Focused Ultrasound Surgery for Parkinson's Disease

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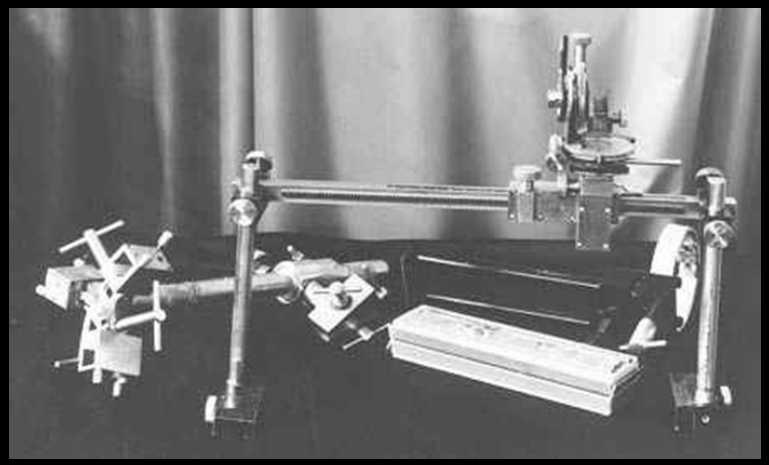
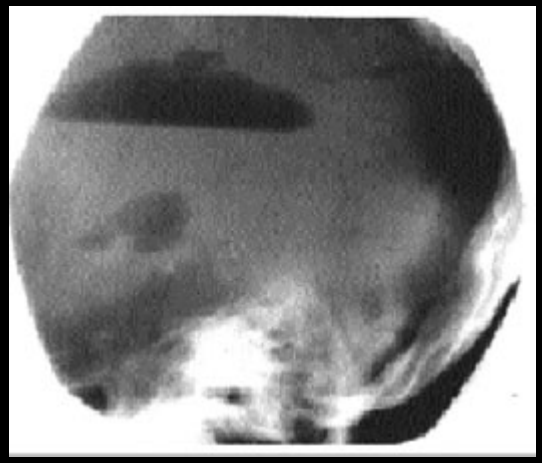
Disclosures

- The University of Maryland has received research support from InSightec
- MRgFUS is FDA approved only for Essential Tremor and Tremor Dominant Parkinson's disease.

Brain Surgery for Parkinson's Disease

- **Era I, 1960s**: Cryo-Thalamotomy for PD tremor, Pallidotomy. Effective, but unexpected complications from bilateral procedures on speech and swallowing.





Irving Cooper began with homemade equipment guided by pneumoencephalography

Brain Surgery for Parkinson's Disease

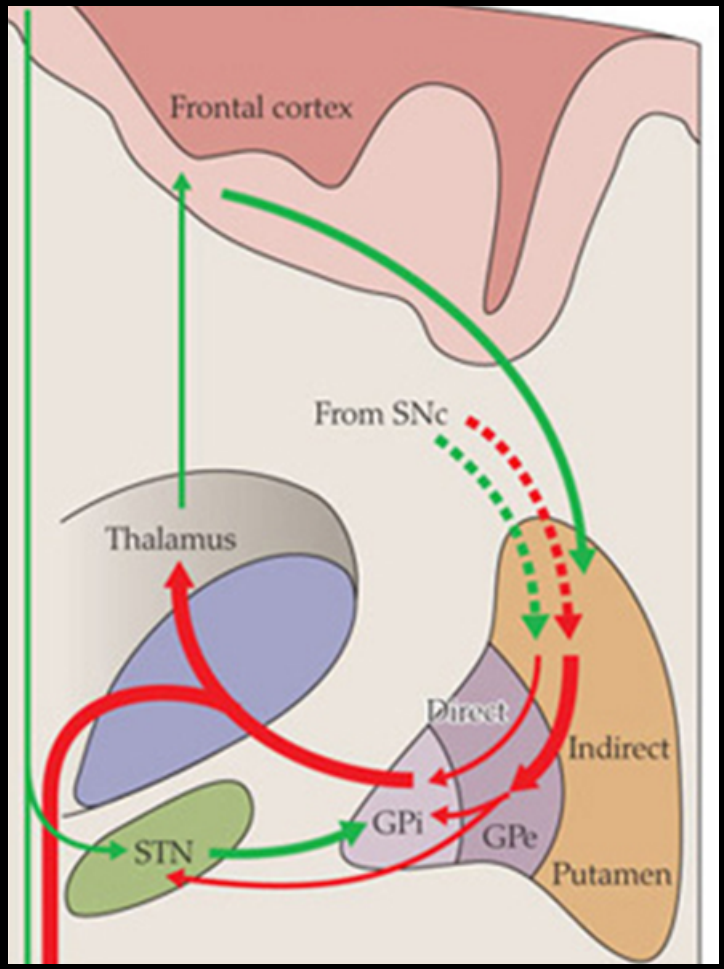
- **Era II, 1990s**: DBS to VIM, STN, GPi for PD . Effective, bilateral, adjustable with no ***intentional*** brain lesion but unintended surgical complications of bleeding (1%) and infection (2%).
- Possible with advanced stereotactic apparatus, MRI, and intra-operative neurophysiology

Deep Brain Stimulation (DBS): The Standard of Surgical Therapy

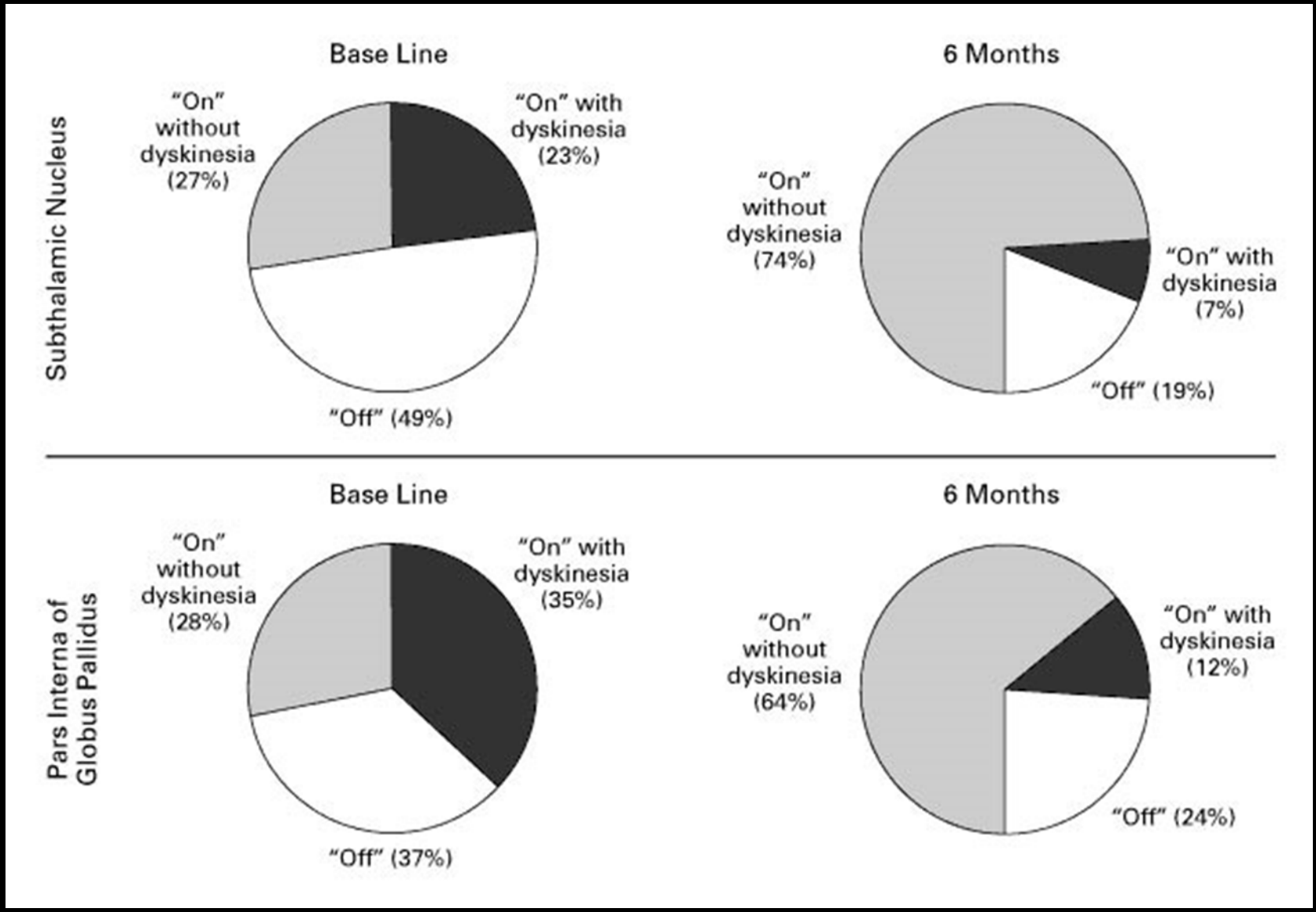
- An implantable electronic device that interacts with brain activity to improve motor symptoms of Parkinson's disease
- FDA approved since 1997
- Over 200,000 patients implanted world-wide (mostly for PD)
- The commonest form of brain surgery for PD

