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Magnetic Resonance-guided Focused Ultrasound (MRgFUS)

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Magnetic Resonance-guided Focused Ultrasound (MRgFUS)

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Editorial: Magnetic Resonance-guided Focused Ultrasound (MRgFUS)

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KEYWORDS

Magnetic Resonance-guided Focused Ultrasound Surgery (MRgFUS), Parkinson's disease, essential tremor, disability, quality of life

Editorial on the Research Topic
Magnetic Resonance-guided Focused Ultrasound (MRgFUS)

Magnetic Resonance-guided Focused Ultrasound (MRgFUS) has emerged over the past decade as one of the most promising innovations in functional neurosurgery. This Research Topic presents a comprehensive exploration of MRgFUS across 13 peer-reviewed contributions that explore MRgFUS across a broad spectrum: clinical outcomes, patient experience, neurophysiological mechanisms, targeting strategies, cognitive safety, and healthcare system integration. Together, these articles chart the maturation of MRgFUS from a novel incisionless ablative technique to a mainstream therapeutic option for movement disorders such as essential tremor (ET) and Parkinson's disease (PD).

Longitudinal studies confirm the sustained efficacy of unilateral MRgFUS thalamotomy in ET, with significant improvements in tremor severity and quality of life maintained over 3 years. Tamburin et al. report durable tremor reduction and manageable side-effect profiles in a cohort of 49 patients, reinforcing the long-term benefit of this approach. In PD, Tian et al. provide safety and efficacy analysis, while Saporito et al., in the COGNIFUS Part 2 study, demonstrate cognitive stability and mood improvements one-year post-treatment—addressing an important concern in lesional neurosurgery.

Targeting strategies are central to therapeutic success. Jameel et al., through an international survey, observe a trend toward targeting above the intercommissural plane in ventral intermediate nucleus (VIM) thalamotomies. Buch et al. further show that smaller, well-placed lesions within network-based hotspots yield greater subjective quality-of-life improvements, underscoring that "more" is not necessarily better. Complementing these findings, Blitz et al. report that the lesion size and its evolution over time as seen in MR images does not correlate with tremor control, while Bruno et al. analyze nine patients with tremor recurrence after VIM thalamotomy to extrapolate optimal targeting location. Low skull density ratio (SDR) has been and still is a limiting factor in patient eligibility due to concerns about acoustic energy transmission. Ng et al. challenge this paradigm by demonstrating that patients with an SDR <0.40 can still benefit—albeit requiring higher sonication energy and experiencing slightly increased failure rates—prompting a re-evaluation of strict exclusion criteria.

On the neurophysiological front, Visani et al. present novel Magnetoencephalography (MEG) data indicating that MRgFUS thalamotomy induces early cortical reorganization,

including reduced beta-band cortico-cortical coupling and adjusted cortico-muscular coherence. These findings offer potential early biomarkers of treatment response.

The phenomenological study by Stoycheva et al. reminds us that outcome metrics must encompass not just tremor scores but also the patient's lived experience.

Liang et al. provide a network meta-analysis comparing MRgFUS and deep brain stimulation (DBS), showing comparable efficacy in motor symptom control and quality-of-life enhancement. While DBS remains the gold standard for many, MRgFUS is increasingly validated as a viable alternative, particularly for patients ineligible for implants. Cesarano et al. further support MRgFUS's potential through a systematic review of staged bilateral treatments in both ET and PD, demonstrating encouraging safety and efficacy profiles.

Finally, Rinaldo et al. outlie a structured diagnostic-therapeutic pathway (DTP) for integrating MRgFUS into clinical workflows. Their experience with over 600 cases offers a practical and scalable model for institutions aiming to adopt or expand MRgFUS programs.

In conclusion, MRgFUS is maturing into a safe, effective, and patient-centered modality for the treatment of movement disorders. The contributions in this Research Topic highlight both technological progress and humanistic insight, reaffirming the growing role of MRgFUS in modern functional neurosurgery.

Author contributions

FP: Writing – original draft, Conceptualization, Writing – review & editing. MG: Writing – review & editing, Conceptualization, Writing – original draft. MT: Conceptualization, Writing – original draft, Writing – review & editing.

Conflict of interest

MG was employed by SIFUS AG.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Longitudinal MR imaging after unilateral MR-guided focused ultrasound thalamotomy: clinical and radiological correlation

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Introduction: Magnetic-resonance-guided focused ultrasound (MRgFUS) thalamotomy uses multiple converging high-energy ultrasonic beams to produce thermal lesions in the thalamus. Early postoperative MR imaging demonstrates the location and extent of the lesion, but there is no consensus on the utility or frequency of postoperative imaging. We aimed to evaluate the evolution of MRgFUS lesions and describe the incidence, predictors, and clinical effects of lesion persistence in a large patient cohort.

Methods: A total of 215 unilateral MRgFUS thalamotomy procedures for essential tremor (ET) by a single surgeon were retrospectively analyzed. All patients had MR imaging 1 day postoperatively; 106 had imaging at 3 months and 32 had imaging at 1 year. Thin cut (2 mm) axial and coronal T2-weighted MRIs at these timepoints were analyzed visually on a binary scale for lesion presence and when visible, lesion volumes were measured. SWI and DWI sequences were also analyzed when available. Clinical outcomes including tremor scores and side effects were recorded at these same time points. We analyzed if patient characteristics (age, skull density ratio), preoperative tremor score, and sonication parameters influenced lesion evolution and if imaging characteristics correlated with clinical outcomes.

Results: Visible lesions were present in all patients 1 day post- MRgFUS and measured 307.4 $\pm$ 128.7 mm^3. At 3 months, residual lesions (excluding patients where lesions were not visible) were 83.6% smaller and detectable in only 54.7% of patients (n = 58). At 1 year, residual lesions were detected in 50.0% of patients (n = 16) and were 90.7% smaller than 24 h and 46.5% smaller than 3 months. Lesions were more frequently visible on SWI (100%, n = 17), DWI (n = 38, 97.4%) and ADC (n = 36, 92.3%). At 3 months, fewer treatment sonications, higher maximum power, and greater distance between individual sonications led to larger lesion volumes. Volume at 24 h did not predict if a lesion was visible later. Lesion visibility at 3 months predicted sensory side effects but was not correlated with tremor outcomes.

Discussion: Overall, lesions are visible on T2-weighted MRI in about half of patients at both 3 months and 1 year post-MRgFUS thalamotomy. Certain sonication parameters significantly predicted persistent volume, but residual lesions did not correlate with tremor outcomes.

KEYWORDS

focused ultrasound, essential tremor, thalamotomy, thermal lesions, lesion persistence

1. Introduction

Magnetic resonance-guided focused ultrasound (MRgFUS) thalamotomy has demonstrated successful treatment of medication-refractory tremor in essential tremor (ET) (1, 2). This technique uses transcranial acoustic energy to ablate the ventral intermediate (Vim) nucleus of the thalamus, allowing for an incisionless approach in an awake patient to relieve debilitating tremor. Clinical neurologic feedback between sonications can guide target placement and other parameters, such as number of sonications, maximum power, and maximum energy. Sonications continue until adequate tremor control is achieved, with the targeted tissue usually reaching a peak temperature of around 55–60°C (3).

Post-procedural imaging is common on the day after the procedure as well as at various time intervals thereafter. T2-weighted imaging 24-h after MRgFUS thalamotomy typically shows a region of ablation with dimensions of 6–8 mm, although specifics can vary depending on the exact time interval and MRI methods used (3). These lesions have distinct concentric zones: a central necrotic core (zone 1), surrounding cytotoxic edema (zone 2), and a larger ring of vasogenic edema (zone 3) (4). At our institution, additional MRI scans are often obtained at 3-months and less frequently at 1-year following the procedure depending on patient availability and ability to return to clinic. On these subsequent T2-weighted images, visible lesions are often substantially smaller or no longer visible despite persistent tremor improvement, which has previously been reported (4–7) (Figure. 1). There is currently no consensus on the frequency of postoperative imaging after MRgFUS thalamotomy, specific sequences to be used, or what these findings may represent. Some studies have looked at variables that correlate with post-procedure lesion persistence, but these have analyzed very few patients, mostly at less than 6 months post-procedure, and some only on two-dimensional axial imaging (4, 6, 8–10). Now that more bilateral thalamotomies are being performed, an understanding of lesion evolution over time will be useful to better assess how the second side target relates to the lesion location on the first side.

In this retrospective analysis of a large single-surgeon consecutive series of unilateral MRgFUS thalamotomy procedures in patients with ET, we aimed to evaluate the evolution and incidence of lesion persistence on T2-weighted MR imaging and correlate this with tremor outcomes and side effects at 3-months and 1-year. Prior studies have demonstrated that larger lesion size on MRI completed 1 day following MRgFUS thalamotomy is correlated with more adverse events (4, 11–13), and that lesion size and tremor control are influenced by various sonication parameters (10, 12, 14, 15). We therefore predicted that increasing sonication parameters (e.g., power, temperature, distance between individual sonications) would create larger lesions that would both persist on imaging as well as lead to more adverse effects, although potentially with improved tremor control.

2. Methods

2.1. Patient selection

We retrospectively identified all patients who underwent unilateral MRgFUS thalamotomy for ET between June 2017 and April 2022 at our institution. Those chosen for treatment included patients that satisfied the following criteria: (1) severe and/or disabling tremor, (2) failed multiple medications, (3) not a candidate for or unwilling to undergo deep brain stimulation (DBS), and (4) skull-density ratio of at least 0.35. All patients had imaging on postoperative day 1. Out of the 215 total patients treated, 121 had imaging at either 3 months, 1 year, or both timepoints following the procedure and were therefore included in the study.

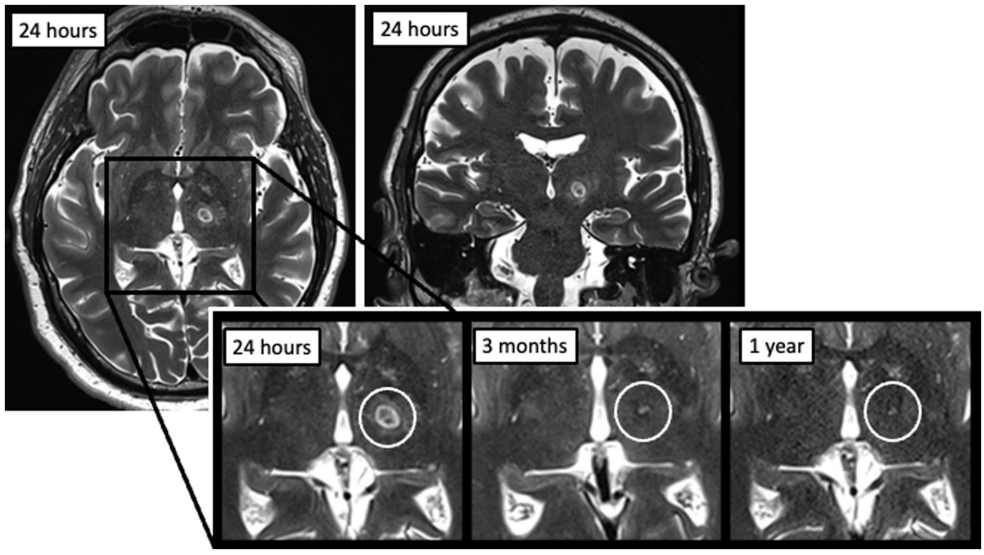

FIGURE 1
Example of an MRgFUS thalamotomy lesion at 24 h post-procedure on axial (left) and coronal (right) T2-weighted imaging, as well as evolution over time at three time points (24 h, 3 months, and 1 year).

2.2. MRgFUS procedure

The detailed MRgFUS thalamotomy procedural workflow at our institution has previously been published (11). Briefly, a patient's head was completely shaved and a modified Codman-Robert-Wells frame (Radionics, Inc.) was applied under local anesthesia. A silicone membrane was stretched over the frame and head before placing the patient in a 3 T MRI (GE Medical Systems) connected to the ExAblate 4,000 MRgFUS transducer (InSightec Inc., Israel). The space between the transducer and the scalp was filled with cooled and degassed water for acoustic coupling. The unilateral Vim was targeted in all patients as previously described (8) using atlas-based coordinates of one quarter of the anterior commissure-posterior commissure (AC-PC) distance anterior to PC, 13–14 mm lateral to midline, and 1.5–2 mm superior to the midcommissural plane, and further refined with direct visualization (16). Subclinical test sonications were used to assess for transient tremor improvement or side effects and target adjustments were made as needed before delivery of high-powered sonications with maximum temperature of around 55–60°C (monitored with real-time MR thermometry). Patients were clinically assessed between each sonication to ensure adequate tremor control and monitor for side effects, including asking about sensory disturbances.

The postoperative focused ultrasound imaging protocol is as follows: 3D plane localizer sagittal and axial T1, axial 3D T1, axial and coronal 2 mm thin-cut T2, axial T2 GRE, axial Flair, axial SWI, and axial DWI. Later patients replaced SWI with WMn MPRAGE sequence on Prisma scanner and replaced DWI with DTI 30 direction (or 18 if 30 was not available).

2.3. Data collection and outcomes

For each procedure, sonication parameters were recorded including the total number of sonications, number of treatment sonications (defined as energy >5,000 J), maximum power, maximum energy, maximum duration, and maximum temperature. Additionally, with adjustment of the sonication target during the procedure to maximally relieve tremor, we recorded the maximum distance between planned targets. Skull-density ratio (SDR), or the ratio of cortical to cancellous bone, was calculated based on preoperative CT imaging. Because SDR is correlated with most sonication parameters given its impact on the required thermal dose to create lesions (10), SDR-normalized values of power, energy, and duration were calculated using a linear regression between the SDR and the respective sonication parameter, and fitting to a linear equation, as previously described (11). For each patient, SDR values were used to calculate the expected value based on the regression equation. Power, energy, or duration values for that patient were divided by the expected value, such that a value >1 corresponded to a value above the expected maximum. We also calculated the number of 'low-power' and 'low-temperature' sonications per treatment, since it was previously described that delivery of high power and temperature earlier in the treatment course led to larger lesions at 24 h (11). Because high-power sonications were previously defined as those within the top 10th percentile, low-power sonications were defined as those within the bottom 90th percentile. This was also the definition used for low temperature sonications.

Postoperative axial and coronal thin-cut (2 mm) T2-weighted images at 3 months and 1 year were analyzed on a binary scale for lesion visibility (authors SEB, MMJC, and DJS). This was done by comparing side-by-side images to the 24-h lesion and directly visualizing if there was any T2 hyper-or hypointense remnant in the location of the lesion. Figure. 2 shows an example of a patient with a lesion that was not present at 1 year (top) compared to a patient with a T2-bright lesion still present at 1 year (bottom). Approximate volumes were calculated for those with lesions still visible at 3 months and 1 year and for all 24-h lesions by measuring the anterior–posterior (AP), transverse (TR), and craniocaudal (CC) diameters calculating the volume of an ellipsoid, where V = volume of an ellipsoid, a = AP radius, b = TR radius, and c = CC radius:

$$V = \frac{4}{3}\pi abc$$

At 24 h, 3 months, and 1 year post-MRgFUS thalamotomy, absolute volume as well as percent of 24-h volume still present were used for calculations.

Fahn-Tolosa-Marin (FTM) tremor scores were assessed preoperatively for baseline comparison, and at 3-month and 1-year postoperative follow-up visits. Tremor on the FTM scale is graded from 0 to 4, with 0 being no tremor, and 4 being severe tremor. FTM components assessed in each patient included head, voice, resting, postural, and intention tremor. Side effects were also recorded, including motor weakness, sensory deficits, dysarthria, fatigue, imbalance, dysgeusia, and coordination issues/dysmetria.

To assess attrition bias for patients with MRI at 1 year, the included patients were separated into 2 groups based on those that had a 1-year MRI versus those that did not. These groups were compared for patient characteristics, total and treatment sonications, volume at 24 h, preoperative total FTM score and FTM intention score, 1-year total FTM and FTM intention score, 1-year total FTM improvement, and 1-year FTM intention improvement.

2.4. Statistical analysis

Chi-squared tests, unpaired t-tests, and Spearman's rank correlations were performed using Python version 3. When calculating Spearman's rank correlations for volume, lesions that were not visible (i.e., volume of 0) were excluded given that the lesions could have become absent at different time points, which could impact the fit of the data. Multiple regressions were also used to determine predictors of lesion absence/presence as well as volume at these timepoints and change in volume at these timepoints. Variables included in the regression were based on previously determined significant predictors of volume at 24 h (11) as well as those found to be significant in simple Spearman's rank correlations. A value of p of less than 0.05 was considered statistically significant. A Bonferroni test was used for post-hoc multiple-comparison correction.

3. Results

3.1. Patient baseline characteristics

Patients' ages ranged from 59 to 94 years (mean ± SD, 75.4 ± 6.7), with most patients being male (71.1%) (Table 1). Baseline preoperative

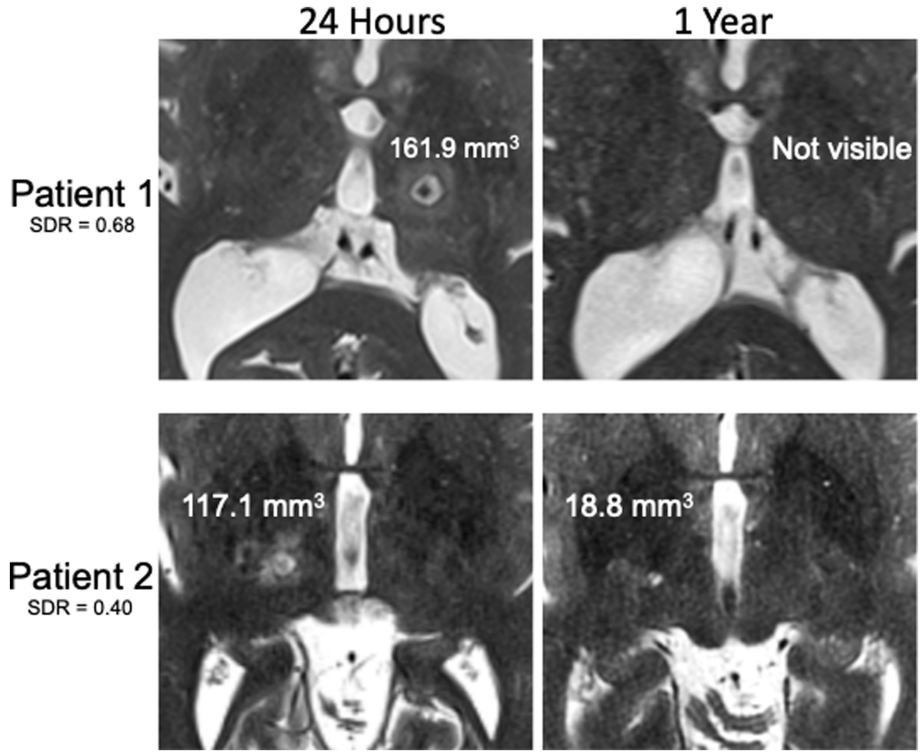

FIGURE 2
Examples of T2-weighted MR images 24 h and 1 year after MRgFUS for essential tremor. Patient with high SDR without visible lesion at 1 year despite large lesion at 24 h (top) compared to patient with low SDR with visible lesion at 1 year despite smaller lesion at 24 h (bottom). Lesion volumes displayed on the images.

TABLE 1 Patient characteristics.

	n = 121
Age, years, mean ± SD (range)	75.4 ± 6.7 (59–94)
Male sex, *n* (%)	86 (71.1)
Dominant hand, *n* (%)	
Left	20 (16.5)
Right	97 (80.2)
Ambidextrous	5 (4.1)
Right hand treatment, *n* (%)	96 (79.3)
Baseline preoperative FTM, median (IQR), range	7 (5–8), 3–16
Baseline preoperative FTM intention, median (IQR), range	3 (3–4), 1–4
3-month total FTM, median (IQR), range	0 (0–1), 0–12
3-month FTM intention, median (IQR), range	0 (0–0), 0–4
3-month FTM intention percent improvement, median (IQR), range	100.0 (100.0–100.0), 0.0–100.0
1-year total FTM, median (IQR), range	0 (0–1), 0–9
1-year FTM intention, median (IQR), range	0 (0–1), 0–4
1-year FTM intention percent improvement, mean ± SD	100.0 (75.0–100.0), 0.0–100.0

FTM scores ranged from 3 to 16 (7.0 ± 2.4) with FTM intention score ranging from 1 to 4 (3.2 ± 0.7).

3.2. Lesion visibility and volume

All patients had visible lesions on 24-h post-procedural T2-weighted MRI, with an average volume of 307.4 ± 128.7 mm^3 [median (IQR), 294.2 (213.9–369.9) mm^3], or 7.7 × 7.9 × 9.2 mm (AP x TR x CC) (Table 2; Figures 1, 3). At 3 months, residual lesions were detectable in 59.0% of patients (n = 69) and were 83.6% smaller on average with a volume of 38.7 (19.2–64.4) mm^3 ($p < 0.0001$), or 3.9 × 4.7 × 4.5 mm. For patients who had SWI sequences (n = 17), visible SWI signal was present in all at 3 months. The majority of lesions were also visible on DWI (n = 38, 97.4%) and ADC (n = 36, 92.3%) at 3 months. Almost half were bright on DWI (42.1%). Lesions at 1 year were detectable in 52.9% of patients (n = 18). Residual lesions [18.9 (12.5–35.9) mm^3 or 3.1 × 3.9 × 3.9 mm] were on average 90.7% smaller than 24 h ($p < 0.0001$), and 46.5% smaller than 3 months ($p = 0.110$).

3.3. Predictors of lesion visibility and size

Independent t-tests between patients with lesions present and those without lesions present at both 3 months and 1 year demonstrated no difference in patient characteristics (age and SDR),

TABLE 2 Lesion characteristics at 3 months and 1 year postoperatively on MRI.

24 h		
T2-weighted lesion presence	*n* = 121 (100%)	
Volume, median (IQR)	294.2 (213.9–369.9) mm^3	

3 months		*p* value (compared to 24 h)
T2-weighted lesion presence	*n* = 58 (54.7%)	**<0.0001**
Volume, median (IQR)	38.7 (19.2–64.4) mm^3	**<0.0001**
SWI lesion presence	*n* = 17 (100%)	
DWI lesion presence	*n* = 38 (97.4%)	
Bright on DWI	*n* = 16 (42.1%)	
ADC lesion presence	*n* = 36 (92.3%)	

1 year		*p* value (compared to 24 h)	*p* value (compared to 3 months)
T2-weighted lesion presence	*n* = 16 (50.0%)	**<0.0001**	0.393
Volume, median (IQR)	18.8 (12.5–35.9) mm^3	**<0.0001**	0.110

The percent of lesions present and volumes of lesions were significantly smaller at 3 months compared to 24 h and 1 year compared to 24 h.

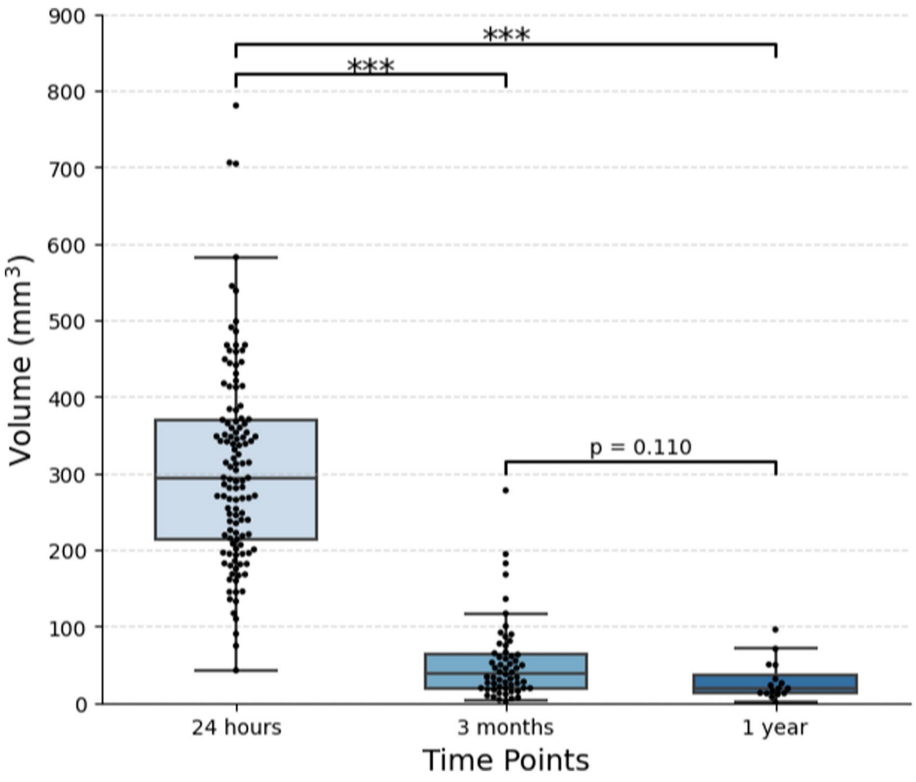

FIGURE 3
Change in lesion volume over time. One hundred and twenty-one patients with essential tremor who underwent MRgFUS thalamotomy were included. Out of 106 patients with imaging at 3 months, 58 had visible lesions. Out of 32 patients with imaging at 1 year, 16 had visible lesions. The plot displays the median and IQR (***$p < 0.001$).

sonication parameters, preoperative tremor scores, or 24-h lesion volume (Supplementary Table S1).

Before multiple-comparison corrections, Spearman's rank correlations found that age predicted the lesion volume at 3 months (rho = −0.302, $p = 0.021$) and SDR predicted the change in volume at 1 year (rho = −0.605, $p = 0.013$) (Figure 4; Supplementary Table S1). However, after Bonferroni corrections, neither of these remained significant (not $p < 0.003$).

Multiple regressions to determine predictors of lesion presence at both 3 months and 1 year did not show any significant variables. A regression of predictors of lesion volume at 3 months showed that the number of treatment sonications (coefficient = −12.7, $p = 0.016$),

normalized maximum power (coefficient = 96.5, $p = 0.048$), and the maximum distance between sonication targets (coefficient = 27.9, $p = 0.013$) predicted volume. Treatment sonications and maximum distance also predicted the percent of lesion volume still present at 3 months compared to 24-h volume (coefficient = −5.7, $p = 0.003$ and coefficient = 10.5, $p = 0.009$, respectively). No variables were significant in the 1-year volume regressions.

3.4. Lesion visibility and volume and outcomes

At 3 months, the total FTM score ranged from 0 to 12 [median (IQR) = 0 (0–1)], and FTM intention ranged from 0 to 4 [0 (0–0)]. At 1 year, the total FTM score ranged from 0 to 9 [0 (0–1)], and FTM intention ranged from 0–4 [0 (0–1)]. Lesion visibility and lesion size at 3 months and 1 year did correlate with some side effects, specifically weakness and sensory deficits (Supplementary Table S3). After Bonferroni corrections, the only significant correlate was that those with sensory deficits at 3 months had larger lesions ($p = 0.001$). Interestingly, tremor outcomes were not found to be related to the presence of the lesion or lesion size.

3.5. Assessing attrition bias at 1 year

Patients who had MRIs at 1 year post-MRgFUS thalamotomy ($n = 34$), compared to those who did not ($n = 87$), were significantly younger (73.2 ± 6.8 vs. 76.3 ± 6.5, $p = 0.019$). There was similar gender distribution ($p = 0.603$) and SDRs ($p = 0.489$). However, those who did have MRIs underwent significantly more total sonications (6 ± 3 vs. 5 ± 2, $p = 0.015$) and treatment sonications (11 ± 5 vs. 9 ± 3, $p = 0.002$). Additionally, patients who did have MRIs were significantly earlier patients in the cohort with lower identification numbers ($p < 0.001$). Preoperative total FTM scores and FTM intention scores were not significantly different ($p = 0.703$ and $p = 0.715$, respectively). Lesion volumes at 24 h were also similar ($p = 0.427$). At 1 year, FTM intention scores and percent improvement were not significantly different ($p = 0.317$ and $p = 0.356$, respectively).

4. Discussion

There is no current consensus on the utility or frequency of postoperative imaging after unilateral MRgFUS thalamotomy. In this single-surgeon series, we show that lesions are visually identifiable on T2-weighted MRI in only about one half of patients at both 3 months and 1 year following MRgFUS thalamotomy (Table 2). This may be slightly higher than would be seen in other cohorts, given our institution's larger 24-h lesions (11). Keil et al. describe similar findings of lesion persistence on T2-weighted imaging in only 40% of their patients at 6 months postoperatively with smaller lesion volumes at all timepoints post-procedurally (3 days, 1 month, and 6 months) (6). These observations demonstrate that while T2-weighted images are very useful during the first few days after MRgFUS to show lesion location, extent and edema, the images may return to normal after 1 month and are inadequate for longer follow-up studies (4, 6). SWI, on the other hand, demonstrates persistent lesions more reliably over long-term follow-up (Table 2) (6). This suggests that SWI could be used in postoperative imaging protocols to localize lesions after extended periods of time, especially when planning retreatments or contralateral treatments.

4.1. Significant predictors of lesion persistence

4.1.1. Some sonication parameters predicted 3-month volume

The multivariate regression for lesion size at 3 months showed that the number of treatment sonications, maximum power, and maximum distance between sonication targets predicted lesion size. A fewer number of treatment sonications was correlated with increased lesion size as well as a larger percentage of lesion volume still present at 3 months confirming what we have previously found: more, lower power sonications does not create as large of a lesion as fewer, higher power sonications (11). Here, we show that this finding seems to persist on imaging past 24 h. Greater maximum power and maximum distance positively predicted lesion volume, which has also previously been shown on 24-h imaging (11). Overall, these known predictors of larger 24-h volume also predict larger 3-month volume.

4.1.2. Increased SDR may lead to greater change in volume at 1 year

Although not significant after post-hoc corrections or within the multivariate regression, when assessed independently, patients with lower SDR had more of their lesion still present at 1 year (Figure 4; Supplementary Table S2). This was not seen at 3 months. Heating efficiency is known to be worse for patients with a lower SDR (17–20). It has previously been demonstrated that the skull along the ultrasound beam paths can cause acoustic parameters to change, leading to blurring (dephasing) of the focus and reduction in treatment efficiency (21). Greater heating efficiency for patients with high SDR may not have the same impact on the tissue, leading to lesions that do not maintain the same volume. At lower SDRs, the ultrasound focus disperses, leading to less precise targeting (21). The impact on the tissue surrounding the lesion may be impacted in a way that maintains the structure of the lesion without collapsing in on itself as quickly at this long-term follow-up.

The multivariate regression at 1 year showed no significant predictors. This is likely because there were very few observations (only 32 patients with 1-year imaging, and only 16 still had lesions present), which would not allow for any smaller associations to be extrapolated.

4.2. Clinical outcomes

4.2.1. Radiological persistence of lesion does not correlate with tremor outcomes

We did not find any correlations between presence or volumes of lesions on 3-months or 1-year T2-weighted MRI with any metrics of tremor improvement (Supplementary Table S1). This may also reflect, as we have suggested previously (11), that lesions at our institution are larger than those reported by several other series, and that even our smaller lesions tend to remain above any threshold that might

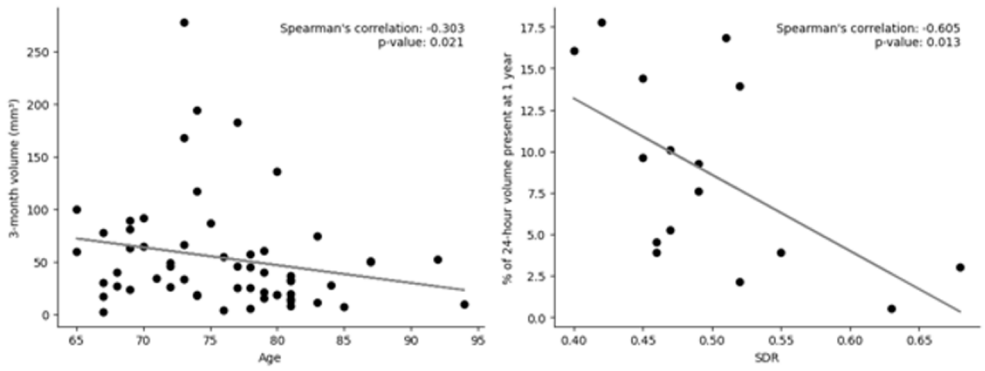

FIGURE 4
Scatter plots of predictors of volume at various timepoints. Left: Lesion volume at 3 months vs. age; out of 106 patients who had imaging at 3 months, 58 still had lesions present. Right: Skull density ration (SDR) vs. change in volume at 1 year; Out of 32 patients who had imaging at 1 year, 16 still had lesions present. Linear trendline and Spearman's rank correlation value and value of p are included. Neither were significant after Bonferroni correction ($p < 0.003$).

correlate with changes in tremor improvement. Although lesion size on 1 day postoperative imaging has been shown to predict tremor outcomes up to 1 year after MRgFUS thalamotomy (4, 11, 12), studies have repeatedly demonstrated that tremor control persists despite lesions disappearing on T2-weighted imaging (4–7). Unlike our results, Keil et al. found that greater lesion shrinkage at 180 days on T2-weighted MRI correlated with increased tremor recurrence on the treated limb (6). It is possible that with additional patients or with imaging at additional timepoints, we too may have seen correlation with tremor outcomes. Additionally, as previously discussed, other imaging sequences, such as SWI where lesions are present for longer, may provide better insight into this question.

4.2.2. Radiological evidence and volume of lesion predicts side effects

After post-hoc analysis, patients with sensory side effects at 3 months had larger lesions (Supplementary Table S3). This was not surprising, given that sensory side effects are very common and related to larger or more posterior lesions at 24-h that overlap with the ventroposterolateral nucleus which lies posterior to the Vim (11, 22). While previous studies have found that larger lesions on 24-h imaging is correlated with more adverse effects (11), to the best of our knowledge, this is the first time that postoperative imaging beyond the first few days has demonstrated a significant correlation with adverse events.

4.3. Limitations and future directions

While we describe a very large cohort with imaging at 24 h after MRgFUS thalamotomy ($n = 121$), this number decreased for those with imaging and FTM scores at 3 months ($n = 99$) and at 1 year ($n = 28$). Analyses with more patients could gain greater statistical power and may elucidate more subtle correlations. Additionally, there were some differences between the patient population that had MRIs at 1 year compared to those that did not, including imaged patients being younger and having undergone more total and treatment sonications. Future studies with more consistent imaging could avoid attrition bias. Another limitation is that the determination of presence or absence of lesions has intrinsic subjectivity which we attempted to mitigate by having a second observer where necessary. Finally, due to the imaging preferences at our institution, SWI sequences were not obtained for many patients, which did not allow for any significant analysis outside of noting presence for all images.

An interesting future direction is analyzing diffusion tensor imaging (DTI) over time. Previous studies have demonstrated persistent changes in tractography up to 1 year after MRgFUS thalamotomy (23). This type of imaging gives much clearer information into the specific fiber tracts that are targeted during FUS procedures to elicit the intended effects. Various features of connectivity have been correlated with better tremor outcomes (24–31). With longitudinal studies, DTI may give insight into the individual changes in functional connectivity of tremor circuitry that lead to persistent adverse effects as well as tremor control and/or recurrence.

5. Conclusion

Lesions are visible on T2-weighted MRI in only about one half of patients at both 3 months and 1 year post unilateral MRgFUS thalamotomy for ET and were significantly smaller over time. At 3 months, multivariate regression showed that fewer treatment sonications, greater maximum power, and larger distance between treatment sonication targets led to more persistent lesions. Independent analyses showed that older patients tended to have smaller 3-month volumes. While the presence or size of lesion at 3 months was not a predictor of tremor outcomes, it did predict sensory side effects. Overall, postoperative T2-weighted MR imaging at 3 months and beyond did not provide significant clinically relevant data and SWI MRI sequences may be better to analyze predictors and significance in volume changes. Moving forward, as we start to perform more bilateral FUS procedures, this study supports relying on early postoperative imaging for procedure planning.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

Ethical approval was not required for the studies involving humans because it was a retrospective review of unidentifiable data. The studies were conducted in accordance with the local legislation and institutional requirements. Written informed consent for participation was not required from the participants or the participants' legal guardians/next of kin in accordance with the national legislation and institutional requirements because it was a retrospective review of unidentifiable data.

Author contributions

SB: Data curation, Formal analysis, Investigation, Methodology, Software, Visualization, Writing – original draft. MC: Data curation, Investigation, Methodology, Writing – review & editing. PN: Data curation, Writing – review & editing. DS: Formal analysis, Writing – review & editing. RJ: Data curation, Writing – review & editing. NM: Data curation, Writing – review & editing. MD: Data curation, Writing – review & editing. JR: Supervision, Writing – review & editing. GC: Conceptualization, Supervision, Writing – review & editing.

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Conflict of interest

GC is a consultant for InSightec. JR was previously a consultant for ClearPoint. NM's laboratory has received research support unrelated to the current study from InSightec.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2023.1272425/full#supplementary-material

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Efficacy and safety of magnetic resonance-guided focused ultrasound for Parkinson's disease: a systematic review and meta-analysis

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Objective: Magnetic resonance imaging-guided focused ultrasound (MRgFUS) is a novel noninvasive treatment for drug-resistant Parkinson's disease (PD) related tremor. This study aims to evaluate MRgFUS's efficacy and safety in PD through a systematic review and meta-analysis, examining pre-and post-treatment MDS-UPDRSIII and/or CRST scores and associated adverse events.

Materials and methods: We conducted an extensive literature search across PubMed, Embase, Web of Science, and Cochrane Library databases, screening studies based on set criteria and analyzing MDS-UPDRSIII, CRST, and adverse events pre- and post-MRgFUS treatment.

Results: Out of 468 retrieved articles, 20 studies involving 258 patients, spanning 2014–2023, were included.17 studies indicated significant MDS-UPDRSIII score reductions post-MRgFUS treatment, while 3 showed significant CRST score declines. In the "on" medication state, pooled MDS-UPDRSIII scores at 1, 3, 6, and 12 months were 12.18 (95% CI: 5.83–18.52), 12.10 (95% CI: 8.22–15.97), 14.85 (95% CI: 9.28–20.41), and 20.65 (95% CI: 12.15–29.14) respectively. In the "off" state, scores were 11.45 (95% CI: −3.50-26.40), 14.71 (95% CI: 4.95–24.46), 21.52 (95% CI: 19.28–23.75), and 22.28 (95% CI: 15.26–29.30). Adverse events were typically mild and transient, with speech disturbances, ataxia, and sensory abnormalities being common post-operative neurological complications.

Conclusion: MRgFUS offers an effective and relatively safe treatment option for patients with drug-resistant PD-related tremor.

Systematic review registration: https://www.crd.york.ac.uk/prospero/, No. CRD42023428332.

KEYWORDS

MRgFUS, Parkinson's disease, efficacy, safety, Meta-analysis

1 Introduction

Parkinson's disease (PD) is a common neurodegenerative disorder, with the risk of onset increasing with age (1). The clinical manifestations of this disease include motor-related symptoms such as bradykinesia, rigidity, and tremor, as well as non-motor symptoms including impaired olfaction, cognitive disorders, and psychiatric disturbances (2). These symptoms significantly impact the quality of life of the patients, bringing immense psychological and medical burdens to their families (3).

The primary treatment strategy for PD is usually pharmacotherapy, which includes anticholinergic agents, dopaminergic receptor agonists and levodopa (4).These medications can help alleviating patients' symptoms and improve their quality of life. For those who do not respond well to medications or experience significant side effects, surgical treatment becomes an alternative option. Currently, Deep Brain Stimulation (DBS) is the predominant surgical approach for treating PD, particularly interventions targeting the ventral intermediate nucleus (VIM), globus pallidus internus (GPI), and subthalamic nucleus (STN) (5, 6). This is suitable for advanced PD, when oral or transdermal treatments are no longer effective (7). However, despite the adjustable advantages of DBS, it is important to note that this method is invasive and quite costly, in addition to the risks associated with device implantation and electrical stimulation, which cannot be ignored (6, 8).

.Magnetic Resonance Imaging-guided Focused Ultrasound (MRgFUS) is a non-invasive neurosurgical technique that offers minimally invasive ablation, paving a new way for the treatment of PD-related tremor (9). This technique is characterized by its non-invasiveness, lack of radiation, and the absence of a need for anesthesia (10, 11). It works by thermally ablating specific brain regions (such as VIM and GPI) during the treatment process, forming a coagulative necrotic focus (12). Compared to traditional invasive surgeries, MRgFUS significantly reduces the risks of infection and cerebral hemorrhage (13). Studies have demonstrated its safety and efficacy in treating Essential Tremor (ET) (14, 15). However the safety and efficacy of MRgFUS in treating PD related tremor and in improving other PD symptoms need to be better elucidated. Currently, there is a relatively limited literature review on the efficacy and safety of MRgFUS in the treatment of Parkinson's disease (16, 17). In terms of relevant reports for which meta-analysis was performed, only one article exists, and that article included only two papers (18). In contrast, our study employs a single-arm meta-analysis approach that encompasses a wider range of research literature and takes into account a longer span of years to provide a more comprehensive and in-depth analysis. This will help to fill the knowledge gap in the existing literature. Therefore, our research aims to systematically review relevant literature to assess the safety and efficacy of MRgFUS in treating drug-resistant PD-related tremor. Our study results may provide a scientific basis for the clinical application of MRgFUS in the treatment of drug-resistant PD-related tremor.

2 Methods and analysis

2.1 Purpose and registration

A systematic review and meta-analysis will be performed to synthesize the evidence and assess the efficacy and safety of MRgFUS for the treatment of drug-resistant PD-related tremor. This protocol is registered in PROSPERO (No. CRD42023428332). This study followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyzes (PRISMA) statement (19).

2.2 Information sources and search strategies

A systematic search was conducted on August 6, 2023, using PubMed, Embase, Web of science, and Cochrane Library electronic databases for the keywords ("MRgFUS" or "HIFU" or "focused ultrasound") AND ("Parkinson disease").

Inclusion criteria: articles must report on the efficacy and/or safety of MRgFUS treatment in patients with PD. For efficacy: quantitative or qualitative data on major symptoms such as tremor, bradykinesia, and rigidity need to be included. For safety: need to include the incidence and detailed description of complications, adverse events associated with MRgFUS therapy; the intervention in the study was the administration of MRgFUS treatment to the study cases. Exclusion criteria: studies with less than 3 patients, case reports, experimental animal studies, reviews, conference abstracts, duplicate publications, or literature with missing data.

2.3 Data extraction and analysis

Two independent researchers undertook the literature search. After deduplicating with NoteExpress, abstracts and titles were preliminarily screened based on inclusion criteria. Relevant full-text articles were further assessed, and in cases of data overlap, only the most updated or comprehensive study was retained. Disparities between researchers were reconciled through consultation with a third expert. Subsequently, a collective in-depth analysis and data extraction from the selected studies were done, ensuring unanimous agreement on divergences. The selection process is illustrated in the PRISMA flow diagram (Figure 1). Essential details for each study, such as authorship, publication date, study design, sample demographics, PD duration, follow-up duration, efficacy metrics (including both on- and off-medication Movement Disorder Society Unified Parkinson's Disease Rating Scale part III (MDS-UPDRSIII) scores, and/or pre- and post-treatment Clinical Rating Scale for Tremor (CRST) scores), recurrent events of tremor and postoperative adverse events, were systematically recorded. The MDS-UPDRSIII scale usually covers a comprehensive assessment of hand movements, upper extremity movements, and lower extremity movements. Increased patient scores in these areas usually reflect severe impairments in movement in patients with PD. The CRST score is primarily used to assess resting and locomotor tremor at different sites, as well as other symptoms associated with tremor. Higher MDS-UPDRSIII scores indicate more severe impairment of motor function in patients with PD, and higher CRST scores indicate more significant symptoms of resting and motor tremor in patients with PD.

2.4 Statistical analysis

Meta-analysis was performed using the R language (v4.2.2) meta-function package to meta-analyze the data, with measurements expressed as mean difference and standard deviation (MD ± SD), and dichotomous data expressed as proportions and 95% confidence intervals. Heterogeneity among the results of the included studies was tested with I^2 and p-values, and if there was good statistical homogeneity among the studies ($p > 0.1$; $I^2 \leq 50\%$), Meta-analysis was performed using a fixed-effects model; if there was statistical heterogeneity ($p < 0.1$;

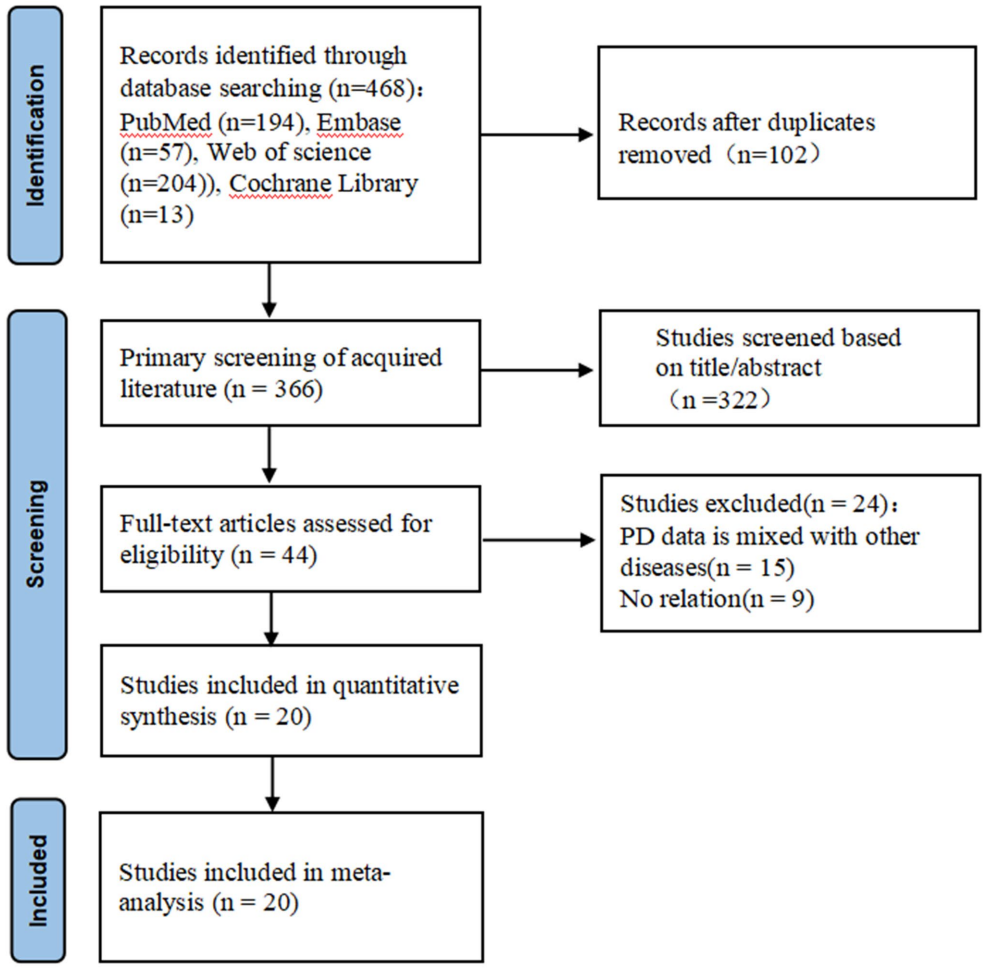

FIGURE 1
Flowchart of literature search and study selection process.

$I^2 > 50\%$), Meta-analysis could be performed using a random-effects model. The level of test for Meta was $\alpha = 0.05$ with a statistically significant $p < 0.05$.

3 Results

3.1 Study characteristics

This meta-analysis included 20 studies published between 2014 and 2023 (5, 9, 11, 20–36), encompassing 258 patients. Among these, two were retrospective studies and 18 were prospective. Table 1 provides a detailed breakdown of the characteristics of each study. The participants were primarily middle-aged and elderly, with a majority being male. The follow-up duration varied across studies, ranging from as short as 1 month to as long as 3 years. Three studies (21, 27, 29) documented cases of bilateral pallidothalamic tractotomy (PTT) ablation, while the rest reported unilateral ablations (5, 9, 11, 20, 22–26, 28, 30–36). Regarding the surgical targets: 11 studies (5, 9, 11, 22, 23, 30–32, 34–36) selected the VIM nucleus; PTT was chosen as the target in 4 studies (20, 21, 27, 29); whereas STN (24, 33) and GPI (25, 28) were each selected in 2 studies.

3.2 Tremor scores

3.2.1 MDS-UPDRSIII scores (on-medication and off-medication states)

The mean MDS-UPDRSIII score for drug-resistant PD patients in the on-medication states on the treatment side at baseline was 27.77 ± 13.03. Five studies (5, 9, 25, 26, 36) involving 47 patients reported the mean MDS-UPDRSIII scores at 1 month from baseline to non-pharmacological status, which showed that the scores showed a high degree of heterogeneity ($I^2 = 96.9\%$, $p < 0.05$), and the pooled standard mean difference was 12.88 (95% CI:5.32–20.44).Four studies (20, 23, 25, 32) involving 34 patients reported mean MDS-UPDRS III scores at 3-month postoperative follow-up, showing a high degree of heterogeneity ($I^2 = 72.71\%$, $p < 0.05$), with a combined score of 12.10 (95% CI: 8.22–15.97). Ten studies (5, 9, 21, 22, 24–26, 31, 33, 34) involving 120 patients reported mean MDS-UPDRSIII scores at 6-month postoperative follow-up, showing a high degree of heterogeneity ($I^2 = 97.86\%$, $p < 0.05$), with a combined score of 14.85 (95% CI: 9.28–20.41). Three studies (5, 32, 33) concerning 51 patients and reporting the mean MDS-UPDRSIII scores at 1-year postoperative follow-up showed a high level of heterogeneity ($I^2 = 96.44\%$, $p < 0.05$), with a pooled result of 20.65 (95% CI: 12.15–29.14) (Figure 2).

TABLE 1 Characteristics of included studies.

Author, year	Study design	Patients	Follow-up	Age (Mean, Sd)	Sex (Male: Female)	PD duration year	Ablation target	Unilateral/ Bilateral	Baseline MDS-UPDRSIII scores (On state)	Baseline MDS-UPDRSIII scores (Off state)	Baseline total CRST scores
Chen et al. (2023) (36)	Retrospective	3	1 month	60.7 ± 6.0	3:0	7.3 ± 4.1	PTT + VIM	Unilateral		37.0 ± 8.0	
Dahmani et al. (2023) (5)	Prospective	10	1 year	55 ± 7.29	8:2	4.92 ± 1.59	VIM	Unilateral	29.7 ± 8.6		
Wang et al. (2023) (35)	Prospective	9	1 year	64.67 ± 6.12	8:1	8.22 ± 7.19	VIM	Unilateral			45.89 ± 8.94
Saporito et al. (2023) (34)	Prospective	18	6 months	65.4 ± 11.4	/	7.8 ± 4.63	VIM	Unilateral	30.0 ± 13.7		35.79 ± 14.39
Martinez-Fernandez et al. (2023) (33)	Prospective	32	36 months	56 ± 10.1	22:10	6.8 ± 2.8	STN	Unilateral	24.7 ± 7.4	36.8 ± 7.4	
Yin et al. (2022) (32)	Prospective	9	1 year	64.7 ± 6.1	8:1	7(5.5,9.0)	VIM	Unilateral	26 ± 7.41	57.33 ± 7.74	20 ± 7.78
Golfrè Andreasi et al. (2022) (31)	Prospective	10	6 months	62.3 (60.2, 72.3)	8:2	3.8(2.4,4.5)	VIM	Unilateral	22.5 ± 8.15		
Stanziano et al. (2021) (30)	Prospective	15	3 months	64 ± 7	13:2	6.8 ± 6	VIM	Unilateral		7.2 ± 1.9	
Eisenberg et al. (2021) (28)	Prospective	20	1 year	56.4 ± 11.3	13:7	9.9 ± 6.4	GPI	Unilateral		20.0 ± 5.6	
Gallay et al. (2021) (29)	Prospective	10	1 year	63 ± 5	5:5	10.2 ± 10.6	PTT	Bilateral		41.0 ± 20.0	
Zur et al. (2020) (26)	Prospective	17	6 months	65 ± 8	13:4	6 ± 3	/	Unilateral	5.4 ± 1.6		
Gallay et al. (2020) (27)	Prospective	51	1 year	67.3 ± 10.1	37:14	10 ± 5.3	PTT	Unilateral/ Bilateral			
Jung et al. (2019) (25)	Prospective	8	6 months	59.8(52–73)	/	10.1(6–14)	GPI	Unilateral	8.5 ± 2.8	30.1 ± 6.2	
Martinez-Fernandez et al. (2018) (24)	Prospective	10	6 months	59.5 ± 10.1	6:4	6.3 ± 2.5	STN	Unilateral	21.5 ± 6.3	32.7 ± 5.4	
Zaaroor et al. (2018) (9)	Prospective	9	2 years	59.4 ± 8.4	8:1	5.3 ± 3.3	VIM	Unilateral	24.9 ± 8.0		
Iacopino et al. (2018) (23)	Prospective	4	3 months	68 ± 4.74	4:0	14 ± 11.3	VIM	Unilateral	36.5 ± 12.5		
Fasano et al. (2017) (22)	Retrospective	3	6 months	76.3 ± 4.0	3:0	10.3 ± 2.1	VIM	Unilateral	27.0 ± 1.0		
Wegener et al. (2016) (21)	Retrospective	3	6 months	61.1 ± 13.7	/	8.9 ± 5.1	PTT	Unilateral/ Bilateral	30.6 ± 10.5		
Schlesinger et al. (2015) (11)	Prospective	7	1 year	59.4 ± 9.8	6:1	5.4 ± 2.8	VIM	Unilateral			
Magara et al. (2014) (20)	Prospective	13	3 months	64.5 ± 12.8	8:5	9.7 ± 6.3	PTT	Unilateral	18.7 ± 7.2		

Pallidothalamic tractotomy (PTT), ventral intermediate nucleus (VIM), globus pallidus internus (GPI), subthalamic nucleus (STN). On state: on- medication states. Off state: off-medication states. Data are expressed as median (interquartile range) and mean ± standard deviation.

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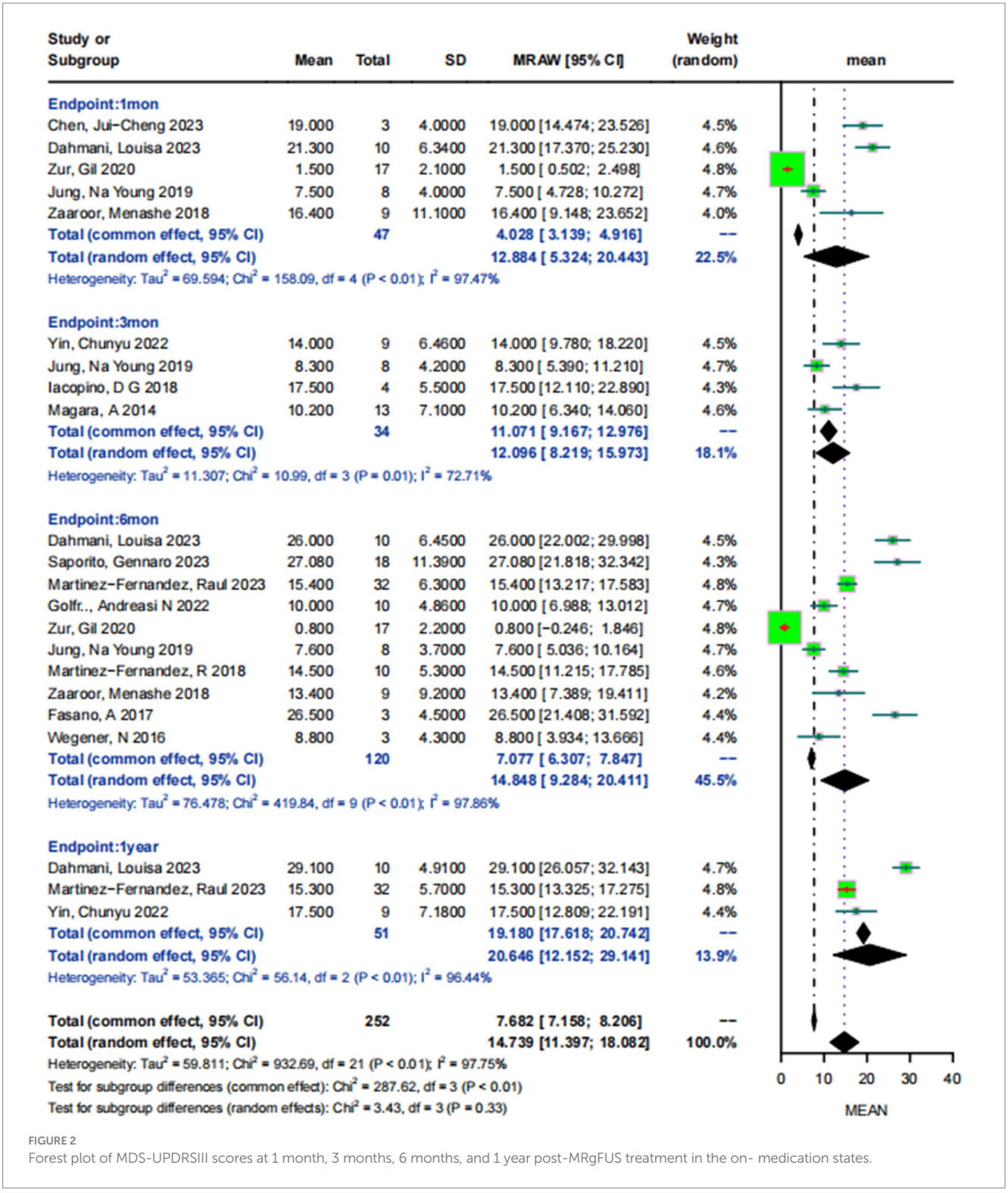

FIGURE 2
Forest plot of MDS-UPDRSIII scores at 1 month, 3 months, 6 months, and 1 year post-MRgFUS treatment in the on- medication states.

Mean MDS-UPDRSIII scores for patients with drug-resistant PD who were off-medication states on the treatment side at baseline were 31.65 ± 12.75. The 2 studies (25, 30) involving 23 patients reported the mean MDS-UPDRSIII scores at 1 month postoperatively, and their results showed a high degree of heterogeneity in the scores ($I^2 = 95.62\%$, $p < 0.05$), with a combined analysis of 11.45 95% CI:−3.50–26.40. Four studies (25, 28, 30, 32), involving 52 patients, reported mean MDS-UPDRSIII scores at 3-month postoperative follow-up exhibited a high degree of heterogeneity ($I^2 = 95.66\%$, $p < 0.05$), and 14.71 (95% CI:4.95–24.46) after combining. Three studies (24, 25, 33) involving 50 patients reported the mean MDS-UPDRSIII score at 6-month postoperative follow-up, showing a heterogeneity of scores of 0 ($I^2 = 0$, $p < 0.05$) and a combined MDS-UPDRSIII score of 21.52 (95% CI:19.28–23.75). Three studies

(29, 32, 33) involving 51 patients reported the mean MDS-UPDRSIII scores at 1-year postoperative follow-up, showing a high degree of heterogeneity ($I^2 = 73.54\%$, $p < 0.05$), with a combined result of 22.28 (95% CI: 15.26–29.30) (Figure 3).

In both states, MRgFUS treatment effectively reduced the MDS-UPDRSIII scores, indicating its efficacy. Comparatively, the baseline score in the "off" medication state was higher, but the post-treatment reduction trend mirrored the "on" state, suggesting a potentially more pronounced effect in the "off" state. This could be attributed to the higher baseline score in the "off" state, offering more room for improvement. Over time, the therapeutic effect diminishes, possibly due to the progressive nature of the disease.

As can be seen from the Table 2, MRgFUS had a positive impact on the treatment of motor symptoms in drug-resistant PD patients, especially in terms of tremor and bradykinesia. It is important to note, however, that the treatment effect was relatively small in stiffness symptoms. These results emphasize the potential of MRgFUS treatment in improving different motor symptoms in patients with Parkinson's disease, but also highlight the variability between different symptoms.

3.3 CRST scores

In three studies, total CRST scores were documented. Wang et al. (35) observed an initial score of 45.89 ± 8.94, which significantly reduced to 17.89 ± 11.92 1 year post-surgery. Saporito et al. (34) recorded a baseline score of 35.79 ± 14.39, which dropped to 23.03 ± 10.95 6 months postoperatively. Similarly, Yin et al. (32) registered an initial score of 20 ± 7.78, declining to 3.44 ± 2.83 1 year post-intervention. Due to the insufficiency of data, a meta-analysis on the aforementioned results could not be conducted.

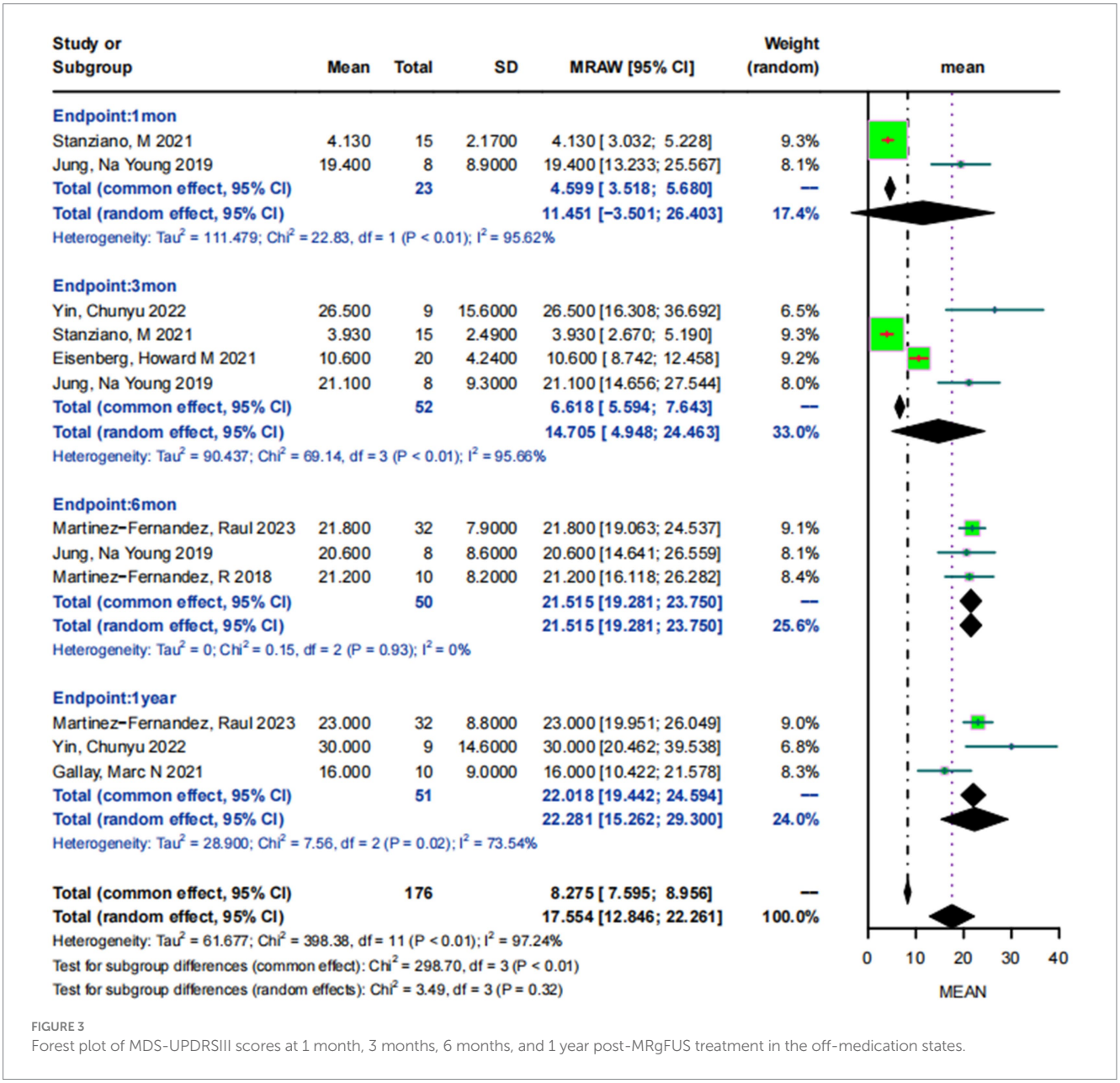

FIGURE 3
Forest plot of MDS-UPDRSIII scores at 1 month, 3 months, 6 months, and 1 year post-MRgFUS treatment in the off-medication states.

