Unilateral Thalamic Deep Brain Stimulation Versus Focused Ultrasound Thalamotomy for Essential Tremor

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BACKGROUND: **The predominant neurosurgical approach to medication-refractory essential tremor is thalamic deep brain stimulation (DBS). The emergence of magnetic resonance-guided focused ultrasound (MRgFUS) thalamotomy has reawakened the debate surrounding the use of DBS versus thalamotomy for this indication. Herein, we aimed to provide a contemporary comparison between DBS and MRgFUS.**

METHODS: **Two controlled trials that evaluated DBS and MRgFUS for the unilateral treatment of refractory essential tremor were compared. Clinical outcomes extracted included postural tremor score in the treated upper extremity, quality of life (QoL), and incidence of adverse events (AE).**

RESULTS: **Baseline patient characteristics were comparable in the 2 studies, except that DBS patients were younger and had more severe baseline tremor. Both DBS- and MRgFUS-treated patients had significant tremor improvement that was sustained for 1-year posttreatment, and significant improvement in QoL. The MRgFUS cohort had higher rates of persistent neurologic AE, whereas the DBS group had higher rates of surgery- and hardware-related AEs, including intracranial hemorrhage.**

CONCLUSIONS: **In context of prior literature, both DBS and MRgFUS significantly improve tremor control and QoL. The 2 approaches are predominantly differentiated by their AE-profile. Additional head-to-head comparison on matched clinical populations are required to more accurately compare clinical efficacy and long-term outcomes.**

INTRODUCTION

Early interventions for medication-refractory essential tremor (ET) were ablative in nature, and included radiofrequency (RF) ablation, cryoablation, and later, gamma-knife stereotactic radiosurgery (SRS), all primarily targeting the ventral intermedius nucleus of the thalamus (Vim). With the development of deep brain stimulation (DBS) in the early 1990s, DBS of the Vim has gradually supplanted the use of ablative procedures in most neurosurgical centers. This transition was based on numerous studies demonstrating the clinical efficacy of DBS treatment, and improved safety compared to thalamotomy.[1-8]

The recent approval of magnetic resonance-guided focused ultrasound (MRgFUS) thalamotomy for the treatment of ET has reignited the debate surrounding the use of thalamotomy versus DBS for this indication.[9,10] Although MRgFUS is an ablative procedure, it is incisionless, which consequently limits the generalizability of available historical comparisons between DBS and RF thalamotomy.[5-8]

To fill this gap, we extracted clinical outcomes from 2 contemporary, prospective, multi-center controlled trials that examined the use of thalamic DBS and MRgFUS thalamotomy for the treatment of medication-refractory ET. The DBS study, by Wharen et al.,[11] and the MRgFUS study, by Elias et al.,[12] both met their primary

Key words
- Deep brain stimulation
- Essential tremor
- Focused ultrasound
- Thalamotomy
- Ventral intermedius nucleus

Abbreviations and Acronyms
AE: Adverse events
CRST: Clinical Rating Scale for Tremor
DBS: Deep brain stimulation
ET: Essential tremor
FDA: Food and Drug Administration
FUS: Focused ultrasound
ICH: Intracranial hemorrhage
MER: Microelectrode recording
MRgFUS: Magnetic resonance-guided focused ultrasound
RF: Radiofrequency
SRS: Stereotactic radiosurgery
QoL: Quality of life
QUEST: Quality of Life in Essential Tremor
Vim: Ventral intermedius nucleus of the thalamus

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Table 1. Patient Characteristics

Characteristics	DBS (n = 127)	MRgFUS (n = 56)	*P* Value
Age (years)	64.6 ± 9.6	70.8 ± 8.7	<0.001
Sex (no. male)	69 (54.3)	37 (66)	0.14
Laterality of treatment			
Unilateral	80 (63%)	56 (100%)	
Bilateral	47 (37%)	N/A	
Years since tremor onset	29.1 ± 17.4	28.3±16.4	0.77
Years since ET diagnosis	14.8 ± 11.8	16.4±13.1	0.42

DBS, deep brain stimulation; MRgFUS, magnetic resonance-guided focused ultrasound; ET, essential tremor.

endpoints and led to the Food and Drug Administration (FDA) approval of their respective technology. Given the study design and FDA oversight, these studies provide high-quality data allowing for a contemporary comparison between the 2 treatments. We examine the results of these studies in context of the existing literature comparing DBS and thalamotomy.

