Archival Report

Biological Psychiatry

Long-Term Safety and Efficacy of Focused Ultrasound Capsulotomy for Obsessive-Compulsive Disorder and Major Depressive Disorder

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ABSTRACT

BACKGROUND: Magnetic resonance–guided focused ultrasound (MRgFUS) trials targeting the anterior limb of the internal capsule have shown promising results. We evaluated the long-term safety and efficacy of MRgFUS capsulotomy in patients with obsessive-compulsive disorder (OCD) and major depressive disorder (MDD).

METHODS: This phase 1, single-center, open-label study recruited patients with treatment-resistant OCD and MDD. Outcomes were measured 6 months, 12 months, and 18 to 24 months (long term) after MRgFUS capsulotomy. Neuropsychological testing and neuroimaging were conducted at baseline and 12 months postoperatively. The primary outcome was safety. The secondary outcome was clinical response, defined for OCD as a ≥35% improvement in Yale-Brown Obsessive Compulsive Scale scores and for MDD as a ≥50% reduction in Hamilton Depression Rating Scale scores compared with baseline.

RESULTS: No serious adverse effects were registered. In patients with OCD (n = 15), baseline Yale-Brown Obsessive Compulsive Scale scores (31.9 ± 1.2) were significantly reduced by 23% (p = .01) at 6 months and 35% ($p < .0001$) at 12 months. In patients with MDD (n = 12), a 26% and 25% nonsignificant reduction in Hamilton Depression Rating Scale scores (baseline 24.3 ± 1.2) was observed at 6 months and 12 months, respectively. Neuropsychological testing revealed no negative effects of capsulotomy. In the OCD and MDD cohorts, we found a correlation between clinical outcome and lesion laterality, with more medial left–placed lesions (OCD, p = .08) and more lateral right–placed lesions (MDD, $p < .05$) being respectively associated with a stronger response. In the MDD cohort, more ventral tracts appeared to be associated with a poorer response.

CONCLUSIONS: MRgFUS capsulotomy is safe in patients with OCD and MDD and particularly effective in the former population.

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Magnetic resonance–guided focused ultrasound (MRgFUS) involves the focal delivery of ultrasound with the goal of creating discrete intracranial lesions (1–5). This technique has several advantages over other ablative modalities. First, it is incisionless and does not require skull opening. Second, it allows real-time thermometry and lesion volume estimation. Finally, patients may be evaluated for efficacy and side effects during the procedure. Historically, lesions for psychiatric disorders were shown to induce side effects that were sometimes noted immediately after the procedure, including apathy and urinary incontinence (6). Examining patients during MRgFUS may help to detect these events while lower-dose sonications are delivered, avoiding permanent damage.

In psychiatry, MRgFUS trials have targeted the anterior limb of the internal capsule (ALIC) (1). Initial results have shown important clinical improvements in patients with obsessive-compulsive disorder (OCD) and major depressive disorder (MDD) (7–9). Most studies, however, have only followed patients in the short term. After either radiofrequency (RF) lesions or deep brain stimulation, clinical results in patients with several psychiatric disorders tend to become more pronounced over time. In our initial report, we presented 6- to 12-month follow-up data on a small number of patients (7). We now report long-term follow-up results in an expanded cohort, correlating clinical scores with the location of the lesions and fibers potentially interrupted by MRgFUS.

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METHODS AND MATERIALS

Participants

This prospective, phase 1, open-label study (NCT03421574, NCT03156335) was approved by the Sunnybrook Research Ethics Board. Patients with severe treatment-refractory OCD and MDD who met inclusion/exclusion criteria (Table S1) were offered capsulotomy (7).

Clinical Outcomes

The primary outcome of our trial was safety, measured by an unstructured detailed clinical evaluation for potential adverse events (7). Patients were directly inquired as to whether they presented cognitive effects or worsening of psychiatric symptoms. Particular attention was paid to suicidality. Whenever patients were accompanied by family members during follow-up appointments, the latter were also inquired about potential side effects. The secondary outcome for OCD was clinical response, defined as a ≥35% improvement in Yale-Brown Obsessive Compulsive Scale (YBOCS) scores compared with baseline (10). Partial response was defined as ≥25% to <35% improvement. For MDD, treatment response was defined as a ≥50% reduction in the 17-item Hamilton Depression Rating Scale (HAMD-17) (11). Other secondary outcomes were the percentage of patients who responded to capsulotomy and changes in quality of life, as measured with the Quality of Life Enjoyment and Satisfaction Questionnaire (QLESQ) (12). Additional scales administered to patients with OCD included the HAMD-17, Beck Depression Inventory (BDI), Beck Anxiety Inventory, and Obsessive-Compulsive Inventory (OCI). In patients with MDD, additional scales were the Montgomery–Åsberg Depression Rating Scale and BDI. Scales were administered at baseline, 6 months, 12 months, and the last follow-up appointment (18–24 months). Medication changes in the postoperative period were allowed at the discretion of the treating psychiatrists. Patients followed over the long term were often those treated first in our series. No patients were lost to follow-up in our trial.

Surgical Procedure

Our MRgFUS capsulotomy technique has been previously described in detail (2,7,13). Briefly, a Cosman-Roberts-Wells headframe (Integra) was used and the patient placed under local anesthesia, following a complete head shave. Surgery was performed under conscious sedation within a 3T MR imaging suite using the ExAblate 4000 system (InSightec). The ventral aspect of the ALIC was targeted by direct visualization (7). Anatomical images included a T1-weighted 3-dimensional fast spoiled gradient echo sequence with 176 slices (echo time = 2.94 ms, repetition time = 7.65 ms, matrix size = 265 × 265, resolution = 0.94 × 0.94 × 1.2 mm) (7). General coordinates were ∼7 mm anterior to the anterior commissure, 12 mm lateral to the midline, at the level of the midcommissural plane (2,7). Low-powered test sonications (40–45 °C) were initially conducted to align the focus and confirm targeting accuracy. These were followed by higher-powered sonications (targeting >53 °C), which were repeated based on temperature rise, estimated thermal dosing, and patient tolerability. Repeating sonications with focal temperatures ≥53 °C and not using much higher temperatures is a strategy used in our center to initially create and consolidate lesions while controlling the thermal dose. As the temperature curve often flattens at high temperatures, we find the thermal dose to be a more accurate estimate of the lesion size than peak temperatures (14,15). It is also used for thalamotomies (15) and unrelated to the fact that we are targeting the ALIC. The accuracy of lesion targeting was confirmed with real-time thermography and T2-weighted imaging conducted after high-powered sonications. Beginning in December 2021, after the safety of single lesions was well established (16), our strategy was modified to include a second contiguous lesion 2 mm dorsal and slightly lateral to the ventral one, along the axis of the internal capsule. This was only attempted in cases in which bilateral ventral lesions were created without reaching maximal energy and power requirements. Four patients with OCD and 1 patient with MDD received double lesions. After failing to create thermal lesions in 8 patients, we have started to select patients with skull density ratio (SDR) ≥0.45 and, if possible, ≥0.5. All patients with an SDR ≥0.5 in our series were successfully treated.

