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Parkinson's Disease

A message of hope

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Disclosures

- I’ve consulted for compensation for Medtronics, Boston Scientific, and Abbott DBS. I’ve received research funding and/or salary support from the NINDS, NIA, NIMH, Parkinson’s Foundation, American Parkinson’s Foundation of America, Parkinson’s Study Group, and the Michael J Fox Foundation.

Main points

- There is more hope for Parkinson's disease than ever before
  - better understanding
  - better treatments
  - treating not just Parkinson's but *your* Parkinson's

What is Parkinson's Disease?

- What's a disease?
  - A disease is a collection of symptoms that can be traced to a cause
- Parkinson's disease is not currently a disease in practice
  - Parkinson's is a syndrome
  - It is a clinical diagnosis
- Why does this matter?
  - Syndromes have symptomatic treatments
  - Diseases have cures
  - e.g .Consumption vs. tuberculosis, dropsy versus edema from congestive heart failure

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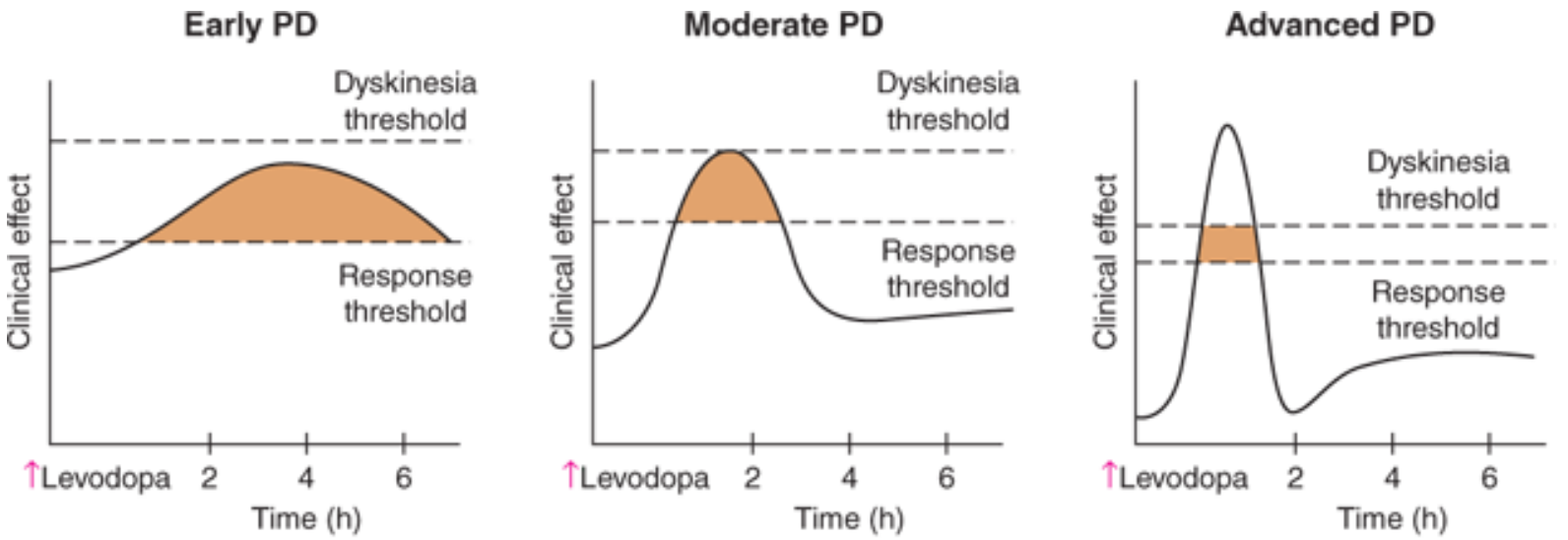
Parkinson's syndrome

Recognizing Parkinson's disease

- Right now treating PD is first recognizing PD
- Cardinal features of PD:
  - Motor:
    - Rest tremor
    - Bradykinesia
    - Rigidity
    - Balance problems

How do we treat Parkinson's syndrome?

- medications are symptomatic.
- They do not have an impact on disease course.
- There are two caveats:
  - Being on medication can allow you to remain more active, which will slow progression
  - Being on medication can allow you to avoid falls



Source: D. L. Kasper, A. S. Fauci, S. L. Hauser, D. L. Longo, J. L. Jameson, J. Loscalzo: Harrison's Principles of Internal Medicine, 19th Edition.
www.accessmedicine.com

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Parkinson's disease

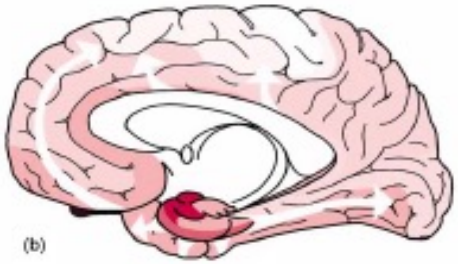
Parkinson's disease

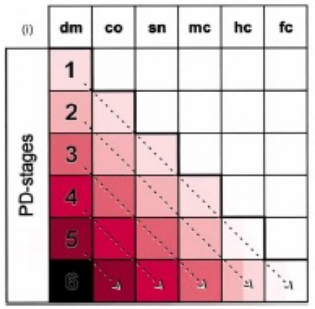
- At least three ways to think of Parkinson's disease
  - A disease of protein accumulation
  - A genetic disease
  - An inflammatory disease

Heiko Braak et al. Staging of brain pathology related to sporadic Parkinson's disease. Neurobiology of Aging. 2003; 24:197-211

Parkinson's disease: a proteinopathy

- What underlies the disease?
- Accumulation of an abnormally folded protein: alpha synuclein
- Accumulation starts in two places simultaneously
  - Olfactory bulb
  - Medulla
- Gradually involves adjacent areas





