Stanford MEDICINE | Neurology & Neurological Sciences

Updates in Parkinson's Disease

Gaurav Chattree, MD
Clinical Fellow – Stanford Movement Disorders
Research Fellow – Schnitzer Lab

March 2022

Types of treatments

Disease Modifying Therapies

- **Slow** or **halt** the progression of neuron dysfunction / neuron death (i.e. therapies that prevent further neurons from being impacted by the disease)

Symptomatic Therapies

- **Improve** / **restore function** for the patient (i.e. therapies that improve motor function, cognitive function, etc)

Disease Modifying Approaches

Hundreds of approaches at some stage in development

Highlights:

- GLP-1R agonists
- Targeting α-synuclein
- LRRK2 inhibition

GLP-1R Agonists

Isolated from Gila Monster venom in 1992 by Dr. John Eng

Commonly used drug class for **diabetes** (and recently, obesity)

- Stimulates the pancreas to release more insulin

Parkinson's animal models showed disease benefit

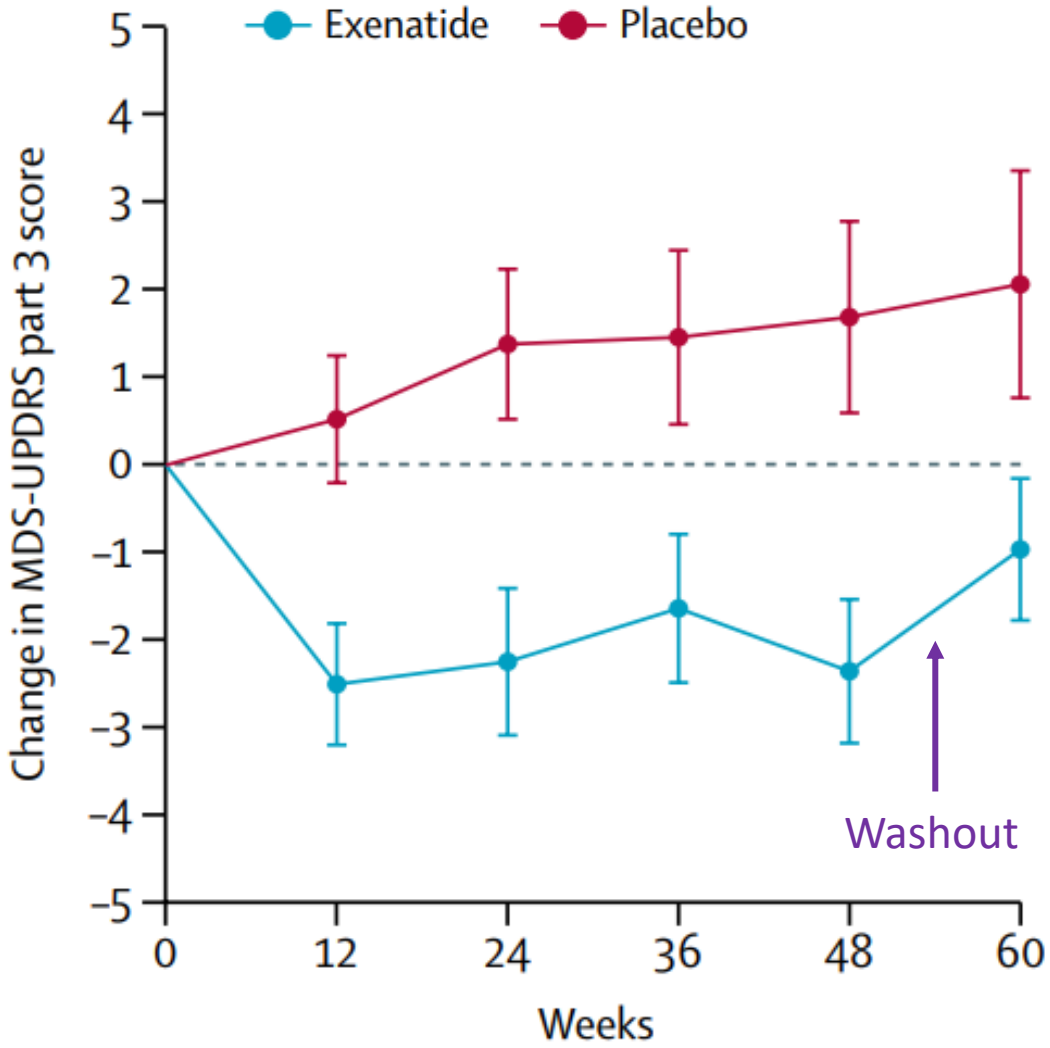
GLP-1R Agonist (Exenatide) Phase 2 Trial

