Jefferson Health®

VICKIE AND JACK FARBER INSTITUTE FOR NEUROSCIENCE
OUTCOMES & RESEARCH: VOLUME 5

ADVANCES

IN PARKINSON'S DISEASE

A MESSAGE FROM THE PRESIDENT/CEO, VICKIE AND JACK FARBER INSTITUTE FOR NEUROSCIENCE

Dear Colleagues,

Thomas Jefferson University Hospital's Departments of Neurology and Neurosurgery and the Vickie and Jack Farber Institute for Neuroscience – Jefferson Health are constantly engaged in research that will help discover innovative treatments for various neurologic conditions, thus improving patient care.

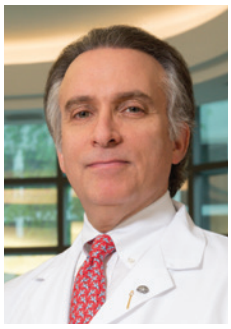
I am pleased to be sending you the fifth volume of our series that describes research and superior patient care that our departments and physicians engage in. In previous brochures, we have described our research in spinal cord injury; cognitive functioning in temporal lobe epilepsy; ALS; and our ongoing clinical trials and treatment for both aneurysm and stroke.

In this current volume, we highlight the work Jefferson Health is doing in the area of the debilitating motor symptoms of advanced Parkinson's disease (PD). Chengyuan Wu, MD, MSBmE; Tsao-Wei Liang, MD; Ashwini Sharan, MD; and others are studying high-frequency deep-brain stimulation and the use of diffusion-weighted imaging to better understand brain microarchitecture in these patients to help lessen some of the symptoms of PD. Richard Smeyne, PhD and his group are examining the signals that lead to initiation of this disease as well as how we might arrest its progression.

At Jefferson Health, we value our clinicians and researchers who contribute to the well-being of patients with neurological impairment and disability. We continue to utilize many different treatments and approaches for patients with various neurologic conditions. Substantive research informs all of our treatment modalities.

Now, I invite you to explore current research and treatment options for patients with advanced PD. I hope you will find it informative to read about the ways we are working to enhance the quality of life for these and other patients.

Sincerely,



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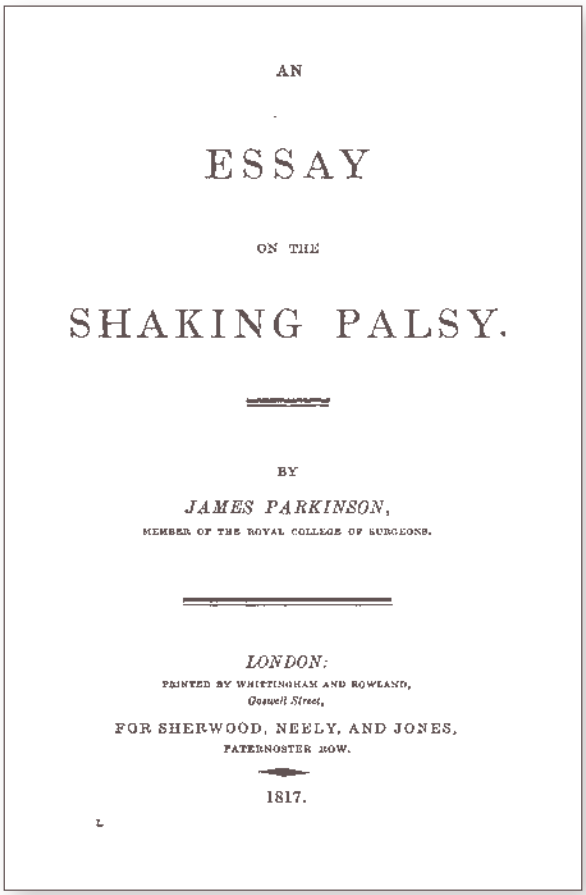
A Brief History of PD

As early as AD 175, Parkinson's disease (PD), a disabling motor and neurologic condition, was identified and named, the "shaking palsy" (see Figure 1). Yet, it was not until 1817 that James Parkinson, a London physician, published a detailed article titled "An Essay on the Shaking Palsy," which established PD as a distinct medical condition. Since those early times, much has been learnt about the disease; yet much still remains a mystery.



AN

ESSAY

ON THE

SHAKING PALSY.

BY

JAMES PARKINSON,

MEMBER OF THE ROYAL COLLEGE OF SURGEONS.