TABLE 2 Detailed changes in specific sections of MDS-UPDRSIII.

Author, year	Locomotor condition		Baseline	3-month follow-up	6-month follow-up	1-year follow-up
Martinez-Fernandez et al. (2023) (33)	Tremor	OFF	5.2 + 2.3		1.2 + 1.4	1.1 + 1.6
		ON	3.7 + 1.9		0.9 + 1.3	0.5 + 1.0
	Bradykinesia	OFF	10.3 + 2.5		5.0 + 2.8	5.4 + 3.0
		ON	7.3 + 2.4		3.6 + 2.8	3.9 + 2.6
	Rigidity	OFF	3.5 + 0.9		1.5 + 1.3	1.7 + 1.2
		ON	2.8 + 1.1		0.9 + 1.0	1.1 + 1.2
Yin et al. (2022) (32)	Tremor	OFF	19.0 (14.5, 21.0)	8.0 (5.0, 10.5)		7.0 (4.0, 12.5)
		ON	6.0 (1.5, 11.0)	2.0 (0.0, 2.5)		0.0 (0.0, 2.5)
	Bradykinesia	OFF	23.0 (16.5, 25.0)	16.0 (9.5, 19.5)		17.0 (10.0, 23.5)
		ON	8.0 (6.5, 12.0)	6.0 (4.5, 10.5)		9.0 (5.5, 10.5)
	Rigidity	OFF	9.0 (7.0, 11.0)	8.0 (7.0, 11.0)		9.0 (7.0, 11.5)
		ON	6.0 (5.5, 6.5)	6.0 (5.5, 8.5)		7.0 (6.0.10.0)
Golfrè Andreasi et al. (2022) (31)	Tremor	ON	8.0 (7.0; 9.8)		3.0 (1.5; 4.8)	
	Bradykinesia	ON	6.5 (4.5; 8.75)		6.0 (3.0; 6.8)	
	Rigidity	ON	2.0 (2.0; 3.0)		0.5 (0.0; 2.0)	
Gallay et al. (2021) (29)	Tremor	OFF	13 ± 6			0.9 ± 2.1
		ON	11 ± 6			–
	Bradykinesia	OFF	14.0 ± 7.7			5.8 ± 4.5
		ON	12.6 ± 6.9			–
	Rigidity	OFF	6.4 ± 3.8			1.8 ± 1.8
		ON	5.3 ± 3.2			–
Martinez-Fernandez et al. (2018) (24)	Tremor	OFF	4.2 ± 2.1		1.2 ± 1.8	
		ON	3.7 ± 1.9		0.9 ± 1.7	
	Bradykinesia	OFF	9.4 ± 2.7		5.6 ± 2.9	
		ON	6.5 ± 2.0		4.7 ± 2.1	
	Rigidity	OFF	2.9 ± 0.7		0.8 ± 0.8	
		ON	2.2 ± 1.2		5.8 ± 3.5	

OFF, off-medication states; ON, on- medication states. Data are expressed as median (interquartile range) and mean ± standard deviation.

3.4 Recurrent events of tremor

Eisenberg et al. (28) reported a recurrence of tremor in a PD patient at month 3 after GPI-targeted surgery. Zaaroor et al. (9) mentioned 2 patients experiencing tremor recurrence, one with significant recurrence within 3 months of undergoing the VIM procedure and the other with minor recurrence within 6 months. Schlesinger et al. (11) documented that 1 patient each experienced transient mild tremor recurrence at various time points after VIM surgery, including 1 week, 1 month, and 6 months. Magara et al. (20) noted that four patients experienced tremor recurrence within 3 months of PTT surgery.

3.5 Adverse events

We have summarized the adverse events during and after surgery in the included studies (Table 3). Generally, the procedure was safe for these patients, with the majority of adverse events being mild and transient.

Adverse events from MRgFUS can be primarily categorized into two main types: neurological complications and side effects associated with MRI/ultrasound or the frame. Neurological complications can be further delineated into: sensory deficits (e.g., taste disturbances, sensory loss, visual field defects, paresthesia, numbness, or burning sensations, total of 20 cases), motor disturbances (e.g., facial or limb weakness, eyelid spasms, total of 12 cases), ataxia (e.g., unsteady gait, hand coordination difficulties, total of 18 cases), speech disorder (total of 18 cases), cognitive and emotional disturbances (e.g., anxiety, depression, fatigue, and behavioral changes, total of 10 cases), hypertension (total of 5 cases), and thalamotomy-related dizziness ($n = 5$) and headache ($n = 4$). Side effects related to MRI/ultrasound or the frame primarily included: headache (30 cases), dizziness (10 cases), head burning sensation (3 cases), facial swelling (4 cases), nausea and vomiting (total of 4 cases), pain induced by ultrasound (8 cases), and back pain (6 cases). Additionally, the studies reported instances of hiccupping, respiratory difficulties (2 cases), weight gain (5 cases), and swallowing difficulties (1 case).

TABLE 3 Summary of adverse events during and after the procedure.

Author, year	Adverse events during the procedure	Adverse events after the procedure
Chen et al. (2023) (36)	Headache ($n = 1$), dizziness/vertigo ($n = 2$), head pain/heat sensation ($n = 1$), not persistent at the follow-up.	0
Dahmani et al. (2023) (5)	0	At 6 months: target hand's inflexible movement and slow reaction ($n = 1$), slight shaking in the treated leg ($n = 1$). By 12 months, all adverse effects resolved. Other complications were discussed with the conditions of ET patients.
Wang et al. (2023) (34)	0	Mild dizziness ($n = 4$), which was relieved within 24 h.
Saporito et al. (2023) (35)	#	#
Martinez-Fernandez et al. (2023) (33)	0	4–6 months post-treatment AE included dyskinesias ($n = 3$), clumsiness/weakness ($n = 1$), facial asymmetry ($n = 1$), dysarthria ($n = 2$), reduced verbal fluency ($n = 1$), unsteady gait ($n = 1$), weight gain ($n = 3$). Most were mild. At 3 years, issues were reduced verbal fluency ($n = 1$), mild dysarthria ($n = 1$), and clumsy hand ($n = 1$).
Yin et al. (2022) (32)	Headache ($n = 1$) and dizziness ($n = 2$), which disappeared after the operation was completed.	Post-operation, patients reported gait disturbance ($n = 3$), tongue tip numbness ($n = 4$), and hypogeusia ($n = 1$). Two had gait issues and one had tongue tip numbness resolve in a month. All other symptoms improved within 3–12 months. All responses were mild to moderate.
Golfrè Andreasi et al. (2022) (31)	No serious AEs (i.e., associated with new or prolonged hospitalization, permanent disability, or death) were found in either MRgFUS VIM thalamotomy.	
Stanziano et al. (2021) (30)	NA	NA
Eisenberg et al. (2021) (28)	Related to placement of the stereotactic frame (headache, facial edema) ($n = 4$), 17 of the AEs were transient, which included the only severe AEs (2 with transient sonication-related head pain, 1 with transient nausea and vomiting).	Nausea/vomiting and headache affected 3 patients each, while 7 had sonication-related head pain. Neurological AEs from the procedure: visual field deficit (1 mild, transient), dysarthria ($n = 4$; 2 mild, 2 moderate), cognitive disturbance (1 mild), fine motor deficit (2 mild), facial weakness (1 mild), balance difficulties (1 moderate). 20 AEs persisted: fine motor difficulties (1 mild), dysarthria (3; 1 mild, 2 moderate), balance difficulties (1 mild)
Gallay et al. (2021) (29)	Sonications were painful for a few seconds ($n = 1$).	Hiccup, breathing and speech issues ($n = 1$, regressed at 10 months); gait disturbance ($n = 1$, normalized at 3 months). At 1 year, uncontrollable laughter and blepharospasms ($n = 1$).
Zur et al. (2020) (26)	NA	NA
Gallay et al. (2020) (27)	Sonications were painful ($n = 7$, for a few seconds), scalp hypoesthesia ($n = 1$, recovered after 3 months).	Intense anxio-depressive episode ($n = 1$, relapsed after 1 year post-op). At 3 months: speech difficulties ($n = 7$), hiccup with breathing and speech issues ($n = 1$, persisted for months), gait disturbance ($n = 1$).
Jung et al. (2019) (25)	Mild headache ($n = 8$).	After frame removal, pin-site pain occurred ($n = 8$, typically no medication needed for pain). Back pain from fixed positioning ($n = 4$, alleviated with analgesics). Neurological issues, dysarthria, and grade-III right motor hemiparesis noted ($n = 1$, fully resolved in 2 days).
Martinez-Fernandez et al. (2018) (24)	Transient cranial warmth ($n = 2$), pin-site head pain ($n = 6$), nausea ($n = 4$), back pain ($n = 2$), anxiety ($n = 2$), and high blood pressure ($n = 5$).	Transient gait ataxia ($n = 6$) and facial palsy ($n = 1$, resolved during follow-up). Post-discharge behavioral changes like impulsivity ($n = 2$, resolved in a month). Off-drug choreic dyskinesias in shoulder/arm ($n = 1$, gone by 6 months) and involuntary movements in treated arm ($n = 1$). Subjective speech disturbance ($n = 1$). Weight gain ($n = 2$), fatigue ($n = 1$), and anxiety ($n = 1$).
Zaaroor et al. (2018) (9)	#	Gait ataxia ($n = 1$). Other complications were discussed alongside ET patient conditions.
Iacopino et al. (2018) (23)	#	#
Fasano et al. (2017) (22)	0	Transient local pain/burning ($n = 2$), dizziness ($n = 1$) and headache ($n = 1$), dysarthria ($n = 1$) and eyelid weakness ($n = 1$). Persistent numbness/paresthesia ($n = 1$) and hemiparesis ($n = 1$).
Wegener et al. (2016) (21)	0	Transient dysphagia ($n = 1$).
Schlesinger et al. (2015) (11)	Headache ($n = 3$), dizziness ($n = 2$), vertigo ($n = 4$), and lip paresthesia ($n = 1$, resolved after target was repositioned 1 mm anteriorly).	Hypogeusia ($n = 1$), subjective unsteady feeling when walking ($n = 1$, resolved), and disturbance when walking tandem ($n = 1$, resolved at 2-month follow-up).
Magara et al. (2014) (20)	0	0

Studies with no complications are labeled "0." If no data on complications was given for a time period, it's marked "NA." #Adverse events for PD were grouped with other diseases, so exact PD numbers are unknown. Adverse event severity was categorized: mild (minimal impact), moderate (interferes with daily activities), or severe (prevents daily activities).

Out of the total, 65 patients (representing 25.2%) experienced side effects associated with MRI/ultrasound or the frame, with headache and dizziness being the most common. These events usually subsided on their own within a few days without the need for specialized intervention. The most commonly reported neurological adverse events were sensory abnormalities, ataxia, and speech disorders, which generally improved within 3 months post-operation and had a minimal impact on patients' daily lives. The severity of most adverse reactions ranged from mild to moderate. The only three severe adverse events reported were by Eisenberg et al. (28), which included two cases of transient headache related to ultrasound and one case of transient nausea and vomiting; neither of these met the United States Food and Drug Administration (FDA) definition for severe adverse reactions. In a study by Gallay et al. (29), one patient experienced uncontrollable laughter and eyelid spasms a year post-operation, and in another of their studies (27), a patient underwent a brief yet intense episode of anxiety and depression, which then recurred after more than a year post-operation. Fasano et al. (22) reported persistent side effects in two patients: numbness and hemiparesis accompanied by hemihypoesthesia. It remains uncertain whether these persistent adverse events will fade with extended follow-up.

3.6 Quality of the evidence

Two researchers independently evaluated the studies using the ROBINS-I scale (37). The included studies were assessed for potential biases in seven areas: confounding bias, selection of participants bias, intervention classification bias, intention to intervene deviation bias, missing data bias, outcome measurement bias, and selective reporting bias. These evaluations are presented in Table 4. In cases of disagreement, the issues were resolved through mutual consultation or determined through a discussion with a third party.

Of the 20 studies selected. A few studies had some quality issues, including potential confounders and selective reporting of risk. However, some studies performed relatively well in certain aspects, such as lower risk bias and better methodological quality. Overall, these studies provide preliminary information about MRgFUS treatment for drug-resistant PD-related tremor, but caution is needed in interpreting the results, especially in the presence of potential wind traps. Future studies should focus more on methodologic quality to further validate the efficacy and safety of this treatment.

TABLE 4 Robins-I quality rating scale.

Author, year	Confounding bias	Selection bias	Intervention classification bias	Intention-to-intervention bias	Missing data bias	Outcome measurement bias	Selective reporting bias	Overall risk of bias
Chen et al. (2023) (34)	2	1	2	1	1	2	1	2
Dahmani et al. (2023) (5)	3	2	1	2	1	2	1	3
Wang et al. (2023) (33)	3	2	1	2	1	2	1	3
Saporito et al. (2023) (32)	4	2	1	1	1	1	2	4
Martinez-Fernandez et al. (2023) (31)	1	2	5	1	1	1	1	1
Yin et al. (2022) (30)	3	2	1	1	1	2	1	2
Golfrè Andreasi et al. (2022) (29)	2	1	1	5	1	2	1	2
Stanziano et al. (2021) (28)	2	5	1	1	2	2	2	2
Eisenberg et al. (2021) (26)	2	1	1	1	1	2	1	2
Gallay et al. (2021) (27)	3	1	1	1	1	2	2	2
Zur et al. (2020) (24)	2	2	1	1	1	2	1	2
Gallay et al. (2020) (25)	2	1	1	1	2	2	2	2
Jung et al. (2019) (9)	2	1	1	1	1	2	2	2
Martinez-Fernandez et al. (2018) (23)	3	2	2	1	1	2	1	3
Zaaroor et al. (2018) (9)	4	2	1	1	1	2	1	2
Iacopino et al. (2018) (22)	3	2	1	2	1	2	1	3
Fasano et al. (2017) (21)	3	2	1	1	1	1	2	3
Wegener et al. (2016) (11)	3	2	1	1	2	2	1	3
Schlesinger et al. (2015) (11)	3	1	1	1	2	2	1	3
Magara et al. (2014) (20)	3	2	1	1	1	1	1	3

Low, 1; Moderate, 2; Serious, 3; Critical, 4; NI, 5.

4 Discussion

MRgFUS as a novel non-invasive intervention technique has gradually become a new option for treating medication-resistant PD patients. To our knowledge, this is the first comprehensive meta-analysis of the efficacy of MRgFUS in the treatment of PD. Overall, this study suggests that MRgFUS treatment for drug-resistant PD is both effective and safe.

In both states, MRgFUS significantly reduced the MDS-UPDRSIII scores. However, as time post-surgery progresses, scores tend to rise, suggesting a potential diminishing therapeutic effect, warranting further longitudinal studies. We recognize this and also consider that Parkinson's disease is a progressive neurodegenerative disease. The progression of this disease may be an important reason for the rise in scores. Given this, MRgFUS's capability for repeated treatments emerges as a distinct advantage. Since MRgFUS primarily targets symptoms unresponsive to medication, improvements during the drug-off state are particularly noteworthy for an accurate assessment of the surgical intervention's benefits. Thus, notable symptom relief by MRgFUS during the off-medication states, given its critical role in patients' daily challenges, represents a crucial therapeutic milestone. Nonetheless, enhancements in the on-medication states also epitomize the overall treatment efficacy. In line with previous reports, our data indicates that speech disorder, ataxia, and sensory abnormalities are the most common adverse events in the neurological system after MRgFUS treatment (16). Complications related to MRI/ultrasound or the frame are typically transient reactions during the treatment process, such as headaches, dizziness, nausea, vomiting, scalp numbness, or a burning sensation. Our findings reveal that over a quarter of patients experienced ultrasound-related complications, with headaches and dizziness being the most frequent. Additionally, the use of anesthetics is avoided during the MRgFUS ultrasound procedure, offering a safer treatment alternative for patients at high risk from general anesthesia. Compared to other therapeutic technologies, an advantage of MRgFUS is that most surgery-related complications can be detected in real-time during surgery. This allows physicians to mitigate or reverse most side effects by adjusting the initial treatment target.

A total of 4 different surgical targets were used in the 20 studies we reviewed, with VIM being the most commonly used surgical target. MRgFUS produces varying effects and potential complications across different targets. VIM therapy is commonly used to suppress tremor symptoms, but may be accompanied by sensory or motor impairment, resulting in sensory abnormalities, muscle weakness, or dyskinesia. Some patients may also experience pain after the procedure, which may require additional management. STN treatment has an ameliorating effect on major motor symptoms, such as rigidity, tremor, and bradykinesia, and also reduces the dose of levodopa-related treatments. However, the treatment may also lead to movement disorders and speech or cognitive problems. GPI treatment provides significant relief from almost all symptoms of drug-resistant PD, especially when accompanied by cognitive decline and mood disorders, but may also trigger motor deficits and language or cognitive dysfunction. PTT treatment produces positive results in dyskinesia and dystonia, but may result in abnormal sensations or increased pain after the procedure, as well as some temporary headaches or discomfort (38). It is important to note that complications of the MRgFUS procedure can vary greatly from patient to patient, and with improvements in surgical techniques, it has become possible to reduce the risk of complications. Future research should be directed toward exploring which target delivers the best results in MRgFUS therapy and whether there are adverse effects associated with target selection. In addition, MRgFUS single-target thalamotomy has not demonstrated significant efficacy in some of the motor symptoms of PD such as rigidity, bradykinesia, and gait disturbances, as well as in a number of non-motor symptoms such as cognitive deficits, affective problems, and sleep disorders. However, Chen et al. (36) have demonstrated that dual-targeted MRgFUS significantly reduced resting and locomotor tremor in drug-resistant PD. Future research directions should focus on exploring the potential benefits of MRgFUS for drug-resistant PD patients in terms of non-motor symptoms in order to improve the overall quality of life of patients.

Moreover, numerous studies have concurrently addressed the efficacy and safety of MRgFUS in treating both ET and drug-resistant PD. This conflation precluded their inclusion in our analysis, potentially affecting the comprehensiveness of our data. Given this backdrop, we advocate for more dedicated clinical studies focusing solely on drug-resistant PD, especially since the safety and efficacy of MRgFUS in treating ET have already been established.

We concluded that selection of appropriate patients for MRgFUS treatment is critical to ensuring the efficacy and safety of the treatment. Current selection criteria may be based primarily on patient history, disease stage, and ancillary tests. However, as our understanding of PD grows, there may be other biomarkers or neuropsychological assessment tools that can more accurately predict which patients are most likely to benefit from MRgFUS therapy. Considering that the duration of PD and lesions vary widely from patient to patient, a uniform treatment approach may not be appropriate for all patients. Therefore, new metrics with predictive value could help to individualize treatment. It is recommended to consider combining MRgFUS with other non-pharmacological treatments (e.g., cognitive rehabilitation, physical therapy, or DBS) to assess whether treatment effects can be further enhanced. In exploring this direction, we should focus on improving the overall quality of life of patients and advancing individualized treatment to ensure the best outcome for each patient.

4.1 Limitations

This study primarily relies on the MDS-UPDRSIII for assessing treatment outcomes. While it is a key tool for evaluating PD, the inclusion of other crucial indicators such as quality of life and mental state was limited by data availability, potentially hindering a comprehensive understanding of the MRgFUS treatment effects. In addition, most of our studies had limited sample sizes and short follow-up periods.

5 Conclusion

MRgFUS is a potential option for the treatment of drug-resistant PD-related tremor with satisfactory efficacy and safety. Speech disorders, ataxia and sensory abnormalities are the most common postoperative side effects, but the symptoms are mild and usually transient. However, because MRgFUS is a relatively new technique, follow-up data and randomized clinical trials are quite limited. More

rigorous study designs, larger sample sizes, and longer follow-up times are needed in the future to further investigate the efficacy, safety, and durability of MRgFUS in the treatment of drug-resistant PD-related tremor in order to determine its long-term benefits in the management of drug-resistant PD-related tremor.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

Author contributions

XT: Conceptualization, Writing – original draft. RH: Formal analysis, Software, Supervision, Writing – review & editing. PH: Formal analysis, Writing – review & editing. JY: Conceptualization, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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'Am I fixed, am I better now?': undergoing MR-guided focused ultrasound for essential tremor: an interpretative phenomenological analysis

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Introduction: Essential tremor (ET) is characterised by postural and intentional tremor typically affecting the upper limbs, which can negatively impact functionality and quality of life. Magnetic Resonance-guided Focused Ultrasound (MRgFUS) is a novel and promising non-invasive treatment for ET which offers instantaneous results.

Methods: Using interpretative phenomenological analysis we explored the experience of undergoing MRgFUS in six ET patients as well as their experiences pre- and post-procedure.

Results: One-time, retrospective semi-structured interviews were conducted and six themes emerged: Life pre-treatment: "It's everyday tasks that get you down" and "Most people who understand, they are okay. Some people aren't"; MRgFUS: Treatment day: "Going into the unknown" and "There's no way I was going to press that button"; and Life post-treatment: "One is good. Two is better" and "Am I fixed, am I better now?."

Discussion: The findings point to a significant period of adjustment associated with living with ET and the effects of undergoing ET MRgFUS treatment. As ET progressed, participants struggled to cope with increasing symptoms and had to develop coping strategies to manage life with ET. The procedure itself was perceived as strange and extraordinary and despite some immediate adverse effects participants were determined to go through with it. Post procedure, all participants reported tremor suppression which was life changing. While some participants still felt burdened by ET, others expressed it took them a while to psychologically adjust to what essentially was their new body. This study has highlighted the need for patients to be supported at all stages of their ET journey.

KEYWORDS

essential tremor, interpretative phenomenological analysis, MR-guided focused ultrasound, patient experience, patient perspective

1 Introduction

Essential tremor (ET) is the most common cause of disabling tremor (1) and The National Tremor Foundation estimates it affects approximately 1 million people in the UK. It is characterised by a postural and intentional tremor typically affecting the upper limbs, with some patients also experiencing head, voice and lower limb tremor (2). Tremor is typically

symmetrical (3), although the higher amplitude of tremor can vary between the dominant and non-dominant arm (4). ET develops insidiously and progresses slowly over time with tremor generally beginning in the arms and spreading to other body parts in some patients. Apart from the location, the amplitude of tremor in someone with ET can also vary from mild to potentially disabling shaking. Despite an increased prevalence among the elderly, ET can occur at any age. It is thought to have a bimodal age of onset – one peak between the ages of 10 and 20 years, and another between 50 and 60 years (5). ET can be a genetically inherited disorder with approximately 50% of people having a positive family history of the condition (2).

Although "benign" in terms of any possible effects on life expectancy, ET's clinical characteristics can negatively impact functionality and quality of life (6). Unlike resting tremor (common in Parkinsonism) which occurs when the muscles are relaxed, intentional and postural tremor can affect tasks of daily living such as eating, drinking, dressing and writing. Thus, the diagnosis is associated with significant impairment of manual function, which affects daily activities and results in varying degrees of disability and social handicap (7).

People with ET have been found to be at increased risk of anxiety and depression (5). Chandran et al. (8) suggested that among other factors, depression and anxiety in ET can be attributed to the impact of tremor on every day and work performance with tremor-associated embarrassment leading to low self-esteem and social isolation.

First line of treatment for ET is pharmacological although even well-established treatments can be ineffective in 25–55% of patients and are often associated with serious adverse events in a large percentage of patients (9). Pharmacological agents can lose their efficacy over the course of long-term therapy and in cases where the condition is medically refractory, neurosurgery such as radiofrequency (RF) ablation thalamotomy and deep brain stimulation (DBS) is considered. Although effective, both interventions are invasive procedures and carry significant risks including infection and intracerebral haemorrhage (10).

To mitigate the risks of surgical interventions, MR-guided Focused Ultrasound (MRgFUS) has recently emerged as a novel and promising non-invasive treatment for ET. Focused ultrasound has been used to treat uterine fibroids and prostate cancer in the past, but the recent introduction of phased-array transducers allows incisionless intracranial lesioning under real-time magnetic resonance thermography (11).

In the treatment of ET, the procedure can be performed as a day case and takes approximately 3–4 h to complete. As part of the preparation, the patient's head is completely shaved, and a stereotactic head frame is attached which aims to eliminate any potential movement during the procedure (12).

Throughout the procedure patients lie supine inside an MRI scanner with their head placed inside a phased-array transducer containing 1,024 elements arranged in a hemisphere. These individual elements are used for beam steering as they focus all ultrasound beams onto a small target to generate heat, which allows thermal ablation of the target brain tissue. To prevent any thermal damage caused by increase in bone temperature, chilled water is constantly circulated around the head (11, 13).

Patients are kept awake throughout the course of the procedure while ultrasound sonications are delivered to ablate the target tissue. An ultrasound sonication lasts 13–24 s on average (11, 13) during which time the patient can press a button to terminate its delivery should they experience any pain or discomfort. Following each sonication the patient is assessed by a neurologist while still lying on the table for any adverse events and tremor suppression. One way of assessing tremor suppression is to ask patients to draw Archimedes' spirals after each sonication, which visually demonstrate the severity of their tremor and help track response to treatment.

Pilot and sham-controlled studies have focused on the safety and effectiveness of MRgFUS with centres worldwide starting to report data on the procedure's long-term effectiveness and impact on quality of life. In 2018, The National Institute for Health and Care Excellence (NICE) issued a positive NICE guidance for unilateral MRgFUS in ET. In 2020, NHS England agreed to fund MRgFUS treatment of ET for NHS patients effective from April 2021. A recent health economic study (14) also demonstrated the favourable cost-effectiveness profile of MRgFUS for the treatment of ET in England. With MRgFUS funding in place for ET, it is important to understand patients' perspectives and experiences of this new type of treatment. Patient-centeredness has been increasingly recognised as a crucial part of quality of care which is sometimes overlooked in the pursuit of treatment efficacy (15). Some evidence suggests that there may be discrepancies between what patients with neurodegenerative conditions and physicians value in terms of the impact of the disease and the focus of treatment (16). While some health professionals may believe that quality of life depends primarily on severity of disease and effectiveness of treatment, patients with neurodegenerative diseases have been found to emphasise other factors including mood (depression) and effective communication with healthcare providers (Janca, 1999, as cited in Findley & Baker, (16)).

In ET, assessing clinical effectiveness and quality of life has often been quantitative in nature. However, considering the complex nature of ET and the novelty of the MRgFUS treatment, qualitative approaches can provide more detailed exploration of patient experience. This article explores the patients' experience of living with a chronic neurological condition and the impact of MRgFUS on quality of life.

2 Methods

An interpretative phenomenological analysis (IPA) approach was used to inform the conceptual background and to guide the study which was conducted between January 2021 and July 2021 at a single centre.

Purposive sampling was adopted with a sample size of 5–15 participants which was in line with an IPA approach. It was anticipated that this sample size would allow gender and age diversity among participants while ensuring sufficient data can be collected to describe in depth the phenomenon under investigation. IPA researchers typically interview small samples, which are fairly homogenous and often chosen through purposive sampling (17). Considering that a small number of interviews is normally sufficient in IPA, the aim is to find a more closely defined group for which the research question will have significance and to understand the perceptions of a particular group rather than make general claims (18).

Potential participants were approached by their healthcare team and those who expressed interest in taking part were interviewed over the phone due to COVID19 restrictions

preventing hospital visits. Consent was obtained over the phone prior to all interviews. Adult participants (18 years and above) with confirmed diagnosis of ET who had undergone a unilateral/bilateral MRgFUS procedure were included in the study after consenting to study participation.

Semi-structured interviews were used in line with IPA and an interview guide was developed formulating three neutral, open-ended questions to reflect the three main areas of interest: Living with ET, Undergoing MRgFUS and Life post-procedure. Further prompting questions and conversation continuers were used flexibly to invite participants to give more detail or clarify what was being discussed. The interview guide was initially piloted with appropriate volunteers who were familiar with the MRgFUS procedure. Participants were interviewed once by the first author and the audio-recorded interviews were transcribed before analysis. All interviews are anonymized, and pseudonyms and identifiers have been omitted.

2.1 Data analysis

In line with IPA, the transcripts were analysed following several steps as defined by Smith et al. (19) (Figure 1): looking for themes in the first case, connecting the themes, continuing the analysis with other cases.

The transcripts were read multiple times, highlighting areas of what was deemed significant discourse. During the process of analytical re-reading notes were made summarising the essence of these excerpts which were then transformed into preliminary themes (phrases best representing what was being said). Through constant comparison, connections were sought between the preliminary themes while referring repeatedly to the transcripts to ensure accuracy. The preliminary themes were then used to form superordinate themes which best capture the essence of patients' experience.

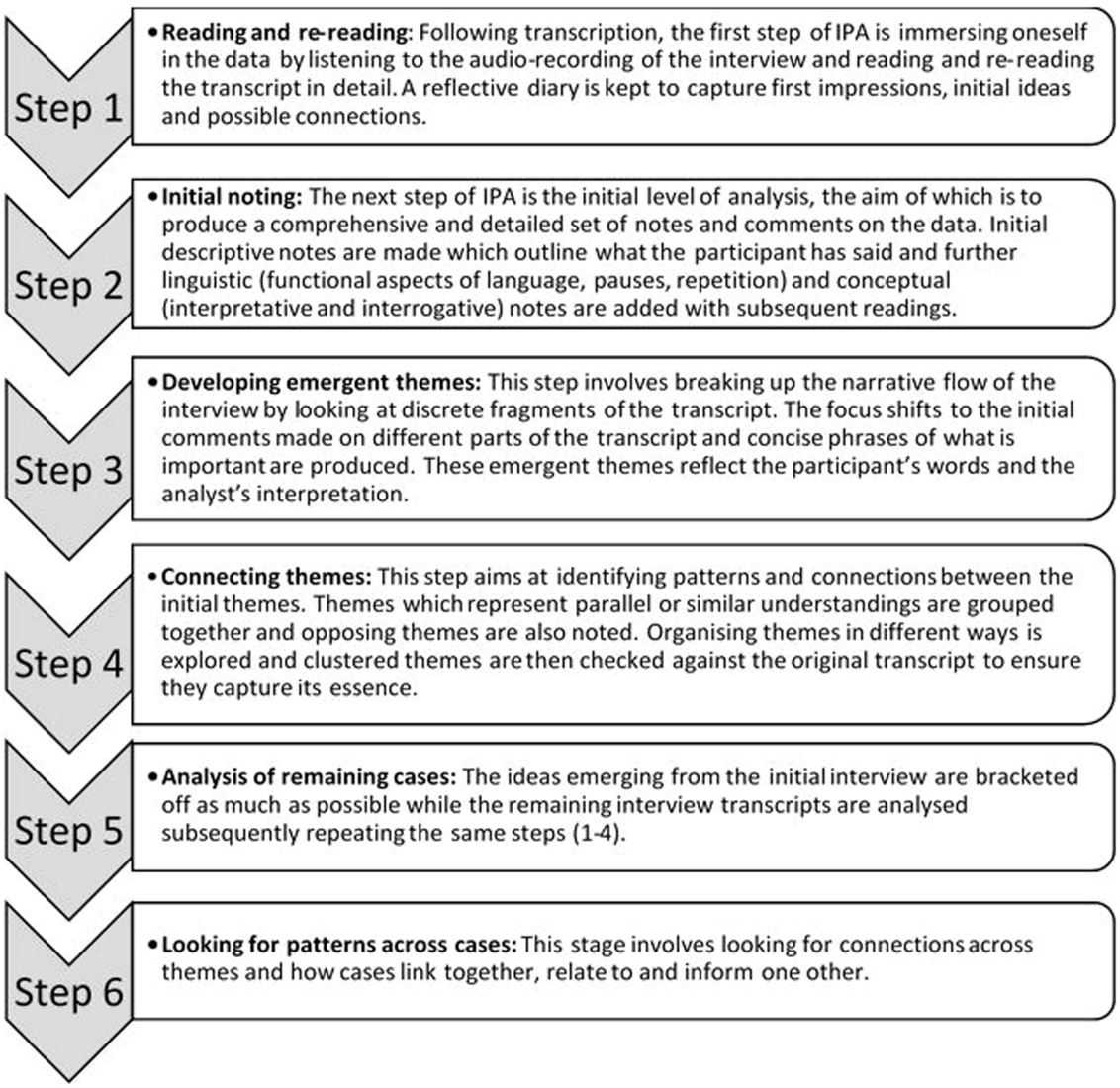

FIGURE 1
Analysis of interview data: Steps to IPA (19).

2.2 Ethical considerations

This study received HRA approval and favourable opinion by the London - Westminster Research Ethics Committee (REC reference: 20/LO/0156) in February 2020.

3 Findings

3.1 Demographic data and clinical outcome

Six patients with ET who had undergone a unilateral or bilateral staged MRgFUS treatment were interviewed. Participants' age at the time of treatment ranged from 59 to 81 years and the duration of tremor pre-treatment ranged from 7 to 71 years. All participants apart from one were male and all participants but one had undergone a unilateral treatment. According to the participants' treatment records, the tremor severity pre-procedure varied from mild to severe while post-treatment tremor severity was mild for all participants. On average, interviews took place roughly three and half years post-treatment and lasted around forty-seven minutes. During the interviews participants demonstrated no difficulty in recalling past events, their pre- and post- treatment narratives were detailed and they provided rich accounts of their experience of undergoing MRgFUS.

3.2 Themes

The following themes emerged from the six interviews and were organised temporally:

- Life pre-treatment: "It's everyday tasks that get you down" and "Most people who understand, they are okay. Some people aren't"
- MRgFUS: Treatment day: "Going into the unknown" and "There's no way I was going to press that button"
- Life post-treatment: "One is good. Two is better" and "Am I fixed, am I better now?"

3.2.1 Life pre-treatment

"It's everyday tasks that get you down"

All participants gave an account of the physical and emotional challenges of living with essential tremor. Regardless of the time of onset, activities of daily living including "*eating, drinking, baking, carrying drinks, cooking*" were adversely affected with some participants describing the need for assistance with practical tasks from family members. The burden of intention tremor was particularly difficult to manage for all participants:

> "*You can't help but concentrate (…) if you've got let's say a hot drink, because you're shaking you might spill a bit and you spill it on yourself, that really makes you concentrate and of course then the whole thing goes up in the air literally.*"

Similarly, another participant noted that it was becoming unsafe for him to sometimes do things around the house and when tasks such as DIY work were not completely impossible, they would take disproportionately long to accomplish. Hobbies also "*fell by the wayside*" and employment was negatively affected with some participants taking early retirement as a result. The multifaceted impact of tremor required adaptations to help navigate life with diminishing functional ability. All participants spoke of strategies and coping mechanisms such as "*holding on to one hand or bracing one hand against the side of a table or pushing it up against your body*" that were necessary to manage unilateral hand tremor. Overall, participants experienced increasing frustration in the face of decreasing functionality: "*when you got it 24/7, yeah it's a different, it's a different ball game*." Feelings of annoyance and low mood were often further exacerbated by misdiagnosis or lack of diagnosis over prolonged periods of time following tremor onset. While some participants ultimately "*recognised it as something in the family*," others were initially struggling to make sense of their ambiguous ill-health experience. The interplay between stress and trembling (typically a physiological sign of stress) was explored to establish a much needed cause-and-effect relationship. For some participants, the strong drive for sense-making served as motivation to gather, attend to and process information in a way which left them questioning the validity of their conclusions:

> "*I remember in my teens (…) listening to a radio lecture (…) that (…) parents who've had malaria (…) there was a relationship in their children of the virus that lead to very mild forms of tremor. (…) I was quite impressed because I thought "hang on, that's me". (…) I've mentioned this, you know, over the years and nobody's ever heard of it. Uhm maybe I was dreaming or hypersensitive.*"

This quote demonstrates the emotional burden of a condition with very intrusive symptomatology and the human drive for knowledge and understanding which might lead to a resolution.

"Most people who understand, they are okay. Some people aren't"

Participants described situations in which they would feel embarrassed as a result of the visibility and unpredictability of their tremor. Social occasions such as religious functions, weddings and funerals brought about great levels of anxiety to the point where some participants completely withdrew and restricted their life to "*home to work, work to home, that's it*." When it did not result in social withdrawal, the tremor-driven social anxiety led to the development of further strategies to adapt and adjust to the demands of a worsening situation - "*you find ways of eating food without people noticing too much*." Some participants, however, felt the need to provide an explanation over concerns their tremor might be misinterpreted as something more sinister – "*always used to be frightened that people would think that I was on drugs like, you know, a junkie type*." While some participants feared the moral judgement associated with society's perceptions of drug users, others were confronted directly with insensitive questions and remarks including: "*You're a young person, why are you shaking like this, what's going on*" and "*you wanna pull yourself together*." Lack of compassion was sometimes even expressed by healthcare professionals: "*I*

remember [a doctor] years ago saying 'Well, I do not think we can be wasting more time so you can do a bit of DIY'." The very visible restrictions essential tremor placed upon participants' social lives similarly affected family members:

> *"…my husband likes, likes me to be perfect [laughing] and I remember having a drink in the interval before an opera (…) and I tried to hold the glass and drink with my right hand and it shook and he said "Use your left hand" because that was better uhm you know, so it did, it did affect him as well really because he's a worrier and he likes everything to be just right"*

The idea that tremor was the kind of imperfection that needed sorting, fixing, correcting or repairing was present in all participants' accounts, carrying a negative undertone and alluding to a sense of guilt.

3.2.2 MRgFUS: treatment day

"Going into the unknown"

While participants generally felt confident about undergoing MRgFUS, everyone described to a certain extent experiencing a natural fear of going into an unknown situation:*"…suppose it's a bit like going to the dentist (…) you do not know what they are going to do until you are in the chair.."* Some participants found themselves feeling uneasy while others had concerns over potential complications during the procedure: "*I was fairly tense wondering what was happening and hoping they'd hit the right spot and were not going to burn my brains out.*"

Participants described that their initial anxiety eased once the pre-operative preparations and set up were completed and they were on the MR table: "*once I been settled down in the MRI machine, it was fine.*" One participant emphasised how once he became familiar with the treatment stages and how the procedure was carried out, it was easier to go through with it:

> *"… one of the things is they fetch you out* [of the MR scanner] *and have a chat and, and they put you back in again and [laughing] once (…) you realise uhm that this bit is going to be where they operate and then they would take you out to say "How do you feel?" and then push you back in and then you get all the process restarting [pause] you get used to it."*

The fact that the treatment itself is delivered in sonications and patients are assessed after each one was experienced as helpful and reassuring: "*the amount of times you are sort of wheeled out (…) to see how you are each time (…) that breaks it up into segments which makes it more acceptable.*" Continued communication with the clinical team throughout the treatment played a key role for participants and having family members present on the day also encouraged them to get through the procedure: "*it was excellent for me to have my wife actually in the magnetic room.*"

"There's no way I was going to press that button"

All participants felt that the "*screwing in of the crown*" (fitting of the stereotactic head frame to the skull) was one of the most painful or uncomfortable parts of undergoing the treatment. Once inside the MRI scanner, participants described the treatment as "*strange*" and "*extraordinary.*" There was a sense of rising up to a challenge with some participants describing that they were "*doing what I could do*" and "*it was all sort of questions and people telling me what to do and trying to do it.*" Sensations during the procedure varied among participants with one participant recalling that he "*did not feel a thing.*" Other participants, however, experienced a burning sensation inside the head during sonication delivery which for one participant became so severe that he had to press an emergency button to terminate the energy delivery. Despite the pain and the treatment interruption, he was determined to persevere and did not terminate the procedure. Similarly, another participant described the burning sensation during sonication delivery as "*quite intense (…) I gave it a 7 out of 10,*" however he was also determined to see it through:

> *"… the nurse gave me the button, I said "I don't want that, I don't want that!". She said "Oh, you've got to have it" cause there's no way I was going to press it, no way. I was so on it to get rid of this tremor."*

Rather than pain, sonication delivery caused two participants to experience a spinning, tumbling sensation: like a "*trapeze artist doing sort of backward somersaults in the air*" which led to dizziness and nausea. Despite this "*sort of disorientation, of tumbling, (…) falling out of control,*" neither of them interrupted a sonication and their treatments were completed. As one participant explained: "*I never thought of stopping, I was determined to see it through.*" Similarly, another participant was so committed to improving his tremor, he felt that going through hardship was worth it: "*mentally once you have built up the confidence, you can write off your pain.*" As one participant suggests: "*I had the tremor bad enough to, to do whatever necessary.*"

Despite these untoward events participants persevered to complete their treatment. The strong drive to go through with the treatment serves to demonstrates the everyday struggle and frustration living with essential tremor brings: "*to be really honest, you get to a position (…) with your tremor that (…) you will have a go with any—most things.*"

3.2.3 Life post-treatment

"One is good. Two is better"

All participants experienced immediate improvement of their tremor which was described as "*revolutionary*" and "*brilliant.*" One participant realised his tremor was improving during the treatment when he was asked to repeatedly draw free hand spirals while lying on the MRI table – "*that's one thing I treasure from both operations (…) my drawings (…) how they got better..*" Similarly, another participant noticed her tremor improving during a different treatment task (pretending to drink from a vitamin bottle): "*it was a sort of pill box with something in it rattling (…) and it rattled less, and then not at all and it was absolutely amazing.*"

Post-procedure side effects from the treatment included fatigue and difficulty with speech and balance which were mild and transient. All participants were adamant that undergoing the treatment and experiencing temporary adverse effects afterwards were worth it considering the tremor reduction they experienced. One participant noticed a big difference post-treatment in small, mundane tasks such as:" *I could put the key in the keyhole straightaway without having to have four goes*" and another

recognised the treatment has improved aspects of everyday life including "*eating and drinking, socialising*." Having one arm treated was very beneficial for participants but those who had bilateral tremor were confined to using their tremor-free side now: "*So I tend to do a lot more things single handed, one handed uhm so the problems arise where I've got to use two hands.*." One participant also agreed that tasks and activities which involved using both hands at the same time were still problematic for her: "*still my left hand if I, if I involve it, it can upset something*." Similarly, another participant struggled with his untreated arm and was disappointed when he was advised not to proceed with a second treatment to address that: "*…I was hoping it could give me that same improvement on the left side which I now cannot really use very much*."

It appears that while regaining functionality in one arm undoubtedly has a positive impact on day to day life, it also inadvertently draws focus to the lack of functionality of the untreated arm in participants with bilateral tremor.

"Am I fixed, am I better now?"

The newly regained functionality in the treated arm also necessitated a period of adjustment for participants. Participants acknowledged they no longer needed their old strategies to cope with the tremor and it took them some time "*to relinquish these habits*" and adjust accordingly which was described as "*a peculiar sensation*":

> *"…the family kept reminding me that I wasn't left handed - I was right handed, because I was trying to do everything with my left hand. It took—It was a psychological [pause] delay [laughing] in relying on my right hand, maybe two weeks…"*

The striking difference between treated and untreated arm in patients with bilateral tremor had to be processed psychologically.

Participant also needed to let go of the tremor and accept their new level of functionality which was not always easy to do. One participant explained that even now, four years after his treatment he would still "*opt out of volunteering to help serve drinks just in case*." It seems that the trauma of past tremor-induced embarrassment had a tight grip and it was difficult for participants to let go and feel confident in social situations which they dreaded before. Similarly, another participant also felt that leaving essential tremor behind did not happen automatically but required some time and active effort. Another participant noticed this was particularly driven by the fact that MRgFUS offered instantaneous tremor reduction in the space of hours and the sudden and abrupt disappearance of tremor, while positive and desired, required to be psychologically processed:

> *"It's difficult to put a finger on it but uhm everything you do, you don't notice these things because they are so gradual uhm and it came to a stop rather suddenly and I thought "Oh, that's not happening and that's not happening" and uhm the things [pause] you know, you just carry on. I don't consciously think all the time about uhm "Am I fixed, am I better now?" or things like that, you haven't got time. I mean there's lots to do in life [laughing]"*

Participants' narratives suggest that a tremor-free hand does not immediately equate a tremor-free mind and fully letting go of the burden of essential tremor comes after some time.

4 Discussion

The findings point to a significant period of adjustment associated with both living with ET and the effects of undergoing MRgFUS treatment for it. As ET progressed, participants struggled to cope with increasing symptoms and the dread and embarrassment tremor brought about in social situations. Participants had to develop coping mechanisms and strategies to manage life with ET and this adjustment period was one of considerable loss of sense of normality. According to Lazarus's stress and coping theory [e.g., (20)], cognitive and behavioural responses are key elements in the adjustment process. Participants in this study demonstrated behavioural changes in order to physically cope with their tremor, and also employed cognitive adaptations especially in social situations. This was mostly evidenced by their need to provide an explanation for their tremor over fears that it might be associated with addiction. Moore et al. (21) also found that ET patients' social anxiety was exacerbated by the prospect of misinterpretation of their uncontrollable shaking and unjust moral judgements on their character. It can be argued that this response in ET patients is a cognitive adjustment in an attempt to restore a sense of control and positive self-view in the face of social judgement.

As was evident in participants' narratives, empirical evidence suggests that living with chronic disease requires adaptations in multiple life domains (22). The restrictions tremor placed on daily practicalities affecting their personal, social and work lives resulted in feelings of annoyance, anxiety, extreme frustration and low mood. A thematic synthesis of the psychological processes of adaptation and hope in MS patients described that the initial cognitive adaptation to multiple sclerosis included similar emotional responses. It also brought feelings of perceived loss of control in life and over disease symptoms and MS patients expressed particularised hopes for improvement or "normality" (23). Similarly, research on the experience of amputation and prosthetic use in adults has identified that initially the key meaning of amputation was a loss of independence and control over life which was sometimes conceived as akin to bereavement (24). The loss of control and independence ET participants reported experiencing also alluded to a sense of loss of normality as often in their narratives they referred to tremor as something that needed to be fixed, sorted or repaired. Similarly, Mathers et al. (25) concluded from their systematic review of PD patients that the feeling of loss takes patients away from a sense of normality which they are trying to regain through treatment. In that sense, participants in the current study, much in keeping with PD patients undergoing DBS (25, 26) did not see MRgFUS as merely an option but rather as an obvious choice.

The procedure itself was perceived as "strange" and "extraordinary" similarly to patients describing DBS as "spectacular" and "mysterious" (26). Participants reported that one of the most uncomfortable parts of the procedure was the placement of the stereotactic head frame. This is somewhat in keeping with Ben-Haim and Falowski's (27) survey of DBS patients who reported an average comfort level with head frame placement of 5.2 (+/− 3.15) out of 10, with 10 representing "very uncomfortable." Nonetheless, being observed by family and clinicians throughout the treatment was experienced as reassuring and helpful. This highlights the importance of continuous and effective communication between treating team and patient but also the value of having family present in the treating room. Indeed, patient-clinician communication has been highlighted as a significant factor in patient

satisfaction and complaints about care (28) and it plays a key role in healthcare service quality (29).

Despite some participants experiencing adverse effects during the treatment, all participants' narratives demonstrated an incredible sense of determination and perseverance throughout the treatment process which can be interpreted as stemming from a life of discomfort and frustration caused by ET.

Post procedure, all participants reported tremor suppression which was life changing. This was very similar to PD patients describing DBS as a "miracle," "life-changing" and "unbelievably wonderful" (30, 31). Both participants in the current study and in the existing DBS literature expressed that the most significant impact of their respective treatments was evident in everyday achievements such as eating, drinking and socialising. While for DBS patients this allowed the return of a much desired sense of normality, for some of the MRgFUS participants in the current study it inadvertently drew attention to the unilaterality of their procedure. The likely explanation for this is that DBS can be performed bilaterally during the same operation if a patient has troublesome symptoms on both sides of their body. MRgFUS, on the other hand, can so far only be performed as a staged bilateral treatment with two separate procedures taking place at least 9 months apart due to concerns over speech adverse effects.

In the current study, the fact that the treated arm brought focus to the untreated one anecdotally resembles patients' initial experience of prosthesis use. For instance, Murray et al. (24) found that introducing prosthesis was often emotionally ambiguous for patients who appreciated the undoubted benefit of added functionality an artificial limb can afford but continued to feel the profound loss of their limb. Perhaps for ET patients, while a one-sided MRgFUS treatment brings back a much desired functionality, they continue to experience a sense of loss of that same functionality on the contralateral side.

Participants overwhelmingly expressed that undergoing the treatment necessitated an unexpected period of adjustment. This is entirely in keeping with previous research on DBS patients who reported difficulty breaking old habits and getting used to a new level of functionality (25, 30). Another form of adaptation which was required post-MRgFUS related to letting go of the tremor altogether and of past negative experiences caused by it. Some participants in the current study still seemed haunted by the burden of ET while others expressed it took them a while to psychologically adjust to what essentially was their new body. In the amputation and prosthesis use literature, the term "embodiment" (the perception of the prosthesis as part of one's body) is often an important component of functional and emotional recovery (32). In an IPA study of the embodiment of artificial limbs, Murray (33) identified time as a crucial component of the adjustment process as with time the use of the prosthesis can become intuitive and more natural. While in ET, regaining functionality is not associated with some of the negatives reported with the use of artificial limbs such as people staring (34), time can still be an important factor in the adaptation process. Indeed, Mathers et al.'s (25) idea that a cured body may not necessarily equate a cured mind post DBS seems to apply to MRgFUS patients alike, signifying a crucial period of adjustment following interventions capable of drastically reducing or completely abolishing very troublesome symptomatology instantaneously.

4.1 Conclusions and limitations

This study has highlighted the need for patients to be supported at all stages of their ET journey by linking them to appropriate resources and existing networks (such as The National Tremor Foundation, The Focused Ultrasound Foundation), creating dedicated support groups and also by easing the adjustment to the very sudden reduction of tremor post-procedure which appears to be both psychological and physiological in nature.

One important consideration for the MRgFUS service outside of the treatment of ET is the sheer determination to be treated ET patients demonstrate during this awake procedure. Due to the chronic nature of ET, these patients may well be more likely to persevere during the MRgFUS procedure, and different patient populations need to be carefully considered for treatment before assuming they will share this similarity. For instance, for applications of MRgFUS in brain tumour work, factors such as patients' psychological and physical adjustment to their diagnosis, prognosis and previous treatments need to be taken into account. Similarly, in PD the "off state" patients experience when they are not taking PD medication needs to be accounted for since it is likely patients would not be on their typical medical management during MRgFUS for the effects of the treatment to be accurately assessed.

The scope of this study was limited by University course requirements and the length of time between the interviews taking place and participants' respective procedures which may have resulted in poorer recall of very specific details and some negative aspects of the procedure being overlooked.

Future research should explore patient experience of MRgFUS as part of the NHS service, including other patient groups and interviewing patients before and after their treatment rather than collecting a retrospective account of all events.

Data availability statement

The datasets presented in this article are not readily available because data are not available due to confidentiality. Requests to access the datasets should be directed to tina.stoycheva@nhs.net.

Ethics statement

The studies involving humans were approved by London - Westminster Research Ethics Committee. The studies were conducted in accordance with the local legislation and institutional requirements. Written informed consent for participation was not required from the participants or the participants' legal guardians/next of kin because Consent was obtained over the phone prior to any study related activity due to COVID19 restrictions preventing hospital visits. This was agreed with the REC.

Author contributions

TS: Conceptualization, Data curation, Formal Analysis, Methodology, Project administration, Writing – original draft, Writing – review & editing. AJ: Writing – review & editing. PB: Conceptualization, Writing – review & editing. DN: Writing – review & editing. BJ: Writing – review & editing. LH: Writing – review & editing. WG: Supervision, Writing – review & editing. JM: Methodology, Supervision, Writing – review & editing.

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Focused ultrasound therapy in movement disorders: management roadmap toward optimal pathway organization

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MRI-guided focused ultrasound (MRgFUS) lesioning is an innovative, safe and effective treatment which provides an innovative development in the field of minimally invasive stereotactic neurosurgery. Based on the application of focused ultrasound energy under full MR planning and thermal imaging control, unilateral lesioning of the thalamus, subthalamic nucleus, and globus pallidus is indicated for the treatment of movement disorders, including essential tremor, Parkinson's disease, and dystonia. We started to apply this technique in February 2019 for the treatment of patients with movement disorders. The authors developed a diagnostic therapeutic care pathway, which is herewith proposed and applied as an explication of standard clinical practice in use. The project was the result of the application of different methods such as Health Technology Assessment (HTA), Strengths, Weaknesses, Opportunities and Threats analysis (SWOT) and Demin -Plan, Do, Check, Act (PDCA) cycle. The aim of this project was to standardize the MRgFUS diagnostic-therapeutic pathway (DTP), describe its application and the appropriateness of different phases (patient selection, intervention phase and follow-up). Here, we described in detail our experience in the DTP application from 2019 up to now in 610 patients with movement disorders.

KEYWORDS

clinical pathways, MRgFUS, focused ultrasound, thalamotomy, essential tremor, Parkinson's disease

Introduction

Improving the quality of life of patients with movement disorders [including Parkinson's disease (PD) and tremor syndromes such essential tremor (ET) and dystonia] is one of the most critical challenges due to their progressive motor and non-motor disability. Therefore, it is essential to implement an integrated and multidisciplinary approach that can reduce the impact of disability on patients' quality of life; depending on the circumstances and stages of the disease, this may involve many professionals. The field of movement disorders management continues to evolve and change at a remarkable pace. Interventional therapies, including surgical options, are increasingly used globally to treat movement disorders, in addition to pharmacological and rehabilitative approaches (1–3).

Among interventional approaches, magnetic resonance-guided focused ultrasound (MRgFUS) ablation therapy is a non-invasive modality requiring neither craniotomy nor skin incision for the treatment of ET, unilateral tremor in PD or dystonia and neuropathic pain (4). It immediately appeared necessary and indispensable to structure a pathway for patients with movement disorders eligible for interventional therapies to offer them the best personalized option based on international guidelines and expert consensus and on the availability of healthcare institute in terms of expertise, facilities, technology, staff available. The comprehensive definition of diagnostic-therapeutic pathways (DTPs) provided during the 2005 Consensus Meeting in Slovenia describes them as a methodology aimed at sharing decision-making processes and organization of care for a specific group of patients during a well-defined period of time. According to the European Pathway Association (EPA), the purpose of DTPs is to increase the quality of care perceived and delivered, improving outcomes and promoting patient safety through the use of the right resources needed.

This manuscript aims to describe the standardized process and to show the results of the application of the DTP that we have used since 2019 targeted to patients with medication-refractory tremor, from the screening for eligibility to MRgFUS treatment to the long-term follow-up. We herewith report the development and application of a specific DTP starting from the identification of a model pathway, then continuing with the analysis of the actual working reality at the given historical moment, to the definition of an actual pathway, which is applicable in real-life and in the context of the specific institutional scenario, considering the environmental reality, skills, knowledge, experience, and competencies at the Foundation IRCCS Carlo Besta Neurological Institute, Milan, Italy (hereinafter referred to as 'our Institute') at the time when the path definition activities began.

The development of a DTP starts from a review of the current literature on assessments programs for interventional procedures in movement disorders, associated with a careful analysis of the existing operative and managerial reality at our Institute. The expected result was to establish a consistent basis for the development of a series of standardized and specific activities referring to the different phases of the DTP. The outcome was the development and application of a DTP embedded within an integrated process mapping for all the 'interventional therapies' available at our Institute.

Materials and methods

Considering that both the technology and the MRgFUS procedure represented two novelties for our center, we deemed it appropriate to carry out a Health Technology Assessment (HTA) before starting to develop the pathway. It is a multidisciplinary process that evaluates the clinical, economic, organizational, social, ethical, and safety implications related to the introduction, diffusion, and use of health technologies.

The objective of the HTA analysis was to assess the actual and/or potential effects of technology, as well as the consequences that the introduction of the specific type of technology could have for the health care system, economy, and society. The evaluation of the effectiveness of health technology was conducted by employing a systematic review of literature, which is the most comprehensive and structured methodological tool.

HTA: literature search

Essential and common elements of the methodological tool used were:

- the literature search, consistent with the research question;
- the selection of studies, based on the predefined inclusion and exclusion criteria;
- the critical analysis of the quality of the included studies and the synthesis of the data.

An analogous consideration was made in setting up the research for the analysis of the safety, organizational, ethical, and social aspects of the specific technology. The instruments were imprinted with the method used for the evaluation of effectiveness; additional and specific aspects were considered, such as the specialized resources to be consulted for information retrieval. As for the evaluation of the "economic" domain, the methodological approaches employed were:

- systematic review of economic studies;
- cost analysis/estimation;
- economic evaluation (with the formulation of an economic model);
- economic analysis (review/research of economic studies and from the economic evaluation).

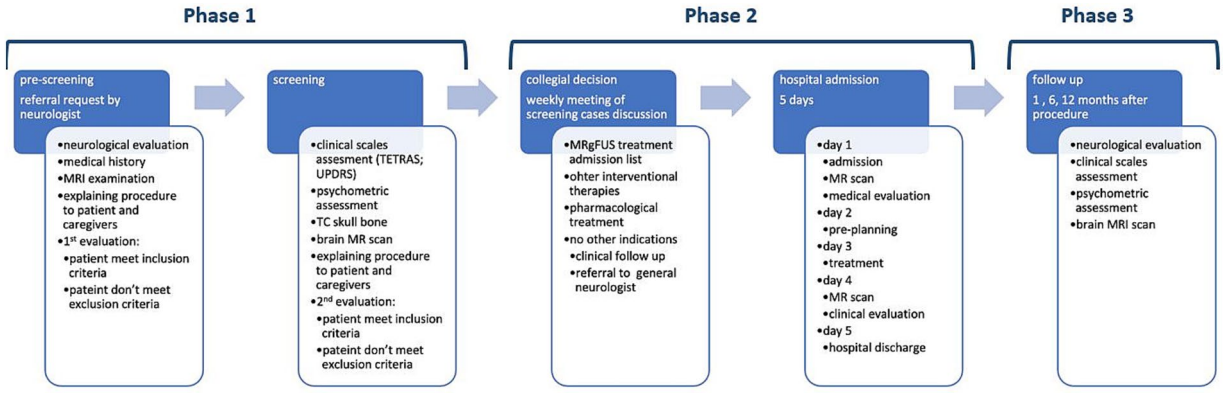

FIGURE 1
Diagnostic care pathway for the treatment of unilateral tremor with MR-guided high-field focused ultrasound.

Case series, observational studies, and randomized controlled trials on focused high-field ultrasound for the treatment of ET and tremor in PD were considered (5–8). Previous HTA research conducted in other countries was also evaluated (9).

Analysis of strengths, weaknesses, opportunities, and threats

The SWOT Analysis was constructed through the classic matrix divided into four fields:

1. Strengths—Factors within the context to be enhanced;
2. Weaknesses—Limits to be considered;
3. Opportunities—Possibilities that are offered by the context and can provide opportunities for development;
4. Threats—Risks to be assessed and addressed because they could worsen and make a situation critical.

For this type of analysis, it is crucial to be specific circumscribing the object and being clear about the objective, because a generic analysis would be ineffective.

The ***advantages*** of such analysis can be summarized in three points:

1. The deep analysis of the context in which one acts made possible by the preliminary observation and collection of data and their skillful interpretation results in a timely delineation of strategies.
2. The continuous comparison between the needs of the organization and the strategies adopted leads to an enhancement of the effectiveness achieved.
3. It allows for a greater consensus on strategies if all parties involved in the intervention participate in the analysis.

The ***limitations*** associated with this type of analysis are the following ones:

1. risk of describing a too simplified reality.
2. its implementation requires a partnership context, which if not realized, runs the risk of a disconnect between the theoretical and the political-pragmatic plan.

Diagnostic therapeutic pathway: working group definition and document drafting

In this DTP, a multidisciplinary and multi-professional team made up of personnel from different Operating Units (Parkinson and Movement Disorders Unit, Functional Neurosurgery Unit, Radiotherapy, Diagnostic and Interventional Neuroradiology, Intensive Care Unit, Neurophysiology Unit, Health Service, Neuropsychology Unit) were responsible for screening, treatment, and monitoring of patients undergoing MRgFUS at our Institute.

The work team consisted of all the professionals involved in the pathway: neurologist, neurosurgeon, radiotherapist, medical physics expert, anesthesiologist, neuroradiologist, clinical psychologist, radiology technician, neurophysiology technician, engineering support staff and administrative.

The DTP is intended as an explication of current practice in a specific institution, in a specific time and in a specific operative contest; it is not intended to be only a systematic review of the literature on the subject and a passive application of founded indications, but an adaptation of it to the existent work frame. In general terms, the DTP procedure verifies the appropriateness of patient selection, the intake of cases selected for the procedure, the stage of the intervention, and the short- and long-term follow-up of patients.

The pathway was developed as being applicable only to patients with ET and unilateral tremor in PD while being part of an operational structure with greater organizational complexity, which is that for advanced therapies in movement disorders.

Three essential phases characterize this DTP are summarized in Figure 1:

- Pre-Treatment Screening Phase (patient selection)
- Intra-hospital Phase (Surgical Procedure)
- Follow-up phase (post-treatment)

The DTP has been diffused through an educational process of all health professionals involved through training meetings and its publication on the Institute Intranet.

A table of responsibilities has been edited and made available in the document, thus that each operator identifies a person or operational unit to interface with. Several clinical studies have been designed and approved by the local Ethics Committee.

Real-world application of the pathway: defining organizational strategy and management of communication

To optimize communication and the acquisition of useful information for work planning, we have activated and widespread a corporate e-mail address to which internal and external neurologists can contact to refer patients they consider to be candidates for MRgFUS. We developed patient-specific information pages, also made available on the Foundation's website, with first-contact information about the procedure. It immediately appeared essential to adopt a waiting list system to ensure that patient's access to the screening pathway is organized in a linear and orderly manner. Therefore, we implemented a database in which to enter, at time of referral, the personal data and specifications regarding pathology and indication for treatment and type of access (whether screening or first neurological pre-screening assessment).

The database works by color code: yellow means awaiting screening, red screening performed with negative results, and green screening performed with positive results, thus to be placed on the waiting list for admission. Once placed on the waiting list in our specific data base management system, the color changes to white.

The Pathway Coordinator manages the database, which is then shared with the neurologists who perform the screening assessments.

Different operative structures are involved in the development of the pathway, each providing necessary primary and secondary processes. Several professionals in many different areas and sectors, even physically separated, must be promptly informed about the work organization, thus it immediately appeared essential to activate an internal communication tool within the Foundation that would allow for a precise, rapid, and effective mass dissemination of work plans to share a weekly organization plan for outpatients.

A similar scheme is necessary for the pathway manager to set up the basic operations required for admission for surgery: verify the list of patients for admission for MRgFUS procedures, availability of beds for admission, availability of high-technology operating rooms, alert the neuroradiology and OR coordinators, verify the availability of disposables, alert administration secretariat for patient-call in time for admission with the possible discontinuation of drug therapies, when indicated.

The planned work-plan for outpatients performing clinical diagnoses and evaluations for screening and follow-up is necessary for pathway coordination to establish the sequence of examinations/visits to be completed in the correct order based on the patient's clinical status, the time of examinations or visits (so that they are performed in the proper clinical timing and without overlapping of schedules).

Once the workflow has been defined, the Pathway Coordinator sends the plan to all the professionals involved. The work plan, sent the week before, reported identification of the outpatient clinic/diagnostic area where the patient will be assessed, type of examination/evaluation, clinical protocol to be applied (screening, follow-up, and timing), the reference Neuroradiology, blood tests and any rapid swab to be carried out in the screening area if the stay in the institute is for more than 4 h. The operating schedule is spread over 4 out of 5 working days.

To verify the process quality of the DTP procedures, the working team defined indicators for each of the three specific stages. The corresponding rationale accompanies each indicator:

i) for *Phase 1 (pre-treatment/screening),* the indicator will be the ratio between the number of cases selected for MRgFUS and the number of cases proposed (total). Rationale: selecting the correct candidate reduces the risk of failure and/or complications. The target value per year is >0.6: the appropriateness of sending is considered adequate if at least 6 out of 10 subjects have an effective indication for treatment.
ii) for *Phase 2 (treatment),* to ensure intra-operative and post-operative complication monitoring, the indicator will be the Number of cases undergoing MRgFUS without complications/Total Number of cases treated. In this case, the Outcome will be the safety of the procedure. The target value per year is >0.85: the procedure is considered adequately safe if at least 8 out of 10 subjects have no major side effects and/or adverse events.
iii) for *Phase 3 (follow-up),* to ensure monitoring of efficacy and long-term complications, the indicator will be the number of cases followed up 1 year after MRgFUS / total number of cases treated. The target value per year is >0.6: the level of clinical and instrumental assessment after treatment is considered adequate if at least 6 out of 10 treated subjects perform follow up visits in the 12 months following the procedure.