METHODS

Sources of Data

Clinical outcomes were compared between 2 recent prospective trials for the treatment of medication-refractory ET. In the Wharen et al.[11] single-blinded trial (NCT02087046), patients received unilateral or bilateral DBS implantation targeting the Vim with the Brio Neurostimulation constant-current stimulation device (St. Jude Medical, Little Canada, Minnesota, USA). In the Elias et al.[12] double-blinded trial (NCT01827904), patients were randomized to either unilateral MRgFUS Vim thalamotomy using the ExAblate Neuro model 4000 type 1.0 system (Insightec Inc., Dallas, Texas, USA) or sham surgery. All data presented in this text, with 1 exception, were extracted either from the publicly available FDA Summary of Safety and Effectiveness Data, or from the peer-reviewed articles reporting on the outcomes of these trials.[11-14]

The postural tremor score in the target extremity from the Clinical Rating Scale for Tremor (CRST) part A is reported as the measure of clinical efficacy and is scored in an ordinal fashion as 0 to 4, with 4 representing maximal tremor.[15] In DBS patients who received bilateral implants, the score used here is for the upper extremity with the most severe baseline tremor, consistent with the original reporting. A total of 42 of the 127 DBS-treated patients did not have full CRST data and were excluded from tremor outcome reporting in the primary study.[11] Quality of life (QoL) is reported using the Quality of Life in Essential Tremor (QUEST) questionnaire, which is a patient-reported assessment of 5 QoL domains (communication, work and finances, hobbies and leisure, physical, and psychosocial), and is reported as the measure of QoL. Clinical efficacy and QoL outcomes are reported for the intent-to-treat MRgFUS-treated cohort (i.e., cross-over patients are not included).

Adverse events (AE) are reported consistent with the original publications and are based on number of individual events as opposed to patients, such that some patients may have had multiple AE and others had none. In the DBS trial, AE were recorded up to 180-days following implantation. Postoperative pain or discomfort, AE that were deemed unrelated to the study by the primary authors, and those which resolved with DBS reprogramming were not reported in this text. Similarly, AE that were categorized as transient are not reported, unless they were categorized by the authors as serious. Serious AE were defined as "AE [that] are/cause: life threatening or fatal, required or prolonged hospitalization (>23 hours), or cause the patient to be disabled."[11] Stimulation-related AE and rates of reoperation were originally reported in a pooled fashion for patients who received unilateral and bilateral implantation (n = 127). Results based on this pooled data are pointed out in the text. Surgery- and hardware-related AE reported here include only the unilaterally treated patients (n = 80).

In the MRgFUS trial, AE were recorded up to 1-year following procedure. AE that were restricted to the intraoperative period, such as discomfort or intraprocedural dizziness, are not included here. AE that did not persist up to the 3-month postprocedure follow-up are categorized as transient and are not included here.

Statistical Analysis

In the absence of individual patient level data to allow for repeated-measures analysis of variance, the Student *t* test was performed for all comparisons using continuous variables. The χ^2 test was performed for comparison of sex distribution between studies. Statistical significance is defined as $P < 0.05$ throughout.

RESULTS

Patient Characteristics

A total of 127 patients received DBS Vim stimulation, 80 of which were treated unilaterally (Table 1). The remaining 47 patients were treated bilaterally; 8 of those underwent simultaneous bilateral implantation and 39 underwent staged implantation with at least 180 days between procedures. A total of 56 patients were treated by unilateral MRgFUS thalamotomy. The sex distribution between the 2 groups was comparable ($P = 0.14$). The MRgFUS cohort was older than the DBS cohort (70.8 ± 8.7 vs. 64.6 ± 9.6, $P < 0.001$). The time since the onset of tremor and since diagnosis was comparable between the groups.

