Targeting the posterior subthalamic area for essential tremor: proposal for MRI-based anatomical landmarks

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OBJECTIVE Deep brain stimulation (DBS) of the posterior subthalamic area (PSA) is an alternative to thalamic DBS for the treatment of essential tremor (ET). The dentato-rubro-thalamic tract (DRTT) has recently been proposed as the anatomical substrate underlying effective stimulation. For clinical purposes, depiction of the DRTT mainly depends on diffusion tensor imaging (DTI)-based tractography, which has some drawbacks. The objective of this study was to present an accurate targeting strategy for DBS of the PSA based on anatomical landmarks visible on MRI and to evaluate clinical effectiveness.

METHODS The authors performed a retrospective cohort study of a prospective series of 11 ET patients undergoing bilateral DBS of the PSA. The subthalamic nucleus and red nucleus served as anatomical landmarks to define the target point within the adjacent PSA on 3-T T2-weighted MRI. Stimulating contact (SC) positions with reference to the midcommissural point were analyzed and projected onto the stereotactic atlas of Morel. Postoperative outcome assessment after 6 and 12 months was based on change in Tremor Rating Scale (TRS) scores.

RESULTS Actual target position corresponded to the intended target based on anatomical landmarks depicted on MRI. The total TRS score was reduced (improved) from 47.2 ± 15.7 to 21.3 ± 10.7 ($p < 0.001$). No severe complication occurred. The mean SC position projected onto the PSA at the margin of the cerebellothalamic fascicle and the zona incerta.

CONCLUSIONS Targeting of the PSA based on anatomical landmarks representable on MRI is reliable and leads to accurate lead placement as well as good long-term clinical outcome.

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KEYWORDS DBS; essential tremor; posterior subthalamic area; functional neurosurgery; targeting

DEEP brain stimulation (DBS) is an effective treatment for essential tremor (ET) in patients who do not tolerate or respond to medication.²⁰ The classical target for DBS treatment of ET is the ventrolateral thalamus (or ventral intermediate nucleus [Vim]) according to Hassler¹⁵.⁴ Thalamic DBS has been demonstrated to improve tremor severity up to 48%–57%.^{3,14,19,29} However, the optimal site is still a matter of debate, and other targets have been suggested for both lesioning and DBS. The posterior subthalamic area (PSA) includes the zona incerta (ZI) and the prelemniscal radiation (RapL), which itself consists of the cerebellothalamic fascicle (fct) (or dentato-rubro-thalamic tract [DRTT]) and pallidothalamic fibers, and was targeted for lesioning as early as 1960 by Wertheimer et al.³⁹ Since then, several studies of DBS

of this region have been published, demonstrating very good results, with up to 80% symptom reduction.^{2,17,26,32,33} However, analysis of the active or stimulating contact (SC) position revealed that stimulation sites within the PSA differed considerably between different studies.¹² More recently, the DRTT has been suggested as the anatomical substrate for stimulation-induced alleviation of tremor on the basis of deterministic and probabilistic diffusion tensor imaging (DTI) studies.^{8,9,37} Anatomical data confirm the close anatomical relationship between the DRTT and the PSA and ZI.^{8,9} However, DTI has some technical limitations with an impact on accuracy of the depicted fiber tracts: due to its low signal-to-noise ratio, relatively large voxel sizes (2–3 mm) have to be selected in clinical practice, which has implications for the depiction of small fiber

ABBREVIATIONS AP = anteroposterior; DBS = deep brain stimulation; DRTT = dentato-rubro-thalamic tract; DTI = diffusion tensor imaging; ET = essential tremor; fct = cerebellothalamic fascicle; LAT = lateral; MER = microelectrode recording; MCP = midcommissural point; PSA = posterior subthalamic area; RapL = prelemniscal radiation; ROI = region of interest; SC = stimulating contact; STN = subthalamic nucleus; TRS = Tremor Rating Scale; VERT = vertical; Vim = ventral intermediate nucleus; ZI = zona incerta.

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tracts such as the DRTT.¹ Additionally, the tensor calculation fails to display crossing fibers within the same voxel, which is a known feature of the DRTT.²⁵ Thus, a targeting strategy based on DTI-based tractography might lead to inaccurate results.

