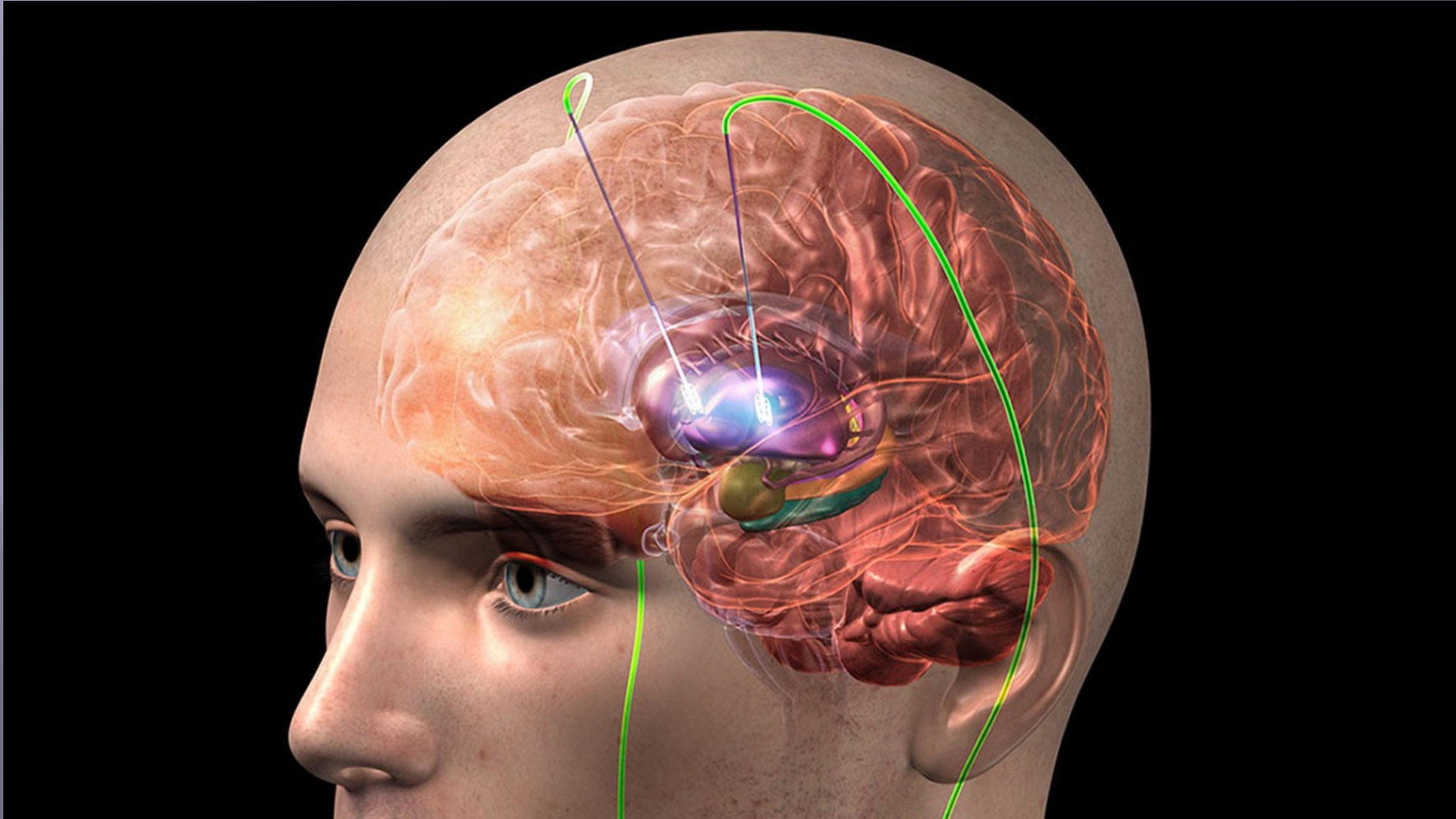


EVOLUTION-REVOLUTION OF DEEP BRAIN STIMULATION (DBS)

Deep Brain Stimulation: Cutting Edge Technology

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Parkinson's Disease and Movement Disorders Center
RWJ Barnabas Health

DBS: What is it?



Deep Brain Stimulation (DBS) Surgery

- ❑ DBS is an effective, long-term treatment for movement disorders like essential tremor, Parkinson's disease and dystonia.
- ❑ Efficacy and safety depend on the spatial restriction of the stimulation field to a functional target responsible for benefit.
- ❑ Side effects emerge if the volume of tissue activated (VTA) spreads into adjacent structures.

Is DBS Effective?

- ▣ DBS is a neurosurgical procedure that involves the implantation of electrodes into specific brain targets to deliver constant or intermittent electricity from an implanted battery
- ▣ The clinical use of DBS is one of the most significant developments in the past 25 years
- ▣ DBS can measure pathological brain activity and deliver adjustable stimulation for therapeutic benefit
- ▣ DBS intervenes directly in pathological neural circuits and has altered the way brain disorders are understood and treated

• <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6397644/>

Deep Brain Stimulation

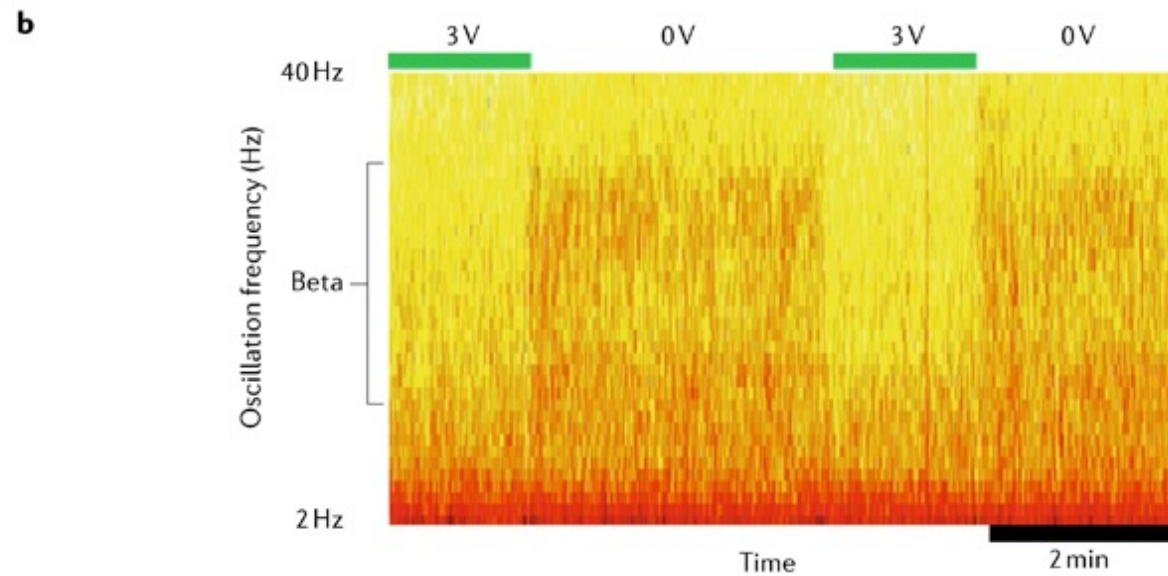
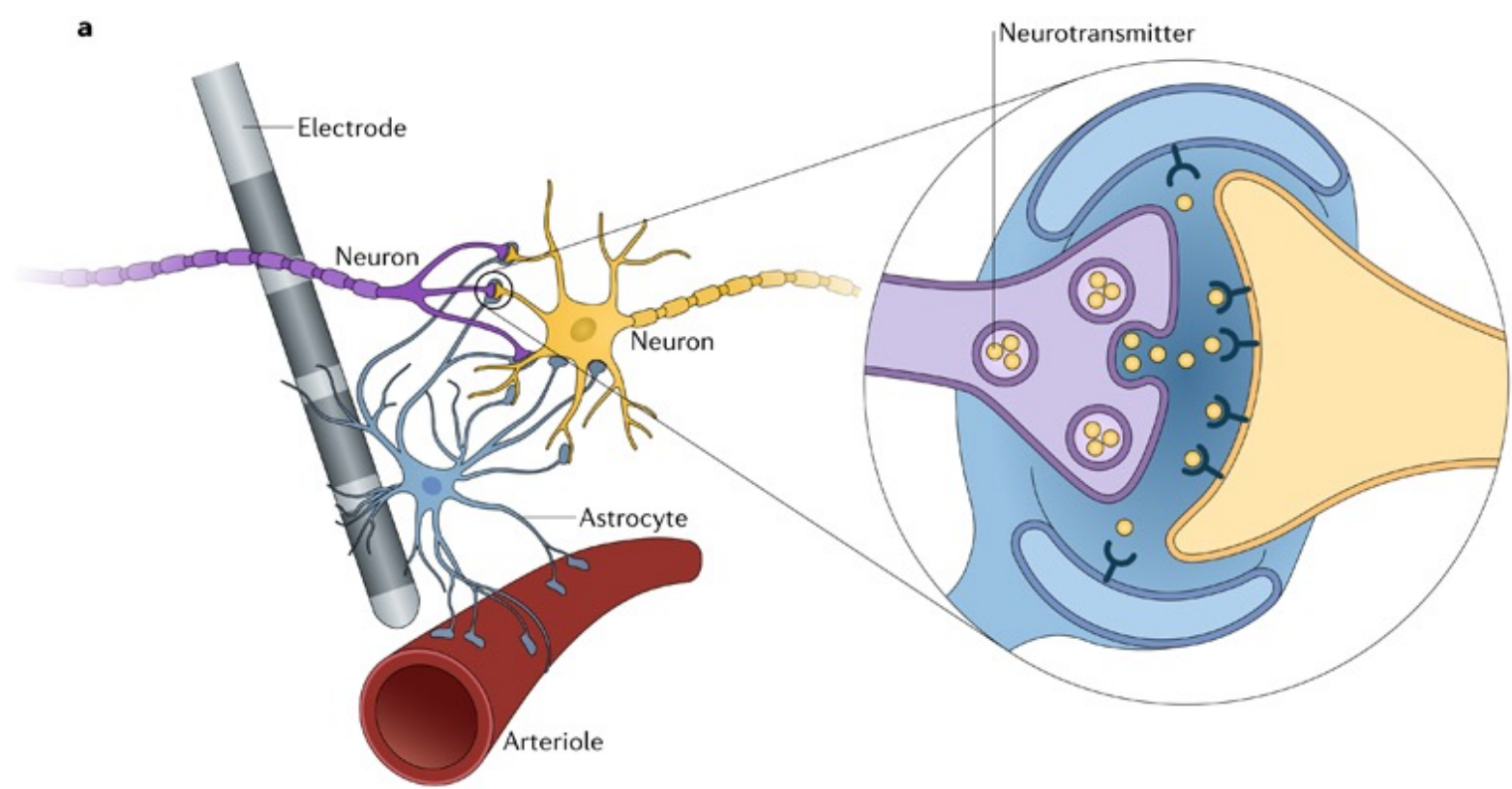
- 1997 FDA approved DBS of the thalamus for treatment of tremor
- 2002: FDA approved DBS of STN for treatment of PD
- 2003: FDA approved DBS of Gpi for treatment Dystonia and/or PD