Results

HTA analysis

Evaluation results in the *clinical* domain:

a) MRgFUS neurosurgery is an effective and generally safe treatment option for moderate to severe, drug refractory ET.
b) It provides a treatment option for people unsuitable for invasive neurosurgery and offers a non-invasive option for all people considering neurosurgery.
c) Patients not eligible or not accepting invasive neurosurgery (e.g., deep brain stimulation), MRgFUS lesioning is cost-effective compared to best medical therapy.
d) In individuals eligible for invasive neurosurgery, MRgFUS may be one of several reasonable options.
e) Patients with ET who underwent MRgFUS neurosurgery reported positive experiences. They appreciated the fact that it was a non-invasive procedure and reported a substantial reduction in tremor that resulted in an improvement in their quality of life.

Evaluation results in the *non-clinical* domain:

a) The funding of MRgFUS neurosurgery for the treatment of moderate to severe, drug refractory ET at the Institute has been partly public and partly private. The economic investment is certainly significant, but the burden of disease estimates for PD and ET are higher.
b) The treatment of tremor has a low care burden and an equally low cost in terms of consumables, with a recognized DRG equal to a craniotomy.

SWOT analysis

Once the issue has been assessed from the point of view of health technology, one must think about the objective while simultaneously considering both internal and external variables: the SWOT analysis. Being specific is critical to this type of analysis: circumscribe the object and be clear about your objective, because a generic analysis would be ineffective.

Table 1 describes the SWOT analysis related to MRgFUS in movement disorders, to identify in depth all contingent factors and carry out an effective cross-reading of them.

Evaluated the context in all his relevant aspects considering the prospect to effectively start the screening pathway, the working group defined shared clinical criteria in inclusion/exclusion from the procedure. Table 2 reported the main grounds considered in deciding whether to proceed with treatment.

Real-world application of the pathway: results

From January 2019 to August 2023, a total of 610 patients affected by unilateral or bilateral drug-refractory tremor in individuals diagnosed with ET, dystonia, or PD, who were referred to our Institute to be screened for MRgFUS treatment. Figure 2 shows the number of accesses to the pathway, completed screenings and referring diagnoses.

Out of 362 screenings performed, 244 tested positive with indication of treatment: 25 refused the surgical procedure, 216 underwent procedure (77 for tremor in Parkinson's disease, 139 for essential tremor). Figure 3 shows details of screening-failure results for the 73 patients that meet some exclusion criteria and did not receive indication for treatment.

Intraoperative workflow was defined as we became familiar with the use of the system (for technicians and health physicists, involved in the functional control phase of MRI and test sonication on a phantom) and the operative sequences to be performed (for radiologists), with the membrane placement phase after the stereotaxic helmet (neurosurgeons), as well as with a clinical tremor assessment system applicable in MRI (for neurologists: rest and action tremor assessment with score from 1 to 4 and paper writing tests with marker, with score from 0 to 4 for free writing, spirals, dot approximation).

After 8 months, the procedure time has been cut in half: to date, there are two procedures performed in one room session. Eighty subjects with drug-refractory diagnosed with ET or ET plus and 53 patients with tremor-dominant PD underwent the procedure.

The inpatient-surgery phase saw the initial need to initiate educational meetings with the inpatient nursing staff, who acquired basic information about the procedure and skills for managing the specific type of patient (surgical but different from oncology): despite the change of inpatient stay on 3 different operating units, due to the reorganization of beds management, there were no adverse events,

TABLE 1 SWOT analysis related to MRgFUS in movement disorders.

STRENGTHS	**WEAKNESSES**
(Factors within the context to be enhanced)	*(Limits to be considered)*
Solid group (long-standing collaboration)	Little time to carry out activities and in addition the project
Opportunities to grow	Dispersion of energy
New knowledge	Clinical/organizational duplication
Conviction	Unready organization (conservatism)
Valid arguments	Inconsistency in actions and different messages to patients
Need to reflect on the DTP	Lack of communication
Comparison	"Sacrifice" and tiredness
Training	Lack of concrete motivation
Experience	Use of computers
Skills	Long-established habits
Flexibility and ability to confront	
Willingness for change	
OPPORTUNITIES	**THREATS**
(Possibilities that are offered by the context and can provide opportunities for development)	**(Risks to be assessed and addressed, because they could worsen and make a situation critical)**
Growth for the group, more dialog	Failure of the project
Social benefit (fewer hospital admissions)	Confusion
Optimization in budget management	Tiredness
Improved forecasting requirements	Conflicts
Greater well-being for patients	Opposition to changes Incompetence
More precise organization	Non-adherence to the project
Greater actual and perceived safety	Physician-centered and not patient-centered view
Computer use	Disorganization
Directing management of screening and planning procedures	Lack of confidence
Optimisation of hospital bed management	

TABLE 2 Inclusion and exclusion criteria for MRgFUS treatment of unilateral tremor in PD and ET.

Inclusion criteria
• Diagnosis of 'Essential Tremor' resistant to at least 2 medications targeting tremor, with medium to severe disability - TETRAS scale (10) Diagnosis of clinically established 'Parkinson's disease' predominantly unilateral tremor' (11), who meet the following criteria: MDS-UPDRS-III scale (12) score ≥ 20 in OFF therapy • Maintain stable medical therapy during the 30-day pre-procedure period • Age > 18 years and ability to provide informed consent • Ability to communicate their symptoms or distress during the procedure
Exclusion Criteria About patient with diagnosis of clinically established 'Parkinson's disease': • Hoehn and Yahr scale modified to ON therapy greater than 3. • Atypical Parkinsonism (multisystem atrophy, progressive supranuclear palsy, corticobasal syndrome); • Secondary Parkinsonism (drug-induced, vascular, normal-pressure hydrocephalus, etc). • Previous CNS surgery including Deep Brain Stimulation; General exclusion criteria: • Clinical Dementia according to the according to MDS criteria (13) or DSM-V (14); • Unstable psychiatric disorders, defined as active and uncontrolled, such as: depression, psychosis, delirium, hallucinations or suicidal ideation, severe mood disorders such as to have required hospitalization in psychiatric settings, electroconvulsive therapy, or Transcranial Magnetic Stimulation in the previous 12 months; • Contraindications deducible from 'neuropsychological evaluation': o Subjects with a history of alcoholism or drug addiction o Presence of significant cognitive impairment (MoCA ≤21) • Serious cardiological pathologies such as: o Unstable angina pectoris in therapy o Recent IMA (within the previous 6 months) o Severe congestive cardiomyopathy (FE < 40) o Unstable cardiac arrhythmias o Atrial arrhythmias not well controlled o Severe arterial hypertension (not well controlled with medical therapy) o Anticoagulant therapy (TAO or NAO) or anti-aggregants. Note: MRgFUS lesioning can be carried out in patients who can tolerate an adequate withdrawal of therapy (at least 7 days before the procedure) in accordance with the most recent guidelines on anticoagulant therapy (15). o Known risk factors for intra- and post-operative bleeding, such as: documented and certain coagulopathy; platelet count <100,000/mmc. • Severe chronic renal insufficiency (glomerular filtrate <30 mL/min) or on dialysis. • Positive history of hemorrhagic or ischemic stroke in the previous 6 months or with MRI images suggestive of 'cerebral amyloidosis' • Drug-resistant epilepsy • Brain tumor or evidence of significant damage in the MRgFUS target areas. • Intra-cranial aneurysms or intracranial arteriovenous malformations (AVMs). • Contraindications to standard MRI, including those with implanted metallic devices, cardiac pacemakers/defibrillators, neurostimulators, shunts/stents, or other metallic implants in the brain. • Severe claustrophobia, which cannot be managed with medication. • Weight (kg) above the upper limit of what is allowed on the MRI table or who cannot be placed on the scanner. • Patients who are unable to tolerate prolonged supine position during the procedure

near misses or sentinel events: side effects reported after the procedure are the same as those reported in the literature, with the same rates of occurrence and regression times.

The application of the PDA in the screening and follow-up phase was the phase of the course that was most informative and most evolved.

There were no major application problems, except for a start that we can describe as "uphill" due to difficulties that were not objective but related to long-standing organizational habits in the institution, which created some resistance. Outpatient activities have been acquired as a standard of care by the staff after a start-up with difficulties in assimilation and accommodation, within an old structure with few and narrow spaces whose management is not always easy: after an initial transition phase in which activities were performed at the day hospital activity area the screening visits and neuropsychological assessments were directed to the actual outpatient area with the identification of its dedicated spaces: this has made it easier for the operators at the administrative reception desk to identify individuals as outsiders and not as sent from Day Hospital and has benefited the patients, especially in the clinical follow-up phases (they already know where to go) and has avoided the continuous access of outsiders to the Day Hospital area, where they perform treatments immunocompromised patients.

The activity communication tool initially had a "chilly" reception because it appeared quite complex for some operators to understand: with a few informational and educational meetings on the subject, the interpretation issue is resolved and it is now a solid working tool. The same applies to communications regarding admissions.

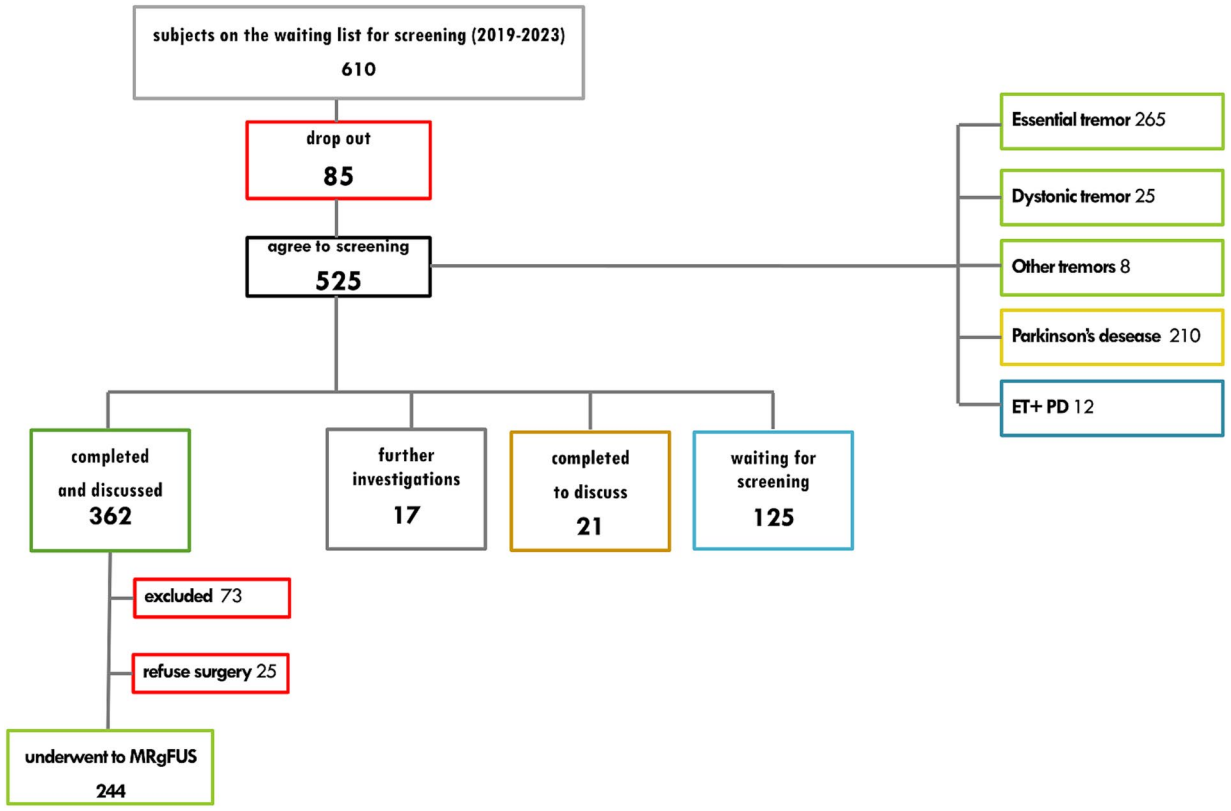

FIGURE 2
Diagnostic care pathway for the treatment of unilateral tremor with MR-guided high-field focused ultrasound: number of accesses, completed screenings and referring diagnoses.

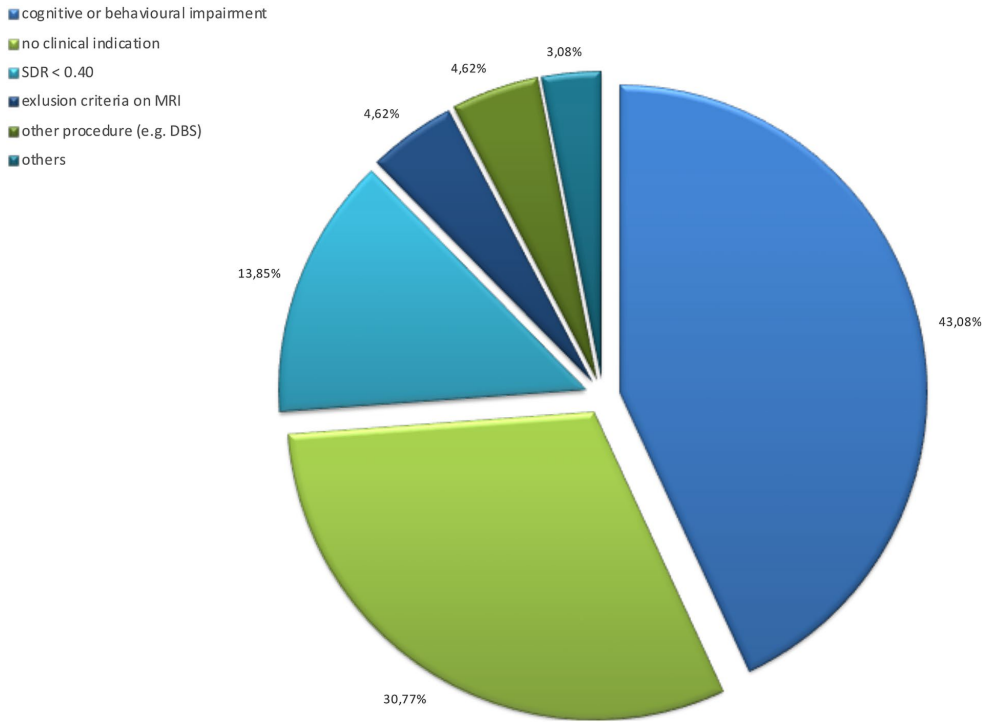

FIGURE 3
Grounds for screening failure: data on 78 assessed and excluded subjects. DBS, deep brain stimulation; SDR, skull density ratio (lower than 0.40).

TABLE 3 Trends for the three most significant indicators for the "DTP MRgFUS."

	Phase 1 (selection)	Phase 2 (surgery)	Phase 3 (follow up)
2019	0.64	0.96	0.68
2020	0.61	0.97	0.97
2021	0.58	0.98	0.85
2022	0.66	0.95	0.82

Phase 1 (pre-treatment/screening): Number of cases selected for MRgFUS / number of cases proposed (total; target > 0.6). Phase 2 (treatment): Number of cases undergoing MRgFUS without complications / total number of cases treated (target > 0.85). Phase 3 (follow-up): Number of cases followed up after 1-year post MRgFUS / total number of cases treated (target > 0.6).

Table 3 shows results for the three most significant indicators for the MRgFUS DTP.

Discussion

The development, implementation and evaluation of a DTP is a continuous process well represented in the Deming's quality cycle (Plan-Do-Check-Act).

Methodically structure of all planning phases was the strategic key for the project's success:

1. Goal setting: the definition of what, as an organization, we want to do.
2. Environmental scan: the assessments the current situation within and outside the organization by the SWOT analysis and verification of the relevance of the results of this internal/external assessment.
3. Defined strategic issues: key factors for developing an operational plan.
4. Development of new pathway and carefully organizing educational program for health professionals.
5. Defining critical success factors: achievement of objectives and implementation of strategy.
6. Development and diffusion of work plans, identification of the resources needed.
7. It was also essential to find and consider the process indicators as effective tools for providing information about the efficiency of the pathway and for adopt corrective interventions.

A coordinating/management professional was introduced for paths of high organizational complexity. This professional figure allows a reference for the definition of strategic orientations aimed at achieving a goal: to highlight the characteristics of the project and the consequent relationships with the context in which it was intended to be inserted. The resistances to development of a new pathway were mainly related to the established habit of "personalized" patient management. However, the feasibility of the pathway and the fact that the cases were already discussed at a collegial meeting made it clear to everyone that it was functional in view of the objectives.

The work plans, meeting reports, operative and discussion meetings rapidly became a solid benchmark for all the operators and operative units involved in this path.

Besides from the results obtained, the introduction of a referent for the coordination of specific DTP represented an opportunity for cultural growth in the management of the interventional therapy pathway and also for professional development. It is not easy to implement a framework aimed at sharing common protocol for screening, clinical and instrumental evaluation. The discussion of the clinical cases, to establish a joint d decision between Neurologist, Neuropsychologist, Neuroradiologist regarding the opportunity to propose the intervention, requires high competence and listening skills.

Medical doctors and staff must be completely convinced: to involve everyone and gather collaboration, it was important to get into the habit of presenting and discussing cases collegially, but also to evaluate together the basic data on the outcomes relating to the current path and communicate gradually, along the way, the clinical results for the operated patients, including the actual and practical ones resulting from the operational change. You can proceed to each discussion meeting, if you wish, with the possibility of expressing opinions and/or difficulties encountered and opening a debate on the merits.

Over time, the awareness has developed that discussing cases through discussion is a strong point: clinical cases discussion meetings have become an unmissable and rich event from a scientific point of view. The mainly practical and organizational part of the workflow is discussed during two meetings, in two key moments of the year (mid-January and early September) in which the situation is taken stock from an operational point of view.

In overcoming any obstacle to implementation, the role of the Operational Unit managers and the project contact is fundamental.

In the application of DTP, differences between the actual and reference pathways were noted, as a matter of course. These have been considered, within certain limits, "physiological" and can be generated by the specific characteristics of patients, which make each healthcare production process a singularity; a second factor considered as generating heterogeneous outcomes with respect to the reference model, are the changing operational and organizational conditions in which the provider finds itself, over time, operating. The deviations recorded, negative and positive, contributed to the refinement (design of ramifications of a basic pathway) and evolution of the reference pathway with the identification of solutions and modifications capable of generating improved results compared to the original one.

The evidences generated by the analysis of actual pathways has been the basis for rethinking the baseline pathway, suggesting the introduction of new or different activities or the elimination of activities that do not generate value (not in a strictly economic sense). Similarly, they suggested the modification of the time placement of some activities and the modulation of

responsibilities in the management and delivery of other activities. In order to arrive at the analysis of deviations between reference and actual pathways, it was essential to undertake a focused study of the care pathway, describing its salient points in detail in some respects but without presumption of exhaustiveness in other respects. The identification of the activities that make up the patient's overall care pathway and that contribute, in a coordinated and finalized form, to the resolution of a need. They have different natures (clinical, care, social, environmental, supportive, direct, indirect, etc.) and can be the most diverse, depending on the specific needs and the institutional entity in charge of them.

Knowing what is carried out during a health care process can lead to questions about how and why certain activities are delivered. Fundamental is to observe how activities are combined, how the organization makes them available, at what times and in what places, and whether with the integration of the different units participating in the overall process. Described the "production" process, in terms of combined activities, the critical activities highlighted in the overall process are highlighted and discussed, making it possible to evaluate production and delivery alternatives.

Some critical issues remain unresolved related to the limited resources available and how/who to involve. In this regard, we are evaluating some possible organizational changes that will allow the project to be more sustainable.

The MRgFUS DTP operating model was adopted as the basis for all complex diagnostic outpatient pathways initiated at the Institute. For interventional therapies, we completed the mapping of the diagnosis and treatment process "Interventional Therapies Movement Disorders" by extending the application of the "model-MRgFUS" to other interventional therapies as well.

Data availability statement

The datasets presented in this article are not readily available because of ethical and privacy restrictions. Requests to access the datasets should be directed to the corresponding author.

Ethics statement

Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

SR: Conceptualization, Data curation, Investigation, Methodology, Project administration, Writing – original draft, Writing – review & editing. RC: Methodology, Supervision, Writing – review & editing. VaL: Writing – review & editing. MGa: Writing – review & editing. NA: Writing – review & editing. FC: Writing – review & editing. AB: Writing – review & editing. RT: Writing – review & editing. MP: Writing – review & editing. ViL: Writing – review & editing. LR: Writing – review & editing. AE: Writing – review & editing. FG: Writing – review & editing. EM: Writing – review & editing. MF: Writing – review & editing. FE: Writing – review & editing. SaP: Writing – review & editing. PA: Writing – review & editing. SyP: Writing – review & editing. GD: Writing – review & editing. VN: Writing – review & editing. EC: Writing – review & editing. MS: Writing – review & editing. MGr: Writing – review & editing. VC: Writing – review & editing. MC: Writing – review & editing. FD: Writing – review & editing. GM: Writing – review & editing. RE: Formal analysis, Funding acquisition, Methodology, Project administration, Resources, Supervision, Validation, Writing – review & editing.

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Early cortico-muscular coherence and cortical network changes in Parkinson's patients treated with MRgFUS

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Introduction: To investigate cortical network changes using Magnetoencephalography (MEG) signals in Parkinson's disease (PD) patients undergoing Magnetic Resonance-guided Focused Ultrasound (MRgFUS) thalamotomy.

Methods: We evaluated the MEG signals in 16 PD patients with drug-refractory tremor before and after 12-month from MRgFUS unilateral lesion of the ventralis intermediate nucleus (Vim) of the thalamus contralateral to the most affected body side. We recorded patients 24 h before (T0) and 24 h after MRgFUS (T1). We analyzed signal epochs recorded at rest and during the isometric extension of the hand contralateral to thalamotomy. We evaluated cortico-muscular coherence (CMC), the out-strength index from non-primary motor areas to the pre-central area and connectivity indexes, using generalized partial directed coherence. Statistical analysis was performed using RMANOVA and *post hoc* *t*-tests.

Results: Most changes found at T1 compared to T0 occurred in the beta band and included: (1) a re-adjustment of CMC distribution; (2) a reduced out-strength from non-primary motor areas toward the precentral area; (3) strongly reduced clustering coefficient values. These differences mainly occurred during motor activation and with few statistically significant changes at rest. Correlation analysis showed significant relationships between changes of out-strength and clustering coefficient in non-primary motor areas and the changes in clinical scores.

Discussion: One day after MRgFUS thalamotomy, PD patients showed a topographically reordered CMC and decreased cortico-cortical flow, together with a reduced local connection between different nodes. These findings suggest that the reordered cortico-muscular and cortical-networks in the beta band may represent an early physiological readjustment related to MRgFUS Vim lesion.

KEYWORDS

Parkinson's disease, cortico-muscular coherence, cortical network, MRgFUS, MEG

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1 Introduction

In Parkinson's disease (PD), resting tremor is a cardinal feature that primarily supports the early diagnosis (1). In addition, postural and kinetic tremors are also common manifestations. In several patients, tremor occurs unilaterally, namely in the relatively early disease stages (2). Tremors can occur in the earliest disease stages, and studies using magnetoencephalography (MEG) have shown that oscillatory activity in the motor cortex, cerebellum, and diencephalic area are tremor-related (3). Cerebello-thalamocortical circuit, the basal ganglia, and the interaction between these two circuits are primarily implicated in the generation of all symptoms (4).

Cortical structures are certainly strongly involved in the disorder, including the motor cortex. Substantia nigra dopaminergic neurons influence the firing rate and synchronization of motor cortical neurons through direct projections and indirect pathways involving the basal ganglia and motor thalamus. Moreover, in PD pathophysiology, the motor cortex is responsible for transferring abnormal activity occurring in the basal ganglia to muscles (5), and is the basis of a positive effect of transcranial magnetic stimulation in PD (6). Moreover, long-range input to the motor cortex originating from other cortical areas may play a role in various movement disorders, including PD (7). These include the primary somatosensory cortex, the contralateral motor cortex, secondary motor cortices [premotor cortex and supplementary motor cortex demonstrated in primates (8, 9)] and other frontal regions (10). These inputs are also probably involved in the side effects of levodopa in PD patients (11).

Among different treatments, surgical options, such as deep brain stimulation and magnetic resonance-guided focused ultrasound (MRgFUS) thalamotomy (12, 13), are a part of the therapeutic opportunities in selected patients, presenting with prominent tremors, as well as in other pathological conditions with tremors, such as essential tremor (14).

We analyzed MEG signals that non-invasively and directly measures the magnetic fields generated by neuronal activity of the cerebral cortex with high spatial and temporal resolution. MEG signals are not distorted by the skull, scalp, and require a simpler head model to apply for source localization. This feature makes MEG a valuable tool that can be used to investigate and disentangle the complex interactions of neural populations, or to localize the physiological and pathological activities.

We are reporting here information concerning the neocortical reorganization involving the motor cortex and non-primary motor cortical areas detected on neurophysiological (MEG) signals in patients with prominently unilateral tremors treated with unilateral VIM thalamotomy using MRgFUS in the absence of other severe symptoms.

2 Materials and methods

2.1 Subjects

We included 16 patients (Table 1) diagnosed with clinically probable PD (1) and tremor-dominant motor phenotype, who showed a clearly prominent tremor on an upper arm and who were followed up for more than 1 year.

TABLE 1 Demographics, clinical scores and adverse events at baseline and 12-months follow-up.

Demographic characteristics		
Sex (M/F)	13/3	
Age (years)	67.1 ± 8.4	
Age at onset (years)	60.5 ± 6.9	
Disease duration (years)	6.7 ± 3.8	
Treated side (left/right thalamus)	8/8	
Baseline MDS-UPDRS-I, median [IQR]		
Total score	2.5 [1.75; 5.3]	
Item 1.1 Cognitive impairment	0 [0; 1]	
Item 1.2 Hallucinations and psychosis	0 [0; 0]	
Item 1.3 Depressed mood	0 [0; 1]	
Item 1.4 Anxious mood	0 [0; 1]	
Item 1.5 Apathy	0 [0; 0]	
Item 1.6 Features of dopamine dysregulation syndrome	0 [0; 0]	
Motor Outcome (MDS-UPDRS-III ON medication)		
	Baseline	*12 months*
Total score	27.6 ± 9.7**	20.3 ± 9.6**
Tremor score[a]	6.1 ± 1.9***	1.6 ± 1.8***
Bradykinesia score[b]	5.1 ± 2.7	4.4 ± 3.1
Rigidity score[c]	2.3 ± 1.0***	0.8 ± 1.1***
Axial score[d]	4.3 ± 2.0*	5.4 ± 2.9*
H&Y, median (IQR) [min-max]	2 (2; 2) [1–2]	2 (2; 2) [2–2]
Pharmacological therapy		
LEDD[e] (mg), mean ± SD (min-max)	570 ± 329 (0–1,350)	572 ± 244 (150–1,000)
Anticholinergic, *n* (%)	3 (19%)	2 (13%)
Beta-blocker, *n* (%)	1 (6%)	1 (6%)
Thalamotomy related adverse events		
Patients with 1 or more AE (*n*)	11	2
Type of AE		
Gait imbalance (*n*)	8	0
Perioral/hand paresthesia (*n*)	6	2
Dysarthria (*n*)	4	0
Inferior limb weakness (*n*)	2	0
Facial asymmetry (*n*)	1	0

Data expressed as mean ± SD unless otherwise specified. AE, Adverse Event; H&Y, Hoehn and Yahr stage; IQR, Interquartile range; LEDD, Levodopa Equivalent Daily Dose, MDS-UPDRS-I Movement Disorder's Society Unified Parkinson's Disease Rating Scale Part I, Non-Motor Aspects of Experiences of Daily Living; MDS-UPDRS-III, Movement Disorder's Society Unified Parkinson's Disease Rating Scale Part III, Motor score. *$p < 0.05$; **$p < 0.010$; ***$p < 0.001$. [a]Sum of items 3.15, 3.16, 3.17 relative to the treated side; [b]Sum of items 3.4–3.8 relative to the treated side; [c]Sum of items 3.3 of upper and lower limbs relative to the treated side; [d]Sum of items 3.1, 3.2, 3.9–3.13; [e]LEDD calculated as previously described (15, 16); LEDD of safinamide was calculated as described in Cilia et al. (17).

The majority of patients were male (13), but there were no obvious differences in both demographic data (age: males = 66.8 ± 2.3 years; females = 68.7 ± 1.7 years; onset age: males = 59.9 ± 1.9 years,

females = 63.0 ± 1.5 years) and data obtained from both clinical and neurophysiological measures.

MDS-UPDRS scores were assessed 24 h before MRgFUS (T0), 24 h after the procedure (T1) and at 12-months follow-up. Detailed pharmacological therapy has been recorded; Levodopa-Equivalent Daily Dose (LEDD), was calculated as previously reported (15, 16), LEDD of safinamide was calculated as recently reported (17) (Table 1). The tremor was scored using the different components of the International Parkinson and Movement Disorders Society version of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS) (18, 19). MDS-UPDRS scores were assessed 24 h before MRgFUS (T0), 24 h after the procedure (T1) and at 12-months follow-up.

We considered eligible for MRgFUS treatment patients with tremor refractory to drug therapy; other significant pathologies or medical risk factors were considered as exclusion criteria, including the presence of cognitive decline and significant psychiatric comorbidities. Detailed MRgFUS eligibility criteria have been previously reported (20). Eight patients underwent MRgFUS treatment on the left thalamus and eight on the right thalamus.

At the time of our evaluation, all patients were on their current home medication regimen and in the "medication-on" condition.

MDS-UPDRS-I and MDS-UPDRS-III were evaluated at T0 and after 1 year of follow-up. The sub scores for tremor (items 3.15, 3.16, 3.17) rigidity (sum of items 3.3 of upper and lower limbs) and bradykinesia (items 3.4–3.8) relative to the treated side and axial score (items 3.1, 3.2, 3.9–3.13) were computed. Only the MDS-UPDRS-III tremor score was evaluated at T1.

We chose the medication-on condition as this was more similar to the daily condition of the patients and avoided an uncomfortable situation during the tests carried out during the MEG recording.

At T1, 11 patient presented symptoms referable to minimal adverse events in the immediate post-treatment, which completely recovered in nine and mitigated in in two (Table 1).

The study was approved by the Ethics Committee of the Fondazione IRCCS Istituto Neurologico C. Besta and was carried out according to the Declaration of Helsinki, and its amendments. All subjects provided their written informed consent before being included in the study.

2.2 MEG signals acquisition and analysis

MEG signals were recorded with a whole-head system (Neuromag Triux, MEGIN; Finland) and pre-processed according to our laboratory procedures [see (21), for details]. For the analyses, we selected an epoch of 60 s at rest and epochs of the MEG and concomitant EMG signals during repeated isometric extensions of the hand contralateral to the ViM target. To limit the presence of tremor that usually appears in the stationary phase of isometric contraction, we selected multiple epochs at the start of each extension (reaching an analysis time of 60 s). Source time series were extracted with a linearly constraint minimum variance beamforming approach using a head model based on individual MRI. Data were normalized to the MNI template to extract the source time series on different cortical areas according to the Automated Anatomical Labeling atlas. The included regions of interest (ROIs) were: Precentral (PreC), Postcentral (PostC), Supplementary Motor (SupM), Parietal (P, including inferior and superior parietal areas), and Frontal (F, including superior and middle gyri) ROI of contralateral (Co) hemisphere with respect to the activated hand. The mean of the values measured on the same ROIs in the ipsilateral hemisphere were grouped into an ROI called Ipsi. We analyzed the MEG signals in different frequency bands: delta (0–4 Hz), theta (>4–8 Hz) alpha (>8–13 Hz), beta (>13–30 Hz), low-gamma (>30–45 Hz).

Cortico-muscular coherence (CMC) between cortical ROIs and muscular activity during isometric contraction was estimated at T0 and T1 using a block-wise bivariate autoregressive parametric model. The CMC values were normalized (nCMC) to the maximum value obtained at different times to better highlighting the coherence reorganization in the different cortical ROIs. To investigate cortical connectivity, generalized partial directed coherence [gPDC, (22)] was applied to the same epochs selected to estimate the nCMC and in the epoch at rest. For CMC and gPDC methods see our previous studies in patients with cortical myoclonus (23–26) and in a population of patients with essential tremor treated with MRgFUS (27). To investigate the regional properties of the network and the unidirectional coupling between ROIs, we calculated the out-degrees (number of edges going out of a node, considering each ROI as a node) and the out-strength index (edges values), respectively. Moreover, we calculated the betweenness centrality, measuring the centrality in a graph of a specific region based on shortest paths, and the clustering coefficient, measuring the degree to which a network organizes into a region. Data analysis was performed using custom-made Matlab (MATLAB 2016a, Mathworks, Inc., Natick, MA, United States) scripts based on the Fieldtrip toolbox (28).

2.3 Statistical analysis

nCMC, out-strength measures, and connectivity indexes obtained in selected cortical ROIs were compared using repeated measures ANOVA (RM ANOVA) at a significance level of $p < 0.05$, using ROIs and Time (T0, T1) as the within-group factor. The sphericity assumption was evaluated using Mauchley's test, and the Greenhouse–Geisser degree of freedom correction was applied when appropriate. Where the RM ANOVA indicates a significant factor or interaction, post-hoc tests using independent and paired samples were performed. Values are expressed as mean ± standard error of the mean.

To test the relationship between clinical scores evaluated at 12-months follow-up and neurophysiological measures linear regression was applied.

3 Results

3.1 Cortico-muscular coherence

At T0, CMC showed a peak in the alpha band in 12 out of 16 patients with a frequency ranging from 10.4 and 11.2 Hz, in the different ROIs. The same occurred at T1, even if in eight patients only. In the delta and theta bands, no patient had detectable CMC peaks at both T0 and T1, while in the low-gamma (30–50 Hz) bands small peaks had variable CMC values and did not show significant differences between T0 and T1.

At T0, in the beta band, six patients showed a CMC peak in one or more of the selected ROIs contralateral with respect to the activated

hand, while at T1 all patients but one showed a CMC peak in one or more Co-ROIs (mean frequency at T0: 23.7 ± 0.4 Hz; at T1: 21.1 ± 1.4 Hz). The frequency did not differ between T0 and T1.

Since CMC, normalized to its main peak (nCMC), was almost exclusively found in the ROIs directly involved motor function, and very rarely in other ROIs, including those of the hemisphere ipsilateral with respect the MRgFUS treatment, the RMANOVA was performed on the beta nCMC values including Co-PreC, Co-PostC, and Co-SupM ROIs. There were significant within-subjects effects for ROIs [$F(3,42) = 7.8$, $p = 0.001$], Time [$F(3,42) = 8.8$, $p = 0.005$] and interaction ROI x Time [$F(3,42) = 9.3$, $p = 0.001$; Figure 1].

Post hoc analyses revealed that, comparing the values recorded at T1 with those recorded at T0, a significant increase in nCMC value occurred in Co-PostC [$t(15) = 3.6$, $p = 0.002$] and Co-PreC ROIs [$t(15) = 3.8$, $p = 0.002$].

3.2 Cortico-cortical out-strength

With the aim of further exploring changes occurring at T1 with respect to T0 in the primary motor cortex, we analyzed the out-strength from Co and Ipsi ROIs toward the Co-PreC ROIs.

During isometric hand extension (action), RMANOVA showed significant within-subjects effects of ROIs but not for Time in theta, alpha, beta, and low-gamma bands. Only in the beta band, RMANOVA revealed a significant within-subjects effect of ROIs [$F(2.23, 33.5) = 19.37$, $p < 0.001$], Time [$F(1, 15) = 29.63$, $p < 0.001$] and ROIs × time $F(4,60) = 4.29$, $p = 0.004$.

Comparing T1 and T0, a reduced out-strength toward Co-PreC ROI occurred from Co-F [$t = 2.9(15)$, $p = 0.011$], Co-P [$t(15) = 3.7$, $p = 0.002$], Co-PostC [$t(15) = 3.1$, $p = 0.007$], and Ipsi ROIs [$t(15) = 2.8$, $p = 0.012$; Figure 2A].

Moreover, the out-strength from the hemisphere ipsilateral with respect the MRgFUS treatment was obviously decreased on the ROIs more involved in motor function [$t(15) = 2.9$, $p = 0.011$], while was at the significance limits from the analyzed F and P ROIs [$t(15) = 2.1$, $p = 0.047$].

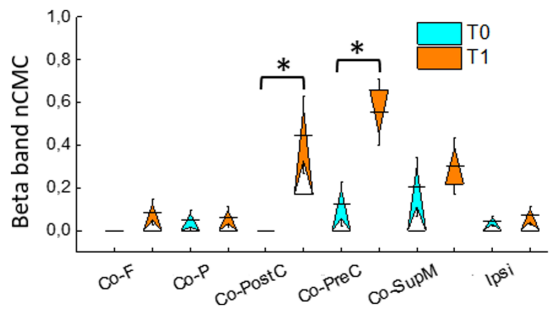

FIGURE 1
Normalized cortico-muscular coherence (nCMC) in the beta band, evaluated during isometric contraction, in different ROIs contralateral (Co) to activated hand (Co-PreC, precentral; Co-PostC, postcentral; Co-SupM, supplementary motor; Co-P, parietal; Co-F, frontal) and in the ipsilateral ROI. Asterisks indicate significant differences between the values assessed at T1 and T0.

When analyzing the epochs at rest, in the beta band, RMANOVA also found a significant within-subjects effect of ROIs, but without the effect of the Time (Figure 2B).

3.3 Connectivity indexes

For the out-degrees, during hand extension, RMANOVA showed significant within-subjects effects of ROIs in the alpha [$F(2.53,38.03) = 5.72$, $p = 0.004$], beta [$F(1.65,24.73) = 225.141$, $p < 0.001$], and low-gamma bands [$F(2.14,32.17) = 23.42$, $p < 0.001$], but no effects of Time. No effects were found for in-degrees, while betweenness centrality showed a within-subject effect of ROIs in the beta band only [$F(3.36, 50.47) = 3.45$, $p = 0.020$], but no effects of Time.

For clustering coefficient, during hand extension, in the beta and low-gamma bands RMANOVA showed a significant within-subjects effect of ROIs [beta: $F(5,75) = 7.14$, $p < 0.001$; low-gamma: $F(2.84,42.64) = 5.17$, $p = 0.004$] and Time [beta: $F(1,15) = 26.26$, $p < 0.001$]; low-gamma: [$F(1,15) = 6.97$, $p = 0.019$]. When examining the clustering coefficient in resting condition, RMANOVA did not show significant differences except for the effect of ROIs in low-gamma band [$F(5,75) = 10.41$, $p = 0.001$].

Comparing T1 and T0 during isometric hand extension, the clustering coefficient decreased in all ROIs including the group of ipsilateral ROIs (with t value ranging from 2.7 to 6.7 and p values ranging from 0.037 to <0.001; Figure 3A).

When grouped together, in the Co ROIs more involved in the motor function, the clustering coefficient decreased in the beta band [$t(15) = 4.8$, $p < 0.001$], as well it decreased in symmetric ipsilateral ROIs [$t(15) = 3.6$, $p = 0.001$]. A similar decrease was found in Co [$t(15) = 2.8$, $p = 0.008$] and ipsilateral (2.7, $p = 0.011$) F ROIs and in Co [$t(15) = 1.6$, $p = 0.011$; $t(15) = 2.6$, $p = 0.012$] and ipsilateral [$t(15) = 2.9$, $p = 0.006$] P ROIs.

In the low-gamma band, the clustering coefficient decreased in Co ROIs more involved in the motor function [$t(15) = 4.3$, $p < 0.001$] and in the same ipsilateral ROIs [$t(15) = 2.7$, $p = 0.009$]; it also decreased in Co [$t(15) = 2.9$, $p = 0.006$] and Ipsilateral [$t(15) = 2.7$, $p = 0.006$] F ROIs, but not significantly in parietal ROIs.

At rest, there was a trend toward reduced value measured a T1, but no difference reached a statistical significance (Figure 3B).

3.4 Correlations between clinical scores and neurophysiological measures

Thirteen patients had a reduction of the total score higher than 30%, while three had a lower reduction.

Linear regression analysis showed a significant relationship between out-strength from the Co-SupM toward Co-PreC ROI [$F(15) = 13.5$, $p = 0.002$] as well as between the collective out-strength from all Co-ROIs and the percentage reduction of the tremors score during hand movement [$F(15) = 9.7$, $p = 0.008$, Figures 4A,B].

A significant relationship was also found between the clustering coefficient and the percentage reduction of the values of the mean score of tremor measured at rest and during motor activation in Co-SupM ROI [$F(15) = 8.3$, $p = 0.012$] and in the Co-PostC ROI [$F(15) = 6.0$, $p = 0.028$; Figures 4C,D].

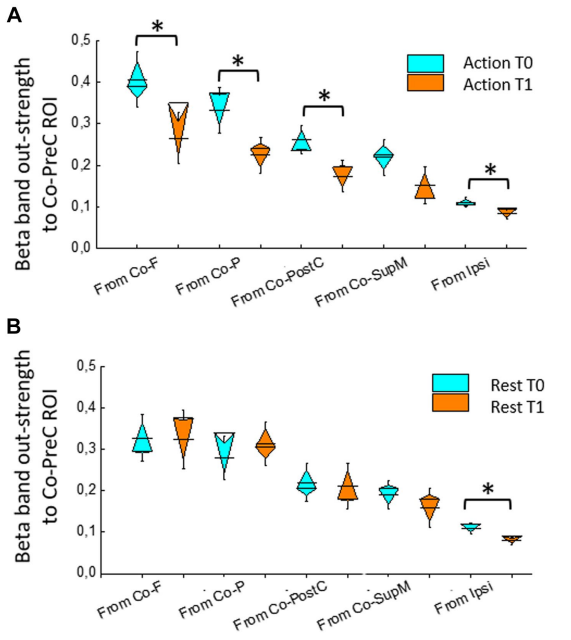

FIGURE 2
Beta band out-strength toward precentral ROI (Co-PreC) from other ROIs (Co-PreC, precentral; Co-PostC, postcentral; Co-SupM, supplementary motor; P, Co-parietal; F, Co frontal) and in the ipsilateral (Ipsi) ROI evaluated during isometric hand extension **(A)** and at rest **(B)**. Asterisks indicate significant differences between T1 and T0.

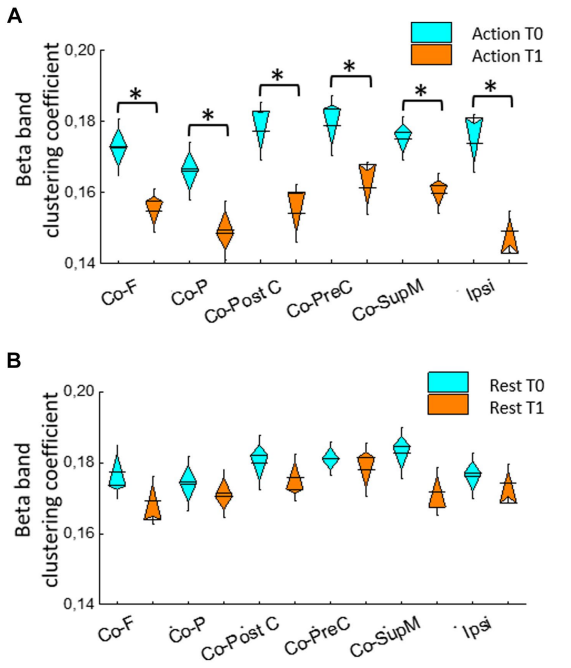

FIGURE 3
Beta band clustering coefficient in different ROIs contralateral to activated hand (Co-PreC, precentral; Co-PostC, postcentral; Co-SupM, supplementary motor; Co-P, parietal; Co-F, frontal) and in the ipsilateral (Ipsi) ROI evaluated during isometric extension of the hand contralateral to treated ViM **(A)** and at rest **(B)**. Asterisks indicate significant differences between T1 and T0.

4 Discussion

Dysfunction of the cerebellum-thalamocortical network and connections to other brain areas is pivotal to many types of tremors. We are reporting here information concerning the cortical reorganization detected on neurophysiological (MEG) signals after unilateral MRgFUS in patients with contralateral tremor in the absence of other severe or prominent symptom in PD patients with a 1 year of post-intervention follow-up.

In the included patients, tremor was the prominent and most disabling symptom and the VIM was selected as target. VIM is a key hub in the cerebello-thalamo-cortical circuit, which has been shown to be impaired in tremor dominant PD (29). This target is the most frequently studied in both functional neurosurgery and lesional approaches in order to treat drug-resistant tremor (30, 31). However, pathophysiology of tremor in PD is complex and involves structures of the basal ganglia-cortical loop (29). In patients with tremor accompanied by other disabling motor symptoms, other targets have been explored and demonstrated efficacy in improving not only tremor but also rigidity, bradykinesia and axial features (32).

Our main evidence concerns the readjustment of a basic mechanism (expressed through cortico-muscular coherence) connecting cortical function with the activated hand, the rearrangement of the cortico-cortical flow toward the precentral area contralateral to lateralized tremor, and the reduction affecting indexes of local cortical trafficking, expressed by clustering coefficient.

The detected changes and the resulting differences were observed the day after the MRgFUS treatment, when the tremor was absent, suggesting that the reordering of cortico-muscular coherence and cortical network in the beta band may represent a very early physiological readjustment of cortico-muscular and cortical relationships. This mainly occurred in the beta band, representing the frequency commonly associated with motor activity (33). The maintenance, in most patients, of the tremor relief 1 year after the MRgFUS treatment and the positive relationship found between changes in tremor scores and neurophysiological parameter assessed at T1 suggest that the early network reordering may also serve as predictors of late outcome.

CMC in the beta band gives information about functional coupling between muscles and the cortex (33). Beta-band CMC became evident when healthy subjects perform isometric contraction and it has been already found reduced in PD patients as a revealing factor of their motor impairment (34). Conversely, it increases after motor improvement in the presence of deep brain stimulation (35) as well as a consequence of effective levodopa treatment (36). We previously found a similar increase at T1 of beta-CMC in patients with essential tremor submitted to MRgFUS treatment, suggesting an immediate reorganization of the cortico-muscular relationship after the tremor relief involving the cortical areas primarily related to the hand movement (27).

Measuring the out-strength from different frontoparietal areas directed toward the precentral area of the hemisphere receiving the Vim thalamotomy, we observed a significant decrease of cortico-cortical flow at T1, suggesting a reordering of cortico-cortical interactions and a reacquired "leadership" of the primary motor cortex recovering at T1, in coincidence with the tremor relief. The same is suggested by the significantly reduced out-strength deriving from the hemisphere ipsilateral with respect the MRgFUS target.

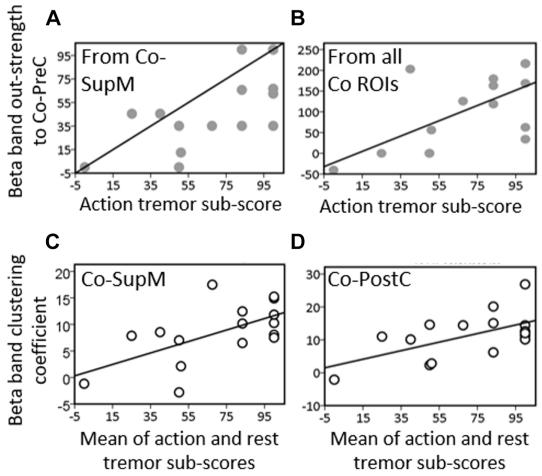

FIGURE 4
Linear regression performed between mean values action tremor sub-scores items and the values of out-strength from **(A)** contralateral supplementary motor ROI (Co-SupM), and **(B)** the sum of the out-strength values from all ROIs toward precentral area contralateral to evaluated hand. Linear regression between mean values of resting and action tremor sub-scores items and **(C)** the values of cluster coefficient on contralateral supplementary motor (Co-SupM) and **(D)** on postcentral (Co-PostC) ROIs.

Changes found in cortico-cortical strength between areas not primarily involved in motor activity appear to be a further indicator of cortical reorganization. Changes in cortico-cortical and cortico-thalamic coupling in the beta band were already reported as excessive in Parkinson's disease patients (37, 38), and suggested as a reliable measure of disease severity.

The reorganization of corticomuscular and cortico-cortical flow appears to a main factor resulting from thalamotomy. Interestingly it appears to be a "precondition" for the following outcome, even if all patients were substantially tremor-free at T1, suggesting that the achievement of a physiological reorganization is important for late prognosis.

The observation of high values of the clustering coefficient was rather noticeable and suggested an augmented tendency of different regions to express a pathological, not efficient, increase of connection between different nodes. This occurred in beta band, but also in low-gamma band. Using EEG signals, an increased local clustering coefficient was already noted in PD patients compared with healthy subjects (39), or the same patients in off with respect to on conditions (40). Similar evidence was obtained comparing PD with healthy subjects using MRI signals (41). This may suggest an increased cortical "pathological trafficking," not limited to the involved motor areas, that is associated with the defective motor activity specific for PD patients and increases during motor activity. The values of the clustering coefficient decreased significantly at T1 both on the hemisphere Co to activated hand on the ipsilateral one. This finding also support the hypothesis that a pathological hyper-connectivity involving beta and low-gamma activity may thus act as a condition rather specific for PD, significantly attenuated after ViM lesion and predicting a better late outcome. In agreement, we did not find a similar connectivity pattern in patients with ET that we examined after MRgFUS in a similar way. We did not investigate frequencies higher than those included in the low gamma, so the involvement of these frequencies may just represent an "extension" of the results obtained in beta frequencies. In fact, the beta-low-gamma frequency range can be generated by the same neuronal systems (42).

Most of our results, including CMC, the out-strength from different cortical areas toward the motor area of the hemisphere with treated Vim (and contralateral to activated hand) mainly involved the beta band frequencies suggesting that the disordered network connecting different ROIs or local hyper-connectivity derive from the pathological organization of these frequencies. Actually, beta frequencies are typically involved in motor function both in healthy and pathological conditions, including PD patients (37, 43).

At rest, a condition in which the tremor had its maximum expression at T0, we did not identify significant relationships with the various indices relating to MEG frequencies, this could suggest that the theta rhythmicity of the tremor mainly involves the basal nuclei and reflects little on the cortical areas.

Regression analysis showed a significant relationship between the reduction of tremor-related scores evaluated at 1-year follow-up during motor activation and the reduction of out-strength from non-primary motor areas and precentral area ipsilateral to treated ViM observed at T1, the same was found between the reduced values of the clustering coefficient values measured in Co-SupM and Co-PostC ROI. This can suggest that excessive cortico-cortical flow is mainly disturbing motor activity, while increased clustering coefficient may influence the movement disorder both a rest and during action. The relationship between the Co-SupM and PostC areas with the primary motor area in PD is variably reported in the literature [see (44) for a review, (45)]. Even if our observation cannot resolve every single interpretation, it may however suggest that interactions and local organization of these areas play a significant role in motor impairment and possibly be "relieved" by ViM lesions.

This study had some limitations deriving from the small sample size and a higher number of patients who maintained a positive outcome 1 year after MRgFUS treatment, while only a few patients had a relevant recurrence of Parkinson's symptoms. The slight number of unsuccessful MRgFUS treatments can be considered as positive result, but did not allow comparisons between groups with different prognosis. However, correlation analyses indicate a positive relationship between the evaluated network measure and the improvement maintained after 1 year of follow-up. This may suggest that the effort of identifying network changes may propose to verify in a more extensive case series of significant outcome-predicting factors.

Our results we obtained were rather clear, but obviously limited to not severe patients with prominently lateralized signs and dominant tremor. The validation of the parameters applied in a more complex series of patients with PD therefore requires further evaluations in order above all to confirm the possible predictive value of the effectiveness of the treatment.

5 Conclusion

Our data suggest that the higher cortico-cortical flow and pathological increased local connection between different nodes, revealed by the values of clustering coefficient, together with topographically disordered cortico-cortical flow and CMC may reveal

an extensive and disarranged cortical defect occurring during motor activity.

The observation that most of the changes in the evaluated measures correlate with the changes in the clinical score related to the active movement may also suggest that MRgFUS Vim thalamotomy may act outside the resting tremor on the more complex motor impairment occurring in PD patients.

Data availability statement

The data and MEG signals supporting the conclusions of this article will be made available by the authors on request.

Ethics statement

The studies involving humans were approved by Fondazione IRCCS Istituto Neurologico Carlo Besta, Milan, Italy. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

EV: Formal analysis, Investigation, Methodology, Validation, Writing – review & editing. FP: Conceptualization, Investigation, Methodology, Software, Validation, Writing – review & editing, Supervision. SF: Conceptualization, Formal analysis, Methodology, Supervision, Validation, Writing – original draft, Writing – review & editing. NG: Data curation, Investigation, Validation, Writing – review & editing, Methodology. RC: Data curation, Formal analysis, Validation, Writing – review & editing, Investigation. SR: Data curation, Validation, Writing – review & editing. DR: Data curation, Validation, Writing – review & editing. PL: Data curation, Resources, Validation, Writing – review & editing, Methodology. RE: Investigation, Project administration, Validation, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be considered as a potential conflict of interest.

The author(s) declared that they were an editorial board member of Frontiers, at the time of submission. This had no impact on the peer review process and the final decision.

Publisher's note

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The evolution of ventral intermediate nucleus targeting in MRI-guided focused ultrasound thalamotomy for essential tremor: an international multi-center evaluation

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Background: The ventral intermediate nucleus (VIM) is the premiere target in magnetic resonance-guided focused ultrasound (MRgFUS) thalamotomy for tremor; however, there is no consensus on the optimal coordinates for ablation. This study aims to ascertain the various international VIM targeting approaches (VIM-TA) and any evolution in practice.

Methods: International MRgFUS centers were invited to share VIM-TAs in 2019 and 2021. Analyses of any modification in practice and of anatomical markers and/or tractography in use were carried out. Each VIM-TA was mapped in relation to the mid-commissural point onto a 3D thalamic nucleus model created from the Schaltenbrand–Wahren atlas.

Results: Of the 39 centers invited, 30 participated across the study period, providing VIM-TAs from 26 centers in 2019 and 23 in 2021. The results are reported as percentages of the number of participating centers in that year. In 2019 and 2021, respectively, 96.2% ($n = 25$) and 95.7% ($n = 22$) of centers based their targeting on anatomical landmarks rather than tractography. Increased adoption of tractography in clinical practice and/or for research was noted, changing from 34.6% to 78.3%. There was a statistically significant change in VIM-TAs in the superior-inferior plane across the study period; the percentage of VIM-TAs positioned 2 mm above the intercommissural line (ICL) increased from 16.0% in 2019 to 40.9% in 2021 (WRST, $p < 0.05$). This position is mapped at the center of VIM on the 3D thalamic model created based on the Schaltenbrand–Wahren atlas. In contrast, the VIM-TA medial-lateral and anterior-posterior positions remained stable. In 2022, 63.3% of participating centers provided the rationale for their VIM-TAs and key demographics. The centers were more likely to target 2 mm above the ICL if they had increased experience (more than 100 treatments) and/or if they were North American.

Conclusion: Across the study period, FUS centers have evolved their VIM targeting superiorly to target the center of the VIM (2 mm above the ICL) and increased the adoption of tractography to aid VIM localization. This phenomenon

is observed across autonomous international centers, suggesting that it is a more optimal site for FUS thalamotomy in tremors.

KEYWORDS

magnetic resonance guided focused ultrasound (MRgFUS), essential tremor (ET), movement disorders, tremor, ventral intermediate nucleus (VIM), thalamotomy, stereotactic targeting, tractography

Introduction

The ventral intermediate nucleus (VIM) of the thalamus is currently established as the premiere target for magnetic resonance-guided focused ultrasound (FUS) thalamotomy in essential tremor (ET). Over the past decade, the efficacy of FUS VIM ablation has been proven in multiple international studies (1–3) and recent systematic reviews, which demonstrated pooled tremor suppression of 56.7%, 62.4%, and 61.5%, respectively (4–7). Although other tremor-specific targets such as the cerebellothalamic tract (8) or even a combination of targets such as the VIM with the posterior subthalamic area (PSA) (9, 10) have been explored, the VIM alone remains the most frequently used target in FUS treatment for ET (11, 12). Several alternative targets have been considered in Parkinson's disease (PD) (13–16), but the VIM remains the target of choice for FUS treatment of tremor-dominant PD (17). The success of VIM ablation can be readily seen with its global adoption and the growth in the number of FUS centers performing thalamotomy for tremors (18).

The VIM, a motor nucleus within the lateral thalamic subgroup of nuclei, is a proven tremor-sensitive nucleus within the cerebello-thalamo-cortical network (19, 20). In FUS thalamotomy, accurate targeting of the VIM is crucial to ensure adequate tremor suppression while avoiding the erroneous ablation of adjacent structures, risking motor and sensory adverse effects. The VIM is predominantly bordered anteriorly by the ventral oralis posterior (VOP), a motor nucleus in the pallidothalamocortical pathway (21, 22), and posteriorly by the ventralis caudalis (VC), a large sensory nucleus (21, 23). The medial border of the VIM is less well defined, but on the Schaltenbrand–Wahren (S-W) atlas (21), it includes the ventro-oralis internus, the lamella medialis interpolaris, and the nuclei centrales thalami. The VIM's lateral border is the nucleus reticularis, a thin strip of tissue separating the VIM from the internal capsule (IC), which contains the pyramidal tracts. On the S-W atlas, the superior border of VIM is predominantly formed by the nucleus zentrolateralis intermedius. The fasciculus interstitio-thalamicus, the zona incerta (ZI), and the prelemniscal radiation (RAPRL) form the inferior border of the VIM and are included on the coronal plates of the S-W atlas. The ZI and RAPRL are often considered together as the PSA. Although some centers deliberately target PSA, a cautious approach should also be taken to inferior lesioning as there is a risk of chorea (9, 10). Consideration of the posterior and lateral borders is also crucial in VIM targeting to minimize the risk of ablation of key adjacent structures and associated adverse sensory and motor effects.

Unfortunately, current clinical MRI scanners at 1.5 and 3 Tesla (T) cannot delineate the VIM on conventional MRI pulse sequences. Although post-processing techniques have allowed the demarcation of thalamic nuclei subgroups on 3T MRI (20), individual nuclei cannot be determined. Therefore, VIM targeting in FUS traditionally relies on anatomical landmarks to infer the VIM position. The key structures used are demonstrated across all brain cross-sectional imaging modalities and include the third ventricle and internal capsule (IC). The cerebrospinal fluid-filled third ventricle borders the thalamus medially. The IC is a large confluence of white matter tracts that, on CT and MRI, form a distinct lateral border to the thalamus, which itself is a large confluent region of gray matter. The anterior commissure (AC) and posterior commissures (PC) are relatively thin white matter tracts that cross the cerebral hemispheres, which can be visualized on specific MRI sequences, including the Fast Gray Matter Acquisition T1 Inversion Recovery (FGATIR) sequence (24) or the Magnetization Prepared RApid Gradient Echo sequence (MP-RAGE) (25). In the midline, the AC–PC line or intercommissural line (ICL) is an imaginary line joining these two structures and is widely used as an imaging plane and as the baseline for stereotactic neurosurgery. As the inferior border of the VIM lies close to the axial plane projected at the level of the ICL, it can readily be inferred on an MRI.

The traditional approach to VIM targeting in FUS thalamotomy utilizes the ICL to set the superior-inferior (SI) position with pre-determined measurements in anterior-posterior (AP) and medial-lateral (ML) positions along this trajectory. FUS treatment allows the target to be adjusted according to patient response, in sub-millimeter increments, before a permanent ablation is performed. This technique has been well described in the literature (26) and allows the tailoring of treatments to individual neuroanatomy. The most commonly published or "traditional" VIM targeting approach (VIM-TA) utilizes the following trajectories: (AP) 25% of ICL length, anterior to PC; (ML) 14–16 mm lateral; and (SI) on the ICL plane. However, as clinical experience grows, FUS centers naturally adapt their VIM-TA. For example, our centre's approach has evolved over 7 years of practice from the described traditional VIM-TA to (AP) 3–5 mm posterior to MCP; (ML) 3–5 mm medial to IC; and (SI) 2 mm above ICL in 2023. At this site, we achieve better tremor control with minimal adverse effects and are completing treatments in fewer sonications with a shorter procedural time. This learning from experience, or "evolution", will have occurred at every FUS center; however, there is currently no published data describing the various VIM-TAs used internationally, and an update is vital.

Diffusion tensor imaging (DTI) or "tractography" is an imaging technique that utilizes the anisotropic diffusion properties of water in the white matter tracts to create three-dimensional maps of neural pathways and provide information on directionality. As the VIM lies between several large white matter tracts, the medial

lemniscus, the pyramidal tract, and the dentatorubothalamic tract, some FUS centers use tractography to infer the VIM position (27–30). Tractography promises highly individualized VIM-TA; however, it is not yet universally adopted. Of note, tractography does not directly visualize the VIM, but an ultrahigh-field strength MRI at 7T can provide enough contrast between thalamic nuclei to delineate the VIM (31). Current clinical scanners operate at 1.5T and 3T; unfortunately, 7T MRIs are not readily available in healthcare institutions, so direct VIM visualization remains within the research space. DTI and ultrahigh-field MRI offer patient-specific targeting, and future developments in these and other advanced imaging techniques may lead to higher adoption.

Early FUS publications focused on the safety and efficacy of this novel treatment for tremor, with a paucity of data on the technique itself. With safety and efficacy established (1, 2), there has been a notable trend in scientific output from FUS centers with more detailed technical methodology, including closer reporting of their approach to VIM targeting (32, 33). There has also been further enquiry into improving FUS treatments from a technical perspective (34), including specific consideration of skull factors (29, 35–37), thermal dose and lesion size (38–41), and imaging aspects (42–45). However, there has not yet been a review or consensus on the optimum location for FUS VIM ablation. To establish this, an evaluation of VIM-TAs utilized internationally and documentation of the evolution of FUS centres' practice are the natural first step. Furthermore, sharing any such analysis based on clinical experience gained with the optimal FUS technique is vital to ensure improved tremor suppression and minimization of adverse effects for ET patients treated with FUS.

Aims

This article aims to ascertain the various international approaches to targeting the VIM (VIM-TA) in magnetic resonance-guided focused ultrasound (FUS) thalamotomy for essential tremor (ET) and consider how targeting has evolved internationally as experience develops.

Materials and methods

Between July 2019 and July 2021, all 39 MRgFUS centers from the Insightec Limited (Haifa, Israel) international FUS tremor database were invited to participate in this study and share their VIM targeting approach (VIM-TA). Each FUS center was contacted at least three times via email. Invitations included reassurance that participating FUS centres' contributions would be acknowledged in any subsequent academic output from this study, but individual VIM-TAs would remain anonymous. Where possible, the system operator (neurosurgeon and/or neuroradiologist) was contacted directly. At many centers, correspondence was first conducted through clinical or research administrators before reaching the appropriate clinician. The best efforts were made to ensure the system operator provided the VIM-TA where initial contact was via a third party. Written informed consent from the participants was not required to participate in this study in accordance with national legislation and institutional requirements. Ethical review and approval were not required for the study in accordance with the local legislation and institutional requirements.

Participants were invited to share their VIM-TA for 2019 and 2021 with open correspondence rather than a rigid questionnaire to encourage the sharing of information and discussion.

1. Please describe your approach to VIM targeting.
    - *If anatomical targeting is used, what landmarks and distances (in mm) are used?*
    - *If there is an alternative targeting method, please describe.*
2. Do you use tractography?

Where the VIM-TA was anatomical, coordinates were calculated with respect to the mid-commissural point (MCP) to allow 3D modeling and mapping graphically. Coordinates were determined in three planes, namely, anterior-posterior (AP), medial-lateral (ML), and superior-inferior (SI), with the MCP considered coordinate 0 in all three axes. Positive numbers were assigned to anterior, lateral, and superior movements. Negative numbers were assigned for medial, posterior, and inferior movements. This method was chosen to accommodate various ICL lengths. Where centers provided a range (mm) for a specific plane, the mid-point was taken.

Where tractography-based targeting was reported, technical details of the methodology were requested. Where tractography was used to complement anatomical-based targeting, the primary anatomical-targeting method was mapped.