At this stage, no systematic approach based on MRI-depictable landmarks to target the PSA has been proposed. Motivated by the excellent results of PSA DBS reported by different groups and the inhomogeneity of targeting approaches across these studies, our objective in the current work is to present a systematic and reproducible targeting strategy for DBS of the PSA based on anatomical landmarks. We were interested in the reliability of the targeting method and its long-term clinical effectiveness in patients treated with bilateral DBS. Furthermore, we analyzed the anatomical position of the stimulation site as well as its relation to DTI tractography results to evaluate the proposed current concept of the DRTT as the underlying neural structure responsible for the tremor-suppressive effect of DBS in patients with ET.

Methods

Patients

This is a retrospective, single-center study of a series of 11 consecutive ET patients (7 male, 4 female; mean age 67 ± 14 years) who underwent bilateral DBS of the PSA, with the DBS units being implanted between June 2014 and December 2016. Eligibility criteria based on ET diagnosis were assessed by specialized movement disorder neurologists according to the accepted guidelines.¹⁰ Patients were discussed by a multidisciplinary team and deemed suitable candidates for surgery if 1) they had severe, functionally disabling tremor impairing activities of daily living and quality of life, 2) they did not tolerate or respond to medical treatment (i.e., propranolol or primidone), and 3) they had no contraindications for surgery. No patients were excluded from the final analysis. The study was approved by the local ethics review board.

Target Planning

Preoperative imaging was performed with a 3-T MRI system (MAGNETOM Trio Tim, Siemens). A standard gadolinium-enhanced T1-weighted protocol (160 sagittal slices, 1-mm thickness) was followed by T2-weighted sequences (FOV 220 mm, acquisition matrix 128 × 128, TR 2000 msec, and multiple TE values ranging from 12 msec to 96 msec in steps of 12 msec) and DTI (number of gradient directions 12, 2.2-mm slice thickness; 55 slices, TR 10,100 msec, TE 88 msec, field of view 280 mm, matrix 256 × 256, b value 1305 sec/mm²). Target planning was based on iPlan NET software 3.0 (Brainlab AG).

The target was defined visually on T2-weighted axial slices based on anatomical landmarks (Fig. 1A and B): a horizontal line was constructed through the equator of the red nucleus at the level of its maximum diameter. A second line was drawn from the most anteromedial to the most posterolateral point of the subthalamic nucleus (STN), representing the STN axis. A third line, perpendicular to the axis of the STN, was constructed to cross the first line at the lateral border of the red nucleus. The

target point was selected on that third perpendicular line halfway between the lateral border of the red nucleus and the medial border of the STN. The entry point was selected near the coronal suture. Trajectories were planned to avoid crossing sulci, blood vessels, and the ventricles.

A Leksell G frame (Elekta Instruments) was placed, and a high-resolution, stereotactic CT scan was performed and co-registered with the preoperative MRI.

Electrophysiology Protocol and Intraoperative Clinical Testing

Patients were operated on under local anesthesia. Intraoperative microelectrode recording (MER) (FHC microTargeting electrodes) and clinical testing were performed as described recently.²⁷ Recording was typically performed on 3 parallel trajectories (central, anterolateral, and posteromedial). From 10 to 5 mm above the target, electrophysiological activity was recorded in 1-mm steps, and from 5 mm above the target it was recorded in 0.5-mm steps. Specialized movement disorder neurologists analyzed the electrophysiological pattern. The trajectory *without* electrophysiological STN activity (typically marked by increased baseline signal amplitude and sustained irregular neuronal activity with increased spike frequency, as well as bursting cells) that yielded the best intraoperative clinical testing results was used for implantation of the permanent DBS lead. The DBS lead model Activa 3389 (Medtronic) was implanted in 7 patients, and the directional DBS lead model Boston Vercise (Boston Scientific) was implanted in 5 patients.

Fiber Tracking

DTI sequences were automatically corrected for eddy current distortions and head motion. Deterministic fiber tractography was performed using Brainlab software iPlan NET 3.0 by applying 3 different regions of interest (ROIs): the manually segmented dentate nucleus of the ipsilateral cerebellum, a second manually segmented ipsilateral region in the PSA defined on T2-weighted imaging, and a cubic box including the ipsilateral precentral gyrus according to the Yousry criteria.⁴⁰ The minimum fiber length was set at 30 mm, and the fractional anisotropy (FA) value was adjusted to display 1 homogeneous fiber bundle included in both ROIs.

