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MRgFUS subthalamotomy in Parkinson's disease: an approach aimed at minimizing Lesion Volume

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Idiopathic Parkinson's Disease (PD) is a neurodegenerative disorder characterized by tremor, rigidity, bradykinesia, and postural instability. Magnetic Resonance-guided high-intensity focused ultrasound (MRgFUS) of the subthalamic nucleus (STN) is gaining recognition as a minimally invasive surgical option. This study assesses the safety and efficacy of unilateral MRgFUS subthalamotomy, aiming to create the smallest effective lesion. Between June 2021 and October 2023, twelve PD patients underwent the procedure, with primary outcomes focused on safety and motor improvements after six months. Results indicated significant motor improvements, with over 50% reduction in tremor, rigidity, and bradykinesia, while balance and gait remained stable. Quality of life also improved. Side effects were generally mild and transient, though some patients experienced involuntary movements, managed through medication adjustments. Despite limitations, this technique appears to offer a promising, less-invasive alternative for managing PD symptoms with a favorable risk-benefit profile. Further research is necessary to refine the procedure and assess long-term outcomes.

Idiopathic Parkinson's Disease (PD) is a neurodegenerative disorder characterized by tremor, rigidity, bradykinesia and postural instability. Surgical interventions to address PD motor symptoms have a rich history dating back to the 1940s[1]. High-Intensity Focused Ultrasound (HIFU) was explored for cerebral ablations by the Fry brothers and Russel Meyers[2,3]. Advances in transducer, amplifier and neuroimaging allowed the development of the new high intensity focused ultrasound treatment era[4]. The ventralis intermedius nucleus (VIM) of the thalamus was the first and most frequently target used in PD. A randomized controlled trial of VIM Magnetic resonance guided high-intensity focused ultrasound (MRgFUS) in PD-Tremor led to FDA approval in 2017[5]. However, the restricted benefit on tremor of thalamotomies, prompted the exploration of other brain targets to address the different motor symptoms of PD. Previous experience with both, ablation and neuromodulation procedures had confirmed that subthalamic nucleus (STN) and Globus Pallidus internus (GPi) are more suitable targets for PD[6]. GPi procedures have a main impact on dyskinesia whereas, its effects on cardinal motor symptoms can be more modest when compared with subthalamotomies or STN DBS[3,6]. Additionally, unilateral radiofrequency subthalamotomies have shown significant improvements in motor symptoms with an acceptable risk profile[7]. More recently, a correlation between lesion size and side effects has been identified[8]. New evidence supports the efficacy of incisionless subthalamotomy MRgFUS in substantially improving PD motor features[9,10]. The advantages of the MRgFUS technique over radiofrequency are evident in terms of invasiveness, accuracy, and control of lesion size.

Despite the potential of targeting one of the most effective neurosurgical targets for Parkinson's Disease through an incisionless procedure, further research is required, and several clinical and technical considerations remain. A comprehensive understanding of the regional anatomy surrounding the STN is crucial for optimal preoperative and intraoperative planning[8]. The sensorimotor part of the STN, corresponding to the dorsolateral part of the nucleus, has been

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reported as the most clinically effective zone for lesioning[11]. The risk of developing involuntary movements after subthalamotomy is well known, leading some investigations to include the pallidothalamic Tract (PTT), an antidyskinetic target, within the lesion area[12]. However, it has been suggested that the threshold for ballism in parkinsonian STN is higher than in normal STN, and the risk of inducing dyskinesia is related to location and volume of the lesion[13,14]. Therefore, the necessity of systematically targeting PTT is questioned. Furthermore, side effects in neurosurgical ablative procedures are largely related to lesion size, suggesting that smaller lesions may be advisable[5,9,13,14]. Thus, a fine balance between benefits and risks must be considered during each procedure.

Gait disturbance is another significant concern in functional neurosurgery, with up to 48% of MRgFUS-treated patients reporting issues, depending on the series and targets[10]. Although objective balance evaluation in MRgFUS thalamic procedures for Essential Tremor (ET) has been considered relevant[15], no references are available for subthalamotomies in PD.

This study aimed to investigate the safety and efficacy of unilateral MRgFUS subthalamotomy, following a protocol for individualized STN targeting. The objective was to perform the smallest lesion that provided optimal clinical benefit by targeting the appropriate STN subregion for each individual patient. Additionally, a detailed assessment of the impact on balance and gait was conducted.

Methods

Between April 2019 and October 2023, individuals meeting the U.K. Brain Bank Clinical criteria for Parkinson's Disease[16], determined by a movement disorders specialist, were eligible for inclusion in this study. For those who declined DBS treatment, the option of MRgFUS subthalamotomy was offered.

Inclusion criteria were: Asymmetric parkinsonism at the screening visit (Asymmetry Index (AI) scores above 1 were considered asymmetric, and scores higher than 2 were categorized as markedly asymmetric)[17], motor signs on the more affected side not well controlled despite optimized dopaminergic medication and aged > 18 years old. Patients were excluded if they presented with history of uncontrolled troublesome dyskinesia, cognitive decline, brain hemorrhage, diagnosis of an unstable cardiac or psychiatric disease, a Skull Density Ratio (SDR) ≤ 0.35 calculated from the CT screening scan or conditions that contraindicated magnetic resonance image (MRI). Other, exclusion criteria included clinically significant gait or balance problems, speech impairment or inability to comply with the scheduled follow-up. Patients were classified based on the most distressing motor symptomatology and MDS-UPDRS III motor subscores. Levodopa Equivalent Daily Dose (LEDD) was calculated according to established equivalences[18]. Levodopa dosage was deemed optimized when the patient exhibited dyskinesia while on medication or when the total daily dose reached 5–6 mg/kg, as higher doses are associated with an increased risk of dyskinesia[19]. To consider treatment fully optimized, the patient should have been receiving or have trialed other antiparkinsonian treatments (e.g., MAO inhibitors, COMT inhibitors, dopamine agonists) up to a reasonable maximum dose. For patients experiencing "wearing off," the number of levodopa doses were at least four per day. A suboptimal motor control of symptoms was defined as partial improvement while on medication or the presence of motor fluctuations affecting one side of the body, indicating a short-duration response to medication.

