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Deep brain stimulation for epilepsy: A systematic review and meta-analysis of randomized and non-randomized studies of thalamic targeting

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ABSTRACT

Introduction: Deep Brain Stimulation (DBS) of the thalamus for drug-resistant epilepsy (DRE) is an emerging treatment modality. This systematic review and meta-analysis sought to evaluate the efficacy of stimulating different targets within the thalamus.

Methods: A systematic search of four databases was conducted. Rates for overall seizure reduction (SR), responder rate (RR ≥50 % SR), and seizure freedom (SF) were evaluated at a minimum time point of 12 months post-stimulation commencement in the anterior (ANT) and centro-median (CMN) thalamic nuclei. Subgroup analyses for a minimum 24 months follow up, sensitivity analyses, and funnel plots to assess for publication bias were also performed. Risk of bias was assessed using the ROBINS-I tool.

Results: Fourty-nine articles met the inclusion criteria. The mean seizure reduction (SR) across 21 studies was 62.31 % (95 % CI: 55.99–68.62, $p < 0.01$). Specifically, SR was 64.28 % for ANT (95 % CI: 57.55–71.01, $p < 0.01$) and 69.11 % for CMN (95 % CI: 58.14–80.09, $p < 0.01$). Meta-analyses of 41 ANT studies and 12 CMN studies reported a response rate (RR) of 61.51 % (95 % CI: 54.11–68.9, $p < 0.01$) and 69.09 % (95 % CI: 54.01–84.16, $p < 0.01$), respectively. Overall seizure freedom (SF) was 3.57 % % for ANT (95 % CI: 1.86–5.28, $p = 0.45$) and 1.32 % for CMN(95 % CI: 0–4.45, $p = 0.81$). For ANT, RR was 67.63 % (95 % CI: 61.04–74.23) for follow-up periods longer than 24 months, and 44.05 % (95 % CI: 26.73–61.38) for periods shorter than 24 months. The SF rate for ANT was 3 % (95 % CI: 1–4 %) for follow-up under 12 months. For CMN, RR was 70 % (95 % CI: 53–87 %) for periods over 24 months, and 68 % (95 % CI: 31–100 %) for periods under 24 months. The SF rate for CMN was 1 % (95 % CI: 0–4 %) for periods under 12 months. There was no strong evidence of publication bias based on funnel plot analysis, and results were consistent across sensitivity analyses. Insufficient data precluded meta-analysis for other nuclei.

Conclusion: These findings demonstrate efficacy of ANT and CMN DBS for patients with DRE, defined by responder rate and seizure reduction. Further research is required to optimize patient selection, predict individual response, and assess non-seizure related outcomes.

1. Introduction

Approximately 1 % of the global population is affected by epilepsy, resulting in reduced quality of life of affected individuals, increased mortality risk and in significant healthcare resource utilization (Beghi, 2020). Despite the availability of antiseizure medications, approximately 30–40 % of patients present with drug resistant epilepsy (DRE) (Deutschová and Rektor, 2022). Epilepsy surgery, a successful intervention for selected DRE cases, targets the epileptogenic zone, the area of the cortex that needs to be resected or completely disconnected to produce seizure freedom (Kahane et al., 2016). However, nearly 50 % of DRE patients do not meet the criteria for resective surgery (Jobst and Cascino, 2015). Consequently, almost one-third of patients with epilepsy continue to experience seizures despite medical management (Kwan and

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Brodie, 2000).

Neuromodulation is an alternative therapeutic option (Deutschová et al., 2021; Zangiabadi et al., 2019). Recent decades have witnessed the advent of differing neuromodulation options, including deep brain stimulation (DBS), vagal nerve stimulation (VNS), and responsive neurostimulation (RNS), specific to patients with epilepsy ineligible for surgical interventions (Saillet et al., 2009; Nagel and Najm, 2009). DBS of the Anterior Nucleus of the Thalamus (ANT) has sparked considerable interest as a treatment for DRE, showing a significant reduction in seizure frequency, with a 20 % decline at 1 month and a 14 % decrease at 3 months, as evidenced by the SANTE trial (Fisher et al., 2010; Kaufmann et al., 2020a). ANT DBS is seen as a treatment option for focal epilepsies. There has also been a growing interest in DBS of the centromedian nucleus (CMN). For instance, the ESTEL study, a double blind, randomized, controlled trial of CMN stimulation in Lennox-Gastaut Syndrome (LGS) patients achieved a median seizure reduction of 50 % at the conclusion of the 3-month blinded phase (Dalic et al., 2022a). The pulvinar nucleus (PN) is also considered a potential neuromodulatory target due to its extensive connectivity with the contralateral PN and significant connections to the hippocampus. This connectivity is particularly relevant for treating drug-resistant focal epilepsy originating from the posterior quadrant, as the pulvinar has robust connections with visual and memory-associated cortical regions, suggesting its involvement in seizure propagation and potential effectiveness as a neurostimulation target (Burdette et al., 2021).

Considering the various targets utilized in thalamic DBS, our inquiry revolved around whether the precise thalamic target yields differential outcomes. It is essential to establish target-specific efficacy to provide guidance for evidence-based decision-making. However, given the different indications for each nucleus, a direct comparison of efficacy was not conducted.

Although previous reviews have examined different targets, the field continually evolves with new data and insights, necessitating an updated synthesis of evidence. Our approach also differs from previous reviews by including non-randomized studies and specifically comparing the effectiveness of targeting different thalamic nuclei (Sprengers et al., 2017; Vetkas et al., 2022; Haneef and Skrehot, 2023). This systematic review and meta-analysis aims to evaluate the target-specific differential efficacy of DBS in various thalamic nuclei and provide a current informative landscape regarding optimal thalamic target selection to guide clinical decision-making.

2. Methods

This systematic review followed PRISMA-P and Cochrane Handbook guidelines and was registered with PROSPERO (registration no. CRD42024493696).

2.1. Search Strategy and Information Sources

A literature search was conducted independently by two reviewers (J.D. and M.R.P.). Medline (Ovid), Embase (Ovid), Web of Science, and Scopus were systematically searched for published articles. The specific parameters used for article searches in each database were outlined. Initial results were obtained through a thorough search strategy (see supplementary material).

2.2. Inclusion & exclusion criteria

The systematic review included all patients who underwent DBS for DRE in randomized controlled trials, observational studies, retrospective chart studies, and other observational studies published in English since the year 2000. Studies targeting the thalamus and adjacent diencephalic nuclei were included. Articles were eligible for inclusion in the systematic review if the cohort consisted of at least three patients. We did not include thalamic RNS, as this was considered a different therapeutic strategy. Randomized studies were screened regardless of publication year or cohort size. Cohorts with multiple publications were analyzed separately in the meta-analysis, to account for censoring in long term follow-up. Case reports and studies with outcomes other than postoperative success rates expressed as a percentage were excluded from the meta-analysis. The article selection process is summarized in the PRISMA flow diagram (Fig. 1).

2.3. Definitions

Definitions of terminology such as responder rate, seizure reduction and seizure freedom were discussed between reviewers and established based on current International League Against Epilepsy (ILAE) guidelines (Kwan et al., 2010). Seizure freedom was defined as patients who had gone without a seizure for at least 12 months (Infographic: What Does Seizure Freedom Really Mean? - European Medical Journal, 2024). To account for variations in seizure freedom definitions across studies, we extracted the 12-month seizure freedom data, even in cases where studies reported multiple seizure freedom intervals (e.g., 6, 12, and 18 months). Responder rate was defined as the proportion of patients with $\geq$ 50 % seizure frequency reduction after DBS.