❖ ***THIS IS NOT A NEW THERAPY OR A LAST RESORT!***

DBS – How we got here

- ▣ 1949: Treatments for various movement and psychiatric disorders involve surgical lesions to brain areas, using electrical stimulation in awake patients to identify targets
- ▣ 1986-90: French neurosurgeon and scientist Alim-Louis Benabid reports that DBS in the ventral intermediate nucleus of the thalamus (VIM) can reversibly decrease tremors in patients with PD
- ▣ 1994-2000: Benabid and colleagues use DBS to inactivate the STN in patients with PD. They report improvement in tremor, rigidity, slowed or reduced movement, and gait. Larger clinical trials to assess DBS in the STN and GPi follow.
- ▣ **1996**: The FDA approves VIM-DBS for **essential tremor** and severe tremor in PD
- ▣ **2000**: The FDA approves its use in the STN or GPi in advanced **PD**
- ▣ **2003**: The FDA allows DBS for **dystonia** under a Humanitarian Device Exemption (HDE)

Deep brain stimulation mechanisms



PD - Epidemiology

- ▣ 2nd most common neurodegenerative disease after Alzheimer's Disease
- ▣ Affects 1% of population over age 65
- ▣ 4-10% are young onset (diagnosed prior to age 40)
- ▣ US – half a million people diagnosed with PD
- ▣ Predicted to triple over next 50 years
- ▣ Slightly more common in men

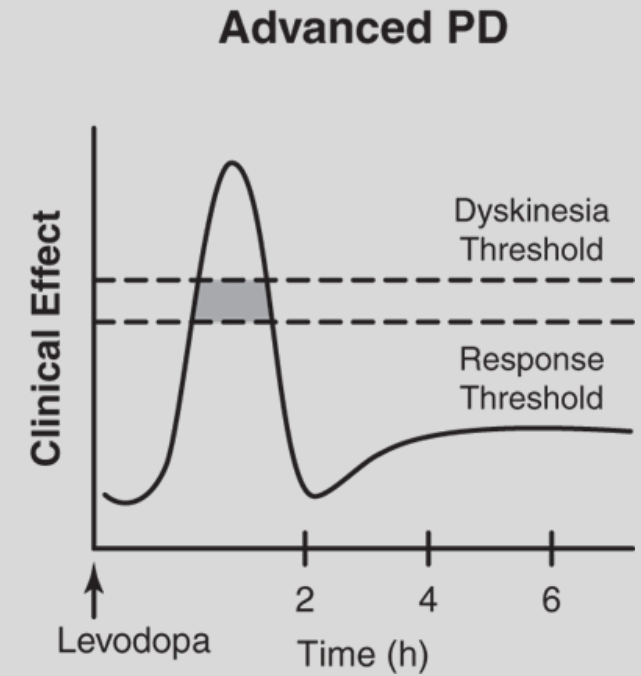
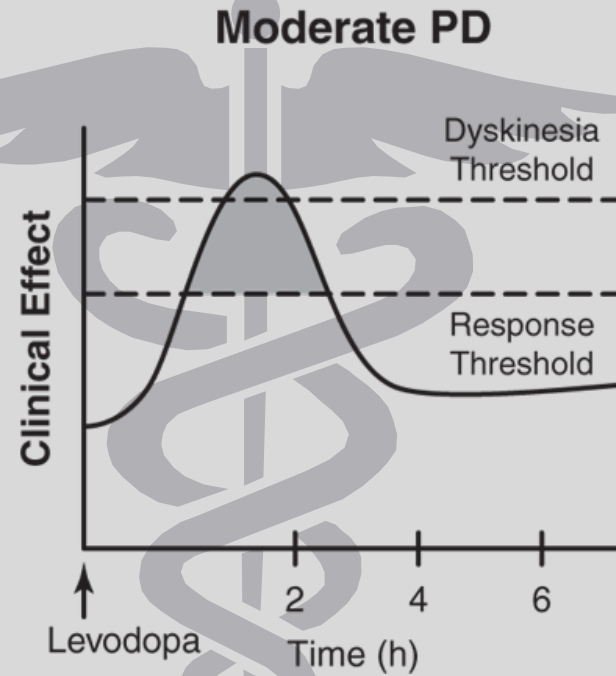
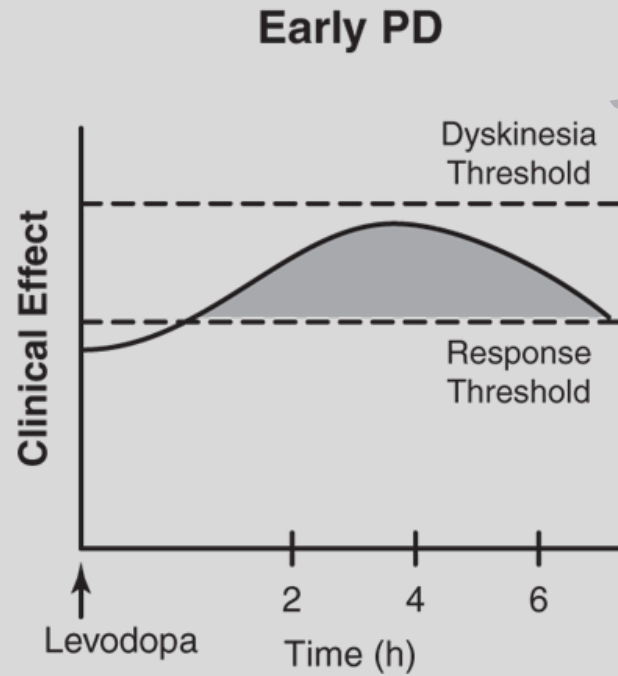
Diagnosing PD

- ▣ Clinical diagnosis
- ▣ Based on signs and symptoms
- ▣ DaTscan – first and only FDA-approved visual adjunct imaging agent for adult patients with suspected Parkinsonian syndromes (PS)
- ▣ May help differentiate essential tremor from tremor due to PS

Pharmacotherapy

- ▣ Levodopa remains the mainstay of PD therapy
- ▣ Robust response typical, with marked reduction in motor symptoms
- ▣ Motor complications frequently emerge over time

Therapeutic Window of Levodopa



ATYPICAL PARKINSONISM

- ▣ PD – IDIOPATHIC Parkinson's disease – appropriate candidate
- ▣ Not appropriate candidates if diagnosis is:
 - MSA – Multiple System Atrophy (MSA)
 - Progressive Supranuclear Palsy (PSP)
 - Corticobasal degeneration (CBD)
- ▣ All are associated with dopaminergic neurodegeneration