Neuropsychology

To assess cognitive changes following MRgFUS, we administered a battery of neuropsychological tests at baseline and 12 months following treatment, except for 1 patient who was tested 6 months posttreatment. The following domains were assessed: processing speed (Symbol Digit Modalities Test), executive function (Delis-Kaplan Executive Function System Sorting Test), verbal memory (California Verbal Learning Test–Second Edition), and nonverbal memory (Brief Visuospatial Memory Test–Revised). The battery also included a measure of self-report changes in frontal behaviors, including apathy, executive dysfunction, and disinhibition [Frontal Systems Behavior Scale: self-report scale (7)]. The Wechsler Test of Adult Reading was administered at baseline to provide a measure of estimated premorbid intellectual functioning.

Location of Lesions and Fiber Tracking

Lesions were manually traced using a postoperative day 1 T1-weighted magnetic resonance imaging scan, to include the necrotic core but not surrounding edema (17). Lesion volumes in native space were calculated using FSL (18). Postoperative MR images for each patient were normalized to Montreal Neurological Institute 2009b Nonlinear Asymmetric Space (Montreal Neurological Institute space) using Advanced Normalization Tools (19). The x/y/z coordinate of the centroid of each normalized lesion was calculated using FSL.

To compare lesion location with clinical response, response-map images were generated using an approach based on that described by others (20). Each patient's lesions were scaled based on how the patient responded relative to the group mean. For example, if an OCD patient's YBOCS improved by 25%, which is 15% below the group mean of 40%, their binarized lesion would be multiplied by a weighting factor of −0.15. Weighted lesions were then summed, averaged, and thresholded by a lesion frequency map, such that the final response maps represented voxels lesioned in at least 90% of patients. We also utilized a second probabilistic lesion-

mapping technique modified from the probabilistic stimulation mapping described by others (21). Demeaned response values were normalized by lesion volume, averaged, and masked by lesion frequency maps at 90%. At each voxel, a Wilcoxon signed rank test was then carried out, generating a p-map in which significant voxels suggest that a lesion is associated with above-average response. In order to compare tracts associated clinical response, normative tractography was performed (22). Response maps were thresholded at 99% and used to seed streamlines using DSI-Studio (https://dsi-studio.labsolver.org/). Deterministic tractography was performed with quantitative anisotropy (23). The following tracking parameters were held constant: angular threshold = 40, step size = 0.4 mm, minimum length = 10 mm, maximum length = 200 mm, seed number = 100,000.

Statistical Analyses

Because the distribution of YBOCS scores at baseline did not follow a normal distribution (Kolmogorov-Smirnov test, $p = .02$) and our sample size was relatively small, comparisons of secondary outcome over time were conducted with a Friedman test. The chi-square test was used to compare the percentage of responders at different follow-up periods. The Mann-Whitney *U* test was used to compare the percentage of response in patients with single or double lesions and SDRs, and *t* tests were used to compare pre- and posttest neuropsychological data. Lesion volumes between sides and lesioning approaches (single vs. double) were compared using the Wilcoxon signed rank test. Unless otherwise specified, data are presented as mean and standard error. Percentages were derived from the ratio of preoperative mean values for each scale relative to baseline.

RESULTS

Baseline Demographics

Between June 2017 and January 2023, 44 patients were evaluated by our multidisciplinary psychiatric surgery team in consideration of bilateral MRgFUS capsulotomies. Eight patients who underwent a computed tomography scan were excluded prior to treatment due to low SDR (<0.40), and 1 patient did not return for the appointments. Thirty-five patients were assigned to treatment. In 7 of these individuals, heating was insufficient to create a lesion (all with SDR scores <0.45). In 1 additional patient, the postoperative lesion was <1 mm. These patients were excluded from analysis, as they did not receive the intended treatment. Overall, 18% of the patients initially enrolled had an SDR <0.40 and were not amenable for treatment. Another 18% of patients were excluded after receiving sonications that could not properly raise the thermal dose. None of these patients had an SDR >0.50.

Because failure to properly sonicate the patients was related to technical difficulties, we report a per-protocol analysis of 27 patients (15 OCD, 12 MDD) with lesions larger than 2 mm, 19 of whom were followed over the long term (12 OCD, 7 MDD). In 1 patient, only a right-sided lesion could be made in an initial lesion attempt. After 6 months of minimal response, the procedure was repeated for contralateral lesioning. The follow-up regimen was considered to begin after the second lesion. All patients in our series had lesions in the ventral aspect of the capsule, near the nucleus accumbens (Figure 1). In 4 patients with OCD and the 1 patient with depression, 2 lesions were made per hemisphere along the axis of the internal capsule. Results of all OCD patients were grouped for analysis. The SDR in patients with OCD (0.55 ± 0.03) was similar to that in patients with depression (0.56 ± 0.02) ($p = .57$).

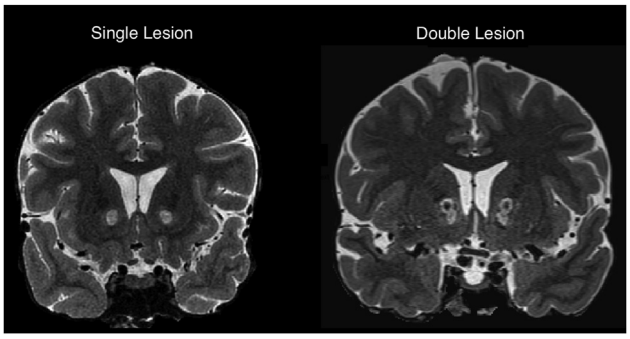

Figure 1. Coronal magnetic resonance imaging showing single and double lesions in the anterior capsule.