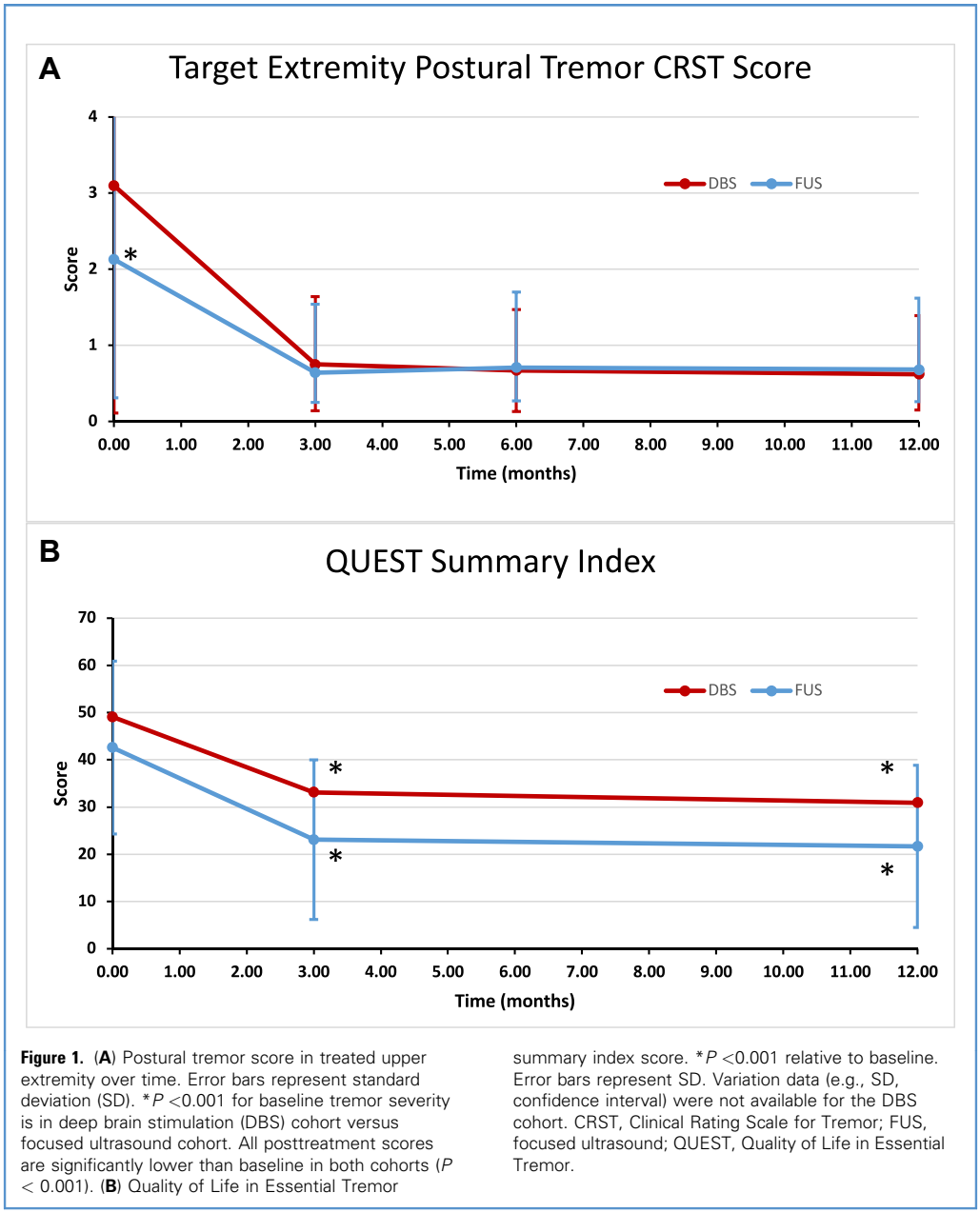

Figure 1. (**A**) Postural tremor score in treated upper extremity over time. Error bars represent standard deviation (SD). *P <0.001 for baseline tremor severity is in deep brain stimulation (DBS) cohort versus focused ultrasound cohort. All posttreatment scores are significantly lower than baseline in both cohorts (P < 0.001). (**B**) Quality of Life in Essential Tremor summary index score. *P <0.001 relative to baseline. Error bars represent SD. Variation data (e.g., SD, confidence interval) were not available for the DBS cohort. CRST, Clinical Rating Scale for Tremor; FUS, focused ultrasound; QUEST, Quality of Life in Essential Tremor.

