Comparative Efficacy of Neuromodulatory Strategies for Drug-Resistant Epilepsy: A Systematic Review and Meta-Analysis

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Key words
- Drug-Resistant Epilepsy
- Meta-analysis
- Neuromodulation
- Neurosurgery
- Seizure frequency reduction

Abbreviations and Acronyms
ASM: Anti-seizure medication
ATL: Anterior temporal lobectomy
CI: Confidence interval
DBS: Deep brain stimulation
DRE: Drug-resistant epilepsy
inVNS: Invasive vagal nerve stimulation
NMA: Network meta-analysis
OR: Odds ratio
RCT: Randomized controlled trial
RNS: Responsive neurostimulation
SAH: Selective amygdalohippocampectomy
SFR: Seizure frequency reduction
SUCRA: Surface under the cumulative ranking curve
SE: Surgical excision
SMA: Single-arm meta-analysis
tACS: transcranial alternating current stimulation
tDCS: transcranial direct current stimulation
taVNS: Transcutaneous auricular VNS
tnVNS: transcutaneous auricular nonvagal nerve stimulation
TMS: Transcranial magnetic stimulation
TNS: Trigeminal nerve stimulation

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OBJECTIVE: **The study aims to evaluate the efficacy of neuromodulatory strategies for people who have drug-resistant epilepsy (DRE).**

METHODS: **We searched electronic repositories, including PubMed, Web of Science, Embase, and the Cochrane Library, for randomized controlled trials, their ensuing open-label extension studies, and prospective studies focusing on surgical or neuromodulation interventions for people with DRE. We used seizure frequency reduction as the primary outcome. A single-arm meta-analysis synthesized data across all studies to assess treatment effectiveness at multiple time points. A network meta-analysis evaluated the efficacy of diverse therapies in randomized controlled trials. Grading of Recommendations, Assessment, Development, and Evaluations was applied to evaluate the overall quality of the evidence.**

RESULTS: **Twenty-eight studies representing 2936 individuals underwent 10 treatments were included. Based on the cumulative ranking in the network meta-analysis, the top 3 neuromodulatory options were deep brain stimulation (DBS) with 27% probability, responsive neurostimulation (RNS) with 22.91%, and transcranial direct current stimulation with 24.31%. In the single-arm meta-analysis, in the short-to-medium term, seizure control is more effective with RNS than with invasive vagus nerve stimulation (inVNS), which in turn is slightly more effective than DBS, though the differences are minimal. However, in the long term, inVNS appears to be less effective than both DBS and RNS. Trigeminal nerve stimulation, transcranial magnetic stimulation, and transcranial alternating current stimulation did not demonstrate significant seizure frequency reduction.**

CONCLUSIONS: **Regarding long-term efficacy, RNS and DBS outperformed inVNS. While transcranial direct current stimulation and transcutaneous auricular VNS showed promise for treating DRE, further studies are needed to confirm their long-term efficacy.**

INTRODUCTION

Drug-resistant epilepsy (DRE) remains a challenge, affecting approximately one-third of people with epilepsy.[1] According to International League Against Epilepsy criteria, DRE, is an inability to achieve sustained seizure freedom despite adequate trials of 2 or more anti-seizure medication (ASM), inflicting significant clinical, psychological, and social burdens.[2,3] A recent study highlighted the complex interplay between clinical and psychological factors contributing to drug resistance.[4] While surgical interventions have been proven effective for seizure control in DRE, postoperative neuropsychological sequelae often complicate them. The efficacy of emerging neuromodulation techniques remains unknown.[5] This highlights the need for full evaluations to guide clinicians in the nuanced management of DRE.

Surgical excision (SE) of an epileptogenic zone remains a cornerstone in managing focal DRE.[6] Various surgical procedures, such as anterior temporal lobectomy (ATL) and selective amygdalohippocampectomy (SAH), offer curative potential but are limited to specific individuals with well-localized seizure foci.[7,8] In recent years, neuromodulatory technologies based on brain network modulation have undergone enhancements, increasing the therapeutic options. Vagus nerve stimulation (VNS) is the less invasive alternative, available as an implantable and transcutaneous device.[9] Specifically, the implantable VNS involves a pulse generator placed subcutaneously within the thoracic region, enhancing neural activity via the vagus nerve. There is a noninvasive VNS transcutaneous options, broadening its applicability.[10] Deep brain stimulation (DBS) targets various thalamic nuclei, predominantly the anterior nucleus of the thalamus and centromedian thalamic nucleus.[9] Centromedian thalamic nucleus has demonstrated efficacy in generalized epilepsy. Closed-looped responsive neurostimulation (RNS) is a real-time modality designed to identify abnormal electrical activity and deliver targeted stimulation to abort seizures.[9] It is capable of concurrently targeting up to 2 epileptogenic foci.

Emerging noninvasive neurostimulation therapies, including trigeminal nerve stimulation (TNS), transcranial magnetic stimulation (TMS), and transcranial electrical stimulation are entering clinical practice. TNS, which modulates the trigeminal nerve, influences critical brain regions such as the solitary tract nucleus, the locus coeruleus, and the reticular formation—structures likely critical to seizure inhibition.[11] Early clinical investigations suggest TNS holds promise.[11,12] TMS, conventionally utilized for functional delineation of epileptogenic regions, has been scrutinized for potential antiepileptic effects, with some modest reports of seizure reduction.[13] Transcranial electrical stimulation, encompassing transcranial direct (tDCS), and alternating current stimulation (tACS), employs specified current waveforms applied to the scalp to modulate neural excitability.[14,15] Transcranial electrical stimulation aims to attenuate neuronal hyperactivity within targeted epileptogenic zones or intermediary structures, such as the thalamus, mitigating the likelihood of seizure onset.

These modalities present advantages and may expand the therapeutic arsenal for DRE. Individual outcomes can vary based on a myriad of factors, including the duration of epilepsy and the presence of comorbidities. Given this variability and the interest in neuromodulatory therapies, we conducted a systematic review and meta-analysis to evaluate the comparative efficacy of current neuromodulatory interventions for DRE. To ensure the robustness and comprehensiveness of our approach, we have structured it into 2 distinct segments. The first employs a Bayesian network meta-analysis (NMA) incorporating randomized controlled trials (RCTs). The second is a single-arm meta-analysis (SMA), which broadens the scope of the analysis to include RCTs, their open-label extensions, and prospective studies, offering a cross-sectional comparison at different follow-up periods. Recognizing open surgical resection as the first choice for people with DRE (where indicated), we also included it in our study to evaluate the comparative efficacy of current neuromodulatory treatments against this benchmark.

METHODS

Study Design and Search Strategy

We followed the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) extension statement, inclusive of NMA (Appendix S1).[14] The study was listed in the International Prospective Register of Systematic Reviews—PROSPERO (CRD42023405725). We devised a search strategy incorporating MeSH terms, Emtree headings, and free-text keywords specifically tailored for surgical and neuromodulatory modalities in epilepsy (**Appendix S2**). We searched PubMed, Web of Science, Embase, and Cochrane Library from January 1990 to April 2024. Three investigators (Jianwei Shi, Dafeng Lu, and Yanfeng Yang) reviewed the reference lists of included studies, relevant reviews, and other items to identify additional studies missed by the initial search. We did not include items from the gray literature.

Eligibility Criteria

The initial screening involved reviewing the titles and abstracts of all identified studies to assess their relevance based on the following preset eligibility criteria: 1) Definition of DRE: Studies must define DRE as the failure of at least 2 adequate trials of ASM, with "adequate" defined according to the International League Against Epilepsy criteria for drug resistance. 2) Efficacy and Tolerability Reporting: Studies had to report on the efficacy (e.g., seizure frequency reduction, seizure freedom rates) and tolerability of interventions (e.g., dropout rates due to side effects) in people with DRE. 3) Participant Age: Studies should focus on adults over the age of 18 years, pediatric studies on participants under 18 were excluded to maintain a consistent study population. 4) Follow-Up Duration: A minimum follow-up of one month postintervention was needed to ensure sufficient time to assess the efficacy. 5) Sample Size: At least 10 participants, with more than 5 in any single treatment or control arm are required to ensure adequate statistical power. 6) Data Availability: Studies had to provide extractable or convertible data of mean, standard deviation/95% confidence intervals (CIs), or median, interquartile range for seizure frequency reduction (SFR). 7) Study Design: Only RCTs, subsequent open-label extensions, and prospective studies were included. 9) Comparator Groups: RCTs should clearly define the comparator groups, whether it is a sham procedure, standard medical therapy, or another neuromodulatory technique, to ensure comparability across studies. 10) Intervention Details: Studies must provide a comprehensive description of the surgical or neuromodulatory intervention, including procedural details, stimulation parameters (e.g., frequency, amplitude for neuromodulation), and any pre- or postintervention care protocols. 11) Baseline Characteristics: Studies should include detailed baseline characteristics of participants and report outcomes stratified by key demographic and clinical variables (e.g., age, sex, epilepsy duration). 12) Seizure Type: Studies must specify the type of seizures (e.g., focal, generalized)

and the epilepsy syndrome (if applicable). If these details are not available, they should at least provide information on the location of the seizure focus.

Full-text reviews were then conducted (Jianwei Shi) for studies that appeared to meet the inclusion/exclusion criteria. The selection of specific neuromodulatory interventions was based on their clinical relevance, established use in treating DRE, and the availability of sufficient data for analysis. Substantial clinical evidence was needed to support their safety. Interventions that lacked sufficient clinical evidence, or did not provide extractable data for main outcomes were excluded to maintain the integrity and comparability of the meta-analysis.

Data Extraction

Data on trial details (e.g., first author, publication year, number of participants, and individual characteristics), treatments, follow-up, and outcomes were independently extracted by 2 reviewers (Jianwei Shi and Dafeng Lu) to ensure accuracy and minimize bias. Following the initial extraction, the data were reviewed and censored by another reviewer (Yanfeng Yang). Unavailable information on the above categories was documented as not reported.

While the ultimate goal in epilepsy treatment is achieving seizure freedom, this outcome is relatively less frequent in neuromodulatory therapies, particularly in short-term follow-ups.[9] The reduction in seizure frequency may serve as a reliable indicator of the dynamic efficacy of the neuromodulatory therapies.[9,15,16] Thus, the primary outcome of our study was the converted odds ratio (OR) for mean percentage in SFR compared to the baseline. The OR reflects the ratio of outcomes between the intervention group and the control group, and the relationship between the OR and SFR can be expressed as SFR = ((OR - 1)/OR) * 100%. When the data provided were in the form of medians, interquartile ranges, or ranges, we converted these to means and standard deviations as required for the pooled analysis.[17]

Given the bifurcated structure of our study, in the Bayesian network meta-analysis focusing on RCTs, data from the final follow-up period were exclusively extracted if multiple follow-up periods existed in one study. For the SMA encompassing all study types, data at various follow-up intervals were extracted and categorised into 3 groups: from one month up to 18 months (short term-group year 1), from beyond 18 months up to 30 months (mid-term-group year 2), and beyond 30 months (long term-group year 3). In the overall efficacy analysis of the SMA, we aggregated data from different time points over a short-to-long period, which is represented as "person-times." If data were solely available in graph format, they were extracted using WebPlotDigitizer.[18]

Quality and Risk Bias in Studies

Quality assessment was independently conducted by Jianwei Shi Yanfeng Yang, and Dafeng Lu in a blinded fashion. Any divergences were reconciled through consensus. We employed the revised Cochrane risk-of-bias tool for RCTs, tailored to specific outcomes.[19] Without a standardized metric for observational studies, we used a customized assessment tool.[20] Items were considered as high, low, or uncertain risk of bias. Any discrepancies were resolved by consensus. The study used the Grading of Recommendations, Assessment, Development, and Evaluations to systematically evaluate the overall quality of evidence from both the NMA. The following factors were assessed: Within-study bias, inconsistency, indirectness, imprecision, heterogeneity and across-studies bias,. The Grading of Recommendations, Assessment, Development, and Evaluations system evaluates the quality of evidence at 4 levels: high, moderate, low, and very low. For the design and quality of individual studies, a modified quality rating scheme from the Oxford Center for Evidence-Based Medicine was used to assess the strength of evidence.[21-23]

Statistical Analysis

Considering the clinical implications and the statistical distribution characteristics of SFR, we applied log-transformation before conducting statistical.[24] The results were back-transformed and presented in an anti-logarithmic scale for statistical interpretation. Converting SFR to OR provides a more robust representation of therapeutic efficacy.[24,25] Additionally, if the SFR data were not normally distributed, transformation is also required to meet the assumptions for analysis.[24] Evidence to compare different treatments in terms of SFR was synthesized, and these parameters were reported as OR and 95% CI for each study. To avoid confusion, the term "OR" in the NMA represents the odds ratio between different treatment effects (ORn), while in the SMA, the "OR" refers to the odds ratio comparing post-treatment to pretreatment outcomes (ORs). Study heterogeneity was assessed via the Q test and I^2 statistic, with significance set at $P \leq 0.05$. Given that this NMA primarily analyzes direct evidence, we used a random effects model. The choice of the SMA model was determined through a heterogeneity test. In the NMA, we assumed that each treatment arm had a stable but heterogeneous variance.[21,26] We used the generalized method of moments to estimate the between-study variance and applied adjustments for multi-arm studies. For the SMA, we applied the DerSimonian-Laird method to estimate the between-study variance, which was then used to calculate heterogeneity (I^2).[21,26] Levels of heterogeneity were stratified as low ($I^2 < 25\%$), moderate ($25\% \leq I^2 \leq 50\%$), or high ($I^2 > 50\%$). When $I^2 > 50\%$, the combined proportion and 95% CI are calculated by the random effects model. Otherwise, a fixed effect model is used. The statistical significance level was set to $P \leq 0.05$.

