Thalamic Deep Brain Stimulation for Essential Tremor: Recommendations for Long-Term Outcome Analysis

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ABSTRACT: ***Objectives:*** Determine the efficacy of thalamic deep brain stimulation (DBS) for tremor control among individuals with essential tremor (ET). ***Methods:*** A clinical series of 52 consecutive individuals undergoing placement of a DBS system for treatment of ET completed an unblinded battery of subjective and objective measures at postoperative intervals of one, three, and 12 months, and annually thereafter up to three years. The assessment battery included measures of tremor and activities of daily living. ***Results:*** Both subjective and objective measures showed that stimulation was associated with significant improvement at nearly every postoperative interval as compared to pre-operative and stimulation 'off' ratings of activities of daily living functioning, midline tremor, contralateral upper extremity tremor, and contralateral lower extremity tremor. Ipsilateral tremor showed some improvement with stimulation, but only within the first three months. Trend analysis showed stable tremor control. Stimulation settings remained largely unchanged after the first three months. Dysarthria was more common among those with bilateral stimulation. A range of missing data estimation methods were performed, and subsequent analyses corroborated the main findings of the study. ***Conclusion:*** Thalamic DBS is generally a well-tolerated and effective treatment for ET. Methodological and analytical recommendations are provided for the evaluation of long-term outcome.

RÉSUMÉ: Stimulation cérébrale profonde au niveau du thalamus dans le traitement du tremblement essentiel: recommandations pour l'analyse des résultats à long terme. *Objectif:* Déterminer l'efficacité de la stimulation cérébrale profonde (SCP) au niveau du thalamus pour maîtriser le tremblement chez les individus présentant un tremblement essentiel (TE). *Méthodes:* Une série de 52 patients consécutifs, chez qui un dispositif SCP a été installé pour traiter le TE, ont complété une batterie de mesures subjectives et objectives au su, 1, 3 et 12 mois après la chirurgie et annuellement par la suite pendant trois ans. La batterie de tests comprenait des mesures du tremblement et du fonctionnement dans les activités de la vie quotidienne (AVQ). *Résultats:* Tant les mesures subjectives qu'objectives ont montré que la stimulation était associée à une amélioration significative au moment de presque toutes les évaluations par rapport aux mesures préopératoires et aux mesures sans stimulation quant aux AVQ, au tremblement axial, au tremblement du membre supérieur contralatéral et du membre inférieur contralatéral. On a observé une légère amélioration du tremblement ipsilatéral par la stimulation, mais seulement pendant les trois premiers mois. Une analyse de tendance a montré que l'effet sur le tremblement était stable à long terme. Le réglage des conditions de stimulation n'a à peu près pas été modifié après trois mois. La dysarthrie était plus fréquente chez les patients dont la stimulation était bilatérale. Les résultats des analyses effectuées selon l'intention de traitement à la fin du suivi de trois ans corroboraient les principales observations de l'étude. *Conclusion:* La SCP est généralement bien tolérée et constitue un traitement efficace du tremblement essentiel. Nous fournissons des recommandations méthodologiques et analytiques quant à l'évaluation des résultats à long terme.

Essential tremor (ET) is a commonly diagnosed movement disorder,[1] typically involving postural and kinetic tremor. Individuals with essential tremor can experience progressively disabling tremor resistant to pharmacological treatment in up to 50% of cases.[2] Surgical intervention has generally targeted the ventral intermediate (Vim) nucleus of the thalamus for

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management of tremor. As compared to lesioning techniques, deep brain stimulation (DBS) has become increasingly employed due to a reduced risk of adverse effects (e.g., dysarthria, paresis) with similar or better tremor control outcomes.[3-6] The relative advantages associated with DBS include minimal lesioning secondary to lead placement, reversibility, ability to employ treatment bilaterally, and flexibility in tremor and side effect management through changes in parameters settings (i.e., electrode use, amplitude, pulse width, rate).

Multiple studies have demonstrated beneficial, short-term (i.e., 12 months or less) efficacy of Vim stimulation among individuals with ET across a broad range of outcome domains including subjective and objective tremor ratings, functional (e.g., activities of daily living (ADL)) and emotional (e.g., depressive symptomatology) status, and clinician and patient-based global disability ratings.[5,7-22] In comparison, there are relatively few studies examining Vim stimulation over longer intervals (i.e., greater than 12 months).[4,12,23-28] As seen in Table 1, there is inconsistent evidence regarding long-term DBS outcomes. Some studies show decreased efficacy over time,[23,25,26] while others indicate stable tremor control.[4,12,24,27,28] Surgical trials involve several methodological challenges that complicate interpretation of results which may, in part, account for these inconsistent findings.

Potential bias in data collection over time is the primary methodological concern that complicates interpretation of DBS outcome results. Specifically, dropout rates, variable data collection, and limited analyses that account for missing data are

three methodological concerns that have received inadequate attention within the DBS literature. The current study was designed to extend previous Vim DBS outcome studies by 1) reporting the results based on standardized data collection intervals [i.e., one, three, 12 months and annually thereafter], 2) examining dropout characteristics, and 3) including a range of estimation methods and subsequent analyses to account for missing data.

METHODS

Participants and procedures

A clinical series of 55 consecutive individuals with ET undergoing thalamic DBS for intractable tremor were included for study. Diagnosis of ET was made by one neurologist (RJU) based on the criteria by Louis.[29] Surgical indications included disabling tremor despite optimal medical therapy, which included trials of propranolol, primidone, and gabapentin at maximal tolerable doses. Bilateral surgery was performed in cases of severe bilateral tremor. All patients discontinued pharmacological anti-tremor therapy before pre-operative tremor assessment. One patient who underwent previous stimulator placement at another institution, and one patient with a previous history of left temporal lobectomy were excluded from study. In addition, a DBS system was not placed in one individual secondary to seizures during surgical placement. Thus, 52 individuals were included for analyses (note: the seizure case was included in the missing data estimation methods).