2.3.1. Risk of bias

The risk of bias in the individual studies included was evaluated using the Risk of Bias in Nonrandomized Studies of Interventions (ROBINS-I) tool. Two reviewers (J.D. and M.R.P.) independently assessed the studies and resolved any differences in judgment through discussion or referring this query to another independent reviewer (A. C.).

2.3.2. Statistical analysis

Statistical analysis was conducted using R version 4.0.4, employing the Metafor 3.0–2 and Meta 4.19–0 packages for the meta-analysis (Schwarzer et al., 2024). For studies that reported median and range of seizure reductions, conversion to mean ± SD was performed using established methods (Wan et al., 2014; Hozo et al., 2005). Both fixed and random effects models were applied in the analysis, with an assessment of outcome and heterogeneity based on 95 % confidence intervals (CIs) and I^2. Funnel plots were utilized to evaluate publication bias, considering the effect size estimates derived from the random-effects model. Funnel plots are scatter plots of the effect estimate (x-axis) against the standard error of the study (y-axis). They allow the inspection of small-study effects and possible publication bias. In the absence of bias, the plot should approximately resemble an inverted funnel. To test funnel plot asymmetry, we used egger's regression test

3. Results

3.1. DBS of all thalamic nuclei

In total, we identified 49 studies including 1125 patients (Fig. 1). Targets included the anterior nucleus of the thalamus (ANT), centromedian nucleus (CMN), and pulvinar (PN).

Study participants' median ages ranged from 15.5 to 35.8 years (overall range: 5–71 years) and mean ages ranged from 20.9 to 42.8 years. Most study populations (38/49, 77.6 %) centered in the 30–38 year range. Standard deviations varied from ±8.6 to ±12.18 years. A minority of studies (7/49, 14.3 %) examined younger cohorts, with median ages of 18 years (IQR: 10–24) and 15.5 years (range: 5–29). The remaining studies (4/49, 8.1 %) either did not report age data or reported age ranges without means or medians.

The mean duration of epilepsy across studies ranged from 12.76 ± 7.28–27.4 years (range 10–56 years). Among studies reporting mean values with standard deviations (n = 14), the weighted average duration was 20.9 ± 10.8 years. Median durations, when reported (n = 4), varied from 9 to 25 years (IQR 21–27 in one study). The overall range of

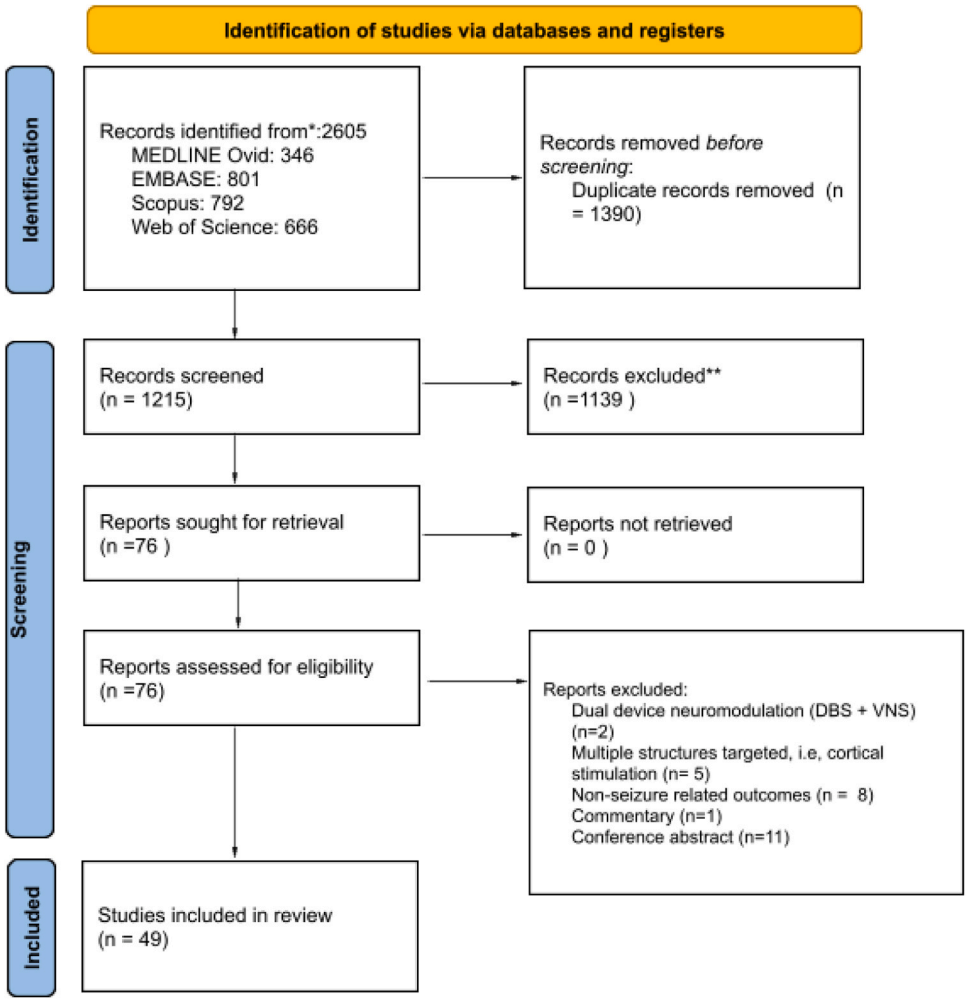

Fig. 1. PRISMA flow diagram. *Records identified from each database. **The Rayyan automation tool was used. Data added to the PRISMA template (from Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ*. 2021;372:n71) under the terms of the Creative Commons Attribution (CC BY 4.0) License (https://creativecommons.org/licenses/by/4.0/).

epilepsy duration across all studies spanned from 2 to 60 years, demonstrating considerable heterogeneity among study populations. The majority of studies (68.2 %) reported mean durations between 19 and 24 years, suggesting that most research was conducted in populations with long-standing epilepsy.

3.2. DBS of ANT

A total of 41 studies focusing on DBS in the ANT, involving 981 patients, were included in the meta-analysis (Fig. 2) (Fisher et al., 2010; Alcala-Zermeno et al., 2021; Andrade et al., 2006; Sitnikov et al., 2018; Passamonti et al., 2021; Chua et al., 2023; Costa-Gertrudes et al., 2022; Tassigny et al., 2020; Kaufmann et al., 2020b; Schaper et al., 2020; Freund et al., 2022; Miron et al., 2022; Yan et al., 2023; Herrman et al., 2019a; Hodaie et al., 2002; Park et al., 2019; Koeppen et al., 2019; Olaciregui Dague et al., 2023; Kerrigan et al., 2004; Krishna et al., 2016; Lee et al., 2012; Lim et al., 2007; Piacentino et al., 2015; Sobstyl et al., 2023; Herrera et al., 2021; Oh et al., 2012; Osorio et al., 2021, 2007a; Parisi et al., 2023; Peltola et al., 2023; Poulen et al., 2022; Järvenpää et al., 2020, 2018; Kim et al., 2017; Salanova et al., 2021, 2015; Guo et al., 2020; Yang et al., 2022a; Zhu et al., 2021; Lee et al., 2006; Lim et al., 2008). The most common epilepsy type was focal epilepsy, in 85.7 % of patients (Table 1) (ILAE, 2017). The analysis revealed a 64.28 % (95 % CI: 57.55–71.01, $p < 0.01$) mean seizure reduction (SR) based on the random effects model. The overall responder rate was 61.51 % (95 % CI: 54.11–68.9, $p < 0.01$). Subgroup analysis for follow-up duration revealed a responder rate of 67.63 % (95 % CI: 61.04–74.23, $p < 0.01$) for follow-up periods exceeding 24 months, and 44.05 % (95 % CI: 26.73–61.38, $p < 0.01$) for those under 24 months (Fig. 3).The difference between subgroups was statistically significant ($p = 0.0127$). The seizure freedom at 12 months was 3.57 % (95 % CI: 1.86–5.28, $p = 0.45$) (Fig. 4). The mean maximum follow-up duration was approximately 52 months (range 12–168 months).

