Clinical and Electrophysiological Investigation of the Influence of Tempo in Music Therapy for Epilepsy

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Alan C. Evans and Paule-J Toussaint: Suggested corrections to the experiment design, provided guidance on statistical analysis, assisted in the interpretation of results, and helped with manuscript writing.

Jing Lu: Assisted in the experiment design, give suggestions on data calculation and helped with the interpretation of results.

The following co-authors, also made significant contributions to the manuscripts:Ying Liu: Assisted in the preprocessing of the EEG data. Xiaoting Hao and Huajuan Tang: Assisted in the data acquisition in hospital.

Abstract：

Background: Music listening is thought to be effective as alternative therapy in intractable epilepsy, but little is understood about the underlying biological mechanisms or which musical feature could be driving this therapeutic effect. This study explored whether tempo is an important component for driving the observed therapeutic effect of listening to music.

Methods: We used two widely cited classical compositions: Mozart's sonata K448 and Haydn's Symphony no. 94. We measured the effects of tempo in both music pieces on clinical and electroencephalographic parameters of 147 epilepsy patients who listened to the Mozart's music at original, slow, or accelerated speed and Haydn at original speed.

Results: Listening to Mozart's sonata at original speed reduced the number of interictal epileptic discharges. There was decreased beta power in the frontal, parietal, and occipital regions, suggesting increased auditory attention and reduced visual attention. Phase-amplitude coupling results showed significant decline in the parietal and occipital regions. These effects were not observed after patients listened to the slow or fast version of Mozart's sonata, or to Haydn's symphony at normal speed.

Conclusions: Our results suggest that Mozart's Sonata for two pianos may exert therapeutic effects by regulating attention when played at its original tempo, but not slower or faster. These findings may help guide the design and optimization of music therapy against epilepsy.

Résumé:

Contexte: L'écoute de musique est considérée comme une thérapie alternative efficace dans l'épilepsie intraitable, mais peu est compris sur les mécanismes biologiques sous-jacents ou sur les caractéristiques musicales qui pourraient entraîner cet effet thérapeutique. Cette étude a exploré si le tempo est un composant important pour entraîner l'effet thérapeutique observé de l'écoute de musique.

Méthodes: Nous avons utilisé deux compositions classiques largement citées : la sonate K448 de Mozart et la symphonie n° 94 de Haydn. Nous avons mesuré les effets du tempo dans les deux morceaux de musique sur les paramètres cliniques et électroencéphalographiques de 147 patients atteints d'épilepsie qui ont écouté la musique de Mozart à une vitesse originale, lente ou accélérée et celle de Haydn à vitesse normale.

Résultats: L'écoute de la sonate de Mozart à une vitesse originale a réduit le nombre de décharges épileptiques intericales. Il y a eu une diminution de la puissance bêta dans les régions frontale, pariétale et occipitale, suggérant une attention auditive accrue et une attention visuelle réduite. Les résultats de couplage phase-amplitude ont montré une diminution significative dans les régions pariétale et occipitale. Ces effets n'ont pas été observés lorsque les patients ont écouté la version lente ou rapide de la sonate de Mozart, ou la symphonie de Haydn à vitesse normale.

Conclusions: Nos résultats suggèrent que la sonate pour deux pianos de Mozart pourrait exercer des effets thérapeutiques en régulant l'attention lorsqu'elle est jouée à son tempo original, mais pas plus lentement ou plus rapidement. Ces résultats pourraient aider à guider la

conception et l'optimisation de la thérapie musicale contre l'épilepsie.

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Introduction

Epilepsy

Epilepsy is a chronic and common brain disorder characterized by uncertain seizure duration and recurrent episodes, caused by highly synchronized bursts of neuronal discharges in the brain. In 2014, the International League Against Epilepsy (ILAE) stated that the diagnosis of epilepsy should meet at least one of the following criteria (Fisher et al., 2014): 1) at least two unprovoked seizures occurring more than 24 hours apart; 2) one unprovoked seizure with a probability of recurrence within the next 10 years that is similar to the recurrence risk after two unprovoked seizures (at least 60%); or 3) epilepsy symptoms present. Epilepsy can be divided into three subtypes based on seizure origin: focal, generalized, and unknown. Focal seizures are characterized by flattening, fast discharges, bursts of spikes in localized areas, while generalized seizures feature synchronized spike and slow wave bursts in all leads. Existing research attributes epileptic seizures to several factors and some of the most studied are: 1) genetic influences (Pitkänen et al., 2016). Some types of epilepsy are hereditary within families. Certain genes may make individuals more sensitive to environmental conditions that trigger seizures. 2) Head trauma (Immonen et al., 2019). Head injuries resulting from traffic accidents or other traumatic events can lead to epilepsy. 3) Malformation of brain development (Hong et al., 2019; Thom, 2014). This includes focal cortical dysplasia(Hong et al., 2019; Lee et al., 2023), hippocampal sclerosis(Bernhardt et al., 2016; Bernhardt et al., 2019), periventricular heterotopia and polymicrogyria(Sisodiya,

2004), which can cause epilepsy. 4) Infections (Singhi & Neurology, 2011). Meningitis, HIV, viral encephalitis, and certain parasitic infections may cause cellular damage that leads to epilepsy. 5) Prenatal injury (Lilienfeld & Pasamanick, 1954). Babies are very sensitive to brain injury before birth, which can be caused by various factors such as maternal infection, malnutrition, or hypoxia. This type of brain injury can lead to epilepsy or cerebral palsy. 6) Developmental disorders (Symonds & McTague, 2020). Epilepsy may sometimes be associated with developmental disorders such as autism.

Epilepsy is one of the five major neurological diseases whose prevention and treatment have been prioritized by the World Health Organization, affecting approximately 50 million people worldwide and constituting a serious burden for affected individuals, their families, and society (Moshé et al., 2015) The symptoms of various types of seizures vary, with transient symptoms such as loss of consciousness or awareness, and impairment of motor, sensory functions. In addition, recurrent seizures also cause the impairment of cognition, including the working memory, attention and executive function, as epileptic seizures are caused by an imbalance between neural excitability and inhibition, and excessively excited neurons can disrupt neuronal networks, leading to neuronal death and consequent cognitive impairments (Fisher et al., 2005; Holmes, 2015; Iori et al., 2016). Moreover, epileptic seizures can also cause psychological stress, as individuals with epilepsy may face discrimination in their work or marital life (Verrotti et al., 2014). Research has shown that the incidence of anxiety, depression, and other mental illnesses is much higher in epileptic patients than in healthy individuals (Davies et al., 2003; Kwon & Park, 2014). Epileptic seizures can result in accidents and even life-threatening situations, as patients may fall,

drown, or be involved in traffic accidents during a seizure. If a seizure lasts for more than 5 minutes or if seizures occur frequently without full recovery of consciousness between them, there is an increased risk of permanent brain damage and death. Epilepsy accounts for over 0.5% of the global burden of disease, a time-based measure that combines years of life lost due to premature death and years lived with disability. Epilepsy has significant economic impacts in terms of healthcare needs, premature mortality, and loss of work productivity, which impose a heavy burden on families and society. Therefore, research on the mechanisms and intervention methods for epileptic seizures is crucial.

Neuroimaging and Electroencephalography (EEG) are the most relevant methods during presurgical investigation of the drug resistant epilepsy patients, who account for 30% of all epilepsy patients and can not be cured by medication. These methods have revealed alterations in the brains of people with epilepsy compared to healthy individuals. Recurrent seizures in epilepsy can lead to structural changes in certain brain regions and functional abnormalities such as the activation and connectivity of brain regions. These structural and functional alterations in the brain can result in reduced cognitive function. Resting-state brain networks exhibit different connectivity patterns in patients with epilepsy compared to healthy individuals. The main manifestations are functional connectivity changes in the Default Mode Network (DMN), the attention network, the executive control network, and the reward emotion network (Cataldi et al., 2013; in temporal lobe epilepsy), which may have an impact on the cognitive ability of epilepsy, including memory retrieval, attention span, working memory, and affective behavior (Cataldi et al., 2013; Constable et al., 2013; Royer et al., 2022) . Specifically, changes of functional connectivity in executive control network of

temporal lobe epilepsy(TLE) may be related to working memory impairment (Vlooswijk et al., 2011). In addition, studies in childhood absence epilesy (CAE) patients also observed attention impairment, which is associated with declined functional connectivity between the right anterior insula/frontal operculum (In/FO) and the medial frontal cortex (MFC), or with increased fronto-parietal connectivity (Killory et al., 2011). In addition, functional connectivity changes have been found to be related to the severity of epilepsy. Englot et al. (2015) found that decreased functional connectivity mainly occurred in the frontal cortex and it may be related to longer epilepsy duration or higher seizure frequency.

