Deep Brain Stimulation for Arm Tremor: A Randomized Trial Comparing Two Targets

Nadja Kvernmo, MD,[1,2] Ane E. Konglund, MD, PhD,[3] Martin M. Reich, MD,[4,5] Jonas Roothans, MSc,[5] Are H. Pripp, PhD,[6] Espen Dietrichs, MD, PhD,[1,2] Jens Volkmann, MD, PhD,[4,7] and Inger Marie Skogseid, MD, PhD [1]

Objective: Deep brain stimulation (DBS) of the thalamic ventral intermediate nucleus (VIM) effectively suppresses arm tremor. Uncontrolled studies suggest the posterior subthalamic area (PSA) may be superior. We compared the intra-individual efficacy of VIM- versus PSA-DBS on tremor suppression and arm function.
Methods: We performed a randomized, double-blind, crossover trial at Oslo University Hospital in patients (18–80 years) with isolated or combined action tremor affecting at least one arm. Four-contact DBS leads were implanted (bi- or unilaterally) with a trajectory to cover the VIM (upper two contacts) and PSA (lower two contacts). Patients were randomized (1:1 ratio) post-surgery to: Group 1, VIM-stimulation months 0–3 (period 1), then PSA-stimulation months 4–6 (period 2); Group 2, PSA-stimulation first, then VIM-stimulation. Primary endpoint was the difference in improvement from baseline to the end of the VIM- versus PSA-period in the sum of the dominant arm tremor scores of the Fahn-Tolosa-Marin Tremor Rating Scale (FTMTRS), items 5/6 + 10−14.
Results: Forty-five patients were randomized to Group 1 ($n = 23$) or 2 ($n = 22$). In the primary endpoint per-protocol analysis (mixed model, n = 40), mean difference in the sum FTMTRS score improvement for the dominant arm was −2.65 points (95% CI −4.33 to −0.97; $p = 0.002$). The difference in favour of PSA stimulation was highly significant in period 2, but not period 1.
Interpretation: Our randomized trial demonstrated that PSA stimulation provided superior tremor suppression compared with VIM stimulation. A period effect reducing tremor for up to three months in both groups was most likely attributed to a post-surgery stun effect.

ANN NEUROL 2022;91:585–601

Tremor is defined as rhythmic and oscillatory involuntary movements of a body part. Action tremor occurs when maintaining a posture against gravity (postural) and/or when making a dynamic movement (kinetic).[1,2]Upper limb (UL) action tremor is the most frequent movement disorder and may profoundly impact dexterity. The prevalence of the isolated tremor syndrome essential tremor (ET) alone is around 1% (5% in patients >60 years old).[3] UL action tremor is also frequent in combined tremor syndromes, Parkinson's disease (PD), dystonia and cerebellar syndromes.[2–5] The pharmacological management of disabling hand tremor is notoriously difficult, because normal hand function requires near complete tremor suppression and is not proportional to documented reductions in tremor amplitude.[6–8] Functional stereotactic surgery, which provides more reliable and profound control of tremor than any drug therapy, has therefore been part of the treatment algorithm of severe tremor since the 1950s.

View this article online at wileyonlinelibrary.com. DOI: 10.1002/ana.26317

Received Aug 27, 2021, and in revised form Jan 14, 2022. Accepted for publication Feb 7, 2022.

Address correspondence to Dr Skogseid Department of Neurology, Oslo University Hospital, PO box 4950, Nydalen, 0424 Oslo, Norway. E-mail: skogseidingermarie@gmail.com

[Correction added on March 29, 2022, after first online publication: The copyright line was changed.]

From the [1]Department of Neurology, Oslo University Hospital, Oslo, Norway; [2]Institute of Clinical Medicine, University of Oslo, Norway; [3]Department of Neurosurgery, Oslo University Hospital, Oslo, Norway; [4]Department of Neurology, University Hospital of Wuerzburg, Wuerzburg, Germany; [5]Visual DBS lab, University Hospital of Wuerzburg, Wuerzburg, Germany; [6]Department of Biostatistics, Oslo University Hospital, Oslo, Norway; and [7]Institute of Clinical Medicine, University of Wuerzburg, Germany

Additional supporting information can be found in the online version of this article.

Two decades ago, deep brain stimulation (DBS) of the thalamic ventral intermediate nucleus (VIM) (or ventrolateral posterior) was established as a potent treatment alternative for tremor patients, with superior functional outcomes compared to thalamotomy and a high responder rate.[9,10] However, the efficacy depends on the site and intensity of stimulation, and must be balanced against potential stimulation-induced adverse effects such as dysarthria and gait ataxia during neurological follow-up.[11,12] VIM-DBS has proved less efficient in reducing intention tremor, and loss of sustained tremor control over time (habituation) has been observed in a varying proportion of patients (0–73%).[13]

Several groups have therefore pioneered DBS in the posterior subthalamic area (PSA) – localized below the thalamic VIM and ventro-oral nuclei, posteromedial to the subthalamic nucleus (STN), and lateral to the red nucleus (RN). The PSA contains grey matter, eg, zona incerta (ZI), surrounded by large fibre bundles, such as the prelemniscal radiation (RaPrl). Open-label case series have indicated very good UL tremor suppression from PSA-DBS, including proximal kinetic and intention components, both in ET and more heterogenous clinical populations.[14–16] In a systematic study that tested each contact of quadripolar DBS leads targeted to the VIM nucleus in ten ET patients and eleven multiple sclerosis (MS) patients, stimulation of the contacts below the AC-PC line, covering the ZI and RaPrl, yielded significantly more improvement of UL action tremor in clinical ratings and objective kinematic recordings than those above.[17] Quantitative measures of ataxic tremor components also improved to a greater extent.[17] This indicated that stimulating the dentato-rubro-thalamic tract, as it runs through the anatomical "bottle-neck" of PSA, could yield better tremor suppression than stimulating the VIM proper.

In 2018, a randomized, double-blind, crossover trial comparing DBS of the PSA to VIM using a single lead in each hemisphere in 13 ET patients reported a trend towards more pronounced improvement in arm tremor with PSA-DBS ($p = 0.086$).[18] In our controlled, randomized trial, the main aim was to evaluate whether PSA-DBS was more effective than VIM-DBS at suppressing UL action tremor in the most common tremor syndromes. We studied this by placing a single lead bilaterally (or unilaterally) to cover both targets, and stimulating each target consecutively in a randomized, controlled, crossover design, to compare their efficacy and safety profile.

Methods

Study Design and Participants

This randomized, double-blind, crossover study compared the efficacy of VIM-DBS versus PSA-DBS in patients with UL action tremor as a symptom of the most common tremor syndromes. All patients were operated and followed at the DBS center at Oslo University Hospital (OUH), Oslo, Norway. Ethical approval was obtained from the Privacy Ombudsman, OUH and the Regional Committee for Medical Ethics of South-Eastern Norway (2013/1013). The study was purely investigator-initiated. Link to protocol online: https://www.ous-research.no/skogseid.

Patients were randomized post-surgery to receive either stimulation in VIM first then PSA, or PSA first then VIM, for three months each. After these randomized periods, stimulator settings could be further optimized during the following six months. Blinded evaluations of the endpoints were performed at the end of each randomized period and one year post-surgery.

We chose a crossover design to allow direct comparison of stimulating the two targets in each patient, who served as their own control. This design was suitable because action tremor presents with variable severity and additional symptoms difficult to control for in a parallel design study. Moreover, natural disease progression is unlikely to confound the analysis of such a short crossover-period. Action tremor severe enough to indicate surgery has a low prevalence; a crossover design can yield sufficient statistical power with fewer patients. We did not include a washout period because the tremor-suppressing effects from stimulation in each target are known to be rapid. Cerebellar gait ataxia, a feared side effect of DBS in both VIM and PSA, can last for 72 hours or longer after turning off stimulation, but has been observed mostly with supratherapeutic stimulation.[19] Due to protocol restrictions of the stimulation parameters allowed during the randomized periods, supratherapeutic stimulation would be unlikely to occur.

Study participants were recruited consecutively from patients with severe tremor evaluated and accepted for DBS treatment at our center. Eligible patients were males and females, aged 18 to 80 years, with chronic action UL tremor interfering with work performance and/or activities of daily living, and insufficient relief from adequate trials of recommended medications. Prior diagnostic work-up included brain MRI in all, DATscan in patients with rest tremor, and blood and urine tests to exclude medically-treatable disorders. Eligible tremor disorders were ET/ET plus,[2] PD, dystonic tremor, and cerebellar tremor (idiopathic or secondary to MS or spino-cerebellar ataxia). Exclusion criteria included the usual contraindications to DBS surgery,[20] and comorbidities which would make evaluation of the beneficial and adverse stimulation effects challenging (eg, severe peripheral neuropathy, chronic pain syndrome with opioid use). Written informed consent was obtained from each patient before enrolment. The study

was performed according to the Helsinki declaration. Trial registration: ClinicalTrials.gov (NCT03156517).