Atypical Parkinsonism - PSP

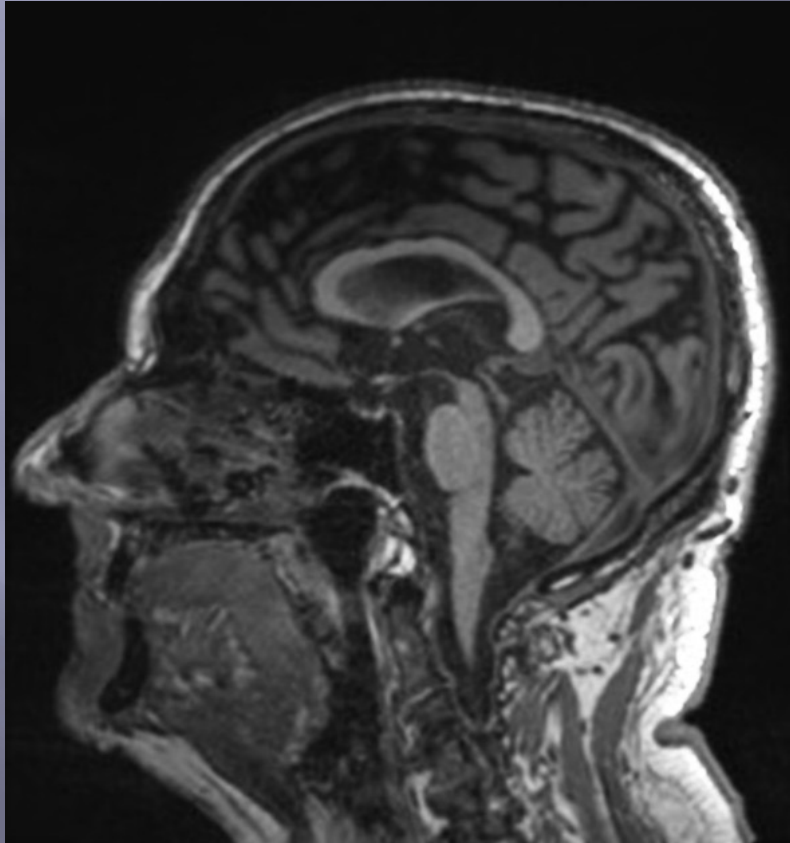
- ▣ Difficult to diagnose: characteristic symptoms may develop late or not at all
 - ▣ Unexplained falls, personality changes, dysarthria, dysphagia, cognitive changes, inability to maintain eye contact
 - ▣ MRI findings: midbrain atrophy
-
- ▣ Research: <http://www.curepsp.org>, 410-785-7004,, 800-457-4777, Fax: 410-785-7009

Atypical – Progressive Supranuclear Palsy

- ▣ Gait and balance – frequent falls, stiff, broad-based gait, extension of knees and trunk and neck (“frankenstein gait”)
- ▣ Lack of insight regarding equilibrium
- ▣ Paralysis of downgaze (ophthalmoparesis) – may be overcome with “doll’s eye maneuver”
- ▣ Pseudobulbar affect, depression
- ▣ Dysarthria

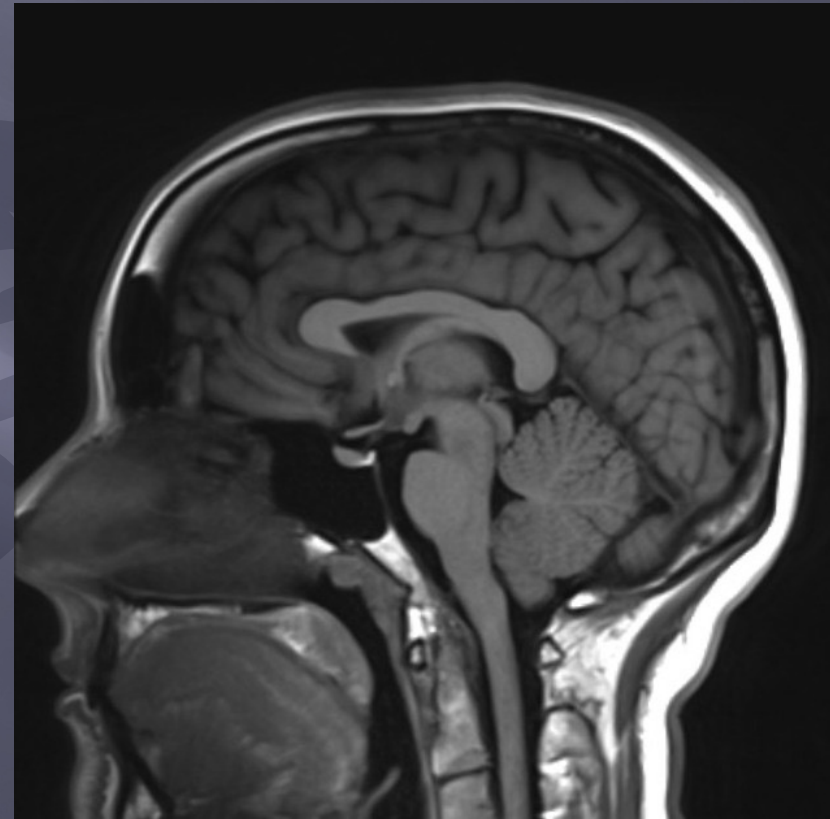
PSP – Hummingbird Sign

HUMMINGBIRD SIGN



Sagittal T1 Image
Atrophy of midbrain

NORMAL BRAIN



Atypical Parkinsonism - MSA

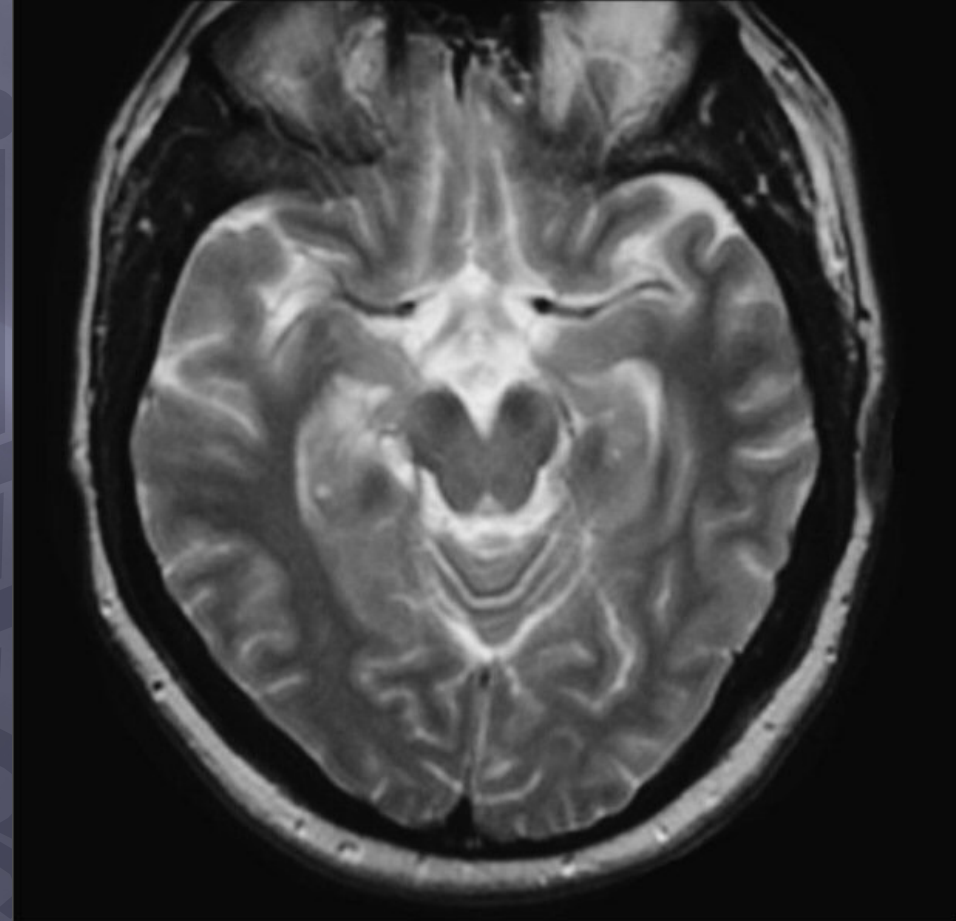
- ▣ Characterized by symptoms of **autonomic nervous system failure**: orthostatic syncope, impotence, bladder dysfunction
- ▣ Motor control symptoms: tremor, rigidity, loss of muscle coordination
- ▣ Affects both men and women primarily in their 50s
- ▣ Loss of nerve cells in brain and spinal cord: build-up of protein alpha-synuclein in dopamine producing cells

MSA – Hot Cross Bun Sign

HOT CROSS BUN SIGN



NORMAL MIDBRAIN



Axial T2-weighted MR image (MSA-c) shows the "Hot Cross Bun" sign as a cruciform hyperintensity in an atrophied pons (arrow)

VASCULAR PARKINSONISM

- ▣ 2.5 – 5% of all cases of Parkinsonism
- ▣ Risk factor: cerebrovascular disease
- ▣ AKA: multi-infarct parkinsonism, lower body parkinsonism
- ▣ Postural instability & falls
- ▣ Gait: short-stepped, may be wide-based, lead pipe rigidity, no resting tremor (Parkinsonian-ataxic gait)
- ▣ Levodopa response: poor
- ▣ MRI of brain: diffuse white matter changes

