Objective Neurophysiological Indices for the Assessment of Chronic Tinnitus Based on EEG Microstate Parameters

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***Abstract*— Chronic tinnitus is highly prevalent but lacks precise diagnostic or effective therapeutic standards. Its onset and treatment mechanisms remain unclear, and there is a shortage of objective assessment methods. We aim to identify abnormal neural activity and reorganization in tinnitus patients and reveal potential neurophysiological markers for objectively evaluating tinnitus. By way of analyzing EEG microstates, comparing metrics under three resting states (OE, CE, and OECEm) between tinnitus sufferers and controls, and correlating them with tinnitus symptoms. This study reflected specific changes in the EEG microstates of tinnitus patients across multiple resting states, as well as inconsistent correlations with tinnitus symptoms. Microstate parameters were significantly different when patients were in OE and CE states. Specifically, the occurrence of Microstate A and the transition probabilities (TP) from other Microstates to A increased significantly, particularly in the CE state (32-37%, $p \leq 0.05$); and both correlated positively with the tinnitus intensity. Nevertheless, under the OECEm state, increases were mainly observed in the duration, coverage, and occurrence of Microstate B (15-47%, $p < 0.05$), which negatively correlated with intensity ($R < -0.513$, $p < 0.05$). Additionally, TPx between Microstates C and D were significantly reduced and positively correlated with HDAS levels ($R > 0.548$, $p < 0.05$). Furthermore, parameters of Microstate D also correlated with THI grades ($R < -0.576$, $p < 0.05$). The findings of this study could offer compelling evidence for central neural reorganization associated with chronic tinnitus. EEG microstate parameters that correlate with tinnitus symptoms could serve as neurophysiological markers, contributing to future research on the objective assessment of tinnitus.**

***Index Terms*— Chronic tinnitus, EEG microstates, objective assessment, various resting states, abnormal central neural activity.**

I. Introduction

THE auditory system is a complex network of structures responsible for perceiving sound stimuli and processing auditory information, enabling human beings to hear and interpret a wide range of sounds. There are several physiological structures that consists of the auditory system, namely the outer ear, middle ear, inner ear, auditory nerve, brainstem, and auditory cortex. However, when the functions of the auditory system are disrupted, several diseases and symptoms can occur, among which tinnitus is one of the most common. Tinnitus refers to the perceived sound without any external sound stimuli, and has become the first of the three major problems (tinnitus, deafness, vertigo) in otology, and is a global health problem that cannot be ignored [1]. According to epidemiological data, subjective tinnitus is more common, especially chronic tinnitus (with a course longer than three months), has a prevalence rate of about 11.9-30.3% globally [2], [3], [4]. The proportion of patients with severe tinnitus is constantly increasing and the trend towards youthfulness is obvious. Chronic tinnitus patients can be accompanied by depression, anxiety, irritability, sleep disorders, etc. Some patients may even have suicidal tendencies, which seriously affect their lives, work, and learning [5], [6]. However, due to the diversified and complex etiology of tinnitus, the current clinical treatment effect is limited [7]. Therefore, there is an urgent need to explore efficient treatments to improve tinnitus rehabilitation in clinical practice.

An auditory-somatosensory bimodal stimulation method was proposed by Shore and Wu and verified the performance through animal experiments [8]. The results showed that the proposed method could facilitate the reconstruction of the brain function, and therefore improve the rehabilitation

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of chronic tinnitus [9]. Later, the auditory-somatosensory bimodal stimulation method was applied to human subjects, and the results were promising [10], [11]. The introduction of this technique opens new avenues for the treatment of tinnitus. However, the lack of an objective evaluation method for tinnitus hampers the further development of the auditory-somatosensory bimodal stimulation technique, as it requires precise identification of the stimulation position and the physiological structures related to tinnitus [12], [13]. The commonly used evaluation methods for tinnitus are functional magnetic resonance imaging (fMRI), electroencephalograph (EEG), and functional near-infrared spectroscopy (fNIRS), within those, EEG draws a lot of attention due to its high time resolution and non-invasive [14], [15], [16], [17].

Recent studies have indicated that subjective tinnitus may be related to abnormal firing of central neurons. EEG microstate analysis, as a novel analysis method and capable of representing the spatiotemporal activity of the brain, focuses on brain activity in a short time frame. Their high temporal resolution enables a rapid understanding of how the brain processes information and forms connections, crucial for comprehending cognition and behavior [18], [19]. They have gradually proven valuable in diagnosing and evaluating tinnitus caused by various diseases affecting the auditory system [20]. Cai et al. applied 128-channel EEG on tinnitus subjects and found their transitions between Microstate D to B were reduced when compared to the control group [21]. Further, they studied on idiopathic sudden sensorineural hearing loss (SSNHL) patients with tinnitus. The results showed that SSNHL with tinnitus patients were with reduced amplitude, coverage, mean duration, and occurrence of Microstate A while Microstate B was increased [22]. Furthermore, Sven et al. investigated the EEG microstate in patients with tinnitus and chronic pain. Tinnitus patients' Microstate C mainly involved the left anterior temporal gyrus, with the activities of δ-band and γ-band dominated, while those of healthy subjects mainly involved the central posterior cingulate cortex and insula. It was believed that the left middle temporal gyrus affected tinnitus by affecting sound detection and suppression [23]. Cao et al. studied on the EEG microstate of subjective tinnitus patients in resting state and found that the duration time of Microstates A, C, and D had statistical differences when compared to healthy subjects. Also, EEG microstates A and D were linearly related to the visual analogue scale of tinnitus patients [24]. Zhang et al. studied on the patients with vestibular schwannoma (VS) and tinnitus. They found that compared to the patients with VS and no tinnitus, the EEG microstate C of the patients with VS and tinnitus showed an increment of frequency, and the score of tinnitus handicap inventory (THI) was negatively correlated with the duration of Microstate A and positively correlated with the frequency of Microstate C [25]. De Ridder and Vanneste suggested that the pain and tinnitus patients were in a specific Microstate for half of the time [26], [27]. Therefore, it has been proved that EEG microstates could potentially serve as meaningful indices for evaluating tinnitus. However, to our knowledge, very few studies have utilized EEG microstate parameters to analyze the central neural causes of subjective tinnitus, particularly in cases where the root cause cannot be definitively diagnosed. Although these limited studies suggest that EEG microstate parameters may have value in diagnosing subjective tinnitus, the existing evidence is still insufficient. Additionally, subjective tinnitus symptoms are influenced by patients' physical and mental health, and environment, causing rapid and complex neural changes [28]. Moreover, the unique complexity and individual variability of tinnitus present challenges for its neural study and objective diagnosis.

