Brain Stimulation 9 (2016) 268–275

Contents lists available at ScienceDirect

Brain Stimulation

journal homepage: www.brainstimjrnl.com

Outcome based definition of the anterior thalamic deep brain stimulation target in refractory epilepsy

K. Lehtimäki [a,*], T. Möttönen [a], K. Järventausta [b], J. Katisko [c], T. Tähtinen [a], J. Haapasalo [a], T. Niskakangas [a], T. Kiekara [d], J. Öhman [a], J. Peltola [a]

[a] Department of Neurosciences and Rehabilitation, Tampere University Hospital, Finland
[b] Department of Psychiatry, Tampere University Hospital, Finland
[c] Department of Neurosurgery, Oulu University Hospital, Finland
[d] Imaging Centre, Tampere University Hospital, Finland

ARTICLE INFO

Article history:
Received 24 June 2015
Received in revised form 19 September 2015
Accepted 30 September 2015
Available online 9 October 2015

Keywords:
Refractory epilepsy
Targeting
Deep brain stimulation
Seizure
Anterior nucleus of the thalamus

ABSTRACT

Background: Deep brain stimulation of the anterior nucleus of the thalamus (ANT) is an emerging therapy for refractory focal epilepsy. However, the most optimal target for stimulation has not been unambiguously described.
Objective: In the present study, we investigated the correlation between the stimulation site and outcome in order to define the optimal target for deep brain stimulation in refractory epilepsy.
Methods: The locations of 62 contacts used in 30 treatment attempts in 15 prospectively followed patients during a 5 year period were assessed. Treatment attempts were classified into responding and non-responding trials using seizure reduction and side effect profile as criteria. The locations of active contacts were calculated with respect to mid-commissural point and visible borders of ANT in 3T MRI (ANT-normalized coordinate system) aiming to minimize the confounding effect of individual variation in the location and size of the ANT.
Results: Contacts in successful treatment trials were located significantly more anterior and superior both in AC–PC and ANT-normalized coordinate systems. Favourable outcome was observed at 3T MRI based location of ANT but not at location predicted by Schaltenbrandt atlas sagittal data. Contacts used in successful trials were at anterior aspect of the ANT complex evidenced by the ANT-normalized coordinate system.
Conclusion: The anti-epileptic effect of anterior thalamic DBS may be dependent on stimulation site especially in the anterior to posterior axis. Extensive anatomical variation confounds severely the targeting of ANT. Therefore, direct visualization of the desired target for stimulation is essential for favourable outcome in refractory epilepsy.

Introduction

Deep brain stimulation (DBS) of the anterior nucleus of the thalamus (ANT) was first introduced by Cooper and Upton [1–4] followed by several pilot studies reporting safety and potential efficacy in refractory epilepsy [5–10]. This pioneering work motivated performing a large scale controlled multicentre trial (SANTE trial) with a 29% greater seizure reduction in the active stimulation group compared to sham stimulation and a median of 56% seizure reduction compared to baseline at 2 years [11]. Recent 5-year results of the SANTE trial showed slightly improved outcome with a median of 69% seizure reduction [12]. Finally, favourable long-term efficacy of ANT-DBS was also reported by Lee et al. with a mean of 70% seizure reduction [13].

Abbreviations: 3T, three tesla; 18-F-FDG-PET, 18-fluoro-deoxyglucose-positron-emissio-tomography; AC, anterior commissure; AM, anteromedial nucleus; ANT, anterior nucleus of thalamus; Apr, anterior principal nucleus; DBS, deep brain stimulation; IPG, internal pulse generator; MCP, midcommissural point; MRI, magnetic resonance imaging; MTT, mamillo-thalamic tract; PC, posterior commissure; PTZ, pentylenetetrazole; SANTE, stimulation of anterior nucleus of thalamus in epilepsy; SPSS, statistical package for social sciences; STIR, short tau inversion recovery; SWA, Schaltenbrant–Wahren atlas; T1WI, T1 weighted image; T2WI, T2 weighted image; VAT, volume of activated tissue; X_R, relative X coordinate in ANT-normalized coordinate system; Y_R, relative Y coordinate in ANT-normalized coordinate system; Z_R, relative Z coordinate in ANT-normalized coordinate system.

* Corresponding author. Tel.: +358 3 311 69412; fax: +358 3 31164373.
E-mail address: kai.lehtimaki@pshp.fi (K. Lehtimäki).

Data presented previously in scientific meetings (oral presentations): European Society for Stereotactic and Function Neurosurgery, Maastricht, The Netherlands, 2014; Brain Stimulation Conference, Singapore, March 2015.

http://dx.doi.org/10.1016/j.brs.2015.09.014

The selection of ANT as a potential target nucleus for stimulation was based on data suggesting crucial role for ANT in seizure spread [14–17]. Available studies including the SANTE trial have tested this hypothesis by assessing seizure reduction compared to baseline after implantation of leads aiming at ANT. However, the specific effect of active contact location on outcome has not been addressed previously. Therefore, the specific anterior thalamic region being responsible for the favourable outcome has not been unambiguously defined.

The targeting method of choice for DBS depends largely on the visualization of the target structure. Poor visualization of the desired target in MRI encourages the use of indirect atlas based targeting using stereotactic coordinates. Importantly, a high degree of anatomical variation has been reported in the location of ANT in stereotactic space in non-epileptic subjects [18]. We have recently confirmed this finding using 3T MRI in patients with epilepsy [19]. These data suggest that atlas based targeting may not be unquestionably feasible to ANT targeting. Fortunately, recent developments in the imaging of the ANT suggest that ANT can be delineated using 3T MRI techniques visualizing the white matter structures enveloping ANT [19,20] enabling direct DBS targeting of ANT.

The present study investigates the relationship between the stimulation site at ANT vicinity and outcome in patients with refractory epilepsy. We specifically asked whether a region associated with the most optimal outcome can be defined in stereotactic space. Secondly, we tested whether a region of the most favourable outcome can be directly defined relative to visible ANT borders. Finally, we sought for evidence suggesting that stimulation specifically at ANT is more effective than stimulation of adjacent thalamic structures.

Materials and methods

Patients

A total of 15 patients underwent ANT-DBS for refractory epilepsy. All patients were evaluated using inpatient video-EEG telemetry, 18-F-FDG-PET and 3T MRI to identify potential epileptogenic zone/epileptic syndrome and evaluated for resective surgery. Clinical features of the patients are summarized in Table 3. Study plan was approved by the Ethical Committee of Tampere University Hospital.

