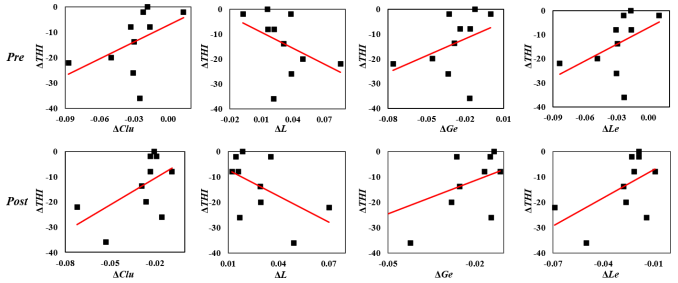

Fig. 6. The correlation between network property changes and *ΔTHIs* calculated from S1 and S6 for the nine subjects in the *Pre* and *Post* stages.

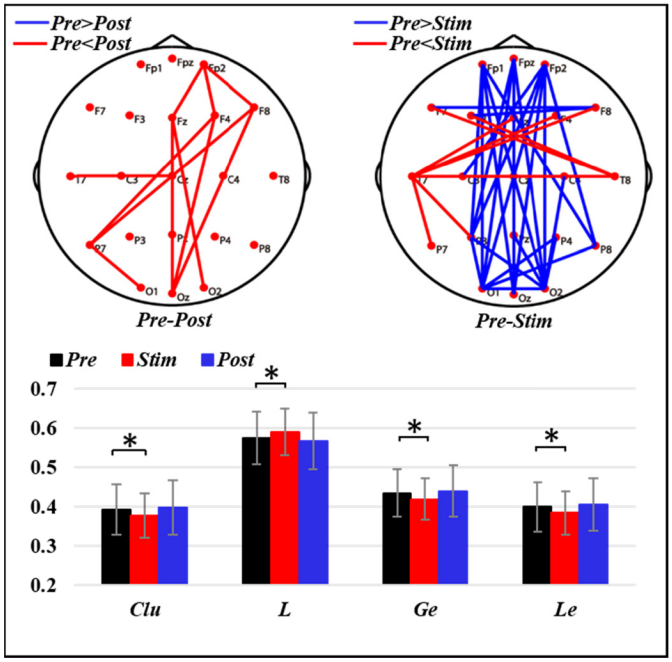

Fig. 7. The difference between network patterns and properties before, during, and after stimulation within one session. *Pre-Post* is the comparison of network topology between the *Pre* stage and the *Post* stage within one session, and *Pre-Stim* is the comparison of network topology between the *Pre* stage and the *Stim* stage within the same session. The blue line indicates enhancement (*Pre*>*Post*/*Stim*) while the red line indicates reduction. For network properties, the vertical axis is the average of nine subjects, and the symbol * denotes the significant difference between the *Pre* stage and the *Stim* stage ($^*p < 0.05$).

ulation, and an over 5% network properties improvement could be achieved after the long-term stimulation as shown in Table I. Previous studies have revealed that the interference between thalamus-cortex causes tinnitus and tinnitus conversely amplifies the effect of auditory nerve activity through thalamus-cortex global brain network by top-down influence [35]–[38], i.e., tinnitus patients usually show the enhanced linkages among those related brain areas. Therefore, decreased network patterns and properties consistently demonstrate that acoustic stimulation could improve impaired brain networks. As for S5's network properties differences between the *Post* stage and *Pre* stage, a decrease of *Clu, Le, and Ge* and an increase of *L* are observed in the *Pre* stage compared to the *Post* stage, while no difference is revealed in the other 5 sessions between these two stages. This difference is due to the abnormality of one subject who did not follow the acoustic stimulation treatment exactly as required during the 15 days interval at home before the 5th session data collection. Fig. 3 also shows the gradual improvement of the brain networks, and the long-term stimulation obviously shaped the brain networks with the decreased linkage patterns as shown in Fig. 4. We assume this reshaped network patterns after long term stimulation treatment is the accumulation of those short-term stimulations. Therefore, we further compared the network topology and properties for *Pre* vs *Post* and *Pre* vs *Stim*, i.e., the difference of networks before, during, and after stimulation within one session (Fig. 7). As displayed in the upper part of Fig. 7, *Pre* stage showed enhanced network connectivity compared to *Stim*, mainly manifested as the long-range connections between the frontal lobe and parietal-occipital lob; and in the lower part, the obvious difference of network properties between both stages could also be found, which might be attributed to the modulation effect of the acoustic stimulation that has an obvious inhibitory effect on the information interaction between frontal and parietal lobes in tinnitus patients ($p < 0.05$). Unfortunately, after the acoustic stimulation, the *Post* stage did not show too much difference from the *Pre* stage for both network patterns and properties, as shown in Fig. 7. This might be due to that the short-term treatment by using acoustic stimulation is not long enough to significantly affect the brain of tinnitus patients, and fails to improve the structure and function of the auditory system. Moreover, by designing our 75-days experiments, our present study further validated that the long-term intervention did work, and could affect and promote the brain network, as our current study found that the EEG network becomes significantly weaker after long-term treatment.

The EEG network analysis shows the improved network patterns during the acoustic stimulation. To further investigate if the EEG network is correlated with the clinical THI scores, we performed two correlation analysis. The first is the correlation between the network properties and the corresponding THI scores across the six sessions. As shown in Fig. 5(a), the THI scores show a decreasing trend during the acoustic stimulation, inferring the chronic tinnitus degree is alleviated after the modulation stimulus. The strong correlation between the network properties and THI scores proves that the network properties can reflect the clinical chronic tinnitus severity degree. The second correlation analysis is further applied to probe if the improved THI scores could be also reflected by the network properties after the long-term stimulation. The corresponding correlation analysis in Fig. 6 demonstrates that a higher degree of THI improvement is accompanied by larger changes in network properties. Combing the two correlation analysis, we conclude that the EEG network may be served as a potential biomarker to reflect the chronic tinnitus severity degree and objectively evaluate the neuromodulation treatment efficacy, and also as a feedback metric to guide developing the more effective acoustic stimulation therapy in the future.

One possible limitation would be that, as our present study lasted a long duration of 75 days, although a relatively large

sample size (i.e., 30 patients) was recruited at first, only a few of the recruited tinnitus patients could adhere to our experimental protocols and finish the data collection, which led to the small size of tinnitus patients. In the future, more patients will be recruited to further validate our findings.

V. Conclusion

Based on the EEG coherence analysis, the changes in the brain network could be observed during the 75-days acoustic therapy. EEG network becomes significantly weaker after long-term periodic treatment, and THI scores are strongly correlated with the brain network properties. This finding indicates that the EEG network provides a relatively reliable and quantitative analysis approach for objective evaluation of tinnitus clinical diagnosis and treatment.

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