In order to comprehensively analyze EEG microstate parameters in individuals with subjective tinnitus compared to a control group, this study incorporated different observation conditions that accounted for the potential influence of varying neural activities. These conditions included common resting states, namely opening-eyes (OE), closing-eyes (CE), and the transition from opening-eyes to closing-eyes (OECEm). Recent studies have shown significant differences in brain network activities between OE and CE resting states [29], [30]. These variations under each condition provides a novel approach to detect sensory-related brain abnormalities, contributing to the quantitative monitoring of neurological disorders [31], [32]. Additionally, research has identified complex interactions between brain sensory systems, such as vision and hearing, even though the full details of these interactions remain unclear [33]. Variations in ocular states have been found to influence auditory perception and sensitivity, leading to different brain neural activities [34], [35]. Building on these previous findings, it can be hypothesized that analyzing EEG microstates in tinnitus patients across different ocular states could offer deeper insights into their resting-state brain activities. Furthermore, some investigations into the mechanisms of tinnitus have revealed that its onset and development involve a dynamic process, characterized by abnormalities in local neural activity and dysfunctional connections within multifunctional brain networks [36]. Moreover, it has been suggested that the occurrence of chronic subjective tinnitus could be associated with integrative changes throughout the cerebral cortes [37]. Considering these findings, a detailed analysis of EEG microstates in tinnitus patients under different ocular conditions may reveal unique brain activity patterns, thereby deepening our understanding of the associated neurological changes. Such studies, however, are currently rare. Our preliminary experiments found that subjective perception of tinnitus patients can change with shift in attention, psychological stress, and relaxation levels. Closing eyes, which reduces visual stimuli, might influence tinnitus perception by altering the information integration processing of external inputs to internal auditory systems in brains. Besides, the transition between OE and CE could also influence the perception of tinnitus via inducing changes in cognitive and neurophysiological states. Therefore, we hypothesized that identifying unique EEG microstate patterns in tinnitus patients under different eye conditions could discover crucial objective biomarkers for diagnosing and understanding the neurophysiological mechanisms of subjective tinnitus.

Given the variability in treatment effectiveness for subjective tinnitus due to individual differences, analyzing EEG microstates associated with tinnitus under various eye states, including OE, CE, and OECEm, might contribute to finding

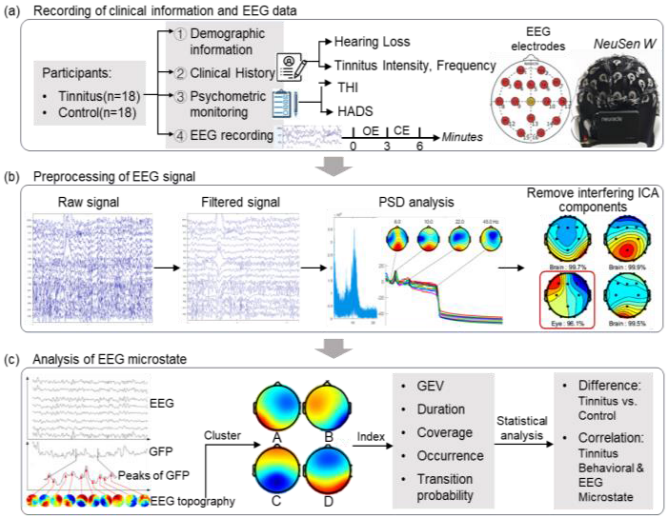

Fig. 1. The overall experimental process.

objective and individualized physiological markers. In addition to comparing parameter differences between the tinnitus and control groups under various experimental conditions, this study also conducted a between-state comparison of EEG microstate parameters for both groups of participants. The aim was to investigate the potential specific changes more precisely in the neural networks of patients with chronic subjective tinnitus. Furthermore, the subjective characteristics of tinnitus in patients, including tinnitus frequency and intensity as well as the HADS and THI scores, were also executed to a correlational analysis with EEG microstate parameters under different resting states. Subsequently, the potential association between the significant differences in EEG microstate activities in tinnitus relative to controls and the anticipated changes in neural network activities was discussed to explore potential specific reorganization in neural networks of tinnitus patients. Finally, a comprehensive discussion of the different results in the EEG microstate parameters and the correlation results between these parameters and subjective tinnitus characteristics was carried out, to achieve the purpose of finding neurophysiological markers and methods for the objective characterization of chronic subjective tinnitus.

II. Materials and Methods

A. Participants

The process for the acquisition of participants' clinical information was shown in Fig. 1(a). This study involved a total of 36 participants: 18 were chronic subjective tinnitus with normal audition, and 18 were healthy volunteers, categorized respectively into the *tinnitus group* and the *control group*. The dataset for the entire tinnitus group and 14 of the healthy volunteers (8 males and 6 females, with ages between 22 and 70 years old) in the *control group* were sourced from datasets previously published in *www.nature.com/scientificdata.* The database was available at *https://doi.org/10.17632/kj443jc4yc.1*. Participants with tinnitus (8 males and 10 females, aged 37 to 80 years) were recruited from the National Institute of Rehabilitation (NIR) in Mexico City, all of them have no clinical history of otitis, cerebellopontine angle tumors, psychiatrist pathologies, demyelinating diseases of the nervous system or epilepsy. In addition, the NIR provided the audiology evaluation of all the tinnitus (as shown in TABLE I), including audiometry (hearing loss, HL), tinnitus characteristics (laterality, frequency, and intensity), psychometric-based on tinnitus handicapped inventory (THI) and hospital anxiety and depression scale (HADS), as well as electroencephalographic (EEG) information [38]. This experimental procedure was formerly approved by the Ethical Committee (The registration trial number was ISRCTN14553550) [39]. The data for the remaining 4 healthy subjects (one male and three females, with ages from 24 to 26 years old) were collected from the Department of Otolaryngology at Peking University Shenzhen Hospital. All of them were informed about the protocol and signed a consent form. They were additionally informed that their head physician was also checking up on the procedure. The experimental procedure was formerly approved by the hospital ethical committee with the ethical review approval number of PKU Shenzhen Hospital Ethics Committee (Research) [2022] No. (060).

