Clinical Neurology and Neurosurgery 185 (2019) 105466

Contents lists available at ScienceDirect

Clinical Neurology and Neurosurgery

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

Comparison of posterior subthalamic area deep brain stimulation for tremor using conventional landmarks versus directly targeting the dentatorubrothalamic tract with tractography

Hu Liang Low[a,b,*], Mohd. Nasir bin Mohd Ismail[c], Ahsan Taqvi[a], Jacquie Deeb[d], Charlotte Fuller[e], Anjum Misbahuddin[f]

[a] Department of Neurosurgery, Queen's Hospital Romford, London, UK
[b] Department of Neurosurgery, Sunway Medical Centre, Bandar Sunway, Malaysia
[c] Clinical Service, Sunway Medical Centre, Bandar Sunway, Malaysia
[d] Department of Neurophysiology, Queen's Hospital Romford, London, UK
[e] Department of Neuropsychology, Queen's Hospital Romford, London, UK
[f] Department of Neurology, Queen's Hospital Romford, London, UK

ARTICLE INFO

Keywords:
Posterior subthalamic area deep brain stimulation
Tremor
Diffusion tensor imaging and tractography
Functional outcome
Randomised study

ABSTRACT

Objective: To compare posterior subthalamic area deep brain stimulation (PSA-DBS) performed in the conventional manner against diffusion tensor imaging and tractography (DTIT)-guided lead implantation into the dentatorubrothalamic tract (DRTT).

Patients and Methods: Double-blind, randomised study involving 34 patients with either tremor-dominant Parkinson's disease or essential tremor. Patients were randomised to Group A (DBS leads inserted using conventional landmarks) or Group B (leads guided into the DRTT using DTIT). Tremor (Fahn-Tolosa-Marin) and quality-of-life (PDQ-39) scores were evaluated 0-, 6-, 12-, 36- and 60-months after surgery.

Results: PSA-DBS resulted in marked tremor reduction in both groups. However, Group B patients had significantly better arm tremor control (especially control of intention tremor), increased mobility and activities of daily living, reduced social stigma and need for social support as well as lower stimulation amplitudes and pulse widths compared to Group A patients. The better outcomes were sustained for up to 60-months from surgery. The active contacts of Group B patients were consistently closer to the centre of the DRTT than in Group A. Speech problems were more common in Group A patients.

Conclusion: DTIT-guided lead placement results in better and more stable tremor control and fewer adverse effects compared to lead placement in the conventional manner. This is because DTIT-guidance allows closer and more consistent placement of leads to the centre of the DRTT than conventional methods.

1. Introduction

Deep brain stimulation (DBS) is now an accepted treatment for medication-refractory tremor. The most common surgical target is the ventral intermediate (Vim) nucleus of the thalamus [1] but other targets have been used with good effect including the globus pallidus interna (GPi) [1], subthalamic nucleus (STN) [1], prelemniscal radiation (RaPRL) [2], caudal zona incerta (cZI) [3], Voa/Vop thalamic nuclei [4] and the posterior subthalamic area [5,6]. In recent years, there has been increased interest in targeting sub-thalamic structures for tremor control especially the posterior subthalamic area (PSA). The PSA is an area bounded superiorly by the thalamus, inferiorly by the substantia nigra, posteriorly by the medial lemniscus, anterolaterally by the subthalamic nucleus, laterally by the posterior limb of the internal capsule and medially by the red nucleus [6]. It is closely related to the aforementioned surgical targets and contains the cZI, the cerebellothalamic tracts

Abbreviations: AC-PC, anterior commissure-posterior commissure; ADL, activities of daily living; CBTT, cerebellothalamic tract; DBS, deep brain stimulation; DRTT, dentatorubrothalamic tract; DTIT, diffusion tensor imaging and tractography; ET, essential tremor; FOV, field of view; FTMTS, Fahn-Tolosa-Marin Tremor Score; MER, microelectrode recording; PD, Parkinson's disease; PDQ-39, Parkinson's disease questionnaire-39; PSA, posterior subthalamic area; TDPD, tremor dominant Parkinson's disease; TE, time of excitation; TR, relaxation time; TTS, treated tremor score

* Corresponding author at: Department of Neurosurgery, Queen's Hospital, Rom Valley Way, Romford, London RM7 0AG, UK.
E-mail address: lowhli@hotmail.com (H.L. Low).

https://doi.org/10.1016/j.clineuro.2019.105466
Received 23 April 2019; Received in revised form 19 July 2019; Accepted 6 August 2019
Available online 12 August 2019
0303-8467/ Crown Copyright © 2019 Published by Elsevier B.V. All rights reserved.

(CBTT) including the dentatorubrothalamic tract (DRTT) and RaPRL [6–8].

Modern histological methods [7] and diffusion tensor imaging and tractography (DTIT) [8] show that the surgical targets used in tremor are either connected to the CBTT (cZI, RaPRL, ventral thalamic nuclei) or very close to it (STN, GPi and pallidothalamic projections). Tractography has also demonstrated lesions within the CBTT [9] in patients with ataxia and tremor. Worsening abnormalities within this structure are associated with tremor progression [10]. Better tremor control is also observed whenever DBS contacts [8,11] or radiofrequency lesions [12] are closer to the DRTT. These provide indirect evidence that the CBTT, especially its DRTT component, plays an important role in tremor modulation probably by acting as a common 'superhighway' connecting the neural centres involved in tremorgenesis.

Studies where the DRTT is directly targeted are limited. Coenen reported a 90% reduction in myoclonic head tremor 3-months after DBS leads were placed in the DRTT under DTIT-guidance [13]. Similar procedures performed on twenty essential tremor (ET) patients in a prospective observational study with a "minimum" follow-up period of 6-months reported equally good results [14]. DTIT-guided magnetic resonance focused ultrasound lesioning of the DRTT on four ET patients resulted in a 85–95% tremor reduction but there was no long-term follow-up [15]. These studies show that directly targeting the DRTT can result in good tremor control.

However, is DTIT-guided PSA-DBS better than PSA-DBS performed conventionally? Can the technique be used for non-ET tremor especially Parkinsonian tremor? The latter is important as Parkinson's disease (PD) is probably the second most common neurological condition with tremor [16] and there are very few studies on the surgical treatment of tremor-dominant Parkinson's disease (TDPD). To answer this, we carried out this randomised, double-blinded 5-year study with the primary goal being to determine if DTIT-guided PSA-DBS conveys any clinical advantage to conventional' PSA-DBS.

2. Materials and methods

The study was performed in accordance to the Declaration of Helsinki and approved by the Institutional Review Board (No. 230313) with all patients giving informed, written consent.

2.1. Patient selection

Patients with confirmed medication-refractory ET and TDPD and who met the criteria for DBS [17] were included. The diagnosis of ET and TDPD was made by two movement disorder neurologists. Tremor was considered 'medication-refractory' if there was moderate to severe disruption of the patient's activities of daily living (ADL) despite trying 3 or more medications at the highest tolerated dose for a minimum of 6-months. TDPD patients were only included if tremor was the main complaint and there was minimal progression of non-tremor PD symptoms for at least 8 years or more. Patients were recruited and operated-on between 2009 and 2013 and followed for 5 years.

2.2. Study design

The CONSORT flowchart is shown in Fig. 1. Suitable candidates underwent assessments, MRI scanning and tractography at least 2-weeks before surgery. On the morning of surgery, patients were randomised to Group A where the brain electrode was inserted in the conventional manner [4] or Group B where electrode insertion was DTIT-guided. Randomisation was performed using a random sequence generator with even and odd numbers being allocated to Groups A and B respectively. Results of randomisation was concealed to everyone except the operating surgeon. Surgery was performed according to the groups patients were randomised to. Post-lead implantation MRI scans were obtained to determine the locations of the lead contacts and to allow post-surgical assessment of the lead location relative to the centre of the DRTT. Assessments and DBS programming were performed by a neurologist blinded to the outcome of patient randomisation at 6-, 12-, 36- and 60-months post-surgery. Details of any adverse effects and stimulation parameters were also recorded..

