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Perspective

# A systematic review of the Mozart effect in adult and paediatric cases of drug-resistant epilepsy: A sound approach to epilepsy management

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ABSTRACT

*Objectives:* In recent years, adjunctive therapies for epilepsy management are being explored due to considerable side effects carried by antiepileptic drugs (AEDs) and widespread reports of drug-resistant epilepsy. One such approach is non-invasive musical neurostimulation. Within this context, Mozart's sonata K448 has received particular attention following reports of reduced seizure frequency and a decrease in epileptiform discharges during and after music exposure; often described as the 'Mozart effect'. However, controversy exists around the effectiveness of K448 in epilepsy and the strength and quality of the evidence supporting it. Therefore, this study aims to systematically review the available literature around the Mozart effect, in both adult and paediatric cases of epilepsy.

*Methods:* We carried out a literature search on PubMed, Science Direct, Scopus and Web of Science using the query string ALL= (Mozart AND epileps*). Selected clinical studies were classified based on the age of the population studied, as paediatric (0–18 years), adult (19 years or older) or a combination of the two. All the studies were evaluated using the Johns Hopkins Nursing Evidence-Based Practice (JHNEBP) rating scale to determine the strength of the evidence (level) and the quality of the research evidence.

*Results:* Out of 538 records, 25 studies were selected, grouped based on the age of the population studied and evaluated using the JHNEBP rating scale. Ten level 1 studies, which represent the strongest evidence, were identified, including six RCTs and three *meta*-analyses. Nine of these ten studies show a decrease in epileptiform discharges and in seizure frequency following exposure to Mozart's K448. One multiverse analysis reported lack of statistically significant evidence to support the use of K448 in epilepsy or any other medical condition.

*Conclusions:* A growing body of evidence supports the Mozart effect on epilepsy, with notable studies including RCTs and comprehensive *meta*-analyses. This review identified nine level 1 studies, conducted by research groups worldwide, which endorse the use of Mozart's music to reduce seizures and epileptiform discharges in adult and paediatric epilepsy patients. However, existing research exhibits limitations like varying protocols, small sample sizes and diverse treatment regimens. Additionally, studies that combine adult and paediatric patients fail to take account of developmental differences between these two groups – particularly with regards to brain maturation and neurophysiology – which could negatively impact upon the accuracy of findings by obscuring important age-related differences in response to intervention. Adequately addressing these limitations will be crucial to demonstrating proof of concept; otherwise, a potentially valuable, non-invasive, accessible, and affordable therapeutic option for drug-resistant epilepsy will remain on the medical fringe. Further research with larger samples and stricter protocols, particularly considering patient age and drug regimens, is required.

## 1. Introduction

In 1993, Rauscher and colleagues reported that listening to Mozart's sonata for two pianos in D major, K488, for 10 min, resulted in a transient improvement in spatial-reasoning skills compared to listening to a relaxation tape or sitting in silence [1]. Studying thirty-six college students, they specifically described an increase of 8–9 points in the IQ of the subjects exposed to Mozart's music, compared to the other two conditions [1]. These findings started to receive media attention in 1994 and the hypothesis that listening to Mozart could improve cognitive

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abilities became known as the 'Mozart effect'. However, multiple laboratories failed to replicate the initial findings of Rauscher *et al.*, leading to strong scepticism among the scientific community about the Mozart effect's validity in healthy subjects [2,3].

In 1998, Hughes and colleagues started exploring whether listening to Mozart's K448 could affect the electroencephalograms (EEGs) of patients with epilepsy [4]. When listening to Mozart's K448, 23 out of 29 patients affected by seizures (of different severity) displayed a decrease in the number and amplitude of interictal epileptiform discharges (IED) [4]. Following this seminal study, multiple case reports and prospective studies (including randomized control trials: RCTs) have been published describing the anti-seizure and anti-epileptiform effect of Mozart's music in both paediatric and adult cases of epilepsy [5–19]. Consequently, there are now systematic reviews and *meta*-analyses covering the topic area [20–29]; the latter represent the most rigorous form of evidence and currently amount to three. However, differences in study design, methodology and clinical populations, limit our ability to draw definitive conclusions about the effectiveness of Mozart's music in the management of epilepsy. This, in turn, presents a barrier to the intervention's use as a tool for the clinical management of epilepsy. Currently, in the United Kingdom (UK), 633,000 people have a known diagnosis of epilepsy with, on average, 79 people receiving an epilepsy diagnosis every day[30]. Epilepsy frequently affects the physical and mental well-being of patients. According to a recent survey conducted across five European countries, the condition itself, along with certain treatments, disrupts daily activities, leading to a diminished quality of life for individuals with epilepsy when compared to those without the condition [31]. Significantly, the 2019 Global Burden of Diseases, Injuries, and Risk Factors Study (GBD) reports that, globally, idiopathic epilepsy accounts for 0.52 % of all disability adjusted life years (DALYs) [32]. Perhaps unsurprisingly, given such a statistic, the economic costs of epilepsy to healthcare systems across the world is not insubstantial [33]. Unfortunately, a definitive cure based on aetiology is not available, although most cases remit or resolve after childhood if adequate treatment aimed to reduce seizure frequency is set [34]. However, antiepileptic medications carry considerable side effects and for one third of epilepsy patients worldwide these medications show limited to no effectiveness [35,36]. For this reason, there is a pressing need to explore new therapeutic options for the management of epilepsy; with musical neurostimulation, through Mozart's music, representing a promising line of enquiry due to apparent neuromodulation effects, its non-invasive nature, and minimal costs.

The last comprehensive review of the Mozart effect in epilepsy dates to 2020 [27]. Since then, four additional studies have been published, contributing to our knowledge on the topic [9,15,17,25]. This paper will update and extend our knowledge in this area by conducting a systematic review of the current literature base, encompassing both paediatric and adult patients, with the goal of providing clinicians and researchers with a comprehensive overview of the field as it stands.

## 2. Methods

A research question was formulated following the population, intervention, comparison, outcome (PICO) strategy [37]. The chosen patient (P) group were children and adults with epilepsy; the intervention (I) was exposure to one/a set of Mozart's compositions; comparison (C) between exposure to Mozart's music and other musical stimuli was included when possible; and the outcome (O) was changes in seizure frequency and/or in IEDs.

The inclusion criteria involved clinical, peer-reviewed, English language studies of the Mozart effect on epilepsy, where (i) the treatment music was by a single composer, (ii) the control was either silence or a musical stimulus (if present) and (iii) the outcome was a change in seizure or IED frequency. Preclinical studies involving animal models, systematic and narrative reviews, abstracts submitted to conferences, letters to the editor and comments, were omitted. The literature search was carried out on PubMed, Science Direct, Scopus and Web of Science databases, with the query string ALL= (Mozart AND epileps*) (adapted based on database-specific setting), producing 54, 200, 422 and 72 results, respectively. After removal of duplicates, 538 records were screened based on title and abstract, then 65 full-text records were screened for eligibility criteria, leading to the final selection of 25 studies (Fig. 1). Reference lists of selected studies were screened for relevant citations, producing one additional paper to review [13]. All studies were evaluated using the Johns Hopkins Nursing Evidence-Based Practice (JHNEBP) rating scale [38] to determine the strength (level) and the quality of the research evidence (Table 1). Importantly, the decision on the study's quality was dependent on the study level. For example, a level I study could be deemed of low quality if it had a small sample size, while a level V study, such as a case report, would be considered high quality despite small sample size.

