Surgical Treatment of Parkinson Disease

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Conflict of Interest Statement

No drug (or medical device) company pays me any money

Surgical Treatment of Parkinson Disease

- **Ablative surgical intervention:**
  - **Pallidotomy**
  - **Thalamotomy**
- **Deep brain stimulation:**
  - **Subthalamic nucleus (STN)**
  - **Internal segment of the globus pallidus (GPi)**
  - **Thalamic ventral intermediate nucleus (Vim)**
- **Fetal tissue transplantation (into the striatum):**
  - **Human fetal dopaminergic neurons**
  - **Pig dopaminergic neurons**

Ablative Surgical Intervention

- **The "Abandoned Pallidotomy":**
  - **Transient improvement of rigidity, bradykinesia and tremor (for about 2 years)**
  - **Heterogeneous outcome depending on location of lesion (ideal location is posteroventral GPi)**
  - **Definite long-lasting anti-dyskinetic effect**
  - **Irreversible side effects (visual field defects, hemiparesis and hemorrhage)**
  - **Bilateral pallidotomy causes:**
    - **Postural instability, worsening of gait freezing**
    - **Dysphagia, dysarthria**
    - **Cognitive deficits**

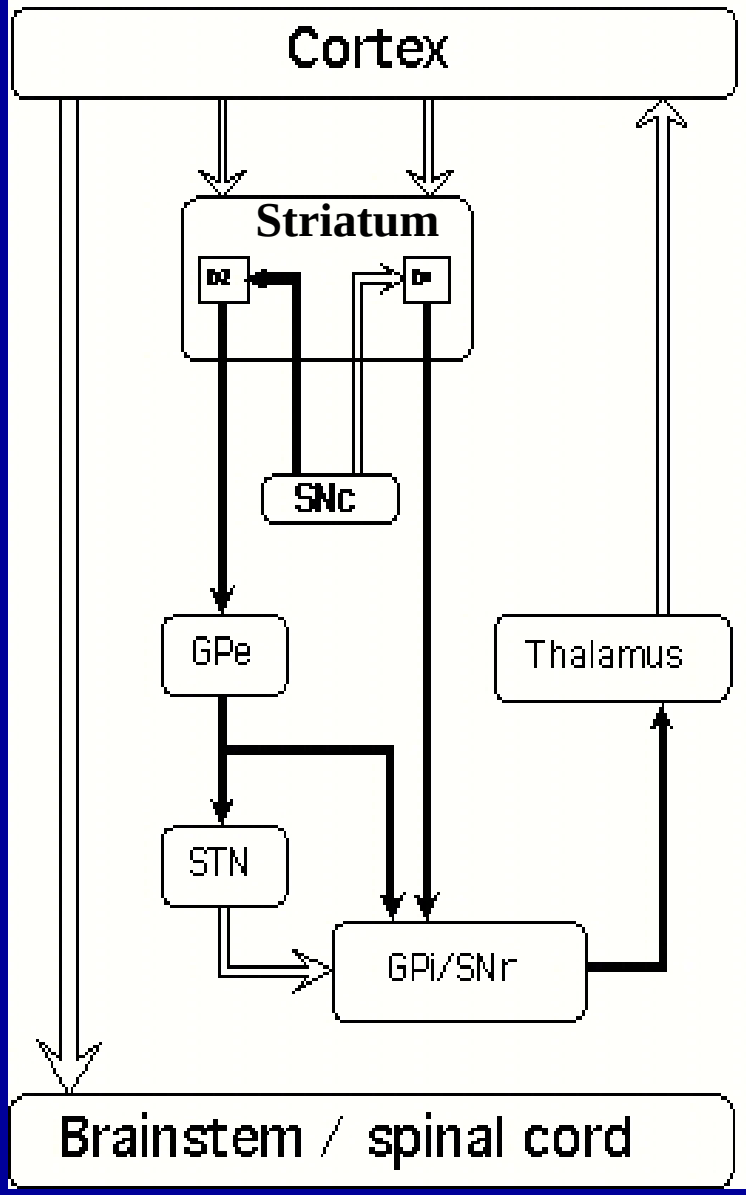
Ablative Surgical Intervention (cont´d)

- **Thalamotomy:**
  - **Improves rest tremor and rigidity, bradykinesia**
  - **Irreversible side effects (hemiparesis, hemiparesthesia and hemorrhage)**
  - **Bilateral thalamotomy causes:**
    - **Postural instability, worsening of gait freezing**
    - **Dysphagia, dysarthria**
    - **Cognitive deficits**
- **Resurrected by High-Intensity Focused Ultrasound (HIFU): short-lived benefit, irreversible adverse effects**

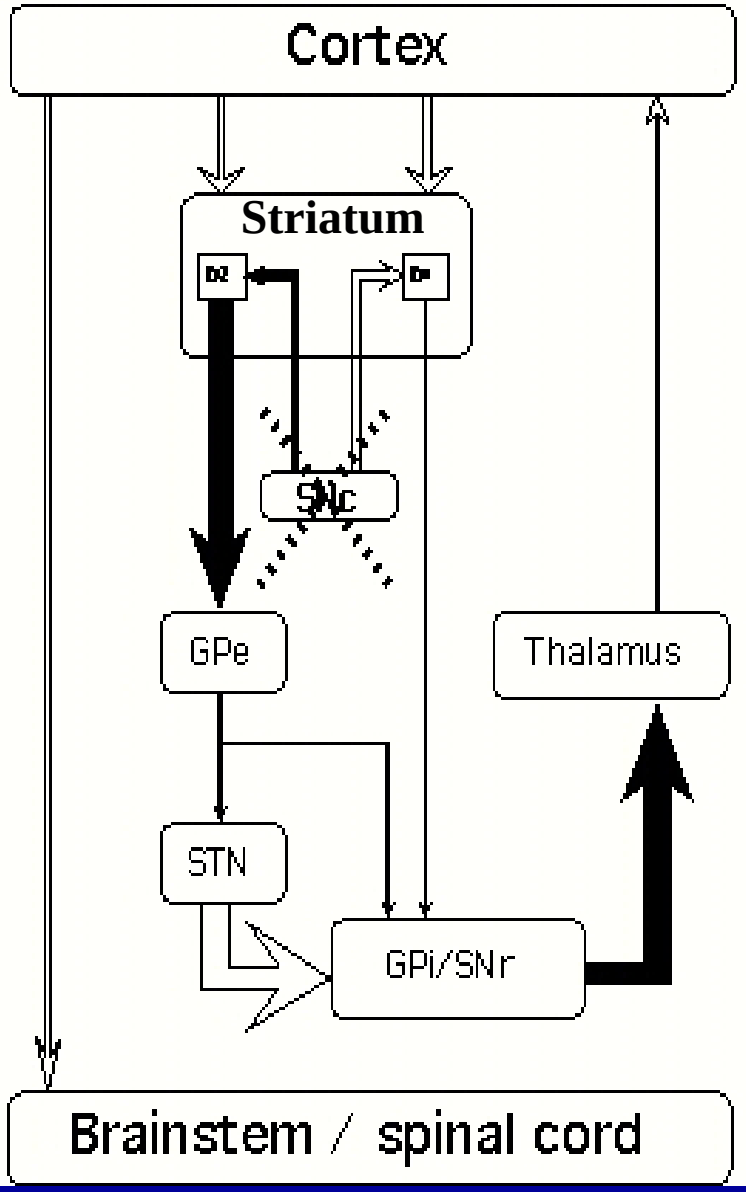
Deep Brain Stimulation in Parkinson Disease

- **Deep brain stimulation targets:**
  - **Sensorimotor subthalamic nuclei (STN) -1994**
  - **Internal segment of the globus pallidus (GPi)**
  - **(Thalamic ventral intermediate nucleus (Vim) -1987)**
- **All DBS procedures:**
  - **are expensive and labor intensive**
  - **share surgical risks**
  - **share reversible adverse effects from excessive stimulation at variable degrees:**
    - **Sensory adverse effects (paresthesias, visual hallucinations…)**
    - **Motor adverse effects (peak-dose dystonias, diplopia, eyelid apraxia, dysarthria, ataxia…)**
    - **Cognitive changes**
    - **Behavioral changes (depression, mania, psychosis…)**

