Deep Brain Stimulation for the Treatment of Parkinson's Disease

Jeff Elias, MD

University of Virginia Health System

Disclosures

FDA approvals:

- Unilateral thalamic DBS for ET/PD tremor: 1997 (*Medtronic*)
- DBS for PD: 2002 (*Medtronic*)
- Bilateral STN DBS for PD: 2016 (*Abbott*)
- Bilateral STN DBS for PD: 2017 (*Boston Scientific*)

Funding (PD)

- FUS Foundation
- Commonwealth of Virginia
- Diane & David Heller
- Robert & Molly Hardie
- Prince Charitable Trust

Funding (Neuromodulation)

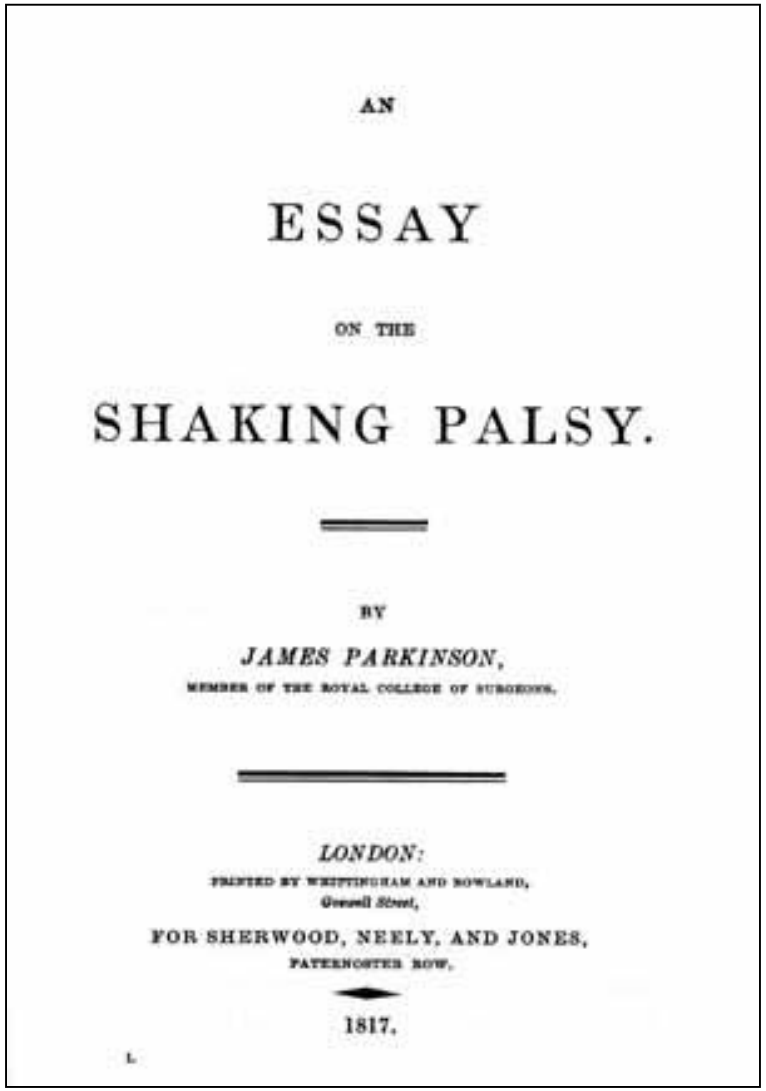
- NIH
- UVA Brain Institute

Objectives

1. Parkinson’s disease overview

2. History of surgery for movement disorders

3. Contemporary Deep Brain Stimulation



AN

ESSAY

ON THE

SHAKING PALSY.

BY

JAMES PARKINSON,

MEMBER OF THE ROYAL COLLEGE OF SURGEONS.

LONDON:

PRINTED BY WHITTINGHAM AND ROWLAND,

Goswell Street,

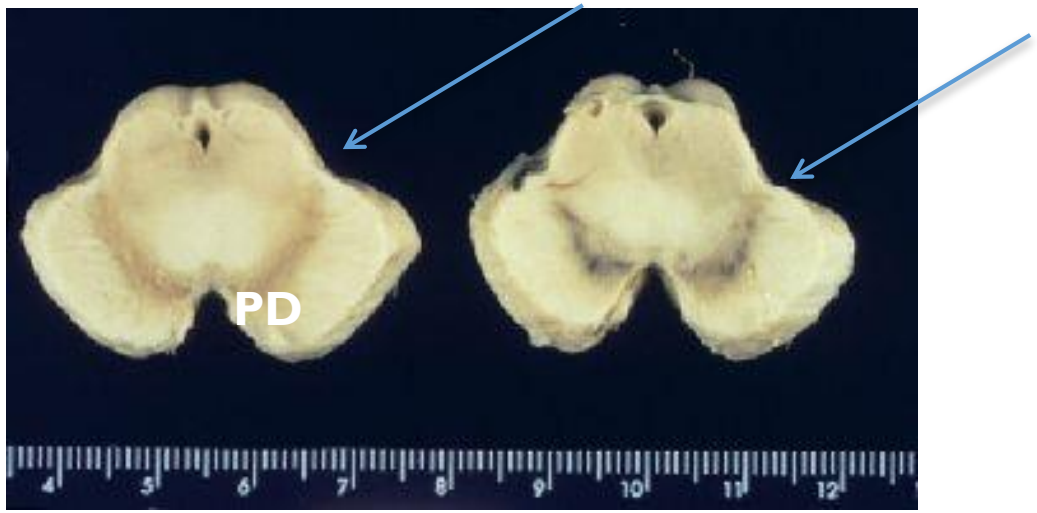
FOR SHERWOOD, NEELY, AND JONES,

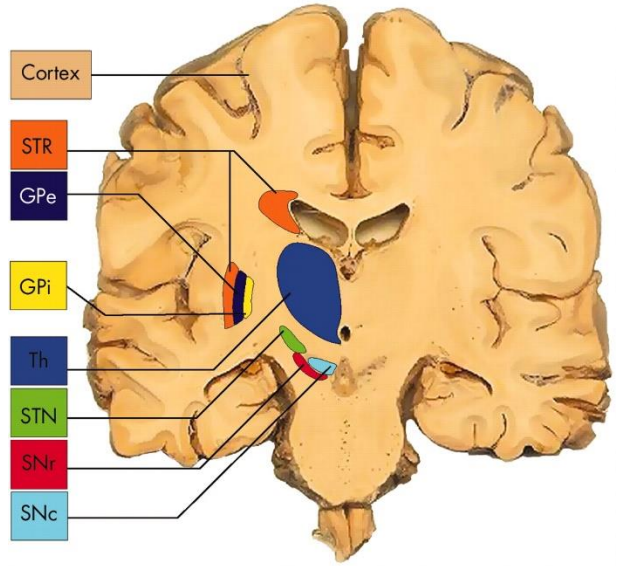
PATERNOSTER ROW.

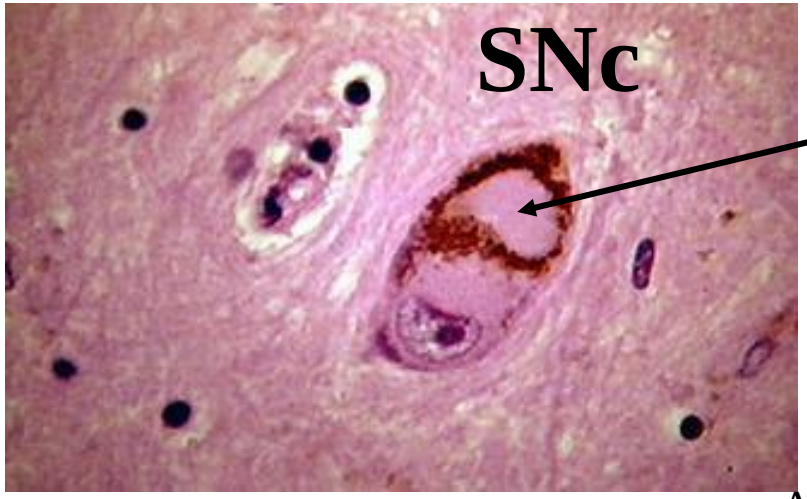
1817.

"….this affection is distinguishable from tremor, by the agitation, in the former, occurring whilst the affected part is supported and unemployed … whilst in the latter, the tremor is induced immediately on bringing the parts into action."

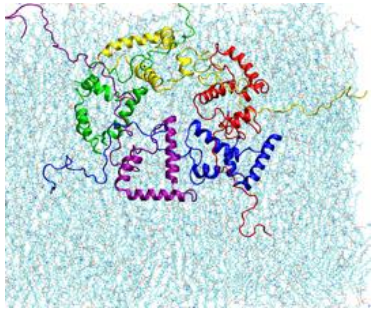
Parkinson's Disease – Pathology







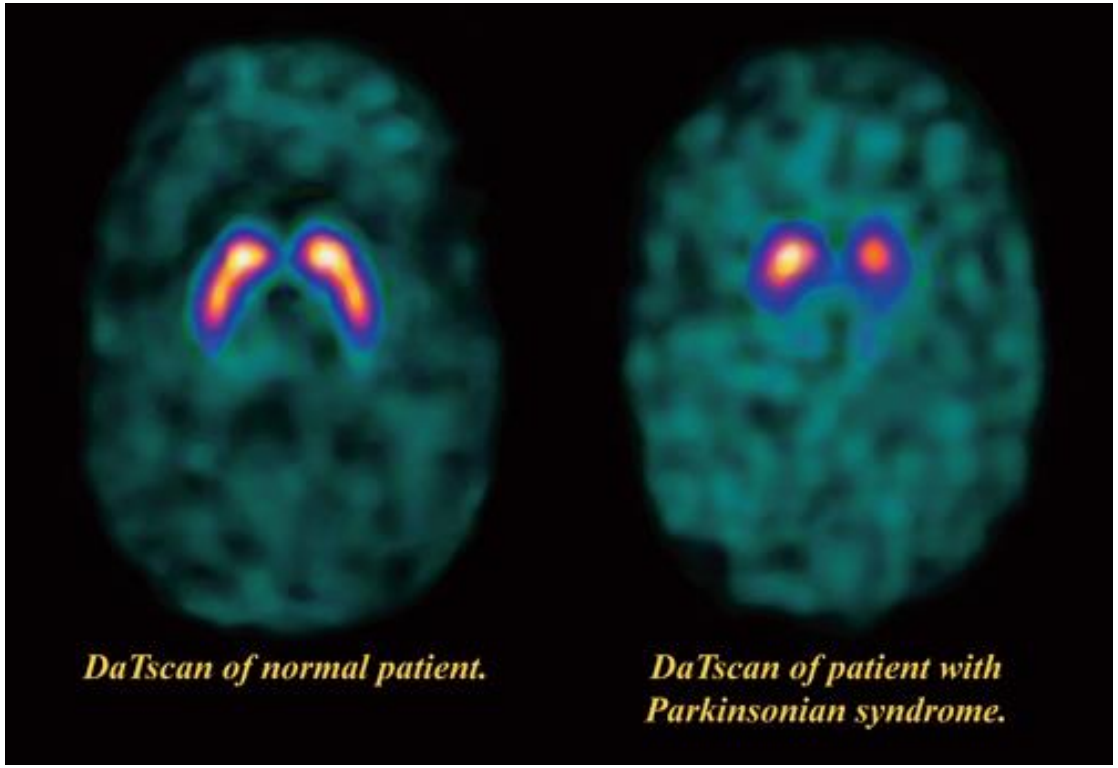
Lewy Body



Alpha-synuclein

Diagnosis:

