

## Long-term Anterior Thalamus Stimulation for Intractable Epilepsy

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**Background:** Deep brain stimulation (DBS) has re-emerged as an alternative therapy for intractable epilepsy. In this study, we investigated the feasibility, efficacy and safety of long-term anterior thalamic nucleus (ATN) stimulation for intractable epilepsy.

**Methods:** In this open-label pilot study of electrical stimulation of the ATN, we investigated four cases of intractable epilepsy (one man with generalized seizure, and three woman with partial seizure and secondary generalization; age range, 18-45 years), with a follow up of 2 years. Under the indication of bilateral or nonlocalized epileptic foci, each patient underwent stereotactic implantation of a quadripolar stimulating electrode in the bilateral ATN, guided by single-unit microelectrode recording. The stimulator was turned on after a sham period of 2-4 weeks. Seizure frequency was monitored and compared with the pre-implantation baseline. Twenty-one similar cases reported in the literature during the past 20 years were reviewed.

**Results:** Insertion into and stimulation through electrodes implanted in the ATN decreased seizure frequency, with a mean reduction rate of 49.6% in the current series. Two patients had seizure reductions of  $\geq 60\%$ , with complete remission achieved in one patient. These findings were consistent with those in four other investigations of intractable epilepsy, which showed an overall rate of 45-55% in seizure reduction. One of our patients suffered a small frontal hemorrhage, and a second patient had extension erosion over the scalp; however, no resultant major or permanent neurological deficits were observed.

**Conclusions:** Based on our study results and literature review, it appears reasonable to conclude that long-term ATN stimulation is a safe and effective treatment for seizure reduction in patients with intractable epilepsy.

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**Key words:** electrical stimulation, anterior thalamic nucleus, intractable epilepsy, deep brain stimulation

Many patients with epilepsy continue to have disabling seizures despite the use of medica-

tion with optimal antiepileptics drugs (AEDs). In addition, some are not suitable candidates for current

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conventional surgical treatment. The search for alternative therapies for such patients is needed, including for patients with multifocal seizure onset, inability to localize seizure onset zone, and seizure onset zone that co-localizes with eloquent brain. The recent success of brain stimulation for the treatment of movement disorders and pain, together with the advantages of reversibility and adjustability, have driven the application of these procedures for patients with intractable epilepsy.<sup>(1,2)</sup> A variety of brain regions have been targeted for this treatment modality, including the amygdalohippocampus,<sup>(3-5)</sup> cerebellum,<sup>(6-8)</sup> caudate nucleus,<sup>(9)</sup> subthalamic nucleus (STN),<sup>(10,11)</sup> centromedian thalamic nucleus (CM),<sup>(12-15)</sup> and anterior thalamic nucleus (ATN).<sup>(16-20)</sup> Despite encouraging results, the optimal brain target for seizure control remains unknown.

The ATN projects largely to the cingulate gyrus, via the cingulate gyrus, to limbic structures and wide regions of the neocortex. Thus, it was believed that stimulation of a relatively small ATN would influence physiologic activity in widespread areas of the cortex and limbic system; and would influence the propensity of seizures based on the connectivity. Historically, Upton and his colleagues introduced ATN stimulation for epilepsy in 1985,<sup>(16,17)</sup> and subsequent development work has been performed by other researchers.<sup>(18-20)</sup> During recent years, great improvements have been achieved in the accuracy of ATN targeting and implantation of electronic devices of programmable pulse generators. To date, we have implanted deep brain stimulation (DBS) electrodes for ATN stimulation in four patients with intractable epilepsy. In this report, we describe the preliminary results of this ATN stimulation and also review relevant cases we found in the literature.