TABLE I
The Information of Audiology Evaluation of Tinnitus Involved in This Study

Patient	Gender	Tinnitus			HL-D	HL-I	Scales for THI and HADS		
		Laterality	Frequency (Hz)	Intensity (dB)			HADS-D	HADS-A	THI
Sub1	F	L	6000	30	11	16	1	1	3
Sub2	F	L	8000	50	22	26	1	1	3
Sub3	M	L	10000	50	11	18	1	1	2
Sub4	M	L	1500	15	6	8	2	1	2
Sub5	F	R	8000	15	18	21	1	1	2
Sub6	F	L	11200	90	8	12	1	1	3
Sub7	F	R	2000	35	18	16	1	1	2
Sub8	M	R	8000	20	41	46	1	1	3
Sub9	F	R	6000	10	15	16	1	1	3
Sub10	M	R	4000	10	20	19	3	2	2
Sub11	M	L	6000	50	14	15	1	2	2
Sub12	F	R	8000	15	11	15	1	1	2
Sub13	F	R	12500	50	26	18	1	2	2
Sub14	F	B	4000	25	25	34	1	1	4
Sub15	F	L	10000	45	15	15	-	-	-
Sub16	M	L	3000	40	25	24	-	-	-
Sub17	M	B	6000	35	13	12	1	2	2
Sub18	M	R	6000	80	59	16	1	1	3

B. EEG Recording

EEG signals at sixteen channels were recorded from all participants while they were at rest in both opening-eyes (OE) and closing-eyes (CE). During this procedure, each participant was asked to sit in a comfortable chair in a quiet room. They were instructed to keep their eyes open and focus on a fixed white wall continuously for three minutes, followed by closing their eyes for another three minutes. The positions of the

sixteen EEG channels conformed to the 10/20 international system. The Cz channel served as the reference, and the left earlobe channel aced as the ground, as shown in Fig. 1(a).

In [38], for each of eighteen tinnitus and fourteen healthy subjects, the EEG signal was recorded at a sampling frequency of 256 Hz by using a high-performance and high-accuracy biosignal *USBamp amplifier*. EEG electrodes were connected to the amplifier via the *GAMMAbox*. The *USBamp* was connected to the computer via *OpenViBE* platform, which was used to measure electrode impedance ($\leq$5kΩ should be accepted) before each recording. Besides, the *OpenViBE* was also configured to digitally filter EEG signals by an 8th-order band-pass filter with cut-off frequencies between 0.1-100Hz and a 4th-order notch filter of 60 Hz. Then the EEG files were provided in GDF formats in the scientific database. Furthermore, EEG signals for the other four healthy subjects were collected with a sampling frequency of 1000Hz by using the wireless EEG collection system *NeuSen W* (*Neuracle. Co., Ltd, Changzhou, China*), as shown in Fig. 1(a).

C. EEG Data Preprocess

Preprocessing is critical in EEG data analysis, significantly impacting the quality of subsequent analysis and interpretation. In this study, all EEG data were read and prepared using the EEGLAB 2023 toolbox in MATLAB 2021b software. The preprocessing steps are detailed in Fig. 1(b).

1) An FIR band-pass filter, with a passband frequency range of 1 to 45Hz, was designed to eliminate low-frequency interferences, including motion and baseline drift, as well as high-frequency noises, such as electromyographic interference. Additionally, for the EEG data collected in this experiment using *NeuSen W* system, it was necessary to be down-sampled to 256Hz before performing filtering, then a notch filter was designed to eliminate the 50Hz noise introduced by the electrical line. Furthermore, frequency and power spectral density (PSD) plots for each channel were generated and observed, then frequencies with abnormally high energy were eliminated by a designed precise FIR filter.
2) Afterward, data segments with poor quality were removed, and damaged data channels were repaired by an interpolation method. Subsequently, the whole-brain average method was used to reference the modified data. The filtered data was saved separately according to three different rest states of opening-eyes, closing-eyes, and the mixed condition of opening-eyes and closing-eyes. Therefore, three datasets of EEG data under different nuanced states were saved and labeled as OE, CE, and OECEm, respectively.
3) To further reduce the impact of the volume conduction effect in signals from the scalp, an independent component analysis (ICA) algorithm was used to calculate independent components for each dataset. The ICLabel plugin in EEGLAB was then employed to cluster each component, followed by calculating the probability of each component belonging to EEG, EOG (eye movement), EMG (muscle), ECG (heart), and line noise categories. Components with a probability of more than 90% belonging to categories other than EEG were considered as interference components and removed. Finally, the preprocessed data was reconstructed and ready for the subsequent microstate analysis.

D. EEG Microstates Analysis

This study analyzed four classic EEG microstates (A, B, C, and D) and their metrics using the Microstate 1.0 plugin of EEGLAB, the analysis process was indicated in Fig. 1(c).

1) First, the preprocessed data was passed through a band-pass filter with a frequency range from 2 to 20Hz to extract the frequency band required for EEG microstate analysis.
2) Second, the global field power (GFP) of the EEG signal at a certain moment was calculated based on the potential value of each electrode channel of each subject. Since the brain topographic map at the time of the GFP maximum value has the largest signal-to-noise ratio, the time series (with 1000 random points for each subject) of the GFP maximum value was further extracted.
3) Third, an improved K-means clustering algorithm, named '*Modkmean*', was used to obtain the '*microstate model*'. Four brain topographic maps from the GFP maximum time series were randomly selected as the '*initial cluster center*'. It was then compared with the rest topographic maps, and the one map that was most similar to it was marked, from which a '*new cluster center*' was calculated. This step was repeated a hundred times until the percentage of EEG signals represented by the cluster centers no longer improved, the four cluster centers obtained at that time were the '*microstates model*' for one subject. Finally, the EEG microstates A, B, C, and D were calculated according to the '*microstates model*' of all subjects in the group.

The analysis of EEG microstate time series could be useful for understanding rich neurophysiological information. In general, EEG microstate indexes about describing brain state changes mainly include the global explained variance (*GEV/%*, the percentage of total EEG signals that a given microstate can represent), mean duration (*ms*, the average length of time for a given microstate to appear and remain stable in), coverage (%, it refers to the ratio of the duration of a given microstate to the total duration of the microstate), frequency (*Time/s*, it is the average number of occurrences per second during which a microstate appears and remains stable), and transition probability (TP/%, it is transition probability from one microstate to any other microstate).

E. Statistical Analysis

To explore nervous system abnormalities associated with chronic tinnitus, this study analyzed statistical differences in brain activity across three resting states (OE, CE, and OECEm) between individuals with tinnitus and healthy controls, with the SPSS 27.0 software. On the other hand, an objective assessment method for chronic tinnitus was researched in the MATLAB 2021 software by the statistical correlation analysis

between the neural activity and the symptoms (including tinnitus laterality, intensity, and frequency, as well as subjective scales liked THI, HADS) of tinnitus at three rest states. Among them, the HADS scale included HADS-A and HADS-D, which were used to measure the degree of attention and depression respectively, as shown in TABLE I. The statistical analysis process also was shown in Fig. 1(c).

