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

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Summary

Background Efficacy in previous studies of surgical treatments of refractory multiple sclerosis tremor using lesioning or deep brain stimulation (DBS) has been variable. The aim of this study was to investigate the safety and efficacy of dual-lead thalamic DBS (one targeting the ventralis intermedius–ventralis oralis posterior nucleus border [the VIM lead] and one targeting the ventralis oralis anterior–ventralis oralis posterior border [the VO lead]) for the treatment of multiple sclerosis tremor.

Methods We did a single centre, single-blind, prospective, randomised pilot trial at the University of Florida Center for Movement Disorders and Neurorestoration clinic (Gainesville, FL, USA). We recruited adult patients with a clinical diagnosis of multiple sclerosis tremor refractory to previous medical therapy. Before surgery to implant both leads, we randomly assigned patients (1:1) to receive 3 months of optimised single-lead DBS—either VIM or VO. We did the randomisation with a computer-generated sequence, using three blocks of four patients, and independent members of the Center did the assignment. Patients and all clinicians other than the DBS programming nurse were masked to the choice of lead. Patients underwent surgery 1 month after their baseline visit for implantation of the dual lead DBS system. A pulse generator and two extension cables were implanted in a second surgery 3–4 weeks later. Patients then received an initial 3-month period of continuous stimulation of either the VIM or VO lead followed by blinded safety assessment of their tremor with the Tolosa-Fahn-Marin Tremor Rating Scale (TRS) during optimised VIM or VO lead stimulation at the end of the 3 months. After this visit, both leads were activated in all patients for an additional 3 months, and optimally programmed during serial visits as dictated by a prespecified programming algorithm. At the 6-month follow-up visit, TRS score was measured, and mood and psychological batteries were administered under four stimulation conditions: VIM on, VO on, both on, and both off (the order of testing was chosen by a computer-generated random sequence, assigned by independent members of the centre, and enacted by an unmasked DBS programming nurse). Each of four stimulation settings were tested over 4 consecutive days, with stimulation settings held constant for at least 12 h before testing. The primary outcome was change in mean total TRS score at the 6-month postoperative assessment with both leads activated, compared with the preoperative baseline mean TRS score. Analysis was by intention to treat.Safety was analysed in all patients who received the surgical implantation except in one patient who discontinued before the safety assessment. This trial is registered with ClinicalTrials.gov, number NCT00954421.

Findings Between Jan 16, 2007, and Dec 17, 2013, we enrolled 12 patients who were randomly assigned either to 3 initial months of VIM-only or VO-only stimulation. One patient from the VO-only group developed an infection necessitating DBS explantation, and was excluded from the assessment of the primary outcome. Compared with the mean baseline TRS score of 57·0 (SD 10·2), the mean score at 6 months decreased to 40·1 (17·6), –29·6% reduction; t=–0·28, p=0·03. Three of 11 patients did not respond to surgical intervention. One patient died suddenly 2 years after surgery, but this was judged to be unrelated to DBS implantation. Serious adverse events included a superficial wound infection in one patient that resolved with antibiotic therapy, and transient altered mental status and late multiple sclerosis exacerbation in another patient. The most common non-serious adverse events were headache and fatigue.

Interpretation Dual lead thalamic DBS might be a safe and effective option for improving severe, refractory multiple sclerosis tremor. Larger studies are necessary to show whether this technique is widely applicable, safe in the long-term, and effective in treating multiple sclerosis tremor or other severe tremor disorders.

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Research in context

Evidence before this study

Deep brain stimulation (DBS) of the ventral intermediate nucleus (VIM) of the thalamus is a well established therapy for patients with treatment-refractory essential tremor and tremor-dominant Parkinson's disease. However, studies of lesioning and DBS to treat severe multiple sclerosis tremor have produced variable results. We searched PubMed for reports of clinical trials published in English up to March 6, 2017, with the terms "multiple sclerosis", "deep brain stimulation", and "tremor", and identified eight reports. Four studied multiple sclerosis tremor with other forms of tremor and did not directly address the challenges posed by the treatment of multiple sclerosis tremor. Three studies examined multiple sclerosis tremor directly, comparing thalamotomy to traditional VIM DBS; in one of these studies, approximately half of the ten patients included derived some initial benefit from VIM DBS after surgery but a sustained benefit of more than 50% tremor reduction only occurred in 30% of patients. The eighth report identified in our search was a case series published by our group, which showed clinical efficacy in the treatment of three patients with post-traumatic tremor and one with multiple sclerosis tremor using dual-thalamic DBS with one lead in the VIM and another in the VO. Findings from small case studies have suggested that successful treatment of parkinsonian, essential, and post-stroke tremor occurred with dual VIM or ventralis oralis (VO) stimulation achieved with either non-traditional single-lead trajectories or dual-lead implantation; these reports were excluded from our primary search for multiple sclerosis tremor therapy.

Added value of this study

In our randomised pilot trial, we treated patients with debilitating multiple sclerosis tremor with dual-lead thalamic DBS, which was well tolerated and might result in improvement of tremor. Our results suggested that dual-lead DBS was well tolerated and improved mean tremor rating scale scores at 6 months in this small cohort. Adverse events were infrequent and similar to those noted with routine DBS therapy, although we did identify three non-responders to dual-lead therapy. No substantial deleterious cognitive changes were observed postoperatively with an extensive neuropsychological battery, and only modest postoperative mood effects were observed using an extensive mood battery. This is the first study to show a possible lasting clinical efficacy in surgical treatment of multiple sclerosis tremor, and also (to our knowledge) the first to systematically investigate the use of dual-lead thalamic deep brain stimulation to treat a severe tremor disorder.

