Epilepsy Research 153 (2019) 1–6

Contents lists available at ScienceDirect

Epilepsy Research

journal homepage: www.elsevier.com/locate/epilepsyres

# Targeting analysis of a novel parietal approach for deep brain stimulation of the anterior nucleus of the thalamus for epilepsy

Yu-Chi Wang[a,e,1], Sanjeet S. Grewal[b,1], Erik H. Middlebrooks[b,c,1], Gregory A. Worrell[d], Matt Stead[d], Brian N. Lundstrom[d], Jeffrey W. Britton[d], Min-Hsien Wu[e], Jamie J. Van Gompel[f,*]

[a] Department of Neurosurgery, Chang Gung Memorial Hospital in Linkou, Chang Gung University, Taiwan
[b] Department of Neurosurgery, Mayo Clinic, Jacksonville, FL, USA
[c] Department of Radiology, Mayo Clinic, Jacksonville, FL, USA
[d] Department of Neurology, Mayo Clinic, Rochester, MN, USA
[e] Program of Biomedical Engineering, Graduate Institute of Biomedical Engineering, Chang Gung University, Taiwan
[f] Department of Neurosurgery, Mayo Clinic, Rochester, MN, USA

ARTICLE INFO

*Keywords:*
Anterior nucleus of thalamus
Deep brain stimulation
Epilepsy
Trajectory

ABSTRACT

*Purpose:* Deep brain stimulation (DBS) of the anterior nucleus of the thalamus (ANT) is a promising treatment for refractory epilepsy; however, it remains challenging to successfully target the ANT. The results of Medtronic Registry for Epilepsy (MORE) supported a frontal transventricular(TV) compared to frontal extraventricular (EV) lead trajectory for ANT DBS may have better coverage of the ANT. Here we report the safety and targeting efficacy of a novel, posterior parietal extraventricular (PEV) approach to the ANT.

*Methods:* We conducted a retrospective analysis of ten patients who underwent bilateral ANT DBS (20 total trajectories) for medically-refractory epilepsy. Similar targeting methodology as the MORE trial was used, and the DBS Intrinsic Template Atlas (DISTAL) was utilized for ANT localization and contact position relative to ANT. Clinical data were assessed for DBS targeting efficacy and surgical complications.

*Results:* The demonstrated PEV trajectory showed a successful ANT targeting rate of 90% bilaterally. Two or more contacts within ANT were presented in 75% of all leads. Mean contact number in ANT was 2.2± 1.2. There were no intracranial hemorrhages, cerebrospinal fluid leakage, or permanent neurologic deficits.

*Conclusion:* In this small series, the novel PEV for ANT DBS is feasible with good targeting accuracy and potential safety advantages. The high accuracy of the PEV trajectory suggests that it is a reasonable alternative trajectory for ANT DBS. Larger studies will be needed to assess this trajectory on clinical outcome of DBS treatment to epilepsy.

## 1. Introduction

Epilepsy affects approximately 65 million people globally, and up to one third are refractory to medical therapy and may be considered for surgical therapy.(Thurman et al., 2011) Deep brain stimulation (DBS) of the Anterior Nucleus of the Thalamus (ANT) has been approved for use in Europe for an extended period of time and recent approval in the United States by the Food and Drug Administration (FDA) has rekindled interest in the treatment of epilepsy patients with DBS who are not candidates for resection.(Cukiert and Lehtimaki, 2017) Of potential DBS targets, the anterior nucleus of the thalamus (ANT) has been the most studied and may function to modulate the limbic seizure network or the default mode network.(Bouwens van der Vlis et al., 2018; Laxpati et al., 2014; Wang et al., 2018) The Stimulation of the Anterior Nucleus of the Thalamus for Epilepsy (SANTE) trial demonstrated a significant seizure reduction in the active stimulation group compared to sham stimulation at the end of a 3-month blinded period. There was a 41% decrease in median seizure frequency at 13 months and a 56% decrease at 25 months.(Fisher et al., 2010; Lega et al., 2010) Long-term follow-up showed the responder rate (defined as > 50% reduction in seizure frequency) in open-label stimulation at 5 years was 68%, and 16% of subjects were seizure-free for at least 6 months.(Salanova et al., 2015)

Two main transfrontal trajectories for targeting the ANT have been utilized in previous studies, the transventricular (TV) and the extra-ventricular (EV) trajectories. The SANTE trial specifically utilized the TV trajectory mostly.(Lehtimaki et al., 2018) Importantly, 8.2% of the

* Corresponding author at: Department of Neurosurgery and Otorhinolaryngology, Mayo Clinic, 200 First Street SW, Rochester, MN, 55905, USA.
*E-mail address:* vangompel.jamie@mayo.edu (J.J. Van Gompel).
[1] Wang, Grewal and Middlebrooks contributed equally to the manuscript.