## METHODS

### Patient selection and presurgical evaluation

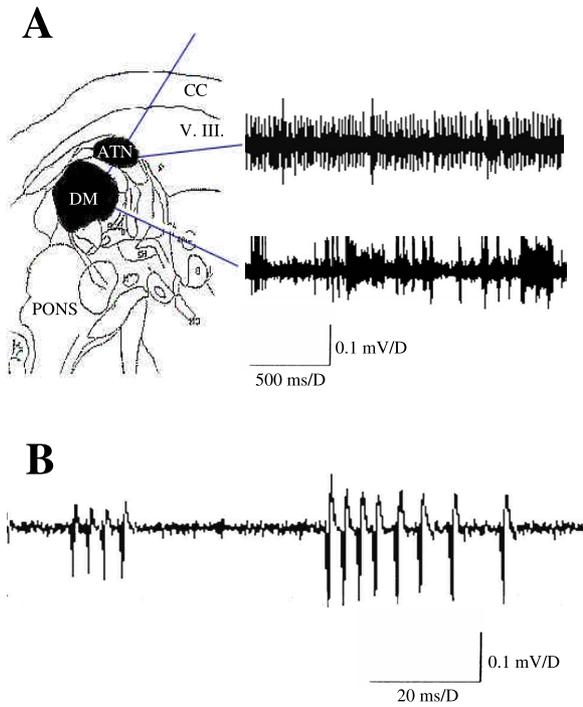
Four patients with long histories of frequent intractable seizures were enrolled in this pilot study. The patients were receiving multiple AEDs for seizure control. No structural abnormalities were detected in their brain magnetic resonance imaging (MRI) studies, and the patients underwent long-term video-electroencephalogram (EEG) monitoring to characterize the seizure types and to locate the epileptic foci which were: generalized tonic-clonic

seizures (GTCS;  $n = 1$ ); and partial seizures with secondary generalization ( $n = 3$ ). The bilateral and/or nonlocalized findings for the epileptic foci, which were verified using long-term video-EEG recording, precluded the surgical resection of the epileptic foci. The protocol was reviewed and approved by our institutional ethics board. Informed consent was obtained from each patient after complete disclosure of the salient features to the patients and their families.

Daily seizure diaries were recorded by the patients and caregivers for at least 9 months before enrollment and then after electrode implantation and extending through the study period. Intelligence (IQ) testing and auditory P300 measurements were performed before and after electrode implantation to evaluate the effects of ATN stimulation on cognitive processing.

### Surgical methods

Patients underwent preoperative cerebral computed tomography (CT) using a stereotactic frame to determine the targets and anterior commissure/posterior commissure (AC/PC) reference line. Surgery was performed under local anesthesia using bilateral burr holes at the coronal sutures, with a guiding cannula inserted through the burr hole to the desired target. Single-unit microelectrode recording was performed to characterize the physiology of the neuronal environment and to determine the proper target location of the dorsal and ventral borders of the ATN. The microelectrode recordings were extracellular via the FHC (Bowdoinham, ME, U.S.A.) platinum-iridium microelectrode (0.3-0.5 M $\Omega$  impedance), and the guiding cannula was used as the reference electrode. Extracellular action potentials were amplified using an amplifier (GS3000, Axon Instruments, or, Leadpoint, Medtronic) and simultaneously recorded using standard recording techniques (300-10000 Hz) together with a descriptive voice channel. The electrode tip was slowly advanced and various signals encountered. It was initially advanced to the lateral ventricle where no signals were recorded, then advanced until a first signal was first detected (superficial surface of the ATN), and then advanced until the signals were lost (intralaminar region) and then the signals were detected again at the dorsal median nucleus of the thalamus (Fig. 1). The microelectrodes were then



