Anterior Nucleus Deep Brain Stimulation for Refractory Epilepsy: Insights Into Patterns of Seizure Control and Efficacious Target

BACKGROUND: Anterior nucleus (AN) deep brain stimulation (DBS) is a palliative treatment for medically refractory epilepsy. The long-term efficacy and the optimal target localization for AN DBS are not well understood.

OBJECTIVE: To analyze the long-term efficacy of AN DBS and its predictors.

METHODS: We performed a retrospective review of 16 patients who underwent AN DBS. We selected only patients with reliable seizure frequency data and at least a 1-year follow-up. We studied the duration of the seizure reduction after DBS insertion and before stimulation (the insertional effect) and its association with long-term outcome. We modeled the volume of activation using the active contacts, stimulation parameters, and postoperative imaging. The overlap of this volume was plotted in Montreal Neurological Institute 152 space in 7 patients with significant clinical efficacy.

RESULTS: Nine patients reported a decrease in seizure frequency immediately after electrode insertion (insertional or microthalamotomy effect). The duration of insertional effect varied from 2 to 4 months. However, 1 patient had a long-term insertional effect of 36 months. Altogether, 11 patients reported a 50% decrease in seizure frequency with long-term stimulation. The most common pattern of seizure control was immediate and sustained stimulation benefit (n = 8). In patients with long-term stimulation benefit, the efficacious target was localized in the anteroventral AN in close proximity to the mammillothalamic tract.

CONCLUSION: AN DBS is efficacious in the control of seizure frequency in selected patients. An insertional effect is commonly observed (56%). The most efficacious site of stimulation appears to be the anteroventral AN.

KEY WORDS: Anterior nucleus, Deep brain stimulation, Efficacious stimulation target, Neuromodulation, Refractory epilepsy, Stereotactic targeting

ABBREVIATIONS: AN, anterior nucleus; DBS, deep brain stimulation; MNI, Montreal Neurological Institute; MRE, medical refractory epilepsy; MT, mammillothalamic tract; SANTE, Stimulation of the Anterior Nucleus of the Thalamus for Epilepsy; VNS, vagal nerve stimulation

Medically refractory epilepsy (MRE) presents a significant unmet need in clinical neuroscience.1,2 Some patients with MRE are suitable for resective surgery; however, many continue to have seizures that adversely affect their quality of life.3 Electric modulation of epileptic neural circuits is a palliative option to decrease seizure frequency and to improve quality of life.4,5 The targets for neuromodulation can be classified as either central or peripheral. The cranial targets for neuromodulation include the epileptogenic zone and the anterior nucleus (AN) of the thalamus.6,7 Vagal nerve stimulation (VNS) and more recently trigeminal nerve stimulation have also been applied for seizure control.8-10

The AN is a central node in the circuit of Papez.11 It receives input from the mesial temporal structures via the fornix, mammillary body, and mammillothalamic tract (MT).12,13 It projects to the ipsilateral cingulate cortex, medial frontal lobe, and temporal lobe. The AN is also implicated in seizure generalization and propagation.14,15 A combined ictal electroencephalogram functional magnetic resonance imaging (fMRI) study in
patients with idiopathic generalized epilepsy revealed hemodynamic changes in the AN, suggesting a role in seizure propagation. Therefore, modulation of AN with deep brain stimulation (DBS) is an attractive option. The uncertainty surrounding the mechanism of efficacy of AN DBS is still unresolved.

In this report, we analyzed the patterns of seizure control and distinguished the insertional effect (ie, the effects of microthalamotomy) from the stimulation benefits. We investigated whether an acute insertional effect is predictive of long-term efficacy after AN DBS. We also determined an efficacious site of stimulation using volume of activation modeling from postoperative imaging and stimulation parameters.

**METHODS**

**Study Design**

In addition to patients included in previously published prospective trials (early cohort, n = 5), we analyzed all subsequent patients (recent cohort, n = 11) who underwent DBS for MRE at our center.

