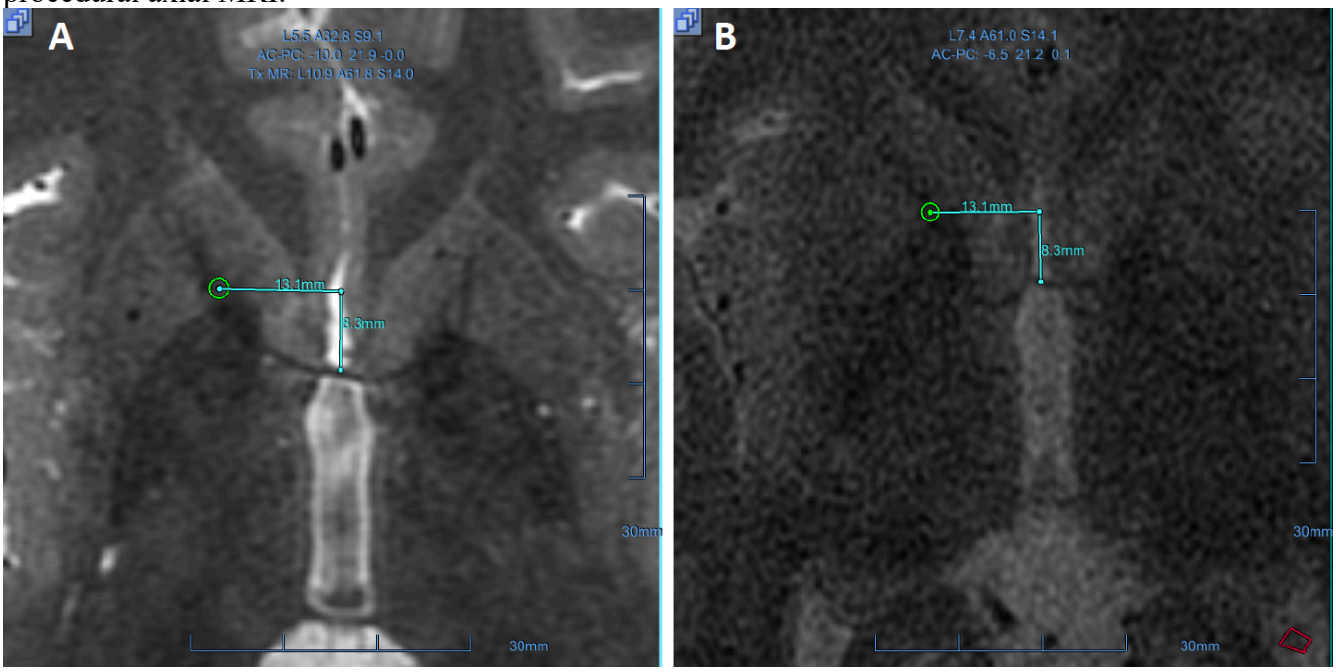
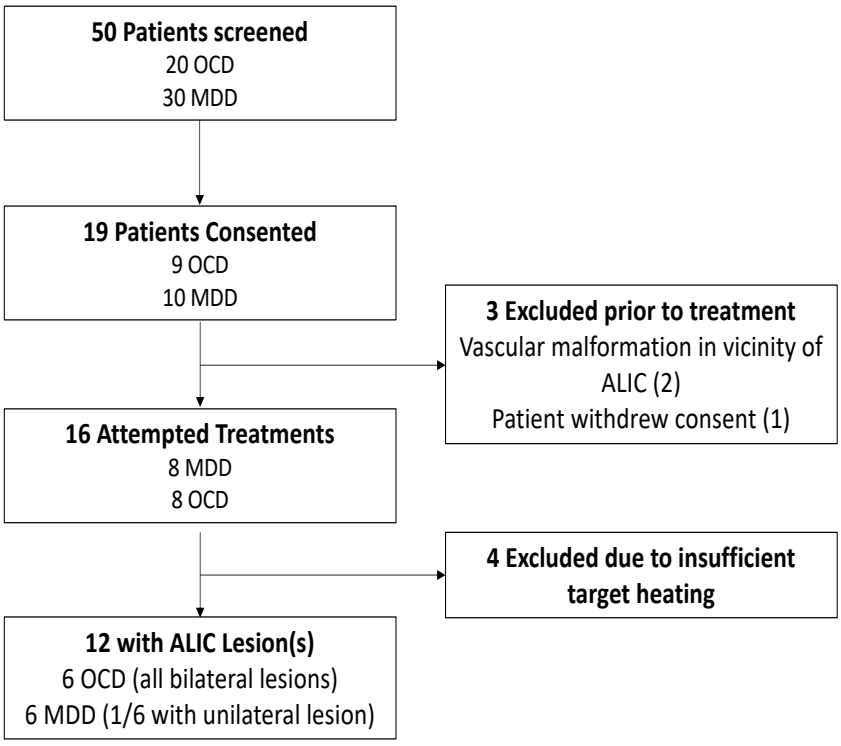
Supplementary Material

