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SHORT RESEARCH ARTICLE

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Responsive neurostimulation targeting the anterior nucleus of the thalamus in 3 patients with treatment-resistant multifocal epilepsy

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Summary

Electrical stimulation in the anterior nucleus of the thalamus (ANT) has previously been found to be efficacious for reducing seizure frequency in patients with epilepsy. Bilateral deep brain stimulation (DBS) of the ANT is an open-loop system that can be used in the management of treatment-resistant epilepsy. In contrast, the responsive neurostimulation (RNS) system is a closed-loop device that delivers treatment in response to prespecified electrocorticographic triggers. The efficacy and safety of RNS targeting the ANT is unknown. We describe 3 patients with treatment-resistant multifocal epilepsy who were implanted with an RNS system, which included unilateral stimulation of the ANT. After >33 months of follow-up, there were no adverse effects on mood, memory or behavior. Two patients had ≥50% reduction in disabling seizures and one patient had a 50% reduction compared to pretreatment baseline. Although reduction in seizure frequency has been modest to date, these findings support responsive neurostimulation of the ANT as feasible, safe, and well-tolerated. Further studies are needed to determine optimal stimulation parameters.

KEYWORDS

anterior nucleus thalamus, epilepsy surgery, multifocal epilepsy, responsive neurostimulation, Treatment-resistant epilepsy

1 | INTRODUCTION

The anterior nucleus of the thalamus (ANT) is considered a promising site for neurostimulation in epilepsy due to its connections to hippocampal outflow in the Papez circuit, an important pathway in seizure propagation. Experimental studies of ANT stimulation have been performed in animal models of epilepsy with mixed but generally positive results.[1–6] Although Lado et al[5] found that bilateral ANT deep brain stimulation (DBS) actually reduced seizure threshold in kainic acid model rats, numerous studies have supported the efficacy of bilateral ANT stimulation in increasing seizure threshold, including in pentylenetetrazole-induced, amygdala-kindled, and pilocarpine-induced models.[1–3] Of interest, the latter 3 studies also showed that unilateral ANT stimulation in each model did not affect seizure threshold. Two other studies found that unilateral stimulation in the ANT increased seizure threshold in pilocarpine-induced and amygdala-kindled rat models.[4,6] Human studies of the ANT have been more consistent, identifying significant reductions in seizure frequency with bilateral ANT DBS.[7–12]

Although these studies found a benefit of stimulation beyond implantation, one human study of ANT DBS found that stimulation provided no additional benefit above implantation alone,[13] with another study showing unclear benefit of stimulation.[12] In the multicenter, randomized, double-blinded stimulation of the anterior nucleus of the thalamus for epilepsy (SANTE) trial,[14] patients with focal epilepsy who were randomized to bilateral ANT stimulation with intermittent stimulation by implanted DBS experienced significant long-term reduction in seizure frequency, reduced seizure-related injuries, and improvement in epilepsy-related quality of life scores. On long-term follow-up, these patients experienced significant improvement in neuropsychological outcomes including depression, anxiety, attention, and executive function.[15] There was a trend toward decreased seizure frequency in a subgroup of patients with multifocal epilepsy, but the subgroup was too small to identify conclusive results.[14]

The responsive neurostimulation, or RNS, system (NeuroPace, Mountain View, CA), was approved by the US Food and Drug Administration (FDA) in 2013 for treatment-resistant focal epilepsy in patients ≥18-years-old with ≤2 seizure-onset zones based on the positive results of controlled trials.[16,17] With few treatment-related adverse events and known feasibility of early seizure detection[17] and abatement by stimulation[18] of the ANT, RNS is considered a potentially attractive alternative to DBS. This closed-loop system delivers therapeutic stimulation dependent on seizure detection by electrocorticographic correlate; this selectivity may result in improved efficacy and avoid some adverse effects associated with open-loop stimulation systems like DBS. Unlike DBS of the ANT, RNS electrodes are typically implanted in or adjacent to the presumed epileptogenic focus. To date, published data on the safety and efficacy of the RNS system have been limited to patients with ≤2 seizure foci with treatment targeting the seizure-onset zone. It is unknown if the therapeutic effects of the RNS system require direct stimulation of the cerebral cortex or if stimulation of subcortical brain regions such as the ANT—with its thalamocortical projections to the cortical seizure foci—can also exert beneficial neuromodulatory effects. If RNS of a brain region with diffuse cortical projections can influence activity at distant cortical seizure foci, it may facilitate effective treatment options for patients with multifocal or generalized-onset seizures.