Studies were also divided (based on the population studied) into paediatric (0–18 years), adult (19 years and older) or a combination of both. The 27-item checklist from the PRISMA 2020 statement for transparent and clear reporting of systematic reviews was followed throughout [39,40].

## 3. Results

The 25 selected studies were classified based on the population of interest (paediatric, adult, paediatric-adult combined). The JHNEBP rating scale was applied to evaluate the strength (level) and quality of the evidence for all studies [38]. A comprehensive summary of all the studies, including sample characteristics, inclusion criteria, protocols, findings and level and quality of the evidence according to the JHNEBP scale, can be found in Tables 2-5.

### 3.1. Paediatric studies

Nine studies involving a paediatric population were analysed, comprising three Level I studies [23,25,28], five Level II studies [10–12,14,16], and one Level V study [6](Table 2). All three Level I studies were RCTs. The RCT by Lin and colleagues [23] reported that after 6 months of listening to K448 the seizure recurrence rate was lower in the treatment group compared to the control group (silence); 22.7 % for the treatment group versus 58.3 % for the control group. The same authors also observed a significant decrease in IEDs after 1, 2 and 6 months of listening to K448, when compared to baseline. Patients in the control group reported no significant changes in IEDs during the average period of 3.3 months.

Paprad and colleagues [25], meanwhile, reported a significant decrease in IEDs in 67 % of patients during single 8 min exposure to K448, compared to an increase in IEDs observed in 42 % of patients in the control group (silence). They also observed an increase in IEDs after exposure to K448, suggesting the lack of a carry-over effect. Furthermore, they described a 34 % decrease in parasympathetic activity during music exposure in the treatment group.

Turner [28] also described a significant decrease from baseline in mean IEDs during exposure to K448 (33.7 %, 50.6 % and 33.9 % for three epochs, respectively). No significant IEDs decrease was reported during exposure to control music (Beethoven's Für Elise).

In line with this, Grylls and colleagues [14] reported observing a lower number of IEDs during exposure to K448 for 5 min when comparison was made to those exposed to age-appropriate control music. A statistically significant difference in the frequency of IEDs was found between baseline and exposure to K448 ($p < 0.0005$).

A further study by Lin and colleagues [16] described a significant decrease in IEDs during a single exposure to either K448 or Mozart's Sonata K545, compared to IED frequency before music exposure (33.3 $\pm$ 31.1 reduction, $p < 0.001$ during K448 and 38.6 $\pm$ 43.3 % reduction, $p < 0.001$ during K545). The same research group noted a significant reduction in IEDs immediately after a single exposure to K448 and K545;

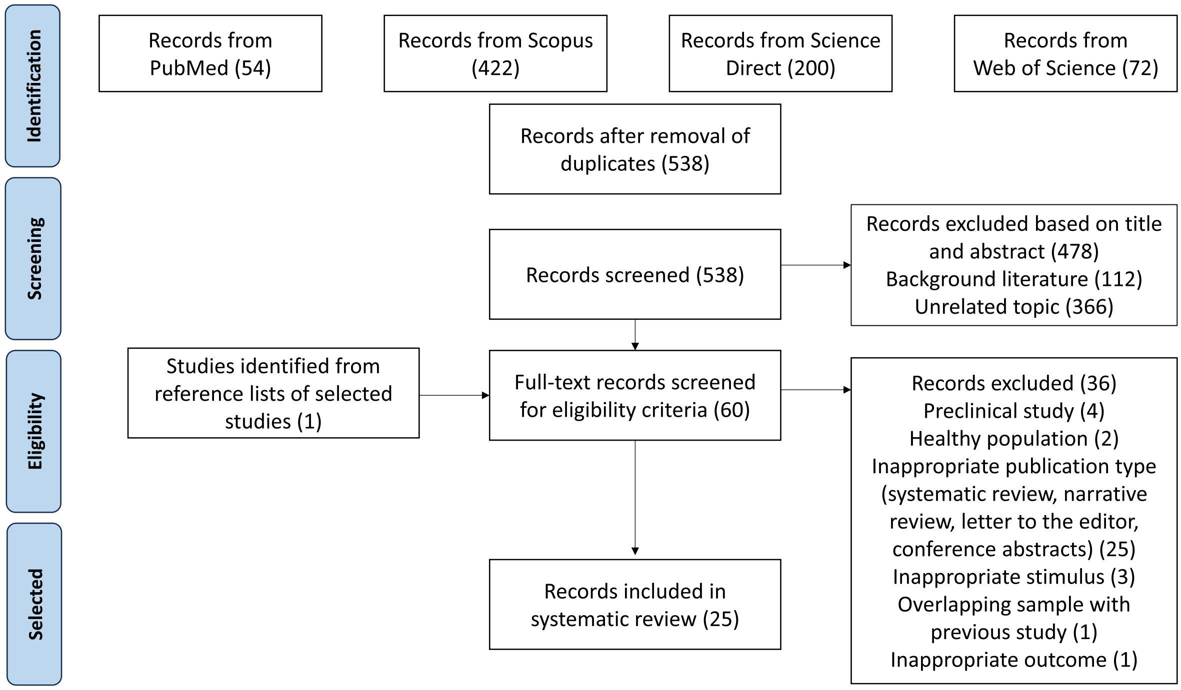


**Fig. 1.** PRISMA flowchart illustrating the process of identification and selection of studies.

30.3 ± 44.4 % after K448 and 31.8 ± 39.2 % after K545 [10]. A decrease in IEDs was also observed in most patients during exposure to either K448 or K545 (84.6 % reduction during K448 and 82.1 % reduction during K545).

In an extension of previous studies, Lin and colleagues [12] evaluated the longer-term effects of listening to K448 and found a distinct decrease in IEDs after 1, 2 and 6 months of exposure (IEDs decreased by 53.2 ± 47.4, 64.4 ± 47.1, and 71.6 ± 45.8 %, respectively, $p < 0.001$). In another study on the same topic, Lin and colleagues [11] described a greater than 50 % reduction in seizure frequency in 72.7 % of patients following 6 months exposure to K448. This reduction was statistically significant compared to baseline seizure frequency ($p < 0.05$).

In line with the above reports, a single-case study (of a patient with Lennox-Gastaut Syndrome) by Hughes and colleagues [6] also described a decrease in seizure activity (from 9 to 7 to 1), as well as in generalised discharges, during three periods of wakefulness in a 24-hour period while the patient listened to K448 for 10 min during every waking hour. The number of seizures recorded by the patient's parent on the following day was 1 (as opposed to 9, during the same time period the day before), while the patient kept listening to K448 following the same schedule as the day before.