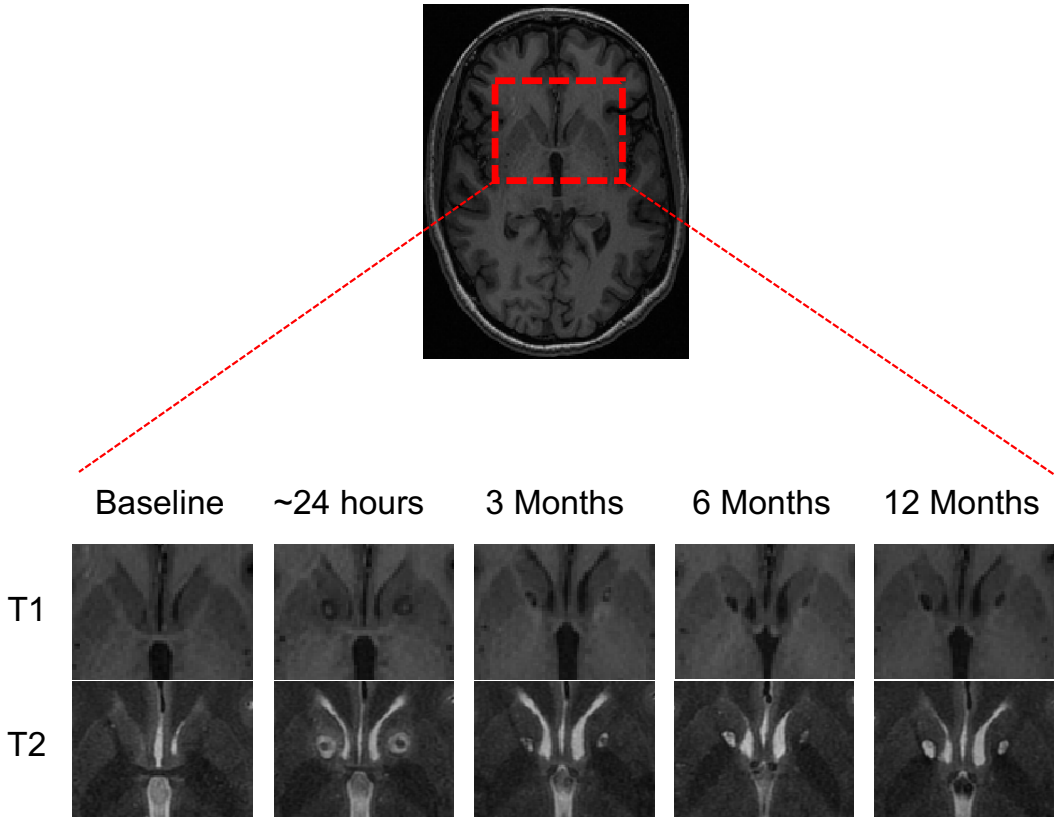
Supplementary Figure 1. Example of direct targeting of the anterior limb of the internal capsule. Panel A shows a pre-treatment high-resolution 3-tesla axial MRI, and panel B displays the intra-procedural axial MRI.



