UNIVERSITY of MARYLAND
SCHOOL OF MEDICINE

Overview of surgical options for Parkinson's disease

Parkinson's Foundation of the North Capital Area 2022 Annual Symposium

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Disclosures

NewTouch Digital, Inc. – Chief Scientific Officer
Zimmer Biomet – surgical advisory board

Objectives

DBS surgery - stages

- Phase 1: awake DBS surgery (frame-based and frame-less)
- Phase 1: asleep DBS Surgery
- Phase 2: IPG implantation

Other surgical options

- Focused ultrasound

Goal of stereotactic surgery (unchanged since 1908)

Place a small wire (1.3mm) or lesion into a small group of cells (3mm)

1908 – Clark and Horsley (England) First "stereotaxic" apparatus for animal research

1918 – Mussen (England) introduces first human stereotactic apparatus but never caught on

1947 – Spiegel (Philadelphia) First human stereotactic frame used, based on intracranial imaging

1949 – Talairach (Paris) proposed coordinate system to gain access to deep brain structures from lateral approach

1951 – Lars Leksell (Sweden) Introduced Leksell frame, first to use Arc-radius system

1977 – Roberts and Brown (Salt Lake City) Develop **BRW** frame which was then modified to simpler **CRW** frame **1988** To be used with CT (Edwin Todd and Trent Wells – **(Los Angeles)**

2002 – Peter Konrad (Nashville) Develops frameless STarFix personalized frame

2004 – Kathryn Holloway (Richmond) Develops frameless Nexframe

2005, 2013 – Paul Larson (San Francisco) Develops MRI-guided asleep DBS (ClearPoint)

2016 – Jeff Elias (UVA) FUS for ET

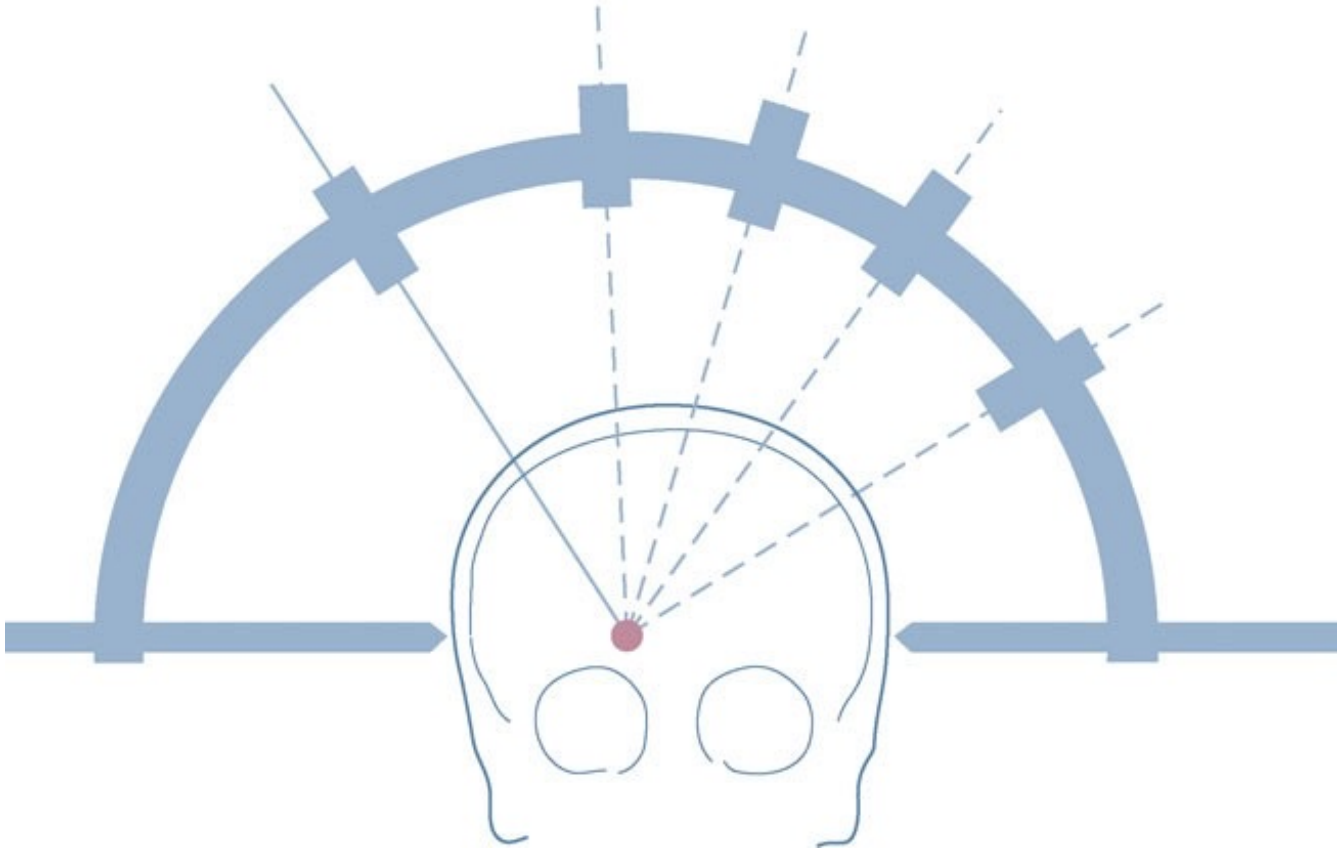
Murad et al.
Early history of stereotactic apparatus in neurosurgery

Two major stages in DBS surgery

1. Placement of electrode leads into nucleus of interest (STN, GPi, Vim)
    - Awake vs. asleep
    - Frame-based (or Robotic) vs. frameless
    - Image-guided

2. Placement of internal pulse generator (IPG)
    - Single procedure (during lead placement)
    - Separate procedure

Awake frame-based surgery



Awake frame-based surgery – technical overview

1. Preoperatively - trajectory toward target planned using indirect (AC/PC coordinates) and direct preoperative imaging (MRI)

2. Frame (CRW vs. Leksell) fixed to patient's head using scalp pins

3. Imaging (CT or MRI) performed to match pre-operative MR-space with trajectory plan to patient's 3D space
   - Used to obtain coordinates (Leksell frame)
   - Robot-guided coordinate system (Rosa-guided DBS surgery)

4. Patient fixed to bed and incision made to access skull

5. Burr hole created / dura cut to access brain

Awake frame-based surgery – technical overview

6. Micro-electrode recordings used to localize nucleus of interest (1-5 electrodes)

7. Macro-electrode stimulation while testing for symptom improvement or stimulation side-effects

8. Placement of permanent lead to depth of target based on recording and stimulation

9. Permanent lead stimulation to test for symptom improvement or stimulation side-effects

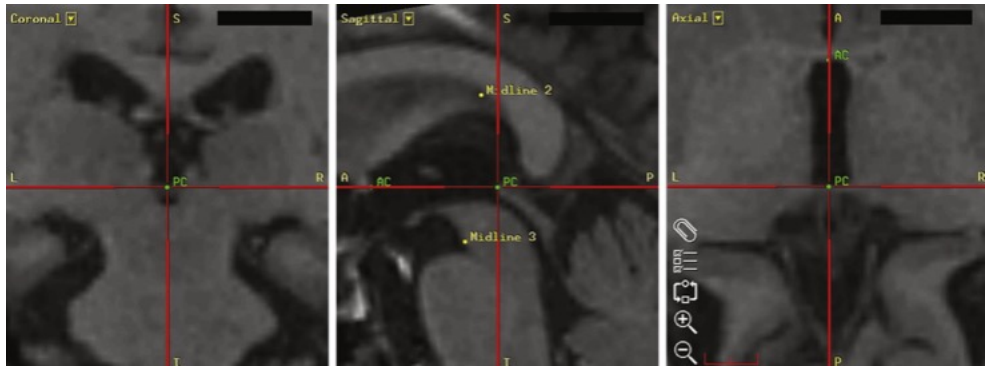
10. Intra-operative CT to localize and confirm lead placement within target

11. Closure of skin, repeat on other side

Awake frame-based surgery – preoperative planning

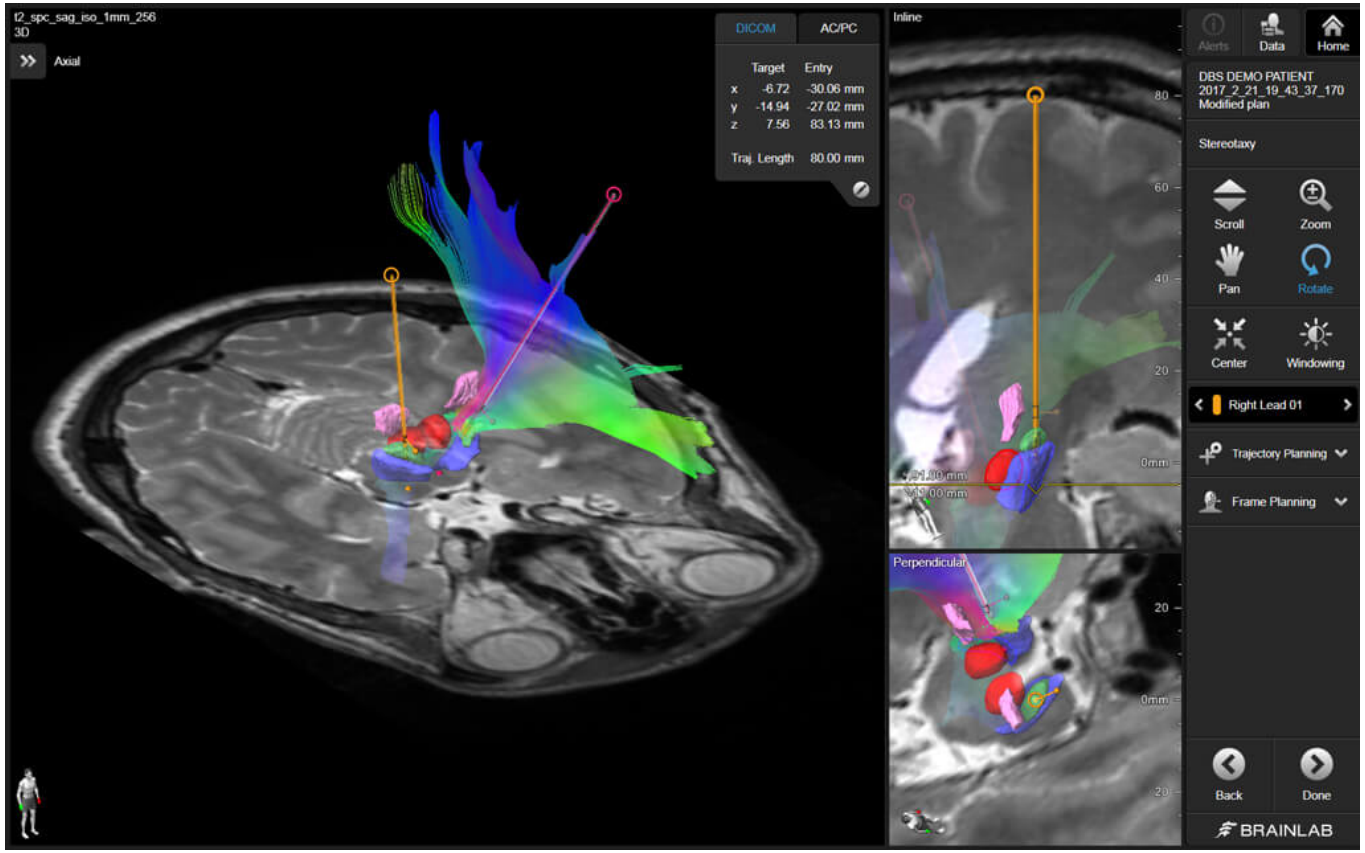
Preoperatively - trajectory toward target planned on BrainLab or Medtronic Stealth software

