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# Staged Bilateral Magnetic Resonance-Guided Focused Ultrasound Thalamotomy for Essential Tremor: Prospective Single-Centre Cohort and Systematic Review With Meta-Analysis

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## ABSTRACT

**Background:** Staged bilateral Magnetic Resonance–guided Focused Ultrasound (MRgFUS) thalamotomy is an incisionless option for medication-refractory essential tremor (ET). While the efficacy and safety of unilateral MRgFUS are established, evidence for bilateral treatment remains limited.

**Objective:** To evaluate the efficacy and safety of staged bilateral MRgFUS in a prospective single-centre observational cohort and to perform a systematic review and meta-analysis of the literature.

**Methods:** Consecutive ET patients undergoing second-side MRgFUS were prospectively assessed. The primary efficacy endpoint was the longitudinal change in Clinical Rating Scale for Tremor (CRST) A + B scores for the treated hand after FUS2, while safety was evaluated by collecting and grading adverse events (AEs). A systematic review identified published bilateral MRgFUS series; efficacy data were meta-analysed, while AEs were reported descriptively.

**Results:** Fifteen patients (60% men; mean age 74.1 ± 8.9 years) underwent FUS2 28.9 ± 22.5 months after first-side treatment. At the 12-month evaluation, CRST A + B decreased from 21.0 to 8.8 (−58%), CRST C from 7.3 to 1.9 (−74.2%), and QUEST from 30.5 to 9.5 (−68.7%). Head and voice tremor were reduced by 73.8% and 40.3%, respectively. AEs were predominantly mild (95.2%) and transient (88%). Cognition at 1 year was globally preserved, with a selective decline in verbal episodic memory. Meta-analysis confirmed significant improvement in tremor severity.

**Conclusion:** Staged bilateral MRgFUS thalamotomy was associated with sustained tremor reduction, including midline tremor, functional improvement and acceptability, with a manageable safety profile. Overall, consistent with literature, these findings support its potential role as a therapeutic option in selected ET patients.

## 1 | Introduction

Magnetic Resonance-guided Focused Ultrasound (MRgFUS) thalamotomy is an incisionless treatment for medication-refractory tremor syndromes, including essential tremor (ET) and tremor-dominant Parkinson's disease. In ET, randomised and prospective studies have demonstrated significant and durable tremor reduction and quality-of-life (QoL) improvement, with benefits sustained for up to five years [1, 2]. Despite these advances, unilateral thalamotomy often leaves residual tremor in the contralateral upper limb, head and voice, leading to persistent disability [3]. MRgFUS renewed interest in bilateral thalamotomy that traditionally was associated with a high risk of adverse events (AEs) (i.e., dysarthria and imbalance) [4] and therefore was replaced by deep brain stimulation (DBS) [5]. Prospective trials and multicentre studies have supported staged bilateral MRgFUS thalamotomy, which may offer additional functional improvement to single side treatment, with an overall favourable safety profile, with most AEs being mild and transient [6, 7]. These results supported FDA approval in late 2022 and CE mark certification in mid-2023 [8].

Nevertheless, evidence for staged bilateral MRgFUS thalamotomy is currently based on a limited number of cohorts with heterogeneous design, follow-up duration, and outcome reporting. Additional prospective series and quantitative synthesis of available data are needed to further refine estimates of efficacy and safety, including midline tremor. To contribute additional prospective data to the current evidence, we conducted a prospective single-centre observational study to evaluate the efficacy and safety of staged bilateral MRgFUS thalamotomy in patients with medication-refractory ET, with 12 months follow-up after FUS2. We also performed a systematic review and meta-analysis of the available literature to place the present findings within the context of published evidence.

## 2 | Methods

### 2.1 | Study Design and Population

This was a prospective, single-centre, observational study conducted at the University Hospital of Verona within routine clinical practice as standard-of-care. Consecutive patients with ET undergoing second side MRgFUS thalamotomy (FUS2) were included from November 2023 to March 2025. All patients had previously received first side MRgFUS thalamotomy (FUS1) from July 2018 to May 2024. Eligibility for FUS2 were (1) minimum interval of 9 months since the first procedure, (2) Clinical Rating Scale for Tremor (CRST) [9] part A score $\geq 2$ in the untreated upper limb, (3) CRST part C score $\geq 2$ in at least one item, (4) Montreal Cognitive Assessment (MoCA) score $\geq 18$, (5) no clinically significant persistent AEs related to FUS1. Access modalities to FUS2 and general exclusion criteria for MRgFUS thalamotomy are provided in the Supporting Information.

Before FUS2, patients underwent neurological and neuropsychological evaluations, CT scan for SDR calculation, and structural brain MRI to rule out contraindications to MRgFUS. Follow-up visits were scheduled at 1, 6, and 12 months after FUS2, including a full neuropsychological battery at 12 months. Pre-FUS1 and pre-FUS2 refer to the clinical assessments before FUS1 and FUS2, respectively.

### 2.2 | Outcomes

The primary efficacy outcome was defined as the longitudinal change in tremor severity after FUS2, assessed using the CRST at available follow-up timepoints. Parts A (tremor amplitude) and B (motor task performance) were administered, and composite CRST A + B scores were calculated for the hand treated by FUS2. Secondary outcomes for efficacy included midline tremor (head and voice), assessed using CRST part A subscores, functional disability and QoL, assessed using CRST part C and the Quality of Life in Essential Tremor (QUEST) questionnaire [10], administered pre-FUS2 and at follow-up visits. Retrospective pre-FUS1 data were extracted when available. Moreover, patients were asked at every follow-up visit whether they would choose to undergo FUS2 again (yes/no) to support the interpretation of functional benefit and patients' preferences.

Safety was evaluated by assessing AEs at 1, 6, and 12 months after FUS2, categorised by domain (i.e., motor, sensory, cerebellar), graded according to the Common Terminology Criteria for Adverse Events, version 5 (CTCAEv5) [11] (Table S1), and classified by severity and persistence over time. Safety on axial function and balance was also evaluated with items 1–4 of the Scale for the Assessment and Rating of Ataxia (SARA) [12], administered pre-FUS2 and at follow-up visits. Safety on cognition was assessed with a standardised neuropsychological battery administered by experienced neuropsychologists pre-FUS2 and at 12 months post-FUS2.

### 2.3 | MRgFUS Procedure

All procedures were performed using the Exablate Neuro system 4000 (Insightec, Haifa, Israel) integrated with a 3 T MRI scanner (Signa Architect; GE Healthcare, Milwaukee). Premedication and patient preparation followed our standard protocols that were reported in detail elsewhere [13, 14] and are reported in the Supporting Information, as well as standard targeting strategy. For FUS2, the initial target was generally set as the mirror image of the first side lesion, using the final stereotactic coordinates of FUS1 as reference. Final targeting was subsequently refined based on clinical response after each low power sonication. When test sonications confirmed effective tremor suppression, the definitive lesion was intentionally placed slightly dorsal to the mirrored FUS1 target—typically within the submillimetric range—to minimize the risk of AEs [6].

Treatment parameters for FUS1 and FUS2 were selected intraprocedurally based on real-time thermal and clinical feedback.

### 2.4 | Statistics

Analyses were conducted using R software (version 4.5.0; R Foundation for Statistical Computing, Vienna, Austria) [15]. Longitudinal changes in tremor severity, functional disability,

and quality of life after FUS2 were analysed using linear mixed-effects models, with timepoint as a fixed effect and subject as a random intercept, to account for unbalanced follow-up and missing observations under a missing-at-random assumption. Model assumptions were checked and found to be satisfactory. Estimated marginal means with 95% confidence intervals were derived, and post hoc pairwise comparisons were Bonferroni-adjusted. Unless otherwise specified, results are reported as model-based estimates. Observed values (mean ± SD) were used only for descriptive and graphical purposes. Axial SARA subscores were summarised descriptively. Neuropsychological outcomes were compared between baseline and 12 months using paired parametric or non-parametric tests, as appropriate. Statistical significance was set at $p < 0.05$ (two-tailed). Full description of statistical methods is provided in the Supporting Information.

### 2.5 | Systematic Review and Meta-Analysis

We conducted a systematic review and meta-analysis of staged bilateral MRgFUS thalamotomy for medically refractory essential tremor in accordance with PRISMA 2020 guidelines [16]. PubMed, Web of Science Core Collection, and the Cochrane Library were searched up to 15th July 2025, with citation tracking through 15th January 2026. Studies reporting clinical outcomes after bilateral MRgFUS with pre- and post-FUS2 assessment were included. Random-effects meta-analyses were performed for pre-specified efficacy outcomes (CRST A + B, CRST C, and CRST A head and voice subscores) focusing on 6- and/or 12-month follow-up. Secondary exploratory analyses extended follow-up windows to 3–6 months and ≥ 12 months. AEs were summarised descriptively. Full methodological details are provided in the Supporting Information.