VIM-TAs were mapped graphically and on a 3D model created from the S-W atlas (21). The model was created from Brain LXXVIII, Axial Plates 53–55. Images were stacked in MATLAB (R2021a, MathWorks Inc.) to obtain uniform resolution in three dimensions, and using the 3D slicer (v4.11.2021022), key thalamic nuclei were segmented, including VIM, VOP, and VC, and the model surfaces were smoothed. The model ICL length was scaled to a modern average of 27.8 mm (based on the last 30 MRgFUS patients at our center), and the model coordinates were scaled accordingly prior to mapping.

The results were first analyzed with regard to VIM-TA, whether anatomical and/or using tractography. Further analysis considered VIM-TA coordinates in relation to MCP, both graphically and within key nuclei on the 3D model. Finally, any change, trend, or evolution in VIM-TA across the study period was determined.

In 2022, all participating centers were invited to share further details on their experience with FUS thalamotomy, the rationale for their VIM-TA, and any change in practice. Further analysis of the centres' years of experience, number of treatments performed, and geography was conducted to determine whether any correlation to the trends in VIM-TA is ascertained.

Results

Across the study period, a total of 30 participants from the database of 39 centers participated (Table 1), with a response rate of 76.9%. Complete VIM-TA was reported by 26 centers for 2019 (Appendix 1), 23 centers for 2021 (Appendix 2), and 20 centers provided data for both years. For each year cohort (2019 and 2021), the results are provided as percentages of the

TABLE 1 List of participating FUS centers in alphabetical order (please note this does not correlate to center number).

Country	Participating MRgFUS centers (in Alphabetical Order)
Italy	Azienda Ospedaliera Universitaria Integrata Verona
USA	Brigham and Women's Hospital
Taiwan	Chang Bing Show Chwan Memorial Hospital
Taiwan	CMUH (China Medical University Hospital)
Italy	Fondazione IRCCS Istituto Neurologico Carlo Besta Milano
Spain	HM CINAC, Hospital HM Puerta del Sur
Japan	Hokuto Hospital
UK	Imperial College Healthcare NHS Trust
USA	Mayo Clinic
Canada	Montreal Neurological Institute and Hospital
USA	NYU Langone Health
USA	Ohio State University
USA	Penn Medicine
Israel	Rambam Medical Center
Japan	Sadamoto Hospital
Japan	Saito Yukokai Hospital
Israel	Sheba Medical Center
USA	Sperling Medical Center
Australia	St. Vincent's Hospital, Sydney
USA	Stanford University Hospital
USA	Swedish Hospital
USA	University of Maryland
USA	University of Utah
Italy	University Degli Studi Di Palermo
Switzerland	University Hospital Zurich
Germany	University of Bonn
Canada	University of Calgary
Italy	University of L'Aquila
Canada	University of Toronto
South Korea	Yonsei University College of Medicine

number of participating centers in that year. The majority of the centers replied with direct answers describing VIM-TA, but some provided presentation slides, unpublished data summaries, and published papers. Where appropriate, replies were clarified with responders directly before converting VIM-TAs to coordinates for mapping. Two centers were excluded from the coordinate analysis as complete VIM-TAs could not be determined.

The vast majority of FUS centers used anatomical VIM-TAs: 96.2% in 2019 ($n = 25$) and 95.7% in 2021 ($n = 22$), with only one center using primarily tractography-based VIM-TA. However, across the study period, more centers incorporated tractography in conjunction with or as an adjunct to their anatomical targeting (Figure 1). In 2019, only 30.7% were utilizing tractography in their clinical practice, and in 2021, this doubled to 60.8% (total groups T1–T3). Participating centers using tractography only for research increased more than four-fold across the study period, from only 3.8% in 2019 to 17.4% in 2021 (Group T-5). Furthermore, the percentage of centers not using tractography in any role decreased from 65.4% to 21.7%. The one center with a tractography-based VIM-TA shared its published papers, which included a well-described methodology (27, 28). As the S-W atlas does not delineate individual white matter tracts, this centre's VIM-TA was not mapped onto the 3D model.

All anatomical VIM-TAs were calculated in relation to the MCP (considering ICL length) prior to analysis. The distribution of anatomical VIM-TA coordinates in the AP, ML, and SI planes was tabulated and graphically demonstrated (Figures 2A–C). All VIM-TAs were mapped onto the axial and sagittal graphs (Figures 3A, B) and the 3D thalamic nucleic model (Figures 4A–C); full coordinates are listed in Appendices 1, 2.

Anterior-posterior plane

For both 2019 and 2021, the majority of centers targeted the VIM from −6 to −6.9 mm posterior to the MCP (Group AP-3), accounting for 72% of centers in 2019 ($n = 18$) and 68.2% of centers in 2021 ($n = 15$) (Figure 2A). Of note, the AP position was relatively fixed over the study period, with no statistically significant change noted on a Wilcoxon Signed Rank Test (WRST) ($p = 0.865$), although some centers diverged slightly along the ML and SI planes (Figures 3A, B).

Medial-lateral plane

The majority of centers targeted VIM between 11.0 and 14.9 mm lateral to the MCP (Groups ML-1 to ML-4), accounting for 88% of centers in 2019 ($n = 22$) and 90.9% of centers in 2021 ($n = 20$) (Figure 2B). For both years, 14.0–14.9 mm lateral to the MCP (Group ML-4) was the most common position (Figure 3B). The distribution of ML coordinates was stable across the study period, with no statistically significant change in WRST ($p = 0.779$).

Superior-inferior plane

Across the study period, there was a statistically significant superior migration in VIM targeting in the SI plane (Figures 2B, C). In 2019, there were only 16% of centers ($n = 4$) targeting 2 mm above the ICL; this increased to 40.9% of centers ($n = 9$) in 2021 (group SI-5) [WRST, $p = 0.046$ ($p < 0.05$)]. Conversely, 28% of centers ($n = 7$) targeted the ICL in 2019, and this decreased to 13.6% of centers ($n = 3$) in 2021. Of note, those who were already targeting at 2 mm did not move, suggesting that this location is viewed as the optimal tremor lesioning site. One center moved inferiorly (from 1.5 mm to ICL).

Group	DTI role	2019	2021
T-1	primary	3.80	4.30
T-2	conjuction	11.50	26.10
T-3	adjunct	15.40	30.40
T-4	research	3.80	17.40
T-5	no	65.40	21.70

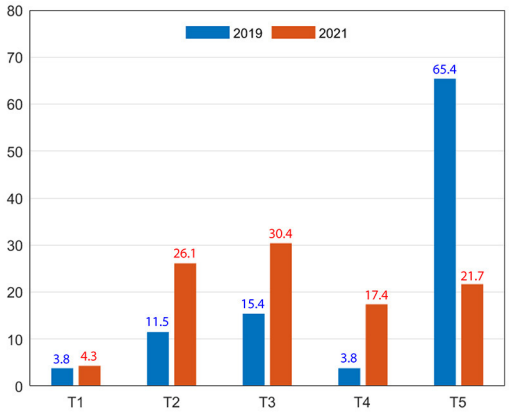
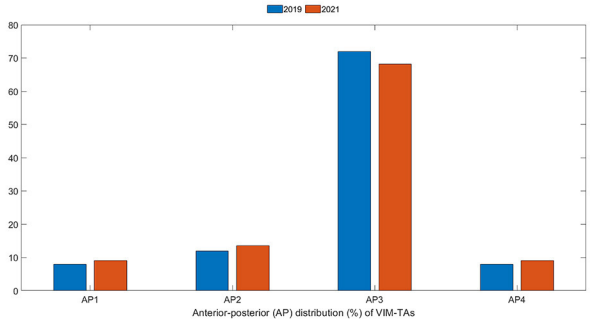


FIGURE 1
Use of tractography in FUS thalamotomy for tremor.

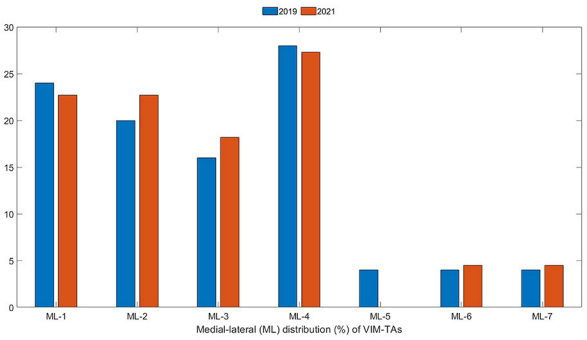
A

Group	AP to MCP	2019 %	2021 %
AP-1	-4.0 to -4.99	8.00	9.1
AP-2	-5.0 to -5.99	12.0	13.6
AP-3	-6.0 to -6.99	72.0	68.2
AP-4	-7.0 to -7.99	8.0	9.1



B

Group	ML to MCP	2019%	2021%
ML-1	11.0-11.99	24.0	22.7
ML-2	12.0-12.99	20.0	22.7
ML-3	13.0-13.99	16.0	18.2
ML-4	14.0-14.99	28.0	27.3
ML-5	15.0-15.99	4.0	0.0
ML-6	16.0-16.99	4.0	4.5
ML-7	>17	4.0	4.5



C

Group	SI to MCP	2019%	2021%
SI-1	0	28.0	13.6
SI-2	0.5	4.0	4.5
SI-3	1	24.0	22.7
SI-4	1.5	28.0	18.2
SI-5	2	16.0	40.9

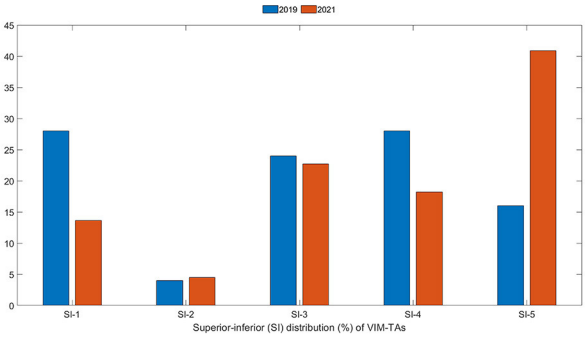


FIGURE 2
Distribution of VIM-TA coordinates in relation to the Midcommissural point (MCP) as a **(A)** Anterior-Posterior (AP) % distribution, **(B)** Medial-Lateral (ML) % distribution, and **(C)** Superior-Inferior (SI) % distribution.

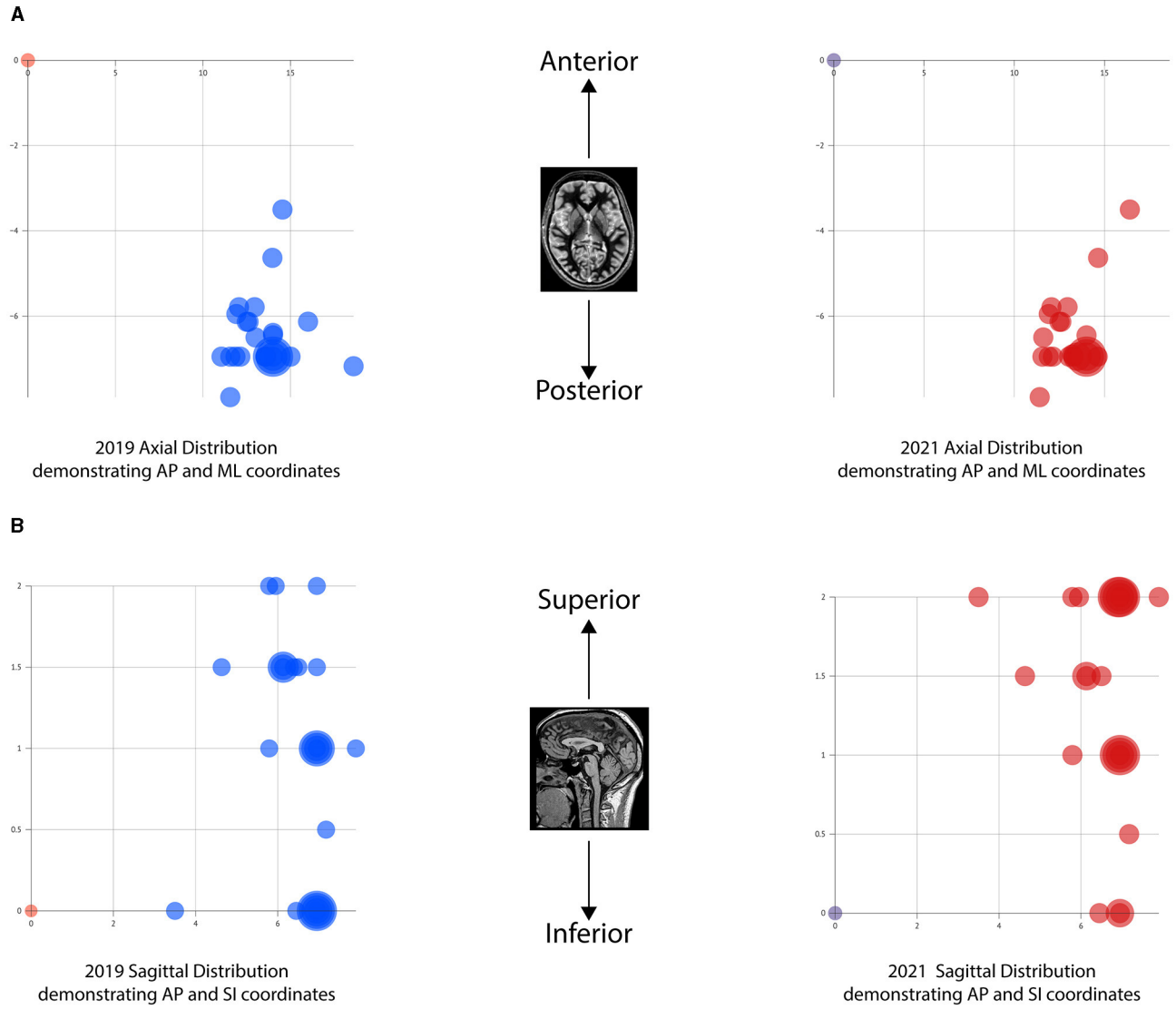


FIGURE 3
Graphical mapping of the VIM-TAs. **(A)** Axial graphs of VIM-TA coordinates in relation to midcommissural point, demonstrating anterior-posterior (AP) and medial-lateral (ML). **(B)** Sagittal graphs of VIM-TA coordinates in relation to midcommissural point, demonstrating anterior-posterior (AP) and superior-lateral (SI).

3D model

All FUS centers utilizing an anatomical VIM-TA were mapped onto a 3D model created from the S-W Brain LXXVIII (as described in methodology), whose VIM measures approximately 5 mm (AP) × 8 mm (ML) × 5.5 mm (SI) (17). The model demonstrates the non-uniform shape of the VIM, with smooth tapering inferiorly in both the AP and ML dimensions. The model includes the anterior VOP and the larger posterior VC nuclei. Of note, the size and shape of the thalamic nuclei modeled are specific to the S-W Brain LXXVIII. The VIM-TAs (Appendices 1, 2) were mapped onto the model in relation to MCP for 2019, 2021, and both years combined (Figure 4, Appendix 3).

On Brain LXXVIII, the most common AP position (Group AP-3), between −6 and −6.9 mm posterior to MCP, lies within the anterior VC. There are several centers that target more anteriorly to this position at the VIM/VC junction, but only two centers where model coordinates lie within VIM itself on Brain LXXVIII (AP-1). No VIM-TAs were modeled within the VOP. In the ML plane, the most common position (ML-4) lies within the medial aspect of the key nuclei; there were no laterally placed VIM-TAs to suggest encroachment on IC.

The superior trend for targeting in the SI plane, from the ICL to 2 mm above the ICL, is well demonstrated in the model (Figures 4A, B) by the number of centers moving from the inferior border of VIM (Group SI-1) to the middle of VIM (Group SI-5) across the study period. Given the inferior tapering of the VIM in the AP and ML planes, targeting at 2 mm above the ICL is shown to be more centrally placed within the VIM. The dark green dots represent our centre's VIM-TA (Imperial),

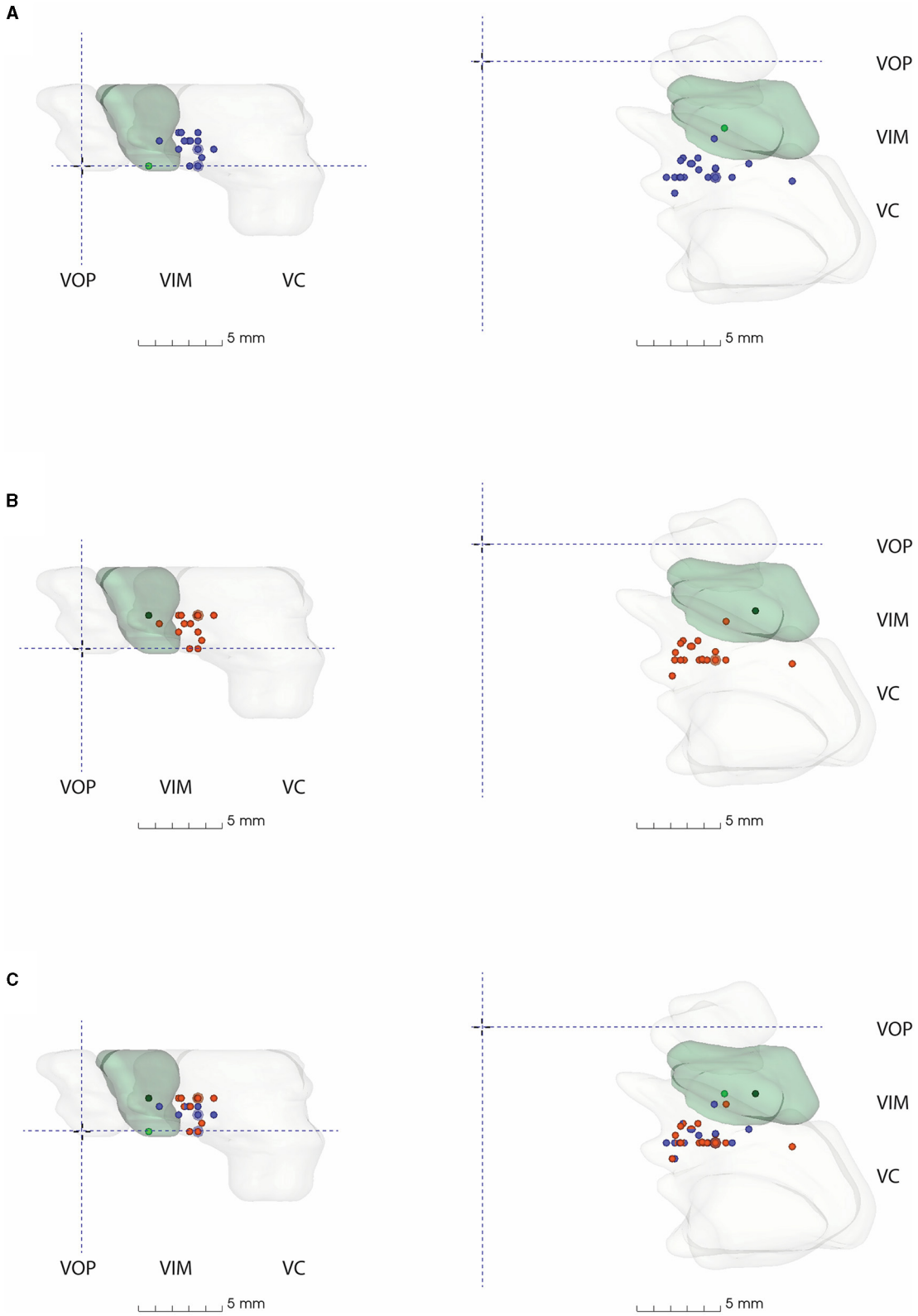


FIGURE 4
3D model of thalamic nuclei with participating centre's VIM-TAs mapped **(A)** 2019, **(B)** 2021, and **(C)** 2019 + 2021. MCP, Mid-commissural point; VOP, Ventral oralis posterior; VIM, Ventral Intermediate Nucleus; VC, Ventral Caudalis.

TABLE 2 FUS Center experience.

(A) FUS Center experience (to date 1st January 2022) in relation to SI co-ordinates.						
No. procedures	Total centers	On ICL	0.5 mm above	1 mm above	1.5 mm above	2 mm above
>100	7	28.8%	0%	0%	14.3%	57.1%
50–100	7	0%	0%	42.9%	14.3%	42.9%
<50	3	0%	33.3%	0	33.3%	33.3%

(B) FUS Center experience (to date 1st January 2022) and movement over the study period.		
No. procedures	Total centers	Movement
>100	7	0%
50–100	7	28.7%
<50	3	66.7%

which evolved from the ICL in 2019 to 2 mm above the ICL in 2021.

Discussion

Across the study period, the VIM-TAs evolved more superiorly to 2 mm above the ICL. This movement occurred independently across autonomous international FUS centers, with a combined experience exceeding 1,800 treatments. This change developed as experience accrued, presumably reflecting the view that this superior target provides better tremor suppression and/or minimizes adverse effects. The S-W 3D model also supports this concept, demonstrating the natural inferior tapering of VIM in the AP and ML planes (Figure 4). As VIM-TAs at 2 mm above the ICL lie more centrally within the VIM, sonications here will ablate more VIM tissue than at the ICL. Interestingly, centers with the least experience were most likely to move their VIM-TA across the study period, suggesting that the evolution of VIM-TAs tends to occur within the first 100 FUS treatments (Table 2B).

In 2022, 63.3% of participating centers ($n = 19$) provided the rationale for their VIM-TAs and key demographics, including the number of treatments performed (to date, 1 January 2022); a detailed analysis of this data is provided in Appendix 5. In summary, in 2021, the centers were more likely to target 2 mm above the ICL if they had increased experience (more than 100 treatments) (Table 2A) and/or if they were North American (rather than European or Asian) (Table 3, Figure 5). The reported rationales for VIM-TAs (Table 4, Appendix 4) included improved tremor suppression and a reduction in adverse effects or safety. Some centers reported that their VIM-TAs were influenced by their prior experience with deep brain stimulation (DBS) or gamma knife (GK). Others discussed the size, shape, and risk of cranial-caudal extension of the FUS sonication spot. Many centers reported that moving superiorly allowed them to perform a second, more inferior lesion in the same FUS procedure (which is also the practice at our centre at Imperial). The solitary center that moved inferiorly from 2019 to 2021 reported in their rationale high sensory adverse effects and a possible second ablation below ICL (Table 4, Appendices 4, 5). Interestingly, of the three centers targeting ICL who provided their rationale, all reported performing a second target (in the same FUS procedure) if tremor suppression was inadequate, either superior or inferior to ICL (Table 4B). Although these findings are of interest, not all participating centers provided a rationale for their VIM-TA, reducing the significance of these summations, and thus, clinical conclusions can only be drawn to a limited extent.

Tractography

Although the vast majority of the centers used anatomical VIM-TAs (96.2% in 2019; 95.7% in 2021), there was an increase in the adoption of tractography in clinical practice as an adjunct or in conjunction with anatomical targeting from 26.9% in 2019 to 56.5% in 2021 (Figure 1). Many centers reported specific challenges in incorporating tractography into their practice, including being time-consuming with mixed reliability, requiring specific software and expertise, and having difficulty integrating it with the current FUS systems. Some centers only utilized tractography retrospectively to review challenging cases; however, many centers reported its potential benefits and/or a desire to use tractography when it became more reliable and easier to incorporate. Future developments in DTI and/or other imaging techniques may change the preferred choice between anatomical and tractography-based VIM-TA. Future advanced imaging may allow precise target planning, for example, by combining DTI with high-field strength MRI 7T, which allows direct visualization of individual thalamic nuclei anatomy.

Targeting vs. clinical outcomes (tremor suppression/adverse effects)

There is an ongoing debate on the classification and functional anatomy of thalamic nuclei (46), and this study reveals several interesting findings, specifically the 3D modeling of S-W Brain LXXVIII (Figure 4). Of note, it was beyond the scope of this study to collate technical data on energy delivered, ablative spot size, and clinical outcomes. Thus, analyses of final ablation locations and clinical outcomes, including adverse effects, were not performed.

1. Targeting in the traditional AP location (25% of ICL, anterior to PC) is demonstrated on the 3D model to lie within the anterior VC, which is understood to be a sensory nucleus, yet multiple

TABLE 3 FUS center regional demographics.

(A) 2019 Regional VIM-TA SI co-ordinate distribution (mm above ICL).						
Center geography	Number of centers	0.0 mm	0.5 mm	1 mm above	1.5 mm above	2 mm above
R-1	10	30%	0%	40%	10%	20%
R-2	8	25%	0%	25%	25%	25%
R-3	1	100%	0%	0%	0%	0%
R-4	6	16.7%	16.7%	0%	66.7%	0%
(B) 2021 Regional VIM-TA SI co-ordinate distribution (mm above ICL).						
Center geography	Number of centers	0.0 mm	0.5 mm	1 mm	1.5 mm	2 mm
R-1	9	0%	0%	33.3%	0%	66.7%
R-2	7	28.6%	0%	28.6%	14.3%	28.6%
R-3	0	0%	0%	0%	0%	0%
R-4	6	16.7%	16.7%	0%	50%	16.7%

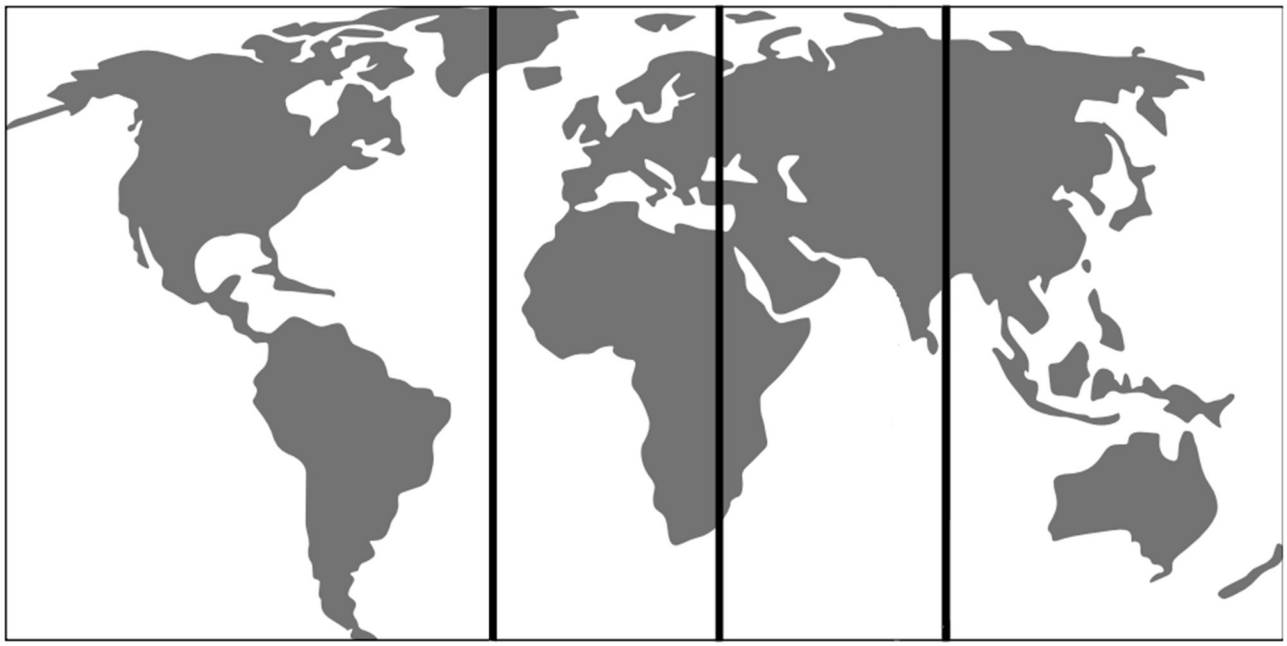


FIGURE 5
World Map demonstrating the 4 regions used for geographical analysis of VIM-TAs. R1 = Region 1 which includes North American centers, R2 = Region 2 which includes European centers, R3 = Region 3 which includes West Asian centers, R4 = Region 4 which includes East Asian and Australian centers.

studies targeting at this location report good tremor suppression (4, 5). This finding can be explained by the size of the sonication spot created, typically approximately 3.9 mm (38), which would include the adjacent motor VIM and cause the reported tremor suppression. Interestingly, multiple studies that describe targeting based on the traditional method have reported high rates of paraesthesia; meta-analyses by Mohammed et al. and Giordano et al. observed 15.3% and 36.7% paraesthesia, respectively, which correlates with the 3D model findings (4, 5) demonstrating VIM-TAs in the anterior VC and at the VIM/VC junction. Given the ongoing discussion on the optimal AP position, the 3D model supports the suggestion that targeting anterior to the traditional location would avoid paraesthesia while achieving good tremor suppression (9).

2. Targeting in the traditional ML location (14–16 mm lateral to the ICL) has a comfortable margin from the IC. Therefore, sonication spot size should be considered when reviewing the reported 10.5% and 34.4% ataxia/gait disturbance reported in the aforementioned meta-analyses (4, 5, 9). Of note, the more modern "2–4 mm from IC" approach lies in a similar position to traditional VIM-TAs on 3D modeling. Although the 3D model did not include changes secondary to age-related brain

parenchymal atrophy (which can be observed in older ET patients who undergo FUS treatment), this was considered by many centers that reported their VIM-TAs with allowances for an enlarged third ventricle, providing coordinates from its lateral border rather than the MCP itself.

3. Targeting in the traditional SI location, on the ICL plane, is demonstrated on the 3D model to lie at the inferior border of VIM. The more modern VIM-TA, 2 mm above ICL, is demonstrated at the midpoint of VIM in the SI axis. Outcomes from this study show the international evolution of VIM-TAs to this location, where there is more VIM tissue. Interestingly, depending on sonication spot size, traditional VIM ablation at ICL may extend superiorly to mid-VIM or inferiorly to the posterior subthalamic area, which includes the zona incerta, a known tremor sensitive tissue targeted in DBS and FUS (9, 47).

Understanding the FUS lesion morphology

The results of this study should be considered in the historical context of stereotactic neurosurgical treatments for tremors. At centers with experience in radiofrequency ablation (RFA) or DBS, one would typically place the tip of the probe or electrode at the ICL to target the VIM. In RFA, the lesion created could be extended superiorly by withdrawing the probe, thereby ablating the more central portions of VIM. With DBS, this position sited the most effective electrode contacts at the center of VIM. However, in FUS, the sonication creates a sphere that expands concentrically around the target. Haray et al. have neatly demonstrated the average FUS lesion volume on immediate post-procedure MRI to be ∼3.9 mm (range 1.5–6.3 mm) (38), and Gallay et al. have described their FUS targeting accuracy between 0.29 and 0.44 mm in the three dimensions of space (48). Thus, if the FUS target coordinates are placed at the ICL, the average FUS lesion would extend beyond the inferior margins of the VIM into the PSA. As demonstrated by the 3D model in this study, moving the VIM-TA to 2 mm above the ICL corresponds to a more centrally placed lesion within the VIM and, equally importantly, creates a lesion that is almost completely confined to the borders of the VIM in the superior-inferior plane. Similarly, consideration of the AP and ML dimensions of VIM and appropriate placement of the target in these planes would ensure the lesion remains within all the borders of VIM. It is important to note that ensuring a controlled, uniform expansion of the sonication spot and the ablation confined to the VIM is crucial to reducing adverse effects in FUS tremor treatments. Thus, as well as locating the best targeting coordinates, further research on optimizing sonication parameters, controlling the accumulated thermal dose, and sonication spot size and shape is required before FUS thalamotomy can be truly optimized.

Limitations

COVID-19

There are several limitations to this study. First, the COVID-19 pandemic interrupted normal medical practice, including FUS treatments, across the world (49, 50), disrupting the experience and, therefore, the evolution of VIM-TAs. As global experience develops, it would be interesting to ascertain any further trends in VIM-TAs.

The Schaltenbrand-Wahren atlas 3D model

The accuracy of the 3D thalamic nucleus model relies on the accuracy of Brain LXXVIII from the S-W atlas (17, 34). It is important to consider that any model created from one person's brain cannot be representative of all demographics. Less information is provided about LXXVIII beyond its own demographics of a 40-year-old woman. Of note, its AC-PC length is 23 mm, which is short compared to modern brains (35); thus, the model was scaled accordingly, as described in the methodology. There are a number of brain dissections in the S-W atlas, and the VIM itself was delineated into two further dissections, one conducted in the sagittal plane and one in the coronal plane. However, as other key structures required for VIM-TA mapping were not delineated in those dissections (either VOP or MCP), the axially dissected Brain LXXVIII was chosen for the 3D model. Previous studies have demonstrated the variability in VIM size and shape within the different dissections of the S-W atlas (36), further suggesting that a variation in individual neuroanatomy should be considered in modeling.

For the macroscopic dissection of axial brain LXXVIII, the authors of the S-W model performed the dissection in Reid's plane, which differs from the AC-PC plane used for the atlas's individual plate dissections and that used in modern MRI (51). For this study, to account for various ICL lengths, all VIM-TAs were mapped in relation to MCP in the AC-PC plane. However, given the central location of the thalamus, any discrepancy between macroscopic Reid's plane and microscopic dissections in the AC-PC plane is minimal and unlikely to affect the model or VIM-TA mapping.

Debate on thalamic nucleic classification

There is a historical lack of consensus on thalamic nuclei classification with implications for the nomenclature of tremor targets in FUS and stereotactic neurosurgery. Although modern neurosurgery favors the Hassler classification (based on the S-W atlas), there remains considerable debate, as described by Mai et al. (46). Future studies could explore VIM-TAs mapped on other established classification systems, such as Morel's (46, 52, 53), or on individualized patient imaging, as 7T MRI allows direct VIM visualization (31). Following this, highly individualized functional thalamic neuroanatomy maps could be modeled, which when correlated with several key technical factors (including initial VIM-TA position, final VIM ablation position, sonication spot size, and clinical outcomes) would be of great value in identifying the optimal coordinates for FUS tremor treatment in ET. Recent studies have performed retrospective analyses of FUS-treated VIM positions with interesting results (54, 55); however, further research is required, including prospective studies and analyses that consider individual 3D thalamic neuroanatomy alongside tractography to better understand the optimal VIM-TA.

TABLE 4 FUS centers rationale for 2021 VIM-TA.

(A) Table of FUS centers with rationale.		
Center Number	SI coordinate 2021	Rationale
1	2 mm	1 + 2 + 5
4	2 mm	2
10	2 mm	1 + 2 + 5
12	2 mm	2
13	2 mm	4
14	2 mm	2 + 5
15	2 mm	1 + 5
26	2 mm	1 + 2
28	2 mm	1 + 2 + 3 + 5
27	1.5 mm **moved to 2mm in 2022 for safety*	2
19	1.5 mm	4 + 5 (avoid the lesion extending below AC-PC.)
21	1.5 mm	1 + 3
5	1 mm	5 (target higher (2 mm) for 2nd side)
22	1 mm	1
23	1 mm	2 + 4 + 5
20	0.5 mm	1
8	0 mm	1 + 2 + 3 + 5
9	0 mm	1 + 3
17	0 mm	1 + 2 + 3 + 4

Rationale categories:
1, improved tremor suppression.
2, reduce adverse effects/safety.
3, to allow a second target.
4, based on previous neurosurgical experience (DBS/GK).
5, other.

(B) FUS centers rationale with VIM-TA 2021 SI co-ordinate distribution (mm above ICL).						
2021 SI coordinates	Total center number	Rationale category				
		1	2	3	4	5
0 mm	3	100%	66.7%	100%	33.3%	33.3%
0.5 mm	1	100%	0%	0%	0.%	0%
1 mm	3	33.3%	33.3%	0%	33.3%	66.7%
1.5 mm	3	33.3%	33.3%	33.3%	33.3%	33.3%
2 mm	9	55.6%	77.8%	11.1%	11.1%	55.6%

1, improved tremor suppression.
2, reduce adverse effects/safety.
3, to allow a second target.
4, based on previous neurosurgical experience (DBS/GK).
5, other.

Conclusion

This study demonstrates that anatomical-based targeting of VIM is the most widely utilized methodology internationally for FUS thalamotomy despite recent advances in tractography. Over the study period, there was a statistically significant superior movement to target the VIM 2 mm above the intercommissural line. This superior evolution of VIM targeting has occurred independently across autonomous international centers, suggesting that it is an optimized site for FUS thalamotomy in the treatment of tremors.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary material, further inquiries can be directed to the corresponding author.

Author contributions

AJ: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Resources, Supervision, Validation, Visualization, Writing—original draft, Writing—review & editing. SA: Data curation, Formal analysis, Investigation, Methodology, Visualization, Writing—review & editing. NY: Conceptualization, Data curation, Formal analysis, Methodology, Software, Validation, Visualization, Writing—review & editing. JS: Conceptualization, Methodology, Software, Visualization, Writing—review & editing, Formal analysis. BJ: Supervision, Methodology, Validation, Writing—review & editing. DN: Resources, Supervision, Writing—review & editing, Formal analysis, Methodology. PB: Resources, Supervision, Writing—review & editing, Formal Analysis, Methodology, Validation. WG: Conceptualization, Investigation, Methodology, Project administration, Resources, Supervision, Validation, Writing—review & editing, Data curation, Formal analysis.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2024.1345873/full#supplementary-material

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Magnetic resonance-guided focused ultrasound thalamotomy for essential tremor patients with low skull density ratio: a case-matched analysis

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Introduction: Skull density ratio (SDR) is the ratio between the mean Hounsfield units of marrow and cortical bone, impacting energy transmission through the skull. Low SDR has been used as an exclusion criterion in major trials of magnetic resonance-guided focused ultrasound (MRgFUS) thalamotomy for medication-refractory essential tremor (ET). However, some studies have suggested that patients with low SDR can safely undergo MRgFUS with favorable outcomes. In this case-matched study, we aim to compare the characteristics, sonication parameters, lesion sizes, and clinical outcomes of patients with low SDR vs. patients with high SDR who underwent unilateral MRgFUS thalamotomy for medication-refractory ET.

Methods: Between March 2016 and April 2023, all patients ($n = 270$) who underwent unilateral MRgFUS thalamotomy for medication-refractory ET at a single institution were classified as low SDR (<0.40) and high SDR (≥0.40). All clinical and radiological data was prospectively collected and retrospectively analyzed using non-case-matched and 1:1 case-matched methodology.

Results: Thirty-one patients had low SDR, and 239 patients had high SDR. Fifty-six patients (28 in each cohort) were included in 1:1 case-matched analysis. There were no significant differences in baseline characteristics between the two groups in both non-case-matched and 1:1 case-matched analyses. In both analyses, compared to patients with high SDR, patients with low SDR required a significantly higher maximum sonication power, energy, and duration, and reached a lower maximum temperature with smaller lesion volumes. In the non-case-matched and case-matched analyses, low SDR patients did not have significantly less tremor control at any postoperative timepoints. However, there was a higher chance of procedure failure in the low SDR group with three patients not obtaining an appropriately sized lesion. In both analyses, imbalance was observed more often in high SDR patients on postoperative day 1 and month 3.

Discussion: ET patients with SDR <0.40 can be safely and effectively treated with MRgFUS, though there may be higher rates of treatment failure and intraoperative discomfort.

KEYWORDS

focused ultrasound, thalamotomy, essential tremor, skull density ratio, case match

1 Introduction

Magnetic resonance-guided focused ultrasound (MRgFUS) thalamotomy is an FDA-approved, minimally invasive therapy for the treatment of medication refractory Essential Tremor (ET) (1, 2). With MRgFUS thalamotomy, high-intensity ultrasound beams are focused on the ventralis intermedius nucleus (VIM), creating a thermal lesion that has been shown to reduce pathological tremors (3). In the pivotal, randomized, sham-controlled trial that led to FDA-approval of MRgFUS thalamotomy for ET, hand tremor was improved by 47% at 3 months, and clinical benefits were sustained at 5 years with no progressive or delayed complications (4–6). Patient outcomes with MRgFUS have continued to improve in more recent trials (7).

Among several preoperative criteria used to select patients for MRgFUS, skull density ratio (SDR) has been one of the most widely applied and debated (8). SDR is defined as the ratio between the mean values (in Hounsfield units) of marrow and cortical bone as measured by preoperative computed tomography (CT) scans (9). Lower SDR has been postulated to interfere with transcranial energy transmission via greater attenuation and reflection of ultrasonic energy at the marrow/cortical bone interface (9). Indeed, clinical studies have shown that SDR affects energy delivery and efficiency (9, 10). Based in part on the inclusion criteria of the pivotal trial (4), the FDA has established an SDR of 0.45 (±0.05) or less as a contraindication for MRgFUS (1). While SDR is an important factor in determining technical feasibility of MRgFUS, some studies have demonstrated no significant associations between SDR and clinical outcomes at one year follow-up (8, 11–13). Additionally, while SDR may impact the ability to reach high maximum temperatures, multiple lower-temperature sonications have been demonstrated to reach a high enough accumulated thermal dose to create an appropriate lesion (14). Furthermore, patients with SDR <0.45 may represent 30–40% of ET patients who could potentially benefit from MRgFUS, especially East Asian patients who tend to have lower SDRs (15–17). The FDA's SDR cutoff of 0.45 (±0.05) may therefore exclude a significant proportion of patients who could benefit from an effective therapy with a growing number of indications (18).

A recent report by Vetkas et al. (19) analyzed differences in MRgFUS in patients with low SDR and high SDR, but very few patients had follow up of tremor scores and adverse events. In our large patient population, we aimed to better characterize these differences and complete a case-matched cohort analysis to more directly understand the effect of SDR on tremor outcomes. We report a study comparing the characteristics, sonication parameters, lesion sizes, and clinical outcomes of patients with low SDR vs. patients with high SDR and present one illustrative case.

2 Methods

This case-matched cohort study was designed to compare the clinical characteristics, sonication parameters, lesion size, and tremor outcomes of patients with low SDR vs. patients with high SDR. This study was conducted at a single center (Brigham and Women's Hospital, Boston, MA, United States) with local institutional review board approval.

2.1 Patient selection

Between March 2016 and April 2023, all patients ($n = 270$) who underwent unilateral MRgFUS thalamotomy for medication-refractory ET had their clinical and radiological data prospectively collected. All patients with an SDR < 0.40 were assigned to the low-SDR cohort ($n = 31$). For non-case-matched analyses, all remaining patients were assigned to the high-SDR cohort ($n = 239$). Patients who did not achieve a goal lesion of at least 4 mm ($n = 3$) were excluded from analyses of sonication parameters, tremor control, side effects, and lesion volume. For a supplemental analysis, patients were also grouped into low (< 0.40), medium (≥ 0.40, < 0.60), and high (≥ 0.60) SDR groups, and tremor control and sonication parameters between these three groups were compared. For case-matched analyses, we conducted a 1:1 matching between low-SDR and high-SDR cohorts with the following variables: age (within 2 years), sex, and date of procedure (within 7 months) ($n = 28$ in each cohort).

2.2 Prospective database

The following variables were prospectively collected for every patient: demographics (age, sex, handedness), disease characteristics (family history, tremor duration, baseline tremor scores), SDR, treatment laterality, presence of intraoperative side effects, sonication parameters (sonication number, maximum power, maximum energy, number of sonications with energy >5000 J, maximum sonication duration, maximum temperature), follow-up tremor scores, follow-up percent improvement in tremor scores relative to baseline scores, and adverse events (fatigue, weakness, dysarthria, dysgeusia, sensory changes including numbness and/or paresthesia, and imbalance).

Tremor scores were measured using the Fahn-Tolosa-Marin (FTM) scale (20). We report total FTM score, which is a composite score of the following categories with 0 to 4 points (no tremor – 0; slight tremor – 1; moderate tremor – 2; marked tremor – 3; severe tremor – 4) assigned to each category, yielding a maximum total score of 20: vocal tremor, head tremor, resting tremor of the affected limb, intention tremor of the affected limb, and postural tremor of the affected limb. We also report intention + posture FTM score, which combines 0-to-4-point scores for intention and postural tremors of the affected limb, yielding a maximum total score of 8. Tremor scores were recorded at baseline and postoperatively on day 1, 3 months, 1 year, and each annual follow-up thereafter. Adverse events were also documented at these follow-up timepoints. Not all patients had follow-up data at all timepoints. Only available data was included in analyses at each timepoint.

2.3 Procedure

The procedural workflow at our institution has been previously reported (21). In brief, all patients underwent preoperative CT scans to measure SDR. On the day of treatment, the patient's head was shaved, and a modified Cosman-Roberts Wells frame (Radionics, Inc.) was secured low enough on the patient's head to accommodate the silicone membrane associated with the ExAblate system. The patient was positioned on a 3T magnetic resonance imaging (MRI) table (GE Medical Systems) and connected to the ExAblate 4000 MRgFUS

TABLE 1 Characteristics of low SDR vs. high SDR patients in the non-case-matched analysis.

Variable	Low SDR	High SDR	*p* value
Number of patients	31	239	
SDR (mean ± SD)	0.36 ± 0.02	0.51 ± 0.08	
Sex (females) (%)	41.9	31.8	1.0
Dominant hand (right) (%)	93.6	81.6	1.0
Duration of tremor (years) (mean ± SD)	23.8 ± 18.1	28.0 ± 18.5	0.292
Preop FTM score (total) (mean ± SD)	7.1 ± 2.0	7.0 ± 2.3	0.773
Preop FTM score (intention + posture) (mean ± SD)	5.9 ± 1.2	5.8 ± 1.2	0.680
Age at treatment (mean ± SD)	76.0 ± 8.1	74.7 ± 7.0	0.361
Treatment laterality (left) (%)	83.9	78.7	1.0
Intraoperative side effects (%)	6.5	9.2	1.0
3 month postop FTM score (intention + posture) (mean ± SD)	0.6 ± 1.1 ($n = 19$)	0.4 ± 1.0 ($n = 176$)	0.30
1 year postop FTM score (intention + posture) (mean ± SD)	0.9 ± 2.0 ($n = 15$)	0.8 ± 1.5 ($n = 156$)	0.73

Continuous variables were analyzed with independent *t*-tests, while categorical variables were analyzed with Chi-squared tests. Significance was set at $p < 0.05$.

hemispheric transducer operating at 650 Hz (InSightec, Inc.). The space between the patient's head and the transducer was then filled with cooled, degassed water. Baseline MRI sequences were obtained to assist with indirect targeting via standardized stereotactic coordinates and anatomical landmarks. Initial target coordinates for the VIM were set at 25% of the anterior commissure-posterior commissure (AC-PC) distance anterior to the PC, 1.5–2 mm superior to the AC-PC plane, and 14 mm lateral to the midline or 11 mm lateral to the wall of the third ventricle. Low-energy test sonications were delivered under MR thermometry guidance to confirm appropriate alignment. With confirmed targeting, high-energy sonications were delivered sequentially to a maximum temperature goal of 55–60°C. Clinical exams were conducted after each treatment to monitor for side effects and tremor improvement.

2.4 Lesion analysis

Thin-cut (2 mm) axial and coronal T2-weighted MRI slices were obtained within 24 h postoperatively. Lesions were manually segmented in 3D slicer.[1] A lesion was defined as combined Wintermark zones 1 and 2, which represent coagulative necrosis and cytotoxic edema, respectively (22). Segmented lesion volume data was analyzed in MATLAB 2022a (The MathWorks, Inc., Natick, Massachusetts, United States). Two patients did not have a T2-weighted MRI at 24 h and were therefore excluded from volumetric analyses.

2.5 Statistical analysis

Statistical analyses were conducted within Microsoft Excel (Microsoft Corporation, Redmond, WA), and Python version 3 (Python Software Foundation, Fredericksburg, VA). Continuous variables were reported as mean (± SD) or median (range) and were analyzed with independent t-tests, while categorical variables were analyzed with Chi-squared tests. Statistical significance was set at $p < 0.05$.

3 Results

3.1 Non-case-matched analysis

Overall, thirty-one patients had low SDR (i.e., SDR < 0.40), and two hundred and thirty-nine patients had high SDR. Median (range) SDRs in the low-SDR and high-SDR groups were 0.36 (0.32–0.39) and 0.49 (0.40–0.76), respectively. There were no significant differences between the two groups in the following characteristics: sex, handedness, duration of tremor, total preoperative FTM score, intention + posture preoperative FTM score, age at treatment, treatment laterality, and rate of intraoperative side effects (Table 1).

Except for number of treatment sonications with energy >5000 J, all other sonication parameters, including sonication number, maximum power, maximum energy, maximum duration, and maximum temperature, differed significantly between low-SDR and high-SDR cohorts (Figure 1). Patients with low SDR required a lower sonication number ($p < 0.05$) and a higher maximum power ($p < 0.001$), energy ($p < 0.001$), and duration ($p < 0.001$), and reached a lower maximum temperature ($p < 0.001$). There was a significant difference in the mean lesion volumes (± SD) with low-SDR patients demonstrating a smaller lesion volume (302.5 ± 150.4 mm^3, $n = 28$) than high-SDR patients (435.8 ± 185.9 mm^3, $n = 237$) ($p = 0.0003$).

Although patients with low SDR tended to have lower tremor control at all timepoints, there were no significant differences in the absolute intention + posture FTM scores and % improvement in intention + posture FTM scores relative to baseline between low-SDR and high-SDR patients (Figures 2, 3). Regarding adverse events, there were significant differences between low-SDR and high-SDR cohorts in postoperative day 1 imbalance (low-SDR: 32.1%; high-SDR: 66.0%; $p = 0.002$) and postoperative month 3 imbalance (low-SDR: 5.6%; high-SDR: 31.8%; $p = 0.04$) (Table 2).

1 https://www.slicer.org

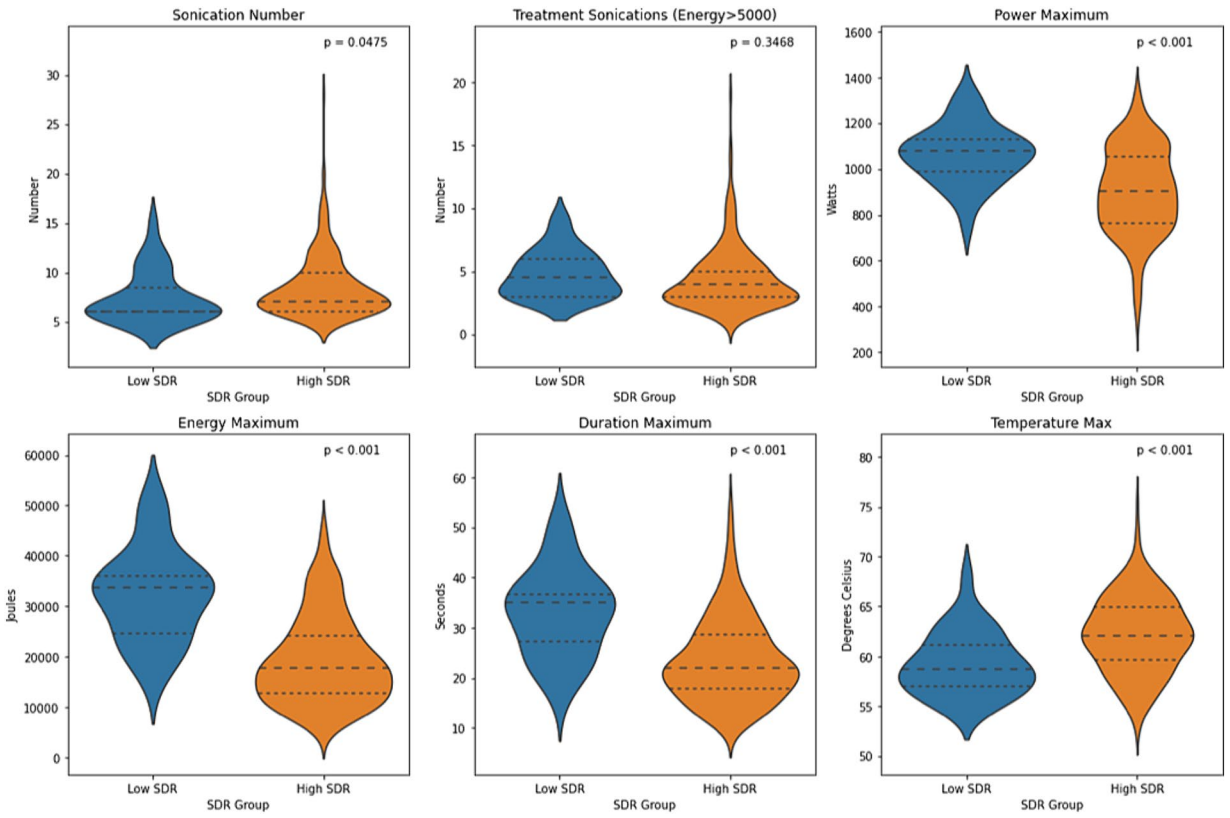

FIGURE 1
Violin plots of sonication number, treatment sonications with energy >5000 J, mean maximum power, mean maximum energy, mean maximum sonication duration, and mean maximum temperature between low-SDR ($n = 28$) and high-SDR ($n = 239$) cohorts. Continuous variables were analyzed with independent t-tests. Significance set at $p < 0.05$. SDR: skull density ratio.

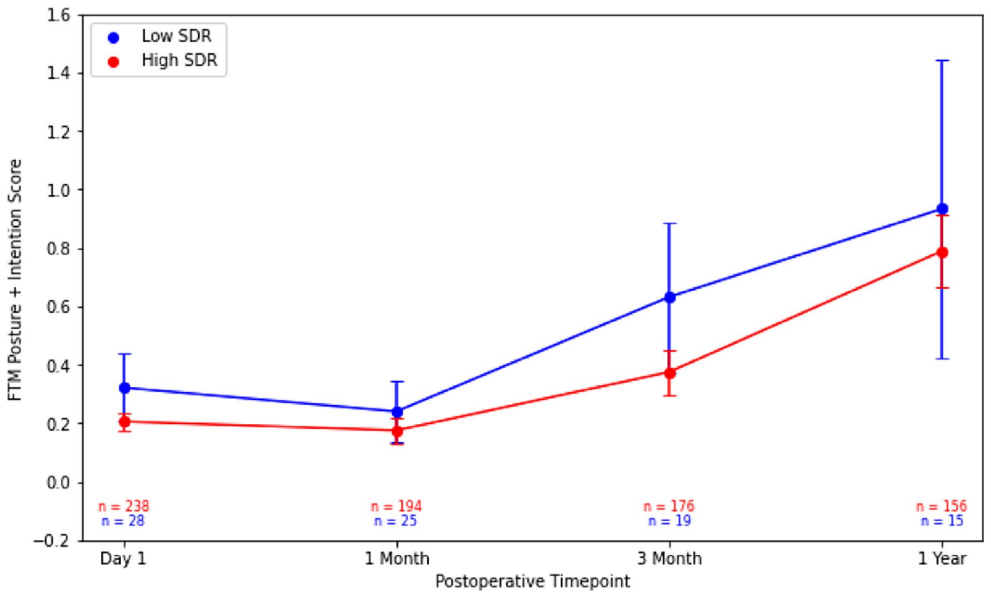

FIGURE 2
Post-operative Fahn-Tolosa-Marin (FTM) intention + posture scores over time after MRgFUS for essential tremor comparing all patients with low SDR ($n = 28$) to all patients with high SDR ($n = 239$). Continuous variables were analyzed with independent t-tests. Significance set at $p < 0.05$. SDR: skull density ratio.

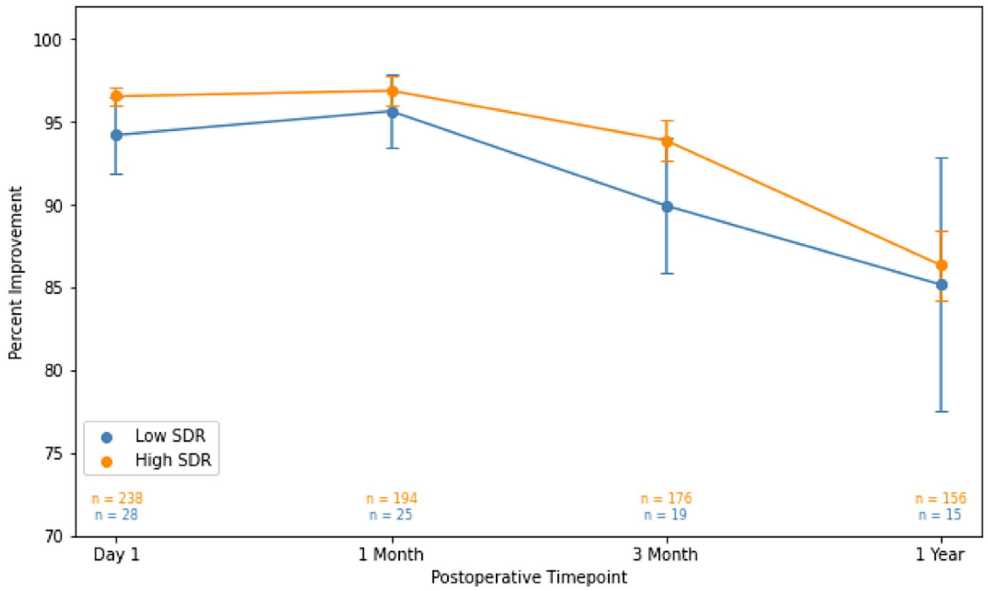

FIGURE 3
Percent improvement in essential tremor (intention + posture FTM scores) for patients at various timepoints after MRgFUS for essential tremor comparing all patients with low SDR ($n = 28$) to all patients with high SDR ($n = 239$).Populations compared using independent t-tests. Significance set at $p < 0.05$. SDR: skull density ratio.

TABLE 2 Side effects over time after MRgFUS for essential tremor comparing all patients with low SDR ($n = 28$) to patients with high SDR ($n = 239$).

	%	Overall	Weakness	Sensory	Dysarthria	Imbalance	Dysmetria/ Discoordination	Dysgeusia
Day 1	Low SDR ($n = 28$)	57.1	3.6	25.0	7.1	32.1	3.6	3.6
	High SDR ($n = 238$)	76.9	11.3	26.1	16.8	66.0	15.1	2.1
	p-value	0.030	0.244	0.700	0.180	0.002	0.104	1.000
1 Month	Low SDR ($n = 25$)	88.0	4.0	32.0	8.0	64.0	12.0	24.0
	High SDR ($n = 194$)	86.1	17.0	32.5	15.5	57.2	31.4	13.4
	p-value	1.00	0.146	1.000	0.448	0.836	0.062	0.309
3 Months	Low SDR ($n = 18$)	38.9	0	22.2	0	5.6	5.6	11.1
	High SDR ($n = 176$)	60.2	6.2	27.8	4.5	31.8	14.8	10.8
	p-value	0.134	0.577	0.817	0.763	0.040	0.472	1.000
1 Year	Low SDR ($n = 15$)	20.0	0	6.7	0	6.7	13.3	0
	High SDR ($n = 156$)	42.3	3.8	15.4	4.5	18.6	10.3	7.1
	p-value	0.160	0.969	0.596	0.876	0.421	1.000	0.608

Categorical variables were analyzed with Chi-squared tests. Significance was set at $p < 0.05$.

An analysis comparing patients with low (< 0.40), medium (≥ 0.40, < 0.60), and high (≥ 0.60) SDR showed that all of the differences in sonication parameters are graded (Supplementary Figure S1). When looking at tremor control, patients with medium and high SDR had extremely similar outcomes (Supplementary Figure S2). These groups both tended to have better percent improvement than those with low SDR, but there were no statistically significant differences.

3.2 Case-matched analysis

The low-SDR and high-SDR case-matched cohorts included twenty-eight patients each. Median (range) SDR in the low-SDR and high-SDR groups were 0.36 (0.32–0.39) and 0.48 (0.41–0.67), respectively. There were no significant differences between the two groups in the following characteristics: sex, handedness, duration of tremor, total preoperative FTM score, intention + posture preoperative FTM score, age at treatment, treatment laterality, and rate of intraoperative side effects (Table 3).

Except for sonication number and number of treatment sonications with energy >5000 J, all other sonication parameters, including maximum power, maximum energy, maximum duration, and maximum temperature, differed significantly between low-SDR and high-SDR cohorts (Figure 4). Patients with low SDR required a higher maximum power ($p < 0.001$), energy ($p < 0.001$), and duration ($p = 0.001$), and reached a lower maximum temperature ($p = 0.002$). There was a significant difference in the mean lesion volumes (± SD) between low-SDR patients (293.7 ± 153.7 mm^3, $n = 28$) and high-SDR patients (433.7 ± 265.8 mm^3, $n = 28$) ($p = 0.02$).

Absolute intention + posture FTM scores between low-SDR and high-SDR cohorts were not significantly different at every follow-up time point (Figure 5). Percent improvements in intention + posture FTM scores relative to baseline preoperative scores between low-SDR and high-SDR cohorts were also not significantly different at every follow-up time point (Figure 6). Regarding adverse events, there were significant differences between low-SDR and high-SDR cohorts in postoperative day 1 imbalance (low-SDR: 29.6%; high-SDR: 63.0%; $n = 27$; $p = 0.03$) and postoperative month 3 imbalance (low-SDR: 0%; high-SDR: 33.3%; $n = 15$; $p = 0.05$).

3.3 Illustrative case

A 74-year-old right-handed female presented with essential tremor, diagnosed 30 years prior. On presentation, she reported difficulty with buttons, make-up, writing, and inability to use a keyboard. At the time of presentation, she stated she no longer ate in public. She had tried a variety of medications but still had persistent tremor. She was on propranolol, which was initially very helpful when she started it 20 years prior but had lost most of its effect despite high dosing. On exam, she had full strength and normal gait with no evidence of bradykinesia or increased tone. She had mild head and vocal tremor with no rest tremor, as well as a moderate postural tremor (right greater than left) with an inability to draw a spiral or write legibly (rated head 1/4, vocal 1/4, postural 2/4, intentional 4/4). CT revealed an SDR of 0.33. After a discussion on the implications of her low SDR, she agreed to proceed with left-sided MRgFUS thalamotomy for treatment of right-sided tremor.

During the procedure, other than severe headache, no complications ensued. She had complete tremor abolition immediately after the procedure. At day 1, she had continued abolition of tremor in the right hand as well as improved vocal tremor (from 1/4 to 0/4) with no side effects. At 1 week, she maintained tremor response, but had a slightly unsteady gait and some fatigue. At 1 month, her fatigue resolved, and her gait was almost completely back to normal. At most recent follow-up of 1 year, she continued to demonstrate no tremor in the right hand with improvement in vocal tremor, and she felt her side effects had completely resolved.

4 Discussion

Overall, in this large single-center analysis, unilateral MRgFUS thalamotomy was feasible and effective in patients with SDR <0.40. There were some important differences to consider between patients with low and high SDR, including some significant differences in sonication parameters, lesion volumes, and side effects. While patients with low SDR had slightly lower tremor control, there was no significant difference at any timepoint. In the case-matched analysis, patients with high and low SDR showed similar tremor outcomes, although the patient populations were smaller.

The overall analysis showed that patients with low SDR required greater maximum power, energy, and duration and reached lower maximum temperature. This has been previously demonstrated, as patients with lower SDR have lower heating efficiency (8–11, 21, 23,

TABLE 3 Characteristics of low SDR vs. high SDR patients in the case-matched analysis.

Variable	Low SDR	High SDR	*p* value
Number of patients	28	28	
SDR (mean ± SD)	0.36 ± 0.02	0.50 ± 0.06	
Sex (females) (%)	42.9	42.9	1.0
Dominant hand (right) (%)	89.3	82.1	1.0
Duration of tremor (years) (mean ± SD)	21.3 ± 16.7	27.9 ± 19.5	0.29
Preop FTM score (total) (mean ± SD)	6.89 ± 1.57	7.00 ± 2.52	0.85
Preop FTM score (intention + posture) (mean ± SD)	6.00 ± 1.28	5.82 ± 1.28	0.60
Age at treatment (mean ± SD)	74.4 ± 6.9	74.2 ± 6.6	0.92
Treatment laterality (left) (%)	78.6	75.0	1.0
Intraoperative side effects (%)	0.0	7.1	1.0
3 month postop FTM score (intention + posture) (mean ± SD)	0.4 ± 0.8 ($n = 15$)	0.8 ± 1.7 ($n = 15$)	0.42
1 year postop FTM score (intention + posture) (mean ± SD)	1.3 ± 2.4 ($n = 10$)	0.5 ± 1.1 ($n = 10$)	0.34

Continuous variables were analyzed with independent *t*-tests, while categorical variables were analyzed with Chi-squared tests. Significance was set at $p < 0.05$.