Seizures cause a massive abnormal discharge of neurons, which causes dramatic changes in neuronal potentials. EEG monitoring during seizures will show sudden abnormal EEG changes, reflected in the frequency and time domains by the appearance of waveforms with different frequencies from normal EEG signals and a sudden increase or decrease in EEG amplitude, respectively. Epileptic seizures are mainly manifested as rhythmic bursts of waveforms such as spikes, and spike-slow complex (Mălîia et al., 2016). However, Ictal EEG might be very difficult to analyze because of motion / muscle artifacts. Interictal EEG which is very short hundreds of ms and not associated with clinical manifestation is also very critical: interictal epileptiform discharges (IEDs) are the most common clinical markers of epilepsy physiology, including spike and waves . This can be used for epilepsy type diagnosis, epileptic and non-epileptic seizure identification, the prediction of seizure recurrence, and can localize the epileptic focus as a possible target for surgery(Brodbeck et al., 2011; Cuello-Oderiz et al., 2017b). EEG can also detect the onset and spatiotemporal (location and time) evolution of epileptic seizures (Abbasi & Goldenholz, 2019; Acharya et

al., 2013; Cuello-Oderiz et al., 2017a). In addition, the source image of EEG and MEG also play an essential role in localizing seizure onsets as well as revealing alterations in the function of resting-state networks(Mégevand & Seeck, 2018). Therefore, EEG can provide support for the localization of epilectic foci and the prediction of epileptic seizures. In addition, EEG is often used to evaluate the effectiveness of a certain treatment for patients with epilepsy, and indicators such as power spectrum and brain network are widely used for assessing the treatment effect of epilepsy. Patients with juvenile myoclonic epilepsy (JME) exhibit a higher beta power spectrum compared to healthy controls(Niso et al., 2015), probably due to the synchronous firing of seizure neurons, which results in cortical hyperexcitability and thus enhanced power spectrum (Clemens et al., 2000). The higher power spectrum is also an indicator of epilepsy susceptibility.. After taking medicine or receiving other disease modifying treatment, the power spectrum will decline compared with before (Amorim et al., 2015b; Tong et al., 2022; Wu & Xiao, 1997b). Seizures also affect functional connectivity, and are linked to the epileptic network causing the disease seizures, rather than being associated with a single lesion (Burns et al., 2014; van Blooijs et al., 2018). A study found that, compared to the interictal period, the functional connectivity significantly reduced during epileptic seizures, indicating a decrease in synchrony among the electrodes during seizures (Kramer et al., 2008). Clemens et al (Clemens et al., 2011) compared the brain electrical activity of patients with epilepsy during interictal periods with that of healthy individuals, using source-based connectivity analysis on EEG recordings in 19 adolescents with myoclonic epilepsy. They found that, compared to the control group, patients with epilepsy had increased alpha-band connectivity and decreased beta-band connectivity

dominated among the frontal region. After receiving medication treatment, the functional connectivity in epilepsy was also altered.

Conventional methods for the treatment of epilepsy

There is a marked increase in the types of anti-epileptic drugs (AEDs) available, such as sodium valproate, carbamazepine, lamotrigine, levetiracetam, topiramate. AEDs act by altering the levels of chemicals in the brain. They prevent neuronal depolarization by blocking sodium or calcium channels, enhance potassium channel function, inhibit neurotransmitter glutamate-mediated excitatory effects, or promote GABA-mediated inhibitory effects (Bui et al., 2015). AEDs cannot cure epilepsy, but can reduce the frequency and intensity of seizures. However, approximately one third of people with epilepsy experience seizures even after taking medication (Kwan & Brodie, 2000; Moshé et al., 2015). Simultaneous use of multiple anti-epileptic drugs may cause a variety of side effects such as skin rashes, osteoporosis, psychiatric symptoms, intellectual impairment, as well as fetal malformations and spontaneous abortion (Alsaad & Koren, 2014; Kwan & Brodie, 2000; Moshé et al., 2015). Surgery to remove potentially causative lesions in the brain is another therapeutic option that can cure around 25-30% of patients, following a surgical ablation technique pioneered by Dr Wilder Penfield (Ontario, 2012), reflecting the high cost of the procedure and the difficulty of resecting lesions without harming normal brain activity if the focus is located in the deep brain region. Electrical stimulation therapy may also be attempted, including Vagus Nerve Stimulation (VNS), which involves sending regular and

mild electric pulses to the brain through the vagus nerve to prevent or reduce the number of seizures. Deep Brain Stimulation (DBS) involves implanting tiny electrodes in certain parts of the brain and stimulating these brain regions by adjusting the voltage and other parameters of the electrodes. The ketogenic diet is also a treatment method to control seizures, primarily by reducing the amount of glucose in the blood, which prevents the seizures from receiving the energy they require. Apart from these mainstream therapeutic methods, there are alternative treatment approaches such as music therapy which is also used to assist in alleviating the symptoms of epilepsy(Lin et al., 2011; Quon et al., 2021).

Alternative remedy: Music therapy

Music interventions have been used as a non-invasive, non-side effect alternative approach for the treatment of neurodegenerative diseases. Several studies have shown the effect of listening to music on cognitive improvement in Parkinson's disease, Alzheimer's disease, and attention deficits, as well as evaluating the therapeutic potential of music listening (Foster & Valentine, 2001; Pacchetti et al., 2000; Rickson & Watkins, 2003). In addition, research has shown that rats exposed to the complex music of Mozart in utero and 60 days postnatally performed better in the T-maze tests than those who listened to silence, minimalist music, or white noise, with the enhanced memory and spatial-temporal learning effect lasting for several days in some cases (Rauscher et al., 1998). Research at microscopic level have also indicated that exposure to music can enhance dendritic branching, cell proliferation, and neurogenesis in the hippocampus and amygdala, thus obtaining a positive effect of musical intervention (Kim et al., 2006).

Previous studies have explored the therapeutic effect of music on epilepsy. Lin et al. (Lin et al., 2011) found that listening to Mozart music for 8 min daily over a 6-month period could decrease the number of IEDs, a potential marker of epilepsy treatment. This approach produced an effect comparable to that of anti-epileptic drugs and other treatment methods (Hallböök et al., 2007; Stodieck et al., 2001). Other studies have explored the potential brain mechanisms underlying the therapeutic effects of music on epilepsy. One such study found that after listening to music, rats suffering from epilepsy showed a significant decline of power spectrum in gamma band, which was previously shown to increase in epilepsy compared with healthy controls (Xu et al., 2022). In addition, studies explored the possible brain networks regulated by music treatment in epilepsy and found that after listening to music the patients showed a significant change of IEDs and EEG indexes which mainly happened in the frontal regions, which led them to speculate that music treatment may preferentially regulate epilepsy via the emotional network (Quon et al., 2021). Another study compared the difference between musician / non-musician patients with epilepsy and healthy controls, and found that healthy controls have significantly higher verbal cognition ability compared to non-musicians with epilepsy, whereas there was not much difference compared to musicians with epilepsy. These findings suggest that music training may regulate the cognitive abilities in epilesy via the fronto-temporal regions (Bird et al., 2019). Guaranha et al. (Guaranha et al., 2009) investigated the effect of cognitive tasks on epileptiform discharges in patients with JME. They found that motor tasks activated epileptiform discharges, while thinking tasks suppressed them. The authors speculated that motor tasks that activate the motor pathway are more likely to trigger seizures, while spatial thinking tasks that involve activating non-motor areas in the parietal

lobe may suppress activity in adjacent motor cortices, thereby inhibiting epileptic activity. Therefore, they suggested that music may have an anti-epileptic effect by activating and enhancing cortical areas involved in cognitive processes, which can directly inhibit adjacent motor areas or produce greater inhibition through inhibitory cortical-thalamic feedback loops (Maguire, 2012). Microscopic studies also suggest that music may intervene in epilepsy primarily by affecting dopamine secretion in the dorsal and ventral striatum following music listening, and the anti-epileptic effects of dopamine are attributed to stimulation of D2 receptors in the prefrontal cortex. Further research has identified that D2 receptor stimulation may have neuroprotective effects in the neurodegenerative processes induced by glutamate (Bozzi et al., 2000). Therefore, music could, like anti-epileptic drugs, increase dopamine levels in the brain, leading to upregulation and activation of D2 receptors in the striatum, thereby enhancing thalamic-cortical inhibition in the seizure-prone brain (Maguire, 2012).