Surgery for PD: A Tale of Three Targets

- Thalamus (ViM) for refractory tremor
- Subthalamic Nucleus (STN) for fluctuating response to medications – most common target
- Globus Pallidus (GPi) also for dose fluctuations but best for dyskinesias and dystonia



DBS of STN and GPI Give Similar Results



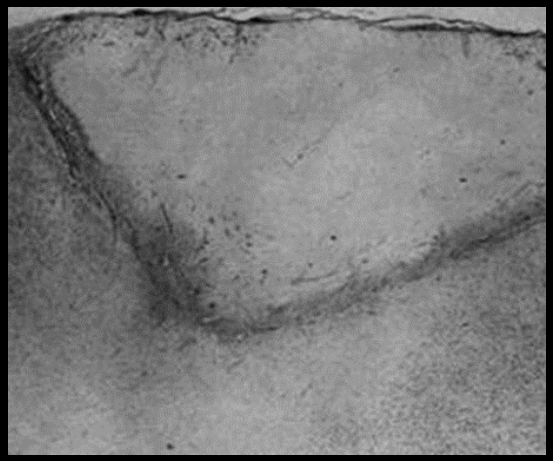
Similar improvement in “On” without Dyskinesia

Brain Surgery with Focused Ultrasound

Three major technical advances after 70 years

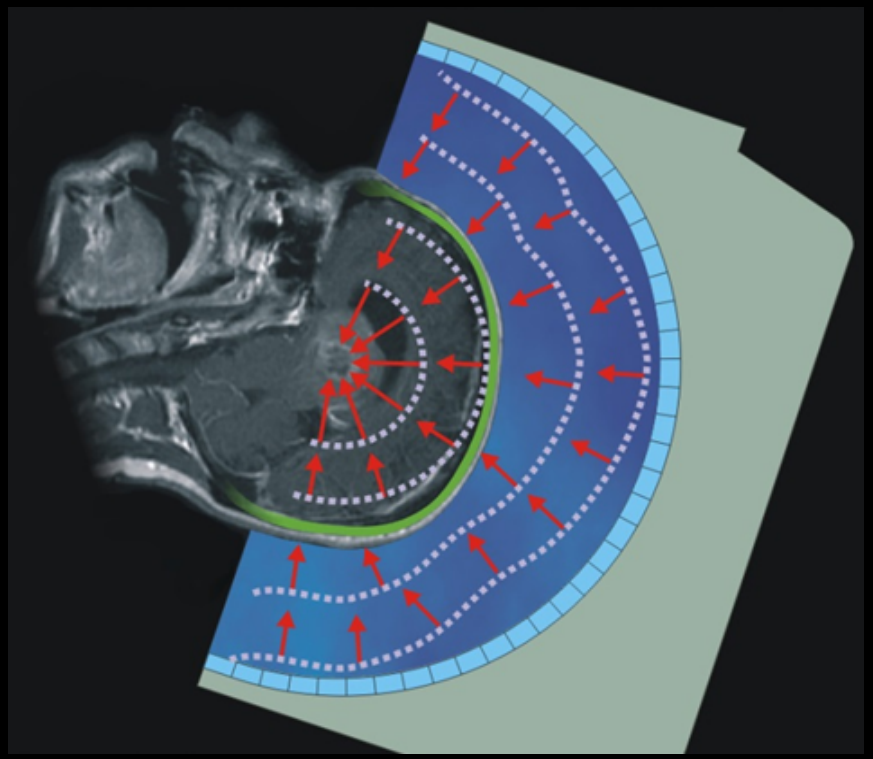
- MRI stereotactic localization
- Temperature sensitive MRI
- Capacity to focus sonic energy in spite of absorption and distortion by the skull

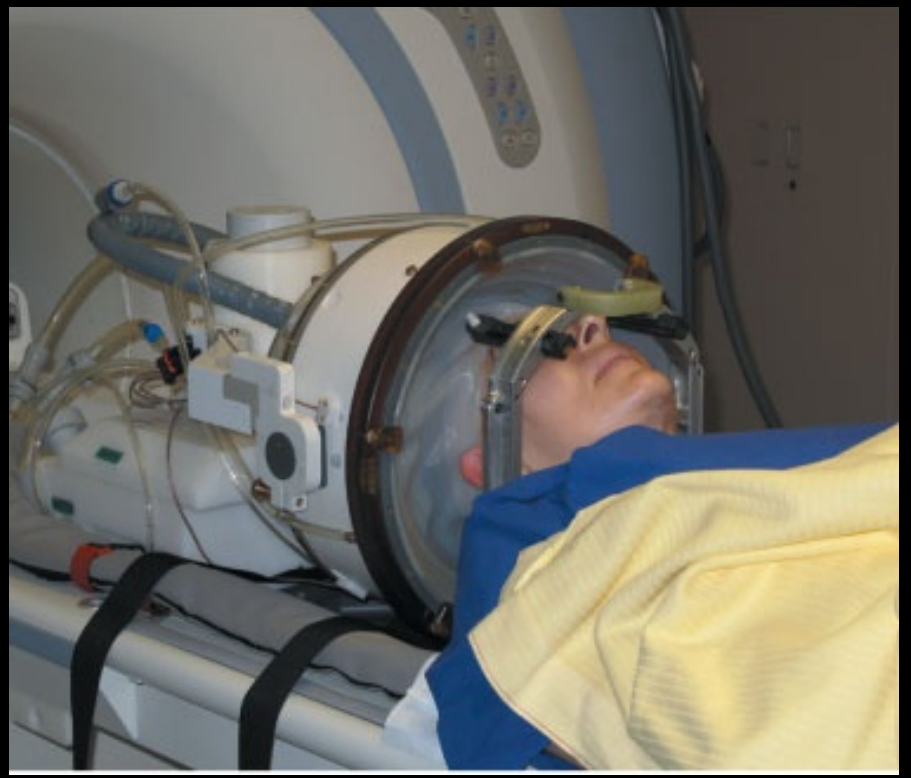
1950's Frey brothers- coagulation lesions in monkey brain but needed to remove the skull



Current Therapeutic Ultrasound to Brain

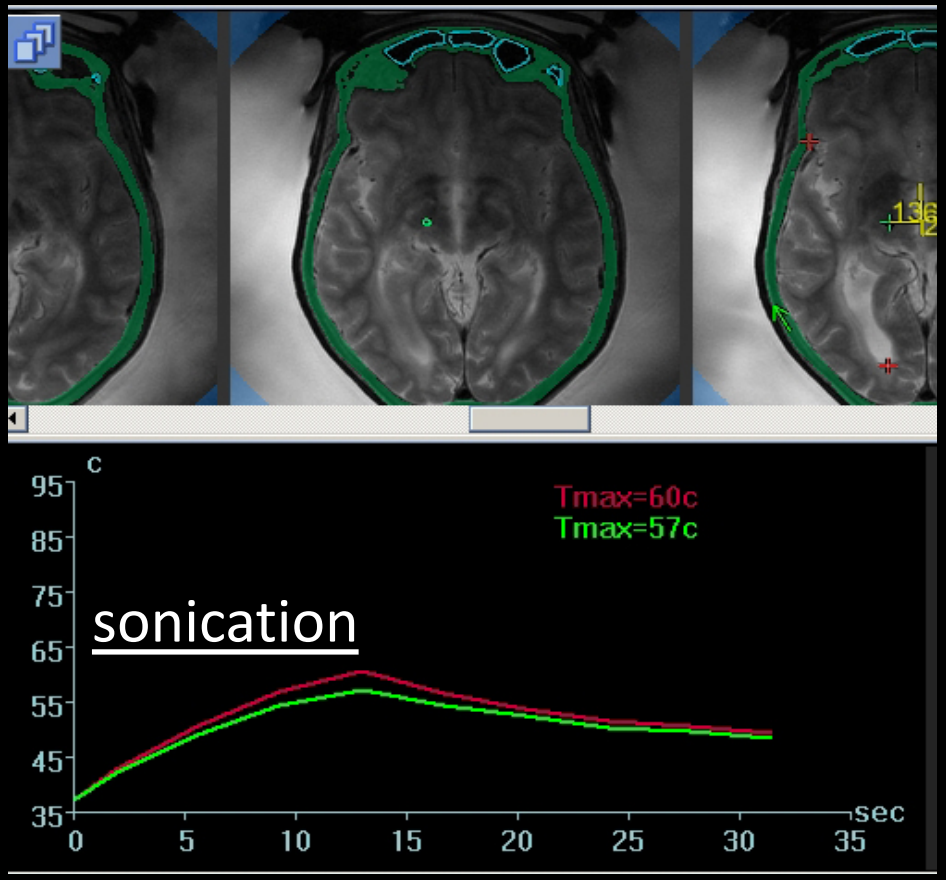
Accuracy of targeting is enhanced by using a focusable array of aligned sonic emitters (1000) where the point of intersection receives 1000 times the sonic energy. (same principle as Gamma Knife)