A random effects model was employed, and the Deviance Information Criterion assessed its fitness.[27] For the primary outcome, 110,000 iterations were run with 100,000 burn-ins. Convergence was confirmed visually and via the Brooks-Gelman-Rubin diagnostic. Once convergence was established, the posterior distributions for the model parameters were obtained as the output of the NMA estimate. With minimal priors, credible intervals were interpreted as CI. NMA estimated the overall rankings of treatments by calculating the surface under the cumulative ranking curve (SUCRA) for each.[28] Statistical analyses were performed using the gemtc, multinma, and netmeta packages of R Language (version 4.3.1) to generate network plots to illustrate the geometry and to clarify which treatments were directly or indirectly compared in the included studies.

RESULTS

Included Studies

Figure 1 presents the PRISMA flowchart delineating the study selection process. The search initially yielded 2051 items, from which 460 articles were identified as potentially eligible and subsequently reviewed in full text. Eventually, 28 articles met the inclusion criteria, covering data from 2936 individuals with a similar proportion of men and women, including 16 RCTs.[29-56] There was one article on SE, 8 on VNS (5 invasive and 3 noninvasive), 6 on RNS, 5 on DBS, 4 on tDCS, 2 on TNS, and single articles on TMS and tACS. The duration of the trials spanned from one month to nine years. Characteristics of the included trials were summarized in Table 1, specific details (including data used for analysis) were provided in Appendix S3. The overall methodologic quality of the included studies was summarized in Supplementary Table 2. It is worth noting that VNS can be categorized into invasive (inVNS) and noninvasive forms. Within the noninvasive category, the treatment for transcutaneous auricular non-VNS involved an initial 8 weeks of sham stimulation followed by 16 weeks of true transcutaneous auricular VNS (taVNS).[57] As a result, we did not consider it a separate "treatment modality" for further detailed discussion.

NMA in Treatments for DRE

The network meta-analysis included data from 11 treatments for DRE (Supplementary Figure 1). An NMA was considered appropriate for synthesizing the evidence, as most RCTs exhibited a low risk of bias (Supplementary Figure 2).

In terms of head-to-head comparisons for ORn of the 11 interventions (Appendix S4 and Figure 2A), the analysis indicated varying levels of benefit in SFR versus control-ASM. Specifically, SE showed a notably higher ORn of 55.72 (95% CI: 18.90 to 158.68), followed by DBS (ORn: 1.55, 95% CI: 0.88 to 3.61), RNS (ORn: 1.55, 95% CI: 0.77 to 3.10), tDCS (ORn: 1.52, 95% CI: 1.06 to 2.27), TNS (ORn: 1.46, 95% CI: 0.84 to 2.45), taVNS (ORn: 1.23, 95% CI: 0.69 to 2.22), inVNS (ORn: 1.17, 95% CI: 0.59 to 2.28), and TMS (ORn: 1.05, 95% CI: 0.53 to 2.10). tACS (ORn: 0.81, 95% CI: 0.18 to 3.53) seems to have limited efficacy and is underperforming if compared to controls on ASM only.

The Gelman-Rubin-Brooks diagnostic plots indicate a convergence model (Supplementary Figure 3). The Bayesian ranking profiles of comparable treatments are shown in Figure 3A, Supplementary Table 1, and Supplementary Figure 4. The 66.7% and 95% CI of SUCRA was presented to quantify the uncertainty of ranking (Figure 3B). The Bayesian ranking results are almost in line with the pooled analyses of SFR. The cumulative ranking probability plots for patients with DRE show that SE had the highest cumulative probability (99.86%) of being the most effective treatment in reducing seizure frequency, with a SUCRA value of 99.97%. In addition to SE (Rank 1), the top 3 neuromodulation treatments are ranked as follows: DBS (Rank 2 with a cumulative probability of 26.74%), RNS (Rank 3 with a cumulative probability of 22.91%), and tDCS (Rank 4 with a cumulative probability of 24.31%), with SUCRA values of 66.83% for DBS, 67.26% for RNS, and 66.72% for tDCS. tACS ranked last with the highest cumulative probability of 44.83% and a SUCRA value of 26.90%.

SMA in Treatments for DRE

3986 "person-times" were included from 28 studies for the overall efficacy analysis, accounting for repeated counts across different periods (short-, medium-, and long term). Most non-RCTs exhibited low to moderate risk of bias (Supplementary Figure 5). The overall heterogeneity was substantial (all >50%), requiring the use of a random-effects model for analysis. Summary of the overall efficacy of different treatments across all time periods is presented in Figure 2B. SE (ORs=47.5, 95% CI: 27.86 to 80.45), RNS (ORs=2.37, 95% CI: 2.09 to 2.7), DBS (ORs=2.13, 95% CI: 1.54 to 2.95), inVNS (ORs=1.83, 95% CI: 1.58 to 2.13), taVNS (ORs=1.73, 95% CI: 1.06 to 2.83), and tDCS (ORs=1.67, 95% CI: 1.41 to 1.97) showed significant improvements in SFR. In contrast, TNS (ORs=1.38, 95% CI: 0.82 to 2.33), TMS (ORs=1.05, 95% CI: 0.73 to 1.13), tACS (ORs=0.88, 95% CI: 0.25 to 3.12), and ASM controls

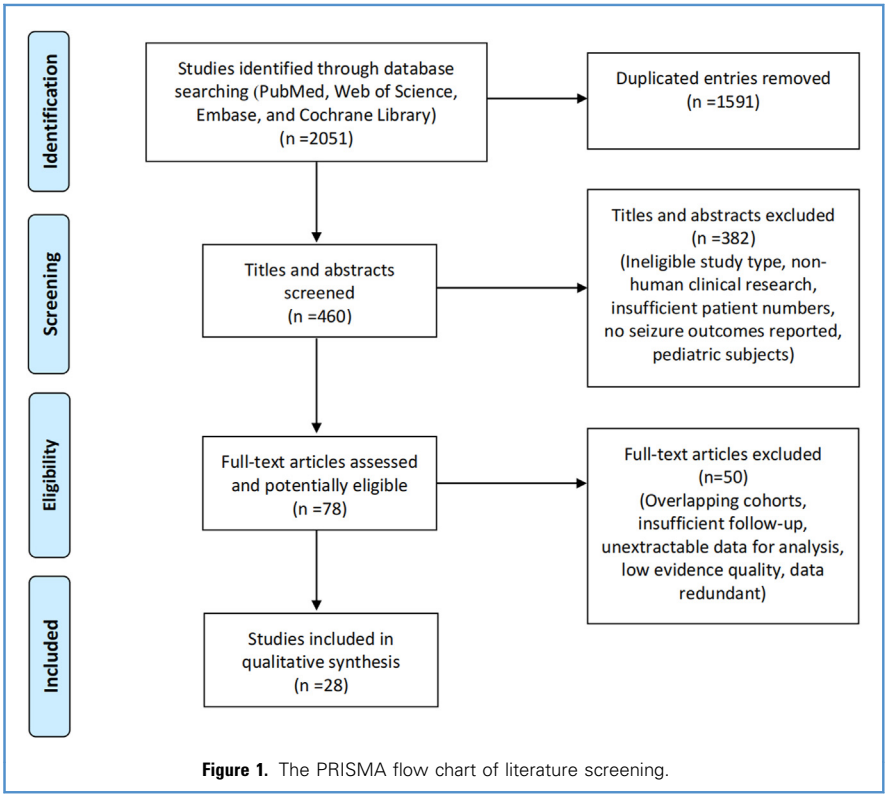


Figure 1. The PRISMA flow chart of literature screening.

Table 1. Characteristics of Studies Included in the Final Analysis

Year; Name	Modality/Group	Number of participants	Seizure type (subtypes noted where provided)	Seizure Reduction %: mean ± SD or median (IQR)	Mean follow-up (months)	Quality Rating
1 Year (or less)						
1998; Handforth	in-VNS	94	FS (AB), GS(TS)	27.9 ± 34.3	3	1
	Control-ASM	102		15.2 ± 39.2	3	1
2001; Scherrmann	in-VNS	85	FS (FA), GS	32.5 ± 41.9	15.8	3
2016, García-Pallero	in-VNS	85	GS	45.6 ± 30.3	18	2
2017; Kawai	in-VNS	357	FS (FIA, FBTC), GS (TC, AB, TS)	27.7 ± 40.5	36	2
2016; Bauer	taVNS	27	FS (FA, FIA)	23.4 ± 47.2	4.7	1
	Control-ASM	31		2.9 ± 94.4	4.7	1
2023; Yang H	taVNS	76	NR	30.8 ± 54.3	4.7	1
	Control-ASM	36		15.7 ± 44.9	4.7	1
2014; Rong-b	taVNS	98	FS (FA)	62.5 ± 23.4	2	2
2019; Herrman	DBS	8	FS	23.0 ± 27.0	6	1
	Control-ASM	10		-11.0 ± 28.0	6	1
2017; Cukiert	DBS	8	FS (FA, FIA, FBTC)	50.0 (0.0, 100.0)	6	1
	Control-ASM	8		-26.3 (-91.3, 20.6)	6	1
2015; Salanova	DBS	99	FS (FA, FBTC)	41.0 (12.0, 76.5)	60	1
2023; Peltola	DBS	163	FS (FA, FIA, FBTC)	25.3 (-11.6, 51.9)	60	2
2011; Morrell	RNS	97	FS (FA, FIA, FBTC)	41.5 (28.7, 52)	3	1
	Control-ASM	94		9.4 (-16.4, 29.5	3	1
2014; Heck	RNS	181	FS (FA, FIA, FBTC)	40.2 (33.6, 46.7)	24	1
2013; DeGiorgio	TNS	25	FS (FA, FBTC)	5.9 ± 67.6	4	1
	Control-ASM	25		2.1 ± 44.1	4	1
2020; Gil-López	TNS	16	FS (FIA, FBTC), GS (TC, AB, TS)	43.5 (10.0, 66.7)	12	1
	Control-ASM	13		0.0 (-20.0, 0.0)	12	1
2012; Jerome	Surgical Excision	14	NR	98.8 (94.12, 100.0)	36	1
	Control-ASM	20		-10 (-26.2, 6.2)	36	1
2002; Theodore	TMS	12	FS (FIA, FBTC)	4.5 ± 13.0	2	1
	Control-ASM	12		-0.4 ± 20.0	2	1
2022; Rezakhani	tDCS	10	FS	30.5 ± 13.0	2	1
	Control-ASM	10		-4.8 ± 2.9	2	1
2020; Yang	tDCS	49	FS (FA, FIA, FBTC)	35.2 (12.6, 57.8)	2	1
	Control-ASM	21		12.5 (-12.5, 57.5)	2	1
2017; San-Juan	tDCS	20	FS (FIA), TCS*	47.9 (37.2, 58.6)	2	1
	Control-ASM	8		6.3 (-30.8, 43.3)	2	1
2006; Fregni	tDCS	10	NR	41.7 (7.3, 76.2)	1	2
	Control-ASM	9		-5.4 (-33.6, 22.7)	1	2
2022; San-Juan	tACS	16	FS (FA, FIA, FBTC), GS	-13.2 ± 111.9	2	1
	Control-ASM	7		7.3 ± 40.4	2	1
2-3 Years						
2017; Kawai	in-VNS	348	FS (FA, FIA, FBTC), GS (GTC, AB, TS, MYO, AT)	47.2 ± 50.2	36	2
2015; Salanova	DBS	82	FS (FA, FIA, FBTC), GS	56 (25.5, 79.1)	60	1
2023; Peltola	DBS	155	FS (FA, FIA, FBTC)	33.11 (-6.87, 57.93)	60	2
2014; Heck	RNS	174	FS (FA, FIA, FBTC)	49.9 (42.6, 57.2)	24	1
2017; Geller	RNS	102	NR	50.0 (27.8, 73.6)	24	1
2017; Jobst	RNS	114	NR	44.0 (8.8, 81.2)	73.2	1
2012; Jerome	Surgical Excision	14	NR	98.33 (8.8, 81.2)	36	1
	Control-ASM	19		-35.5 (-47.0, -24.0)	36	1
3 Years (or more)						
2013; Marras	in-VNS	35	FS (FA, FIA, FBTC), GS (GTC, AB, TS, AT)	68.0 (50.0, 90.0)	36	2
2017; Kawai	in-VNS	333	FS (FA, FIA, FBTC) , GS (GTC, AB, TS, MYO, AT)	53.3 ± 51.5	36	2
2015; Salanova	DBS	59	FS (FA, FIA, FBTC), GS	69 (42.6, 96.4)	60	1
2021; Salanova	DBS	73	FS (FA, FIA, FBTC), GS	67.9 (58.6, 75.9)	84	1
2015; Bergey	RNS	191	FS (FA, FIA, FBTC)	65.7 (30.6, 80.1)	64.8	2
2017; Geller	RNS	82	NR	66.5 (31.8, 93.7)	24	1
2017; Jobst	RNS	87	NR	58.0 (-11.0, 95.0)	73.2	1
2020; Nair	RNS	162	FS (FA, FIA, FBTC)	73.0 (47.0, 93.0)	90	1

The studies were rated using a modified quality scheme from the Oxford Center for Evidence-Based Medicine.

