European Journal of Neurology

european journal of neurology
the official journal of the european academy of neurology

ORIGINAL ARTICLE OPEN ACCESS

Toward a Tailored Acoustic-Based Approach in Music Neuromodulation in Epilepsy

Ondřej Strýček[1,2] | Jiří Mekyska[2,3] | Štěpán Miklánek[3] | Michal Fusek[4] | Klára Štillová[1,2] | Martin Mazánek[5] | Ivan Rektor[1,2]

[1]Brno Epilepsy Centre, First Department of Neurology, St. Anne's University Hospital and Faculty of Medicine, Masaryk University, Member of ERN-EpiCARE, Brno, Czech Republic | [2]Central European Institute of Technology (CEITEC), Masaryk University, Brno, Czech Republic | [3]Faculty of Electrical Engineering and Communication, Department of Telecommunications, Brno University of Technology, Brno, Czech Republic | [4]Faculty of Electrical Engineering and Communication, Department of Mathematics, Brno University of Technology, Brno, Czech Republic | [5]Faculty of Arts, Department of Musicology, Masaryk University Symphony Orchestra, Masaryk University, Brno, Czech Republic

Correspondence: Ivan Rektor (ivan.rektor@fnusa.cz)

Received: 31 August 2024 | **Revised:** 23 February 2025 | **Accepted:** 1 April 2025

Funding: This work was supported by project no. LX22NPO5107 (MEYS): Funded by the European Union—Next Generation EU.

Keywords: acoustic properties | epilepsy | iEEG | interictal epileptiform discharges | music

ABSTRACT

Background: Music-based neuromodulation has garnered interest as a potential therapeutic approach for drug-resistant epilepsy. This study expands on prior research by examining the effects of different musical features on interictal epileptiform discharges (IEDs) within intracerebral EEG (iEEG).

Methods: Twenty-five patients with drug-resistant epilepsy undergoing presurgical iEEG evaluation participated in the study. Over 2 days, patients listened to various musical compositions characterized by distinct acoustic properties. EEG measurements were recorded before and after each listening session to evaluate IED changes.

Results: The study identified individualized patterns in IED reduction, with certain acoustic properties showing consistent effects across musical genres. Mozart's "Piano Concerto No. 27" K 595c globally reduced IEDs by 28% while listening to music ($p = 0.0191$) and 19% in the postmusic resting state ($p = 0.0111$); relaxation music increased IEDs by 55% ($p = 0.0197$). Based on the acoustic analysis of individuals, we identified compositions that significantly reduced IEDs, with reductions ranging from 32% to 44% ($p = 0.0001$). In contrast, compositions with differing acoustic properties did not result in significant changes in IEDs. These results suggest that specific acoustic properties, rather than genre, primarily influence IEDs.

Conclusions: The findings suggest that specific acoustic properties can influence brain activity in a reproducible manner at the individual level, modulating IEDs based on personalized testing and selection across a spectrum of musical genres. These results suggest the potential for music-based neuromodulation as a personalized therapeutic approach in epilepsy management, emphasizing the importance of acoustic features over musical genre. Further research is needed to explore individual aspects of music-based interventions.

1 | Introduction

Epilepsy is a chronic neurological disorder characterized by recurrent, unprovoked seizures. Despite advancements in antiseizure medications (ASMs), approximately 30% of patients have drug-resistant epilepsy. For these patients, nonsurgical palliative treatments, such as neuromodulation techniques, are explored. Among these, music-based interventions have recently emerged as a promising avenue.

The most substantial evidence supporting the role that listening to music plays in patients with epilepsy is associated with Mozart's "Sonata for Two Pianos in D Major" (K 448), which has been shown to reduce interictal epileptiform discharges (IEDs) in EEG studies and demonstrate seizure-reducing effects with regular listening [1–6]. Other compositions have been investigated; similarly, promising results were predominantly observed with Mozart's "Piano Sonata No. 16 in C Major" (K 545) [7]. The uniqueness of K 448 and the mechanism of its effect on IEDs or seizures are subjects of ongoing research, with hypotheses proposing mechanisms such as positive emotional responses to music [8, 9] and the presence of long-term periodicities (lasting 10–60 s) within the composition, which are thought to be associated with cerebral coding [10].

The Mozart effect has garnered significant attention in both the scientific community and popular media over the past 3 decades. A recent meta-analysis based on eight studies involving 207 subjects casts doubt on the evidential value of the Mozart effect for epilepsy [11]. The analysis revealed nonsignificant, trivial-to-small summary effects of listening to K 448 or other musical stimuli on epilepsy or other medical conditions. These results, coupled with inconsistent evidential patterns from multiverse analyses and low primary study power, indicate limited reason to suspect a specific Mozart effect in epilepsy treatment.