In the statistical differences analysis, at each rest state, the average and standard deviation values of each EEG microstate index were calculated in turn. In addition, the normality test was carried out on the average value series of each index. Then the mean difference between tinnitus and control groups was analyzed using a two-tailed independent sample t-test (in the case where samples from both groups were normally distributed) or the *Kruskal-Wallis* test (*KW*-test). Furthermore, the differences between OE and CE states of tinnitus and control groups were respectively calculated and compared. Furthermore, the relative difference between the two samples under the target EEG microstate parameter was computed by using equation (1). In where, *Sample1* and *Sample2* respectively represented the tinnitus and control groups, or the CE and OE states. $Index_m$ denoted the mth target parameter among the twenty-five microstate parameters, including GEV, durations of A-D microstates, coverage, occurrence, and TP between any two EEG microstates. $Diff\_Index_m$ represented the ratio of changes in *Sample1* relative to *Sample2* in terms of the parameter of $Index_m$.

$$Diff\_Index_m = \frac{Index_m Sample1 - Index_m Sample}{2 Index_m Sample2}, \quad m = 1, 2, 3, \ldots n, n = 25 \tag{1}$$

In addition, the Pearson and Spearman coefficients were used to calculate the correlation coefficient and p-value matrix between each EEG microstate index and each subjective tinnitus score in the tinnitus group.

III. Results

A. Topological Maps of EEG Microstates

After preprocessing and quality screening of the data, EEG data from 18 patients in the *tinnitus group* and 15 participants in the *control group* were ultimately selected for EEG microstate analysis. Fig. 2 shows the average microstate topographies within each of the two groups obtained when participants were in three rest states of OE, CE, and OECEm respectively. Similar to previous studies (Cai et al., [21]), four typical Microstate maps were found and clustered into microstates A, B, C, and D.

B. Average Value Differences of Microstate Indicators

The average and standard deviation values as well as the two-tailed independent sample t-tests and *KW*-tests for EEG microstate parameters, such as the GEV, duration, coverage, and occurrence, between the tinnitus and control groups were given in TABLE II. It can be seen from TABLE II that the average values of occurrence for Microstate A in tinnitus and control groups were significantly different in rest states of OE

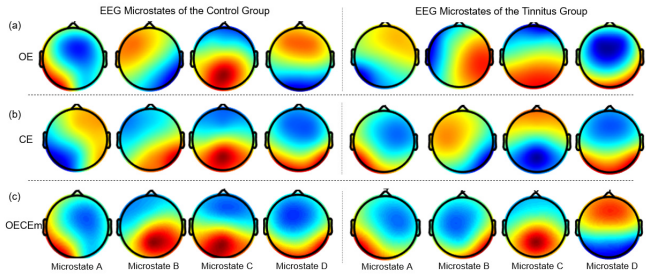

Fig. 2. Topological maps of clustering microstates in rest states of OE, CE, and OECEm for tinnitus and control groups.

TABLE II
THE MEAN ± STANDARD DEVIATION VALUES OF MICROSTATE PARAMETERS (GEV, DURATION, COVERAGE, AND OCCURRENCE) FOR THE TINNITUS AND CONTROL GROUPS

	Mean ± SD					
	OE		CE		OECEm	
	Control	Tinnitus	Control	Tinnitus	Control	Tinnitus
GEV	0.644±0.082	0.637±0.067	0.687±0.073	0.701±0.082	0.719±0.053	0.741±0.045
Microstate Duration (ms)						
A	60.56±14.96	67.34±13.15	65.91±18.34	70.60±15.49	62.19±23.67	72.05±19.36
B	64.18±9.28	62.49±12.44	67.03±17.91	65.39±6.333	61.29±11.36	70.58±7.89*
C	73.13±17.45	71.84±22.77	88.47±20.58	75.34±17.56	84.24±25.22	66.42±7.94*
D	71.77±15.98	71.66±13.56	76.29±20.53	76.21±18.71	73.83±16.22	74.08±14.71
Microstate Coverage (%)						
A	0.189±0.131	0.242±0.099	0.187±0.142	0.255±0.112	0.182±0.176	0.261±0.115*
B	0.232±0.092	0.204±0.112	0.207±0.096	0.216±0.063	0.180±0.098	0.266±0.073*
C	0.299±0.134	0.260±0.151	0.334±0.105	0.273±0.098	0.349±0.154	0.225±0.062*
D	0.280±0.130	0.293±0.111	0.272±0.123	0.255±0.086	0.289±0.135	0.248±0.074
Microstate Occurrence (Times/s)						
A	2.854±1.443	3.475±0.801**	2.613±1.177	3.506±0.849*	2.458±1.580	3.510±0.728
B	3.513±0.922	3.067±1.203	2.986±0.795	3.276±0.729	2.735±1.298	3.708±0.729*
C	3.903±0.980	3.408±0.934	3.736±0.696	3.553±0.564	4.004±0.680	3.340±0.549
D	3.693±1.111	3.941±0.940	3.424±0.968	3.296±0.564	3.668±1.383	3.305±0.520

** and ** indicated the t-tests (or KW-tests) were significant ($p < 0.05$, $p < 0.01$, respectively).*

(p <0.01) and CE (p <0.05). In addition, for the OECEm state, the significant difference (p <0.05) in the average values of parameters between the two groups was reflected in the three Microstates A (coverage), B (duration, coverage, and occurrence), and C (duration and coverage).

The specific values of difference ratios for each EEG microstate index between the two groups have been calculated by using equation (1) and listed in TABLE III, where the positive value indicates the increased ratio of this parameter in the tinnitus group relative to that in the control group. The table shows that under all three resting conditions, the duration and coverage of EEG microstate A in the tinnitus group are both extended and increased, respectively, compared to the control group, and the occurrence is higher (significantly so in the OE and CE states, with p-values of 0.007 and 0.017). In contrast, the results for Microstate C are opposite to those of A; that is, all parameters for the *tinnitus group* are

TABLE III
THE AVERAGE VALUE DIFFERENCES OF MICROSTATE PARAMETERS BETWEEN THE TINNITUS AND CONTROL GROUPS (*Diff_Tinnitus Vs. Control*) UNDER ALL CONDITIONS

	Index Diff _ Tinnitus Vs. Control		
	OE	CE	OECEm
GEV	-0.01	0.02	0.03
Duration (ms)			
Microstate A	0.11	0.07	0.16
Microstate B	-0.03	-0.02	0.15*
Microstate C	-0.02	-0.15	-0.21*
Microstate D	0.00	0.00	0.00
Coverage (%)			
Microstate A	0.28	0.36	0.43*
Microstate B	-0.12	0.05	0.47*
Microstate C	-0.13	-0.18	-0.35*
Microstate D	0.05	-0.06	-0.14
Occurrence (Times/s)			
Microstate A	0.22**	0.34*	0.43
Microstate B	-0.13	0.10	0.36*
Microstate C	-0.13	-0.05	-0.17
Microstate D	0.07	-0.04	-0.10