In this article, we describe 3 patients with treatment-resistant multifocal epilepsy who were implanted with RNS in cortical epileptogenic zones and ANT in an attempt to palliate debilitating seizures through the institution's off-label compassionate-use policy. This case series provides insight into the feasibility, safety, and potential efficacy of this treatment approach.

2 | METHODS

A retrospective chart review was performed on 3 patients with treatment-resistant multifocal epilepsy who received care at NYU Langone Medical Center and underwent RNS system implantation involving the ANT under the institution's compassionate-use policy. Demographic, magnetic resonance imaging (MRI), electroencephalography (EEG), electrocorticography (ECoG), neuropsychological testing, and follow-up data were abstracted according to institutional review board (IRB)–approved protocol. All patients had ≥33 months of follow-up after RNS system implantation. Seizure frequency estimates were based on ECoG data and seizure diaries. Baseline seizure frequency was determined by patient and caregiver report from the year before RNS implantation as well as documentation of seizure frequency as summarized in the patients' multidisciplinary surgical conference presentations. Medication adjustments were performed at the discretion of the patients' epileptologists in conjunction with regular modifications to RNS detection and therapy settings.

3 | RESULTS

All 3 patients were male, aged 26- to 30-years-old, with a duration of epilepsy ranging from 9 to 23 years. Each patient had a diagnosis of multifocal epilepsy confirmed by intracranial EEG monitoring. Patient 1 had ANT depth electrode implantation by a transventricular approach. Patients 2 and 3 had ANT depth electrodes placed by an extraventricular approach. Patients 1 and 3 had bilateral ANT implantation, whereas Patient 2 had unilateral ANT implantation. In Patient 3, the depth electrode was identified postoperatively in the ANT-ventral lateral nucleus border with remaining contacts in the ventral lateral and ventral anterior thalamic nucleus. Postoperative electrode reconstructions also confirmed implantation of depth electrodes in the ANT in Patients 1 and 2 (see Figure 1). Each patient also had a cortical strip placed in the region of the most clinically disabling seizures, or most robust electrographic ictal evolution. Each patient had one ANT depth and one ipsilateral cortical strip connected to the RNS generator for detection and stimulation. Thalamic depth electrode locations for each patient are shown in Figure 1.

ECoG demonstrated spread of ictal activity to the ANT as well as seizure activity independently within the ANT (Figure 1). No adverse effects including mood, memory, or behavioral changes have been reported in more than 33 months of postoperative follow-up.

All patients underwent medication adjustments during the follow-up period at the discretion of their epileptologists while undergoing regular refinements of RNS detection and