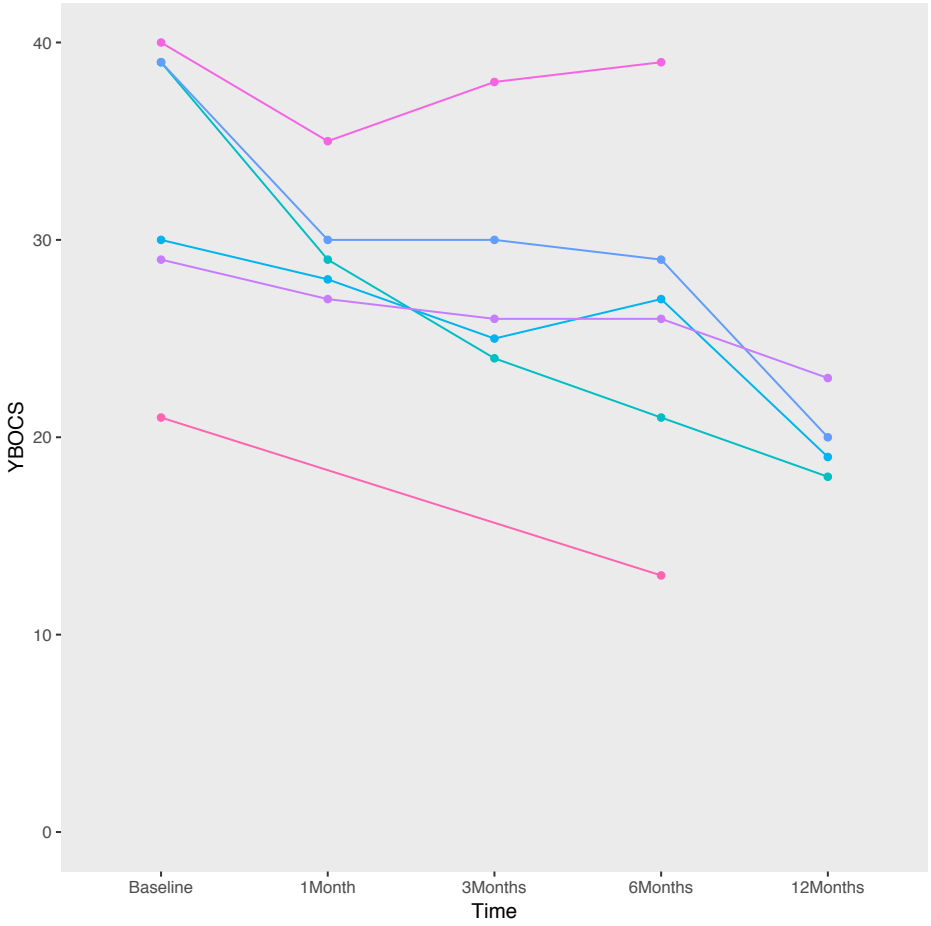
Supplementary Figure 2. Patient Flow Diagram



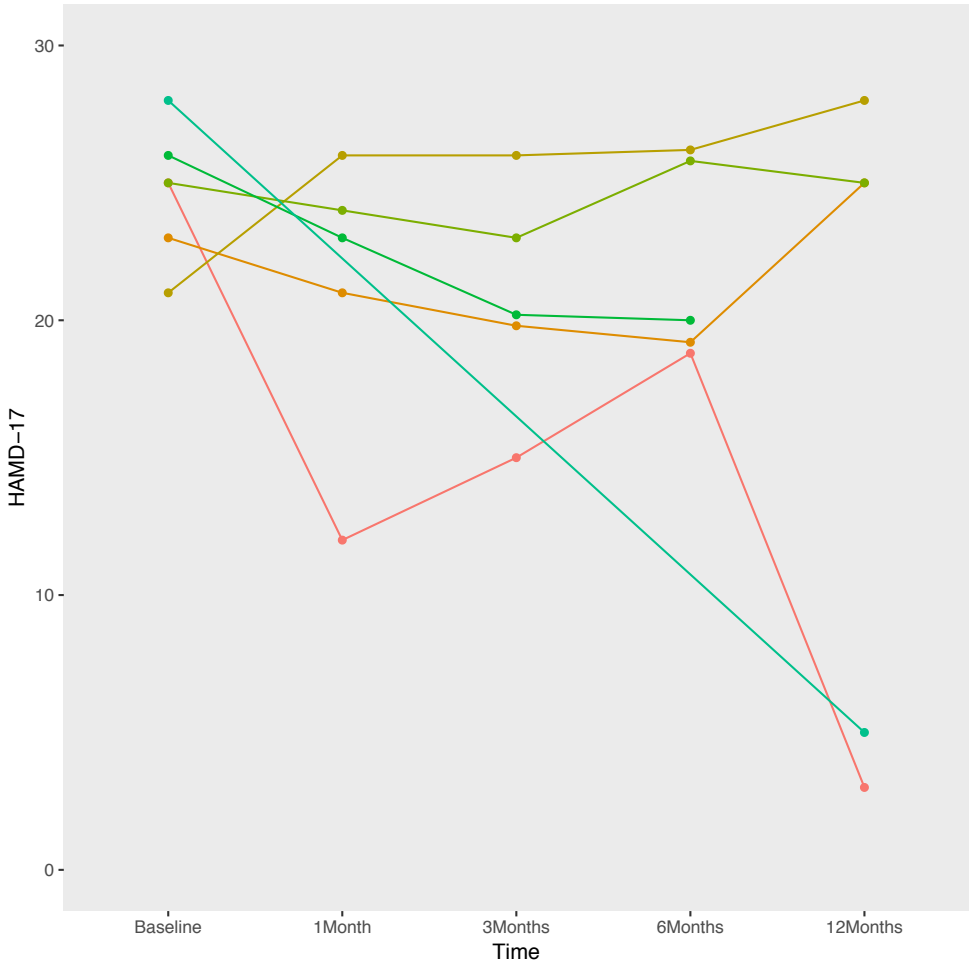
Supplementary Figure 3. MRgFUS capsulotomy lesion evolution on T1 and T2 MRI



