ORIGINAL RESEARCH

Multimodal MRI for MRgFUS in essential tremor: post-treatment radiological markers of clinical outcome

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ABSTRACT

Background MRI-guided focused ultrasound (MRgFUS) thalamotomy is a promising non-invasive treatment option for medication-resistant essential tremor. However, it has been associated with variable efficacy and a relatively high incidence of adverse effects.

Objectives To assess the evolution of radiological findings after MRgFUS thalamotomy and to evaluate their significance for clinical outcomes.

Methods Ninety-four patients who underwent MRgFUS between 2012 and 2017 were retrospectively evaluated. Lesion characteristics were assessed on routine MRI sequences, as well as with tractography. Relationships between imaging appearance, extent of white matter tract lesioning (59/94, on a 4-point scale) and clinical outcome were investigated. Recurrence was defined as >33% loss of tremor suppression at 3 months relative to day 7.

Results Acute lesions demonstrated blood products, surrounding oedema and peripheral diffusion restriction. The extent of dentatorubrothalamic tract (DRTT) lesioning was significantly associated with clinical improvement at 1 year (t=4.32, p=0.001). Lesion size decreased over time (180.8±91.5 mm^3 at day 1 vs 19.5±19.3 mm^3 at 1-year post-treatment). Higher post-treatment oedema (t=3.59, p<0.001) was associated with larger lesions at 3 months. Patients with larger lesions at day 1 demonstrated reduced rates of tremor recurrence (t=2.67, p=0.019); however, lesions over 170 mm^3 trended towards greater incidence of adverse effects (sensitivity=0.60, specificity=0.63). Lesion encroachment on the medial lemniscus (Sn=1.00, Sp=0.32) and pyramidal tract (Sn=1.00, Sp=0.12) were also associated with increased adverse effects incidence.

Conclusion Lesion size at day 1 predicts symptom recurrence, with fewer recurrences seen with larger lesions. Greater DRTT lesioning is associated with treatment efficacy. These findings may have implications for lesion targeting and extent.

Trial registration number NCT02252380.

INTRODUCTION

Essential tremor (ET) is the most common movement disorder.[1] Medical management improves symptoms in approximately 50% of patients. Patients who are refractory or unable to tolerate medical management can be considered for invasive neurosurgical intervention with deep brain stimulation, radiosurgery or radiofrequency thalamotomy.[2] Recent technological advances have also led to the development and approval of intracranial MRI-guided focused ultrasound (MRgFUS) as a minimally invasive ablative treatment for ET. This procedure specifically ablates the ventral intermediate nucleus (VIM) of the thalamus with the aim of disrupting the dysfunctional tremor network implicated in ET pathophysiology.[3] Patients typically undergo a follow-up MRI scan to confirm lesion location and to assess for potential complications. Prior work has assessed the characteristics of the early post-treatment changes in imaging within the first 3 months,[3] finding the early lesion appearance to be characterised by the presence of blood products, oedema and peripheral diffusion restriction.[4] Changes over time have also been documented in the first 3 months; both the oedema and diffusion restriction appear to rapidly resolve after the acute post-treatment period, while the lesion volume progressively decreases at a slower rate.[4 5] Whether or not the imaging appearance of MRgFUS lesions and its evolution could serve as a surrogate for treatment efficacy or adverse outcomes has not yet been determined.[3]

VIM cannot be visualised on routinely acquired clinical MRI.[6] As such, indirect targeting techniques reliant on anatomical landmarks have been used to infer target coordinates for MRgFUS ablation, with intraprocedural clinical response feedback from the patient used to further refine lesion location. It is conceivable that this limitation—especially when compounded by the difficulty associated with controlling and predicting final lesion volume—leads to suboptimal lesion location, resulting in less desirable therapeutic outcomes and adverse neurological effects.[2 7] Post-treatment neurological adverse effects may be short-lived or persistent and most commonly are sensory, motor or ataxia-related in nature.[2] Prior work suggests lesion impingement on surrounding white matter tracts, such as the medial lemniscus (ML) and pyramidal tract (PT) within the internal capsule, may be related to the incidence or severity of adverse effects.[5]

