



Deep Brain Stimulation and Focused Ultrasound for Parkinson's Disease

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Outline

- Overview of Deep Brain stimulation
- Overview of Focused Ultrasound
- DBS vs FUS: a direct comparison
- Questions!

What is Deep Brain Stimulation?

- ◆ Therapy using an implantable electronic device that interacts with brain activity to improve some of the motor symptoms of Parkinson's Disease, Essential Tremor, and Dystonia.
- ◆ Benefits
 - Reversible.
 - Adjustable.





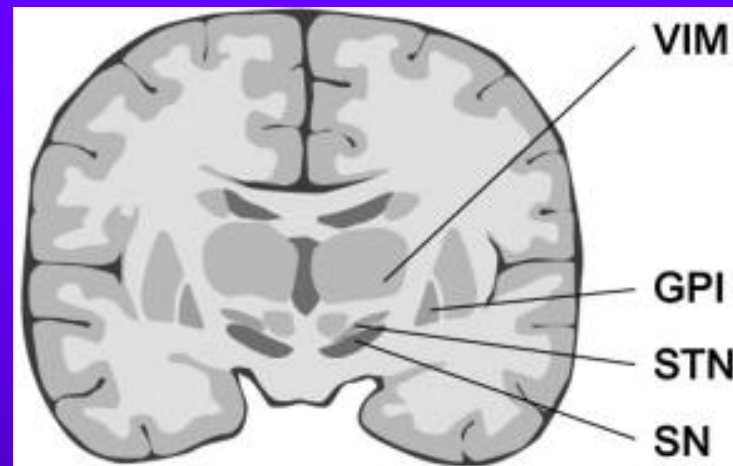
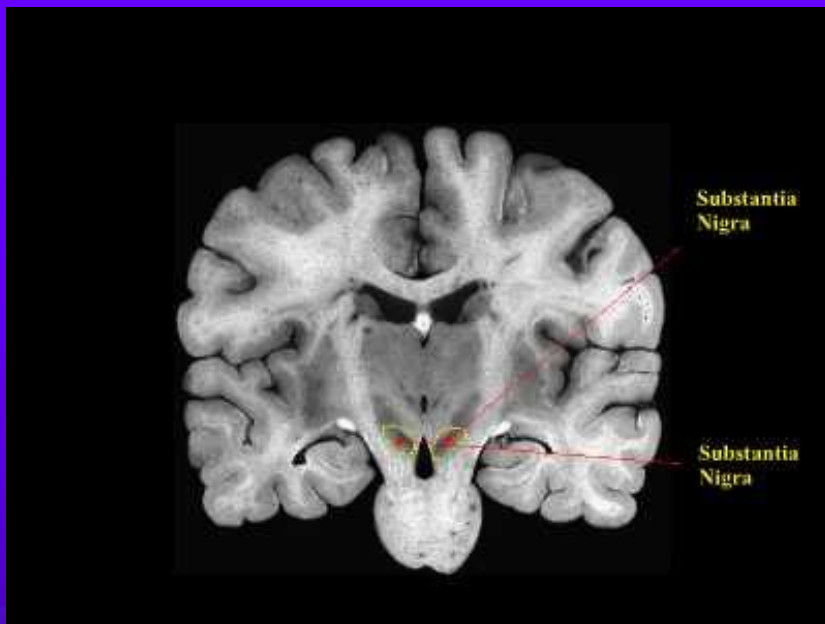
Deep Brain Stimulation (DBS): A “New Standard” Therapy

- ◆ An implantable electronic device that interacts with brain activity to improve motor symptoms of Parkinson Disease
- ◆ FDA approved since for Essential Tremor in 1997, for PD in 2002
- ◆ The commonest form of brain surgery for Parkinson’s disease and Essential Tremor



What is Deep Brain Stimulation?

- ◆ The DBS lead can be implanted in a number of different locations in the brain, with different therapeutic effects.