The study received ethics approval by the local Institutional Review Board (IIS La Fe), and informed consent was obtained from all participants.

All patients underwent a preoperative neuronavigation T1, T2, and diffusion tensor imaging with a conventional 3 Tesla MRI scanner prior to surgery. Images were then processed using a clinically approved stereotactic software platform (StealthStation S7 and S8 Medtronic). The preoperative MRI scans were performed using a Philips Medical Systems Achieva MRI scanner with a 3 T magnetic field. MRI parameters are displayed in Supplementary table 1. The target was the contralateral STN nucleus to the desired body side to treat. Briefly, the dorsolateral subthalamic nucleus (STN) was directly targeted using the anterior border of the red nucleus as a landmark, which is recognized as the central reference point for the STN along the rostrocaudal axis[20]. From this position, the target coordinates were adjusted rostrally and posteriorly on the visualized STN to maintain a safe distance from the nucleus's center, as proximity may increase the risk of dyskinesia. Lateral adjustments were also made based on the visualization of the STN. A tractography-based method for STN targeting was subsequently employed, visualizing the pyramidal and cerebellothalamic tracts to ensure a safe distance from these structures. The day of the treatment a sequence of the preoperative MRI is uploaded in the MRgFUS equipment. This sequence is corregistrated with the prior CT scan and intraprocedural MRI. Pre-planned target's coordinates are transposed into the uploaded sequence and readjusted according to image if necessary.

Based on previous experience with ET patients, our group adopted some procedural changes that included increasing the rate at which sonication power is raised over the course of the treatment[21]. The first low-power sonication (duration, 10–20 s; average peak temperatures, 40 °C–45 °C) was used to confirm alignment. The power was increased to reach temperatures of between 50 °C and 53 °C which induced transient clinical effects. Intraprocedural clinical monitoring was conducted throughout the procedure. If clinical improvement was observed (defined as a decrease of at least one point in the assessed MDS-UPDRS subscore items) and no adverse events (AEs) occurred, the subsequent high-power sonication was initiated to achieve a mean target temperature between 55 °C and 60 °C, which is known to induce thermal ablation. This temperature range typically yields greater improvement than what is observed during the verification process. Once the initial ablative lesion was completed, a second sonication at increased power was performed to enlarge and consolidate the lesion at the same site. If temperatures needed for lesion were not attained, the exposure time for the last sonication was extended up to 50 s. The emergence of side effects or the lack of motor improvement prompted adjustments to the target coordinates. Treatment was concluded when sufficient clinical improvement was deemed to have been achieved, defined as at least a 30% improvement from baseline for rigidity and bradykinesia, and a 50% improvement for tremor. Therefore, two key methodological considerations were taken into account. First, the goal was to minimize the number of sonications required for thermoablation, aiming for a more focused lesion which may reduce the risk of oedema. Second, emphasis was placed on executing the minimum number of lesions within the STN/STN area to achieve a favorable risk/benefit profile.

Lesion coordinates were calculated from the center of the lesion as seen on T2-weighted MRI obtained immediately after the procedure and values were normalized to a 25 mm ACPC distance. Lesion volumes were measured by manual segmentation (from axial, coronal and sagittal T2-weighted slices) in the 3D post-immediate and six months brain MRI (additional MRI details are available in Supplementary information file). All the interventions took place in off-medication condition and in an ambulatory setting. After the procedure, dopaminergic drugs were adjusted according to patients' needs.

Clinical visits comprised baseline, one week, one-, three- and six-months follow-ups after subthalamotomy. Clinical assessments were completed at baseline and six months follow-up and included: complete neurological examination and MDS-UPDRS part II (Activities of daily living Off and On-state) and III in Off (after a minimum 12 h overnight withdrawal of standard-release anti-parkinsonian drugs or 24 h withdrawal of prolonged-release anti-parkinsonian drugs) and On-medication state (60–90 min after the administration of the dopaminergic medication), MDS-UPDRS part IV, PDQ39, EQ-5D questionnaires and Berg Balance Scale (BBS). The percentage of the patient's self-reported overall improvement compared to baseline was noted for each visit. One-week, one- and three-months visits after subthalamotomy were programed to asses side effects and to allow for

further dopaminergic medication adjustment. Formal neuropsychological evaluation was undertaken in the On-medication state at baseline and at six months. Cognitive battery tests included memory, language, visuo-spatial, attention and executive functions evaluation.

The primary endpoints were efficacy and safety.

Primary efficacy endpoint was defined as the change in the motor score for the treated side, using MDS-UPDRS III in the Off-medication state after six months of the procedure compared with baseline. A change of 30% in the motor score of MDS-UPDRS III was considered clinically meaningful[22].

Safety was determined by the frequency and severity of any adverse event observed during the procedure and on clinical examinations after the procedure. Severity was predefined as mild (minor inconvenience), moderate (bothersome), or severe (in-capacitating). AE were characterized as transient or persistent (presented at the six months follow-up visit). AE were also grouped into two categories:

1. Sonication-related: including nausea, vomiting, dizziness and scalp burn.
2. Subthalamotomy-related, subdivided into six categories: sensory, motor, speech, dyskinesia, balance and gait difficulties and dysmetria.

Secondary outcomes included: change from baseline in the MDS-UPDRS III score for the treated side in On-medication state; change in the MDS-UPDRS III rigidity, bradykinesia and tremor for the more affected side and gait and axial specific subscores in both the Off and On-medication states; change in general motor condition assessed by MDS-UPDRS III total score in both the Off-medication and On-medication states; activities of daily living assessed by MDS-UPDRS II and motor complications rated by MDS-UPDRS IV. Quality of life was assessed with the use of EQ-5D and the 39-item Parkinson's Disease Questionnaire summary index[23].

