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**Title of manuscript:** DEEP BRAIN STIMULATION FOR DRUG-RESISTANT EPILEPSY

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**Summary and key words**

OBJECTIVES: To review clinical evidence on the anti-epileptic effects of deep brain stimulation (DBS) for drug-resistant epilepsy, its safety, and factors influencing individual outcomes.

METHODS: A comprehensive search of the medical literature (PubMed, Medline) was conducted to identify relevant articles investigating DBS therapy for drug-resistant epilepsy. Reference lists of these articles were used to source further articles.

RESULTS: Stimulation of the anterior nucleus of the thalamus (ANT) and hippocampus (HC) has been shown to decrease the frequency of refractory seizures. Half of all patients from clinical studies experienced a 46 – 90% seizure reduction with ANT-DBS, and a 48 – 95% seizure reduction with HC-DBS. The efficacy of stimulating other targets remains inconclusive due to lack of evidence. Approximately three-quarters of patients receiving ANT, HC or centromedian nucleus of the thalamus (CMT) stimulation are responders – experiencing a seizure reduction of at least 50%. Time course of clinical benefit varies dramatically, with both an initial lesional effect and ongoing stimulation effect at play. Improved quality of life and changes to cognition or mood may also occur. Side effects are similar in nature to those reported from DBS therapy for movement disorders. Several factors are potentially associated with stimulation efficacy, including an absence of structural abnormality on imaging for ANT and HC stimulation, and electrode position relative to the target. Certain seizure types or syndromes may respond more favorably to specific targets, including ANT stimulation for deep temporal or limbic seizures, and CMT stimulation for generalized seizures and Lennox-Gastaut syndrome.

SIGNIFICANCE: We have identified several patient, disease, and stimulation factors which potentially predict seizure outcome following DBS. More large-scale clinical trials are needed to explore different stimulation parameters, re-evaluate the indications for DBS, and identify robust predictors of patient response.

KEY WORDS: refractory, intractable, seizures, efficacy, predictors

**OUTLINE**

1. INTRODUCTION

## 1. INTRODUCTION

Approximately 50 million people have epilepsy worldwide, of whom more than 20% suffer from drug-resistant epilepsy.[1] The International League Against Epilepsy proposed that drug-resistant epilepsy be defined as a failure of adequate trials of at least two anti-epileptic drugs which are appropriately chosen, used and tolerated.[2] People with refractory seizures carry a great burden of disability, with poor quality of life as well as increased morbidity and mortality. The first-line treatment for drug-resistant epilepsy is resective surgery. However, when surgery is contraindicated or ineffective, deep brain stimulation (DBS) has emerged as an important treatment option, along with other neurostimulation therapies including vagal nerve stimulation (VNS) and responsive neurostimulation (RNS).

Deep brain stimulation involves the delivery of a pre-determined (open-loop) program of electrical stimulation to deep brain structures via implanted electrodes connected to a pulse generator. Following a recent clinical trial,[3] DBS of the anterior nucleus of the thalamus (ANT) has been approved for the treatment of refractory epilepsy in Europe, Canada and Australia.[4] DBS is also used therapeutically in movement disorders such as Parkinson's disease, essential tremor and dystonia, and has shown potential in treating neuropsychiatric disorders such as depression and obsessive-compulsive disorder.[5]

The anti-epileptic effects of DBS were first studied in the 1970s and 80s,[6–8] yet the current evidence base remains modest with only one large-scale randomized controlled trial (RCT) of ANT stimulation – the SANTE trial.[3] Promising though variable anti-epileptic effects have been observed from smaller studies of stimulation targets including thalamic nuclei, the hippocampus, and the cerebellum. Most

significantly, it remains a mystery why some epileptic patients respond well to DBS but others do not, and the exact mechanisms by which DBS ameliorates seizures are also poorly understood.

Currently, a clinician may consider DBS for patients with drug-resistant epilepsy when they have failed reasonable attempts at anti-epileptic drugs and are unsuitable for surgery. Reasons for surgical contraindication include bilateral or widespread seizure activity, proximity of ictal zone to important functional areas, and lack of anatomical abnormality on imaging. Appropriateness of DBS therapy also depends on other factors, including failure or contraindication to other neurostimulation therapies, and the lower surgical risk of electrode implantation compared with resective surgery.[9–11]

Although DBS for drug-resistant epilepsy is prescribed with palliative rather than curative intent, better epileptic control may lead to improvements in quality of life, independence, and cognition.[3,9,12] Seizure reductions may also allow the tapering of anti-epileptic drugs, reducing medication side effects.[13–15] Surgical and stimulation-related adverse effects are similar to those observed from DBS for movement disorders.[4] However, more large-scale clinical trials are needed, especially investigation of factors which might predict or improve individual patient responses to DBS.

This review focuses on clinical studies investigating DBS in patients with drug-resistant epilepsy. Results are organized by DBS target, with emphasis on controlled clinical trials over less rigorous open-label studies. Safety data is also reviewed, followed by discussion of DBS efficacy and factors which may influence this.

## 2. CLINICAL STUDIES ON DBS FOR DRUG-RESISTANT EPILEPSY

We identified 10 RCTs and 48 non-controlled studies investigating DBS for drug-resistant epilepsy. Seizure outcomes from RCTs are shown in Table 1. Study characteristics and primary outcomes are summarized in Table 2 (ANT), Table 3 (Hippocampus), Table 4 (Centromedian nucleus of thalamus), Table 5 (Cerebellum), and Supplementary Table 1 (Other targets). Other notable observations from non-controlled studies are listed in Supplementary Table 2.

### i. Anterior nucleus of the thalamus (ANT)

As part of the medial limbic (Papez) circuit, the ANT connects to the hippocampus via the mammillo-thalamic tract and fornix, before projecting to the cingulate cortex and neocortex. Given this circuit is thought to be involved in emotional processing and seizure propagation, high frequency ANT stimulation may inhibit the spread of focal seizures to cortical areas.[4,10,11,16,17] Current evidence for ANT-DBS includes one large-scale RCT[3,18] and 16 non-controlled studies[8,9,19–33] (Table 2).

*Controlled clinical trials*

In 2010, the landmark SANTE (Stimulation of Anterior Nucleus of Thalamus for Epilepsy) trial was published. This was a multi-center RCT where 110 adult patients suffering refractory focal seizures with

or without bilateral spread received DBS of the ANT.[3]After the three-month blinded phase, seizure frequencies fell by a median of 40% in the stimulation group versus 15% for controls when compared with baseline. The stimulated group were also more likely to report subjective depression and memory impairment. Interestingly, seizures were reduced by around 22% in both groups during the one month post-implantation pre-stimulation phase, perhaps reflecting a "lesional effect" – an immediate seizure reduction caused by lesioning of neural tissue from electrode implantation.[3]

All participants then received unblinded DBS therapy for long-term follow-up, which revealed ongoing and progressive seizure improvement with a median seizure frequency reduction of 69% after five years. 68% of patients achieved seizure reductions of at least 50%, and there were significant improvements in seizure severity and quality of life scores across the cohort.[3,18]

Subgroup analysis showed that treatment efficacy varied with the region of seizure origin. Temporal onset epilepsies were more responsive, with a 44.2% improvement with stimulation during the blinded phase compared with 40% for the whole stimulation group. Similarly, after five years, patients with temporal seizure onset experienced a 76% improvement, compared with 59% for frontal epilepsies and 68% for other locations.[3,18] The adverse effects from this trial will be discussed later.