Clinical Effect

The postural tremor score on part A of the CRST represented a component of the primary outcome in both studies. The DBS cohort had a significantly more severe tremor at baseline (3.1 ± 0.62) compared to the MRgFUS cohort (2.13 ± 1.15, P < 0.001). In the DBS group, the tremor score at 3 months, 6 months, and 1 year was 0.75 ± 0.78, 0.67 ± 0.70, and 0.62 ± 0.79, respectively (Figure 1A). In comparison, the MRgFUS group score at those time points was 0.64 ± 0.99, 0.71 ± 1.07, and 0.68 ± 0.99, respectively. The posttreatment scores were significantly lower than baseline for both cohorts (P < 0.001), signifying clinical improvement. This represents an average 80% and 68% improvement at 1 year in the DBS and MRgFUS cohorts, respectively. The posttreatment scores were comparable between the DBS and MRgFUS groups at each of the follow-up time points (P > 0.40). None of the MRgFUS patients underwent repeat lesioning.

QoL

Both DBS and MRgFUS achieved a significant and sustained improvement in QoL, as measured by the QUEST summary index (Figure 1B). In absolute terms, the DBS group had a worse QoL at baseline compared to the MRgFUS cohort, however, because standard deviation was not reported numerically for this score in

Table 2. Adverse Events Reported in Deep Brain Stimulation Cohort within 6-Months Postoperatively

Adverse Events Reported in DBS Cohort	n	%
Stimulation-related* (uni+bi)†		
Speech disturbance	12	9.4
Gait/postural disturbance	3	2.4
Cognitive change	1	0.8
Dysphagia or dysgeusia	1	0.8
Tinnitus	1	0.8
Surgery-related (uni)‡		
Misplaced lead	5	6.3
Infection	2 | **3**	2.5 | **3.8**
Intracranial hemorrhage	**3**	3.8
Paresis (symptomatic and transient)	**1**	1.3
Wound dehiscence	2 | **2**	2.5 | **2.5**
Pocket hematoma	1	1.3
Seizure (transient)	**1**	**1.3**
Stroke (symptomatic and persistent)	**1**	**1.3**
Intracranial edema (symptomatic and transient)	**1**	**1.3**
Worsening of preexisting condition (dystonia and possible TIA)	1 | **1**	1.3 | **1.3**
Dysarthria (persistent)	1	1.3
Other	5 | **1**	6.25 | **1.3**
Hardware-related (uni)		
Extension malfunction	4	5.0
Gait disorder including balance problem	1	1.3
Shocking or jolting sensation	1	1.3
IPG malfunction	3	3.8
Hemiparesis	**1**	1.3
Re-operation§ (uni+bi)		
Complete removal	**3**	**2.4**
Lead reposition	**2**	**1.6**
Extension lead replacement	**3**	**2.4**
Early need for IPG replacement	**3**	**2.4**

Numbers in **bold type** represent serious adverse events.
DBS, deep brain stimulation; TIA, transient ischemic attack; IPG, implantable pulse generator.
*Adverse events that did not resolve with reprogramming.
†Uni+bi represents pooled data from unilaterally and bilaterally implanted patients (n = 127).
‡Uni represents data only from unilaterally implanted patients (n = 80).
§Causes for reoperation typically also appear under surgery-related or hardware-related adverse events.

the DBS study, a statistical comparison between the 2 groups could not be done. The DBS group, including both unilaterally and bilaterally treated patients, went from a baseline score of 49.1 to 30.9 at the 1-year mark, in which a lower score represents improved QoL. In comparison, the MRgFUS group went from a baseline of 42.6 ± 18.3 to 21.7 ± 17.2 at the 1-year posttreatment. This represents an average 37% and 49% improvement in the DBS and MRgFUS cohorts, respectively.

AE

AE in the DBS group can be largely subdivided into 3 subcategories as being related to stimulation, surgery, or hardware (Table 2). In the first 6 months following DBS implantation, the rate of neurologic stimulation-related AE that were not transient and did not resolve with reprogramming was 14.2%, none of which was rated as serious. In the MRgFUS group, the rate of neurologic AEs that persisted at 3-months posttreatment was 66%, 1 of which was rated as serious (Table 3). This diminished to 34% by 1-year posttreatment.