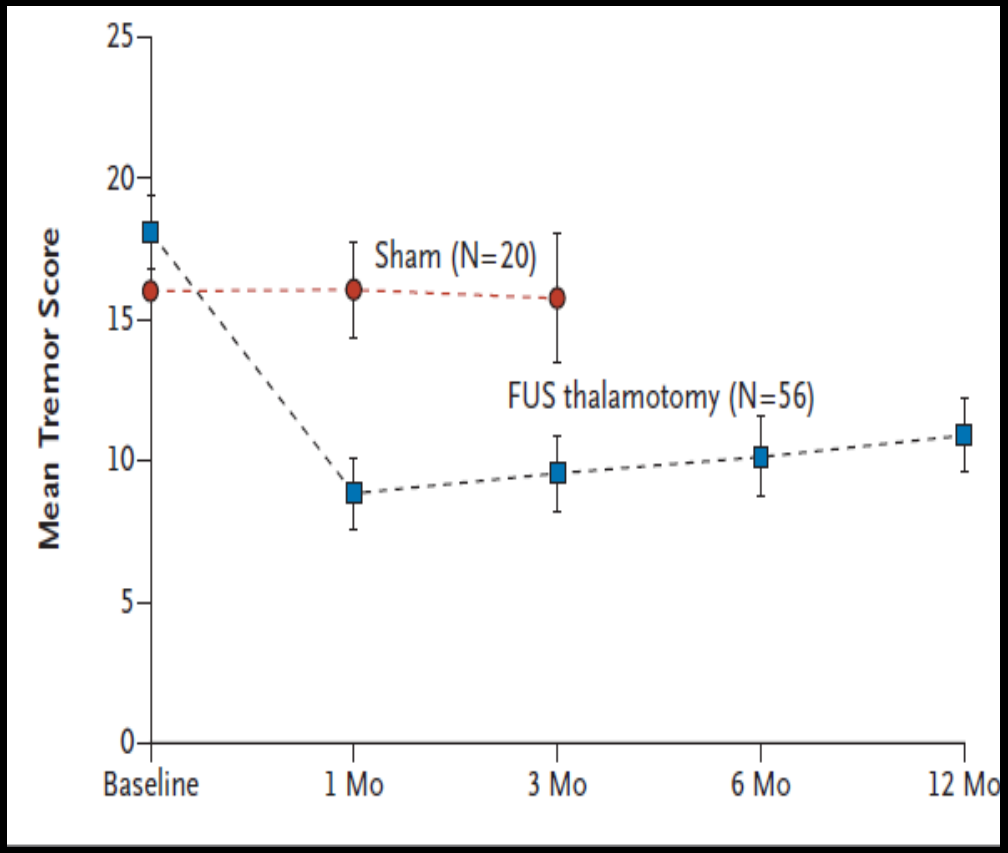
MRI can measure local brain temperature after each sonic treatment in real time

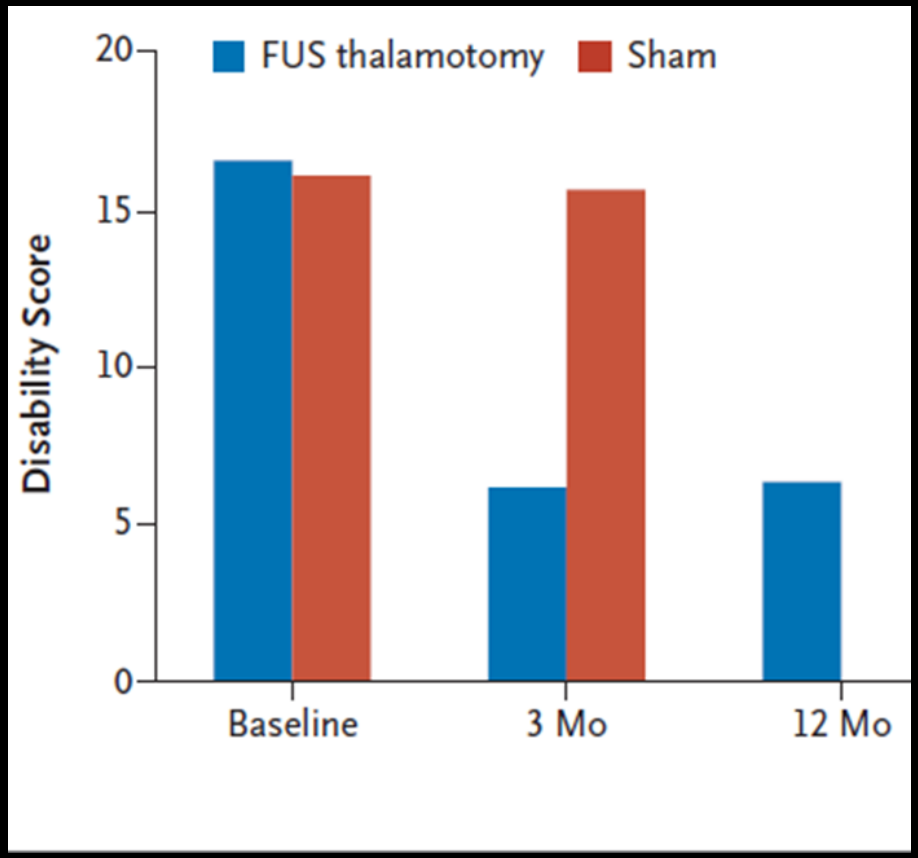
37C Normal
47C Temporary
57C Permanent



Controlled creation of a temporary and then permanent lesion monitoring of both brain temperature and patient response for both symptom relief and side effects (like DBS)

FUS to ViM for Treatment of Essential Tremor: First FDA Brain Indication Approved in 2016





About 50% Reduction In Tremor Amplitude and Disability

Side Effects after FUS for ET (186 Patients) Are Common, But Mostly Mild

Adverse event	Mild	Moderate	Severe
• Speech	8	1	
• Numbness/Parasthesia	75	6	1
• Gait Disturbance/ataxia	70	8	3 Persistent
• Weakness	8	1	
• Headache	25	18	1
• Total	186 (83%)	34 (15%)	5 (2%)

Serious Adverse Events (SAEs) FUS ET Trials (N=186)

- 1 Severe hand numbness
- 1 CVA (unrelated- 6wks. Later)
- 1 Severe lip and tongue numbness
- 1 MI related to anxiety during the procedure
- 1 Syncope/Fall (unrelated)
- 1 Arrhythmia (8 mos. Later – unrelated)
- Frequency of related SAEs – 1.6%

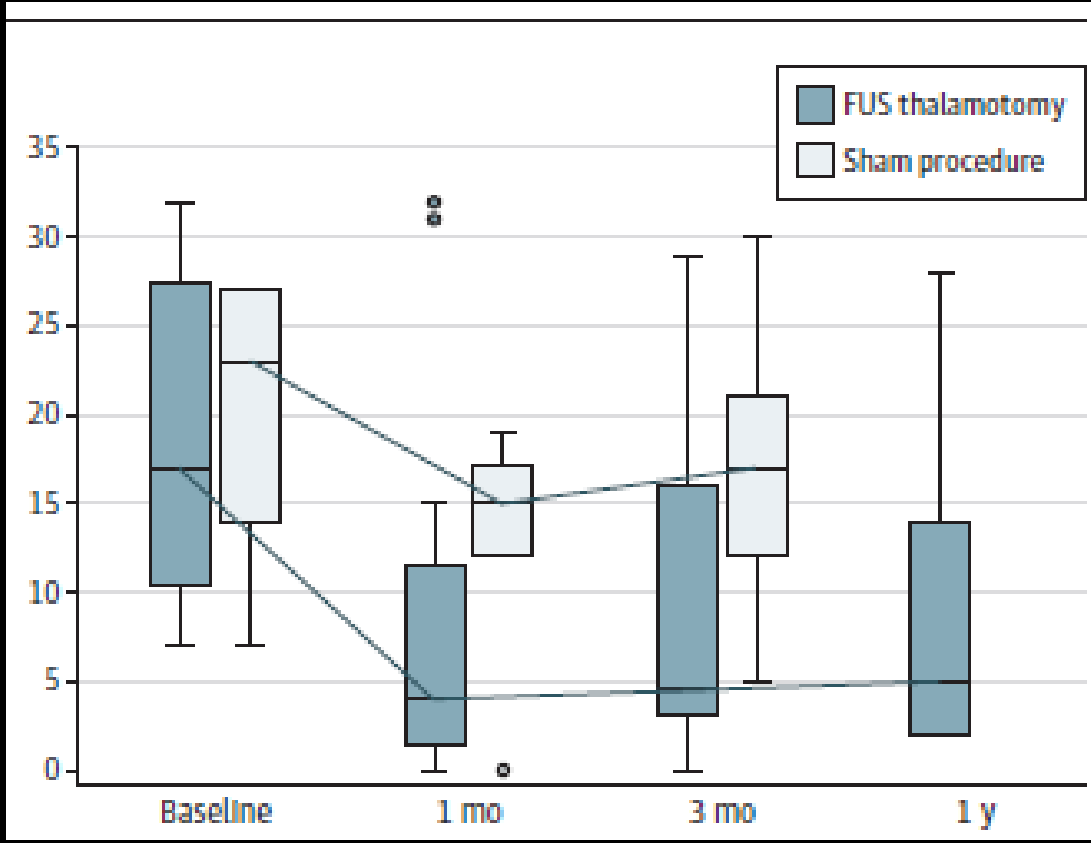
Serious Adverse Events St. Jude DBS ET Trial (N=127 Patients, 166 implants)