Gait function was specifically investigated using the Berg Balance Scale (BBS)[24]. Higher scores reveal better balance. For this analysis, scores of less than 45 on the BBS after six months were considered a harsh impact on patient's balance and were rated as a severe AE. A change in the BBS score of 4 points or greater was rated as a mild AE if it did not affect daily activities, and it was rated as a moderate AE if it interfered with daily activities. A change of 3 or less was not considered clinically relevant[25].

The change from baseline to six months in levodopa equivalent daily dose was also analyzed.

Post-treatment and six months after surgery MRI imaging were obtained to document the natural evolution of the lesion.

Statistical analysis

The descriptive analysis provides the most relevant statistics for each of the parameters and differences: mean, standard deviation, minimum, maximum, 25th percentile, median (50th) and 75th percentile. As the cohort size is small, the results of continuous variables are presented in terms of median and interquartile range (25th and 75th percentiles). For the motor scales and the Berg scale parameters, the percentage difference of the final measurement with respect to baseline was determined. Regarding the EQ-5D-5L scale, the severity index (ISEV) was calculated from the score of the individual scores of the five dimensions. For the PDQ-39 scale, absolute variations were used. Given the small sample size, the analysis approach was non-parametric. Wilcoxon test was used to study changes in the distribution of parameters between six months and baseline scores. The level of significance used in the analysis was 5% ($\alpha = 0.05$). A Wilcoxon test applied to the sample of 12 patients reaches a power of 68.9% in order to detect a significant variation compatible with a large effect size ($d = 0.8$) for a confidence level of 95%. Statistical analyses were conducted with the use of SPSS software, version 15.0.

Results

Patients

From April 2019 to December 2023, one hundred ninety patients underwent ablative procedures with MRgFUS at our center for ET or PD. In June 2021 the first unilateral subthalamotomy was performed and, since then twenty-three patients underwent unilateral subthalamotomy. Fourteen patients completed six month follow up and two of them were excluded from the analysis because previous DBS in one (Patient 7, DBS explanted due to suture dehiscence and infection) and advanced PD with complex motor fluctuations with high concerns for DBS surgery in the other (Patient 14). Therefore, as of the preparation of this manuscript, baseline and six-month follow-up assessments are available for twelve participants. Eleven patients presented with a PD-tremor phenotype, while one had a rigid-akynetic PD phenotype. Demographics and cohort characteristics are summarized in Table 1.

Table 1 | Demographics

Age – yr	59.5 (54.7–67.2)
Sex - no, (%)	
Male	9 (75)
Female	3 (25)
Hand Dominance - no, (%)	
Right-handed	12 (100)
Left-handed	0 (0)
Phenotype - no, (%)	
Tremoric	11 (91.6)
Rigid-Akinetic	1 (8.4)
Disease duration - yr	8.0 (6.0–9.0)
MDS-UPDRS III total score[a,b]	
Off-medication state	45.5 (34.7–51.2)
On-medication state	22.0 (12.0–29.0)
Baseline Hoehn and Yahr	
Off-medication state	2.0 (2.0–2.0)
On-medication state	1.5 (1.0–2.0)
Off-medication Asymmetry Index[c]	2.0 (1.3–2.4)
Baseline LEDD[d]	816.0 (641.0–895.0)

Continuous values are expressed in median and interquartile range (IQR). $n = 12$.
[a]Total scores on the Movement Disorder Society–Unified Parkinson's Disease Rating Scale (MDS-UPDRS), part III, range from 0 to 132, with higher scores indicating more severe clinical features.
[b]The Off-medication state was defined as a minimum 12-hour overnight withdrawal of antiparkinsonian drugs and a 24 h withdrawal of prolonged-release formulations. The On-medication state was determined by both the patient and the clinician and indicated that the medication had been effective for at least 30 min after ingestion.
[c]Asymmetric parkinsonism is defined by the Off-state Asymmetry Index which is the ratio of the motor score on the Movement Disorder Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS, part III) for the more affected side of the body to the score on the less affected side, with an index of 1 indicating symmetric parkinsonism.
[d]LEDD refers to Levodopa Equivalent Daily Dose.

Surgical data

Surgical data are described in Table 2. Median average peak target temperature of 57.5 °C (range, 56.0–60.25) to induce a subthalamic ablation was reached with an average of 5 sonications. In two patients the sonication between 52 and 53 °C with an increased time of exposure was considered thermoablative[26]. The overall duration of the sonication procedure was short, lasting approximately 20 minutes (median duration 18 min; range 15.75–23.25 min). No further adjustments to the target coordinates were needed, except in one patient in whom a readjustment was required after the fourth sonication (average temperature 52 °C) induced dyskinesia in the right hand. The target was shifted 0.7 mm rostrally and 0.9 mm laterally. Examples of brain magnetic resonances can be seen in Fig. 1 (twelve patient images are available in the Supplementary Fig. 1). Mean postoperative lesion volume was 207.89mm^3 (range 124.07–389.53)

Table 2 | Surgical data

Target (STN) - no, (%)	
Left	10 (80)
Right	2 (20)
Skull Density Ratio - SDR	0.55 (0.53–0.62)
Baseline M-L coordinate[a]	11.92 (11.70–12.51)
Baseline A-P coordinate[b]	10.82 (9.43–11.52)
Baseline S-I coordinate[c]	−2.71 (−3.09 to −2.36)
Sonications - no	5.0 (4.75–6.0)
Thermoablative sonications[d] - no	2.0 (2.0–2.0)
Coordinates adjustmentse[e]- no	0.0 (0.0–0.0)
Sonication duration - min	18.0 (15.75–23.25)
Final Energy[f] - Jules	13392.5 (9603–20975.7)
Final Power[f] - Wats	752.0 (735.7–812.7)
Final Average Temperature[f] - °C	57.5 (56-60.25)
Final Maximum Temperature[f] - °C	62.0 (59.5–65)
Immediate post-treatment M-L coordinate[a]	12.68 (11.43–13.01)
Immediate post-treatment A-P coordinate[b]	10.87 (9.18–11.87)
Immediate post-treatment S-I coordinate[c]	−2.48 (−2.98 to −1.55)
Immediate post-treatment volume[g] - mm^3	207.89 (124.07–389.53)
Six months volume[g] - mm^3	95.90 (41.62–145.89)