As the main cerebellar input to the VIM, the dentatorubrothalamic tract (DRTT) has been hypothesised to play a key role in mediating tremor relief from neuromodulatory procedures targeting the thalamus.[8 9] Indeed, DRTT has been prospectively targeted for both deep brain stimulation and MRgFUS for tremor to good effect.[10–12] Proximity of active contacts to DRTT may also be associated with greater efficacy in patients with tremor treated with deep brain stimulation targeting the posterior subthalamic area.[13] The relevance of DRTT to tremor relief is also corroborated by its relationship to long-term maintenance of symptom relief, an important element given that many patients experience progressive loss of efficacy and return of tremor over time.[14 15] White matter integrity in the treated area has been suggested to reflect persistent tremor improvement up to 6 months after MRgFUS treatment,[15] and reduced VIM region fractional anisotropy at day 1 post-treatment has been correlated with both short-term and long-term treatment efficacy.[16 17] In addition, one case report described a patient with tremor whose recurrence of symptoms after MRgFUS treatment was accompanied by the reappearance of the DRTT on tractography.[18] Most recently, white matter changes at various segments of the DRTT have been described following MRgFUS.[17] Taken together, these findings suggest a role of major white matter tracts in treatment efficacy, as well as adverse effects after treatment.

This study sought to (1) define the radiological features of MRgFUS thalamotomy lesions, particularly with respect to their temporal evolution following the procedure; (2) evaluate the relationship of both these radiological features and the degree of lesion encroachment on tractography-defined major white matter tracts (DRTT, PT and ML) with clinical outcomes.

MATERIALS AND METHODS

Patient population

Ninety-four patients who underwent MRgFUS thalamotomy at Sunnybrook Health Sciences Centre (n=55) and Toronto Western Hospital (n=39) between May 2012 and October 2017 (prior to regulatory agency approvals, patients were enrolled in the clinical trial, clinicaltrials.gov; principal investigators: AML and MLS) were included. Patients with clinical follow-up of less than 3 months or sham procedures (as part of the clinical trial) were excluded. Patients underwent MRgFUS with inclusion and exclusion criteria as previously described.[3 19] Typically, patients underwent postprocedural assessment at days 1 and 7, 3 months and 1 year postoperatively. Using the standard Clinical Rating Scale for Tremor (CRST), we recorded the patients' tremor scores in the treated hand (ie, the hand contralateral to the lesion) at baseline, 3 months and 1 year.[20] A percentage improvement of the treated hand using CRST as compared with pre-treatment baseline was calculated at 3 months and 1 year of follow-up. In order to capture patients with only short-lived tremor relief, tremor recurrence was documented; on the basis of prior clinical experience, this was defined as loss of >33% of the efficacy at 3 months relative to a short time after the treatment (ie, 7 days). The presence or absence of adverse effects—specifically sensory, motor, speech and ataxia (dysmetria or gait disturbance)—was determined based on notes made prospectively at each follow-up visit. Only adverse effects persisting at 3 months of follow-up were included for this analysis, as most early symptoms are known to be transient and self-resolving.[20] Indeed, previous analysis of patients treated at our institution found that rates of adverse effects decreased substantially from the immediate post-treatment period to 3 months of follow-up.[5]

Imaging acquisition

Images were acquired at day 1, 3 months and 1 year post-treatment at one of two sites: Sunnybrook Health Sciences Centre (GE 3T MR650 Discovery) and Toronto Western Hospital (GE 3T HDx scanner). Standard MRI sequences (pregadolinium 3D T1-weighted, gradient echo (GRE) T2*-weighted, radiological diffusion-weighted imaging (DWI), fluid-attenuated inversion recovery (FLAIR) and postgadolinium T1-weighted sequences) were acquired. In addition, 60 and 30 direction research DWI sequences (the former acquired at Sunnybrook Health Sciences Centre and the latter at Toronto Western Hospital) were acquired for tractography as previously described.[5] DWI image acquisition for tractography was as follows: Sunnybrook Health Science Centre GE 3T MR650 Discovery 1 b=0 images, 60 directions at b=1000 s/mm^2, repetition time: 9000 ms, echo time: 83 ms, isotropic voxel: 2 mm; Toronto Western Hospital GE 3T HDx scanner 3 b=0 images, 30 directions at b=1000 s/mm^2, repetition time: 11 700 ms, echo time: 108 ms, isotropic voxel: 2 mm.[5] Because tractography was used only to generate major white matter tracts and to assess for overlap with thalamotomy lesions, the difference in acquisition parameters between sites, although a limitation, was not deemed prohibitive.

