In memory of
Leyla deToledo Morrell, PhD
1941–2015

A leader in the field of Alzheimer’s disease research, Leyla deToledo Morrell was a part of the Rush family for more than 35 years. She was among the first to use modern imaging techniques to report that shrinkage in the medial temporal lobe marks the transition from prodromal to Alzheimer’s disease. Medial temporal lobe atrophy is now a major biomarker for the disease.
THE 2015
RUSH NEUROSCIENCE REVIEW

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Aimee Szewka, MD

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To view The 2015 Rush Neuroscience Review online, visit www.rush.edu/neurosciencereview.
Chairmen’s Letter

As we look back over the last year, one research study in particular—the SWIFT-PRIME stroke trial—demonstrates the multidisciplinary approach to achieving clinical excellence that is the hallmark of our two departments. Rush was one of 39 centers in the U.S. and Canada that participated in the SWIFT-PRIME trial, the results of which appeared this summer, coauthored by our faculty, in the New England Journal of Medicine.

The results showed significantly higher functional outcomes in stroke patients who received IV tPA plus mechanical thrombectomy vs. IV tPA alone, the current standard. We hope that these findings serve as a foundation for nationwide changes in the way stroke patients receive emergency care—changes that could one day lead to less patient disability from stroke.

And we are particularly gratified by the recognition our stroke team received for the way they routinely deliver this improved level of care:

- Of all the participating sites in the SWIFT-PRIME trial, Rush had the fastest times from patient arrival to insertion of the catheter (door to groin).
- Rush also had the fastest initiation of the procedure to restoration of blood flow (groin to recanalization).
- The Rush team was recognized for having the best workflow among a larger group of 203 sites in the U.S., Australia, Canada, and Europe that participated in SWIFT-PRIME and two other affiliated stroke studies.

In addition to the above, we are pleased to share highlights from the last year that further exemplify multidisciplinary approaches to providing excellent care:

**Alzheimer’s disease protection research:**
Drawing on years of prior nutrition and Alzheimer’s research, clinicians at Rush developed the Mediterranean-DASH Intervention for Neurodegenerative Delay, or MIND, diet. The MIND diet is a hybrid of the Mediterranean and DASH (Dietary Approaches to Stop Hypertension) diets, both of which have been found to reduce the risk of cardiovascular conditions.

Researchers at Rush compared the MIND diet with Mediterranean and DASH diets. While people with high adherence to either the DASH or the Mediterranean diet had reductions in their risk of developing Alzheimer’s, those who moderately adhered had negligible benefits. However, the MIND diet lowered Alzheimer’s risk by as much as 53 percent for those who had high adherence and by about 35 percent in those who followed it only moderately well.

**Improving access for movement disorders:**
Physicians from our movement disorders program are piloting a way to make follow-up visits easier for select patients who live outside the Chicago area. The physicians can now “see” a patient in his or her own home—or in some cases a remote
provider clinic—using special monitors. On their end, patients will use their MyChart accounts to access the appropriate software to make the telemedicine process possible.

**Huntington’s Disease Center of Excellence:**
The Huntington’s Disease Society of America named Rush one of 29 Centers of Excellence for 2015. Facilities that receive the designation must demonstrate a team approach to Huntington’s disease care and research driven by “expert neurologists, psychiatrists, therapists, counselors, and other professionals who have deep experience” working with families affected by the disease.

**New developmental synaptopathies consortium:** Rush is a founding member of the new Developmental Synaptopathies Consortium, which aims to deepen researchers’ understanding of rare genetic diseases that disrupt synapse formation and can cause autism spectrum disorder and intellectual disability. As part of this aim, the consortium will launch a five-year study at 10 medical centers, enlisting children ages 3 to 21 for the purpose of tracing the “natural history” of the progression of tuberous sclerosis complex, Phelan-McDermid syndrome, and PTEN-associated autism and hamartoma tumor syndrome. The National Institutes of Health has pledged $6 million to the consortium and will also participate as a member.

In addition to the above achievements, our faculty were lauded for their contributions to our field.

We are proud to share with you a few of these honors from the last year:

- *Orthopedics This Week* named Vincent Traynelis, MD, to its list of 18 of the best North American spine surgeons for 2014.
- Thomas Bleck, MD, was named a Master of Critical Care Medicine by the Society of Critical Care Medicine and the American College of Critical Care Medicine.
- Thompson Reuters named David Bennett, MD, and Julie Schneider, MD, of the Rush Alzheimer’s Disease Center, among the most influential researchers in the world.
- Neuropsychologist Christopher Grote, PhD, was elected as president of the Association of Postdoctoral Programs in clinical neuropsychology.
- Christopher Goetz, MD, received the Movement Disorders Research Award from the American Academy of Neurology.
- Spine neurosurgeon Richard Fessler, MD, PhD, received the 2015 Neurosurgical Society of America Meritorious Service Medal for contributions that have significantly changed the field of neurosurgery.

We invite you to read on to learn more about our faculty’s robust research and clinical contributions to the neurosciences.

Regards,

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

Jacob Fox, MD
Chairperson, Department of Neurological Sciences
The Joseph and Florence Manaster Foundation Professor of Multiple Sclerosis
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
- Neuro-ophthalmology Service

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

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**Neurology**
- 28,986 outpatient visits
- 2,528 inpatient discharges

**Neurological Surgery**
- 3,420 outpatient visits (brain)
- 5,086 outpatient visits (spine)

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**Inpatient Facilities**

<table>
<thead>
<tr>
<th>Beds</th>
<th>General Neurology</th>
<th>Neuro ICU</th>
<th>Psychiatric Rehabilitation</th>
<th>Epilepsy (adult)</th>
</tr>
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<tbody>
<tr>
<td>32</td>
<td>28</td>
<td>67</td>
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**Faculty physicians and researchers**
- 120

**Residents and fellows**
- 51

**Advanced practice nurses and physician assistants**
- 24

For additional volume and quality data, see pages 66-67.
In 2014, Rush received the University HealthSystem Consortium’s Quality Leadership Award, ranking fifth among more than 100 academic medical centers.

The Rush stroke program is certified by the Joint Commission as a comprehensive stroke center.

Rush has earned Magnet status—the highest honor in nursing—three times from the American Nurses Credentialing Center.

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

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.

