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# Electrical Stimulation of the Anterior Nucleus of the Thalamus for the Treatment of Intractable Epilepsy

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**Summary:** *Purpose:* Animal studies and sporadic case reports in human subjects have suggested that intermittent electrical stimulation of the anterior nucleus of the thalamus reduces seizure activity. We embarked on an open-label pilot study to determine initial safety and tolerability of bilateral stimulation of the anterior nucleus of the thalamus (ANT), to determine a range of appropriate stimulation parameters, and to begin to gather pilot efficacy data.

*Methods:* We report an open-label pilot study of intermittent electrical stimulation of the anterior nucleus of the thalamus in five patients (three men, two women; age range, 24–47 years), with follow-up between 6 and 36 months. All patients had intractable partial epilepsy. Four of the five patients also had secondarily generalized seizures. Stimulation was delivered by bilateral implantable, programmable devices by using an intermittent, relatively high-frequency protocol. Stimulation parameters were 100 cycles per second with charge-balanced alternating current; pulse width, 90 ms; and voltages ranging between 1.0 and 10.0 V. Seizure counts were monitored and compared with preimplantation baseline.

*Results:* Four of the five patients showed clinically and statistically significant improvement with respect to the severity of their seizures, specifically with respect to the frequency of secondarily generalized tonic–clonic seizures and complex partial seizures associated with falls. One patient showed a statistically significant reduction in total seizure frequency. No adverse events could clearly be attributed to stimulation. None of the patients could determine whether the stimulator was on or off at these parameters.

*Conclusions:* Electrical stimulation of the ANT appears to be well tolerated. Preliminary evidence suggests clinical improvement in seizure control in this small group of intractable patients. Further controlled study of deep brain stimulation of the anterior nucleus is warranted. **Key Words:** Thalamus—Anterior nucleus—Electrical stimulation—Deep brain stimulation—Intractable epilepsy.

Many patients with epilepsy remain inadequately controlled despite optimal use of antiepileptic medications (AEDs) and also are not candidates for resective brain surgery. The search for alternative therapies for such patients has renewed interest in electrical stimulation of deep brain structures for treating intractable epilepsy.

The rationale that electrical stimulation of the nervous system can be effective in treating epileptic seizures is based on both animal data and preliminary human studies. In animal models, electrical stimulation of the thalamus at slow frequencies drives or synchronizes activity in distant brain regions (1,2), whereas stimulation at fast frequencies (>60 cycles/s; cps) can desynchronize intrinsic cortical activity in distant areas (3). High-frequency stimulation of the medial thalamus can block epileptiform activity in cortex (4). The thalamus was chosen for these studies because stimulation of a relatively small anatomic region can influence physiologic activity in more widespread areas of cortex. For example, the anterior nucleus of the thalamus (ANT) projects largely to the cingulate gyrus, and via the cingulate gyrus, to limbic structures and wide regions of neocortex (5).

In humans with intractable epilepsy, stimulation of thalamus (specifically, the centromedian nucleus) has induced synchronized driving (recruiting response) of cortex at frequencies ~6 cps, and desynchronization of intrinsic cortical activity at frequencies >60 cps (6). Previous trials of deep brain electrical stimulation in patients with intractable epilepsy, with intermittent stimulation of the centromedian nucleus, have shown mixed results.

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Velasco et al. (7) reported a favorable experience, particularly for patients with generalized tonic–clonic seizures (GTCSs) and atypical absence seizures, including patients with Lennox–Gastaut syndrome. A randomized, double-blind, crossover study of centromedian stimulation in seven patients with intractable partial epilepsy failed to show a statistically significant benefit (8). However, several of the patients in that study appeared to show improvement in seizure frequency with stimulation, including one patient who withdrew consent for crossover (placebo) treatment.

Based on the data from both the experimental models and limited clinical trials, and the expectation that stimulation of the ANT may be more effective at desynchronizing widespread areas of cortex, we performed an open-label, pilot study of intermittent high-frequency electrical stimulation of the ANT in five patients with intractable epilepsy.

## METHODS

### Design

Seizure frequency and intensity during stimulation were compared with preimplantation baseline seizure characteristics.

### Subjects

Patients included in this study had poorly controlled seizures, despite optimal medication management, and were not candidates for surgical resection of an identifiable seizure focus. All patients had undergone previous scalp video-EEG monitoring to characterize seizure types and localization. Informed consent was obtained. This study was approved by the Institutional Review Boards of the participating institutions.

Clinical features for each of the five patients in this study are shown in Table 1.

### Surgical implantation of stimulation leads

The intracranial stimulation leads were Medtronic 3387 DBS Medtronic, (Minneapolis, MN, U.S.A.) depth electrodes with 4 platinum–iridium stimulation contacts (each contact 1.5 mm wide with 1.5 mm edge-to-edge separation). Stimulation lead implantation was achieved by using a CRW stereotactic frame. Target sites were selected from magnetic resonance (MR) images, by using 1-mm-thick axial, coronal, and sagittal spoiled gradient echo (SPGR) pulse sequences. The target site (ANT) was identified on each side by visual selection, with reference to a standard stereotactic atlas (9).