Image preprocessing and lesion segmentation

Image preprocessing, registration and lesion segmentation methods were detailed in a previous study.[5] Briefly, immediate post-operative 3D T1-weighted fast spoiled gradient echo (FSPGR) images were used for manual lesion segmentation and were registered to their corresponding pre-treatment 3D T1-weighted FSPGR (acquired with the same MRI parameters as the immediate post-treatment images) via rigid registration (6 df) in FMRIB software library (FSL) using FLIRT V.5.0 (FMRIB, Oxford, UK, http://www.fmrib.ox.ac.uk/fsl/).[21] Using MincTools software, the necrotic lesion centre was manually delineated in the axial plane on the 3D T1-weighted images, as previously defined by Wintermark *et al*.[4] It should be noted that the lesion size can vary slightly depending on the MRI sequence and that use of T1-weighted sequences for demarcation purposes has been validated.[22] The volume of each lesion mask was obtained. Research DWI acquisitions were adjusted for motion and eddy-current correction in FSL, and for b-vector rotational corrections. Anisotropic power (AP) images were generated to more accurately coregister the DWI images with the pre-treatment 3D T1-weighted FSPGR images. Advanced normalization tools (ANTs; http://stnava.github.io/ANTs/) were used to non-linearly register the 3D T1 FSPGR images to these AP images. The transforms from this non-linear registration were then applied to the lesion masks in order to move each lesion from post-treatment 3D T1-weighted FSPGR space into the corresponding pre-treatment DWI space.

Tractography

As previously described,[5] fibre tracking was performed in DWI space using a deterministic tractography approach as implemented in Mrtrix3 (http://www.brain.org.au/software/).[23 24] Specifically, the ML, PT and DRTT white matter tracts were generated from pre-treatment DWI images. Tracking parameters included step size of 1 mm, minimum radius of curvature of 1 mm, fractional anisotropy (FA) cut-off threshold of 0.2 and tracking angles at 45°. For subjects whose ML, PT or DRTT tracts could not be traced with these settings, we first attempted to generate missing tracts by using probabilistic tractography with the same tracking parameters described previously and then by

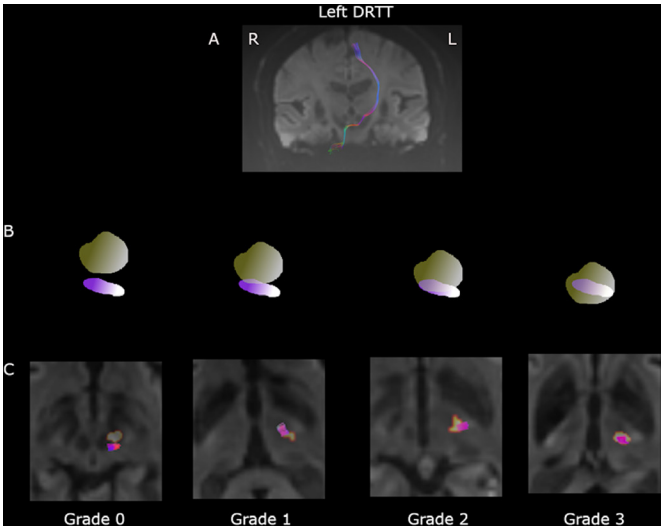

Figure 1 Semiquantitative grading of MRI-guided focused ultrasound lesion overlap with white matter tracts (eg, left DRTT, A) using a 4-point scale (0–3); presented with schematic (B) and representative cases (C). Grade 0=no overlap, grade 1<50% overlap, grade 2≥50% overlap, grade 3=complete overlap. Lesion=yellow and tract=pink/purple. DRTT, dentatorubrothalamic tract; L, left, R, right.

lowering the FA cut-off threshold to 0.1. A total of 59 patients had DWI data that were adequate for analysis. Fibre tracks were subsequently overlaid with each subject's lesion mask in native pre-treatment DWI space for overlap analysis.