Table 1: Long-term (greater than 12 months) efficacy of VIM DBS for essential tremor

Author	n	Description of last follow-up group	n at last follow-up (% retained)	Results of long-term assessment
Benabid et al.[23] & Benabid et al.[25]	23	"at least 6 months" (maximum 7 years)	20 (87)[1]	Proportion of those with little or no upper extremity tremor decreased from 75% to 61%, and proportion with 'no benefit' increased from 0% to 17% at 3 months vs. last follow-up, respectively; rebound tremor upon stimulation discontinuation in 10%; stable stimulation settings after first few months.
Blond et al.[7]	4	ranged from 6 to 16 months (mean 11 months)	4 (100)	Long-term tremor control maintained; rebound tremor upon stimulation discontinuation in 57% (not separated by diagnosis); Voltage increased over time.
Hariz et al.[26]	36	"more than 12 months", average = 28 months	16 (44)	Proportion with 'poor' effect increased from 3 to 22%, at 1 week to last follow-up respectively; persistent rebound tremor upon stimulation discontinuation in 11%; amplitude and frequency increased over time.
Koller et al.[27]	49	"At least 24 months", mean = 40 months	25 (51)	Maintained tremor control with no loss of effect long-term, no change in stimulation settings.
Krauss et al.[12]	42	Not stated, mean = 12 months	NR	Marked or excellent tremor control in 93% at last follow-up.
Kumar et al.[28]	9	"every 6 months after the first year", mean = 15 months	NR	Long-term efficacy maintained for tremor control and ability to perform day-to-day tasks (pouring, writing, drawing), amplitude increased over time, rebound effect with discontinuation of stimulation in 22%.
Pahwa et al.[18]	17	"annually", mean of 27 months	17 (100)[2]	Long-term tremor control maintained.
Rehncrona et al.[24]	19	"6 to 7 years"	13 (68)	Action and postural control maintained long-term.

NR= not reported. VIM = Ventral intermediate nucleus. DBS = Deep brain stimulation.
[1]All individuals with a six month or greater postoperative assessment included in follow-up. [2]A matched, retrospective study.

The surgical procedures have been previously described in detail.[15,30] In brief, a stereotactic target in the Vim was planned with magnetic resonance guidance. Microelectrode recording was used for the first 13 patients. In all patients, test stimulations were performed to evaluate tremor relief and side effects. After determining optimal position, the stimulation electrode (Model 3387, Medtronic, Minneapolis, MN) was secured to the skull. The electrode was connected to the infraclavicular pulse generator under general anesthesia immediately following optimal lead positioning.

Initial stimulation programming occurred the day following surgery and within two weeks after surgery for further stimulator programming. If necessary, stimulation settings 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 paresthesias, occurring when the stimulator was turned 'on' and subsiding within a few seconds, were not considered side effects. After the initial two week period, clinic visits to assess tremor control and side effects were scheduled at one, three, and 12 months, and then annually thereafter. Follow-up scores were measured with the stimulator switched 'off' and 'on.' All scores were recorded prior to any adjustments being made to the stimulation settings, thus providing a conservative estimate of efficacy. 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.

Individuals were separated into 1 of 5 mutually exclusive and collectively exhaustive groups based on their evaluation status at each post-operative interval. The 5 status groups were those 1) whose evaluations were not due yet, 2) whose evaluations were due and outcome measures were obtained, 3) whose evaluations were due and outcome measures were not obtained, 4) lost to follow-up, and 5) deceased. For clarification, the 'evaluation not due yet' group includes those who have yet to reach a particular post-operative interval (e.g., a patient who is 3 months out from their initial lead placement would be considered in the 'evaluation not due yet' group at the 12 month interval). Table 2 presents several summary characteristics including the number of individuals in the various status groups at each post-operative interval, the mean days from the expected date the evaluation was performed, the number of individuals from whom quantitative outcome measures were obtained, and the proportion of evaluations due that were actually obtained (range 47 to 98%). Two individuals died of unrelated causes (i.e., lung cancer, gunshot wound). One of the initial individuals was not followed according to the standard clinical protocol intervals until after the placement of their second DBS lead 14 months later. No data were available between the first and second placement. For analysis, post-operative intervals were considered to start after the second DBS placement. An attempt was made to complete all the measures at each assessment. However, between 3-5% of participants did not complete all measures at each assessment interval for various reasons (e.g., refusal to turn the stimulator 'off', time limitations).

Measures

The Tremor Rating Scale (TRS)[31] is a validated patient and clinician-based rating scale of tremor and ADL. The TRS contains 21 items that use a 5-point Likert scale (i.e., 0 = no tremor/disability, 4 = severe tremor/disability), as well as a global disability item (0 = no functional disability, 4 = severe disability).

After the first seven patients, a battery of objective tests were added to the assessment protocol. The Purdue Pegboard Test required participants to place as many pegs onto a board as possible within 30 seconds. In three separate trials, the right hand, the left hand, and both hands were used. The movement monitor/accelerometer (MM-1 Movement Monitor; Axon Instruments, Foster City, CA) allowed measurements of reaction and movement time (milliseconds), rotation dexterity (rotations per second), tremor frequency, and tremor power. Hand/finger reaction times were measured in response to audible and visible stimuli. Rotation dexterity involved timed rotation of 2 inch pegs (about half the width of a pencil). The predominant tremor frequency (Hz) was calculated after attachment of the accelerometer to the participant's hand. Two measures of tremor power are calculated by the device including 1) the root mean square of the acceleration (in milligravities) associated with the predominant frequency band, and 2) the total root mean square power over the 15 second interval. Bi-variate correlations between the two measures of tremor power were $r = .95$ and above. Thus, only the root mean square of the acceleration associated with the predominant frequency band was reported for consistency with our previous research.

Statistical procedures

Outcome measures collected under both the stimulation 'on' and 'off' condition at each postoperative interval were compared to pre-operative functioning (i.e., baseline). Similarly, the 'on' and 'off' stimulation condition was compared at each postoperative interval. Change over time was assessed by five paired comparisons between adjacent postoperative intervals (i.e., presurgical – month 1, month 1 – month 3, month 3 – year 1, year 1 – year 2, year 2 – year 3). The Wilcoxon sign rank test was used for each comparison due to the non-normal distribution of outcome measure. Significance was set at $p<.05$, however, three significance levels were reported ($p<.05$, $p<.01$, $p<.001$) so that results could be evaluated according to various correction methods (e.g., Bonferroni).