Implications of all the available evidence

The results of this pilot trial indicate that dual-lead thalamic DBS represents a potential new option for patients with multiple sclerosis tremor, a condition that has previously been considered to respond poorly to surgical intervention. Larger studies of patients with multiple sclerosis tremor and other severe tremor disorders will be necessary to assess long-term safety and efficacy, and better predict responsiveness to dual-lead thalamic DBS.

Introduction

Around 25–58% of patients with multiple sclerosis develop tremor,[1–3] which is typically pharmacoresistant and can be profoundly disabling.[2,4] An estimated 10% of patients with multiple sclerosis become incapacitated by their tremor,[5] which can be widespread, but most typically affects the upper extremities, is often high-amplitude, and is comprised of both kinetic and postural components.[2] This form of tremor is inherently complex and commonly involves superimposed ataxia. While treatment of essential or parkinsonian tremor with stereotactic lesioning and deep brain stimulation (DBS) has been successful, results for similar treatment of multiple sclerosis tremor have been inconsistent.[3,6–10] Traditional ventralis intermedius (VIM) nucleus stimulation has been initially successful for some patients[3] but, over weeks to months, the tremor frequently returns or even worsens despite subsequent repeated DBS treatments.

We previously reported[10,11] findings from the use of two ipsilateral thalamic DBS leads (one targeting the VIM nucleus–ventralis oralis posterior (VOP) nucleus border, referred to from here as the VIM lead, and one targeting the ventralis oralis anterior [VOA]–VOP nucleus border, referred to from here as the VO lead, to treat a few patients with severe post-traumatic tremor,[10,11] and a single case of multiple sclerosis tremor.[11] In this group of patients, tremor suppression was sustained for at least 6 months without rebound. Here, we report a prospective pilot study to investigate the safety and efficacy of dual lead thalamic VIM plus VO DBS for treatment of severe, treatment-refractory multiple sclerosis tremor. Since VIM plus VO DBS increases the volume of both thalamic stimulation and thalamic microinjury, we also examined its effects on cognition and mood.

Methods

Study design and participants

We did a single centre, single-blind, prospective, randomised pilot trial at the University of Florida Center for Movement Disorders and Neurorestoration clinic (Gainesville, FL, USA). The study protocol and ethics were approved by the University of Florida Institutional Review Board. Data were monitored by a Data Safety and Monitoring Committee that met quarterly, led by an independent chairman. There were open and closed sessions for each meeting. The reports were prepared by an unblinded study coordinator who was not otherwise involved with study implementation. Regular progress and safety data reports were submitted by the investigators to the Committee throughout the duration of the study.

The original study protocol intended for recruitment of ten patients with multiple sclerosis tremor and ten patients with post-traumatic tremor to undergo dual thalamic DBS therapy starting in November, 2006. Because of low recruitment for the post-traumatic tremor group, the US National Institutes of Health (NIH) granted a protocol change to enrol only patients with multiple sclerosis tremor starting in April 6, 2010. This protocol change also recommended increased enrolment for patients with multiple sclerosis tremor from the planned ten patients to 12, to increase statistical power. The few patients with post-traumatic tremor initially recruited into the study were excluded from any analysis.

Patients who were referred to the Center for neurological or neurosurgical therapy were approached about the study by study coordinators if they met inclusion criteria. A movement disorders neurologist from our study (MSO or RLR) assessed each patient to confirm the diagnosis of multiple sclerosis tremor and to ascertain that all previous treatment had been effectively administered, but failed. Patients who agreed to participate in the study were also assessed by a psychiatrist and a neuropsychologist at the University of Florida (Gainesville, FL, USA) to assess baseline mood and cognitive function. We included patients if they had a clinical diagnosis of multiple sclerosis tremor characterised by the presence of severe and disabling rest, postural, or action tremor (or a combination thereof); were aged between 18–79 years; had unsatisfactory clinical response to maximum medical therapy; and had a stable, optimised medical regimen of drug therapy for at least 1 month before surgery. We excluded patients who had a clinically significant medical disease that would excessively increase the risk of developing perioperative complications; severe cerebellar dysfunction in the arm ipsilateral to the side of the brain being considered for surgery; evidence of secondary or atypical movement disorder; severe brain atrophy or other prohibitive structural abnormality; diagnosed dementia; or an uncontrolled major psychiatric disorder. Patients with psychiatric disorders identified on initial screening were treated for these conditions before DBS and enrolled only if deemed psychiatrically stable for at least 3 months before entry. Written informed consent was obtained from every patient, indicating their willingness to both participate in the study and to undergo the surgical procedure, understanding the associated risks, benefits, and alternative treatments.

Randomisation and masking

Two randomisation events occurred during the study. First, before surgery, we randomly assigned patients (1:1) to optimised single-lead stimulation (VIM or VO) for the first 3 months after surgery. Blocked randomisation (three blocks of four patients) was determined by a computer-generated sequence using standard methods of the University of Florida Clinical Research Center Data Services Laboratory. Members of the Center who did not participate in the study assigned participants to one of the two stimulation groups, which was enacted by an unmasked nurse after assignment during the first DBS programming session.

