“Medicine is a science, but there is also an art, and the approach has to be customized depending on the patient, their background, and where they are in their lives. We help them understand what’s in the future, and we help walk this path with them.”

– Aikaterini Kompoliti, MD, movement disorders specialist
THE 2016 RUSH NEUROSCIENCE REVIEW

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Chairpersons’ Letter

You may notice something different about this year’s letter: After 26 years of distinguished service to Rush, our esteemed colleague Jacob Fox has retired. (See page 63 for an interview with Dr Fox.) And I am pleased to introduce you to my new fellow chairperson and coauthor, Igor Koralnik, who has accepted the position of chairperson for the Department of Neurological Sciences.

If you will permit me, a brief introduction: Koralnik has spent the last 25 years studying how viruses affect the nervous system in immunosuppressed individuals, with an emphasis on progressive multifocal leukoencephalopathy. In bringing his clinical expertise in neuroimmunology, along with his research laboratory and fellowship to Rush, he will continue Rush’s strong tradition of patient care, education, and translational research.

As you know, this intersection of education, patient care, and research is particularly critical now as we face an aging population and a national focus on cost-effective health management strategies. Neuroscientists are critical to the management of complex chronic conditions—and to spreading this expertise to the many areas in our country and beyond that lack neurologists and neurosurgeons. Rush’s focus on translational research, in particular, is a key component to fulfilling these needs.

Here are several examples from the last year at Rush of clinical progress toward these goals:

**Movement disorders fellowship and research:**
Our movement disorders program is one of the few that focuses on the nonmotor aspects of Parkinson’s disease along with the motor aspects, including training interns and residents in both aspects of the disease. In recognition of our program’s strengths, the Michael J. Fox Foundation recently announced that Rush was one of only six academic medical centers selected to host a Safra Fellowship in Movement Disorders. The fellowship is designed to further the growth of movement disorders specialists and potential clinical breakthroughs.

**Telehealth access to epilepsy specialists:** Rush’s epilepsy program, in collaboration with the Epilepsy Foundation of North/Central Illinois, is developing portable communication technologies that will allow epileptologists to take specialized epilepsy care to refractory patients in rural communities that lack this expertise—and to help these patients avoid going to the ER. Two examples of these technologies are micro-EEGs that can be put on a patient’s head within minutes and relay information remotely, and biosensors that can be placed on the body to watch a patient walk around in their own homes in case of falls.

The program is also developing implantable nanotechnology the size of a pin tip. Currently in preclinical stages, this patented technology can be injected into the brain to facilitate sensing early seizure activity. This technology can amplify both stimulation therapy in tandem with therapeutic drug delivery to stabilize otherwise uncontrolled seizures.

**Expanding quick access to stroke neurologists:**
For the last 5 years, our stroke program has been busy demonstrating the great possibilities for raising the health of a whole community through telemedicine. The TeleStroke program will soon have 13 affiliated hospitals participating in its stroke network, the largest such network in the Chicago area.
Stroke neurologists from Rush have remotely examined more than 2700 stroke patients at community hospitals across Chicago—an indication of the tremendous need for stroke neurologists not only in rural areas, but in urban settings as well.

The team has honed their processes for quickly treating these emergencies to the point where their door-to-needle times are routinely under one-third of the national average for this measure. (See page 17 for more on the stroke team’s processes and page 49 for quality data.)

Alzheimer’s NIA research funding: The National Institute on Aging has recently awarded the Rush Alzheimer’s Disease Center $14.3 million over the next 5 years. This award is a renewal of continuous grant funding—now extending to 30 years—for the center that has supported the collection of pathology samples and health data from longitudinal research of individuals with and without Alzheimer’s.

This information is available to researchers at Rush, 11 strategic partner programs at other major academic medical centers, and other researchers worldwide. In the last 5 years alone, researchers in the Alzheimer’s center have published more than 225 papers in peer-reviewed journals.

Extending neurosurgery access: Our Department of Neurological Surgery has strengthened its affiliation with John H. Stroger, Jr Hospital, Chicago’s public hospital and Rush’s neighbor in the Illinois Medical District. The affiliation involves a collaboration as the primary academic partner of the Stroger Division of Neurosurgery. In the spirit of the larger academic affiliation between Rush and Stroger, Rush neurosurgery plans to offer more subspecialty clinical services to patients at this safety net hospital while improving the educational experience for Rush neurosurgery residents.

And our faculty continue to further their respective fields in a variety of other ways:

- Neurologist Neelum Aggarwal, MD, received the 2016 Women in Science Award from the American Medical Women’s Association in recognition of her exceptional contributions to medical science, and specifically women’s health, through her research and leadership. Among Aggarwal’s research interests is the intersection between cognitive decline and cardiology among women, an interest that is manifest in the neurocognitive cardiology clinic that is part of the Rush Heart Center for Women.

- Rush hosted several conferences last year, including the first World Live Neurovascular conference to be held in the United States in June 2015. Co-directed by neuroendovascular surgeon Demetrius Lopes, MD, the conference showcased new developments in neurointerventional and cerebrovascular surgery. Rush also hosted the American Association of Neurological Surgeons annual conference and the First International Brain Mapping Course.

- Our spine neurosurgeons continue to pursue new treatment possibilities for spine patients, particularly in the area of spinal cord injuries. Richard Fessler, MD, PhD, is leading an exciting stem cell therapy trial for traumatic spinal cord injuries (see page 12 for more).

We invite you to read more about the contributions of our departments to further the reach of translational research so that it is truly bench to bedside—whether the bedside is at Rush, in community hospitals, in rural communities across Illinois, or even around the world.

Regards,

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

For additional volume and quality data, see pages 48-49.

28,709 | Neurology outpatient visits

2,717 | Neurology inpatient discharges

3,638 | Neurological surgery outpatient visits (brain)

5,068 | Neurological surgery outpatient visits (spine)

Attending physicians 120
Residents and fellows 57
Advanced practice nurses and physician assistants 25
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 U.S. National Institutes of Health.

No. 2 in the Nation: In 2015, Rush received the University HealthSystem Consortium’s Quality Leadership Award, ranking No. 2 among more than 100 academic medical centers.

Comprehensive Stroke Center: The Rush stroke program is certified by the Joint Commission as a comprehensive stroke center.

CARF accreditation: Rush’s rehabilitation program, including general inpatient and stroke specialty rehab, is fully accredited by the Commission on Accreditation of Rehabilitation Facilities.

Huntington’s Disease Center of Excellence: The Huntington’s Disease Society of America named Rush one of its Centers of Excellence for 2015.

AAHRPP accreditation: Rush’s research program is fully accredited by the Association for the Accreditation of Human Research Protection Programs.

Nursing Excellence: Rush has earned Magnet status—the highest honor in nursing—four times from the American Nurses Credentialing Center.
Primary and Associated Faculty (2015)

Department of Neurological Sciences

Chairperson: Igor Koralnik, MD

Alzheimer’s disease

Neelum Aggarwal, MD
Konstantinos Arfanakis, PhD
Zoe Arvanitakis, MD
Lisa Barnes, PhD
David Bennett, MD
Patricia Boyle, PhD
Aron Buchman, MD
Ana Capuano, PhD
Robert Dawe, PhD
Debra Fleischman, PhD
S. Duke Han, PhD
Bryan James, PhD
Sue Leurgans, PhD
Sukriti Nag, MD, PhD
Julie Schneider, MD
Raj Shah, MD
Rita Shapiro, DO
Robert Wilson, PhD
Lei Yu, PhD

Not pictured:
Denis Evans, MD
Christopher Gaiteri, PhD
Jingyun Yang, PhD

Cerebrovascular disease

Laurel Cherian, MD
James Conners, MD, MS
Shawna Cutting, MD
Michael Kelly, MD
Vivien Lee, MD
Sarah Song, MD

Clinical neurophysiology and epilepsy

Antoaneta Balabanov, MD
Donna Bergen, MD
Lawrence Bernstein, MD
Adriana Bermeo-Ovalle, MD
Thomas Hoeppner, PhD
Maggie McNulty, MD
Serge Pierre-Louis, MD
Marvin Rossi, MD, PhD
Michael Smith, MD

Not pictured:
Esmeralda Park, MD
Travis Stoub, PhD
Critical care neurology

Thomas Bleck, MD  Torrey Boland, MD  Katharina Busl, MD  Rajeev Garg, MD  Diana Goodman, MD  Sayona John, MD  George Lopez, MD, PhD  Sebastian Pollandt, MD

General neurology

Jonathan Cheponis, MD  Jacob Fox, MD  Carrie Grouse, MD  Steven Lewis, MD  Megan Shanks, MD  Jordan Topel, MD  Allison Weathers, MD  Felise Zollman, MD

Movement disorders

Sharlet Anderson, PhD  Brandon Barton, MD, MS  Bryan Bernard, PhD  Cynthia Comella, MD  Christopher Goetz, MD  Jennifer Goldman, MD, MS  Deborah Hall, MD, PhD  Aikaterini Kompoliti, MD  Gian Pal, MD, MS  Kathleen Shannon, MD  Glenn Stebbins, PhD  Leonard Verhagen, MD, PhD  Not pictured:
Melany Danehy, MD  Bichun Ouyang, PhD

Multiple sclerosis

Roumen Balabanov, MD  Rajendra Goswami, PhD  Dusan Stefoski, MD  Not pictured:
Michael Ko, MD
Primary and Associated Faculty (2015)

Department of Neurological Surgery

**Chairperson:** Richard Byrne, MD

[Images of faculty members]

**Research faculty**

- Roberta Glick, MD
- Terry Lichtor, MD, PhD
- Richard Penn, MD

**Associated faculty at Rush University Medical Center**

- Pete Batra, MD (Otorhinolaryngology)
- Aidnag Diaz, MD, MPH (Radiation oncology)
- Sheila Dugan, MD (Physical medicine and rehabilitation)
- R. Mark Wiet, MD (Neurology)

[Images of faculty members]

**Not pictured:**
- David Rothenberg, MD, anesthesiology
- Mary Sturaitis, MD, anesthesiology

**Associated clinical faculty***

- Jerry Bauer, MD
- Martin Luken, MD
- Tibor Boco, MD
- Patricia Raksin, MD
- George Bovis, MD
- Szymon Rosenblatt, MD
- Martin Herman, MD, PhD
- John Ruge, MD
- Juan Jimenez, MD
- Andrew Zelby, MD

*Primary appointment is not at Rush University Medical Center
Residents and Fellows (2015)

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 at Tulsa

Ankush Bhatia, MD
Medical school: Rush Medical College

Hunan Chaudhry, MD
Medical school: Rush Medical College

Christine Chuck, MD
Medical school: Indiana University School of Medicine

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

Kathryn Ess, MD
Medical school: Indiana University School of Medicine

Avram Fraint, MD
Medical school: Rush Medical College

Sabreena Gillow, MD
Medical school: University of Colorado School of Medicine

Breyanna Grays, MD
Medical school: Indiana University School of Medicine

Ryan Hanson, MD
Medical school: Rush Medical College

Christian Hernandez, MD
Medical school: Louisiana State University School of Medicine–New Orleans

Emily Hill, MD
Medical school: Rush Medical College

Zehra Husain, MD
Medical school: Wayne State University School of Medicine

Samantha LoRusso, MD
Medical school: Wake Forest University School of Medicine

Brian Marcus, MD
Medical school: Medical College of Wisconsin

Colin McLeod, MD
Medical school: University of Florida College of Medicine

Michael Mercurio, MD
Medical school: State University of New York Upstate College of Medicine

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

Jeremy Pruzin, MD
Medical school: The Chicago Medical School at Rosalind Franklin University of Medicine and Science

Benjamin Savage, DO
Medical school: Chicago College of Osteopathic Medicine, Midwestern University

Dan Schachter, MD
Medical school: New York Medical College

Ruby Upadhyay, MD
Medical school: Rush Medical College

David Whitney, MD
Medical school: Temple University School of Medicine

Fellows

Justin Abraham, MD
Medical school: Penn State College of Medicine
Residency: Thomas Jefferson University Hospital

Hesham Allam, MD
Medical school: Ain Shams University Faculty of Medicine
Residency: Saint Louis University Hospital

Ameer Al Wafai, MD
Medical school: Beirut Arab University School of Medicine
Residency: University of Tennessee Health Science Center

Fatmah Al Zahmi, MBBS
Medical school: United Arab Emirates University
Residency: University of Connecticut

Meagan Bailey, MD
Medical school: Texas Tech University Health Sciences Center
Residency: Wake Forest School of Medicine

Ian Bledsoe, MD
Medical school: University of Pittsburgh School of Medicine
Residency: Stanford Hospital and Clinics

Kyle Carpenter, DO
Medical school: Des Moines University College of Osteopathic Medicine
Residency: University of Kansas Medical Center

Mohamad Ezzeldin, MD
Medical school: Cairo University Faculty of Medicine
Residency: University of Texas Medical Branch
Mineshkumar Morker, MD  
Medical school: Northwestern University Feinberg School of Medicine  
Residency: Northwestern University Feinberg School of Medicine

Nicholas Osteraas, MD  
Medical school: George Washington University School of Medicine and Health Sciences  
Residency: Rush University Medical Center

Atul Ramesh, MD  
Medical school: University of Toledo College of Medicine  
Residency: Albert Einstein College of Medicine

Kapil Sachdeva, MD  
Medical school: Northwestern University Feinberg School of Medicine  
Residency: Northwestern University Feinberg School of Medicine

Varoon Thavapalan, MD  
Medical school: John A. Burns School of Medicine  
Residency: Thomas Jefferson University Hospital

Jessica Walter, MD  
Medical school: Georgetown University School of Medicine  
Residency: Mount Sinai Hospital, New York

Department of Neurological Surgery

Residents

Owoicho Adogwa, MD  
Medical school: Vanderbilt University School of Medicine

Sumeet Ahuja, MD  
Medical school: Indiana University School of Medicine

Bledi Brahimaj, MD  
Medical school: University of Cincinnati College of Medicine

Daniel DiLorenzo, MD, PhD, MBA  
Medical school: Harvard Medical School

Daniel Eddelman, MD  
Medical school: Indiana University School of Medicine

Carter Gerard, MD  
Medical school: University of Louisville School of Medicine

Manish Kasiwal, MBBS, MCh  
Medical school: All India Institute of Medical Sciences

Mena Kerolus, MD  
Medical school: University of Missouri–Kansas City School of Medicine

Kapil Sachdeva, MD  
Medical school: Northwestern University Feinberg School of Medicine  
Residency: Northwestern University Feinberg School of Medicine

Varoon Thavapalan, MD  
Medical school: John A. Burns School of Medicine  
Residency: Thomas Jefferson University Hospital

Jessica Walter, MD  
Medical school: Georgetown University School of Medicine  
Residency: Mount Sinai Hospital, New York

Fellow

Danilo Marques Nogueira, MD  
Medical school: Federal University of Grande Dourados, Brazil  
Residency: Hospital de Base do Distrito Federal, Brazil
Introduction

The personal and societal impact of traumatic spinal cord injury (SCI) is often tremendous. Affected individuals are disproportionately young and healthy, and this devastating injury is common. Recent estimates suggest an annual incidence of 30 to 49 cases per million in North America. This incidence has compelled clinicians and basic scientists to search for strategies to optimize neurological recovery after these life-changing events. One area of active research is stem cell transplantation therapy, which holds promise to enhance sensorimotor recovery and improve functional outcomes through multiple mechanisms of neural protection and plasticity.