**Participants and Setting**

Our criteria for patient selection and AN DBS implantation have been published previously. Briefly, all patients with MRE (failed at least 3 adequate trials of antiepileptic drugs) underwent a multidisciplinary evaluation with video electroencephalography, high-resolution MRI, neuropsychological evaluation, and intracranial electroencephalography if indicated. Patients who either were not suitable for resective surgery or had failed resective or disconnection surgery were considered for AN DBS. Patients were requested to maintain a seizure diary for 3 months before and at least 12 months after AN DBS implantation. Most patients provided their own informed consent. In patients with significant developmental disabilities, the caregiver was involved in the consent process. The AN implantation was performed with either local or general anesthesia using a Leksell frame. We targeted the AN on the parasagittal MRI as a prominence in the inferior wall of the lateral ventricle. The trajectory was chosen to place the distal 2 contacts in the dorsomedial nucleus and the proximal 2 electrodes within the AN. Microelectrode recording was performed to confirm passage of the trajectory from the ventricle into the substance of the thalamus and to obtain direct recordings of thalamic neurons. We confirmed the electrode placement within the AN with postoperative imaging (MRI for most and computed tomography if MRI contraindicated). Stimulation was routinely started at a scheduled time postoperative imaging and stimulation parameters.

**Inclusion and Exclusion Criteria**

For the purpose of this study, we included only patients who had at least 1 year of follow-up after AN DBS and a reliable documentation of seizure frequency. We excluded patients who had electrode implantation at other targets with and without AN (eg, centromedian nucleus, hippocampus).

**Variables**

Standardized data abstraction sheets were used to collect data on the basic demographics, seizure characteristics, and treatment received (medical and operative). Other collected information included the postoperative seizure frequency, changes in antiepileptic drugs, adverse effects, and stimulation parameters. We categorized patients with >50% decrease in seizure frequency as responders and patients with <50% decrease in seizure frequency as nonresponders.

**Volume of Tissue Activation of the Active Contact**

Postoperative high-resolution T1-weighted spoiled gradient recall echo scan (repetition time/echo time = 12/5 milliseconds; field of view = 260 mm, reconstructed voxel = 0.5 × 0.5 × 0.7 mm3) was acquired with a 1.5-T scanner (Signa Excite, General Electric, Milwaukee, Wisconsin) for each patient in the immediate postoperative period. For spatial normalization, these structural images were registered to the Montreal Neurological Institute (MNI) 152 template with a 12-parameter affine transformation and a nonlinear warping algorithm using Analysis of Functional NeuroImages software (http://afni.nimh.nih.gov/afni; National Institutes of Mental Health, Bethesda, Maryland).

The location of the active contact, defined as the cathode, was determined in MNI152 space. To account for a multipolar configuration of stimulation (multiple cathodes), all active contacts on a single DBS electrode were included for analysis. Similarly, to account for the bilateral implantation of DBS electrodes, both sides of the brain were mapped to 1 side of the MNI152 template. The volume of tissue activation surrounding an active contact was modeled with an ellipsoid based on a simplified method performed with Matlab (Mathworks, Natick, Massachusetts). Briefly, the volume of the ellipsoid was determined from the individual stimulation parameters of the active contacts (varying voltage of stimulation; pulse width, 90 microseconds; and frequency, 130 Hz). For this volume calculation, we assumed constant medium impedance (1 kΩ) across all contacts. Similar methodology has also been incorporated into other commercially available systems for the calculation of volumes of tissue activation.

All volumes were analyzed in MNI space such that the probability of each voxel being activated, out of the whole cohort of volumes of tissue activated, was calculated as an activation threshold. To be included in the final activated volume, a minimum activation threshold of 75% was selected. In other words, the volume included in the final hot-spot calculation had a ≥75% probability of being stimulated across the whole group. This volume was spline interpolated and mapped onto the Schaltenbrand-Wahren brain atlas and the MNI152 template brain.

