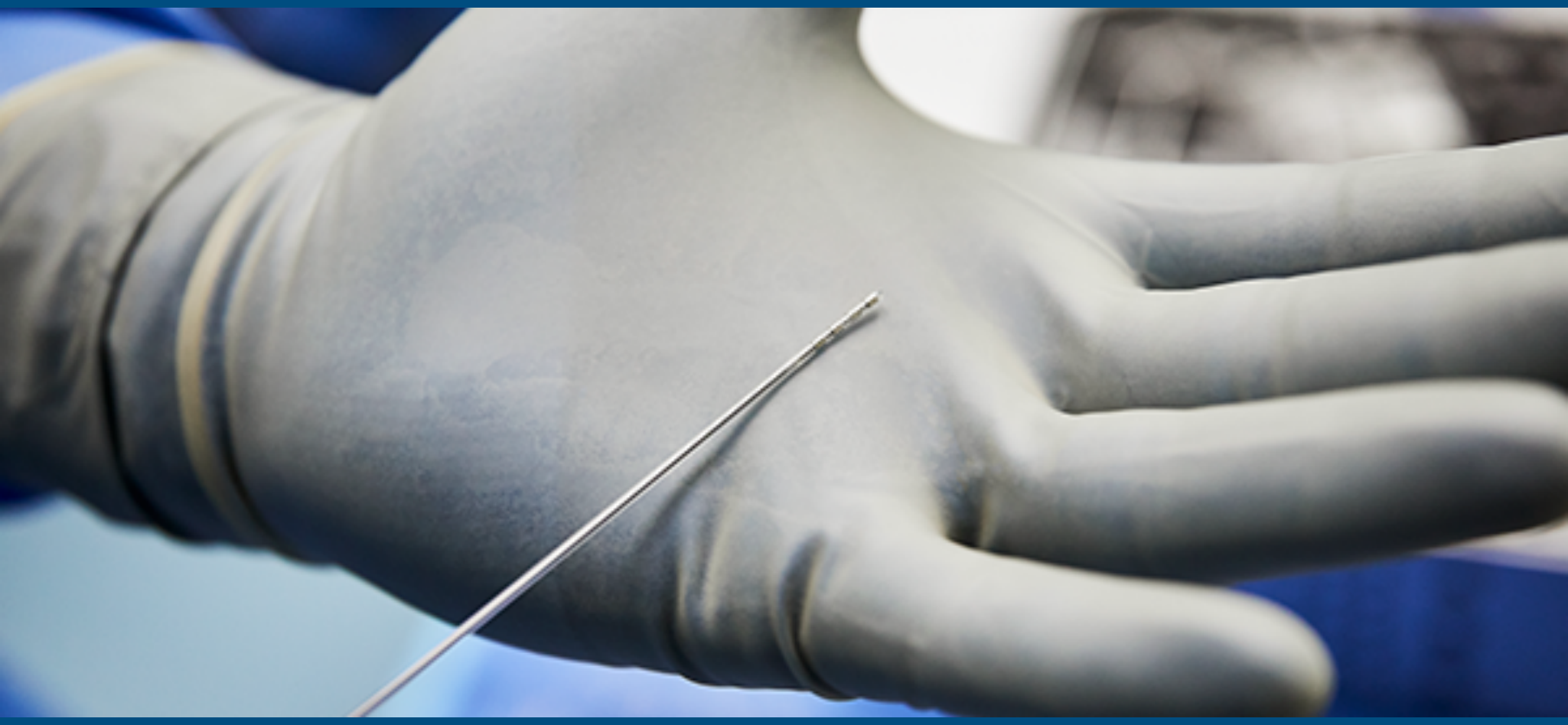
Dr. Richardson's Patient Guide

IMPROVING QUALITY OF LIFE IN MOVEMENT DISORDERS WITH DEEP BRAIN STIMULATION "DBS"



Mark Richardson, MD, PhD

Director of Functional Neurosurgery at the Massachusetts General Hospital
Professor of Neuroscience at Harvard Medical School

WELCOME TO DBS!