Measurements

A postoperative high-resolution CT scan was performed and fused to the preoperative target plan. The postoperative lead tip and SC position as well as the vector of error were determined as described previously by our group.²⁸ Images were reconstructed according to the anterior commissure–posterior commissure plane. The distance between the center of the SC and the center of the DRTT tractography model was measured in each individual patient (Fig. 1C and D).

Atlas- and MRI-Based Anatomy Analysis

The lateral (LAT), anteroposterior (AP), and vertical (VERT) stereotactic coordinates of each DBS lead tip as well as each SC with reference to the midcommissural

FIG. 1. Targeting strategy for the PSA and determination of the distance between the SC and the center of gravity of the DRTT. The theoretical target point at the center of the PSA is based on the stereotactic atlas of Morel (A). The applied targeting strategy based on 3-T T2-weighted MRI sequences leads to the planned target (B). The distance between the SC and the center of the tractography-based DRTT (1.5 mm in this case) was measured with iPlan 3.0 software (C and D). al = ansa lenticularis; fct = cerebellothalamic fascicle; fl = fasciculus lenticularis; GPi = globus pallidus interna; ic = internal capsule; mcl = midcommissural line; MGN = medial geniculate nucleus; ml = medial lemniscus; mtt = mammillothalamic tract; PAG = periaqueductal gray; pc = posterior commissure; Po = posterior nucleus; RN = red nucleus; SG = supragenicular nucleus; STh = subthalamic nucleus; VPI = ventral posterior inferior nucleus; VPMpc = ventral posterior medial nucleus, parvocellular division; ZI = zona incerta. Panel A modified from Gallay MN, Jeanmonod D, Liu J, Morel A: Human pallidothalamic and cerebellothalamic tracts: anatomical basis for functional stereotactic neurosurgery. *Brain Struct Funct* 212:443–463, 2008, with kind permission of the authors. Copyright the authors. CC BY-NC (<https://creativecommons.org/licenses/by-nc/3.0/>).

point (MCP) were determined as described previously by our group.²⁸ Mean target coordinates, lead tip coordinates, and SC coordinates were projected onto axial and sagittal planes of the Morel stereotactic atlas.¹³

On axial planes, the smallest distance from the center of the SC to the center of gravity of the DTI-based depicted DRTT was measured.

Clinical Assessment

Preoperative “medication-off” and postoperative “stim-

ulation-on, medication-off” tremor severities were assessed “nonblinded” based on the Fahn-Tolosa-Marin Tremor Rating Scale (TRS) by specialized movement disorder neurologists at 6 and 12 months postoperatively.³⁸ Two patients were lost to the 12-month follow-up as they were followed up in another clinic, but their 6-month follow-up data were available and used in our final analysis. The part A and part B subscores were determined separately for each hemibody. At each follow-up, side effects attributable to stimulation were recorded. We determined the difference

TABLE 1. Clinical and demographic characteristics of the study cohort

Patient No.	Age (yrs)*	Stimulus Parameter						% Improvement				SC Location		
		Amplitude (mA)		Pulse Width (μsec)		Frequency (Hz)		TRS A	TRS B	TRS C	TRS Total	Lt	Rt	Side Effects
1	73	1.7	1.8	60	60	130	130	16.7	52	70.6	39.0	ZI	ZI/fct	None
2	53	1.6	2.1	60	60	130	130	66.7	18.2	50	36.3	fct	fct	Paresthesia
3	80	2.3	1.9	60	60	130	130	32	63	62.5	52.6	fct	ZI/fct	Mild dysarthria
4	79	1.6	1.5	60	60	120	120	47.6	70.6	60	58.6	fct	fct	None
5	69	1.6	1.5	60	60	130	130	75	70	84.6	75.6	fct	fct	None
6	73	2.3	2.9	60	60	130	130	100	80	92.3	89.2	ZI	ZI	None
7	71	1.5	4	60	60	119	119	75	16.7	58.3	50.0	ZI	fct	Dysarthria
8	35	2.7	2	60	60	149	149	42.8	0	100	56.3	ZI	ZI	Mild dysarthria
9	72	3.7	2.6	60	60	136	136	23.1	29.4	69.2	39.5	ZI	ZI	None
10	53	2.6	2.3	60	60	185	185	50	54.5	90.9	61.7	ZI	Vim	None
11	80	2	3.5	60	60	185	185	58.8	58.6	43.7	54.8	fct	Vim	Mild dysarthria

* Age at surgery.

between each corresponding pre- and postoperative TRS subscore (part A, part B, part C, and total).