Randomization and Masking

Patients were randomized (1:1 allocation) post-surgery to receive two different interventions (AB:BA crossover design). Group 1 received VIM-DBS for the first three months (period 1) then PSA-DBS for the next three months (period 2). Group 2 received PSA-DBS during period 1 and VIM-DBS during period 2. Randomization took place with a computer-generated, secured, web-based service provided by The Norwegian University of Science and Technology, Trondheim, Norway, which had no other role in the study. The sequence was yielded through block randomization. After operation, each included patient was entered for randomization by the project leader (IMS), who received the group assignment by secured message through password-protected email. She also programmed the stimulators. The physician who performed the blinded clinical scoring (NK) had no role in randomization or programming, and was not allowed to read the electronic charts from the operation before completion of the last blinded follow-up visit, one-year post-surgery. No masking was used as all patients were operated, and the target sequence concealed for the blinded rater and patients.

Neurological Evaluation and Scoring

The examination at inclusion included a comprehensive medical history and neurological examination. One blinded physician performed the tremor scoring/other clinical evaluations preoperatively, at the end of each three-month randomized period and the one-year follow-up.

The Fahn-Tolosa-Marin Tremor Rating Scale (FTMTRS) was used to score tremor,[21] containing 21 items scored from 0 = no tremor/disability to 4 = severe tremor (constant/marked amplitude/inability to perform a task due to tremor). For each limb, rest tremor, postural, and kinetic/intention tremor are scored and summed (items 5 (right UL), 6 (left UL) and 8/9 for legs; maximum score 12/ limb). UL tremor was also scored during handwriting (dominant hand only, item 10), drawing spirals, straight lines and pouring water from one plastic cup to the other (both hands, items 11–14). Evaluation of each arm was done separately, with stimulation on in both hemispheres in bilaterally-implanted patients. Items 16 to 21 score disability caused by UL tremor during feeding, drinking, hygiene, dressing, writing, and working, and the remaining FTMTRS items tremor in the face, tongue, voice, head, and trunk, and disability in speech.

Each study visit also included interview for the Quality of life in Essential Tremor-Questionnaire (QUEST), Visual Analog Scale (VAS) score of Global Burden of Disease/tremor (GBD) and tremor-related pain, Hospital Anxiety and Depression Scale (HADS), and clinical interview/examination for type/severity of adverse events (AEs) and complications, using standardized forms. QUEST is a 30-item questionnaire developed and validated for ET patients. Its five domains evaluate physical aspects, communication, work, hobbies/leisure, and psychosocial aspects of the tremor.[22] A Summary Index can be calculated (Sum of the five domain scores/5). VAS-GBD is a patient-evaluated measure consisting of a 0 to 100-mm continuous line on which patients mark their disease burden with a cross (0 = no burden; 100 = maximum burden the patient can imagine). HADS is a well-established and validated self-report questionnaire that contains 14 items expressing emotions, alternating between seven emotions of anxiety and seven of depression (each item scored 0–3, higher scores indicate more emotional distress).[23]

Surgical Procedure

Preoperative axial MRI sequences (T2-weighted fast-spin-echo (SE), diffusion-weighted SE-planar imaging, and 3D inversion prepared T1-weighted gradient-echo) were obtained on a 3 Tesla MRI scanner. Under local anaesthesia, a stereotactic head ring was mounted in parallel with the intercommissural line (ICL) before performing a stereotactic computed tomography (CT) scan. The iPlan™ (version 3.0 or later) computer-aided neuronavigation system (BrainLab, München, Germany) was used to merge the CT and MRI scans, and to plan the targets based on predefined stereotactic coordinates for VIM (indirect targeting) and structural/anatomical guidance (direct targeting) for PSA. Our definition of the VIM target point was $X = 50\%$ of the ICL length lateral to the ICL, $Y = 30\%$ anterior to the posterior commissure, and $Z =$ the level of the ICL-plane.[24,25] The PSA was targeted slightly posterior and medial to the STN, at the level of the maximal diameter of RN, aligned with published coordinates.[15,16] A trajectory angle was applied to allow the two most dorsal contacts of a four-contact lead to cover the VIM and the two most ventral contacts to cover the PSA. Trajectories were designed to avoid vessels, sulci and ventricles. The surgery was performed in awake patients using the CRW™ (Radionics, MA, USA) or Leksell® Vantage™ (Elekta AB, Stockholm, Sweden) stereotactic system for electrode placement.

Clinical test stimulation to define the threshold for action tremor suppression and adverse effects (dysarthria, hand paresthesias) was performed at four steps: 2 mm above and at the ICL-plane (VIM), and 2 and 4 mm inferior (cranial and caudal ZI), using the permanent electrode (Medtronic® 3389, $n = 38$ patients; Boston® Cartesia, $n = 7$). Placement was accepted if we observed good tremor suppression and no unacceptable side effects. Intraoperative

fluoroscopy was used to evaluate the final electrode position. The electrodes were connected via extensions to a pulse generator (Activa PC®, Medtronic; Gevia®, Boston) implanted in the subclavicular region. Prophylactic antibiotics were administered the first 24 hours.

Initiation and Modulation of Stimulation Parameters

For the VIM period, the two upper contacts of the lead were tested with monopolar review; the one yielding the best clinical results was chosen for further treatment. For the PSA period, the contact yielding the better tremor suppression among the two lower contacts of the lead was determined accordingly. As predefined in the protocol, stimulator settings were kept as similar as possible in the two randomized periods: monopolar and ring-stimulation mode, pulse width 60 μs, frequency 130 Hz (up to 145 Hz), current ≤3 mA. One mid-period reprogramming visit was allowed in each period to refine the parameter settings. Protocol deviations of parameter settings occurred only if the clinical result was deemed clearly unsatisfactory by the patient.

After blinded scoring at the end of period 2 (six months postoperatively), the contact that yielded the best tremor reduction with no or only minor side effects was selected for subsequent treatment. Two additional programming visits could be scheduled flexibly until the one-year follow-up.

Outcomes

In the protocol, primary endpoints were defined as the differences from baseline to the end of each three-month randomized treatment period in the objectively-observed tremor scores of the contralateral arm(s) for VIM-DBS versus PSA-DBS, as evaluated by the sum of FTMTRS items 5/6 and 10−14 (dominant arm) or 11−14 (non-dominant arm). From power calculations, 45 patients needed to be included. Only the dominant arm was treated in all patients. Thus, our main primary endpoint was the sum FTMTRS score of the dominant arm. Functional disability of arm tremor (FTMTRS item 16–21) was also included among the primary endpoints.

Pre-specified secondary endpoints were the improvement from baseline to the 12-month blinded evaluation in the following scores: UL tremor (same items as for primary endpoints), tremor scores for face/tongue/voice/head/trunk/lower limb(s), total FTMTRS score, patient-rated measures (QUEST Summary Index, VAS GBD of tremor), and frequency/severity of AEs.

To localize the active contacts, the preoperative MRI and post-surgical volume CT scans (obtained median 155 days post-surgery (10^{th}-90^{th} percentile: 7–479) were merged using the SureTune software version 3 (Medtronic®) as previously described.[26] Lead localizations were linearly normalized to MNI-space (ICBM 2009b NLIN asymmetric) based on the local Yelnik atlas registration (Yelnik et al., 2007) using an in-house MATLAB toolbox (Arena; https://github.com/JonasRoothans/ArenaToolbox).

Statistical Analysis

Based on earlier research concerning VIM- and PSA-DBS for tremor, we assumed a mean improvement of 16 points (standard deviation (SD): 5) in the dominant arm sum score (items 5/6 + 10−14) of UL tremor. We defined a clinically-significant difference as 1.8 (4) points between the two interventions. A 2x2 crossover design with 41 patients in each period would then have 80% power to detect a clinically-significant difference using a paired t-test. To account for potential drop-outs and missing data, we planned to include 45 patients.

A basic statistical analysis of the 2 × 2 crossover design assumes no period (systematic difference between periods) or carryover effects (systematic difference between sequences of interventions). The period effect was assessed by comparing the mean response of the two periods using a paired t-test and the carryover effect by comparing the mean response of the two sequences of interventions using an independent t-test. We conducted a linear mixed-model approach using a random intercept with maximum likelihood estimation to account for within-subject correlations. Both a model with fixed effects for treatment, period, and carryover (interaction between period and treatment) and a model with only fixed effects for treatment were estimated. The period and carryover effect were then assessed from the linear mixed-model estimates. Results from the linear mixed models are presented with estimated means, 95% confidence intervals (CI), and *p*-values. These analyses were performed both on the per-protocol and intention-to-treat populations. A p-value <0·05 was considered statistically significant.

Continuous data are presented as mean (SD), or median (10^{th}–90^{th} percentile) if clearly skewed, and categorical data with number of observations (percentage). Statistical analyses were performed using IBM SPSS Statistics for Windows, version 26.0 (IBM Corp, Armonk, NY) 26 and STATA/SE 16.1 for Windows (StataCorp LLC, College Station, TX, USA).

Results

Study Population

Between April 1, 2014, and December 11, 2018, we assessed 56 patients for eligibility and enrolled 45 patients (male:female: 25:20), who were operated and randomized to Group 1 ($n = 23$) or Group 2 ($n = 22$) (Fig 1).