Mozart's sonata for two pianos in D major (Mozart K 448) is a prevalent musical stimulus which has been used in the music treatment of epilepsy, and there are several speculations related to the mechanism of the effect of this particular composition on epilepsy. The most widely cited hypothesis is that the positive emotional response elicited by sonata music may lead to the release of dopamine, modulating dopamine neurotransmitter pathways, which may have an anti-epileptic effect (Maguire, 2017; Maguire, 2012). Additionally, the super organized stimulus of music may lead to innate memory patterns, which decreases the excitability of epileptogenic focus. Then, the music feature itself may also be a potential factor that influences the epilepsy (Hughes et al., 1998). Previous studies (Štillová et al., 2021) explored the difference between Mozart K 448 and Haydn No 94 as they share emotion and period of

creation, and they found that the decline of IEDs number is more significant after listening to Mozart K 448 compared to Haydn, potentially related to music feature differences between these two compositions. Hughes et al. (Hughes, 2001) have explored the so-called Mozart effect on epilepsy and compared to other kind of music composition including Haydn, Beethoven, Chopin, J.S. Bach and others, and they found that Mozart may be associated with best anti-epileptic effect, potentially due to its highest repetition of note sequence. Therefore, musical features may be related to the anti-epileptic effect.

Rationale, Hypotheses and Aims

There is increasing evidence to suggest that music listening is an essential alternative stimulus that can be applied to the epilepsy treatment. Some studies have explored the potential clinical and brain mechanism related to the therapeutic effect. However, there is a lack of study exploring which feature -or features- in music could influence the therapeutic effect, and the brain mechanism behind it.

A critical feature in music is tempo, which has been shown to play an essential role in the treatment of neurodegenerative diseases such as Parkinson and stroke. After rhythmic auditory stimulation (RAS) training, which involves training with music played at different tempos, the gait of Parkinson’s disease patients becomes more stable and less asymmetrical. This may be due to the tempo perception in rhythm that activates structures in key motor networks, many of which are damaged to varying degrees in Parkinson's disease (Rodriguez-Fornells et al., 2012; Thaut, 2005; Thaut & Abiru, 2010). Studies showed that tempo variations might have an

effect on the change of epileptic discharges (Štillová et al., 2021). The different rhythmic structure of music might activate large neuronal networks and evoke specific oscillatory periodicities, which may activate or inhibit the seizure-susceptible neural networks (Anderson et al., 2009; Maguire, 2015; Sesso & Sicca, 2020). Therefore, *we hypothesize that tempo in musical composition plays an important role in its treatment effect on epilepsy by impacting the attention ability of epileptic patients.*

To resolve this hypothesis, we altered the music stimulus into different tempos to compare the difference of resting-state EEG before and after listening to music. The specific aims of the project are as follows: i) to conduct an experiment collecting EEG data before and after listening to two widely cited classical compositions: Mozart's sonata K448 whose tempo has been altered into fast/slow/original, and Haydn's Symphony no. 94 with its original tempo, ii) to examine the clinical characteristics and changes in EEG indexes for power spectrum or/and phase-amplitude coupling of the participants, and iii) to investigate the therapeutic effect of musical tempo and its underlying neural mechanisms.

Method

Ethical statement

This prospective cohort study was approved by the Medical Ethics Committee of Sichuan University (approval K2021037). Written informed consent was obtained from all participants involved in the study or from their legal guardians.

Participants

This study consecutively screened patients who were monitored at the video-EEG monitoring unit of the Epilepsy Center, West China Hospital, Sichuan University from January 19 to July 20, 2022. The inclusion criteria consisted of epilepsy patients aged between 13 to 68 who were diagnosed according to the criteria established by the International League Against Epilepsy (ILAE), had IQ scores greater than 70, and had no definite seizure within 24 hours prior to musical stimulation. The very large age range may be seen as a shortcoming, however, our four groups of patients showed no significant difference in terms of age. Therefore, we think that age may not be an influencing factor in the main aim of our experiment. During the study, each patient remained quiet and awake. The exclusion criteria were as follows: No seizures in the past two years, the presence of systemic or progressive neurological disease (including deafness, intracranial infection, intracranial tumor, acute cerebral infarction, etc.), the existence of uncontrolled psychiatric diseases, patients who failed to adhere to the complete

the study, and patients who have experienced epileptic surgery before. The type of epilepsy includes generalized, focal, and unknown (Scheffer et al., 2017). The drug response was based on the level 1 and level 2 outcomes for each AED as defined by ILAE 2010 (Kwan et al., 2010). Data were collected on the etiology, seizure characteristics, and any unspecified level 1 outcomes for patients with a level 2 outcome classification of seizure-free, unspecified, or drug-resistant. Patients were classified as drug- resistant epilepsy or not according to drug response (Kwan et al., 2010). We initially enrolled 226 individuals with epilepsy for our study, of whom we excluded 16 individuals who had experienced seizures during the past 24 hours, 14 individuals who had a history of epileptic surgery, 30 individuals whose electroencephalographic data were of insufficient quality, and 19 individuals whose Patient Health Questionnaire (PHQ-9) and General Anxiety Disorder (GAD-7) (Kroenke et al., 2001; Spitzer et al., 2006) were higher than 12 to eliminate the effects of anxiety. In total, 147 individuals were included in the final analysis. The participant enrollment process is illustrated in the Fig 1. We firstly use the G power(Faul et al., 2009) to conduct a prior, we assumed an effect size of 0.5(paired t-test). $\alpha = 0.05$; With a power of 0.9, this indicated a total sample size of at least 36. We then assumed an effect size of 0.4(one-way ANOVA). $\alpha = 0.05$; With a power of 0.95, the number of groups is 4, which indicated a total sample size of at least 112. Therefore, our participants fulfill the standard.

Composition of the final analysis groups is shown in Table 1. The four groups showed similar clinico-demographic characteristics in terms of the gender, marital status, age, duration of illness, epilepsy type, whether they are drug-resistant epilepsy, occurrence of

seizures in the past month, number of AEDs taken and values of GAD-7 and PHD-9 (Table 1). These similarities indicate that the baseline characteristics of participants in the four groups were consistent and there were no significant differences among them.

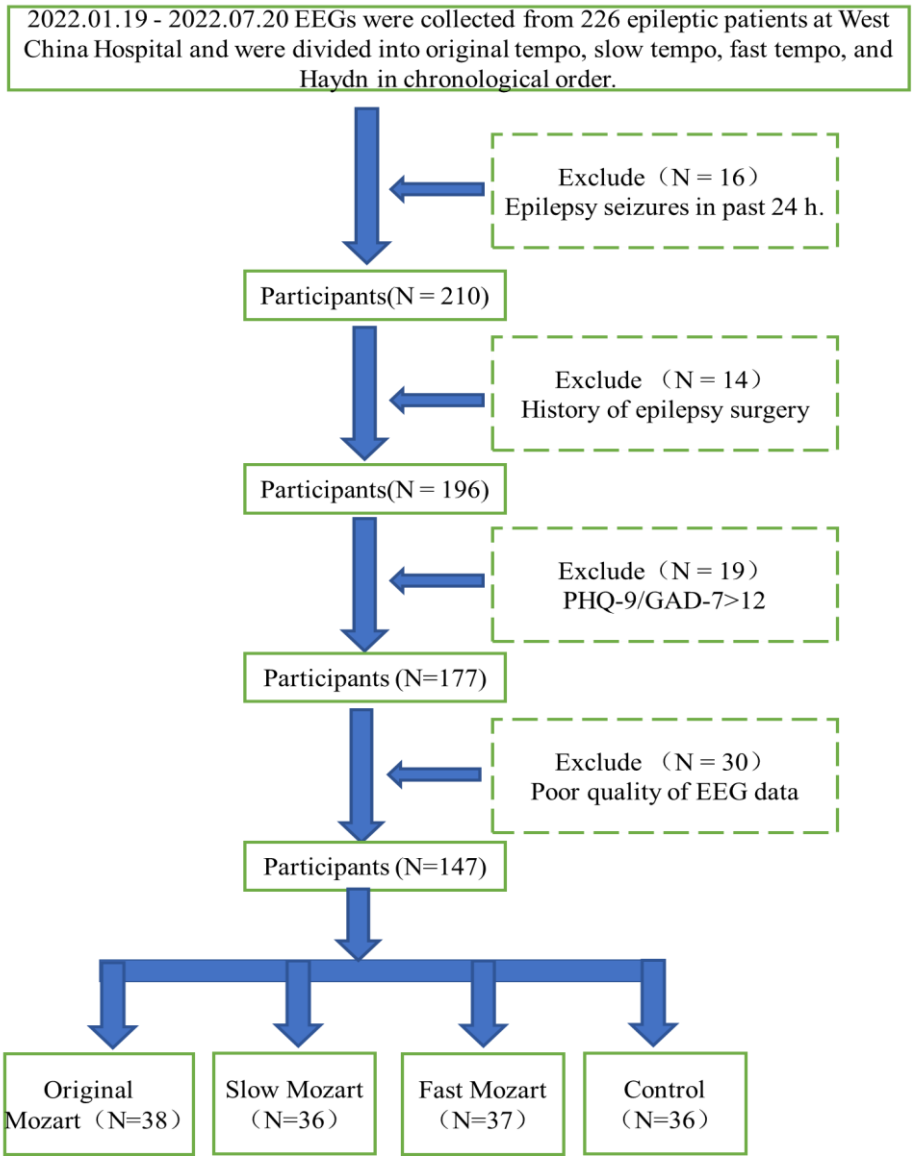

Figure 1 Participant Enrollment Process.