LONDON:

PRINTED BY WHITTINGHAM AND ROWLAND,

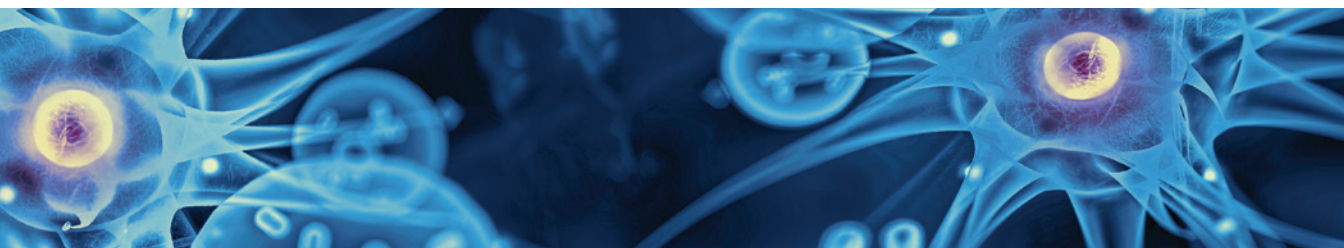
Goswell Street,

FOR SHERWOOD, NEELY, AND JONES,

PATERNOSTER ROW.

1817.

Figure 1. "An Essay on the Shaking Palsy," by James Parkinson, was originally published as a monograph by Sherwood, Neely, and Jones, London, 1817. (From Wikimedia Commons, the free media repository.)



The symptoms of PD are progressive and degenerative and tend to occur in older individuals. We now know that the symptoms of PD affect both motor and non-motor activities, leading to cognitive dysfunction, interference with normal sleep cycles, mood and vision issues as well as a number of other neurologic symptoms.

Parkinson's disease is currently the second most common neurodegenerative disorder and the leading movement disorder. We know that the motor problems of PD are, for the most part, caused by a loss of dopaminergic neurons in the midbrain and their projections to the striatum. Why this process occurs is not yet clear.

While many treatments over the years have been investigated for the symptomatic treatment of PD, the treatment of choice – the "gold standard" – remains levodopa (L-dopa). Although research continues at a rapid pace in an attempt to better understand the mechanism of action of PD, the search for both a cure and better treatments continue, including surgical options. At Jefferson Health, a comprehensive team of basic scientists and clinicians are continuing to lead the way.

The following pages describe some of the work currently taking place within the Jefferson Comprehensive Parkinson's Disease Center (JCPDC) in the Vickie and Jack Farber Institute of Neuroscience at Jefferson Health. To see timelines of both the history of PD treatment over the centuries and the advancements Jefferson has made, please see Table 1 and Table 2 inside the back cover.

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Parkinson J. An essay on the shaking palsy. 1817. J Neuropsychiatry Clin Neurosci 2002; 14:223-236. Discussion 2.

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JEFFERSON'S COMPREHENSIVE MOVEMENT DISORDERS CENTER

In 2005, Abdolmohamad Rostami MD, PhD, Chair, Department of Neurology, and Robert Rosenwasser, MD, MBA, FACS, FAHA, Chair, Department of Neurological surgery, recruited two young neurologists to develop a specialized program for the treatment of PD and related movement disorders. Founded that year by Tsao-Wei Liang, MD, and Daniel E. Kremens, MD, JD, the Jefferson Health Comprehensive Movement Disorders Center has developed into one of the largest and most highly regarded centers in the Greater Philadelphia region, including the most advanced neurosurgical treatments led by Ashwini Sharan, MD, and Chengyuan Wu, MD, MSBmE. It is staffed by a multidisciplinary team consisting of movement disorder neurologists, nurses, a social worker, functional neurosurgeons, neuropsychologists and allied health professionals. (See Table 3.) Between 2006 and 2018, the Center evaluated over 6,000 patients with PD and related disorders, and currently treats over 2,500 patients in the clinic. In addition, Center leaders are consistently ranked in the top 5% of providers in the nation by Press Ganey surveys.

Table 3. Clinical Staff

Tsao-Wei Liang, MD *Medical Director, Division Chief*	Mary Kate Maloney, MSN, CRNP
Daniel Kremens, MD, JD *Co-medical Director*	Kim Stoveld, BSN, RN
Jeffrey Ratliff, MD *Residency and Fellowship Program Director*	Teresa Beasley *Care Coordinator*
Melissa Heiry, MD	Lance Wilson, MSW, LCSW *Social Worker/Outreach/Education Coordinator*
Anh Thu Vu, MD	Teresita Devera, CRNP
Ashwini Sharan, MD *Department of Neurosurgery*	Darniece Alsop *Administrative Assistant*
Chengyuan Wu, MD, MSBmE *Department of Neurosurgery*	Abigail Lyons, DSc *Neuropsychology*
Andrew Newberg, MD *Marcus Institute for Integrative Health*	Gregory Seidel, PhD *Neuropsychology*
Jared Ellman, MD *Department of Psychiatry*	Joseph McCoy, PT, MSPT, NC *Physical Therapy*
Marc Zisselman, MD *Department of Psychiatry*	John Kardine, MS, OTR/L *Occupational Therapy*
Sirisha Thumalapenta, MD *Movement Disorders Clinical Fellow 2020-21*	Adeline Schultz, MA, CCC-SLP, BCS-S *Speech Therapy*
Michael Kogan, MD *Neurosurgery Clinical Fellow 2020-2021*	

A Parkinson's Foundation Center of Excellence

In 2017, Jefferson's Health's CEO, Stephen K. Klasko, MD, highlighted the importance of research in advancing the system's clinical program by designating the JCPDC a CRISP program (Clinical Research Integrated Strategic Program). Shortly thereafter, Richard Smeyne, PhD, was recruited to lead and facilitate the integration of its already well-established basic research and clinical endeavors to a comprehensive center. The goal of this integration was to help Jefferson move the Center to the level of a world-class leader in PD care.

