New Frontiers in Advanced Therapeutic Options for Parkinson Disease:

Asleep DBS, Robotic Surgery, Advanced Imaging

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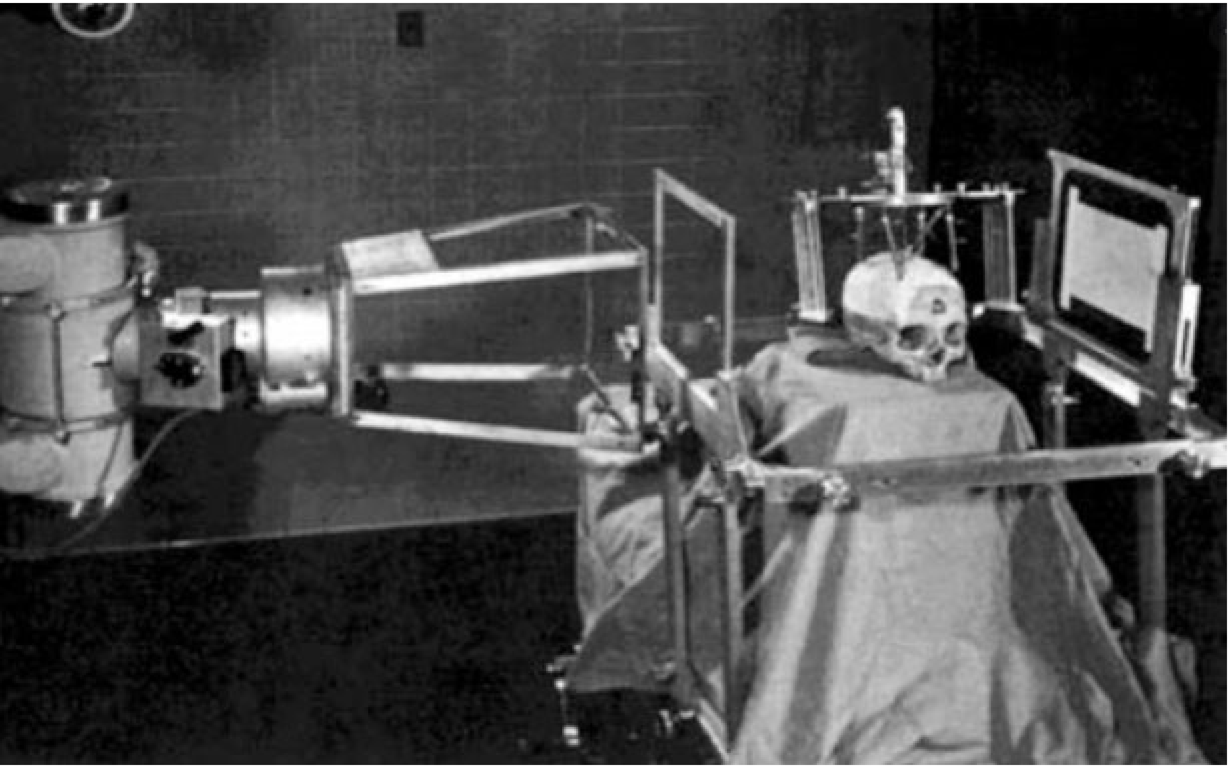
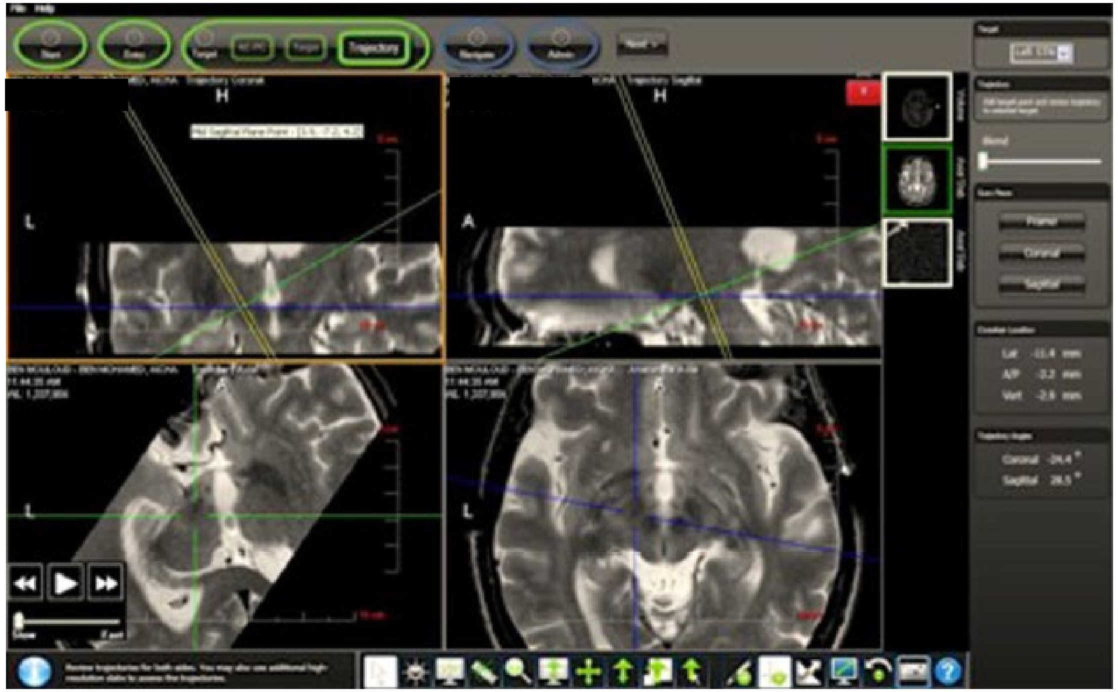
Evolution of DBS Surgery