During surgery, a guide cannula was inserted through a burr hole, and advanced to a point 10 mm from the desired target. In three of five patients, a monopolar single-unit recording electrode (Advanced Research Systems, Atlanta, GA, U.S.A.) was initially introduced to confirm the anatomic depth for entry into thalamic tissue after traversing the lateral ventricle (Fig. 1). The electrode tip was initially positioned within the lateral ventricle, where no units were recorded, then advanced until units were first recorded (superficial surface of ANT), and then advanced until units ceased (intralaminar region) and then recommenced [dorsomedian (DM) nucleus of thalamus]. The single-unit recording electrode was removed, and a temporary stimulation lead (Radionics Stimulation/Lesioning Probe, Burlington, MA, U.S.A.) was then introduced to elicit the driving response (see later). This was then removed, and the Medtronic 3387 DBS stimulation lead, with an internal stylet, was then inserted through the guide cannula to the desired target. The stylet and cannula were then withdrawn under fluoroscopy, after test stimulation demonstrated no adverse events.

The programmable pulse generators (Medtronic 7424 ITREL II Pulse Generator, Medtronic, Minneapolis, MN, U.S.A.) were surgically placed into a subcutaneous pocket

**TABLE 1.** *Patient characteristics*

| Patient | Age (yr) | Gender | Age at onset (yr) | Etiology | Seizure type(s) | Localization of seizure onset | Medications during study |
|---|---|---|---|---|---|---|---|
| 1 | 44 | Male | 3 | Cryptogenic | 1. Simple and complex partial seizures, and 2. secondarily generalized tonic–clonic seizures | Poorly localized: probable frontal or bifrontal onset | Topiramate, phenobarbital, clorazepate |
| 2 | 47 | Male | 4 | Cryptogenic, possible measles encephalitis | 1. Simple and complex partial seizures, and 2. secondarily generalized tonic–clonic seizures | Bilateral independent temporal onset | Carbamazepine, gabapentin, clorazepate |
| 3 | 41 | Female | 9 | Cryptogenic, possible head trauma | 1. Complex partial seizures, and 2. secondarily generalized tonic seizures | Poorly localized: probable frontal or bifrontal onset | Phenytoin, lamotrigine, topiramate |
| 4 | 24 | Male | 8 | Cryptogenic | 1. Complex partial seizures, and 2. secondarily generalized tonic seizures | Right hemispheric multifocal | Topiramate, lamotrigine, clonazepam |
| 5 | 25 | Female | 12 | Bilateral cortical dysplasia and heterotopias | 1. Simple partial seizures, and 2. complex partial seizures | Bilateral independent onset | Topiramate, oxcarbazepine, lorazepam |

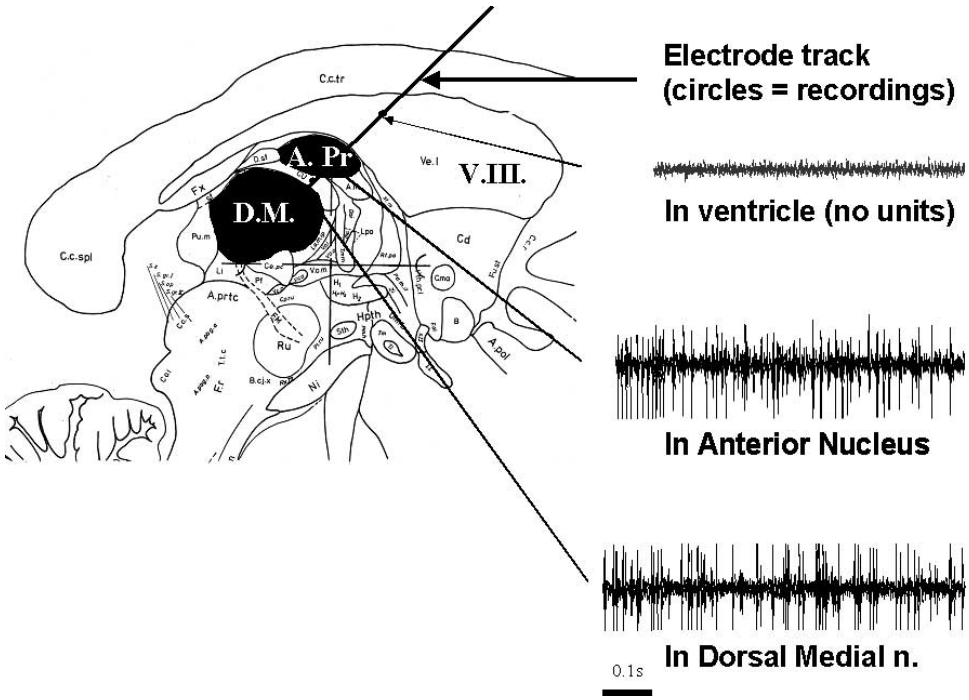



**FIG. 1.** Sagittal representation with trajectory of implantation for anterior nucleus of the thalamus electrodes. Recordings from single-unit monopolar electrode shown at right from various depth levels, identifying entry into thalamic tissue after traversing the lateral ventricle.

in the subclavicular region and connected to the stimulation leads by means of a lead extension (Medtronic 7495 Lead Extension, Medtronic, Minneapolis, MN, U.S.A.), which was tunneled under the skin of the neck and scalp. Electrically independent pulse-generation systems were placed on each side (i.e., bilateral ANT implantation). Placement location of the stimulation leads was confirmed with either cranial computed tomography (CT; n = 1) or MR imaging (n = 4) (Fig. 2).