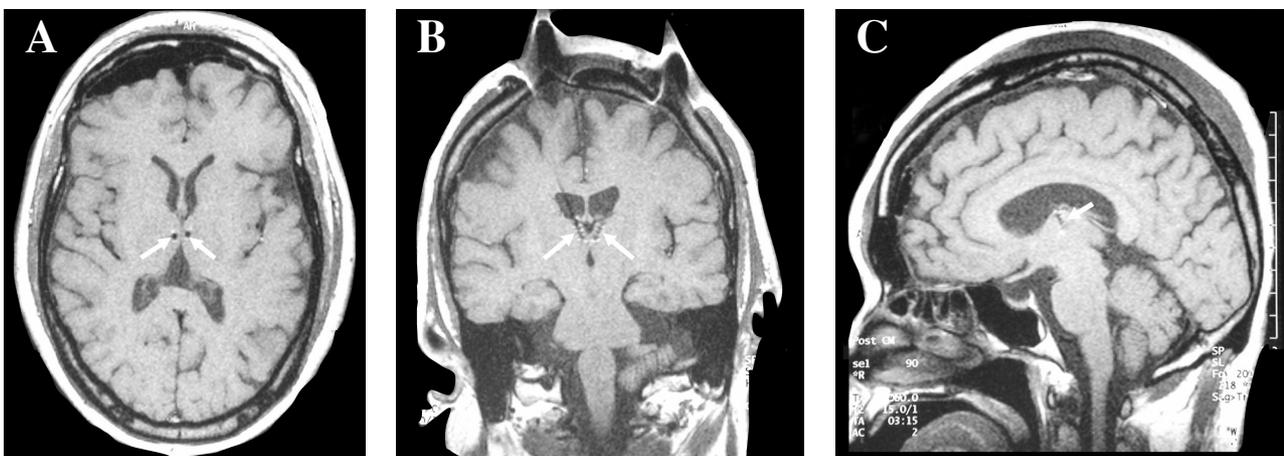
**Fig. 1** Electrode trajectory targeting the anterior nucleus (ATN) and dorsal median nucleus (DM) of the thalamus. Recording from a single-unit monopolar electrode (shown at left) at various depth levels, identifying entry into thalamic tissue after traversing the lateral ventricle, including the ATN (upper trace) and DM (lower trace), with the interposed nucleus cecularis separating these two structures (A). The characteristic of ATN neurons showed regular firing pattern with interspike interval for each firing increase in length (B).

removed and each received a DBS quadripolar stimulation electrode (Medtronic 3387, Minneapolis, MN, U.S.A.), comprising four platinum-iridium stimulation contacts (1.5 mm wide with 1.5 mm edge-to-edge separation) along with an internal stylet, inserted through the guiding cannula to the ATN. Since the long axis of the ATN is around 6 mm in humans and the quadripolar electrode span is 10.5 mm, the bottom one or two contacts were in the dorsal median nucleus of the thalamus (DM), and the upper two or three, in the ATN. Electrodes were temporarily connected to transcutaneous leads to record thalamic EEG activities concomitant with scalp EEG monitoring. Placement of the stimulation leads were further verified using postoperative brain MRI. Brain MRI scans from Patient 2, illustrating placement of the DBS electrodes in the ATN in transverse, coronal and sagittal views, are presented in Fig. 2.

The patient subsequently underwent postoperative video-EEG monitoring for 5-7 days, where scalp and thalamic EEGs were recorded through the implanted leads. One week after the procedure, the electrodes were internalized and connected to a subclavicular internal pulse generator (IPG, 7428 Kinetra Neurostimulator; Medtronic, Minneapolis, MN, U.S.A.), via a lead extension (7482; Medtronic).

#### Post-implantation management and follow-up study

Each patient had 2-4 weeks without stimulation



**Fig. 2** Post-implantation brain MRI (Patient 2) showing stimulation electrodes in the ATN (arrows). Localization of bilateral ATN electrodes in transverse view (A); four contacts of the quadripolar electrode are clearly visible in the coronal view (B); sagittal view demonstrating localization of quadripolar electrodes in ATN (C).

(sham period) following the electrode implantation. Bipolar stimulation to the pairs of electrode contacts was subsequently initiated at a high-frequency stimulation rate of 90-110 Hz, standard pulse width of 60-90  $\mu$ s, and pulse amplitude of 4-5 V. These parameter settings were based on the results of earlier studies of DBS in Parkinson's disease,<sup>(21)</sup> and of other brain structures in epilepsy.<sup>(12)</sup> Continuous stimulation was used initially, based on the clinical experience in the treatment of movement disorders.<sup>(22)</sup> Later the stimulation mode was changed to intermittent (cycling), as this modality prolonged battery life and offered the theoretical advantage of less potential injury to surrounding tissue. No significant seizure frequency differences were determined between the two stimulation modes.

Patients were followed monthly at outpatient clinics. The possible occurrence of adverse events was carefully monitored after DBS implantation and at each follow-up visit. Anticonvulsant treatment was kept unchanged for the first month of stimulation; however, adjustment was permitted subsequently to reduce side effects or to improve seizure control in individual cases. Adjustment of the stimulation parameters (frequency, pulse width, intensity, bi/monopolar, continuous/intermittent mode) responsive to the relevant clinical conditions occurred for each patient.

