BACKGROUND

Deep brain stimulation (DBS) of the anterior nucleus of thalamus (ANT) is an evolving treatment option in refractory focal epilepsy.1,2 The SANTE study3 was for a long time the only randomized double-blinded trial with bilateral implantation of DBS electrodes to the ANT. They found that bilateral ANT stimulation reduced seizures with a sustained effect for 2 years. An open follow-up continuation of the study showed reduction in the median seizure frequency by 69% from baseline after 5 years of stimulation.4

Objectives: Deep brain stimulation (DBS) of the anterior thalamic nucleus (ANT) may be used against refractory focal epilepsy, but only two randomized double-blinded trials have been performed. The Oslo study was discontinued prematurely since reduction in seizure frequency was less than expected. The aim of the present study was to review the targeting used in the Oslo study and to identify the actual positions of the contacts used for stimulation.

Material and methods: BrainLab MRI data were available from 12 Oslo study patients. Based on MRI the coordinates of the center of the ANT were identified. The coordinates were considered as the visually identified preferred target and were compared with the target originally used for ANT electrode implantation and with the actual electrode positions estimated from post-operative CT scans.

Results: We found considerable differences between the visually identified preferred target, the originally planned target, and the actual electrode position. The total distance between the active electrode position and the visually identified preferred target was on average 3.3 mm on the right and 2.9 mm on the left side.

Conclusion: Indirect targeting based on preset coordinates may contribute to explain the modest effect of ANT-DBS on seizure frequency seen in the Oslo study. Observed differences between the center of the ANT and the actual electrode position may at least in part be explained by variations in position and size of the ANT. Direct identification of the target using better MRI imaging protocols is recommended for future ANT-DBS surgery.

Keywords
anterior nucleus of thalamus, deep brain stimulation, epilepsy
Between April 2010 and March 2015, 18 patients with refractory focal epilepsy were operated with bilateral DBS electrodes to the ANT at Oslo University Hospital. The aims of this Oslo study were to investigate the possible effect of ANT-DBS on seizure frequency and on the burden of epileptic seizures (as measured by the Liverpool seizure severity scale) and to evaluate possible adverse effects and peri- and post-operative complications. The study had a prospective double-blinded randomized design, very similar to the SANTE study, but with a longer blinded period. The first 6 months represented the double-blinded part of the study. Half of the patients received active stimulation from the day of operation. All patients received active stimulation from 6 months post-operatively. However, this study could not reproduce the good results of the SANTE study, neither after the 6-month double-blinded period or after the next 6 months with open continuation. Inclusion of new patients to the Oslo study was therefore discontinued prematurely after a half-way interim analysis, but patients already included finished the study as planned. We found no significant difference between the 2 groups at the end of the blinded period at 6 months, but when considering all patients and comparing 6 months of stimulation with baseline, there was a significant, 22% reduction in the frequency of all seizures (P = .009). However, this mean reduction in the frequency of all seizures in the Oslo study was somewhat less than that seen after 3 months in the SANTE study (29%), and some patients even reported higher seizure frequency with ANT-DBS.

Later studies have discussed the importance of a correct implantation site and advocated that direct MRI visualization of the desired target is essential for a favorable outcome in ANT-DBS. ANT target identification in the Oslo patients was performed in the same way as in the SANTE study, using the same coordinates that were described in the pilot studies listed in the original SANTE article, and that were confirmed through personal communication with the SANTE authors. Thus, preset coordinates were used, but small adjustments were allowed to compensate for anatomical variations. An extraventricular trajectory was chosen in order to reduce the risk of hemorrhage and avoid implantation through prominent veins located close to the ANT. One reason for the inferior results of the Oslo study could be suboptimal electrode positioning. In order to analyze this and to find possible explanations for the different treatment effects between the two existing double-blinded DBS studies, we have tried to identify the actual positions of the active contacts and performed a retrospective review of the ANT targeting used in the Oslo study.