Our study aimed to build upon findings by exploring the impact of specific musical features on IEDs. Research by Štillova et al. showed in intracerebral EEG (iEEG) that certain musical properties like rhythm, melody, harmony, dynamics, and timbre can influence IEDs in epilepsy patients [12].

Based on those results, we conducted a study testing the prediction of music's IED-reducing effect based on its acoustic properties. We did not include K 448 in our study, as we aimed to explore whether there might be other compositions suitable for IED reduction. Our study hypothesized that the IED-reducing effect is not because of Mozart's music; the effect is individual and based on the acoustic parameters of the music. We posited that patients who respond to a particular type of music with an IED reduction would experience a similar effect when exposed to acoustically similar music, while the effect would be absent with acoustically contrasting music. In this way, we aimed to predict the effects of music on patients with epilepsy. Our study was designed specifically for patients with iEEG, as many IEDs do not propagate to scalp-EEG.

2 | Methodology

2.1 | Patients

We included 25 patients with drug-resistant epilepsy, undergoing iEEG during presurgical evaluation. All patients had iEEG implanted using a stereotactic frame, with position verified by MRI (for details see Supplementary). The cohort had limited exposure to classical music and no serious visual or hearing disturbances. Those with a seizure less than 6 h prior to or during study recordings were excluded. Three patients were excluded due to recent seizures, in accordance with these criteria. The study adhered to ethical standards and all patients provided informed consent. For the patient characteristics see Supporting Information.

2.2 | EEG And Music Recordings

Recordings were conducted at the Brno Epilepsy Centre's video-EEG unit. Patients listened to music through headphones during sessions conducted over two consecutive days. On the first day, the session included a premusic resting-state EEG, during which patients listened to five original compositions (OCs), followed by a postmusic resting-state EEG. The OC that elicited the lowest number of IEDs was identified for further analysis. On the second day, patients listened to the OC identified from the first day (with the lowest IED count) along with four additional compositions selected according to the methodology. These sessions were also flanked by premusic and postmusic resting-state EEGs. The order of music presentation was randomized, and two epileptologists independently analyzed the recordings, focusing specifically on IEDs within the irritative zone. IEDs were counted within a 5-min interval for each composition (for details see Supporting Information) Additionally, after the recordings, patients were asked to rate the compositions on a scale from 1 to 5, with 1 indicating "I like this the most" and 5 signifying "I did not like this." This subjective assessment was used to gain insights into the patients' personal preferences and enjoyment of the music, which is considered a crucial element in evaluating music therapy as a potential treatment option.

2.3 | Selection of Music Compositions

Our evaluation involved five different types of music, each represented by a group of compositions: movie soundtrack, relaxation music, minimalistic music, rapid and dynamic music, and Mozart's music. A professional musician selected one original composition per group, and each was acoustically compared with the others using acoustic parameters identified as important in our previous study [12]. For the selection of compositions see Table 1; for the complete procedure for selecting compositions based on acoustic analysis and the acoustic properties of the selected compositions, please refer to the Supporting Information. The compositions were 5–5.5 min in length.

For each group, four additional compositions were chosen based on acoustic similarity to or difference from the original composition

(the most IED-reducing composition from the first day): the most similar composition from the same group (sSG), the most similar composition from all compositions outside the group (sOG), the most contrasting composition from the same group (cSG), and the most contrasting composition from all groups (cOG).

2.4 | Statistical Analysis

The number of IEDs and changes between the premusic and postmusic resting states were summarized as medians. Absolute and relative changes were calculated; relative changes were calculated as absolute changes divided by the number of IEDs in the premusic resting state. The effects of listening to compositions were compared using a paired-sample Wilcoxon test. The changes in IEDs between men and women were evaluated using the Mann–Whitney *U* test. The effects on IEDs of the acoustic properties of the compositions that were listened to on the first day were analyzed based on Pearson correlation coefficients. The coefficients were calculated between musical features and median numbers of IEDs in the selected parts (equally long sections of the compositions within the first 5 min from the start).

3 | Results

3.1 | Results of the First Day

The analysis of the music compositions that led to the lowest number of IEDs showcased varied results across different genres: Relaxation music led to the lowest number of IEDs in 1 patient, minimalistic music in 5 patients, rapid and dynamic music in 6 patients and Mozart's music in 13 patients. However, statistical significance across the entire group of patients was observed only in two categories: Mozart's music, which showed a significant reduction in IEDs, and relaxation music, which, conversely, increased IEDs.

