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SURGICAL NEUROLOGY INTERNATIONAL

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Editor: **Antonio F. DeSalles,** M.D., University of California at Los Angeles, Los Angeles, CA, USA

SNI: Stereotactic

Original Article

Bilateral stereotactic lesions and chronic stimulation of the anterior thalamic nuclei for treatment of pharmacoresistant epilepsy

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Received: 21 January 17 Accepted: 21 June 18 Published: 19 July 18

Abstract

Background: The use of the anterior nucleus of thalamus (ANT) as a target for treatment of pharmacoresistant epilepsy is based on its crucial role in seizure propagation. We describe results of chronic bilateral ANT stimulation and bilateral ANT lesions in 31 patients with refractory epilepsy.

Methods: ANT DBS was performed in 12 patients (group I) and bilateral stereotactic radiofrequency lesions of ANT were performed in 19 patients (group II). Targeting was based on stereotactic atlas information with correction of the final coordinates according to the location of anatomical landmarks and intraoperative microelectrode recording data.

Results: Both groups were similar in age, gender, seizures frequency, and duration of disease. The median *x*, *y*, and *z* coordinates of ANT were found to be 2.9, 5, and 11 mm anterior, lateral, and superior to the mid-commissural point, respectively. Mean seizures reduction reached 80.3% in group of patients with ANT DBS with two nonresponders and 91.2% in group of patients with lesions. Five patients from group I and three patients from group II became seizure-free. The morbidity rate was low in both groups.

Conclusions: Stereotactic anterior thalamotomy and chronic ANT stimulation are both effective for seizure control in epilepsy originated from frontal and temporal lobes. ANT lesions and stimulation were more effective for secondary-generalized seizures compared to simple partial seizures.

Key Words: Anterior thalamic nucleus, deep brain stimulation, epilepsy, microelectrode recording seizures, stereotactic lesion

Access this article online

Website: www.surgicalneurologyint.com

DOI: 10.4103/sni.sni_25_18

Quick Response Code:

INTRODUCTION

Pharmacoresistant epilepsy can be defined as failure of adequate trials of two tolerated and appropriately chosen and used antiepileptic drugs schedules (whether as monotherapies or in combination) to achieve sustained seizure freedom.[20] Several potential stereotactic targets have been suggested for the treatment of pharmacoresistant epilepsy, including the medial parts of temporal lobes, caudate nucleus, cerebellum,

How to cite this article: Sitnikov AR, Grigoryan Yu A, Mishnyakova LP. Bilateral stereotactic lesions and chronic stimulation of the anterior thalamic nuclei for treatment of pharmacoresistant epilepsy. Surg Neurol Int 2018;9:137.

http://surgicalneurologyint.com/Bilateral-stereotactic-lesions-and-chronic-stimulation-of-the-anterior-thalamic-nuclei-for-treatment-of-pharmacoresistant-epilepsy/

centromedian nucleus of the thalamus, subthalamic nucleus, and anterior thalamic nucleus (ANT).[1,2,7,15,47,49,53] Although the majority of publications focus on defining an optimal target for neuromodulation, the stereotactic lesions are rarely reported and most of these reports are dedicated to stereotactic amygdalohippocampectomy and destructions of epileptogenic foci identified by stereoencephalography.[8,25,26]

ANT represents a promising target because of their widespread projections to various cortical and subcortical structures and involvement in the process of generation and spreading of epileptic activity.[32,45]

ANT consist of 3 subnuclei (anteromedial nucleus, anterodorsal nucleus, and anteroventral nucleus) widely projecting predominantly to frontal and temporal lobes, including frontal area 2, frontal polar and medial orbital cortex, anterior cingulate and dysgranular retrosplenial cortex, entorhinal cortex, perirhinal cortex, presubiculum and subiculum, temporal area 2, and secondary motor cortex [Figure 1].[5,56] Afferent input comes from mammillary bodies, limbic cortex, prelimbic and medial orbital cortices, and many other areas. Due to involvement of ANT in seizure propagation and spreading via corticothalamic connections, mammillary bodies (or mammillothalamic tracts), and the circuit of Papez, their lesion or stimulation result in suppression of abnormal neural activity originated from frontal or temporal lobes.

