Bilateral thalamic deep brain stimulation: midline tremor control

J D Putzke, R J Uitti, A A Obwegeser, Z K Wszolek, R E Wharen

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See end of article for authors' affiliations

Correspondence to:
Dr R J Uitti, Department of
Neurology, Davis Bldg E-
8, Mayo Clinic
Jacksonville, 4500 San
Pablo Road, Jacksonville,
FL 32224, USA; uitti@
mayo.edu

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Objectives: To determine the efficacy of bilateral deep brain stimulation (DBS) for management of midline tremor (head, voice, tongue, trunk) in patients with essential tremor.

Design: Prospective assessment of tremor at baseline (presurgical), and postoperatively at 1, 3, and 12 months, and annually thereafter.

Methods: A clinical series of 22 individuals undergoing staged, bilateral DBS for treatment of essential tremor. The tremor rating scale was the primary outcome measure.

Results: Midline tremor showed significant improvement with stimulation "on" at nearly every postoperative interval when compared with stimulation "off" and with baseline tremor. Bilateral stimulation was associated with a significant incremental improvement in midline tremor control compared with unilateral stimulation: average "stimulation on" percentage change in midline tremor from the unilateral to bilateral period was 81%. Head and voice tremor showed the most consistent improvement. Among those requiring a change in stimulation parameters because of side effects, dysarthria, disequilibrium, motor disturbances, and paraesthesiae were the most common. Dysarthria was more common with bilateral (n=6; 27%) than with unilateral (n=0) stimulation. Stimulation parameters remained largely unchanged after the first three months. Nine of 44 leads placed (20%) required subsequent repositioning or replacement.

Conclusions: Unilateral thalamic stimulation significantly improves midline tremor, and subsequent bilateral thalamic stimulation offers an additional incremental improvement in midline tremor control.

Essential tremor is a commonly diagnosed movement disorder¹ typically involving high frequency postural and intention tremor. It predominantly affects the distal upper extremities, but may also affect midline structures and functions, including the head, face, voice, and trunk (range 5–34% with various midline tremors).² Deep brain stimulation (DBS) of the ventral intermediate (Vim) nucleus of the thalamus has been shown to be effective at reducing disabling tremor in the contralateral distal upper and lower extremities among individuals with essential tremor.^{3,4} In some cases stimulation may also reduce ipsilateral tremor; however, the magnitude of effect is substantially smaller, of marginal clinical significance,⁵ and not sustained over the long term (that is, more than 12 months).^{6,7}

There is increasing evidence that thalamic stimulation also improves midline tremor.^{4,5,8–14} The ability to control midline tremor tends to be associated with symptom severity such that more severe tremors show the greatest improvement with stimulation,⁸ whereas mild tremor shows little or no change.¹⁵ Although several studies have shown that unilateral DBS may improve midline tremor,^{4,5,8,13} the most consistent effects occur with bilateral Vim stimulation.¹⁵ Indeed, studies of staged, bilateral DBS have shown that improvement in midline tremor tends to occur primarily after placement of the second lead.^{4,9,12,14} Unfortunately, potential bias in dropouts, variable data collection, and limited analyses that account for missing data are three methodological concerns that have limited our understanding of midline tremor control with thalamic DBS.

Our current study was designed to extend previous research on midline tremor control by including a standardised data collection protocol (that is, at one, three, and 12 months and annually thereafter), an examination of dropout characteristics, and a range of missing data estimation methods to account for missing data.

METHODS

Participants and procedures

A clinical series of 24 consecutive individuals with essential tremor undergoing bilateral thalamic DBS for intractable tremor was considered for study. The diagnosis of essential tremor was made by one neurologist (RJU), based on the Louis criteria.¹⁶ The indication for surgery was disabling tremor despite optimal medical treatment, which involved individual and combination trials of propranolol, primidone, and gabapentin at maximum tolerated doses. All patients discontinued pharmacological antitremor therapy before preoperative tremor assessment. One patient who underwent previous stimulator placement at another institution was excluded from the study. One of the initial individuals was not followed according to the standard protocol (that is, one, three, and 12 months and annually thereafter) until after the placement of the second DBS lead 14 months later. No data were available between the first and second placement, and the patient was therefore not included in the study. One individual had simultaneous bilateral lead placement and was only included in the analyses of bilateral DBS and midline tremor. In all, therefore, 22 individuals were included, representing a subset of the 52 patients previously reported with unilateral and bilateral stimulation.⁶ More specifically, the current study is a detailed report of midline tremor control among those individuals with bilateral stimulation.

