Supplementary Online Content

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This supplementary material has been provided by the authors to give readers additional information about their work.

eMethods 1. Inclusion and Exclusion Criteria

Adult patients over 30 years with idiopathic PD were included if their subtype was tremor-dominant that was deemed medication-refractory, severe, and disabling. The diagnosis was confirmed using the UK Brain Bank Criteria by a movement disorder neurologist. The tremor-dominant subtype was determined in the on-medication state when the ratio of the mean UPDRS tremor scores (items 16,20,21) to the mean UPDRS postural instability/gait disorder scores (items 13-15,29,30) was ≥ 1.5.[1] Patients were deemed medication-refractory if trials of levodopa or its equivalent medications (LEDD) ≥ 900 mg did not suppress the tremor, or if intolerant side effects developed. LEDD was not fixed during the trial. Severe and disabling tremor was defined by cutoff scores for on-medication UPDRS items and part C of the CRST.

Neurological exclusion criteria included central neurodegenerative disease other than PD, drug-induced parkinsonism, cognitive impairment defined as Montreal Cognitive Assessment score (MoCA) ≤ 21, unstable psychiatric disease, depression from the Beck Depression Inventory score (BDI-II) > 14, history of seizures, brain tumors, intracranial aneurysms or arteriovenous malformations requiring treatment, and a history of deep brain stimulation (DBS) or prior stereotactic ablation.

Non-neurologic exclusion criteria included unstable cardiac status, behavior consistent with ethanol abuse as defined by the DSM-IV, hypertension (diastolic BP>100 on medication), contraindication to obtaining an MRI, intolerance or allergies to MRI contrast agents, claustrophobia, bleeding abnormalities, anticoagulant or antiplatelet usage, elevated INR or low platelet levels, history of intracranial hemorrhage or strokes, weight > 285lbs, unwilling to tolerate prolonged stationary position in the supine position, participation in another clinical trial in the last 30 days, legal incapacity or an inability to communicate, and overall skull density ratio ≤0.45 as calculated from the screening CT.

eMethods 2. Details of the MR-Guided FUS Thalamotomy Procedure

The patient is first prepared by shaving their scalp. A Radionics™ Cosman-Roberts-Wells (CRW®) stereotactic 4 pin headframe (Integra LifeSciences, USA) is then applied under local anesthesia. The headframe is placed as low on the skull as possible to maximize the scalp area and number of ultrasound elements available for transcranial sonication. A rubber membrane is then fitted to the patients scalp as close to the headframe pins as possible minimizing folds in the membrane. The patient is then positioned supine with the headframe secured in place and the membrane sealed to the ExAblate 4000 mid frequency head transducer (InSightec, Haifa, Israel). The mid frequency head transducer is 30cm in diameter and movable in X,Y,Z and gantry relative to the patients head. There are 1024 individually controlled phase adjusted transducers operating at 710kHz. Degassed and chilled water, maintained at a temperature of 17°C, is then circulated in the space between the cranium and the transducer, and any excess air bubbles are removed. The transducer is fixed to the table of a 3T MRI system (GE medical, Milwaukee, WI, USA) to enable precise MRI monitoring of the procedure.

The preoperative CT scan is used to identify exclusion zones for the beam path including intracranial calcifications and air sinuses. An MRI is obtained at the beginning of the procedure to center the transducer on the target and to identify additional exclusion zones related to the membrane folds. Usually, at least 800 of the 1024 transducer elements were available for the treatments. Our initial target coordinates for Vim thalamotomy is anterior to the posterior commissure by 25% of the AC-PC line and lateral to midline 14mm, or in the case of a large 3rd ventricle, 10.5mm lateral to the lateral border of the 3rd ventricle.

The ExAblate system uses proton chemical shift techniques to determine the relative change in temperature from baseline.[2] The baseline temperature is assumed to be 37°C. The system reports a peak temperature at a single voxel (1x1x3mm) and an average temperature of 9 voxels. We routinely use the average temperature when making decisions on adjusting power for future sonications. Low energy sonications are performed in the sagittal, coronal, and axial planes to verify that the two dimensional MR thermometry plane is centered at the focus of the pressure wave. Peak temperatures during the setup or calibration phase are kept low to avoid generation of a permanent lesion.

