Music as medicine: a literature review on the effectiveness of Mozart's music on epilepsy

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Music, in particular Mozart's K448 Sonata for Two Pianos, has been said to have a potential to alleviate epilepsy, hence it has potential as a non-pharmacological intervention or therapy. This effect is termed the "Mozart effect": listening to Mozart's K448 was associated with a reduction in epileptic activity on the electroencephalograms of epileptic patients. Thus far, no literature was found summarizing and analyzing the relevant literature in this topic, exploring the different characteristics that could affect the effectiveness of music therapy in alleviating epilepsy. This literature review therefore aimed to consolidate and discuss the literature surrounding this issue. The literature review was conducted using six databases: DOAJ, Google Scholar, JSTOR, PubMed, ScienceDirect and Scopus. Key terms "Mozart", "Music", "Epilepsy", "Seizure" and "Epileptic" were included in the search strategy, and relevant articles were shortlisted based on the title and abstract. 22,410 articles were found in total. Only English articles found in the six databases were shortlisted for this review. 13 articles were shortlisted for final review. The 13 shortlisted articles were classified to discuss one or more of the following topics: Investigating the effectiveness of music in reducing the occurrence of epilepsy for peoples of different age groups, effectiveness of music in reducing the occurrence of different types of epilepsy and seizures, effectiveness of different types of music in reducing the occurrence of epilepsy, and theories behind K448 as a potential treatment for epilepsy. In conclusion, all the studies showed that Mozart's K448 music seems to be a potentially effective and affordable option of an alternative or additional therapy for epileptic patients that causes little to no harm.

Keywords: Mozart, Epilepsy, Seizure, Music, Electroencephalogram

1. Introduction

Epilepsy is a disease of the brain which is distinguished by repeated seizures, and is defined as having two or more unprovoked seizures (Epilepsy, 2019). Numerous types of epilepsy have been studied, and their treatments have also been widely explored. Types of epilepsy can be classified into:

> Focal seizures, and generalised-onset seizures which includes: absence seizures, myoclonic seizures, tonic and atonic seizures, tonic, clonic and tonic-clonic seizures. (Types of Seizures, n.d., Shorvon, 2010)

Epilepsy treatments can be grouped into 2 broad categories: pharmacological and non-pharmacological. Pharmacological treatments involve anti-epileptic drugs, whereas non-pharmacological treatments can include ketogenic diets, deep brain and vagal nerve stimulation, transcranial magnetic stimulation as well as epilepsy surgery (Parakh and Katewa, 2014).

Besides commonly used antiseizure drugs such as sodium valproate, phenobarbital, clobazam, and clonazepam (Stephen and Brodie, 2010), of interest is an area of non-pharmacological intervention: music as a potential form of therapy for epileptic patients, in particular, Wolfgang Amadeus Mozart's music: Sonata for two pianos in D major (K448). This piece for two pianos comprises of 3 movements and was composed in 1784, and later revised by Alfred Dörffel and published by C.F. Peters. The three movements of the piece are: Allegro con spirito, Andante, and Molto Allegro (Mozart, n.d.).

Hughes et al., 1998 first discovered the "Mozart effect" in epilepsy whereby listening to Mozart's K448 was associated with a reduction in epileptic activity on the electroencephalograms of 23 out of 29 patients. This was an exceptional and valuable finding as music was found to potentially serve as a cheaper and safer alternative treatment for epileptic patients, especially those with drug-resistant epilepsy. There is, by far, no precise definition of "drug-resistant epilepsy" (French, 2006). However, an epilepsy is generally considered as "refractory," or "drug-resistant" when seizures cannot be managed by at least two anti-seizure drugs suitable for the kind of epilepsy (Soranzo, Goldstein and Sisodiya, 2005, Sisodiya, 2003, French et al., 2004, Schiller and Najjar, 2007).

Many more studies on the promising potential of Mozart's music to serve as an alternative therapy had since been produced.

2. Literature Review

In the area of music and seizures, several studies were found discussing topics such as non-pharmaceutical interventions to treating seizures, triggers of musicogenic seizures, the "Mozart

Effect" as a potential form of therapy for seizures, and potential of music therapy in alleviating cognitive impairment in epileptic patients. There was robust research in music therapy for epileptic patients, particularly on Mozart's Sonata for two pianos in D major (K448). However, no literature was found summarizing and exploring the different characteristics that could affect the effectiveness of music therapy in alleviating epilepsy. This literature review therefore aimed to consolidate and discuss the literature surrounding this issue.