A BRIEF HISTORY OF DEEP BRAIN STIMULATION

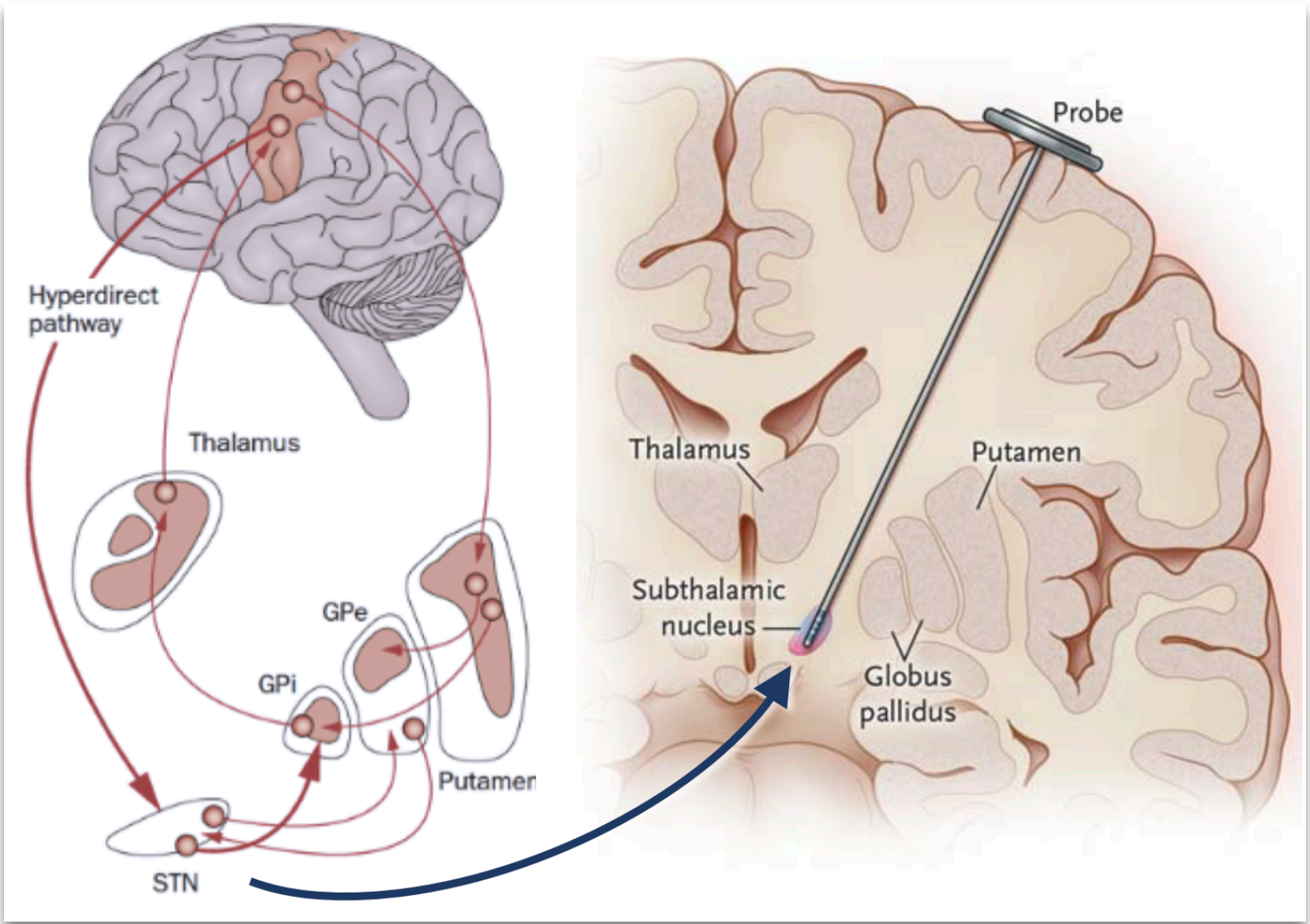
Deep brain stimulation (DBS) is not a new therapy. The earliest studies of chronic brain stimulation began in the 1950s, in the United States. Our modern form of DBS therapy was created in the 1980s in Grenoble, France, starting with DBS of the thalamus in patients with tremor. The same group introduced subthalamic nucleus DBS in the early 1990s, for patients with Parkinson's disease. Functional neurosurgery (the specialty aimed at improving quality of life for people with chronic brain diseases) now has 30 solid years of DBS experience under its belt.

Birthplace of modern DBS. The *30 year anniversary* of subthalamic nucleus DBS was celebrated in Grenoble, France in June 2023.

HOW DOES DBS WORK?

Studies conducted in the operating room with DBS patients during test stimulation have indicated that DBS works by *reducing abnormally synchronous brain activity* in loop circuits that connect cortical (outer) and subcortical (deep) areas of the brain responsible for specific types of behavior, like control of movement. These areas usually coordinate their activity like sections of an orchestra, to produce fluid transitions between complex movements. Abnormally repetitive rhythms of electrical activity that disrupt this coordination are present in many brain diseases. *DBS counteracts these abnormal brain rhythms, without affecting healthy brain activity, to reduce symptoms.*

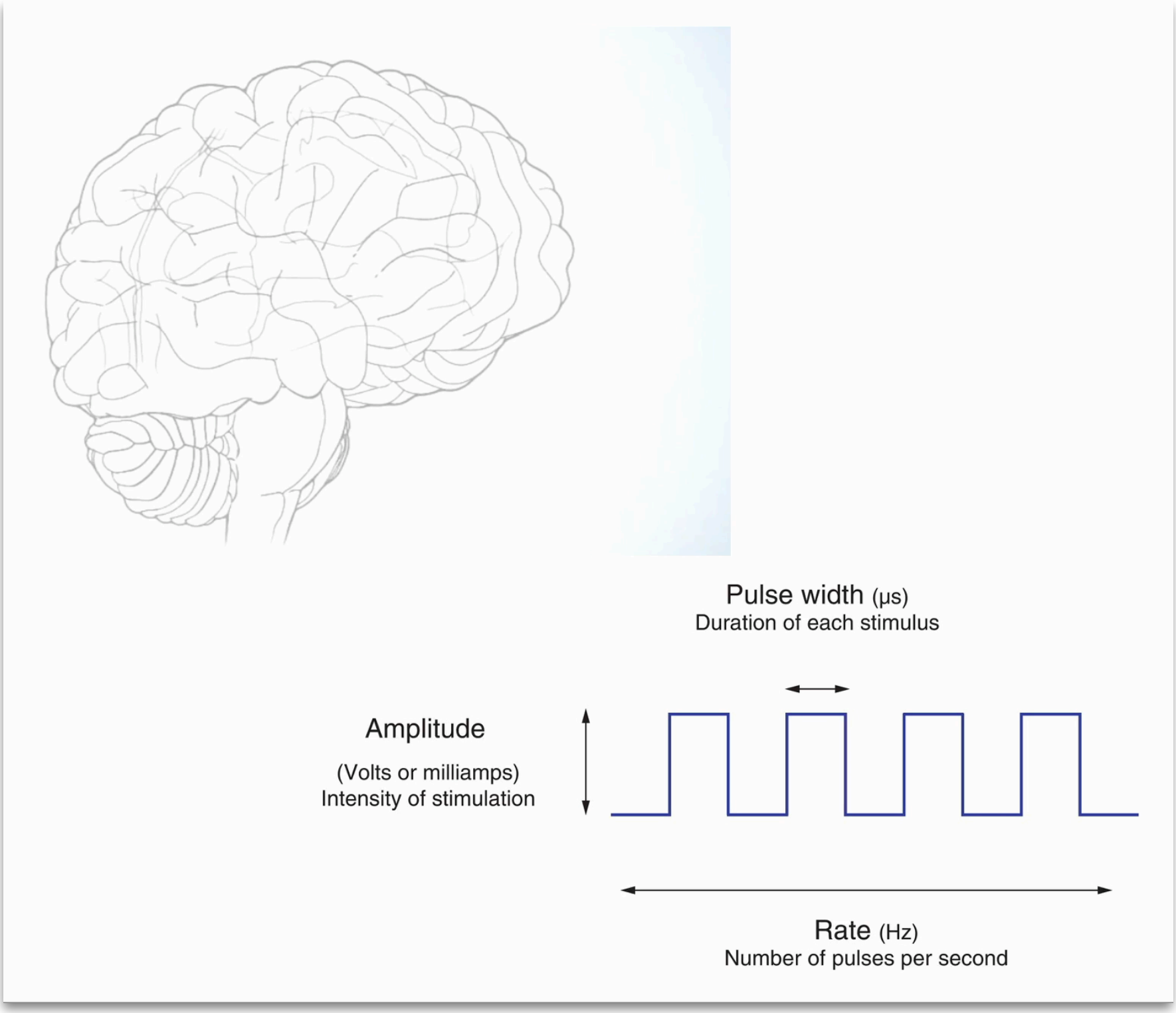
The DBS lead is implanted in a specific subcortical node the relevant behavioral circuit, including the subthalamic nucleus (STN) or globus pallidus (GP) for Parkinson's disease, the thalamus for tremor, or the nucleus accumbens for obsessive compulsive disorder.