3.3. DBS of CMN

A total of 12 studies involving 135 patients undergoing CMN DBS were incorporated into the meta-analysis (Fig. 5) (Alcala-Zermeno et al., 2021, 2022; Andrade et al., 2006; Passamonti et al., 2021; Chua et al., 2023; Yan et al., 2023; Son et al., 2016; Cukiert et al., 2020; Dalic et al., 2022b; Yang et al., 2022b; Valentín et al., 2013; Velasco et al., 2006). The most common epilepsy type was focal epilepsy, in 41.5 % of patients (Table 2) (ILAE, 2017). A mean seizure reduction (SR) of 69.11 % (95 % CI: 58.14–80.09, $p < 0.01$) was calculated based on the random effects model. The responder rate was found to be 70 % (95 % CI: 53–87, $p < 0.01$) for follow-up periods exceeding 24 months, and 68 % (95 % CI: 31–100, $p < 0.01$) for those under 24 months (Fig. 6). The overall responder rate was 69 % (95 % CI: 54.01–84.16, $p < 0.01$). The seizure freedom was found to be 2.80 % [95 % CI: 1.43–4.18, $p < 0.01$] (Fig. 7). The average maximum follow-up duration was approximately 65.25

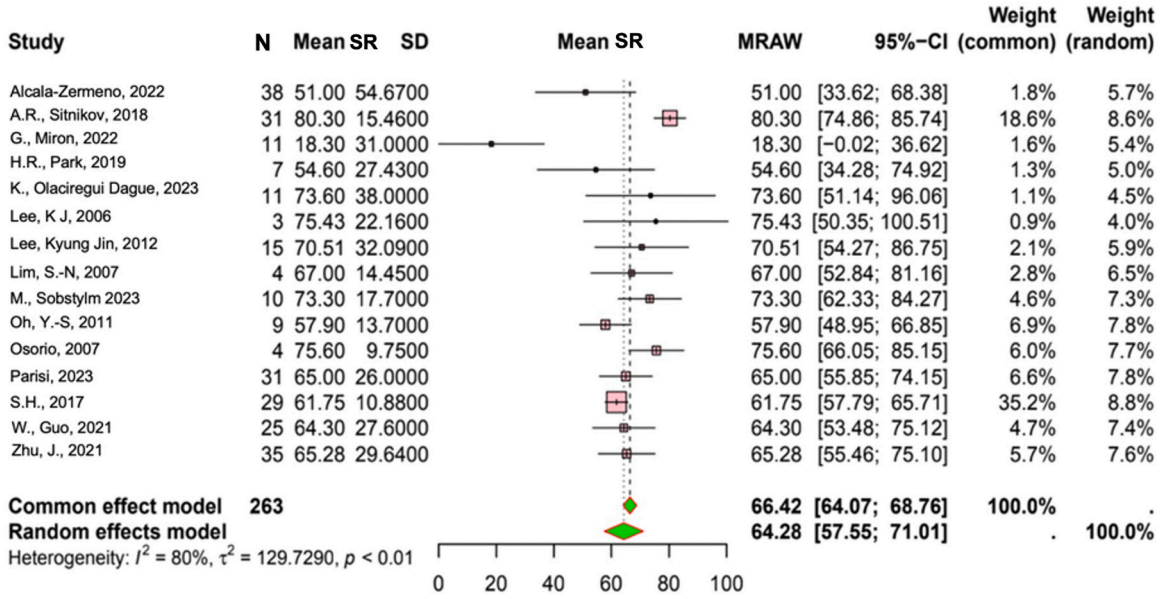

Fig. 2. Pooled mean seizure reduction after deep brain stimulation (DBS) of the anterior thalamic nucleus in epilepsy. N, total number of patients; Mean SR, mean seizure reduction; SD, standard deviation; MRAW, raw mean; CI, confidence interval; Weight (common), study weight in fixed-effect model; Weight (random), study weight in random-effects model.

Table 1
Table displaying the distribution of patients across different epilepsy subtypes according to the ILAE 2017 guidelines for ANT-DBS (ILAE, 2017).

Focal		Generalized		Unknown	
Seizure type	Number of patients	Seizure type	Number of patients	Seizure type	Number of patients
Aware	263	Motor	38	Motor	0
Impaired awareness	447	Non-motor (Absence)	0	Non-Motor	1
Motor onset	3	Not specified	30	Unknown	7
Nonmotor onset	9	Total	68	Total	8
Focal to bilateral tonic-clonic	403				
Not specified	95				
Total	841				

months (range 12–132 months).

3.4. Other

Only 2 studies reported DBS targeting the PN nucleus, with a total of 9 patients (Yan et al., 2023; Yang et al., 2023) Given the limited data in the literature, a meta-analysis was precluded due to inadequate data availability. Multiple thalamic nuclei targeting was observed in patients, with 1 patient receiving stimulation in both the PN and CMN, and 7 patients receiving stimulation in both the CMN and ANT. Although the data was too varied to meta-analyze, it is valuable to understand the range of combined nuclei and the number of patients involved.

3.5. Serious adverse events (SAE)

Serious adverse events were inconsistently reported. The reported SAE included those related to the implantation surgical procedure, device related, stimulation related and psychiatric. Amongst the most important ones to mention are intracranial bleeding, depression and psychosis. Other common SAE were paresthesia and changes to behavior. We summarized these events in Table 3.

3.6. Risk of bias assessment and sensitivity analysis

There was significant heterogeneity for data in this meta-analysis, especially for the ANT and CMN responder rates (I^2 83.9 % and 75 % respectively). Sensitivity analysis results for responder rates and seizure freedom indicate that the effect sizes remained stable after sequential exclusion of studies, confirming robustness of the meta-analysis. Overall risk of bias was moderate for most studies, although a few had critical risk of bias in relation to missing data and patient selection. Risk of Bias is presented in Fig. 8. Funnel plots are presented on Fig. 9. These are symmetrical and egger's regression tests were not statistically significant for funnel plot asymmetry. Thus, there is no strong evidence of publication bias for the meta-analysis conducted.