Corticobasal degeneration (CBS)

- ▣ Most common cognitive abnormalities in CBD-Cog were executive and visuospatial dysfunction.
- ▣ Dementia is now recognized as a presenting and predominant feature in many cases of CBD.
- ▣ Alien limb phenomena (including complex unintentional limb movements interfering with normal tasks and the sensation that a limb was foreign or had a will of its)

DEEP BRAIN STIMULATION (DBS)

- ▣ Appropriate candidates:
 - Idiopathic Parkinson's disease
 - Essential Tremor
 - Dystonia



Over the past 25 years, DBS has become the standard of care for patients with treatment-refractory motor circuit disorders — most commonly PD, dystonia and essential tremor. DBS is highly effective at controlling motor symptoms

Deep brain stimulation

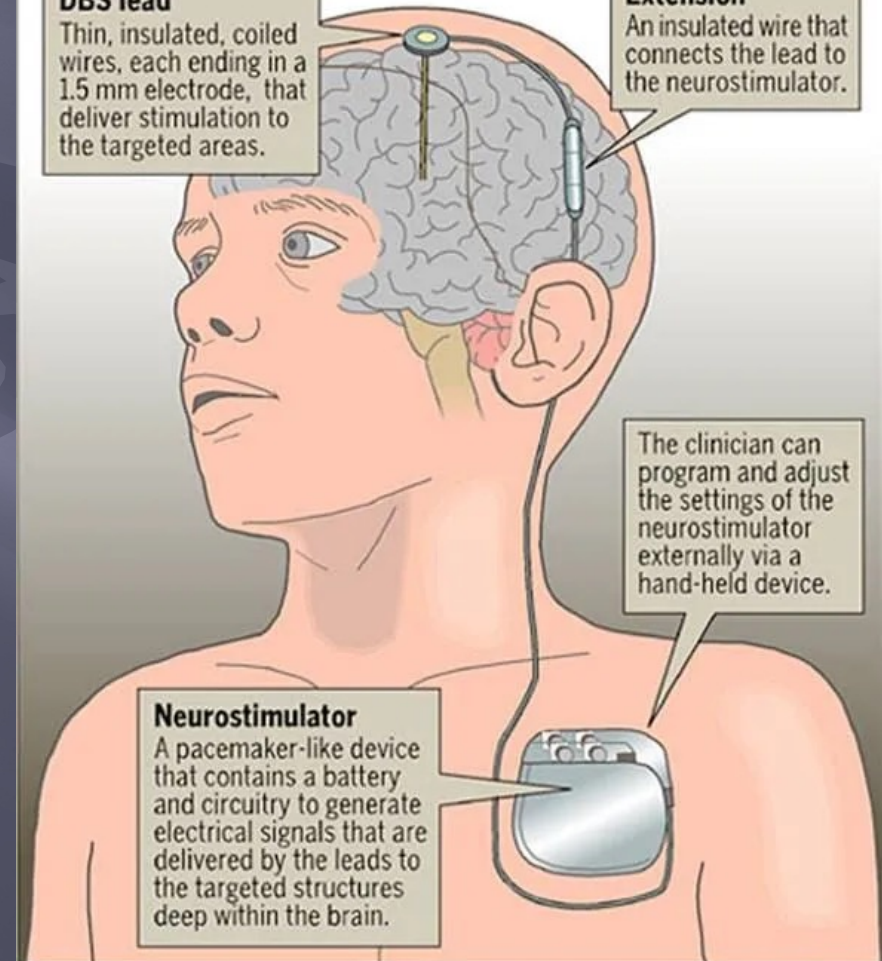
The Deep Brain Stimulation (DBS) system is used to help control tremors and chronic movement disorders. Tiny electrodes are surgically implanted in the brain and are connected via a subcutaneous wire to a neurostimulator (or two, for some diseases) implanted under the skin near the clavicle.

DBS lead

Thin, insulated, coiled wires, each ending in a 1.5 mm electrode, that deliver stimulation to the targeted areas.

Extension

An insulated wire that connects the lead to the neurostimulator.



Neurostimulator

A pacemaker-like device that contains a battery and circuitry to generate electrical signals that are delivered by the leads to the targeted structures deep within the brain.

Source: Medtronic Inc.

Steve Greenberg / Star staff

DBS: Window of Opportunity

- “On” time with disabling dyskinesias or other nonmotor side effects
- “Off” time characterized by disabling tremor, rigidity, or akinesia/bradykinesia
- Unpredictable, “on/off” motor fluctuations
- Medication-resistant tremor

“DBS”

- ▣ KEYS TO SUCCESS
 - PATIENT SELECTION
 - PRECISION OF ELECTRODE TARGETING
 - EXPERIENCED STIMULATION AND MEDICATION ADJUSTMENTS



DBS Technological Advances

- ▣ Within past several years there have been many technological innovations
- ▣ Electrode designs now allow programmer to direct the current flow in vertical and horizontal planes
- ▣ There are now more programming options to compensate for a small deviation from the optimal target
- ▣ Initial settings usually need adjusting, based on the clinical course and the predominant symptoms.
- ▣ Complex clinical problems such as gait or speech problems may require multiple adjustments

How will the new technological innovations in DBS programming change patient outcomes?

- Newer contact designs now allow directional (steering) stimulation with segmented contacts.
- Despite accurate placement of DBS leads, side effects may result due to unwanted neuronal stimulation.
- Primarily, this technology permits the steering of current to the desired areas and avoids unintended stimulation to neighboring areas.

Patient selection for STN DBS

- ▣ Earlier is better (EARLYSTIM STUDY)
- ▣ Improved quality of life compared to BMT (best medication therapy)
- ▣ Less anti-PD medication complications
- ▣ Improved social and occupational activities

- ▣ STN = subthalamic nucleus

- ▣ Subthalamic stimulation was superior to medical therapy in patients with Parkinson's disease and early motor complications. (Funded by the German Ministry of Research and others; EARLYSTIM ClinicalTrials.gov number, NCT00354133.).

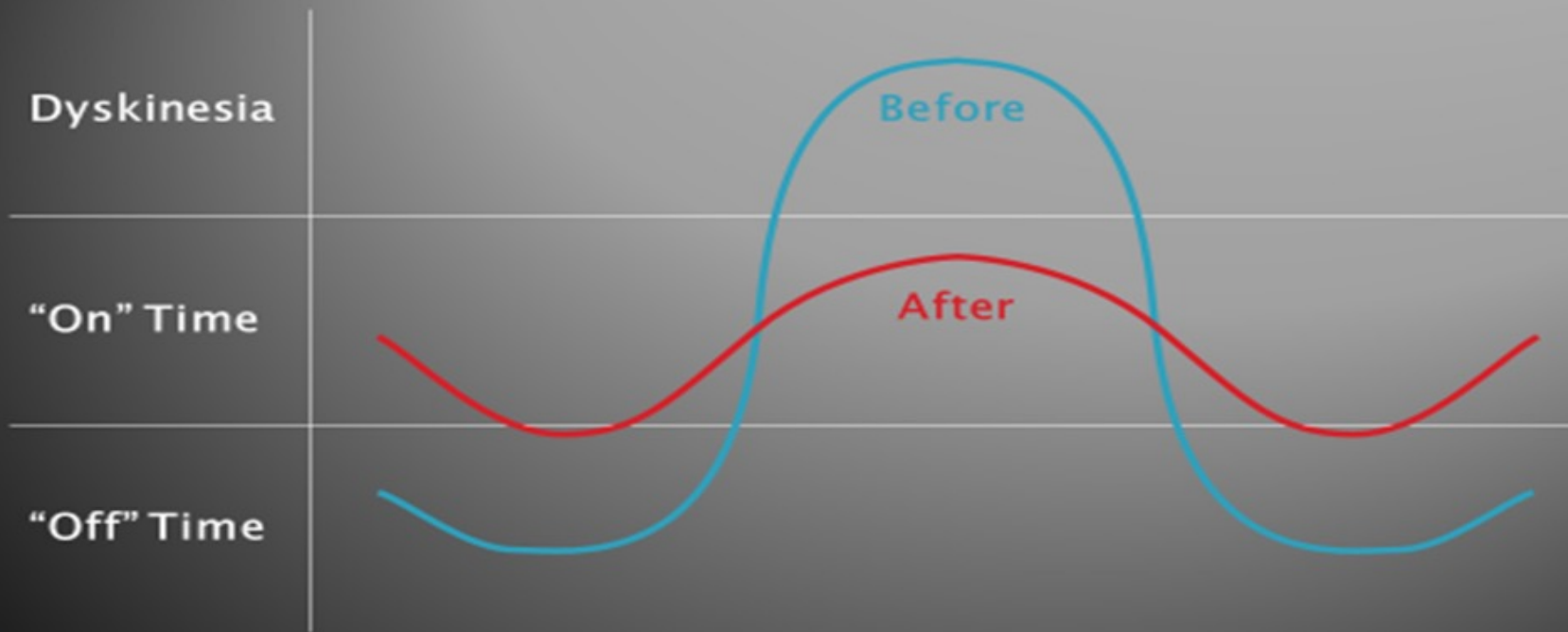
Selection Criteria for STN/GPi DBS

- ▣ Idiopathic Parkinson's Disease / Dystonia
- ▣ No significant comorbidities
- ▣ No severe depression, psychosis or cognitive impairment
- ▣ Troublesome symptoms despite optimal pharmacological management
 - (on/off fluctuations, dyskinesia, tremor)
 - Disabling side effects related to medications
 - Gpi = globus palidus intermedius