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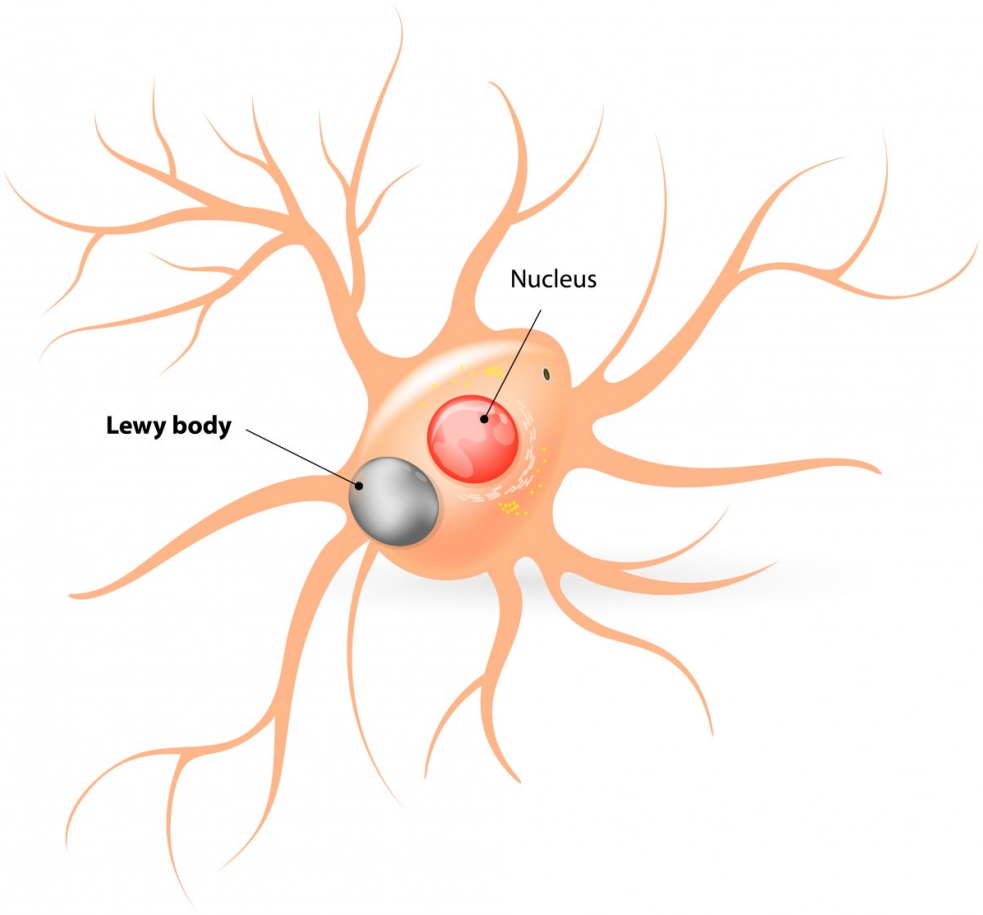
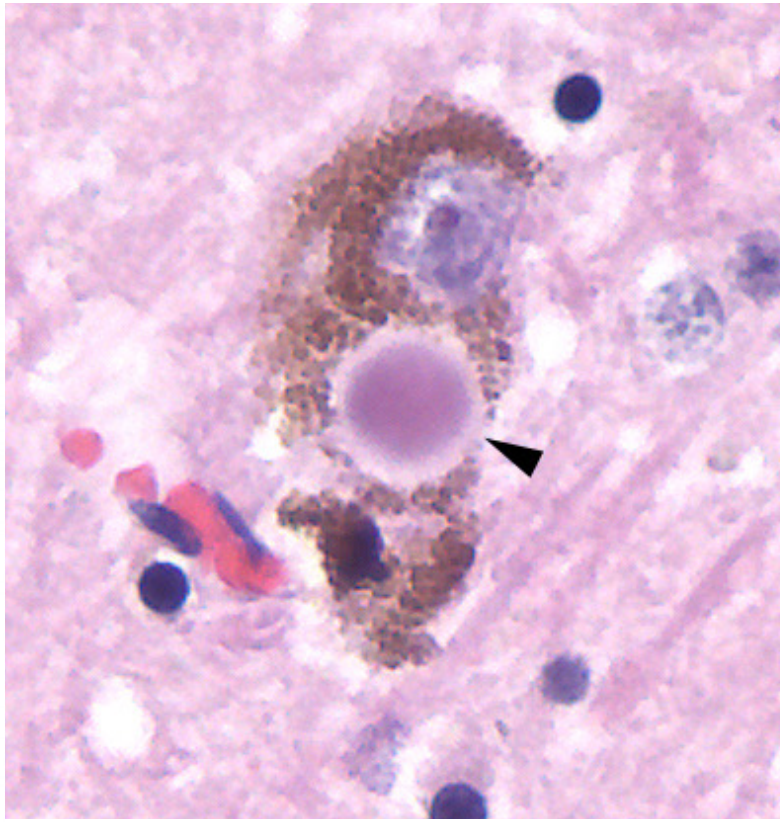

Nucleus
Lewy body



α-synuclein seed amplification: a cross-sectional study of the PPMI

- PPMI: large registry of clinical and biomarker data: 33 clinical sites, 11 countries, 1,400 participants
- 1123 participants from 2010 to 2019: 545 with PD, 163 controls, 51 prodromal, 310 carriers
- Sensitivity for Parkinson's disease was 88%
- sensitivity in sporadic Parkinson's disease with typical olfactory deficit was 99%
- Lower in subgroups including LRRK2 Parkinson's disease at 68%
- sporadic Parkinson's disease without olfactory deficit at 78%
- LRRK2 variant and normal olfaction had an even lower α-synuclein SAA positivity rate 35%