## 3 | Results

### 3.1 | Study Population

Fifteen right-handed patients (60% men; mean age at FUS2 74.1 ± 8.9) underwent FUS2 (Table 1). One patient lacked baseline data from FUS1, which was performed at another site. The mean interval between FUS1 and FUS2 was 28.9 ± 22.5 months. At 12 months, data were available for 10 out of 15 patients; no patients were lost to follow-up.

The limb treated by FUS1 showed a mean improvement of 81% at the last assessment before FUS2 (i.e., CRST A + B scores decreased from 22.6 ± 3.4 at pre-FUS1 to 4.2 ± 2.6) remaining stable throughout follow-up (Table S3). Head tremor was present in 14 patients pre-FUS2 while voice tremor was present in all patients.

Full estimates of mean differences and observed data are reported in Table 2.

Overall CRST scores across treatments are detailed in the Supporting Information.

**TABLE 1** | Baseline demographic and clinical features of the study population.

| | Baseline |
|---|---|
| Gender (men/women) | 9/6 (60/40%) |
| Dominant hand (right/left) | 15/0 (100/0%) |
| Age at onset (years) | 31.1 ± 18.8, 10–60 |
| Disease duration (years) | 40.7 ± 18.3, 10–67 |
| Age at FUS1 (years) | 71.8 ± 8.6, 51–84 |
| Age at FUS2 (years) | 74.1 ± 8.9, 52–89 |
| Interval between FUS1 and FUS2 (months) | 28.9 ± 22.5, 10–69 |
| SDR at FUS1 | 0.53 ± 0.07, 0.46–0.69 |
| SDR at FUS2 | 0.53 ± 0.07, 0.43–0.68 |

*Note:* Data are presented as mean ± standard deviation, range or number (%). Abbreviations: CRST, Clinical Rating Scale for Tremor; *n*, number of patients; pre-FUS1 and pre-FUS2, baseline assessment before first and second side procedure, respectively; SDR, skull density ratio.

Final stereotactic coordinates and treatment parameters are reported in Table S2.

### 3.2 | Tremor Outcomes for the Treated Hand

Following FUS2, model-estimated CRST A + B composite scores for the treated hand (100% left-sided) decreased from 21.0 to 7.1 at 1 month (−13.9 [95% CI −15.4, −12.5]; $p < 0.001$ vs. baseline), corresponding to a 66.3% improvement. This effect was sustained at 6 months (8.5, −12.5 [−14.0, −11.0]; $p < 0.001$) and 12 months (8.8, −12.2 [−13.9, −10.5]; $p < 0.001$), reflecting 59.4% and 58% reductions, respectively, with no significant differences between post-treatment timepoints (Figure 1A).

### 3.3 | Midline Tremor

Head tremor showed minimal change after the FUS1 but improved significantly after FUS2. CRST part A scores decreased from 1.7 at baseline pre-FUS2 to 0.3 at 1 month (−1.47 [95% CI −1.76, −1.17]; $p < 0.001$ vs. baseline), corresponding to an 84.6% improvement, and remained significantly lower at 6 and 12 months (0.3, 80.8% reduction; 0.5, 73.8% reduction; $p < 0.001$; Figure 1B).

Voice tremor followed a similar course, with CRST part A scores improving from 1.6 to 0.9 at 1 month (−0.73 [−0.94, −0.53]; $p < 0.001$), reflecting a 45.8% reduction. Score remained stable at 6 and 12 months (0.9, 41.7% reduction; 1.0, 40.3% reduction; $p < 0.001$; Figure 1C).

### 3.4 | Functional Outcome and Acceptability

Functional disability improved significantly after FUS2. CRST part C scores decreased from 7.3 at baseline pre-FUS2 to 1.3 at

**TABLE 2** | Observed and model-estimated CRST and QUEST mean scores across different timepoints.

| | Pre-FUS1 ($n=14$) | Pre-FUS2 ($n=15$) | 1 Month ($n=15$) | 6 Months ($n=15$) | 12 Months ($n=10$) |
|---|---|---|---|---|---|
| CRST total score | 65.3 ± 8.3 | 36.5 ± 9.0 | 14.4 ± 7.0 | 16.1 ± 7.4 | 15.8 ± 6.7 |
| | 65.9 (61.5–70.3) | 36.5 (32.1–40.9) | 14.4 (10.0–18.8) | 16.1 (11.8–20.8) | 16.4 (11.8–20.9) |
| Hand treated by FUS2[a] | | | | | |
| CRST A | 7.6 ± 2.0 | 8.0 ± 2.1 | 1.6 ± 1.1 | 2.2 ± 1.2 | 1.7 ± 0.8 |
| | 7.7 (6.9–8.6) | 8.0 (7.2–8.8) | 1.6 (0.8–2.4) | 2.2 (1.4–3.0) | 1.7 (0.8–2.7) |
| CRST B | 12.5 ± 2.5 | 13.0 ± 2.4 | 5.5 ± 2.6 | 6.3 ± 3.3 | 6.6 ± 3.1 |
| | 12.8 (11.3–14.3) | 13.0 (11.5–14.5) | 5.5 (4.0–7.0) | 6.3 (4.8–7.8) | 7.1 (5.5–8.7) |
| CRST A + B | 20.1 ± 3.9 | 21.0 ± 4.1 | 7.1 ± 3.4 | 8.5 ± 4.2 | 8.3 ± 3.7 |
| | 20.5 (18.3–22.6) | 21.0 (18.9–23.1) | 7.1 (5.0–9.2) | 8.5 (6.4–10.6) | 8.8 (6.6–11.1) |
| Head tremor CRST A | 1.9 ± 0.8 | 1.7 ± 0.8 | 0.3 ± 0.5 | 0.3 ± 0.5 | 0.4 ± 0.5 |
| | 2.0 (1.6–2.3) | 1.7 (1.4–2.1) | 0.3 (0.07–0.6) | 0.3 (0.0–0.7) | 0.5 (0.1–0.9) |
| Voice tremor CRST A | 1.6 ± 0.5 | 1.6 ± 0.5 | 0.9 ± 0.4 | 0.9 ± 0.3 | 0.9 ± 0.3 |
| | 1.7 (1.4–1.9) | 1.6 (1.4–1.8) | 0.9 (0.7–1.1) | 0.9 (0.7–1.2) | 1.0 (0.7–1.2) |
| Functional disability CRST C | 18.4 ± 2.5 | 7.3 ± 2.7 | 1.3 ± 1.3 | 1.7 ± 1.6 | 2.0 ± 1.7 |
| | 18.5 (17.4–19.6) | 7.3 (6.2–8.4) | 1.3 (0.2–2.3) | 1.7 (0.7–2.8) | 1.9 (0.6–3.2) |
| QUEST | 57.1 ± 16.2 | 30.5 ± 13.5 | 9.5 ± 8.5 | 9.6 ± 8.7 | 10.8 ± 11.4 |
| | 56.9 (50.4–63.4) | 30.5 (24.1–36.9) | 9.5 (3.1–16.0) | 9.6 (3.3–16.0) | 9.7 (2.8–16.7) |

*Note:* For each outcome, the first row reports observed means ± standard deviation (SD), while the second row reports model-estimated means with 95% confidence intervals (CIs) from linear mixed-effects models. Pairwise comparisons and statistical significance across timepoints, for the most clinically relevant variables, are illustrated in Figure 1. Pre-FUS1 = baseline data before first side thalamotomy; Pre-FUS2 = baseline data before second side thalamotomy; 1, 6, 12 months = follow-up visits after the second procedure.

Abbreviations: CRST, Clinical Rating Scale for Tremor; FUS2, second side thalamotomy; *n*, number of patients; QUEST, Quality of Life in Essential Tremor Questionnaire.

[a]All second side procedures were performed on the right thalamus to treat left-hand tremor.

1 month (−6.1 [95% CI −7.3, −4.9]; $p<0.001$ vs. baseline), corresponding to an 82.7% reduction and remained low at 6 and 12 months (1.7 and 1.9, corresponding to 76.4% and 74.2% reductions; both $p<0.001$; Figure 1D).

QoL, as measured by QUEST, followed a similar course, improving from 30.5 to 9.5 (68.7% reduction) at 1 month (−21.0 [−25.9, −16.1]; $p<0.001$) and remaining stable thereafter (9.6 at 6 months and 9.7 at 12 months, reflecting a 68.4% and 68.7% reduction, respectively; both $p<0.001$) (Figure 1E).

Improvements in functional disability and QoL were paralleled by a high patient acceptability, with all participants reporting, at every timepoint, that they would choose to undergo the procedure again.

