Parkinsonism and Related Disorders 60 (2019) 126–132

Contents lists available at ScienceDirect

Parkinsonism and Related Disorders

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

Benefits and risks of unilateral and bilateral ventral intermediate nucleus deep brain stimulation for axial essential tremor symptoms

Kyle T. Mitchell[a,*], Paul Larson[b], Philip A. Starr[b], Michael S. Okun[c], Robert E. Wharen Jr.[d], Ryan J. Uitti[o], Barton L. Guthrie[e], DeLea Peichel[f], Rajesh Pahwa[g], Harrison C. Walker[p], Kelly Foote[q], Frederick J. Marshall[h], Joseph Jankovic[i], Richard Simpson[j], Fenna Phibbs[k], Joseph S. Neimat[l], R. Malcolm Stewart[m], Khashayar Dashtipour[n], Jill L. Ostrem[r]

[a] Department of Neurology, University of California San Francisco and the San Francisco Veteran's Affairs Medical Center, 1635 Divisadero Street, 5th Floor, Suite 520, San Francisco, CA 94115, USA
[b] Department of Neurological Surgery, University of California San Francisco and the San Francisco Veteran's Affairs Medical Center, 1635 Divisadero Street, 5th Floor, Suite 520-530, San Francisco, CA, 94115, USA
[c] Departments of Neurology and Neurosurgery, University of Florida Fixel Center for Neurological Diseases and the Movement Disorders and Neurorestoration Program, 3450 Hull Road, 4th Floor, Gainesville, FL, 32607, USA
[d] Department of Neurosurgery, Mayo Clinic, 4500 San Pablo Road, Jacksonville, FL, 32224, USA
[e] Department of Neurosurgery, University of Alabama Birmingham, School of Medicine, 510 20th Avenue South, FOT 1038, Birmingham, AL, 35234, USA
[f] Abbott, Clinical Research Department, 6901 Preston Road, Plano, TX, 75024, USA
[g] Department of Neurology, University of Kansas Medical Center, Parkinson's Disease and Movement Disorder Center, 3599 Rainbow Blvd, Mailstop 2012, Kansas City, KS, 66160, USA
[h] Department of Neurology, University of Rochester, 919 Westfall Rd., Bldg C, Suite 220, Rochester, NY, 14618, USA
[i] Department of Neurology, Baylor College of Medicine, Parkinson's Disease Center and Movement Disorders Clinic, 7200 Cambridge, Suite 9A, Houston, TX, 77030, USA
[j] Department of Neurosurgery, The Methodist Hospital Physician Organization, 6560 Fannin, Suite 944, Houston, TX, 77030, USA
[k] Department of Neurology, Vanderbilt University, A-0118 Medical Center North, Nashville, TN, 37232-2551, USA
[l] Department of Neurosurgery, Louisville Neuroscience, USA
[m] Department of Neurology, Institute of Bioinformatics and Computational Biology, Tandy School of Computer Science, The University of Tulsa, 800 South Tucker Drive, Tulsa, OK, 74194-9700, USA
[n] Department of Neurology, Loma Linda University Health System, 11370 Anderson St, Suite B-100, Loma Linda, CA, 92354, USA
[o] Department of Neurology, Mayo Clinic, 4500 San Pablo Road, Jacksonville, FL 32224, USA
[p] Department of Neurology, University of Alabama Birmingham, School of Medicine, 510 20th Avenue South, FOT 1038 Birmingham, AL 35234, USA
[q] Department of Neurosurgery, University of Florida Fixel Center for Neurological Diseases and the Movement Disorders and Neurorestoration Program, 3450 Hull Road, 4th Floor, Gainesville, FL 32607, USA
[r] Department of Neurology, University of California San Francisco, 1635 Divisadero Street, 5th Floor, Suite 520-530, San Francisco, CA 94115, USA

ARTICLE INFO

Keywords:
Axial tremor
Midline tremor
Essential tremor
Deep brain stimulation
Thalamic DBS
Unilateral
Clinical outcomes

ABSTRACT

Introduction: Many experts assume bilateral deep brain stimulation (DBS) is necessary to improve axial tremor in essential tremor (ET). In the largest clinical trial of DBS for ET to date evaluating a non-directional, constant current device, we studied the effects of unilateral and staged bilateral DBS on axial tremor.

Methods: We included all participants from the original trial with unilateral ventral intermediate nucleus (VIM) DBS and 90-day follow up at minimum. Primary outcomes were changes in pooled axial subscores in the Clinical Rating Scale for Tremor (CRST) at 90 and 180 days after activation of unilateral VIM DBS compared to pre-operative baseline (n = 119). Additionally, we performed within-subject analyses for unilateral versus bilateral DBS at 180 days in the cohort who underwent staged surgery to bilateral DBS (n = 39).