- 3 Infections
- 3 Intracranial hemorrhages
- 2 Wound dehiscences
- 1 Air embolus
- 1 Intracranial edema
- 1 Seizure
- 1 Stroke
- 1 Hemiparesis
- 1 Condition worsening
- Frequency of related SAEs – **8.4%**

Surgery and Device Related Only

Plus patients with lead (6) extension (9) IPG (6) revisions and 3 with the system removed = another 15.1% over 2 years

FUS Thalamotomy for PD Tremor: FDA Approved in 2019 (but not yet covered by insurance)

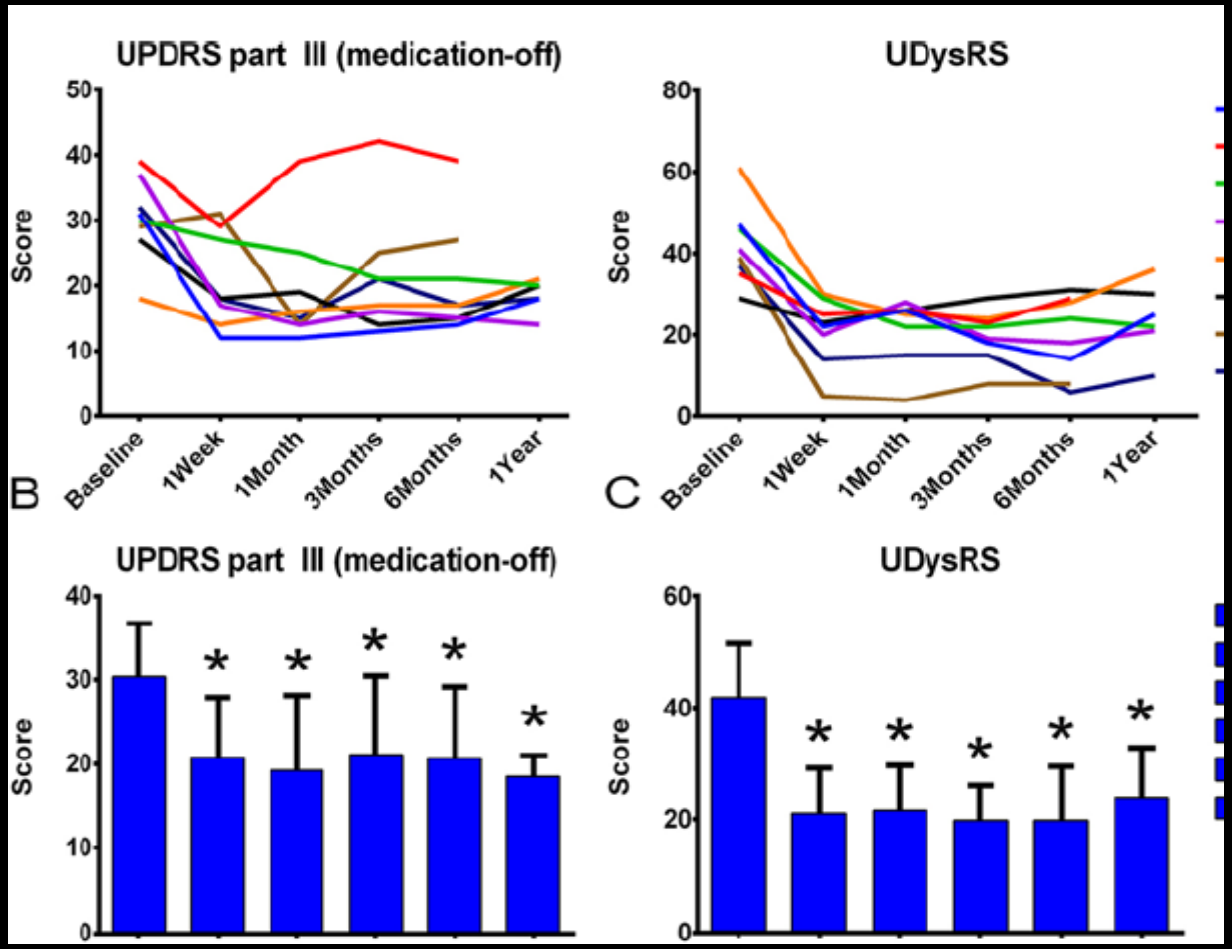


Event	No. (%) FUS Thalamotomy (n = 20)
Thalamotomy Related[a]	
Finger paresthesia	
Transient[b]	7 (35)
Persistent[c]	1 (5)
Orofacial paresthesia	
Transient	1 (5)
Persistent	4 (20)
Ataxia	
Transient	8 (40)[d]
Persistent	1 (5)
Hemiparesis	
Transient	2 (10)
Persistent	2 (10)[e]
Dysmetria, transient	1 (5)
Mild vocal change, persistent	1 (5)

Tremor Reduction

Side Effects

First FUS-PD Pallidotomy Trial 2018



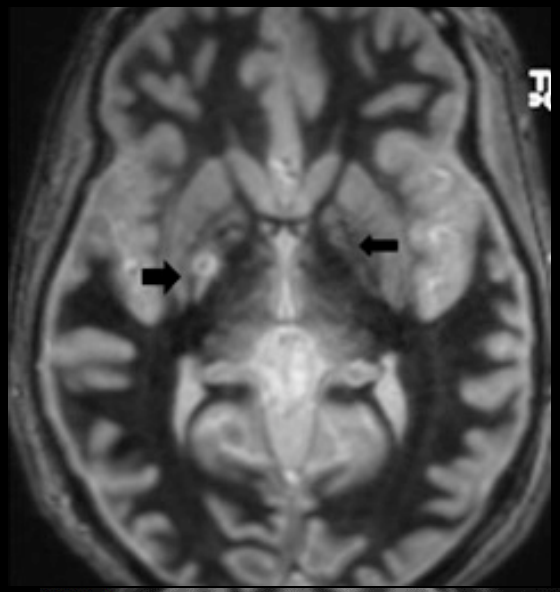
34% improvement in "OFF" severity on treated side and 47% improvement in dyskinsias at 1 year for 8 of 10 patients with 2 treatment failures

Treatment failure is usually due to skull characteristics (SDR) that can be screened out with CT (about 10%)

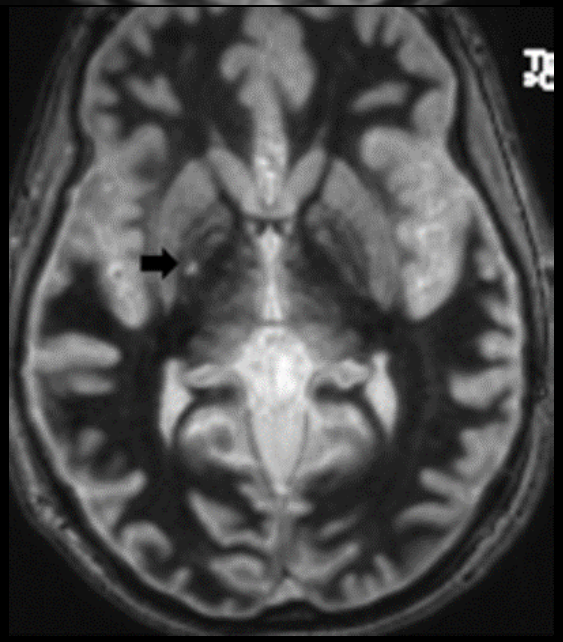
First US Trial of FUS Pallidotomy for PD 2021

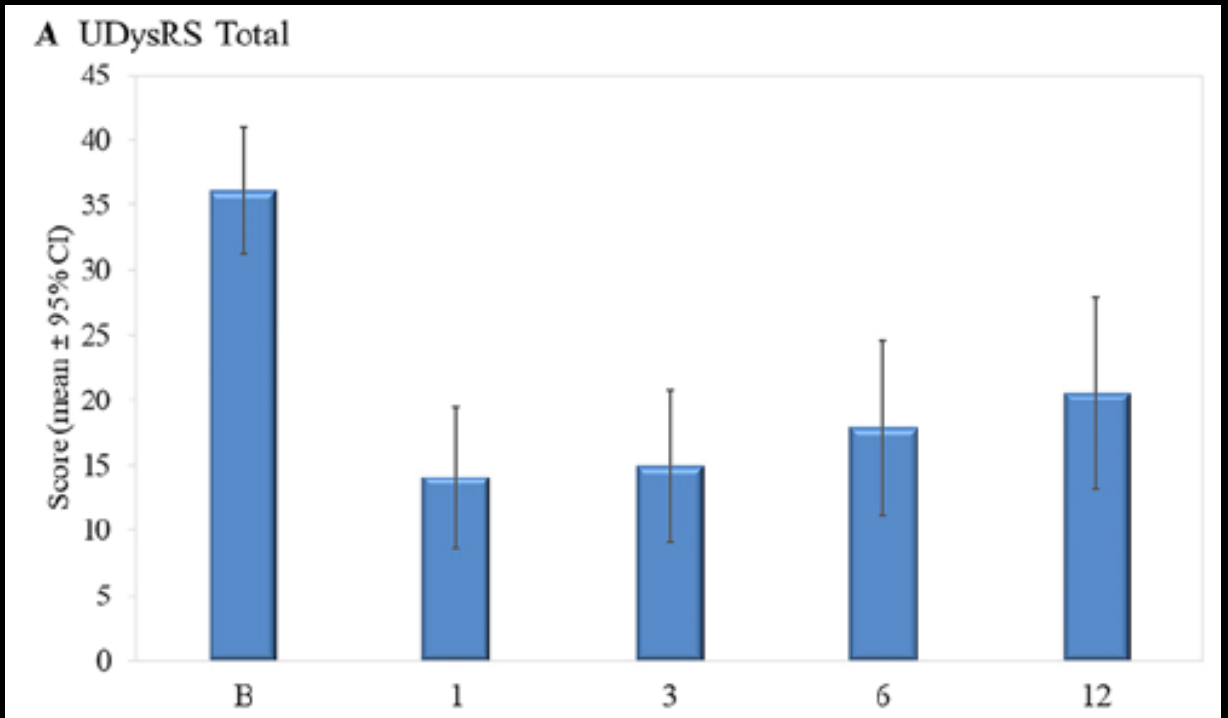
- PD patients with dose fluctuations and dyskinesia with significantly one-sided symptoms, since treatment would only be on one side of brain
- 20 patients for at least one year (13 at U. of Maryland)