https://doi.org/10.1016/j.eplepsyres.2019.03.010
Received 26 October 2018; Received in revised form 2 February 2019; Accepted 18 March 2019
Available online 19 March 2019
0920-1211/ 

subjects in the SANTE trial had revisions due to an absence of lead contacts within the ANT on postoperative imaging.(Salanova et al., 2015) Additionally, there was a 4.5% incidence of intracranial hemorrhage with the TV trajectory, higher than commonly reported in other DBS applications and this increase is believed to be due to passage through the ependymal to a target in which the choroid plexus and thalamostriate vein overlies. In comparison, the EV trajectory was previously shown to reduce the likelihood of lead contacts in the ANT compared to the TV trajectory and, therefore, associated with inferior outcomes.(Lehtimaki et al., 2016) More recently, the Medtronic Registry for Epilepsy (MORE) trial compared the TV and EV trajectories and found a higher probability of successfully targeting the ANT with the TV lead trajectory.(Lehtimaki et al., 2018)

Based on the prior studies, there are potential advantages and disadvantages for both the frontal TV and EV trajectories. As such, there is currently no consensus as to the optimal trajectory for placement of ANT leads. We previously described (Van Gompel et al., 2015) a parietal extraventricular (PEV) trajectory that mimics a posterior shunt surgery. In this study, we showed in a consecutive patient experience the relative value of this approach and analyzed the targeting results with our coregistration, normalization and image process.

## 2. Materials and methods

### 2.1. Patients

This retrospective study was approved by the Mayo Clinic Institutional Review Board. Ten patients with medically intractable epilepsy were recruited who met the inclusion criteria of drug-resistant epilepsy, defined as refractory to trials of at least three appropriately chosen anticonvulsant medications, and not suitable candidates for resection. After evaluation and recommendations from a multidisciplinary epilepsy surgery conference that included epileptologists, neuroradiologists, and neurosurgeons, all patients consented to ANT DBS for treatment of epilepsy.

### 2.2. Surgical approach and trajectory planning

The details of our implantation have been previously described. (Grewal et al., 2018; Van Gompel et al., 2015) In brief, stereotactic 3 T MR images were performed after Leksell (Elekta) frame fixation. The image data were then **co-**registered and aligned with the anterior commissure - posterior commissure (AC-PC) plane. The ANT was targeted semidirectly, by using a Schaltenbrand and Wahren stereotactic atlas overlay and anatomical landmark, like mammillothalamic tract (MTT). The coordinates used were modified based on anatomy to allow contact 0 to be as anterior and medial in the ANT as possible. A parietal entry site was chosen resulting in a trajectory from superior posterior to inferior anterior (Fig. 1). Entry points were selected to be posterior enough to reach associative areas posterior to sensorimotor cortices. Medtronic 3389 leads were used in all cases. The patient was taken immediately for postoperative CT to confirm localization. After confirmation of the electrode location, the patient returned to the operating room where the leads were attached to extensions and tunneled to a battery in the standard infraclavicular pocket.

### 2.3. Implantation analysis

All patients had pre-operative MRI and post-operative CT performed according to a previously published protocol.(Van Gompel et al., 2015) Briefly, the protocol contained high-resolution MP-RAGE and turbo spin-echo T2-weighted imaging used for targeting purposes. Post-operatively, high-resolution CT was obtained for localization of final lead position.

The post-operative CT and pre-operative MP-RAGE MRI were co-registered using a two-stage linear registration consisting of a rigid linear registration followed by affine registration in Advanced Normalization Tools (http://stnava.github.io/ANTs/)(Avants et al., 2008) The pre-operative T2-weighted MRI was then linearly co-registered to the MP-RAGE using SPM12 (http://www.fil.ion.ucl.ac.uk/spm/software/). Next, using the MP-RAGE and T2-weighted MRI, transformation matrices were derived for normalization of all pre- and post-operative images into Montreal Neurologic Institute atlas space (MNI_ICBM_2009b_NLIN_ASYM)(Fonov et al., 2011) using the SyN registration approach in Advanced Normalization Tools.(Avants et al., 2008) A nonlinear deformation was performed in several steps: 1) two linear (rigid followed by affine) steps, 2) nonlinear (whole brain) SyN-registration, 3) two nonlinear SyN-registrations focusing subcortical masks defined by Schoenecker, et al.(Schonecker et al., 2009) A brain shift correction was performed on the postoperative CT images by calculation of a focused affine transform between pre- and post-operative acquisitions restricted to subcortical structures in Lead-DBS software (http://www.lead-dbs.org).(Horn and Kuhn, 2015) Electrodes were then localized and contacts manually corrected using Lead-DBS software.

Comparison of contact position relative to the ANT was performed in Lead-DBS software by means of the DBS Intrinsic Template Atlas (DISTAL).(Ewert et al., 2018) The center of each contact was localized in MNI space, and a threshold of radius 0.635 mm was applied to account for contact diameter. A 3-D Euclidean distance to the ANT border was calculated for all four contacts of each Medtronic 3389 lead.