ASM, anti-seizure medication; DBS, deep brain stimulation; inVNS, invasive vagal nerve stimulation; RNS, responsive neurostimulation; SE, surgical excision; tACS, transcranial alternating current stimulation; tDCS, transcranial direct current stimulation; taVNS, transcutaneous auricular VNS; tnVNS, transcutaneous auricular non-vagal nerve stimulation; TMS, transcranial magnetic stimulation; TNS, trigeminal nerve stimulation; FS, focal seizures; GS, generalized seizures; NR, not reported (note: NR indicates that the article does not specify the type of seizures, but it includes other information such as the localization of the epileptic focus); AB, absence; AT, atonic seizure/drop attack; DRA, Dravet syndrome; FA, focal aware—previously simple partial; FIA, focal impaired awareness—previously complex partial; FBTC, focal to bilateral tonic–clonic—previously secondarily generalized tonic–clonic; GTC, primary generalized tonic–clonic; MYO, myoclonic seizure; SBH, subcortical band heterotopia; TCS, tonic-clonic seizure; TS, tonic seizure.

(ORs=0.99, 95% CI: 0.92 to 1.07) did not show significant differences in SFR before and after treatment. Below are the specific results for different time periods.

In the short-term efficacy analysis (group year 1), 22 studies involving 1956 individuals were included, spanning 10 treatments. Apart from TNS (ORs=1.38, 95% CI: 0.82 to 2.33), TMS (ORs=1.05, 95% CI: 0.97 to 1.13), tACS (ORs=0.88, 95% CI: 0.25 to 3.12), and ASM controls (ORs=1.01, 95% CI: 0.96 to 1.08), all other treatments (inVNS, taVNS, DBS, RNS, SE, and tDCS) demonstrated significant efficacy (Figure 4A).

The medium-term efficacy analysis (group year 2) included 7 studies involving 1008 participants, covering 5 treatments

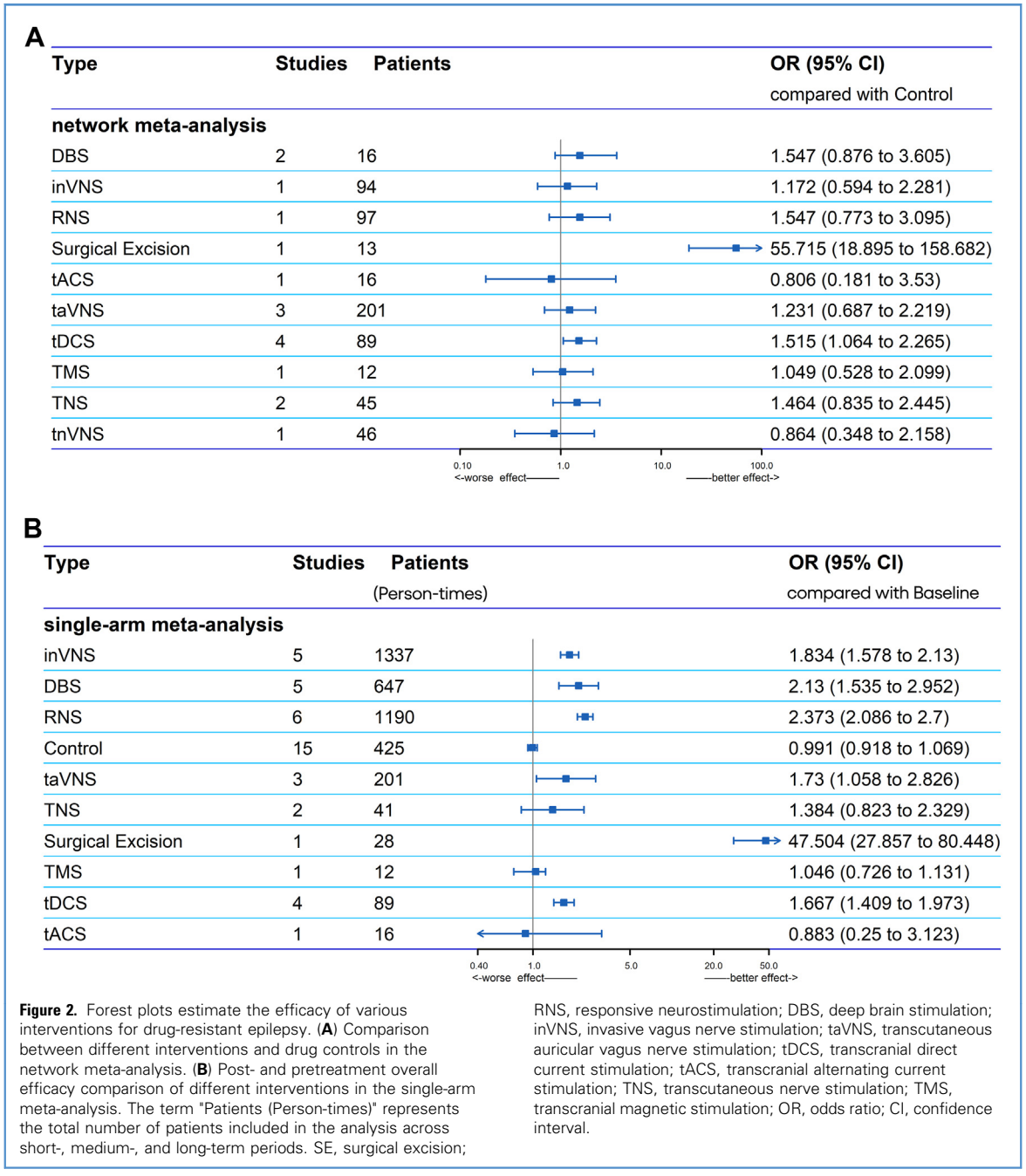


Figure 2. Forest plots estimate the efficacy of various interventions for drug-resistant epilepsy. (**A**) Comparison between different interventions and drug controls in the network meta-analysis. (**B**) Post- and pretreatment overall efficacy comparison of different interventions in the single-arm meta-analysis. The term "Patients (Person-times)" represents the total number of patients included in the analysis across short-, medium-, and long-term periods. SE, surgical excision; RNS, responsive neurostimulation; DBS, deep brain stimulation; inVNS, invasive vagus nerve stimulation; taVNS, transcutaneous auricular vagus nerve stimulation; tDCS, transcranial direct current stimulation; tACS, transcranial alternating current stimulation; TNS, transcutaneous nerve stimulation; TMS, transcranial magnetic stimulation; OR, odds ratio; CI, confidence interval.

(inVNS, DBS, RNS, SE, and ASM control). All other treatments showed significant efficacy except for ASM controls (Figure 4B).

In the long-term efficacy analysis (group year 3), 8 studies involving 1022 people were included in 3 different treatments: DBS (ORs=3.87, 95% CI: 2.32 to 6.45), RNS (ORs=3.65, 95% CI: 2.66 to 5.00), and in VNS (ORs=2.84, 95% CI: 1.55 to 5.18) (Figure 4C). All 3 demonstrated effective control of seizures.

In terms the efficacy changes for RNS, DBS, and inVNS across different follow-up stages, these were illustrated in Figure 5. All 3 treatments exhibited a statistically significant, yet heterogeneous, trend of gradual improvement in efficacy. Within the first three years, the effectiveness of RNS, DBS, and invasive VNS was very similar, with RNS > inVNS > DBS. However, in the long-term (three years and beyond), the efficacy of inVNS gradually lagged behind that of DBS and RNS.

DISCUSSION

Our meta-analysis compared the relative efficacy of neuromodulatory strategies in SFR among people with DRE. These

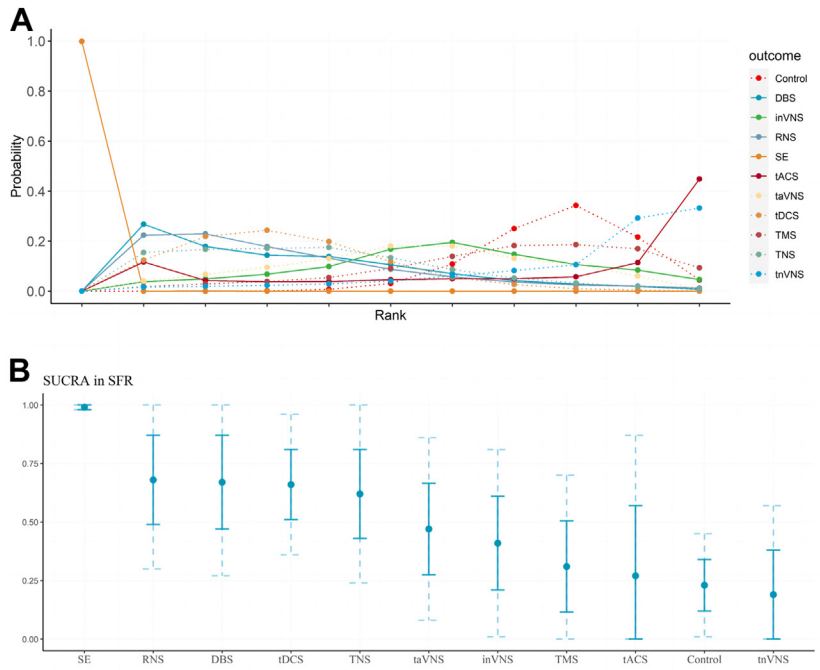


Figure 3. (**A**). The Bayesian ranking profile of comparable treatments on efficacy for people with drug-resistant epilepsy according to seizure frequency reduction. Profile indicates the probability of each comparable treatment being ranked from first to last on seizure frequency reduction. (**B**). SUCRA plot of all interventions with 95% and 66.7% confidence interval. SE, surgical excision; RNS, responsive neurostimulation; DBS, deep brain stimulation; inVNS, invasive vagus nerve stimulation; taVNS, transcutaneous auricular vagus nerve stimulation; tDCS, transcranial direct current stimulation; tACS, transcranial alternating current stimulation; TNS, transcutaneous nerve stimulation; TMS, transcranial magnetic stimulation; SUCRA, surface under the cumulative ranking curve.

individuals were treated with various interventions including ASMs, epilepsy surgery and different forms of neuromodulation. Our work is one of the first NMA to assess the impact of nonpharmacologic treatments on SFR in people with DRE. By converting SFR values to ORs and incorporating findings from SMA, we specifically focus on the overall and time-specific efficacy of various neuromodulatory techniques in treating DRE. Our findings suggest epileptogenic focus resection remained the most effective intervention for controlling epileptic seizures, yet it may not necessarily be the optimal choice for all cases.

Regarding overall ORn and ORs, the efficacy hierarchy may follow: RNS ≈ DBS > inVNS. In terms of temporal ORs, the efficacy of RNS, DBS, and inVNS improves with extended follow-up time. RNS demonstrated stable and better outcomes in the short and medium-to-long term. The short-to-medium term efficacy of DBS may lag behind RNS and inVNS, but long-term outcomes significantly improved; inVNS seemed to be less effective in the long term compared to RNS and DBS.