## 3.5 | Safety Profile

### 3.5.1 | Patient-Reported AEs

A total of 42 AEs were reported across 15 patients, mostly grade 1 (95.2%) with two grade 2 events (4.8%) (Table 3), all managed conservatively, resolved or improved by the 6-month follow-up. Transient gait disturbance was the most frequent AEs, occurring in up to 12 out of 15 patients (80%) within the first few days and gradually resolving over the follow-up. At last follow-up, only five mild AEs persisted: two at 6 months (i.e., dysarthria and dysgeusia) and three at 12 months (i.e., dysarthria, dysgeusia, finger hypoesthesia).

### 3.5.2 | Axial Function

SARA showed a transient worsening after FUS2 (Figure 1F). SARA total score for axial items (1–4) rose from 0.5 at baseline to 2.1 at 1 month, then decreased to 0.9 at 6 months and 0.7 at 12 months. The mean gait subscore increased from 0.3 to 1.0 at 1 month, then decreased to 0.4 at 6 and 12 months. Stance and speech showed similar patterns, while sitting balance remained unaffected.

### 3.5.3 | Neuropsychological Testing

Cognitive performance was globally preserved at 12 months ($n=10$). No significant changes were observed in global cognition, attention/working memory, visuospatial abilities, visual memory, executive functions, or language. In contrast, performance on the Rey Auditory Verbal Learning Test documented

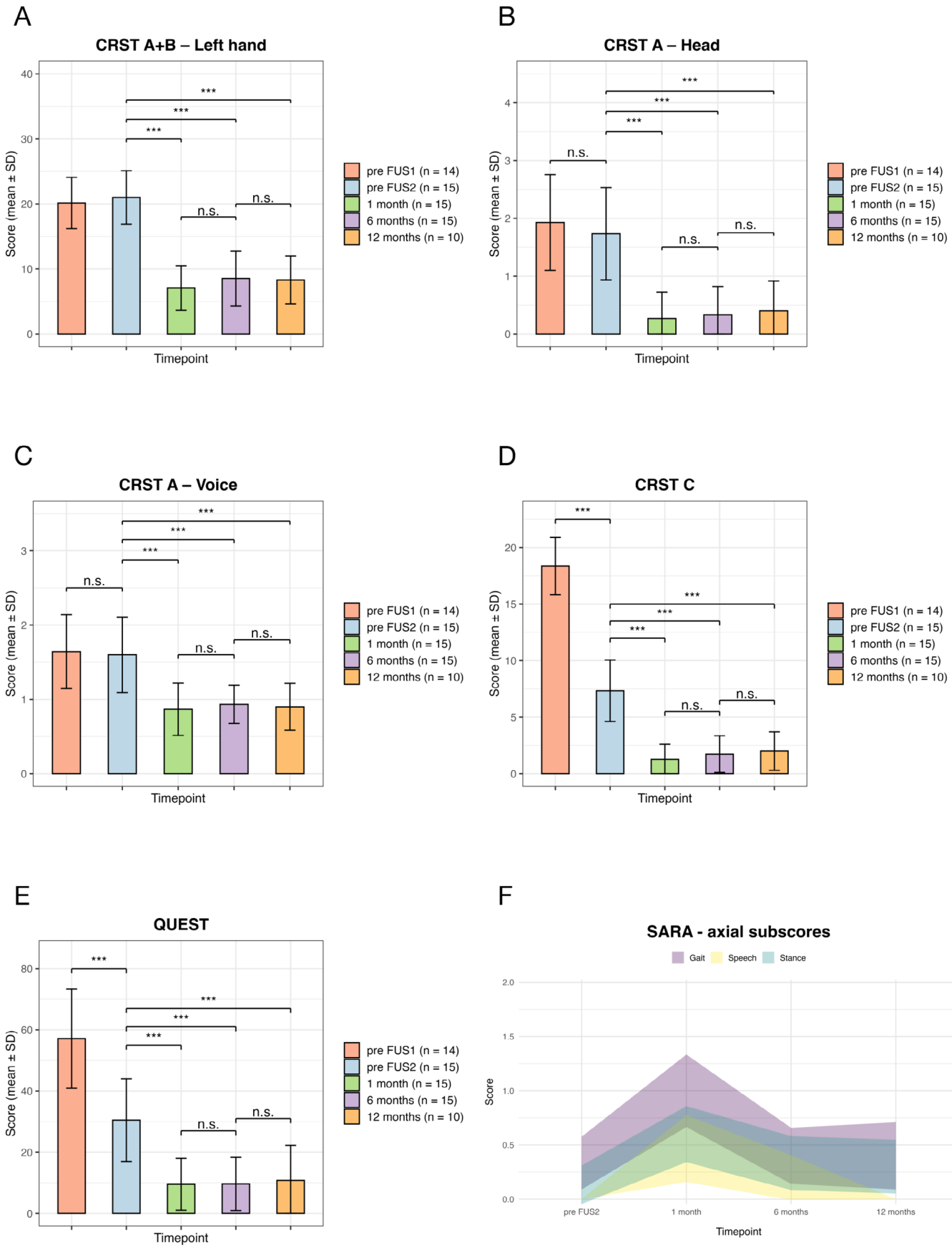


**FIGURE 1** | Legend on next page.

**FIGURE 1** | Efficacy outcomes and axial impairment after second side thalamotomy (FUS2). (A–E) display observed group data (mean ± SD) across study visits: Pre-FUS1 = baseline before first side thalamotomy; pre-FUS2 = baseline before second side thalamotomy; 1 month, 6 months, 12 months = follow-up visits after second side thalamotomy. Statistical comparisons were obtained from linear mixed-effects models with Bonferroni-adjusted post hoc contrasts. Panel F shows SARA axial sub-items mean values with 95% confidence intervals derived from group-level summary data. CRST, Clinical Rating Scale for Tremor; MRgFUS, Magnetic resonance-guided focused ultrasound; n, Number of patients; n.s., Not significant; QUEST, Quality of Life in Essential Tremor Questionnaire; SARA, Scale for the Assessment and Rating of Ataxia; SD, Standard deviation.

**TABLE 3** | Adverse events by frequency and severity after second side MRgFUS thalamotomy.

| | 1 month ($n = 15$) | 6 months ($n = 15$) | 12 months ($n = 10$) |
|---|---|---|---|
| Gait disturbance | | | |
| Grade 1 | 8 (53.3%) | 3 (20%) | 0 |
| Grade 2 | 0 | 0 | 0 |
| Grade 3 | 0 | 0 | 0 |
| Dysarthria | | | |
| Grade 1 | 3 (20%) | 4 (26.7%) | 1 (10%) |
| Grade 2 | 2 (13%) | 0 | 0 |
| Grade 3 | 0 | 0 | 0 |
| Dysphagia | | | |
| Grade 1 | 1 (6.7%) | 1 (6.7%) | 0 |
| Grade 2 | 0 | 0 | 0 |
| Grade 3 | 0 | 0 | 0 |
| Grade 4 | 0 | 0 | 0 |
| Grade 5 | 0 | 0 | 0 |
| Dysesthesia | | | |
| Grade 1 | 2 (13%) | 1 (6.7%) | 1 (10%) |
| Grade 2 | 0 | 0 | 0 |
| Grade 3 | 0 | 0 | 0 |
| Dysgeusia | | | |
| Grade 1 | 2 (6.7%) | 2 (13.3%) | 1 (10%) |
| Grade 2 | 0 | 0 | 0 |
| Muscle weakness | | | |
| Grade 1 | 0 | 0 | 0 |
| Grade 2 | 0 | 0 | 0 |
| Grade 3 | 0 | 0 | 0 |
| Other | | | |
| Fatigue | 4 (26.7%) | 2 (13.3%) | 0 |
| Steroid-related[a] | 3 (20.0%) | 0 | 0 |
| Difficulty in word finding | 1 (6.7%) | 0 | 0 |

Abbreviation: *n*, number of patients.
[a]Tachycardia ($N = 1$), mild hyperglycaemia ($N = 1$), oral candidiasis ($N = 1$). Values are reported as the number (%) of patients at each visit for each adverse event and severity grade, classified according to the Common Terminology Criteria for Adverse Events, version 5 (CTCAEv5) [11], across all follow-up assessments.

a significant decline in verbal episodic memory, with a marked increase in recognition errors (+4.5 vs. baseline, $p = 0.02$). The results also showed a decline in both immediate and delayed recall ($p = 0.01$ and $p = 0.03$, respectively), although above the normality cut-off limit (Table S4).