2 | MATERIAL AND METHODS

Eighteen patients (11 women, seven men) with refractory focal epilepsy were operated with bilateral DBS electrodes to the ANT in the Oslo study. The operation was performed in general anesthesia. Prior to the operation a stereotactic frame was fastened to the skull and a preoperative CT scan performed. The CT data were transferred to an iPlan stereotaxy v2.6 digital workstation (BrainLab AG, Feldkirchen, Germany), and the images were fused with earlier MRI scan. The target in the ANT was calculated according to the anterior commissure-posterior commissure line (AC-PC line), within the following range of coordinates: 1-2 mm anterior to the mid-commissural point, 4-6 mm lateral to the AC-PC line, and 10-12 mm cranial to the commissure plane. Further adaptations to these preset coordinates were made when divergent anatomy, such as enlargement of the lateral ventricles or brain asymmetry was identified. The electrodes (Medtronic 3389) were inserted into the ANT by a lateral approach to avoid transventricular access.

The study was double-blinded. Eight of the 18 patients were randomized to receive active stimulation from the day of operation. Stimulation in the remaining 10 patients was turned on after 6 months. The lowest contact on the electrode (“target”) was always used. Stimulation was given in a cyclic manner, 1 minute on and 5 minutes off, with 5 V amplitude, 90 μs duration of each stimulus, and 150 Hz frequency. For further details concerning stimulation procedures, see reference 5.

Dataset from BrainLab with the original target in the ANT were available in 12 of the 18 patients from the Oslo study. All datasets included a 3D-T1W MRI sequence. Due to long inclusion time the MRI studies were carried out on different scanners using different protocols. Three different MRI scanners, MAGNETOM Symphony 1.5T (Siemens, Erlangen, Germany), MAGNETOM Sonata 1.5T (Siemens, Erlangen, Germany), and MAGNETOM Skyray 3T (Siemens, Erlangen, Germany) were used. Six patients had a 3D-T1W sequence with voxel size of 1 mm × 1 mm × 2 mm. Six patients had an isotropic 3D-T1W sequence with a voxel size of 1 mm or 1.25 mm.

The ANT is located at the anterior superior medial aspect of the thalamus and constitutes its anterodorsal border (Figure 1). The mammillothalamic tract (MTT) is pointing up toward the ANT. Fibers of the MMT together with the medullary layers of thalamus are myelin-rich structures which partially envelope the ANT and define the border toward adjacent thalamic nuclei. Two readers (TN/ KL), both experienced with direct targeting of the anterior thalamic area, evaluated the 3D-T1W MRI dataset using BrainLab iPlan stereotactic planning software and identified the MTT. By following the MTT in the cranial direction, the ANT was found on axial images at the anterior medial border of thalamus immediately medial and posterior to the caudothalamic groove. The center of the nucleus and its coordinates were estimated from reformatted images in three orthogonal planes, and these coordinates were considered as the visually identified preferred target.

Subsequently, the coordinates from the visually identified preferred target (VIT) were compared with the coordinates from the originally planned target (OPT) used for the DBS electrode implantation and with the actual position of the active electrodes (AEP). The differences between these coordinates on each side were calculated in the anterior-posterior, crano-caudal, and lateral-medial directions, and the total distances (vectors) were calculated as √(x² + y² + z²). All values are given as means in Tables 1 and 2.

All patients had CT scans within 4 weeks following surgery. The CT scan protocol was focused on the assessment of post-operative complications rather than localizing the electrode. Hence, the scans
The study was approved by the Regional Committee for Medical and Health Research Ethics, REC South East, Norway.

3 | RESULTS

The coordinates of the originally planned target, the visually identified preferred target, and the actual electrode position are given in Table 1. Table 2 shows the distance in each of the three planes and the total distance between the originally planned target and the visually identified preferred target, between the visually identified preferred target and actual electrode position, and between the originally planned target and the actual electrode position.

Mean actual electrode position was 0.3 mm lateral to the visually identified preferred target on the left side and 0.6 mm on the right side. In the antero-posterior plane, the electrodes were located 0.4 and 1.6 mm behind the preferred target on the left and right side, respectively. Along the vertical axis, electrodes were on average 0.7 mm below the preferred target on the left side (Figure 2A), 0.1 mm on the right. The total distance between the active electrode position and the visually identified preferred target was on average 3.3 mm on the right and 2.9 mm on the left side.