Indirect targeting (AC-PC coordinates)



Target	Lateral (*x*) to MCP	Anterior/Posterior (*y*) to MCP	Vertical (*z*) to MCP
Vim	0.55 (AC-PC length)	0.25 (AC-PC length) posterior	0
STN	12 mm	3 mm posterior	4 mm below
GPi	21 mm	2 mm anterior	4 mm below

Direct targeting (MR-imaging)



Awake frame-based surgery – frame placement

Frame (CRW vs. Leksell) fixed to patient's head using scalp pins

CRW Frame

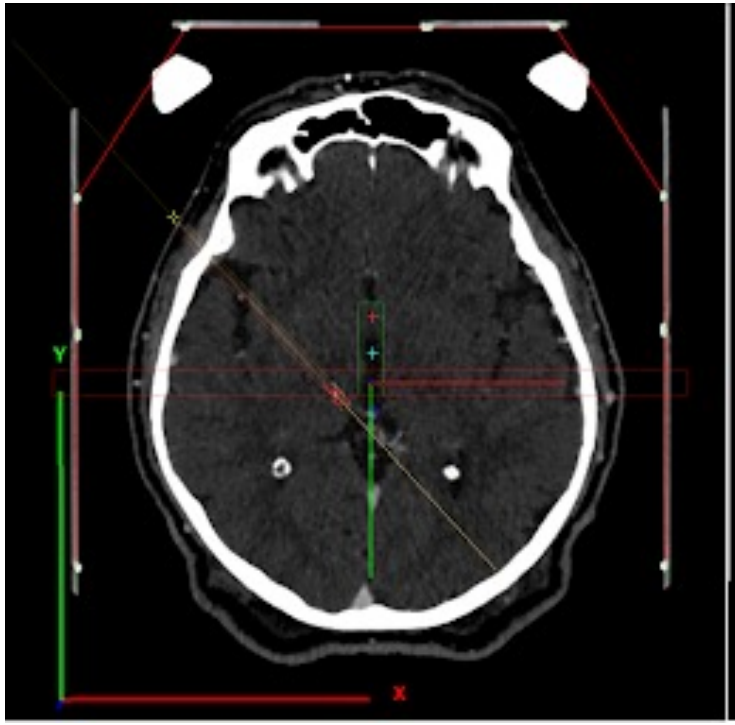
Leksell Frame

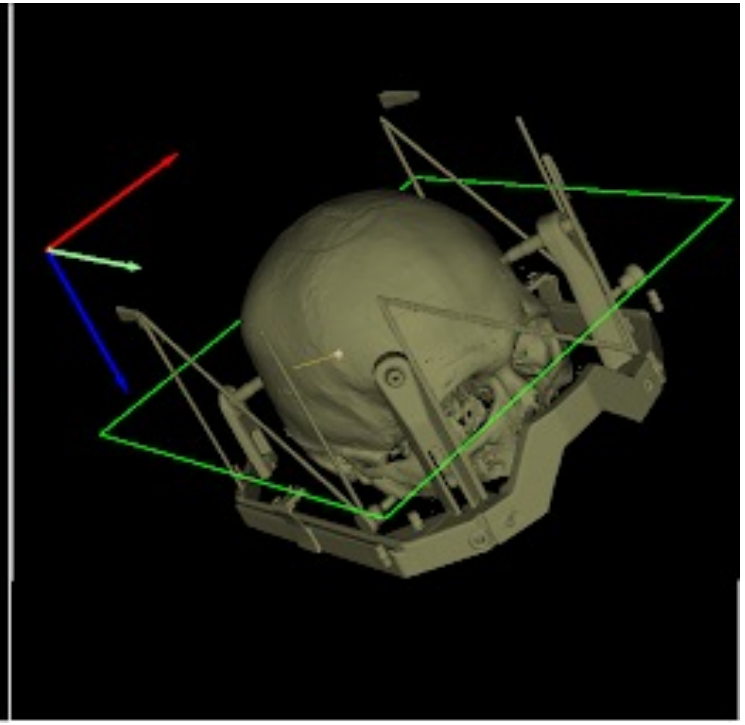
Cohen-Gadol et al.
The neurosurgical atlas

Awake frame-based surgery – post-frame imaging

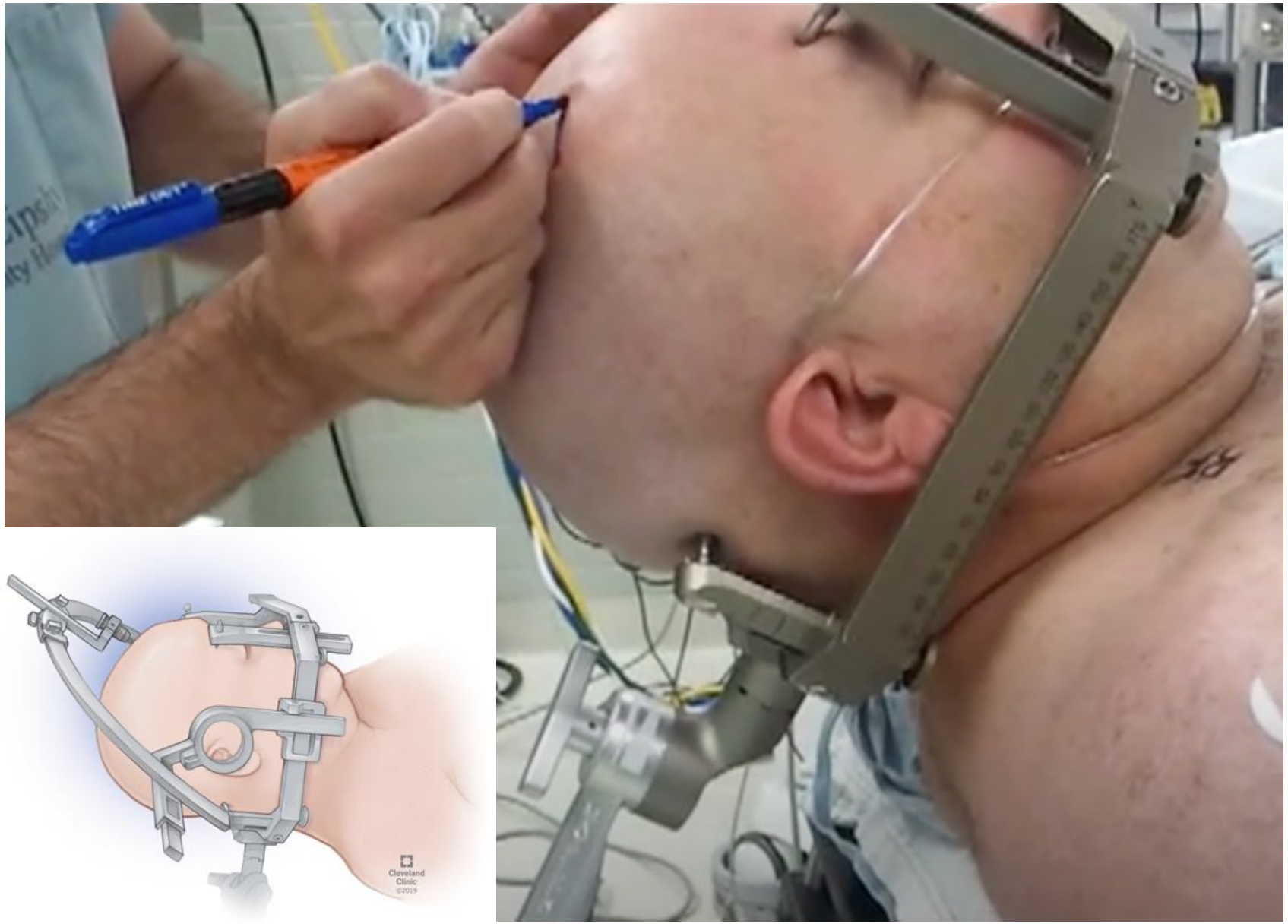
Imaging (CT or MRI) performed to match pre-operative MR-space to patient's 3D space

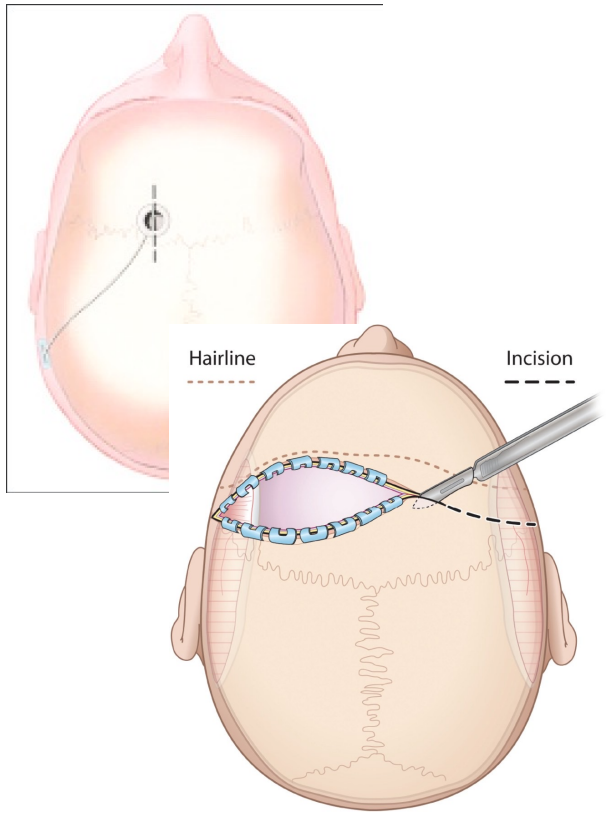
- Intraoperative vs. extraoperative CT/MRI





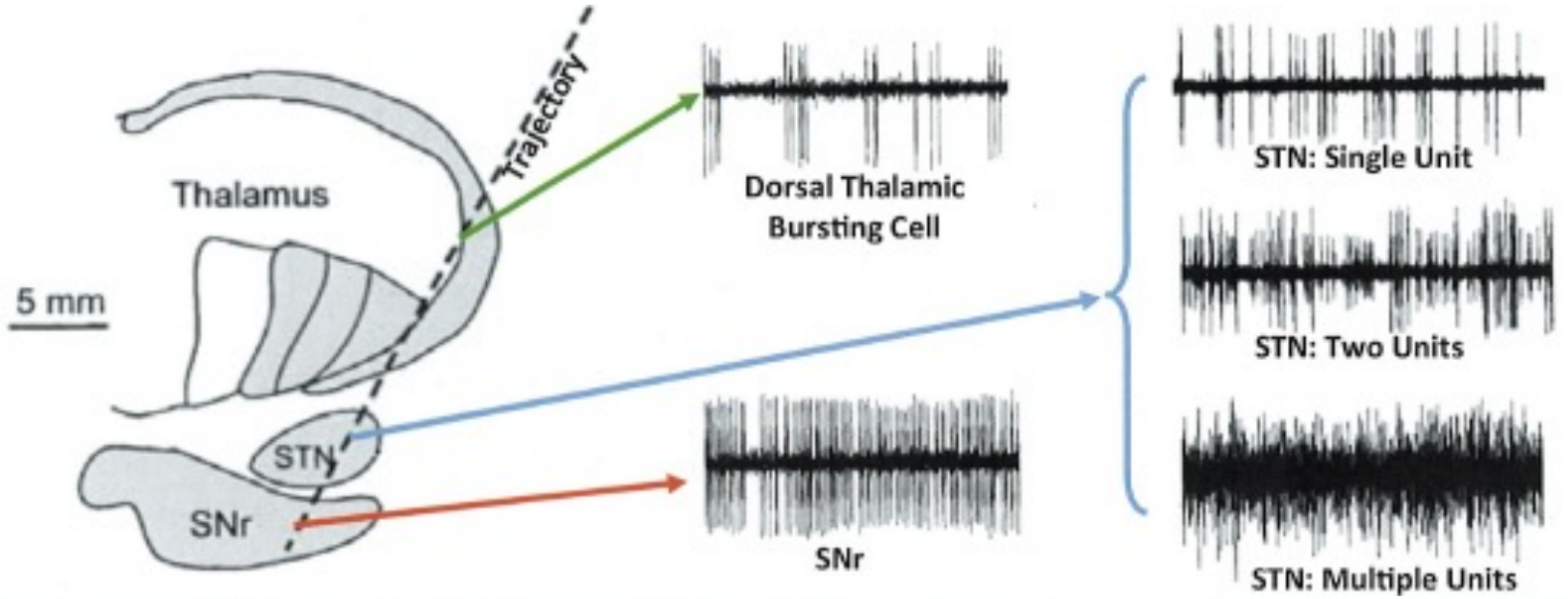
Awake frame-based surgery – attach to bed and incision