The surgical procedures have been described in detail previously.¹⁷ In brief, a stereotactic target in the Vim was planned with magnetic resonance guidance. In all patients test stimulations were carried out intraoperatively to evaluate tremor relief and side effects. After determining the optimal

Abbreviations: DBS, deep brain stimulation; IPG, implantable pulse generator; TRS, tremor rating scale; Vim, ventral intermediate (nucleus)

Table 1 Electrode position across various groups

	Distal electrode	Proximal electrode
<i>All leads</i>		
Laterality from PC	14.4 (1.9)	16.6 (2.1)
Anterior distance from PC	5.9 (2.3)	11.5 (2.6)
Distance above (–) or below (+) AC/PC line	0.3 (2.6)	–6.2 (2.5)
<i>Leads not requiring repositioning</i>		
Laterality from PC	14.4 (1.9)	16.6 (2.1)
Anterior distance from PC	6.0 (2.1)	11.6 (2.2)
Distance above (–) or below (+) AC/PC line	0.3 (2.6)	–6.3 (2.5)
<i>Leads requiring repositioning</i>		
Laterality from PC	14.2 (2.4)	16.6 (2.7)
Anterior distance from PC	5.0 (4.0)	10.6 (4.6)
Distance above (–) or below (+) AC/PC line	0.5 (2.5)	–6.1 (2.5)

Values are distances in mm (mean (SD)). There were no significant differences across groups.

AC, anterior commissure; PC, posterior commissure.

position, the stimulation electrode (model 3387, Medtronic, Minneapolis, Minnesota, USA) was secured to the skull and connected to the infraclavicular pulse generator under general anaesthesia.

Initial stimulation programming occurred the day after surgery and within two weeks after surgery for further stimulator programming. If necessary, stimulation parameters were adjusted for optimal tremor control with minimal side effects. If patients later observed side effects or a loss of tremor control, they returned for further pulse generator adjustment. Initial paraesthesiae, occurring when the stimulator was turned “on” and subsiding within a few seconds, were not considered side effects. Clinic visits to assess tremor control and side effects were scheduled after the initial lead placement for each side at one, three, and 12 months, and then annually thereafter. Follow up scores were measured with the stimulator switched “off” and switched “on.” Typically, the stimulator was deactivated overnight before the patient was examined in the morning. In cases in which the patient did not deactivate the stimulator overnight, it was deactivated for at least one hour before tremor assessment. All scores were recorded before any adjustments were made to the stimulation parameters, thus providing a conservative estimate of efficacy.

The tremor rating scale (TRS)¹⁸ is a well established patient and clinician based rating scale of tremor and activities of daily living. The TRS contains 21 items that use a five point Likert scale (0, no tremor/disability; 4, severe tremor/disability) as well as a global disability item (0, no functional disability; 4, severe disability). The midline tremor total score (possible range 0 to 32) was the sum the five tremor location scores: face, tongue, voice, head, and trunk tremor. The types of tremor assessed for each location included resting tremor for the face (possible range 0 to 4), intention tremor for voice (0 to 4), and postural and resting tremor for the tongue, head, and trunk (0 to 8). The activities of daily living (ADL) score (possible range 0 to 32) summed eight items involving the ability to carry out day to day tasks (dressing, writing, hygiene, and so on).

Statistical procedures

The Wilcoxon signed rank test was used for three primary sets of comparisons. First, baseline functioning was compared with both the “on” and the “off” stimulation condition at each postoperative interval. Second, the stimulation “on” versus “off” condition was compared at each postoperative interval. Third, the unilateral three month “on” stimulation condition was compared to bilateral “on” stimulation scores

at each postoperative bilateral interval in order to determine whether bilateral DBS offers a significant incremental effect over unilateral DBS. Significance was set at $p < 0.05$; however, three significance levels are reported ($^1p < 0.05$, $^2p < 0.01$, $^3p < 0.001$) so that results could be evaluated according to various correction methods (for example, Bonferroni).

RESULTS

Sample characteristics

Examination of demographic characteristics indicated that the group was mostly male ($n = 12$, 55%), with a mean (SD) age of 70.3 (9.0) years and a tremor duration of 30.0 (14.3) years at the time of the first surgery. Left sided brain stimulation was carried out first in the majority of cases ($n = 20$, 91%). As part of a staged bilateral DBS placement, the mean duration between placement of the first and second lead was 223 days, most being undertaken within five months or less ($n = 17$; 77%) following initial surgery. The mean time between the initial lead placement and last available follow up was 29 months. Over the course of follow up, seven leads required repositioning owing to loss of effect, and two leads were broken and subsequently replaced. Other surgical procedures included replacement of one implantable pulse generator (IPG) and one DBS system (right side) was explanted because of infection after 22 months.

Table 1 presents a summary of the electrode position separated into three groups: all leads combined; leads that did not require repositioning; and leads requiring repositioning. In general, results suggest that most distal lead positions were in one of the usual Vim thalamic locations. Lead position was not significantly different between the leads that did or did not require repositioning.