Preoperative and postoperative seizure frequencies were tabulated from daily diaries and expressed as a mean number per month and percentage change compared with baseline. SPSS 10.0 software (Statistical Package for the Social Sciences) was used for statistical analysis.

## RESULTS

### Individual patients

#### *Patient 1*

An 18-year-old man was diagnosed with medically intractable GTCS at the age of 3.5 years. Despite various treatment regimes including carbamazepine (CBZ), vigabatrin (VGB), topiramate (TPM), gabapentin (GBP) and clonazepam (CNZ) in different combinations, his seizure frequency remained at  $26.2 \pm 9.8$  per month.

He underwent bilateral electrode implantation in the ATN and STN. No immediate complications were observed and the postimplantation brain MRI

did not show evidence of hemorrhage. The patient received continuous stimulation to the bilateral ATN and STN alternatively for 6 days while blind to the protocol. Under video-EEG monitoring, one GTCS was noted during ATN stimulation and four GTCS were recorded during the STN stimulation. One week after the electrode insertion, the quadripolar electrodes placed into the STN were removed. The IPG was connected to the ATN electrode. However, acute weakness in the left hand was noted 2 days after the connection. A brain MRI revealed a small right frontal hematoma. The weakness recovered in 2 months without functional impairment.

A 69% reduction in seizure frequency was noted for the 3-weeks of the sham stimulation (8 vs 26/month, stimulator OFF and baseline, respectively). Parameter adjustments including stimulating modes (bipolar or monopolar), voltages (5-7 V), frequency (100-110 Hz) and duration (90  $\mu$ s) were performed to optimize therapeutic response. Total post-implantation seizure frequency was  $13.9 \pm 4.1$  (mean  $\pm$  SD), which was a 47% reduction compared with the baseline.

#### *Patient 2*

A 45-year-old woman had been diagnosed with intractable upper limbs and/or lower limbs motor seizures accompanied by uncontrollable crying for 6 years. Initially, seizures occurred during her sleep, and later occurred mostly during the daytime. Treatment consisted of CBZ, valproic acid (VPA), GBP, lamotrigine (LTG), TPM and CNZ in different combinations. However, seizure frequency increased (from 5 to 10 per day) and the duration increased (from 10 to 30 minutes) during a 2-year period, with a mean seizure frequency of  $216.7 \pm 63.2$  per month.

During the 4-week sham period, a double-blind trial of ATN stimulation during the motor seizures was evaluated using video-EEG monitoring. In all of the 14 trials involving true ATN stimulation, the motor seizures stopped 1-5 seconds after the stimulation was activated. In contrast, the motor seizures and EEG findings remained unaffected in the 19 false analogs. A 94% reduction in seizure frequency was noted during the sham period (14 vs 216.7/month at baseline). Stimulation modes (bipolar or monopolar), voltage (4-7 V), frequency (100-110 Hz) and amplitude (90  $\mu$ s) were adjusted in an attempt to enhance seizure control. The total post-

implantation seizure frequency was  $84.3 \pm 48.4$  (mean  $\pm$  SD), which was a 61% reduction compared with baseline.

#### **Patient 3**

A 21-year-old woman, whose seizures started at 13 years of age, had simultaneous and alternative clonic jerks of the four limbs with clear consciousness. Occasionally, seizures were followed by secondary GTCS. The AEDs consisted of various combinations of VPA, CNZ, CBZ and TPM. Seizure frequency increased (from 5 to 12 per month) and their durations were prolonged. Intravenous injections of benzodiazepine had been administered to stop the prolonged seizures in emergency departments during the 3 years prior to this study.

The stimulator was activated after a 2-week sham period. Extension erosion of the scalp was noted during a routine follow-up examination 5 months after the electrode implantation. Exposure of the connecting wire developed 1 week after that, and surgical intervention was subsequently required to remove the right stimulation electrode and connecting wire. Stimulation of the left ATN electrode was continued. At 10 months after the initial implantation, a second extension erosion developed at the scalp around the left connecting wire. The IPG, left electrode, and connecting wire were removed. A total of 1500 mg VPA per day added to the CBZ and TPM. Her seizure frequency gradually decreased, and the patient ultimately became seizure free at 22 months after initial implantation.