Demographics and medication changes are presented in Tables S2 and S3. The mean age of patients with OCD and depression was 41.9 ± 3.6 years and 46.7 ± 3.6 years, respectively. Disease duration at the time of surgery was 22.7 ± 2.7 years and 25.2 ± 2.3 years, respectively. Forty percent of patients with OCD and 50% of patients with depression were female.

Adverse Effects

No serious adverse effects were registered in our trial. Nonserious adverse events occurred in 7 patients. These included transient headaches that lasted for a few hours after the procedure and pin-site swelling. Three patients with MDD reported a subjective sensation of fogginess in the immediate postoperative period that sometimes lasted for a few weeks. No clinical signs or symptoms of mania/hypomania were observed. No patient presented with new or active suicidal ideation during the study follow-up.

Outcome

The mean pretreatment YBOCS score in the 15 patients with OCD was 31.9 ± 1.2. In this group, a significant effect of capsulotomy was observed ($p < .0001$). Six months and 12 months after surgery, YBOCS scores were reduced by 23% (24.6 ± 1.7; $p = .01$) and 35% (20.7 ± 1.7; $p < .0001$) compared with baseline, respectively (Figure 2, Table 1). At 6 months, the percentage of responders, partial responders, and nonresponders was 27% ($n = 4$), 13% ($n = 2$), and 60% ($n = 9$), respectively. At 12 months, 47% ($n = 7$) of patients were considered to be responders, 13% ($n = 2$) were partial responders, and 40% ($n = 6$) nonresponders (Figure 1). Despite the substantial increase in responders at 12 months compared with 6 months, values did not reach significance ($p = .49$). A significant clinical improvement was also observed in HAMD-17 (32%) and Beck Anxiety Inventory scores (33%) at 12 months compared with baseline (Table 1). Quality-of-life

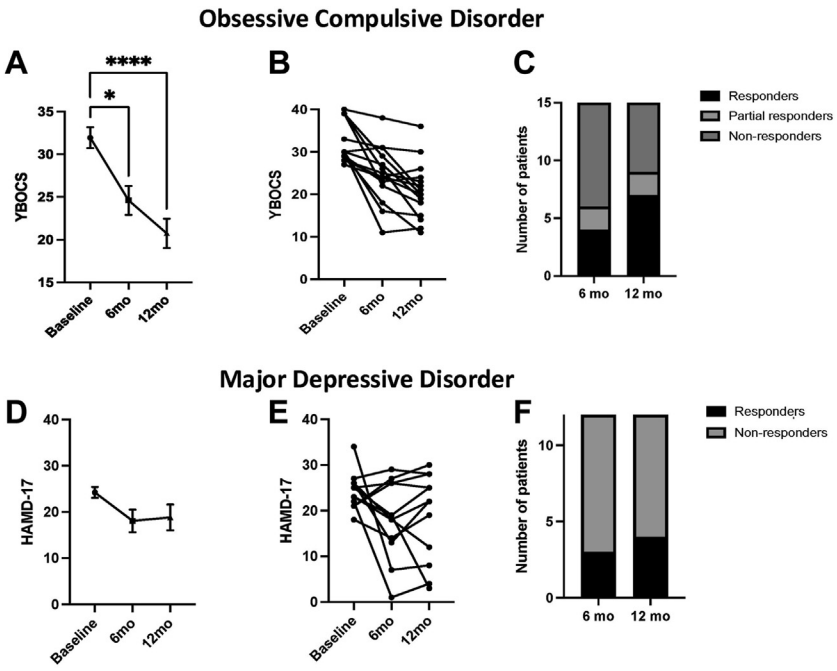

Figure 2. Outcome of focused ultrasound capsulotomy in patients with obsessive-compulsive disorder (OCD) and major depressive disorder (MDD). Average **(A)** Yale-Brown Obsessive Compulsive Scale (YBOCS) scores and **(D)** 17-item Hamilton Depression Rating Scale (HAMD-17) scores at 6 months' and 12 months' follow-up in patients with OCD and MDD. Individual **(B)** YBOCS and **(E)** HAMD-17 scores over time in patients with OCD and MDD. The number of responders, partial responders, and nonresponders in patients with **(C)** OCD and **(F)** MDD. *$p < .05$, ****$p < .0001$.

changes measured with QLESQ were only modest and did not reach statistical significance ($p = .55$).

In patients with MDD ($n = 12$), the mean pretreatment HAMD-17 score was 24.3 ± 1.2. No significant effect of capsulotomy was observed over time ($p = .35$) (Figure 2, Table 2). At 6 months and 12 months, mean HAMD-17 scores were nonsignificantly reduced by 26% and 25% compared with baseline, respectively. Despite the increase in responders at 12 months ($n = 4$) compared with at 6 months ($n = 3$; 33% vs. 25%), values did not reach significance ($p = .65$) (Figure 2). Two patients were in remission (HAMD-17 score <8) at 12 months (Table S3). Changes observed in other clinical scales, including the QLESQ, were also not significant ($p = .77$) (Table 2).

Long-Term Outcome

Nineteen patients were followed for 18 to 24 months. The mean pretreatment YBOCS score in 12 patients with OCD was 31.8 ± 1.4. In this group, a significant improvement was observed over time ($p < .0001$). Postoperative YBOCS scores at 6 months, 12 months, and over the long term were reduced by 19% (25.7 ± 1.7; $p = .16$), 32% (21.6 ± 1.9; $p = .002$), and 47% (16.9 ± 3.0; $p < .0001$), respectively, compared with baseline (Figure 3, Table 1). Though improvements were seen in most scales when long-term outcomes were compared with those achieved at 6 months and 12 months, significant results were only recorded when HAMD-17 scores (43%) over the long term were compared with baseline (Table 1). The percentage of responders at 6 months, 12 months, and over