Published in 2017

32 PD patients received Exenatide, 30 PD patients received placebo

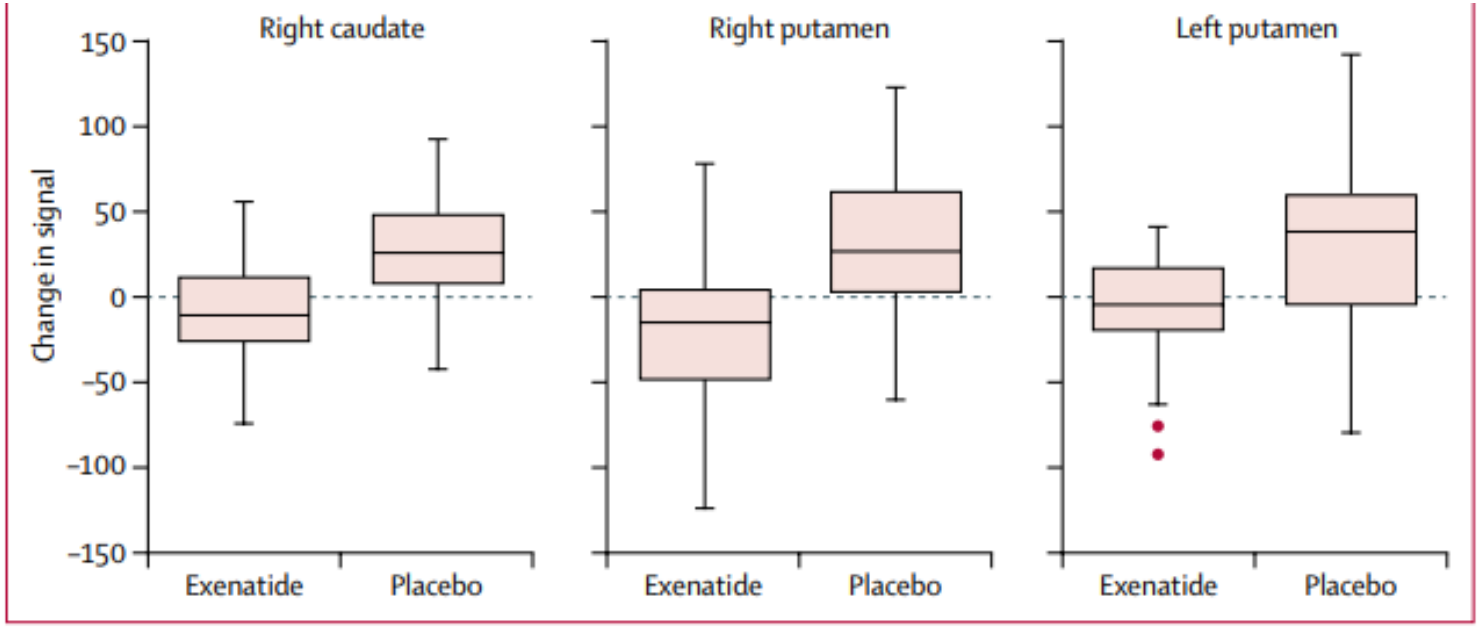
- 48 weeks on medication, 12-week washout period