**Statistical Methods**

The clinical data analysis was performed with SPSS version 19 (IBM Corp, Armonk, New York). Measures of central tendency (mean and median) and dispersion (standard deviations and range) were calculated for continuous variables, and proportions were calculated for categorical variables. We used the Student t test and Mann-Whitney U test for comparison of continuous variables and the Fisher exact test for categorical variables. Values of P < .05 were considered significant. For the seizure frequency data, median seizure reduction at each time point was calculated for the whole cohort and compared with the baseline seizure frequency with the use of the Wilcoxon signed-rank test.
RESULTS

Participants

We identified 21 patients with AN DBS for MRE. Sixteen patients were included in the final analysis. Five patients were excluded because of a follow-up <1 year (n = 2), targets other than AN (n = 2), and unreliable seizure frequency data (n = 1).

Descriptive Data

All patients underwent bilateral AN implantation except 1 patient who received left-sided DBS only. Outcome data from the 5 patients in the early cohort (patients 1-5) were presented previously (AN1, AN3, AN4, and AN5 in Hodaie et al17 and AN6 in Andrade et al18). The mean age of the combined (early plus recent) cohort was 32.3 ± 10.1 years; 50% were female. The mean follow-up was 4.3 ± 3.8 (range, 1-14 years). The mean duration of epilepsy was 21.8 ± 10.1 years, and most patients had failed several antiepileptic drugs in the past (Table 1). Most patients had partial-onset seizures with secondary generalization (68.8%), although some patients with generalized epilepsies (25%) were also implanted.

Outcome Data

Insertional Effect

We observed an insertional effect in 9 patients (56%). The reduction in seizure frequency varied from 32% to 99% (Figure 1). The insertional effect on seizure frequency in 1 patient was not included because of an unreliable seizure diary.

In the early cohort (AN1 and AN3-5 from Hodaie et al17 and AN6 from Andrade et al18) stimulation was preplanned to start 1 and 3 months after DBS insertion, respectively. In the recent cohort, we observed an insertional effect in 4 patients and programmed their DBS only after a return of seizure frequency to baseline. In this group, the typical duration of insertional effect was 2 to 4 months. However, in 1 patient, we have observed a long-term insertional effect lasting >3 years after electrode insertion.

Six of these 9 patients reported >50% reduction in seizure frequency at the last follow-up. The association between insertional effect and responder status (>50% reduction in seizure frequency) was not statistically significant (Fisher exact test, \( P = .84 \)).

Effect of Stimulation

In 11 of the 16 patients (68.8%) in total were considered responders (>50% improvement in seizure frequency). Among