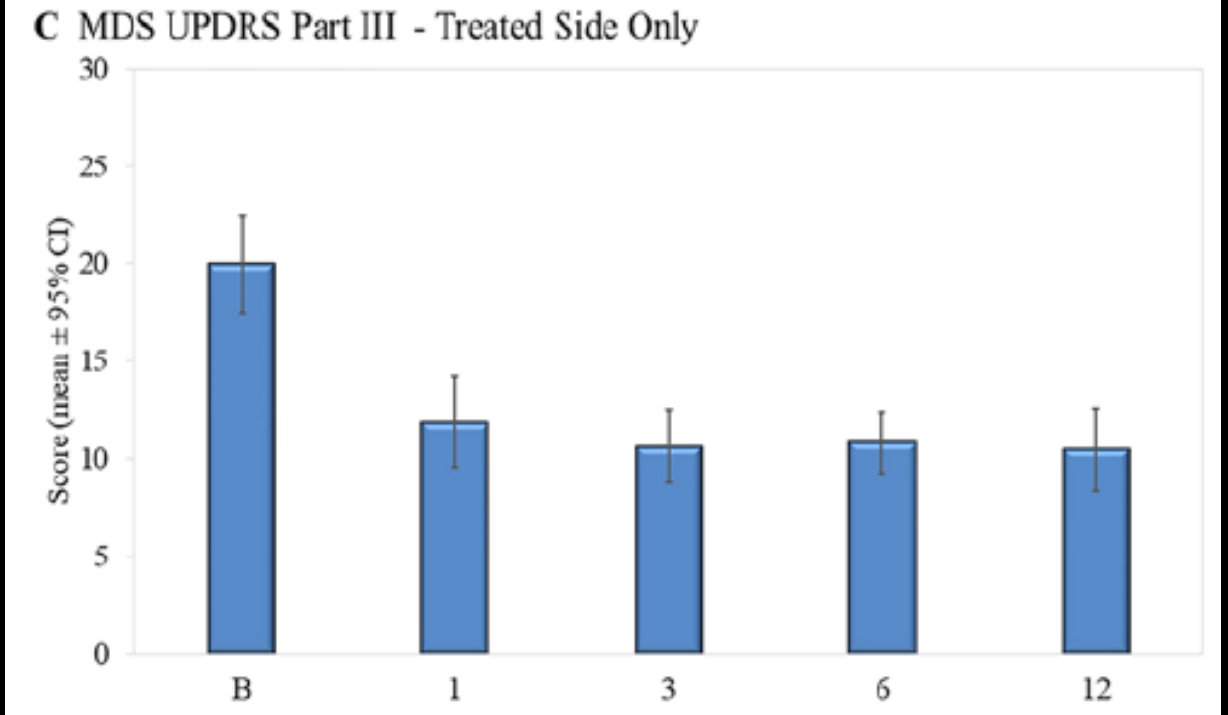
After 1 Day



After 6 mos.





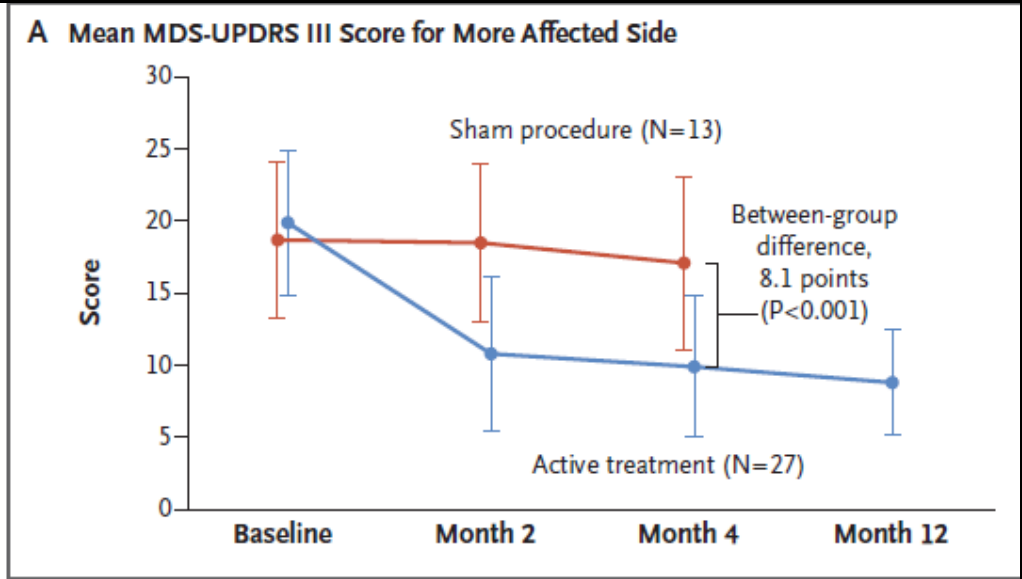


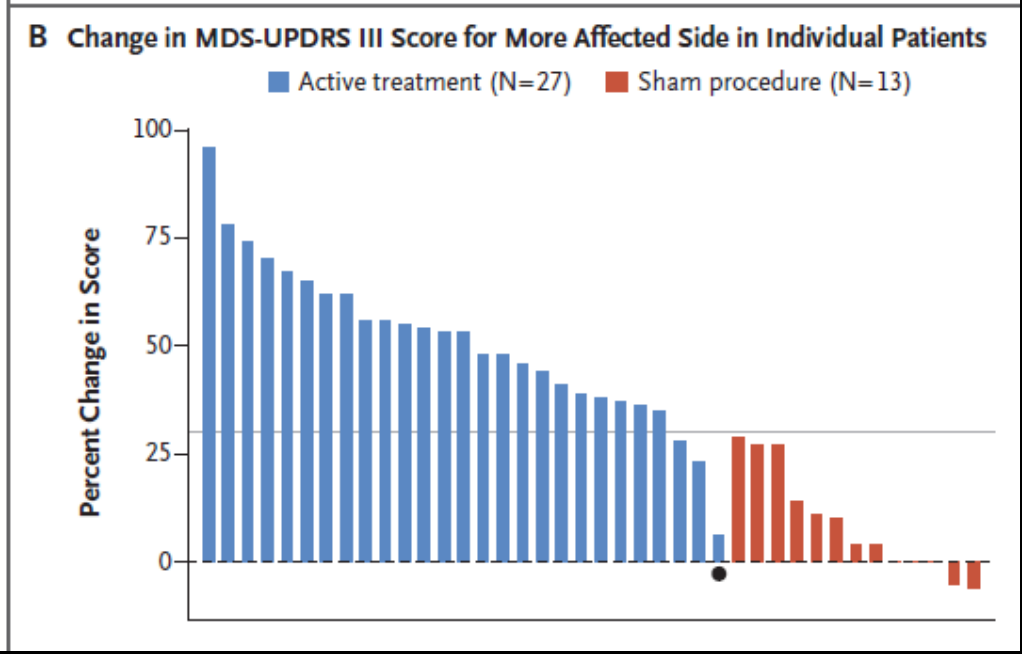
Clinically Significant Reductions in Both Dyskinesias and “Off” Severity on treated side for at least one year

No Serious or Severe Adverse Events

			MILD	MOD.	SEVERE
Procedure Related	General	Fatigue	1	0	0
	Musculoskeletal	Facial weakness	1	0	0
		Facial tic	0	1	0
	Neurological	Cognitive disturbance	1	0	0
		Fine motor problems	2	0	0
	Pain/Discomfort	Headache	4	1	0
	Psychological	Anxiety		2	0
Procedure-related subtotal			9	4	0
Pallidotomy Related	Neurological	Dysarthria	2 (3%)	2	0
	Vision	Visual field deficit	1 (2%)	0	0

First Sham-Controlled Trial of FUS to the STN (2021)





50% Improvement in severity of "off" on the treated side, but the effect is highly variable

Neurologic Side Effects Were Common, but Mostly Temporary and Not Severe (2 at 12 mos.)