Awake frame-based surgery – burr hole and MER

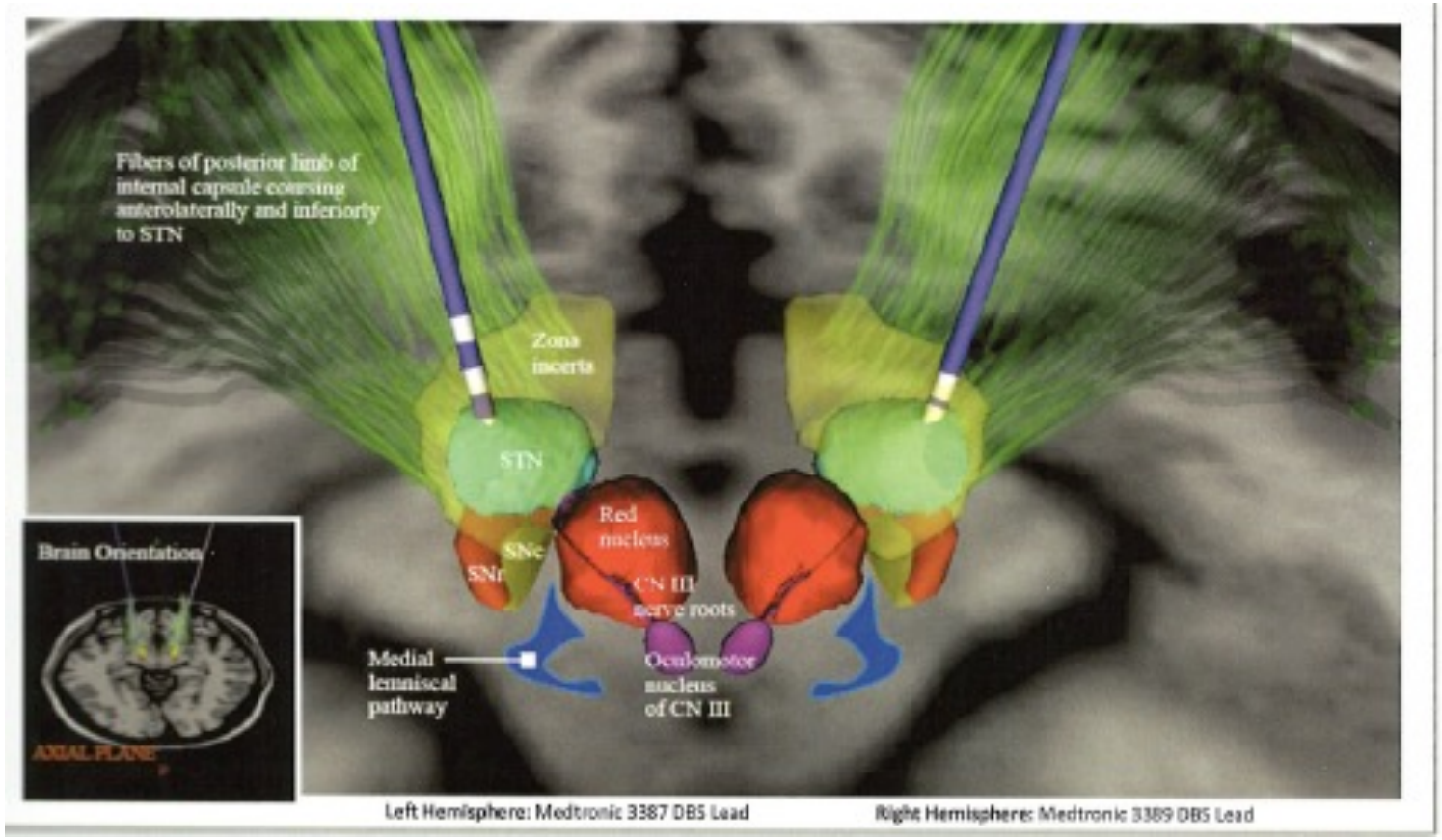
Surgical technique – STN MER and macrostimulation



		Location*	Stimulation Effects (& *Anatomical Correlate*)
Dorsal or Reticular Thalamus	- Low density of spontaneously firing neurons, not movement-responsive		
Ventral Oralis anterior **(VOa) Nucleus of the Thalamus***	- Low density of sporadically firing neurons, not movement-responsive	**Posterior**	- Paresthesias (*Medial lemniscus*)
OR ***Ventral Oralis posterior*** **(VOp) Nucleus of the Thalamus***	- Moderate density and discharge frequency, voluntary movement-responsive cells - Presence of cells with bursting activity	**Anterior**	- Muscle Contractions, Dysarthria (*Internal Capsule*)
Base of Thalamus	- Marked decrease or cessation of neuronal activity	**Lateral**	- Muscle Contractions, Dysarthria, Contralateral Gaze Deviation (*Internal Capsule*)
Zona Incerta	- Low frequency units, low cellular density		
STN	- Significant increase in background activity and neuronal density - Very active with possible tremor cells - Movement-responsive neurons in dorsal 2/3 of STN - Dramatically elevated background	**Medial**	- Diplopia, deviation of ipsilateral eye, dizziness, ALO (*CN III*) - Personality/impulsivity changes, depression (*Limbic STN*) - Sweating, nausea, extreme discomfort, paresthesias, warm sensations (*Red nucleus, posteromedial*)
White Matter (Quiet zone)	- Quiet zone of variable thickness between STN and SNr	**Superior†**	- Possible impact on dyskinesias and/or tremor (*Zona incerta*)
SNr	- High-frequency activity with regular discharge rates, lower background	**Inferior†**	- Possible mood changes, akinesias (*SNr*)

* *dependent on trajectory and angle. A more anterior approach may traverse VOa while a more posteriorly-positioned approach may encounter VOp*

Surgical anatomy – STN macrostimulation



2.1 ANATOMY SURROUNDING STN:

Posterior Limb of Internal Capsule
Lateral, anterior and ventral to dorsolateral STN

Zona incerta
Dorsal to dorsolateral STN

Substantia Nigra
Ventral to dorsolateral STN

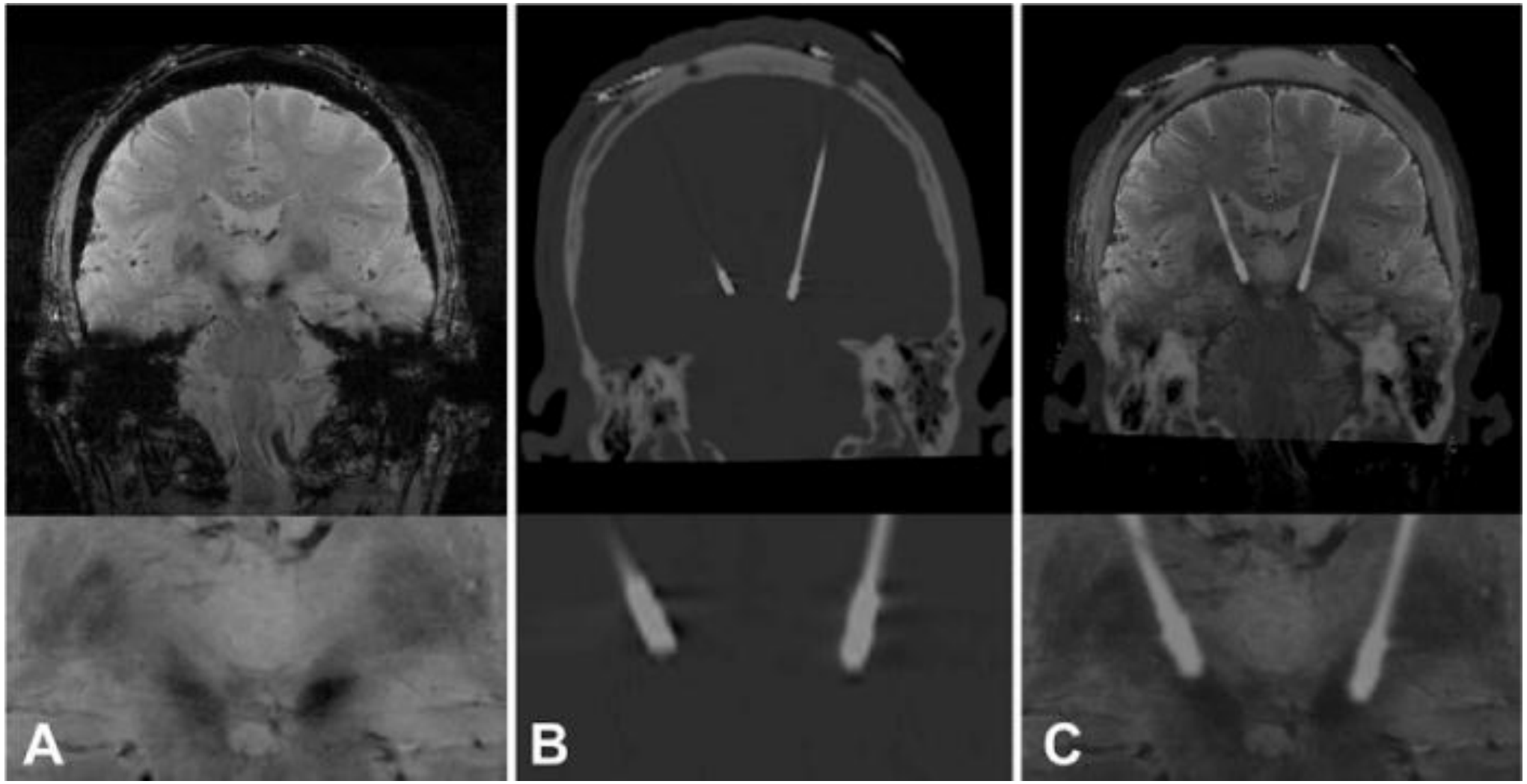
Medial Lemniscus
Posterior to dorsolateral STN