## 3. Results

Demographic information of the ten patients is included in Table 1. Patient age ranged from 19 to 56 years at the time of DBS surgery with a median age of 34.5 years. Median duration of epilepsy 30 years. Mean follow up time was 26 months. A list of final used target coordinates relative to AC-PC line was showed in Table 2.

### 3.1. Success rate of ANT-targeting

Bilateral ANT DBS in all ten patients resulted in a total of 20 trajectories. At least one contact was present within the ANT in 90% (n = 18). Additionally, 80% (n = 8) of patients were successfully targeted on both sides, with only two patients categorized as a unilateral ANT miss. There was no difference of ANT hit rate between the right side (90%) and left side (90%). The relationship of all contacts with the ANT is demonstrated in Fig. 2 (3D reconstruction data showing each implant is in supplemental figure). The number of trajectories that included 1, ≥2 or ≥ 3 contacts within the ANT were 3, 15, and 9, respectively. Notably, left-sided leads showed a greater number of contacts within the ANT compared to the right side (26 vs. 18). The mean contact number at ANT was 2.2± 1.2. (Table 3)

### 3.2. Lead misplacement

A total of two leads within two patients had no contacts in the ANT on postoperative CT. One missed on the right side lead (patient 9) and one missed on the left (patient 6). The ANT misplacement rate was 10% of trajectories. The displacement of the right lead in patient 9 was slightly lateral to the ANT with the most distal lead contact only 0.5 mm from the ANT border. Displacement of the left lead in patient 6 was related to a deflection of the lead along the posterior trajectory that resulted in a more superior and medial positioning of the lead than anticipated. (Fig. 3)

### 3.3. Surgery-related complications

There were no post-operative intracranial hemorrhages identified on follow-up imaging for our patient cohort. No CSF leakage happened. There were no intracranial infections, however one patient experienced

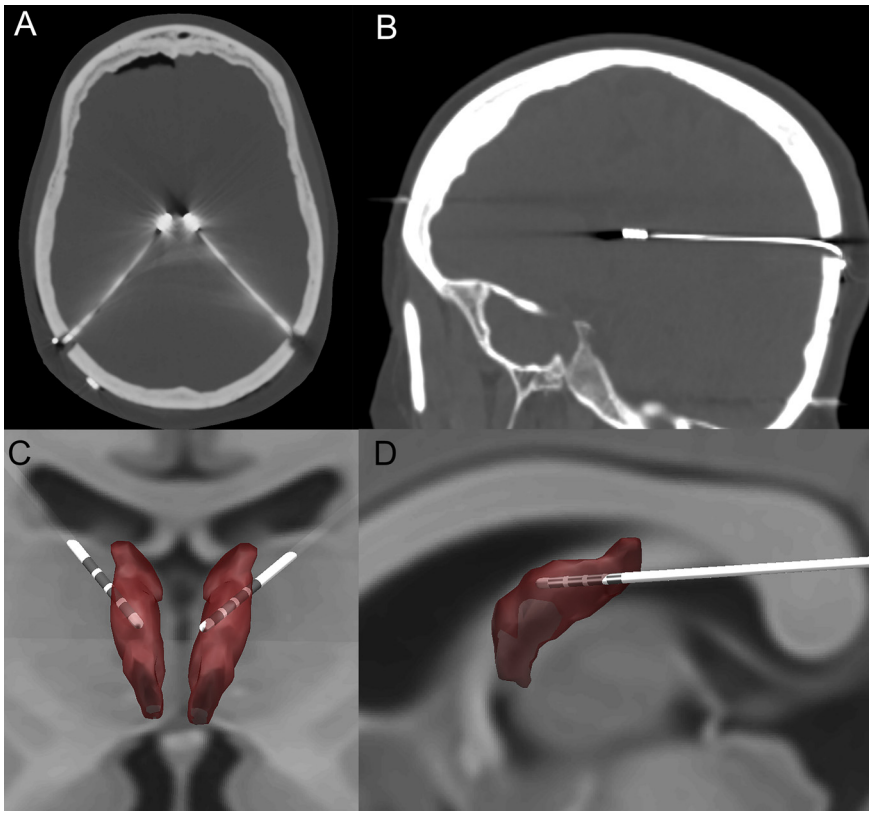


**Fig. 1.** Exemplary subject illustrating the current parietal extraventricular trajectory in axial (A) and oblique sagittal (B) post-operative non-contrast CT. Electrodes in the same subject co-registered to the Montreal Neurological Institute atlas space are shown in the oblique coronal (C) and left sagittal (D) views highlighting the relationship of the electrode contacts with the anterior nucleus of the thalamus (red).

a battery site infection 9 months following surgery resulting in explantation of the battery and lead extensions. The cause of the delayed infection was unknown but did have dental work one month prior to infection. One patient developed transient contralateral motor weakness after implantation lasting 1 week, which was attributed to a centromedian intra-laminar parafascicular complex (CMpF) lead that was placed through the motor cortex rather than related to the ANT lead. One right-sided lead fracture was noted in one patient 18 months after the DBS surgery, which was subsequently replaced.