4. Discussion

In this systematic review, we analyzed data from 1125 patients with DRE who underwent DBS, sourced from 49 studies. A total of 981 patients underwent ANT-DBS (Fisher et al., 2010; Alcala-Zermeno et al., 2021; Andrade et al., 2006; Sitnikov et al., 2018; Passamonti et al., 2021; Chua et al., 2023; Costa-Gertrudes et al., 2022; Tassigny et al., 2020; Kaufmann et al., 2020b; Schaper et al., 2020; Freund et al., 2022; Miron et al., 2022; Yan et al., 2023; Herrman et al., 2019a; Hodaie et al., 2002; Park et al., 2019; Koeppen et al., 2019; Olaciregui Dague et al., 2023; Kerrigan et al., 2004; Krishna et al., 2016; Lee et al., 2012; Lim et al., 2007; Piacentino et al., 2015; Sobstyl et al., 2023; Herrera et al., 2021; Oh et al., 2012; Osorio et al., 2021, 2007a; Parisi et al., 2023; Peltola et al., 2023; Poulen et al., 2022; Järvenpää et al., 2020, 2018; Kim et al., 2017; Salanova et al., 2021, 2015; Guo et al., 2020; Yang et al., 2022a; Zhu et al., 2021; Lee et al., 2006; Lim et al., 2008), while CMN-DBS was performed on 135 patients (Alcala-Zermeno et al., 2021, 2022; Andrade et al., 2006; Passamonti et al., 2021; Chua et al., 2023; Yan et al., 2023; Son et al., 2016; Cukiert et al., 2020; Dalic et al., 2022b; Yang et al., 2022b; Valentín et al., 2013; Velasco et al., 2006), and PN DBS was conducted on 9 patients, with 1 patient receiving stimulation in both the PN and CMN (Yan et al., 2023; Yang et al., 2023). The pooled SR and responder rate was higher in patients who underwent CMN DBS.

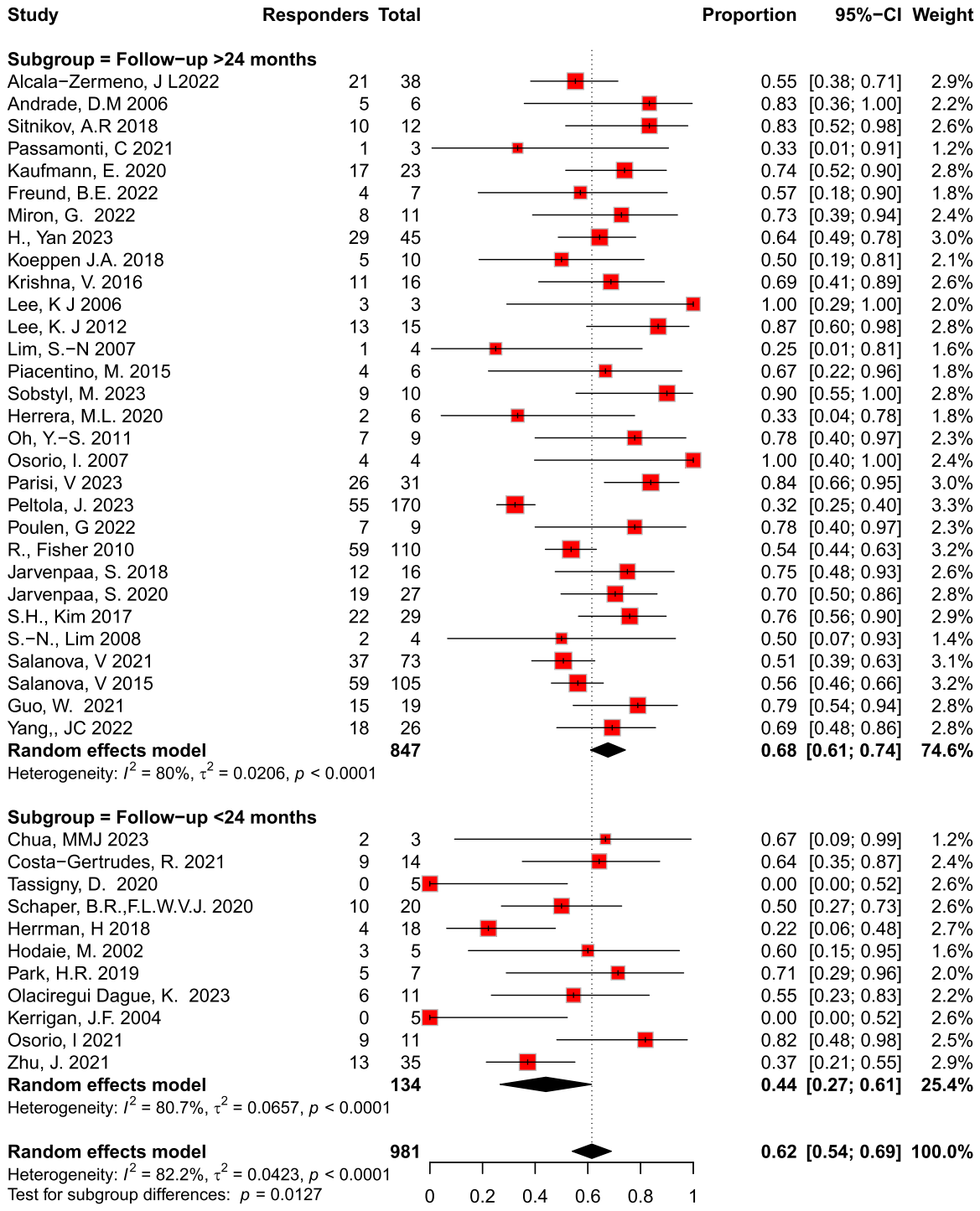

Fig. 3. Responder rate after deep brain stimulation (DBS) of the anterior thalamic nucleus in epilepsy. CI, confidence interval; *P*, *P*-value.

Seizure freedom was higher for the ANT stimulated cohort. The risk of bias was deemed to be moderate and critical for a significant proportion of the included studies.

Subsequent to the SANTE trial, further studies have corroborated a responder rate of 50 % on average but have highlighted significant heterogeneity in effect size (Krishna et al., 2016; Lee et al., 2012; Lehtimäki et al., 2016a; Herrman et al., 2019b). Several determinants, including patient characteristics, the location of the seizure onset zone (SOZ), and the specific stimulation site, contribute to the varied outcomes of DBS (Krishna et al., 2016; Lehtimäki et al., 2016a). A narrative review of the included studies suggests that patients whose epileptogenic zones are outside the temporal lobes or multifocal have exhibited a comparatively less efficacious response to ANT DBS in contrast to those with onset solely within the temporal lobes (Fisher et al., 2010; Osorio et al., 2007b). Furthermore, some studies suggest that ANT-DBS may be more effective in treating focal (limbic) seizures, whereas CMN-DBS appears to be better suited for generalized seizures (Vetkas et al., 2022). CMN-DBS for instance has been noted to be specifically beneficial for individuals with generalized epilepsy, particularly those diagnosed with Lennox–Gastaut syndrome or those predominantly experiencing tonic-clonic or other generalized seizures (Haneef and Skrehot, 2023; Kulju et al., 2018; Velasco et al., 1993).