Rather than arbitrarily establishing a cut off date for study inclusion, all available data at the time of analysis were included. Thus individuals were separated into mutually exclusive and collectively exhaustive status groups based on their evaluation status at each postoperative interval. Three status groups were defined several months after the initial lead placement: those whose evaluation was obtained; those whose evaluation was not obtained; and those in whom a second lead was already placed. For the period after placement of the second lead, the five status groups were as follows: those with evaluations not due yet; those with evaluations due and outcome measures obtained; those with evaluations due and outcome measures not obtained; lost to follow up; and deceased. For clarification, the “evaluation not due yet” group included those who had yet to reach a particular postoperative interval. For example, an individual who was three months out from their second lead placement would be considered in the “evaluation not due yet” group at the 12 month bilateral postoperative interval. Table 2 presents several summary characteristics including the number of individuals in the various status groups at each postoperative interval, the mean days from the expected date the evaluation was carried out, and the proportion of evaluations due that were actually obtained. Three individuals died of unrelated causes (lung cancer, gunshot wound, and colon cancer). One was considered lost to follow up because of transfer of care. During a structured telephone interview the individual lost to follow up reported continued good tremor control and improvement in activities of daily living with stimulation, and no subsequent device related surgery (for example, lead repositioning, battery replacement).

Two sets of comparisons were made to determine whether those available for analysis at each postoperative interval were representative of the overall sample. First, the demographic characteristics (sex, duration of symptoms, and age at first surgery) of those with completed evaluations at each postoperative interval were compared with the overall group

Table 2 Summary of data collection at various intervals (n = 22 patients)

	Baseline	1 Month	3 Months	12 Months	24 Months	36 Months
Unilateral DBS (period between first and second lead placement)						
Evaluation obtained	21 (96)	21 (96)	16 (73)	4 (18)	0 (0)	0 (0)
Evaluation not obtained	1 (4)	0 (0)	0 (0)	0 (0)	2 (9)	0 (0)
Second lead already placed	–	1 (4)	6 (27)	18 (82)	20 (91)	22 (100)
Days from expected date (mean (SD))	1.2 (1.0)	4.2 (3.2)	14.4 (22.5)	11.0 (9.8)	–	–
Bilateral DBS (period after placement of second lead)						
Evaluation not due yet	–	0 (0)	0 (0)	2 (9)	5 (23)	12 (54)
Evaluation obtained	–	18 (82)	20 (91)	12 (54)	13 (59)	5 (23)
Evaluation not obtained	–	4 (18)	2 (9)	5 (23)	0 (0)	1 (4)
Deceased	–	0 (0)	0 (0)	3 (14)	3 (14)	3 (14)
Lost to follow up	–	0 (0)	0 (0)	0 (0)	1 (4)	1 (4)
Percentage of evaluations due that were obtained	–	82%	91%	60%	76%	50%
Days from expected date (mean (SD))	–	3.4 (2.5)	9.9 (12.2)	63.0 (101.9)	75.7 (118.4)	42.0 (42.9)

Values are n (%) except where indicated.

characteristics at baseline. Second, the demographic characteristics of those with complete versus incomplete evaluations (lost to follow up, evaluation not obtained, deceased) at each postoperative interval were compared to assess differential drop out rates. None of the demographic comparisons examined was significant ($p > 0.05$).

Efficacy over time

As previously shown,⁶ contralateral upper extremity tremor was significantly improved with stimulation “on” at nearly every postoperative interval when compared with the stimulation “off” condition and with baseline tremor (fig 1). An additional incremental effect following placement of the second lead was not observed. However, contralateral upper extremity tremor remained consistently controlled with stimulation during the bilateral stimulation period.

The extent of midline tremor was evaluated at baseline. Results indicated that 95% of the sample had a score of 1 or more on the TRS midline tremor total score, and 57% had a score of 4 or more. The midline tremor total score showed significant improvement with stimulation “on” at nearly every postoperative unilateral and bilateral interval when compared with the stimulation “off” condition and with baseline tremor. Moreover, placement of the second lead was associated with incremental improvement in midline tremor control as compared with unilateral stimulation (the three month postoperative unilateral interval was chosen so as to be outside the window of possible microthalamotomy effects)

at most postoperative bilateral intervals (fig 2). Indeed, the average “on” percentage change from the unilateral to the various bilateral follow up periods was 81% (range 59% to 100%) and the average effect size estimate (the difference between the unilateral and bilateral mean divided by the pooled average standard deviation) was 1.3 (range 0.77 to 1.95), representing a large effect size difference. Bivariate correlations were calculated between baseline midline tremor score, and the “off” v “on” stimulation difference score at each postoperative interval in order to determine the relation between initial tremor severity and treatment effect. (Correlations not generated for the 36 month postoperative bilateral stimulation interval due to small sample size.) With one exception (that is, 12 months postoperative bilateral stimulation, $r = 0.12$, $p = 0.74$), the correlation coefficients were all significant (mean $r = 0.69$; range = 0.57 to 0.82).