### 3.2. Adult studies

Six studies including an adult only population were selected once study inclusion and exclusion criteria had been applied. Of these, there was one RCT (level I), two prospective studies (level II) and three case reports (level V) (Table 3). In their RCT, Rafiee and colleagues [26] reported a 35 % decrease in seizure frequency during daily exposure to K448 for 3 months compared to daily listening to a non-rhythmic control piece.

A case report by Bedetti and colleagues [8] described a similar decrease in seizure frequency (46.6 % reduction) following daily exposure to K448, but this time coverage was over six months. The authors also reported a significant decrease in frequency of IEDs on EEGs that were performed on the last day of listening to music when this was compared to the EEG recording undertaken on the day prior to the patient starting music exposure (160 vs 540).

A prospective study by Štillová and colleagues [17] also reported a decrease in IEDs, recorded with intracerebral EEGs, both during and after a single exposure to K448, when compared to IED frequency during and after exposure to Haydn's symphony No.94. They also reported persisting effects on IEDs 10 min after music exposure, however differences between K448 and No.94 did not reach statistical significance.

Quon and colleagues [15] also took intracerebral EEG recordings during exposure to K448 (for as short as 30 s), this time in a group of 16 neurosurgical patients and, likewise, found a significant reduction in IEDs (RR = 0.31, $p < 0.001$). Moreover, a significant reduction in IEDs during 90 s exposure to the original K448 was observed both inside and outside the seizure onset zone (SOZ) (SOZ RR = 0.33, $p < 0.001$; non-SOZ RR = 0.34, $p = 0.0013$), compared to a non-significant change observed for the filtered version of K448 (SOZ RR = 0.95, $p = 0.48$; non-SOZ RR = 0.82, $p = 0.23$).

The case report by Kuester and colleagues [5] on a patient with non-convulsive status epilepticus also describes a marked reduction in IEDs during exposure to K448 (for 30 min a day during a 5-day period) when compared to IED frequency before music exposure.

Meanwhile, another case report [7] describes a decrease in the severity of gelastic seizures and the frequency of secondary tonic-clonic seizures in a 56-year-old male with refractory gelastic epilepsy following 45 min daily exposure to different compositions by Mozart over a 3-month period.

### 3.3. Paediatric-adult combined studies

A total of 7 studies involved both paediatric and adult subjects (Table 4). Among those, three were Level I studies, encompassing one RCT [20] and two prospective randomized studies [19,21]. The remaining four studies were Level II prospective studies [4,9,13,18].

The RCT by Bodner and colleagues [20] reported a significant 24 % decrease in seizures from baseline when patients were exposed to K448 during sleeping hours for 1 year. Controls who received no music treatment and continued regular AEDs had a 9.6 % increase in seizures from baseline. At 1 year follow up, the treatment group showed a 33 % decrease in seizures compared to a 25.6 % increase in the control group.

In the prospective randomised study by Coppola and colleagues [19],

**Table 1**
JHNEBP scoring tool.

| Evidence level | Types of evidence | |
|---|---|---|
| Level I | • Experimental study<br>• Randomised controlled trial (RCT)<br>• Systematic review of RCTs with or without *meta*-analysis | |
| Level II | • Quasi-experimental study<br>• Systematic review of quasi-experimental studies and/or RCTs | |
| Level III | • Non-experimental study<br>• Qualitative study<br>• Meta-synthesis | |
| Level IV | • Clinical practice guidelines<br>• Consensus panels/position statements | |
| Level V | • Scoping review<br>• Literature reviews<br>• Case reports<br>• Opinion of nationally recognised expert(s) based on experiential evidence | |
| Research studies | A High quality | Consistent results with sufficient sample size; adequate control and definitive conclusions; and recommendations based on extensive literature review. |
| | B Good quality | Reasonably consistent results; sufficient sample size; some controls; fairly definitive conclusions; reasonably consistent recommendations based on a fairly comprehensive literature review that includes reference to scientific evidence. |
| | C Low quality | Little evidence with inconsistent results; insufficient sample size; conclusions cannot be drawn. |
| Summative reviews | A High quality | Topic clearly defined; literature search methods are clear and appropriate; literature thoroughly appraised and synthesized; recommendations consistent with findings; definitive conclusions can be drawn. |
| | B Good quality | Topic defined; literature search methods are clear and appropriate; literature appraised and reasonably synthesized; recommendations consistent with findings; fairly definitive conclusions can be drawn. |
| | C Low quality | Topic not well defined; search methods lack clarity; literature appraisal and synthesis insufficient; recommendations inconsistent with findings; conclusions cannot be drawn. |
| Case reports | A High quality | Expertise is clearly evident; draws definitive conclusions and provides scientific rationale. |
| | B Good quality | Expertise appears to be credible; draws fairly definitive conclusions and provides a logical argument for opinions. |
| | C Low quality | Expertise is not discernible or is dubious; conclusions cannot be drawn. |

Studies are evaluated for strength (level) and quality of evidence. Evaluation criteria are illustrated in the tables below. Tables adapted from (38).

22.9 % of patients exposed to K448 for 2 h a day for 15 days had a > 75 % seizure decrease while 70 % of patients exposed to a set of Mozart's works for the same length and frequency of time had a significant seizure reduction (>50 % seizure reduction in 1/10, > 75 % in 4/10 patients, 100 % in 2/10). The difference in seizure reduction between the two groups (K448 vs set of Mozart's work) was significant ($p < 0.05$), suggesting a possible greater effect for the Mozart set protocol, compared to the K448 one.

The study by D'Alessandro and colleagues [21] reported an average 20.5 % reduction in seizure frequency compared to baseline during 6-month exposure to K448. None of the patients worsened in seizure frequency during exposure. Statistically significant differences existed between treatment and baseline ($p = 0.009$) and between treatment and control ($p = 0.003$). No statistical significance was reported between baseline and control period, suggesting that the treatment effect did not persist over time.

Coppola and colleagues [13] described a 51.5 % decrease in total seizure number compared to baseline during 15-day exposure to Mozart's compositions and a 20.7 % decrease in the two weeks after treatment completion, suggesting a potential carry-over effect.

Ding and colleagues [9] reported a significant decrease in IEDs after single exposure to the original K448 composition, while no significant changes in IEDs were observed after exposure to K448 delivered at a slower and faster tempo. Similarly, no statistically significant changes in IEDs were observed following exposure to Haydn's symphony No.94.

The seminal study by Hughes and colleagues [4] reported a decrease in IEDs in 79 % of patients (23/29 patients) during single exposure to K448 for 10 min, compared to exposure to control music (Old Piano Pop Tunes).

Lastly, Lin and colleagues [18] reported a decrease in IEDs in 81 % of patients after a single exposure to K448, when IED frequency was compared to baseline records. The effect on IED frequency persisted in the 8 min after exposure to music, hence displaying a carry-over effect (compared to baseline IED frequency). Patients who had a positive response to piano K448 were exposed to string K448; however, recordings did not show significant changes in IEDs during or after exposure to this alternative K448 composition.