Second, the order of four testing conditions (VIM-only on, VO-only on, both on, or both off) at the 6-month final assessment was chosen by a computer-generated random sequence using standard methods of the University of Florida Clinical Research Center Data Services Laboratory. Members of the Center who did not participate in the study assigned the order of the conditions, which were programmed into the patient's DBS device by an unmasked nurse the night before the motor, neuropsychological, and mood assessments, ensuring that settings had been constant for at least 12 h before each round of testing. No emergency code break was necessary. Because the tests needed to be administered in four conditions at this visit, equivalent forms for each neuropsychological test were produced and the battery was designed to be short to minimise practice effects and testing fatigue.

The patient and all other clinicians involved in the patient's care were masked to the results of randomisation. The unmasked surgical team had no part in any stage of clinical assessment. Every effort was made to ensure that patients and clinicians remained masked; however, the necessary involvement of an unmasked nurse required that the study be designated as single-blinded, since this individual routinely interacted with the investigators for other clinical duties outside the study.

Procedures

Within 1 month after their baseline visit, each patient underwent surgery for implantation of the dual-lead thalamic DBS system contralateral to their most symptomatic upper extremity. Surgical procedures were done as previously described[10] by one surgeon (KDF). A high-resolution, volumetric brain MRI was obtained 1 day before the procedure and, on the morning of surgery, a high-resolution stereotactic head CT scan was obtained after application of a Cosman-Roberts-Wells head ring. By use of software developed at our institution, the CT and MRI scans were combined and stereotactic targeting was done with T1+ gadolinium and FGATIRMRI sequences[12] coupled with a three-dimensional deformable, patient-specific brain atlas[13] to clarify thalamic and basal ganglia anatomy (appendix). Detailed microelectrode recording confirmed the location of the anterior border of the ventralis caudalis, as well as the sensory and sensorimotor hand regions of the ventralis caudalis and VIM, respectively. Two Medtronic 3387 DBS electrodes (Medtronic, Minneapolis, MN, USA) were implanted (figure 1): the first electrode was placed 2 mm anterior to the anterior border of the ventralis caudalis (the VIM

See Online for appendix

lead). The second electrode was then implanted through the same burr hole on a parallel trajectory 2 mm anterior and 1 mm medial to the first (the VO lead). The ventral tips of both DBS leads were positioned at the level of the anterior-posterior commissural line (appendix).

Patients were observed overnight in the hospital prior to a typical discharge home on postoperative day one. A dual channel implantable pulse generator and two extension cables were implanted in a second staged outpatient procedure under general anaesthesia 3–4 weeks later (appendix). We then initiated a randomised 3-month period of VIM-only or VO-only stimulation using a fixed algorithm to determine optimal stimulation parameters. We used a fixed algorithm for determining optimal stimulation parameters (appendix).

After 3 months of single-lead stimulation, each patient underwent blinded assessment of their tremor for safety analysis using the full Tolosa-Fahn-Marin Tremor Rating Scale (TRS, including both the semiquantitative bilateral exam and the disability questionnaire portions). After this visit, all patients had both leads activated for 3 months and optimally programmed during serial visits as indicated by the programming algorithm before returning for a follow-up assessment 6 months after implantation. During the 6-month assessment TRS was measured by the investigators MSO and RLR, and mood and neuropsychological batteries were administered by DB, under each condition of VIM on, VO on, both on, and both off. One stimulation setting was tested per day for 4 consecutive days, based on the assumption that 24 h was a sufficient period to ensure proper washout (pulse width between 60–180 µs and rate 135 or 185 Hz; appendix). Each stimulation condition was initiated at least 12 h before testing. In the neuropsychological battery, we tested frontal lobe function with the Stroop Color Word Naming Test and the Letter Fluency Task. We also tested non-frontal lobe function for comparison using the Hopkins Verbal Learning Test (HVLT, a measure of working and episodic memory) and the Paced Auditory Serial Addition Test (PASAT, a measure of attention and working memory). The mood battery consisted of several standardised, validated instruments to thoroughly assess the underlying components of mood. These included the Visual Analog Mood Scale (VAMS), the Profile of Mood States (POMS), the Spielberger State-Trait Anger Expression Inventory (STAXI) and the Beck Depression Inventory (BDI).

Tremor-suppressing medications were held stable at the preoperative optimised dose for the duration of the study. Before both the 3-month and 6-month assessments, medications were withheld for 12 h. All data from clinical assessments were uploaded via remote data capture to the University of Florida Interdisciplinary Florida Registry of Movement Disorders (UF-INFORM) Database, a prospective registry and database maintained by the University of Florida Center for Movement Disorders and Neurorestoration.