Red Nucleus
Posteromedial to dorsolateral STN

Nerve Roots of CN III
Ventromedial to dorsolateral STN

Awake frame-based surgery – permanent lead and test

Awake frame-based surgery – final CT and skin closure



Awake frame-less surgery

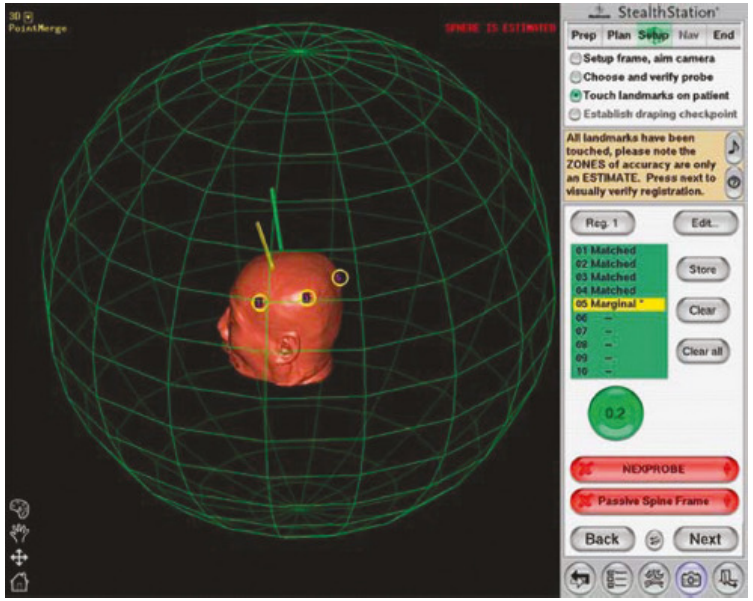
Awake frame-less surgery – technical overview

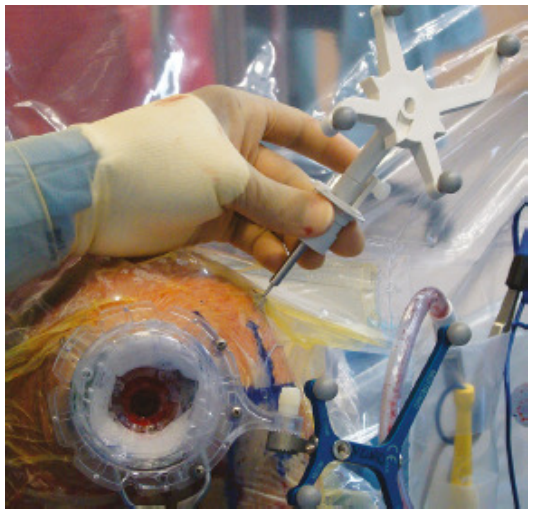
1. Preoperatively **(NexFrame)** – Bony fiducials placed into skull, CT and MRI performed, trajectory planned
2. No further imaging necessary, patient goes directly to OR.
3. Patient not fixed to bed, head supported by padded headrest, incision made to access skull
4. NexFrame registered to arc
5. Rest of procedure same as awake frame-based surgery

1. Preoperatively **(StarFix)** – Bony fiducials placed into skull, CT and MRI performed, trajectory planned and sent to company → custom frame built and sent back (3 days)
2. No further imaging necessary, patient goes directly to OR.
3. Patient not fixed to bed, head supported by padded headrest, incision made to access skull
4. Rest of procedure same as awake frame-based surgery

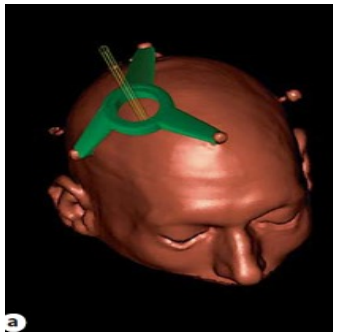
Awake frame-less surgery – technical overview

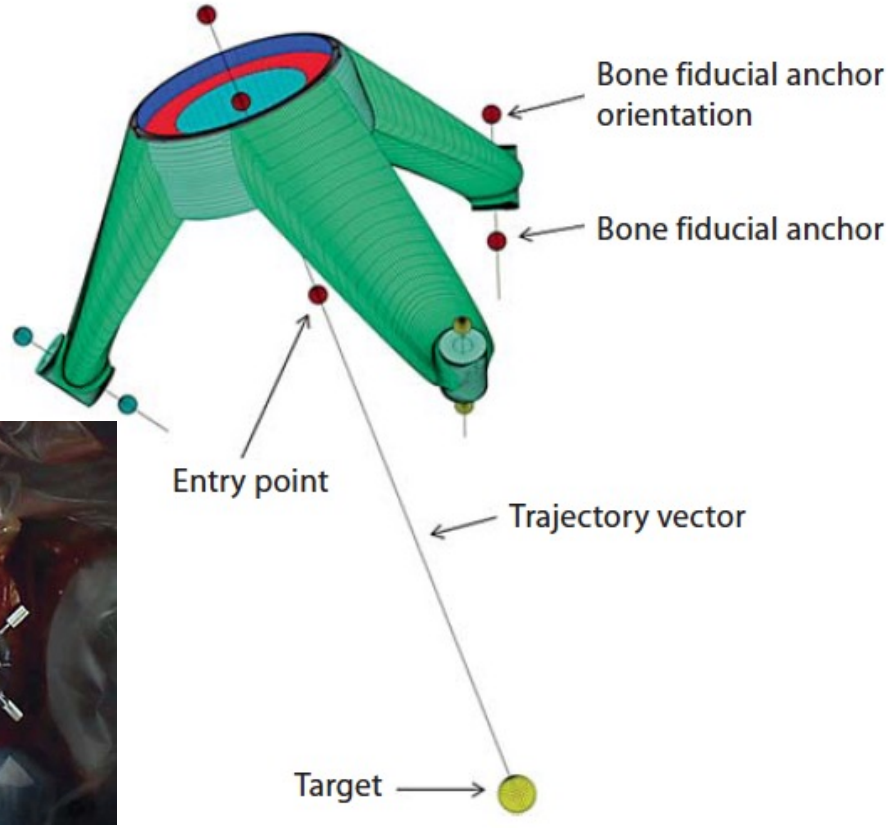
NexFrame





StarFix





Awake frame-based vs frame-less surgery

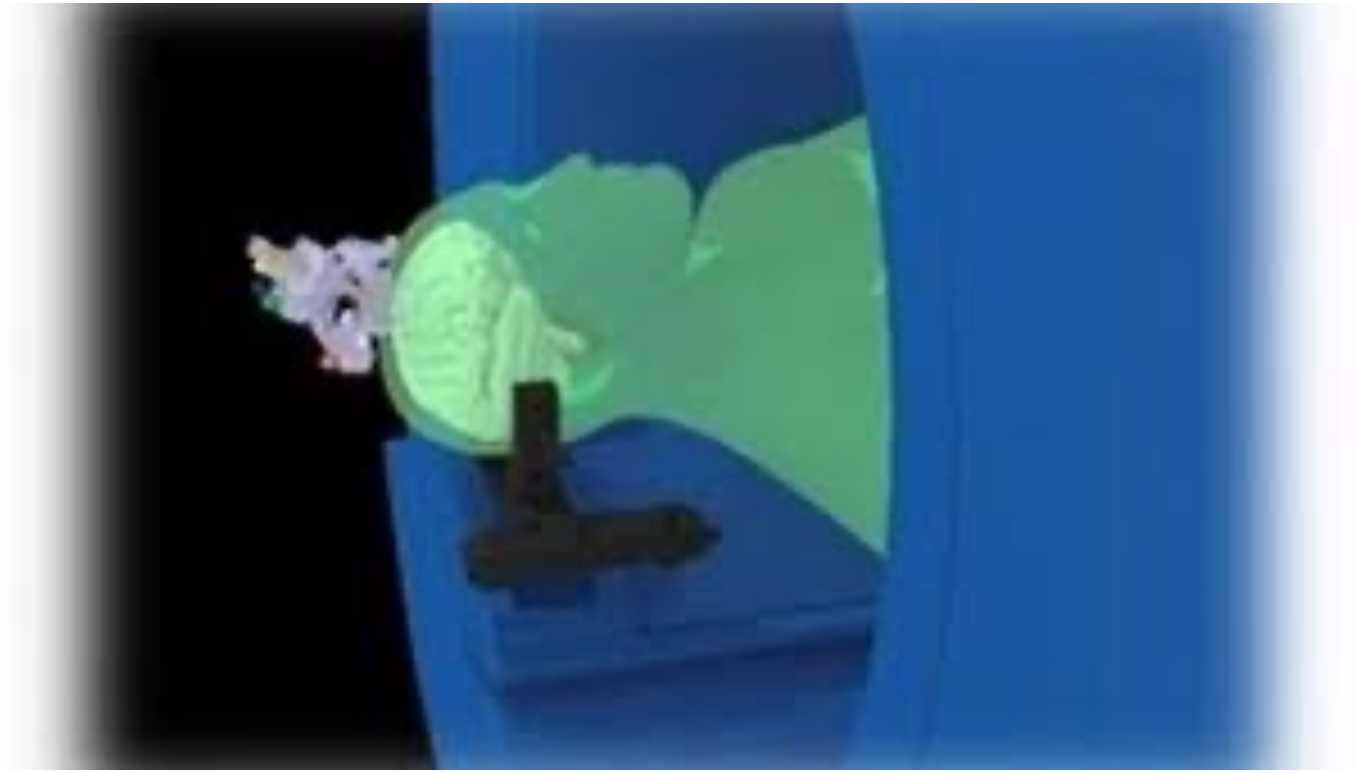
Frame-based

1. Tried and true targeting, used since 1950s
2. Most literature showing sub-millimeter accuracy
3. Versatile – can change trajectory on day of surgery if needed
4. Not dependent on integrity of bony fiducials (can be displaced / moved leading to loss of accuracy)

Frame-less

1. Bony fiducials placed pre-operatively and all imaging and targeting is based on fiducials
2. No imaging needed on day of surgery
3. No placement of stereotactic frame to patient head
4. No fixation of patient head to bed
5. Recent publications suggest similar accuracy to frame-based

Asleep frame-less surgery (ClearPoint)



Asleep frame-less surgery – technical overview

1. Preoperatively - trajectory toward target planned using indirect (coordinates) and direct preoperative imaging (MRI)

2. Patient anesthetized with general anesthesia

3. MRI (intra-operative vs. clinical) performed to localize burr hole placement

4. Skin incision and burr hole

5. ClearPoint frame attached to each side of patient head

Asleep frame-less surgery – technical overview

6. MRI-based targeting performed with patient in MRI scanned
   - Macro- and micro-adjustments performed based on trajectory toward desired target

7. Placement of permanent lead to depth of target based on final position on MRI

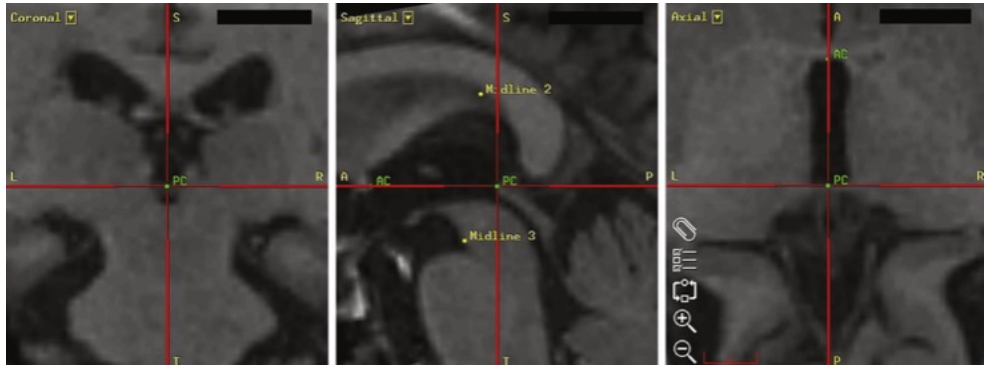
8. Final MRI to confirm placement

9. Closure of skin, repeat on other side

Asleep frame-less surgery – preoperative planning

Preoperatively - trajectory toward target planned on BrainLab or Medtronic Stealth software (same planning step and system as awake frame-based)

Indirect targeting (AC-PC coordinates)