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Parkinson's disease

as an inflammatory disease

Overlap with Autoimmune

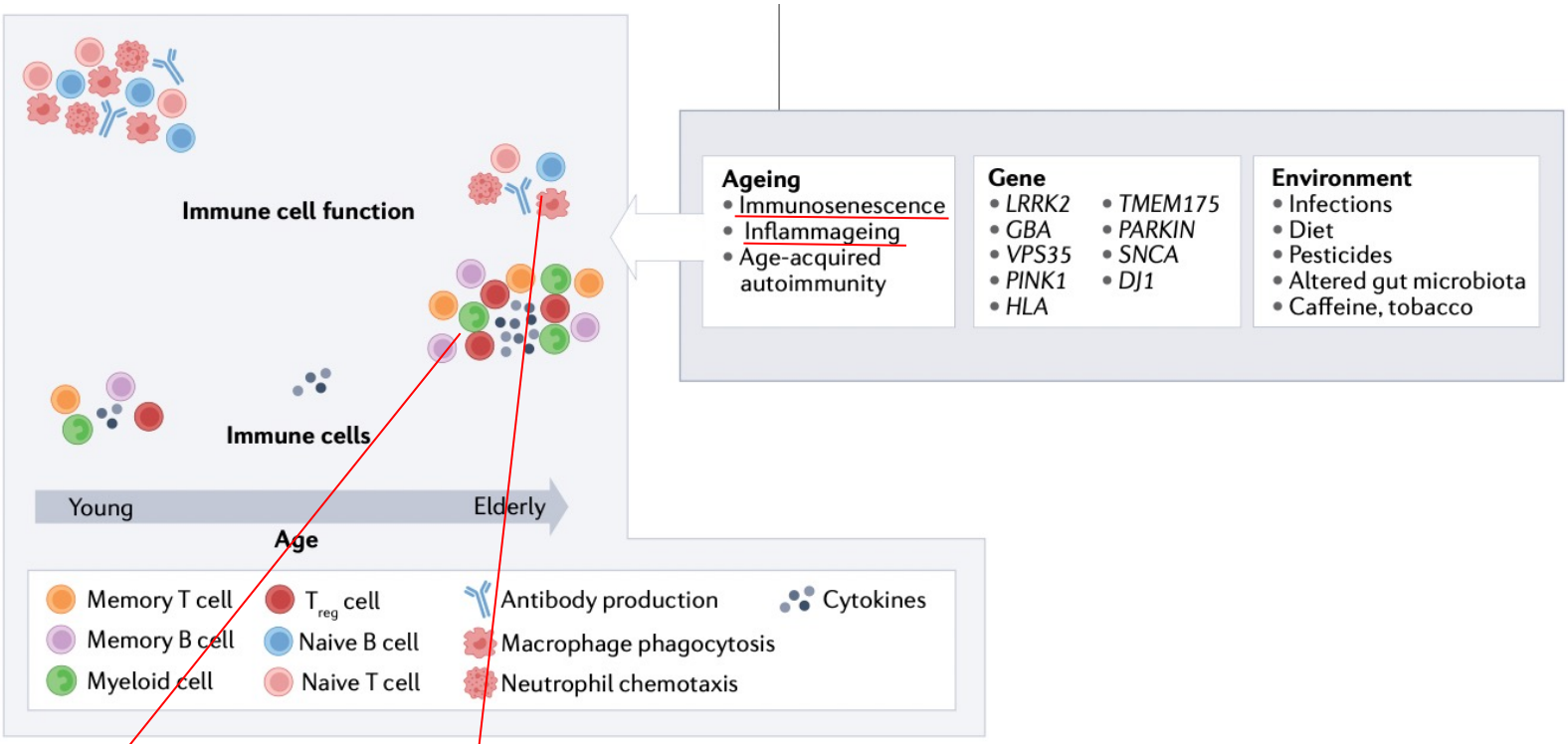
- Patients with autoimmune disease have a 33% increased risk of developing PD
- Gene analyses identified 17 shared loci between PD & 7 autoimmune diseases
- Both *GBA* and *LRRK2* affect inflammation and immune function

PD as an inflammatory disorder

- PET studies have shown that microglia are activated early in the PD disease process
- Neuro-inflammation & immune dysfunction may be responsible for the non-motor symptoms of PD (which tend to occur in the prodromal phase)
  - GI dysfunction, sleep disorders, etc

anti-inflammatories

- In animal models, sodium salicylate, aspirin & meloxicam protect against MPTP-induced dopaminergic neurotoxicity
- pts w/ regular use of non-aspirin NSAIDs (≥2 tablets per day) had a lower risk of developing PD relative to non-regular users
- Follow up studies indicated that ibuprofen had a slightly protective effect on risk for PD
- Possible difference of effect between males & females



Accumulation of memory cells + Decreased # naïve B & T cells + Reduced B & T cell receptor diversity & sensitivity to stimuli = Impaired adaptive Immune system

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Parkinson's disease

as a genetic disease

Article | Open access | Published: 02 October 2023

Mitochondrial DNA damage triggers spread of Parkinson's disease-like pathology

Emilie Tresse, Joana Marturia-Navarro, Wei Qi Guinevere Sew, Marina Cisquella-Serra, Elham Jaberi, Lluis Riera-Ponsati, Natasha Fauerby, Erling Hu, Oliver Kretz, Susana Aznar & Shohreh Issazadeh-Navikas

Molecular Psychiatry (2023) | Cite this article

BACKGROUND: MITOCHONDRIAL DNA

- Genetic variations of mtDNA increase with age and are reported to be associated with PD
- Strong evidence from PD animal models supports the involvement of mitochondrial disturbances including mtDNA packaging