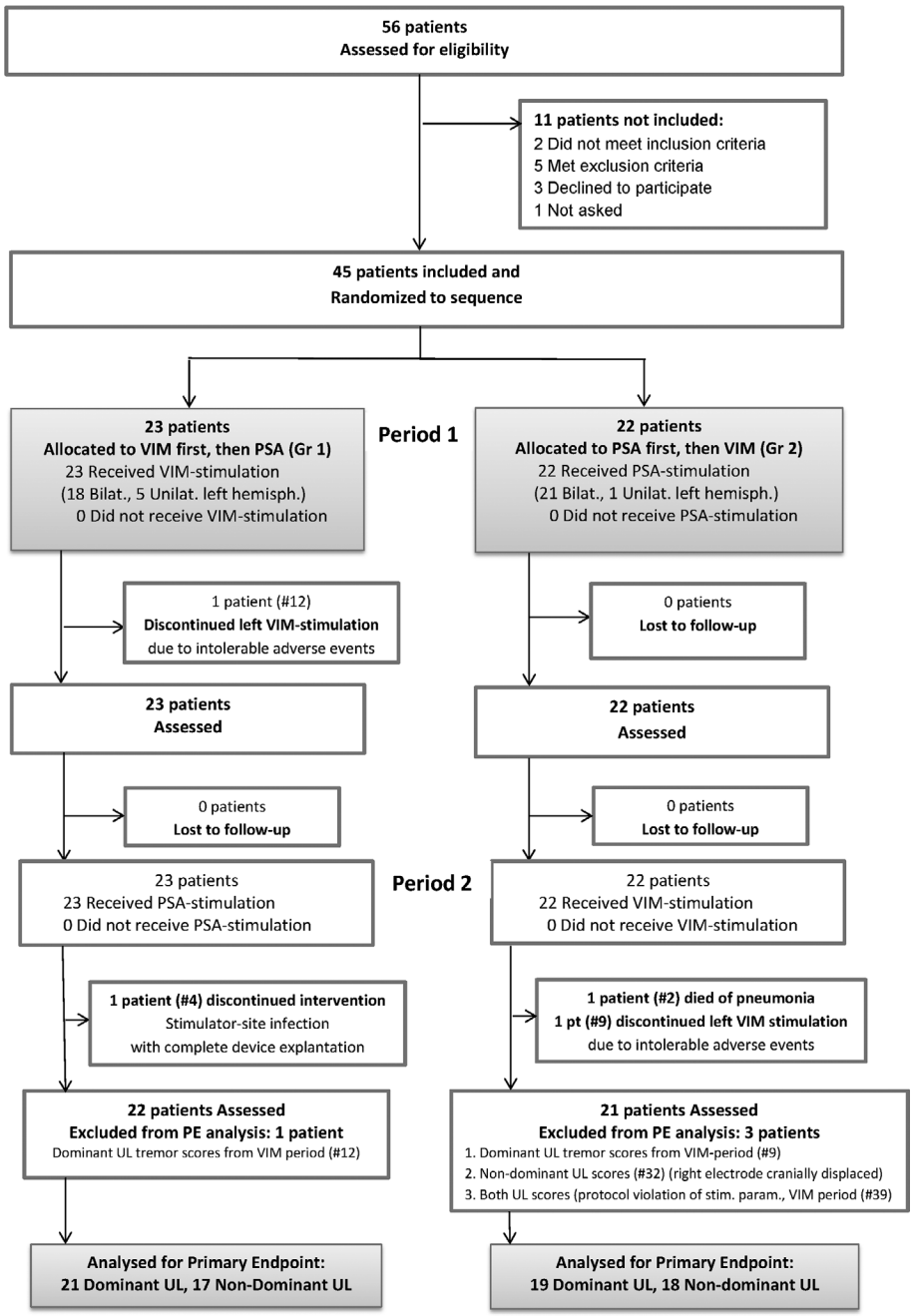

FIGURE 1: Trial profile.

Electrodes were implanted bilaterally in 39 patients and unilaterally in six (all in the left hemisphere, for dominant arm PD tremor). At surgery, mean age was 62.8 (11.5) years and disease duration 25.0 (16.0) years. Tables 1 and 2 summarizes the baseline clinical characteristics.

During period 1 (0–3 months post-surgery), a woman with cerebellar tremor and mild MS in Group 1 had to discontinue left VIM-DBS due to worsened gait unsteadiness (compared to preoperative), which then improved immediately (Fig 1). All patients in Group 2 tolerated PSA-DBS. During period 2 (4–6 months post-surgery), all patients in Group 1 tolerated PSA-DBS, but a woman with dystonic tremor developed a stimulator-site infection that necessitated device removal, and was lost to follow-up. In Group 2, a man (aged 58 years) with severe cerebellar tremor secondary to advanced primary progressive MS (of 24 years duration) died of pneumonia (after 2.5 months with stable stimulation parameters). In a woman with severe MS, left VIM-DBS had to be discontinued due to dyskinesias of the right arm, which then improved immediately. We also excluded the following scores from the

TABLE 1. Baseline demographics and diagnoses in the intention-to-treat population

	Treatment sequence/ Group		Total
	1	2	
	VIM first, then PSA (n=23)	PSA first, then VIM (n=22)	(n=45)
Gender			
Female	9 (39)	11 (50)	20 (44)
Male	14 (61)	11 (50)	25 (56)
Age at tremor onset (years)	44.0 (20.1)	31.3 (18.0)	37.8 (19.9)
Age at surgery (years)	63.1 (11.9)	62.3 (11.4)	62.7 (11.5)
Disease duration (years)	19.4 (12.5)	31.0 (17.3)	25.0 (16.0)
Tremor classification, axis 1			
Isolated; essential tremor	8 (35)	8 (36)	16 (36)
(w/comorbidity Polyneuropathy)	(0)	(3 (14))	(3 (7))
Combined	15 (65)	14 (64)	29 (64)
with parkinsonism/PD[a]	7 (30)	3 (14)	10 (22)
with cerebellar deficits	5 (22)	5 (23)	10 (22)
with dystonia	3 (13)	3 (14)	6 (13)
with dystonia + cerebellar deficits	0 (0)	2 (9)	2 (4)
with dystonia + parkinsonism[a]	0 (0)	1 (4)	1 (2)

Data are mean (standard deviation) for continuous variables and number (%) for categorical variables.
DaT = dopamine transporter; FTM, PD = Parkinson's disease; PSA = posterior subthalamic area.
[a]Pathological DaT scan.

per-protocol analysis: 1) non-dominant (left) arm scores from a woman with ET because image analysis showed clearly misplaced right electrode (too cranially: tip above the ICL-plane); 2) bilateral arm scores from the VIM period of a woman with severe PD tremor (on ET) (Period 2/Group 2) because the protocol-defined stimulation parameter limits had to be significantly violated to obtain acceptable tremor suppression. All patients excluded from the per-protocol analyses received bilateral stimulation and were right-handed. Thus, in the per-protocol analysis for the dominant arm/non-dominant arm, we had valid scores in 41/36 patients, respectively, from the VIM period, 44/37 from the PSA period, and 40/35 from both periods (Group 1: 21/17; Group 2: 19/18, Fig 1).

Outcomes

The primary endpoint analysis for the dominant arm in the per-protocol population ($n = 40$) is shown in Table 3. For the two treatment periods combined, the improvement in sum FTM arm tremor score was significantly better with PSA-DBS than VIM-DBS; mean paired differences (VIM – PSA) −2.65 points (95% CI −4.33 to −0.97), $p = 0.002$. When items 5/6 and 10 to 14 were evaluated separately, improvements were also significantly better with PSA-DBS. Table 3 and Figure 2 both show that PSA-DBS yielded significantly better improvements in arm tremor scores than VIM-DBS in period 2, but not in period 1. This period effect was, however, significant only for item 5/6 ($p < 0.05$). Findings were similar for the intention-to-treat population (Table 4).

Disability caused by arm tremor (FTMTRS items 16–21) improved by mean (standard error of the mean) 10.08 (0.87) points with VIM-DBS versus 11.90 (0.87) points with PSA-DBS; mean paired differences −1.82 (95% CI −3.89 to −0.55), $p = 0.005$ (both periods combined, per-protocol population).

TABLE 2. Baseline tremor characteristics and scores in the intention-to-treat population

	Treatment sequence/ Group		Total
	1	2	
	VIM first, then PSA (n=23)	PSA first, then VIM (n=22)	(n=45)
Body distribution of tremor			
Segmental			
UL only	4 (17)	5 (23)	9 (20)
UL + head	1 (4)	3 (14)	4 (9)
UL + head + voice/other cranial	3 (13)	4 (18)	7 (16)
Generalized			
LL, no trunk	10 (43)	5 (23)	15 (33)
LL + trunk	4 (17)	4 (18)	8 (18)
Trunk, no LL	0 (0)	1 (5)	1 (2)
Hemi (unilat. UL + LL)	1 (4)	0 (0)	1 (2)
Preop. UL FTM tremor scores			
Dominant UL	n=23	n=22	n=45
Sum items 5/6+10-14 (0-32)	21.78 (6.04)	21.86 (6.05)	21.82 (5.97)
Items 5/6 (0-12)	8.74 (2.14)	8.09 (2.11)	8.42 (2.13)
Items 10-14 (0-20)	13.04 (5.40)	13.77 (5.03)	13.40 (5.8)
Non-dominant UL	n=18	n=21	n=39
Sum items 5/6+11-14 (0-28)	18.50 (4.49)	18.76 (5.66)	18.64 (5.09)
Items 5/6 (0-12)	7.94 (2.15)	7.62 (2.06)	7.77 (2.08)
Items 11-14 (0-16)	10.56 (3.29)	11.14 (4.53)	10.87 (3.97)
FTM items 16-21 (0-24)	15.00 (4.37)	17.23 (3.62)	16.09 (4.13)

Data are mean (standard deviation) for continuous variables and number (%) for categorical variables. Fahn-Tolosa-Marin tremor rating scale; FTM tremor scores: Items 5/6, sum score for rest+postural+kinetic tremor for right/left arm; Item 10, handwriting (dominant arm only); Item 11, Drawing large spiral; Item 12, Drawing small spiral; Item 13, Drawing continuous lines; Item 14, Pouring; Items 16-21, Disability of arms in daily activities.
LL = lower limb; PSA = posterior subthalamic area; UL = upper limb; VIM = ventral intermediate nucleus.

