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Application of Neurofeedback in Treating Epilepsy: A Systematic Review and Meta-Analysis

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Review Article

Abstract

Background: To investigate the evidence related to the effectiveness of neurofeedback (NF) treatment in patients suffering from epilepsy, a meta-analysis of randomized controlled trials (RCTs) for people suffering from epilepsy was conducted in different research sources.

Methods: This research was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols (PRISMA) guidelines and Meta-Analysis of Observational Studies in Epidemiology (MOOSE) guidelines. Original research studies that were published in valid electronic sources from March 1975 to March 2022 were included in the study; 15 original studies (including 330 patients) were finally analyzed. To achieve this objective, the primary outcome measure was the ratings of epilepsy symptoms in subjects based on assessments of patients. The Cambridge Neuropsychological Test Automated Battery (CANTAB), Wechsler Intelligence Scale for Children-Second Edition (WISC-II), and the Attention Span Test were regarded as primary outcomes. The required data from the desired studies were putted in the Review Manager Software to perform a systematic analysis of trial characteristics.

Results: The findings showed that the mean level had significantly dropped by about 4.064 units in the intervention group (MD = -0.4.064; 95% CI = [-4.909, -3.22]; $P < 0.001$). However, the mean difference was not statistically significant within the subgroups. No significant heterogeneity or publication bias was detected.

Conclusion: The results of the meta-analysis offer preliminary evidence that, based on the assessment of patients, NF is a beneficial clinical method for epilepsy. However, more RTCs are required to compare standard treatments such as medication, and neurological and behavioral interventions.

Keywords: Epilepsy; Neurofeedback; EEG biofeedback; Slow cortical potentials; Sensory motor rhythm; Meta-analysis

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Introduction

Neurofeedback (NF) training is designed to collect and analyze information, and provide “feedback” on an individual’s electroencephalogram (EEG) signals so that the individual can learn to modify their brain activity. Individual therapeutic training goals are based upon significant abnormalities in a baseline quantitative EEG (QEEG). Repeated exercise of the brain pathways needed to reach feedback goals stimulates synaptic and network plasticity and long-term and sometimes permanent changes in brain functioning. Increasing amounts of information illustrate that the application of an EEG to educate specific brain rhythms is a functional, inexpensive, low-risk, and reassuring medication for patients suffering from epilepsy (Sterman & Egner, 2006).