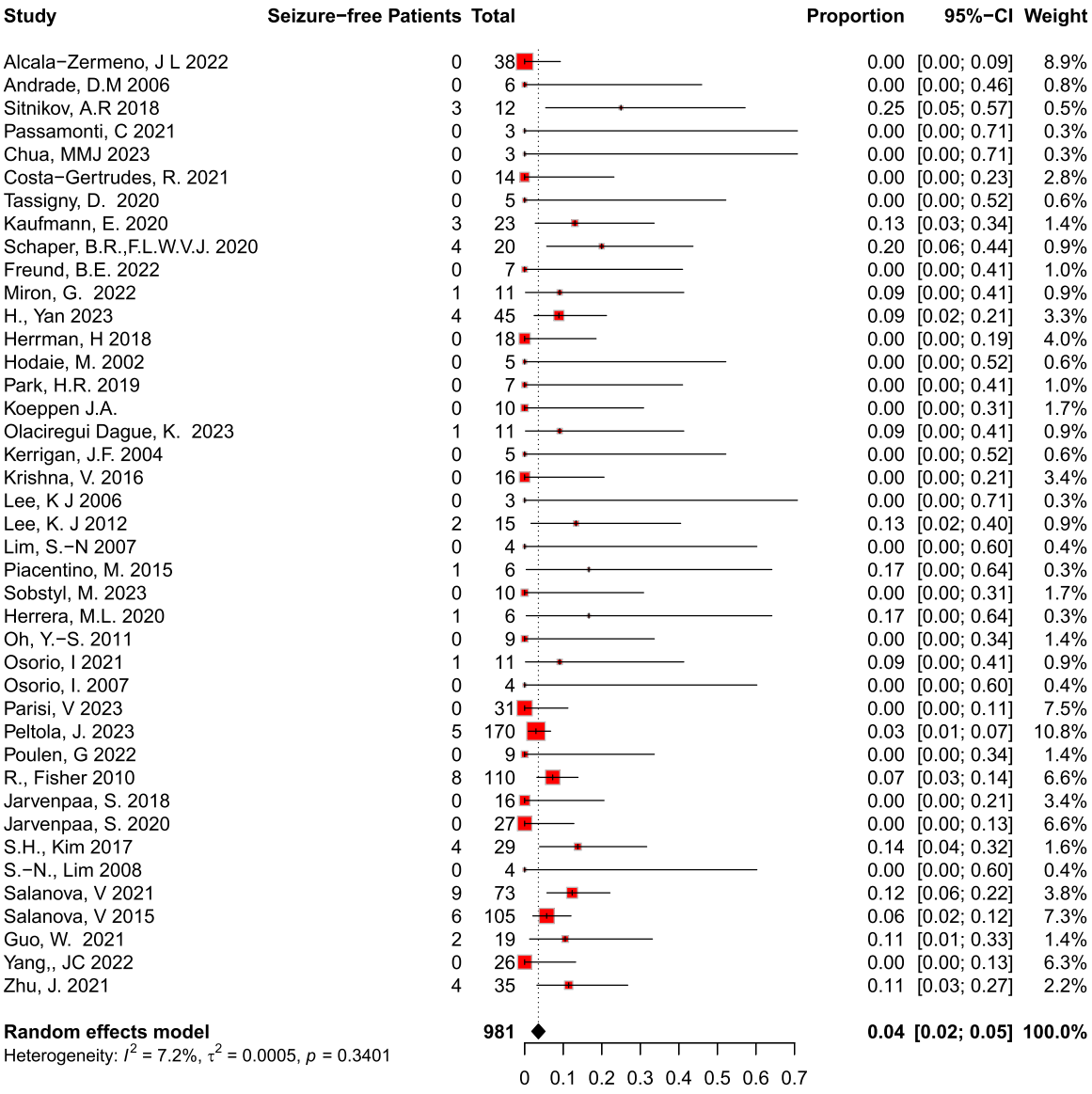

Fig. 4. Seizure freedom (100 % seizure reduction for at least 12 months) after deep brain stimulation (DBS) of the anterior thalamic nucleus in epilepsy. CI, confidence interval; *P*, *P*-value.

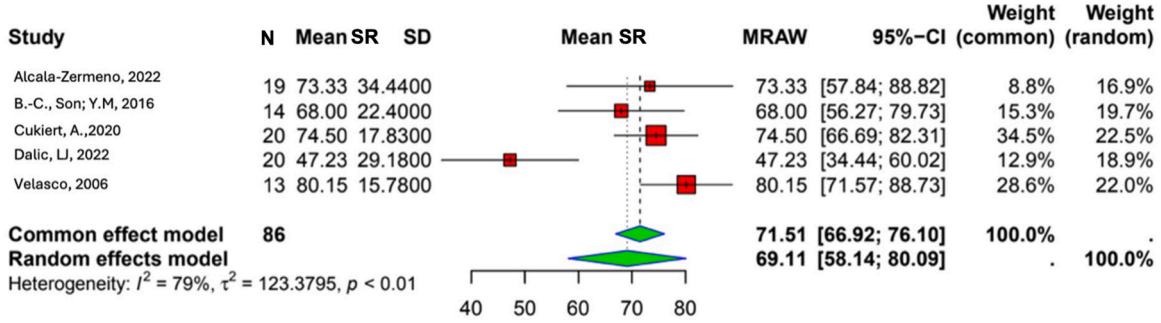

Fig. 5. Pooled mean seizure reduction after deep brain stimulation (DBS) of the centromedian nucleus in epilepsy. N, total number of patients; Mean SR, mean seizure reduction; SD, standard deviation; MRAW, raw mean; CI, confidence interval; Weight (common), study weight in fixed-effect model; Weight (random), study weight in random-effects model.

However, in our analysis, patients with LGS were grouped alongside those with genetic/idiopathic generalized epilepsy syndromes. Given the distinct underlying pathophysiology of LGS, this categorization could introduce confounding effects. Future studies should consider analyzing LGS as a separate subgroup to better delineate treatment outcomes.

Our review found that focal epilepsy was the most common type to undergo DBS, present in 41.5 % of patients across the literature. The

Table 2
Table displaying the distribution of patients across different epilepsy subtypes according to the ILAE 2017 guidelines for CMN-DBS (ILAE, 2017).

Focal Epilepsy		Generalized Epilepsy		Unknown	
Seizure type	Number of patients	Seizure type	Number of patients	Seizure type	Number of patients
Aware	1	Motor	15	Motor	0
Impaired awareness	5	Non-motor (Abscence)	4	Non-Motor	0
Motor onset	0	Not specified	5	Unknown	29
Nonmotor onset	9	Total	24	Total	29
Focal to bilateral tonic-clonic	11				
Not specified	31				
Total	56				

relatively higher success rates and clearer clinical outcomes in focal epilepsy compared to generalized epilepsy perhaps are likely to contribute to this trend. This predominance underscores the need for further research and tailored strategies when considering DBS for other types of epilepsy, ensuring treatment protocols are optimized for a broader range of epileptic disorders. Furthermore, to enhance alternative treatment approaches, additional studies on the PN nucleus are necessary to identify the specific patient cohort that would benefit most from this stimulation.

4.1. Optimization of DBS target placement and stimulation parameters

Improving outcomes of DBS for epilepsy requires a multifaceted approach involving individualized optimization of stimulation parameters and lead placement, alongside a thorough understanding of the clinical effectiveness across different seizure types (Järvenpää et al., 2020). However, not all studies included in this study provided detailed stimulation parameters, limiting the ability to perform a meta-analysis on their specific effects. Given the potential influence of contact location, intensity levels, and directionality on outcomes, future studies with standardized reporting of these parameters would enable a more comprehensive assessment.

Due to the diverse anatomical features found among patients, along with the complexities arising from inconsistencies among atlases and surgical methods, achieving optimal ANT targeting poses a significant challenge (Wu et al., 2017; Lehtimäki et al., 2016b; Gross et al., 2021). Schaper et al. conducted a study indicating that DBS targeting near the mammillothalamic tract within the anterior ventral nucleus led to improved outcomes, a conclusion further supported by a meta-analysis (Schaper et al., 2020; Ilyas et al., 2022). Likewise, active contact locations within the dorsal CMN have indicated improved seizure outcomes (Warren et al., 2020; Grant et al., 2015; Funct et al., 2016). Therefore, evidence suggests successful outcomes are highly contingent upon accurate targeting. The challenge presents when patients who have undergone previous resections (e.g., temporal resection, callosotomy) exhibit anatomical distortions that complicate the alignment process to a standardized atlas, leading to imprecise results (Ilyas et al., 2022). Whilst indirect targeting via extraventricular trajectories may be influenced by systemic bias, both indirect and direct targeting methods face challenges, such as structural distortions in the brain.