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Vim	0.55 (AC-PC length)	0.25 (AC-PC length) posterior	0
STN	12 mm	3 mm posterior	4 mm below
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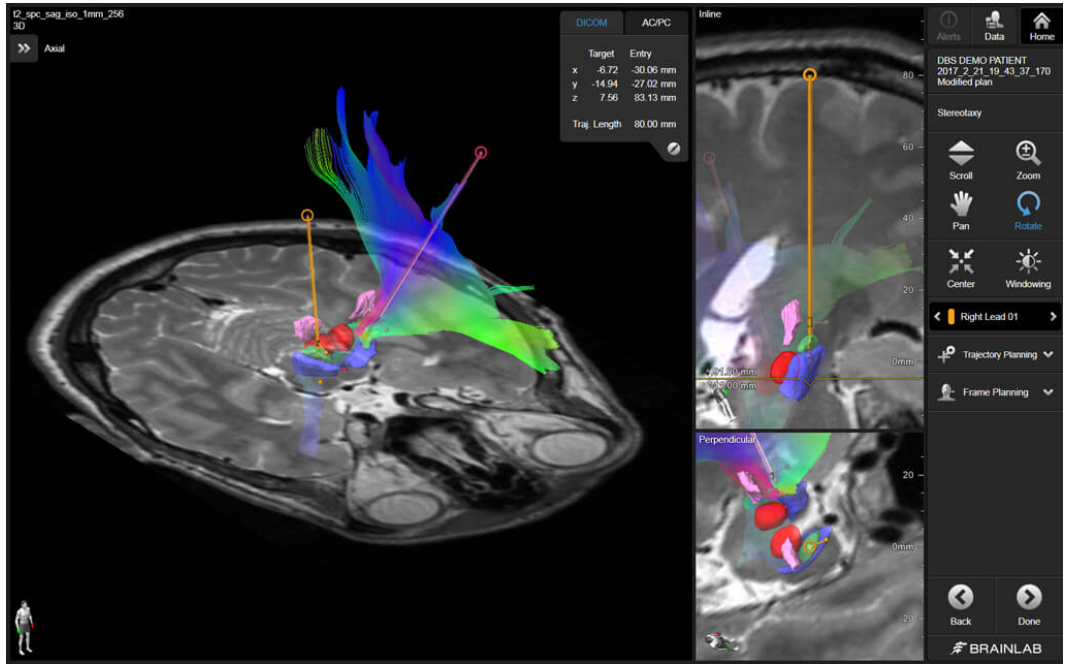
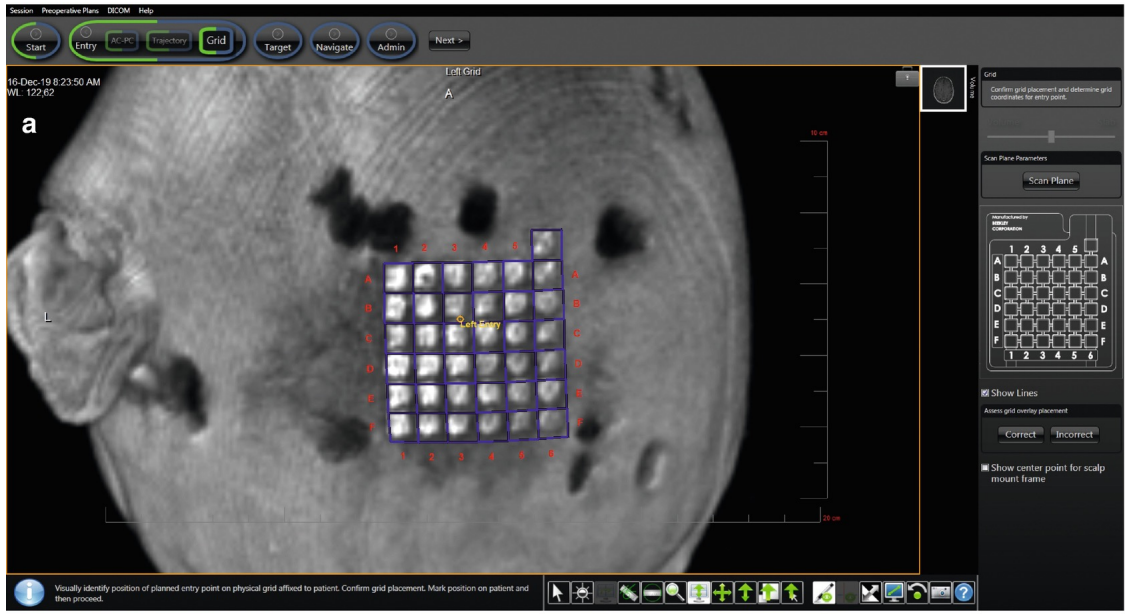
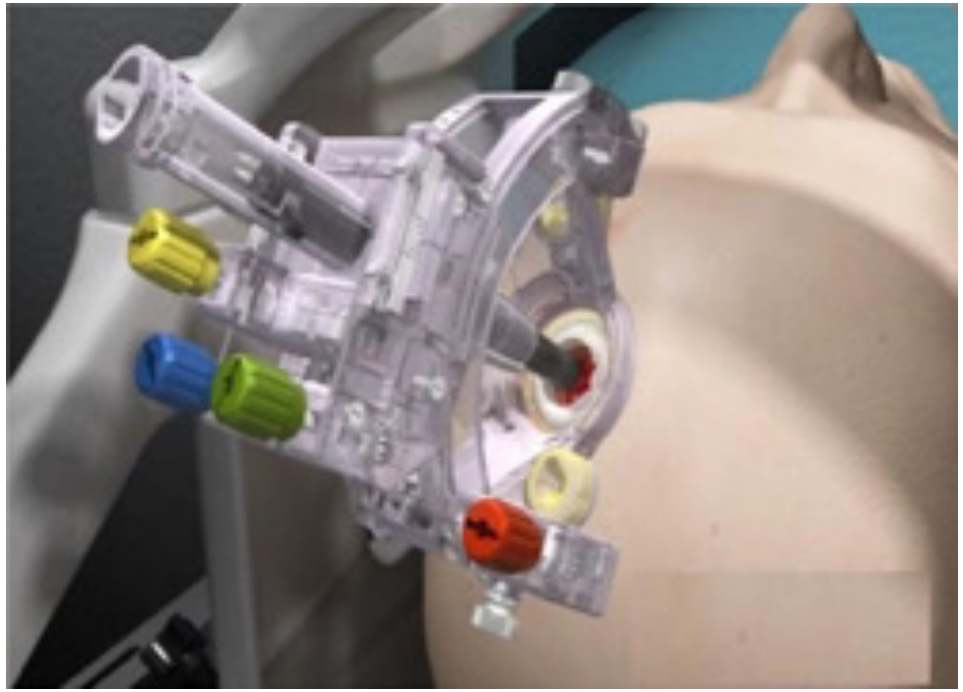
Direct targeting (MR-imaging)



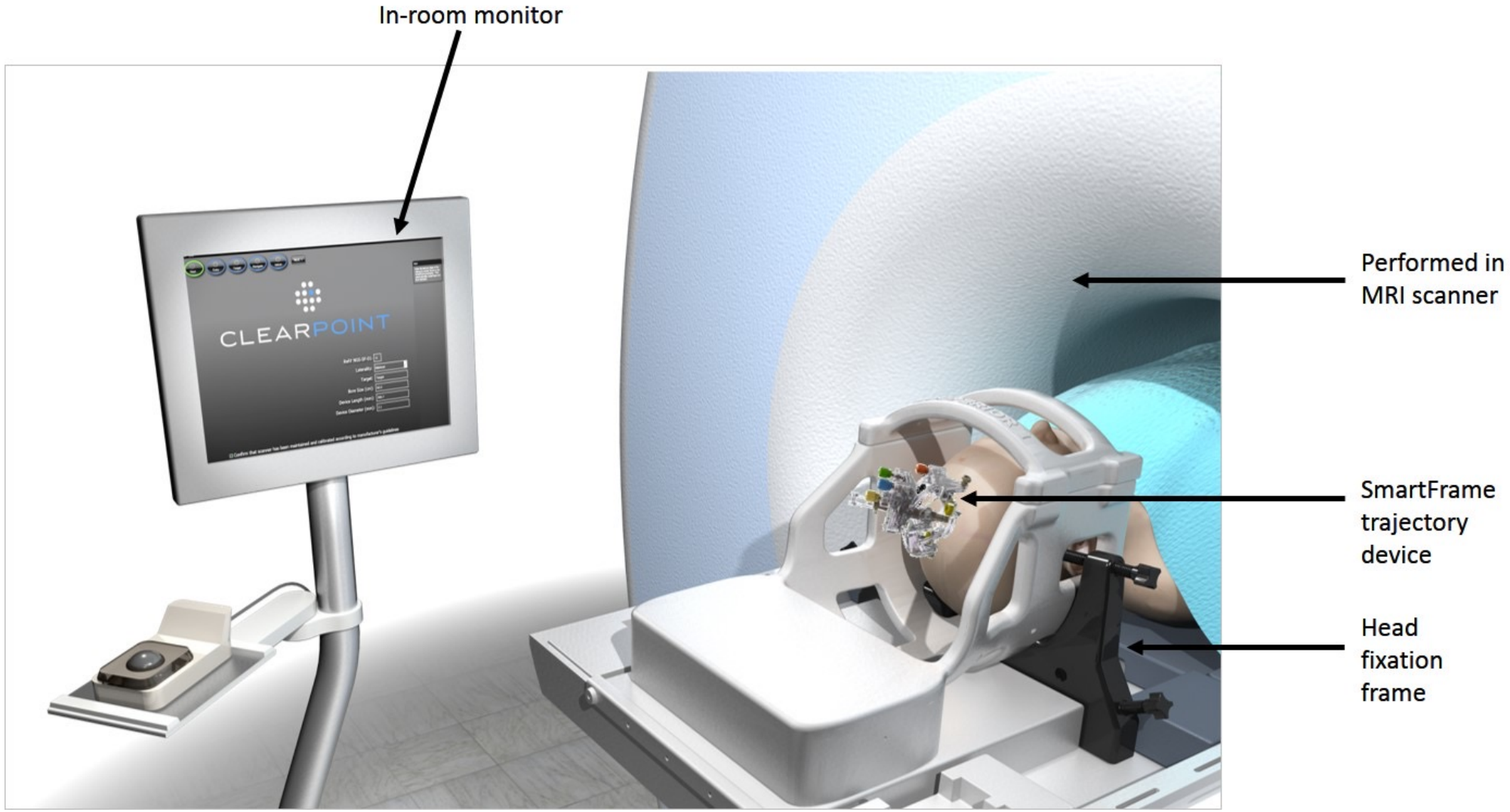
Asleep frame-less surgery – MRI, burr hole, frame



MRI (intra-operative vs. clinical) performed to localize burr hole placement, frame placed