2.3. Preoperative magnetic resonance imaging and tractography

MRI scans were obtained 2-weeks before surgery (1.5 T Siemens Magnetom, Germany). T2-weighted, axial images of the whole brain (TR 3890 msec, TE 101 msec, FOV 260 mm, slice thickness 2 mm, distance factor 0 mm, voxel size 0.9 × 1.0 × 2 mm) and spin-echo echo-planar imaging pulse sequences (TR 6004 msec, TE 97 msec, FOV 260 mm, slice thickness 2 mm, 0 mm gap, voxel size 2 × 2 × 2 mm, number of gradient directions 20, b-value 1000 sec/mm^2, matrix 128 × 128) were obtained parallel to the anterior commissure- posterior commissure (AC-PC) plane.

Following corrections for movement artefacts, T2 and spin-echo images were co-registered and tensor calculations performed (fractional anisotropy level 0.2, angle threshold 30°, minimum fibre length 10 mm, seed density 5.0) using Syngo DTI-tractography software (Siemens, Germany).

Deterministic tractography was performed using Kwon's technique [18]. The DRTT was defined as the fibre tract connecting three regions of interest: the cerebellar dentate nuclei, superior cerebellar peduncle and midbrain tegmentum at the level of the equator of the red nucleus before ending in the motor-premotor cortex. The individually defined DRTT images were co-registered with the preoperative T2-scans using Syngo DTI software (Fig. 2A-B) before being imported to FrameLink 5.0 neuronavigation software (Medtronic, USA) for further processing.

2.4. Surgical procedure

All patients were operated by the same surgeon (LHL) and assessed by the same neurologist (AM). Following general anaesthesia, a Cosman-Robert-Wells (CRW) headframe was attached. T2- images extending from the dorsal thalamic surface to the midbrain-pons border (TR 3890 msec, TE 101 msec, FOV 260 mm, slice thickness 2 mm, distance factor 0 mm, voxel size 0.9 × 1.0 × 2 mm) and gadolinium-enhanced T1-images of the whole brain (TR 554 msec, TE 17 msec, FOV 270 mm, slice thickness 2 mm, 0 mm gap, voxel size 1.4 × 1.0 × 2.0 mm) were obtained parallel to the AC-PC plane. The images were imported into FrameLink5.0 software for determination of target coordinates and trajectory planning. Blomstedt's technique was used to target the PSA in Group A patients [5]. In Group B, the centre of the DRTT (hereafter known as the DRTT-core) at the level of the equator of the red nucleus contralateral to the side of the tremor was the initial target. The trajectory was adjusted to avoid critical structures and the lateral ventricles and to allow the posterolateral STN to touch at least one of the two most proximal contacts.

Baseline arm tremor scores (FTMTS and Bains-Findley) were obtained. A single, centrally located microelectrode and cannula (FHC Inc,USA) was inserted and advanced towards the target using a microdrive. The microdrive was positioned such that its anteroposterior axis lay parallel to the patient's mid-sagittal plane. Continuous microelectrode recordings were obtained from 10 mm above ($T = -10$ mm) to 3 mm below ($T = +3$ mm) the proposed target using a Leadpoint-4 platform (Medtronic). As the microelectrodes pass to the target, MER recordings typically revealed STN-spiking (especially laterally placed microelectrodes) before becoming silent on entering the PSA. This is often accompanied by a reduction in arm tremor. Next, the guide tube advanced in 1 mm increments from $T = -5$ mm to $T = +3$ mm. Test macrostimulation (0–5 mA, 60microsec, 100 Hz) was performed through the guidetube until a satisfactory response was obtained as shown by i) a reduction in arm tremor by at least 90% compared to baseline at 1 mA, 60 μs, 120 Hz, ii) the ability to draw spirals of grade 4

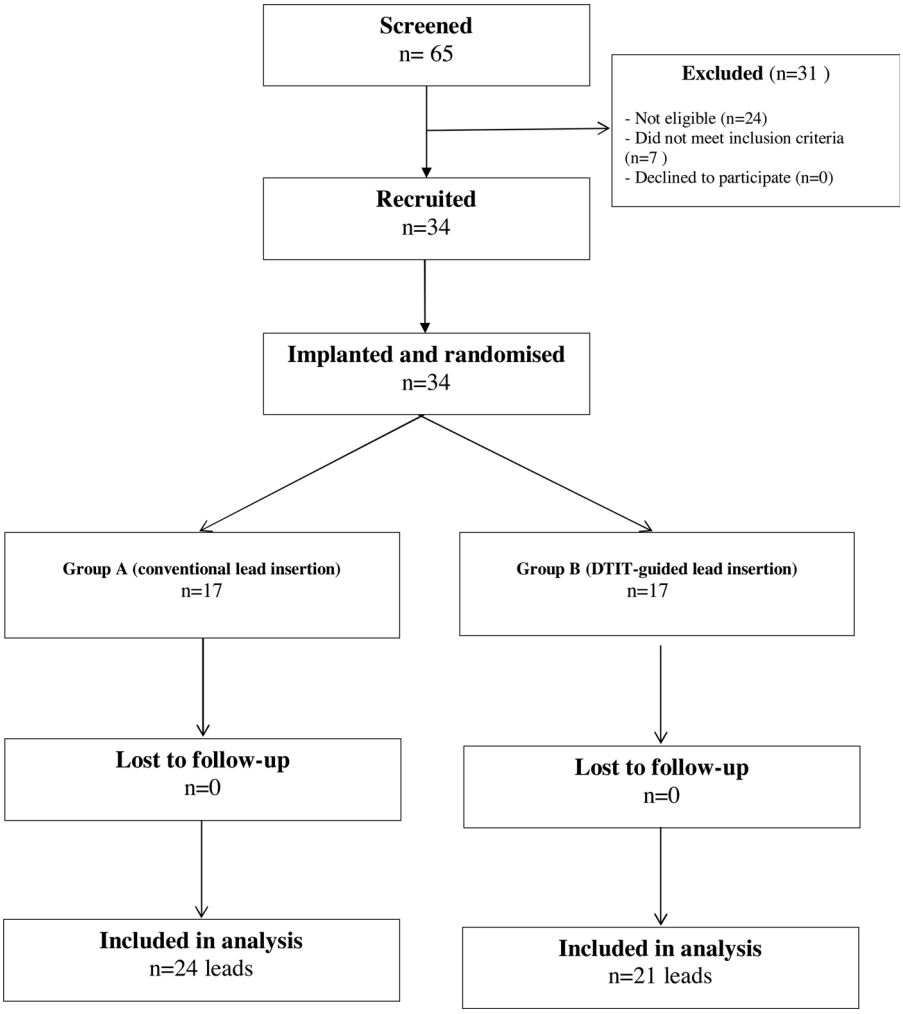

Fig. 1. CONSORT (Consolidated Standards of Reporting Trials) diagram showing all phases of the trial.

and below on the Bains-Findley scale using the treated arm at 1 mA, 60 μs, 120 Hz and iii) absence of significant and permanent side effects at 5 mA, 60 μs, 120 Hz. The microelectrode-macroelectrode was re-positioned and the above repeated until a satisfactory response was obtained.

On eliciting the desired response, the macroelectrode was exchanged for a Medtronic 3389-40 lead under fluoroscopic guidance with the penultimate lead contact (contact 1) being placed where tremor control was best during testing. The electrode was secured and the incision closed. The above was repeated on the opposite side for bilateral procedures.

Intraoperative T2-weighted images were obtained whilst the patient was still in the CRW frame (TR 3890 msec, TE 101 msec, FOV 260 mm, slice thickness 2 mm, 0 mm gap, low SAR setting < 2.4 W/kg)) to determine the position of the electrode contacts. An Activa PC (Medtronic) pulse generator was implanted in the infraclavicular subcutaneous region under general anaesthesia if the lead positions were satisfactory. Patients were discharged the next day. Stimulator adjustments were initiated 2–3 weeks later and continued until a satisfactory outcome was achieved.

2.5. Assessments and outcome measures

Assessors and patients were blinded to the outcome of randomisation. A movement disorder specialist performed assessments pre-operatively and 6-, 12-, 36- and 60-months post-operatively. Tremor severity was assessed using the Fahn-Tolosa-Marin tremor scale (FTMTS) and reported in two ways: an overall FTMTS score and the treated tremor score (TTS). As the FTMTS contains scores from treated and untreated sides, the TTS is more representative of tremor control following surgery. The TTS is derived from the sum of the scores for the treated side using FTMTS questions 11–14 and either questions 5 and 8 (right side) or 6 and 9 (left side). The TTS was sub-divided into the scores for the treated arm (TTS-a), leg (TTS-l) and combined arm and leg (TTS-al).Tremor affecting the face, tongue, voice, head and trunk were grouped under ‘axial’ tremor (TTS-ax). The treated arm tremor score (TTS-a) was sub-divided further into resting (TTS-ar), postural (TTS-ap) and intention (TTS-ai) tremor scores.