Stereotactic Neurosurgery

- Historical context
- Modern advancements
- Adaptation to modern technologies

Stereotactic Neurosurgery

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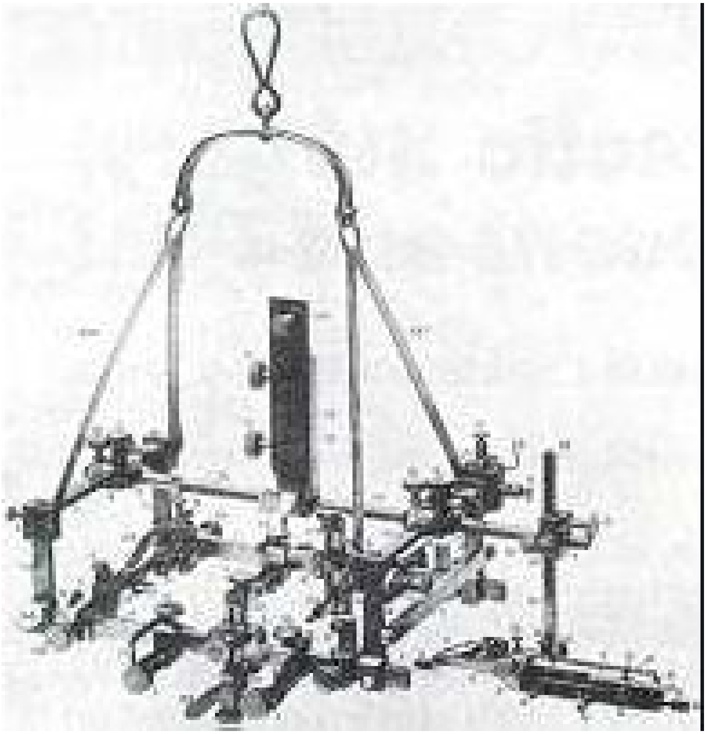
Stereotaxy

- Three-dimensional target localization referenced to a Cartesian coordinate system
  - X, Y, Z
- 1908 – Horsley and Clarke developed head frame
- Introduction of stereotactic techniques
- Developed atlas for monkey brain
- Used bone landmarks
- Does not account for skull anatomy variability



Gildenberg. Movemt Disord Surg. 15:1-20, 2000

Stereotaxy

- 1961 – Albe-Fessard et al. first to report technique of intra-op microelectrode recording (MER)
- Numerous iterations over next ten years; ~40 devices
  - Leksell – first arc-centered apparatus
  - Talairach – laterally fixed grid system; prequel to SEEG
  - Riechert and Wolff – arc-centered device with phantom base
- Several stereotactic atlases created
- 37,000 operations performed by 1969

Stereotaxy

- Limitations:
  - Poor image quality
  - Indirect targeting based off of brain atlas cartesian coordinates
  - Intra-op x-rays may infer Z- errors or Y- errors, but not X- errors
  - Large variations in surgical techniques

Stereotactic Neurosurgery

- Historical context
- Modern advancements
- Adaptation to modern technologies

Computed Tomography and MRI

- John Shea, MD – single greatest advancement in neurosurgery was the development of the CT scan in 1972
- MRI technology developed around same time
- Three dimensional cartesian coordinates paired well with three dimensional anatomical structures now visualized on CT imaging