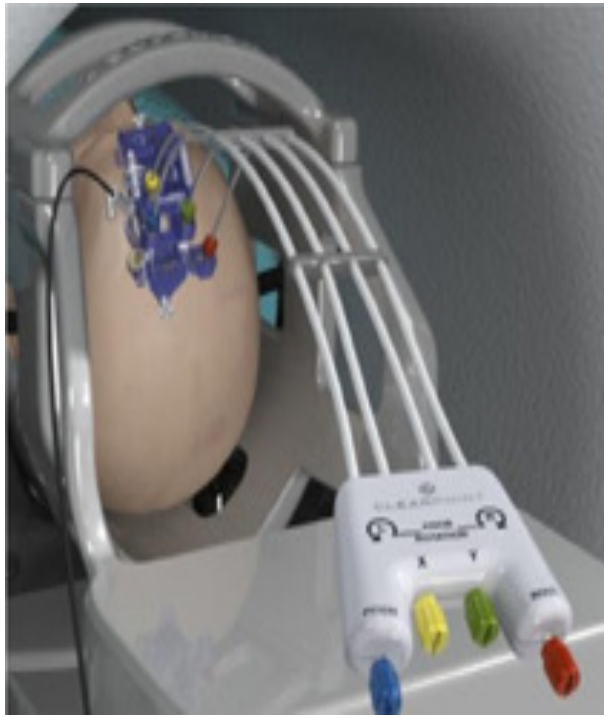
Asleep frame-less surgery – imaging

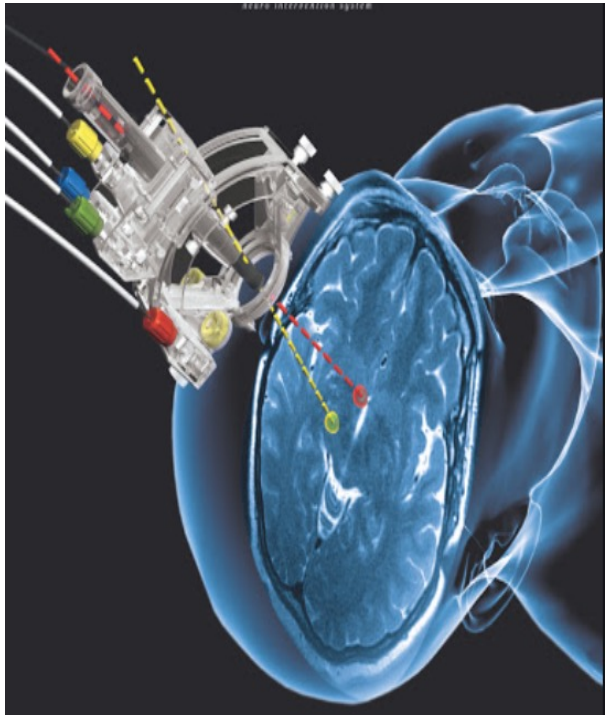


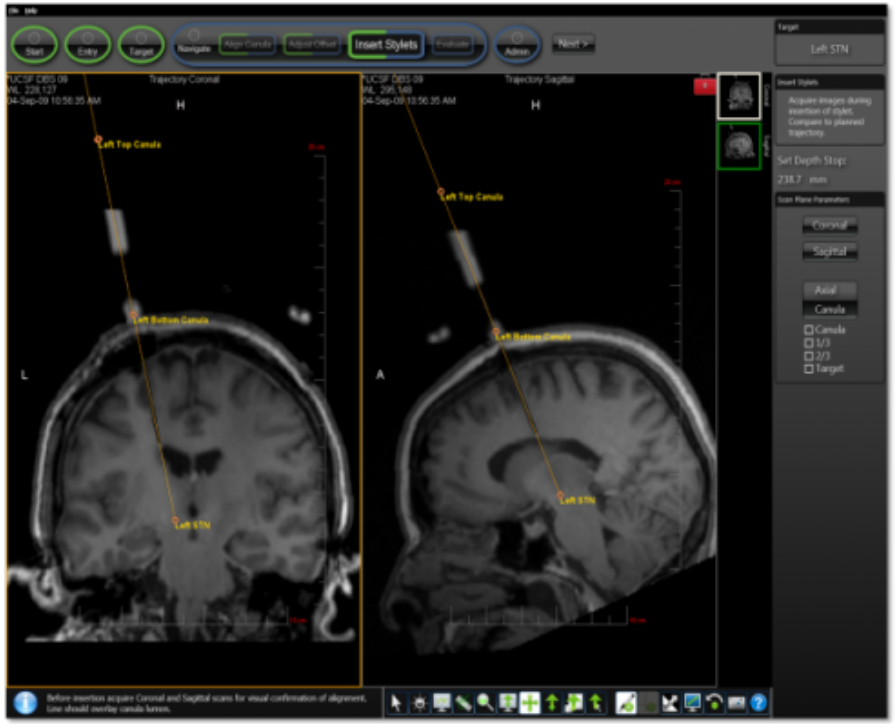
Asleep frame-less surgery – MR-based targeting

MRI-based targeting performed with patient in MRI scanned

- Macro- and micro-adjustments performed based on trajectory toward desired target







Asleep frame-less surgery – technique

Awake frame-less/based vs asleep MRI-based

Awake frame-less/based

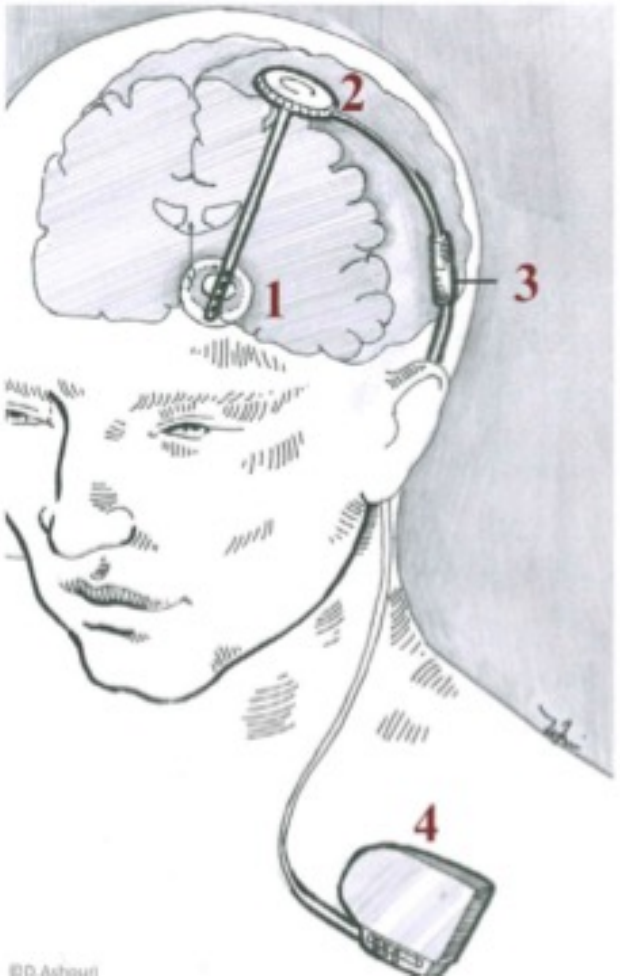
1. Uses pre-defined trajectory (direct vs. indirect) which is aligned to stereotactic space (fiducials vs. frame)
2. Awake allows for MER (neurophysiological targeting)
3. Awake allows for symptom testing prior to final electrode
4. Extremely accurate (1mm)
5. Can be uncomfortable if anxious or claustrophobic
6. Recover quicker without general anesthesia

Asleep MRI-based

1. Uses intraoperative imaging with frame attached to define stereotactic space
2. Uses imaging ONLY as targeting (no neurophysiological targeting)
3. No symptom testing
4. Extremely accurate placement of electrode (0.6 – 1.2mm) based on desired imaging
5. More comfortable surgery
6. Could be slightly longer recovery from general anesthesia

- No direct (prospective) comparisons
- Similar UPDRS outcomes
- Similar complications (although trend toward ClearPoint being slightly safer)
- Mostly depends on patient comfort and training / expertise of surgeon

Surgery details – stage 2



1 Stimulation probe

2 Fixation cap

3 Extension lead

4 Pulse generator (IPG)

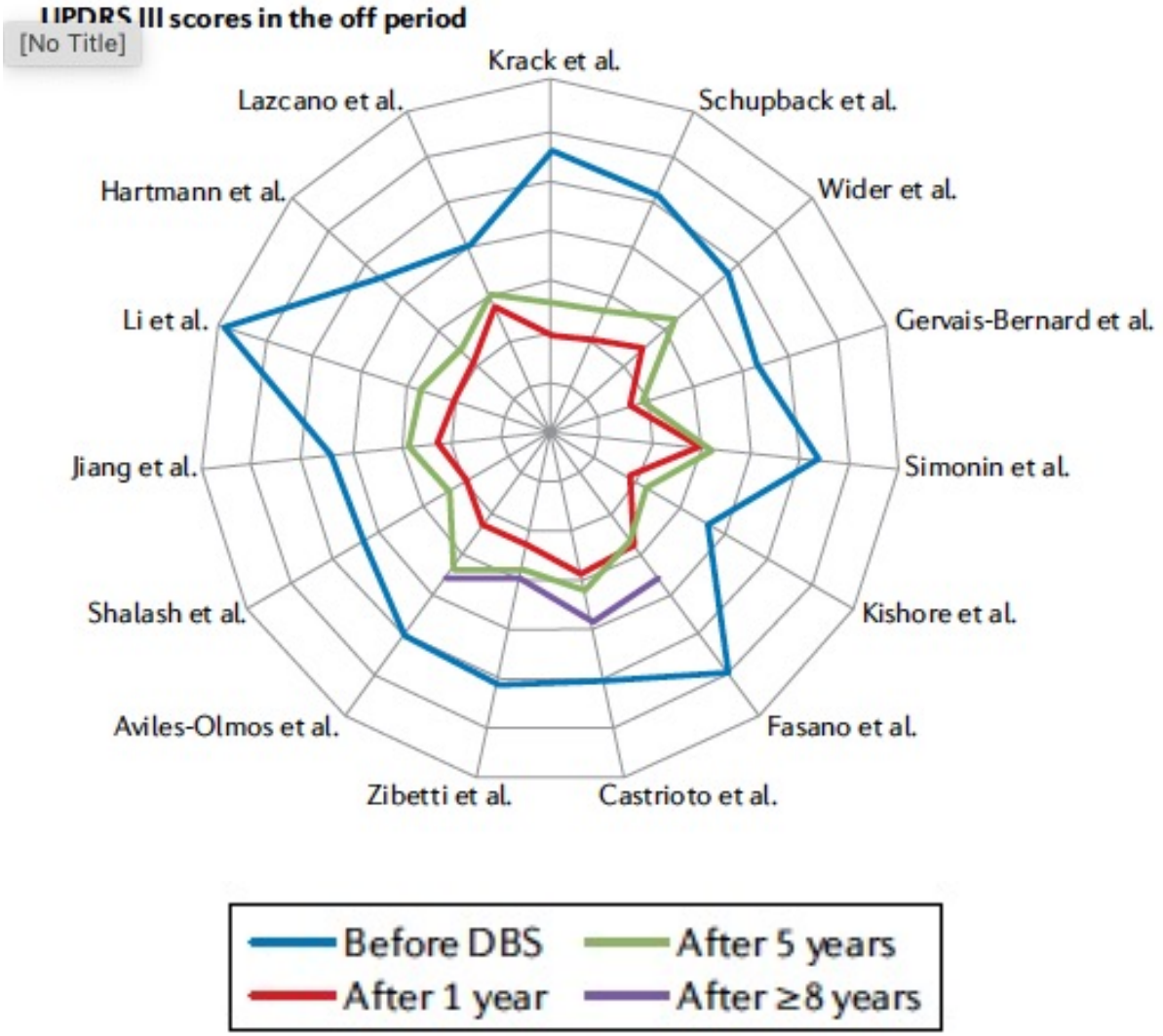
- DBS internal pulse generator (battery) placement

- Same day vs. outpatient procedure on separate day

1. Implanted DBS leads exposed
2. Extension leads tunneled under scalp → behind ear → to chest
3. IPG implanted under clavicle in subcutaneous pocket

Long-term DBS outcomes (PD) (STN)

- Significant improvement in UPDRS-3 at 1 and 5 years and even 10 years
- Slight decrease in benefit over years
  - Tremor and rigidity significantly improved and stayed over 5 years
  - Bradykinesia and axial symptoms show less improvement over 5 years
- Significant improvement in at 5 years and even at 10 years (but less)
- Significant improvement quality of life at 1 years but less at 5 years
- Medication reduction = 52% at 1 year, 45% at 5 years