## 3.6 | Literature Review

The study selection process is summarised in the PRISMA flow diagram (Figure S1). The systematic review identified 12 studies with relevant outcomes of interest [6, 7, 17–26] (Table 4), 4 of which [7, 18, 22, 23] were eligible for the primary meta-analysis and 2 additional ones [6, 21] for the explorative analysis with extended follow-up; data from the present study were also included.

### 3.6.1 | Meta-Analysis of Efficacy Outcomes

The primary meta-analysis demonstrated a significant and sustained reduction in treated-hand tremor severity (CRST A + B) at both 6 and 12 months after FUS2 (Figure 2A,B). Functional disability (CRST C) improved significantly at 6 months but not at 12 months (Figure 2C,D). Head tremor did not reach statistical significance at either timepoint, whereas voice tremor showed a significant and persistent improvement (Figure 2E–H). Exploratory meta-analyses using extended follow-up windows confirmed a consistent reduction in hand tremor severity across timepoints (Figure 3A,B). Functional disability improved at earlier follow-up but not at the longest timepoint, while head tremor reached statistical significance only at ≥ 12 months. Voice tremor remained significantly reduced throughout (Figure 3C–H). Sensitivity analyses by setting a lower correlation coefficient (i.e., $r = 0.5$) yielded similar estimates (Figures S2 and S3). Detailed results are provided in the Supporting Information.

### 3.6.2 | Descriptive Analysis of Adverse Events

A total of 134 patients with the longest available follow-up were analysed (included studies, $n = 124$, Table 5; present cohort, $n = 10$). The most frequently reported persistent AEs were sensory disturbances ($n = 25$), followed by gait disturbance ($n = 18$), dysarthria ($n = 16$), dysgeusia ($n = 15$), and dysphagia ($n = 7$). Overall, persistent AEs at last follow-up were 1.5%–18.6% of all treated patients and were mostly mild.

## 4 | Discussion

In this prospective single-centre study, staged bilateral MRgFUS thalamotomy for medication-refractory ET was associated with additional and sustained improvements in tremor severity, functional disability, and QoL, persisting up to 12 months after FUS2. FUS2 was associated with a marked contralateral hand tremor reduction (58% of CRST A + B) and relevant functional gains vs. FUS1. In the context of the high acceptability observed in our cohort, all patients who underwent FUS2 experienced a marked and sustained clinical benefit after FUS1 and had not developed persistent severe AEs, likely contributing to their motivation. Notably, none of the patients in our cohort reported persistent disabling AEs or substantial decline in tremor control after FUS2. This may have contributed to the high acceptability in our series, in contrast with reports of declining satisfaction over longer follow-up [26]. Although the magnitude of improvement observed for the treated hand after FUS2 was, on average, lower than that achieved after FUS1—as also reported by other studies [22, 26]–patient satisfaction remained consistently high. This suggests that perceived clinical benefit may not scale linearly with absolute tremor severity scores, particularly for the non-dominant hand, but may instead reflect functional relevance in daily activities and individual patient expectations.

Reports on the effect of FUS2 on axial tremor are inconsistent, with some series describing benefit and others showing limited or no improvement [21, 23]. Consistent with prior reports [6, 7, 18, 20, 22], our cohort showed sustained improvements in head (~74%) and voice (~40%) tremor through 12-month follow-up.

According to the meta-analysis, FUS2 consistently reduced hand tremor severity, whereas heterogeneity was greater for tremor-related disability and midline symptoms. This variability likely reflects differences in patient phenotype, outcome measures (i.e., CRST subscores), across studies [7, 18, 23], and, importantly, the limited sample size available for some outcomes. In particular, head tremor did not reach significance either at 6 or 12 months in the primary meta-analysis, whereas a significant reduction emerged at 12 months only in the exploratory analysis. This difference is most likely driven by increased sample size rather than a true delayed clinical response.

In our cohort, AEs were common but mainly mild and self-limiting. Transient gait disturbance was the most frequent, affecting up to 80% within the first days and gradually and completely resolving over the follow-up. Accordingly, axial function, captured by SARA, showed a predictable transient worsening at 1 month with near-complete resolution by 6–12 months. Overall, at 12 months, only three mild (grade 1 CTCAE) AEs persisted (dysarthria, finger hypoesthesia, and dysgeusia).

Findings from the systematic review and descriptive aggregate analysis of staged bilateral MRgFUS treatment demonstrated similar trends. Sensory and gait/balance disturbances were the most frequently reported persistent AEs, followed by dysarthria and dysgeusia. Most AEs were transient, although heterogeneity in follow-up duration and AE grading across studies limits direct comparison.

Historically, persistent dysarthria discouraged bilateral thalamotomy and contributed to the shift toward DBS [4, 27]. A large meta-analysis of lesioning procedures (i.e., radiofrequency, Gamma Knife radiosurgery) and DBS reported higher rates of persistent speech disturbance after bilateral than unilateral thalamotomy (40.6% vs. 15.0%), with a similar pattern for DBS (34.6% vs. 10.2%) [28]. Interestingly, the highest risk occurred in patients with Parkinson's disease in the lesioning group and for patients with ET in the DBS group. Against this background, both our cohort and the provided aggregate analysis of AEs suggest lower rates of persistent dysarthria (i.e., 9%–11.9%)

**TABLE 4** | Features of the studies included in the systematic review.

| Study | Design | Follow-up (months) | Sample size | Sex | Minimum interval (months) | Mean interval (months) | Mean age (years) | Targeting strategy |
|---|---|---|---|---|---|---|---|---|
| Ito et al. [24] | Case report | 1 | $n=1$ | M | 8 | 8 | 57 | Symmetric |
| Bruno et al. [17] | Case report | 1, 6 | $n=1$ | N.R. | 24 | 24 | 63 | Asymmetric |
| Martínez-Fernández[a] et al. [18] | Prospective, open-label, multicentre study | 6 | $n=9$ | 5 M, 4 F | 5 | 24 ± 18 | 71 ± 6 | Symmetric |
| Fukutome et al. [19] | Retrospective case series | 3 | $n=5$ | 4 M, 1 F | 12 | 27.8 ± 11.5[b] | 57.6 ± 17.5[b] | Asymmetric |
| Iorio-Morin et al. [6] | Prospective, single-arm, single-blinded, multicentre, phase 2 trial | 3 | $n=10$ | 7 M, 3 F | 6 | Median 9, Range 7–56 | 71.2 ± 7.5[b] | Asymmetric |
| Pearce et al. [20] | Case report | 3, 6 | $n=1$ | M | 7 | 7 | 69 | Asymmetric |
| Scantlebury et al. [21] | Prospective, open-label, single-centre study | Median 4.4, Range 3–6 | $n=11$ | 7 M, 4 F | 12 | 35.3 ± 23.6[b] | 69.6 ± 8.6[b] | N.R. |
| Kaplitt[a] et al. [7] | Prospective, open-label, multicentre study | 1, 3, 6, 12 | $n=51$ | 44 M, 7 F | 9 | 26.4 ± 19.2[d] | 73 ± 9.3 | Standardised targeting framework based on predefined stereotactic coordinate range |
| Sarica[c] et al. [22] | Retrospective-prospective case series | 23.4 ± 13.3 | $n=19$ | 13 M, 6 F | 6 | 17.3 ± 15.7 | 69.8 ± 10.3 | Asymmetric |
| Campins-Romeu[a] et al. [23] | Prospective, open-label, single-centre study | 6 | $n=20$ | 12 M, 8 F | 9 | 17.8 ± 7.6 | 66.5 ± 9.2 | Asymmetric |
| Boshmaf[e] et al. [25] | Prospective, open-label study | 4.3 ± 1.8 | $n=21$ | 14 M, 7 F | 12 | 30 ± 18[d] | 69 ± 12 | N.R. |
| Pertsch et al. [26] | Retrospective case series | 3, 6, 12, 24+ | $n=30$ | 22 M, 8 F | 6 | Median 11.6 Range 6–21.6 | 71.2 ± 8.2 | Symmetric |

*Note:* Data are reported as mean ± SD unless otherwise stated.
Abbreviations: F, female; M, male; n, number of patients; N.R., not reported; SD, standard deviation.
[a]Included in the meta-analysis.
[b]Calculated from the original dataset.
[c]Includes data from Iorio-Morin et al., prospective phase 2 trial (NCT04501484) [6].
[d]Interval originally reported in years and converted to months.
[e]Includes data from Scantlebury et al. [21].