Outcomes

The primary outcome measure was the change in mean TRS score at the 6-month postoperative assessment with both VIM and VO leads activated, compared with baseline TRS measured before implantation. Secondary outcome measures were the change in 6-month postoperative mean TRS scores in each of the other stimulation conditions (VIM-only, VO-only, and both

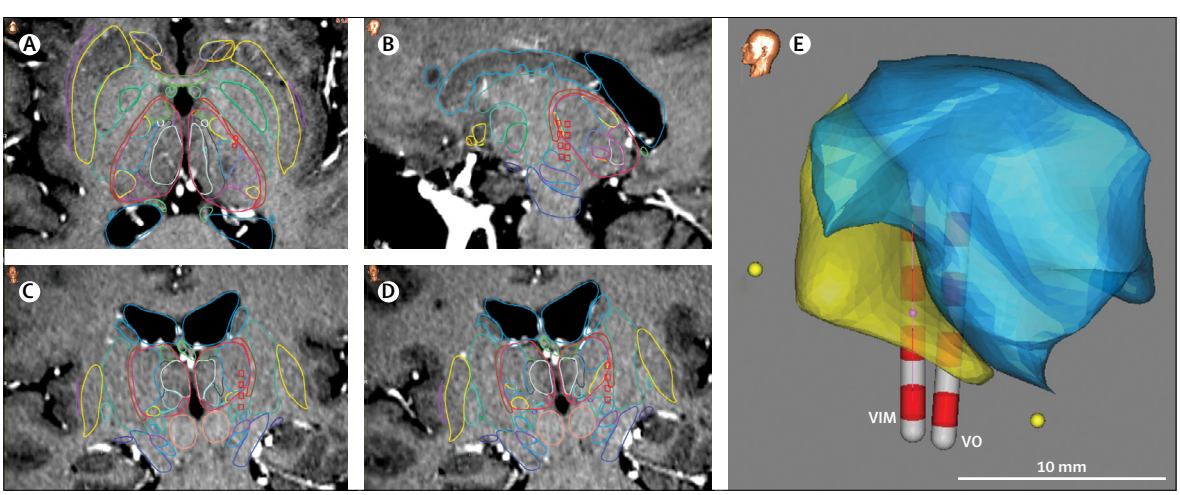

Figure 1: **Deep brain stimulation lead localisation measurements**
Deep brain stimulation (DBS) lead localisation was precisely measured by fusing postoperative high resolution CT images to preoperative MR images fit with a deformable atlas, which was applied using Cranial Vault Explorer software (version 5.6.3, Neurotargeting, LLC, USA). A–E are representative images from patient 10. The coloured outlines in A–D show the basal ganglia and surrounding structures, and represent the fit of the deformable atlas to the individual patient MRI. (A) Axial representation of ventral intermediate nucleus (VIM; posteromedial) and ventralis oralis (VO; anterolateral) leads. (B) Sagittal representation of VIM (posterior) and VO (anterior) leads. (C) Coronal representation of VIM lead. (D) Coronal representation of VO lead. (E) Three-dimensional representation of VIM and VO leads. Yellow shows the ventral lateral anterior thalamus and blue shows the ventral lateral posterior thalamus. Active contact position coordinates and lead configurations for each patient are presented in the appendix.

leads off) compared with preimplantation baseline TRS score, and the change in 6-month postoperative mean neuropsychological and mood battery measures in the four stimulation conditions, compared with baseline preoperative measures. TRS was also measured at 3 months after surgery during single-lead stimulation as a prespecified portion of the safety analysis; however, no analysis of this subgroup data was anticipated because of the shortage of statistical power. For the purposes of this study, we made the explicit assumption that the initial 3-month single-lead stimulation period had no effect on the 6-month primary or secondary outcome measures. Safety was assessed monthly by telephone checks, in addition to the 3-month assessment visit (appendix).

Statistical analysis

Our initial study design included two groups: ten patients with post-traumatic tremor and ten with multiple sclerosis tremor. We intended to do a primary outcome analysis comparing mean TRS at baseline with dual-lead thalamic stimulation (ie, both leads on) at 6 months by the exact Wilcoxon Sign-Rank test. Since the results represented two discrete distributions (one for each group), a normality assumption needed for the classic *t*-test was not considered viable. On the basis of preliminary results from our previous case reports, we considered two alternative distributions: one with a strong effect (baseline – 6-month change in TRS of –1 [20%], 0 [20%], +1 [20%], +2 [20%], or +3 [20%]) or with a moderate effect (baseline – 6-month change in TRS of –1 [15%], 0 [40%], +1 [15%], +2 [15%], or +3 [15%]). For each distribution, we did a simulation study of 10 000 replications with 20 simulated patients per run. The power of the exact two-sided test at p=0·05 was 91% for the strong-effect distribution and 82% for the moderate-effect distribution, indicating good power to detect these probabilistic changes based on a sample of 20. However, a protocol change was granted to enrol only patients with multiple sclerosis tremor, and enrolment was increased from the planned ten patients to 12. A second power analysis was not done after this protocol change. In light of the protocol change to include only patients with multiple sclerosis tremor, we chose to do repeated measures ANOVA to identify a difference for the primary and secondary outcome measures. Subsequently we did post-hoc paired-samples *t*-tests to compare preoperative and postoperative values as indicated by the ANOVA results. All patients were included in the primary analysis per protocol on an intention-to-treat basis. Statistical analyses were done using SSPS version 22.0.

This trial is registered with ClinicalTrials.gov, number NCT00954421.