	Total	At 24 Hr	At 2 Mo	At 4 Mo	At 12 M
Dyskinesia on the more affected side, in the off-medication state — no. of patients (%)					
Any event, regardless of severity	6 (22)	0	6 (22)	3 (11)‖	0‖
Chorea	5 (19)	0	5 (19)	3 (11)	0
Ballism	1 (4)	0	1 (4)	0	0
New-onset dyskinesia on the more affected side, in the on-medication state — no. of patients (%)	6 (22)	0	6 (22)	1 (4)	2 (7)
Weakness on the more affected side — no. of patients (%)	5 (19)	5 (19)	2 (7)	2 (7)	2 (7)*
Isolated facial asymmetry — no. of patients (%)	3 (11)	3 (11)	3 (11)	1 (4)	0
Speech disturbance — no. of patients (%)					
Any objective or subjective event†	15 (56)	6 (22)	12 (44)	3 (11)	1 (4)
Dysarthria, assessed objectively on examination	7 (26)	6 (22)	5 (19)	3 (11)	1 (4)
Slurred speech, as reported by the patient	8 (30)	0	7 (26)	0	0
Gait disturbance — no. of patients (%)					
Any objective or subjective event‡	13 (48)	8 (30)	7 (26)	2 (7)	1 (4)
Ataxia, assessed objectively on examination	3 (11)	2 (7)	1 (4)	0	0
Unsteady gait, as reported by the patient	10 (37)	6 (22)	6 (22)	2 (7)	1 (4)
Upper limb dysmetria — no. of patients (%)	2 (7)	0	2 (7)	0	0

DBS and FUS: Similarities and Differences

DBS

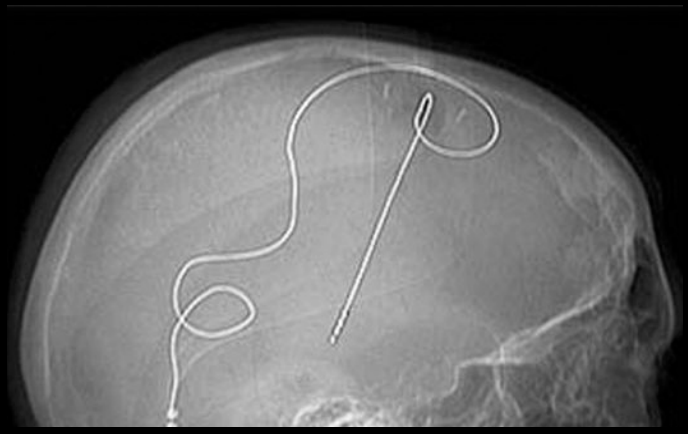
- "Standard of Care"(200Kpatients)
- Head Frame (Standard or Mini)
- Patient cooperation needed with pain
- No Intentional brain injury, but surgical placement (two stages) with known serious risks of bleeding , infection
- Adjustable device to maximize long-term benefit, with programming, battery replacement with risk of breakage and malfunction
- Treats both sides

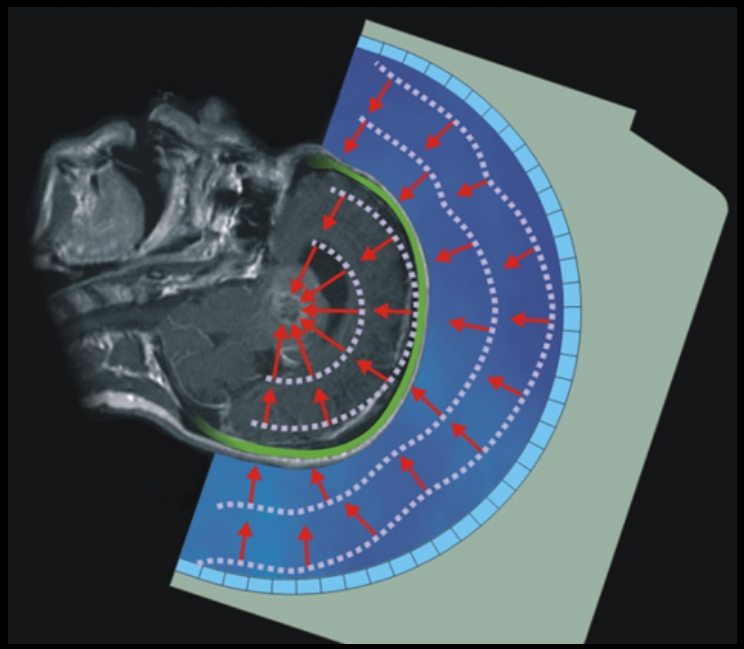
FUS

- FDA approved 2016 for ET, PD tremor 2019, more than 1000 ET about 200-300 PD
- Head Frame
- Patient cooperation needed with less pain and less total procedure time. (3-4 hours)
- Non- Incisional brain destruction with frequent mild deficits, but without bleeding of infection
- One time treatment – no device, no battery, but little experience with retreatment if loss of benefit
- Treats one side *(currently)*

Could MRgFUS Be **Less Harmful** to Brain than DBS?

- MRgFUS makes a brain lesion while DBS does not require an ***intentional*** brain injury
- All of the FUS lesion is at/near the target (5mm diam. = $50mm^3$), while DBS makes 1.5 passes with a 2x50mm rigid probe = $500mm^3$ of potentially compromised non-target brain tissue.
- Many reports of worsening gait and cognition in PD patients years after DBS. Is this a “pass effect” on damaged sub-cortical fibers?





MgFUS: Multiple Brain Indications Using Different Levels of Energy

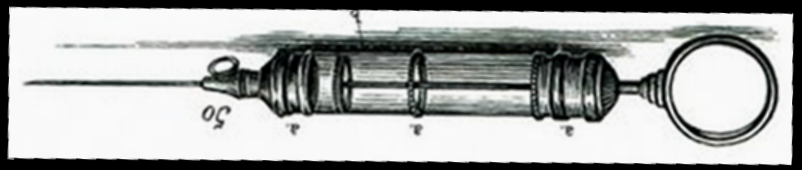
- **High Intensity (HIFU): Lesioning**: ET, PD, Chronic Pain, OCD, Epilepsy, Tumors
- **Medium Intensity: Opening the BBB**, Enhanced chemotherapy for brain tumors, Cell and Molecular therapies
- **Low intensity: Neuro-modulation,** Neuronal inhibition or excitation, modification of behavior

The Blood-Brain Barrier: Obstacle to Restorative Therapy of PD

- **Proteins**: Enzymes, Trophic factors and Anti-Synuclein Antibodies
- **Gene** therapy
- **Stem Cells**: ESC, MSC, NPCs

"High Tech" therapies are too large get into brain

Current technology: Sophisticated variations on the hypodermic needle (1835) with risk of bleeding and infection

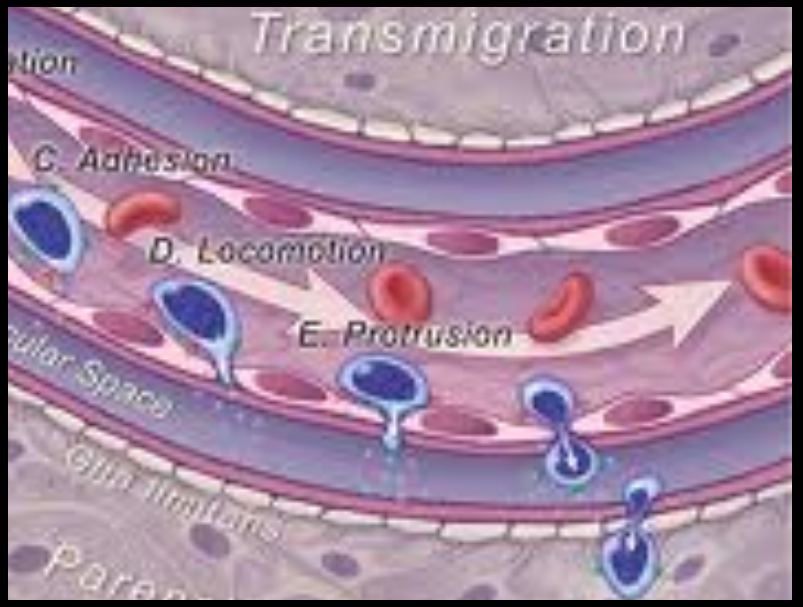


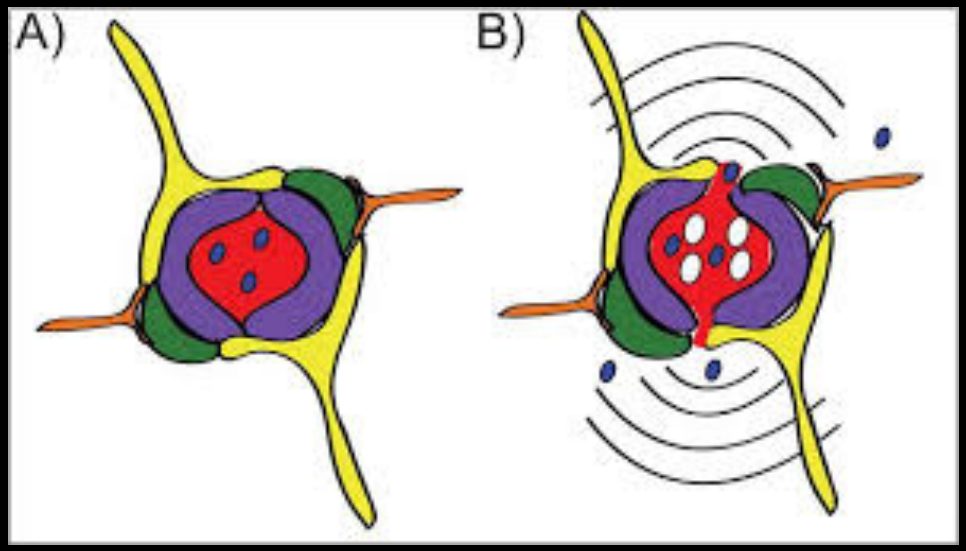
FUS Can Open the Blood-Brain Barrier to Deliver Proteins, Genes and Even Cells