Imaging

The MRI sequences obtained for surgical planning included sagittal T1WI with thin slices for multiplanar reconstruction, axial T2WI, and STIR in all three orientations in majority of the patients [19]. All images were obtained using a 3T scanner (MAGNETOM Trio 3T, Siemens Healthcare Sector, Erlangen, Germany) with a 12-channel head matrix coil. The STIR sequence used was a 2D turbo inversion recovery sequence with short inversion time (TR/TE/TI = 8300 ms/22 ms/120 ms: acquisition time 7:05 minutes), with a slice thickness/gap of 2.0/0.2 mm, matrix size 256 × 256 and FOV of 235 mm.

During surgery, patients underwent stereotactic CT followed by co-registration of the previously performed surgical plan. Few days after surgery, patients underwent postoperative thin slice CT followed by image fusion to the preoperative STIR images using Elekta software (Elekta AB, Stockholm, Sweden).

Planning of the procedure

Surgical plan was performed using Elekta Surgiplan software. The preliminary surgical target was at 5–6 mm lateral, 12 mm superior and 0–2 mm anterior to MCP. The target was then individually adjusted according to individual anatomy using the mamillothalamic (mtt) tract as a landmark. The trajectory was planned to run primarily transventricularly (24 out of 30) avoiding major visible vascular structures in contrast enhanced T1 images. Paraventricular trajectory was selected as a secondary option (6 out of 30) due to rich ventricular veins. Paraventricular approach to the central part of ANT was found to be challenging due to course of thalamostriatal vein at superior, lateral and anterior aspect of ANT. Keeping in mind the hippocampal input to ANT via mtt, the trajectory in these cases was planned to run at inferior–lateral aspect of ANT, aiming to stimulate mtt–ANT junction.

Surgery

Surgery was performed under general anesthesia except patient number 1. DBS electrodes (Medtronic 3387 in patient 1 and 3389 in consecutive 14 patients) were implanted via insertion cannula extending 10 mm level above planned target under intra-operative fluoroscopy control and fixed to the skull. Extension cables and Activa PC (Medtronic) internal pulse generator (IPG) were implanted in the same procedure.

Stimulation parameters

Stimulator was typically turned on in the fifth postoperative day using 1 min ON and 5 min OFF cycle, 140 Hz, 90 μs pulse width. The stimulation amplitude was elevated to 5 V during a period from 5–6 postoperative days to 2–3 weeks. The initial contacts for cathodal monopolar stimulation were selected by neurosurgeon using preoperative MRI–postoperative CT fusion images. Changes in active contacts were later made due to lack of response or side effects (Table 1). In one patient, bipolar stimulation was used due to implanted cardiac pacemaker.

Evaluation of the outcome

First 3 months after implantation were excluded from the analysis due to a potential lesion effect [11]. Contact pairs were classified as a responding contact pair or non-responding contact pair using a >50% reduction in seizure frequency and side-effect profile as a criteria. Seizure frequency assessment was based on patient's seizure diaries. An episode of status epilepticus or intolerable side-effects during contact pair stimulation led to classifying the treatment trial as a non-responding trial. Characteristics of the treatment trials and therapy response are presented in Table 2.

Evaluation of contact locations

The locations of contacts relative to MCP were calculated from postoperative CT–preoperative 3T MRI fusion images using FrameLink software (Medtronic). Contact locations were superimposed onto a sagittally oriented overlap model of left ANT delineations (n = 8) based on 3T MRI STIR images described previously [19] to demonstrate the relationship between mean contact locations with respect to Schaltenbrant–Wahren atlas (SWA) [21] and 3T MRI based location of ANT.

To evaluate the location of contacts with respect to boundaries of ANT, a proportional coordinate system normalized to ANT dimensions was developed (Fig. 1). The relative coordinates of each contact were then calculated in the ANT-normalized coordinate system. In one patient (responder) the locations of contacts were calculated only in AC–PC coordinate system due to lack of 3T MRI images (cardiac pacemaker). In the case that no response was observed using a particular contact pair but clear response was observed after adding more cranial contacts bilaterally, the initial

Table 1
The contact combinations and therapy response.

Patient	Contacts	Seizure reduction	Side effects	Pre-DBS mean seizure interval	Period duration	Response
1	2/10	≈50%		1.3 days	4 months	Yes
	1/9	≈50%	Psychiatric		1.4 years	No
	3/11	>50%			2.8 years	Yes
2	2/10	NC		<1 days	6 months	No
	1/9	NC	Psychiatric		7 months	No
	0–1/8–9	NC	Psychiatric		2 months	No
	3/11	NC			3.5 months	No
3	2/10	>50%		<1 days	3.3 years	Yes
4	3/11	NC		1 days	1.5 years	No
	2/10	NC			5 months	No
	0/8	NC			4 months	No
5	2/10	NC		3 days	3.5 months	No
	1/9	SE			2 weeks	No
	3/11	>50%			2.7 years	Yes
6	2/10	NC		<1 day	5 months	No
	3/11	NC			8 months	No
7	3/11	>50%		1.7 days	2 years	Yes
8	3/11	>50%		<1 day	2.3 years	Yes
9	2/10	NC		<1 day	1.8 years	No
	3/11	>50%			7 months	Yes
10	2/10	NC		<2 day	2 years	No
	3/11	>50%			9 months	Yes
11	3/10–11	>50%		15 days	1.7 years	Yes
12	1/9	NC		<2 day	1.3 years	No
	2/10–11	NC			5 months	No
13	3/11	NC	Obsessions	7.5 days	9 months	No
14	2/10	>50%	Confusion	2.5 days	4 months	Yes
	3/11	>50%			1 year	Yes
15	2/10	NC		2 days	4 months	No
	2-3/11	>50%			6 months	Yes

The relationship between active contacts, side-effects and response are presented together with the mean seizure interval and the duration of the treatment trials. The cumulative duration of stimulation in whole patient group was 378 months (31.5 years). Contact combinations are shown in chronological order in each patient.
NC, no change; SE, status epilepticus.

contacts were classified as non-responders and secondary contacts as responders.

Statistical analysis

SPSS version 17.0 (IBM, Armonk, NY, USA) was used in statistical analysis. In patients without a change in response status (being responder with all contacts tested or being non-responder with all contacts tested) independent samples t-test was used to compare mean location of contacts. In patients with a change in response status (response with some contact pair and non-response with other contact pair) paired samples t-test was used to compare mean location of contacts.

Results

The locations of 62 contacts used in 30 treatment trials were analyzed. Twenty-five contacts were associated with therapy response and 37 contacts were non-responders. The mean duration of stimulation in responding trials was 18.3 ± 12.9 months and the mean

Table 2
The mean location of contacts.