Therapeutic sonications are administered at the target location with incrementally increasing energy. Our primary goal during treatment is to achieve elimination of the patient's tremor. Tremor was assessed by the neurosurgeon in the resting and postural states, as well as with finger-to-nose and drawing tasks following each treatment sonication. The target is routinely adjusted based on clinical feedback. Our final goal is to achieve an adequate temperature / thermal dose to the region; however, this is still under investigation.[3-6] The mean energy administered during this study during therapeutic sonications (average temperature > 50°C) was 8977 joules (SD 5277 joules). The mean average temperature achieved was 52.4°C (SD 2.2°C). The mean number of therapeutic sonications was 3.6 (SD 2.0), the mean number of total sonications (including targeting) was 13.2 (SD 4.0). Once a significant reduction in tremor is noted, a T2 MRI was obtained for a qualitative assessment of the lesion size and location. The MRI results evolve over time as the lesion matures. MRI on the day of the procedure are not good indicators of final lesion size; however, MRI performed the next day correlates with studies obtained at 1 month. In this trial, MRI was obtained on the day of procedure, the day after the procedure, at one month follow up, and at one year. Mean lesion diameters at each of these times were (3.6 mm, SD 1.2), (5.3 mm, SD 1.6), (4.8mm, SD 1.1), (2.7mm, SD 1.3), respectively at the level of the ACPC on T2 axial images.

At the conclusion of the treatment, the headframe is disconnected from the transducer and is removed from the patient. The procedure lasts approximately 3-5 hours inside of the MRI. Following an MRI the day after the procedure, the patient was discharged from the hospital.

The sham patients were randomized after the headframe was attached to the transducer. These patients underwent all the stages of a treatment (targeting, MRI, assessments); however, the sonication power was set to zero watts. The number of sham sonications were also randomized after their treatment assignment and ranged from 10-15 sonications.

eTable 1. Screen Failures

	No (%)[a]
MRI contraindication	2 (8)
Patient withdrawal	8 (31) [b]
Abnormal MRI finding	2 (8)
Failed minimum tremor criteria	1 (4)
Not proven medication refractory	8 (31) [c]
Failed MOCA and/or BDI-II criteria	3 (12)
Failed tremor dominant criteria	4 (15)
SDR out of range	2 (8)

Abbreviations: MoCA, Montreal Cognitive Assessment; BDI-II, Beck Depression Inventory; SDR, Skull Density Ratio; [a]Four patients failed for more than one reason. [b]Patients withdrew after they changed their mind owing to either opting for DBS (2/8), claustrophobia (1/8), travel requirements (1/8), or not specified (4/8). [c]During screening, the patient had not attempted a medication dosage which was intolerable, or they were in fact medication responsive which was not clear in the pre-screening assessment

eTable 2. Clinical Outcomes

FUS thalamotomy	**Baseline N=20**	**1 Month N=20 (blinded)**	**3 Months N=20 (blinded)**	**1 Year N=14 (unblinded)**
CRST				
Tremor subscore (CRST A+B)[a], *treated hand*	17 (10.5-27.5)	4 (1.5-11.5)	4.5 (3.0-16.0)	5.0 (2.0-14.0)
Total CRST[b]	41.5 (28.0-65.0)	14.5 (7.0-43.5)	18.0 (8.0-52.0)	18.0 (7.0-42.0)
UPDRS				
Resting tremor (item #20), *treated hand*[b]	4.0 (3.0-4.0)	1.0 (0-2.0)	1.0 (0.5-3.5)	1.5 (1.0-3.0)
Postural or action tremor (item #21), *treated hand*[b]	4.0 (1.5-4.0)	0 (0-1.0)	1.0 (0-2.5)	0.5 (0-1.0)
Motor (part III) subsection[b]	23.0 (15.5-34.0)	14.5 (5.0-25.0)	16.5 (8.0-27.5)	13.0 (5.0-28.0)
Total UPDRS	37.5 (32.5-44.5)	N/A[c]	27.0 (11.5-41.0)	19.5 (9.0-36.0)
Quality of life				
PDQ-39[b]	21.2 (12.6-32.0)	N/A[c]	7.9 (4.8-23.5)	7.5 (3.4-22.2)
CRST disability (part C)[b]	13.0 (10.0-18.5)	2.0 (0.5-8.0)	3.5 (1.0-10.0)	2.5 (0-11.0)
Neuropsychological				
MoCA	25.5 (23.0-28.0)	N/A[c]	25.5 (23.5-26.5)	25.0 (24.0-26.0)
BDI-II	5.0 (2.5-9.0)	N/A[c]	6.0 (1.5-9.0)	5.0 (3.0-8.0)
LEDD (mg)	751 (450-950)	573 (400-950)	500 (400-836)	550 (400-800)
Sham procedure	**Baseline, N=7**	**1 Month, N=7 (blinded)**	**3 Months, N=7 (blinded)**	
CRST				
Tremor subscore (CRST A+B)[a], *treated hand*	23 (14-27)	15 (12-17)	17 (12-21)	
Total CRST[b]	48 (43-62)	39 (27-54)	37 (29-53)	
UPDRS				
Resting tremor (item #20), *treated hand*[b]	4 (3-4)	3 (2-4)	4 (4-4)	
Postural or action tremor (item #21), *treated hand*[b]	4 (2-4)	4 (0-4)	4 (1-4)	
Motor (part III) subsection[b]	25 (15-33)	10 (5-34)	15 (11-21)	
Total UPDRS	39 (25-53)	N/A[c]	24 (21-50)	
Quality of life				
PDQ-39[b]	25.0 (14.8-27.7)	N/A[c]	17.4 (1.8-20.6)	
CRST disability (part C)[b]	17 (13-20)	16 (11-18)	16 (13-18)	
Neuropsychological				
MoCA	27 (23-28)	N/A[c]	26 (23-28)	
BDI-II	5 (4-8)	N/A[c]	8 (2-9)	
LEDD (mg)	640 (550-1250)	640 (550-1250)	840 (550-1250)	