#### **Patient 4**

A 22-year-old woman had febrile convulsions since she was 3 months old. She began having various types of partial and generalized seizures since the age of 9 months, and was treated with various combinations of phenobarbital (PB), phenytoin (PHT), VPA, CBZ and TPM; however, her seizure frequency had risen to 5-15 per month during the 3 years prior to her operation.

Seizure control improved after electrode implantation (sham period) with a seizure frequency of 5/month vs. baseline of 9/month (44% reduction). The stimulator activated was accidentally turned off at 7-12 months, causing an increasing seizure frequency to 9.6/month during this period. Seizure frequency reduced after the stimulator was reactivated.

Stimulation modes (bipolar or monopolar, from continuous to cycling), voltage (3-5 V), frequency (110-130 Hz) and duration (60-90  $\mu$ s) were changed to optimize seizure control. The total post-implantation seizure frequency was  $6.3 \pm 2.8$  (mean  $\pm$  SD), which was a 30% reduction compared with baseline.

#### **Case analysis and general results**

The four cases presented herein bring the total number of reported ATN stimulations to 25 for intractable epilepsy documented in the world literature. A breakdown of the seizure onset ages and types, and post-implantation follow-up, as well as outcomes and complications are summarized in Table 1. Patient ages ranged from 15-47 years; 22 of the cases involved partial seizures with or without secondary generalization, and three GTCS. The follow-up time ranged from 6 months to a period of over 36 months.

Baseline seizure frequency for our four patients ranged from 7.8-216.7 per month; overall seizure reduction was 49.6% (30-61%) during the 2-year follow-up period (Table 2). Two patients experienced  $\geq 60\%$  reductions in seizure frequency, with complete remission in one patient. Fig. 3 shows that simple insertion of the ATN electrodes reduced mean seizure frequency to 67% during the sham period (range, 44-94%), and that this improvement was maintained at 47.3% (range, 28-60%) during the subsequent stimulation period.

## **DISCUSSION**

ATN stimulation for intractable epilepsy has been performed previously, with an overall 45-55% reduction in seizures demonstrated for intractable epileptic patients.<sup>(2,16-20)</sup> In our present study, high-frequency ATN stimulation produced a mean seizure reduction of 49.6% during 2 years of follow-up, with seizure reduction rates of more than 60% in two of the cases. These findings, which are consistent with those of four previous studies, offer evidence that ATN stimulation is an effective treatment for intractable epilepsy.

#### **Mechanism of DBS stimulation for intractable epilepsy**

The mechanism of seizure reduction in DBS remains unclear, and controversy about the mecha-

**Table 1.** Clinical Patient Characteristics and Outcomes in the Present Series Compared with Four Other Series

Report	Case	Age (years)/ Sex	Onset age (years)	Etiology	Seizure type	Localization of seizure onset	Follow up time (month)	Outcome (seizure reduction)	Side effect
Upton (1987)	1	26 / M	8	-	CPS	-	Over 3 years	4 patients showed seizure reduction (seizure free in 1 patient)	No
	2	21 / M	10	-	CPS	-			
	3	32 / F	17	-	CPS	Temporal			
	4	23 / M	1	-	CPS	-			
	5	15 / M	4.5	-	CPS	-			
	6	25 / M	8	-	CPS	-			
Sussman (1988) Abstract	1	-	-	-	CPS	Temporal	12-24	3 patients showed improvement (generalized epilepsy free in patient)	-
	2	-	-	-	CPS	Temporal			
	3	-	-	-	CPS	Temporal			
	4	-	-	-	CPS	Temporal			
	5	-	-	-	Secondarily generalized	-			
Hadaie (2002)	1	45 / F	1	-	GTCS	Generalized	20.7	33%	1 patient had skin erosion over the DBS site
	2	36 / F	2	-	GTCS	Generalized	12.8	24%	
	3	22 / M	1	-	Atonic drop attack, CPS vs atypical absence, secondarily GTCS	Generalized	10.6	52%	
	4	30 / F	5	-	CPS, secondarily GTCS	Right hemisphere	18.3	89%	
	5	19 / M	1	-	SPS, secondarily GTCS	Right fronto-central	12.1	75%	
Kerrigan (2004)	1	44 / M	3	Cryptogenic	SPS and CPS, secondarily GTCS	Poorly localized	36	75% reduction in serious seizure	No
	2	47 / M	4	Cryptogenic, possible measles encephalitis	SPS and CPS, secondarily GTCS	B independent temporal	30	76% reduction in serious seizure	No
	3	41 / F	9	Cryptogenic, possible head trauma	CPS, secondarily	Poorly localized	18	60% reduction in serious seizure	No
	4	24 / M	8	Cryptogenic	CPS, secondarily GTCS	Right hemisphere multifocal	12	98% reduction in serious seizure	No
	5	25 / F	12	Bil cortical dysplasia and heteropias	SPS and CPS	Bilateral independent	6	Increased seizure frequency	No
Current series	1	18 / M	3.5	Cryptogenic	GTCS	Bilateral fronto-temporal	24	37%	Small ICH
	2	45 / F	41	Cryptogenic	Prolonged SMS, with secondarily GTCS	Generalized	24	48%	No
	3	21 / F	13	Cryptogenic	SMS, secondarily GTCS	Bilateral frontal	24	75%	Allergic reaction
	4	22 / F	0.25	Cryptogenic	CPS, secondarily GTCS	Bilateral fronto-temporal	24	43%	No