Various animal studies demonstrated the efficacy of bilateral lesions and stimulation of ANT in prevention of seizure propagation with superiority of lesions in terms of epilepsy control.[14,28,30,31] Currently bilateral stimulation of ANT using the Medtronic DBS System approved by FDA on April 27, 2018 as an adjunctive therapy for reducing the frequency of seizures in individuals 18 years of age or older in cases of medically refractory epilepsy.[55]

The only research regarding the ANT lesions in humans was published by Mullan *et al*. in 1967. Using the strontium needle with exposition for 15 min he performed unilateral lesions in nine patients resulted in seizures-freedom in two patients, and seizures frequency reduction in four.[34] Based on this research and several animal studies, we started using bilateral stereotactic anterior nucleothalamotomy for treatment of pharmacoresistant epilepsy in humans.[40]

The article summarizes results of chronic electrical stimulation and bilateral radiofrequency lesion of the ANT in our series of patients with pharmacoresistant epilepsy.

MATERIALS AND METHODS

We operated on 31 patients with pharmacoresistant epilepsy (age 16–48 years). Twelve patients (group I) underwent bilateral ANT DBS and 19 patients (group II) underwent bilateral stereotactic radiofrequency ANT lesions. The major reasons for selecting patients for lesioning were as follows: 1) the patients' disinclination to have the implantable devices, 2) the inability to come for

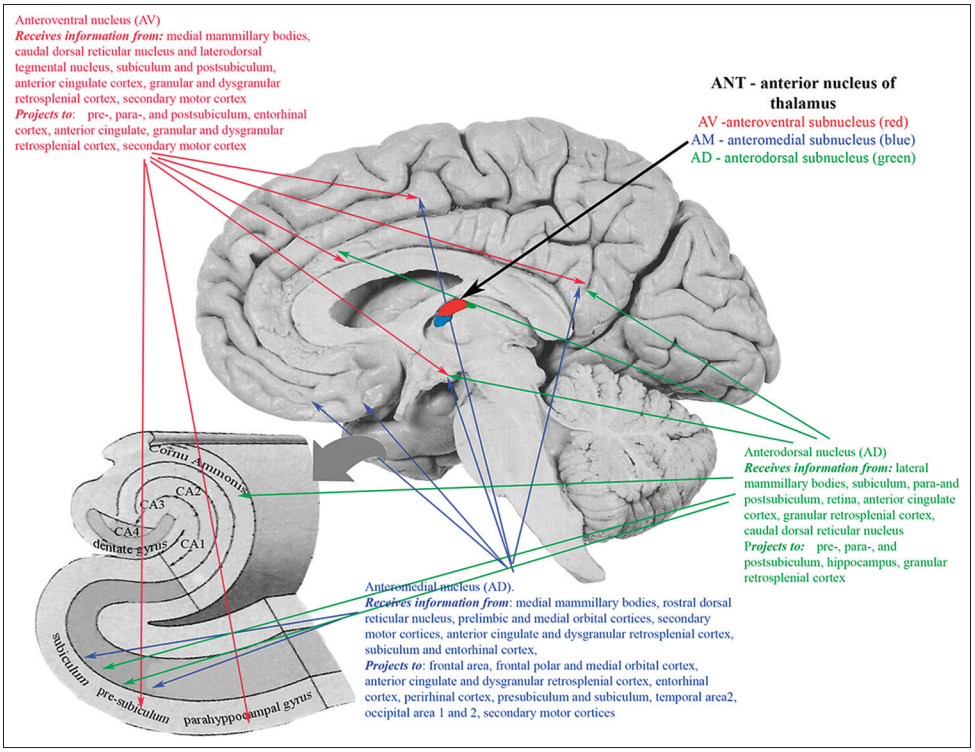

Figure 1: Schematic representation of major projection of ANT

reprogramming and stimulation settings checkup due to remote location from implanting center, 3) the inability to use the patients' programmer due to intellectual decline.

Due to lack of clearly identifiable anatomical borders of ANT on 3 Tesla MRI (GE Discovery MR750w), the patients were scanned day before surgery according to a standardized MR-protocol to visualize well-defined anatomical structures—subthalamic nucleus, red nucleus, and substantia nigra. The CT-scan with stereotactic frame (CRW® System, Integra™) was performed on the day of surgery using a routine protocol followed by the fusion of CT and MRI images. The combined stereotaxic targeting (anterior part of ANT) was performed using the Schaltenbrand and Wahren stereotaxic atlas with correction of final coordinates according to the deviation of visible anatomical targets (red nucleus, subthalamic nucleus) from the coordinates provided by atlas.