Current State of Knowledge

Presently, stem cell therapy for traumatic SCI is focused on 3 specific cell types: (1) mesenchymal stem cells (MSCs), (2) embryonic stem cells (ESCs), and (3) induced pluripotent stem cells (IPSCs). Each has been shown to hold promise for enhancing recovery through neuroprotection, axonal regeneration, and cellular replacement at the injury site.

Mesenchymal Stem Cells

The sources of adult mesenchymal stem cells (MSCs) are numerous, but they are most commonly derived from bone marrow and after appropriate processing may be stimulated for neuroglial differentiation. These differentiated cells may then be transplanted into the injured spinal cord of the same patient from whom they came. It is generally thought that MSCs act primarily through modulation of the immunogenic response, a part of the secondary injury phase of SCI that occurs after the initial traumatic insult. By preventing the deleterious effects of T-cell activation at the injury site, MSCs exert a neuroprotective effect at the cellular level. This theory is supported by observations of significantly higher levels of neuron preservation and axonal myelination in animal models of traumatic SCI treated with MSCs. These findings suggest a potential for the enhancement of neurological function after injury, and a number of studies conducted on rat models have identified this effect after implantation of MSCs in the acute and subacute phases after injury.
The encouraging results of animal investigations have been translated into a number of human trials. Here, the results have been mixed, but some have found clinically meaningful improvement in neurological function in certain patients after MSC therapy. The neuroprotectant properties of MSCs are likely to have the greatest benefit during the early phases of the secondary injury process, but because most human studies have focused on the chronic phase of injury, the full potential of MSCs may not have been observed. The authors of 1 particular trial reported that nearly one-third of their study cohort with loss of all sensorimotor function treated in the acute or subacute period with MSCs regained a clinically significant amount of neurological function. This finding suggests that timing of administration may be an important factor, although the results should be interpreted with caution because the single-arm nature of the study does not allow for a clear distinction between gains attributable to therapy and those resulting from the evolution of and recovery from the injury. At present, the efficacy of MSCs for treatment of SCI remains to be fully defined, and further study is needed.

Embryonic Stem Cells

ESC are generally classified as those of the inner cell mass within a blastocyst. These cells are pluripotent cells that differentiate into multipotent cells of the 3 germ layers: ectodermal (the origin of neural tissue), mesodermal, and endodermal. During the differentiation process, progenitor cells that are capable of self-renewal are formed. Neural progenitors become the neuron and glial cells of the central nervous system, and it is these cells that are of specific interest for SCI therapies. The process of differentiation is illustrated in Figure 1.Implanted progenitor ESCs have been shown to have neuroprotectant properties by acting to reduce inflammation and mitigate cell death, along with axonal regeneration through remyelination following the injury. Although these effects have been noted with MSCs, a further and potentially substantial advantage of ESCs over adult MSCs is their potential to act as cellular replacements. Whereas adult MSCs do not appear to harbor this ability, ESC-derived neurons have been shown to survive and integrate after injection into animal models of SCI.

The synergistic combination of neuroprotective effects in the earlier stages of injury coupled with cellular replacement has led to excitement and active research in both animal models and human trials of ESCs for the treatment of SCI. However, the use of these cells is not without challenges. One particular issue with ESCs is immunogenicity. ESCs are not autologous (adult MSCs are), and thus transplantation of ESCs stimulates an immune response that places the transplanted cells at risk for rejection. For this reason, all patients receiving ESCs require immunosuppression. Furthermore, there have been concerns regarding the potential for teratogenicity with ESC implantation because of uncontrolled cellular proliferation. However, this concern has been greatly reduced through differentiation of the ESCs to neural progenitor cells prior to implantation. Ethical dilemmas are also commonplace when discussing ESCs. The concerns largely focus on the creation of human embryos specifically for scientific research and the identification of the point when a human life begins.

Notwithstanding these challenges, the effects of ESCs on inflammation, axonal remyelination, and cellular replacement have led to significant neurological improvement after SCI in animal models. This finding has spurred active research in human SCI. A phase I/IIa study of ESC therapy for traumatic thoracic SCI (ClinicalTrials.gov identifier NCT01321333) was initiated in 2011 and reached completion in mid-2015, but the publication of the results is pending. Around the time of completion of this trial, another study of ESC therapy following traumatic SCI was initiated. Rush University Medical Center is currently involved with this promising phase I/IIa multicenter study, and the details are outlined in the final section of this review.
Induced Pluripotent Stem Cells

IPSCs are derived from adult cells that are “reprogrammed” to behave as immature stem cells, which differentiate into cells of any germ line, including neurons, oligodendrocytes, and astrocytes. Figure 2 summarizes the harvesting and reprogramming process. The cells are easily accessible, and because they are autologous, immunosuppression is not needed. The ethical issues inherent with embryonic cells are avoided because IPSCs are derived from adult cells instead. Because these cells appear to behave similarly to ESCs, they may offer the same benefits. Encouraging results suggest improved motor function after IPSC therapy in animal models of SCI. Currently, no human trials are underway to assess the role of IPSCs in SCI; however, future research in this area is likely.

The Role of Rush University Medical Center

The Department of Neurological Surgery at Rush University Medical Center is currently at the forefront of clinical trials of stem cell therapy in traumatic SCI. Rush is actively recruiting patients as a part of the SCiStar study (ClinicalTrials.gov identifier NCT02302157). This multicenter phase I/IIa open-label, single-arm study is testing AST-OPC1, a population of oligodendrocyte progenitor cells derived from human ESCs, as a potential therapy to enhance neurological recovery following SCI.

Potential Reparative Mechanisms

Oligodendrocyte progenitor cells have been shown to enhance survival and regrowth of axons following SCI through neurotrophic factor production, stimulation of vascularization, and remyelination of denuded axons. Specific testing involving AST-OPC1 cells injected in rodent models 7 days after SCI revealed appropriate in situ differentiation into mature oligodendrocytes and encouraging findings of reduced spinal cord cavitation, remyelination, and, most important, enhanced functional recovery.

Study Recruitment

The overall aim of the SCiStar study is to test the safety of stem cell therapy with AST-OPC1 and to evaluate if the neurological gains observed in animal models may be translated to humans. To this end, 13 participants will be recruited, each between 18 and 65 years of age. Those with a blunt traumatic SCI within the past 14 to 30 days are eligible. The clinical neurological
exam must be consistent with a sensorimotor complete traumatic spinal cord injury, and the last fully preserved single neurological level must be between C5 and C7. In effect, this requirement represents a state of absent neurological function below the level of injury in the cervical spine. These individuals are profoundly affected by the injury, and it is here where the greatest potential gains are thought to be achievable.

**Stem Cell Transplantation**

These progenitor cells are differentiated from an undifferentiated population of human embryonic stem cells after a controlled and specialized differentiation protocol.24 The early-stage oligodendrocyte progenitor cells are cryopreserved, forming the AST-OPC1 investigational product. AST-OPC1 is injected directly into the spinal cord parenchyma at the site of injury. This procedure requires surgical removal of the lamina overlying the injured segment of the spinal cord and opening of the dura mater to provide access for administration of AST-OPC1 through a single-use, sterile syringe (Figure 3). Each participant will receive a single dose, and the study will follow a sequential dose escalation protocol, testing 3 escalated dose cohorts ranging from 2 million cells to 20 million cells.

**Outcomes and Follow-up**

The treatment and observation period is set for 12 months, and the total duration of the study is planned to be approximately 3 years. The primary end points are focused on safety and include tracking the incidence and severity of adverse events as well as untoward changes in serum laboratory values and changes at the injection site through monitoring with periodic magnetic resonance imaging studies. The secondary end points pertain to efficacy of the treatment and are focused on changes in sensorimotor neurological function. Finally, exploratory testing will include changes in aspects of daily living and lower urinary tract and bowel function over the 12-month follow-up period. The participants will then be enrolled in a separate long-term safety protocol that is planned for a duration of 14 years.

**Conclusions**

Stem cells hold tremendous promise to enhance functional neurological recovery after traumatic SCI through mechanisms of neuroprotection, axonal regeneration, and cellular replacement. Future SCI management is quite likely to involve stem cell transplantation therapies; however, much more remains to be learned. Investigations such as the SCiStar study and the contributions made by the Department of Neurological Surgery at Rush may play an important role in mitigating the devastating impact of the injury.
References

THE JOIN APP FOR ACUTE STROKE:
Mobile Real-Time Tracking of Patients With Instant Interteam Communication

Daniel J. DiLorenzo, MD, PhD, MBA; Lee A. Tan, MD; Danilo Marques Nogueira, MD; Kiffon M. Keigher, ACNP; Demetrius K. Lopes, MD

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Introduction

Concurrent with technological advances in therapy for acute emergencies has been the development of an infrastructure to support time-efficient delivery of care and the education of physicians, patients, and other stakeholders on the need and availability of promptly delivered therapy. Prompt treatment is particularly important in the management of ischemic conditions, such as myocardial infarction and stroke, in which irreversible organ damage begins shortly after onset of the condition. Over the past decade, to address this growing need, our institution has designed and implemented a multidisciplinary and multi-institutional workflow and infrastructure to support streamlined treatment of stroke patients. One novel component of this process is a mobile smartphone software application (app), the features, functionality, and benefits of which are the focus of this article.

More than two-thirds of physicians now regularly use smartphones, and mobile smartphone applications are beginning to be used broadly in disease management, in a variety of indications and spanning the chronology from prevention to management to long-term follow-up. In the cardiovascular and stroke space, recent promise has been shown across this time frame, including the use of digital health interventions in the reduction of vascular stroke risk factors, prevention of cardiovascular disease, diagnosis of stroke in telestroke centers, and postdischarge follow-up with automated assessment of modified Rankin scores. With the refinement of streamlined acute stroke management workflows and the realization that improved interinstitutional communication, such as telestroke processes, improves outcomes, the time has come for the introduction of a new wave of technologies and processes that further improve communication and reduce time to treatment delivery.

Figure 1. A time series of screenshots from the Join app (Allm Inc) is shown, beginning with A and progressing in time from A to F. Each screenshot has a time stamp in the upper center. A mobile beacon with GPS tracking communicates the location of the patient. In this series, a patient is picked up and tagged by emergency medical services at 10:46 pm (A), followed by rapid transport from the suburbs by helicopter, over the congested Chicago highway and street system, to a helipad in the Illinois Medical District by 10:59 pm and then via ambulance to Rush University Medical Center minutes later (F).
Methods

Clinical Workflow for Acute Stroke Management

Our Stroke60 acute stroke workflow begins with a call or page from a physician from an outside facility who has a patient in whom a stroke is suspected. This communication is early and usually occurs immediately after the physician’s assessment of the patient, often before computed tomography (CT) imaging is performed. Our stroke neurologist receives the call, discusses the patient, reviews the imaging when available, and discusses the case with the neurosurgeon or interventional neurologist to decide whether the patient meets criteria and would benefit from an intervention such as mechanical thrombectomy. Immediately upon an affirmative decision, a page is sent to the entire on-call stroke team, which includes the neurology and neurological surgery stroke fellows, the circulating nurse, the scrub technician, and the room technician. The procedure is scheduled emergently in the neurointerventional suite, and the anesthesia team on call is immediately notified. Others who are notified or paged include the neuroscience intensive care unit (NSICU) charge nurse to facilitate timely staffing and bed availability for the patient after the procedure. This notification typically occurs 45 minutes prior to the arrival of the patient at our institution. A series of subsequent pages are sent at specific time points, including confirmation of the name and date of birth of the patient, an update with the medical record number of the patient, notification of the arrival of the transport team (helicopter or ambulance) to the referring facility, and a heads-up usually 15 minutes and then several minutes prior to arrival.

The patient is admitted upon entry through the emergency department bay doors with prompt placement of a wristband. A rapid neurological assessment, including the National Institutes of Health Stroke Scale, is performed; orders for emergent computed tomography (CT), CT arthrography, and CT perfusion study are entered; and the patient is wheeled directly to the CT scanner. On the basis of the examination, the patient’s ASPECTS (Alberta Stroke Program Early CT Score) assessment, the presence of large-vessel occlusion, and other factors including medical comorbidities, a decision whether to perform mechanical thrombectomy is made, and the patient is taken immediately to the neurointerventional suite or NSICU.

Figure 2. A, A time-stamp sequence for a Stroke60 patient from arrival at Rush University Medical Center to recanalization is shown, including the following events: arrival to hospital, start of CT/MRI imaging, end of CT/MRI imaging, entrance into angiography suite, and recanalization. B, The Rush University Medical Center stroke team, after waiting in the emergency department (ED) before arrival of the ambulance, meets the ambulance in the ED bay before the patient is unloaded, and assists in the unloading and expeditious transport of the patient through the ED directly to the CT scanner. C, The team in the neurointerventional suite after successful thrombectomy. D, Close-up photograph depicts the retrieved thrombus and the stent retriever.
A customized mobile application called Join (Allm Inc) has been developed to further streamline our acute stroke workflow. The app provides the following helpful features: (1) real-time secure communication among team members, (2) automated time-stamping of events, (3) generation of a summary document in PDF for uploading into the electronic medical record (EMR), and (4) real-time monitoring and communication of patient’s exact position during transport using GPS. All events receive a time stamp that is visible to all team members, obviating the need for a recording person to be appointed and a specific clock to be chosen. Time-stamped events include “Time of Onset / Last Known Well,” “Time of tPA Administration,” “Time Consent Obtained,” “Time of Arrival / Door Time,” “Imaging Complete Time,” “Procedure Start Time,” “First Pass Time,” and “Recanalization Time.”

After the treatment process is completed and the patient is admitted to the NSICU, the information that was transmitted, with associated time stamps, is summarized in a document, outputted as a PDF, and uploaded to the patient’s EMR. A unique feature of this application and our workflow is the incorporation of a real-time GPS-based patient tracking system. A precise estimated time of arrival for a patient is difficult to determine because of the multiple stages in evaluation and transport, each of which has considerable variability. Therefore, to best inform the stroke team of the patient’s status, a graphical representation of the patient’s position in the city or surrounding region is transmitted.

