Open-loop deep brain stimulation for the treatment of epilepsy: a systematic review of clinical outcomes over the past decade (2008–present)

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OBJECTIVE The field of deep brain stimulation (DBS) for epilepsy has grown tremendously since its inception in the 1970s and 1980s. The goal of this review is to identify and evaluate all studies published on the topic of open-loop DBS for epilepsy over the past decade (2008 to present).

METHODS A PubMed search was conducted to identify all articles reporting clinical outcomes of open-loop DBS for the treatment of epilepsy published since January 1, 2008. The following composite search terms were used: ("epilepsy" [MeSH] OR "seizures" [MeSH] OR "kindling, neurologic" [MeSH] OR epilep* OR seizure* OR convuls*) AND ("deep brain stimulation" [MeSH] OR "deep brain stimulation" OR "DBS") OR ("electric stimulation therapy" [MeSH] OR "electric stimulation therapy" OR "implantable neurostimulators" [MeSH]).

RESULTS The authors identified 41 studies that met the criteria for inclusion. The anterior nucleus of the thalamus, centromedian nucleus of the thalamus, and hippocampus were the most frequently evaluated targets. Among the 41 articles, 19 reported on stimulation of the anterior nucleus of the thalamus, 6 evaluated stimulation of the centromedian nucleus of the thalamus, and 9 evaluated stimulation of the hippocampus. The remaining 7 articles reported on the evaluation of alternative DBS targets, including the posterior hypothalamus, subthalamic nucleus, ventral intermediate nucleus of the thalamus, nucleus accumbens, caudal zone incerta, mammillothalamic tract, and fornix. The authors evaluated each study for overall epilepsy response rates as well as adverse events and other significant, nonepilepsy outcomes.

CONCLUSIONS Level I evidence supports the safety and efficacy of stimulating the anterior nucleus of the thalamus and the hippocampus for the treatment of medically refractory epilepsy. Level III and IV evidence supports stimulation of other targets for epilepsy. Ongoing research into the efficacy, adverse effects, and mechanisms of open-loop DBS continues to expand the knowledge supporting the use of these treatment modalities in patients with refractory epilepsy.

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KEYWORDS DBS; deep brain stimulation; epilepsy; seizures; Stimulation of the Anterior Nucleus of the Thalamus for Epilepsy (SANTE)

EPILEPSY affects around 50 million people worldwide;⁵⁸ it is estimated that 30% to 40% of these patients are medically refractory to treatment.^{26,27,41} It is well documented that uncontrolled seizures cause significant morbidity and mortality,⁴⁵ and while a large portion of these patients are candidates for surgical resection, a critical need exists for alternative treatment modalities for those who are not. In recent years, neurostimulation

for the treatment of medically refractory epilepsy has gained considerable interest among patients and providers.^{14,22,28,46,47}

Deep brain stimulation (DBS) for the treatment of medically refractory epilepsy was pioneered in the 1970s and 1980s, with early studies on the effects of cerebellar and anterior thalamic stimulation in patients with epilepsy.^{8,9,50} Since then, a growing body of literature has further sup-

ABBREVIATIONS ANT = anterior nucleus of the thalamus; CMT = centromedian nucleus of the thalamus; DBS = deep brain stimulation; HCP = hippocampus.

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FIG. 1. Flowchart depicting literature search keywords, methodology, and number of studies found for clinical outcomes of open-loop DBS for the treatment of epilepsy.

ported the safety and efficacy of established targets such as the anterior nucleus of the thalamus (ANT), while simultaneously exploring alternative targets such as the centromedian nucleus of the thalamus (CMT), and the hippocampus (HCP).^{6,24,25,35,52} This review focuses on studies of clinical outcomes of open-loop DBS published during the last 10 years.

Methods

Search Methodology

MEDLINE and PubMed inquiries of all studies reporting clinical outcomes of open-loop DBS since January 1, 2008, were performed (Fig. 1). Articles were included if they reported on at least one patient who underwent DBS for epilepsy and reported clinical outcomes. Articles were excluded if they reported nonclinical outcomes (i.e., electrographic or imaging findings), included nonhuman subjects, or were not published in English.

The following composite search terms were used: ("epilepsy" [MeSH] OR "seizures" [MeSH] OR "kindling, neurologic" [MeSH] OR epilep* OR seizure* OR convuls*) AND ("deep brain stimulation" [MeSH] OR "deep brain stimulation" OR "DBS") OR ("electric stimulation therapy" [MeSH] OR "electric stimulation therapy" OR "implantable neurostimulators" [MeSH]). The composite search term yielded 2134 articles. Of these, 536 articles were excluded because they were duplicates and 402 ar-

ticles were excluded because they did not deal with human subjects. Another 88 non-English language publications were excluded, yielding a total of 1108 articles for final review. A title and abstract review, followed by a full-text review of selected articles, was subsequently conducted to identify publications for final inclusion. We evaluated each study for overall epilepsy response rates as well as for adverse events and other significant nonepilepsy outcomes.