Analysis of midline tremor at the longest postoperative interval (that is, 36 months post bilateral stimulation) was limited owing to the small sample size ($n = 5$) and attrition (50%). Intention to treat analyses were carried out in an attempt to account for missing data at the year 3 bilateral stimulation interval. More specifically, all those with evaluations due at the 36 month bilateral interval were included for analysis (that is, those with evaluations obtained and not obtained, deceased, and lost to follow up). A range of liberal to conservative estimates for the total midline tremor score was used for missing data. The most conservative technique was the “insert baseline functioning” method, followed by

Figure 1 Contralateral tremor.

[†] $p < 0.05$ v baseline;
^{††} $p < 0.01$ v baseline;
^{†††} $p < 0.001$ v baseline;
^{*} $p < 0.01$ v “on” stimulation;
^{†††} $p < 0.001$ v “on” stimulation.

Figure 2 Midline tremor.

¹ $p < 0.05$ v baseline;
² $p < 0.01$ v baseline;
³ $p < 0.001$ v baseline;
^{*} $p < 0.01$ v "on" stimulation;
^{††} $p < 0.001$ v "on" stimulation;
^{‡‡} $p < 0.05$ v "on" stimulation;
^{§§} $p < 0.05$ v "on" stimulation unilateral month 3;
^{¶¶} $p < 0.01$ v "on" stimulation unilateral month 3.

the "carry forward the worst stimulation on and off score"; the most liberal estimate of missing data was the "carry forward the most recently available stimulation on and off score" technique. In all, three comparisons were made for each intent to treat technique: the stimulation "on" condition at 36 months was compared with both the stimulation "off" condition and baseline, and the stimulation "off" condition was compared with baseline. None of the three comparisons was significant using the most conservative approach ($p > 0.05$); two of the three were significant using the next most conservative approach, and all three were significant using the most liberal approach ($p < 0.05$).

Table 3 (unilateral stimulation) and table 4 (bilateral stimulation) provide a more detailed summary of the individual items that comprise the TRS midline tremor total score for the stimulation "on" and "off" conditions at the various postoperative intervals. Upper extremity ipsilateral tremor and ADL scores are also provided. As can be seen, the most consistent improvement during both unilateral and bilateral stimulation was found for head and voice tremor. Moreover, the bilateral stimulation "on" condition for head and voice tremor showed a significant incremental improvement over unilateral stimulation through the first 12 months of bilateral stimulation. Small sample size limited power for these analyses at 24 and 36 months after the second DBS placement. It should be noted, however, that effect size estimates (mean of unilateral "on" stimulation mean minus mean of bilateral "on" stimulation divided by pooled standard deviation) remained largely the same. Trunk, tongue, and face tremor also showed significant improvement with stimulation, although floor effects and the small number of individuals with these types of tremor limited statistical power. For example, only three individuals at baseline were rated with observable trunk tremor. These three individuals had no observable trunk tremor with stimulation during both the unilateral and bilateral period.

Table 3 Summary of clinical tremor rating scale (unilateral stimulation)

Tremor location	Baseline	Month 1	Month 3
Head			
Off stimulation	2.1 (2.1)	1.4 (2.0) ^{1*}	1.2 (1.6) ¹
On stimulation		0.8 (1.2) ³	0.9 (1.1) ²
Voice			
Off stimulation	1.7 (1.2)	1.7 (1.0) [†]	1.1 (1.1)
On stimulation		0.7 (1.0) ¹	1.1 (1.1)
Tongue			
Off stimulation	0.9 (1.4)	0.6 (1.2)	0.4 (0.7)
On stimulation		0.2 (0.4) ¹	0.3 (0.6)
Face			
Off stimulation	0.7 (1.1)	0.6 (0.8) [‡]	0.6 (0.8) [*]
On stimulation		0.1 (0.3) ²	0.1 (0.3) ¹
Trunk			
Off stimulation	0.4 (1.0)	0.3 (1.1)	0.4 (0.7)
On stimulation		0.0 (0.0)	0.0 (0.0)
Ipsilateral UE tremor			
Off stimulation	6.4 (2.2)	6.4 (2.5) [*]	5.8 (3.0)
On stimulation		5.7 (2.3) ¹	5.1 (2.9)
ADL			
Off stimulation	18.0 (3.3)	—	—
On stimulation		7.1 (5.3) ³	6.4 (6.0) ³

Values are mean (SD).

¹ $p < 0.05$ v baseline; ² $p < 0.01$ v baseline; ³ $p < 0.001$ v baseline;

^{*} $p < 0.05$ v "on" stimulation; ^{††} $p < 0.001$ v "on" stimulation; ^{‡‡} $p < 0.01$ v "on" stimulation.

ADL, activities of daily living; UE, upper extremity.