<table>
<thead>
<tr>
<th>TABLE 1. Demographics and Seizure Characteristics in the Cohorts of Patients Undergoing AN DBS</th>
<th>Early Cohort (Patients 1-5)</th>
<th>Recent Cohort (Patients 6-16)</th>
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</thead>
<tbody>
<tr>
<td>Patient Characteristic</td>
<td></td>
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<tr>
<td>Mean age, y</td>
<td>31.8 ± 12.4</td>
<td>32.5 ± 9.6</td>
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<tr>
<td>Female sex, %</td>
<td>40</td>
<td>54.5</td>
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<tr>
<td>Mean follow-up, y</td>
<td>8.2 ± 4.6</td>
<td>2.4 ± 1.2</td>
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<tr>
<td>Mean seizures per month, n</td>
<td>61.2 ± 57.2</td>
<td>72 ± 89.3</td>
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<tr>
<td>Epilepsy origin, n</td>
<td></td>
<td></td>
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<tr>
<td>Genetic syndromes (MECP-2 duplication, Dravet syndrome)</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>After encephalitis</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Idiopathic/cryptogenic</td>
<td>3</td>
<td>10</td>
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<tr>
<td>Age at seizure onset, n</td>
<td></td>
<td></td>
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<tr>
<td>Pediatric</td>
<td>4</td>
<td>11</td>
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<tr>
<td>Adult</td>
<td>1</td>
<td>0</td>
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<tr>
<td>Mean duration of epilepsy, y</td>
<td>21.4 ± 9.5</td>
<td>22 ± 10.8</td>
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<tr>
<td>Seizure types, n</td>
<td></td>
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<tr>
<td>Complex partial</td>
<td>5</td>
<td>10</td>
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<tr>
<td>Focal motor</td>
<td>1</td>
<td>2</td>
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<tr>
<td>Primary (idiopathic) generalized</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Secondary (symptomatic) generalized</td>
<td>1</td>
<td>2</td>
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<tr>
<td>Myoclonic</td>
<td>1</td>
<td>0</td>
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<tr>
<td>Drop attacks</td>
<td>3</td>
<td>3</td>
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<tr>
<td>Secondarily generalized</td>
<td>4</td>
<td>7</td>
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<tr>
<td>Mean seizure medications, n</td>
<td></td>
<td></td>
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<tr>
<td>Current</td>
<td>2.8 ± 0.4</td>
<td>2.8 ± 1.1</td>
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<tr>
<td>Previous</td>
<td>5 ± 1.4</td>
<td>5.3 ± 2.2</td>
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<tr>
<td>Previous epilepsy surgery, n</td>
<td></td>
<td></td>
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<tr>
<td>Vagus nerve stimulator</td>
<td>0</td>
<td>1</td>
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<tr>
<td>Corpus callosotomy</td>
<td>0</td>
<td>3</td>
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</table>
the 5 nonresponders, 4 did not experience a decrease in seizure frequency, whereas 1 patient reported an increase in seizure frequency (from 1 seizure per month at baseline to 3 seizures per month, an increase of 200% from baseline seizure frequency). For the whole cohort (n = 16), the median decrease in seizure frequency at 1, 2, and 3 years and at last follow-up was 65.7% (range, −300% to 99%; $P = .02$), 57.4% (range, 0%-100%), 64.8% (range, −500% to 99%; $P = −.002$), and 11.5% (range, −400% to 99%; $P = .2$), respectively (Figure 2). The distribution of patients with >50% reduction in seizure frequency is shown in Figure 2. Fifty-six percent of patients (9 of 16) reported >50% reduction in seizure frequency at the 1-year follow-up. At subsequent follow-up, 66.7% (8 of 12) at 2 years, 54.5% (6 of 11) at 3 years, and 37.5% (3 of 8) reported >50% reduction in seizure frequency. Overall, 5 patients did not experience a significant benefit in seizure reduction. A majority (4 of 5) of these patients had no stimulation benefit at 1 year after implantation. In 2 of these patients, the DBS system was explanted because of infection (n = 1) or cosmetic concern (n = 1). In our case series, only 1 patient experienced delayed failure (4 years after implantation), resulting not from change in seizure frequency but from increased agitation that responded to cessation of stimulation.

We observed 3 patterns of seizure control after AN DBS (Figure 3). One patient experienced a prolonged insertional effect that persisted for >3 years after electrode implantation. This patient has not required DBS programming. Most patients (n = 8) had a decrease in seizure frequency that was time locked with AN DBS electrode implantation and subsequent stimulation. We categorized this pattern as an immediate benefit. Finally, in 2 other patients, the benefit was delayed for up to 6 months to 1 year after implantation (delayed stimulation benefit).

**Volume of Activation and Site of Efficacious Stimulation**

Postoperative imaging was available for review in 10 patients (7 responders and 3 nonresponders). As a result of recent changes in institutional policy on record storage, imaging data obtained before 2008 were no longer available in the archives for analysis. In the group of patients with available imaging data, the AN was atrophied either unilaterally or bilaterally in 4 patients and could not be reliably visualized for stereotactic targeting.