*Non-controlled studies*

See Table 2.

ii. Hippocampus (HC)

The hippocampus is an attractive target for DBS given its role in the Papez circuit. Hippocampal stimulation may directly attenuate (at low frequencies) or interrupt (at high frequencies) epileptic activity originating from the medial temporal region – the origin of most focal impaired awareness seizures.[4,10,16,17] Thus, researchers have empirically trialed HC-DBS exclusively in patients with medial temporal lobe epilepsy (MTLE), some with MRI evidence of medial temporal (hippocampal) sclerosis. Current evidence includes four RCTs (one trialing RNS),[34–38] and nine non-controlled studies[13,14,39–47] (Table 3).

*Controlled clinical trials*

In 2006, Tellez-Zenteno and colleagues conducted a double-blind, multiple cross-over RCT involving four patients with refractory MTLE suffering at least four seizures per month. A 15% (-13 to 47%) median seizure reduction was reported when comparing stimulation directly with sham stimulation, though this was not statistically significant. Possible explanations include attenuation of stimulation effect due to changes to anti-epileptic drugs, treatment and washout periods being too short to detect a full effect, and small sample size. Additionally, HC stimulation did not modify the severity, impact or symptoms of seizures, nor improve quality of life or depression measures.[34]

Velasco's month-long double-blind randomized trial in 2007 on nine refractory MTLE patients found that seizure frequencies decreased by a median of 40% in the stimulation group versus 0% in the control group (values estimated from graphs). All patients achieved seizure reductions of at least 50% during unblinded follow-up. Notably, patients with a normal MRI experienced a faster and more significant seizure decrease compared to patients with hippocampal sclerosis – 99% versus 63% respectively at 18 months. Neuropsychological outcomes trended towards improvement, with no memory decline attributed to hippocampal implantation and stimulation.[35,36]

In another double-blind, cross-over randomized trial, stimulation reduced seizures in two MTLE patients by an average of 33%.[37] The modest response was attributed to shorter follow-up, and selection bias (e.g. pre-selection of patients based on positive responses to earlier trial stimulation).[41] The patient with a normal MRI responded better than the patient with medial temporal sclerosis, supporting Velasco's earlier observations.[35,36] However, findings from this trial are limited by its small sample size.[37]

These three RCTs all concur that HC stimulation decreases seizures, though sample sizes were small, and there was between-study variability in the placebo effect (Table 1).[34–37] The trial with the largest sample size (N=9) did not report values from its blinded phase directly, nor their clinical significance.[35,36] Thus, larger well-designed trials may be required to prove clinical efficacy.

It is worth noting a recent multi-centre RCT (N=191) which demonstrated that RNS of seizure foci (HC or otherwise) is efficacious for refractory epilepsy.[38] RNS employs a closed-loop paradigm where stimulation is delivered only in response to epileptiform activity, as opposed to scheduled (open-loop) DBS. Seizures were decreased by 38% in treated individuals versus 17% among the sham group during the 3-month blinded phase,[38] with a subsequent reduction of 53% after two years of open-label stimulation.[48] Notably, comparable results were observed among the subset of MTLE patients (N=95), further supporting the therapeutic value of HC stimulation.[38,48]

*Non-controlled studies*

See Table 3.

iii. Centromedian nucleus of the thalamus (CMT)

The CMT is connected to the ascending reticular system, with wide projections to cortical regions (especially frontal), insula, and basal ganglia. CMT stimulation may desynchronize and inhibit electrical conduction through these pathways, potentially interrupting or decreasing the risk of seizure activity.[10,16,17] Current evidence consists of two small RCTs[49,50] and seven non-controlled studies[12,22,32,51–54] involving patients with refractory epilepsy, some of whom suffer from, or have characteristics of Lennox-Gastaut syndrome – a childhood epilepsy featuring tonic and atonic seizures (Table 4).

*Controlled clinical trials*

In 1992, Fisher and colleagues published the results of a double-blind cross-over study involving seven patients with focal and generalized epilepsy, of which two had Lennox-Gastaut syndrome. Though seizures were reduced by 30% with stimulation compared with 8% for sham stimulation, these results did not reach significance.[49].

Velasco's group also found that CMT stimulation did not significantly reduce the frequency of total seizures or specific seizure types. However, EEGs revealed a significant decrease in generalized spike-wave and secondary synchronous discharges, and focal spikes from frontal areas. Long-term unblinded stimulation was more efficacious in patients with Lennox-Gastaut syndrome, with an average 81.6% seizure reduction versus 57.3% for patients with primarily focal epilepsies. Additionally, better outcomes were associated with radiological and electrophysiological confirmation of correct electrode placement on at least one side.[50]

Both RCTs failed to produce evidence in support of CMT stimulation for refractory seizures, although Velasco's trial revealed better long-term responses in patients with Lennox-Gastaut syndrome.[50]

*Non-controlled studies*

See Table 4.

iv. Cerebellum (CB)

Low or high frequency stimulation of the CB is thought to activate inhibitory outputs of the superomedial cerebellar cortex, regulating electrical activity within motor cortical and amygdalo-hippocampal regions.[16,17] Current evidence includes two small RCTs[55,56] and six open-label studies involving patients with refractory focal and generalized seizures[6,7,52,57–59] (Table 4).

*Controlled clinical trials*

Wright's 1984 trial found that CB stimulation did not ameliorate seizures among nine patients with quantifiable results. Although the authors note that 11 of their 12 patients thought "the trial had helped them", these subjective statements cannot be validated.[55]

A more recent RCT by Velasco's group in 2005 treated five epileptic patients with bilateral superomedial CB-DBS. Compared to baseline, a 67% mean seizure reduction with stimulation versus 7% without stimulation was observed during the blinded period. These benefits carried over into the long-term, with a 76% reduction in generalized tonic-clonic seizures, and a 57% reduction in tonic seizures.[56]

Notably, the findings from these two RCTs are discordant, which could have several explanations. Wright's trial added some observer-recorded major seizures to patient seizure diaries, after noting that patients were less likely to record major seizures than minor seizures, and vice versa for observers.[55] Given that three patients were also excluded from analysis due to incomplete records or unquantifiable seizures, Wright's results may be affected by the unreliable nature of seizure records[60] – to be discussed

later. Though Velasco's trial was more stringent, using a parallel rather than cross-over protocol, the effect of selection bias cannot be excluded as there were only five patients (3 treated, 2 control).[56] Due to these limitations, the benefits of CB stimulation remain uncertain.

*Non-controlled studies*

See Table 5.

v. Other DBS targets

Other stimulation targets have been explored for the treatment of drug-resistant epilepsy. The subthalamic nucleus (STN) plays a critical role in motor control and modulation. Indeed, STN stimulation is used clinically in the treatment of movement disorders such as Parkinson's disease. Therefore, STN-DBS may de-synchronize motor circuits,[16,17] and has been empirically trialed in patients with motor-related seizures.[15,21,61–65]

Additional targets studied include the caudate nucleus[52,66] and nucleus accumbens (NA)[67,68] in the basal ganglia, the posterior hypothalamus (PH),[69,70] caudal zona incerta,[69] and fornix[71] (Supplementary Table 1).