Role of the funding source

The funders of this study had no role in study design, data collection, data analysis, data interpretation, patient recruitment, or any other aspect pertinent to the study. The US National Institutes of Health provided standard trial oversight and was contacted for approval when a protocol change was required. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Between Jan 16, 2007, and Dec 17, 2013, we enrolled 12 patients into our study (table 1, figure 2). Baseline neuropsychological and mood measures, including percentiles as appropriate, are presented in the appendix. We noted baseline cognitive deficits in several areas that were tested by the neuropsychological battery, as expected for this cohort of patients with cognitive symptoms secondary to multiple sclerosis. One patient in the VO-only initial stimulation cohort did not complete the study because of a hardware infection requiring explantation of his DBS system before assessment. 11 patients completed the study and were included in the safety and efficacy analyses.

Repeated measures ANOVA provided evidence to suggest a difference in mean TRS score at 6 months compared with baseline between the conditions tested (F [4–36]=3·82, p=0·01, $\eta p2$=0·30), followed by post-hoc paired-samples *t*-tests. Compared with the mean baseline TRS score of 57·0 (SD 10·2), the mean TRS score at 6 months decreased to 40·1 (17·6), –29·6% reduction; t=–0·28, p=0·03. Three of 11 patients did not respond to surgical intervention.

The 6-month reduction in mean TRS score during VO-only stimulation (45·6 [SD 18·4], –20·0% reduction) was similar to that with VIM-only stimulation (45·0 [18·9], –21·1% reduction). Likewise, there was a –12·8% absolute reduction in mean TRS scores with both leads turned off, but the study was not powered to detect significant differences in these measures (TRS score baseline 57·0 [SD 10·2], both leads turned off 49·7 [18·0]).

Figure 3 shows individual TRS scores with single-lead stimulation at 3 months and with dual-lead stimulation at 6 months. For the eight patients who responded to DBS therapy, no rebound tremor was observed at 6 months. A review of the baseline characteristics and medical history in the three patients who were non-responders (identification numbers 4, 12, and 7) revealed that patients 4 and 12 both had previously unidentified severe ataxia, obscured by their severe tremor, that could not be captured during DBS programming sessions. Despite dual-lead DBS programming, patient 7 reported poor contralateral upper extremity tremor control, worsening ipsilateral upper extremity tremor, and exacerbation of her baseline lower extremity weakness and gait instability with stimulation. This worsening might have represented progression of multiple sclerosis, but this could not be definitively diagnosed. The postoperative CT to MRI or atlas fusion and programming thresholds showed that the positioning of both leads for all non-responders was adequate (appendix).

	Age at DBS implantation (years)	Sex	Multiple sclerosis subtype	Disease duration (years)	Tremor duration (years)	Baseline TRS score	Single-lead stimulation group
Patient 2	30	Female	Relapsing-remitting	7	6	53	VIM
Patient 4	27	Male	Relapsing-remitting	19	1·5	66	VIM
Patient 6	49	Female	Relapsing-remitting	15	7	50	VO
Patient 7	54	Female	Primary-progressive	8	8	50	VO
Patient 9	47	Female	Relapsing-remitting	28	17	68	VIM
Patient 10	51	Female	Relapsing-remitting, gradual progression	18	17	60	VO
Patient 11	26	Male	Primary-progressive	1·5	1·5	62	VO
Patient 12	72	Female	Primary-progressive	13	3	81	VO
Patient 13	23	Female	Primary-progressive *vs* secondary	3	2	55	VIM
Patient 14	40	Female	Relapsing-remitting, progressing to secondary	20	11	50	VO
Patient 15	36	Female	Relapsing-remitting	7	5	76	VIM
Patient 16	58	Female	Relapsing-remitting	30	8	46	VIM

Duration of disease and tremor are relative to the time of DBS implantation. Patient 11 did not complete the trial because of a hardware infection requiring DBS explantation. Baseline neuropsychological and mood measures are presented in the appendix. DBS=deep brain stimulation. TRS=tremor rating scale. VIM=ventral intermediate nucleus. VO=ventralis oralis.

Table 1: **Patient demographic and baseline clinical characteristics**

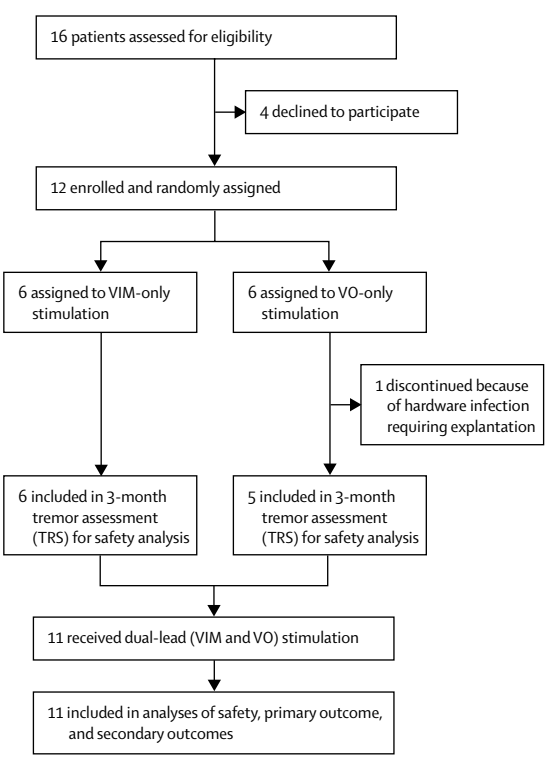

Figure 2: **Trial profile**
VIM=ventral intermediate nucleus. VO=ventralis oralis. TRS=tremor rating scale.