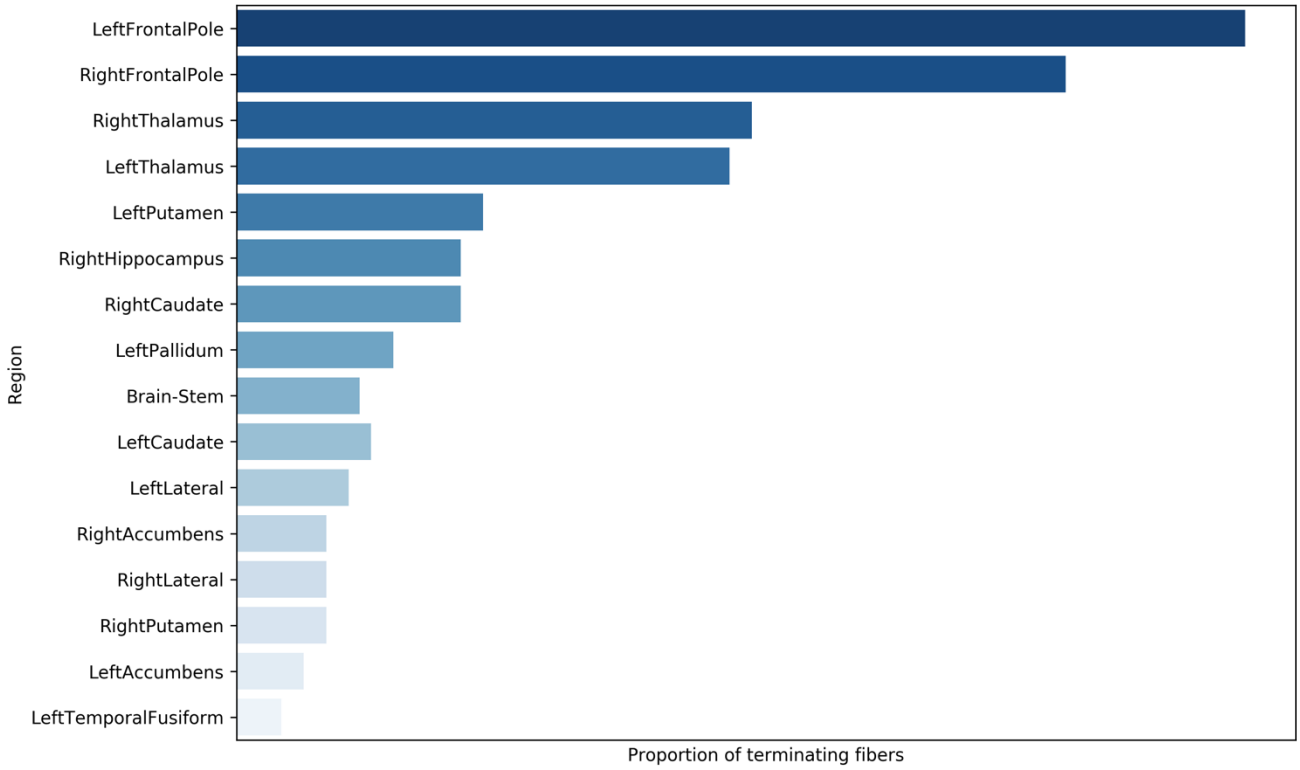
Supplementary Figure 4. Patient-level YBOCS Response Following MRgFUS Capsulotomy for OCD



Supplementary Figure 5. Patient-level HAMD-17 Response Following MRgFUS Capsulotomy for MDD



Supplementary Figure 6. Locations of terminating fibers based on the Harvard-Oxford Cortical and Subcortical Atlases.