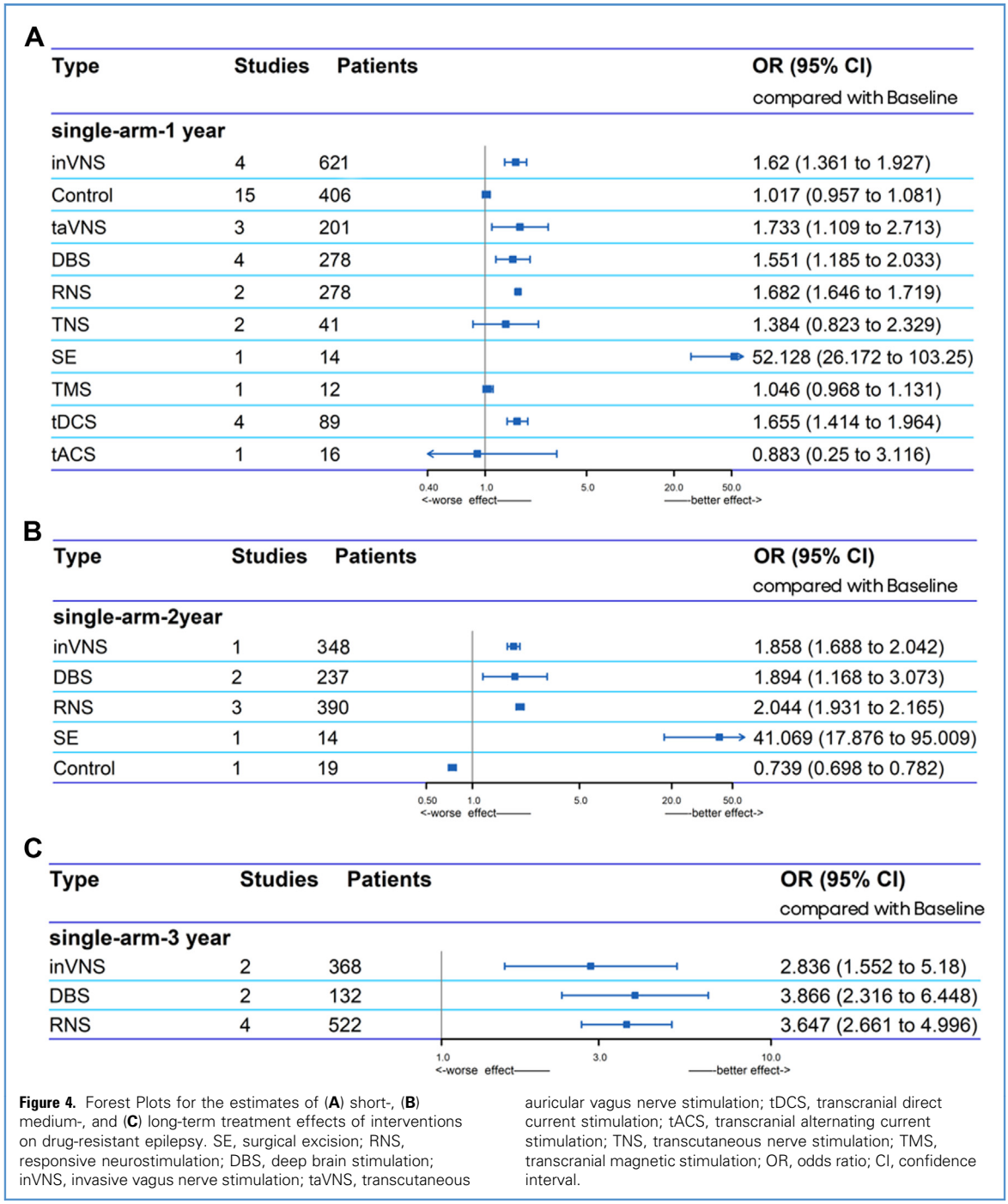
Among other neuromodulatory strategies, tDCS and taVNS emerged as promising noninvasive neuromodulatory techniques in the short term follow-up. TNS showed some therapeutic potential but has not yet demonstrated outstanding efficacy; The efficacy of TMS was generally mild. tACS seemed to be less effective, even compared to pharmacologic control.

Efficacy of Open Surgery

Temporal lobe epilepsy is the most common type of focal epilepsy.[58] For drug-resistant temporal lobe epilepsy, ATL is the predominant choice for SE, with SAH as an alternative option. In cases involving multiple foci or generalized epilepsy, corpus callosotomy may also be an option. Standardized ATL entails the resection of 4–6 cm of the anterior temporal lobe, including medial temporal structures such as the amygdala and hippocampus. SAH encompasses various surgical approaches such as transsylvian, transcortical/transtemporal, and subtemporal to preserve the temporal neocortex and underlying white matter. This is an attempt to improve postoperative cognitive function and minimize complications. Despite some evidence suggesting that SAH has a lower incidence of postoperative visual field defects compared to ATL,[59] SAH demands higher surgical skill and its effectiveness versus ATL in seizure control remains contentious.[60,61]

Additionally, SAH also demonstrated superior cognitive outcomes,[62] but no significant difference was observed between ATL and SAH,[55,63] regarding overall seizure freedom. There is still a lack of consensus on the neuropsychological outcomes in post-ATL and SAH surgeries.[64] For SE, we included a high-quality RCT on ATL for treating drug-resistant temporal lobe epilepsy, which provided extractable data on SFR.[55] In alignment with current mainstream perspectives,[9] our NMA and SMA results indicated that SE remained unparalleled in its efficacy for DRE, but it may not necessarily be the optimal choice. For example, DRE patients with eloquent brain involvement and those at high risk for postsurgical neurological complications are not suitable candidates for invasive surgical excision. Factors such as age, pathologic conditions (e.g., hippocampal sclerosis), the location and number of the epileptic focus, and imaging findings (e.g., whether magnetic resonance imaging-negative) should be considered for personalized planning.

Based on current experience, SE, particularly ATL, remains the most effective means of improving focal DRE. We included SE as one of the interventions in our analysis and a primary reason for this inclusion was to indirectly compare the efficacy gap between neuromodulation and SE through NMA. In fact, minimally invasive neurosurgical procedures for DRE, such as laser interstitial thermal therapy, radiofrequency ablation, stereotactic radiosurgery, and focused ultrasound, are gradually being implemented.[65]



Efficacy of RNS, DBS, and VNS

Neuromodulatory strategies offer less invasive alternatives, particularly for patients who are not suitable candidates for surgery. Among these, RNS, DBS, and VNS are mainstream neuromodulatory technologies approved by the U.S. Food and Drug Administration for treating DRE. Using a closed-loop approach, the RNS system dynamically monitors intracranial EEG at seizure onset zones, with remote access to long-term data for treatment guidance.[9,66] DBS primarily targets the anterior nucleus of the thalamus, centromedian thalamic nucleus, and hippocampus, disrupting neural synchronization in the Papez circuit and epileptic networks to achieve efficacy in epilepsy.[9,63] VNS mainly targets catecholaminergic nuclei and limbic structures, with recent advancements introducing transcutaneous alternatives.[9,67]

RNS demonstrated stable and better outcomes in the short and medium-to-long term, likely due to its closed-loop

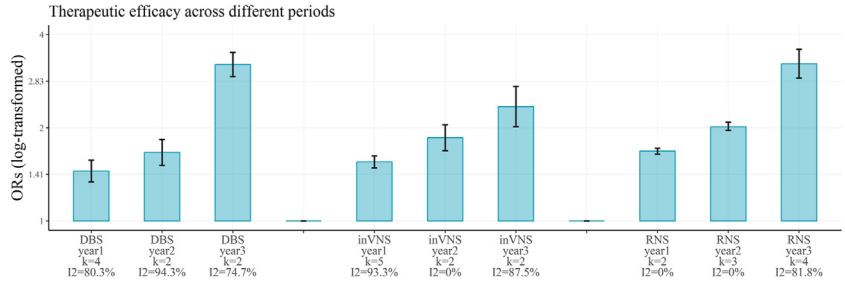


Figure 5. Dynamic changes in the short-term (year 1), medium-term (year 2), and long-term (year 3) efficacy of DBS, inVNS, and RNS. RNS, responsive neurostimulation; DBS, deep brain stimulation; inVNS, invasive vagus nerve stimulation; OR, odds ratio.

system that dynamically adjusts to detected seizure activity in real-time.[68,69] This adaptive approach allows RNS to intervene more precisely at the onset of seizures. In contrast, DBS, which delivers continuous or periodic stimulation, takes longer to induce neuroplastic changes in the brain, which may explain its improved long-term efficacy.[68,69] In contrast, VNS operates intermittently, which may limit its long-term efficacy as the stimulation is not directly synchronized with seizure activity. Moreover, VNS predominantly targets broad networks like the brainstem and limbic system, rather than modulating specific seizure onset zones, which could explain why it is less effective in the long-term compared to the more targeted approaches of RNS and DBS.[25] In ranking neuromodulatory treatments, DBS and RNS occupied the first and second positions. According to the overall efficacy of the SMA, RNS, DBS, and inVNS ranked as the top 3 neuromodulatory treatments, consistent with the findings of the NMA. Across the 3 distinct phases in the SMA, the efficacy of RNS, DBS, and inVNS progressively increased. Specifically, RNS exhibited consistent and favorable efficacy in the short-, medium-, and long-term follow-ups. While DBS showed efficacy comparable to, but slightly less than, inVNS in the short and medium term, it significantly improved in the long term and demonstrated the best performance. inVNS showed relatively poorer outcomes in the long term compared with RNS and DBS. A single-center retrospective study recently compared the effectiveness of RNS and DBS in treating drug-resistant temporal lobe epilepsy, with a 12–15 months follow-up.[70] Their findings were consistent with our overall results and the trends in the therapeutic efficacy of RNS and DBS during the short term.

Both RNS and DBS systems involve adaptive neuromodulation, where the stimulation parameters are continuously adjusted based on real-time monitoring of the patient's brain activity.[68,69] Over time, the cumulative effect of neuromodulation appears to enhance the brain's ability to resist seizure activity. Studies have shown that patients often experience a progressive reduction in seizure frequency with continued use of these devices.[37,71] This could be due to a combination of neuroplasticity, where the brain gradually adapts to the stimulation, and the system's ability to fine-tune its responses based on long-term data. In some studies, patients have shown significant improvements even several years after the initial implantation, suggesting that these devices contribute to a long-term stabilization of seizure activity.[32,71] It is noteworthy that in our study, DBS demonstrated the best long-term efficacy. DBS modulates subcortical targets connected to the cortical seizure network, including the anterior thalamic nucleus, centromedian thalamic nucleus, and hippocampus,[16,72,73] and is effective in treating focal epilepsy that is not suitable for resection as well as multifocal epilepsy. Advancements in medical engineering and imaging have driven the continuous development of DBS. Although currently, closed-loop RNS is the only method that has shown substantial progress in clinical practice for treating epilepsy,[32] the advent of flexible bidirectional devices for chronic implantation, combined with long-term neurophysiological recordings and machine learning, is expected to significantly enhance the development of closed-loop, adaptive DBS. In addition to stimulation patterns that respond to potential epileptic signals in the nervous system, the feed-forward regulation and short-term responses to biological rhythms, such as circadian and diurnal rhythms, also warrant attention. These could be potential directions for future DBS interactions with brain dynamics and therapeutic strategies.

We could not conduct a unified, effective analysis of adverse events reported in the included studies. Nonetheless, stimulation-related adverse events are generally mild and manageable. Implant-related complications are primarily characterized by infection and pain at the implantation site, with severe instances necessitating device removal.[9,38,56] Non–seizure-related hemorrhage is a frequent issue associated with RNS and DBS, typically without resulting in neurological sequelae.[9,38,56] Emotional and memory disorders are most observed in DBS therapy,[38] whereas dysphonia is prevalent among people treated with VNS.[74] VNS is generally more cost-effective and does not require intracranial surgery.[75] The stable efficacy of RNS is contingent upon long-term clinician programming and maintenance. Consequently, therapeutic choices can be tailored to individual needs.