The procedure of implantation of electrodes or radiofrequency lesions was performed under a local anesthesia through bilateral 14 mm but holes located 3–3.5 cm posteriorly to the coronal suture and approximately 4 cm from midline. Microelectrode recording was performed in 11 patients from group I and in 18 patients in group II to differentiate the border between the lateral ventricle and the thalamus and define the length of ANT.

In 11 cases, four-contact electrodes (Medtronic 3389) were implanted and in one case eight-contact electrodes (Boston Scientific Vercise™ DBS system) were used.

For lesioning we used CSK-3M radiofrequency electrode (Cosman) with tip diameter 1.1 mm (the diameter of the insulated part of the electrode 1.24 mm, the length of the active tip is 3 mm) connected to G4 four-electrode RF generator (Cosman).

The position of electrodes after ANT DBS and location of lesions after bilateral thalamotomy were confirmed with MRI scan on the same day.

The results of surgical treatment were assessed with Engel and ILAE outcome scales, basing on the seizure diaries and control EEG.

RESULTS

Both groups of patients were comparable in average age, gender, duration of seizure history, and frequency of seizures [Table 1].

In ANT DBS group, one patient diagnosed with idiopathic-generalized epilepsy, three had focal and eight had multifocal epilepsies. In ANT lesioning group, one patient had focal temporal epilepsy and 18-multifocal epilepsy with location of seizure onset zone(s) within frontal and/or temporal lobes, confirmed by continuous EEG-video monitoring.

Two of the patients in group I previously underwent resective surgery due to lesional epilepsy. One of them had focal cortical dysplasia resection (FCD) accompanied by multiple subpial transections in the right frontal lobe, resulting in incomplete seizure control for 2 years and subsequent increase in seizure frequency and severity. The second patient underwent incomplete FCD resection in the posterior part of the left temporal lobe with subsequent clinical and electroencephalographic remission and recurrence of symptoms 3 years later.

According to MRI data, structural abnormalities were noted in three patients from group II: in one patient posttraumatic gliotic changes in the left frontal, temporal, and parietal lobes, in one-transmantle FCD of the right parietal lobe, located in the eloquent area and one patient presented with multiple FCD in the left frontal, left temporal, and left insular lobes not eligible for surgical resection due to high risk of developing irreversible neurological deficit.

The estimated commissural coordinates of the targets (anterior thalamic nuclei) for implantation of stimulating electrodes and stereotaxic ATN lesion are presented in Table 2.

The AP coordinates demonstrated the highest degree of variability due to the significant inter-hemispheric asymmetry of the foramen of Monroe and anatomy of the venous angle, formed by internal vein of the brain, thalamostriate vein, and the anterior septal vein, behind

Table 1: Clinical data of patients

	Group I (12 patients)	Group II (19 patients)
Average age, years	28.9	31.5
Male:female ratio	1:0.41	1:0.36
Age of the seizure onset, years	12.7	12.9
Epilepsy duration, years	18.7	19.4
Frequency of partial seizures per month (median)	9	4
Frequency of generalized seizures (median)	4	4

Table 2: Midcomissural coordinates of the anterior thalamic nuclei

	Anteroposterior (*y*)	Lateral (*x*)	Vertical (*z*)
Average value	3.34210526	4.86315789	11.0105263
Median	2.9	5	11
Standard deviation	1.26109115	0.533552587	0.810962896
Minimum	1.6	3.7	9.6
Maximum	5.7	5.6	12.8

which is located the anterior tubercle of thalamus that contains ANT.

Microelectrode recording data were obtained from 56 trajectories; the clear signal from ANT was noted in 48 trajectories. The frequency of irregular high-amplitude spikes recorded when the microelectrode was passing ANT ranged from 15 to 29 Hz [Figure 2] and did not change with intraoperative motor or sensory testing. The clear signal was not obtained in four patients due to high level of artifacts. According to the MER data, the average length of ATN was 4.1 mm on the left (range 4.0–5.2 mm) and 4.5 mm on the right (range 3.1–4.7 mm).

Group I

The postoperative MRI prior to IPG implantation confirmed correctness of bilateral electrode location in 11 patients [Figure 3]. In one patient, who was implanted without MER, one of the electrodes was found to be 2 mm away from the intended target.

Monopolar cathode stimulation started in the early postoperative period (2–3 days after surgery) with the initial parameters of 1.5 V, 110 Hz, 90 μs and subsequent adjustment of parameters based on clinical and EEG observation. At the time of hospital discharge, the average stimulation parameters were 4 V, 130 Hz, 90 μs.