Side effects and stimulator settings

In all, 225 clinic visits (both scheduled and unscheduled) were made, and 81% ($n = 182$) involved a change to the stimulator settings for at least one IPG. Of the 182 changes made, the stimulator setting adjustment was required in order to eliminate side effects in 17% ($n = 31$), to improve tremor control in 68% ($n = 124$), or both in 8% ($n = 15$), or else data were missing (7% ($n = 12$)). The most common self reported problems among those undergoing a stimulation change to eliminate side effects were dysarthria (45%), disequilibrium (41%), motor disturbances (32%), and paresthesiae (23%). The side effect profile during unilateral and bilateral stimulation was compared. In order to control for variability in time between the staged procedure, the interval over which side effects were examined was standardised for each patient as the shorter of two periods: either the number of days between the placement of the first and second lead, or the number of days between placement of the second lead and the date of the last available assessment of side effects. Thus intervals of similar length were compared during periods with unilateral and bilateral DBS. McNemar's test

Table 4 Summary of clinical tremor rating scale (bilateral stimulation)

Tremor location	Month 1	Month 3	Year 1	Year 2	Year 3
<i>Head</i>					
Off stimulation	1.1 (1.3) ¹ ‡	1.0 (1.3) ¹ ‡	1.3 (1.4) ¹ ‡	0.8 (1.0) ¹	0.3 (0.5)
On stimulation	0.1 (0.3) ³ §	0.2 (0.4) ³ §	0.1 (0.3) ² §	0.2 (0.4) ²	0.0 (0.0)
<i>Voice</i>					
Off stimulation	1.5 (0.9) [†]	1.4 (1.2) [†]	1.6 (0.9) [‡]	1.3 (0.8) [*]	1.0 (0.8)
On stimulation	0.6 (0.8) ³ ¶	0.3 (0.7) ³ ¶	0.3 (0.7) ² §	0.6 (0.7) ²	0.0 (0.0)
<i>Tongue</i>					
Off stimulation	0.3 (0.6)	0.3 (0.7) ¹	0.5 (1.0)	0.5 (0.8)	0.0 (0.0)
On stimulation	0.1 (0.3) ¹	0.0 (0.0) [†]	0.0 (0.0) ¹	0.3 (0.5)	0.0 (0.0)
<i>Face</i>					
Off stimulation	0.3 (0.7)	0.2 (0.5) ¹	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)
On stimulation	0.1 (0.2) ¹	0.0 (0.0) ¹	0.0 (0.0)	0.0 (0.0) ¹	0.0 (0.0)
<i>Trunk</i>					
Off stimulation	0.1 (0.5)	0.1 (0.2)	0.0 (0.0)	0.1 (0.3)	0.0 (0.0)
On stimulation	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)
<i>Ipsilateral UE tremor</i>					
Off stimulation	5.2 (2.3) ¹ ‡	5.2 (2.5) [†]	4.2 (2.5) ¹ ‡	5.6 (2.2) [‡]	4.0 (2.0)
On stimulation	1.2 (1.3) ³ ¶	1.0 (1.4) ³ ¶	0.6 (0.8) ² ¶	1.3 (1.2) ² §	1.0 (0.7)
<i>ADL</i>					
Off stimulation	–	–	–	–	–
On stimulation	4.6 (5.1) ³	4.3 (5.7) ³	3.3 (4.5) ²	5.5 (4.4) ²	2.6 (1.5)

Values are mean (SD).

¹p<0.05 v baseline; ²p<0.01 v baseline; ³p<0.001 v baseline; ^{*}p<0.05 v "on" stimulation; [†]p<0.001 v "on" stimulation; [‡]p<0.01 v "on" stimulation; [§]p<0.05 v "on" stimulation; [¶]p<0.01 v "on" stimulation unilateral month 3.

ADL, activities of daily living; UE, upper extremity.

Table 5 Side effects reported during staged bilateral lead placement over standardised intervals

Side effect	Unilateral	Bilateral
Dysarthria	0 (0)	6 (27) [*]
Disequilibrium	2 (9)	5 (23)
Paraesthesiae	3 (14)	1 (5)
Motor disturbance	1 (5)	2 (9)

Values are n (%).

Average standardised interval length = 146 days; total n = 22.

^{*}p = 0.03 v unilateral.

for symmetry was used to compare the proportion of individuals experiencing each side effect during unilateral v bilateral stimulation (table 5). Dysarthria was more common after bilateral than after unilateral stimulation (p<0.05). None of the other comparisons was significant.

Stimulation parameters were recorded both as part of the standard clinical protocol and during patient initiated visits for parameter adjustments. Stimulator settings closest to the expected standard clinical protocol (that is, 1, 3, 12, 24, 36 months) were used for analysis. Two sets of analyses were carried out using the Wilcoxon signed rank test. First, the stimulation parameters (amplitude, rate, pulse width) for each DBS system (right and left) were compared between each adjacent postoperative interval (for example, year 1 v year 2). Second, stimulation parameters at month 1 were compared with all other intervals for each DBS system. Overall, a total of 18 unique comparisons was made for each stimulation parameter.