3. Methods

3.1 Search Strategy

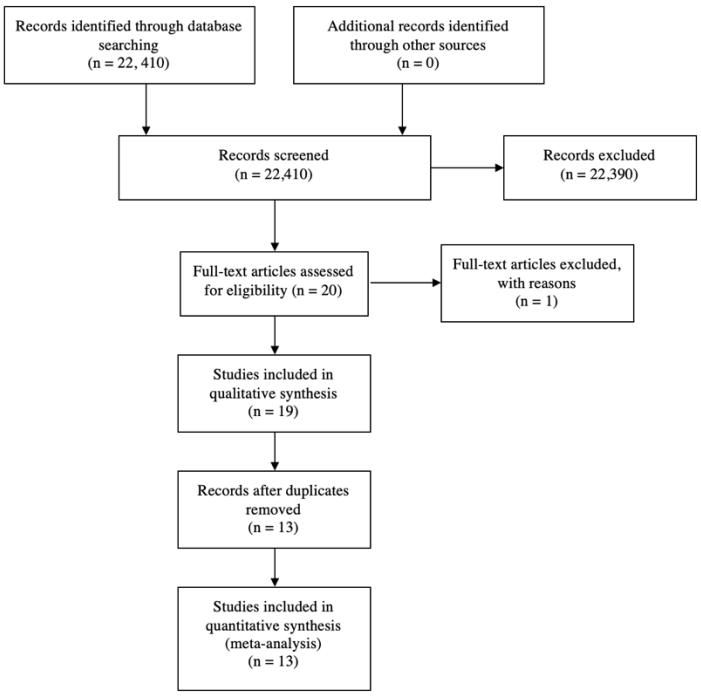

DIAGRAM 3.1. *PRISMA flowchart on search strategy.*

The literature review was conducted using six databases: DOAJ, Google Scholar, JSTOR, PubMed, ScienceDirect and Scopus. Key terms "Mozart", "Music", "Epilepsy", "Seizure" and "Epileptic" were included in the search strategy, and relevant articles were shortlisted based on the title and abstract. 22,410 articles were found in total. Only English articles found in the six databases were shortlisted for this review.

3.2 Inclusion Criteria

Articles discussing forms of music with the potential to serve as therapy for epileptic patients were shortlisted for review, through

the following search means: ("music" OR "mozart") AND ("epilepsy" OR "seizure" OR "epileptic"). Other criteria of inclusion includes articles written in English, research on experiments based on controlled randomized trials and clinical trials, as well as articles that measured the effectiveness of music on epileptic patients through quantitative means. Other relevant articles were also hand-searched from bibliographies of shortlisted articles.

3.3 Exclusion Criteria

13 articles were shortlisted for final review. In choosing the articles for final review, the following exclusion criteria were used: articles dated before 2011, systematic reviews and reviews, articles not written in the English Language, articles on other forms of treatment for epilepsy and articles that investigated the potentiality of music as a potential trigger for epilepsy.

4. Results

The 13 shortlisted articles were classified to discuss one or more of the following topics:

1. Investigating the effectiveness of music in reducing the occurrence of epilepsy for peoples of different age groups
2. Investigating the effectiveness of music in reducing the occurrence of different types of epilepsy and seizures
3. Investigating the results of the effectiveness of different types of music in reducing the occurrence of epilepsy
4. Theories behind K448 as a potential treatment for epilepsy

4.1 Investigating the Effectiveness of Music in Reducing the Occurrence of Epilepsy for Peoples of Different Age Groups

In the studies of the effectiveness of music in reducing the occurrence of epilepsy with a target age group in mind, 1 study was conducted on infants, 7 were conducted on children, 1 on both children and adults and 2 on adults. Across the board, it can be concluded that music is equally effective in reducing the occurrence of epilepsy for peoples of different age groups, such as infants, children and adults.

4.1.1 Infants

H. Ren et al.'s 2019 research evaluated the effects of Mozart music on cerebral hemodynamics in preterm infants and the statistical analysis results showed that when comparing the experimental group with the control group in resting state, the sample entropy of the experimental group was significantly lower. This means that the cerebral activity had strong regularity and consistency, thereby implying the positive effects of Mozart’s music on reducing brain activity.