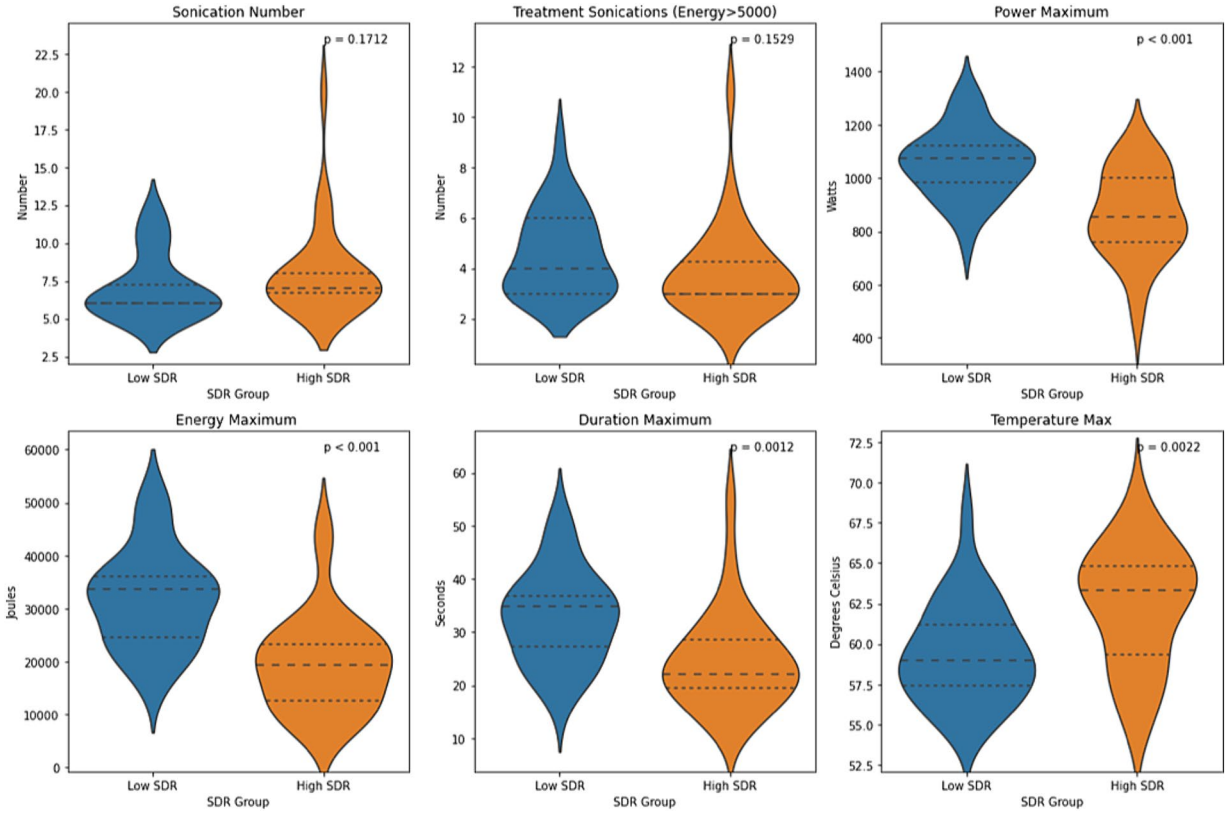

FIGURE 4
Violin plots of sonication number, treatment sonications with energy >5000 J, mean maximum power, mean maximum energy, mean maximum sonication duration, and mean maximum temperature between case-matched low-SDR ($n = 28$) and high-SDR ($n = 28$) cohorts. Continuous variables were analyzed with independent t-tests. Significance set at $p < 0.05$. SDR: skull density ratio.

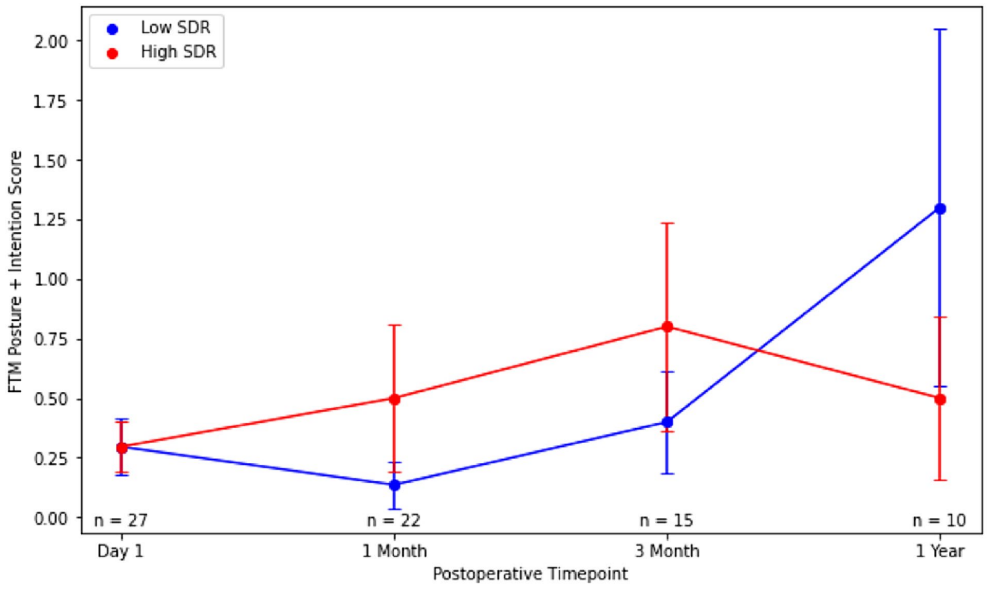

FIGURE 5
Post-operative Fahn-Tolosa-Marin (FTM) intention + posture scores over time after MRgFUS for essential tremor comparing case-matched cohorts with low SDR ($n = 28$) and high SDR ($n = 28$). Continuous variables were analyzed with independent t-tests. Significance set at $p < 0.05$. SDR: skull density ratio.

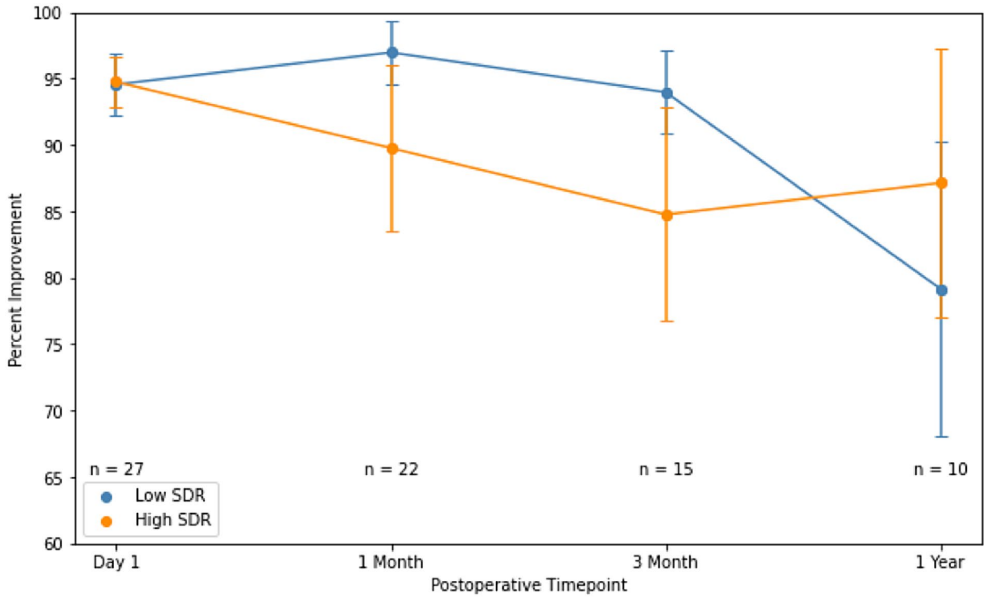

FIGURE 6
Percent improvement in essential tremor (intention + posture FTM scores) for patients at various timepoints after MRgFUS for essential tremor comparing case-matched cohorts with low SDR ($n = 28$) and high SDR ($n = 28$). Populations compared using independent t-tests. Significance set at $p < 0.05$. SDR: skull density ratio.

24). A potential cofounder is skull thickness, which has also been shown to impact ultrasound energy efficiency (25). Although increasing sonication power and duration for lower SDR patients has the potential to overheat the skin and skull (9), no significant adverse effects were seen with these parameter changes. Nevertheless, patients with low SDR can experience more side effects during treatment, such as severe headache or nausea and vomiting, which may prohibit successive sonications and prevent tremor from being completely abolished. Anecdotally, the surgeons here confirm that higher treatment parameters result in much higher discomfort during the procedure, although no formal analysis was performed.

Thalamotomy lesion volumes were significantly smaller in patients with lower SDR. This trend has been previously demonstrated by Vetkas et al. (19), although the difference was not significant in their population (150 ± 94 mm^3 vs. 131 ± 98 mm^3, $p = 0.401$). The lesions created in that study were much smaller than in our population, which may explain the difference. Reasonably sized lesions can be created in patients with low SDR, but this becomes more difficult as the lesion gets larger. We also found, as demonstrated in recent reports by D'Souza et al. (11) and Vetkas et al. (19), that low SDR patients had slightly lower side effect profiles. We also demonstrated no difference in long-term tremor control. The effect of SDR on tremor outcomes and side effects has been debated, but the significance here is likely a consequence of volume discrepancies (8, 11–13, 16, 26, 27). The case-matched analysis also supports that there are no major differences between the tremor outcomes in the two populations, although there were fewer patients in this analysis. Additionally, because population sizes diminished at later follow-up timepoints, tremor outcomes at long-term follow-up cannot be as confidently assessed.

The findings here may seem to suggest that contrary to current thinking, patients with lower SDR are better candidates given the insignificantly lower tremor control and lower side effect profile. However, it is important to consider that three patients with low SDR were excluded given the inability to create a satisfactory lesion. Patients with low SDR need to be counseled properly on the requirement for longer, potentially more uncomfortable sonications that still may result in treatment failure. If a lesion is able to be created, the outcomes will be more closely correlated with lesion size rather than SDR. Additionally, practitioners should be wary that it is easier to make a lesion that is too large in patients with higher SDR, potentially leading to a greater side effect profile.

The main limitation, as aforementioned, is the loss of patient follow-up at later timepoints. There was no clear explanation for the loss to follow up. Additionally, it is difficult to compare our population to other studies because MRgFUS technique, goal lesion size, and subjective follow-up measures can vary between institutions. Another limitation of our dataset is the omission of the FTM disability subscale, which measures the impact of tremor on activities of daily living and is therefore an informative marker of treatment success. Finally, although SDR is the main measure used to exclude patients from undergoing MRgFUS thalamotomy, the skull features that impact effective lesioning is likely more complex, including volume, shape, and presence of hyperostosis and skull thickness. Future studies should look into these characteristics to get a more comprehensive analysis of factors affecting lesioning.

5 Conclusion

In summary, ET patients with SDR <0.40 can be safely and effectively treated with MRgFUS. Sonication parameters need to be adjusted accordingly to create effective lesions, including higher energy, power, and duration. Maximum temperatures may be lower in patients with low SDR than in patients with high SDR resulting in smaller thalamotomy lesion volumes on postoperative MR imaging.

The smaller lesion volume may explain lower adverse event profiles, but tremor control appears to be comparable. As MRgFUS technology expands to include additional patient populations and indications, patients with low SDR can be considered for treatment but should be advised on potential treatment discomfort and slight outcome differences.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving humans were approved by Brigham and Women's Hospital Institutional Review Board. The studies were conducted in accordance with the local legislation and institutional requirements. Written informed consent for participation was not required from the participants or the participants' legal guardians/next of kin due to the retrospective nature of the study.

Author contributions

PN: Conceptualization, Investigation, Writing – review & editing, Writing – original draft, Methodology, Data curation. SB: Writing – review & editing, Writing – original draft, Visualization, Software, Methodology, Investigation, Formal Analysis, Data curation. MC: Writing – review & editing, Methodology, Data curation, Conceptualization. GC: Writing – review & editing, Supervision, Resources, Project administration, Conceptualization.

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Conflict of interest

GC is a consultant for InSightec.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2024.1370574/full#supplementary-material

SUPPLEMENTARY FIGURE S1
Violin plots of sonication number, treatment sonications with energy >5000 J, mean maximum power, mean maximum energy, mean maximum sonication duration, and mean maximum temperature between low-SDR (n=28), medium-SDR (n=202) high-SDR (n=37) cohorts. Continuous variables were analyzed with independent t-tests. Significance set at p<0.05. SDR: skull density ratio.

SUPPLEMENTAL FIGURE S2
Percent improvement in essential tremor (intention + posture FTM scores) for patients at various timepoints after MRgFUS for essential tremor comparing all patients with low SDR (n=28), medium SDR (n=202), and high SDR (n=37). Populations were compared using independent ANOVAs. Significance set at p<0.05. SDR: skull density ratio.

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Magnetic resonance-guided focused ultrasound unilateral thalamotomy for medically refractory essential tremor: 3-year follow-up data

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Introduction: Magnetic resonance–guided focused ultrasound (MRgFUS) thalamotomy of the ventralis intermediate (Vim) nucleus is an "incisionless" treatment for medically refractory essential tremor (ET). We present data on 49 consecutive cases of MRgFUS Vim thalamotomy followed-up for 3 years and review the literature on studies with longer follow-up data.

Methods: A retrospective chart review of patients who underwent MRgFUS thalamotomy (January 2018–December 2020) at our institution was performed. Clinical Rating Scale for Tremor (CRST) and Quality of Life in Essential Tremor (QUEST) scores were obtained pre-operatively and at each follow-up with an assessment of side effects. Patients had post-operative magnetic resonance imaging within 24h and at 1 month to figure out lesion location, size, and extent. The results of studies with follow-up ≥3 years were summarized through a literature review.

Results: The CRST total (baseline: 58.6 ± 17.1, 3-year: 40.8 ± 18.0) and subscale scores (A + B, baseline: 23.5 ± 6.3, 3-year: 12.8 ± 7.9; C, baseline: 12.7 ± 4.3, 3-year: 5.8 ± 3.9) and the QUEST score (baseline: 38.0 ± 14.8, 3-year: 18.7 ± 13.3) showed significant improvement that was stable during the 3-year follow-up. Three patients reported tremor recurrence and two were satisfactorily retreated. Side effects were reported by 44% of patients (severe: 4%, mild and transient: 40%). The improvement in tremor and quality of life in our cohort was consistent with the literature.

Conclusion: We confirmed the effectiveness and safety of MRgFUS Vim thalamotomy in medically refractory ET up to 3 years.

KEYWORDS
functional neurosurgery, MRgFUS, non-invasive, thalamus, thalamotomy, tremor

Introduction

First ablative magnetic resonance–guided focused ultrasound (MRgFUS) thalamotomy dates to around 15 years ago, although its use has experienced exponential growth in recent years (1). MRgFUS is an "incisionless" technique that uses ultrasound from an array of transducers around the skull to induce focal thermal ablation lesions in the brain during an awake outpatient procedure and magnetic resonance imaging (MRI) for target definition, treatment planning, and closed-loop control of energy deposition (2, 3).

MRgFUS is applied to patients with medically refractory essential tremor (ET), who are not suitable for or refuse an invasive surgical procedure, to target the ventralis intermediate (Vim) nucleus of the thalamus (2). A randomized controlled trial showed that unilateral MRgFUS Vim thalamotomy may induce nearly 50% reduction in contralateral tremor in patients with moderate to severe medically refractory ET 1 year after treatment (4) and a sustained clinical benefit at 2 years (2). The benefit up to 1 year has been confirmed by many studies and summarized in two systematic reviews (5, 6) and some reports confirmed the positive effect at 2-year follow-up according to a meta-analysis with meta-regression (6). Only few studies explored the MRgFUS thalamotomy outcomes at longer time points, i.e., 3- (7, 8), 4- (9), and 5-year follow-ups (10, 11) in ET, offering a less definitive scenario of its longer-term benefit.

Factors that influence MRgFUS outcome include skull density ratio [SDR; (2)], lesion location and volume (12–14), patient age, disease duration, peak temperature, and number of sonications (15).

The aim of this study is two-fold. The first aim is to report data of a retrospective single-center observational study from our Institution's experience with MRgFUS Vim thalamotomy in patients with medically refractory unilateral ET followed-up over a period of 3 years. Our data may offer a "real-world" clinical experience to confirm the clinical efficacy of this procedure and help to identify areas for future research. The second aim is to summarize the results of studies with follow-up of at least 3 years through a discussion of the literature.

Methods

Subjects

We retrospectively reviewed prospectively collected data of 49 patients, who were consecutively treated between January 2018 and December 2020 at Verona University Hospital, Verona, Italy. Therefore, inclusion and exclusion criteria align with the eligibility criteria for MRgFUS thalamotomy. We treated adult patients (>18 y/o) with disabling ET unresponsive to at least two classes of medication, who could tolerate and cooperate during the procedure and were unwilling or ineligible for deep brain stimulation. Exclusion criteria included general MRI contraindications, impossibility to avoid sonication of sensitive brain/skull structures, SDR value <0.40, patients on anticoagulant and/or antiplatelet therapy with no possibility of temporary suspension, and those with significant and active comorbidities.

All patients signed an informed consent before MRgFUS thalamotomy and provided a specific informed consent to participate in the observational study, delivered either upon admission to the Hospital or during one of the follow-up visits. The study was conducted according to the Declaration of Helsinki and approved by the local ethical committee (Ethical Committee of the Veneto Region South-West Area at the Verona University Hospital – CET-ASOV; approval number 133CET).

A detailed chart review was performed to extract demographics (age, gender), disease characteristics (ET duration, baseline ET severity and quality of life, treated side), and radiological parameters such as SDR and lesion volume at the 1-month MRI. As previous described by other authors (16), volume was determined based on the 2-mm slice axial and coronal T2-weighted images, considering the three maximum diameters [latero-lateral (x), anterior-posterior (y), and cranio-caudal (z)] and estimated by using the ellipsoid approximation formula: $4/3 \times \pi \times (x/2) \times (y/2) \times (z/2)$.

MRgFUS procedure

All patients underwent a prophylaxis protocol with corticosteroids, with the administration of intravenous dexamethasone 4 mg every 8 h on the day of the thalamotomy (i.e., one administration before and two administrations after the procedure) followed by slow tapering with oral prednisone in the next 2–3 weeks.

Details of the MRgFUS procedure have been previously published elsewhere (2, 4). Briefly, the patient's head was shaved, and a modified stereotactic frame was affixed on the patient's skull after infiltration with local anesthetic. A flexible rubber gasket was placed over the frame and the patient's head rigidly fixed to the MRI table. The space between the patient's head and the MRgFUS transducer was filled with circulating, degassed water and T2-weighted MRI images were obtained in sagittal, coronal, and axial planes. Standard stereotactic coordinates were used to locate the thalamic Vim nucleus, i.e., X: 11 mm from the lateral wall of third ventricle, Y: average of one third/one fourth distance of the anterior commissure-posterior commissure (AC-PC) distance in front of the PC, Z: 1–2 mm above the intercommissural plane. Minor corrections to the initial target were made to adjust for individual patient anatomy. The sonication procedure, i.e., the administration of thermal energy to the brain target by the array of ultrasound transducers, consists of several phases (1, 17). In the alignment phase, brief low-energy sonications aim to reach a temperature of approximately 40–45°C without biological effects and thermometric maps are acquired to confirm the accuracy of the sonication point. The verification phase involves sonications reaching higher temperatures (46–54°C) for neuromodulation and testing potential adverse events. In the verification phase, serial neurological examinations allow for probing

the magnitude of postural and intentional tremor response (writing, spiral and line drawing, drinking from a bottle) and to assess possible side effects (motor and sensory function, speech, coordination). Once the 'sweet spot' that maximizes clinical benefit and cuts adverse effects has been found, the procedure moves to the final ablation phase, which involves modulating the energy to achieve effective temperatures for coagulative necrosis (55–60°C) leading to an irreversible lesion. Each phase can be repeated to ensure correspondence between target coordinates and the focal point, check for adverse effects, and confirm effectiveness in treating the patient's tremor.

Clinical assessment

Clinical assessments were performed at baseline (T0), and 1 (T1), 3 (T2), 6 (T3), 1 year (T4), 2 years (T5) and 3 years (T6) after the treatment. Tremor was evaluated with the Clinical Rating Scale for Tremor (CRST) (18), which measures the severity of resting, postural and intention tremor (Part A), the severity of upper limb intention tremor during writing, drawing and pouring (Part B), the functional disability related to tremor (Part C) and the subjective % of tremor improvement. Quality of life was explored with the Quality of Life in Essential Tremor (QUEST) questionnaire (19). Side effects and their duration were also recorded. Outcome measures of the treated side were CRST part A and B score, while overall outcome measures included CRST part C and total score, and QUEST score.

Statistics

Statistical analysis was performed with SPSS version 21.0 (SPSS, Chicago, United States). For continuous variables, normality of distribution was tested with the Shapiro-Wilks test. Differences in outcome measures (CRST, QUEST) at various assessment timepoints were analyzed with repeated measures ANOVA with Greenhouse–Geisser correction (within-group variable: time, T0-T6 for CRST A, B, C and total and QUEST; time, T1-T6 for CRST subjective improvement that was not administered to baseline) followed by post-hoc paired Student's t-test in case of normal distribution, or the non-parametric Wilcoxon signed-rank order test when the distribution was not normal. $p < 0.05$ (two-tailed, with Bonferroni's correction as needed) was the significance threshold for all the tests.

Review of studies with follow-up of at least 3 years

To integrate data derived from the systematic review and meta-analysis by Miller et al. (6) and provide an updated overview (i.e., from 2019 onwards) of the outcomes of unilateral MRgFUS thalamotomy in medically refractory ET, we searched studies with long-term follow-ups (i.e., ≥ 3 years). PubMed/MEDLINE was consulted using the following search string: ("magnetic resonance guided focused ultrasound" OR "MRgFUS" OR "focused ultrasound") AND ("essential tremor"). Studies were considered eligible if they included measures of ET severity (e.g., CRST) or ET impact on quality of life (e.g., QUEST) assessed prior to and at regularly scheduled follow-up intervals after MRgFUS intervention.

TABLE 1 Demographic and baseline clinical characteristics of the patients and treatment parameters.

Variable	Overall patients ($N = 49$)	Patients with 3-year follow-up ($N = 35$)
Demographic characteristics		
Sex (M/F)	30/19	21/14
Age (years)	72.8 ± 6.9, 73, 49–85	72.7 ± 7.2, 74, 49–85
Baseline clinical characteristics		
ET duration (years)	22.7 ± 14.1, 20, 5–60	22.7 ± 13.0, 20, 5–55
CRST part A, treated side	9.0 ± 3.0, 10, 3–18	8.5 ± 3.7, 9, 4–15
CRST part B, treated side	15.4 ± 4.1, 16, 5–20	15.4 ± 4.2, 17, 5–20
CRST part C	12.7 ± 4.3, 12.5, 4–24	12.2 ± 4.3, 12, 4–24
CRST total severity	58.9 ± 17.1, 59, 22–94	57.5 ± 18.3, 55, 22–94
Quality of life (QUEST)	38.0 ± 14.8, 34, 14–78	37.2 ± 15.7, 32, 14–78
Treated side (R/L)	45/4	31/4
Treatment parameters		
SDR	0.58 ± 0.09, 0.56, 0.41–0.75	0.57 ± 0.10, 0.55, 0.41–0.75
Number of sonications	12.0 ± 3.4, 12, 7–19	11.8 ± 4.2, 11, 7–19
Max temperature (°C)	57.7 ± 1.8, 57, 55–62	57.4 ± 2.0, 57, 55–61
Lesion volume (mm^3) at 1 month	11.9 ± 17.9, 5.0, 1.3–83.7	12.1 ± 18.5, 6.3, 1.3–83.7

Data are reported as mean ± SD, median, range for continuous variables. CRST, clinical rating scale for tremor; ET, essential tremor; L, left; R, right, QUEST, quality of life in essential tremor; SDR, skull density ratio.

Results

Baseline demographic and clinical characteristics of the overall patients and those with 3-year follow-up data and treatment parameters are reported in Table 1.

The CRST (repeated measures ANOVA: CRST A; $F = 84.1$, $p < 0.001$; CRST B: $F = 30.0$, $p < 0.001$; CRST C: $F = 61.7$, $p < 0.001$; CRST total: $F = 53.4$, $p < 0.001$) and the QUEST score (repeated measures ANOVA: $F = 34.7$, $p < 0.001$) showed a significant and consistent improvement of the treated side outcome measures (tremor severity: CRST A: 54–77% across different follow-ups vs. T0, $t = 9.4–17.7$, $p < 0.001$; CRST B, 41–65%, $t = 5.5–16.2$, $p < 0.001$), overall tremor outcome measures (impairment due to tremor: CRST C, 55–78% across different follow-ups vs. T0, $t = 10.2–14.7$, $p < 0.001$; overall tremor score: CRST total, 31–50%, $t = 7.1–18.4$, $p < 0.001$), and quality of life (QUEST: 51–66% across different follow-ups vs. T0, $t = 6.0–12.2$, $p < 0.001$) that was stable in comparison to baseline during the three-year follow-up period (Figure 1). Subjective improvement (CRST subjective: range, 53–74%) showed a reduction over time (repeated measures ANOVA: $F = 5.3$, $p = 0.01$) that was not significant across different follow-ups vs. T1 ($t = 1.0–3.2$, n.s.; Figure 1).

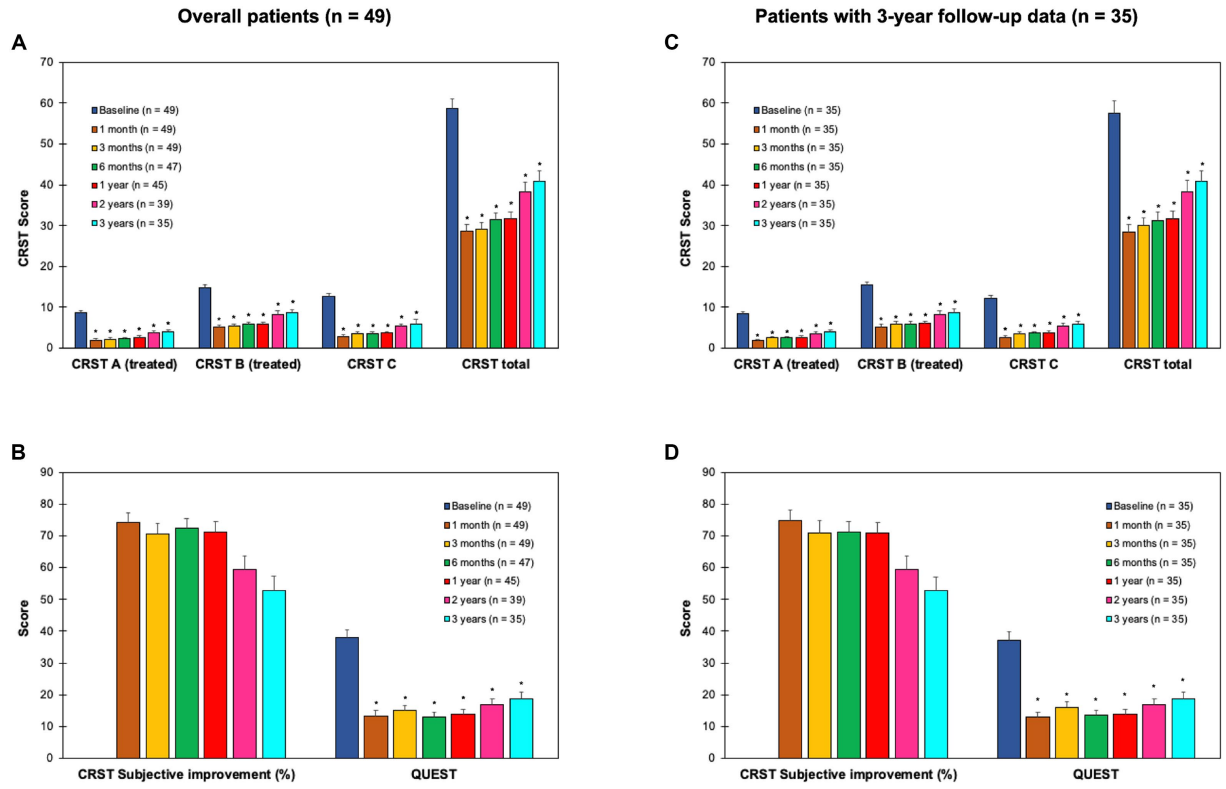

FIGURE 1
Clinical outcome measures at baseline (T0), and 1 (T1), 3 (T2), 6 months (T3), 1 year (T4), 2 years (T5) and 3 years (T6) after the treatment in objective (upper panels) and subjective measures (lower panels) of tremor in the overall population of patients (n = 49; panels **A,B**) and in the patients with 3-year follow-up data (n = 35; panels **C,D**). CRST, clinical rating scale for tremor (18) that is composed by part A (tremor severity, treated side), part B (upper limb intentional tremor severity, treated side), part C (functional disability related to tremor; panels **A,C**), and subjective improvement % (panels **B,D**). QUEST: quality of life in essential tremor questionnaire (19) (panels **B,D**). *p < 0.008 (i.e., Bonferroni's corrected p) for T1-T6 vs. T0 comparisons. CRST subjective improvement was stable across time (i.e., *post-hoc* comparisons not significant for T2-T6 vs. T1). Error bars equal 1 SEM.

TABLE 2 Side effects to treatment and their duration.

Side effect	Duration
Severe	
Ballism (N = 1)	36 months
Hemiparesis (N = 3)	1–24 months
Mild	
Ataxia (N = 14)	15 days-12 months
Subjective cognitive impairment (N = 1)	3 months
Dysarthria (N = 4)	15 days
Paresthesia (N = 3)	7–15 days
Corticosteroid related (N = 3)	15 days-1 month

At 1-year follow-up, 3 patients reported loss of benefit with <30% CRST overall score reduction, while 2 and 1 additional patients reported recurrence of tremor with less than 30% benefit on CRST score at 2- and 3-year follow-up, respectively. Two patients were retreated after 13 and 35 months, respectively, with CRST reduction >50%. In one of the retreated patients, the lesion after first treatment was undetectable in T2-weighted images, while the first lesion size was within normal range in the other retreated patient.

Severe and mild side effects are reported in Table 2. Severe side effects included ballism lasting up to 36 months and hemiparesis lasting 1–24 months. The most common mild side effect was ataxia that was short-lasting (i.e., 2 weeks- 3 months) in all cases, except one who reported partial amelioration after 1 month, but persistence up to 1 year. Other mild and transient side effects included short-lasting (i.e., 2 weeks), dysarthria and paresthesia, corticosteroid-related effects (overall, N = 3; nocturnal restlessness, N = 1; annoying hiccups, N = 1; mild transitory hyperglycemia; N = 2) that were limited to the corticosteroid administration and then vanishing, and subjective cognitive impairment, without changes to standard neuropsychological testing.

Five studies were identified that provided data at 3, 4, and 5-year follow-ups (see Table 3 for details).

Discussion

This retrospective report of 49 patients who underwent unilateral MRgFUS Vim thalamotomy for medically refractory ET, with follow-up data for up to 3 years in 35 of them, documented an overall consistent improvement in the tremor scores on the treated side, the impairment due to tremor, the overall tremor, and the subjective experience of tremor, as well as tremor-related quality of life. Some patients reported reappearance of tremor during follow-up, of whom

TABLE 3 MRgFUS thalamotomy studies providing long-term clinical data (i.e., follow-up ≥3 years).

Ref.	Study design	Site (s)	Sample size		FU duration	ET severity (CRST)						QoL (QUEST)	
						CRST part A + B (hand tremor-motor score)		CRST part C		CRST total			
			BL	FU		BL	FU	BL	FU	BL	FU	BL	FU
Halpern et al. (7)[#]	Prospective, controlled, multicenter clinical trial	USA Canada Japan South Korea	*N* = 76 (M: 52, F: 24; age: 71.0 ± 3.8)	*N* = 52	3 y	20.1 ± 4.7	9.5 ± 5.4	16.4 ± 4.6	7.5 ± 6.1	NR	NR	43.1 ± 18.3	23.8 ± 19.6
Peters et al. (8)	Prospective, monocenter clinical trial	Australia	*N* = 30 (M: 23, F: 7; age: 74.5 ± 7.53)	*N* = 6	3 y	21.2 (12.5–30.0)[§]	8.6 (0.2–17.1)[§]	NR	NR	43.8 (21.3–66.4)[§]	23.3 (1.2–45.4)[§]	43.8 (21.3–66.4)[§]	23.3 (1.2–45.4)[§]
Park et al. (9)	Randomized, controlled, monocenter clinical trial	South Korea	*N* = 15	*N* = 12 (M: 10, F: 2; age: 61.7 ± 8.1)	3 y 4 y	17.4 ± 3.8	3 y: 7.5 ± 5.3 4 y: 7.7 ± 4.1	12.7 ± 3.0	3 y: 4.4 ± 3.3 4 y: 4.7 ± 3.0	NR	NR	NA	NA
Cosgrove et al., (10)[#]	Long-term, multicenter, postinterventional clinical trial	USA Canada Japan South Korea	*N* = 76 (M: 52, F: 24; age: 71.0 ± 3.8)	*N* = 52 (3 y) *N* = 45 (4 y) *N* = 40 (5 y; M: 30, F: 10; age: 75 ± 8.4)	3 y 4 y 5 y	20 ± 4.7	3 y: 9.5 ± 5.4 4 y: 9.6 ± 5.8 5 y: 11.0 ± 6.5	16 ± 4.6	3 y: 7.5 ± 6.1 4 y: 8.4 ± 6.9 5 y: 8.9 ± 6.6	NR	NR	43 ± 18	3 y: 26 ± 21 4 y: 28 ± 19 5 y: 30 ± 20
Sinai et al. (11)	Prospective, monocenter clinical trial	Israel	*N* = 44 (M: 27, F: 17; age: 70.5, 63–87*)	*N* = 10 (3 y) *N* = 6 (4 y) *N* = 2 (5 y)	3 y 4 y 5 y	NR	NR	NR	NR	46.0 (16–74)*	3 y: 16.0 (9–57)* 4 y: 14.0 (6–74)* 5 y: 8.0 (6–10)*	41.5 (15–93)*	3 y: 15.5 (8–59)* 4 y: 14.5 (4–28)* 5 y: 11.0 (6–16)*
Present study	Retrospective, monocenter clinical trial	Italy	*N* = 49 (M: 30, F: 19; age: 72.8 ± 6.9)	*N* = 35	3 y	23.5 ± 6.3	12.8 ± 7.9	12.7 ± 4.3	5.8 ± 3.9	58.6 ± 17.1	40.8 ± 18.0	38.0 ± 14.8	18.7 ± 13.3

[#]Refer to the same cohort followed over time (registration no: NCT01827904). *Median, range. [§]Estimated marginal mean with 95% CI. BL, baseline; CI, confidence interval; CRST, clinical rating scale for tremor; ET, essential tremor; F, females; FU, follow-up; M, males; MRgFUS, magnetic resonance-guided focused ultrasound; N, number; NA, not assessed; NR, not reported; QoL, quality of life; QUEST, Quality of Life in Essential Tremor Questionnaire; y, years.

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two were retreated with success. We considered the first case as a 'technical failure' because the patient experienced an 'early' recurrence of tremor, in the absence of a detectable lesion on MRI. At variance, in the second patient, who exhibited a 'late' recurrence of tremor even in the presence of the lesion, it is conceivable that the diminished efficacy was, at least in part, due to worsening of ET because of its natural course.

There are robust data in the literature, supported by meta-analyses, demonstrating the sustained efficacy of MRgFUS treatment at short-term follow-up [i.e., 6 months, 1 year; (5, 6)]. On the other hand, limited and diverse data are accessible for a longer-term follow-up (i.e., > 3 years), as indicated in Table 3. Of the 115 patients with ET, for whom there is a follow-up of at least 3 years, approximately one-third of them come from our cohort. When comparing our data to those previously published, the tremor improvement in our cohort was consistent to that in previously reported ones.

It can be pointed out that this is still a relatively shorter follow-up compared to that of alternative neurosurgical procedures, such as deep brain stimulation, radiofrequency and radiosurgery ablation of the Vim (20, 21). Considering that the MRgFUS literature reports 5-year follow-up data only for 57 patients, there is a need for longer studies to confirm the duration of its effects for longer time periods. In this context, our follow-up data may offer interesting insight, compared to the brief history (i.e., around 10 years) of MRgFUS thalamotomy for refractory ET treatment.

More severe side effects occurred in a minority of treated patients. Mild adverse events were common, but transitory or rapidly improving in most of the cases. The most common ones, in line with previous literature (22) were mild ataxia, dysarthria and paresthesia, which are related to the proximity of the Vim to other thalamic nuclei and the internal capsule. Some patients also reported side effects related to the use of corticosteroids, which are routinely prescribed in our center on the day of the treatment and the following 2–3 weeks to reduce edema secondary to the procedure. These side effects led to a modification of the corticosteroid protocol. Nowadays we administer the same high dose of steroid on the day of the procedure followed by a shortened tapering period (i.e., prednisolone 25 mg for 3 days, then 12.5 mg for 2 days).

The routine use of corticosteroid may account for the significantly lower rate of adverse events, in particular sensory ones, and/or - if present - their rapid resolution (< 15 days) in most cases, when compared to other studies (23). Moreover, the use of steroid may explain the why our lesion volume at 1-month follow-up is much smaller when compared to that reported by other studies that used the same method to measure the size of the lesion (2, 23). We speculate that premedication and an immediate post-procedure protocol with high-dose steroid could mitigate the development of vasogenic edema in the outermost zone [zone III of Wintermark; (24, 25)] thereby explaining the relatively low incidence of adverse effects in the postoperative period. Moreover, it is conceivable that corticosteroids might have reduced cytotoxic edema (zone II of Wintermark) and contributed to reduce the size of the lesion at 1-month follow-up [zone I + zone II of Wintermark; (24, 25)]. Along this line, larger lesion size at 3 months was reported to be heralded by increased edema in the acute phase (26). Admittedly, proving this hypothesis is challenging due to the lack of comparative studies and the limited radiological follow-up data of our cohort, but we consider this is a starting point for future studies. Indeed, quantitative automated methods were not employed and the intrinsic limitations in the methods used to estimate the lesion size might have influenced our findings. Also, we did not systematically assess the lesion size at longer follow-ups. Regardless of the reasons why our lesions appear smaller, the lesion size did not seem to affect our clinical outcomes that are comparable with the literature. This finding is in line with the hypothesis that small lesion size seems not to affect the treatment's efficacy, as previously reported (14, 27). However, there is no consensus on the use of corticosteroids among centers, and its significance should be better investigated in future multicenter studies.

Finally, SDR was on average high in our patients in that it ranged from 0.41 to 0.75. Some Authors suggest that SDR > 0.45 should predict MRgFUS treatment success and side effects (28), but other studies reported contrasting findings, in that SDR was reported not to influence clinical outcome (2, 29).

Strength and limitations

The main strength of our study is that it reports a real-world clinical experience that confirms the generalizability of the data on the efficacy of MRgFUs thalamotomy that was previously documented in various reports.

We acknowledge some limitations of this report. First, the study was retrospective and the unblinded evaluation of the patients at different follow-ups carried the risk of positive reporting bias both by observer and patients. Second, the loss of some patients to follow-up because they came from other regions of Italy, and/or the COVID-19 pandemics, might have influenced the statistical analysis, but results did not change when examining patients with 3-year follow-up. Third, the small number of patients impeded the exploration of factors potentially influencing clinical outcomes. Fourth, we did not explore the spread of the lesion to other structures in single patients reporting side effects and did not systematically perform MRI tractography, which was reported to improve MRgFUS targeting, in all the patients (30). Finally, our review of previous studies was not systematic, as it was meant to provide an updated overview of the outcomes of unilateral MRgFUS thalamotomy in medically refractory ET, with long-term follow-ups. Future studies should better explore whether the site and the size of the lesion, as well as the involvement of specific tracts according to tractography predict side effects and their duration.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving humans were approved by the Ethical Committee of the Veneto Region South-West Area at the Verona University Hospital – CET-ASOV. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

ST: Writing – review & editing, Writing – original draft, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. FP: Writing – review & editing, Writing – original draft, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. TB: Writing – review & editing, Methodology, Investigation, Data curation. GB: Writing – review & editing, Methodology, Investigation, Data curation. ML: Writing – review & editing, Methodology, Investigation, Data curation. RF: Writing – review & editing, Supervision, Project administration, Methodology, Investigation, Funding acquisition, Data curation, Conceptualization. EM: Writing – review & editing, Writing – original draft, Methodology, Investigation, Formal analysis, Data curation. PP: Writing – review & editing, Methodology, Investigation, Data curation. MAT: Writing – review & editing, Methodology, Investigation, Data curation. EZ: Writing – review & editing, Methodology, Investigation, Data curation. CZ: Writing – review & editing, Methodology, Investigation, Data curation. CC: Writing – review & editing, Supervision, Methodology, Data curation. AN: Writing – review & editing, Supervision, Methodology, Data curation. BP: Writing – review & editing, Supervision, Methodology, Data curation. FS: Writing – review & editing, Supervision, Methodology. BB: Writing – review & editing, Supervision, Project administration, Methodology, Conceptualization. MHT: Writing – review & editing, Supervision, Project administration, Methodology, Conceptualization. SM: Writing – review & editing, Supervision, Project administration, Methodology, Conceptualization. GR: Writing – review & editing, Writing – original draft, Supervision, Software, Project administration, Methodology, Investigation, Data curation, Conceptualization.

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Publisher's note

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Early re-emerging tremor after MRgFUS thalamotomy: case–control analysis of procedural and imaging features

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Purpose: This study aimed to identify possible prognostic factors determining early tremor relapse after Magnetic Resonance guided Focused Ultrasound Surgery (MRgFUS) thalamotomy in patients with essential tremor (ET) and Parkinson's disease (PD).

Methods: Nine patients (six ET and three PD) who underwent Vim MRgFUS thalamotomy in a single institution and developed early re-emergent tremor were analyzed. A control group of patients matched pairwise for sex, pathology, age, disease duration, and skull density ratio (SDR) was selected to compare the technical-procedural data and MR imaging evidence. MR imaging findings compared between groups included lesion shape and volume in multiparametric sequences, as well as Fractiona Anisotropy (FA) and Apparent Diffusion Coefficient (ADC) values derived from Diffusion Tensor Imaging Diffusion Weighted Imaging (DTI) and Diffusion Weighted Imaging (DWI) sequences.

Results: We did not find statistically significant differences in gender and age between the two groups. Technical and procedural parameters were also similar in both treatment groups. In MRI analysis, we found lesions of similar size but with greater caudal extension in the control group with stable outcomes compared to patients with tremor relapse.

Conclusion: In our analysis of early recurrences after thalamotomy with focused ultrasound, there were neither technical and procedural differences nor prognostic factors related to lesion size or ablation temperatures. Greater caudal extension of the lesion in patients without recurrence might suggest the importance of spatial consolidation during treatment.

KEYWORDS

essential tremor, Parkinson's disease, MRgFUS, MRI, tremor recurrence

Introduction

Vim thalamotomy using focused ultrasound is a well-established method for the treatment of Parkinson's and essential tremor (ET) (1–3). Numerous studies have confirmed the indications, clinical findings, and complications. The results of efficacy in reducing tremors with follow-up up to 5 years are now available, with a known occurrence of recurrence in

approximately 10% of cases (4–6). Many cases have also been retreated with the method or subsequently subjected to Deep Brain Stimulation (DBS) to consolidate the result (7–9). Although numerous factors that contribute to successful long-term treatment have been proposed and identified, including in previous studies by the authors, what is a common experience in many centers is the possible occurrence of tremor reoccurrence very early, within 1 month of treatment. In these cases, the determining factors often remain unclear (8, 10, 11).

Therefore, our study aimed to evaluate the influence of procedural and imaging parameters on the early recurrence of tremor in patients submitted to MRgFUS Vim thalamotomy, compared to those with a sustained optimal outcome.

Materials and methods

We retrospectively evaluated all patients submitted to MRgFUS Vim thalamotomy at our institution between March 2018 and January 2023. From clinical reports, we retrieved patients with early tremor relapse (It is defined as an increase in the Fahn–Tolosa–Martin (FTM) part A score of ≥3 points after the post-procedural clinical assessment at 24 h.) that occurred within 1 month after treatment. According to our protocol, all patients are subjected to clinical and instrumental follow-up 1 day, 1 month, and 6 months after treatment.

All procedures were performed as explained in detail in other publications (1). In particular, Vim targeting was performed with indirect coordinates as follows:

- Halfway between one-third and one-fourth of the Anterior Commissure - Posterior Commissure (AC-PC) distance from the PC.
- Halfway between 14 mm from the AC-PC line and 11 mm from the lateral wall of the third ventricle.
- 2 mm above the AC-PC line.

In all patients, we recorded clinical-demographic features, procedural data, and MR findings. Patients with missing or incomplete clinical data, procedural reports, and MRI follow-up were excluded.

Clinical and demographic characteristics included as follows: underlying pathology, age, gender, disease duration, and skull density ratio (SDR).

Procedural data were retrieved from treatment reports and were included as follows:

- Ablative sonications, i.e., the number of sonications performed during the treatment reaching a mean target temperature of ≥54°C.
- Mean temperature (°C), i.e., the highest value of mean temperature reached during sonications.
- Maximum temperature (°C), i.e., the highest value of maximum temperature reached during sonications.

Imaging evaluation included the measurement of the lesion size and shape at the thalamus level, expressed in millimeters, measured as the maximum diameter on Fluid Attenuation Inversion Recovery (FLAIR), T1, T2, Susceptibility Weighted Imaging (SWI), and DWI-weighted sequences in the axial plane. For the evaluation of the shape, on the coronal sequences, the lesion cranial and caudal extension were measured in millimeters with respect to the AC-PC plane. In the same plane as the spatial measurements, an ROI was placed on the thalamotomy lesion for the quantitative measurement of FA and ADC values, respectively, in DWI- and DTI-weighted sequences. All MRI examinations were performed using a 3-Tesla MR-scanner (MR750w, GE Healthcare) with a 32-channel head coil. Acquisition parameters were as follows: slice 3.0–0.3, TR 7854, freq. FOV 26, and phase FOV 0.8. The same MRI protocol was applied for the follow-up examinations at 24 h, 1 month, and 6 months after treatment. Thalamotomy lesions were manually measured on a PACS workstation (Vue Motion, Carestream Health) by two neuroradiologists (AC, FB, with 16 and 4 years of experience in neuroimaging, respectively) using a digital ruler tool. The slice at the thalamus level that showed the greatest extent of the lesion and edema was chosen. Both readers were blinded to clinical and procedural information.

All procedural and imaging data were compared with a selected control group of patients without tremor relapse at the same follow-up interval, matched pairwise for age, sex, pathology, years of disease, pre-treatment FTM score, and SDR values (Table 1).

Statistical analysis

Data analyses were performed by using XLSTAT 2017: Data Analysis and Statistical Solution for Microsoft Excel (Addinsoft, Paris, France, 2017). Qualitative variables were summarized as frequency and proportions. Values of continuous variables were tested for normal distribution with Shapiro–Wilk's test and reported as mean and standard deviation (SD) or median and interquartile range (IQR), according to their distribution. Differences in quantitative values between groups were compared using the *t*-test or Wilcoxon test.

Results

Out of a total of 175 patients treated during the study period, 9 patients (8 men, mean age 68.44 ± 10.38 years) showed evidence of early tremor relapse. All patients had been treated in the right hand with left thalamotomy. No adverse effects or complications were recorded in all patients at the time of follow-up.

The clinical characteristics of the study group are summarized in Table 1.

As illustrated in Table 2, the analysis of the trend of the assessment of tremor intensity through the FTM scale demonstrated a reduction in tremor part A of approximately 85% at 24 h, reduced at 1-month follow-up to 78%. In part B of the tremor, there was a reduction of approximately 30% at 24 h and then reduced to 7% at 1 month.

TABLE 1 Clinical data of the study population and control group.

	Study group	Control group
Sex (M/F)	8/1	8/1
Pathology (ET/PD)	6/2	6/2
Disease Duration	10.67 ± 5.92 (5–20)	9.89 ± 6.68 (6–18)
Age	68.44 ± 10.38 (47–74)	67.52 ± 11.23 (45–76)
SDR	0.45 ± 0.09 (0.35–0.58)	0.47 ± 0.11 (0.38–0.56)

TABLE 2 Tremor intensity trend with FTM scale (treated side).

	FTM
Pre tot	44.18 ± 11.93 (27–68)
Pre part A	13.36 ± 4.27 (7–22)
Pre part B	16.01 ± 6.54 (6–24)
24 h tot	25.73 ± 8.96 (12–43)
24 h part A	7.55 ± 3.72 (2–13)
24 h part B	11.64 ± 4.84 (4–19)
1mo tot	31.36 ± 9.43 (19–51)
1mo part A	10.45 ± 3.27 (5–16)
1mo part B	15.18 ± 5.17 (9–24)

TABLE 3 Thalamotomy lesion size at 1 month.

	Study group	Control group	*p*-value
T1 1mo	5.11 ± 1.45 (3–7)	5.22 ± 1.39 (4–8)	0.253
FLAIR 1mo	6.22 ± 1.3 (4–8)	6.44 ± 1.33 (5–8)	0.365
T2 1mo	5.67 ± 1.22 (3–7)	6.22 ± 1.72 (4–9)	0.625
DWI 1mo	6.11 ± 1.05 (5–8)	6.67 ± 1.41 (5–9)	0.732
SWI 1mo	6.11 ± 1.62 (4–9)	6.56 ± 1.94 (2–8)	0.196
AC-PC 1mo	1.83 ± 0.87 (0.5–3)	0.44 ± 1.74 (−3–2)	**0.021**

Statistically significant results in bold.

In both groups, we found a progressive decrease in the thalamotomy lesion size (Table 3). In assessing the size of the lesion, we also considered the total brain volume of the patients, which showed no statistically significant differences between the two study groups (1397.22 ± 74.64 mL in the study group vs. 1403.25 ± 59.25 mL in the control group, $p = 0.855$). However, we did not find significant size differences between the study (relapse) group and the controls. In the analysis of the lesion shape, patients without recurrence showed a more elongated shape, with significantly more caudal extension below the AC-PC ($p = 0.02$) (Table 3 and Figure 1).

Quantitative evaluation of ADC values demonstrated the presence of residual signal restriction with decreased ADC values in both groups. There was also a decrease in AF values in both cohorts, which was statistically lower in the study group than in the control group (Table 4).

Regarding the analysis of procedural data, we did not find statistically significant differences between the two groups (Table 5).

Discussion

The occurrence of extremely early recurrences is the common experience of many centers performing high-volume MRgFUS; however, still, limited information is discussed in the literature except in a few case reports (4, 7–9).

In fact, most of the recurrences described in trials and observational studies involve those arising within 6–12 months, which is known to occur in approximately 10–11% of cases. Some factors influencing this type of recurrence, which can also be partially considered a "loss of efficacy," involve demographic factors, primarily the underlying pathology, where tremor recurrence is more frequent in patients affected by Parkinson's disease (PD) or long-standing essential tremor (ET) before developing PD symptoms. In our cases with early recurrence, however, only two were affected by PD (1, 2, 5, 6, 12–14).

According to numerous authors, including our previous experience, it is crucial to consider the size of the lesion in order to achieve a durable and established outcome. In our cohort, there were no statistically significant differences in lesion size at 1 month. However, a noteworthy imaging finding was the caudal extent of the lesion. This finding is particularly intriguing. It is a common approach for many centers to set the initial coordinates of their target at 2 mm above the AC-PC plane in order to minimize the risk of adverse effects. Nevertheless, lesions that are positioned too high in relation to the AC-PC plane appear to be more closely linked to recurrence (14–17).

No dissimilarities in lesion size were detected between the two groups during the MRI follow-up after 1 month. This contrasts partially with the findings of Atkinson et al.'s study, which revealed that patients who achieved excellent post-treatment outcomes displayed larger lesions. Nevertheless, in both groups, the lesion size—measured as the maximum diameter—fell within the normal range when compared to the accepted standards for a sufficiently ablative lesion (18–20).

Some previous studies in the literature have evaluated changes in DWI and DTI metrics after MRgFUS. In particular, it is known that at the lesion level, there is evidence of necrosis with the restriction of diffusivity and reduction of ADC values. The changes in FA values measured at the level of the Vim could be indicative of the actual disruption of the fiber bundles involved in tremor and in particular, the dentato-rubro-thalamic tract (DRTT) bundle (21). In the paper by Hori et al., researchers found that TcMRgFUS thalamotomy resulted in a significant decrease in relative FA (rFA) values in the targeted Vim at 1 day and 1 year after treatment. These changes in rFA values also showed a significant correlation with clinical outcomes measured by the Clinical Rating Scale for Tremor scores at 1 year follow-up. This implies that FA may be a potential imaging biomarker for early prediction of clinical outcomes after TcMRgFUS thalamotomy for ET (10).

In partial disagreement with what was expected, in our study, we did not show a lower reduction in FA values compared with patients in the control group.

Some other previous observations suggest that the disruption of the DRTT is only partially a prognostic element of stable tremor reduction. According to Maamary et al., who reported two instances of early tremor recurrence in PD patients following MRgFUS thalamotomy, the disruption of the DRTT may only partially and temporarily halt tremor outflow, allowing other circuits, particularly the PTT, to persist in propagating tremors. A possible explanation for the recurrence of tremors following VIM thalamotomy is that although the interruption of major pathways, such as the DRTT, initially suppresses tremors, re-routing through unaffected parts of the tremor network, specifically the PTT, could potentially lead to tremor recurrence (8, 22, 23).

The above would not only be applicable to Parkinson's tremors, in which recurrence is more frequent in the literature than in ETs but also in the latter, which were found to account for the majority of recurrences in the present study. Indeed, the experience of Gallay et al.

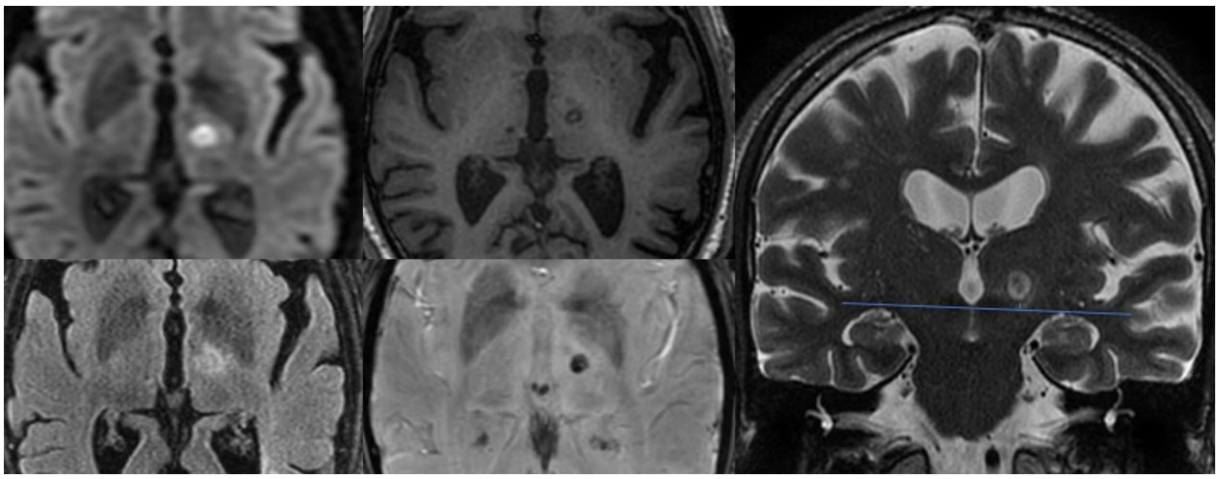

FIGURE 1
Evaluation of thalamotomy lesion axial plane diameter on DWI, FLAIR, T1 and SWI sequences, and caudal extension with respect to the AC-PC plane visualized on coronal T2 images.

TABLE 4 ADC and FA values at 1 month.

	Study group	Control group	*p*-value
ADC 1mo	0.55 ± 0.16 (0.33–0.85)	0.56 ± 0.13 (0.36–0.71)	0.978
FA 1mo	0.13 ± 0.03 (0.08–0.17)	0.25 ± 0.11 (0.12–0.41)	**0.008**

Statistically significant results in bold.

TABLE 5 Procedural and sonication parameters in the study and control group.

	Study group	Control group	*p*-value
Ablative sonications (N)	2.38 ± 1.06 (1–4)	2.86 ± 1.57 (1–5)	0.979
Mean temperature (°C)	55.75 ± 1.67 (53–58)	54.86 ± 1.21 (1–41)	0.689
maximum temperature (°C)	61.38 ± 1.85 (58–64)	58.43 ± 0.98 (57–60)	0.715

in performing cerebellothalamic tractotomy, ablation with a target placed 3 mm below the ICP was found to have improved target coverage and procedural efficacy, with tremor relief of up to 90% at 1 year follow-up (23).

The hypothesis is bolstered by various factors, such as the case where repeat Vim MRgFUS thalamotomy did not offer additional advantages, but targeting the subthalamic area proved to be effective (8, 17). Furthermore, there have been inconsistent findings regarding lesion overlap and the visualization of the DRTT bundle after thalamotomy, both in patients with recurrence and in those with stable outcomes.

Accuracy in targeting, the operator's experience with the method, and intraoperative monitoring are key factors in achieving an ablative and established lesion (14, 24–26).

In a recent commentary, Önder proposed a hypothesis regarding the recurrence of tremors after MRgFUS thalamotomy in PD patients. The hypothesis suggests that the histopathological effects of MRgFUS treatment may differ from other techniques, such as RF and gamma knife thalamotomy. Specifically, a unique post-mortem histopathological examination of a patient who underwent MRgFUS revealed demyelination, abundant lipid-laden macrophages, and relatively preserved neurons and axons in the lesion. Therefore, MRgFUS is hypothesized to preferentially cause demyelination rather than necrosis. It is suggested that the decline in the benefit of MRgFUS on tremors over time in PD patients may be related to possible amelioration of the demyelinating injury (27).

Although MRgFUS is a repeatable technique in cases of recurrence, it, therefore, remains to be clarified what is the best strategy used for targeting in these cases, whether to consider vim recentering by imaging and direct targeting or to choose another target, or to prefer a different method such as DBS (7, 27, 28).

The current research has certain limitations that warrant acknowledgment. First, the sample size of the study group is modest, given that the incidence of relapse after MRgFUS thalamotomy is relatively low. Additionally, the follow-up duration was restricted to only 1 month. Conducting future studies with a larger participant pool and an extended follow-up duration may be advantageous to validate our findings.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

FB: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. PB: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. AI: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. GS: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. AC: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. PS: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. AB: Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing, Conceptualization, Data curation, Formal analysis. EC: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. CM: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. FP: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. AS: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Cognitive safety of focused ultrasound thalamotomy for tremor: 1-year follow-up results of the COGNIFUS part 2 study

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Introduction: In the COGNitive in Focused UltraSound (COGNIFUS) study, we examined the 6-month cognitive outcomes of patients undergoing MRgFUS thalamotomy. This study endorsed the safety profile of the procedure in terms of cognitive functions that cannot be evaluated in real-time during the procedure unlike other aspects. The aim of the COGNIFUS Part 2 study was to investigate the cognitive trajectory of MRgFUS patients over a 1-year period, in order to confirm long-term safety and satisfaction.

Methods: We prospectively evaluated the cognitive and neurobehavioral profile of patients with essential tremor (ET) or Parkinson's Disease (PD) related tremor undergoing MRgFUS thalamotomy at 1 year-follow-up following the treatment.

Results: The sample consists of 50 patients (male 76%; mean age ± SD 69.0 ± 8.56; mean disease duration ± SD 12.13 ± 12.59; ET 28, PD 22 patients). A significant improvement was detected at the 1 year-follow-up assessment in anxiety and mood feelings (Hamilton Anxiety rating scale 5.66 ± 5.02 vs. 2.69 ± 3.76, $p \leq <0.001$; Beck depression Inventory II score 3.74 ± 3.80 vs. 1.80 ± 2.78, $p = 0.001$), memory domains (Rey Auditory Verbal Learning Test, immediate recall 31.76 ± 7.60 vs. 35.38 ± 7.72, $p = 0.001$ and delayed recall scores 5.57 ± 2 0.75 vs. 6.41 ± 2.48), frontal functions (Frontal Assessment Battery score 14.24 ± 3.04 vs. 15.16 ± 2.74) and in quality of life (Quality of life in Essential Tremor Questionnaire 35.00 ± 12.08 vs. 9.03 ± 10.64, $p \leq 0.001$ and PD Questionnaire −8 7.86 ± 3.10 vs. 3.09 ± 2.29, $p \leq 0.001$).

Conclusion: Our study supports the long-term efficacy and cognitive safety of MRgFUS treatment for ET and PD.

KEYWORDS

tremor, cognitive outcomes, Parkinson disease, essential tremor, MRgFUS

1 Introduction

Tremor is the cardinal sign of essential tremor (ET) and one of the most disabling symptoms of Parkinson's disease (PD). When tremor is refractory to pharmacological therapy, it may benefit from surgical approaches like radiofrequency thalamotomy, gamma knife thalamotomy, and thalamic stimulation (1). Magnetic resonance-guided focused ultrasound (MRgFUS) thalamotomy is a more recent approach that combines two technologies: magnetic resonance (MR) imaging and focused ultrasound (FUS). This combination allows obtaining a precise targeting of the ventral intermediate (Vim) nucleus and subsequent Vim ablation through high-intensity ultrasound waves. To date, many studies confirmed the efficacy and safety of MRgFUS thalamotomy for the treatment of medically refractory ET and PD-related tremor (2–5). Since the thalamus also plays an important role in cognition, evaluating the patient's cognitive dimension is considered worthy of careful assessment both in the short and long term. In this respect, some studies reported a worsening in processing speed, executive function, memory and verbal fluency following unilateral thalamotomy using various techniques (6–10). Other reported stable or even improved cognitive performances in these same domains (11, 12). Moreover, a recent metanalysis analyzed the results of eight studies in this field, including 193 patients with ET, PD, or multiple sclerosis managed with MRgFUS, Radiofrequency ablation or Gamma Knife radiosurgery (13). When considering the whole sample, regardless of the technique used, a small but significant decline in phonemic fluency and a trend toward a decline in semantic fluency were observed, while the other domains remained unchanged (13). Conversely, when restricting the analysis to studies using MRgFUS, no evidence of cognitive decline across any domain was found (13). In the *COGNitive in Focused UltraSound (COGNIFUS)* study, we later investigated the 6-month cognitive outcomes of patients undergoing MRgFUS thalamotomy, showing an improvement in anxiety feelings and in quality of life without changes in frontal and executive functions, verbal fluency and memory, and abstract reasoning and problem-solving abilities (14). The aim of the COGNIFUS Part 2 study was to investigate the cognitive trajectory of MRgFUS patients over a 1-year period, in order to confirm long-term safety and satisfaction.

2 Materials and methods

2.1 Protocol and study population

This prospective study included patients who underwent MRgFUS VIM thalamotomy for medically refractory ET and PD-related tremor within a 2-year period and receiving a complete neuropsychological and behavioral assessment at 6-month and at 1 year following the treatment. Criteria to be included in the study were: (i) age > 18 years, (ii) signed informed consent to be enrolled in the study, and (iii) availability to attend the intermediate 6-month visit and the final 1-year visit following MRgFUS thalamotomy. Exclusion criteria were a previous history of neurological or psychiatric disorders, and a history of deep brain stimulation (DBS) or previous stereotactic ablation. The study was approved by the Internal Review Board of the University of L'Aquila (n. 08/22) and performed according to the declaration of Helsinki. An informed consent to participate in the study was signed by all the included patients.