Efficacy of Other Alternative Neuromodulation Strategies

The promising therapeutic effects of tDCS and taVNS warranted our attention. Evidence-based guidelines have accorded tDCS a level B recommendation for conditions including fibromyalgia, depression, and cravings for alcohol, drugs, and smoking.[76] In head-to-head comparisons within our NMA, tDCS was the only treatment, aside from SE, to significantly outperformed control-ASM. tDCS ranked just behind RNS and DBS in the overall efficacy of neuromodulatory treatments. In SMA, the short-term efficacy of tDCS was significant and ranked just behind taVNS and RNS. The most common adverse events associated with tDCS were headaches and mild itching sensations.[45,48]

A recent study demonstrated that high-definition tDCS can acutely reduce

epileptic spike rates both during and after stimulation in patients with refractory status epilepticus.[77] The treatment not only significantly lowered epileptic spiking rates, potentially maintaining these reductions in the stimulated area, but also notably improved clinical outcomes for refractory status epilepticus patients in the ICU.[77] These findings highlight the potential for a sustained therapeutic effect, underscoring its clinical significance. Although tDCS effectively modulates cortical excitability by altering membrane potentials, which contributes to short-term seizure reduction, its long-term efficacy may be limited due to its non-targeted nature. taVNS has received European approval for the treatment of epilepsy and depression.[78] In the short term, taVNS appeared to offer the best efficacy among these alternative neuromodulations. Common adverse events in taVNS included headaches, insomnia, and nasopharyngitis.[39,53] Although taVNS serves as a noninvasive and easy-to-apply alternative to inVNS, capable of reducing seizure frequency and improving patient quality of life, its efficacy is influenced by anatomical complexities.[39,53] The outer ear is innervated by several sensory nerves, such as the auricular branch of the vagus nerve, which vary in fiber density and have significant overlap. VNS requires the activation of Aβ fibers, which are far less abundant in the auricular branch of the vagus nerve than the cervical vagus nerve. This may also explain why taVNS did not demonstrate significant efficacy in the NMA. Thus, further investigation is needed to determine the optimal stimulation sites, parameters, and taVNS algorithms.

TNS has been approved for use in Europe, Australia, and Canada. Current research on TNS primarily focused on focal epilepsy and has shown promising results in TLE[33,47,79]。 Compared to control-ASM, TNS was ranking behind RNS, DBS, and tDCS. However, in the short-term outcomes of the SMA, the efficacy of TNS was not prominent and lacked statistical significance. The most common adverse events for TNS were skin irritation and headache.[33,47] To date, no abnormal changes in neurophysiological parameters of the trigeminal nerve have been observed following long-term stimulation.[33,47]

A study using neuronavigated TMS for treating focal neocortical epilepsy,[80] incorporating factors previously associated with reasonable epilepsy control with TMS found no significant impact of TMS on SFR, with some participants having seizure aggravation. In our analysis, the ORn of TMS compared to ASM suggesting the limited efficacy of TMS. tACS has been used in people with neuropsychiatric disorders and has been shown to enhance cognitive function or improve behavioral outcomes.[81-83] However, its efficacy in epilepsy control may even be less than that of ASM alone, with no significant improvement observed pre- and post-treatment.

TNS and TMS may be limited in their efficacy due to their inability to penetrate deep epileptic networks. These noninvasive techniques mainly affect superficial cortical areas, which might explain their milder efficacy compared to more targeted neuromodulatory strategies. tACS, which delivers alternating current, appears to have minimal influence on reducing seizure frequency. Its primary mode of action is likely more suited for cognitive and behavioral improvements, making it less effective in epilepsy control compared to pharmacologic treatments. Overall, these interventions are well-tolerated cost-effective, and some hold significant therapeutic potential. While our analysis offered some insights into applying these neuromodulation technologies in treating DRE, their maturity for widespread use remains limited. Specifically, long-term research on their effectiveness in controlling seizures, improving cognitive function, and enhancing mental well-being is lacking.

Future Prospects of Neuromodulation

Neuromodulatory therapies treat DRE by directly altering the excitability of affected brain circuits. The mechanisms contributing to long-term improvement are not yet fully understood, but may involve factors such as neuroinflammation,[84] upregulation of GABA function,[85] chronic glial changes,[86] gene induction,[87] neurogenesis,[88] and among others. While the efficacy of RNS is well-established, it relies on the ongoing involvement of experienced neurologists, and active individual cooperation. DBS offers the advantage of targeting multiple focal epilepsy lesions, whereas the minimally invasive nature and cost-effectiveness of inVNS make it more readily accepted by people.[75] Additionally, inVNS is the only neurostimulation method approved by the FDA for use in children, making it the standard initial choice for treating pediatric epilepsy. Thus, more high-quality clinical studies are needed to support the clinical application of RNS and DBS in children. Importantly, prior surgical treatments or other neuromodulatory interventions do not appear to alter the efficacy of current neuromodulatory therapies.[89]

Our meta-analysis also identified tDCS and taVNS as neuromodulatory approaches with promising research and clinical potential. Overall, one of the major challenges in the field of neuromodulation remains the optimization of stimulation parameters and the modulation of a multitude of variables. Clinical trials need to consider multiple factors such as the treatment target, voltage versus current-controlled stimulation, continuous versus intermittent stimulation, pulse width and frequency, and the characteristics of the stimulation sequence. Large-scale, multicenter studies are needed to validate biomarkers that can provide helpful predictions of neuromodulatory responses in individuals most likely to benefit.[90] The choice of stimulation parameters may vary across different countries and medical institutions, making it challenging to conduct comparative efficacy between different neuromodulatory therapies.

Despite the promising results of neuromodulatory techniques, there remain several areas for further investigation. First, RCTs with head-to-head comparisons of different neuromodulatory strategies are necessary to directly assess their relative efficacy and identify patient-specific factors influencing treatment outcomes. Second, longer-term studies are critical to evaluating the durability of seizure control provided by these interventions, particularly some techniques which may show delayed benefits due to neuroplastic changes over time. Finally, future research should focus on identifying biomarkers or clinical predictors of response to neuromodulation, which could enable more personalized treatment approaches. Understanding how variables

like seizure onset zone, patient age, and comorbid conditions influence response could refine patient selection and optimize therapeutic outcomes. Addressing these gaps will be key to maximizing the benefits of neuromodulation for drug-resistant epilepsy.

Strengths and Limitations

Our work has several strengths. Drawing on high-quality RCTs and prospective studies, we employed a nuanced measure of efficacy—SFR converted to OR—to ensure clinical relevance and statistical reliability. This was further enhanced by the integration of NMA with SMA, which allowed for comparisons between nonpharmacologic interventions for DRE. Lastly, we captured the dynamic changes in the efficacy of RNS, DBS, and inVNS across different follow-up periods, providing an understanding that could be invaluable for clinical decision-making.

Our study has several limitations. First, the inclusion of open-label extension studies may introduce potential biases, particularly the lack of blinding, which could overestimate treatment efficacy. Second, the variability in follow-up durations across studies may affect the consistency of results, as long-term effects may be captured in some studies but not in others. Third, the SMA lacks a control group, which limits the ability to assess relative treatment effects fully and introduces potential selection bias, thereby reducing the generalizability of our findings. Moreover, the limited number of studies restricted our ability to extract and analyze data on adverse events, quality of life, and cognitive function. Additionally, some nonpharmacologic treatments were not considered, such as stereotactic radiosurgery, stereotactic radiofrequency thermocoagulation, and the modified Atkins diet. Although the vast majority of studies focus on focal DRE, we did not focus on applying different treatments in specific types of DRE. Another key limitation is the short-term follow-up for some neuromodulation techniques beyond mainstream therapies like RNS, DBS, and VNS, restricting our ability to assess their long-term efficacy. The heterogeneity in treatment efficacy may be increased by varying stimulation parameters across interventions. Finally, the small pool of RCTs, coupled with the inherent limitations of single-arm meta-analyses, leads to some degree of uncertainty in our estimates.

CONCLUSION

For clinical practice, RNS and DBS may offer superior overall and long-term efficacy and be recommended as preferred interventions for DRE patients who are not candidates for resective surgery, particularly for those with multiple epileptic foci or eloquent cortex involvement. While inVNS, it remains a cost-effective option for patients, offering reliable results with a more favorable price-performance. tDCS and taVNS may offer a viable alternative for patients who are seeking less invasive options or cannot tolerate intracranial procedures. However, high-quality studies with long-term follow-up, especially those comparing different neuromodulatory therapies, are needed to confirm their effectiveness. The identification of patient-specific factors that may predict response to each neuromodulatory approach remains a crucial area for future research.

CRediT AUTHORSHIP CONTRIBUTION STATEMENT

Jianwei Shi: Data curation, Formal analysis, Investigation, Writing — original draft. **Dafeng Lu:** Formal analysis. **Penghu Wei:** Data curation, Formal analysis. **Yanfeng Yang:** Data curation, Investigation. **Hengxin Dong:** Data curation. **Lei Jin:** Data curation. **Josemir W. Sander:** Supervision, Writing — review & editing. **Yongzhi Shan:** Visualization, Writing — review & editing. **Guoguang Zhao:** Resources, Supervision, Writing — review & editing, Conceptualization, Project administration.

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SUPPLEMENTARY DATA

Search Strategy

Pubmed. (("Drug Resistant Epilepsy"[MeSH Terms] OR ("drug"[All Fields] AND "resistant"[All Fields] AND "epilepsy"[All Fields]) OR "drug resistant epilepsy"[All Fields] OR ("refractory"[All Fields] AND "epilepsy"[All Fields]) OR "refractory epilepsy"[All Fields]) AND (("surgery"[Subheading] OR "surgery"[All Fields] OR "surgery"[MeSH Terms]) OR neuromodulation [All Fields] OR ("vagus nerve stimulation"[MeSH Terms] OR ("vagus"[All Fields] AND "nerve"[All Fields] AND "stimulation"[All Fields]) OR "vagus nerve stimulation"[All Fields]) OR ("deep brain stimulation"[MeSH Terms] OR ("deep"[All Fields] AND "brain"[All Fields] AND "stimulation"[All Fields]) OR "deep brain stimulation"[All Fields]) OR ("responsive neurostimulation"[MeSH Terms] OR ("responsive"[All Fields] AND "neurostimulation"[All Fields]) OR "responsive neurostimulation"[All Fields]) OR ("trigeminal nerve"[MeSH Terms] OR ("trigeminal"[All Fields] AND "nerve"[All Fields]) OR "trigeminal nerve"[All Fields] AND "stimulation"[All Fields]) OR ("transcranial magnetic stimulation"[MeSH Terms] OR ("transcranial"[All Fields] AND "magnetic"[All Fields] AND "stimulation"[All Fields]) OR "transcranial magnetic stimulation"[All Fields]) OR ("transcranial electrical stimulation"[MeSH Terms] OR ("transcranial"[All Fields] AND "electrical"[All Fields] AND "stimulation"[All Fields]) OR "transcranial electrical stimulation"[All Fields])) AND ("Randomized Controlled Trial"[Publication Type] OR ("randomized"[All Fields] AND "controlled"[All Fields] AND "trial"[All Fields]) OR "randomized controlled trial"[All Fields] OR "open-label"[All Fields] OR "prospective studies"[MeSH Terms] OR ("prospective"[All Fields] AND "studies"[All Fields]) OR "prospective studies"[All Fields]))

Web of Science. # Drug-Resistant Epilepsy Types

TS=("Drug-Resistant Epilepsy" OR "Refractory Epilepsy" OR "Intractable Epilepsy" OR "Pharmacoresistant Epilepsy" OR "Focal Epilepsy" OR "Generalized Epilepsy" OR "Temporal Lobe Epilepsy" OR "Frontal Lobe Epilepsy" OR "Occipital Lobe Epilepsy" OR "Parietal Lobe Epilepsy")

Treatment Modalities

TS=("Surgery" OR "Surgical Resection" OR "Anterior Temporal Lobectomy" OR "Selective Amygdalohippocampectomy" OR "Neuromodulation" OR "Neurostimulation" OR "Vagus Nerve Stimulation" OR "VNS" OR "Implantable VNS" OR "Non-Implantable VNS" OR "Transcutaneous VNS" OR "Deep Brain Stimulation" OR "DBS" OR "Responsive Neurostimulation" OR "RNS" OR "Trigeminal Nerve Stimulation" OR "TNS" OR "Transcranial Magnetic Stimulation" OR "TMS" OR "Transcranial Electrical Stimulation" OR "TES" OR "Transcranial Direct Current Stimulation" OR "tDCS" OR "Transcranial Alternating Current Stimulation" OR "tACS")

Study Types

TS=("Randomized Controlled Trial" OR "RCT" OR "Open-Label Extension" OR "OLE" OR "Prospective Studies" OR "Prospective Cohort Studies" OR "Clinical Trials" OR "Pilot Studies")