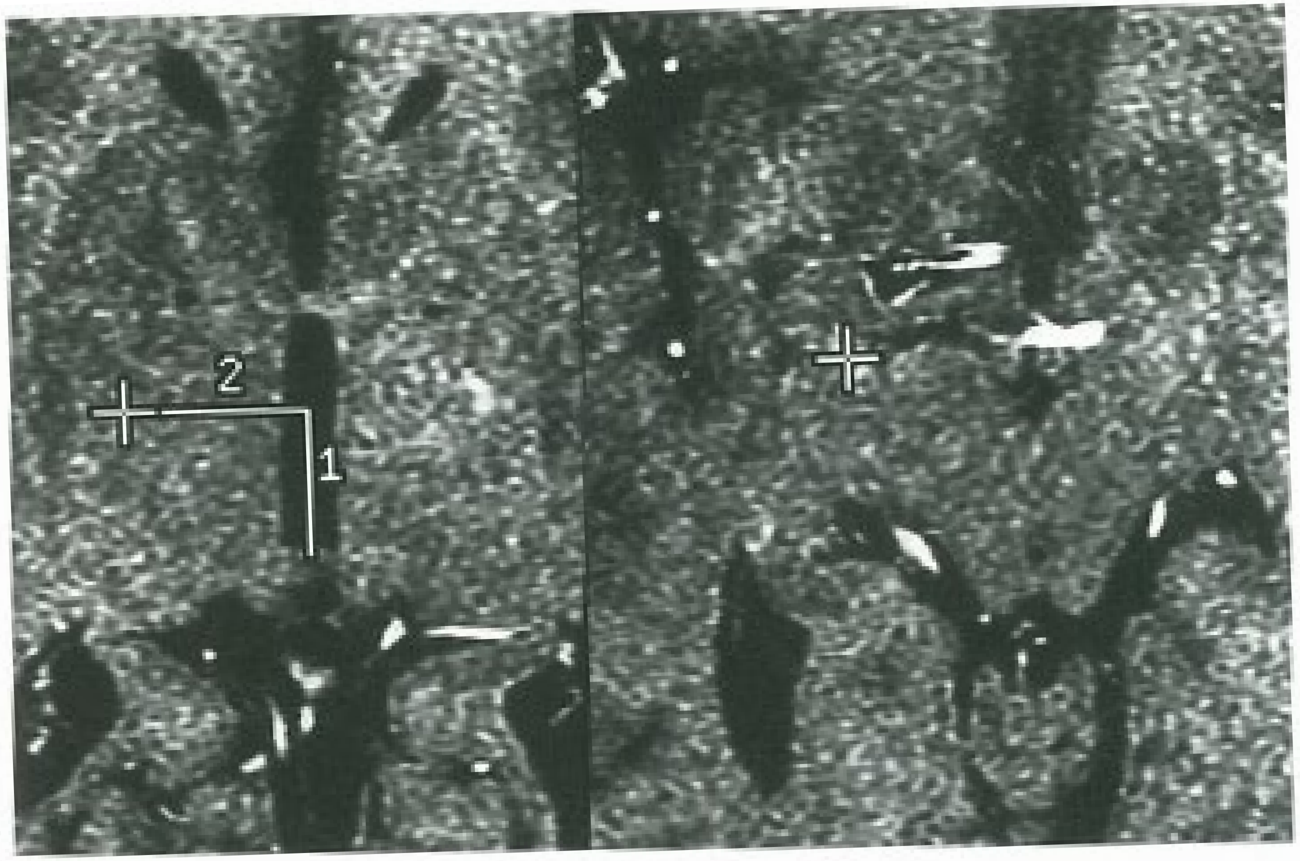
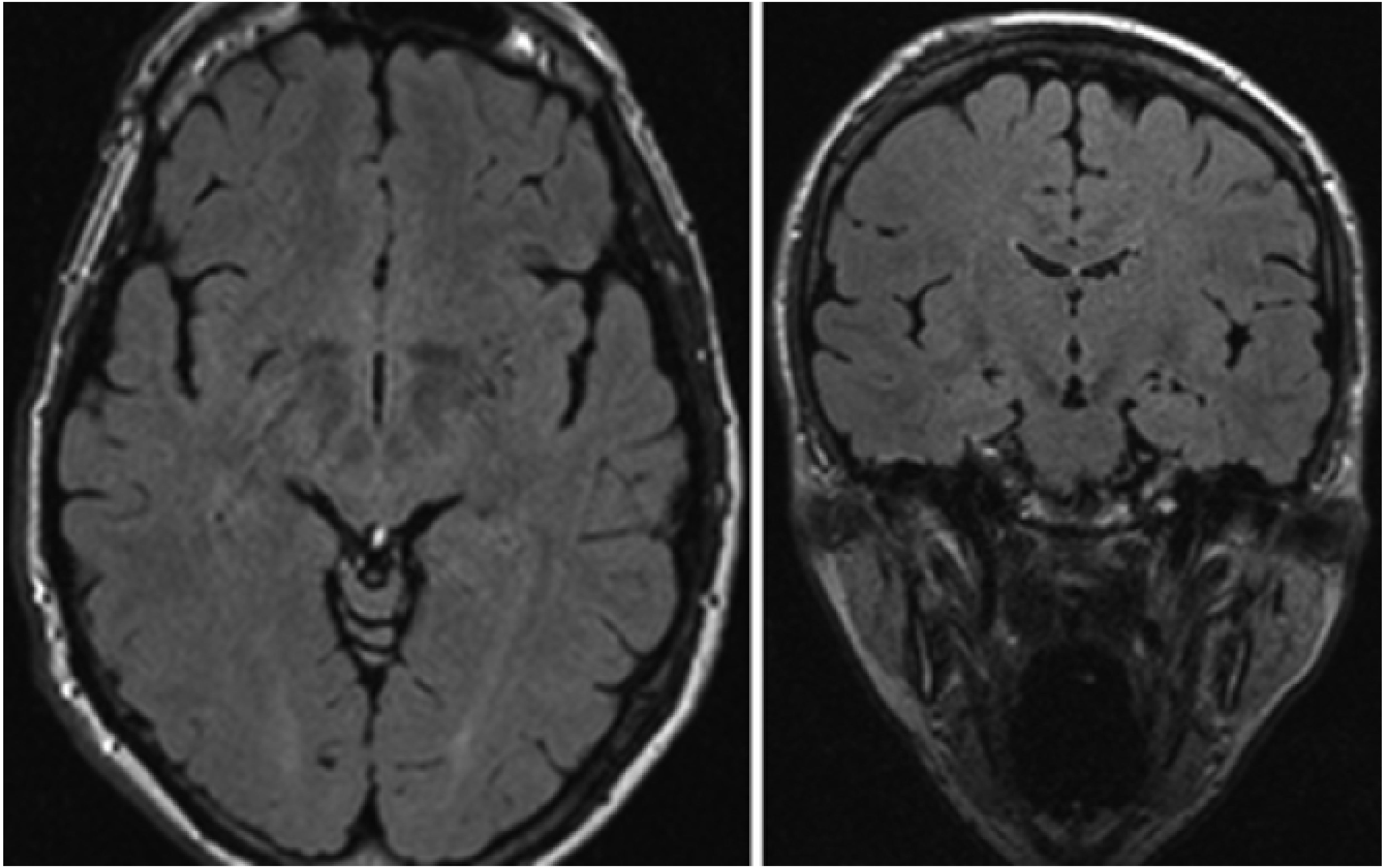


Fig. 4. Target localization for a GPi lesion demonstrates the X and Y coordinates in the intercommissural plane. The right image demonstrates the final target in the appropriate Z plane, 2 mm above the right optic tract.

Fig. 3. A coronal image obtained with the inversion recovery signal clearly demarcates the internal, external, and extreme capsules (arrows right to left), the optic tract, putamen and globus pallidus.

Thompson et al. Movemt Disord Surg. 15:1-20, 2000



Stereotactic Neurosurgery

- Historical context
- Modern advancements
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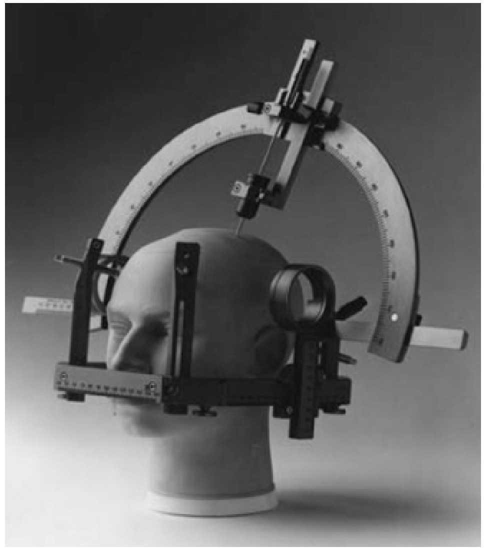
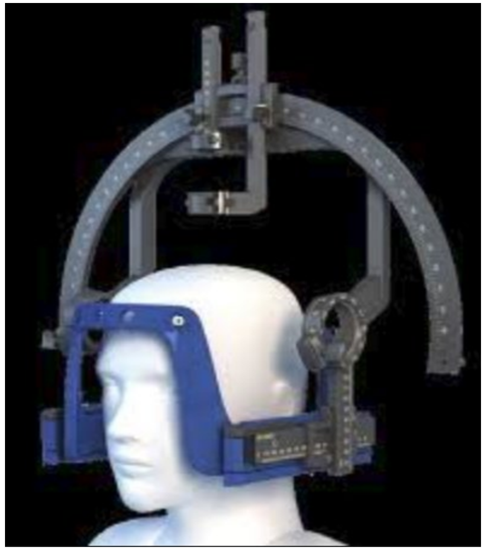
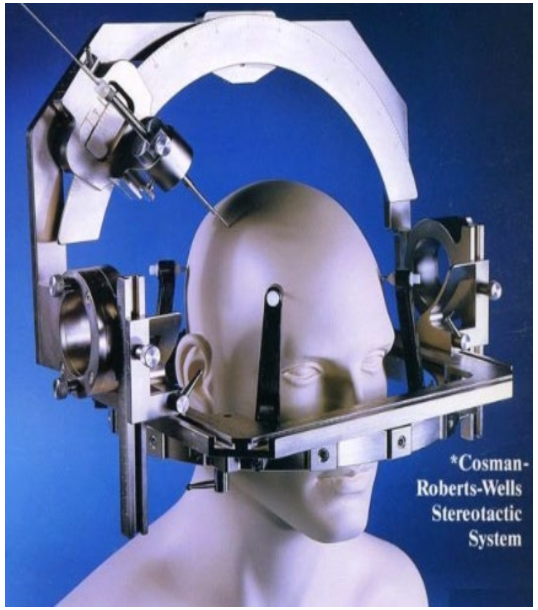
Stereotactic Frames