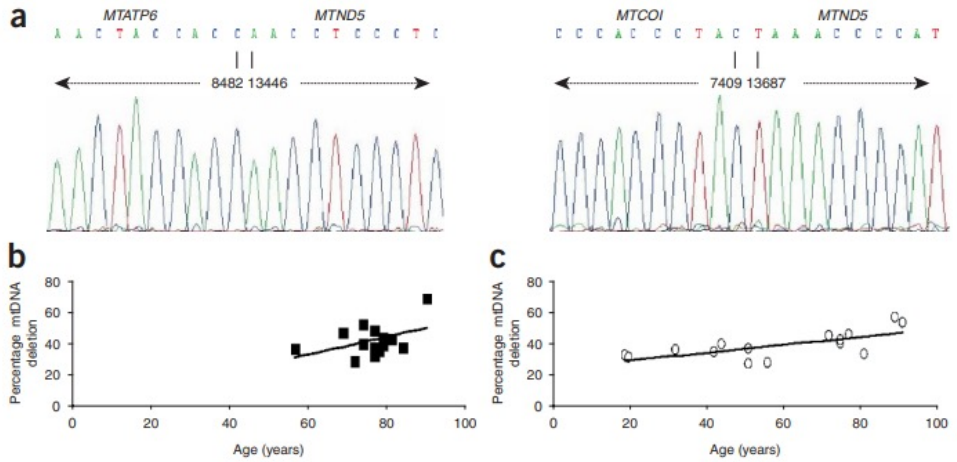

Figure 2 Characterization and quantification of mtDNA deletion in substantia nigra neurons from individuals with Parkinson disease and from age-matched controls. (**a**) Breakpoint sequences of cloned products of mtDNA deletions generated from long-range PCR of individual neurons. Both breakpoints show tandem repeat sequences at the site of the mtDNA deletion, with the left panel illustrating the well-characterized 'common deletion'. (**b**) Levels of deleted mtDNA in collections of 25 individual substantia nigra neurons from individuals with Parkinson disease. The amount of deletion tended to increase with age, but the overall level of deleted mtDNA was high. (**c**) Correlation of level of deletion with age in substantia nigra neurons from control subjects.

BACKGROUND: PD & MITOCHONDRIA

Gene	Mechanism	Complex I	Complex II	Complex III	Complex IV	Complex V	References
PRKN and PINK1	Protein turnover	+	+	+	+	+	Vincow et al., 2013
	Translation derepression	+		+		+	Gehrke et al., 2015
PINK1	Phosphorylation	+					Morais et al., 2014
PARK7	Chaperone	+			+	+	Hayashi et al., 2009; Heo et al., 2012; Chen et al., 2019
PLA2G6	Ceramide metabolism	+	+				Kinghorn et al., 2015
GBA	Unknown, probably regulating mitophagy, GlcCer metabolism, and NAD + production	+	+	+			Osellame et al., 2013; Schöndorf et al., 2018
LRRK2	Unknown, probably regulating mitophagy	+	+		+		Mortiboys et al., 2010
SNCA	Mutant monomers or oligomers	+				+	Chinta et al., 2010; Reeve et al., 2015; Ludtmann et al., 2018
	Fibril-induced Lewy body formation	+	+			+	Mahul-Mellier et al., 2020
CHCHD2	Chaperone				+		Aras et al., 2015; Meng et al., 2017
	Transcription factor				+		Aras et al., 2015
UQCRC1	cIII core subunits			+			Unni et al., 2019; Lin et al., 2020

" + " indicates evidence of direct or indirect interactions but the exact involved subunits are still unclear.

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LRRK2

- Most common cause of familial PD; ~1% of sporadic cases
- Member of family ofProteins that detect & respond to cellular stress by regulating cell death & immune system activation
- LRRK2 is recruited to ruptured lysosomal membranes & induces lysosomal tubule formation
  - Lysosomal tubules critical for phagocytosis & antigen presentation
- LRRK2 expression ↑ in response to microbial pathogens

GBA

- *GBA* encodes 'glucocerebrosidase'
- *GBA* mutations most common genetic risk factor for PD
- *GBA* mutations cause cell inflammation
- Induced macrophages from individuals with GBA mutations showed ↑ pro-inflammatory cytokines (TNF, IL-6, IL-1B)
- Enzymatic GBA activity significantly ↓ in monocytes from patients w/ idiopathic PD & GBA-associated PD

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Parkinson's disease

Treating *your* Parkinson's disease

What are we trying?

- New treatments
- Preventative therapies
  - Anti a-synuclein therapies
  - exercise
- Surgical therapies
  - Deep Brain Stimulation
  - Focused ultrasound
  - Dopamine pumps
- Stem Cell therapies
- Gene based therapies
- Personalized assessment

Personalized therapy

- Gene-driven treatments
  - Biogen: LUMA
    - small molecule designed to cross the blood-brain barrier and block LRRK2 activity
    - This could restore lysosomal function
    - This could potentially slow Parkinson's progression

Personalized therapy

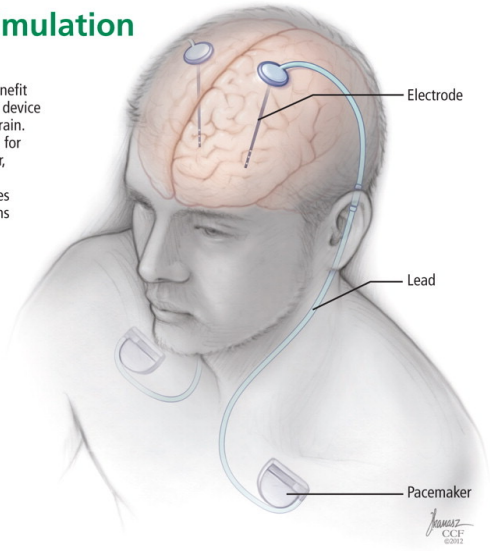
- Gene-driven treatments
  - Bial: Activate
    - BIA 28-6156
    - activator of the enzyme beta-glucocerebrosidase (GCase) for the treatment of patients with Parkinson's disease (PD) who have a mutation in the glucocerebrosidase 1 (GBA1)
    - This could modulate lysosomal function and slow Parkinson's progression

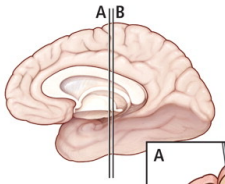
Personalized therapy

Deep brain stimulation

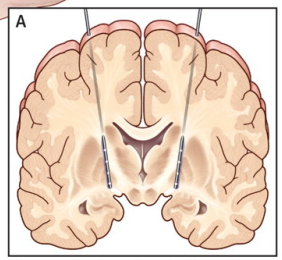
Carefully selected patients may benefit from implantation of a pacemaker device to stimulate precise areas of the brain. This treatment, currently approved for Parkinson disease, essential tremor, primary dystonia, and intractable obsessive-compulsive disorder, does not cure but can improve symptoms and quality of life.

The pacemaker is implanted in the chest, with a lead tunneled beneath the skin of the neck to the scalp and an electrode implanted in the target area of the brain. Batteries last 3–5 years.