The PDQ-39 questionnaire was used to assess the quality of life of the subjects as more than 50% of the patients had TDPD. Although designed for use in patients with Parkinson's disease, PDQ-39 has been used to assess the quality of life in ET patients following DBS [19,20]. The questionnaire contains 8 domains corresponding to patients’ mobility (Qs. 1–10), activities of daily living (Qs 11–16), emotional well-being (Qs. 17–22), stigma of disease (Qs 23–26), social support (Qs. 27–29), cognition (Qs. 30–33), ability to communicate (Qs. 34–36) and bodily discomfort (Qs 37–39). The PDQ39-SI is an average of all 8 domain scores and reflects the overall quality of life as perceived by the patient. The scores are expressed in percentages with a lower score denoting a better outcome.

Adverse effects were recorded on a binary scale (‘present’ or ‘absent’).

The primary outcome measures were the differences in tremor and PDQ-39 scores between Groups A and B at 6-, 12-, 36- and 60-months

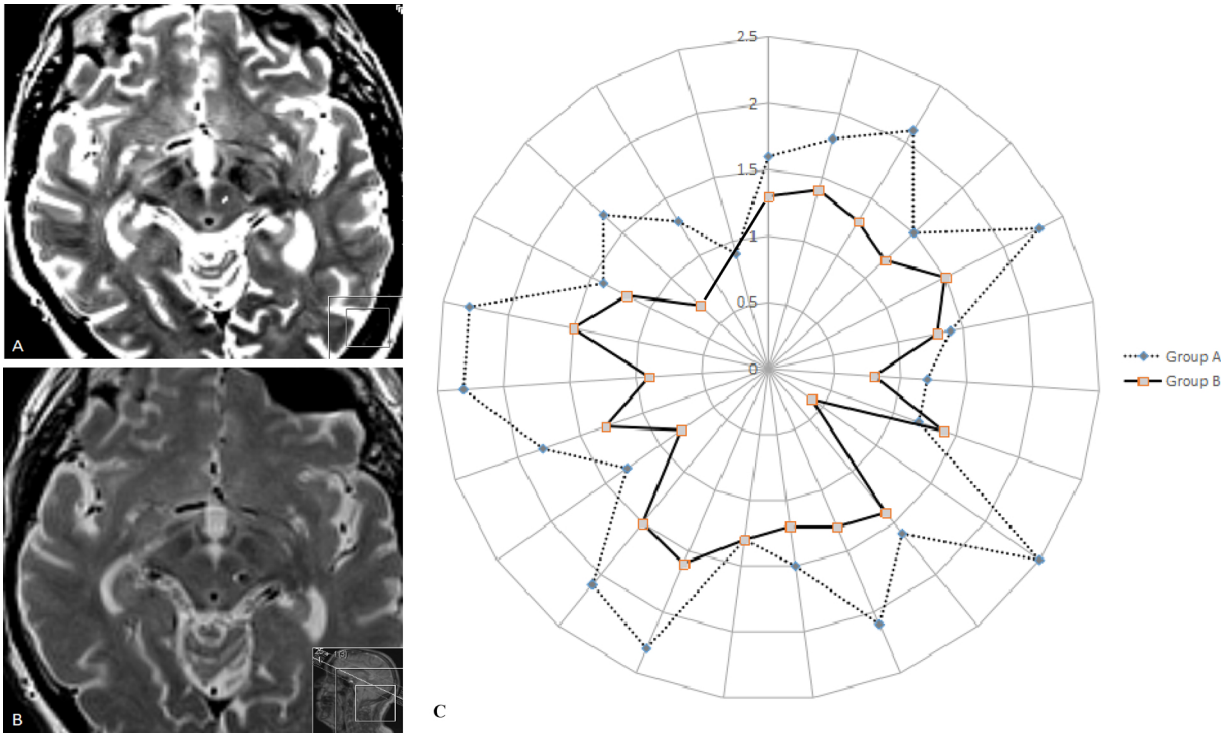

Fig. 2. Relationship of active DBS contact from the centre of the DRTT (DRTT-core). (A) Location of the DRTT as shown by DTIT at the level of the equator of the left red nucleus. The DTIT images had been fused to T2-weighted axial images and was to guide lead implantation into the DRTT. (B) Intraoperative axial T2-images showing a lead contact within the DRTT. The distance between the centre of the contact and the DRTT was measured. Incidentally, this patient exhibited a profound microlesioning effect and has no tremor in the treated arm even though his neurostimulator has not been activated for the last 5 years. (C) Radar plot of the distances between Group A and B active contacts and the centre of the DRTT (referred to as the DRTT-core). The concentric circles denote distances in 0.5 mm increments from the DRTT-core. Each marker is an active contact from either Group A or B. All active contacts were located within 2.5 mm of the DRTT-core. The majority of Group B contacts were within a 1.5 mm radius of the DRTT-core which is only slightly greater than the diameter of a 3389-brain electrode (1.27 mm) whereas Group A contacts were more widely dispersed.

after surgery. Secondary outcome measures were the effect of PSA-DBS on the control of different tremor types, on axial tremor, differences in stimulation parameters between groups, adverse effects of treatment and the distance between the active contact and the DRTT-core.

2.6. Determination of location of active contact and distance from the DRTT-core

Post-implantation scans were co-registered with the scans containing the location of the DRTT using FrameLink software which allowed determination of contact coordinates were determined relative to the mid-commissural point and the measurement of distances between the centre of the active contact to the DRTT-core.

2.7. Sample size and statistical analysis

Calculation of sample size was based on Blomstedt's study[6]. With a power of 0.8, alpha 0.05 and equal proportions of patients in each group, we calculated that a minimum of 12 patients in total with at least 6 in each group was required to detect a mean difference of 0.5 standard deviation.

Statistical analysis was carried with IBM SPSS version 20. Wilcoxon signed-rank tests were used as the data was not normally distributed. Statistical significance was set at $P < 0.05$.

3. Results

3.1. Patient demographics

These are summarised in Table 1. Of the 65 patients screened, 31 were excluded as they did not have ET or TDPD (24) or did not meet the inclusion criteria despite having ET/TDPD (7). Thirty-four patients were included in the study of which 17 were randomised to the group where lead implantation was carried out conventionally (Group A) and 17 underwent DTIT-guided lead implantation (Group B). No patients dropped-out or were lost to follow-up throughout the study.

Table 1
Patient demographics in Group A (conventional lead implantation) and Group B (DTIT-guided lead implantation) at baseline.

	Group A	Group B	P-value
Number	17	17	NS
Sex (Male:Female)	10:7	13:4	NS
TDPD:ET	7: 10	10:7	NS
Age at tremor onset (years)	53.00 ± 15.90	54.18 ± 18.70	NS
Age when DBS performed (years)	70.41 ± 8.46	54.18 ± 18.70	NS
Duration of symptoms before DBS (years)	17.41 ± 14.72	12.94 ± 12.57	NS
Laterality of procedure- Unilateral: Bilateral	10:7	13:4	NS
Side of lead insertion (Right: Left)	11:13	7:14	NS
Total number of leads inserted	24	21	

NS = not statistically significant.

3.2. Primary outcome measures

3.2.1. Tremor scores following PSA-DBS are significantly better than baseline and remains so until 60-months

Tremor scores are summarised in Table 2. At all post-surgical time-points, conventional and DTIT-guided PSA-DBS resulted in significantly

Table 2
Tremor scores comparing Group A and Group B tremor scores relative to baseline scores and between groups before surgery and at 6-, 12-,36- and 60-months after PSA-DBS.