Observing only those patients who received unilateral DBS, the rate of serious AE was 17.5%, which included infection (3 cases), intracranial hemorrhage (ICH) (3 cases), wound dehiscence (2 cases), seizure, stroke, paresis, and intracranial edema (1 case each). In the entire DBS cohort, the rate of reoperation owing to surgery or hardware-related complications was 8.7%. With the exception of 1 instance of paresthesia that was categorized as serious (mentioned earlier), there were no other cases of serious AE reported in the MRgFUS cohort, as well as no reoperations.

DISCUSSION

Since the development of DBS, the use of ablative Vim thalamotomies for medication-refractory ET has largely given way to DBS.[16,17] The recent emergence of incisionless MRgFUS thalamotomy as a potential alternative to DBS has created a need for a contemporary comparison between these 2 approaches. Comparison of the 2 prospective trials with regard to clinical efficacy demonstrate that both DBS and MRgFUS thalamotomy lead to significant improvement in tremor severity. The DBS cohort had a greater percent improvement in tremor than the focused ultrasound (FUS) group, suggesting superior clinical efficacy; this must, however, be interpreted with caution because the cohorts were unmatched at baseline with the DBS group having more severe tremor at baseline.

The difference in relative tremor improvement between the groups can be interpreted in 2 ways; first, that the DBS cohort has a larger percent improvement and therefore DBS is more efficacious than MRgFUS. Alternatively, because all posttreatment scores were statistically comparable between the 2 cohorts, interventions to the Vim may only able to reduce tremor to a certain level in an affected population. Earlier studies comparing DBS and RF thalamotomy in comparable clinical populations support the latter (Table 4), demonstrating similar rates of tremor reduction between the 2 techniques.[5-7,18] Moreover, in their recent single-center retrospective study, Kim et al.[18] reported equivalent clinical efficacy between DBS, RF thalamotomy, and MRgFUS thalamotomy when all groups had comparable baseline tremor

Table 3. Adverse Events Reported in Deep Brain Stimulation Cohort within 3-Months and 1-Year Postoperatively

Adverse Events Reported in MRgFUS Cohort

	AE Persistent at 3-Months		AE Persistent at 1-Year	
Adverse Event	**n**	**%**	**n**	**%**
Gait/postural disturbance	9	16.1	5	8.9
Dysphagia or dysgeusia	2	3.6	2	3.6
Paresthesia or numbness	14 | **1**	25.0 | **1.8**	7| **1**	12.5 | **1.8**
Dysmetria (limb)	5	8.9	2	3.6
Disequilibrium	3	5.4	1	1.8
Paresis (symptomatic and transient)	2	3.6	1	1.8
Dysarthria (persistent)	1	1.8	-	

Numbers in **bold type** represent serious adverse events.
MRgFUS, magnetic resonance-guided focused ultrasound; AE, adverse events.

Table 4. Summary of Studies Reporting on Head-to-Head Comparison of Ventral Intermedius Nucleus of the Thalamus Deep Brain Stimulation Versus Thalamotomy in Essential Tremor Patients. Some Studies Report Results on Pooled Cohorts Including Patients with Tremor Secondary to Parkinson Disease, Multiple Sclerosis, or Other

Comparative Studies on DBS and Thalamotomy for ET

Study	Patient Population	Clinical Efficacy	Safety
Tasker et al., 1997[7]; Tasker 1998[8,*] Design: single surgeon retrospective cohort	DBS (n = 20): PD (13), ET (3), CT (4) RF (n = 35): PD (23), ET (2), CT (10)	■ Total or near-total control of tremor achieved in DBS (62.5%) and RF (63.7%) ET+PD patients. ■ These rates represent response after repeated surgery, when needed.	■ DBS: Lead extrusion requiring replacement (1, 5%). ■ RF: ICH (1, 3%), repeated lesioning (6, 17%), persistent neurologic AE[†] in RF group (12, 34%).
Schuurman et al., 2000[6] Design: RCT	DBS (n = 34): PD (22), ET (7), MS (5) RF (n = 34): PD (23), ET (6), MS (5)	■ Functional status improvement is superior in the DBS group ($P < 0.05$). ■ Abolition of tremor in all ET patients in both cohorts by 6-month postoperative.	■ DBS: Surgery-related death (1, 3%), hardware-related AE (2, 6%). ■ RF had higher rates of persistent neurologic AE at 6-month follow-up compared to DBS.
Pahwa et al., 2001[5] Design: single surgeon retrospective cohort	DBS (n = 17) RF (n = 17) (all ET patients)	■ Comparable improvement in tremor severity (CRST) between the 2 cohorts.	■ DBS: Seizure (1, 6%), reoperation for reoperation for hardware-malfunction (5, 29%), no benefit with consequent conversion to RF (1, 6%). ■ RF: ICH (6, 35%), repeated lesioning (1, 6%). ■ No persistent neurologic AE in either group.
Kim et al., 2017[18] Design: single center retrospective cohort	DBS (n = 19) RF (n = 17) MRgFUS (n = 23) (all ET patients)	■ Rates of treatment success were comparable between the DBS, RF, and MRgFUS cohorts ($P < 0.05$). ■ There was some recurrence in all cohorts by 1-year posttreatment, with no significant difference between the groups ($P > 0.05$).	■ DBS: No persistent neurologic AE. ■ RF: ICH (1, 5%), persistent neurologic AE (2, 11%). ■ MRgFUS: persistent neurologic AE (1, 4%).

