Parkinson's Foundation
CENTER OF EXCELLENCE

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Department of Neurology-
Parkinson's Center of Excellence
DARTMOUTH HITCHCOCK MEDICAL CENTER

DHMC's 2025 Parkinson's Symposium:

New Technologies and Adaptive Treatments

August 1, 2025

Remember:

- **Welcome!**
- **Please silence your phones and devices**
- **Recording in progress**
- **Save questions for Q&A portion**
- **No personal or identifying information**

Save the Date, for our Next Symposium!

Friday April 24, 2026

10:30 – 10:45	**Opening Remarks**	Jillian Carpenter, MHA, CMOM Mary Feldman, DO Stephen Lee, MD, PhD
10:45 – 11:00	**Opportunities and Resources Local to You**	Tamara Berry, FNP, President of Upper Valley Programs for Parkinson's
11:00 – 11:05	Q&A and Discussion: Resources	
11:05 – 11:35	**Nutrition for Parkinson's Disease**	Birgit Humpert, RND, LD
11:35 – 11:45	Q&A and Discussion: Nutrition	
11:45 – 12:00	**Parkinson's Dance Group**	Diane and Richard Caruso PD Dance Group
12:00 – 1:00	Lunch and Exhibit Hall	
1:00 – 1:30	**What To Know When Considering Participating in Clinical Trials**	Rebecca "Becky" Thompson, MD
1:30 – 1:35	Q&A and Discussion: What to Know	
1:35 – 2:05	**Clinical Trials: Disease Modifying Therapies—Stem Cells, Synuclein, and Other Targets**	Stephen Lee, MD
2:05 – 2:10	Q&A and Discussion: Disease Modifying Therapies	
2:10 – 2:40	**Clinical Trial Update: Role of Exercise in Parkinson's Patients**	Mary Feldman, DO
2:40 – 2:45	Q&A and Discussion: Exercise	
2:45 – 3:00	**Tai Chi Quan Exercise**	Katie Weathers, PT
3:00 – 3:20	**Non-Motor Manifestations of Parkinson's Disease**	Corie Crane, DNP
3:20-3:25	Q&A and Discussion: Non-Motor Manifestations	
3:25 – 4:15	**Deep Brain Stimulation and Focused Ultrasound for Parkinson's Disease**	Xiaonan "Richard" Sun, MD
4:15 – 4:25	Q&A and Discussion: DBS and Focused Ultrasound	
4:25-4:30	Closing Remarks	Jillian Carpenter, MHA, CMOM

Resources for People with Parkinson's in the Upper Valley and Beyond

TAMARA BARRY

PRESIDENT, UPPER VALLEY PROGRAM'S FOR PARKINSON'S

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Medical

- Dartmouth Health, Department of Neurology, Movement Disorder Specialists
- Center for Excellence in Parkinson’s by the Parkinson’s Foundation

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Physical

- Physical Therapy and Occupational Therapy
- LSVT Big and Loud
- RSB, PWR, Pedaling for Parkinson’s, Dancing for Parkinson’s, Up Ending, Tai Ji Quan

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Psychological/Emotional

- Neuropsychologist
- Social Worker
- Support groups
- Exercise groups
- Parkinson’s Social Hour
- Mentor’s

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Parkinson's Organizations and Foundations

- Parkinson's Foundation
- American Parkinson's Disease Foundation
- Michael J. Fox Foundation
- Davis Phinney Foundation
- Twitchy Woman
- Pass to Pass

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Books

- Parkinson's: How to Reduce Symptoms Through Exercise by Kristine Meldrum, BA, ACE
- Every Victory Counts, Davis Phinney Foundation For Parkinson's
- Not Afraid to Fall, by Brian Hall

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Questions?

Nutrition and Healthy Eating in Parkinson's Disease

BIRGIT HUMPERT, RDN, LD

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Outline for today:

- What do we know about the effect of dietary patterns on PD progression?
  - Mediterranean Diet and MIND Diet
- Complications and how to manage them with nutrition
  - constipation
  - gastroparesis or delayed gastric emptying
  - swallowing issues
  - low blood pressure (orthostatic hypotension)
  - unintended weight loss
  - medication and protein intake

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Dietary Patterns

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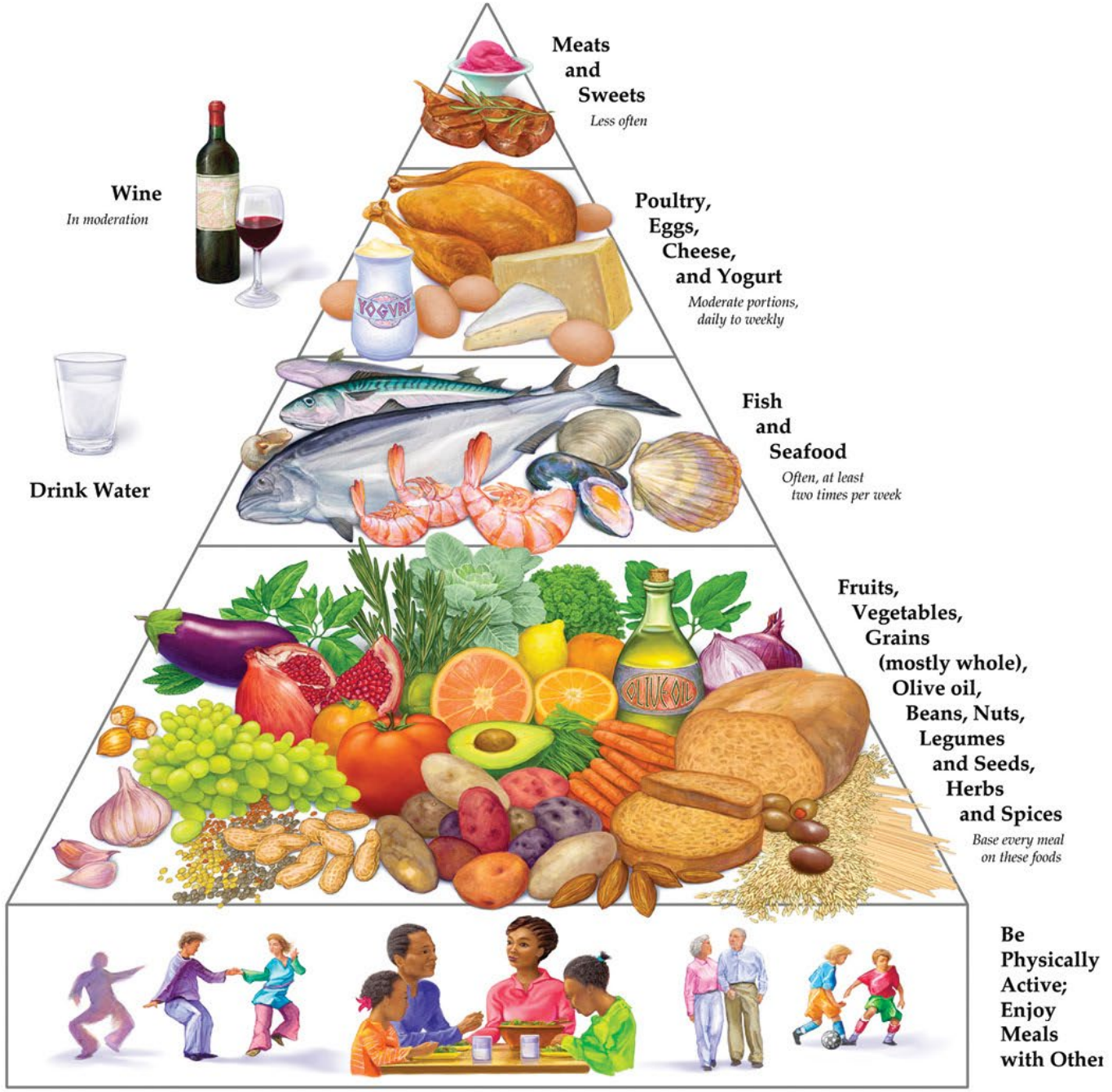
The Mediterranean Diet



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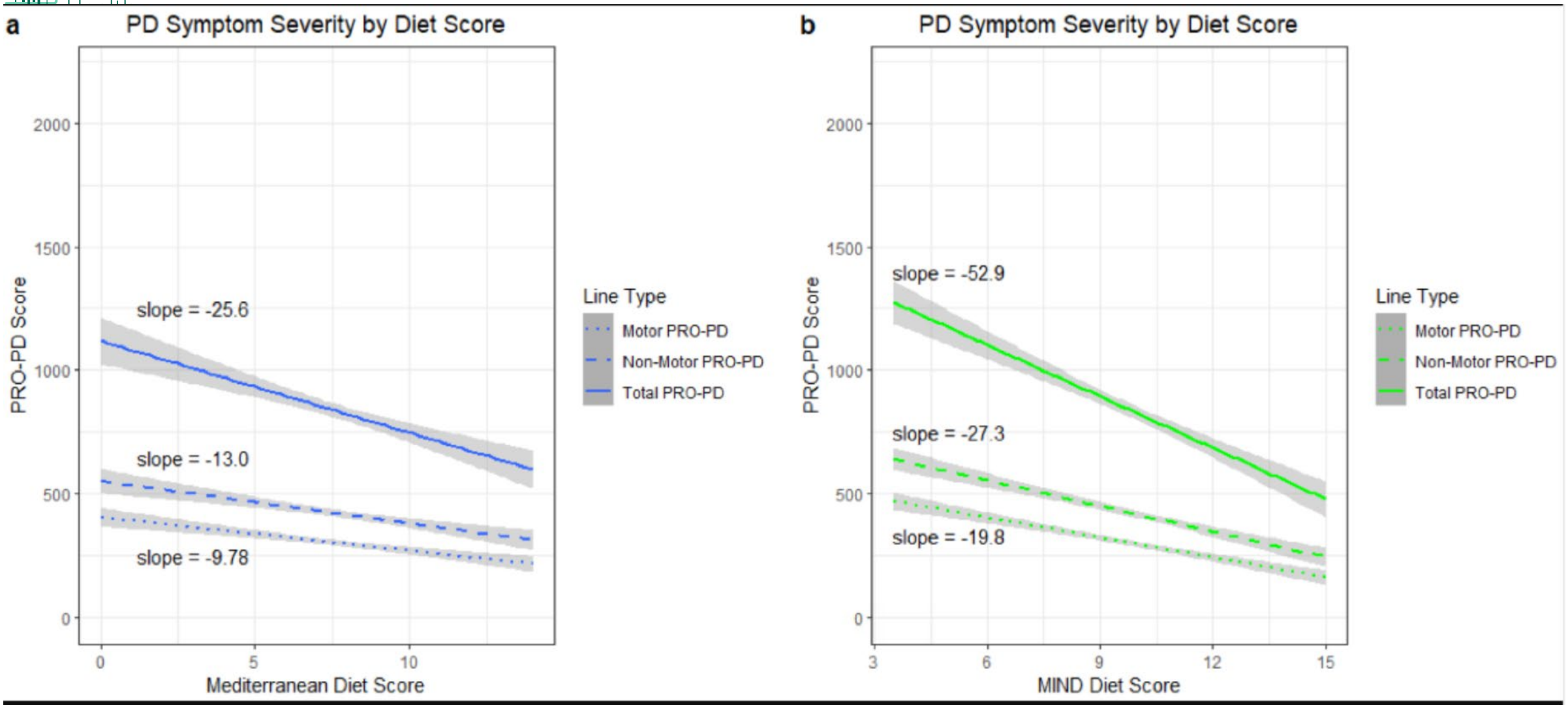
MIND Diet

Mediterranean Diet + DASH Diet

= **M**editerranean-DASH **I**ntervention for **N**eurodegenerative **D**elay



- Fox DJ, Park SJ, Mischley LK. Comparison of Associations between MIND and Mediterranean Diet Scores with Patient-Reported Outcomes in Parkinson's Disease. Nutrients. 2022 Dec 6;14(23):5185. doi: 10.3390/nu14235185. PMID: 36501214; PMCID: PMC9739738.

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Conclusion

- Both diet patterns improved symptoms
- Both diet patterns improved motor and non-motor symptoms
- Higher consumption levels of butter/margarine, red meat, cheese, fast food, carbonated/sweet beverages, and pastries and sweets were associated with greater severity of PD symptoms.
- Higher consumption of nuts, vegetables, berries, beans and non-fried fish were associated with lesser severity of PD symptoms.

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How do they work?

- Rich in antioxidants
- Rich in omega-3 fatty acids
- Anti-inflammatory properties
- Benefits for the gut bacteria

Make colorful plates!

https://www.themediterraneandish.com/red-lentil-soup-recipe/

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Principles of the MIND Diet

- Less ….
- Less than 5 servings/week of pastries and sweets
- Less than 4 servings/week of red meat (including beef, pork, lamb, and products made from these meats)
- Less than one serving/week of cheese and fried foods
- Less than 1 tablespoon/day of butter/stick margarine

- More…
- 6+ servings/week of green leafy vegetables
- 1+ servings/day of vegetables (other than green leafy)
- 3+ servings/day of whole grains
- 5+ servings/week of nuts
- 4+ meals/week of beans
- 2+ servings/week of berries
- 2+ meals/week of poultry
- 1+ meals/week of fish
- Mainly olive oil if added fat is used

Complication and how to manage them with nutrition:

- Constipation
- Gastroparesis or delayed gastric emptying
- Swallowing issues
- Low blood pressure (orthostatic hypotension)
- Medication and protein intake
- Unintended weight loss

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Constipation

- The gut is slowing down as waste products move through
- Reasons:
  - changes due to Parkinson's Disease itself
  - medication
  - dehydration
  - less activity

Slow transit through the gut can also lead to SIBO (Small Intestinal Bacterial Overgrowth)

Probiotics?

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Fiber, Fluid and Fitness

Sweet Potato Chili:

- Fiber from beans, bell peppers, tomatoes, corn
- Can be made soft
- Provides some hydration as well
- Provides salt from canned products but also other electrolytes
- Lots of antioxidants in the vegetables and beans

https://cookieandkate.com/sweet-potato-chili-recipe/

Be consistent!
Start increasing fiber slowly!
Drink lots of water!

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Delayed Gastric Emptying

- Foods stays in the stomach longer
  -> feeling full, nausea, vomiting
  -> delayed action of medication
- Small meals (1 – 1.5 cups) but more frequently
- Soft, blenderized foods
- Chewing well
- More solid foods earlier in the day (making dinner a lighter meal)
- Lower fat, fat in liquids better tolerated
- Might need lower fiber
- Drink small sips of water during the meal, but drink the majority of your water in between meals
- Gentle walking or at least sitting up after a meal
- In severe cases might need a liquid diet

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Tuna Pasta Salad:

- Lower in fiber with white pasta
- Soft consistency
- Protein from tuna
- Uses pantry staples
- Make with light mayonnaise

https://www.budgetbytes.com/tuna-pasta-salad-wpeas/

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Swallowing Issues

- Soft consistencies
- Eating slow and mindfully, chewing well
- Ground up meats, mashed veggies/steamed soft veggies
- Soups, but avoiding mixed consistencies

- Speech Language Pathologists give recommendation for consistency

Berry-Kefir-Smoothie:

- Fiber from berries and almond butter
- Antioxidants from berries
- Extra hydration
- Protein from the kefir and the almond butter
- No chewing
- Thicker consistency is easier to swallow
- Liquid calories usually don’t make us feel as full
- Faster transition through the stomach

A personal blender is lightweight, easier to clean and great for making individual portions!

https://www.eatingwell.com/recipe/257793/berry-kefir-smoothie/

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Orthostatic Hypotension

-
  - at least 2 liters of water
  - starting with some ice cold water in bed
  - add sodium and other electrolytes
  - small, frequent meals

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Hydration

- water, water, water!
- sparkling water, seltzer
- adding lemon for flavor
- sports drinks could be useful
- tea and coffee
- diluted juice

Monitor your intake and set reminders!

https://www.acouplecooks.com/cucumber-lemon-water-recipe/

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Cheddar & Spinach Twice Baked Potatoes:

- Potassium in the potatoes
- Magnesium in the spinach
- Sodium in the cheese
- Calcium and phosphorus in the cheese

Also
- Soft, easy to chew
- High in calories

https://www.tasteofhome.com/recipes/cheddar-spinach-twice-baked-potatoes/

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Unintended Weight Loss

Can be due to

- Aging
- Changes in appetite
    - Changes in smell
    - Gastrointestinal issues like swallowing issues, nausea, delayed stomach emptying, constipation
    - Depression, fatigue
- Food avoidances
- Dyskinesia – extra movements
- Tremor, difficulty preparing food

-> reduced muscle mass and stre
-> risk for reduced bone density
-> lower quality of life

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What to do to avoid weight loss?

- Swallowing evaluation
- Talk to your doctor about your medication and other reasons for weight loss
- Treat depression
- Think about food shopping and food preparation
- Increase number of “Eating Events”, small frequent meals
- Liquid calories like homemade smoothies, supplements like Boost or Ensure
- Increase foods that are calorie dense, this often means more fat

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Make every meal count!

<u>High-calorie snack plate:</u>

- Nuts
- Nut butter (peanut butter, almond butter) with pretzels
- Fruit
- Cheese and crackers

Have easy to eat foods on hand and in sight!

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Protein and Medication

- Levadopa and protein use the same transporter in the intestine and into the brain
- This could lead to medication working less effective
- This is not an issue for everybody, might be more common later in the disease
- Not as important with multiple small doses
- If you suspect that your mediation does not work as effectively, try
  taking it 30-60 minutes before (or 1 hour after) a meal and/or
  taking it with mostly carbohydrates and eat a protein rich meal later


QUESTIONS

Break Lead By: Parkinson's Dance Group

A very special thanks to:

Kevin & Sharon Thomson
Mary Ellen & John Ketz
Mary Sue Turner
Ann Cioffi
Miriam & Gary Durkee
Dick & Bobbi Roy
Diane & Richard Caruso
Peter Rogers
Kristina & Lynn Cole
Libby Edson
Patti Hardenberg
Betsy Warren
Tony Palazzo

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Lunch and Exhibit Hall

Be sure to visit our partners and sponsors today!

-

Program resumes promptly at 1:00 p

What to know when Considering Participation in Clinical Trials

REBECCA THOMPSON, MD

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What is a clinical trial?

- A research study involving human volunteers
- Tests new ways to prevent, detect, treat or manage disease
- Follows strict ethical and scientific standards

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Why participate in a clinical trial?

- Contribute to medical knowledge and future patient care
- Access to new treatments before they are widely available
- Receive expert medical attention during the trial
- Help others by advancing science

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Types of clinical trials

- Treatment trials
- Prevention trials
- Diagnostic trials
- Quality of life trials

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Phases of a clinical trial

- Phase I: safety and efficacy, smaller group, 1st time in humans
- Phase II: effectiveness, does it work, is it safe?
- Phase III: comparison- compare to standard treatment, try different doses
- Phase IV: post approval long term effects and monitoring

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What are my rights as a participant?

- Voluntary participation- you can withdraw any time
- Informed consent- detailed explanations before you agree
- Privacy protection- our health information is secure
- Access to support- ask questions anytime

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What should I ask before joining?

- What is the purpose of this study?
- What are the risks and potential benefits?
- How long will the study last?
- How frequently will I need to have visits?
- Will I be paid?
- What happens if I stop participating?