- Bradykinesia
- *AND* at least one:
  - Muscle rigidity
  - 4-6 Hz resting tremor
  - Postural instability

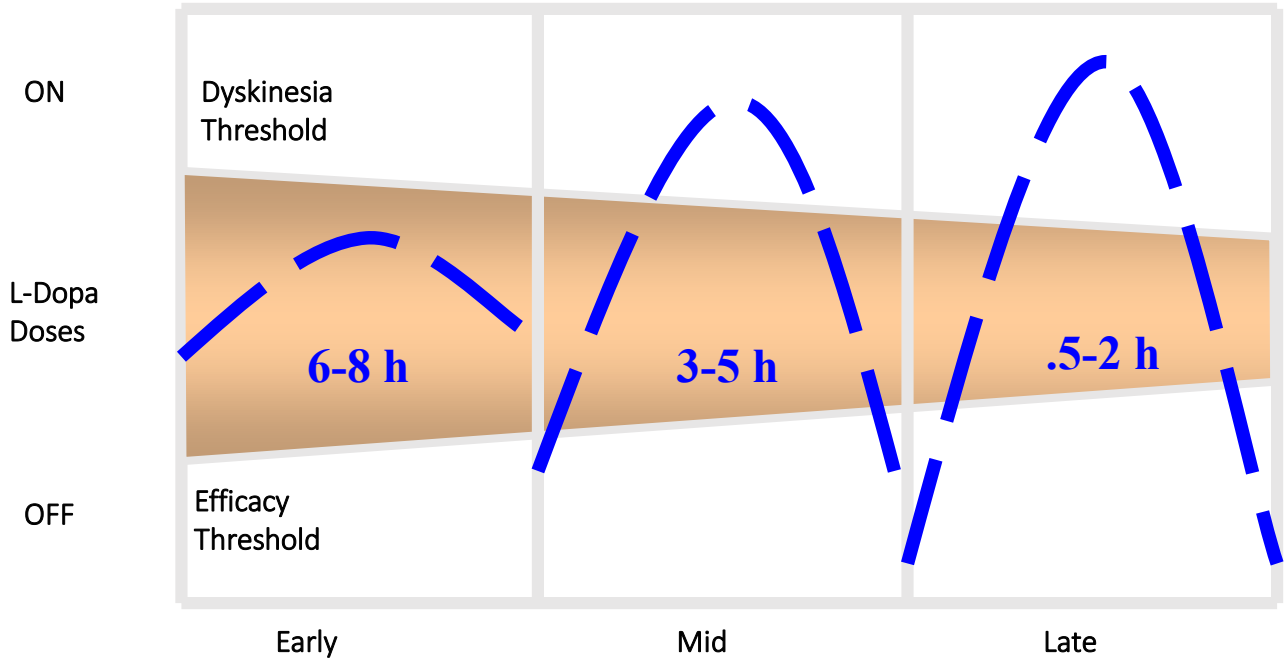


Parkinson's Disease – Early Symptoms

- At least 3 of the following:
    - Bradykinesia (slowness)
    - Rigidity (cogwheel rigidity)
    - rest tremor,
    - **asymmetric** onset;
- Levodopa responsive
- No evidence of atypical parkinsonism
    - Incontinence
    - Early balance difficulty
    - Autonomic dysfunction

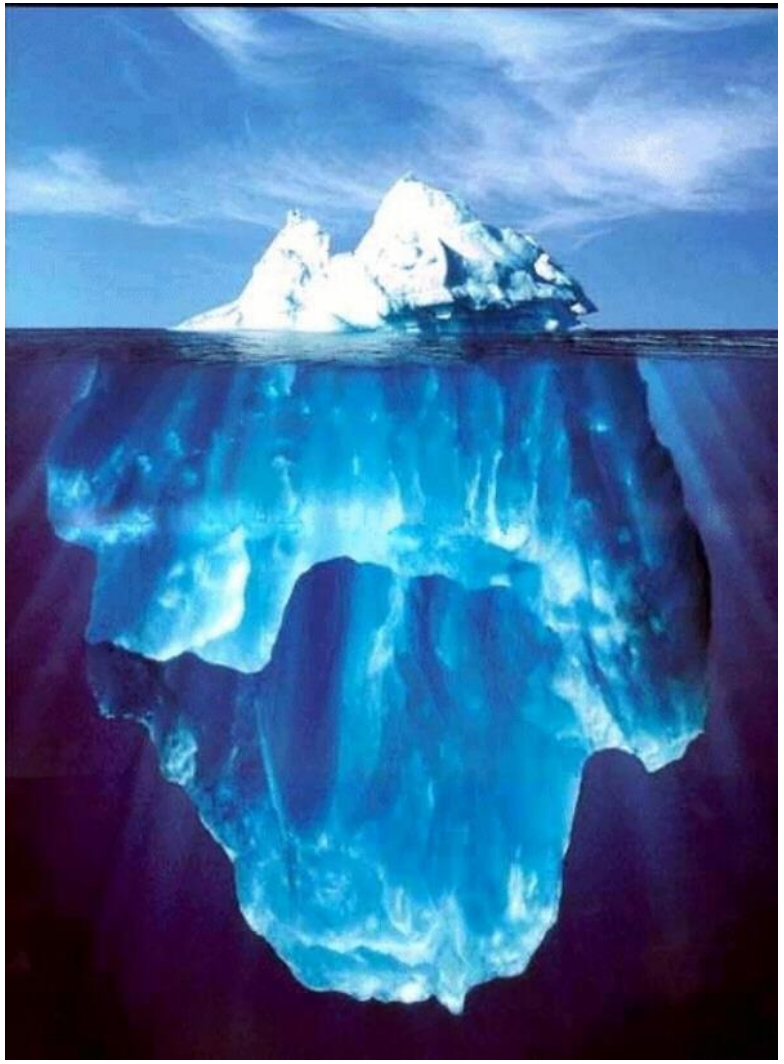
Parkinson's Disease – Late(r) Symptoms

- Dyskinesias: excess, uncontrolled movements that may develop later in disease
- Wearing off
- Dystonia: cramping of muscles (typically feet)
- Gait problems: Shuffling, freezing
- Balance difficulties



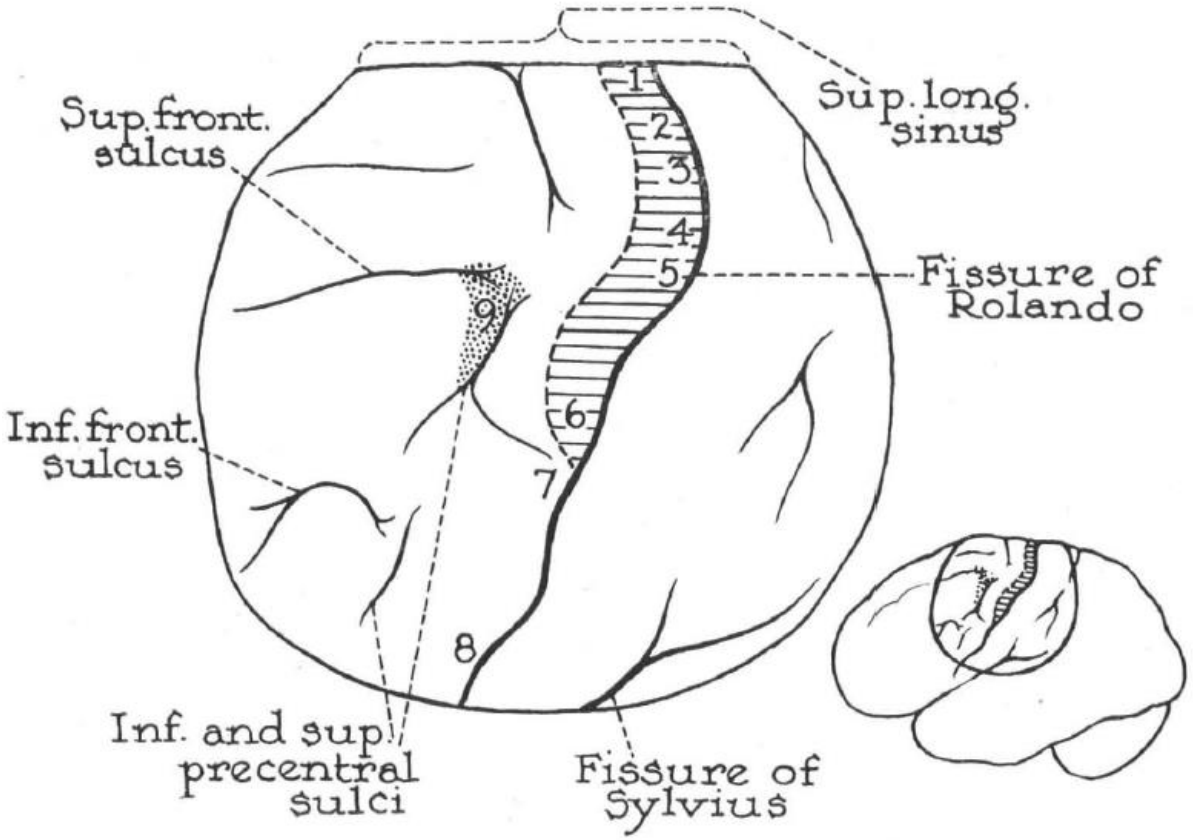
Non-motor (Non-dopamine response) Symptoms

- **Non-Motor**
  - Depression
  - Anxiety
  - Loss of sense of smell
  - Constipation
  - Sleep Disorders
  - Incontinence
  - Low blood pressure
  - Memory problems
- Motor – not DOPA responsive
  - Freezing of gait
  - Postural instability



Surgical relief of tremor at rest.