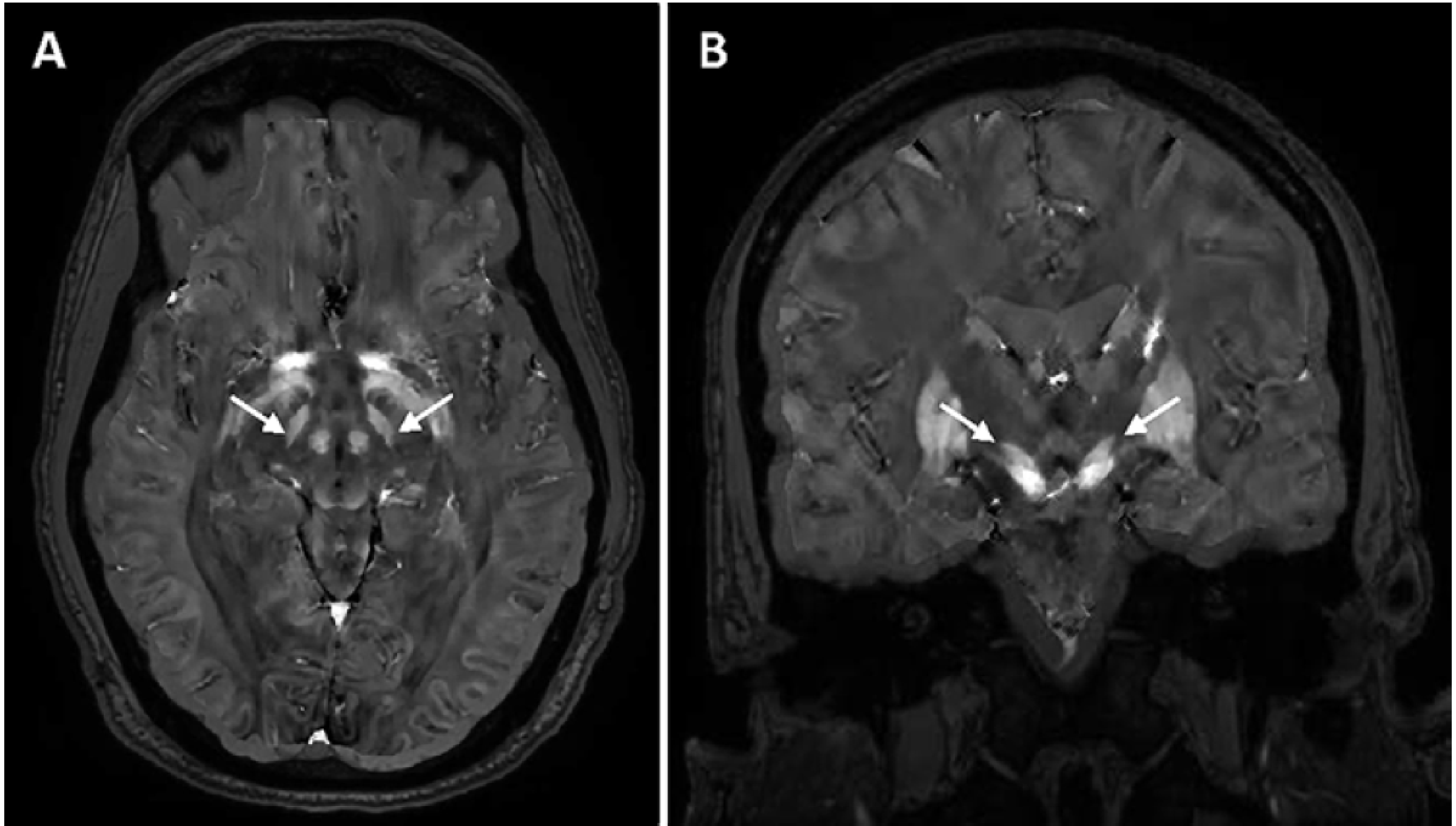






Intra-op Stereotactic Accuracy

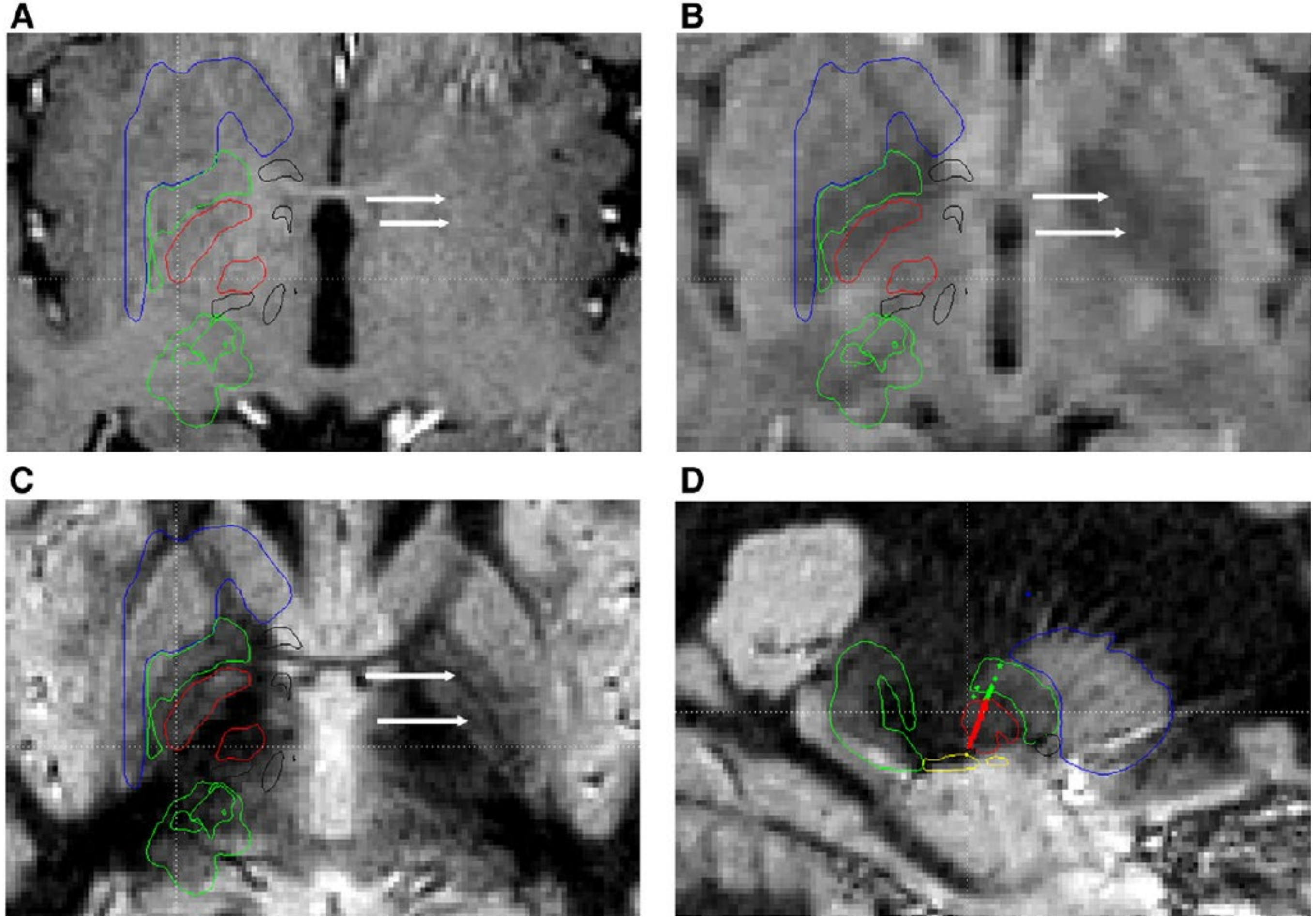
- Quantitative Susceptibility Mapping