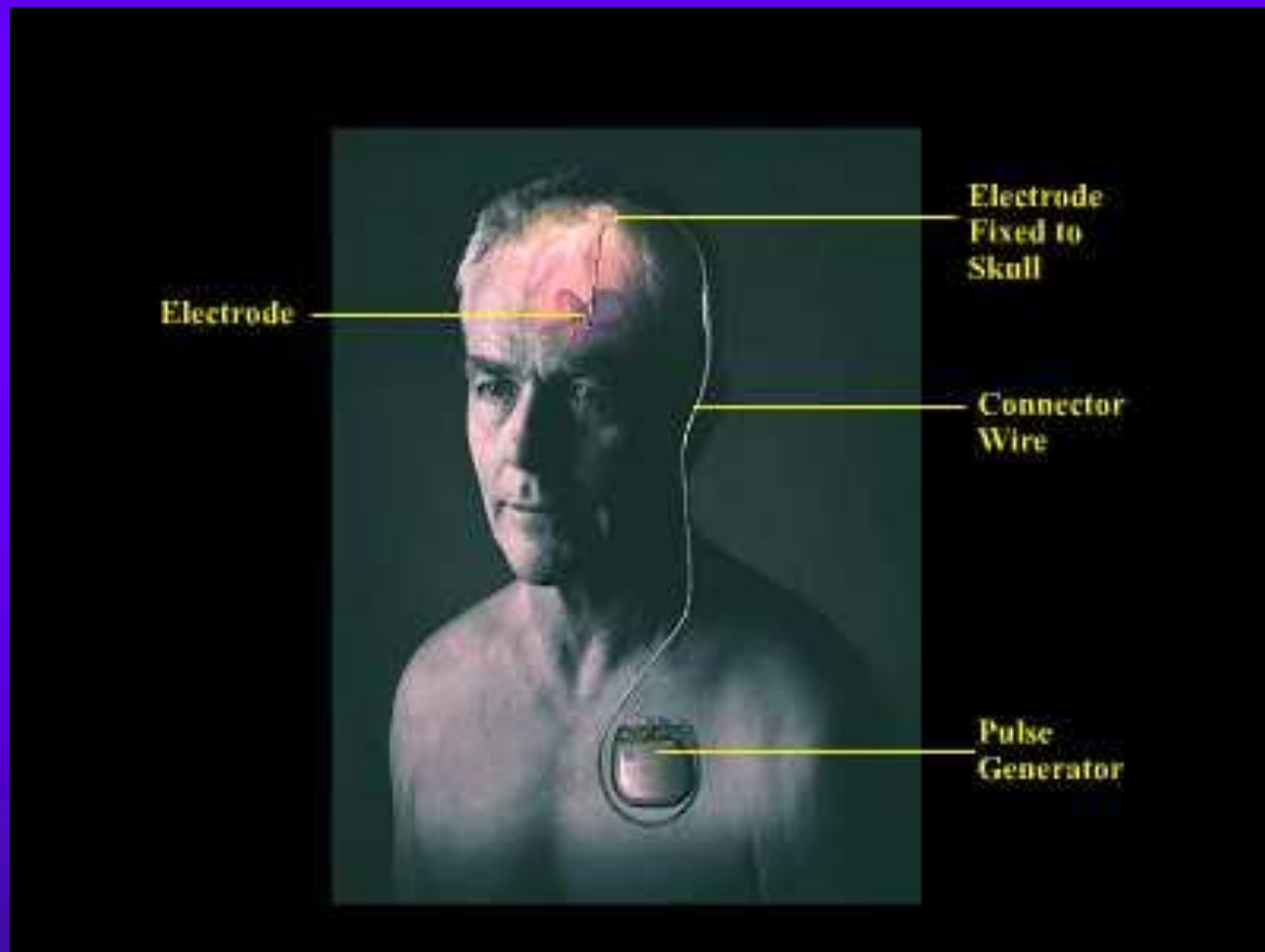
The Subthalamic Nucleus (STN) is a small, almond-shaped structure located deep in the brain, adjacent to the Substantia Nigra. As a result of dopamine deficiency in the Substantia Nigra, the Subthalamic Nucleus is overactive. This is the most common site for DBS lead placement in Parkinson's disease




The key element of DBS is the lead. Currently, the most commonly used lead has 4 electrodes, the two middle ones are directional. The lead is placed into the subthalamic nucleus or the thalamus during a precise surgical procedure.



The other key element is the pulse generator, similar to a pacemaker, which is implanted below the collarbone. The pulse generator drives current through the electrodes, and reduces hyperactivity of certain brain cells.



The lead is fixed to the skull by means of a cap to prevent movement. The lead is connected by means of a connector wire which runs underneath the skin of the scalp and neck to the pulse generator.



What Symptoms are Improved by Surgery?

- ◆ Symptoms improved by surgery are those symptoms that are best improved with medication:
 - Tremor.
 - Tremor reduction can be superior than achieved with medication
 - Slowness (Bradykinesia).
 - Stiffness (Rigidity).
 - Gait freezing.
 - Dyskinesias and Dystonia.
- ◆ Motor fluctuations can often be improved, allowing function at best current level without the interference of dyskinesias



What Symptoms Will Not Be Improved with Surgery?

Deep Brain Stimulation Surgery is Not a Cure



What Symptoms Will Not Be Improved by Surgery?

Parkinson Patients Will Not Be Better Than


YOUR BEST ON TIME

(exception is tremor)



What Symptoms Will Not Be Improved by Surgery?