Group	AC–PC			ANT-normalized		
	X (mm ± SD)	Y (mm ± SD)	Z (mm ± SD)	X_R ± SD	Y_R ± SD	Z_R ± SD
Response with initial contacts						
Responding contacts (n = 13)	*5.3 ± 1.0*	*4.1 ± 1.1* } ***	*11.6 ± 1.1*	*0.64 ± 0.33*	*0.65 ± 0.33* } *	*0.27 ± 0.29*
No response using any of the contacts						
Non-responding contacts (n = 25)	*3.7 ± 4.6*	*1.0 ± 2.5* } ***	*9.6 ± 2.7*	*0.84 ± 0.45*	*0.39 ± 0.25* } *	*0.09 ± 0.31*
Non-responder to responder after programming						
Responding contacts (n = 12)	*5.6 ± 1.0* } †	*2.7 ± 1.7*	*12.9 ± 2.0* } †	*0.68 ± 0.32*	*0.62 ± 0.08* } ††	*0.35 ± 0.30* } ††
Non-responding contacts (n = 12)	*4.8 ± 1.0* } †	*2.0 ± 2.0*	*11.1 ± 2.1* } †	*0.52 ± 0.29*	*0.48 ± 0.07* } ††	*–0.04 ± 0.33* } ††
All						
Responding contacts (n = 25)	*5.4 ± 1.0*	*3.4 ± 1.6*	*12.2 ± 1.7*	*0.66 ± 0.3*	*0.63 ± 0.2*	*0.31 ± 0.3*
Non-responding contacts (n = 37)	*5.3 ± 1.7*	*1.4 ± 2.4*	*10.1 ± 2.6*	*0.73 ± 0.4*	*0.42 ± 0.2*	*0.05 ± 0.3*

Two parallel analyses were performed to compare contact locations between responders and non-responders. Patients with therapy response using initial (and final) contacts were compared to patients without therapy response using any of the contacts tested (independent samples t-test, 2-tailed) and presented as (*$p > 0.05$; ***$p < 0.001$). The location of contacts in patients who became responders after re-programming of the IPG was tested separately using paired samples t-test (2-tailed) and presented as (†$p < 0.05$; ††$p < 0.01$; †††$p < 0.001$). We observed that responding contacts were significantly more anterior and superior compared to non-responding contacts in patients who became responders after re-programming of the IPG. Contacts in patients with initial response were also significantly more anterior than in patients without response using any of the contacts. We observed also a trend in more superior location of responding contacts in patients with initial response compared to non-responding contacts in patients who did not benefit any of the contacts tested ($p = 0.09$, independent sample's t-test).
X_R, relative X coordinate; Y_R, relative Y coordinate; Z_R, relative Z coordinate; SD, standard deviation; AC, anterior commissure; PC, posterior commissure; ANT, anterior nucleus of thalamus; IPG, internal pulse generator.

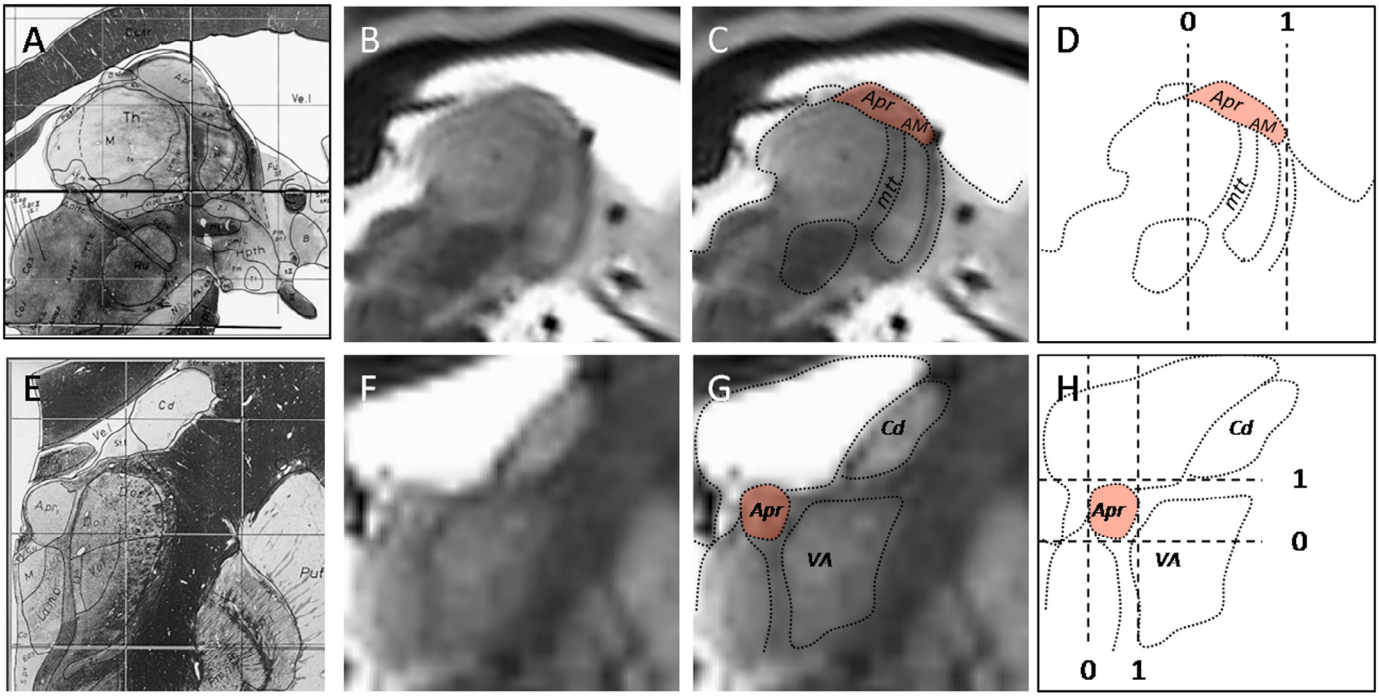

Figure 1. The principle of ANT normalized coordinate system. ANT normalized coordinate system is based on direct visualization of ANT in 3T STIR images. Sagittal (A) and coronal (E) images from SWA are shown for comparison with 3T MRI STIR images (B–C, F–G). In ANT-normalized coordinate system the most posterior border of ANT is defined as 0 and most anterior border as 1 (D). The medial and inferior borders are defined as 0 and the lateral and superior border as 1 in coronal image through the mamillo-thalamic tract where ANT is most reliably visualized (H). The anterior–posterior axis of ANT-normalized coordinate system is oriented along AC–PC line and both medial–lateral axis and inferior–superior axis are perpendicular to AC–PC line. Abbreviations: Apr, anterior principal nucleus; AM, anteromedial nucleus; VA, ventral anterior nucleus; Cd, nucleus caudatus; mtt, mamillo-thalamic tract, SWA, Schaltenbrandt–Wahren atlas. Printed with permission.

duration of side-effect free non-responding trial was 9.5 ± 7.5 months. The total duration of stimulated periods was 378 months (31.5 years). Table 1 presents treatment trials in a chronological order for each patient (baseline seizure frequency, response and potential side-effect).