Basal ganglia-thalamus-cortex loop circuit. The left drawing shows the motor control circuit including the basal ganglia nodes STN and GPi. The right drawing shows a DBS lead implanted in the STN.

DBS is nondestructive, adaptable, and reversible. Leads are implanted on both sides of the brain during *one minimally invasive* procedure. Stimulation is controlled by a pulse generator (a small computer and battery combined in one module) implanted in the right chest under the collar bone. Four stimulation parameters are set by the programming physician using an external programming device: intensity, frequency, duration, and location. DBS settings are programmed to optimize the "therapeutic window," or the amount of stimulation that produces the best reduction in symptoms without significant side-effects.

DBS Lead. The DBS lead is thin, only 1.3 mm in diameter, shown here to scale with a dime.



Stimulation Parameters. We use DBS leads that allow us to "steer" the current in a shape that best fits the stimulation target.

DBS AT THE MASSACHUSETTS GENERAL HOSPITAL

INTRODUCTION

Welcome to the DBS program at the Massachusetts General Hospital, one of the world's premier centers for neuromodulation! The purpose of this book is to introduce you to topics I discuss with patients during our introductory visits, and to introduce you to myself and my team, and leave you with resources to help you in your DBS decision-making.

My own introduction to DBS occurred as a medical student in Virginia, and I've been hooked ever since, performing over 500 DBS cases in my practice thus far. My PhD and postdoctoral research centered on two additional types of functional neurosurgery: cell transplantation and gene therapy, which are covered briefly in the research section of this guide. After residency training at the University of California San Francisco, I lead the DBS program at the University of Pittsburgh Medical Center for 8 years. In 2019, I joined MGH to direct the division of Functional Neurosurgery. I am also a neuroscientist who founded the Brain Modulation Lab, which studies brain recordings from DBS and other types of implanted electrodes. Our work has received funding from the NIH every year since 2014.

My MGH clinical partners are Drs. Jeff Schweitzer and Ziv Williams in the Department of Neurosurgery, and Dr. Todd Herrington who leads a team of movement disorders DBS experts in our Department of Neurology, including Drs. Alice Flaherty, Nutan Sharma, Grace Crotty, and Emily Ferrence. Our goal is to provide DBS evaluation, surgery, and programming with a level of expertise that is among the best in the world.

Mark Richardson, MD, PhD
Director of Functional Neurosurgery, MGH
Charles Pappas Professor of Neurosciences, Harvard Medical School
Visiting Professor of Brain and Cognitive Sciences, MIT

NEUROSURGERY PROGRAM STAFF

CLINICAL TEAM

Tatyana Pearson - Administrative Coordinator for Functional Neurosurgery

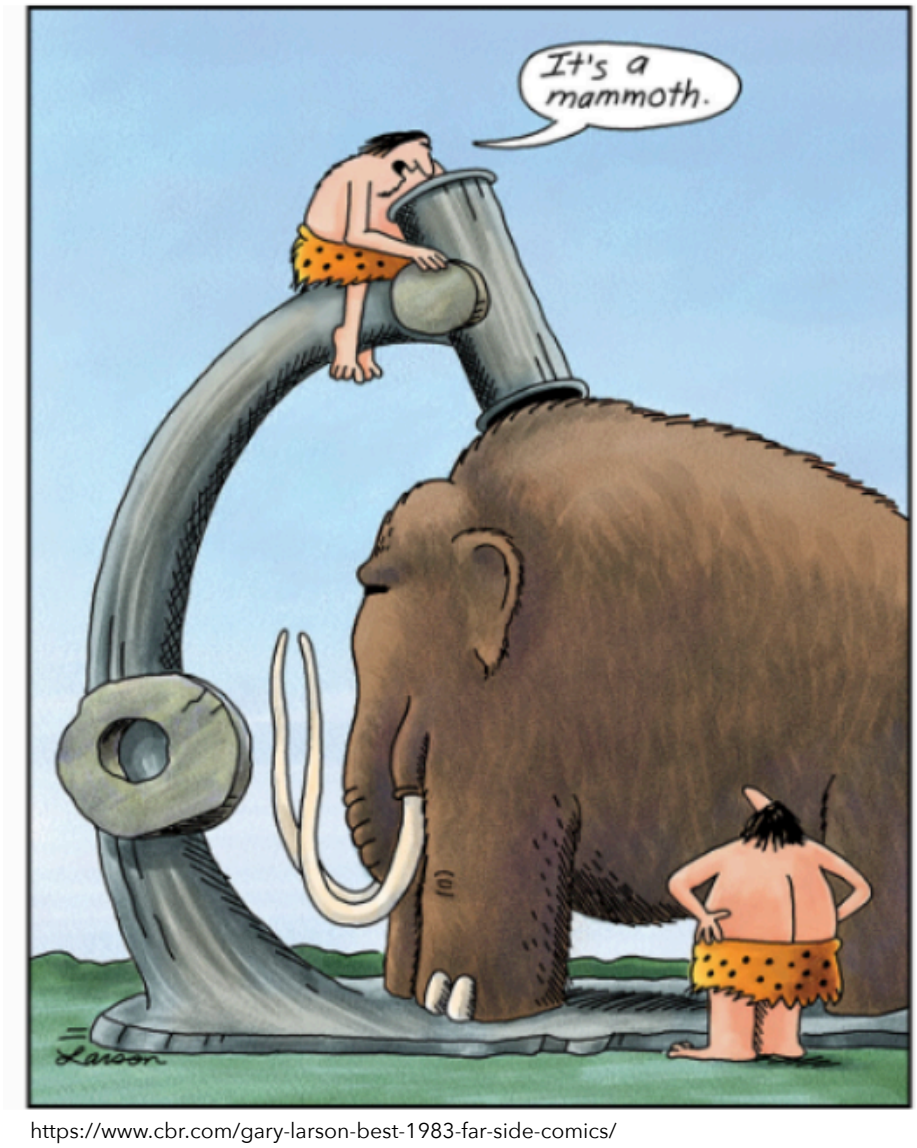
Ari Philbin - Physician Assistant for Functional Neurosurgery.