Epilepsy is often comorbid with other cognitive and behavioral issues that are more disabling than seizures (Doyle, 2004). Community-based studies document the prevalence of such neurobehavioral comorbidities in epilepsy, which are divided into psychiatric, cognitive, and social categories (Josephson et al., 2017). It is worth highlighting the fact that epilepsy is a heterogeneous condition and most samples are also heterogeneous. A significant potential complication of epilepsy is impairment in some aspects of objectively assessed cognition including intelligence, language, perception, learning and memory, executive function, and/or processing speed (Kerick et al., 2023; Lin, Mula, & Hermann, 2012). Noticeably, NF protocols have been utilized with patients suffering from a wide range of disorders, including attention deficit hyperactivity disorder (ADHD) (Lubar & Bahler, 1976; Rahmani et al., 2022), obsessive-compulsive disorder (OCD) (Zafarmand, Farahmand, & Otared, 2022), epilepsy (Andrews & Schonfeld, 1992; Brogin, Faber, & Bueno, 2022; Cott, Pavloski, & Black, 1979; Frey & Koberda, 2015; Kaplan, 1975; Khaksarian, Hasanvandi, Piri, & Sohrabifard, 2020; Kotchoubey et al., 2001; Kuhlman & Allison, 1977; Lantz & Sterman, 1988; Morales-Quezada, Martinez, El-Hagrassy, Kaptchuk, Sterman, & Yeh, 2019; Quy, Hutt, & Forrest, 1979; Rotondo et al., 2022; Sterman & Macdonald, 1978; Sterman & Egner, 2006; Strehl, Birkle, Worz, & Kotchoubey, 2014; Tozzo, Elfner, & May, 1988; Walker & Kozlowski, 2005; Weber, Koberl, Frank, & Doppelmayr, 2011), autism (Kang, Zhang, Wan, Casanova, Sokhadze, & Li, 2022; Seok, 2022), Asperger’s syndrome (Thompson & Thompson, 2009), stroke (Girges, Vijiaratnam, Zrinzo, Ekanayake, & Foltynie, 2022; O'Donoghue, Leahy, Boland, Galvin, McManus, & Hayes, 2022), tinnitus (Czornik, Malekshahi, Mahmoud, Wolpert, & Birbaumer, 2022; Sadeghijam, Moossavi, Akbari, Yousefi, & Haghani, 2022), and emotional disturbances (Hesam- Shariati et al., 2022; Russo, Balkin, & Lenz, 2022; Yonah, 2023). Strehl et al. (2014) reported sustained reduction of epilepsy after self-regulation education of slow cortical potentials (Kotchoubey et al., 2001; Strehl et al., 2014). Sterman and Egner (2006) classified peer-reviewed neurofeedback epilepsy studies from 1972 to 1996 and declared that 4 out of 5 individuals who participated in the mentioned trials showed improvement (142 of 174 patients, or 82%), and nearly all (66% of reported cases) presented "contingency-related EEG changes and a shift towards EEG normalization". Trials applying slow cortical potentials (SCP) education, although the number of studies is limited, also show positive results. Kotchoubey et al. (2001) reported reduced seizure frequency following SCP education (Le Breton, 2022; Souza, Navegantes, Miranda, Fiel, & Pereira, 2022), which was related to SCP range (Kotchoubey et al., 2001). Rotondo et al. (2022) reported notable seizure reductions, with 6 patients having more long-term seizure-free times. Eventually, Hesam-Shariati et al. (2022) illustrated reductions in seizure frequencies following SCP education in a patient experiencing generalized tonic-clonic seizures while taking anticonvulsant medications and after an anterior colostomy.

In light of previous studies, about one-third of patients with epilepsy do not benefit from medical treatment (Zafarmand et al., 2022). New automated external defibrillators (AEDs) and surgery are the standard treatment for those patients, but still a considerable percentage of patients are left drug-resistant (Autenrieth, Kober, & Wood, 2022). For these patients, EEG biofeedback is a viable alternative (Turner, Wilson, Gunkelman, Harvison, & Walker, 2023). EEG biofeedback, or NF, normalizes or enhances EEG activity by means of operant conditioning. While dozens of scientific reports have been published on neurofeedback for a seizure disorder, most have been case series with too few subjects to establish efficacy (Patil et al., 2023). Applied Psychophysiology and Biofeedback and the International Society for Neurofeedback have proposed criteria for evaluating evidence of NF efficacy. To be considered efficacious, treatment must be proven superior or equivalent to a control group using a randomized design with sufficient power to detect differences, a population clearly identified through operational definition, valid outcome measures, and independent replication of effect (Sho'ouri, 2023). This standard would have to be amended to include studies like those in this meta-analysis which were of necessity limited to small sample sizes and only one group for which pre-treatment and post-treatment consequences were considered (Fleury, Figueiredo, Vourvopoulos, & Lécuyer, 2023).

In spite of the mentioned restrictions, results have been consistent across trials, basically proposing that neurofeedback leads to a decrease in seizures (Adhia et al., 2023; Lyle, 2022; White, Turner, Arnold, Bernica, Lewis, & Swatzyna, 2022). Despite the success documented in the abovementioned studies, which have demonstrated the positive consequences of neurofeedback education on epilepsy, most of these studies lacked careful experimental methods. While mentioned results in these and other trials are optimistic, any study alone is inadequate to decide whether neurofeedback is beneficial for medicating epilepsy. The goal of the current paper is to combine the appropriate literature into a single evaluation of seizure control (i.e., meta-analysis), which may allow a firm conclusion. The purpose of the current article is to provide the quantitative integration of controlled research on the NF treatment of epilepsy.