Dimov et al. J Neurosurg. 131:360-367, 2019

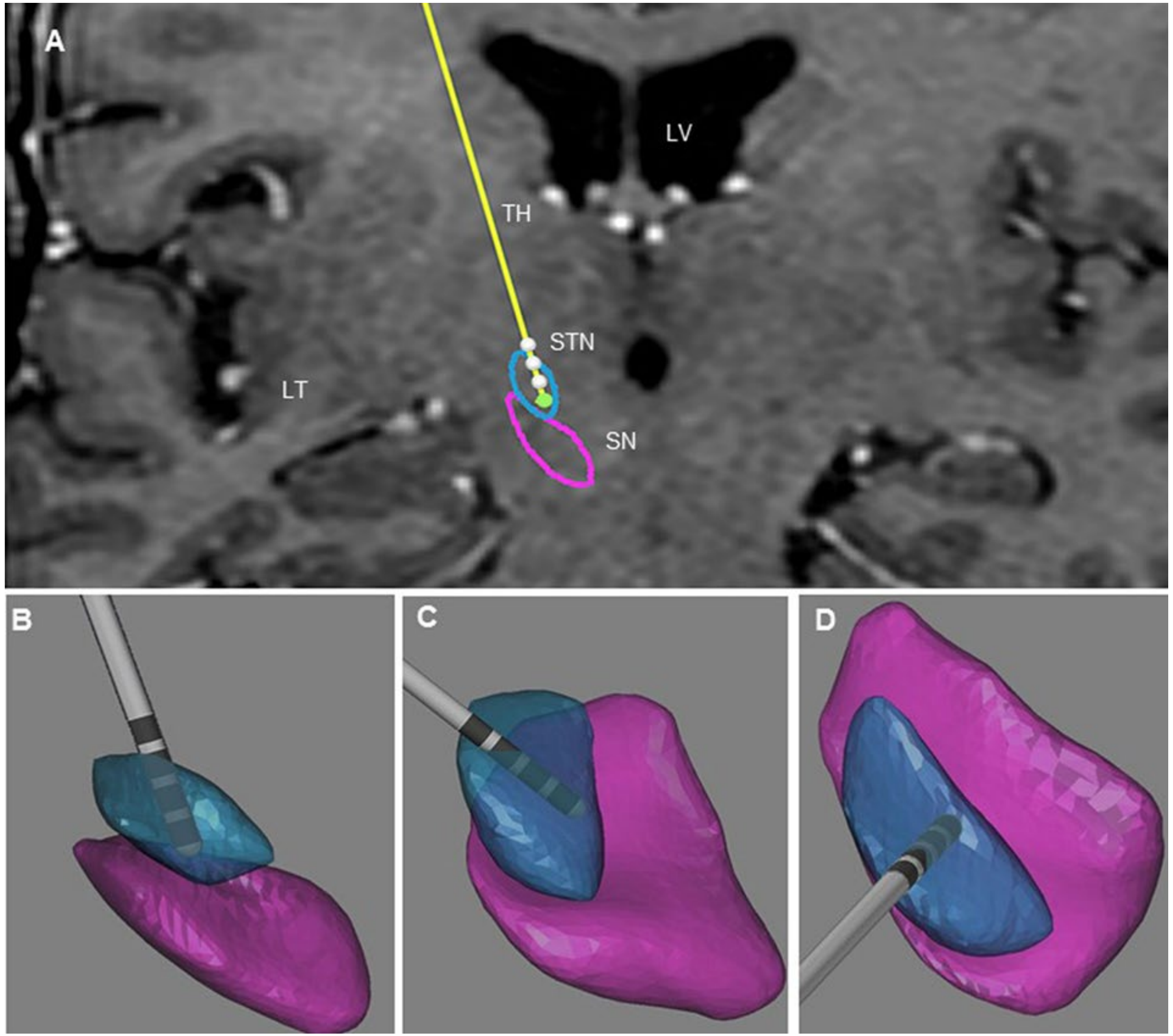
Intra-op Stereotactic Accuracy

- Fast Gray Matter Acquisition T1 Inversion Recovery (FGATIR)