Table 1. Outcome of Capsulotomy in Patients With Obsessive-Compulsive Disorder

Patients	Follow-Up	YBOCS	HAMD-17	BDI	BAI	OCI	QLESQ
All Patients, $n = 15$	Baseline	31.9 ± 1.2	18.3 ± 2.1	28.8 ± 3.1	30.8 ± 4.0	84.1 ± 6.3	40.3 ± 3.5
	6 mo	24.6 ± 1.7 (23%)[a]	15.2 ± 1.8 (17%)	24.1 ± 2.9 (16%)	25.3 ± 3.7 (18%)	70.2 ± 5.8 (17%)	40.8 ± 3.2 (1%)
	12 mo	20.7 ± 1.7 (35%)[b]	12.5 ± 1.6 (32%)[a]	22.1 ± 2.8 (23%)	20.5 ± 2.9 (33%)[a]	57.8 ± 7.3 (31%)	42.7 ± 3.3 (6%)
Long-Term Patients, $n = 12$	Baseline	31.8 ± 1.4	17.8 ± 2.5	28.6 ± 3.6	29.4 ± 4.5	82.1 ± 7.6	39.6 ± 3.6
	6 mo	25.7 ± 1.7 (19%)[a]	16.3 ± 2.1 (8%)	25.6 ± 3.5 (10%)	27.2 ± 3.9 (7%)	71.5 ± 6.7 (13%)	38.1 ± 3.5 (−4%)
	12 mo	21.6 ± 1.9 (32%)[b]	13.0 ± 1.9 (27%)	22.3 ± 3.2 (22%)	20.7 ± 3.4 (30%)	58.3 ± 8.6 (29%)	41.2 ± 3.8 (4%)
	Long-term	16.9 ± 3.0 (47%)[b]	10.2 ± 2.0 (43%)[a,c]	20.1 ± 3.9 (30%)	21.4 ± 4.3 (27%)	59.7 ± 10.3 (27%)	45.9 ± 4.9 (16%)

Values are mean ± SE. Percentages represent the percent change compared with baseline.

BAI, Beck Anxiety Inventory; BDI, Beck Depression Inventory; HAMD-17, 17-item Hamilton Depression Rating Scale; OCI, Obsessive-Compulsive Inventory; QLESQ, Quality of Life Enjoyment and Satisfaction Questionnaire; YBOCS, Yale-Brown Obsessive Compulsive Scale.

[a]$p \leq .05$ compared with baseline.

[b]$p \leq .01$ compared with baseline.

[c]$p \leq .05$ compared with 6 months.

Table 2. Outcome of Capsulotomy in Patients With Major Depressive Disorder

Patients	Follow-Up	HAMD-17	MADRS	BDI	QLESQ
All Patients, *n* = 12	Baseline	24.3 ± 1.2	34.7 ± 1.7	38.7 ± 2.5	31.1 ± 1.6
	6 mo	18.1 ± 2.4 (26%)	23.7 ± 3.7 (32%)	29.4 ± 4.1 (24%)	38.9 ± 3.3 (25%)
	12 mo	18.3 ± 2.8 (25%)	25.2 ± 4.8 (27%)	29.1 ± 4.4 (25%)	36.4 ± 3.5 (17%)
Long-Term Patients, *n* = 7	Baseline	22.0 ± 0.9	33.1 ± 1.7	35.4 ± 3.5	32.0 ± 2.5
	6 mo	16.9 ± 3.3 (23%)	22.6 ± 5.0 (32%)	27.7 ± 5.7 (22%)	38.9 ± 4.0 (21)
	12 mo	21.4 ± 3.2 (3%)	30.0 ± 5.7 (9%)	31.4 ± 5.2 (11%)	33.6 ± 4.2 (5%)
	Long-term	15.4 ± 4.1 (30%)[a]	21.7 ± 6.9 (34%)	15.4 ± 1.3 (56%)[a]	42.1 ± 4.4 (32%)

Values are mean ± SE. Percentages represent the percent change compared with baseline.

BDI, Beck Depression Inventory; HAMD-17, 17-item Hamilton Depression Rating Scale; MADRS, Montgomery–Åsberg Depression Rating Scale; QLESQ, Quality of Life Enjoyment and Satisfaction Questionnaire.

[a]Trend toward significance compared with baseline.

the long term was 25% (*n* = 3), 42% (*n* = 5), and 67% (*n* = 8), respectively, and the percentage of partial responders was 8% (*n* = 1), 16% (*n* = 2), and 0% (*n* = 0), respectively. The percentage of nonresponders at these respective time frames was 67% (*n* = 8), 42% (*n* = 5), and 33% (*n* = 4) (Figure 3, Table 1). Despite the substantial increase in responders over time, values did not reach significance (*p* = .21). A long-term improvement was observed in most scales (e.g., values recorded at 18–24 mo were lower than those recorded at 6 mo and 12 mo), but only HAMD-17 scores reached significance (Table 1). Quality of life increased by 16%, but values did not reach statistical significance (*p* = .13).

In patients with MDD (*n* = 7), the mean pretreatment HAMD-17 score was 22.0 ± 0.9. A general trend toward significance was recorded over time (*p* = .08) (Figure 3). Yet, reductions in scores recorded at 6 months (23%; 16.9 ± 3.3), 12 months (3%; 21.4 ± 3.2), and over the long term (30%; 15.4 ± 4.1) were not found to be significant compared with baseline. Despite the substantial increase in responders at long-term follow-up (43% [*n* = 3]) compared with 12 months (14% [*n* = 1]) and 6 months (29% [*n* = 2]), values did not reach significance (*p* = .50) (Figure 3). Additional scales have shown an overall improvement over time, but a trend toward significance was only recorded in the BDI (56%) (Table 2). Quality of life increased by 32%, but values did not reach significance (*p* = .25).

No long-term responder relapsed during the study follow-up.

Single Versus Double Lesions

In patients with OCD, no differences in the percentage of improvement were found between patients treated with single (*n* = 11) or double (*n* = 4) lesions at 6 months (24% vs 19%;