DBS – Candidate Selection

- ▣ 1. Dopamine challenge (not applicable for ET)
 - If tremor predominant – may see minimal improvement in tremor
- ▣ 2. Neuropsychological evaluation
- ▣ 3. MRI of brain – DBS protocol
- ▣ 4. Referral to neurosurgery
- ▣ 5. Anatomical brain targeting (STN v GPI for PD, Vim for ET)

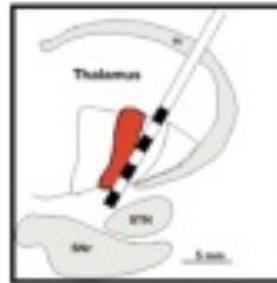
Benefits of DBS: Mobility



Anatomical Targets

DBS ANATOMICAL TARGETS

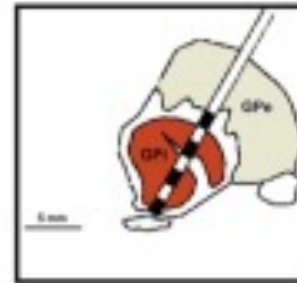
Target Sites for DBS Therapy



Vim Thalamus:
Essential Tremor



Subthalamic Nucleus:
Parkinson's disease
and Dystonia



Globus Pallidus:
Parkinson's disease
and Dystonia

Challenge v Opportunity

- ▣ The advent of directional leads is a recent technological advance and has the potential to expand the capabilities of DBS. The ability to more accurately target and precisely control stimulation can theoretically improve the effectiveness of DBS while avoiding side effects, given the novelty of this approach there is currently no firm clinical evidence.

- ▣ Directional Leads for Deep Brain Stimulation: Opportunities and Challenges. Schupbach, et al. *Movement Disorders*, Vol. 32, No. 10, 2017

Awake v Asleep

- ▣ Advancements in neuroimaging have led to a trend toward direct, image-based targeting under general anesthesia without the use of microelectrode recording (MER) or intraoperative test stimulation, also referred to as “asleep” deep brain stimulation (DBS) surgery. Asleep DBS, utilizing imaging in the form of intraoperative computed tomography (iCT) or magnetic resonance imaging (iMRI), has demonstrated reliable targeting accuracy of DBS leads implanted within the globus pallidus and subthalamic nucleus while also improving clinical outcomes in patients with Parkinson’s disease.
- ▣ Currently studies provide evidence that asleep DBS techniques are highly accurate and confer at least equal efficacy in terms of outcomes in comparison to awake surgery. To date, no randomized trials comparing the two techniques have been performed.

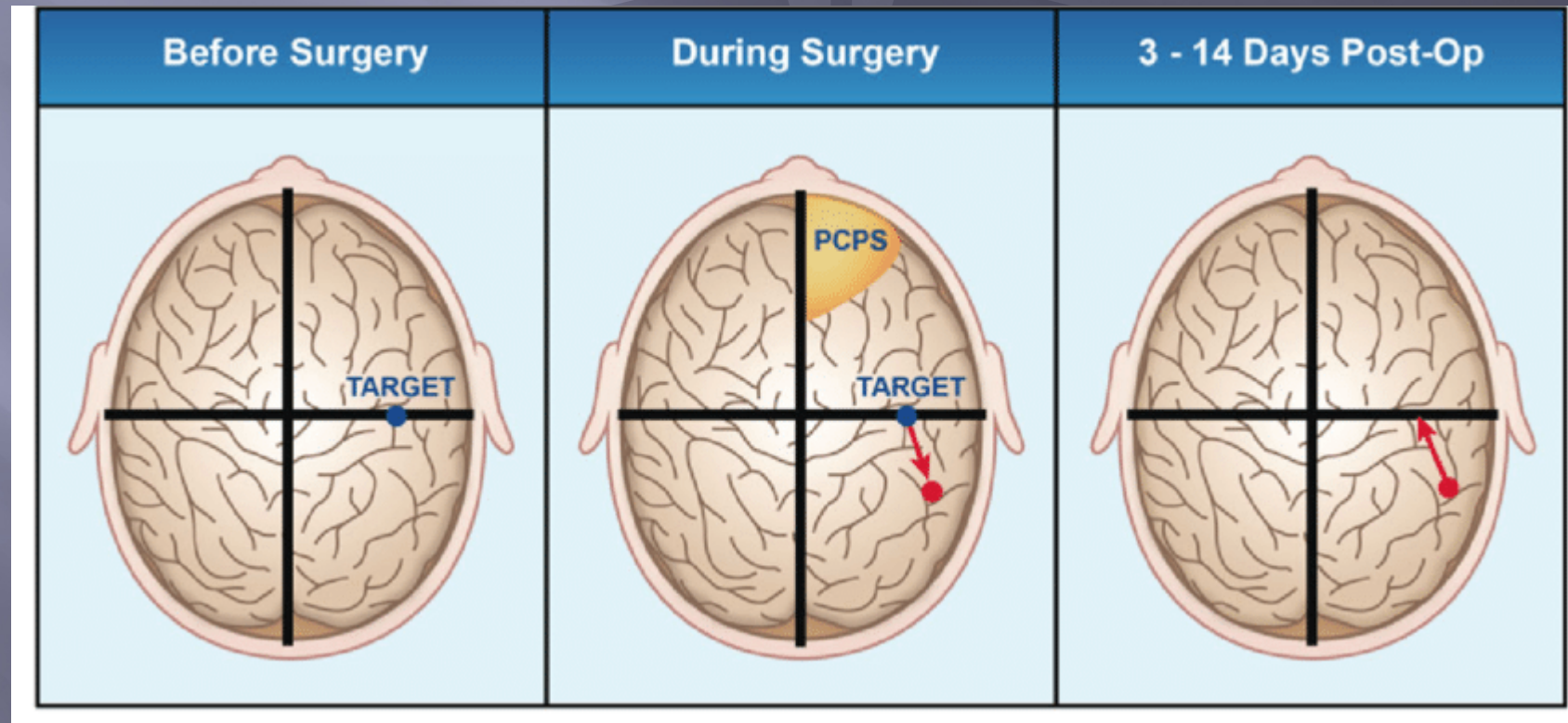
• <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5789348/>

DBS Radiographic Imaging

- ▣ MR imaging has made tremendous progress in recent years
- ▣ MR/CT high resolution imaging fusion has enabled improved visualization of target structure for stereotactic planning
- ▣ Precise contact placement translates to good clinical response