Results: Unilateral VIM DBS improved midline tremor by 58% at 90 days (median[IQR]) (3[3] to 1[2], $p < 0.001$) and 65% at 180 days (3[3] to 1[2], $p < 0.001$) versus pre-op baseline. In the staged to bilateral DBS cohort, midline tremor scores further improved after bilateral DBS at 180 days by 63% versus unilateral DBS

* Corresponding author. Duke University Movement Disorders Center, DUMC 3333, 932 Morreene Rd Durham, NC, 27705, USA.
E-mail addresses: kyle.mitchell@duke.edu (K.T. Mitchell), paul.larson@ucsf.edu (P. Larson), philip.starr@ucsf.edu (P.A. Starr), okun@neurology.ufl.edu (M.S. Okun), wharen.robert@mayo.edu (R.E. Wharen), Uitti.ryan@mayo.edu (R.J. Uitti), bguthrie@uabmc.edu (B.L. Guthrie), deleapeichel@yahoo.com (D. Peichel), RPAHWA@kumc.edu (R. Pahwa), hcwalker@uabmc.edu (H.C. Walker), foote@neurosurgery.ufl.edu (K. Foote), Frederick_marshall@urmc.rochester.edu (F.J. Marshall), josephj@bcm.edu (J. Jankovic), RSimpson@houstonmethodist.org (R. Simpson), fenna.phibbs@Vanderbilt.edu (F. Phibbs), joseph.neimat@louisvilleneuroscience.com (J.S. Neimat), stewart4765@sbcglobal.net (R.M. Stewart), KDashtipour@llu.edu (K. Dashtipour), jill.ostrem@ucsf.edu (J.L. Ostrem).

https://doi.org/10.1016/j.parkreldis.2018.09.004
Received 12 June 2018; Received in revised form 9 August 2018; Accepted 4 September 2018

Table 1
Prior studies of unilateral DBS and midline tremor.

Study by First Author	Axial Tremor Studied	N with unilateral outcomes	Follow up	Contralateral arm tremor (mean CRST or % improvement unless noted, all improvement significant)	Axial results (mean CRST or % improvement unless noted, statistically significant unless specified)
Carpenter (1998)	Voice	5	Not specified	33–75% improvement	1 of 2 bilateral improved, 2 of 5 unilateral improved to a lesser degree
Ondo (1998)	Head and voice	14	3 months	82% improvement	No improvement voice tremor, 55% non-significant (NS) trend in head tremor
Koller (1999)	Head	38	3,6,12 months	Total CRST 26→16 at 1 year	75% of participants had improved head tremor at 1 year
Limousin (1999)	Head and voice	26	3 and 12 months	Essential Tremor Rating Scale (ETRS) Items 1-9 19.21→8.65 at 1 year	NS in unilateral, ETRS 2.22→0.44 at 3 months in bilateral (only significant timepoint)
Obwegeser (2000)	Head, voice, tongue, face, and trunk	27	3 months after unilateral, 12 months after bilateral	6.7→1.2	7.3→3.7 unilateral pooled axial tremor. All individual axial subscores improved 7.3→1.8 Bilateral pooled axial tremor.
Ondo (2001a)	Head	41	3 months	7.7→2.9	Head 1.9→1.3
Ondo (2001b)	Head	11 (staged to bilateral from Ondo 2001a)	3 months	6.8→2.2	Head 2.0→1.4 (first side, NS) →0.7 (second side, sig.)
Sydow (2003)	Head and voice	14	1 and 6 years	3.4→1.0 at 1 year, 1.7 at 6 years	NS in unilateral, 1.9→0.3 in head tremor in bilateral (sig only at 6 years, NS for voice)
Putzke (2004)	Pooled axial tremor	29	1 and 3 months	6.9→0.9 at 3 years	4.1→1.2 at 3 months
Putzke (2005)	Head, voice, tongue, face, and trunk	22 (staged to bilateral from Putzke 2004)	1 and 3 months	Not studied	**Baseline→Unilateral 3 mos→Bilateral 3 mos** Head: 2.1→1.2→0.2 Face: 0.7→0.3→0.0 Voice: 1.7→1.1→0.3 Tongue: 0.9→0.3→0.0, Trunk: NS
Mandat (2011)	Head	6	3 months	79%	3 of 6 unilateral and 6 of 8 bilateral had 1 point head subitem improvement
Moscovich (2013)	Head	23	6 and 12 months	Not studied	2.2 point improvement for both unilateral and bilateral

(3[3] to 1[3], p = 0.007). There were, however, 35 additional DBS and surgery-related adverse events, 14 related to incoordination, gait impairment, or speech impairment, versus 6 after unilateral DBS.
Conclusion: Unilateral VIM DBS for ET significantly improved associated axial tremor. Staged bilateral DBS was associated with additional axial tremor improvement but also additional adverse events. Unilateral VIM DBS may be sufficient to achieve a goal of contralateral limb and axial tremor attenuation.

1. Introduction

High frequency (> 100 Hz) deep brain stimulation (DBS) of the ventral intermediate nucleus (VIM) of the thalamus is an effective therapy for medication refractory essential tremor (ET) [1]. Chronic thalamic DBS typically provides a robust improvement in contralateral limb tremor [2–5]. The efficacy of unilateral thalamic DBS for disabling midline symptoms of head, voice, face, tongue, and trunk tremor remains controversial. While some small studies revealed no significant improvement in axial tremor [4,6–8], others, including the largest unilateral VIM DBS published cohort (n = 41), have demonstrated modest improvement with unilateral DBS. This improvement was inferior to bilateral DBS (Table 1) [3,9–13]. One small retrospective study revealed similar head tremor improvement when comparing unilateral and bilateral DBS [14].