Paul Bucy. Annals of Surgery, 1945



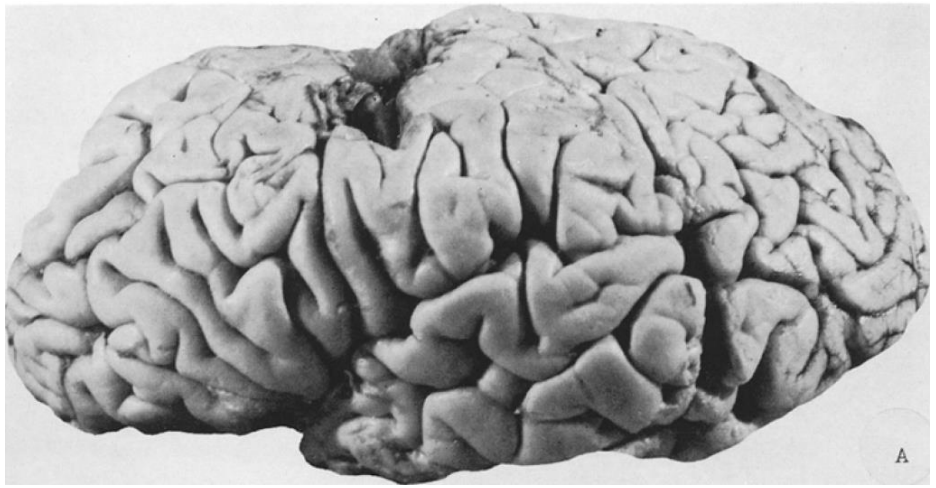
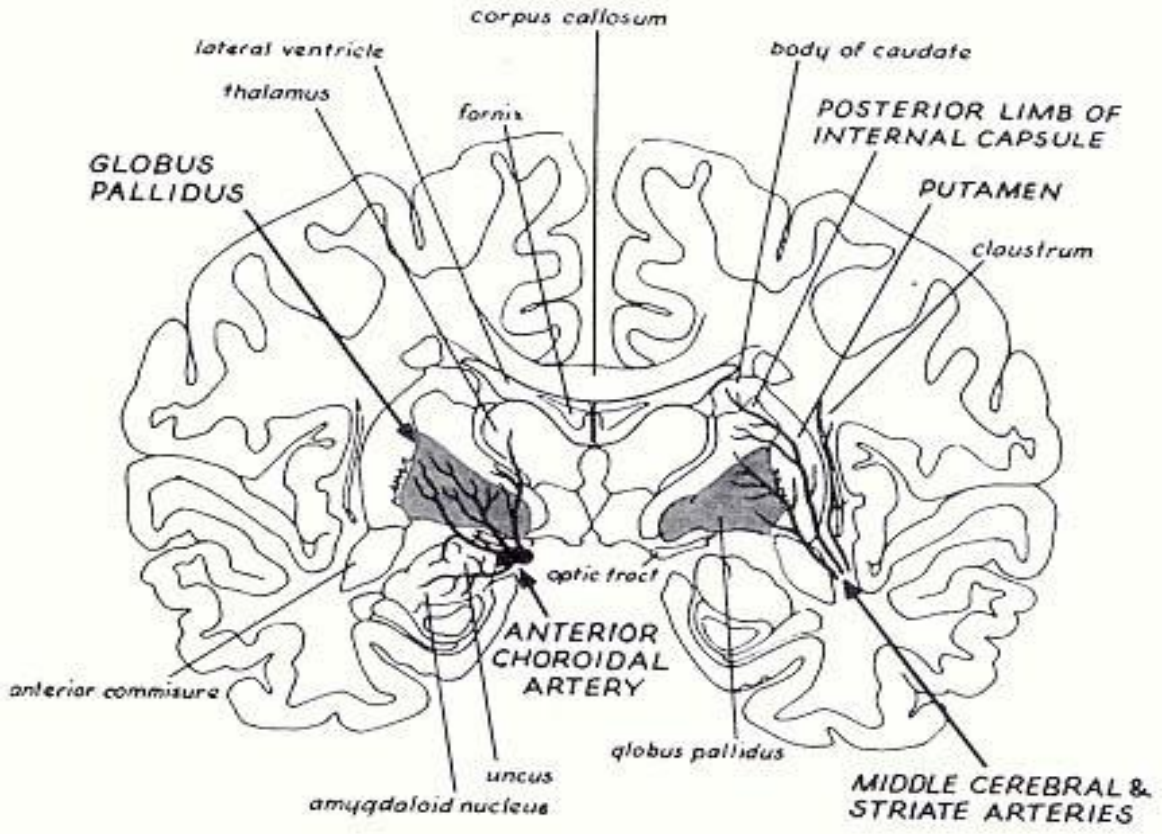


Illustration by Percival Bailey

Pallidotomy - *a famous surgical accident*

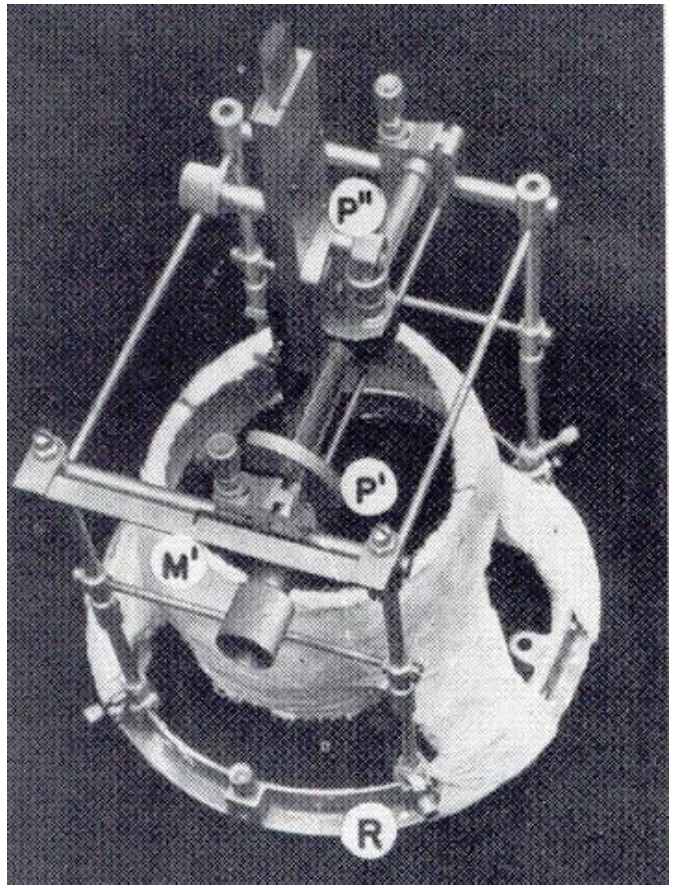


… more than 10,000 cases of diverse dyskinetic syndromes have been studied…. Received its major impetus and direction when, in 1952, during a craniotomy in which I planned to incise the cerebral peduncle, I was obliged to occlude the anterior choroidal artery.

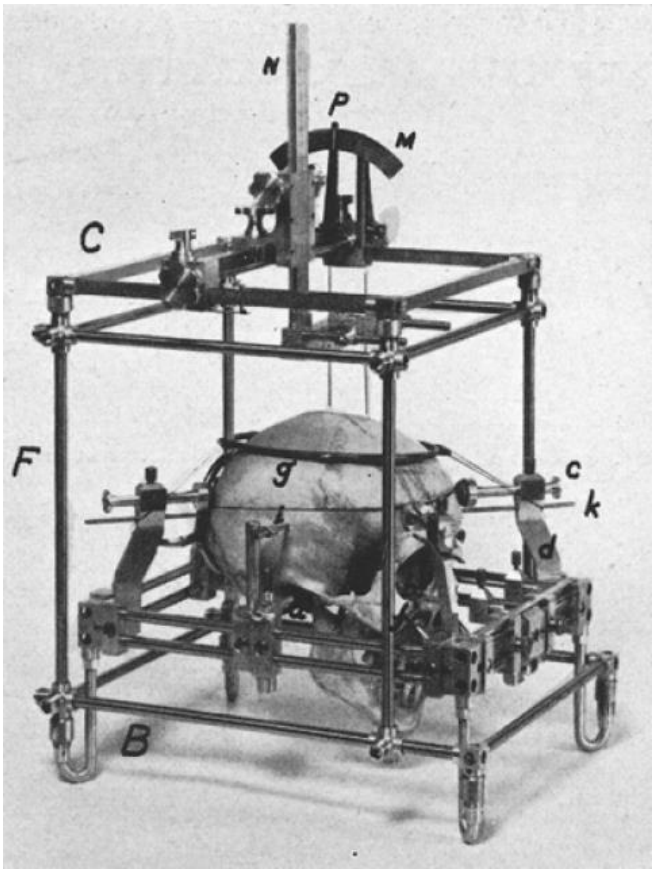
- IS Cooper

Stereotactic surgery

- 1908 stereotaxic frame
- 1946 ‘Stereoencephalotome’
- 1957 AC-PC reference (Talairach)
- 1959 Shaltenbrand & Bailey atlas
- 1958/64 Microelectrode recordings
- 1970s CT
- 1980s MRI



Science 1947



JNS 1951

Origin of contemporary DBS therapy

- DBS for chronic pain (1982): improves PD tremor

  Siegfried & Lippitz; Benabid

- Combined (thalamotomy and stimulation) stereotactic surgery of the Vim thalamic nucleus for bilateral Parkinson disease

  AL Benabid, et al: Appl Neurophysiol 50:344–346, 1987

- Long term suppression of tremor by chronic stimulation of the Vim nucleus.

  Benabid. Lancet 337:403, 1991

1. **'High' frequency stimulation (~130 Hz) for tremor suppression**
2. **Chronic stimulation with implanted devices became accepted**
3. **Led to the replacement of lesioning surgery**

First DBS in the US

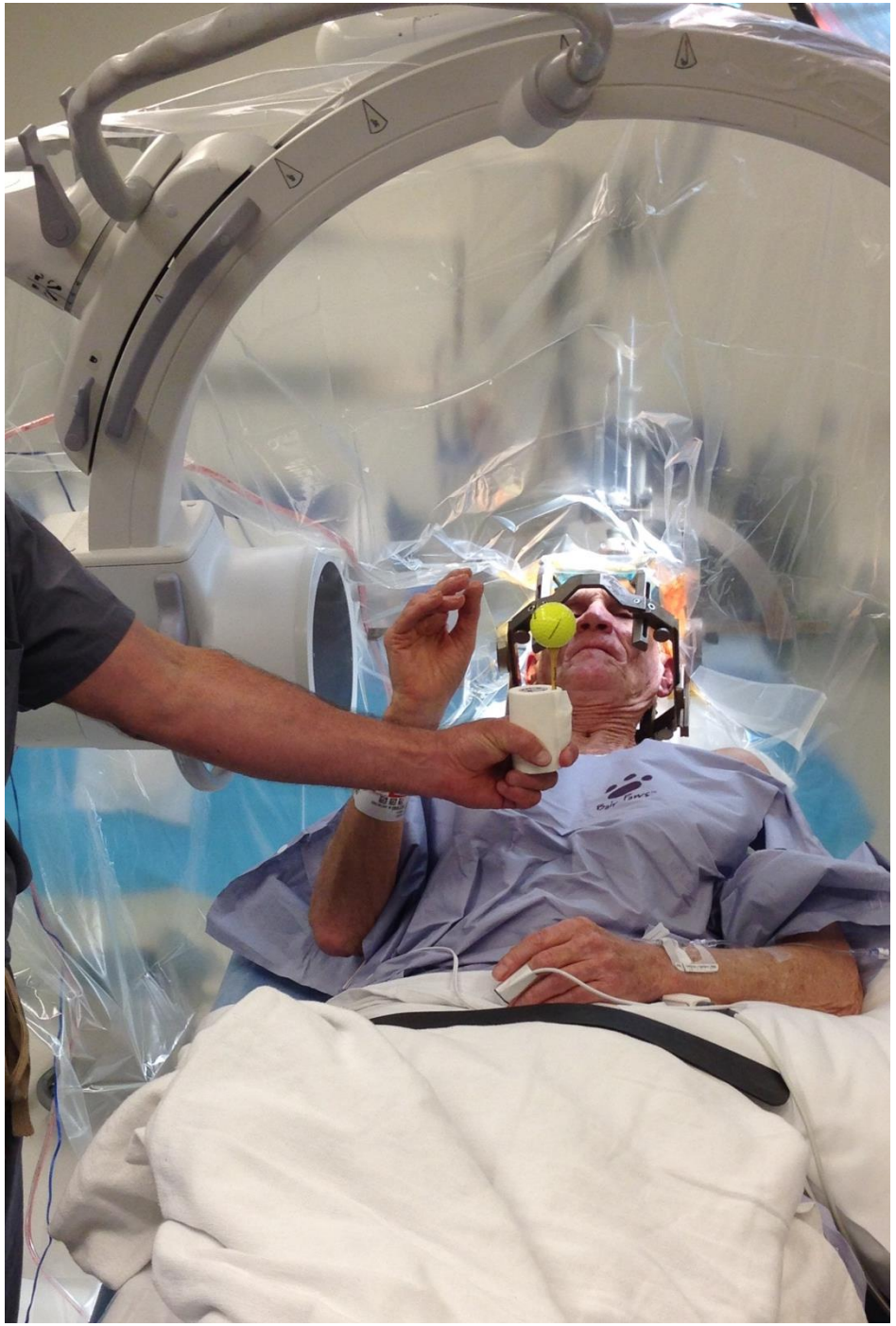
DBS: the surgical procedure

Part 1 (awake, IV sedation)