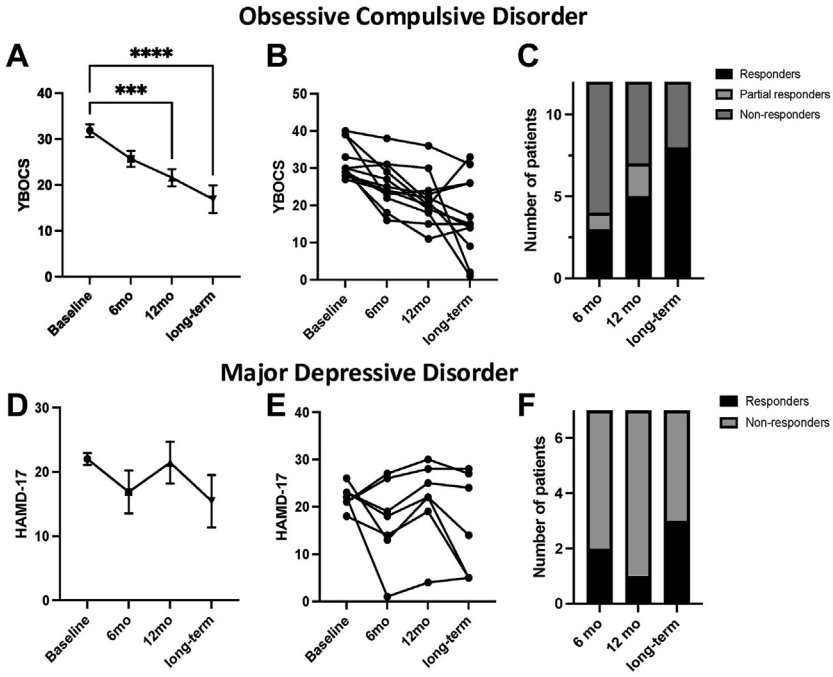

Figure 3. Outcome of focused ultrasound capsulotomy in patients with obsessive-compulsive disorder (OCD) and major depressive disorder (MDD) followed over the long term. Average **(A)** Yale-Brown Obsessive Compulsive Scale (YBOCS) scores and **(D)** 17-item Hamilton Depression Rating Scale (HAMD-17) scores at 6 months, 12 months, and over the long term in patients with OCD and MDD. Individual **(B)** YBOCS and **(E)** HAMD-17 scores over time in patients with OCD and MDD. The number of responders, partial responders, and nonresponders in patients with **(C)** OCD and **(F)** MDD. ***$p < .001$, ****$p < .0001$.

p = .93) or 12 months (36% vs 29%; p = .66). As only 1 patient with depression was treated with double lesions, statistical analyses were not conducted. The percentage of improvement in patients with depression treated with single lesions (n = 11) at 6 months and 12 months was 23% and 20%, respectively. The percentage of improvement in the depressed patient with double lesions at 6 months and 12 months was 22% and 4%, respectively. Three of the 4 patients with OCD treated with double lesions were followed over the long term. In this subgroup of patients, the percentage of responders, partial responders, and nonresponders at 6 months was 33%, 0%, and 67%, respectively. At 12 months, 33% were responders, 33% were partial responders, and 33% were nonresponders. At long-term follow-up, all patients responded to treatment. The only patient with depression treated with double lesions responded to treatment over the long term.

Neuropsychology

Baseline and follow-up neuropsychological data were available for 12 patients with OCD and 12 patients with MDD. Among the 3 patients with OCD who did not complete the testing (2 nonresponders and 1 responder), 2 declined to join in-person sessions and 1 patient was unable to attend due to a scheduling error on the patient's part. There were no negative effects of MRgFUS capsulotomy on cognitive or behavioral functioning (Tables S4 and S5). Notably, significant improvements were observed on select tests of cognition in both patient groups. Furthermore, patients with OCD endorsed less apathy postoperative compared with baseline on the Frontal Systems Behavior Scale.

Lesion Analysis

The mean lesion volume on the right and left hemispheres was 117.8 ± 13.1 mm^3 and 111.1 ± 6.91 mm^3, respectively (p = .83). The mean volume of single and double lesions was 88.4 ± 8.4 mm^3 and 223.8 ± 18.0 mm^3, respectively ($p < .01$). When the OCD and MDD cohorts were considered separately, there was no significant correlation between lesion volume and clinical response (Figure S1). When these cohorts were considered together, however, a significant correlation was found between right-sided lesion volume and clinical response ($p < .05$) (Figure S1).

In the OCD cohort, we found a tendency for more medial lesions to correlate with stronger clinical response (p = .08) (Figure 4A). In the MDD cohort, there was a significant relationship between the right mediolateral coordinate and the HAMD-17 response ($p < .05$). Both yielded significant clusters using the probability-mapping technique.

Tracts seeded from the 99th percentile of the lesion response maps are displayed in Figure 4B. Clearly distinguished positive and negative tracts were not revealed for OCD, whereas more ventral tracts appeared to be associated with a poorer response compared with more dorsal/superior tracts in the MDD cohort.

DISCUSSION

Our study suggests that MRgFUS is safe in patients with OCD and MDD and is particularly effective in the former population. In patients with severe, chronic, and highly refractory OCD and depression, capsulotomy led to gradual and sustained improvements over 12 months to 24 months.

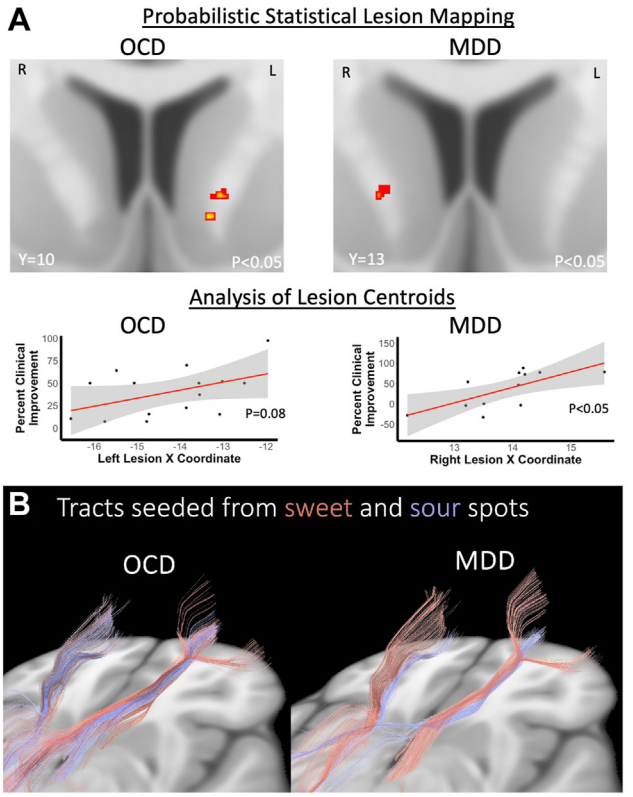

Figure 4. Response maps and tractography in patients with obsessive-compulsive disorder (OCD) and major depressive disorder (MDD) treated with focused ultrasound capsulotomy. **(A)** Correlations were found between the left (L) x-coordinate and clinical response in patients with OCD and the right (R) x-coordinate and clinical response in patients with MDD. **(B)** No distinguished positive and negative tracts were found in patients with OCD. In the MDD cohort, more ventral tracts appeared to be associated with poorer response.