The evaluation of IEDs during the music-listening sessions and the corresponding premusic and postmusic resting states are detailed in Tables 2 and 3. For K 595c, there was approximately a

TABLE 1 | Compositions.

First day **Original compositions**	
Movie	J. Horner—*Bicentennial Man*
Relaxing	Music for healthy sleep
Minimalism	P. Glass—"Metamorphosis Three"
Rapid and dynamic	C. Saint-Saëns—"Danse Bacchanale"
Mozart	W. A. Mozart—"Piano Concerto 27" K 595
Second day **Acoustically based selection**	
The most IED-reducing composition from the first day	
The most similar composition from the same group (sSG)	
The most similar composition from all compositions outside the group (sOG)	
The most contrasting from the same group (cSG)	
The most contrasting from all groups (cOG)	

Note: The original compositions listened to on the first day and the principle of the selection of the acoustic parameters.

TABLE 2 | Results of the first day of the study.

Composition	Subjective rating (average)	Premusic resting state—number of IEDs (median, minimum; maximum)	Music—number of IEDs (median, minimum; maximum)	Postmusic resting state—number of IEDs (median, minimum; maximum)
Movie	1.6	29 (4; 254)	38 (5; 248)	43 (2; 214)
Relaxing	1.96		45 (4; 272)	29 (0; 268)
Minimalism	3.64		37 (4; 268)	36 (4; 255)
Rapid and dynamic	3.76		46 (2; 257)	36 (2; 290)
Mozart	4.08		27 (0; 185)	22 (1; 227)

Note: The subjective ratings of the compositions, presented as average numbers on a scale ranging from 1 to 5. In this scale, 1 represents "I like this the most" and 5 denotes "I did not like this."

TABLE 3 | Comparison of the effects of the compositions on the first day of the study.

	Change in IEDs while listening to music and in the postmusic resting state compared to in the premusic resting state (median, minimum; maximum)				
	Movie	**Relaxing**	**Minimalism**	**Rapid and dynamic**	**Mozart**
Absolute change—premusic resting state and listening to the music—number of IEDs	1 (−61; 22) $p=0.5853$	**7 (−57; 28)** $p=0.9815$, $\boldsymbol{p^*=0.0197}$ (for increase)	0 (−66; 67) $p=0.5228$	−2 (−55; 37) $p=0.1355$	**−6 (−81; 30)** $\boldsymbol{p=0.0191}$
Relative change—premusic resting state and listening to the music	0.01 (−0.63; 0.65)	0.12 (−0.7; 2.56)	0 (−0.8; 1.47)	−0.17 (−0.82; 1.61)	−0.28 (−1; 1.04)
Absolute change—premusic and postmusic resting state—number of IEDs	0 (−74; 40) $p=0.1435$	−6 (−62; 59) $p=0.2076$	−4 (−68; 82) $p=0.1265$	−4 (−92; 68) $p=0.1728$	**−6 (−114; 36)** $\boldsymbol{p=0.0111}$
Relative change—premusic and postmusic resting state	0 (−0.88; 2)	−0.17 (−1; 1.87)	−0.13 (−0.71; 1.62)	−0.21 (−0.82; 2.96)	−0.19 (−0.89; 1.48)

Note: Changes in the number of IEDs while listening to the music and in the postmusic resting state compared with the premusic resting state. The reduction of IEDs is represented by negative values and the increase by positive values. The null hypothesis of no difference is tested against the alternative that there is a decrease in IEDs (*p* value *p*), or an increase in IEDs (*p* value *p**). Statistically significant changes are shown in bold.

7% decrease in the median of IEDs between the premusic resting state and while listening to the music, and approximately a 24% decrease in the median of IEDs between the premusic and postmusic resting states; see Table 3. Table 4 shows that K 595c led to a significant reduction in IEDs between the premusic resting state and while listening to the music ($p=0.0191$) with a median decrease of six IEDs and a median relative decrease of 28%, but there was negligible effect size (Cliff's delta = 0.1088). Moreover, there was a significant reduction in IEDs between the premusic and postmusic resting states ($p=0.0111$), with a median decrease of six IEDs and a median relative decrease of 19%, see Table 4. A small effect size (Cliff's delta = 0.1856) was observed for this comparison, indicating a minor but consistent reduction in IEDs.