*Controlled clinical trials*

A double-blind, cross-over trial (N=4) found that refractory seizures were decreased by 48% during stimulation periods versus 14% during placebo periods (values derived from authors' data). However, the frequency of seizures with impaired awareness increased markedly in one individual. Neither additional nor alternative ANT stimulation improved efficacy, suggesting both ANT and NA stimulation are equally effective in some patients. Mean seizure reduction over the entire follow-up period was 23%.[68]

*Non-controlled studies*

See Supplementary Table 1.

**3. SAFETY AND ADVERSE EFFECTS**

i. Safety of DBS in general

The main complications of DBS can broadly be divided into three categories – surgical, stimulation-related, and equipment-related. Surgical complications include hemorrhage, wound infection, and implant site pain. Stimulation effects include worsening or new seizures, neurological symptoms (e.g. paresthesias and dizziness), and neuropsychological changes (e.g. memory and cognitive changes). Equipment-related effects may include lead displacement or migration, lead fracture, erosions, and equipment infections.[16]

Most DBS safety data comes from patients with movement disorders such as Parkinson's disease. In one study of 728 patients receiving DBS for various movement disorders, the main surgical complications were hemorrhage (4.9%) and wound infection (1.7%). Equipment-related complications included loss of effect (2.6%), lead malposition or migration (1.7%), and hardware discomfort (1.1%).[72] Another article

looked at a stratified sample of 20% of all patient discharges across the US. Out of 332 patients, they reported an overall complication rate of 6.5%, with hemorrhage or infarction in 1.2% of patients, and mechanical complications in 3.1% of patients.[73] A detailed single-center report of 319 patients reported headache (15%) and confusion (5%) as the most common post-surgical adverse events, along with stimulation-related dysarthria (4%) and cognitive disturbances (4%), and equipment-related complications such as infection (4.4%) and lead fracture (3.8%).[74] Three more articles describe similar rates of equipment-related side effects including equipment infection, electrode fracture, skin erosions, and lead migration or displacement.[75–77] Overall, DBS presents minimal rates of short and long-term complications.

ii. Safety of DBS for drug-resistant epilepsy

The safety of DBS for drug-resistant epilepsy is less well documented due to limited patient data. Nonetheless, similar adverse effects were observed over five-year follow-up of the SANTE study population.[18] The most common device or stimulation-related side effects were paresthesias (22.7%), implant site pain (20.9%), and implant site infection (12.7%). Other common complications included hardware discomfort (9.1%), ineffective product (8.2%), lead misplacement (8.2%) and sensory disturbances (8.2%).[18] Extended follow-up revealed no significant deterioration in cognition or depression scores.[78] Importantly, two deaths due to sudden unexpected death in epilepsy (SUDEP) were reported, consistent with the expected rate amongst the underlying population, and three others died of unrelated causes.[3,18]

Of the smaller clinical trials, one reported implant site infections in three patients who received HC stimulation,[35,36], and another reported an asymptomatic intracranial hemorrhage in one patient receiving CMT stimulation.[49] Across two small-scale trials of CB stimulation, CSF leak occurred in one, wound or equipment infections occurred in three, and three patients had lead displacement requiring re-positioning.[6,55,56]

The most common complications among non-controlled studies were intracranial hemorrhage (often asymptomatic),[23,41,43] lead displacement,[42,43] and skin erosions[12,19,23] or implant site infection[33,54,61] often requiring explantation. Additionally, one study noted reversible memory impairment with strong HC stimulation,[42] and another reported transient psychiatric symptoms in 3 of 15 patients receiving ANT stimulation.[30] The risk of complications may decrease as equipment and surgical techniques continue to improve over time.

## 4. DISCUSSION

i. Efficacy of DBS for drug-resistant epilepsy

The most frequently studied DBS targets are the ANT and HC. Robust clinical trials demonstrate seizure frequency reductions of 40% following short-term ANT stimulation,[3] and 26 – 40% following short-term HC stimulation,[34–37] in patients with primarily focal epilepsies. In the long-term, reductions range from 50%[20] – 76%[24] for ANT-DBS, and 45%[47] – 93%[46] for HC-DBS among non-controlled studies spanning months to years. Indeed, a recent meta-analysis found statistically significant reductions in seizure frequency secondary to ANT-DBS (high-quality evidence) and HC-DBS (moderate-quality evidence), but not for any other targets.[79] Our pooled analysis of patients for whom individual data was available (Figure 1) revealed that half of all ANT-DBS patients experienced a 46 – 90% decline[9,18,19,21–24,26,27,31] in seizures, and half of all HC-DBS patients experienced a 48 – 95% decrease[13,34–36,41–47] (interquartile ranges). Pooled responder rates (seizure reduction ≥50%) were greater than 70% for both ANT[9,18,19,21–24,26–33] and HC-stimulated[13,14,34–36,41–47] patients. Notably, there is marked variability across individual responses.

Stimulation of the CMT, CB, STN, and other targets remains inconclusive due to a lack of evidence. Small-scale controlled trials failed to demonstrate benefit from CMT-DBS,[49,50] were contradictory for CB-DBS,[55,56] and showed a favorable outcome for NA-DBS.[68] Other open-label pilot studies show promise over longer periods of stimulation,[15,21,52,61,64,69,70] but should be interpreted very cautiously.

Given the evidence base consists primarily of open-label studies rather than double-blind RCTs (listed in Table 1), there are many limitations to the discussion points raised in this article. Open-label DBS studies are exposed to confounders, investigator and patient biases when recording seizures, and the potential selection of patients more likely to respond (e.g. due to seizure type, epilepsy history, or demographic factors). They also cannot distinguish between placebo effect and true treatment effect. A combination of these factors may explain why outcomes from non-controlled studies vary substantially, and tend to be greater than controlled trials. For instance, the SANTE RCT noted a 40% decrease in seizures with ANT stimulation (versus 15% for controls),[3] compared with reductions of 53% and 80% in an open-label study of two patients over an equivalent 3-month period.[27] Additionally, changes to stimulation parameters and anti-epileptic medications were often allowed at will, potentially influencing individual responses.

The most robust RCTs to date are the SANTE trial[3] (N=110) and the RNS trial[38] (N=191), reporting remarkably similar responses during blinded evaluation and long-term follow-up periods. Both RCTs provide Class I evidence supporting ANT-DBS and HC-RNS respectively for the treatment of refractory focal seizures. In contrast, smaller studies (controlled and non-controlled) are more vulnerable to selection bias, and the unpredictable temporal course of seizure activity.

Moreover, all studies of DBS for drug-resistant epilepsy are limited by the unreliable nature of patient-recorded seizure events, known to be markedly inconsistent with events detected by an implanted seizure advisory system.[60] Therefore, our observations and conclusions should be interpreted with caution, as they are drawn from a heterogenous collection of studies which vary in quality, patient characteristics, follow-up times, data collection, and outcome reporting.