In each patient, we compared the distances between the visually identified preferred target and the actual electrode positions to the changes in epileptic seizure frequency after 6 months of active stimulation as reported in the Oslo study (also shown in Table 2). No correlations were found, neither when calculating the results for each side separately, nor when calculating the sum of distances from both sides versus change in seizure frequency (Pearson correlation statistics, SPSS ver. 25). The best seizure reduction (to 33% of baseline seizure frequency) was seen in patient 9 where the actual stimulation site was 1.9 and 2.3 mm from the preferred target on the right and left sides, respectively, but no seizure reduction was seen in patient 4 with deviations of only 1.2 and 2.2 mm. Also, some seizure reduction (to 70%) was seen in patient 7, with 5.9 and 4.5 mm deviations.

In the mediolateral direction, the biggest deviation from the visually identified preferred target was seen in patient 1, who had a marked seizure reduction (to 44% of baseline; see Table 2). No clear differences could be seen concerning anterior or posterior deviations of the electrodes. As an example, only very small antero-posterior deviations were seen in patients 2 and 4, with seizure frequencies of 40% and 100%, respectively. Along the vertical axis, there may be a trend toward better results when the actual stimulation site is not too far below the visually identified preferred target. This was true for all the four patients that reported most reduction of seizure frequency (patients 1, 2, 5, and 9), and patient 8 with an increased seizure frequency (to 123% of baseline) had both electrodes placed in a more caudal position. However, even the patient with the most caudally located electrodes reported some reduction in seizure frequency (patient 6, to 67% of baseline).
On the left side, the visually identified preferred target was on average 0.3 mm lateral to, 1.2 mm in front of, and 1.2 mm above the originally planned target used for electrode implantation. Similar figures for the right side were 0.1 mm lateral, 2.6 mm in front, and 1.2 mm above.

Our analysis also shows that there are differences between the original coordinates used for electrode implantation and the final position of the electrodes (see Table 2). On average, the deviations of the actual electrode position from the originally planned coordinates on the left and right sides are 0.6 and 0.7 mm in the mediolateral direction, 0.8 and 1.0 mm in the anterio-posterior direction, 0.5 and 1.1 mm in the vertical plane, and 2.8 and 3.2 in total length.

The analysis also revealed anatomical variations among the patients. There was a tendency that the ANT on the right side was located more anterior than the left ANT, on average 1.3 mm in our patients (Table 1).

### DISCUSSION

The first patients included in the Oslo study were operated in 2010. The study design aimed at reproducing the results of the SANTE study that had just been published, and indirect targeting based on preset coordinates were therefore used. Besides, the ANT is not readily visible in the traditional MRI sequences that were in normal use for DBS surgery, for example, in patients with Parkinson’s disease and other movement disorders. However, more recent studies with better imaging protocols including short...
### TABLE 2  Differences between originally planned target, the visually identified preferred target, and the actual electrode position