Lesion–tract overlap analysis

Building on prior analyses,[5] semiquantitative analysis of lesion overlap with ML, PT and DRTT was performed in native pre-treatment DWI space. For each white matter tract, a grade ranging from 0 to 3 was assigned to capture the degree to which a given lesion impinged on the tract cross-section. These grades were operationally defined as follows: grade 0=no overlap between tract and lesion, grade 1<50% of tract overlapping with lesion, grade 2≥50% of tract overlapping with lesion and grade 3=complete tract overlap with lesion (figure 1). Lesion–tract overlap analysis was performed independently by two raters (ANK and GJBE) with discrepancies resolved via consensus.

Statistics

Statistical analysis was performed in R V.5.3.0 using a statistical significance level of $p<0.05$. The relationships between lesion radiological characteristics or lesion–tract overlap and symptom improvement were assessed using either linear (for continuous outcome variables) or logistic regression (for categorical or ordinal outcome variables). Sensitivity/specificity analysis was performed to investigate the relationship between lesion–tract overlap and adverse effects. Receiver operating characteristic (ROC) curves were used to examine for lesion volume thresholds for treatment response and occurrence of adverse effects.

RESULTS

Demographics and clinical outcomes

A total of 94 patients with ET who underwent MRgFUS thalamotomy treatment were included in this analysis. Patient demographics, including patient age, gender, disease duration, 1 day, 3 months and 1-year post-treatment clinical improvement in tremor relative to baseline are summarised in table 1. Technical

Table 1 Patient demographics and summary of clinical outcomes

	Total cohort (n=94)
Age (years)	70.8±9.2
Female	32%
Duration of disease (years)	31.5±17.4
Treated hand CRST % improvement at clinical follow-up times	
1 day*	70.0%±27.0%
3 months* (n=78)	67.6%±17.6%
12 months* (n=48)	56.0%±20.4%
Post-treatment adverse effects at clinical follow-up times	
3 months (n=76)†	
Gait	46%
Motor	13%
Sensory	12%
Dysmetria	17%
Ataxia‡	50%
Speech	7%
12 months (n=44)†	
Gait	29%
Motor	10%
Sensory	8%
Dysmetria	10%
Ataxia‡	33%
Speech	8%

Data are presented as mean±SD or percentage of the total cohort.
*CRST improvement calculated as percentage improvement from baseline.
†A number (n=40) of patients had multiple different adverse effects.
‡Ataxia is the presence of dysmetria or gait disturbance.
CRST, Clinical Rating Scale for Tremor.

treatment parameters are summarised in online supplementary table 1. Following MRgFUS treatment, tremor scores improved from baseline, without significant loss of efficacy between early post-treatment and 3 months (table 1). Some loss of efficacy was observed between 3 months and 1 year of follow-up (table 1). At 3 months post-treatment, 68% of patients had at least one persistent adverse effect, regardless of its severity. This was reduced to 42% at 1 year. The most common adverse effects were related to gait abnormality (46%) and ataxia (50%), as observed at 3 months. A smaller proportion of patients developed motor, sensory or speech deficits (table 1).