In our trial, not only was the incidence of side effects minimal, but neuropsychological testing revealed no adverse cognitive effects. Indeed, performance on several tests improved. Given the open-label design of our study, it is unclear whether this reflects practice effects or true improvements. Furthermore, the latter could be due to a direct circuit-level effect on cognitive processes, off-target benefits of reduced symptomatology, or an indirect effect of reduced medication usage that may occur following symptomatic amelioration. The precision of MRgFUS ablation allowed us to make relatively smaller lesions compared with historical RF lesions. We believe that doing so helped avoid the cognitive sequelae previously described in capsulotomy patients (24). A recent RF series noted a few occurrences of permanent frontal lobe dysfunction (apathy or disinhibition), particularly in patients with larger lesions (25). This is the opposite of the improvements observed in our study. Despite reports of transient urinary incontinence, somnolence, and amotivation in OCD patients treated with RF and gamma knife, recent studies have shown either no neuropsychological changes (26) or an improvement in

several cognitive functions (e.g., fluency, inhibitory function, set shifting, decision making, IQ scores) after capsulotomy with and without a rehabilitation program (27).

Therapeutic effects of both lesional and deep brain stimulation treatments for OCD and MDD have been known to gradually accrue over 3 months to 12 months, or even longer in some cases (9,28,29). When analyzing our data, we noticed a particular trend in patients with OCD. Though a few nonresponders converted into responders, the main changes in outcome were related to the fact that most partial responders became responders, and that responders had a progressive improvement over time (Table S2). In contrast, patients with depression tended to present more protracted responses, with a substantial reduction in clinical scores only being documented at long-term (Table S3).

Clinical outcomes in our study are comparable with other published open-label series for OCD and are on the lower end of the range reported in MDD studies. In OCD, a large gamma-knife capsulotomy series reported a long-term response rate of 56% (28). A meta-analysis comparing ablative procedures (both capsulotomy and cingulotomy) and deep brain stimulation for OCD noted long-term response rates of 53% and 57%, respectively (30). On the other hand, 2 open-label series reporting the effects of RF capsulotomy on patients with MDD noted long-term response rates of 54% and 60% (31,32), seemingly superior to our response rate. An explanation for this lower response rate in MDD is yet to be determined but further emphasizes the importance of identifying preoperative predictors of response (33).

In several fields of functional neurosurgery, outcome metrics have progressively changed from clinical variables to the assessment of quality of life. As factors driving the latter are often complex, a better appraisal of quality-of-life changes was only possible when the clinical response was well characterized. In our study, symptomatic improvements recorded with validated scales, particularly in OCD, were not associated with parallel changes in QLESQ scores. One possibility is that the clinical improvement obtained in patients with severe and very severe OCD and MDD recruited in our trial may not have been sufficient to drive quality-of-life changes of a similar magnitude. However, it is also possible that patients may have underappreciated some of the improvements acquired when executing daily activities. Self-reported metrics, such as the QLESQ, BDI, and OCI, tend not to closely follow clinician-administered scales, such as the YBOCS and HAMD-17. Anecdotally, family members accompanying the patients during regular appointments often stressed that they were more participative and engaged at home and socially compared with prior to the procedure. Unfortunately, the data captured in our study do not allow a clear identification of potential reasons for the discrepancy between clinical and quality-of-life scores.

With the current iteration of commercially available high-intensity MRgFUS devices, creating bilateral capsulotomy lesions is highly feasible in patients with an SDR >0.5 but more challenging for those with an SDR <0.5. The likelihood of successful lesioning in patients with an SDR in this range is likely related to additional skull factors beyond the SDR, including skull thickness and overall skull shape (5). Patients with an SDR <0.5 should be cautioned that there is a chance of insufficient heating and therefore incomplete lesioning. Although the current use of MRgFUS capsulotomy may only be helpful for up to 70% of the population, the future use of newer techniques of lesioning, such as microbubble cavitation lesioning (34), may increase the number of patients suitable for the procedure.

In our trial, multiple scales were intentionally recorded to gather as much information as possible. While capsulotomy improved HAMD-17 and BDI scores in both the MDD and OCD groups, improvements on the BDI tended to be less prominent. This discrepancy is a known occurrence, related in part to the fact that the BDI is a patient-reported questionnaire, while the HAMD-17 is a clinician-administered scale. More severely depressed patients tend to underreport their symptoms, while less severely depressed patients tend to overreport their symptoms, reducing expected change scores on the BDI (35). Furthermore, on factor-analysis items of the BDI tend to load on a single factor, likely related to negative self-perception, whereas the HAMD-17 loads on to several factors (neurovegetative, mood, anxiety) (36). A similar trend is present in YBOCS versus OCI analyses (YBOCS being clinician administered and OCI being self-reported). Not surprisingly, self-reported measures, such as the BDI and OCI, are more correlated with quality-of-life measures than clinician-administered metrics (37). While acknowledging that any scale that aims to quantify the severity of a psychiatric illness will have flaws, our group and others continue to search for improved ways to measure outcome in these patients (38,39).

In our trial, we found no correlation between lesion volume and response when considering OCD and MDD cohorts separately. This is consistent with lesion analyses from 3 other OCD capsulotomy cohorts treated using MRgFUS (40), RF (25), and gamma knife (20), in which lesion volume was not correlated with response. However, a recent cohort of patients treated using laser interstitial thermal therapy employed comparatively large lesion volumes, based on earlier findings suggesting stronger responses (41). When combining our OCD and MDD cohorts, we detected a slight signal toward larger right-sided lesions correlating with better response. The lesions produced in our trial were smaller than those in the previously mentioned studies, although response rates in our OCD cohort were similar. Along this line, we did not observe significant differences in response when patients treated with single and double MRgFUS lesions were compared. We note, however, that all patients with double lesions in our series responded to treatment over the long term. That said, the number of individuals in this subgroup of patients was too small for any meaningful conclusions. We suspect that there is a minimum lesion volume necessary to disrupt the abnormal circuitry driving OCD and/or MDD, but higher volumes may be associated with more sustainable results. However, this is yet to be confirmed.