Tables 6 and 7 present a summary of the stimulation parameters at each postoperative interval for the two DBS systems placed. As can be seen, most of the comparisons were non-significant. Indeed, none of the comparisons was

Table 6 Summary of stimulator settings over time, unilateral stimulation

Setting	Month 1	Month 3
<i>Amplitude</i>		
First side	2.6 (0.8)	2.8 (1.1)
Second side	–	–
<i>Rate</i>		
First side	160.0 (20.9)	158.3 (30.8)
Second side	–	–
<i>Pulse width</i>		
First side	78.5 (19.5)	80.9 (33.0)
Second side	–	–
Days from expected date	6.4 (5.9)	7.6 (6.2)

Values are mean (SD).

significant for pulse width. Only two of the 18 paired comparisons were significant for both amplitude and rate (both showing an increase between month 1 and month 3 for the second DBS system). Amplitude at year 2 was higher than at month 1, and rate at year 1 was higher than at month 1.

Lastly, change in parameter settings in the first DBS system after surgical placement of the second DBS system was further examined by using the closest evaluation (rather than the evaluation closest to the clinical protocol) just before and after the placement of the second DBS system. This approach served to control for interval length variability between placement of the first and second DBS systems. None of the three comparisons (amplitude, rate, pulse width) showed a difference in the stimulation parameters of the first DBS system after the second DBS system was placed (p>0.05).

Table 7 Summary of stimulator settings over time (bilateral stimulation)

Setting	Month 1	Month 3	Year 1	Year 2	Year 3
<i>Amplitude</i>					
First side	2.8 (1.3)	2.8 (1.2)	2.3 (1.1)	3.1 (0.9)	2.8 (1.0)
Second side	2.0 (0.7)	2.5 (0.7)*	2.5 (0.8)	2.8 (0.9)*	2.4 (0.7)
<i>Rate</i>					
First side	152.4 (37.3)	160.0 (27.0)	167.0 (21.8)	172.5 (20.4)	168.1 (19.8)
Second side	147.9 (31.9)	152.5 (26.5)*	163.0 (20.1)*	163.8 (19.4)	158.8 (19.4)
<i>Pulse width</i>					
First side	93.8 (33.0)	96.3 (38.2)	96.9 (21.8)	95.0 (25.0)	97.5 (26.6)
Second side	86.8 (19.9)	78.0 (15.2)	94.7 (36.4)	87.7 (19.2)	97.5 (31.1)
Days from expected date	6.3 (7.1)	10.2 (10.5)	47.8 (60.0)	26.5 (6.2)	40.9 (38.3)

* $p < 0.05$ v month 1. None of the adjacent pairs was significantly different except as noted between month 1 and month 3.

DISCUSSION

Between 5% and 34% of individuals with essential tremor may present with midline tremor. Both unilateral and bilateral thalamic stimulation have been shown to improve this condition. However, methodological limitations have complicated interpretation of the data. The current study was designed to improve the methodological approach of previous research by incorporating additional analytical (missing data estimation methods, examination of drop outs) and design related techniques (results reported according to a standardised clinical protocol). Three main findings emerged.

First, unilateral thalamic stimulation was associated with significant improvement in midline tremor when compared both with the “off” stimulation condition and with baseline tremor.^{4 5 8 9 13} The reported follow up period for unilateral stimulation in the current study was relatively short (three months); however, others have shown stable midline tremor control with unilateral stimulation for 12 months or more.^{6 13}

Second, bilateral stimulation was also associated with a significant improvement in midline tremor when compared both with the “off” stimulation condition and with baseline tremor. In fact, bilateral stimulation offered an additional incremental effect in midline tremor control over unilateral stimulation. For instance, the average “stimulation on” percentage change from the unilateral to the various bilateral follow up periods was 81%.

Third, the effect of stimulation on midline tremor was stable over time, although results at the longest postoperative interval were limited owing to the small sample size and missing data. In order to further examine the results at the longest postoperative interval, missing data estimation methods were undertaken using a range of liberal to conservative estimates. Results were mixed, with the more liberal intention to treat analysis (carry forward the most recent) confirming midline tremor control, whereas the other two more conservative techniques failed to show consistent statistical support. Thus results at the 36 month bilateral stimulation interval are speculative.