For the non-dominant arm (per-protocol population: $n = 35$, Table 5), the score improvement for item 5/6 was also significantly better with PSA-DBS. The sum score of items 11−14 (spiral and line drawing plus pouring) significantly improved with both targets, with no significant difference between them. The sum of items 5/6 + 11−14 for the non-dominant arm improved significantly more with PSA- than VIM-DBS in period 2, but not period 1 (Table 5).

VAS-GBD of tremor and the QUEST physical domain score also improved significantly more with PSA-DBS ($p = 0.003$ and $p = 0.004$, respectively). A trend in favour of PSA-DBS was observed for the QUEST Summary Index ($p = 0.059$).

Improvement of tremor scores in other body regions was significant with both targets, with a trend towards better improvement with PSA-DBS for head tremor ($p = 0.083$). However, with $n = 26$ for head tremor at baseline, the power was insufficient to evaluate this properly.

The secondary endpoints at the 12-month follow-up all improved significantly. These results will be discussed in detail in a separate paper.

TABLE 3. Primary endpoint analysis (dominant arm) in the per-protocol population

	Baseline – VIM Mean (SE)	Baseline – PSA Mean (SE)	Δ VIM – Δ PSA Mean difference (95% CI)	*p**
Sum FTMTRS score[a]				
Treatment period 1	(n=21) 16.14 (1.55)	(n=19) 15.21 (1.63)	0.93 (-3.49 to 5.35)	0.679
Treatment period 2	(n=19) 13.53 (1.63)	(n=21) 19.67 (1.55)	-6.14 (-10.56 to -1.72)	**0.006**
Treatment periods 1 and 2 combined	(n=40) 14.90 (1.16)	(n=40) 17.55 (1.16)	-2.65 (-4.33 to -0.97)	**0.002**
	Mixed model p-value for period effect =0.091			
FTMTRS items 5/6[b]				
Treatment period 1	(n=21) 6.95 (0.58)	(n=19) 5.84 (0.61)	1.11 (-0.53 to 2.75)	0.186
Treatment period 2	(n=19) 5.21 (0.61)	(n=21) 7.95 (0.58)	-2.74 (-4.39 to -1.10)	**0.001**
Treatment periods 1 and 2 combined	(n=40) 6.13 (0.45)	(n=40) 6.95 (0.45)	-0.83 (-1.35 to -0.30)	**0.002**
	Mixed model p-value for period effect =**0.016**			
FTMTRS items 10-14[c]				
Treatment period 1	(n=21) 9.19 (1.22)	(n=19) 9.37 (1.28)	0.18 (-3.63 to 3.28)	0.920
Treatment period 2	(n=19) 8.32 (1.28)	(n=21) 11.71 (1.22)	-3.40 (-6.86 to 0.06)	0.054
Treatment periods 1 and 2 combined	(n=40) 8.78 (0.89)	(n=40) 10.60 (0.89)	-1.83 (-3.17 to -0.48)	**0.008**
	Mixed model p-value for period effect =0.322			

Primary Endpoint was the difference in improvement of Sum FTMTRS score for dominant arm between baseline and the VIM versus PSA treatment periods.

[a]Sum FTMTRS score represent the improvement of the sum of scores for items 5/6+10-14.

Treatment period 1: 0-3 months post-surgery; treatment period 2: 4-6 months post-surgery. * p <0.05 considered statistically significant (in bold).

[b]Items 5/6: sum of arm tremor at rest+postural+kinetic. In this study, the postural tremor score was the worst score obtained from examining the patient both with arms outstretched forward, in the wing-beating position, and when holding a water-filled plastic cup. The kinetic tremor score was the worst score from examining the finger-to-nose and Barany's tests, plus drinking from a water-filled plastic cup.

[c]Items 10-14: 10, Hand-writing; 11, Drawing large spiral; 12, Drawing small spiral; 13, Drawing continuous lines; 14, Pouring from one plastic cup to the other. CI, confidence interval; FTMTRS, Fahn-Tolosa-Marin Tremor Rating Scale; PSA, posterior subthalamic area; SE, standard error of the mean; VIM, ventral intermediate nucleus.

Localization of Active Contacts and Stimulation Parameters

Figure 3 shows the localization of the leads. Figure 4 depicts the localization of the active contacts in the VIM and PSA randomized periods and at one year, in a coronal and sagittal view of the ventro-lateral thalamic and subthalamic area. In the legend their mean (SD) coordinates are referred, both AC-PC based and in MNI space. In the VIM period, the most dorsal contact was used in 19.5%/19.4% in left/right hemisphere, respectively, and the one below in the remaining patients. In the PSA period, the most ventral contact was used in 54.5%/59.5% in left/right hemisphere, respectively, and the one above in 45.5%/40.5%. At one year, one of the two most ventral contacts were used in 91% of patients (the most ventral in 52%, and the other in 39% of total). While the pulse width was kept constant (60 μs) and frequency at 130 Hz (with few exceptions), the effective current was significantly lower in the PSA versus VIM period: mean difference 0.37 (0.61) mA in the left hemisphere ($p < 0.001$), 0.37 (0.42) mA in the right ($p < 0.001$).

TABLE 4. Primary endpoint analysis (dominant arm) in the intention-to-treat population

	Baseline – VIM Mean (SE)	Baseline – PSA Mean (SE)	Δ VIM – Δ PSA Mean difference (95% CI)	*p**
Sum FTMTRS score[a]				
Treatment period 1	(n=23) 15.5 (1.5)	(n=22) 13.9 (1.5)	1.6 (-2.7 to 5.8)	0.468
Treatment period 2	(n=21) 12.8 (1.6)	(n=22) 18.9 (1.5)	-6.1(-10.4 to -1.8)	**0.005**
Treatment periods 1 and 2 combined	(n=44) 14.2 (1.1)	(n=44) 16.4 (1.1)	-2.3 (-3.9 to -0.6)	**0.007**
	Mixed model p-value for period effect =0.057			
FTMTRS Item 5/6[b]				
Treatment period 1	(n=23) 6.6 (0.6)	(n=22) 5.5 (0.6)	1.1 (-0.5 to 2.7)	0.180
Treatment period 2	(n=21) 5.0 (0.6)	(n=22) 7.6 (0.6)	-2.6 (-4.2 to – 1.1)	**0.002**
Treatment periods 1 and 2 combined	(n=44) 5.8 (0.4)	(n=44) 6.5 (0.4)	-0.7 (-1.3 to -0.2)	**0.004**
	Mixed model p-value for period effect =**0.018**			
FTMTRS items 10-14[c]				
Treatment period 1	(n=23) 8.9 (1.2)	(n=22) 8.4 (1.2)	0.5 (-2.8 to 3.8)	0.784
Treatment period 2	(n=21) 7.8 (1.2)	(n=22) 11.3 (1.2)	-3.5 (-6.8 to -0.1)	**0.041**
Treatment period 1 and 2 combined	(n=44) 8.4 (0.9)	(n=44) 9.9 (0.9)	-1.5 (-2.8 to -0.2)	**0.024**
	Mixed model p-value for period effect =0.206			

Primary Endpoint was the difference in improvement of Sum FTMTRS score for dominant arm between baseline and the VIM versus PSA treatment periods.

[a]Sum FTMTRS score represent the improvement of the sum of scores for items 5/6+10-14.

Treatment period 1: 0-3 months post-surgery; treatment period 2: 4-6 months post-surgery. * p <0.05 considered statistically significant (in bold).

[b]Items 5/6: sum of arm tremor at rest+postural+kinetic. In this study, the postural tremor score was the worst score obtained from examining the patient both with arms outstretched forward, in the wing-beating position, and when holding a water-filled plastic cup. The kinetic tremor score was the worst score from examining the finger-to-nose and Barany's tests, plus drinking from a water-filled plastic cup.

[c]Items 10-14: 10, Hand-writing; 11, Drawing large spiral; 12, Drawing small spiral; 13, Drawing continuous lines; 14, Pouring from one plastic cup to the other. CI, confidence interval; FTMTRS, Fahn-Tolosa-Marin Tremor Rating Scale; PSA, posterior subthalamic area; SE, standard error of the mean; VIM, ventral intermediate nucleus.