In the 6-month postoperative neuropsychological battery, no major deleterious postsurgical effects occurred. A numerical reduction occurred in Stroop colour naming under VO-only stimulation (table 2), and a numerical increase occurred in the HVLT Recognition Discrimination Index with either both leads off or both leads on; however we do not present any comparative statistical tests here.

At the 6-month postoperative mood battery assessment, compared with preoperative baseline there was a numerical reduction in the Visual Analog Mood Scale (appendix) happy scores with both leads on or VIM on. There was also a numerical increase in the Profile of Mood States (appendix) Inertia/Fatigue scores with both leads off or both leads on. Finally, a reduction occurred in Profile of Mood States Anger/Hostility scores with both leads off, both leads on, and VIM-only on.

One patient suddenly died 2 years after surgery; this case was reviewed by the University of Florida Institutional Review Board and was judged to be unrelated to DBS implantation. A cumulative list of all adverse and unanticipated events is presented in table 3 and the appendix. Two infections occurred: first, a single deep surgical infection that necessitated the explantation of the entire DBS system; second, a superficial postoperative wound infection that resolved with a course of antibiotics. Neither of these patients were using immunomodulatory therapy that would predispose them to infection. One patient developed self-limited postoperative altered mental status. There was a single brief intraoperative seizure. An extension cable was replaced after it fractured approximately 1 year after surgery. Finally, a single new multiple sclerosis plaque was identified during the study after the patient developed increased hemiparesis and spasticity more than 1 year after DBS implantation. Several other routine postoperative complaints and stimulation-related

symptoms were also addressed. The most common non-serious adverse events were headache and fatigue.

Discussion

The preliminary findings of our study, plus findings from previous reports, support further research into the use of VIM plus VO stimulation to treat severe tremors in patients with multiple sclerosis that are not reliably controlled with traditional single-lead VIM DBS. Additionally, despite baseline cognitive deficits in several neuropsychological areas in our cohort, only slight changes occurred from baseline after dual-lead thalamic DBS. Our study built on results from our previous case series using dual thalamic DBS to treat multiple sclerosis tremor and post-traumatic tremor,[10,11] as well as work from Yamamoto and colleagues[14,15] who used two thalamic leads to treat severe essential tremor, parkinsonian tremor, and post-stroke tremor. In addition, several small case reports[16–18] have also described a role for VIM plus VO stimulation for treatment of severe tremor disorders, albeit with varying degrees of efficacy.

The poor efficacy of single-lead DBS in multiple sclerosis tremor might be related to differences in tremor pathophysiology when compared with more readily treated disorders, such as essential tremor or parkinsonian tremor.[10] Multiple sclerosis is a multifocal disease and its tremor pathology might involve pallidal circuitry in addition to the cerebello-thalamo-cortical loop; thus, dual-lead thalamic DBS might be advantageous because both the cerebellar receiving area (VIM) and the pallidal receiving area (VO) are targeted for stimulation. A second explanation, which does not exclude the first, is that dual-lead stimulation increases the volume of stimulation to more adequately influence the widely distributed thalamic somatotopy representing both the proximal shoulder and distal hand. This explanation is supported by findings from a case series where increased lesion volume was necessary to suppress post-traumatic and post-stroke tremors that involved the proximal muscles.[19] Although the efficacy of increased lesion volume is unfortunately closely associated with increasing side-effects, dual-lead thalamic DBS offers the opportunity to reversibly increase the volume of affected tissue in a controlled manner that can both optimise tremor control and minimise undesirable effects related to stimulation.

In addition to the complexities of multiple sclerosis tremor pathophysiology, other factors contribute to the inconsistency of DBS effectiveness in this disorder. Substantial variability exists among patients in the location and burden of demyelinating lesions, degree of neurological deficit, and rate of multiple sclerosis progression. Although no evidence exists to suggest that DBS surgery might induce an multiple sclerosis exacerbation, we were still concerned about this possibility—however, in our series only one confirmed