The other musical categories did not demonstrate significant changes in IEDs across the entire group of patients, except for the relaxing music category. This music significantly increased IEDs ($p=0.0197$), with a median increase of seven IEDs between the premusic resting state and while listening to the music. Moreover, there was approximately a 55% increase in the median of IEDs between the premusic resting state and while listening to the music. In the relaxing music category, small effect sizes were observed for both comparisons: between the premusic resting state and while listening to the music, and between the premusic and postmusic resting states. For complete results of effect size results see the Supporting Information. Boxplots illustrating the reduction in IEDs across patients, specifically comparing the premusic resting state with the music-listening state, are included in Supporting Information.

Table 2 also includes the subjective ratings of the compositions presented as average numbers on a scale ranging from 1 to 5. In this scale, one represents "I like this the most" and five denotes "I did not like this." Generally, not compared with the premusic resting state, movie soundtrack compositions did not lead to the lowest IEDs in any of the patients, relaxation music in one patient, minimalistic music in five patients, rapid and dynamic music in six patients, and Mozart's music achieved the lowest IED count most frequently, in 13 patients. We conducted an additional analysis of the combined effect of the randomized sequence of music, showing that there was no effect of the order of listening to compositions We analyzed the relationship between music-induced spike reduction and epilepsy types, music preferences, and subjective ratings using Fisher's exact test. Furthermore, we analyzed the relationship between the type of music that induced IED reduction and participants' age using ANOVA. No significant associations were found for epilepsy types ($p=0.3350$), music preferences ($p=0.8012$), subjective ratings ($p=0.1329$), or age ($p=0.7400$), suggesting that the observed effects were independent of these factors (all these analyses are included in Supporting Information). We did not find any effect of acoustic properties of compositions listened to on the first day on IEDs. We did not find any gender differences in the effect of different music on the number of IEDs.

3.2 | Results of the Second Day

On the second day, the musical compositions were set to assess the impact of various acoustic properties on IEDs. This

TABLE 4 | Results of the second day of the study.

Composition	Premusic resting state—number of IEDs (median, minimum; maximum)	Listening to the music—number of IEDs (median, minimum; maximum)	Postmusic resting state – number of IEDs (median, minimum; maximum)
The most IED-reducing composition from the first day	32 (2; 235)	26 (0; 196)	24 (0; 171)
The most similar composition from the same group (sSG)		21 (1; 184)	25 (1; 208)
The most similar composition from all compositions outside the group (sOG)		25 (0; 154)	25 (2; 264)
The most contrasting composition from the same group (cSG)		26 (2; 200)	24 (0; 170)
The most contrasting composition from all groups (cOG)		38 (2; 215)	29 (1; 290)

analysis was grounded in evaluating the acoustic properties of these compositions, categorizing them based on their similarity to or difference from the most effective composition (the composition with the lowest number of IEDs while listening to it) from the first day. That was relaxation music in one patient, minimalistic music in five patients, rapid and dynamic music in six patients, and Mozart's music in 13 patients. The findings from this day's analysis are summarized in Table 5. The most IED-reducing composition from the first day exhibited a significant decrease in IEDs between the premusic resting state and while listening to the music ($p = 0.0001$) with a median decrease of nine IEDs and a median relative decrease of 40%, and between the premusic and postmusic resting states ($p = 0.0003$) with a median decrease in 13 IEDs and a median relative decrease of 43%.

The most similar composition from the same group (sSG) demonstrated a significant decrease in IEDs between the premusic resting state and while listening to the music ($p = 0.0001$) with a median decrease of 12 IEDs and a median relative decrease of 32%, and between the premusic and postmusic resting states ($p = 0.0107$) with a median decrease of nine IEDs and a median relative decrease of 33%.

The most acoustically similar composition from all compositions outside the group (sOG) showed a significant reduction in IEDs between the premusic resting state and while listening to the music ($p < 0.0001$) with a median decrease of 12 IEDs and a median relative decrease of 44%, and between the premusic and postmusic resting states ($p = 0.0108$) with a median decrease of 12 IEDs and a median relative decrease of 39%.

The most contrasting composition from the same group (cSG) indicated a significant decrease in IEDs between the premusic resting state and while listening to the music ($p = 0.0033$) with a median decrease of six IEDs and a median relative decrease of 25%, and between the premusic and postmusic resting states ($p = 0.0005$) with a median decrease of 13 IEDs and a median relative decrease of 43%.

On the contrary, the most contrasting composition from all compositions outside the group (cOG) showed an insignificant decrease in IEDs between the premusic resting state and while listening to the music ($p = 0.1187$) and between the premusic and postmusic resting states ($p = 0.1265$). Boxplots illustrating the reduction in IEDs across patients, specifically comparing the premusic resting state with the music-listening state, are included in Supporting Information

Findings collectively underscore that, except for the most contrasting from all compositions outside the group (cOG), all other compositions led to a significant reduction in IEDs compared with the premusic resting state. But in all these results, we find small size effects. For complete results of size effect results, see the Supporting Information. We did not find any gender differences in the effect of different music on the number of IEDs. For the study design and outcomes summarization, see Figure 1.