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Risks and considerations

- Possible side effects or no benefit
- Extra time for visits or procedures
- Uncertainty of outcomes

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How to find a clinical trial

- Ask your neurologist if you qualify for any ongoing trials
- Sign up for DH Parkinson newsletter
- Visit www.clinicaltrials.gov

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Your role in the process

- Understand the study and your responsibilities
- Communicate with your care team
- Follow study instructions
- Ask questions any time

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Our team is here to support you

- Dedicated clinical research staff
- Ethical oversight by institutional review board (IRB)
- You are never alone in the process

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Questions?

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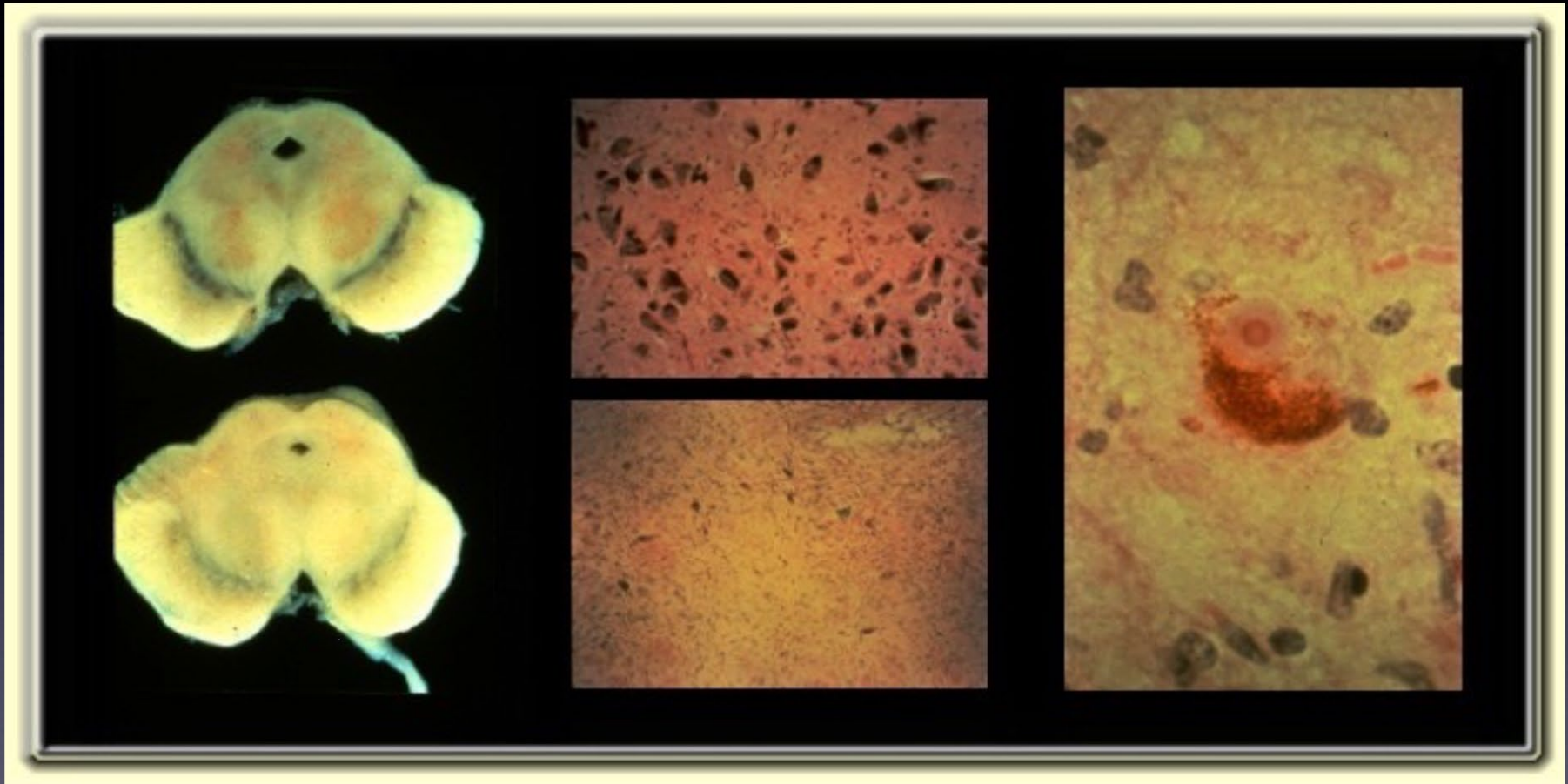
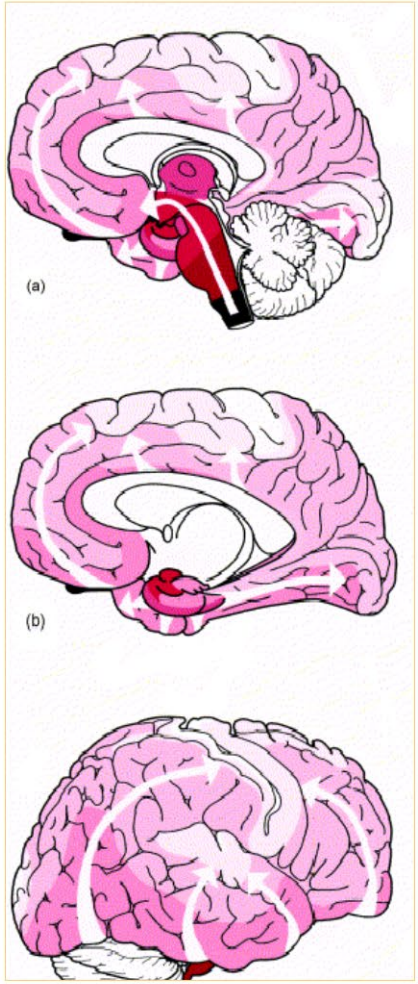
Disease Modifying Clinical Trials Update 2025

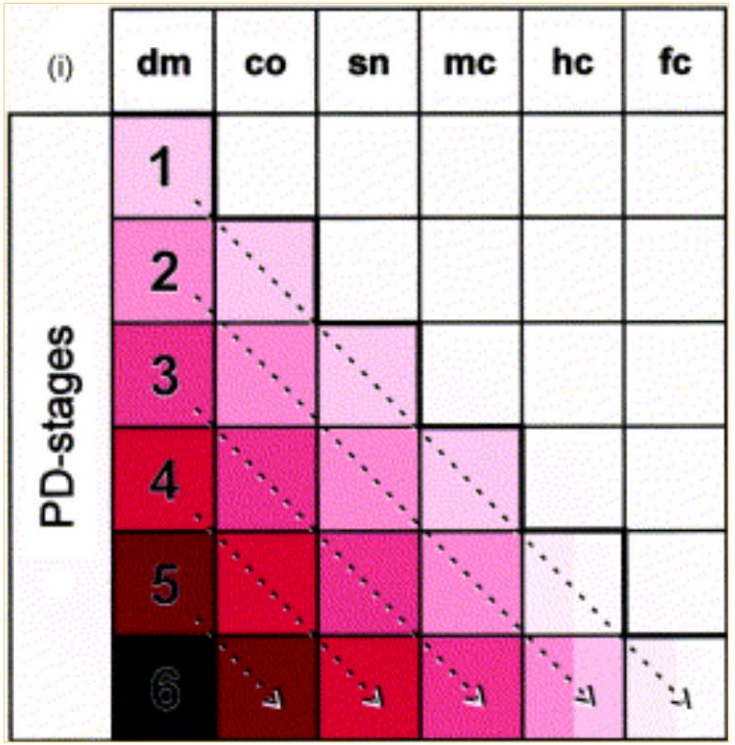
Stephen L. Lee MD PhD
Co-Medical Director of Movement Disorders Center
Assistant Professor of Neurology
Dartmouth Hitchcock Medical Center

Pathology of Parkinson's Disease



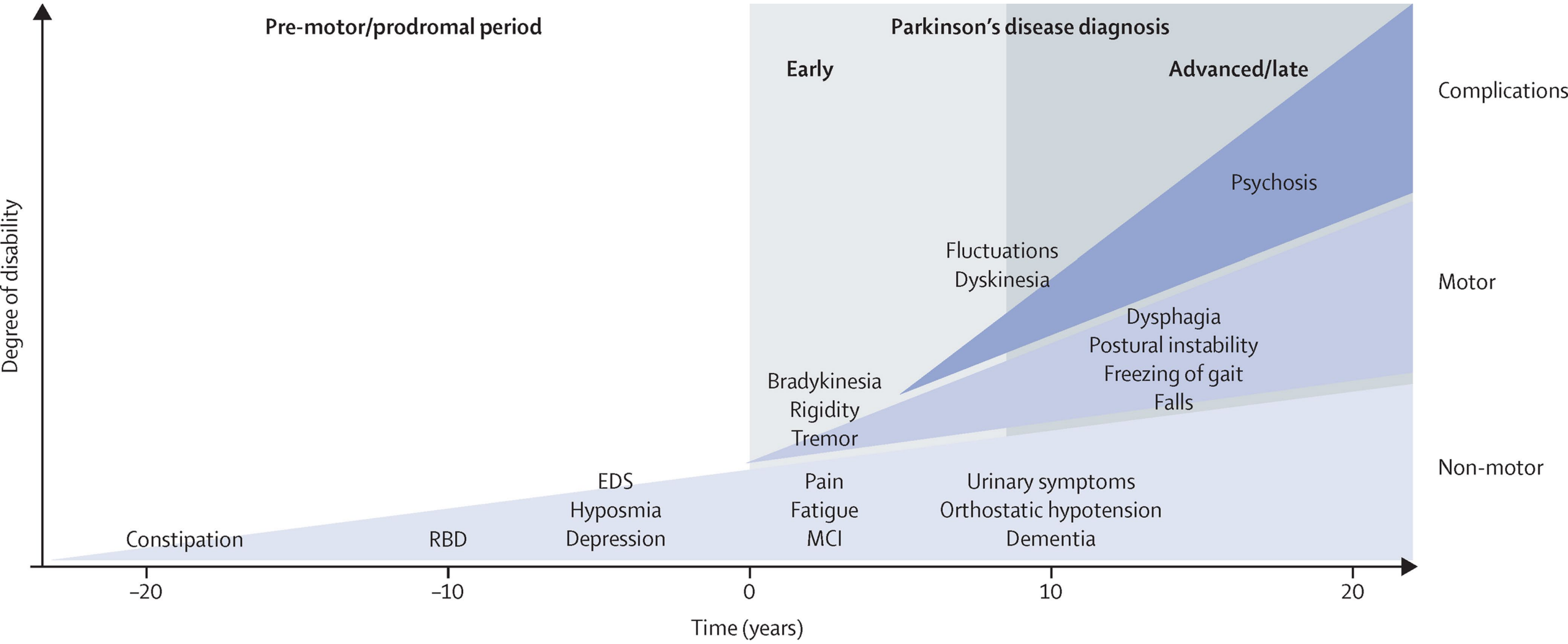
Pathological Staging in PD





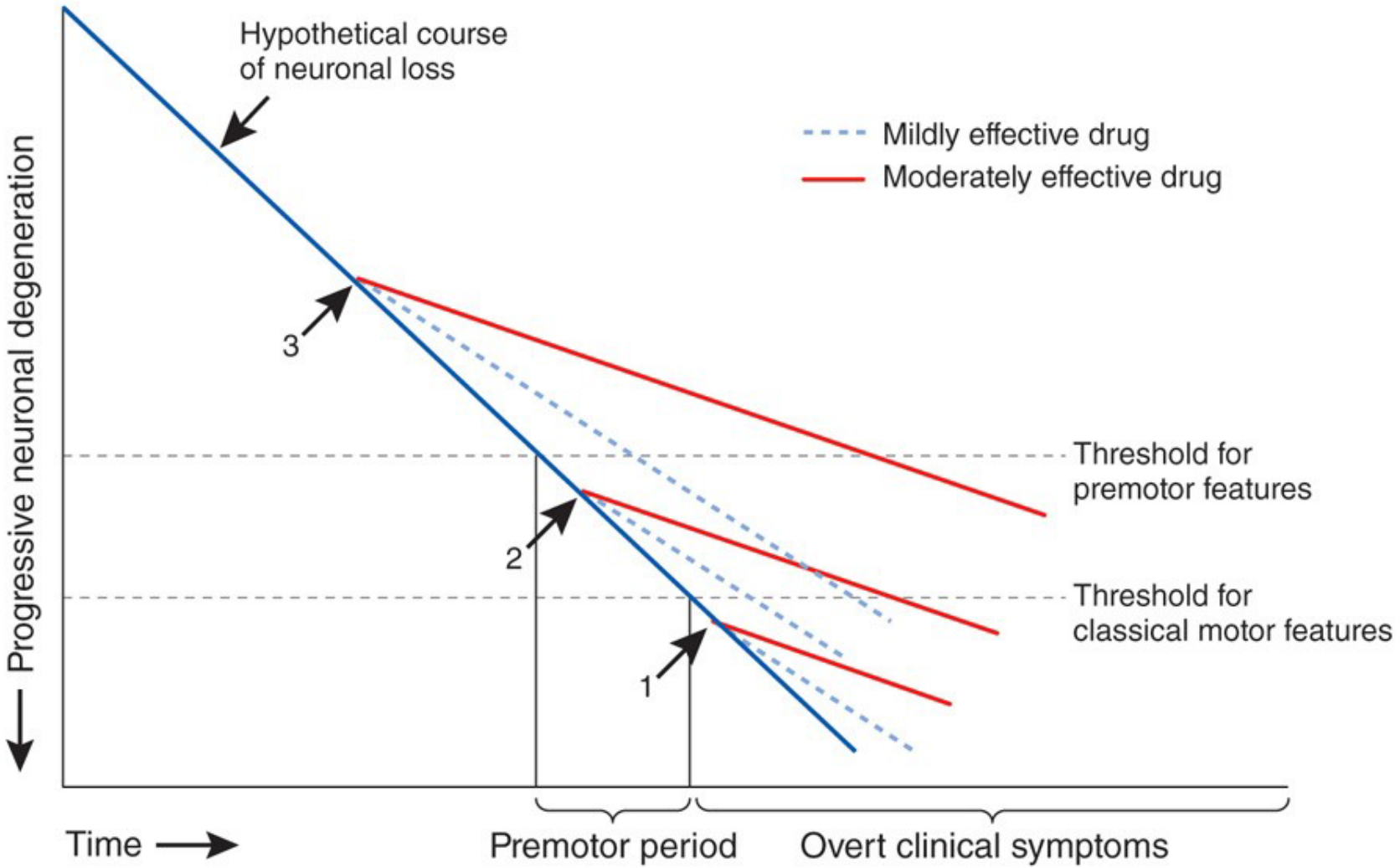
Braak et al. Neurobiol Aging 2003;24:197-211

Disease Progression in PD

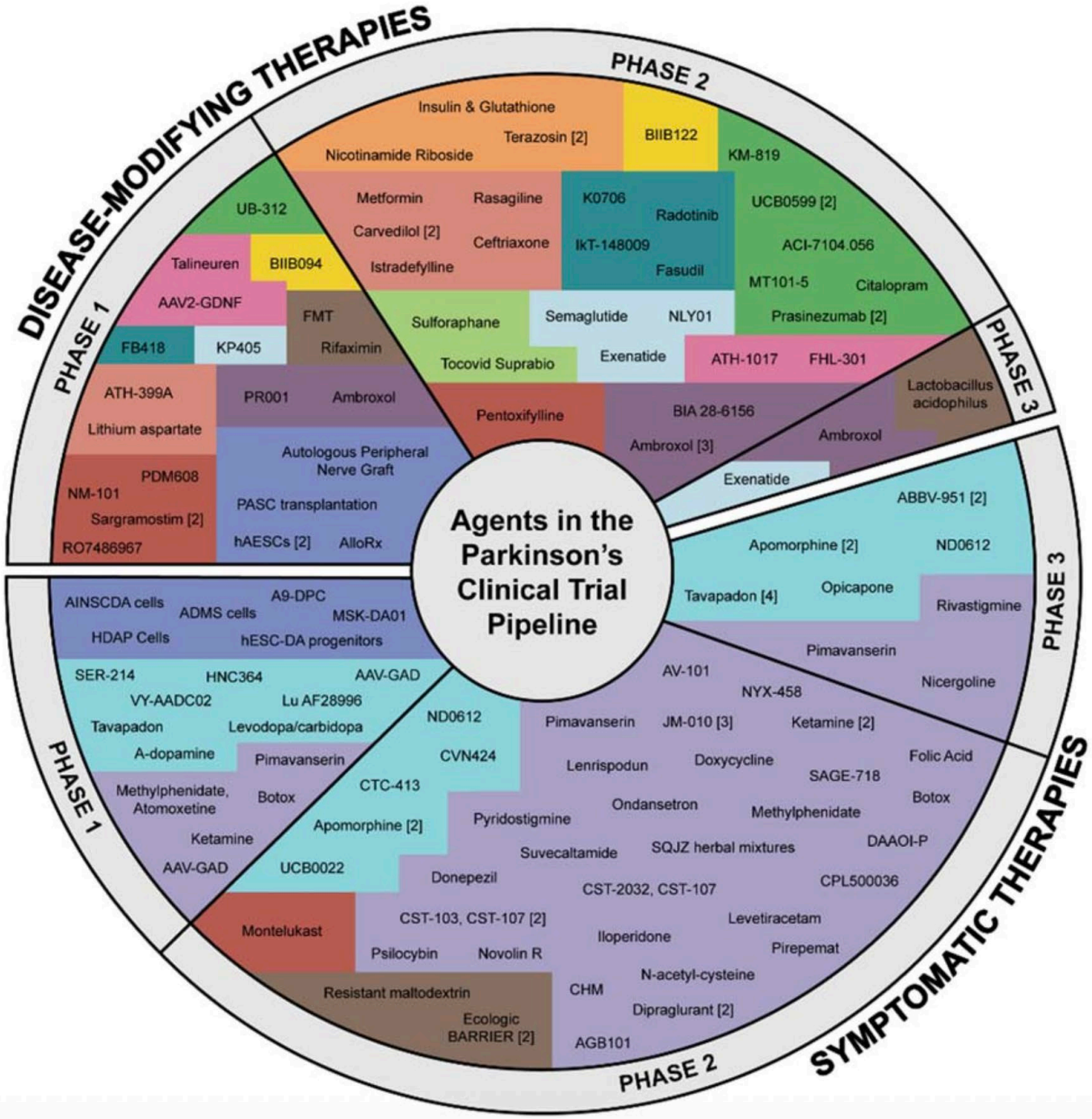


adapted from Kalia and Lang, Lancet 2015

Clinical Trials in Disease-Modifying Therapies



Lang, Nat Med 2010



McFarthing et al. J Neurol 2024

Therapy Targets

- Anti-inflammatory
- Antioxidant
- Cell Therapy
- DMT Other
- Dopaminergic Symptom Relief
- Energy and Mitochondria
- GBA
- GLP-1R Agonist
- Kinase Inhibitor
- LRRK2
- Microbiome/GIT
- Neurotrophic Factors
- Non-dopaminergic Symptom Relief
- Targeting aSN

Cell Stem Cell

Volume 28, Issue 2, 4 February 2021, Pages 182-183

In Translation

Clinical Trial for Parkinson's Disease Gets a Green Light in the US

Jun Takahashi [1]

[1] Department of Clinical Application, Center for iPS Cell Research and Application, Kyoto University, Kyoto 606-8507, Japan

Available online 4 February 2021, Version of Record 4 February 2021.