Stimulation parameters including voltage and frequency are also key factors that influence outcome measures. Zumsteg et al. conducted a study whereby various paradigms were applied including monopolar or bipolar stimulation through neighboring contacts, stimulus frequency 2–130 Hz and voltage 1–10 V for ANT-DBS. The study found that varying stimulation voltage and pulse width significantly influenced cortical responses, with higher settings correlating with increased response amplitudes and current density, while electrode impedance exhibited an inverse relationship (Zumsteg et al., 2006). A case series for CMN-DBS found that specific parameters, including 60 pulses per second frequency, 0.09 s pulse duration, and intensity adjusted just below subjective responses, led to significant reductions in seizure frequency and interictal EEG abnormalities in patients with incapacitating seizures (Velasco et al., 1995). Although some data has demonstrated the effect of programming changes, studies have also shown the minimal impact they can have; in the long-term phase of the SANTE study, changing

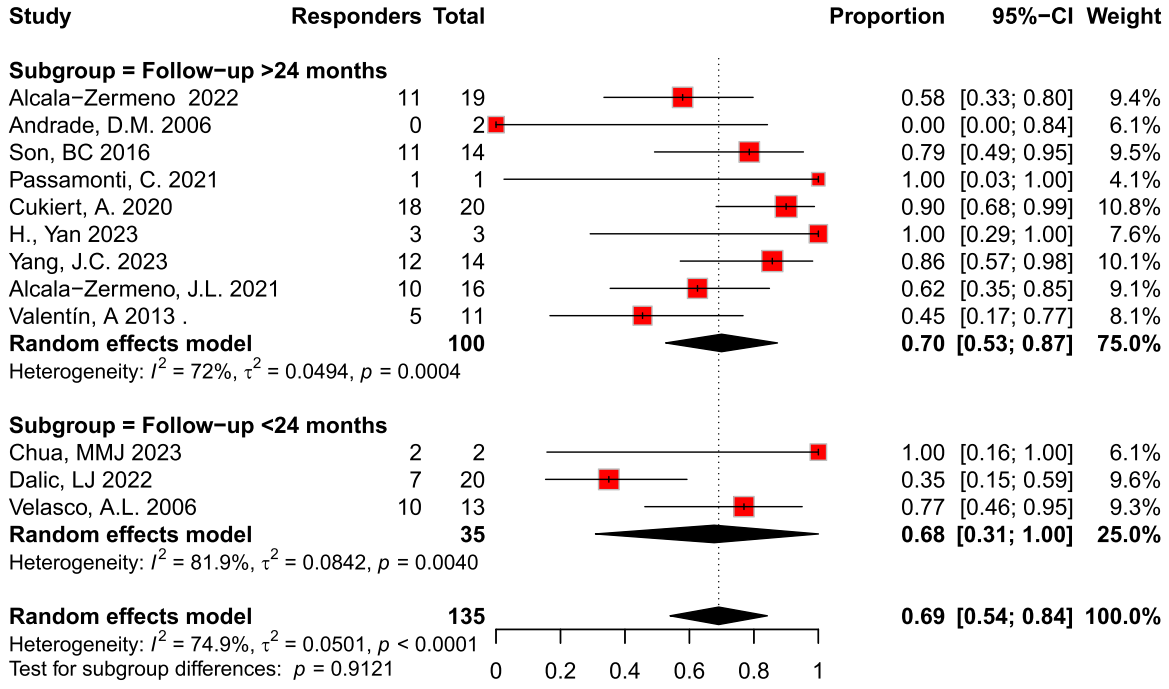

Fig. 6. Responder rate after deep brain stimulation (DBS) of the Centromedian nucleus in epilepsy. CI, confidence interval; *P*, *P*-value.

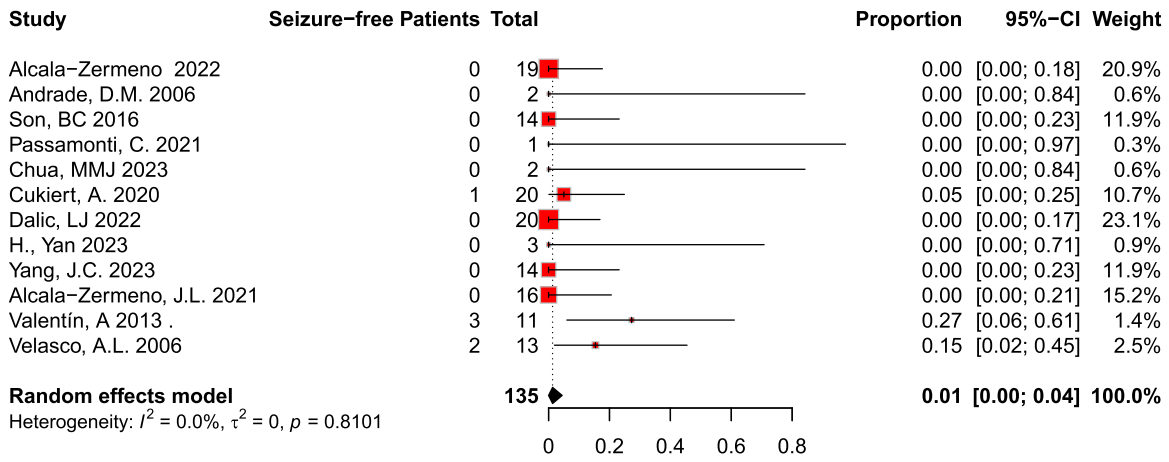

Fig. 7. Seizure freedom (100 % seizure reduction for at least 12 months) after deep brain stimulation (DBS) of the centromedian thalamic nucleus in epilepsy. CI, confidence interval; *P*, *P*-value.

stimulation voltage from 5.0 to 7.5 V or frequency from 145 to 185 Hz did not show an effect on seizure frequency beyond the initial settings (Fisher et al., 2010).

4.2. PN-DBS

The PN presents a promising target for neuromodulation in epilepsy, given its extensive cortical connections, including those with the cingulate gyrus and mesial temporal lobes, and its dense connectivity with the ipsilateral hippocampus (Burdette et al., 2021; Barron et al., 2014). Moreover, there is evidence of distinct functional connectivity patterns of the PN, which reflect its heterogeneous and widespread projections to the cortex and the role of distinct sub-regions in separate networks and cognitive domains (Guedj and Vuilleumier, 2020). The significance of these connections suggests a role of the PN in the propagation of temporal lobe seizures (Rosenberg et al., 2006). A systematic review has demonstrated that stimulating this region in patients with epilepsy resulted in a clinical response, showing a reduction in seizures of over 50 % (Wong et al., 2023). Specifically, optimal efficacy has been demonstrated in treating posterior quadrant regional neocortical epilepsy, with responders experiencing seizure reductions of 90 % or greater (Burdette et al., 2021).Further studies, however, are required to confirm the clinical significance of PN-DBS, and currently there are far few studies of this target than others.

4.3. Serious adverse events (SAEs)

Consideration of the adverse effects associated with thalamic DBS is essential; these effects can be attributed to the surgical procedure, hardware, and stimulation-related complications and are crucial for identifying suitable candidates for the procedure.