2.2 Procedures

A complete clinical, neurobehavioral, and neuropsychological assessment was performed in all included patients before MRgFUS thalamotomy (baseline, t0), at 6 months (t1) and 1 year after the procedure (t2). All three assessments were performed in the ON state for the PD group. Main clinical variables were recorded at baseline (24–48 h before the treatment), at 6-month (t1) and at the 1-year follow-up visit (t2). The tremor improvement was quantified by assessing changes in the Fahn-Tolosa-Marin (FTM) Clinical Rating Scale for tremor (CRST) in all patients: the FTM is a scale initially designed to assess ET, that has been later validated to assess PD tremor (15, 16). The Movement Disorder Society-Sponsored Revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS) part III [MDS-UPDRS-III] was also administered to patients with PD (17). The neuropsychological battery included the following tests: the Montreal Cognitive Assessment (MOCA) test, the Mini Mental State Examination (MMSE), the Frontal Assessment Battery (FAB), the Rey Auditory Verbal Learning Test (RAVLT), the Single Letter-cued (phonemic) fluency (FAS) test, the Categorical Verbal Fluency test, the Raven's Progressive Matrices (RPM), the Hamilton Anxiety rating scale (HAM-A), the Beck Depression Inventory-II (BDI-II), the Quality of life in Essential Tremor Questionnaire (QUEST), and the Parkinson's disease Questionnaire-8 (PDQ-8) (18–30). The MOCA test and the MMSE are cognitive screening tools with good reliability in ET and PD patients: attention and concentration, executive functions, memory, language, visuoconstructional skills, conceptual thinking, calculations, and orientation are some of the cognitive domains examined (18–20). The FAB is one of the most widely used screening tool to assess executive functions: conceptualization processes, abstract reasoning, mental flexibility, motor programming, executive control, resistance to interference, inhibitory control, and environmental autonomy are some of the cognitive skills examined (21, 22). The RAVLT investigates the person's ability to codify, consolidate, store, and retrieve verbal information depending on the integrity of attention, concentration, and short-term memory (23). The FAS test investigates executive functions and processing speed by requiring patients to name as many words as possible starting with F, A, and S in 60 s, respectively (24) while the Categorical Verbal Fluency test explores lexical retrieval and production by requiring patients to say as many words as possible belonging to the "colors," "animals," and "fruits" categories in three different trials, which also last 60 s each (25). Finally, the RPM test provides a non-verbal estimate of fluid intelligence and reasoning (26). The HAM-A scale and the BDI-II were

Abbreviations: ET, Essential tremor; PD, Parkinson's disease; MRgFUS, Magnetic resonance imaging-guided ultrasound; MR, Magnetic resonance; FUS, Focused ultrasound; VIM, Ventral intermediate thalamus; COGNIFUS, Cognitive in focused ultrasound; DBS, Deep brain stimulation; CRST, Clinical rating scale for tremor; MDS-UPDRS, MDS-Unified Parkinson's Disease Rating Scale; MDS-UPDRS-III, MDS-Unified Parkinson's Disease Rating Scale part III; SDR, Skull density ratio; ATD, Accumulate thermal dose; SD, Standard deviation; HAM-A, Hamilton anxiety-rating scale; BDI-II, Beck depression inventory II; PDQ-8, Parkinson disease questionnaire-8; QUEST, Quality of Life in Essential Tremor Questionnaire; RAVLT, Rey auditory verbal learning test; FAB, Frontal assessment battery; fNIRS, functional Near-infrared spectroscopy.

used to investigate anxiety and depressive feelings (27, 28) while the QUEST and the PDQ-8 were used to measure the perceived quality of life in ET and PD patients, respectively, (29, 30). The standardization and calibration of the neuropsychological tests used, as well as the interpretation of the results according to the reference cut-off values, were carried out in accordance with the guidelines provided by the reference standards (31). The neuropsychological assessment was conducted by a certified psychologist (GS) in accordance with testing conditions ensuring privacy, adequate illumination, and a distraction-free environment, with a duration typically lasting 30–40 min.

2.3 Neuroradiological assessment and high intensity focused ultrasound treatment

All patients were subjected to brain CT and MRI before MRgFUS treatment to evaluate the eligibility to the procedure based on neuroimaging findings and skull density ratio (SDR) computation. The whole HIFU procedure is described in a previous publication (14). Figure 1 graphically displays the evolution of a typical lesion on MRI at 24 h, 6 months, and 1 year after the procedure.

3 Statistical analysis

To compare preprocedural and postprocedural scores, either a paired *t*-test or Wilcoxon signed-rank test was employed based on the normal distribution status. Pearson and Spearman correlation coefficients were calculated to examine associations between motor tests and neuropsychological or neurobehavioral tests. Repeated measures ANOVA was utilized to analyze data within the same subjects. Continuous variables were expressed as the mean ± standard deviation (SD), while categorical variables were presented as frequency or percentage. Results were deemed significant if they surpassed an alpha level of 0.003, which was adjusted according to the Bonferroni correction for the number of tests (0.05/14). Statistical analyses were conducted using JAMOVI 2.2.24 software.

4 Results

One hundred patients were screened for the inclusion in the study. Out of them, 50 patients were excluded as unavailable to attend the 1-year follow-up assessment. The 50% drop-out rate was mainly due to the geographic distance of patients from the location where the procedure was performed, resulting in difficulty returning 1 year later for clinical follow-up. Overall, 50 patients (males 76%; mean age ± SD 69.0 ± 8.56 years; mean disease duration ± SD 12.13 ± 12.59 years; mean education ± SD 9.58 ± 3.9 years) completed the clinical, neurobehavioral, and neuropsychological assessment at baseline, at 6-month and at the 1-year follow-up visit. The final sample was different from that reported in our previous study, making this study not a strict follow-up continuation of the previous one (14). The main clinical indication to perform thalamotomy under MRgFUS guidance was ET ($n = 28$; mean age ± SD 69.04 ± 8.0 years, mean disease duration 15.41 ± 15.0 years, mean education 9.43 ± 3–95 years) and PD-related

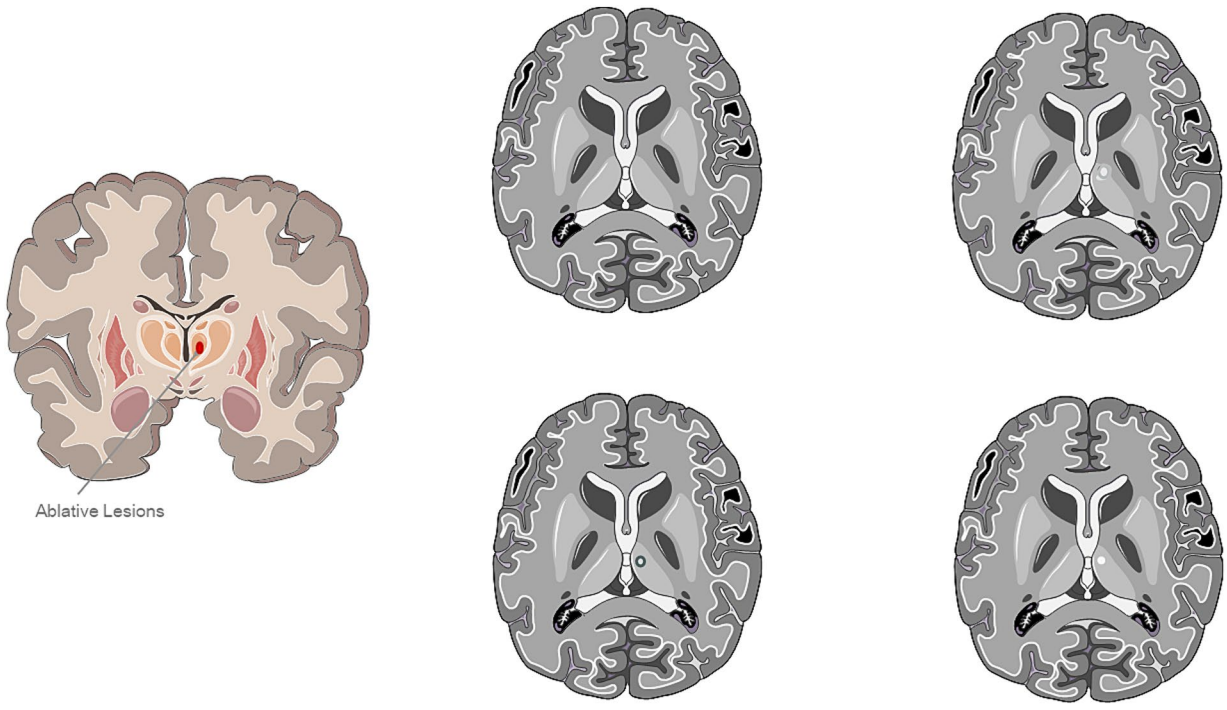

FIGURE 1
Evolution of a typical lesion on MRI at 24 h, 6 months, and 1 year after the procedure. **(A)** Ablative Lesion of Ventral Intermediate Nucleus (VIM). **(B)** A typical MRI sequence prior to ultrasound treatment. **(C)** Representation of a characteristic lesion of the VIM at 24-h after treatment. **(D)** Panel **(C)** depicts a standard MRI T2-weighted sequence obtained 6 months post-treatment. **(E)** Representation of a typical left ventral intermediate nucleus lesion 1-year post-treatment In panels **(C,D)**, a hypointense lesion characteristic of the ventral intermediate nucleus is evident. The image was partly generated using Servier Medical Art, provided by Servier, licensed under a Creative Commons Attribution 3.0 unported license.

tremor ($n = 22$; mean age ± SD 68.95 ± 9.42 years, mean disease 7.90 ± 6.85 years, mean education 9.77 ± 3.91 years). A left VIM thalamotomy was performed in 43 patients and a right VIM thalamotomy in the remainder. For the majority of patients ($n = 45$; 90%), the treated hemisphere was also the dominant one.

4.1 Tremor improvement

When considering the entire sample without differentiating by subgroups, an improvement of the CRST total score was observed at 6 months (42.94 ± 13.67 to 27.02 ± 11.41; *Post-hoc*, $p < 0.001$) as well at 1 year (from 42.94 ± 13.67 vs. 28.68 ± 9.85, *Post-hoc*, $p \leq 001$) following MRgFUS (Figure 2A). Conversely, the postprocedural MDS-UPDRS-III total score did not show a significant improvement at 6 months (from 31.23 ± 13.50 to 28.71 ± 10.40; *post-hoc*, $p = 0.577$) and at 1 year (from 31.23 ± 13.50 to 30.90 ± 9.46; *post-hoc* $p = 1.000$) following the treatment. When stratifying the whole sample by clinical diagnosis, the *post-hoc* comparisons (Figures 2B,C) indicated a significant improvement in total CRST score among patients with PD ($p < 0.001$) and ET ($p < 0.001$) at both 6 months and 1 year after treatment (Figures 2B,C).

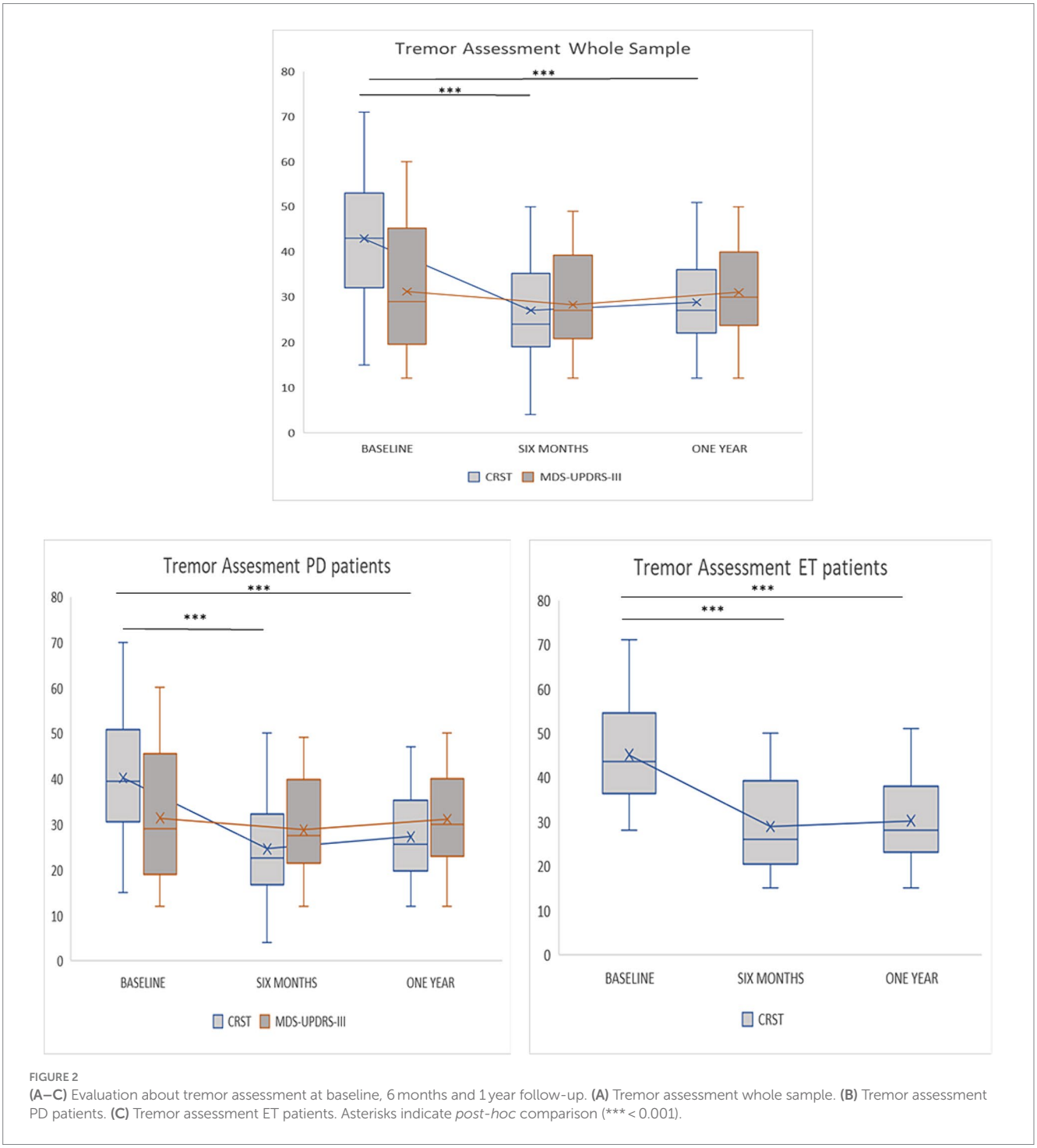

FIGURE 2
(A–C) Evaluation about tremor assessment at baseline, 6 months and 1 year follow-up. **(A)** Tremor assessment whole sample. **(B)** Tremor assessment PD patients. **(C)** Tremor assessment ET patients. Asterisks indicate *post-hoc* comparison (*** < 0.001).

4.2 Cognitive and behavioral changes

When considering the entire sample without differentiating by subgroups, the following changes in behavioral and cognitive domains were observed at 6 months and 1 year, respectively: at 6 months, a statistically significant improvement was detected in anxiety feelings (HAM-A 5.66 ± 5.02 vs. 2.70 ± 4.09, $p < 0.001$) and in cognitive domains including memory (RAVLT: immediate recall 31.76 ± 7.60 vs. 35.51 ± 8.38; $p \leq 0.001$; RAVLT: delayed recall 5.57 ± 2.75 vs. 7.03 ± 3.85; $p \leq 0.001$) and frontal functions (14.24 ± 3.04 vs. 15.24 ± 2.38; $p = 0.003$). At 1 year following the treatment, an improvement was detected in anxiety and mood feelings (HAM-A 5.66 ± 5.02 vs. 2.69 ± 3.76, $p \leq 0.001$; BDI-II 3.74 ± 3.80 vs. 1.80 ± 2.78, $p = 0.001$) and memory domains (RAVLT: Immediate recall 31.76 ± 7.60 vs. 35.38 ± 7.72, $p = 0.001$). Comparison between the mean scores is shown in Figures 3A–E. Moreover, an improvement in quality of life was detected both at 6 months (QUEST: 35.00 ± 12.08 vs. 8.93 ± 9.86, $p \leq 0.001$; PDQ-8 7.86 ± 3.10 vs. 3.10 ± 1.52, $p \leq 0.001$) and at 1 year (QUEST 35.00 ± 12.08 vs. 9.03 ± 10.64, $p \leq 0.001$; PDQ-8 7.86 ± 3.10 vs. 3.09 ± 2.29, $p \leq 0.001$) after the treatment (Figures 3F,G). Psychometric tests exploring executive functions, verbal fluency, abstract reasoning, and problem-solving abilities revealed no significant changes across multiple evaluations (Table 1).

When stratifying the entire sample by subgroups, PD patients showed an improvement of anxiety feelings (HAM-A 6.14 ± 4.51 vs. 2.55 ± 2.91; $p = 0.002$) and in quality of life (PDQ-8 8.10 ± 2.97 vs. 3.11 ± 1.56; $p \leq 0.001$) at 6-month following the procedure. The quality of life continued to show improvement at 1-year (PDQ-8 8.10 ± 2.97 vs. 3.10 ± 2.34; $p \leq 0.001$), in combination with mood improvements (BDI-II 4.73 ± 3.30 vs. 1.68 ± 2.43; $p = 0.003$). ET patients showed an improvement of anxiety feelings (HAM-A 5.29 ± 5.44 vs. 2.50 ± 4.76; $p = 0.001$), quality of life (QUEST 34.93 ± 12.54 vs. 8.85 ± 10. 22; $p \leq 0.001$) and mnestic domains (RAVLT: immediate recall 31.25 ± 7.31 vs. 36.28 ± 7.66; $p = 0.001$; RAVLT: delayed recall 5.60 ± 2.21 vs. 7.01 ± 2.10; $p \leq 0.001$) at 6-month following the procedure. Additionally, ET patients show an improvement in memory domains (RAVLT: immediate recall 31.25 ± 7.31 vs. 36.73 ± 6.26; $p \leq 0.001$; RAVLT: delayed recall 5.60 ± 2.21 vs. 7.02 ± 1.73; $p \leq 0.001$) and in quality of life (QUEST 34.93 ± 12.54 vs. 9.77 ± 11.20; $p \leq 0.001$) at 1-year following MRgFUS (Table 2).

When stratifying neuropsychological and neurobehavioral findings based on the treatment side, we observed distinct patterns of improvement depending on the targeted VIM (Table 3): when a left VIM thalamotomy was performed, a significant improvement was found in mnestic functions [(RAVL: immediate recall 31.26 ± 7.40 vs. 35.09 ± 8.63; $p = 0.002$; RAVLT: delayed recall 5.31 ± 2.58 vs. 6.98 ± 4.06; $p \leq 0.001$; FAB 14.12 ± 3.01 vs. 15.21 ± 2.45; $p = 0.003$)], QUEST (36.27 ± 11.80 vs. 9.88 ± 9.99; $p \leq 0.001$), PDQ-8 (7.47 ± 2.76 vs. 3.06 ± 1.53; $p \leq 0.001$), HAM-A (6.02 ± 5.09 vs. 2.86 ± 4.36; $p \leq 0.001$) at 6 months as well at 1 year [(RAVL: immediate recall 31.26 ± 7.40 vs. 34.89 ± 7.40; $p = 0.003$), BDI-II (3.84 ± 3.79 vs. 1.71 ± 2.73; $p \leq 0.001$), HAM-A (6.02 ± 5.09 vs. 2.74 ± 3.91; $p \leq 0.001$), QUEST (36.27 ± 11.80 vs. 9.48 ± 11.07; $p \leq 0.001$), PDQ-8 (7.47 ± 2.76 vs. 3.11 ± 2.35; $p \leq 0.001$)]. When a right VIM thalamotomy was performed, an improvement in the quality of life and in anxiety-depressive symptoms was observed, although it did not reach statistical significance (Table 3).

When assessing correlations between motor tests and neuropsychological or neurobehavioral tests at 1 year after treatment, a moderate negative correlation was found between the PDQ-8 score and the CRST total score ($r = -0.467$; $p = 0.028$), as well as between CRST total score and FAB score ($r = -0.408$; $p = 0.004$). A strong negative correlation was found between the FAB score and the MDS-UPDRS-III score at 1 year ($r = -0.745$; $p \leq 0.001$).

5 Discussion

Our results support the long-term efficacy and cognitive safety of the MRgFUS treatment for ET and PD related tremor. Indeed, MRgFUS is recognized as an emerging procedure for treating tremor and other neurological disorders, gaining popularity in clinical and research settings worldwide (32). Its main advantage over other lesion techniques lies in its capability to promptly detect potential complications through real-time intraprocedural monitoring. This enables operators to address any adverse effects by adjusting the initial target position as needed. Persistent side effects and symptoms following the procedure, whenever present, typically remain mild and resolve within a few weeks due to the resorption of perilesional edema (33, 34). However, identifying potential cognitive disturbances following thalamotomy can be challenging since cognitive changes may emerge later and necessitate longitudinal evaluation for detection. The only way to exclude interference from the lesion with normal cognitive performances is to provide the patient with longitudinal follow-up evaluations at predetermined intervals. As previously discussed, although the VIM is mainly considered a motor relay station, it might secondarily contribute to cognitive functions since it is integrated into the indirect pathway connecting the prefrontal cortex and deep cerebellar nuclei (35, 36). Possible subtle cognitive complications after unilateral thalamotomy using different techniques have been described: unilateral gamma knife thalamotomy and radiofrequency thalamotomy may cause a decline in phonetic verbal fluency and deficits in visuospatial memory (6–9). On the other hand, MRgFUS has been associated with a higher cognitive safety profile as compared to other techniques (8, 10, 12–14, 37). As highlighted by a recent meta-analysis, preserved cognition following MRgFUS might be due to the generation of smaller, more precise lesions, due to real-time monitoring of the lesion and thermographic feedback (13). An intriguing comparison has also been made regarding the cognitive effects of thalamotomy vs. thalamic stimulation, leading to the conclusion that both techniques carry minimal overall risk of cognitive decline (7). Additionally, it was found that verbal fluency is more likely to decrease following both left-sided thalamotomy and thalamic stimulation (7). Results of the COGNIFUS part 1 study added further insight to the discussion by revealing the absence of cognitive dysfunctions at 6 months and showing an improvement in feelings of anxiety and quality of life in patients treated with MRgFUS (14).

The *COGNIFUS part 2 study* extended the cognitive follow-up to 1 year and showed an improvement in specific cognitive domains and skills including working memory, verbal memory, attention and cognitive flexibility. Specifically, from the comparison of the results obtained at 6 months and 1 year, some differences emerge. While at 6 months specific cognitive functions remained largely unchanged with an improvement in anxious symptoms, at 1 year a significant

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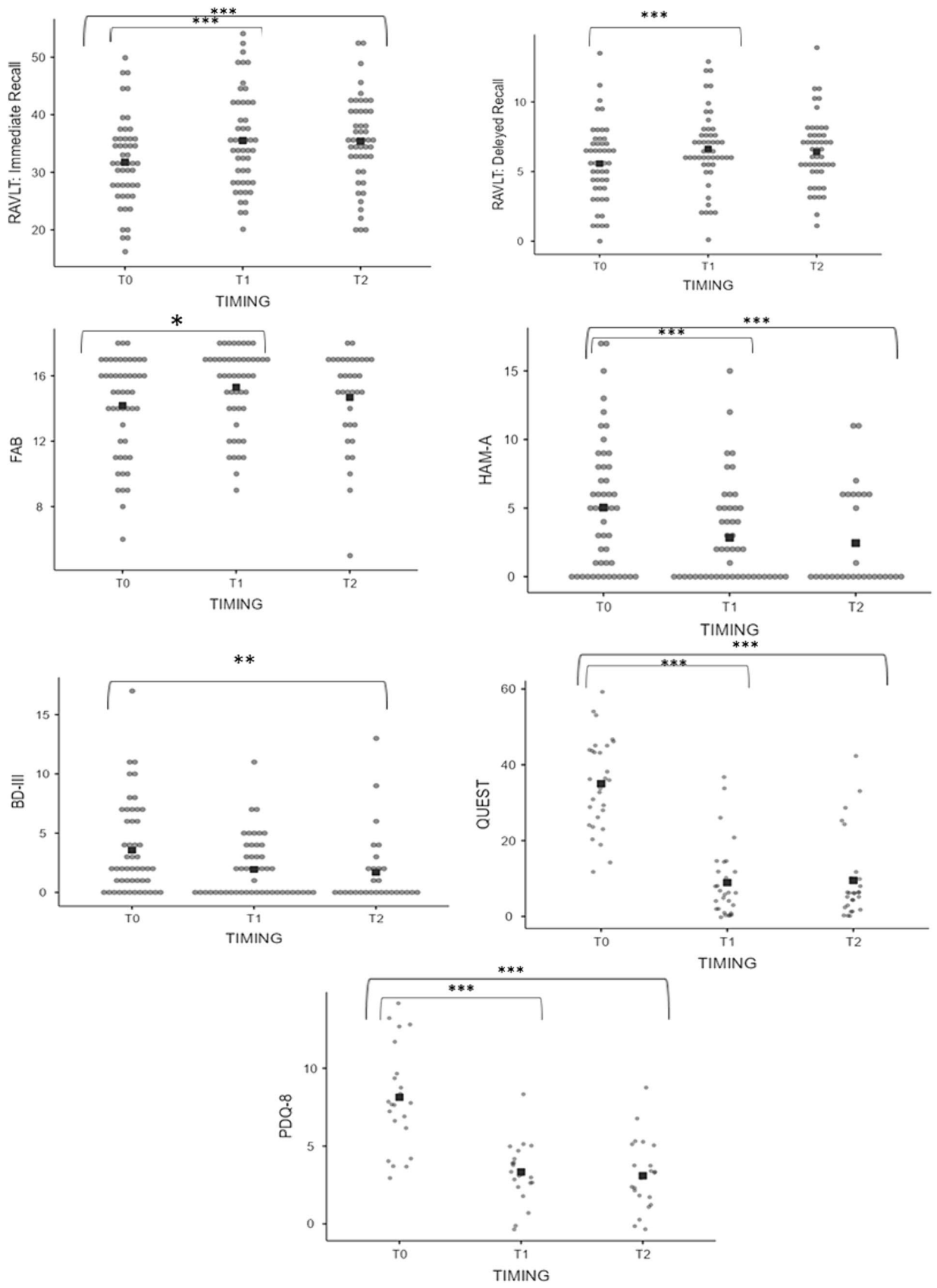

FIGURE 3
(A–G) Pre and postprocedural scores on neuropsychological assessment of the whole sample. **(A)** RAVLT: Immediate Recall. **(B)** RAVLT: Delayed Recall. **(C)** FAB. **(D)** HAM-A. **(E)** BDI-II. **(F)** QUEST. **(G)** PDQ-8. Asterisks indicate significant *p* value (*** < 0.001, **0.001, and *0.003).

TABLE 1 Changes in neuropsychological and neurobehavioral scores across baseline, 6-month, and 1 year follow-up for the whole sample.

Neuropsychological and neurobehavioral tests	Baseline	6-month follow-up	1 year follow-up	*p* value 6 months	*p* value 1 year
Mini Mental State Examination	27.38 ± 2.39	28.29 ± 1.70	28.33 ± 1.69	0.012	0.005
Montreal Cognitive Assessment	23.23 ± 4.93	23.78 ± 3.62	23.90 ± 3.63	0.053	0.004
Frontal Assessment Battery	14.24 ± 3.04	15.24 ± 2.38	15.16 ± 2.74	0.003	0.023
Single letter-cued (phonemic) fluency test	27.30 ± 9.76	28.32 ± 10.38	28.85 ± 9.62	0.336	0.090
Single letter-cued (semantic) fluency test	10.42 ± 2.70	10.50 ± 2.77	10.47 ± 2.85	0.774	0.908
Rey Auditory Verbal Learning Test R.I	31.76 ± 7.60	35.51 ± 8.38	35.38 ± 7.72	<001	0.001
Rey Auditory Verbal Learning Test R.D	5.57 ± 2.75	7.03 ± 3.85	6.41 ± 2.48	<001	0.011
Raven's Progressive Matrices	28.66 ± ±4.72	28.90 ± 5.15	28.86 ± 5.15	0.460	0.686
Hamilton Anxiety rating scale	5.66 ± 5.02	2.70 ± 4.09	2.26 ± 3.76	<001	<001
Beck Depression Inventory-II	3.74 ± 3.80	1.90 ± 2.70	1.80 ± 2.78	0.006	<001

improvement was observed not only in anxiety and mood feelings but also in the memory domains and in frontal functions. In this regard, this study took a step forward in establishing nonmotor outcomes of unilateral MRgFUS thalamotomy, by supporting a potential role of the procedure in preventing the development of cognitive complications mediated by the establishment of maladaptive networks. The most immediate hypothesis to explain the improvement in cognitive performances in treated patients is that an improvement or cessation of tremor may result in greater well-being for the patients, with positive effects on their attentional state. Just recently, a study based on interpretative phenomenological analysis has explored the experiences of ET patients undergoing the treatment throughout the entire surgical process, from the days leading up to the procedure to those following it (33): after the procedure, all participants described the suppression of tremors as life-changing, with some expressing that it took them some time to psychologically adjust to what essentially became their new body (33). This demonstrates that tremor suppression has effects on the patient that go beyond the motor dimension and can significantly influence the psychological and cognitive spheres. An alternative hypothesis, which requires further confirmation from studies specifically designed for this purpose, is that thalamotomy may influence the functioning of subcortical networks that modulate the patient's cognition, particularly in terms of cognitive flexibility and attentional tone. Our findings and previously available evidence do not support suggesting a reconfiguration of brain networks following thalamotomy. However, some clinical elements suggest further investigation in this direction. Indeed, it is known that the prefrontal cortex has wide projections to the mesolimbic, amygdala, and thalamic areas. Various studies investigated cortical activity changes associated with MRgFUS thalamotomy (38, 39). A recent study, based on the investigation of neural activity-related brain dynamic changes in regional cerebral blood flow through functional near-infrared spectroscopy (fNIRS), suggested that therapeutic MRgFUS can promote the remodeling of neuronal networks and changes in cortical activity in association with tremor improvement (38). Similarly, another study using fMRI demonstrated that MRgFUS thalamotomy not only suppress tremor symptoms but also rebalances atypical functional hierarchical architecture in ET patients (39). Specifically, MRgFUS VIM thalamotomy appears to perturb the global brain functional scaffold by influencing spatial information exchange and processing across modalities and areas (38). Other fMRI study in MRgFUS patients suggested that a temporary reconfiguration of the whole brain network occurs following the procedure, although the modalities of the subsequent reorganization are not still clearly understood (40, 41). Overall, this evidence indicates that the effect of VIM thalamotomy is not limited to the lesion in the target but also depends on the reorganization of extensive networks encompassing cerebello-striatal-thalamo-cortical circuits. However, a possible reorganization occurring after a temporary diaschisis remains only a hypothesis that should be investigated through further longitudinal network analysis studies. Another issue that deserves further discussion is the difference in cognitive changes observed in the two subgroups, patients with ET and PD, respectively. While in patients with PD the improvement primarily concerned quality of life and mood, a real enhancement in specific cognitive domains, particularly in memory, was confined to patients with ET. This likely reflects the underlying differences between the two disorders. Although sharing tremor, some cognitive dysfunction and personality changes, patients with ET and PD are profoundly different. Available scientific literature shows that patients with PD perform more poorly than ET patients in cognitive tasks such as attention, executive function, memory, and naming (42). Therefore, the effect of the procedure on cognitive functions may be more uncertain and weaker in patients with PD, requiring further evidence.

Strengths of our study include the prospective design, the longitudinal follow-up, the rigorous criteria adopted for the inclusion of patients and the use of a comprehensive neuropsychological battery for assessment. A limitation of the study is the potential occurrence of a learning effect when longitudinally assessing cognitive performances: however, setting the reassessment at 6 months and at 1 year appears to be the best compromise to ensure a sufficiently long follow-up without interference from potential learning effects or disease progression, the latter of which inherently carries the risk of independent cognitive decline. Although the utilization of alternate forms, which are accessible for most tests, may be proposed to mitigate any potential learning effect, it is primarily recommended for tests not encompassed in the current neuropsychological battery, such as the Paced Auditory Serial Addition Test (PASAT) and the Stroop Color and Word Test (SCWT) (43). Furthermore, subgroup analysis revealed that improvement in memory domains exclusively pertained to patients with ET. This allows us to exclude a learning effect at 6-month and 1 year, which would have been expected to manifest in both subgroups. In any case, caution is mandatory in interpreting the results, which

TABLE 2 Change in neuropsychological and neurobehavioral scores between baseline, 6-month, and 1 year follow-up for PD and ET patients.

		PD patients				ET patients				
Neuropsychological and neurobehavioral tests	Baseline	6-month follow-up	1 year follow-up	*p* value 6 months	*p* value 1 year	Baseline	6-month follow-up	1 year follow-up	*p* value 6-month	*p* value 1 year
Mini Mental State Examination	26.64 ± 2.71	28.13 ± 1.99	28.09 ± 1.98	0.014	0.022	27.95 ± 1.96	28.42 ± 1.46	28.52 ± 1.42	0.186	0.063
Montreal Cognitive Assessment	22.64 ± 4.30	23.27 ± 4.05	23.41 ± 3.78	0.162	0.081	23.89 ± 5.39	24.18 ± 3.27	24.30 ± 3.53	0.777	0.737
Frontal Assessment Battery	14.18 ± 3.03	14.73 ± 2.62	14.82 ± 3.10	0.194	0.294	14.29 ± 3.10	15.64 ± 2.13	15.44 ± 2.44	0.004	0.023
Single letter-cued (phonemic) fluency test	28.56 ± 10.55	28.84 ± 13.30	30.10 ± 11.48	0.881	0.316	26.31 ± 9.17	27.91 ± 7.59	27.83 ± 7.87	0.199	0.164
Single letter-cued (semantic) fluency test	10.36 ± 2.89	10.41 ± 2.78	10.12 ± 3.16	0.919	0.592	10.46 ± 2.60	10.58 ± 2.82	10.76 ± 2.60	0.773	0.515
Rey Auditory Verbal Learning Test R.I	32.40 ± 8.07	34.52 ± 9.32	33.74 ± 9.08	0.185	0.356	31.25 ± 7.31	36.28 ± 7.66	36.73 ± 6.26	0.001	< 001
Rey Auditory Verbal Learning Test R.D	5.54 ± 3.38	7.05 ± 5.38	5.65 ± 3.04	0.150	0.962	5.60 ± 2.21	7.01 ± 2.10	7.02 ± 1.73	< 001	< 001
Raven's Progressive Matrices	28.39 ± 4.84	28.00 ± 6.23	28.29 ± 6.33	0.278	0.808	28.87 ± 4.71	29.63 ± 4.05	29.35 ± 3.95	0.127	0.520
Hamilton Anxiety rating scale	6.14 ± 4.51	2.95 ± 3.12	2.55 ± 2.91	0.002	0.006	5.29 ± 5.44	2.50 ± 4.76	2.81 ± 4.39	0.001	0.015
Beck Depression Inventory-II	4.73 ± 3.30	2.86 ± 3.23	1.68 ± 2.46	0.081	0.003	2.96 ± 4.04	1.14 ± 1.96	1.89 ± 3.07	0.023	0.112
Quality of life in Essential Tremor Questionnaire	-	-	-	-	-	34.93 ± 12.54	8.85 ± 10.22	9.77 ± 11.20	< 001	< 001
Parkinson's disease Questionnaire-8 (PDQ-8)	8.10 ± 2.97	3.11 ± 1.56	3.10 ± 2.34	< 001	< 001	-	-	-	-	-

TABLE 3 Change in neuropsychological and neurobehavioral scores between baseline, 6-month, and 1 year follow-up finding by side (left/right).

		LEFT VIM thalamotomy				Right VIM thalamotomy				
Neuropsychological and neurobehavioral tests	Baseline	6-month follow-up	1 year follow-up	*p* value 6 months	*p* value 1 year	Baseline	6-month follow-up	1 year follow-up	*p* value 6 months	*p* value 1 year
Mini Mental State Examination	27.34 ± 2.42	28.45 ± 1.51	28.33 ± 1.68	0.004	0.010	27.54 ± 2.35	27.31 ± 2.51	28.31 ± 1.86	0.750	0.293
Montreal Cognitive Assessment	23.40 ± 4.99	23.77 ± 3.77	23.95 ± 3.41	0.080	0.008	23.00 ± 4.96	23.85 ± 5.27	23.57 ± 5.09	0.457	0.174
Frontal Assessment Battery	14.12 ± 3.02	15.21 ± 2.45	15.05 ± 2.87	0.003	0.032	15.00 ± 3.31	15.42 ± 1.98	15.85 ± 1,77	0.824	0.548
Single letter-cued (phonemic) fluency test	27.25 ± 9.93	28.24 ± 10.64	28.95 ± 10.00	0.381	0.077	27.61 ± 9.42	28.81 ± 9.36	28.24 ± 7.51	0.725	0.835
Single letter-cued (semantic) fluency test	10.41 ± 2.77	10.52 ± 2.92	10.46 ± 3.04	0.695	0.932	10.46 ± 2.47	10.39 ± 1.73	10.55 ± 1.43	0.957	0.939
Rey Auditory Verbal Learning Test R.I	31.26 ± 7.40	35.09 ± 8.63	34.89 ± 7.40	0.002	0.003	34.81 ± 8.68	38.04 ± 6.60	38.35 ± 9.50	0.189	0.241
Rey Auditory Verbal Learning Test R.D	5.31 ± 2.58	6.98 ± 4.05	6.24 ± 2.17	< 001	0.007	7.20 ± 3.42	7.32 ± 2.44	7.40 ± 3.96	0.688	0.813
Raven's Progressive Matrices	28.69 ± 4.24	29.41 ± 3.98	29.10 ± 3.97	0.074	0.427	28.45 ± 7.44	25.81 ± 9.54	27.50 ± 10.01	0.059	0.611
Hamilton Anxiety rating scale	6.02 ± 5.09	2.86 ± 4.36	2.74 ± 3.91	< 001	< 001	3.42 ± 4.15	1.71 ± 1.49	2.42 ± 2.93	0.462	0.684
Beck Depression Inventory-II	3.84 ± 3.79	1.84 ± 2.81	1.71 ± 2.73	0.004	< 001	3.14 ± 4.10	2.28 ± 2.05	2.28 ± 2.30	0.833	0.684
Quality of life in Essential Tremor Questionnaire	36.27 ± 11.80	9.88 ± 9.99	9.48 ± 11.07	< 001	< 001	24.00 ± 10.00	1.66 ± 0.57	5.00 ± 4.58	0.250	0.250
Parkinson's disease Questionnaire-8 (PDQ-8)	7.47 ± 2.76	3.06 ± 1.53	3.11 ± 2.35	< 001	< 001	9.50 ± 4.35	3.35 ± 1.70	3.00 ± 2.30	0.125	0.098

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need to be confirmed in studies with larger samples. Another limitation lies in the high drop-out rate among patients initially screened for inclusion in the study. This drop-out rate was mainly due to the geographic distance of patients, resulting in difficulty returning 1 year later for clinical follow-up. However, we must consider that this drop-out rate could also introduce a bias in our results. Some open questions remain and should be the focus of further investigations. For the majority of patients, the treated hemisphere was also the dominant one. When stratifying neuropsychological and neurobehavioral findings based on the treatment side, we observed significant changes only when a left VIM thalamotomy was performed. Interpretation of these results must be cautious because patients with right-sided lesions are much less represented in the included sample. Future studies with a larger sample size are needed to better examine the effect of the lesion side on cognitive performances and emotional state. Moreover, the recent authorization for staged bilateral MRgFUS thalamotomies further underscores the importance of longitudinal studies in assessing patients beyond their motor dimension: the ideal studies should combine clinical evaluation of patients, both in terms of motor and cognitive aspects, with analysis of functional changes within cortico-subcortical networks whose functioning appears to be influenced by VIM thalamotomy.

Data availability statement

The data that support the findings of this study are available from the corresponding author GS, upon reasonable request.

Author contributions

GS: Conceptualization, Formal analysis, Writing – original draft, Writing – review & editing, Data curation, Investigation, Methodology. PS: Conceptualization, Writing – original draft, Writing – review & editing, Investigation, Data curation, Formal analysis, Methodology. FB: Conceptualization, Writing – original draft, Writing – review & editing, Investigation. AC: Conceptualization, Writing – original draft, Writing – review & editing, Investigation. CMas: Conceptualization, Writing – original draft, Writing – review & editing, Investigation. MP: Conceptualization, Writing – original draft, Writing – review & editing, Investigation. AS: Conceptualization, Writing – original draft, Writing – review & editing, Investigation. AR: Conceptualization, Writing – original draft, Writing – review & editing, Investigation. EC: Conceptualization, Writing – original draft, Writing – review & editing, Investigation. CMar: Conceptualization, Writing – original draft, Writing – review & editing, Investigation. MM: Writing – original draft, Writing – review & editing, Conceptualization, Investigation. RT: Writing – original draft, Writing – review & editing, Conceptualization, Investigation. FP: Conceptualization, Investigation, Writing – original draft, Writing – review & editing, Data curation, Formal analysis, Methodology, Supervision.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2024.1395282/full#supplementary-material

SUPPLEMENTARY FIGURE 1
Statistically significant changes in neuropsychological and neurobehavioral scores following the procedure in PD patients. Asterisks indicate significant *p* value (***< 0.001, **0.003).

SUPPLEMENTARY FIGURE 2
Statistically significant changes in neuropsychological and neurobehavioral scores following the procedure in ET patients. Asterisks indicate significant *p* value (***< 0.001, **0.001).

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Staged magnetic resonance-guided focused ultrasound thalamotomy for the treatment of bilateral essential tremor and Parkinson's disease related tremor: a systematic review and critical appraisal of current knowledge

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Introduction: Essential tremor (ET) and Parkinson's Disease (PD) are debilitating neurodegenerative disorders characterized by tremor as a predominant symptom, significantly impacting patients' quality of life. Magnetic Resonance-guided Focused Ultrasound (MRgFUS) Thalamotomy is an innovative therapeutic option for the treatment of unilateral medically refractory tremor with fewer adverse effects compared to traditional surgical interventions. A recent CE approval allows appropriate patients to have their second side treated.

Objective: The objective of this systematic review was to analyze available current knowledge about the use of MRgFUS for the treatment of bilateral ET and PD related tremor, to identify the effectiveness and the risks associated with bilateral treatment.

Methods: Eligible studies were identified by searching published studies in PubMed and Scopus databases from May 2014 to January 2024 and by identifying ongoing studies registered on the clinicaltrials.gov website. Data were summarized by considering the following information topics: the number of patients involved, the selected lesion target, the assessment tool used to evaluate clinical changes, the observed improvement, the reported side effects, and the time interval between the two treatments. The study was registered in PROSPERO (ID: CRD42024513178).

Results: Nine studies were eligible for this review, 7 for ET and 2 for PD. The involved population included a variable number of patients, ranging from 1 to 11 subjects for ET and from 10 to 15 subjects for PD. The main lesional targets were the ventral intermediate nucleus of the thalamus, the pallidothalamic tract and the cerebellothalamic tract bilaterally. All studies investigated the tremor relief through the Clinical Rating Scale for Tremor (CRST) in patients with ET,

and through the Unified Parkinson's Disease Rating Scale (UPDRS) in patients with PD. A variable degree of improvement was observed, with all patients expressing overall satisfaction with the bilateral treatment. Adverse events were mild and transient, primarily involving gait disturbances, dysarthria, and ataxia. A standardized protocol for administering the two consecutive treatments was not identifiable; typically, the timing of the second treatment was delayed by at least 6 months.

Conclusion: Available evidence supports the effectiveness and safety of staged bilateral MRgFUS treatments for ET and PD-related tremor.

KEYWORDS

MRgFUS, tremor, essential tremor, Parkinson's disease, focused ultrasound, thalamotomy

Introduction

Essential tremor (ET) and Parkinson's Disease (PD) are two neurodegenerative disorders characterized by a symptomatic framework where tremor often assumes a predominant role (1). Tremor significantly impacts the patient's quality of life, limiting autonomy and participation in social activities, and causing disability and social embarrassment (1, 2). Essential tremor is associated with a condition of slowly progressive action tremor, in the absence of other significant symptoms or a clear etiology, although recent evidence suggests, in some cases, an involvement of NOS3 or FUS genes mutations (3). It is a common disorder, affecting approximately 1% of the general population and 5% of those over 65 years of age. A family history is often reported, and a male predisposition to the development of ET is recognized in terms of both frequency and severity (4, 5). On the other hand, PD is a more complex disease, due to the degeneration of dopaminergic neurons within the nigrostriatal system. It is one of the most common causes of neurological disability, affecting approximately 1% of the population over 55 years of age, with a higher prevalence in males than females (6). Tremor may be variably combined with other symptoms such as bradykinesia and rigidity, so that different PD subtypes can be identified such as tremor-dominant PD, postural instability and gait disturbances (PIGD) PD and mixed forms (6). Both in ET and PD, pharmacological therapy has a poorly predictable effect on tremor. Moreover, the effect of pharmacological therapy tends to diminish as the disease progresses, especially in PD, following the end of the so-called honeymoon period during which the disease is still responsive to oral and transdermal therapy. As the disease progresses, motor fluctuations emerge, and tremor often become not satisfactorily controlled with oral medications. At that stage, advanced therapies should be offered to eligible patients. Traditional methods of surgical and radiotherapy treatment of tremor include deep brain stimulation (DBS), stereotactic radiosurgery (SRS) and radiofrequency thalamotomy (RF). These treatments target specific anatomical structures involved in motor control, primarily at the level of the thalamus which regulates the motor component through the pallidothalamo-cortical (extrapyramidal system) and cerebello-thalamo-cortical (muscle tone regulation) circuits. Specifically, the ventral intermediate nucleus (Vim) of the thalamus is the main target for ET patients and for some patient with tremor dominant PD. Although very effective, these procedures are associated with some risks related to surgical access and positioning of intracranial electrodes, particularly bleeding and infections (7). MRI-guided Focused Ultrasound (MRgFUS) is a new technology that enables non-invasive focal treatment within the brain, showing promising results (8–10). This technique uses a focused ultrasound beam that passes through the skull to reach the target area, without the need for anesthesia or craniotomy (11). Furthermore, the patient is awake and responsive throughout the whole procedure, allowing real-time assessment of any potential side effects (11). The same technique allows for the delivery of either low-intensity focused ultrasounds (LIFU) or high-intensity focused ultrasounds (HIFU) (12). The former may be used for transiently and non-invasively disrupting the blood brain barrier (BBB), allowing for localized delivery of drugs, genes, or other therapeutic agents. The latter are used for ablative purposes in the treatment of medically refractory tremor and neuropathic pain (13–17). During HIFU sessions, the patient's head is shaved and fixed to a stereotactic frame, a flexible silicone membrane is applied to seal the space between the head and the transducer, and water at 15°C–20°C is used to reduce scalp overheating (13). Before the procedure, specific sequences of images are acquired, and the target to be treated is planned. Low-power sonifications are initially administered for 10–20 s to achieve a maximum temperature between 40°C and 42°C and assess the effect of sonification on the target. Once the choice of the target corresponds to the desired therapeutic effect without side effects, high-power sonifications (below 54°C) causing coagulative necrosis are administered (14). Possible complications include periprocedural transient symptoms that may occur during sonifications, such as headache, dizziness, vertigo, nausea, vomiting, scalp warmth sensation, and paraesthesia. These symptoms usually resolve within a few hours. In some cases, thalamotomy-related effects, due to the creation of a thalamic lesion, including gait disturbances or weakness of a limb, may persist longer, usually resolving within 3 months (17). Cognitive outcomes following unilateral MRgFUS thalamotomy have been also investigated, with findings indicating no deterioration, but rather a tendency toward slight improvement (18). The characteristics of this technique allow for immediate therapeutic effects and a rapid return to normal activities. Moreover, a significant advantage that has facilitated its rapid dissemination is the possibility of real-time feedback from the patient during the procedure, allowing for intraoperative evaluations (19).

The aim of this review was to systematically analyze the current knowledge about the use of MRgFUS for the bilateral treatment of ET and PD related tremor. The review focuses on the benefits and risks associated with bilateral procedures, the selection of anatomical therapeutic targets, and the strengths and limitations of the available studies in this field.

Methods

This systematic review was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines, updated to 2020 (20). The study was registered in PROSPERO (ID: CRD42024513178) and the protocol can be found at the PROSPERO database. Data were analyzed and summarized using the Population, Intervention, Comparison, and Outcome (PICO) framework. The PICO question was as it follows: which is the efficacy and safety profile (outcome) of bilateral MRgFUS (intervention) in patients with ET and PD (population)? Comparison with unilateral MRgFUS was also reported where available. The research was conducted on PubMed and Scopus, by identifying articles indexed from May 2014 to January 2024. We conducted a search on both databases using the search terms "MRgFUS," "focused ultrasound," "thalamotomy," combined with the terms "tremor," "Parkinson's disease" and "Essential tremor." The search was restricted to humans and articles published in English. Only studies focusing on the bilateral application of MRgFUS have been considered. Specifically, original studies, including clinical trials, observational studies, case series and case reports addressing HIFU bilateral MRgFUS for ET or PD were eligible for this review. Studies lacking a clear definition of the study design and settings, letters, abstracts, studies not performed on humans, unpublished studies, and studies in which MRgFUS was used outside the neurological context were excluded. Duplicate publications were removed by manual check. The study selection process occurred through 2 phases: in the first phase, studies were selected through the reading of titles/abstracts, and in the second phase, through the reading of full texts. All articles were imported into an online software[1] used during the screening process. The article selection process was carried out independently by two investigators (SC and GS) who initially assessed the study eligibility by screening titles and abstracts. Disagreements were resolved through discussion with a third investigator (FP). In the second phase, the full texts of the selected articles were evaluated. To also include ongoing studies, we conducted an additional search on the clinicaltrials.gov database from the beginning of indexing up to January 2024, using the same terms as those used for the database search. The included studies were individually described, and data were summarized based on the following main domains: the number of subjects treated bilaterally, the selected intracranial target, the interval between the two treatments, the clinical tool used to evaluate tremor, the degree of observed improvement, and the occurrence of adverse events. Additional information regarding patients' satisfaction with the treatment, cognitive status, and quality of life was provided where available.

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Results

A total of 403 records were identified through the search on PubMed and Scopus. After removing duplicates, 214 articles underwent screening, with 57 considered relevant for full-text analysis. Forty-eight studies were subsequently excluded: 20 did not meet the eligibility criteria in terms of study design, 27 did not focus on bilateral MRgFUS application, and 1 was excluded because the full text was in a language other than English. Regarding ongoing studies, a search on clinicaltrial.gov identified 14 articles, none of which met the criteria for inclusion in this review as they did not focus on bilateral MRgFUS application. At the end of the selection process, 9 studies were considered eligible (Figure 1 and Tables 1, 2).

Both for ET and PD data were summarized according to the PICO framework (Population of involved patients, Intervention, Comparison with unilateral treatment where available, Outcome identified by the efficacy and safety profile of the intervention). Individual studies were described in chronological order, according to the year published, from the oldest to the most recent ones.

Bilateral MRgFUS in ET

Among the identified studies, 7 papers focused on the bilateral application of MRgFUS for the treatment of medically refractory ET.

In the prospective study by Gallay et al. (21), 21 patients treated with cerebellothalamic tractotomy (CTT) 5.0 mm posterior to the mid-commisural line (MCL) in the anteroposterior (AP) direction, 8.0 mm lateral to the thalamo-ventricular border in the mediolateral (ML) direction, and 3 mm below the intercommissural plane, were described: a subsample of patients (n = 3) underwent bilateral treatments, with a one-year interval between the two sessions. Tremor reduction was assessed through the Clinical Rating Scale for Tremor (CRST). Measures of tremor relief were not provided separately for patients undergoing unilateral and bilateral treatments, respectively: a 55% global CRST reduction was reported at the 1-year follow-up. Bilateral treatment did not produce side effects apart from a persistent slight worsening of pre-existent gait instability in a patient with concomitant documented polyneuropathy and cervical canal stenosis.

In the case-report by Ito et al. (22), a 57-year-old patient treated with bilateral thalamotomy was described. The selected intracranial target was the Ventral Intermediate (VIM) nucleus bilaterally, targeting a point 6.0 mm anterior to the posterior commissure (PC) and 14.5 mm left of the midline, and 1.5 mm above the anterior commissure (AC)-PC plane. The interval between the two treatments was 8 months. Tremor was assessed using the CRST, which revealed complete tremor remission in both hands (no specific percentages of reduction are reported). With respect to side effects, the patient reported dysesthesia in the right occipital region following the first treatment, which spontaneously disappeared 1 month later. No other adverse events occurred following the second treatment. The patient expressed global satisfaction with the treatment, as endorsed by the reported improvement of the EuroQOL (Quality of life) 5-dimension 3-level (EQ-5D-3L) score.

In the case-report by Bruno et al. (23), a 63-year-old patient with an 8-year history of essential tremor with progressive resistance to pharmacological therapy was described. The patient received a bilateral MRgFUS treatment. The selected intracranial target was the

VIM bilaterally, 14 mm laterally from the AC-PC line, 6.7 mm anteriorly from the PC (halfway between 1/3 and 1/4 of the AC-PC distance), 1 mm above the AC-PC line. The time interval between the two treatments was 24 months. Tremor was assessed through the CRST, with scores significantly decreasing following both the procedures (from 48 to 23 for the right side at 6 months and from 36 to 18 for the left side at 6 months). No side effects were reported. Cognitive functions, as assessed through the Montreal Cognitive Assessment (MoCA) scale, remained unchanged following bilateral thalamotomy. The quality of life, investigated through the Quality of Life in Essential Tremor Questionnaire (QUEST), showed a 86% improvement after the treatment of the left VIM and a further 70% after the treatment of the right VIM.

In the prospective study by Iorio-Morin et al. (24), 10 patients receiving bilateral MRgFUS thalamotomy were described. The selected intracranial target was the Vim nucleus bilaterally: the coordinates were 15 mm lateral to the midline or 11 mm lateral to the wall of the third ventricle, 25 mm anterior to the PC along the intercommissural line between the AC and PC and 3 mm superior to the AC-PC plane. The median interval between the two treatments was 9 months. Overall tremor was assessed through the CRST, which revealed a relevant global improvement following the second procedure (38.1 ± 7.5) before the second procedure vs. 20.9 ± 6.4 after the second procedure ($p < 0.0001$) at the 3-month follow-up. Adverse events included transient limb ataxia, dizziness, or neglect, all of which fully resolved by the 3-month follow-up. However, two patients experienced persistent dysphagia at the 3-month follow-up. Quality of life, as assessed through the QUEST, significantly improved after the second-side thalamotomy (mean QUEST score decreased from 35.1 after the first procedure to 15.4, $p = 0.004$ at 3 months following the second procedure).

In the prospective study by Martinez-Fernàndez et al. (25), 9 patients receiving bilateral MRgFUS treatment were described. The selected intracranial target was the thalamus bilaterally and the mean interval between the two treatments was 24 months. Specific target coordinates are not reported in the study. Tremor

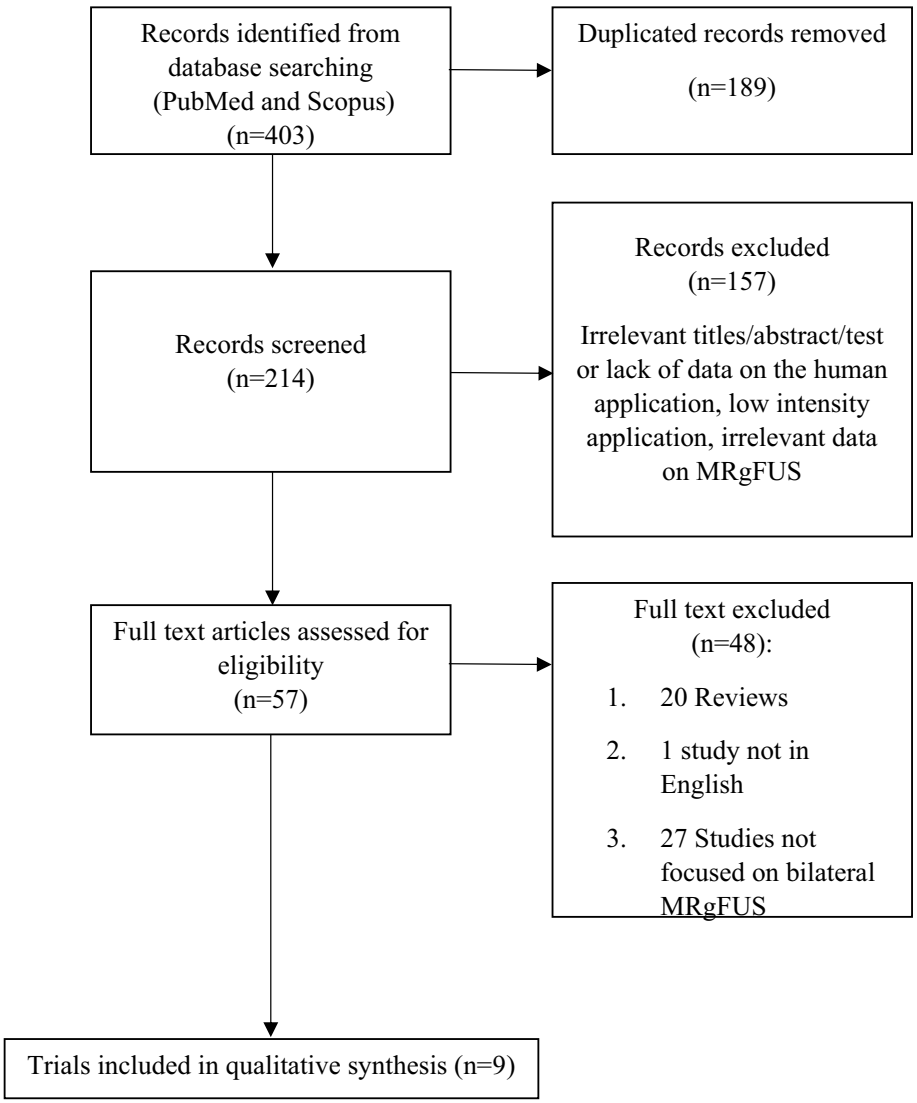

FIGURE 1
Flow diagrams of studies selected.

TABLE 1 Bilateral MRgFUS in ET.

Study	Design, country	Included subjects/ number of treatments	Age range	Disease treated	Disease duration (year)	Target of MRgFUS	Interval between procedures	Temperature achieved	Outcomes	Assessment time points	Results	Adverse events
Gallay et al., 2016	Case series, Switzerland	21 (3 bilateral treatment)	69 ± 9.2	Essential bilateral tremor	29.9 ± 15	Cerebellothalamic tract	1 year	54–60°C	- -ERTS (HF16; HF32) - MoCA - HADS	3 months; 1 year	Mean improvement HF16: - Group 1: 40% - Group 2: 90% Improvement patient treated bilaterally HF16: 75% e 88%, respectively. MoCA and HADS not significantly changed	Worsening of pre-existing gait instability in one patient at 1 year.
Ito et al., 2020	Case report, Japan	1	57	Essential bilateral tremor	1	Ventral intermediate thalamic nucleus (Vim)	8 months	Lefts side: 47.3 ± 6.9°C (range: 40–60°C) Right side: 48.2 ± 6.1°C (range: 43–59°C)	- CRST - EQ-5D-3L	1 month after second treatment	Tremor disappeared in both hands. - EQ-5D-3L: 11112 after first procedure, and 11,111 after the second	none

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TABLE 1 (Continued)

Study	Design, country	Included subjects/ number of treatments	Age range	Disease treated	Disease duration (year)	Target of MRgFUS	Interval between procedures	Temperature achieved	Outcomes	Assessment time points	Results	Adverse events
Bruno et al., 2020	Case report, Italy	1	36	ET	8	Vim	24 months	Not reported	- CRST - QUEST - MoCA	24 h; 1 month; 6 months, 1 year after right side treatment 24 h; 1 month; 6 months after the second treatment	Right side: - CRST: 15, 68.7% reduced. - QUEST: 7, 86% reduced. - MoCA: 30, 11.11% improved. Left side: - CRST: 18, 50% reduced. - QUEST: 3, 70% reduced. - MoCA: no difference	none

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TABLE 1 (Continued)

Study	Design, country	Included subjects/ number of treatments	Age range	Disease treated	Disease duration (year)	Target of MRgFUS	Interval between procedures	Temperature achieved	Outcomes	Assessment time points	Results	Adverse events
Iorio-Morin et al., 2021	Prospective single-arm, single-blinded trial, Canada	10	71.5 ± 7	Essential tremor	>3	Vim	Median 9 months (range, 7–56 months)	62°C (range, 59°C–63°C)	Quality of life and disability: - QUEST - EQ-5D-5L - CRST	2 h; 1 month and 3 months	- QUEST 15.4 ± 11.3 (95%; $p = 0.004$) - CRST part c: 2.4 ± 2.2 (mean difference, 4.2; 95%; $p = 0.005$) - EQ-5D-5L: 80.5 16.1 (mean difference, 6.9; 95%; $p = 0.013$)	dysphagia occurred in 2 patients, only reported the symptom after 3 months.3 of the 10 patients experienced a lasting grade 1 or 2 complication: 4 had transient events that recovered, and 3 did not experience any complication.

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TABLE 1 (Continued)

Study	Design, country	Included subjects/ number of treatments	Age range	Disease treated	Disease duration (year)	Target of MRgFUS	Interval between procedures	Temperature achieved	Outcomes	Assessment time points	Results	Adverse events
Martinez-Fernandez et al., 2021	Prospective case series, Spain and Switzerland	9	71 ± 6	ET	31 ± 15	Vim	24 ± 18 months	Not reported	Safety and efficacy: - CRST - Incidence and severity of treatment related complication	4 weeks ± 14 before second thalamotomy; 6 months ±30 after second thalamotomy	- CRST: 15.5 ± 9.4 (71%; $p < 0.001$)	Five out of nine patients developed transient gait instability. One patient showed dysarthria, remitted in 4 weeks. Three patients developed mild perioral sensory disturbances
Fukutome et al., 2022	Retrospective observational, Japan	5	57.4 ± 17	ET	>6	Vim	27.8 ± 11.48 months	55°C	- CRST and part C - VAS - MMSE - FUJISHIMA GRADE	3 months after each operation	- CRST: 21.8 (65.72% reduction) - CRST part C: 2.6 (85.87% reduction) - MMSE: 28–30 - FUJISHIMA GRADE: 10 - VAS: 74 ± 19.7	None after the first operation. After second operation 3 patient experienced permanent slight dysarthria and dysthesia of the complement.

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TABLE 1 (Continued)

Study	Design, country	Included subjects/ number of treatments	Age range	Disease treated	Disease duration (year)	Target of MRgFUS	Interval between procedures	Temperature achieved	Outcomes	Assessment time points	Results	Adverse events
Scantlebury et al., 2023	Prospective case series, Canada	11	71 ± 8	ET	33 ± 18	Vim	35.27 ± 23.59 months	Not reported	- CRST part A-B - FDA-2 - QUEST - Gait and Stance itemo from SARA	3–6 months	- CRST: 8 ± 4.95; $p < 0.001$ - QUEST improved in "financial," $p = 0.0043$; "Hobbies," $p = 0.007$; "physical," $p = 0.001$; "psychosocial" $p = 0.002$	Short lasting (<24 h) shoulder pain, nausea, headache

was assessed through the CRST, showing improvement in all patients: the total CRST score decreased by 71% from baseline to the second procedure, with a 44% reduction after the first thalamotomy ($p = 0.004$) and an additional decrease of 50% after the second procedure ($p = 0.008$). Adverse events following the second treatment were mild and transient, including gait instability in five patients, worsening of pre-existing gait instability in one patient, dysarthria in one patient, and mild perioral sensory disturbances in two patients. All these symptoms showed full improvement within a few weeks after the last treatment. No differences after the second thalamotomy were observed in cognitive functions. In addition, the evaluation of voice through the Voice Handicap Index-30 (VHI) revealed a 40% improvement (25).

In the retrospective study by Fukutome et al. (26), 5 patients treated with bilateral VIM thalamotomy were described: the target was 11 mm lateral to the third ventricle wall, 5–5.5 mm posterior to the midcommissural point (MCP) at the level of the intercommissural line. The second procedure was performed slightly anteriorly and superiorly to the first, to avoid symmetrical lesioning. An average interval of 27.8 months between the two procedures was reported. Tremor reduction was assessed through the CRST. Significant improvement was observed after both the first and the second procedure, with the CRST score decreasing from 63.6 at baseline to 49.2 before the second intervention and to 21.8 after the second intervention (no significance level values were reported). No patients reported adverse events after the first sonification. However, following the second procedure, three patients experienced transient symptoms, including numbness of the lips, paresthesia, or limb weakness, lasting from a few days to 3 weeks. One patient reported permanent dysarthria and paraesthesia of the tongue. All patients expressed satisfaction with the treatment, as evidenced by an average visual analog scale (VAS, range 0–100) score of 74. Cognitive functions were assessed using the Mini-Mental State Examination (MMSE), with scores consistently maintained between 28 and 30 even after the second intervention. Quality of life, as assessed through part C of the CRST, improved by 85.87%, decreasing from a baseline value of 18.4 to 8.2 after the first procedure and to 2.6 following the second MRgFUS procedure (no significance level values were reported).

