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Impedance Characteristics of Stimulation Contacts in Deep Brain Stimulation of the Anterior Nucleus of the Thalamus and Its Relationship to Seizure Outcome in Patients With Refractory Epilepsy

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ABSTRACT

Background: Deep brain stimulation (DBS) of the anterior nucleus of the thalamus (ANT) is an emerging form of adjunctive therapy in focal refractory epilepsy. Unlike conventional DBS targets, the ANT is both encapsulated by white matter layers and located immediately adjacent to the cerebrospinal fluid (CSF) space. Owing to the location of the ANT, implantation has most commonly been performed using a transventricular trajectory. Previous studies suggest different electrical conductivity between gray matter, white matter, and CSF.

Objectives: In this study, we asked whether therapeutic impedance values from a fully implanted DBS device could be used to deduce the actual location of the active contact to optimize the stimulation site. Secondly, we tested whether impedance values correlate with patient outcomes.

Materials and Methods: A total of 16 patients with ANT-DBS for refractory epilepsy were evaluated in this prospective study. Therapeutic impedance values were recorded on regular outpatient clinic visits. Contact locations were analyzed using delayed contrast-enhanced postoperative computed tomography–3T magnetic resonance imaging short tau inversion recovery fusion images previously shown to demonstrate anatomical details around the ANT.

Results: Transventricularly implanted contacts immediately below the CSF surface showed overall lower and slightly decreasing impedances over time compared with higher and more stable impedances in contacts with deeper parenchymal location. Impedance values in transventricularly implanted contacts in the ANT were significantly lower than those in transventricularly implanted contacts outside the ANT or extraventricularly implanted contacts that were typically at the posterior/inferior/lateral border of the ANT. Increasing contact distance from the CSF surface was associated with a linear increase in therapeutic impedance. We also found that therapeutic impedance values were significantly lower in contacts with favorable therapy response than in nonresponding contacts. Finally, we observed a significant correlation between the left- and right-side averaged impedance and the reduction of the total number of seizures.

Conclusions: Valuable information can be obtained from the noninvasive measurement of therapeutic impedances. The selection of active contacts to target stimulation to the anterior nucleus may be guided by therapeutic impedance measurements to optimize outcome.

Keywords: Deep brain stimulation, drug-resistant epilepsy, electric impedance, epilepsy, thalamus

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INTRODUCTION

Deep brain stimulation (DBS) of the anterior nucleus of the thalamus (ANT) is an emerging form of adjunctive therapy in focal refractory epilepsy. The efficacy of ANT-DBS has been documented by pilot studies,[1–6] one large-scale randomized controlled multicenter trial,[7,8] and several single-center open-label studies.[9–11]

The ANT is located at the anterior and superior aspect of the thalamus at the floor of the lateral ventricle. According to the stereotactic atlas[12] and 3T magnetic resonance imaging (MRI) data,[13] the ANT comprises an approximately 4- to 5-mm-thick strip of thalamic tissue immediately below the cerebrospinal fluid (CSF) surface of the lateral and third ventricle. Because of this location, the transventricular (TV) approach has been almost exclusively used in ANT-DBS.[1–11] The location of the active contact at the ANT, ie, within a few millimeters of range from the CSF surface, has been reported to be associated with a favorable outcome, whereas stimulation of contacts located more deeply in the brain parenchyma has had a poor outcome.[11]

Impedance is a measure of brain tissue resistance.[14] Impedance between every DBS lead contact pair or between a contact and the implantable pulse generator (IPG) can be measured using currently available programming devices to check their integrity. Electrode impedance refers to impedances between contacts and/or IPG using standardized parameters, whereas therapeutic impedance refers to impedance using the parameters and contact combination currently in therapeutic use.[14]

Impedance values have been reported to correlate with the microelectrode registration (MER)–based brain anatomy but not with imaging data around the subthalamic nucleus (STN).[15] Impedance values also differ between movement disorder targets.[16,17] According to the pioneering work by Latikka et al,[18] impedance is low in CSF compared with brain tissue and is slightly higher in white matter than in gray matter when measured during a neurosurgical procedure. On the contrary, measurements around STN using chronically implanted devices showed higher impedance in gray matter than in white matter, potentially reflecting the differences in capsule formation and/or perielectrode fluid accumulation processes between the white and gray matter.[15]

The location of the stimulation target immediately below the CSF space along the lead trajectory is a unique feature of ANT-DBS therapy compared with any other DBS target and may therefore have clinically relevant implications. For instance, the proximity of the CSF space may shape the current field and consequently influence the clinical effect and/or side-effect profile. Furthermore, the ANT is encapsulated by an incomplete white matter laminar layer identifiable in 3T MRI and MER, potentially affecting impedance values.[13]

Here, we sought to determine the relationship between the anatomical location of the active contact and therapy impedance values in patients with chronic ANT-DBS for refractory epilepsy. Impedance data were analyzed with respect to MRI data especially designed for visualization of the ANT.