WHEN IS THE RIGHT TIME FOR DBS?

The answer to this question is often more simple than anticipated. The right time for DBS is when quality of life is deteriorating, despite adequate medication management. The following indicate that the timing may be right for a given person:

- Medications are not working as well.
- Medications are wearing off much faster.
- Side effects are limiting the medication that can be used.
- Botox is not working, not possible, or too involved.
- Dyskinesias are occurring when taking medication (Parkinson's disease).
- The person is withdrawing socially due to difficulty controlling symptoms.
- Any important aspect of a person's quality of life has declined significantly.

The right time for DBS often is obvious.



https://www.cbr.com/gary-larson-best-1983-far-side-comics/

THE DBS EVALUATION PROCESS

Evaluation for DBS surgery is a multidisciplinary process. Neurologists and/or psychiatrists, neurosurgeons, neuropsychiatrists and other staff work together on a team dedicated to considering the whole patient. It can take between 3-12 months to be evaluated and scheduled for DBS surgery, depending on provider and facility availability.

I. Initial Clinic Visits

A. Movement disorders neurologist (Parkinson's, dystonia, essential tremor)

   1. OFF-ON testing with UPDRS (Unified Parkinson's Disease Rating Scale), or TRS (tremor) rating scale for essential tremor, or Fahn-Marsden (BFM) dystonia rating scale.

B. Psychiatrist: Yale-Brown Obsessive-Compulsive Scale rating (YBOCS)

C. Neurosurgeon

D. Neuropsychologist

E. Speech evaluation at Mass Eye and Ear Institute

II. Additional Studies

A. MRI: special sequences are required for surgical planning

EXPECTED OUTCOMES

Parkinson's

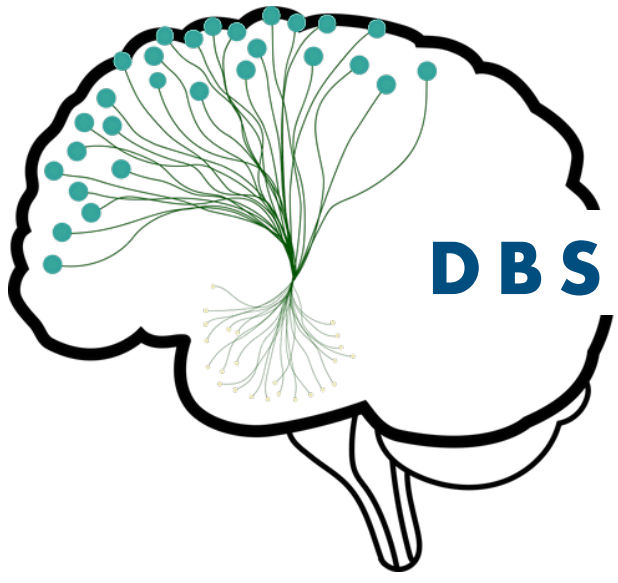
- 4 hours more of "ON" time each day, on average.
- Less motor fluctuations.
- 40-70% improvement in tremor, slowness, and/or stiffness. The extent of improvement in motor symptoms is best predicted by your best "on-medication" state.

Dystonia

- 40-60% improvement, on average.
- Patients with DYT1 mutations can experience 90% improvement.

Essential Tremor

- 50-90% improvement.
- Axial symptoms like head and voice tremor should improve, although typically not to the same extent as hand tremor.



DBS SURGERY

STAGE 1: "AWAKE" PHYSIOLOGICAL MAPPING OPTION

DBS lead implantation traditionally occurred with patients awake, in order to optimize the lead implantation location by performing functional brain mapping. Functional brain mapping involves recording from microelectrodes that are lowered into the brain prior to inserting the DBS leads. These very thin electrodes can record the activity of single neurons, which help us determine when we are in the anatomic target. A robotic stereotactic assistant (ROSA) robot arm is used to position the trajectory guides and electrode holders, to ensure maximum implantation accuracy.