Results

Overall Findings

Of the 1108 articles identified in the literature search, 41 articles met the inclusion criteria of both 1) reporting clinical outcomes and 2) including at least one patient who underwent DBS for epilepsy. The remaining 1067 articles were excluded on the basis of not meeting one or both of these criteria. Results of all 41 studies are summarized in Table 1^{1–6,10–13,15–17,19,20,23–25,29–40,42,44,48,49,51–57} and the most frequently studied stimulation targets were the ANT (20 studies^{1,5,11,15,16,19,25,29,30,32,34,37–40,48,49,53–55}), the CMT (7 studies^{10,11,31,44,51–53}), and the HCP (10 studies^{3,4,11,12,13,20,33,35,36,56}). It is noteworthy that some articles evaluated multiple targets and are included more than once. The remaining 7 articles^{2,6,17,23,24,42,57} investigated alternative targets. The most relevant studies for ANT, CMT, and HCP are discussed in further detail in the following sections. As commonly defined in the literature, a clinical responder refers to a pa-

TABLE 1. Summary of literature review findings

Target/Authors & Year	Study Type	No. of Pts	Target	Stimulation Parameters	FU Duration	DBS Response Rate	Other Outcomes	Adverse Events
ANT								
Lim et al., 2008	CS	4	Bilat ANT	4–5 V; 90–110 Hz; 60–90 μ sec; continuous/ intermittent	2 yrs	50% (2/4)		1 pt developed asymptomatic hemorrhage; 1 pt developed erosion of extension wire through scalp, requiring surgical repair
Andrade et al., 2010	CS	1	ANT	Not described	9.5–10 yrs	50% (1/2)	No changes in behavior or cognitive status	None described
Fisher et al., 2010 (SANTÉ trial)	RCT	110	Bilat ANT	5 V; 145 Hz; 90 μ sec; intermittent (1 on, 5 off)	24 mos	53% (43/81)	Stimulated participants were more likely to report depression or memory impairment as adverse events during the blinded phase	12.7% of pts developed infections (7.3% stimulator pocket, 5.5% lead extensions, 1.8% bur hole), & 8.2% required removal of hardware; 8.2% of pts required lead repositioning; 4.5% of pts developed asymptomatic hemorrhage; 1 participant developed status epilepticus associated w/ stimulation
Lee et al., 2012	CS	15	Bilat ANT	1.5–3.1 V; 100–185 Hz; 90–150 μ sec; continuous	24–67 mos	87% (13/15)		1 pt developed wound infection requiring explantation
Oh et al., 2012	CS	9	Bilat ANT	1.5–3.1 V; 100–185 Hz; 90–150 μ sec; continuous	Mean 15.9 mos	78% (7/9)	Improved performance in verbal fluency tasks & delayed verbal memory after ANT DBS; improvement not correlated to Sz reduction. No significant changes in IQ, MMSE score, information processing, or executive function. No significant cognitive decline after DBS	None described
Penn et al., 2012	CR	1	Bilat ANT	Not described	10 mos	NA		Pt developed Twiddler syndrome, requiring revision of IPG & extension wires. After revision op, pt developed a wound infection requiring explantation
Hartikainen et al., 2014	CT	12	Bilat ANT	5 mA; 145 Hz; continuous	NA	NA	ANT DBS stimulation increased the frequency of commission errors & slowed reaction time in the presence of threat-related distractors	None described
Bucurenciu et al., 2015	CR	1	Bilat ANT	3–7.5 V; 145–180 Hz; 90–120 μ sec; intermittent (1 min on, 5 mins off to 20 sec on, 20 sec off)	11 mos	NA	Stimulation voltages >3 V were associated w/ subclinical Szs in the anterior & temporal regions	None described

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TABLE 1. Summary of literature review findings