A total of 10 patients out of 15 underwent stimulation using multiple contact pairs. After changes in the active contacts, 10 patients out of 15 (67%) became eventually responders. Six patients were responders using the first contact pairs, whereas 4 patients were initially non-responders but were classified as responders after activating the most proximal contacts at ANT. Two patients were responders using the first contact pair but better seizure control with more favourable side effect profile was observed after programming more proximal contacts at ANT.

The patients were treated with antiepileptic drugs (AEDS) according to standard clinical practice. At the time of ANT-DBS treatment initiation one patient was on monotherapy, four patients on two AEDs, eight patients on three AEDs and two patients on four AEDs reflecting the refractory nature of their epilepsy. During the ANT-DBS treatment phase changes to their AED regiment were done in 11 patients. AED changes were done in five patients due to intolerable side-effects which lead to worsening of seizure control in two patients with the remaining patients had unchanged seizure frequency. In one patient one of her three AEDs was withdrawn due to wishes of pregnancy leading to slight worsening of seizure control with restoration of the same AED after pregnancy restoring the previous seizure frequency. In another patient carbamazepine dose was unintentionally halved leading to worsening of seizure control. In four patients in non-responding stage new AED treatment was initiated or dose of pre-existing AED increased with intention of decreasing the seizures, none of these patients improved. In four patients the AED treatment remained constant during the whole follow-up period. AED changes were not responsible for the responder status in any of our patients.

Contact distribution in stereotactic space

Analysis of the contact locations revealed that the responding contacts located significantly more superior and anterior compared to the non-responding contacts in AC–PC coordinate system (Fig. 2A, Table 2). Patients without a change in their response status showed significantly more anterior responding contact locations compared to non-responding contacts, whereas patients with a change in their response status showed significantly more superior and lateral responding contact locations compared to non-responding contacts.

A subgroup of eight patients underwent more detailed modelling of ANT delineations and used for demonstration of mean contact locations together with MRI based variation of ANT location. The distribution of the responding contacts matched closely to the most frequently overlapped area in an overlap model of left ANT delineations in 3T MRI, whereas the non-responding contacts were at more posterior and inferior aspect of this area (Fig. 2A). Noteworthy, the mean location of non-responding contacts correlated highly with location of ANT in SWA sagittal plates [21].

The location of contacts in ANT normalized coordinate system

To study whether responding contacts are located at some specific part of ANT complex, contact locations were calculated with respect to visible boundaries of ANT using ANT normalized coordinate system (Fig. 1). We found that responding contacts were significantly more anterior both in patients with or without a change