Cell Stem Cell

Volume 28, Issue 2, 4 February 2021, Pages 217-229.e7

Clinical and Translational Report

Preclinical Efficacy and Safety of a Human Embryonic Stem Cell-Derived Midbrain Dopamine Progenitor Product, MSK-DA01

Jinghua Piao [1 2], Susan Zabierowski [1 3], Brittany N. Dubose [1 3 11], Ellen J. Hill [1 3], Monalisa Navare [1 2], Nidia Claros [1 2], Siera Rosen [1 3], Kiran Ramnarine [1 3], Callie Horn [1 3], Craig Fredrickson [1 3], Karen Wong [1 3], Brent Safford [5 6], Sonja Kriks [1 8], Abderrahman El Maarouf [1 9], Urs Rutishauser [1], Claire Henchcliffe [7 10], Yongzeng Wang [5 6], Isabelle Riviere [5 6], Shannon Mann [1 3 12], Vladimir Bermudez [5 6], Stefan Irion [1 4 12], Lorenz Studer [1 4 13] ✉, Mark Tomishima [1 3 12 13] ✉, Viviane Tabar [1 2 13 14] ✉

1 Center for Stem Cell Biology, Memorial Sloan Kettering Cancer Center, New York, NY 10065, USA
2 Department of Neurosurgery, Memorial Sloan Kettering Cancer Center, New York, NY 10065, USA
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4 Developmental Biology Program, Memorial Sloan Kettering Cancer Center, New York, NY 10065, USA
5 Center of Cell Engineering, Memorial Sloan Kettering Cancer Center, New York, NY 10065, USA
6 Cell Therapy and Cell Engineering Facility, Memorial Sloan Kettering Cancer Center, New York, NY 10065, USA
7 Department of Neurology, Weill Cornell Medical College, New York, NY 10065, USA

Cell Stem Cell

Volume 28, Issue 2, 4 February 2021, Pages 343-355.e5

Resource

Biphasic Activation of WNT Signaling Facilitates the Derivation of Midbrain Dopamine Neurons from hESCs for Translational Use

Tae Wan Kim [1 2 13], Jinghua Piao [1 3 13], So Yeon Koo [1 2 5], Sonja Kriks [1 10], Sun Young Chung [1 2], Doron Betel [6], Nicholas D. Socci [7], Se Joon Choi [8], Susan Zabierowski [1 2 4], Brittany N. Dubose [1 2 4 12], Ellen J. Hill [1 2 4], Eugene V. Mosharov [8], Stefan Irion [1 2 11], Mark J. Tomishima [1 2 4 11], Viviane Tabar [1 3 9 14] ✉, Lorenz Studer [1 2 14 15] ✉

1 Center for Stem Cell Biology, Memorial Sloan Kettering Cancer Center, New York, NY, USA
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4 SKI Stem Cell Research Facility, Memorial Sloan Kettering Cancer Center, New York, NY, USA
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6 Institute for Computational Biomedicine, Division of Hematology/Oncology, Department of Medicine, Weill Cornell Medical College, New York, NY, USA
7 Bioinformatics Core, Memorial Sloan Kettering Cancer Center, New York, NY, USA
8 Department of Neurology, Columbia University Medical Center, New York, NY, USA
9 Cancer Biology & Genetics Program, Memorial Sloan Kettering Cancer Center, New York, NY, USA

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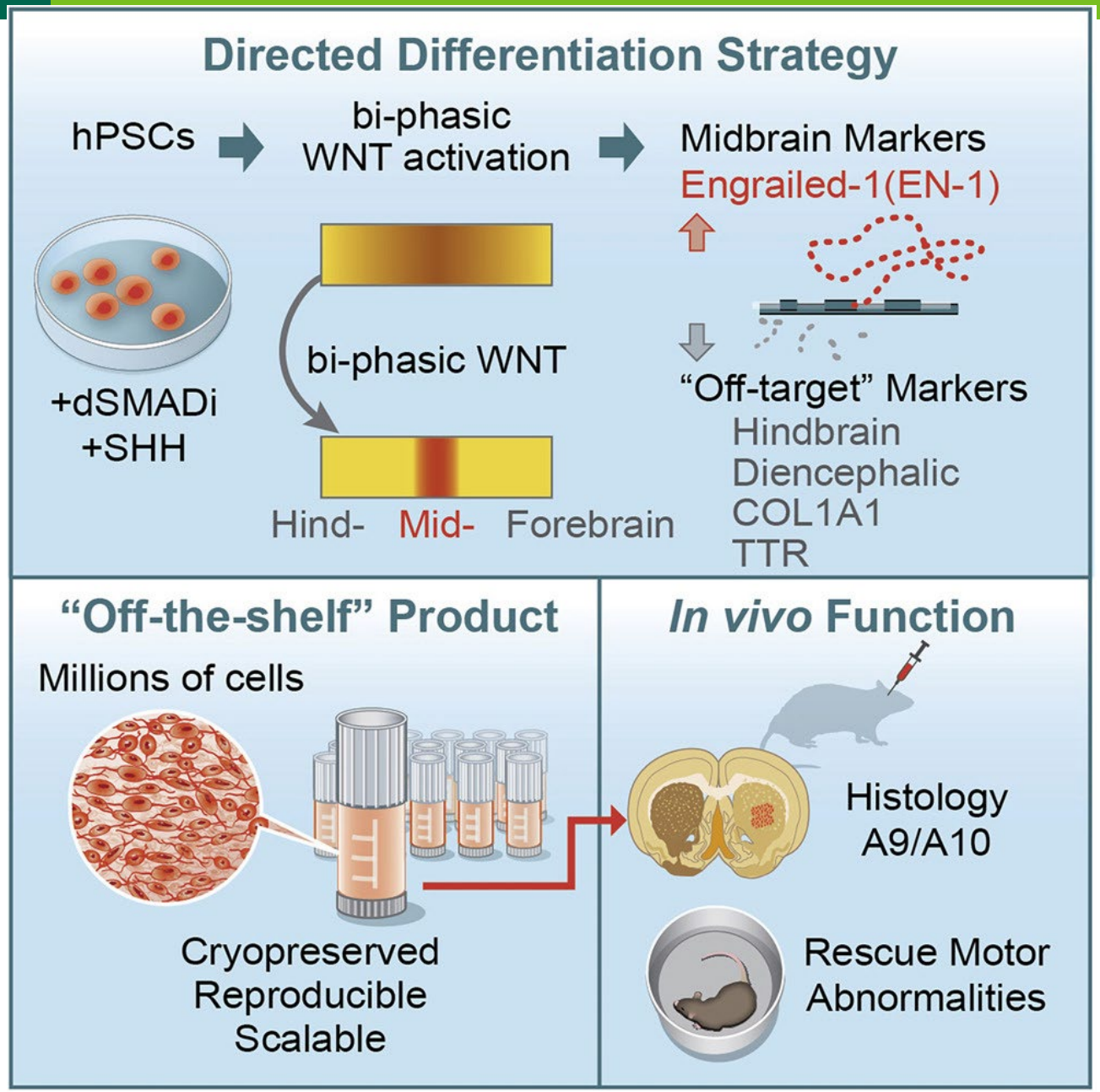

Kim et al., Cell Stem Cell 2021

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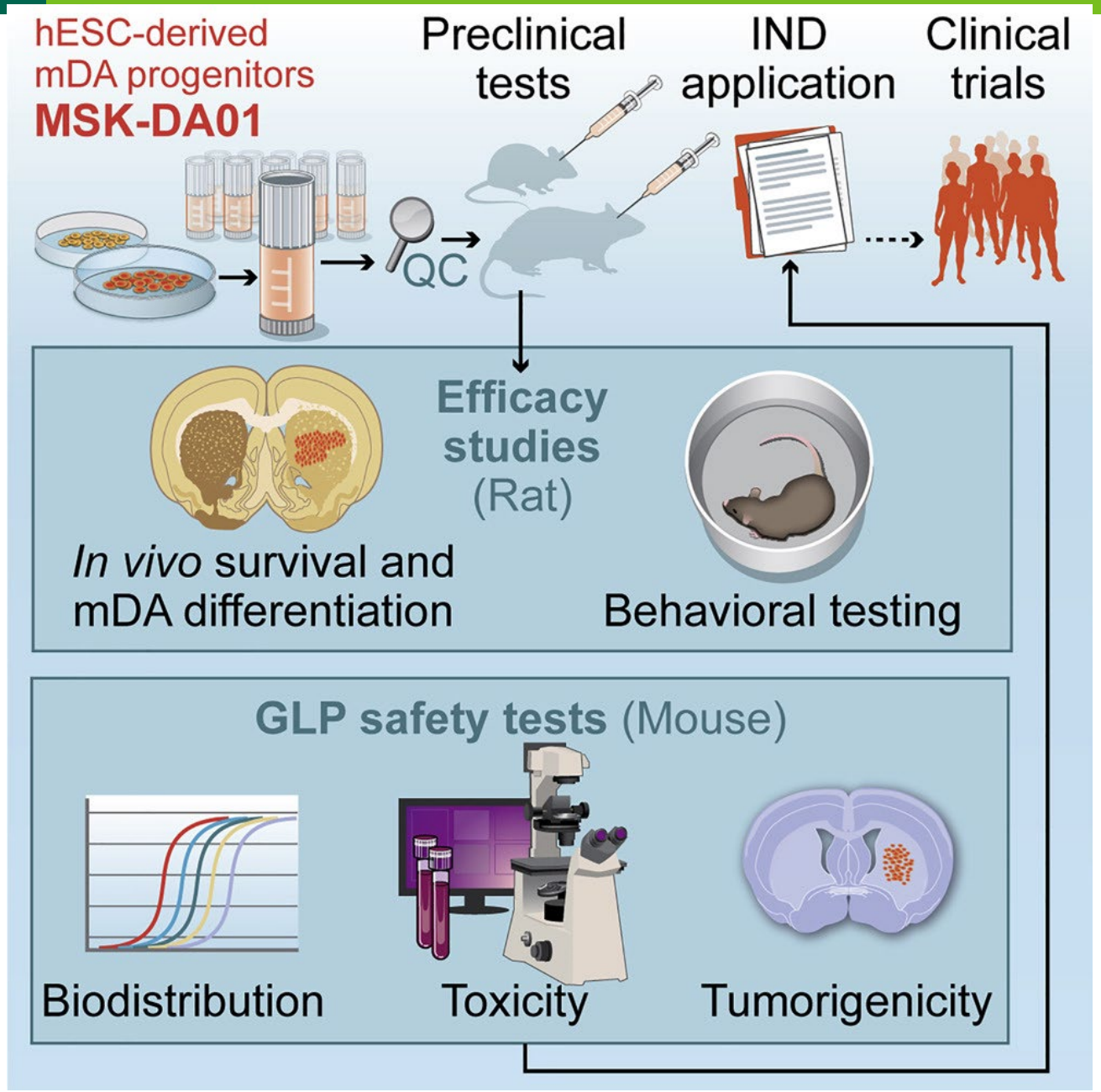

Piao et al, Cell Stem Cell 2021

Article

Phase I trial of hES cell-derived dopaminergic neurons for Parkinson's disease

https://doi.org/10.1038/s41586-025-08845-y

Received: 26 July 2024

Accepted: 26 February 2025

Published online: 16 April 2025

Open access

Check for updates

V. Tabar[1,2,3]✉, H. Sarva[4], A. M. Lozano[5,6], A. Fasano[6,7,8], S. K. Kalia[5,6], K. K. H. Yu[1], C. Brennan[1], Y. Ma[9,10], S. Peng[9], D. Eidelberg[9,10], M. Tomishima[11], S. Irion[11], W. Stemple[11], N. Abid[11], A. Lampron[11], L. Studer[2,12,14] & C. Henchcliffe[13,14]

Parkinson's disease is a progressive neurodegenerative condition with a considerable health and economic burden[1]. It is characterized by the loss of midbrain dopaminergic neurons and a diminished response to symptomatic medical or surgical therapy as the disease progresses[2]. Cell therapy aims to replenish lost dopaminergic neurons and their striatal projections by intrastriatal grafting. Here, we report the results of an open-label phase I clinical trial (NCT04802733) of an investigational cryopreserved, off-the-shelf dopaminergic neuron progenitor cell product (bemdaneprocel) derived from human embryonic stem (hES) cells and grafted bilaterally into the putamen of patients with Parkinson's disease. Twelve patients were enrolled sequentially in two cohorts—a low-dose (0.9 million cells, $n = 5$) and a high-dose (2.7 million cells, $n = 7$) cohort—and all of the participants received one year of immunosuppression. The trial achieved its primary objectives of safety and tolerability one year after transplantation, with no adverse events related to the cell product. At 18 months after grafting, putaminal ^{18}Fluoro-DOPA positron emission tomography uptake increased, indicating graft survival. Secondary and exploratory clinical outcomes showed improvement or stability, including improvement in the Movement Disorder Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS) Part III OFF scores by an average of 23 points in the high-dose cohort. There were no graft-induced dyskinesias. These data demonstrate safety and support future definitive clinical studies.

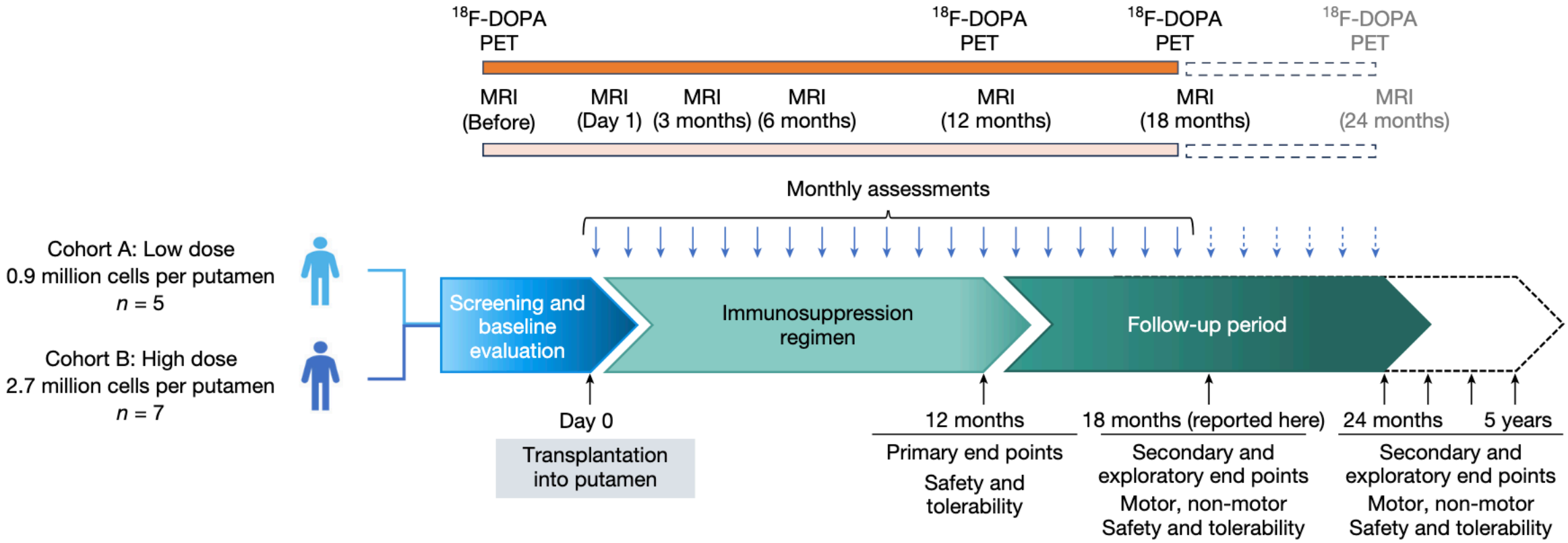

Fig. 1 | The study design. Summary of the study design. Patients were enrolled sequentially into a low-dose then a high-dose cohort. The diagram indicates the timeline of immunosuppression, monthly laboratory and clinical assessments, and imaging studies throughout the study. Ongoing follow-up is anticipated for a minimum of 5 years.

Tabar et al, Nature 2025

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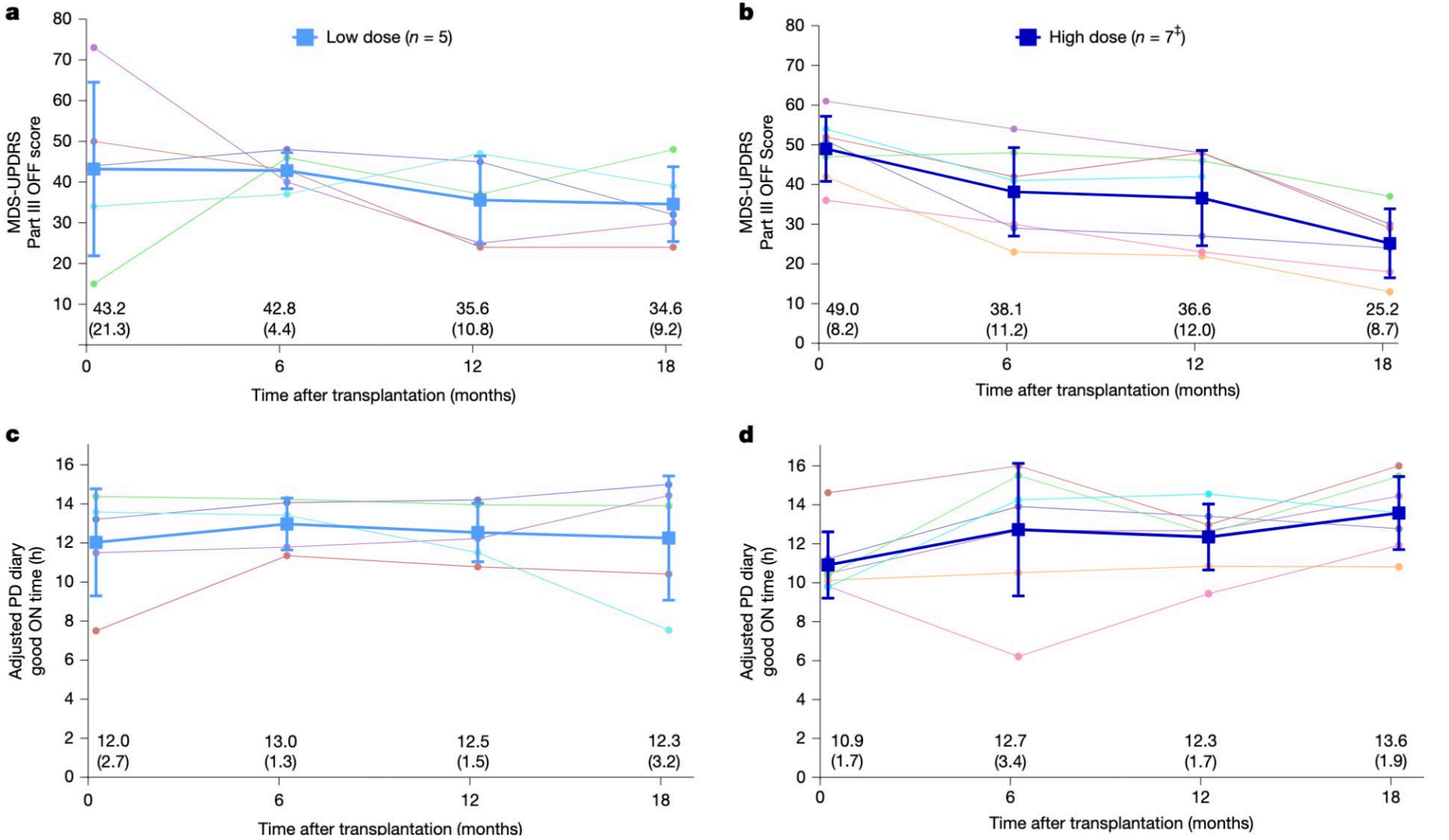
Table 1 | Summary of treatment-emergent SAEs at 12 months post transplantation

	Low dose (*n*=5)			High dose (*n*=7)		
Participants reporting, *n* (%) (total number of events)						
	0 events	1 event	≥2 events	0 events	1 event	≥2 events
TESAE	4 (80.0)	1 (20.0) (1)	0	6 (85.7)	1 (14.3) (1)	0
Related to surgery	5 (100)	0	0	6 (85.7)	1 (14.3) (1)	0
Related to transplanted cells	5 (100)	0	0	7 (100)	0	0
Related to immunosuppressive drugs	5 (100)	0	0	7 (100)	0	0
Tumour or abnormal tissue overgrowth related to presence of transplanted cells	5 (100)	0	0	7 (100)	0	0
Intracerebral haemorrhage that is deemed life threatening	5 (100)	0	0	7 (100)	0	0
Deaths	0			0		

Summary of treatment-emergent SAE (TESAE) for all patients, according to dose group.