Figure 1 shows a series of screenshots of the Join app during a Stroke60 event. In Figure 2, a set of time stamps from the Join app is shown along with corresponding components of the workflow in our institution, including the team awaiting and greeting the arriving ambulance and patient, rapid transport to the CT (or MRI) scanner and then to the neurointerventional suite for thrombectomy. Figure 3 depicts the interrelated stroke response team entities.

Results

We have found the Join app to be a helpful tool in providing real-time communication among team members, all of whom are on call and may be up to 60 minutes away from the hospital. The secure text communication feature facilitates rapid delegation of tasks and confirmation of their completion to the entire team. Automated time-stamping eliminates inefficient
scribing of times and the risk of losing paper time-stamp notes. Automated generation of a summary report provides further robust documentation of time stamps and communication. Real-time patient location tracking with GPS is valuable to on-call and in-house team members in ensuring that appropriate personnel are ready prior to the arrival of the patient, thereby minimizing delay in delivery of therapy.

Discussion

The Rush University Medical Center Stroke60 workflow and associated mobile application represent, to our knowledge, the first integration of a mobile application with GPS functionality that coordinates the activities and travel logistics of all stakeholders in acute stroke treatment, including the patient, the staff at the initial presenting hospital, the transportation service (ambulance or helicopter service), and the receiving hospital and associated physicians and on-call team members.

In real time, we are able to receive text and image updates, delegate responsibility for tasks (scheduling the procedure in the interventional suite, calling the anesthesia team, obtaining telephone consent from family, obtaining patient handoff from the transferring hospital, and others) and confirm their completion, and ensure that all on-call staff are on site and systems are ready before arrival of the patient. Rather than utilizing an estimated time of arrival with an unknown level of uncertainty, the visual GPS tracking, with an icon trail showing the trajectory history and velocity, provides a clear big-picture view of the patient’s present location and likely time to arrival. Usually, the stroke neurointerventional team has 45 to 60 minutes of advance notice from the first page to arrival of the patient at the emergency department bay, but the variability is large, and occasionally less than 30 minutes of notice has been given. A real-time visual representation is helpful so that the need for backup staff may be quickly appreciated and their activation commenced if needed.

Static use of GPS has been described in stroke treatment. Nam et al. described a consumer mobile smartphone application that provides guided questioning to enable patients to self-diagnose acute ischemic stroke and uses GPS in a static fashion to calculate distances to hospitals to determine the closest hospital offering thrombectomy services. Demaerschalk et al. described the use of a smartphone application, ResolutionMD, to facilitate secure remote viewing of neuroradiological images from an outside hospital for stroke diagnosis.

Conclusion

In our pilot study, the Join app has provided reliable real-time communication among Stroke60 team members, reliable graphical representation of patient location during transport, time-efficient time-stamping, and summaries of these and other metrics for uploading into the EMR. This pilot experience is qualitative in nature, and further quantitative study with metrics is planned. This is the first reported use of real-time GPS tracking of patient transfer for acute stroke treatment. Our experience has been positive, and further quantitative evaluation of this and other mobile applications is warranted and planned.

Acknowledgments

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References


DEEP BRAIN STIMULATION FOR MAJOR DEPRESSION

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Introduction
Major depressive disorder (MDD) is a ubiquitous affective disorder with debilitating symptoms that severely hampers quality of life. Population studies have reported the lifetime prevalence of MDD to be 16.2%.1 Symptoms of depression include depressed mood, changes in sleep patterns, loss of interest in daily activities, fatigue, excessive guilt, and suicidal ideation. Pharmacotherapy is commonly effective; however, 20% to 30% of patients remain refractory to medical treatment.2,3

In addition to pharmacotherapy, contemporary noninvasive treatments for MDD include psychotherapy and electroconvulsive therapy. Surgical treatments in the form of ablation, including anterior capsulotomy, anterior cingulotomy, and subcaudate tractotomy, have been reported with varying degrees of success.4,7 Neuromodulation therapies including vagal nerve stimulation and epidural cortical stimulation have also been trialed.8,9 With increasing interest and improvement in reported outcomes, deep brain stimulation (DBS) for MDD is becoming a field of heightened interest.

The departments of neurological surgery, neurological sciences, and psychiatry at Rush University Medical Center are high-volume clinical practices with the requisite patient population and resources to conduct continued research regarding DBS for MDD. In this review we intend to illustrate how Rush is in a unique position to advance the field of neuromodulation for psychiatric conditions and improve the quality of life for those with refractory MDD.

Current State of Knowledge
MDD is a multifactorial disease process predicated around the monoamine and catecholamine hypotheses for affective disorders.10 Simply stated, affective disorders such as MDD are observed to exist in a state of relative amine deficiency (serotonin and norepinephrine). Conversely, drugs or therapies that potentiate amine availability produce an antidepressant effect. Additional factors contributing to MDD include stress, neurodegeneration, and possibly genetic components.11-13

Neurocircuitry
The neurocircuitry relating to MDD and other affective disorders is complex. Previous studies have implicated various components of the cortico-striato-thalamo-cortical (CSTC) pathway and subcomponents thereof.14-18 The CSTC pathway can be subcategorized into dorsal, modulatory, and ventral components.16 The dorsal component consists of the thalamus, prefrontal cortices, premotor cortex, dorsal cingulate cortex, dorsal striatum, and dorsal pallidum. The dorsal structures are believed to contribute to the cognitive and motor symptoms of MDD. The ventral compartment consists of the thalamus, orbitofrontal cortex, subgenual cingulate cortex (SCC), insular cortex, ventral striatum, and ventral pallidum. These structures contribute to the vegetative state observed in MDD. The modulatory component, consisting of the hippocampus, amygdala, and hypothalamic-pituitary-adrenal axis, completes the circuit and aids in communication and relaying information between the dorsal and ventral structures.16

Review of DBS for MDD
A total of six stimulation sites have been trialed for the treatment of MDD, including the SCC, nucleus accumbens (NAcc), ventral capsule/ventral striatum (VA/VS), lateral habenula (LHb), inferior thalamic peduncle, and medial forebrain bundle (MFB). In a series of patients undergoing DBS
Deep Brain Stimulation for Major Depression

of the NAcc, long-term follow-up revealed that approximately 50% of the cohort had a successful response. DBS of the VA/VS has been reported with a response rate of 71% in 1 trial of 17 patients with a mean follow-up of 37.4 months. Response rates have ranged from 29% to 92% across multiple studies. However, despite success with open-label VA/VS DBS, a prospective randomized trial failed to show significant improvement in the VA/VS stimulation group when compared with the sham stimulation group. Stimulation of the SCC was initially described in 1997, and, more recently, a single-blinded study of 17 patients with bipolar disorder and MDD demonstrated a response rate of 92% with full remission in 58% of patients. However, a multicenter, prospective, randomized trial for DBS of the SCC was initiated by St. Jude Medical and stopped early because the 6-month results failed to show utility.

At Rush, current efforts to treat MDD are focused on targeting of the LHb and MFB. DBS of the LHb has been reported with success in a single patient with therapy-refractory MDD, and increased activation of the LHb has been implicated in the downregulation of serotonergic, noradrenergic, and dopaminergic systems and stimulation of the HPA axis. An increase in peripheral brain-derived neurotrophic factor, a neuronal growth factor involved in maintenance of synaptic function and neural plasticity, with long-term DBS of the LHb has also been demonstrated. At Rush, we have utilized MRI tractography to identify the major afferent pathway to the LHb, the stria medullaris thalami, in 5 patients, which could provide utility for direct targeting in DBS surgery (Figure 1).

The MFB (Figure 2) interconnects various centers of the reward pathway, including the NAcc, ventral tegmental area (VTA), hypothalamus, and amygdala. The VTA is central to the processing of inputs from various parts of the brain to generate motivated behavior based on reward designation and is believed to be dysfunctional in patients with MDD. Therefore, it stands to reason that stimulation of the MFB may alter the function of the VTA, leading to improvement in mood. This hypothesis has undergone preliminary testing in Germany, where 7 patients underwent bilateral DBS implantation of the superolateral branch of the medial forebrain bundle (sLMFB), a structure with proven convergence on the prefrontal cortex and close functional connection to the anterior limb of the internal capsule and the NAcc. Preliminary results show that 6 of 7 patients studied achieved a 50% decrease in the Montgomery-Asberg Depression Rating Scale, a very encouraging result so far.

Figure 1. Diffusion tensor imaging of the stria medullaris in axial (A), sagittal (B), and coronal (C) views.

The Role of Rush University Medical Center

The departments of neurological surgery, neurological sciences, and psychiatry at Rush are at the forefront of researching new and evolving uses of DBS. In addition to efforts targeting the LHb via the stria medullaris using MRI tractography, Rush is also currently recruiting patients with refractory MDD for treatment with DBS targeting the sLMFB in a randomized, blinded, placebo-controlled trial.

Study Design

Twenty patients age 18 to 70 years with refractory MDD will be identified by the Department of Psychiatry at Rush. Those included in the study must carry the diagnosis of MDD as defined by DSM-IV (Diagnostic and Statistical Manual of Mental Disorders, 4th ed) standards. Symptoms must be present for greater than 2 years, with a current episode lasting longer than 12 months. Standardized Hamilton Depression Rating Scale (HDRS) and computerized adaptive testing (CAT) will be used for inclusion criteria, and all patients must have exhausted trials of at least 3 antidepressants used independently or in combination with each other. Lifetime failure or intolerance of electroconvulsive therapy is also required. Both patients with bipolar disorder and those with MDD will be included.

Excluded from the study are those with concomitant nonaffective psychiatric disorders such as schizophrenia,
schizoaffective disorder, or personality disorders. Organic neurologic disorders such as dementia, stroke, or medical illness affecting brain function will preclude enrollment in the study. Additionally, previous brain surgery or abnormal preoperative cranial imaging will negate enrollment.

Initial baseline testing will take place 3 weeks after DBS implantation within the sMFB. Patients will be randomized into 2 groups (10 patients each). The DBS system will be turned on for 1 cohort and kept off for the other cohort, and no changes will be made over a 6-month period during the blinded evaluation phase. Following the blinded evaluation phase, the open-label phase, during which all patients will have their DBS system turned on and settings optimized over an 18-month period, will ensue.

**Outcome Measures**

The primary outcome measure will be evaluated by CAT scoring, which will be used to record response and remission rates. Response to stimulation will be defined as a CAT severity score of moderate or better, while remission will be defined as a severity score of mild or better. Secondary outcome measures will be defined by HDRS scoring. A response in HDRS measures will be defined as a 50% change in HDRS score compared with the baseline score. Remission will be defined as an HDRS score of 8 or less at the end point.

**Conclusions**

Treatment-refractory MDD is a common clinical occurrence with debilitating symptomatology. A variety of stimulation targets exist for select patients with refractory MDD. At Rush, the departments of neurological surgery, neurological sciences, and psychiatry are changing the way MDD is managed and will continue to do so in the prospective, randomized clinical trial of DBS of the sMFB.

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*Figure 2.* Diffusion tensor imaging of the medial forebrain bundle in axial (A), sagittal (B), and coronal (C) views.
References


OUTCOME FOLLOWING INTRACRANIAL HEMORRHAGE ASSOCIATED WITH NOVEL ORAL ANTICOAGULANTS

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Introduction

Anticoagulants are frequently used for various indications, including prevention of venous thromboembolism after orthopedic surgery, treatment of acute venous thromboembolism, and prevention of arterial thromboembolism in atrial fibrillation.1-3 Warfarin has been the most commonly prescribed anticoagulant to treat and prevent thrombosis for many decades. Three novel oral anticoagulants (NOAC), dabigatran, rivaroxaban, and apixaban, have recently been approved by the US Food and Drug Administration for the prevention of arterial thromboembolic events in nonvalvular atrial fibrillation as an alternative to warfarin.4-6 As the use of these NOAC increases over time, neurosurgeons will be confronted with managing patients receiving these medications more often, secondary to the risk of development of intracranial hemorrhage (ICH) while on these NOAC.7 We report our experience in 2 patients who sustained ICH while on NOAC, along with a review of the literature.

Case Descriptions

Patient 1

An 83-year-old man presented with acute onset of weakness for 1 day. Computed tomography (CT) scan of the head revealed an ICH involving the left basal ganglia (Figure 1). Past medical history was significant for well-controlled hypertension and nonvalvular atrial fibrillation.1-3 Warfarin has been the most commonly prescribed anticoagulant to treat and prevent thrombosis for many decades. Three novel oral anticoagulants (NOAC), dabigatran, rivaroxaban, and apixaban, have recently been approved by the US Food and Drug Administration for the prevention of arterial thromboembolic events in nonvalvular atrial fibrillation as an alternative to warfarin.4-6 As the use of these NOAC increases over time, neurosurgeons will be confronted with managing patients receiving these medications more often, secondary to the risk of development of intracranial hemorrhage (ICH) while on these NOAC.7 We report our experience in 2 patients who sustained ICH while on NOAC, along with a review of the literature.

Case Descriptions

Patient 1

An 83-year-old man presented with acute onset of weakness for 1 day. Computed tomography (CT) scan of the head revealed an ICH involving the left basal ganglia (Figure 1). Past medical history was significant for well-controlled hypertension and nonvalvular atrial fibrillation for which he was receiving rivaroxaban 20 mg daily, the last dose being taken about 12 hours prior to the onset of symptoms. Neurological examination at presentation was within normal limits except for a subtle right-sided pronator drift. Laboratory analysis showed serum creatinine, prothrombin time/international normalized ratio (PT/INR), and activated partial thromboplastin time (APTT) to be within normal limits. He was immediately treated with factor VIII inhibitor bypassing activity (FEIBA) 30 international units/kg in consultation with a hematologist and monitored in the neuroscience intensive care unit. Repeat CT scan performed 24 hours after admission showed no expansion in the size of the hematoma with stable neurological exam. He was subsequently discharged home and was doing well at last follow-up at 3 months.

Patient 2

An 80-year-old man with a significant past medical history of deep vein thrombosis on dabigatran 150 mg every 12 hours presented to an outside hospital after 2 days of altered mental

Figure 1. Axial noncontrast CT scan of the head showing an acute hemorrhage in the left thalamus measuring 2×1 cm in axial section with no significant mass effect or midline shift (A). Repeat CT scan done after 24 hours demonstrating stable hemorrhage (B).
status and right-sided weakness. He was taking dabigatran as prescribed, with the most recent dose taken the morning of presentation. CT scan of the head showed a left-sided acute-on-chronic subdural hematoma (SDH) with significant mass effect and midline shift (Figure 2). Laboratory analysis showed serum creatinine within normal limits with PT, INR, and APTT on admission being 14.8 seconds (normal range, 9.5-13.2 seconds), 1.48 (normal range, 0.8-1.2), and 45.8 seconds (normal range, 23-33 seconds) respectively. Surgical treatment was deemed appropriate, but because he recently took dabigatran, it was deferred considering his good neurological examination apart from minimal right pronator drift. The family was informed about the risk and benefits, and a collective decision to delay the surgery (reserving it for acute deterioration) was made. He was closely monitored in the neuroscience intensive care unit with repeat CT scan of the head performed at 6 and 24 hours after admission showing stable SDH (Figure 2) with no worsening of neurological examination. Because he was more than 96 hours out from his last dose of dabigatran and his PT/INR and APTT normalized, surgery was performed with successful removal of the SDH through a mini craniotomy. Excessive bleeding was not encountered during surgery, and hemostasis was achieved without difficulty. Throughout the inpatient stay, he did not experience neurological deterioration attributable to rebleeding, and subsequent postoperative CT scans showed good decompression with resolution of the mass effect and midline shift. However, he experienced a prolonged postoperative recovery and required a tracheostomy because he could not be weaned off the ventilator. He was finally transferred to a nursing home.