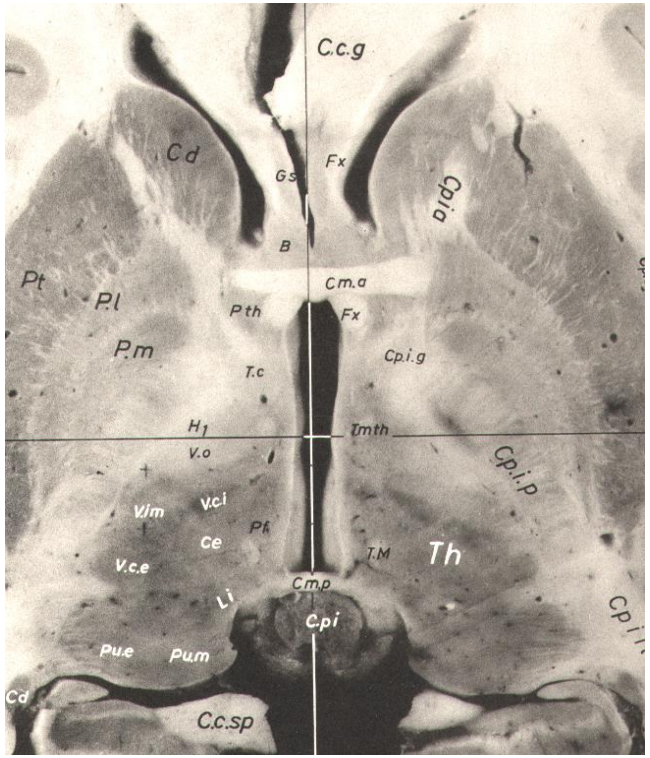
- Frame placement
- Burr holes
- Electrode recordings
- Awake testing

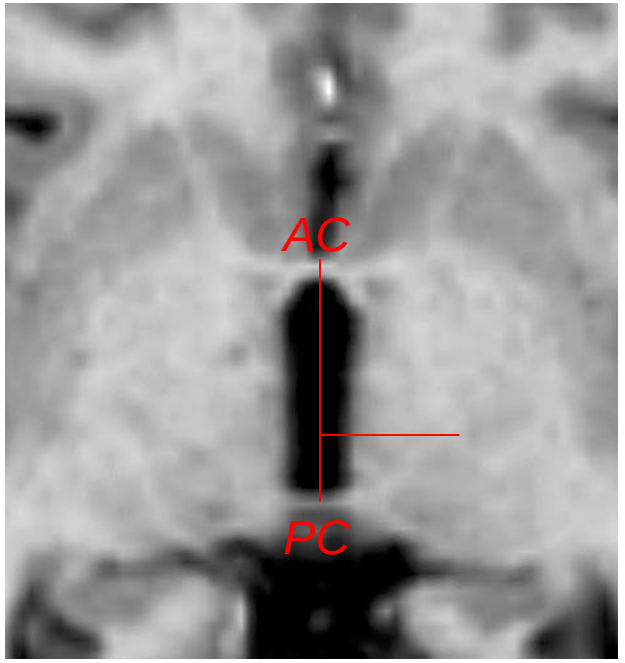
Part 2 (General anesthesia)