4.1.2 Children

Studies have also shown that music can significantly decrease the frequency of occurrence of seizures in children. With reference to Table 1 in Annex A, it can be seen in the studies of E. Grylls et al. (2018), L. Lin et al. (2010), L. Lin et al. (2012), L. Lin et al. (2013), L. Lin et al. (2014) and T. Paprad, M. Veeravigrom, T. Desudchit (2020) that a good majority of patients exhibited decreased epileptiform discharges while listening to music. The studies of Coppola, G. et al. (2018), L. Lin et al. (2011), L. Lin et al. (2014) and M. Bodner et al. (2012) also show that the recurrence of seizures in patients who have listened to music is lowered in frequency. This shows that music is largely effective as a non-invasive treatment for epilepsy or as a means to reduce epilepsy for children.

4.1.3 Adults

As with the children and infants, a reduction in seizure count can also be seen in the studies conducted for adults. The studies of C. Bedetti et al. (2019), Coppola, G. et al. (2018), D'Alessandro, P. et al. (2017), M. Bodner et al. (2012) and M. Rafiee et al. (2020) shows statistical evidence that a good majority of adults who have been exposed to Mozart's music showed an improvement in epileptic conditions.

4.2 Investigating the Effectiveness of Music in Reducing the Occurrence of Different Types of Epilepsy and Seizures

Generally, music showed promising effectiveness across both drug-resistant epilepsy as well as general epilepsy, although some studies reported higher effectiveness in certain groups of epileptic patients. There were a total of 5 studies (D'Alessandro et al., 2017, L. Lin et al., 2011, Coppola et al., 2018, Bedetti et al., 2019, Paprad et al., 2020) that investigated the effect of music on drug-resistant epilepsy, and a total of 8 studies on general epilepsy, 3 of which (Grylls et al., 2018, M. Rafiee et al., 2020, H. Ren et al., 2019) did not discuss the effect of music on any type of specified epilepsy and were hence not included in this segment.

4.2.1 Investigating the effectiveness of music in improving drug-resistant epilepsy

Drug-resistant, refractory or pharmacoresistant epilepsy is defined by the International League against Epilepsy (ILAE) as:
failure of adequate trials of two tolerated and properly selected and utilized anti-epileptic drug schedules (whether as monotherapies or in combination) to achieve sustained seizure freedom (Kwan et al., 2010).

In the 5 studies that discussed drug-resistant epilepsy, all postulated that listening to Mozart's K448 music had an effect of a significant reduction in seizure frequency in patients with drug-resistant epilepsy.

D'Allesandro et al.'s 2017 study was conducted on subjects with drug-resistant and symptomatic epilepsy. Overall, half of all the subjects in the study exhibited a very good response to treatment whereby subjects listened to Mozart's sonata for two pianos in D major, K448, once a day for six months. There were no patients who experienced a worsening of their seizure frequencies. One patient was found to be free of seizures, five patients attained a more than half times reduction in seizure frequency, while the rest of the patients experienced no significant changes. The treatment effect however did not persist over time. This was also seen in Coppola et al.'s 2017 study, where all studied patients had drug-resistant epilepsy. In both groups where patients listened to Mozart's K448 and Mozart's other compositions, there were positive impacts on seizure frequency reduction, apart from few patients who experienced no change. One study had found that effectiveness of music therapy could be higher in patients with generalized seizures as compared to focal seizures: in L. Lin et al.'s 2011 study, 6 patients with generalized seizures and 2 with focal seizures became seizure free or had a very good response to listening to Mozart K.448 during 6 months of music therapy. 85.7% of patients with generalized seizures had effective outcomes while 50% of patients with focal seizures experienced effective outcomes. Therefore, it can be seen that patients with generalized seizures responded better towards Mozart K.448 music treatment. Another study found that tonic-clonic seizures in drug-refractory epilepsy patients were more effectively reduced than atonic seizures through music therapy. In C. Bedetti et al.'s 2019 study, one subject with drug-resistant epilepsy with atonic and tonic-clonic seizures was studied. There was a significant decrease of 46.6% in the frequency of generalized epileptiform discharges after listening to Mozart's K448 music compared to the day before the music therapy, where tonic-clonic seizures have been found to be reduced to a greater extent than atonic seizures. Lastly, one study found that music therapy did not have lasting improvements on drug-refractory epilepsy. In Paprad et al.'s 2020 study, 96% of the participants had pharmacoresistant epilepsy. This study found that allowing children with pharmacoresistant epilepsy to listen to Mozart K.448 for 8 minutes induced significant decreases in the numbers of interictal epileptiform discharges. However, after the music therapy, there was an increase in the number of interictal epileptiform discharges, which indicates short-term effects of the music.