All assessments on medications. Data are median (IQR). Abbreviations: CRST, Clinical Rating Scale for Tremor; UPDRS, Unified Parkinson's Disease Rating Scale; PDQ, Parkinson's Disease Questionnaire; LEDD, Levodopa Equivalent Daily Dosage. [a]Primary outcome. [b]Predefined secondary outcome. [c]Partial UPDRS performed at 1 month (UPDRS III), PDQ-39 and BDI-II not assessed at 1 month.

eTable 3. Adverse Events for Open-Label Crossover Patients

Thalamotomy Related[a]	**FUS Thalamotomy (N=6, unblinded)**
Finger paresthesia	
Transient[c]	2 (33)
Persistent[d]	0 (0)
Orofacial paresthesia	
Transient	2 (33)
Persistent	0 (0)
Ataxia	
Transient	0 (0)
Persistent	0 (0)
Hemiparesis	
Transient	0 (0)
Persistent	0 (0)
Dysmetria Transient	0 (0)
Mild vocal change Persistent	0 (0)
MRI/Ultrasound Related[b] **(All Transient)**	
Scalp numbness	0 (0)
Headache	2 (33)
Dizziness / vertigo	2 (33)
Head pain / heat sensation	2 (33)
Stomach pain / nausea / emesis	0 (0)
Tinnitus	1 (17)
Periorbital swelling	0 (0)
Neck / back / shoulder pain	2 (33)
Decline in mental status	2 (33)
Pin site pain	3 (50)
Anxiety	1 (17)
Light headedness	0 (0)
Right sided ecchymosis	0 (0)
Spot in visual field	0 (0)
Unrelated	
Decline in visuospatial abilities	0 (0)
Decline in executive function	1 (17)[e]
Transient ischemic attack	1 (17)[e]
Brief loss of reality	0 (0)
Increased daytime sleepiness	0 (0)
Decreased hand dexterity	0 (0)
Worsening degenerative knee disease	0 (0)
Cholecystitis / cholecystectomy	0 (0)
Worsening of depression	0 (0)

Data is No (%).[a]From the creation of a thalamic lesion. [b]From the procedure environment. [c]Transient AEs resolved during the one year study. [d]Persistent AEs were still present at one year. [e]Same patient, unrelated to procedure, reported as SAEs.

eTable 4. Clinical Outcomes of Open-Label, Crossover FUS Thalamotomy

	Baseline, N=6	**3 Months, N=6**	**1 Year, N=5**
CRST			
Tremor subscore (CRST A+B), *treated hand*	21 (14-24)	5.5 (4-11)	6 (4-12)
Total CRST	47 (43-53)	14 (10-17)	21 (16-27)
UPDRS			
Resting tremor (item #20), *treated hand*	4 (4-4)	3 (1-4)	3 (3-3)
Postural or action tremor (item #21), *treated hand*	4 (2-4)	1 (0-4)	2 (1-3)
Motor (part III) subsection	27.5 (15-33)	9 (7-29)	23 (15-25)
Total UPDRS	43 (25-53)	16.5 (12-41)	37 (19-39)
Quality of life			
PDQ-39	25.0 (21.6-27.7)	14.5 (3.4-21.7)	18.8 (10.4-28.6)[a]
CRST disability (part C)	18.5 (15.0-20.0)	1.5 (0-8.0)	6.0 (5.0-7.0)
Neuropsychological			
MoCA	26.5 (23.0-28.0)	28.0 (27.0-28.0)[b]	24.0 (21.0-27.0)
BDI-II	6 (4-8)	1 (1-5)[b]	7 (5-7)
LEDD (mg)	620 (550-775)	694 (400-1000)	1000 (400-1010)[c]

All assessments were unblinded and made during the on medication condition. Data are median (IQR). Abbreviations: CRST, Clinical Rating Scale for Tremor; UPDRS, Unified Parkinson's Disease Rating Scale; PDQ, Parkinson's Disease Questionnaire; LEDD, Levodopa Equivalent Daily Dosage. [a]N=4. [b]N=5. [c]Patient lost to follow up had LEDD of 500mg.

eReferences

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