Postoperative MRI revealed subcortical asymptomatic hematoma of the right frontal lobe with a volume of up to 3 cm^3 located along the electrode track in one patient.

After implantation, all the patients went through adjustment of anticonvulsant therapy based on their seizure type and individual tolerance. Six patients were converted to monotherapy, six to a combination of two AEDs.

Follow-up evaluations and EEG—video monitoring were conducted in 3 months, with final correction of stimulation parameters at 6 months depending on its effectiveness.

There were no neurological side effects from stimulation. Two patients experienced "current leak" at the IPG site with monopolar mode stimulation; this phenomenon disappeared after the stimulation was changed to a bipolar mode.

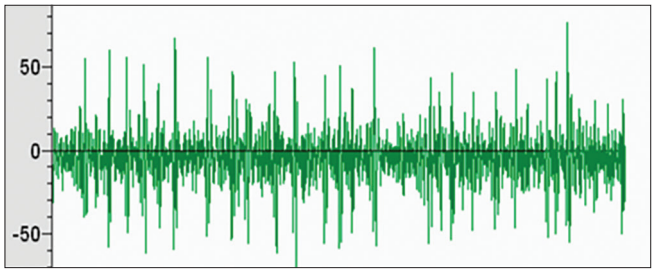

Figure 2: Signal from the anterior thalamic nucleus

Follow-up ranged from 7 months to 5.2 years. The average reduction in seizure frequency a year after the start of stimulation was 80.3%, with three patients becoming seizure-free and four patients having only rare seizures (one of these patients has only night seizures), which are significantly lower in their duration and strength compared to preoperative period. One patient with positive MRI and extensive brain lesions did not respond to stimulation well [Table 3]. The patient discontinued stimulation 2 years after the surgery due to the subjective unsatisfactory assessment of its effectiveness leading to subsequent explantation of the DBS system.

One patient with a unilaterally displaced electrode failed to achieve significant improvement in terms of seizures; however the patient's quality of life improved as a result of objective improvement in cognitive and psychoemotional status.

One patient had an infection along his extension cables resulted in explantation of IPG and the extension cables lines with the preservation of intracranial electrodes.

Group II

In group II patients, postoperative MRI confirmed the location of the lesions zones within ANT on both sides with average diameter of the lesion zone 4.1 mm (range 3.8–5.2 mm) [Figure 4].

In one patient the postoperative MRI scan revealed noticeable lesion only on one side due to technical mistake (mismeasurement of RF-electrode length) requiring repeated unilateral radiofrequency lesion the next day with successfully placed lesion within ANT borders.

During early postoperative period, 16 of the 19 patients experienced a significant reduction in seizures ranging from 50% to 90%. Two patients with a previously registered photoparoxysmal response demonstrated