Limousin et al. *Nature Reviews Neurology*

Long-term DBS outcomes (PD) – adverse events

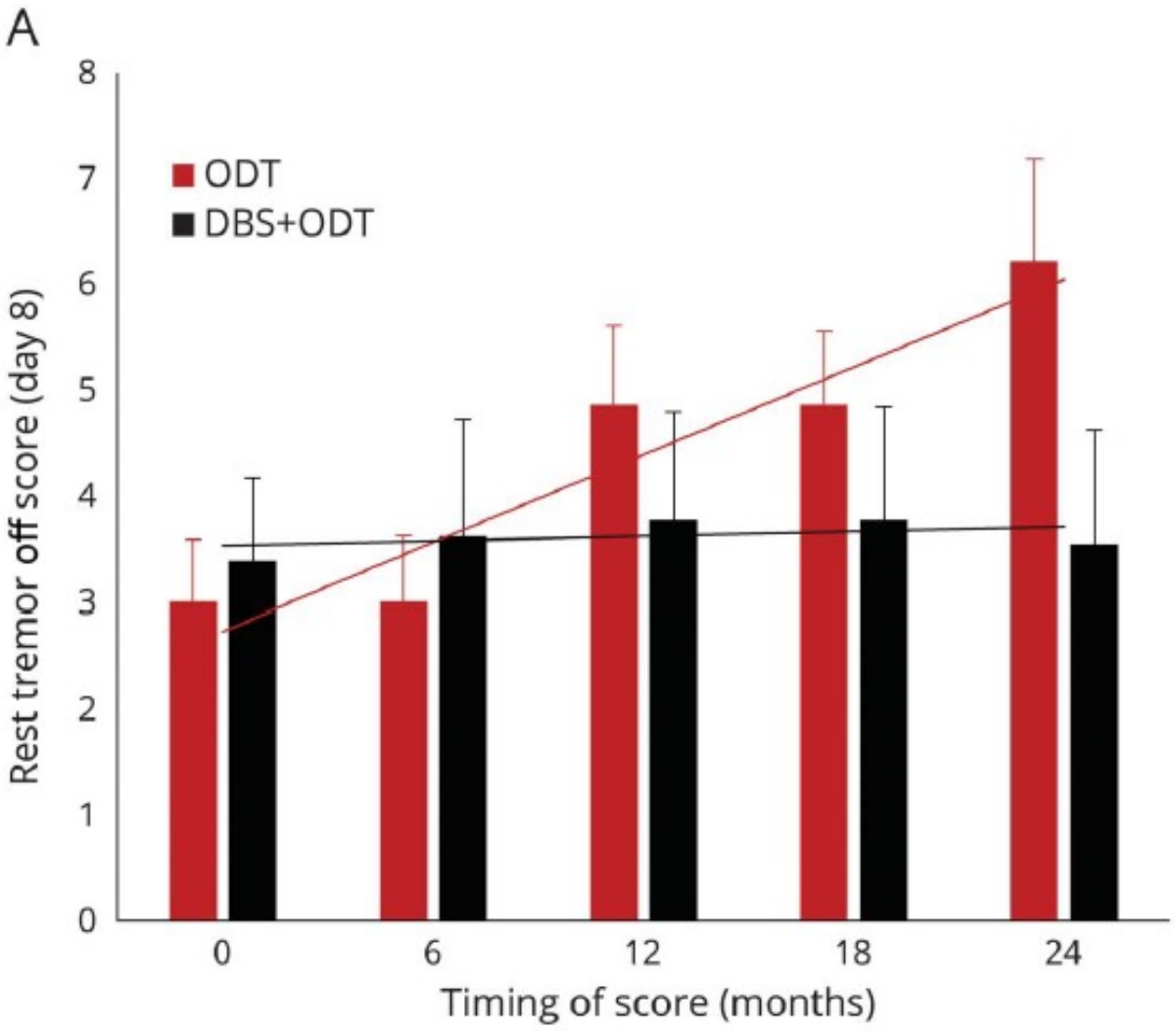
- No adverse effect on overall survival

- Total = 5% patients have long-term problems after DBS
  - Speech decline
  - Weight gain
  - Withdrawal

- Unclear if from PD progression or consequence of DBS

Early DBS and outcomes (tremor)

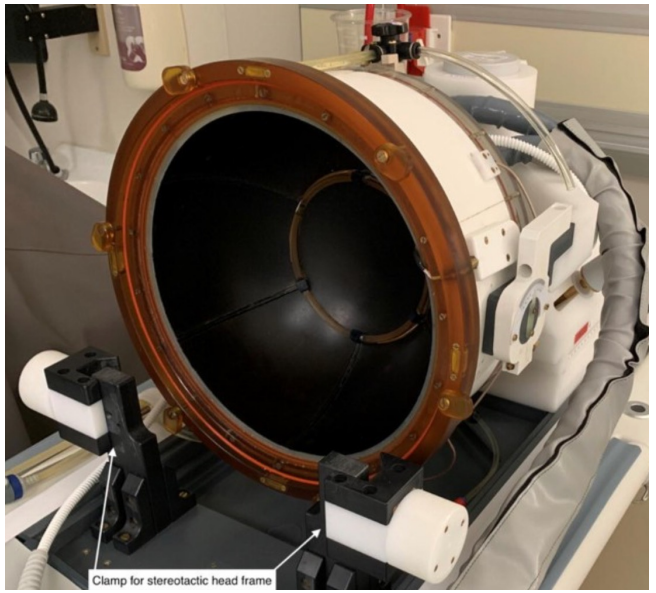
- Patients with PD for 6mo – 4 years enrolled
- Optimal drug therapy vs. optimal drug therapy + DBS → 7 day washout and then UPDRS-3 tremor score
- No change in tremor off score (off meds) up to 24 months with DBS
- Suggests decrease in degenerative tremor symptoms with DBS therapy

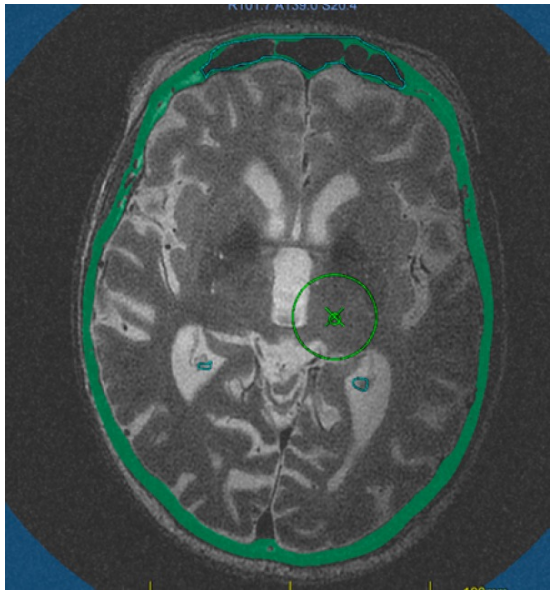


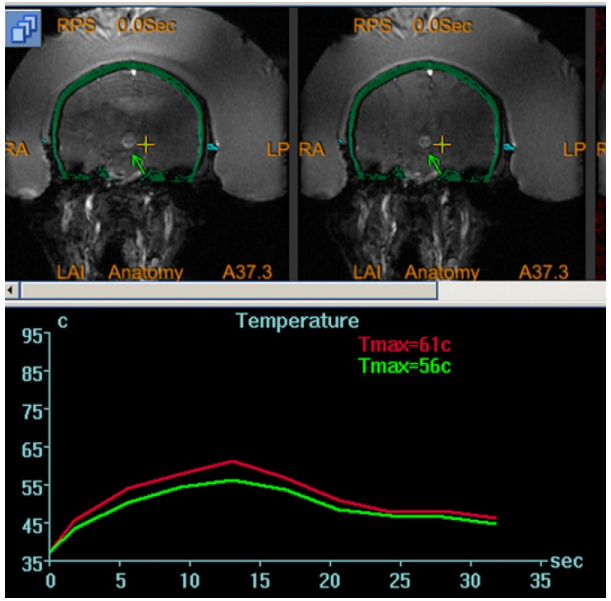
Focused ultrasound

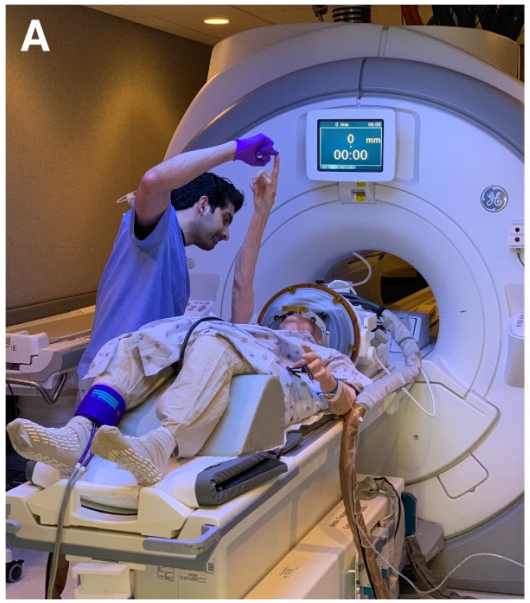
- Non-invasive technology that uses ultrasound therapy for therapeutic benefit
- Focusing 1024 beams of ultrasound into 1 point to achieve heating temperatures
- Originally discovered in 1944
- Recent advances allow for intracranial use
  - MR guided thermography
  - Correction for ultrasound attenuation at the skull