### Scalp EEG changes with ANT stimulation

Intracranial electrode contacts were electrically stimulated, with simultaneous recording with scalp EEG, to determine whether a driving response could be elicited. Standard 10–20 electrode placement and conventional bipolar and referential montages were used for scalp EEG recording.

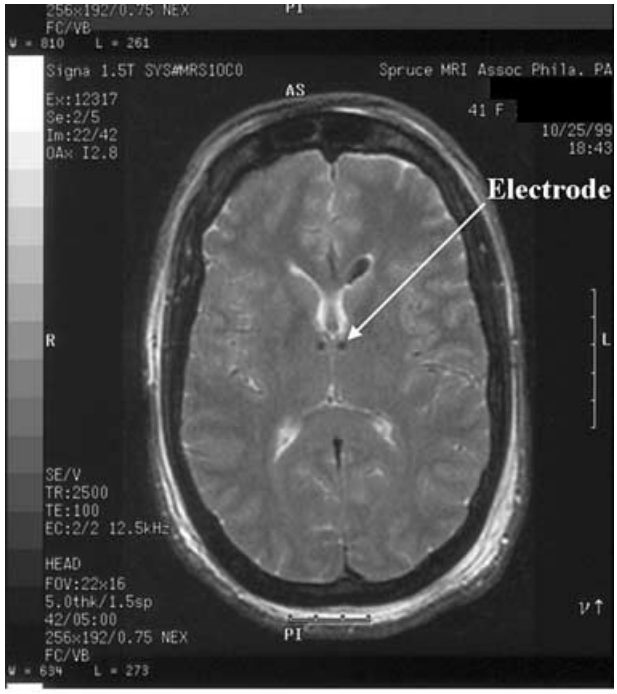
A bipolar alternating current using adjacent electrode contacts was applied unilaterally, with stimulation intensities between 1 and 10 V, individual pulse widths between 90 and 330 microseconds, and total pulse durations between 3 and 10 s. A "slow frequency" stimulation rate of 5 to 10 cycles/s was used to make a visual determination as to the presence or absence of a scalp EEG driving response, and threshold parameters were determined, if possible.

### Prolonged stimulation parameters

Long-term ANT stimulation was performed intermittently, with the stimulation system on each side set to deliver 1 min of stimulation every 10 min. Stimulation on one side was offset by 5 min from stimulation on the opposite side.

A bipolar, alternating current, usually between adjacent electrode contacts, was performed. A "high-frequency" stimulation rate of 100 cycles/s was used, with a standard pulse width of 90 microseconds. Stimulation intensity with the Medtronic ITREL system is set by changing the stimulation voltage, and this parameter varied between 1.0 and 10.0 V (using 1.0-V increments) during this pilot study. Stimulation voltage was incrementally increased for each patient over a period of 12 to 30 weeks, with prolonged stimulation performed with a voltage setting that accompanied a satisfactory clinical response, determined individually for each patient. Ongoing adjustments also could be made, in response to clinical conditions, at the discretion of the study investigators at each site. Stimulation parameters were derived from earlier human studies using deep brain stimulation (DBS) for epilepsy (8).

To monitor for adverse changes, scalp EEG recordings were performed in three of the study patients for 1 h during and immediately after reprogramming the stimulation parameters with each outpatient visit. In all cases, with "high-frequency" stimulation at 100 cps; pulse width, 90 microseconds; and stimulation voltages $\leq$5 V, no observable change in EEG background or in the frequency of interictal spikes was found by standard visual analysis. No seizures were noted during any of these 1-h monitoring periods after reprogramming.

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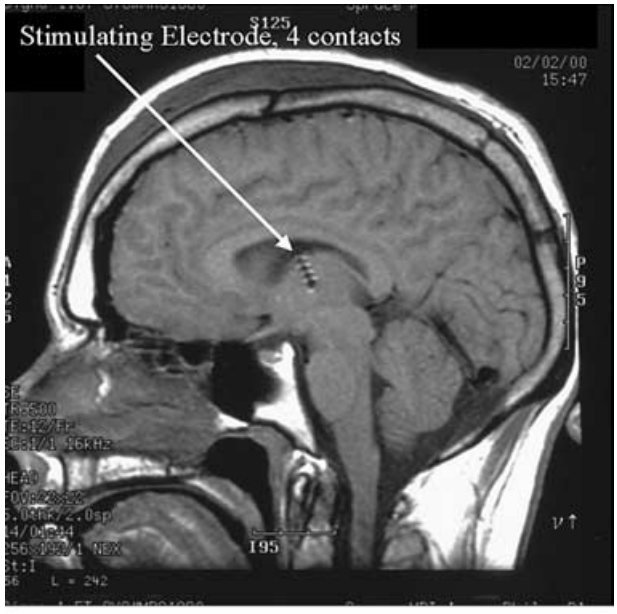


