THE 2017 RUSH
NEUROSCIENCE REVIEW
Forward Progress: Neurologists at Rush, including Dusan Stefoski, MD (right), and Michael Ko, MD, have played a vital role in advancing treatment for patients with multiple sclerosis. Learn how on page 59.
THE 2017
RUSH NEUROSCIENCE REVIEW

Faculty editors
Sepehr Sani, MD
Aimee Szewka, MD

CHAIRPERSONS’ LETTER 2

NEUROSCIENCES AT RUSH: AT A GLANCE 4

PRIMARY AND ASSOCIATED FACULTY
Department of Neurological Sciences 6
Department of Neurological Surgery 7

RESIDENTS AND FELLOWS
Department of Neurological Sciences 8
Department of Neurological Surgery 9

ARTICLES
Preimplantation Modeling of Electrode Lead Implant Sites to Predict the Extent of Cortical Activation During Direct Neurostimulation Therapy 10
Leopoldo Cendejas-Zaragoza; Richard W. Byrne, MD; Marvin A. Rossi, MD, PhD
Improvement of Brain Function by a Lipid-Lowering Factor 18
Kalipada Pahan, PhD
Predictors of False-Positive Stroke Thrombectomy Transfers 23
Julia Yi, MD; Danielle Zielinski, RN, MSN, AG-ACNP; Bichun Ouyang, PhD; James Conners, MD, MS; Rima Dafer, MD, MPH, FAHA; Michael Chen, MD
Dramatic Reductions in Spine Surgery Infection Rates 29
Harel Deutsch, MD
Moving Pictures and Moving Targets in the Care of Patients With Movement Disorders 33
Jennifer G. Goldman, MD, MS; Brandon R. Barton, MD, MS; Gian D. Pal, MD, MS

PUBLICATIONS 39

RESEARCH GRANTS 53

VOLUME AND QUALITY DATA
Volumes, neurology and neurological surgery 57
Mortality, neurology and neurological surgery 58
Quality indicators, stroke 58

INTERVIEW: Game-Changers 59
Multiple sclerosis specialists Dusan Stefoski, MD, and Michael Ko, MD, discuss Stefoski's and Rush's roles in bringing novel therapies to the market to advance care for patients with multiple sclerosis.
Chairpersons’ Letter

Both of us were early in our careers when President George H. W. Bush proclaimed the 1990s the “Decade of the Brain.” In the years between 1990 and 1999, neuroscience research flourished in the US and abroad. The decade also forced a confrontation with an uncomfortable fact: With the steady aging of the nation’s population, the high cost of caring for neurological diseases would only get higher. By the end of the 1990s, the cost to treat neurological diseases in the US was approximately $400 billion a year; by 2014, according to a recent study published in the *Annals of Neurology*, the country was spending close to $800 billion annually.

Today, the challenge for the neuroscience program at Rush—as for programs throughout the country—is twofold. We must continually innovate to offer high-quality care as efficiently as possible while enhancing the vital relationship between patient and physician. We must also strive to foster a rich intellectual and clinical environment to engage our faculty and nurture the next generation of physicians and researchers.

The following selected highlights from 2016 and early 2017 demonstrate how we’re facing these challenges.

**Mobile stroke unit:** In October 2016, Rush unveiled its mobile stroke treatment unit—a specially built, state-of-the-art ambulance outfitted with telemedicine technology and a CT scanner to enable brain imaging that is critical to accurate stroke diagnoses and treatment. The unit, one of only a handful of its kind in the US, will serve Chicago’s western suburbs from a base at Rush Oak Park Hospital.

**Regenerative research institute:** Rush has raised $2 million to fund a regenerative research institute at Rush that will be led by neurosurgeon Richard G. Fessler, MD, PhD, who has vast experience in research on using stem cells to treat patients with spinal cord injuries. With Fessler’s expertise in the treatment of spinal cord injury as a springboard, the institute will ultimately encompass all areas of regenerative research at Rush, including neurological conditions, cartilage repair, heart disease, and macular degeneration.

**Neurology elective in Zambia:** Starting in the 2017-2018 academic year, 2 3rd-year residents received a stipend to travel to Zambia’s capital city for a 1-month elective at the University Teaching Hospital in Lusaka. The elective provides a vital service for Zambia, which faces a significant deficit of neurologists—there are only 4 neurologists in the country the size of Texas. And it provides a vital global outlook for Rush residents, who have the opportunity to practice medicine in another country with a significantly different population in a hospital with limited resources.

**New neuroimmunology fellowship:** Rush has established a 2-year neuroimmunology fellowship that combines training in clinical care and research in the fields of multiple sclerosis and related demyelinated and autoimmune diseases, neurological complications of HIV, and infectious diseases of the nervous system.

**Delivering high-quality care in Chicago—and beyond:** Over the next 2 years, the Department of Neurological Sciences will be expanding services at Rush offices in the South Loop, River North, Oak Park, and Oakbrook, and at Rush Copley Medical Center in Aurora.

**Research highlights**

With a growing number of clinical trials in both neurosurgery and neurology, faculty at Rush continue to make substantial contributions to the understanding of neurological disease. Here are just a few examples:

- **Hope for patients with spinal cord injuries.** Four of 6 people with paralyzing spinal cord injuries who were treated with a new cell therapy have recovered a significant level of movement on at least one side, new study results show. This 67 percent recovery rate is more than double the rates of recovery seen in both matched historical controls and published data in a similar population. Each of the 6 participants in the study had lost all motor function below the location of the spinal injury. They each received a surgical injection of 10 million oligodendrocyte progenitor cells, or AST-OPC1, which potentially can make poorly working nerves function better. Asterias Biotherapeutics, the California-based biotechnology company that manufactures the cell therapy, reported the 12-month results of the study.

Igor Koralnik, MD (left), and Richard Byrne, MD.
in October 2017. Neurosurgeon Richard G. Fessler, MD, PhD, is the principal investigator of the study at Rush, one of 9 clinical sites in the US.

- **Disease-modifying therapy for multiple sclerosis.** Ocrevus (ocrelizumab), the first and only disease-modifying therapy for both primary progressive and relapsing forms of multiple sclerosis (MS) was approved by the US Food and Drug Administration in late March. Learn how Rush helped pioneer the use of Ocrevus in the interview feature on page 54.

- **Clot removal can be effective, even after 6 or more hours.** Mechanical thrombectomy, a treatment to remove a stroke-causing blood clot in the brain, is effective in some patients even when performed within 6 to 24 hours after a stroke, according to the results of an international, randomized controlled research study. Neurointerventionalist Michael Chen, MD, the principal investigator of the study at Rush, presented the findings in May 2017 at the European Stroke Organization Conference in Prague. Rush is the only Illinois site, one of 7 sites in the US, and one of only 22 sites in the world to participate in the international study, called the DAWN trial.

**Faculty awards and recognition**

Each year, many of our faculty members are recognized for their achievements locally, nationally, and internationally. The following are just a few examples:

**Department of Neurological Surgery**

- Richard W. Byrne, MD, served as co-president at the second annual Chinese and American Neurosurgery Meeting in Harbin, China, and was named president-elect of the Neurosurgical Society of America.

- Among his many honors, Richard G. Fessler, MD, PhD, was listed in the 9th edition of 2000 Outstanding Intellectuals of the 21st Century and was named chairman and president-elect of the International Society for Minimal Intervention in Spinal Surgery.

**Department of Neurological Sciences**

- Thomas Pritchett Bleck, MD, will be honored with the Lifetime Achievement Award for 2018 from the Society of Critical Care Medicine.

- Kalipada Pahan, PhD, earned the Zenith Fellows Award from the Alzheimer’s Association for researchers who have made a substantial personal commitment to the advancement of Alzheimer’s disease research.

- Christopher Goetz, MD, was elected president of the International Parkinson and Movement Disorder Society and became a member of the Académie Nationale de Médecine (French National Medical Academy).

- Jeffrey Kordower, PhD, was named vice chairman of the board of directors of the National Association for Biomedical Research.

- Cynthia Comella, MD, was named president-elect of the International Neurotoxin Association and chair-elect of the International Parkinson and Movement Disorders Society, Pan American Section.

- Deborah Hall, MD, received recognition in 2017 for having one of the top 10% of posters at the American Academy of Neurology and an exceptional poster at the Movement Disorder Society International Meeting in Vancouver for her poster titled “Fragile X Gray Zone Alleles Are Associated With Higher Global Motor Function in an Elderly Community Population.”

- Brandon Barton, MD, published a textbook, Non-Parkinsonian Movement Disorders, with Hall.

- Igor Koralnik, MD, was named chair of the international outreach committee of the American Neurological Association.

- The Huntington’s Disease program at Rush, led by Jennifer G. Goldman, MD, MS, was named a Center of Excellence by the Huntington’s Disease Society of America.

- Matthew Meriggioli, MD, was awarded a Muscular Dystrophy Association (MDA) grant, and Rush was designated as an official MDA Care Center.

- James Conners, MD, MS, and the stroke team have been honored with the 2017 Excellence in Telehealth Achievement Award for Improved Care for Underserved Populations.

- Sayona John, MD, was recognized as a Lifesaving Partner by Gift of Hope Organ & Tissue Donor Network for going above and beyond to make donations possible.

- Aimee Szewka, MD, was awarded for outstanding achievement in receiving an A.B. Baker Teacher Recognition Award from the American Academy of Neurology.

We hope you will explore the rest of this publication to learn about our faculty’s many contributions to research and clinical care in the neurosciences.

Richard Byrne, MD  
Chairperson, Department of Neurological Surgery  
The Roger C. Bone, MD, Presidential Chair  

Igor Koralnik, MD  
Chairperson, Department of Neurological Sciences  
The Jean Schweppe Armour Professor of Neurology
# Neurosciences at Rush: At a Glance

## Department of Neurological Sciences
- Rush Alzheimer’s Disease Center
- Section of Cerebrovascular Disease
- Section of Clinical Neurophysiology and Epilepsy
- Section of Cognitive Neurosciences
- Section of Critical Care Neurology
- Section of General Neurology
- Section of Movement Disorders
- Rush Multiple Sclerosis Center
- Section of Pediatric Neurology
- Section of Neuromuscular Diseases
- Section of Neuro-oncology
- Section of Neuro-ophthalmology

## Department of Neurological Surgery
- Neuroendovascular Surgery Center
- Skull Base and Pituitary Surgery Center
- Spine and Back Care

<table>
<thead>
<tr>
<th>Service</th>
<th>Volume</th>
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<tr>
<td>Neurology outpatient visits</td>
<td>29,635</td>
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<tr>
<td>Neurology inpatient discharges</td>
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<tr>
<td>Neurological surgery outpatient visits (brain)</td>
<td>39,585</td>
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<td>Neurological surgery outpatient visits (spine)</td>
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For additional volume and quality data, see pages 52-53.

## Inpatient Facilities

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<td>Psychiatric</td>
<td>67</td>
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<tr>
<td>Rehabilitation</td>
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<tr>
<td>Epilepsy (adult)</td>
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## Professional Staff

<table>
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<tr>
<td>Attending physicians</td>
<td>112</td>
</tr>
<tr>
<td>Residents and fellows</td>
<td>58</td>
</tr>
<tr>
<td>Advanced practice nurses and physician assistants</td>
<td>33</td>
</tr>
</tbody>
</table>
**NIA-designated Alzheimer’s Research Center:** The Rush Alzheimer’s Disease Center is a designated Alzheimer’s disease research center, funded by the National Institute on Aging of the US National Institutes of Health.

**No. 4 in the Nation:** In 2017, Rush University Medical Center received Vizient’s (formerly University HealthSystem Consortium’s) Quality Leadership Award, ranking No. 4 among 107 academic medical centers nationwide. It is the 5th consecutive time Rush has been ranked in Vizient’s top 5, and the 9th since 2005.

**Comprehensive Stroke Center:** Rush’s stroke program received the Get With the Guidelines Gold Plus Award from the American Heart Association and earned a place on the American Stroke Association’s Target: Stroke Elite Plus Honor Roll.

**MDA Care Center:** In January 2017, the Muscular Dystrophy Association (MDA) named Rush University Medical Center an MDA Care Center, elevating Rush to an elite group of just over 150 providers who have this designation.

**Parkinson’s Foundation Center of Excellence:** The Parkinson’s Foundation added Rush University Medical Center to the global network of institutions the foundation has designated as Centers of Excellence. The designation builds upon Rush’s longstanding history and recognition as a Parkinson’s Foundation Research Center.

**NIA-designated Alzheimer’s Research Center:** The Rush Alzheimer’s Disease Center is a designated Alzheimer’s disease research center, funded by the National Institute on Aging of the US National Institutes of Health.

**Nursing Excellence:** Rush University Medical Center has earned Magnet status—the highest recognition for nursing excellence—4 consecutive times from the American Nurses Credentialing Center.
Faculty (2016)
Department of Neurological Sciences

Chairperson: Igor Koralnik, MD

Aging and neurodegenerative diseases
Neelum Aggarwal, MD
Zoe Arvanitakis, MD, MS
Lisa Barnes, PhD
David Bennett, MD
Katherine Blizinsky, PhD
Aron Buchman, MD
Ana Capuano, PhD
Debra Fleischman, PhD
Chris Gaiteri, PhD
Duke Han, PhD
Namhee Kim, PhD
Sue Leurgans, PhD
Julie A. Schneider, MD
Robert Wilson, PhD
Lei Yu, PhD

Cerebrovascular disease
Laurel Cherian, MD, MS
James Conners, MD, MS
Rima Dafer, MD, MPH, FAHA
Michael Kelly, MD*
Neha Kramer, MD
Nick Osteraaas, MD
Sarah Song, MD, MPH
Alejandro Vargas, MD, MS

Clinical neurophysiology and epilepsy
Antoaneta Balabanov, MD
Adriana Bermeo-Ovalle, MD
Lawrence Bernstein, MD
Amar Bhatt, MD
Thomas Bleck, MD
Elia DeSavino, MD*
Thomas Hoeppner, PhD
Maggie McNulty, MD
Rebecca O’Dwyer, MD
Esmeralda Park, MD*
Serge Pierre-Louis, MD*
Lubov Romantseva, MD
Marvin Rossi, MD, PhD
Michael Smith, MD
Travis Stoub, PhD

Critical care neurology
Thomas Bleck, MD
Torrey Boland, MD
Michael Chen, MD
Ivan DaSilva, MD
Rajeev Garg, MD, MS
Sayona John, MD
Lauren Koffman, DO
George Lopez, MD, PhD
Sebastian Pollandt, MD
Starane Shepherd, MD

Cognitive neurosciences
Christopher Grote, PhD
Duke Han, PhD
Richard Peach, PhD
Robert Wilson, PhD

General neurology
Amar Bhatt, MD
Richard Brannegan, MD*
Jon Cheponis, MD
James Dorman, MD*
Andrew Dorsch, MD
Katey Ess, MD
Jacob Fox, MD
Laura Goldstein, MD
Christopher Muth, MD
Ligia Rioja, MD
Sava Saeed, MD*
Megan Shanks, MD
Lafayette Singleton, MD*
Milena Stosic, MD
Aimee Szewka, MD
Jordan Topel, MD
Jessica Wilson, MD
Robert Wright, MD