Continuous values are expressed in median and interquartile range (IQR). $n = 12$.
Baseline normalized coordinates refer to those coordinates determined at the beginning of the procedure. Coordinates were normalized to 25 mm ACPC distance.
Immediate post-treatment coordinates refer to those coordinates that were calculated from the center of the lesion as seen on T2-weighted MRI obtained immediately after the procedure. Values were normalized to a 25 mm ACPC distance.
[a]*M-L* Medial-Lateral.
[b]*A-P* Anterior-Posterior.
[c]*S-I* Supero-Inferior.
[d]Refers to the number of sonications that met mean target temperatures between 55 °C and 60 °C.
[e]Refers to the number of adjustments of the target coordinates if intraprocedural involuntary movements or adverse events were encountered.
[f]Refers to those values applied at the last sonication.
[g]Lesion volumes were measured by manual segmentation (from axial, coronal and sagittal T2-weighted slices) in the 3D post-immediate and six months brain MRI.

and decreased up to 95.90mm^3 (range 41.62–145.89) after six months of the subthalamotomy.

Efficacy

Treated side Off-medication MDS UPDRS-III scores significantly improved by 56.5% at six months follow-up (baseline 20.5 points (range 17.0–23.5) and six months 6.5 points (range 5.0-11); $p = 0.006$). Ten out of twelve patients achieved more than 30% reduction in motor scores at 6 months. The total Off-MDS UPDRS-III scores significantly improved by 39.2% ($p = 0.002$). At six months, Off-treated side rigidity, bradykinesia, tremor, significantly improved by 58.3% ($p = 0.007$), 52.3% ($p = 0.005$), 64.6% ($p = 0.015$), respectively compared to baseline, as did Off-MDS UPDRS III axial subscores (29.2% ($p = 0.049$)). Off-Gait subscores remained stable. Treated side On-medication MDS UPDRS-III scores significantly improved by 58.3%. and the total On-MDS UPDRS-III scores significantly improved by 46.7%. At six months follow-up On-treated side rigidity and bradykinesia improved by 75% ($p = 0.02$), 60.7% ($p = 0.014$), respectively; and axial subscores by 25% ($p = 0.024$). On-medication tremor showed a tendency towards improvement (100% improvement; $p = 0.072$). On-medication gait subscore remained stable throughout the follow-up. BBS scores did not decline throughout the study. Additionally, significant improvement in patients' ratings of their activities of the daily living (MDS UPDRS II) and quality of life (PDQ39), was found. The mean Off and On-MDS-UPDRS II total scores improved 66.7% ($p = 0.005$) and 73.3% ($p = 0.008$) at six months. For PDQ-39 total score, a mean change of 18.6 points (95% CI; $p = 0.013$) in the total score at six months compared to baseline was found. No differences were elicited in ISEV EQ-5D 5 L results. MDS-UPDRS IV scores showed a tendency to decrease by 50% ($p = 0.062$) at six months. LEDD decreased by 16.6% at six months follow up (p = 0.021). Median self-reported improvement of 95% (range 87.5-100) was found. Detailed analysis can be found in Table 3 and Fig. 2. Six months follow-up MRI are displayed in Fig. 1.

Safety

Sonication related adverse events were all mild and transient (Table 4). Overall, dizziness, headache and scalp burn were reported. Regarding subthalamotomy related side effects, mild facial asymmetry was detected after the last sonication in one patient and persisted at six months follow-up. Additional intraprocedural facial asymmetry in one patient resolved within the first month. One patient presented mild limb weakness after the procedure which resolved by the one-month visit. Subjective gait unsteadiness was reported by five patients at one month and by three at six months. No objective gait disturbance on examination (gait and tandem gait) was observed at any timepoint and BBS scores did not decline over follow-ups (Table 3). Three patients showed mild dysarthria at one month which persisted in two at six months. Detailed subthalamotomy-related adverse events data are summarized in Table 4.

Intraprocedural involuntary movements were observed in four patients (Patient 4, 6, 8 and 13). At the first month follow-up, three patients presented with On-dyskinesia (Patient 4, 11 and 12). Patient 11, who additionally presented Off-state involuntary movements, had not showed dyskinesia neither at baseline nor intraprocedural. In Patient 4 and 12 dyskinesia occurred only in the On-state and of note, in patient 4 they were already present at baseline. All of them underwent dopaminergic medication adjustment which led to improvement at six months. Thus, at six months, new onset mild On-dyskinesia were present in three patients (25%) and none had Off-state dyskinesia. Dyskinesia outcomes are described in Table 5.

Unilateral subthalamotomy did not affect neuropsychological tests (neuropsychological data are available in Supplementary information file).

Discussion

MRgFUS subthalamotomy is a novel surgical option for PD patients, and thus, literature in this field is scarce. The CINAC group has made significant contributions to this area helping us to understand the impact of lesioning the STN using a method other than the previous radiofrequency subthalamotomies. However, delineating the optimal surgical approach remains challenging. Our study aimed to contribute to this understanding by advocating for the performance of the smallest lesion possible. The patients presented here were successfully treated with a single lesion within the STN, corresponding to a mean volume of 95.90 mm^3 at six months after the procedure. Lesion volume following MRgFUS subthalamotomy has not been systematically reported in the literature. The pilot study from the CINAC group, however, documented a mean lesion volume of 132 mm^3 (SD 55) at the 6-month follow-up. In their study, the mean number of sonications per procedure was 23.4, with an average of 8.4 sonications exceeding 55 °C[9]. This approach targeted a larger volume of the STN/STN area (including the PTT) compared to our current approach. Larger lesions are typically associated with a higher risk of side effects[13]. Nevertheless, the rate of side effects and clinical outcomes in our study are comparable to those observed in the CINAC group's study[9], suggesting that both methodologies represent valuable options.