Supplementary Methods

Diffusion MRI Analysis (Figure 1)

Day 1 post-treatment structural T1 scans were registered and warped into MNI-space using SPM12 (https://www.fil.ion.ucl.ac.uk/spm/). Lesions were then manually traced in MNI space using freeview as implemented through Freesurfer (https://surfer.nmr.mgh.harvard.edu/). Lesions were summated and using as seeds in a tractography analysis implemented in DSI-Studio (http://dsi-studio.labsolver.org/). Fiber tracking was performed on a large normative averaged diffusion dataset of 1021 subjects from the human connectome project (HCP), as described elsewhere.[1] The diffusion imaging was constructed from scans acquired with a multi-shell diffusion scheme was used, and the b-values were 990 ,1985 and 2980 s/mm2. The number of diffusion sampling directions were 90, 90, and 90, respectively, and the slice thickness was 1.25 mm. Diffusion data was reconstructed using q-space diffeomorphic reconstruction. The anisotropy threshold was 0.156397. The angular threshold was randomly selected from 15 degrees to 90 degrees. The step size was randomly selected from 0.5 voxel to 1.5 voxels. 50000 seeds were placed within the whole brain, and the whole-brain tractography was filtered to only tracts passing through the left summated lesion, or the right summated lesion. Tracks with length shorter than 30 or longer than 300 mm were discarded.

MRI preprocessing and subject template generation (Figure 2)

Each patients' baseline and 6-month T1 MRI scan was processed using FreeSurfer (v6.0-Linux, https://surfer.nmr.mgh.harvard.edu). Briefly, the cross-sectional pre-processing of T1-weighted scans included motion correction, skull-stripping, transformation to Talairach space, intensity normalization, hemispheric separation, and tissue segmentation and parcellation.[2-4] After cross-sectional processing, each subject was processed through the longitudinal pipeline.[5] An unbiased within-subject template space and image was created using robust, inverse consistent registration.[6] Several processing steps, such as skull stripping, Talairach transforms, atlas registration, as well as spherical surface maps and parcellations were then initialized with common information from the within-subject template, significantly increasing reliability and statistical power.[5] After longitudinal processing, visual inspection was conducted in order to ensure optimal skull-stripping and reconstruction of pial and white matter surfaces.

For the voxel-wise subcortical analysis, each subject's PVC subcortical volume was sampled into the 2mm space of the MNI305 template in FreeSurfer. Subcortical regions of interest were created from FreeSurfer's subcortical and tissue segmentation (aseg.mgz) in MNI305 space and 5mm FWHM smoothing kernel was applied to the volume maps using the regions of interest as a mask.

Resting-State fMRI Analysis (Figure 3)

After discarding the first two volumes of each rs-fMRI scan to ensure a steady state, preprocessing was carried out using SPM12 (Wellcome Department of Imaging Neurosciences, London, United Kingdom) using slice timing/motion correction, realignment to the first scan, co-registration to session-specific structural scans, normalization to the MNI152 template, and spatial smoothing using a 2-mm gaussian kernel. Artifact detection was conducted using the *art* tool (https://www.nitrc.org/projects/artifact_detect). Each scan was segmented into grey matter, white matter (WM), and cerebrospinal fluid (CSF). In order to reduce partial volume effects, the first three principal components of each rs-fMRI scan's WM and CSF masks were regressed out using aCompCor.[7] Each scan was then subjected to a temporal bandpass filter of 0.009-0.08Hz. A seed-to-whole-brain voxelwise analysis was carried out using a priori defined seeds commonly used in the literature (ventral striatum: x = +/-9, y = 9, z = -8; dorsal striatum: x = +/-13, y = 15, z = 9; ventral putamen:

x = +/-20, y = 12, z = -3; dorsal putamen: x = +/-28, y = 1, z = 3; and subcallosal cingulate: x = +/-6, y = 24, z = -11).[8,9] 3.5mm spherical binary regions of interest (ROI) were constructed using the WFU PickAtlas (https://www.nitrc.org/projects/wfu_pickatlas/). First-level correlation maps were constructed by computing Pearson's correlation coefficient between the average timeseries within each seed ROI and every other voxel in the brain. [8,9] These correlation maps were Fisher-transformed to normalized z-scores.