To localize the most efficacious site of stimulation, we modeled the volume of tissue activation in the 7 patients who had >50% reduction in postoperative seizure frequency. We identified the hot spot of activation (75% overlap in volume of activation) in the basolateral part of AN. The corresponding coordinates of the

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**FIGURE 1.** Reduction in seizure frequency (y axis) was observed after the insertion of deep brain stimulation electrodes and before activation of stimulation in 9 patients (insertional effect). The percentage reduction in seizure frequency varied from 32% to 99%. Insertional effect data from 1 patient were not included here because of unreliable seizure documentation in the immediate postoperative phase.
efficacious stimulation site (defined at the intersection of the 97% activation volumes) in relation to the anterior commissure were 
\[ x = 7 \text{ mm (lateral to midpoint of anterior commissure)}, \ y = +14 \text{ mm (posterior to anterior commissure)}, \ z = -12 \text{ mm (superior to anterior commissure; Figure 4)}. \]
This hot spot is localized in the anteroventral subdivision of AN, which lies immediately posterior and superior to the entry of the MT into the AN. On the basis of these findings, we suggest that the MT may serve as a new internal landmark that neurosurgeons can use for direct stereotactic targeting of the AN. A similar analysis of the 3 nonresponders was not performed, given that just 1 patient had appropriate imaging (1 had only computed tomography scan owing to an indwelling VNS device; the other was the patient with unilateral AN DBS).

**Adverse Effects**

Two patients developed infection, 1 deep at the cranial implantation site (3 years after implantation) and the other

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**FIGURE 2.** Seizure control with anterior nucleus (AN) deep brain stimulation (DBS). 

**A,** the median reduction in seizure frequency is plotted at various time points after DBS surgery. The bar graphs represent the median reduction for the whole group. 

**B,** the number of patients with >50% reduction in seizure frequency and the failures (increase, no reduction, or <50% reduction in seizure frequency) plotted at various time points after AN DBS. At long-term follow-up (>3 years), 3 patients reported >50% reduction in seizure frequency, and 5 patients reported <50% reduction. Most patients in the latter category (4 of 5) reported no stimulation benefit within the first year after DBS implantation. In 1 patient, the stimulator was turned off in a delayed fashion (because of worsened agitation) with return of seizure frequency to preoperative levels.
superficial. The hardware was removed in the patient with deep infection, whereas a wound revision was sufficient in the patient with superficial infection. This occurrence of infectious complication could be related to seizure monitoring with externalized DBS leads in these patients. No intracranial hemorrhages were observed in this patient population. One patient had a self-limited episode of postoperative psychosis in the context of a rapid correction of electrolyte imbalance. In 1 patient, severe postoperative agitation was observed on an increase in the voltage of stimulation to achieve better seizure control. The agitation improved after cessation of stimulation. At the caregiver’s request, the DBS was permanently switched off in this patient. We also observed a transient increase in seizure frequency in the immediate postoperative period in 2 patients. There were no episodes of status epilepticus.

DISCUSSION

Key Results and Interpretation

In this case series, we observed 11 patients who experienced >50% reduction in seizure frequency, whereas 5 patients failed to have significant stimulation benefit. Among the patients with available long-term follow-up data (mean duration, 6.9 years), 3 patients (of 8 in total) had >50% reduction in seizure frequency. We report the temporal patterns of seizure control and the significance of the insertional effect. We also define what appears to be the most efficacious target for seizure control and propose an internal landmark for targeting of AN.

Our group has contributed to the reappraisal and reintroduction of AN DBS for refractory epilepsy.17,18 The initial prospective studies paved the way for the large, multicenter, sham-controlled randomized trial (Stimulation of the Anterior Nucleus of the Thalamus for Epilepsy [SANTE]).6,24 AN DBS is currently not approved by the US Food and Drug Administration for the treatment of MRE; however, the recent approval of responsive neurostimulation (Neuropace, Mountain View, California) has renewed interest in studying the long-term outcomes after AN DBS.