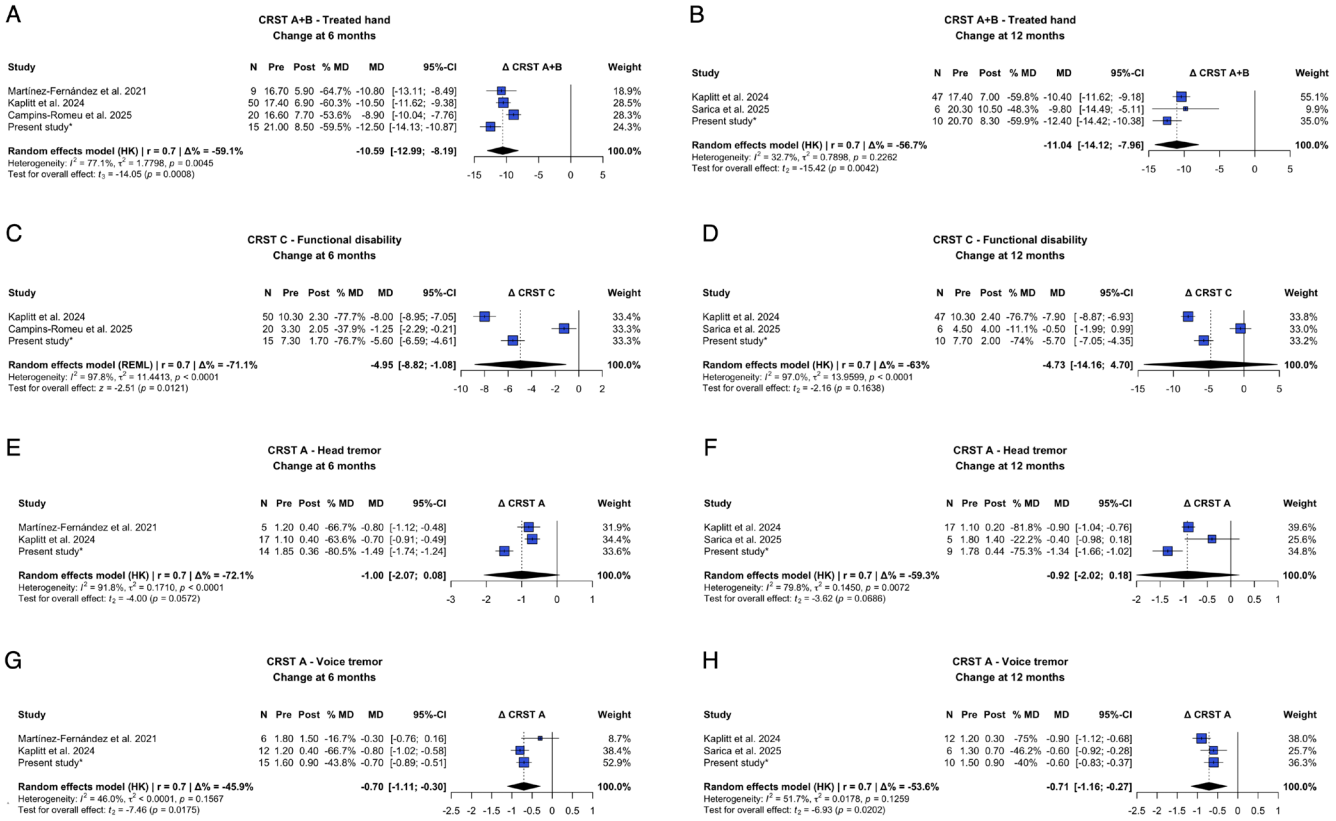


**FIGURE 2** | Meta-analysis of efficacy outcomes at 6- and 12-month follow-up. Forest plots (A–H) depict pre- and post-treatment mean scores and standard deviations for the Clinical Rating Scale for Tremor (CRST) following second side MR-guided focused ultrasound (MRgFUS) thalamotomy. Pooled absolute mean differences, corresponding to 95% confidence intervals (CIs), and mean percentage changes (Δ%) were calculated using random-effects models, assuming a within-subject correlation coefficient of $r = 0.7$. Panels show changes in CRST composite scores for the treated hand (part A + B, panels A and B), functional disability (part C, panels C and D), and head and voice tremor subscores (part A, panels E–H) at 6 and 12 months post-procedure. Heterogeneity across studies is expressed as $I^2$. *Data from the present study. For the study by Sarica et al. [22], only participants with a 12-month follow-up were included.

compared with bilateral thalamotomy using other lesioning techniques, and rates that are comparable—or in some recent series [22] even lower—than bilateral DBS. These observations are contextual rather than based on head-to-head comparisons and should be therefore interpreted with caution, particularly considering the potential reversibility of speech-related AEs with DBS. Nevertheless, compared with aggregate data from multiple unilateral MRgFUS cohort [29], bilateral staged procedures appear to carry a higher prevalence of persistent dysarthria consistent with meta-analytic estimates from a study on unilateral MRgFUS [30] in which dysarthria was usually transient (1–3 months), while persistent sensory (19%–18%) and cerebellar (13%–10%) disturbances at 6–12 months were broadly similar to those observed for bilateral procedures.

Although based on a limited subsample with 12-month follow-up—redetermined to limit practice effects—global cognition in our cohort was preserved, with a highly selective decline in verbal episodic memory and no detectable impact on ecological functioning. These preliminary findings partially diverge from preliminary investigations of cognitive outcomes following both unilateral [31–36] and bilateral MRgFUS thalamotomy [7, 18, 21, 23, 25] which generally reported a normal cognitive profile, or isolated mild decline affecting a small proportion of cognitive measures at the individual level [25]. However, most unilateral studies [31, 33, 35] and all published bilateral series [7, 18, 21, 23, 25] assessed patients within a relatively short interval after the procedure (typically 4–6 months), a timeframe susceptible to practice effects [37] and potentially insufficient to detect subtle and delayed changes. Nevertheless, our results are congruent with DBS literature, in which modest, lateralised effects—often in verbal fluency or memory—may occur without global deterioration [38, 39] and are consistent with a network-level mechanism involving cerebello–thalamo–cortical circuits [40]. Overall, these findings support a favourable cognitive safety profile while underscoring the need for systematic, longer-term monitoring to define trajectory, mechanisms (i.e., lesion location/extent), and clinical salience.

Taken together, literature data suggest that staged bilateral MRgFUS may offer tremor control comparable to DBS [22], with a broadly similar safety profile, while avoiding some of the morbidity associated with older bilateral lesioning. However, as with all surgical approaches, bilateral treatment appears to carry a higher risk of AEs compared with unilateral procedures, particularly in axial domains. Importantly, some AEs observed after staged bilateral procedures can be attributed to lesion topography, rather than bilaterality itself. By contrast, other AEs (i.e., axial symptoms, dysgeusia), may be more sensitive to procedural factors that systematically differ between first- and second-side