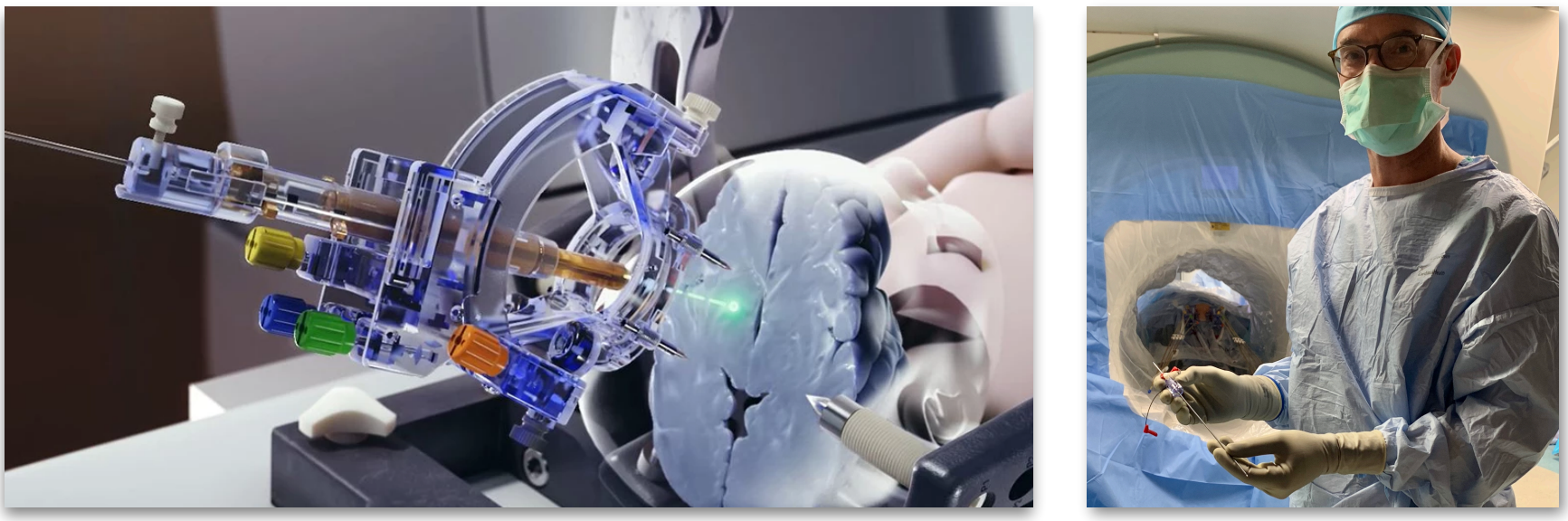
We also stimulate through these mapping electrodes to confirm the best trajectory in which to place the DBS lead, based on thresholds for side effects and symptom improvement. Next, we place the DBS lead through the trajectory with the best mapping result, and then we test that location with stimulation through the DBS lead. When we're happy with the result on the first side, we move to the second side. The patient is awake for mapping and stimulation testing, but typically asleep at the beginning and end of the procedure.

Dr. Richardson connecting the microelectrodes.

Dr. Herrington testing the effects of stimulation.

STAGE 1: "ASLEEP" REAL-TIME MRI OPTION

Since 2010, we have implanted DBS leads using real-time MRI visualization with patients under general anesthesia. Instead of using intra-operative microelectrode recording and stimulation testing, we verify accurate lead placement using direct anatomic visualization with intra-operative MRI. We use a targeting system called ClearPoint. Dr. Richardson helped launch this system during its preclinical development at the University of California San Francisco, and he established one of the earliest intra-operative MRI DBS programs at the University of Pittsburgh Medical Center in 2011. The video below shows highlights of this procedure being performed at the MGH, where we have an intra-operative-MRI suite.



The ClearPoint System. Illustration of the SmartFrame and trajectory (left). Dr. Richardson in the intraoperative-MRI OR (right).

Video. Aspects of asleep iMRI-DBS at MGH. The surgery is performed within an intraoperative 3-Tesla MRI suite.

AWAKE VS. ASLEEP SURGERY: WHICH IS BEST?

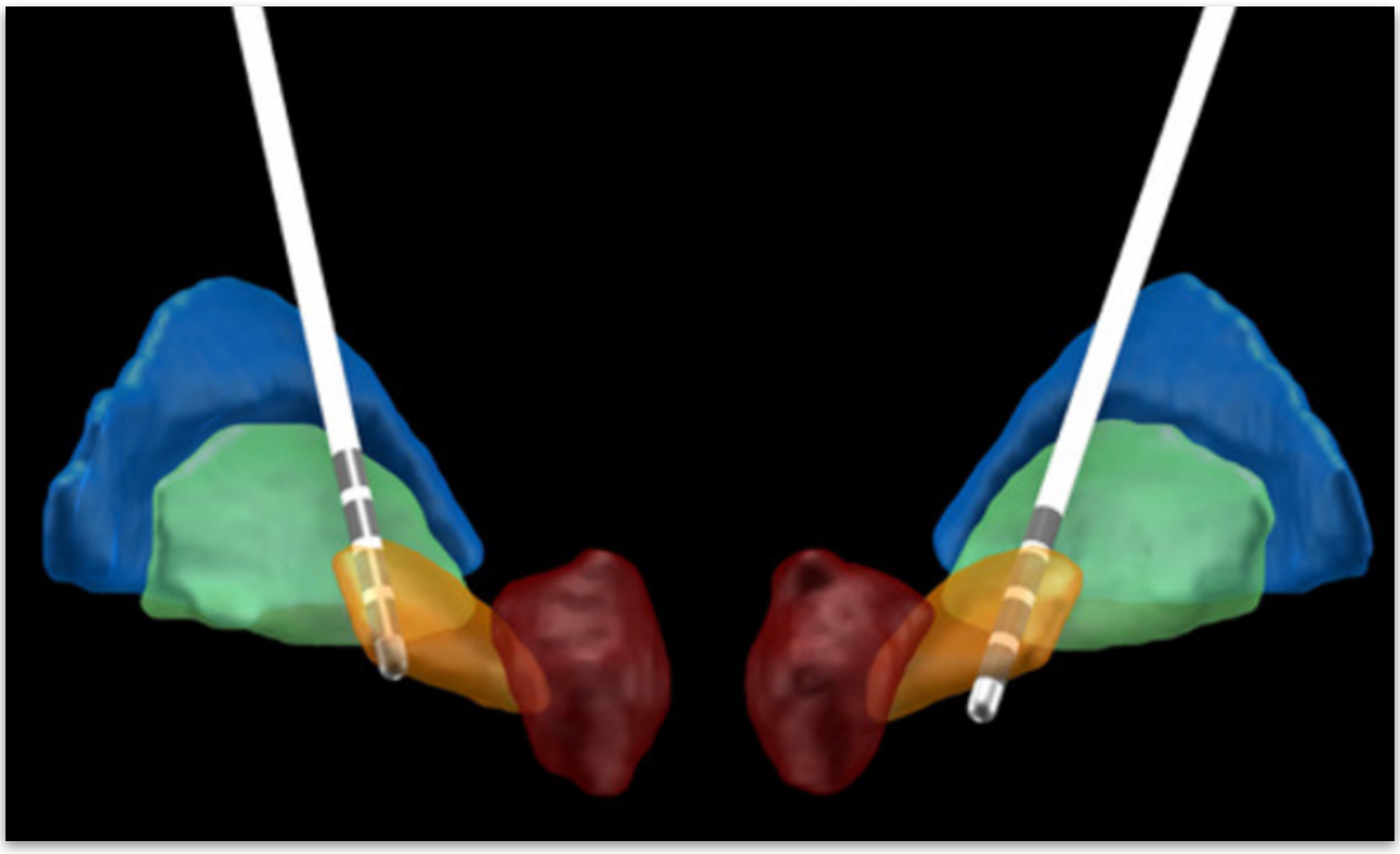
Patients undergoing DBS surgery are expected to do **equally well**, whether they undergo "awake" implantation with functional brain mapping or "asleep" implantation with real-time MRI visualization. In fact, Dr. Richardson and others have published data from case series showing that outcomes are similarly excellent with both options (**click here for article**). Given our extensive expertise with both methods, we allow patients to choose which method they prefer. How do you know which option is right for you? This chart may help…