4 | Discussion

The results of our 2-day iEEG study on music modulation of IEDs in patients with epilepsy provide insights into the potential effects of music on IEDs and emphasize that reproducibility relies on individualized testing and selection, as no universal acoustic properties or ideal compositions were identified as effective for all patients.

On the first day, the only significant IED-reducing effect was with K 595c (a median relative decrease of 28% during the music session and a 19% decrease in the postmusic resting state). This effect is less than was reported with K 448 in the iEEG study by Quon, in which they observed an average global IED reduction of 66.5% [9]. Štillová et al. (2021) also used iEEG to report a median IED reduction of 32% [12]. A meta-analysis of other scalp-EEG studies reported an average IED reduction of approximately 35% while listening to K 448 [13]. Comparing these findings to our study, it is evident that the effect of K 448 on IEDs is

TABLE 5 | Comparison of the effects of the compositions on the second day of the study.

	Change of IEDs while listening to the music and in the postmusic resting state compared to in the premusic resting state (median, minimum; maximum)				
	The most IED-reducing composition from the first day	**The most similar composition from the same group (sSG)**	**The most similar composition from all compositions outside the group (sOG)**	**The most contrasting composition from the same group (cSG)**	**The most contrasting composition from all groups (cOG)**
Absolute change—premusic resting state and while listening to the music—number of IEDs	**−9 (−167; 17)** ***p*** **= 0.0001**	**−12 (−163; 26)** ***p*** **= 0.0001**	**−12 (−159; 3)** ***p*** **= 0.0000**	**−6 (−67; 40)** ***p*** **= 0.0033**	0 (−76; 31) $p = 0.1187$
Relative change—premusic resting state and while listening to the music	−0.4 (−1; 1.06)	−0.32 (−0.86; 1.63)	−0.44 (−1; 0.43)	−0.25 (−0.71; 2.5)	0 (−0.62; 1.94)
Absolute change—premusic and postmusic resting states—number of IEDs	**−13 (−100; 13)** ***p*** **= 0.0003**	**−9 (−136; 69)** ***p*** **= 0.0107**	**−12 (−125; 42)** ***p*** **= 0.0108**	**−13 (−91; 56)** ***p*** **= 0.0005**	−3 (−123; 91) 0.1265
Relative change—premusic and postmusic resting states	−0.43 (−1; 1.57)	−0.33 (−0.9; 4.31)	−0.39 (−0.79; 2.31)	−0.43 (−1; 3.5)	−0.11 (−0.78; 2.75)

Note: Changes in the number of IEDs while listening to the music and in the postmusic resting state compared to the premusic resting state. The reduction of IEDs is represented by negative values, the increase is represented by positive values. The null hypothesis of no difference is tested against the alternative that there is a decrease in IEDs. Statistically significant changes are shown in bold.