Tabar et al, Nature 2025

Secondary end points



Tabar et al, Nature 2025

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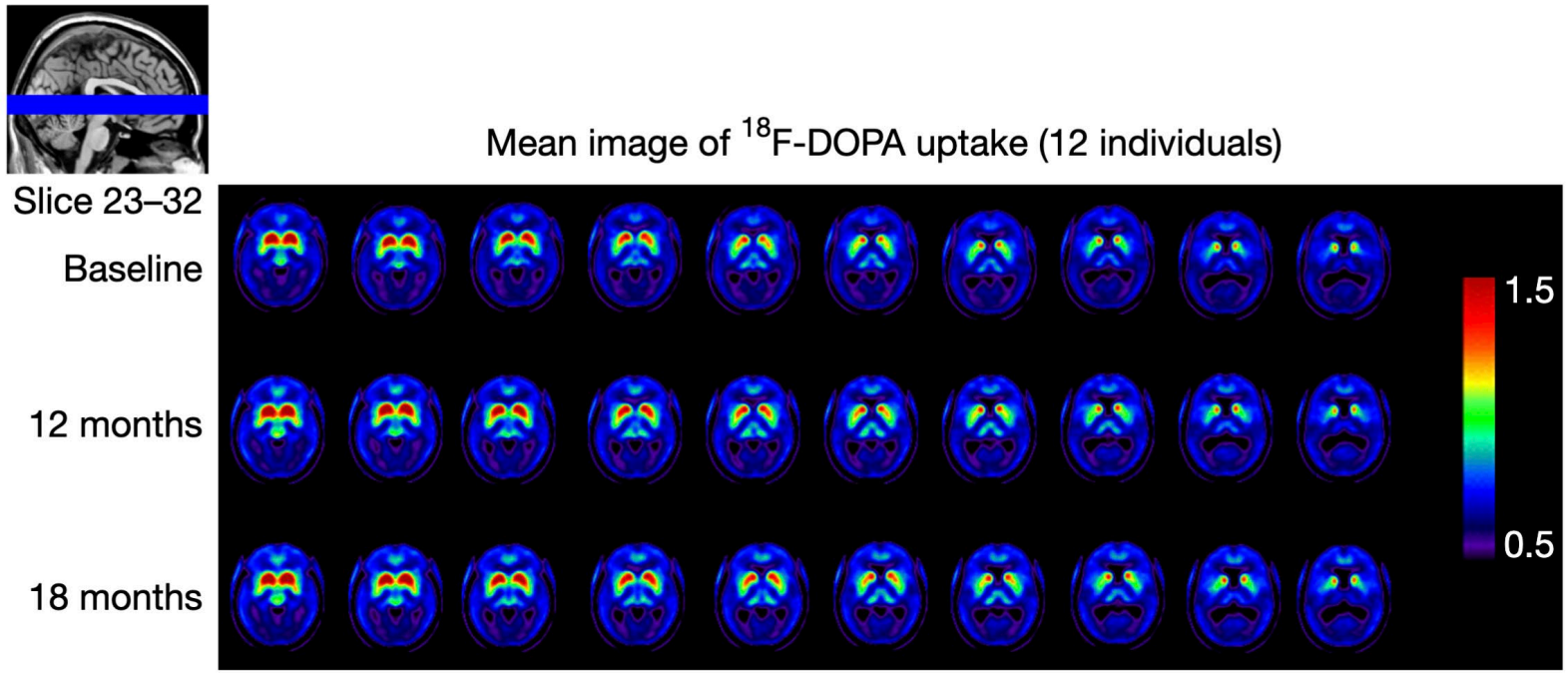


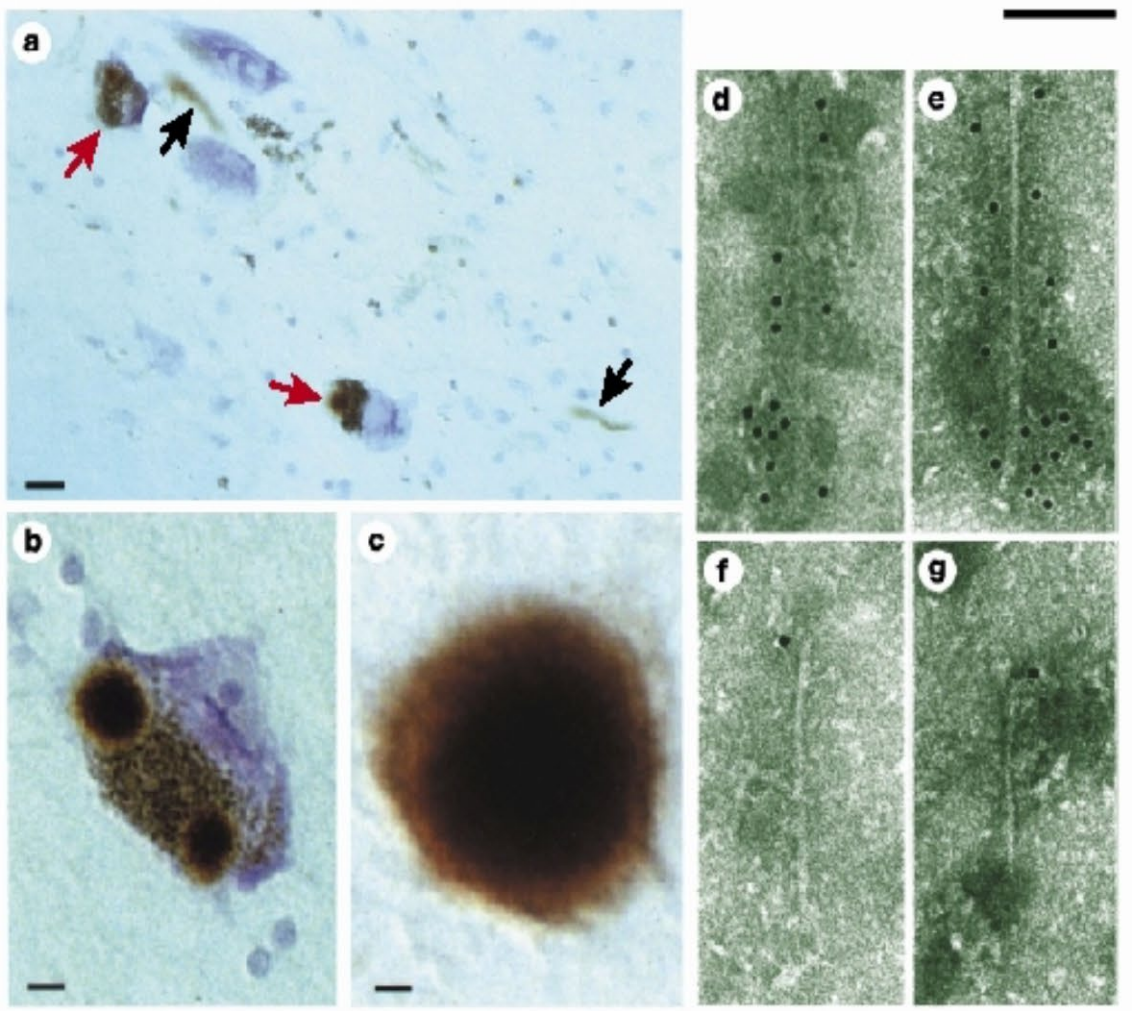
Fig. 3 | PET images of ^{18}F-DOPA uptake signal in the striatum. Images of the ^{18}F-DOPA PET uptake signal at multiple sections through the striatum, presented as the mean uptake of all patients (n = 12 at all timepoints except at 18 months, for which n = 11). Images of ^{18}F-DOPA uptake were produced by dividing each original PET image by the occipital count and then subtracting 1. Formula: image of ^{18}F-DOPA uptake = (PET image/occipital count − 1).

Tabar et al, Nature 2025

PARK1: Alpha Synuclein

(Polymeropoulos et al., *Science* 1997)

- Autosomal dominant with variable penetrance
- A30P and A53T mutations discovered in Italian, Greek and German pedigrees.
- Exhaustive search for mutations in common forms of PD have been negative.
- Discovery of this gene facilitated the key discovery that alpha synuclein was a key component of Lewy bodies.

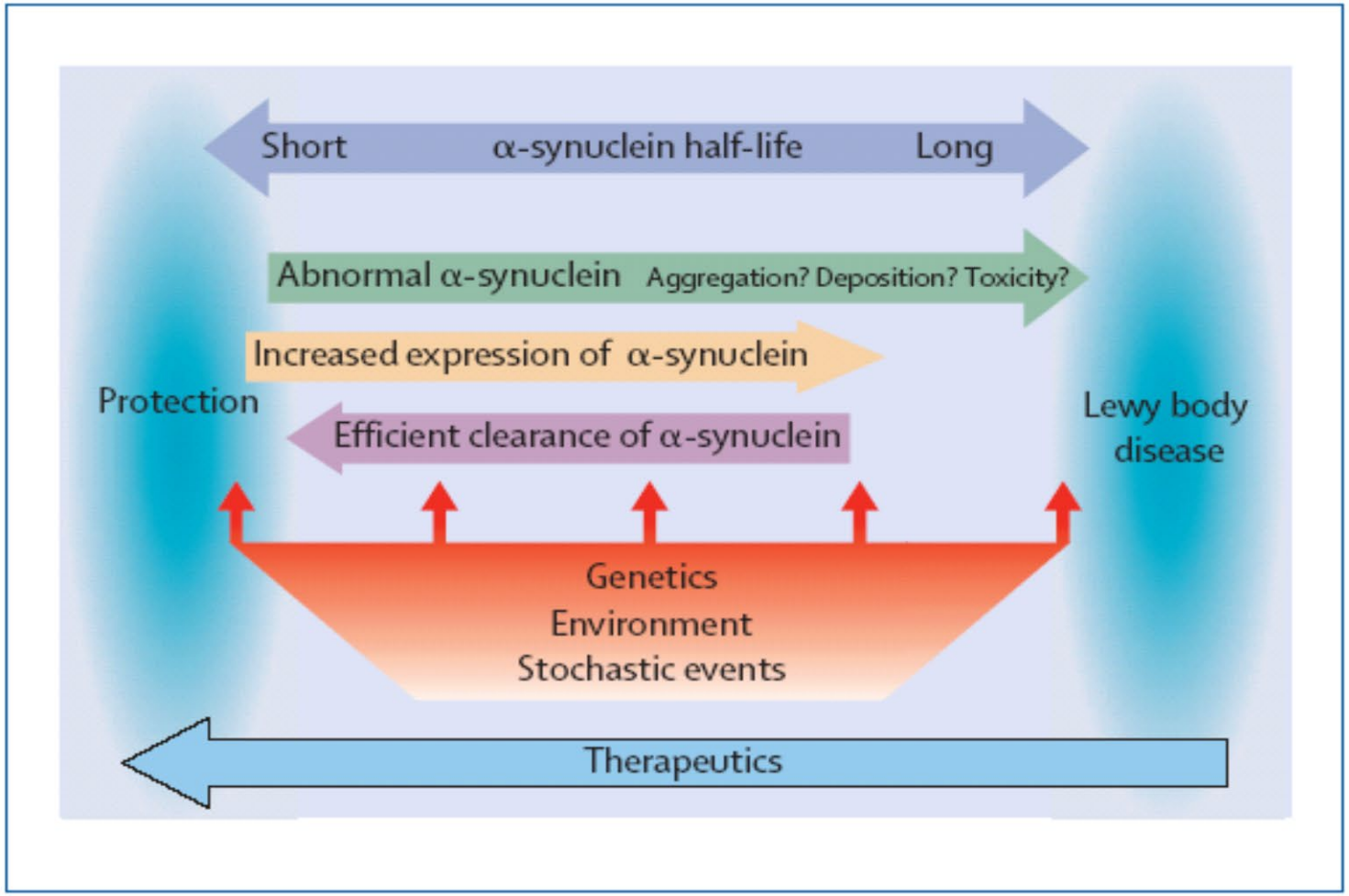


(Spillantini et al. *Nature* 1997)

PD Genetics: From Genes to Therapeutics

Year	Locus	Mode	Gene/locus	Protein	Pathogenic Role
1997	PARK1	AD	SNCA	α-synuclein	Fibril formation
1998	PARK2	AR	PARK2	Parkin	Ubiquitin Proteasome / Mitochondria
	PARK3				
2003	PARK4	AD	SNCA	α-synuclein	Protein dosage?
1999	PARK5		UCH-L1	UCH-L1	Ubiquitin Proteasome
2004	PARK6	AR	PINK1	PINK1	Mitochondria
2002	PARK7	AR	DJ-1	DJ-1	ROS
2004	PARK8	AD	LRRK2	dardarin	GTPase
2006	PARK9	AR	ATP13A2	ATP13A2	Protein trafficking/degradation
2002	PARK10	sporadic	1p32	unknown	
2008	PARK11	?	GIGYF2	GIGYF2	??
2003		AR/AD/sp	NR4A2	Nurr1	Drives DA differentiation
		AD	MAPT	Tau	Protein accumulation
2008		AD	GBA	glucocerebrosidase	Protein trafficking
2002	PARK12		Chr X		
2005	PARK13	AR	Omi/HtrA2	HTRA2	Serine protease: Mitochondria
2010	PARK14	AR	PLA2G6		
2009	PARK15	AR	FBX07		
	PARK16		1q32		
2011	PARK17	AD	VP35, MEM3	VP35	Protein trafficking in trans golgi
2011	PARK18	AD	EIF4G1		
2012	PARK19	AR	DNAJC6	DNAJC6	endosome trans golgi network
2013	PARK20	AR	SYNJ1	SYNJ1	Protein trafficking in synaptic vesicles
2014	PARK21	AD	DNAJC13	DNAJC13	Protein trafficking

α-synuclein: a matter of dose?



Singleton, Lancet 2004

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RESEARCH SUMMARY

Trial of Prasinezumab in Early-Stage Parkinson's Disease

Pagano G et al. DOI: 10.1056/NEJMoa2202867

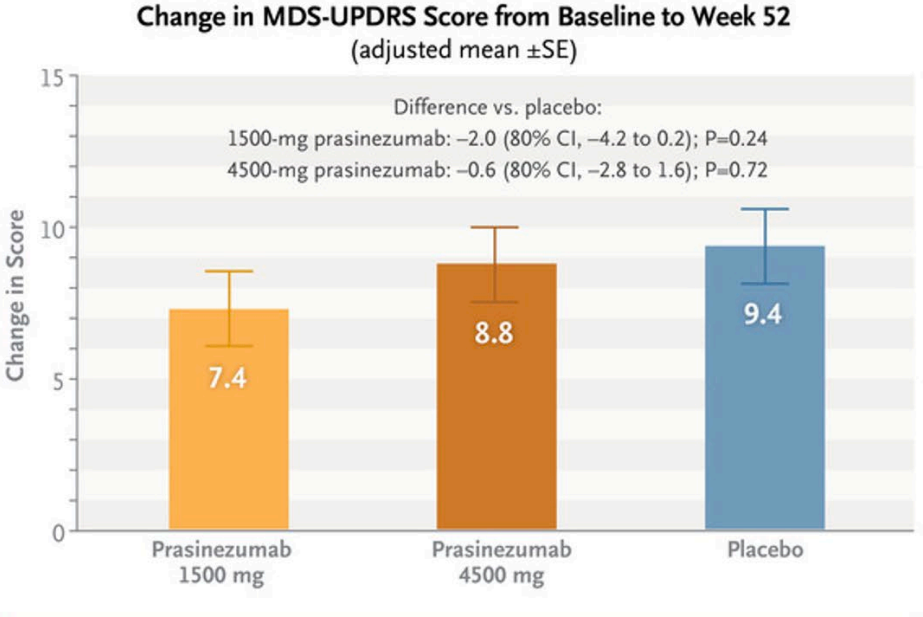
CLINICAL PROBLEM

Aggregated α-synuclein has a prominent role in the pathogenesis of Parkinson's disease. Prasinezumab, a humanized monoclonal antibody that binds to aggregated α-synuclein, has been proposed as a potential treatment for Parkinson's disease, but clinical trial data are needed.

CLINICAL TRIAL

Design: A phase 2, multinational, double-blind, randomized, placebo-controlled trial examined the efficacy and safety of low- and high-dose prasinezumab in patients with early-stage Parkinson's disease.

Intervention: 316 patients who had not previously received treatment for symptoms of Parkinson's disease or who were receiving stable doses of a monoamine oxidase B inhibitor were assigned to receive intravenous prasinezumab (1500 mg or 4500 mg) or placebo every 4 weeks for 52 weeks. The primary end point was the change from baseline to week 52 in the Movement Disorder Society–sponsored revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS) total score; scores range from 0 to 236, with higher scores indicating greater symptom severity.



