

Deep brain stimulation for treatment-resistant major depressive disorder: a network meta-analysis of stimulation targets

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OBJECTIVE Major depressive disorder is a significant cause of disability, impacting an estimated 193 million individuals worldwide. Forty percent are estimated to have little to no response to standard pharmacological therapies. Deep brain stimulation (DBS) has emerged as a favorable neuromodulation therapy for treatment-resistant depression, but it remains unclear which brain targets are optimal.

METHODS The authors performed a systematic literature review and meta-analysis of articles published through January 2022 to examine the efficacy of DBS targets in reducing depressive symptoms in patients with treatment-resistant depression. The primary outcome was the reduction in depression severity measured by the Montgomery-Asberg Depression Rating Scale and Hamilton Rating Scale for Depression. Secondary outcomes were responder and remission rates.

RESULTS The authors analyzed 22 trials, 15 of which were sham-controlled studies. This network meta-analysis identified that stimulation of the medial forebrain bundle (MFB) was associated with the greatest reduction in depressive symptoms, compared with stimulation of the subcallosal cingulate gyrus (SCG) and ventral capsule/ventral striatum (VC/VS). Stimulation of the MFB also exhibited a higher responder rate (86%) than stimulation of the SCG or anterior limb of the internal capsule. Stimulation of the rostral extension of the prefrontal cortex was associated with the highest remission rate (60%), but this was not statistically significant compared with stimulation of other brain regions.

CONCLUSIONS The MFB shows promise as a DBS target for treatment-resistant depression, possibly a result of its involvement in the mesocortical and mesolimbic pathways mediating depression. However, additional trials directly comparing stimulation of different brain regions are necessary to establish MFB as the optimal neurostimulation target.

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KEYWORDS depression; deep brain stimulation; functional neurosurgery; psychiatry

MAJOR depressive disorder is the leading cause of disability in adults.¹ Treatments include psychotherapy, antidepressants, ketamine, transcranial magnetic stimulation, electroconvulsive therapy, and vagus nerve stimulation. Most patients will achieve a satisfactory response early in the clinical algorithm; however,

the minority of patients who do not often struggle to find an effective but tolerable treatment strategy. Aggressive pharmaceutical management is often accompanied by poor tolerability and limited efficacy, with remission rates reaching single digits following three medication trials.² Transcranial magnetic stimulation, vagus nerve stimula-

ABBREVIATIONS ALIC = anterior limb of the internal capsule; DBS = deep brain stimulation; EPFC = epidural prefrontal cortex; HAM-D = Hamilton Rating Scale for Depression; ITP = inferior thalamic peduncle; MADRS = Montgomery-Asberg Depression Rating Scale; MFB = medial forebrain bundle; NMA = network meta-analysis; RCT = randomized controlled trial; ROM = ratio of mean; SCG = subcallosal cingulate gyrus; SMD = standardized mean difference; TRD = treatment-resistant depression; VC = ventral capsule; VS = ventral striatum.

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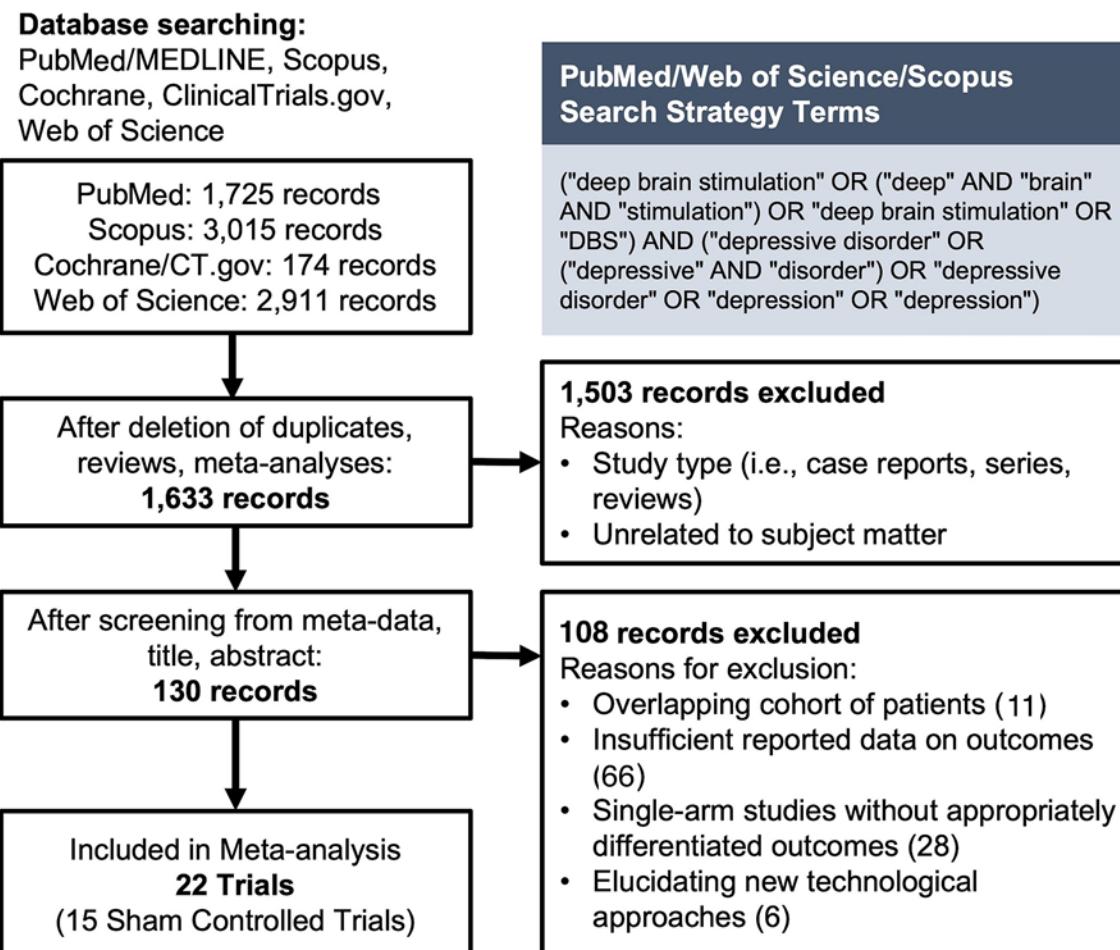