Mild adverse effects, not worse than placebo

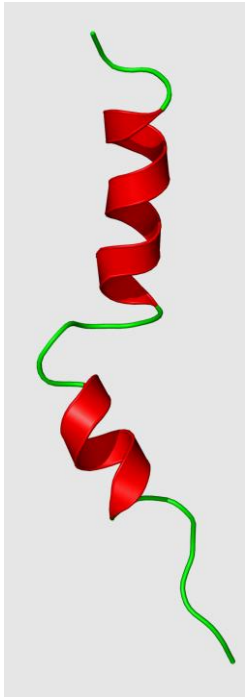


GLP-1R Agonist (Exenatide) Phase 2 Trial

Reduced rate of decline in DAT Scan



GLP-1R Agonists – What's Next



- 2019 to 2024: Exenatide Phase III (UK)
  - 200 patients, each patient followed over 24 months
- 2020 to 2023: Pegylated Exenatide Phase II (US)
  - 240 patients, each patient followed for 9 months
  - UC Davis, UCSF, UCLA all participating and **recruiting**
  - https://clinicaltrials.ucsf.edu/trial/NCT04154072
- 2020 to **2022**: Exenatide in new PD – Phase II (Sweden)
  - 60 patients, each patient followed over 18 months
- 2018 to **2022**: Lixisenatide Phase II (France)
  - 156 patients, each patient followed over 12 months
- 2017 to **2022**: Liraglutide Phase II (US – Cedars Sinai)
  - 63 patients, each patient followed over 12 months
- Studies in Norway and S. Korea as well, to be reported in **2022**

All eyes on these in 2022

Targeting α-synuclein

Hypothesis:

- Various triggers cause the α-synuclein protein to misfold
- This misfolded protein propagates throughout the brain causing neuron dysfunction and neuron death resulting in PD

Goal:

- Stop α-synuclein misfolding and propagation

Strategies:

- Passively provide antibodies against α-synuclein
- Have the body generates its own antibodies to α-synuclein (i.e. an α-synuclein vaccine)
- Have a small molecule interfere with α-synuclein
- Create a protein that breaks misfolded α-synuclein

Targeting α-synuclein

Mixed results so far (mostly negative, but some signs of small benefit in post-hoc analysis)

Concern: Once a patient is showing signs of PD lots of neuronal injury has already occurred and many biological pathways throughout the brain are behaving abnormally. Misfolded α-synuclein may have *triggered* the cascade, but the cascade is already in motion and removing misfolded α-synuclein at this stage may not stop it

This appears to be the case in Alzheimer's disease and β-Amyloid

Studies will need to be done in *prodromal* patients (patients who are likely to develop PD but do not meet the diagnosis yet)

Targeting α-synuclein – What's next

- 2019 to 2022: UB-312 (α-synuclein vaccine) Phase I
  - 70 patients
- 2021 to 2024: Prasinezumab (α-synuclein antibody) Phase II
  - 575 patients, each patient followed over 18 months
- Many other Phase I trials in this category underway or to be initiated soon

LRRK2 Inhibitors

Hypothesis:

- Certain mutations in the gene LRRK2 contribute to the development of PD
- The enzyme encoded by the mutated gene is hyperactive
- This LRRK2 enzyme hyperactivity leads to PD (exactly how is unclear)

Goal:

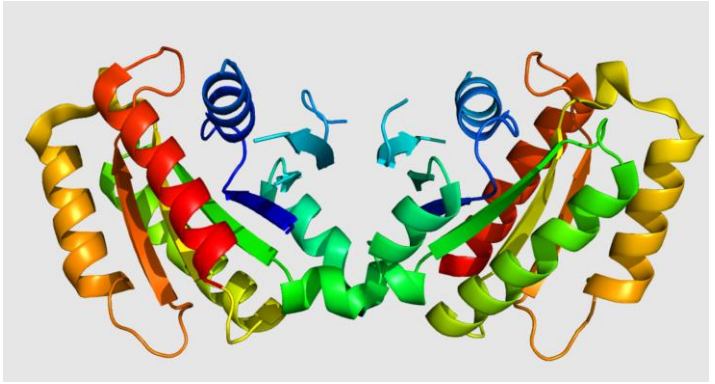
- Design a way to slow down the LRRK2 enzyme

Strategies:

- Small molecules
  - Phase 1 study of the drug DNL151 was safe (reported in 2021, Denali Therapeutics)
- Genetic modifications