Multiple sclerosis
Michael Ko, MD
Danielle Rice, MD*
Fabian Sierra-Morales, MD
Dusan Stefoski, MD
Neurobiology
Yaping Chu, PhD
Malabendu Jana, PhD
Jeffrey Kordower, PhD
Susanta Mondal, PhD
Dan Nicholson, PhD
Kalipada Pahan, PhD
Avik Roy, PhD

Neuroinfectious diseases
Igor Koralnik, MD
Fabian Sierra-Morales, MD
Lakshmi Warrior, MD*

Neuromuscular diseases
Reena Ghode, MD*
Rabia Malik, MD
Matthew Meriggioli, MD
Irwin Siegel, MD
Madhu Soni, MD

Neuro-oncology
Joo Yeon Nam, MD
Clement Pillainayagam, MD

Neuro-ophthamology
Thomas Mizen, MD
Milena Stosic, MD
Aimee Szewka, MD

Parkinson’s disease and movement disorders
Sharlet Anderson, PhD
Meagan Bailey, MD
Brandon Barton, MD, MS
Bryan Bernard, PhD
Cynthia Comella, MD
Melany Danehy, MD
Jori Fleisher, MD
Christopher Goetz, MD
Jennifer Goldman, MD, MS
Deborah A. Hall, MD, PhD
Aikaterini Kompoliti, MD
Bichun Ouyang, PhD
Gian Pal, MD, MS
Glenn Stebbins, PhD
Leonard Verhagen Metman, MD, PhD

Pediatric neurology
Elizabeth Berry-Kravis, MD
Peter Heydemann, MD
Meryl Lipton, MD
Lubov Romantseva, MD

Department of Neurological Surgery
Chairperson: Richard Byrne, MD

Richard Byrne, MD
Michael Chen, MD
R. Webster Crowley, MD
Harel Deutsch, MD
Richard Fessler, MD, PhD
Ricardo Fontes, MD, PhD
Demetrius Lopes, MD
Lorenzo Munoz, MD
John O’Toole, MD, MS
Sepehr Sani, MD
Vincent Traynelis, MD

Research faculty
Roberta Glick, MD
Richard Penn, MD

Associated faculty at Rush University Medical Center
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Aidnag Diaz, MD, MPH – Radiation oncology
Sheila Dugan, MD – Physical medicine and rehabilitation
David Rothenberg, MD – Anesthesiology
Mary Sturaitis, MD – Anesthesiology
R. Mark Wiet, MD – Neurotology

Associated clinical faculty, neurosurgery*
Jerry Bauer, MD
Tibor Boco, MD
George Bovis, MD
Martin Herman, MD, PhD
Juan Jimenez, MD
Martin Luken, MD
Patricia Raskin, MD
Szymon Rosenblatt, MD
John Ruge, MD
Andrew Zelby, MD

*Primary appointment is not at Rush University Medical Center
Residents and Fellows (2016)

Department of Neurological Sciences

Residents

Zeeshan Ali, MD  
Medical school: Indiana University School of Medicine

Bahar Beaver, MD  
Medical school: University of Oklahoma College of Medicine

Hannah Breit, MD  
Medical school: Loyola University Chicago Stritch School of Medicine

Dana Cooper, MD  
Medical school: Loyola University Chicago Stritch School of Medicine

Catherine Daley, MD  
Medical school: University of Toledo College of Medicine and Life Sciences, Ohio

Gregory Fenton, MD  
Medical school: Boston University School of Medicine

Rachel Forman, MD  
Medical school: Chicago Medical School

Edie Graham, MD  
Medical school: Loyola University Chicago Stritch School of Medicine

Christopher Green, MD  
Medical school: Rush Medical College

Emily Grodinsky, MD  
Medical school: Weill Cornell Medicine, New York

Ryan Hanson, MD  
Medical school: Rush Medical College

Emily Hill, MD  
Medical school: Rush Medical College

Teresa Lee, MD  
Medical school: Georgetown University School of Medicine, Washington, DC

Stephanie Lyden, MD  
Medical school: University of Washington School of Medicine, Seattle

Fiona Lynch, MD  
Medical school: Rush Medical College

Jacob Manske, MD  
Medical school: Rush Medical College

Kristin Miller, MD  
Medical school: George Washington University School of Medicine and Health Sciences, Washington, DC

Jeremy Pruzin, MD  
Medical school: Chicago Medical School

Jeffrey Quinn, MD  
Medical school: Loyola University Chicago Stritch School of Medicine

Daniel Schachter, MD  
Medical school: New York Medical College

Kathy Slota, MD  
Medical school: Chicago Medical School

Tammy Smith, MD, PhD  
Medical school: University of Utah School of Medicine

Maggie Stepien, MD  
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Jake Torrison, MD  
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Fellows

Fawaz Ahmad, MD  
Medical school: University of Arkansas College of Medicine  
Residency: Greater Baltimore Medical Center

Hunan Chaudhry, MD  
Medical school: Rush Medical College  
Residency: Rush University Medical Center

Yoon Jae Choi, MD  
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Residency: University of Chicago Medical Center  
Fellowship (neuro-oncology): University of California, Los Angeles

Christine Chuck, MD  
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Residency: Rush University Medical Center

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Residency: University of Illinois at Chicago

Avram Fraint, MD  
Medical school: Rush Medical College  
Residency: Rush University Medical Center

Anjali Gera, MD  
Medical school: University of Illinois at Chicago  
Residency: University of Illinois at Chicago

Ajit Indavarapu, MD  
Medical school: Osmania Medical College, Hyderabad, India  
Residency: University of Wisconsin - Madison
Asma Moussaoui, MD
Medical school: V.N. Karazin Kharkiv National University, Ukraine
Residency: University of Minnesota Medical Center
Benjamin Savage, DO
Medical school: Chicago College of Osteopathic Medicine, Midwestern University, Downers Grove, Ill.
Residency: Rush University Medical Center
Arpan Shrivastava, MD
Medical school: American University of Antigua, Coolidge, Antigua
Residency: University of Kentucky Medical Center
Ruby Upadhyay, MD
Medical school: Rush Medical College
Residency: Rush University Medical Center

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Medical school: Baghdad College of Medicine, Iraq
Residency: Baghdad Teaching Hospital, Iraq
Fellowship (epilepsy): Detroit Medical Center, Michigan
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Medical school: Boston University School of Medicine
Residency: University of California, San Francisco
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Residency: National Hospital, Hamah, Syria

Department of Neurological Surgery

Residents
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Sumeeet Ahuja, MD
Medical school: Indiana University School of Medicine
Andre Beer Furlan, MD
Medical school: University of Sao Paulo Faculty of Medicine, Brazil
Bledi Brahimaj, MD
Medical school: University of Cincinnati College of Medicine
Daniel Eddelman, MD, PhD, MBA
Medical school: Harvard Medical School
R. David Fessler, MD, PhD
Medical school: University of Cincinnati College of Medicine
Mena Kerolus, MD
Medical school: University of Missouri - Kansas City School of Medicine
Ryan Khanna, MD
Medical school: Northwestern University Feinberg School of Medicine, Chicago

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Krishna Joshi, MD, MBBS, MS, MCh
Medical school: Govind Ballabh Pant Institute of Postgraduate Medical Education and Research, Maulana Azad Medical College, New Delhi, India
Residency: Govind Ballabh Pant Hospital, New Delhi
Hani Malone, MD
Medical school: Columbia University College of Physicians and Surgeons, New York
Residency: Columbia University Medical Center, New York

Ryan Kochanski, MD
Medical school: Wayne State University School of Medicine, Detroit
Joseph Edward Molenda, MD
Medical school: Johns Hopkins University School of Medicine, Baltimore
Stephan Munich, MD
Medical school: University at Buffalo Jacobs School of Medicine and Biomedical Sciences, New York
Ravi Nunna, MD
Medical school: University of Cincinnati College of Medicine
Joshua Wewel, MD
Medical school: University of Nebraska College of Medicine
Andrew Wong, MD
Medical school: University at Buffalo Jacobs School of Medicine and Biomedical Sciences, New York
Josha Woodward, MD
Medical school: Oregon Health and Science University School of Medicine

Mazda Turel, MD
Medical school: Grant Medical College, Mumbai, India
Residency: Christian Medical College (CMC), Vellore, India
PREIMPLANTATION MODELING OF ELECTRODE LEAD IMPLANT SITES TO PREDICT THE EXTENT OF CORTICAL ACTIVATION DURING DIRECT NEUROSTIMULATION THERAPY

Leopoldo Cendejas-Zaragoza // Richard W. Byrne, MD // Marvin A. Rossi, MD, PhD

Author Affiliations: Department of Neurological Sciences (Mr Cendejas-Zaragoza and Dr Rossi) and Department of Neurological Surgery (Dr Byrne), Rush University Medical Center, Chicago, Illinois.

Corresponding Author: Marvin A. Rossi, MD, PhD, Rush University Medical Center, Department of Neurological Sciences, 1725 W Harrison St, Suite 885, Chicago, IL 60612 (marvin_a Rossi@rush.edu).

Introduction

The RNS System (Responsive Neurostimulation System; NeuroPace) is a neuromodulation technology that was approved in 2013 by the US Food and Drug Administration as an adjunctive therapy for patients with refractory focal-onset epilepsy. This technology is based on delivering direct brain stimulation therapy using a closed-loop on-demand approach to revert a pathological epileptic network to a nonpathophysiological state.

The efficacy of the RNS System has been evaluated and followed in multicenter clinical trials.1-3

Neuromodulation therapy has been shown to demonstrate both acute and chronic efficacy. Proposed mechanisms explaining the acute efficacy of local or direct brain stimulation include conduction blockade,4 synaptic inhibition,5 synaptic depression,6 and overriding of pathophysiological neural network activity.7-10 In addition, chronic exposure to direct neurostimulation has been associated with distant cortical synaptic proliferation.11

Several elements must be considered in the clinical response to stimulation delivered directly to neuronal populations. These variables include stimulation parameter settings,12 the number and interdependence of anatomical targets, electrode number,

Figure 1. A, A lumped model for an axon oriented in the x direction is presented at the level of a node of Ranvier during bipolar stimulation. Each compartment (red box) is considered to be composed by a membrane capacitance (cM), connected in parallel with the membrane resistance (rM). Compartments are connected to others through resistors in the extracellular space (rE) and intracellular space (ri). The transmembrane voltage (VM) is defined as the potential difference between the extracellular and intracellular fluid (\(VM = Vi - VE\)). In the figure, \(\Delta x\) is the length of the compartment. Note that the extracellular potential (VE) is modified by the electric stimulation produced by the electrode (see the isopotential lines produced during a bipolar stimulation of 4.3 mA). Also note how VE changes with the distance. B, The structural MRI was used to create a 3D computational model for the patient. C, Segmentation of the patient’s MRI data set was performed manually by using colored masks (blue, cerebrospinal fluid; gray, gray matter; white, white matter).
Preimplantation Modeling of Electrode Lead Implant Sites

Electrode location and orientation, geometry or shape of the electrode contacts, distribution of the cathode and anode, and the biophysical properties of the stimulated medium.

A critical step toward effectively applying direct brain stimulation therapy in patients with focal-onset epilepsy is to effectively interface with epileptogenic neural circuits. Therefore, the objective of this study was to predict preoperatively the extent to which direct stimulation therapy, using a limited set of active electrode contacts, can propagate through white matter to influence the maximal extent of an epileptic circuit.

A patient-specific preimplant model was generated to calculate the volume of cortical activation (VOCA) in a patient who was a candidate for treatment with the RNS System. This model comprises an iterative, computationally intensive process that calculates regions of hyperpolarization and depolarization in axon bundles immediately surrounding the active electrode contacts, at the gray–white matter interface, using a so-called activation function.

Our center has successfully implanted RNS System depth leads in juxtacortical epileptogenic mesial temporal white matter since 2004. Our goal has been to influence contralateral homotopic mesial temporal regions with a limited set of active electrode contacts. We employed parahippocampal white matter as robust afferent and efferent hippocampal pathways for strategic propagation of direct stimulation therapy. Our goal in the present study was to maximize the extent to which preimplant modeling of four cylindrical depth electrode contacts placed in extratemporal basal frontal white matter can enable modulation of distant epileptic tissue in a complex epileptogenic network. Achieving such distant activation can be improved with patient-specific lead placement planning. For this purpose, our model has been incorporated into a preimplant workflow at our institution using novel neuroimaging techniques. Postimplant validation of the preimplant modeling predicting the extent to which distant targeted brain regions would be influenced was performed using subtracted activated SPECT (single-photon emission computed tomography), referred to herein as SAS.

Methods

The preimplantation workflow that was established to predict the extent to which direct stimulation therapy can be strategically guided through white matter was based on an iterative computational model that involved the following 6 steps: (1) description of an activation function derived from the cable equation of axons; (2) calculation of the extracellular electric potential, $V_E$, through the construction of a patient-specific finite element method (FEM) model; (3) identification of axon bundle directionality by means of diffusion tensor imaging (DTI); (4) computation of the activation function using the values of $V_E$ and axon directionality, to differentiate among the regions of depolarization and hyperpolarization; (5) generation of regions of interest (ROIs) that were constructed according to the numerical values of the activation function; and (6) identification of influenced tracts by exporting the ROIs as seeds into a tractography algorithm. The model was validated after implantation using SAS. This technique captured transient blood flow changes during delivery of neurostimulation therapy using a relatively high therapeutic charge density delivered through adjacent electrode contacts without generating an afterdischarge.

Patient

The patient was a 19-year-old left-handed woman who experienced a left temporal hemorrhage in utero, secondary to maternal blood incompatibility. Infantile spasms were noted when the patient was 6 months of age, with subsequent frequent

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Figure 2. A, The CAD electrode model consisted of 4 conductive cylinders (1.27 mm diameter × 2 mm height) separated by insulators (10 mm between cylinder midpoints). The numbers in the figure indicate the depth electrode conductors from anterior to posterior. B and C, The +CAD module in Simpleware was used to place the electrodes in white matter.
nocturnal seizures since that time. A left posterior temporal ventriculoperitoneal shunt was placed at the age of 10 months. Seizure semiology included quickly sitting up in bed with right head deviation followed by loud vocalization. Triggers included menstruation and stress. During wakefulness, she reported an aura of sensations that she described as the feeling of “spiders” in her stomach.

Activation Function Definition

The activation function was derived by analyzing a lumped element model of an axon compartment, which is placed within a Cartesian coordinate system in a specific direction, at the level of a node of Ranvier (Figure 1A). A nonhomogenous partial differential equation was derived by applying the Kirchhoff current law. This partial differential equation, known as the cable equation, is as follows:

$$\lambda \frac{\partial V_M}{\partial t} - \tau \frac{\partial V_M}{\partial x} - V_M = -\lambda \frac{\partial V_E}{\partial x},$$

where $\lambda$ is the length constant and $\tau$ is the time constant for the membrane. The solution of this equation describes the transmembrane voltage ($V_M$) as a function of time and geometry. The activation function (the right-hand side of the equation) is proportional to the 2nd derivative of the extracellular voltage ($V_E$) with respect to the $x$ direction; thus the activation function is proportional to $\frac{\partial^2 V_E}{\partial x^2}$.