Although ET typically presents with bilateral symptoms including midline tremor, not all ET patients will require bilateral surgery to have meaningful tremor control (i.e. dominant hand improvement may be enough). Bilateral VIM DBS is more invasive than unilateral surgery, so defining potential incremental benefits and risks is important. A five year follow-up study reported 63% (dysarthria), 38% (incoordination), and 25% (abnormal gait) adverse event rates in patients with bilateral thalamic DBS compared to 17%, 17%, and 0% in a unilateral cohort [15]. In one study, 25% patients who proceeded from unilateral to bilateral thalamic DBS developed new onset dysarthria [11]. The decision to add a second, contralateral lead is often driven by ipsilateral refractory arm tremor, but in many patients, axial tremor symptoms can also be bothersome and contribute to disability [16]. A better understanding of benefits and risks of unilateral versus bilateral VIM DBS for ET with axial tremor can help guide clinical decision-making and patient counseling. We hypothesize that unilateral VIM DBS alone will have a significant benefit on axial tremor with a lower risk of the side effects associated with bilateral DBS.

A recent large prospective controlled study of VIM DBS for ET using non-directional leads [17] focused on upper extremity tremor improvement. Here, we performed post-hoc analyses to better understand the impact of unilateral VIM DBS on axial tremor and adverse events. We systematically evaluated the effects of isolated unilateral DBS on axial tremor as well as potential predictors of axial tremor improvement. We further examined outcomes following a contralateral VIM implant in a subset of patients who elected to undergo staged bilateral DBS to treat residual tremor.

2. Methods

Detailed methods of the original 12 center prospective, controlled trial were previously published [17]. At the beginning of the trial, all participants underwent unilateral VIM thalamus DBS surgery with an option for second sided surgery a minimum of 6 months later pending response and patient preference. As the study progressed, there was an amendment to the protocol allowing patients to have bilateral simultaneous implants upfront (for purposes of this sub study, these patients were excluded from the analysis; N = 8). Implantation of the Libra DBS system (St. Jude Medical/Abbott Neuromodulation Division, Plano, TX, USA) was performed according to the standard surgical procedures at each center. Participants were evaluated at baseline, post-operative day 90 (± 14 days) and day 180 (± 14 days) (primary outcome time point). A day 365 (± 30 days) unilateral DBS follow-up evaluation was also performed if the patient did not elect to have a contralateral VIM lead placed. If a second lead was placed, additional evaluations occurred at day 180 (± 14 days) and day 365 (± 30 days) after the second sided implant. Study visits included Fahn and Tolosa Clinical Rating Scale for Tremor (CRST) in both the off- and on-DBS states, documentation of DBS programming parameters, and assessment for adverse events. Participants arrived at each visit with DBS switched "off" for 4 h prior to each visit. On-DBS CRST was performed after DBS was switched back "on" for approximately 10 min. Patients were programmed by expert clinicians using standard troubleshooting strategies to minimize stimulation-induced side effects and maximize efficacy as part of standard clinical care.

We measured effects of unilateral DBS on axial tremor in all participants. Primary outcome measures were change in on-DBS pooled CRST axial tremor subscores at 90 and 180 days compared to baseline and the off-DBS condition. Axial tremor subscores include CRST Part A Items 1–4 and 7, all postural tremor only except voice (action tremor). Secondary outcomes included changes in individual midline CRST subscores of head, face, tongue, voice, and trunk tremor.

The subgroup of participants who later underwent second sided surgery (all had 180 days follow up visits after unilateral DBS) was analyzed using a within-group comparison of unilateral versus bilateral thalamic DBS. Primary outcomes were change in pooled CRST axial tremor subscores 180 days after second sided DBS placement compared to 180 days after unilateral DBS placement. We also compared change in CRST axial tremor scores from baseline to the off-DBS state at each timepoint. Adverse events after unilateral and bilateral DBS placement in the staged cohort at 180 days were collected and compared.

We repeated the above primary analyses excluding participants with no axial tremor at baseline (pooled axial CRST score of 0) to assess for potential dilution effects altering any observed data trends.

To evaluate for selection bias based on axial tremor influencing those subjects who ultimately received bilateral DBS, baseline pooled CRST axial tremor subscores were compared between the unilateral-only DBS and the staged bilateral DBS cohorts. We also compared percent improvement of midline tremor after 180 days of unilateral DBS between the two cohorts.

To identify potential predictors of improvement in midline tremor after unilateral DBS, we measured the percent improvement of pooled CRST axial tremor subscores at 90 days and 180 days after unilateral DBS compared to baseline for the following: gender, dominant handedness, hemisphere of lead placement, baseline overall tremor severity (based on total CRST score), disease duration, age at surgery, and degree of tremor asymmetry (difference of pooled arm rest, action, and postural tremor scores between sides).

The study was approved by the United States Food and Drug Administration (FDA), and registered with clinicaltrials.gov (NCT02087046). All sites received Institutional Review Board approval prior to consenting patients. Written informed consent was obtained prior to study procedures and device implantation.

Abbott (formerly St Jude Medical) was the sponsor of the original trial [17]. This current substudy was conducted with in collaboration with Abbott. Abbott provided the raw clinical data but analysis, interpretation, funding, and manuscript preparation were conducted by the investigators independent of Abbott.