Target/Authors & Year	Study Type	No. of Pts	Target	Stimulation Parameters	FU Duration	DBS Response Rate	Other Outcomes	Adverse Events
<i>ANT (continued)</i>								
Cukiert et al., 2015	CS	6	ANT	5 V; 130 Hz; 300 μ sec; continuous	Up to 6 mos after battery depletion	100% (9/9)	1 pt did not experience increased Sz frequency after battery depletion; 5 pts experienced increased Sz frequency after battery depletion, 3 of whom had lower Sz frequency than at pre-DBS baseline, while 2 returned to pre-DBS baseline	None described
Piacentino et al., 2015	CS	6	ANT	4 V; 140 Hz; 90 μ sec; not specified	24 mos	50% (3/6)	1 pt died 40 days postop due to a myocardial infarction (unrelated to op)	None described
Salanova et al., 2015 (SANTE study w/ 5-yr FU)	CS	74	Bilat ANT	Not described	5 yrs	69% (51/74)	Significant improvement in neuropsychological testing at 5 yrs, specifically in attention, executive function, depression, tension/anxiety, total mood disturbance, & subjective cognitive function. Significant improvement in QOL (QOLIE-31) at 5 yrs	Implant site infection in 12.7% of pts; 9 required full/partial system explantation. Lead not w/in target in 8.2% of pts
Van Gompel et al., 2015	CS	2	Bilat ANT (stimulation) + bilat HCP (recording)	4 V; 7–8 Hz; 90 μ sec; intermittent (0.4 on, 0.1 off) or continuous	12 wks	100% (2/2)		None described
Voges et al., 2015	CS	9	ANT	4 V; 145 Hz; 90 μ sec; intermittent (1 on, 5 off)	1–21 mos	44% (4/9)	2 pts excluded because of technical artifacts; remaining 7 pts demonstrated DBS-related arousal w/ maximal voltage. At 5 V, DBS-related arousal occurred w/ 14.0%–67.0% of all DBS stimuli. Reduction of DBS voltage to btwn 1 & 4 V led to decrease in DBS-related arousals to btwn 9.0% & 33.0% of all stimuli. Reduction of nocturnal DBS voltages resulted in no worsening of Sz frequency & incomplete/complete remission of neuropsychiatric symptoms	None described
Franco et al., 2016	CS	2	ANT	5 V; 145 Hz; 90 μ sec; continuous	12–18 mos	100% (2/2)	Both pts experienced new-onset or worsening depressive symptoms after ANT DBS	None described

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TABLE 1. Summary of literature review findings

Target/Authors & Year	Study Type	No. of Pts	Target	Stimulation Parameters	FU Duration	DBS Response Rate	Other Outcomes	Adverse Events
ANT (continued)								
Krishna et al., 2016	CS	16	ANT	2.4–7 V; >100 Hz; 90 μ sec; not specified	1–14 yrs (mean 4.3 $\pm$ 3.8)	69% (11/16)		1 pt developed a deep infection requiring explantation; 1 developed a superficial infection requiring wound revision; 1 experienced severe postop agitation requiring cessation of stimulation
Lehtimäki et al., 2016	CS	15	Bilat ANT	5 V; 140 Hz; 90 μ sec; intermittent (1 on, 5 off)	5 yrs	67% (10/15)		None described
Sweeney-Reed et al., 2016	CS	8	Unilat/ bilat ANT/ DMNT	Not described	6 mos	50% (4/8)		None described
Lee et al., 2017	CR	1	Bilat ANT	8 V; 145 Hz; 120 μ sec; continuous	45 days	NA	Immediate resolution of RSE after DBS placement & stimulation; 100% decrease in GTCS & "head nodding" events & 90% decrease in staring episodes & myoclonic jerks during FU	None described
Valentin et al., 2017	CS	1	Bilat ANT	Not described	12–48 mos	100% (1/1)	Pt w/ bilat ANT DBS developed increased aggression	None described
Tröster et al., 2017 (SANTE trial w/ 7-yr FU)	RCT	67	Bilat ANT	Not described	7 yrs	NA	Stimulated participants were more likely to report depression or memory impairment as adverse events, but no objective cognitive decline or worsening of depression was observed in this group during the blinded phase. No overall cognitive decline or worsening of depression scores was observed 7 yrs into the open-label period. Self-reported depression & memory impairment adverse events were not associated w/ reliable changes on objective neuropsychological measures or overall 7-yr neurobehavioral outcome	See Fisher et al., 2010 ¹⁵
CMT								
Cukiert et al., 2009	CS	4	Bilat CMT	2 V; 130 Hz; 300 μ sec; continuous	1–2 yrs	100% (4/4)	Clinically relevant increase in attention level in 4/4 pts after CMT DBS	None described

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TABLE 1. Summary of literature review findings