CONSIDERATION	AWAKE	ASLEEP
Anesthesia for Stage 1	General anesthesia	Conscious sedation
Anesthesia for Stage 2	General anesthesia	General Anesthesia
Target verification with real-time MRI	No	Yes
Target verification with functional mapping	Yes	No
Minimally invasive	Yes	Yes
Amount of hair shaved	Less	More
Patients with severe anxiety	No	Yes
Off medications for surgery	Yes	No
Patients with chronic neck pain	Not ideal	No problem
Children	Not ideal	No problem
Patients who want to participate in brain research	Possible	Possible

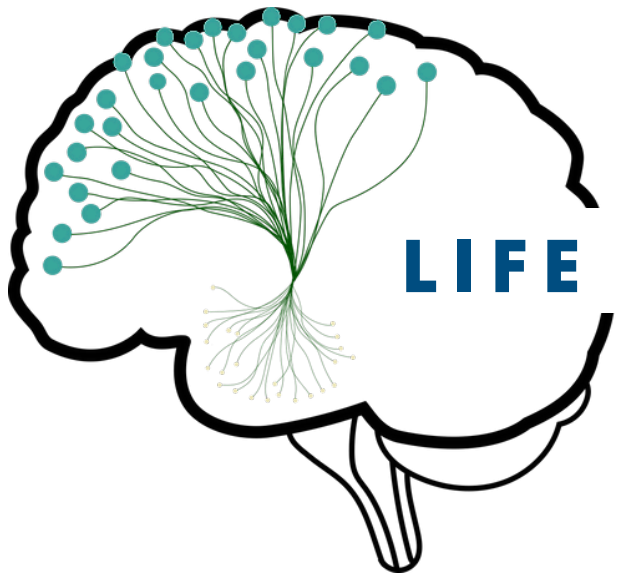
STAGE 2: IMPLANTING THE IPG AND CONNECTORS

Stage 2 surgery involves implanting connector cables from the DBS leads to the battery, or implantable pulse generator (IPG), which is placed in a skin pocket on the surface of the pectoralis muscle in the chest, just below the level of the collar bone. The IPG is almost always placed on the right side of the chest, to reserve the ability for a cardiac pacemaker to be placed on the left side, if one was ever needed in the future.

Stage 2 surgery is performed under general anesthesia for all patients and is typically separated from Stage 1 surgery by about two weeks. The stages are separate due to the length of time required to perform both stages together, as well as to provide a window in which to evaluate the placement of the DBS leads with a postoperative CT scan. Every patient will get a CT scan after Stage 1 surgery to generate an image that is fused to the preoperative MRI in order to model the position of the DBS leads. In less than 10% of cases, Dr. Richardson will identify an opportunity to change the depth placement of the DBS lead, which can easily be modified at the time of Stage 2 surgery.



DBS Lead Reconstruction. Using special software, the post-operative CT is combined with the pre-operative MRI to generate an estimation of the lead locations with the target structure, for each patient. Here, the contacts of bilateral DBS leads are shown within the subthalamic nucleus (orange volume).



LIFE AFTER SURGERY

RECOVERY FROM SURGERY

Most patients spend one night in the hospital and go home the next day. Patients can expect to experience a headache for a few days after surgery and mild pain at the incision site. It's important to note that patients with Parkinson's disease do have a bit more chance of experiencing post-operative confusion for one or a few days, sometimes in the context of a hospital-acquired delirium.

All surgical incisions are closed with absorbable suture and skin glue. Patients should shower daily upon returning home. It is difficult to disrupt the incisions with normal activity and impossible to hurt the device. The general recommendation is to refrain from high-intensity exercise until the incisions have healed, which is about two weeks after the last surgery. Activities like walking, riding a stationary bike, using a treadmill, etc. are all encouraged.

DBS PROGRAMMING

Surgery is just half of the process required to initiate DBS therapy. Programming is the other key element, which will be performed by your neurologists, although in some cases this can be performed by our neurosurgery team. Typically, it takes a few visits over several months to fine-tune your DBS for optimal symptom control, but often patients will experience a significant benefit after their first programming visit. The exception are dystonia symptoms, which can take several months to improve. Programming visits are in-person, unless you are implanted with a DBS system approved for remote programming.

DBS MAINTENANCE

Non-rechargeable IPGs need to be replaced every 2-5 years, with dystonia patients tending to need IPGs replaced in the shorter time frames because high settings typically

are used. Rechargeable IPGs will last approximately 20 years, but require 45 total minutes of charging per week.