LRRK2 Inhibitors – What's Next

- FDA has approved Denali to move to the next stage of clinical trials
  - Enrollment will begin in 2022
  - Learn more: https://www.engageparkinsons.com/
- Ionis Pharmaceuticals has an Antisense Oligonucleuotide (ASO) that blocks the neurons from making the LRRK2 enzyme
  - Phase 1 will be complete in 2023



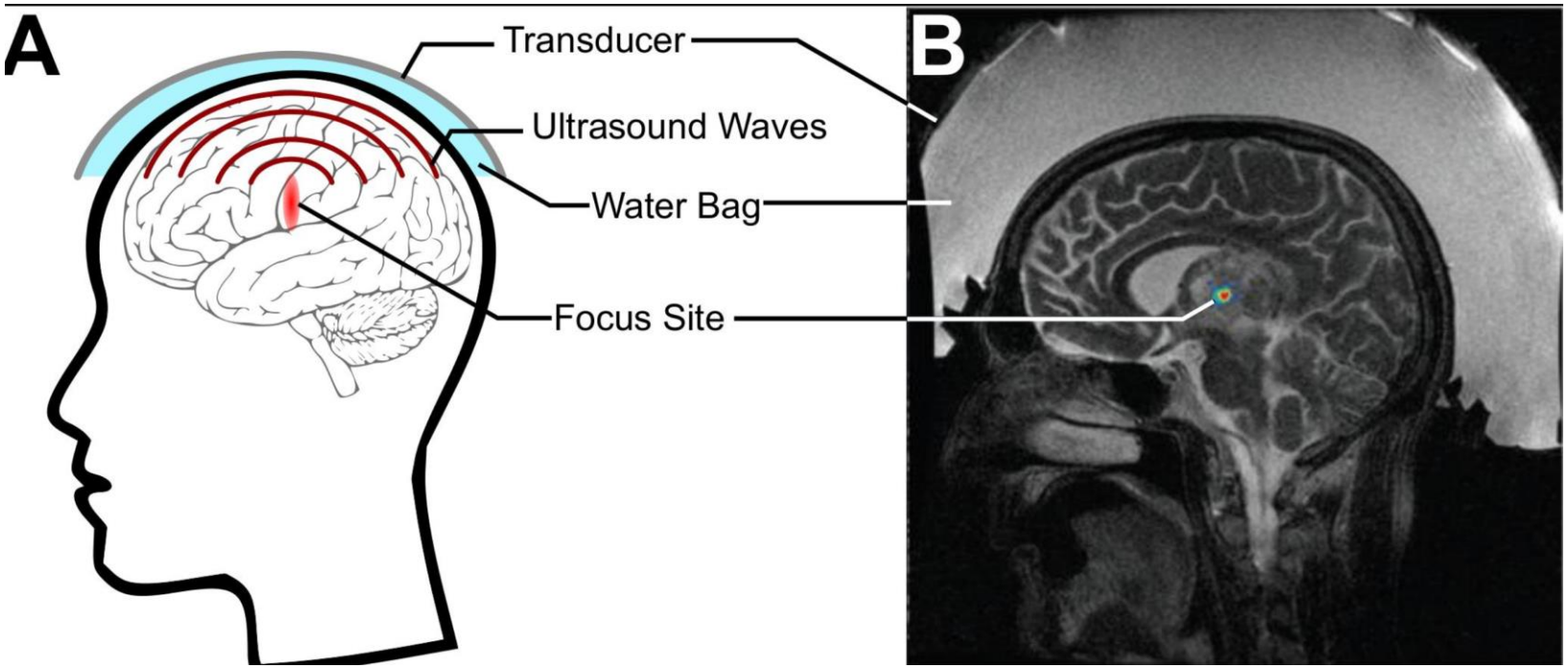
Symptomatic Therapies

New formulations of old drugs:	Opicapone, Safinamide, Levodopa inhalation powder, Apomorphine sublingual film, long-acting Amantadine
	Useful in special cases, but does not change treatment for most patients
New interventional approaches:	Ultrasound lesion of the Subthalamic Nucleus (STN) (approved)
	Dopamine neuron stem cell implantation (in trials)
	Adaptive Deep Brian Stimulation (aDBS) (in trials)