Rush’s research program is fully accredited by the Association for the Accreditation of Human Research Protection Programs.
Primary and Associated Faculty (2014)

Department of Neurological Sciences

Chairperson: Jacob Fox, 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  Michael Stein, MD  Travis Stoub, PhD
Cognitive neurosciences

Christopher Grote, PhD  Richard Peach, PhD

Critical care neurology

Thomas Bleck, MD  Torrey Boland, MD  Katharina Budl, 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  Laura Jawidzik, MD  Steven Lewis, MD  Megan Shanks, MD  Jordan Topel, MD

Allison Weathers, MD

Movement disorders

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:
Mehul Trivedi, PhD
Margaret Park, MD
Robert Wright, MD
Melany Danehy, MD
Bichun Ouyang, PhD
Multiple sclerosis

Roumen Balabanov, MD  Rajendra Goswami, PhD  Dusan Stefoski, MD  James Stewart, PhD

Not pictured: Michael Ko, MD

Neurobiology

Yaping Chu, PhD  Bin He, PhD  Jeffrey Kordower, PhD  Kalipada Pahan, PhD  Sylvia Perez, PhD

Not pictured: Malabendu Jana, PhD  Elliott Mufson, PhD  Dan Nicholson, PhD  Avik Roy, PhD  Dustin Wakeman, PhD

Neuromuscular disease

Rabia Malik, MD  Matthew Meriggioli, MD  Irwin Siegel, MD  Madhu Soni, MD

Neuro-oncology

Robert Aiken, MD  Nina Paleologos, MD

Neuro-ophthalmology

Thomas Mizen, MD  Aimee Szewka, MD

Pediatric neurology

Elizabeth Berry-Kravis, MD, PhD  Peter Heydemann, MD  Meryl Lipton, MD

Not pictured: Lubov Romantseva, MD
Primary and Associated Faculty (2014)

Department of Neurological Surgery

**Chairperson:** Richard Byrne, MD

Richard Byrne, MD  Michael Chen, MD  Harel Deutsch, MD  Richard Fessler, MD, PhD  Ricardo Fontes, MD, PhD  Demetrius Lopes, MD

Roham Moftakhar, MD  Lorenzo Muñoz, MD  John O’Toole, MD, MS  Sepehr Sani, MD  Vincent Traynelis, MD

Research faculty

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

Associated faculty at Rush University Medical Center

Pete Batra, MD  Aidnag Diaz, MD, MPH  Sheila Dugan, MD  R. Mark Wiet, MD  Not pictured: David Rothenberg, MD, anesthesiology  Mary Sturaitis, MD, anesthesiology

Otorhinolaryngology  Radiation oncology  Physical medicine and rehabilitation  Neurology

Associated clinical faculty*

Jerry Bauer, MD  Martin Herman, MD, PhD  Patricia Raksin, MD

Tibor Boco, MD  Juan Jimenez, MD  John Ruge, MD  Andrew Zelby, MD

George Bovis, MD  Martin Luken, MD

*Primary appointment is not at Rush University Medical Center
Residents and Fellows (2014)

Department of Neurological Sciences

Residents

Anik Amin, MD  
Medical school: Baylor College of Medicine

Stuart Bergman-Bock, MD  
Medical school: University of Louisville School of Medicine

Ankush Bhatia, MD  
Medical school: Rush Medical College

Michael Boffa, MD  
Medical school: New York University School of Medicine

Hunan Chaudhry, MD  
Medical school: Rush Medical College

Arun Chhabra, MD  
Medical school: Eastern Virginia Medical School

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

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

Avram Fraint, MD  
Medical school: Rush Medical College

Michael Gibbs, MD  
Medical school: Northwestern University Feinberg School of Medicine

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

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

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

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

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

Brian Marcus, MD  
Medical school: Medical College of Wisconsin

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

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

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

Sarah Sung, MD  
Medical school: University of Oklahoma College of Medicine

Jaspreet Thiara, MD  
Medical school: Rush Medical College

Ruby Upadhyay, MD  
Medical school: Rush Medical College

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

Fellows

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

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

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

Elizabeth Flaherty, MD  
Medical school: Rush Medical College  
Residency: Rush University Medical Center

Joseph Kipta, MD  
Medical school: New York Medical College  
Residency: McGaw Medical Center of Northwestern University

Melissa Mercado, MD  
Medical school: Boston University School of Medicine  
Residency: Boston University Medical Center

Matthew Raday, MD  
Medical school: Rush Medical College  
Residency: Rush University Medical Center

Rochelle Sweis, DO  
Medical school: Chicago College of Osteopathic Medicine, Midwestern University  
Residency: Froedtert Memorial Lutheran Hospital

Padmina Vittal, MD  
Medical school: M.S. Ramaiah Medical College, India  
Residency: Tulane University School of Medicine

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

Residents

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

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

Ricardo Fontes, MD, PhD
Medical school: University of Sao Paulo School of Medicine

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

Manish Kasliwal, MD
Medical school: All India Institute of Medical Sciences

Rob Kellogg, MD
Medical school: Indiana University School of Medicine

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

Ryan Kochanski, MD
Medical school: Wayne State University School of Medicine

Joseph Molenda, MD
Medical school: Johns Hopkins University School of Medicine

Stephan Munich, MD
Medical school: University at Buffalo School of Medicine and Biomedical Sciences

David Straus, MD
Medical school: University of Chicago Pritzker School of Medicine

Lee Tan, MD
Medical school: Indiana University School of Medicine

David Wallace, MD
Medical school: Rush Medical College

Joshua Wewel, MD
Medical school: University of Nebraska College of Medicine

Fellows

Christopher Gillis, MD
Medical school: Schulich School of Medicine and Dentistry, University of Western Ontario, Canada
Residency: University of British Columbia Faculty of Medicine, Canada

Andrew Johnson, MD
Medical school: Columbia University College of Physicians and Surgeons
Residency: Rush University Medical Center

Erwin Mangubat, MD
Medical school: University of Illinois College of Medicine at Chicago
Residency: Rush University Medical Center
THE EVOLUTION OF NEUROCRITICAL CARE

Georgia Korbakis, MD; Thomas Bleck, MD, MCCM, FNCS

Author Affiliations: Department of Neurological Sciences (Dr Korbakis) and Departments of Neurological Sciences, Neurological Surgery, Anesthesiology, and Internal Medicine (Dr Bleck), Rush University Medical Center, Chicago, Illinois.

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Key Points
1. Head trauma is a major aspect of neurocritical care, and the management of cranial injuries can be traced back to 2000 BC.
2. The first contemporary neurointensive care units using mechanical ventilation developed after the poliomyelitis epidemic of the 1920s.
3. Modern neurointensive care units use multiple modalities to monitor a diverse patient population.
4. The Neurocritical Care Society was founded in 2002 and is a multidisciplinary organization dedicated to progress in the field of neurocritical care and improvement in patient outcomes.

Historical Aspects
The history of neurocritical care begins in antiquity, as documented in the Edwin Smith surgical papyrus. This text, named for a 19th-century Egyptologist who purchased the document in Luxor or Thebes in 1862, is an unfinished textbook on bodily injuries written circa 1700 BC. It is believed to be a copy of an original manuscript written 1000 years prior and describes 48 case reports, including 27 head injuries and 6 spinal cord injuries, many with documented interventions by the investigator. The Edwin Smith papyrus is remarkable in that it not only gives the first anatomical description of the brain, cerebrospinal fluid, and meninges but also describes conditions such as tetanus and aphasia.