Supplementary Table 1. Inclusion & exclusion criteria for OCD and MDD trials

MRgFUS capsulotomy for OCD	
Inclusion criteria	Exclusion criteria
1. Men and women ≥20 and ≤80 years of age. 2. Patients who are able and willing to give consent and able to attend study visits, as determined by both study Psychiatrist and the surgeon. 3. Diagnostic and Statistical Manual of Mental Disorders (DSM-V) diagnosis of Obsessive Compulsive Disorder (OCD), at least 5-year illness history with a minimum score of 28 on the Yale-Brown Obsessive Compulsive Scale (Y-BOCS). 4. Medication-refractoriness as determined by an adequate dose and duration of standard psychiatric treatments (including psychotherapy and/or pharmacology) as determined by two psychiatrists associated with the study. Including specifically: a. Failed adequate trial of three or more medications accepted as first line in the treatment of OCD b. Attempted augmentation, if tolerated, by at least 2 medications known to be first line treatments for OCD c. An adequate trial of cognitive behavioural therapy, delivered by a therapist experienced in treating OCD 5. Able to communicate sensations during the ExAblate MRgFUS treatment 6. A consistent dose of all medications in the 30 days prior to study entry.	1. Patients with unstable cardiac status [e.g. Unstable angina pectoris on medication, Patients with documented myocardial infarction within six months, Congestive heart failure requiring medication (other than diuretic), Patients on anti-arrhythmic drugs, Severe hypertension (diastolic BP > 100 on medication)] 2. Patients with standard contraindications for MR imaging such as non-MRI compatible implanted metallic devices including cardiac pacemakers, size limitations, etc. 3. Known intolerance or allergies to MRI contrast agent (e.g. Gadolinium or Magnevist) including advanced kidney disease 4. Severely impaired renal function (estimated glomerular filtration rate < 30ml/min/1.73 m2) or receiving dialysis 5. Laboratory biochemical evidence of abnormal bleeding and/or coagulopathy, including risk factors for intraoperative or postoperative bleeding (platelet count less than 100,000 per cubic millimeter or abnormal INR) 6. Cerebrovascular disease (e.g. cerebrovascular accident within 6 months) or history of intracranial hemorrhage 7. Untreated, uncontrolled sleep apnea 8. Receiving anticoagulant (e.g. warfarin) or antiplatelet (e.g. aspirin) therapy within one week of focused ultrasound procedure or drugs known to increase risk or hemorrhage (e.g. Avastin) within one month of focused ultrasound procedure 9. Individuals who are not able or willing to tolerate the required prolonged stationary supine position during treatment 10. Are participating or have participated in another clinical trial in the last 30 days

	11. Patients unable to communicate with the investigator and staff. 12. Presence of significant cognitive impairment 13. Presence of psychosis on clinical evaluation. 14. Patients with brain tumors already known or revealed on pretreatment MRI 15. Currently pregnant (as determined by history and serum HCG) or lactating. 16. Chemical abuse or dependence within the previous six months
MRgFUS capsulotomy for MDD	
Inclusion criteria	Exclsion criteria
1. Men and women ≥20 and ≤80 years of age. 2. Patients who are able and willing to give consent and physically and practically able to attend study visits, as determined by both study Psychiatrist and the surgeon. 3. DSM-V diagnosis of major depressive episode, as a component of an Axis I disorder, such as Major Depressive Disorder, Bipolar Disorder, Anxiety Disorder, Eating Disorder, Substance Abuse/Dependence Disorder ,or Personality Disorder 4. At least 5-year illness history of the primary disorder and at least 6 months since the onset of the first episode of major depression. 5. A minimum score of 20 on the Hamilton Depression Rating Scale (HAMD) when depressed (patients with bipolar disorder may be rapid cycling, but have to have at least 2 weeks of major depression at the time the HAMD is conducted) 6. Medication-refractoriness as determined by an adequate dose and duration of standard psychiatric treatments (including psychotherapy and/or pharmacology) as determined by two psychiatrists associated with the study. Including specifically:	1. Patients with unstable cardiac status [e.g. Unstable angina pectoris on medication, Patients with documented myocardial infarction within six months, Congestive heart failure requiring medication (other than diuretic), Patients on anti-arrhythmic drugs, Severe hypertension (diastolic BP > 100 on medication)] 2. Patients with standard contraindications for MR imaging such as non-MRI compatible implanted metallic devices including cardiac pacemakers, size limitations, etc. 3. Severely impaired renal function (estimated glomerular filtration rate < 30ml/min/1.73 m2) or receiving dialysis 4. Laboratory biochemical evidence of abnormal bleeding and/or coagulopathy, including risk factors for intraoperative or postoperative bleeding (platelet count less than 100,000 per cubic millimeter or abnormal INR) 5. Cerebrovascular disease (e.g. CVA within 6 months) or history of intracranial hemorrhage 6. Untreated, uncontrolled sleep apnea 7. Receiving anticoagulant (e.g. warfarin) or antiplatelet (e.g. aspirin) therapy within