Because of Jefferson Health's commitment to both expert patient care (under the leadership of Drs. Liang and Kremens) and research (under the leadership of Dr. Lorraine Iacovitti), the Parkinson's Foundation named Jefferson Health's JCPDC a Center of Excellence. Jefferson Health is now home to one of approximately 48 centers in the world – with only 33 in the United States – all focused exclusively on PD. This designation recognizes the successful integration of multiple disciplines, including neurology, neurosurgery, neuropsychology, physical, speech, and occupational therapy, basic science researchers, and others, all with deep expertise in the latest PD medications, therapies, and research that provides the best care for Jefferson Health's movement disorder patients. When patients do not respond to medications, our expert neurosurgeons Drs. Sharan and Wu provide deep brain stimulation (DBS) to reduce symptoms of Parkinson's disease and tremors by improving mobility, reducing involuntary movements and increasing an overall quality of life. Through the collaboration of the Center's leadership, the Jefferson team continues to demonstrate a high level of coordinated care and programmatic integration.

Research Highlights

Jefferson Health's approach to research and treatment of PD brings together its multi-disciplinary team; the goal being to understand how this disease manifests, which could lead to the pioneering of new treatments for this degenerative disease. The following pages describe some of the innovative research and treatments currently happening at Jefferson. These include basic research that attempts to understand how PD starts as well as clinical studies that look for better methods for the therapeutic and surgical treatment of the disease.

The following sections review and illustrate the important work our research and clinical staff are involved in, including but not limited to the work of Richard Smeyne, PhD; Tsao-Wei Liang, MD; and Chengyuan Wu, MD, MSBmE.

Research on Immune System Interactions in PD

Two studies conducted under the direction of Richard Smeyne, PhD, suggest that peripheral immune signaling (T- and B-cells in the blood) plays an unexpected, but important role in the regulation of neurodegeneration in at least one form of PD – that mediated by a mutation in the leucine-rich repeat kinase 2- (LRRK2) gene. Dysfunction of this gene is thought to underlie about 20% of all PD (and perhaps higher levels in those with a heritage of Ashkenazi Jews, Arab Berbers, and Basques). Understanding how mutations in this gene lead to PD will allow Jefferson Health researchers to identify new targets that can be modified by both life-style changes as well as drugs.

Study #1: Mutant LRRK2 Mediates Immune Response

One of the most common pathologies seen in PD is that of neuroinflammation. When this inflammation occurs, specialized cells in the brain (microglia and astrocytes) release chemicals that eventually lead to neuron death. To examine how this inflammation starts, as well as how it is regulated, researchers in the Smeyne laboratory at Jefferson Health used specialized mice that have the same mutations in the LRRK2 gene as humans to look at how these mutations affect inflammation. They administered a compound called lipopolysaccharide (LPS), which mimics bacterial infections, to mice into the gut and found that only mice whose DNA contained the LRRK2 mutations showed any brain effects that looked like PD, including an exacerbated inflammation in the brain.

Although LPS was administered to the body of the animal, scientists saw inflammation both in the body as well as the brain. This suggested to them that the inflammation in the brain had to arise from signals that initiated in the blood. This finding for a critical role for peripheral immune signaling has the potential to both provide new targets for interfering with the onset and progression of the disease but also the ability to identify blood-based biomarkers of the disease that could provide an "early warning" that a person may develop PD.

So, how was this done? As mentioned earlier, LPS was injected into the gut of either normal (what we call wild-type) or LRRK2 mutant (what we call transgenic) mice. After allowing enough time for LPS to cause its effects, the team at Jefferson Health looked at microscope sections from these animals' brains and using specialized stains counted the number of neurons in the part of the brain that contain the dopaminergic neurons lost in PD (called the substantia nigra pars compacta [SNpc]). Results from these studies showed that 7 days after LPS, only mice with the mutation in the LRRK2 gene showed loss of SNpc dopamine neurons while no death was seen in the wild-type mice. Associated with the cell loss in these LRRK2 mutants was a dramatic increase in both the number of inflammatory cells (activated microglia) in the brain and the levels of inflammatory chemicals (called cytokines). This can be seen in Figure 2.

One of the unique aspects of Thomas Jefferson University is that students from the Kanbar College of Design, Engineering and Commerce have the opportunity to interact and work with neurologist Tsao-Wei Liang, MD, to develop novel and practical devices to help patients with PD. Through a summer work study program, design students have been invited to the Movement Disorders clinic to evaluate the daily struggles of patients, return to the studio and then brainstorm to create and develop prototypes that have the potential to improve the quality of life of persons with Parkinson's.