In the model depicted in Figure 1A, the axon is oriented in the $x$ direction. However, axons can be oriented in any spatial direction in a 3-dimensional (3D) space. Therefore, the activation function should be computed with respect to the axon direction. The activation function is relevant because previous work has determined that qualitative predictions of neural activation by extracellular sources can be evaluated by direct computation of this parameter. It can be assumed that regions of depolarization can be identified where the activation function is positive, whereas regions of hyperpolarization can be identified where the activation function is negative. Also, note that the activation function can be computed if the extracellular potential ($V_E$) and the axon orientation are known.

Image Sequences

High-resolution DTI sequences were obtained for the patient with a 3-T magnetic resonance imaging (MRI) scanner using 2-mm-thick oblique axial slices. Diffusion measurements were performed in 60 noncollinear directions with a diffusion weighting factor of 900 s/mm$^2$. Six nondiffusion weights (b values) were used.

In addition, a T1-weighted SPACE MRI sequence and a T2-weighted FLAIR sequence were acquired. The resulting images were used to perform eddy current and distortion corrections for the DTI volumes using TORTOISE version 2.0.1. The DTI and T2 images were later resampled and registered to the T1-weighted SPACE image.

Construction of the 3D Model

The structural MRI was used to construct a 3D model of the brain tissue using ScanIP version 6.0 (Simpleware); see Figure 1B. Segmentation of cerebrospinal fluid, gray matter, and white matter was performed manually by creating masks using solid-color filled regions (Figure 1C). This segmentation was later used to compute the solution for $V_E$.

Further resampling of the structural image was performed by means of linear interpolation between neighboring voxels to generate cubic voxels of 0.2 mm. This resolution was necessary to include the depth electrode models. These models were constructed in a computer-aided design (CAD) platform, according to geometric specifications provided by NeuroPace. Specifically, each model had 4 platinum/iridium conductive cylinders (1.27 mm diameter × 2 mm height) separated by insulators (10 mm between the midpoints of the cylinders); see Figure 2A. The CAD electrode lead models were later strategically positioned in the white matter of the segmented MRI data set, within 4-5 mm of the gray–white matter interface, using the +CAD module in Simpleware (Figure 2B and 2C).

The depth electrode placement sites were chosen using 2 functional imaging techniques: subtracted ictal SPECT coregistered to the patient’s MRI (SISCOM), and subtracted postictal DTI (spiDTI). The former was used to identify the ictal onset zones through transient changes in blood perfusion caused during an ictal event. The latter technique, which was developed by researchers at our center to delineate and visualize the epileptic circuit, was performed by capitalizing on the transient directionality of water diffusion following a focal-onset seizure. Specifically, acute or transient but evolving postictal changes in fractional anisotropy (FA) could be identified when compared with interictal DTI FA. This technique can be utilized to visualize the subacute remnants of the directionality of an epileptic circuit recruited by focal-onset seizures. These transient postictal measures are not typically useful in those patients in whom secondarily generalized seizures have occurred. Such widespread propagation pathways may become too complex to analyze. Both SISCOM and spiDTI complemented our standard presurgical scalp video-electroencephalographic monitoring, magnetoencephalography, positron emission tomography, and observed semiology.

The composite model, which included the 3D brain model and the depth leads, was used to construct a variable FEM tetrahedral mesh using ScanIP.

Solving for $V_E$

The FEM mesh was then exported to COMSOL Multiphysics version 4.4 (COMSOL Inc.), in which isotropic electric properties were assigned to each segmented tissue and material (Table 1). Bipolar stimulation, between two adjacent depth lead contacts, was simulated in the electrodes by applying direct current at
4.3 mA. The UMFPACK linear solver was used within COMSOL to compute the extracellular electric potential ($V_E$) by solving a Poisson-like equation derived from electric quasistatic conditions. The solution was performed on a 64-bit dual-processor, 16-core, Windows 7 workstation with 192 GB of accessible RAM.

**Calculation of the Activation Function, Generation of ROIs, and Tractography**

The patient’s DTI data set was used to construct an approximation for the 3D axon orientation field. This approximation delivered the orientation of bundles (collection of axons) rather than a specific axon direction. This approximation was necessary because it was not possible to extract directional information of individual axons with the current DTI protocols because of limited resolution (the size of a voxel is approximately 2 mm). Therefore, a voxel in a DTI data set may contain axons with different directions.

The values of the activation function were computed within the patient’s 3D model using the $V_E$ results and the axon directionality field. As discussed previously, regions of depolarization and hyperpolarization were identified where the value of the activation function was positive or negative, respectively. These regions were used to construct 3D ROIs adjacent to the electrode. These ROIs constituted the VOCA solution and were imported as seeds into TrackVis version 0.6 (TrackVis.org).

Finally, Diffusion Toolkit software was used to track DTI fibers using the FACT (Fiber Assignment by Continuous Tracking) algorithm with an angle threshold of 70°. TrackVis was then used to visualize tracts and filter those that entered the imported ROIs.

**Postimplant Validation**

SAS was used to validate, in vivo, the preoperatively modeled VOCA and white matter propagation circuit. This validation was done 6 months after stereotactic implantation of the depth lead in the patient’s right temporal and left frontal white matter. The stimulation parameters used in the presurgical simulation were delivered during postimplantation testing through contacts 1 and 2 in a bipolar configuration of the left frontal depth electrode. A peripheral intravenous injection of a 5-mL bolus of technetium-99m ethyl cysteinate dimer ($^{99m}$Tc-ECD) was...
completed during delivery of 20 bursts of high-frequency stimuli (200 Hz) at approximately 2-second intervals (0.5 Hz) for acquisition of an activated SPECT data set. To produce the SAS image, this data set was normalized and subtracted from a baseline SPECT data set obtained 12 hours after the stimulation session. The SAS and the T1 MRI data sets were coregistered using the ITK coregistration algorithm in Analyze version 10 (AnalyzeDirect, Inc).

Results and Validation

The activation function model was used to predict the extent to which direct stimulation therapy can propagate during electrical stimulation for the proposed depth electrode position as follows. The solution for $V_E$ was obtained by applying direct current at 4.3 mA between contacts 3 and 4 of the right temporal electrode and between contacts 1 and 2 of the left frontal electrode. This was achieved through construction of a 3D mesh and application of the FEM. The computation in a cross-sectional 2-dimensional (2D) slice can be observed in Figure 3A, where the maximum value observed for $V_E$ was 7.5 V. In addition, this extracellular potential produced a related $E_{→}$ field (Figure 3A). The magnitude of the $E_{→}$ field was >1000 mV/mm in areas within 3-4 mm from the center of the electrodes, as expected.

Following this computation, the DTI was used to create a directionality vector field, $\hat{n}$ (Figure 3B). Then, the values of both $V_E$ and $\hat{n}$ were used to compute the activation function. Two cross-sectional 2D sagittal slices of the value of the activation function are presented in Figure 3C and Figure 3D, with areas of depolarization and hyperpolarization identified according to the positivity or negativity of the activation function. Two threshold values were applied to identify the boundaries of the regions of depolarization and hyperpolarization. This generated nonspherical 3D ROIs, with a volume that varied from 40 mm$^3$ to 84 mm$^3$, surrounding the active electrode contacts (Figure 4A and 4B). These ROIs were exported to TrackVis as seeds, wherein the influenced tracts were identified.
by filtering those that entered the polarization region. In these tracts, shown in Figure 4C, the ROIs from the left frontal electrode (red and blue) influenced the genu, left forceps minor, and anterior body of the corpus callosum. Importantly, some of the influenced fibers reached the contralateral hemisphere through the splenium of the corpus callosum. Specifically, some of the fibers that crossed the corpus callosum ended at the contralateral temporal lobe. The ROIs from the right temporal lobe (orange and light blue) influenced the ipsilateral uncinate fasciculus, the inferior longitudinal fasciculus (reaching the right occipital lobe), and the fornix tracts.

Stereotactic implantation of two RNS depth leads was guided by our preimplant electrode lead plan. A 4-contact, 1-cm center-to-center depth lead was placed in the right paramesial temporal region using a posterior-to-frontal longitudinal approach in paramesial white matter (Figure 4D). A 4-contact, 2.5-mm center-to-center depth lead was placed using a lateral-to-medial approach in the left frontal lobe targeting the white matter (Figure 4E). The trajectories were guided by our preimplantation model and were facilitated by a Stealth (Medtronic) MRI navigational system. The final positions of the electrode contacts are shown in Figure 4F.

Proof of the principle is demonstrated electrophysiologically in Figure 4F, in which electrocorticography obtained by the implanted RNS System shows propagation between contralateral epileptic sources interconnected by white matter pathways, as predicted by the tractography model. Propagation from the left frontal source to the right temporal source is illustrated.

A SAS study performed during stimulation of distal contacts 1 and 2 of the depth frontal electrode demonstrated transient hyperperfusion and hypoperfusion changes beyond the immediately surrounding tissue. No afterdischarge was recorded by electrocorticography at the site of stimulation. Therefore, these transient hyper- and hypoperfusion-related changes were due to direct stimulation itself and not produced by epileptiform activity. The results of the SAS study are presented next to the preimplant model of the left frontal depth electrode in Figure 5. The gray matter regions of transient hypoperfusion included the contralateral (right) frontal lobe and the ipsilateral (left) parietal cortex, whereas the gray matter regions of transient hyperperfusion included the contralateral (right) anterior temporal region, the ipsilateral (left) head of caudate near the electrode contacts stimulated during the SAS protocol, the contralateral (right) frontal pole, and the contralateral (right) frontal operculum.

Figure 5. A comparison between the preimplant modulated circuit tractography model of the left frontal depth electrode (A) and postimplant SAS (B and C) is presented. The SAS regions of transient hypoperfusion (B) and hyperperfusion (C) coregistered to MRI are displayed separately. Contacts 1 and 2 of the left frontal depth electrode were stimulated without causing a seizure (afterdischarge). The gray matter regions of transient hypoperfusion included the contralateral (right) frontal lobe (1) and the ipsilateral (left) parietal cortex (2), whereas the gray matter regions of transient hyperperfusion included the contralateral (right) temporal region (3), the ipsilateral (left) head of caudate (4), the contralateral (right) frontal pole (5), and the contralateral (right) frontal operculum (6). Note that the tractography in the preimplant plan terminated near or within the regions concordant with the SAS study.
Because the stimulation in the left frontal lead produced transient hyperperfusion in the contralateral temporal lobe, these data suggest communication between the epileptic sources that was predicted by the modulated circuit tractography model. This communication was evident in the electrocorticography presented in Figure 4F, which was discussed previously.

**Conclusion**

This practical application of the activation function model, which is based on the second directional derivative of the extracellular potential, demonstrates the ability to generate a timely preimplant depth electrode planning map for a patient with a refractory epileptogenic circuit. This simulation predicted the white matter tracts that were influenced by direct neurostimulation therapy. That is, the VOCA and modeled modulated circuit tractography map can be visualized before implantation, thereby enabling their inclusion in the final RNS System lead placement plan. Furthermore, the application of the activation function offers an improvement over previously reported activation regions produced by the magnitudes of the $\vec{E}$ fields. This model offers the potential for steering the VOCA to predict the optimal electrode contact implant sites. It considers not only the magnitude of the $\vec{E}$ field, but also directionality effects in relation to the orientation of the axon bundle.

The electrode placement model, seen as a specialized type of brain–computer interface planning, may improve the probability of modulating the maximal extent of an epileptic network with minimum electrode contacts by targeting white matter, not simply the presumed gray matter focus. Moreover, the demonstration of a mechanistic interplay between cortical and subcortical structures, such as the thalamus, may provide a basis for future clinical trials combining stimulation of both regions. Further development of this strategy will clarify and lead to a better understanding of the individual differences seen when direct cortical stimulation is delivered through white matter pathways to distant epileptogenic neural tissue. The data obtained with this model emphasize the need to recognize localization-related epilepsies as being potentially extensive pathophysiologic neural networks.
References


IMPROVEMENT OF BRAIN FUNCTION BY A LIPID-LOWERING FACTOR

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Introduction

Although brain function decreases with age, in some people the brain functions normally until death. Several risk factors may contribute to decelerated brain function. Among these factors, it has been demonstrated that people with high amounts of abdominal fat in middle age are 3.6 times more likely to develop memory problems later in life than people with less abdominal fat in middle age are. Accordingly, a diet rich in saturated long-chain fatty acids decreases memory and learning in mice. Although the mechanisms by which abnormal fat metabolism interacts with brain function are not yet fully understood, recent research at our institution has shed some light on a lipid-lowering factor that appears to have various effects on the brain.

This factor, peroxisome proliferator-activated receptor α (PPARα), is a nuclear hormone receptor family transcription factor that controls the metabolism of fatty acids in the liver. Although the brain is not a metabolic organ, we have recently demonstrated that PPARα is constitutively expressed in different parts of the hippocampus. PPARα is also constitutively present in neurons and astrocytes. Various functions in the brain are controlled and coordinated at the transcriptional level by CAMP response element-binding protein (CREB). We have found that PPARα controls the transcription of CREB and regulates memory and learning.

The action of PPARα is affected by statins, which are cholesterol-lowering drugs that are widely used throughout the world. Statins have been found to bind to PPARα and protect memory in an animal model of Alzheimer’s disease. One of the pathologic hallmarks of Alzheimer’s disease is the presence of extracellular amyloid plaques (Figure 1) containing amyloid β peptides, which originate from the amyloidogenic proteolytic processing of amyloid precursor protein (APP) through the sequential action of β- and γ-secretases. In contrast, APP can also be cleaved in a nonamyloidogenic pathway by α-secretase, precluding the formation of amyloid β peptides. We have found that activation of PPARα stimulates the transcription of ADAM10 α-secretase and lowers the level of amyloid plaques in an animal model of Alzheimer’s disease.

Normal and pathologic aging are often linked to reduction in autophagic potential. Moreover, reduced autophagy is also a hallmark of different neurodegenerative disorders. Lysosomes are classically considered to be central to autophagy and the mechanisms of cellular waste management. We have seen that PPARα controls the activity of tripeptidyl peptidase 1 (TPP1) via transcriptional control of the Cln2 gene and stimulates lysosomal biogenesis in astrocytes via direct transcriptional
regulation of transcription factor EB (TFEB), the master regulator of lysosomal biogenesis, thereby contributing to autophagy. Therefore, the activation of PPARα can lower the production of amyloid plaques, stimulate lysosomal clearance mechanisms, and protect memory and learning. Moreover, PPARα may play a role in controlling sleep.

PPARα and Lipid Metabolism

Whereas mitochondria catalyze the β-oxidation of most short-, medium-, and long-chain fatty acids derived from diet, peroxisomes are responsible for β-oxidation of very long-chain fatty acids. After chain shortening of very long-chain fatty acids via β-oxidation, these fatty acids are transported to mitochondria for complete metabolism. Although activation of PPARα stimulates the β-oxidation pathway in both mitochondria and peroxisomes (Figure 2A), its effects are more specific in peroxisomal β-oxidation than in mitochondrial β-oxidation. It has been shown that upon activation of PPARα by different ligands (gemfibrozil, fenofibrate, clofibrate, etc), PPARα is recruited to the promoters of genes encoding fatty acid β-oxidation.