a. Failed to respond or tolerate adequate trial of three or more medications accepted as first line in the treatment of depression b. Failed to respond or tolerate augmentation with or combination, of at least 2 medications known to be first line treatments for depression c. An adequate trial of cognitive behavioural therapy or other evidence-supported psychotherapy, delivered by a therapist experienced in treating depression 7. Able to communicate sensations during the ExAblate MRgFUS treatment 8. A consistent dose of any and all medications in the 30 days prior to study entry. 9. Women of childbearing potential must agree to use a contraception method throughout the study.	one week of focused ultrasound procedure or drugs known to increase risk or hemorrhage (e.g. Avastin) within one month of focused ultrasound procedure 8. Individuals who are not able or willing to tolerate the required prolonged stationary supine position during treatment 9. Are participating or have participated in another clinical trial in the last 30 days 10. Patients unable to communicate with the investigator and staff. 11. Presence of significant cognitive impairment 12. Presence of psychosis on clinical evaluation. 13. Patients with brain tumors already known or revealed on pretreatment MRI 14. Currently pregnant (as determined by history and serum HCG) or lactating.

Supplementary Table 2. Medication changes

Patient	Diagnosis	Psychiatric medications at time of MRgFUS	Medication changes during follow-up period
1	OCD	Amitriptyline 150mg BID, citalopram 40mg OD, risperidone 1.5mg OD	-
2	OCD	Sertraline 250mg OD, risperidone 2mg OD, lorazepam 0.5mg BID, clonazepam 0.5 md TID,	-
3	OCD	Paroxetine 40 mg OD, clonazepam 0.5mg BID, memantime 10 mg OD	Added trazodone 75 mg OD PRN for sleep
4	OCD	Clomipramine 300mg OD, desvenlafaxine 200mg OD, lurasidone 40 mg OD, lorazepam 1mg OD	Stopped lurasidone, tried on risperidone but that was stopped, Lurasidone replaced with risperidone Clomipramine decreased to 50mg OD
5	OCD	Nil$^{\tau}$	Started lurasidone 20 mg OD
6	OCD	Fluoxetine 60mg OD, nortriptyline 20mg OD, clonazepam 0.75mg TID, clonidine 0.025mg OD, trazodone 50mg OD, lorazepam 1mg QID PRN	Fluoxetine decreased to 40 mg OD, Nortriptyline increased to 40mg OD, Clonazepam discontinued, Added topiramate 25mg OD
7	MDD	Risperidone 4.5mg daily (divided), ketamine 0.01mg twice weekly, desipramine 40mg OD, clonazepam 1.75 mg OD.	Decreased risperidone to 3.0mg daily (divided) Added clonazepam 0.25mg BID PRN, Decreased desipramine to 20mg OD, Added vilazadone 2.5mg OD
8	MDD	Quetiapine 50mg OD, buproprion 150mg OD, ketamine nasal spray 150mg weekly, gabapentin 2000 daily (divided), trazodone 50mg OD	-
9	MDD	Nil$^{\tau}$	Added chlorpromazine 12.5mg every other day
10	MDD	Levomilnacapran 120mg OD, asenapine 5mg OD, clonazepam 1mg OD	Increased levomilnacapran to 140mg OD,
11	MDD	Duloxetine 60 mg OD, quetiapine 25mg OD	-
12	MDD	Duloxetine 120mg OD, lurasidone 80mg OD, mirtazapine 15mg OD, temazepam 15mg OD, trazodone 150mg OD	Reduced trazodone to 100mg OD,

Supplementary Table 3. YBOCS Change Over Time in OCD Patients

Patient	Preoperative	1 Month	3 Month	6 Month	12 Month
1	39	29	24	21	18
2	30	28	25	27	19
3	39	30	30	29	20
4	29	27	26	26	23
5	40	35	38	39	-
6	21	*	*	13	*

* only preoperative and 6 month scores were collected on patient 6, who was treated on humanitarian grounds outside of the trial protocol; "-" indicates a patient had not yet reached that timepoint

Supplementary Table 4. HAMD-17 Change Over Time in All Patients

Patient	Preoperative	1 Month	3 Month	6 Month	12 Month
1	25	12	11	12	9
2	8	18	10	10	7
3	22	12	15	18	16
4	21	20	13	23	16
5	28	23	26	28	-
6	13	*	*	5	*
7	25	12	15	19	3
8	23	21	20	19	25
9	21	26	26	26	28
10	25	24	23	26	25
11	26	23	20	20	-
12	28	*	*	*	5

* only preoperative and a single postoperative HAMD-17 were collected on patients 6 and 12, who were treated on humanitarian grounds outside of the trial protocol.