Methods

Search strategy and study selection: Original research studies from March 1975 to March 2022 that were published on English and Persian electronic databases were searched in the systematic review process (Figure 1). Initial keywords search was done to identify the literature associated with neurofeedback treatment for patients with epilepsy. Several electronic searches were conducted in various databases, including PubMed, Scopus, Google Scholar, Web of Science, Google Scholar Cochrane Library, Science Citation Index Expanded (SCI-Expanded), Arts & Humanities Citation Index (AHCI), Social Sciences Citation Index (SSCI), Conference Proceedings Citation Index–Science (CPCI-S), Conference Proceedings Citation Index–Social Sciences & Humanities (CPCI-SSH), Index Chemicus (IC), Current Contents Connect, Derwent Innovations Index (DII), Biological Abstracts, BIOSIS Previews, CAB Abstracts and Global Health, Current Chemical Reactions (CCR-Expanded), EMBASE Classic+EMBASE, Food Science and Technology Abstracts (FSTA), Inspec, MEDLINE, Zoological Record, Ovid MEDLINE(R), PsycINFO, Education Resources Information Center (ERIC), and CINAHL, and Persian electronic databases (i.e., Magiran, SID, Iran Medex, IranDoc).

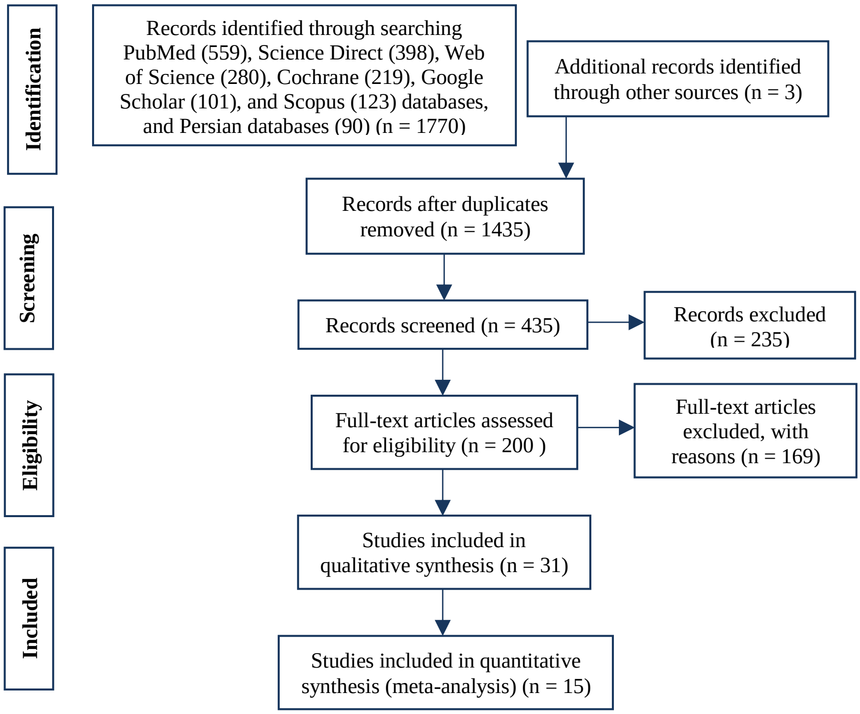

Figure 1. Flow diagram for the study selection process through the different phases of a systematic review

Similar search strategies and combination of keywords were used in all English and Persian databases. We conducted a comprehensive search using combinations of the following keywords: "Randomized controlled trial (RCT)" OR "cluster RCT" OR "clinical trial" OR "controlled clinical trial" OR "double-blind procedure" OR "double blind method" OR "double blind study" OR "single blind procedure" OR "single blind method" OR "single blind study" OR "random allocation" OR "randomization" OR "random assignment" OR "randomized controlled trial" AND "Neurofeedback" OR "Slow Cortical potentials" OR "EMG" OR "EEG" OR "biofeedback" OR "theta -beta protocol" OR "SMR protocol (Neurofeedback intervention)".