We determined the difference in the mean stereotactic SC position between the more effective SCs (defined as percentage improvement of part A and part B TRS subscores for the corresponding contralateral hemibody greater than 60%) and less effective SCs (defined as percentage improvement of part A and part B TRS subscores for the corresponding contralateral hemibody less than 30%).

Outcome Measures and Statistical Analysis

The primary outcome was the difference of means between preoperative “medication-off” and postoperative

“medication-off, stimulation-on” TRS total scores. Secondary outcomes were the difference of means between preoperative “medication-off” and postoperative “medication-off, stimulation-on” TRS subscores; the mean target and SC position with reference to the MCP and DRTT; and the difference in the mean stereotactic SC position and distance to DRTT between the most and least effective SCs.

Data were analyzed with descriptive/parametric statistics using Prism software (GraphPad Prism 6). The Shapiro-Wilk normality test was used to test for normal distribution of data sets. Student’s unpaired t-test was applied to compare the mean coordinates of independent groups. One-way ANOVA was applied to compare pre- and postoperative tremor subscores. Data are presented as mean $\pm$ standard deviation or 95% confidence interval. Correlation analysis was tested by Spearman’s R and linear regression analysis. A p value < 0.05 was considered statistically significant.

Results

Clinical Outcome Assessment

Table 1 summarizes the stimulation parameters as well as the percentage improvement in TRS subscores for each patient. The mean preoperative global TRS score was 47.2 ± 15.7 . The mean postoperative TRS score was 21.3 ± 10.7 , demonstrating a significant reduction. The mean percentage improvement was 55.1% (95% CI 30.9%–59.3%). Figure 2 shows the mean pre- and postoperative TRS subscores for the study cohort. The most common stimulation-induced side effects were dysarthria (36%) and paresthesia (9%). No postoperative hemorrhage, infection, granuloma, or DBS device malfunction occurred within the 12-month follow-up time in our series of patients.

Target, Lead Tip, and SC Position

The mean preoperative target coordinates were LAT 10.57 ± 0.81 , AP -5.20 ± 0.71 , and VERT -3.17 ± 0.53

FIG. 2. Box and whiskers plot showing the pre- and postoperative total scores and subscores from the Fahn-Tolosa-Marin Tremor Rating Scale (TRS). Part A scores improved from 14.3 ± 5.2 to 7 ± 4.7 , part B scores improved from 19 ± 7.4 to 9.2 ± 4.6 , and part C scores improved from 14.8 ± 4.9 to 4.8 ± 3.5 postoperatively. There was a statistically significant reduction of the total TRS and the 3 TRS subscores ($p < 0.001$; 2-way repeated measures ANOVA). The boxes indicate IQRs, the horizontal lines within the boxes indicate the median values, and the whiskers indicate the minimum and maximum values.

FIG. 3. Mean target (A) and SC (B and C) position projected onto the stereotactic atlas of Morel. The mean target point (A) was slightly posterior to the theoretically expected target point according to MRI-based anatomical landmarks and projected onto the center of the PSA at the margin of the cerebellothalamic fascicle (fct) and zona incerta (ZI). The mean SC position was superior with respect to the planned target and projected onto the PSA at the margin of the fct and ZI on both axial (B) and sagittal (C) images. ft = fasciculus thalamicus; R = reticular thalamic nucleus; sPf = supraparafascicular nucleus; VApC = ventral anterior nucleus, parvocellular division; VLPv = ventral lateral posterior nucleus, ventral division; VPLp = ventral posterior lateral nucleus, posterior division; VPM = ventral posterior medial nucleus. Adapted from Gallay MN, Jeanmonod D, Liu J, Morel A: Human pallidothalamic and cerebellothalamic tracts: anatomical basis for functional stereotactic neurosurgery. *Brain Struct Funct* 212:443–463, 2008, with kind permission of the authors. Copyright the authors. CC BY-NC (<https://creativecommons.org/licenses/by-nc/3.0/>).

mm. Projected onto the stereotactic atlas of Morel, the mean target position showed a good correspondence with the intended target based on MRI anatomical landmarks (Fig. 3A).

The mean vector of error between the intended target and actual lead tip position was 1.01 ± 1.10 mm. The mean SC coordinates were LAT 10.92 ± 1.50 , AP -3.92 ± 0.97 , and VERT -1.85 ± 1.37 mm. The mean SC position projected onto the anterior aspect of the fct at the margin of the ZI (Fig. 3B and C).