**Figure 2.** Diagrams depicting the PPARα signaling pathways leading to fatty acid oxidation in the liver (A) and synaptic plasticity in the hippocampus (B). A, Short-chain fatty acids and omega-3 polyunsaturated fatty acids are known to activate the PPARα:RXRα (retinoic acid X receptor α) heterodimeric complex in hepatocytes, which binds to promoters of genes encoding fatty acid β-oxidation. B, In the hippocampus, the endogenous ligands octadecenamide, hexadecanamide, and 3-hydroxy-(2,2) dimethyl butyrate activate PPARα, which is recruited to the promoter of CREB in hippocampal neurons. CREB turns on the transcription of molecules associated with plasticity.

**PPARα in the Hippocampus**

PPARα is known to be present in metabolically active organs, and the hippocampus does not produce energy from fat metabolism; however, we have demonstrated the presence of PPARα in different subfields of the hippocampus of rodents. Although humans and other primates have been reported to have considerably lower levels of PPARα in the liver than rodents have, PPARα has been found in the hippocampus of theses monkeys.

**Control of Learning and Memory by PPARα**

Whereas metabotropic receptors (eg, NR2A, GluR1) play a crucial role in hippocampal plasticity, voltage-gated ion channel molecules such as Kv1.1 and Scn1a contribute to neuronal excitability and discharge behavior. Interestingly, knockdown of PPARα decreases the expression of various plasticity-associated molecules (NR2A, NR2B, GluR1, and Arc), but not voltage-gated ion channel molecules, in hippocampal neurons, indicating a selective role of PPARα in plasticity (Figure 2B). Consistent with this finding, PPARα-null hippocampal neurons exhibit a weaker calcium influx and a smaller amplitude.
Hippocampal Memory Not Directly Controlled by Hepatic PPARα

PPARα is present in both periphery (eg, the liver) and the brain (Figure 3). To understand which type of PPARα participates in regulation of memory, we dissected peripheral PPARα from CNS PPARα by generating bone marrow chimeric mice. Analyses of bone marrow chimeric mice demonstrated that the hippocampal memory apparatus is not regulated by peripheral PPARα. Interestingly, hippocampal NR2A and spatial memory ability remained intact in animals when peripheral PPARα was ablated, whereas NR2A expression in the hippocampus and the ability to consolidate spatial memory were markedly reduced when PPARα was ablated in the CNS. Therefore, PPARα in the hippocampus has a substantial direct effect on spatial memory, and its absence hinders the learning and memory acquisition process by inhibiting Creb transcription and suppressing various molecules associated with plasticity.

Because PPARα affects the expression of genes involved in lipid metabolism, overweight people may have abnormal lipid metabolism and decreased PPARα in the liver. However, not all overweight people have memory loss. Many overweight people have normal memory probably because they have normal PPARα in the hippocampus. On the other hand, memory loss may be attributable to abnormal hippocampal PPARα, which could be the result of a genetic polymorphism in PPARα or altered expression of the gene because of hormonal imbalances or epigenetic mechanisms.

Identification of Physiologically Available Ligands of PPARα in the Hippocampus: An Avenue for Possible New Drugs

Being a nuclear hormone receptor, PPARα depends on ligands to function. Therefore, ligands must be present in the brain for PPARα to function properly there. Using PPARα ligand-binding domains as bait, we have discovered 3 endogenous PPARα ligands [3-hydroxy-(2,2)-dimethyl butyrate, hexadecanamide, and 9-octadecenamide] in the mouse brain hippocampus (Figure 2B), and we identified specific PPARα ligand-binding domains (Tyr 464 and Tyr 314) involved in binding these ligands. Because these compounds were isolated from the hippocampus, we examined their effect in hippocampal neurons and found that these ligands activated PPARα and upregulated the synaptic function of hippocampal neurons. Identification of drugs that have the potential to improve synaptic plasticity is an important area of research.

Binding of Statins to PPARα

Statins are widely used as cholesterol-lowering drugs throughout the world. For the last 30 years, these drugs have been considered to be competitive inhibitors of HMG-CoA (3-hydroxy-3-methylglutaryl-coenzyme A) reductase. Although it was not known previously whether statins bind to any
receptor protein, we have recently discovered that statins bind to the ligand-binding domain of PPARα and serve as ligands of PPARα. Among simvastatin, mevastatin, pravastatin, atorvastatin, and rosuvastatin, simvastatin was found to be the strongest ligand of PPARα, followed by mevastatin. The ligand-binding efficacies of pravastatin, atorvastatin, and rosuvastatin were similar to each other. Interestingly, statins upregulate neurotrophins in brain cells via PPARα-mediated transcriptional activation of CREB. Neurotrophins are important for neuronal health and function. Simvastatin treatment also increased BDNF (brain-derived neurotrophic factor) in the hippocampus and cortex and improved memory and learning in an animal model of Alzheimer’s disease via PPARα. These findings disclose a new site of action (PPARα) for statins that could offer the potential for therapeutic benefit in patients with Alzheimer’s disease.

**PPARα and Plaque Formation**

Understanding how plaques are formed is important for the development of effective drugs that lower plaques and stop the progression of Alzheimer’s disease. In the brain of patients with Alzheimer’s disease, pieces of beta-amyloid protein clump together to form hard, insoluble plaques. The beta-amyloid protein pieces come from a parent protein called amyloid precursor protein. In a healthy brain, this precursor protein is broken down by another protein, called ADAM10, in such a way as to preclude the formation of beta-amyloid. We have found that neurons from mice lacking PPARα contain less ADAM10 than is found in neurons from normal mice. Our results also indicate that mice lacking PPARα produce more beta-amyloid than normal mice, and in a mouse model of Alzheimer’s disease, the PPARα-deficient mice have more amyloid plaques in their brains and shorter life expectancies than normal mice have. We have seen that a combination of gemfibrozil (a lipid-lowering drug approved by the US Food and Drug Administration) and the vitamin A derivative retinoic acid induces the activation of PPARα, increases ADAM10, and reduces amyloid plaques in the brain in a mouse model of Alzheimer’s disease. Replication of these results in human patients with Alzheimer’s disease would open up a promising avenue of treatment for patients with this devastating neurodegenerative disease.

### Possible Role of PPARα in Sleep

Despite intense investigation, sleep remains a poorly understood process, and the mechanisms by which it is regulated are unclear. Notably, 9-octadecenamide or oleamide, one of the three hippocampal ligands that we recently isolated, is a sleep-inducing supplement. Therefore, it is possible that PPARα plays a role in sleep as well. However, at present, detailed mechanisms are not known. Because 9-octadecenamide and the related compounds 3-hydroxy-(2,2)-dimethyl butyrate and hexadecanamide are constitutively present in the hippocampus as PPARα ligands, an area of future research would be to determine whether these compounds contribute to sleep via PPARα.

### Conclusion

These studies illustrate a far-reaching possibility of improving hippocampal functions and preventing memory loss by restoring and/or maintaining normal PPARα activation in the hippocampus. In this respect, our newly discovered physiological ligands of PPARα from the hippocampus may serve as novel brain-derived drugs for maintaining normal brain functions. At present, our lab is involved in investigating this avenue of research.

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References

Introduction

For nearly 20 years, hospitals caring for acute stroke patients have been organized to deliver intravenous thrombolysis. Although robust level 1a evidence demonstrating a clinical benefit of mechanical thrombectomy in patients with acute anterior circulation large vessel occlusions (LVOs) was published in 2015, over the last 2 years, our stroke team has noticed a large number of patients transferred for thrombectomy who do not end up undergoing the procedure. To minimize time to recanalization, the decision to transfer a patient for thrombectomy is often based on the severity of the clinical examination rather than on brain vascular imaging. As suggested by American Heart Association/American Stroke Association guidelines, a National Institutes of Health Stroke Scale (NIHSS) score >6 is often used as a surrogate marker for the presence of LVO. Turc et al evaluated the ability of 13 clinical scores to predict large artery occlusions in more than 1000 patients and found false-negative and false-positive rates that were higher than expected. Furthermore, patient transfers for potential thrombectomy have considerable costs, which include but are not limited to ambulance/helicopter services, call pay for the neuroendovascular and stroke neurology team, repeat imaging, and the cost of the temporary suspension of the team members’ other activity as they await the patient’s arrival.

Sonig et al evaluated 1311511 National Inpatient Sample stroke admissions from 2008 to 2010 and found that the mean expenditure for transferred patients undergoing intravenous thrombolysis and thrombectomy was $27,000 more than that of those who were not transferred. Thus, despite the potential to incur substantial unnecessary costs, the decision to transfer is currently based on an oblique measure suggesting the presence of LVO.

In this study, we measured the frequency of nontreatment transfers since the publication of the positive thrombectomy trials in 2015 and evaluated the most common reasons why transferred patients did not undergo thrombectomy. The purpose of the study was to find potential predictors of nontreatment transfers based on the limited clinical information available during the initial evaluation at the transferring hospital. Our hope is that identifying these predictors may enable the development of strategies to improve the transfer decision process.
Methods

Stroke Transfer Process

The stroke service is staffed with 5 stroke neurologists who provide 24/7 coverage, 365 days per year, via a dedicated telephone hotline or telestroke system, which uses customized videoconferencing technology. In each consultation, the initial determination is the patient’s eligibility for intravenous thrombolysis. If the stroke neurologist finds clinical suspicion of a potentially disabling stroke due to LVO, arrangements are made for transfer. Considerations for transfer include all of the following criteria: NIHSS score >6; neurologic examination findings suggestive of cortical involvement, such as gaze preference, neglect, or motor deficit with language impairment; time since onset of symptoms <6 h; and initial head computed tomography (CT) with Alberta Stroke Program Early CT Score (ASPECTS) ≥6, or a dense middle cerebral artery or basilar sign suggestive of LVO. Patients with serious medical comorbidities, including severe dementia, terminal illness, or prestroke modified Rankin scale score ≥3, are usually not transferred.

Conventionally, brain vascular imaging has not been recommended at the transferring hospital because the acquisition and interpretation of the images can be unpredictable and potentially time-consuming. If the stroke neurologist deems the patient a candidate for thrombectomy, after discussion with the neurointerventionalist, the stroke code group page is activated, and relevant team members aim to meet at the emergency department bay prior to the patient’s arrival. Every activation of the stroke code group page constituted the denominator for this study. Upon the patient’s arrival, the neurologic examination is repeated by the stroke team. If a potentially disabling deficit persists, brain parenchymal and vascular imaging are immediately obtained to determine if the ASPECTS score is ≥6 and to confirm the presence of LVO before the decision is made to proceed with thrombectomy.

Data Collection

Institutional Review Board approval was not necessary because the data were obtained as a part of a collaborative quality improvement project for our hospital’s Joint Commission stroke center certification program. Records of consecutive patients transferred to our urban, tertiary care academic medical center between January 2015 and December 2016 were reviewed. Every stroke transfer is coordinated through the hospital transfer center, which records demographic data on the patient. Reports of all transfers are then sent to the stroke program data analyst, who then adds additional predetermined clinical information from our hospital’s electronic medical record system (Epic) for the purposes of the hospital’s stroke program certification. An on-call advanced practice nurse practitioner also responds to every stroke alert and records details of the transfer, time stamps for hospital arrival and imaging, and the reason why the patient did not undergo thrombectomy, if applicable. The prospectively recorded data served as the source of data for this study. Independent variables were the date, patient age, method of transportation, initial NIHSS score at the transferring hospital, telestroke video use, whether the transfer call was placed after hours (defined as 7 PM to 7 AM), whether the patient arrived at our hospital within 5 hours since

Figure 2. Angiograms showing large vessel occlusion (A) and restoration of blood flow after thrombectomy (B). C, A large clot retrieved using thrombectomy.
the last known well time, and whether the referring hospital was a Joint Commission–certified primary stroke center. Outcomes included the total number of transfers, the number of nontreatment transfers, and the reasons why those patients were not treated. We used chi-square tests and multivariate logistic regression analysis to compare demographic and clinical variables, including age, NIHSS score, and other variables, between patients with and without thrombectomy. All statistical analyses were performed with SAS 9.3 (SAS Institute). P < .05 was considered statistically significant.

Table 1. Reasons for No Treatment Among Consecutive Patients Transferred for Mechanical Thrombectomy

<table>
<thead>
<tr>
<th>Reason</th>
<th>No. (%) (n = 106)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No large vessel occlusion on imaging</td>
<td>71 (67%)</td>
</tr>
<tr>
<td>Substantial improvement on examination</td>
<td>19 (18%)</td>
</tr>
<tr>
<td>ASPECTS &lt;6</td>
<td>10 (9%)</td>
</tr>
<tr>
<td>Premorbid disability discovered</td>
<td>3 (3%)</td>
</tr>
<tr>
<td>Patient unstable</td>
<td>3 (3%)</td>
</tr>
</tbody>
</table>

Abbreviation: ASPECTS, Alberta Stroke Program Early CT Score.

Table 2. Predictors of No Treatment Among Consecutive Patients Transferred for Mechanical Thrombectomy

<table>
<thead>
<tr>
<th>Variable</th>
<th>All Transferred Patients (n = 194)</th>
<th>Not Treated (n = 106)</th>
<th>Treated (n = 88)</th>
<th>P value&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD), y</td>
<td>67.3 (14.0)</td>
<td>66.8 (13.9)</td>
<td>67.8 (14.2)</td>
<td>.850</td>
</tr>
<tr>
<td>Age &gt;80 y</td>
<td>42 (21.9%)</td>
<td>18 (17.3%)</td>
<td>24 (27.3%)</td>
<td>.100</td>
</tr>
<tr>
<td>Helicopter transfer</td>
<td>67 (34.9%)</td>
<td>46 (44.2%)</td>
<td>21 (23.9%)</td>
<td>.003</td>
</tr>
<tr>
<td>Intravenous thrombolysis given</td>
<td>140 (72.9%)</td>
<td>73 (70.2%)</td>
<td>67 (76.1%)</td>
<td>.360</td>
</tr>
<tr>
<td>NIHSS score&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;10</td>
<td>16 (8.3%)</td>
<td>14 (13.5%)</td>
<td>2 (2.3%)</td>
<td>.010</td>
</tr>
<tr>
<td>10-20</td>
<td>98 (51.0%)</td>
<td>53 (51.0%)</td>
<td>45 (51.1%)</td>
<td>.0005</td>
</tr>
<tr>
<td>&gt;20</td>
<td>78 (40.6%)</td>
<td>37 (35.6%)</td>
<td>41 (46.6%)</td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>18.8 (6.2)</td>
<td>17.5 (6.8)</td>
<td>20.5 (4.8)</td>
<td></td>
</tr>
<tr>
<td>Telestroke video used</td>
<td>94 (49.0%)</td>
<td>53 (51.0%)</td>
<td>41 (46.6%)</td>
<td>.550</td>
</tr>
<tr>
<td>Time of transfer call 7 PM to 7 AM</td>
<td>69 (35.9%)</td>
<td>33 (31.7%)</td>
<td>36 (40.9%)</td>
<td>.190</td>
</tr>
<tr>
<td>Arrival within 5 hours</td>
<td>136 (70.8%)</td>
<td>63 (60.6%)</td>
<td>73 (83.0%)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Referred from primary stroke center</td>
<td>154 (80.2%)</td>
<td>81 (77.9%)</td>
<td>73 (83.0%)</td>
<td>.380</td>
</tr>
</tbody>
</table>

Abbreviation: NIHSS, National Institutes of Health Stroke Scale.
<sup>a</sup> All values are given as number and percentage except as noted.
<sup>b</sup> Statistically significant at P < .05.