In terms of lesion location, the literature suggests a trend toward targeting the ventral-most aspect of the capsule, especially in OCD (28,42,43). In a large gamma knife cohort, a single shot to the mid-ALIC yielded a very low response in the initial 15 patients treated. As a result, a double-shot technique covering the ventral and mid-ALIC was employed (28). A later analysis including a subset of gamma knife–treated patients suggested that in fact the mid-ALIC is still the target most associated with treatment response (20). This finding was also demonstrated in a post hoc analysis of capsulotomy lesions

from the first published MRgFUS trial (40). It is difficult to know if these findings represent a true lesioning sweet spot or a trend toward larger lesions having better clinical outcomes (surgeons generally lesion the ventral-most capsular region and then expand the lesion dorsally).

Limitations

Although our series is the largest published to date, it has a few caveats. First, the number of patients is relatively small. Second, patients with single and double lesions were grouped for analysis. Third, only patients with lesions larger than 2 mm were included. Our initial patients were treated with a single-shot ventral capsulotomy for the preliminary assessment of safety. Once this was confirmed, treatment with double-shot lesions was commenced. Though we found no substantial differences in outcome between lesioning strategies, treatment with double-shot lesions has to be considered with caution, as the number of double lesions in our study was small. MRgFUS has introduced a new way of performing a long-established treatment to the field. However, it is important to continue perfecting this therapy. Our trial only included patients with a skull density ratio >0.4. As the anterior capsule is more distant from the center of the brain than the thalamus, values above this threshold are key for the successful development of lesions in the former target. As described previously, this problem should be mitigated and MRgFUS should be potentially offered to more patients when new technology is implemented to avoid skull density–related difficulties and facilitate the development of lesions with lower power. Our series was preliminary and had an open label design. Though blinded studies comparing the effects of capsulotomy with sham lesions are of importance, several parameters derived from studies such as ours are crucial for the proper design of randomized clinical trials. Based on our data, we can better define aspects of lesion location and volume, the time frame required for a clinical response, and the safety of the procedure.

Conclusions

We show that MRgFUS is safe and potentially effective in patients with refractory OCD. In MDD, the procedure was shown to be safe and not as effective in most patients. These results are encouraging and need to be corroborated in additional studies. The optimal volume and site required for effective capsulotomies are still unclear.

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REFERENCES

1. Krishna V, Sammartino F, Rezai A (2018): A review of the current therapies, challenges, and future directions of transcranial focused ultrasound technology: Advances in diagnosis and treatment. JAMA Neurol 75:246–254.
2. Davidson B, Hamani C, Huang Y, Jones RM, Meng Y, Giacobbe P, *et al.* (2020): Magnetic resonance-guided focused ultrasound capsulotomy for treatment-resistant psychiatric disorders. Oper Neurosurg (Hagerstown) 19:741–749.
3. Meng Y, Hynynen K, Lipsman N (2021): Applications of focused ultrasound in the brain: From thermoablation to drug delivery. Nat Rev Neurol 17:7–22.
4. Davidson B, Meng Y, Giacobbe P, Hamani C, Lipsman N (2019): Magnetic resonance-guided focused ultrasound for psychiatric disorders. Clin Pharmacol Ther 106:720–722.
5. Davidson B, Mithani K, Huang Y, Jones RM, Goubran M, Meng Y, *et al.* (2020): Technical and radiographic considerations for magnetic resonance imaging-guided focused ultrasound capsulotomy. J Neurosurg 135:291–299.
6. Davidson B, Eapen-John D, Mithani K, Rabin JS, Meng Y, Cao X, *et al.* (2022): Lesional psychiatric neurosurgery: Meta-analysis of clinical outcomes using a transdiagnostic approach. J Neurol Neurosurg Psychiatry 93:207–215.
7. Davidson B, Hamani C, Rabin JS, Goubran M, Meng Y, Huang Y, *et al.* (2020): Magnetic resonance-guided focused ultrasound capsulotomy for refractory obsessive compulsive disorder and major depressive disorder: Clinical and imaging results from two phase I trials. Mol Psychiatry 25:1946–1957.
8. Kim M, Kim CH, Jung HH, Kim SJ, Chang JW (2018): Treatment of major depressive disorder via magnetic resonance-guided focused ultrasound surgery. Biol Psychiatry 83:e17–e18.
9. Kim SJ, Roh D, Jung HH, Chang WS, Kim CH, Chang JW (2018): A study of novel bilateral thermal capsulotomy with focused ultrasound for treatment-refractory obsessive-compulsive disorder: 2-year follow-up. J Psychiatry Neurosci 43:327–337.
10. Goodman WK, Price LH, Rasmussen SA, Mazure C, Delgado P, Heninger GR, *et al.* (1989): The Yale-Brown Obsessive Compulsive Scale. II. Validity. Arch Gen Psychiatry 46:1012–1016.
11. Hamilton M (1967): Development of a rating scale for primary depressive illness. Br J Soc Clin Psychol 6:278–296.
12. Endicott J, Nee J, Harrison W, Blumenthal R (1993): Quality of Life Enjoyment and Satisfaction Questionnaire: A new measure. Psychopharmacol Bull 29:321–326.
13. Davidson B, Hamani C, Rabin JS, Meng Y, Richter MA, Giacobbe P, *et al.* (2021): Magnetic resonance-guided focused ultrasound capsulotomy for musical obsessions. Biol Psychiatry 90:e49–e50.
14. Huang Y, Lipsman N, Schwartz ML, Krishna V, Sammartino F, Lozano AM, *et al.* (2018): Predicting lesion size by accumulated thermal dose in MR-guided focused ultrasound for essential tremor. Med Phys 45:4704–4710.