**Abbreviations:** CPS: complex partial seizures; GTCS: generalized tonic-clonic seizures; SPS: Simple partial seizures; SMS: Simple motor seizures; DBS: deep brain stimulation; ICH: Intracerebral hemorrhage.

nism persists in the literature. Some reports have raised the hypothesis that the efficacy is based on the lesions resulting from physical placement of the electrodes, referred as the microthalamotomy or lesioning effect. This observation was described by Hodaie et al., who demonstrated that there were no differences in seizure reduction between the ATN stimulation-on and stimulation-off periods.<sup>(19)</sup> In patients with movement disorders, this microthalam-

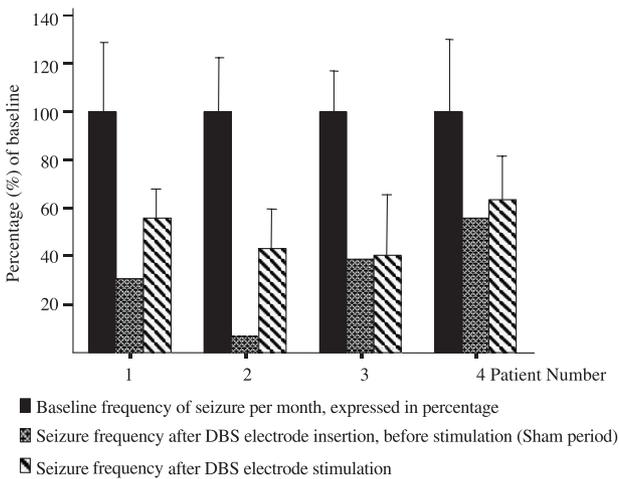
otomy effect was observed in  $\leq 53\%$  of DBS electrode insertions for tremors, persisting up to 1 year in some cases.<sup>(23)</sup> A second hypothesis was that DBS may act through local inhibition induced by a current applied to a specific CNS structure, the so-called reversible functional lesion effect. By targeting crucial structures in a network, nuclei that were involved in sustaining, propagating, or triggering epileptic activity are inhibited. In four patients

**Table 2.** Comparison of Seizure Control Effects of Anterior Thalamic Nucleus (ATN) Stimulation in Each Phase

Patient age (year) / sex	Baseline seizure Frequency / month	Post-DBS (Sham period) seizure frequency / month (Mean seizure reduction*)	Post-DBS (stimulation ON) seizure frequency / month (Mean seizure reduction*)	Total post-DBS (Sham + ON) seizure frequency / month (Mean seizure reduction*)
18 / M	26.2 ± 9.8	8 (69%)	14.6 ± 3.8 (44.3%)	13.9 ± 4.1 (47.0%)
45 / F	216.7 ± 63.2	14 (94%)	93.1 ± 43.4 (57%)	84.3 ± 48.4 (61.1%)
21 / F	7.8 ± 1.7	3 (61%)	3.1 ± 2.3 (60.3%)	3.1 ± 2.2 (60.3%)
22 / F	9.0 ± 3.5	5 (44%)	6.5 ± 3.0 (27.8%) <sup>†</sup>	6.3 ± 2.8 (30%) <sup>b</sup>

Seizure frequency expressed as mean ± standard deviation.