Finally, in the prospective study by Scantlebury et al. (27), 11 patients undergoing a second MRgFUS intervention were described. The selected intracranial target was the thalamus bilaterally and the mean interval between the two treatments was 35 months. Specific target coordinates are not reported in the study. Tremor severity was assessed using the CRST scale, which revealed a significant improvement after both the first and the second procedure: CRST scores for the targeted hand improved after each MRgFUS ($p < 0.001$), while the untargeted-hand tremor had no significant change. Many periprocedural adverse effects were detected, including transient shoulder pain in two patients, headaches in two patients, and nausea in one patient, all of which resolved quickly. Persistent perioral or finger paraesthesias were identified in four patients at the 6-month follow-up, although the symptoms did not impact their activities of daily living. Concurrent improvements in QUEST scores in the "financial," "hobbies/leisure," "physical," and "psychosocial" domains were recognized.

TABLE 2 Bilateral MRgFUS in PD.

Study	Design, country	Included subjects/ number of treatments	Age range	Disease treated	Disease duration (year)	Target of MRgFUS	Interval between procedures	Temperature achieved	Outcomes	Assessment time points	Results	Adverse events
Gallay et al., 2020	Prospective case series, Switzerland	52 (15 bilateral treatment)	67 ± 10	Chronic therapy resistant PD	10 ± 5.3	Pallidothalamic tract	At least 6 months	43°, 240 CEM	Primary: UPDRS; GSRt; GSRb; reduction drug intake; off dystonia; on dyskinesias; sleep disturbances; pain; Secondary: MoCA; WHOQOL; HADS	2 days; 3 months; 1 year	At 1 year: - UPDRS—UPDRS reduction: 46% on-medication ($n = 21$; $p < 0.001$) and 51% off-medication ($n = 25$; $p < 0.001$); - GRSb: 69 ± 27 ($n = 27$, median: 80, 85% improved by ≥50%) - GSRt 82 ± 22 ($n = 29$, median: 90, 93% improved by ≥50%). Secondary outcomes did not reached statistically significance differences	One patient with scalp hypoesthesia fully recovered in 3 months. One patient suffered from a short-lived intense anxio-depressive episode from which he rapidly and completely recovered. Seven patients reported increased (two patients) or new (five patients) speech difficulties (UPDRS II, item 5); at 1 year, they were 2 and 4, respectively.

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TABLE 2 (Continued)

Study	Design, country	Included subjects/ number of treatments	Age range	Disease treated	Disease duration (year)	Target of MRgFUS	Interval between procedures	Temperature achieved	Outcomes	Assessment time points	Results	Adverse events
Gallay et al., 2021	Retrospective observational, Switzerland	10	63 ± 5	Chronic therapy resistant PD	10.2 ± 4.6	Pallidothalamic tract	20 ± 10 months (median: 16.5; range: 5–38)	43240CEM	Primary: - UPDRS-dyskinesias - off- and on-dystonia - drug intake Secondary: - MoCA - WHOQOL - . HADS	before second side treatment; 1 year	- UPDRS 29 ± 11 (52% reduction; $p < 0.007$) - dyskinesias (choreoathetosis) were suppressed in four over four, dystonia in four over five patients - 7/10 stopped al drug intake, alla stopped dopamine agonist. Secondary outcomes changes were not statistically significant.	One patient suffered hiccup and breathing difficulties, regressed in 10 months. One patient reported to be slightly dragged to his right side, improved after bilateral PTT. At 1 year after bilateral PTT, one patient experienced episodes of uncontrollable laughter.

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Bilateral MRgFUS in PD

In the prospective study by Gallay et al. (28), a series of 52 patients was described. Among them, 15 patients underwent bilateral MRgFUS, with two patients receiving the treatment in a single session and the others undergoing staged sessions. The selected intracranial target was the pallidothalamic tract 6.5 mm from the medial thalamic border and 1 mm posterior to the MCL (28). The time interval between the two procedures was at least 6 months. Tremor was evaluated using the Unified Parkinson's Disease Rating Scale (UPDRS). Measures of tremor relief were not provided separately for patients undergoing unilateral and bilateral treatments, respectively: a 37% total UPDRS III score reduction was reported at 3 months ($p < 0.01$) and a 46% reduction at 1 year ($p < 0.001$). Irregular final follow-ups were obtained for the different patients: a small group of patients receiving bilateral treatment had a 1-year follow-up (only four patients), showing similar results compared to patients receiving unilateral treatment. A 55% reduction of the mean L-Dopa intake was also observed. No adverse effects related to the bilateral nature of the procedure were identified. Regarding the perception of quality of life, statistical significance was only reached for the World Health Organization Quality of Life (WHOQOL) item 2 (How satisfied are you with your health?) at 3 months ($p < 0.001$) and at 1 year ($p < 0.005$) and for the WHOQOL item 1 (how would you rate your quality of life) at 3 months ($p = 0.002$).

In a retrospective study by Gallay et al. (29), data confined to 10 patients with PD treated with bilateral MRgFUS are reported. The selected intracranial target was the pallidothalamic tract using the same targeting protocol as in the previous study (28). Tremor was assessed through the UPDRS, whose total score decreased from 65 ± 25 at baseline to 29 ± 11 1 year after the second intervention (52% reduction, $p < 0.007$). A reduction of the mean L-Dopa intake was also observed, from 690 ± 250 mg to 110 ± 190 mg 1 year after the second treatment. Seven patients had completely discontinued pharmacological therapy, and all 10 included patients had stopped using dopaminergic agonists. Regarding adverse events, one patient experienced respiratory and language difficulties, which resolved after 10 months. Another patient reported episode of falls and a deviation to the right while walking, with all symptoms resolving within 1 week. Cognitive effects were evaluated using the MoCA, but no cognitive changes were observed after the two procedures. The mean WHOQOL score showed a slight improvement, increasing from 93 ± 11 to 95 ± 11, but these changes were not statistically significant.

Discussion

Our systematic review indicates that bilateral MRgFUS treatment could be an effective and promising clinical option for managing patients with ET and PD when tremor is refractory to pharmacological therapy. Available studies suggest that bilateral MRgFUS often yields better results compared to unilateral treatment, particularly in terms of improvements in quality of life, with an additional positive effect being observed after the second procedure (22, 24, 26, 28). The time elapsed between the first and the second intervention can vary from 6 months to 3 years, with significant heterogeneity observed across the studies. The limb initially treated typically continues to benefit from the effects of the first procedure, and no severe or persistent adverse effects have been observed following the treatment of the second limb. It can be hypothesized that postponing the second procedure ensures that the circuits involved, which were modulated during the first lesion, undergo stabilization before proceeding with contralateral treatment. This is contrary to what occurs with the MRgFUS management of refractory pain, where bilateral lesioning is performed in a single session. The difference is likely attributable to the fact that both ET and PD, unlike pain syndromes, are neurodegenerative diseases with a progressive and somewhat unpredictable natural history: thus, staging the second procedure may be preferable and more cautious. Staging the second treatment allows employing a waiting period to monitor the stability of the effects achieved with the initial procedure and to evaluate potential responses, including adaptive or maladaptive changes, in the broader neuronal circuits passing through the lesion site but extending beyond it (23, 29). The selected intracranial target is almost always the VIM. However, Gallay et al. (28) suggested the utility of targeting the pallidothalamic tract, particularly in bilateral procedures, to preserve the integrity of the thalamocortical network, thereby reducing motor and cognitive adverse events: however, their findings are too much preliminary and heterogenous to draw conclusions and deserve further investigations through specifically designed longitudinal case–control studies.

Overall, patient's satisfaction following the second procedure and the safety profile are high, due to the minimally invasive nature of the technique and the rapid recovery of autonomy in activities of daily living. Given the rapid increase in the incidence of neurodegenerative diseases (30), ensuring a bilateral solution to the problem of medically refractory tremor significantly improves the quality of life of affected patients. The reduction in tremor, along with the preservation of all neurological functions, including cognitive functions, is an important objective in managing patients with ET or tremor-dominant PD. In the latter, of course, other motor symptoms and signs of the disease such as bradykinesia and rigidity are not influenced by MRgFUS, even some improvements following the second procedure have been reported (28): however, whether these improvements have been causally related to the procedure is yet to be determined. Nevertheless, the reduction in tremor alone can positively impact patients' autonomy and quality of life. Some studies addressing unilateral MRgFUS thalamotomy confirmed the safety of the MRgFUS approach even with respect to cognitive functions (18). The contribution of these studies in the assessment of cognitive functions after unilateral MRgFUS was important in planning bilateral procedures. Indeed, while any adverse effects related to motor or sensory functions, language, or coordination can be directly ruled out during intraoperative monitoring, the same cannot be done for cognitive adverse events, which may manifest weeks or even months after the procedure. The data obtained in this context are highly reassuring because they not only indicate the absence of cognitive complications, even in the long term, but also suggest that there may be a slight improvement in overall cognitive performances of patients managed with unilateral MRgFUS thalamotomy. This improvement is likely driven by a reduction in patient distractibility due to the tremor itself, a reduction in social embarrassment caused by the tremor

and an improvement in anxiety levels. The studies included in this systematic review confirm this aspect, regardless of the site of sonification treatment; in fact, the cognitive performance of the patients examined has never been affected, and in most cases, it has even been enhanced. Regarding adverse effects, the most frequent ones were dysarthria, ataxia, and gait disturbance. However, both the percentage and severity of adverse effects are progressively decreasing. This trend can be attributed to improved localization techniques, which enhance precision, and a more accurate differentiation from pre-existing symptoms related to the disease, thereby excluding them from consideration as adverse events (31). Given the heterogeneity of intervention protocols in various studies, it was not possible to highlight an optimal protocol for the bilateral administration of MRgFUS. However, all studies were based on the evaluation of functional and cognitive outcomes of the first treatment before deciding to proceed with contralateral sonification. Therefore, there is still no strong recommendation for the use of bilateral thalamotomy to date: attention must be paid to patient selection criteria for this procedure, preferably identifying those who have not experienced adverse effects after the first sonification session and who have maintained good neuropsychological performance in the following months (26).

In conclusion, this systematic review suggests that bilateral thalamotomy treatment with MRgFUS represents an effective and safe alternative approach in the treatment of patients diagnosed with medically refractory ET or PD related tremor. The data were collected in a limited and heterogeneous sample, but they are promising and encouraging. Overall, the studies are too heterogeneous to allow for a robust comparison of the data and generalization of the results to all patients with ET and PD. High-quality evidence is crucial to reach higher levels of evidence and standardizing the protocols used.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

Author contributions

SC: Writing – original draft, Data curation, Formal analysis, Investigation, Methodology. GS: Conceptualization, Data curation, Formal analysis, Writing – original draft. PS: Formal analysis, Investigation, Writing – review & editing. FB: Conceptualization, Writing – review & editing. AC: Conceptualization, Writing – review & editing. MP: Conceptualization, Writing – review & editing. AS: Conceptualization, Writing – review & editing. AR: Conceptualization, Writing – review & editing. EC: Conceptualization, Writing – review & editing. RT: Conceptualization, Writing – review & editing. FP: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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"Quality over quantity:" smaller, targeted lesions optimize quality of life outcomes after MR-guided focused ultrasound thalamotomy for essential tremor

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Introduction: MRI-guided focused ultrasound (MRgFUS) thalamotomy of the nucleus ventralis intermedius (VIM) has emerged as a powerful and safe treatment modality for refractory essential tremor. While the efficacy of this technique has been extensively described, much remains unclear about how to optimize MRgFUS for patient quality of life (QoL), which may depend as much on a patient's adverse effect profile as on the magnitude of tremor suppression. Diffusion tensor imaging (DTI) has been used to help guide targeting strategies but can pose certain challenges for scalability.

Methods: In this study, we propose the use of a simplified patient-reported change in QoL assessment to create an unbiased representation of a patient's perception of overall benefit. Further, we propose a large-sample-size, high-resolution, 7 T DTI database from the Human Connectome Project to create a normative tractographic atlas (NTA) with representations of ventral intermediate nucleus subregions most likely to be structurally connected to the motor cortex. The NTA network-based hotspots are then nonlinearly fitted to each patient's T1-weighted MRI.

Results and discussion: We found that smaller lesion size and higher extent to which the lesion is within the NTA hotspot predicted patients' change in QoL at last follow-up. Though long-term change in clinical rating scale for tremor (CRST) impacted QoL, neither intraoperative tremor suppression nor the patient's long-term perception of tremor suppression correlated with QoL. We provide an intraoperative threshold for accumulated dose volume (<0.06 cc), which along with the network-based hotspot in the NTA, may facilitate an easily scalable approach to help limit treatment to small, safe yet effective lesions that optimize change in QoL after MRgFUS.

KEYWORDS

MRI-guided focused ultrasound surgery, quality of life, thalamotomy, essential tremor, normative tractographic atlas

Introduction

Essential tremor (ET) is the most common movement disorder, estimated to affect approximately 5–6% of adults over the age of 60 (1). Up to half of patients remain debilitated despite medical management (2, 3, 56), leading to referral for treatment with deep brain stimulation (DBS) or thalamotomy targeting the nucleus ventralis intermedius (VIM) of the thalamus, a sensorimotor integration center connecting the cerebellum to cortical motor pathways (3–5).

MRI-guided focused ultrasound (MRgFUS), an incision-less approach, is increasingly used to treat essential tremor of the hands. While prior studies have established improvement in tremor from and the safety profile of MRgFUS thalamotomy (6–8), less emphasis has been placed on overall post-procedural quality of life (QoL), which likely reflects a subjective combination of tremor relief, freedom from debilitating side effects, and overall impact of the procedure. The relationship between tremor control and QoL can be highly variable between different cohorts and studies (9–15), likely driven by a patient-specific subjective balance between the impacts of tremor suppression and potential side effects on a patient's quality of life. For example, ataxia, the most frequent side effect after MRgFUS thalamotomy, may be sustained in 18% of patients long term (6); such a side effect may outweigh alleviation of tremor in patients' own assessment of their overall treatment-induced change in QoL. The Fahn-Tolosa-Marin Clinical Rating Scale for Tremor (CRST) typically used to quantify the results of MRgFUS thalamotomy (57) does not address patient satisfaction. The Quality of Life in Essential Tremor (QUEST) questionnaire (16) asks about QoL only in terms of the impact of tremor on specific daily functions and overall health status. Without a more directed question about treatment-induced change in QoL, patients may not know to report the impact of any non-tremor related effects on current QoL. This introduces a potential limitation for understanding the relative impact of tremor suppression versus non-tremor related effects on quality of life. Therefore, we introduced a simplified, patient-reported impression of change in overall QoL after their procedure to measure how patients qualitatively assess the impact of the procedure as a whole.

Traditionally, MRgFUS thalamotomy targeting has relied on canonical, indirect targeting to estimate the location of the VIM nucleus, as it is not readily visible on MRI (17). Due to uncertainty regarding the location of the VIM, patients are kept awake and frequently examined to solicit immediate clinical feedback, facilitating rapid adjustment of the target (18). With this approach, if ablation at the canonical target produces incomplete tremor suppression, then target adjustment is based entirely on clinical feedback, increasing lesion size and prolonging procedure time. Patient-specific diffusion tensor imaging (DTI) can optimize targeting (4, 19, 20, 58) however, high-resolution DTI is technically challenging to acquire, and non-uniform fiber tracking algorithms across both deterministic and probabilistic approaches may lead to a lack of reliability and overall accuracy (21), which may contribute to difficulty with scaling this approach across academic and non-academic hospital settings. Here, we propose the use of a large-sample-size, high-resolution, 7 T DTI database from the Human Connectome Project to create a normative tractographic atlas (NTA) to identify VIM subregions likely to be structurally connected to the motor cortex. The NTA network-based hotspots are then nonlinearly fitted to each patient's imaging. In a retrospective cohort, we investigated the relationships between MRgFUS treatment-related QoL change and lesion characteristics, as well as the extent to which the lesion fell within the patient-fit NTA hotspot.

Methods

Patient selection

This study included 60 patients who were treated with commercial (post-FDA-approval) MRgFUS ablation for disabling upper extremity tremor at Stanford University prior to July 2020, before implementation of some of the advanced targeting techniques highlighted, enabling unbiased review of clinical QoL outcomes and lesion/hotspot characteristics. Medical records and imaging were retrospectively reviewed and processed. Inclusion criteria included age at least 18 years, diagnosis of ET with or without Parkinsonian features confirmed by a movement-disorders-trained neurologist and the treating neurosurgeon, and post-treatment follow-up of at least 90 days. Patients without a preoperative noncontrast magnetization-prepared rapid gradient-echo (MPRAGE) scan acquired at 3 T were excluded (see Table 1 for imaging parameters). This study was approved by the Stanford University Institutional Review Board.

Tremor suppression and QoL assessment

Participants were seen for a preoperative visit, where their symptoms and the effects on activities of daily living were evaluated using the Fahn-Tolosa-Marin Clinical Rating Scale for Tremor (CRST; Fahn et al., 1988). On the day of treatment, CRST parts A (limited to tremor amplitude) and B were repeated immediately prior to treatment, with part B being repeated after each ablative sonication and at the end of the treatment session. The part B assessment included drawing an Archimedes spiral, drawing three straight lines, and writing their name. MRgFUS therapy was delivered according to standard-of-care treatment guidelines as outlined in Elias et al. (7, 22). Lesion characteristics, including accumulated dose volume (in cc), were recorded. Participants were reached for an initial telephone call an average of 4.89 ± 1.35 days after their procedure, followed by up to two additional calls in the weeks after the day of treatment to assess for rapid development of side effects. Participants were then seen in the clinic for a first follow-up visit an average of 144 ± 21 days after the day of treatment, followed by up to two additional clinic visits; CRST assessments were repeated at in-person clinic appointments. Participants were discharged from the study after three follow-up visits without a need for ongoing treatment, after they could no longer be reached for further follow-up, or at the end of study enrollment, whichever occurred last. Because the Clinical Rating Scale for Tremor typically used to quantify the results of MRgFUS thalamotomy does not address patient satisfaction, and because the Quality of Life in Essential Tremor (QUEST) questionnaire (16) asks about QoL only in terms of the impact of tremor on overall health status, we introduced a simplified, patient-reported, subjective change in QoL after their procedure to measure how patients qualitatively assess the impact of the procedure. At last follow-up, participants were asked to holistically assess their quality of life compared to before treatment in terms of tremor relief, side effects, and impacts on activities of daily living, and

TABLE 1 MRI sequence parameters.

	Preoperative MPRAGE (BRAVO or T1-FFE)	Postoperative T2-weighted CUBE	Postoperative FGATIR
Echo time (or Effective Echo Time)	3.0–3.5 ms	84–96 ms	3.9–5.4 ms
Repetition time	7.9–8.2 ms	2,502 ms	9.7–12.7 ms
Inversion time	400 ms		300 ms
Echo train length		100	
Flip angle	8-13°	90°	7°
Reconstructed matrix size	512 × 512 × 170–344	512 × 512 × 121	512–568 × 512–568 × 178–232
Field of view	240 × 240 × 170–188 mm	240 × 240 × 242 mm	200–260 × 200–260 × 155–178 mm

The typical parameters used to acquire and reconstruct the preoperative T1-weighted MPRAGE and postoperative T2-weighted CUBE and FGATIR images in the patients in this study.

choose "better," "approximately the same," or "worse". Any adverse effects experienced were documented at each postoperative contact.

Lesion segmentation

Approximately 30 min after treatment (after removal of the ultrasound transducer helmet), MRI, including volumetric T2-weighted fast spin echo (CUBE) and fast gray matter acquisition T1 inversion recovery (FGATIR) (3 T Discovery MR 750, GE Healthcare) sequences (Table 1), were acquired using an 8-channel head coil. These MRIs were manually segmented using ITK-SNAP software (23). Zones I and II, corresponding to durable lesions, were segmented; zone III, corresponding to vasogenic edema (24), was excluded.

Normative tractographic atlas creation

Normative tracts were identified using probabilistic tractography on high-resolution 7 T diffusion data from the Human Connectome Project (HCP) (25). This data has 1.05 mm isotropic resolution and approximately 65 diffusion weighting directions spread over two shells with b-values of 1,000 and 2000 s/mm^2. For each of the 178 subjects in the HCP dataset, a nonlinear (i.e., deformable) transform mapping from the MNI152 nonlinear 2009c brain (59) to that subject's brain was found using image registration tools from the ANTs software package (26) after brain extraction. Each patient's transform was used to warp the VIM region of interest (ROI) from the DISTAL Medium atlas (27), and the precentral gyrus ROI from the Harvard-Oxford atlas (28–31), from MNI space to the subject's brain to serve as the seed and terminus regions, respectively, for tractography. Probabilistic tractography from VIM to the precentral gyrus (VIM-precentral) (Figure 1a) was performed using FSL software (60). FSL bedpostx determines the distribution of diffusion parameters at each voxel, automatically determining the number of and modeling crossing fibers. The subject's network-based VIM-precentral hotspot was created as follows: for each voxel within the subject-fit VIM ROI, the intensity of the VIM-precentral hotspot is the percent of streamlines launched from that voxel that reached the ipsilateral precentral gyrus ROI (determined using FSL probtrackx2's "--os2t" output seeds to terminus option). The inverse of the MNI-to-subject transform was applied to the subject's network-based hotspots to warp them back to MNI space. Finally, the 178 MNI-space network-based VIM-precentral hotspots (each specific to one of the 178 HCP subjects) were median-averaged to create normative, network-based VIM-precentral hotspot objects. The normative VIM-precentral hotspot object was divided by its maximum values to form the VIM-precentral regions in the NTA, which thus ranges from 0 to 1. Note that for the NTA we are using VIM-precentral to refer to the normative representation of the seeds to termini, not the tract itself. These NTA regions (Figure 1b) are shared at https://github.com/adatta92/VIM2precentral.

Patient-fitting of NTA regions and calculation of normative tractographic coefficients

After FSL brain extraction of both the MNI152 and patient preoperative T1 images, a nonlinear transform mapping from the MNI brain to each patient's brain was found using ANTs image registration tools. The inverse of this transform was used to warp the NTA VIM-precentral objects to each patient's T1-space. A rigid transform between the patient's postoperative (either T2-weighted-CUBE or FGATIR) MRI and preoperative T1-weighted MRI was also found using ANTs (no brain extraction). The manually segmented FUS thalamotomy lesions (as described in the "lesion segmentation" subsection above) were coregistered to the patient-fit NTA hotspots using this transform. To quantify the degree to which the lesion falls within the patient-fit NTA VIM-precentral regions, we calculated the average value of the patient-fit NTA object over the voxels of the coregistered lesion segmentation. This quantity was named the normative tractography coefficient (NTC). A lesion that only contained the voxel where the patient-fit NTA hotspot is at its maximum would thus have an NTC of 1, while a lesion that does not overlap with any of the patient-fit NTA object would have an NTC of 0. In practice, none of our NTC values reached either of these extremes.

Use of standard clinically acquired DTI for probabilistic tractography

The clinically acquired (lower resolution) DTIs (3 T, 1 mm x 1 mm x 2 mm resolution, 30 diffusion weighting directions, b-value of 1,000 s/mm^2), were used to run patient-specific probabilistic tractography using FSL. Tracking was performed from the patient-fit VIM to the patient-fit precentral gyrus, as done in the 7 T HCP datasets. Dentatorubrothalamic

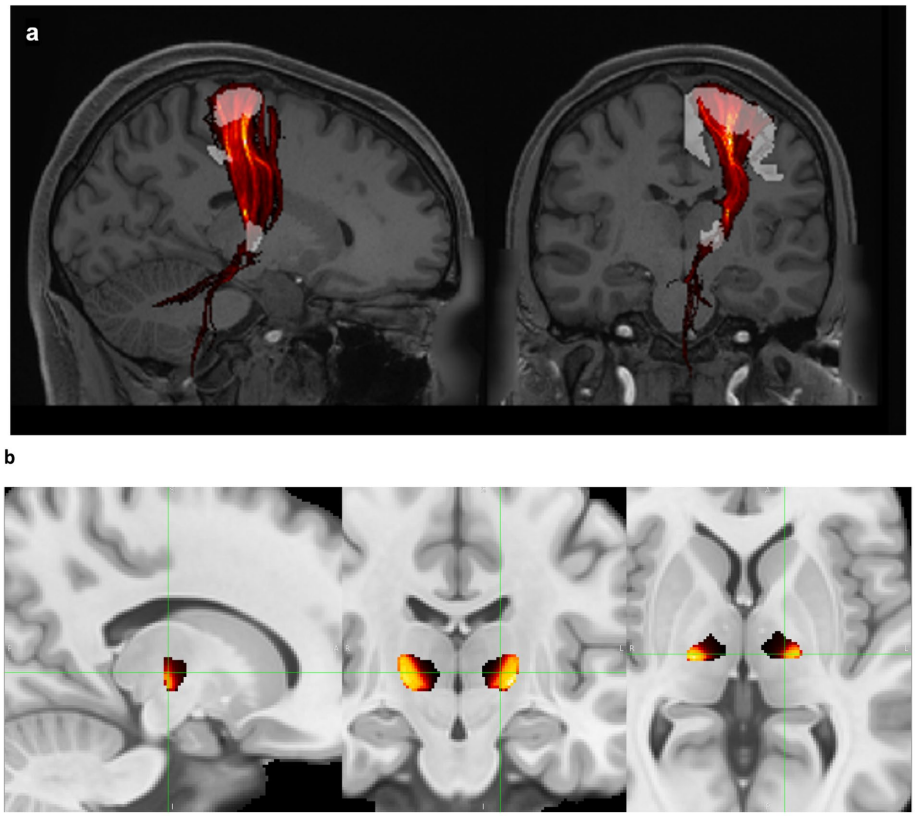

FIGURE 1
Normative tractographic atlas. (a) VIM-precentral streamlines (red, thresholded and displayed as a maximum intensity projection) connect the brainstem, cerebellum, VIM (white), and motor cortex (white) in a subject in the Human Connectome Project 7 T database. (b) Normative VIM-precentral objects (the seeds most likely to project to motor cortex) in hot colors within the entire VIM (black) in MNI space. In MNI space, the green crosshairs are at the medial apex of the hottest voxels (15 mm lateral to midcommissural plane, 1 mm anterior to the 25% ACPC distance from PC, and 2 mm superior), which represents the MNI-space target for MRgFUS due to the predominant inferoanteriolateral spread of sonication energy. Exact coordinates of this point vary for each patient based on the nonlinear transform back to individual native space.

probabilistic fiber tracking was also attempted from the thalamus to the hand knob region of the motor cortex to mirror the probabilistic tractography performed with high-resolution DTIs in (32). We tabulated the number of patients in whom probabilistic tracking from the VIM to the precentral gyrus was successful.

Results

Tremor suppression and relationship to patient-reported QoL outcome

Sixty patients (76.0 ± 1.10 years) reported their self-assessed change in QoL at last follow-up (405 ± 44 days) post-treatment. Of those, 37 (61.7%) rated their QoL as "better," 14 (23.3%) rated their QoL as "approximately the same," and 9 (15%) rated their QoL as "worse" since treatment. On the day of each patient's MRgFUS procedure, scores from CRST part B drawings sections A and C were calculated immediately before and after treatment. Each group of patients stratified by patient-reported QoL assessment at last follow-up had significant reduction in tremor on the day of treatment (QoL "better": CRST-B section A + C 5.5 ± 0.31 to 2.1 ± 0.17; QoL "approximately the same": 6.2 ± 0.36 to 1.7 ± 0.29; QoL "worse": 6.0 ± 0.47 to 2.6 ± 0.73; all $p = 0.009$), with similar tremor reduction across all groups (Kruskal-Wallis $H = 3.5697$, $p = 0.168$; Figure 2). Thus, immediate post-procedure tremor reduction did not vary between categories of patient-reported change in QoL at last follow-up. At last follow-up, 31/32 (96.9%), 36/44 (81.8%), and 21/23 (91.3%) patients had improved scores on CRST parts A (in the treated hand only), B (treated hand only without pouring), and C (function only, not including global assessment), respectively. Five of the part A, four part B, and two part C scores were measured at less than 90 days after the patient's procedure, but all were at greater than 30 days post-procedure. There was a significant association between level of tremor reduction at last follow-up as measured by CRST subpart scores and QoL category (part A: $H = 6.6039$, $p = 0.036$; part B: $H = 6.5706$, $p = 0.037$; part C: not enough respondents; Figures 3a–c).

At last follow-up, patients reported an average subjective tremor suppression of 78.4 ± 4.1%, with the majority reporting ≥80% reduction (Figure 4a). While there is significant interaction between subjective tremor suppression magnitude and QoL category ($H = 15.923$, $p = 0.0003$; as there were only four reported

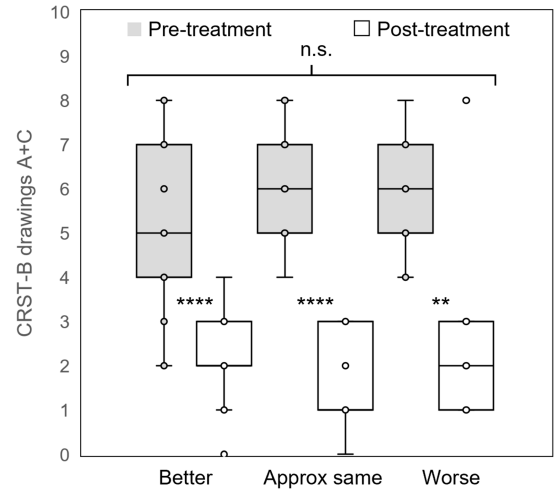

FIGURE 2
Immediate post-procedural tremor reduction. Groups of patients who self-assessed their quality of life as "better," "approximately the same," or "worse" at last follow-up all experienced significant reduction tremor as measured by the CRST part B Archimedes spiral and straight-line drawings on the day of treatment; however, there was no difference in tremor reduction between groups. CRST: Clinical Rating Scale for Tremor; **: $p < 0.01$; ****: $p < 0.001$; n.s.: not significant.

tremor suppression scores in the "worse" QoL group, an additional value equivalent to the mean of the four "worse" QoL tremor suppression scores was added to the "worse" QoL group in order to obtain the requisite five values necessary for Kruskal-Wallis testing), there is no significant difference between the subjective tremor reduction for patients who rated their QoL "better" versus for those who rated their QoL "worse" ($p = 0.44$; Figure 4b). Both groups reported relatively high subjective tremor suppression ("better": 86.8 ± 3.1% versus "worse": 93.2 ± 3.5%), whereas the group rating their subjective QoL as "approximately the same" by last follow-up reported less subjective tremor reduction (46.7 ± 10.4%).

Adverse effects and QoL outcomes

Most patients (50/60, 83.3%) experienced some adverse effect (AE) at the time of the first follow-up phone call (4.89 ± 1.35 days). All patients in this cohort received intraoperative steroids and a standard, postoperative one-week steroid taper. Thirteen patients (21.6%) had persistent self-reported sensorimotor AEs at the time of last follow-up. The most frequent sensorimotor AE experienced by patients was gait ataxia (8/60, 13.3%), followed by contralateral limb ataxia or weakness (5/60, 8.3%), dysarthria (4/60, 8.3%), and decreased sense of taste or smell (2/60, 3.3%); one patient each (1.7%) experienced tongue numbness, contralateral limb numbness, dysphagia, or fatigue (Figure 5a). Additionally, four patients self-reported cognitive or behavioral changes after the procedure (6.7%). The AEs with the highest proportion of patients experiencing that AE who reported "worse" QoL at last follow-up were dysarthria (3/4, 75%), limb ataxia/weakness (3/5, 60%), cognitive/behavioral changes (2/4, 50%), decreased taste/smell (1/2, 50%), and gait ataxia (2/8, 25%) (Figure 5c). Additionally, no patients who experienced dysarthria at last follow-up rated their QoL as "better" than before the procedure.

Effect of skull density ratio, dose volume, lesion size, and normative tractographic coefficients on QoL outcomes

Stratified by patient QoL assessment at last follow-up, the skull density ratio (SDR) of "worse" patients was highest (0.64 ± 0.03), followed by "better" (0.58 ± 0.02), and lastly "same" (0.53 ± 0.03), with the group differences trending toward significance (Kruskal-Wallis $H = 4.7705$, $p = 0.09$). For most patients, SDRs were calculated from preoperative CT scans acquired using a GE Revolution CT at our institution. For any patient's imaged elsewhere using non-GE CT scanners, a correction factor is utilized by Insightec to attempt to normalize SDRs to the GE-derived standard.

Lesion characteristics were calculated and stratified by patient QoL assessment at last follow-up (Figures 6a,b). Smaller accumulated dose volume (Kruskal-Wallis $H = 14.2693$, $p = 0.0008$; Figure 6a) was significantly associated with greater subjective QoL assessment. FUS thalamotomy lesions (green) and NTA hotspots thresholded to >0.6 (hot colors) are shown for exemplar patients who self-assessed their QoL at last follow-up to be "better" (Figure 6c), "approximately the same" (Figure 6d), and "worse" (Figure 6e). Despite having similar treatment-day reductions in tremor, the lesion of the patient whose QoL improved was smaller and best encapsulated by the NTA hotspot, while the lesion of the patient whose QoL decreased was largest, with much of the ablated volume superior and medial to the hotspot. The "same" QoL patient had the smallest lesion of the three, located slightly medial to the brightest voxels of the hotpot.

To facilitate calculation of classifiers that would allow us to avoid worse QoL outcomes, we binarized QoL outcomes by combining patients who self-assessed as "better" and "approximately the same" into a single "better/same" group. "Better/same" QoL outcomes were significantly associated with smaller lesion volume ($p < 0.0001$; Figure 7a), smaller accumulated dose volume ($p < 0.0001$; Figure 7b), and higher normative tractographic coefficient with the NTA VIM-precentral hotspot (NTC; $p = 0.046$; Figure 7c).

To determine values of intraprocedural treatment parameters and of normative tractographic coefficients that might optimize for better QoL outcomes, receiver operating characteristic curves were generated and optimization points with maximum Youden index were identified that maximize the balance between sensitivity and specificity (Table 2). Immediate post-operative lesion volume less than 127 mm^3, intraprocedural accumulated dose volume less than 60 mm^3, and lesion/VIM-precentral coefficient (NTC) greater than 0.54 were all associated with "better/same," versus "worse," QoL outcome.

Since late 2018, the stereotactic coordinate that was used for targeting has been 11 mm from the lateral wall of the third ventricle, ¼ of the anterior commissure-posterior commissure (AC-PC) distance anterior to PC, and 2 mm above the intercommissural plane, similar to (33). There is no association between the Euclidean distance

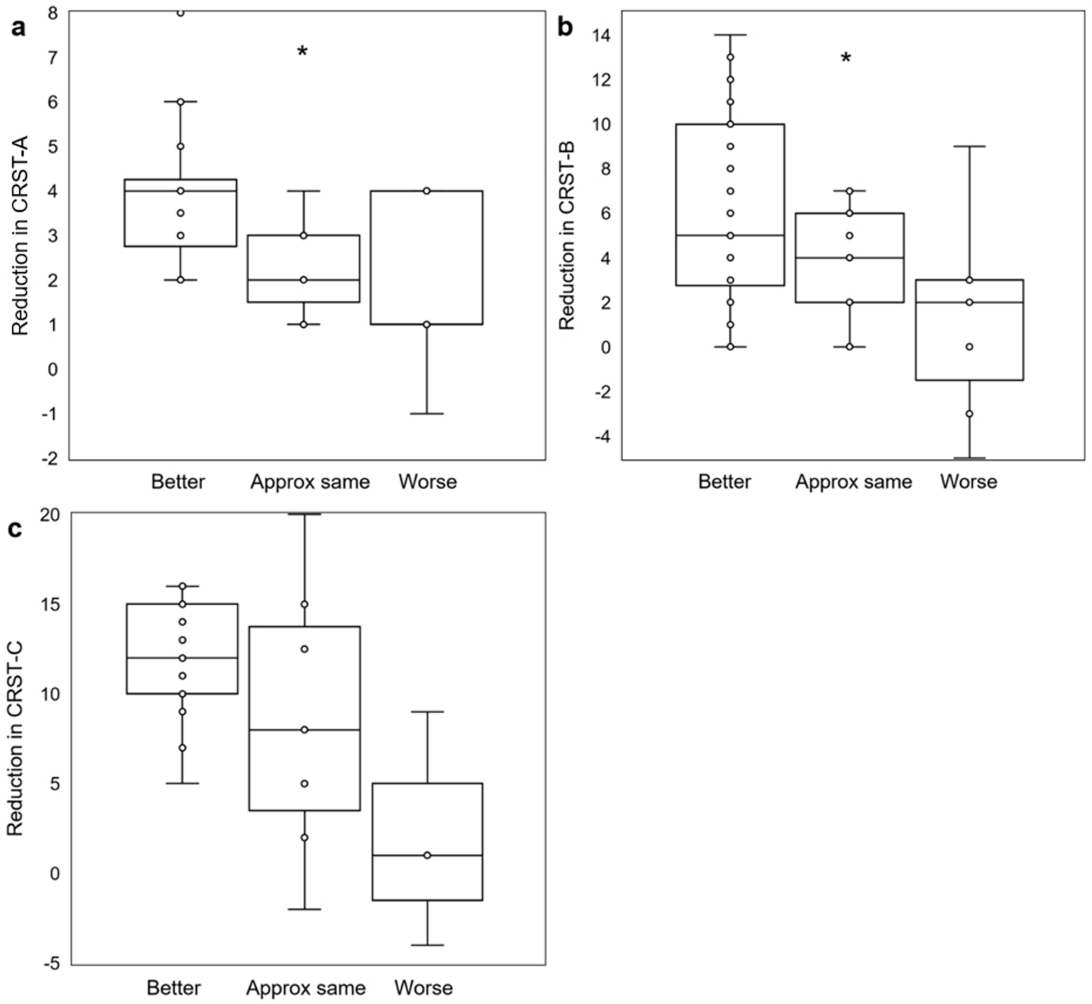

FIGURE 3
Objective post-MRgFUS tremor reduction and association with QoL self-assessment. Box and whisker plots demonstrate significant associations (by Kruskal-Wallis test) between objective measures of tremor reduction (a: CRST part A, treated hand only; b: CRST part B, treated hand only, without pouring; c: CRST part C, function only) and QoL outcomes. CRST: Clinical Rating Scale for Tremor; *: $p < 0.05$.

from the stereotactic coordinate to the center of mass of the lesion and QoL status (Kruskal-Wallis H = 1.4206, $p = 0.49$).

Relationship between lesion volume and self-reported and clinically rated tremor suppression

In the setting of our finding that smaller lesions (less than 127 mm^3) were associated with better QoL outcomes, we next examined the relationship between lesion size and both objective and subjective measures of tremor suppression. There was no significant association between lesion size and changes in CRST part A (treated hand only), part B (treated hand only without pouring), or part C (function only) ($R^2 = 0.0123$, $R^2 = 0.0271$, $R^2 = 0.0412$, and $R^2 = 0.0756$, respectively; Figure 8a), or between lesion size and self-reported tremor suppression at last follow-up ($R^2 = 0.01039$; Figure 8b). With lesions greater than 180 mm^3, all patients reported effective subjective tremor control at last follow-up and objectively scored at or above the predicted tremor reduction trendline on CRST subscales, but they were more likely to report "worse" QoL.

Effect of procedural characteristics on lesion volume

No direct correlation was found between the number of sonications with temperature above 50°C and lesion volume, nor between the total energy applied and lesion volume.

Use of clinically acquired low-resolution DTI for creation of probabilistic dentatorubrothalamic tracts

Using the clinically acquired low-resolution DTIs (3 T, 1 mm x 1 mm x 2 mm resolution, 30 diffusion weighting directions, b-value of 1,000 s/mm^2), probabilistic tractography from the VIM to the precentral gyrus using FSL was successful in only 44 of the 60

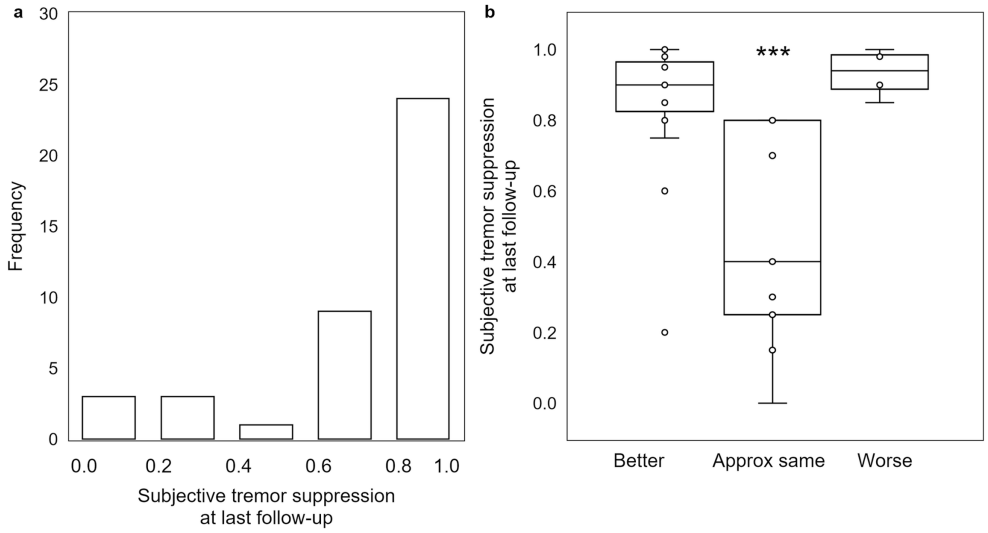

FIGURE 4
Subjective assessment of tremor reduction at last follow-up does not follow the expected pattern. (a) While the majority of patients experienced between 80% and 100% subjective tremor suppression, (b) there is no significant difference in degree of subjective tremor suppression between patients self-assessing as "worse" and those self-assessing as "better." Those that self-assess as "approximately the same" had a significantly lower degree of subjective tremor suppression. ***: $p < 0.001$.

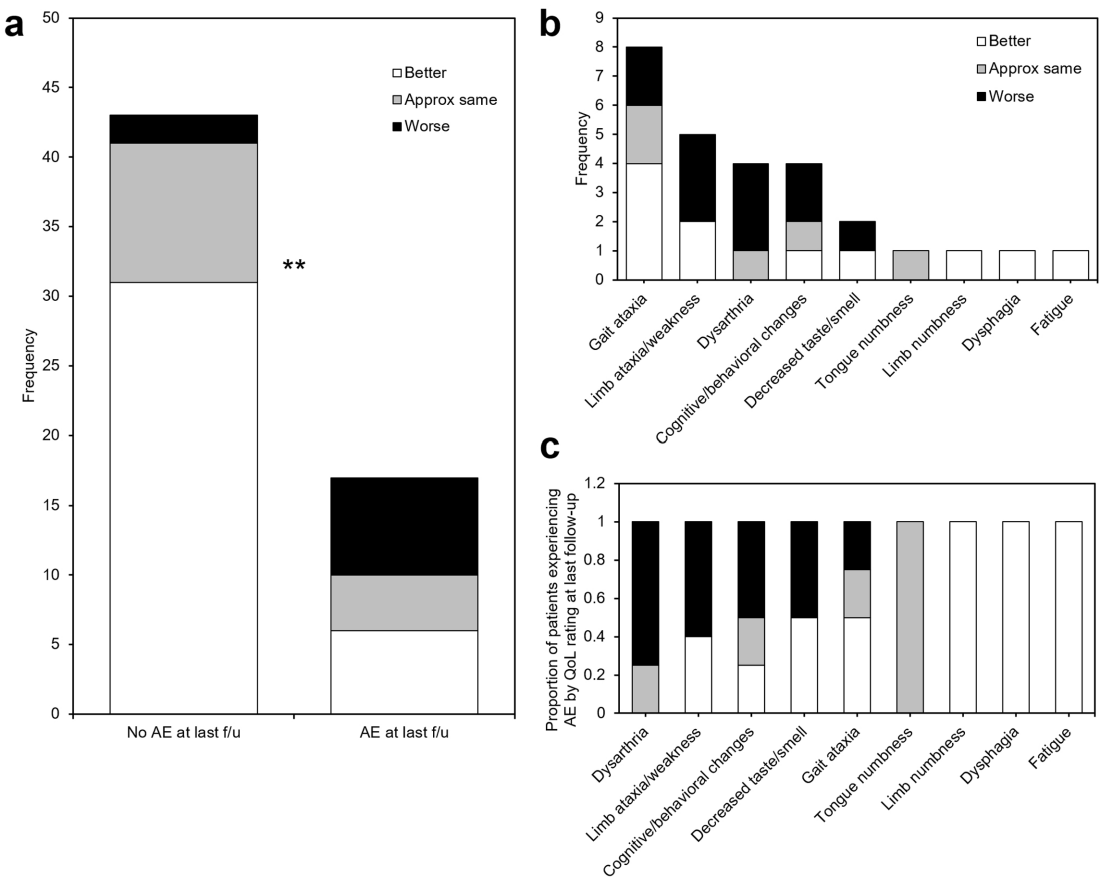

FIGURE 5
Adverse effects after MRgFUS VIM thalamotomy. (a) histogram of adverse effects experienced by patients at last follow-up, stratified by study-end QoL self-assessment. (b) A significantly larger proportion of patients who reported unchanged or worse QoL experienced persistent adverse effects at last follow-up. (c) Adverse events ranked in order of proportion of patients experiencing that AE reporting worse (black), same (gray), or better (white) QoL at last follow-up. AE: adverse event; f/u: follow-up; **: $p < 0.01$.

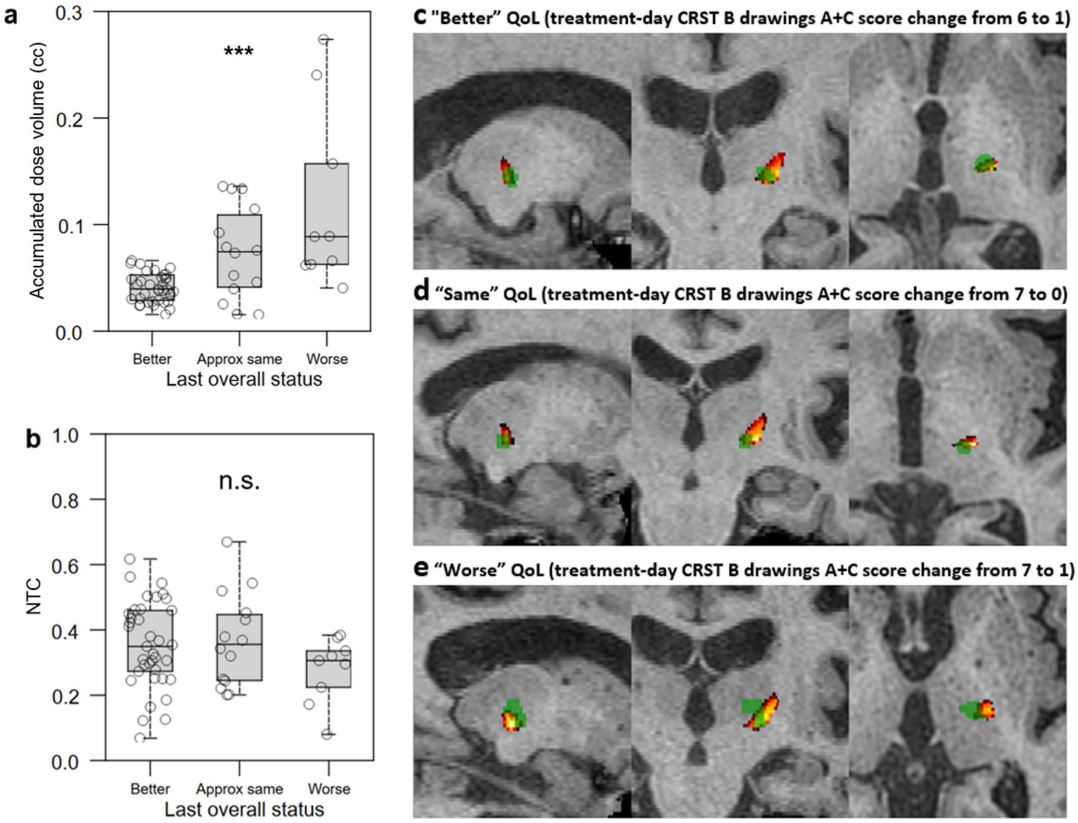

FIGURE 6
Relationship between lesional characteristics and QoL outcomes. (a,b) Lower accumulated dose volume (a) but not greater normative tractographic coefficient (NTC) between the lesion and VIM-precentral NTA hotspot (b) was significantly associated with difference between all three subjective QoL assessment groups. c-e: FUS thalamotomy lesions (green) and NTA hotspots (hot colors, thresholded to >0.6 to minimize the black/empty VIM component) for exemplar patients who self-assessed their QoL at last follow-up to be "better" (c), "approximately the same" (d), and "worse" (e); despite having similar treatment-day reductions in tremor, the lesion of the patient whose QoL improved was smaller and best encapsulated by the NTA hotspot, while that of the patient whose QoL decreased was largest, with much of the ablated volume superior and medial to the hotspot. The "same" QoL patient had the smallest lesion of the three, and it is slightly medial to the brightest voxels of the hotpot. NTC: normative tractography coefficient for VIM-precentral hotspot; QoL: quality of life; CRST: Clinical Rating Scale for Tremor; ***: $p < 0.001$; n.s.: not significant.

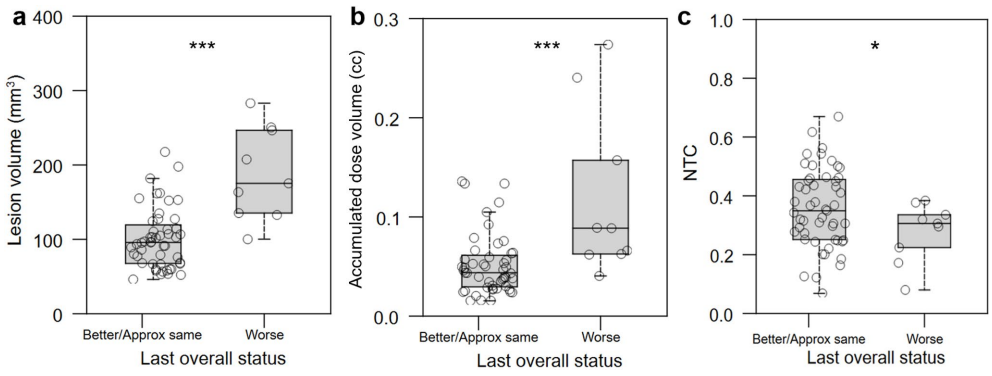

FIGURE 7
Relationship between lesional characteristics or normative tractography coefficient and binary QoL outcome. (a,b) Better/same QoL outcomes were significantly associated with smaller lesion volume (in mm³) and accumulated dose volume (in cc). (c) Improved or unchanged QoL was significantly associated with normative tractographic coefficient (NTC) with the NTA VIM-precentral hotspot. *: $p < 0.05$; ***: $p < 0.001$.

patients in this cohort. In 11 patients, the format of the "blip-down" acquisition used for artifact correction before fiber tracking precluded use. In another five cases, the DTIs had too much artifact for reasonable fiber tracking. However, even in the 44 patients with adequate DTIs, specialized tracking to the hand-knob subregion of precentral gyrus, which was found by (32) to be the

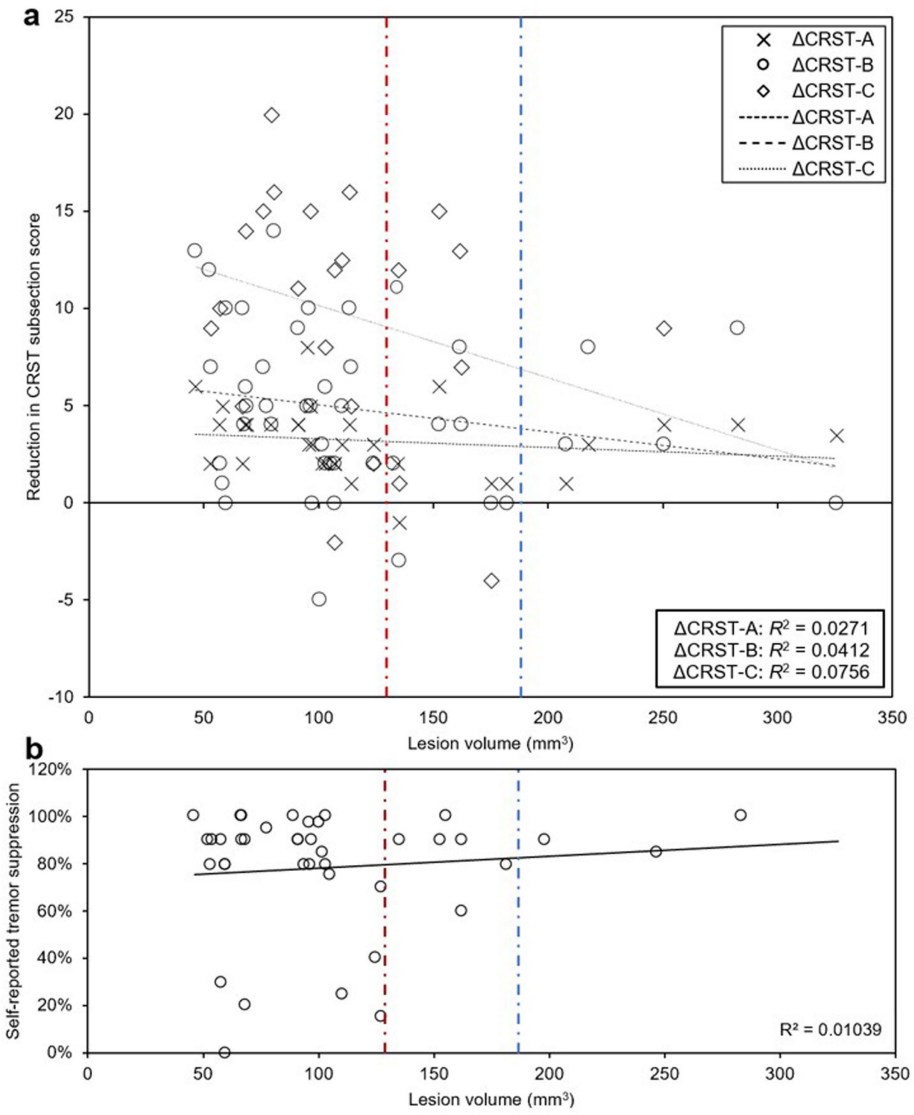

FIGURE 8
Relationship between lesion size and clinically rated and self-reported tremor suppression. (a, b) There were no significant associations between lesion volume and CRST part A (treated hand only), part B (treated hand only, no pouring), part C (functional assessment only) (a), or self-reported tremor suppression (b) at last follow-up. Above lesion volume of 180 mm^3, no patients had lower than expected subjective or objective tremor suppression at last follow-up (blue dashed line). All patients that had less than 50% subjective tremor suppression had lesion volumes < 127.4 mm^3 (red dashed line), which represents the lesion volume threshold below which patients were more likely to have "better" or "same" QoL.

most predictive DRTT methodology, was unsuccessful in all patients.

Effect of lesion size and normative tractographic coefficient on adverse effects

We examined the relationship between lesion characteristics and the presence of AEs at time of last follow-up. Larger lesion volume, larger accumulated dose volume, and lower NTC were associated with presence of AEs at last follow-up ($p = 0.002$, Figure 9a; $p = 0.002$, Figure 9b; $p = 0.020$, Figure 9c, respectively).

Discussion

In this retrospective study, we sought to investigate the relationship between subjective QoL outcome and tremor suppression (both subjectively reported and clinically measured), and to determine the feasibility of a scalable approach to MRgFUS thalamotomy lesioning that could potentially optimize QoL outcome. We focused on subjective, qualitative, patient-reported QoL instead of the Quality of Life in Essential Tremor (QUEST) questionnaire (16) because QUEST frames QoL chiefly in terms of the impact of tremor, while we hypothesized that the degree of tremor suppression is not necessarily entirely predictive of post-treatment QoL, with the impact of adverse side effects also playing a role.

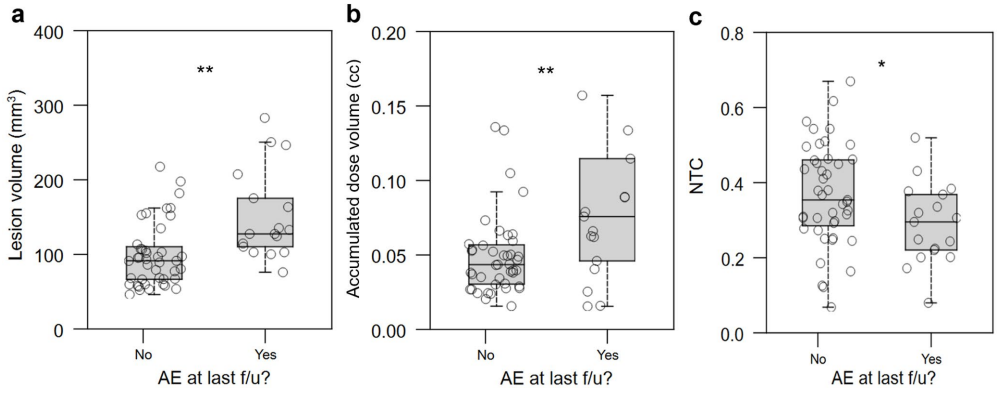

FIGURE 9
Relationship between lesional characteristics and presence of persistent AEs at last follow-up. Larger lesion volume, (a) accumulated dose volume (in cc) (b), and normative tractographic coefficient (c, NTC) with the VIM-precentral projection-based hotspot in the NTA were significantly associated with the presence of persistent AEs at last follow-up. AE: adverse effect; NTC: normative tractography coefficient. *: $p < 0.05$; **: $p < 0.01$; n.s.: not significant.

TABLE 2 Test performance of lesional characteristics as univariate predictors of QoL outcomes.

Variable	AUC	Youden Index	Sensitivity	Specificity	Optimal Cutoff	*p*
Lesion volume (mm³)	0.880	0.692	0.804	0.889	<127.4	<0.0001
ADV (cc)	0.826	0.634	0.745	0.889	<0.0594	<0.0001
NTC [0–1]	0.723	0.438	0.549	0.889	>0.544	0.015

AUC: area under curve; ADV: accumulated dose volume; NTC: normative tractography coefficient for VIM-precentral hotspot. Receiver operating curves were generated for lesion volume and degree to which the lesion is within the NTA VIM-precentral projection-based hotspot. Optimization by setting a threshold at maximum Youden index to maximize the balance between sensitivity and specificity yielded optimal cutoff values for lesion characteristics.

What is the relationship between subjective QoL outcome and tremor suppression?

On the day of MRgFUS thalamotomy, all patients tested immediately post-procedure had improved tremor scores, regardless of QoL outcome at last follow-up. For the majority of patients, improvement was durable through last follow-up. At last follow-up, objective, quantitative tremor suppression correlated with QoL outcome (Figure 3); this is unsurprising, as a patient without significant objective improvement in tremor is unlikely to rate their QoL as "better" after their procedure. However, patients with *either* "better" or "worse" QoL after treatment *perceived* similarly high levels of subjective tremor improvement (approximately 80–100%), while patients who rated their QoL as "approximately the same" *perceived* an average of only approximately 50% (Figure 4b). In other words, a group of patients who *perceived* strong improvement in tremor nevertheless rated their QoL as "worse" after treatment. We hypothesized that the distinguishing factor between these patients and others is the set of adverse effects (AEs) they experienced; indeed, 77.8% (7/9) of patients reporting "worse" QoL (with or without tremor improvement at last follow-up) had persistent AEs at last follow-up, compared to just 16% (6/37) of patients stating "better" QoL ($p = 0.001$; Figure 5). Of the two" worse" patients without AEs at last follow-up, one had worsened tremor relative to before procedure as quantified by CRST parts A (treated hand only) and B (treated hand only, without pouring). The other was later diagnosed with normal pressure hydrocephalus, so the cause of their worsened QoL could be multifactorial. The relative impact of AEs versus tremor control on a patient's self-assessed QoL rating may depend on the type and severity of their persistent AEs, as well as the effect that their AEs have on their lifestyle. Interestingly, even though gait ataxia was the most common, dysarthria and limb ataxia/weakness were the most likely AE's leading to "worse" QoL assessments, while gait ataxia was better tolerated (Figure 5). Overall, though a high degree of subjective tremor suppression appears necessary for achieving the highest QoL outcome, it is not sufficient, and minimizing AEs may be required to promote higher QoL ratings.

How can AEs be avoided during FUS procedures? Larger lesions are thought to contribute to a higher side effect profile (33, 34). We identified that large lesion volume strongly differentiated patients with persistent AEs at last follow-up (Figure 9a) as well as the "worse" QoL outcome group (Figure 7a). However, given that final lesion size may continue to develop for days after treatment, a proxy quantity is needed that can be measured and monitored in real time during treatment and that also correlates with AE frequency and QoL. Accumulated dose volume is an intraprocedural metric that is strongly correlated with postoperative lesion volume (35). Both larger lesion size measured on immediate post-treatment MRI (Figure 7a) and higher intraprocedural accumulated dose volume (Figure 7b) strongly distinguished worse QoL outcome. Cutoff values were found, with lesion size above 127 mm³ and accumulated dose volume of greater than 0.06 cc (60 mm³) strongly predicting "worse" QoL outcome (Table 2).

However, we also found that patients with lesions larger than approximately 180 mm^3 uniformly had both subjective and objective improvement in tremor, while some patients with lesions smaller than 180 mm^3 had less effective tremor control (Figure 8). This value contrasts with 127 mm^3, the lesion size below which patients are more likely to have "better/same" than "worse" QoL outcomes (Table 2). At first glance, these data are contradictory – why do lesions larger than 180 mm^3 predict the best subjective and objective tremor suppression, while lesions *smaller* than 127 mm^3 predict better QoL? We hypothesized that even more important for predicting QoL than the size of the lesion is the precise location of the lesion and the clinical consequences thereof. Presumably, a well-placed lesion under 127 mm^3 in size will target the putative "sweet spot" that optimizes for tremor control, improves QoL, and minimizes AEs; a lesion larger than this might improve tremor but cause AEs and therefore diminish QoL, while a smaller lesion that misses the "sweet spot" may not be large enough to improve tremor, even if it spares the patient of AEs.

Is there a scalable approach to MRgFUS thalamotomy lesioning that can optimize QoL outcome?

Central to improving patient satisfaction with MRgFUS thalamotomy is devising an approach that can be used to model the small target zone within each patient's imaging space that will lead to a superior QoL outcome (which incorporates maximizing subjective and objective tremor suppression). Distance between the stereotactic coordinate and lesion center-of-mass was not associated with QoL outcome, suggesting that canonical targeting does not provide this. Though studies have highlighted the utility of personalized DTI in predicting putative ablation zones within VIM (19, 20, 36, 37), the acquisition and processing of high-resolution personalized DTI may be costly, technically challenging, and resource-intensive. As such, the ability to scale across centers may be limited, particularly in more community-based settings. Lower resolution DTI acquisition may be more achievable due to the decreased time and resources required, but may lack reliability. Using our clinically acquired (lower resolution) DTIs (3 T, 1 mm x 1 mm x 2 mm resolution, 30 diffusion weighting directions, b-value of 1,000 s/mm^2), we were only able to successfully run probabilistic tractography on less than 3/4 of the patients in this cohort. Since patients with ET often also have head tremor, we presume that acquiring reliable DTI, which is extremely susceptible to motion artifact, may be more challenging in this patient population than in the general population. Further, even in the patients with adequate DTIs, specialized tracking to the hand-knob subregion of precentral gyrus, as done with the higher resolution research DTIs in (32), and found to be the most reliable methodology for generating outcome-predictive streamlines, was unsuccessful in all patients in this cohort. This may be due to the non-isotropic resolution, inferior angular resolution (lower number of diffusion weighting directions), and lower b-value of the clinical-grade DTIs, which are not optimal for tractography. Together, these challenges highlight the need for a scalable, resource-light approach utilizing high-resolution DTIs.

Here, we propose the use of a large-sample-size, high-resolution DTI database from the Human Connectome Project to create a normative tractographic atlas (NTA) to provide representations of VIM subregions with high probability of streamlines to the motor cortex that are then fit to each patient. This approach is directly scalable as it does not require any DTI acquisition, can be performed using the standard volumetric preoperative T1 imaging, and only requires freely available coregistration algorithms to MNI space. Our data demonstrate that smaller lesions (measured both intraprocedurally with accumulated dose volume and at time of immediate postoperative imaging with lesion segmentation) and higher NTC independently predict superior QoL outcomes. Furthermore, our analyses yield a set of threshold values for immediate postoperative lesion size (< 127.4 mm^3), accumulated dose volume (< 0.06 cc) and NTC (> 0.54) that select against worse QoL outcomes and that could one day be used prospectively, at time of treatment, to plan a lesion that maximizes the chance of improving overall QoL by optimizing the tradeoff between maximum tremor suppression and minimum AEs.