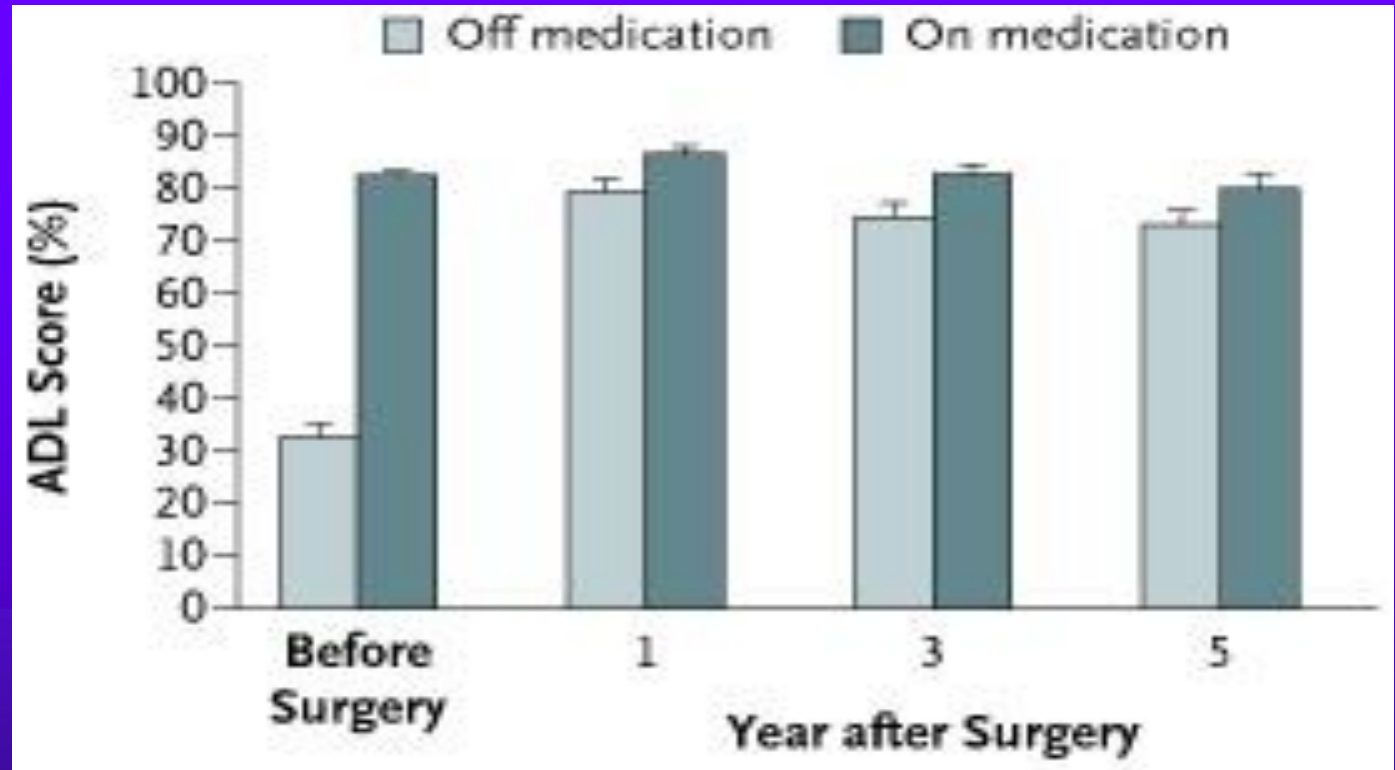
- ◆ Cognitive and Psychiatric Symptoms.
- ◆ On-Period Freezing.
- ◆ Swallowing Difficulties.
- ◆ Speech Problems.
- ◆ Poor Balance.




How Long Will the Benefits of Surgery Last?

In the vast majority of appropriately selected DBS cases, the patients continue to have improved functioning for at least 16 years*.

How Long Will Benefits Last?



- ◆ Patients who have undergone DBS on both sides continue to be improved beyond their pre-op state for at least 5 years.



How Long Will the Benefits of Surgery Last?

Batteries for the pulse generators will need to be recharged at differing intervals depending on the generator settings. *



What Are the Risks of Surgery?

Hemorrhage (1-2%).

Infection (1-2%).

Mechanical Hardware Problems (1-5%).

Short Term Changes in Thinking and Behavior (5%).



Indications for Deep Brain Stimulation for Parkinson's Disease

- ◆ Suffers from idiopathic Parkinson's Disease.
- ◆ “On-Off” phenomena and/or dyskinesia.
- ◆ Troubling motor symptoms despite optimized pharmacotherapy.
- ◆ Highly responsive to levodopa, with good motor function in best “on” state.
- ◆ Doesn't suffer from dementia.
- ◆ Doesn't suffer from untreated depression.



What Should I expect from the Surgery?