4.2.2 Investigating the effectiveness of music in improving generalized epilepsy

3 studies found that the effectiveness of Mozart music in improving generalized epilepsy, as compared to focal epilepsy, was higher. In L. Lin et al.'s 2012 study, over 80% of patients had experienced decreased interictal discharge frequencies when listening to either Mozart's K.448 or K.545 music pieces. However, the patients with generalized epilepsy were found to have lower interictal discharge frequencies as compared to patients with focal seizures towards the aforementioned two music pieces. With regards to the epileptiform discharge foci in patients who listened to both music pieces, the mean decreases in epileptiform discharges when comparing against records before music therapy were greater in patients who had central and generalized discharges. Likewise in L. Lin et al.'s 2013 study, the effect of Mozart music listening decreasing epileptiform discharges was particularly greater in patients with generalized seizures or discharges. As for L. Lin et al.'s 2010 study, following therapy with Mozart's K448, it was found that patients with generalized epilepsy experienced higher effectiveness of the music in decreasing interictal discharge frequencies as compared to patients with focal seizures, although the difference was insignificant. The largest decrease in interictal discharge frequencies was found to be with discharges from the central cortex or with generalized discharge.

With regards to whether etiology of seizures affects the effectiveness of music therapy in improving epilepsy in patients, 2 studies had found no significant effect while 1 study found that idiopathic seizures had a higher rate of effectiveness than symptomatic seizures. As seen in M. Bodner's 2012 study, both groups of subjects with symptomatic and idiopathic seizures demonstrated a significant decrease in seizures after listening to Mozart's K448, but there was a greater reduction in both music therapy and subsequent follow-up years in patients with idiopathic seizures, as compared to patients with symptomatic seizures. However, in L. Lin et al.'s 2012 and 2014 studies, there were no significant differences in gender, seizure type, and etiology between the seizure recurrence and non-recurrence subjects, and no significant differences in epileptiform discharges by epilepsy etiology as well.

4.3 Investigating the Results of the Effectiveness of Different Types of Music in the Reducing the Occurrence of Epilepsy

There were 3 studies that have introduced other forms of music (other than Mozart's K448) in the experimental set-up to investigate the effectiveness of different types of music in reducing the occurrence of epilepsy.

The findings of E. Grylls et al. (2018) had also pointed out that as of present times, the "Mozart Effect" is unique to Sonata in D Major for 2 Pianos (K. 448) and music of similar structure and composition. L. Lin et al. (2012) and Coppola G. et al. (2018) have shown in their research that other pieces by Mozart were equally effective (and in certain conditions, more effective) in reducing the frequency of epileptic discharges. Coppola G. et al. (2018) have also reported other behavioral improvements in the experimental group that had listened to other types of Mozart music, such as:

> less irritability and tearfulness, reduced self-/heteroaggression, a better daytime vigilance, and nighttime sleep quality.

This then shows the possibility of using other types of Mozart music that is of similar characteristics to that of K. 448 in the treatment of epilepsy.

However, as mentioned before, the "Mozart Effect" is not seen or present in pieces of other make. E. Grylls et al. (2018) cited the example of Bodner et al. and Hughes et al. whose studies in Beethoven's "Fur Elise" and "old time pop piano tunes" have proven ineffective in the frequency of seizures or reduced epileptic discharges. This is also confirmed by M. Rafiee et al. (2020) who had conducted the experiment over two phases: first (treatment period) with patients listening to the first six minutes of Sonata for two pianos in D major for three months; the second (control period) with patients listening to a phase-scrambled version of the aforementioned piece. Results have shown that a reduction in seizure count was observed in the treatment period but not the control period. A further study by L. Lin et al. (2010) had also conducted a study using a computerized string version of K. 448 and results show that the epileptic discharges were not reduced at all. This therefore shows that melody, harmony, form, structure and timbre of the piece could have a part to play in the possibility of reducing the frequency of seizures and/or epileptic discharge.