Target/Authors & Year	Study Type	No. of Pts	Target	Stimulation Parameters	FU Duration	DBS Response Rate	Other Outcomes	Adverse Events
CMT (continued)								
Valentin et al., 2012	CR	1	Bilat CMT	5 V; 6 Hz; 90 μ sec; continuous	6 mos	NA	Immediate resolution of tonic-clonic Sz's & epileptiform discharges after DBS placement & stimulation. Further resolution of myoclonic jerks 4 wks after initiation of DBS	Electrodes explanted at 6 mos due to infection
Cukiert et al., 2015	CS	2	CMT	5 V; 130 Hz; 300 μ sec; continuous	Up to 6 mos after battery depletion	100% (2/2)	1 pt did not experience increased Sz frequency after battery depletion; 1 pt experienced increased Sz frequency after battery depletion, but the frequency was lower than pre-DBS baseline	None described
Valentin et al., 2013	CT	11	Bilat CMT	5 V; 60–130 Hz; 90 μ sec; continuous	12–66 mos	64% (7/11)		1 pt required device explantation because of infection; 1 experienced transient agraphia immediately after implantation
Son et al., 2016	CS	14	Unilat/bilat CMT	2.2 ± 0.41 V; 129.3 $\pm$ 2.7 Hz; 124.4 $\pm$ 23.0 μ sec; continuous	9–25 mos	79% (11/14)	No correlation btwn calculated coordinates & percentage of Sz reduction	1 pt required lead repositioning
Lehtimäki et al., 2017	CR	1	Bilat CMT	7 V; 180 Hz; 150 μ sec; continuous	7 mos	NA	Resolution of RSE w/ high-frequency stimulation combined w/ S-ketamine infusion; RSE returned when stimulation switched from continuous to intermittent but resolved again w/ continuous stimulation; 2–4 focal Sz's per mo on continuous stimulation (baseline frequency not noted)	None described
Valentin et al., 2017	CS	2	Bilat CMT	Not described	12–48 mos	50% (1/2)		None described
HCP								
McLachlan et al., 2010	CT	2	Bilat HCP	0.5+ V; 185 Hz; 90 μ sec; continuous	12 mos	NA	Subjective memory improvement in 1 pt during stimulation period	None described
Boex et al., 2011	CS	8	Unilat/bilat HCP/AMG	0.5–2 V; 130 Hz; 450 μ sec; continuous	12–74 mos	75% (6/8)	Reversible memory impairments w/ high-voltage or quadripolar stimulation in 2 pts; otherwise, no significant neuropsychological outcomes	None described

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TABLE 1. Summary of literature review findings

Target/Authors & Year	Study Type	No. of Pts	Target	Stimulation Parameters	FU Duration	DBS Response Rate	Other Outcomes	Adverse Events
HCP (continued)								
Miatton et al., 2011	CS	10	Unilat/bilat HCP/AMG	1–2.5 V; 130 Hz; 450 µsec; continuous	6 mos	70% (7/10)	Pts w/ both unilat & bilat HCP/AMG DBS reported significantly fewer somatic complaints & feelings of insufficient mental/physical functioning. Unilat HCP/AMG DBS in dominant hemisphere was associated w/ significantly lower verbal IQ. No overall pattern of change in cognitive measures w/ DBS	None described
Bondallaz et al., 2013	CS	8	HCP	0.5–2 V; 130 Hz; 450 µsec; continuous	10–74 mos	75% (6/8)		1 pt required reimplantation of an electrode due to lead fracture
Vonck et al., 2013	CS	11	Unilat/bilat HCP/AMG	1–6 V; 130 Hz; 450 µsec; continuous +/- day/night cycling	67–120 mos	82% (9/11)		1 pt had asymptomatic intracranial hemorrhage; 1 pt required cable revision due to hardware failure; 1 pt required pulse generator removal due to local infection
Cukiert et al., 2014	CS	9	Unilat/bilat HCP	1–3.5 V; 130 Hz; 300 µsec; continuous	15–50 mos	78% (7/9)		1 pt required explantation due to infection related to trauma directly to the generator
Cukiert et al., 2015	CS	1	1	2 V; 130 Hz; 300 µsec; continuous	Up to 6 mos after battery depletion	100% (1/1)	Sz frequency increased after battery depletion but was lower than pre-DBS baseline	None described
Jin et al., 2016	CS	3	Bilat HCP	1–2.5 V; 130–170 Hz; 450 µsec; continuous	26–43 mos	100% (3/3)	No postop neuropsychological deterioration at 1 yr as measured by Wechsler Adult Intelligence Scale & Wechsler Memory Scale	None described
Lim et al., 2016	CS	5	Unilat/bilat HCP	Low frequency: 1–6 V; 3–5 Hz; 90–120 µsec; intermittent (1 on, 5 off)	30–42 mos	60% (3/5)		None described
Cukiert et al., 2017	RCT	16	Unilat/bilat HCP	2 V; 130 Hz; 300 µsec; continuous	8 mos	87.5% (7/8)		2 pts presented w/ local wound erosions & were treated successfully w/ antibiotics
Other								
Franzini et al., 2008	CS	4	Bilat pHyp (2), unilat Czi (2)	pHyp: 1.5–3.5 V; 185 Hz; 90 µsec; continuous	6 mos–5 yrs	75% (3/4)	2 pts who had significant behavior comorbidity before pHyp DBS experienced dramatic improvement in disruptive behavior	None described

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TABLE 1. Summary of literature review findings