Controversy exists regarding the mechanisms of efficacy after AN DBS and whether microthalamotomy or stimulation accounts for a majority of the effects.6,18,25 The SANTE trial reported a decrease in seizure frequency in the sham group (20% decline at 1 month and 14% at 3 months).6 However, the proportion of patients experiencing an insertional effect was not reported. Lim et al26 also reported an overall reduction in seizure frequency (67%; range, 44%-94%) without stimulation (Table 2). We observed an insertional effect in 56% of patients. The duration of insertional effect varied from 2 to 4 months, followed by the return of seizure frequency to baseline, as observed in the recent cohort of patients. However, a long-term insertional effect was also seen in 1 patient. High-frequency AN DBS may decrease cortical excitability, potentially mediated through γ-aminobutyric acid.31 In a rat model of epilepsy, muscimol (γ-aminobutyric acid agonist) microinjection into the AN provided protection from
pilocarpine-induced seizures. Another mechanism may involve interruption of seizure propagation via the MT. The initial animal studies reported protection from seizures with high-fidelity lesions of the MTs not involving the surrounding nuclei. In 2 patients with hypothalamic hamartomas and gelastic seizures, Khan et al recently reported successful seizure control after MT stimulation.

Accurate targeting of AN remains challenging in patients with MRE. Most published studies describe AN targeting on the basis of the formulaic method or direct visualization. The formulaic method does not account for the individual variability in the localization of AN. Postoperative analysis reveals significant variability in electrode placement, requiring electrode revision in some cases. Even superimposition of the Schaltenbrand-Wahren atlas during targeting may be of limited help. Osorio et al reported that despite superimposition of the Schaltenbrand-Wahren atlas, the final electrode location was quite variable. The direct visualization of AN on MRI can also be difficult in patients with long-standing epilepsy; Mueller et al reported significant atrophy of AN, especially in patients with mesial temporal lobe epilepsy. In our series, we found that visual identification of AN was difficult in a significant number of these patients (ie, 4 of 10). Therefore, a consistent and reliable methodology for targeting AN is desirable. We identified the basolateral part of AN as the most efficacious site of stimulation. This area corresponds to the anteroventral subdivision of AN. This subdivision has a consistent relation posterior and superior to the MT. We suggest that targeting of this area may be performed with the MT used as an internal landmark because it is visible in the majority of these patients.

Generalizability

The mechanisms underlying AN DBS efficacy are not well understood. As summarized in Table 2, several studies have evaluated outcomes after AN DBS for MRE. The similarities and differences in outcomes may be attributed to patient selection, targeting of AN, and the stimulation parameters. At our center, we have offered AN DBS to patients with partial-onset seizures with or without secondary generalization and to patients with primary or secondary (symptomatic) generalized epilepsy. The localizations of seizure onset in these patients included temporal, bitemporal, frontal, multifocal, and nonlocalizable (generalized).