\*: Represents reduction in seizure frequency after ATN DBS implantation in each phase, and the reductions are expressed as percentage reduction compared with baseline; †: In this patient, stimulator accidentally turned off from 7<sup>th</sup> to 12<sup>th</sup> month, increased seizure frequency to 9.6 ± 3.2 per month in this period; the accidentally OFF period was eliminated.



**Fig. 3** Comparison of seizure frequency at baseline (BL), and in the sham (no stimulation) and after stimulation periods. The reduction in seizure frequency after ATN electrode implantation is expressed as percentage of baseline. Error bars represent standard deviations.

receiving ATN stimulation, immediate increases in seizure frequency and intensity occurred when the ATN stimulation was turned off, followed by improvement once the stimulator was resumed.<sup>(20)</sup> In contrast to the microthalamotomy effect, the authors suggest that stimulation-induced inhibition was the active factor in the therapeutic efficacy.

In our small group of patients, simple insertion of the ATN electrodes resulted in a mean reduction in seizure frequency of 67% during the sham and 47.3% during the stimulation period. The seizure reduction during the sham period may be due to the microthalamotomy or “carry-over” effect of the brief test stimulation. Continuous improvement in seizure

frequency and eventual seizure-free status was observed in Patient 3 even after the removal of the intracranial electrodes which further supports the hypothesized microthalamotomy or “carry-over” effect. In contrast, Patient 2 underwent repeated double-blind randomized trials of ATN stimulation where the motor seizures stopped 1-5 sec after stimulation commenced. Further, increased seizure frequency was noted in Patient 4 when the stimulator was accidentally turned off; with the seizure frequency reduced again once the stimulator was reactivated. The responsiveness to active stimulation in these two patients tends to argue against the lesion-related hypothesis, and supports the proposed role of active ATN stimulation for reducing seizure frequency. In conclusion, evidence from our patients suggests that either microthalamotomy or direct ATN stimulation contributes to the seizure reduction effect of DBS. We cannot distinguish whether the implantation itself or the subsequent stimulation had the greatest impact in seizure reduction. An extended double-blind controlled study comparing stimulation paradigms following electrode implantation (3-6 months) may further clarify this issue and provide insight into the possible mechanisms underlying the therapeutic effect.

**Seizure type and stimulation effect**

Of the 25 patients that received ATN stimulation during the past 20 years, 22 had partial seizures with or without secondary generalization and three had GTCS. Analysis of the cumulative data showed a 24-37% (mean 31.3%) seizure reduction in the three cases of generalized epilepsy. Although the small sample size limits any meaningful conclusion with

respect to the general efficacy of ATN stimulation, based on our findings it appears reasonable to suggest that patients with partial seizures appear to have better responses. This contrasts the results of another study that CM stimulation was more suitable for the control of the absence and generalized seizures in primary/secondary Lennox-Gastaut syndrome, but not for complex partial seizures.<sup>(14)</sup>

### **Selection of stimulation parameters**

The ideal DBS parameters for patients with epilepsy remain unclear. In animal studies, low-frequency ATN stimulation synchronized the EEG activity making the cortex more susceptible to seizures. A similar effect has also been noted in human studies, with low-frequency stimulation producing EEG synchronization in the form of recruiting rhythm, and sometimes inducing spike-waves.<sup>(19,20)</sup> Whereas, in animal models high-frequency stimulation leads to EEG desynchronization, thought to render the cortex less susceptible to seizures.<sup>(24)</sup> Therefore, high-frequency stimulation is currently being widely used for DBS treatment in patients with refractory epilepsy. The choices with respect to stimulation intensity (including voltage and pulse width) were based on the results of previous studies of movement disorders. Low-intensity stimulation may produce no effect, whereas high intensity may spread the stimulating current outside the nucleus under study. Intermittent rather than continuous stimulation was selected by most epilepsy specialists, possibly due to previous experience with vagus nerve stimulation. The advantages include less potential causes for injury to the surrounding brain tissue and prolongation of battery life. However, there is no definite conclusion with respect to the selection of current flow models, with researchers using both bipolar and monopolar (referential) stimulation. The current generated from bipolar stimulation is more localized and maximized around each electrode, whereas the monopolar variant generates a wider current field. Typical settings for DBS stimulation for intractable epilepsy are 100-165 Hz, 1-10 V, 90  $\mu$ s, running either continuously or in 1/5 min on/off cycles.<sup>(1)</sup> These settings may be adjusted dynamically according to the clinical response.