Adverse Events

Intervention withdrawals because of AEs during the randomized study periods are reported above and in Fig 1. The frequency of serious AEs by target and treatment period are summarized in Table 6. Surgical complications and serious AEs requiring intervention were more frequent postoperatively/during period 1, but with no significant differences between the two targets.

Table 7 shows AEs that were registered and evaluated to have a possible link to the surgical lesion or stimulation. Such AEs were more frequent in the VIM period. However, factors related to the underlying tremor disorder, comorbidities or change in medication (eg, reduction of dopaminergic drugs in PD) might have been the only cause or important contributors to these events. Regarding the use of tremor-suppressing drugs during VIM/PSA randomized periods, respectively, 57%/58% used no drug, 30%/27% reduced the dose or stopped completely, 7%/7% used stable medication, and 7%/7% increased the dose or started new drug.

Discussion

We report the results of the first large, randomized, double-blind, crossover trial to intra-individually compare the effects of PSA-DBS versus VIM-DBS on UL action tremor in patients with various drug-refractory tremor syndromes (isolated tremor or combined tremor with dystonia, parkinsonism, or cerebellar deficits). We found that PSA-DBS was superior to VIM-DBS at reducing tremor

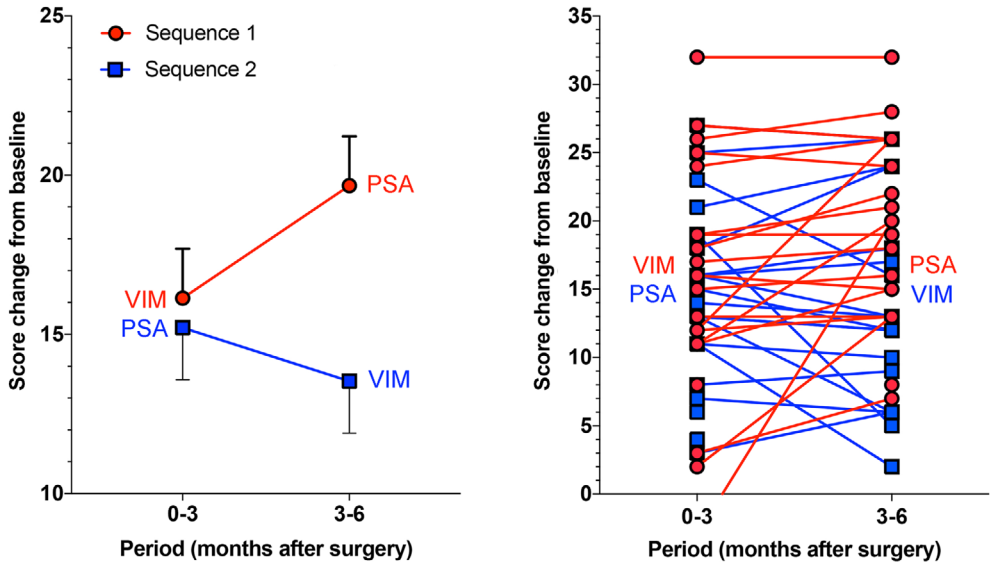

FIGURE 2: Primary endpoint by sequence and period. Left panel shows the mean of individual patient score changes from baseline in the sum of the dominant arm FTMTRS items (5/6 + 10–14), for Group 1/Sequence 1 (stimulation first in the VIM, then PSA; red-filled circles) and Group 2/Sequence 2 (stimulation first in the PSA, then VIM; blue-filled squares). Bars represent standard error of the mean. Right panel shows score changes in each individual patient. In four patients of each group in whom tremor improvement favoured PSA the most (difference > 6 points), diagnoses were cerebellar tremor ($n = 5$), essential tremor ($n = 2$) and segmental dystonic tremor ($n = 1$). (Non-parametric tests comparing these four patients with the remaining patients of their respective group showed no significant differences in active contact coordinates for the VIM- or PSA-period (left hemisphere), stimulation current applied, age at surgery, disease duration or gender). PSA, posterior subthalamic area; VIM, ventral intermediate nucleus; FTMTRS, Fahn-Tolosa-Marin Tremor Rating Scale.

severity and tremor-associated disturbance of hand function. Our results were obtained by comparing monopolar ring stimulation of a dorsal contact (VIM) to a caudal contact (PSA) in two three-month periods in each patient, who therefore acted as their own control. Imaging analyses of the active contact locations showed good segregation on a group level between the anatomical targets.

Only one other controlled study used a similar crossover design, comparing VIM- with PSA-DBS by switching from an upper to a lower contact on a single DBS lead in 13 patients with ET.[18] They found a trend ($p = 0.086$) for better improvement in the PSA (68%) versus VIM (54%) for hand tremor scores (FTMTRS items 5/6 + 11−14). In our mixed patient population, percentage improvement for the dominant hand (items 5/6 + 10−14) was mean 78% (median 88%) in the PSA versus mean 69% (median 80%) in VIM, applying a lower mean current both in the VIM and the PSA compared with their study.

The percentage improvement from VIM-DBS in our study is comparable to the mean 53 to 75% improvement in studies that targeted VIM alone and reported location of their active contacts.[27–30] The location and variability of the stereotactic coordinates for active contacts used for VIM- versus PSA-DBS in our study also correspond well with other groups that targeted VIM[27–30] or PSA alone.[15] When comparing the mean coordinates of our VIM target (AC-PC-based, left hemisphere) with the average from these four groups,[27–30] the mean differences (95% CI) in mm were *X*: −0.81 (−1.39 to −0.23), *Y*: 0.16 (−0.35 to 0.67), and *Z*: −1.85 (−2.58 to −1.12). Thus, it can be concluded that our VIM target is comparable to these centers, with our mean Z-coordinate being at the ventral end of the variability of the studies targeting VIM alone.[27–30] We are fully aware that such a comparison can only be used to exclude a gross targeting bias because of the large variability in clinical inclusion and exclusion criteria, observational period and visit schedule, and the imaging and atlas tools used to visualize the active contacts and retrieve their coordinates.[27–30]

The strengths of our study are the crossover design, allowing a direct intra-individual comparison of two stimulation sites, and a sufficient power to detect a significant difference between them. A possible limitation may be that a substantial number of patients were treated with the second contact from the top in the VIM period and third contact (from the top) in the PSA period, implying some overlap between the volume of tissue activated (VTA) in the two periods. It could therefore be argued that these patients have not really been stimulated in two separate targets. Also, as shown

TABLE 5. FTMTRS Score Improvement for the Non-Dominant Arm in the Per-Protocol Population

	Baseline – VIM Mean (SE)	Baseline – PSA Mean (SE)	Δ VIM – Δ PSA Mean difference (95%CI)	*p**
Sum FTMTRS score[a]				
Treatment period 1	(*n* = 17) 13.59 (1.25)	(*n* = 18) 11.33 (1.22)	2.25 (–1.17 to 5.67)	0.196
Treatment period 2	(*n* = 18) 10.78 (1.22)	(*n* = 17) 14.47 (1.25)	–3.69 (–7.11 to –0.27)	**0.034**
Treatment period 1and 2 combined	(*n* = 35) 12.14 (0.91)	(*n* = 35) 12.86 (0.91)	–0.71 (–1.92 to 0.49)	0.244
	Mixed model *p*-value for period effect = 0.069			
FTMTRS items 5/6[b]				
Treatment period 1	(*n* = 17) 6.12 (0.52)	(*n* = 18) 5.17 (0.51)	0.95 (–0.47 to 2.38)	0.191
Treatment period 2	(*n* = 18) 4.44 (0.51)	(*n* = 17) 6.76 (0.52)	–2.32 (–3.75 to –0.89)	**0.001**
Treatment period 1and 2 combined	(*n* = 35) 5.26 (0.39)	(*n* = 35) 5.94 (0.39)	–0.69 (–1.21 to –0.16)	**0.010**
	Mixed model *p*-value for period effect = **0.016**			
FTMTRS items 11–14[c]				
Treatment period 1	(*n* = 17) 7.47 (0.93)	(*n* = 18) 6.17 (0.91)	1.30 (–1.25 to 3.85)	0.316
Treatment period 2	(*n* = 18) 6.33 (0.91)	(*n* = 17) 7.71 (0.93)	–1.37 (–3.92 to 1.18)	0.292
Treatment period 1 and 2 combined	(*n* = 35) 6.89 (0.66)	(*n* = 35) 6.91 (0.66)	–0.03 (–0.86 to –0.81)	0.947
	Mixed model *p*-value for period effect = 0.276			

[a]Sum FTMTRS score represent the improvement of the sum of scores for items 5/6 + 11–14, for the non-dominant arm. Treatment period 1: 0–3 months post-surgery; treatment period 2: 4–6 months post-surgery. * $p < 0.05$ considered statistically significant (in bold).
[b]Items 5/6: sum of arm tremor at rest+postural+kinetic. In this study, the postural tremor score was the worst score obtained from examining the patient both with arms outstretched forward, in the wing-beating position, and when holding a water-filled plastic cup. The kinetic tremor score was the worst score from examining the finger-to-nose and Barany's tests, plus drinking from a water-filled plastic cup.
[c]Items 11 to 14: 11, Drawing large spiral; 12, Drawing small spiral; 13, Drawing continuous lines; 14, Pouring from one plastic cup to the other.
CI = confidence interval; FTMTRS = Fahn-Tolosa-Marin Tremor rating scale; PSA = posterior subthalamic area; SE = standard error of the mean; VIM = ventral intermediate nucleus.

by image fusion, some patients were stimulated slightly below the ICL during the VIM period, indicating a coverage of subthalamic fibre pathways by the VTA. However, as all patients acted as their own control, a significantly better improvement when stimulating the ventral versus the dorsal contact pair of the lead strongly supports the notion that it is easier to achieve good tremor suppression within PSA than more dorsally in the VIM area. Moreover, the predefined coverage of two target sites with a single trajectory may lead to a compromise for optimal targeting of VIM or PSA depending on the entry point, which needs to respect the cortical gyration and vascularization along the electrode path. We observed a slightly larger variance in the *Y*- and *Z*-coordinates of active contacts in the VIM versus PSA period, which could bias results in favour of PSA, but these differences in the variance were not statistically significant. We cannot, however, exclude the possibility that a comparative trial targeting VIM and PSA separately, using two electrodes on each side or two groups in a parallel design, could yield different results, but such trials would need much larger power and control adequately for inter-individual variability.