A. Normal Basal Ganglia Circuitry



B. PD Basal Ganglia Circuitry



Basal Ganglia Circuitry After Subthalamic Nucleus Lesion

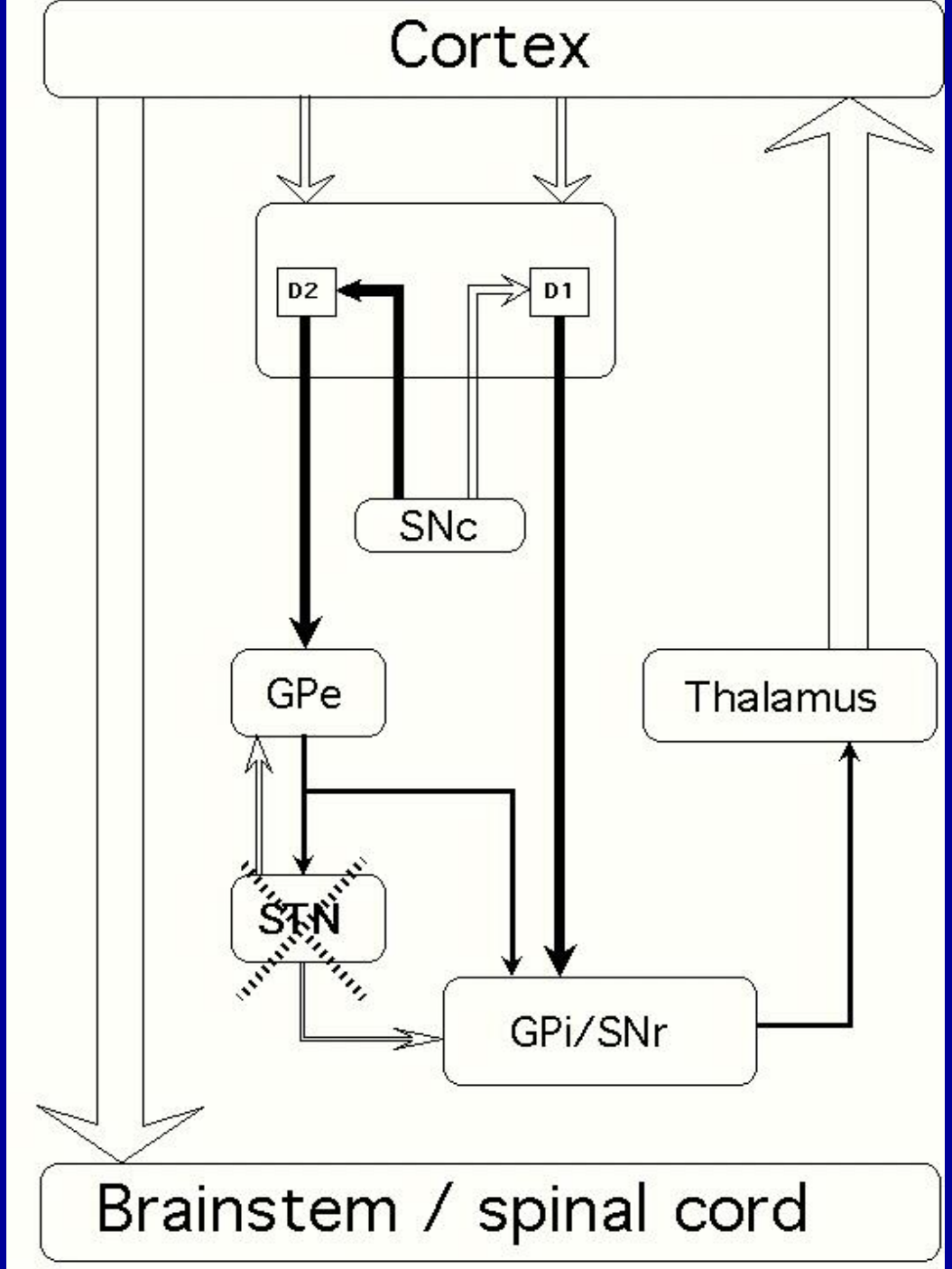


Figure 5a

Ideal Candidate for DBS

- **Parkinson disease patient who, despite best drug therapy, still has:**
  - **Disabling OFF states: painful rigidity, difficulty walking, falls, tremor …**
  - **Frequent or prolonged OFF states: wearing off less than 3 hours**
  - **Peak-dose adverse effects: severe dyskinesia**
  - **No significant dementia**

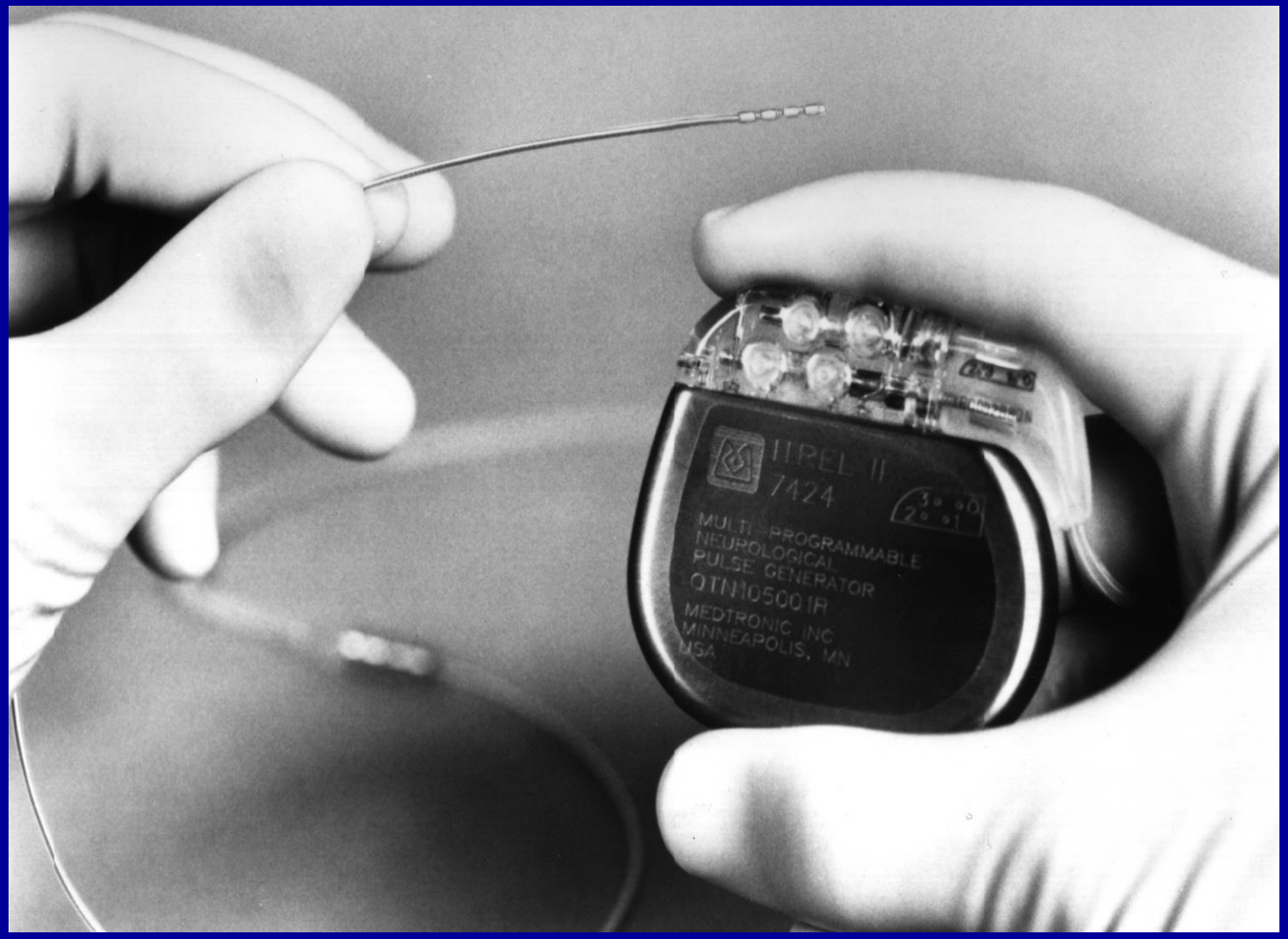
Bilateral STN DBS in PD

- **Effective & Safe :**
  - **Improved UPDRS scores**
  - **Improved motor fluctuations:**
    - **Decreased OFF time**
    - **Improved dyskinesia**
  - **DECREASED daily dose of levodopa and other PD medications**
  - **(Improved sleep)**
  - **(Weight gain)**
- **Variable surgical technique**
- **Ideal candidate: medically-optimized PD patients with:**
  - **disabling OFF states: painful rigidity/dystonia, gait freezing, falls, tremor …**
  - **Frequent or prolonged OFF states: wearing off around 2-3 hours**
  - **Peak-dose adverse effects: severe dyskinesia, mental adverse effects**

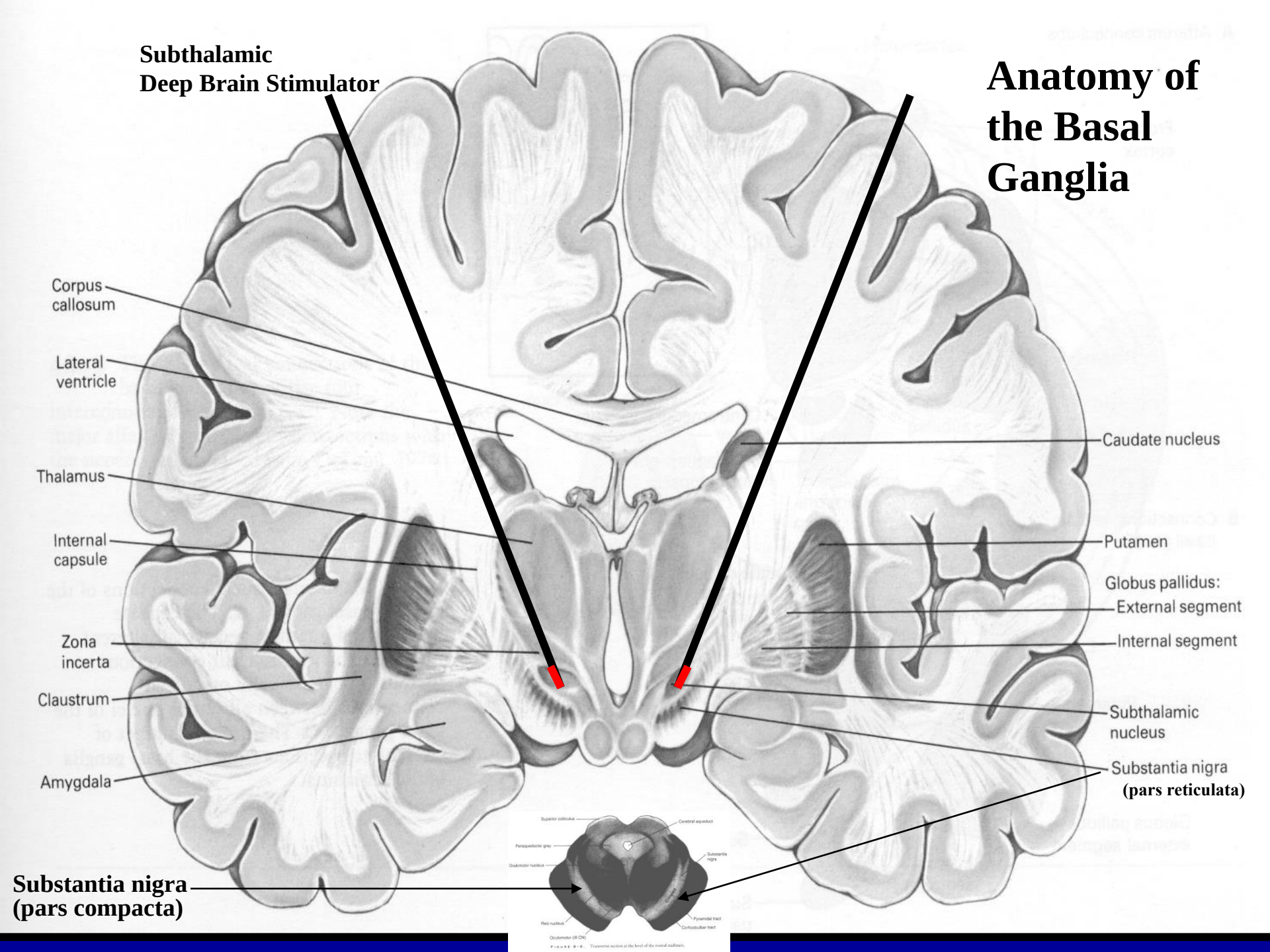
Bilateral GPi DBS in PD

- **Effective & Safe:**
  - **Improved UPDRS scores similar to STN DBS**
  - **Improved motor fluctuations:**
    - **Decreased OFF time**
    - **Improved dyskinesia**
  - **INCREASED daily dose of levodopa-equivalent**
- **Clinical effects depends on location of DBS lead:**
  - **Ventral stimulation:**
    - **improves rigidity and dyskinesia**
    - **may worsen bradykinesia**
  - **Dorsal stimulation:**
    - **improves bradykinesia**
    - **may worsen dyskinesia**