### 3.4. Meta-analyses

Three comprehensive *meta*-analyses have been conducted on the Mozart effect in epilepsy (Table 5). The work by Dastgheib and colleagues included three *meta*-analyses [22]. The first *meta*-analysis evaluated the percentage of patients who responded to musical neurostimulation and included four studies. It showed that 84 % of patients had a decrease in epileptic discharges following musical neurostimulation. The second *meta*-analysis evaluated the percentage of reduction in IEDs during music exposure across three studies and reported a 31.24 % (95 % CI: 23.057–39.423) reduction in IEDs. Lastly, the third *meta*-analysis evaluated carry-over effect in two studies and yielded a 23.74 % (95 % CI: 14.199–33.288) reduction in IEDs after music exposure. Sesso and Sicca conducted nine *meta*-analyses evaluating percent changes in seizure frequency after long-term intervention with Mozart's K448, IED frequency during and following a single musical stimulation with K448, and after a long-term intervention with K448 [27]. They also assessed percentage changes in IED frequency after a long-term and single exposure to K545. Additionally, they compared the percentage differences in IED frequency during and after a single music stimulation with K545 versus K448. Lastly, they examined the percentage change in seizure frequency during extended exposure to a set of Mozart's works. The *meta*-analyses revealed, compared to baseline, a significant reduction in seizure frequency during (mean difference- MD: 31.7 %, 95 % CI: 20.70–41.64) and after (MD:79.29 %, 95 % CI: 68.35–90.23) a period of listening to K448. They also reported a significant reduction in IED frequency during (MD: 28.21 %, 95 % CI: 17.62–38.80), and after single exposure to K448 (MD: 20.12 %, 95 % CI: 7.76–32.48). A significant reduction in IEDs was also observed during (MD: 35.51 %, 95 % CI: 25.36–45.67) and after (MD:37.78 %, 95 % CI:24.04–51.52) single exposure to K545. Additionally, a reduction in seizure frequency was noted after 15-day long exposure to a set of Mozart's works (MD:66.17 %, 95 % CI: 38.99–93.36). Lastly, non-significant difference was detected between IED changes during and after single exposure to K448 or K545.

In 2023, Oberleiter and Pietschnig conducted three *meta*-analyses [24]. Initially, they examined primary studies focusing on epilepsy, blood pressure in stroke, and premature infant pain, comparing the effects of K448 to silence in studies with a treatment–control design. The outcome measures were IED frequency, systolic blood pressure and the premature infant pain profile, respectively. Subsequently, they assessed the impact of listening to K448 versus silence in studies where patients were exposed to both conditions. Lastly, they analysed the effect of listening to any music versus no stimulus in studies with both conditions. Their hypothesis posited that if musical neurostimulation was effective, significant changes would only manifest in the second *meta*-analysis, not

**Table 2**
Paediatric studies of the Mozart effect in epilepsy.

| Study | Sample size | Sample characteristics | Intervention | Main findings | JHNEBP Rating Scale | |
|---|---|---|---|---|---|---|
| | | | | | Level | Quality |
| Lin et al., 2014 [23] | 46 | 25 male and 21 female. Age 8 years 7 months to 13 years. Idiopathic (n = 41), symptomatic (n = 5). Focal seizures (n = 3, generalised seizures (n = 11). First unprovoked seizure with epileptiform discharges, treatment not commenced until second seizure. | Children randomly assigned to treatment (n = 22) or control group (n = 24). The treatment group listened to K448 for 8 min before going to bed for at least 6 months. The control group did not receive any intervention. | Significant decrease in IEDs on after 1, 2 and 6 months of listening to K448 and significantly lower recurrence rate of seizures in treatment group (22.7 %) compared to control (58.3 %) at 6 months follow up. | Level I RCT | C (Low) Small sample size and some patients have experienced only one seizure |
| Paprad et al., 2021 [25] | 26 | 13 male and 13 female. Age 1 year 2 months to 13 years 5 months. Idiopathic (n = 14), symptomatic (n = 12). Patients on variable number of AEDs during the study. Per ILEA definition, 96 % of participants had drug resistant epilepsy. Normal intelligence (n = 1), mild developmental delay (n = 3), moderate developmental delay (n = 11), severe developmental delay (n = 11). Generalised seizures (n = 6), focal seizures (n = 20). | Children randomly assigned to treatment (n = 15) or control group (n = 15). EEG of all children were recorded in 3–8 min blocks: before, during and after listening to K448 for the treatment group and 3–8 min blocks of silence for the control group. | Significant decrease in IEDs in 67 % of patients in treatment group while listening to K448, compared to 42 % of patients in the control group. | Level I RCT | B (Good) Small sample size |
| Turner 2004 [28] | 4 | 2 male and 2 female. Age range 5 to 9 years. Participants affected by Rolandic epilepsy. Two patients were on AEDs and two were on no medications. | EEGs were recorded for 4 h. Each hour was split accordingly: silence/baseline (15 min); exposure to K448 or control music (Beethoven's Für Elise) (18 min); washout period (27 min). | A 25 % decrease in IEDs was observed during exposure to K448, compared silence. No decrease observed during exposure to control music. | Level I RCT with crossover design | C (Low) Insufficient sample size and no follow up. |
| Grylls et al., 2018 [14] | 45 | 22 male and 23 female. Age 2 to 18 years. Structural/unknown aetiology (24) and genetic aetiology (21). Participants were on 0 to 4 AEDs. | Patients were exposed to 5 states with no breaks in between, each lasting 5 min: before K448, during K448, after K448/before age-appropriate control music, during control music and after control music. EEGs were recorded throughout. | Statistically significant decrease in IEDs between exposure to K448 and control music and between exposure to K448 and baseline. | Level II Prospective study | B (Good) |
| Lin et al., 2012 [10] | 39 | 19 male and 20 female. Age 2 years 9 months to 17 years 3 months. Idiopathic (n = 29), probably symptomatic (n = 2), symptomatic (n = 8). Normal intelligence (n = 32), reduced IQ (n = 5), undetermined IQ (n = 2). | EEGs were recorded before, during, and after listening to Mozart K448 and K545 in random order, one week apart, respectively. A result was considered 'effective' if it led to a greater than 20 % reduction in IEDs. | Significant decrease in IEDs during and after listening to K448 and K545. Patients with generalised epilepsy had a greater reduction in IEDs than those with focal epilepsy, when listening to both pieces. | Level II Prospective study | B (Good) |
| Lin et al., 2013 [16] | 64 | 31 male and 33 female. Age 2 years 11 months to 15 years 4 months. Focal seizures (n = 31), generalised seizures (n = 33). Normal intelligence (n = 54), mental retardation (n = 9), undetermined (n = 1). Idiopathic (n = 51), symptomatic (n = 12), probable symptomatic (n = 1). | EEG and ECGs were recorded for all patients before, during and after listening to Mozart K448 or K545, based on the patient's preference. Forty-one patients listened to K448, and 23 patients listened to K545. | A significant reduction in IEDs compared to baseline was observed during both Mozart K448 and Mozart K545 in most patients (90.2 % during K448 and 82.6 % during K545). A decrease in IEDswas observed also after music exposure. Increased parasympathetic activity, based on ECG data, was observed during music exposure. | Level II Prospective study | C (Low) Randomisation is preferred in assigning treatment music (K448 or K545). |
| Lin et al., 2011b [12] | 18 | 8 male and 10 female. Age 7 months to 14 years 4 months. Patients were on 1 to 3 AEDs. Idiopathic (n = 10), symptomatic (n = 8). Focal seizures (n = 16), generalised seizures (n = 2). Normal intelligence (n = 11), mental retardation (n = 7). | All participants were asked to listen to K448 for 8 min once daily before bed for 6 months. They were reviewed monthly as outpatients. | There was significant decrease in IED frequency after 1, 2, and 6 months of listening to K448, compared to baseline. The decreases in IEDs significantly differed between 1, 2, and 6 months of listening to Mozart K448, with the greatest decrease observed after 6 months. | Level II Prospective study | B (Good) Small sample size |
| Lin et al., 2011a [11] | 11 | 6 male and 5 female. Age 2 years 9 months to 14 years 4 months. | Parents/caregivers were provided with a seizure diary to record participants' seizure | During the 6 months of listening to K448, 72.7 % of patients reported a greater than 50 % reduction in | Level II Prospective study | C (Low) Insufficient sample size and unclear about daily |