FIG. 1. Diagram for flow of evidence in meta-analysis. Figure is available in color online only.

tion, and ketamine are well tolerated, although they also have limited efficacy, with approximately one-third or fewer of patients experiencing remission.^{3–6} Electroconvulsive therapy offers the greatest odds of remission, although adverse cognitive effects are concerning for otherwise highly functioning patients or patients requiring long-term maintenance treatments. Additional therapeutic options are thus required to maximize patient outcomes.

Deep brain stimulation (DBS) is primarily indicated for movement disorders; however, recent efforts have attempted to use DBS as a treatment modality for psychiatric disorders including treatment-resistant depression (TRD).⁷ Randomized controlled trials (RCTs) have targeted several different neuroanatomical locations to treat TRD with varying success. Understanding which stimulation target offers the greatest reduction in symptoms is critical to guide future research and eventually clinical efforts. Unfortunately, small sample sizes associated with most trials have prevented within-trial target comparisons. Furthermore, few existing meta-analyses compare the efficacy of different targets in treating depression.

The present study performed a network meta-analysis (NMA) of existing clinical trials to determine the func-

tional target that most effectively treats depression. The primary aim was to compare mean improvement in clinical measurements of depression across targets. Secondary aims included comparisons of responder and remitter rates across targets.

Methods

Search Strategy and Selection Criteria

A systematic search adherent to PRISMA guidelines was performed in January 2022. This review was not registered. An a priori search strategy was designed to include PubMed, MEDLINE, Scopus, Cochrane, ClinicalTrials.gov, and Web of Science, using search terms including “deep brain stimulation,” “DBS,” and “depression.” The selection criteria were as follows: 1) sham-controlled and non-sham-controlled randomized trials evaluating DBS of a clearly specified region of the brain for major depressive disorder, and 2) enrollment of human subjects with TRD (those who had previously undergone unsuccessful medical management prior to the DBS trial). No clear language restrictions were placed. Only full-length articles were considered for inclusion in analysis. All authors contributed to article selection and screening against