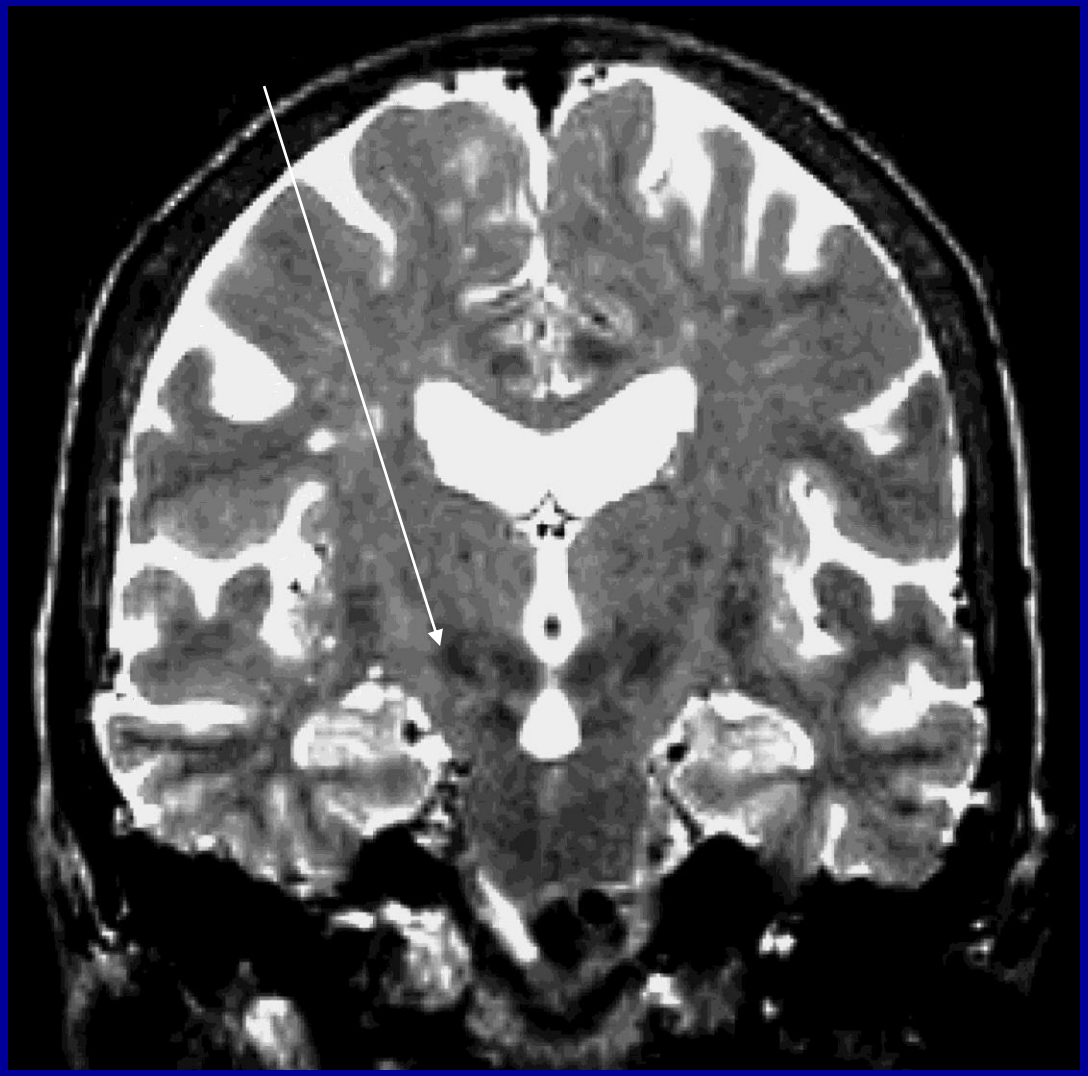
Deep Brain Stimulation
Hardware

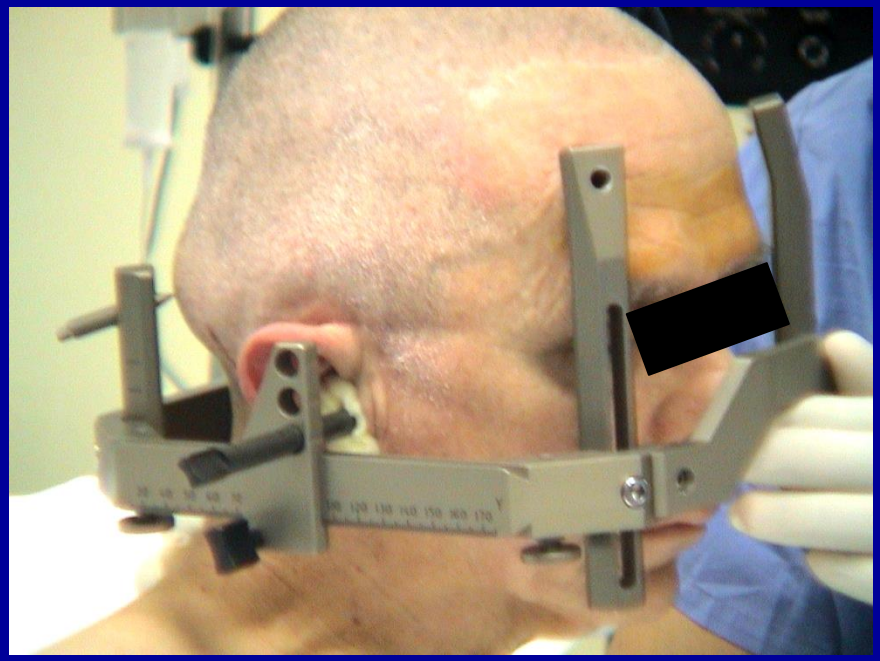


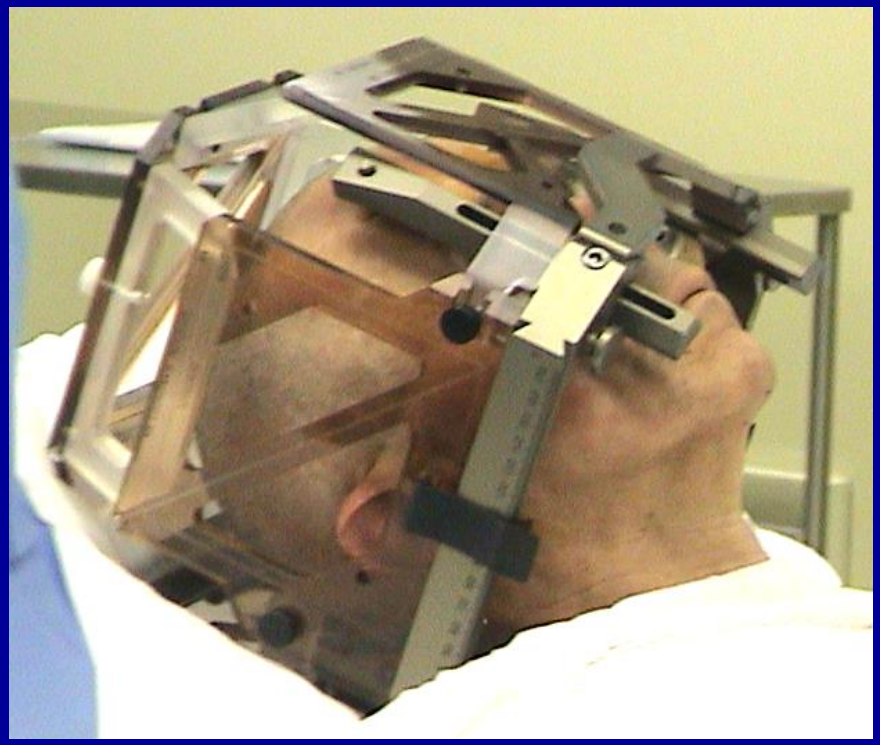
Anatomy of the Basal Ganglia



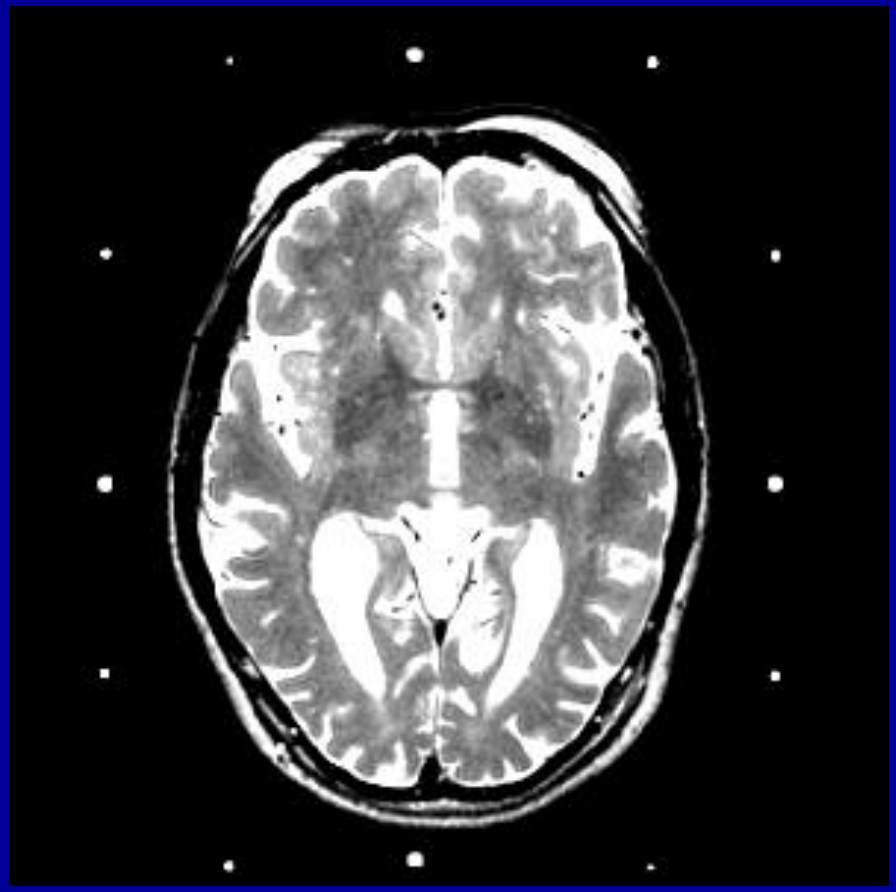
Subthalamic Nucleus

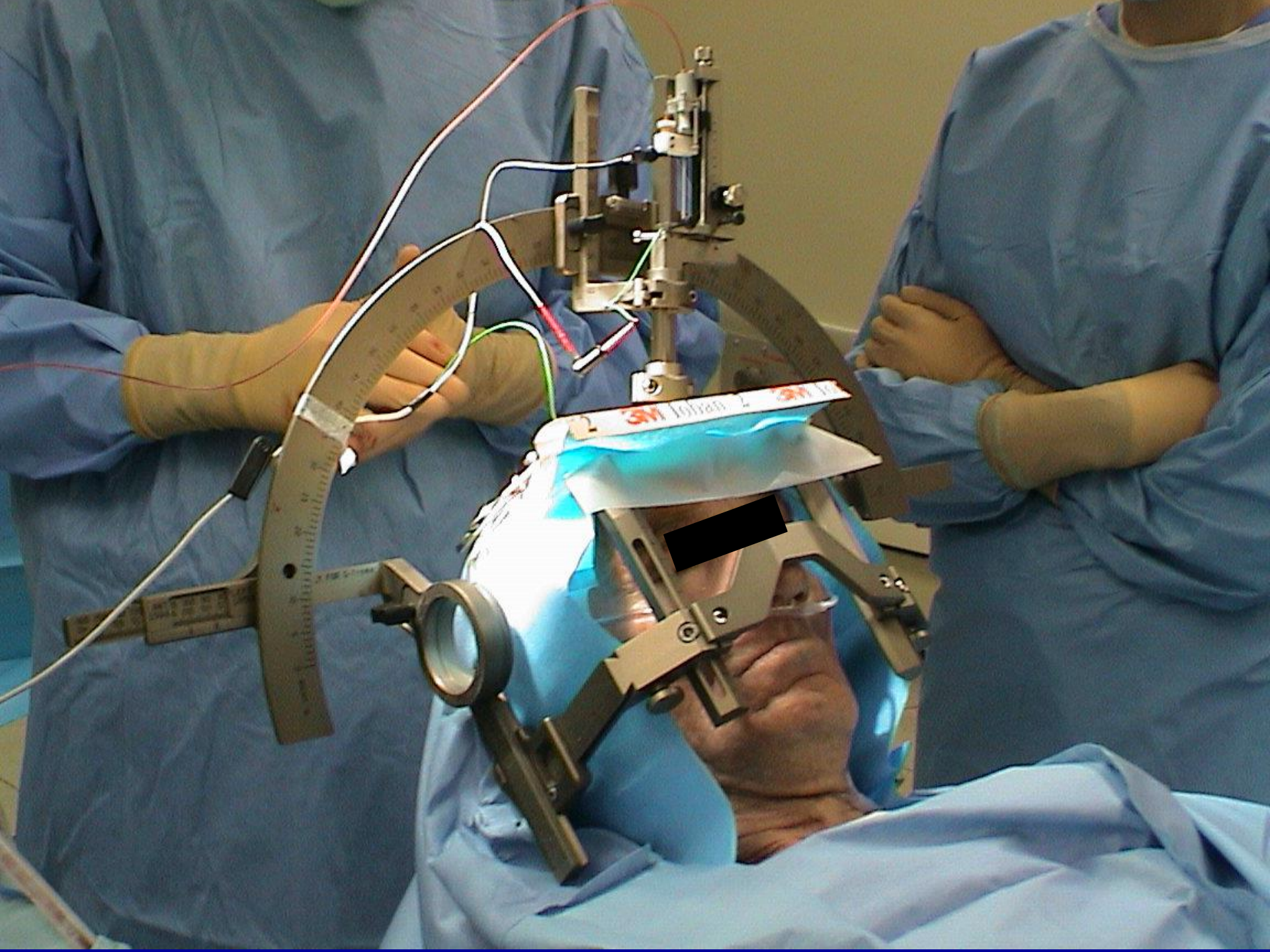






Stereotaxic frame

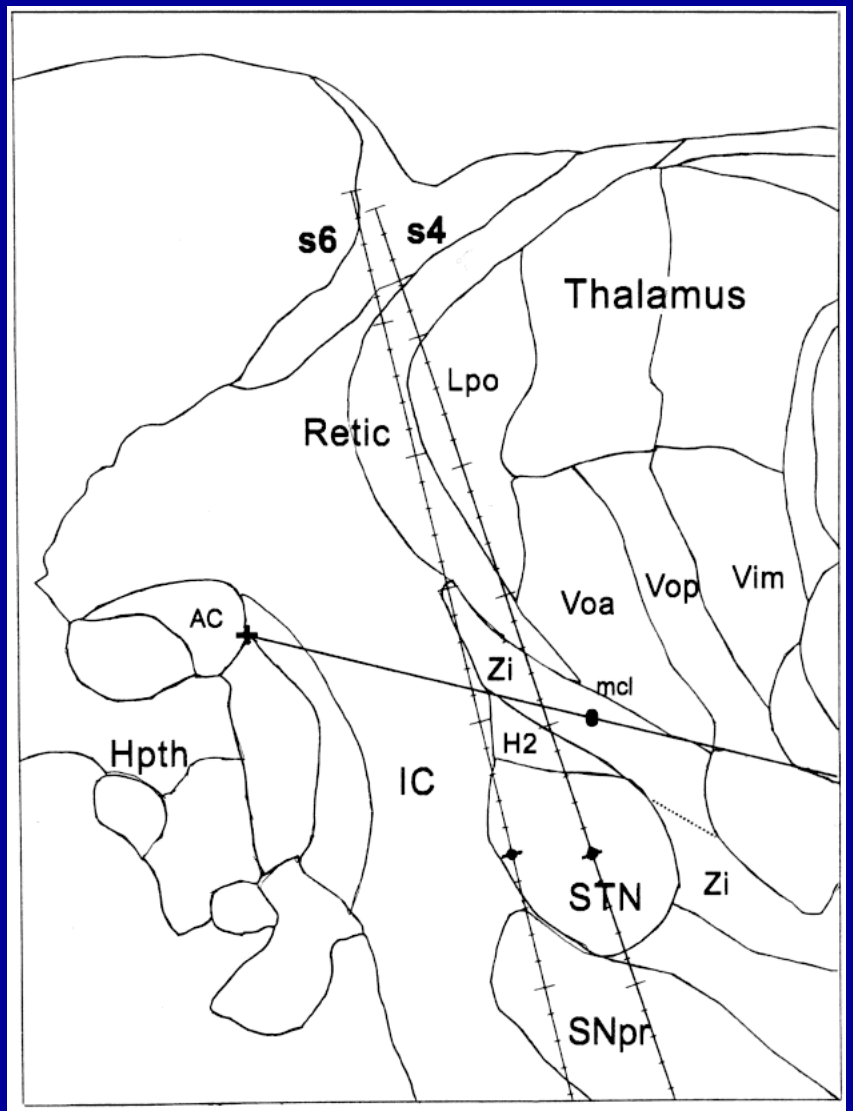


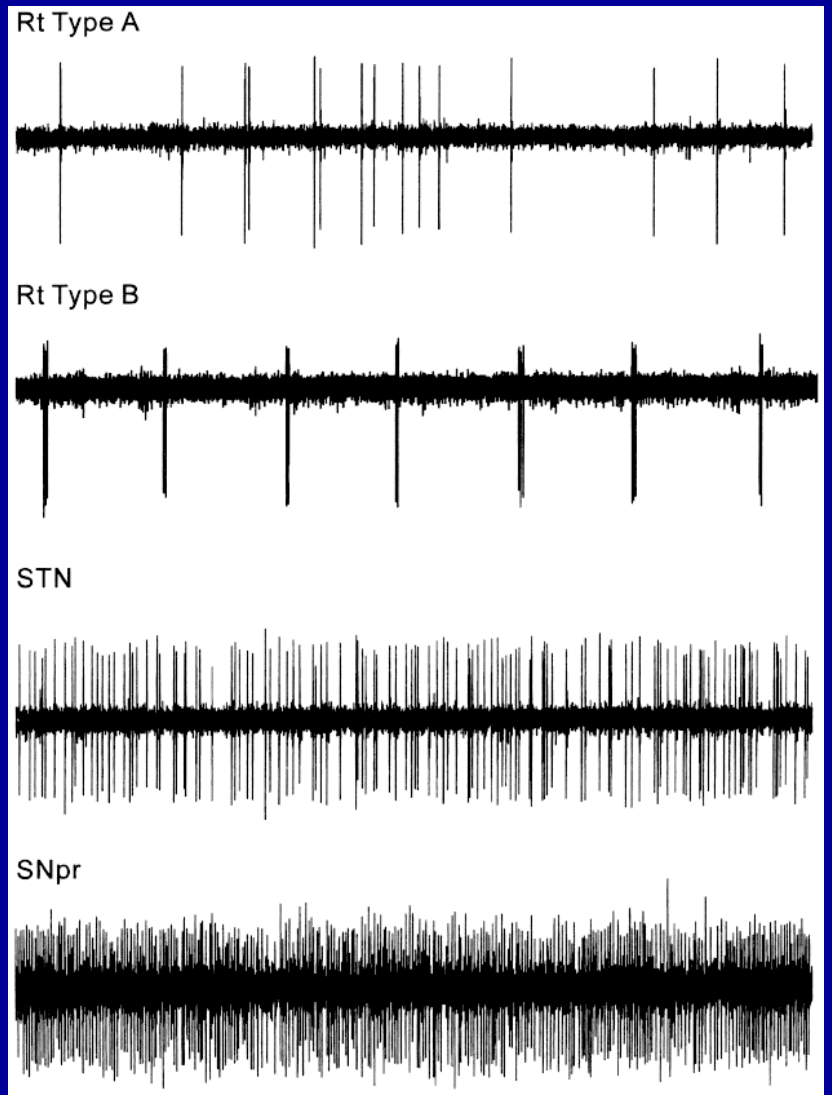

3M Tegaderm 2 3M

Microelectrode targeting -

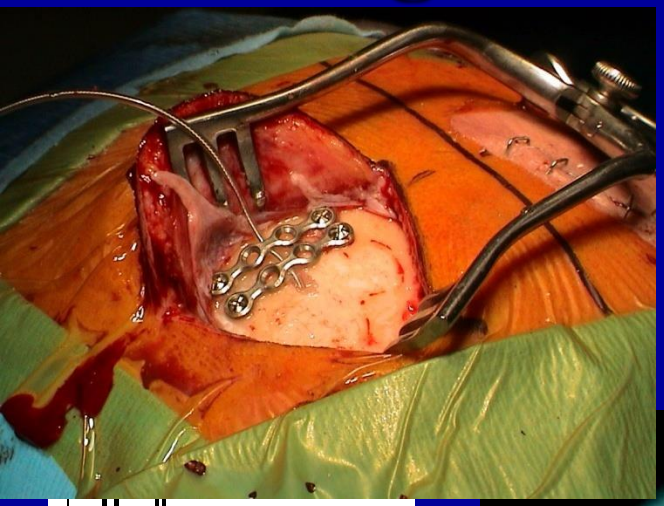
Sagittal view: Schaltenbrand atlas

Hutchison: Ann Neurol, 44: 1998.622-628

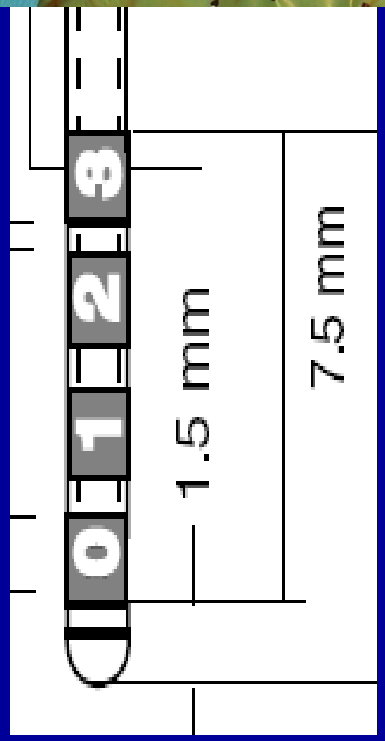




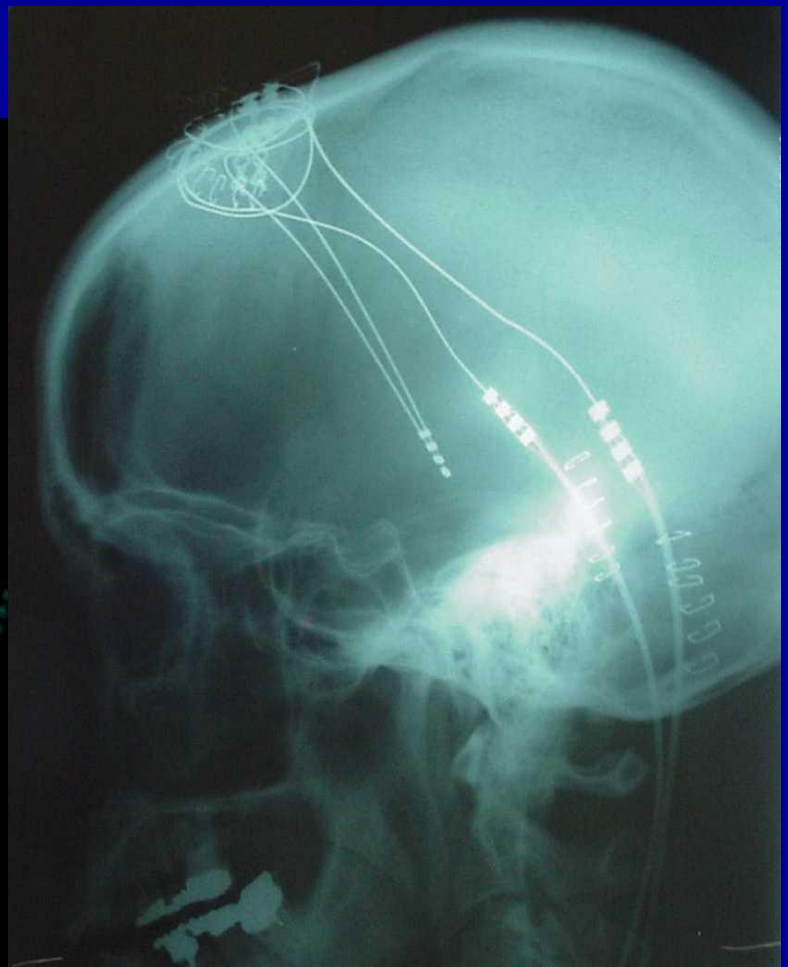
Surgical Technique of STN DBS



Stage I: Electrode implantation
Stage II: Pulse generator implantation







Deep Brain Stimulation Hardware