RESULTS

Sample characteristics

The study sample included men (n = 30, 58%) and women (n = 22, 42%), with a mean age of 72.3 (SD = 8.4) and tremor duration of 24.6 (SD = 16.2) years at the time of surgery. A total of 75 operative sides were placed, about half (n = 29; 56%) were unilateral placements, largely on the left side (left = 25, 86%, right = 4; 14%). Over the course of follow-up, eight leads required repositioning due to loss of effect (i.e., eight patients total, one repositioned lead per patient), two leads were broken and subsequently replaced (i.e., two patients total, one broken lead per patient), and initial placement of one lead was not done due to insufficient effect during surgery (lead was subsequently placed six months later, unilateral). For the 10 patients with repositioned or broken leads, replacement occurred an average of 385 days (range: 84 to 950 days) from initial placement. Surgical replacement of components included one connector lead, and
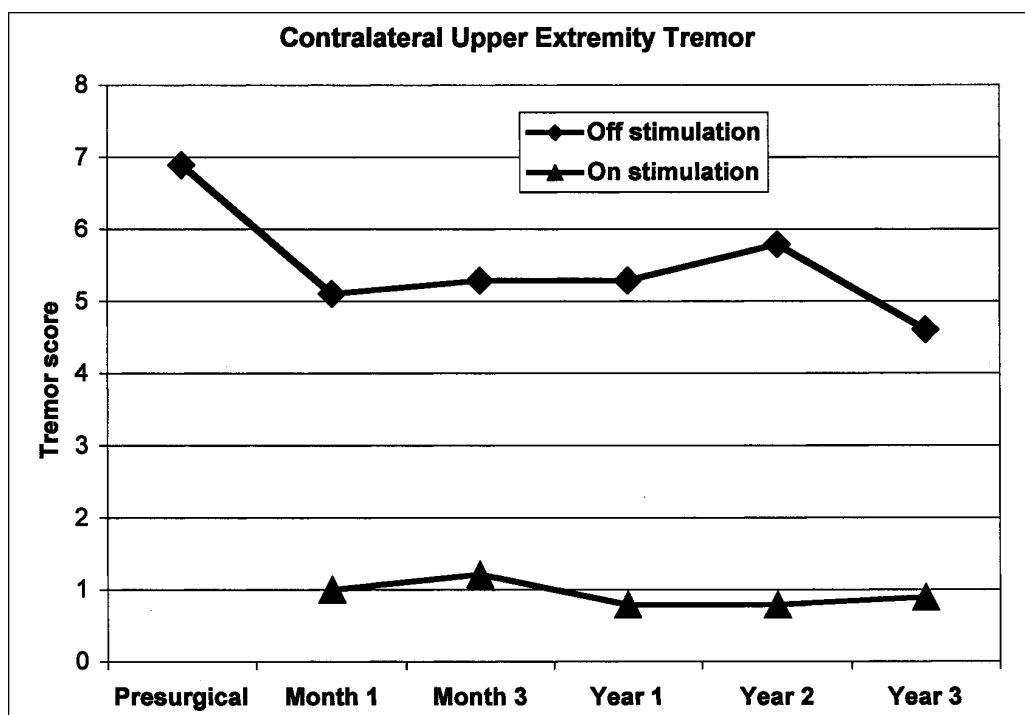
Figure: *Long-term contralateral upper extremity tremor control with deep brain stimulation.*

three implantable pulse generators. One DBS system was explanted due to infection after 22 months in an individual with bilateral stimulation. The overall mean duration between the initial lead placement and last follow-up was 19.8 months, and was significantly longer among individuals with bilateral (28.9 months) as compared to unilateral (12.5 months) DBS, $F(1,50) = 20.9$, $p<.001$. A structured telephone interview was obtained for three of the six individuals lost to follow-up (five individuals transferred care, one due to medical noncompliance). All three individuals indicated that their devices had not been explanted, one individual reported continued good tremor control and improvement in ADLs with stimulation, two individuals reported no benefit, and all three reported no other subsequent device related surgeries (e.g., lead repositioning, battery replacement).

Two sets of comparisons were made in order to determine whether those available for analysis at each post-operative interval were representative of the overall sample (see Table 2). First, the demographic characteristics of those with completed evaluations at each postoperative interval were compared to the overall group characteristics at baseline. Second, the demographic characteristics of those with complete (i.e., evaluation obtained) versus incomplete (i.e., lost to follow-up, evaluation not obtained, deceased) evaluations at each postoperative interval were compared to assess differential dropout rates. Only one of the 40 comparisons was significant, $p<.05$. That is, a significantly lower proportion of individuals with unilateral placement were assessed at year 2 (31%) compared to baseline (57%), $\chi^2(1) = 4.70$, $p = .03$.

Tremor control efficacy

Results of tremor control were separated out between those with unilateral vs. bilateral stimulation. Table 3 presents a summary of the mean scores for the TRS at the various postoperative intervals. Three consistent findings emerged. First, the stimulation 'on' condition showed significant ($p<.001$) improvement at nearly every postoperative interval as compared to pre-operative ratings of ADL functioning, midline tremor, contralateral upper extremity tremor, and contralateral lower extremity tremor (e.g., see Figure). Second, comparisons between the stimulation 'on' versus 'off' condition indicated significant improvement associated with stimulation at nearly every postoperative interval for midline tremor, contralateral upper extremity tremor, contralateral lower extremity tremor. Third, ipsilateral upper and lower extremity tremor in the stimulation 'on' condition showed some improvement compared to baseline over the first three months. However, little or no improvement was observed after 12 or more months, $p>.05$. It should be noted that staged, bilateral placement was performed in 21 of the 23 individuals with bilateral DBS which likely contributes to the decrease in 'off' state midline tremor ratings over time (233 mean days between placements).