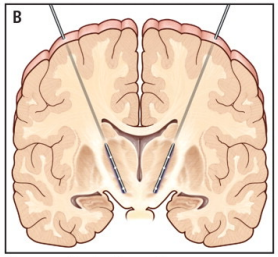




Millimeters matter. The leads are inserted under stereotactic guidance with computed tomography and magnetic resonance imaging, and their location is confirmed by "listening" to brain activity.



Placement for dystonia or Parkinson disease



Placement for Parkinson disease

Medical Illustrator: Joseph Kanasz CCF ©2012

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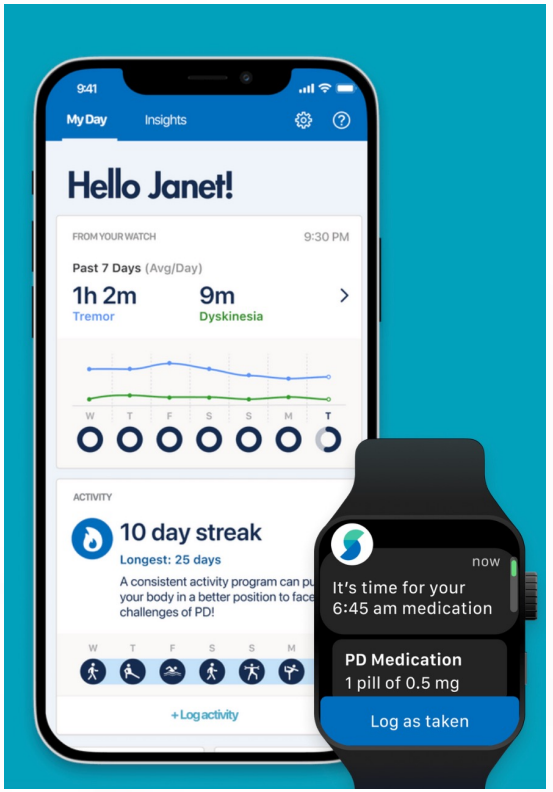
Pre-Op Assessment

PKG Watch

Source: pkghealth.com

StrivePD App



Source: strive.group

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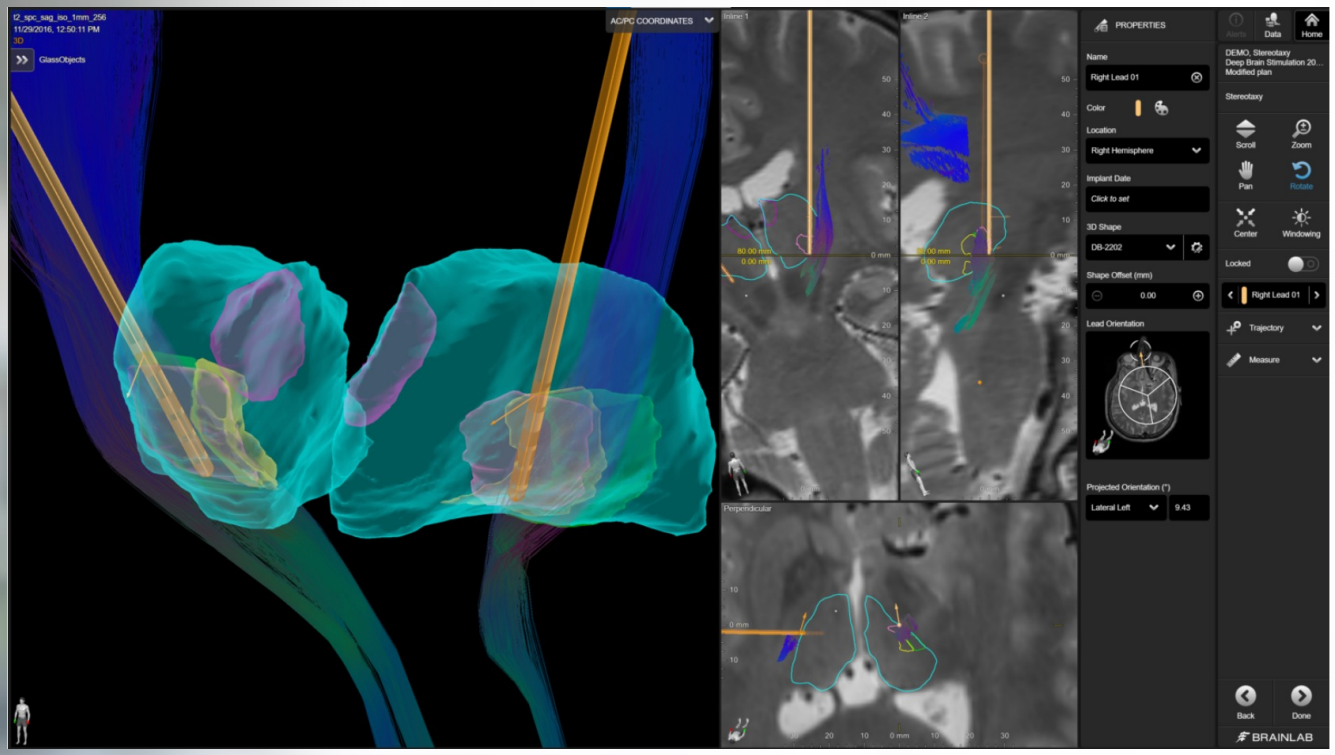
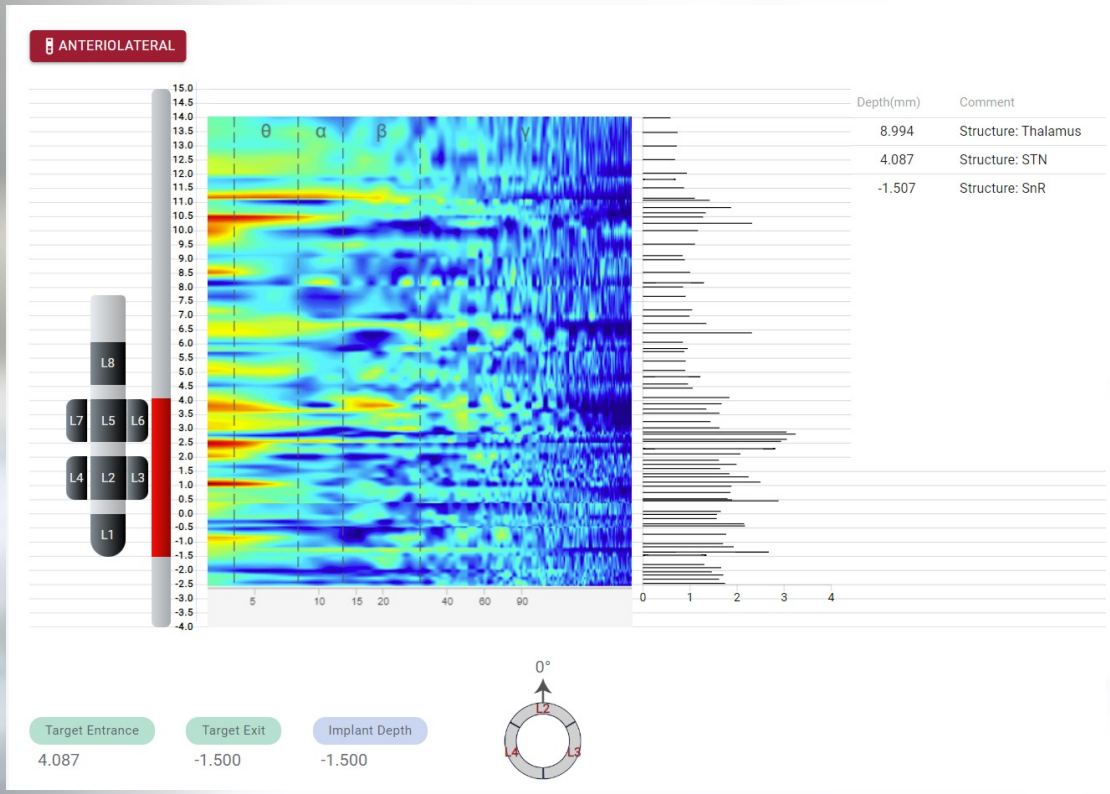
Intra-Op Assessment