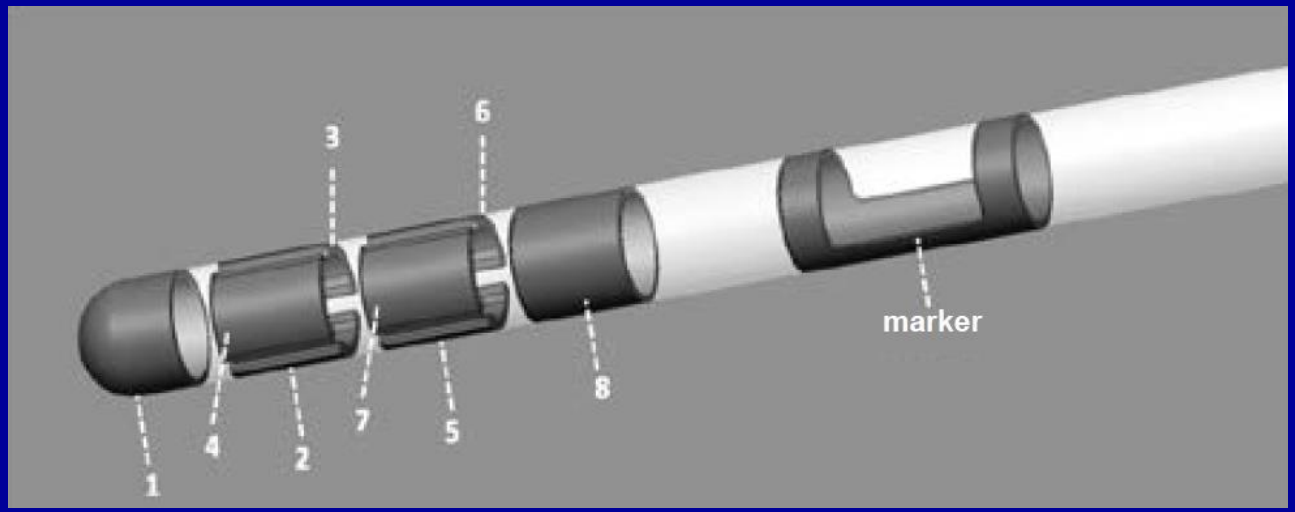




DBS Non-Directional Lead

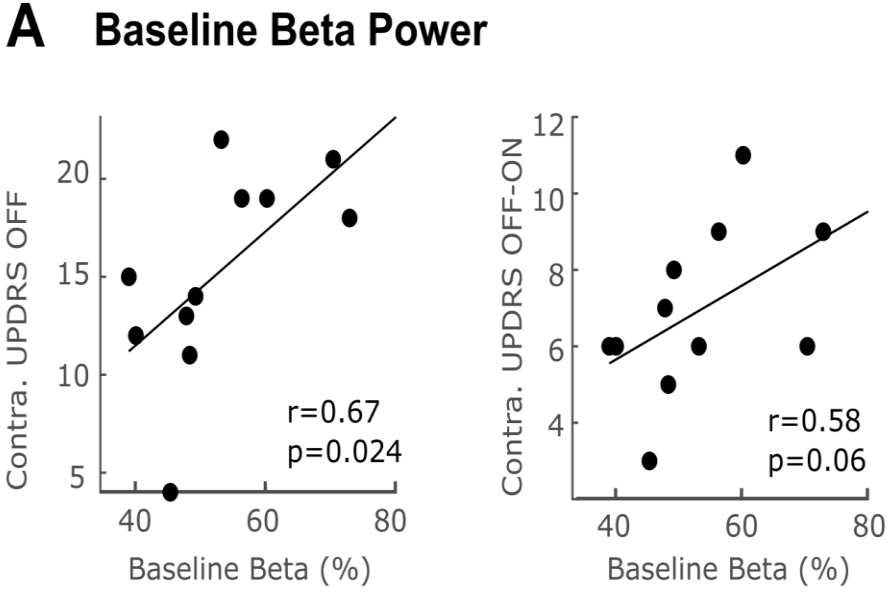


DBS Directional Lead

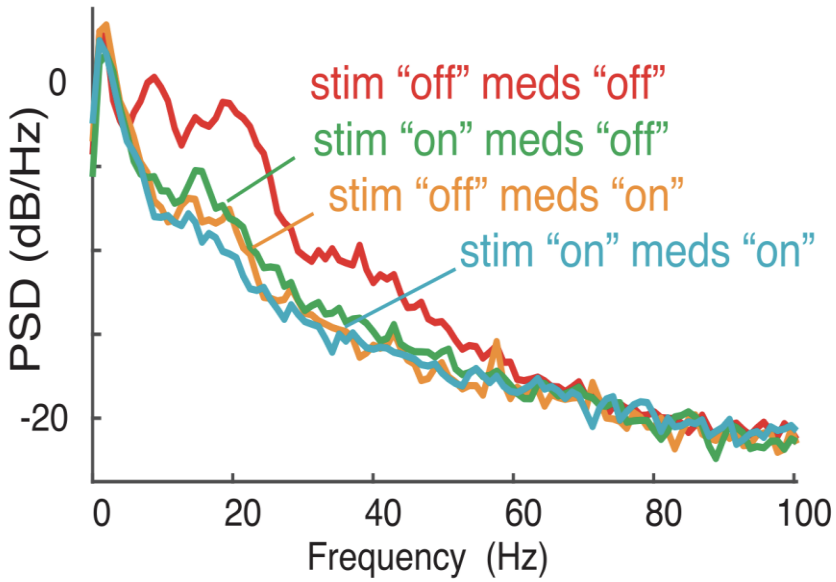


DBS Electrodes That Measure Local Field Potentials for Guiding DBS Programming

Beta correlation with symptoms



Beta LFPs are attenuated with medication and stimulation



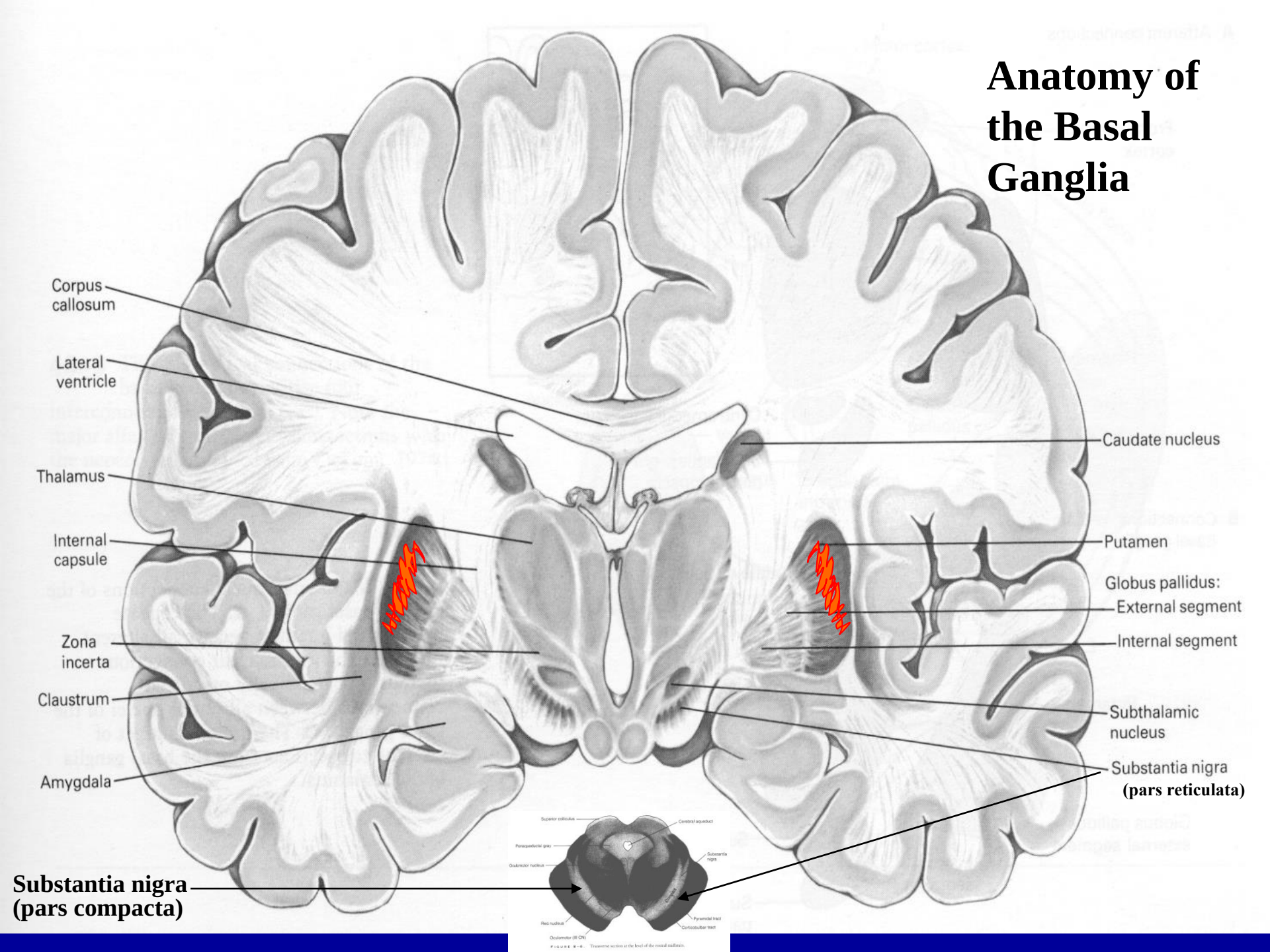
Research on brain sensing and BrainSense™ technology, Scientific Compendium, Medtronic 2022

Fetal Tissue Transplantation in PD

Implanting dopaminergic neurons into critical structures originally innervated by degenerating dopaminergic neurons of the substantia nigra pars compacta

Chosen Target: Striatum

Anatomy of the Basal Ganglia



Methodological Issues of the Fetal Transplantation Procedure