Combine All Criteria

#1 AND #2 AND #3 #

Embase. # Drug-Resistant Epilepsy Types

('drug resistant epilepsy' OR 'refractory epilepsy' OR 'intractable epilepsy' OR 'pharmacoresistant epilepsy' OR 'focal epilepsy' OR 'generalized epilepsy' OR 'temporal lobe epilepsy' OR 'frontal lobe epilepsy' OR 'occipital lobe epilepsy' OR 'parietal lobe epilepsy')/exp OR ('drug resistant epilepsy' OR 'refractory epilepsy' OR 'intractable epilepsy' OR 'pharmacoresistant epilepsy' OR 'focal epilepsy' OR 'generalized epilepsy' OR 'temporal lobe epilepsy' OR 'frontal lobe epilepsy' OR 'occipital lobe epilepsy' OR 'parietal lobe epilepsy')

Treatment Modalities

('surgery' OR 'surgical resection' OR 'anterior temporal lobectomy' OR 'selective amygdalohippocampectomy' OR 'neuromodulation' OR 'neurostimulation' OR 'vagus nerve stimulation' OR 'VNS' OR 'implantable VNS' OR 'non-implantable VNS' OR 'transcutaneous VNS' OR 'deep brain stimulation' OR 'DBS' OR 'responsive neurostimulation' OR 'RNS' OR 'trigeminal nerve stimulation' OR 'TNS' OR 'transcranial magnetic stimulation' OR 'TMS' OR 'transcranial electrical stimulation' OR 'TES' OR 'transcranial direct current stimulation' OR 'tDCS' OR 'transcranial alternating current stimulation' OR 'tACS')/exp OR ('surgery' OR 'surgical resection' OR 'anterior temporal lobectomy' OR 'selective amygdalohippocampectomy' OR 'neuromodulation' OR 'neurostimulation' OR 'vagus nerve stimulation' OR 'VNS' OR 'implantable VNS' OR 'non-implantable VNS' OR 'transcutaneous VNS' OR 'deep brain stimulation' OR 'DBS' OR 'responsive neurostimulation' OR 'RNS' OR 'trigeminal nerve stimulation' OR 'TNS' OR 'transcranial magnetic stimulation' OR 'TMS' OR 'transcranial electrical stimulation' OR 'TES' OR 'transcranial direct current stimulation' OR 'tDCS' OR 'transcranial alternating current stimulation' OR 'tACS')

Study Types

('randomized controlled trial' OR 'RCT' OR 'open-label extension' OR 'OLE' OR 'prospective studies' OR 'prospective cohort studies' OR 'clinical trials' OR 'pilot studies')/exp OR ('randomized controlled trial' OR 'RCT' OR 'open-label extension' OR 'OLE' OR 'prospective studies' OR 'prospective cohort studies' OR 'clinical trials' OR 'pilot studies')

Combine All Criteria

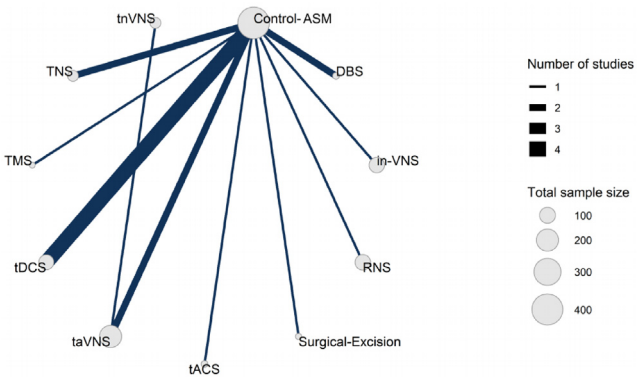
#1 AND #2 AND #3

Cochrane Library. # Drug-Resistant Epilepsy Types

("Drug-Resistant Epilepsy" OR "Refractory Epilepsy" OR "Intractable Epilepsy" OR "Pharmacoresistant Epilepsy" OR "Focal Epilepsy" OR "Generalized Epilepsy" OR "Temporal Lobe Epilepsy" OR "Frontal Lobe Epilepsy" OR "Occipital Lobe Epilepsy" OR "Parietal Lobe Epilepsy"):ti,ab,kw.

Treatment Modalities

("Surgery" OR "Surgical Resection" OR "Anterior Temporal Lobectomy" OR "Selective Amygdalohippocampectomy" OR "Neuromodulation" OR "Neurostimulation" OR "Vagus Nerve Stimulation" OR "VNS" OR "Implantable VNS" OR "Non-Implantable VNS" OR "Transcutaneous VNS" OR "Deep Brain Stimulation" OR "DBS" OR "Responsive Neurostimulation" OR "RNS" OR "Trigeminal Nerve Stimulation" OR "TNS" OR "Transcranial Magnetic Stimulation" OR "TMS" OR "Transcranial Electrical Stimulation" OR "TES" OR "Transcranial Direct Current Stimulation" OR "tDCS" OR



Supplementary Figure 1. Network meta-analysis of eligible comparisons for efficacy. Width of the lines is proportional to the number of trials comparing every pair of treatments. Size of every circle is proportional to the number of randomly assigned participants (i.e., sample size). ASM, anti-seizure medication; DBS, deep brain stimulation; inVNS, invasive vagal nerve stimulation; RNS, responsive neurostimulation; SE, surgical excision; tACS, transcranial alternating current stimulation; tDCS, transcranial direct current stimulation; taVNS, transcutaneous auricular VNS; tnVNS, transcutaneous auricular non-vagal nerve stimulation; TMS, transcranial magnetic stimulation; TNS, trigeminal nerve stimulation.

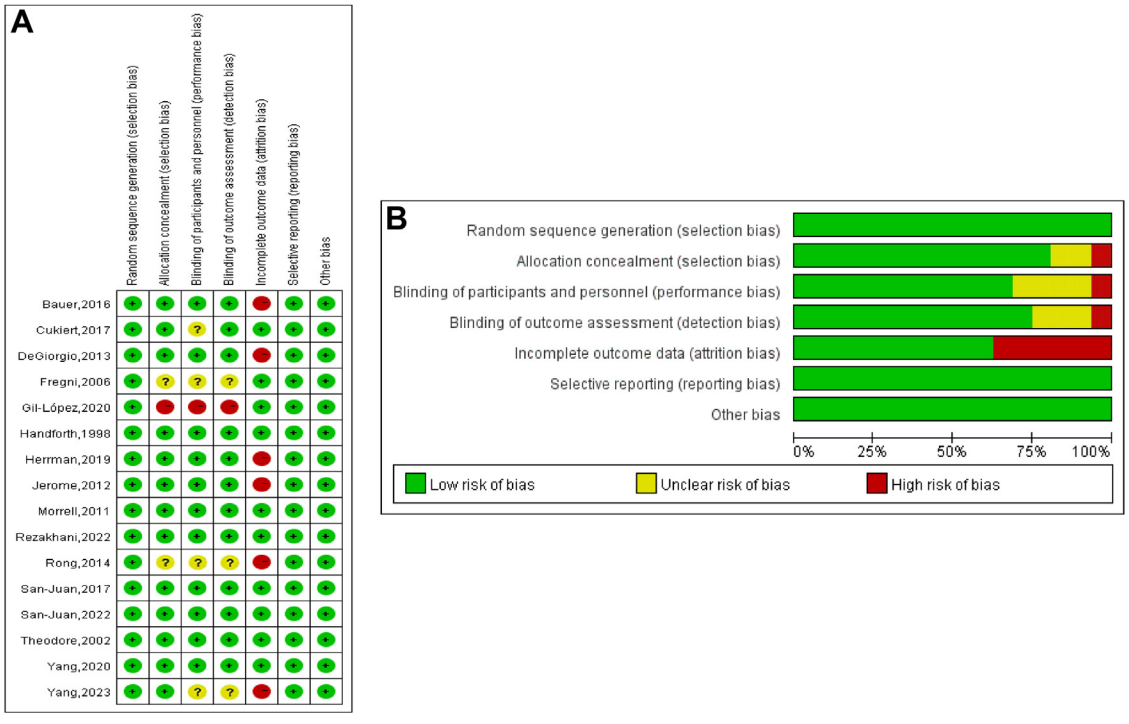
"Transcranial Alternating Current Stimulation" OR "tACS"):ti,ab,kw.

Study Types

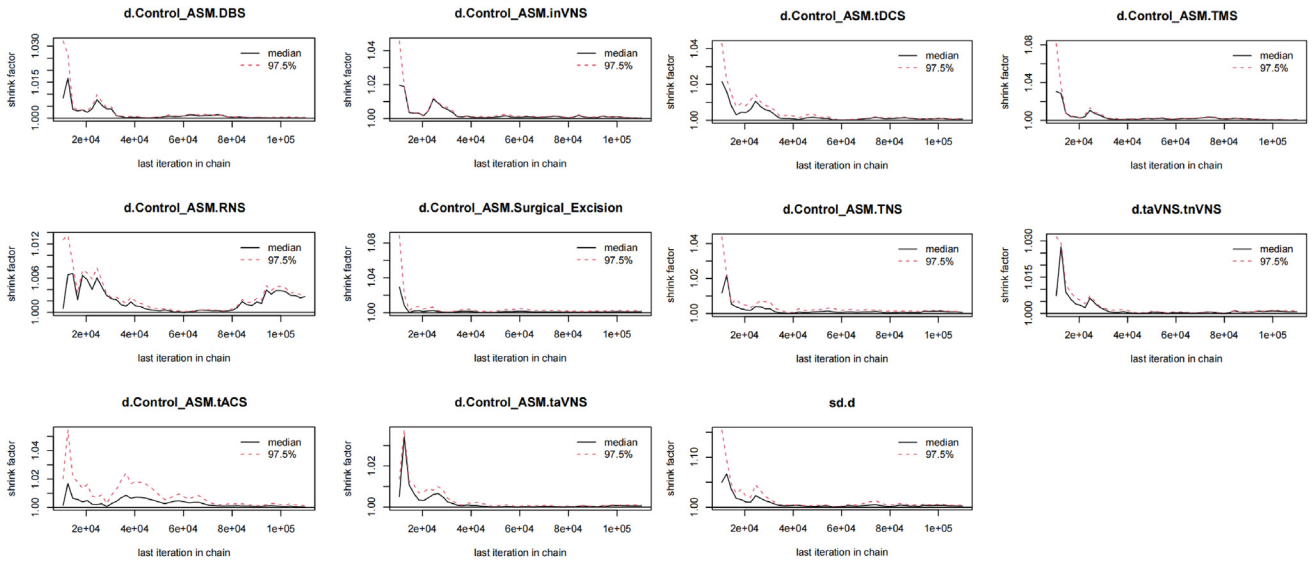
("Randomized Controlled Trial" OR "RCT" OR "Open-Label Extension" OR "OLE" OR "Prospective Studies" OR "Prospective Cohort Studies" OR "Clinical Trials" OR "Pilot Studies"):ti,ab,kw.

Combine All Criteria

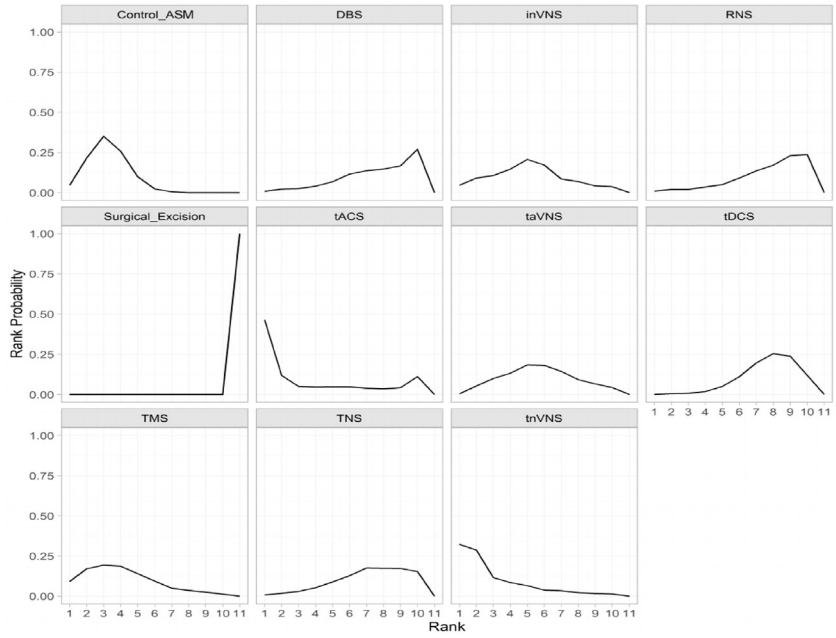
#1 AND #2 AND #3



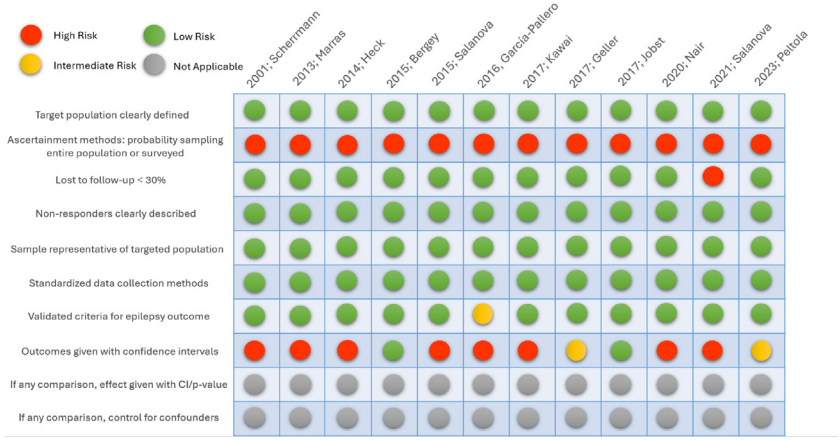
Supplementary Figure 2. Risk of bias assessment for RCTs. Risk of bias graph (**A**) and summary (**B**) for RCTs of various surgical and neuromodulatory strategies for DRE. DRE, drug-resistant epilepsy; RCT, randomized controlled trial. Green: low risk of bias; yellow: unclear risk of bias; red: high risk of bias.