Search strategies were conducted in different databases. Moreover, the reference lists of the obtained articles and published reviews were also searched for additional studies. Expert researchers with specialized knowledge on this topic were also queried for the existence of unpublished articles (gray literature). After removing duplicate articles, the remaining articles were assessed according to title and abstract by two independent reviewers (S.H. and M.R). The clinical trial was selected because it is a representative of better control and has a logically better estimate of the effectiveness rate of NF. The other inclusion criteria were randomized sampling, diagnosis based on the DSM criteria, and cognitive-behavioral and neurological tests. Studies conducted on specific groups (such as brain injury and stroke patients), papers published before 1975, letters or editorial articles, and reviews without original data were excluded. In addition, of the studies published several times for a given population, only the valid and the most complete publication was included in the analyses. Moreover, articles must have been peer-reviewed and presented in English or Persian. Patients either had an epilepsy diagnosis or were above the cutoff point on an approved epilepsy measure on an extensive rating scale, for example, the Test of Variables of Attention (T.O.V.A.) and Integrated Visual and Auditory (IVA) test (Goodman, 1997). All age groups with epilepsy participated in this study. Trials had to be randomized controlled trials (RCTs). All studies were included irrespective of intervention quality/characteristics. Trials were only excluded if a specific comorbidity was an inclusion criterion in the trial (e.g., autism). Only studies that evaluated outcomes of epilepsy symptoms were included. Furthermore, studies in which no epilepsy outcome was evaluated or other interventions were combined with NF treatment so that the specific impact of NF treatments could not be illustrated were excluded.

All trials meeting the above criteria were included irrespective of the focus of the study design (e.g., type of pharmacotherapy, etc.) and/or outcomes evaluated (as long as there was at least one epilepsy-specific outcome). Figure 1 illustrates the number of articles recognized in the primary search and the process of characterizing the final articles included in this study. All trials were assessed by two independent researchers at each phase, and any inconsistencies were resolved through argument within the research group. Although there is no specific minimum number of studies necessary for a meta-analysis, the literature propose that the median number of studies included in meta-analyses tends to be 3 (Davey, Turner, Clarke, & Higgins, 2011).

Screening and data Extraction: The design and sample data on the included studies was entered into Review Manager Software (RevMan 5.1; Nordic Cochrane Center, Copenhagen, Denmark) to create a systematic record of study features. All information on study characteristics, year of publication, gender, participant characteristics, medication and control characteristics, consequences, and main findings were excerpted. Data were extracted by one author and independently checked by another. Variables assessed for the meta-analysis were based on a pragmatic evaluation of the outcomes included in each trial.

Quality assessment of studies: To assess the quality of the articles, 2 investigators (A. M. and M. R.) reviewed all the original articles and assessed them according to the Joanna Briggs Institute (JBI) Prevalence Critical Appraisal Tool (Munn, Moola, Lisy, & Riitano, 2014). The quality assessment scores ranged between 55% and 100%. All the articles with a low score (score < 60%; n = 3) were excluded from the analyses. Disagreements between investigators in the quality assessment process were resolved through the opinion of a third person (S. H.) and consensus of all the authors. To ensure that up-to-date publications were obtained, searches were carried out several times. The final search was conducted on 8 April 2022. All publications related to our keywords were attained.

All analyses were separately conducted on epilepsy symptoms. Random effect models were utilized to calculate pooled prevalence and 95% confidence intervals (CI). For this purpose, a mean command was used in Stata software (version 14; StataCorp, College Station, TX, USA). Heterogeneity among studies was appraised using Cochran's Q test and I^2 statistics (Riahi & Mokhayeri, 2017). I^2 statistics ranges between 0 and 100%, and values of 50% or higher were considered heterogeneous (Freeman & Tukey, 1950).