Unilateral MRgFUS subthalamotomy led to a significant contralateral improvement over 50% in all cardinal motor symptoms—tremor (64.4%), rigidity (58.3%) and bradykinesia (52.3%)—in the Off-medication state. Ten patients achieved more than 30% reduction in motor scores at 6 months. STN4 exhibited a worsening in motor scale performance at 6 months. However, the annual motor assessment continues to show an improvement of over 30% compared to baseline data.

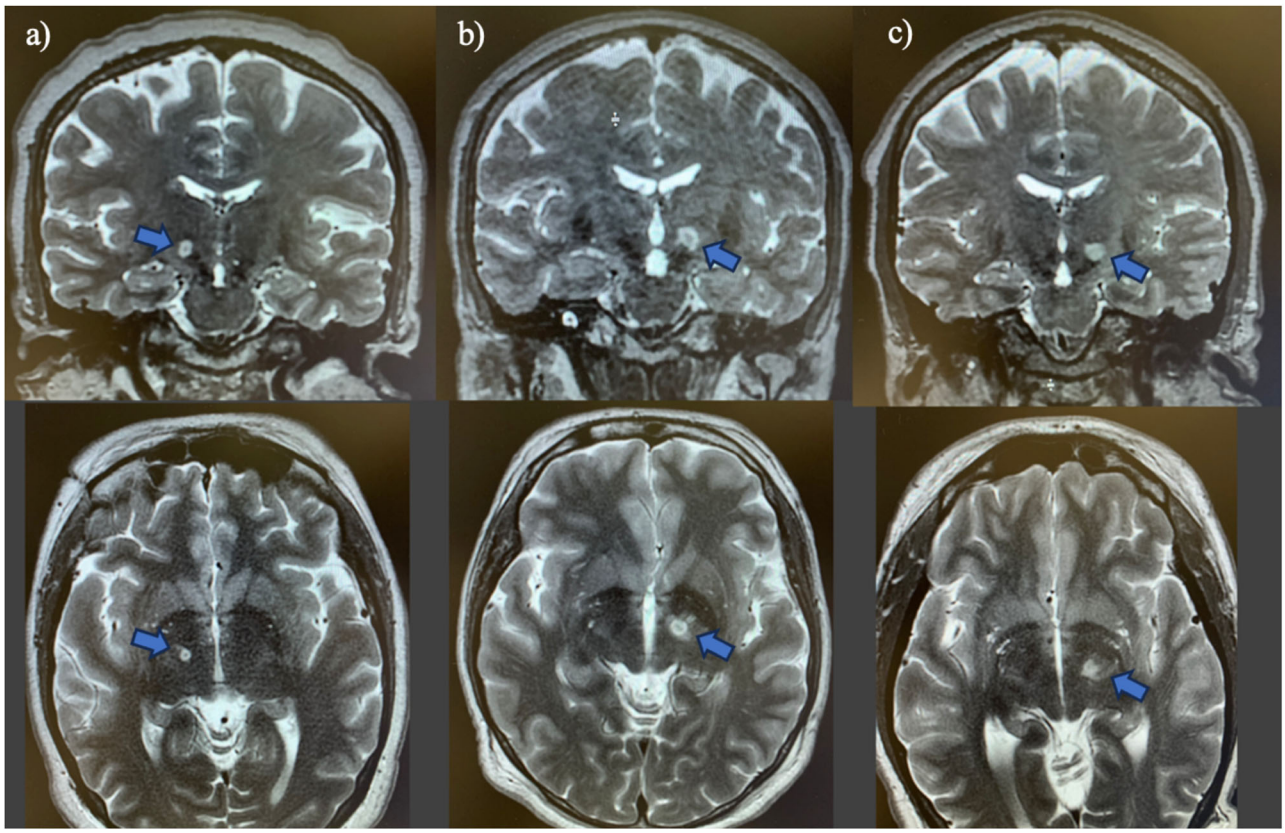

Fig. 1 | Immediate post-treatment unilateral subthalamotomies. Examples of coronal and axial T2-weighted MRI views obtained immediately after the procedure from STN10 (**a**), STN5 (**b**) and STN12 (**c**) participants (with different degrees of cytotoxic oedema). The site of the lesion is recognizable by a heterogeneous central area corresponding to tissue necrosis which is typically hypointense on T2-weighted image. This zone is delimited by a rim of perilesional cytotoxic oedema. The subthalamic lesions are marked with blue arrows.

STN13 achieved an improvement of 27% (improvement on rigidity 17%; bradykinesia 50% and, tremor 34%).

Our results align with those of previous studies with some subtle differences. For instance, Martínez-Fernandez observed a superior impact on tremor (77% and 83.3% in pilot and randomized studies, respectively) but a lower improvement in bradykinesia (37% and 33%) when performing two or more lesions within the STN/STN area which included the PTT (mean number of lesions 3.2)[9,10]. The inclusion of the PTT aims to prevent dyskinesia, given the known antidyskinetic properties of this structure[12]. Experience in STN DBS shows that stimulation of this structure can improve tremor and dyskinesia but may worsen bradykinesia[27]. This could explain the greater improvement on tremor and the more restricted impact on bradykinesia seen with previous MRgFUS subthalamotomies where the PTT was included in the surgical plan[9,10]. Recently, the CINAC group, in view of their ongoing experience, maintained the attitude of performing at least three lesions within the subthalamic area but with a slight target coordinates modification in an early PD cohort[28]. This led to a larger improvement on bradykinesia (64.2%) as well as for other symptoms (rigidity 69.6% and tremor 90.3%). However, it is important to note that patients treated with this approach had shorter disease duration and were therefore less affected, making direct comparison difficult.

The growing knowledge in STN functional anatomy, along with the accuracy and the capability of producing small lesion with MRgFUS, opens the door towards a tailored subthalamotomy[29–31]. Beside the classical segregation in sensorimotor, associative and limbic areas within the basal ganglia nuclei[32], a further segregation can be found within the sensorimotor area in terms cortical connectivity and somatotopy. The more rostral part of the sensorimotor STN displays connectivity with the primary sensorimotor cortex (SMC), whereas the more ventral part connects mainly with the supplementary motor area (SMA)[29,33]. This is relevant as different spots for tremor, rigidity and bradykinesia have been identified within the sensorymotor STN[29–31]. Moreover, hand and leg somatotopy are, as well, segregated[29,34,35].