Strategies that are now used at our institution to limit lesion size include the use of fewer total sonications, increasing power instead of duration to reach the desired sonication energy, targeting a lower peak temperature of about 55°C rather than 57-60°C, and the application of masks that deactivate elements primarily transmitting through the temporal bones, thereby limiting medial-lateral spread of the thermal spot. Fewer sonications are achieved by aligning with minimal power and then rapidly ramping the power to treatment power levels. Prior to July 2020, when the patients in this study were treated, only the application of masks was routinely used. In addition, in this cohort, we did not find a direct correlation between the number of sonications with temperature above 50°C and lesion volume, nor between the total energy applied and lesion volume. The lack of relationship between total energy applied or number of sonications and lesion volume may be a result of the numerous differences between patients and their treatment parameters that are challenging to control for, including the number, magnitude, and direction of target adjustments, as well as SDR distribution over the skull.

Many centers offering MRgFUS for ET acquire postoperative imaging approximately 24 h after treatment. We expect that the segmented regions (zones I and II) grow during the first 24 h postop, so the lesion volumes in this study may not be directly comparable to those stated in studies from other institutions. In addition, note that the NTC is not a similarity metric – our hypothesis was that an adequate portion of the patient-fit NTA object needs to be ablated, not its entirety. Too large of a lesion may increase the likelihood of adverse side effects, and too small of a lesion may lead to suboptimal subjective tremor suppression.

Within the range of last follow-ups for which we have data, patients with longer follow-up did not have less tremor improvement at last follow-up, even when considering only subjects with smaller lesions (Supplementary Figure S2). This suggests that most patients, including those with smaller lesions, did not have tremor recurrence during the study period, but future work looking at longer follow-up (e.g., > 5 years) is merited.

Finally, it is important to note that though the desired ablation volume may coincide strongly with the NTA network-based hotspot, we do not recommend targeting at the center of mass of the NTA object as this is likely to result in ablative ultrasonic dose in the internal capsule. Due to the predominant inferoanteriolateral spread of ultrasonic energy during most MRgFUS procedures, our current practice is to target at the medial apex of the NTA (typically about 15 mm lateral to midcommissural plane, 1 mm anterior to the 25%

ACPC distance from PC, and 2 mm superior, Figure 1b). This is approximately 3.5 mm away from the thalamocapsular border at 2 mm above ACPC, and approximately 2.5 mm away from the thalamocapsular border at ACPC. The thalamocapsular border is best seen on FGATIR imaging, though it can also be seen on T1-weighted imaging with appropriate contrast windowing. The exact location and relative ACPC coordinates of this medial apex varies on an individual patient basis due to the nonlinear coregistration from MNI space to each patient's native T1 space.

Limitations and future directions

The primary limitations of our study include the relatively low number of patients available for purely unbiased retrospective analysis (patients treated prior to the creation of the NTA hotspot pipeline at our center), and incomplete data due to lack of consistent follow-up in this cohort. The relatively short follow-up period (405 ± 44 days) limits our ability to assess the durability of tremor improvement (or the likelihood of AEs resolving) in the long run, and how this impacts QoL.

Another limitation of the proposed NTA method is that the HCP 7 T datasets used to determine the normative VIM-to-precentral hotspots were acquired from healthy adults. While the nonlinear registration used to warp the NTA from the MNI brain to each patient's T1-weighted MRI has some capacity to account for differences in ventricular size and morpohology commonly seen with aging, it is possible that our proposed method would be less reliable if a patient has other pathology, such as tumor, large stroke, encephalomalacia, or other structural abnormalities. In such cases, patient-specific tractography may likely be an important adjunct.

Future directions could include obtaining both subjective, qualitative, patient-reported QoL data and QUEST data in patients to compare our simplified scale, which is intended to include the impact of both tremor reduction and any adverse side effects, to QUEST, which focuses on the effect of tremor on specific ADLs and functional aspects. Qualitative data could also probe more subjective insights from patients based on their experience including whether or not they would have decided to undergo MRgFUS in the first place, or why they would or would not undergo MRgFUS in the future for the second side. Additionally, future work might include refining the NTA by focusing on only the most efficacious components of the VIM to precentral fibers in order to get a tighter normative hotspot. Tracking to the hand-knob region instead of all of the motor cortex could possibly accomplish this (as shown in (32)). This would be aided by an effective method for automatically segmenting the hand-knob region in the HCP dataset subjects and is thus outside of the scope of this manuscript. Finally, in this study, intraoperative imaging used the body RF coil; future work could include using a 2-channel head coil designed to be compatible with the transcranial MRgFUS setup, which has been shown to enable better visualization of the thalamus and other structures, and more precise MR thermometry (38).

Our data nevertheless suggest that this relatively simple approach can be used to optimize patient QoL and satisfaction with MRgFUS thalamotomy. Future work to validate our findings prospectively and to automate the computational aspects of our approach will be important to facilitate wider adoption of this approach.

Conclusion

Though tremor suppression is certainly required for achieving the best QoL outcome after MRgFUS thalamotomy for ET, paying particular attention to minimizing adverse effects may be more impactful to QoL than the exact degree of tremor suppression achieved. We find that small lesions (both as predicted by accumulated dose volume at time of treatment and on postoperative imaging) that fall within the sweet spot of our NTA may provide this optimal balance. Of particular interest, we find a cutoff value of intraprocedural accumulated dose volume < 0.06 cc as optimal to avoid poor QoL outcome. Furthermore, since generating the NTA volume requires only routine, preoperative T1-weighted imaging and is not dependent on resource-intensive high-resolution DTI acquisition, the NTA represents a reliable and easily scalable method that can be implemented anywhere MRgFUS is performed. Eventually, such reliable and scalable image-guided targeting techniques, in addition to patient-specific modeling when available, with predictive intraprocedural metrics such as accumulated dose volume, may obviate the current need for an awake, interactive patient. This may lead to the ability to perform asleep MRgFUS, enhancing patient comfort and increasing access to this life-changing therapy.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving humans were approved by Stanford University Institutional Review Board. The studies were conducted in accordance with the local legislation and institutional requirements. The ethics committee/institutional review board waived the requirement of written informed consent for participation from the participants or the participants' legal guardians/next of kin due to the retrospective nature of the study.

Author contributions

VB: Conceptualization, Funding acquisition, Supervision, Writing – original draft, Writing – review & editing. DP: Data curation, Formal analysis, Methodology, Visualization, Writing – original draft, Writing – review & editing. AD: Visualization, Writing – original draft, Writing – review & editing, Formal analysis, Methodology, Software, Validation. AW: Data curation, Formal analysis, Writing – review & editing. DB: Methodology, Software, Writing – review & editing. YC: Data curation, Writing – review & editing. LL-T: Writing – review & editing. CL: Writing – original draft. CH: Writing – review & editing. JH: Writing – review & editing. JM: Writing – review & editing. RB: Writing – review & editing. PG: Funding acquisition, Writing – review & editing.

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Conflict of interest

PG and VB report receiving research funding for clinical trials from INSIGHTEC. PG previously served on the medical advisory board of INSIGHTEC for a prostate cancer application.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2024.1450699/full#supplementary-material

SUPPLEMENTARY FIGURE S1
Relationship between NTC and CRST scores. Higher NTC was weakly correlated with CRST score reduction for CRST part A (treated hand only), part B (treated hand only, no pouring), and part C (functional assessment only). CRST: Clinical Rating Scale for Tremor; NTC: normative tractography coefficient for VIM-precentral hotspot.

SUPPLEMENTARY FIGURE S2
CRST B scores vs. length of time to last follow-up. (a) Patients with longer follow-up do not have less tremor improvement at last follow-up as measured by reduction in CRST part B (treated hand only, no pouring) scores. (b) This is also true when considering only subjects with smaller lesions (lesion volume < 127.4 mm^3, the cutoff below which patients are more likely to have "better" or "approximately the same" QoL at last follow-up). This suggests that most patients, including those with smaller lesions, did not have tremor recurrence during the study period, but future work looking at longer follow-up (e.g., > 5 years) is merited. CRST: Clinical Rating Scale for Tremor.

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Ameliorating motor performance and quality of life in Parkinson's disease: a comparison of deep brain stimulation and focused ultrasound surgery

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Introduction: Deep brain stimulation (DBS) and magnetic resonance-guided focused ultrasound surgery (MRgFUS) have emerged as valuable treatment options for Parkinson's disease (PD) with drug-resistant symptoms. However, comparative studies of various DBS targets and MRgFUS are still limited.

Methods: We reviewed three databases for trials on the effects of DBS or MRgFUS on PD patients, focusing on motor performance and quality of life (QoL). A frequentist network meta-analysis was conducted to estimate the treatment effects.

Results: There were 39 trials in this study, comprising 3,002 patients. In the off-phase, subthalamic nucleus_DBS (STN_DBS [SMD, −0.94; 95%CI, −1.40 to −0.48]) significantly improved the UPDRS-III Total score compared to medication treatment alone (MT). In the on-phase, STN_DBS (SMD, −0.83; 95%CI, −1.13 to −0.53), internal globus pallidus_DBS (GPi_DBS [SMD, −0.80; 95%CI, −1.20 to −0.40]), and STN_Focused Ultrasound (STN_FUS [SMD, −1.83; 95%CI, −2.97 to −0.68]) significantly improved the UPDRS-III Total score. Regarding QoL, STN_DBS (SMD, −0.75; 95% CI, −1.46 to −0.05) and GPi_DBS (SMD, −0.58; 95% CI, −0.96 to −0.21) demonstrated better outcomes compared to MT. The SUCRA plot indicated that the top three treatments for UPDRS-III Total score in the off-phase were STN_FUS (79.6%), STN-GPi_DBS (73.7%), and STN_DBS (69.1%). In the on-phase, the top three treatments were STN_FUS (95.7%), STN_DBS (69.6%), and GPi_DBS (66.9%). Regarding QoL, GPi_DBS (77.2%) ranks first, followed by STN_DBS (67.3%), STN_FUS (56.9%) ranks third.

Conclusion: STN_DBS, GPi_DBS, and STN_FUS have exhibited efficacy in ameliorating motor performance and enhancing QoL in PD patients. Nevertheless, as a potential alternative to STN_DBS with comparable efficacy, STN-FUS may serve as another treatment option.

KEYWORDS

deep brain stimulation, magnetic resonance-guided focused ultrasound surgery, network meta-analysis, Parkinson's disease, quality of life

Introduction

Parkinson's disease (PD) is a neurodegenerative disorder characterized by resting tremors, bradykinesia, rigidity, and postural disturbances typically progressing over time (1). As the most common movement disorder, PD currently affects approximately 6.2 million individuals, with the figure projected to double by 2040 (2, 3). As PD evolves, motor complications can appear and progressively worsen, substantially affecting not only the general quality of life (QoL) but also the daily routines of those afflicted.

Dopamine-based medications are essential for alleviating both motor and non-motor symptoms in individuals with PD (4). However, prolonged administration of these medications frequently gives rise to drug-induced dyskinesias and motor fluctuations. These complications pose significant challenges in achieving optimal management through pharmacological interventions (5, 6).

Hence, interventions such as deep brain stimulation (DBS) or the more novel method of magnetic resonance-guided focused ultrasound surgery (MRgFUS) are increasingly selected as approaches for patients resistant to medication or experience disabling motor complications. Numerous studies have shown that DBS and MRgFUS may be more effective than dopamine-related drugs in improving motor symptoms and QoL in PD (7–9).

Individuals who experience motor complications from drug therapy and undergo DBS often exhibit superior outcomes compared to those solely reliant on medication. Improvements include reduced motor symptoms, decreased dependence on dopaminergic medications, and enhanced self-assessed QoL (10, 11). Over the years, it has proven that DBS of the internal globus pallidus (GPi_DBS) and the subthalamic nucleus (STN_DBS) serves as an effective surgical procedure for managing motor fluctuations in PD patients (5, 12–15).

The academic literature widely accepts that GPi stimulation improves tremor, rigidity, and bradykinesia, whereas STN stimulation demonstrates comparable efficacy in symptom control while allowing for a reduction in dopaminergic therapy. In contrast, the ventral intermediate nucleus (VIM) holds a slight advantage in tremor control (7). To date, the use of DBS targeting both STN and GPi remains the leading surgical approach for managing PD.

Furthermore, the advent of MRgFUS, a novel incisionless technique capable of targeting the STN, GPi, or other brain regions, may advance its utilization (8, 16). The actions of MRgFUS in the brain are diverse, encompassing neuromodulation, opening of the blood–brain barrier, and thermal ablation of targeted tissues (17). In contrast to DBS, MRgFUS carries a minimal risk of hardware-related infection and hemorrhage. In recent years, some clinical studies have observed that VIM_MRgFUS can improve tremor-dominated Parkinson's disease, while MRgFUS targeting STN and GPi can provide better performance for the motor symptoms (18).

Despite existing evidence, the safety and efficacy of MRgFUS remain limited, but the use of DBS in PD may offer valuable insights for clinicians in identifying potential targets for MRgFUS. Consequently, MRgFUS holds promise for greater adoption in clinical practice.

So far, clinical research has rarely compared the effectiveness of DBS targeting different brain regions with MRgFUS for PD. Unlike a pairwise meta-analysis, which compares two treatments, a network meta-analysis (NMA) evaluates the effectiveness of more than two treatments simultaneously. Previous research performed a network meta-analysis on the efficacy of DBS and MRgFUS in controlling PD-induced tremors, revealing a comparable potency in tremor reduction (7). Moreover, treatments such as GPi_DBS, GPi_MRgFUS, STN_DBS, and caudal zona incerta (cZi_DBS) showed noticeable improvements in motion-related symptoms compared to baseline (7).

However, this study did not compare these two surgical techniques directly with sole medical treatment (MT), nor did it focus on the aspect of quality of life (QoL). An analysis found that when it came to enhancing patient QoL in parkinsonism, both GPi_DBS and STN_DBS outperformed pharmacological therapy (19). Yet, there was no statistically significant difference between these DBS treatments, with the ranking probability showing that GPi_DBS was second to STN_DBS.

In the light of this background, we performed a NMA to indirectly compare the efficacy of DBS, MRgFUS and MT on motor performance and quality of life in PD patients. Subsequently, a comparative analysis was conducted to rank the efficacy of DBS and MRgFUS targeting various brain regions, along with medical treatment, in improving motor performance and quality of life.

Methods

The current NMA adhered to the guidelines specified in the expanded checklist for preferred reporting items in systematic reviews and meta-analyses.

Prospero registration number

PROSPERO CRD42024521903.

Data sources and searches

To facilitate this meta-analysis, an extensive literature search was conducted, covering articles published from January 1998 to October 2023. Three prominent databases, namely PubMed, Embase, and Cochrane Library, were utilized for this purpose. The search included literature in multiple languages; however, only English-language publications was deemed appropriate for inclusion. The complete strategy is described in the Supplementary material.

Inclusion criteria

1. Study subjects: individuals who have received a clinical diagnosis of PD.
2. Intervention: Patients with PD were divided into two groups: the intervention group received either DBS or MRgFUS, and the control group received medication treatment alone (MT). The specific therapeutic methods are as follows: STN_FUS, Gpi_FUS, VIM_FUS, STN_DBS, Gpi_DBS, STN-Gpi_DBS, STN-SNr_DBS, SNr_DBS, cZi_DBS, NBM_DBS, MT.
3. Outcomes: The studies employed the Unified Parkinson's Disease Rating Scale, Part III (UPDRS-III or MDS-UPDRS-III), to assess motor symptoms, and evaluated quality of life using instruments such as the Parkinson's Disease Questionnaire (PDQ-39/PDQ-8) and Sickness Impact Profile (SIP), to measure therapy effectiveness.

Exclusion criteria

1. The exclusion criteria encompassed secondary parkinsonism, severe dementia, and significant concurrent depression.
2. If data extraction was not feasible or if the data lacked integrity.
3. Studies that were not clinical trials or those involving non-human subjects (such as mice or dogs), were excluded from the review.

Evaluation of quality and information gathering

We used the Cochrane Collaboration's tool to assess the quality of all trials, which consists of seven domains: generation of random sequences, concealment of allocations, blinding of personnel and outcome assessors, incomplete outcome data, selective reporting, and other biases. Two researchers from our team independently scrutinized the complete text of all suitable studies. In instances of discord, a third team researcher was involved in discussions to reach a final agreement. Based on the trials included, we gathered the subsequent data: the principal author's identity, year of publication, demographic details, objectives, disease progression, UPDRS-III, and QoL scores.

Outcome measures

The UPDRS and MDS-UPDRS (revised version) are widely used to assess functional status and motor symptoms in PD patients. Part III of both scales was utilized to evaluate motor function, with total scores ranging from 0 to 108 for the UPDRS-III and 0 to 132 for the MDS-UPDRS-III. The PDQ-39, its abbreviated version (PDQ-8), and the SIP are commonly used and important tools for assessing the QoL. Higher scores on these scales indicate greater severity of impairment.

Statistical analysis

We used Stata Statistical Software, V.17 (StataCorp) for statistical analysis. Our approach involved conducting a frequentist meta-analysis, which does not require a prior distribution, thus avoiding subjective bias and simplifying implementation. To visualize each outcome, we used the 'network plot' command in Stata. The results of the NMA are presented as standardized mean differences (SMDs), which quantify the difference between two means on a unified scale, with 95% confidence intervals. The ability to assess the consistency assumption was limited because the networks did not include any closed loops. Using the Surface Under the Cumulative Ranking (SUCRA) method, we evaluated treatments, assigning each a score from 0 (least effective) to 100% (most effective) based on overall ranking. An investigation into the influence of the small sample size was performed by using funnel charts.

Results

A thorough literature search initially identified 4,506 studies, from which 1,354 duplicates were removed. After applying inclusion and exclusion criteria, 39 of the remaining 204 studies were selected for inclusion in this NMA, encompassing 3,002 patients with PD (Figure 1).

Basic characteristics

Table 1 summarizes baseline characteristics of the participants in the included trials. Figures 2A–C presents the network plots for each treatment target of DBS, FUS or MT.

Risk of bias

Figures 3A–C shows no significant publication bias; the effect of small sample effect is minimal. The risk of bias for the included trials is displayed in Figures 4A,B.

UPDRS-III total score (off-phase)

The analysis included a total of 31 studies (29 two-arm and 2 three-arm) examining the UPDRS III scores in the off-phase. These studies involved 11 treatment modalities, encompassing a total of 2,350 patients: STN_DBS, GPi_DBS, STN-GPi_DBS, substantia nigra pars reticulata_DBS (SNr_DBS), STN-SNr_DBS, cZi_DBS, nucleus basalis of Meynert_DBS (NBM_DBS), STN_FUS, GPi_FUS, VIM_FUS, and MT.

In comparison, treatment with STN_DBS resulted in significant improvements in UPDRS-III scores compared to MT (SMD, −0.94; 95% CI, −1.40 to −0.48) in the off-phase (Figure 5A). According to the SUCRA plot (Figure 6A), the top three treatments were as follows: STN_FUS (79.6%) ranked first, followed by STN-GPi_DBS (73.7%) in second place, and STN_DBS (69.1%) in third, while SNr_DBS (18.2%) ranked last.

UPDRS-III total score (on-phase)

The comparison of UPDRS-III in the on-phase incorporated 30 studies (28 two-arm and 2 three-arm) and 9 treatments used in 2184 patients, including STN_DBS, GPi_DBS, SNr_DBS, STN-SNr_DBS, cZi_DBS, NBM_DBS, STN_FUS, VIM_FUS, and MT.

In the on-phase, significant improvements in UPDRS-III scores were observed with STN_DBS (SMD, −0.83; 95% CI, −1.13 to −0.53), GPi_DBS (SMD, −0.80; 95% CI, −1.20 to −0.40), and STN_FUS (SMD, −1.83; 95% CI, −2.97 to −0.68) compared to MT (Figure 5B). According to the SUCRA plot (Figure 6B), the top three techniques were STN_FUS (95.7%) in first place, followed by STN_DBS (69.6%), GPi_DBS (66.9%) in third place, while NBM_DBS (17.9%) was in the last position.

Quality of life

The QoL assessment included 22 studies, involving 2085 patients, and compared seven two-arm treatment strategies: STN_DBS, GPi_DBS, cZi_DBS, NBM_DBS, STN_FUS, VIM_FUS, and MT.

Among all treatments, significant improvements in QoL were observed with STN_DBS (SMD, −0.75; 95% CI, −1.46 to −0.05) and GPi_DBS (SMD, −0.58; 95%CI, −0.96 to −0.21) compared to MT

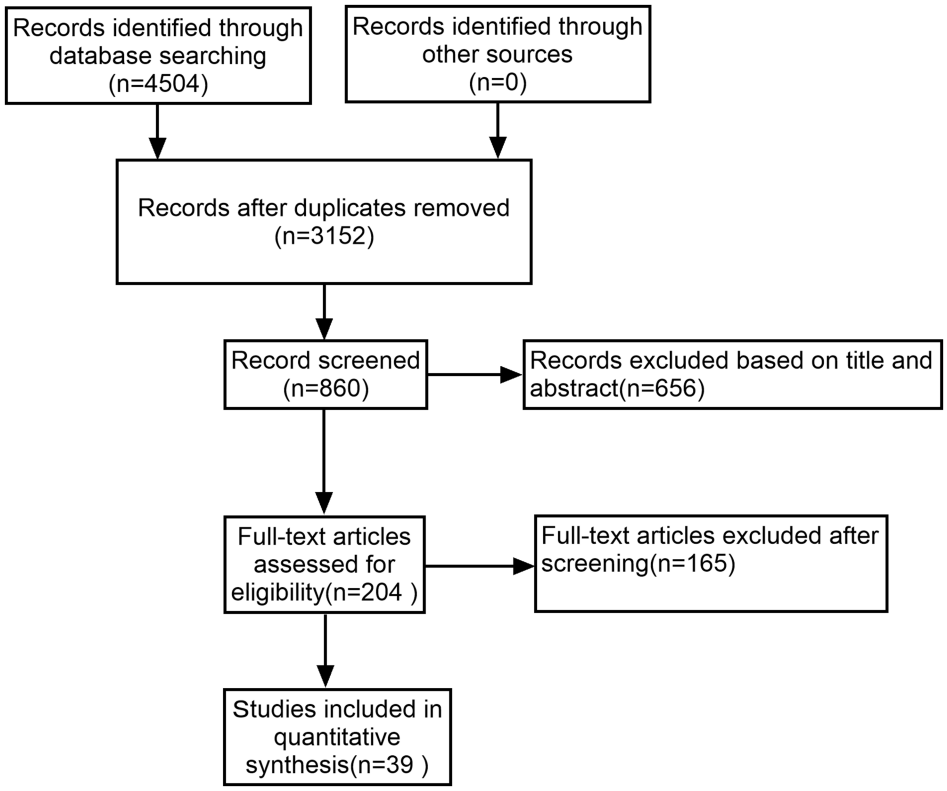

FIGURE 1
Flow diagram.

(Figure 5C). According to the SUCRA plot (Figure 6C), the top three interventions were: GPi_DBS (77.2%) in first place, followed by STN_DBS (67.3%) in second place, and STN_FUS (56.9%) in third place, with MT (27.5%) ranking last.

Adverse event

The included studies generally reported nucleus-related, PD-related, Procedure or device-related, dopaminergic therapy-related or other adverse events. Certain studies differentiate between severe and non-severe adverse events, while others omit the inclusion of adverse effects altogether. A range of adverse events noted in the included studies is detailed in the Supplementary material.

Discussion

We analyzed 39 clinical trials involving 3,002 PD patients and compared different targets of DBS and MRgFUS. This study found that STN_DBS significantly enhanced motor symptoms in both the off-phase and on-phase compared with MT. Additionally, both GPi_DBS and STN_FUS demonstrated significant improvement in the on-phase.

We utilized the Surface Under the Cumulative Ranking curve (SUCRA) to assess the probability of each treatment being the most effective option. SUCRA values range from 0 to 100%, with a value closer to 100% indicating a higher likelihood of being the most effective intervention.

Although not statistically significant in the off-phase, STN_FUS consistently ranked the top position in the SUCRA ranking in both the on-phase and off-phase, hinting at potential advancements in motor symptoms. Additionally, it is important to note that STN_DBS and GPi_DBS significantly impact QoL, with STN_DBS ranking first, GPi_DBS ranking second, and STN_FUS ranking third in effectiveness.

Numerous clinical studies have substantiated the significant contribution of STN_DBS and GPi_DBS in ameliorating motor behavior compared to dopaminergic medications alone (5, 9, 10, 20). A network meta-analysis, comparing various targets of DBS, indicated that both STN_DBS and GPi_DBS exhibit potential for enhancing both motor and non-motor symptoms (21). It is highly plausible that STN_DBS yields equivalent outcomes to GPi_DBS in the treatment of motor performance and QoL (22, 23). However, our research could not clarify the differential impacts of STN_DBS and GPi_DBS for their effectiveness in augmenting exercise performance and quality of life.

There is a currently prevailing belief that STN_DBS is more efficient than GPi_DBS in reducing reliance on dopaminergic medications, although it has a higher propensity to impair cognitive function. This potential effect may arise because the lesion locations affecting cognitive function and the STN_DBS target area is part of the same brain network. Consequently, connectivity between STN_DBS sites and cognition-related region was significantly associated with cognitive decline following DBS (24). Meanwhile, blocking dopamine terminals in the STN boosts its activity, showing dopamine's direct influence on the STN (25).

TABLE 1 Comparative characteristics of distinct targets.

Number	Author & Year	Treatment	Surgical modus	Sample size, n	Age, years	Male/ female, n	Disease duration, years	LEDD at base line, mg	Follow-up periods, months	Outcomes
1	Krishna 2023 (8)	GPi_FUS	uni	65	64.20 ± 9.60	43/25	NA	1051.60 ± 473.80	3	MDS–UPDRS–III
		MT*	–	22	63.30 ± 9.20	14/10	NA	1044.70 ± 660.60		
2	Andreasi 2022 (38)	VIM_FUS	NA	10	62.30 (60.20; 72.30)	8/2	3.80 (2.40; 4.50)	472.50 (300.00; 650.00)	6	MDS–UPDRS–III
		MT	–	20	62.87 (59.50; 72.10)	16/4	3.20 (2.80; 4.10)	400.00 (285.00; 525.00)		
3	Weiss 2022 (9)	STN_DBS	NA	84	52.40 ± 7.00	66/18	7.20 ± 2.70	942.30 ± 47.00	24	UPDRS–III, PDQ39
		MT	–	89	52.30 ± 5.80	59/30	7.60 ± 2.60	980.30 ± 46.00		
4	Zeng 2022 (39)	STN_DBS	uni	8	66.13 ± 6.71	5/3	10.13 ± 7.85	616.97 ± 276.04	24 ~ 36	UPDRS–III
		GPi_DBS	uni	8	66.13 ± 6.71	5/3	10.13 ± 7.85	616.97 ± 276.04		
5	Jost 2021 (40)	STN_DBS	bi	40	62.20 ± 8.60	25/15	9.70 ± 4.70	1066.00 ± 468.20	36	PDQ8
		MT	–	40	63.80 ± 10.40	27/13	8.30 ± 4.90	885.20 ± 355.30		
6	Dafsari 2020 (41)	STN_DBS	bi	28	58.50 ± 12.40	19/11	10.40 ± 5.60	1164.10 ± 449.20	6	PDQ8
		GPi_DBS	bi	18	58.10 ± 9.10	11/7	11.00 ± 4.00	1166.20 ± 563.20		
7	Hacker 2020 (42)	STN_DBS	bi	14	NA	NA	NA	526.7 ± 313.0	24	PDQ39
		MT	–	14	NA	NA	NA	705.2 ± 377.1		
8	Li 2020 (43)	STN_DBS	bi	16	60.25 ± 5.56	8/8	10.38 ± 4.33	1225.63 ± 714.81	6	MDS–UPDRS–III, PDQ39
		MT	–	20	57.88 ± 6.98	8/12	12.85 ± 4.25	1200.80 ± 714.81		
9	Martínez-Fernández 2020 (44)	STN_FUS	uni	27	56.60 ± 9.30	16/11	5.60 ± 2.50	729.70 ± 328.30	4	MDS–UPDRS–III, PDQ39
		MT*	–	13	58.10 ± 8.80	10/3	7.30 ± 3.80	881.70 ± 407.90		
10	Martinez-Martin 2020 (45)	STN_DBS	NA	120	NA	NA	NA	NA	24	PDQ39
		MT	–	123	NA	NA	NA	NA		
11	Vitek 2020 (46)	STN_DBS	bi	121	60.70 ± 7.90	90/31	10.00 ± 3.60	1252.20 ± 843.00	3	UPDRS–III, PDQ39
		MT*	–	39	57.50 ± 7.70	26/12	10.20 ± 3.60	1456.00 ± 1004.00		
12	Zhang 2020 (47)	STN–GPi_DBS	bi	8	67.38 ± 4.81	7/1	10.13 ± 4.36	777.34 ± 264.11	6	UPDRS–III
		MT	–	8	67.38 ± 4.81	7/1	10.13 ± 4.36	777.34 ± 264.11		
13	Valldeoriola 2019 (48)	STN_DBS	bi	6	59.10[43–70.00]	5/1	16.1.[10.00–20.00]	1250.00 ± 427.00	3	UPDRS–III
		SNr_DBS	bi	6	59.10[43–70.00]	5/1	16.1.[10.00–20.00]	1250.00 ± 427.00		
		STN–SNr_DBS	bi	6	59.10[43–70.00]	5/1	16.1.[10.00–20.00]	1250.00 ± 427.00		

(Continued)

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TABLE 1 (Continued)

Number	Author & Year	Treatment	Surgical modus	Sample size, n	Age, years	Male/ female, n	Disease duration, years	LEDD at base line, mg	Follow-up periods, months	Outcomes
14	Blomstedt 2018 (49)	cZi_DBS	bi	9	57.00 ± 11.40	7/2	6.40 ± 3.00	1376.00 ± 883.00	6	UPDRS–III, PDQ39
		MT	–	10	60.90 ± 9.20	8/2	10.30 ± 5.60	1043.00 ± 516.00		
15	Gratwicke 2018 (50)	NBM_DBS	bi	6	65.20 ± 10.70	6/0	12.70 ± 2.30	646.90 ± 204.70	1.5	MDS–UPDRS–III, PDQ39
		MT*	–	6	65.20 ± 10.70	6/0	12.70 ± 2.30	646.90 ± 204.70		
16	Bond 2017 (51)	VIM_FUS	uni	20	68.1 (63.70;73.30)	19/1	5.90 (3.40;9.20)	751.00 (450.00;950.00)	3	UPDRS–III, PDQ39
		MT*	–	7	62.40 (50.20;76.20)	7/0	6.70 (5.40;8.10)	640.00 (550.00;1250.00)		
17	Hacker 2015 (52)	STN_DBS	bi	9	60.00 ± 5.60	9/0	2.70 ± 1.30	475.70 ± 323.10	12	UPDRS–III, PDQ39
		MT	–	11	60.00 ± 7.50	9/2	2.10 ± 0.90	479.30 ± 242.70		
18	St George 2015 (53)	STN_DBS	bi	11	62.00 ± 5.70	9/2	13.30 ± 5.00	1349.00 ± 668.00	6	UPDRS–III
		GPi_DBS	bi	10	62.80 ± 8.20	9/1	15.40 ± 8.70	1412.00 ± 887.00		
		MT	–	8	60.00 ± 8.50	7/1	12.10 ± 6.00	1253.00 ± 47.00		
19	Charles 2014 (54)	STN_DBS	bi	15	60.00 ± 6.80	14/1	2.20 ± 1.40	417.20 ± 306.60	24	UPDRS–III, PDQ39
		MT	–	14	60.00 ± 7.00	NA	2.10 ± 1.10	494.00 ± 208.70		
20	Okun 2014 (55)	STN_DBS	bi	16	58.00 ± 10.70	13/3	12.10 ± 4.50	805.40 ± 434.70	4	UPDRS–III
		GPi_DBS	bi	14	58.00 ± 10.70	8/6	11.50 ± 3.30	1037.10 ± 647.80		
21	Schuepbach 2013 (10)	STN_DBS	bi	124	52.90 ± 6.60	94/30	7.30 ± 3.10	918.80 ± 412.50	24	UPDRS–III, PDQ39
		MT	–	127	52.20 ± 6.10	85/42	7.70 ± 2.70	966.90 ± 416.50		
22	Chang 2012 (56)	STN_DBS	bi	31	58.32 ± 4.18	20/11	NA	814.31 ± 195.49	7	PDQ39
		MT	–	31	57.83 ± 4.23	20/11	NA	826.86 ± 218.05		
23	Okun 2012 (57)	STN_DBS	bi	100	60.60 ± 8.30	NA	12.10 ± 4.90	1311.00 ± 615.00	3	UPDRS–III
		MT	–	35	59.50 ± 8.20	21/14	11.70 ± 4.10	1459.00 ± 991.00		
24	Rocchi 2012 (58)	STN_DBS	bi	15	61.40 ± 5.50	11/4	11.90 ± 4.80	1313.10 ± 670.20	6	UPDRS–III
		GPi_DBS	bi	14	61.10 ± 8.40	13/1	12.90 ± 10.17	1305.90 ± 667.40		
25	Weaver 2012 (20)	STN_DBS	NA	67	60.70 ± 8.90	NA	NA	1270.00 ± 570.00	6	UPDRS–III, PDQ39
		GPi_DBS	NA	83	60.40 ± 8.30	NA	NA	1365.00 ± 543.00		
26	Robertson 2011 (59)	STN_DBS	bi	14	63.80 ± 6.30	13/1	16.80 ± 6.20	1289.00 ± 652.00	6	UPDRS–III
		GPi_DBS	bi	13	65.50 ± 8.60	12/1	15.10 ± 10.20	1306.00 ± 667.00		

(Continued)

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TABLE 1 (Continued)

Number	Author & Year	Treatment	Surgical modus	Sample size, n	Age, years	Male/ female, n	Disease duration, years	LEDD at base line, mg	Follow-up periods, months	Outcomes
27	Smeding 2011 (60)	STN_DBS	bi	99	57.90 ± 8.10	58/41	13.70 ± 6.10	899.30 ± 498.00	6	PDQ39
		MT	–	36	63.00 ± 9.10	21/15	10.40 ± 4.60	629.60 ± 304.90		
28	Follett 2010 (61)	STN_DBS	bi	147	61.90 ± 8.70	116/31	NA	1118.00 ± 562.00	24	UPDRS–III, PDQ39
		GPi_DBS	bi	152	61.80 ± 8.70	133/19	NA	1361.00 ± 545.00		
29	Moro 2010 (62)	STN_DBS	bi	31	59.30 ± 9.47	NA	15.30 ± 6.51	1709.30 ± 986.80	3	UPDRS–III
		GPi_DBS	bi	15	56.00 ± 8.40	NA	15.10 ± 6.00	1417.80 ± 612.00		
30	Montel 2009 (63)	STN_DBS	NA	40	56.00 ± 9.20	22/18	11.90 ± 5.00	975.00 ± 443.80	12	UPDRS–III
		MT	–	40	55.80 ± 9.30	22/18	11.00 ± 4.40	1065.00 ± 576.80		
31	Volkmann 2009 (64)	STN_DBS	bi	45	58.50 ± 9.80	22/23	15.30 ± 6.30	NA	6	UPDRS–III, SIP
		GPi_DBS	bi	20	55.80 ± 9.40	7/13	15.40 ± 6.20	NA		
32	Zahodne 2009 (65)	STN_DBS	uni	20	61.30 ± 9.00	14/6	13.57 ± 3.88	935.90 ± 374.00	6	UPDRS–III, PDQ39
		GPi_DBS	uni	22	61.30 ± 5.50	16/6	12.36 ± 3.58	1199.80 ± 576.90		
33	Zangaglia 2009 (66)	STN_DBS	bi	32	58.84 ± 7.70	18/14	11.84 ± 5.07	617.19 ± 303.57	36	UPDRS–III
		MT	–	33	62.52 ± 6.82	20/13	9.97 ± 4.86	647.73 ± 243.78		
34	Witt 2008 (67)	STN_DBS	bi	60	60.20 ± 7.90	36/24	13.80 ± 6.30	1203.00 ± 535.00	6	UPDRS–III
		MT	–	63	59.40 ± 7.50	41/22	14.00 ± 6.10	1142.00 ± 463.00		
35	Deuschl 2006 (68)	STN_DBS	bi	71	60.50 ± 7.40	NA	NA	1176.00 ± 517.00	6	UPDRS–III, PDQ39
		MT	–	73	60.80 ± 7.80	NA	NA	1175.00 ± 461.00		
36	Anderson 2005 (69)	STN_DBS	bi	10	61.00 ± 9.00	NA	15.60 ± 5.00	NA	12	UPDRS–III
		GPi_DBS	bi	10	54.00 ± 12.00	NA	10.30 ± 2.00	NA		
37	Capecci 2005 (70)	STN_DBS	bi	23	59.50 (7.50)	12/11	12.80 (4.20)	987.87 (427.00)	12	UPDRS–III
		MT	–	16	62.20 (6.50)	6/10	10.30 (4.20)	961.19 (474.00)		
38	Just 2002 (71)	STN_DBS	bi	11	59.80 (6.80)	8/3	14.00 (6.00)	NA	6	PDQ39
		MT	–	13	61.40 (5.70)	7/6	16.00 (6.00)	NA		
39	Obeso 2001 (14)	STN_DBS	bi	91	59.00 ± 9.60	NA	NA	1218.80 ± 575.00	6	UPDRS–III
		GPi_DBS	bi	36	55.70 ± 9.80	NA	NA	1090.90 ± 543.00		

Data are expressed as number, mean±SD, median (interquartile range), mean [range]. *: medical treatment & sham procedure or off stimulation. NA, not available. DBS, deep brain stimulation; FUS, focused ultrasound surgery; STN, subthalamic nucleus; Gpi, internal globus pallidus; cZi, caudal zona incerta; NBM, nucleus basalis of Meynert; SNr, substantia nigra pars reticulata; VIM, ventral intermediate nucleus; MT, medication treatment; uni, unilateral; bi, bilateral; UPDRS-III, Unified Parkinson's Disease Rating Scale, Part III; PDQ, Parkinson's Disease Questionnaire; SIP, Sickness Impact Profile.

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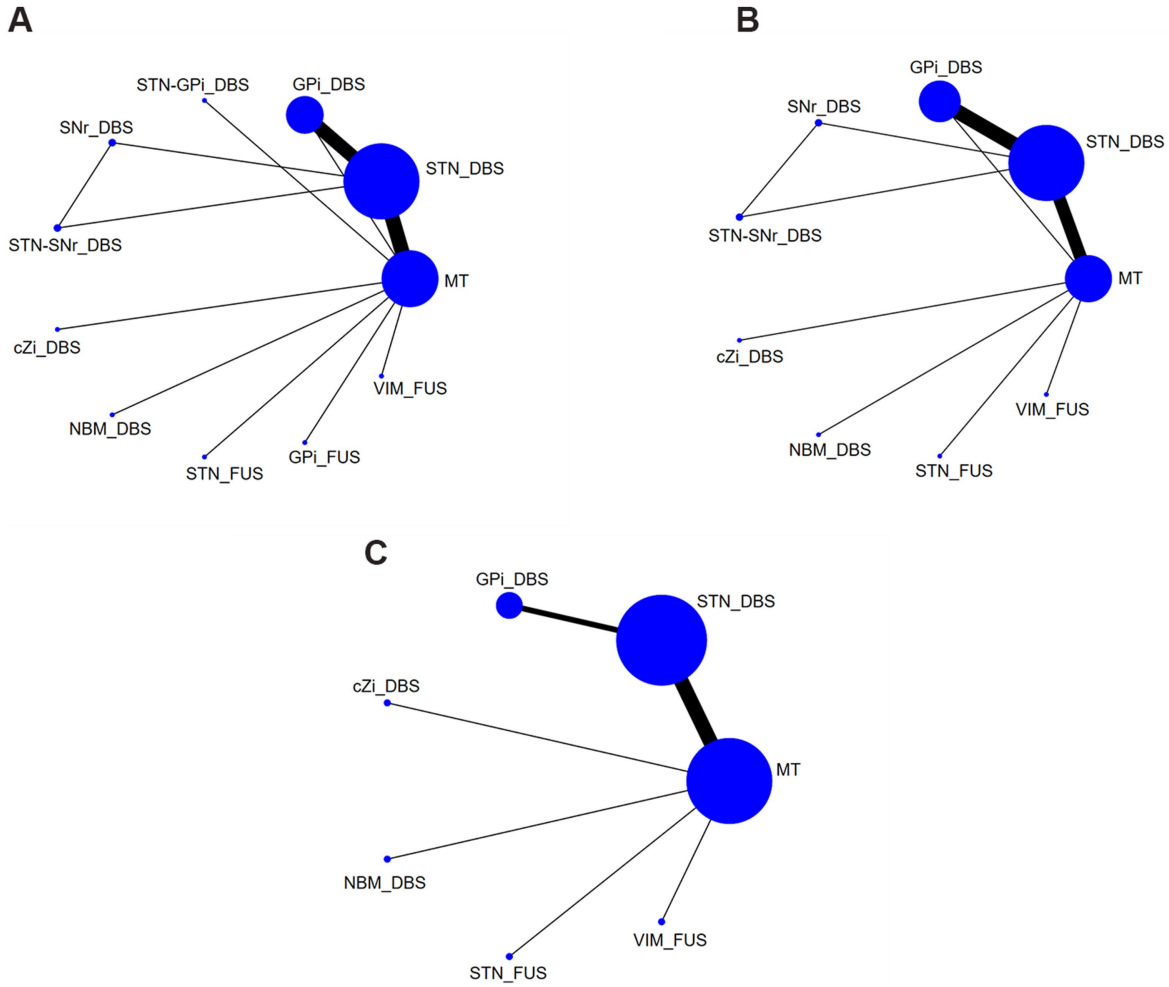

FIGURE 2
Network plots of each evaluation. **(A)** UPDRS-III Total score (off-phase); **(B)** UPDRS-III Total score (on-phase); **(C)** QoL. DBS, deep brain stimulation; FUS, focused ultrasound surgery; STN, subthalamic nucleus; Gpi, internal globus pallidus; cZi, caudal zona incerta; NBM, nucleus basalis of Meynert; SNr, substantia nigra pars reticulata; VIM, ventral intermediate nucleus; MT, medication treatment.

While a definitive cure for PD continues to be elusive, there exist effective treatments to manage the symptoms. DBS is one such treatment that has consistently proven its effectiveness. Thalamic DBS is optimal for handling tremors. Pallidum DBS has been shown to be excellent for rigidity and dyskinesias. STN DBS can manage a range of symptoms and decrease the requirement for medications, thereby earning recognition as a favored DBS focus area (5).

Despite its benefits, DBS carries the risk of certain complications, which discourages many patients from opting for the invasive procedure (26, 27). Adverse reactions of DBS include dysarthria, changes in mood or cognition impairment, implant infection, and other adverse outcomes (10). A small number of patients may experience serious adverse effects related to the device (28).

Nonetheless, our study focused more on STN_FUS. MRgFUS generates extracorporeal ultrasound to deliver ultrasonic energy precisely to specific brain regions through the skull, allowing for incision-free lesion treatment and real-time monitoring (29). Different points of focus have been employed for MRgFUS in the handling of PD; these include areas like the ventral lobe of VIM, STN, GPi, along with pallidothalamic tractotomy (PTT) (17). In comparison to DBS, MRgFUS does not necessitate implantation of a device and presents a minimal risk of hemorrhage and infection (30, 31).

The case series by Schlesinger et al. pointed out that VIM_FUS can simultaneously improve tremor severity, UPDRS-III and PDQ-39 scores in PD individuals (32), while Moosa et al. summarized previous studies in a review and concluded that MRgFUS of the VIM, STN, and GPi all can improve patients' motor symptoms and produce fewer adverse reactions than DBS (29).

Parkinsonian symptoms occur when output from the GPi or SNr is excessively inhibited, affecting thalamic cortical projections, which is induced by an increase in STN excitatory activity (33). Therefore, MRgFUS is theoretically feasible and effective for STN and GPi targets.

Because we only included one study on the effect of GPi_FUS on motor symptoms, our results on FUS are limited; this study has only found that STN_FUS may improve motor symptoms and QoL. Due to its anatomical position relative to the STN or VIM, targeting the GPi may require steeper angles of the ultrasound beam,

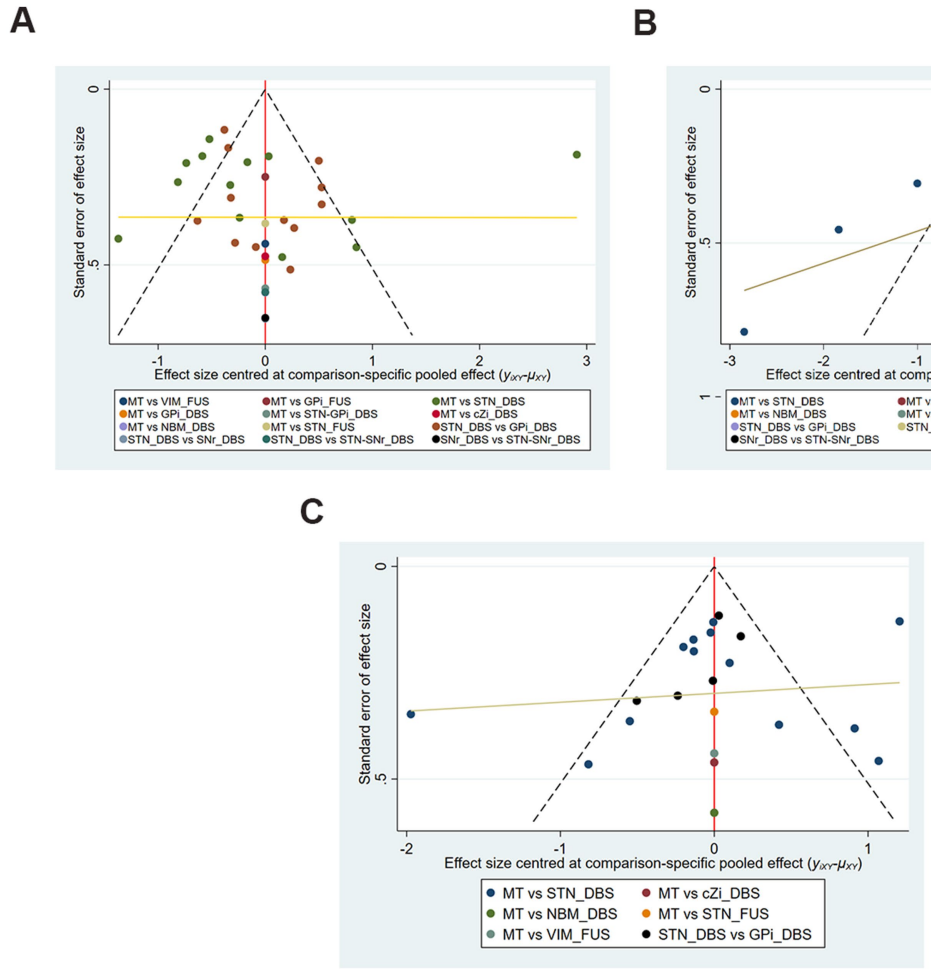

FIGURE 3
Funnel plots of each evaluation. **(A)** UPDRS-III Total score (off-phase); **(B)** UPDRS-III Total score (on-phase); **(C)** QoL.

which could reduce energy transfer efficiency (17). Hence these potential problems limit the current results. Additionally, the outcomes of our VIM_FUS procedure did not yield favorable results, possibly due to the anatomical challenges associated with targeting this region. In contrast to our findings, Schlesinger and colleagues reported notable improvements in motor abilities and Quality of Life in a group of seven patients suffering from PD, who had undergone unilateral VIM-MRgFUS treatment for managing tremors (32).

The STN_FUS improves both dyskinesia and QoL, which aligns with the conclusions of many advanced studies (18, 34, 35). Regrettably, only one study concerning STN_FUS was included in our analysis. In addition, we failed to find that GPi_FUS and VIM_FUS have a meaningful effect on motor function and QoL, which is contrary to the conclusions of other studies (36, 37).

Given the limited research on MRgFUS and smaller sample sizes, and lack of in-depth follow-up period, interpreting the results requires caution. Besides, MRgFUS treatment involves creating a lesion in the target region, precluding postoperative adjustments. In conclusion, despite certain drawbacks, MRgFUS represents a promising, less invasive alternative for treating PD, with the potential to offer benefits comparable to those of DBS.

Limitations

Certain limitations are inevitable in this study. Currently, RCT studies on FUS are very rare. Our study includes only 27 patients targeting STN and 65 patients targeting GPi, hence the conclusions drawn from this may not be highly reliable. However, future RCT studies are expected to increase, and this new surgical technique sure will bring about new hope. We did not conduct rigorous subgroup analysis based on follow-up times, which could potentially limit comparisons of different outcomes. In addition, we did not perform statistical analysis on adverse reactions to surgery. Future studies should consider these variables.

In this study, we employed a frequentist NMA to evaluate the effects of different treatments on Parkinson's disease patients. This approach allows for effective comparisons between treatments, providing interpretable effect sizes (e.g., SMD) and confidence intervals. However, it has limitations regarding sample heterogeneity and missing data. Although most studies included were of high quality, caution is warranted due to potential publication bias from lower-quality studies. Additionally, NMA relies on indirect comparisons from existing literature, lacking direct support from randomized controlled trials, which necessitates careful interpretation

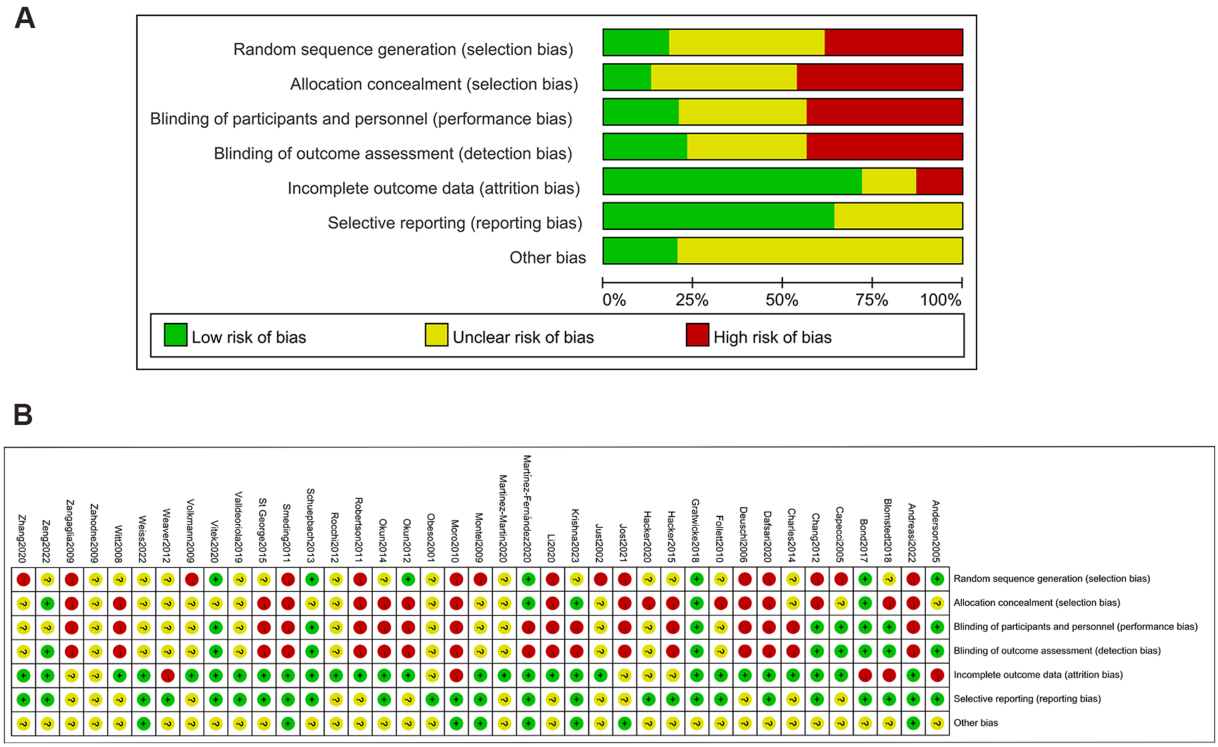

FIGURE 4
Risk of bias assessment. **(A)** Risk of bias graph; **(B)** Risk of bias summary.

A

STN_FUS										
-0.20 (-2.79,2.39)	STN-GPi_DBS									
-0.58 (-2.38,1.22)	-0.38 (-2.36,1.60)	STN_DBS								
-0.61 (-3.25,2.03)	-0.41 (-3.18,2.36)	-0.03 (-1.96,1.91)	STN-SNr_DBS							
-0.84 (-3.37,1.68)	-0.64 (-3.29,2.01)	-0.26 (-2.14,1.62)	-0.23 (-2.93,2.47)	cZi_DBS						
-0.91 (-2.77,0.95)	-0.71 (-2.74,1.32)	-0.33 (-0.81,0.16)	-0.30 (-2.30,1.70)	-0.07 (-2.01,1.87)	Gpi_DBS					
-1.03 (-3.43,1.36)	-0.83 (-3.36,1.70)	-0.45 (-2.16,1.26)	-0.42 (-3.01,2.16)	-0.19 (-2.65,2.27)	-0.12 (-1.90,1.65)	Gpi_FUS				
-1.37 (-3.97,1.23)	-1.17 (-3.90,1.56)	-0.79 (-2.78,1.20)	-0.76 (-3.54,2.02)	-0.53 (-3.19,2.14)	-0.46 (-2.50,1.59)	-0.33 (-2.88,2.21)	NBM_DBS			
-1.67 (-4.17,0.82)	-1.47 (-4.10,1.16)	-1.09 (-2.94,0.76)	-1.06 (-3.74,1.62)	-0.83 (-3.39,1.73)	-0.76 (-2.67,1.14)	-0.64 (-3.07,1.79)	-0.30 (-2.94,2.34)	VIM_FUS		
-1.52 (-3.26,0.22)	-1.32 (-3.24,0.60)	**-0.94 (-1.40,-0.48)**	-0.91 (-2.90,1.08)	-0.68 (-2.50,1.15)	-0.61 (-1.27,0.05)	-0.49 (-2.13,1.16)	-0.15 (-2.09,1.79)	0.15 (-1.64,1.94)	MT	
-2.10 (-4.80,0.61)	-1.89 (-4.72,0.94)	-1.51 (-3.54,0.51)	-1.48 (-3.51,0.54)	-1.25 (-4.02,1.52)	-1.19 (-3.27,0.90)	-1.06 (-3.71,1.59)	-0.73 (-3.57,2.11)	-0.42 (-3.17,2.32)	-0.58 (-2.65,1.50)	SNr_DBS

B

STN_FUS								
-1.00 (-2.18,0.18)	STN_DBS							
-1.03 (-2.24,0.18)	-0.03 (-0.30,0.24)	Gpi_DBS						
-1.25 (-3.09,0.59)	-0.25 (-1.66,1.16)	-0.22 (-1.65,1.21)	STN-SNr_DBS					
-1.44 (-3.28,0.41)	-0.44 (-1.85,0.97)	-0.41 (-1.85,1.03)	-0.19 (-1.59,1.22)	SNr_DBS				
-1.48 (-3.09,0.13)	-0.48 (-1.65,0.69)	-0.45 (-1.65,0.75)	-0.23 (-2.06,1.60)	-0.04 (-1.88,1.79)	VIM_FUS			
-1.67 (-3.34,0.01)	-0.67 (-1.93,0.59)	-0.64 (-1.93,0.65)	-0.42 (-2.31,1.47)	-0.23 (-2.13,1.67)	-0.19 (-1.85,1.48)	cZi_DBS		
-1.83 (-2.97,-0.68)	**-0.83 (-1.13,-0.53)**	**-0.80 (-1.20,-0.40)**	-0.58 (-2.02,0.86)	-0.39 (-1.84,1.06)	-0.35 (-1.48,0.78)	-0.16 (-1.39,1.07)	MT	
-2.16 (-3.97,-0.34)	-1.16 (-2.60,0.29)	-1.13 (-2.60,0.34)	-0.91 (-2.92,1.11)	-0.72 (-2.74,1.30)	-0.68 (-2.48,1.13)	-0.49 (-2.36,1.38)	-0.33 (-1.74,1.08)	NBM_DBS

C

Gpi_DBS						
-0.17 (-0.76,0.43)	STN_DBS					
-0.30 (-1.88,1.28)	-0.13 (-1.60,1.33)	STN_FUS				
-0.55 (-2.24,1.14)	-0.38 (-1.97,1.20)	-0.25 (-2.34,1.84)	cZi_DBS			
-0.56 (-2.38,1.27)	-0.39 (-2.12,1.33)	-0.26 (-2.46,1.94)	-0.01 (-2.29,2.27)	NBM_DBS		
-0.88 (-2.55,0.79)	-0.71 (-2.27,0.85)	-0.58 (-2.65,1.49)	-0.33 (-2.48,1.83)	-0.32 (-2.58,1.94)	VIM_FUS	
-0.75 (-1.46,-0.05)	**-0.58 (-0.96,-0.21)**	-0.45 (-1.86,0.96)	-0.20 (-1.74,1.34)	-0.19 (-1.87,1.49)	0.13 (-1.38,1.64)	MT

FIGURE 5
League tables of the NMA outcome. **(A)** UPDRS-III (off-phase); **(B)** UPDRS-III (on-phase); **(C)** QoL.

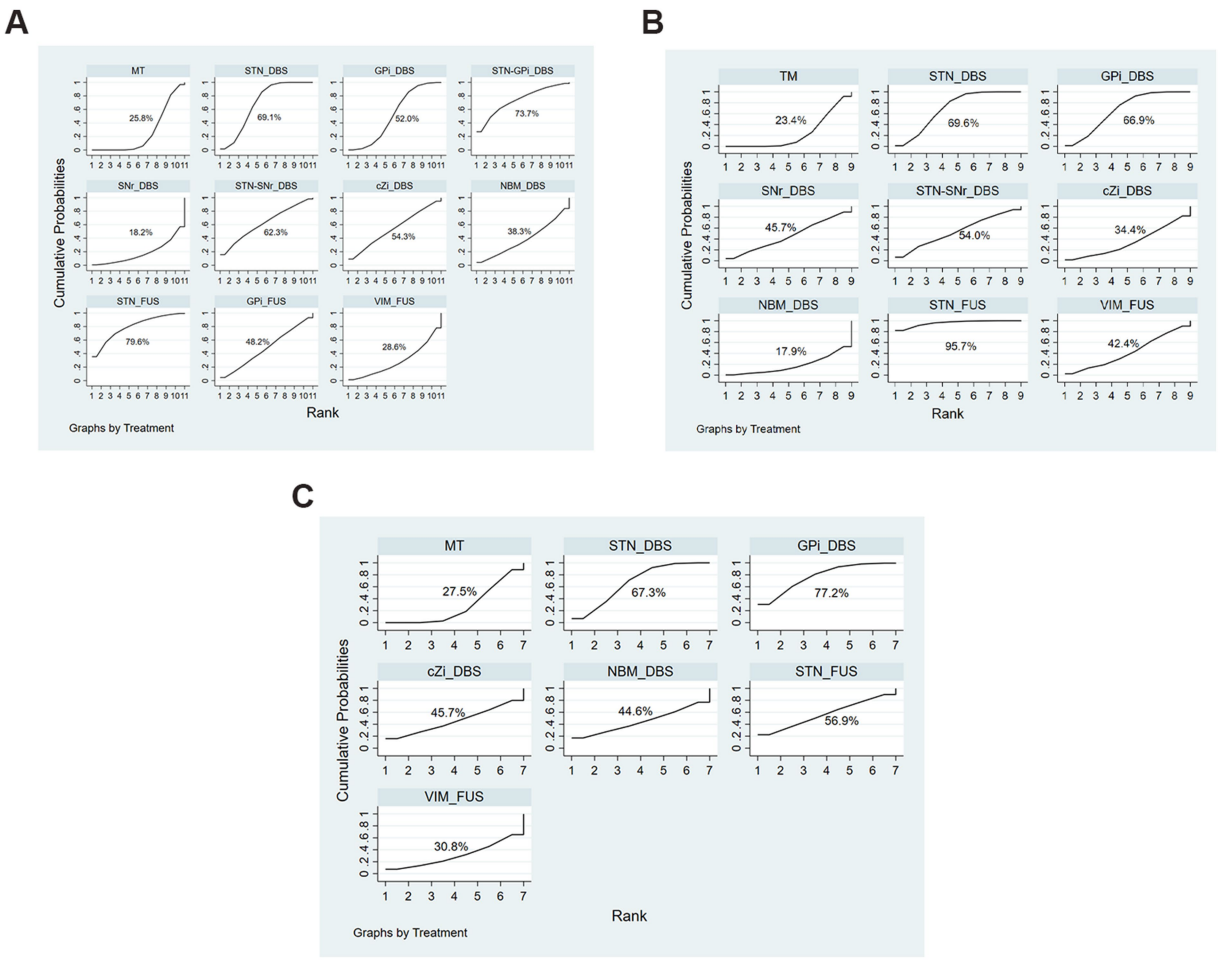

FIGURE 6
SUCRA Plots of each evaluation. **(A)** UPDRS-III Total score (off-phase); **(B)** UPDRS-III Total score (on-phase); **(C)** QoL.

of treatment effects, particularly regarding their applicability to diverse patient populations.

Conclusion

Surgical interventions such as STN_DBS, GPi_DBS, and STN_FUS have exhibited efficacy in ameliorating motor symptoms, alongside enhancing quality of life in parkinsonism. Moreover, indirect evidence from our study indicates that STN-FUS is not inferior to STN-DBS in both aspects for PD. Therefore, STN-FUS may serve as a second alternative with comparable efficacy to STN-DBS in the management of PD. In conclusion, based on the assessment of motor function improvements and quality of life, we provide recommendations for surgical treatment options. For motor symptoms in the off-phase, STN-DBS is the preferred approach. In the on-phase, STN-DBS, GPi-DBS and STN_FUS, are considered viable options. Regarding improvements in quality of life, STN-DBS and GPi-DBS are the preferred treatments. Taking all factors into account, STN-DBS is ultimately recommended as the optimal surgical intervention.

Author contributions

ML: Data curation, Methodology, Software, Validation, Visualization, Writing – original draft. LH: Formal analysis, Investigation, Software, Writing – original draft. JL: Conceptualization, Methodology, Writing – original draft. SB: Conceptualization, Supervision, Writing – review & editing.

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Conflict of interest

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Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2025.1449973/full#supplementary-material

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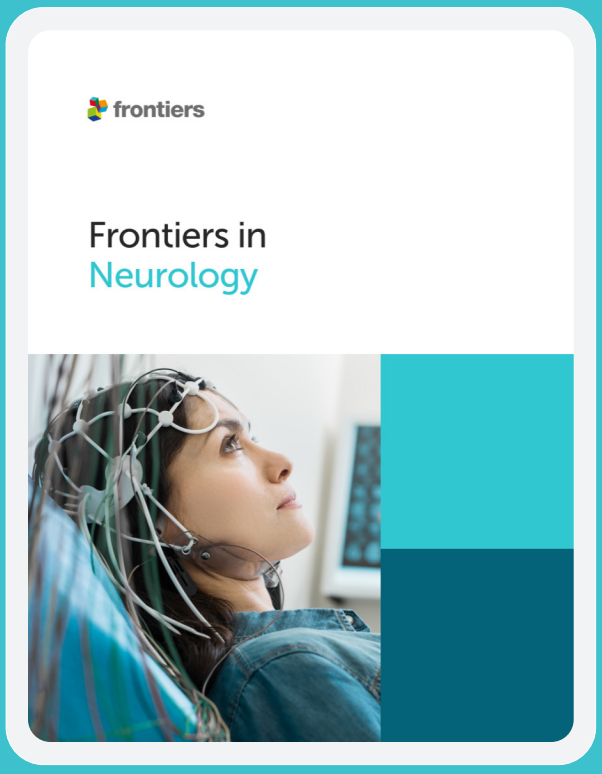

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