- ◆ Surgery is usually (but not always) performed as a two-step procedure:
 - The leads will be implanted.
 - You will be discharged from the hospital the next morning.
 - About one week later, the pulse generator will be implanted under general anesthesia as an outpatient procedure.
- ◆ The Stimulator will be turned on 2-6 weeks after implantation of the pulse generator.



Placing the Electrodes

- ◆ You usually will arrive early on the day of surgery.
- ◆ Nothing to eat or drink on the surgical morning. Some medications will be allowed as discussed in your pre-op physical
- ◆ Surgery may be performed while you are asleep



Frame Application

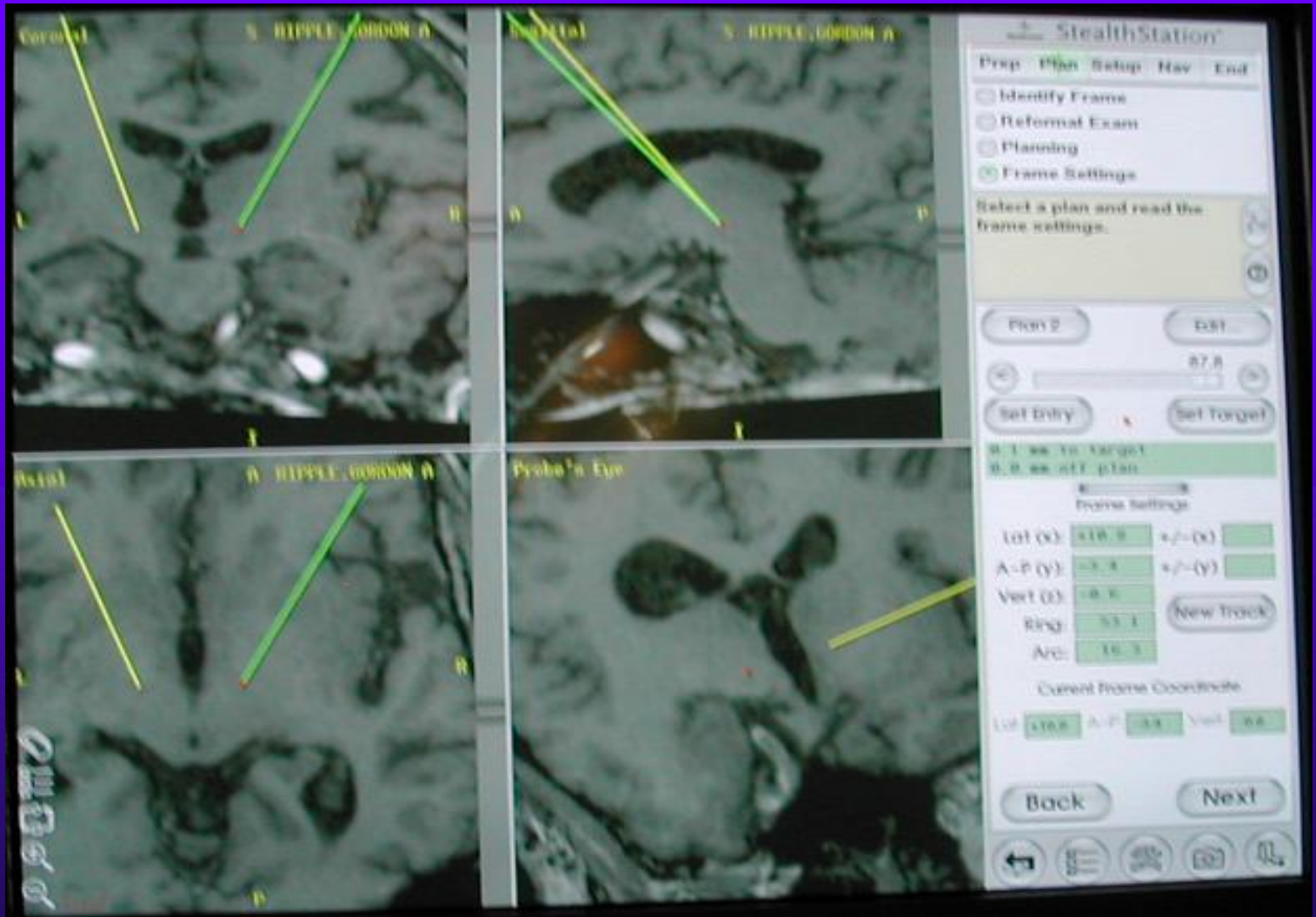


The first step is the application of a frame, which is tightly applied under local anesthesia. It is NOT screwed into your skull. The frame allows identification of the relationships of various brain structures to the position of the frame on the skull. An MRI scan and CT scans will be used to locate landmarks. Another box is attached to the frame.