		FTMTS/144 (Grp A n = 17; Grp B n = 17)	P value (Grp A vs Grp B)	TTS-al/40 (Grp A n = 24; Grp B n = 21)	P value (Grp A vs Grp B)	TTS-a/28 (Grp A n = 24; Grp B n = 21)	P value (Grp A vs Grp B)	TTS-ar/4 (Grp A n = 24; Grp B n = 21)	P value (Grp A vs Grp B)
Preop	Group A	57.47 ± 16.90	0.421	21.46 ± 5.54	0.793	20.17 ± 5.33	0.278	2.33 ± 1.58	0.736
	Group B	51.88 ± 19.78		21.10 ± 5.92		17.90 ± 5.48		2.19 ± 1.54	
6-mths	Group A	15.00 ± 10.37	0.776	3.75 ± 3.42	**0.047***	3.33 ± 3.24	**0.081***	0.08 ± 0.41	0.059
	Group B	12.82 ± 8.60		2.10 ± 2.32		1.90 ± 2.10		0.24 ± 0.54	
	P value (Grp A vs preop)	< **0.001***		< **0.001***		< **0.001***		< **0.001***	
	P value (Grp B vs preop)	< **0.001***		< **0.001***		< **0.001***		< **0.001***	
12-mths	Group A	17.18 ± 11.70	**0.041***	4.00 ± 4.64	**0.018***	3.75 ± 4.47	**0.019***	0.13 ± 0.34	0.157
	Group B	7.47 ± 3.95		1.52 ± 2.46		1.24 ± 2.30		0.14 ± 0.36	
	P value (Grp A vs preop)	< **0.001***		< **0.001***		< **0.001***		< **0.001***	
	P value (Grp B vs preop)	< **0.001***		< **0.001***		< **0.001***		< **0.001***	
36-mths	Group A	18.12 ± 14.35	**0.032***	3.79 ± 4.74	**0.016***	3.67 ± 4.76	**0.016***	0.04 ± 0.20	0.317
	Group B	6.88 ± 4.17		1.05 ± 2.11		1.00 ± 2.12		0.05 ± 0.22	
	P value (Grp A vs preop)	< **0.001***		< **0.001***		< **0.001***		< **0.001***	
	P value (Grp B vs preop)	< **0.001***		< **0.001***		< **0.001***		< **0.001***	
60-mths	Group A	19.94 ± 14.64	**0.026***	3.67 ± 4.10	**0.013***	3.58 ± 4.16	**0.017***	0.13 ± 0.34	0.194
	Group B	10.00 ± 7.66		1.29 ± 2.67		1.19 ± 2.32		0.24 ± 0.62	
	P value (Grp A vs preop)	< **0.001***		< **0.001***		< **0.001***		< **0.001***	
	P value (Grp B vs preop)	< **0.001***		< **0.001***		< **0.001***		< **0.001***	

	TTS-ap/4 (Grp A n = 24; Grp B n = 21)	P value (Grp A vs Grp B)	TTS-ai/20 (Grp A n = 24; Grp B n = 21)	P value (Grp A vs Grp B)	TTS-l/12 (Grp A n = 8; Grp B n = 15)	P value (Grp A vs Grp B)	TTS-ax/28 (Grp A n = 13; Grp B n = 10)	P value (Grp A vs Grp B)
Preop	3.25 ± 0.74	0.869	14.58 ± 5.36	0.217	3.88 ± 2.64	0.223	3.69 ± 2.06	0.237
	3.19 ± 0.93		12.52 ± 5.38		4.47 ± 3.40		3.20 ± 2.35	
6-mths	0.25 ± 0.68	0.763	3.00 ± 2.86	**0.028***	0.38 ± 0.74	1.000	0.79 ± 1.75	0.863
	0.29 ± 0.46		1.38 ± 1.66		0.27 ± 0.59		0.54 ± 0.78	
	< **0.001***		< **0.001***		**0.018***		**0.002***	
	< **0.001***		< **0.001***		**0.001***		**0.012***	
12-mths	0.17 ± 0.48	0.705	3.46 ± 4.22	**0.014***	0.25 ± 0.46	1.000	0.32 ± 1.16	0.18
	0.14 ± 0.36		0.95 ± 1.96		0.13 ± 0.34		0.31 ± 0.48	
	< **0.001***		< **0.001***		**0.017***		**0.001***	
	< **0.001***		< **0.001***		**0.001***		**0.007***	
36-mths	0.17 ± 0.14	0.414	3.54 ± 4.47	**0.012***	0.25 ± 0.71	0.317	0.58 ± 1.26	0.546
	0.10 ± 0.30		0.86 ± 1.77		0.07 ± 0.26		0.69 ± 1.11	
	< **0.001***		< **0.001***		**0.011***		**0.001***	
	< **0.001***		< **0.001***		**0.001***		**0.009***	

(*continued on next page*)

Table 2 (*continued*)

	TTS-ap/4 (Grp A n = 24; Grp B n = 21)	P value (Grp A vs Grp B)	TTS-ai/20 (Grp A n = 24; Grp B n = 21)	P value (Grp A vs Grp B)	TTS-l/12 (Grp A n = 8; Grp B n = 15)	P value (Grp A vs Grp B)	TTS-ax/28 (Grp A n = 13; Grp B n = 10)	P value (Grp A vs Grp B)
60-mths	0.17 ± 0.48	0.572	3.38 ± 4.06	**0.010***	0.25 ± 0.71	0.317	0.32 ± 0.95	0.655
	0.10 ± 0.44		0.86 ± 1.74		0.20 ± 0.77		0.23 ± 0.83	
	< 0.001*		**< 0.001***		**0.020***		**0.001***	
	< 0.001*		**< 0.001***		**0.001***		**0.005***	

FTMTS = Fahn-Tolosa-Martin tremor score; TTS-al = treated tremor score for arm and leg; TTS-a = treaed tremor score for arm; TTS-ar = treated tremor score for resting arm tremor; TTS-ap = treated tremor score for postural arm tremor; TTS-ai = treated tremor score for intentional arm tremor; TTS-l = treated tremor score for leg; TTS-ax = treated tremor score for axial tremor (head, neck, torso). Lower scores denote better tremor control. Statistically significant results are denoted in bold with an asterisk*.

improved tremor control over baseline ($p < 0.001$). The tremor reduction was greatest in the first 6-months after which they remained stable up to 60-months.

3.2.2. DTIT-guided lead insertion is associated with better long-term arm tremor control (especially the control of intention tremor) than conventional lead insertion

The pre-surgical Group A and B tremor scores were not statistically different. The tremor scores began to diverge within 6-months of surgery with Group B mean tremor scores being lower than those of Group A. However only TTS-al scores were significantly different ($p = 0.047$) at 6-months. The FTMTS, TTS-al and TTS-a scores in Group B were significantly lower than that of Group A from 6 to 60- months (Table 2). The total (FTMTS). treated tremor scores for the arm and leg (TTS-al) and arm (TTS-a) were 65.30%, 82.90% and 82.25% better than baseline for Group A patients at 60-months. Similar scores in Group B patients at 60-months were 80.72%, 93.89% and 93.35% respectively above baseline.

Resting (TTS-ar), postural (TTS-ap) and intention (TTS-ai) arm tremor scores were significantly lower than baseline following surgery ($p < 0.001$) but inter-group differences were not significant except for the TTS-ai scores which were better in Group B ($p < 0.001$).

3.2.3. Patients who underwent DTIT-guided lead implantation reported better quality of life especially in the domains of activities of daily living, mobility, social stigma and social support compared to patients who underwent conventional lead implantation

The results from the patient-reported PDQ-39 questionnaire are summarised in Table 3 with lower scores denoting a better outcome. Group B patients returned significantly better scores compared to Group A patients in the following domains: PDQ-39SI, mobility, ADL, stigma, social support and communication especially after the first year of surgery. The difference in scores was not significant in the remaining domains.

The impact of DTIT-guided lead implantation was most clearly shown Group B patients activities of daily living. Group A patients reported improvements in ADL scores over baseline of 76.13%, 73.33%, 59.22%, 50.50% at 6-, 12-, 36- and 60-months after surgery. In contrast, improvements over a similar period in Group B patients were of the order of 88.55%, 93.13%, 91.98% and 87.03%.

Group B patients also experienced statistically significant improvements in mobility, stigma and social support from 12- to 60- months compared to Group A patients. These were all responsible for the better quality of life experienced by Group B patients as reflected by the lower PDQ-39SI score.