More and Less Effective SC Positions

The mean stereotactic coordinates for the more effective SC (leading to more than 60% TRS part A and B improvement on the contralateral side) were LAT 10.54 ± 0.71 , AP -4.32 ± 0.64 , and VERT -2.14 ± 1.50 mm. The mean stereotactic coordinates for the less effective SC (leading to less than 30% TRS part A and B improvement on the contralateral side) were LAT 10.08 ± 1.70 , AP -4.46 ± 0.72 , and VERT -2.32 ± 1.92 mm. There was no statistically significant difference between the most and least efficient SC LAT, AP, and VERT coordinates, and both projected onto the atlas-based border of the fct and ZI (data not shown).

DRTT Tractography Results

The DRTT could not be tracked in an anatomically plausible way in 4 patients (4 hemispheres, 36%). The mean distance of the SC to the center of the DRTT tractography model was 1.29 ± 1.22 mm. The most and least efficient SC showed no difference between their distance to the tracked DRTT (1.84 ± 1.24 vs 0.92 ± 1.21 mm, $p = 0.22$).

Discussion

Our targeting approach to the PSA is based on anatom-

ical landmarks in combination with MER showing a typical pattern of missing spiking activity to confirm targeting outside the STN and red nucleus. The results show that application of this technique leads to precise and accurate positioning of the DBS lead within the PSA with a small mean targeting error of 1.01 mm. Projected onto the stereotactic atlas of Morel, the mean SC position lies within the PSA at the margin of the fct and ZI. Furthermore, we can show that bilateral DBS of the PSA is clinically effective, leading to a mean tremor reduction of 55.1% based on the TRS. Despite the well-known technical limitations of DTI-based tractography, our tractography results show that the SC position is in close spatial proximity to the tracked DRTT. We could not demonstrate a difference in position between the SCs that was clinically more or less effective based on stereotactic and atlas data or tractography results.

Clinical Outcome

Our study was motivated by previous work of different groups presenting good outcomes of PSA DBS for tremor.^{5,7,17,26,31–33} Until recently, only 5 studies included ET patients exclusively. Murata et al. presented a series of 8 ET patients who underwent unilateral DBS of the PSA with a mean reduction of 81% on a modified tremor scale.²⁶ Plaha et al. reported on 4 ET patients with bilateral PSA DBS who had a mean reduction of 80.1% based on the TRS.³³ Later, the same group presented results for ET patients in whom DBS was targeted more specifically in the caudal ZI. The authors reported a mean reduction of 75.9% in 6 patients and 73.8% in 15 patients after a mean follow-up of 32 months.^{31,32} Blomstedt and coworkers presented the largest series of patients undergoing unilateral DBS of the PSA for treatment of ET (21 patients). According to their results, a tremor reduction of 60% on the TRS after 1 year of clinical follow-up was achieved.⁵ The mean tremor reduction of 55% in our cohort is in line with previous

FIG. 4. Comparison of the mean SC position. The stereotactic coordinates of the mean SC position of our results and those of other groups are projected onto the stereotactic atlas of Morel. Modified from Gallay MN, Jeanmonod D, Liu J, Morel A: Human pallidothalamic and cerebellothalamic tracts: anatomical basis for functional stereotactic neurosurgery. *Brain Struct Funct* 212:443–463, 2008, with kind permission of the authors. Copyright the authors. CC BY-NC (<https://creativecommons.org/licenses/by-nc/3.0/>).

studies. No relevant complication occurred in our series of patients. However, 36% of the patients showed stimulation-induced mild dysarthria, which prevented application of higher stimulation amplitudes and thus limited further tremor suppression.