TABLE 1. Features of included studies

Authors & Year	Mean Age ± SD, yrs	% Females in Tx	Pts in Control	Stim Location	Stim Details	Outcomes Measured	Study Length, mos	FU, yrs
Bergfeld et al., 2016 ¹⁷	53.2 ± 8.4	68	16	vALIC	Optimization phase: 2.5–6 V, 90-μsec PW, 130 or 180 Hz; crossover phase: 2 blocks of 6 wks during which DBS stimulator was on (active) or off (sham)	HAMD-17, MADRS, IDS-SR	48	NR
Coenen et al., 2019 ¹⁸	51.6 ± 10.2	37.5	8	MFB	Active group received stim for 8 wks, then both groups received stim for up to 12 mos (3–5 V, 60-μsec PW, 130 Hz) w/ therapeutic target current of 2.5–3 mA	MADRS	12	4
Dougherty et al., 2015 ¹⁹	47.7 ± 12.0	43	16	VC/VS	2 different pulses (90 μsec, 210 μsec), tested up to a threshold of 8 V	MADRS	4	2
Fenoy et al., 2018 ²⁰	50.2 ± 10.2	66	6	MFB	3.8 ± 1.2 V, 64 ± 8.4-μsec PW, 130 Hz	MADRS, HAMD-24, YMRS, CGI	13	NR
Holtzheimer et al., 2012 ²¹	42.0 ± 8.9	59	17	SCG	4–8 mA, 90-μsec PW, 130 Hz, approx 2–5 mins of active stim at each contact	HAMD-24, BDI-II, GAF	7	2
Holtzheimer et al., 2017 ²²	Tx: 50.53 ± 9.73; control: 48.70 ± 0.56	52	60	SCG	4 mA (increased to 8 mA if not adequate), 130 Hz, 91-μsec PW	MADRS, GAF, QIDS-SR, HAMD-17, IDS-C30	12	2.5
Merkle et al., 2013 ²³	50.6 ± 9.2	66	6	SCG	2.5–10 V, 90-μsec PW, 130 Hz, then set at a constant 5 V	HAMD-24, MADRS, BDI, YMRS	6–9	4
Merkle et al., 2018 ²⁴	48.2 ± 12.9	25	4	SCG	2.5–10 V, 90-μsec PW, 130 Hz, then set at a constant 5–7 V	HAMD-24, BDI, MADRS	2	2.3–4
Puigdemont et al., 2015 ²⁵	42.0 ± 9.9	NR	5	SCG	3.5–5 V, 120- to 240-μsec PW, 130–135 Hz	HAMD-17, MADRS	6	NR
Ramasubbu et al., 2013 ²⁶	50.25 ± 4.2	75	4	NA	SCG Wk 1: 2.7–5 V, 90-μsec PW, frequency changed weekly (0, 5, 20, 50, 130, 185 Hz); wks 8–11: 130 Hz, PW randomized (0, 90, 150, 270, 450 μsec), 5 V for PWs up to 150 μsec, 3 V for higher PWs	PANAS, VAS, HAMD-17	9	NR
Raymaekers et al., 2017 ²⁷	50.0 ± 5.6	43	6	ALIC	4.5–8 V, 130 Hz	HAMD-24, IDS, BHS, HAMD-17, GAF, CGI-S, PGI-S, CGI-I, PGI-I, SCL-90	15	3–8
Raymaekers et al., 2017 ²⁷	50.0 ± 5.7	43	5	ITP	4.5–9 V, 130 Hz	HAMD-24, IDS, BHS, HAMD-17, GAF, CGI-S, PGI-S, CGI-I, PGI-I, SCL-90	16	3–8
van der Wal et al., 2020 ²⁸	53.2 ± 8.4	68	25	NA	ALIC 130, 180, or 190 Hz, 60- to 120-μsec PW	HAMD-17, MADRS, IDS-SR, CGI	24	2
Mayberg et al., 2005 ²⁹	46 ± 8	50	6	NA	SCG Voltage was progressively increased up to 9 V, 60-μsec PW, 130 Hz	HAMD-17, HAMD-24, MADRS, CGI	6	NR
Lozano et al., 2003 ³⁰	47.4 ± 10.4	55	20	NA	SCG 3.5–5.0 V, 90-μsec PW, 130 Hz	HAMD-17, CGI-S	12	NR
Kennedy et al., 2011 ³¹	47.7 ± 10.4	55	20	NA	SCG Mean stim parameters: 4.3 V, 70.6-μsec PW, 124.7 Hz	HAMD-17, SF-36	12	3–6
Lozano et al., 2012 ³²	47.3 ± 6.1	62	21	NA	SCG Average 6-mo parameters: 4.9 mA, 100.5-μsec PW, 130.5 Hz; average 12-mo parameters: 5.2 mA, 93.9-μsec PW, 128.1 Hz	HAMD-17, CGI	12	NR
Malone et al., 2009 ³³	46.3 ± 10.8	NR	15	NA	VC/VS Average at last FU: 6.7 V, 113-μsec PW, 127 Hz	HAMD-17, MADRS, GAF	6	0.5
Nahas et al., 2010 ³⁴	44.2 ± 9.4	80	5	NA	EPFC 2–4 V, 60 Hz; on for 30 mins every 2.5 hrs, off from 8 AM to 10 PM	HAMD-24, MADRS, IDS-SR	7	NR

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TABLE 1. Features of included studies

Authors & Year	Mean Age ± SD, yrs	% Females	Pts in Tx	Pts in Control	Stim Location	Stim Details	Outcomes Measured	Study Length, mos	FU, yrs
Williams et al., 2016 ³⁵	44.4 ± 9.7	80	5	NA	EPFC	4.5–6.5V, 210 µsec (except 1 pt w/ a PW of 90 µsec), 130Hz for the last 2–3 yrs; initial frequency was 60 Hz	HAMD-24, MADRS, IDS-SR, YMRS, CGI-S, CGI-I, Q-LES	7	5
Schlaepfer et al., 2013 ³⁶	42.6 ± 9.1	42.9	7	NA	MFB	2–3 mA, 2–3 V, 130 Hz, 60-µsec PW	MADRS, HAMD-24, HAMD-17, GAF, SF-36	12	0.25
Accolla et al., 2016 ³⁷	45.2 ± 12.8	20	5	NA	SCG	5 V, 90-µsec PW, 130 Hz	HAMD-24, BDI	6	1

BDI = Beck Depression Inventory; BHS = Beck Hopelessness Scale; CGI = Clinical Global Impressions; CGI-I = Clinical CGI-Improvement; CGI-S = CGI-Severity; FU = follow-up; GAF = Global Assessment of Functioning; HAMD-17 = 17-item HAM-D; HAMD-24 = 24-item HAM-D; IDS-C30 = Inventory of Depressive Symptomatology, Clinician-Rated; IDS-SR = IDS, Self-Report; NA = not applicable; PANAS = Positive and Negative Affect Schedule; PGI-I = Patient Global Impression of Improvement; PGI-S = PGI of Severity; pt = patient; PW = pulse width; Q-LES = Quality of Life Enjoyment and Satisfaction; QIDS-SR = Quick Inventory of Depressive Symptomatology Self-Report; SCL-90 = Symptom Checklist-90; stim = stimulation; Tx = treatment; VAIIC = ventral ALIC; VAS = visual analog scale; YMRS = Young Mania Rating Scale.

inclusion criteria. Disagreements, if any, were resolved by consensus discussion with senior authors.