Brainlab Anatomical Segmentation



Source: Brainlab.com

Intra-Op Assessment: LFPs



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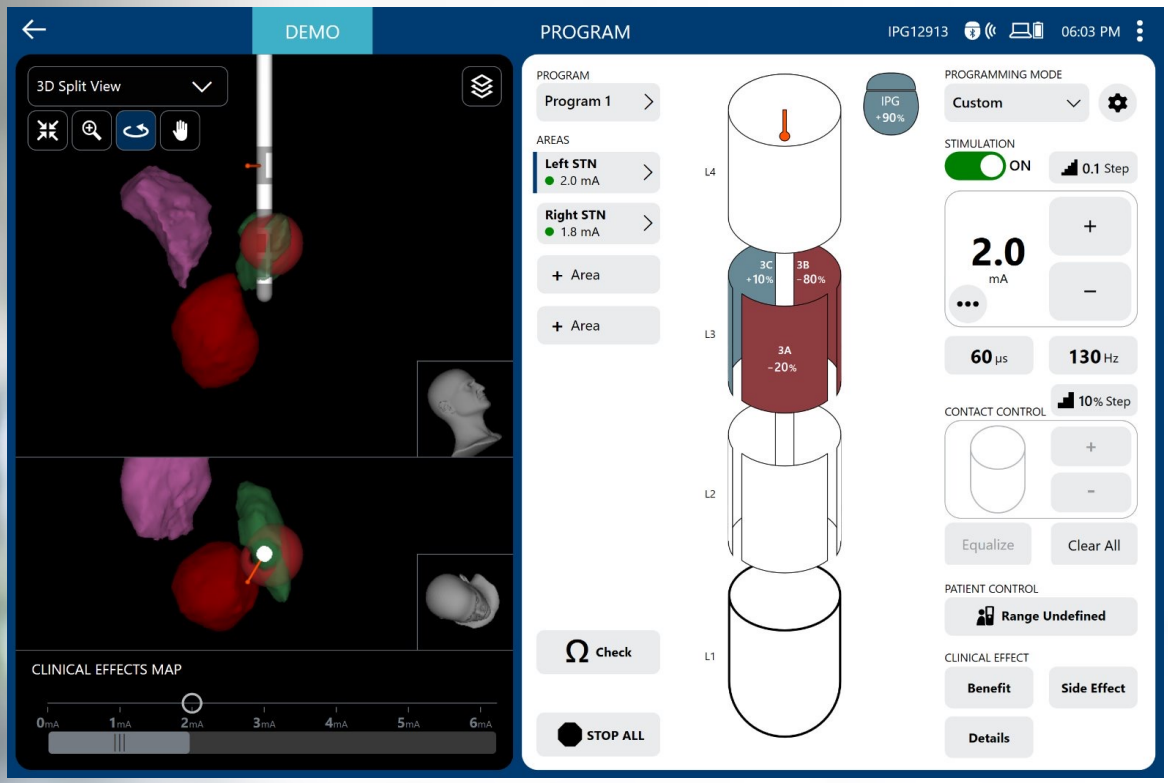
Post-Op Programming