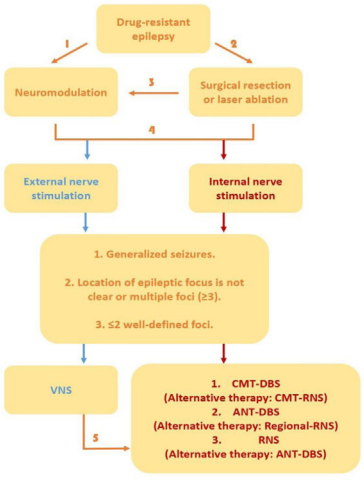
Supplementary Figure 3. Brooks-Gelman-Rubin diagnostic plots for seizure frequency reduction. ASM, anti-seizure medication; DBS, deep brain stimulation; inVNS, invasive vagal nerve stimulation; RNS, responsive neurostimulation; SE, surgical excision; tACS, transcranial alternating current stimulation; tDCS, transcranial direct current stimulation; taVNS, transcutaneous auricular VNS; tnVNS, transcutaneous auricular non-vagal nerve stimulation; TMS, transcranial magnetic stimulation; TNS, trigeminal nerve stimulation.



Supplementary Figure 4. The rankogram of different treatments. ASM, anti-seizure medication; DBS, deep brain stimulation; inVNS, invasive vagal nerve stimulation; RNS, responsive neurostimulation; SE, surgical excision; tACS, transcranial alternating current stimulation; tDCS, transcranial direct current stimulation; taVNS, transcutaneous auricular VNS; tnVNS, transcutaneous auricular non-vagal nerve stimulation; TMS, transcranial magnetic stimulation; TNS, trigeminal nerve stimulation.



Supplementary Figure 5. Risk of bias assessment for nonrandomized controlled trials.



1. Unable to localize or surgical contraindications
2. Clearly localized non-functional zone single epileptic focus.
3. Failure of surgical resection (or persistent seizures after resection)
4. Long-term intracranial EEG monitoring unable to locate the epileptic focus.
5. Failure of VNS therapy.

(Abbreviations: VNS, vagal nerve stimulation; RNS, responsive neurostimulation; SE, surgical excision; DBS, deep brain stimulation; ANT, anterior nucleus of the thalamus; CMT, centromedian thalamic nucleus.)

Supplementary Figure 6. Simple overview of neuromodulation treatment options for people with drug-resistant epilepsy. 1. Unable to localize or surgical contraindications. 2. Clearly localized nonfunctional zone single epileptic focus. 3. Failure of surgical resection (or persistent seizures after resection). 4. Long-term intracranial EEG monitoring unable to locate the epileptic focus. 5. Failure of VNS therapy. VNS, vagal nerve stimulation; RNS, responsive neurostimulation; SE, surgical excision; DBS, deep brain stimulation; ANT, anterior nucleus of the thalamus; CMT, centromedian thalamic nucleus.

Supplementary Table 1. Ranking Data of Different Treatments for Drug-Resistant Epilepsy

Intervention/Rank	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11
Control- ASM	0	0	7.50E-05	0.001025	0.00695	0.0306	0.108325	0.250075	0.3429	0.215925	0.044125
DBS	4.00E-04	0.267375	0.178875	0.14375	0.1381	0.10545	0.069625	0.042425	0.027725	0.018775	0.0075
inVNS	0.00015	0.0381	0.049075	0.06755	0.09845	0.167475	0.194825	0.147425	0.106075	0.0844	0.046475
RNS	0.000275	0.223625	0.2291	0.177925	0.13195	0.087225	0.05655	0.0363	0.024975	0.01995	0.012125
SE	0.99855	8.00E-04	0.000275	0.000125	0.000175	0	2.50E-05	2.50E-05	2.50E-05	0	0
tACS	0.000125	0.1167	0.0424	0.03805	0.038325	0.0456	0.04925	0.049575	0.0574	0.1143	0.448275
taVNS	7.50E-05	0.040025	0.06725	0.095425	0.12995	0.181025	0.18015	0.131425	0.106625	0.060925	0.007125
tDCS	0	0.1241	0.2185	0.243125	0.198425	0.117875	0.055225	0.026825	0.0099	0.0046	0.001425
TMS	0.00015	0.0183	0.0287	0.03865	0.05385	0.0906	0.13875	0.1821	0.18595	0.169925	0.093025
TNS	5.00E-05	0.1546	0.1669	0.17125	0.17485	0.133875	0.0866	0.05195	0.0329	0.01915	0.007875
tnVNS	0.000225	0.016375	0.01885	0.023125	0.028975	0.040275	0.060675	0.081875	0.105525	0.29205	0.33205

ASM, anti-seizure medication; DBS, deep brain stimulation; inVNS, invasive vagal nerve stimulation; RNS, responsive neurostimulation; SE, surgical excision; tACS, transcranial alternating current stimulation; tDCS, transcranial direct current stimulation; taVNS, transcutaneous auricular VNS; tnVNS, transcutaneous auricular non-vagal nerve stimulation; TMS, transcranial magnetic stimulation; TNS, trigeminal nerve stimulation.

Supplementary Table 2. Evidence Profile (GRADE) for Network Meta-Analysis and Single Arm Meta-Analysis.

Network Meta-analysis

Comparison	No of Studies	Within-Study Bias	Imprecision	Heterogeneity	Incoherence	Indirect-ness	Across-Studies Bias	Confidence Rating
DBS versus. Control ASM	2	Major	Major	Low	Low	Low	Low	Very Low
inVNS versus. Control ASM	1	Low	Major	Moderate	Low	Low	Low	Low
RNS versus. Control ASM	1	Low	Major	Moderate	Low	Low	Low	Low
SE versus. Control ASM	1	Major	Major	Moderate	Low	Low	Low	Very Low
tACS versus. Control ASM	1	Low	Major	Moderate	Low	Low	Low	Low
taVNS versus. Control ASM	2	Major	Major	Low	Low	Low	Low	Very Low
tDCS versus. Control ASM	4	Low	Major	Low	Low	Low	Low	Moderate
TMS versus. Control ASM	1	Low	Major	Moderate	Low	Low	Low	Low
TNS versus. Control ASM	2	Major	Low	low	Low	Low	Low	Moderate
tnVNS versus. taVNS	1	Low	Major	Moderate	Low	Low	Low	Low

Single Arm Meta-analysis

Quality Assessment	Participants (Studies)	Study Design	Risk of Bias	Inconsistency	Indirectness	Imprecision	Other Considerations	Overall Quality
Seizure Frequency Reduction	2936[28]	Single Arm	Low	Serious	Moderate	Low	None	Moderate

Within-study bias: Using the results of the Cochrane risk-of-bias tool to evaluate within-study bias, if a study in a group exhibits high risk bias, then the entire group of studies is rated as a major concern; if not, it is rated as a low concern; **Imprecision**: To assess imprecision of the estimates, we set the threshold for the smallest worthwhile difference at 1 point in each term. A rating of "major concerns" is assigned to a treatment effect if the 95% confidence interval extends beyond the area of equivalence on the opposite side of the no effect line as the point estimate, so that the estimated treatment effect is compatible with clinically important effects in both directions. A rating of "some concerns" is assigned if the confidence interval extends into but not beyond the area of equivalence on the opposite side of the no effect line. There are "No concerns" if the confidence interval is entirely on one side of the no effect line, or if it is entirely within the area of equivalence. If there are 0 studies in a term, it is rated as a 'Major concern'. **Heterogeneity**: Heterogeneity was considered "No concerns," "Some concerns," "major concerns" for estimated I2 under 25%, between 25% and 50%, and over 50% in each term. The heterogeneity evaluation of the network meta-analysis is 5%, which is less than 20%. However, due to the presence of multiple groups in the study that only include one paper, the heterogeneity of these groups is upgraded to moderate. Incoherence: Incoherence was assessed by the global test of inconsistency (design-by-treatment test) and the local tests of inconsistency (back-calculation). **Indirectness**: We judged that there was no indirectness because the included studies all fit our research questions. **Across-studies bias**: There was no evidence of publication bias, as the funnel plot did not suggest the absence of any bias ($P > 0.05$). The included studies had few missing outcomes and we judged the potential for reporting bias was low. Therefore, all trials were at low risk of across-studies bias.

ASM, anti-seizure medication; DBS, deep brain stimulation; inVNS, invasive vagal nerve stimulation; RNS, responsive neurostimulation; SE, surgical excision; tACS, transcranial alternating current stimulation; tDCS, transcranial direct current stimulation; taVNS, transcutaneous auricular VNS; tnVNS, transcutaneous auricular non-vagal nerve stimulation; TMS, transcranial magnetic stimulation; TNS, trigeminal nerve stimulation.

Characteristics

Year; Name	Patients Number	Male/Female	Age (Mean ± SD or Median with Range)	Follow-Up (months)	Intervention 1 (N1)	Intervention 2 (N2)	Design
1998; Handforth	196	93/105	33.19	3	in-VNS	Control-ASM	RCT
2001; Scherrmann	85	49/36	34.9 ± 10.4	15.8	in-VNS	NR	Prosp
2002; Theodore	24	11/13	40±14	1.9	TMS	Control-ASM	RCT
2006; Fregni	19	11/8	24.16	1	tDCS	Control-ASM	RCT
2011; Morrell	191	91/100	34.9±11.6	84	RNS	Control-ASM	RCT-PIVOTAL
2012; Jerome	38	18/20	33.5	24	Surgical Excision	Control-ASM	RCT
2013; Marras	35	18/17	30.4±12	36	in-VNS	NR	Prosp
2013; DeGiorgio	50	23/27	33.65	4.2	TNS	Control-ASM	RCT
2014; Heck	191	91/100	34.9±11.6	24	RNS	NR	OLE of PIVOTAL
2014; Rong	144	93/51	23.72	5.6	taVNS	tnVNS	RCT
2015; Bergey	256	125/131	34±11.4	64.8±25.2	RNS	NR	OLE of PIVATOL
2015; Salanova	110	55/55	36.1 (18.2-60.9)	60	DBS	NR	OLE of SANTE
2016, García-Pallero	85	49/36	33 (25-37)	18	in-VNS	NR	Prosp
2016; Bauer	76	45/31	38.8±12.5	4.7	taVNS	Control-ASM	RCT
2017; Kawai	362	215/147	24.8±14.7	36	in-VNS	NR	Prosp
2017; Cukiert	16	5/11	38.4±14.6	6	DBS	Control-ASM	RCT
2017; Geller	111	53/58	37.3±11.3	24	RNS	NR	Prosp
2017; Jobst	126	63/63	30.4±10.1	73.2	RNS	NR	Prosp
2017; San-Juan	28	16/12	26-65	2	tDCS	Control-ASM	RCT
2019; Herrman	18	7/11	18-52	12	DBS	Control-ASM	RCT
2020; Nair	256	131/125	34±11.3	90±34.8	RNS	NR	OLE of PIVOTAL
2020; Gil-López	40	16/24	40.65±12.24	12	TNS	Control-ASM	RCT
2020; Yang D	70	42/28	30.9	1.9	tDCS	Control-ASM	RCT
2021; Salanova	73	35/38	37.1 ±11.8	84	DBS	NR	OLE of SANTE
2022; Rezakhani	20	9/11	27.9	2	tDCS	Control-ASM	RCT
2022; San-Juan	23	9/14	30.6±9.2	2	tACS	Control-ASM	RCT
2023; Peltola	170	97/73	35.6±10.7	24-60	DBS	NR	Prosp
2023; Yang H	123	62/61	30.77	4.7	taVNS	Control-ASM	RCT