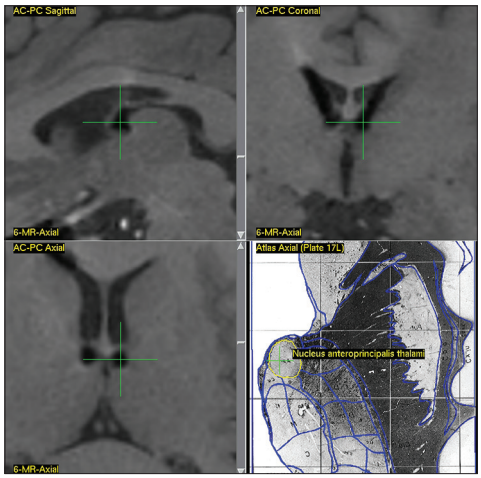

Figure 3: Location of the stimulating electrodes in ANT

Table 3: Results of the anterior thalamic nuclei stimulation

Number (gender)	Reduction of seizure frequency (%)		Side effects		Engel outcome scale (12 months)	ILAE outcome scale (12 months)	AED before surgery mg/day	AED after surgery mg/day
	6 months	12 months	6 months	12 months				
1 (M)	47	21	-	-	IV A	5	Fl-2000	Fl-800
2 (F)	82	88	-	-	I C	2	Fl-800	En-1000
3 (F)	73	77	Current leak	-	I C	2	Lam-300, Top-200	Lam-300, Top-200
4 (F)	69	74	-	-	II B	3	Tri-1800	Vim-2000, Teg-800
5 (M)	79	100	-	-	I A	1	Fl-1600	Ke-2750
6 (M)	56	63	Current leak	-	II D	4	Fl-800, Si -10, Fe-1	De-1000
7 (M)	61	94	-	-	II A	3	Teg-800, Ke-1000	Teg-800, Ke-1000
8 (M)	97	100	-	-	I A	1	De-1500, Tri-1000	De-1500
9 (M)	100	100	-	-	I A	1	Fl-800	Fl-800, De-750
10 (F)	64	86	-	-	IIB	3	Fl-800, Bz-300	Ke-2000, Tri-900
11 (M)	80	80	-	-	I C	2	Sa-300, De-1500	De-1500
12 (F)	75	n/a	-	n/a	n/a	n/a	Fl-1200, Lam-300	Lam -100, Ke-1000

*AED: Antiepileptic drug, Bz: Benzonal, De: Depakine, En: Encorate, Fe: Fenazepam, Fl: Finlepsin, Ke: Keppra, Lam: Lamotrigin, Sa: Sazar, Si: Sibazon, Teg: Tegretol, Top: Topamax, Tri: Trileptal, Vim: Vimpat

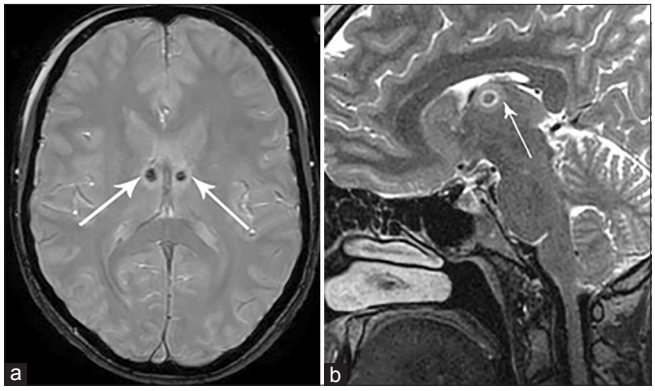

Figure 4: MRI of the patient on the first day after bilateral radiofrequency anterior nucleothalamotomy, axial (a) and sagittal (b) projections. Lesions located in the anterior thalamic nuclei are marked by arrows

increased resistance to photic stimulaiton. In one case, the EEG obtained 12 months after the surgery did not show any pathological activity [Table 4].

The average seizure frequency reduction among the responders with available follow-up exceeded 91.2%. Currently, five patients remain completely seizure-free.

The postoperative period was uneventful in all patients except one who developed a small right-sided subcortical hematoma and transient left-side hemiparesis that resolved in 4 weeks.

No side effects or any significant changes in mental and emotional status were observed after the lesions.

DISCUSSION

Stimulation of the anterior thalamic nuclei for the treatment of epilepsy was first performed in 1980s by Cooper I.S. and Upton A.R. and soon thereafter by Sussman N.M.[7,44,46,47] The choice of ANT as potential stimulation target was primarily based on animal studies of Mirski M.A. *et al.*, demonstrating the leading role of ANT in the distribution of the pathological epileptic activity.[28-30]

In most studies, the authors observed effective suppression of the seizures frequency using high-frequency stimulation in a cyclic mode [Table 5].[1,10,17,21,22,35-38,41,42]

The exact mechanism of action of ANT DBS remains poorly understood. First, the explanation of mechanism of action has to be thought as a result of inactivation of stimulated structures due to the similarity in therapeutic effects with DBS and lesions. However, the possible mechanism of action seems to be more complicated. Model-based analysis of the cellular effects of DBS provided by McIntyre C.C. *et al.* revealed both excitatory and inhibitory effects on the thalamic neurons located near the electrode.[27] It has been shown that response of the neuron to stimulation was dependent on the position and orientation of the axon to the electrode and the stimulation parameters. High-frequency stimulation caused suppression of firing activity during the applying stimulus due to activation of presynaptic terminals. Suprathreshold stimulation caused suppression of firing in the neuron's soma and the same time generated axonal output at the stimulus frequency. The distance from the electrode was predicting the effect of stimulation cells within 2 mm outside of the electrode generated axonal output at the stimulus frequency and neurons stimulated at subthreshold levels (above 2 mm from electrode) were suppressed.[27]

Griffin D. M. *et al.* and later Cheney P. D. *et al.* described the mechanism of "neural hijacking" during intracortical microstimulation and recording the action