2.1. Data collection and statistical analysis

Each individual center entered data into a combined electronic database with automated data checks for expected value ranges and audit trails for any manual changes to the data.

Baseline demographics of age, gender, race, disease duration, disease severity, dominant handedness, and hemisphere of first implant for the two cohorts were tabulated.

Two-tailed Wilcoxon Rank sum tests for non-parametric data were performed for CRST comparisons within cohorts at 90, 180, and 365 days including all primary outcomes with significance at $p < 0.01$ as this was a post-hoc analysis. Two-tailed Mann Whitney U tests were performed for comparisons of baseline axial tremor severity and percent improvement at 180 days of unilateral DBS between the unilateral-only and eventual bilateral DBS cohorts with significance also at $p < 0.01$.

Two-tailed Mann Whitney U tests were also performed to evaluate potential predictive factors for percent pooled axial tremor improvement for gender, dominant handedness, hemisphere of lead placement, baseline overall tremor severity, and degree of tremor asymmetry with significance at $p < 0.01$ to adjust for multiple comparisons. Regression analyses were performed to evaluate age at surgery and disease duration as potential predictive factors.

3. Results

Baseline characteristics of age, gender, race, disease duration, disease severity, dominant handedness, and target limb are provided in Table 2. Follow-up was high for participants with unilateral DBS (95.8% at day 90; 93.3% at day 180). In the bilateral staged cohort, all 39 patients (100%) followed up at 180 days after unilateral DBS placement, and 89.7% followed up at 180 days after the second sided surgery. The mean time between initial and second-sided surgery in the staged cohort was 309 days (range 161–918 days).

The primary outcome was met with pooled midline CRST scores, which significantly improved after unilateral DBS at 90 days (median [IQR]) (3 [3] to 1 [2], 58% mean improvement, $p < 0.001$) and 180 days (3 [3] to 1 [2], 65% improvement, $p < 0.001$) (Fig. 1). The subgroup of patients who remained with unilateral DBS at 365 days ($n = 80$) demonstrated continued improvement in midline CRST compared to baseline (3 [3] to 1 [2], 64% improvement, $p < 0.001$) and no difference compared to outcomes at 180 days (1 [2] vs 1 [2], $p = 0.886$). The off-DBS state also improved in midline CRST comparisons at 90 days (3 [3] to 2 [3], 30.6% improvement, $p < 0.001$) and 180 days (3 [3] to 2 [4], 25.6% improvement, $p < 0.001$) compared to baseline (Fig. 1).

After unilateral DBS, most individual CRST axial tremor subscores improved at 180 days, although median baseline values were already low (face (median[IQR] (0[0] to 0[0], 73.9% improvement, $p = 0.001$), tongue (0 [1] to 0[0], 70.8% improvement, $p < 0.001$), voice (1 [2] to 0 [1], 58.3% improvement, $p < 0.001$), and head tremor (1 [2] to 0 [1], 65.2% improvement, $p < 0.001$)) with a non-significant trend toward improvement in trunk tremor (0[0] to 0[0], 64.3% improvement, $p = 0.05$).

In the staged cohort, axial tremor further improved after 180 days of bilateral DBS compared to unilateral DBS (1 [3] to 0 [1], 63.2% additional improvement, $p = 0.007$) (Fig. 1). This change was largely driven by head tremor (0 [1] to 0[0], 86.0% additional improvement, $p = 0.07$) which was the only subscore that significantly improved with bilateral compared to unilateral DBS at 180 days. Excluding patients without axial tremor at baseline revealed a similar improvement. Staged participants also had improved off-DBS midline CRST subscores at 180 days after unilateral (3 [3] to 2 [4], 24.0% improvement, $p = 0.004$), and 180 days after second sided surgery (3 [3] to 2 [4], 28.4% improvement, $p = 0.003$) compared to baseline.

Baseline axial tremor severity was comparable between the unilateral DBS only cohort (median[IQR]) (3 [3]) and the staged bilateral DBS cohort (3 [3]) ($p = 0.230$), as was the percent improvement after unilateral DBS at 180 days (61.9%[75.0%] unilateral only vs 66.7%[66.7%] staged, $p = 0.724$). In the unilateral only cohort, 14 of 76 subjects (18.4%) had no axial tremor at baseline compared to 5 of 39 subjects (12.8%) in the staged cohort.

Adverse effects in the staged cohort are reported in Table 3. There were 24 DBS and surgery-related adverse effects after unilateral DBS, 6 of which were associated with speech or balance. After second DBS implant, 35 additional DBS, surgery-related, or serious adverse events were reported. These included 14 related to incoordination, gait impairment, or speech impairment, and only 2 resolving with reprogramming. The remainder of these adverse events could not be avoided after programming sessions that resulted in satisfactory contralateral limb tremor control as determined by the clinicians. Of note, several serious adverse events occurred after second implant in the staged cohort including death unrelated to surgery (1), hemiparesis (1), and infection (1), while none occurred in these participants after the first implant.

We detected no significant predictors for improvement in axial tremor following unilateral DBS at 180 days follow up (data not shown); this included gender, dominant handedness, hemisphere of lead placement, baseline overall tremor severity (based on total CRST score), disease duration in number of years, age at surgery, and degree of tremor asymmetry.