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RESULTS

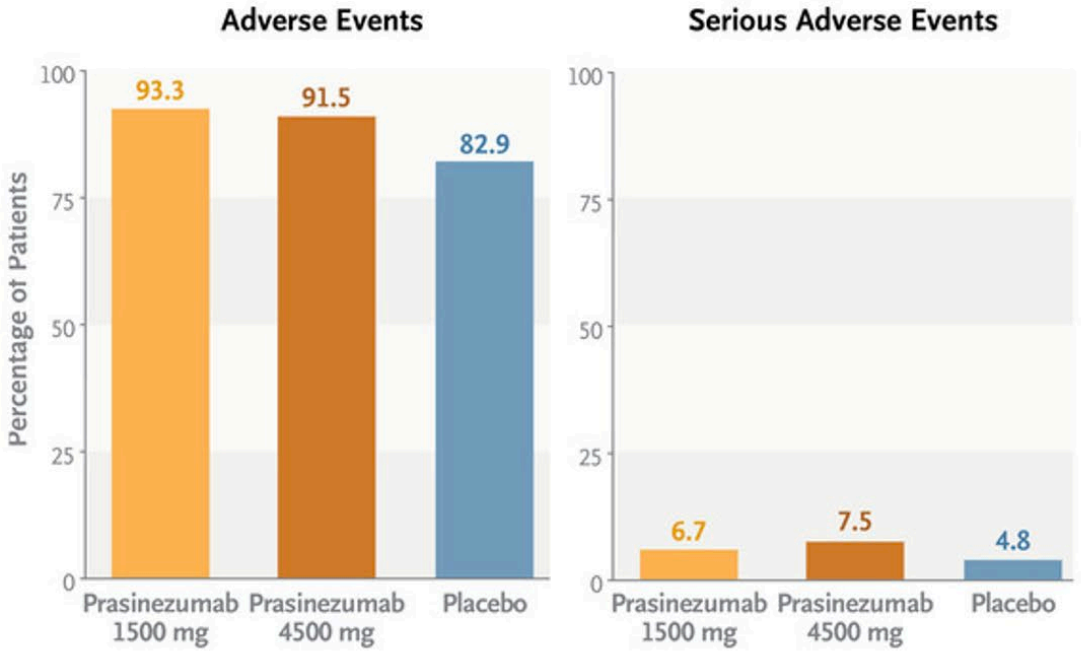
Efficacy: The mean change in the MDS-UPDRS score at week 52 did not differ significantly between either prasinezumab dose and placebo.

Safety: Infusion reactions were common and were reported most frequently in the 4500-mg group. Serious adverse events occurred more often with prasinezumab than with placebo.

LIMITATIONS AND REMAINING QUESTIONS

- Nearly one third of the participants were excluded from the 52-week efficacy analysis because they had started treatment for symptoms of Parkinson's disease.
- Non-White and non-U.S. or non-European populations were underrepresented in the trial.
- Testing for target engagement of prasinezumab was not performed.

Links: Full Article | NEJM Quick Take | Editorial



CONCLUSIONS

The monoclonal antibody prasinezumab, as compared with placebo, did not slow disease progression in patients with early-stage Parkinson's disease over a 52-week treatment period.

Parkinsonism & Related Disorders
Volume 132, March 2025, 107257

A Phase 2b, multicenter, randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of intravenous prasinezumab in early-stage Parkinson's disease (PADOVA): Rationale, design, and baseline data

Tania Nikolcheva [a], Gennaro Pagano [b c], Nathalie Pross [a], Tanya Simuni [d], Kenneth Marek [e], Ronald B. Postuma [f], Nicola Pavese [g], Fabrizio Stocchi [h], Klaus Seppi [i], Annabelle Monnet [j], Nima Shariati [j], Benedicte Ricci [b], Loes Rutten-Jacobs [a], Gesine Respondek [a], Thomas Kustermann [b], Kirsten I. Taylor [b], Dylan Trundell [k], Paulo Fontoura [a], Rachelle Doody [a l], Hanno Svoboda [b m], Azad Bonni [b], for the PADOVA Investigators and Prasinezumab Study Group

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[m] Roche Diagnostics GmbH, Penzberg, Germany

npj | parkinson's disease

Perspective

Published in partnership with the Parkinson's Foundation

https://doi.org/10.1038/s41531-025-00886-4

Prasinezumab slows motor progression in Parkinsons disease: beyond the clinical data

Bin Xiao [1,2] ✉ & Eng-King Tan [1,2,3] ✉

A post hoc subgroup analysis has suggested potential therapeutic benefits of prasinezumab, a humanized monoclonal anti-α-synuclein antibody, in patients with rapidly progressing Parkinson's disease (PD), despite initial trials showing limited impact on primary outcomes. Caution is needed due to the retrospective nature of subgroup analyses, and potential confounding factors that may have influenced the observed treatment effects in specific patient subsets. Critical considerations are provided here for designing and implementing preclinical studies and clinical trials involving monoclonal antibodies, suggesting that future research should prioritize refining preclinical models and optimizing biomarker-based patient selection to reduce risks of false trial outcomes, eventually advancing antibody-based therapies in PD effectively and safely.

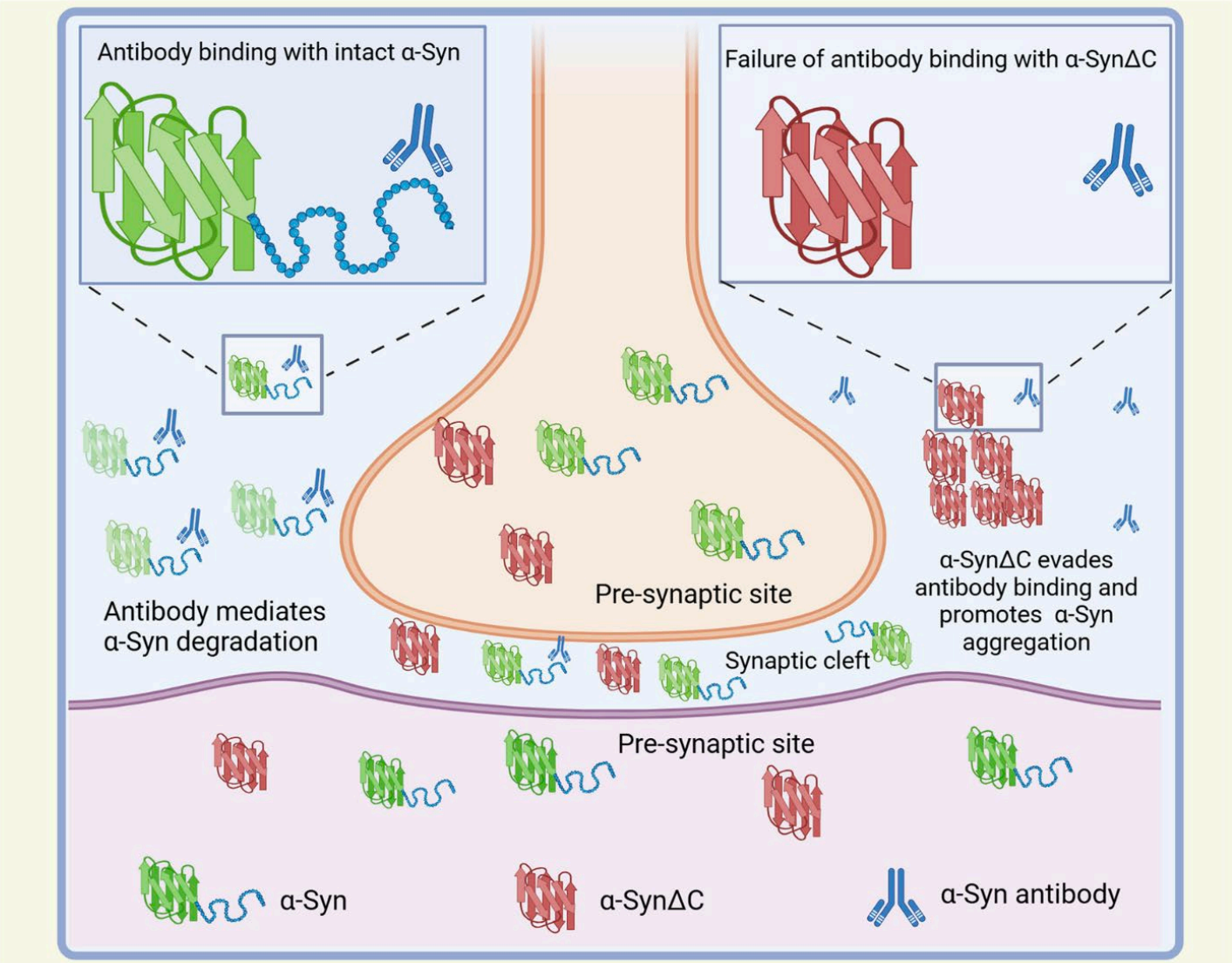

Fig. 1 | Factors that may affect target engagement of α-synuclein (α-syn) monoclonal antibody. C-terminus truncated α-synuclein (α-SynΔC) can evade the antibody binding and promote α-syn aggregation, resulting in neurodegeneration. Antibodies may find it difficult to enter the narrow synaptic cleft where there may be enriched spreading α-syn.

Xiao and Tan, NPJ 2025

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Dartmouth GEISEL SCHOOL OF MEDICINE

Conclusion:

Several Phase III DMT Clinical Trials hold promise

Academic Medical Center such as DH aim to bring clinical trials the community

National Institutes of Health and our basic science research is vital to these developments

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Questions?

Exercise is Medicine: *Modifying Parkinson's Disease*

Mary S. Feldman, DO,
Co-Director of Movement Disorders Center,
Director of the Neurology Residency Program
Dartmouth Health

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What is Exercise?

A type of physical activity that consists of planned, structured, and repetitive body movements that are performed to improve or maintain 1 or more components of physical fitness

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Disease Modification

Slowing Clinical Decline is the Ultimate Goal of Parkinson's Therapy!!

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Jay Alberts, PhD
Cleveland Clinic Foundation

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Jay Alberts…
Yearly RAGBRAI

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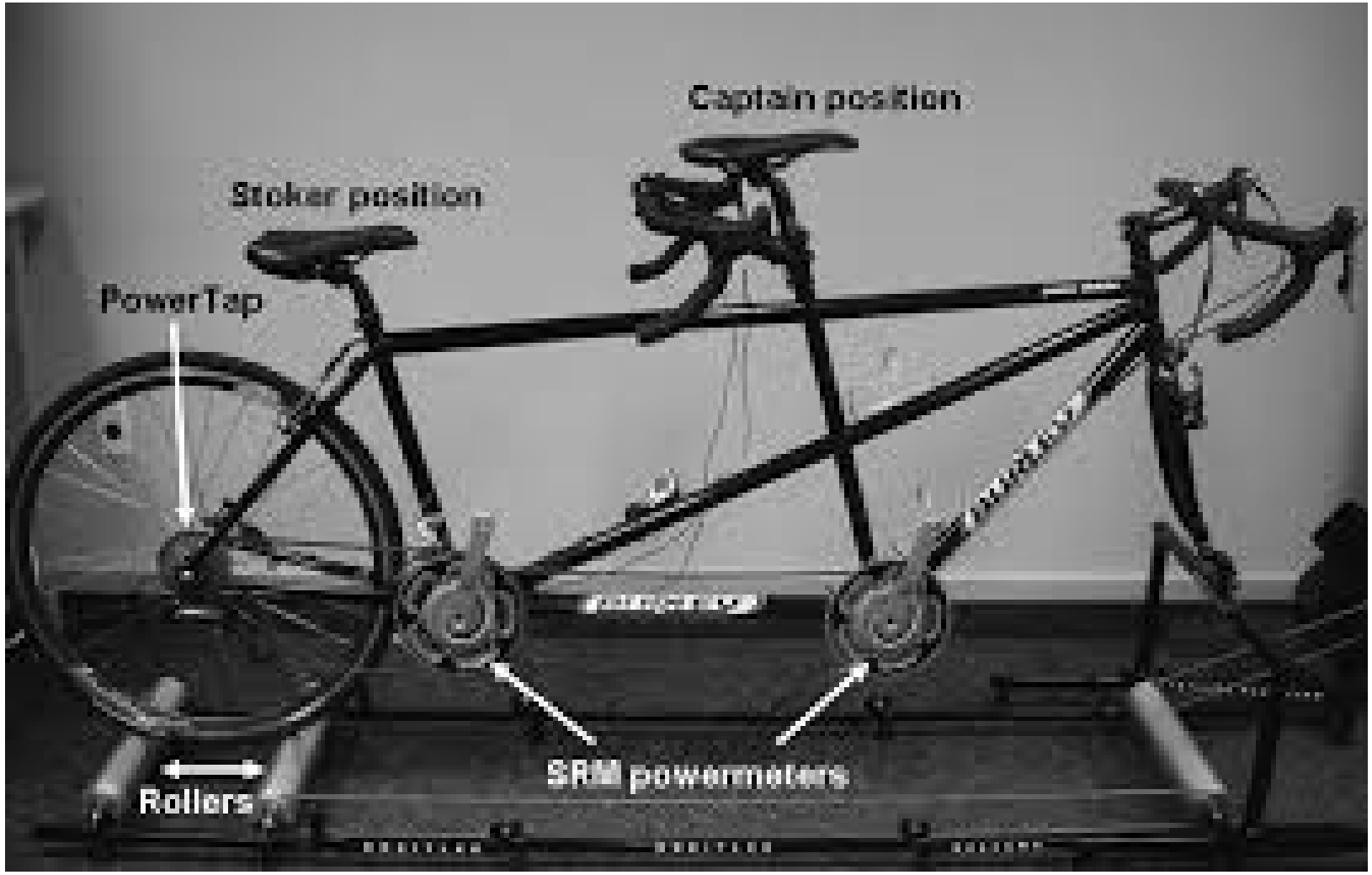
Modified



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Forced Exercise Study

- Participants ride for 1 hour: 10 min warm up at 60 RPMs, 40 min. ride at 80-90 RPMs, 10 min cool down at 60 RPMs

- Patient's heart rate (effort) kept between 60-80% of their max heart rate by the Karvonen formula ((HRmax – HRrest) × % Intensity) + HRrest

- 3 Times/week x 8 weeks x 1 hour of exercise

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Forced Exercise Study

- FE groups maintained a cadence of about 86 rpm's; avg heart rates were around 117 BPM

- Voluntary maintained a cadence of about 60 rpm's; avg heart rates were around 121 BPM

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Forced Exercise Study

- A movement disorders specialist (myself, and 2 of my partners) would examine the patients symptoms
- On meds
- Off meds
- After forced Exercise

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Forced Exercise Study

- In the FE group:
  - 41% ***improvement*** in rigidity,
  - 38% ***improvement*** in tremor, and
  - 28% ***improvement*** in bradykinesia

  (very similar improvements on levodopa)

- Voluntary groups improved, but only about half as much.

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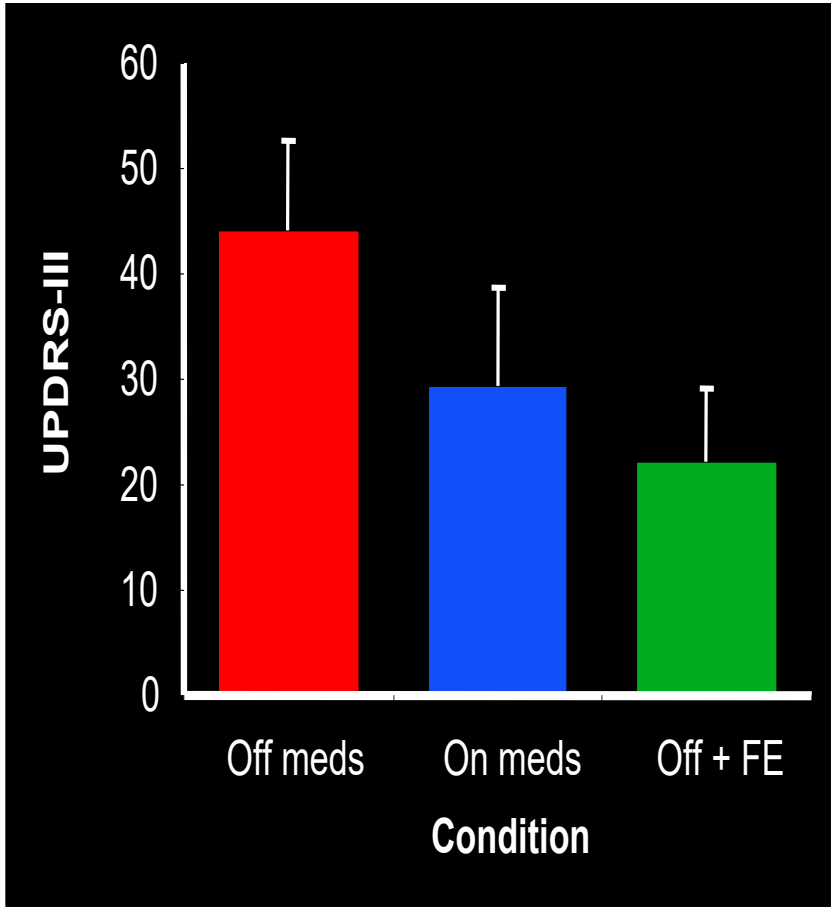
Forced Exercise Study

UPDRS Motor Score was significantly reduced with medication (41%) and following forced-exercise (46%).

(FE BETTER than exercise)



Alberts et al. Forced, Not Voluntary, Exercise Improves Motor Function in Parkinson's Disease Patients. Neurorehabil Neural Repair. 2009. 600-608.

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Forced Exercise Study - fMRI

- **Functional MRI** scanning was done 3 hours after a 40 minute session of forced exercise, as well as “on” and “off” meds.

- The pattern of cortical and subcortical activation was similar while patients were **on levodopa** and **3 hours post FE** – indicating that medications and FE utilize similar pathways to produce symptomatic relief.

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Cortical and Motor Responses to Acute Forced Exercise in Parkinson's Disease

Jay Alberts; Michael Phillips, Mark Lowe, Anneke Frankemolle, Anil Thota, Erik Beall, Mary Feldman, Anwar Ahmed, Angela Ridgel

Parkinsonism and Related Disorders 24 (2016) 56-62

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Cycle II Study

- Peloton cycling - High intensity cycling vs casual cycling
- Results show HIGH INTENSITY AEROBIC EXERCISE SLOWS THE DISEASE COURSE
- ”Prescription” for slowing appears to be cycling at about 75 RPMs for about 1 hour three times weekly

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Types of Exercise with Proven Benefits…

Tai Chai

- There have been 7 RCT's published in the past decade on the PD population.
- Studies consistently demonstrate Tai Chai groups have consistently better scores on measures of postural stability, recorded fewer falls, had better motor outcomes, and had better quality of life scores (QOL) than control groups (no exercise).
- Safe, feasible. Class I evidence by AAN guidelines.

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Types of Exercise…

Dance

- 6 published RCT's of Tango dancing in PD within the last decade – one group comparing to conventional exercise and only the Tango group showing improved balance scores, all others compared to "no exercise".

- Motor, balance, and gait scores improved in all patients who were exercising regardless of what exercise they were performing.

- Good quality studies; Class I or II AAN evidence

Duncan et al, 2014. The Journal of Alternative and Complementary Medicine; Bega, et al. Curr Treat Options Neurol, 2014. 16: 314.

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Other Exercise Types…

Yoga

- One small RCT – 13 patients over 12 weeks comparing yoga to “no exercise” control group.
- No comparisons were made for Yoga vs other exercise.
- Patients doing yoga vs no exercise had better UPDRS motor scores and balance scores.

Colgrove et al. 2012; Effect of Yoga of on motor function in people with Parkinson’s disease: a randomized controlled pilot study. J yoga Phys Ther. 2012; 2(112).