Table 4: Results of bilateral radiofrequency lesions of ANT

Number	Sex	Follow up (months)	Reduction of seizures frequency (%)		Engel outcome scale (12 months)	ILAE outcome scale (12 months)	AED before surgery mg/day	AED after surgery mg/day
			3 months	6 months				
1	M	17	-	-	-	-	De-1500, Fl-800	De-2000
2	F	35	-	100	I A	1	Vim-400, De-1000	Vim-400
3	M	33	80	100	I A	1	Fl-400, Tri-1200, Ke-1000, Lam-175	Ke-2500
4	M	33	-	-	-	-	Lam-300	Lam-250
5	M	31	95	100	I A	1	Ke-1000	Ke-1500
6	F	11	-	-	-	-	Fl- 800, Sa-100, Top-200	Fl-800, Sa-100
7	F	30	95	95	I B	2	Fl-600, Lam-200, En-1000	De-1250, Lam-275
8	M	10	-	-	-	-	De-600	Ke-3000, Vim-400
9	M	28	70	80	IIB	2	Fl-1600	Fl-800
10	M	27	50	70	III A	3	Top-200, De-1500, Ke-2000	De-1500, Ke-2000
11	F	24	100	100	I B	2	Lam-200	Lam-200
12	F	5	0	-	-	-	De-1000, Fl-800	De-1000, Fl-800
13	F	24	100	100	I B	2	Ke-3000	Ke-3000
14	M	18	100	100	I A	1	De-1000	No therapy
15	M	16	80	80	I B	2	Sa-200, Tri-1800, Bz-0.04, Re-0.01	Sa-200, Tri-1800
16	M	15	85	85	I B	2	Fl-800, Sa-100, Top-200	Fl-800, Top-200
17	M	11	90	100	I A	1	Lam-200, Tri-600, De-900, Top-125	Tri-600, De-1200
18	M	2	-	-	-	-	De-1000, Ke-1000	De-1000, Ke-1000
19	F	1	-	-	-	-	Fl-800	Fl-800

*AED: Anti-epileptic drug, Bz: Benzonal, De: Depakine, En: Encorate, Fe: Fenazepam, Fl: Finlepsin, Ke: Keppra, Lam: Lamotrigin, Re: Relanium, Sa: Sazar, Si: Sibazon, Teg: Tegretol, Top: Topamax, Tri: Trileptal, Vim: Vimpat

Table 5: Effectiveness of anterior thalamic stimulation in the treatment of pharmacoresistant epilepsy

Author	Number of patients	Reduction of seizures frequency
Upton *et al*., 1987[47]	6	4 out of 6 patients-clinical response
Hodaie *et al*., 2002[15]	5	54% (24-89%)
Kerrigan *et al*., 2004[17]	5	48% (−57 to 98%)
Lee *et al*., 2006[21]	3	75.4% (50-90.6%)
Lim *et al*., 2007[24]	4	49% (35-76%)
Osorio *et al*., 2007[36]	4	75.6% (53-92%)
Andrade *et al*., 2009[1]	2	98% in one patient, 66% in the second patient
Fisher *et al*., 2010 (SANTE)[10]	110	56% average frequency after 2 years and 68% after 5 years 31
Lee *et al*., 2012[22]	15	70.51% (0-100%)
Oh *et al*., 2012[35]	9	57.9% (35.6-90.4%)
Piacentino *et al*., 2015[37]	6	More than 50%
Van Gompel *et al*., 2015[49]	2	More than 50%
Sitnikov *et al*., 2013[42], 2015[41]	10	64% after 6 months and 86% after 12 months, three patients without seizures
Lehtimäki *et al*., 2016[23]	15	10 out of 15 patients (67%) reached the reduction of seizures frequency more than 50%
Krishna *et al*., 2016[19]	15	50% and more reduction of seizures frequency in 11 of 15 patients

potentials from single neurons.[4,13] They showed that high-frequency stimulation not inhibits but eliminates and replaces natural activity. The mechanism proposed by authors was described as "excitation of axons by intracortical microstimulation and elimination of natural spikes by antidromic collision with stimulus-driven spikes evoked at high frequency." This hypothesis can explain the modulation of pathological activity in cortical neurons involved in epileptic circuity with ANT DBS through cortico–thalamo–cortical excitatory loops. ANT projections are mostly represented in hippocampus, mammillary bodies, temporal and frontal lobes as shown on Figure 2 and this can be a reason of sensitivity of temporal and frontal epilepsy to ANT DBS.