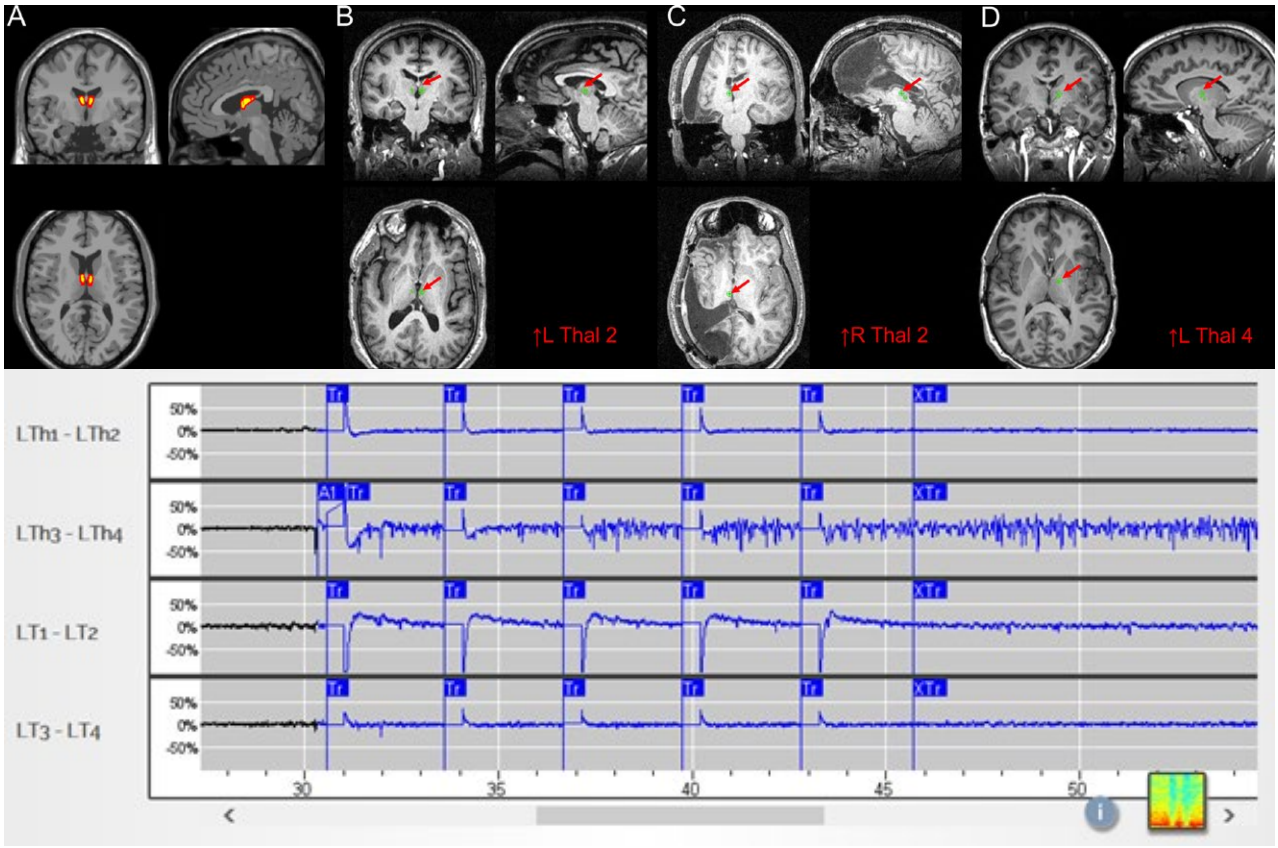

FIGURE 1 Localization of thalamic electrodes and electrocorticography of seizure detection in thalamic electrodes. Top Panel: (A) Location of ANT based on a standard subcortical MRI atlas (Ewert et al, 2017) superimposed on an Montreal Neurological Institute (MNI) template MRI. Location of select thalamic RNS electrodes (green) obtained from postimplant computed tomography (CT) coregistered to the preimplant MRI for Patient 1 (B), Patient 2 (C), and Patient 3 (D). Contact number identified by the red arrow is indicated in the text box. Bottom Panel: ECoG recording of ictal onset in Patient 1 with initial electrographic changes seen in thalamic electrodes. (LTh, Left thalamic electrode; LT, Left temporal electrode)