## 4. Discussion

The ANT has proven challenging to reliably target in multiple prior studies.(Bouwens van der Vlis et al., 2018; Jiltsova et al., 2016) Targeting difficulty could be due to a relatively large degree of variation in the structure of the ANT in anatomical and radiological studies. (Mottonen et al., 2015; Van Buren and Borke, 1972) The results of the MORE trial supported that a TV trajectory is more likely to deliver an electrode into the ANT when compared to a frontal EV trajectory. The

**Table 2**
Target Coordinates to AC-PC Line.

| Patient No. | Anterior MCP offset (mm) | Laterality offset (mm) | Superior offset (mm) |
|---|---|---|---|
| 1 | 4.50 | 4.25 | 13.50 |
| 2 | 3.50 | 3.50 | 14.75 |
| 3 | 3.75 | 4.25 | 14.00 |
| 4 | 1.50 | 4.25 | 14.25 |
| 5 | 4.00 | 4.00 | 14.00 |
| 6 | 3.50 | 4.25 | 14.00 |
| 7 | 2.00 | 4.00 | 14.75 |
| 8 | 1.50 | 5.00 | 12.00 |
| 9 | 3.00 | 5.50 | 14.00 |
| 10 | 1.50 | 5.00 | 12.00 |

AC: anterior commissure; PC: posterior commissure; MCP: mid-commissural points.

**Table 1**
Demographics of Patients.

| Patient No. | Age at Surgery | Gender | Seizure Duration (Years) | Follow up (Months) | Complication |
|---|---|---|---|---|---|
| 1 | 36 | M | 33 | 16 | Battery site infection at 9 months |
| 2 | 54 | F | 31 | 10 | none |
| 3 | 47 | M | 44 | 28 | none |
| 4 | 32 | F | 8 | 33 | Fracture of right side lead |
| 5 | 39 | M | 30 | 38 | none |
| 6 | 33 | F | 21 | 28 | none |
| 7 | 32 | F | 30 | 39 | none |
| 8 | 25 | M | 14 | 39 | none |
| 9 | 50 | M | 49 | 16 | Transient left hemiparesis (suspected from entry site of CMpf Electrode) |
| 10 | 19 | F | 9 | 11 | none |

ANT: Anterior nucleus of the thalamus.
CMpf: Centromedian intra-laminar parafascicular complex.

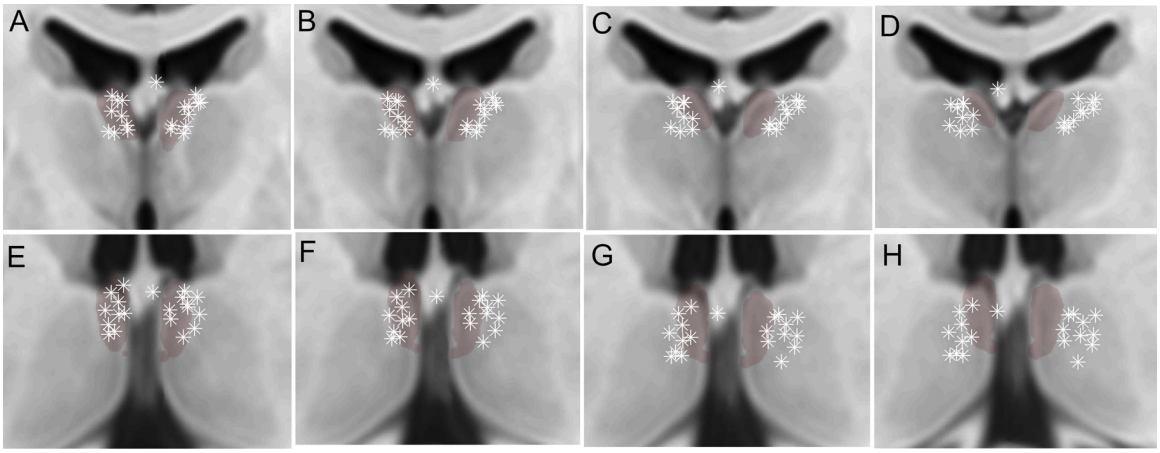


**Fig. 2.** Relationship of all contacts with the anterior nucleus of the thalamus (red). Coronal views show the most distal contact (A), second most distal contact (B), third most distal contact (C), and proximal contact (D). Axial views show the most distal contact (E), second most distal contact (F), third most distal contact (G), and proximal contact (H).