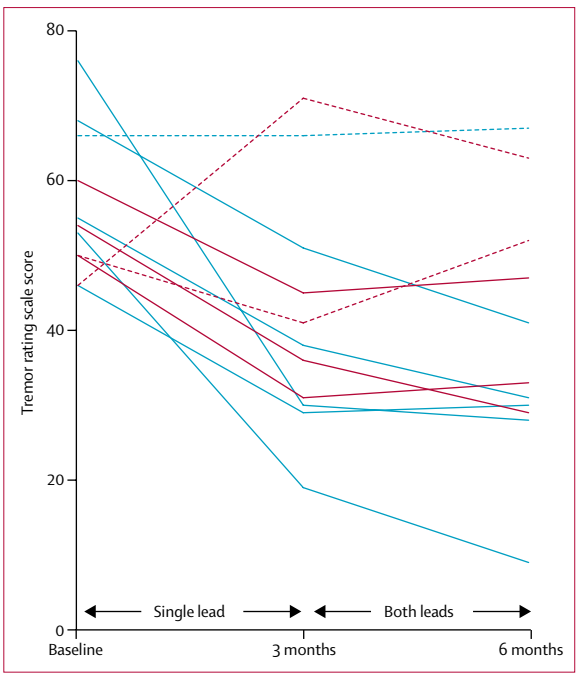

Figure 3: **Individual tremor rating scale scores over time**
Scores are shown for each individual patient measured at their preoperative baseline, at 3 months with single-lead activation, and at 6 months with dual-lead activation. Blue lines indicate patients assigned to ventral intermediate nucleus (VIM) stimulation for the first 3 months. Red lines indicate patients assigned to ventralis oralis (VO) stimulation for the first 3 months. Dashed lines indicate patients identified as non-responders to deep brain stimulation (patient identification numbers 4, 7, and 12). Data are for 11 patients, six in the VIM-only initial stimulation group and five in the VO-only initial stimulation group.

	Baseline	Both leads off	VIM lead only initially	VO lead only initally	Both leads on
Stroop					
Word	55·7 (24·0)	54·4 (20·1)	56·1 (22·7)	56·5 (15·9)	58·7 (14·7)
Colour	46·7 (15·4)	41·1 (16·4)	39·6 (21·2)	39·2 (16·3)	40·0 (15·3)
Colour-Word	30·4 (16·3)	25·9 (12·6)	26·8 (14·4)	23·8 (12·1)	26·3 (11·5)
Interference	3·2 (7·4)	3·9 (8·4)	5·7 (6·7)	2·7 (6·1)	4·2 (5·4)
PASAT					
Trial	24·3 (13·1)	24·7 (15·0)	25·1 (15·8)	27·5 (16·9)	26·2 (15·3)
Total	41·4 (25·6)	47·3 (30·8)	47·4 (30·5)	43·8 (27·9)	50·3 (28·5)
Fluency					
Letter	31·1 (7·6)	28·2 (8·6)	28·4 (5·5)	28·4 (5·6)	29·3 (6·6)
Semantic	14·5 (5·2)	21·6 (13·2)	14·8 (6·7)	16·1 (5·3)	16·1 (4·4)
HVLT					
Trial 1	6·4 (1·6)	6·8 (1·8)	6·8 (1·3)	6·9 (2·4)	6·7 (1·9)
Total recall	24·1 (3·9)	25·3 (5·2)	25·7 (3·6)	23·9 (6·6)	25·2 (4·7)
Delayed recall	6·8 (3·4)	8·6 (3·3)	7·8 (3·7)	7·9 (2·7)	8·3 (3·7)
Percentage retention	68·0% (31·9)	86·1% (25·2)	75·0% (31·8)	84·4% (16·1)	79·4% (27·5)
RDI	10·3 (1·8)	11·0 (2·0)	10·9 (2·3)	10·3 (2·5)	10·9 (1·6)

Data are mean (SD) for 11 patients, six in the VIM-only stimulation group and five in the VO-only stimulation group. VIM=ventral intermediate nucleus. VO=ventralis oralis. Stroop=Stroop Color-Word Naming Test. PASAT=Paced Auditory Serial Addition Test. HVLT=Hopkins Verbal Learning Test. RDI=Recognition Discrimination Index.

Table 2: **Neuropsychological battery results**

	Serious adverse events	Other adverse events
Patient 2	Superficial wound infection	*Clostridium difficile* infection, headache, lightheadedness, leg weakness*, and speech difficulty*
Patient 4	Transient altered mental status, late multiple sclerosis exacerbation	Nausea, vomiting, constipation, headache, paresthesias*, arm weakness*, and facial pulling*
Patient 6	Self-limited intraoperative seizure	Balance difficulty, headache, fatigue, incisional tenderness, and falling*
Patient 7	None	Headache, fatigue, insomnia, decreased mobility*, and dysarthria*
Patient 9	Sudden death >1 year after operation	Headache
Patient 10	None	Trigeminal neuralgia, headache or scalp tenderness, fatigue, insomnia, leg weakness*, and dysarthria*
Patient 11	Deep infection or DBS system explantation	Slow or stuttering speech, and fever
Patient 12	None	Arm weakness*
Patient 13	Extension fracture	Tenderness at implantable pulse generator, and UTI
Patient 14	None	Scarring along extension cable
Patient 15	None	Dysphagia
Patient 16	None	UTI, pseudobulbar symptoms, irritability, and dysarthria*

A cumulative list of adverse events is presented. DBS=deep brain stimulation. UTI= urinary tract infection.
*Stimulation-related symptoms, which resolved with additional DBS programming.

***Table 3*: Adverse events**

new multiple sclerosis plaque occurred, more than 1 year after surgery. A second transient worsening of multiple sclerosis symptoms was also reported, also more than 1 year after surgery, but this was self-limited and of unclear significance. Many patients have ataxia associated with their tremor, which can also be severe. In some instances, clinical differentiation between the rhythmic tremor component of a patient's movement disorder (which typically responds to DBS) and the ataxic component (which would not be expected to respond to DBS) can be challenging. We sought to exclude patients with ataxia-predominant multiple sclerosis from our study, however, in practice we found it challenging to clinically predict the response to DBS in patients with coexistent tremor and ataxia. Indeed, two of the non-responders to dual-lead thalamic DBS in our study were retrospectively determined to have a predominant debilitating ataxia of their affected extremity. In future studies, the use of more sophisticated analytical tools to distinguish these clinical events might improve patient selection and therefore improve outcomes for patients with multiple sclerosis tremor.