Although this extraordinary work gives us a view of ancient medical practices, it does not mention the earliest known neurosurgical procedure of trepanation, which appears to have originated in the Neolithic Era after the discovery of a trephinated skull dating back to 10 000 BC. Hippocrates, frequently hailed as the “father of medicine,” clearly documented and advocated trepanation as a management for certain head injuries including skull fractures and contusions. He also documented neuroanatomical observations, categorized different skull fractures, suggested treatment for such injuries, and recognized deleterious complications such as fever and inflammation. About 300 years later, Aulus (Aurelius) Cornelius Celsus of Alexandria promoted the work of Hippocrates, but additionally described epidural and subdural hematoma evacuation via trepanation. In the 2nd century AD, another titan in the field of medicine, Galen of Pergamon, further expanded on the technique of trepanation and described innovative new tools. This ancient era also heralded the initial management for spinal cord injury, and Hippocrates is credited for one of these early treatments: traction. By using an extension bench he was able to reduce spinal deformities. Celsus and Galen further advanced the understanding of the pathophysiology of spinal cord injury by recognizing that damage to the “spinal marrow” or cord, and not the vertebrae, leads to deficits.

The medieval times following the flourishing of science and medicine in the Greco-Roman epoch lacked major advances, excepting those described by one famous Persian intellectual, Avicenna. His Canon of Medicine was used as a medical text throughout Europe up until the 18th century, and he may have been the first to realize that stroke was due to blockage of the cerebral vessels, offering remedies for management of acute stroke including venesection.
Mechanical Ventilation and the Birth of Critical Care Medicine

A complete discussion of the history of mechanical ventilation is beyond the scope of this article; however, many key elements in the development of artificial respiration are relevant to critical care medicine as a subspecialty, and particularly neurocritical care. Galen first described using a bellows to ventilate a dead animal artificially through the trachea; later, the Renaissance physician Andreas Vesalius documented the use of a tracheostomy with artificial respiration by inserting a reed tube into the trachea of animals and blowing in air to observe the heart and thoracic cavity during vivisection. More than a century later, in 1744, the first report of positive pressure ventilation by mouth-to-mouth resuscitation was described by the surgeon William Tossach during the successful revival of a suffocated miner. Around the same time, several methods regarding the resuscitation of humans were in practice, including insufflating tobacco smoke through the anus, and rolling a barrel against a victim’s thorax.

The next great stride was in respiratory physiology with the discovery of carbon dioxide by Joseph Black. He demonstrated that carbon dioxide was the product of respiration through experiments with caustic alkali. The discovery of oxygen by Joseph Priestley and Carl Wilhelm Scheele soon followed through tests involving heating mercuric oxide. Antoine-Laurent de Lavoisier repeated these experiments and named the gas “oxygen.” He also realized that oxygen was necessary for respiration or “internal combustion.” By the end of the 18th century, bellows and pistons were favored over mouth-to-mouth resuscitation for both aesthetic reasons and concern over lack of effectiveness when using expired air containing carbon dioxide. Despite this trend, positive pressure ventilation was strongly criticized after experiments on drowned animals in the 1800s demonstrated emphysema when the lungs were inflated forcibly, and thus this practice fell out of favor.

In the early 19th century, attention was directed toward negative pressure ventilation. Dr Dalziel introduced the tank respirator, which enclosed the patient in a cylindrical tube and used bellows to reduce the pressure within the tank to subatmospheric levels. In 1929, Drinker and Shaw published their work on a new tank respirator that used electrically operated pumps to create negative and positive pressure within the tank. This respirator became known as the “iron lung” and was used extensively throughout the United States to provide ventilatory support for respiratory paralysis during the poliomyelitis epidemic of the late 1940s. The poliomyelitis epidemic in Copenhagen in 1952 prompted the use of intermittent positive pressure ventilation.

Primary credit is given to anesthesiologist Bjørn Ibsen, who treated a patient with tracheotomy followed by manual positive pressure bag ventilation using humidified oxygen. This technique was applied to several patients, and a large staff, including 250 medical students, worked in relays to provide uninterrupted ventilation for patients. The mortality rate in Copenhagen was cut to 39%. Knowledge spread throughout Europe, and quickly intermittent positive pressure ventilation became standard practice.

The Copenhagen poliomyelitis epidemic provided the catalyst for the development of dedicated respiratory care units—the first true intensive care units (ICUs)—to treat patients with respiratory failure of various etiologies, although Florence Nightingale is customarily regarded as the first to have established an ICU during the Crimean War. Nightingale clustered the sicker patients in a “monitoring unit.” Dr Dandy Walker created a specialized unit for his postoperative neurosurgical patients at the Johns Hopkins Hospital in 1929.

With the subsequent development of respiratory and cardiac ICUs, a decrease in mortality rate between mechanically ventilated patients treated in traditional general hospitals compared to those in new ICUs was quickly identified and provided convincing evidence for the establishment of these units, despite higher costs. In 1971, the Society of Critical Care Medicine was founded to promote the field and define core competencies. The three founding physicians came from different medical specialties: cardiology, anesthesiology, and trauma surgery. ICUs today remain diverse, and neurocritical care units represent yet another important subspecialty linking the care of the damaged nervous system to other organs.
Head Trauma

Traumatic brain injury (TBI) has gained much attention in the news recently, especially regarding sports-related injuries; however, severe TBI due to injuries sustained during periods of war has been a topic of study since antiquity. One of the main indications for trepanation is thought to have been TBI. Trepanation could be performed by scraping, grooving, or boring and cutting, as was performed by the Greeks, using an instrument called a trepanon. Interestingly, many of the ancient skulls discovered showed postoperative changes in the bone, indicating survival after the procedure. Hippocrates was the first to systematically document skull fractures and emphasized the importance of history taking and careful physical examination.23 Rhazes, a Muslim physician practicing in the 9th century, was the first to define concussion in the modern sense, recognizing that brain injury could occur without skull fracture. In the 14th century, Guy de Chauliac further elaborated this concept. He described the term commotio cerebri, a transient cerebral dysfunction caused by the brain being shaken and not necessarily related to structural pathology.24 The next great work regarding head trauma, Tractatus de Fractura Calvae sive Cranii (Treatise on Fractures of the Calvaria or Cranium) was written by Berengario da Carpi in the 16th century. He noted the difference between injuries involving the dura mater, as opposed to the pia mater (the latter also involving the underlying brain parenchyma), and described surgical treatments for head trauma including a description of contemporary instruments.25

The prevalence of wars in the next few centuries along with the increased use of firearms during warfare ushered in a new era of TBI medicine. The American Civil War (1861-1865) saw a great deal of head injury, but unfortunately, because of lack of aseptic technique, surgery frequently met with significant infection and subsequent mortality. The medical “pocket manuals” of the time served as guides for military doctors. They classified injuries into blunt or penetrating wounds and distinguished between immediate concussion and delayed compression, now recognized as herniation. Advances in anesthesia, such as the use of ether, allowed advances in surgery as well.26 World War I (1914-1918) advanced the treatment of brain wounds as both the Allied and Central powers dealt with trench warfare and focal brain injury due to smaller ammunition. The English neurosurgeon Percy Sargent and neurologist Gordon Holmes emphasized the importance of a detailed neurologic examination prior to operation, gave indications for different procedures, and described rises in intracranial pressure (ICP) as well as the underlying causes and treatment.27 The topic of increased ICP was further expanded on by Harvey Cushing, who went to France in 1917 as part of the war effort. Dr Cushing’s experiences in Europe rapidly advanced the field of neurosurgery and the treatment of TBI by addressing hemostasis and aseptic technique. Additionally, his contributions regarding the use of radiographs and the Riva-Rocci pneumatic device for recording blood pressure during anesthesia were particularly valuable.28 George Tabuteau was a proponent of the then-controversial issue of opening the dura to remove clot, which subsequently lowered infection rates and improved outcomes.29 Robert Bárány, a surgeon in the Austro-Hungarian army, described the importance of primary wound closure after thorough débridement to prevent infection.30 Over the remainder of the 20th century, advances in evacuation times from the battlefield and improvement in our understanding of the pathophysiology and monitoring of TBI decreased the mortality rates of head wounds from 74% in the Crimean War to 10% in the Korean and Vietnam wars.31