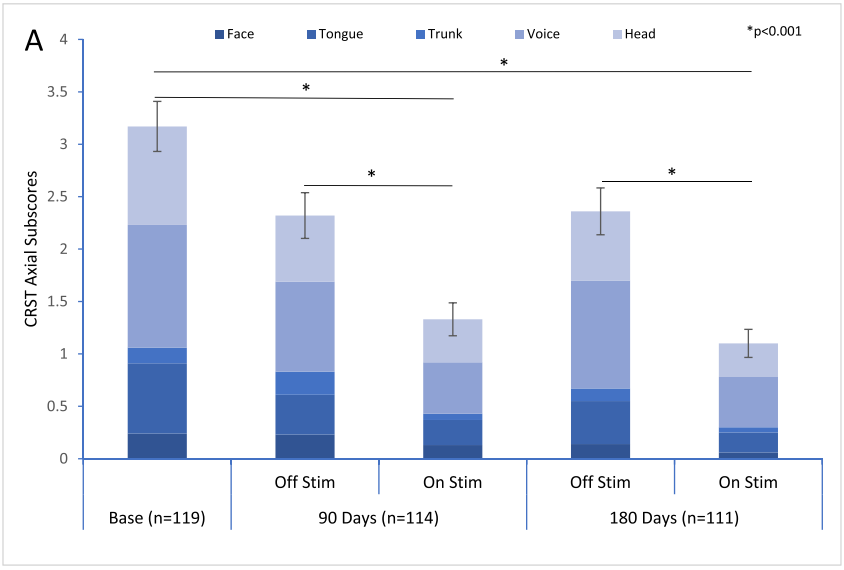
4. Discussion

This study revealed a significant benefit in midline tremor when applying only unilateral VIM DBS for ET. Participants had an improvement of more than 50% in axial tremor following a single DBS lead, which persisted at one year of follow-up. This degree of improvement is comparable to several smaller studies [3,11,13]. Bilateral DBS offered some incremental benefit in axial tremor, which was primarily driven by improvement in head tremor. This additional improvement was minimal given the already low pooled axial tremor midline subscore after unilateral DBS. Prior studies that suggested significant improvement in midline tremor only after bilateral stimulation had smaller sample sizes, and most focused on head and vocal tremor rather than all midline tremor symptoms [4,6–8].

We did not identify predictors for improvement in axial tremor following unilateral DBS. Heterogeneity of this population in terms of age, gender, tremor severity, and disease duration may have factored

Table 2
Baseline characteristics.

	All Unilateral (N = 119)	Bilateral Staged (N = 39)
Gender: n (%)		
Males	67 (56.3%)	23 (59.0%)
Females	52 (43.7%)	16 (41.0%)
Age (at surgery): Mean ± SD	65.1 ± 9.3	64.9 ± 9.5
Race: n (%)		
Caucasian	116 (97.5%)	37 (94.9%)
African American	1 (0.8%)	2 (5.1%)
Hispanic	2 (1.7%)	
Years since onset of tremor	29.6 ± 17.5	28.1 ± 16.0
Years since initial diagnosis of ET	15.2 ± 11.9	16.7 ± 11.9
Dominant hand: n (%)		
Right	102 (88.7%)	33 (84.6%)
Left	17 (14.3%)	6 (15.4%)
Target extremity: n (%)		
Right arm	100 (84.0%)	33 (84.6%)
Left arm	19 (16.0%)	6 (15.4%)
Total CRST at baseline	55.7 ± 13.4	58.1 ± 12.6