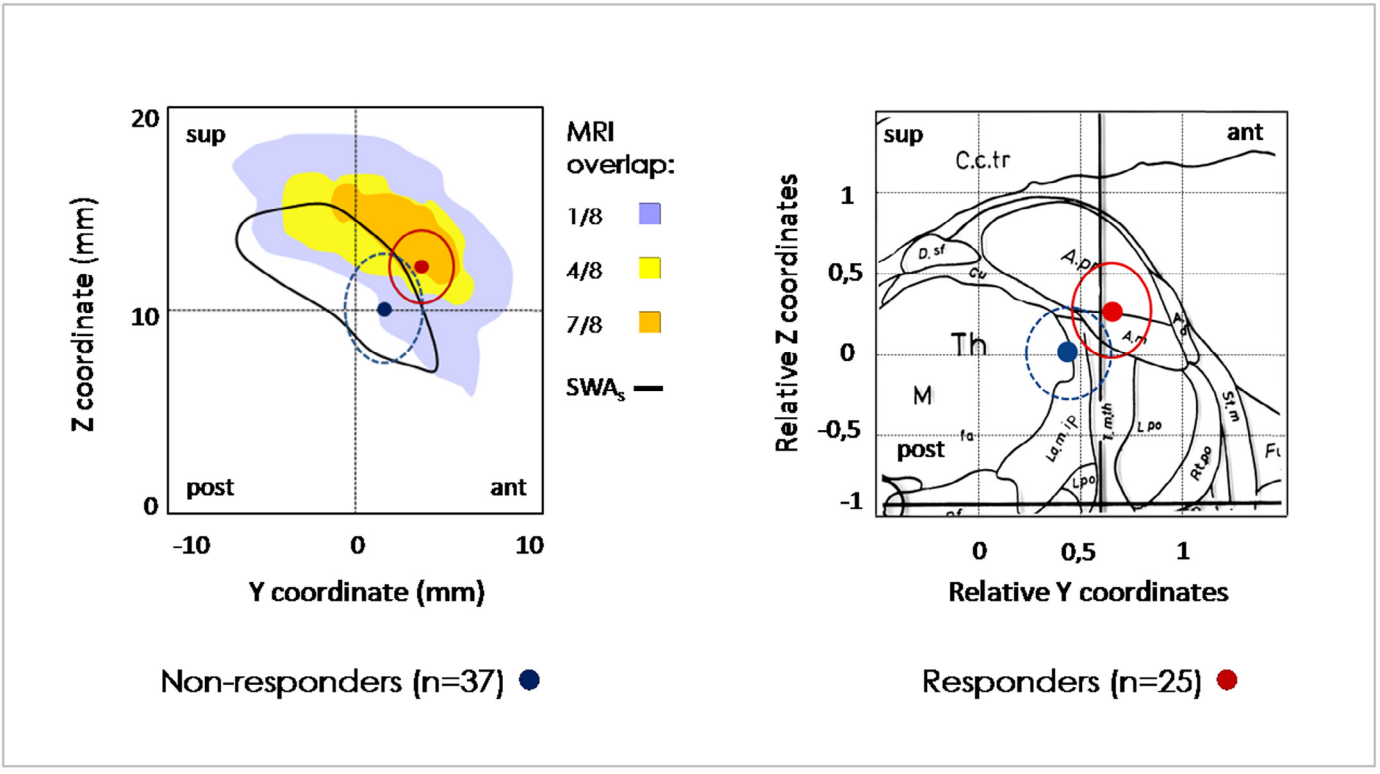

Figure 2. The mean location of responding and non-responding contacts in stereotactic space. The relationship between responding (red) and non-responding (blue) contacts is presented with respect to SWA (sagittal image 5.5 mm lateral from midline) and 3T MRI based location of ANT [19]. Area overlapped by 1 out of 8 cross-sectional models of ANT in 3T MRI in the left hemisphere is shown in light blue, area overlapped by 4 out of 8 cross-sectional models is shown in yellow and most frequently overlapped area (7 out of 8) cross-sectional models is shown in orange (2A). The responding contact location correlates highly with the most frequently overlapped area from cross-sectional models from individual patients. The mean non-responding contact location correlates with the SWA sagittal information (black solid line in 2A). ANT-normalized coordinate system reveals that responding contacts are located at the anterior aspect of ANT complex at the border between anterior principal nucleus (Apr) and anteromedial nucleus (AM). Note the mean location of responding contacts slightly superior and anterior to mtt termination point. Circles indicate one standard deviation (SD) from mean values. Abbreviations: X_R, relative X coordinate; Y_R, relative Y coordinate; Z_R, relative Z coordinate; Apr, anterior principal nucleus; AM, anteriomedial nucleus, SWA, Schaltenbrandt–Wahren atlas; sup, superior; ant, anterior; post, posterior; mtt, mamillo-thalamic tract. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.) Printed with permission.

in their response status (Fig. 2B, Table 2). Responding contacts were significantly more superior in patients with a change in response status compared to non-responding contacts (Table 2). Fig. 2 demonstrates the mean contact locations with respect to anatomical relationships according to SWA.

When compared to the AC–PC coordinate system, we found that the ANT normalized coordinate system was more robust in differentiating responding and non-responding contacts especially in the anterior–posterior axis (Fig. 3). Seventeen out of 23 (74%) responding contacts were located anterior to Y-axis cut-off level $Y_R = 0.58$, whereas 30 out of 36 (83%) contacts posterior to this cut-off level were classified as non-responders (for more details, see Fig. 3). Furthermore, two non-responding contacts with Y-axis projected location of contact at anterior part of ANT (anterior to $Y_R = 0.58$) were implanted using paraventricular trajectory and had very lateral location ($X_R = 1.4$ and 1.5), thus being clearly lateral to ANT (Fig. 3).

Clinical characteristics and outcome

Table 3 summarizes the clinical characteristics and the most optimal contact locations in individual patients together with clinical characteristics. We observed no clear association between patient's age, sex, MRI pathology, seizure onset zone, aetiology or previous epilepsy surgery and the clinical outcome. To further demonstrate the effect of contact locations on outcome at individual patient level we defined the optimal contact location at anterior aspect of ANT (ANT_a) using the following relative coordinates in ANT-normalized coordinate system: anterior to $Y_R = 0.58$ and medial to $X_R < 1.25$. We observed that seven out of ten responders had contact at ANT_a bilaterally and three patients out of ten responders had a contact at ANT_a at least on the other side. In non-responders ($n = 5$) only one patient had contact at ANT_a bilaterally and one patient had contact at ANT_a on the other side (Table 3).

Discussion

Detailed analysis of the contact locations in anterior thalamic region was carried out to study the structure–function correlation between stimulation site and anti-epileptic effect in refractory epilepsy. We specifically assessed whether the stimulated area associated with a favourable outcome can be neuroanatomically defined in stereotactic space or relative to the borders of ANT to guide targeting and postoperative programming to optimize outcome. We were able to demonstrate that the contacts with an actual location at the anterior aspect of ANT, as demonstrated by ANT-normalized coordinate system, were associated with a favourable outcome. On the other hand, contacts at a location suggested by the SWA sagittal plates were situated at more posterior/inferior aspect of ANT and were associated with a poor outcome. Due to limited number of individual patients in our study, we were not able to observe any association between aetiology, seizure onset zone, MRI findings or demographic factors and outcome.

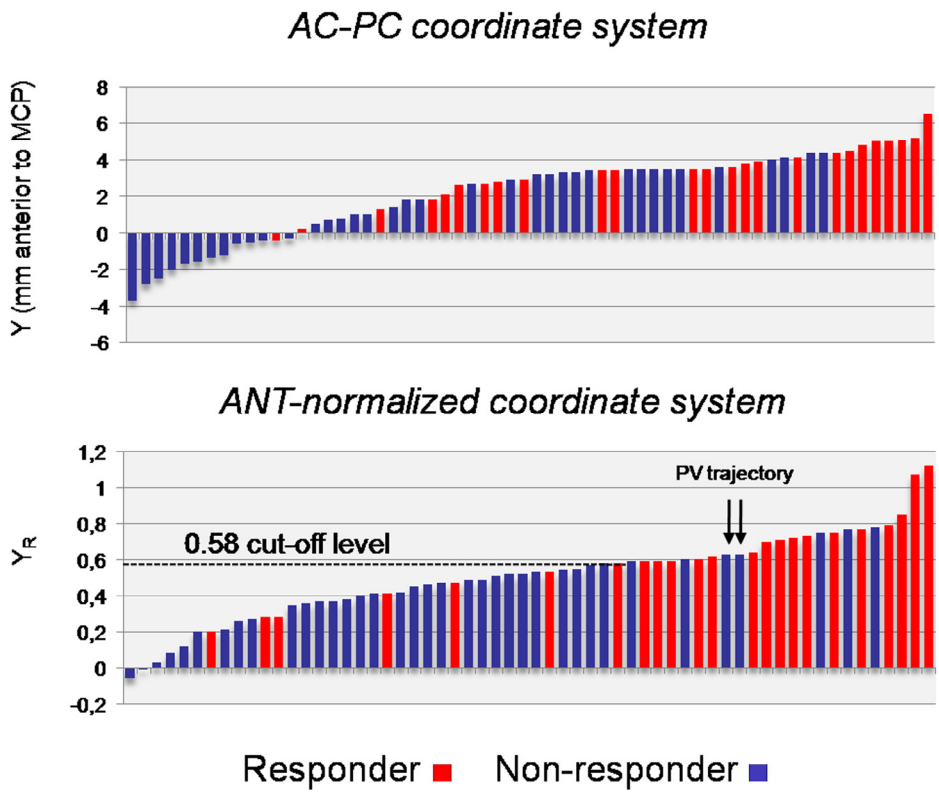

Figure 3. The robustness of ANT-normalized coordinate system compared to AC–PC coordinate system in the evaluation of responding and non-responding contact locations. The isolated Y coordinates of the responding (red) and non-responding (blue) contacts are shown in AC–PC coordinate system (upper panel) and in ANT-normalized coordinate system (lower panel). AC–PC coordinate system shows marked Y coordinate overlap between responding and non-responding contacts whereas ANT-normalized coordinate system shows more robust difference in responding and non-responding Y coordinates. Anterior to cut-off level $Y_R = 0.58$ (dashed line) 74% of the contacts were responders whereas posterior to this level 83% of the contacts were non-responders. Two non-responding contacts (indicated by arrows) implanted using paraventricular approach were at anterior aspect in the Y axis but due to lateral trajectory were clearly lateral to ANT ($X_R = 1.4$ and 1.5). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