The TRS midline tremor total score includes items that assess face, tongue, voice, head, and trunk tremor. The most consistent results were found for head and voice tremor, which were also the most commonly experienced midline tremors (81% and 90% of the sample with a score of 1 or more, respectively, on at least one item).¹⁰ Face, tongue, and trunk tremor were less common in the sample (38%, 47%, and 14% of the sample with a score of 1 or more on at least one item), thus limiting the statistical power to find an effect, but generally showed improvement with stimulation (for example, none of the three individuals with trunk tremor at baseline had observable trunk tremor with stimulation

during both the unilateral and bilateral periods). Related to this, the effect of thalamic stimulation on midline tremor tended to increase with symptom severity. More specifically, those with the most severe midline tremor at baseline had the greatest difference between the stimulation “on” v “off” condition which may explain, in part, the limited effect between stimulation and midline tremor control found in the European trial that reportedly involved primarily those with mild midline tremor.¹⁵ It should be noted, however, that an attenuated relation between baseline tremor, and “on” v “off” difference scores may also be attributed to restricted scaling in the mild tremor range (for example, ceiling effects). Indeed, the psychometric characteristics of the TRS for the various types of midline tremor are limited. Future research on midline tremor would benefit from the development of measures that allow more extensive assessment of the various types and locations of midline tremor.

The mechanisms of action are not well understood, but DBS is generally thought potentially to involve any of the following: stimulation of neural tracts, “depolarisation block”, disruption of neural networks (“neural jamming”), generation of action potentials at the cathode, and build up of neurotransmitters and neuromodulators over time that produce changes to neural network properties.¹⁹

Adverse side effects related to stimulation were generally mild and easily altered by adjusting stimulus parameters. The most common side effects reported were dysarthria, disequilibrium, motor disturbances, and paraesthesiae. Consistent with our previous report,⁶ the proportion of individuals who experienced each side effect at least once during the course of DBS was used as the level of analysis, rather than a simple count of each side effect occurrence. This approach limited the impact of over-representation caused by variation in treatment seeking behaviour (for example, report of the same side effect on repeated occasions by one individual). In order to control for interval variability between the first and second lead placement, the length of time over which side effects were compared under the unilateral v bilateral stimulation condition was standardised for each individual as the shorter of two intervals: time between the first and second surgery, or time between the second surgery and the last available follow up. Results showed that dysarthria appeared only after bilateral stimulation. An increase in adverse events after placement of a second DBS system has been reported previously,^{11 12} although these were not considered serious adverse events. The proportion of individuals who experienced other side effects was not significantly different between the unilateral and the bilateral stimulation periods. Taken together, the increased benefits of tremor control associated with the

placement of a second lead should be weighed against the increased risk of dysarthria.

Examination of the stimulator settings at adjacent postoperative intervals for each DBS system (left and right) showed little or no change over long term follow up intervals. Moreover, the stimulation parameters of the initial DBS system did not change after placement of the second stimulator lead. The rate and amplitude of the second stimulator showed some change, mostly over the first three months, levelling off thereafter. Pulse width remained largely unchanged across all postoperative intervals. These findings are consistent with other studies that showed an increase in stimulation parameters only within the first several months after surgery,^{3 20 21} although others have shown evidence of the need for a systematic increase in stimulation parameters to maintain tremor control.^{14 22 23}

An attempt was made to determine whether the results at each postoperative interval were representative. In fact, analyses of the demographic characteristics of those whose midline tremor evaluations were obtained at each postoperative interval showed no difference when compared with those whose evaluations were not obtained, or with the overall sample at baseline. The lack of differences in demographic characteristics served to minimise concerns that selective attrition may have influenced the results, and increased the likelihood that they can be generalised to apply to the overall sample. It should be noted, however, that the small sample size at the longer postoperative intervals limits the power to detect differences.

If one considers the nine leads that required reoperation as failures, then the failure rate for tremor control in this series was 20% (9/44). In our experience, lead fractures that had been occurring in the extreme proximal region of the brain electrode (close to the extension lead connector site) happened in this historic cohort but not since we have employed the revised smaller profile connector, which has also shown less propensity to migrate. In all patients, however, long term tremor control was achieved and stimulation tolerance to the extent of preventing tremor control was not observed. Moreover, the vast majority of patients have maintained stable tremor control. Examination of lead position showed no differences between leads that did or did not require repositioning. In general, the benefits of stimulation are thought to outweigh health care provider and patient burden costs related to device maintenance and failure.²⁴ However, the costs associated with DBS, particularly over the long term, have yet to be clearly determined and will be an important focus of future research.

Conclusions

Thalamic stimulation is generally an effective approach for management of midline tremor associated with essential tremor. Although unilateral stimulation results in improvement, bilateral stimulation offers a significant further increment in midline tremor control. The results tend to be maintained over time and do not require a systematic increase in stimulation parameters. Adverse affects are generally mild and can be controlled by adjustment to the stimulation parameters. Bilateral stimulation, however, may be associated with modest speech difficulties that can typically be minimised with adjustment in stimulation parameters.