A forest plot in the random effect model was applied to calculate the pooled measure and 95% CI (Harris, Deeks, Altman, Bradburn, Harbord, & Sterne, 2008). To assess the sources of heterogeneity meta-regression analyses were performed.

Univariate meta-regression (UMR) models were separately used for examining the year of publication, mean age, sex, and duration of follow-up. In all statistical analyses, the significance level was considered as P value < 0.05, and all statistical analyses were done in Stata software. Publication bias was assessed using both graphical method (funnel plot by plotting the effect size against standard error for each trial) and statistical tests (Egger's test and Begg's test).

Statistical Analysis: Mean difference and standard error for each study was calculated based on the mean change and its standard deviation. The fixed effects model was used to pool the mean differences. Heterogeneity between the studies was evaluated using chi-squared test and I^2 statistic. Subgroup analysis was performed based on study type and duration of intervention. Publication bias was assessed using Begg's and Egger's tests. All analyses were performed in Stata software (version 11.2; StataCorp, College Station, TX, USA). P-values of less than 0.05 were considered as statistically significant.

Results

A total of 15 studies were included in the analysis. It was found that the mean level of outcome had significantly decreased for about 4.064 units in the intervention group (MD = -0.4.064; 95% CI = [-4.909, -3.22]; P < 0.001). However, the mean difference was not statistically significant within the subgroups. No significant heterogeneity was found neither across the studies nor between the subgroups (Tables 1 and 2). Furthermore, funnel plot along with Begg's and Egger's tests revealed no significant publication bias (Figure 2). Selectivity analysis also showed that the results are robust. The results of study subgroups are displayed in table 3. Moreover, meta-regression results between the effect of NF and year of publication in studies are illustrated in figure 3.

Table 1. Characteristics of the clinical trials included in the meta-analysis based on eligibility criteria (Part I)

Language	Study	Gender	Sample size	Control (n)	Treatment (n)	Before intervention
EN	Seifert and Lubar (1975)	3	12	6	6	9
EN	Lubar and Bahler (1976)	3	16	8	8	11
EN	Kuhlman and Allison (1977)	2	20	10	10	7
EN	Sterman and Macdonald (1978)	3	16	8	8	6
EN	Cott, Pavloski, and Black (1979)	3	14	7	7	9
EN	Lubar et al (1981)	1	20	10	10	10
EN	Tozzo et al. (1988)	2	12	6	6	5
EN	Lantz and Sterman (1988)	3	24	12	12	12
EN	Andrews and Schonfeld (1992)	3	83	40	43	8
EN	Walker and Kozlowski (2005)	3	10	5	5	11
EN	Strehl et al. (2014)	3	32	16	16	9
EN	Morales-Quezada et al. (2019)	2	29	13	16	13
Persian	Khaksarian et al (2020)	3	30	15	15	13
EN	Frey and Koberda (2015)	3	12	6	6	9
EN	Weber et al. (2011)	3	24	12	21	12

Gender: 1: Woman, 2: Man, 3: Both

Table 1. Characteristics of the clinical trials included in the meta-analysis based on eligibility criteria (Part II)