B

**FIG. 2.** **A.** Axial $T_2$-weighted brain magnetic resonance imaging (MRI; spin echo TR, 2500; TE, 100) of patient 3 demonstrating localization of stimulation electrodes after implantation. The artifact of electrode on image is larger than actual size. (Small amount of air in left frontal horn.) **B.** Sagittal $T_1$-weighted brain MRI (TR, 500; TE, 12) of patient 4 demonstrating localization of stimulation electrodes in anterior nucleus of the thalamus.

### Seizure counts, concomitant medications, and adverse events

Seizure counts for each individual seizure type were maintained with the use of a daily diary by each patient, with the assistance of family, throughout the duration of the study period. Seizure counts during the period of intervention were compared with baseline seizure frequencies. Baseline seizures were recorded either prospectively (n = 2) or by using historical seizure diaries (n = 3) over a 2-month period.

Concomitant antiepileptic drugs (AEDs) were unchanged during the first 3 months of electrical stimulation, but subsequently could be adjusted or changed according to the discretion of the study investigators at each site. The possible occurrence of adverse events was monitored with each clinic visit.

## RESULTS

### Safety

Surgical implantation and prolonged intermittent electrical stimulation of the ANT was well tolerated by all five patients in this open-label pilot trial. None of the postplacement neuroimaging studies showed evidence of hemorrhage, and none of the five patients experienced any site infections.

A single patient (patient 1) showed incorrect positioning of the depth electrodes at the time of initial placement (incorrectly positioned in the pulvinar nuclei bilaterally, due to a frame calculation error). These were removed and reimplanted 2 days later. No associated complications or neurologic symptoms resulted from this. No adverse events or complications were otherwise reported.

Patients were unaware of device activation with the stimulation parameters used during long-term treatment in this study.

### Scalp EEG changes ("driving response") with ANT stimulation

All patients demonstrated scalp EEG driving in response to low-frequency stimulation of the ANT electrodes. The driving response was time and frequency locked to ANT stimulation, was maximal in the frontal (F3 and F4) and frontopolar (Fp1 and Fp2) electrodes, and was greatest in amplitude ipsilateral to the stimulus (Fig. 3). During intraoperative recording in two patients, scalp electrode placement sites lateral to the typical 10–20 positions for F3 and F4 were used, to prevent interfering with the operative field for intracranial stimulation electrode placement.

Two techniques were tested for evoking the recruiting response: stimulation directly through adjacent pairs of DBS electrode contacts (all five patients) and intraoperative stimulation through a monopolar macroelectrode used for localization of deep structures before placement of the DBS electrode (three patients). In each case stimulation was applied in 0.5-V increments until the driving response was seen in scalp EEG channels, to determine the "threshold" voltage for driving the ANT. The relation between stimulation voltage, pulse width, and frequency were

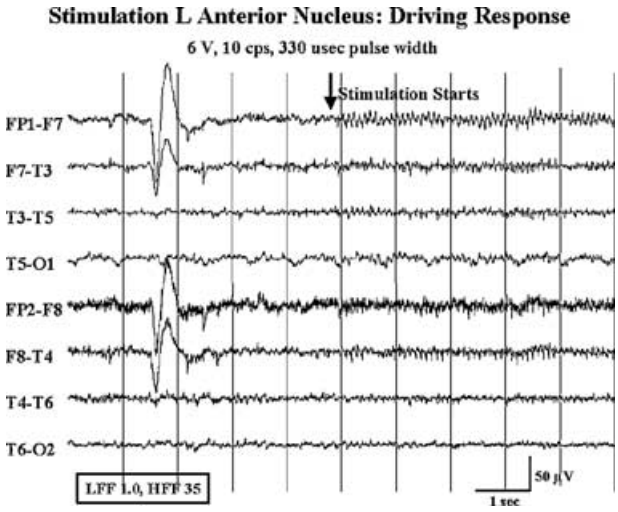


**FIG. 3.** Scalp EEG driving response to left-sided anterior nucleus of the thalamus electrical stimulation, demonstrating frontal and ipsilateral maximum. (Patient 1, LFF 1.0, HFF 35).