Technically, the addition of a second thalamic DBS lead is straightforward. The second lead is placed along a parallel trajectory close to the VIM lead, through the same burr hole, after the location of the ventralis caudalis and VIM have been confirmed with microelectrode recording. Nevertheless, risks are associated with an additional brain penetration—albeit small—and additional costs for a dual-lead DBS system. We believe our results show that, for carefully selected patients with severe multiple sclerosis tremor, dual-lead (VIM plus VO) thalamic DBS provides some clinical benefit over traditional VIM DBS. None of the patients in our study who responded to DBS therapy showed any appreciable tremor rebound at 6 months with dual lead stimulation, which has been common in previous reports of DBS for multiple sclerosis tremor. This finding suggests that the dual-lead strategy might improve the durability of the therapeutic effect of DBS in these difficult cases. Overall, the risks of the procedure and side-effects appear to be similar to those of standard VIM DBS. No major deleterious cognitive postoperative changes were observed in the neuropsychological battery (table 2) and only minor changes in the fatigue or inertia and happiness subscores occurred in the mood battery (appendix).

Intriguing questions are raised by our trial for further study. First, is VO-only stimulation equivalent to VIM-only stimulation for severe multiple sclerosis tremor? Second, is dual-lead thalamic DBS truly superior to VIM-only or VO-only stimulation? Finally, did any improvement in the mean TRS from baseline with both leads implanted but off underlie a robust lesional microthalamotomy effect as a result of placing two ipsilateral DBS leads into the thalamus? Unfortunately, these questions could not be addressed in the current study because of the small size and will require further investigation.

Our study had several limitations. First, our sample size was small. As discussed previously, the initial trial was designed to include a cohort of 20 patients divided equally between post-traumatic and multiple sclerosis tremor. However, a protocol change was granted to restrict the study to 12 patients with multiple sclerosis tremor because of slow recruitment in the post-traumatic group. Additionally, one patient was excluded from the safety and efficacy analyses after undergoing explantation of their DBS system because of postoperative infection. Although our final cohort was sufficient to assess the feasibility of the intervention and could inform trial design in future, larger trials are needed. Because of the small sample size in our study—noting also that the three DBS non-responders were included in the primary outcome analysis—it can't be determined whether dual-lead treatment was effective, although our preliminary results suggest further research is warranted. Second, the follow-up period was limited to 6 months. Although we think that this was an appropriate period to assess tremor improvement after surgery or potential tremor rebound, late progressive loss of efficacy has also been reported over 1–3 years after DBS[3]—presumably due to multiple sclerosis disease progression. By contrast, some patients have late improvements in tremor in the 1–3 year range in the setting of thalamic DBS.[20] Finally, we chose to measure the full Tolosa-Fahn-Marin TRS (including both the semiquantitative bilateral motor exam and the disability questionnaire components) preoperatively and postoperatively because it is

well known, widely used, and has been extensively validated.[21] However, although the strength of the TRS is its multimodal assessment of tremor by both the clinician and the patient, this might obscure contralateral tremor responsiveness to DBS and thus underestimate the motor response to surgery. Likewise, the disability score is arguably the best indicator of DBS effect on quality of life, but this indicator is obscured when included as part of the total TRS score. However, TRS subscores were not prespecified outcome measures and have not been validated for standalone use.

The results of this study might also have relevance beyond the treatment of multiple sclerosis tremor. First, as in this study, dual-lead thalamic DBS might be used as a first-line surgical option for patients with severe multiple sclerosis tremor who have a known high risk of DBS failure with traditional single-lead VIM DBS. Second, placement of an additional rescue lead in VO could be considered intraoperatively for other cases of severe tremor when macrostimulation in VIM does not achieve adequate tremor suppression. Based on the clinically significant benefit observed in this cohort of patients with multiple sclerosis tremor—a frail population with the most severely debilitating and treatment refractory of tremors—it may be justified to consider expanded investigation of this technique for treatment of other severely debilitating and difficult-to-control tremor types, including post-traumatic, post-stroke, and severe essential tremor.

The preliminary findings of this pilot study underscore the potential use of dual-lead thalamic DBS for well selected individuals. Additional investigation with larger sample sizes and longer follow-up periods are necessary to establish the general applicability of this technique to large numbers of patients with refractory multiple sclerosis tremor or other severe tremor disorders. Our experience with this cohort has addressed the feasibility objectives of this study, which were to assess the safety and efficacy of dual-lead thalamic DBS and to determine suitable clinical endpoint measures. We therefore conclude that large-scale investigation of dual lead thalamic DBS is feasible, but that the limitations of this pilot study should be taken into consideration for future trial design.

Contributors

SFO contributed to the literature search, figures, data analysis, data interpretation, and writing. RLR contributed to the study design, data collection, data analysis, data interpretation, and writing. DB and DK contributed to the study design, data collection, data analysis, data interpretation, and writing. EHM contributed to the figures, data analysis, and writing. JDH and BMS contributed to the figures and data analysis. MSO and KDF contributed to the literature search, study design, data collection, data analysis, data interpretation, and writing.

Declaration of interests

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