After intervention	Age range	Seizure type	Neurofeedback protocol	Outcome measure	Duration
5	19-57	varied	SMR	Seizure, frequency; EEG	10-20 weeks
6	29-65	varied	SMR	Seizure, frequency	80-260 days
7	17-66	4 partials, 1 generalized, myoclonic	SMR	Seizure, frequency; EEG	A:9 sessions, sham B:24 sessions
2	15-40	varied	SMR	Seizure, frequency	12 months, (2-week intervals)
8	16-31	varied	SMR	Seizure frequency	210 days, (2 sessions per week)
10	13-52	varied	SMR	Seizure, frequency; EEG	10 months
3	18-29	Absence, Atonic, Tonic-clonic	SMR	Seizure, frequency	5 weeks SMR; 3 weeks "auditory biofeedback"
13	10-53	varied	SMR	Seizure, frequency	6 Weeks
7	12-67	Complex-partial, Secondarily, Generalized	SMR	Seizure, frequency	12 Sessions
9	10-62	Varied	QEEG Biofeedback	Seizure, frequency	
3		varied	QEEG Biofeedback	Seizure, frequency	
4	18-70	Absence, Atonic, Tonic-clonic	SMR/SCP	The attention switching task (AST), Liverpool Seizure Severity Scale, (LSSS), seizure frequency (SF), EEG power spectrum, and coherence	30-, minute sessions, 5 consecutive days/week over 5 weeks)
7	12-66	varied	SMR	Seizure, frequency	
6	33	Focal	SMR	Seizure, frequency	125 sessions
3	12-64	Focal	SMR	Seizure, frequency	25 sessions/ 30 mins

Gender: 1: Woman, 2: Man, 3: Both
SMR: Sensory motor rhythm; SCP: Slow cortical potentials; EEG: Electroencephalogram; QEEG: Quantitative EEG

Discussion

The aim of the present study was to investigate the evidence related to the effectiveness of NF treatment for patients suffering from epilepsy. The results showed that this treatment has a positive and significant effect on the improvement of epilepsy symptoms.

Table 2. Weighted Mean for studies

Study	MD	95% CI		Weight (%)
		L	U	
Seifert and Lubar (1975)	-4.77	-9.027	-0.513	3.94
Lubar and Bahler (1976)	-7.14	-11.656	-2.624	3.5
Kuhlman and Allison (1977)	-4.98	-8.539	-1.421	5.63
Sterman and Macdonald (1978)	-5.83	-10.518	-1.142	3.25
Cott, Pavloski, and Black (1979)	-6.68	-11.59	-1.77	2.96
Lubar et al. (1981)	-4.69	-8.552	-0.828	4.78
Tozzo et al. (1988)	-4.3	-9.206	0.606	2.96
Lantz and Sterman (1988)	-5.41	-8.526	-2.294	7.35
Andrews and Schonfeld (1992)	-4.05	-5.866	-2.234	21.64
Walker and Kozlowski (2005)	-3.4	-8.33	1.53	2.94
Strehl et al. (2014)	-1.57	-4.163	1.023	10.61
Morales-Quezada et al. (2019)	-2	-5.076	1.076	7.54
Khaksarian et al. (2020)	-3.85	-6.653	-1.047	9.08
Frey and Koberda (2015)	-3.41	-8.297	1.477	2.99
Weber et al. (2011)	-4.29	-6.856	-1.724	10.83
Pooled MD	-4.064	-4.909	-3.22	100

Heterogeneity chi-squared = 10.08 (df = 14), P = 0.756
I-squared (variation in ES attributable to heterogeneity) = 0%
Test of MD = 0: Z = 9.43, P < 0.001

This result is consistent with that of prior studies (Adhia et al., 2023; Le Breton, 2022; Lyle, 2022; Souza et al., 2022; White et al., 2022). Despite certain limitations, the results were quite similar across all studies included in our meta-analysis as well as the majority of case reports and case series, sensory motor rythm (SMR) or SCP training consistently decreased epilepsy rate among all patients. As nearly all patients underwent lengthy unsuccessful medication therapies for epilepsy prior to any NF session, and the placebo effect had minimal impact in these previous therapies, its presence in NF training is just as unlikely and probably negligible (Lyle, 2022). While we can clearly state that NF is useful for patients with uncontrolled epilepsy, this may also suggest a promising avenue for future research and treatment for many patients whose epilepsy does respond to other forms of treatment as well (Patil et al., 2023).