Interestingly, for the improvement of item 5/6 there was a significant period effect, as PSA-DBS yielded significantly larger arm tremor suppression than VIM-DBS in period 2, but not in period 1. Our interpretation of this period effect is that it could mainly be explained

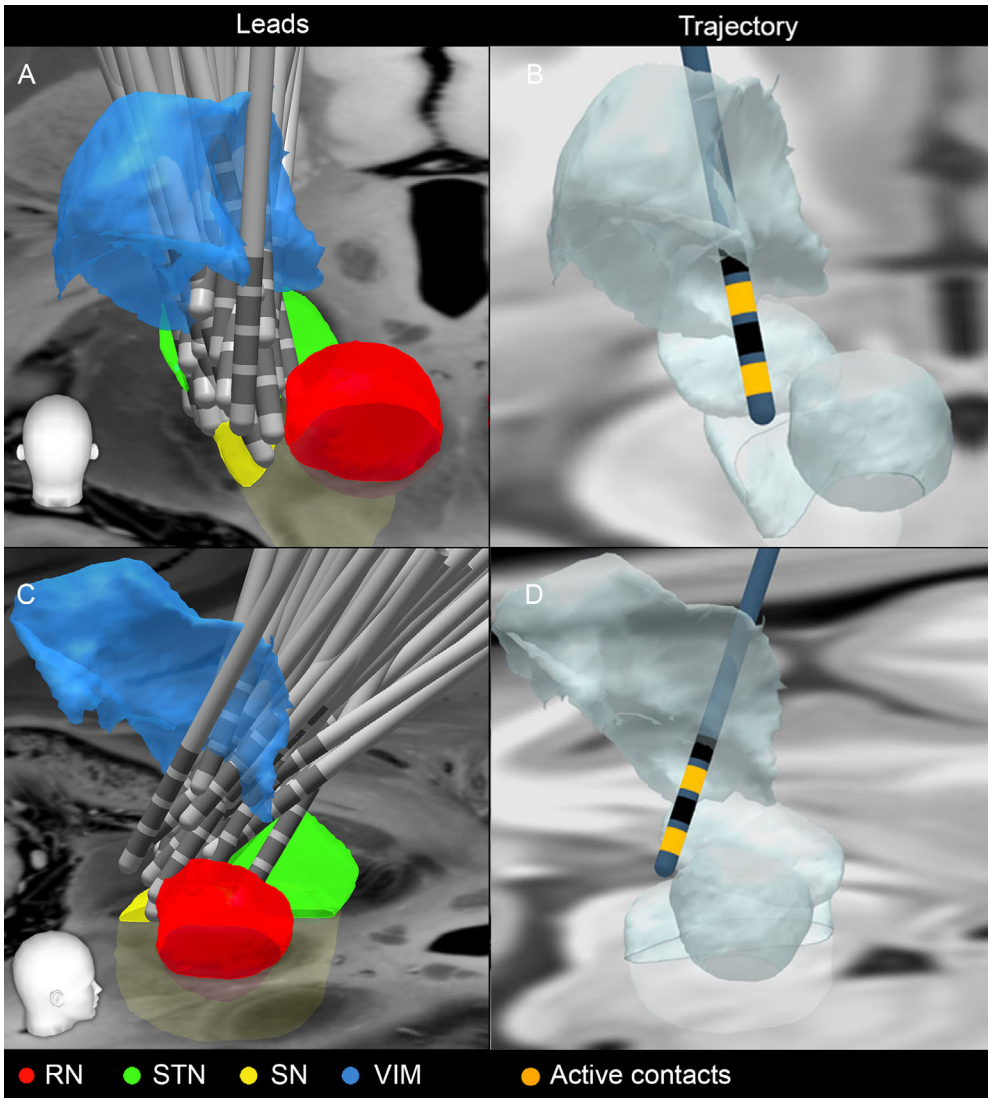

FIGURE 3: Lead location of individual patients, and an example of an 'ideal' trajectory. Left hemisphere is shown anatomically, but all leads are shown, with those in the right hemisphere projected onto the left hemisphere. Upper panels: coronal plane, lower panels: sagittal plane. Panels A and C show lead locations. Panels B and D show an example of a study patient (male 54 years, diagnosis essential tremor) with an "ideal" left trajectory, with coordinates of the active contact used in the VIM-period: *X* = 12.61 mm (lateral to the ICL-line (48.5% of the ICL-length), Y = −5.36 mm (posterior) to MCP (;29.4% anterior to PC), *Z* = 0.80 mm above the AC-PC plane, and in the PSA-period: *X* = 11.55, *Y* = −7.25, *Z* = −2.57 (ICL-length 26.0 mm). His tremor improved very well with both targets, but 2 points better in the PSA versus VIM. AC, anterior commissure; ICL, intercommissural line; MCP, mid-commissural point; PC, posterior commissure; PSA, posterior subthalamic area; RN, red nucleus; SN, substantia nigra; STN, subthalamic nucleus; VIM, ventral intermediate nucleus.

by a residual surgical lesion effect, the benefit of which may have obscured a possible difference in the effect of the stimulation alone in period 1. It is plausible that this effect may have become larger in our patients due to the double targeting. However, at the end of period 2 (6 months post-surgery), the tremor suppression observed must be regarded as almost exclusively due to stimulation – and was then observed to be significantly better in the PSA.

Increasing evidence for the mechanisms of DBS indicates that the effect of this high-frequency, low-current stimulation with relatively short pulse widths is exerted mainly on the large, myelinated axons passing through the targets.[31,32] Thus, focus has shifted from targeting nuclei to targeting fibre tracts. In DBS for tremor, direct targeting of fibre tracts was pioneered by Coenen et al, through his first case report on direct targeting of the DRT tract, and