Target/Authors & Year	Study Type	No. of Pts	Target	Stimulation Parameters	FU Duration	DBS Response Rate	Other Outcomes	Adverse Events
<i>Other (continued)</i>								
Wille et al., 2011	CS	5	Bilat SNr/ STN ± bilat VIM	1–4 V; 100–160 Hz; 60–120 µsec; continuous	12–42 mos	NA	Improvement in HRQoL in 4/5 pts, predominantly in overall, energy/fatigue, & emotional well-being domains	1 pt developed hardware failure due to unilat electrode dislocation
Capecci et al., 2012	CS	2	Bilat STN	2–3 V; 130 Hz; 60 µsec; continuous ± day/night cycling	12–48 mos	50% (1/2)	Both pts exhibited neuropsychological decline w/ DBS, including worsening attention, apathy, & mood changes. No improvement in functional status or QOL noted in either case	None described
Koubeissi et al., 2013	CS	11	Fornix	8 mA/phase; 5 Hz; 0.2 µsec; 4-hr sessions	48 hrs	NA	LFS of the fornix resulted in a significant increase in MMSE scores, mostly due to improvement in delayed recall scores	None described
Schmitt et al., 2014	CS	5	Bilat NAC + bilat ANT	5 V; 125 Hz; 90 µsec; intermittent (1 on, 5 off)	6 mos	40% (2/5)	No significant differences in neuropsychological measures at 6 mos; 1 pt experienced resolution of major depressive symptoms after NAC DBS & 2 pts developed new-onset generalized anxiety disorder after DBS	None described
Benedetti-Isaac et al., 2015	CS	5	Bilat pHyp	3 V; 185 Hz; 90 µsec; intermittent (1 on, 5 off)	2 mos–4 yrs (mean 2.83 yrs)	100% (5/5)		None described
Kowski et al., 2015	CT	4	Bilat NAC + bilat ANT	5 V; 125 Hz; 90 µsec; intermittent (1 on, 5 off)	15 mos	75% (3/4)		1 pt developed subcutaneous infection requiring explantation & reimplantation at a later date

AMG = amygdala; CR = case report; CS = case series; CT = crossover trial; CZI = caudal zone incerta; DMNT = dorsomedial nuclei of the thalamus; FU = follow-up; GTCS = generalized tonic-clonic seizure; HRQoL = health-related quality of life; IPG = implantable pulse generator; MMSE = Mini-Mental State Examination; NA = not available; NAC = nucleus accumbens; pHyp = posterior hypothalamus; Pt = patient; QOL = quality of life; QOLIE-31 = Quality of Life in Epilepsy Inventory-31; RCT = randomized controlled trial; RSE = refractory status epilepticus; SNr = substantia nigra pars reticulata; STN = subthalamic nucleus; Sz = seizure; VIM = ventral intermediate nucleus of the thalamus.

tient who experienced at least a 50% reduction in seizure frequency with DBS.

Anterior Nucleus of the Thalamus

Seizure Outcomes

Interest in ANT DBS for epilepsy has increased substantially since Kerrigan et al.²¹ published an open-label trial demonstrating its efficacy in 2004. Over the past decade, 20 studies have been published, reporting on 220 patients who underwent ANT DBS for the treatment of epilepsy.^{1,5,11,15,16,19,25,29,30,32,34,37–40,48,49,53–55} These studies have reported responder rates ranging from 44% to 100%. Patients from the largest series (n = 110) were reported to have median seizure reduction rates of 56% at 2 years¹⁵ and 69% at 5 years.⁴⁰ The Stimulation of the Anterior Nucleus of the Thalamus for Epilepsy (SANTE) trial was the first randomized controlled trial investigating ANT DBS for the treatment of intractable epilepsy. As described by Fisher et al.¹⁵ in 2010, a total of 110 patients underwent bilateral ANT DBS, of whom 109 were then randomized to receive stimulation or no stimulation during a 3-month blinded phase. Patients randomized to stimulation experienced a 29% greater reduction in seizures compared to the control group (p = 0.002); median declines at the end of the blinded phase were 40.4% and 14.5%, respectively. After the 3-month blinded phase, all patients received stimulation as part of an open-ended unblinded phase. At 2-year follow-up, the authors reported a median 56% reduction in seizure frequency, with a 54% response rate. Overall, 808 adverse events were documented during the first 13 months of follow-up, 55 of which were considered serious. Implant site infection developed in 14 participants (12.7%), 9 of whom required full or partial removal of the hardware. Five hemorrhages (4.5%) were detected incidentally on imaging, none of which were symptomatic. In 2015, Salanova et al.⁴⁰ published 5-year outcomes of the SANTE trial patients (n = 74) and found a median 69% reduction in seizure frequency, with 68% of patients classified as responders.