- Tunnel lead extension wire(s)
- Placement of pulse generator



‘Indirect’ stereotactic targeting: Vim thalamus

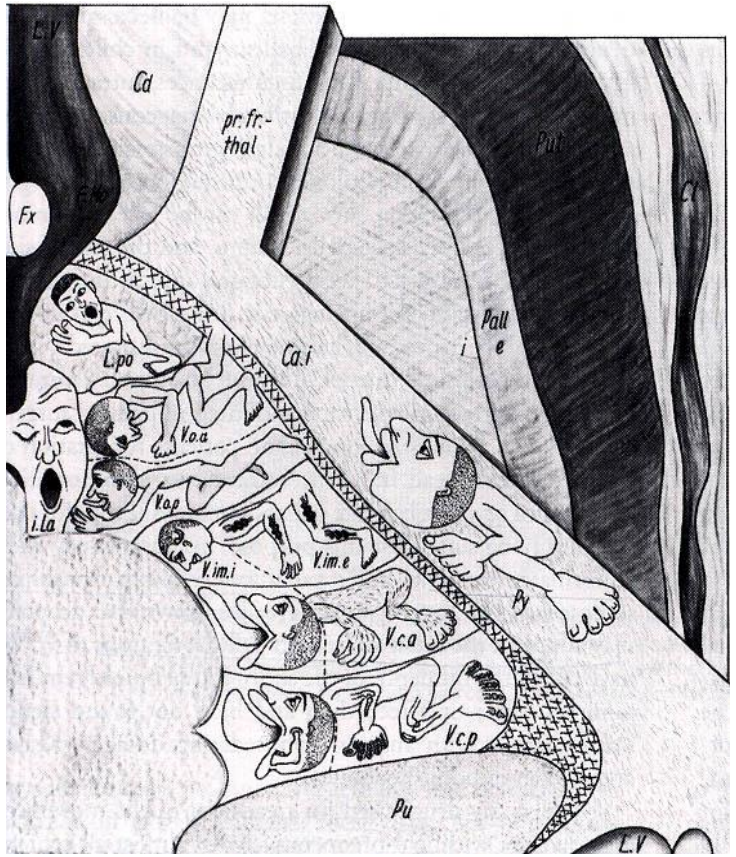




- Schaltenbrand-Wahren atlas

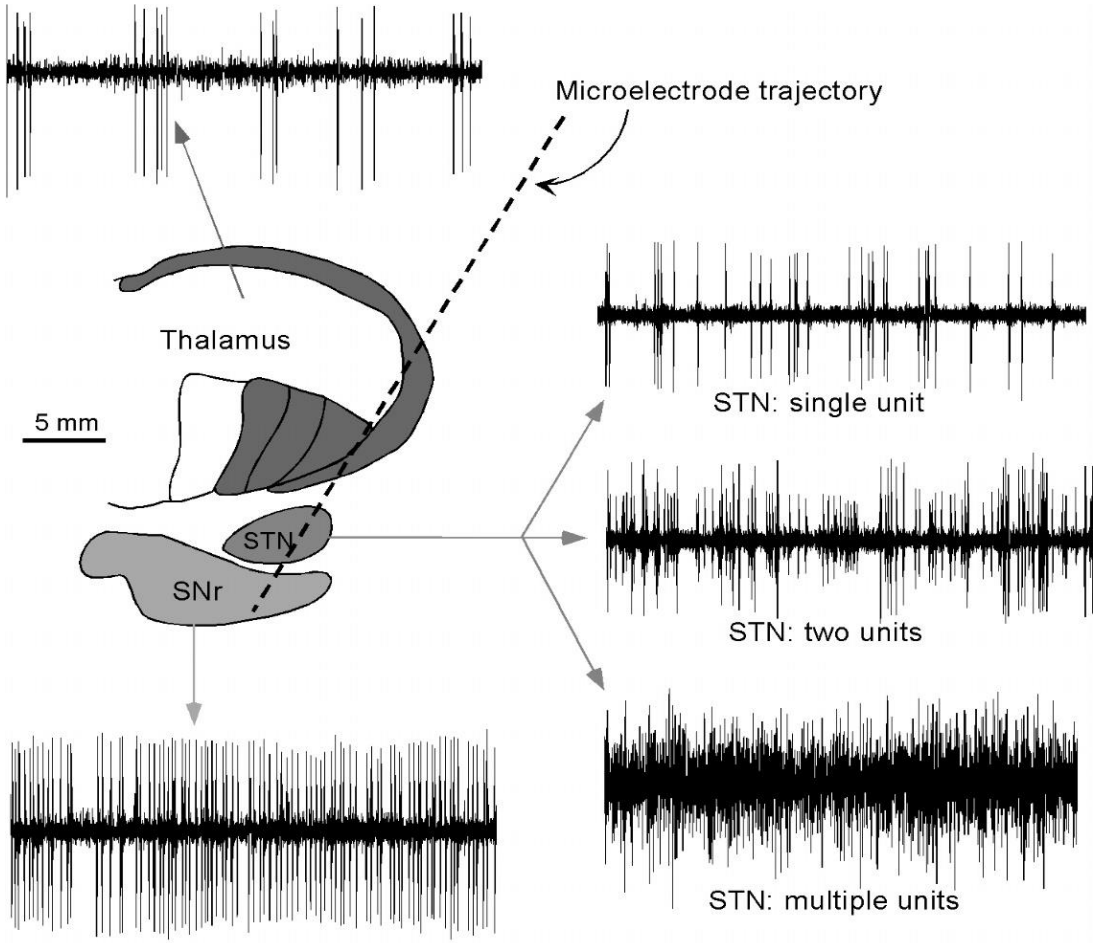
Rationale for awake surgery

Stimulation mapping

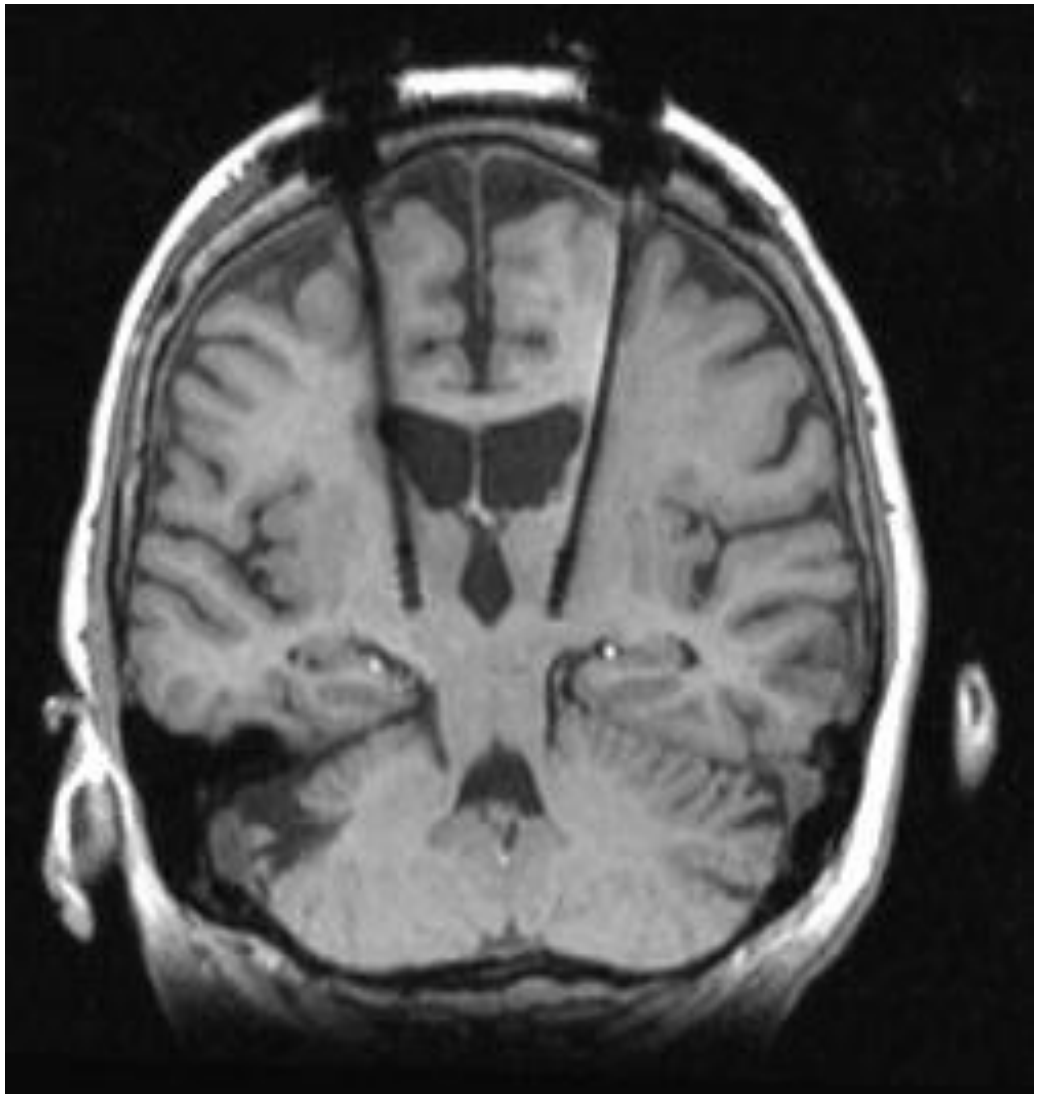


- Hassler

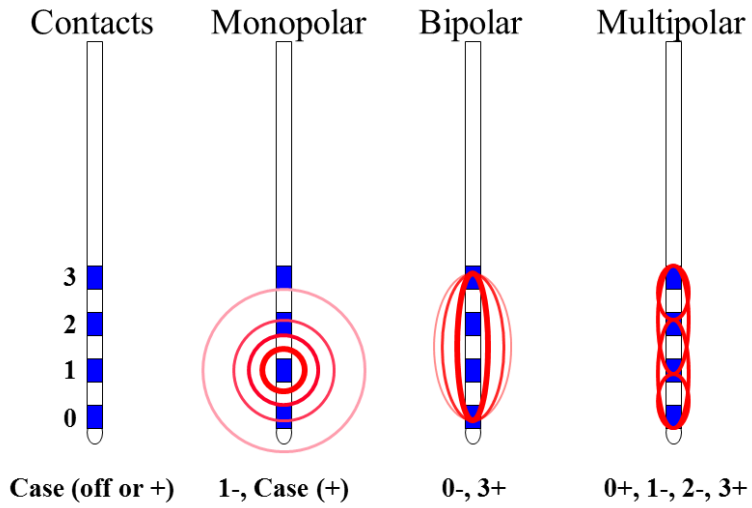
Microelectrode recordings



Deep Brain Stimulation: "shaping the therapy"



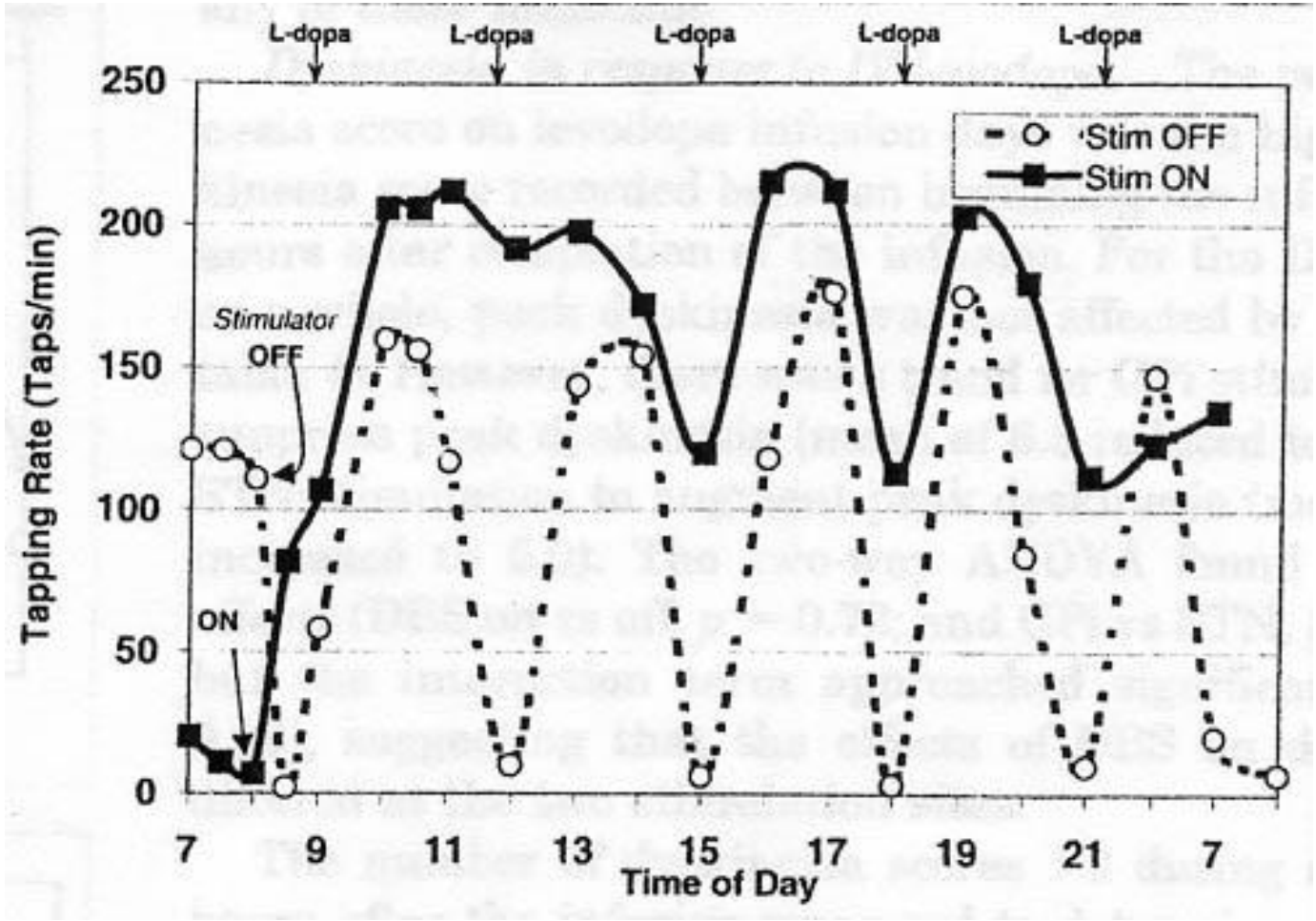
1. Amplitude (mA or volts)
2. Pulse width (msec)
3. Frequency (130-185 Hz)
4. Electrode configuration
   - Pseudomonopolar (-)
   - Bipolar (+-)
   - Guarded cathode (+-+)



DBS for Parkinson's disease: *indications*

- Tremor
- Bradykinesia
- Rigidity
- Postural instability

- Motor fluctuations
- Dyskinesia



JAMA®

Online article and related content current as of July 17, 2010.

Bilateral Deep Brain Stimulation vs Best Medical Therapy for Patients With Advanced Parkinson Disease: A Randomized Controlled Trial

Frances M. Weaver; Kenneth Follett; Matthew Stern; et al.

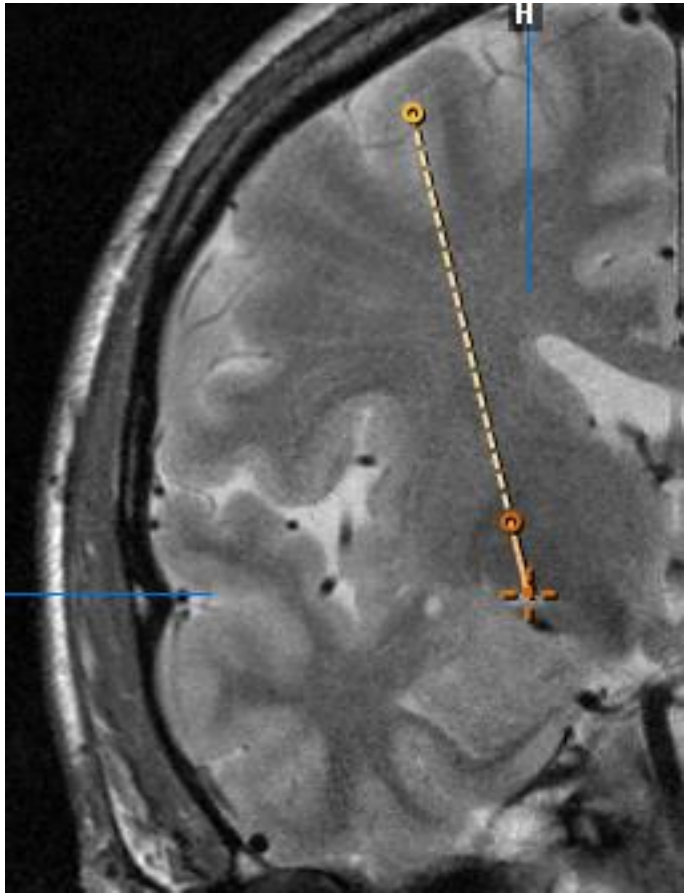
JAMA. 2009;301(1):63-73 (doi:10.1001/jama.2008.929)