Discussion

Neurosurgeons and neurointensivists are frequently involved in the management of anticoagulant-related ICH. Pharmacologic strategies are available to reverse the effect of traditional anticoagulants such as warfarin, unfractionated heparin, and low-molecular-weight heparin, which may improve the overall outcome by reducing hematoma expansion, related mass effect, and midline shift.12,8 This may involve reversal with fresh frozen plasma, phytonadione, prothrombin complex concentrates (PCC), and recombinant activated factor VII (rVIIa). Regardless of the availability of reversal agents and their efficacy in reversing the anticoagulation effect of warfarin, reversal of anticoagulation may not always translate to good clinical outcome, which is probably related to the severity of initial hemorrhage.9 Likewise, even though platelets are often administered in patients who sustain ICH on antiplatelet agents such as aspirin and clopidogrel, there is no true antidote for these agents either. As compared to warfarin, where reversal strategies for preventing expansion of ICH in the event of bleeding are well defined, pharmacologic strategies to reverse NOAC in cases of life-threatening hemorrhage are lacking and experience is limited mostly to animal studies, in vitro studies, and case reports.2,10-21 In addition, coagulation assays used to confirm the anticoagulant effect of NOAC are limited to clinical studies and not commercially available at this time.22 This makes it very difficult to confirm the effect of the various pharmacologic agents used to reverse these agents in clinical practice.

Upon our review of all the reported cases of NOAC-associated ICH at the time of writing (total 18 patients, including this study), there were 7 deaths, leading to an overall mortality rate of 39% (7 of 18 patients).10,12,13,16,19-21 Previous reports have focused mainly on dabigatran-associated hemorrhages. The management of these patients who sustained ICH while on dabigatran varied among institutions and reflects the problems associated with incomplete dabigatran reversal (Table 1). Even though various pharmacologic agents such as PCC and rVIIa have been administered to patients who sustained a dabigatran-associated ICH, it is unknown whether they are effective in fully reversing the anticoagulant effect of dabigatran.10,12,13,20,23 Dialysis is an alternative for drug clearance and can remove approximately 35% to 60% of the drug in 2 to 3 hours and at present may be the only option to enhance the removal of
However, it is not proven whether patients with normal renal function should undergo hemodialysis to expedite clearance of dabigatran. Since the patient receiving dabigatran was conscious with very subtle pronator drift and had normal renal function, we elected not to proceed with the emergent surgery to allow time for dabigatran to be fully excreted. The use of dabigatran did delay the surgery in this case and could have precipitated an adverse outcome if the hematoma expanded with subsequent deterioration of the neurological examination.

On the other hand, there is growing evidence that PCC may be beneficial and have been found to reverse the anticoagulant activity of rivaroxaban. Our patient receiving rivaroxaban prior to admission was treated with FEIBA, which may have contributed to his favorable outcome. He maintained his neurological examination status throughout the hospital stay without evidence of hematoma expansion on serial imaging at 6 and 24 hours and was discharged home.

### Table 1. Summary of Reported Cases of Intracranial Hemorrhage in Patients Treated With Novel Oral Anticoagulants

<table>
<thead>
<tr>
<th>No.</th>
<th>Authors (Year)</th>
<th>Age/Sex</th>
<th>Anticoagulant</th>
<th>Type of ICH</th>
<th>Reversal Strategy</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Garber et al (2012)</td>
<td>83/M</td>
<td>Dabigatran</td>
<td>Parenchymal/subdural/subarachnoid</td>
<td>rFVIIa</td>
<td>Death</td>
</tr>
<tr>
<td>2</td>
<td>Chen et al (2012)</td>
<td>80/M</td>
<td>Dabigatran</td>
<td>Subdural</td>
<td>Phytonadione</td>
<td>Stable hemorrhage</td>
</tr>
<tr>
<td>3</td>
<td>Chang et al (2013)</td>
<td>94/M</td>
<td>Dabigatran</td>
<td>Subdural</td>
<td>FEIBA, hemodialysis</td>
<td>Stable hemorrhage</td>
</tr>
<tr>
<td>4</td>
<td>Awad et al (2013)</td>
<td>85/F</td>
<td>Dabigatran</td>
<td>Subdural</td>
<td>Hemodialysis attempted</td>
<td>Surgery due to hemorrhage expansion; neurologically intact at discharge</td>
</tr>
<tr>
<td>5</td>
<td>Faust and Peterson (2014)</td>
<td>85/M</td>
<td>Dabigatran</td>
<td>Parenchymal</td>
<td>FEIBA</td>
<td>Death secondary to ischemic stroke; hemorrhage stable</td>
</tr>
<tr>
<td>6</td>
<td>Wassef et al (2013)</td>
<td>79/F</td>
<td>Dabigatran</td>
<td>Parenchymal</td>
<td>None</td>
<td>Death secondary to expansion of hemorrhage</td>
</tr>
<tr>
<td>7</td>
<td>Wassef et al (2013)</td>
<td>72/M</td>
<td>Dabigatran</td>
<td>Chronic subdural</td>
<td>None</td>
<td>Surgery; discharged home</td>
</tr>
<tr>
<td>8</td>
<td>Wassef et al (2013)</td>
<td>72/M</td>
<td>Dabigatran</td>
<td>Subarachnoid</td>
<td>None</td>
<td>Stable hemorrhage; discharged home</td>
</tr>
<tr>
<td>9</td>
<td>Ross et al (2014)</td>
<td>NR</td>
<td>Dabigatran</td>
<td>NR</td>
<td>None</td>
<td>Stable hemorrhage; discharged home</td>
</tr>
<tr>
<td>10</td>
<td>Ross et al (2014)</td>
<td>NR</td>
<td>Dabigatran</td>
<td>NR</td>
<td>FFP, platelets</td>
<td>Death</td>
</tr>
<tr>
<td>11</td>
<td>Ross et al (2014)</td>
<td>NR</td>
<td>Dabigatran</td>
<td>NR</td>
<td>None</td>
<td>Stable hemorrhage; discharged home</td>
</tr>
<tr>
<td>12</td>
<td>Ross et al (2014)</td>
<td>NR</td>
<td>Dabigatran</td>
<td>NR</td>
<td>FFP, platelets, dialysis</td>
<td>Surgery; death</td>
</tr>
<tr>
<td>13</td>
<td>Ross et al (2014)</td>
<td>NR</td>
<td>Dabigatran</td>
<td>NR</td>
<td>None</td>
<td>Stable hemorrhage; discharged home</td>
</tr>
<tr>
<td>14</td>
<td>Ross et al (2014)</td>
<td>NR</td>
<td>Dabigatran</td>
<td>NR</td>
<td>FFP, vitamin K, rFVIIa, dialysis</td>
<td>Surgery; death</td>
</tr>
<tr>
<td>15</td>
<td>Ross et al (2014)</td>
<td>NR</td>
<td>Dabigatran</td>
<td>NR</td>
<td>None</td>
<td>Stable hemorrhage; rehabilitation</td>
</tr>
<tr>
<td>16</td>
<td>Simonsen et al (2014)</td>
<td>75/M</td>
<td>Dabigatran</td>
<td>Parenchymal</td>
<td>None</td>
<td>Death due to hematoma expansion</td>
</tr>
<tr>
<td>17</td>
<td>Present study</td>
<td>83/M</td>
<td>Rivaroxaban</td>
<td>Parenchymal</td>
<td>FEIBA</td>
<td>Stable hemorrhage; discharged home</td>
</tr>
<tr>
<td>18</td>
<td>Present study</td>
<td>80/M</td>
<td>Dabigatran</td>
<td>Subdural</td>
<td>None</td>
<td>Surgery; rehabilitation</td>
</tr>
</tbody>
</table>

Abbreviations: F, female; FEIBA, factor VIII inhibitor bypassing activity; FFP, fresh frozen plasma; ICH, intracranial hemorrhage; M, male; NR, not reported; PCC, prothrombin complex concentrates; rFVIIa, coagulation factor VIIa (recombinant).
Conclusion

With the introduction of NOAC, the low risk of ICH provides a favorable alternative to warfarin. The use of NOAC comes with a greater risk for hematoma expansion and death if suitable reversal agents are not found. Current strategies to reverse the NOAC with PCC, fresh frozen plasma, and rVIIa are limited by the inability to measure their clinical effect with the available coagulation assays. The need to develop antidotes for NOAC and reliable laboratory tests to measure anticoagulation effects related to them cannot be overemphasized. Understanding the potential salvaging reversal strategies and knowledge of the outcome following ICH in patients receiving NOAC is of utmost importance for any practicing neurosurgeon and neurointensivist to envisage the expected outcome and prognosticate following this catastrophic event.

Conflict of Interest

The authors M.K.K., N.G.P., and L.F.M. have no disclosures or conflict of interest. R.W.B. is a consultant for Integra and Stryker. R.M. is a consultant for Covidien and Penumbra Inc. D.K.L. has financial and research relationships with Penumbra, Covidien, and Stryker.
References


Epilepsy is estimated to affect between 2.5 and 3 million people in the United States, with a prevalence of 5 to 10 persons per 1,000.1 It has been shown that about 47% of patients with a new diagnosis of focal-onset epilepsy are successfully treated with the first antiepileptic drug (AED) prescribed.2 Therapeutic failure of 2 AEDs is defined as drug-resistant epilepsy.3,4 Approximately 20% to 40% of patients with epilepsy are likely to have drug-resistant epilepsy.5-7 Patients with a unilateral lesion on high-resolution MRI that is concordant with the electroencephalography (EEG) findings and seizure semiology have the best outcomes after resection.8-10 Unfortunately, 20% to 30% of temporal lobe epilepsy (TLE) patients and 20% to 50% of extratemporal lobe epilepsy (ETLE) patients demonstrate the absence of an underlying lesion on high-resolution MRI.11-13 Lesional TLE patients have seizure-free rates (Engel Class I) of around 60% (at 1-year follow-up).3,14-16 In contrast, patients with nonlesional TLE have seizure-free rates (Engel Class I) ranging from 41% to 65% (at 2-year follow-up).14-16 Patients with nonlesional ETLE have the lowest seizure-free outcomes, ranging from 24% to 42% (at 2-year follow-up).17-22 A better understanding is necessary to evolve our approach toward recognizing the IOZ as a critical node in a larger epileptogenic network in order to achieve better seizure-free rates, particularly in nonlesional focal-onset epilepsy.

In the present study, we retrospectively analyzed the clinical history profiles including duration of epilepsy, video EEG (noninvasive and invasive) and MRI findings, subtraction ictal SPECT coregistered to MRI (SISCOM) data, seizure semiology, sites and sizes of resection, pathological findings, and postsurgical seizure outcomes in a cohort of patients with lesional and nonlesional ETLE and TLE. The aim of our study was to assess the positive predictive value of resecting SISCOM regions of transient hyperperfusion that were associated with the IOZ. Also, the long-term postsurgical outcomes in patients with both MRI-positive and MRI-negative ETLE and TLE were compared.

**Methods**

**Patients**

A total of 567 presurgical SPECT studies (243 patients) were performed at our center between 2002 and 2013. Our study included a cohort of 44 patients from this presurgical group who underwent resective epilepsy surgery. The mean age of the patients in our cohort was 29 years (range, 11-57 years; SEM, 1.8) (Table 1). Patients underwent follow-up for a mean of 5 years (range, 2-10 years). All patients in our cohort were assessed using chronic intracranial electrocorticography (ECoG) monitoring and/or acute intraoperative electrocorticography (aECoG). The placement of the electrodes for invasive monitoring was determined during the epilepsy surgery management conference at our institution. Multiple factors were analyzed to generate the hypothesis for intracranial electrode placement and targeting the IOZ. To facilitate localization of the IOZ, we employed seizure semiology, MRI,
chronic noninvasive scalp video-EEG monitoring, magnetoencephalography, SISCOM, positron emission tomography, and neurocognitive testing (Table 2).

We included patients based on the following inclusion criteria: (1) diagnosis of drug-resistant, focal-onset epilepsy based on the presurgical evaluation that included SISCOM; and (2) resective epilepsy surgery performed with a postoperative follow-up of at least 24 months (mean follow-up, 5 years). The predominant reasons for exclusion from the study were (1) patient underwent less than 24 months of follow-up (except patients who remained as Engel Class IV), or (2) no interictal SPECT was acquired. Forty-four patients met all of the inclusion criteria and were analyzed in this study. One ETLE patient in the study had undergone a previous resection prior to a second resection. In 25 patients (61%), postresection MRI was performed. Preresection subtraction ictal SPECT was coregistered to the patient's postresection MRI study, which was acquired at least 12 months postoperatively. This strategy was used to determine the regions of transient hyperperfusion in comparison with the extent of resection.

### High-Resolution MRI

High-resolution, gapless, pregadolinium and postgadolinium, volumetric, spoiled gradient recalled (SPGR) MR images of the brain were obtained for each patient. The MRI examination was performed using a 1.5-T or 3-T scanner (Siemens). A gapless, SPGR, T1-weighted sequence data set for each patient was acquired at a slice thickness of 1.0 or 1.6 mm.

### Noninvasive Video-EEG Monitoring

Chronic, noninvasive video-EEG monitoring was performed in each patient using the International 10-20 system for electrode placement, including anterior temporal and sphenoidal electrodes if appropriate. AEDs were lowered during chronic monitoring, all patients were electrographically monitored to record the typical seizures, and video recordings were generated to monitor semiology.