- Source of fetal tissue
- Donor age
- Number of donor cells
- Post-transplantation immunosuppression
- Type of transplant
- Strategies of enhancing viability of the transplanted cells
  - Neurotrophic factors
  - Free radical scavengers
  - Genetically engineered cells

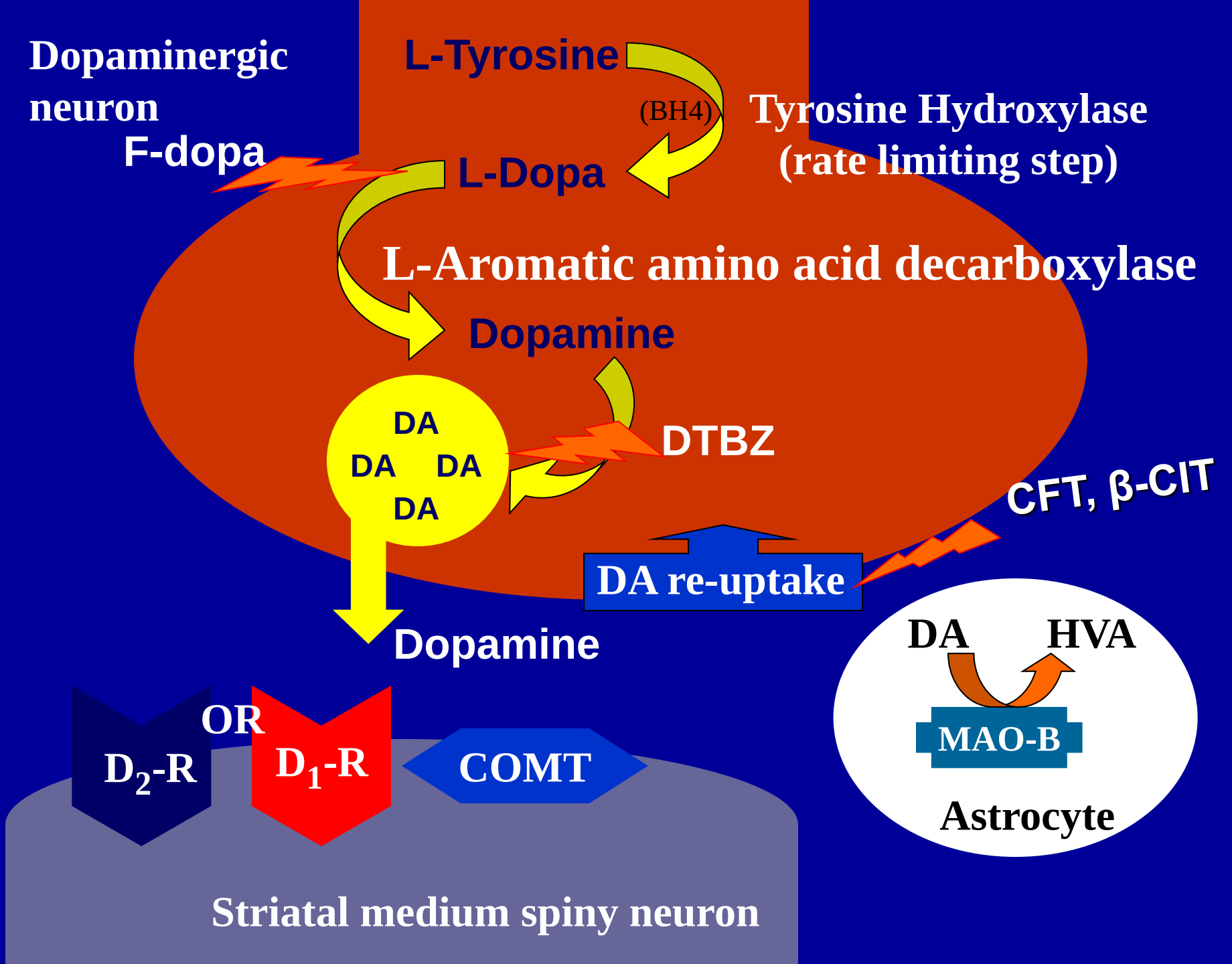
Fetal Tissue Transplantation in Humans

Fetal dopaminergic neuron transplants:

- **survive long-term**
- **innervate the striatum**
- **form synaptic connections**
- **Miserable clinical outcome (understatement):**
  - **Runaway dyskinesia**
  - **Intractable dystonias**
  - **Bizarre phenomenology never seen in the natural history of PD**

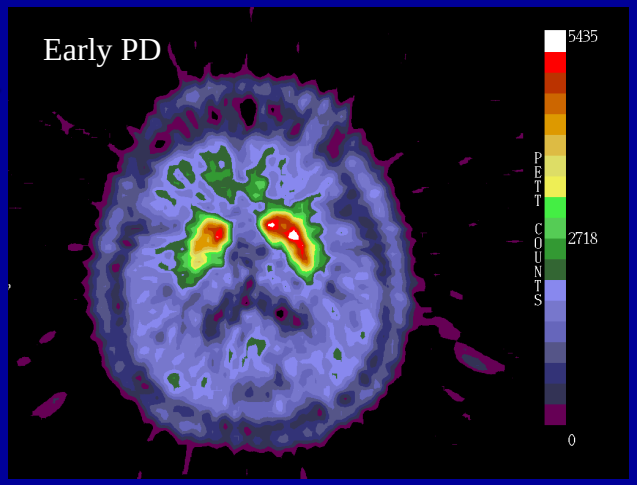
Imaging of Dopamine Terminals

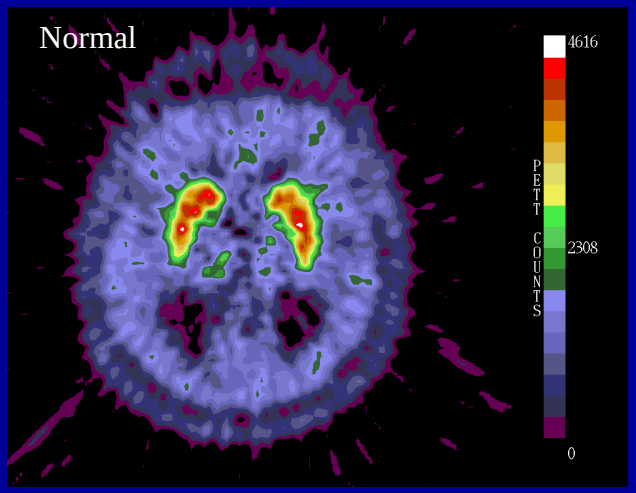
- **PET ligands:**
  - **6-^{18}F-fluorodopa (FD) binds:**
    - **L-aromatic amino acid decarboxylase**
  - **^{11}C dihydrotetrabenazine (DTBZ) binds:**
    - **VMAT 2 receptor on vesicles**
  - **^{11}C 2-β-carbomethoxy-3-β-4-fluorophenyltropane (CFT) binds:**
    - **dopamine reuptake transporter**
  - **Other radioligands:**
    - **^{11}C raclopride, ^{18}F-fallypride and ^{18}F-desmethoxyfallypride bind dopamine D2/D3 receptors**
    - **^{11}C McN 5652 and ^{11}C DASB bind serotonin transporters**
    - **^{18}F-Mefway bind serotonin 5HT1a receptors**
    - **^{18}F-Nifene bind nicotinic acetylcholine receptors**
- **SPECT ligand:**
  - **^{123}I-2-β-carbomethoxy-3-β-[4-iodophenyl] tropane (β-CIT) binds:**
    - **dopamine reuptake transporter**
    - **FDA-approved as DaTscan in 2012**