4.4 Theories Behind the K448 as a Potential Treatment for Epilepsy

There are several theories for the effectiveness of Mozart's K448 on improving epilepsy and seizures.

One of the theories for the "Mozart Effect" is the musical enhancement of parasympathetic tone. Mozart music has been found to possibly cause parasympathetic activation (L. Lin et al., 2013). Listening to Mozart music could regulate the thalamic region, increasing parasympathetic tone, thereby resulting in the benefits experienced by patients with generalized epilepsy (L. Lin et al., 2014).

The "Mozart Effect" might also occur with the help of sensorimotor circuits by "mirror neurons", where such "mirror

neurons" help regulate neuron activity through connecting auditory stimulation straight to the motor cortex (L. Lin, 2011).

Another theory involves neurotransmitter pathways (L. Lin et al., 2014). Listening to music increases the expression of dopamine levels in the brain, and contributes to effectiveness of music therapy as it enhances the neuroplasticity of the brain (Stegemöller, 2014). Listening to music could change the dopaminergic pathways contributing to the effectiveness of music therapy in epileptic patients (L. Lin et al., 2014)

Overall, more research has to be done to determine the mechanism of Mozart's K448 on improving epilepsy, by delving into the musical traits of K448 that cause parasympathetic activation, musical effects that regulate neuron activity and musical material that increases the expression of dopamine levels in the brain.

5. Discussion

The overall effectiveness and limitations of different areas in this topic of music therapy on epileptic patients is summarized in the table below:

Method / Topic of Interest	**Effectiveness**	**Limitations**
Study on infants	Effective	Small sample size Limited studies on infants
Study on children	Effective	Some subjects were prescribed sedation medication prior to EEG, which might have caused some effects on EEG frequency. The studies were also limited by the limited number of test subject patients and the lack of diversity in backgrounds of them. Some studies had not used a control music in their setup, which did not eliminate the possibility of the placebo effect. There was not a follow-through on the EEG in all patients of the control group for some studies.
Study on adults	Effective	The sample size of studies conducted on adults was small. Limited studies conducted on adults.

Study on improving drug-resistant epilepsy	Effective	Small sample sizes Short duration of follow-ups following music therapy
Study on improving generalized epilepsy	Effective	Small sample sizes Some studies did not have a control setup with other music to eliminate potential of a placebo effect
Study on re-orchestrated version of K. 448	Not Effective	Limited studies on the effectiveness on re-orchestrated pieces of Mozart
Study on other Mozart pieces	Little Effectiveness	Limited studies on other Mozart pieces except for K. 554, symphony No. 41, K551; piano concerto No. 22, K482; violin concerto No. 1, K207; violin concerto No. 4 in D major, K218, allegro aperto; symphony No. 46 in C major, KV96, allegro; and flute concerto in D major K314, allegro aperto.
Study on music of other composers	Not effective	Little research was conducted on other types of music by other composers except "Fur Elise" by Beethoven and "old time pop piano tunes"

6. Conclusion

In conclusion, all the studies showed that Mozart's K448 music seems to be a potentially effective and affordable option of an alternative or additional therapy for epileptic patients that causes little to no harm. We found that in all of the studies, there was a short duration for follow-ups for music therapy, small sample sizes (with the biggest group being 64 subjects), and there were very few studies on other forms of music on whether they might also potentially be effective at alleviating seizures. Not much is also known about the mechanisms behind the effectiveness of Mozart K448. Hence, future research in this topic could focus on the following areas:

1. Determining if there are other forms of music (classical or others) that result in improvements in epileptic patients
2. Determining if music therapy has potential to result in long-lasting impacts through longer follow-up periods of time following music therapy
3. Determining if music therapy is effective in larger sample sizes

These could shed light on the reasons behind why music therapy is effective, which could potentially aid future research in

coming up with treatments for epilepsy or other similar diseases. We conclude that while music therapy using Mozart's music seems to be harmless and at least partially effective for alleviating epilepsy, there is more room for further research to be conducted to find out how it works and improve future epilepsy treatments.