Imaging findings

Table 2 describes the imaging appearance of MRgFUS thalamotomy lesions (n=94) at day 1, 3 months and 1 year post-treatment. On 3D T1-weighted images, all lesions demonstrated a hypointense necrotic appearance. At day 1 post-treatment, the degree of perilesional oedema seen on FLAIR images varied between a subjectively limited or more extensive appearance based on extent beyond lesion core (online supplementary figure 1). Thirty-six per cent of patients demonstrated more extensive perilesional oedema. Average lesion volume (as measured on these T1-weighted images) decreased considerably over time ($180.8\pm91.5\,mm^3$ at day 1 vs $19.5\pm19.3\,mm^3$ at 1 year post-treatment). Up to 28% of lesions become too small to measure at 1 year of follow-up. Nearly all patients (96%) demonstrated blood products on GRE images at day 1 post-treatment; residual hemosiderin at the lesion site was seen on GRE images at subsequent follow-up for all patients with blood products seen at day 1. All acute lesions, at day 1, were associated with a characteristic zone II, rim-like, diffusion restriction on DWI; this

Table 2 Imaging appearances at day 1, 3 months and 1 year post-procedure

	Day 1	3 months	1 year
Imaging			
FLAIR oedema (day 1)	100% (36% extensive, 64% limited)	0%	0%
Blood products (%)			
No	5 (n=4)	5 (n=3)	7 (n=3)
Yes	95	95	93
Zone II diffusion restriction (%)	100	0	0
Size measurable	100	80	72
Average lesion size (mm^3, mean±SD)	180.8±91.5	40.0±42.8	19.5±19.3

Percentages indicate the proportion of patients who have the specific imaging findings.
FLAIR, fluid-attenuated inversion recovery.

Table 3 Extent of lesion overlap with major white matter tracts, a semiquantitative grading by two observers obtained by consensus

Extent of tract overlap	ML (%)	PT (%)	DRTT (%)
Grade 0	25.5	8.7	22.0
Grade 1	27.3	60.3	17.0
Grade 2	29.1	29.3	14.6
Grade 3	18.2	17.2	46.3

Percentages indicate the proportion of patients who demonstrated each particular grade of lesion/tract overlap. Grade 0=no overlap between tract and lesion, grade 1<50% of tract overlapping with lesion, grade 2≥50% of tract overlapping with lesion; grade 3=complete tract overlap with lesion (see figure 1).
DRTT, dentatorubrothalamic tract; ML, medial lemniscus; PT, pyramidal tract.

had invariably resolved by the subsequent follow-up scan at 3 months. Many patients additionally demonstrated focal hyperintensity on FLAIR images at 3 months and 1 year post-treatment. Figure 2 demonstrates the typical appearance of the thalamotomy lesions.

ML (56/59) and PT (59/59) were consistently visualised in patients with adequate DWI acquisitions (n=59), while DRTT (41/59) could only be visualised in 70% of patients due to its smaller size and tortuous course. The average lesion location of patients who underwent tractography was 6.9±1.0 mm anterior to the posterior commissure and 14.8±1.1 mm lateral to the anterior commissure–posterior commissure line. MRgFUS lesions were found to variably overlap with these neighbouring white matter tracts (table 3 and online supplementary table 2). DRTT demonstrated the most pronounced lesion involvement; >50% lesion overlap of DRTT was observed in 60.6% of patients, and complete cross-sectional involvement of this tract was common (46.3%). Semiquantitative lesion–tract overlap grading demonstrated an inter-rater agreement of 84%, 95% and 88% for ML, PT and DRTT, respectively. The two raters never disagreed by more than 1 point on the rating scale.

Relationships between imaging findings and clinical outcome

Patients with larger MRgFUS lesions at day 1 demonstrated significantly greater improvement in treated hand CRST at both 3 months (t=2.67, p=0.0093, R=0.30) and 1 year post-treatment (t=2.65, p=0.01, R=0.36). Larger lesions at day 1 were also associated with reduced rates of tremor recurrence (t=2.59, p=0.019, mean lesion volume at day 1: 186 mm^3 in non-relapse vs 135 mm^3 in relapse). Similarly, patients with larger lesions at 3 months demonstrated significantly greater clinical improvement at 3 months (t=2.04, p=0.047, R=0.29), as well as reduced rates of recurrence (t=3.75, p=0.001, mean lesion volume at 3 months: 43 mm^3 in non-relapse and 12 mm^3 in relapse). No other conventional imaging parameters were associated with improvement of clinical tremor score. Since larger lesions were associated with clinical efficacy, other imaging parameters were assessed for their association with lesion volume. Higher degree of oedema (t=3.59, p<0.001) at day 1 was associated