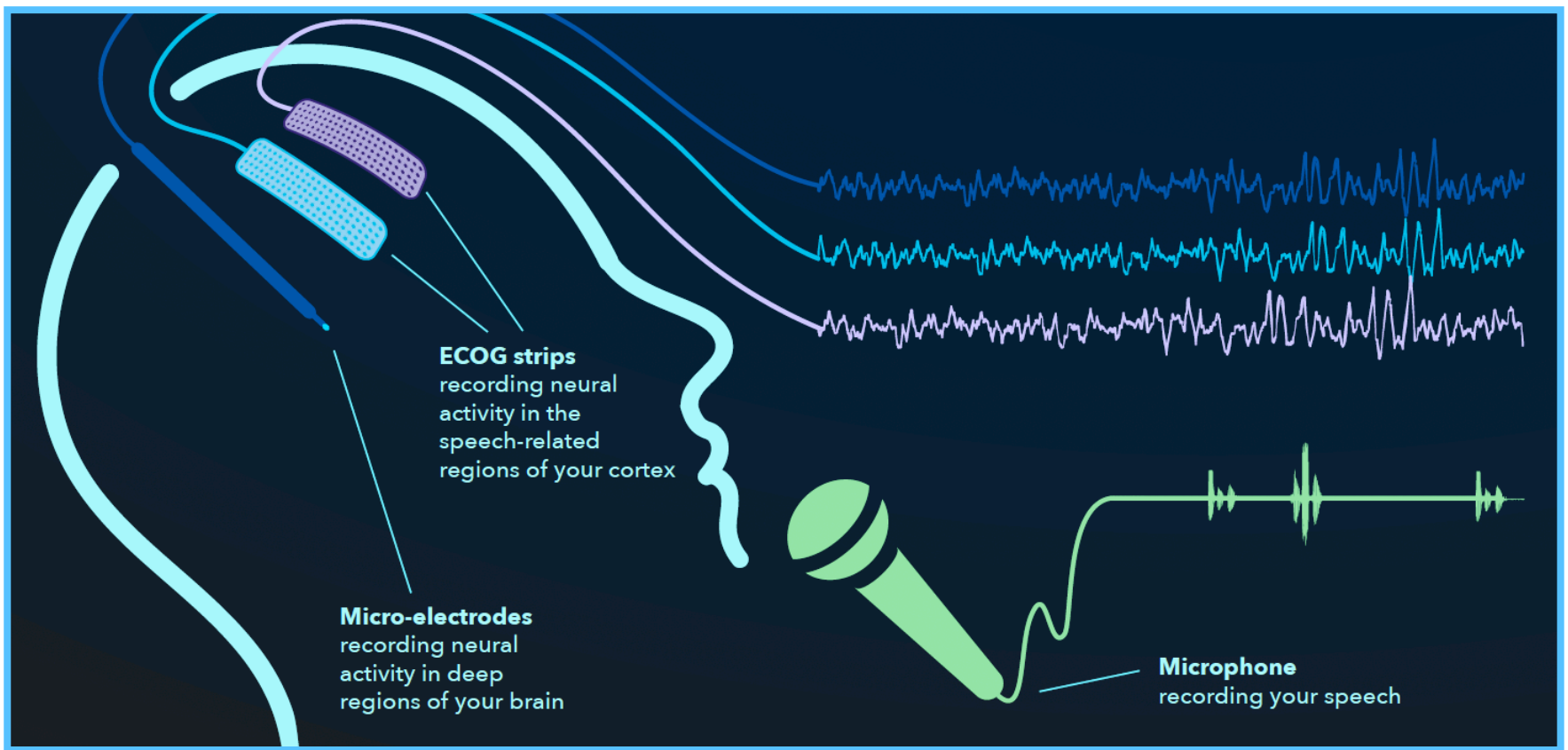
RESEARCH

NIH-FUNDED RESEARCH IN SPEECH PRODUCTION

DBS offers the only opportunity to observe speech-related electrical activity directly within target areas of the brain called the basal ganglia and thalamus. Dr. Richardson's research team in the Brain Modulation Lab developed a way to do this while recording from the cortex (outer command layers of the brain) at the same time. These studies, funded by the U.S. BRAIN Initiative, are improving our understanding of how the brain enables us to speak. We are grateful to patients for partnering with us on our journey to understand the human brain – how it works, and potentially how we can make it work better for patients with disorders that are treated with DBS.

Patients who volunteer to participate in this study have their brain activity recorded using electrodes while they are performing speech tasks during their DBS surgery. This brochure includes more information about the data we collect as part of this study and how we use this data to better

PET scans showing the putamen before and after gene therapy for PD. *From* Richardson et al., 2022