We found statistically significant and systematic differences in the contact locations between responding and non-responding contacts. AC–PC coordinate system revealed approximately 2 mm overall differences both in Y and Z coordinates between responding and non-responding contacts (Table 2), resulting in approximately 2.9 mm difference in the sagittal plane. In the ANT-normalized coordinate system we observed a mean of 0.21 and 0.26 unit difference in the relative Y and Z coordinates respectively (Table 2). Using average

Table 3
The effect of MRI pathology, aetiology, previous epilepsy surgery and DBS lead location on outcome.

Patient	Sex	Age	Response	MRI	VNS	Aetiology	Seizure onset zone	Best contact location	
								Left	Right
1	M	32	Yes	Occipital bilateral subependymal heterotopia	No	CD	Multifocal	ANT_a	ANT_a
3	F	28	Yes	Bilateral perisylvian polymicrogyria	Yes	CD	Multifocal	ANT_a	Post
5	M	32	Yes	Occipital bilateral heterotopia	Yes	CD	Multifocal	ANT_a	Post
7	M	24	Yes	Normal	Yes	Encephalitis	Multifocal	ANT_a	ANT_a
8	F	38	Yes	Right hemimegencephalia	Yes	CD	Right frontotemporal	ANT_a **	ANT_a **
9	F	24	Yes	Fronto-parietal bilat gliosis	Yes	Encephalitis	Multifocal	ANT_a	ANT_a
10	F	32	Yes	Normal	No	Encephalitis	Multifocal	ANT_a	ANT_a
11	M	48	Yes	Normal	No	Unk	Frontal lobe, side unknown	ANT_a	ANT_a
14	M	50	Yes	Right temporal and frontal atrophy	No	Encephalitis	Right temporal lobe	ANT_a	Post
15	M	40	Yes	Bilat perisylvian polymicrogyria	Yes	CD	Multifocal	ANT_a	ANT_a
2	F	34	no	CD left frontal lobe; left temporal resection	No	CD	Left frontal lobe	Post	Post
4	M	23	No	Normal	Yes	Encephalitis	Multifocal	Post	Post
6	M	49	No*	Bilat perisylvian polymicrogyria	Yes	CD	Multifocal	ANT_a	Lat
12	M	24	No	Normal	Yes	Encephalitis	Left frontotemporal	Post/inf	Post/inf
13	M	44	No	Normal	Yes	Unk	Frontal lobe, side unknown	ANT_a	ANT_a

Responders are shown at upper part of table (red rectangle) in a chronological order and non-responders at the bottom part of the table (blue rectangle) in a chronological order. Cortical dysplasia and encephalitis were most common aetiologies both in responders and non-responders. Normal MRI was found in both groups. The deviation of leads from anterior aspect of ANT (ANT_a; defined as anterior to $Y_R = 0.58$; medial to $X_R = 1.25$) was the most evident factor explaining the lack of response.
* The patient number 6 had left sided lead at ANT_a and showed reduction of most severe seizures. ** The patient had cardiac pacemaker and therefore only 1.5T MRI. The patient number 13 had leads optimally at ANT_a but was classified as a non-responder.
Post, posterior; inf, inferior; lat, lateral; CD, cortical dysplasia; unk, unknown; VNS, vagal nerve stimulation.

ANT dimensions in 3T MRI (10 mm × 4 mm in Y and Z axes [19]), this gives approximately 2.3 mm difference in the sagittal plane. In the field of DBS surgery these distances are generally regarded clinically relevant. For instance, in DBS of subthalamic nucleus (STN), such deviation from target is very likely to be associated with lack of clinical effect.

The classical spherical model of current spread from DBS electrode (volume of activated tissue (VAT)) is dependent on the stimulation parameters but its radius is thought to be within a few millimetre range. A matter of particular interest is the effect of white matter structures at the posterior and inferior aspects of ANT separating ANT, DM and VA nuclei. It may be speculated that relatively small deviation from ANT into posterior/inferior direction could prevent current spread into ANT by insulating white matter layers to activate sufficient number of ANT neurons. Interestingly, this hypothesis is supported by recent report using posterior trajectory to ANT together with hippocampal DBS capable of registering of evoked potentials [22]. They implanted electrodes along the posterior–anterior axis of ANT and found that only the most anterior contacts within ANT caused hippocampal evoked potentials while more posterior contacts did not. They also reported favourable effect in these two patients, although follow up was relatively short.

Our data suggest that stimulation at the anterior part of ANT complex has powerful anti-epileptic effect. It is conceivable that stimulation site at the anterior part of ANT complex modulates the critical nodes in the seizure propagation pathways. In fact, experimental evidence suggests that ANT plays a major role in seizure spread and generalization in pentylenetetrazole (PTZ) model in rats [16,23]. Stimulation at anterior aspect of ANT using currently available DBS devices reaches most likely the anteriomedial (AM) and the anterior principal (Apr) subnuclei (Fig. 2B). AM has well established connections to frontal cortex, anterior cingulum, retrosplenial cortex, amygdala and hippocampus [24], while Apr is particularly well connected to hippocampal area and posterior cingulum [24,25]. Furthermore, studies tracking axonal transport have demonstrated that AM has connections to orbitofrontal, frontopolar and medial prefrontal cortex in rhesus monkeys [26] and in rodents [27]. AM has also connections to amygdala, hippocampus, temporal lobe cortex and mamillary bodies in rhesus monkeys [28]. In the light of our results, it is attractive to hypothetize that stimulation at more anterior aspect of ANT complex, presumably extending also to AM subnucleus, may have capacity to modulate more broad range of epileptic networks involving frontal and temporal lobe structures.