Table 4 presents a summary of the mean scores for the objective test battery at the various postoperative intervals. As can be seen, the stimulation 'on' condition for reaction time, movement time, rotational dexterity, ipsilateral tremor measurements, and Purdue Pegboard (i.e., ipsilateral and contralateral hand) scores showed little or no differences when compared to baseline functioning or when compared to the stimulation 'off' condition at each postoperative interval. As expected, 'on' stimulation measurements of frequency (Hz), power (milligravities), and total power (milligravities) for both contralateral resting and postural tremor showed significant improvement when compared to baseline functioning and when

336

Table 2: Summary of Data Collection at Various Intervals

	Presurgery n (%)	Month 1 n (%)	Month 3 n (%)	Year 1 n (%)	Year 2 n (%)	Year 3 n (%)	Year 4 n (%)
Evaluation not due yet	–	1 (2)	4 (8)	14 (27)	20 (38)	31 (59)	42 (80)
Evaluation obtained	51 (98)	45 (86)	47 (90)	36 (69)	26 (50)	11 (21)	2 (4)
Evaluation not obtained	1 (2)	6 (12)	1 (2)	1 (2)	0 (0)	2 (4)	0 (0)
Deceased	-	0 (0)	0 (0)	0 (0)	2 (4)	2 (4)	2 (4)
Lost to follow-up	-	0 (0)	0 (0)	1 (2)	4 (8)	6 (12)	6 (12)
Number with quantitative data	n	n	n	n	n	n	n
	45	36	35	27	23	7	1
Percentage of evaluations due obtained	%	%	%	%	%	%	%
	98	88	97	94	81	47	20
Days from expected date							
Mean	1.0	4.4	16.5	76.4	111.5	79.0	22.5
Standard deviation	1.6	3.6	20.9	67.3	83.6	76.0	7.8

Note: Quantitative measures added to assessment protocol in 1998. Total Sample: n = 52

Table 3: Summary of Clinical Tremor Rating Scale

	Presurgerical M ±SD	Month 1 M ±SD	Month 3 M ±SD	Year 1 M ±SD	Year 2 M ±SD	Year 3 M ±SD
CLupper extremity						
Off stimulation	6.9 ±2.0	5.1 ±2.5[3]	5.3 ±2.6[3]	5.3 ±2.5[2]	5.8 ±2.6	4.6 ±2.0
On stimulation		1.0 ±1.5[3, b]	1.2 ±2.2[3, b]	0.8 ±1.1[3, b]	0.8 ±1.0[3, b]	0.9 ±1.1[3, b]
ILupper extremity*						
Off stimulation	5.5 ±1.7	4.6 ±2.4[1]	4.7 ±1.8[1]	4.6 ±1.7	4.1 ±2.3	4.3 ±1.5
On stimulation		4.6 ±1.9[3]	4.3 ±2.0[2]	3.9 ±1.9[1]	4.1 ±2.0	4.3 ±0.6
CL lower extremity						
Off stimulation	0.7 ±1.1	0.4 ±1.0[1]	0.4 ±1.0[1]	0.7 ±1.2	0.4 ±0.6	0.2 ±0.6
On stimulation		0.1 ±0.3[3, b]	0.1 ±0.4[3, b]	0.0 ±0.0[3, c]	0.0 ±0.0[2, b]	0.0 ±0.0
ILlower extremity*						
Off stimulation	0.6 ±1.3	0.5 ±1.1	0.3 ±0.7[1]	0.5 ±0.9	1.0 ±1.4	0.7 ±1.2
On stimulation		0.4 ±0.9	0.2 ±0.7[1]	0.3 ±0.9	0.5 ±1.4	0.3 ±0.6
Midline tremor**						
Off stimulation	5.6 ±5.1	4.4 ±3.9[1]	3.4 ±3.4[2]	3.4 ±3.9[1]	3.0 ±2.5[1]	1.2 ±0.8[1]
On stimulation		1.6 ±2.0[3, c]	2.0 ±2.4[3, b]	0.9 ±1.9[3, c]	0.8 ±0.8[3, b]	0.9 ±1.5[2]
Midline tremor*						
Off stimulation	4.1 ±3.1	3.8 ±2.7	3.2 ±2.5	2.7 ±2.3	3.5 ±1.9	2.0 ±2.0
On stimulation		1.7 ±1.7[3, c]	1.2 ±1.3[3, c]	1.8 ±1.3	1.8 ±1.9	1.0 ±1.7
ADL						
Off stimulation	17.8 ±3.7	-	-	-	-	-
On stimulation		7.7 ±5.6[3]	6.5 ±6.5[3]	5.5 ±5.1[3]	6.5 ±5.3[3]	5.3 ±4.5[2]

Note: CL = Contralateral. IL = Ipsilateral. ADL = Activities of Daily Living. Summary of tremor scores represent all forms of tremor (rest, postural, kinetic).
*Only those with unilateral DBS. **Only those with bilateral DBS. [1]$p < .05$ versus baseline. [2]$p < .01$ versus baseline. [3]$p < .001$ versus baseline.
[a]$p < .05$ versus off. [b]$p < .01$ versus off. [c]$p < .001$ versus off.