Boston Scientific Stimview



Source: Boston Scientific

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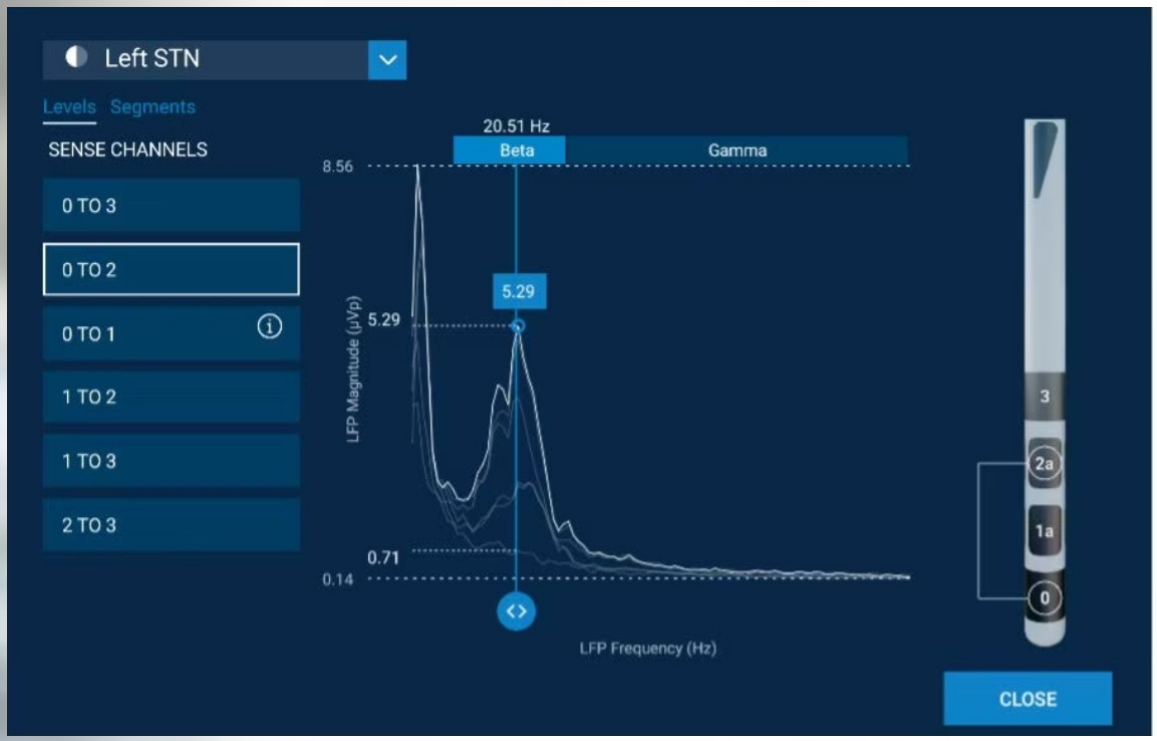
Post-Op Assessment

Medtronic BrainSense Technology



Source: Medtronic.com

What are we trying?

- Cell therapies
  - Bluerock therapeutics (phase 1, 2)
    - MSK-DA01 Cell Therapy
    - surgical transplantation of the dopamine-producing cells into the putamen. Subjects then take medicines to partially suppress their immune system (aimed to prevent the body from rejecting the cells) for 1 year. Assessed for 2 years post-transplant.

Why do I have hope?

- We're better able to see and understand PD than ever before
- We're moving PD from a syndrome to a disease
- Diseases have cures
- We're developing personalized treatments for Parkinson's disease

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Our Team


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MD PhD


Jason Margolesky
MD

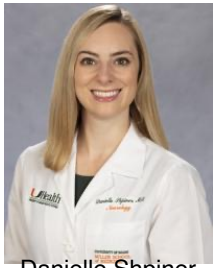

Bonnie Levin PhD


Jonathan Jagid MD


Sarah Marmol
MD


Henry Moore MD


Angela Russell
APRN FNP PhD


Danielle Shpiner
MD


Carlos Singer MD


Victor Riquelme
BSN MBA

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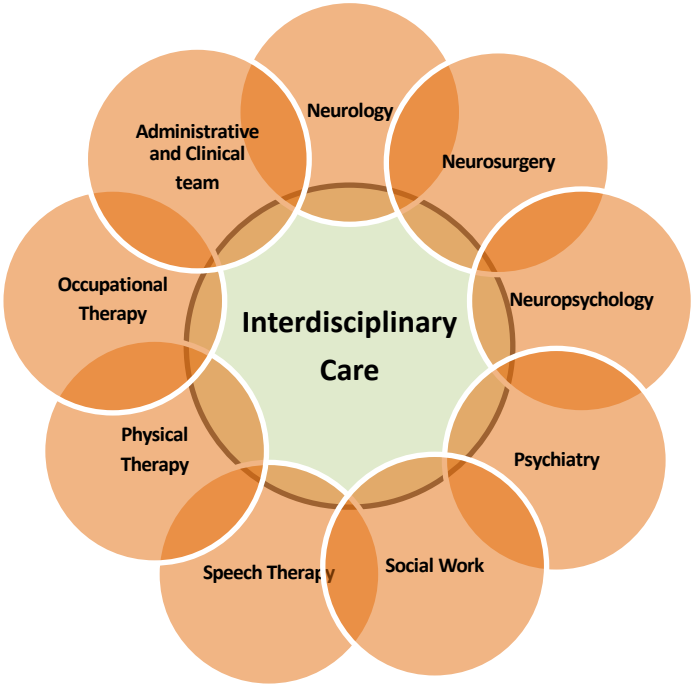
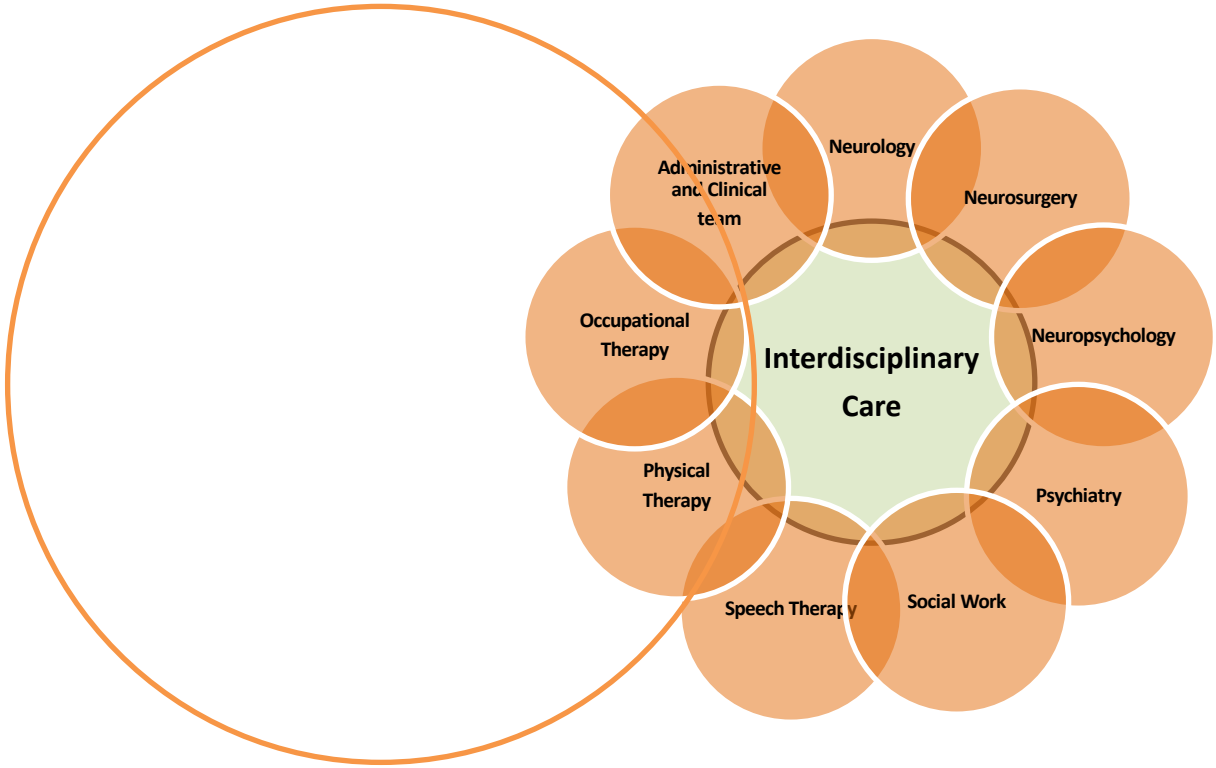
Clinical team