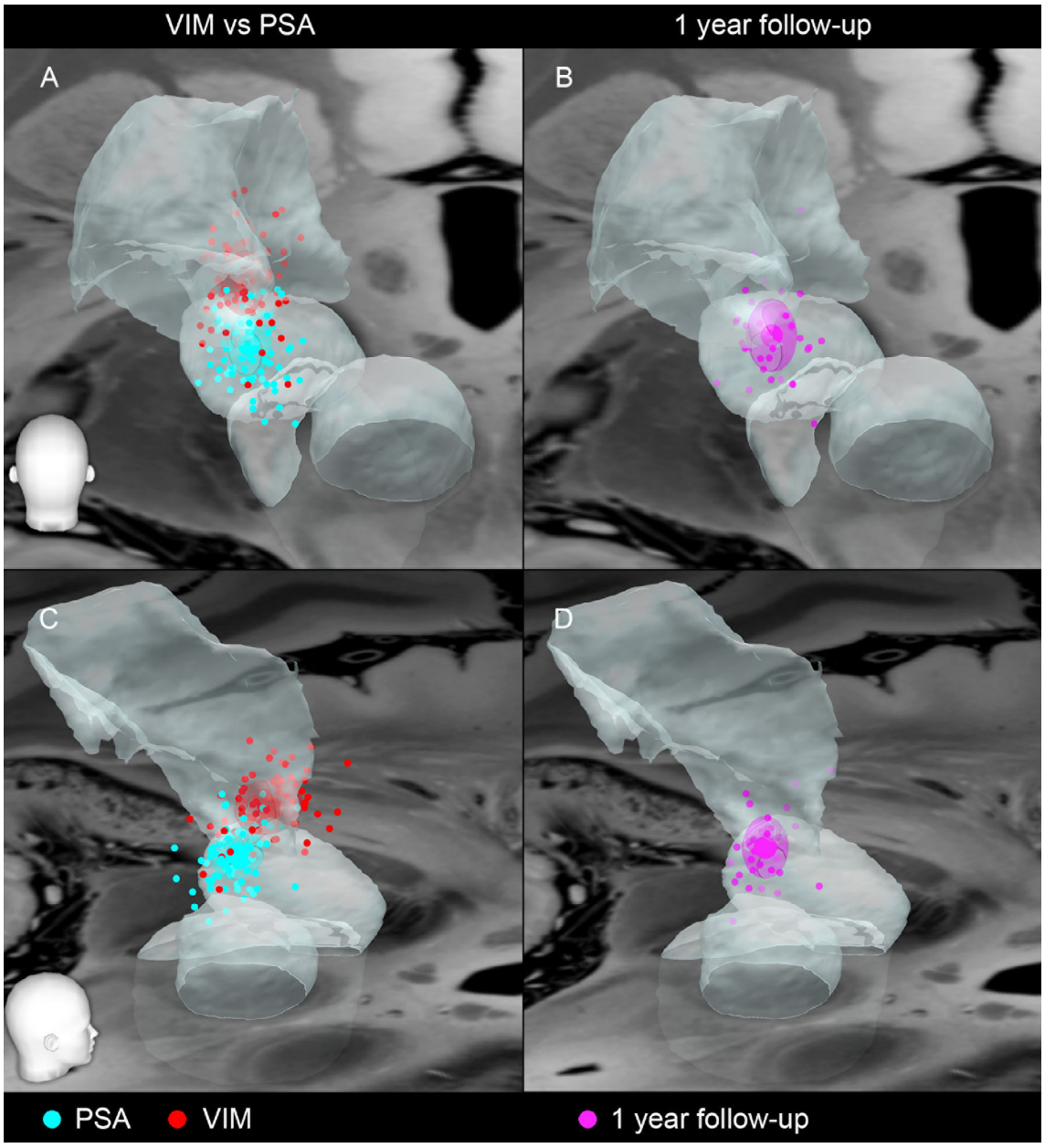

FIGURE 4: Active contact location of individual patients in each randomized period and at one-year follow-up. Left hemisphere is shown anatomically, but all contacts are shown, with those in the right hemisphere projected onto the left hemisphere. Upper panels: coronal plane, lower panels: sagittal plane. Panels A and C show the location of each patient's active contact used in the VIM treatment period (red dots) and PSA period (light blue dots); panels B and D show the active contact used at the one-year follow-up (pink dots). The mean (standard deviation) AC-PC-based coordinates for the active contacts were in the left/right hemispheres for the VIM period: *X* (mm lateral to the ICL-line) = 13.29(1.45)/−13.10 (1.32), *Y* (mm anterior–posterior relative to MCP) = −4.74(1.83)/−4.85 (1.51), *Z* (mm superior/inferior to the ICL-plane) = −0.25(1.67)/−0.24(1.44); for the PSA period: *X* = 12.25(1.37)/−11.90(1.13), *Y* = −6.58(1.52)/−6.88(1.20), *Z* = −3.02 (1.40)/−3.04(1.32). Coordinates in the MNI-space were in the left/right hemispheres for the VIM-period: *X* = 12.47 (1.21)/12.65 (1.11), *Y* = −15.28 (2.28)/−16.43(1.84), *Z* = −3.22 (1.71)/−3.15 (1.84); for the PSA-period: X = −12.05 (1.20)/11.95 (0.93), Y = −17.64 (1.74)/−18.54 (1.35), *Z* = −5.61 (1.61)/−5.94 (1.53). AC, anterior commissure; MCP, mid-commissural point; MNI, Montreal Neurological Institute; PC, posterior commissure; PSA, posterior subthalamic area; VIM, ventral intermediate nucleus.

developed further as recently reported in an observational series, although without reporting longer-term outcomes.[33–35] Furthermore, a recent important study on the functional and structural connectivity of the network involved in ET, and of the sweet spot for the suppression of ET by DBS, confirms the essential role of the fibres of the cerebello-thalamic pathway inferior to the VIM, as it traverses the ZI/PSA after passing

TABLE 6. Serious Adverse Events by Intervention and Period

	VIM		PSA		Total	
	Period 1 *n* = 23	Period 2 *n* = 22	Period 1 *n* = 22	Period 2 *n* = 23	Period 1 *n* = 45	Period 2 *n* = 45
Death	0	1 (4.5)	0	0	0	1 (2.2)
Hospitalization – total:	2 (8.7)	1 (4.5)	3 (13.6)	1 (4.3)	5 (11.1)	2 (4.4)
Increased peri-lead oedema	1	0	2	0	3	0
Increased gait ataxia in MS patient	1	0	0	0	1	0
Increased neuropathic pain in MS patient	0	0	1	0	1	0
Transient reduction of arm function	0	1	0	0	0	1
Fall without injury in PD patient	0	0	0	1	0	1
Required intervention – total:	2 (8.7)	2 (9.1)	0 (0.0)	1 (4.3)	2 (4.4)	3 (6.7)
Postoperative pneumonia, iv AB	1	0	0	0	1	0
Scalp wound revision, oral AB	1	0	0	0	1	0
Stimulator-site infection, device explanted	0	0	0	1	0	1
Arm dyskinesias in MS patient, active contact changed	0	1	0	0	0	1
Fall with shoulder injury, physiotherapy required	0	1	0	0	0	1
Total SAE	4 (17.4)	4 (18.2)	3 (13.6)	2 (8.7)	7 (15.6)	6 (13.3)
No SAE	19 (82.6)	18 (81.8)	19 (86.4)	21 (91.3)	38 (84.4)	39 (86.7)

Numbers are *n* (%). Treatment period 1: 0 to 3 months post-surgery; treatment period 2: 4 to 6 months post-surgery.
AB = antibiotics; MS = multiple sclerosis; PD = Parkinson's disease; PSA, posterior subthalamic area; SAE = serious adverse events; VIM = ventral intermediate nucleus.

the RN.[36] This indeed corroborates our findings that stimulation of the PSA is superior to the VIM nucleus proper. It is possible that the superiority of PSA may be partly driven by a better suppression of cerebellar tremors, which are known to respond poorly to VIM-DBS.

In conclusion, we have shown that PSA-DBS resulted in significantly better tremor suppression than VIM-DBS when studied in a randomized, crossover design covering the first six months post-surgery, with each patient acting as their own control. The superiority of PSA-DBS was convincing in the second study period (4–6 months post-surgery), when the surgical lesion effect was no longer present and the observed tremor suppression was purely an effect of stimulation. Good tremor suppression was sustained at the one-year blinded follow-up, with PSA-DBS in >90% of patients. Our findings may have important implications for the future of tremor surgery, because it may foster the application of modern neuroimaging methods including tractography to further refine the definition of the PSA target, which could now be considered clinically preferable according to our data. The long-term adverse effects of PSA-DBS, however, have not yet been fully elucidated because few long-term studies have been published for this target. Future long-term studies of VIM- and PSA-DBS should explore further the potential advantage of using segmented DBS leads to shape and direct the current field more accurately[37] and to apply lower pulse widths if gait ataxia (or another limiting adverse event) appears.[38]

TABLE 7. Adverse Events by Intervention

Type adverse event	VIM ($n = 45$)	PSA ($n = 45$)
No adverse event	7 (15.6)	17 (37.8)
Gait/balance	**23 (51.1)**	**17 (37.8)**
Subjective dysequilibrium	12 (26.7)	6 (13.3)
Impaired tandem gait, normal gait	1	1
Moderate gait ataxia or fall	9 (20.0)	10 (22.2)
Severe gait ataxia	1	0
Speech/voice	**24 (53.3)**	**10 (22.2)**
Subjective dysarthria	3 (6.7)	5 (11.1)
Objective dysarthria	17 (37.8)	5 (11.1)
Hypophonia/hoarse voice	4 (8.9)	0
Motor, other	**5 (11.1)**	**1 (2.2)**
Dysphagia	2 (4.4)	0
Reduced dexterity (c.lat.)	1	0
Dyskinesias	1	0
Peripheral paresis	1	1
Somatosensory disturbances (c.lat.)	**7 (15.5)**	**4 (8.9)**
Paraesthesias	4 (8.9)	2 (4.4)
Numbness	3 (6.7)	2 (4.4)
Dysgeusia	2 (4.4)	1 (2.2)
Fracture	1	0
Fatigue	1	1
Dizziness	1	1
Headache	0	1
Improved mood/reduced anxiety	0	1

Numbers are *n* (%).
$n = 45$ because the two complete drop-outs from each intervention both occurred late in the second treatment period, after the mid-period control at which adverse events could be registered.
PSA = posterior subthalamic area; VIM = ventral intermediate nucleus.

Acknowledgements

We thank all patients that contributed to this study. We also thank doctors, nurses and other health-care workers at Oslo University Hospital that assisted in the care of these patients.

We are very grateful for the grant from the South-Eastern Regional Health Authorities awarded to Inger Marie Skogseid. She was also supported by private donations (from two patients outside the study) to the Department of Neurology, Research section. Editorial assistance was provided by a native English speaker (Deborah Nock, Medical WriteAway, Norwich, UK).

Author Contributions

IMS, AEK, ED and JV contributed to the conception and design of the study; NK, IMS, AEK, MMR, JV AHP and JR, contributed to the acquisition and/or analysis of data; NK, IMS, MMR, JV and JR contributed to drafting the text

or preparing the figures. All authors contributed with review and critique and accepted the final version of the paper.