STN Focused Ultrasound

Focused non-ionizing ultrasonic waves to lesion tissue

- In this case, the subthalamic nucleus in the brain



STN Focused Ultrasound Trial (2020)

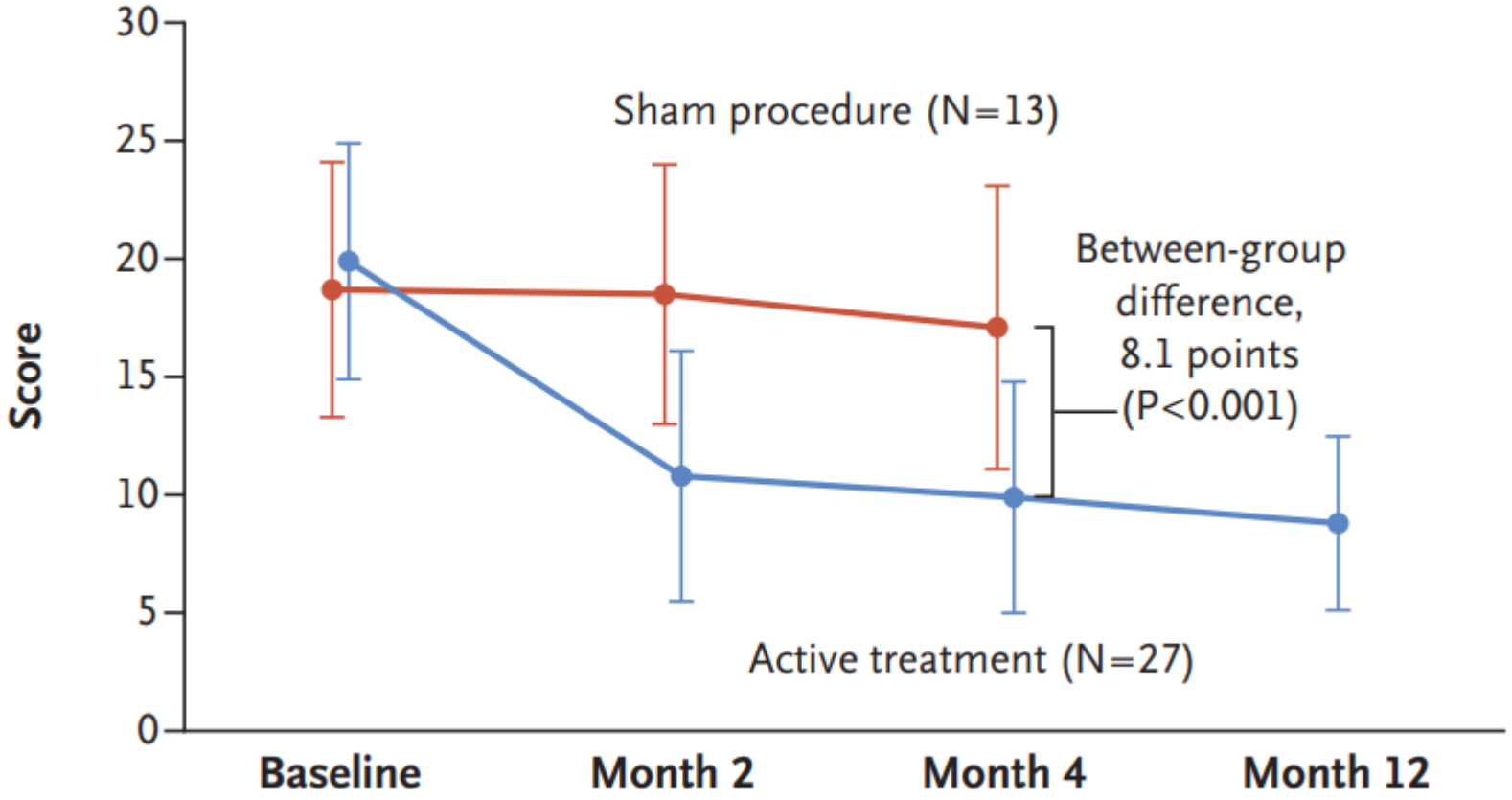
The NEW ENGLAND JOURNAL of MEDICINE
ESTABLISHED IN 1812 DECEMBER 24, 2020 VOL. 383 NO. 26