** and ** indicated the t-tests (or KW-tests) were significant (p < 0.05, p < 0.01, respectively).*

TABLE IV
THE AVERAGE VALUE DIFFERENCES OF MICROSTATE PARAMETERS OBTAINED UNDER OE AND CE CONDITIONS (*Diff_OE Vs. CE*), FOR THE TINNITUS AND CONTROL GROUPS RESPECTIVELY

	Index Diff _ OE Vs. CE	
	Tinnitus	Control
GEV	-0.09**	-0.06
Duration (ms)		
Microstate A	-0.05	-0.08
Microstate B	-0.04*	-0.04
Microstate C	-0.05	-0.17*
Microstate D	-0.06	-0.06
Coverage (%)		
Microstate A	-0.05	0.01
Microstate B	-0.05*	0.12
Microstate C	-0.05	-0.11
Microstate D	0.15	0.03
Occurrence (Times/s)		
Microstate A	-0.01	0.09
Microstate B	-0.06*	0.18
Microstate C	-0.04	0.04
Microstate D	0.20**	0.08

** and ** indicated the t-tests (or KW-tests) were significant (p < 0.05, p < 0.01, respectively).*

reduced relative to the *control group*, and these differences are statistically significant under the OECEm condition. However, the results for EEG microstate B are inconsistent across the OE, CE, and OECEm conditions. Specifically, in the CE and OECEm conditions, the parameter values for Microstate B in the *tinnitus group* are greater than those in the *control group* and are statistically significant in the OECEm condition. In contrast, they are opposite and not statistically significant in the OE condition.

TABLE IV shows the average value differences between the EEG microstate parameters under OE and CE conditions, for the tinnitus and control group respectively. Where the positive value indicates the increased ratio of this parameter under the OE state relative to that under the CE state. From the table, for the control group, there is no significant difference in the parameters obtained under the OE and CE states, except that the duration of EEG microstate C under OE state is shorter than that under the CE state. Nevertheless, for the *tinnitus group*, the values of GEV (p <0.01) as well as all the parameter values for EEG microstate B (p <0.05), which were calculated under the OE condition, are significantly lower compared to those calculated under the CE condition. Conversely, the occurrence value of EEG microstate D under the OE state is significantly higher than its value under the CE state (p <0.01).

C. Differences of TP Among EEG Microstates

Fig. 3 shows the difference ratios in the transaction probabilities (TP) between the four EEG microstates A, B, C, and D in the *tinnitus group* relative to the *control group*. In this figure, arrows represent the transition direction between two

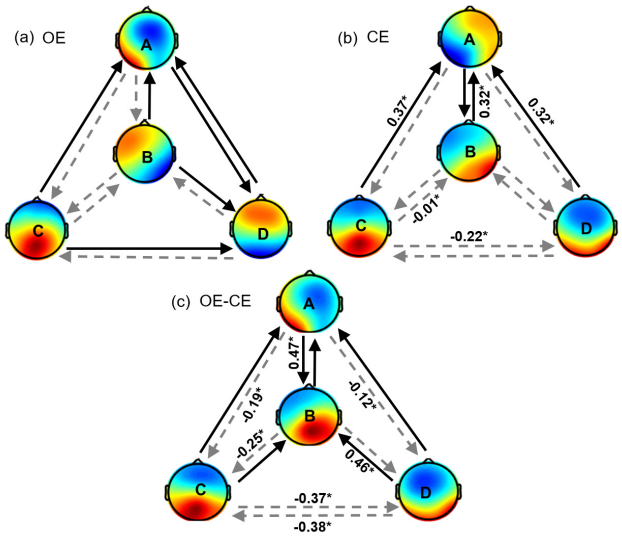

Fig. 3. The differences in TP maps for EEG microstates (A-D) between tinnitus and control groups, under three resting states: (a) OE, (b) CE, and (c) OECEm. The direction of the arrow is the state transition direction. Black solid lines indicate '+', which means that the TP in the tinnitus group is higher compared to the control group; gray dashed lines indicate '-', which means the conversion rate is lower.

microstates and identify signs of difference ratios ('+' or '-'). In addition, the significant difference ratios in TP between the two groups are marked in the figure, black solid arrows indicate that the TP in the tinnitus group is higher compared to the control group, and gray dashed arrows mean the conversion rate is lower than the control group. It can be seen from the figure that the TP of three EEG microstates B, C, and D to microstate A in the tinnitus group all increase, while the mutual conversion rate between EEG microstates C and D decreases, especially under the CE and OECEm conditions, the difference is greater and significant.

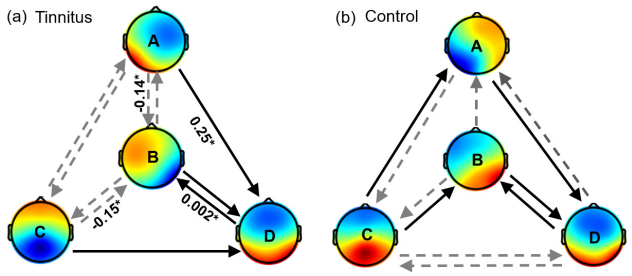

Fig. 4. The TP differences of EEG microstates (A-D) between OE and CE conditions, for (a) tinnitus group and (b) control group. The direction of the arrow is the state transition direction. Black solid lines indicate '+', which means that the TP obtained in the OE state is higher compared to that obtained in the CE state; gray dashed lines indicate '-', which means the conversion rate in OE state is lower than that in CE state.

Fig. 4 shows the difference ratios in the TP between the four EEG microstates A to D obtained under the OE condition compared with those obtained under the CE condition, for both the tinnitus and control group. Similar to Fig. 3, difference ratio values with statistically significant in TP between OE and CE states are marked in Fig. 4. It can be seen from the figure that the transition rate between each EEG microstate of the *control group* has no significant difference in conditions of OE and CE. But apparently different from the *control group*, there are significant differences between TPs of different EEG microstates obtained in the *tinnitus group* under OE and CE conditions. For the *tinnitus group*, compared with the CE state, the TP from EEG microstates A and C to the Microstate B was significantly reduced (with difference ratios of -14% and -15%, p <0.05) under the OE state, while the TP from microstate D to C is slightly increased (with the difference ratio of 0.2%, p <0.05). Besides, there is a significant increase (with the difference ratio of 25%, p <0.05) in the TP of EEG microstate A to D calculated under the OE condition relative to that obtained in the CE condition.