Certain seizure types and syndromes appear more amenable to stimulation of specific targets. For instance, HC stimulation has been empirically trailed for temporal epilepsies,[13,14,34–37,39–47] and CMT stimulation seems more effective for Lennox-Gastaut syndrome and in generalized seizures.[50,54] PH stimulation may also reduce aggressive behaviours.[69,70] Furthermore, the efficacy of DBS is comparable to other forms of neurostimulation, with an average one-year seizure reduction of 41% for ANT-DBS, versus 36% for VNS, 37% for trigeminal nerve stimulation, and 44% for RNS.[11]

Many studies observed a lesional effect, that is, an immediate decrease in seizures after implantation but before stimulation, possibly due to local tissue damage from electrode implantation.[39] The SANTE trial reported a median post-implantation seizure reduction of 22% alongside a stimulation benefit, with the control group experiencing additional improvement after initiation of unblinded stimulation.[3] However, two small RCTs of HC stimulation found no lesional effect.[36,37] Simple electrode insertion also decreased seizures by 67% in one open-label study,[23] and by 32-99% for 2–4 months in more than half the participants of another study.[33] To what extent the clinical benefits of DBS are derived from an initial lesional effect or an ongoing stimulation effect remains to be elucidated.

DBS may continue to reduce seizures for up to 10 years,[25] with progressive improvements reported across the SANTE cohort – 41% after one year, 56% after two years, and 69% after five years of DBS.[3,18] However, there is evidence of temporal variation in response among individuals. For instance, seizure frequencies in one study were initially variable before stabilizing after 15 months of stimulation.[23] Possible reasons include differences in patient characteristics, changes to anti-epileptic medications or DBS parameters during stimulation, and adverse events requiring cessation of DBS.

Another question, is whether chronic DBS has any permanent effect on epileptogenesis besides network modulation. A recent study observed the effect of battery depletion in nine patients with refractory epilepsy treated with at least three years of DBS. After six months of battery depletion, some patients' seizures returned to pre-DBS baseline levels, some experienced a partial rebound, whereas others noted no change in seizure frequency.[80]

Some studies also highlight changes in secondary outcomes. ANT stimulation reduces seizure severity and improves quality of life, but worsens subjective depression and memory impairment[3] – however these measures may be unreliable.[29] Reduction of myoclonic seizures with STN stimulation may improve gross

and fine motor skills.[64] Cognitive improvements have also been reported in ANT, CMT and STN stimulation.[9,15,42] Despite the role of the hippocampus in memory processing, transient memory impairment was only observed following strong HC-DBS.[42] Neuropsychiatric symptoms and sleep arousals both decreased with nocturnal DBS voltage reduction, suggesting cognitive side effects may be, in part, a consequence of stimulation-induced sleep disruption.[28]

ii. Predictors of efficacy

The anti-epileptic effects of DBS vary extensively among individuals from existing studies, yet the reasons remain unknown. We attempted to identify potential factors associated with the efficacy of DBS, in the hopes of guiding further research (Table 6). Understanding these determinants will enable clinicians to better predict which patients will respond well, and to select the most suitable DBS target and parameters for each patient.

*Demographic factors*

No studies have explicitly reported an association between stimulation efficacy and demographic characteristics such as age and gender. However, inspection of individual patient data in two open-label studies, one of HC-DBS[47] and another of CMT-DBS[53], revealed an apparent relationship between younger age and greater seizure reduction. A better response in the younger of two patients with Dravet's syndrome receiving ANT-DBS was attributed to an "aging effect", whereby a longer duration of refractory seizures may render them more resistant.[25] Conversely, some studies found no association between favorable outcome and demographic factors.[26,30]

*Epilepsy history*

Patient responses to DBS treatment may be influenced by features of their epilepsy history, including seizure type or onset zone, etiology, duration of epilepsy, and age at onset. There is evidence that ANT stimulation is more effective for temporal epilepsies. Subgroup analysis of the SANTE study population revealed a marginally better response in patients with temporal seizure onset (44% after one year, 76% after five years) versus the whole cohort (41% after one year, 69% after five years).[3,18] An open-label study found that ANT stimulation was more effective for temporal or limbic-related epilepsies versus extra-temporal epilepsies. Specifically, those suffering focal impaired awareness seizures of deep temporal or frontal limbic origin without anatomical abnormality on MRI (e.g. dysplasia or atrophy) responded better, and those with fronto-temporal ictal onset and limbic spread due to neo-cortical lesions responded poorer.[29]

Additionally, CMT stimulation is more effective in Lennox-Gastaut syndrome compared with focal onset seizures,[50] and in generalized seizures compared with frontal seizures.[54] Unilateral focal epilepsies also respond better to HC stimulation than bilateral onset epilepsies.[43] However, the investigation of HC-

DBS exclusively in temporal epilepsy, and STN-DBS primarily in seizures with motor features, precludes observation of associations between response and seizure syndrome.

Previous VNS or resective surgery did not affect efficacy, and patients who added medication while receiving DBS performed no different from those who did not.[3,18] There were also no correlations between outcome and seizure onset zone or etiology (cortical dysplasia versus encephalitis),[30] nor age of onset or prior duration of epilepsy.[26]

*Investigation findings*

Concerning MRI findings, follow-up from two small RCTs of HC stimulation revealed strong correlations between MRI normality and outcome.[35–37] In one, patients with a normal MRI (non-lesional medial temporal epilepsy) had an impressive 99% mean seizure reduction after 18 months, compared with 63% for patients with MRI evidence of medial temporal sclerosis.[35,36] Perhaps for HC stimulation, it is worthwhile considering two distinct subpopulations – one with normal MRIs, and the other with hippocampal sclerosis – with the hypothesis that neuronal reduction and/or electrical resistance in sclerosed neural tissue may hinder stimulation.[35,36] In contrast, the inverse relationship was true of participants in an open-label study.[47] Patients without structural abnormality on MRI also responded better to ANT-DBS,[29] though another study found no such association.[30]

The clinical utility of "evoked potentials" has been gathering interest. Evoked potentials are EEG waveforms recorded in response to a triggering electrical stimulus, such as stimulation of a deep brain structure. An early study found that low-frequency ANT stimulation (2–10Hz) elicited a "recruiting rhythm" on EEG only in those participants who went on to achieve ≥50% seizure reduction.[19] More recently, hippocampal evoked potentials were used to confirm proper placement of ANT electrodes.[27] However, it has been argued that evoked potentials are of little localizing value, as reproducible evoked responses of variable morphology failed to correspond with correctly positioned electrodes.[24]

To date, evoked potentials have been employed as a means of confirming correct electrode placement. The idea that evoked potentials might somehow predict DBS efficacy in humans with drug-resistant epilepsy is yet to be explored.

*DBS-related factors*

Stimulation parameters have thus far been chosen empirically based on previous studies and investigator experience. The effects of frequency, voltage, current, pulse width, unilateral versus bilateral stimulation, and cycling versus continuous stimulation on efficacy are poorly understood.