Problems with communication were encountered in both groups. Indeed, speech problems were the most common adverse effect in our study. However, significant worsening of postoperative 'communication' scores were only present in Group A patients and manifested as early as 6-months after surgery. Verbal problems, whilst present in Group B patients, were not as marked and did not reach statistical significance. There were no significant differences between groups or against baseline in the 'emotional well-being', 'cognition' and 'discomfort' domains.

3.3. Secondary outcome measures

3.3.1. PSA-DBS is very effective in controlling leg and axial tremor

Both groups demonstrated significant improvement in leg (TTS-l) and axial (TTS-ax) tremor following surgery when compared to baseline (Table 2). However, there was no statistical difference in the mean TTs-l and TTS-ax scores of Group A and B patients.

We investigated the effect of unilateral or bilateral PSA-DBS on axial tremor. Bilateral procedures had lower mean axial tremor scores but the differences between unilateral and bilateral lead insertion on axial tremor control were not statistically significant (Table 4).

Table 3
PDQ-39 scores comparing the quality of life of patients in Group A and B before surgery and at 6-, 12-,36- and 60-months after PSA-DBS.

		PDQ-39SI	P value (GrpA vs B)	Mobility (Qs 1–10)	P value (GrpA vs B)	ADL (Qs 11–16)	P value (GrpA vs B)	Emotional well-being (Qs 17–22)	P value (GrpA vs B)	Stigma (Qs 23–26)
Preop	Group A	26.21 ± 12.83	0.287	27.98 ± 21.07	0.309	62.50 ± 24.21	0.796	21.32 ± 21.89	0.254	48.16 ± 31.47
	Group B	33.24 ± 13.66		37.21 ± 21.70		64.21 ± 21.40		28.92 ± 12.37		59.93 ± 31.02
6-mths	Group A	22.22 ± 12.90	0.554	22.50 ± 17.92	0.604	17.37 ± 15.62	**0.046***	24.26 ± 21.66	0.468	28.31 ± 27.43
	Group B	18.79 ± 14.50		18.68 ± 13.44		7.35 ± 6.34		19.12 ± 19.27		23.90 ± 26.63
	P value (Grp A vs preop)	0.326		0.233		**0.001***		0.777		**0.009***
	P value (Grp B vs preop)	**0.002***		**0.002***		< **0.001***		0.088		**0.002***
12-mths	Group A	22.75 ± 14.07	**0.044***	27.35 ± 18.95	**0.033***	16.67 ± 22.49	**0.020***	24.27 ± 24.39	0.276	23.04 ± 25.54
	Group B	13.88 ± 10.72		14.58 ± 11.67		4.41 ± 4.53		15.69 ± 17.02		8.46 ± 9.87
	P value (Grp A vs preop)	0.332		0.679		**0.001***		0.646		**0.013***
	P value (Grp B vs preop)	< **0.001***		**0.001***		< **0.001***		0.051		**0.001***
36-mths	Group A	28.49 ± 15.34	**0.044***	38.68 ± 24.50	**0.007***	25.49 ± 24.11	**0.005***	28.43 ± 24.04	0.320	33.09 ± 23.36
	Group B	17.11 ± 14.47		14.71. ± 11.59		5.15 ± 5.21		18.63 ± 21.00		9.56 ± 13.64
	P value (Grp A vs preop)	0.723		0.121		**0.001***		0.209		**0.05***
	P value (Grp B vs preop)	**0.001***		**0.002***		< **0.001***		0.107		< **0.001***
60-mths	Group A	37.52 ± 13.45	**0.009***	51.32 ± 21.54	**0.024***	40.93 ± 26.97	< **0.001***	37.26 ± 25.24	0.070	43.01 ± 34.37
	Group B	21.58 ± 15.22		30.88 ± 27.73		8.33 ± 6.91		21.81 ± 22.46		11.03 ± 14.58
	P value (Grp A vs preop)	**0.011***		**0.005***		**0.028***		0.051		0.537
	P value (Grp B vs preop)	**0.006***		**0.049***		< **0.001***		0.288		**0.001***

	P value (GrpA vs B)	Social support (Qs 27–29)	P value (GrpA vs B)	Cognition (Qs. 30–33)	P value (GrpA vs B)	Communication (Qs. 34–36)	P value (GrpA vs B)	Discomfort (Qs. 37–39)	P value (GrpA vs B
Preop	0.245	13.73 ± 18.39	0.959	21.32 ± 21.89	0.937	6.86 ± 11.87	0.070	18.14 ± 20.88	0.512
		13.24 ± 19.56		21.69 ± 19.40		17.65 ± 24.81		23.04 ± 26.11	
6-mths	0.906	19.61 ± 28.10	0.722	23.53 ± 19.46	0.259	20.59 ± 19.35	0.944	27.94 ± 21.03	0.825
		15.20 ± 29.64		16.54 ± 20.48		21.57 ± 24.31		27.94 ± 26.01	
		0.574		0.817		**0.008***		0.091	
		0.611		0.233		0.385		0.218	
12-mths	**0.044***	17.15 ± 17.03	**0.026***	27.57 ± 23.08	0.450	15.07 ± 15.53	0.504	30.39 ± 21.03	0.115
		5.39 ± 9.29		22.06 ± 21.55		19.85 ± 23.17		20.10 ± 21.05	
		0.529		0.306		**0.049***		0.065	
		0.135		1.000		0.755		0.427	
36-mths	**0.010***	22.43 ± 20.08	**0.039***	22.43 ± 16.54	0.795	23.04 ± 19.21	0.637	34.31 ± 29.45	0.563
		6.86 ± 12.92		26.10 ± 25.60		27.45 ± 30.73		28.43 ± 28.12	
		0.275		0.899		**0.007***		0.078	
		0.271		0.342		0.113		0.284	
60-mths	**0.006***	26.96 ± 29.98	**0.023***	30.88 ± 21.02	0.932	37.25 ± 21.67	0.704	37.26 ± 22.84	0.507
		5.10 ± 7.95		31.25 ± 25.10		32.84 ± 28.64		31.37 ± 27.41	
		0.161		0.131		**0.001***		0.065	
		0.139		0.070		0.057		0.223	

Scores are expressed as percentages with a lower score denoting a better outcome. Statistically significant results are denoted in bold with an asterisk*.

Table 4
Axial tremor scores following unilateral and bilateral PSA-DBS.

		TTS-ax/28	P value
Preop	Group A: unilateral (n = 7)	3.57 ± 1.90	0.916
	Group A: bilateral (n = 6)	3.83 ± 2.40	
	Group B: unilateral (n = 7)	5.00 ± 2.00	0.109
	Group B: bilateral (n = 3)	2.43 ± 2.15	
60-mths	Group A: unilateral (n = 7)	0.86 ± 1.43	0.102
	Group A: bilateral (n = 6)	0.00 ± 0.00	
	Group B: unilateral (n = 7)	0.43 ± 1.13	1.000
	Group B: bilateral (n = 3)	0.00 ± 0.00	

TTS-ax = treated tremor score for axial tremor (head, neck, torso)

3.3.2. DRTT stimulation is equally effective in controlling tremor essential tremor or tremor-dominant Parkinson's disease patients

We sought to determine if there was a difference in outcomes in DTIT- guided lead implantation on ET and TDPD patients. Group B contained seven patients with ET and ten with TDPD. The TTS-al scores at 0-, 6-, 12-, 36- and 60-months in Group B patients with ET were 23.90 ± 4.68, 3.00 ± 2.36, 1.90 ± 2.88, 1.80 ± 2.78 and 2.70 ± 5.19 respectively. The scores for Group B patients with TDPD during the same time-points were 18.55 ± 5.96, 1.27 ± 2.05, 1.18 ± 2.09, 0.36 ± 0.92 and 0.64 ± 1.29. Group B TTS-al scores were significantly better after surgery ($p < 0.001$) for both ET and TDPD patients. However when the postoperative TTS-al scores for ET patients were not statistically different to those with TDPD between 12- to 60-months ($p = 0.079$, 0.066, 0.176 respectively). This meant that targeting the DRTT in ET patients results in as good an outcome as targeting this structure in patients with TDPD.