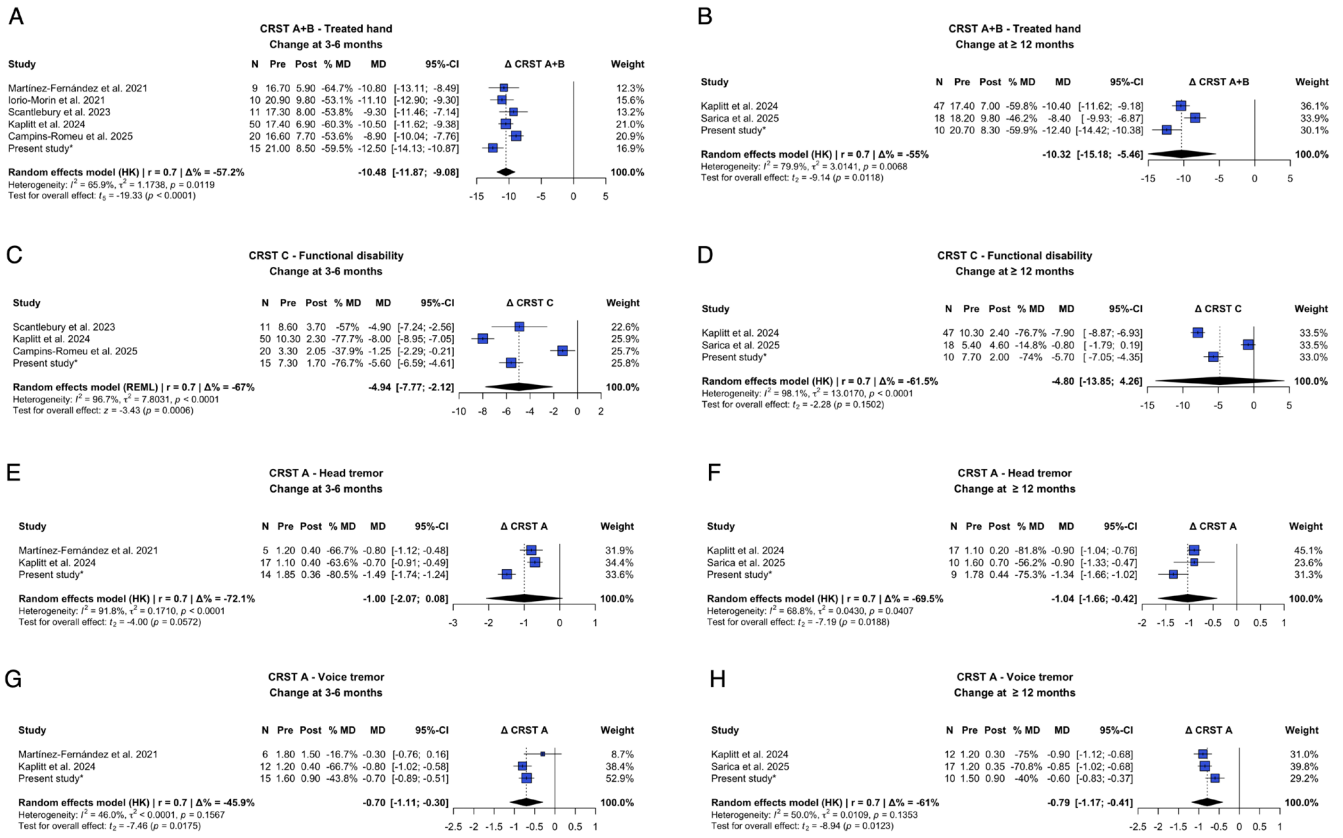


**FIGURE 3** | Exploratory meta-analysis of efficacy outcomes with extended follow-up windows. Forest plots (A–H) depict pre- and post-treatment mean scores and standard deviations for the Clinical Rating Scale for Tremor (CRST) following second side MR-guided focused ultrasound (MRgFUS) thalamotomy. Pooled absolute mean differences, corresponding to 95% confidence intervals (CIs), and mean percentage changes (Δ%) were calculated using random-effects models, assuming a within-subject correlation coefficient of $r = 0.7$. Panels show changes in CRST composite scores for the treated hand (part A + B, panels A and B), functional disability (part C, panels C and D), and head and voice tremor subscores (part A, panels E–H) at 3–6 months and ≥ 12 months post-procedure. Heterogeneity across studies is expressed as $I^2$. *Data from the present study. For the study by Iorio-Morin et al. [6]. 2021, contralateral CRST A + B scores (including lower-limb items) were used as a proxy for upper-limb tremor severity in the exploratory analysis, as no hand-specific subscore was separately reported. For the study by Sarica et al. [22] only participants with follow-up ≥ 12 months were included.

treatments. In this context, targeting strategy represents a key variable warranting consideration.

Available evidence indicates that staged bilateral MRgFUS is performed using heterogeneous targeting strategies, with substantial variability in both procedural details and reporting. Several series reported asymmetric targeting, whereas others used symmetric strategies or did not provide sufficient information to determine lesion symmetry. This limitation applies also to the largest available cohort [7], which adopted a standardised targeting framework without specifying whether lesions were symmetric across sides. Although a tendency toward asymmetric targeting emerges, current evidence remains insufficient to define an optimal strategy. Similarly, the interval between the two procedures varied widely across cohorts and was not systematically investigated as a determinant of outcome and safety. Longer inter-procedural intervals may allow partial functional compensation, particularly for axial domains, although this hypothesis remains speculative and should be interpreted alongside lesion topography and patient-related factors (e.g., age and baseline axial functioning). Overall, these observations underscore the exploratory nature of the current evidence and highlight the need for better reporting of targeting strategies, procedural timing, and lesion characteristics to understand if these variables may influence efficacy and safety of staged bilateral MRgFUS.

## 4.1 | Strengths and Limitations

This study benefits from a prospective design with systematic assessment of motor, functional, and quality-of-life domains, alongside longitudinal structured collection of AEs.

Nonetheless, several limitations warrant consideration. The study was conducted outside a formal clinical trial framework and was not prospectively registered; although outcomes and follow-up assessments were defined a priori within routine clinical care, this may increase susceptibility to bias and should be considered when interpreting the results. The series was observational, single-centre, and lacked a control group or blinded tremor ratings, with a small sample size and relatively limited follow-up. Objective quantitative measures for voice tremor and gait analysis were not included, and no baseline neuropsychological data were available before FUS1. Also, correlations with procedural or imaging parameters were not explored, as

**TABLE 5** | Summary of adverse events reported in the studies included in the systematic review.

| Study | Last FU (months) | Gait disturbance | Dysarthria | Dysphagia | Sensory disturbances | Dysgeusia | Muscle weakness | Other | Standardised NPS evaluation |
|---|---|---|---|---|---|---|---|---|---|
| Ito et al. [24] | 1 ($n=1$) | None | None | None | None | None | None | None | No |
| Bruno et al. [17] | 6 ($n=1$) | None | None | None | None | None | None | None | MoCA and extensive battery (no change) |
| Martínez-Fernández et al. [18] | 6 ($n=9$) | 4 (0) mild; 2[a] (0) requiring walking assistance | 1[a] (0) | None | 2 (2) | 1 (0) | None | 2 (0) limb dysmetria | Extensive battery (no change) |
| Fukutome et al. [19] | 6 ($n=5$) | None | 1 (0) | None | 2 (1) | None | 1 (0) limb | None | MMSE only after the procedure (normal) |
| Pearce et al. [20] | 6 ($n=1$) | 1 (0) mild | 1 (0) mild | 1 (0) mild | None | None | None | None | No |
| Scantlebury[b] et al. [21] | 6 ($n=11$) | 4 (0) mild to moderate | None | 1 (0) | 4 (4) mild | 1 (0) mild, 3 (3) moderate | None | 1 (0) shoulder pain, 1 (0) word-finding difficulty | Extensive battery (no change) |
| Kaplitt et al. [7] | 12 ($n=47$) | 16 (7) mild, 1 (0) moderate | 14 (7) mild, 1 (0) moderate | 3 (2) mild, 1 (1) moderate | 18 (9) mild | 10 (5) mild, 1 (1) moderate | 1 (0) mild facial, 1 (0) mild limb | 1 (1) sialorrhea, 1 (1) decreased synchronicity, 2 (0) dysmetria, 1 (0) voice change, 2 (0) fatigue, 1 (0) severe UTI due to catheter during the treatment | MoCA (no change) |
| Sarica[c] et al. [22] | Mean 23.4 ($n=19$) | 4 (3) grade 1 | 2 (2) grade 1 | 5 (3) grade 1 | 2 (1) grade 1 | 4 (3) grade 1, 1 (1) grade 2 | 1 (0) limb grade 2 | N.R. | N.R. |
| Campins-Romeu et al. [23] | 6 ($n=20$) | 3 (3) mild | 2 (1) mild | None | 5 (5) mild | None | 1 (0) mild facial asymmetry | None | Extensive battery (no change) |
| Pertsch[e] et al. [26] | 24+ ($n=10$) | 12 (4) grade 1 1 (1) grade 2 | 21 (4) grade 1 3 (1) grade 2 | 9 (1) grade 1 1 (0) grade 2 | 15 (2) grade 1 | 7 (0) grade 1 1 (1) grade 2 | None | Possible cognitive changes[d] | No |

*Note:* Values are expressed as total events (persisting events at last follow-up available). AEs severity grading was available only in some studies, either through formal scales (e.g., Common Terminology Criteria for Adverse Events, version 5.0) or descriptive qualifiers (mild, moderate, severe) as reported by the Authors, often without explicit definitions. When absent, severity grading was not inferred or reclassified.

Abbreviations: AEs, adverse events; FU, follow-up; MMSE, Mini-Mental Status Examination; MoCA, Montreal Cognitive Assessment; MRgFUS, MR-guided focused ultrasound; N.R., not reported; *n*, number of patients; NPS, neuropsychological.

[a]Worsening of pre-existing symptoms.

[b]The cohort reported by Scantlebury et al. [21] is included within that of Boshmaf et al. [25]; therefore, only the former was reported, as the latter did not provide data on overall AEs and focused primarily on cognition, which is discussed in the main text.

[c]The cohort of Sarica et al. [22] included patients from Iorio-Morin et al. [6] thus not listed separately to avoid duplication.

[d]Although the Authors reported that 5 patients experienced mild or possible cognitive changes (e.g., mental fatigue, memory decline, and word-finding difficulties) at 3 months, and symptoms persisted at 6 months in 3 patients; however, only 2 and 1 patient attributed these changes to the MRgFUS procedure at the 3- and 6-month follow-up, respectively.

[e]For this study, total events were derived from the first available follow-up (3 months; $n=30$), whereas AEs were considered persistent only if reported at the last available follow-up ($\geq 24$ months).

the study was primarily designed to assess clinical, functional, and cognitive outcomes. In addition, the systematic review and meta-analysis was not pre-registered in a database. At the meta-analytic level, inference was constrained by the small number of eligible studies contributing to substantial heterogeneity, the inclusion of our cohort, and the absence of randomised controlled trials in the literature.