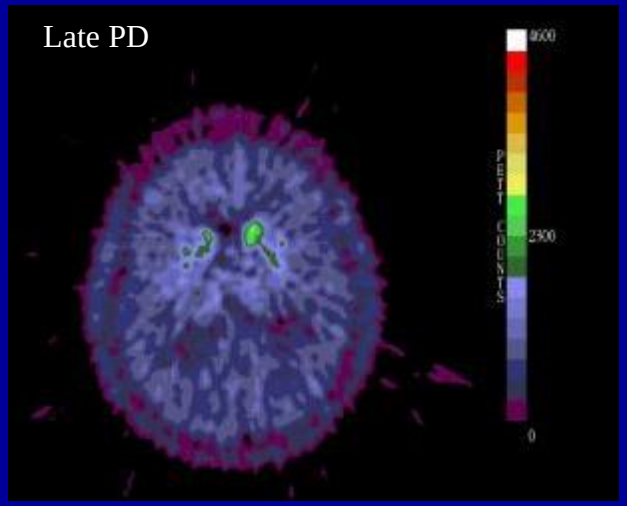

Dopaminergic neuron
L-Tyrosine
(BH4)
Tyrosine Hydroxylase (rate limiting step)
F-dopa
L-Dopa
L-Aromatic amino acid decarboxylase
Dopamine
DA
DA DA
DA
DTBZ
CFT, β-CIT
DA re-uptake
Dopamine
DA
HVA
MAO-B
Astrocyte
OR
D2-R
D1-R
COMT
Striatal medium spiny neuron

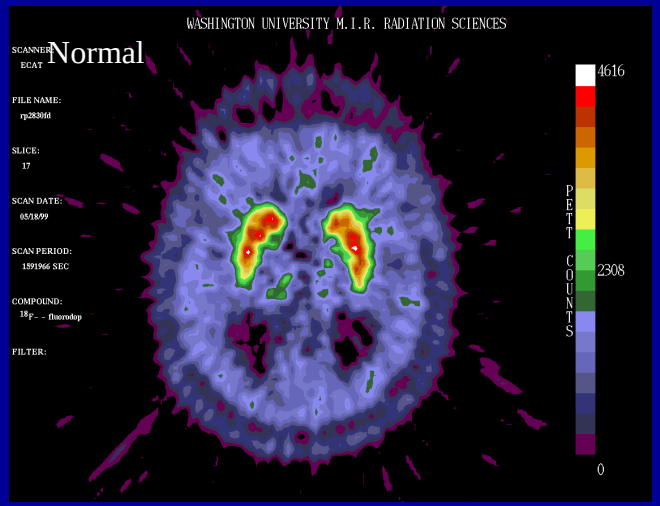
18-Fluorodopa Positron Emission Tomography in Parkinson Disease