TBI in the civilian population remains a serious epidemiological issue with an annual incidence of 1.7 million and a mortality rate of 52,000 per year.31 In 1996, the Brain Trauma Foundation published the first set of guidelines for the management of severe TBI. These guidelines were most recently revised in 2007. Current recommendations focus on avoiding hypotension and hypoxia while managing ICP and maintaining cerebral perfusion and oxygenation.32 Adherence to these guidelines significantly improves survival among TBI patients.33,34

Intracranial Pressure

Assessment and management of ICP remains one of the main responsibilities of neurointensivists practicing today. In 1901, Cushing published a landmark study demonstrating the “Cushing response”: a triad of hypertension, bradycardia, and irregular respirations related to intracranial hypertension. Increasing ICP in dogs via infusion of a salt solution directly
into the subdural space and recording several physiologic measures. Cushing noted a direct correlation of the rise in arterial blood pressure with ICP elevation and determined this was a regulatory mechanism to maintain perfusion to the brainstem. The recognition of this triad of symptoms remains crucial to clinical intensive care.35

Evaluation of elevated ICP was traditionally assessed by clinical examination, measurement of vitals, and inference from lumbar puncture. In 1953, Ryder et al46 published a case series recording cerebrospinal fluid pressure continuously in a few patients following acute brain injury, and in 1965 Lundberg et al37 published the first report of continuous ICP monitoring using ventricular cannula in patients with TBI and nontraumatic cases of intracranial hypertension.38 This article demonstrated the variations in ICP following head injury and provided a targeted approach for the management of elevated ICP. Continuous ICP monitoring remains an integral aspect in the care of the critically ill neurologic patient, extending beyond traumatic injuries, and is discussed in a later section.

Although identification of elevated ICP is critical, treatment options are scarce and reveal the tremendous gaps in our current knowledge of the pathophysiology and management of intracranial hypertension. Cushing was truly a pioneer in this field and was the first to describe palliative subtemporal decompression to relieve elevated ICP prior to brain tumor resection, thus lowering the risk of herniation during the resection.39 Decompressive hemicraniectomy remains one of the few tools to definitively manage elevated ICP. A modern application of this concept frequently encountered in neurologic ICUs today is evident in the recent publications of 3 randomized controlled trials from Europe (HAMLET, DESTINY, and DECIMAL) showing that early decompressive hemicraniectomy reduces mortality in patients with large hemispheric ischemic stroke.40

The use of chemical agents to lower elevated ICP was developed in the early 20th century. In 1919, Weed and McKibben41 published a study on ICP changes following intravenous injection of solutions with varying concentrations. They recorded cerebrospinal fluid (CSF) pressures in cats and demonstrated a sustained elevation following infusion of hypertonic distilled water and conversely a marked and rapid decrease in ICP with administration of hypertonic saline and other highly concentrated salt solutions. Fremont-Smith and Forbes42 found that hypertonic urea lowered ICP in animals. Initially used in humans in the 1950s, urea soon fell out of favor because of difficulties in preparation.43 Mannitol was first studied in dogs in 1961; subsequently, Wise and Chater44 published their report of lowering CSF pressure in 24 patients with various causes of intracranial hypertension using mannitol. In the 1990s, there was a resurgence of interest in other hypertonic solutions after several studies demonstrated improved survival in patients treated with hypertonic saline mixed with dextran for hemorrhagic shock following trauma, termed “small volume resuscitation.” Some investigators deemed the improvement to be due to rapid increase in systemic arterial pressure and reduction in cerebral edema, with subsequent increase in cerebral perfusion.45,46 The use of hyperosmolar agents either as continuous infusions or as boluses is still in practice today in the management of elevated ICP.

Since the 1930s, the correlation between barbiturates and lowered ICP has been identified, by their effect on reducing cerebral metabolism.47 Their use, however, was limited because of side effects of hypovolemia and respiratory depression. In 1988, Eisenberg et al48 compared patients with elevated ICP receiving conventional therapy (hyperventilation, neuromuscular junction blockade, sedation, mannitol, and ventricular drainage) to those receiving conventional therapy plus pentobarbital and found high-dose pentobarbital to be an effective adjunctive therapy for elevated ICP. Currently, high-dose barbiturates used to achieve a burst-suppression pattern on continuous electroencephalography (EEG) are used to lower ICP in medically refractory cases.

Therapeutic hypothermia has also been used for the management of elevated ICP. The most evidence comes from TBI studies where it is used in medically refractory cases.49 It has also been effective at controlling ICP in acute hepatic failure.50

Neuromonitoring

The field of neurocritical care is relatively young but has quickly evolved over the last 30 years to involve a multidisciplinary approach to the management of acute neurologic injury. The term multimodal monitoring refers to measuring and recording neuropsyche variables in real time, in addition to the patient’s cardiac and pulmonary status.

The oldest and most dependable of these variables is the neurologic examination. Vigilant bedside monitoring for neurologic deterioration is difficult but remains vital in the care of the neurologically ill patient. Serial clinical neurologic examinations remain crucial in the ICU. Although several coma scales have been documented,51 the Glasgow coma scale is one of the most commonly used tools in the neurologic ICU. Introduced in 1974 by Teasdale and Jennett, it is extensively used worldwide to classify the level of consciousness. Clinical parameters measure the best motor, verbal, and eye opening responses; a summed score of 8 or less suggests coma and the need for intubation.52 This scale has become increasingly useful in communication during patient transfer (eg, from a community hospital to a tertiary care center).53

More recently, the FOUR (Full Outline UnResponsiveness) score was developed by Wijdicks et al,44 assigning a score from 1 to 4 to each of 4 components: eye response, motor response,
brainstem reflexes, and respiration. This score was validated in 2005 and allows for greater neurologic detail during evaluation, remaining testable in intubated patients as well.

