Pain related to MRgFUS: a merely minor transient adverse event?

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Supplementary materials

Supplementary material S1: Materials and Methods

Patients

Patients admitted to Fondazione IRCCS Istituto Neurologico C.Besta from July 2020 to October 2022 for unilateral MRgFUS thermoablation of the VIM were enrolled in the present study. All patients had a diagnosis of TDPD [1] or ET [2] based on current diagnostic criteria, had tremor resistant to the best medical therapy causing disability in everyday activities, and fulfilled inclusion and exclusion criteria as described elsewhere [3,4]. MRgFUS thalamotomy was performed using the InSightec ExAblate 4000 Transcranial System interfaced with a 1.5 T GE Medical System MRI machine. The scalp was razor-shaved in all cases, prepped with povidone-iodine and infused with local anesthetic at the pin sites for placement of the CRW frame (Integra LifeSciences). All patients were awake throughout the procedure. An intravenous catheter was used to promptly administer analgesic treatment (paracetamol) in case of pain caused by the prolonged stationary position of the body and sedative treatment (dexmedetomidine) in case of severe anxiety or agitation. All patients gave written informed consent to participate, and the Ethical Committee of Fondazione IRCCS Istituto Neurologico C.Besta approved the study (soFUS-study; n.74, 15th of July 2020).

Assessment

Clinical assessments were performed at baseline, during hospitalization for MRgFUS treatment, and at one-month follow-up. At baseline, tremor severity was evaluated with the Movement Disorder Society-Unified Parkinson's Disease Rating Scale (MDS-UPDRS; items from 3.15 to 3.18) [5] in TDPD patients and with the Essential Tremor Rating Assessment Scale (TETRAS; items 4,6,7 and 8) [6] in ET patients. Global cognitive status was assessed with the Montreal Cognitive Assessment (MoCA) [7] and symptoms of depression with the Beck Depression Inventory-II (BDI-II) [8].
The main MRgFUS treatment parameters were collected, including the skull density ratio (SDR) [9], the number of sonications, the duration of sonications, the peak of the temperature, the total amount of energy delivered (Joules), the maximum power (peak Watt), and the skull surface (cm^2).
During hospitalization, head pain associated with sonication and pain associated with frame placement were assessed separately within 48 hours after MRgFUS. Since most patients had tremor of the dominant hand, we decided to use a verbal rating scale (VRS) to avoid difficulties or distortions in responding. Patients had to select the most appropriate among eight adjectives (no pain, just noticeable, weak, mild, moderate, strong, severe, and excruciating) to characterize pain intensity associated with sonication and frame placement. During hospitalization, the Peritraumatic

Dissociative Experiences Questionnaire (PDEQ-10) [10] was used to assess the occurrence of peri-operative (during or immediately after MRgFUS) dissociative symptoms (a score above 14 was considered clinically significant).

One-month after MRgFUS, tremor was re-assessed with MDS-UPDRS and TETRAS, and symptoms of acute stress disorder related to the procedure were evalueted with the Impact of Event Scale–Revised (IES-R; a score above 33 was considered clinically significant) [11].

Statistical analysis

The normality of data distribution was checked with the Kolmogornov-Smirnov test. As almost all the variables had non-normal distribution, we used non-parametric statistics. Categorical data were expressed as frequency and continuous data as means±SD [median(IQR)]. Patients were split into two groups according to the rating of head pain intensity during sonication: patients who scored from “strong” to “excruciating” were assigned to the high pain (HP) group, and patients who scored from “no pain” to “moderate” were assigned to the low-medium pain (LMP) group (Supplementary Figure 1). The Chi-squared and the Mann-Whitney tests were used for between-group comparisons. The Wilcoxon Signed-ranks test was used for within-group comparisons. The Benjamini-Hochberg procedure was used to control the false discovery rate in multiple hypothesis testing. Univariate and multivariate logistic regressions were used to evaluate the influence of baseline demographic and clinical features on high-intensity head pain during sonications; the two-level variable representing head pain during sonications (HP coded as 1 and LMP coded as 0) was the dependent variable. The SDR was multiplied by 10 to rescale the scale of the coefficient in the logistic regression; of note, this procedure has no impact on statistical inference or the p-values which remained the same. We also assessed the performance of the univariate and multivariate logistic regression models in correctly predicting head pain during sonication based on the significant features identified at the previous step of analysis. We calculated area under the curve, sensitivity, and specificity along with their 95% confidence intervals with bootstrapping using 2000 stratified resamples. Sensitivity and specificity values were calculated fixing the threshold to the best cut-off according to the Youden’s index as obtained by bootstrapping. The significance level was set at $p<0.05$. SPSS (version 25) and R (version 4.3.1) softwares were used for statistical analysis.