Optimal Stimulation Site

The PSA contains the zona incerta (ZI) as well as white matter tracts considered the prelemniscal radiation (RapRL) and fields of Forel (fields H1 and H2). Whereas the RapRL contains fct, the fields of Forel consist of the ansa lenticularis and fasciculus lenticularis, which form pallidothalamic fibers.¹² Thus, the PSA contains different fiber pathways that convey information within cortico-cerebello-thalamic and cortico-striato-pallido-thalamic loops. The anatomical complexity of the PSA will have implications on the neuromodulatory effects of DBS in this area and might determine the relationship between the exact lead location and the therapeutic window in each patient. In previous studies the exact SC position within the PSA differed significantly between groups.^{5,26,30} Despite the fact that different subareas of the PSA seemed to be stimulated, our group has previously suggested that the DRTT might be the common stimulated anatomical structure.¹²

Figure 4 reviews the mean SC positions of the above-cited studies (if applicable) and our results projected onto the stereotactic atlas of Morel. The mean SC position of each of the cited studies covers the fct, but at the margin of the ZI in the case of findings by Plaha et al.³² and our group. The hypothesis that the DRTT might mediate the stimulation-induced tremor-suppressive effect is also postulated by recent work based on DTI tractography.^{9,11} On the other hand, Plaha et al. suggested that stimulation of the ZI is effective to suppress tremor in ET patients. The ZI is a heterogeneous reticular nucleus of primarily GABAergic neurons with reciprocal connections to the basal ganglia, cerebellum, thalamus, and brainstem nuclei.^{18,23,34,35} ZI neurons probably play a role in mediating neuronal synchronization in the subcortical motor network, resulting in tremor oscillations.^{16,32}

To confine the optimal stimulation site within the PSA subregions in our series of patients, we analyzed the anatomical position of the clinically most effective SCs and compared these positions to the position of the least effective SCs. No significant differences were found between the most and least effective SC positions and their distance to the tractography-based DRTT. Thus, the question of an optimal stimulation site within the PSA remains unanswered at this point and needs to be addressed in future studies with a bigger sample size and stimulation field models.

Limitations

Our study has some limitations. First, the sample size is too small to allow generalization of our results to a broader population. Second, the postoperative clinical testing was not performed in a blinded manner. Third, we have not included the analysis of stimulation volumes based on stimulation field models such as proposed by McIntyre and coworkers or Butson and coworkers to further define the volume of tissue activated.^{6,21,22} Furthermore, we implanted 2 different types of DBS leads in our study population. As there is no study directly comparing constant voltage source-driven (CV) omnidirectional DBS leads with constant current source-driven (CC) directional DBS leads, we cannot exclude the introduction of a potential bias. Our targeting approach was based on anatomical landmarks visible on T2-weighted MRI rather than tractography of the DRTT. Despite the application of tractography-guided targeting of the DRTT by several groups, its accuracy for displaying the anatomical DRTT has yet to be validated. Only probabilistic DTI-based tractography of the DRTT has so far been validated in a postmortem anatomical study, with 7-T MRI revealing moderate concordance of the tracked and anatomical DRTT at the level of the midbrain.²⁴ Moreover, application of deterministic DTI-based tractography to display the DRTT has some limitations that shall be mentioned only cursorily. The relatively low resolution of our DTI sequences and the small number of gradients that we used (only 12) in order to achieve compatibility with the Brainlab software algorithm has implications for the reliability of the DRTT tractography results. The tensor calculation model fails in cases of voxels containing 2 or more fiber tracts with different orientations. These theoretical limitations are practically relevant and are reflected by the

high percentage (36%) of anatomically implausible tracking results. This reflects the main reason why we prefer to rely on anatomical landmarks rather than tractography as a targeting strategy for the PSA. The question of whether application of higher angular resolution published by other groups is more accurate remains to be determined.^{8,36}

Due to these limitations, our results do not allow reliable conclusions about an optimal stimulation target within the PSA and whether this is confined to one of its substructures. Furthermore, due to the study design our results do not contribute to disentangling one of the most relevant questions—whether there are differences between Vim and PSA targeting for ET in terms of clinical outcome and side effects.

Conclusions

Targeting of the PSA based on anatomical landmarks on MRI is accurate and leads to good long-term clinical results. Although our results support the concept of the DRTT to mediate the tremor-suppressive effect of DBS, the optimal stimulation site within the PSA still has to be further defined in future studies of directional leads and reliable electric field models.

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Conception and design: Pollo. Acquisition of data: Nowacki, Debove, Rossi, Schlaeppli, Petermann, Wiest, Schüpbach. Analysis and interpretation of data: Nowacki, Pollo. Drafting the article: Nowacki, Pollo. Critically revising the article: Debove, Rossi, Wiest, Schüpbach. Approved the final version of the manuscript on behalf of all authors: Nowacki. Statistical analysis: Nowacki. Administrative/technical/material support: Petermann, Wiest. Study supervision: Pollo.

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