Normal BBB consists of brain endothelial cells sealed together with continuous tight junctions

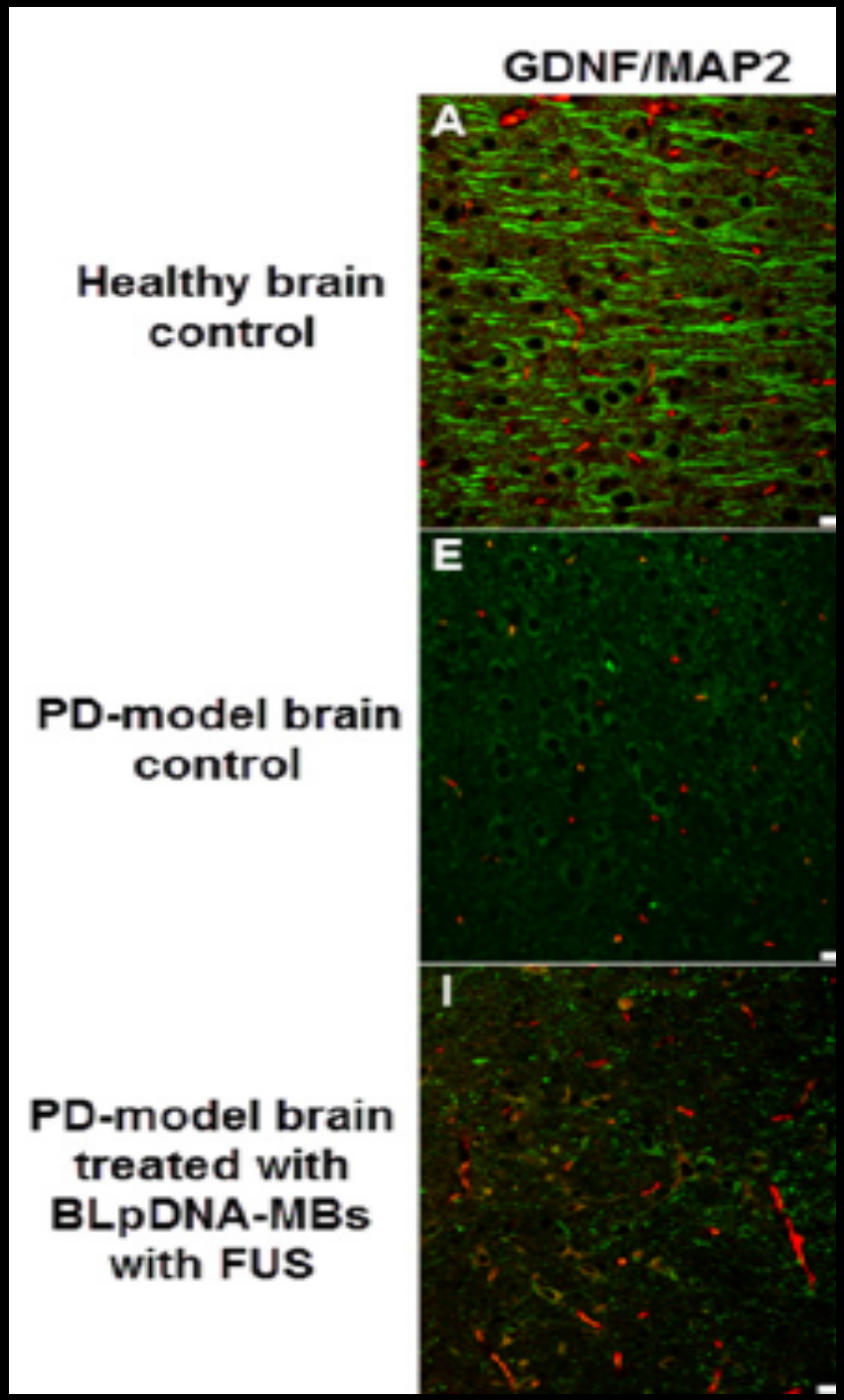
Commercial solutions of microbubbles - used as a contrast agent in diagnostic ultrasound.

When activated by FUS can safely open the BBB for a short time and allow large molecules and cells to enter

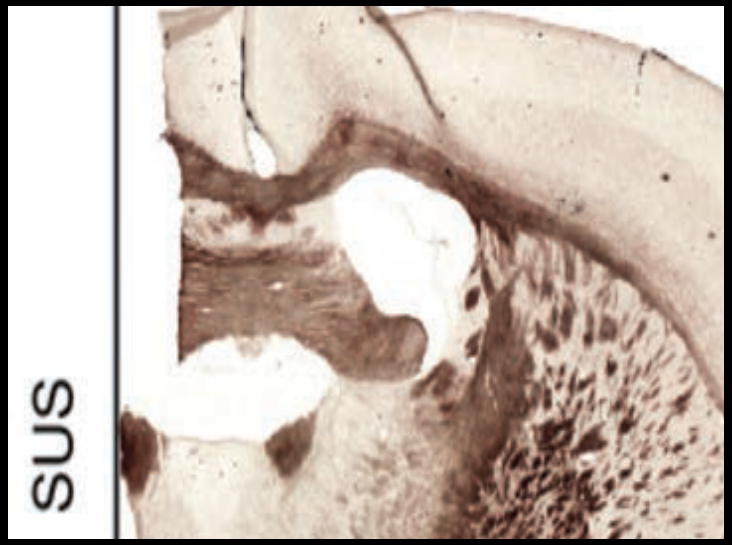


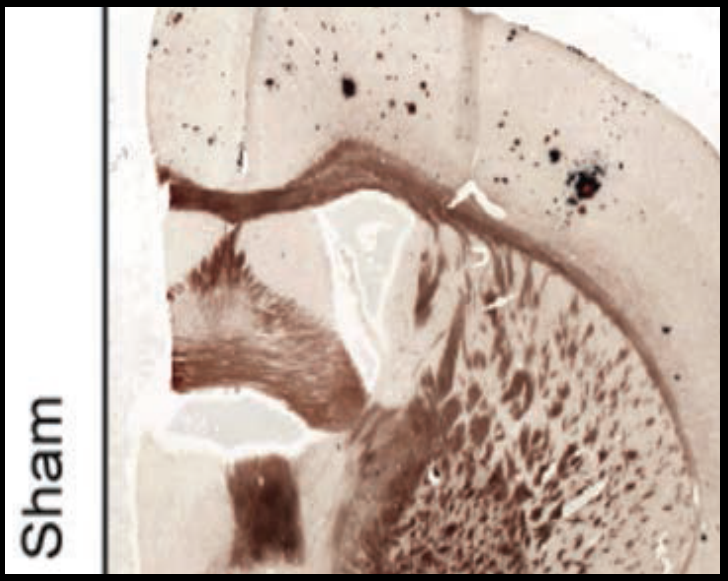


FUS mediated BBBD can allow IV Gene therapy for GDNF in a mouse model of PD with improvement in brain cell function