3.3.3. DTIT-guided lead implantation results in fewer macrostimulation passes and lower stimulation amplitudes and pulse widths to obtain satisfactory tremor control

Group B patients required fewer macroelectrode passes before satisfactory tremor control was achieved (1.75 ± 0.79 versus 2.67 ± 0.97 for Group A; $p = 0.007$), had more instances of significant microlesioning effect and required fewer programming sessions (results not shown) compared to Group A patients. Although the stimulation frequency was not significantly different in either group, satisfactory long-term tremor control was achieved at a lower amplitudes and pulse widths in Group B (Table 5). Incidentally, a Group B patient experienced tremor arrest during microelectrode insertion and has remained tremor-free for 5-years despite his neurostimulator not being switched on! (Fig. 2A-B).

3.3.4. Adverse effects of PSA-DBS

There were no brain haemorrhages on the post-implantation scans, surgical infections or lead revisions. Only four adverse effects were noted: speech difficulties, a sensation of unsteadiness (dysequilibrium), paraesthesia in the treated limb and discomfort over the extension cable and neurostimulator.

Speech difficulties, especially verbal fluency, were reported by 6 patients from Group A (35.29%) and 3 patients from Group B (17.65%). The problem invariably disappeared when the neurostimulator was switched off and more frequent at amplitudes above 3.0 V. In the majority of cases, the speech disturbance was not apparent to people surrounding the patient.

A concern when performing PSA-DBS was the risk of unsteadiness due to the proximity of the red nucleus. Dysequilibrium was the second most common adverse effect and was experienced by all patients but only at amplitudes above 4.0 V. In only 1 case (Group A, 5.88%) was dysequilibrium clinically significant at less than 3.5 V. Since the mean amplitude was less than 3 V in practically all other cases, dysequilibrium did not prove a significant problem. Contact between the lead and the red nucleus per se did not necessarily result in unsteadiness as demonstrated in one patient (Fig. 2A-B). In this case, the lead touched the lateral border of the red nucleus. This resulted in such a profound microlesioning effect that the neurostimulator was not (and has still not been) activated. The patient has no tremor, speech problems or dysequilibrium.

Transient paraesthesias when the amplitude was changed quickly was common but not considered a significant adverse effect as it invariably lasted seconds. We noted that patients experiencing transient paraesthesia in the thumb and index finger on the treated side during macrostimulation almost invariably had excellent arm tremor control following surgery. The final adverse effect was discomfort over the extension cables and neurostimulator. However, the discomfort was sufficiently mild not to warrant the use of oral analgesics. No case required cable repositioning.

Table 5
Number of test insertions, stimulation parameters, coordinates of the active contacts and distance between the centre of the active contact to the DRTT core in Group A and B patients.

	Group A (n = 24 leads)	Group B (n = 21 leads)	P-value (Grp A vs B)
Number of macroelectrode tests before satisfactory tremor control achieved	2.67 ± 0.96	1.75 ± 0.79	**0.007***
Number of significant microlesioning effects observed during macroelectrode insertion	4	12	
Stimulation parameters at 5 years			
Amplitude (V)	2.48 ± 0.77	1.83 ± 0.77	**0.004***
Pulse width (μs)	98.75 ± 36.99	76.36 ± 15.29	**0.005***
Frequency (Hz)	120.83 ± 2.82	120.48 ± 2.18	0.564
Coordinates of active contacts relative to AC-PC plane			
AC-PC distance (mm)	25.87 ± 1.31	25.19 ± 1.62	0.463
Right x-coordinates	10.92 ± 1.45	10.04 ± 0.87	
Left x-coordinates	10.54 ± 1.53	10.62 ± 1.05	
Right y-coordinates	−7.32 ± 1.84	−7.37 ± 1.37	
Left y-coordinates	−7.62 ± 1.18	−7.71 ± 1.56	
Right z-coordinates	−4.05 ± 0.74	−3.99 ± 0.57	
Left z-coordinates	−3.91 ± 0.62	−3.80 ± 0.57	
Mean distance of centre of active contact from DRTT-core (mm)	1.72 ± 0.45	1.21 ± 0.31	< **0.001***

The coordinates are relative to the mid-commissural point. Statistically significant results are denoted in bold with an asterisk*.

3.3.5. Group B active contacts are closer to the centre of the DRTT compared to Group A contacts

Tremor control in all cases was achieved with only monopolar stimulation. Table 5 summarises the mean coordinates of the active contacts. In Group A, the target for DBS lead placement was the white matter just lateral to the equator of the red nucleus as this was the presumed location of the DRTT. In our patients, tractography confirmed that a portion of the DRTT always passed through this area (data not shown). However, the centre of the DRTT (DRTT-core) could be slightly more posterior, medial or anterior and may differ on either side even in the same patient. There was more variation in the distance between the contact and the DRTT-core in Group A (Fig. 2C). The average distance between the contact and the DRTT-core was 1.72 ± 0.45 mm and eight out of 24 contacts (33%) were located more than 2 mm from the DRTT-core.

The DRTT-core was the target in Group B patients. The mean distance between the contact and DRTT-core was 1.21 ± 0.31 mm which was significantly lower than that of Group A ($p < 0.001$). All Group B active contacts were located within 2 mm of the DRTT-core (Fig. 2C).

4. Discussion

The DRTT is largest and most extensively studied component of the cerebellothalamic tract [18,21,22]. Fibres from the cerebellar dentate nuclei ascend through the superior cerebellar peduncle into the caudal mesencephalon where the majority decussate to reach the contralateral red nucleus and caudal thalamus. A smaller, non-decussating DRTT continues to the ipsilateral red nucleus and thalamus before terminating. The ascending DRTT fibres must pass through the relatively narrow posterior subthalamic area before fanning out and ending in the caudal thalamus. The close proximity of DRTT fibres in the PSA makes it a good target for surgical intervention and excellent tremor control has been reported after DBS or lesioning in this area [11–15,25–28].

4.1. Given that PSA-DBS is already so effective in controlling tremor, is there any clinical justification in making the procedure more complex by directly targeting the DRTT?

This was the main objective of our study. Group A leads were inserted using Blomstedt's technique [5] which assumes that the fibre tracts involved in tremor control was fixed in its location hence could be targeted using conventional landmarks on MRI scans. However, our results and that of others [23] show that there is actually slight variation in the position of the DRTT between individuals and even between sides. This leads to differences in the distance between the active DBS contact and the DRTT-core. This difference is smallest when DTIT is used to guide lead implantation into the DRTT. In this study, all Group B contacts and only two-thirds of Group A contacts were within a 2 mm radius of the DRTT-core. The area occupied by the PSA is small and all leads were either in contact with a portion of the DRTT which probably explains why tremor was less postoperatively in both groups. However the slightly better placement of Group B leads relative to the DRTT-core resulted in superior short and long term tremor control, patient-rated quality of life scores, fewer test macroelectrode passes, lower stimulation amplitudes and pulse widths and fewer problems with speech and dysequilibrium compared to patients who underwent lead implantation using conventional methods (Group A).

4.2. Is there evidence to support the hypothesis that the cerebellothalamic tract (especially the DRTT) plays a major role in the generation and modulation of tremor?

Although there is a wealth of studies providing indirect evidence that the CBTT (especially the DRTT) is important in tremorgenesis, direct evidence is limited to three clinical studies [13–15] with no more than 20 patients and review periods under 2-years. Our study provides direct evidence of the importance of the DRTT in tremorgenesis and shows that directly targeting the DRTT results in stable long-term tremor control.

The cerebellothalamic tract (especially the DRTT) is a hypothesised 'superhighway' connecting centres responsible for the generation and control for tremor regardless of aetiology. For this hypothesis to be correct, tremor control should be the same if the DRTT was targeted in patients with ET or TDPD. This was indeed the case. Our results, together with reports that PSA-DBS has been successfully used to control tremor in other neurological conditions such as multiples sclerosis [4], dystonia [11], Wilson's disease [24] and Ehlers–Danlos Syndrome (own case- unpublished) lends credence to this hypothesis.

PSA-DBS was very effective in controlling resting and postural arm tremor but targeting the DRTT did not convey any additional advantage. However, intention tremor was significantly better controlled when the DRTT was targeted. The reason for this is unclear. The threshold for inhibiting the neural networks controlling resting and postural tremor may be lower than that of intention tremor hence such types of tremor are more easily suppressed. Alternatively, the mechanisms by which resting and intention tremors differ [25] with the DRTT playing a major role mainly in the latter.