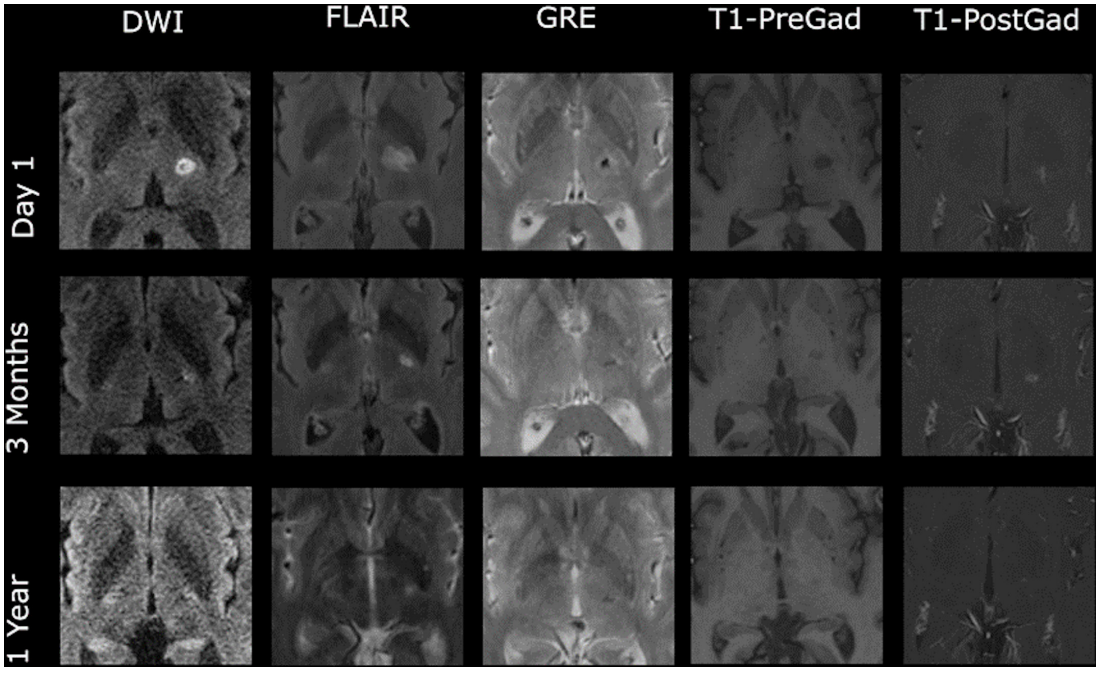

Figure 2 MRI appearance of thalamotomy lesions at day 1, 3 months and 1 year post-treatment. Representative axial DWI, FLAIR, T2*-weighted (GRE), pre-Gad T1-weighted and post-Gad T1-weighted images are shown at each timepoint. DWI, diffusion-weighted imaging; FLAIR, fluid-attenuated inversion recovery; Gad, gadolinium; GRE, gradient echo.

with larger lesion volumes at 3 months (mean lesion volume at 3 months: 62 mm^3 in more extensive oedema and 25 mm^3 in limited oedema).

Tractography assessment demonstrated a positive association between the degree of lesion overlap with DRTT and tremor improvement; this was trending at 3 months (t=1.9, p=0.067, R=0.33; online supplementary figure 2) and significant at 1 year post-treatment (t=3.8, p=0.001, R=0.65; online supplementary figure 3). In particular, efficacy at 1 year was significantly associated with those lesions demonstrating >50% overlap (grade 2 and grade 3) with DRTT (t=4.32, p=0.0003; mean improvement of 69% in high overlap vs 42% in low overlap), and a trend towards this association was seen at 3 months (t=1.91, p=0.065; mean improvement of 74% in high overlap vs 63% in low overlap). Parallel, although non-significant, associations between DRTT overlap and efficacy were observed when tracts obtained through probabilistic and deterministic tractography were analysed separately (online supplementary figures 4,5). Lesion overlap with ML and PT were not associated with efficacy of tremor reduction.