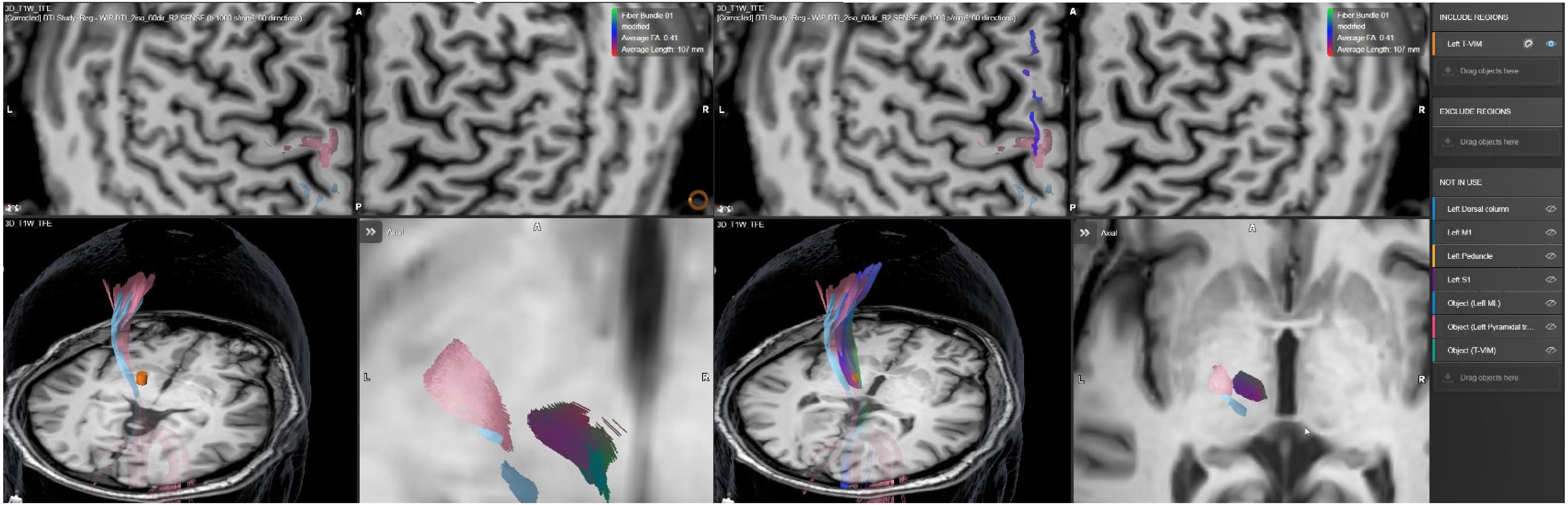
Sudhyandhom et al. NeuroImage. 47:44-52, 2009