RCT-total

Year; Name	Intervention	Number	Age	Seizure Reduction % (Mean)	SD, IQR or CI (%)
1998; Handforth	in-VNS	94	13-54	27.9	34.3
1998; Handforth	Control-ASM	102	15-60	15.2	39.2
2002; Theodore	TMS	12	40±14	4.5	13
2002; Theodore	Control-ASM	12	40±14	-0.4	20
2006; Fregni	tDCS	0.1	24.3±6.4	41.7	(7.3, 76.2)
2006; Fregni	Control-ASM	9	24±9.8	-5.4	(-33.6, 22.7)
2011; Morrell	RNS	97	34±11.5	41.5	(28.7, 52)
2011; Morrell	Control-ASM	94	35.9±11.6	9.4	(-16.4, 29.5)
2012; Jerome	Surgical Excision	13	37.5±11.1	98.33	(91.39, 100)
2012; Jerome	Control-ASM	18	30.9±10.1	-35.47	(-47, -23.95)
2013; DeGiorgio	TNS	25	33.1 (20-58)	5.9	67.6
2013; DeGiorgio	Control-ASM	25	34.2 (14-52)	2.1	44.1
2014; Rong-b	taVNS	98	24.4±12.1	62.5	23.4
2014; Rong-b	tnVNS	46	22.2±15.4	46.7	14.3
2016; Bauer	taVNS	27	40.1±12.7	23.4	47.2
2016; Bauer	Control-ASM	31	37.5±12.2	2.9	94.4
2017; Cukiert	DBS	8	38.3±12.3	50	(0, 100)
2017; Cukiert	Control-ASM	8	39.9±14.5	-26.3	(-91.3, 20.6)
2017; San-Juan	tDCS	20	26-65	47.9	(37.2, 58.6)
2017; San-Juan	Control-ASM	8	28-55	6.3	(-30.8, 43.3)
2019; Herrman	DBS	8	18-52	23	27
2019; Herrman	Control-ASM	10	18-52	-11	28
2020; Yang	tDCS	49	31.2±9.9	35.2	(12.6, 57.8)
2020; Yang	Control-ASM	21	31.8±9.3	12.5	(-12.5, 57.5)
2020; Gil-López	TNS	20	44.2±11.0	43.5	(10, 66.7)
2020; Gil-López	Control-ASM	20	37.1±12.7	0	(-20, 0)
2022; Rezakhani	tDCS	10	26.5±6.5	30.5	13
2022; Rezakhani	Control-ASM	10	29.3±9.2	-4.8	2.9
2022; San-Juan	tACS	16	31.7±9.1	-13.2	111.9
2022; San-Juan	Control-ASM	7	28±9.9	7.3	40.4
2023; Yang H	taVNS	76	33.3±11.3	30.8	54.3
2023; Yang H	Control-ASM	36	34±10.8	15.7	44.9

Year 1

Year; Name	Intervention	N (X excluded)	Seizure Reduction % (Mean or Median)	SD, IQR or CI %
1998; Handforth	in-VNS	94	27.9	34.3
1998; Handforth	Control-ASM	102	15.2	39.2
2001; Scherrmann	in-VNS	85	32.5	41.9
2016, García-Pallero	in-VNS	85	45.6	30.3
2017; Kawai	in-VNS	357	27.7	40.5
2016; Bauer	taVNS	27	23.4	47.2
2016; Bauer	Control-ASM	31	2.9	94.4
2023; Yang H	taVNS	76	30.8	54.3
2023; Yang H	Control-ASM	36	15.7	44.9
2014; Rong-b	taVNS	98	62.5	23.4
2019; Herrman	DBS	8	23	27
2019; Herrman	Control-ASM	10	-11	28
2017; Cukiert	DBS	8	50	(0, 100)
2017; Cukiert	Control-ASM	8	-26.3	(-91.3, 20.6)
2015; Salanova	DBS	99	41	(12, 76.5)
2023; Peltola	DBS	163	25.3	(-11.6, 51.9)
2011; Morrell	RNS	97	41.5	(28.7, 52)
2011; Morrell	Control-ASM	94	9.4	(-16.4, 29.5)
2014; Heck	RNS	181	40.2	(33.6, 46.7)
2013; DeGiorgio	TNS	25	5.9	67.6
2013; DeGiorgio	Control-ASM	25	2.1	44.1
2020; Gil-López	TNS	16	43.5	(10, 66.7)
2020; Gil-López	Control-ASM	13	0	(-20, 0)
2012; Jerome	Surgical Excision	14	98.8	(94.12, 100)
2012; Jerome	Control-ASM	20	-10	(-26.2, 6.2)
2002; Theodore	TMS	12	4.5	13
2002; Theodore	Control-ASM	12	-0.4	20
2022; Rezakhani	tDCS	0.1	30.5	13
2022; Rezakhani	Control-ASM	10	-4.8	2.9
2020; Yang	tDCS	49	35.2	(12.6, 57.8)
2020; Yang	Control-ASM	21	12.5	(-12.5, 57.5)
2017; San-Juan	tDCS	20	47.9	(37.2, 58.6)
2017; San-Juan	Control-ASM	8	6.3	(-30.8, 43.3)
2006; Fregni	tDCS	10	41.7	(7.3, 76.2)
2006; Fregni	Control-ASM	9	-5.4	(-33.6, 22.7)
2022; San-Juan	tACS	16	-13.2	111.9
2022; San-Juan	Control-ASM	7	7.3	40.4

Year 2

Year; Name	Intervention	N (X excluded)	Seizure Reduction % (Mean or Median)	SD, IQR or CI %
2017; Kawai	in-VNS	348	47.2	50.2
2015; Salanova	DBS	82	56	(25.5, 79.1)
2023; Peltola	DBS	155	33.11	(-6.87, 57.93)
2014; Heck	RNS	174	49.9	(42.6, 57.2)
2017; Geller	RNS	102	50	(27.8, 73.6)
2017; Jobst	RNS	114	44	(8.8, 81.2)
2012; Jerome	Surgical Excision	14	98.33	(8.8, 81.2)
2012; Jerome	Control-ASM	19	-35.47	(-47, -23.95)

Year 3

Year; Name	Intervention	N (X excluded)	Seizure Reduction % (Mean or Median)	SD, IQR or CI %
2013; Marras	in-VNS	35	68	(50, 90)
2017; Kawai	in-VNS	333	53.3	51.5
2015; Salanova	DBS	59	69	(42.6, 96.4)
2021; Salanova	DBS	73	67.9	(58.6, 75.9)
2015; Bergey	RNS	191	65.7	(30.6, 80.1)
2017; Geller	RNS	82	66.5	(31.8, 93.7)
2017; Jobst	RNS	87	58	(-11, 95)
2020; Nair	RNS	162	73	(47, 93)

Appendix S4. The head-to-head comparisons for the odds ratio between different treatment effects of the interventions in the network meta-analysis.

Control_ASM	1.547 (0.876 to 3.605)	1.172 (0.594 to 2.281)	1.547 (0.773 to 3.095)	55.715 (18.895 to 158.682)	0.806 (0.181 to 3.53)	1.231 (0.687 to 2.219)	1.515 (1.064 to 2.265)	1.049 (0.528 to 2.099)	1.464 (0.835 to 2.445)	0.864 (0.348 to 2.158)
0.646 (0.277 to 1.14)	DBS	0.757 (0.244 to 1.753)	1 (0.32 to 2.329)	35.506 (9.063 to 115.36)	0.51 (0.096 to 2.479)	0.79 (0.281 to 1.753)	0.979 (0.392 to 1.945)	0.678 (0.223 to 1.58)	0.946 (0.327 to 1.958)	0.558 (0.154 to 1.547)
0.852 (0.438 to 1.681)	1.319 (0.57 to 4.084)	in-VNS	1.319 (0.506 to 3.555)	47.176 (13.269 to 163.143)	0.687 (0.134 to 3.434)	1.042 (0.432 to 2.584)	1.283 (0.611 to 2.907)	0.895 (0.348 to 2.361)	1.248 (0.517 to 2.928)	0.737 (0.236 to 2.297)
0.646 (0.323 to 1.292)	1 (0.429 to 3.116)	0.757 (0.281 to 1.972)	RNS	35.753 (10.056 to 125.365)	0.521 (0.102 to 2.657)	0.79 (0.327 to 1.958)	0.972 (0.453 to 2.203)	0.678 (0.253 to 1.79)	0.946 (0.392 to 2.188)	0.558 (0.181 to 1.729)
0.017 (0.006 to 0.052)	0.028 (0.008 to 0.11)	0.021 (0.006 to 0.075)	0.027 (0.007 to 0.099)	Surgical Excision	0.014 (0.002 to 0.09)	0.022 (0.006 to 0.074)	0.027 (0.009 to 0.087)	0.018 (0.005 to 0.067)	0.026 (0.007 to 0.085)	0.015 (0.003 to 0.062)
1.239 (0.283 to 5.502)	1.958 (0.403 to 10.41)	1.453 (0.291 to 7.412)	1.918 (0.376 to 9.781)	69.07 (11.004 to 424.611)	tACS	1.515 (0.316 to 7.464)	1.879 (0.411 to 8.754)	1.292 (0.258 to 6.543)	1.802 (0.376 to 8.633)	1.057 (0.196 to 5.979)
0.812 (0.45 to 1.453)	1.265 (0.57 to 3.555)	0.959 (0.386 to 2.313)	1.265 (0.51 to 3.052)	45.254 (13.361 to 151.167)	0.659 (0.133 to 3.16)	taVNS	1.231 (0.628 to 2.514)	0.852 (0.343 to 2.084)	1.189 (0.532 to 2.531)	0.702 (0.346 to 1.394)
0.659 (0.441 to 0.939)	1.021 (0.514 to 2.549)	0.779 (0.343 to 1.635)	1.028 (0.453 to 2.203)	36.758 (11.471 to 110.66)	0.532 (0.114 to 2.428)	0.812 (0.397 to 1.591)	tDCS	0.697 (0.307 to 1.484)	0.965 (0.473 to 1.777)	0.57 (0.21 to 1.494)
0.952 (0.476 to 1.892)	1.474 (0.632 to 4.469)	1.117 (0.423 to 2.867)	1.474 (0.558 to 3.944)	53.076 (14.825 to 182.278)	0.773 (0.152 to 3.863)	1.172 (0.479 to 2.907)	1.433 (0.673 to 3.249)	TMS	1.394 (0.562 to 3.249)	0.823 (0.262 to 2.62)
0.683 (0.408 to 1.197)	1.057 (0.51 to 3.052)	0.801 (0.341 to 1.931)	1.057 (0.456 to 2.549)	38.054 (11.712 to 125.365)	0.554 (0.115 to 2.657)	0.84 (0.395 to 1.879)	1.035 (0.562 to 2.114)	0.716 (0.307 to 1.777)	TNS	0.59 (0.211 to 1.765)
1.156 (0.463 to 2.867)	1.79 (0.646 to 6.453)	1.356 (0.435 to 4.228)	1.79 (0.578 to 5.502)	64.445 (16.111 to 254.231)	0.946 (0.167 to 5.098)	1.424 (0.716 to 2.887)	1.753 (0.668 to 4.756)	1.214 (0.381 to 3.81)	1.693 (0.566 to 4.723)	tnVNS

(Abbreviations: ASM, anti-seizure medication; DBS, deep brain stimulation; inVNS, invasive vagal nerve stimulation; RNS, responsive neurostimulation; SE, surgical excision; tACS, transcranial alternating current stimulation; tDCS, transcranial direct current stimulation; taVNS, transcutaneous auricular VNS; tnVNS, transcutaneous auricular non- vagal nerve stimulation; TMS, transcranial magnetic stimulation; TNS, trigeminal nerve stimulation.)

ASM, anti-seizure medication; DBS, deep brain stimulation; inVNS, invasive vagal nerve stimulation; RNS, responsive neurostimulation; SE, surgical excision; tACS, transcranial alternating current stimulation; tDCS, transcranial direct current stimulation; taVNS, transcutaneous auricular VNS; tnVNS, transcutaneous auricular non-vagal nerve stimulation; TMS, transcranial magnetic stimulation; TNS, trigeminal nerve stimulation.

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