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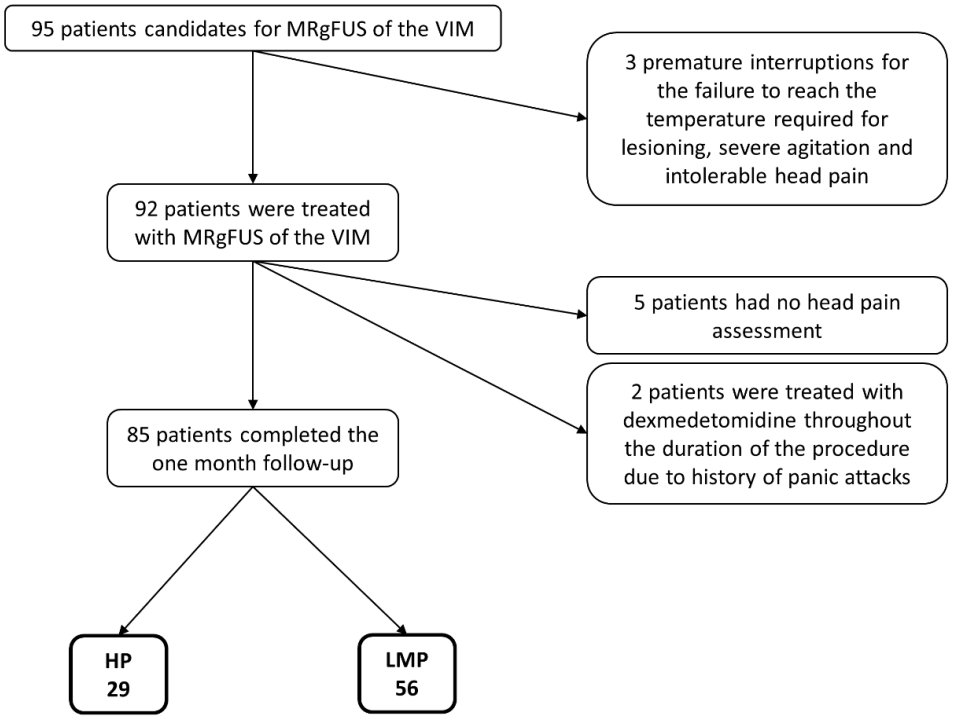
Supplementary figure S2: Flowchart of the study



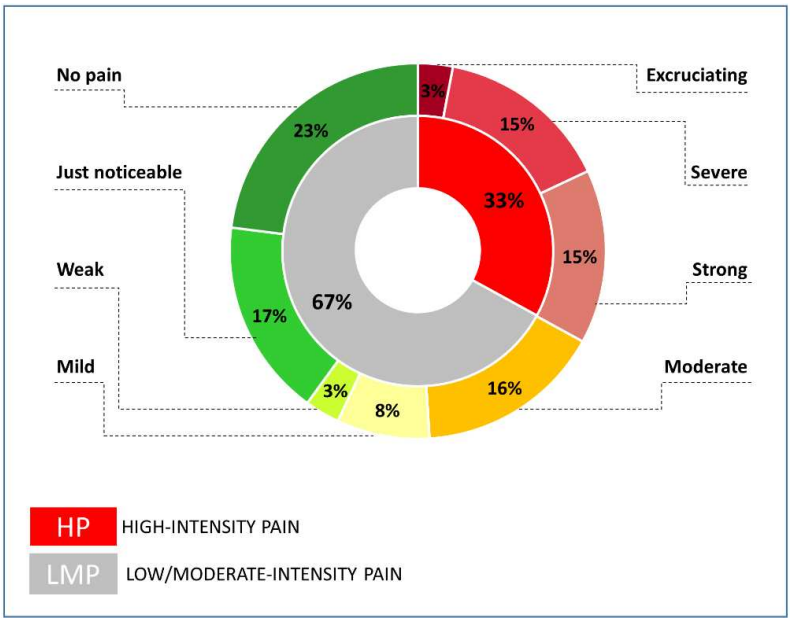
Supplementary table S3: Baseline demographic and clinical features of patients treated with MRgFUS