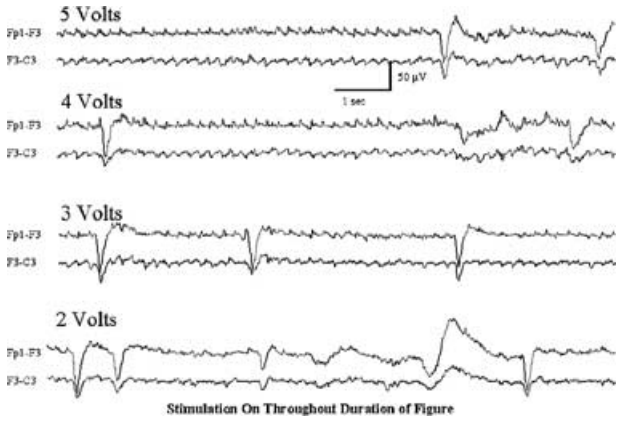


**FIG. 4.** Driving of the scalp EEG response to unilateral monopolar anterior nucleus of the thalamus stimulation (5 cps) at 2 V, establishing threshold, and increasing to 5 V for suprathreshold stimulation. Increasing amplitude and sharpness of the driving response are noted.

systematically explored in the monopolar stimulation group. Placement of DBS electrodes was verified in all patients by eliciting the recruiting response from all DBS contacts and by postoperative brain MRI.

The ability to evoke a driving response correlated with electrode placement in the thalamus. Two patients had electrodes placed so that the most distal electrode contacts did not extend deeper than the calculated border of the anterior nucleus. Consequently electrode placement in these two patients resulted in the most proximal contact on one side in each patient landing outside of the tissue, within the lateral ventricle, as verified by postoperative MRI. No driving response could be elicited from these contacts during the operative procedure, although the response could be elicited from all contacts imbedded in thalamic tissue. The presence of a recruiting response was not interpreted as evidence that electrodes were placed specifically in ANT, but rather that they were placed in thalamic tissue, given reports that the driving response can be elicited from nuclei other than ANT, including centromedian (CM) (6) and dorsomedian (DM) nuclei (personal communication, A. Lozano 2002).

Monopolar stimulation evoked the driving response at lower threshold voltages (0.5–2.5 V) than did bipolar stimulation (5–10 V). Suprathreshold stimulation enhanced the amplitude of the recruiting response (Fig. 4). In the patient with the lowest stimulation threshold (0.5 V), stimulation at 5 V provoked a recruiting response with a spike-and–slow wave morphology that was time and frequency locked to the stimulus. This discharge was asymptomatic and did not persist beyond stimulation. The recruiting rhythm was evoked by stimulation frequencies of 2–20 cps. No clear relation was seen between stimulation threshold and frequency of stimulation, although the recruiting rhythm was of highest amplitude between 7 and 10 cps in all patients (Fig. 5). Longer pulse-widths lowered the stimulation threshold for evoking the recruiting response, when a range of values between 90 microseconds and 330 microseconds was tested. This effect was observed to peak at pulse-widths of 180 microseconds in the two patients in whom this was systematically tested.

One patient underwent 12 h of continuous video-EEG monitoring with both scalp and DBS electrodes. During this period, several of the patient's typical tonic seizures were recorded. Figure 6 displays a typical seizure for this patient manifested as an electrodecremental pattern and artifact on the scalp, and as several polyspikes and then high-frequency tonic spiking in the referentially recorded thalamic electrodes bilaterally. This recording verifies the feasibility of using the DBS electrode to record high-fidelity intracranial EEG signals as well as to stimulate thalamic tissue.

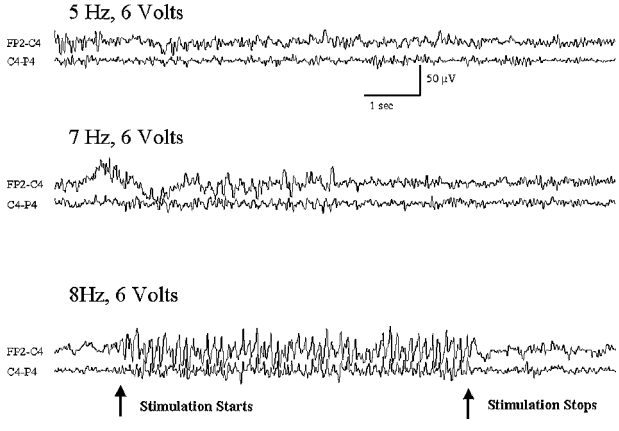


**FIG. 5.** Driving response to three stimulation frequencies. An intermittent response is noted at 5 cps, which becomes much more robust and well delineated with increasing frequency to 8 cps. The recruiting rhythm peaked at 10 cps in this patient, before gradual reduction in amplitude was noted, with stimulation ≤20 cps.

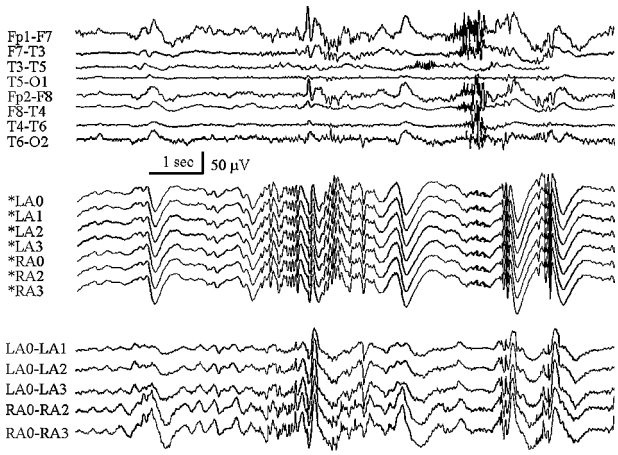


**FIG. 6.** A habitual tonic seizure recorded from scalp (top) and anterior thalamic electrodes (bottom) in patient 3 during video-EEG monitoring before internalization of stimulator units and tunneling of electrode leads. Scalp recording demonstrates flattening of background, while thalamic electrodes record a tonic, high-frequency ictal discharge. This demonstrates the ability of deep brain stimulation electrodes to record high-quality intracranial EEG while the leads remain externalized. *The EEG reference was linked ears (A1 + A2) for these channels. The RA1 contact/wire was nonfunctional and omitted from the figure.