D. Correlation Between Tinnitus and EEG Microstates

Fig. 5 demonstrates the Pearson correlation coefficient matrixes between the tinnitus frequency/intensity and all parameters of EEG microstates, which are calculated under the CE and OECEm conditions for 18 tinnitus. In this figure, the more yellow the grid is, the more it indicates a strong positive correlation, while the blue indicates a negative correlation relationship. Factors with significant positive and negative correlations are marked with red and white circles, respectively. It can be concluded from this figure that tinnitus intensity shows a significant positive correlation with the duration of EEG microstate A (R=0.529, p = 0.024) and the TP from Microstate C to A (R=0.533, p = 0.023), while it shows a strongly significant negative correlation with the occurrence of Microstate D (R=-0.68, p = 0.002) and the TP from Microstate B to D (R=-0.596, p = 0.036), under the CE condition. In the case of OECEm, in addition to arriving the same conclusion as in the CE state, the intensity of tinnitus is also significantly negatively correlated with the duration (R=-0.534, p = 0.033), coverage (R=-0.527, p = 0.035), occurrence (R=-0.513, p = 0.042) of state B, occurrence of state D (R=-0.59, p = 0.016), and the TP from Microstate D to B (R=-0.649, p = 0.007). It shows a significant positive correlation with the TP between Microstates A and C (R=0.597, p = 0.015). Furthermore, the frequency of tinnitus has a significant negative correlation with the duration and coverage of Microstate D (R=-0.506, p = 0.046, and R=-0.576, p = 0.019), as well as the TP from Microstate C to D (R=-0.554, p = 0.026) under the OECEm condition. While it shows a positive correlation with the coverage of Microstate A (R=0.514, p = 0.042) and the TP from Microstate B and C to A (R=0.498, p = 0.049, and R=0.51, p = 0.044).

Fig. 6 shows the Spearman correlation coefficient matrixes between the HADS/THI scores for 16 tinnitus (in TABLE I) and all parameters of EEG microstates, which are calculated under the OECEm condition. The green grid represents a positive correlation, while the blue indicates a negative correlation relationship. The results shown in the figure suggest that there is a positive correlation between the score of psychological depression (HADS-D) of tinnitus patients and the coverage of Microstate D (R=0.602, p = 0.023) and the mutual TP between Microstates D and C (R=0.602, p = 0.023, and R=0.548, p = 0.042). Conversely, the tinnitus handicap inventory (THI) level in tinnitus patients shows a negative correlation with the duration (R=-0.653, p = 0.011), coverage (R=-0.623, p = 0.017) and occurrence (R=-0.576, p = 0.031) of EEG microstate D, as well as with the TP from Microstate B to D (R=-0.64, p = 0.014).

IV. Discussion

Tinnitus, especially chronic subjective tinnitus, is a common problem. However, as of the time of writing this article, the latest global Clinical Practice Guideline for the diagnosis and treatment of Chronic Tinnitus still do not offer a definitively effective treatment approach. Current recommendations primarily focus on relieving the psychological stress caused by tinnitus, but with limited success [1]. This is mainly because the causes of tinnitus are diverse and vary among patients, making its pathogenesis still unclear. At the same time, there is a lack of objective criteria for assessment. As scientific research progresses, the theory of 'centralization of tinnitus' has been proposed and is gradually gaining increasing attention from scholars. Through neurophysiological examinations on animals exhibiting behavioral characteristics of tinnitus, researchers have found that specific changes related to tinnitus do indeed occur in the brains of these animals. Majority of current animal research assumes that the onset of chronic subjective tinnitus is related to the synchronization and spontaneous firing of neurons in the auditory system. Therefore, by analyzing central neural activity, we may be able to delve deeper into understanding the mechanisms underlying the development of tinnitus [8]. In human research, techniques such as functional magnetic resonance imaging (fMRI) and electroencephalography (EEG) are commonly employed to analyze the neural activity of the brain in patients. EEG can provide real-time reflections of neural oscillations and has a relatively low cost in signal acquisition and system

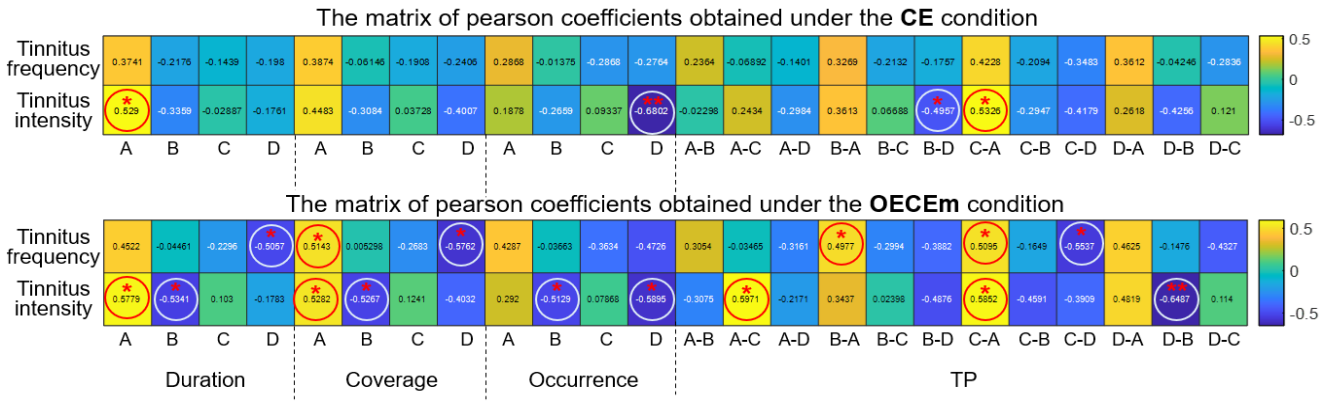

Fig. 5. The matrixes of the Pearson correlation coefficient between tinnitus frequency/intensity and EEG microstate parameters for the tinnitus group, under the CE and OECEm conditions. The red and white circles represent positive and negative correlations respectively. Besides, * and ** indicated the Pearson correlation was significant ($p < 0.05$, $p < 0.01$, respectively).

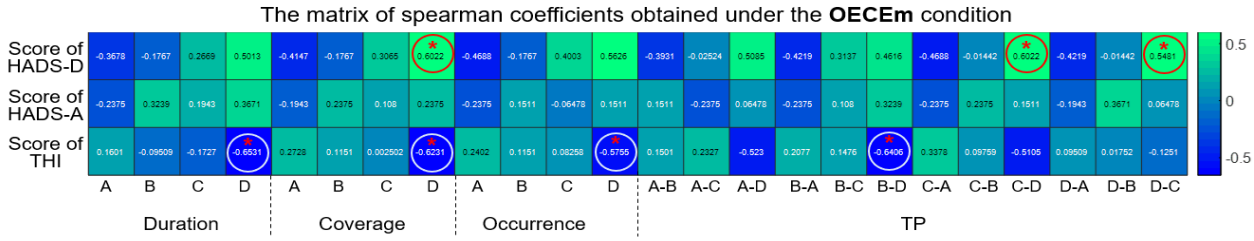

Fig. 6. The matrixes of Spearman correlation coefficient between tinnitus HADS/THI scores and EEG microstate parameters for the tinnitus group, under the OECEm conditions. The red and white circles represent positive and negative correlations respectively. Besides, *indicated the Spearman correlation was significant ($p < 0.05$).