Pre-SANTE pilot studies reported 14–76% seizure reduction in a relatively small number of patients [5–10]. These studies are subject to several reviews [29–33]. SANTE trial reported median of 56% seizure reduction in a group of 81 patients at 2 years with a 54% responder rate (>50% seizure reduction) [11] and 69% seizure reduction with 68% responder rate at 5 years [12]. Lee et al. reported results from chronic stimulation in 15 patients, where 80% of patients reached >50% seizure reduction level [13]. Our data are consistent with these available studies with respect to the responder rate (68%). Importantly, our primary scope is entirely different from these previous studies: We aimed to study and define the most optimal target for DBS at anterior thalamus using outcome data instead of assessing outcome in the individual patients with DBS aimed at ANT. As a contrary, we have evaluated the response for stimulation focusing on detailed analysis of individual contact locations in multiple treatment trials. Post-hoc analysis of the lead locations in individual patients showed that a lead location deviating from most optimal target area defined in the present study (anterior aspect of ANT) was associated with poor outcome (Table 3), being the only identifiable factor differentiating responders from non-responders. A total of six patients improved after activation of the most cranial contacts at ANT, indicating that contact location plays a critical role in therapy outcome, and that a significant improvement can be achieved after re-programming of the device after relatively long periods of time.

There is ongoing debate about the most optimal trajectory to the ANT among neurosurgical centres currently performing this procedure. Available literature describes transventricular approach to ANT [6,8,11,13]. However, several functional neurosurgeons experience this approach susceptible to lead misplacement due to penetration of the lateral ventricle, or susceptible to intraventricular bleeding due to choroidal plexus vessels, and prefer transparenchymal lateral approach to reach ANT. In the present study, 6 electrodes were implanted using paraventricular trajectory (bilaterally in two patients) whereas 24 electrodes were implanted using transventricular trajectory. Importantly, none of the contacts implanted paraventricularly was clearly at the ANT. It is vitally important to understand that the most optimal trajectory is highly dependent on the definition of the target. Trajectory to the indirect ANT target using atlas based coordinates using tranventricular trajectory from routine pre-coronal entry point most likely traverses ANT with a relatively high success rate. However, the lateral paraventricular approach may reach the identical “surgical” target point, but due to a more lateral course of the electrode, may not traverse ANT properly. Therefore, it is important to acknowledge that surgery performed in the absence of clearly defined neuroanatomical target, and using indirect targeting method (especially based on SWA sagittal plates) together with lateral paraventricular approach, may be very potent cause of inconsistent results. Furthermore, lateral paraventricular trajectory results in extremely lateral entry point and most likely penetration of the eloquent cortex. One patient with bilateral lateral paraventricular approach showed cortical infarct together with aphasia postoperatively which eventually recovered. It may be speculated that lateral paraventricular approach is not only less feasible in reaching optimal stimulation site but also may have increased risk for neuronal deficits.

Indirect targeting method is a remnant of the stereotactic technique used in the ventriculography era, but it is still widely used with success especially in the movement disorder targets. While DBS for movement disorders is performed only to patients with relatively undisturbed brain MRI, this requirement is not realistic in a patient group suffering from refractory epilepsy. The patient group in the need of more effective form of therapy such as DBS consists both from developmental and acquired lesions like cortical dysplasia or various postoperative states severely disturbing the architecture of the brain. Our data strongly suggest that stereotactic coordinates should be used cautiously, and corrections should be made according to individual patient’s anatomy.

Several experimental studies support our finding that stimulation specifically at the ANT is essential for the antiepileptic effect. Mirski et al. showed that high frequency stimulation of ANT had an anti-epileptic effect in a PTZ seizure model in rats by increasing seizure threshold level via serotonergic mechanism [34]. Rats with stimulating electrode outside ANT (including dorsomedial nucleus and ventral thalamic nucleus) showed seizure threshold level similar to non-ANT-stimulation group [34]. Stimulation of the dorsomedial nucleus lying at posterior–inferior aspect of ANT was not antiepileptic in a kindling model of epilepsy [35]. In a study by Stypulkowski et al., authors observed powerful inhibitory effect upon hippocampal electrical activity using most cranially located contacts at ANT, whereas adjacent more deeply located contact was not associated with suppression of neuronal activity [36]. Hamani et al. reported in pilocarpine model of SE in rats that the latency for SE onset was increased after stimulation of all different subnuclei in ANT complex (anteromedial, anterior principal and anterior dorsal nucleus) [37]. Finally, in an earlier study by Mirski et al., behavioural seizure scores were decreased with high frequency ANT

stimulation compared to stimulation at striatum or posterior thalamus in a PTZ model in rat [17].

Conclusions

Our data demonstrate that contact location may be a critical factor determining therapy response in refractory epilepsy. Present study provides further evidence for proof of principle in ANT-DBS and offers new insight into the definition of the most optimal DBS target at the anterior aspect of ANT in refractory epilepsy. Our results highlight the importance of direct targeting based on individual patient's anatomy in ANT targeting.

Acknowledgements

We thank MRI physicist Pertti Ryymin for his work in development of 3T MRI protocols for thalamus. We thank Heini Huhtala for supervision in statistical analysis.

Funding

The study was financially supported by competitive EVO funding of Pirkanmaa Hospital District and Finnish Epilepsy Foundation.