### SISCOM

SPECT was performed on each patient during video-EEG monitoring using Cerecet (Tc-HMPAO) or Neurolite (Tc-ECD) at a dose of 24 to 26 mCi (adjusted for body weight). The radiotracer was injected for the ictal SPECT studies with an autoinjector (MedRad) used by a specially trained nuclear medicine technologist (V.P.) while at the patient's bedside during seizure onset. The technologist was trained to inject at the clinical and/or electroencephalographic seizure onset, whichever came first. The seizure-onset and ending times were always noted. Also, the time from the beginning of injection up to the complete depression of the syringe plunger was noted. We retrospectively calculated the time of the radiotracer injection following seizure onset by reviewing the video-EEG recordings for all patients. To avoid injection during the postictal state, a minimum of 15 seconds was required between the end of radiotracer injection and the end of the seizures, as described above. Baseline SPECT was obtained by performing an interictal injection after a seizure-free period of at least 24 hours. Brain SPECT scans were obtained within 2 hours after injection using a Siemens E.CAM Dual-Detector gamma camera with BiOCORE fan beam collimators. Thirty-two views per detector (total 64) were acquired using 80 000 counts per view, circular orbit, and “step and shoot” mode. Images were reconstructed by Synogy Siemens AG software using a 128x128 matrix with a Butterworth filter. DICOM isotropic datasets with a voxel size of 3.9 mm were created and transferred to Analyze software (AnalyzeDirect). Analyze version 10 was used to perform ictal and interictal SPECT thresholding, normalization, subtraction, and coregistration to the patient's MRI study. Finally, the brain was segmented from the extracerebral structures, as identified on the patient’s volumetric MRI study. The cerebral surface of the binary ictal SPECT was matched to the cerebral surface of the binary MRI. The resulting registered transformation matrix was then applied to the subtraction SPECT data set in order to coregister it to the processed MRI study. Complete, gapless, SISCOM image sets were presented to a blinded, board-certified epilepsy neurologist (M.A.R.), who determined the SISCOM region of transient hyperperfusion for each patient in this study.

### Invasive Recording

The ECoG electrode placement plan (subdural grid electrodes and/or depth electrodes) was confirmed using head CT. In 41 patients, chronic bedside ECoG monitoring was performed to investigate the clinical electrocerebral IOZ based on the patient’s stereotypic seizure. For 3 patients, aECoG monitoring alone provided enough information to establish the IOZ.
A pathological diagnosis of the resected specimens, such as gliosis, focal cortical dysplasia, heterotopias, tumor, or mesial temporal sclerosis, was determined for 38 of 44 patients (86%) (Table 2).

Postoperative Seizure Outcomes

Postoperative outcomes were determined by following 38 patients for a period greater than 24 months (mean follow-up, 5 years; range, 2-10 years) after resection. We classified the postresection outcomes into 4 classes and subclasses according to Engel’s classification (Table 3). At the time of our analysis, 5 patients in our study received a follow-up period of 17 to 18 months. However, these patients remained classified as Engel Class IV. One of the patients in our study was observed for only 12 months. However, this patient remained Engel Class IVc (no worthwhile improvement, worsening of seizures after surgery).

Postresection MRI

We obtained postresection MRIs for 34 of 44 patients (77%). We coregistered the preresection SISCOM on postresection MRI in order to evaluate the extent of resection of the identified SISCOM region of hyperperfusion. Using traditional SISCOM processing with Analyze, we could not achieve accurate registration of the preresection SISCOM signals on the postresection MRI studies for all patients. Postresection MRI findings were considerably different from preresection MRI findings because of the creation of new cortical boundaries, particularly in the area of resection. In addition, the craniotomy flap altered the skull shape in some patients. Consequently, clean object extraction could not be achieved in several postresection MRI data sets, resulting in poor registration. To solve this problem, we employed a different postprocessing method. We performed 3-dimensional voxel registration using Analyze between the original fused preresection SISCOM, which was used as the base, and the postresection MRI, which was used as the match. We first performed manual registration to achieve similar alignment in all 3 planes (transverse, coronal, and sagittal). We then performed autoregistration using the register tab in the 3-dimensional voxel registration window in Analyze. This process perfectly aligned the 2 3-dimensional objects, so that the each voxel in the new fused image represented the same voxel of the base (preresection SISCOM) and match (postresection MRI).

The intensities of the base and match were modified as follows. The minimum intensity of the base image was increased in order to make the preresection MRI disappear and reduce the maximum of the base in order to improve the SPECT signal. This technique prevented the preresection brain tissue boundary from filling the resection site. Thus, the fused image demonstrated the properties of the SPECT signal of the base, but not the MRI properties of the base. Lastly, we reduced the maximum intensity of the match to intensify the postresection MRI. This technique enabled us to better visualize the resection site. This process resulted in the accurate

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**Figure 1.** Classification hierarchy of patient outcomes after resective epilepsy surgery. Three main groups are represented: (1) subtraction ictal SPECT coregistered to MRI (SISCOM) concordant with electrocorticography (ECoG) and overlapping with the resection site; (2) SISCOM nonconcordant with ECoG and nonoverlapping with the resection site in temporal lobe epilepsy (TLE) patients; and (3) SISCOM nonconcordant with ECoG and overlapping with the resection site. aECoG, acute intraoperative electrocorticography.
Table 2. Clinical Data of All Patients Included in the Study

<table>
<thead>
<tr>
<th>Pt No.</th>
<th>Age/y/</th>
<th>Sex</th>
<th>Side</th>
<th>Duration of Epilepsy</th>
<th>MRI Finding</th>
<th>Pathology</th>
<th>Scalp EEG</th>
<th>ECoG Onset</th>
<th>Injection Time, s</th>
<th>No. of Seizures During Injection</th>
<th>SISCOM Focus</th>
<th>Surgery</th>
<th>ECoG/ SISCOM Concordance</th>
<th>Complete Partial Resection</th>
<th>Outcome (Engel Class)*</th>
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<td>(1) SFG, MFG, sparing lt MFG; (2) lt anterior frontal</td>
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<td>Rt mesiofrontal</td>
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<td>11</td>
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<td>cyst</td>
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<td>Ischemia or denyelination</td>
<td>NA</td>
<td></td>
<td>Rt frontal, lt post quadrant</td>
<td>Rt mesial frontal</td>
<td>9</td>
<td>4</td>
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<td>MSt, leg area over to the lateral convexity rt frontal</td>
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<td>Rt mesiofrontal, also bilat frontal spikes</td>
<td>129</td>
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<td>Lt dorsolateral frontal</td>
<td>Rt frontal-SFG using bipolar &amp; resection</td>
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<td>Age</td>
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<td>Laterality</td>
<td>Lesion Site</td>
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<td>Surgical Outcome</td>
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<tr>
<td>33</td>
<td>41M</td>
<td>Rt</td>
<td>Rt temp, rt occipital, &amp; rt parietal FCD</td>
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<td>Rt parietal quadrant</td>
<td>28 2</td>
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<td>Rt</td>
<td>Lt temp tumor</td>
<td>Old hemorrhage</td>
<td>Lt temp, rt frontal</td>
<td>76 5</td>
<td>Rt STG</td>
<td>(1) Lt temp; (2) Rt neurospace concordant w/ SISCOM</td>
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<td>Rt</td>
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<td>13 5</td>
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Abbreviations: aECoG, acute intraoperative electrocorticography; AHC, amygdalohippocampectomy; ant, anterior; bilat, bilateral; ECoG, electrocorticography; FCD, focal cortical dysplasia; H, hemisphere; HE, hippocampus; IFG, inferior frontal gyrus; ITG, inferior temporal gyrus; Lt, left; MFG, middle frontal gyrus; midpost, midposterior; MST, multiple subpial transection; MTG, middle temporal gyrus; MTS, mesial temporal sclerosis; NA, not available; NR, not resected; post, posterior; pt, patient; rt, right; SFG, superior frontal gyrus; SISCOM, subtraction ictal SPECT coregistered to MRI; STG, superior temporal gyrus; temp, temporal.

* Engel classification: Ia, completely seizure free since surgery; Ib, nondisabling, simple partial seizures only after surgery; Ic, some disabling seizures after surgery, but free of disabling seizures for at least 2 years; IId, generalized convulsions with antiepileptic drug discontinuation only; IIa, initially free of disabling seizures, but has rare seizures now; IIIa, worthwhile seizure reduction; IIIb, prolonged, seizure-free intervals amounting to greater than half of the follow-up period, but for less than 2 years; IVa, significant seizure reduction; IVb, no appreciable change; IVc, seizures worse after surgery.

Analysis and Statistics

Concordance was determined between SISCOM localization and ECoG on the basis of an overlapping IOZ and called "concordance with the ECoG." Concordance was also determined between SISCOM localization and the resection site, or "concordance with the resection site." Two different concordance types are designated since resection usually involves a larger area than the IOZ, as determined by ECoG. Strict concordance criteria were used, where greater than 90% of the resected area must overlap with the SISCOM signal to be considered concordant. Concordance was determined by a blinded, board-certified epilepsy neurologist (M.A.R.).

We coregistered preresection and subtracted ictal SPECT on postresection MRI to determine if the SISCOM signal was completely or partially removed. We determined if complete or partial resection impacted postoperative outcomes.

Our cohort of 44 patients underwent resective epilepsy surgery. All patients underwent follow-up for at least 2 years (mean follow-up, 5.0 years; range, 2-10 years). Five patients received only 17 to 18 months of follow-up at the time of our analysis, but these patients demonstrated Engel Class IV outcomes. One of the patients completed a follow-up of only 12 months, but achieved Engel Class Ivc. The mean radiotracer injection time for all patients was 45 seconds (SEM, 11.4) after electrocerebral seizure onset. In our cohort, all SPECT studies were performed during the patient’s stereotypic seizures, as measured electrographically or clinically.

Results

ECoG Monitoring

ECoG concordant tissue was completely resected from all 44 patients. Of these 44 patients, 24 of 44 (55%) became seizure free (Engel Class I) after at least 2 years of follow-up after resection.

SISCOM Concordance

SISCOM was concordant with ECoG and the resection site in 32 of 44 patients (73%), and 20 of these 32 (63%) became seizure free (Engel Class I after greater than 2 years of follow-up). Of these, 32 patients, 19 of 32 (59%) had ETLE and 13 of 32 (41%) had TLE (Figure 1). The mean injection time was 46 seconds in the SISCOM ECoG concordant group (SEM, 14.5).
SISCOM Concordant ETLE Group

In 19 ETLE patients with concordant SISCOM and ECoG results, ECoG delineated the epileptogenic source or focus, which was completely resected in all patients; 11 of 19 patients (58%) became seizure free (Engel Class I) (Table 3).

Among these 19 ETLE patients, 8 patients exhibited a lesion on MRI (focal cortical dysplasia, tumor, double cortex, or encephalomalacia). Only 6 of these 8 patients exhibited an MRI lesion and SISCOM focus that were both concordant with the ECoG results; only 3 of these 6 patients (50%) became seizure free (Engel Class I) (Table 3).

Also, among these 19 ETLE patients, 11 patients were MRI negative for lesions. For these patients, SISCOM facilitated the placement of the intracranial electrodes; 7 patients (64%) became seizure free (Engel Class I) (Table 3).

SISCOM Concordant TLE Group

In the 13 TLE patients with concordant SISCOM and ECoG results, the indicated ECoG focus was completely resected; 9 of 13 patients (69%) became seizure free (Engel Class I) (Table 3).

Among these 13 TLE patients, 11 patients had a lesion (mesial temporal sclerosis, focal cortical dysplasia, or tumor) on MRI.
Only 8 of these 11 patients demonstrated an MRI lesion and SISCOM focus that were both concordant with the ECoG results; 7 of these 8 patients (88%) became seizure free (Engel Class I) (Table 3).

Also, among these 13 TLE patients, 2 patients were MRI negative. For these patients, SISCOM guided the placement of the intracranial electrodes; 1 patient (50%) became seizure free (Engel Class I) (Table 3).

Nonconcordant Group

SISCOM was nonconcordant with ECoG but overlapped with the resection site in only 1 of 44 patients. This patient was diagnosed with nonlesional ETLE but did not have a lesion on MRI. This patient demonstrated a worse outcome after resection and achieved Engel Class IV (greater than 2 years of follow-up, Figure 1).

SISCOM was nonconcordant with ECoG and nonoverlapping with the resection site in 11 of 44 patients (Figure 1). In the nonconcordant group, 4 of 11 patients (36%) achieved Engel Class I, 1 of 11 patients (9%) achieved Engel Class II (rare disabling seizures), 2 of 11 patients (18%) achieved Engel Class III (worthwhile improvement), and 4 of 11 patients (36%) achieved Engel Class IV. All of these 11 patients exhibited lesions on MRI (Table 4).

For the SISCOM nonconcordant group, the average injection time was 37 seconds (SEM, 11.3).

Resection of SISCOM Focus

We coregistered the preresection subtraction ictal SPECT to each patient’s postresection MRI in order to determine if the SISCOM signal(s) used to guide the placement of the intracranial electrodes preresection was completely, partially, or not resected. A 10% shifting of the adjacent brain postresection was assumed in the postresection MRI coregistrations. Postresection MRI studies were completed in 35 of 44 patients (80%). Complete resection of the SISCOM signal was found in 7 of 34 patients (21%). Of these 7 patients, 5 patients (72%) were seizure free (Engel Class I). Partial resection of the SISCOM signal was found in 16 of 34 patients (47%); 10 of these 16 patients (62%) were seizure free (Engel Class I) after more than 24 months of follow-up (Table 5).

The SISCOM signal was not resected in 11 of 34 patients (32%). Four of these 11 patients (36%) were seizure free (Engel Class I) after more than 24 months of follow-up.

Pathology

The pathological findings (gliosis and focal cortical dysplasia) were not significantly correlated with the outcomes of epilepsy surgery ($P=.1007$; Table 2).

Discussion

The success of epilepsy surgery depends on the accurate anatomical localization of the IOZ, which is indispensable to contributing to favorable outcomes. The IOZ is a component of the ictal circuitry that is critically involved in the initiation of seizures. Scalp EEG and semiology are often not sensitive enough to accurately delineate the IOZ in rapidly propagating seizures. Consequently, the development of novel neuroimaging approaches is required to facilitate visualizing the IOZ, particularly in patients with ETLE. SISCOM can help identify the IOZ, though its limitations as an indirect measure of increased metabolic demand in the nearby epileptogenic cortex must be kept in mind. The probability of seizure freedom in our cohort is highest for lesions identified on MRI. Patients with MRI findings showing lesions in 1 temporal lobe that are concordant with ipsilateral ictal activity on EEG have the highest rate of seizure freedom after resective epilepsy surgery.8,9 In our cohort, 7 patients demonstrated underlying lesions in 1 temporal lobe (predominantly mesial temporal sclerosis), and a concordant abnormality on scalp EEG was noted in 6 of these patients; all 7 of 7 patients (100%) achieved Engel Class I with longer than 3 years of follow-up (mean follow-up, 4.9 years).
SISCOM was concordant with the resection site in 6 of 8 (75%) of these patients.