Table 4: Summary of Objective Hand Measure Assessments

	Baseline M ±SD	Month 1 M ±SD	Month 3 M ±SD	Year 1 M ±SD	Year 2 M ±SD	Year 3 M ±SD
CLreaction time (ms)						
Off stimulation	510.8 ±188.5	512.2 ±197.2	454.9 ±124.0	467.9 ±102.5	482.4 ±164.2	460.3 ±130.1
On stimulation		484.5 ±137.1	475.0 ±165.4	450.7 ±82.4	471.2 ±153.1	460 ±134.0
ILreaction time (ms)*						
Off stimulation	481.4 ±182.0	501.9 ±236.8	485.5 ±222.7	474.4 ±190.7	464.2 ±122.7	405.6 ±57.2
On stimulation		484.7 ±129.8	464.1 ±286.7	412.4 ±102.8	402.2 ±81.5	375.0 ±45.9
CL movement time (ms)						
Off stimulation	422.8 ±202.5	438.6 ±170.2	471.7 ±241.4	488.6 ±274.6[1]	528.1 ±204.8	579.0 ±260.7
On stimulation		411.9 ±146.0	418.3 ±165.9	451.7 ±147.9	540.0 ±446.2	413.3 ±72.2
ILmovement time (ms)*						
Off stimulation	373.6 ±128.3	340.4 ±134.4	394.0 ±178.7	389.3 ±119.8	333.8 ±70.8	379.0 ±89.4
On stimulation		387.1 ±114.9	382.1 ±180.6	396.6 ±128.6	342.4 ±115.4	379.0 ±63.0
CLrotations						
Off stim	1.4 ±1.2	1.6 ±1.8	1.4 ±1.1	1.5 ±0.8	1.2 ±0.8[2]	1.6 ±0.9
On Stim		1.7 ±1.4	1.5 ±0.9	1.6 ±0.9[a]	1.3 ±0.8	1.9 ±1.0
ILrotations*						
Off stimulation	1.2 ±0.9	1.3 ±1.0	1.5 ±1.2	1.2 ±0.9	1.3 ±0.8	1.5 ±1.0
On stimulation		1.6 ±1.4	1.4 ±0.8	1.7 ±0.9 [a]	1.4 ±0.5	2.0 ±1.0
CLresting tremor frequency (Hz)						
Off stimulation	2.8 ±2.5	2.1 ±2.4	1.4 ±2.2 [3]	1.1 ±2.2 [3]	1.6 ±2.1	1.4 ±2.2
On stimulation		0.5 ±1.4 [3,c]	0.4 ±1.2 [3,c]	0.6 ±1.8 [3]	0.0 ±0.0 [2, b]	0.0 ±0.0
ILresting tremor frequency (Hz)*						
Off stimulation	3.2 ±2.8	3.2 ±2.9	1.6 ±2.4	3.1 ±3.3	4.2 ±2.5	1.9 ±3.1
On stimulation		3.1 ±3.0	1.1 ±2.2[2]	2.5 ±2.9	1.6 ±2.3	3.0 ±2.6
CLresting tremor power (mgrav)						
Off stimulation	45.7 ±91.3	60.5 ±192.1	41.0 ±144.9	27.7 ±66.5	44.0 ±164.7	38.0 ±69.4
On stimulation		2.0 ±5.2[3,c]	2.8 ±10.8[3,b]	2.0 ±4.3[3,b]	4.9 ±13.7	0.8 ±2.1
ILresting tremor power (mgrav)*						
Off stimulation	15.7 ±20.7	75.2 ±123.2[1]	12.8 ±33.3	38.8 ±87.4	18.6 ±20.5	12.7 ±12.5
On stimulation		24.6 ±59.6[a]	11.7 ±23.2	23.8 ±47.0	5.0 ±4.8	6.3 ±6.5
CLpostural tremor frequency (Hz)						
Off stimulation	4.7 ±1.1	4.6 ±1.4	3.9 ±1.9[3]	4.1 ±1.6[2]	4.3 ±0.9[2]	4.3 ±0.9
On stimulation		2.3 ±2.6[3,c]	2.2 ±2.4[3,c]	1.4 ±2.1[3,c]	1.7 ±2.4[3,c]	1.3 ±2.4[a]
ILpostural tremor frequency(Hz)*						
Off stimulation	5.3 ±1.1	6.9 ±8.9	5.0 ±1.7	5.3 ±1.0	4.3 ±2.6	5.0 ±0.4
On stimulation		5.0 ±2.1	4.8 ±2.1	5.0 ±1.9	4.4 ±2.7	5.0 ±1.0
CLpostural tremor power (mgrav)						
Off stimulation	547.8 ±689.2	490.4 ±705.0	493.0 ±665.1	236.2 ±224.6	207.4 ±210.4	249.9 ±456.8
On stimulation		42.6 ±153.2[3,c]	60.3 ±197.9[3,c]	6.6 ±9.6[3,c]	11.4 ±26.6[3,c]	2.1 ±4.2[a]
ILpostural tremor power (mgrav)*						
Off stimulation	279.1 ±549.1	251.2 ±420.5	124.3 ±215.7	87.8 ±64.5	95.2 ±81.5	64.7 ±50.0
On stimulation		259.8 ±527.2	136.2 ±296.2[a]	47.5 ±23.2[a]	72.4 ±48.0	43.7 ±21.6
Purdue Pegboard						
Off stimulation						
CLhand	7.1 ±3.2	7.2 ±4.0	7.3 ±4.0	7.8 ±3.8	5.6 ±3.5[2]	7.6 ±3.5
ILhand	7.1 ±3.2	6.9 ±3.9	7.6 ±3.5	7.3 ±4.0	6.6 ±2.0[a]	9.7 ±1.2
Both hands	5.4 ±2.8	5.1 ±3.7	5.9 ±3.7	5.3 ±2.8	4.6 ±3.2	6.3 ±3.2
On stimulation						
CLhand		7.8 ±3.6[a]	7.7 ±3.5	8.3 ±3.6	8.2±3.7[c]	8.7 ±2.9
ILhand		7.4 ±3.4	7.6 ±3.5	7.8 ±3.9	8.5 ±2.6	9.0 ±3.6
Both hands		6.0 ±3.2[1]	5.8 ±3.1	6.3 ±3.2[b]	6.6 ±3.2[c]	7.4 ±3.1[a]

Note: CL = Contralateral. IL= Ipsilateral. *Only those with unilateral DBS. Higher Purdue Pegboard scores reflect better functioning.
[1]p < .05 versus baseline. [2]p < .01 versus baseline. [3]p < .001 versus baseline.
[a]p < .05 versus off. [b]p < .01 versus off. [c]p < .001 versus off.

compared to the 'off'stimulation condition at most postoperative intervals. In addition, 'on' stimulation Purdue Pegboard scores using both hands showed significant improvement as compared to the 'off'stimulation condition for evaluations at year 1, 2, and 3.