Our experience with the driving response in these five pilot subjects suggests the following conclusions: (a) that the recruiting response can be used to verify placement of stimulating electrodes in thalamic tissue; (b) that good initial parameters for eliciting a driving response from these electrodes consist of the following: voltage, 5 to 10 V (DBS electrode) or 1.5 to 5 V (monopolar macroelectrode); pulse width, 90 to 200 microseconds; stimulation frequency, 5 to 10 cps (maximal amplitude at 7–10 cps); (c) that the recruiting rhythm can be elicited at lower threshold voltages by stimulation with a monopolar macroelectrode than with bipolar stimulation using adjacent pairs of DBS electrode contacts; and (d) that DBS electrodes can be used for high-quality intracranial EEG recording.

## Efficacy

In this open-label, unblinded study, each patient acted as his or her own control. After implantation, stimulators were placed in bipolar mode using the two contacts that seemed either anatomically or physiologically best placed in the ANT. During the course of the study, after predetermined protocols were followed, stimulation parameters were changed to try to optimize therapeutic responses. Such changes included monopolar stimulation, changes in cycling times, and adjustments of stimulation voltage and duration, all within specified parameters determined before the implantations were performed and approved by relevant oversight groups. In addition, during the course of the study, each patient's medications were individually adjusted, either to reduce side effects or to attempt better seizure control. Therefore rather than try to illustrate each patient's response graphically, or simply provide data about reductions in different seizure types collectively in the five patients, we present narrative descriptions of each patient's course after stimulation. These narratives emphasize what the patients and their care providers thought were the most significant results of ANT stimulation. It should be emphasized again that no adverse events attributable to the implantation or stimulation occurred in any of the five patients, and none was able to determine when the stimulators were on or off.

**TABLE 2.** *Mean seizure frequency per month (total seizures) at baseline, and subsequent treatment intervals, for each study subject*

| Patient | Baseline | 3 mo | 6 mo | 12 mo |
|---|---|---|---|---|
| 1 | 65.0 | 7.2 | 0.0 | 45.2 |
| 2 | 13.6 | 10.9 | 16.8 | 13.3 |
| 3 | 27.5 | 35.7 | 28.1 | 38.8 |
| 4 | 77.9 | 21.9 | 22.4 | 14.9 |
| 5 | 50.0 | 30.8 | 39.4 | 50.4 |

Table 2 shows the mean for total seizure counts (all seizure types) per month for the 2-month baseline and the mean for the subsequent treatment intervals assessed 3 months, 6 months, and 12 months after the start of ANT stimulation.

The baseline monthly seizure frequency for total seizures averaged for the five subjects was 46.8 ± 26.4 (mean ± SD). The mean of the collective (or pooled) 12-month treatment period for all five study subjects was 25.0 ± 11.5 (mean ± SD) seizures per month, which was not significantly different from baseline. However, it should be noted that seizure frequency during this pooled 12-month treatment interval included periods of increased seizure activity in several patients when stimulators were accidentally or intentionally turned off, or when medications were tapered. See individual case descriptions for details.

Evaluating each patient individually, with comparison of baseline total seizure frequency against the pooled 12-month treatment period, by using a two-tailed single-value *t* test, yielded the following p values for patients 1 through 5, respectively: 0.08, 0.97, 0.17, 0.002, and 0.23. Therefore only one subject (patient 4) demonstrated a statistically significant ($p < 0.05$) decrease in total seizure frequency.

Figure 7 plots the percentage reductions in tonic–clonic seizures or partial seizures resulting in falls. By 3 months after implantation, potentially injurious seizures (which we call "serious" seizures) had decreased to <50% of their baseline value in four of the five patients. In this sample, no patient showed a significant trend of seizure frequencies over time during the postimplantation period, so postimplantation seizure frequencies were pooled for each patient. The decrease in seizures potentially resulting in falls was significant in all four of these subjects (see

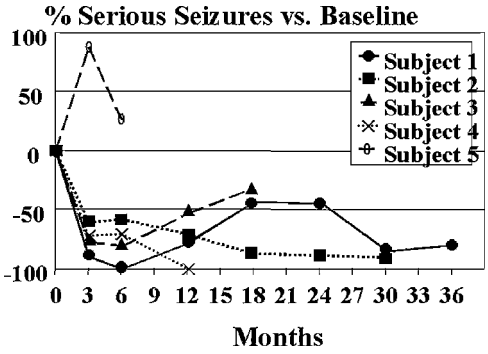


**FIG. 7.** Frequencies over time after implantation of the stimulator as a percentage of baseline for tonic–clonic seizures or partial seizures resulting in falls.

case details), by comparing the pooled postimplantation seizure frequencies with the baseline frequency, patient by patient, by using a two-tailed single-value *t* test, with the SPSS statistics package.