When lesion encroachment was examined in a binary touch (grades 1–3)/no-touch (grade 0) manner, encroachments on ML and PT were found to be sensitive but not specific markers for sensory and motor adverse effects at 3 months post-treatment, respectively. No patients without ML involvement exhibited sensory adverse effects, while 21% (n=9) of patients with ML involvement had sensory adverse effects (Sn=1.00, Sp=0.32). Similarly, no patients whose lesion spared PT had motor adverse effects, but 14% (n=7) of those with PT overlap did show motor deficits (Sn=1.00, Sp=0.12). No tract overlap trends were identified with respect to gait abnormalities, dysmetria or ataxia. Finally, ROC curve analysis indicated a trend towards adverse effects when lesion volume at day 1 post-treatment equalled or exceeded 170 mm^3 (Sn=0.60, Sp=0.63, p=0.07). A nearly significant difference in terms of day 1 lesion volume (t=1.85, p=0.07) was moreover identified between patients with adverse effects at 3 months (204±99 mm^3) and those without (166±79 mm^3).

DISCUSSION

In this analysis of 94 MRgFUS patients with ET, we described the typical imaging appearance of MRgFUS thalamotomy lesions and its evolution in the months following the procedure. We also identified important relationships between imaging findings and clinical outcomes. Specifically, larger lesions at post-treatment day 1 were associated with improved tremor reduction at 3 months and 1 year post-treatment, as well as with reduced rates of tremor recurrence. Lesions above 170 mm^3, however, demonstrated a trend towards increased adverse effects. Finally, degree of lesion overlap with DRTT correlated with extent of tremor reduction, while involvement of ML or PT portended adverse effects.

This work deepens existing knowledge about the radiological appearance of MRgFUS thalamotomy lesions, contributing new insights about its dynamic course and clinical implications. In keeping with previous qualitative observations of typical post-MRgFUS imaging findings in a small cohort,[4] we found lesions at day 1 post-treatment to demonstrate blood products, surrounding oedema, and a peripheral rim of DWI restriction. By 3 months, the DWI signal had normalised with resolution of oedema; only residual FLAIR signal, possibly gliosis, and chronic hemosiderin deposit were noted. All lesions decreased in size considerably over time, tending to be roughly one-tenth of their initial size at 1 year post-treatment. Notably, we observed a parallel tendency for loss of clinical efficacy over time, in accordance with prior findings.[15] A larger lesion size both acutely and at 3 months post-treatment was associated with tremor improvement and decreased rate of tremor recurrence, while a larger lesion size at 3 months was itself heralded by increased acute oedema. These factors may serve as potential early surrogate markers of efficacy; however, more work is required, given the complex interplay between lesion location and size, and the effects of lesion size on both efficacy and adverse effects. The aetiology for loss of treatment efficacy and tremor recurrence is not clear at this point. Although it is possible that benefits are mediated by both acute and transient tissue changes (ie, oedema), the timelines for symptom recurrence and relevant imaging findings do not overlap. Alternatively, the efficacy of treatment is a by-product of tissue necrosis either at the level of the VIM or communicating white matter tracts. In this case, the regeneration of necrosed tissue or replacement of its function by non-lesioned brain could be responsible for symptom recurrence.[25] This presents another avenue to avoid recurrence that could be pursued in future work.

Novel tractography-based techniques have been proposed to more precisely target the VIM and to optimise clinical outcomes.[10–12 26–28] However, most of these studies have used small cohorts and have not yet established the superiority of tract-based VIM targeting in a statistically rigorous manner. We observed that DRTT was frequently involved by MRgFUS lesions; over three quarters of patients had lesions that impinged on this tract, and nearly half had lesions that involved its entire cross-section. Interestingly, lesion involvement of DRTT at post-treatment day 1 was found to be associated with improvement in clinical outcome at 3 months and 1 year post-treatment. Given that DRTT is directly connected with VIM and posited to play a central role in ET pathophysiology,[29] it is not surprising that lesioning this tract may be beneficial in terms of tremor control.[9 12 30] Indeed, these results are consistent with prior evidence.[16 18] In the present study, greater lesion volume was also associated with more improvement in the total tremor score at 1 year. It is unclear whether this association simply reflects involvement of a greater proportion of VIM itself or whether it relates to increased encroachment on DRTT. Further work is needed to probe this relationship and also to prospectively validate whether using DRTT tractography to guide or refine MRgFUS targeting translates to improved clinical outcomes.