Intra-op Stereotactic Accuracy

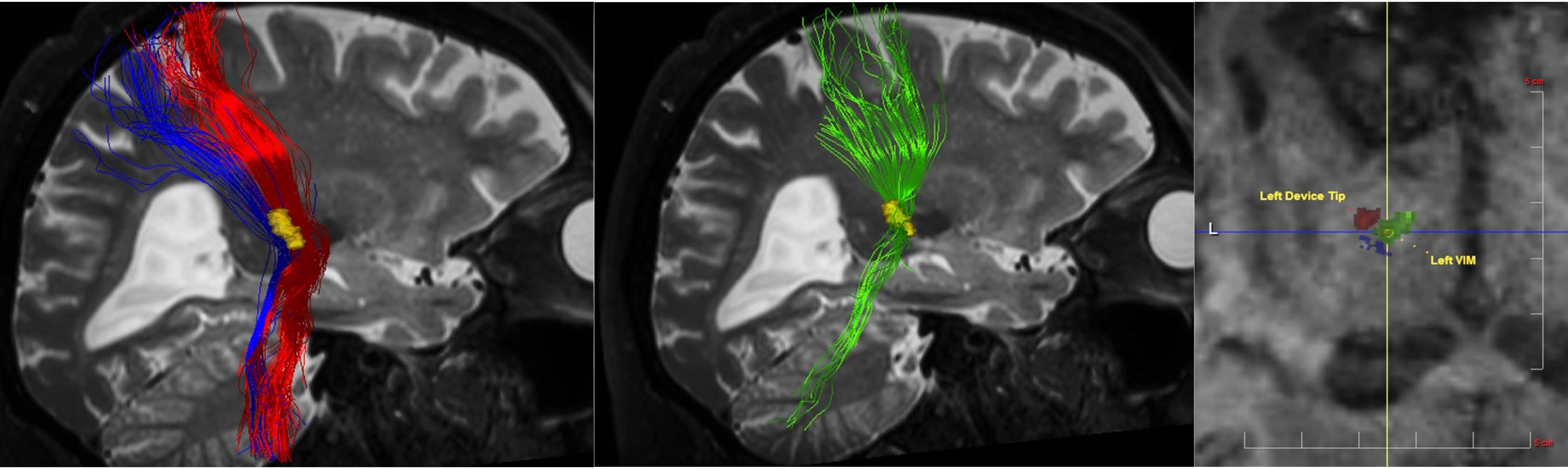


Huang, et al. Font. Neurol. 9:1-6 2018

Intra-op Stereotactic Accuracy: Tractography



Tractography



Robotics in DBS

Intraoperative Lead Confirmation

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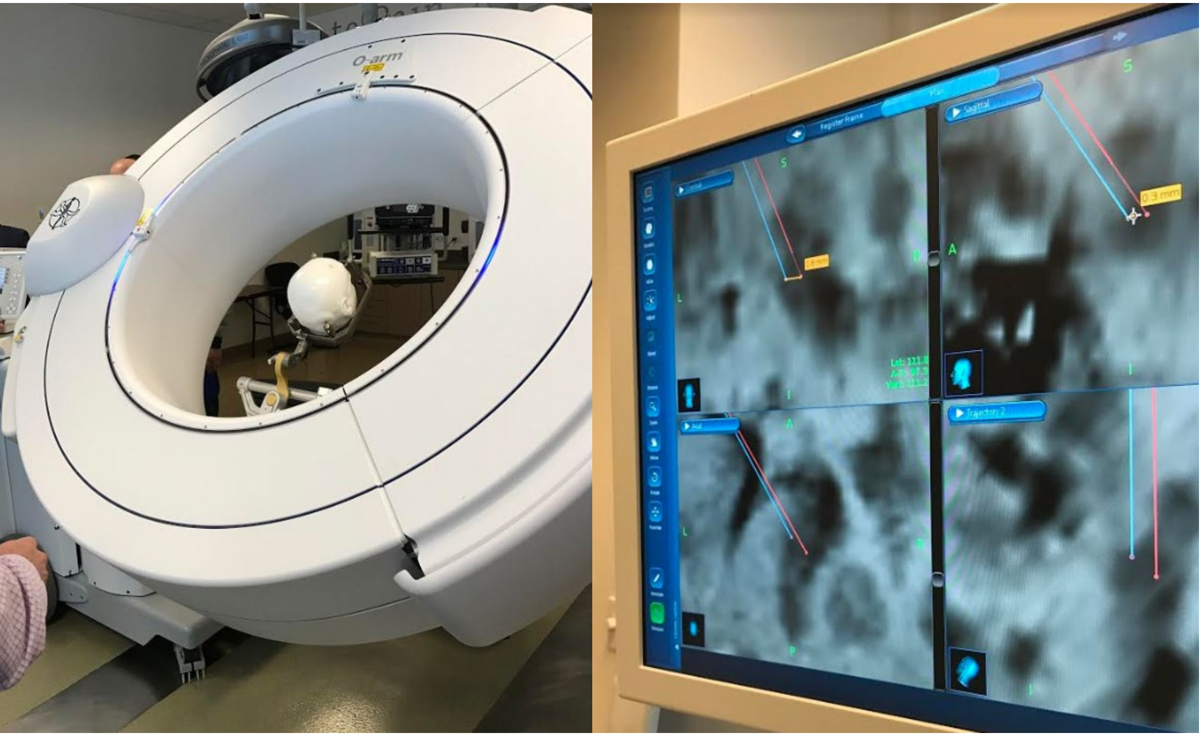
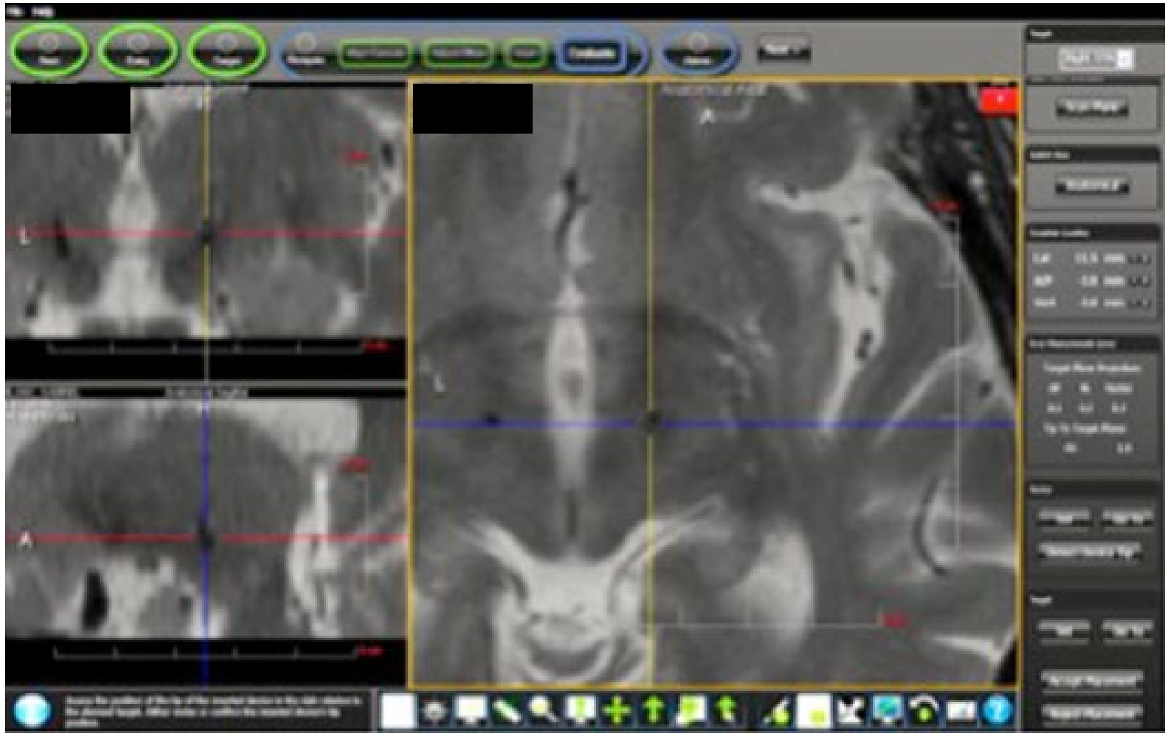
Intra-op Stereotactic Accuracy

- All these modalities help to visualize and predict the appropriate target
- Intra-op confirmation of lead placement accuracy is paramount

Intra-op Stereotactic Accuracy

- CT Guided
- MRI Guided





Intra-op Stereotactic Accuracy

- Accuracy of lead placement
  - Frame Based: average no more than 1.7 mm in any direction
  - MRI guided: 0.6 ± 0.3 mm
  - CT guided: 0.8-1.24 mm
  - Renishaw Robot: 0.86 ± 0.32 mm