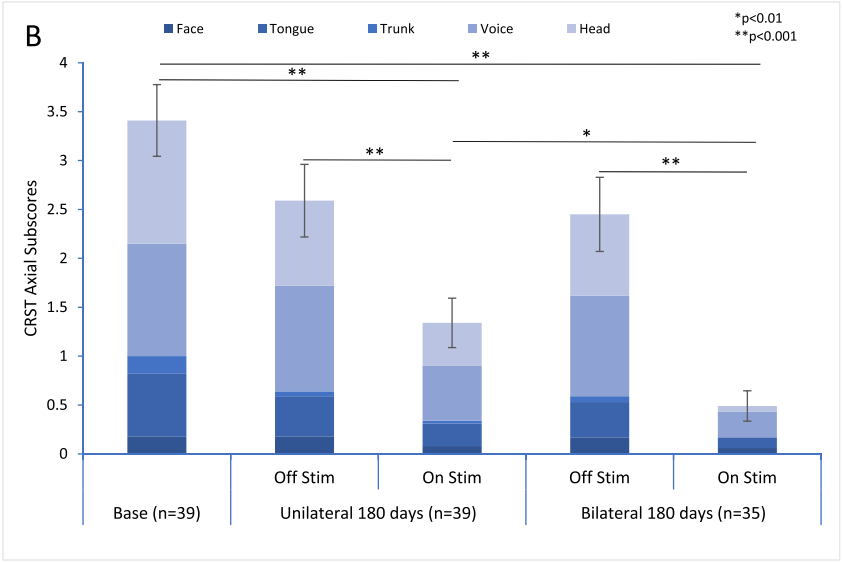


Fig. 1. Effects of unilateral and bilateral DBS on pooled midline tremor severity.
A: Unilateral DBS only cohort. All patients receiving unilateral DBS for essential tremor. Error bars represent standard error of mean (SEM). Midline tremor improved at 90 (median [IQR]) (3 [3] to 1 [2], 58% improvement, $p < 0.001$) and 180 days (3 [3] to 1 [2], 65% improvement, $p < 0.001$) compared to baseline as well as the off-DBS state at 90 (2 [3] to (1 [2], $p < 0.001$) and 180 days (2 [4] to 1 [2], $p < 0.001$).
B: Staged bilateral DBS cohort. All patients in staged cohort. Error bars represent SEM. Midline tremor improved at 180 days after unilateral DBS compared to baseline (median [IQR]) (3 [3] to 1 [3], 61% improvement, $p < 0.001$) and the off-DBS state (2 [4] to 1 [3], $p < 0.001$). Tremor further improved at 180 days after bilateral DBS compared to unilateral DBS (1 [3] to (0 [1], 63.2% improvement, $p = 0.007$) and the off-DBS state (2 [4] to 0 [1] $p < 0.001$).

Table 3
Surgery-related, DBS-related, and all serious adverse events in staged cohort after each DBS lead placement (n = 39).

Adverse Event (AE)	Unilateral		Bilateral	
	N	Resolved with Reprogramming	N	Resolved with Reprogramming
Incoordination and/or gait impairment	3	1	4	1
Dysarthria	3	1	10	1
Cognitive and psychiatric	2	1	10	0
Post op pain, headache, jolting	16		8	
Serious AE	0		3 • 1 unrelated death • 1 infection • 1 hemiparesis	
Total	24	3	35	2

into the failure to uncover predictive factors. Lead location and trajectory information were not available for our analyses, but there is recent evidence that lead trajectory (more vertically placed with a larger angle in relation to the AC-PC line) correlates with degree of axial tremor benefit [14]. Future studies should evaluate whether these parameters consistently predict midline tremor improvement in large data sets.

An important aspect of this study was the inclusion of a staged bilateral DBS cohort. These data provided valuable information on additional side effect risk after a second contralateral implant. Though adverse events remained low overall, participants in the staged cohort after second sided implants reported 14 new side effects involving gait/balance (n = 4) and dysarthria (n = 10) in addition to the 6 similar adverse events after their first implants. This trend fits prior observations of these side effects occurring more frequently following bilateral VIM DBS [15]. Further, several serious adverse events occurred after

second surgery versus none after the initial implant in the staged cohort.

A modest degree of midline tremor improvement was maintained after the DBS was switched off for 4 h as part of the protocol. Reasons for this benefit in the off-DBS state remain unknown but could be due to washout issues or due to the long-term effects from a microlesion. Waning long-term microthalamotomy effects and disease progression have both been previously associated with higher amplitude DBS requirements at one year and beyond [18]. Rebound limb tremor when DBS is switched off has been occasionally reported in Parkinson's disease and ET [19], though it was not observed in this study and likely did not affect midline tremor in the off-DBS state.

The data from this study are strengthened by the sample size, which is the largest to date examining axial ET symptoms. Low attrition and multicenter participation are also strengths that should increase the likelihood of reproducibility of these results. The staged cohort uniquely facilitated direct comparison of unilateral to bilateral DBS implantation. A final strength was the lack of observed investigator driven selection bias for the decision to pursue unilateral versus staged bilateral implantation based on axial tremor. Participants in both cohorts had similar baseline axial tremor scores and percent improvement following the first intervention.

Although the study was large it had several key limitations. These were post-hoc analyses, and while statistical significance was adjusted for multiple comparisons, the original clinical trial was not designed to evaluate unilateral DBS and midline tremor. Unilateral DBS was implanted to target dominant hand tremor in the vast majority of cases (115/119), so this substudy does not address whether initial target of a non-dominant hand would have the same effect on axial tremor. Additionally, tremor subscores were rated in an unblinded fashion at baseline and scheduled follow-up visits, potentially introducing rater bias. The trial lacked racial diversity (97.5% Caucasian) and addressed only axial tremor as a symptom of ET (not other etiologies such as dystonic head tremor and orthostatic tremor) which could impact generalizability.

Finally, while there were additional side effects after bilateral DBS, this study used non-directional leads. Directional leads have recently shown promise for expanding the DBS therapeutic window primarily by improving side effect thresholds in the intended target [20–22].

5. Conclusion

Unilateral VIM DBS provided significant benefit in axial tremor symptoms in this large ET cohort. The placement of a second contralateral DBS lead provided some additional axial tremor improvement but was associated with additional adverse events. When evaluating a patient with the primary goal of improving disabling contralateral limb and axial tremor, initial unilateral DBS placement may provide significant improvement in both and may allow avoidance of a second sided DBS surgery.

Disclosures

Kyle Mitchell has no conflicts of interest to disclose.

Paul Larson has received honoraria from Medtronic and serves on the advisory board for Abbott.

Philip Starr has received fellowship and research support from Medtronic and research support from Boston Scientific.