18-Fluorodopa PET

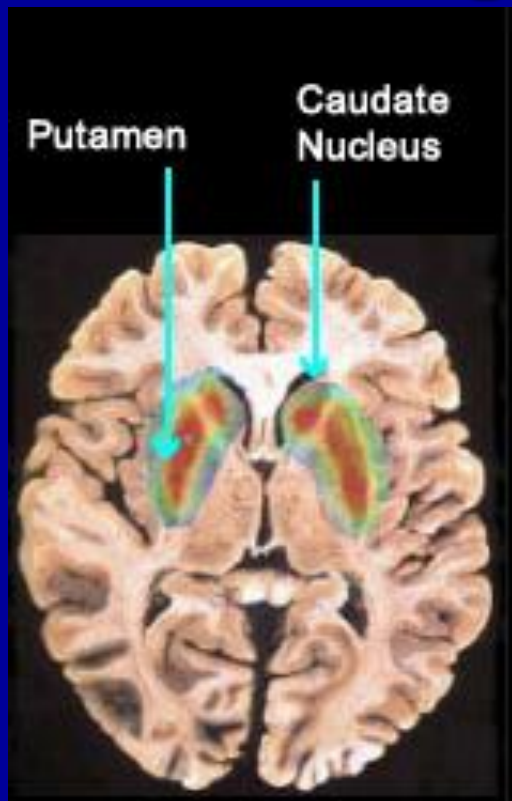


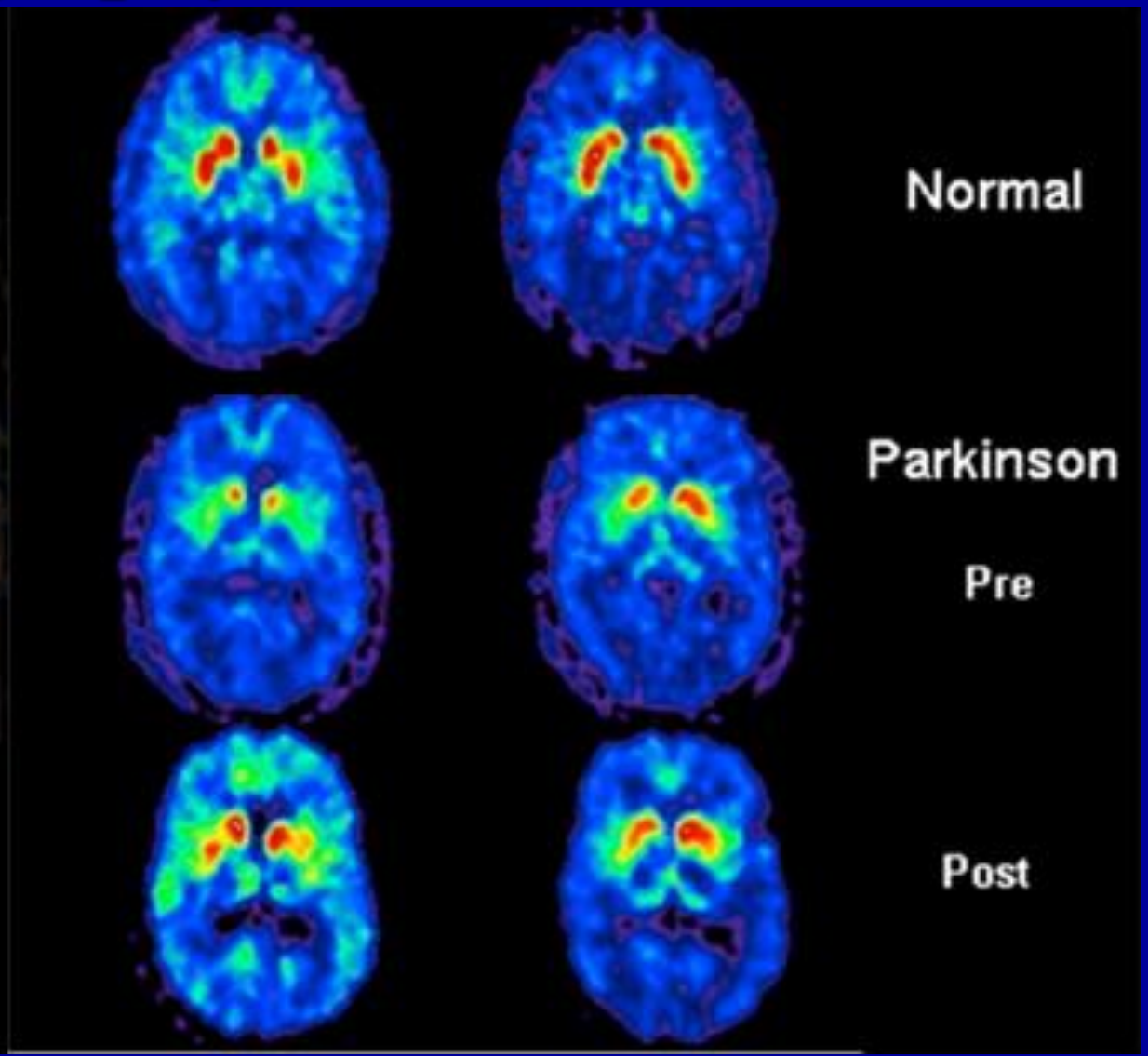






^{123}Beta-CIT Single Photon Emission Tomography (SPECT) in PD

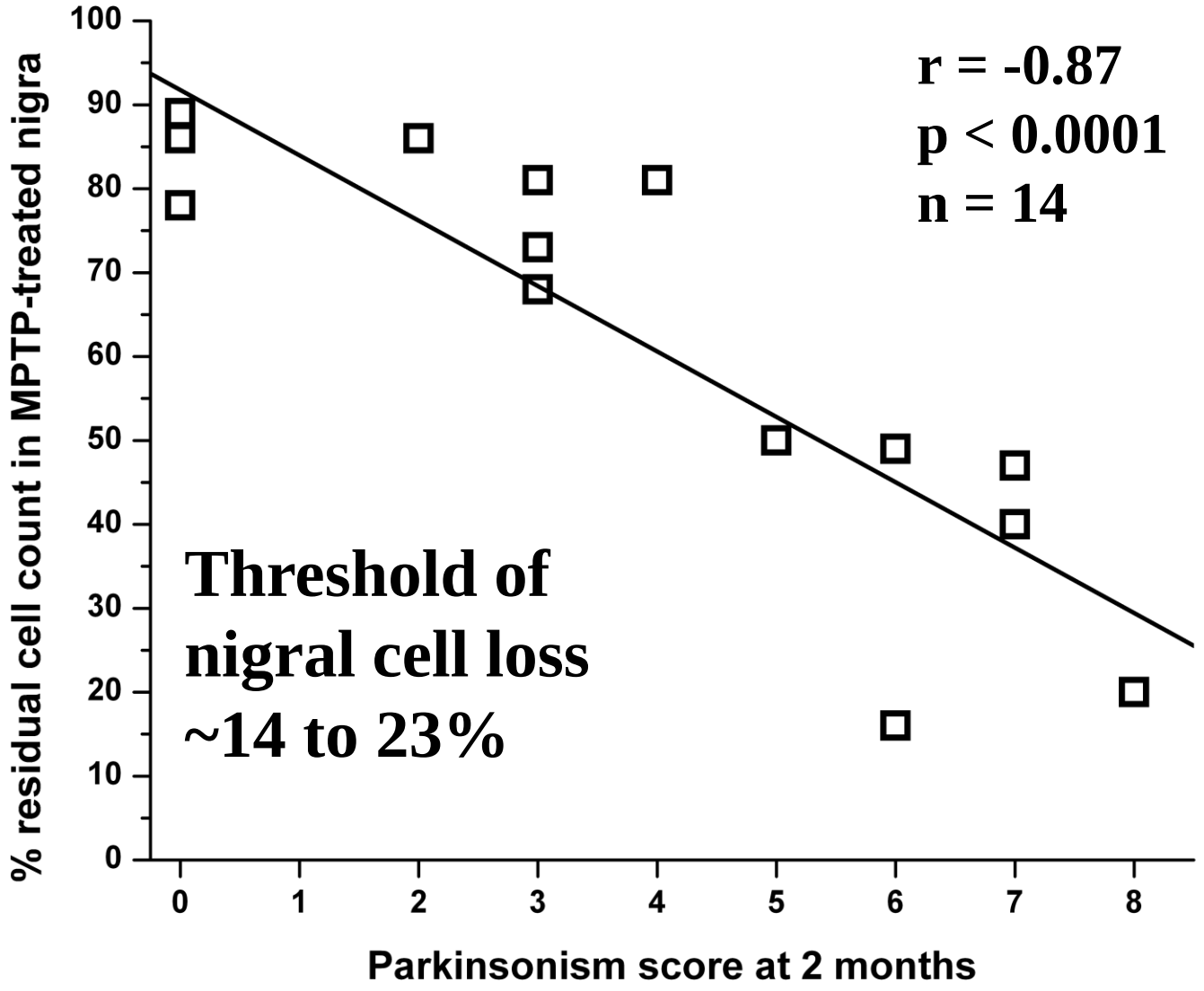




Imaging of Dopamine Terminals

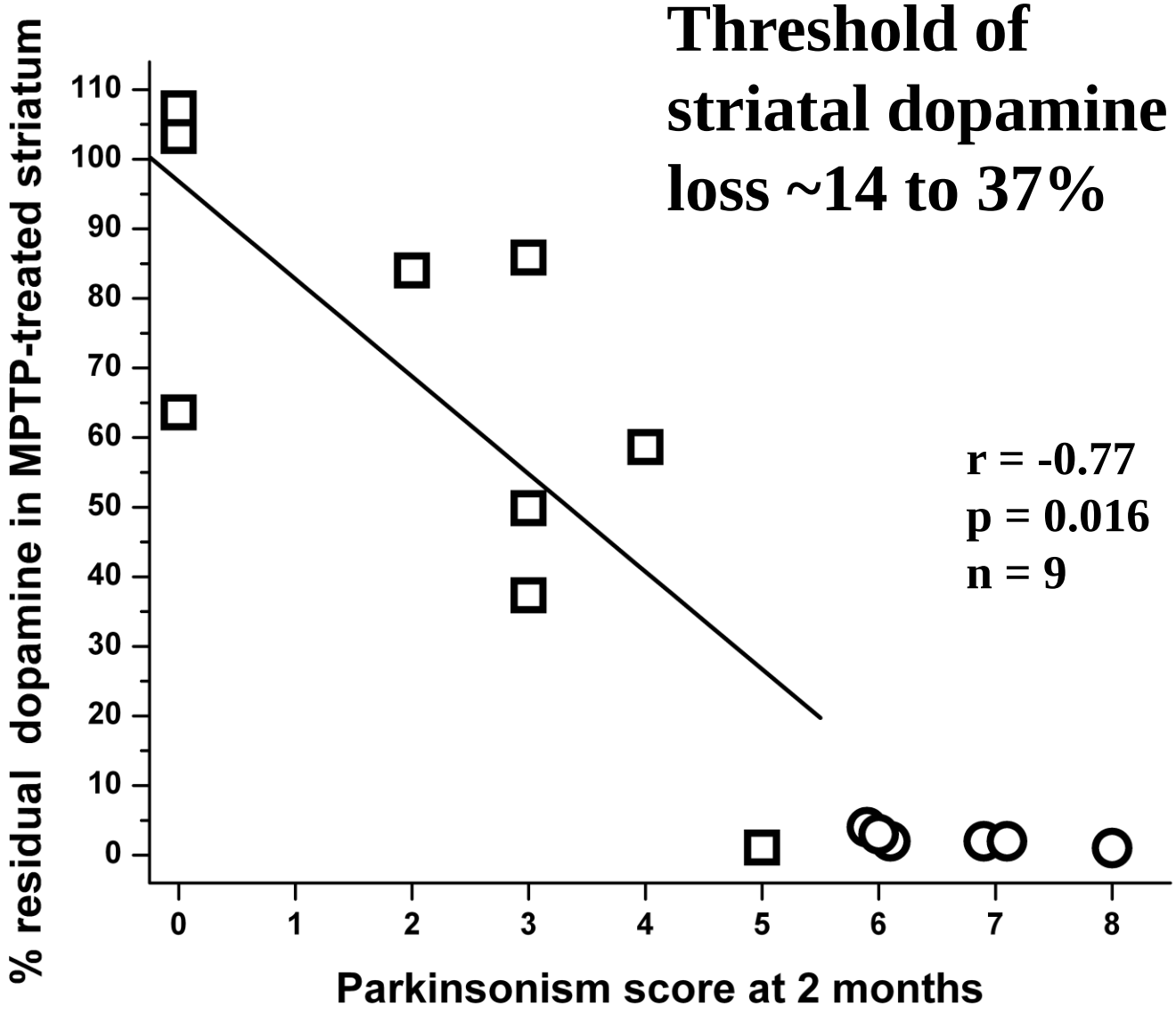
- **NONE are good biomarkers for disease:**
  - **Do not correlate with motor function**
  - **Do not correlate with number of dopamine terminals**
  - **Ligand binding sites affected by medications?**
- **Useless for diagnosis:**
  - **False positives: e.g, drug-induced parkinsonism**
  - **False negatives: Parkinson disease with normal β-CIT scans**
  - **Cannot differentiate:**
    - **Parkinson disease vs Parkinson Plus syndromes**
    - **Diffuse Lewy body disease vs Alzheimer dementia (?)**

PD Score vs % Residual Cell Count



Tabbal 2012, *Experimental Neurology*, vol 237: 355–362

PD Score vs % Residual Striatal Dopamine



Tabbal 2012, *Experimental Neurology*, vol 237: 355–362

Experimental Neurology 237 (2012) 355–362

Contents lists available at SciVerse ScienceDirect

Experimental Neurology

journal homepage: www.elsevier.com/locate/yexnr

Low nigrostriatal reserve for motor parkinsonism in nonhuman primates

Samer D. Tabbal [a], LinLin Tian [a], Morvarid Karimi [a], Christopher A. Brown [a], Susan K. Loftin [a], Joel S. Perlmutter [a,b,c,d,e,*]

Results

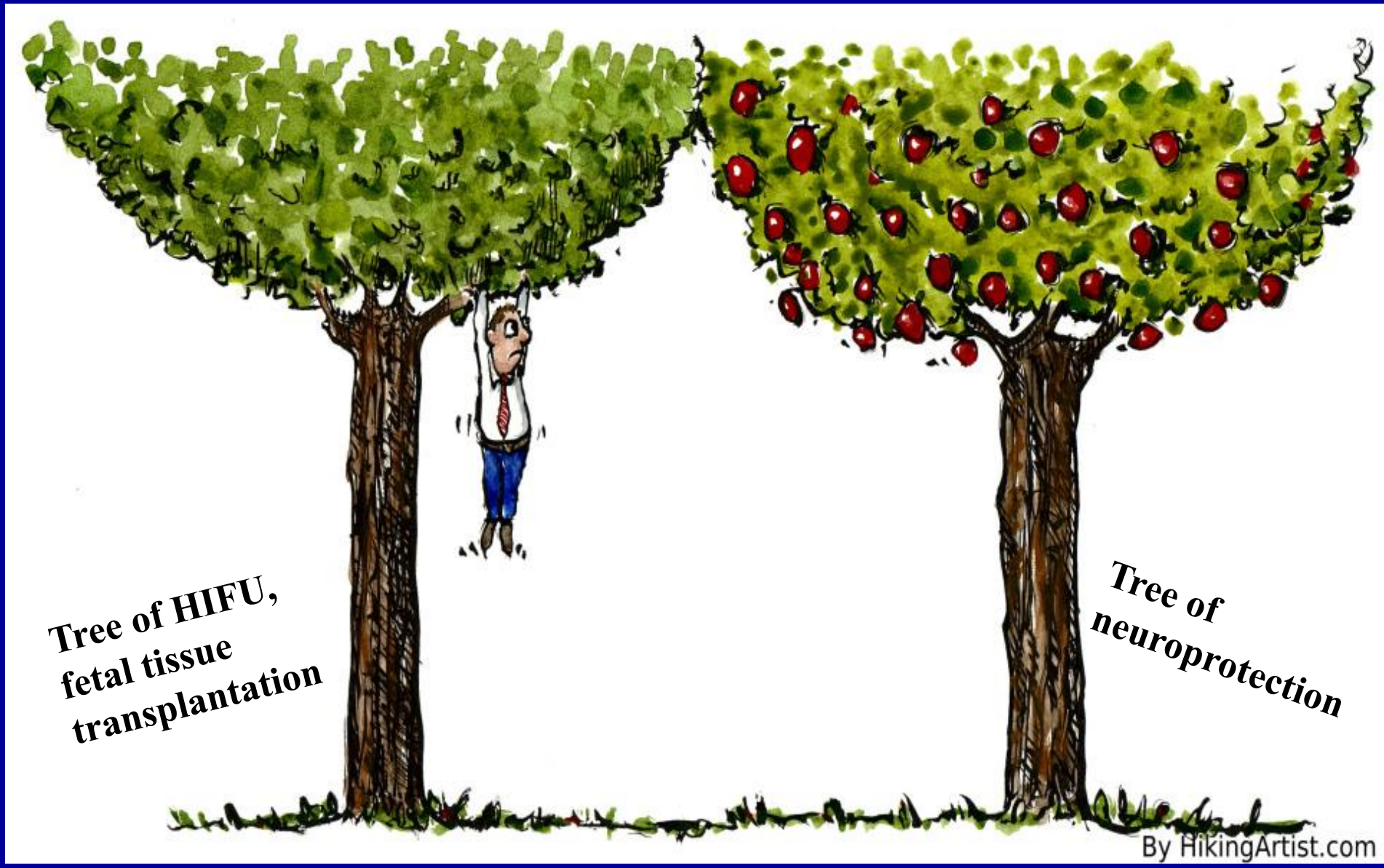
The percent of residual cell counts in lesioned nigra correlated linearly with the parkinsonism score at 2 months ($r = -0.87$, $p < 0.0001$). The parkinsonism score at 2 months correlated linearly with the percent residual striatal dopamine ($r = -0.77$, $p = 0.016$) followed by a flooring effect once nigral cell loss exceeded 50%. A reduction of about 14 to 23% of nigral neuron counts or 14% to 37% of striatal dopamine was sufficient to induce mild parkinsonism.

Motor symptoms develop after loosing >80% of dopaminergic neurons

Conclusions

- PD is readily treatable in the first 15-20 years of disease: medications then DBS surgery
  - No dopamine agonists for patients > 70 years, if at all
  - No D2-dopamine receptors blocking drugs EVER!
  - DBS is good, ablation is bad
  - Fetal tissue transplantation is a disaster
- Forget the Myth: motor symptoms >80% dopaminergic neuron loss
- PET and β-CIT scans:
  - Not adequate biomarkers
  - Not useful for diagnosis
- No proven neuro-protective drugs yet, but:
  - Eat less
  - Exercise more
  - Invest in research and …

Conclusion


Tree of HIFU, fetal tissue transplantation
Tree of neuroprotection
By HikingArtist.com

… And Above All…