MATERIALS AND METHODS

Patients

A total of 16 patients with refractory epilepsy not amenable to surgical resection underwent ANT-DBS surgery at Tampere University Hospital. All patients underwent 3T MRI and video-electroencephalogram investigations as a part of presurgical evaluation. No invasive investigations were performed. One patient had previous resection of the temporal lobe (patient number 9). Clinical characteristics are shown in Table 1. Surgery was planned using the Surgiplan software (Elekta AB, Stockholm, Sweden) based on preoperative 3T MRI, enabling direct visualization of the ANT.[11,13] In patients with intact vagus nerve stimulation (VNS) therapy, 1.5T MRI was used using a comparable imaging protocol.[19] Surgery was performed under general anesthesia using a Leksell frame (Elekta AB) after coregistration of the preoperative MRI and stereotactic contrast-enhanced thin-slice computed tomography (CT). Two patients underwent bilateral lead revision surgery, and impedance measurements from both implants were included in the analysis (correction of the lead depth bilaterally in one patient and replacement of leads bilaterally in one patient). The default stimulation parameters were 1 minute on/5 minutes off cycle, 140 Hz, 90 μs, and 5 V amplitude but were individually adjusted to optimize the therapy. The most common adjustment, in addition to a change in the active contacts, was an increase in amplitude or pulse width. Parameters deviating from default parameters are shown in Table 2. The ANT-DBS study protocol was approved by the Ethics Committee of Tampere University Hospital. Clinical characteristics of the patients are shown in Table 1, and lead contacts used are shown in Table 3. The therapeutic response was classified as a response or nonresponse for a given chronically stimulated contact combination of sufficient duration, using a >50% reduction in seizure count of the dominant or most severe seizure type as a criterion. Absolute seizure reductions (total seizure count) are shown in Table 3.

Therapy Impedance Measurements

Therapy impedances from the contacts selected for active stimulation were measured using a fully implanted DBS device (Medtronic 3389 leads connected to extension cables and Activa PC neurostimulator [Medtronic, Dublin, Ireland]) using an N'Vision clinical programmer (Medtronic) and recorded prospectively on follow-up visits approximately every three months. Periods of bipolar stimulation and stimulation of multiple monopolar contacts were omitted from the analysis. To study the correlation between the anatomical location of a contact and therapy impedance values, the mean therapy impedance value during stimulation of a given contact was first calculated. Next, these values were plotted together with the distance from the CSF surface to test the correlation between impedance and distance from CSF. The mean therapeutic impedance values also were compared between groups based on the MRI-based classification of contact location.

Assessment of Contact Location

The imaging parameters enabling delineation of the ANT have been reported previously in detail.[11,13,19] The precise location of a given contact was classified into ANT or outside-ANT groups based on preoperative MRI short tau inversion recovery (STIR)–postoperative CT fusion images. The contacts at the ANT were further divided into superficial and distal contact at the ANT. The distance of each contact implanted using the TV trajectory from the "second entry point" at the floor of the lateral ventricle was measured in preoperative 3T MRI T1-weighted magnetization-prepared gradient echo images. To allow comparison between extraventricularly implanted contacts and transventricularly implanted contacts, an

Table 1. Patient Demographics and Clinical Characteristics.

Patient no.	Sex	Age at implantation (y)	Epilepsy duration (y)	Etiology	MRI findings	Epileptic zone	Seizure types	Previous VNS
1	M	48	37	CD	Bilateral perisylvian polymicrogyria	Right temporal	FIAS	No
2	M	24	5	Unknown	Normal	Left parietal	FIAS, FBTCS	Yes
3	M	45	9	Unknown	Normal	Right frontal	FIAS, FBTCS	Yes
4	M	50	49	Ischemic lesion	Right parietal hypoxic or ischemic lesion	Right frontal	FAS, FIAS	Yes
5	M	22	10	Encephalitis	Normal	Multifocal	FIAS, FBTCS	Yes
6	F	24	7	Encephalitis	Bilateral parietal inflammatory lesion	Multifocal	FAS, FIAS, FBTCS	Yes
7	F	31	3	Encephalitis	Normal	Multifocal	FAS, FIAS	No
8	M	40	32	CD	Bilateral perisylvian polymicrogyria	Multifocal	FIAS	Yes
9	F	32	31	CD	Left frontal cortical dysplasia	Left frontal	FIAS	Yes
10	F	26	19	CD	Bilateral perisylvian polymicrogyria	Multifocal	FAS, FIAS	Yes
11	M	47	38	Unknown	Normal	Frontal	FIAS, FBTCS	No
12	M	49	44	Encephalitis	Right parietal & temporal inflammatory lesion	Right temporal	FIAS, FBTCS	No
13	M	56	42	Unknown	Normal	Multifocal	FIAS, FBTCS	Yes
14	M	29	20	Unknown	Normal	Right frontal	FIAS, FBTCS	
15	M	30	18	CD	Bilateral periventricular heterotopy	Multifocal	FIAS, FBTCS	Yes
16	M	24	14	Encephalitis	Normal	Multifocal	FIAS	Yes