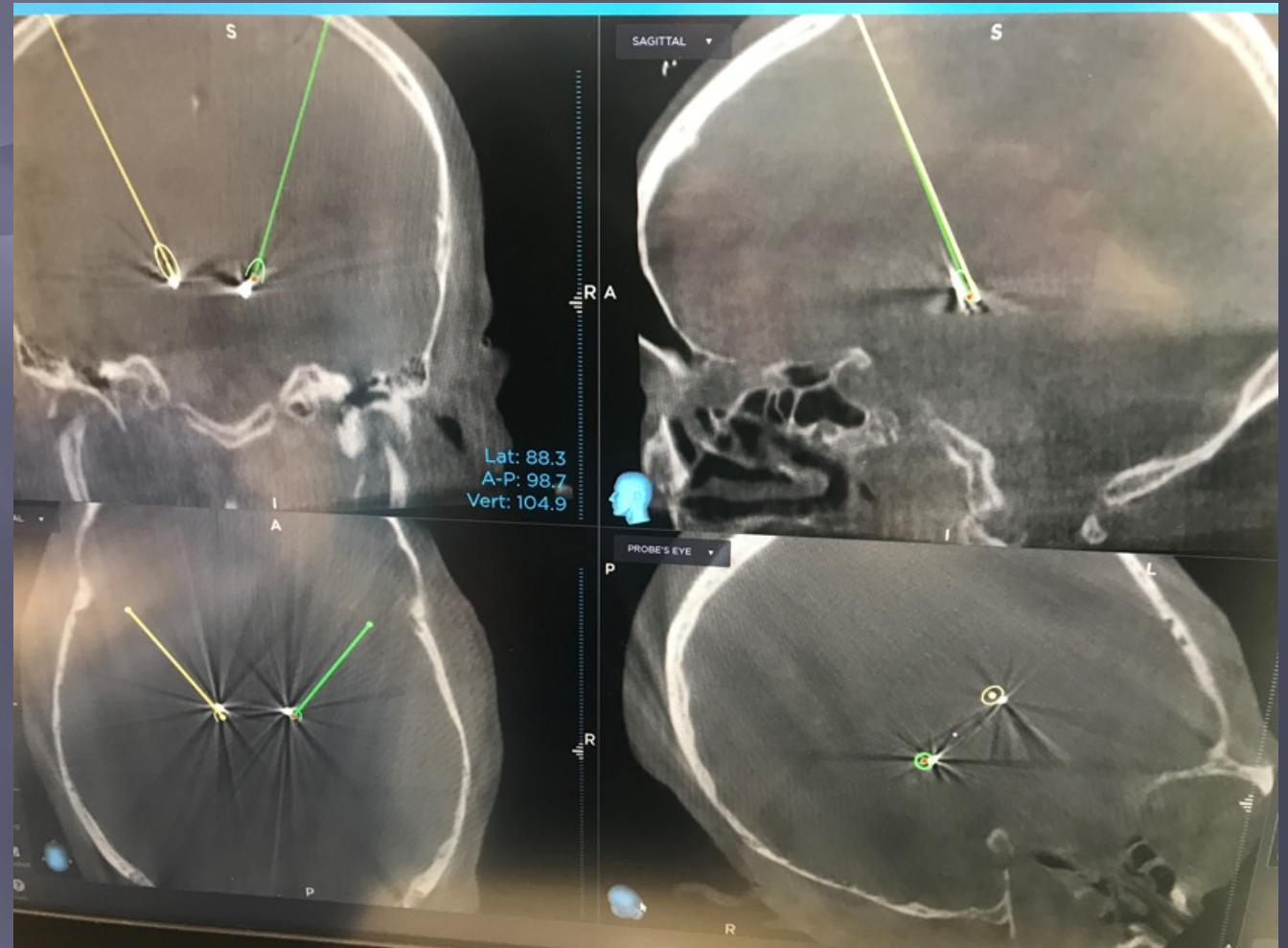
Imaging Accuracy

- Brain shift due to intraoperative CSF leakage:

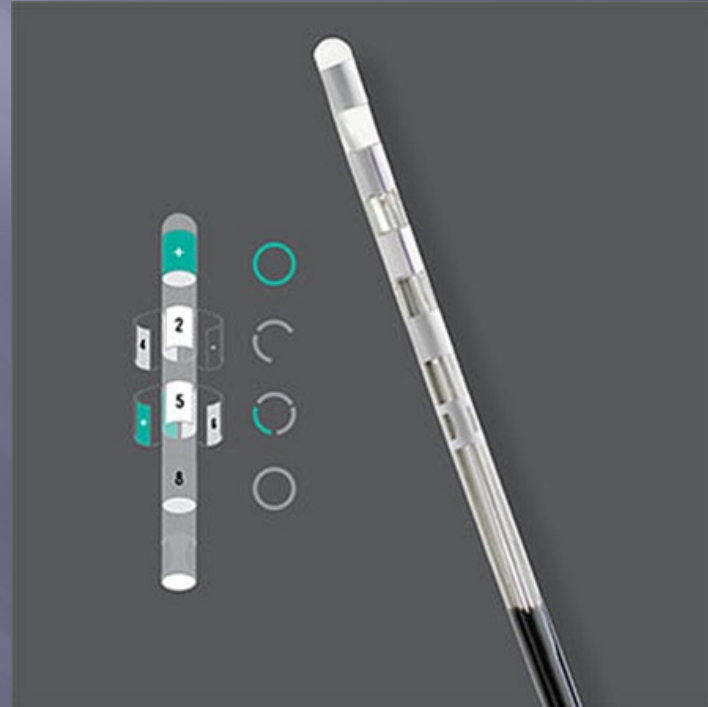


Post-op Imaging

O-Arm images fused to Postoperative MRI and CT scan of DBS electrodes in bilateral subthalamic nucleus in patient with tremor-dominant Parkinson's disease.



Electrodes



Boston Scientific System



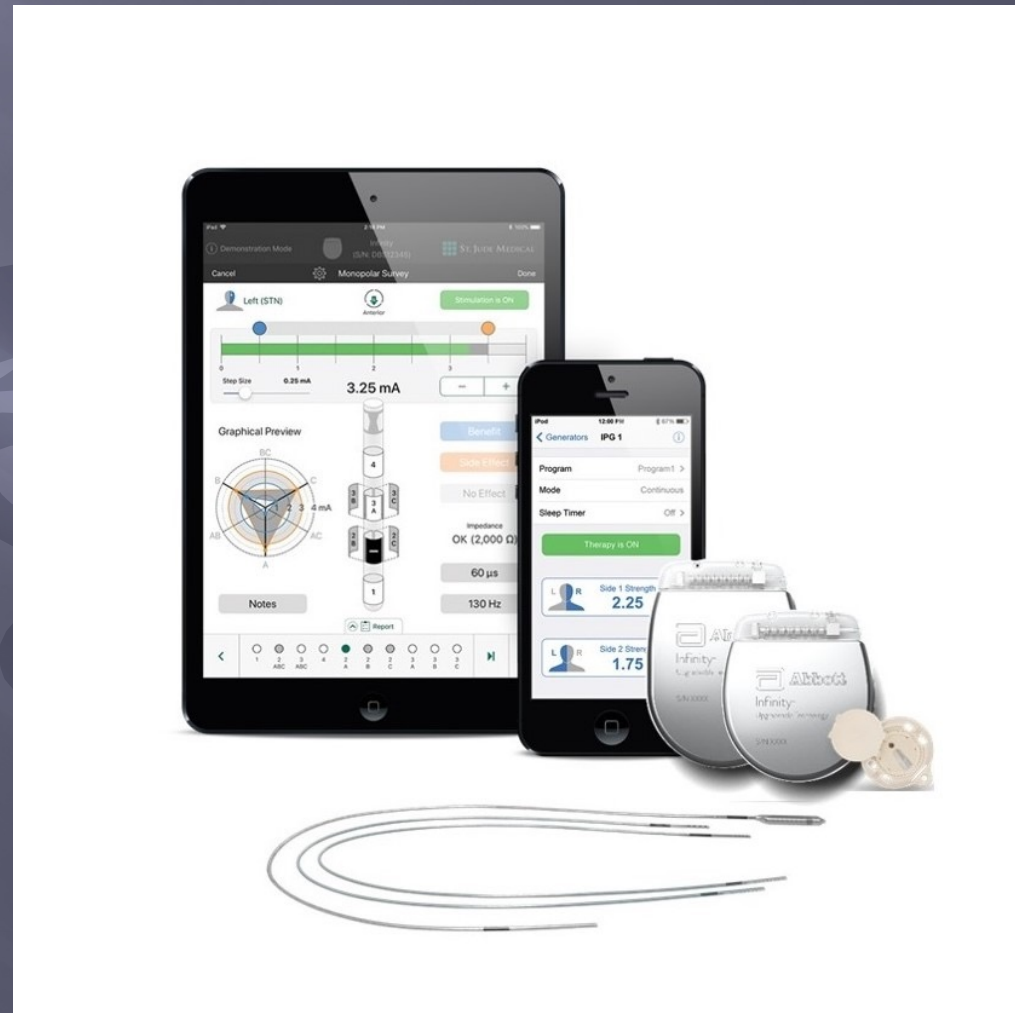
The IPGs come equipped with Bluetooth® connectivity for greater data transfer speed, longer telemetry and unencumbered DBS programming. The rechargeable batteries offer a lifespan of at least 15 years to lessen the risks associated with repeat surgeries.

Intuitive controls and a broad telemetry range simplify the patient experience.

Wireless Charging System
Many patients find that charging the completely wireless system can be completed in as little as one hour a week

Abbott DBS System

- 1st with directional leads
- Patients can download an app on phone
- Allows **virtual programming**
- No rechargeable battery



Medtronic System



SureTune™ 4 software patient-specific anatomy, lead location and orientation can be pulled into the DBS Clinician Programmer.



The only complete DBS system with sensing, directionality, and visual programming giving you access to data-driven insights you need to make informed decisions.



The first-of-its-kind sensing-enabled directional leads with benefits of directionality plus the power of sensing.

Improved Technology



4 = full-ring contact

3 = contact with equally spaced segments

2 = contact with equally spaced segments

1 = full-ring contact

DBS Programming

- ▣ Stimulation of single lead segments may result in an improved therapeutic window
- ▣ Threshold for achieving therapeutic benefit may be lower with the optimal direction stimulation (less energy=longer battery life)
- ▣ To obtain optimal clinical effect, certain stimulation parameters have been determined empirically for STN-DBS.