The bidirectional association between depression and epilepsy highlights the importance of considering potential exacerbation of psychiatric adverse effects when performing DBS (Salanova et al., 2021; Hesdorffer et al., 2012; Josephson et al., 2017). Long-term results from the SANTE trial validate this relationship, reporting 37.3 % of subjects presented with depression, 9.3 % presented with anxiety, and 10 % experienced suicidality; although, it is important to note that two-thirds of these subjects had a history of depression. Additional adverse effects comprised paresthesia around the incision sites (9 %), dizziness (5.6 %), headache (3.7 %), and infection (12.7 %) (Salanova et al., 2021). The ESTEL trial, looking at specifically CMN-DBS, reported 35 % (n = 7) of participants having serious adverse events (SAE) of which the following were included: cerebral Staphylococcus aureus infection necessitating DBS hardware removal (n = 1), prolonged seizures/status epilepticus requiring hospital admission (n = 2), drop seizures leading to facial laceration (n = 1), and postoperative seizures during hospital admission (n = 14). It is important to note that many of these SAEs were related to the unique characteristics of the population studied, such as prolonged status epilepticus and injury from drop seizures. As such, these adverse events may not necessarily be applicable to every CMN-DBS implant. The ESTEL trial, originally designed with a focus on effect size and safety rather than the primary outcome, suggests caution is warranted in interpreting adverse effects associated with CMN DBS. Despite negative primary outcomes, the trial revealed multiple positive secondary outcomes, indicating the need to carefully consider the significance of these findings. The change in secondary outcomes primarily reflects their frequency and underscores the importance of robust study designs in future research (Dalic et al., 2022a). The observed significant improvement in electrographic seizures (secondary outcome) compared to diary-recorded seizures (primary outcome) reflects the vast difference in seizure detection rates between these measures. With EEGs capturing approximately 100 times more seizures than diaries, this discrepancy underscores the importance of objective measurements in future LGS studies The reported complications of PN-DBS are limited; one case series however showed that after two patients underwent pre- and post-surgical neuropsychiatric evaluations, no evidence of cognitive decline or complications were detected (Wong et al., 2023). Further investigations are required to fully confirm the complications and long-term adverse effects of PN-DBS.

4.4. Limitations

Although our study represents a novel approach to analyzing DBS targeting across three distinct thalamic nuclei for epilepsy, this comes with some limitations. The heterogeneity of included studies, spanning randomized and non-randomized designs, poses methodological challenges for meta-analysis, further compounded by variability in patient populations, epilepsy syndromes, stimulation parameters, and outcome measures, as well as inconsistent reporting of patient- and procedure-related factors, all of which contribute to the high I^2 and limit the generalizability of pooled estimates. Moreover, due to the heterogeneous and mixed nature of the cohorts included, as well as the inconsistent reporting of the SOZ location, we were unable to conduct subgroup analysis based on these characteristics, thus limiting our conclusions regarding DBS effectiveness for one specific epilepsy type. We also did not establish the risk of bias as an exclusion criterion, allowing for a more comprehensive synthesis of available evidence. However, we acknowledge that the inclusion of studies with a critical risk of bias may influence our findings, and this should be considered when interpreting the results. These factors may include seizure etiology, variations in stimulation parameters, differences in surgical

Table 3
Summary of major complications in deep brain stimulation studies for epilepsy.

Study Author(s)	Total number of patients (n)	Infection	Haemorrhage	Depression/ Mood Disorders	Memory/ Cognitive Impairment	Hardware Issues	Seizure Increase	Paraesthesia	Suicidality	Serious Unexpected Death in Epilepsy (SUDEP)	Targeting / Lead Revision
Alcala-Zermeno et al. (2022)	159	1	-	-	-	1 (pulse generator rotation)	-	1 (transient hemiparesis)	-	-	-
Yan et al. (2023)	8	-	-	-	-	-	-	1 (hand tingling)	-	-	-
Andrade et al. (2006)	8	-	-	-	-	-	-	1 (paresthesias)	-	-	-
Sitnikov et al. (2018)	31	-	-	-	-	2 (current leak)	-	-	-	-	-
Son et al. (2016)	14	-	-	-	-	1 (lead misplacement)	-	-	-	-	1
Passamonti et al. (2021)	6	-	-	1	-	-	-	-	-	-	-
Chua et al. (2023)	5	-	-	-	1	-	-	-	-	-	-
Fisher et al. (2010)	110	1	5	8	7	2 (targeting issues)	1 (new seizure types)	1 (paresthesias)	-	-	1
Kim et al. (2017)	29	2	1	5	7	5 (targeting issues, hardware)	-	1 (sensory changes)	2	1 (SUDEP)	1
Salanova et al. (2015)	105	14	-	41	33	9	-	1 +	11	2	1
Salanova et al. (2021)	73	17	-	1	1	33	-	1 +	-	-	1
Valentín et al. (2013)	11	1	-	-	-	-	-	-	-	-	-
Parisi et al. (2023)	31	1	-	4	1	2 (fractured electrode, removal)	-	3 (stimulation side effects)	-	-	1
Peltola et al. (2023)	191	1	-	1	1	2 (misplacement, dislocation)	1 (seizure increase)	-	1	-	1
Jarvenpaa et al. (2020)	27	-	-	-	-	1 (mistargeting)	-	-	-	-	1
Yang et al. (2023)	14	-	2	-	-	2 (wound complications)	-	1 (sensorimotor changes)	-	-	1