maintenance, has become the most common method for analyzing the mechanisms of tinnitus onset and treatment at the cortical level [17]. Some traditional static EEG features such as absolute and relative power, coherence, entropy, and event-related positive are often calculated to analyze abnormal activity of cortical neurons in patients. Recent studies have shown that through EEG microstate analysis, spontaneous brain electrical activity can be segmented at the microsecond level, thereby enabling fine analysis of cortical quasi-steady states. In particular, the four classical EEG microstates and their parameter characteristics could potentially be used to assess the dynamic activity performance of cortical neurons [40]. To our knowledge, Cai et al. calculated four classic EEG microstates from patients with chronic subjective tinnitus by collecting high-density EEG signals with 128 channels. For the first time, they discovered a correlation between the tinnitus intensity and the duration of EEG microstate C. Besides, they proposed the possibility of using EEG microstate parameters as an objective metric for evaluating tinnitus [21].

In this study, the four classical EEG microstates (as shown in Fig. 2) were also successfully obtained from the EEG signals of 18 chronic tinnitus patients using just 16 channels. These results are consistent with previous studies [21], [22], [24], [41], even though they typically required at least 64 channels. One significant reason for achieving reliable results from the limited 16-channel data could be the meticulous preprocessing we applied to the raw EEG data during the initial stages. This involved a thorough analysis of the spectral content for each channel and designing high-precision FIR filters in EEGLAB to accurately eliminate specific interference frequencies.

Furthermore, we conducted a deeper analysis of the neural aberrant discharge activity in chronic tinnitus patients through EEG microstate features. Considering the varying impact on the neuron activity by the complexity of tinnitus etiology and the subjectivity of tinnitus symptoms, we paid special attention to the EEG microstates of patients in different resting states, including OE, CE, and OECEm. Subsequently, we used the results from healthy participants as a *control group* to examine how the tinnitus-related EEG microstate features undergo abnormal changes under each of these states, as shown in Fig. 2. EEG microstates are generated by coordinated neural activity across brain regions, forming stable whole-brain patterns. Based on the framework proposed by Britz et al., EEG microstates may have specific associations with resting-state networks: Microstate A is related to auditory and semantic processing, Microstate B is linked to visual processing, Microstate C involves the salience network, responsible for information filtering and response, while Microstate D connects to the attention network [42]. Therefore, resting-state EEG microstates capture the rapid sequential activation and transitions between various neural networks. Specific metrics shed light on characteristics of these networks: the average duration of a microstate indicates neural stability; its frequency points to activation tendencies; and its coverage and GEV indicate its time relevance compared to other neural activities; moreover, transitions between

microstates generally reveal an orderly activation of neural components [20].

TABLE II presents the results of the average values and variances for four EEG microstate metrics (GEV, duration, coverage, and occurrence) in both the tinnitus and the control groups under three different resting states (OE, CE, and OECEm). It reveals a consistent ranking pattern in the parameter values of four EEG microstates four the control group under all three resting states. Specifically, Microstate C consistently had the longest duration, largest coverage, and highest occurrence frequency. In contrast, Microstate A had the lowest occurrence frequency, as well as the shortest duration and smallest coverage in OE and CE states. However, for the tinnitus group, this established ranking pattern has changed, potentially suggesting a reorganization of the connections between neurons in different brain regions for tinnitus patients. All parameter values for the EEG microstate A have risen, pushing it further down the rankings. Conversely, Microstate C has seen a reduction in all its parameter values, leading to its upward movement in the rankings. Especially under the OECEm condition, its duration and coverage values are the lowest among the four EEG microstates, this result is completely opposite to the control group and statistically significant (p<0.05). This conclusion is consistent with the data result obtained under the OE state in the previous study [22]. However, there were several inconsistent findings observed in the analysis of microstate parameters relative to the previous published illustrates. These differences may be attributed to variations in the study population, EEG signal analysis methods, and research aims. In our study, we focused on investigating the impact of visual stimuli on auditory transmission pathways, conducting comprehensive EEG microstate analyses under different eye conditions. We conducted multiple comparative analyses, including comparisons between tinnitus patients and healthy controls under three different eye conditions (OE, CE, and OECEm), as well as comparisons of EEG microstate parameters between OE and CE conditions for different groups. The aim was to achieve a more comprehensive analysis of the EEG microstate characteristics in tinnitus patients to identify specific physiological indicators of tinnitus.

The specific ratios of the changed EEG microstate parameters for the tinnitus group relative to the control group are also presented in TABLE III, along with their significance. In tinnitus patients compared to controls, the occurrence of Microstate A significantly increased by 22% (OE state, p<0.01) and 34% (CE state, p<0.05). Based on the topography results of four EEG microstates in Fig. 2, increased neural activity in the right frontal and left occipital lobes for Microstate A indicates heightened activity in these brain areas for tinnitus patients during rest. If the interpretation proposed by Britz et al. holds accurate, this implies enhanced auditory and language neural networks, evident through increased activation duration, coverage, and occurrence within each brain activity cycle. Meanwhile, the duration and coverage of Microstate C dropped significantly by 21% and 35% (OECEm state, p<0.05). Combining the topological map results in Fig. 2 and Britz's functional interpretation of brain areas for the EEG microstate C, it can be revealed that neural activity in the frontal and parieto-occipital regions of tinnitus patients are reduced compared to control groups. This may suggest a weakened capacity of centralized processing and responding to external environmental stimuli. Notably, some tinnitus patients do experience heightened auditory focus but diminished responsiveness to other environmental factors. While EEG microstate B in the tinnitus group has the lowest parameters among all under both OE and CE conditions, its occurrence and coverage still exceeded those in the control group (CE state). Besides, its duration, coverage, and occurrence are significantly 15%, 47%, and 36% higher than controls (OECEm state, p<0.05). These findings reflect that in tinnitus patients, compared to controls, the differences of neural activities in brain regions represented by EEG microstate B (upper left frontal and lower right occipital lobes) vary across three resting states (OE, CE, and OECEm). This variation might align with Britz's proposal that Microstate B signifies the activity of vision-related neural networks. Furthermore, the tinnitus group shows significant differences in the way visual-related processing networks handle information between the OE and CE resting states. In contrast, the control group does not exhibit such differences. The conclusion is supported by the results in TABLE IV, which demonstrate the difference rates between under OE and CE states in the duration, coverage, and occurrence of EEG microstate B for tinnitus patients: 4%, 5%, and 6% (p<0.05), respectively. This conclusion also suggests that the differences in parameters of Microstate B between OE and CE states could potentially serve as a stable indicator for the objective assessment of tinnitus. Moreover, significant differences between OE and CE states are also observed in the GEV values (9%, p<0.01) and the occurrence of Microstate D (20%, p<0.01). Similarly, these could also serve as objective indicators for distinguishing tinnitus patients. At the same time, Fig. 5 indicates that under the OECEm, the duration, coverage, and occurrence of EEG microstate B, as well as the occurrence of Microstate D in tinnitus patients, are negatively correlated with tinnitus intensity. Therefore, these could also be objective physiological indicators for assessing tinnitus intensity. In addition, Fig. 6 shows that parameters of EEG microstate D under the OECEm state have a significant negative correlation with THI levels in tinnitus patients, indicating their potential as objective measures.