We observed a number of adverse effects related to the procedure. Transient side effects encountered in our study resolved within a few weeks, with persistent effects at six months rated as mild. Objective balance showed no decrease in stability during the follow-up period. However, it is possible that BBS may not be sensitive enough to detect very mild stability impairments.

The occurrence of chorea-ballism remains a significant concern during subthalamotomies. Previous studies on radiofrequency subthalamotomies have demonstrated a higher risk of dyskinesia in patients with larger lesions[13]. However, even small lesions may still pose a risk of dyskinesia, as observed in our cohort, where 25% of patients developed mild, new-onset, on-medication dyskinesia at six months. On the other hand, 75% of patients did not experience any new involuntary movement, despite marked improvement in bradykinesia. Thus, there is still potential for refining the targeting of the STN and the precise delineation of the lesion. Whether the PTT should always be included within the lesion plan or addressed on demand during the procedure or afterward remains an open question. Furthermore, it is important to be aware of the ongoing necessity of dopaminergic medication which may complicate the management of subthalamotomy-induced involuntary dyskinesia.

It is crucial for patients to be aware of the risks (as they may be permanent) as well as of the necessity of a neurosurgical procedure for the non-treated side in the long-term. Recently, a pilot study showed that staged bilateral MRgFUS subthalamotomy may be an option for selected patients[36]. Therefore, comprehensive discussions with patients should precede MRgFUS treatment.

Table 3 | Primary and Secondary Efficacy Outcomes

	Baseline	Six months follow-up	Improvement (%)	*P*-value
MDS-UPDRS II total score[a]				
Off-medication state	17.0 (14.5–19.0)	5.0 (5.0–10.0)	66.7	*0.005**
On-medication state	6.5 (2.0–10.0)	1.0 (0.0–3.0)	73.3	*0.008**
MDS-UPDRS III total score[b,c]				
Off-medication state	45.5 (34.5–53.0)	21.0 (317.0–39.5)	39.2	*0.002**
On-medication state	22.0 (10.0–30.0)	4.0 (2.5–5.0)	58.3	*0.007**
MDS-UPDRS III score for untreated side[d,c]				
Off-medication state	9.5 (7.0-20.5)	7.0 (6.0-12.5)	22.2	*0.028**
On-medication state	5.0 (2.0-10.0)	3.5 (2.0-8.5)	33.3	*0.469*
MDS-UPDRS III score for treated side[d,c]				
Off-medication state	20.5 (17.0–323.5)	6.5 (5.0–11.0)	56.5	*0.006**
Rigidity	4.0 (2.0–4.5)	1.0 (0.5–3.0)	58.3	*0.007**
Bradykinesia	10.5 (8.0–12.5)	4.5 (2.5–5.0)	52.3	*0.005**
Tremor	5.5 (3.5–7.0)	1.5 (0.5–3.5)	64.6	*0.015**
Gait	1.0 (1.0–2.5)	0.5 (0.0–1.5)	45.8	*0.234*
Axial	9.0 (7.5–12.0)	6.0 (3.0–8.0)	29.2	*0.049**
On-medication state	12.0 (5.0–14.0)	4.0 (2.5–5.0)	58.3	*0.007**
Rigidity	2.0 (1.0–3.0)	1.0 (0.0–1.5)	75.0	*0.020**
Bradykinesia	6.0 (4.0–8.0)	2.0 (1.5–4.0)	60.7	*0.014**
Tremor	2.0 (1.0–4.0)	0.0 (0.0–0.5)	100	0.072
Gait	0.0 (0.0–1.0)	0.5 (0.0–1.0)	87.5	0.336
Axial	4.0 (2.0–6.0)	2.0 (1.0–5.0)	25.0	*0.024**
MDS-UPDRS IV score[e]				
Total score	4.0 (0.5–4.5)	1.5 (0.5–2.5)	50.0	0.062
Dyskinesia	0.0 (0.0–0.5)	0.0 (0.0–1.0)	0.0	0.890
Motor fluctuations	2.5 (0.75–4)	0.5 (0.0–2.25)	20.0	*0.049**
Dystonia, in the off-medication state	0.0 (0.0–0.0)	0.0 (0.0–0.0)	00	0.072
PDQ-39 total score[f]				
Total score	22.4 (16.0–37.5)	5.8 (0.6–19.2)	18.6 (73.75)	*0.013**
Mobility	21.3 (7.5–46.3)	0.0 (0.0–22.5)	10 (100)	*0.006**
Activities of daily living	20.8 (12.5–54.2)	0.0 (0.0–20.8)	12.5 (100)	*0.005**
Emotional well-being	25.0 (17.2–31.3)	8.3 (0.0–20.8)	11.5 (66.8)	0.075
Social stigma	15.6 (6.5–28.1)	0.0 (0.0–0.0)	12.5 (100)	0.622
Social Support	0.0 (0.0–37.5)	0.0 (0.0–8.3)	0 (0)	0.058
Cognition	18.8 (9.4–25.0)	6.3 (0.0–18.8)	6.3 (66.49)	0.095
Communication	16.7 (4.2–25.0)	0.0 (0.0–33.3)	8.3 (100)	0.095
Bad physical condition	45.8 (16.7–62.5)	25.0 (0.0–41.7)	33.3 (45.42)	0.108
EQ-5D (ISEV)[g]				
	20.0 (15.0–35.0)	15.0 (0.0–35.0)	5 points	0.438
Berg Balance Scale[h]				
	56.0 (55.0–56.0)	56.0 (56.0–56.0)	0%	0.655
LEDD[i]				
	816.0 (641.0–895.0)	669.0 (575.0–840.0)	16.6	*0.021**

Continuous values are expressed in median and interquartile range (IQR).

[a]Total scores on the Movement Disorder Society–Unified Parkinson's Disease Rating Scale (MDS-UPDRS), part II, range from 0 to 52, with higher scores indicating more severe impairment in activities of daily living.