In general, it is thought that low frequency stimulation increases seizure risk by lowering seizure threshold and enhancing epileptogenic discharges, whereas higher frequencies desynchronize electrical activity and reduce seizure risk.[11,16,19] Common stimulation parameters are ≥100Hz at 1–10V for ANT

stimulation, ≥130Hz at 1–5V for HC and STN stimulation, moderate to high frequency stimulation at 1–10V for CMT stimulation, and low (10Hz) or high (200Hz) stimulation for the CB (Tables 2 to 5). Low frequency (4–8 Hz) high cycling ANT stimulation could also be effective.[27]

Most significantly, descriptive analysis of stimulation parameters used during the long-term follow-up of the SANTE cohort found no favorable parameters in frequency, voltage, or pulse width.[3] Among non-controlled studies, evidence suggests that hippocampal sclerosis patients may require "stronger" stimulation – either higher voltage or quadripolar stimulation – to achieve a response.[42] Yet, low frequency (5 Hz) HC stimulation seemed optimal in other patients with hippocampal sclerosis.[47]

There were no differences between cycling and continuous stimulation,[23] nor an association between output voltage and seizure reduction.[43] Comparison of unilateral to bilateral stimulation also yielded conflicting results.[43,45] Interestingly, concordance between response to closed-loop (responsive) stimulation and long-term DBS suggests that inpatient closed-loop trials may help identify optimal DBS parameters.[24] It is difficult to draw conclusions without more rigorous investigation of stimulation parameters.

Positioning of DBS electrodes appears significant, as ANT-DBS electrodes located anteriorly,[30] or in the antero-ventral subdivision of the ANT,[33] were correlated with a better outcome. For HC stimulation, one study found no relationship between response and distance from active electrodes to ictal focus, though good responders had active contacts <3mm from the subiculum.[44] Another study noted that all responders to HC-DBS had electrode contacts within the hippocampal formation and the gyrus.[39] Correct electrode placement as confirmed radiologically (MRI) and electrophysiologically (EEG) was also important for CMT stimulation.[12,50]

## 5. CONCLUSION

Deep brain stimulation (DBS) is an important treatment option to consider for patients suffering drug-resistant epilepsy unsuitable for resective surgery. Current evidence demonstrates that stimulation of the ANT and HC reduces the frequency of refractory seizures, though the benefits of stimulating other targets remains inconclusive. An ensemble of patient and procedural factors may influence the efficacy of DBS. Seizures of deep temporal or limbic onset are perhaps more amenable to ANT stimulation,[3,18,29] and Lennox-Gastaut syndrome and generalized seizures may respond better to CMT stimulation.[50,54] Lack of structural abnormality on MRI could favor better outcomes,[29,35–37] along with higher voltage or quadripolar HC stimulation in patients with hippocampal sclerosis,[42] and correct electrode positioning.[12,30,33,39,44,50] The limitations of these conclusions are discussed earlier.

Given the infancy of the current evidence base, more large-scale clinical trials are needed in this area. In the era of personalized medicine, the ability to tailor DBS therapy to the individual is imperative. This

includes refining investigations to help select the most suitable patients, and developing a better understanding of the stimulation targets best geared towards treating specific seizure types. A range of different stimulation parameters should be explored, as innovation ought not be impeded by onerous regulations. Of course, the accessibility of bulk data is crucial – improved data collection and aggregation will greatly assist the identification of potential factors associated with efficacy.

Novel strategies of predicting a patient's response to DBS, such as the use of evoked potentials, or inpatient trials of open-loop stimulation, should also be explored. It will be worthwhile investigating combined stimulation of multiple targets, and RNS of deep brain structures. Ongoing development of surgical implantation techniques and improvements to software and hardware will also be important.

Current indications recommend DBS only in patients with drug-resistant epilepsy unsuitable for resective surgery, but we might be missing the opportunity to modify the disease earlier in its course. Perhaps failure of drug therapy itself increases the likelihood of subsequently failing DBS therapy – a reflection of the increased treatment resistance of seizures secondary to the natural progression of epilepsy. As such, widening the indications for DBS or prescribing it earlier in the disease process may be more beneficial, targeting seizures when they are most susceptible to modulation.

Future research will hopefully sharpen the role of DBS as a valuable tool in the clinician's arsenal for tackling drug-resistant epilepsy and its debilitating consequences.

**KEY POINTS**

- Long-term ANT and HC stimulation decreased seizures by 46 – 90% and 48 – 95% among half of all patients studied; DBS of other targets remains inconclusive.
- More than 70% of patients receiving ANT or HC stimulation among existing studies are responders (experiencing a seizure reduction of at least 50%).
- Side effects and complications of DBS for drug-resistant epilepsy are similar in nature to those observed from DBS therapy for other indications.
- Individual responses vary markedly – potential predictors of efficacy include seizure syndrome, absence of structural abnormality, and electrode position.
- More robust clinical trials are needed to investigate the determinants of efficacy, and personalize DBS therapy for patients with drug-resistant epilepsy.

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## SUPPORTING INFORMATION

SUPPLEMENTARY TABLE 1: Clinical data on other targets for drug-resistant epilepsy.

SUPPLEMENTARY TABLE 2: Other notable observations from non-controlled, open-label studies.

SUPPLEMENTARY TABLE 3: Detailed clinical data on DBS for drug-resistant epilepsy for all targets showing individual results where possible.

TABLE 1: Summary of data from randomised controlled trials

| DBS target | RCT | Outcomes during the blinded phase | |
|---|---|---|---|
| | | Stimulation compared with baseline | Sham stimulation compared with baseline |
| ANT | Fisher et al. 2010[3] | 40.4% median SR | 14.5% median SR |
| HC | Tellez-Zenteno et al. 2006[34] | 26% median SR | -49% median SR |
| | A. Velasco et al. 2007[35,36] | 40% median SR | 0% median SR |
| | McLachlan et al. 2010[37] | 33% mean SR | 4% mean SR* |
| | (Morrell et al. 2011[38]) [#] | 37.9% mean SR | 17.3% mean SR |
| CMT | Fisher et al. 1992[49] | 30% mean SR | 8% mean SR |
| | F. Velasco et al. 2000[50] | No statistically significant SR (values not reported) | |
| CB | Wright et al. 1984[55] | No statistically significant SR (values not reported) | |
| | F. Velasco et al. 2Focal onset005[56] | 67% GTC mean SR | 7% GTC mean SR |
| NA | Kowski et al. 2015[68] | 48% mean SR* | 14% mean SR* |

*Values calculated from data or graphs presented in the original article.

[#]50% of participants received HC-RNS; the remainder received RNS of cortical areas.

SR (seizure reduction), ANT (anterior nucleus of the thalamus), HC (hippocampus), CMT (centromedian nucleus of the thalamus), CB (cerebellum), NA (nucleus accumbens).