	N 85
Gender (f/m)	18/67
Education	12±3.98) [13(8-13)]
Hand dominance (r/l)	82/3
Diagnosis (ET/TDPD)	42/43
Age at disease onset	47.5±20.2 [55(34-62)]
Disease duration	19.9±19.6 [9(5-31)]
MoCA (raw score)	23.9±3 [24(22-26)]
BDI-II	5.4±4.1 [4(3-9)]
Categorical variables are expressed as frequency and continuous variables as means±SD [median(IQR)]. Abbreviation: BDI-II, Beck Depression Inventory II; ET, essential tremor; MoCA, Montreal Cognitive Assessment; TDPD, tremor-dominant Parkinson disease.	

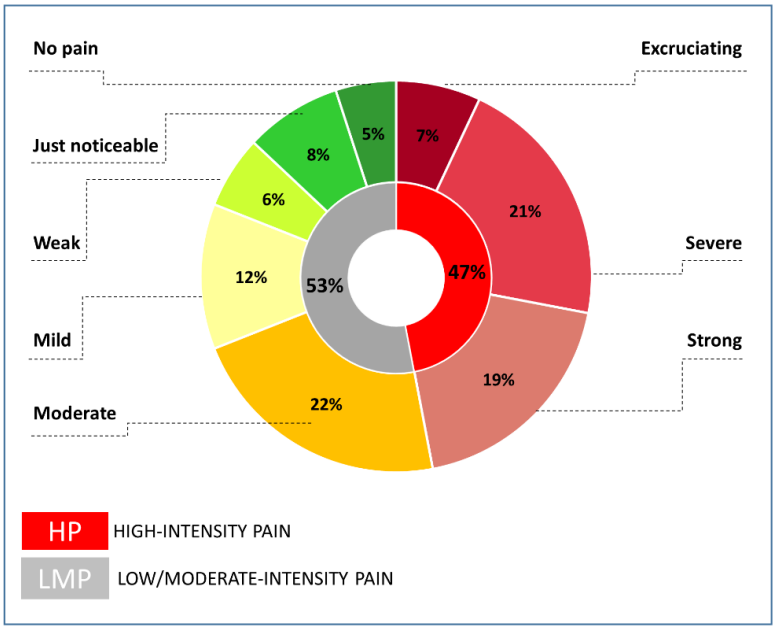
Supplementary table S4: MRgFUS-related features and treatment parameters

	N 85
Age at MRgFUS	67.5±10.8 [70(63-74)]
Treated hemisphere (r/l)	25/60
Medications during sonications (no/dexmedetomidine/paracetamol)	59/13/13
SDR	0.56±0.10 [57(50-63)]
Number of sonications	10.1±3.1 [10(8-12)]
Sonication duration (sec)	169.3±75 [152(112-210)]
Peak temperature (°Celsius)	62.9±3.7 [62(60-66)]
Total energy delivered (Joules)	93375.2±67442.1 [70677(43335-126586)]
Maximum power delivered (Watt)	845±115.7 [854(789-906)]
Skull surface (cm^2)	352.1±32.5 [358(335-367)]
Tremor reduction (%)	55%
PDEQ	11.1±2.3 [10(10-12)]
IES-R	2.9±7.7 [0(0-2)]
Categorical variables are expressed as frequency and continuous variables as means±SD [median(IQR)]. Abbreviation: IES-R, Impact of event scale-revised;MRgFUS, magnetic resonance-guided focused ultrasound; PDEQ, Peritraumatic dissociative experiences questionnaire; SDR, skull density ratio.	