### **Complications and safety considerations**

Risks estimated for DBS are mainly derived

from the results of studies of movement disorders. The studies of STN stimulation in Parkinson's disease indicate that adverse events may be related to the DBS surgery, hardware, stimulation, or disease progression, with overall complication rates of DBS can exceed 25%.<sup>(25)</sup> The rate of hemorrhage was 3% to 5% for bilateral procedures. Long-term follow-up demonstrated that hardware complications including lead migration, lead fracture, extension erosion, extension fracture, and IPG malfunction were relatively common, having occurred in 26.2% of 82 patients receiving STN stimulation.<sup>(26)</sup> From literature review, skin erosion over the DBS site has only been reported in one patient with ATN electrode placement,<sup>(19)</sup> with no DBS-related deaths. In our series, one patient had a small frontal hemorrhage possibly related to the removal of the STN stimulation electrode and another subject experienced extension erosion of the scalp, resulting in subsequent removal of the two electrodes, connecting wires and IPG. The complication of frontal hemorrhage and extension erosion in our patients was similar to that seen in patients receiving STN stimulation for Parkinson's disease. No other adverse events or complications were noted during the follow-up period. Postoperative IQ index and auditory P300 response were not significantly different compared with the baseline.

### **Conclusions**

In this open pilot study, insertion and stimulation through electrodes implantation in the ATN appeared effective in terms of reduction in seizure frequency in patients with intractable epilepsy. Therefore, ATN stimulation may be considered a valuable therapeutic alternative where patients are not candidates for epilepsy surgery. Longer follow-up studies of our current cohort and further double-blinded clinical trials using a larger population are necessary to clarify the long-term efficacy and optimal stimulation paradigms for DBS-based control of intractable epilepsy.

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## 長期視丘前核刺激治療頑固型癲癇症

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**背景：**近年來深部腦刺激術再度成爲治療頑固型癲癇症的其中一種方法。本研究的目的是在於探討長期視丘前核刺激術治療頑固型癲癇症的可行性、有效性及安全性。

**方法：**本研究包含了4名頑固型癲癇症的病人(分別爲1名全身性癲癇症的男性病人及3名局部性合併次發性全身性癲癇症的女性病人；病人年齡介於18-45歲)，追蹤期爲期2年。所有病人具有兩側性或無法定位的癲癇病灶，皆進行立體定位手術將一永久性之刺激電極植入雙側的大腦視丘前核，並在術後接受腦部磁共振造影的檢查以進一步確定電極的位置。在電極植入術後，所有的病人皆有二到四個星期的不刺激期(Sham period)，之後開始接受長期的視丘前核刺激。我們比較病人手術前、後的癲癇發作頻率，同時回顧過去廿年文獻上總共記載的21例接受視丘前核刺激術治療癲癇的病例。

**結果：**我們的研究顯示植入電極及長期刺激視丘前核皆明顯的降低病人的癲癇發作頻率，並達到平均減少49.6%的效果。其中兩個病人的癲癇發作頻率降低大於60%，包括其中一個病人完全沒有再發作。回顧文獻上其他四篇報導，總共達到平均減少45-55%的癲癇發作頻率，這一結果和我們的研究成果是一致的。在我們的病人當中，其中一個病人出現輕微的額葉出血，另外一個病人則併發刺激部位的感染，但是沒有一個病人出現重大的或永久性的功能障礙。

**結論：**根據本研究的結果及文獻的回顧，長期視丘前核刺激術是一個有效且安全的治療頑固型癲癇症的方法。在未來，需要更大型控制組的研究去驗證視丘前核刺激術降低癲癇發作頻率的結果。

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**關鍵詞：**電刺激術，視丘前核，頑固型癲癇症，深部腦刺激術

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