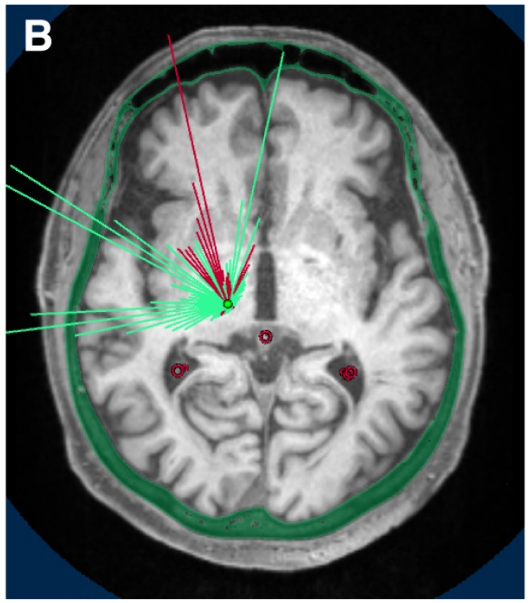
Focused ultrasound - technique

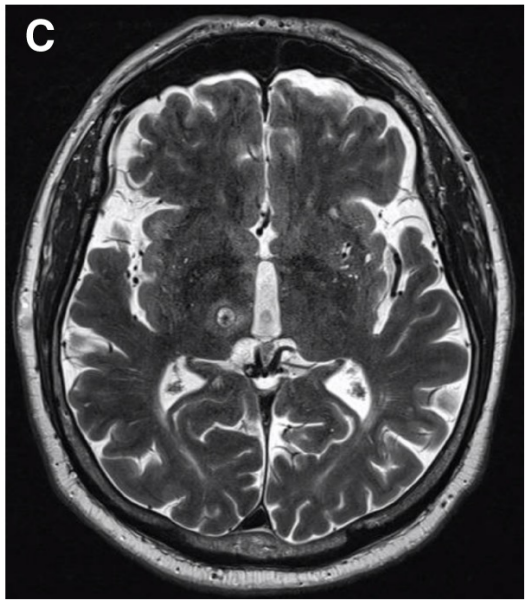






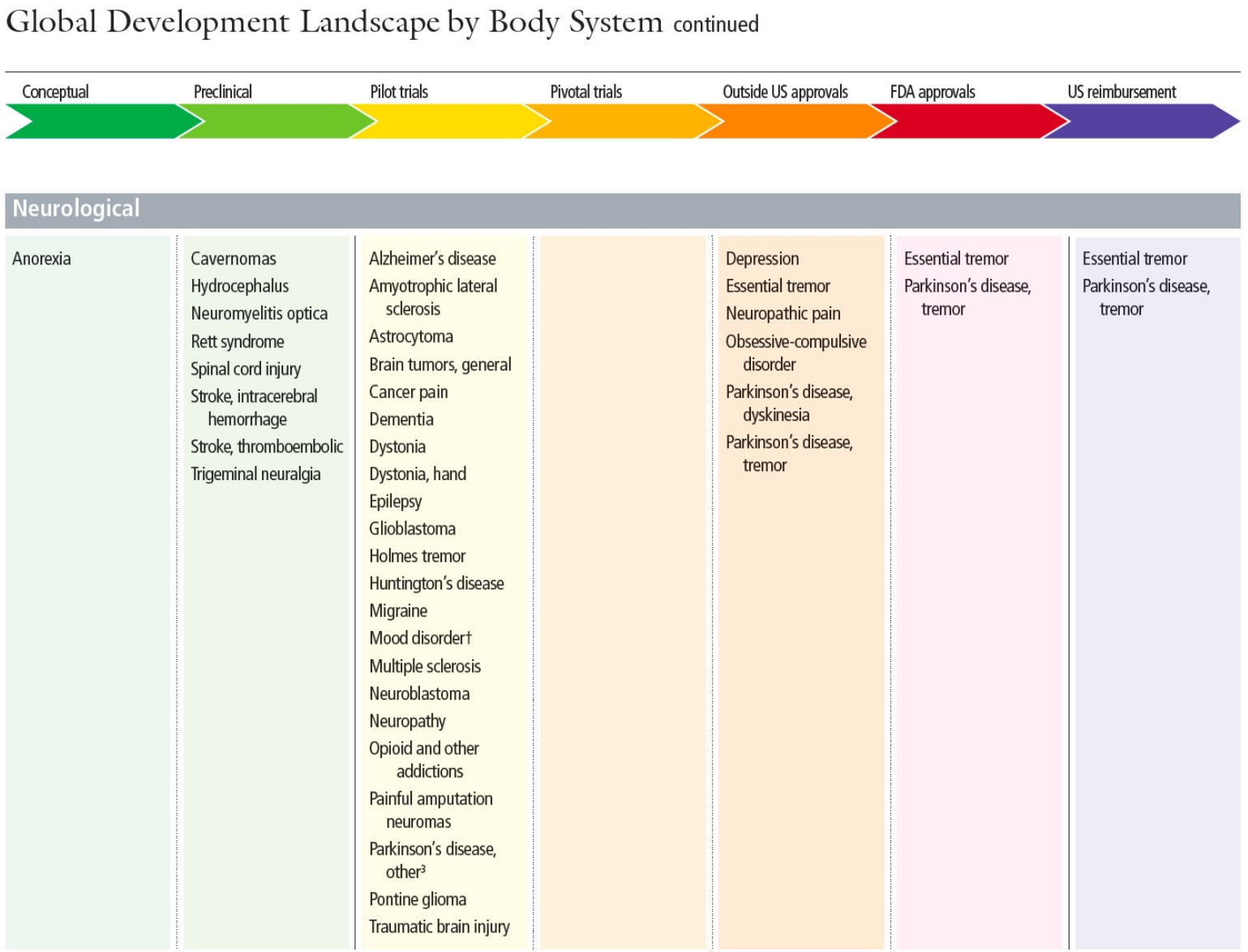






Focused ultrasound – state of the field (neuro)

- Currently approved for unilateral Vim for tremor-dominant PD and unilateral GPi for motor fluctuations
- Trials underway for bilateral (pallidothalamic tract) ablations (staggered over 6 months)



Global Development Landscape by Body System continued

Conceptual → Preclinical → Pilot trials → Pivotal trials → Outside US approvals → FDA approvals → US reimbursement

Neurological

Conceptual	Preclinical	Pilot trials	Pivotal trials	Outside US approvals	FDA approvals	US reimbursement
Anorexia	Cavernomas Hydrocephalus Neuromyelitis optica Rett syndrome Spinal cord injury Stroke, intracerebral hemorrhage Stroke, thromboembolic Trigeminal neuralgia	Alzheimer's disease Amyotrophic lateral sclerosis Astrocytoma Brain tumors, general Cancer pain Dementia Dystonia Dystonia, hand Epilepsy Glioblastoma Holmes tremor Huntington's disease Migraine Mood disorder† Multiple sclerosis Neuroblastoma Neuropathy Opioid and other addictions Painful amputation neuromas Parkinson's disease, other[3] Pontine glioma Traumatic brain injury		Depression Essential tremor Neuropathic pain Obsessive-compulsive disorder Parkinson's disease, dyskinesia Parkinson's disease, tremor	Essential tremor Parkinson's disease, tremor	Essential tremor Parkinson's disease, tremor

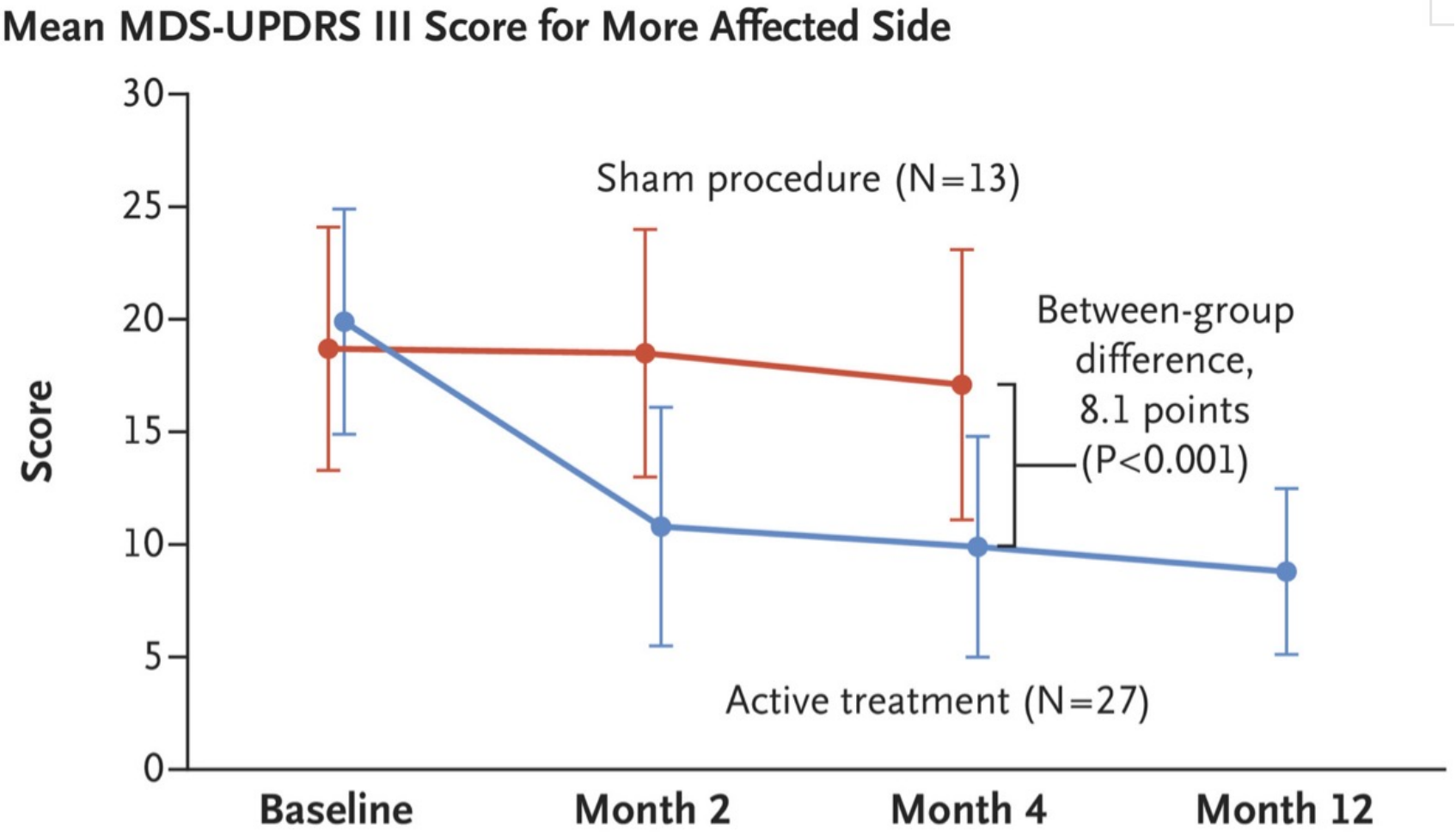
Focused ultrasound – PD outcome (tremor dominant)

- Tremor-dominant PD (unilateral symptoms) – Vim target
  - Efficacy – 51.9% reduction in tremor (vs. 12.7% in sham group) at 3 month
  - Trend for improved tremor at 12 months

  - Safety – 7% numbness and tingling; 4% imbalance, 2% gait disturbance and 1% unsteadiness
    - 58% resolved on same day
    - 1 patient with weakness improved after 30 days
    - 1 patient with hemiparesis

Focused ultrasound – PD outcome (motor fluctuations)

- Motor symptoms PD (unilateral STN) – efficacy (40 patients)



Focused ultrasound – PD outcome (motor fluctuations)

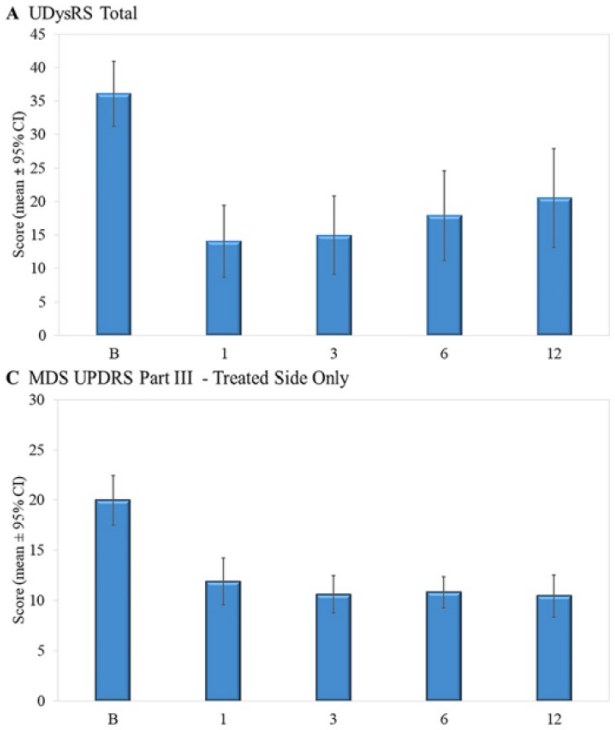
- Motor symptoms PD (unilateral STN) - safety

Adverse Event	Focused Ultrasound Subthalamotomy (N=27)				
	Total	At 24 Hr	At 2 Mo	At 4 Mo	At 12 Mo
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‖
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)
Gait disturbance — no. of patients (%)					
Any objective or subjective event‡	13 (48)	8 (30)	7 (26)	2 (7)	1 (4)

Focused ultrasound – PD outcome (motor fluctuations)

- Motor symptoms PD (unilateral GPi) – (20 patients)
- Safety
  - Headache, n/v, headache
  - Neurological (persisted)
    - 1 patient motor difficulty (mild)
    - 3 patients with speech alteration (mild to mod)
    - 1 patient with balance (mild)

- Efficacy
  - Unified dyskinesia rating scale improved 59% at 3mo
  - UPDRS-III improved by 44% at 3mo



Conclusions

DBS surgery is safe and effective for PD and should be considered early in disease progression

Efficacy of DBS can last 5 – 10 years but start to wane

Focused ultrasound is an emerging technology for PD

Thank You

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