Results

Between January 2015 and December 2016, 106 of the 194 patients transferred for potential thrombectomy (55%) did not undergo thrombectomy. Brain vascular imaging upon arrival—usually computed tomography angiography (CTA)—showing no LVO was by far the most common reason for not undergoing thrombectomy (71 of 106 transfers [67%]). A substantially improved neurologic examination and Alberta Stroke Program Early CT Score (ASPECTS) <6 were the next two most common reasons for nontreatment but were far less common than the first reason (Table 1). Approximately one-third of all transfers were by means of air transport, and approximately one-third occurred during the evening hours. Nearly half of the transferred patients were first evaluated with telestroke video. Most patients received intravenous thrombolysis, most arrived within 5 hours, and most came from a Joint Commission–certified primary stroke center.

The strongest predictor of no treatment was the initial NIHSS score; 14 of 16 patients (88%) with NIHSS score <10 did not undergo thrombectomy, whereas 41 of 78 patients (53%) with NIHSS score >20 underwent thrombectomy (P < .001). Helicopter use was significantly associated with no treatment (P = .003). Arrival within 5 hours was significantly associated with treatment (P < .001); see Table 2. The NIHSS score (as a continuous variable), helicopter use, and arrival within 5 hours were all identified as predictors in multivariate logistic regression analysis (Table 3).
Discussion

Our results show that more than half of the patients transferred for potential thrombectomy between January 2015 and December 2016 did not end up undergoing thrombectomy. The most common reason (67%) for a nontreatment transfer was brain vascular imaging after transfer showing absence of LVO. A minority of patients did not undergo thrombectomy because of a substantial improvement on examination or ASPECTS score <6. Because the majority of patients (73%) received intravenous thrombolysis before transfer, improved findings on examination could be explained by vessel recanalization that occurred while the patient was en route. However, intravenous thrombolysis effectively recanalizes LVOs in only a minority of patients, with larger and longer clots shown to be recalcitrant. Hence, it is possible that an even larger proportion of the patients transferred because of suspected LVO based on clinical examination and evaluation scale scores may not have had LVO in the first place.

Prior studies have reported that up to one-third of transferred patients demonstrated so-called ASPECTS decay, or rapid progression of cerebral infarction during transfer. A high NIHSS score on admission was found to be a predictor. A noncontrast head CT scan is a standard part of our evaluation after transfer showing absence of LVO. A minority of patients did not undergo thrombectomy because of a substantial improvement on examination or ASPECTS score <6. Because the majority of patients (73%) received intravenous thrombolysis before transfer, improved findings on examination could be explained by vessel recanalization that occurred while the patient was en route. However, intravenous thrombolysis effectively recanalizes LVOs in only a minority of patients, with larger and longer clots shown to be recalcitrant. Hence, it is possible that an even larger proportion of the patients transferred because of suspected LVO based on clinical examination and evaluation scale scores may not have had LVO in the first place.

The time of day, telestroke use (Figure 3), and origination of the transfer at a primary stroke center did not appear to affect the rate of nontreatment transfers. We identified 3 predictors of whether the patient underwent treatment: helicopter use, patient arrival within 5 hours, and NIHSS severity on admission. Helicopter transportation costs alone can range from $12 000 to $25 000 at our institution, and two-thirds of patients who arrived in this fashion did not undergo thrombectomy. One explanation for this finding that may be unique to our hospital is its urban location and the location of the helipad 2 city blocks away from the hospital. A separate ambulance transfer is necessary to transport the patient to our hospital after landing. This association of no treatment with helicopter use warrants additional investigation, including the possibility of ASPECTS decay as a mechanism.

A NIHSS score <10 at the transferring hospital reliably predicted a nontreatment transfer. Therefore, for patients in this subgroup, it may be particularly worthwhile to take the added effort and time to perform CTA before transfer. Despite the American Heart Association/American Stroke Association recommendation to use NIHSS score >6 as a criterion to select patients for treatment of LVO, our observations over the past 2 years are more consistent with the results of the study by Turc et al showing that modification of the NIHSS cutoff below a threshold of NIHSS score >11 would result in sending almost every stroke patient to a center capable of endovascular treatment. Although in our cohort NIHSS score <10 was predictive, NIHSS score 10-20 (51%) and NIHSS score >20 (36%) had a substantial proportion of patients not undergoing thrombectomy.

The ability to rapidly obtain and interpret brain vascular imaging not only speeds the treatment process for patients with actual LVO, but also, as our data suggest, could reduce the number of nontreatment transfers by reliably detecting the most common reason for not undergoing treatment after transfer.

Table 3. Multivariate Logistic Regression

<table>
<thead>
<tr>
<th>Variable</th>
<th>Odds Ratio (95% CI)</th>
<th>P Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &gt;80 y</td>
<td>1.82 (0.84, 3.92)</td>
<td>.130</td>
</tr>
<tr>
<td>NIHSS scoreb</td>
<td>1.09 (1.03, 1.15)</td>
<td>.004</td>
</tr>
<tr>
<td>Intravenous thrombolysis given</td>
<td>0.79 (0.35, 1.77)</td>
<td>.570</td>
</tr>
<tr>
<td>Helicopter transfer</td>
<td>0.29 (0.14, 0.61)</td>
<td>.001</td>
</tr>
<tr>
<td>Telestroke video used</td>
<td>1.01 (0.53, 1.92)</td>
<td>.970</td>
</tr>
<tr>
<td>Time of transfer call 7 pm to 7 am</td>
<td>1.33 (0.69, 2.59)</td>
<td>.400</td>
</tr>
<tr>
<td>Arrival within 5 hours</td>
<td>4.28 (1.88, 9.71)</td>
<td>.0005</td>
</tr>
<tr>
<td>Referral from primary stroke center</td>
<td>1.29 (0.56, 2.95)</td>
<td>.550</td>
</tr>
</tbody>
</table>

Abbreviation: NIHSS, National Institutes of Health Stroke Scale.

*Statistically significant at P < .05.

As a continuous variable.
One concern related to performing CTA at the transferring hospital is the unpredictability of acquisition and interpretation of the images. Liang et al.\(^1\) investigated the feasibility of outreach efforts to improve the performance of transferring hospitals in rapidly obtaining CTA prior to transfer. After their efforts, among 57 consecutive transfers, the time from stroke onset to groin puncture was similar regardless of whether CTA was done at the transferring hospital or at the hospital capable of endovascular treatment.

Having the expertise available at the transferring hospital to interpret CTA images immediately after acquisition can be a challenge. Particularly for images that can be automatically and immediately uploaded, the use of telesstroke technology may allow for rapid interpretation of CTA images by the receiving hospital before the decision is made to transfer the patient. Anecdotally, to save time, some stroke neurologists at our hospital have asked the physician at the transferring hospital to take HIPAA-compliant mobile phone videos or snapshots of the CTA as the images are being acquired. The ability of stroke neurologists to reliably and accurately interpret CTA images to detect LVO is therefore obviously critical in this time-sensitive process that demands instant availability. A study by Bar et al.\(^1\) validated this practice by finding strong interrater agreement in CTA evaluation for occlusion in 75 acute stroke patients between stroke neurologists and neuroradiologists. Their study provides data to support practices that are likely already in place to improve triage efficiencies.

Another consideration related to evaluation of the necessity of transfer is that the transfer of patients with L VOs to a comprehensive stroke center may have benefits for the patient in addition to thrombectomy. Advanced neurocritical and neurosurgical care may not be available at the transferring hospital, potentially justifying the transfer. However, because 67% of transferred patients in our study were found not to have LVO, our data suggest that these patients may in fact be effectively managed without advanced neurocritical and/or neurosurgical care.

A limitation of our study consists of the variability in clinical examination methods to determine stroke severity. Among the 5 stroke neurologists involved in the transfer decision process over the past 2 years, there was no uniform agreement on which clinical scale to use or what cutoff to use as a screen for LVO. It is possible that the use of standardized criteria would have yielded a lower number of nontreatment transfers. However, approximately half of the transfers did not involve the use of telesstroke technology, and it may be challenging to achieve an accurate, consistent neurologic assessment in consultation with an emergency physician over the telephone, often in the middle of the night. Additional limitations include the limited perspective from a single center’s experience. The sample size is of course limited, but reflects actual experience over 2 years at an urban tertiary care comprehensive stroke center.

**Conclusion**

Stroke centers capable of endovascular treatment should reconsider their usual practice of accepting a substantial rate of overdiagnosis in stroke patients considered potential candidates for thrombolysis prior to transfer. Overdiagnosis in this fashion is costly, and our data suggest that the rate of unnecessary transfer may be effectively minimized by obtaining brain CTA before transfer. These findings justify efforts to develop and potentially mandate workflows at the more than 1000 primary stroke centers in the United States that would enable physicians at these facilities to quickly acquire and interpret brain CTA images to efficiently and accurately diagnose LVO as early as possible. If such efforts can be realized, much like other workflow goals that have been mandated for delivery of intravenous thrombolysis, improved diagnostic accuracy could be obtained while minimizing both elapsed time and the costs associated with unnecessary transfers. Our data suggest that the use of clinical scales, particularly the identification of patients with NIHSS score <10, who are likely to undergo unnecessary transfer for thrombectomy, can help to avoid unnecessary transfers that could be obviated by performing CTA prior to transfer.

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**Competing Interests:** Michael Chen, MD, is a consultant for General Electric, Genentech, Penumbra, Stryker, and Medtronic. None of the other authors have competing interests.

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**Contributorship Statement:** All listed authors (J.Y., D.Z., B.O., J.C., R.D., and M.C.) contributed to the design, data collection, data analysis, and drafting of the manuscript.

**Data Sharing:** The authors agree to share any data on request.
References


Introduction

Infection remains one of the most common complications related to spine surgery (Figure 1). A postoperative infection may result in substantial increased cost to the procedure and can also result in significant worsening of overall patient outcomes. In a large review of 108,419 spine cases published in 2011, investigators found an overall 2.1% infection rate.\(^1\) Factors associated with increased rate of infection were revision surgery (\(P < .001\)), spinal fusion (\(P < .001\)), and the use of spinal implants (\(P < .001\)). Minimally invasive surgery was found to have lower infection rates, with 0.4% for minimally invasive lumbar diskectomies and 2.9% for minimally invasive interbody fusion surgeries.\(^1\)

Recent introduction of the application of vancomycin powder has been suggested to decrease the incidence of spine infections. Chotai et al showed in 2017 that the use of intraoperative vancomycin was associated with significantly lower infection rates (1.6% [20 of 1215 patients] with vancomycin vs 2.5% [40 of 1587 patients] without vancomycin; \(P = .02\)).\(^2\) Other investigators have also found a reduction in surgical site infections (SSIs) with the use of vancomycin powder. Ghobrial et al published a review of the literature and found no evidence of adverse effects of vancomycin use in lumbar spine surgery.\(^3\) They found mean infection rates among the control patients and vancomycin-treated patients of 7.47% and 1.36%, respectively.\(^3\)

At Rush University Medical Center, surgeons have adopted the use of vancomycin powder over the past 2 years. Encouraged by early data that showed decreased infection rates with vancomycin powder, more surgeons included the use of vancomycin powder in their procedures, especially during those that pose a higher risk of postoperative infection. Vancomycin powder was used exclusively in spinal procedures and was not used in cranial procedures. The purpose of the study was to compare the infection rates after cranial procedures and spinal procedures to determine whether the use of vancomycin powder resulted in decreased spine surgery infection rates.
Methods

This retrospective review examined morbidity and mortality data of all patients who underwent neurological surgery at our institution from 2010 to 2016. Data collected included prior infection, organism, and surgery type. Overall numbers and types of procedures performed in each year were obtained from neurosurgery department records. Endovascular procedures were excluded from cranial procedures in the computation of cranial infection rates. In the review of spinal procedures, lumbar microdiscectomies and anterior cervical diskectomies were excluded because they had extremely low infection rates and their overall numbers skewed the data for spinal procedures. The numbers of gram-negative and gram-positive infections were also tallied for each of the years.

Results

Infection rates after both cranial and spinal procedures have decreased over the years. There has been a notable greater decrease in the infection rates for spinal procedures than for cranial procedures over the period of the study. Figure 2 shows the overall infection rates for cranial and spinal procedures in 2011 to 2016. We were not able to calculate infection rates for 2010 because the numbers and types of cases were not available for that year. The infection rates for spinal procedures and cranial procedures have converged. The number of gram-negative infections has remained essentially unchanged from 2010 to 2016 for both cranial and spinal procedures, albeit at low levels. The number of gram-positive infections decreased by a greater amount for the spinal procedures than for the cranial procedures. Figure 3 shows the number of gram-positive bacterial infections from 2010 to 2016 for both cranial and spinal procedures, and Figure 4 shows the number of gram-negative bacterial infections over the same period.

Discussion

Infections are well-known complications of all surgical interventions. The occurrence of SSIs prolongs hospitalization and increases costs. SSIs can also cause disability and worsened overall outcome for patients (Figure 5). Badia et al. found in a meta-analysis of European hospitals that the cost of the treatment of a patient with SSI is almost 3 times as high as that of other patients. Hospital stays were 2.3 times greater in patients who had SSIs, compared with other patients. Half of neurosurgery patients who had SSIs required reoperation. Schweizer et al. found that patients with SSIs in the Veterans
Affairs hospital system incurred costs up to 1.93 times greater than those of other patients. Patients who had SSIs after undergoing neurosurgery had the greatest cost burden, compared with patients who had SSIs after other types of surgery.

Our data show an overall decrease in SSIs at our institution over time but a greater decrease in the number of SSIs attributable to spine surgery, compared with cranial surgery. The decrease in spine surgery SSIs may be attributable to several general trends in spine surgery. Minimally invasive spine surgery has been correlated with a decreased rate of SSIs after spine surgery. Some spinal procedures, such as anterior cervical discectomies or lateral interbody fusion surgeries, may have a decreased incidence of infection; thus a general shift to those procedures may also be responsible for the decreased rate of infection. On the other hand, the increased use of spine instrumentation (Figure 6) would be expected to result in increased infection rates related to spine surgery.

The utilization of intraoperative vancomycin powder in spine surgeries has been shown recently to decrease the rate of SSIs. Surgeons adopted the use of intraoperative vancomycin early, before studies conclusively showed its effectiveness, and subsequent data have shown a substantial decrease in SSIs with the use of vancomycin powder. The infection rates in spinal procedures in this study are consistent with the new infection rates documented in other studies of 1%-2%, which are an improvement over prior studies showing a 3%-5% infection rate. Our data show a substantial decline in gram-positive bacterial infections, while the rate of gram-negative infections has remained relatively constant, which is consistent with the effect we would expect to see with vancomycin powder.