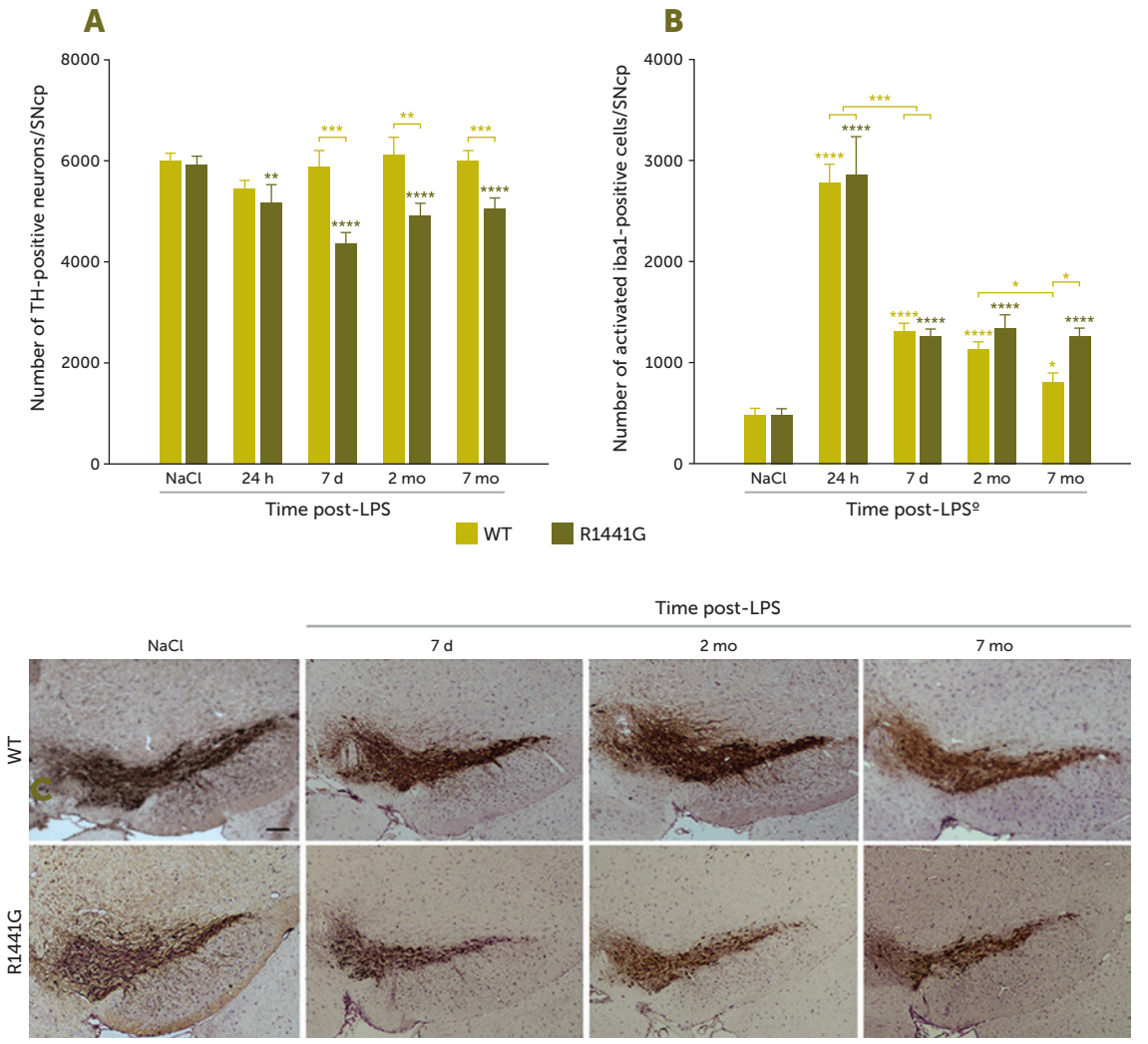

Figure 2. Systemic inflammation causes neuronal loss in the SNpc of mutant LRRK2 R1441G mice but not wild-type. (A) Loss of TH-positive dopaminergic neurons in the SNpc of R1441G mice starts at 7 days and lasts through 7 months after systemic LPS injection. Data are mean _ SEM, n = 16 for NaCl group; n = 3–5 for each post-LPS group. **P50.005, ***P50.001, ****P50.0001. (B) Number of activated Iba1-positive microglial cells (inflammatory cells in the brain) in the SNpc of LRRK2 R1441G mice and background matched nontransgenic litter-mates (wild-type) following systemic LPS injection. Data are mean _SEM, n = 15 for NaCl group; n = 3–5 for each post-LPS group. *P50.05, ***P50.001, ****P50.0001. (C) Representative images of TH-positive dopaminergic neurons in the SNpc of wild-type and R1441G mice 7 days, 2 and 7 months after LPS injection. Sections are matched at the same level of the substantia nigra (Bregma _3.08–3.16 mm) (Paxinos and Franklin, 2001). Scale bar = 100 mm. Source: Image taken from Kozina E, Sadasivan S, Jiao Y, Dou Y, Ma Z, Kodali HK, Sha T, Peng J, Smeyne RJ. Mutant LRRK2 mediates peripheral and central immune response leading to neurodegeneration in vivo. Brain.2018;141:1753-1769, Figure 1