It has been previously shown that the probability of seizure freedom (Engel Class I) at the 12-month follow-up after surgery is 2.7 times higher in TLE patients with MRI lesions in comparison with TLE patients without MRI lesions. Moreover, the probability of seizure freedom (Engel Class I) at the 12-month follow-up after surgery is 2.9 times higher in ETLE patients with MRI lesions in comparison with ETLE patients without MRI lesions. SISCOM impacted our postresection outcomes in the nonlesional ETLE and TLE patient groups. Also, the complete or partial resection of the SISCOM region of transient hyperperfusion plays a role in seizure freedom; 5 of 7 patients (72%) were seizure free after complete resection of SISCOM hyperperfusion-related signaling, and 10 of 16 patients (63%) were seizure free after the partial resection of similar SISCOM signals. In our study, 6 patients exhibited SISCOM signal foci localized with the resection site; these patients demonstrated poor surgical outcomes (Engel Class IV), and at least 1 SISCOM region not overlapping with the resection site (Figure 2). Concordance between SISCOM and ECoG had a sensitivity of 72.7%, specificity of 100%, positive predictive value of 100%, and negative predictive value of 14.3%.

Improved outcomes were seen with earlier surgery for intractable frontal lobe epilepsy. In our study, the mean duration of frontal lobe epilepsy was 19.17 years. When the duration of frontal lobe epilepsy was less than 5 years, 75% became seizure free (n=4; 3 MRI lesion-positive patients and 1 MRI lesion-negative patient) (Engel Class I, mean year of follow-up postresection, 7.7 years; range, 6-10 years; SD, 2.08). However, when the duration of frontal lobe epilepsy was at least 5 years, 59% became seizure free (n=17; 7 MRI lesion-positive and 10 MRI lesion-negative patients) (Engel Class I, mean year of follow-up postresection, 7.3 years; range, 3-11; SD, 2.8).

According to previously published success rates for partial frontal lobectomy, favorable outcomes (Engel Class I) range from 15% to 35% in these trials. The only variable that was significantly associated with a favorable surgical outcome was a focal MRI abnormality in frontal lobe epilepsy. Elsharkawy et al published a retrospective study investigating 97 patients with lesional frontal lobe epilepsy who underwent
This study reported the seizure freedom rates (Engel Class I) to be 54.6% at 6 months, 49.5% at 2 years, 47% at 5 years, and 41.9% at 10 years. In yet another series, 41% of nonlesional TLE patients showed excellent outcomes versus 72% when an MRI abnormality was present. Previous studies that report favorable (Engel Class I) outcomes investigated patients with frontal lobe tumors or focal cortical dysplasias. Other factors that predict seizure recurrence include incomplete resection of the epileptogenic lesion, predominantly generalized or poorly localized ictal EEG patterns on surface EEG, the lack of a subdural grid evaluation, acute postresection seizures, postoperative persistence of prolonged auras, history of febrile seizures, and the lack of a distinct MRI lesion.

The SISCOM results in our study patients influenced the planning of intracranial electrode placement. Therefore, our ECoG results were, in part, influenced by our SISCOM data. Also, all patients in our cohort underwent SISCOM as part of the presurgical evaluation. Therefore, potential selection bias toward patients with more localizable IOZ has to be regarded, and consequently resulted in more favorable postresection outcomes.

**Conclusions**

The goal of resective epilepsy surgery is long-term seizure freedom (Engel Class I or II). Seizure outcomes are time dependent and dynamic. All prognostic factors converge into one central theme: an epileptogenic zone that is well visualized and also electrically and semio logically restricted, in that its extent offers the best chance of seizure freedom when resected completely. However, SISCOM provides an indirect measure of localizing the IOZ, which often coincides with the critical nodes within the epileptogenic network.

These data confirm previous studies that demonstrate the utility of SISCOM by improving the outcomes of drug-resistant, focal-onset epilepsy in both ETLE and TLE patients. Concordance between SISCOM and ECoG and/or aECoG in this refractory epilepsy cohort provide useful additional information for predicting postresection outcomes. In addition, the limitations in SPECT scanner technology may contribute to the sensitivity of SISCOM for identifying the maximal extent of the critical nodes or the generators of the epileptogenic circuit. The predominant limitation of conventional SPECT technology is the voxel resolution, which is limited to 8 to 12 mm with inadequate attenuation correction. The limitations of the spatial resolution of SPECT are related to using only 2-head and 3-head photon detectors to record low-energy single-photon events. Next-generation SPECT scanner systems with significantly improved resolution and complementary postprocessing techniques will facilitate identifying a greater extent of critical nodes in the epileptogenic network. Such technology will augment guiding of ECoG electrode placement in potentially extensive epileptogenic networks.

**Conflict of Interest**

Dr Byrne reports that he is a consultant for Stryker and Integra.
References


Introduction

Cognitive impairment, including attention and working memory deficits, is frequently observed in Parkinson disease (PD). It is estimated that 78% of patients with PD will develop dementia. Treating cognitive impairment is a challenge given that it is often unresponsive to dopaminergic therapies. Recent work from the 90+ Study suggests that poor overall physical performance is a strong predictor of cognitive decline. The beneficial effects of exercise training on cognitive performance are well recognized in aging, as well as in individuals with dementia. In PD, preliminary research on the effects of exercise on cognition is promising, but long-term randomized controlled trials (RCTs) are needed.

Recently, the Progressive Resistance Exercise Training in PD (PRET-PD) trial reported that, compared to modified Fitness Counts (mFC), Progressive Resistance Exercise Training (PRET) reduced the off-medication motor section of the Unified Parkinson’s Disease Rating Scale (UPDRS-III) at the study endpoint of 24 months by 7.3 points. More recently, we also reported our findings associated with physical function, a secondary outcome. Here, we examine the cognitive domain and report the effect of mFC and PRET on cognitive outcomes related to attention and working memory. This article addresses the following questions at the 12-month and 24-month time points: Relative to baseline, does exercise improve cognitive function, and is one type of exercise modality better at improving cognitive function in mild-to-moderate PD? Because of the known benefits of exercise on cognitive performance, we hypothesized that exercise would improve cognitive function in mild-to-moderate PD.

Patients and Methods

Study Design and Participants

The PRET-PD trial was a prospective, parallel-group, single-center RCT between September 2007 and July 2011. Patients with idiopathic PD, confirmed by a movement disorders specialist, were self-referred or recruited from Rush University Medical Center (Chicago, IL). Patients were eligible if they were 50 to 67 years of age (the Physical Activity Readiness Questionnaire [PAR-Q], a screening tool used for exclusion, was only validated for use with persons younger than 69 years, the maximum age at study completion); on stable dopaminergic therapy; and able to walk for 6 minutes. Patients were ineligible if they had a neurological history other than PD; had significant arthritis; failed the PAR-Q; had a Mini–Mental State Examination score less than 23; were already exercising; or had deep brain stimulation surgery for PD. Patients were followed every 6 months for 24 months or until they withdrew from the study. Each participant provided written informed consent approved by the local institutional review boards.

Interventions

Details of the exercise intervention used in the PRET-PD trial have been published previously. In brief, the mFC was an exercise program recommended by the National Parkinson...
Foundation and focused on stretches, balance exercises, breathing, and nonprogressive strengthening (manual chapters 2 and 3). PRET was a weight-lifting program in which the load against which the muscle worked was systematically and progressively increased. The PRET program consisted of strengthening exercises that were directed at all the major muscle groups. The programs were identical in all aspects (duration of exercise, number of exercise sessions, and time with the personal trainer), except for the specific exercises. Patients participated in their respective interventions twice a week for 24 months. One-on-one exercise with a certified personal trainer was provided for both weekly exercise sessions during the first 6 months; the trainer-assisted sessions were reduced to once per week after 6 months. Patients in the mFC and PRET groups were instructed not to engage in additional exercise.

Study Procedures

All cognitive assessments were performed after 12-hour overnight withdrawal of dopaminergic medication by individuals trained in administering standardized cognitive assessments and blinded to group assignments at the clinical motor control laboratory at the University of Illinois at Chicago. Off-medication assessment was completed in the morning. The cognitive outcomes were one of many outcome domains tested; they were clinical status, the primary outcome, and bradykinesia and strength, tremor, physical function and gait, quality of life, and cognition, which were secondary outcomes. The order of testing was pseudorandomized between outcome domains and between cognitive outcomes. The off-medication testing session lasted for approximately 3 hours. It was followed by ingestion of antiparkinsonian medication, a break for lunch, confirmation of a clinical response to the medication, and then repetition of the entire testing procedure while on antiparkinsonian medication. In this article, we report findings related to the cognitive outcomes only while off medication for the following reasons: first, the effects of antiparkinsonian medication on cognitive outcomes are not well understood; second, antiparkinsonian medication could possibly mask the effects of exercise; and third, because on-medication testing was always conducted in the afternoon after off-medication testing in the morning, fatigue was a potential confound with respect to cognitive performance.

Cognitive Outcomes

The cognitive outcomes were the Digit Span Forwards and Backwards to assess working memory, which had a sum score that ranged from 0 to 30; the Stroop Color-Word Interference to measure selective attention and conflict resolution, which had a T score, a standardized normative metric, with a mean of 50 and a standard deviation (SD) of 10; and the Brief Test of Attention (BTA) to assess selective attention, which had a sum score that ranged from 0 to 20.

Follow-up

Patients in the mFC and PRET groups returned to the laboratory at 6, 12, 18, and 24 months for follow-up. The entire baseline assessment procedure was repeated at each follow-up visit.

Randomization and Blinding

The statistician matched the enrolled patients in pairs by sex and off-medication UPDRS-III scores and randomly assigned one member of each pair to PRET and the other member to mFC using a random-length permuted block design. Randomization resulted in a parallel-group design with a 1:1 allocation ratio. Patients started exercising within 1 month of randomization. Research personnel involved in data collection were blinded to group assignment. The patients knew their treatment assignment but were unaware of the study hypothesis and were explicitly instructed not to discuss their exercise program with the raters.
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<td>Right</td>
<td>22 (91.7)</td>
<td>23 (95.8)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left</td>
<td>2 (8.3)</td>
<td>1 (4.2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Clinical</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Years since diagnosis</td>
<td>6.5 ± 4.7</td>
<td>6.5 ± 4.1</td>
<td>0.0 (−2.5 to 2.6)</td>
<td>0.97c</td>
</tr>
<tr>
<td>MMSE</td>
<td>29.1 ± 1.4</td>
<td>29.3 ± 1.1</td>
<td>−0.2 (−0.9 to 0.5)</td>
<td>0.56c</td>
</tr>
<tr>
<td>Most affected side, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Right</td>
<td>17 (70.8)</td>
<td>13 (54.2)</td>
<td></td>
<td>0.37c</td>
</tr>
<tr>
<td>Left</td>
<td>7 (29.2)</td>
<td>11 (45.8)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Motor status</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unified Parkinson Disease Rating Scale, part III,</td>
<td>34.7 ± 11.5</td>
<td>34.5 ± 11.9</td>
<td>−0.2 (−7.0 to 6.6)</td>
<td>0.95c</td>
</tr>
<tr>
<td>motor subscale score (range, 0-108) (off medication)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hoehn and Yahr Staging Scale (disability; range, 0-5;</td>
<td>2 (2, 2.5)</td>
<td>2 (2, 2.5)</td>
<td>0 (0 to 0)e</td>
<td>0.85f</td>
</tr>
<tr>
<td>off medication)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Medication, n (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dopamine precursors</td>
<td>19 (79)</td>
<td>17 (71)</td>
<td></td>
<td>0.51d</td>
</tr>
<tr>
<td>Dopamine agonists</td>
<td>16 (67)</td>
<td>17 (71)</td>
<td></td>
<td>0.76d</td>
</tr>
<tr>
<td>Adjuncts</td>
<td>12 (50)</td>
<td>10 (42)</td>
<td></td>
<td>0.56d</td>
</tr>
<tr>
<td><strong>Cognitive outcomes, median (IQR)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Digit Span Forwards and Backwards Sum Score (range, 0-30;</td>
<td>17 (14.5, 19)</td>
<td>17 (15, 19.5)</td>
<td>0 (−2 to 2)e</td>
<td>0.84f</td>
</tr>
<tr>
<td>off medication)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stroop Color-Word Interference T Score (mean, 50;</td>
<td>47.5 (41, 53)</td>
<td>41 (33, 51)</td>
<td>−3 (−11 to 4)e</td>
<td>0.41f</td>
</tr>
<tr>
<td>SD, 10; off medication)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Brief Test of Attention Sum Score (range, 0-20;</td>
<td>16 (13, 18.5)</td>
<td>17 (13.5, 18)</td>
<td>0 (−2 to 2)e</td>
<td>0.75f</td>
</tr>
<tr>
<td>off medication)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; IQR, interquartile range; mFC, modified Fitness Counts; MMSE, Mini-Mental State Examination; PRET, Progressive Resistance Exercise Training.

a Plus-minus values are mean ± 1 SD.

b Representing significance of a test that was performed to determine if values were the same across the mFC and PRET groups.

c P values calculated using t test.

d P values calculated using chi-square test (expected cell count ≥ 5) or Fisher exact test (expected cell count <5).

e Hodges-Lehman estimate of location shift.

f P values calculated using Wilcoxon rank-sum test.
Statistical Analysis

All raw scores were converted to z scores. For the Digit Span and the Stroop, published norms were used to calculate z scores. For the BTA, the pooled baseline mean and SD was used to calculate z scores. To reduce type I errors, we used only the 12- and 24-month change from baseline z scores. The distributional assumptions for parametric testing were not met; therefore, nonparametric methods were used. The Wilcoxon rank-sum test was used to analyze the differences between the mFC and PRET groups at 12 and 24 months. The Wilcoxon signed-rank test was used to analyze change from baseline at 12 and 24 months. We also calculated correlations of changes in cognitive outcomes with changes in clinical and functional outcomes published previously. In addition, a sensitivity analysis using the last available observation carried forward (LOCF) was performed to evaluate the impact of missing data. Since these outcomes were not used to power the original RCT, we did not adjust the significance level for multiple outcomes. All statistical tests were 2-tailed, with \( P < .05 \) for statistical significance.

Results

Of the 51 patients enrolled, 46 patients (mFC, \( n = 23 \); PRET, \( n = 23 \)) completed the 12-month follow-up and 38 patients (mFC, \( n = 18 \); PRET, \( n = 20 \)) completed the 24-month follow-up. At baseline, the mFC and PRET groups did not differ on demographic, clinical, and cognitive outcomes (Table 1).

Difference Between mFC and PRET Groups at 12 and 24 Months

There were no differences between the mFC and PRET groups at 12 and 24 months on any of the cognitive outcomes measured in this study (Table 2).

Change From Baseline: The Effect in Each Intervention Arm at 12 and 24 Months

Digit Span Forwards and Backwards Sum Score

The mFC and PRET groups improved their Digit Span scores at 12 (mFC: estimated difference, 0.3; interquartile range [IQR], 0, 0.7; \( P = .04 \); PRET: 0.7; IQR, 0.3, 1; \( P < .01 \); Table 3; Figure 1A) and at 24 months (mFC: 0.7; IQR, 0.3, 1.7; \( P < .01 \); PRET: 0.5; IQR, 0.2, 0.8; \( P < .01 \); Table 3; Figure 1A).