Table 1: Clinico-demographic characteristics of study participants.

characteristic	Mozart's Sonata, tempo			control (n=36)	*p*-value
	Original(n=38)	Fast(n=37)	Slow(n=36)		
Gender[a]					
Male	20(52.63%)	19(51.35%)	19(52.78%)	18(50%)	0.99
Marital status[a]					
Married	22(57.89%)	23(62.16%)	13(36.11%)	20(55.56%)	0.12
Age[b]	30.39±12.06	36.46±13.31	30.43±13.95	35.23±15.35	0.12
Duration of illness	7.05±7.90	5.00±5.48	6.91±7.34	7.65±7.60	0.42
Epilepsy type[a]					
Partial original	20(52.63%)	25(67.57%)	21(58.33%)	22(61.11%)	0.62
General original	15(39.47%)	11(29.73%)	13(36.11%)	14(38.89%)	0.81
Unknown original	3(7.89%)	1(2.70%)	2(5.56%)	0	0.34
Drug-resistant epilepsy[a]	5(13.16%)	3(8.11%)	5(13.89%)	2(5.56%)	0.59
Seizure in 30 days[a]	17(44.74%)	21(56.76)	22(61.11%)	19(52.78%)	0.54
Number of AEDs[b]	1.34±1.07	1.38±0.95	1.11±0.89	1.06±0.89	0.38
GAD-7[b]	3.97±3.99	2.73±3.38	2.75±3.11	2.00±2.14	0.10
PHD-9[b]	3.84±3.82	2.46±2.90	3.44±2.98	2.25±2.36	0.10

Abbreviations: AEDs, anti-epilepsy drug; GAD-7, General Anxiety Disorder; PHD-9, Patient Health Questionnaire.

Values are shown as mean ± SD, unless otherwise noted. P values refer to significance across all four groups.

a: Chi square test was used.

b: One-way analysis of variance was used.

Auditory stimuli

The stimulus for the original/fast/slow Mozart group was the first movement of Mozart's K448 sonata (Allegro con spirito), with a tempo of 138 beats per minute. The tempo of slow (64 beats/min) and fast (188 beats/min) Mozart music was 0.5 and 1.5 times that of original Mozart music, respectively. The stimulus for the control group (96 beats/min) is the first movement of Haydn No 94 (Surprise Symphony). The reason for choosing Haydn as the control group is that both Mozart and Haydn were from the same period and had shared

musical styles, and their music may also have a similar emotional effect (Štillová et al., 2021). The duration of stimuli last for nearly 8 min. In addition, we compared the difference in the musical features of these stimuli. We used the MIR toolbox in MATLAB (MathWorks, Natick, MA, USA) (Lartillot & Toiviainen, 2007) to parameterize the composition in terms of tempo part, spectrum, low energy rate (dynamics), inharmonicity (pitch), entropy (timbre), and tonal centroid (tonality). The low energy rate, entropy, and inharmonicity are global values, so no statistical analysis was necessary for these features. For tempo, spectrum, and tonal centroid, the MIR toolbox divided the musical stimulus into several "frames", resulting in a vector of several values. We sorted the vector in ascending order and then reduced the dimensionality using the mean method by calculating of the mean of several values, resulting in a vector with fewer values. After confirming that these values obey the normal distribution and homogeneous variance, we conducted an ANOVA to implement statistical analysis. We found that apart from tempo, which has a significant difference between the original Mozart and the other three types of musical stimuli presented, the other musical features were similar among these stimuli (Fig. 2).

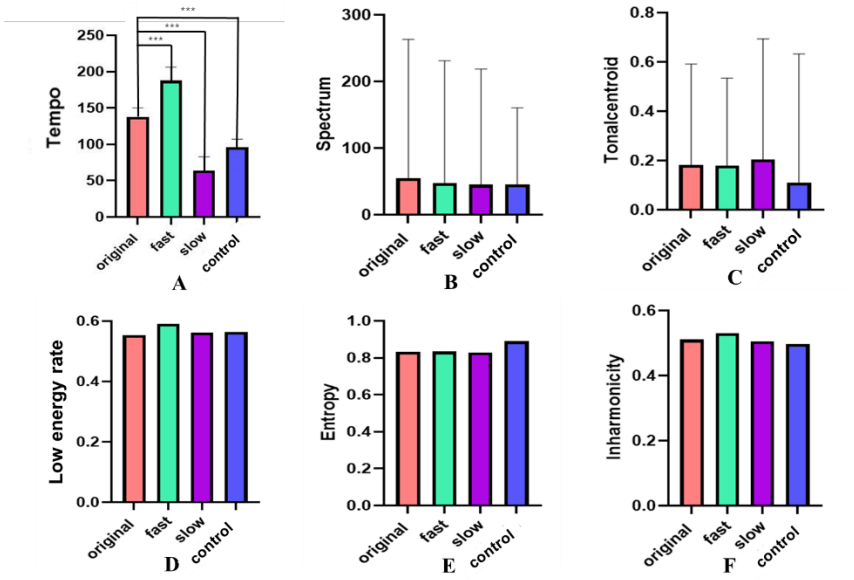

Figure 2 Comparison of musical features among the four music recordings played for study participants. Mozart's "Sonata for Two Pianos" (K. 448) was played at one of three tempos (original, fast, slow), while Haydn's Symphony no. 94 was played as a control. (A) Tempo. (B) Spectrum. (C) Tonality (measured as tonal centroid). (D) Dynamics (measured as low energy rate). (E) Timber (measured as entropy). (F) Pitch (measured as inharmonicity). *** $p < 0.01$.

Experimental procedure

We collected the data of these four groups in the following sequence: original Mozart, slow Mozart, fast Mozart, and control (original speed Haydn). Participants were randomly assigned to their groups and were asked to listen once to their assigned music while lying in an otherwise quiet room. Prior to the music starting, participants were instructed to relax, remain quiet and awake. Then patients had a pre-listening period of 8 min when they remained in place without music, followed by approximately 8 min of listening to the first movement of Mozart's sonata or Haydn's symphony, and finally another 8 min of post-listening rest without music (Fig. 3). Electroencephalograms were recorded on the scalp during the whole process using a 23-

channel (i.e., Fp1/2, F3/4, F7/8, FT9/10, Fz, C3/4, Cz, P3/4, Pz, O1/2, T3/4, and T5/6, TP9/10) instrument EEG-1200C electroencephalograph (Nihon Kohden, Tokyo, Japan) and the International 10–20 System of Electrode Placement (Fig. 4).

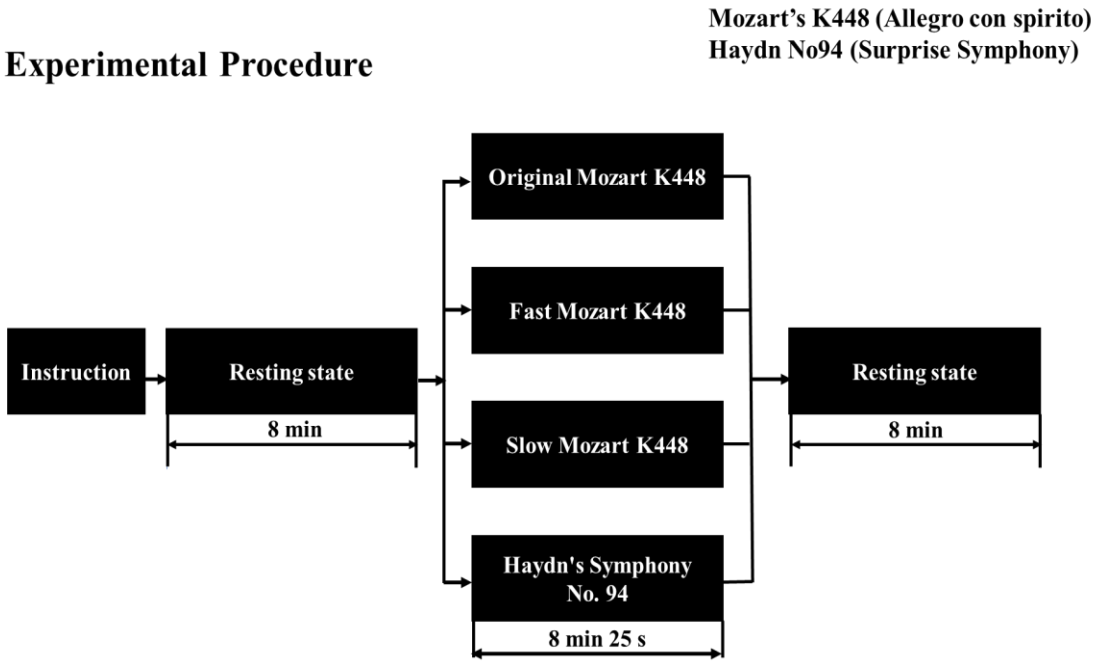

Figure 3 Experimental protocol. There are four groups: original/fast/slow Mozart (Mozart K448) and control group (Haydn No 94). The procedure includes three stages: before and after listening to music and during active music listening.