Outcome Measures

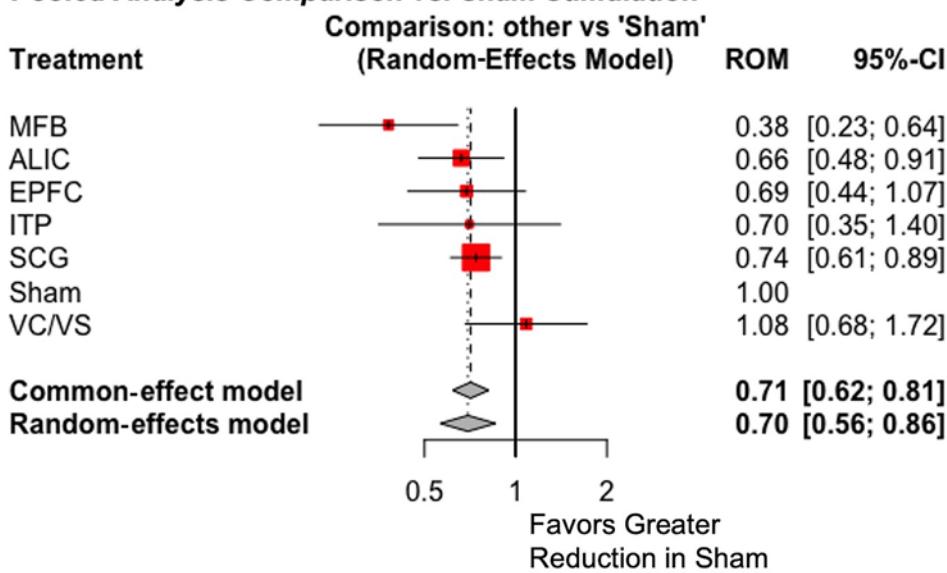
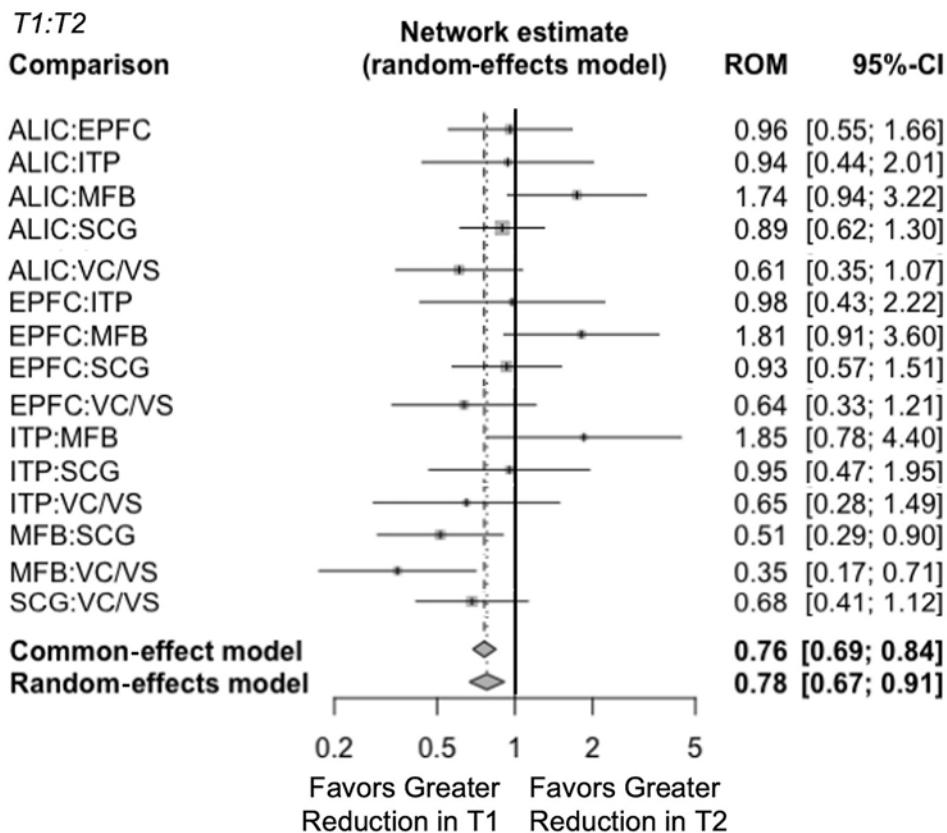
For the primary outcome, we used the ratio of mean (ROM) of two well-established measures and scales of depression, the Montgomery-Asberg Depression Rating Scale (MADRS) and the Hamilton Rating Scale for Depression (HAM-D), to evaluate the comparative impact of DBS targeted to different regions of the brain. Both scales are the most common standardized clinical tools for the assessment of depressive symptom severity. The MADRS was developed for and has demonstrated greater reliability in detecting symptoms of depression when compared with the HAM-D.^{8,9} The MADRS score consists of a 10-item questionnaire that allows for monitoring of depressive symptoms over time. The scores range from 0 to 60 with higher scores reflecting a greater severity of depression.¹⁰ The HAM-D is the most widely used clinical depression assessment scale.^{11,12} For secondary outcomes, we examined responder and remission rates. A responder was defined as a patient with ≥ 50% reduction in the depression measure of interest.¹³ Remission was defined as a complete resolution of depressive symptoms.¹⁴

Quality Assessment and Publication Bias

For all RCTs, the Cochrane Risk of Bias tool was used to assess risk of bias attributable to randomization, allocation concealment, and other possible factors. Quality assessment was performed and cross-validated by all authors. Publication bias for NMA was assessed using Egger's test for NMAs.