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Other Exercise Types…

- Rock Steady Boxing improves depressive symptoms and motor signs

- (Meyers et al., 2024)

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Sparx Trial

- 2017
- Phase 2 multi-center clinical trial with 3 groups assessing stage 1 to 2 PD patients over 6 months (40-80 years), not on dopaminergic medications
- 128 patients randomly assigned - high intensity exercise, moderate intensity or control group.
- Treadmill

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Sparx trial results

- High intensity group progressed less in terms of their symptoms over 6 month period on the UPDRS

- Adverse events (joint/musculoskeletal) were not significant

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Sparx 3 trial (follow up trial)

- SPARX3 trial: high-intensity treadmill as disease-modifying therapy (Corcos et al., 2022, Trials)

- Meta-analysis: aerobic exercise improves UPDRS-III (SMD −0.40), BBS (SMD 0.99)

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Park in Shape Trial (2019)

- Effectiveness of home-based and remotely supervised aerobic exercise in Parkinson's disease: a double-blind, randomized controlled trial
- 2019 clinical trial, looking at 130 PD patients, randomized to aerobic exercise (stationary bike) vs control group (stretching) 6 months
- UPDRS scores measured in off state > 12 hours after dose of dopamine medications
- Those in aerobic exercise group performed better in the “off” state

Aerobic Exercise Alters Brain Function and Structure in Parkinson's Disease: A Randomized Controlled Trial

Martin E. Johansson, MSc,[1,2†] Ian G. M. Cameron, PhD,[3,4,5†]
Nicolien M. Van der Kolk, MD, PhD,[2] Nienke M. de Vries, PhD,[2] Eva Klimars, MSc,[1,2]
Ivan Toni, PhD,[1] Bastiaan R. Bloem, MD, PhD,[2] and Rick C. Helmich, MD, PhD[1,2]

Objective: Randomized clinical trials have shown that aerobic exercise attenuates motor symptom progression in Parkinson's disease, but the underlying neural mechanisms are unclear. Here, we investigated how aerobic exercise influences disease-related functional and structural changes in the corticostriatal sensorimotor network, which is involved in the emergence of motor deficits in Parkinson's disease. Additionally, we explored effects of aerobic exercise on tissue integrity of the substantia nigra, and on behavioral and cerebral indices of cognitive control.
Methods: The Park-in-Shape trial is a single-center, double-blind randomized controlled trial in 130 Parkinson's disease patients who were randomly assigned (1:1 ratio) to aerobic exercise (stationary home trainer) or stretching (active control) interventions (duration = 6 months). An unselected subset from this trial (exercise, n = 25; stretching, n = 31) underwent resting-state functional and structural magnetic resonance imaging (MRI), and an oculomotor cognitive control task (pro- and antisaccades), at baseline and at 6-month follow-up.
Results: Aerobic exercise, but not stretching, led to increased functional connectivity of the anterior putamen with the sensorimotor cortex relative to the posterior putamen. Behaviorally, aerobic exercise also improved cognitive control.

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Testing -

- f MRI
- MRI scans
- MOCA/cognitive testing done at baseline and 6 months on both groups

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Results:

- The aerobic exercise group had a positive shift in balance of connectivity from the sensory motor region of the cortex to the putamen. (Normally disrupted in PD due to depletion of dopamine)

- The brain atrophy worsened with time in the stretching group compared to the aerobic group.

- The aerobic exercise group experienced improved cognitive control compared to the stretching group.

- The aerobic exercise group had a significantly larger change in functional connectivity within the right frontoparietal network, (a cognitive control network)

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Results: (2022)

Results: Aerobic exercise, but not stretching, led to increased functional connectivity of the anterior putamen with the sensorimotor cortex relative to the posterior putamen. Behaviorally, aerobic exercise also improved cognitive control. Furthermore, aerobic exercise increased functional connectivity in the right frontoparietal network, proportionally to fitness improvements, and it reduced global brain atrophy.

Interpretation: MRI, clinical, and behavioral results converge toward the conclusion that aerobic exercise stabilizes disease progression in the corticostriatal sensorimotor network and enhances cognitive performance.

ANN NEUROL 2022;91:203–216

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Parkinson's Outcome Project

- Largest ever study conducted of Parkinson's disease
- Began in 2009, Parkinson's Foundation
- > 13,000 participates in more than 5 countries
- Parkinson's Foundation and Centers of Excellence track and monitor care of People with Parkinson's over time

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Parkinson’s Outcome Project and Exercise

Those patients with Parkinson’s disease who exercise more than 2.5 hours per week can slow Parkinson's decline and have better quality of life

This appears to provide neuroprotective benefits and can change the course of the disease

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Exercise is medicine!

- Exercise is now considered a cornerstone in Parkinson's Rehabilitation

- Chronic exercise delays motor decline and preserves mobility (Corcos et al., 2023, Front Aging Neurosci)

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What is exercise doing to slow PD?

- Exercise increases BDNF, mitochondrial function, and anti-inflammatory exerkines and cytokines (Aguiar et al., 2023, Front Aging Neurosci)

- Biomarker shifts linked to clinical improvement (Iseki et al., 2023, Front Aging Neurosci)

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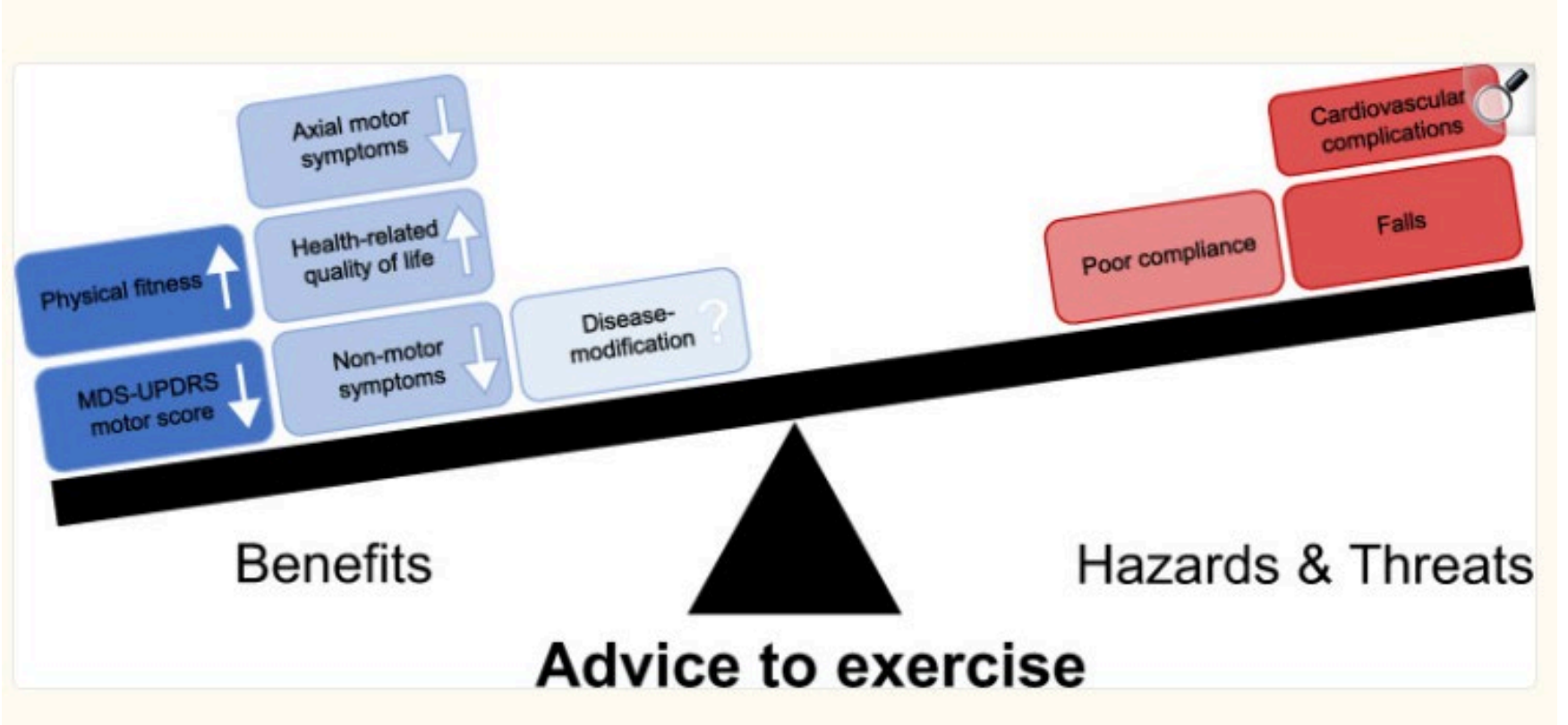

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Current Exercise Recommendations - FITT

- **F**requency – Three times per week
- **I**ntensity – 70-85% of maximum heart rate (if you could hold a conversation while exercising you need to increase the intensity)
  - 220-age then whatever # is multiple by 70-85% and that is your range.
- **T**ime – 30-40 min sessions
- **T**ype -- cycling, treadmill walking, rowing, etc.

OVERVIEW: *BENEFITS OF EXERCISE*

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Questions?

Tai Ji Quan Exercise Break

Katie Weathers, PT

New London Hospital

Parkinson's Foundation
CENTER OF EXCELLENCE

Tai Ji Quan: Moving for Better Balance® (TJQMBB)

- Hybrid approach, tailored toward balance training
  - TJQ Breathing, mindfulness, forms
  - Postural control science
    - Sensory, motor and cognitive challenge
- 1 hour classes, 2x/week x 24 weeks
  - Seated, standing and stepping
  - Remote and in-person delivery

tai ji quan
Moving for Better Balance

Expert Panel Q&A

Mary Feldman, DO

Stephen Lee, MD

Rebecca Thompson, MD

Oliver Phillips, MD

Richard Wang, DO

Non-Motor Manifestations of Parkinson's Disease

Corie Crane, DNP, APRN, PMHNP-BC

Nurse Practitioner, Geriatric Psychiatry

- No conflicts of interest
- I will discuss off-label use of medications
- All content and data presented my own viewpoints, not those of Dartmouth Health

Neuropsychiatric Symptoms

Depression
Anxiety
Apathy
Psychotic Symptoms
Impulsivity and Compulsions
Cognitive Impairment

Why these symptoms matter

- Neuropsychiatric symptoms are common!
- Functional impairment, loss of independence can be distressing
- Can lead to earlier and longer hospitalization or need for higher level of care

Depression

- Common, approximately 35%
  - 60% of people with advanced disease
- Ranked as one of the most troubling non-motor symptoms
- Including: sadness, depressed mood, loss of pleasure, guilt, worthlessness
- May be an early or first sign of Parkinson’s
- Chronic, frequent throughout course of illness
- Often improves with dopaminergic medication treatment

Depression

- Full biology of depression in Parkinson's is unknown
- Result of off-period fluctuations or secondary to long-term levodopa
- Symptom overlap with key Parkinson's features can be challenging (weight loss, sleep changes, slowed moving and thinking)
  - Can mean it can be left untreated or undertreated
- Negatively impacts motor symptoms and quality of life
- Evidence-based and effective treatment options

Anxiety

- Common, approximately 30 - 40%
- Including nervousness, worry, fear, sense of physical or emotional distress, avoiding everyday situations or socialization
    - Generalized anxiety (excessive worry)
    - Social anxiety (anxiety in social situations)
    - Panic (abrupt onset of anxiety)
- Early, chronic, frequent
- Can improve with dopaminergic medication

Anxiety

- Biology is unclear
- Can be in relation to off-periods of medication, or potentially triggered by medication
- Parkinson's related fears: Falling, drooling, slurring words, pronounced Parkinsonian symptoms, worry of medication wearing off
- Negatively impacts motor symptoms & quality of life
- Medications & psychotherapy can be helpful

Apathy

- Common, approximately 40 - 60%
- Including: low interest, low participation, lack of initiative, low motivation, indifference
- Worsens with disease progression
- Often improves with dopaminergic medication
  - Correlates to decreased medication adherence and response
- Not well studied, but treatable!

Apathy

- What apathy isn’t: laziness, poor initiative, depression
- Differences from depression include indifference and lack of drive
- Can lead to decreased physical activity and decreased socialization!
- Great impact to quality of life for both the patient and their care partners

Managing Apathy

- Encouragement
- Routine
- Exercise
- Sleep well!
- Attainable goal setting
- Prompting
- Focus on achievements
- Create a schedule

- Ask for support!

Psychosis & Hallucinations

- Common, approximately 20 - 40%
- Visual hallucinations most common (including illusions)
  - Begin minor, non-threatening but can progress into more troublesome
- Auditory hallucinations occur in a small percentage of persons with PD
- Rarely olfactory, tactile, or gustatory
- Can be precipitated by drug treatment
- Treatable!

Psychosis & Delusions

- Illogical, irrational, dysfunctional views or thoughts, not based in reality
- Not deliberate
- Including: jealousy, persecutory, somatic

Impulse control Disorders

- Occurs in 5 - 15% of patients treated for PD
- Including failure to resist temptation, impulsive actions, repetitive behaviors interfering with daily life
    - Excessive cleaning, eating, gambling, hypersexuality
- Range of intensity – non-bothersome to destructive
- Generally improve with medication adjustments

Cognitive Impairment

- Subjective cognitive impairment: approximately 16 - 45%
- Mild cognitive impairment: approximately 25 - 40%
- Dementia: approximately 24 - 41%
- Including memory loss, functional difficulties, word-finding, slowed processing speed
- Gradual onset and progression

Cognitive Impairment

- Not impacted by dopaminergic medications
- Parkinson's disease dementia is considered a type of Lewy body dementia
- May co-occur with other forms of dementia
- Neuropsychiatric symptoms are considered to be a risk factor for developing cognitive impairment
- Impacts quality of life, ability to complete activities of daily living, impacts social function, contributes to care partner distress

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Treatment Considerations

- Safety is always the priority

- May not always require medication intervention!
- First-line interventions include psychotherapy, behavioral interventions based on patient's ability to learn and apply these interventions
  - Patient, care partner, environment
- One size does not fit all

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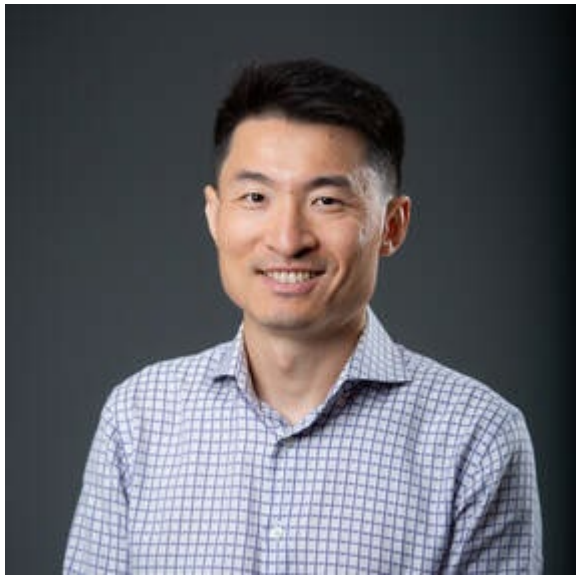
Treatment Considerations

- Neuropsychiatric symptoms can overshadow motor symptoms and become distressing
- They occur throughout the course of the disease, often worsening with illness progression
- Distressing to patient and care partners, leading to higher occurrence of hospitalizations or escalating level of care needs
- May include: antidepressants, antipsychotics, stimulants, dementia drugs, etc

Questions?



Deep Brain Stimulation and Focused Ultrasound for Parkinson's Disease

RICHARD SUN, MD, PHD, NEUROSURGEON

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Deep brain stimulation (DBS)

- Neuromodulation: an established approach for treating neurological disorders
- A device implanted into the brain to improve motor symptoms of Parkinson Disease and Essential Tremor
  - Benefits: (1) reversible and (2) adjustable
- > 180,000 patients with Essential Tremor, Parkinson's, and dystonia treated with DBS worldwide
- > 2000 scientific articles published on DBS
- **FDA-approved: Essential Tremor in 1997, Parkinson's in 2002**
- Best outcomes: expert/experienced team/center for standardized & consistent approach to DBS patient selection and management

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PD: Indications for Deep Brain Stimulation

- Idiopathic Parkinson's Disease.
- "On-Off" phenomena and/or dyskinesia.
- Troubling motor symptoms despite optimized medication regimen.
- Highly responsive to levodopa, with good motor function during "on" state.
- Doesn't suffer from dementia or untreated depression.

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DBS is not a cure: what symptoms are improved by surgery?

- Motor fluctuations in response to medications (e.g. levodopa)
- Surgery can help with symptoms that responds to medication (unlikely to be better than your best on-time):
  - Tremor: reduction can be superior to medication
  - Slowness (Bradykinesia)
  - Stiffness (Rigidity)
  - Freezing of gait
  - Dyskinesias and Dystonia

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What symptoms will unlikely improve?