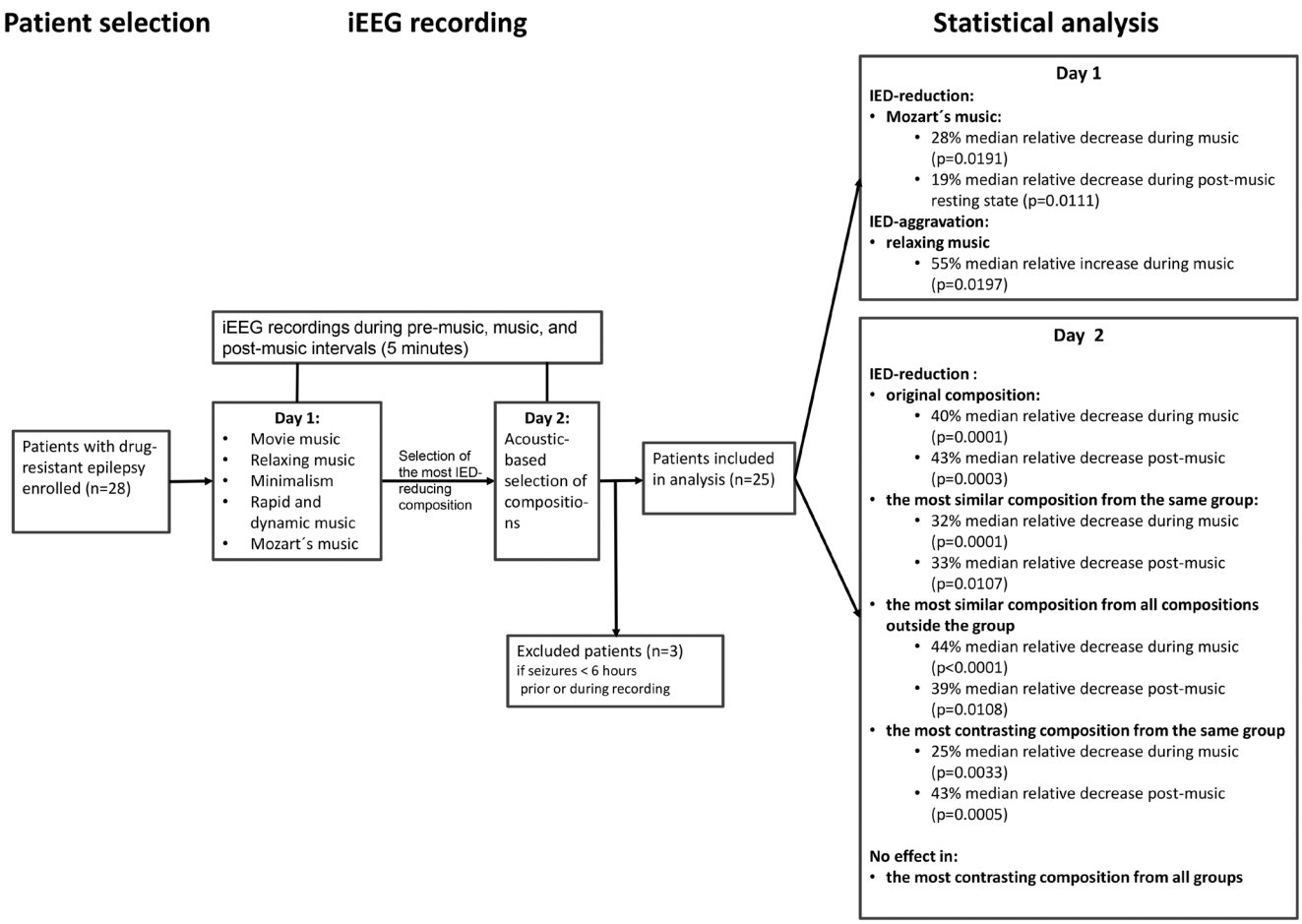

FIGURE 1 | Study design and outcomes summarization. iEEG, intracerebral EEG; IEDs, interictal epileptiform discharges.

more pronounced than that of K 595c. The remarkable reduction observed with K 448, as highlighted in Quon's study, suggests a more profound influence of this specific composition on neural activities, probably due to its unique structural, rhythmic, and harmonic characteristics.

Furthermore, Quon's study highlighted the importance of the duration of the musical stimulus, as a short exposure of 90 s to K 448 did not carry over its effect into the poststimulus periods. We found a modest but still significant carry-over effect after 5 min of exposure, resulting in reduced IEDs even in the post-music interval.

Interestingly, the results from our study revealed a counterintuitive trend regarding the subjective popularity of compositions and their effect on IEDs. From the selected compositions, those that were the most favored by patients either had no significant effect or even a worsening effect on IEDs. On the other hand, the compositions that patients favored less, particularly those in the Mozart and rapid dynamic genres, demonstrated the most significant reduction of IEDs. This finding suggests that the effect of music on reducing IEDs in epilepsy might not necessarily correlate with emotional responses or personal preferences for the music. It indicates that other factors, possibly specific acoustic properties inherent in certain types of music, could play a more crucial role in modulating IEDs.

The relationship between music and brain dynamics could be further explored in the context of findings by Teixeira Borges et al. (2019) [14], which suggest that changes in the scaling exponent of neuronal activity (1/f resonance) during music listening are linked to pleasure. The lack of such scaling effects in certain compositions might also contribute to their therapeutic impact. While our study was not designed to investigate this phenomenon, the lack of 1/f scaling resonance in specific compositions could potentially explain the observed IED-reducing effects.

The second day's results further extend these findings by demonstrating that not just Mozart's compositions but also other musically varied pieces. The median relative decrease in IEDs for various compositions ranged from 0% to 44%, highlighting the nuanced role of specific acoustic features. Notably, there was a reduction in IEDs across almost all compositions tested on the second day, including the original composition from the first day, sSG, sOG, and cSG. The significance of these results lies in their validation of the idea that even compositions that are musically different can reduce the number of IEDs if they are acoustically similar to a composition that has previously shown a positive impact. In contrast, the lack of IED reduction in response to the most acoustically contrasting composition from all groups (cOG) further validates our hypothesis. This composition, which differed significantly in acoustic properties from the original effective composition, did not produce the same

therapeutic effect, highlighting the specific nature of acoustic influence on neural modulation in epilepsy.