Subjective and objective measures showing a consistent significant improvement with stimulation for at least four of the five post-operative intervals were examined using missing data estimation methods to determine a conservative estimate of long-term efficacy at year 3. More specifically, all those with evaluations due at year 3 were included in the analyses (i.e., those whose evaluations were and were not obtained, deceased, and lost to follow-up). A range of liberal to conservative estimation methods were used to estimate at year 3 data. The most conservative technique was the 'carry-forward the worst 'on' and 'off' stimulation score' technique, followed by the 'carry-forward-baseline-functioning' technique, and the most liberal estimate was the 'carry-forward the most recent 'on'and 'off' stimulation score' technique. Comparisons between baseline and 'on'stimulation were performed for each measure. A comparison between 'on'and 'off' stimulation was also made for the 'carry-forward-most-recent'technique. However, an 'on' vs. 'off' comparison was not used for the other two techniques since the 'off' condition would be biased toward finding an effect (i.e., the 'off' condition would generally tend to be worse). The outcome measures examined included midline tremor (bilateral placement only), contralateral lower extremity subjective ratings, and contralateral tremor measures of upper extremity 1) subjective ratings, 2) resting frequency, 3) resting power, 4) postural frequency, and 5) postural power. Six of the seven comparisons were significant for both the 'carry-forward most recent' technique, p<.05. In contrast, only two of the seven comparisons were significant for the 'carry-forward baseline'

and 'carry-forward worse' technique (contralateral upper extremity subjective ratings and postural power).

Trend analysis

Five paired comparisons between adjacent postoperative intervals were performed for both the 'on'and 'off' stimulation condition in order to determine trends over time (note: for the presurgical vs. month 1 comparison both the 'on' and 'off' condition were compared to presurgical functioning). Thus, a total of 10 comparisons were made (i.e., five stimulation 'on'and five stimulation 'off' comparisons) for each the 45 outcome measures (listed in Tables 3 and 4). The overwhelming majority of significantly different paired intervals were comparisons between the presurgical and month 1 interval. Also, none of the outcome measures in either the 'on' or 'off' state had four or more (maximum of five) significant differences between adjacent intervals, even at the most liberal alpha level. In fact, most outcome measures had either 0 or 1 significantly different adjacent pairs. Thus, a consistent increase or decrease over time was not found for any of the outcome measures.

Side effects and stimulator settings

A total of 367 clinic visits (i.e., both scheduled and unscheduled patient visits) were made and 63% (n = 231) involved a change to the stimulator settings for at least one implantable pulse generator. Of the 284 changes made, the stimulator setting adjustment was required in order to eliminate side effects 15% (n = 42), improve tremor control 70% (n = 198), or both 9% (n = 26), or missing data 6% (n = 18). The most common self-reported side effects among those undergoing a stimulation change to eliminate side effects were dysarthria 40%, disequilibrium 31%, motor disturbances (e.g., eye deviation, pulling or tightness in limbs or face) 24%, and paresthesias 16%.

Table 5: Side Effects Reported During Staged, Bilateral Lead Placement Over Standardized Interval

Side effect	Unilateral n (%)	Bilateral n (%)
Dysarthria	0 (0)	6 (27)*
Disequilibrium	2 (9)	5 (23)
Paresthesia	3 (14)	1 (5)
Motor disturbance	1 (5)	2 (9)

Note: Average standardized interval length = 146 days. Motor disturbance included eye deviation, pulling or tightness in limbs or face. Total n = 22.
*p =.03.

Table 6: Summary of Stimulator Settings Over Time

	Month 1 M ±SD	Month 3 M ±SD	Year 1 M ±SD	Year 2 M ±SD	Year 3 M ±SD
Amplitude (v)	2.9 ±1.1	3.1 ±1.0*	3.1 ±1.0	3.3 ±1.2	3.0 ±1.3
Rate (Hz)	154.3 ±26.1	161.8 ±25.5*	162.7 ±26.3	169.0 ±21.4	170.7 ±19.3
Pulse Width (msec)	85.9 ±28.6	81.1 ±21.9	92.8 ±29.9	93.5 ±24.5	87.9 ±27.5

*p < .05, significantly different from month 1.

McNemar's test for symmetry was used to compare the proportion of individuals with staged bilateral DBS that experienced each side effect during unilateral vs. bilateral stimulation period (see Table 5; note: one individual had simultaneous bilateral lead placement and was not included in the analysis of side effects). Results showed dysarthria was significantly more common after bilateral as compared to unilateral stimulation. All other comparisons were not significant.

Paired comparisons between adjacent postoperative intervals showed that both rate and amplitude significantly increased from month 1 to month 3, p = .022 and .016, respectively. All other paired comparisons were not significant, p > .05 (see Table 6).

DISCUSSION

Consistent with previous research,[4,5,7-23,25-28] analysis of subjective measures indicated that thalamic stimulation was associated with a significant reduction in tremor ratings and improvement in ADL functioning. Indeed, the stimulation 'on' condition showed significant improvement as compared to both the pre-surgical and 'off' stimulation condition ratings at nearly every post-operative interval. As expected, ratings of contralateral tremor showed the most consistent improvement. As found in other studies (e.g., head and voice tremor),[10,32] midline tremor also showed significant improvement with stimulation as compared to presurgical ratings and the 'off' stimulation condition, with the most consistent improvement among those with bilateral DBS. In contrast, measures of ipsilateral tremor generally showed no difference between the 'on' and 'off' stimulation condition at nearly every postoperative interval, and, when compared to presurgical ratings, some improvement in ipsilateral tremor was noted with stimulation, but only during the first three months.

Analysis of objective measures corroborated with the results of the subjective measures. More specifically, contralateral postural and resting tremor, as measured by frequency (Hz) and power (milligravities), showed significant improvement with stimulation as compared to presurgical levels and to the 'off' stimulation condition at nearly every postoperative interval. Again, ipsilateral tremor measures were largely unrelated to stimulation status and were unchanged from baseline at nearly every postoperative interval. Consistent with our previous research,[15] measures of reaction time, movement time, and finger dexterity showed little or no change with stimulation. The significant effects of stimulation were re-examined using a range of liberal to conservative estimates for missing data at year 3. The results generally confirmed the main findings without using data estimation methods, however, the more conservative techniques showed inconsistent support.