Clinical team



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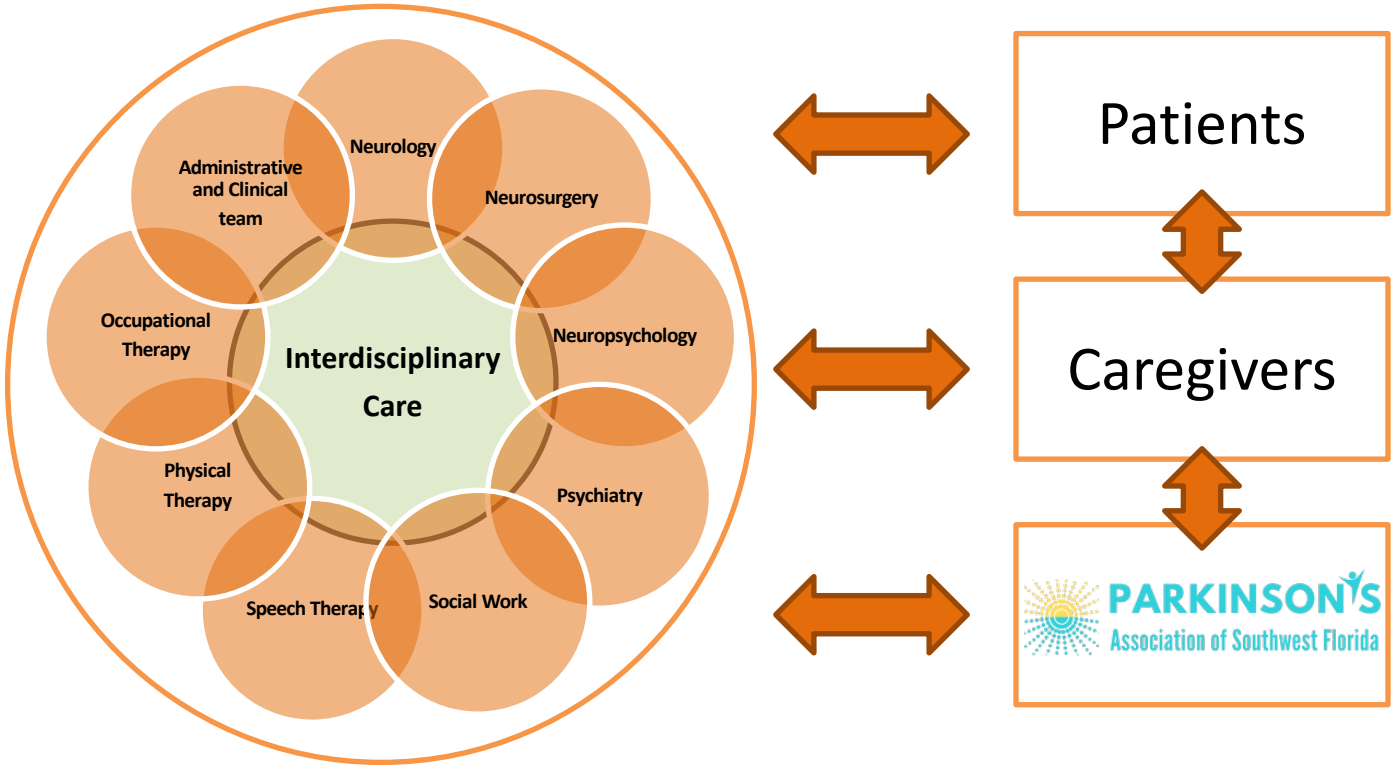

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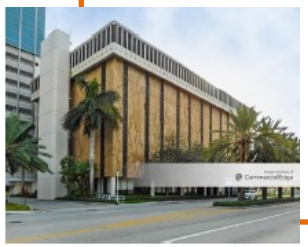
Where we are

Sylvester at Plantation

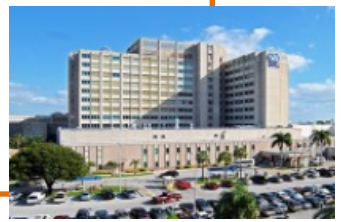


Desai Sethi Medical Center

The Lennar Foundation Medical Center

UHealth at Boca Raton

UHealth at Fort Lauderdale



Bruce Carter VA Medical Center

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