PSA-DBS was very effective in controlling leg and axial tremor. Although the mean axial tremor scores following bilateral lead implantation were lower than after unilateral procedures, the difference was not significant whether or not lead implantation was DTIT-guided. Our numbers were too small to allow us to determine if there was a difference in results between unilateral procedures on the left or right sides of the brain. However, we confirmed that unilateral lead implantation had bilateral effects which lends support to the existence of a non-decussating DRTT [21].

We found strong correlation between tremor control and the position of the active contact along the *z*-axis. Active contacts associated with best tremor control in our study were more caudal than that reported by others [26–29]. However other authors noted similar findings to ours [27–29]. This is perhaps not surprising given that the DRTT decussates through an area extending from the pontomesencephalic to the subthalamic region [21,22].

4.3. PSA-DBS is very effective in controlling tremor in TDPD but can its use in PD patients be justified as PD is a progressive disorder?

Our study purposely made a distinction between patients with TDPD and PD patients with tremor as one of the motor symptoms. TDPD is a unique phenotype of idiopathic PD characterised by moderately severe asymmetric limb tremor with mild and very slow progression of the other non-tremor motor symptoms [30]. The cZI and RaPRL are part of the DRTT whereas the Vim and STN are very close to it. It is therefore not surprising that all stimulation of these targets have been previously used to control PD-tremor [30–32]. Velasco [31] and Blomstedt [32] have also shown that stimulation of the RaPRL and cZI not only decreases tremor but also rigidity and bradykinesia in PD. Indeed, the "cZI" target used by Blomstedt [32] is identical to ours.

None of our TDPD patients exhibited significant progression of non-tremor motor symptoms during the study. Although not part of this study, we noted that UPDRS-III scores improved after surgery due to the very significant tremor reduction but also from moderate improvements in the rigidity and bradykinesia. With the exception of tremor scores, the decrease in rigidity and bradykinesia scores between Group A and B patients were not statistically significant. We do not consider PSA-DBS a contraindication in TDPD patients.

4.4. Limitations and strengths of the study

A limitation was that we used deterministic rather than probabilistic tractography. The latter has been shown to have greater sensitivity and accuracy in delineating fibre tracts [33]. Additionally, there were concerns as to whether fibre tracts shown on tractography are accurate representations of the 'real' tracts in vivo [34]. Coenen et al. has now have provided electrophysiological evidence of concordance between tracts seen on deterministic tractography and 'real' fibre bundles [35]. This has also been our experience. The main difference between our work and Coenen's was that his images were acquired with a 3T-MR scanner and he had more sophisticated tractography software. These were not available to us when this project started in 2009. We had difficulty imaging crossing fibres and small tracts and used long scanning times which increased the probability of movement artefacts, bias in the assessment of fibre orientation and fusion errors. Nevertheless we have shown that with great care, these errors could be minimised and that good results following DTIT-guided lead implantation can be achieved even with 1.5T-MRI scanning. The DRTT being a large and relatively straight fibre bundle and that the PSA was relatively confined made targeting the DRTT easier. However we would be hesitant in performing this procedure in fully anaesthetised patients given the technical challenges described.

We used the PDQ-39 rather than the QUEST questionnaire to assess quality of life after surgery as almost half of our patients had TDPD.

Although QUEST is a more sensitive instrument it has never been used to assess the tremor of Parkinson's disease unlike the PDQ-39 which has been used on both ET and PD patients [19,20]. Differences between questionnaires were reduced as many questions were shared.

Finally, the inclusion of more patients and more participating centres will result in better and more generalisable data. That being said, there are very few prospective studies on tremor containing as many participants as ours let alone a double-blind, randomised study over 5-years. By way of comparison, a recent randomised, double-blind study comparing tremor control in Vim-DBS with PSA-DBS only had 13 patients with a follow-up of 1-year [26]. This study should hopefully act as a spring-board to larger multi-centre collaborations with longer follow-ups.

5. Conclusion

The DRTT is an important component in tremorgenesis and is the likely stimulation substrate during PSA-DBS. Due to slight inter-individual variation in the location of the DRTT, the placement of leads in the conventional manner may not always yield optimal results. DTIT-guidance allows more consistent and accurate lead placement during PSA-DBS which in turn results in better and more stable long-term tremor control.

Funding source

None.

Disclosures and declarations of interest

None.

Authors' roles

HLL was responsible for the overall conception of the study, writing, acquisition and analysis of data and revision of the manuscript for intellectual content. MNMI was involved in the writing, statistical analysis and revision of the manuscript. AT, JD, CF and AM were involved in data acquisition, analysis and revision of the manuscript.

Acknowledgement

We thank Sr J Foley for her help in completing this article.

References

[1] J.K. Wong, J.H. Cauraugh, K.W.D. Ho, M. Broderick, A. Ramirez-Zamora, L. Almeida, A. Wagle Shukla, C.A. Wilson, R.M. de Bie, F.M. Weaver, N. Kang, Okun. STN vs. GPi deep brain stimulation for tremor suppression in Parkinson disease: A systematic review and meta-analysis, Parkinsonism Relat. Disord. 58 (2019) 56–62, https://doi.org/10.1016/j.parkreldis.2018.08.017.

[2] G. Castro, J.D. Carrillo-Ruiz, V. Salcido, J. Soto, G. García-Gomar, A.L. Velasco, F. Velasco, Optimizing prelemniscal radiations as a target for motor symptoms in Parkinson's Disease treatment, Stereotact. Funct. Neurosurg. 93 (2015) 282–291, https://doi.org/10.1159/000433446.

[3] P. Plaha, N.K. Patel, S.S. Gill, Bilateral stimulation of the caudal zona incerta nucleus for tremor control, J. Neurol. Neurosurg. Psychiatry 79 (2008) 504–513, https://doi.org/10.1136/jnnp.2006.112334.

[4] S.F. Oliveria, R.L. Rodriguez, D. Bowers, D. Kantor, J.D. Hiliard, E.H. Monari, B.M. Scott, M.S. Okun, K.D. Foote, Safety and efficacy of dual-lead thalamic deep brain stimulation for patients with treatment-refractory multiple sclerosis tremor: a single-centre, randomised, single-blind, pilot trial, Lancet Neurol. 16 (2017) 691–700, https://doi.org/10.1016/S1474-4422(17)30166-7.

[5] P. Blomstedt, A. Fytagoridis, S. Tisch, Deep brain stimulation of the posterior subthalamic area in the treatment of tremor, Acta Neurochir. (Wien). 151 (2009) 31–36, https://doi.org/10.1007/s00701-008-0163-7.

[6] P. Blomstedt, U. Sandvik, S. Tisch, Deep brain stimulation in the posterior subthalamic area in the treatment of essential tremor, Mov. Disord. 25 (2010) 1350–1356, https://doi.org/10.1002/mds.22758.

[7] M.N. Gallay, D. Jeanmonod, J. Liu, A. Morel, Human pallidothalamic and cerebellothalamic tracts: anatomical basis for functional stereoctactic neurosurgery, Brain Struc. Funct. 212 (2008) 443–463, https://doi.org/10.1007/s00429-007-0170-0.

[8] V.A. Coenen, B. Mädler, H. Schiffbauer, H. Urbach, N. Allert, 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 68 (2011) 1069–1076, https://doi.org/10.1227/NEU.0b013e31820a1a20.

[9] M. Marek, S. Paus, N. Albert, B. Mädler, T. Klockgether, H. Urbach, V.A. Coenen, Ataxia and tremor due to lesions involving cerebellar projection pathways: a DTI tractographic study in six patients, J. Neurol. 262 (2012) 54–58, https://doi.org/10.1007/s00415-014-7503-8.

[10] S.H. Jang, H.G. Kwon, Aggravation of an injured dentato-rubro-thalamic tract in a patient with mild traumatic brain injury: a case report, Medicine 96 (2017) e8253, https://doi.org/10.1097/md.0000000000008253.

[11] V.A. Coenen, N. Albert, S. Paus, M. Kronenbürger, H. Urbach, B. Mädler, Modulation of the cerebello-thalamo-cortical network in thalamic deep brain stimulation for tremor: a diffusion tensor imaging study, Neurosurgery 75 (2014) 657–670, https://doi.org/10.1227/NEU.0000000000000540.