Table 2. Patient Motor Diary Outcomes

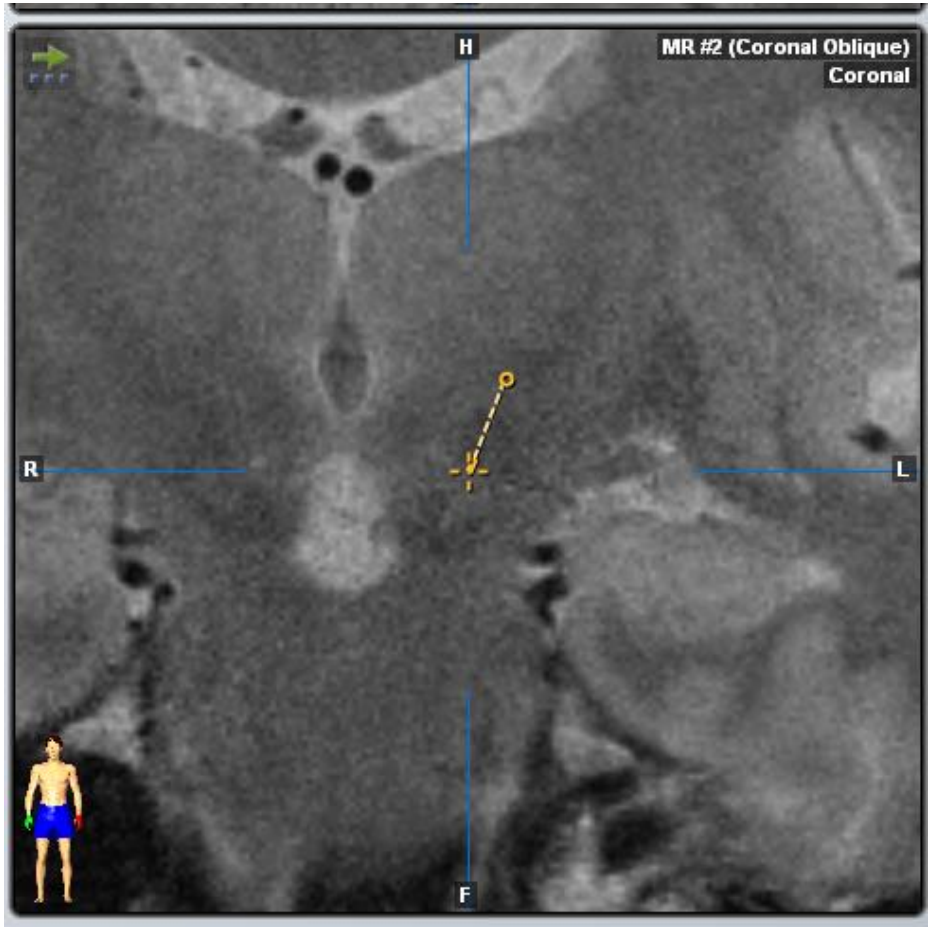
Time	Best Medical Therapy (n = 134)			Deep Brain Stimulation (n = 121)			Best Medical Therapy Minus Deep Brain Stimulation	
	Baseline, Mean (SD)	6 mo, Mean (SD)	Mean Difference (95% CI)	Baseline, Mean (SD)	6 mo, Mean (SD)	Mean Difference (95% CI)	Mean Difference (95% CI)	*P* Value[a]
On, h/d[b]								
Without troublesome dyskinesia	7.0 (2.9)	7.1 (3.3)	0 (–0.5 to 0.5)	6.4 (2.7)	10.9 (4.2)	4.6 (3.8 to 5.3)	–4.5 (–5.4 to –3.7)	<.001
With troublesome dyskinesia	4.2 (3.1)	3.9 (3.3)	–0.3 (–0.8 to 0.3)	4.4 (3.1)	1.8 (3.0)	–2.6 (–3.3 to –2.0)	2.3 (1.5 to 3.2)	<.001
Off, h/d[b]	5.6 (2.9)	5.7 (2.8)	0 (–0.4 to 0.5)	5.9 (2.6)	3.4 (3.1)	–2.4 (–3.1 to –1.8)	2.5 (1.7 to 3.2)	<.001
Asleep, h/d	7.1 (1.7)	7.3 (2.0)	0.3 (0 to 0.6)	7.3 (1.8)	7.7 (2.0)	0.4 (0 to 0.7)	–0.1 (–0.6 to 0.4)	.66

Abbreviation: CI, confidence interval.
[a] Test for the change scores from baseline to 6 months between the best medical therapy group and the deep brain stimulation group.
[b] "On" and "off" time are described in the "Study Procedures" section of the "Methods."

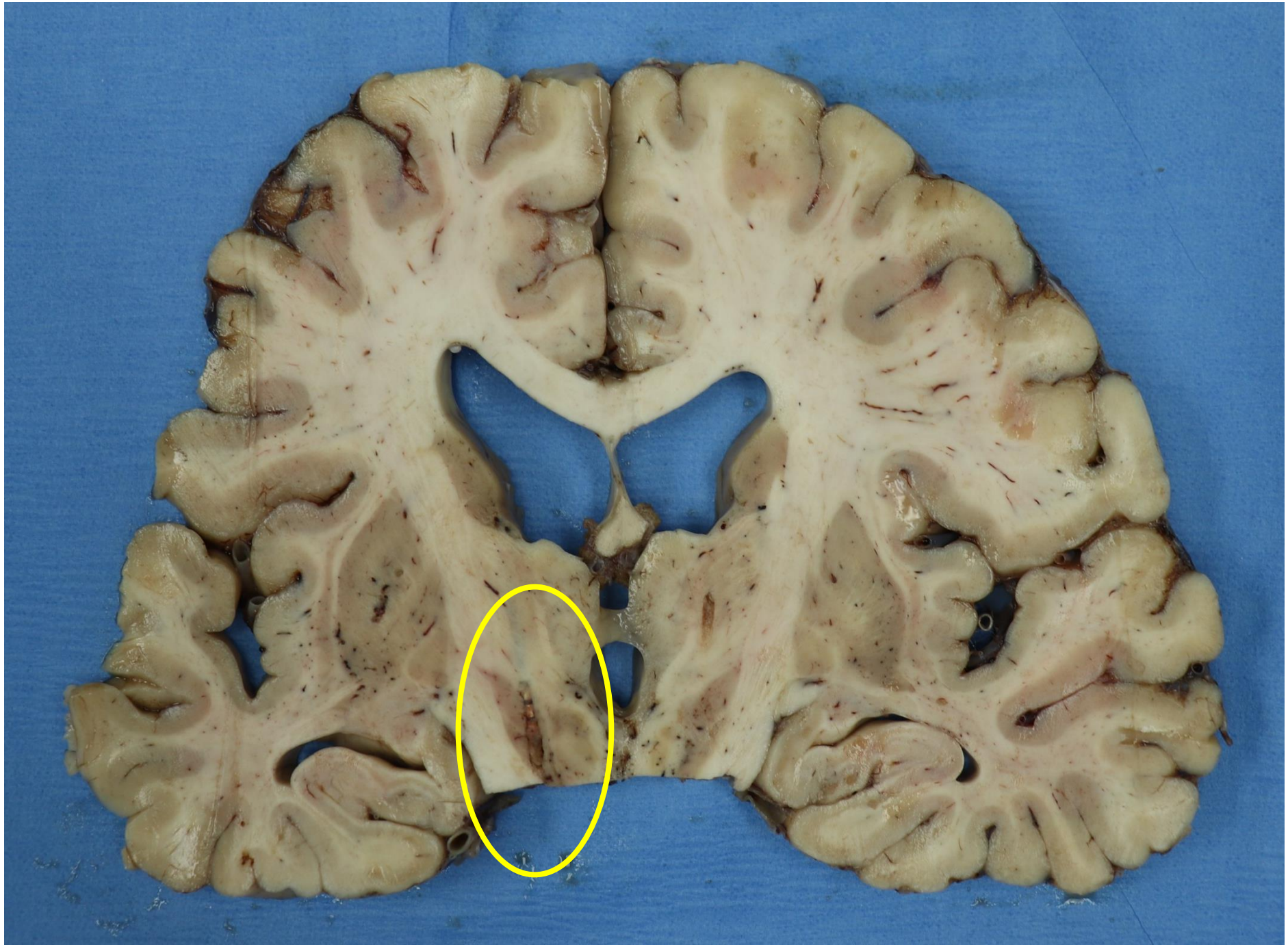
DBS targets for Parkinson's disease



Globus pallidus (Gpi)



Subthalamic nucleus (STN)



Subthalamic DBS

Baseline
Off meds

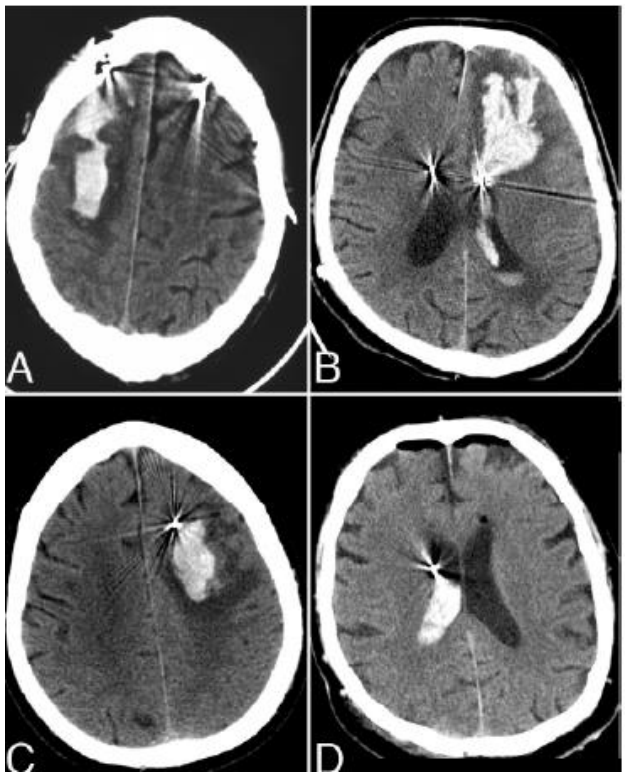
6 months
Off meds, *on* stim

J Neurosurg 107:998–1003, 2007

Incidence of symptomatic hemorrhage after stereotactic electrode placement

CHARLES A. SANSUR, M.D., M.H.SC., ROBERT C. FRYSINGER, PH.D., NADER POURATIAN, M.D., PH.D., KAI-MING FU, M.D., PH.D., MARKUS BITTL, M.D., ROD J. OSKOUIAN, M.D., EDWARD R. LAWS, M.D., AND W. JEFFREY ELIAS, M.D.

Department of Neurological Surgery, University of Virginia Health System, Charlottesville, Virginia



N = 567 electrodes

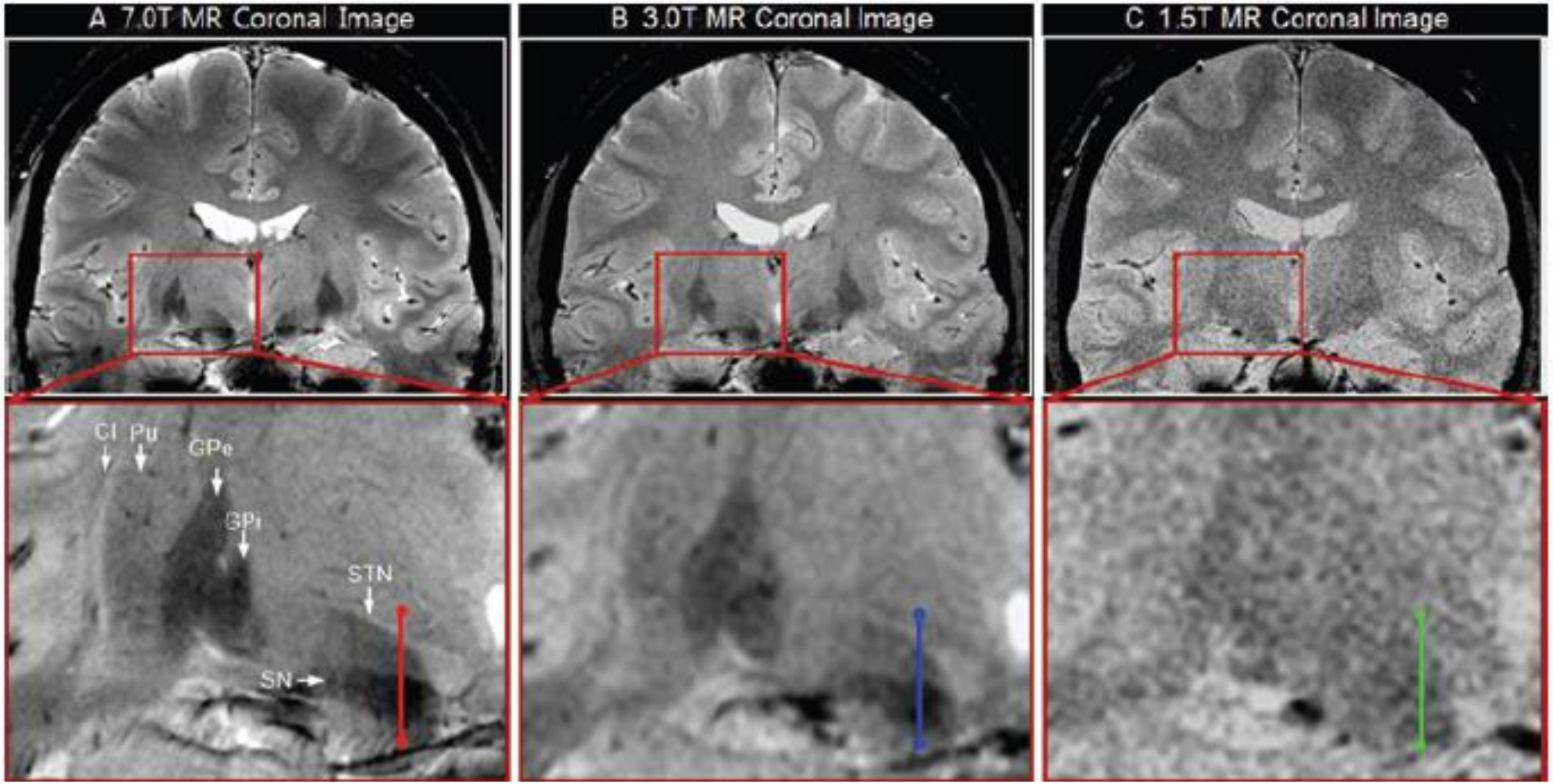
1.2% symptomatic ICH rate

0.7% permanent neuro deficit

Prognostic factors and influence on rate of symptomatic hemorrhage in all patients