Randomized Trial of Focused Ultrasound Subthalamotomy for Parkinson's Disease

R. Martínez-Fernández, J.U. Máñez-Miró, R. Rodríguez-Rojas, M. del Álamo, B.B. Shah, F. Hernández-Fernández, J.A. Pineda-Pardo, M.H.G. Monje, B. Fernández-Rodríguez, S.A. Sperling, D. Mata-Marín, P. Guida, F. Alonso-Frech, I. Obeso, C. Gasca-Salas, L. Vela-Desojo, W.J. Elias, and J.A. Obeso

40 patients

- 27 treated
- 13 'sham' treatment (control)



STN Focused Ultrasound Adverse Effects

7% chance of weakness is relatively high for a unilateral lesions

Will be higher for bilateral lesions

Adverse Event	Focused Ultrasound Subthalamotomy (N=27)					Sham Procedure (N=13)
	Total	At 24 Hr	At 2 Mo	At 4 Mo	At 12 Mo	At 4 Mo
Dyskinesia on the more affected side, in the off-medication state — no. of patients (%)						
Any event, regardless of severity	6 (22)	0	6 (22)	3 (11)	0	0
Chorea	5 (19)	0	5 (19)	3 (11)	0	0
Ballism	1 (4)	0	1 (4)	0	0	0
New-onset dyskinesia on the more affected side, in the on-medication state — no. of patients (%)	6 (22)	0	6 (22)	1 (4)	2 (7)	0
Weakness on the more affected side — no. of patients (%)	5 (19)	5 (19)	2 (7)	2 (7)	2 (7)**	0
Isolated facial asymmetry — no. of patients (%)	3 (11)	3 (11)	3 (11)	1 (4)	0	0
Speech disturbance — no. of patients (%)						
Any objective or subjective event†	15 (56)	6 (22)	12 (44)	3 (11)	1 (4)	0
Dysarthria, assessed objectively on examination	7 (26)	6 (22)	5 (19)	3 (11)	1 (4)	0
Slurred speech, as reported by the patient	8 (30)	0	7 (26)	0	0	0
Gait disturbance — no. of patients (%)						
Any objective or subjective event‡	13 (48)	8 (30)	7 (26)	2 (7)	1 (4)	0
Ataxia, assessed objectively on examination	3 (11)	2 (7)	1 (4)	0	0	0
Unsteady gait, as reported by the patient	10 (37)	6 (22)	6 (22)	2 (7)	1 (4)	0

STN Focused Ultrasound - What's next

- Centers will test out unilateral STN Focused Ultrasound and report their experiences
  - Side effect profile will likely improve as centers get experienced

- 2019 to 2022: STN Focused Ultrasound – Both sides of brain
  - 10 patients

Thoughts:

- May be useful for patients who cannot get DBS (e.g. patients > 80 years of age), but at this time unlikely to be superior to DBS for most patients

Stem Cells for PD

Unfortunately, symptomatic only

- *Not* being used as a cure
- Replaces dopamine, does not prevent spread of disease

Logic:

- Dopamine cells are dying, let's replace them

Trials done in 1980s and 1990s with mixed effects

- Some benefited, some had no effect, and some worsened due to uncontrollable dyskinesias

Trying again with argument that we have better quality stem cells and surgical techniques

Stem Cells for PD – What's Next

- 2021 to 2024: iPSC Dopamine Neurons implantation into Putamen – Advanced PD – Phase 1 (US, Memorial Sloan Kettering)
  - 12 patients
- Australia, Japan, UK/Sweden, China all have started or will start soon Phase 1 clinical trials for Dopamine Neuron Stem Cell implantation