However, our findings also indicate that the relationship between music's acoustic properties and its impact on epilepsy is not entirely straightforward. An intriguing observation was the reduction in IEDs during the listening session to the most contrasting composition from the same group (cSG), a composition that was acoustically different from the original composition identified on the first day. Despite being acoustically distinct, this composition still reduces IEDs, suggesting that there are additional factors beyond the acoustic properties we initially set out to examine.

Interestingly, the study did not find any significant gender differences in response to music, which could indicate a more universal applicability of music-based interventions irrespective of gender. This finding is somewhat in contrast with earlier studies, including the one by Štillová et al., that suggested gender-specific responses to different acoustic properties in music.

Our findings contribute to the ongoing debate about the effect of music on the brains of patients with epilepsy. While a recent meta-analysis cast doubt on the specific effects of Mozart's music on epilepsy, suggesting that the reported effects could be driven by isolated factors, our study indicates that the therapeutic potential of music might extend beyond Mozart's compositions. The remarkable reduction in IEDs observed on the second day indicates that the acoustic properties of the music, rather than the music of Mozart per se, are instrumental in modulating epileptiform activity. This aligns with theories suggesting the involvement of complex neural networks in response to musical stimuli [8, 15]. However, the observed small effect sizes warrant careful consideration before generalizing these findings to broader clinical applications.

Moreover, the first-day results present a novel finding: the significant increase in the number of IEDs when patients listened to relaxing music. This result is particularly intriguing as it challenges the commonly held notion that all forms of relaxing music inherently have a calming or stabilizing effect on the brain's electrical activity, especially in the context of epilepsy. We hypothesize that contrary to expectations, certain characteristics of what is typically categorized as “relaxing” music might contribute to increased neural excitability in individuals with epilepsy.

In this study, we also investigated whether specific acoustic properties contributed to the reduction of IEDs across groups of patients. Specifically, we stratified patients based on the recording that was most beneficial on the first day and then performed Spearman's correlation (with Bonferroni correction) between acoustic features extracted from the contrasting parts of recordings and their associated IEDs within each group. However, we did not identify any significant correlations, suggesting that the effect of specific acoustic features on the reduction of IEDs is likely individual rather than global. Although the findings suggest that the effect of musical features on IEDs is individual, this conclusion was reached indirectly by exploring the global effect of features across all participants. These results should be interpreted with caution, as only 25 patients participated in this study.

In our study, due to the highly varied locations of iEEG electrodes within the brain, we did not analyze the impact of IED reduction in specific brain areas. The diversity in electrode placement, even within the same brain lobe, likely would have led to insufficient statistical significance in such an analysis.

It is important to emphasize that while our findings are promising, they should be interpreted with caution in terms of their implications for seizure reduction. The exact mechanism by which different acoustic properties influence the epileptic brain, particularly in reducing IEDs, remains an area for further exploration. Recording iEEG during music presentation provides an opportunity to assess alignment between the auditory envelope and EEG features, as well as amplitude modulation and simple measures of autonomic arousal. Additionally, measures of connectivity, such as global synchrony or temporary decoherence promoted by specific musical features, could provide insights into the therapeutic mechanisms.

Author Contributions

Ondřej Strýček: conceptualization, methodology, investigation, writing – review and editing, writing – original draft, validation, formal analysis, data curation. **Jiří Mekyska:** conceptualization, methodology, supervision, formal analysis, writing – review and editing. **Štěpán Miklánek:** writing – review and editing. **Michal Fusek:** validation, formal analysis, writing – review and editing. **Klára Štillová:** writing – review and editing, conceptualization, methodology, investigation, validation. **Martin Mazánek:** writing – review and editing, methodology. **Ivan Rektor:** conceptualization, methodology, writing – review and editing, supervision.

Acknowledgments

We would like to express our gratitude to the epileptologists Dr. Irena Doležalová, Dr. Jitka Kočvarová, and Dr. Martin Pail for their significant contributions to patient data collection and analysis. The authors wish to thank Dr. Martin Pail and Dr. Robert Roman for help with the localization of the intracerebral electrode contacts and Anne Johnson for grammatical assistance.