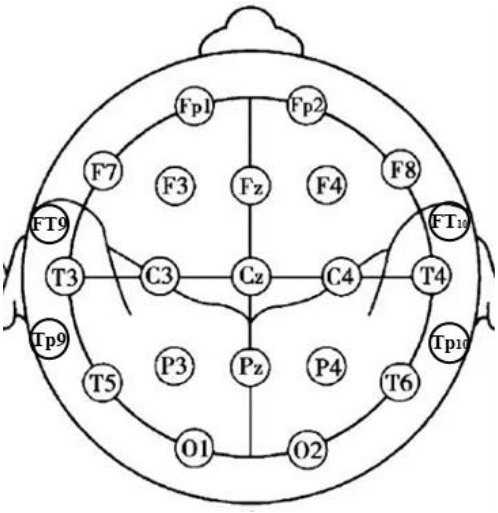

Fig 4 Placement of surface electrodes.

Data Analysis

Analysis of IEDs

All recordings were analyzed in the bipolar montage independently by two experienced epilepsy specialists at West China Hospital, who were blinded to other data about the participants. The number of IEDs recorded 8 min before and after listening to music were also counted by them. The Lilliefors test(Lilliefors, 1967) was used to confirm that the data were normally distributed, and the Bartlett test(Bartlett, 1937) was used to determine the homogeneity of variance. As the data did not satisfy the homogeneity of variance, the Wilcoxon rank test(Mann & Whitney, 1947) was used to compare the number of IEDs before and after listening to music.

Preprocessing of electroencephalography data

EEG data were preprocessed using the "EEGLAB" toolbox in MATLAB 2018b and the "zero reference" procedure based on the reference electrode standardization technique which translates EEG with reference at Infinity where the potential is zero/constant, whose merit is its ability to recover the true waveform and so to get correct estimate of various EEG/ERP features related to waveform (http://www.neuro.uestc.edu.cn/rest/)(Dong et al., 2017; Yao, 2001), followed by decomposition of the signal into functionally distinct frequency bands using bandpass filtering (1-45 Hz). Ocular artifacts were removed using independent component analysis (ICA). Signals were divided into 5-second segments, and other types of artifacts were removed using a threshold of ± 100 μV. These data were then used to calculate the indicated electroencephalographic parameters.

Analysis of power spectral density

Power spectral density (PSD), which describes the distribution of power as a function of frequency, is widely used to analyze therapeutic effect in epilepsy (Amorim et al., 2015a; Hurless et al., 2013; Wu & Xiao, 1997a). The PSD was calculated using Welch's method (Welch, 1967) after dividing the electroencephalographic signals into segments using a Hamming window, then performing fast Fourier transformation to calculate the power spectrum and calculating the average of the result of every window to obtain the final results. Beta power is known to be elevated in tonic-clonic epilepsy, and can be dampened by anti-epileptic drugs and deep brain stimulation (Amorim et al., 2015a; Hurless et al., 2013; Wu &

Xiao, 1997a), which may be an indicator of the therapeutic effect on epilepsy. In addition, beta oscillation is also changed most when changing the tempo (Hurless et al., 2013). Therefore, we calculated whole brain beta power spectrum(13-30 Hz) before and after individuals listened to music. The results were normally distributed and satisfy the homogeneity of variance in beta power, and we compared pre- and post-listening values using a paired *t* test in every electrode. The change of power spectrum may be influenced by the change of IEDs number, Therefore, we calculated the segments of power spectrum with no IEDs to regress out the influence of IEDs number changes. In addition, in order to know if listening to music with different tempo will cause a variation in power spectrum, we further compare the difference among the four groups after listening to music using Welch ANOVA(Tamhane, 1977) as it does not assume that all groups have equal variance. After verifying that the population means of the four groups at baseline were similar, we used the Game-Howell test(Toothaker, 1993) to conduct post-hoc multiple comparisons.

In order to understand how the tempo has a potential influence on epilepsy treatment, we further explored how the music with different tempos corresponded to the IEDs and PSD change in all participants. The individual IEDs change was the difference between before and after listening to music. We calculated the power spectrum density in the frontal-parietal region, because of its close association with attention (Zatorre et al., 1999). We used recordings from the electrodes FP1, FP2, C3, C4, P3, and P4. The final individual PSD change was calculated based on the change of average value for these electrodes.

Analysis of phase amplitude coupling (PAC)

Studies have shown that brain function is mediated by simultaneous oscillations in different frequency bands (Schutter et al., 2012) . Classical studies in this field have focused only on oscillations in single frequency bands, which have been reported to be relevant for perception and cognition (Cohen, 2008). However, it has been demonstrated that the interactions between oscillations in different frequency bands can also provide information for understanding brain function. Therefore, this concept has gained increasing attention, especially in the field of cognitive neuroscience. The interaction between several oscillations is also called cross-frequency coupling (CFC). The two recognized forms of CFC in brain rhythms are phase-amplitude coupling (PAC) and phase-phase coupling (PPC). In PAC, the phase of low-frequency oscillations drives the amplitude of high-frequency oscillations, resulting in a faster frequency amplitude envelope synchronized with a slower frequency phase. Studies have shown that behavioral tasks can modulate PAC (Voytek et al., 2010), which may involve sensory integration, memory processes, and attentional selection (Axmacher et al., 2010; Lisman & Idiart, 1995; Schroeder & Lakatos, 2009). This coupling has been observed in several regions of the brain, including the hippocampus, basal ganglia, and neocortex; these observations have been reported in various species, including rats, mice, sheep, monkeys, and humans (Tort et al., 2010). In the rodent hippocampus, a similar coupling between θ and γ oscillations is associated with learning. The strength of θ/γ PAC increases with rodent performance, providing evidence that PAC plays a functional role in the learning in hippocampus. Recently, disruptions in PAC patterns have been shown to be

associated with various neurological disorders, such as autism spectrum disorders, schizophrenia, and Parkinson's disease(Fujita et al., 2022a). PAC has also been applied to epilepsy, where the coupling between low and high-frequency bands has been found to be related to seizure dynamics (Hashimoto et al., 2021; Ibrahim et al., 2014; Weiss et al., 2020). Ibrahim et al (Ibrahim et al., 2014) showed that in the seizure state and seizure onset zone (SOZ), the phase of low-frequency bands such as θ and α modulates the amplitude of high-frequency bands. In particular, the intensity of PAC increases more in the SOZ than in the non-SOZ, which helps to identify the SOZ(Amiri et al., 2016; Cámpora et al., 2019). In addition, coupling between β-phase and γ-amplitude has been shown to help distinguish between seizure and interictal states (Edakawa et al., 2016; Zhang et al., 2017b). It has also been found that interictal PAC is greater in epileptic patients than in normal subjects (Fujita et al., 2022b)

To estimate the coupling between the phase of low frequency oscillations and the amplitude of high frequency oscillations, it is necessary to extract these oscillations from the signal. Traditional methods rely on bandpass filtering combined with Hilbert transform (Canolty et al., 2006; Penny et al., 2008), and wavelet transform (Caiola et al., 2019; Nakhnikian et al., 2016). However, these methods rely on bandpass filtering, so there are several limitations in evaluating these PAC methods, including limited frequency resolution and sensitivity to noise, data length, and sampling rate. Alternatively, we utilized the method proposed by Munia in 2019 (Munia & Aviyente, 2019) , which does not rely on bandpass filtering and offers desirable time-frequency distribution properties, such as high frequency resolution. The instantaneous phase and amplitude are first estimated based on the Reduced

Interference Rihaczek (RID-Rihaczek) distribution, which extracts both the envelope of the high-frequency amplitude component and the low-frequency phase component . The Rihaczek approach employs a complex signal formulation to define the signal energy in time and frequency distribution(Aviyente et al., 2011).

$$C(t,f) = x(t)X*(f)e^{-j2pft}$$

where $X(f)$ is the Fourier transform of the signal $x(t)$. Then we extract the high frequency amplitude component, $Af_a(t)$ and $\varphi f_p(t)$, where f_{a1} and f_{a2} define the bandwidth around the high frequency of interestf_a.

$$Af_a(t) = \int_{f_{a1}}^{f_{a2}} C(t,f)df$$

$$\varphi f_p(t)_{arg\left[\frac{C(t,f_p)}{|C(t,f_p)|}\right]}$$

The mean vector length (MVL) is then calculated based on the extracted amplitude $Af_a(t)$ and phase time series $\varphi f_p(t)$, in order to quantify the PAC.

$$MVL(f_a, f_p) = \left|\frac{1}{N}\sum_{t=1}^{N} Af_a(t)e^{j\varphi f_p(t)}\right|$$

In this way, a matrix is obtained for each channel of the subject, and the values in the matrix represent the coupling values of the high and low frequency bands. We first conducted the normalization. Then, we averaged all channels for each subject and compared the coupling values before and after listening to music using a paired t-test as it obeys the normal distribution and homogeneous variance, which would yield coupling values for α/γ, β/γ, and θ/γ (α:8-13Hz,

θ:4-8 Hz, β:13-30Hz, γ:30-45Hz). To further demonstrate which brain regions were changed, the coupling values of each channel before listening to music were compared using paired t-test. The resulting p-values were corrected for multiple hypothesis testing using the False Discovery Rate (FDR) method (Benjamini & Hochberg, 1995), and the results were displayed in the topographic map (p<0.05). Similar with the power spectrum, we also calculated the segments of PAC with no IEDs to regress out the influence of IEDs number changes on PAC changes.