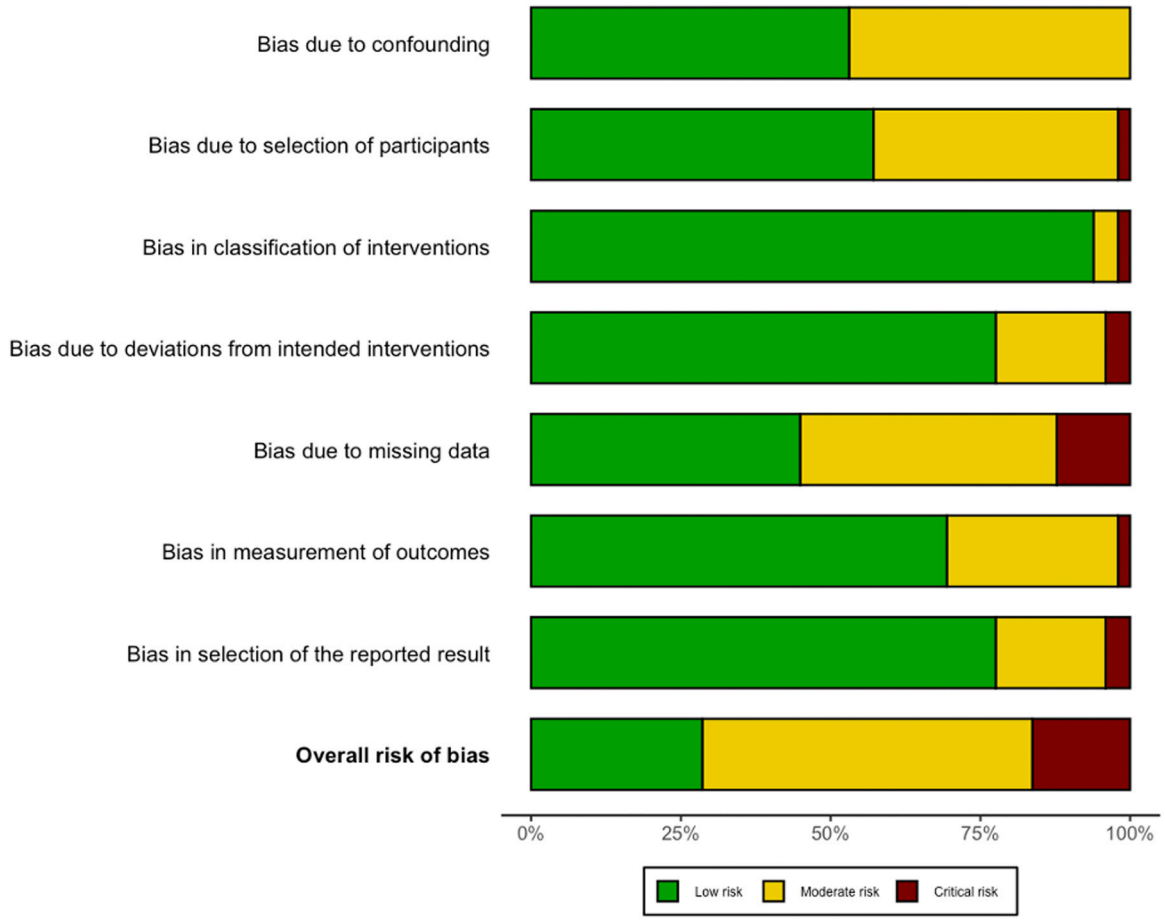

Fig. 8. ROBINS- I. Risk of bias, as determined according to the Cochrane ROBINS-I tool. Risk of bias in each domain is classified as serious, moderate, low, or no information, as shown in the legend.

techniques, recordings of implantation effects and prior neurostimulation interventions. Further, to ensure robust and representative data, we set a cutoff of three patients per study. This minimized bias from single-case studies while avoiding the exclusion of significant data from smaller studies.

Determining clear definitions for seizure terminology also proved to be a challenge due to the considerable variability across the literature, particularly when considering the diverse range of seizure types. Despite the clarity provided by ILAE guidelines, determining a consistent time frame for responder rates proved challenging. Some studies spanned over decades, whilst others only a couple of months, leading us to subgroup our outcomes into those with follow-up within 24 months and those observed for more than 24 months following a comprehensive review of the literature. Moreover, risk of bias was deemed to be moderate and critical for a significant proportion of the included studies, further limiting the generalizability of the findings for wider clinical practice. We did not include health related quality of life outcomes for our analysis, as this was inconsistently measured and reported in the included studies. Furthermore, poor results are less likely to be published; this significant issue highlights why outcomes from randomized controlled trials often appear less favorable than those from case series, a factor not addressed by examining bias in published studies alone.

5. Conclusion

Our findings demonstrate high responder rates and reductions in seizure frequency for DBS targeting the ANT or CMN of the thalamus with low rates of seizure freedom. Further investigations are required to explore PN-DBS to fully understand the extent of its efficacy and utility. Research should be focused on refining patient selection criteria, discovering biomarkers to predictive individual response, and evaluating outcomes beyond seizure control.

CRediT authorship contribution statement

Dhaliwal Jasneet Kaur: Writing – original draft, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Tisdall Martin:** Writing – review & editing, Supervision, Project administration, Methodology, Formal analysis, Data curation, Conceptualization. **Piper Rory:** Writing – review & editing, Visualization, Validation, Methodology, Conceptualization. **Aswin Chari:** Writing – review & editing, Visualization, Validation, Methodology, Conceptualization. **Michelle Ruiz-Perez:** Writing – review & editing, Visualization, Validation, Methodology, Data curation, Conceptualization. **Michael Hart:** Writing – review & editing, Supervision, Project administration, Methodology, Formal analysis, Data curation, Conceptualization.

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N/A.

Declaration of Competing Interest

All authors declare no conflicts of interest.

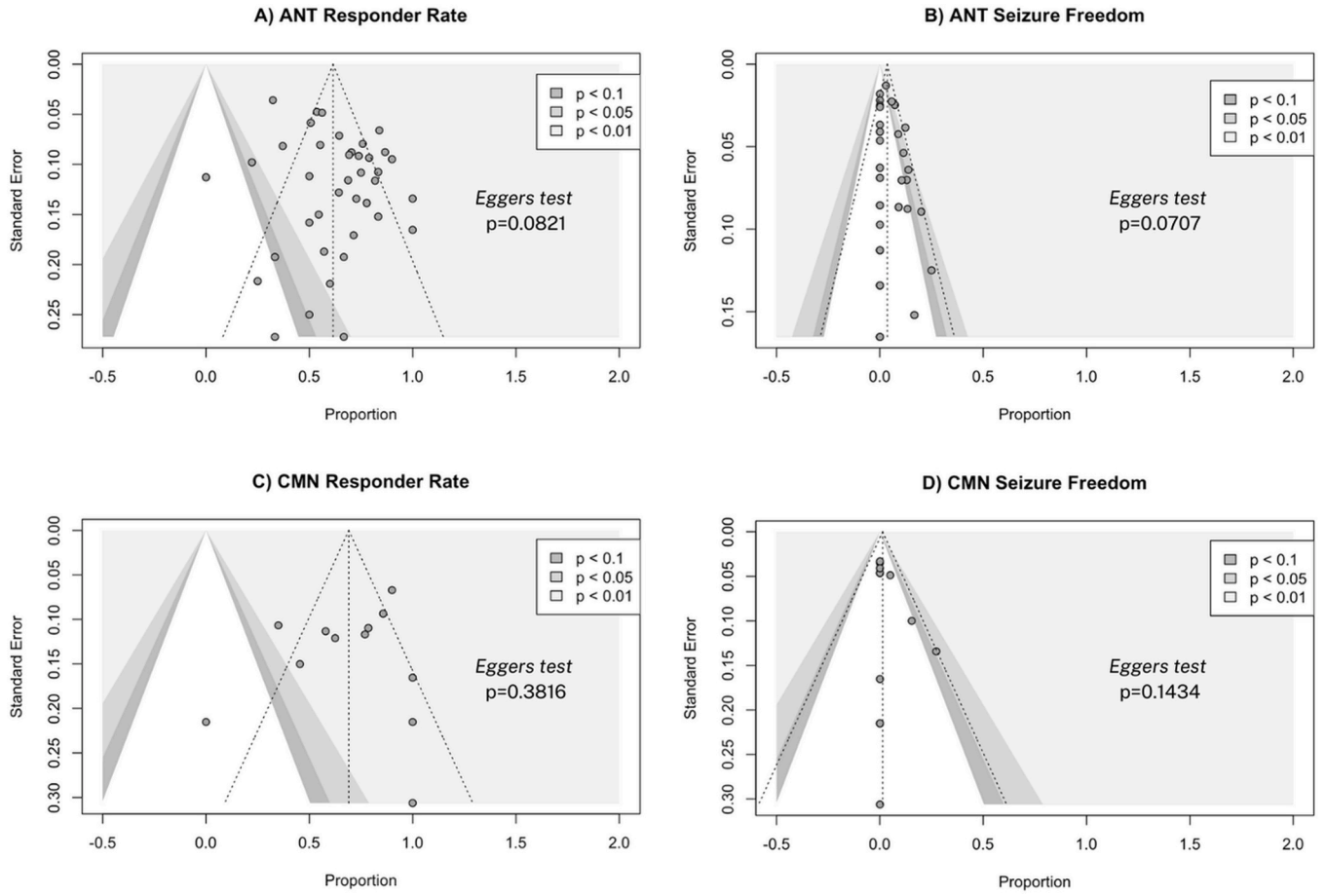

Fig. 9. Funnel Plots-Publication Bias. A) ANT Responder Rate. B) ANT Seizure Freedom. C) CMN nucleus responder rate. D) CMN nucleus seizure freedom.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.eplepsyres.2025.107607.

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