Stroop Color-Word Interference T-Score

The mFC group improved performance on the Stroop at 12 months (mFC: 0.3; IQR, 0, 0.6; \( P = .04 \); Table 3; Figure 1B), whereas the PRET group presented with no change (0.2; IQR, −0.1, 0.8; \( P = .08 \); Table 3; Figure 1B). At 24 months, the mFC and PRET groups improved their Stroop scores (mFC: 0.3; IQR, 0.1, 0.5; \( P = .03 \); PRET: 0.2; IQR, −0.1, 0.6; \( P = .048 \); Table 3; Figure 1B).

Brief Test of Attention Sum Score

At 12 months, the mFC (0.3; IQR, −0.3, 1; \( P = .07 \); Table 3; Figure 1C) and the PRET (0; IQR, −0.3, 0.5; \( P = .11 \); Table 3; Figure 1C) groups did not change on the BTA. At 24 months, the mFC group remained unchanged, whereas the PRET group improved on the BTA (mFC: 0.1; IQR, −0.3, 0.8; \( P = .50 \); PRET: 0.3; IQR, 0, 0.8; \( P = .048 \); Table 3; Figure 1C).

Table 2. Difference Between Groups in Change From Baseline in Cognitive Outcomes at 12 and 24 Months

<table>
<thead>
<tr>
<th>Outcome</th>
<th>PRET vs mFC (95% CI)*</th>
<th>( P ) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Digit Span Forwards and Backwards (z score)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>12 mo</td>
<td>−0.3 (−0.7 to 0.3)</td>
<td>0.32</td>
</tr>
<tr>
<td>24 mo</td>
<td>0.3 (−0.3 to 1)</td>
<td>0.27</td>
</tr>
<tr>
<td>Stroop Color-Word Interference (z score)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>12 mo</td>
<td>0.1 (−0.5 to 0.5)</td>
<td>0.81</td>
</tr>
<tr>
<td>24 mo</td>
<td>0 (−0.4 to 0.5)</td>
<td>0.77</td>
</tr>
<tr>
<td>Brief Test of Attention (z score)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>12 mo</td>
<td>0 (−0.5 to 0.5)</td>
<td>0.77</td>
</tr>
<tr>
<td>24 mo</td>
<td>0 (−0.8 to 0.5)</td>
<td>0.83</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; mFC, modified Fitness Counts; PRET, Progressive Resistance Exercise Training.

*Hodges-Lehman estimate of location shift and \( P \) values calculated using Wilcoxon rank-sum test.
Associations of Change in UPDRS-III, Function, and Cognition

There were no significant relationships between change in the cognitive outcomes and the UPDRS-III. With respect to the relationships between change in cognitive outcomes and change in physical function outcomes, only the relationship between the Digit Span and walking speed was significant (rho=0.46, P=0.004).

In summary, there are 2 findings of importance at the study endpoint. First, there are no differences between mFC and PRET for all cognitive outcomes measured in this study. Second, the PRET and mFC groups presented with substantial within-group improvement in cognitive performance; that is, at 24 months, relative to baseline, the PRET group improved on all three of the cognitive outcomes (Digit Span, Stroop, and BTA) measured in this study, while the mFC group improved on two of the three cognitive outcomes (Digit Span and Stroop) measured in this study. These results did not change with LOCF sensitivity analyses (Supporting Tables e-1 and e-2 are available in the published version online).

Adverse Events

Adverse events related to this trial have been previously published. Of note, there were no neurological or cognitive adverse events reported.

Discussion

This clinical trial demonstrated that 24 months of exercise, twice a week, may be effective in improving attention and working memory in patients with mild-to-moderate PD without dementia when evaluated off medication. Relative to baseline, mFC and PRET improved performance on the Digit Span and Stroop, whereas PRET also improved performance on the BTA. This study is the first RCT to examine the effects of 24 months of exercise on cognitive functions in patients with mild-to-moderate PD. The findings from this clinical trial extend the previously known cognitive benefits of exercise in Alzheimer’s disease and in normal aging to PD. In addition, improvements in Digit Span scores were associated with improvements in walking speed. Given the recently published finding that physical activity reduces major mobility disability in older adults at risk for disability, taken together with our recently published findings that exercise improves motor signs of PD and physical function, and our current finding that exercise might improve cognitive function, the evidence for the benefits of exercise across domains is accumulating.

This clinical trial demonstrates the likely beneficial effects of 24 months of structured exercise on attention and working memory, which are cognitive domains that are frequently impaired in patients with PD. This finding is especially important for the Stroop because impaired performance on the Stroop has been shown to be associated with greater risk of subsequent dementia in patients with PD without dementia. Consequently, the finding that structured exercise might improve Stroop scores might indicate that exercise may reduce the risk of subsequent dementia in patients with PD. This possibility is clinically relevant because the cumulative incidence estimates from longitudinal studies indicate that up to 78% of patients with PD will develop dementia.

PRET was significantly better than mFC at improving motor signs of PD, and PRET and mFC were efficacious at improving

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### Table 3. Cognitive Outcomes at Baseline, 12 Months, and 24 Months, and Change From Baseline at 12 and 24 Months

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Z Score at Visit: Median (IQR)</th>
<th>Change From Baseline: Median (IQR), P Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>mFC</td>
<td>PRET</td>
</tr>
<tr>
<td>Digit Span Forwards and Backwardsb</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>0 (−0.3, 0.6)</td>
<td>0.3 (−0.3, 0.8)</td>
</tr>
<tr>
<td>12 mo</td>
<td>0.3 (−0.3, 1.3)</td>
<td>1 (0, 1.7)</td>
</tr>
<tr>
<td>24 mo</td>
<td>1 (0, 2)</td>
<td>0.7 (0.3, 1.7), P=0.01</td>
</tr>
<tr>
<td>Stroop Color-Word Interferenceb</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>−0.3 (−0.9, 0.3)</td>
<td>−0.9 (−1.7, 0.1)</td>
</tr>
<tr>
<td>12 mo</td>
<td>−0.1 (−0.8, 0.8)</td>
<td>−0.2 (−1.2, 0.4)</td>
</tr>
<tr>
<td>24 mo</td>
<td>−0.1 (−0.8, 0.8)</td>
<td>−0.1 (−1.7, 0.4)</td>
</tr>
<tr>
<td>Brief Test of Attentionb</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>0.1 (−0.7, 0.8)</td>
<td>0.4 (−0.5, 0.7)</td>
</tr>
<tr>
<td>12 mo</td>
<td>0.4 (−0.4, 1.2)</td>
<td>0.4 (−0.4, 0.9)</td>
</tr>
<tr>
<td>24 mo</td>
<td>−0.1 (−0.4, 0.9)</td>
<td>0.4 (0.1, 1.2)</td>
</tr>
</tbody>
</table>

Abbreviations: IQR, interquartile range; mFC, modified Fitness Counts; PRET, Progressive Resistance Exercise Training.

*P values calculated using the Wilcoxon signed-rank test.

b Positive change score from baseline is indicative of improvement.
physical function\textsuperscript{15} and cognitive outcomes in patients with PD, with neither being better than the other. One possible explanation is that because the mFC protocol included nonprogressive resistance exercises, it could be considered a low-dose resistance exercise regimen, whereas the PRET protocol could be considered a high-dose resistance exercise regimen. It has been shown that both low- and high-dose PRET have similar beneficial effects on cognitive outcomes.\textsuperscript{30} It could be that there is a threshold for a treatment effect on cognitive function. Our findings suggest that PRET and mFC exceeded a threshold for an effect on cognitive function. Further research is needed to understand the mechanisms by which exercise improves cognition and whether different doses of exercise and different types of exercise have the same or different effects on cognition.

In general, repeated administrations of cognitive assessments in healthy individuals are known to have practice effects, and these practice effects are affected by factors such as age, task difficulty,\textsuperscript{31,32} and IQ.\textsuperscript{33} We recognize that the improvements observed in this study could have been driven by practice effects. However, there are two arguments that favor the idea that the improvements in cognitive outcomes observed in this study were, at least partially, attributable to the effect of exercise and not simply an effect of practice. First, cognitive function has been shown to decline with increasing age, and the magnitude of this decline is approximated by the improvement in cognitive function owing to repeated testing.\textsuperscript{33} Second, in patients with PD, the neurodegenerative disease process augments the cognitive decline that accompanies the aging process. In fact, earlier work has shown that when cognitive tests are administered approximately 36 months apart, more cognitive decline occurs in patients with PD than in age-matched controls.\textsuperscript{33} Consequently, combining the effects of aging and the neurodegenerative disease process, one would expect cognitive function to decline or, at best, remain unchanged over time in patients with PD. However, we observed improvements in performance in the mFC and PRET groups in cognitive outcomes at 12 and 24 months. This finding might be suggestive of an effect of exercise beyond that of practice alone.

Another factor that is a potential confound is the increased social and cognitive engagement by virtue of mere participation in the PRET-PD study. The very fact that these patients went out of their houses to the gyms provides for greater opportunities for social and cognitive engagement with others, including their family, personal trainers, and the study personnel. The extent to which this increased social and cognitive engagement confounds our findings is unknown. This is a limitation of this study. In addition, because the study included a relatively younger group of patients with mild-to-moderate disease and an above-average level of education, the lack of generalizability is a limitation. Given these limitations and the fact that we did not adjust our alpha level for multiple outcomes, our findings should be interpreted with caution. Despite these limitations, the PRET-PD trial is similar to a phase II study that supports the concept of exercise as an adjunct therapy for PD and demonstrates feasibility,\textsuperscript{16} thereby providing a rationale for larger-scale, multicenter trials that could extend our findings across geographical locations, clinical practices, and a wider group of patients with PD.

In conclusion, this clinical trial found that 24 months of PRET or mFC exercise may improve cognitive outcomes in patients with mild-to-moderate PD while off medication. Our findings suggest that patients with mild-to-moderate PD without dementia might be able to improve cognitive performance by engaging in either mFC or PRET for two 60- to 90-minute sessions a week.

Supporting Data

Additional supporting information may be found in the online version of this article at the publisher’s website.

Funding

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Conflict of Interest

Nothing to report. Full financial disclosures and author roles may be found in the online version of this article.
References

Volume and Quality Data

Volumes, neurology and neurological surgery

Neurology volumes*, fiscal years 2011-2015

Neurology outpatient visits, fiscal years 2011-2015

*Includes neuro-oncology discharges

Rush had the highest volume of general neurology discharges in the Chicago region for fiscal years 2014 and 2015.

Neurological surgery outpatient visits, fiscal years 2011-2015

Volume of patients monitored for epilepsy, calendar years 2011-2015

*Includes all nonspine procedures

Rush had the highest volume of neurosurgical discharges in the Chicago region for fiscal years 2011-2015.

Neurological surgery volume of major cases by area, fiscal year 2015

Rush had the highest volume of neurosurgical discharges in the Chicago region for fiscal years 2011-2015.
Mortality, neurology and neurological surgery

Neurological surgery mortality o/e, fiscal years 2011-2015

Source: University HealthSystem Consortium clinical database

Quality indicators, stroke

Median times to endovascular recanalization treatment at Rush

Stroke IV tPA rate, fiscal year 2015

Stroke inpatient mortality, fiscal year 2015

Sources: Get With the Guidelines and internal data

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

2Administered at Rush and outside hospitals combined

3Includes all U.S. hospitals participating in Get With the Guidelines stroke data registry

Stroke case volumes, fiscal year 2015

<table>
<thead>
<tr>
<th>Condition</th>
<th>Cases</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intracerebral hemorrhage</td>
<td>273</td>
<td>(24.14%)</td>
</tr>
<tr>
<td>Ischemic stroke</td>
<td>596</td>
<td>(52.70%)</td>
</tr>
<tr>
<td>Subarachnoid hemorrhage</td>
<td>158</td>
<td>(13.97%)</td>
</tr>
<tr>
<td>Transient ischemic attack (&lt;24 hours)</td>
<td>104</td>
<td>(9.20%)</td>
</tr>
</tbody>
</table>

Total: 1131 Cases


Kasiwai MK, Dua SG, Mangubat EZ, Lopes DK. Compersive cervical myelopathy secondary to totally extradural spinal arteriovenous fistula. Neurol India. 2015;63(5):790-792.


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The 2016 Rush Neuroscience Review
Select Research Grants (2015)

Department of Neurological Sciences

Neelum Aggarwal, MD
- Community Engagement for Early Recognition and Immediate Action in Stroke (CEERIAS)
- Community-Based End-of-Life Intervention for African American Dementia Caregivers
- Study in Patients With Mild to Moderate Alzheimer's Disease

Zoe Arvanitakis, MD, MS
- Vascular Cognitive and Motor Decline: Impact of aPL
- Mechanisms Linking Insulin Resistance to Brain Structure, Pathology, and Function

Lisa Barnes Young, PhD
- Risk Factors for Cognitive Decline in African Americans
- Rush Center of Excellence on Disparities in HIV and Aging (CEDHA)

David Bennett, MD
- Epidemiologic Study of Neural Reserve and Neurobiology of Aging
- National Alzheimer's Coordinating Center
- Risk Factors, Pathology, and Clinical Expressions of Alzheimer's Disease
- Altered Monocyte Function in Relation to the CD33 Alzheimer's Disease Locus
- Targeted Proteomics of Resilient Cognition in Aging
- Transcriptional Regulation and Novel Therapeutic Targets for Alzheimer's Disease
- Neurobiology of Mild Cognitive Impairment in the Elderly
- The Brain Transcriptome and Lifetime Obesity Measures: The Framingham Study
- Development of Lewy Bodies Biofluid Signatures by Targeted Proteomics
- Clinical-Pathological Study of Cognitive Impairment in Essential Tremor

Patricia Boyle, PhD
- Epidemiologic Study of Impaired Decision-Making in Preclinical Alzheimer's Disease

Aron Buchman, MD
- Brain and Spinal Cord Microvascular Pathology in Late-Life Motor Impairment
- Spinal Cord and Brainstem Pathology Contributions to Late-Life Gait Impairment
- The Clinical Profile of Parkinson's Disease Pathology

James Conners, MD, MS
- Stroke Trials Network-Regional Coordinating Stroke Centers

Jennifer Goldman, MD
- Assessing Aberrant Motor Learning in Parkinson's Disease Patients
- Study of Dual Antagonist in Parkinson's Disease Dementia

Diana Goodman, MD
- Futility Study of Deferoxamine Mesylate in Intracerebral Hemorrhage

Deborah Hall, MD, PhD
- RECRUIT: A Randomized Recruitment Intervention
- Adult Neurological Phenotypes of Fragile X Gray Zone Expansion
- Study of Different Doses of Endurance Exercise in People With Parkinson's Disease