**Table 3**
Success Rate of Placing Contacts at ANT.

| Trajectories | Left side N (%) | Right Side N (%) | Both Sides N (%) |
|---|---|---|---|
| ANT-hit | 9 (90%) | 9 (90%) | 18 (90%) |
| ANT-miss | 1 (10%) | 1 (10%) | 2 (10%) |
| 1 Contact ANT | 1 (10%) | 2 (20%) | 3 (15%) |
| > 2 Contacts ANT | 8 (80%) | 7 (70%) | 15 (75%) |
| > 3 Contacts ANT | 7 (70%) | 2 (20%) | 9 (45%) |
| Total Contacts in ANT | 26 | 18 | 44 |
| Mean ANT Contacts per Trajectory (SD) | 2.6 (1.3) | 1.8 (0.9) | 2.2 (1.2) |

ANT: Anterior Nucleus of the Thalamus.
SD: Standard Deviation.

success rate for placing at least 1 contact at ANT bilaterally was 84% for TV implants and 58% for EV implants.(Lehtimaki et al., 2018) We modified the trajectory at our institution to allow full access to the ANT, and our proposed PEV trajectory revealed a 90% success rate for placing at least one contact within ANT, bilaterally. The MORE trial found a greater accuracy with the TV trajectory (ANT hit rate of 82.8%) compared with the EV trajectory (ANT hit rate of 70.3%). Results of similar measures of our targeting results with the MORE trial using 3389 leads were summarized in supplemental table (Lehtimaki et al., 2018).

A notable consideration is the contact number inside the ANT. The current PEV trajectory acquired an average number of contacts as 2.2 within ANT by using Medtronic 3389 leads. Since ANT is longer in A–P direction than in superior-inferior or medial to lateral aspect, it is reasonable that lead trajectory along that axis implants more lead contacts in ANT. So far there is no direct evidence to prove that more contacts in ANT benefits on clinical outcome. However, it is reasonable that the higher ANT contact density definitely provide more flexibility with stimulation program in the treatment of epilepsy, and as we collect more data, this will be an important analysis on seizure outcome. In addition, Satzer et al. demonstrated the impedance of DBS electrode varied over time, and contact number and electrode model were significant predictors (Satzer et al., 2014). Since the likelihood of a given contact being active in any given programming varied significantly between contacts, more contacts in the attempted target area would have significant implications for long-term DBS programming and efficacy.

Despite the relatively low incidence, intracranial hemorrhages carry the highest risk of devastating neurological outcome for DBS (Zrinzo et al., 2012). In the current study, no patient had intracranial hemorrhages after the surgeries. In the SANTE trial, five asymptomatic intracranial hemorrhages (4.5% of patients) occurred after DBS implantation via the TV trajectory (Fisher et al., 2010). Importantly, Elias et al. and Ben-Haim et al. reported the hemorrhage rate to be significantly associated with a surgical trajectory traversing the ventricle (Ben-Haim et al., 2009; Elias et al., 2009). Zrinzo et al. concluded that the TV approach was a technical factor increasing the risk of hemorrhage in DBS surgeries (Zrinzo et al., 2012). The consideration to the risk of ICH by going through lateral ventricle motivated the search for alternative surgical approaches. It is reasonable that an EV trajectory for DBS placement may have a lower potential risk for an intracranial hemorrhage compared to a TV trajectory since the electrode does not penetrate the ependyma twice. As such, the PEV trajectory which passes

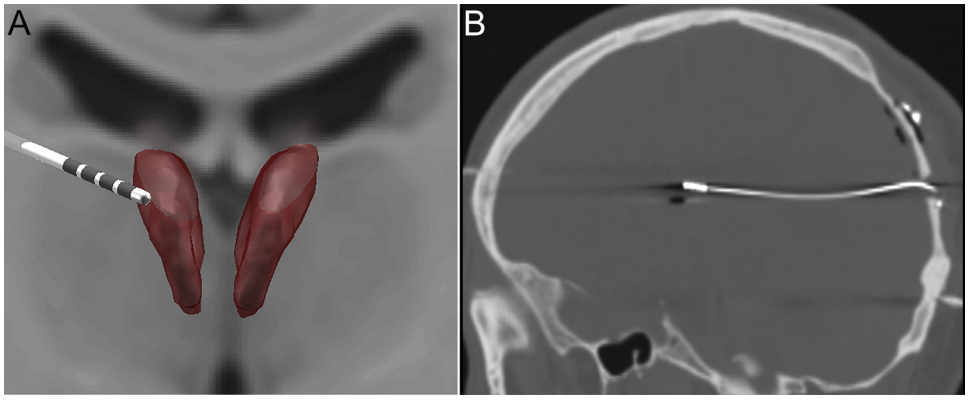


**Fig. 3.** Image of two patients with anterior thalamic nucleus misses. The right electrode position in Patient 9 (A) was located slightly lateral to the margin of the anterior nucleus of the thalamus (red). Oblique sagittal CT in the patient 6 (B) shows a superior deflection of the electrode beginning near the margin of the atrium of the lateral ventricle.

extraventricularly should theoretically further reduces the risk of hemorrhage as the ependyma should not be violated. Notably, the thalamostriate vein at anterior aspect of ANT would never be a problem on pathway since we inserted the electrode posteriorly.