DBS, deep brain stimulation; ET, essential tremor; RCT, randomized controlled trial; PD, Parkinson disease; CT, cerebellar tremor; RF, radiofrequency; MS, multiple sclerosis; MRgFUS, magnetic resonance-guided focused ultrasound; CRST, Clinical Rating Scale for Tremor; ICH, intracranial hemorrhage; AE, adverse events.
*Patients in these series were included in 2 reports; 1 that included computed tomography patients,[7] and a subsequent 1 that did not.[8]
†Neurologic adverse events include paresthesia, hand ataxia, dysarthria, and gait disturbance.

Table 5. Summary of Studies Reporting on Long-Term Outcomes Following Deep Brain Stimulation or Thalamotomy for Essential Tremor

	Long-Term Follow-Up of DBS and Thalamotomy for ET			
	Study	**Number of Patients**	**LTFU (months)**	**Long-Term Outcomes**
DBS	Blomstedt et al., 2007[20]	19	89 ± 9	■ Persistent clinical benefit relative to baseline ($P < 0.01$), but not as much as at initial postoperative score ($P = 0.037$). ■ Lead breakage (6, 32%), IPG replacement (12, 63%).
	Koller et al., 2001[21]	46	40	■ Persistent clinical benefit ($P < 0.001$) in 25 patients returning for LTFU. ■ Reoperations (20, 43%): lead replacement/repositioning owing to loss of effect (10, 22%) or breakage (1, 2%); extension wire or IPG replacement (2, 4%); explantation (7, 15%) owing to: infection (1), no benefit (2), lost benefit then converted to thalamotomy (3), persistent thalamotomy effect with no need for stimulation (1).
	Sydow et al., 2003[22]	17	78 ± 7.2	■ Persistent clinical benefit ($P < 0.001$). ■ Unresolved stimulation-related neurologic AE* (7, 41%), IPG replacement (5, 29%), loss of effect (2, 11%).
Thalamotomy	Nagaseki et al., 1986[23] (RF)	16	36–120	■ Persistent clinical benefit in 15 of 16 (absent or slight residual tremor). ■ Early re-lesioning (≤2 weeks) owing to recurrence (1, 6%). ■ In larger cohort containing PD patients (total n = 43), persistent neurologic AE (3, 7%).
	Young et al., 2010[24] (SRS)	161	56 ± 31	■ Persistent clinical benefit ($P < 0.0001$). ■ Persistent neurologic AE (8, 2%). ■ Absence or loss of effect (>10, >6%; portion patients lost to follow-up [n = 42] was due to treatment failure).
Comparative	Schuurman et al., 2008[25,†]	DBS (n = 26) RF (n = 22)	60	■ 64% (DBS) and 72% (RF) of patients tremor free at LTFU compared to 76% 6-months postoperative in both groups. Functional status higher in DBS group relative to RF at LTFU ($P < 0.05$). ■ Persistent neurologic AE in both DBS (2, 8%) and RF (7, 32%) cohorts. Hardware-related complications requiring surgery in DBS cohort (6, 18%).