FIGURE 4. The combined activation maps from 7 patients (with >50% seizure reduction in seizure frequency) were plotted on the Montreal Neurological Institute 152 space. The coordinates of the hot spot (intersection of the 97% activation volumes) in relation to the anterior commissure are x = 7 mm, y = +14 mm, z = −12 mm. These coordinates were plotted on the Schaltenbrand-Wahren atlas (sagittal 6.5-mm plate). Of note, the hot spot is located in the inferior and lateral part of anterior nucleus (AN) in close relation to the mammillothalamic tract as it enters the inferior border of AN.
<table>
<thead>
<tr>
<th>Study</th>
<th>Participants</th>
<th>Targeting</th>
<th>Stimulation</th>
<th>Outcomes</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fisher et al\textsuperscript{6} and Salanova et al\textsuperscript{27}</td>
<td>110 Patients with partial-onset seizures. Mainly frontal and temporal localization. 3-mo blinded and 9-mo unblinded phase.</td>
<td>Visually chosen target. Postoperative confirmation with MRI.</td>
<td>Monopolar, 145 Hz, 90 µs, 5 V. Duty cycle (1 min on, 5 min off).</td>
<td>In blinded phase, 36.3% vs 12.1% mean seizure reduction (P = .04). The 50% responder rate was 43% (n = 99) at 13 mo, 54% (n = 81) at 25 mo, and 68% (n = 83) at 5 y.</td>
<td>Predictor of good outcome temporal origin of seizures. Insertional effect observed (seizure frequency decreased in sham group 20% at 1 mo and 14% at 3 mo).</td>
</tr>
<tr>
<td>Kerrigan et al\textsuperscript{28}</td>
<td>5 Patients with partial-onset seizures. Multifocal epilepsy. 6-36 mo of follow-up.</td>
<td>Visual selection compared with Schaltenbrand-Wahren atlas.</td>
<td>Bipolar, 100 Hz, 90 µs, 1-10 V. Duty cycle (1 min on, 9 min off).</td>
<td>No significant differences in mean seizure frequency. Seizures resulting in falls decreased in 60% of patients.</td>
<td>No reported insertional effect. No other predictors.</td>
</tr>
<tr>
<td>Lim et al\textsuperscript{26}</td>
<td>4 Patients with partial-onset and generalized seizures. Multifocal epilepsy. 43.8 mo of follow-up.</td>
<td>No coordinates provided. Targeting methodology unclear.</td>
<td>Bipolar, 90-110 Hz, 60-90 µs, 4-5 V. Continuous and cycling.</td>
<td>Mean seizure reduction 51% (37%-75%), 50% of patients with &gt;50% reduction.</td>
<td>Insertional effect observed (mean reduction without stimulation 67%; range, 44%-94%).</td>
</tr>
<tr>
<td>Osorio et al\textsuperscript{25}</td>
<td>4 Patients with partial-onset seizures. Bitemporal origin. 36 mo of follow-up.</td>
<td>1 mm posterior, 4 mm lateral, and 9 mm superior to MCP.</td>
<td>Monopolar or multipolar, 145-170 Hz, 90 µs, 1.5-5 V. Duty cycle (1 min on, 5 min off).</td>
<td>84%-92% seizure reduction.</td>
<td>Delayed response in 1 patient. No insertional effect. No consistent target. 3 of 16 electrodes in AN. Other stimulated nuclei: ventroanterior and reticular nuclei.</td>
</tr>
<tr>
<td>Khan et al\textsuperscript{29}</td>
<td>2 Patients with gelastic seizures from hypothalamic hamartoma. 13-21 mo of follow-up.</td>
<td>Ipsilateral MT.</td>
<td>Multipolar 140 Hz, 90 µs, 3-3.5 V. Duty cycle (2 min on, 1 min off).</td>
<td>Both patients with &gt;50% seizure reduction.</td>
<td>MT easily visualized on MRI. Insertional effect seen in 1 patient.</td>
</tr>
<tr>
<td>Lee et al\textsuperscript{30}</td>
<td>15 Patients with partial-onset and generalized seizures. Multifocal epilepsy. 24-67 mo of follow-up.</td>
<td>5 mm lateral and 12 mm superior to MCP, along with direct visualization.</td>
<td>Monopolar or multipolar. 100-185 Hz, 90-150 µs, 1.5-3.1 V. Continuous stimulation.</td>
<td>Mean reduction 70.51 ± 32.09%.</td>
<td>No predictors. Response at 3 mo predicted long-term effect. Insertional effect not measured.</td>
</tr>
<tr>
<td>Present study</td>
<td>16 Patients with partial-onset and generalized seizures. Multifocal epilepsy. 1-13 y of follow-up.</td>
<td>Direct visualization in relation to MT. Proximal 2 contacts in AN and distal 2 in dorsomedian nucleus.</td>
<td>Monopolar or multipolar. 100-185 Hz, 90 µs, 2.4-7 V. Duty cycle (1 min on, 5 min off).</td>
<td>11 of 16 patients with &gt;50% seizure reduction. Median reduction, 11.5% in long term.</td>
<td>The active contact hot spot localized to the basolateral part of the AN in proximity to the MT. Insertional effect seen in 56% of patients.</td>
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</table>