Leakage of CSF through the lead was a rare but possible hardware complication in DBS surgeries. Due to pulsation-induced hydrostatic pumping, CSF would leak outside the brain or accumulate around the electrode through a fine, tiny slit between the lead and the targeted thalamus, especially when a lead passes through lateral ventricle. Son et al. reported a patient underwent ANT DBS with TV approach and got CSF egress through fine gaps between the metallic electrode contacts and electrode spacing (Son et al., 2018). There is no evidence currently to prove this CSF accumulation around the lead would contribute to malfunction. However, given all the currently available DBS electrodes are not waterproofed, it should be concerned that TV approach would cause long-term impedance changes in ANT DBS for refractory epilepsy. Since the leads are designed for intraparenchymal use, the EV approach would be a reasonable choice for the long-term stability of electrical current delivery.

ANT targeting is augmented by identification of the MTT, which joins ANT at its inferior border slightly anterior to the midpoint of ANT in the anterior–posterior axis (Jiltsova et al., 2016). It is notable that MTT has parallelly anatomic orientation with TV trajectory. Parallel approaches are more likely to miss the tract, especially when anatomical targeting of the MTT intentionally avoids this tract. On the contrary, targeting via the posterior approach is placement of the lead more perpendicular to MTT. Although ANT stimulation is a key to seizure treatment in this strategy, the supplementary antiseizure effect of MTT stimulation was discussed in the literature. Previous studies with animal models showed that ablation of the MTT provides a treatment advantage in medically induced seizures (Mirski and Ferrendelli, 1984). Therefore, a separate advantage of the PEV Trajectory targeting is being perpendicular to the MTT. This would increase the probability that the DBS lead crosses the tract and further enable electric stimulation of the MTT.

Many functional neurosurgical centers apply semidirect or indirect approximations of stereotactic targets, and the difficulty associated with directly visualizing deep thalamic nuclei is a major concern (Andrade-Souza et al., 2005; Bejjani et al., 2000; Benabid et al., 2000). Despite we showed the good accuracy to target hit, semidirect or indirect targeting methods face the obstacle of known unpredictability in spatial localization of thalamic structures in each individual given their reliance on standardized coordinates (Kelly et al., 1978). In the field of epilepsy, volumetric MRI studies have demonstrated that hippocampal, amygdalar, and thalamic atrophy increases with longer duration of disease in patients with drug-refractory epilepsy (Bernasconi et al., 2005; Natsume et al., 2003; Tasch et al., 1999; Theodore and Gaillard, 1999). Inter-individual variations could be distinguished with direct visualization of neural structures based on brain images. Therefore, direct targeting is an alternative method of targeting ANT, particularly for patients with long-term epilepsy. Recently, Grewal, et al. have shown improved ability to directly identify and target the ANT using a high-resolution Fast Gray Matter Acquisition T1 Recovery (FGATIR) MRI sequence (Grewal et al., 2018). The integration of such improvements in direct targeting, combined with our proposed surgical approach, may allow further increases in targeting accuracy and higher mean contact number within the ANT.

### 4.1. Limitations

Several limitations of our study are noteworthy. The smaller patient sample compared to the SANTE and MORE trial may result in more variance, however notably these were large multicenter trials allowing the higher numbers. Additionally, the method for assessing lead accuracy is not fully identical between the MORE trial and the current series. The different way of visualization of contact position relative to the ANT potentially affect the comparison. Further, a single center study comparing data with a multi-center study might cause selection bias. Additional patients and longer follow-up would allow us to assess seizure outcomes of the PEV trajectory.

## 5. Conclusions

In the present case series, we present our institutional experience with ten adult patients treated with the PEV Trajectory to electrode placement in the ANT, a novel posterior parietal approach. The current study provides evidence that the PEV Trajectory is a safe procedure in appropriately selected patients with no hemorrhage or permanent neurologic deficit. The results indicate comparable high accuracy to target the ANT. Multicenter, prospective studies with more patients may be needed to clarify the benefit of this surgical approach.

## Conflict of interest disclosures

The authors have no conflicts of interest to declare relevant to this study.

## Disclosure of funding

The authors have no specific sources of funding to disclose relevant to this study.

## Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.eplepsyres.2019.03.010.

## References

Andrade-Souza, Y.M., Schwalb, J.M., Hamani, C., Eltahawy, H., Hoque, T., Saint-Cyr, J., Lozano, A.M., 2005. Comparison of three methods of targeting the subthalamic nucleus for chronic stimulation in Parkinson's disease. Neurosurgery 56, 360–368 discussion 360-368.

Avants, B.B., Epstein, C.L., Grossman, M., Gee, J.C., 2008. Symmetric diffeomorphic image registration with cross-correlation: evaluating automated labeling of elderly and neurodegenerative brain. Med. Image Anal. 12, 26–41.