Monitoring and measuring changes in ICP are crucial parts of neurocritical care and are fundamental in the management of patients with subarachnoid hemorrhage (SAH), TBI, hydrocephalus, stroke, central nervous system infection, and hepatic failure. The importance of ICP was recognized more than 2 centuries ago by Alexander Monro, and advances in monitoring and managing ICP and related measures are in continuous evolution. Claude-Nicolas Le Cat first documented the placement of an external ventricular drain after specially devising a cannula with a stopple that was placed in the lateral ventricle and used to drain small volumes of CSF in an infant with hydrocephalus. William Williams Keen, Emil Theodor Kocher, and Hermann Tillmanns made significant advances in approach and aseptic technique. Throughout the 20th century, advances in materials proved most noteworthy, from horsehairs and catgut to metals and modern plastic catheters. However, as mentioned previously, Lundberg was one of the first physicians to continuously measure and document ICP using a ventricular catheter. This procedure continues to be used in neurologic ICUs today. This device is easily placed at the bedside using anatomic landmarks and has the added benefit of being able to treat elevations in ICP via drainage of CSF. The most significant complications include malposition, occlusion, hemorrhage, and infection. Current studies examine the use of silver or antibiotic-coated catheters to reduce the risk of ventriculitis, but a consensus has yet to be determined.

Fiberoptic, transducer-tipped monitors were developed in the 1980s, and experience with these devices continues to build. Again, the device is easily inserted at the bedside and can be left in place for continuous ICP measurement. The intraparenchymal monitors have lower complication rates, but major issues include transducer disconnection and drift. Additionally, a significant fraction of patients with an intraparenchymal monitor will require external ventricular drainage placement to treat elevated ICP.

Several other modalities have been developed to continuously monitor the neurologically ill patient. EEG, traditionally used for the analysis of seizures, provides a continuous, noninvasive approach to determine brain function, specifically cerebral ischemia. In the 1970s, changes in cerebral blood flow during carotid endarterectomy were noted to correlate with EEG changes, specifically a replacement of faster alpha range frequencies for slower theta and delta range components. Quantitative EEG transforms EEG waves into numerical values that are compressed over a large period of time to form visual graphs, allowing the reader to compare one cerebral hemisphere to the other. This technique has been increasingly used in the management of SAH to detect delayed cerebral ischemia in the comatose patient and has shown accuracy in predicting ischemia prior to clinical or radiographic changes. It provides the added benefit of continuous monitoring, rather than the routine daily transcranial Doppler ultrasounds, which provide data for only one time point. Quantitative EEG continues to be limited by artifact and requires an experienced electroencephalographer to interpret. Use of intracortical EEG via a depth electrode has recently been documented in 5 poor-grade SAH patients and shows some promise in detecting ischemia by reducing EEG artifact.

Several new methods for measuring cerebral oxygenation are available, and a few are discussed here. Near-infrared spectroscopy was described in the 1970s and was clinically used to monitor cerebral ischemia during carotid and cardiac surgery. The device measures the transmission and absorption of near-infrared-frequency light and is used as an indirect measure of oxygenation. The monitor is noninvasive, and although it has been used with increasing frequency in SAH and TBI patients, the research is limited and sometimes contradictory. Jugular venous bulb oximetry has been used to measure jugular venous oxygen saturation, which is the result of oxygen delivery to the brain minus the cerebral metabolic rate of oxygen. It has mainly been applied to comatose patients following TBI to identify global cerebral ischemia, and desaturations have been associated with poor neurologic outcome. The use of jugular venous bulb oximetry has several risks, including insertion complications and low sensitivity.

Brain tissue oxygen monitors were first used in the 1990s and involve insertion of a small catheter directly into the brain parenchyma. Benefits of these monitors include that they can be placed in an area of interest to determine regional ischemia. They have been studied mainly in TBI, SAH, and large hemispheric infarctions and offer real-time information that can guide management of these patients.

Since 1992, cerebral microdialysis, a technique for continuous monitoring of cerebral chemistry and metabolism, has been used in neurologic ICUs. A thin catheter with a semipermeable membrane is inserted into the brain parenchyma, and perfusate is infused. Chemicals from the interstitial space diffuse through the membrane, and the fluid is collected and analyzed. The main markers investigated are glucose, lactate, pyruvate, and glutamate. Levels and ratios of these metabolic substances have been studied, and correlation with outcomes after severe TBI has been identified. Additionally, changes in these values have been shown to be early predictors of vasospasm in SAH. Microdialysis has furthered our understanding of brain energy metabolism following severe neurologic injury and may be used as a tool in the future for the direct delivery of substances to damaged tissue or for measuring drug concentrations in brain tissue.
Brain Death

With the increasing use of mechanical ventilation in the 1950s, patients who would have previously died from respiratory arrest were being kept alive in ICUs around the world. This situation resulted in a widely cited French study on *coma dépasse* (a state beyond coma, or irreversible coma) by Mollaret and Goulon published in 1959.74 This study documented 23 patients who lost consciousness and other brainstem function and reflexes but maintained a heartbeat while being kept on mechanical ventilation. This finding later prompted an ad hoc committee of anesthesiologists, neurologists, neurosurgeons, ethicists, public health and biochemistry professors, and transplant surgeons to convene at Harvard Medical School and define criteria for what was then termed brain death.75 The clinical criteria included unresponsivity, absence of movement and brainstem reflexes, areflexia, and apnea in the context of an identified cause for coma.76 In 1976, the Conference of Medical Royal Colleges and their Faculties in the United Kingdom issued a statement defining brain death as the loss of all brainstem reflexes.77 Shortly thereafter, the President’s Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research published the Uniform Determination of Death Act providing either cardiopulmonary or neurologic criteria for the legal determination of death.78

The American Academy of Neurology conducted an evidence-based review and published guidelines defining death by neurologic criteria in 1995 focusing on the clinical examination and apnea testing.79 Although all 50 states have adopted the Uniform Determination of Death Act, there remains great variability among different states and different institutions regarding the guidelines for diagnosing brain death.80 This variability holds true regarding the diagnostic criteria for brain death worldwide as well.81 Ancillary testing such as cerebral angiography, EEG, transcranial Doppler sonography, and nuclear imaging are available, but there are no clear guidelines regarding their use.

This concept of brain death remains controversial. Some have argued that the Harvard report was devised as a way to ensure organ donors in the new era of transplant medicine. Others have taken a more philosophic approach and have promoted the term *total brain failure* instead.82

Cardiopulmonary Resuscitation and Hypothermia for Cardiac Arrest

A synopsis regarding the evolution of critical care medicine as a specialty would not be complete without a discussion of cardiopulmonary resuscitation (CPR). Details regarding positive pressure ventilation were discussed earlier. Peter Safar, an anesthesiologist named the “father of CPR,” first introduced the concept of mouth-to-mouth resuscitation with the head-tilt-chin-lift method to open the patient’s airway, publishing his work in a landmark study in the *Journal of the American Medical Association* in 1958.83 Combining the findings of closed-chest cardiac massage by W. B. Kouwenhoven, James Jude, and G. Guy Knickerbocker, which showed that a pulse could be generated on dogs by external chest compressions,84 Safar united this information and came up with the “ABCs” of basic life support. Safar realized that patients surviving cardiac arrest and his own postoperative patients needed closer monitoring and thus established the first multidisciplinary physician-staffed ICU in the United States at Baltimore City Hospital in 1958.85 Dr Safar’s attention then turned toward cerebral resuscitation following cardiopulmonary arrest and included investigations into hypothermia.17

Hypothermia had been used in the 1940s to reduce cerebral edema during neurosurgery, and it was around that time that interest began to build regarding the use of hypothermia following cardiac arrest, with case series publishing successful outcomes in patients who were cooled.86 In February 2002, two studies published in the *New England Journal of Medicine* demonstrated improved neurologic outcomes in patients treated with hypothermia shortly after cardiac arrest.87,88 The 2010 practice guidelines for advanced cardiac life support include induced hypothermia to a temperature of 32°C to 34°C for 12 or 24 hours in the algorithm for post-cardiac arrest care in a patient who does not follow commands following return of spontaneous circulation.89 In many institutions, the neurocritical care team is responsible for therapeutic hypothermia following cardiac arrest.