While the SANTE trial is the only randomized controlled trial on ANT DBS for epilepsy, several other studies have evaluated the safety and efficacy of this therapy. In 2008, Lim et al.³⁴ reported a mean 49.6% reduction in seizures with stimulation (range 35%–61%) at the 2-year follow-up for 4 patients. One patient achieved complete remission, and 2 other patients were responders, defined as a seizure reduction rate $\geq 60\%$. However, the complication rate was 50%. One patient developed a frontal hematoma and transient left-sided weakness, and a second patient developed extension lead erosion through the scalp that ultimately required removal of the entire DBS system. In 2012, Lee et al.³⁰ monitored 15 patients for an average of 27 months and noted a mean 70.4% reduction in seizure frequency; 13 of the 15 patients (87%) experienced $> 50\%$ reduction in seizures. The authors reported that only one major adverse event occurred in a patient who developed a wound infection requiring system explantation.

In 2015, Cukiert et al.¹¹ studied the effects of battery depletion on seizure frequency in 6 patients treated with ANT DBS for intractable epilepsy. They demonstrated that when battery depletion occurred after 3 years of continu-

ous ANT DBS, 5 patients experienced increased seizure frequency and 1 did not. Of the 5 patients who experienced an increase in seizure frequency after battery depletion, 3 patients still had a lower seizure rate than they did at their pre-DBS baseline, whereas 2 patients returned to their pre-DBS baseline seizure rate. The authors posited that, in those patients who did not experience a full return to pre-DBS baseline seizure frequency, some degree of network neuromodulation may have occurred with prolonged continuous DBS.

Neuropsychological and Cognitive Outcomes

Although patients enrolled in the SANTE trial exhibited no objective differences in neuropsychological testing for cognition or mood during the blinded phase of the study, significantly more patients reported subjective adverse events related to depression (p = 0.02) and memory impairment (p = 0.03).¹⁵ Gradual improvement in neuropsychological outcomes was noted at the 5-year follow-up, specifically in attention, executive function, depression, tension/anxiety, total mood disturbance, and subjective cognitive function.⁴⁰ At 7-year follow-up, Tröster et al.⁴⁹ noted that no patients (n = 67) experienced significant worsening of cognition or depression on objective testing. Patients achieved significantly higher scores on objective measures of executive function and attention. They also noted that self-reported depression and memory-related adverse events were not associated with declines in neuropsychiatric testing.

In 2012, Oh et al.³⁷ reported 12-month cognitive and behavioral outcomes after bilateral ANT DBS for epilepsy in 9 patients. They found significant improvements in verbal fluency tasks (p < 0.05) and delayed verbal memory (p = 0.017) but saw no overall change in general measures of intelligence, information processing, and executive functioning. There was also no evidence of significant cognitive decline 1 year after ANT DBS. They postulated that cognition may have improved directly through stimulation of the medial temporal structures via the Papez circuit and indirectly through reductions in seizure frequency and antiepileptic drug use.

In 2014, Hartikainen et al.¹⁹ studied the effects of threat-related emotional distractors and rule switching in 12 patients using a computer-based executive function test and found that stimulation increased commission error frequency and slowed participant reaction times in the presence of threat- or emotion-related distractors. They speculated that ANT DBS affected response inhibition and emotional reactivity modulation through indirect stimulation of limbic structures such as the nucleus accumbens and orbitomedial prefrontal cortex via the Papez circuit.

Surgical Considerations

As ANT DBS has become an increasingly accepted therapy for epilepsy, interest has focused on refining targeting and patient selection. Van Gompel et al.⁵⁴ recently reported on 2 such novel targeting techniques. First, electrodes were placed along a posterior inferior parietal route, to avoid intraventricular hemorrhage and lead misplacement associated with transventricular and lateral transcortical approaches. Second, they used recordings from

concomitantly placed hippocampal electrodes to verify accurate lead placement. Both patients in this series experienced > 50% reduction in seizures over a 3-month follow-up period, and no adverse events, including lead misplacement, were reported.

Piacentino et al.³⁹ classified 6 patients based on preoperative imaging and continuous video electroencephalography, and they demonstrated that ANT DBS was most effective in patients with epileptic origins strictly in the limbic system who had no discrete anatomical lesions. Lehtimäki et al.³² analyzed the placement of 62 contacts in 15 patients, 10 of whom were responders. Using an ANT-normalized coordinate system, they found that contacts in responders were placed significantly more anteriorly and superiorly than they were in nonresponders. They hypothesized that the white matter structures at the inferior and posterior aspects of the ANT prevented the spread of stimulation current into the ANT, which limited the utility of electrodes placed in that region. Krishna et al.²⁵ found similar results, noting that patients with the most long-term stimulation benefit had electrodes placed in the anteroventral ANT in close proximity to the mammillothalamic tract.

Centromedian Nucleus of the Thalamus

Seven studies over the past decade have investigated the use of CMT DBS for the treatment of epilepsy in 35 patients.^{10,11,31,44,51–53} Treatment response rates range from 50% to 100%, depending on the study and the type of epilepsy being treated. The largest series, published by Son et al. in 2016,⁴⁴ reported a 79% response rate (11 of 14 patients), with a mean seizure frequency reduction of 68%. They did not find any correlation between lead positioning and the magnitude of seizure reduction on regression analysis.