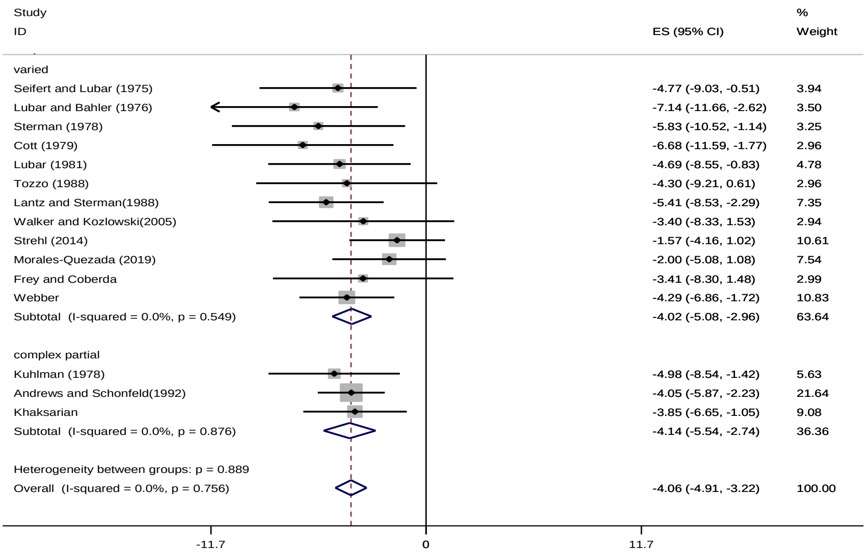

Figure 2. Forest plot diagram for effectiveness of NFB on epilepsy

Table 3. Results of study subgroups

Subgroup by	No of studies	MD	95% CI L	95% CI U	Weight (%)	I^2	P_1	P_2
Study type								
Varied	12	-4.019	-5.077	-2.960	63.64	0%	0.549	0.889
Complex partial	3	-4.144	-5.545	-2.743	36.36	0%	0.876	
Duration								
Short	4	-4.267	-5.586	-2.949	41.04	0%	0.883	0.694
Long	11	-3.923	-5.023	-2.823	58.96	0%	0.507	

MD: Mean Difference; CI: Confidence Interval
P_1: P-value of test for heterogeneity between studies within sub-group
P_2: P-value of test for heterogeneity between sub-groups

The current research on utilizing NF for epilepsy has included children and adolescents in the participant samples; however, no specific effects of age have been reported. Since none of the above studies have documented potential age effects, one cannot make any assumptions regarding the efficacy of NF training for children with epilepsy (Turner et al., 2023). Although the growing amount of literature in the field of NF in epilepsy disorder demonstrates the usefulness of NF in the pediatric population, there will hopefully be continued research involving RCTs to document the effectiveness of NF in pediatric epilepsy (Yonah, 2023).