CD, cortical dysplasia; F, female; FAS focal aware seizure; FBTCS, focal to bilateral tonic-clonic seizure; FIAS, focal impaired awareness seizure; M, male.

imaginary TV trajectory was created, and the distance between the imaginary "second entry point" and the contact was calculated.

Statistical Analysis

SPSS (version 26.0; IBM, Armonk, NY) was used for the statistical analysis. Therapeutic impedances were not normally distributed in most analyses. Therefore, the statistical difference between multiple related samples was tested using the Friedman test, between two related samples using the Wilcoxon signed-rank test and between two independent groups using the Mann-Whitney *U* test. The correlation between continuous scale variables was tested using Spearman's test.

RESULTS

A total of 57 contacts were used for active stimulation trials and thus had available therapeutic impedance measurements that were analyzed with respect to distance from the CSF border and the MRI-based classification of location. A total of 51 contacts were analyzed in different time points (constant stimulation and contact change analysis, Table 3). A total of 25 leads were placed using a TV lead trajectory, with the most superior contact being immediately below the CSF surface, whereas nine leads had a longer parenchymal course either owing to the placement of the TV lead more deeply than anticipated (deep TV [dTV]; $n = 3$) or to the extraventricular (EV) lead trajectory ($n = 6$). In one patient (patient number 5), deeply located TV leads were repositioned and after revision classified as optimal TV lead category (Table 3). A total of 37 contacts with available therapy impedance measurements were at the ANT (including two contacts close to the CSF border), 19 contacts were outside the ANT (ten EV implanted contacts at the ANT border and nine contacts with deep TV implantation), and one contact was most likely in the CSF. The two most proximal contacts in optimally placed TV leads were typically at the ANT. The contacts from EV leads with available therapy impedance measurements were at the posterior, inferior, and lateral border of the ANT.[11] The contacts from TV leads implanted more deeply than anticipated with available therapy impedance measurements were deep to the ANT in the dorsomedial nucleus of the thalamus. A total of 17 contacts were stimulated chronically (a mean of 27.5 ± 12.7 months) without evidence of lead migration or changes in the active contact, allowing the assessment of stability of the impedances. In 17 leads, the active contact was changed during the therapy, and the total number of lead contacts in contact change analysis was 36 (Table 3).

The Effect of Contact Location on Impedance Values

We found that contact location had a profound effect on impedance values. The contacts in TV leads implanted immediately below the CSF surface showed impedances that were overall lower and slightly decreasing over time compared with higher and more stable impedances shown in contacts from leads with a deeper parenchymal course (Fig. 1a). Therapeutic impedance decreased slowly during chronic stimulation without a change in stimulation site, with an average rate of 87.3 Ω/year during 27.8 months of stimulation (TV and EV lead contacts combined; $n = 17$). Therapeutic impedances were significantly different between time points when all leads were analyzed as a group ($p < 0.05$; df 3; Friedman test). The last therapeutic impedance was significantly lower in TV leads than in the first measurement ($p < 0.05$; Wilcoxon signed-rank test; $Z = -2.118$), whereas EV or dTV lead impedances were not significantly changed. Reprogramming of the more proximal

Table 2. Individual Stimulation Parameters.