There is disagreement regarding the stability of DBS for tremor control with some studies suggesting between 10-20% of individuals may experience reduced efficacy over time.[23,25,26] Other evidence suggests a systematic increase in 'off' state tremor over time with subsequent 'rebound tremor' found in as many as 57% of individuals with DBS.[7,25] In the current study, a consistent increase or decrease over time was not found for any of the outcome measures in either the 'on' or 'off' condition. The current design lacked both pre-operative rates of decline and a

control group of ET patients without DBS. Thus, assertions regarding the possible influence of DBS on disease progression are limited. For instance, the lack of significant change in 'off' stimulation tremor scores may suggest a potential effect on slowing progression, but could also be explained as a prolonged washout effect from the 'on' stimulation state, a 'ceiling effect' in patients with severe tremor, or merely too short of an interval to identify progression. Similarly, stimulator settings showed little or no change after the first three months. These findings are consistent with other studies that showed an increase in stimulation settings only within the first several months after surgery,[23,25,27] although others have shown evidence of the need for a systematic increase in stimulation settings to maintain tremor control.[7,26,28]

Adverse side effects related to stimulation were generally mild and easily altered by adjusting stimulus parameters. Consistent with previous reports,[15,33] the most common side effects reported were dysarthria, dysequilibrium, motor disturbances, and paresthesias. The proportion of individuals that 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 due to variation in treatment seeking behavior (e.g., report of same side effect on repeated occasions by one individual). Using this method, the four most common side effects were experienced by 5-15% of individuals.

It has been argued that unilateral and bilateral DBS placement in the Vim may be associated with the same risks of side effects.[19] In contrast, our previous short-term study (i.e., three-month follow-up)[15] showed dysarthria to be significantly more common among individuals with bilateral DBS. However, several confounding factors may limit the utility of a straight forward comparison of side effects between individuals with unilateral versus bilateral stimulation. For instance, the mean duration between the initial lead placement and the last available assessment was significantly longer among individuals with bilateral (28.9 months) versus unilateral (12.5 months) stimulation. Since the risk of experiencing any given side effect at least once increases over time, the extent to which variation in side effects may be attributed to differences in stimulation duration is unknown. Relatedly, the interval between the first and second lead placement varied considerably (0 to 27 months, average seven months) among those with bilateral DBS. Therefore, a within subjects analysis using only individuals with staged, bilateral lead placement was considered to be the best approach to control for variability in patient characteristics and assessment intervals. The length of time over which side effects were compared was standardized for each individual as the shorter of two intervals: 1) time between the first and second surgery, or 2) time between the second surgery and the last available follow-up. Results showed that dysarthria was more common after bilateral stimulation. The proportion of individuals who experienced other side effects was not significantly different between unilateral and bilateral stimulation. Future research would benefit from the measurement and control of other patient-related characteristics that may influence self-report behavior (e.g., proximity to clinic, previous learning, side effect tolerance threshold for treatment seeking behavior, etc.)[34] in order to more specifically distinguish

340

the side effect profile associated with unilateral vs. bilateral DBS.

Due to the differences in analyses employed in the current study as compared to the bulk of the DBS literature, it is important to summarize the follow-up approach taken here. As traditionally done, the effect of DBS for tremor control was examined using paired comparisons between baseline and post-operative tremor measures. In addition, several other methodological (i.e., standardized intervals) and analytical (e.g., missing data estimation methods) procedures were utilized to 1) minimize confounds in data collection, 2) examine the potential impact of differential dropout rates, and 3) account for missing data. Taken together, these additional steps allow for a better understanding and more accurate interpretation of the available follow-up data, which in turn facilitates a more informed assessment of the conclusions asserted.

Certainly, the report of follow-up data from clinical series involves numerous potential confounds that need to be carefully considered. Several other recommendations follow regarding the analysis and report of prospective clinical outcome data.

(1) *Standardized assessment scheme.* A consistent attempt to capture all patients at each defined interval serves to minimize variation in postoperative assessment length, particularly in the longest follow-up intervals, and decreases the risk of unrepresentative samples at each postoperative interval [e.g., over-sampling treatment seeking individuals].

(2) *Full disclosure of the clinical dataset.* This method is most consistent with actual data collection associated with a clinical series. That is, patients are entered into the series on an ongoing basis, and are in one of five status groups (described above) at any particular postoperative interval. The alternative approach is to arbitrarily set a postoperative cut-off interval and only report data on individuals that have reached the chosen interval. Unfortunately, there may be an extended period while waiting for a sufficient number of individuals to reach the defined cut-off interval, no information is provided on those significantly past the cut-off interval even though they continue to be followed clinically, the rationale for determining the cut-off interval is arbitrary by definition, and failure to include those who have yet to reach the cut-off interval foregoes the opportunity to obtain better estimates of outcome at the intermediate intervals prior to cut-off.

(3) *Multi-modal tremor assessment.* The assessment battery should incorporate both subjective and objective measures of tremor, and possibly alternate source ratings (e.g., caregiver), in an attempt to minimize participant and experimenter bias. The most convincing evidence would be consistent results across measurement modalities.

(4) *Examination of dropout characteristics.* Analyses should include examination of dropout characteristics at each postoperative interval to more specifically determine the extent to which the results can be generalized. More specifically, demographic characteristics of those with complete evaluations should be compared to both those with incomplete evaluations at each post operative interval and to the overall sample at baseline.

(5) *Missing data estimation methods.* Unfortunately, missing data is a typical component of clinical research. Thus, statistical attempts should be made to account for missing data. A range of liberal to conservative estimation methods should be used.

(6) *Pre-operative symptom progression and controls.* Ideally, inclusion of tremor ratings prior to placement of the DBS system, as well as the use of a comparative ET group not undergoing DBS would help clarify the extent to which DBS may influence disease progression.