(continued on next page)

**Table 2** (*continued*)

| Study | Sample size | Sample characteristics | Intervention | Main findings | JHNEBP Rating Scale | |
|---|---|---|---|---|---|---|
| | | | | | Level | Quality |
| | | Symptomatic (n = 6), probably symptomatic (n = 4), idiopathic (n = 1). Participants were on 2 to 6 AEDs. Focal seizure (n = 4), generalised tonic-clonic (n = 4), atypical absence (n = 2), myoclonic (n = 1). Normal intelligence (n = 2), mild mental retardation (n = 1), moderate mental retardation (n = 1), severe mental retardation (n = 4), profound mental retardation (n = 3). | frequency 6 months before listening to K448 and 6 months while listening to K448. | seizure frequency, including 2 patients who were seizure free. The remaining 27.3 % showed minimal or no effect (effectiveness < 50 %; unmodified or worsened seizure frequency). | | frequency and length of listening to K448. |
| Hughes et al., 1999 [6] | 1 | 8-year-old female with Lennox-Gastaut Syndrome on 2 AEDs at the time of the study (Topomax and Klonopin). Seizures commenced following surgery for removal of arteriovenous malformation on the right posterior temporal area. | An EEG recording was produced over 24 h while the patient listened to K448 every hour for 10 min. Seizure frequency was recorded by the mother and teacher while the child attended school. | The patient had fewer seizures and fewer generalised bilateral spikes and wave complexes over a 24-h period, when listening to K448 every hour for 10 min during wakefulness hours. | Level V Case report | B (Good) It is un clear how long the seizure frequency was recorded for by the child's mother and teacher. |

in the third.

The first *meta*-analysis favoured listening to Mozart over silence, although the authors attributed this to low power and denied a meaningful beneficial effect. The second and third *meta*-analyses revealed non-significant trivial summary effects, indicating no significant positive influence of K448 or listening to any music versus no stimulus on epilepsy, respectively.

## 4. Discussion

This study aimed to conduct a comprehensive analysis of the Mozart effect in both childhood and adult epilepsy. The objective was to evaluate the efficacy of musical neurostimulation using Mozart's music, whether as a single-exposure treatment or a long-term intervention. Four previous systematic reviews have been carried out on the topic; three of which included a *meta*-analysis [22,24,27] and have therefore been included in this review. The fourth systematic review focused on childhood epilepsy and was primarily directed at a nursing audience [29]. This review was not part of our analysis because it did not include a *meta*-analysis. The most recent systematic review with *meta*-analysis includes papers to 2020 only [27]. Since then, four new papers addressing the Mozart effect in epilepsy have been published. Notably, two of these papers feature an evaluation of the Mozart effect using stereo electroencephalography, marking a novel approach [15,17]. The remaining two studies consist of an RCT [25] and a prospective study, specifically exploring the impact of tempo in the Mozart effect on epilepsy [9].

Additionally, we classified papers into three distinct groups: paediatric, adult, and mixed. This is something that the 2020 review did not achieve. We emphasise the importance of classifying studies based on the age group of the population, as this links back to our suggestion for future studies to ensure that age groups are not combined, to prevent the introduction of additional developmental variables. On this basis, an up-to-date review of the literature appeared warranted in order to bridge the time gap and contribute further to our current understanding of the evidence base for musical neurostimulation in epilepsy. Within this context, it was expected that critical appraisal of relevant studies would provide knowledge that could help identify future objectives and prospects in this area of enquiry.

Utilizing the JHNEBP rating scale [41], ten level I studies, considered the most robust evidence, were identified. Out of these, nine described a decrease in seizure frequency and/or IEDs following exposure to K448 or other compositions by Mozart [19–23,25–28]. The *meta*-analysis by Oberleiter reported no positive effect of listening to K448 or any other type of music in epilepsy compared to no stimulus [24]. This Oberleiter review, however, did not include all the available, clinical randomised studies on the Mozart effect in epilepsy due to apparently insufficient statistical information. Thus, this presents a limited view of research on the topic, which, in our opinion, cannot fully support the authors' claims concerning the research's validity.

Eleven level II studies were identified and out of these, nine reported an immediate decrease in IEDs [4,9,10,12,14–18] and two described a decrease in seizure frequency during exposure to K448 or other works by Mozart [11,13]. Four level V studies were identified; one study described a decrease in both seizure frequency and IEDs during exposure to K448 [6], two studies described an immediate decrease in IEDs during exposure to K448 [5,8] and one study reported a decrease in seizure frequency following exposure to various works by Mozart [7].

In 11 of the 25 chosen studies, musical neurostimulation was employed as a prolonged repeated stimulus [5,7,8,11–13,19–21,23,26]. Three of these studies conducted follow-ups to explore potential carry-over effects [20,23,26]. An RCT by Lin *et al.* [23] revealed a significant increase in seizure recurrence in the control (silence) group compared to the treatment group (exposed to K448 daily for 6 months) at the 6-month follow-up. Similarly, Bodner *et al.'s* RCT [20] described a 33 % decrease in seizure frequency in the treatment group compared to a 25.6 % increase in the control group (silence) at the 1-year follow-up. However, Rafiee *et al.'s* RCT [26] reported an increase in the average seizure count in both treatment and control (non-rhythmic K448) groups at the 3-month follow-up.