Patient	Trajectory L/R	All contacts and outcome classification (responder/nonresponder)	Contacts with impedance and seizure reduction data	First contacts	Second contacts	Third contacts	SR first contacts (%)	SR second contacts (%)	SR third contacts (%)	L/R mean impedance first contacts (Ω)	L/R mean impedance second contacts (Ω)	L/R mean impedance third contacts (Ω)
								*			ns	
1	EV/TV	2, 10, 11 (NR)	2, 10, 11	2/10 (5–7 V)	2/11 (150 μs; 180 Hz)		−6.1	3.0		1083	987	
2	EV/EV	0, 1, 8, 9 (NR[†])	1, 9	1/9 (6/6 V)			−63.4			1074		
3	TV/TV	3, 11 (NR)	3, 11	3/11			21.4			877		
4	TV/TV	2, 10 (NR)	No (lead migration)									
5	dTV/dTV	3, 11, 0, 8 (NR)	3, 11, 0, 8	3/11 (4–6 V; 180 Hz)	0/8		23.0	16.5		1283	1308	
Reposit	TV/TV	2, 10 (NR)	2, 10	2/10			12.6			792		
6	TV/TV	2, 10 (NR), 3, 11 (R)	2, 3, 10, 11	2/10 (150 μs)	3/11		−15.9	−69.6		960	717	
7	TV/TV	2, 10 (NR), 3, 11 (R)	2, 3, 10, 11	2/10 (5–7 V)	3/11		−18.0	−47.8		889	625	
8	TV/TV	2, 10 (NR), 3, 11 (R)	2, 3, 10, 11	2/10	3/11		−32.5	−83.1		1020	854	
9	dTV/EV	2, 1, 3, 10, 9, 11 (NR)	2, 1, 3, 10, 9, 11	2/10 (5–7 V)	1/9 (150 μs)	3/11	24.5	−16.9	−26.7	953	1066	1043
Reimpl	TV/TV	2, 11 (R)	2, 11	2/11			−54.2			769		
10	EV/EV	2, 10 (R)	2, 10	2/10 (5–6.5 V)			−96.9			849		
11	TV/TV	3, 10 (NR)	3, 10	3/10 (5–7 V)			−16.7			966		
12	TV/TV	2, 3, 10, 11 (R)	2, 3, 10, 11	2/10	3/11		−58.3	−88.9		842	606	
13	TV/TV	2, 10 (NR), 3, 11 (R[‡])	3, 11	3/11			−38.7			583		
14	TV/TV	2, 10 (R)	2, 10	2/10			−50.0			663		
15	TV/TV	2, 10 (NR), 3, 11 (R[‡])	3, 11	2/10	3/11 (5–6 V)			−18.4			996	
16	TV/TV	3, 11 (R)	3, 11	3/11			−79.1			509		
Total	36	57 (NR, n = 35; R, n = 22)	49				−28.0	−38.2	ND	882	895	ND

Default stimulation parameters were 5 V/5 V; 90 μs; 140 Hz; 1 minute on-5 minutes off cycling. Parameters different from these default settings are shown in parentheses after contact combinations. L/R, left/right; ND, not determined; NR, nonresponder; ns, not significant; R, responder; Reimpl, after lead reimplantation; Reposit, after lead repositioning; SR, seizure reduction.

*Wilcoxon signed-rank test, $p < 0.05$; $Z = -2.028$.

[†]Nonresponder caused by episodes of status epilepticus.

[‡]More than 50% reduction in most disabling seizure type (focal to bilateral tonic-clonic seizure).

Table 3. Overview of Contact Changes and Analyses.

Patient	Trajectory L/R	Contact changes	CSF distance analysis (all contacts)	Time course analysis	Constant	Contact change	ANT (TV)	ANT border (EV)	dTV (inferior to ANT)	CSF
1	EV/TV	2/10 → 11	2, 10, 11	2, 10, 11	2	10, 11	10, 11	2		
2	EV/EV	0 → 1/8 → 9	0, 1, 8, 9	0, 1, 8, 9		0, 1, 8, 9		0, 1, 8, 9		
3	TV/TV	3/11	3, 11	3, 11	3, 11		3, 11			
4	TV/TV	2/10	2, 10	No (migration)			2, 10			
5	dTV/dTV	3/11; 3 → 0/11 → 8	3, 11, 0, 8	3, 11, 0, 8	3, 11*	3, 11, 0, 8			0, 3, 8, 11	
Reposit	TV/TV	2/10	2, 10	2, 10	2, 10		2, 10			
6	TV/TV	2 → 3/10 → 11	2, 3, 10, 11	2, 3, 10, 11		2, 3, 10, 11	3, 10, 11		2	
7	TV/TV	2 → 3/10 → 11	2, 3, 10, 11	2, 3, 10, 11		2, 3, 10, 11	2, 3, 10, 11			
8	TV/TV	2 → 3/10 → 11	2, 3, 10, 11	2, 3, 10, 11		2, 3, 10, 11	3, 10, 11		2	
9	dTV/EV	2 → 1/10 → 9; 1 → 3/9 → 11	2, 1, 3, 10, 9, 11	2, 1, 3, 10, 9, 11		2, 1, 3, 10, 9, 11		9, 10, 11	1, 2, 3	
Reimpl	TV/TV	2/11	2, 11	No			2, 11			
10	EV/EV	2/10	2, 10	2, 10	2, 10			2, 10		
11	TV/TV	3/10	3, 10	3, 10	3, 10		3, 10			
12	TV/TV	2 → 3/10 → 11	2, 3, 10, 11	2, 3, 10, 11		2, 3, 10, 11	2, 3, 10, 11			
13	TV/TV	2 → 3/10 → 11	2, 3, 10, 11	2, 3, 10, 11		2, 3, 10, 11	2, 10, 11			3
14	TV/TV	2/10	2, 10	2, 10	2, 10		2, 10			
15	TV/TV	2 → 3/10 → 11	2, 3, 10, 11	2, 10 (no 3, 10)	2, 10		2, 3, 10, 11			
16	TV/TV	3/11	3, 11	3, 11	3, 11		3, 11			
Total	36		57	51	17*	36	37	10	9	1