Ten leads were replaced due to a loss of effect (n = 8) or broken lead (n = 2). A consensus regarding how to manage the outcomes in such cases has yet to be firmly established. These cases were considered to be more of a 'cost' than an 'efficacy' issue for three reasons: 1) the overwhelming majority of the overall sample, including those with lead replacement, experienced consistent tremor control throughout follow-up, 2) all 10 patients showed good response after replacement, and 3) the duration between loss of tremor control and replacement was generally short [i.e., less than six weeks]. Thus, the time since the initial placement of the DBS system was not considered changed after replacement. As with most potential confounds in clinical studies, there is not a clear solution to the problem and it is likely best to err on the conservative side. Along those lines, results did not change when excluding follow-up tremor assessments made after lead replacement. Future research on long-term efficacy, adverse affects, and device maintenance cost will help further characterize the utility of DBS for management of tremor among individuals with ET.

REFERENCES

1. Findley LJ, Koller WC. Essential tremor: a review. Neurology 1987; 37(7):1194-1197.
2. Koller WC, Busenbark K, Miner K. The relationship of essential tremor to other movement disorders: report on 678 patients. Essential Tremor Study Group. Ann Neurol 1994; 35(6):717-723.
3. Pahwa R, Lyons K, Koller WC. Surgical treatment of essential tremor. Neurology 2000; 54(11):S39-S44.
4. Pahwa R, Lions KE, Wilkinson SB, et al. Comparison of thalamotomy to deep brain stimulation of the thalamus in essential tremor. Mov Disord 2001; 16(1):140-143.
5. Schuurman PR, Bosch DA, Bossuyt PMM, et al. A comparison of continuous thalamic stimulation and thalamotomy for suppression of severe tremor. N Eng Med 2000; 342(7):461-468.
6. Tasker RR. Deep brain stimulation is preferable to thalamotomy for tremor suppression. Surg Neurol 1998; 49(2):145-153.
7. 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(1):62-68.
8. Hubble JP, Busenbark KL, Wilkinson S, et al. Deep brain stimulation for essential tremor. Neurology 1996; 46(4):1150-1153.
9. Hubble JP, Busenbark KL, Wilkinson S, et al. Effects of thalamic deep brain stimulation based on tremor type and diagnosis. Mov Disord 1997; 12(3):337-341.
10. Koller WC, Lyons KE, Wilkinson SB, Pahwa R. Efficacy of unilateral deep brain stimulation of the VIM nucleus of the thalamus for essential head tremor. Mov Disord 1999; 14(5):847-850.
11. Koller W, Pahwa R, Busenbark K, et al. High-frequency unilateral thalamic stimulation in the treatment of essential and parkinsonian tremor. Ann Neurol 1997; 42(3):292-299.

12. Krauss JK, Simpson RK, Ondo WG, et al. Concepts and methods in chronic thalamic stimulation for treatment of tremor: technique and application. Neurosurgery 2001; 48(3):535-541.

13. Mobin F, De Salles AAF, Behnke EJ, Frysinger R. Correlation between MRI-based stereotactic thalamic deep brain stimulation electrode placement, macroelectrode stimulation and clinical response to tremor control. Stereotact Funct Neurosurg 1999; 72(2-4):225-232.

14. Obwegeser AA, Uitti RJ, Turk MF, Strongosky AJ, Wharen RE. Thalamic stimulation for the treatment of midline tremors in essential tremor patients. Neurology 2000; 54(12):2342-2344.

15. 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(2):274-281.

16. Ondo W, Jankovic J, Schwartz K, Almaguer M, Simpson RK. Unilateral thalamic deep brain stimulation for refractory essential tremor and Parkinson's disease tremor. Neurology 1998; 51(4):1063-1069.

17. Ondo W, Almaguer M, Jankovic J, Simpson RK. Thalamic deep brain stimulation - comparison between unilateral and bilateral placement. Arch Neurol 2001; 58(2):218-222.

18. Pahwa R, Lyons KL, Wilkinson SB, et al. Bilateral thalamic stimulation for the treatment of essential tremor. Neurology 1999; 53(7):1447-1450.

19. Taha JM, Janszen MA, Favre J. Thalamic deep brain stimulation for the treatment of head, voice, and bilateral limb tremor. J Neurosurg 1999; 91(1):68-72.

20. Troster AI, Fields JA, Pahwa R, et al. Neuropsychological and quality of life outcome after thalamic stimulation for essential tremor. Neurology 1999; 53(8):1774-1780.

21. Vesper J, Funk T, Kern BC, et al. Thalamic deep brain stimulation: present state of the art. Neurosurgery Quarterly 2000; 10(4):252-260.

22. Limousin P, Speelman JD, Gielen F, Janssens M. Multicentre European study of thalamic stimulation in parkinsonian and essential tremor. J Neurol Neurosurg Psychiatry 1999; 66(3):289-296.

23. 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(2):203-214.

24. Rehncrona S, Johnels B, Widner H, et al. Long-term efficacy of thalamic deep brain stimulation for tremor: double-blind assessments. Mov Disord 2003; 18(2):163-170.

25. 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 in Neurosurgery 1999; 5(1):5-30.

26. Hariz MI, Shamsgovara P, Johansson F, Hariz GM, Fodstad H. Tolerance and tremor rebound following long-term chronic thalamic stimulation for parkinsonian and essential tremor. Stereotact Funct Neurosurg 1999; 72(2-4):208-218.

27. Koller WC, Lyons KE, Wilkinson SB, Troster AI, Pahwa R. Long-term safety and efficacy of unilateral deep brain stimulation of the thalamus in essential tremor. Mov Disord 2001; 16(3):464-468.

28. 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(1):47-61.

29. Louis ED, Ford B, Lee H, Andrews H, Cameron G. Diagnostic criteria for essential tremor: a population perspective. Arch Neurol 1998; 55(6):823-828.

30. Obwegeser AA, Uitti RJ, Turk MF, et al. Simultaneous thalamic deep brain stimulation and implantable cardioverter-defibrillator. Mayo Clin Proc 2001; 76(1):87-89.

31. 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 & Schwarzenberg, 1993: 271-280.

32. Carpenter MA, Pahwa R, Miyawaki KL, et al. Reduction in voice tremor under thalamic stimulation. Neurology 1998; 50(3):796-798.

33. Starr PA, Vitek JL, Bakay RAE. Deep brain stimulation for movement disorders. Neurosurg Clin N Am 1998; 9(2):381-402.