Other thalamic nuclei also have been proposed for DBS in refractory epilepsy. Velasco F. *et al*. reported five cases of centro-median thalamic nucleus (CMT) DBS in 1987

showing the significant reduction in seizures frequency.[51] Subsequent series with higher number of patients also demonstrated the great efficacy of CMT DBS especially in patients with Lennox–Gastaut syndrome.[50,52-54] The results in patients with partial epilepsy were less favorable comparatively to patients with generalized seizures only two from five achieved more than 80% seizure reduction.[53,54]

Fisher R. S. *et al*. in 1992 also reported at least a 50% decrease in seizure frequency in three of six patients with CMT DBS with no side effects.[11] And once more the tonic-clonic generalized seizures seemed to be more sensitive to stimulation.

More recent study published by Valentín A. in 2013 included 11 patients (five with frontal lobe epilepsy, six with primary-generalized epilepsy) treated with CMT DBS.[48] All six patients with generalized epilepsy had more than 50% seizure reduction during the blinded phase, and 5/6 maintained more than 50% seizure reduction during the long-term extension phase. Five patients with frontal lobe epilepsy patients did not respond so well, with only one patient with more than 50% improvement in seizure frequency during the blinded phase. During the long-term follow-up, three patients with frontal lobe epilepsy demonstrated 50–90% reductions in seizure frequency with two nonresponders.

All published data regarding to CMT DBS clearly showing the great efficacy for primary-generalized seizures, especially in cases of Lennox–Gastaut syndrome with less prominent effectiveness in cases of frontal or temporal lobe partial epilepsy in contrast with ANT DBS that is more suitable for cases of secondary-generalized seizures originated from temporal/frontal lobes.

The parameters of ANT stimulation still remain empirical. In the SANTE trial the stimulation with 5V 145Hz 90 μs in cycling mode (1 min on/5 min off) resulted in 76% median reduction in seizure frequency at 5 years.[10,38] In our patients we started stimulation from 1.5 V, 110 Hz, 90 μs with gradual increasing up to 4 V, 130 Hz, 90 μs relying on video-EEG data and seizures diary. In first four cases we used cycling mode (2 min on/2 min off), subsequently changed to continuous stimulation due to better respond in terms of seizure control.

Animal study provided by Gibson W. S. *et al*. showed an amplitude-dependent increase activation within temporal, prefrontal, and sensorimotor cortex in at 60 Hz and 145 Hz stimulation, but not with 2 Hz stimulation.[12] Those findings supporting the hypothesis that ANT DBS has an amplitude and frequency dependent effects on cerebral cortex and epileptic seizures. However, there is still some uncertainty about the adjusting the stimulation in patients with different seizure types and origin.

The use of various electrodes and modes for stimulation also can be an issue. In most studies the majority of patients were implanted with Medtronic 3387 leads following by monopolar stimulation. Patients in our study were implanted with Medtronic 3389 leads (one case eight-Boston Scientific Vercise™ DBS electrodes) with shorter inter-contact spacing (0.5 mm) and were stimulated with monopolar configuration. The use of electrodes with shorter spacing more likely allows to implant two contacts within ANT and change parameters to bipolar mode if needed without current spreading on adjacent thalamic nuclei. In two patients from our group who experienced current leak with monopolar stimulation, we achieved the parameters correction from monopolar to bipolar configuration without reducing the amplitude/frequency and with the same efficacy in seizures reduction.

The issue of stereotactic planning in the anterior thalamic nuclei is extremely important, because effective seizure frequency reduction is possible only with bilateral ANT stimulation or lesion.[14,24,28]

Möttönen T., Lehtimäki K. *et al*. demonstrated the possibility of a precise delineation of the ANT anatomical boundaries using STIR and T1-MPRAGE MR-sequences.[15,16,23,33] The authors believe that the most important anatomical landmarks in the planning are mammillothalamic tract, the external, and internal medullary lamina. Buentjen L. also indicated the possibility of visualizing ANT anatomical boundaries for direct targeting.[3] However, even on the MR images published by these authors, the clear visualization of the real boundaries of the nuclei is difficult and requires considerable skills. In our series of 31 patients using 3 Tesla MRI (GE Discovery MR750w) for stereotactic planning with T1, T2, SWAN, FLAIR, and DWI sequences we failed to obtain the reliable anatomical borders of ANT in vast majority of cases, even with STIR sequence. In some cases, ANT could be recognized usually unilaterally, however this did not provide the strong bases for direct anatomical targeting. It is also important to consider the imperfect match of visible anatomical boundaries on MRI and physiological boundaries of targets, similar to what is observed with subthalamic nucleus or the internal segment of globus pallidus.