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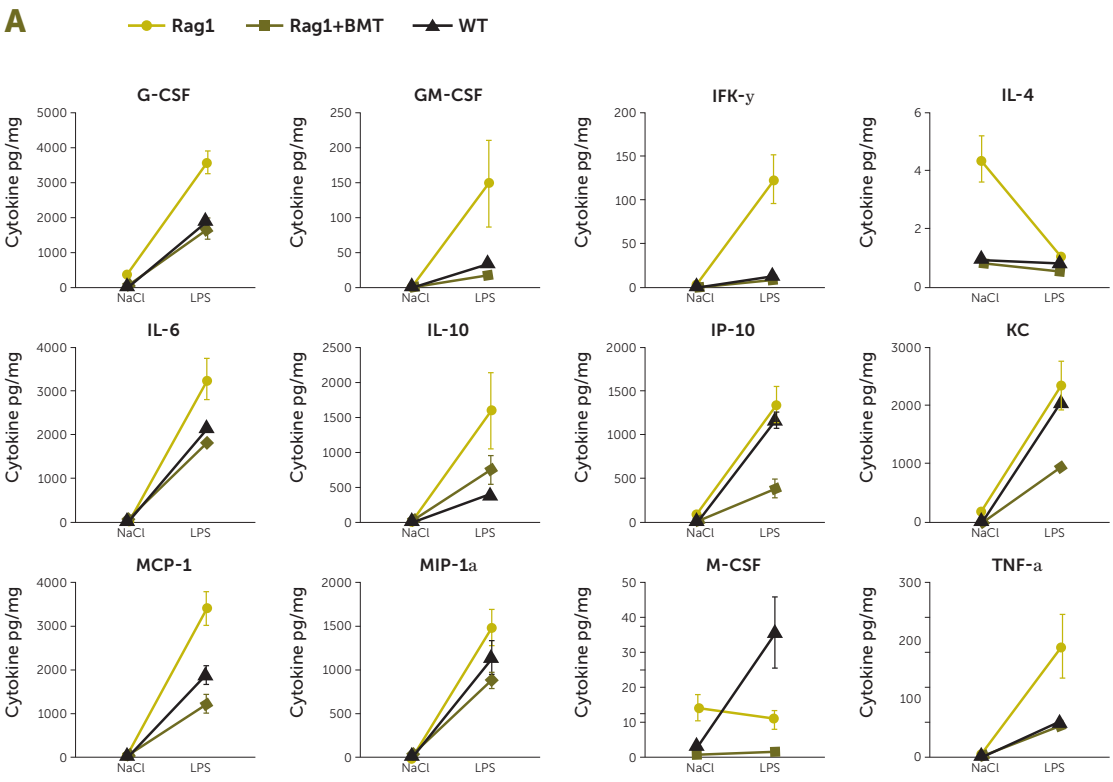
Study #2: The Role of T- and B-Lymphocytes in LRRK2-Mediated PD

Earlier studies from Richard Smeyne, PhD's lab at Jefferson Health, supported by research from other labs around the world, suggested that the immune system of mice carrying a LRRK2 mutation were supercharged. If this is the case, Jefferson investigators wondered if replacing the abnormal immune system seen in LRRK2 mice with a normal immune system of wild-type mice could "rescue" the PD pathology induced by LPS. This was done by generating a new strain of mice that contained LRRK2 mutations in all cells, but lacked an immune system. Once these mice were bred, researchers used bone marrow transplantation to introduce a normal immune system into these animals. These animals are called "chimeras" since they contain a combination of cells from two different animals. In this case, an animal with normal LRRK2 in their T- and B-cells, but whose other cells (including neurons, astrocytes, and microglia) contain the LRRK2 mutation. After comprehensive experimentation, the Smeyne lab was successful in regenerating the peripheral immune system in these mice. These chimeric mice could then be used to directly test the hypothesis that signals from the peripheral immune system (T- and B-cells) control what happened in the brain. Chimeric mice had LPS administered to their gut, and after 7 days (the time necessary to see cell loss), the lab examined the brain's immune response to see if the LPS induced neuron loss. Figure 3 shows that much of the brain's immune response was normalized and, despite the brain cells having a LRRK2 mutation, no neuron death was seen. This important finding points to a new way to think about how PD starts, and the Smeyne lab is continuing to examine if this peripheral immune system to brain crosstalk is important in other forms of PD.