The differences in these results regarding potential carry-over effects could be attributed to the duration of exposure to the musical stimulus. Lin *et al.'s* study lasted 6 months, while Bodner *et al.'s* extended to a year, whereas Rafiee *et al.'s* study only covered 3 months. It is plausible that the 3-month exposure was insufficient to observe a significant carry-over effect. Moreover, differences in control interventions and population demographics among those studies further contribute to the variation in outcomes. Bodner *et al.* and Lin *et al.* used silence as the control, while Rafiee *et al.* employed a non-rhythmic version of K448. Additionally, the study design in Rafiee *et al.* differed from the others by applying a cross-over design instead of a parallel one. The heterogeneity among those studies impedes the drawing of definitive conclusions regarding the potential carry-over effect.

Studies have been carried out to determine the specific features of K448 responsible for its potential anti-epileptic properties. A RCT by Rafiee *et al.* analysed the anti-epileptic effect of K448 compared to a non-

**Table 3**
Adult studies of the Mozart effect in epilepsy.

| Study | Sample size | Sample characteristics | Intervention | Main findings | JHNEBP Rating Scale | |
|---|---|---|---|---|---|---|
| | | | | | Level | Quality |
| Rafiee et al., 2020 [26] | 13 | 5 male and 8 female. Age range 26 to 75 years. Patients on an average of 2.3 AEDs per individual. Seizure control not achieved despite medication and at least three seizures during baseline period (at least one of three seizures happened 2 months prior). Complex partial seizure (n = 11), generalised tonic-clonic (n = 4), absence (n = 1), nocturnal (n = 3), simple partial (n = 1). Multiple seizure types present in the same patient. | Participants were randomly assigned to two groups (A and B). Group A listened to the first 6 min of K448 (treatment) once daily for three months, then switched to a non-rhythmic version of K448 (control) once daily for 3 months. Group B started with the control piece and then switched to the treatment. Participants recorded seizures using a seizure dairy. | Individuals had a 35 % reduction on average in seizure count when listening to daily Mozart K448 for 3 months compared to the control. Increase in average seizure count was observed during at 3-months follow up. | Level I RCT with crossover design | C (Poor) Insufficient sample size |
| Štillová et al., 2021 [17] | 18 | 9 male and 9 female Age range 19 to 49 years All participants were candidates for surgery. Patients are on different combinations of AEDs. Left temporal lobe epilepsy (n = 11), right temporal lobe epilepsy (n = 4), bitemporal epilepsy (n = 1), cingular right (n = 1), fronto-insular right (n = 1). | Patients had deep electrodes implanted in the medial and lateral temporal cortex and were monitored for 2 days using video EEG. EEGs were recorded for 10 min of resting state, while listening to either K448 or symphony No.94 by Haydn and for 10 min post-music. Participants also completed a questionnaire about their musical preference. | Listening to K448 resulted in a 32 % median decrease in IEDs, while listening to symphony No.94 by Haydn led to a 45 % increase in IEDs. The musical preference questionnaire revealed that all the participants were emotionally indifferent to both pieces. | Level II Prospective study | C (Poor) Small sample size and poorly described methods. |
| Quon et al., 2021 [15] | 16 | 10 male and 6 female. Age range 24 to 68 years. All patients had refractory focal epilepsy, AED regimens not reported. Seizure onset zone: mesial (n = 7), temporal cortex (n = 7), frontal cortex (n = 1), hippocampus (n = 1). | Patients were divided into groups 1 and 2. Group 1 was exposed to 15 s clips of K448, and 40 Hz modulated K448, while group 2 was exposed to 90 s of K448 and filtered K448. Violet noise and Wagner were controls for group 2. Intracerebral EEGs were recorded. | Exposure to K448 for 90 s led to significant global IED reduction, while non-significant IEDs reductions were seen in exposure to K448 for 15 s. | Level II Prospective study | B (Good) Some controls and small sample size. |
| Bedetti et al., 2019 [8] | 1 | 27-year-old male affected by profound intellectual disability, autism spectrum disorder, intermittent explosive disorder, drug-resistant epilepsy with atonic and tonic-clonic seizure, microcephaly, facial and limb dysmorphism. | EEGs were recorded for 180 min during wakefulness before and after six months of listening to K448 for 30 min once daily. Brain MRIs were performed before and after 6 months of daily listening to K448. | Significant decrease in IEDs after 6 months of daily listening to K448 compared to before music (160 vs 540) and a reduction of 46.6 % in seizure frequency. Data from brain MRIs regarding changes post musical exposure were inconclusive. | Level V Case report | B (Good) Recommendations for further research are only very briefly mentioned. |
| Kuester et al., 2010 [5] | 1 | 22-year-old male with severe brain trauma with non-convulsive status epilepticus. Treated unsuccessfully with midazolam, levetiracetam, valproic acid and topiramate. | After 5 days of refractory status epilepticus, the patient was exposed to K448 for 30 min once daily. His EEG was monitored before and during music exposure in a blinded fashion. | Reduction in IEDs during exposure to K448. After 5 days of music exposure, anti-convulsant drugs were progressively withdrawn and patient recovered from his coma. Daily listening to K448 was continued as part of rehabilitation programme. | Level V Case report | A (High) |
| Lahiri and Duncan, 2007[7] | 1 | 56-year-old male with refractory gelastic epilepsy (laughing fits), secondarily generalised tonic clonic seizures and complex partial seizures. Underwent surgery for hypothalamic hamartoma and brachytherapy. Memory impairment. | The patient spontaneously started listening to Mozart's works for an average of 45 min/day for 3 months. | During the 3 months of exposure to Mozart's music, he did not experience any secondarily generalised tonic clonic seizures and the gelastic seizures continued but presented as a brief smile (5–9 s) that he could easily conceal if in social situations. | Level V Case report | C (Low) The intervention was not overseen by healthcare professionals, giving poor control over variables, hence conclusions cannot be drawn. |

rhythmic version of K448, where the periodicity was altered but the spectral properties remained unchanged. They described a reduction in seizure count during the treatment period, thus suggesting that the long-term periodicity characteristic of K448 could be one of the features responsible for a potential anti-epileptic effect, as it may reflect the organisation of the cerebral cortex [26].

Ding *et al.* focused on the effect of tempo of K448, by using versions of K448 with slower or faster tempos as controls. A significant decrease in IEDs was observed in patients exposed to the original K448, compared to slow or fast tempo K448. The authors suggest that Mozart's K448 original tempo underlies its effect, because the original tempo of Mozart's K448 facilitated concentration, whereas the slower tempo was not engaging, and the faster tempo was too complex, affecting participants' attention [9].