[b]Total scores on the Movement Disorder Society–Unified Parkinson's Disease Rating Scale (MDS-UPDRS), part III, range from 0 to 132, with higher scores indicating more severe clinical features.

[c]The Off-medication state was defined as a minimum 12-hour overnight withdrawal of antiparkinsonian drugs and a 24-hour withdrawal of prolonged-release formulations. The On-medication state was determined by both the patient and the clinician and indicated that the medication had been effective for at least 30 min after ingestion.

[d]The MDS-UPDRS III score of each hemibody side was calculated as the sum of the assessments for rigidity (item 3.3; assessment on one side includes evaluation of rigidity in the upper and lower limbs on a scale from 0 to 8, with higher scores indicating higher rigidity) plus bradykinesia (items 3.4 to 3,8; assessment on one side includes evaluation of the upper and lower limbs on a scale from 0 to 20, with higher scores indicating more severe bradykinesia) plus tremor (items 3.15 to 3.17; assessment on one side includes evaluation of rest tremor in the upper and lower limbs and of postural and kinetic tremor in the upper limb on a scale from 0 to 16, with higher scores indicating more severe tremor). Thus, the overall score for one side ranges from 0 to 44, with higher scores indicating a worse motor condition.

[e]The score on the MDS-UPDRS, part IV, for levodopa-related motor complications ranges from 0 to 24, with higher scores indicating more severe or disabling motor complications. The score is calculated as the sum of the scores for dyskinesia in the on-medication state (items 4.1 and 4.2; range, 0–8), for motor fluctuations (items 4.3 through 4.5; range, 0–12), and for dystonia in the off-medication state (item 4.6; range, 0–4).

[f]The PDQ-39 total score (Parkinson´s Disease Questionnaire) for assessment of quality of life (range 0–100 with higher score indicating worse quality of life and greater disability).

[g]EQ-5D 5 L severity index. The severity index (ISEV) was calculated from the score of the individual scores of the 5 dimensions; It is a percentage on a scale 0–100%, where 0 represents the absence of severity and 100 the maximum possible severity.

hBerg Balance Scale (BBS) is a fourteen-item objective measure that assesses static balance and fall risk in adults. Higher scores reveal better balance (range 41-56 indicating independent walking). A score of less than 45 indicates that individuals may be at greater risk of falling.

iLEDD refers to Levodopa Equivalent Daily Dose.

* *P*value < 0.05.

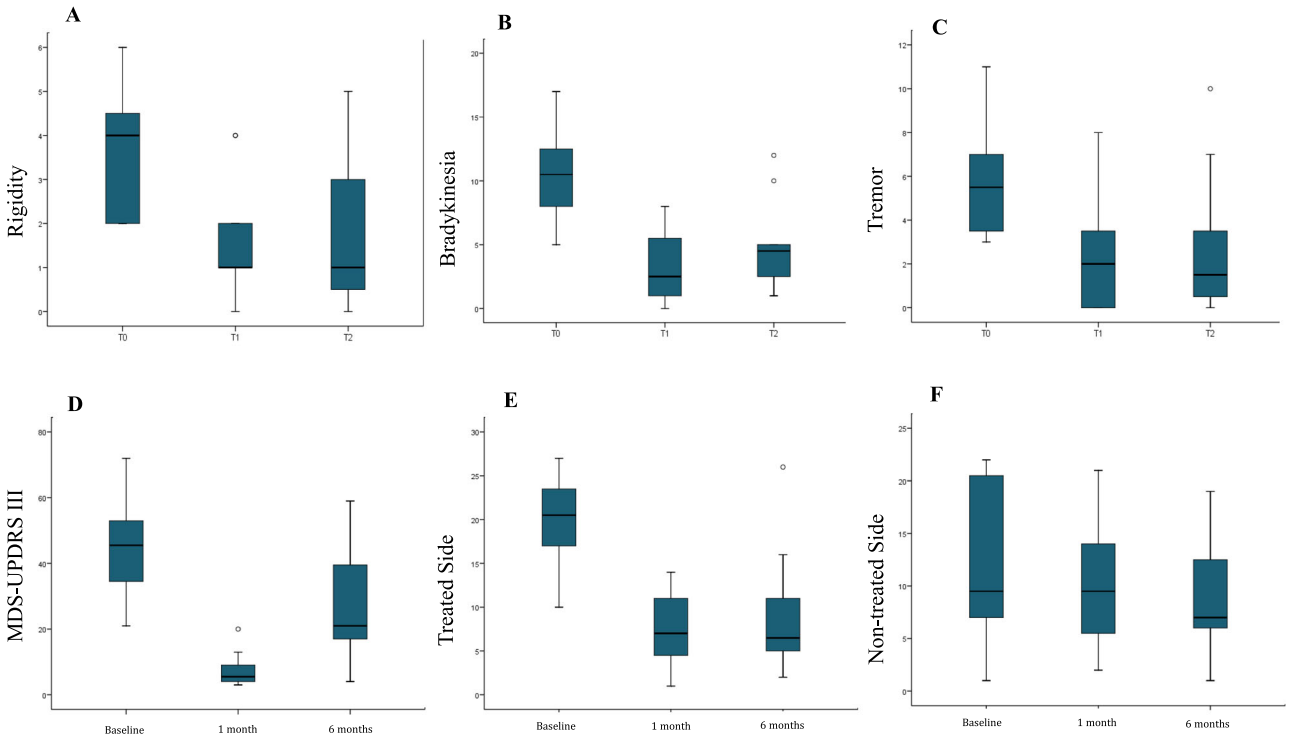

Fig. 2 | Effect of unilateral subthalamotomy on motor features during the 6-months follow-up. Off-medication rigidity (**A**), bradykinesia (**B**) and tremor (**C**) MDS-UPDRS III subscores of the treated side (contralateral to subthalamotomy) throughout the evaluation period. Off-medication MDS-UPDRS III (**D**), treated side (**E**) and non-treated side (**F**). Sustained improvement was seen after subthalamotomy. Off-medication state was defined as a minimum 12 h withdrawal of standard-release anti-parkinsonian drugs and a minimum of 24 h with prolonged release formulations. Continuous values are expressed in medians, empty dots refer to extreme values. *$p < 0.05$; **$p < 0.01$; ***$p < 0.001$.