**Patient 1** had a mean of 2.4 total seizures/day (including 1.6 GTCSs/day) during a prospective baseline period of 2 months. Seizure control was improved after device implantation and activation, including one 4-month seizure-free interval. Preexisting problems with anxiety worsened. Topiramate (TPM) was tapered and discontinued ~9 months after implantation. Total seizure frequency returned to baseline, although secondarily GTCS frequency remained below baseline. Subsequently (~20 months after implantation), the devices were turned off temporarily, with increased seizure frequencies, followed by improvement (GTCS frequency <50% of baseline) once the devices were reactivated. The mean (± SD) postimplantation serious seizure frequency was 12.1 ± 10.5 per month, versus baseline of 48 serious seizures per month ($t = -9.06$; $p < 0.001$, paired *t* test against a single value).

**Patient 2** had a mean of 0.4 total seizures/day (including 0.15 secondarily GTCSs/day) during the preimplantation baseline period. After implantation, total seizure frequency was not consistently changed from baseline, although the frequency of GTCSs did remain below baseline subsequent to the 5-month postimplantation time point. An increase in total seizure frequency (but not GTCSs) was seen when the devices were turned off temporarily at ~14 months, with return to previous seizure frequencies when the devices were reactivated. The mean (± SD) postimplantation serious seizure frequency was 1.1 ± 0.7 per month, versus baseline of 4.5 serious seizures per month ($t = -12.3$; degree of freedom, 5; $p < 0.001$, paired *t* test against a single value).

**Patient 3** had a baseline frequency of 0.95 total seizures/day and 0.20 seizures with falls/day. During the first 5 months of stimulation, total seizure frequency increased [predominantly complex partial seizures (CPSs)], although shortly after the ANT stimulators reached a stimulation setting of 3 V, her falls disappeared. After ~6 months, her total seizure frequency returned to baseline, although seizures associated with falls remained absent. Twice in the ensuing 6 months, her left thalamic electrode was accidentally turned off, and she began experiencing seizures with falls again. Each time it was restarted, these seizures disappeared. The patient and her family were unaware of the status of the electrodes, and only on testing was it discovered that the stimulator was off. After another period of rare falls, the patient's TPM was tapered and discontinued because of excessive weight loss. She remained with only rare generalized seizures. After 14 months, her phenytoin (PHT) was tapered, and at that time, her generalized seizures began to return. The mean (± SD) postimplantation serious seizure frequency was 2.4 ± 1.4 per month versus baseline of 6.0 serious seizures per month ($t = -5.1$; degree of freedom, 3; $p = 0.015$, paired *t* test against a single value).

**Patient 4** had a baseline frequency of 2.3 total seizures/day and 1.8 GTCSs/day before ANT implants. His seizure frequency for the next 10 months ranged between none and one total seizures per day with only one GTCS during that period. Approximately 10 months after electrode placement, an exacerbation of delayed gastric emptying developed, a problem that he had had before ANT placement. Extensive evaluation failed to show a cause for this condition, and his ANT stimulators were turned off 13 months after placement. No improvement was seen in his gastrointestinal symptoms, but both his CPS and GTCS frequency worsened. After 3 months, his ANT stimulators were turned on again, and both total seizures and GTCS frequencies were reduced below preimplantation baselines. After a period of 2 months with no seizures, the patient began to experience CPSs again. It was quickly determined that one ANT electrode had spontaneously stopped stimulating. When this electrode was turned back on, the patient's generalized seizures again disappeared. CPSs were initially reduced, but then slowly returned to near preimplantation levels over several months, but were less intense (no falling). Once again, the patient began experiencing more-severe CPSs with falling and it was again determined that one of his ANT electrodes had stopped stimulating. When it was restarted, both GTCSs and CPSs once again disappeared for >5 months. The mean (± SD) postimplantation serious seizure frequency was 0.9 ± 1.3 per month, versus baseline of 54 serious seizures per month ($t = -59$; degree of freedom, 1; $p = 0.011$, paired *t* test against a single value).

**Patient 5** had a small initial reduction in her total seizure frequency and a small increase in her CPSs associated with falls. She continues to show no benefit from the ANT. She is the only patient in this series who had previously undergone a temporal lobectomy, which also failed to reduce her seizures significantly. The mean (± SD) postimplantation serious seizure frequency was 28.3 ± 7.9 per month,

versus baseline of 18 serious seizures per month ($t = 1.84$; degree of freedom, 1; $p = 0.317$, not significant by paired $t$ test against a single value).