Future Direction

Since its inception, the field of neurocritical care has grown dramatically. Much of this article has focused on TBI and multimodal monitoring where the goal is to prevent secondary injury. An emerging specialty, neurocritical care bioinformatics, attempts to use all the data gathered through multimodal monitoring and analyze these parameters at the bedside in real time to aid in decision making for complicated cases.90 This specialty may prove to be an exciting new development as we continue to understand the complex physiologic relationships following brain injury.

Although over the last several years we have learned that oxygen free radicals are a common pathway leading to neuronal dysfunction, further research is needed to identify targets to prevent cerebral reperfusion injury. One such target includes modulation of the mitochondrial permeability transition pore.91 More practical studies are currently underway as well. For example, the ATACH II study is designed to determine the ideal systolic blood pressure goal for patients experiencing acute intracranial hemorrhage.92
Several advances have been made in ischemic stroke in the last few decades. The major advance to date was in 1995 with the publication of the National Institute of Neurological Disorders and Stroke rt-PA trial supporting the use of intravenous tissue plasminogen activator (t-PA) for ischemic strokes, which demonstrated improved clinical outcomes in treated patients at 3 months. A major role of the neurocritical care unit now is to admit patients who have received rt-PA for close monitoring for at least 24 hours given the risk of bleeding. With the invention of several clot retrieval devices, endovascular treatment of stroke in addition to t-PA was becoming popular; recently, however, 3 studies (MR RESCUE, IMS III, SYNTHESIS Expansion) have not shown any benefit in clinical outcomes for ischemic stroke patients undergoing endovascular treatment with or without rt-PA. Nevertheless, further studies are in process to identify stroke patients who may benefit from endovascular therapies.

Patients in the neurologic ICU also have fascinating nonvascular pathologies, particularly the immune-mediated disorders. Guillain-Barré syndrome or acute inflammatory demyelinating polyneuropathy is perhaps one of the more common immune-mediated disorders requiring ICU admission when neuromuscular respiratory failure or autonomic instability occurs. Intravenous immunoglobulin or plasmapheresis is the preferred treatment. An interesting variant, the Miller-Fisher syndrome, was described in the 1950s as a triad of ophthalmoplegia, ataxia, and areflexia. Around the same time, Bickerstaff proposed a brainstem encephalitis. The two syndromes are now felt to represent a spectrum of the same disease process.

Another great stride in antibody-mediated diseases is seen with the paraneoplastic syndromes. Onconeural antibodies were first discovered in the 1980s, and some classic examples include Lambert-Eaton myasthenic syndrome, subacute cerebellar degeneration, and dermatomyositis. These syndromes are believed to be caused by an immune response directed against neuronal proteins expressed by a malignant tumor. Recently, the anti-N-methyl-D-aspartate receptor antibody was discovered in young women presenting with prominent psychiatric symptoms, seizures, orofacial dyskinesias, dysautonomia, and decreased level of consciousness, who were later found to have ovarian teratomas. Although this condition can be lethal, several patients who required ventilatory support, immunotherapy, and tumor resection survived with marked neurologic improvement. Several antibodies against neuronal antigens continue to be discovered, and prompt identification and tumor screening are crucial.

Conclusion

Neurocritical care is a diverse and fascinating field that has quickly blossomed from a small group of interested physicians in the 1980s to an established subspecialty encompassing doctors trained in neurology, neurosurgery, internal medicine, and emergency medicine. In 2002 the Neurocritical Care Society was founded in San Francisco, California, by a small group of neurointensivists; the group held its inaugural meeting in Phoenix, Arizona, in 2003. The United Council of Neurological Subspecialties, founded in 2005, formally recognized neurocritical care as a subspecialty fellowship. As diagnostic and therapeutic modalities continue to be developed, highly trained individuals with a profound understanding of cerebral physiology and metabolism are crucial. Neurologic ICUs are now present in most major medical centers across the United States, and several studies have demonstrated improved outcomes when neurologically ill patients are cared for by specially trained staff. As the field continues to grow, and with the support of an established professional society, advances will hopefully continue along with development of new technologies and improved clinical trial design. However, the roots of neurocritical care—mainly improving outcomes in disorders of the nervous system—can be traced back for thousands of years.
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SURGICAL MANAGEMENT OF LOW-GRADE GLIOMAS

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Low-grade gliomas represent a wide spectrum of intra-axial brain tumors with diverse presentations, radiographic and surgical appearances, and prognoses. By necessity, the goals of surgical treatment of low-grade gliomas are correspondingly wide, ranging from simple biopsy for diagnosis, to subtotal resection for relief of presenting symptoms, to attempted surgical cure. We review the indications for surgery, surgical techniques, adjuncts, and surgical goals and limitations.

As with most neurosurgical procedures, a judicious balancing of potential risks and benefits is necessary, and involvement of the patient in the process is appropriate (Figure 1).

Tumor Classifications and Epidemiology

Gliomas are intrinsic brain tumors arising from the glial cell lines, including astrocytes, ependymal cells, and oligodendrocytes. The current World Health Organization (WHO) classification uses histology to classify tumors and determine grade. The tumors are grouped by the most commonly encountered cell type and graded by the presence

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**Figure 1.** Decision algorithm for surgical intervention in low-grade gliomas. Abbreviations: CS, cortical stimulation; CSM, cortical stimulation mapping; MEP, motor-evoked potential; MRI, magnetic resonance imaging; MRS, magnetic resonance spectroscopy; SSEP, somatosensory-evoked potential.
or absence of necrosis, mitotic activity, nuclear atypia, and endothelial cell proliferation. Low-grade gliomas are classified as WHO grade I or II. Although WHO grades I and II are both considered low grade, the natural history and, therefore, the management of each group of lesions varies greatly. Intracranial WHO grade I gliomas include pilocytic astrocytomas, subependymal giant cell astrocytomas, gangliogliomas, and subependymomas. These lesions may be diffuse but are usually well defined with a benign clinical course. Patients with these lesions are often cured with a successful resection alone. We will focus primarily on the management of WHO grade II astrocytomas, pleomorphic xanthoastrocytomas, oligodendrogliomas, and oligoastrocytomas because these tumors are common in adults and present the greatest clinical challenges.