Supplementary figure S5: Pie chart of the intensity of head pain suffered during sonications.



Supplementary figure S6: Pie chart of the intensity of head pain suffered during frame positioning.



Supplementary table S7: Univariate logistic regression analysis.

Variables	Exp(B)	95% CI	*p-value*	Exp(B)	95% CI	*p-value*
	Univariate			*Multivariate*		
Gender	0.768	0.262 – 2.253	0.631			
Age at MRgFus	0.970	0.930 – 1.012	0.154			
Diagnosis	1.115	0.469 – 2.823	0.759			
Baseline MoCA	1,124	0.955 – 1.323	0.159			
Baseline BDI-II	0.948	0.847 – 1.062	0.359			
SDRx10	0.367	0.207 – 0.652	**0.001**	0.381	0.210 – 0.689	**0.001**
Pain during frame positioning	3.187	1.255 – 8.093	**0.015**	2.714	0.990 – 7.437	0.052

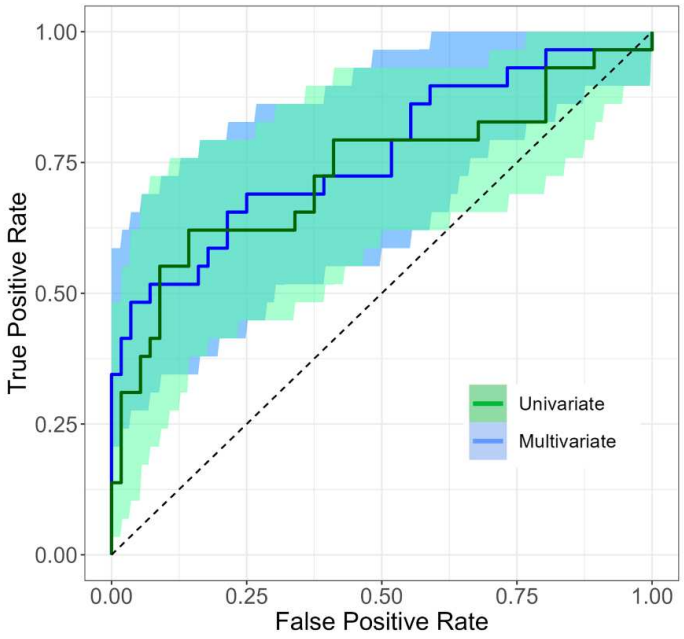
The two-level variable head pain during sonications was the dependent variable: HP group was the reference. The female group was the reference for geneder, TDPD was the reference for diagnosis and HP group was the reference for pain during frame positioning. The SDR was multiplied by 10 to rescale the scale of the coefficient in the logistic regression; of note, this procedure has no impact on statistical inference or the p-values which remain the same. Statistical significance ($p < .05$) is expressed in bold.
Abbreviation: BDI-II, Beck depression inventory II; MoCA, Montreal cognitive assessment; SDR, Skull density ratio.

Supplementary table S8: Classification performance of the univariate model (based only on SDR) and multivariate model (based on SDR and pain during frame positioning).

Logistic regression model:	AUC (95%CI)	Threshold	Sensitivity (95%CI)	Specificity (95%CI)
Univariate (SDR)	0.740 (0.615 – 0.865)	≤0 .515	85.7 (76.8 – 94.6)	62.1 (44.8 – 79.3)
Multivariate (SDR and pain during frame positioning)	0.768 (0.645 – 0.875)	≥ 0.505	92.7 (85.7 – 98.2)	51.7 (34.4 – 69)

Data are median values over 2000 bootstrap resamples (95% CI); the threshold for the univariate model was reported on the scale of SDR, while the threshold of the multivariate model was reported in terms of probability.
Abbreviations: AUC, area under the curve; SDR, skull density ratio.

Supplementary figure S9: ROC curve of the univariate and multivariate logistic regression models with 95% confidence intervals.



Supplementary material S10: References

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