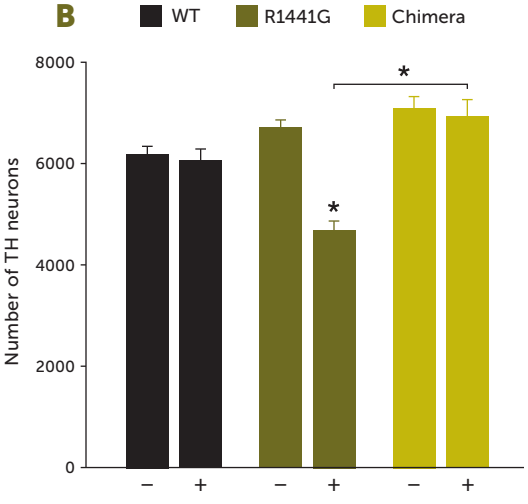


Figure 3. Rescue of PD phenotype by bone marrow transplant. (A) The immune response from mutant mice lacking T- and B-cells (called RAG-1 mice) following LPS (orange lines) are returned to normal levels (black lines) in mice after bone marrow transplants (red lines). (B) LRRK2 mutation mice, normal (WT), and chimeric mice were given LPS. After 7 days, the number of dopamine neurons (TH-positive) were counted, and researchers found that animals with a normal immune system (both WT and chimeric mice) independent of the cells having the LRRK mutations did not show any of the neuron loss associated with PD. Source: Image taken from Kozina E, Byme M, Oakley L, Smeyne RJ. The role of peripheral T-and B-lymphocytes in LRRKs-mediated Parkinson's disease. Poster, Thomas Jefferson University, 2020.

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Kozina E, Byme M, Oakley L, Smeyne RJ. The role of peripheral T-and B-lymphocytes in LRRKs-mediated Parkinson's disease. Poster, Thomas Jefferson University, 2020.

Feasibility of Diffusion and Probabilistic White Matter Analysis

Other Jefferson faculty are also conducting research. Shown below is a study conducted by Chengyuan Wu, MD, MSBmE, and his team on diffusion weighted imaging (DWI) and deep brain stimulation (DBS). Dr. Wu serves as the clinical director of the Jefferson Magnetic Resonance Imaging Center and focuses his research on clinical and translational applications of advanced MR imaging

DBS is an established therapy that produces therapeutic effects through high-frequency stimulation. Although this option does lead to improved clinical outcomes, the mechanisms of the underlying efficacy of the therapy are not well-understood. Investigation of DBS and its postoperative effects on brain architecture continues to be of great interest and a focus of research at Jefferson Health.

DWI, another technique used by Jefferson Health clinicians, involves using advanced imaging to estimate the structure of white matter fibers; however, clinical application of DWI after DBS implantation is challenging due to the strong susceptibility artifacts caused by implanted devices.

This study aims to evaluate the feasibility of generating meaningful white matter reconstructions after DBS implantation. It also attempts to subsequently quantify the degree to which these tracts are affected by postoperative device-related artifacts.

In one study, DWI was safely performed before and after implanting electrodes for DBS (N=9). Differences within each patient between pre- and post-implantation measures for 123 regions of interest (ROIs) were calculated. While differences were noted globally, they were larger in regions directly affected by the artifact. White matter tracts were generated from each ROI with probabilistic tractography, which revealed significant differences in the reconstruction of several white matter structures after DBS. Most importantly, tracts pertinent to PD, such as regions of the substantia nigra and nigrostriatal tract, were largely unaffected.

The aim of the study was to demonstrate the feasibility and clinical applicability of acquiring and processing DWI postoperatively in PD patients after DBS implantation. The presence of global differences provides an impetus for acquiring DWI shortly after implantation to establish a new baseline against which longitudinal changes in brain connectivity in DBS patients can be compared. Understanding that postoperative fiber tracking in patients is feasible on a clinically-relevant scale has significant implications for increasing our current understanding of the pathophysiology of movement disorders, and may provide insights into better defining the pathophysiology and therapeutic effects of DBS. (see Figures 4, 5)