Results

The original tempo Mozart was associated with a decrease in the number of IEDs (p=0.03) (Fig. 5) and a reduction in beta power spectrum (p< 0.05) (Fig. 6), especially in the following regions: frontal (FP2), parietal (P4), occipital (O1, O2), and temporal-parietal (T5). In contrast, no changes in IEDs or beta power spectrum were observed in the three other groups. In addition, the results of beta power spectrum excluding the IEDs changes are shown in Fig.7. Comparison of the PSD among those four groups after listening to music found that after listening to the original Mozart, beta power was lower compared to slow Mozart, mainly in the temporal and tempo-parietal regions (T6, TP10) (Fig.8). Compared to the control group, original tempo music had lower beta power in the occipital and temporal regions (O1, O2, T3).

Analysis of music stimuli with different tempos corresponding to IEDs and PSD change indicated that the original tempo Mozart has a significant decrease of IEDs and PSD, whereas the tempo of fast, slow and control had no effect on the IEDs and beta oscillatory power decline (Fig.9).

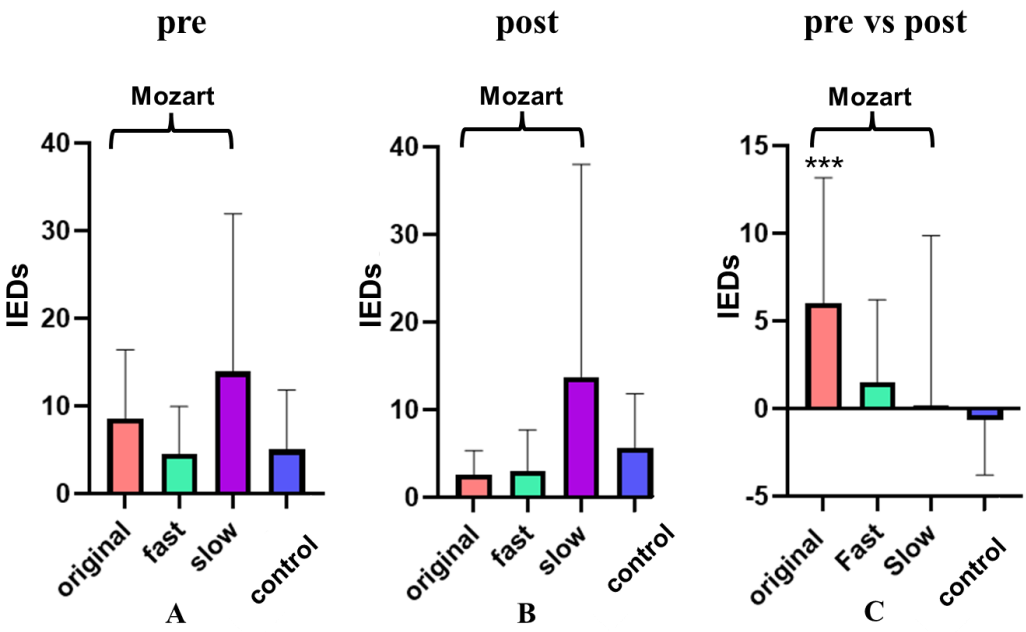

Figure 5 IEDs numbers during 8 min of resting state. (A)Number of IEDs before listening to music. (B)Number of IEDs after listening to music. (C)Change in number of IEDs (pre vs post). *** p<0.05.

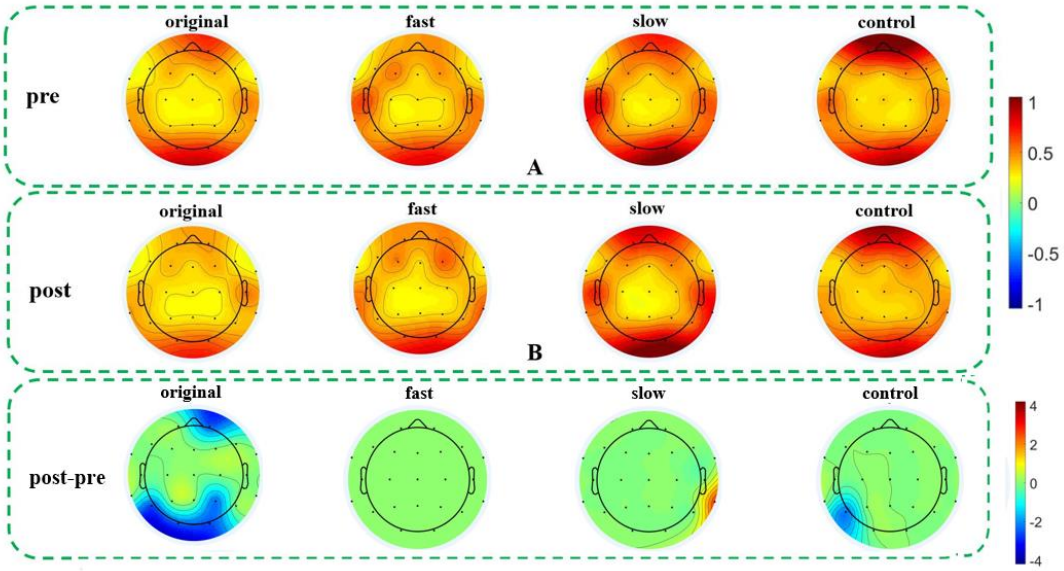

Figure 6 Global distribution of beta power spectrum. (A)Beta power spectrum before listening to music. (B) Beta power spectrum after listening to music. (C)Change of beta power spectrum (pre vs post). Blue indicates beta power decline and red represents increase.

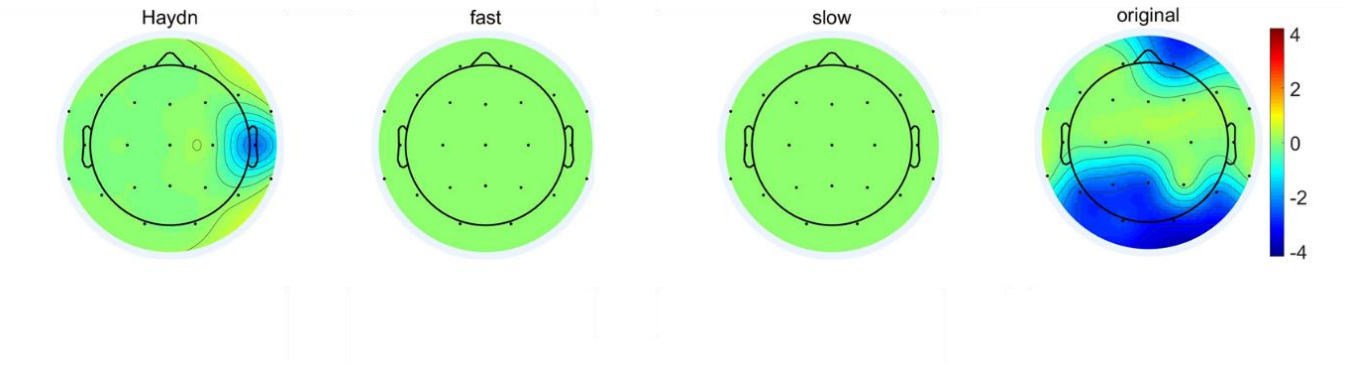

Figure 7 Global distribution of beta power spectrum after excluding the effect of IEDs

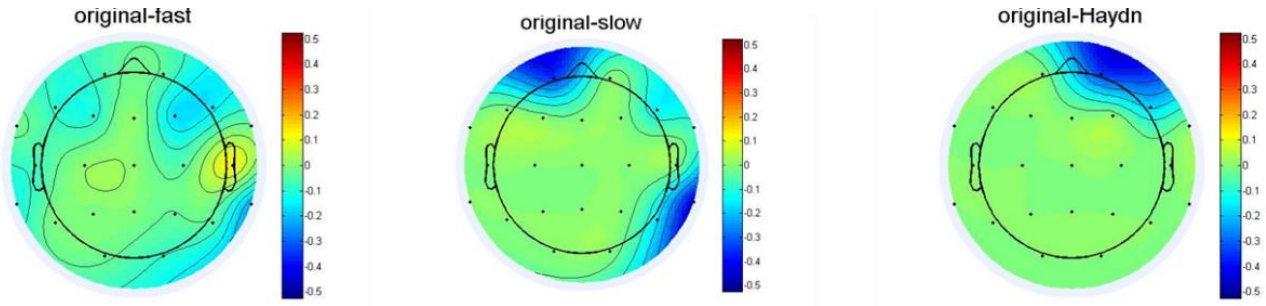

Figure 8 Global distribution of beta power spectrum comparison of after listening to music. (A)Comparison between original Mozart and fast Mozart. (B)Comparison between original Mozart and slow Mozart. (C)Comparison between original Mozart and Haydn. Blue indicates that the PSD of the former is lower.