DBS, deep brain stimulation; ET, essential tremor; LTFU, long-term follow-up; RF, radiofrequency; SRS, stereotactic radiosurgery; IPG, implantable pulse generator; AE, adverse events; PD, Parkinson disease.
*Neurologic adverse events include paresthesia, hand ataxia, dysarthria, and gait disturbance.
†Reporting on mixed population of essential, Parkinsonian, and multiple sclerosis tremor.

severity. It should be noted that in the Tasker et al.[7] study, the thalamotomy cohort required repeat lesioning at a rate of 23.7% to match the clinical efficacy of DBS.

Long-term follow-up for the MRgFUS cohort is available up to 2-years postoperatively for 67 of 76 treated patients (initial cohort plus cross-over patients); these data suggest sustained efficacy between 1 and 2 years after treatment.[19] Of the 9 patients excluded at the 2-year assessment, 3 decided to undergo DBS-implantation in the interim. Although no follow-up data for FUS exists beyond 2 years, thalamotomy data from other ablative techniques can be used as a proxy for understanding recurrence risks in the FUS population. Using the long-term data available for DBS, RF, and SRS thalamotomies, it seems that long-term tremor recurrence may be seen with either treatment (**Table 5**), although some literature suggests higher recurrence rates in thalamotomy-treated patients.[9,10] Blomstedt et al.[20] report persistent clinical benefit relative to preoperative baseline at approximately 7 years after DBS implantation; however, tremor severity is higher relative to the early postoperative evaluation. This may indicate either progression of underlying tremor or loss of clinical benefit. Although Koller et al.[21] similarly show persistent clinical effect of DBS in patients returning for long-term follow-up, they also report a 28.3% reoperation rate in the original cohort, specifically for reasons pertaining to the loss of clinical benefit. Sydow et al.[22] also report a recurrence rate of 11%.

Studies reporting on long-term outcomes following thalamotomy tell a similar story. Although Nagaseki et al.[23] show persistent effects in their small series of RF-treated patients, Young et al.[24] reported absence or loss of effect in at least 6% of SRS-treated patients. The long-term follow-up of the Schuurman et al.[25] trial, comparing DBS and RF, showed a mild decrease in tremor control over time in both groups, but similar to the early

Table 6. Differentiating Factors in Each Treatment that Have the Potential to Negatively Affect Patient Quality of Life

Potential Factors Negatively Affecting QoL		
DBS		**MRgFUS**
Need for craniotomy	Procedure-related	Need for total head-shave
Clinic visits for reprogramming to maximize effect	Clinical effect	Repeat treatment to maximize clinical effect
Stimulation-related AE (mostly manageable with reprogramming) Surgery-related AE Management of hardware-related AE	Adverse events	Risk of persistent neurologic AE
Need long-term access to DBS center	Other	

QoL, quality of life; DBS, deep brain stimulation; MRgFUS, magnetic resonance-guided focused ultrasound; AE, adverse events.

postoperative outcomes, functional status of DBS-treated patients remained superior to the RF group. Taken together, it seems that both thalamotomy and DBS are associated with some tremor recurrence over time; current literature does not provide enough evidence to determine whether 1 treatment is more efficacious as the disease progresses.

Accuracy of Localization

One of the common arguments for the superiority of DBS to incisionless interventions, such as SRS and MRgFUS, is the ability to use physiologic mapping techniques, including microelectrode recording (MER) or macro-electrode stimulation, to assist with the localization of Vim. MRgFUS differs from SRS by supplementing traditional anatomic targeting with the use of preablative low temperature simulations at the ultrasound focus. Similar to macro-stimulations for DBS, subthreshold sonications allow real-time assessment of clinical effect and AE, and the target can be adjusted accordingly prior to delivering permanent ablations. MRgFUS is further enhanced by real-time monitoring of the lesioning using MR thermometry, which provides an additional checkpoint for target verification. In DBS surgery, MER can help identify Vim and the borders of adjacent structures through recognition of characteristic neuronal firing patterns. This can be supplemented by macro-electrode stimulation. Gross et al.[26] examined the use of physiologic mapping in DBS surgery for Parkinsonian and ET in 28 centers in Europe and North America. They note that although 40% of centers use MER for Vim targeting, there was no statistical difference in outcomes between centers using MER and those relying purely on macro-stimulation and stereotaxy. Therefore, they suggest that use of MER should be balanced against the associated elevated bleeding risk.[27] It is important to note that the appropriate role of MER remains an active area of debate in DBS literature.