Recently, Krishna V. *et al*. showed that microelectrode recording can be used to identify the nature of the signal from the ANT, however it is not mandatory due the signal nonspecificity.[19] A number of other authors pointed to the possible higher accuracy of electrodes location in the anterior thalamic nuclei using for EEG-driving response and microelectrode recording and as a consequence—improvement of surgical treatment results.[18,33] It is expected that the final role of microelectrode recording in ANT stimulation will

be refined, and it is obvious that any additional data obtained during the surgical intervention may improve the results.

The characteristic data of the ANT signal and anterior ventral thalamic nuclei (VA) (three spike per 2 s for ANT and seven spikes per 2 s for VA), shown in work of Lehtimäki *et al*., are similar to what we saw in our cases and confirm the theory that firing rate is more specific for ANT than the signal shape and/or interspike interval.[33] It is worth mentioning, however, that there may be a difference MER data obtained from the patients under general anesthesia, as described by Lehtimäki K. *et al*., and our patients that were operated under local anesthesia.

Due to presumably higher risk of hemorrhagic complications the use of microelectrode recording in ANT DBS still controversial, especially considering the transventricular trajectory of electrode placement. However, recent data showing the minimal, if not a zero risk of microelectrode recording-associated hemorrhages.[6,9,39] The precise targeting with respect of venous anatomy of ventricles and one-pass trajectory of microelectrode can prevent the intraventricular hemorrhages. We had only one case of subcortically located small asymptomatic hemorrhage in patients with ANT DBS could equally happen during the MER or insertion of stimulating electrode. Second case was presented with symptomatic hemorrhage in patients with ANT lesions and was not related to MER, the hemorrhage occurred after removing the canula from the brain few minutes after second lesion.

Another technical complication noted in patients with ANT DBS was unilateral misplacement of DBS electrode. The possibility of electrode misplacement during ANT DBS also was specified by other studies, resulted in recommendation of obligatory postoperative MRI to confirm the electrodes location, irrespective of neurophysiological conformation and preoperative targeting.[43]

Stereotactic lesioning of anterior thalamus predates ANT DBS by about 20 years. The first report on unilateral stereotactic lesion of the anterior thalamus in humans for the treatment of epileptic seizures was published in 1967 by Mullan S. *et al*.[34] Despite unpredictability of size of radiation necrosis with the use of a strontium needle, the imprecision of stereotactic calculations based on pneumoventriculography and angiography data, a seizure freedom achieved in two of nine patients, a significant improvement was noted in four cases and there was no response in one patient. Six of nine patients developed complications associated with injury of the internal capsule and various subcortical structures manifested in severe hemiparesis, aphasic, and visual disturbance and one hemorrhage in the subcortical nuclei. The authors stated that in each case the lesion zone included the additional damage of internal capsule, lateral group of nuclei, the field of Forel, mammillothalamic tract, and in some cases the subthalamic nuclei. With this extensive spread of the lesions, it is not possible to judge antiepileptic effectiveness of selective ANT lesioning.

With modern MRI and targeting techniques the precise placement of lesions gives the alternative to ANT DBS in some selected cases as has been shown in our study. The same efficacy of bilateral ANT stimulation and lesions in terms of seizures control confirm the major role of ANT in propagation of epileptic activity originated from temporal/frontal lobes. However, more studies needed to specify the indications to both procedures and to define best candidates for ANT DBS/ANT lesions among patients suffering from medically intractable seizures.

CONCLUSION

Stereotactic radiofrequency anterior nucleotalamotomy and high-frequency ANT stimulation appear to have similar efficacy in terms of seizures control in patients with pharmacoresistant epilepsy with single or multiple sources of pathological activity located in the frontal and temporal lobes. The maximum efficiency of both approaches is observed in the suppression of secondarily generalized seizures, whereas simple partial seizures are less responsive.

Use of microelectrode recording facilitates accurate determination of neurophysiological borders of the anterior thalamic nuclei and appears to improve surgical treatment results.

Financial support and sponsorship
Nil.

Conflicts of interest
There are no conflicts of interest.

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