After DBS surgery, a special cover will be required for all MRI scans – which can be done only at major centers.

Navigation to the Target





- ◆ Surgery begins with opening the skull with a tiny hole about the size of a dime.
- ◆ The drilling takes about 10 seconds.
- ◆ A small circle is placed inside this opening to allow the electrodes to be inserted.
- ◆ After testing, the circular device is closed allowing the electrodes to be held in place.

The Surgery

◆ The DBS Surgical Team:



Microelectrode Recording





After Lead Placement

- ◆ You will go to the recovery room or to ICU.
- ◆ Usually, you go home the next morning.



Placing the Pulse Generator

- ◆ After the leads are implanted in the brain, the second procedure is sometimes performed approximately 1 week later.
- ◆ This procedure is performed under general anesthesia to implant the pulse generator.
- ◆ This is done as an outpatient procedure. Overnight stay is usually not required.



Turning On the Stimulator

- ◆ The stimulator will be turned on 4-6 weeks after placement of the leads.
- ◆ This will take place in an office visit.
- ◆ The stimulator is programmed specifically to treat your symptoms.
- ◆ The visit will take about 1-2 hours. Following visits will be 30min-1 hour.
- ◆ *Parkinson's patients are usually asked to be OFF medication for DBS visits.*



Results of Surgery

- ◆ Some patients note improvement after surgery even before the stimulator is turned on. This is a temporary condition we call “the honeymoon period” or lesional effect.
- ◆ After the stimulator is turned on, an immediate effect is usually apparent.
- ◆ Most patients require multiple programming sessions over the first 3-6 months to optimize the therapy.



Results of Surgery

- ◆ Off time reduced for Parkinson's patients
 - 83% reduction in off time¹
- ◆ Medication requirements on average are decreased by 30-40%.
- ◆ The reduced requirement for medications results in better quality “on” time with less dyskinesia.
 - 86% reduction in incidence and duration of dyskinesias.¹
 - Average daily increase of 4.6 hours on time without troubling dyskinesia.²

¹Ostergard, et al. *Mov Disord*. 2002 Jul;17(4):693-700.

²Weaver, et al, *JAMA*, Jan 7, 2009 Vol 301, No 1: 63-73.



Results of the Surgery

- ◆ Remember, Deep Brain Stimulation does not cure the disease, nor does it inhibit the progression of the disease.
- ◆ The stimulator can be adjusted over time to treat changing symptoms.



Results of Surgery?

For Parkinson's Patients:

YOU WON'T BE BETTER THAN

YOUR BEST ON TIME

What is Focused Ultrasound?

- ◆ Therapy using an implantable electronic device that interacts with brain activity to improve some of the motor symptoms of Parkinson's Disease, Essential Tremor, and Dystonia.
- ◆ Benefits
 - Reversible.
 - Adjustable.





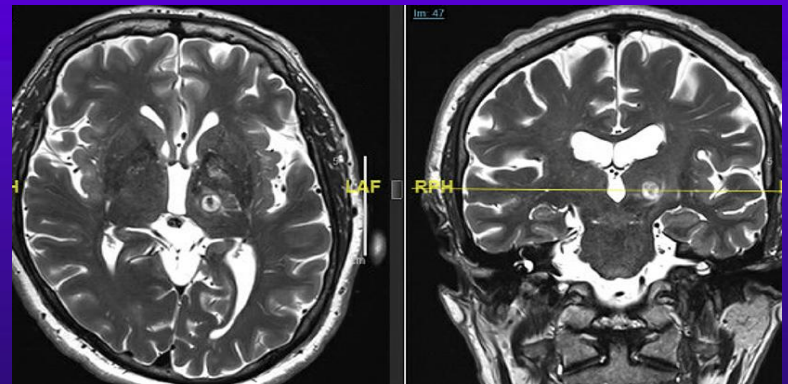
Focused Ultrasound: An emerging treatment

A rapidly evolving, noninvasive, therapeutic technology with the potential to improve the quality of life for patients with Parkinson's disease. This novel technology focuses beams of ultrasonic energy precisely and accurately on targets deep in the brain without damaging surrounding normal tissue.



What is Focused Ultrasound?

- ◆ Uses 1024 high frequency sound waves to lesion brain
- ◆ Relatively non-invasive
- ◆ Outpatient procedure





What is it currently used for?

1. Unilateral Thalamotomy (ViM) for Essential Tremor

Approved by FDA and Medicare for medication intractable moderate/severe ET

Insurance will pay

2. **Bilateral** Thalamotomy (ViM) for Essential Tremor

Trial no longer recruiting.