Michael Okun serves as a consultant for the National Parkinson Foundation, and has received research grants from NIH, NPF, the Michael J. Fox Foundation, the Parkinson Alliance, Smallwood Foundation, the Bachmann-Strauss Foundation, the Tourette Syndrome Association, and the UF Foundation. His DBS research is supported by: R01 NR014852 and R01NS096008. Michael Okun has previously received honoraria, but in the past > 60 months has received no support from industry. He has received royalties for publications with Demos, Manson, Amazon, Smashwords, Books4Patients, and Cambridge (movement disorders books). He is an associate editor for New England Journal of Medicine Journal Watch Neurology. Michael Okun has participated in CME and educational activities on movement disorders (in the last 36) months sponsored by PeerView, Prime, QuantiaMD, WebMD, Medicus, MedNet, Henry Stewart, and by Vanderbilt University. The institution and not Dr. Okun receives grants from Medtronic, Abbvie, Allergan, and ANS/St. Jude, and the PI has no financial interest in these grants. He has participated as a site PI and/or co-I for several NIH, foundation, and industry sponsored trials over the years but has not received honoraria.

Robert Wharen has no conflicts of interest to disclose.

Ryan Uitti serves as an associate editor for Neurology and receive compensation from the AAN for this service.

Barton Guthrie has no conflicts of interest to disclose.

Delea Peichel is was an employee of Abbott (formerly St Jude Medical) during the majority of her contribution to this study.

Frederick Marshall has received an unrestricted educational grant from Medtronic.

Fenna Phibbs has served as a consultant for Medtronic and Boston Scientific.

Rajesh Pahwa has received honorarium/consulting fees from AbbVie, ACADIA, Acorda, Adamas, Alexza, Abbott, Global Kinetics, Ionis, Lundbeck, Neurocrine, St Jude Medical, Sunovion, Teva Neuroscience, UCB, and US World Meds. He has received research support from Abbott, AbbVie, Acorda, Adamas, BMS, Boston Scientific, Cala Health, Cavion, Cynapsus, Intec, Jazz, Kyowa, Lilly, NIH/NINDS, NPF, PSG, Pfizer, Prexton, Roche, Sunovion, and US WorldMeds.

Harrison Walker has no conflicts of interest to disclose.

Kelly Foote has received research support from Medtronic, Boston Scientific, Abbott/St. Jude, Neuropace, and Functional Neuromodulation. He has received fellowship support from Medtronic. He has received personal payment for consulting work for Medtronic on one occasion in the past three years.

Joseph Jankovic has received research and training grants from Medtronic.

Richard Simpson has no conflicts of interest to disclose.

Joseph Neimat serves as a member of the advisory board for Abbott.

R. Malcolm Stewart has no conflicts of interest to disclose.

Khashayar Dashtipour has received honorarium and consulting fees from Abbvie, ACADIA, Adamas, Allergan, Cynapsus, Ipsen, Lundbeck, Merz, Neurocrine Biosciences, Sunovion, Teva Neuroscience, and US World Meds. He has received research grants from Abbott, Acorda, Adamas, Allergan, Intec, Ipsen, Lundbeck, Merz, Teva, and US WorldMeds.

Jill Ostrem has received research support from NIH grants R01NS090913, UH3NS100544, DARPA contract W911NF1420043, and PCORI contract 782.002 as a co-investigator. She also has received research grant support from The National Parkinson Foundation, Michael J. Fox Foundation, Boston Scientific, St Jude Medical, Cala Health, Google, Sangamo, and Biogen. She has been a consultant for Abbvie, Neurocrine, Medtronic, and Adamas Pharmaceutics. She receives programmatic fellowship training support from Medtronic, Abbvie, Boston Scientific, and Allergan.

Acknowledgements

This substudy used data from the cited original controlled trial, which was funded by Abbott (formerly St Jude Medical). This substudy did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

References

[1] A.L. Benabid, P. Pollak, C. Gervason, D. Hoffmann, D.M. Gao, M. Hommel, J.E. Perret, J. de Rougemont, Long-term suppression of tremor by chronic