Statistical Analysis

A frequentist approach toward NMA was used for the comparative impact of stimulation location on reduction of depression. This analysis was performed only on sham-controlled trials. Because multiple scales were used in the literature to ascertain reduction in depression, the ROM was used as the primary comparative effect for the NMA. The ROM method has been shown to be an effective way to aggregate outcomes and has been found to be more interpretable compared with other metrics such as standardized mean difference, while still minimizing sources of bias across studies.¹⁵ The Mantel-Haenszel method was used to pool the ROM and corresponding standard error for each study. The Der Simonian-Laird method was used to measure internal and external heterogeneity. In the case of significant heterogeneity, an adjusted random-effects model was used. Indirect and direct ROM measurements were used to calculate a hierarchical ranking using the P-scoring method for frequentist NMA, with a high P-score indicative of a more preferable outcome.¹⁶ For the pooling of responder and remission rates, a proportional meta-analysis of sham-controlled and non-sham-controlled studies was performed using the inverse-variance method. Rates for each region were compared using Welch's two-sample t-test, adjusted for multiple comparisons using the Bonferroni correction. A superiority diagram was con-

Direct Comparisons***Pooled Analysis Comparison vs. Sham Stimulation******Indirect Comparisons******Pooled Analysis Comparisons vs. Other Regions*****FIG. 2.** Frequentist NMA for ROM comparison between brain regions. Figure is available in color online only.

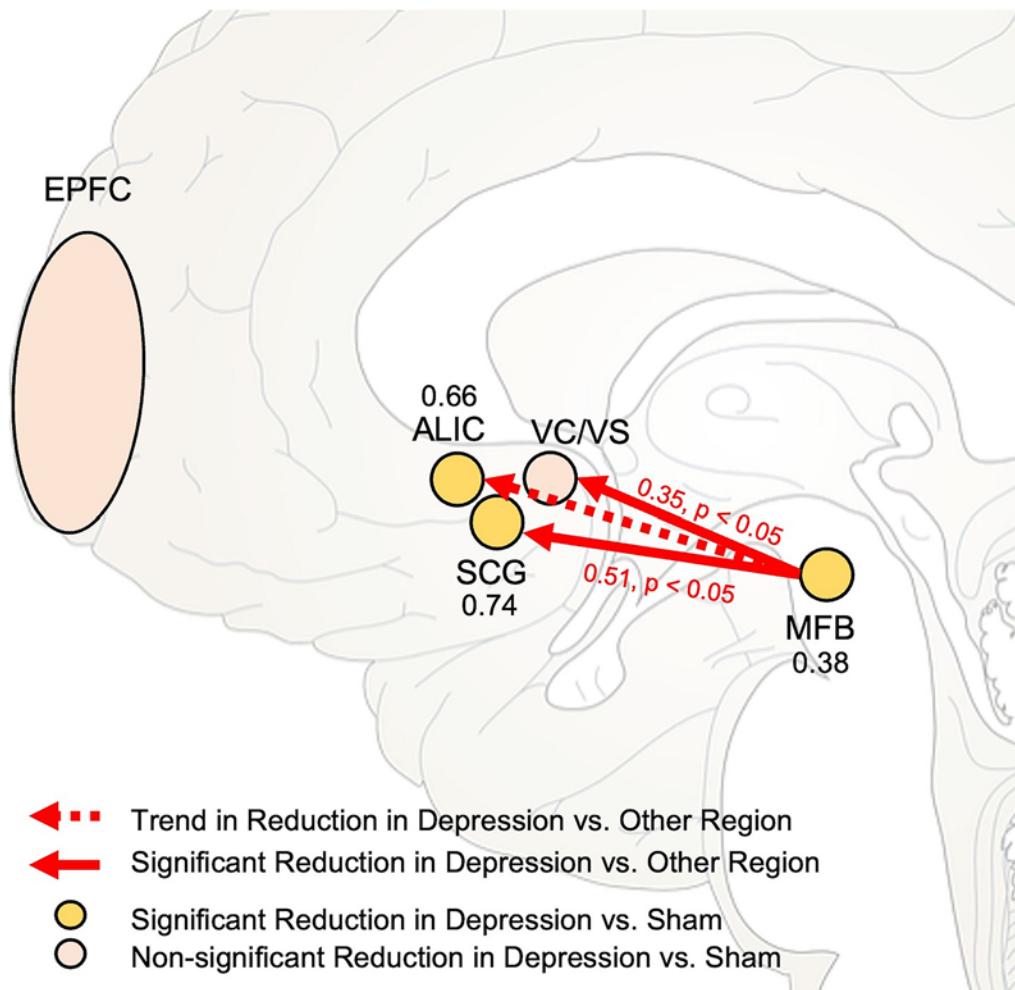


FIG. 3. Superiority diagram comparing regions of stimulation for reduction in depression. Figure is available in color online only.

structured to visualize comparative differences in stimulation by location.