WHO grade II gliomas have an incidence of 1 to 2 per 100,000 people per year and are most likely to affect young adults. The vast majority of patients, up to 80%, present with seizures. Lesions may be either well defined, involving two or fewer lobes with clear margins on fluid-attenuated inversion recovery (FLAIR), or diffuse, with poorly defined FLAIR borders or involving more than two lobes.

**Surgical Indications for Biopsy**

When a patient is found to have a lesion consistent with a low-grade glioma, a decision must be made between surgical intervention and observation. In cases where a tissue diagnosis is thought to be useful to direct therapy, stereotactic or open biopsy may be performed. As more and more evidence argues for resection first, biopsy of low-grade gliomas is used in limited scenarios such as when a tumor is inaccessible or diffuse, or when there is a poor functional status or uncertain pathology. Open biopsy with image guidance is appropriate in cases where the lesion approaches or reaches the cortical surface in a safe, accessible area. Stereotactic biopsy is most appropriate for deep-seated or small lesions (Figure 2). Depending on the surgeon’s experience and comfort with each technique, frame-based or frameless stereotactic biopsy can be performed. Frameless stereotaxy has gained popularity as its reliability has been shown in large series.

**Technical Aspects of Stereotactic and Open Biopsy**

The goal of a biopsy is to acquire sufficient tissue to obtain a diagnosis while minimizing the risk to the patient. Prior to any biopsy, imaging is obtained for use in neuronavigation and the stereotactic targeting system in the operating room. The most common study is magnetic resonance imaging (MRI; T2-weighted images and T1-weighted with contrast) 1-mm slices; thin-cut computed tomography (CT) with contrast may be used if MRI cannot be used. Once the patient is sedated and positioned, the tumor is localized using neuronavigation and cranial landmarks. Lesions that arrive at or are close to the surface of the cortex can be accessed with a single 1-cm burr hole or with a small craniotomy. Once the dura is opened, the cortex is inspected for abnormal appearance, and biopsies are taken, then sent for frozen and permanent pathology. If the surgeon is satisfied with the tissue sample, the surgery is complete and the wound is closed. Although the goals of a stereotactic biopsy are the same, the technique requires some additional planning. Prior to incision, a plan is defined in the neuronavigation computer, including the entry point and the trajectory of the needle to the target. Several general principles are used when making any stereotactic plan, whether for stereotactic biopsy or deep brain stimulator lead placement. The trajectory should avoid sulci in order to prevent vascular injury and should try not to pass through the ventricle because of the risk of intraventricular hemorrhage and subsequent hydrocephalus. Generally, lesions involving the basal ganglia are approached with a frontal entry point; the precentral gyrus can be avoided by placing the burr hole anterior to its location. Brainstem lesions, such as pontine gliomas, can be accessed with a burr hole in the suboccipital area, with a

![Figure 2. A, A lesion involving the midbrain and pons. This deep-seated lesion involving multiple eloquent structures is an ideal candidate for stereotactic needle biopsy. B, A superficial lesion involving bilateral frontal lobes, more so on the left. This lesion involves the cortex and is easily accessed via an open biopsy.](image)
Surgical Indications for Resection

The indications for surgical resection include diagnosis, relief of neurological deficits, medically uncontrolled epilepsy, relief of mass effect, and possible improvement in progression-free survival (PFS) or overall survival (OS). The usefulness of surgical resection for diagnosis and relief of mass effect are self-evident. If mass effect is causing neurological deficits, removing the majority of the mass is likely to aid in relief of neurological deficits. If the tumor is infiltrative of demonstrably functional areas, but does not cause mass effect, surgical resection is unlikely to relieve symptoms and may bring a high risk of postoperative deficit. Surgical resection of a low-grade glioma in a patient who has medically intractable epilepsy related to the glioma is a common indication for surgery. In patients with low-grade glioma-associated seizures, surgical resection results in seizure improvements in almost all patients: Engel class 1 outcome (seizure-free) in 67% to 70% of patients and improvement in seizure frequency in another 20% to 25%.16-19 Moreover, increased extent of tumor resection was found to be an important factor in multivariate analysis of seizure outcome in low-grade glioma.16-18

There has been significant historical discussion regarding the influence of the extent of resection (EOR) and overall survival in the treatment of low-grade gliomas.20 Arguments for biopsy alone or radiographic monitoring have been purported since the advent of CT and MRI technologies. Similarly, as our ability to detect these lesions has grown with increasingly sensitive neuroimaging modalities, we have been forced to scrutinize our management approaches to these lesions. Our diagnostic and surgical treatment algorithm has been outlined above. Older retrospective studies comparing subjective EOR parameters (eg, “gross total resection” vs “subtotal resection” vs “biopsy”) have yielded variable results.20-21 However, recent literature examining volumetric EOR data has identified consistent associations between increased EOR and increased patient PFS and OS.22-27 On the basis of these data, a growing number of surgeons pursue a maximal resection of low-grade gliomas. In cases without mass effect and where the expected volumetric resection of tumor is less than 50%, it may be appropriate to consider biopsy or radiologic monitoring as outlined above.21-24 Although minor transient deficits are common after surgery for eloquent low-grade glioma,21,28,29 most resolve over the first several months postoperatively and thus yield a low rate of permanent neurologic morbidity and consequent functional impairment.28

Preoperative Evaluation of the Surgical Patient

The most critical factor in surgical planning for resective surgery in low-grade gliomas is the neuroanatomic milieu within which the neoplastic lesion exists. The intuitively obvious evidence of this fact has been demonstrated in numerous large case series,21-25,30,32 each of which has shown the prognostic importance of the anatomic location of low-grade gliomas. Preoperative MRI (T2-weighted images and T1-weighted with contrast) with 1-mm (or smaller) slices is used to evaluate and categorize lesions into 3 groups: presumed eloquent location, near-eloquent location, and noneloquent location. Our definition of topographic regions of the brain with presumed eloquence is in line with previously published studies20,31 and includes the primary sensorimotor cortex of the precentral and postcentral gyri, the Wernicke area (posterior portion of the superior temporal gyrus and the inferior parietal lobule), the Broca area (inferior dominant frontal lobe), the calcarine visual cortex, the basal ganglia, the internal capsule, the thalamus, and the white matter paths of each. If any part of the lesion is found to infiltrate these regions, it is regarded as being located in...
presumed eloquent brain; if it approaches but does not clearly involve these regions, it is considered near eloquent; and if it is situated in a separate anatomic location, it is considered noneloquent. The preoperative MRI also is used to identify functionally important vessels that will be encountered and must be spared during the operation.