In 2009, Cukiert et al.¹⁰ evaluated the use of CMT DBS for refractory generalized epilepsy in 4 patients who previously underwent corpus callosotomies. At 1 to 2 years of follow-up, seizure reduction rates ranged from 65% to 95%. No significant morbidity or mortality was reported other than transient contralateral paresthesia. Valentín and colleagues⁵¹ published results from a single-blinded, non-randomized, crossover trial of 11 patients with generalized or frontal epilepsy who were treated with bilateral CMT DBS in which they found that CMT DBS was more effective in treating generalized epilepsy than frontal lobe epilepsy. In this study, 40% (2/5) of patients with frontal lobe epilepsy and 83% (5/6) of patients with generalized epilepsy responded to DBS therapy, for a total overall response rate of 64% (7/11).

Two case reports of CMT DBS used in patients with status epilepticus have been published. In 2012, Valentín et al.⁵² described the successful use of CMT DBS to treat a 27-year-old patient with 5-week history of refractory status epilepticus. Electroencephalography findings were consistent with resolution of status epilepticus on initiation of low-frequency 6-Hz CMT DBS. The patient developed a wound infection 6 months postprocedure and required device explantation; however, symptoms reportedly did not recur. In 2017, Lehtimäki et al.³¹ reported the case of a 17-year-old male patient with refractory status

epilepticus thought to be secondary to common variable immunodeficiency-associated encephalomyelitis. Bilateral high-frequency 180-Hz DBS, coupled with a continuous S-ketamine infusion, proved effective in terminating the status epilepticus. However, all attempts to wean the patient from continuous to intermittent stimulation resulted in relapse.

Hippocampus

Over the past decade, 10 studies have been published on the use of HCP DBS for the treatment of epilepsy in 73 patients.^{3,4,11,12,13,20,33,35,36,56} The reported response rates have ranged from 60% to 100%.

In 2014, Cukiert and colleagues¹² published the results of a prospective study investigating the effects of unilateral or bilateral HCP DBS in 9 consecutive patients with refractory temporal lobe epilepsy (TLE). At a mean follow-up of 30.1 months, 2 of 2 patients with unilateral temporal lobe sclerosis responded to unilateral DBS therapy, with a mean reduction in seizure frequency of 78%. Three of 4 patients with bilateral mesial temporal lobe sclerosis responded to unilateral stimulation, whereas 1 patient did not respond even when advanced to bilateral stimulation; these patients experienced a mean reduction in seizure frequency of 63%. Similarly, 2 of 3 patients with normal MRI results responded to unilateral DBS therapy, whereas 1 did not respond to both unilateral and bilateral stimulation; these patients experienced a mean reduction in seizure frequency of 58%. One patient in the study developed a wound infection related to a direct impact to the stimulator and subsequently required device explantation; otherwise, no adverse events were reported. Cukiert and colleagues¹³ then reported in 2017 on the results of a prospective, double-blind, randomized controlled trial evaluating the efficacy of unilateral and bilateral HCP DBS in 16 patients with refractory TLE. Two months after surgery, all patients were randomized to stimulation on or off for a 6-month blinded period. The authors reported that, of the 8 patients randomized to the on-stimulation group, 4 became seizure free and 7 were defined as responders, whereas 1 patient did not respond to DBS therapy. The investigators further noted that the experimental group experienced significantly fewer simple partial and complex partial seizures than the control group throughout the blinded period. Two patients with superficial wound infections were successfully treated with antibiotics, and no other complications were noted.

Vonck et al.⁵⁶ reported on 11 patients who underwent bilateral HCP DBS electrode implantation, with stimulation laterality applied based on seizure localization. After 2.5–3 years of follow-up, patients who were initially started on unilateral stimulation were converted to bilateral stimulation if seizure reduction of > 90% had not been achieved. At final follow-up, and after switching to bilateral stimulation as necessary, 6 patients achieved ≥ 90% seizure reduction, 3 patients achieved seizure reduction rates ranging from 40% to 70%, and 2 patients achieved < 30% seizure reduction. Importantly, the authors found that switching from unilateral to bilateral stimulation further improved seizure outcomes in 3 of 5 patients with unilateral ictal onset. Implementing day-night cycling after attaining treat-

ment stability did not affect seizure control, and no changes in neuropsychological testing were noted after DBS therapy. One patient developed an asymptomatic intracranial hemorrhage diagnosed incidentally on imaging, 1 patient required cable revision because of hardware failure, and 1 patient developed a wound infection requiring system explantation; otherwise, no serious adverse events were reported.