Bejjani, B.P., Dormont, D., Pidoux, B., Yelnik, J., Damier, P., Arnulf, I., Bonnet, A.M., Marsault, C., Agid, Y., Philippon, J., Cornu, P., 2000. Bilateral subthalamic stimulation for Parkinson's disease by using three-dimensional stereotactic magnetic resonance imaging and electrophysiological guidance. J. Neurosurg. 92, 615–625.

Benabid, A.L., Krack, P.P., Benazzouz, A., Limousin, P., Koudsie, A., Pollak, P., 2000. Deep brain stimulation of the subthalamic nucleus for Parkinson's disease: methodologic aspects and clinical criteria. Neurology 55, S40–44.

Ben-Haim, S., Asaad, W.F., Gale, J.T., Eskandar, E.N., 2009. Risk factors for hemorrhage during microelectrode-guided deep brain stimulation and the introduction of an improved microelectrode design. Neurosurgery 64, 754–762 discussion 762-753.

Bernasconi, N., Natsume, J., Bernasconi, A., 2005. Progression in temporal lobe epilepsy: differential atrophy in mesial temporal structures. Neurology 65, 223–228.

Bouwens van der Vlis, T.A.M., Schijns, O., Schaper, F., Hoogland, G., Kubben, P., Wagner, L., Rouhl, R., Temel, Y., Ackermans, L., 2018. Deep brain stimulation of the anterior nucleus of the thalamus for drug-resistant epilepsy. Neurosurg. Rev.

Cukiert, A., Lehtimaki, K., 2017. Deep brain stimulation targeting in refractory epilepsy. Epilepsia 58 (Suppl 1), 80–84.

Elias, W.J., Sansur, C.A., Frysinger, R.C., 2009. Sulcal and ventricular trajectories in stereotactic surgery. J. Neurosurg. 110, 201–207.

Ewert, S., Plettig, P., Li, N., Chakravarty, M.M., Collins, D.L., Herrington, T.M., Kuhn, A.A., Horn, A., 2018. Toward defining deep brain stimulation targets in MNI space: a subcortical atlas based on multimodal MRI, histology and structural connectivity. NeuroImage 170, 271–282.

Fisher, R., Salanova, V., Witt, T., Worth, R., Henry, T., Gross, R., Oommen, K., Osorio, I., Nazzaro, J., Labar, D., Kaplitt, M., Sperling, M., Sandok, E., Neal, J., Handforth, A., Stern, J., DeSalles, A., Chung, S., Shetter, A., Bergen, D., Bakay, R., Henderson, J., French, J., Baltuch, G., Rosenfeld, W., Youkilis, A., Marks, W., Garcia, P., Barbaro, N., Fountain, N., Bazil, C., Goodman, R., McKhann, G., Babu Krishnamurthy, K., Papavassiliou, S., Epstein, C., Pollard, J., Tonder, L., Grebin, J., Coffey, R., Graves, N., 2010. Electrical stimulation of the anterior nucleus of thalamus for treatment of refractory epilepsy. Epilepsia 51, 899–908.

Fonov, V., Evans, A.C., Botteron, K., Almli, C.R., McKinstry, R.C., Collins, D.L., 2011. Unbiased average age-appropriate atlases for pediatric studies. NeuroImage 54, 313–327.

Grewal, S.S., Middlebrooks, E.H., Kaufmann, T.J., Stead, M., Lundstrom, B.N., Worrell, G.A., Lin, C., Baydin, S., Van Gompel, J.J., 2018. Fast gray matter acquisition T1 inversion recovery MRI to delineate the mammillothalamic tract for preoperative direct targeting of the anterior nucleus of the thalamus for deep brain stimulation in epilepsy. Neurosurg. Focus 45, E6.

Horn, A., Kuhn, A.A., 2015. Lead-DBS: a toolbox for deep brain stimulation electrode localizations and visualizations. NeuroImage 107, 127–135.

Jiltsova, E., Mottonen, T., Fahlstrom, M., Haapasalo, J., Tahtinen, T., Peltola, J., Ohman, J., Larsson, E.M., Kiekara, T., Lehtimaki, K., 2016. Imaging of anterior nucleus of thalamus using 1.5T MRI for deep brain stimulation targeting in refractory epilepsy. Neuromodulation 19, 812–817.

Kelly, P.J., Derome, P., Guiot, G., 1978. Thalamic spatial variability and the surgical results of lesions placed with neurophysiologic control. Surg. Neurol. 9, 307–315.

Laxpati, N.G., Kasoff, W.S., Gross, R.E., 2014. Deep brain stimulation for the treatment of epilepsy: circuits, targets, and trials. Neurotherapeutics 11, 508–526.

Lega, B.C., Halpern, C.H., Jaggi, J.L., Baltuch, G.H., 2010. Deep brain stimulation in the treatment of refractory epilepsy: update on current data and future directions. Neurobiol. Dis. 38, 354–360.