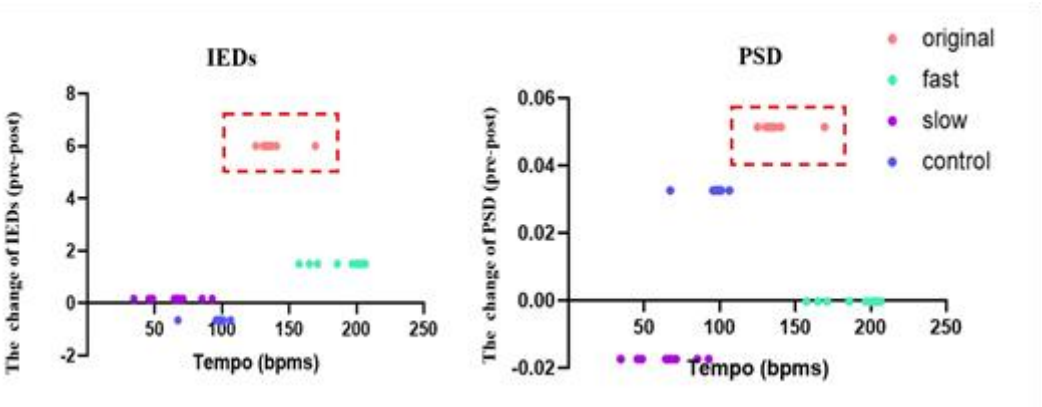

Figure 9 Tempo corresponding to IEDs and PSD change (pre - post). (A) IEDs changes after listening to different music. (B) Beta power spectrum change in the frontal-parietal region after listening to different music. The red dotted boxes represent the change in both IEDs and PSD. $p<0.05$. The results indicated that only the tempo of the original Mozart corresponded to a decline in IEDs and PSD.

The results of PAC analysis revealed that compared with before listening to original Mozart, the mean PLV value of the whole brain decreased in the θ/γ and α/γ band after listening to original Mozart (p =0.04, t = 2.11, d = 0.13; p = 0.01, t = 2.70, d = 0.23)(Cohen, 2013) (Fig. 10). The global distribution of the decrease in PAC value was mainly in the parietal-occipital region in δ/γ band (P4), parietal and frontal-temporal regions in θ/γ band (Pz, FT10) and frontal, parietal and occipital regions in α/γ band (P3,T5,Pz,FP2,P4,O2). (Fig. 11). The results of PAC excluding the IEDs changes are shown in Fig.12. These results were corrected for multiple hypothesis testing using the FDR method.

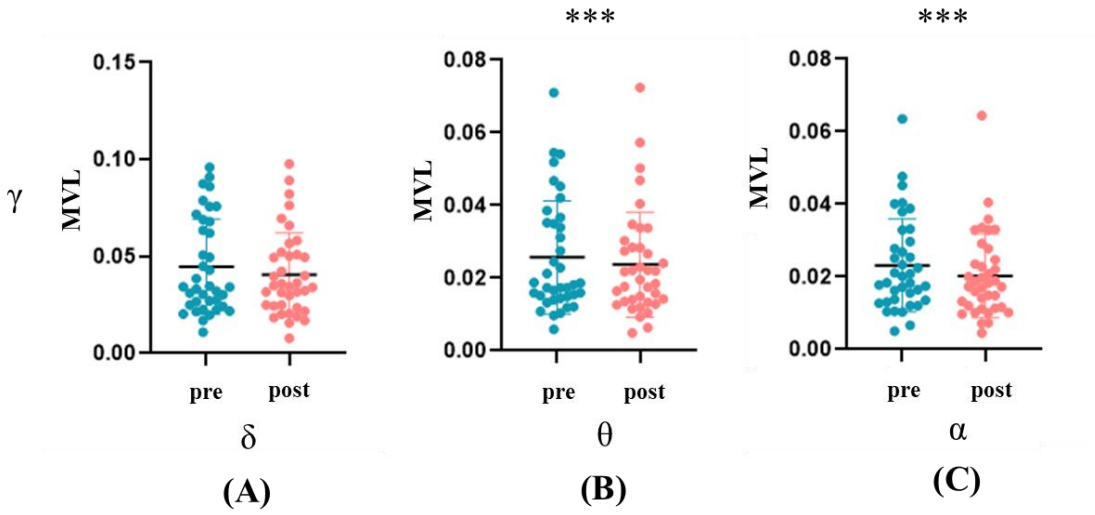

Figure 10 Mean PAC value before and after listening to original Mozart in the (A)δ/γ, (B)θ/γ, (C)α/γ(C). Blue represents before listening to music whereas red represents after listening to music*** $p<0.05$

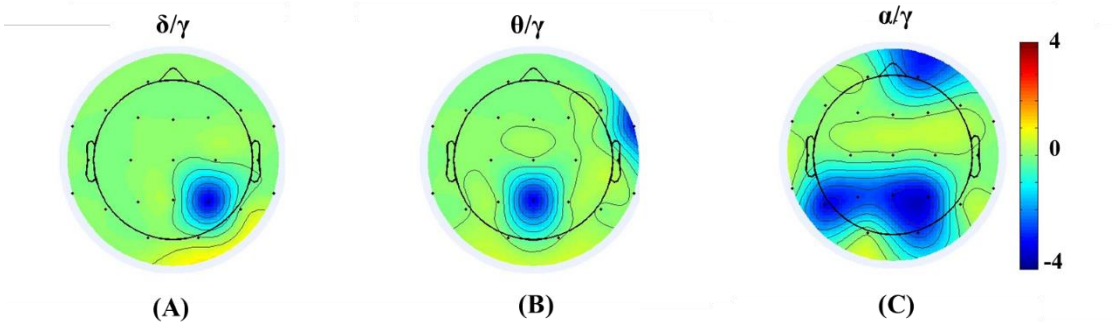

Figure 11 Global PAC value before and after listening to original Mozart in (A)δ/γ, (B)θ/γ, (C)α/γ. Blue indicates that the connectivity declined whereas red represents increase. $t>2.72$; $p<0.01$ (FDR-Corrected).

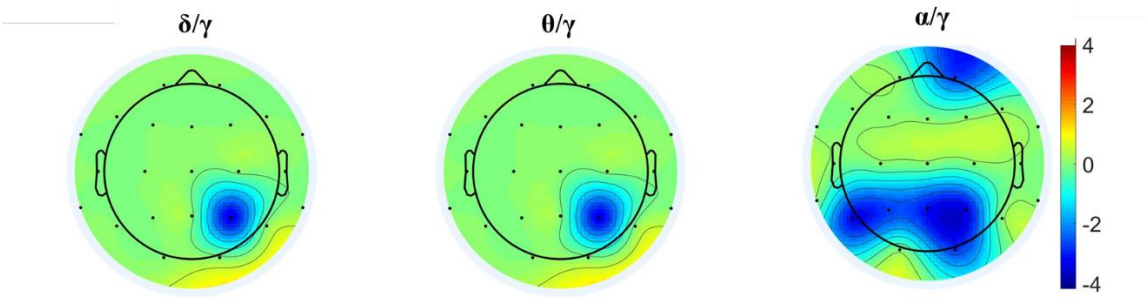

Figure 12 Global PAC value before and after listening to original Mozart in (A)δ/γ, (B)θ/γ, (C)α/γ after excluding the effect of IEDs number changes(FDR-Corrected).