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Appendix A: Summary of Studies

Authors (Year)	Age of Target Group	Type of epilepsy investigated	Number of test subjects	Method	Results
C. Bedetti et al. (2019)	Adults	drug-resistant/refractory epilepsy	1	The patient listened to Mozart's K448 while his brain activity was recorded. Differences in epileptiform activity before and after music therapy were analyzed.	Significant decrease in frequency of generalized epileptiform discharges after music therapy was observed.
Coppola, G. et al. (2018)	Children Adults	drug-resistant/refractory epilepsy	19	About half the subjects listened to Mozart's sonata in D major for two pianos (K448) while the other group listened to a set of Mozart's other compositions. Seizure frequency, type, and duration were manually recorded. Patients were later clinically reassessed.	With Mozart's K448, there was either seizure reduction in the children or no observed changes. With other Mozart music, a significant number of children had seizure reduction.
D'Alessandro, P. et al. (2017)	Adults	drug-resistant/refractory epilepsy	12	Patients were assigned into two groups in a crossover design study. Patients listened to Mozart K448 for six months.	During the music period, patients were either seizure-free, did not show significant changes, or experienced great

				Frequency of seizures was recorded through manual means.	reduction in seizure frequency.
E. Grylls et al. (2018)	Children	general epilepsy	45	Patients listened to Mozart's Sonata for two pianos in D major (K448), while the control group listened to other age-appropriate music. Frequency of seizures was recorded through manual means.	A significant reduction in the frequency of epileptic discharges was found during listening to the Mozart music as compared to without the music.
L. Lin et al. (2010)	Children	general epilepsy	58	Patients listened to Mozart's Sonata for two pianos in D major, K.448, as well as a digitally devised string version of K448, and the frequencies of epileptic discharges were compared.	Interictal discharges were reduced in most patients. Decrease in epileptiform discharges persisted after the music therapy in most patients.
L. Lin et al. (2011)	Children	drug-resistant/refractory epilepsy	11	Patients listened to Mozart K.448 once a day before bedtime for 6 months. Frequencies of seizures were compared before and	Majority of patients were seizure free or had very good responses while others showed minimal effect.

				after listening to Mozart K.448.	
L. Lin,et al. (2012)	Children	general epilepsy	39	Patients listened to Mozart K.448 and K.545, one week apart Frequencies of epileptiform discharges were compared before, during and after the music treatment.	Significant decrease in the frequency of epileptiform discharges was observed in both the K448 and K545 groups.
L. Lin et al. (2013)	Children	general epilepsy	64	Patients' EEGs were monitored before, during and after listening to Mozart K.448 or K.545 and analyzed.	Epileptiform discharges were significantly reduced after listening to Mozart Music.
L. Lin et al. (2014)	Children	general epilepsy	46	Children in the treatment group listened to Mozart K.448 daily before bedtime for at least six months and rates of seizures recurrence were analyzed.	Significant decreases in epileptiform discharges were observed after listening to Mozart K.448 compared to the time without music therapy.
M. Bodner et al. (2012)	Children Adults	general epilepsy	36	Treatment group subjects were exposed to specific music at regular intervals while control	Subjects who underwent music treatment showed significant decreases in

				subjects had no music. Seizure rates were recorded and analyzed.	seizures both during and after the treatment was over. A few subjects were observed to be seizure-free.
M. Rafiee et al. (2020)	Adults	general epilepsy	13	Each participant was exposed to both three months of Sonata for two pianos in D major by Mozart and three months of a phase-scrambled version as control. Seizure rates were recorded manually throughout, and the results were compared.	The results revealed a reduction in seizure counts during the treatment period, which was not observed in the control period.
Ren, H. et al. (2019)	Infants	general epilepsy	16	Control group was without music. In the music therapy group, Mozart's Sonata for Two Pianos in D, K448 was played with headphones. Cerebral hemodynamics were then analyzed.	Sample entropy of experimental group was significantly lower than that of control group after music intervention.
T. Paprad, M. Veeravigrom, T.	Children	drug-resistant epilepsy and general epilepsy	32	Treatment group: listened to Mozart K.448	Majority of patients in the music group exhibited

Desudc hit (2020)				during EEG recording Control group: underwent an EEG recording of the same duration IED frequency was manually determined and EEG and heart rate variability were analyzed.	significantly decreased IEDs while listening to music.

Abbreviations: EEG: electroencephalogram; ECG: electrocardiogram; MRI: Magnetic resonance imaging; IEDs: interictal epileptiform discharges