Just FDA Approved, insurance not yet paying

3. Unilateral Thalamotomy (ViM) for **Parkinson's Disease**

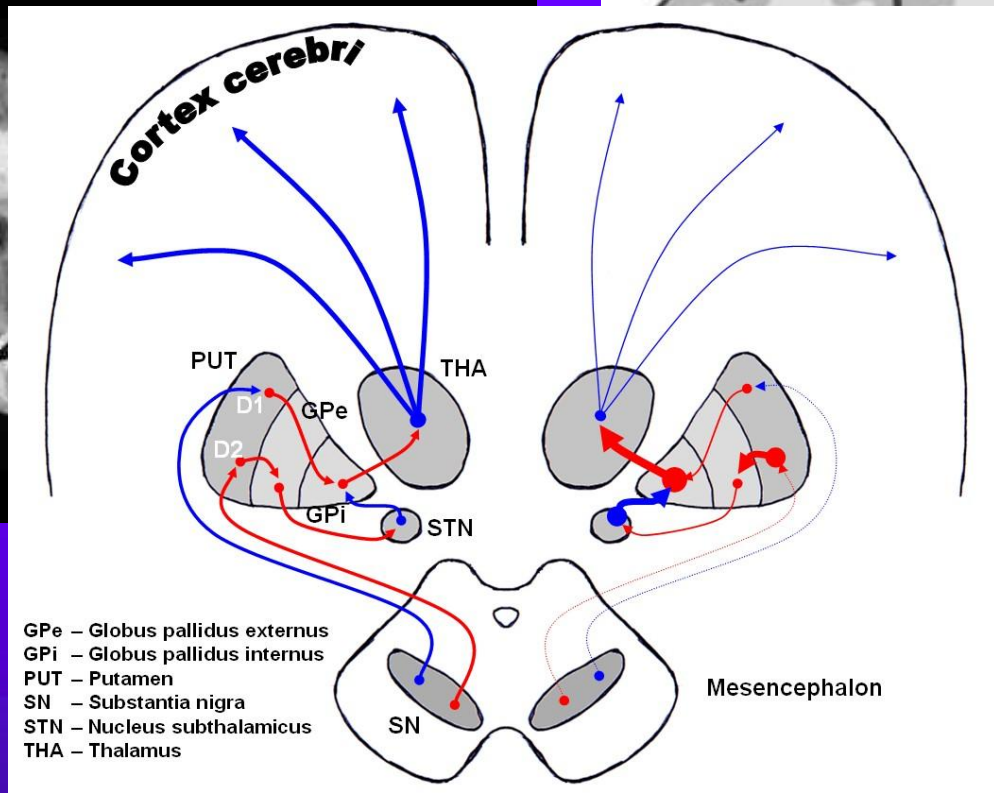
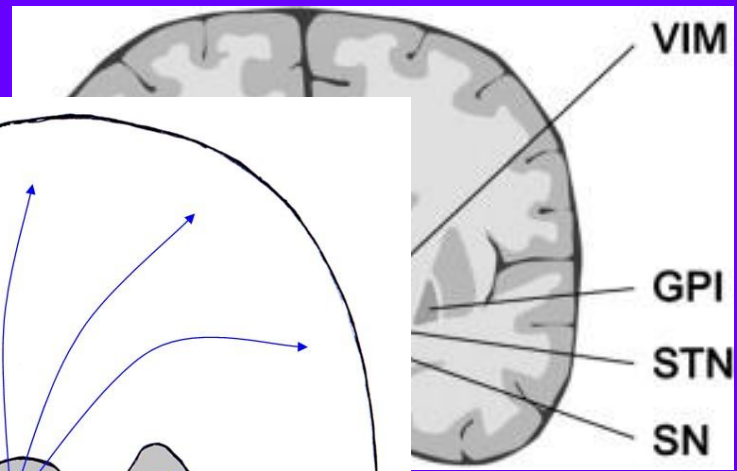
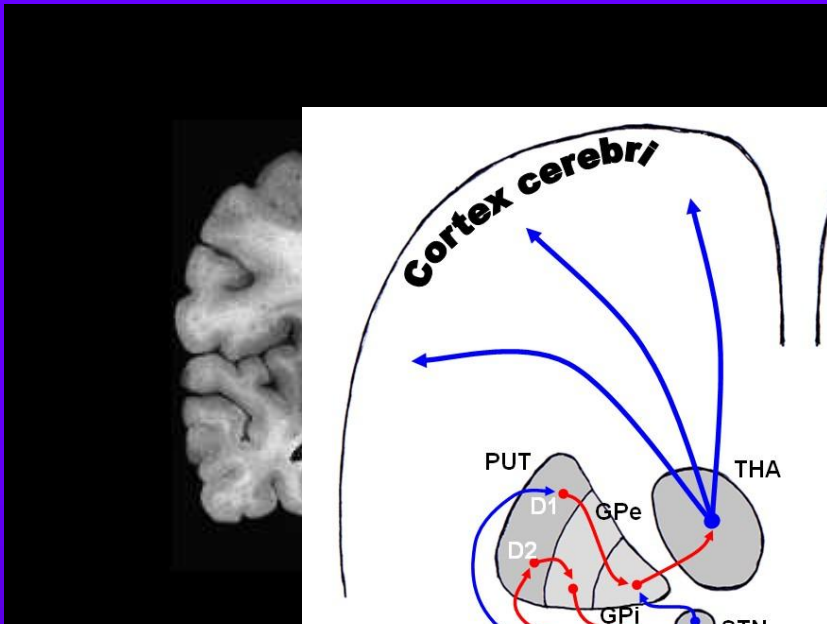
Approved by FDA for Tremor Dominant PD
NOT approved by Maryland Medicare