Ethics Statement

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

References

1. G. Coppola, A. Toro, F. F. Operto, et al., “Mozart's Music in Children With Drug-Refractory Epileptic Encephalopathies,” *Epilepsy & Behavior* 50 (2015): 18–22, https://doi.org/10.1016/j.yebeh.2015.05.038.

2. G. Coppola, F. F. Operto, F. Caprio, et al., "Mozart's Music in Children With Drug-Refractory Epileptic Encephalopathies: Comparison of Two Protocols," *Epilepsy & Behavior* 78 (2018): 100–103, https://doi.org/10.1016/j.yebeh.2017.09.028.

3. L. C. Lin, W. T. Lee, H. C. Wu, et al., "The Long-Term Effect of Listening to Mozart K.448 Decreases Epileptiform Discharges in Children With Epilepsy," *Epilepsy & Behavior* 21, no. 4 (2011): 420–424, https://doi.org/10.1016/j.yebeh.2011.05.015.

4. M. Rafiee, K. Patel, D. M. Groppe, et al., "Daily Listening to Mozart Reduces Seizures in Individuals With Epilepsy: A Randomized Control Study," *Epilepsia Open* 5, no. 2 (2020): 285–294, https://doi.org/10.1002/epi4.12400.

5. J. R. Hughes, Y. Daaboul, J. J. Fino, and G. L. Shaw, "The "Mozart Effect" on Epileptiform Activity," *Clinical Electroencephalography* 29, no. 3 (1998): 109–119, https://doi.org/10.1177/155005949802900301.

6. L. C. Lin, M. W. Lee, R. C. Wei, H. K. Mok, and R. C. Yang, "Mozart K.448 Listening Decreased Seizure Recurrence and Epileptiform Discharges in Children With First Unprovoked Seizures: A Randomized Controlled Study," *BMC Complementary and Alternative Medicine* 14, no. 1 (2014): 17, https://doi.org/10.1186/1472-6882-14-17.

7. L. C. Lin, M. W. Lee, R. C. Wei, et al., "Mozart K.545 Mimics Mozart K.448 in Reducing Epileptiform Discharges in Epileptic Children," *Evidence-Based Complementary and Alternative Medicine* 2012 (2012): 1–6, https://doi.org/10.1155/2012/607517.

8. A. J. Blood and R. J. Zatorre, "Intensely Pleasurable Responses to Music Correlate With Activity in Brain Regions Implicated in Reward and Emotion," *Proceedings of the National Academy of Sciences* 98, no. 20 (2001): 11818–11823, https://doi.org/10.1073/pnas.191355898.

9. R. J. Quon, M. A. Casey, E. J. Camp, et al., "Musical Components Important for the Mozart K448 Effect in Epilepsy," *Scientific Reports* 11, no. 1 (2021): 16490, https://doi.org/10.1038/s41598-021-95,922-7.

10. J. R. Hughes, "The Mozart Effect," *Epilepsy & Behavior* 2, no. 5 (2001): 396–417, https://doi.org/10.1006/ebeh.2001.0250.

11. S. Oberleiter and J. Pietschnig, "Unfounded Authority, Underpowered Studies, and Non-Transparent Reporting Perpetuate the Mozart Effect Myth: A Multiverse Meta-Analysis," *Scientific Reports* 13, no. 1 (2023): 3175, https://doi.org/10.1038/s41598-023-30206-w.

12. K. Štillová, T. Kiska, E. Koriťáková, et al., "Mozart Effect in Epilepsy: Why Is Mozart Better Than Haydn? Acoustic Qualities-Based Analysis of Stereoelectroencephalography," *European Journal of Neurology* 28, no. 5 (2021): 1463–1469, https://doi.org/10.1111/ene.14758.

13. G. Sesso and F. Sicca, "Safe and Sound: Meta-Analyzing the Mozart Effect on Epilepsy," *Clinical Neurophysiology* 131, no. 7 (2020): 1610–1620, https://doi.org/10.1016/j.clinph.2020.03.039.

14. A. F. Teixeira Borges, M. Irrmischer, T. Brockmeier, D. J. A. Smit, H. D. Mansvelder, and K. Linkenkaer-Hansen, "Scaling Behaviour in Music and Cortical Dynamics Interplay to Mediate Music Listening Pleasure," *Scientific Reports* 9, no. 1 (2019): 17700, https://doi.org/10.1038/s41598-019-54,060-x.

15. J. R. Hughes and J. J. Fino, "The Mozart Effect: Distinctive Aspects of the Music—A Clue to Brain Coding?," *Clinical Electroencephalography* 31, no. 2 (2000): 94–103, https://doi.org/10.1177/155005940003100208.

Supporting Information

Additional supporting information can be found online in the Supporting Information section.