| ID | Difference OPT-VIT | Difference VIT-AEP | Difference OPT-AEP | Seizure frequency, % of baseline |
|----|--------------------|--------------------|--------------------|---------------------------------|
|    | Anterior | Lateral | Vertical | Vector | Anterior | Lateral | Vertical | Vector | Anterior | Lateral | Vertical | Vector |                          |
| Pat 1 | Right | -5.3 | 1.8 | -1.2 | 5.7 | 2.9 | -3.6 | -1.2 | 4.8 | -2.4 | -1.8 | -2.4 | 3.8 | 44 |
| Pat 2 | -2.0 | 0.1 | -1.7 | 2.6 | 0.1 | -2.4 | -1.7 | 2.9 | -1.9 | -2.3 | -3.4 | 4.5 | 40 |
| Pat 3 | -3.6 | 0.3 | -0.8 | 3.7 | 0.2 | -1.0 | -1.2 | 1.6 | -3.4 | -0.7 | -2.0 | 4.0 | 71 |
| Pat 4 | 0.4 | -1.3 | 0.3 | 1.4 | 0.5 | -1.0 | -0.3 | 1.2 | 0.9 | -2.3 | 0.0 | 2.5 | 100 |
| Pat 5 | -3.8 | -0.8 | -0.2 | 3.9 | 3.0 | -0.8 | -1.3 | 3.4 | -0.8 | -1.6 | -1.5 | 2.3 | 61 |
| Pat 6 | -3.7 | -0.7 | -2.4 | 4.5 | 3.1 | 0.9 | 3.1 | 4.5 | -0.6 | 0.2 | 0.7 | 0.9 | 67 |
| Pat 7 | -3.9 | 0.5 | 0.4 | 4.0 | 4.4 | -0.3 | -3.9 | 5.9 | 0.5 | 0.2 | -3.5 | 3.5 | 70 |
| Pat 8 | -1.5 | -0.2 | -1.6 | 2.2 | 1.3 | -1.9 | 2.5 | 3.4 | -0.2 | -2.1 | 0.9 | 2.3 | 123 |
| Pat 9 | -3.4 | -1.4 | -1.9 | 4.1 | 0.5 | 1.6 | 0.9 | 1.9 | -2.9 | 0.2 | -1.0 | 3.1 | 33 |
| Pat 10 | -3.3 | -1.3 | -1.1 | 3.7 | -1.6 | 0.8 | 0.8 | 2.0 | -4.9 | -0.5 | -0.3 | 4.9 | 87 |
| Pat 11 | -0.6 | 0.3 | -1.0 | 1.5 | 2.2 | 3.0 | 0.1 | 3.7 | 1.6 | 3.3 | -0.9 | 3.8 | 100 |
| Pat 12 | -0.9 | 1.4 | -2.7 | 3.2 | 3.1 | -2.3 | 2.8 | 4.8 | 2.2 | -0.9 | 0.1 | 2.4 | 101 |
| Mean | Left | -2.6 | -0.1 | -1.2 | 3.4 | 1.6 | -0.6 | 0.1 | 3.3 | -1.0 | -0.7 | -1.1 | 3.2 | |
| Pat 1 | -1.4 | -0.1 | -0.4 | 1.5 | -0.8 | -2.6 | -0.4 | 2.7 | -2.2 | -2.7 | -0.8 | 3.6 | 44 |
| Pat 2 | -0.7 | -0.8 | -2.9 | 3.1 | -0.3 | -1.3 | 0.9 | 1.6 | -1.0 | -2.1 | -2.0 | 3.1 | 40 |
| Pat 3 | -1.7 | 0.8 | -0.7 | 2.0 | 1.0 | -3.6 | -1.2 | 3.9 | -0.7 | -2.8 | -1.9 | 3.5 | 71 |
| Pat 4 | -0.2 | -1.2 | 0.1 | 1.2 | 0.0 | -1.9 | -1.1 | 2.2 | -0.2 | -3.1 | -1.0 | 3.3 | 100 |
| Pat 5 | -2.3 | -1.2 | 0.3 | 2.6 | 1.7 | -1.6 | -1.2 | 2.6 | -0.6 | -2.8 | -0.9 | 3.0 | 61 |
| Pat 6 | 1.2 | -1.1 | -3.3 | 3.7 | -0.7 | 1.0 | 3.5 | 3.7 | 0.5 | -0.1 | 0.2 | 0.5 | 67 |
| Pat 7 | -3.6 | -0.5 | -0.9 | 3.7 | 2.7 | 3.1 | 1.8 | 4.5 | -0.9 | 2.6 | 0.9 | 2.9 | 70 |
| Pat 8 | -0.5 | -0.1 | -0.5 | 0.7 | 0.2 | 0.3 | 1.7 | 1.7 | -0.3 | 0.2 | 1.2 | 1.3 | 123 |
| Pat 9 | -1.8 | -0.4 | -1.5 | 2.4 | 1.9 | 1.3 | 0.0 | 2.3 | 0.1 | 0.9 | -1.5 | 1.8 | 33 |
| Pat 10 | -1.1 | -1.0 | -1.4 | 2.0 | -1.9 | 2.1 | 2.2 | 3.6 | -3.0 | 1.1 | 0.8 | 3.3 | 87 |
| Pat 11 | -2.2 | 0.8 | -0.6 | 2.4 | -2.1 | 0.9 | 0.3 | 2.3 | -4.3 | 1.7 | -0.3 | 4.6 | 100 |
| Pat 12 | 0.3 | 1.4 | -2.6 | 3.0 | 2.7 | -1.3 | 2.1 | 3.7 | 3.0 | 0.1 | -0.5 | 3.0 | 101 |
| Mean | -1.2 | -0.3 | -1.2 | 2.4 | 0.4 | -0.3 | 0.7 | 2.9 | -0.8 | -0.6 | -0.5 | 2.8 | |