**Conclusions**

Neurosurgical infection rates have decreased over time, both at our institution and in other studies. The dramatic reduction in the rate of SSI after spine surgery at our institution is likely attributable to the use of intraoperative vancomycin powder in spine surgical procedures.

**Disclosures:** Dr Deutsch receives consulting royalties from RTI Surgical Inc.
References


MOVING PICTURES AND MOVING TARGETS IN THE CARE OF PATIENTS WITH MOVEMENT DISORDERS

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Introduction

In the field of movement disorders, many clinical and research advances have been made over the years. These advances include pivotal clinical treatments, such as the use of levodopa, deep brain stimulation, infusion pumps for the management of Parkinson’s disease, and the use of botulinum toxin for the management of dystonia. Other advances include the identification of specific genes linked to Huntington’s disease, Parkinson’s disease, dystonia, spinocerebellar ataxia, and other disorders. However, our quest for a cure for these movement disorders remains unfulfilled, and we are continuing to search for sensitive and specific biomarkers (eg, blood tests, imaging, and other clinical markers) to help clinicians render more accurate diagnoses and provide important prognostic information for patients and families. Thus, a large part of the evaluation of a patient’s movement disorder symptoms continues to be based on the patient’s history and clinical examination, which shows demonstrable, visible signs of involuntary or abnormal movements. Indeed, the keen observation of patients’ symptoms led the physician James Parkinson to write his famous “Essay on the Shaking Palsy” in 1817, exactly 200 years ago.¹ Thus, the recognition of visual cues (or phenomenology) of movement disorders and their documentation by videography play important historical and current roles in the field of movement disorders. In this article, we highlight advances in movement disorder videography, its use in clinical care and education, and video techniques and protocols developed at the Parkinson’s Disease and Movement Disorders Program at Rush University Medical Center (Figure 1).

The ever-growing field of technology has brought not only advances in movement disorder videography, but also novel ways to measure and quantify involuntary or abnormal movements. A wide array of wearable devices, sensors, and monitoring devices is now available, and others are under development. These technologies can offer the clinician a glimpse into the patient’s symptoms outside of the clinic setting.

Figure 1. The Rush Parkinson’s Disease and Movement Disorders Program has a large staff who work together to fulfill the clinical, research, and educational missions of the group.
and on a more continuous and objective basis. In addition, technology has driven changes in our delivery of care services to patients and the education and support that we give them. The Parkinson’s Disease and Movement Disorders Program provides care for several thousand patients with movement disorders each year, with patients coming to Rush University Medical Center from near and far. We continuously strive to offer accessible and efficient services to patients and their families, with programs ranging from comprehensive on-site clinics and in-person support groups to our telemedicine services and virtual education and support groups (Figure 2). Our novel telehealth programs extend our reach well outside of the Rush University Medical Center setting.

**Videography: Pictures Are Worth a Thousand Clinic Notes**

Movement disorder neurology as a subspecialty focuses on patients with many kinds of abnormal movements, including Parkinson’s disease, other parkinsonian syndromes, choreas, tics, tremors, dystonia, and myoclonus. It is an inherently visual subspecialty wherein the type of movement, its distribution, and its effect on activities or rest are the most important elements that lead to accurate diagnosis. Since the 19th century, visual documentation has been the technological anchor of movement disorder patient care and research.²

No words in a clinic chart can convey more useful information than that obtained by direct visualization of the patient. Videography or video recordings help to document the type of movements, their anatomic distributions, their effect on standard activities of daily living, and the response to treatment. Video recordings provide a visual document that the clinician can review and discuss with peers. The most important overall effect of careful video recording is improved patient care.
Additionally, video recordings can be used as teaching tools to help educate health professionals to properly rate the severity of a given disorder. Unique or informative videos may be published in academic journals or textbooks. Historical videos can help researchers understand disorders that are rare or have become obsolete (such as kuru). Video-recorded case presentations of patients serve as a core of educational presentations at movement disorder teaching conferences and are invaluable for learning the common and rare manifestations of each disorder.

Despite the importance of video recording to the field of movement disorders, no standardized protocols for the video recording of movement disorder patients have been developed. Because patient video recordings enable progress in the study of movement disorders, allowing for better global efforts to diagnose, treat, and research both rare and common conditions, standardization of the approach to video recording should be an essential part of improving this effort. Internal consistency is important when health care providers film a patient at multiple times because inconsistencies in video recording can make it difficult to compare the same examination longitudinally or to compare the outcomes of different treatments. Although many considerations affect the movements that patients should perform on video, certain common features should be observed in every video (Table 1).

Each type of movement disorder requires a different approach in order to capture the key elements of the disorder. Different scenarios and different patients can also necessitate variation in video-recording techniques. Although the challenges of video recording are several, the Rush University Medical Center movement disorders group has mastered these techniques over many years of experience in evaluating patients with movement disorders and with the practice of regularly filming patients as part of their office visits. The physicians in our practice have often been asked by local, national, and international colleagues to share our filming strategies. For this reason, the book Video Protocols and Techniques for Movement Disorders, by Brandon R. Barton, MD, MS, and Deborah A. Hall, MD, PhD, shares our experience in movement disorder videography. The publication covers technical issues of filming (space, lighting, and equipment), rating scales, and medical decisions regarding exactly what to film and how to capture the essential features of a given patient’s disorder (Figure 3). For each disorder, the publication gives a suggestion on where to focus the camera, followed by specific tasks that can be done when focusing on that body area. It offers examples chosen from our practice that represent the real-world, practical application of video recording in practice. The reader can learn a great deal by observing how experienced videographers efficiently and politely carry out the protocols.

Ultimately, videotaping allows physicians to improve their ability to observe, a critical skill, as Jean-Martin Charcot noted in 1888: “Let someone say of a doctor that he really knows his physiology or anatomy, that he is dynamic—these are not real compliments; but if you say that he is an observer, a man who knows how to see, this perhaps the greatest compliment one can make.”

**Telemedicine: The Future of Patient Interactions**

Telemedicine—the delivery of health care using internet-based communication—has been discussed for years, and now technological advances and lower internet costs have made this service a reality. Many patients have been willing to travel long distances to be treated by health care providers including specialists, such as in our clinic. However, visits to the clinic may carry a substantial burden for patients and their families. Such factors include travel time, expenses (eg, gas, time off from work), and the inconvenience of having to leave home to receive care. Telemedicine offers the potential to reduce these burdens by allowing patients to receive care from the comfort of their own homes. In addition, telemedicine can be used to facilitate communication between patients and their providers, allowing for more frequent and convenient interactions. This can be especially beneficial for patients with movement disorders, who may require frequent follow-up appointments and may live far from their treatment centers.

**Figure 3.** The Rush Parkinson’s Disease and Movement Disorders Program has a dedicated video room to create patient-specific video recordings. For every patient, the video recording serves as a visual document to accompany the written chart. The videos can be used for clinical, research, or educational purposes (with appropriate consent).
work, parking), and fatigue of making a long journey, especially for patients with impaired mobility and advanced disease. The availability of telemedicine has had an immediate effect on this burden because telemedicine appointments avoid the need for the patient to travel outside of the home.

Movement disorders are particularly well-suited for telemedicine because the diagnosis and monitoring of the progression of disorders such as Parkinson’s disease is based almost entirely on visual observation. Nearly 10 years ago, Rush University Medical Center’s Christopher G. Goetz, MD, and colleagues helped establish and test the visual criteria used to assess Parkinson’s disease in the home setting. Furthermore, the features of Parkinson’s disease and treatment decisions are largely based on visual information about the patient’s function. As discussed above, physicians at Rush have been using videography for decades to track progression of the disease. Therefore, features such as worsening of tremor, changes in gait, or bradykinesia can be accurately assessed via telemedicine from a patient’s home in real time.

In the past year, the movement disorders program at Rush has successfully piloted a telemedicine program that allows clinicians to deliver expert care to patients while they are in the comfort of their own home (Figure 4). More than 20 patients have enrolled in the pilot project, and both patients and physicians have expressed a high degree of satisfaction. Rather than signing in at the front desk of the clinic, patients sign in to MyChart, a patient portal that provides a secure video feed using a standard webcam. After that, the flow of the appointment mirrors that of the typical appointment. Because insurance companies are not currently covering telemedicine visits, enrollment in this pilot program has been offered free of charge for patients. Patient feedback has been very positive (Figure 5). Though some health care organizations have not yet developed telehealth capabilities, Rush is preparing proactively for the widespread implementation of telemedicine because this technology is readily available and offers a substantial opportunity to deliver expert health care remotely to an expanded patient population. Illinois is expected to join approximately half of the states that currently require private insurers to cover telehealth services the same as in-person services.10,11 When this technology is formally approved for private insurance payment, the movement disorders program at Rush will be ready.

Additionally, Rush is paving the way for the study and use of telemedicine in other movement disorders besides Parkinson’s disease. Avram Fraint, MD, a movement disorders fellow at Rush, received a grant from the Dystonia Medical Research...
Foundation to study the utility of telemedicine in patients with cervical dystonia under the mentorship of Cynthia L. Comella, MD, and Gian D. Pal, MD, MS. This study will determine the feasibility of using telemedicine to evaluate patients with cervical dystonia, the reliability of a cervical dystonia rating scale in telemedicine visits, and patient and clinician satisfaction with telemedicine compared with standard clinical visits. Such studies will be important in establishing telemedicine as an acceptable alternative to standard clinical care.

### Education and Support: Targeting a Wider Audience

Technology-based tools have tremendous potential not only for clinical care, but also for education and research. From an education standpoint, technology-based solutions can support the education and training of health care professionals, patients, and caregivers. To this end, with a grant from the National Parkinson Foundation, Jennifer G. Goldman, MD, MS, is using technology as a platform to deliver education and support group programs virtually to patients with Parkinson's disease and their caregivers. The program also compares the standard model of live, in-person education and support group sessions to those sessions held online. This program specifically focuses on the neuropsychiatric features of Parkinson's disease, an area in which there is a great unmet need for education and support for Parkinson's disease patients and caregivers. Cognitive, behavioral, and emotional features, despite their frequency in patients with Parkinson's disease, are underreported by patients and caregivers and underrecognized by health care providers. Through this novel program, patients and caregivers have access to educational talks by Parkinson's disease experts followed by online, virtual support groups and discussions with our nurse, neuropsychologist, and social worker. These sessions offer patients and caregivers a way to interact with our experts and other attendees in a format that can be conveniently accessed online from one's home. With this type of technology-based program, we will be able to provide education, support, and resources to a broad community of people with Parkinson's disease and reach well beyond the walls of our hospital.

### Conclusion

Technology holds great promise for the future of patients with movement disorders by providing improved diagnostics and therapeutics as well as enhanced access to care and support. Videography contributes greatly to our patient care and educational efforts, merging the legacy of our field and the importance of acute observational skills with innovative tools that improve accessibility and communication. Telehealth delivery systems will enhance our ability to provide clinical care, research, and educational opportunities to patients who do not have access to a specialist, patients who live far away, and patients who cannot travel to the office setting. In keeping with our center's three-part mission of excellence in patient care, research, and education, the movement disorders program at Rush University Medical Center is paving the way for crucial improvements in how patients experience health care, research, and education in the near future and beyond.

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**Figure 5.** Patient satisfaction with the telemedicine program is high, as is shown in this bar graph depicting results of a patient satisfaction questionnaire, adapted from a study of telemedicine outcomes by Ryan Hansen, MD, and Christopher G. Goetz, MD. Responses are on a Likert scale, with 1 indicating “highly disagree” and 10 indicating “highly agree.” The top bar represents the median of the medians on all satisfaction subdomain items of the questionnaire. The remaining bars show the medians of other selected subdomain items. Response ranges are given in parentheses.
References


*This is a partial list of published works of the neurosciences faculty at Rush University Medical Center (indicated in bold). The departments gratefully acknowledge the coauthorship of students, nurses, practitioners, therapists, residents, fellows, and other colleagues at Rush.


Bartolotti N, Bennett DA, Lazarov O. Reduced pCREB in Alzheimer’s disease prefrontal cortex is reflected in peripheral blood mononuclear cells. Mol Psychiatry. 2016;21(9):1158-1166.


Bermeo-Ovalle A. Do we know what we think we know? reconciling subjective complaints and objective cognitive testing in older adults with epilepsy. Epilepsy Curr. 2016;16(4):230-231.


Kovacheva VP, Aglio LS, Boland TA, Mendu ML, Gibbons


Select Research Grants (2016)

Department of Neurological Sciences

Antoaneta Balabanov, MD
• Outcomes and Management of Dietary Treatments of Epilepsy
• Impact of a Low-Carbohydrate, High-Fat Diet on Epileptic Seizures, Gut Milieu, and Metabolic Health
• Epilepsy After the Implantation of a Vagal Nerve Stimulator (VNS)

Brandon Barton, MD
• Impulse Control Disorders in Parkinson’s Disease: Prevalence and Clinical Features in the Rush University Medical Center Movement Disorders Clinic

Adriana Bermeo-Ovalle, MD
• Use of EEG in Patients With Intracerebral Hemorrhage

Bryan Bernard, PhD
• Correlation of MDS-UPDRS Nonmotor Symptoms With Cognitive Functioning in Parkinson’s Disease

Torrey Boland Birch, MD
• Predictors of Outcome in HSV Encephalitis

Cynthia Comella, MD
• Dystonia Coalition Project 1: Natural History and Biospecimen Repository for Dystonia
• Study of Tozadenant as Adjunct Therapy in Levodopa-Treated Patients With PD Experiencing End of Dose “Wearing-Off”
• RTT150 for Injection in Isolated Cervical Dystonia
• ParkinStim: Transcranial Direct Current Stimulation for PD
• Study of Perampanel (E2007) in Subjects With Cervical Dystonia (SAFE-Per CD)
• Diagnostic and Rating Tools for Blepharospasm
• RE-024 for the Treatment of Pantothenate Kinase-Associated Neurodegeneration
• Neuroimaging Biomarkers in Parkinsonism: Differentiating Subtypes and Tracking Disease Progression

James Conners, MD
• Platelet-Oriented Inhibition in New TIA and Minor Ischemic Stroke (POINT) Trial
• ARAMIS: Addressing Real World Anticoagulant Management Issues in Stroke

Rima Dafer, MD
• Study to Assess the Safety, Pharmacokinetics, and Pharmacodynamics of DS-1040b in Subjects With Acute Ischemic Stroke

Rajeev Garg, MD
• Prospective Neurosciences Intensive Care Unit Outcomes Research Database
• Assessment of Cerebral Blood Flow by Quantitative Perfusion MRI in Patients With Spontaneous Intracerebral Hemorrhage and Its Effect on DWI Abnormalities
• Retrospective Acute Spontaneous Intracerebral Hemorrhage Data Abstraction
• The Effect of Diffusion Weighted Imaging (DWI) Lesion on Global Cognitive Outcomes in Patients With Primary Spontaneous Intracerebral Hemorrhage