Adverse effects were not uncommon in our MRgFUS patients, likely due to the complex locoregional neuroanatomical relationships of grey matter nuclei and white matter tracts. Indeed, the incidence of adverse effects reported here is perhaps higher than is customarily reported in the literature. There are several possible explanations for this, including more sensitive detection of adverse effects given the targeted and prospective manner in which these were surveilled in our trial. Differences between our cohort and others previously described in the literature, such as more advanced age, higher incidence of comorbidities, and reduced neurophysiological reserves, may also have contributed to higher rates of adverse effects. In keeping with prior analyses,[5] adverse effects occurred more frequently when lesions overlapped with certain nearby white matter tracts and also trended towards increased frequency when lesions exceeded 170 mm^3 in volume. Unsurprisingly, given their anatomical location and known function, involvement of PT and ML corresponded to incidence of motor and sensory deficits, respectively. Although gait abnormalities and ataxia were common post-treatment, these were not robustly associated with a specific white matter

tract. This may reflect the multifactorial nature or more subjective assessment of gait disturbances, as well as the high prevalence of gait abnormalities at baseline in patients with ET.[31] In addition to limiting lesion size, it may be desirable to use PT and ML fibre tracking to demarcate the border of VIM and thereby guide MRgFUS targeting to avoid adverse effects. Indeed, initial prospective applications of this targeting method to small patient cohorts have shown it to be safe and potentially associated with decreased adverse effects compared with conventional targeting.[26 28] Similarly, a prior large-scale retrospective analysis indicates this tractography-guided approach moves lesions away from probabilistic zones associated with motor and sensory complications.[32]

This paper does have certain limitations. Because patients were scanned at two separate centres using different hardware and acquisition parameters, there were unavoidable inhomogeneities in the DWI data. These was exacerbated by other difficult-to-control factors (eg, excessive patient movement due to tremor and time restraints) inherent to clinical scans. A stepwise approach of increasingly permissive tracking algorithms was used to generate tracts that proved difficult to trace with deterministic tractography and allow for maximisation of the number of tracts for analysis. While this did introduce further heterogeneity into the tractography analysis, as demonstrated by prior work which has demonstrated subtle but meaningful differences in streamline termination between deterministic (prone to false negatives) and probabilistic (more susceptible to false positives) algorithms,[33] robust quality control was implemented at every stage of data processing to attempt to minimise this. First, careful visual inspection was conducted to ensure the legitimacy and accuracy of every tract employed for analysis. In addition, tract-overlap analysis was performed in a semiquantitative fashion, taking into account only the coarse relative position of the tracts and lesions in order to mitigate the impact of different tracking methods and to avoid overinterpretation. Finally, we repeated our analysis of the relationship between lesion–DRTT overlap and tremor improvement using the probabilistic and deterministic datasets separately, finding that each corroborated the primary result.

In summary, these results suggest early MRI employing a combination of conventional radiological sequences and DWI tractography can serve as an early surrogate for long-term treatment efficacy, symptom recurrence and adverse effects in patients with ET undergoing MRgFUS thalamotomy.

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Contributors ANK: conception, organisation and execution of the project; design and review of the statistical analysis; and writing of the first draft and revisions. GJBE: organisation and execution of the project, design and review of the statistical analysis, and revision of the drafts. AB: conception, organisation and execution of the project; design and review of the statistical analysis, and revision of the drafts. JG: design, execution and review of the statistical analysis; and revision of drafts. AP, PC, JZ and CC: project execution and review of the manuscript. MLS, AF, RM, WK, MH and AML: project supervision, organisation and review of manuscript.

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