Comparative Adverse Event Profile

Although MRgFUS is incisionless, it is nevertheless an ablative procedure consisting of creating a parenchymal lesion. Accordingly, when discussing AE, it is perhaps best compared to SRS thalamotomy rather than RF thalamotomy. Like SRS, MRgFUS obviates the risks associated with surgical and hardware-related complications, however, the risk of neurologic complications remains—including gait disturbance and paresthesia—owing to the disruption of nuclei or tracts neighboring the target. Unlike thalamotomy, DBS can be reprogramed to address stimulation-related neurologic complications. Based on the 2 trials examined here and prior literature, thalamotomy seems to be associated with higher rates of persistent neurologic AE compared to DBS, reaching 2%–34%.[6-8,11,12,18,19,22-25,28] The high rate of neurologic AE in the MRgFUS cohort early on is, in part, attributable to the spread of perilesional edema that dissipates over several months following treatment.[19,29-31] This edema, however, does not explain the presence of persistent neurologic AEs at 1-year time. Centers experienced with SRS thalamotomy have, over time, achieved low rates of persistent neurologic AE, which suggests that additional experience using MRgFUS may lead to reduced AEs.[24]

ICH is presumably the most serious complication of invasive stereotactic interventions. This risk primarily arises from the introduction of the DBS or RF electrode and the potential disruption of vessels along the trajectory, and can be minimized through careful trajectory planning and fewer electrode passes. The Wharen et al.[11] DBS study reported a 3.9% ICH rate, which is consistent with the literature-reported rate of about 1%–4%.[4,6,8] RF thalamotomy may have a slightly increased ICH risk associated with traction on coagulated tissue at the target during lead withdrawal.[5] In the MRgFUS literature reporting on the lesioning in about 270 patients, with targets including Vim,[12,32-35] pallidothalamic tract,[36,37] anterior capsule,[38] and the posterior part of the central lateral thalamus,[39] there has been only 1 case of ICH. In a 2012 pilot study examining the use of MRgFUS for neuropathic pain, Jeanmonod et al.[39] reported 1 case of bleeding within the target (posterior part of the central lateral thalamus) resulting in ischemia in the motor thalamus. The authors postulated that excessive temperature elevation caused cavitation damage, leading them to implement a maximum temperature cutoff of 60°C as well as the use of a cavitation detector.

QoL

After safety and clinical efficacy, the effect of the treatment on QoL is of most importance to both patients and clinicians. Both MRgFUS and DBS led to significant and sustained improvement in QoL, but unfortunately, a strict statistical comparison between the cohorts was not possible. Broadly speaking, both treatment options have potential risk factors that may attenuate the QoL benefit

provided by the procedure (Table 6). For DBS, the most prominent aspects include the need for long-term hardware management, including multiple clinic visits for reprogramming and potential reoperations for implantable pulse generator exchange or hardware-related AE. For MRgFUS-treated patients, there is the risk for persistent AE. These factors must be weighed in the context of patients' goals and circumstances.

CONCLUSIONS

In this article, we have compared clinical outcomes following DBS or MRgFUS thalamotomy for the treatment of medication refractory ET. The 2 trials examined were contemporary and used the same outcome measure scales, making them well-suited for comparison. This study is, however, limited by the several factors including the difference in baseline patient characteristics between the 2 trials in terms of age and tremor severity, and the exclusion of a significant number of patients from the primary outcome reporting in the DBS trial. Additionally, not enough data were available to make statistical comparison for all outcome metrics.

Nevertheless, examination of these 2 trials in the context of the existing literature on the topic suggests that DBS and thalamotomy may be comparable in terms of short- and long-term efficacy. Thalamotomy, in general, including MRgFUS, is associated with higher rates of persistent neurologic AE compared to DBS. In contrast, DBS may be associated with higher rates of ICH relative to MRgFUS, although this remains to be verified as more MRgFUS reporting is generated. Another important difference between the approaches is that DBS is associated with non-negligible rates of reoperation for hardware maintenance or hardware-related AE. There remains a need for longer-term follow-up data on MRgFUS-treated patients, as well as a prospective comparative investigation of MRgFUS thalamotomy versus DBS in matched ET cohorts.

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