Table 2: Clinical data on ANT-DBS for drug-resistant epilepsy

| **Study (RCTs in bold)** | **N** | **Mean age (yrs)** | **Seizure types & onset** | | | **DBS parameters** | | | | **Results** | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | Focal onset seizures | Generalized onset seizures | Onset zone | Freq (Hz) | Voltage (V) | Pulse width (μs) | Timing (mins) | Mean FU (mo) | Primary outcomes **(Bold if during blinded phase)** |
| Upton, 1987[8] | 6 | 24 | FIA | — | NR | 60-70 | 3.5-3.8 | 300 | NR | >36 | 4/6 "significant clinical control" |
| Hodaie, 2002[19] Andrade, 2006[22] | 5 (+1) of 8 | 30 | FIA, FBTC | GTC, AB, AT | Uni-F, GN | 100 | 10 | 90 | 1 on/5 off Alt sides | 4-7 years | 55% (24-89%) MSR after 15mo; 5/6 RR |
| Kerrigan, 2004[20] | 5 | 36 | FA, FIA, FBTC | — | Uni/Bi-F, Bi-T, Multi | 100 | 1-10 | 90 | 1 on/4 off Alt sides | 20 | 50% (-57 to 98%) MSR in "serious seizures" assoc with falls |
| Lee, 2006[21] | 3 | 22 | FIA, FBTC | TS | Bi-F, Multi | 130 | 3-7 | 90 | 1 on/5 off Alt sides | 6 | 75% (50-91%) MSR<br>3/3 RR |
| Lim, 2007[23] | 4 | 27 | FA, FIA, FBTC | GTC | Bi-F/T, Bi-F, Bi-T, GN | 90-110 | 4-5 | 60-90 | Cont & Cycling | 42 | 51% (37-75%) MSR<br>1/4 RR |
| Osorio, 2007[24] | 4 | 31 | FA, FIA, FBTC | AT | Bi-T | 175 | 4.1 | 90 | 1 on/5 off | 36 | 76% (53-93%) MSR<br>4/4 RR |
| Andrade, 2010[25] | 2 DRA | 29, 45 | FA, FBTC | GTC, MYO | Bi-F, GN | NR | NR | NR | NR | 10 years | 98% FBTC SR in 29yo<br>66% total SR in 45yo |
| **Fisher, 2010[3] (SANTE trial)** | 110 | 36 | FA (67.3%)<br>FIA (92.7%)<br>FBTC (77.3%) | GTC (4.5%) | T (60.0%); F (27.3%); GN (9.1%);<br>Other (9.1%);<br>P (4.5%); O (3.6%) | 145 | 5 | 90 | 1 on/5 off | 3 blind<br>24 total | **40%(ON) vs 15%(OFF) MDSR**<br>56% MDSR & 54% RR by 2yrs |
| Salanova, 2015[18] (FU of SANTE) | 83^ | NR | NR | NR | NR | | | | | 60 | 69% MSR<br>68% RR |
| Lee, 2012[26] | 15 | 31 | FA, FIA, FBTC | GTC | Various: Multi, F, T, F/T, C/P, P/O | 100-185 | 1.5-3.1 | 90-150 | Cont | 39 | 71% (0-100%) MSR<br>13/15 RR |
| Oh, 2012[9] | 9^ | 33 | FIA, FBTC | — | Various: Multi, F, T, F/T, C/P, P/O | 100-185 | 1.5-3.1 | 90-150 | Cont | 35 | 58% (36-90%) MSR<br>7/9 RR |
| Van Gompel, 2015[27] | 2 | 26, 32 | FA, FIA, FBTC | — | NR | 4-8 | 3.5-4 | 90 | 0.4s on /0.1s off | 3 | 80% SR in 26yo<br>53% SR in 32yo |
| Piacentino, 2015[29] | 6 | 38 | FIA, FBTC | GTC | T, F/P, F/T, GN | 140 | 4 | 90 | 1 on/4 off | >36 | 3/5 “responders” (1 died) |
| Voges, 2015[28] | 9 | 37 | FIA, FBTC | — | T, F, P, F/T, T/P, I | 145 | 5 | 90 | 1 on/5 off | 28 | 7/9 RR; Nocturnal voltage reduction ↓ sleep disruption |
| Lehtimäki, 2016[30] | 15 | 35 | NR | NR | Multi, F, T, F/T | 140 | 5 | 90 | 1 on/5 off | 25 | 10/15 RR |
| Krishna, 2016[33] | 16 | 32 | FA, FIA, FBTC | GTC, MYO, AT | NR | >100 | 2.4-7 | 90 | NR | 52 | 65% (-500 to 99%) MSR at 3yrs; 11/16 RR |
| Franco, 2016[31] | 2 | 51, 48 (SBH) | FIA, FBTC | — | Uni-F/T, Uni-T/P/C | 145 | 5 | 90 | NR | 18, 12 | 61% SR in 51yo<br>75% SR in 48yo |
| Valentin, | 1 of 3 | 15 | FA | — | NR | NR | NR | NR | NR | 12 | >60% SR |

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 2017[32] | | | | | | | | | | | |

Seizure types: GTC (primary generalized tonic-clonic); AB (absence); AT (atonic seizure / drop attack); TS (tonic seizure); MYO (myoclonic seizure); FA (focal aware – previously simple partial); FIA (focal impaired awareness – previously complex partial); FBTC (focal to bilateral tonic-clonic – previously secondarily generalized tonic-clonic); DRA (Dravet's syndrome); SBH (subcortical band heterotopia).

Seizure onset: GN (generalized or not localized); Multi (multifocal); F (frontal); P (parietal); O (occipital); T (temporal); C (central); I (insular); Uni (unilateral); Bi (bilateral).

DBS parameters: Alt (alternating sides); Cont (continuous).

Results: FU (follow-up); mo (month); yo (years old in age); SR (seizure frequency reduction); MSR (mean seizure frequency reduction); MDSR (median seizure frequency reduction); RR (responder rate (≥ 50% reduction).

Other: NR (Not reported); — (seizure type not present).

^All 83 patients in Salanova et al. 2015 are followed up from Fisher et al. 2010; 6 patients in Oh et al. 2012 are from Lee et al. 2012.