Discussion

Changes in number of IEDs

Our clinical results showed that only after listening to the original Mozart, there was a decrease of IEDs whereas the other types of music (different tempo or different compositor) have no effect on the IEDs. This result was consistent with the treatment effect on epilepsy. The efficacy of anti-epileptic drugs (AEDs) has been tested by the IEDs. After taking AEDs, a decrease of IEDs happened in the patients (Stodieck et al., 2001). After experiencing 3 months ketogenic diet, the number of IEDs of children suffering from intractable epilepsy also declined (Hallböök et al., 2007). As for music therapy of epilepsy, IEDs is also an index that assesses the availability of music. Lin et al. showed a decrease of IEDs in idiopathic epilepsy patients whose seizures were clinically well controlled with epileptic drugs after listening to Mozart K448 (Lin et al., 2013; Lin et al., 2011). This may be a clinical index that showed the original Mozart's therapeutic effect, which was more pronounced in patients with generalized epilepsy. Only the original tempo had the therapeutic effect whereas other tempos had no such clinical

effect. This result showed the effect of tempo preliminary. As for the brain mechanism behind it, we further calculated the power spectrum and PLV results.

Changes in beta power spectrum

After listening to original Mozart music, a decrease in beta power was observed in the frontal, parietal and occipital regions. The beta power spectrum of epilepsy patients is typically higher than in healthy controls, which may reflect greater neuronal synchronization (Clemens et al., 2000; Michel et al., 1992). This synchronization is thought to be due to an altered neuronal extracellular ionic environment (Willoughby et al., 2003), leading to hyperexcitability of the cortex. An increase in power across all frequency bands has been observed immediately before myoclonic seizures, which supports the notion of higher spectral power indicating seizure susceptibility (Sun et al., 2016). Beta power decrease has been proven to be an indicator of epilepsy therapeutic effect as indicated in previous literature where, after taking medicine or receiving DBS treatment, the beta power decreased in epilepsy patients (Amorim et al., 2015a; Tong et al., 2022; Wu & Xiao, 1997a). Previous studies (Bauer et al., 2015; Rodriguez-Fornells et al., 2012) have shown that the coupling of auditory to motor cortex is important in neurological music therapies, and that a significant relation exists between preferred tempo which proved around 120 bpm (Bauer et al., 2015; Moelants, 2002) and the frequency of motor beta oscillation . These studies found that coupling between auditory and motor cortex can only be achieved if the respective areas share the same frequency or an integer relation of it (i.e., 1:8 or 8:1). The tempo of original Mozart which is closest to the preferred tempo may have the best music therapeutic effect on epilepsy. The therapeutic effect may be influenced by the attention alteration after listening to music, as previous literature has suggested that beta power

is inversely related to the attention. In individuals with ADHD, who often have lower attention abilities, higher beta power is commonly observed in the frontal, parietal, and occipital regions. After taking medicines, the beta power decreased in the frontal and parietal region (Clarke et al., 2003; Poil et al., 2014).Our results were in accordance with these studies. Furthermore, previous literature has indicated that beta power reduction is relevant to the deactivation of the default mode network (DMN) (Mantini et al., 2007; Neuner et al., 2014). Activation of DMN was negatively correlated with attention. For instance, an investigation of meditation practice found that the DMN was significantly less activated during focused attention compared to mind wandering (Scheibner et al., 2017). Our results also suggested that decreased beta power in the occipital region may be related to the decreased visual attention ability in epilepsy patients, which was in line with literature showing that the greater attention and quicker response to visual targets was relevant to higher beta activation (Kamiński et al., 2012). It is possible that increased auditory attention ability can compensate for decreased visual attention ability. Previous studies also showed that music with different tempos could modulate attention via the DMN. A study explored the difference between happy and sad music which were typically different in tempo. They found that after listening to sad music with a lower tempo, the DMN centrality is higher with stronger mind-wandering whereas happy music with a higher tempo has more attention (Taruffi et al., 2017).

Correlation between the different tempo with beta power and IED number change

The frontal-central region of the brain is critical for the attention (Marek & Dosenbach, 2018; Zatorre et al., 1999). Our findings suggested that both the decrease in interictal

epileptiform discharges (IEDs) number and beta power indicate a therapeutic effect in epilepsy patients. Interestingly, we found that only the tempo of original Mozart was associated with a decrease in IEDs number and beta power. This could be interpreted as the tempo of original Mozart helps keep epilepsy patients more concentrated. On the other hand, the tempos of control and slow Mozart are lower which may lead to more spontaneous thoughts and mind-wandering, while with the fast playing Mozart, the tempo is too fast to facilitate attention. It is worth noting that epilepsy patients often have lower cognitive abilities which are associated with seizure duration and frequency (Black et al., 2010; Elger et al., 2004; Gavrilovic et al., 2019), which may indicate that attention is related to epilepsy severity (Black et al., 2010). Thus, increased attention may be related to the impairment linked to epilepsy severity.

Changes in Phase-Amplitude Coupling (PAC)

After listening to original Mozart, the mean PAC in the whole-brain decreased in θ/γ, α/γ. Fujita et al (Fujita et al., 2022a) found that healthy controls had significantly lower PAC than epilepsy patients by using magnetoencephalography during the interictal period, and the difference of the PAC during the interictal period between the epileptic patients and controls may increase the correct classification rate between them. Therefore, the results may indicate that listening to original Mozart can help epilepsy patients converge towards a healthy state. The high-frequency band directly reflects local cortical functions, such as motor cortex, while the low-frequency band reflects the coordination of functions across the cortical network. PAC has been reported to reflect the interaction between local cortical functions and the cortical network (Canolty & Knight, 2010). In addition, PAC has also been reported as a biomarker to predict seizure outcome after callosal stripping and corticotomy (Uda et al., 2021; Zhang et al.,

2017a). Therefore, we speculate that changes in PAC after listening to music may reflect changes in resting-state network function induced by neurological disease and treatment. We were also interested in gaining a better understanding of the changes in PAC in various brain regions, and for this a decrease in θ/γ in the parietal and temporal frontal lobes after listening to original Mozart was obtained. Previous research has suggested that elevated PAC in the θ/γ band may represent the pathology of epilepsy, as epilepsy patients were found to exhibit elevated PAC during interictal period in θ/γ band compared with that of healthy controls (Fujita et al., 2022a). Our findings also suggest that listening to original music may lead to a decrease in visual attention, a finding supported by a previous study showing that θ/γ, δ/γ PAC predicts visual attention (Szczepanski et al., 2014), with high PAC in the frontoparietal and occipital lobes indicating faster reaction times and low PAC reflecting slower reaction times during visuospatial attention allocation. Consequently, this reallocation of attentional resources results in more attention being allocated to auditory, so there may be a boost in auditory attention.

In addition, we also calculated the change of beta power spectrum and PAC after regressing out the effect of IEDs number, and found that the trend of the change is similar with the PSD and PAC change without regressing it. Therefore, we believe that the change of PSD and PAC may not be influenced by the change of IEDs number.

Conclusion

To summarize, our results advance our mechanistic understanding of how music features

such as tempo could influence the treatment effect. Few studies have previously explored which music features have a treatment effect on epilepsy. The present study explored the effect of a variation in music tempo on the treatment response as determined by IEDs, PSD, and PAC. All of these measurements suggested that the original tempo in the selected Mozart composition could be driving the putative therapeutic effect. The PSD change also suggest that the therapeutic effect may be mediated through regulating attention ability. The other music stimuli with different tempo selected for our study did not show this effect. This supports our hypothesis that the tempo in the classical Mozart K 448 might play an important role in the conjectured therapeutic effect. Our study provides circumstantial evidence that selected musical features could be influencing the therapeutic effect.

Limitations

There are several limitations to our study. Firstly, our patient groups may have not been entirely comparable in terms of seizure frequency and medication history. However, we conducted the statistical analysis and found no significant differences in clinical characteristics among the four groups, which indicates that the baseline is consistent. Secondly, the number of patients with frontal or temporal lobe epilepsy is not clear. The focus origin may influence the ability of music perception. We need to make sure the baseline is consistent. Thirdly, our classification of epilepsy could be more precise to explore which subtype of epilepsy patients have the most sensitive response to the music tempo change, based on the epileptic seizure focus. Fourthly, other musical indexes which we did not measure may also change after altering

the tempo. Therefore, we need to add a group that would be listening to the pure percussion whose tempo is similar to the Mozart K 448 to eliminate the influence of other musical features in the future. Fifthly, we should clarify the issue of providing data from the scalp level only, not taking into account variability in the shape of the heads of the subjects. Sixthly, the approach did not measure the lasting time of the potential therapeutic effect, the potential therapeutic effect may be temporary. Seventhly, all previous studies and our studies have flaws: none of these studies have accounted for "subconscious familiarity" the effects due to prior unacknowledged or forgotten exposure to the music of Mozart. Some participants may have been unknowingly exposed to the melody before, either on the radio, on television, in a movie or in other public spaces. Finally, the effect regulated by the attention ability is our speculation, it may be that it is regulated by some other cognitive ability, therefore this needs to be further evaluated by adding cognitive tasks.

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