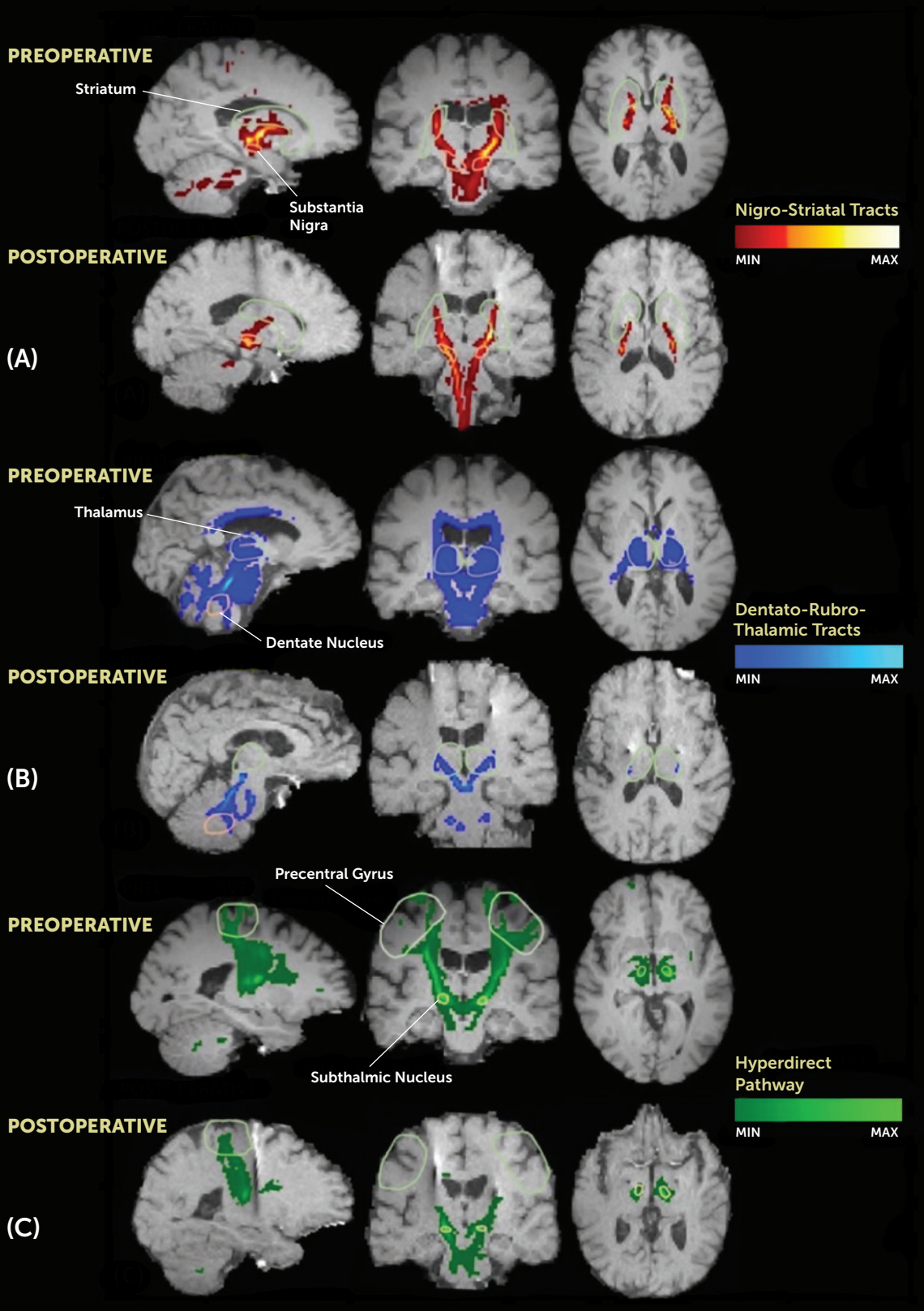

Figure 4. Pre and post-operative tractography of the dentato-rubro-thalamic tracts of the hyperdirect pathway, and nigrostriatal tracts for a single subject (subject 3). Source:_ Image taken from Muller J, Alizadeh M, Lucy L, Thalheimer S, Matias C, Tantawi M, Jingya M, Silverman M, Veronica Z, Grace Yun, ROmo V, Mohamed FB, Chengyuan W. Feasibility of diffusion and probabilistic white matter analysis in patients implanted with deep brain stimulator. NeuroImage Clinical. 2020;25:1-13, Figure 4.