Christopher Goetz, MD
• Topiramate as an Adjunct to Amantadine in the Treatment of Dyskinesia in Parkinson’s Disease
• Study of Urate-Elevating Inosine Treatment to Slow Clinical Decline in Early Parkinson’s Disease
• Validation of the Movement Disorders Society PD Diagnostic Criteria
• APL-130277 in Levodopa Responsive Patients With Parkinson’s Disease Complicated by Motor Fluctuations (“OFF” Episodes)
• Comparing the Efficacy and Safety of Gastric Retentive, Controlled Release Accordion Pill Carbidopa/Levodopa (AP-CD/LD) to Immediate Release CD/LD in Fluctuating PD Patients
• Evaluating the Long-Term Effects of AP-CD/LD in Fluctuating Parkinson’s Disease Subjects Who Completed Study IN 11 004

Jennifer Goldman, MD, MS
• Fox Investigation for New Discovery for Biomarkers (Biofind)
• Clinical and Neuroimaging Predictors of Cognitive Decline in Parkinson’s Disease
• Study of 5-HT6/5-HT2A in the SYNAPSE Parkinson’s Disease Dementia Trial
• Evaluation of the Parkinson’s Disease Psychosis Virtual Reality Simulator Experience
• Study of RVT-101 in Subjects With Dementia With Lewy Bodies (DLB)
• Dementia With Lewy Bodies Consortium
• Mild Cognitive Impairment and Endurance Exercise in Parkinson’s Disease
• Genetic Risk Factors for Cognitive Impairment and Endurance Exercise in Parkinson’s Disease
• Validation of the Movement Disorders Society Criteria for Mild Cognitive Impairment in Parkinson’s Disease
• Parkinson’s Disease, Alpha-Synuclein and Cognitive Decline
• Apathy as a Predictor of Executive Function in Parkinson’s Disease Patients
• Psychosis in Parkinson’s Disease Symptom Identification Tool
• Serotonin Gene Polymorphisms (5-HT6 and 5-HT2A) and Parkinson’s Disease Cognitive Impairment
• Gender Differences in Motor and Non-Motor Features and Dopamine Transporter Imaging in Parkinson’s Disease
• Developing T Cell-Based Biomarkers for Autoimmunity in Parkinson’s Disease
• Improving the Detection of Early Parkinson’s Disease
• Cultural Differences in Japanese and American Populations in the Movement Disorder Society-Sponsored Revision of the Unified Parkinson’s Disease Rating Scale
Deborah A. Hall, MD, PhD
- The Role of Antisense FMR1 in the Development of Fragile X-Associated Tremor/Ataxia Syndrome
- Next Generation Sequencing in Parkinson Disease and Aging
- Citicoline for Neurological Signs in Fragile X-Associated Tremor/Ataxia Syndrome (FXTAS)
- Human Blood to Brain Dopamine Neuron Project
- CVT 301 (Levodopa Inhalation Powder) in Parkinson’s Disease Patients With Motor Response Fluctuations (OFF Phenomena)
- Clinical Phenotype of Parkinson’s Disease in African Americans
- Assessment of ABBV-8E12 in Progressive Supranuclear Palsy
- Evaluation of SAGE-217 in the Treatment of Subjects With Essential Tremor (ET)
- Next Generation Sequencing in Parkinson’s Disease and Aging
- Study of ABBV-8E12 in Progressive Supranuclear Palsy
- Genetic Determinants for Age of Parkinson Disease Onset

Michael Ko, MD
- Study of Montelukast on Gastrointestinal Tolerability in Patients With Relapsing Forms of Multiple Sclerosis Receiving Tecfidera (Dimethyl Fumarate) Delayed-Release Capsules
- Intravenous Infusion Study of rHlgM22 in Patients With Multiple Sclerosis Immediately Following a Relapse
- Study of Tysabri in Early RRMS in Anti-JCV Antibody Negative Patients

Aikaterini Kompoliti, MD
- Multidisciplinary Inpatient Rehabilitation for Functional Movement Disorders
- Study of Isradipine as a Disease Modifying Agent in Patients With Early Parkinson’s Disease (STEADY-PD III)
- Study of SD-809 (Dextefetamine) for the Treatment of Moderate to Severe Tardive Dyskinesia
- Clinical Study of Patients With Symptomatic Neurogenic Orthostatic Hypotension to Assess Sustained Effects of Dr Roxidopa Therapy
- Study of NBI-98854 for the Treatment of Subjects With Tourette Syndrome

Igor Koralnik, MD
- Virus Detection in Patients With Neurological Disorders and Infections
- Epidemiological Studies in Patients With Neurologic Disorders
- Role of Inflammation in Progressive Multifocal Leukoencephalopathy
- Cohort of HIV-Associated Seizures and Epilepsy in Zambia (CHASE): Scale Up and Expansion Informed by R21 Findings
- Cellular Auto-Immune Mechanisms of Narcolepsy
- JC Virus infection of Choroid Plexi and Meninges of Patients With Progressive Multifocal Leukoencephalopathy, JC Virus Granule Cell Neuronopathy, and JC Virus Encephalopathy, and Control Subjects
- Pathogenesis of a JC Virus Variant in Pyramidal Neurons

Jeffrey Kordower, PhD
- Developing a Human ES Cell-Derived Dopamine Neuron Source for Cell Therapy in Parkinson’s Disease
- Implantable Photo-Stimulation System for the Treatment of Parkinson’s Disease
- Evaluation of Alpha-Synuclein Immunohistochemical Methods for the Detection of Lewy-Type Synucleinopathy in Gastrointestinal Biopsies
- Transplantation of Cryopreserved iPSC-Derived Dopamine Neurons for Parkinson’s Disease
- Nortriptyline-Mediated Attenuation of Alpha-Synuclein Pathology in Parkinson’s Disease
- RNAi Therapy for Spinocerebellar Ataxia Type 1
- Human iPSC-Based Personalized Cell Therapy of PD

George Lopez, MD
- Survey on the Use of Hypothermia for Cardiac Arrest Survivors and Updates After Recent Published Trial Results
- INTREPID: Impact of Fever Prevention in Brain Injured Patients
- ESCAPE: Intravenous NA-1 in Subjects With Acute Ischemic Stroke Undergoing Endovascular Thrombectomy
- ACDC: Assessment of Complications Following Decompressive Craniectomy
- Minimally Invasive Surgery Plus Rt-Pa in the Treatment of Intracerebral Hemorrhage
- iDEF Trial: Futility Study of Deferoxamine Mesylate in Intracerebral Hemorrhage
- Comparing EG-1962 to Standard of Care Oral Nimodipine in Adults With Aneurysmal Subarachnoid Hemorrhage
- ASTROH: Aneurysmal Subarachnoid Hemorrhage Trial Randomizing Heparin

Rabia Malik, MD
- Validation of the CAP-PRI (Chronic Acquired Polyneuropathy-Patient Reported Index)

Daniel Nicholson, PhD
- Computational Neurobiology of Hippocampal Dendrites

Rebecca O’Dwyer, MD
- Study of Brivaracetam Administered Intravenously as Treatment for Increased Seizure Activity in an Epilepsy Monitoring Unit Setting
- A Comparison of Epilepsy Surgery Outcomes in Younger and Older Patients
- Characterization of Epilepsy Patients Through the Use of Enhanced Neuroimaging Analysis
- Investigation of Depression and Anxiety in Older Adults With Epilepsy

Nicholas Osteraas, MD
- Predictors of Follow-Up Post-Stroke

Kalipada Pahan, PhD
- Characterizing Novel Hippocampal Drugs for Alzheimer’s Disease
- Identifying Novel PPAR Ligands From Cerebellum
- Dose Reporting Study of Gemfibrozil and Vitamin A Following Oral Administration to Cin2 (+/-) Mice
- PPAR-alpha in APP Metabolism
Gian Pal, MD
- Analysis and Follow-Up on CORE-PD Study
- Technology-Based Tools to Assess Gait After Deep Brain Stimulation in Parkinson's Disease
- Interest in Genetic Testing in Parkinson's Disease Patients Receiving Deep Brain Stimulation
- Quantitative Motion Analysis to Characterize the Motor Phenotype of GBA Mutation Carriers With PD
- Comparison of Striatal Dopamine Levels in DBS and Non-DBS Subjects With Parkinson's Disease
- Parkinson's Disease and DBS: Cognitive Effects in GBA Mutation Carriers
- Determining the Microbiota Composition of the Middle Meatus in Early Parkinson's

Clement Pillainayagam, MD
- DCVax-L, Autologous Dendritic Cells Pulsed With Tumor Lysate Antigen for the Treatment of Glioblastoma Multiforme (GBM)
- A071101: Heat Shock Protein-Peptide Complex-96 (HSPPC-96) Vaccine Given With Bevacizumab vs Bevacizumab Alone in the Treatment of Surgically Resectable Recurrent Glioblastoma Multiforme (GBM)
- Veliparib or Placebo in Combination With Adjuvant Temozolomide in Newly Diagnosed Glioblastoma With MGMT Promoter Hypermethylation

Sebastian Pollandt, MD
- Study of SAGE-547 Injection in the Treatment of Subjects With Super-Refractory Status Epilepticus
- Outcomes in Subdural Hematoma: Experience From a Tertiary Referral Center

Lubov Roman'tseva, MD
- Perampanel as Adjunctive Treatment in Subjects at Least 2 Years of Age With Inadequately Controlled Seizures Associated With Lennox-Gastaut Syndrome

Marvin Rossi, MD, PhD
- Developing an “Activation Function-Dependent” Intra-Operative Depth Lead Guidance System for Direct Neuromodulation Therapy in Patients With Refractory Focal-Onset Epilepsy: A BodyTom CT and O-Arm Comparison
- Interfacing a Mobile Health Delivery Model for Rural Patients With Refractory Epilepsy
- Interfacing a Mobile Health Delivery Model for Pediatric Patients With Refractory Epilepsy
- RNS System Post-Approval Study in Epilepsy

Sarah Song, MD
- The Cardiovascular Health in Asian Elderly Study
- PRISMS Study – Alteplase in Patients With Mild Stroke: Rapidly Improving Symptoms and Minor Neurological Deficits

Glenn Stebbins, PhD
- A New Rating Scale for Focal Task-Specific Dystonia of the Musician's Hand
- Furst 2.0 Rating Scale

Dusan Stefoski, MD
- Ofatumumab vs Teriflunomide in Patients With Relapsing Multiple Sclerosis
- Siponimod (BAF312) in Patients With Secondary Progressive Multiple Sclerosis

Travis Stoub, PhD
- Prediction of Surgical Outcomes After Epilepsy Surgery Using MEG EEG Source Localization
- Brain Network Activation Analysis in Epilepsy
- Complementary Nature of MEG, EEG and SISCOM in Epilepsy
- Markers for Depression and Anxiety in Epilepsy

Leonard Verhagen Metman, MD, PhD
- Analysis of Stereotactic Accuracy of Deep Brain Stimulation Electrode Implantation Using Leksell Frame and Nexframe
- Effect of Unilateral and Bilateral STN Stimulation on Eye-Hand Coordination
- Product Surveillance Registry Base Protocol
- Study of Apomorphine Administered by Continuous Subcutaneous Infusion in Advanced Parkinson's Disease Patients With Unsatisfactory Control on Available Therapy
- PF-06649751 in Subjects With Motor Fluctuations Due to Parkinson's Disease
- Study of Droxidopa in the Treatment of Parkinson's Disease
- PF-06649751 in Subjects With Early-Stage Parkinson's Disease
- Post Market Clinical Follow-Up Evaluating the Infinity Deep Brain Stimulation Implantable Pulse Generator System (PROGRESS Study)
Department of Neurological Surgery

Richard Byrne, MD
- A Retrospective Review on Cortical Stimulation Mapping Techniques in Brain Tumor Patients
- A Retrospective Review of Meningioma Surgery Clinical Outcomes
- Evaluation of Cognitive Function From Subdural Electrodes in Patients Considered as Surgical Candidates for Intractable Epilepsy
- Predictors of Surgical Corridors to the Suprasellar Space
- Temporal Lobectomy, Memory, Sleep, and Dreams

Michael Chen, MD
- DAWN Trial: Diffusion Weighted Imaging (DWI) or Computerized Tomography Perfusion (CTP) Assessment With Clinical Mismatch in the Triage of Wake Up and Late Presenting Strokes Undergoing Neurointervention (DAWN)
- Estrogen Therapy as Prevention in the Progression of Aneurysm (EPPA) Trial
- Post-Aneurysm SAH Memory Loss

R. Webster Crowley, MD
- ARTISSE: Aneurysm Treatment Using Intrasaccular Flow Diversion With the Artisse Device

Harel Deutsch, MD
- A Concurrently Controlled Study of the LimiFlex Paraspinous Tension Band in the Treatment of Lumbar Degenerative Spondylolisthesis With Spinal Stenosis
- Activ-L Lumbar Artificial Disc Trial
- LIFT: Lumbar Interbody Fusion Trial
- Safety and Efficacy of Staphylococcus Aureus Vaccine in Adults Undergoing Elective Posterior Instrumented Lumbar Spinal Fusion Procedures

Richard Fessler, MD, PhD
- A Multi-Center, Randomized, Controlled Study to Evaluate the Safety and Effectiveness of AlloStem vs Non-Cellular Allograft Bone in Single and 2-Level Anterior Cervical Discectomy and Fusion
- Asterias Stem Cell Treatment for SCI: Long Term Follow-Up
- Expectations and Outcomes: MIS vs Open
- Minimally Invasive Surgery for the Treatment of Adult Spinal Deformity: A Multicenter Retrospective Study
- Prospective, Multi-Center Minimally Invasive Adult Spinal Deformity Outcomes Database Registry
- Radiographic Findings After Anterior Cervical Discectomy and Fusion With Translational and Rigid Plating System

Demetrios Lopes, MD
- ANSWER: Adjunctive Neurovascular Support for Wide-Neck Aneurysm Embolization and Reconstruction
- ATLAS: Safety and Effectiveness of the Treatment of Wide-Neck, Saccular Intracranial Aneurysms With the Neuroform Atlas Stent System
- BARREL: Study of the Reverse Medical Barrel® Vascular Reconstruction Device (VRD) for Adjunctive Treatment to Embolic Coils for Wide-Neck, Intracranial, Bifurcating/Branching Aneurysms of Middle Cerebral and Basilar Arteries
- PREMIER Trial: Prospective Study on Embolization of Intracranial Aneurysms With Pipeline Embolization Device
- SCENT Trial: The Surpass IntraCranial Aneurysm Embolization System Pivotal Trial to Treat Large or Giant Wide-Neck Aneurysms
- WEB-IT: The WEB Intrasaccular Therapy Study

John O’Toole, MD, MS
- MITRON: Metastatic Tumor Research and Outcome Network

Sepehr Sani, MD
- Accuracy of Intraoperative CT in Deep Brain Stimulation and Responsive Neurostimulation Surgeries
- High Order Spectral Analysis of Local Field Potential Data in Parkinson’s Disease
- INTREPID: Implantable Neurostimulator for the Treatment of Parkinson’s Disease
- Reclain DBS for Obsessive Compulsive Disorder (OCD) Therapy
- The Effect of Vancomycin Powder on Surgical Site Infections in Deep Brain Stimulation Surgery
- TrueBeam for the Treatment of Trigeminal Neuralgia