## DISCUSSION

The present study establishes stimulation parameters and documents preliminary safety in advance of a future study of anterior thalamic stimulation for epilepsy. The nature of the pilot study precludes any definitive statements about efficacy. Only five patients were enrolled, and they included individuals with frontal, temporal, or multifocal seizure foci. There was no placebo group, and each patient was evaluated with regard to a preimplantation baseline period. In addition, each patient was treated individually after ANT stimulation was in place for several months. However, despite these caveats, in four of the five patients, a clinically and statistically significant benefit appeared to be present, with respect to the frequency of GTCSs or CPSs associated with falls (grouped together as "serious seizures" for the purposes of statistical analysis). One of the five subjects showed a statistically significant decrease in total seizure frequency.

These findings raise questions as to the possible mechanism(s) of action of ANT stimulation. These results would suggest the hypothesis that intermittent ANT stimulation may interfere with seizure propagation, with lesser efficacy on seizure onset. Further study is required to confirm this observation and explore possible mechanisms.

In four patients in whom ANT stimulation was stopped (including two patients who were blinded to the change by virtue of unintended discontinuation of unilateral stimulation), an immediate increase in seizure frequency and intensity occurred. These patients improved when stimulation was resumed. These observations tend to argue that intermittent electrical stimulation of ANT is the active factor in achieving the therapeutic effect (rather than a lesion effect within ANT caused by physical placement of the electrode).

### Prior investigations of ANT stimulation

*Animal models*

High-frequency electrical stimulation of ANT increased the clonic seizure threshold in a pentylenetetrazol (PTZ)-induced seizure model in rats (10). Electrical stimulation in brain structures that project to the ANT can similarly inhibit seizures. High-frequency stimulation (but not low-frequency stimulation) to the mammillary nuclei (MN), which project directly to the ANT via the mammillothalamic tract, can increase seizure threshold in the PTZ model and disrupt the high-voltage synchronized cortical discharges in animals with ongoing seizure activity (11).

Lesion or chemical-inhibition experiments demonstrated the importance of ANT and brain structures that project to the ANT in facilitating seizure activity. Injections of $\gamma$-vinyl aminobutyric acid into the ANT of rats protected against PTZ-induced seizures (12).

*Prior experience in humans*

Implantation and electrical stimulation of the ANT has been performed in a small number of patients with intractable epilepsy. Upton and Cooper (13) reported a series of six patients with intractable partial epilepsy: Four patients experienced a significant reduction in seizure frequency, including one patient who became seizure free. Sussman et al. (14) reported in abstract form a series of five patients with intractable epilepsy (four with CPSs of temporal lobe origin and one with secondary GTCSs). Three of the five patients showed improvement. The patient with GTCSs, representing one of these responders, had complete cessation of drop attacks and GTCSs, although absences and CPSs continued (14). Stereotactic lesions of the anterior thalamus reportedly improved seizure control in human subjects (15).

At the time of writing, we are aware of a total of 20 patients, treated at six institutions, receiving electrical stimulation of ANT to treat seizures. A series of five patients treated at the University of Toronto has recently been reported, demonstrating mean reduction in seizure frequency of 54%, with mean follow-up time of 15 months after ANT implantation (16). These authors raised the possibility that the implantation itself, either via microlesions or placebo effect, could account for some of the benefit. The observation that four of our five patients appeared to worsen when stimulation was discontinued tends to argue against the lesion-related hypothesis. A controlled study will be required to clarify this issue.

### Safety considerations

Safety issues of DBS relate to surgical risks of implantation and the risks associated with electrical stimulation of cerebral tissue. Deep-brain implantation usually is associated with a low incidence of surgical complications (17). Safety experience derives mainly from studies of DBS for movement disorders, and suggests an ~5% risk for significant bleeding or infection associated with electrode placement. Groups of movement disorder patients tend to be older than groups of epilepsy patients, and complication rates may not apply. We are aware of one serious intracerebral hemorrhage in one of 20 patients receiving ANT electrode placement within the past 6 years. Prolonged implantation of deep brain electrodes has also recently been reported with brain injury in association with the therapeutic use of radiofrequency diathermy, presumably due to physical heating of the electrode contacts with this technique (18).

Prior studies suggest that charge densities >30 microcoulombs per square centimeter per phase can damage adjacent neural tissue (19). The charge delivered during a stimulation pulse is the product of the current intensity (voltage divided by resistance) and the duration of

the pulse or pulse width. Charge density is determined by dividing the charge per phase by the surface area of the electrode(s) delivering the charge to the tissue. Although the voltage range used to treat these subjects included values $\leq$10 V, the pulse widths were $\leq$90 microseconds during long-term stimulation. This ensured delivery of charge densities of $<$30 microcoulombs/cm$^2$, given typical values of electrode impedance.

## CONCLUSIONS

Implantation of deep brain electrodes and intermittent high-frequency stimulation of the ANT was well tolerated in this open-label pilot study. Patients were unaware of the presence or absence of intermittent stimulation at the settings used in this study, making a blinded protocol feasible. The changes in seizure frequency, relative to baseline, in this heterogeneous group of patients with severe intractable epilepsy is encouraging and supports the need for further investigation of ANT stimulation, we hope with a multicenter, randomized, blinded study design.

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