Out of pocket only

4. Unilateral Pallidotomy (GPi) for **Parkinson's Disease**

Approved by FDA for PD with Dyskinesias
NOT approved by Maryland Medicare

Out of pocket Only



The UNILATERAL VIM and GPI (also targets of DBS) are the main targets for FUS currently.

There is an ongoing trial using another site called the Palido-thalamic tract, or “PTT.”



Ongoing Research

Unilateral/Bilateral Palido-Thalamic Tractotomy (PTT)

Ongoing **Clinical Trial** for Parkinson's Disease (done recruiting)


Inclusions/Exclusion are very similar to DBS

Eligibility Criteria:

1. >30 yrs old
2. Diagnosis of **PD by a movement disorder neurologist**, with no other diagnostic concerns (no MSA, PSP, CBS, DLB, Alz, etc)
3. Ldopa responsive defined by 30% reduction in UPDRS motor score in On state
4. UPDRS motor score >30 in off state
5. must have dyskinesias or motor fluctuations

Exclusion Criteria:

1. high score on pull test
2. high risk with regard to speech, swallow, saliva.
3. significant cognitive impairment as determined by the neuropsychologist.
4. Subject with unstable psychiatric disease
5. The usual surgical contraindications including substance abuse, bleeding risk, cardiac risk, etc



What Symptoms are Improved by Focused Ultrasound?

- ◆ Similar to DBS, symptoms improved by surgery are those symptoms that are best improved with medication:
 - Tremor (ViM target)
 - Tremor reduction can be superior than achieved with medication
 - Dyskinesias and Dystonia
 - Slowness (Bradykinesia)
 - Stiffness (Rigidity)
 - →decrease in OFF Updrs score and improvement in QOL
- ◆ However, currently it is only approved for treatment on ONE SIDE!



What Symptoms Will Not Be Improved with treatment?

Focused Ultrasound Treatment is Not a Cure



What Symptoms Will Not Be Improved by Treatment?

Parkinson Patients will still need medication (possibly slightly reduced)

But will likely have less dyskinesia, less dystonia, and a lower OFF UPDRS score

(exception is tremor, with ViM target)



What Symptoms Will Not Be Improved by Treatment?


- ◆ Medication Requirement
- ◆ Cognitive and Psychiatric Symptoms.
- ◆ On-Period Freezing
- ◆ Swallowing Difficulties
- ◆ Speech Problems
- ◆ Poor Balance



How Long Will the Benefits of Treatment Last?

This is still being determined...

- ◆ There is evidence that for most people, there will still be benefit at least two years out
- ◆ Some people have transient benefit only (in tremor)
- ◆ We do not have long term data



What Are the Risks of Treatment?

For Pallidotomy:

Procedure related: nausea/vomiting (15%), headache (15%), and sonication-related head pain (35%).

Transient Symptoms during treatment: visual field deficit (1/20)

Transient/Persistent Risks: fine motor difficulties (5%), dysarthria (15%), and balance difficulties (5%), none of which were severe. No AEs fulfilled FDA criteria of an SAE.



Indications for MRgFUS for Parkinson's Disease (currently)

- ◆ Suffers from idiopathic Parkinson's Disease.
- ◆ Asymmetric Dyskinesia or Dystonia limiting or despite optimized pharmacotherapy
- ◆ Highly responsive to levodopa, with good motor function in best “on” state.
- ◆ Doesn't suffer from dementia.*
- ◆ Doesn't suffer from untreated depression.*