- Cognitive and Psychiatric Symptoms
- On-period freezing
- Swallowing difficulties
- Speech problems
- Poor balance

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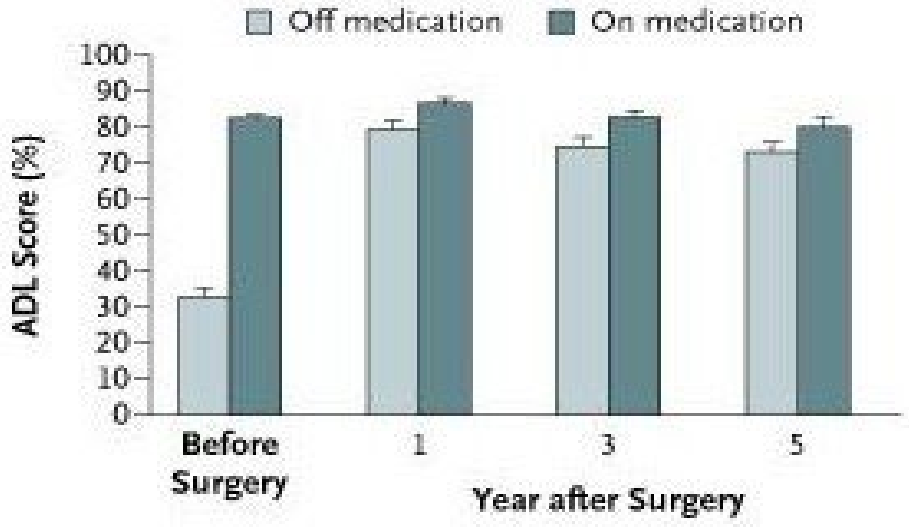
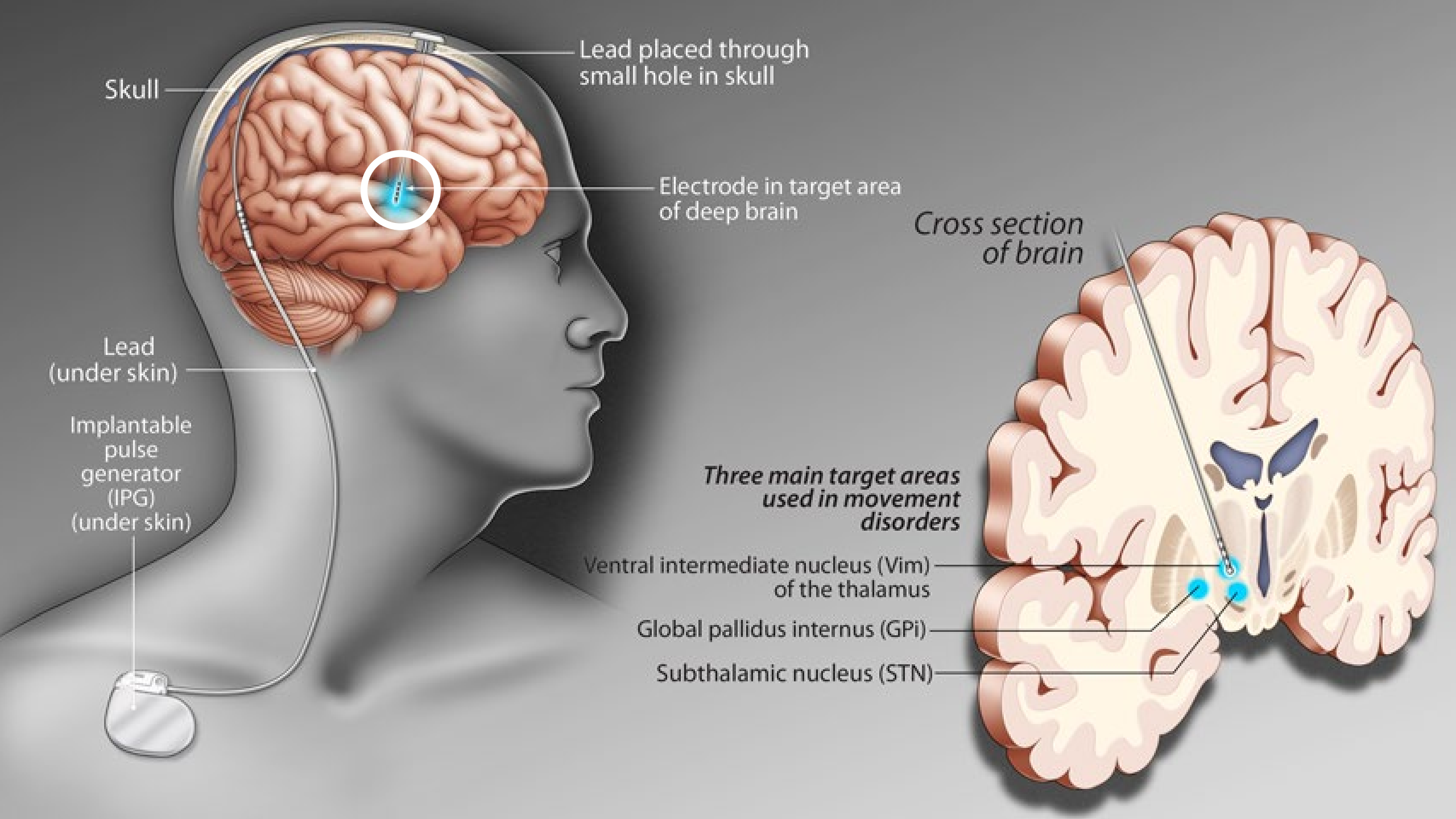
How Long Will the Benefits of Surgery Last?

DBS is adjustable

In most appropriately-selected DBS cases, patients continue to have improved functioning for at least 16 years.

Patients who have undergone DBS on both sides continue to be improved beyond their pre-op state for at least 5 years.




Skull
Lead placed through small hole in skull
Electrode in target area of deep brain
Lead (under skin)
Implantable pulse generator (IPG) (under skin)
Cross section of brain
Three main target areas used in movement disorders
Ventral intermediate nucleus (Vim) of the thalamus
Global pallidus internus (GPi)
Subthalamic nucleus (STN)

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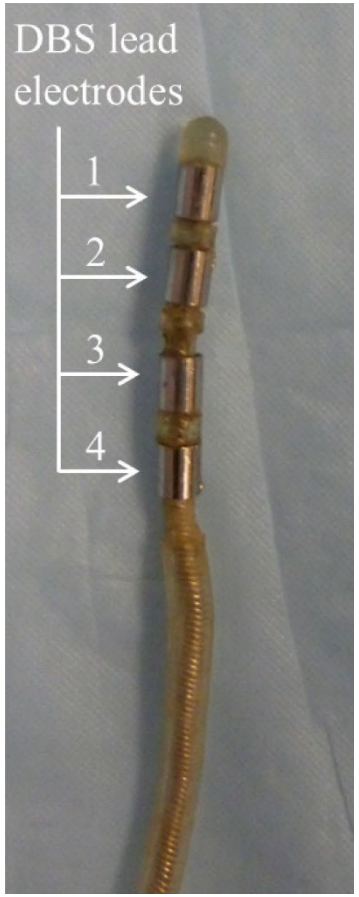
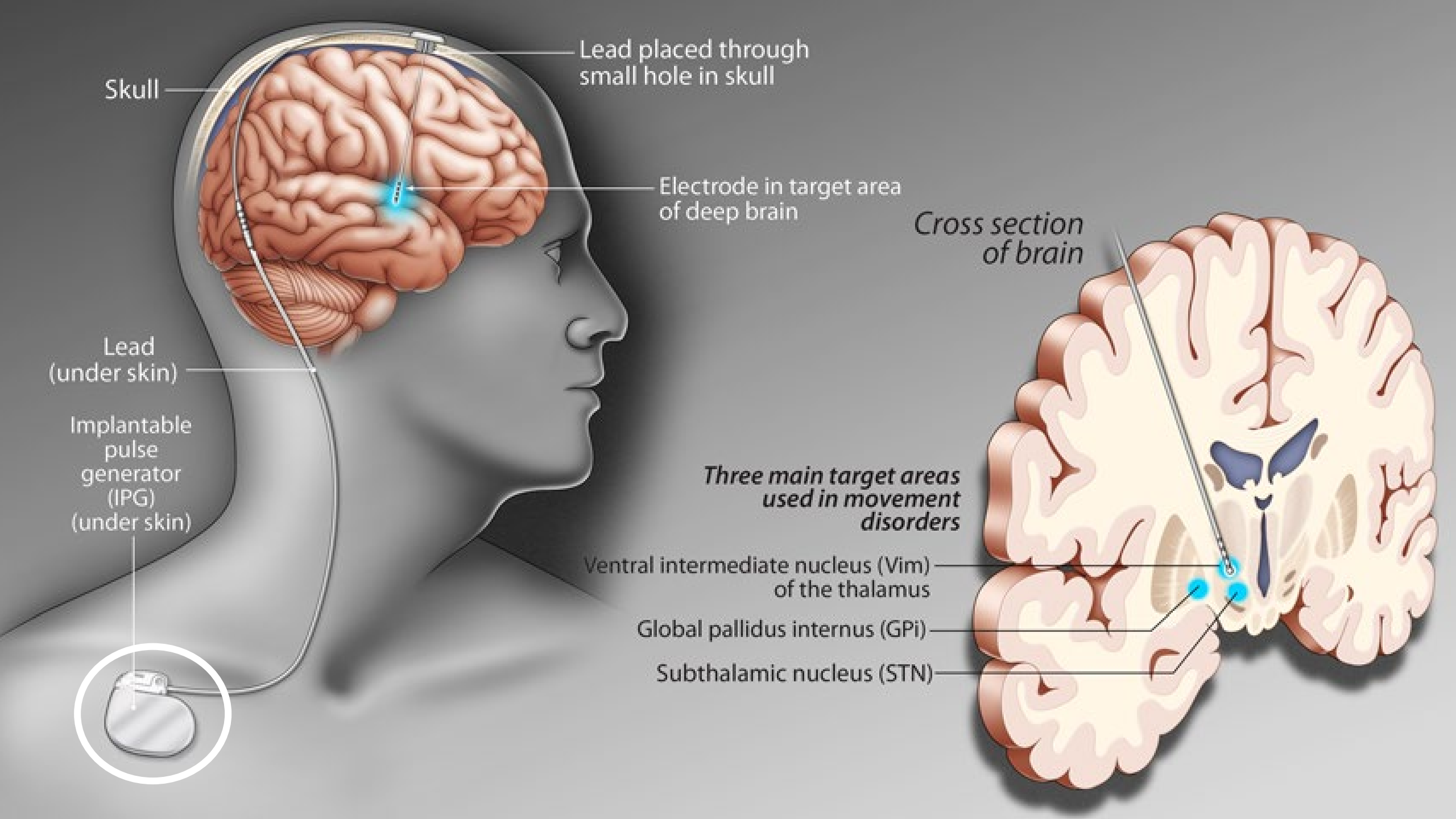
DBS lead implanted into the brain




Skull
Lead placed through small hole in skull
Electrode in target area of deep brain
Lead (under skin)
Implantable pulse generator (IPG) (under skin)
Cross section of brain
Three main target areas used in movement disorders
Ventral intermediate nucleus (Vim) of the thalamus
Global pallidus internus (GPi)
Subthalamic nucleus (STN)

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STN versus GPi DBS

Outcomes	GPi	STN
Bradykinesia	+ +	+ +
Rigidity	+ +	+ +
Tremor	+ +	+ +
Quality of life	+ +	+ +
Dyskinesia reduction	+ +	+
Stimulation-induced dyskinesia	–	––
Medication reduction		+ +
Flexibility of long-term medication adjustments	+ +	
Cognitive adverse effects	–	––
Mood adverse effects	–	––
Gait adverse effects	–	––
Speech and swallowing adverse effects	–	––
Ease of programming	+ +	
Reduced battery consumption		+ +
Ability to use one lead	+ +	

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Implantable pulse generator (IPG) provides electrical power and stimulation

Like a pacemaker, the IPG is implanted below the collarbone on the right or left chest wall. The IPG drives current through the electrodes to alter the activity of small areas of the brain

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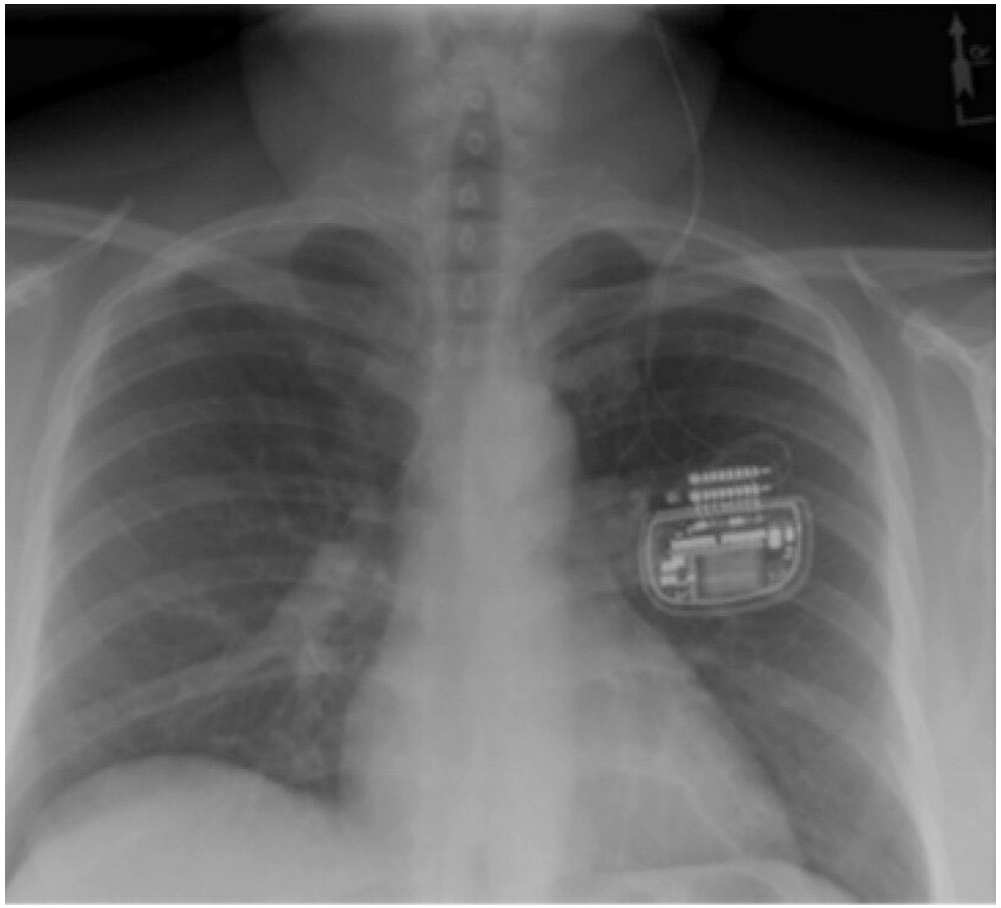
Implantable pulse generator (IPG) provides electrical power and stimulation



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Overview of DBS surgery

- Surgery is a two-stage procedure: (1) lead and (2) generator
- **Stage 1:** leads will be implanted in the brain.
- Discharge from the hospital the following day
- **Stage 2**: pulse generator implantation
- The stimulator will be programmed 2-4 weeks after implantation of the pulse generator

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DBS: local versus general anesthesia

Local anesthesia - awake

- Targeting based on MRI, brain signals, and stimulation-induced effects
- Can test for efficacy and side effects during surgery
- Fewer treatment-related side effects
- Hair shave at incision site
- Generator (battery) implanted during second procedure (1-2 weeks after stage 1)

General anesthesia - asleep

- Targeting based on MRI
- Efficacy and side-effect profile is unknown until device is turned on
- Lower overall complication rates
- Front half of head shaved
- Generator implanted on the same day as stage 1

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DBS: local versus general anesthesia

- No significant differences in overall outcomes at 6 months to 4 years
- A decision based on patient preference, neurologist recommendation, and neurosurgeon input.

Variable	Awake	iMRI
%Δ in UPDRS, off-medication, post-op vs pre-op	**−32.9 (37)**	**−34.1 (28)**
STN	−39.1 (34)	−44.7 (37)
GPi	−17.1 (43)	−30.0 (23)
% Δ in LEDD, postoperative vs preoperative	**−29.4 (42)**	**−15.2 (51)**
STN	−41.9 (37)	−35.8 (41)
GPi	−2.2 (39)	−2.3 (52)

Lee et al., J Neurosurg 2022

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DBS under local anesthesia (awake)
Head frame placement

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DBS under local anesthesia (awake): intraoperative testing

- Surgery begins with incision(s) of the scalp
- Hole(s) are drilled in the skull about the size of a dime.
- The drilling takes about 10 to 30 seconds.
- A small electrode holder is placed inside this opening to allow the electrodes to be inserted.
- Recording of electrical signals and testing the effects of stimulation
- After testing, a plastic cover is placed over the burr holes which secures electrode(s) in place.

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DBS under local anesthesia (awake): testing stimulation effects

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Stage 2: Implantation of the pulse generator

- After stage 1 lead implantation, stage 2 generator implantation is performed approximately 1-2 weeks later.
- Again, if asleep DBS surgery is elected, pulse generator is implanted on the same day as the lead(s)
- This procedure is performed under general anesthesia
- This is done as an outpatient procedure. Overnight stay is usually not required.

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After surgery

- Go to the recovery room or to the ICU.
- Typically, patients feel well enough to go home the next day.

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Turning on the stimulator

- The stimulator will be turned on 4-6 weeks after placement of the leads.
- This will take place in an office visit.
- The stimulator is programmed specifically to treat your symptoms.
- The visit will take about 1-2 hours. Following visits will be 30min-1 hour.
- Parkinson’s patients are usually asked to be OFF medication for DBS visits.

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Results of surgery

- Some patients note improvement after surgery even before the stimulator is turned on. This is a **temporary** condition we call “the honeymoon period” or lesional effect.
- After the stimulator is turned on, an immediate effect is usually apparent.
- Most patients require multiple programming sessions over the first 3-6 months to optimize the therapy.
- DBS does not cure the disease, nor does it inhibit the progression of the disease.
- The stimulator can be adjusted over time to treat changing symptoms.

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Results of surgery – Parkinson's Disease

- Off time reduced for Parkinson's patients
- 83% reduction in off-time
- Medication requirements on average are decreased by 30-40%.
- The reduced requirement for medications results in better quality "on" time with less dyskinesia.
- 86% reduction in incidence and duration of dyskinesias
- Average daily increase of 4.6 hours on time without troubling dyskinesia

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What are the risks of DBS surgery?

- Brain bleed (1-3%).
- Infection (3%).
- Device Failure (1-5%).
- Pain
- Lack of symptom improvement
- Seizures (2%)
- Short-/long-term Changes in cognition, mood, or memory (5%).

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MRI-guided high-intensity focused ultrasound (MRgFUS)

- Incisionless treatment performed as outpatient with the potential to improve the quality of life for patients with essential tremor and Parkinson's disease.
- Hundreds of beams of ultrasonic energy are focused precisely and accurately on small targets deep in the brain without damaging surrounding normal tissue.