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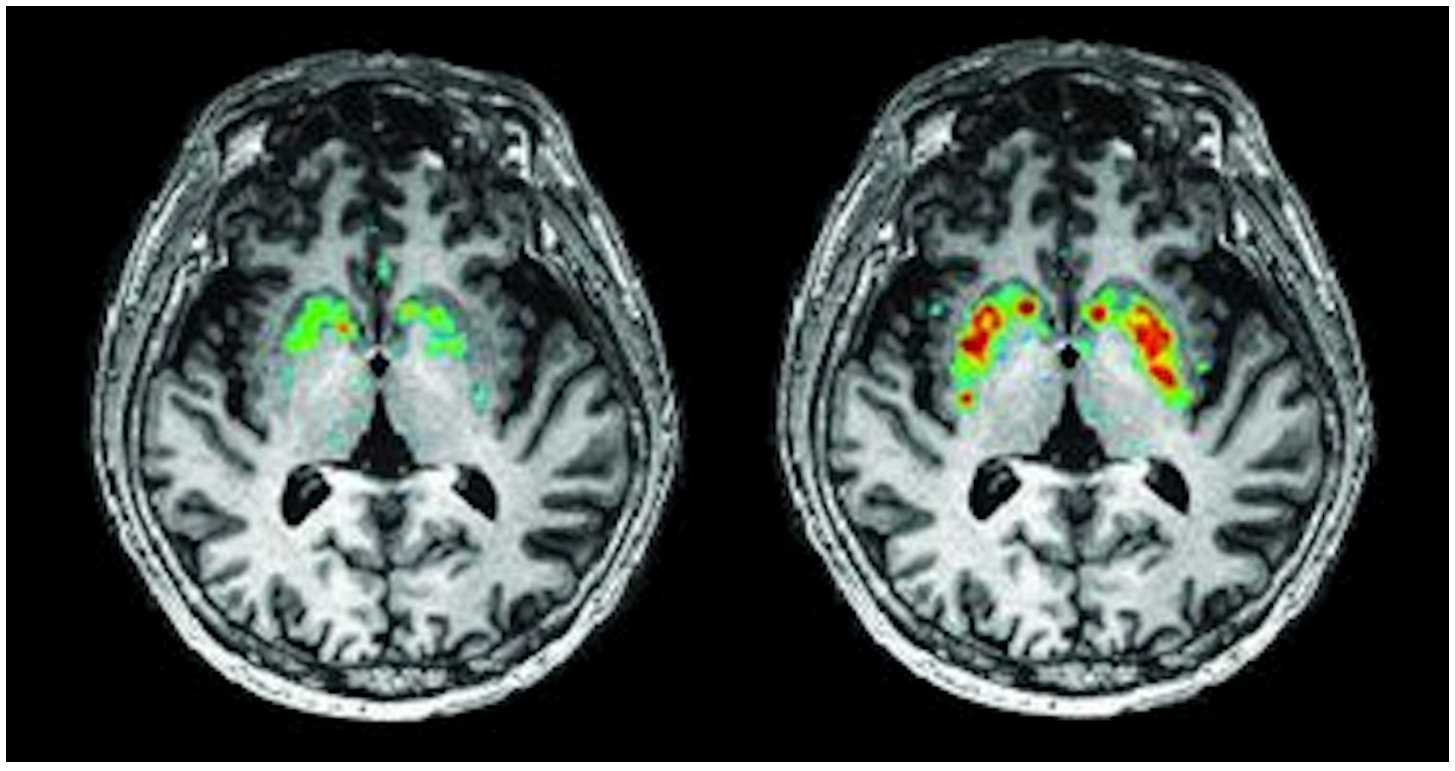
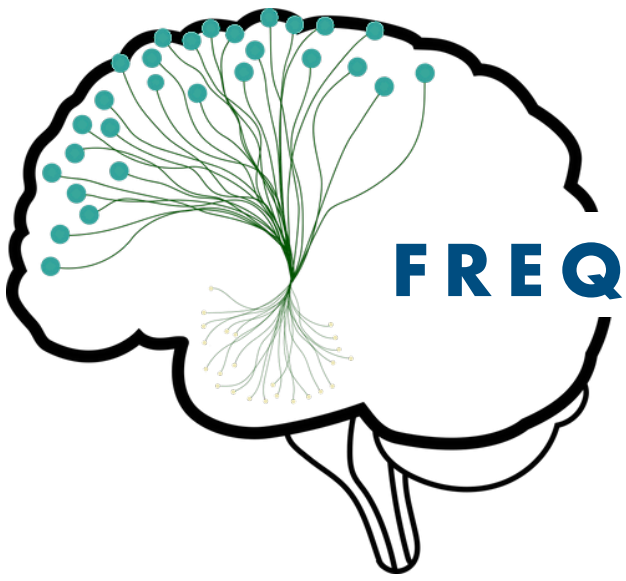
understand the brain:

GENE AND CELL THERAPIES - SHOULD I WAIT?

Dr. Richardson's PhD work was in the field of cell transplantation for Parkinson's disease, and his postdoctoral research was in the field of gene therapy for Parkinson's disease. He has served as a neurosurgeon on clinical trials of both cell and gene therapies and continues to be active in the development of biological therapies. These therapies hold promise for the future, but unfortunately it's the nature of this work to take decades to come to fruition. There are no biological therapies on the near horizon for which anyone who currently qualifies for DBS should wait, given how well DBS can work to improve quality of life.





FREQUENTLY ASKED QUESTIONS

What are the risks of the procedure?

- 1% = bleeding in the brain, or stroke, that would cause a permanent loss of function
- 1% = infection that requires removal of the DBS system
- 3% = infection
- 5% = change in cognition

Are there any external components?

- No.

What physical activities should I avoid after surgery - are there any restrictions because of the device?

- You do not need to avoid any activities, unless you are a scuba diver (cannot descend below 10 meters).

When is it safe to fly and what happens at airport security?

- You can fly anytime.
- The device will not set off a metal detector and is not affected by security machines.
- You can proceed through airport security as usual.

Does DBS help the brain produce dopamine?

- No, DBS quiets down abnormal brain activity that results from a loss of dopamine.

Will DBS improve my memory?

- No.

Is DBS a “last-resort” therapy?

- No, DBS is the gold standard treatment once motor fluctuations develop.

- The earlier DBS is initiated, the more years with better quality of life are experienced.

Can the DBS system be removed?

- Yes.

Do you have to shave my whole head?

- No, we only shave the amount of hair needed.

Can I undergo MRI Scans with a DBS Device?

- Yes, the specifications vary by device.

Are DBS devices compatible with other medical imaging techniques?

- Yes, the only restrictions are related to MRI.

Can I drive after DBS surgery?

- If you were driving before surgery, it is safe to return to driving after your first programming visit. In some cases, it will be safe to drive sooner.
- If you were not driving before surgery, but you feel that DBS has improved your motor symptoms to the point that you can now drive again, we will advise you to undergo a formal driving evaluation.

Will I still need medications after DBS?

- Yes. Although DBS can result in a significant reduction in medication for many patients, the vast majority of DBS patients still need medications for optimal symptom control.

How quickly will I notice improvement after surgery?

- It takes a few visits over several months to fine-tune your DBS, but often patients will experience a significant benefit after their first programming visit.
- For patients with dystonia, we expect symptoms to take several months (up to a year) to improve.

Are there any dietary restrictions after surgery?

- No.

How do I take care of the surgical site?

- No dressing or wound care is required.

- You should shower daily after surgery.
- The incisions are closed with absorbable suture and skin glue, and do not require you to return to the neurosurgery clinic for a wound check.

Can I use electronic devices and appliances safely?

- Yes. There are no restrictions.

How often will I need to replace the DBS device?

- Non-rechargeable (primary cell) = 2-5 years, depending on settings
- Rechargeable = at least 15 years

How do I know when my battery needs to be replaced?

- You will receive a patent programmer that can report the battery life.
- The remaining battery life will also be checked at each programming visit.
- You will have ample notification about impending battery depletion.