Prognostic Factor	p Value	Comments
hx hypertension	0.007	8.6% of hypertensive patients had hemorrhage; 1.0% of normotensive patients had hemorrhage
PD diagnosis	0.007	5 of 7 hemorrhages were in patients with PD
age	0.01	mean 64.6 years compared with 41.2 years
male sex	0.04	all 7 hemorrhages were in men
target location	0.79	no significance
CCI score	0.23	no significance
prior anticoagulant use	0.95	no significance

Image-guided surgery

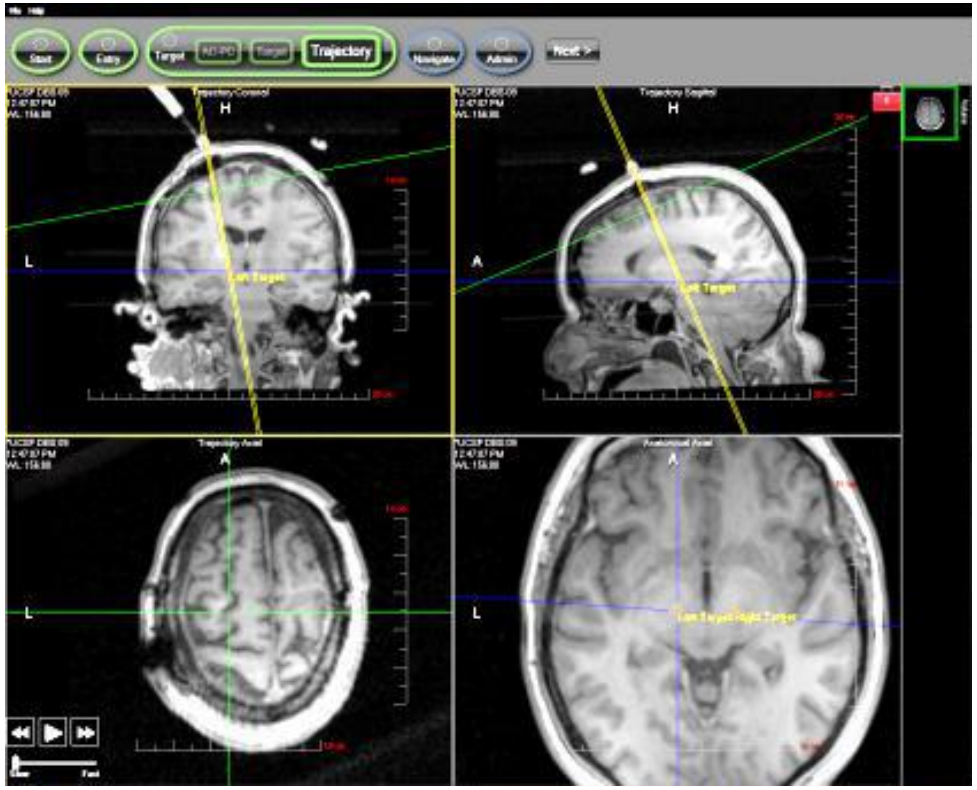


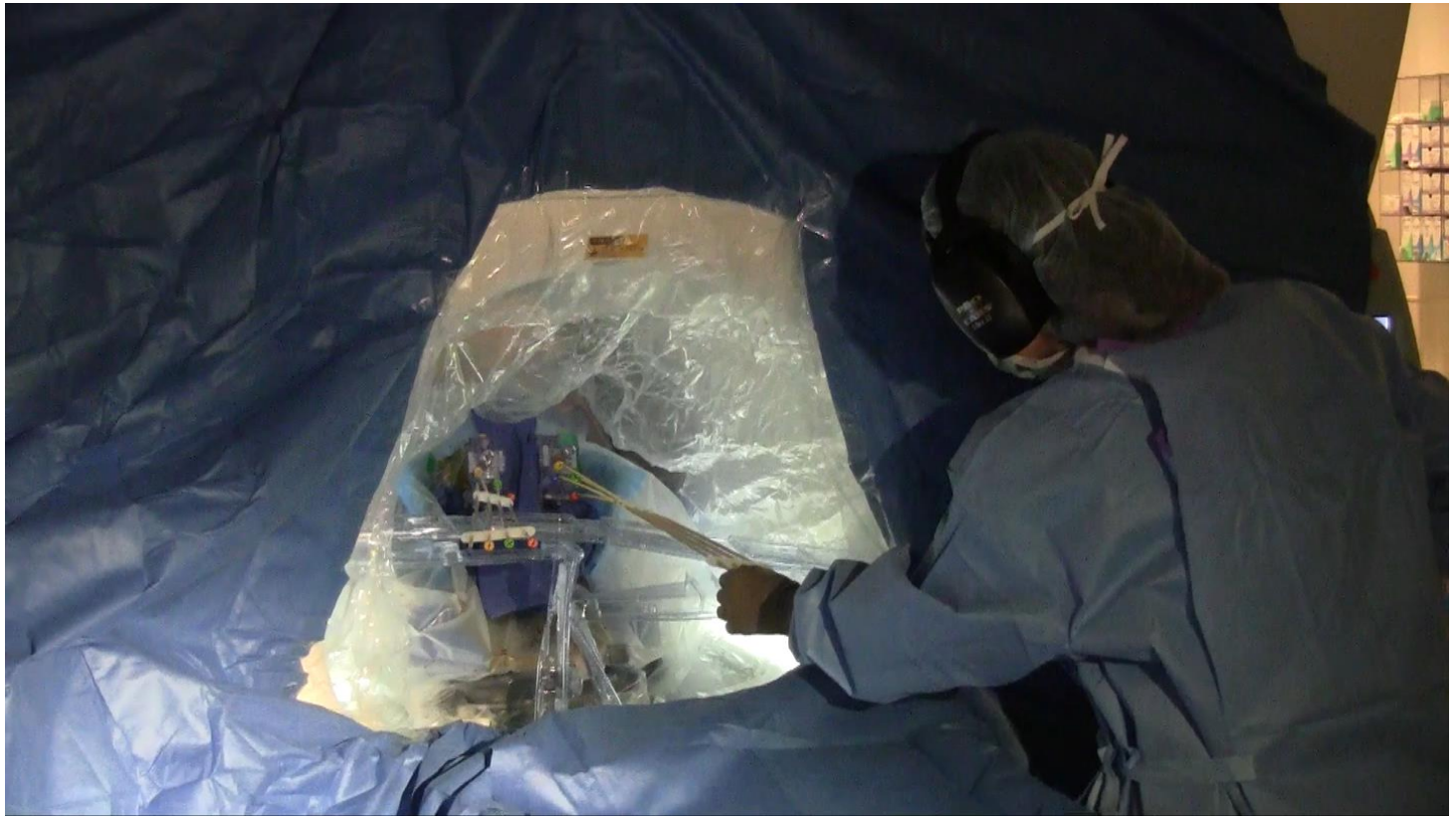
7T MRI. *KH Lee, JNS 2010*

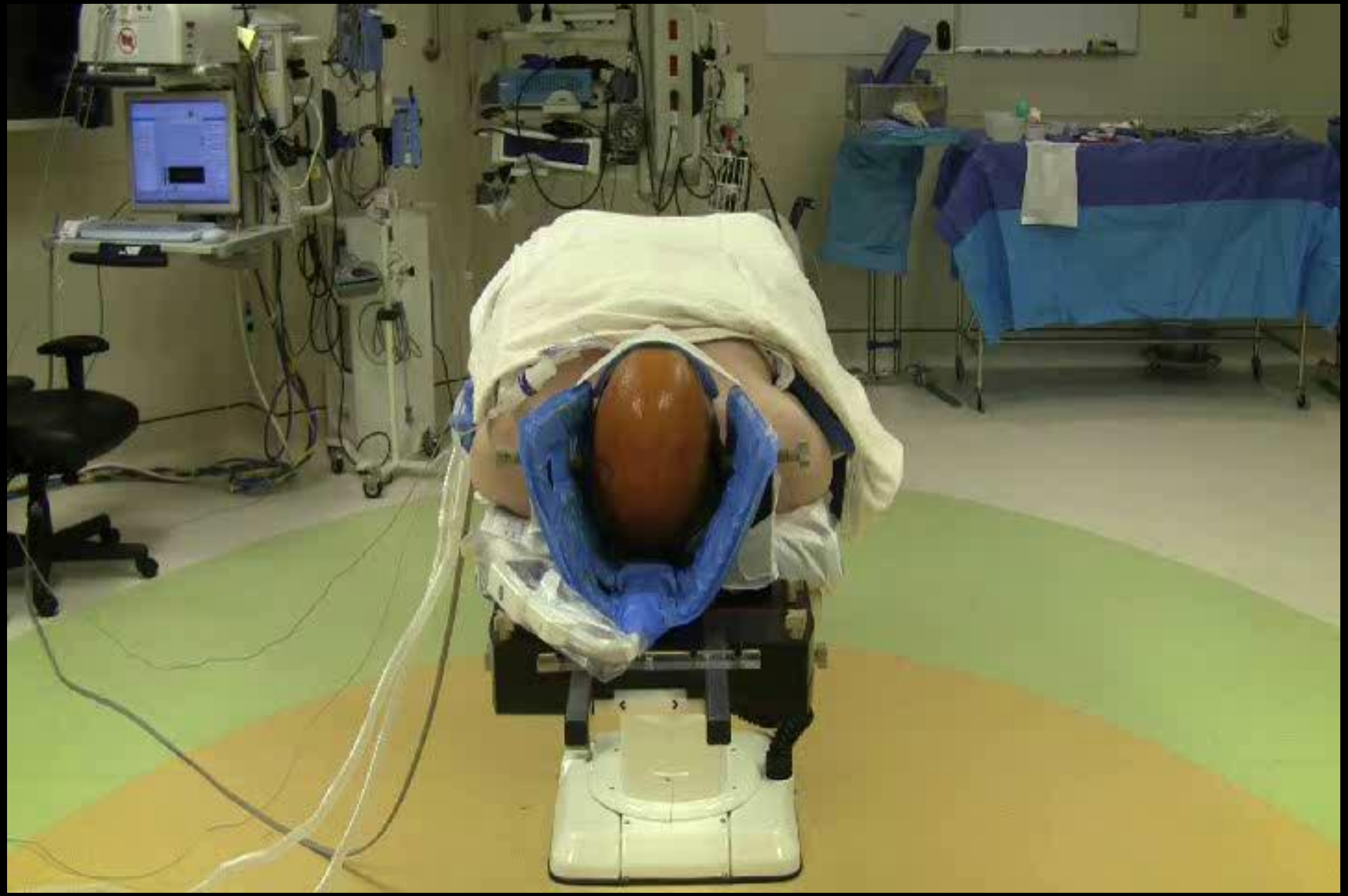
Rationale for image-guided DBS

- Advanced MR imaging = visualized targets
- Awake surgery is difficult (*for everyone*)
    - Anxiety
    - Discomfort
    - ‘off’ state
- Accommodate confounders:
    - Device inaccuracies
    - Image fusion
    - MRI distortion
    - Brain shift
- Anatomic vs physiologic targeting ??