Table 4 | Adverse Events

Subthalamotomy related Adverse Events — no, of patients (%)	Intraprocedure	1 week	1 month	6 months
Dysarthria	1 (8.3)	3 (25)	3 (25)	2 (20)
Facial asymmetry	2 (16.6)	2 (16.6)	1 (8.3)	1 (8.3)
Limb weakness	1 (8.3)	1 (8.3)	0 (0)	0 (0)
Paresthesia	0 (0)	1 (8.3)	1 (8.3)	1 (8.3)
Dysmetria	0 (0)	1 (8.3)	1 (8.3)	0 (0)
Subjective gait disturbance[a]	0 (0)	5 (41)	5 (41)	3 (25)
Objective gait disturbance	0 (0)	0 (0)	0 (0)	0 (0)
Total adverse events, according to severity — no, of events				
Mild	4	13	11	7
Moderate	0	0	0	0
Severe	0	0	0	0
Sonication related Adverse Events — no, of patients (%)				
Nausea	0 (0)			
Vomiting	0 (0)			
Dizziness	1 (5)			
Headache	1 (5)			
Head discomfort	1 (5)			

[a]Patients who reported "unsteady gait" were those who reported having less equilibrium while walking.
Dyskinesia adverse events data are available in Table 5.

Published results in MRgFUS subthalamotomy and the findings we report here, suggest a good balanced risk-benefit ratio. Fine-tuning the sonication process, allowing for a very focused lesion may optimized the impact on edema development and, consequently on the side effect ratio.

This study has limitations which prevent generalizability of the results: it is an open-label study, sample size is small and follow up is only of six months which may be insufficient to conclude persistence of benefit and delay recovery of side effects. Additionally, assessment of the correlation between lesion location and volume and clinical

Table 5 | Dyskinesia outcomes

Subject	Baseline assessment	Intraprocedural	One week		One month		Six months	
			Off	*On*	*Off*	*On*	*Off*	*On*
Patient 1	No	No	No	No	No	No	No	No
Patient 2	No	No	No	No	No	No	No	Yes (1)
Patient 3	No	No	No	No	No	No	No	No
Patient 4	Yes	Yes	No	Yes (1)	No	Yes (1)	No	Yes (1)
Patient 5	No	No	No	No	No	No	No	No
Patient 6	No	Yes	No	No	No	No	No	No
Patient 8	No	Yes	No	No	No	No	No	No
Patient 9	No	No	No	No	No	No	No	No
Patient 10	No	No	No	No	No	No	No	No
Patient 11	No	No	Yes (1)	Yes (2)	Yes (1)	Yes (1)	No	Yes (1)
Patient 12	No	No	Yes (1)	Yes (2)	No	Yes (1)	No	Yes (1)
Patient 13	Yes	Yes	No	Yes (2)	No	No	No	No

Values correspond to functional impact of dyskinesias as calculated through the Movement disorders society Unified Parkinson's Disease Rating Scale IV1, sub-item 4,2, It ranges from 0 to 4, 0= No dyskinesias or no impact from dyskinesias on activities or social interactions; 1= Dyskinesias impact on a few activities, but the patient usually performs all activities and participates in all social interactions during dyskinetic periods; 2= Dyskinesias impact on many activities, but the patient usually performs all activities and participates in all social interactions during dyskinetic periods; 3= Dyskinesias impact on activities to the point that the patient usually does not perform some activities or does not usually participate in some social activities during dyskinetic episodes; 4= Dyskinesias impact on function to the point that the patient usually does not perform most activities or participate in most social interactions during dyskinetic episodes.
Assessment of dyskinesias at baseline, Intraprocedural, 24 h to one week (immediate), one and six months was done in the corresponding follow-up visit.
"On" corresponds to dyskinesias that were observed during the on-medication assessment or that were reported by patients to occur in their daily life while under their regular medication.
"Off" corresponds to dyskinesias that were observed during the off-medication assessment or that were reported by patients to persist after a 12 h withdrawal of medication.

outcome is lacking. Post-treatment image analysis was not performed, and while the target was within the dorsolateral STN we cannot rule out involvement of other structures, such as the PTT. Despite these limitations, the results emphasize the importance of further research on this promising surgical option.

A subthalamotomy aiming for the smallest lesion possible may be a feasible alternative for improving all cardinal features of PD, with a favorable risk/benefit profile. However, the limited experience with the technique emphasizes the need for a learning process and ongoing research. Understanding the functional pathways and interrelations of the STN is crucial for refining optimal targets in functional neurosurgical approaches. In summary, our results align with the experiences of other groups, positioning this surgical procedure as a viable option for medical refractory PD. Future research will undoubtedly enhance the understanding and application of MRgFUS subthalamotomy in the management of Parkinson's disease.

Data availability

The datasets used and/or analyzed during the current study available from the corresponding author on reasonable request.

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Author contributions

1. Research Project: A Conception, B. Organization, C. Execution; 2 Statistical Analysis A. Design, B. Execution, C Review and Critique; 3. Manuscript Preparation: A. Writing the first draft, B: Review and Critique. MCR 1 A, 1B, 1 C, 2 A, 2B, 3 A. ISB 1 A, 1B, 1 C, 2 C, 3B. RCS 1 A, 1B, 2 C, 3B. CMM 1 A, 1B, 1 C, 2 C, 3B. MLL 1 A, 1B, 2 C, 3B. JLLG 1 A, 1B, 2 C, 3B. LRR, 1 C, 1B. JPG 1 A, 1B, 2 C, 3B. AGM 1 A, 1B, 2 C, 3B. AML 2 C, 3B. RBM 1 A, 1B, 2 C, 3B. IMT 1 A, 1B, 2 C, 3B.

Competing interests

The authors declare no competing interests.

Additional information

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