L/R, left/right; Reimpl, after lead reimplantation; Reposit, after lead repositioning.
*Note that contacts 3 and 11 (patient number 5) were included in both constant stimulation analysis and contact change analysis.

contact in optimally placed TV leads resulted in a further decrease in impedance values ($Z = -2.934$; $p < 0.01$; Wilcoxon signed-rank test), whereas contact changes in leads with deep parenchymal course either proximal ($Z = -0.730$, $p = 0.465$; Wilcoxon signed-rank test) or distal ($Z = -1.461$; $p = 0.144$; Wilcoxon signed-rank test) were not significant (Fig. 1b).

Impedance values in contacts at the ANT ($n = 37$) were significantly lower than in the outside-ANT ($n = 19$) location (median 814 Ω vs 1044 Ω; $Z = -3.542$; Mann-Whitney test; $p < 0.001$) (Fig. 2a). Furthermore, the impedance values were significantly lower in the most superficial contacts at the ANT ($n = 24$) than in the more distal contacts at the ANT ($n = 13$) (median 736 Ω vs 929 Ω; $p < 0.001$, $Z = -3.627$; Mann-Whitney test). Contacts implanted using the EV trajectory (being located at the inferior, lateral, and posterior border of the ANT but not clearly at the ANT) showed significantly higher impedance values than did all contacts at the ANT (median 1013 Ω vs 814 Ω) ($p < 0.05$, $Z = -3.041$; Mann-Whitney test) (Fig. 2a).

To further study the relationship between the CSF space and therapeutic impedance, the distance of a given contact from CSF surface was calculated in leads implanted using the TV trajectory. For EV lead contacts, an imaginary TV trajectory was created, and the distance from the CSF surface was calculated to allow comparison with similarly located TV contacts. We found a significant correlation between therapeutic impedance and the distance of the contact from the CSF surface ($n = 57$; correlation coefficient = 0.74; $p < 0.01$; Spearman's test; Fig. 2b,d). EV lead contact impedance values were not statistically different from TV contacts with location at the distal ANT or inferior border of the ANT ($Z = -1.240$; $p = 0.232$; Mann-Whitney test; Fig. 2b).

Impedance Values and Outcome

Ten of 16 patients (62.5%) eventually fulfilled the response criteria, either using the initial settings or after optimization of the stimulation site by reprogramming or reoperation. We found that therapy impedance values were significantly lower in contacts with favorable therapy response ($n = 22$) than in nonresponding contacts ($n = 35$) (median 763 Ω vs 1007 Ω; $Z = -4.524$; $p < 0.001$; Mann-Whitney test) (Fig. 2c). Reflecting the lower impedance in a constant-voltage stimulation setting, the median therapeutic current was significantly higher in responding contacts than in nonresponding contacts (6.5 mA vs 5.3 mA) ($Z = -3.452$; $p < 0.01$; Mann-Whitney test).

To test the correlation between impedance values and the reduction of the total number of seizures, the mean left/right active contact impedance values during chronic stimulation of the most optimal contacts were calculated together with the total seizure reduction compared with baseline during the last three months of stimulation using the same contacts. We observed a significant negative correlation between impedance and the reduction of the total number of seizures ($n = 15$; correlation coefficient = 0.668; $p < 0.01$; Spearman's test) (Fig. 2d). One patient with lead migration was omitted from the analysis. The reduction in the total number of seizures was significantly greater with the second contacts than with the first selected contacts ($p < 0.05$; $Z = -2.028$; Wilcoxon signed-rank test) (Table 2).

DISCUSSION

The location of the target immediately below the CSF surface along with the lead trajectory is a unique feature of ANT-DBS therapy compared with any other commonly used DBS target. We found that therapy impedance values correlate highly with the imaging data of the actual contact location and subsequently with seizure outcome. We demonstrate here that in addition to the traditional use of therapy impedance to check the device integrity, it may be used to optimize the stimulation site in refractory epilepsy. Keeping in mind the desperate lack of easily observable clinical symptoms in refractory epilepsy guiding clinical programming, together with the challenges in defining the detailed location of the contacts in the ANT, this could be of importance.