S. Duke Han, PhD
- Neural Correlates of Impaired Financial and Health Care Decision-Making in Old Age

Aikaterini Kompoliti, MD
- Disease Modifying Agent in Patients With Early Parkinson's Disease
- Group Dosage Study in Subjects With Early Parkinson's Disease
- Trial for Orally Administered Drug in Subjects With Drug-Induced Tardive Dyskinesia
- Study of SCN-102 in Subjects With Tourette Syndrome

Jeffrey Kordower, PhD
- Preclinical Evaluation of miSCA Expression Vectors for SCA1 Therapy
- Intranasal Delivery of Sponsor's Molecules to Target Central Nervous System in Nonhuman Primates

George Lopez, MD, PhD
- Dose Escalation Study in Patients With Aneurysmal Subarachnoid Hemorrhage

Elliott Mufson, PhD
- Basic Neuroscience Training in Age-Related Disorders

Daniel Nicholson, PhD
- Proteomic Reconstructive Microscopy of Health and Diseased Dendrites
- Synaptic Mechanisms Maintaining Persistent Cocaine Craving

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- Cinnamon, Ciliary Neurotrophic Factor (CNTF), and Experimental Autoimmune Encephalomyelitis (EAE)
- RANTES and Eotaxin: New Players in Parkinson's Disease Progression

Sylvia Perez, PhD
- Neuronal Tangle Propagation in Preclinical Alzheimer's Disease

Kathleen Shannon, MD
- Investigation of Levodopa Inhalation Powder in Parkinson's Disease Patients With Motor Response Fluctuations

Julie Schneider, MD
- Epidemiologic Study of TDP-43 Pathology in Aging and Dementia
Raj Shah, MD
- Integrated Inpatient and Outpatient Care for Patients at High Risk of Hospitalization
- Aspirin in Reducing Events in the Elderly

Sarah Song, MD, MPH
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- Safety Registry of Multiple Sclerosis Patients Who Have Participated in Cladribine Clinical Trials
- Impact on Central Nervous System Tissue Damage in Multiple Sclerosis

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- Implantable Neurostimulator for the Treatment of Parkinson’s Disease
- Evaluation of Extended Release Tablets in Parkinson’s Disease Subjects With Levodopa-Induced Dyskinesias

Dustin Wakeman, PhD
- Transplantation of Cryopreserved Induced Pluripotent Stem Cell (iPSC)-Derived Dopamine Neurons for Parkinson’s Disease

Robert Wilson, PhD
- BAILA: Being Active, Increasing Latinos’ Healthy Aging

Lei Yu, PhD
- Role of Impaired Cognitive States and Risk Factors in Conversion to Mixed Dementia

Department of Neurological Surgery

Richard Byrne, MD
- Cortical Stimulation Mapping Techniques in Brain Tumor Patients
- Brain Tumor Database
- Evaluation of Cognitive Function From Subdural Electrodes in Patients Considered as Surgical Candidates for Intractable Epilepsy
- Predictors of Surgical Corridors to the Suprasellar Space

Michael Chen, MD
- 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) Trial
- Estrogen Therapy as Prevention in the Progression of Aneurysm (EPPA) Trial
- Post-Aneurysm Subarachnoid Hemorrhage Memory Loss

Harel Deutsch, MD
- 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
- Asterias Stem Cell Treatment for Spinal Cord Injury
- Minimally Invasive Surgery for the Treatment of Adult Spinal Deformity: A Multicenter Retrospective Study

Demetrius Lopes, MD
- ACE: An Aneurysm Coiling Efficiency Study of the Penumbra Coil 400 System
- Adjunctive Neurovascular Support for Wide-Neck Aneurysm Embolization and Reconstruction (ANSWER) Study
- MicroVention Low-Profile Visualized Intraluminal Support (LVIS) or LVIS Jr Humanitarian Use Device

Leonard Verhagen Metman, MD, PhD
- PREMIER Prospective Study on Embolization of Intracranial Aneurysms With Pipeline Embolization Device
- Safety and Effectiveness of the Treatment of Wide-Neck, Saccular Intracranial Aneurysms With the Neuroform Atlas Stent System
- Solitaire FR With the Intention for Thrombectomy as Primary Endovascular Treatment for Acute Ischemic Stroke (SWIFT PRIME)
- The Surpass IntraCranial Aneurysm Embolization System Pivotal Trial to Treat Large or Giant Wide-Neck Aneurysms (SCENT)

Lorenzo Muñoz, MD
- MISTIE Trial: tPA for Intracerebral Hemorrhage

John O’Toole, MD, MS
- Os Odontoideum in Adults

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- Reclaim Deep Brain Stimulation for Obsessive Compulsive Disorder (OCD) Therapy
- Temporal Lobectomy, Memory, Sleep, and Dreams

Vincent Traynelis, MD
- Assessment of Perioperative Morbidity and Mortality Following Anterior-Posterior Cervical Spine Decompression and Fusion
- Cervical Retraction Study
- Clinical and Radiological Analysis Following Multilevel Anterior or Posterior Cervical Fusion
- Critical Analysis of Extubation Parameters for Patients Undergoing Combined Anterior-Posterior Cervical Spine Surgery ◆
General neurologist Jacob Fox, MD, recently retired after 26 years as chairperson of the Department of Neurological Sciences at Rush University Medical Center. During that time, the department sustained tremendous growth, all while continuing to provide excellent clinical care to patients.

Jacob, or “Jack” to his friends and colleagues, Fox devoted much of his career to the study and treatment of Alzheimer’s disease, for which he was honored by both the Chicago chapter of the Alzheimer's Association and the National Alzheimer's Association.

Fox recently sat down with fellow general neurologist Allison Weathers, MD, to discuss changes in the field of neurology, becoming a chairperson at an academic medical center, and why “legacy” isn’t something this interview should even be called.

**Weathers:** What were the influences that led you to become a neurologist?

**Fox:** When I was in medical school, I really wasn’t interested in anything else. Among the various possibilities, neurology seemed the most interesting, but I doubt I decided until I was a senior medical student. The one thing I knew was that I didn’t care to do surgery. So the limitations would therefore have been something in internal medicine, psychiatry, or neurology.

**Weathers:** Once you decided on neurology, what drew you to study Alzheimer's disease and dementia? How did you end up specializing?

**Fox:** It was purely happenstance. When I was in the military I was stationed at Fort Belfort in northern Virginia. Of course the military then took care of both active duty and retired, and there were many retired military there. After my residency, I accepted a job as the chief of neurology at
DeWitt Army Hospital in Belvoir, Virginia, and I saw a lot of patients there with cognitive dysfunction.

When I came back to Chicago in the early 70s, I took a faculty position at Rush and established my private practice where I just started seeing more patients who had dementia. And as you know, the idea that this dementia was Alzheimer's was something that evolved in clarity through the 70s and early 80s.

But I would say basically I'm a general neurologist. I have always seen everything, except for a period of time shortly after I became chairperson when my clinical time was limited and I was seeing only patients with dementia in the Rush Alzheimer's Disease Center.

And how that happened was I had the busiest Alzheimer practice, I guess you could say, in the area, as a private practitioner. When Rush decided to open the Alzheimer's Disease Center in the mid-80s, they asked me to participate as co-director because I brought all of the patients.

Weathers: So you didn't ever consider other subspecialties?

Fox: No, I'm not nearly as well thought out as that.

On changes in neurology over the last 20-plus years

Weathers: You spoke about it a little bit before, that there wasn't even this realization then that the condition was Alzheimer's. What do you think are the other really significant differences between the care of patients with neurological conditions now compared to the beginning of your career and your practice?

Fox: Unfortunately very little. It's very discouraging. The treatment of Parkinson's disease has improved since the availability of L-dopa, which was available when I finished my residency but not yet widely available and in use.

Headache: not all that much, really. Neuromuscular disease? Actually, during my residency was when it became clear that patients with myasthenia gravis benefited so much from steroids. And those patients do so much better than they did, let's say, in the 40s or 50s.

But in the last couple of decades, I'd say the big things in stroke are first, the use of antiplatelets to prevent stroke, and then tPA to treat it. And particularly the recent advance of doing invasive vascular treatment of major internal carotid and proximal middle cerebral artery strokes: I think that's just amazing. If you had asked me 30 years ago if I was going to be seeing people with major strokes really be helped a lot? I don't think I would have said yes. That's been unbelievable.

And actually the other thing that I really think is quite amazing is the treatment of patients with multiple sclerosis.

Weathers: I was thinking that.

Fox: Yeah, because I know from the early part of my career—of course I took care of hundreds of MS patients—and the fact was that their natural history was determined by their natural history, not by anything I did. And now you can see—whatever the side effects are—drugs like natalizumab really alter the natural history. So improvements in the treatment of stroke and MS in the last couple of decades I think have been truly remarkable and gratifying.

And, of course, neurointensive care didn’t exist when I first started my practice. I’m not sure how much data there is regarding how much better off the patients are in the more formalized neurointensive care compared to the way that it was done before. Undoubtedly they are better off, but I’m not sure there are studies that have been verified.

Weathers: Some interventions, such as with cooling, certainly there are strides.

Fox: Well, yes, but that's very slight.

Weathers: Yes, I know.

Fox: I mean, discouraging, slight, but something. There are a lot of areas where you can say there's something.

Weathers: There's something.

Fox: But I think neurointensive care is certainly the next frontier as far as demonstrating that some of the interventions neurointensivists do really have efficacy in altering the natural history. The clinicians have to do them. And I think
they should. But how one is going to demonstrate efficacy, I think, is challenging.

Weathers: Going back to Alzheimer’s and how you said it’s discouraging that things aren’t that much different. What do you think are the most important areas for future researchers to be focusing on for the treatment and care?

Fox: For sure, biology. The chemistry, the biology: That’s where it’s at. Now whether any of the things that are being planned regarding diminishing amyloid early on in the course of the pathology progression, whether they’re actually going to have efficacy or not, I think remains to be proven. There seem to be some very good studies in progress.

But, I should clarify, when I said I don’t think the care of Alzheimer’s patients has improved, I mean care provided by physicians. I think the recognition of the illness has been beneficial for the patients, for the families, and for how one deals with issues surrounding the disease. And it’s not that physicians have nothing to contribute to those patients; they just aren’t able to do anything to alter the natural history of the disease.

On life as a chairperson at an academic medical center

Weathers: About what you’ve accomplished in your tenure as chair, one of the most notable things is how our volume has grown, the size of our practice.

Fox: It’s exciting.

Weathers: It is. What do you think has contributed to that growth and to sustaining such a successful neurological sciences program?

Fox: We have the best doctors offering the best service. And that’s it. Nothing else. And to the extent that I’ve made any contribution to that is by trying to recruit the best doctors, and by trying to put them in a situation where they can offer the best service.

And by the way, the volumes are astonishing because I figured them out for FY15. We had almost 2900 admissions, and the next closest academic center to us in the area had 1900. I mean, the difference is amazing. And the other academic centers in the area had around 1300. We’re seeing almost 500 new patients per month, which is more than are seen by all of the neurologists in Scotland, as I always point out.

I really do think it’s the best doctors offering the best service. And of course, the best service has to include the opportunity to use the most advanced treatments. So I’ll use as an example—not because it’s the only example, but it’s an obvious recent one—the idea of TeleStroke leading to prompt treatment of patients who are then candidates to get intravascular treatment that has to be done within 6 hours.

In these cases, that better service is even more important. The patients have to be handled quickly and efficiently so that they’re in a position to benefit from that treatment. And that’s very complicated. And that’s not me. That’s a whole group of people who are doing that. My own personal satisfaction is that I’ve allowed them the opportunity to do it, and they’re in a situation where they can.

Weathers: But I think your leadership and your ability to provide those opportunities is what facilitated that.
Weathers: You’ve been here for many years and held many different positions at Rush. Not only chairperson for neurological sciences, but provost, and medical staff president. What has kept you here all these years?

Fox: I like seeing patients and teaching. And I like the people I work with. And Rush is a good place to do those things. As chairperson, I’ve been given an opportunity that I wouldn’t have normally expected with my own background. I’d simply be in private practice. Being able to facilitate some of these advances, like TeleStroke that I mentioned before, has been gratifying. So that’s been an additional opportunity for me, for which I consider myself very lucky.

Weathers: You and I have talked about that before. I think it’s interesting how you feel that your path was unique, and it wouldn’t happen again today.

Fox: I think it’s definitely possible for somebody in private practice to go into academics, but people in private practice are not often considered for chairperson positions in academic institutions. You know, I often say that I happened to be walking on a roof, and a hole opened up, and I landed in the chair. I think people who are primarily clinicians and teachers can end up in charge of large groups of neurologists, but the nature of the academic selection process now is that they’re not the people who are necessarily selected to be chairperson. So, I consider myself particularly lucky in that regard.

On advice for future neurologists

Weathers: Along those lines, what are the biggest challenges you see for future neurologists and trainees who would like to follow in your footsteps?

Fox: I think the main thing is they should not be diverted by all of the things that administration, etcetera, are saying are so important like affiliating with other hospitals. My own opinion is each individual physician has to concentrate exclusively on being the best physician, giving the best service he or she can.

Unless they get into some sort of administrative job, that’s what they should be thinking about. And to the extent they’re diverted from concentrating on being the best physician he or she can be, it’s not beneficial. It’s our job to offer services like TeleStroke or 2-BRAIN [a direct physician transfer service] because that’s what we do.

To the younger physicians, my advice is always the same: Pay much more attention to the history and the physical, and don’t concentrate on the imaging. Not because that’s the only thing we old people used to have for diagnoses, but because that’s how you do the best job as a neurologist. You concentrate on the history and physical, and then you do the imaging to support your suspected diagnosis. That’s what I say all the time to the younger doctors. But I’m not sure they’re really convinced.

Weathers: What would you like your legacy to be?

Fox: This word “legacy” doesn’t mean a thing to me. Honestly, it’s like, if you would ask me, what do you want your legacy to be to your daughter, what does that mean? What I want for my children and grandchildren—my own biological children and grandchildren—is for them to be happy and successful. That’s what I want for our department as well. I want our faculty to continue to be happy and successful. I don’t look at that at all as a legacy.

I want our department to continue to be composed of the best doctors giving the best service. If the department declines after I leave, it will be devastating to me, devastating. Because I truly look at our faculty as my professional family. And therefore, I want for our faculty professionally what I want for my own family personally: I want them to be happy and successful.

Weathers: I talk about that in each residency applicant interview. With every program they say, “What makes your program unique?” And I say, not only are we world-class clinically, but we’re a family.

Fox: Uh huh.

Weathers: And you feel it in everything we do here.

Fox: Yes. And so this legacy stuff—it’s not a word in my lexicon. ♦
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