therapy settings. Patient 1 initially experienced only subclinical seizures after initiating RNS therapy; the first clinically disabling seizures were recorded 4 months after implantation in the setting of a medication taper. Nine months after implantation, this patient experienced an average of 1.5 clinically disabling seizures per month but experienced periodic exacerbations acutely in the setting of additional medication adjustments. Overall, Patient 1 experienced a 50% reduction from preimplant baseline in clinically disabling seizures by the time of last follow-up. Patient 2 experienced near-complete resolution of focal aware sensory seizures 2 months after starting RNS therapy but clinically disabling seizures remained frequent. Ten months after implantation, he underwent significant medication adjustments; 18 months later, seizures were no longer associated with injuries, and at the time of last follow up, clinically disabling seizures decreased from a baseline average of 15 per month to 7 per month (53.3% reduction from preimplant baseline). Seizure frequency and severity were essentially unchanged for Patient 3 until he had some improvement approximately 10 months after RNS implantation after medication changes. Eighteen months after implantation, seizures again worsened in the setting of medication changes, with steady improvement noted 9 months later until the time of last follow-up, with a reduction of average monthly clinically disabling seizures of 56% from baseline. Detailed demographic and clinical information of each patient are summarized in Table 1.

4 | DISCUSSION

These results support the feasibility, safety, and tolerability of RNS in the ANT for treatment-resistant multifocal epilepsy. Although there was only modest improvement in seizure control, no adverse effects related to stimulation were reported by any patient throughout the course of treatment. These results are consistent with a recent report of long-term safety and tolerability of chronic thalamic RNS for intractable Tourette's syndrome in one patient.[19] Although unilateral stimulation of the ANT has been shown to reduce seizures in animal models,[4,6] human studies of subcortical electrical stimulation of the ANT in epilepsy have examined only

TABLE 1 Patient demographic and clinical data

	Patient 1	Patient 2	Patient 3
Age at implant (years)	27	23	24
Age at epilepsy onset (years)	3.5	0.25	15
Sex	M	M	M
Handedness	L	Ambidextrous	R
Clinically disabling seizure types	Focal with impaired awareness; focal to bilateral tonic-clonic	Focal with impaired awareness; focal to bilateral tonic-clonic; atonic	Focal with impaired awareness
Intracranial EEG	Nonlateralized ictal onset with some seizures demonstrating robust evolution in the temporal lobes, left more than right	Bilateral multifocal seizures with a predominance of right frontal and right frontocentral ictal onsets	Bilateral multifocal seizures with majority demonstrating broad left hemispheric onset including the parietal lobe with variable involvement of frontal and temporal cortex
Other interventions	VNS	VNS, R anterior temporal lobectomy, R frontal and parietal corticectomies, anterior 2/3 corpus callosotomy.	None
RNS lead implantation, active leads	L ANT, depth L middle temporal gyrus, strip	R ANT, depth R postcentral gyrus, strip	L ANT, depth L parietal lobe, strip
RNS lead implantation, inactive leads	R ANT, depth R middle temporal gyrus, strip	R anterior precentral gyrus, strip R precentral gyrus, strip	R ANT, depth R parietal lobe, strip
RNS ECoG	Two electrographic seizure types: one characterized by gamma activity in the left temporal cortex with spread of rhythmic spikes to the L ANT, and one characterized by evolution of rhythmic spikes in the L ANT that may or may not spread to temporal cortex	Multiple seizure with initial detection in R postcentral cortex characterized by gamma activity or repetitive spikes, with or without spread to ANT. Not all clinically disabling seizures are detected.	Seizures characterized by bursts of polyspikes in the L parietal cortex with rapid spread to ANT
Current stimulation parameters	Left ANT depth: Config: monopolar Current: 4.5 mA ECD: 2.3 μC/cm^2 Frequency: 142.9 Hz Pulse width: 160 μS Burst duration: 100 msec	Right ANT depth: Config: monopolar Current: 5.5 mA ECD: 2.8 μC/cm^2 Frequency: 142.9 Hz Pulse width: 160 μS Burst duration: 100 msec	Left ANT depth: Config: bipolar Current: 5.0 mA ECD: 5.1 μC/cm^2 Frequency: 142.9 Hz Pulse width: 160 μS Burst duration: 100 msec
	Left temporal strip: Config: monopolar Current: 4.5 mA ECD: 2.8 μC/cm^2 Frequency: 200 Hz Pulse width: 160 μS Burst duration: 100 msec	Right postcentral strip: Config: monopolar Current: 5.5 mA ECD: 2.8 μC/cm^2 Frequency: 200 Hz Pulse width: 160 μS Burst duration: 100 msec	Left parietal strip: Config: monopolar Current: 6.5 mA ECD: 3.3 μC/cm^2 Frequency: 142.9 Hz Pulse width: 160 μS Burst duration: 100 msec
Daily therapies[a]	202	1213	2986
Duration of follow-up	33 mo	33 mo	35 mo
Adverse effects	None	None	None
Outcomes	50% reduction in disabling seizures	53.3% reduction in disabling seizures	56% reduction in disabling seizures