**Table 4**
Adult-paediatric combined studies of the Mozart effect in epilepsy.

| Study | Sample size | Sample characteristics /Inclusion criteria | Intervention | Main findings | JHNEBP Rating Scale | |
|---|---|---|---|---|---|---|
| | | | | | Level | Quality |
| Bodner et al. 2012 [20] | 36 | 16 male and 20 female. Age range 12 to 78 years. Idiopathic (n = 17), symptomatic (n = 19). Regular AEDs maintained for duration of study. Seizure type: focal (n = 17), generalised (n = 6), focal and generalised (n = 5), generalised and myoclonic (n = 8). Cerebral palsy (n = 9), trisomy (n = 4), Angelman syndrome (n = 4), anoxic brain injury (n = 1), Rett syndrome (n = 1). Patients had to exhibit seizures during study. | Participants assigned to either treatment (n = 25) or control group (n = 11). Randomisation ratio 2:1. The treatment group listened to K488 at periodic intervals over 10 h at night for 1 year. The control group did not receive any intervention. | Significant decrease in seizures of 24 % from baseline in treatment group, compared to 9.6 % increase in control group, during treatment phase. At 1 year follow up, 33 % decrease in seizures in treatment group and 25.6 % increase in seizures in control group. Greater decrease in seizure rate for idiopathic subjects during treatment and follow up. | Level I RCT | B (Good) Small sample size |
| D'Alessandro et al., 2017 [21] | 12 | 10 male and 2 female. Age range 5 to 39 years. All participants were symptomatic. Patients were on 2 to 6 AEDs. Seizure type: focal and generalised (n = 10), generalised (n = 2). Intellectual disability: severe (n = 6), profound (n = 6). | Participants were randomly assigned to groups A or B. Group A listened to K448 once daily for 6 months, they then did not receive any treatment for the following 6 months. Group B started with the control intervention for the first 6 months and then switched to the treatment piece for the following 6 months. Baseline seizure frequency was recorded for 6 months prior to the start of the intervention. | There was an average 20.5 % reduction in seizure frequency during the treatment phase compared to baseline. There was no worsening in seizure frequency with one patient becoming seizure free and five patients obtaining a more than 50 % reduction in seizure frequency. However, this effect was lost in the 6 months following the treatment. | Level I Prospective randomised study with crossover design | C (Poor) Insufficient sample size and excessive age spread in the sample. |
| Coppola et al., 2018 [19] | 19 | 13 male and 6 female. Age 1 to 24 years. All participants were suffering from drug resistant encephalopathies or syndromes and were on 2 to 4 AEDs. Intellectual disability: mild (n = 1), severe (n = 9), profound (n = 9). Cerebral palsy: spastic tetraplegia (n = 15), double hemiplegia (n = 1), spastic dyskinetic (n = 1), hemiplegia (n = 1). Epilepsy type: epileptic encephalopathy (n = 16), Lennox-Gastaut syndrome (n = 2), focal epilepsy +/- secondary generalisation (n = 1). Seizure type: spasm (n = 3), tonic (n = 9), atypical absences (n = 4), focal +/- secondary generalised. | Nine patients were randomised to listen to K448 for 2 h/day for 15 days, while the rest listened to a set of Mozart's compositions for the same length of time. Participants reported seizure frequency using a seizure dairy and behavioural parameters (tearfulness, irritability, self/hetero-aggression, day time vigilance). At the end of the 15 days, patients were reassessed. | Among patients exposed to a set of Mozart's compositions, 70 % had a significant seizure reduction (75 % reduction), while among patients exposed to K448 only 22 % had a significant reduction in seizure frequency. Patients exposed to a set of Mozart's compositions showed greater behavioural improvement compared to patients exposed to K448. | Level I Prospective randomised study | B (Good) Small sample size |
| Hughes et al., 1998 [4] | 29 | Age 3 to 47 years. | EEGs were recorded for 10 min before, during K448, after K448, during control music (Old Time Pop Piano Tunes) and after control music. | Decrease in duration of IEDs during K448 in 79 % of patients, compared to before and after Mozart. | Level II Prospective study | C (Low) Insufficient data about sample and excessive age spread. |
| Ding et al., 2023 [9] | 147 | 76 male and 71 female. Age 13 to 68 years old. Patients were on 1 or more AEDs. IQ > 70. Epilepsy type: partial (n = 88), generalised (n = 53), unknown (n = 6), drug-resistant (n = 15). | Patients were divided into 4 groups. Group 1 (n = 38) listened to the Mozart's K448 at the original tempo, group 2 (n = 37) listened to K448 at a fast tempo, group 3 (n = 36) listened to K448 at a slow tempo and group 4 (n = 36) listened to Haydn's symphony No.94 as a control. All participants listened to their assigned music while lying in a quiet room. EEGs were recorded for 24 min (pre/during/post music). | Listening to original K448 resulted in a significant decrease in IEDs, while fast and slow K448 and the control piece did not produce any significant changes in IEDs. | Level II Prospective cohort study | B (Good) Combining adult and paediatric patients introduces developmental variables affecting result accuracy. |
| Coppola et al., 2015 [13] | 11 | 7 male and 4 female. Age 1.5 to 21 years. All patients suffered from drug | Participants completed a diary regarding seizure frequency and behavioural parameters | Overall, 45.5 % (5/11) of participants had a $\geq$ 50 % reduction in seizure | Level II Prospective study | C (Low) Insufficient sample size and inconclusive results. |

(*continued on next page*)

**Table 4** (*continued*)

| Study | Sample size | Sample characteristics /Inclusion criteria | Intervention | Main findings | JHNEBP Rating Scale | |
|---|---|---|---|---|---|---|
| | | | | | Level | Quality |
| | | resistant epileptic encephalopathy and had severe/ profound intellectual disability with cerebral palsy. They had at least four seizures a week in the 6 months before music exposure. | (self/hetero-aggression, irritability) for the 6 months prior to the start of treatment, during the treatment and for 1 month after. They listened to a set of Mozart's composition for 2 h/day for 15 days. Wake EEGs were recorded at each stage for 20 min. | frequency when listening to Mozart's compositions. All participants also showed behavioural improvement according to questionnaires filled in by parents/ caregivers. | | |
| Li et al., 2010 [18] | 58 | 30 male and 28 female. Age 1 year to 19 years 8 months. Idiopathic (n = 38), symptomatic (n = 14) and probably symptomatic (n = 6). Seizure type: generalised (n = 11), focal (n = 47). | Patients were exposed to low harmonic piano K448 for 8 min. EEGs were recorded for 8 min before, during and after music exposure. Patients who benefitted from piano K448 were exposed to high harmonics string K448 after a week and EEGs were recorded. | Decrease in IEDs was observed in 81 % of patients, following exposure to piano K448. The greatest decrease was seen in patients with generalised or central discharge. Non-significant change in IEDs was observed after exposure to string K448. | Level II Prospective study | B (Good) Uses term music therapy instead of non-invasive musical neurostimulation. |