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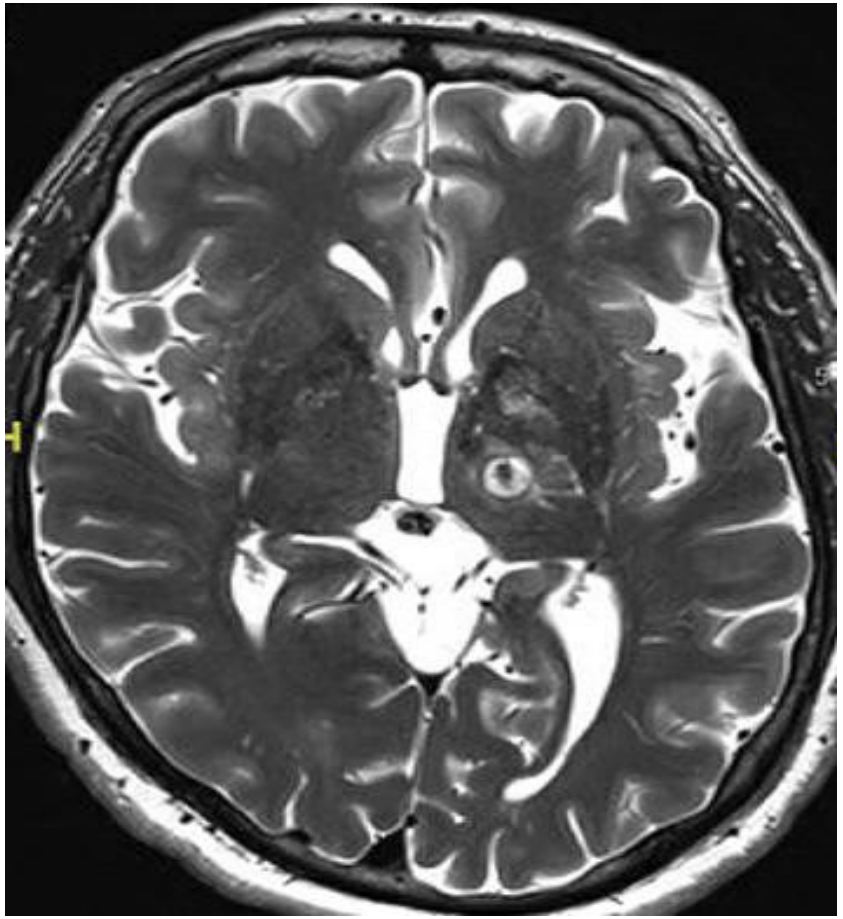
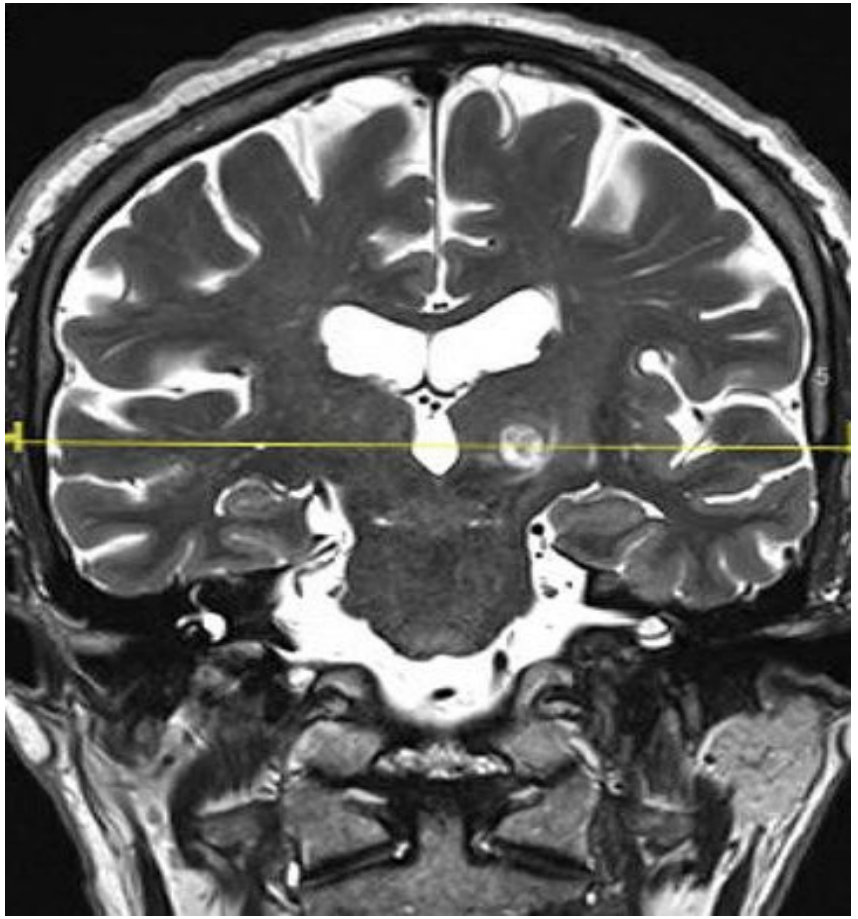
How does focused ultrasound work?

Uses up to 1024 high frequency sound waves to produce a “burn” in the brain





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Current indications for MRgFUS

Diagnosis	Side	Target	Approval date
ET	Unilateral	VIM thalamotomy	July 2016
PD – tremor dominant	**Unilateral**	**VIM thalamotomy**	**December 2018**
ET	Bilateral (staged)	VIM thalamotomy	December 2022
PD	**Unilateral**	**Pallidotomy**	**November 2021**
PD	**Bilateral (staged)**	**Pallidothalamic tractotomy (PTT)**	**July 2025**

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Indications for MRgFUS unilateral thalamotomy

- Patients with Parkinson's disease who regarded arm tremor as the most disabling motor symptom affecting activities of daily living
- Troubling tremors during the "on" state
- Not good candidates: tremors mostly in the "off" state

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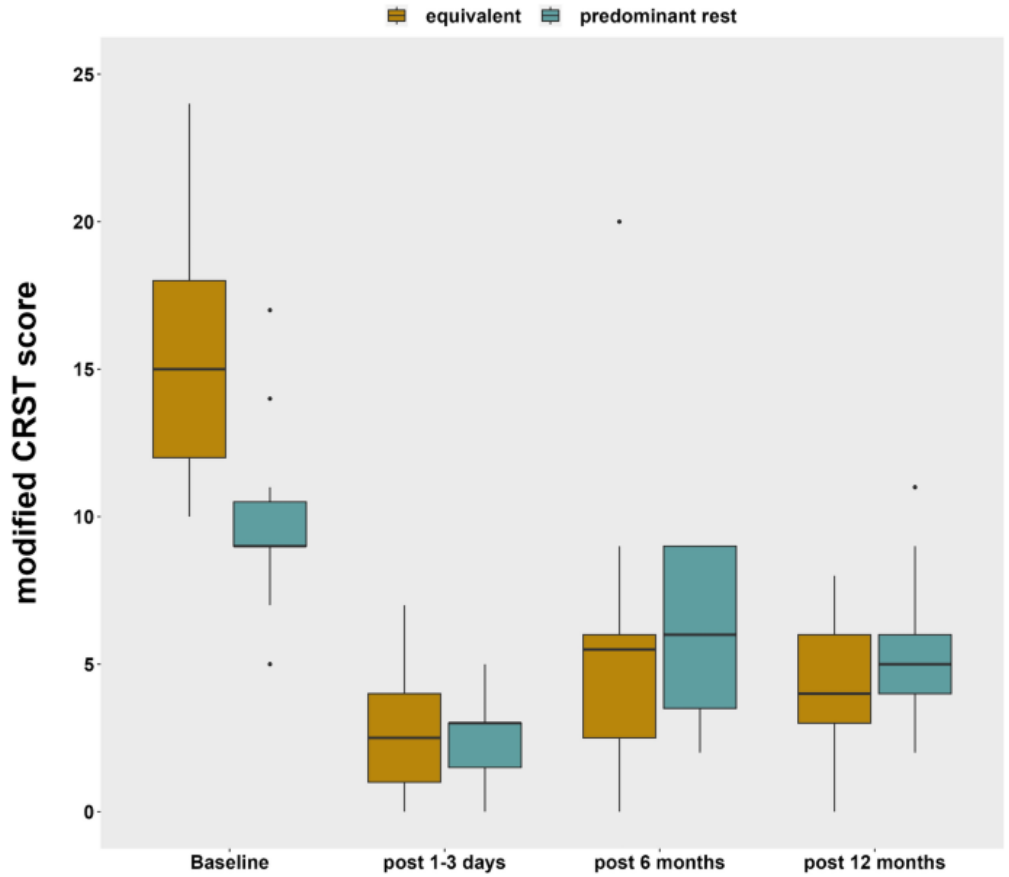
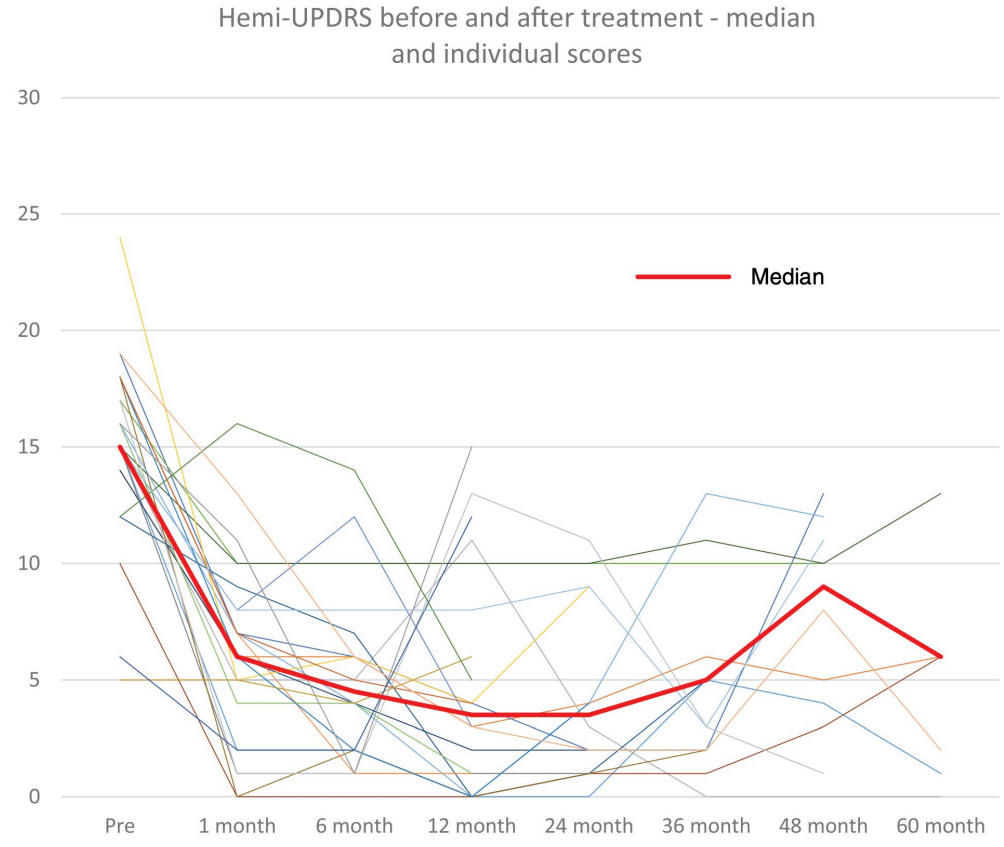
Outcomes of MRgFUS unilateral thalamotomy



Purrer et al., 2024



Sinai et al., 2022

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Side effects of MRgFUS unilateral thalamotomy

- Numbness/tingling
- Dysarthria (speech difficulty)
- Unsteadiness/imbalance
- Abnormal taste
- Gait disturbance (difficulty with walking)
- Dysphagia (swallowing difficulty)
- Fatigue
- Weakness (face or arm/leg)

Indications for MRgFUS staged bilateral pallidothalamic tractotomy

- Advanced idiopathic Parkinson's disease
- Insufficient long-term medication efficacy
- Levodopa responsive patients with severe bilateral symptoms impacting quality of life
- No severe cognitive impairments (MoCA > 20)

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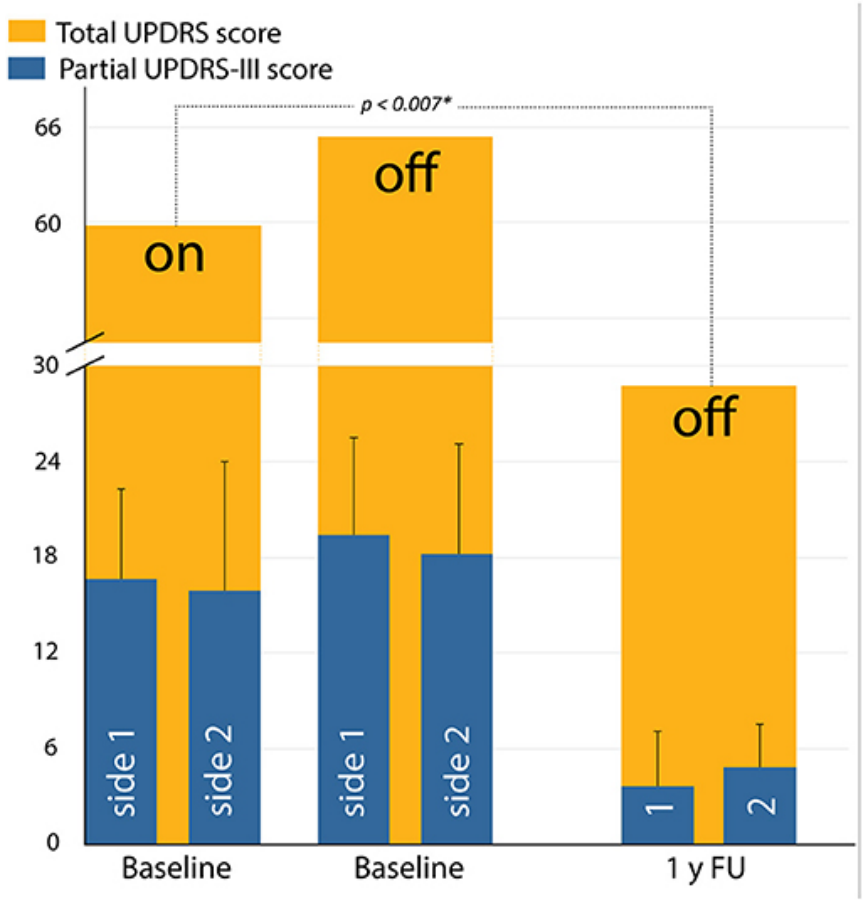
Outcomes of MRgFUS staged bilateral pallidothalamic tractotomy

- Ongoing clinical trial
- Promising outcomes data only from small pilot studies of both unilateral and bilateral cases



Gallay et al., 2021

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Side effects of MRgFUS staged bilateral pallidothalamic tractotomy

- Sonication pain
- Gait instability
- Weakness

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Indications for MRgFUS pallidotomy

- Idiopathic Parkinson's Disease
- Asymmetric dyskinesia or dystonia limiting or despite optimized pharmacotherapy
- Responsive to levodopa, with good motor function in best "on" state
- Doesn't suffer from dementia or untreated depression

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Expected outcomes from FUS pallidotomy

- Motor fluctuations: reduction in “off” time symptoms and dyskinesias
- Off-time dystonia may be improved
- Medication requirements may be decreased
- 70% of clinical trial patients maintained a response at one year
- Long term outcome TBD

Krishna et al., 2023

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PD: what symptoms will not be improved with FUS pallidotomy?

- Medication Requirement
- Cognitive and Psychiatric Symptoms.
- On-Period Freezing
- Swallowing Difficulties
- Speech Problems
- Poor Balance

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PD: risks of FUS pallidotomy

- Procedure related: nausea/vomiting (15%), headache (15%), and sonication-related head pain (35%).
- Visual field deficit (1-5%)
- Transient/Persistent Risks: fine motor difficulties (5%), dysarthria (15%), and balance difficulties (5%), none of which were severe.

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FUS treatment overview

- Initial workup to ensure candidacy
- Treatment is a single-day outpatient procedure
- Typical duration from arrival to discharge: ~ 6 hours
- This is a “one and done” procedure: the goal is to not undergo additional procedures

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Evaluation steps prior to FUS

- Evaluation by with neurosurgeon and team performing the procedure
- Head CT to determine skull density ratio (SDR)
- MRI of the brain: before or on the day of procedure
- Schedule the procedure

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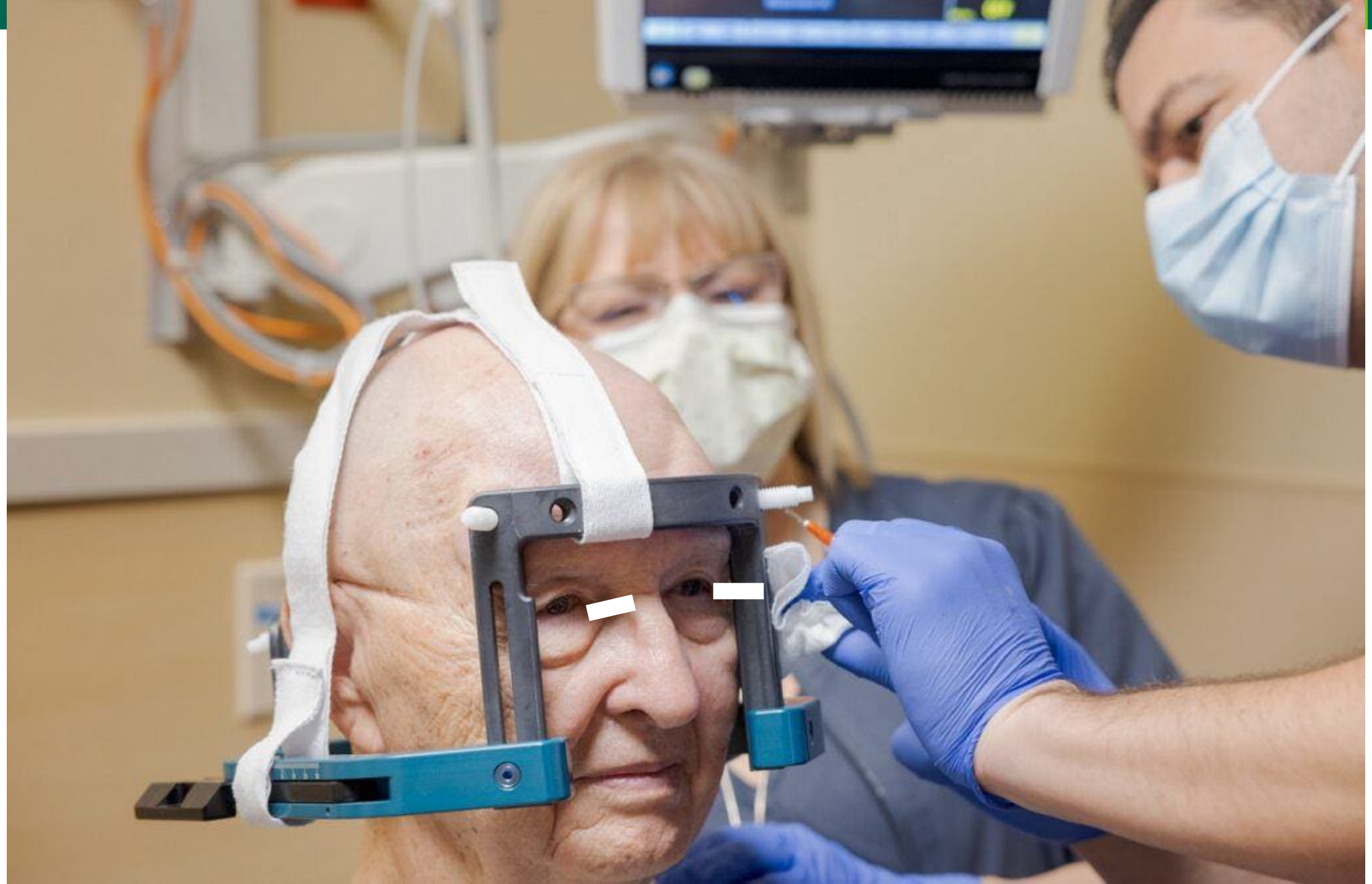
On the day of the procedure

- Complete head shave
- In a procedure room: frame placement with four skull fixation pins
- We will then help you lie down on the MRI table with the frame secured to the ultrasound “helmet”
- We will then do a series of MRI scans
- Then bring you in and out of the scanner to repeatedly test your speech and movement (boring) between sonications
- During sonication, you may feel uncomfortable symptoms or nausea
- The procedure takes 2-4 hours.



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After the procedure

- Recovery room or patient waiting area
- We will make sure you are stable enough to walk
- May require extra time in recovery if dizzy
- Usually, can go home within a few hours
- Reasonable to expect immediate improvement in symptoms

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How does HiFUS compare to DBS?

DBS

- Long-lasting efficacy
- One or both sides
- Adjustable
- Can be turned off
- Surgical risks: bleeding and infection, etc
- Programming and adjustments, multiple surgeries (IPG)

Focused Ultrasound

- May be less durable
- Only one side can be treated at a time
- Unmodifiable
- Side effects can be permanent
- Lower bleeding risk, no infection risk
- One-time outpatient procedure

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Questions?

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Raffle Prize Drawing Time

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Department of Neurology,
Parkinson's Center of Excellence

DARTMOUTH HITCHCOCK MEDICAL CENTER

Thank you!

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