ANT, anterior nucleus of the thalamus; Config, electrode configuration; ECD, estimated charge density; ECoG, electrocorticography; EEG, electroencephalography; L, left; M, male; mA, milliampere; msec, milliseconds; R, right; RNS, responsive neurostimulation (system); VNS, vagus nerve stimulation; μC, microcoulombs.[A]

Daily therapies are calculated as: $\frac{\text{Number of episodes with therapies delivered per epoch}}{\text{Number of hourly bins in epoch}/24}$

bilateral stimulation to date.[7–12] Ideal settings for responsive neurostimulation at this site are currently unknown, and more data must be obtained to accurately characterize its efficacy and optimal programming.

An important complication that occurred in this case series is that one patient was found to have misplacement of a lead that was targeted to the ANT. This electrode was implanted using an extraventricular approach and was placed posterolaterally to the target at the border between the ventral lateral nucleus and the ANT instead of in the ANT proper. In a study of patients who underwent ANT DBS for refractory epilepsy, Lehtimäki et al[20] found that 29.5% of the extraventricular approach DBS placements and 10.3% of the transventricular approach DBS placements were off target. This highlights a relatively common complication of ANT placement of which providers should be aware and illustrates that postoperative imaging is essential in confirming accurate surgical placement. Furthermore, the RNS depth electrodes used have 3.5 mm interelectrode spacing; although these are the smallest electrodes available for the RNS system, they were not well suited for the precision required for a target as small as the ANT.

Limitations of this study include lack of control group, nonblinded nature, and recall bias in reporting seizures. In addition, the small sample size limited our ability to detect statistically significant differences for both treatment efficacy and side effects. Evaluation of therapeutic benefit was also confounded by concomitant medication adjustments that were required by all patients during the postimplant follow-up period. There was a trend for patients in the SANTE trial who had frontal or temporal foci to have greater seizure reduction compared to those with foci in other lobes.[14] It is unclear at this time if this is related to the functional connectivity of ANT, and some authors propose other thalamic targets such as centromedian nucleus for the treatment of extralimbic epilepsies.[21,22]

One key finding in this study was that RNS electrodes placed in the ANT were able to record electrographic correlates and enable visualization of thalamic coupling for many of the seizures in our patients. The ability to record from and therapeutically target major neural network intersections in an individualized, stimulus-dependent manner is particularly appealing in light of the limited treatment options for many patients with refractory multifocal or generalized epilepsy. We are unable to conclude that seizure onset was in the ANT itself, as it is considered more likely that seizure onset was from an unsampled region of cortex with propagation to the ANT. Possible future areas of investigation include evaluation of RNS in bilateral ANT or centromedian nuclei, both of which are thalamic targets with known involvement in seizure networks.[21–23] However, although subcortical seizure detection may prove to be an important treatment option for these patients in the future, more data are necessary to accurately evaluate the true potential of subcortical responsive neurostimulation in epilepsy.

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