Discussion

The role of neuromodulation for the treatment of epilepsy has expanded over the past decade. Vagal nerve stimulation and responsive neurostimulation are approved therapies for epilepsy in the US, and DBS is available in Canada and Europe. To date, the most thoroughly investigated targets in DBS for epilepsy are the ANT, CMT, and HCP, with responder rates of 44%–100%, 50%–100%, and 60%–100%, respectively. Other alternative targets have demonstrated varying degrees of success. Level I evidence from the SANTE trial demonstrates that response rates and seizure-freedom rates of 53% and 13%, respectively, can be achieved with ANT stimulation (2 years after stimulation),¹⁵ with complication rates comparable to those of other large DBS series for movement disorders.^{7,18,43} In contrast to many neuromodulation studies for other non-movement disorder indications, long-term follow-up data are available for this cohort of patients, which supports the safety durability of the therapy over time. Five years after stimulation initiation, a 69% DBS response rate was achieved^{40,49} and no deleterious effects on neuropsychological outcomes were documented.^{40,49} It must be noted, however, that long-term follow-up was obtained only for 74 of the original 110 patients. Additional nonrandomized studies have demonstrated a 44% to 100% seizure response rate.^{1,5,11,16,19,25,29,30,32,34,37–39,48,54,55} Recent innovations in implantation technique, such as the posterior inferior parietal electrode trajectory and concomitant hippocampal electrode placement, warrant additional research and consideration for widespread implementation.^{25,32,54}

CMT DBS has also demonstrated promising results in the treatment of patients with generalized epilepsy.^{10,51} Some studies suggest that patients with generalized epilepsy respond better to CMT DBS than patients with frontal lobe epilepsy; however, the data are still conflicting, and more research is needed to determine whether this is true.^{10,51,53} Overall, most evidence for CMT DBS has come from Level III and IV studies.^{10,51} Studies with higher levels of evidence and with larger patient cohorts and longer follow-up are necessary to determine whether CMT is truly effective in treating the target indications.

Evidence is conflicting in reports on a small number of patients regarding the efficacy of HCP DBS for epilepsy. Response rates range from 78% to 100%, depending on epilepsy etiology,^{12,13,20} and a recently published randomized controlled trial of 16 patients demonstrated that patients who received HCP DBS experienced significantly fewer seizures than controls.¹³ However, data from a crossover study published by McLachlan et al.³⁵ suggested that HCP DBS was clinically ineffective at treating seizures in 2 patients who had refractory TLE. Recent advances in

surgical approaches, including the use of bilateral stimulation in patients with unilateral TLE and the optimization of targeting parameters,^{4,56} warrant further clinical study to determine whether outcomes are improved with these modifications. Investigation of other targets, such as the posterior hypothalamus, nucleus accumbens, and subthalamic nucleus or substantia nigra pars reticulata, is based on small case series and reports and is still in very early and preliminary phases. No definitive conclusions can currently be drawn regarding the efficacy of these targets in treating epilepsy.

Despite the enormous amount of research that has been conducted on DBS for the treatment of epilepsy, countless avenues of inquiry remain open for further investigation. For example, a great deal of uncertainty remains about the efficacy of many of the obscure targets, such as the subthalamic nucleus, nucleus accumbens, and posterior hypothalamus. More data on patient outcomes after DBS of these targets, even in the form of nonrandomized, retrospective case series, may provide more information about whether continued pursuit of these targets is worthwhile. For targets for which outcomes are well defined, such as the ANT, future research may focus on further refining patient selection, targeting, and stimulation parameters, in a manner similar to that in studies conducted by Voges et al.,⁵⁵ Van Gompel et al.,⁵⁴ and Lehtimäki et al.³² Finally, although high-quality, nonrandomized, prospective evidence exists to support the efficacy of CMT DBS for epilepsy, a well-powered, randomized controlled trial is still necessary to establish the clinical efficacy of this target.

Conclusions

The investigation of DBS for the treatment of refractory epilepsy has seen substantial growth and progress in the past decade. Level I evidence supports the efficacy of ANT DBS to treat patients with refractory epilepsy, which has demonstrated continued therapeutic success up to 7 years after surgery. Investigators continue to gather supporting evidence for the safety and efficacy over time of CMT and HCP as stimulation targets, and additional evidence and further study are required for newer targets, such as the nucleus accumbens and posterior hypothalamus, before they are considered for broader therapeutic use.

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Disclosures

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author Contributions

Conception and design: Ponce, Zhou, Chen, Shetter. Acquisition of data: Zhou, Farber. Analysis and interpretation of data: Zhou, Farber. Drafting the article: Zhou, Farber. Critically revising the article: Ponce, Zhou, Chen, Shetter. Reviewed submitted version of manuscript: Ponce, Zhou, Shetter. Statistical analysis: Zhou. Administrative/technical/material support: Zhou. Study supervision: Ponce, Shetter.

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