Typical Side Effects - DBS

- ▣ Most DBS side effects result from current spreading into brain regions bordering target.
- ▣ STN is a small, ovoid structure close to internal capsule, substantia nigra, red nucleus, 3rd cranial nerve
- ▣ Reports suggest that the most effective contacts to relieve PD symptoms are in the dorso-lateral, sensorimotor aspect of the STN

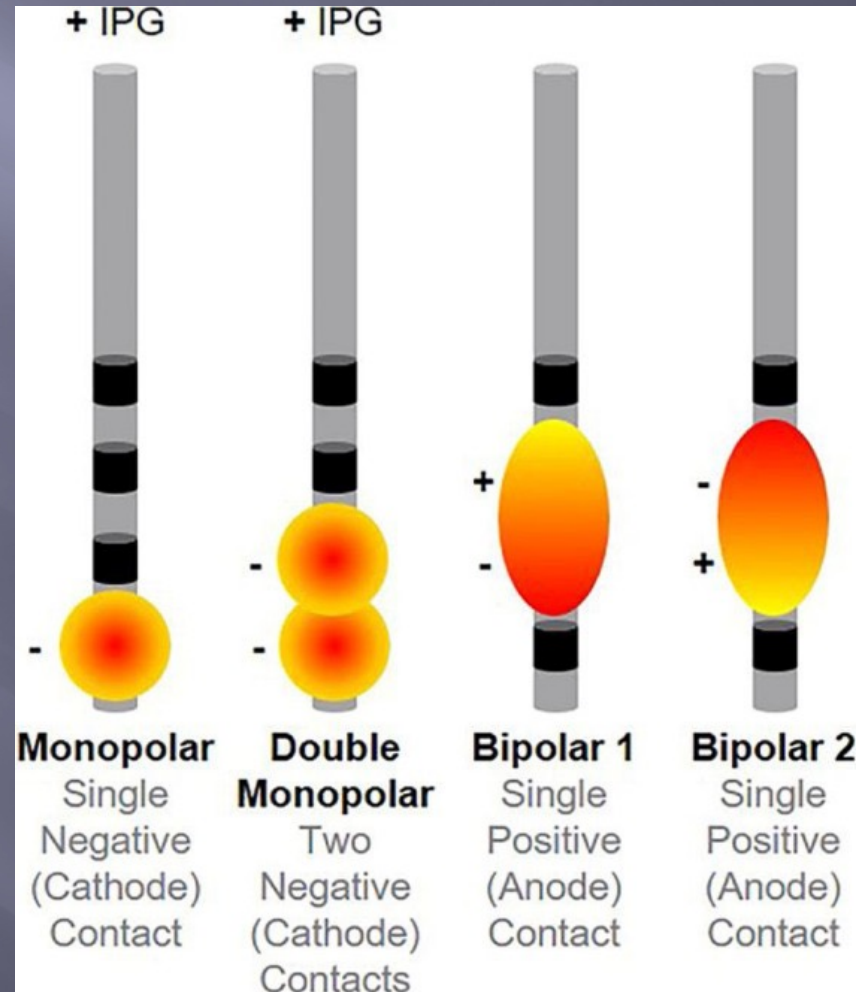
Typical DBS Side Effects

- ▣ Spastic muscle contractions “facial pulling,” current spreading into internal capsule (IC) lateral and anterior to STN
- ▣ Gaze deviation
- ▣ Paresthesia – stimulation of medial lemniscus; usually transient but if persistent, dorsal contact may be better.
- ▣ Speech impairment: frequently occurred during the initial programming
- ▣ Dyskinesia – usually indicate a good outcome and electrode placement
- ▣ Gait impairment/postural instability – may get better, may get worse.

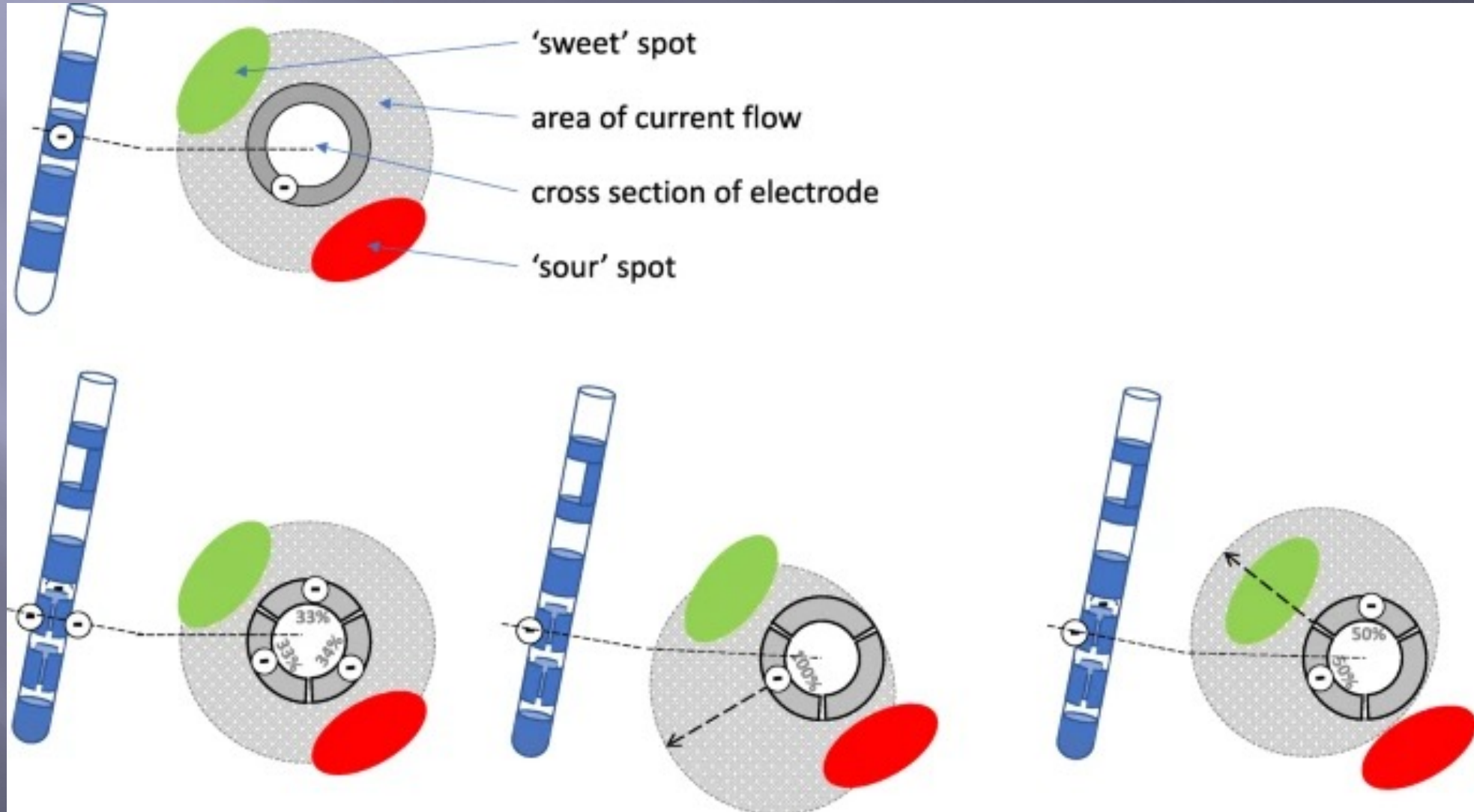
DBS Programming Parameters

- ▣ There are general guidelines available for programming but there are no clear, validated and established programming protocols.
- ▣ The electrical field delivered through the DBS contact is spherical with intensity of field decreasing in proportion to distance from the electrode.
- ▣ The directional lead technology makes it possible to steer different shapes of current at the stimulation contact instead of the conventional spherical shape of current.
- ▣ Primarily, this technology permits the steering of current to the desired areas and avoids unintended stimulation to neighboring areas.