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Authors' affiliations

J D Putzke, R J Uitti, Z K Wszolek, Department of Neurology, Mayo Clinic Jacksonville, Florida, USA

R E Wharen, A A Obwegeser*, Department of Neurosurgery, Mayo Clinic Jacksonville

*Also at Department of Neurosurgery, University Innsbruck, Austria

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REFERENCES

- Findley LJ. Epidemiology and genetics of essential tremor. *Neurology* 2000;**54**:S8–13.
- Elble RJ. Diagnostic criteria for essential tremor and differential diagnosis. *Neurology* 2000;**54**:S2–6.
- Benabid AL, Pollak P, Gao DM, et al. Chronic electrical stimulation of the ventralis intermedius nucleus of the thalamus as a treatment of movement disorders. *J Neurosurg* 1996;**84**:203–14.
- Obwegeser AA, Uitti RJ, Witte RJ, et al. Quantitative and qualitative outcome measures after thalamic deep brain stimulation to treat disabling tremors. *Neurosurgery* 2001;**48**:274–81.
- Ondo W, Dat VK, Almaguer M, et al. Thalamic deep brain stimulation: effects on the nontarget limbs. *Move Disord* 2001;**16**:1137–42.
- Putzke JD, Wharen RE, Uitti RJ, et al. Thalamic deep brain stimulation for essential tremor: recommendations for long-term outcome analysis. *Can J Neurol Sci* 2004;**31**:333–42.
- Kumar R, Lozano AM, Sime E, et al. Comparative effects of unilateral and bilateral subthalamic nucleus deep brain stimulation. *Neurology* 1999;**53**:561–6.
- Carpenter MA, Pahwa R, Miyawaki KL, et al. Reduction in voice tremor under thalamic stimulation. *Neurology* 1998;**50**:796–8.
- Obwegeser AA, Uitti RJ, Turk MF, et al. Thalamic stimulation for the treatment of midline tremors in essential tremor patients. *Neurology* 2000;**54**:2342–4.
- Taha JM, Janszen MA, Favre J. Thalamic deep brain stimulation for the treatment of head, voice, and bilateral limb tremor. *J Neurosurg* 1999;**91**:68–72.
- Ondo W, Almaguer M, Jankovic J, et al. Thalamic deep brain stimulation – comparison between unilateral and bilateral placement. *Arch Neurol* 2001;**58**:218–22.
- Pahwa R, Lyons KL, Wilkinson SB, et al. Bilateral thalamic stimulation for the treatment of essential tremor. *Neurology* 1999;**53**:1447–50.
- Koller WC, Lyons KE, Wilkinson SB, et al. Efficacy of unilateral deep brain stimulation of the VIM nucleus of the thalamus for essential head tremor. *Move Disord* 1999;**14**:847–50.
- Kumar K, Kelly M, Toth C. Deep brain stimulation of the ventral intermediate nucleus of the thalamus for control of tremors in Parkinson's disease and essential tremor. *Stereotact Funct Neurosurg* 1999;**72**:47–61.
- Limousin P, Speelman JD, Gielen F, et al. Multicentre European study of thalamic stimulation in parkinsonian and essential tremor. *J Neurol Neurosurg Psychiatry* 1999;**66**:289–96.
- Louis ED, Ford B, Lee H, et al. Diagnostic criteria for essential tremor: a population perspective. *Arch Neurol* 1998;**55**:823–8.
- Obwegeser AA, Uitti RJ, Turk MF, et al. Simultaneous thalamic deep brain stimulation and implantable cardioverter-defibrillator. *Mayo Clin Proc* 2001;**76**:87–9.
- Fahn S, Tolosa E, Marin C. Clinical rating scale for tremor. In: Jankovic J, Tolosa E, eds. *Parkinson's disease and movement disorders*. Baltimore: Urban and Schwarzenberg, 1993:271–80.
- Benazzouz A, Hallett M. Mechanism of action of deep brain stimulation. *Neurology* 2000;**55**:S13–16.
- Benabid AL, Benazzouz A, Gao DM, et al. Chronic electrical stimulation of the ventralis intermedius nucleus of the thalamus and of other nuclei as a treatment for Parkinson's disease. *Techniques Neurosurg* 1999;**5**:5–30.
- Koller WC, Lyons KE, Wilkinson SB, et al. Long-term safety and efficacy of unilateral deep brain stimulation of the thalamus in essential tremor. *Move Disord* 2001;**16**:464–8.
- Blond S, Caparros-Lefebvre D, Parker F, et al. Control of tremor and involuntary movement disorders by chronic stereotactic stimulation of the ventral intermediate thalamic nucleus. *J Neurosurg* 1992;**77**:62–8.
- Hariz MI, Shamsgovara P, Johansson F, et al. Tolerance and tremor rebound following long-term chronic thalamic stimulation for parkinsonian and essential tremor. *Stereotact Funct Neurosurg* 1999;**72**:208–18.
- Tomaszewski KJ, Holloway RG. Deep brain stimulation in the treatment of Parkinson's disease: a cost-effectiveness analysis. *Neurology* 2001;**57**:663–71.