Potential Conflicts of Interest

Medtronic® and Boston Scientific® are both manufacturers of the DBS devices that have been used in this study. NK reports travel support from Medtronic to participate in a DBS course arranged by them. AEK reports travel support from Boston Scientific to attend a scientific meeting about DBS arranged by them. MMR reports consulting fees and honoraria for lectures from Boston Scientific and Medtronic, and from Boston Scientific also grants, board participation, and travel support for attending meetings, not directly related to the submitted work. JV reports grants and personal fees from Boston Scientific, grants and personal fees from Medtronic, and personal fees from Abbott St. Jude and Newronika (both manufacturers of DBS devices), not directly related to the submitted work. ED reports honoraria for lectures from AbbVie, Lobsor and Nordic Infucare (all manufacturers of dopaminergic medication pumps). IMS reports honoraria for lectures at scientific meetings and courses about DBS from Boston Scientific, arranged by them. None of the activities mentioned above were directly related to the submitted work. JR and AHP report no conflicts of interest.

References

1. Deuschl G, Bain P, Brin M. Consensus statement of the Movement Disorder Society on tremor. Ad Hoc Scientific Committee. Mov Disord 1998;13:2–23.
2. Bhatia KP, Bain P, Bajaj N, et al. Consensus statement on the classification of tremors. From the task force on tremor of the International Parkinson and Movement Disorder Society. Mov Disord 2018;33:75–87.
3. Louis ED, Ferreira JJ. How common is the most common adult movement disorder? Update on the worldwide prevalence of essential tremor. Mov Disord 2010;25:534–541.
4. Dirkx MF, Zach H, Bloem BR, et al. The nature of postural tremor in Parkinson disease. Neurology 2018;90:e1095–e1103. https://doi.org/10.1212/WNL.0000000000005215.
5. Erro R, Rubio-Agusti I, Saifee TA, et al. Rest and other types of tremor in adult-onset primary dystonia. J Neurol Neurosurg Psychiatry 2014;85:965–968. https://doi.org/10.1136/jnnp-2013-305876.
6. Schneider SA, Deuschl G. The treatment of tremor. Neurotherapeutics 2014;11:128–138. https://doi.org/10.1007/s13311-013-0230-5.
7. Fasano A, Bove F, Lang AE. The treatment of dystonic tremor: a systematic review. J Neurol Neurosurg Psychiatry 2014;85:759–769. https://doi.org/10.1136/jnnp-2013-305532.
8. Mittal SO, Lenka A, Jankovic J. Botulinum toxin for the treatment of tremor. Parkinsonism Relat Disord 2019;63:31–41. https://doi.org/10.1016/j.parkreldis.2019.01.023.
9. Benabid AL, Pollak P, Gervason C, et al. Long-term suppression of tremor by chronic stimulation of the ventral intermediate thalamic nucleus. Lancet 1991;337:403–406.
10. Schuurman PR, Bosch DA, Bossuyt PMM, et al. A comparison of continuous thalamic stimulation and thalamotomy for suppression of severe tremor. N Engl J Med 2000;342:461–468.
11. Milosevic L, Kalia SK, Hodaie M, et al. Physiological mechanisms of thalamic ventral intermediate nucleus stimulation for tremor suppression. Brain 2018;141:2142–2155. https://doi.org/10.1093/brain/awy139.
12. Dallapiazza RF, Lee DJ, De Vloo P, et al. Outcomes from stereotactic surgery for essential tremor. J Neurol Neurosurg Psychiatry 2019;90:474–482.
13. Fasano A, Helmich RC. Tremor habituation to deep brain stimulation: underlying mechanisms and solutions. Mov Disord 2019;34:1761–1773.
14. Murata J, Kitagawa M, Uesugi H, et al. Electrical stimulation of the posterior subthalamic area for the treatment of intractable proximal tremor. J Neurosurg 2003;99:708–715.
15. Plaha P, Khan S, Gill SS. Bilateral stimulation of the caudal zona incerta nucleus for tremor control. J Neurol Neurosurg Psychiatry 2008;79:504–513.
16. Blomstedt P, Sandvik U, Tisch S. Deep brain stimulation in the posterior subthalamic area in the treatment of essential tremor. Mov Disord 2010;25:1350–1356.
17. Herzog J, Hamel W, Wenzelburger R, et al. Kinematic analysis of thalamic versus subthalamic neurostimulation in postural and intention tremor. Brain 2007;130:1608–1625. https://doi.org/10.1093/brain/awm077.
18. Barbe MT, Reker P, Hamacher S, et al. DBS of the PSA and the VIM in essential tremor. Neurology 2018;91:e543–e550. https://doi.org/10.1212/WNL.0000000000005956.
19. Reich MM, Brumberg J, Pozzi NG, et al. Progressive gait ataxia following deep brain stimulation for essential tremor: adverse effect or lack of efficacy? Brain 2016;139:2948–2956. https://doi.org/10.1093/brain/aww223.
20. Bjerknes S, Toft M, Konglund AE, et al. Multiple Micorelectrode recording in STN-DBS surgery for Parkinson's disease: a randomized study. Mov Disord Clin Pract 2018;5:296–305. https://doi.org/10.1002/mdc3.12621.
21. Fahn S, Tolosa E, Marin C. Clinical rating scale for tremor. In: Jancovic J, Tolosa E, eds. *Parkinson's disease and movement disorders*. Baltimore, MD: Williams and Wilkins, 1988:225-234.
22. Troester AI, Pahwa R, Fields J, et al. Quality of life in essential tremor questionnaire: development and initial validation. Parkinsonism Relat Disord 2005;11:367–373.
23. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. Acta Psychiatr Scand 1983;67:361–370.
24. Blomstedt P, Hariz G-M, Hariz MI, Koskinen OD. Thalamic deep brain stimulation in the treatment of essential tremor: a long-term follow-up. Br J Neurosurg 2007;21:504–509.
25. Pouratian N, Zheng Z, Bari AA, et al. Multi-institutional evaluation of deep brain stimulation targeting using probabilistic connectivity-based thalamic segmentation. J Neurosurg 2011;115:995–1004.
26. Reich MM, Horn A, Lange F, et al. Probabilistic mapping of the antidystonic effect of pallidal neurostimulation: a multicentre imaging study. Brain 2019;142:1386–1398. https://doi.org/10.1093/brain/awz046.
27. Papavassiliou E, Rau G, Heath S, et al. Thalamic deep brain stimulation for essential tremor: relation of lead location to outcome. Neurosurgery 2008;62:884–894. https://doi.org/10.1227/01.neu.0000316290.83360.7e.
28. Cury RG, Fraix V, Castrioto A, et al. Thalamic deep brain stimulation for tremor in Parkinson disease, essential tremor, and dystonia. Neurology 2017;89:1416–1423. https://doi.org/10.1212/WNL.0000000000004295.
29. Tsuboi T, Jabarkheel Z, Zeilman PR, et al. Longitudinal follow-up with VIM thalamic deep brain stimulation for dystonic or essential

tremor. Neurology 2020;94:e1073–e1084. https://doi.org/10.1212/WNL.0000000000008875.

30. Kuebler D, Kroneberg D, Al-Fatly B, et al. Determining an efficient deep brain stimulation target in essential tremor – cohort study and review of the literature. Parkinsonism Relat Disord 2021;89:54–62. https://doi.org/10.1016/j.parkreldis.2021.06.019.

31. Montgomery EB Jr, Gale JT. Mechanisms of action of deep brain stimulation (DBS). Neurosci Biobehav Rev 2008;32:388–407. https://doi.org/10.1016/j.neubiorev.2007.06.003.

32. Jakobs M, Fomenko A, Lozano AM, Kiening KL. Cellular, molecular, and clinical mechanisms of action of deep brain stimulation-a systematic review on established indications and outlook on future developments. EMBO Mol Med 2019;11:e9575. https://doi.org/10.15252/emmm.201809575.

33. Coenen VA, Maedler B, Schiffbauer H, et al. Individual fiber anatomy of the subthalamic region revealed with diffusion tensor imaging: a concept to identify the deep brain stimulation target for tremor suppression. Neurosurgery 2010;68:1069–1107.

34. Coenen VA, Allert N, Maedler B. A role of DTI fiber tracking in deep brain stimulation surgery: DBS of the dentato-rubro-thalamic tract (drt) for the treatment of therapy-refractory tremor. Acta Neurochir 2011;153:1579–1585.

35. Coenen VA, Sajonz B, Prokop T, et al. The dentato-rubro-thalamic tract as the potential common deep brain stimulation target for tremor of various origin: an observational case series. Acta Neurochir 2020;162:105366:1053–1066. https://doi.org/10.1007/s00701-020-04248-2.

36. Al-Fatly B, Ewert S, Kübler D, et al. Connectivity profile of thalamic deep brain stimulation to effectively treat essential tremor. Brain 2019;142:3086–3098. https://doi.org/10.1093/brain/awz236.

37. Bruno S, Nikolov P, Hartmann CJ, et al. Directional deep brain stimulation of the thalamic ventral intermediate area for essential tremor increases therapeutic window. Neuromodulation 2021;24:343–352. https://doi.org/10.1111/ner.13234.

38. Kroneberg D, Ewert S, Meyer AC, Kühn AA. Shorter pulse width reduces gait disturbances following deep brain stimulation for essential tremor. J Neurol Neurosurg Psychiatry 2019;90:1046–1050. https://doi.org/10.1136/jnnp-2018-319427.