Supplementary Table 5. Disease-specific outcome means

	Mean Preoperative YBOCS	**Mean Last Followup YBOCS**	**% Change**	**Test Statistic**
OCD cohort (n=6)	33.0 +/- 7.6	22.0 +/- 8.9	-33.3	V=21 **p=0.03***
	Mean Preoperative HAMD	**Mean Last Followup HAMD**		
MDD cohort (n=6)	24.67 +/- 2.42	17.83 +/- 11.05	-27.7	V=14 p=0.56

HAM-D: Hamilton depressions scale; YBOCS: Yale-Brown obsessive compulsive scale;
'-' YBOCS is not measured in MDD patients.

Supplementary Table 6. Quality of life and secondary outcomes means

Patient	Diagnosis	Preoperative BDI	Postoperative BDI	Preoperative MADRS	Postoperative MADRS	Preoperative QLESQ	Postoperative QLESQ
1	OCD	33	18	-	-	24	35
2	OCD	14	12	-	-	24	63
3	OCD	41	14	-	-	29	42
4	OCD	26	19	-	-	52	47
5	OCD	38	42	-	-	32	22
6	OCD	*	10	-	-	*	61
7	MDD	42	8	30	2	32	61
8	MDD	35	34	30	40	34	32
9	MDD	45	51	30	38	33	21
10	MDD	36	38	36	38	36	30
11	MDD	45	37	40	26	28	36
12	MDD	*	3	*	2	*	70

BDI: Beck Depression Inventory; MADRS: Montgomery-Asberg depression rating scale; QLESQ: Quality of life enjoyment and satisfaction questionnaire

'-' MADRS is not collected in OCD patients; * preoperative BDI, MADRS, and QLESQ were not collected on the two patients treated outside of the clinical trial

Supplementary Table 7. Beck Anxiety Index scores in OCD patients

Patient	Preoperative	1 Month	3 Month	6 Month	12 Month
1	40	26	16	11	9
2	14	29	15	27	30
3	26	20	22	48	11
4	21	20	18	17	6
5	51	35	40	47	-
6	43	*	*	28	*

Additional References

1. Yeh FC, Tseng WY. NTU-90: a high angular resolution brain atlas constructed by q-space diffeomorphic reconstruction. *Neuroimage* 2011; **58**(1): 91-9.
2. Dale AM, Fischl B, Sereno MI. Cortical surface-based analysis. I. Segmentation and surface reconstruction. *Neuroimage* 1999; **9**(2): 179-94.
3. Fischl B, Dale AM. Measuring the thickness of the human cerebral cortex from magnetic resonance images. *Proc Natl Acad Sci U S A* 2000; **97**(20): 11050-5.
4. Fischl B, Sereno MI, Dale AM. Cortical surface-based analysis. II: Inflation, flattening, and a surface-based coordinate system. *Neuroimage* 1999; **9**(2): 195-207.
5. Reuter M, Schmansky NJ, Rosas HD, Fischl B. Within-subject template estimation for unbiased longitudinal image analysis. *Neuroimage* 2012; **61**(4): 1402-18.
6. Reuter M, Rosas HD, Fischl B. Highly accurate inverse consistent registration: a robust approach. *Neuroimage* 2010; **53**(4): 1181-96.
7. Behzadi Y, Restom K, Liau J, Liu TT. A component based noise correction method (CompCor) for BOLD and perfusion based fMRI. *Neuroimage* 2007; **37**(1): 90-101.
8. Yin D, Zhang C, Lv Q, et al. Dissociable Frontostriatal Connectivity: Mechanism and Predictor of the Clinical Efficacy of Capsulotomy in Obsessive-Compulsive Disorder. *Biol Psychiatry* 2018; **84**(12): 926-36.
9. Dunlop BW, Rajendra JK, Craighead WE, et al. Functional Connectivity of the Subcallosal Cingulate Cortex And Differential Outcomes to Treatment With Cognitive-Behavioral Therapy or Antidepressant Medication for Major Depressive Disorder. *Am J Psychiatry* 2017; **174**(6): 533-45.