Our data can be summarized as follows: 1) the depth of the active contact affects therapeutic impedance values as evidenced by imaging; 2) therapy impedance is significantly lower in contacts at the ANT than in contacts outside the ANT location; 3) contacts

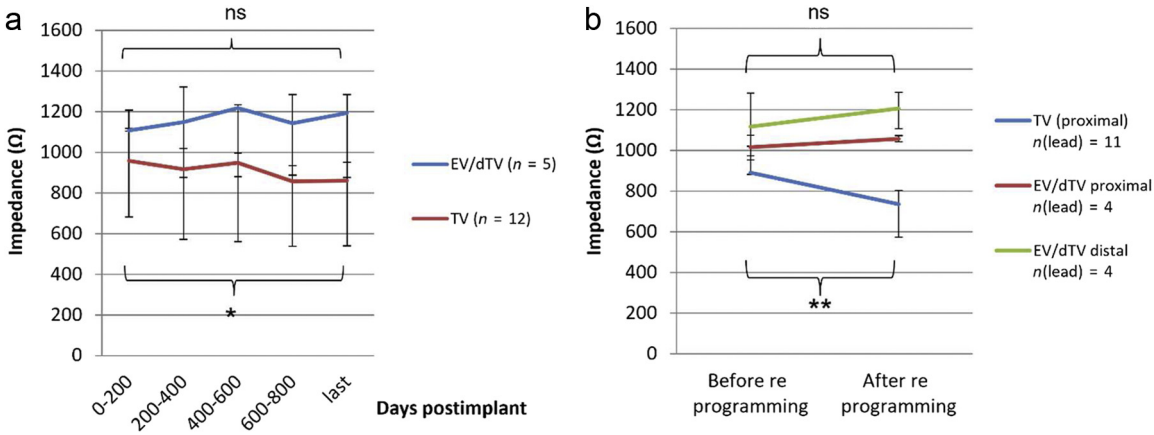

Figure 1. Therapeutic impedance during chronic stimulation and the effect of reprogramming. a. The median therapeutic impedance values during chronic stimulation in TV and EV or dTV leads. Therapeutic impedances differ significantly between time points when all leads are analyzed as a group ($p < 0.05$; Friedman test, not shown). Transventricularly implanted leads at the level of ANT show statistically significant decrease at the last observation compared with initial values ($p < 0.05$; Wilcoxon signed-rank test), whereas EV/dTV leads with longer parenchymal course remain unchanged (panel a). b. The effect of change in the active contact. The change in the active contact in either direction has no statistically significant effect on EV or dTV leads, but activation of more proximal lead contact in TV lead results in statistically significant decrease in impedance ($p < 0.05$; Wilcoxon signed-rank test). *$p < 0.05$; **$p < 0.01$ (Wilcoxon signed-rank test). ns, not significant. [Color figure can be viewed at www.neuromodulationjournal.org]