Results

From an initial search yielding 1633 nonduplicate results, 130 full-length articles were examined against the predefined inclusion and exclusion criteria. Twenty-two trials, of which 15 were sham-controlled RCTs, were included in the final analysis (Fig. 1).^{17–37} Features of included studies have been expanded in Table 1, with a complete quality assessment of each sham-controlled RCT shown in the Supplementary Data. Across all studies, three trials evaluated the medial forebrain bundle (MFB), 11 studies evaluated the subcallosal cingulate gyrus (SCG), and 3 studies evaluated the anterior limb of the internal capsule (ALIC). Other trials evaluated regions such as the epidural prefrontal cortex (EPFC), ventral capsule/ventral striatum (VC/VS), and inferior thalamic peduncle (ITP) (Supplementary Data).

A frequentist NMA of trials for the main effect of the ROM in depression reduction was performed using a random-effects model. Pairwise comparisons versus sham and

other regions are shown in Fig. 2. MFB, ALIC, and SCG stimulation were found to be associated with significant reductions in depression compared with sham stimulation (ROM 0.38 [95% CI 0.23–0.64], 0.66 [95% CI 0.48–0.91], and 0.74 [95% CI 0.61–0.89], respectively), as depicted in the superiority diagram shown in Fig. 3. In aggregate, DBS produced a significant reduction in depression (ROM 0.70 [95% CI 0.56–0.86]). Indirect comparisons revealed the superiority of MFB stimulation compared with SCG stimulation (ROM 0.51 [95% CI 0.29–0.90]) and VC/VS stimulation (ROM 0.35 [95% CI 0.17–0.71]). Other indirect comparisons were found not to be statistically significant. Hierarchical ranking demonstrated the superiority of MFB stimulation (P -score = 0.9702), followed by SCG (P -score = 0.6392) and ALIC stimulation (P -score = 0.5816) (Fig. 4). A comparison of pooled poststimulation scales demonstrated similar findings (Tables 2 and 3). Egger's test did not demonstrate significant publication bias in the data (p = 0.816) (Supplementary Data).

A proportional meta-analysis for responder and remission rates for each brain region was performed. A superiority diagram is shown in Fig. 5. Stimulation of the MFB had the highest pooled responder rate (0.86 [95%

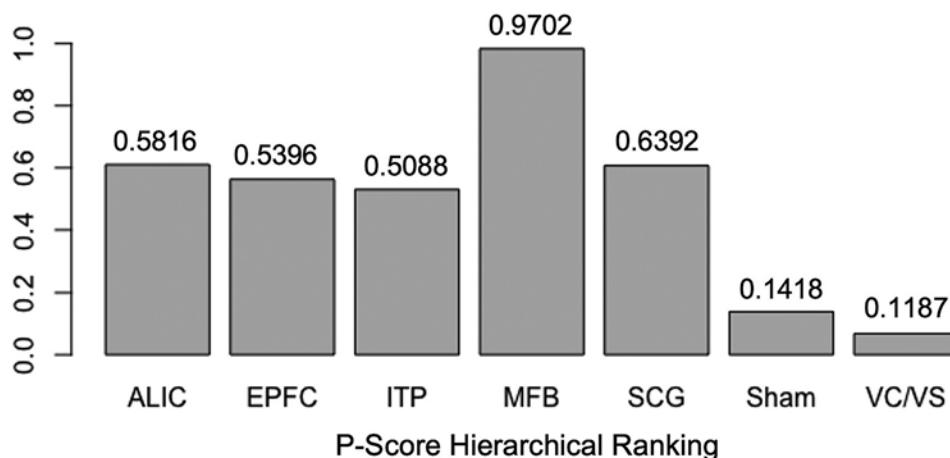


FIG. 4. P-score hierarchical ranking for ROM in depression reduction.

CI 0.64–0.95]), followed by the SCG (0.61 [95% CI 0.40–0.78]). MFB stimulation had a statistically greater pooled responder rate compared with ALIC and VC/VS stimulation ($p < 0.05$). Stimulation of the EPFC yielded the greatest remission rate (0.60 [95% CI 0.20–0.90]), followed by MFB stimulation (0.57 [95% CI 0.36–0.76]). No significant pairwise differences in remission rate were found among targeted regions.

Discussion

While various brain pathways and regions have been explored as targets for electrical neuromodulation in TRD, it is unknown whether a particular target is more effective than others. We performed a frequentist NMA and pooled proportional analysis to compare the reduction in depression and responder and remission rates for electric stimulation of different brain regions. In our study, we found that stimulation of the MFB was most effective for reduction of depressive symptoms, compared with stimulation of the VC/VS and SCG. Additionally, stimulation of the MFB had a superior responder rate compared with stimulation of the ALIC and VC/VS. While stimulation of the EPFC had the highest remission rate, these comparisons were not statistically significant when compared with other regions.