15. Jones RM, Kamps S, Huang Y, Scantlebury N, Lipsman N, Schwartz ML, *et al.* (2019): Accumulated thermal dose in MRI-guided focused ultrasound for essential tremor: Repeated sonications with low focal temperatures. J Neurosurg 132:1802–1809.
16. Davidson B, Hamani C, Meng Y, Baskaran A, Sharma S, Abrahao A, *et al.* (2020): Examining cognitive change in magnetic resonance-guided focused ultrasound capsulotomy for psychiatric illness. Transl Psychiatry 10:397.
17. Wintermark M, Druzgal J, Huss DS, Khaled MA, Monteith S, Raghavan P, *et al.* (2014): Imaging findings in MR imaging-guided focused ultrasound treatment for patients with essential tremor. AJNR Am J Neuroradiol 35:891–896.
18. Jenkinson M, Beckmann CF, Behrens TE, Woolrich MW, Smith SM (2012): FSL. Neuroimage 62:782–790.
19. Avants BB, Tustison NJ, Song G, Cook PA, Klein A, Gee JC (2011): A reproducible evaluation of ANTs similarity metric performance in brain image registration. Neuroimage 54:2033–2044.
20. McLaughlin NCR, Magnotti JF, Banks GP, Nanda P, Hoexter MQ, Lopes AC, *et al.* (2023): Gamma knife capsulotomy for intractable OCD: Neuroimage analysis of lesion size, location, and clinical response. Transl Psychiatry 13:134.
21. Elias GJB, Boutet A, Joel SE, Germann J, Gwun D, Neudorfer C, *et al.* (2021): Probabilistic mapping of deep brain stimulation: Insights from 15 years of therapy. Ann Neurol 89:426–443.
22. Yeh FC (2022): Population-based tract-to-region connectome of the human brain and its hierarchical topology. Nat Commun 13:4933.
23. Yeh FC, Verstynen TD, Wang Y, Fernandez-Miranda JC, Tseng WY (2013): Deterministic diffusion fiber tracking improved by quantitative anisotropy. PLoS One 8:e80713.
24. Ruck C, Karlsson A, Steele JD, Edman G, Meyerson BA, Ericson K, *et al.* (2008): Capsulotomy for obsessive-compulsive disorder: Long-term follow-up of 25 patients. Arch Gen Psychiatry 65:914–921.
25. Li H, Yuan S, Dai L, Huang H, Lin Z, Zhan S, *et al.* (2023): Anterior capsulotomy for refractory obsessive-compulsive disorder: A tractography and lesion geometry study. Stereotact Funct Neurosurg 101:407–415.
26. Csigo K, Harsanyi A, Demeter G, Rajkai C, Nemeth A, Racsmany M (2010): Long-term follow-up of patients with obsessive-compulsive disorder treated by anterior capsulotomy: A neuropsychological study. J Affect Disord 126:198–205.
27. Christmas D, Eljamel MS, Butler S, Hazari H, MacVicar R, Steele JD, *et al.* (2011): Long term outcome of thermal anterior capsulotomy for chronic, treatment refractory depression. J Neurol Neurosurg Psychiatry 82:594–600.
28. Rasmussen SA, Noren G, Greenberg BD, Marsland R, McLaughlin NC, Malloy PJ, *et al.* (2018): Gamma ventral capsulotomy in intractable obsessive-compulsive disorder. Biol Psychiatry 84:355–364.
29. Holtzheimer PE, Husain MM, Lisanby SH, Taylor SF, Whitworth LA, McClintock S, *et al.* (2017): Subcallosal cingulate deep brain stimulation for treatment-resistant depression: A multisite, randomised, sham-controlled trial. Lancet Psychiatry 4:839–849.
30. Hageman SB, van Rooijen G, Bergfeld IO, Schirmbeck F, de Koning P, Schuurman PR, *et al.* (2021): Deep brain stimulation versus ablative surgery for treatment-refractory obsessive-compulsive disorder: A meta-analysis. Acta Psychiatr Scand 143:307–318.
31. Subramanian L, Bracht T, Jenkins P, Choppin S, Linden DE, Phillips G, *et al.* (2017): Clinical improvements following bilateral anterior capsulotomy in treatment-resistant depression. Psychol Med 47:1097–1106.
32. Avecillas-Chasin JM, Hurwitz TA, Bogod NM, Honey CR (2019): An analysis of clinical outcome and tractography following bilateral anterior capsulotomy for depression. Stereotact Funct Neurosurg 97:369–380.
33. Davidson B, Suresh H, Goubran M, Rabin JS, Meng Y, Mithani K, *et al.* (2020): Predicting response to psychiatric surgery: A systematic review of neuroimaging findings. J Psychiatry Neurosci 45:387–394.
34. McDannold N, Zhang Y, Vykhodtseva N (2016): Nonthermal ablation in the rat brain using focused ultrasound and an ultrasound contrast agent: Long-term effects. J Neurosurg 125:1539–1548.
35. Moller HJ (1991): Outcome criteria in antidepressant drug trials: Self-rating versus observer-rating scales. Pharmacopsychiatry 24:71–75.
36. Seemuller F, Schennach R, Musil R, Obermeier M, Adli M, Bauer M, *et al.* (2023): A factor analytic comparison of three commonly used depression scales (HAMD, MADRS, BDI) in a large sample of depressed inpatients. BMC Psychiatry 23:548.
37. Asnaani A, Kaczkurkin AN, Alpert E, McLean CP, Simpson HB, Foa EB (2017): The effect of treatment on quality of life and functioning in OCD. Compr Psychiatry 73:7–14.
38. Rabin JS, Nyman AJ, Davidson B, Zakzanis KK, Giacobbe P, Hamani C, *et al.* (2022): Commonly used outcome measures in neurosurgical trials for major depressive disorder might not capture clinically meaningful treatment effects. J Neurol Neurosurg Psychiatry 93:455–456.
39. Rabin JS, Davidson B, Giacobbe P, Hamani C, Cohn M, Illes J, *et al.* (2020): Neuromodulation for major depressive disorder: Innovative measures to capture efficacy and outcomes. Lancet Psychiatry 7:1075–1080.
40. Germann J, Elias GJB, Neudorfer C, Boutet A, Chow CT, Wong EHY, *et al.* (2021): Potential optimization of focused ultrasound capsulotomy for obsessive compulsive disorder. Brain 144:3529–3540.
41. Satzer D, Mahavadi A, Lacy M, Grant JE, Warnke P (2022): Interstitial laser anterior capsulotomy for obsessive-compulsive disorder: Lesion size and tractography correlate with outcome. J Neurol Neurosurg Psychiatry 93:317–323.
42. Miguel EC, Lopes AC, McLaughlin NCR, Noren G, Gentil AF, Hamani C, *et al.* (2019): Evolution of gamma knife capsulotomy for intractable obsessive-compulsive disorder. Mol Psychiatry 24:218–240.
43. Lopes AC, Greenberg BD, Noren G, Canteras MM, Busatto GF, de Mathis ME, *et al.* (2009): Treatment of resistant obsessive-compulsive disorder with ventral capsular/ventral striatal gamma capsulotomy: A pilot prospective study. J Neuropsychiatry Clin Neurosci 21:381–392.