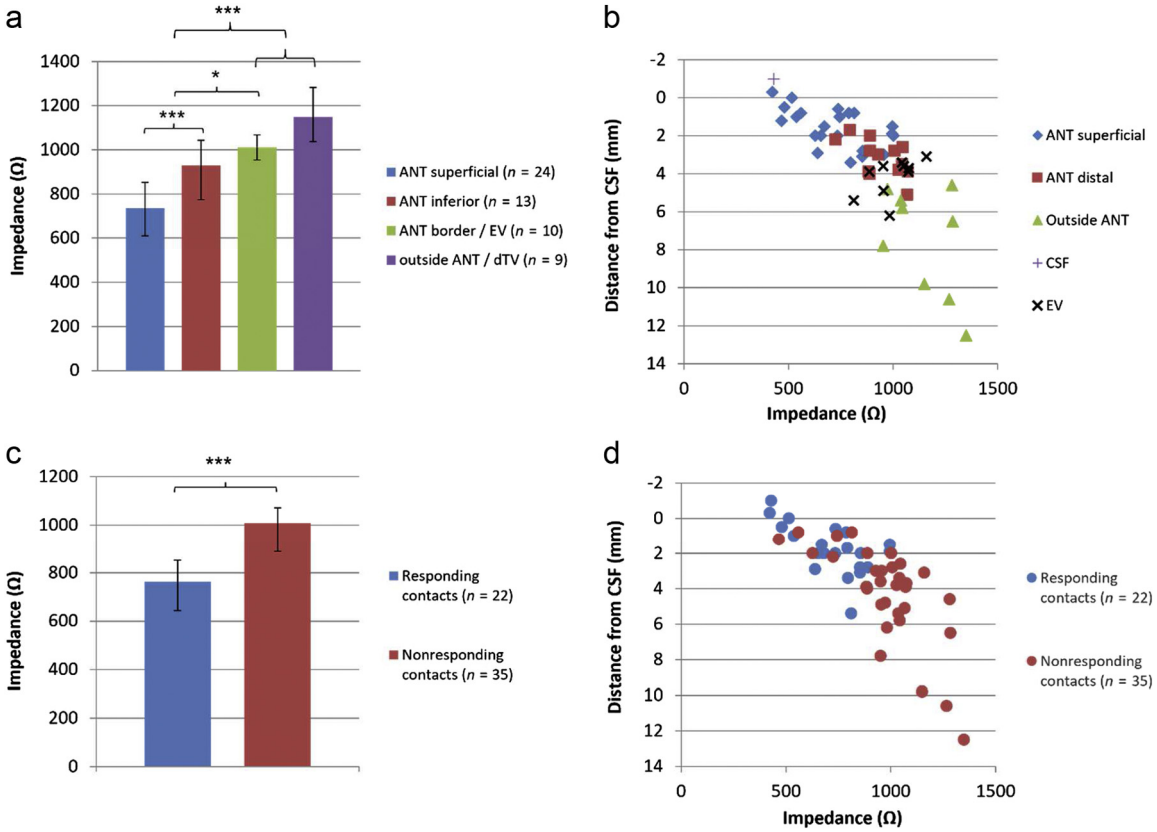

Figure 2. Therapeutic impedance correlates with contact location and therapy outcome. Therapeutic impedance values, contact location with respect to CSF border, and therapy outcome are demonstrated. a. Impedance values and classified contact locations based on MRI (one lead contact was presumably in CSF space and not included in panel a). b. The distance of a given contact from CSF surface, together with MRI-based locations (the distance of contacts implanted using the EV trajectory is calculated using an imaginary TV trajectory). c. Therapy impedance is significantly lower in contacts associated with therapy response. d. Lead contacts associated with therapy response are located within a 4-mm distance from the CSF border. *$p < 0.05$; ***$p < 0.001$; Mann-Whitney test. [Color figure can be viewed at www.neuromodulationjournal.org]

associated with a clinical response show significantly lower therapeutic impedances together with higher therapeutic currents than contacts without a response; 4) low impedance values are associated with greater seizure reduction; 5) therapy impedance tends to decrease slowly during chronic stimulation in contacts at the level of the ANT but not significantly in deeper structures.

The ANT is a 4- to 5-mm-thick shred of tissue bordering the CSF on its superior, anterior, and medial surfaces and the brain parenchyma on its lateral, inferior, and posterior aspects.[12] The Medtronic 3389 lead used in this study has four 1.5-mm-long cylindrical contacts with 0.5-mm interspaces, resulting in a total of 3.5-mm span of two contacts. Because the average height of the ANT in 3T MRI is approximately 4 mm in a plane parallel to a typical TV trajectory,[13] two contacts of 3389 lead may indeed be placed at the ANT. Interestingly, we noted that therapy impedances were significantly lower in both superficial and distal contacts at the ANT than in outside-ANT (deep) location when implanted using the TV trajectory (Fig. 3). The strong correlation between therapy impedance values and the distance from the CSF surface suggests that the presence of the CSF in fact interacts with the DBS lead and results in a local decrease in brain tissue resistance. The effect of the CSF on therapy impedances was noted along the span of two Medtronic 3389 lead contacts, with the distance being 3 to 4 mm in length. Importantly, this distance nearly equals the expected diameters of the ANT from the CSF surface.[13] Contacts implanted using the EV lead trajectory were at the inferior border of the ANT and had impedance values like those of inferior border/distal ANT contacts. However, because no EV implanted contacts were clearly in the ANT, the impact of the TV trajectory per se on a contact in the ANT cannot be fully addressed.

ANT-DBS therapy is challenging compared with traditional movement disorder DBS, not only because of the challenging location of the target but also because of the lack of easily observable symptoms guiding treatment decisions.[13] In a recent pivotal study, impedances were inversely related to the symptom relief in Parkinson disease.[15] At least several months of follow-up are needed to observe any change in seizure counts in contrast to an almost immediate symptom relief in, eg, Parkinson disease or tremor. We have previously recommended image-guided surgery using a specific imaging protocol to identify the ANT, accompanied with image-guided programming to overcome this challenge.[11,19] In the light of our current data, easily performed noninvasive impedance measurement may be of value in optimizing the stimulation site in transventricularly implanted leads to improve outcome. However, it is not a substitute for high-quality imaging and accurate targeting and lead positioning. We recommend that interpreting the impedance data be in relation to imaging and not in a vacuum.