Future research should address these gaps through larger multicentre collaborations, extended follow-up, and harmonised AEs reporting. Objective, instrumental measures for voice tremor and gait, combined with comprehensive cognitive batteries, would better define outcome and safety trajectories. Future studies, integrating imaging-based analyses of lesion location and volume, procedural parameters and patient-related features, may further clarify the relationship between targeting strategies (i.e., symmetrical vs. asymmetrical), thermal delivery, clinical outcomes and AEs. It will also be important to investigate staged bilateral MRgFUS in selected populations, including patients with Parkinson's disease evolving from long-lasting ET, and in younger DBS-eligible individual with ET, to determine whether the favourable safety–efficacy profile observed in older ET cohorts extends to individuals with greater neuroplastic potential, longer life expectancy, and higher functional demands. Finally, prospective observational studies and prospective comparative head-to-head designs versus bilateral DBS could further clarify benefits, risks, and optimal patient selection.

## 5 | Conclusion

In conclusion, findings from this prospective cohort and the systematic review and meta-analysis suggest that staged bilateral MRgFUS thalamotomy may provide additional clinical benefit beyond unilateral treatment in appropriately selected patients, with AEs that are mostly mild and transient.

### Author Contributions

**F. Paio:** conceptualization, writing – original draft, writing – review and editing, data curation, formal analysis, methodology, investigation, validation, supervision. **G. K. Ricciardi:** conceptualization, writing – review and editing. data curation, investigation, validation. **G. Bulgarelli:** writing – review and editing, data curation, investigation. **M. Tagliamonte:** writing – review and editing, data curation, investigation. **E. Mantovani:** writing – review and editing, data curation, investigation, validation, methodology. **C. Zucchella:** writing – review and editing, data curation, investigation, methdology. **T. Bovi:** writing – reveiw and editing, data curation, investigation. **M. Longhi:** writing – review and editing, data curation, investigation. **Z. Lombardi:** writing – review and editing, data curation. **P. M. Polloniato:** writing – review and editing, data curation, investigation. **E. Zivelonghi:** writing – review and editing, data curation, investigation. **C. Cavedon:** writing – review and editing, supervision. **S. Montemezzi:** writing – review and editing, supervision. **A. Nicolato:** writing – reveiw and editing, supervision. **F. Sala:** writing – review and editing, supervision. **B. Petralia:** writing – review and editing, supervision. **B. Bonetti:** conceptualization, writing – review and editing, validation, supervision. **M. Tinazzi:** conceptualization, writing – review and editing, validation, supervision. **S. Tamburin:** conceptualization, writing – review and editing, data curation, investigation, validation, supervision, formal analysis.


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The authors have nothing to report.


### Ethics Statement

The study was conducted in accordance with the Declaration of Helsinki. All participants provided written informed consent before undergoing FUS2. The study protocol was approved by the Ethical Committee of the Veneto Region South-West Area at the Verona University Hospital—CET-ASOV (approval # 133CET).

### Conflicts of Interest

The authors declare no conflicts of interest.

### Data Availability Statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

### References


1. W. J. Elias, N. Lipsman, W. G. Ondo, et al., "A Randomized Trial of Focused Ultrasound Thalamotomy for Essential Tremor," *New England Journal of Medicine* 375, no. 8 (2016): 730–739, https://doi.org/10.1056/NEJMOA1600159.

2. G. R. Cosgrove, N. Lipsman, A. M. Lozano, et al., "Magnetic Resonance Imaging–Guided Focused Ultrasound Thalamotomy for Essential Tremor: 5-Year Follow-Up Results," *Journal of Neurosurgery* 138, no. 4 (2022): 1028–1033, https://doi.org/10.3171/2022.6.JNS212483.

3. W. J. Elias, D. Huss, T. Voss, et al., "A Pilot Study of Focused Ultrasound Thalamotomy for Essential Tremor," *New England Journal of Medicine* 369, no. 7 (2013): 640–648, https://doi.org/10.1056/NEJMOA1300962.

4. J. D. Speelman, R. Schuurman, R. M. A. de Bie, R. A. J. Esselink, and D. A. Bosch, "Stereotactic Neurosurgery for Tremor," *Movement Disorders* 17, no. 3 (2002): S84–S88, https://doi.org/10.1002/MDS.10147.

5. A. L. Benabid, P. Pollak, A. Louveau, S. Henry, and J. de Rougemont, "Combined (Thalamotomy and Stimulation) Stereotactic Surgery of the Vim Thalamic Nucleus for Bilateral Parkinson Disease," *Stereotactic and Functional Neurosurgery* 50, no. 1–6 (1987): 344–346, https://doi.org/10.1159/000100803.

6. C. Iorio-Morin, K. Yamamoto, C. Sarica, et al., "Bilateral Focused Ultrasound Thalamotomy for Essential Tremor (BEST-FUS Phase 2 Trial)," *Movement Disorders* 36, no. 11 (2021): 2653–2662, https://doi.org/10.1002/MDS.28716.

7. M. G. Kaplitt, V. Krishna, H. M. Eisenberg, et al., "Safety and Efficacy of Staged, Bilateral Focused Ultrasound Thalamotomy in Essential Tremor: An Open-Label Clinical Trial," *JAMA Neurology* 81, no. 9 (2024): 939–946, https://doi.org/10.1001/JAMANEUROL.2024.2295.

8. "Insightec Receives CE Mark Approval to Treat Essential Tremor Patients' Second Side, Expanding Treatment Options for People Living With Essential Tremor – Insightec", https://insightec.com/global/news-global/insightec-receives-ce-mark-approval-to-treat-essential-tremor-patients-second-side-expanding-treatment-options-for-people-living-with-essential-tremor/.

9. M. A. Stacy, R. J. Elble, W. G. Ondo, S. C. Wu, and J. Hulihan, "Assessment of Interrater and Intrarater Reliability of the Fahn-Tolosa-Marin Tremor Rating Scale in Essential Tremor," *Movement Disorders* 22, no. 6 (2007): 833–838, https://doi.org/10.1002/MDS.21412.

10. A. I. Tröster, R. Pahwa, J. A. Fields, C. M. Tanner, and K. E. Lyons, "Quality of Life in Essential Tremor Questionnaire (QUEST): Development and Initial Validation," *Parkinsonism & Related Disorders* 11, no. 6 (2005): 367–373, https://doi.org/10.1016/j.parkreldis.2005.05.009.

11. Cancer Institute N, "Common Terminology Criteria for Adverse Events (CTCAE) Common Terminology Criteria for Adverse Events (CTCAE) v5.0", https://www.meddra.org/.

12. A. Weyer, M. Abele, T. Schmitz-Hübsch, et al., "Reliability and Validity of the Scale for the Assessment and Rating of Ataxia: A Study in 64 Ataxia Patients," *Movement Disorders* 22, no. 11 (2007): 1633–1637, https://doi.org/10.1002/MDS.21544.

13. S. Tamburin, F. Paio, T. Bovi, et al., "Magnetic Resonance-Guided Focused Ultrasound Unilateral Thalamotomy for Medically Refractory Essential Tremor: 3-Year Follow-Up Data," *Frontiers in Neurology* 15 (2024), https://doi.org/10.3389/FNEUR.2024.1360035.

14. G. K. Ricciardi, F. Paio, C. Zivelonghi, et al., "MRgFUS Disconnection Surgery for Hypothalamic Hamartoma-Related Epilepsy: Case Report and Literature Review," *Neurological Sciences* 46, no. 3 (2025): 1399–1404, https://doi.org/10.1007/S10072-024-07946-2.

15. Posit team, "RStudio: Integrated Development Environment for R".

16. M. J. Page, J. E. McKenzie, P. M. Bossuyt, et al., "The PRISMA 2020 Statement: An Updated Guideline for Reporting Systematic Reviews," *BMJ* (2021): 372, https://doi.org/10.1136/BMJ.N71.

17. F. Bruno, A. Catalucci, M. Varrassi, et al., "Bilateral MRgFUS Thalamotomy for Tremor: A Safe Solution? Case Report and Review of Current Insights," *Clinical Neurology and Neurosurgery* 197 (2020): 197, https://doi.org/10.1016/j.clineuro.2020.106164.

18. R. Martínez-Fernández, S. Mahendran, J. A. Pineda-Pardo, et al., "Bilateral Staged Magnetic Resonance-Guided Focused Ultrasound Thalamotomy for the Treatment of Essential Tremor: A Case Series Study," *Journal of Neurology, Neurosurgery & Psychiatry* 92, no. 9 (2021): 927–931, https://doi.org/10.1136/JNNP-2020-325278.