*Note:* Anterior: + forward,− backwards. Lateral: + outwards,− inwards toward the midline. Vertical: + upwards,− downwards. Seizure frequency after 6 mo of stimulation, given in % of baseline.

*Abbreviations:* AEP, actual electrode position; OPT, originally planned target; VIT, visually identified preferred target.
tau inversion recovery (STIR) and T1-weighted magnetization prepared gradient echo (MPRAGE) images have enabled direct targeting of the ANT. These studies showed that the ANT could be outlined in stereotactic 1.5T MRI both in STIR and T1-weighted MPRAGE images.

FIGURE 2  A, Merged image from one of our patients showing the position of the left ANT in T1W MRI and the location of the left electrode (light red). Note the extraventricular trajectory and the tip of the electrode located below the caudal border of ANT. B, C, T1W MRI BrainLab iPlan axial and coronal images showing the ANT (pink outline), targeted using extra- and transventricular lead trajectories (in green and yellow, respectively). The contacts of the DBS electrode are in a more inferior and posterior position with respect to the ANT when applying the extraventricular trajectory.
A centrally located ANT stimulation site seems to be important for a good antiepileptic effect of DBS. The Oslo study used an extraventricular approach, which may make it even more difficult to hit the central part of ANT. A consensus report based on an international multicenter registry have recently concluded that direct targeting and a transventricular approach should be preferred for DBS implantations to the ANT. A centrally located ANT stimulation site seems to be important for a good antiepileptic effect of DBS. The Oslo study used an extraventricular approach, which may make it even more difficult to hit the central part of ANT. A consensus report based on an international multicenter registry have recently concluded that direct targeting and a transventricular approach should be preferred for DBS implantations to the ANT. The success rate when placing at least one contact at the ANT target region bilaterally was 84% with a transventricular route, compared to 58% with an extraventricular route.

It is worth noting that the center of the ANT in most patients appears to be located somewhat anterior and superior to the preset target used both in the SANTE and Oslo studies (Möttönen 2015). Figure 2A also shows an example where our extraventricular, more lateral approach has placed the tip of the electrode in a caudal position, while Figure 2B,C shows how the electrode with a transventricular, more vertical approach could have entered the ANT from above. Another advantage with the transventricular approach could thus be that one or two contact points on the electrode would be placed in the ANT superior to our target point, allowing for the use of more cranial contacts.

5 | CONCLUSIONS

This study suggests that the indirect targeting based on preset coordinates may contribute to explain the modest effect of ANT-DBS on seizure frequency seen in the Oslo study. Considerable differences between the preset original targets, the visually identified preferred targets, and the actual electrode positions were seen. These differences may at least in part be explained by the variations both in position and size of the ANT. Direct MRI identification of the target by using better imaging protocols is recommended for future ANT-DBS surgery.

ACKNOWLEDGMENT

We would like to thank professor Mona Skjelland for randomization of patients. The study was supported by a PhD grant from the Dam Foundation, Norway.

CONFLICT OF INTEREST

Dr Ane E. Konglund has received a speaker’s fee from Medtronic.

DATA AVAILABILITY STATEMENT

All data from this study are available in the tables in the article.

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How to cite this article: Nome T, Herrman H, Lehtimäki K, et al. Direct visual targeting versus preset coordinates for ANT-DBS in epilepsy. Acta Neurol Scand. 2020;142:23-29. https://doi.org/10.1111/ane.13233