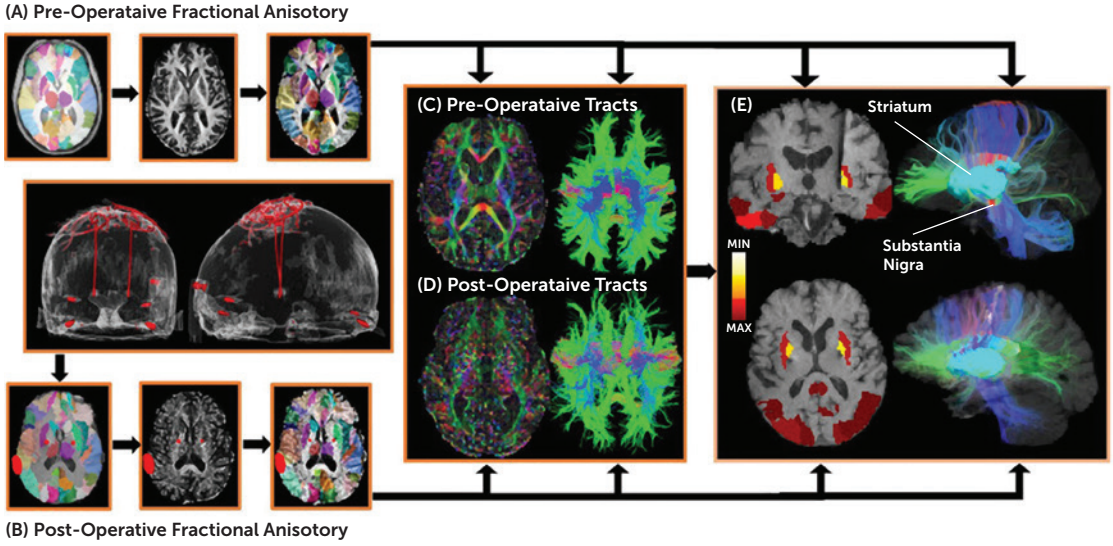

Figure 5. Flowchart of pre and post-operative analysis. The T1 image of the single-subject template in subject space (A) was registered in the pre and post-operative b0 image of each subject in their native space (B) with the transformation T. The atlas labels were transferred to the native space with the transformation T. (C) and (D) show both the pre and post-operative FA map and tractography results in native space, respectively. Pre and post-operative DTI scalars and tractography were compared and analyzed for differences (E). Source: Image taken from Muller J, Alizadeh M, Lucy L, Thalheimer S, Matias C, Tantawi M, Jingya M, Silverman M, Veronica Z, Grace Yun, ROmo V, Mohamed FB, Chengyuan W. Feasibility of diffusion and probabilistic white matter analysis in patients implanted with deep brain stimulator. NeuroImage Clinical. 2020;25:1-13, Figure 1.

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Jefferson Health Parkinson's Disease Clinical Trials

Jefferson Health has a very active clinical research and experimental therapeutics program, with several active and ongoing clinical trials. The variety of trials range from studies evaluating novel delivery systems for levodopa, adjunct medications for motor complications and non-motor symptoms to new DBS systems. Examples of completed and ongoing studies are shown in Table 4

Table 4. Representative Clinical Trials from the Parkinson's Center

Principal Investigator	Name of Trial	Sponsor
Jeffrey Ratliff, MD	A Study to Evaluate the Efficacy, Safety and Tolerability of SEP-363856 in Subjects With Parkinson's Disease Psychosis.	Sunovion
Daniel Monti, MD Andrew Newberg, MD	Physiological Effects of Nutritional Support in Patients with Parkinson's Disease. Sub-Investigator with Daniel Monti, MD (PI)/Andrew Newberg (Co-PI).	
Daniel Kremens, MD	18F-AV-133B04: An open label, multicenter study, evaluating the safety and efficacy of 18F-AV-133 PET imaging to identify subjects with dopaminergic degeneration among subjects presenting to a movement disorder specialist with an uncertain diagnosis.	Avid Radiopharmaceuticals, Inc.
Tsao-Wei Liang, MD	Infusion of Apomorphine, Long-term Safety study (INFUS-ON	US World Meds
Tsao-Wei Liang, MD	Clinical Trial Investigating the Efficacy, Safety, and Tolerability of Continuous Subcutaneous ND0612 Infusion in Comparison to Oral IR-LD/CD in Subjects with Parkinson's Disease Experiencing Motor Fluctuations (BouNDless)	Neuroderm Ltd
Tsao-Wei Liang, MD	A Trial of Zoledronic Acid for the Prevention of Fractures in Patients with Parkinson's Disease (Topaz)	California Pacific Medical Center Research Institute

Table 1. History of Parkinson's Disease and Movement Disorders

AD175	Shaking Palsy Possibly Identified
1755	The birth of James Parkinson
1817	Description of symptoms in the Western world by James Parkinson
1862	Name of disease, Parkinson Disease, coined by Jean-Martin Charcot
1919	Degeneration of substantia nigra identified
1952	Ligation of the anterior choroidal artery discovered as surgical treatment for PD by Irving Cooper
1953	Ablation of the pallidum introduced as a minimally-invasive surgical option for PD
1957	First private Parkinson's Disease Foundation in the US formed
1965	First Levodopa treatments initiated
1968	L-dopa introduced
1979	Discovery of MPTP, a chemical cause of Parkinsonism
1981	Nobel Prize for research into the brain awarded to Dr. Roger Sperry, a neurophysiologist for his work with "split-brain" patients
1987	Popularization of high-frequency deep-brain stimulation by the French neurosurgeon, Dr. Alim Louis Benabid, considered one of the most significant scientific breakthroughs in Parkinson's history
1993	Formation of the European PD Association
1996	Muhammad Ali and his Parkinson's step into the spotlight at the 1984 Olympics
2000	Launch of the Michael J. Fox Foundation
2015	Google joins the fight against PD
2016	Merger to Parkinson's Disease Foundation and National Parkinson's Foundation to form the Parkinson's Foundation
2020	Nobel prize for work on the role of proteins in cells, awarded to Yoshinori Ohsumi, Japanese cell biologist

Table 2. History of Parkinson's Disease and Movement Disorders at Jefferson Health

AD175	Shaking Palsy Possibly Identified
2005	The Parkinson's and Movement Disorders Program created as a Division of the Department of Neurology
2007	First deep-brain simulation procedure for PD performed at Jefferson Health
2013	Clinic expands to second location at Jefferson, Voorhees, NJ
2015	First "asleep" deep-brain stimulation procedure for PD performed at Jefferson Health
2017	Movement Disorders Fellowship established in the Department of Neurology
2018	Stephen Klasko, MD, designates the PD center as a "CRISP" program
2019	Jefferson Health recognized as a Center of Excellence by the Parkinson's Foundation
2020	Clinic expands to third location, Philadelphia Navy Yard

CRISP = Clinical Research Integrated Strategic Program

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