The MFB is a white matter pathway with efferent fi-

bers that project from the ventral tegmental area, anteriorly and superiorly to the nucleus accumbens, to arrive at the prefrontal cortex.³⁸ The ventral tegmental area is a major source of cortical and subcortical dopaminergic innervation and also contains descending fibers directed to the hypothalamus that are less likely to be activated when stimulating near the VTA itself.³⁹ DBS of the MFB is expected to influence dopaminergic neurons and modulate both the mesocortical and mesolimbic pathways that have been implicated in TRD.⁴⁰

Our meta-analysis found that stimulation of the MFB, SCG, and ALIC significantly reduced depression compared with sham, but stimulation of the SCG and ALIC was found not to demonstrate superiority compared with other structures as stimulation of the MFB had. This could be due to the neuroanatomical and functional relation of the SCG and ALIC as downstream structures to the MFB. Because the MFB projects through the SCG and ALIC,⁴¹ its influence is likely to be broader than stimulation at one of the downstream targets alone. This might be relevant to the observed superiority of this upstream target in this meta-analysis.

Stimulation of other structures such as the VS, ITP, and EPFC was not found to be as effective as stimulation of the MFB at reducing depression and did not display superiority over other structures. This could be due to these structures being further downstream from the MFB or influencing pathways related to depression that do not play as

TABLE 2. Pooled poststimulation data of all included studies

Stim Location	No. of Pts	Mean (95% CI)	
		Poststim MADRS	Poststim HAM-D
ALIC	40	19.74 (15.55–23.93)*	—
MFB	21	11.39 (7.24–15.53)*	—
VC/VS	31	23.89 (12.92–34.86)	—
SCG	134	24.73 (21.01–28.45)	13.83 (8.71–18.95)
ITP	5	17.60 (9.10–26.10)*	—
EPFC	10	14.60 (9.25–19.95)*	18.88 (14.04–23.72)
Sham	117	29.51 (26.34–32.68)	24.27 (17.72–30.81)

* Statistically significant from the sham group (t-test).

TABLE 3. Pooled poststimulation data of all included studies

Stim Location	No. of Pts	Pooled Responder Rate (95% CI)	Pooled Remission Rate (95% CI)
ALIC	40	0.45 (0.31–0.60)	0.25 (0.14–0.41)
MFB	21	0.86 (0.64–0.95)	0.57 (0.36–0.76)
VC/VS	31	0.32 (0.18–0.50)	0.19 (0.09–0.37)
SCG	134	0.61 (0.40–0.78)	0.27 (0.15–0.43)
ITP	5	0.60 (0.20–0.90)	0.40 (0.10–0.80)
EPFC	10	0.60 (0.20–0.90)	0.60 (0.20–0.90)

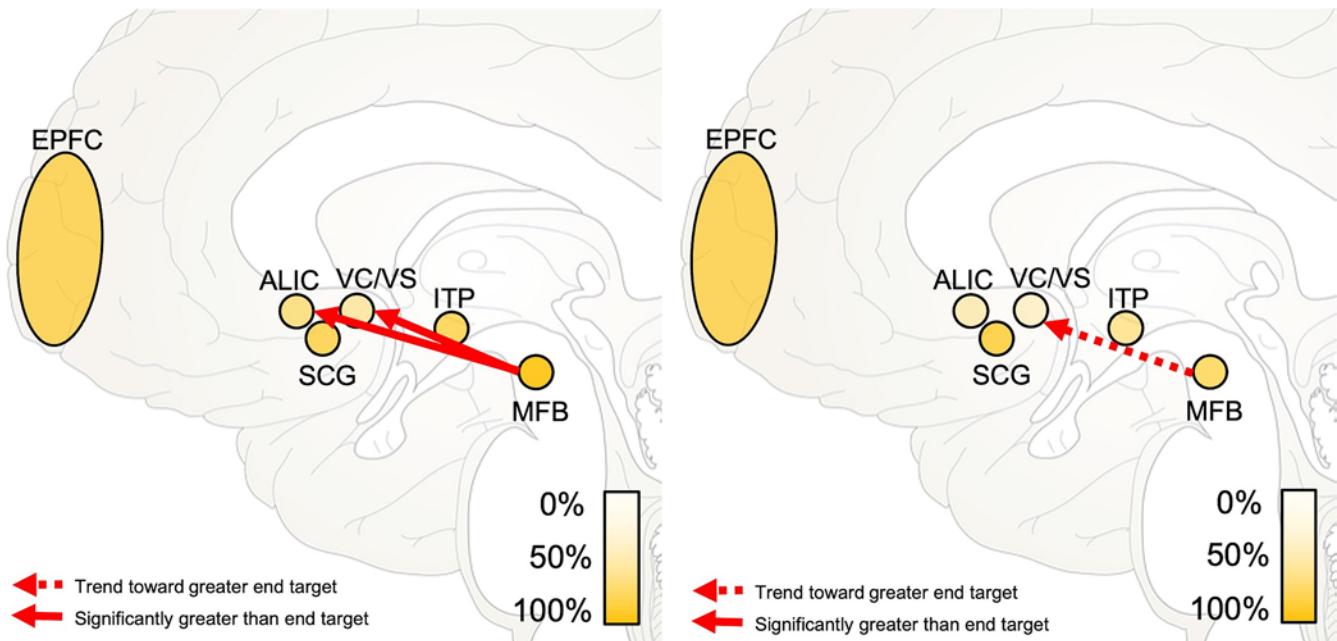


FIG. 5. Superiority diagram comparing regions of stimulation for responder rate (left) and remission rate (right). Figure is available in color online only.

significant a role. The VS is a ventral extension of the striatum and anatomically comprises the shell of the nucleus accumbens, white matter of the ventral ALIC, olfactory tubercle, anterior perforated substance, and medioventral portion of the caudate.⁴² DBS is hypothesized to improve TRD through modulation of neural processes related to emotion and motivation.