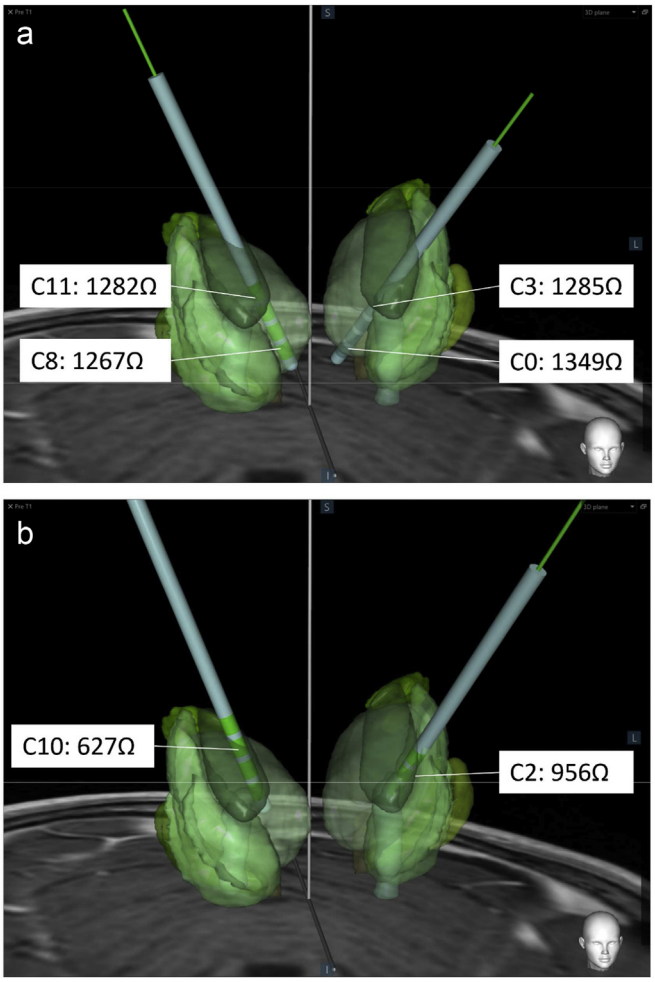

Figure 3. Impedance before and after lead reposition. Therapeutic impedances from TV leads before and after repositioning (case no. 5). a. TV leads implanted more deeply than anticipated. Therapeutic impedances are at the level typically seen in movement disorders (panel a). b. Revision of the leads was performed where leads were pulled upward, aiming the most proximal contacts at the superior border of the ANT. Therapeutic impedances decreased after surgery. Note that lower therapeutic impedances are measured from contact 10 being slightly below the CSF surface. Slightly higher values were measured from contact 2 with a slightly deeper position. Reconstruction of the lead locations was performed using SureTune 3 software (Medtronic). The anterior nucleus was first manually delineated based on 3T MRI STIR images. Paris atlas was then superimposed to manual ANT borders to illustrate the surrounding thalamic nuclei. C, contact. [Color figure can be viewed at www.neuromodulationjournal.org]

We also found evidence that therapy impedance values decrease slightly over time (Fig. 1). Impedance values tend to decrease during chronic DBS in movement disorders, in a manner correlating with stimulation intensity.[16,17,20,21] Impedance also is thought to reflect the foreign-body reaction and capsule formation around the chronically implanted electrodes.[22] The accumulation of peri-electrode fluid has been hypothesized to explain this phenomenon.[17]

However, large and sudden impedance changes may indicate lead withdrawal or migration and should be further examined using CT or MRI. A case of lead migration after ANT-DBS has been reported in a patient with suboptimal initial placement of the lead and enlarged ventricles.[23] Another case of lead migration to the third ventricle and CSF egress through the DBS lead has been reported.[24] A slight decrease of impedances associated with an increase in ventricle size has been reported in three cases with movement disorders without lead migration.[25] Overall, the incidence of lead migration as a hardware complication is approximately 1% to 2% in movement disorders.[26]

It may be concluded that therapy impedance measurement is a useful method to assess contact location with respect to the CSF surface in leads implanted using the standard TV trajectory. Superficial lead contact location with relatively low impedance and high therapeutic current was associated with greatest seizure reduction. The limitation of this study is our small and heterogenous study population, and we encourage others also to explore their therapy impedance data to perhaps corroborate these findings.

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Authorship Statements

Jukka Peltola and Kai Lehtimäki were responsible for the conception and design of the study. Timo Möttönen, Joonas Haapasalo, and Kai Lehtimäki were responsible for the analysis and interpretation of the data. Timo Möttönen and Kai Lehtimäki drafted the manuscript. All authors were responsible for the acquisition of the data. All authors were responsible for the revision of the manuscript. All authors approved the final version of the manuscript.

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COMMENT

I really enjoyed this article. It was very well written and well analyzed. Although my preference is to not use TV approaches, this article provides a great argument based on impedances considering using TV to improve ANT stimulation. The only limitation is the few patients (18) where we have typically response rates around 60%, so it is difficult to ensure the *n* is enough to draw a conclusion, but I really do think the authors did a great job with this paper.

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