Electrode Configurations



Directional DBS



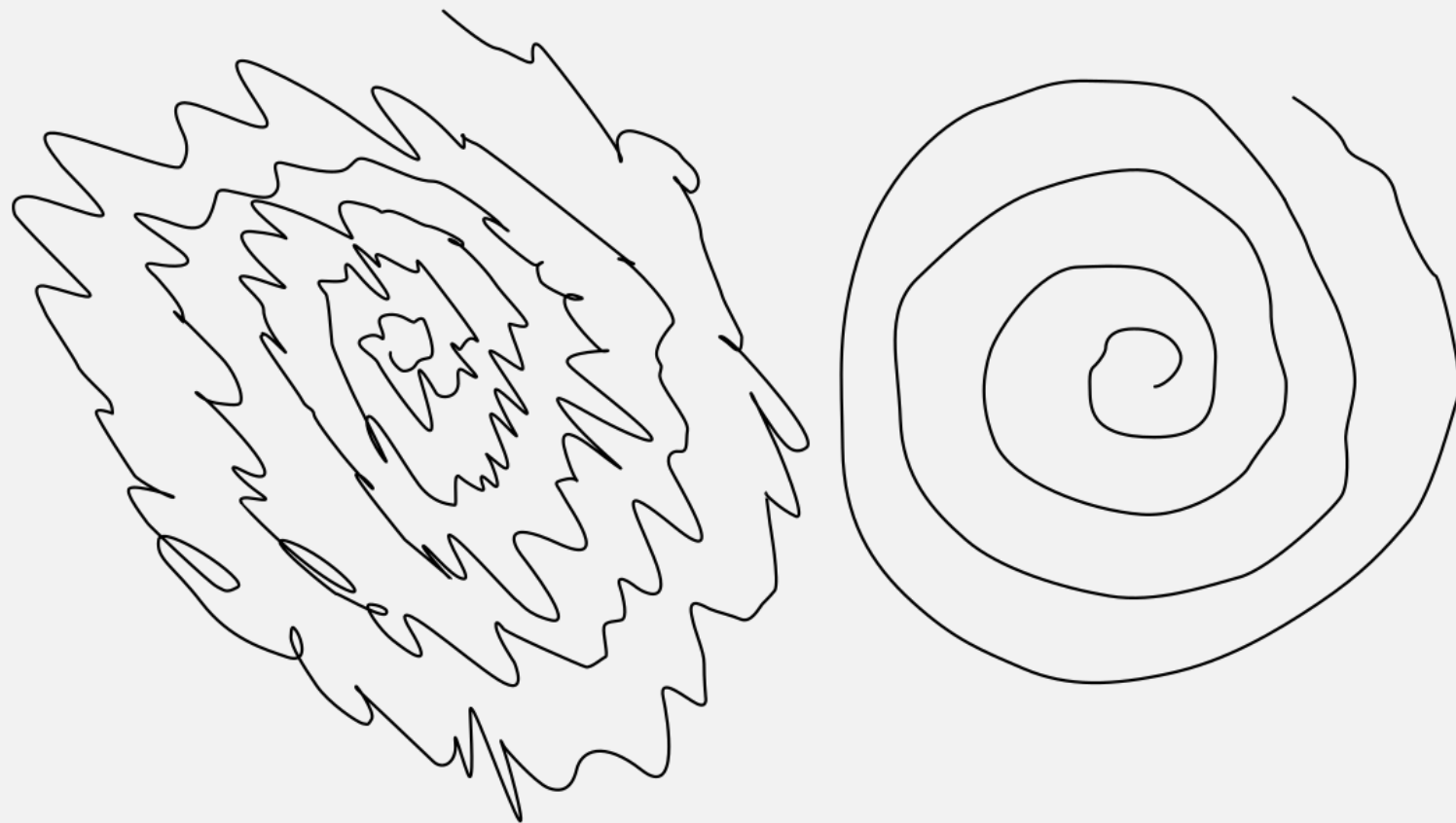
Selection Criteria for Vim (ventralis intermedius)

- ▣ Essential Tremor: the most common form of tremor
 - Involuntary, rhythmic muscle contraction
 - Common movement disorder-usually affects hands but can occur in arms, head, vocal cords, torso, legs
 - May be intermittent or constant
 - Generally affects men and women equally

Essential Tremor

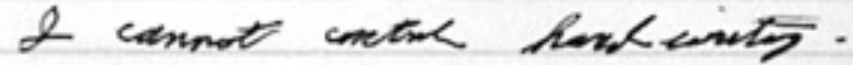
- ▣ Clinical criteria for essential tremor
 - Definite essential tremor
 - ▣ postural tremor of moderate amplitude is present in at least one arm
 - ▣ Tremor of moderate amplitude, present in at least one arm during at least four tasks:
 - pouring water
 - using a spoon to drink water
 - drinking water
 - finger-to-nose movements
 - drawing a spiral.

Archimedes Spiral

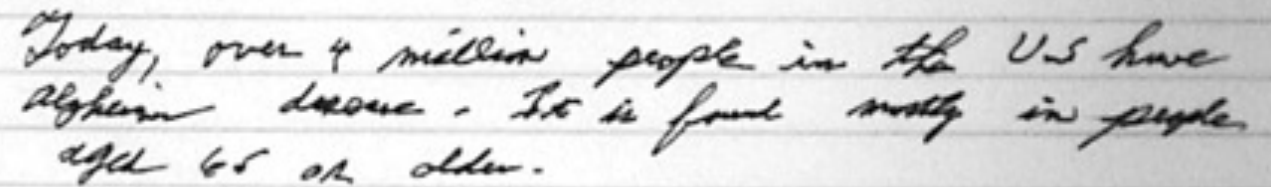


Tremor Comparison

Parkinson's disease

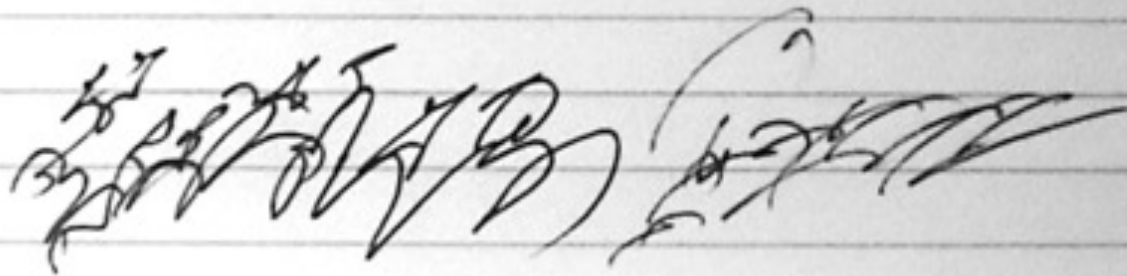


I cannot control handwriting.



Today, over 4 million people in the US have Alzheimer disease. It is found mostly in people aged 65 or older.

Essential Tremor



Handwritten signature showing significant tremor, characterized by large, irregular, and shaky loops and strokes.

Essential Tremor

- ▣ Pharmacological treatment of ET remains unsatisfactory
- ▣ Propranolol, Primidone

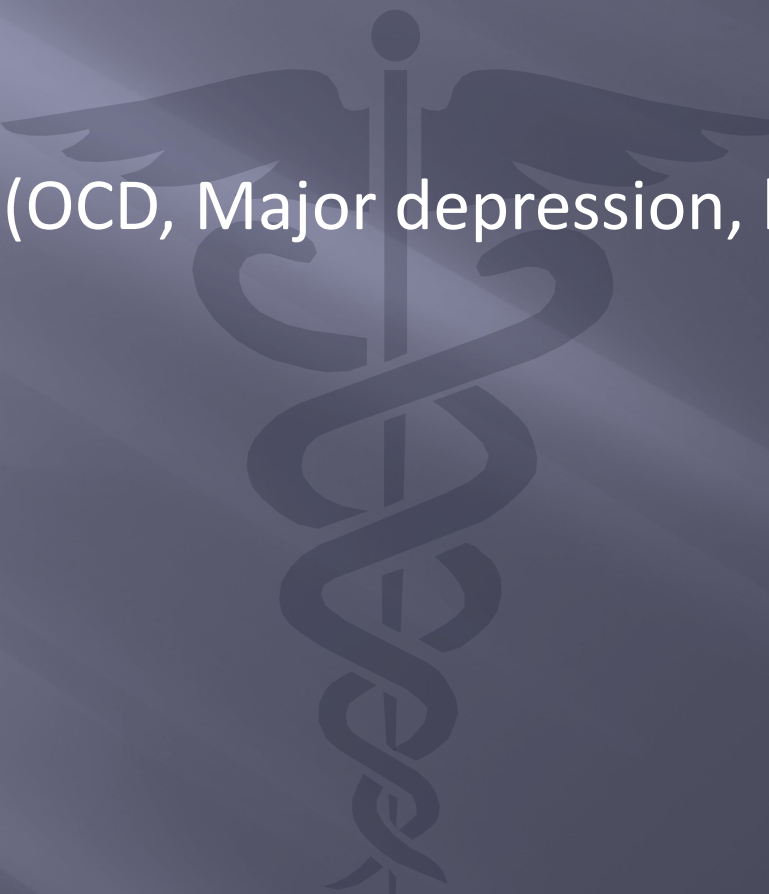
Essential Tremor

- ▣ Most common involuntary movement disorder seen in clinical practice
- ▣ Differential diagnosis is mainly clinical based on the distinction at rest, postural and intention, activation and frequency
- ▣ Essential tremor and the tremor of Parkinson's disease are the most common tremors encountered in clinical practice
 - Action tremor includes postural, isometric, and kinetic tremor
 - Usually bilateral

DBS: LOOKING AHEAD

- ▣ Challenges:
- ▣ Meeting the needs of an aging population and expand indications for DBS, including depression and Alzheimer Disease
- ▣ Biomarkers that predict clinical response
- ▣ Stimulation parameter settings
- ▣ Early intervention is more beneficial than late

Other Indications

- ▣ Epilepsy
 - ▣ Huntington's disease
 - ▣ Psychiatric disorders (OCD, Major depression, bipolar disorder)
 - ▣ Tourette Syndrome
 - ▣ Alzheimer disease
- 

Key Points

- ▣ There is no benefit in waiting when diagnosis is confirmed and symptoms in PD are levodopa responsive
- ▣ DBS is opening new therapeutic possibilities
- ▣ Enabling neuroscientists to obtain direct measures of cellular activity
- ▣ Mechanisms of action of DBS at the cell, molecular and systems level are poorly understood and much work remains to be done