stimulation of the ventral intermediate thalamic nucleus, Lancet 337 (8738) (1991) 403–406.
[2] Z. Peng-Chen, T. Morishita, D. Vaillancourt, C. Favilla, K.D. Foote, M.S. Okun, A. Wagle Shukla, Unilateral thalamic deep brain stimulation in essential tremor demonstrates long-term ipsilateral effects, Park. Relat. Disord. 19 (12) (2013) 1113–1117.
[3] J.D. Putzke, R.E. Wharen Jr., A.A. Obwegeser, Z.K. Wszolek, J.A. Lucas, M.F. Turk, R.J. Uitti, Thalamic deep brain stimulation for essential tremor: recommendations for long-term outcome analysis, Can. J. Neurol. Sci. 31 (3) (2004) 333–342.
[4] O. Sydow, S. Thobois, F. Alesch, J.D. Speelman, Multicentre European study of thalamic stimulation in essential tremor: a six year follow up, J. Neurol. Neurosurg. Psychiatry 74 (10) (2003) 1387–1391.
[5] S. Rehncrona, B. Johnels, H. Widner, A.L. Tornqvist, M. Hariz, O. Sydow, Long-term efficacy of thalamic deep brain stimulation for tremor: double-blind assessments, Mov. Disord. 18 (2) (2003) 163–170.
[6] W. Ondo, J. Jankovic, K. Schwartz, M. Almaguer, R.K. Simpson, Unilateral thalamic deep brain stimulation for refractory essential tremor and Parkinson's disease tremor, Neurology 51 (4) (1998) 1063–1069.
[7] W. Ondo, M. Almaguer, J. Jankovic, R.K. Simpson, Thalamic deep brain stimulation: comparison between unilateral and bilateral placement, Arch. Neurol. 58 (2) (2001) 218–222.
[8] P. Limousin, J.D. Speelman, F. Gielen, M. Janssens, Multicentre European study of thalamic stimulation in parkinsonian and essential tremor, J. Neurol. Neurosurg. Psychiatry 66 (3) (1999) 289–296.
[9] M.A. Carpenter, R. Pahwa, K.L. Miyawaki, S.B. Wilkinson, J.P. Searl, W.C. Koller, Reduction in voice tremor under thalamic stimulation, Neurology 50 (3) (1998) 796–798.
[10] W.C. Koller, K.E. Lyons, S.B. Wilkinson, R. Pahwa, Efficacy of unilateral deep brain stimulation of the VIM nucleus of the thalamus for essential head tremor, Mov. Disord. 14 (5) (1999) 847–850.
[11] J.D. Putzke, R.J. Uitti, A.A. Obwegeser, Z.K. Wszolek, R.E. Wharen, Bilateral thalamic deep brain stimulation: midline tremor control, J. Neurol. Neurosurg. Psychiatry 76 (5) (2005) 684–690.
[12] T. Mandat, H. Koziara, R. Rola, W. Bonicki, P. Nauman, Thalamic deep brain stimulation in the treatment of essential tremor, Neurol. Neurochir. Pol. 45 (1) (2011) 37–41.
[13] A.A. Obwegeser, R.J. Uitti, M.F. Turk, A.J. Strongosky, R.E. Wharen, Thalamic stimulation for the treatment of midline tremors in essential tremor patients, Neurology 54 (12) (2000) 2342–2344.
[14] M. Moscovich, T. Morishita, K.D. Foote, C.G. Favilla, Z.P. Chen, M.S. Okun, Effect of lead trajectory on the response of essential head tremor to deep brain stimulation, Park. Relat. Disord. 19 (9) (2013) 789–794.
[15] R. Pahwa, K.E. Lyons, S.B. Wilkinson, R.K. Simpson, W.G. Ondo, D. Tarsy, T. Norregaard, J.P. Hubble, D.A. Smith, R.A. Hauser, J. Jankovic, Long-term evaluation of deep brain stimulation of the thalamus, J. Neurosurg. 104 (4) (2006) 506–512.
[16] K.P. Bhatia, P. Bain, N. Bajaj, R.J. Elble, M. Hallett, E.D. Louis, J. Raethjen, M. Stamelou, C.M. Testa, G. Deuschl, P. Tremor, Task force of the international, S. Movement disorder, consensus statement on the classification of tremors. From the task force on tremor of the international Parkinson and movement disorder society, Mov. Disord. 33 (1) (2018) 75–87.
[17] R.E. Wharen Jr., M.S. Okun, B.L. Guthrie, R.J. Uitti, P. Larson, K. Foote, H. Walker, F.J. Marshall, J. Schwalb, B. Ford, J. Jankovic, R. Simpson, K. Dashtipour, F. Phibbs, J.S. Neimat, R.M. Stewart, D. Peichel, R. Pahwa, J.L. OstremS.D.E.S. Group, Thalamic DBS with a constant-current device in essential tremor: a controlled clinical trial, Park. Relat. Disord. (2017).
[18] C.G. Favilla, D. Ullman, A. Wagle Shukla, K.D. Foote, C.E.t. Jacobson, M.S. Okun, Worsening essential tremor following deep brain stimulation: disease progression versus tolerance, Brain 135 (Pt 5) (2012) 1455–1462.
[19] M.I. Hariz, P. Shamsgovara, F. Johansson, G. Hariz, H. Fodstad, Tolerance and tremor rebound following long-term chronic thalamic stimulation for Parkinsonian and essential tremor, Stereotact. Funct. Neurosurg. 72 (2–4) (1999) 208–218.
[20] C. Pollo, A. Kaelin-Lang, M.F. Oertel, L. Stieglitz, E. Taub, P. Fuhr, A.M. Lozano, A. Raabe, M. Schupbach, Directional deep brain stimulation: an intraoperative double-blind pilot study, Brain 137 (Pt 7) (2014) 2015–2026.
[21] T.A. Dembek, P. Reker, V. Visser-Vandewalle, J. Wirths, H. Treuer, M. Klehr, J. Roediger, H.S. Dafsari, M.T. Barbe, L. Timmermann, Directional DBS increases side-effect thresholds-A prospective, double-blind trial, Mov. Disord. 32 (10) (2017) 1380–1388.
[22] F. Steigerwald, L. Muller, S. Johannes, C. Matthies, J. Volkmann, Directional deep brain stimulation of the subthalamic nucleus: a pilot study using a novel neurostimulation device, Mov. Disord. 31 (8) (2016) 1240–1243.