\textsuperscript{a}AN, anterior nucleus; MCP, midcommissural point; MRI, magnetic resonance imaging; MT, mammillothalamic tract.
Our patient selection is similar to that of other published case series. In contrast, the SANTE trial included only patients with partial-onset seizures, localized most commonly to the temporal and frontal lobes. In SANTE, the mean reduction in seizure frequency at the end of the blinded phase was 36%. More recently, in the open-label phase, 68% of patients reported >50% seizure reduction at the 5-year follow-up (n = 83). In contrast, we observed >50% seizure reduction in only 37.5% of patients in this cohort. This difference could be related to broader inclusion criteria for AN implantation at our center (ie, inclusion of patients with generalized epilepsy) and a small sample size. Interestingly, other series reporting high seizure control also included patients with temporal-onset partial seizures. These results are in line with the topography of cortical activation with AN DBS. Low-frequency electric stimulation of AN preferentially activates the ipsilateral cingulate gyrus, insular cortex, posterior parietal cortex, and both lateral and medial temporal cortices.

The efficacy of AN DBS is similar to that of other neuromodulation approaches for MRE, including stimulation of the seizure onset zone and VNS. The mean decrease in seizure frequency during the double-blind phase of the Neuropace trial was 37.9% in the stimulation group compared with 17.3% in the sham stimulation group (P = .01). In addition, in the long term (years 3-6), the median percentage reduction in seizure ranged from 48% to 66%. The results of 2 randomized trials evaluating VNS showed significant but modest benefit (24.5% and 27.9% seizure frequency reduction in the high-stimulation groups vs 6.1% and 15.2% in the low-stimulation groups). Any conclusions about the superiority of one target, however, cannot be made without evaluation in a randomized controlled trial.

Limitations

The inclusion criteria for DBS implantation for this study were heterogeneous, and patients with both partial-onset and generalized epilepsy were included. The outcomes for these epilepsy syndromes may be different; however, the small sample size did not allow us to investigate these subgroup differences. Medical management was not standardized in our case series. We maintained all patients on their baseline antiepileptic drug dose in the immediate postoperative phase. In the early cohort, the antiepileptic drug doses were stable for at least the first year after implantation. In the recent cohort, however, medications were sometimes adjusted in the first year if a patient’s seizure frequency either failed to improve or increased despite multiple trials of DBS programming. We generally initiated patients on multipolar stimulation across different combinations of electrodes. Once we obtained a desired response, the field of stimulation was narrowed with the use of a bipolar configuration or a smaller number of active contacts. The clinical outcome data for the recent cohort and for the latest long-term follow-up of the early cohort are based on retrospective review of clinic charts and available seizure diaries and therefore suffer from the measurement and selection biases (secondary to loss of follow-up) often associated with retrospective methodology.

CONCLUSION

AN DBS can be an effective palliative treatment in a select group of patients with MRE. AN DBS was observed in 56% of patients in our series. Although mostly transient (2-4 months), 1 patient experienced sustained seizure reduction after electrode implantation. The most common pattern of seizure control was immediate and sustained benefit. Among patients with successful outcomes, the site of efficacious stimulation was localized to the anteroverentral subdivision of AN. Because of the close proximity of this target with the MT, we recommend future AN targeting based on the location of this tract.

Ongoing work in this field will lead to better understanding of the mechanisms underlying AN DBS efficacy, which will help in the development of effective stimulation parameters and identification of MRE patients most likely to benefit from this therapy.

Disclosure

The authors have no personal, financial, or institutional interest in any of the drugs, materials, or devices described in this article.

REFERENCES


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