**Table 5**
*Meta*-analyses on the Mozart effect in epilepsy.

| Study | Sample size | Sample characteristics /Inclusion criteria | Protocol | Main findings | JHNEBP Rating Scale | |
|---|---|---|---|---|---|---|
| | | | | | Level | Quality |
| Sesso and Sicca, 2020 [27] | k = 12 studies n = 328 | Inclusion criteria were as follows: clinical studies assessing the effect of music exposure on patients with epilepsy which included a pre- to peri-/post-treatment comparison and a quantitative assessment of treatment outcomes. | Nine *meta*-analyses were carried out to determine the percent changes in seizure and IED frequency during long term exposure to K448 or a set of Mozart's compositions, single exposure to K448 or K545, the percent differences in IED frequency during and after a single exposure comparing the effects of K545 versus K448. | The nine *meta*-analyses revealed significant reduction in IEDs and seizure frequency after long-term and single exposure to K448, K545 and a set of Mozart's works, as well as non-significant difference between K448 and K545. | Level I *Meta*-analysis | A (High) |
| Dastgheib et al., 2014 [22] | k = 12 studies n = 257 | Studies on patients with any kind of epilepsy exposed to at least one of Mozart's works (not limited to K448) were included. Case reports and abstracts submitted at conferences were included if they fulfilled the criteria. | Three *meta*-analyses were carried out to determine the percentage of patients who had changes in their IEDs following Mozart's music and the changes in IEDs during and post-exposure to Mozart's music. | The first *meta*-analysis showed that 84 % of patients responded to music exposure, with a decrease in IEDs. The second *meta*-analysis revealed a 31.24 % decrease in IEDs during music exposure, while the third *meta*-analysis showed a 23.74 % decrease in IEDs after music. | Level I *Meta*-analysis | B (Good) Case reports were included, and this decreases the quality of the evidence presented. |
| Oberleiter and Pietschnig, 2023 [24] | k = 8 studies n = 207 | Studies on the effect of Mozart's K448, another musical stimulus, a non-musical stimulus or silence in any medical condition were included. The studies had to include a control condition, provide an appropriate quantitative measure for symptom changes, and include effect sizes or sufficient statistical data to calculate them. | Six studies assessed the Mozart effect in epilepsy, one in stroke and one in premature infant pain. Three *meta*-analyses were conducted. The first one looked at the effect of K448 or silence in different medical conditions with a treatment and control group setup. The second *meta*-analysis analysed the effect of K448 or silence with a one group pre-test/ post-test design. The third *meta*-analysis focused on the effect of other music, versus no-stimulus in a one group pre-test/post-test design. | The three *meta*-analysis yielded non-significant summary effects. | Level I *Meta*-analysis | B (Good) Conclusions drawn are dubious as the Mozart effect cannot be denied based only on the lack of studies with sufficient sample size. |

Despite the encouraging data from the studies included in this systematic review, there are also some limitations which should be discussed and addressed in the design of future studies on the Mozart effect in epilepsy.

Sample sizes tend to be consistently low, with only one study having more than one hundred participants (n = 147) [9] and the remaining sample sizes ranging from 64 [16] to 2 participants [28]. Small sample sizes can lead to underpowered studies [42]. In order to address this, there should be a real effort to recruit more participants in future research on the topic. Multi-centre collaborations should be encouraged, not only to reach adequate sample sizes but also to evaluate the feasibility of a protocol in distinct settings.

Additionally, in 13 of the 25 selected studies [6,9,11–14,17,19–21,25,26,28], patients were reported to be on different numbers and classes of AEDs, thus introducing additional confounding variables and hindering our ability to draw clear conclusions about the anti-epileptic properties of Mozart's music. Importantly, in this context, some AEDs can affect musicality, particularly processing of rhythm and time intervals. For example, carbamazepine can cause reversible disturbances in pitch processing [43].

Variation also exists among the control measures used in level I and some level II studies. Four studies used silence as their control [20,21,23,25], while eleven studies used another piece of music as their control [4,9,10,14–19,26,28]. The latter strategy is preferred as it provides clearer conclusions about the anti-epileptic properties of Mozart's music and should therefore be brought forward in future studies. Combining paediatric and adult patients is another caveat observed in ten out of 25 studies. This might affect result accuracy as research highlights the presence of general maturational differences, such as higher synapse and neuronal density in children, as well as maturational differences related to music processing [44]. Thus, aggregating results at the whole population level risks obscuring important differences in adult versus children response to intervention.

Despite certain limitations in the existing literature, the exploration of musical neurostimulation through K448 opens a promising avenue for clinical research and potential future clinical applications. The interest and willingness displayed by patients, as highlighted in the study conducted by Afra and colleagues in 2018, suggest a positive outlook for incorporating music-based interventions in the treatment of epilepsy [45]. Afra and colleagues designed a proof-of-concept mobile software for the treatment of epilepsy and decided to include music-based interventions for seizure control, based on the evidence available on the Mozart effect in epilepsy. They conducted a survey to understand patients' preferences regarding the interventions included in the mobile software as well as their likelihood to use those interventions long term. From the survey it emerged that 75 % of patients were willing to listen to music that may help with seizure control, while a comparatively lower number of patients was interested in other relaxation techniques such as imagery (40 %), games and puzzles (70 %) and mindfulness (63 %) [45].

Additionally, 65 % of responders were willing to listen to antiseizure music for 10 min daily for several months or longer and out of these responders, 45 % considered adhering to this intervention for 1 year or longer [45]. This suggests that high numbers of patients would be keen to integrate music into their daily routine if this might have positive effect on seizure management. These findings are very promising in relation to public involvement; however, the authors of this study rightfully notice that listening to the same piece of music daily might become unpleasant and result in "desensitisation of physiological effects" [45]. In response to this, it is worth noting that alternative compositions by Mozart, such as K545, K207, K218, K314, K482, have demonstrated anti-epileptic effects. Moreover, music from other renowned composers like Bach, Beethoven, Chopin, and Wagner, exhibiting long-term periodicities similar to K448, may offer a broader repertoire with potentially similar anti-epileptic properties [46]. Interestingly, in this context, a case report by Miranda *et al.* described a patient's remission from status epilepticus following exposure to music by both Mozart and Bach [47]. In their *meta*-analysis, Sesso and Sicca also note that K545 showed a greater, although non-significant, effect on IEDs [27]. While Sonata K448 may not inherently surpass other compositions by Mozart or other composers in its anti-epileptic effectiveness, its prominence as the initial piece linked to the 'Mozart effect', might underlie its association with the strongest bodies of evidence around musical neurostimulation in epilepsy. Therefore, music by other renowned composers represents a promising subject for future research in expanding the available musical repertoire for therapeutic interventions in epilepsy and in elucidating the auditory features and mechanisms responsible for the Mozart effect.

## 5. Conclusion

In conclusion, this systematic review summarises the evidence available on the therapeutic effect of Mozart's music in childhood and adult epilepsy. A total of 25 studies were identified and qualitatively classified using the JHNEBP tool. Most of the available studies are level II, quasi experimental studies (n = 11), followed by level I studies (n = 10) and lastly by level V studies (n = 4). Despite limitations due to small sample size and variation in protocols, musical neurostimulation represents a promising avenue of research for the management of epilepsy, helping to fulfil a pressing clinical need.

- PPI statement

Patients or the public were not involved in the design or conduct of our study.

## CRediT authorship contribution statement

**Lucrezia Maria Piccicacchi:** Writing – review & editing, Writing – original draft, Methodology, Investigation, Formal analysis, Data curation. **Domenico Serino:** Supervision, Conceptualization.

## Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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