Table 3: Clinical data on HC-DBS for drug-resistant epilepsy

| **Study (RCTs in bold)** | **N** | **Mean age (yrs)** | **Seizure types & onset** | | | **DBS parameters** | | | | **Results** | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | Focal onset seizures | Generalized onset seizures | Onset zone | Freq (Hz) | Voltage (V) | Pulse width (μs) | Timing (mins) | Mean FU (mo) | Primary outcomes **(Bold if during blinded phase)** |
| A Velasco, 2000[40] M Velasco, 2000[39] | 10 | 24 | FIA, FBTC | — | T | 130 | 0.2-0.4 mA | 450 | NR | 16 days | 7/10 SF after 6 days |
| Vonck, 2002[13] | 3 | 33 | FIA | — | T | 130 | 1 | 450 | NR | 5 | 78% (50-96%) MSR<br>3/3 RR |
| Vonck, 2005[14] | 7 | NR | NR | NR | T | NR | NR | NR | NR | 14 | 4/7 RR (1/7 SF) |
| **Tellez-Zenteno, 2006[34]** | 4 | 32 | FIA, FBTC | — | Uni-T (3/4), Bi-T (1/4) | 190 | NR | 90 | Cont | 6 blind | **26%(ON) vs -49%(OFF) MDSR** |
| Boon, 2007[41] | 10^ | NR | FA, FIA, FBTC | — | T | 130-200 | 2-3 | 450 | Cont | 31 | 60% (0-100%) MSR<br>7/10 RR (1/7 SF) |
| **A Velasco, 2007[35,36]** | 9 | 29 | FIA, FBTC | — | T | 130 | 0.3 mA | 450 | 1 on/4 off | 1 blind<br>18 total | **40%(ON) vs 0%(OFF) MDSR**<br>83% (50-100%) MSR at 18mo;<br>9/9 RR at 18mo |
| **McLachlan, 2010[37]** | 2 | 45, 54 | Focal - type NR | — | T | 185 | NR | 90 | NR | 3 blind | **33%(ON) vs 4%(OFF) MDSR** |
| Boex, 2011[42] Bondallaz, 2013[44] | 8 | 34 | FIA, FBTC | — | T | 130 | 0.5-2 | 450 | Cont | 44 median | 67% MSR (0-100%);<br>6/8 RR (2/8 SF) |
| **Morrell, 2011[38] (RNS trial)** | 191 (95 HC) | 34.9 (18-66) | FA, FIA, FBTC | — | Bi-T (36%);<br>Uni-T (14%);<br>Other (50%) | 200 | 0.5-12 mA | 160 | RNS; Bursts of 100ms | 3 blind | **38%(ON) vs 17%(OFF) MSR**<br>29%(ON) vs 27%(OFF) RR |
| Heck, 2014[48] (FU of RNS trial) | | | | | | | | | | 48 | 53% MDSR & 55% RR at 2 yrs |
| Vonck, 2013[43] | 11^ | NR | FIA, FBTC | — | T (10/11),<br>Bi-regional (1/11) | 130 | 1-3.1 | 450 | NR | 102 | ≥90% MDSR;<br>8/11 RR (3/11 SF) |
| Cukiert, 2014[45] | 9 | 37 | FA, FIA, FBTC | — | T | 130 | 1-3.5 | 300 | Cont | 30 | 60% MSR (-50 to 100%);<br>7/9 RR |
| Jin, 2016[46] | 3 | NR | FIA, FBTC | — | T | 130-170 | 1-2.5 | 450 | Cont | 35 | 93% (91-95%) MSR |
| Lim, 2016[47] | 5 | 35 | FIA, FBTC | — | T | 145 or 5 | 1 | 90 | 1 on/5 off | 38 | 45% (22-72%) MSR<br>3/5 RR |

Seizure types: GTC (primary generalized tonic-clonic); TS (tonic seizure); FA (focal aware – previously simple partial); FIA (focal impaired awareness – previously complex partial); FBTC (focal to bilateral tonic-clonic – previously secondarily generalized tonic-clonic).

Seizure onset: T (temporal); Uni (unilateral); Bi (bilateral).

DBS parameters: Cont (continuous).

Results: FU (follow-up); mo (month); SF (seizure free); MSR (mean seizure frequency reduction); MDSR (median seizure frequency reduction); RR (responder rate (≥ 50% reduction)).

Other: NR (Not reported); — (seizure type not present).

^3 patients in Boon et al. 2007 from Vonck et al. 2002; 10 patients in Vonck et al. 2013 from Boon et al. 2007.

Table 4: Clinical data on CMT-DBS for drug-resistant epilepsy

| **Study (RCTs in bold)** | **N** | **Mean age (yrs)** | **Seizure types & onset** | | | **DBS parameters** | | | | **Results** | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | Focal onset seizures | Generalized onset seizures | Onset zone | Freq (Hz) | Voltage (V) | Pulse width (μs) | Timing (mins) | Mean FU (mo) | Primary outcomes **(Bold if during blinded phase)** |
| F. Velasco, 1987[51] | 5 | 18 | FIA | GTC, MYO, AT | NR | 60-100 | 0.8-2.0 mA | 100 | 1 on/4 off Alt sides | 3 | 80-100% GTC SR<br>60-100% FIA SR |
| **Fisher, 1992[49]** | 7 (2 LG) | 28 | FIA | GTC, TS | T, F/C, F/T, GN | 65 | 0.5-10 | 90 | 1 on/4 off | 9 blind<br>12-22 total | **30%(ON) vs 8%(OFF) MSR but not statistically significant.**<br>34% (-33 to 92%) MSR;<br>3/6 RR |
| **F. Velasco, 2000[50]** | 13 (8 LG) | 19 | FIA, FBTC | GTC, AB | NR | 60 | 4-6 | NR | 1 on/4 off Alt sides | 3 blind<br>41 total | **No significant SR;**<br>82% (53-100%) MSR for LG;<br>57% (13-99%) MSR for PS |
| Chkenkeli, 2004[52] | 5 of 54 | 21-40 range | FA, FIA, FBTC | GTC, TS | F, F/T, T | 20-130 | 2-4 mA | 200 | Cont OR cycling | ≤18 | 4/5 "worthwhile improvement"<br>1/5 "no improvement" |
| A Velasco, 2006[12] | 13 LG | 13.2 | — | GTC, AB | NR | 130 | 2-3 | 450 | 1 on/4 off Alt sides | 18 | 80% (30-100%) MSR;<br>10/13 RR |
| Andrade, 2006[22] | 2 of 8 | NR | FA, FIA, FBTC | GTC | NR | 100-185 | 1-10 | 90-120 | Cont OR Cycling | ≤7 years | 0/2 RR; no long-term benefit |
| Cukiert, 2009[53] | 4 (1 LG) | 29 | — | GTC, TS, AB, AT, MYO | GN | 130 | 2 | 300 | Cont | 24 | 80% (65-98%) MSR |
| Valentin, 2013[54] | 11 | 37 | FA, FIA | GTC, AB | F, GN | 60 | ≤5 | 90 | Cont | 6 blind<br>35 total | **6/6 RR in GS group;**<br>**1/5 RR in frontal group**<br>84% (49-100%) MSR GS group;<br>47% (0-95%) MSR frontal group |
| Valentin, 2017[32] | 2 of 3 | 10, 8 | — | GTC, TS, AB, AT, MYO | NR | NR | NR | NR | NR | 48, 18 | >60% SR in 10yo<br>No significant SR in 8yo |

Seizure types: GTC (primary generalized tonic-clonic); AB (absence); AT (atonic seizure / drop attack); TS (tonic seizure); MYO (myoclonic seizure); FA (focal aware – previously simple partial); FIA (focal impaired awareness – previously complex partial); FBTC (focal to bilateral tonic-clonic – previously secondarily generalized tonic-clonic); LG (Lennox-Gastaut syndrome).

Seizure onset: GN (generalized or not localized); F (frontal); T (temporal); C (central).

DBS parameters: Alt (alternating); Cont (continuous).

Results: FU (follow-up); mo (month); SR (seizure frequency reduction); MSR (mean seizure frequency reduction); RR (responder rate (≥ 50% reduction)).

Other: NR (Not reported); — (seizure type not present).