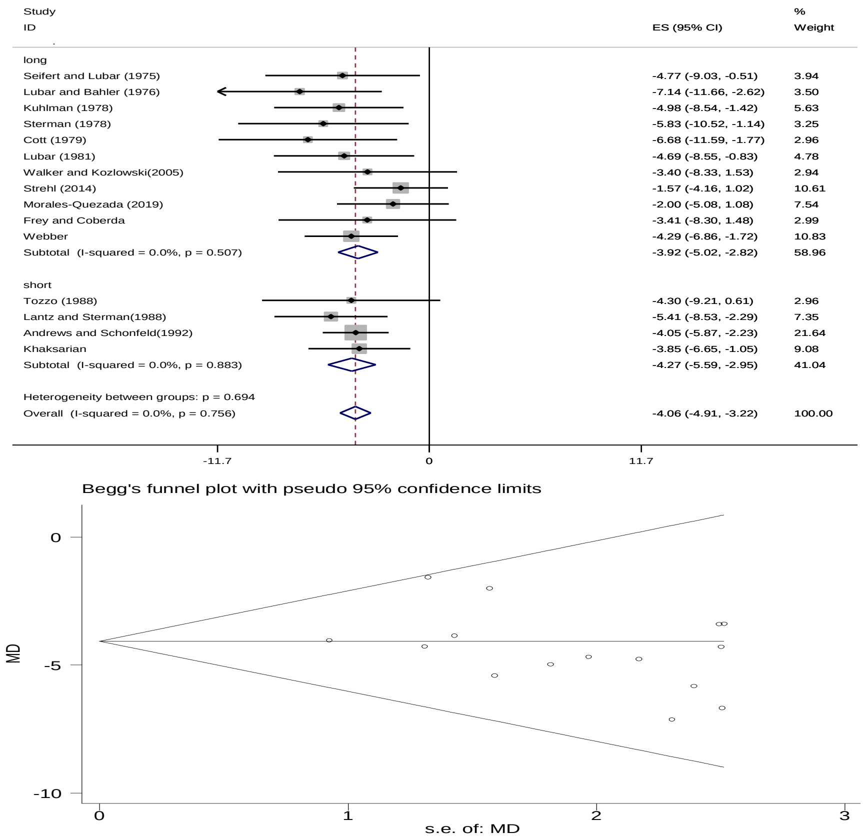

Figure 3. Meta-regression results between effect of neurofeedback and year of publication in studies

Since the latter is associated with many comorbid disorders, such as autism spectrum disorder (ASD) and ADHD, NF can potentially reduce not only epilepsy frequency, but also address the behavioral concerns associated with ASD and ADHD.

Notably, the limited amount of unique studies utilizing NF training in children and adolescents afflicted with epilepsy complicates the endeavor to examine its efficacy in pediatric epilepsy. This problem is also true of AEDs, in that most, if not all, studies assessing their effects were conducted on an adult population; yet this remains the first line of treatment for children diagnosed with epilepsy. In addition, when working with a pediatric population, there are many more regulations concerning their involvement in research, because they are a protected population. All of these factors impact research in this area; therefore, most of the previous research comprised case studies.

More specifically there are a number of factors that limit the span of this meta-analysis and the results of the current meta-analysis which should be interpreted in line with its limitations. First, the simultaneous use of medication and NF in some of the trials included in our meta-analysis may have influenced the results, suggesting it may have affected the expectations of patients. Moreover, these expectations should not bias the data against NF, but rather suggest that the effects of NF may be slightly masked by the increase in expectations seen in the experimental groups. Therefore, the reported consequences may also reflect changes in patients' understanding or tolerance of symptoms rather than real changes in epilepsy behaviors. Nevertheless, the results of the current study do support the role of other factors in assuagement of patients. Moreover, the year of publication is an important factor that must be considered. Some studies have been performed before the development of more accurate types of NF, and the use of more accurate NF protocols may yield different results.

Other authors chose specifically to not run the risk of biased assessment because the patients may underrate recovery for many reasons. Second, no information was accessible to illustrate what effect epilepsy symptoms had on other facets of patient functioning and how the medications might affect this, for example, occupational status, academic status, and social skills. Third, it was not possible to assess the potential role of moderators of the consequences, especially intensity of epilepsy or patients' professionalism which may also affect their assessments. Accordingly, there is a need for vigorous research to evaluate the role of moderators of consequences. Moreover, it still remains necessary to improve the clinical diagnosis procedure in neuropsychology in order to render it useful.

Conclusion

The neurological nature of epilepsy requires the use of low-risk methods that result in less damage. Neurofeedback is based on the principles of conditioning and the use of learning techniques that are implemented in the form of approved protocols. Therefore, in the present meta-analysis, the effectiveness of neurofeedback on the improvement of epilepsy symptoms has been confirmed. It seems that the use of neurofeedback can show a promising perspective in improving and reducing the symptoms of epilepsy.

Conflict of Interests

Authors have no conflict of interests.

Acknowledgments

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All processes conducted in trials involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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