Vincent Traynelis, MD
- Assessment of Peri-Operative Morbidity and Mortality Following Anterior-Posterior Cervical Spine Decompression and Fusion
- Critical Analysis of Extubation Parameters for Patients Undergoing Combined Anterior-Posterior Cervical Spine Surgery
- Critical Analysis of Tracheoesophageal Bundle Retraction Force Pre- and Post-Section of the Omohyoid Muscle During Anterior Cervical Spine Surgery
- Cervical Radiographic Parameters in 1 and 2 Level Anterior Cervical Discectomy and Fusion
- Hyperlordotic Cornerstone Graft Study
Volume and Quality Data

Neurological surgery volume of major cases by area, fiscal year 2016

**Total:** 2165 Surgeries

- Brain tumor: 364 (16.81%)
- Other: 112 (5.17%)
- Functional: 226 (10.44%)
- Cerebrospinal fluid: 206 (9.52%)
- Spine and nerves: 1009 (46.60%)
- Other: 112 (5.17%)
- Open cerebrovascular: 111 (5.13%)
- Trauma: 82 (3.79%)
- Epilepsy and movement disorders: 55 (2.54%)

Rush had the highest volume of neurosurgical discharges in the Chicago region for fiscal years 2011-2016.
Mortality, neurology and neurological surgery

Neurological surgery mortality (observed/expected), fiscal years 2011-2016

Neurology mortality (observed/expected), fiscal years 2011-2016

Quality indicators, stroke

Median times to endovascular recanalization treatment at Rush

Percentage of eligible patients who received IV tPA, fiscal year 2016

Stroke inpatient mortality, fiscal year 2016

Stroke case volumes, fiscal year 2016

Ischemic stroke 571 55.28%
Transient ischemic attack (<24 hours) 73 7.06%
Subarachnoid hemorrhage 124 12.00%
Intracerebral hemorrhage 265 25.66%

Source: Vizient clinical database

Sources: Get With the Guidelines and internal data

1Includes all comprehensive stroke centers participating in Get With the Guidelines stroke data registry

2Includes all US hospitals participating in Get With the Guidelines stroke data registry
Game-Changers

The rapid development of new therapies is giving hope to people with multiple sclerosis—and Rush specialists are among those leading the way

As recently as 40 years ago, people diagnosed with multiple sclerosis (MS) were almost entirely at the mercy of the disease: There were no proven medical interventions that could halt or slow the progression, or even improve symptoms. People with the most severe forms faced certain debility, often in the prime of their lives.

That was the landscape of MS when Dusan Stefoski, MD, completed his residency at what was then Rush-Presbyterian-St Luke’s Medical Center and signed on to the Rush Multiple Sclerosis Center. Four decades later, that landscape is unrecognizable—thanks in large part to the pioneering efforts of Stefoski, now the center’s director, and his Rush colleagues, past and present.

One of those colleagues is Michael Ko, MD, who also trained at Rush before joining Stefoski in practice. Ko recently sat down with his mentor to talk about the rapid evolution of MS treatment, and Rush’s vital role in bringing a slew of promising therapies to the market.
Ko: You first started working with MS patients in 1977. How would you describe the state of MS treatment at that time?

Stefoski: It could best be described as underdeveloped. There was only 1 FDA-approved treatment for MS, adrenocorticotropic hormone (ACTH)—which stimulates the adrenal gland cortex to secrete cortisol and aldosterone, among others, in addition to possibly having a direct ameliorating effect on the immune system. ACTH had some efficacy in terms of speeding up the recovery from acute relapses of MS. But it had no proven efficacy over the long run; it didn’t change the course of the disease.

Ko: There wasn’t another option until Betaseron (interferon beta-1b) was approved in 1993. When you started using it, what was the impact of that medicine?

Stefoski: The impact was relatively modest. People were excited because there was finally a new drug for treatment of MS that held a promise of modest benefit over time. But the availability was initially rather limited, so relatively few people received the drug, and even those who received it often did not experience much in the way of benefit.

But 3 years later, the next interferon, Avonex (interferon beta-1a), was approved. Technically speaking, it showed better long-term efficacy than Betaseron, and Avonex actually began to change the way people felt, meaning they improved some over the long run. We were instrumental in collaborative research to develop Avonex.

Ko: You and your colleagues were also involved in the clinical trials for Tysabri (natalizumab). Was that considered a game-changer when it was approved in 2004?

Stefoski: It was a dramatic game-changer, because that treatment really could halt the disease process in a way that we had not seen before. And it could stop further progression in many people—not all of them, but a large majority of people with MS experienced improvements within the first few months of treatment.

Ko: We’ve treated a lot of people with Tysabri at Rush. Do you think that experience—the high volume of patients—has contributed to a better understanding of how it’s used?

Stefoski: Our initial contribution with Tysabri was collaboratively instrumental in demonstrating its efficacy, because we were part of the phase III trial. But since 2012, we have published a series of pioneering reports on the management of one of the major potential complications of treatment with Tysabri: progressive multifocal leukoencephalopathy (PML), a rare infection of the brain caused by the JC virus. The JC virus is not actually related to MS or to Tysabri. Many healthy people harbor the normally rather innocuous JC virus. However, in people with MS who have the JC virus, treatment with Tysabri creates a situation that allows the virus to establish itself in the brain and cause PML, which can be severely incapacitating or even fatal.

We were the first in the world—and you were part of that whole process—to develop a novel protocol for early detection and treatment for MS patients who contracted PML in association with Tysabri. We monitor patients both clinically and with brain MRI at 3-4 month intervals, which enables early detection of PML and allows for better management outcomes. Our groundbreaking approach consists of accelerated elimination of the JC virus by stimulating the person’s own immune system with filgrastim (G-CSF, Neupogen). This reduces the damage and fosters a faster recovery. Furthermore, we were the first to also administer maraviroc (Selzentry), an antiretroviral that modulates immune T-cell recruitment, in PML patients.

As reported, there were no fatalities among the PML patients we treated, which is significant in that PML used to be considered a fatal disease.

Ko: There has been recent interest in high-dose chemotherapy and hematopoietic stem cell transplantation, or bone marrow transplantation, at Rush and other institutions. What has been your experience with this approach?

Stefoski: High-dose chemotherapy is a very powerful treatment for MS. It is considered induction therapy, because it has an immediate effect of completely stopping the disease process, which can last for quite a while. Although this approach was conceived elsewhere some time ago, we were among the first in the world to start using it, and to date we’ve treated more than 30 patients with excellent results.

As for stem cell transplantation in MS, the treatment is very high-dose chemotherapy using a powerful anti-cancer medication such as cyclophosphamide (Cytoxan), though other drugs or combinations of drugs have been used at other institutions. Chemotherapy is effective for MS and other autoimmune diseases because it kills the attacking cells, but unfortunately, it also kills healthy cells. The patient’s immune system is nearly destroyed and has to be reconstituted, which is achieved by giving them back their own saved bone marrow stem cells, either autologous (their own marrow) or allogeneic (donor marrow). So the stem cells do not actually treat MS, they just restore the immune system that has been badly damaged by the chemo.

Ko: Do you consider high-dose chemo a cure?

Stefoski: No. Most of these people do well for an extended period, up to 5 years following the initiation of treatments, but 25-30 percent of patients begin to experience recurrence of MS at that point, albeit often in a milder form. And
because it’s so harsh, it’s generally a once-in-a-lifetime therapy; if additional treatments are needed later, standard therapies are applied.

**Ko:** In March 2017, ocrelizumab (Ocrevus) became the 15th FDA-approved medication for MS, and Rush was the first center in Illinois and one of the first in the country to use it. It’s been receiving a lot of interest in the MS community. What do you expect to see from it?

**Stefoski:** It’s yet another game-changer for people with MS. It’s the first and only disease-modifying therapy for both primary progressive and relapsing forms of MS, and it has the potential to lead to new avenues of treatment for other diseases as well.

One interesting thing about it is that it treats MS in a way that we never considered would work. The approach is called anti B-cell therapy—Ocrevus is a monoclonal antibody that targets the CD20 molecule on the surface of B cells, allowing for their destruction. The traditional concept of the MS disease process is that T cells are the main culprits, but over the past few years the role of B cells has also emerged.

B cells are best known for their involvement in antibody production through plasma cell formation, but they are also involved in other functions of the immune system, including directing the actions of their counterpart T cells. Research has shown that B cells can induce T cells to attack myelin through a process known as antigen presentation; that’s why eliminating B cells can be effective for MS. Ocrevus removes B cells that would have been bound for the nervous system to orchestrate inflammation.

What this means is that B cells are perhaps just as important as or even more important than T cells in MS. That’s a huge paradigm shift. Anti T-cell drugs do work in MS—cladribine is one such drug—but the vital role of B cells has now been established.

One of the most appealing and impressive facts about Ocrevus is that it’s administered to patients only twice a year, intravenously, in our offices. That is a tremendous benefit for patients.

**Ko:** Your research with Floyd Davis, MD, on dalfampridine (originally known as 4-AP) was truly groundbreaking. How did you start pursuing that line of research when there was not a lot of backing?

**Stefoski:** The initial discovery was really a theoretical one. Some of that work was done here at Rush, when it was realized that blocking the potassium channel on nerves damaged by MS could improve nerve signaling.
In MS, normal electrical nerve signaling fails because the stripping of myelin that coats the nerves leads to their short-circuiting, slowing and even completely blocking the signals. That's why people with MS often develop their problems.

Theoretically, in early computer modeling, it was clear that if we could block the potassium channel, it should improve the signaling. But there were no known potassium channel-blocking drugs, or chemicals for that matter. It turns out that researchers at a physiology laboratory at Duke University had discovered, unrelated to MS, that this chemical known then as 4-aminopyridine (4-AP for short) was a potassium channel blocker on nerve fibers. They cataloged it as such, not anticipating any immediate therapeutic usefulness.

Our team at Rush was able to make the connection between our research and the discovery at Duke, and we began studying 4-AP, initially just in nerves and cells. It worked right away, so we quickly shifted into carefully structured human trials in the early 1980s. There was only one other team of researchers doing similar work, at the National Hospital of Neurology and Neurosurgery (aka Queen Square) in London. Their contemporaneous research looked very good in the laboratory, but their clinical results were unsuccessful, and they never pursued it any further. Ours were successful, and we pressed onward with our efforts that ultimately brought dalfampridine to the market as Ampyra.

Most of our research efforts with this project were funded through private philanthropic donations expressly to the Rush MS Center. Without those generous donations, our work would not have been possible because, as you mentioned, there was no backing from other sources.

**Ko:** What has been the impact of Ampyra in the MS world, and at Rush in general?

**Stefoski:** It's the first and only drug in the history of neurology and MS that can help people who have MS walk better and faster, so it falls into the category of function-restoring drugs, not just symptom-relief drugs.

I'm emphasizing that distinction because while its effects are often misconstrued as symptom relief, Ampyra actually restores function. The difference is clear when we analyze the loosening of spastic muscles by the symptom-relief drug baclofen. Baclofen diminishes stiffness, which is beneficial; but it does not actually improve function in the damaged nerves. Ampyra enables patients to walk better and faster, because it restores the nerves' ability to propagate impulses by making the signals longer and stronger.

Ampyra was the first commercially successful drug ever discovered at Rush, a fairly rare occurrence at any academic institution. Because of its international success, Ampyra has brought significant funds to Rush, which are being reinvested into various research projects that could generate important discoveries.

**Ko:** One of the other medications used almost exclusively at Rush for MS is cladribine, a potent chemotherapy drug that's being investigated as an oral medication. What is your experience with it? Could it eventually get approved in the US for MS?

**Stefoski:** I reckon that it will be. We have been the early proponents and prescribers of cladribine for MS, and it has proven efficacious in halting the destructive processes of MS and lowering the risk of disability progression. The original work was done at Scripps in California, but we may have been the second center in the world to start using it. We were part of the oral cladribine phase III trial, which almost led to its approval, but the company that created it, EMD Serono, did not pursue approval at that time. They are now rekindling their efforts to bring it to market in the US, and it was recently approved in Europe. I think it will be approved fairly quickly in the US because of the efficacy and safety demonstrated in multiple trials worldwide, which included our team at Rush.

**Ko:** Nerve regeneration using stem cell therapy is a very hot topic in the MS community. Do you see that coming to fruition anytime soon?
Stefoski: I do not. The problem with real stem cells is that we don’t know where they go and what they do once they’re put into people’s bodies, at least as far as MS is concerned. Other alleged “stem cell” treatments marketed for MS are actually high-dose chemotherapies, and with those therapies, stem cells serve only to rescue the immune system. The only systematic approach to the treatment of MS with stem cells was done in Israel, with modest benefit. We’re talking about adult mesenchymal stem cells, incidentally, not fetal stem cells. There has been no work with embryonic stem cells for MS.

Unfortunately, since the FDA has relaxed its regulation of adult stem cell treatment centers in the US, they have popped up all over the place. People are going and paying cash up front, but they don’t know what they’re getting. A person with MS is much better off going to a medical facility with a reputation as a leader in MS treatment and research. What does the future hold?

Stefoski: The biggest task now is expansion, to be able to accommodate the increasing numbers of patients receiving intravenous medications. There are 6 IV medications for MS that can be administered on an outpatient basis, so we recently began to expand our infusion facility as well our professional staff. As for research, we are embarking on testing of a few brand-new drugs, some of which have the potential to repair tissues damaged by MS.

Ko: Treatments have advanced significantly in a relatively short period of time.

Stefoski: About 25 years.

Ko: When you started out, did you think there would be this much progress so quickly?

Stefoski: I did, and that’s actually why I went into the field of MS—the potential for innovation was palpable. In 1977, when I was finishing my residency in neurology here at Rush, I was offered the opportunity to stay on by 3 sections within the Department of Neurological Sciences. The first was neuromuscular neurology, which was too intensely reliant on electromyography (EMG). The second was epilepsy, but back then EEGs (electroencephalograms) were these endless reams of paper that you had to read for hours on end. With MS, it was almost exclusively patient work, which I found very engaging. I also realized that I could learn a lot from Dr Floyd Davis, who was the founding director of the Rush MS Center and the only MS specialist in Chicago at that time. He was doing some really interesting MS-directed research, so I joined his team and our work evolved, leading to the development of Ampyra. It turns out I was correct in anticipating such progress.

Ko: When you started out, did you think there would be this much progress so quickly?

Stefoski: Dr Davis taught you, and you, in turn, have taught me and my peers. When you decide to step away from practicing medicine, what will your legacy be?

Stefoski: I believe a legacy is something best left to objective observers to determine. But from a more subjective point of view, there are several things I’m extremely proud to be cultivating here at Rush and teaching to both current and prospective providers of expert MS care: the strong emphasis on compassionate, comprehensive patient care established by Dr Davis decades ago; a forward-thinking and decisive approach to treatment of people with MS; and a steadfast commitment to translational research, which has led—and will, I am confident, continue to lead—to the development of meaningful novel therapies for MS.
For a patient consultation or referral to a neurologist at Rush, please call (312) 942-4500. For a neurosurgeon at Rush, call (312) 942-6644.
Rush is an academic health system comprising Rush University Medical Center, Rush Copley Medical Center and Rush Oak Park Hospital.

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