[12] F. Velasco, M. Esqueda- Liquidano, A.L. Velasco, M.G. García-Gomar, Prelemniscal lesion for selective improvement of Parkinson disease tremor, Stereotact. Funct. Neurosurg. 96 (2018) 54–59, https://doi.org/10.1159/000486318.

[13] V.A. Coenen, N. Albert, B. Mädler, A role of diffusion tensor imaging fiber tracking in deep brain stimulation surgery: DBS of the dentato-rubro-thalamic tract (drt) for the treatment of therapy-refractory tremor, Acta Neurochir. (Wien). 158 (2011) 1579–1585, https://doi.org/10.1007/s00701-011-1036-z.

[14] A. Fenoy, M. Schiess, Deep brain stimulation of the dentato-rubro-thalamic tract: outcomes of direct targeting for tremor, Neuromodulation 20 (2017) 429–436, https://doi.org/10.1111/ner.12585.

[15] J.L. Chazen, H. Sarva, P.E. Stieg, R.J. Min, D.J. Ballon, K.O. Pryor, P.M. Riegelhaupt, M.G. Kaplitt, Clinical improvement associated with targeted interruption of the cerebellothalamic tract following MR-guided focused ultrasound for essential tremor, J. Neurosurg. 129 (2018) 315–323, https://doi.org/10.3171/2017.4.JNS162803.

[16] A.S. Khatter, M.C. Kurth, M.A. Brewer, C.T. Crinnian, J.F. Drazkowski, S.S. Flitman, S. Imke, S.A. Spector, K.L. Wood, A.N. Lieberman, Prevalence of tremor and Parkinson's disease, Parkinsonism Relat. Disord. 2 (1996) 205–208, https://doi.org/10.1016/s1353-8020(96)00027-2.

[17] R.P. Mumhoz, M. Picillo, S.H. Fox, V. Bruno, M. Panisset, C.R. Honey, A. Fasano, Eligibility criteria for deep brain stimulation in Parkinson's Disease, tremor and dystonia, Can J. Neurol Sci. 43 (04) (2016) 462–471, https://doi.org/10.1017/cjn.2016.35.

[18] H.G. Kwon, J.H. Hong, C.P. Hong, D.H. Lee, S.H. Ahn, S.H. Jang, Dentatorubrothalamic tract in human brain: diffusion tensor tractography study, Neuroradiology 53 (2011) 787–791, https://doi.org/10.1007/s00234-011-0878-7.

[19] J.A. Fields, A.I. Tröster, S.P. Woods, C.I. Higginson, S.B. Wilkinson, K.E. Lyons, W.C. Koller, R. Pahwa, Neuropsychological and quality of life outcomes 12 months after unilateral thalamic stimulation for essential tremor, J. Neurol Neurosurg. Psychiatry. 74 (2003) 305–311, https://doi.org/10.1136/jnnp.74.3.305.

[20] J.M. Nazaaro, R. Pahwa, K.E. Lyons, Long-term benefits in quality of life after unilateral thalamic deep brain stimulation for essential tremor, J. Neurosurg. 117 (2012) 156–161, https://doi.org/10.3171/2012.3.JNS112316.

[21] A. Meola, A. Comert, F.C. Yeh, S. Sivakanthan, J.C. Fernandez-Miranda, The non-decussating pathway of the dentatorubrothalamic tract in humans: human connectome-based tractographic study and microdissection validation, J. Neurosurg. 124 (2016) 1406–1412, https://doi.org/10.3171/2015.4.JNS142741.

[22] S.T. Sakai, K. Patton, Distribution of cerebellothalamic and nigrothalamic projections in the dog: a double anterograde tracing study, J. Comp. Neurol. 330 (1993) 193–194, https://doi.org/10.1002/cne.903300204.

[23] C. Listik, N. Santiago, P.R. Reis, F. Godinho, K. Duarte, M.J. Teixeira, E.R. Barbosa, R.G. Cury, Targeting the hot spot in a patient with essential tremor and Parkinson's disease: tractography matters, ClinNeurolNeurosurg. 174 (2018) 230–232, https://doi.org/10.1016/j.clineuro.2018.09.037.

[24] H.L. Low, S.K. Alexander, A. Misbahuddin, G.T. Gillett, Posterior subthalamic area deep brain stimulation for treatment of tremor and dystonia in Wilson's disease, Brain Stimul. (2019), https://doi.org/10.1016/j.brs.2019.05.014.

[25] R.C. Heimlich, M. Hallett, G. Deuschl, I. Toni, B.R. Bloem, Cerebral causes and consequences of parkinsonian resting tremor: a tale of two circuits? Brain 135 (2012) 3206–3226, https://doi.org/10.1093/brain/aws023.

[26] M.T. Barbe, P. Reker, S. Hamacher, J. Franklin, D. Kraus, T.A. Dembek, J. Becker, J.K. Steffen, N. Allert, J. Wirths, H.S. Dafsari, J. Voges, G.R. Fink, V. Visser-Vandewalle, L. Timmermann, DBS of the PSA and the Vim in essential tremor, Neurology 91 (2018), https://doi.org/10.1212/wnl.0000000000005956 e543-e550.

[27] A. Ramirez-Zamora, H. Smith, V. Kumar, J. Prusik, S. Phookan, J.G. Pilitsis, Evolving concepts in posterior subthalamic area deep brain stimulation for treatment of tremor: surgical neuroanatomy and practical considerations, Stereotact. Funct. Neurosurg. 94 (2016) 283–297, https://doi.org/10.1159/000449007.

[28] J.A.H. Holslag, N. Neef, M. Beudel, G. Drost, D.L.M. Oterdoom, N.I. Kremer, T. van Laar, J.M.C. van Dijk, Deep brain stimulation for essential tremor: a comparison of targets, World Neurosurg. 110 (2018), https://doi.org/10.1016/j.wneu.2017.11.064 e580-e584.

[29] T. Xie, J. Bernard, P. Warnke, Post subthalamic area deep brain stimulation for tremors: a mini-review, Transl. Neurodegener. 1 (2012) 20, https://doi.org/10.1186/2047-9158-1-20.

[30] W. Deeb, W. Hu, L. Almeida, A. Patterson, D. Martinez-Ramirez, A.W. Shukla, Benign tremulous Parkinsonism: a unique entity or a facet of Parkinson's disease?

Translational. Neurodegen. 5 (2016) 1, https://doi.org/10.1186/s40035-016-0057-1.

[31] F. Velasco, F. Jiménez, M.L. Pérez, J.D. Carrillo-Ruiz, A.L. Velasco, J. Ceballos, M. Velasco, Electrical stimulation of the prelemniscal radiation in the treatment of Parkinson's disease: an old target revised with new techniques, Neurosurgery 49 (2) (2001) 293–306, https://doi.org/10.1097/00006123-200108000-00009.

[32] P. Blomstedt, R.S. Persson, G. Hariz, J. Linder, A. Fredricks, B. Häggström, J. Philipsson, L. Forsgren, M. Hariz, Deep brain stimulation in the caudal zona incerta versus best medical treatment in patients with Parkinson's disease: a randomised blinded evaluation, J. Neurol. Neurosurg. Psychiatry 89 (7) (2018) 710–716, https://doi.org/10.1136/jnnp-2017-317219.

[33] M. Bucci, M.L. Mandelli, J.I. Berman, B. Amirbekian, C. Nguyen, M.S. Berger, R.G. Henry, Quatifying diffusion MRI tractography of the corticospinal tract in brain tumours with deterministic and probabilistic methods, Neuroimage Clin. 3 (2013) 361–368, https://doi.org/10.1016/j.nicl.2013.08.008.

[34] N. Said, W.J. Elias, P. Raghan, A. Cupino, N. Tutison, R. Frysinger, J. Patrie, W. Xin, M. Wintermark, Correlation of diffusion tensor tractography and intraoperative macrostimulation during deep brain stimulation for Parkinson disease, J. Neurosurg. 121 (2014) 929–995, https://doi.org/10.3171/2014.6.JNS131673.

[35] V.A. Coenen, C. Jenkner, C.R. Honey, B. Mädler, Electrophysiologic validation of diffusion tensor imaging tractography during deep brain stimulation surgery, AJNR Am. J. Neuroradiol. 37 (2016) 1378–1470, https://doi.org/10.3174/ajnr.A4753.