Previous research indicates that the TP between different EEG microstates is not random. The sequence of transitions may reveal the temporal activation patterns of neurons within various networks, holding significant implications. Results from Fig. 3 illustrate the differences in the TP of the four EEG microstates between tinnitus patients and the control group across three distinct resting states of OE, CE and OECEm. Specifically, in all three resting states, we observed an increased probability of transitions from Microstates B, C, and D to A, with this increase being significant in the CE state (0.32, 0.37, and 0.32, p <0.05). Conversely, the TP from Microstates A, B, and D to C decreased and the result is significant in the OECEm state (-0.19, -0.25, and -0.37, p <0.05). These findings are consistent with our previous observations regarding the parameter changes in Microstates

A and C. They further confirm that neural network activity related to auditory and language processing is enhanced in tinnitus patients, while their capability to process external environmental information has declined. Furthermore, a positive correlation result between the TP of EEG microstates A and C with the frequency and loudness of tinnitus (under CE and OECEm states) was revealed in Fig. 5, as well as between the TP from Microstate B to A and the frequency of tinnitus (under the OECEm state). Additionally, under the OECEm condition, the TP between Microstates C and D was significantly reduced in the tinnitus group compared to the control group. Further analysis from Figs. 5 and 6 reveals that this TP is negatively correlated with the tinnitus frequency but shows a positive correlation with the psychological stress levels (HADS-D) in tinnitus patients. These findings indicate that the activity of attention-related neural networks is diminished in tinnitus patients. Furthermore, the interconnectivity and transitional dynamics between attention-related networks and the salience network exhibit reductions in tinnitus patients. These alterations in neurophysiological behavior could be related to the compromised emotional and psychological well-being frequently manifested in these individuals. Such characteristics may function as distinctive biomarkers and quantifiable metrics for differentiating individuals afflicted with tinnitus from those in control groups. Moreover, results from Fig. 3 indicate that TP differences between tinnitus and control groups are not consistently significant across all conditions. Notable differences mainly occur in the CE and OECEm states, whereas in the OE state, no significant discrepancy exists between the two groups. Therefore, the results for the difference ratio in the TPx of EEG microstates under OE and CE states are also presented in Fig. 4. In the tinnitus group, compared to the CE state, the TP from EEG microstates A and C to B significantly decreases under the OE state. Conversely, the TPx from Microstates A to D and D to B are significantly increased by 25% and 0.2%. By combining these results with the correlation analysis in Fig. 5, it is evident that in the CE state, TP from Microstate A to C in tinnitus patients positively correlates with tinnitus intensity, while TP from Microstate D to B negatively correlates (p <0.05). However, no significant correlations exist in the OE state. Therefore, these measures might be able to be used as neurophysiological indicators for assessing tinnitus intensity.

Nevertheless, there are still many limitations in this study. Due to the exceedingly complex neural mechanism of tinnitus, the results of this study merely offer a glimpse into the neural mechanisms underlying tinnitus. Additionally, no findings definitively pinpoint the specific neural changes in tinnitus patients. Furthermore, the neural activity of patients is influenced by multiple factors. Although we innovatively analyzed EEG microstate signals under different eye conditions in this study, it remains insufficient to cover the full impact of natural environmental stimuli on neural signals along the auditory transmission pathway. Hence, we need to consider more environmental factors and refine experimental paradigms accordingly in our future work. Moreover, we did not consider the effects of factors such as age, degree of hearing-loss, and affected laterality on tinnitus-related neural activity in patients, nor did we divide participants based on these factors. Previous studies have suggested possibly complex relationships between these clinical variables and tinnitus, yet these relationships have not been fully elucidated. Thus, we also need to recruit more participants and divide them based on their clinical information to control variables and analyze the neural signal characteristics corresponding to specific clinical manifestations of tinnitus. Besides, to identify specific neurophysiological markers related to tinnitus, the present study, we only focus on the pre-treatment evaluation but not the exploration of treatment strategies. Therefore, we should expand upon the results to conduct a more in-depth analysis of neural signals about therapies, in our future research. This may help us obtain neural activity characteristics to objectively evaluate treatment results, thereby providing better feedback and guidance for formulating clinical treatments.

Overall, this study focuses on the EEG microstate parameters of tinnitus sufferers in various resting states, comparing them with a control group. Results from this research could be extremely useful for gaining a deeper understanding of the physiological mechanisms behind tinnitus. Significant differences in microstate parameters between tinnitus and control groups were identified, which may indicate that tinnitus is associated with specific types of brain activity. This information could be useful for developing future diagnostic tools and treatment methods, as well as for providing a more precise description of tinnitus symptoms. Furthermore, these microstates are correlated with the subjective features of tinnitus. Although this correlation cannot be used to infer a causal relationship between tinnitus symptoms and neural abnormalities, it does indicate that Microstate parameters are related to tinnitus features. This will provide more information that could help with personalized treatments or more accurate predictions of symptom development.

V. Conclusion

In this study, EEG microstate parameters were analyzed under three resting states of OE, CE, and OECEm, to explore specific neural abnormalities and changes in the resting-state network for tinnitus patients. The results showed that tinnitus patients showed significant but inconsistent differences in EEG microstate parameters across various resting states when compared to the control group, hinting at unique neural activity changes under different conditions; For tinnitus sufferers, the differences were especially pronounced in EEG microstates B and D between resting states of OE and CE; Additionally, in the CE and OECEm states, certain EEG microstate parameters correlated significantly with the subjective characteristics of tinnitus and differed notably from controls, suggesting their potential as neurophysiological markers for objective assessment. What distinguishes this study from previous research is the comprehensive analysis across different resting states, revealing that the observed differences and correlations are not consistently uniform across these states. These findings not only strengthen the argument for using Microstate parameters as effective neurophysiological markers but also underscore significant variations in these markers between different resting states. The results of this study could provide valuable

insights for further research into the central neural mechanisms behind tinnitus and help in the development of more precise and effective assessment strategies.

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