Table 5: Clinical data on CB-DBS for drug-resistant epilepsy

| **Study (RCTs in bold)** | **N** | **Mean age (yrs)** | **Seizure types & onset** | | | **DBS parameters** | | | | **Results** | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | Focal onset seizures | Generalized onset seizures | Onset zone | Freq (Hz) | Voltage (V) | Pulse width (μs) | Timing (mins) | Mean FU (mo) | Primary outcomes **(Bold if during blinded phase)** |
| Cooper, 1976[7] | 15 | 29 | FIA, FBTC | GTC, MYO, AB | NR | 10 or 200 | 10 | NR | 8 min intervals | 27 | 10/15 improved (4/15 SF) |
| Van Buren, 1978[6] | 5 | 27 | FIA, FBTC | GTC, MYO | Various, mainly F/T/C | 10 or 200 | 10-14 | NR | 8 min intervals | 15-21 range | No significant SR |
| Levy, 1979[57] | 6 | 29 | — | GTC | Uni-T, GN | 10 | 1-10 | NR | 8 on/8 off Alt sides | 7-20 range | 2/6 RR |
| Bidziński, 1981[58] | 14 | Not available | | | | 10 | 1-7 | 1000 | 30-60 per day | 10-16 days | 13/14 improved (5/14 SF); 1/14 no change |
| **Wright, 1984[55]** | 12 | 30 | FIA | GTC, AT, AB, MYO | F, T, GN | 10 | 1-7 mA | NR | Cont OR int | 6 blind | **No significant SR** |
| Davis, 1992[59] | 27 | Not available | | | | 10-180 | NR | NR | NR | 17 years | 23/27 improved (12/27 SF); 4/27 no improvement |
| Chkenkeli, 2004[52] | 11 of 54 | 21-40 range | FA, FIA, FBTC | GTC, TS | F, F/T, T | 50-100 | 2-4 mA | 200 | Cont OR cycling | ≤18 | 5/11 SF<br>5/11 "worthwhile improvement"<br>1/11 "no improvement" |
| **F. Velasco, 2005[56]** | 5 | 26 | — | GTC, TS, AT, AB, MYO | Bi-P/T, Bi-F/T, Bi-F/P, GN | 10 | 2.28 | 450 | 4 on/4 off | 3 blind<br>24 total | **67%(ON) vs 7%(OFF) GTC SR**<br>76% (62-89%) GTC SR;<br>57% (24-90%) TS SR; |

Seizure types: GTC (primary generalized tonic-clonic); AB (absence); AT (atonic seizure / drop attack); TS (tonic seizure); MYO (myoclonic seizure); FA (focal aware – previously simple partial); FIA (focal impaired awareness – previously complex partial); FBTC (focal to bilateral tonic-clonic – previously secondarily generalized tonic-clonic).

Seizure onset: GN (generalized or not localized); F (frontal); P (parietal); T (temporal); C (central); Uni (unilateral); Bi (bilateral).

DBS parameters: Alt (alternating sides); Cont (continuous).

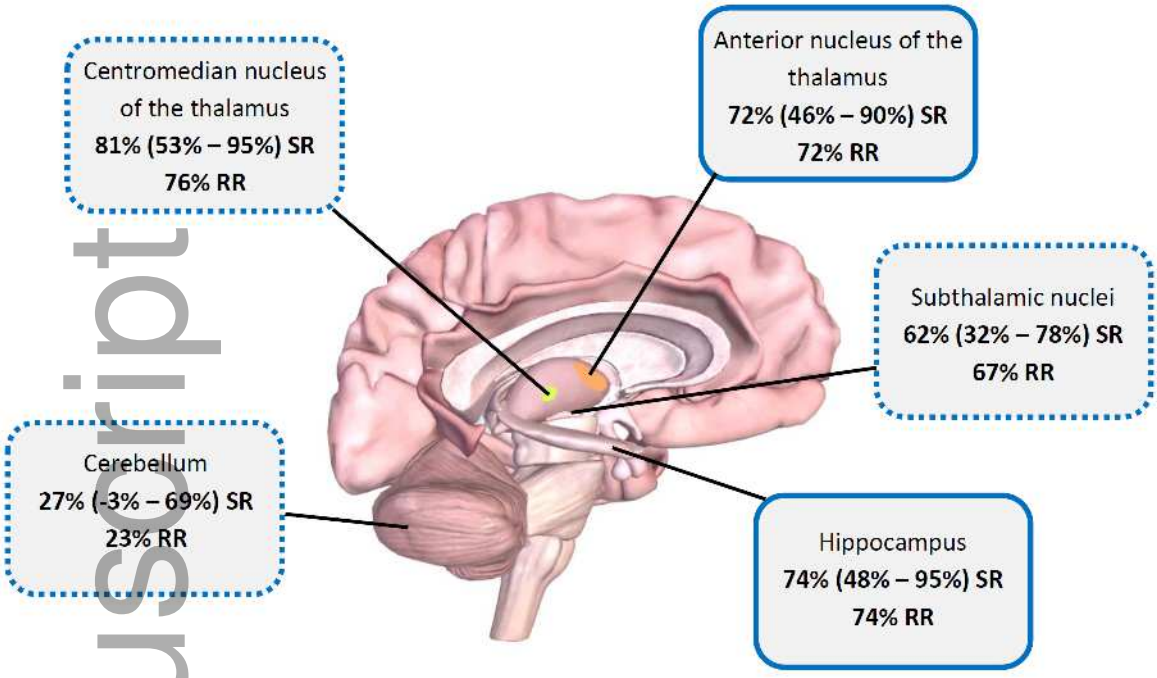
Results: FU (follow-up); mo (month); SF (seizure free); SR (seizure frequency reduction); RR (responder rate (≥ 50% reduction)).

Other: NR (Not reported); — (seizure type not present).

TABLE 6: Possible predictors of the efficacy of DBS for drug-resistant epilepsy

| **Target** | **Evidence base** | **Possible factors associated with efficacy** |
|---|---|---|
| ANT | 1 large RCT<br>16 open-label studies. | • Anterior electrode location[30,33]<br>• Seizures of deep temporal/temporo-frontal limbic onset.[3,18,29]<br>• Normal MRI without structural abnormality.[29]<br>• Efficacy with trial of closed-loop stimulation.[24] |
| HC | 3 small RCTs of HC-DBS<br>(+ 1 large RCT including HC-RNS)<br>9 open-label studies. | • Normal MRI without hippocampal sclerosis.[35–37]<br>• Electrodes close to subiculum,[44] or within hippocampal formation and gyrus.[39]<br>• "Stronger" stimulation for hippocampal sclerosis.[42] |
| CMT | 2 small RCTs.<br>7 open-label studies. | • Electrode placement confirmed radiologically and electrophysiologically.[12,50]<br>• Patients with Lennox-Gastaut syndrome,[50] or generalized epilepsy.[54] |
| CB | 2 small RCTs.<br>6 open-label studies. | • None identified. |
| Others | 1 small RCT for NA.<br>Open-label studies for STN (6), PH (2), CN (2), NA (1), CZI (1), & fornix (1). | • None identified. |

RCT (randomized controlled trial), ANT (anterior nucleus of the thalamus), HC (hippocampus), CMT (centromedian nucleus of the thalamus), CB (cerebellum), STN (subthalamic nuclei), NA (nucleus accumbens), PH (posterior hypothalamus), CN (caudate nucleus), CZI (caudal zona incerta).

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