Lehtimaki, K., Mottonen, T., Jarventausta, K., Katisko, J., Tahtinen, T., Haapasalo, J., Niskakangas, T., Kiekara, T., Ohman, J., Peltola, J., 2016. Outcome based definition of the anterior thalamic deep brain stimulation target in refractory epilepsy. Brain Stimul. 9, 268–275.

Lehtimaki, K., Coenen, V.A., Goncalves Ferreira, A., Boon, P., Elger, C., Taylor, R.S., Ryvlin, P., Gil-Nagel, A., Gielen, F., Brionne, T.C., Abouihia, A., Beth, G., 2018. The surgical approach to the anterior nucleus of thalamus in patients with refractory epilepsy: experience from the international multicenter registry (MORE). Neurosurgery.

Mirski, M.A., Ferrendelli, J.A., 1984. Interruption of the mammillothalamic tract prevents seizures in guinea pigs. Science 226, 72–74.

Mottonen, T., Katisko, J., Haapasalo, J., Tahtinen, T., Kiekara, T., Kahara, V., Peltola, J., Ohman, J., Lehtimaki, K., 2015. 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. 7, 823–829.

Natsume, J., Bernasconi, N., Andermann, F., Bernasconi, A., 2003. MRI volumetry of the thalamus in temporal, extratemporal, and idiopathic generalized epilepsy. Neurology 60, 1296–1300.

Salanova, V., Witt, T., Worth, R., Henry, T.R., Gross, R.E., Nazzaro, J.M., Labar, D., Sperling, M.R., Sharan, A., Sandok, E., Handforth, A., Stern, J.M., Chung, S., Henderson, J.M., French, J., Baltuch, G., Rosenfeld, W.E., Garcia, P., Barbaro, N.M., Fountain, N.B., Elias, W.J., Goodman, R.R., Pollard, J.R., Troster, A.I., Irwin, C.P., Lambrecht, K., Graves, N., Fisher, R., 2015. Long-term efficacy and safety of thalamic stimulation for drug-resistant partial epilepsy. Neurology 84, 1017–1025.

Satzer, D., Lanctin, D., Eberly, L.E., Abosch, A., 2014. Variation in deep brain stimulation electrode impedance over years following electrode implantation. Stereotact. Funct. Neurosurg. 92, 94–102.

Schonecker, T., Kupsch, A., Kuhn, A.A., Schneider, G.H., Hoffmann, K.T., 2009. Automated optimization of subcortical cerebral MR imaging-atlas coregistration for improved postoperative electrode localization in deep brain stimulation. AJNR Am. J. Neuroradiol. 30, 1914–1921.

Son, B.C., Choi, J.G., Ha, S.W., 2018. Cerebrospinal fluid egress from the quadripolar deep brain stimulation electrode for anterior nucleus of the thalamus for refractory epilepsy. Asian J. Neurosurg. 13, 407–410.

Tasch, E., Cendes, F., Li, L.M., Dubeau, F., Andermann, F., Arnold, D.L., 1999. Neuroimaging evidence of progressive neuronal loss and dysfunction in temporal lobe epilepsy. Ann. Neurol. 45, 568–576.

Theodore, W.H., Gaillard, W.D., 1999. Association between hippocampal volume and epilepsy duration. Ann. Neurol. 46, 800.

Thurman, D.J., Beghi, E., Begley, C.E., Berg, A.T., Buchhalter, J.R., Ding, D., Hesdorffer, D.C., Hauser, W.A., Kazis, L., Kobau, R., Kroner, B., Labiner, D., Liow, K., Logroscino, G., Medina, M.T., Newton, C.R., Parko, K., Paschal, A., Preux, P.M., Sander, J.W., Selassie, A., Theodore, W., Tomson, T., Wiebe, S., 2011. Standards for epidemiologic studies and surveillance of epilepsy. Epilepsia 52 (Suppl. 7), 2–26.

Van Buren, J.M., Borke, R.C., 1972. The mesial temporal substratum of memory. Anatomical studies in three individuals. Brain 95, 599–632.

Van Gompel, J.J., Klassen, B.T., Worrell, G.A., Lee, K.H., Shin, C., Zhao, C.Z., Brown, D.A., Goerss, S.J., Kall, B.A., Stead, M., 2015. Anterior nuclear deep brain stimulation guided by concordant hippocampal recording. Neurosurg. Focus 38, E9.

Wang, Y.C., Chuang, C.C., Tu, P.H., Wei, K.C., Wu, C.T., Lee, C.C., Liu, Z.H., Chen, P.Y., 2018. Seizures in surgically resected atypical and malignant meningiomas: long-term outcome analysis. Epilepsy Res. 140, 82–89.

Zrinzo, L., Foltynie, T., Limousin, P., Hariz, M.I., 2012. Reducing hemorrhagic complications in functional neurosurgery: a large case series and systematic literature review. J. Neurosurg. 116, 84–94.