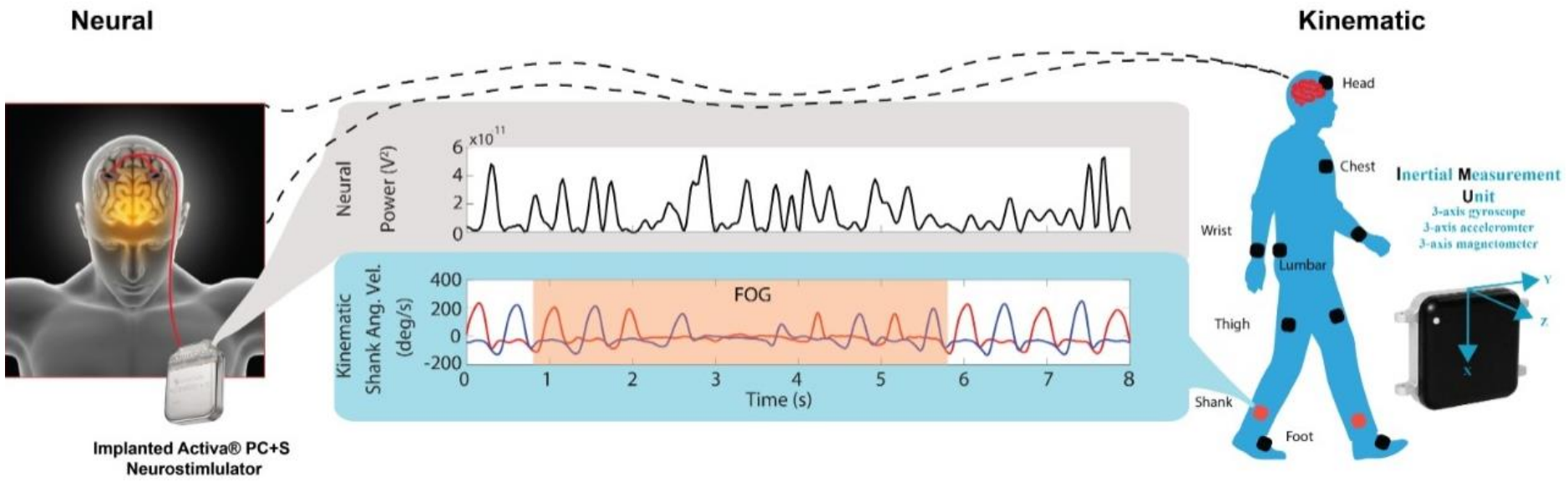
Thoughts:

- Very likely to be succesful initially, allowing patients to come off their Dopamine medications.
- However, at 5 to 10 years post implantation, I suspect we will see difficult to control dyskinesias

Adaptive Deep Brain Stimulation

Use brain and kinematic signals to more optimally control deep brain stimulation

- In order to provide better symptom control, including gait freezing



Adaptive DBS – What's Next

Two trials ongoing at Stanford by Dr. Helen Bronte-Stewart

ADAPT-PD

- Data from this trial will go to the FDA who will then decide if Adaptive DBS will be approved for all patients

SPRING

- Using DBS to improve Gait Freezing

Summary

- Disease Modifying Therapies
  - **GLP-1R agonists (Very exciting – 2022 is a big year)**
  - α-synuclein targeting and LRRK2 inhibitor approaches (early stages)

- Symptomatic Therapies
  - Focused Ultrasound of STN (likely to be beneficial in cases where DBS is not an option)
  - Stem Cells (early stages – will be beneficial initially, but risk of dyskinesias eventually)
  - Adaptive DBS may allow for improved symptom control

Sources:

- Wang, J. B. *et al.* Focused Ultrasound for Noninvasive, Focal Pharmacologic Neurointervention. *Front. Neurosci.* **14**, 675 (2020).
- Takahashi, J. iPS cell-based therapy for Parkinson's disease: A Kyoto trial. *Regen Ther* **13**, 18–22 (2020).
- Athauda, D. *et al.* Exenatide once weekly versus placebo in Parkinson's disease: a randomised, double-blind, placebo-controlled trial. *Lancet* **390**, 1664–1675 (2017).
- Martínez-Fernández, R. *et al.* Randomized Trial of Focused Ultrasound Subthalamotomy for Parkinson's Disease. *New England Journal of Medicine* vol. 383 2501–2513 (2020).
- https://www.nature.com/articles/d41586-021-02622-3
- https://scienceofparkinsons.com/2022/01/20/road2022/
- https://scienceofparkinsons.com/2017/08/04/exenatide-one-step-closer-to-joblessness/

Q&A