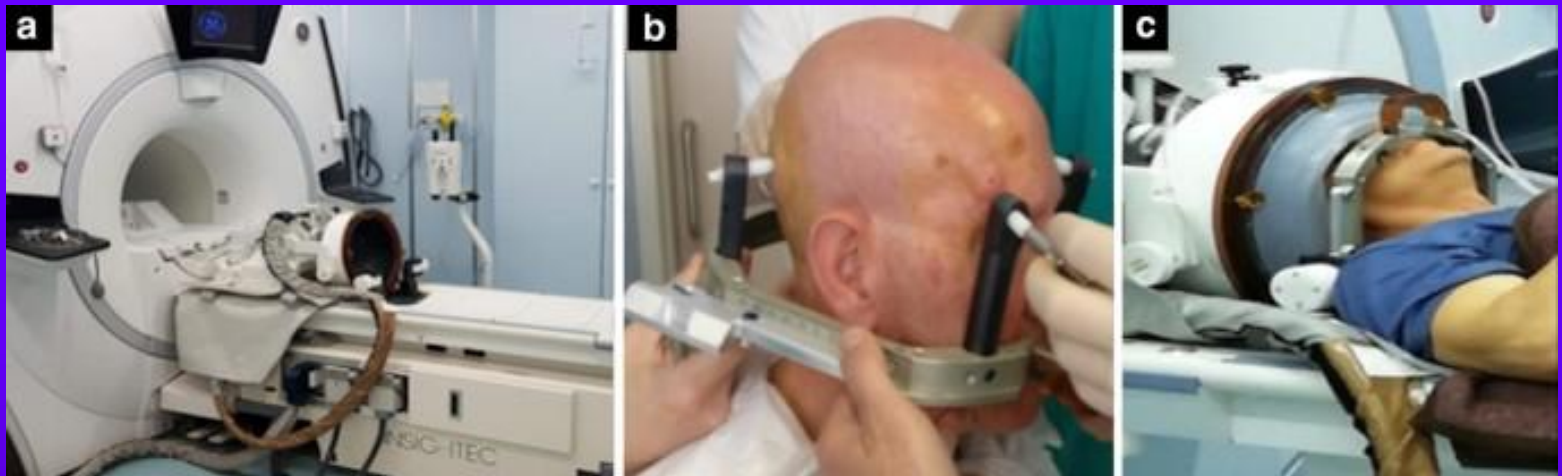
What Should I expect from the Treatment?

- ◆ There is some initial workup to ensure candidacy
- ◆ Treatment is a one day out-patient procedure
 - You will come in morning or afternoon and are usually discharged within 8 hrs
- ◆ This is a “one and done” procedure, meaning you do not have to have further procedures



THE EVALUATION

- ◆ Head CT to determine skull density ratio
- ◆ An MRI of the brain is part of the evaluation, usually day of though sometimes earlier
- ◆ Discuss with Neurosurgery
- ◆ Schedule the procedure



The first step is the application of a frame, which is tightly applied under local anesthesia. It is NOT screwed into your skull. The frame allows identification of the relationships of various brain structures to the position of the frame on the skull. An MRI scan and CT scans will be used to locate landmarks. A flexible rubber gasket will then be attached to the frame posts and your head.

Navigation to the Target





What Should I expect day of?

- ◆ You are asked to come with your head shaved the night before
 - They will usually clean this up day-of
- ◆ You will be brought to the procedure room and have a frame placed on your head
 - ◆ You will then lie down in the MRI and will be asked to do a series of tasks, alternating with going in and out of the machine (boring)
- ◆ During sonication, you may feel uncomfortable symptoms or nausea
- ◆ The procedure will take 2-4 hours.



After the procedure

- ◆ You will go to the recovery room or patient waiting area
- ◆ we will make sure you are stable enough to walk
- ◆ you may need a bit of recovery time if dizzy
- ◆ Usually, you go home fairly quickly, within a few hours
- ◆ You should see immediate improvement in symptoms

Results of Surgery

- ◆ Off time symptoms are reduced
- ◆ Medication requirements may be decreased
- ◆ Dyskinesias or dystonia is improved

¹Ostergard, et al. *Mov Disord.* 2002 Jul;17(4):693-700.

²Weaver, et al, *JAMA*, Jan 7, 2009 Vol 301, No 1: 63-73.



Results of the Procedure

- ◆ Remember, FUS does not cure the disease, nor does it inhibit the progression of the disease.
- ◆ The procedure is a one time procedure—unlike DBS we cannot adjust to improve symptoms again or decrease side effects



How does FUS compare to DBS?

DBS

- ◆ **Very durable**
- ◆ **Bilateral**
- ◆ **Modifiable**
- ◆ **Can turn it off**
- ◆ Bleeding and Infection Risk
- ◆ Multiple surgeries
- ◆ Patient criteria is strict

Focused Ultrasound

- ◆ Probably less durable
- ◆ Unilateral Treatment (for now)
- ◆ Unmodifiable**
- ◆ Side effects can be permanent
- ◆ **Lower bleeding risk, no infection risk**
- ◆ **One time outpatient Procedure**
- ◆ **Patient criteria less strict**

If you are a candidate for DBS, that is probably the better choice!



Questions?