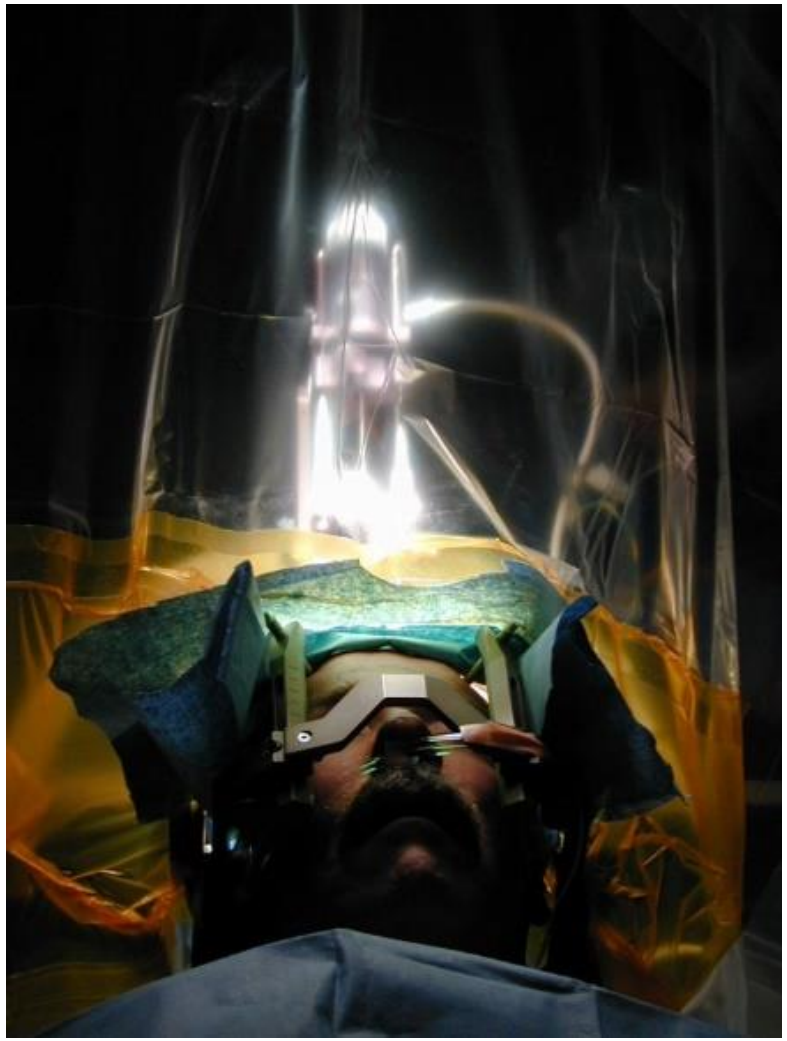
Asleep, MRI-guided DBS







Current state of movement disorder surgery



- Precise stereotactic devices (frame/frameless)
- Class 1 evidence for effectiveness based on awake DBS + MER
- MRI-based targeting
- New technology: multidirectional, rechargeable, closed-loop

doi:10.1093/brain/awu102 Brain 2014: 137; 2015–2026 | 2015

BRAIN
A JOURNAL OF NEUROLOGY

Directional deep brain stimulation: an intraoperative double-blind pilot study

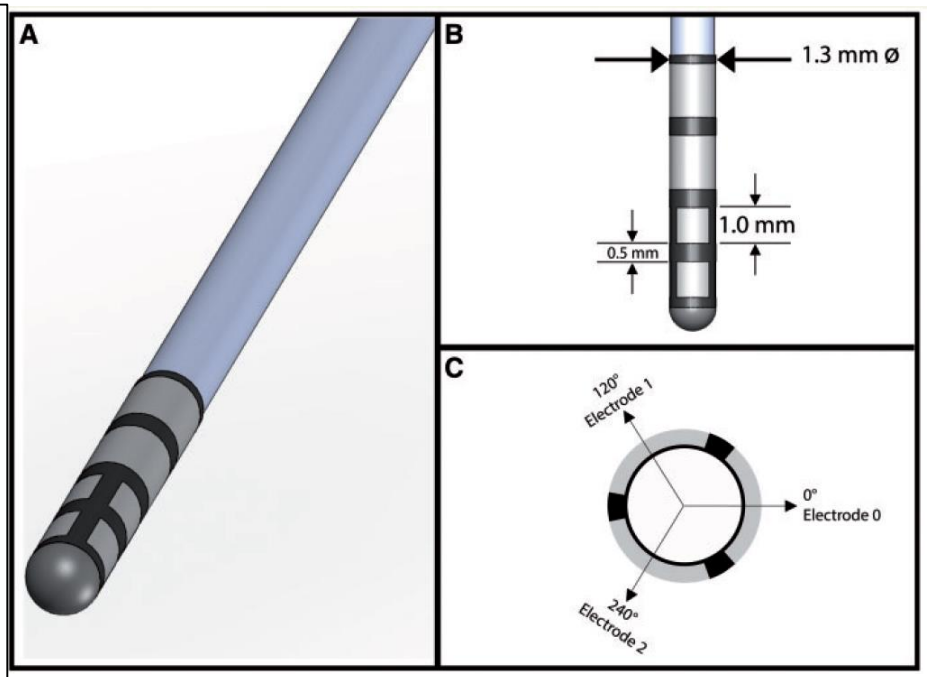
Claudio Pollo,[1] Alain Kaelin-Lang,[2] Markus F. Oertel,[1] Lennart Stieglitz,[1] Ethan Taub,[3] Peter Fuhr,[4] Andres M. Lozano,[5] Andreas Raabe[1] and Michael Schüpbach[2]

directSTNAcute lead

- N=11 PD (STN); N=2 ET (Vim)
- 3 track MER + macrostimulation testing
- Random, acute directional lead testing on most symptomatic side:
    - 0º, 120º, 240º, omnidirectional, best direction

- Therapeutic effect = rigidity relief or good tremor suppression
- Side effects: paresthesia, motor contraction, dysarthria

- <u>Directional stimulation</u> :
    - Superior to omnidirectional (10/11)
    - Best direction (11/11)
    - Therapeutic window 41% wider
    - Current threshold for therapeutic effect in best direction= 0.67mA, 43% less



Parkinson disease

<u>Goals of treatment</u>

1. Cure
2. Neuroprotection
3. **Symptom palliation**

The future of PD treatment is surgery

TABLE 5. Regenerative/restorative therapies

Treatment modality	Proposed mechanism of action	Experience to date	Ongoing/recent studies	Comments
Transplantation of fetal mesencephalic cells into striatum	Replacement of dopaminergic neurons and reinnervation of striatum	2 NIH-funded double blind trials failed to show significant benefit; some patients from these studies did respond[120]; a small number of other patients obtained prolonged benefit (including able withdraw from dopaminergic medications)[121]; transplant-induced dyskinesias a major concern[120]	TRANSEURO program (NCT01898390)[122] attempting to define the optimal transplantation methods using fetal tissue grafts before possibly proceeding to dopaminergic cells derived from stem cells[123]	One very well studied patient with the largest number of surviving dopamine neurons and the densest and most widespread graft-mediated striatal dopamine reinnervation (associated with profound improvement in F-dopa PET scans) failed to obtain any clinical benefit[124]
Trophic factors	Reinnervation of striatum by surviving host dopaminergic cells	Largely unsuccessful[125] including a large double-blind trial of intraputamenal infusion of GDNF[126]; trial of combined intrastriatal and intranigral AAV-neurturin failed to demonstrate any clinical benefit, in contrast to earlier open-label studies[127]	A 12-month double-blind trial with a further 12-month open-label extension of GDNF therapy using a novel convection enhanced delivery system failed to meet its primary endpoint	Failures of trophic factor therapy may relate to the already profound extent of striatal dopamine terminal degeneration within 4 years from clinical disease onset, prior to the intervention[112]
Gene therapy with enzymes involved in dopamine synthesis	Increase and enhance striatal dopamine	Safety and preliminary evidence of efficacy reported from small open label studies using bilateral intraputamenal infusions of AAV vector-mediated gene delivery of AADC[128] and a lentiviral vector-based triple gene therapy (Prosavin) of AADC, TH, and GTP-cyclohydrolase 1.[129]	Safety and efficacy study of intraputamenal VY-AADC01 is currently recruiting for advanced PD (NCT03065192)	Well-designed randomized sham surgery controlled double-blind trials will be necessary to confirm efficacy—many double-blind trials of surgical therapies have failed to confirm important clinical benefits reported in earlier open-label trials
STN DBS	Proposed to have disease-modifying effects distinct from its profound symptomatic benefit: reducing excitotoxic drive from the STN glutamatergic input to the SNc[130]; BDNF signaling through the trkB receptor in SNc neurons[131]; direct effects on α-synuclein toxicity in a AAV1/2-A53T-aSyn rat model.[132]	A group from Vanderbilt University actively pursuing the potential disease-modifying effects of STN DBS in very early-stage PD[133,134]	In planning stages	Challenging population to recruit given mild motor disability at a stage in which surgical intervention is proposed. Lessebo effect in the group allocated to "standard medical care" may further affect validity of the results of subsequent studies if comparison does not include sham surgical arm

AADC, aromatic L-amino acid decarboxylase; AAV,adeno-associated virus; AAV1/2-A53T-aSyn, an adeno-associated virus 1/2-driven human mutated A53T α-synuclein overexpressing rat model; BDNF, brain derived neurotrophic factor; DBS, deep brain stimulation; GDNF, glial derived neurotrophic factor; PET, positron emission tomography; SNc, substantia nigra pars compacta; STN, subthalamic nucleus; TH, tyrosine hydroxylase; trkB, cognate tropomyosin receptor kinase type B receptor; F-dopa, Fluoro-dopa; GTP, Guanosine Triphosphate.

Lang 2018

Deep Brain Stimulation for Parkinson's Disease

1. The patient remains awake during surgery to place the deep brain stimulator leads.
   - True or False?

2. Deep brain stimulation both provides symptomatic relief and slows the underlying neurodegenerative process of Parkinson's Disease.
   - True or False?