Ostrem et al. J. Neurosurg. 124:908-916, 2016
Kochanski et al. Brain Sci. 8(17), 2018
Von Langsdorff et al. J. Neurosurg. 122:191-194, 2015
McClelland et al. Neurosurg Focus. 19(5):E12, 2005
Smith et al. J. Neurosurg. 115:301-309, 2011
Ivan et al. J. Neurosurg. 121:149-160, 2014
Khan et al. Stereotact Funct Neurosurg. 86:44-53 2008

Asleep DBS

- Improved accuracy with MRI, iCT, robotic lead placement
- Decreased pneumocephalus, decreased CSF loss and brain shift
- Correlation of MER with verified correct anatomical placement
- Improved ability to see and direct target deep brain nuclei
- Intra-operative verification of lead accuracy
- MER still possible with asleep DBS surgery
- What is the need for awake DBS surgery?

Ko et al. Stereotact Funct Neurosurg. 2015

Asleep DBS

- Intra-op test stimulation to assess for side effects

Asleep DBS

- Meta analysis by Ho et al. compared 139 awake vs 16 asleep studies
  - No difference in error (1.92 vs 2.27 mm, P=0.557)
  - Fewer lead passes in asleep group (1.4 vs 2.1, P=0.006)
  - Lower ICH (0.3% vs 1.1%, P=<0.001)
  - Lower infection (0.7% vs 1.4%, P=<0.001)
  - **Awake DBS had greater decrease in therapy-related side effects based on UPDRS IV scores in off medication condition (78.4% vs 59.7%, P=0.022)**
    - However, no difference in outcome measured by UPDRS II, III, or LEDD scores
    - Motor outcomes and self evaluation of ADLs were equal
  - Authors suggest asleep DBS is non-inferior to awake DBS but should be considered at highly specialized centers

Ho et al. J. Neurol Neurosurg Psychiatry. 89:687-691, 2018

Asleep DBS

- Blasberg et al. reviewed awake vs asleep PD DBS
  - 140 awake, 48 asleep
  - **Found that UPDRS motor score was better in the awake group at 3 months, but were no different at 12 months** (P=0.006 vs P=0.18)
  - **Freezing and Speech UPDRS scores were worse at 12 months** (P=0.033, P=0.045)
  - **LEDD was no different at 12 months**
  - Authors suggest Asleep DBS is reasonable with similar 12 month UPDRS motor scores

Blasberg et al. Neuromodulation. 21:541-547, 2018

Asleep DBS

- Brodsky et al. found no difference in UPDRS II or III scores at 6 months, but did find improved PDQ-39 and cognition and communication subscores in asleep patients (P=0.004 and P=0.011)
  - Improved ‘on’ time without dyskinesias in asleep group (P=0.002)
  - **Speech was improved in both category** (P=0.0012) **and phonemic fluency** (P=0.038)
- Nakajima et al. found **no difference in UPDRS III motor scores at 12 months**

Brodksy et al. Neurology. 89:1944-1950, 2017
Nakajima et al. Stereotact Funct Neurosurg. 89:318-325, 2011

Asleep DBS

- Matias et al. look at outcomes using iMRI and found UPDRS III off-medication scores, 46.3%, similar to scores reported awake with MER (GPi, single center, 9 mo. avg follow-up)
- Meta analysis by Hamani et al. reported **49% reduction in UPDRS III scores at 5 years in off-medication state** (STN)
- Aviles-Olmos et al. reported 77.2% tremor reduction, 50% rigidity reduction, 23.2% bradykinesia reduction with 8 year follow-up (MRI, awake, without MER)

Matias et al. J Neurosurg. 129:1572-1578, 2018
Hamani et al. Neurosurg. 56(6):1313-1321, 2005
Aviles-Olmos et al. Neurol Neurosurg Psychiatry. 85:1419-1425, 2014

Asleep DBS

- Cost
  - Jacob et al. and Wang et al.
  - Both report **similar costs for asleep vs awake** (38,000±4,500 vs 40,000±6,600)
  - Standard deviation and cost variation for asleep DBS is lower than awake DBS

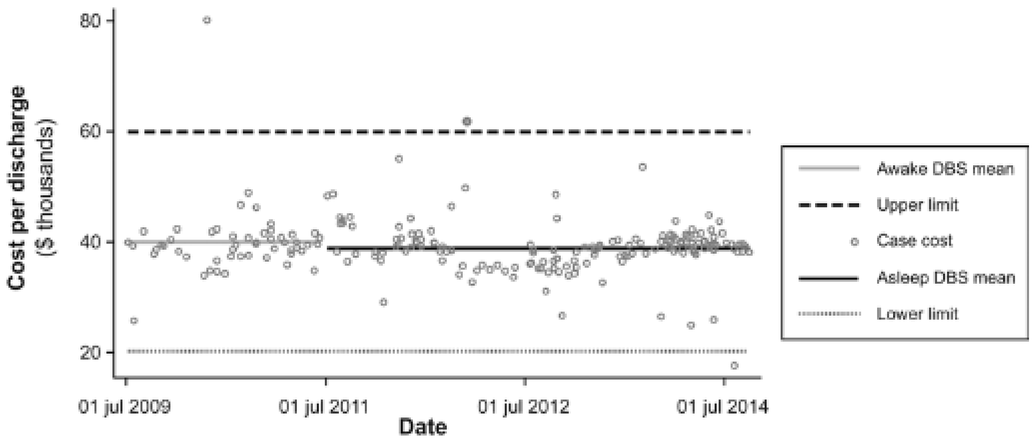


FIG. 3. Total OHSU DBS cost over time with upper and lower 3 standard deviations (July 2009–March 2014). Data source: OHSU.

Jacob et al. J Neurosurg. 124:1517-1523, 2016
Wang et al. Neuromod. 2019

Asleep DBS

- Long term data seems to point to relative equality of outcomes between awake vs asleep groups
- Imaging techniques continue to improve
- Tractography may improve direct targeting and side effects
- Most of data supports that asleep DBS is non-inferior to awake DBS with regards to motor scores and some mixed results with other outcomes

Kochanski et al. Brain Sci. 8(17), 2018