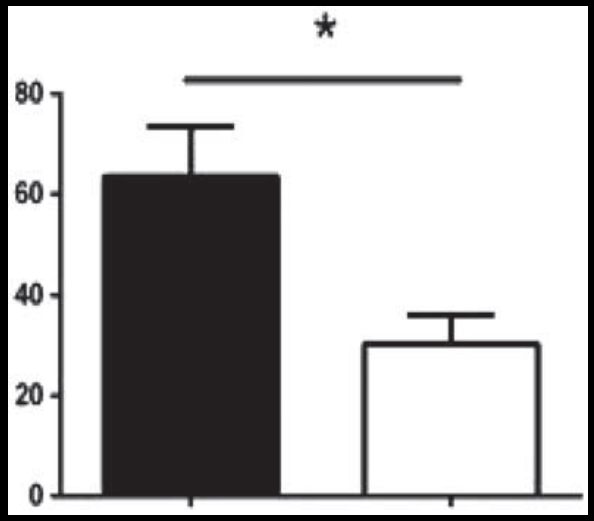
Enhanced Amyloid Clearance with FUS



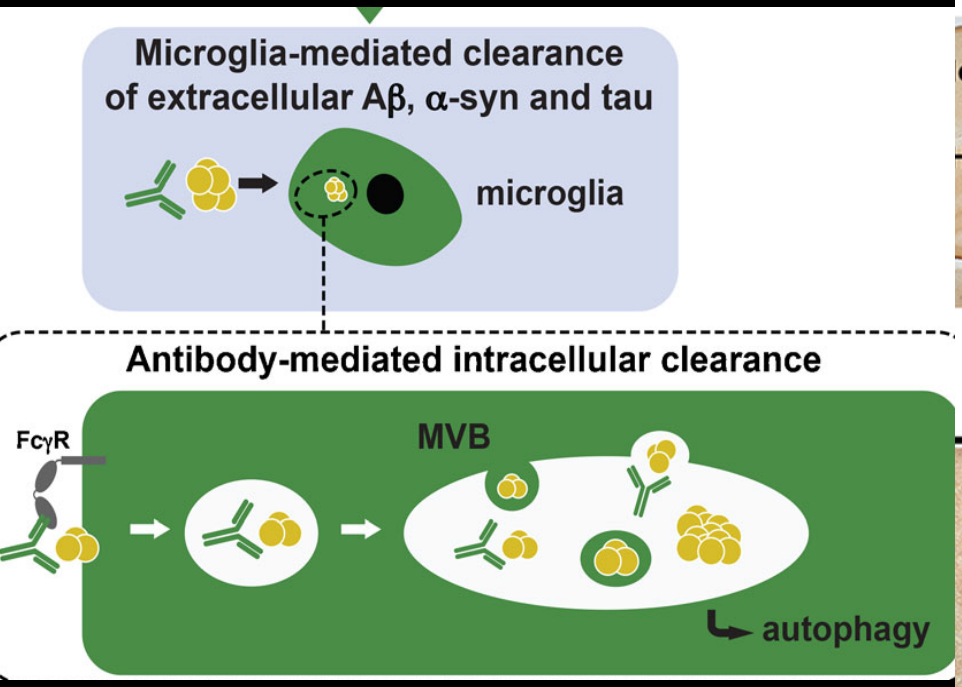


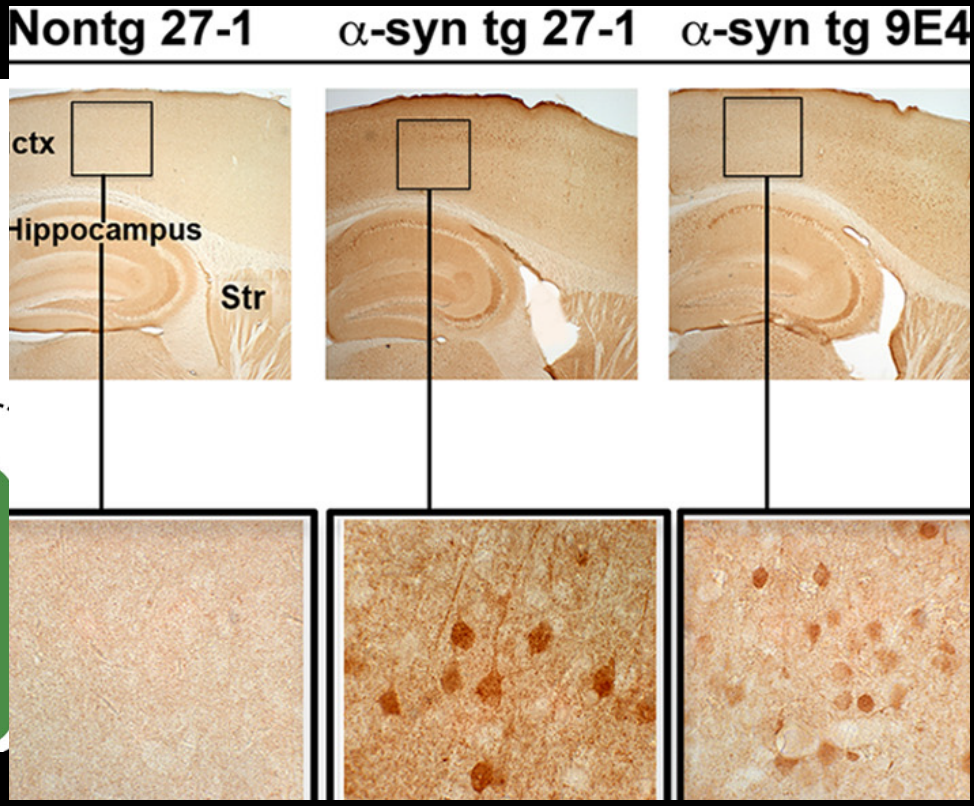
FUS can reduce amyloid plaque burden and improve outcome in a mouse model of Alzheimer's disease

Clinical Trials in Progress both in AD and PD with Dementia



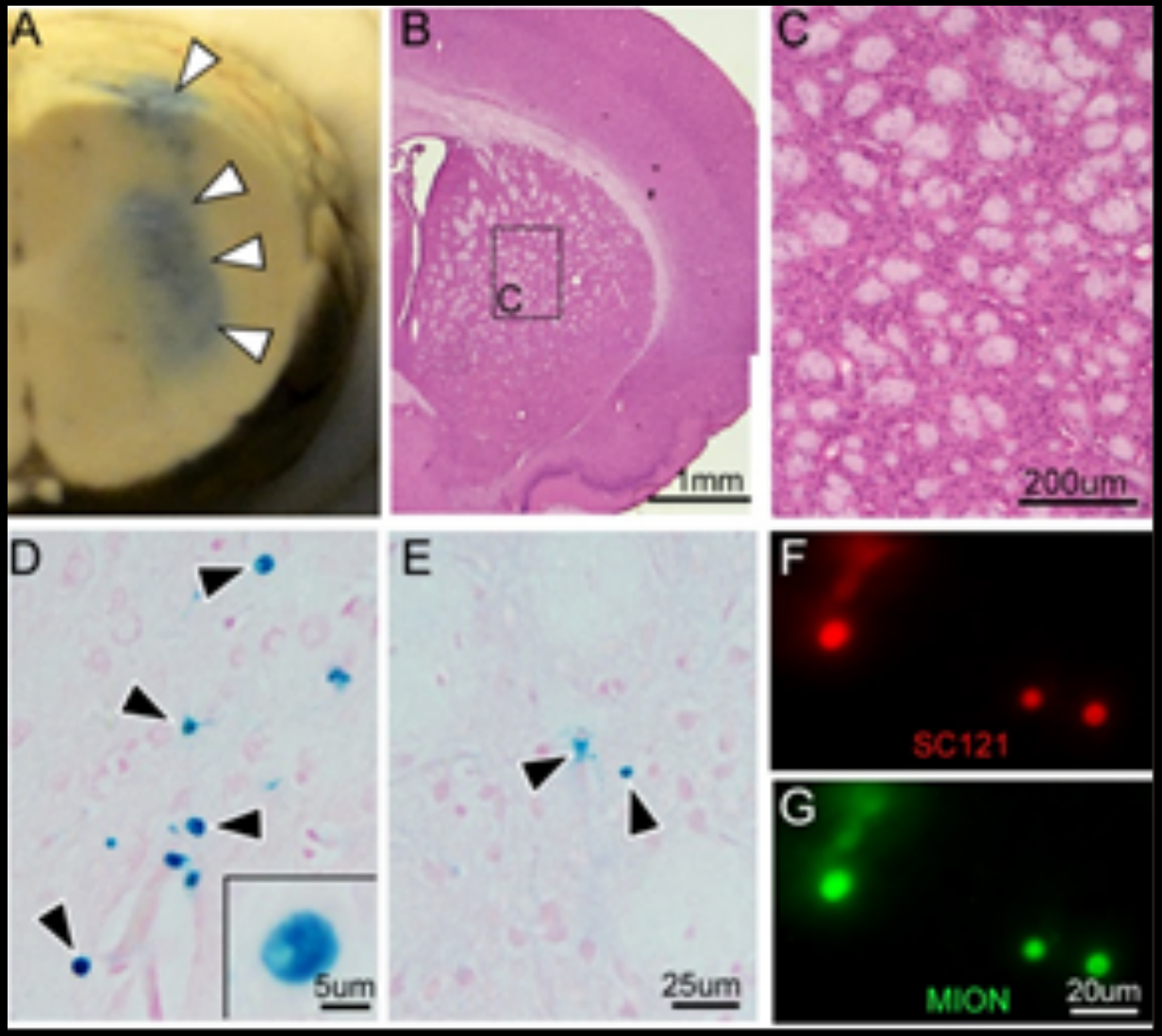
Anti-synuclein antibodies can accelerate the clearance of synuclein in mouse models of PD





Human Trials in Progress. Can FUS Enhance Clearance of Synuclein?

MRgFUS Can Open the BBB without Injury and Allow Stem Cells to Enter the Brain from the Bloodstream



FUS for PD: Work in Progress

- Second Side Treatment for ET – In Progress (U of M)
- Pivotal Trial of Unilateral GPi Treatment – Complete –Under FDA review (U of M)
- Second side GPi Treatment – Planning Stage (U of M), related location (PTT) underway in Europe
- PD Dementia Pilot Trial in Spain
- BBB Opening for Enzyme Delivery (GCase) in England as Disease Modifying Therapy

FUS for PD: It Takes a Team of Different Specialists

- Radiology: Frenkel, Gullapalli, Ghandi, Miller, Melham
- Medical Physics: Dayan (Insightec)
- Neurosurgery: Eisenberg, Woodworth
- Neuroscience: Yarowsky Puche
- Neurology: Fishman, Savitt Von Coelln

University of Maryland is one of only two sites in the US with both a small animal and clinical MRI/FUS systems and is a FUS Foundation Center of Excellence