The ITP consists of bidirectional fibers that radiate from the pulvinar nucleus of the thalamus to the anterior temporal lobe and also contains fibers connecting nonspecific midline thalamic structures⁴³ to the orbitofrontal cortex. The underlying pathophysiology of depression in regard to the ITP is not fully understood; however, the orbitofrontal cortex connects directly and indirectly to several structures that play a role in mood and depression, including the ventral striatum, nucleus accumbens, and ventral tegmental area.⁴⁴ The EPFC was another target for neuromodulation and includes parts of the dorsolateral prefrontal cortex and frontopolar cortex.³⁵ The dorsolateral prefrontal and frontopolar cortices exhibit depression-related changes in activity and have been reported to exhibit hypoactivity on the left and hyperactivity on the right in patients with depression.^{45,46}

Strengths and Limitations

To our knowledge, this NMA is the first study to offer a comparative analysis of DBS efficacy for distinct stimulation targets in TRD. Previous meta-analyses examined the efficacy of DBS for TRD. However, our analytical design allowed us to examine how DBS at specific targets comparatively impacts TRD. Second, our analysis used ROM as the primary measure for depression reduction. There are several benefits of using ROM over other commonly used metrics such as standardized mean difference (SMD).

ROM represents a proportional change in the outcome of interest, allowing for greater clinical interpretability and as such is the preferred test when clinical interpretability is crucial. For example, an ROM value of 0.38 as was observed in the MFB versus sham stimulation comparison can be directly interpreted as the MFB stimulation treatment arm having a mean score that is 38% of sham stimulation. On the other hand, SMD standardizes the difference in means by dividing by the pooled standard deviation. This is beneficial in comparing studies with different clinical scales but makes direct clinical interpretation difficult. As such, the present study should assist providers in understanding the degree of improvement a cohort of patients undergoing specific target stimulation will receive relative to other targets. Additional benefits of using ROM over SMD include suitability for skewed data and avoiding concerns of data heterogeneity. Finally, our study is also the largest meta-analysis to date using high-quality studies, yielding potentially greater statistical power.

Despite these strengths, several important limitations must be noted. First, our analysis did not adjust for stimulation duration. Especially in crossover trials, stimulation duration and study duration were heterogeneous and difficult to factor into the analysis. This element of heterogeneity in study designs was minimized using a random-effects model for analysis. Despite this, because antidepressant effects of DBS can take time to develop, it is possible that some included studies were limited by this factor rather than by the stimulation target. The use of indirect-only (i.e., across-study) comparisons across brain regions also limits the ability of this meta-analysis to detect and precisely quantify relevant differences. Only one study in our analysis directly compared two DBS targets for TRD. All other comparisons were statistically inferred from the direct comparisons to sham stimulation.

This limitation was inherent to the literature available but suggests a greater need for head-to-head trials of different brain regions. Additionally, specific treatment arms observed larger confidence intervals. Although significance could have been reached in comparison with other targets, larger confidence intervals limit a clinician's ability to definitively determine the degree of clinical improvement patients are expected to observe. Furthermore, given the degree of interconnectedness in depression-modulating functional circuits, there could be some overlap in stimulation regions (for instance, ALIC and VC/VS, albeit defined as separate regions in the studies included in our analysis). Finally, sham stimulation was treated as a separate node in our network. This assumption was made for simplicity of the analysis but also is supported by some prior literature. A recent meta-analysis evaluating the reduction in symptomatology for obsessive-compulsive disorder found that sham stimulation in different regions produced a similar effect reduction. However, it is unknown whether this sham stimulation reduction is consistent in TRD and how sham stimulation changes depressive symptomatology.

Conclusions

In this study, we examined how particular neuroanatomical targets comparatively influenced DBS for TRD by pooling the outcomes of multiple RCTs using an NMA approach. We found that stimulation of the MFB yielded a statistically significant improvement in symptoms for patients over other regions. We additionally demonstrated how other regions might not provide a statistically significant benefit for patients with depression with DBS. Direct, within-study comparison of different DBS targets for TRD will be necessary to confirm these findings.

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Conception and design: Cramer, Park, Asaad. Acquisition of data: Saadah, Gangidi. Analysis and interpretation of data: Naik, Chu, Gupta, Gangidi, Cramer, Arnold. Drafting the article: Naik, Chu, Gupta, Saadah, Gangidi, Lee, Lauro, Cramer. Critically revising the article: Naik, Chu, Gupta, Lee, Lauro, Cramer, Park, Arnold. Reviewed submitted version of manuscript: Naik, Chu, Gupta, Gangidi, Lee, Lauro, Cramer, Park, Arnold. Approved the final version of the manuscript on behalf of all authors: Naik. Statistical analysis: Naik, Arnold. Administrative/technical/material support: Park. Study supervision: Cramer, Park, Asaad, Arnold.

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