19. K. Fukutome, H. Hirabayashi, Y. Osakada, Y. Kuga, and H. Ohnishi, "Bilateral Magnetic Resonance Imaging-Guided Focused Ultrasound Thalamotomy for Essential Tremor," *Stereotactic and Functional Neurosurgery* 100, no. 1 (2022): 44–52, https://doi.org/10.1159/000518662.

20. J. J. Pearce, J. Thoma, K. Vinson, and S. Sani, "Treatment of Vocal Tremor With Bilateral Magnetic Resonance Imaging–Guided Focused Ultrasound of the Ventral Intermediate Thalamic Nucleus: Illustrative Case," *Journal of Neurosurgery: Case Lessons* 5, no. 26 (2023), https://doi.org/10.3171/CASE2351.

21. N. Scantlebury, C. R. Rohringer, J. S. Rabin, et al., "Safety of Bilateral Staged Magnetic Resonance-Guided Focused Ultrasound Thalamotomy for Essential Tremor," *Movement Disorders Clinical Practice* 10, no. 10 (2023): 1559–1561, https://doi.org/10.1002/MDC3.13882.

22. C. Sarica, K. Yamamoto, C. Iorio-Morin, et al., "Bilateral Focused Ultrasound Thalamotomy for Essential Tremor: Clinical Outcomes Compared to Bilateral Deep Brain Stimulation and Probabilistic Lesion Mapping," *Movement Disorders* 40, no. 7 (2025): 1265–1278, https://doi.org/10.1002/MDS.30221.

23. M. Campins-Romeu, R. Conde-Sardón, I. Sastre-Bataller, et al., "Safety and Efficacy of Bilateral Staged Focused Ultrasound Thalamotomy in Refractory Essential Tremor," *Brain Communications* 7, no. 3 (2025): fcaf168, https://doi.org/10.1093/BRAINCOMMS/FCAF168.

24. H. Ito, K. Yamamoto, S. Fukutake, T. Odo, T. Yamaguchi, and T. Taira, "Magnetic Resonance Imaging-Guided Focused Ultrasound Bilateral Thalamotomy for Essential Tremor: A Case Report," *Neurology and Clinical Neuroscience* 8, no. 6 (2020): 412–414, https://doi.org/10.1111/ncn3.12438.

25. S. Z. Boshmaf, J. Petersen, R. Kumar, et al., "Cognitive Outcomes Following Second-Sided Focused Ultrasound Thalamotomy for Tremor," *Movement Disorder Clinical Practice* 12 (2025): 1385–1390, https://doi.org/10.1002/MDC3.70095.

26. N. J. Pertsch, K. Sakakura, and J. M. Mueller, "Tremor Control and Patient Reported Outcomes After Bilateral Focused Ultrasound Thalamotomy for Essential Tremor," *Movement Disorder Clinical Practice* (2025), https://doi.org/10.1002/MDC3.70412.

27. J. Alshaikh and P. S. Fishman, "Revisiting Bilateral Thalamotomy for Tremor," *Clinical Neurology and Neurosurgery* 158 (2017): 103–107, https://doi.org/10.1016/j.clineuro.2017.04.025.

28. S. Alomar, N. K. K. King, J. Tam, A. A. Bari, C. Hamani, and A. M. Lozano, "Speech and Language Adverse Effects After Thalamotomy and Deep Brain Stimulation in Patients With Movement Disorders: A Meta-Analysis," *Movement Disorders* 32, no. 1 (2017): 53–63, https://doi.org/10.1002/MDS.26924.

29. M. Giordano, V. M. Caccavella, I. Zaed, et al., "Comparison Between Deep Brain Stimulation and Magnetic Resonance-Guided Focused Ultrasound in the Treatment of Essential Tremor: A Systematic Review and Pooled Analysis of Functional Outcomes," *Journal of Neurology, Neurosurgery, and Psychiatry* 91, no. 12 (2020): 1270–1278, https://doi.org/10.1136/JNNP-2020-323216.

30. A. Shiramba, S. Lane, N. Ray, et al., "Efficacy and Safety of Magnetic Resonance-Guided Focused Ultrasound Thalamotomy in Essential Tremor: A Systematic Review and Metanalysis," *Movement Disorders* 40, no. 6 (2025): 1020–1033, https://doi.org/10.1002/MDS.30188.

31. N. Y. Jung, C. K. Park, W. S. Chang, H. H. Jung, and J. W. Chang, "Effects on Cognition and Quality of Life With Unilateral Magnetic Resonance-Guided Focused Ultrasound Thalamotomy for Essential Tremor," *Neurosurgical Focus* 44, no. 2 (2018): E8, https://doi.org/10.3171/2017.11.FOCUS17625.

32. C. Gasca-Salas, P. Guida, R. Piredda, et al., "Cognitive Safety After Unilateral Magnetic Resonance-Guided Focused Ultrasound Thalamotomy for Essential Tremor," *Journal of Neurology, Neurosurgery, and Psychiatry* 90, no. 7 (2019): 830–831, https://doi.org/10.1136/JNNP-2018-320129.

33. G. Saporito, P. Sucapane, R. Ornello, et al., "Cognitive Outcomes After Focused Ultrasound Thalamotomy for Tremor: Results From the COGNIFUS (COGNitive in Focused UltraSound) Study," *Parkinsonism & Related Disorders* 106 (2023): 105230, https://doi.org/10.1016/j.parkreldis.2022.105230.

34. G. Saporito, P. Sucapane, F. Bruno, et al., "Cognitive Safety of Focused Ultrasound Thalamotomy for Tremor: 1-Year Follow-Up Results of the COGNIFUS Part 2 Study," *Frontiers in Neurology* 15 (2024), https://doi.org/10.3389/FNEUR.2024.1395282.

35. J. Petersen, J. McGough, G. Gopinath, et al., "Cognitive Outcomes Following Unilateral Magnetic Resonance-Guided Focused Ultrasound Thalamotomy for Essential Tremor: Findings From Two Cohorts," *Brain Communications* 6, no. 5 (2024): fcae293, https://doi.org/10.1093/BRAINCOMMS/FCAE293.

36. M. Aubignat, M. Roussel, A. Aarabi, M. Tir, M. Lefranc, and O. Godefroy, "Cognitive Impacts of Unilateral MR-Guided Focused Ultrasound Thalamotomy: A Meta-Analysis and a Call for Systematic Neuropsychological Assessment," *Journal of Neurosurgery* 142, no. 5 (2025): 1271–1279, https://doi.org/10.3171/2024.7.JNS24906.

37. C. Bartels, M. Wegrzyn, A. Wiedl, V. Ackermann, and H. Ehrenreich, "Practice Effects in Healthy Adults: A Longitudinal Study on Frequent Repetitive Cognitive Testing," *BMC Neuroscience* 11 (2010): 11, https://doi.org/10.1186/1471-2202-11-118.

38. K. Dhima, J. Biars, E. Kondylis, S. Nagel, X. X. Yu, and D. P. Floden, "Neuropsychological Outcomes After Thalamic Deep Brain Stimulation

for Essential Tremor," *Parkinsonism & Related Disorders* 92 (2021): 88–93, https://doi.org/10.1016/J.PARKRELDIS.2021.10.026.

39. J. Al Ali, M. Lacy, M. Padmanaban, et al., "Cognitive Outcomes in Patients With Essential Tremor Treated With Deep Brain Stimulation: A Systematic Review," *Frontiers in Human Neuroscience* 18 (2024), https://doi.org/10.3389/FNHUM.2024.1319520.

40. J. D. Jones, T. Orozco, D. Bowers, et al., "Cognitive Outcomes for Essential Tremor Patients Selected for Thalamic Deep Brain Stimulation Surgery Through Interdisciplinary Evaluations," *Frontiers in Human Neuroscience* 14 (2020), https://doi.org/10.3389/FNHUM.2020.578348.

## Supporting Information

Additional supporting information can be found online in the Supporting Information section. **Table S1:** Common Terminology Criteria for Adverse Events (CTCAEv5) definitions and grading. **Table S2:** Summary of final stereotactic coordinates and treatment parameters. **Table S3:** Observed mean values for the first-treated hand. **Table S4:** Neuropsychological testing outcomes. **Figure S1:** PRISMA flow diagram. **Figure S2:** Forest plots from the meta-analysis of efficacy outcomes at 6- and 12-month follow-up (sensitivity analysis, correlation coefficient $r = 0.5$). **Figure S3:** Forest plots from the exploratory meta-analysis of efficacy outcomes with extended follow-up windows (sensitivity analysis, correlation coefficient $r = 0.5$).