References

[1] Cooper IS, Upton AR, Amin I. Reversibility of chronic neurologic deficits. Some effects of electrical stimulation of the thalamus and internal capsule in man. Appl Neurophysiol 1980;43:244–58.
[2] Cooper IS, Upton AR, Amin I, Garnett S, Brown GM, Springman M. Evoked metabolic responses in the limbic-striate system produced by stimulation of anterior thalamic nucleus in man. Int J Neurol 1984;18:179–87.
[3] Upton AR, Cooper IS, Springman M, Amin I. Suppression of seizures and psychosis of limbic system origin by chronic stimulation of anterior nucleus of the thalamus. Int J Neurol 1985–1986;19–20:223–30.
[4] Upton AR, Amin I, Garnett S, Springman M, Nahmias C, Cooper IS. Evoked metabolic responses in the limbic-striate system produced by stimulation of anterior thalamic nucleus in man. Pacing Clin Electrophysiol 1987;10:217–25.
[5] Hodaie M, Wennberg RA, Dostrovsky JO, Lozano AM. Chronic anterior thalamus stimulation for intractable epilepsy. Epilepsia 2002;43:603–8.
[6] Kerrigan JF, Litt B, Fisher RS, Cranstoun S, French JA, Blum DE, et al. Electrical stimulation of the anterior nucleus of the thalamus for the treatment of intractable epilepsy. Epilepsia 2004;45:346–54.
[7] Andrade DM, Zumsteg D, Hamani C, Hodaie M, Sarkissian S, Lozano AM, et al. Long-term follow-up of patients with thalamic deep brain stimulation for epilepsy. Neurology 2006;66:1571–3.
[8] Lee KJ, Jang KS, Shon YM. Chronic deep brain stimulation of subthalamic and anterior thalamic nuclei for controlling refractory partial epilepsy. Acta Neurochir Suppl 2006;99:87–91.
[9] Lim SN, Lee ST, Tsai YT, Chen IA, Tu PH, Chen JL, et al. Electrical stimulation of the anterior nucleus of the thalamus for intractable epilepsy: a long-term follow-up study. Epilepsia 2007;48:342–7.
[10] Osorio I, Overman J, Giftakis J, Wilkinson SB. High frequency thalamic stimulation for inoperable mesial temporal epilepsy. Epilepsia 2007;48:1561–71.
[11] Fisher R, Salanova V, Witt T, Worth R, Henry T, Gross R, et al. Electrical stimulation of the anterior nucleus of thalamus for treatment of refractory epilepsy. Epilepsia 2010;51:899–908.
[12] Salanova V, Witt T, Worth R. and the SANTE study group: long-term efficacy and safety of thalamic stimulation for drug-resistant partial epilepsy. Neurology 2015;84:1017–25.
[13] Lee KJ, Shon YM, Cho CB. Long-term outcome of anterior thalamic nucleus stimulation for intractable epilepsy. Stereotact Funct Neurosurg 2012;90:379–85.
[14] Mirski MA, Ferrendelli JA. Interruption of the mammillothalamic tract prevents seizures in guinea pigs. Science 1984;226:72–4.
[15] Mirski MA, Ferrendelli JA. Anterior thalamic mediation of generalized pentylenetetrazol seizures. Brain Res 1986;399:212–23.
[16] Mirski MA, McKeon AC, Ferrendelli JA. Anterior thalamus and substantia nigra: two distinct structures mediating experimental generalized seizures. Brain Res 1986;397:377–80.
[17] Mirski MA, Rossell LA, Terry JB, Fisher RS. Anticonvulsant effect of anterior thalamic high frequency electrical stimulation in the rat. Epilepsy Res 1997;28:89–100.
[18] van Buren JM, Borke RC. The nuclei and cerebral connections of the human thalamus. In: Variations and connections of the human thalamus. Berlin–Heidelberg–New York: Springer; 1972.
[19] Möttönen T, Katisko J, Haapasalo J, Tähtinen T, Kiekara T, Kähärä V, et al. Defining the anterior nucleus of the thalamus (ANT) as a deep brain stimulation target in refractory epilepsy: delineation using 3 T MRI and intraoperative microelectrode recording. Neuroimage Clin 2015;7:823–9.
[20] Buentjen L, Kopitzki K, Schmitt FC, Voges J, Tempelmann C, Kaufmann J, et al. Direct targeting of the thalamic anteroventral nucleus for deep brain stimulation by T1-weighted magnetic resonance imaging at 3 T. Stereotact Funct Neurosurg 2014;92:25–30.
[21] Schaltenbrand G, Wahren W. Atlas for sterotaxy of the human brain. 2nd ed. Thieme Stuttgart; 1998.
[22] Van Gompel JJ, Klassen BT, Worrell GA, Lee KH, Shin C, Zhao CZ, et al. Anterior nuclear deep brain stimulation guided by concordant hippocampal recording. Neurosurg Focus 2015;38:E9.
[23] Mirski MA, Tsai YC, Rossell LA, Thakor NV, Sherman DL. Anterior thalamic mediation of experimental seizures: selective EEG spectral coherence. Epilepsia 2003;44:355–65.
[24] Jones EG. Anterior nuclei and lateral dorsal nucleus. In: The thalamus. 2nd ed. Cambridge University Press; 2007.
[25] Child ND, Benarroch EE. Anterior nucleus of the thalamus: functional organization and clinical implications. Neurology 2013;81:1869–76.
[26] Xiao D, Barbas H. Pathways for emotions and memory I. Input and output zones linking the anterior thalamic nuclei with prefrontal cortices in the rhesus monkey. Thalamus Relat Syst 2002;2:21–32.
[27] Shibata H, Naito J. Organization of anterior cingulate and frontal cortical projections to the anterior and laterodorsal thalamic nuclei in the rat. Brain Res 2005;1059:93–103.
[28] Xiao D, Barbas H. Pathways for emotions and memory II. Afferent input to the anterior thalamic nuclei from prefrontal, temporal, hypothalamic areas and the basal ganglia in the rhesus monkey. Thalamus Relat Syst 2002;2:33–48.
[29] Halpern CH, Samadani U, Litt B, Jaggi JL, Baltuch GH. Deep brain stimulation for epilepsy. Neurother 2008;5:59–67.
[30] Ellis TL, Stevens A. Deep brain stimulation for medically refractory epilepsy. Neurosurg Focus 2008;25:E11.
[31] Hamani C, Andrade D, Hodaie M, Wennberg R, Lozano A. Deep brain stimulation for the treatment of epilepsy. Int J Neural Syst 2009;19:213–26.
[32] Lega BC, Halpern CH, Jaggi JL, Baltuch GH. Deep brain stimulation in the treatment of refractory epilepsy: update on current data and future directions. Neurobiol Dis 2010;38:354–60.
[33] Pereira EA, Green AL, Stacey RJ, Aziz TZ. Refractory epilepsy and deep brain stimulation. J Clin Neurosci 2012;19:27–33.
[34] Mirski MA, Ziai WC, Chiang J, Hinich M, Sherman D. Anticonvulsant serotonergic and deep brain stimulation in anterior thalamus. Seizure 2009;18:64–70.
[35] Wang S, Wu DC, Fan XN, Zhu MZ, Hu QY, Zhou D, et al. Mediodorsal thalamic stimulation is not protective against seizures induced by amygdaloid kindling in rats. Neurosci Lett 2010;481:97–101.
[36] Stypulkowski PH, Stanslaski SR, Denison TJ, Giftakis JE. Chronic evaluation of a clinical system for deep brain stimulation and recording of neural network activity. Stereotact Funct Neurosurg 2013;91:220–32.
[37] Hamani C, Hodaie M, Chiang J, del Campo M, Andrade DM, Sherman D, et al. Deep brain stimulation of the anterior nucleus of the thalamus: effects of electrical stimulation on pilocarpine-induced seizures and status epilepticus. Epilepsy Res 2008;78:117–23.