The classification of a lesion as located in eloquent, near-eloquent, or noneloquent brain has ramifications for the operative strategy used. Although lesions distant from eloquent anatomic structures do not require further preoperative investigation, it may be prudent to pursue preoperative functional imaging in lesions involving eloquent and near-eloquent brain to help define the critical structures within the proposed operative field. This imaging includes diffusion tensor tractography to define white matter tracts (e.g., the posterior limb of the internal capsule), and functional MRI (fMRI) to localize primary speech and motor cortices (Figure 3, A and B). While the use of fMRI allows the surgeon to better assess the relationship of a lesion to eloquent cortex, there are considerable limitations, especially when mapping language areas. Multiple recent studies have shown relatively reliable motor mapping when compared to intraoperative stimulation. However, while fMRI largely has replaced the Wada test for language lateralization, fMRI does not allow for precise localization of language, which is reflected by the wide range of reported results in the literature. A review of 5 studies showed language mapping sensitivity from 59% to 100% and specificity from 0% to 97% when compared to intraoperative stimulation.34-37 Various authors have used newer noninvasive technologies for anatomic mapping such as magnetoencephalography and transcranial magnetic stimulation. Advanced preoperative functional imaging may serve two important purposes: (1) neuroplasticity may induce migration of functional activity to other neighboring regions in tumor-infiltrated brain, thus providing a better understanding of the true functional eloquence of the anatomically eloquent region under investigation; and (2) it enables the surgeon to understand the most dangerous regions of the tumor with regard to neurological morbidity and to estimate the extent of safe resection prior to the operation, further informing discussions with both the patient and multidisciplinary care providers considering adjuvant and neoadjuvant treatment options.

Intraoperative Monitoring and Cortical Stimulation

The paradigm of noneloquent versus eloquent and near-eloquent lesions is also used to define the extent of intraoperative monitoring and mapping required to safely perform a maximal resection of low-grade gliomas. In noneloquent lesions, the low risk of surgical trauma to anatomically eloquent regions of the brain and the low likelihood of aberrant relocation of functional neural tissue enables a lower level of intraoperative monitoring. Conversely, in eloquent and near-eloquent lesions the potential for neurologic injury is magnified. To maximize safe resection in these cases, awake craniotomy may be employed if the patient is cooperative and capable of tolerating such a procedure.29,30,42,43 This method enables active monitoring of the functional neural tissue in the operative bed and enables intraoperative mapping of functional tissue. Addressing the eloquent region of tumor as the final step of the surgical resection and using cortical and subcortical stimulation to map the eloquent region of tumor during surgery allows a safe, maximal tumor resection. A member of the mapping team is appointed to continuously monitor speech and motor function during the resection. Bipolar electrodes (Integra) are used starting at an amplitude of 2 mA (pulse frequency 60 Hz and 2-3 seconds duration). The surgical team notes where stimulation produces motor reaction, sensory reaction, or speech arrest.28,44 Stimulation levels are raised until a...
physiological response is noted or until an after discharge is noted on electroencephalogram (Figure 4). A stimulation site is considered positive if the response is clear and reproducible. Resection of tumor comes no closer than 1 cm from a positive stimulation site, and the vascular supply to the area must be preserved.\textsuperscript{45,46} In a patient with a near-eloquent lesion who is unable to tolerate awake craniotomy, phase reversal of electrocorticography using subdural electrodes may be used to identify the central sulcus and perirolandic gyri.\textsuperscript{47} Cortical stimulation at increased amplitudes also may be used in the sleeping patient to induce motor activity and to identify motor cortex. During stimulation it is important to be prepared for an induced seizure, the anesthesia team must be informed of stimulation, and cold saline irrigation\textsuperscript{48} should be immediately available to help abort stimulation-induced seizures. The anesthetic course for awake craniotomy with intraoperative mapping involves generous application of local anesthetic to achieve a complete scalp block. During pinning and surgical opening the patient is heavily sedated, typically with propofol and remifentanil.\textsuperscript{28,30,42,44} After exposure is complete, the sedation is lightened to enable patient participation during mapping and tumor resection. Finally the patient is resedated after the tumor resection is completed for final closure.

### Surgical Technique

Surgical exposure depends on the anatomic location and size of the lesion. Intraoperative stereotactic navigation is useful to plan the craniotomy site and dimension. Positioning, skin incision, and type of craniotomy are performed in a manner similar to the treatment of other intracranial lesions. After the craniotomy has been performed and the dural opening made, the next steps in surgical treatment involve localization of the lesion within the surgical field. The margins of the tumor are mapped with the aide of stereotactic neuronavigation, which also provides visual cues to abnormal tissue (edematous regions, grayish discoloration, and increased vascularity) (Figure 5). The borders of the tumor can be defined with surface and depth markers; once resection has begun, the brain can shift, rendering neuronavigation less reliable. For eloquent and near-eloquent lesions, cortical mapping is performed (as described above) to provide an outline of the resection margins and to identify functionally critical cortical regions. Resection should begin at the least eloquent areas and end at the most eloquent areas. The corticotomy is made through noneloquent tissue, with attention to surrounding vascular structures. A sufficient biopsy of the lesion is performed and sent for pathology; care should be taken to obtain tissue from different regions of the lesion and to include samples of any enhancing or visually atypical areas to minimize the risk of misdiagnosing a higher-grade lesion due to sampling error. After sufficient tissue is obtained for pathology, tumor resection is performed with the aide of suction, bipolar electrocautery, and ultrasonic surgical aspirator. The surgeon uses color, firmness, and texture to follow the tumor from sulcus to sulcus. In eloquent and near-eloquent lesions, subcortical mapping is used to define the resection margin and avoid functionally eloquent white matter structures. At the border of the lesion, distinguishing between normal tissue and tumor may become quite difficult. A combination of neuronavigation, visual cues (typical metallic-gray discoloration of the tissue\textsuperscript{49}), various tumor-staining dyes such as 5-aminolevulinic acid,\textsuperscript{50} and intraoperative imaging (ultrasound,\textsuperscript{51} CT,\textsuperscript{52,53} and MRI\textsuperscript{54}) are employed to define the precise margins of resection. Multiple studies have reported increased extent of resection with the use of intraoperative MRI.\textsuperscript{55-60} However, the increased operative times, narrow applicability, and high cost make this technology far from ideal. Intraoperative ultrasound fused with preoperative MRI has been described in the neurosurgical literature and may be beneficial.\textsuperscript{61} Another technique, based on observations in diffuse tumors that abnormal cells can be found up to 20 mm beyond any MRI abnormalities,\textsuperscript{62} is the “supratotal” resection. This technique involves extending the resection around a tumor beyond abnormalities seen on imaging until eloquent areas are localized.\textsuperscript{43} The surgery is ended when maximal resection of the lesion is complete, when there is a new deficit, or when changes in monitoring are noted.

**Figure 4.** A, Cortical mapping with a bipolar stimulator. When eloquent areas are identified, they are marked with the white surface marker that is seen on the field. During stimulation, the electroencephalogram is monitored. B, The recording shows the effect of induced regional activation and not focal activation between the bipolar stimulator probes. This induced activation may lead to both false positive localization and generalized seizures.
The goals of surgery must always remain in the forefront of the surgeon’s mind during the preoperative and operative phases of treating patients with low-grade gliomas. Along these lines, surgical intervention can offer a number of benefits to patients with low-grade gliomas. First, the most modest, but critical, function of surgery is to obtain tissue to provide the patient and oncology team with a definitive histopathologic and molecular diagnosis of the lesion. This diagnosis is critical in planning subsequent chemotherapy or radiotherapy where appropriate and also may help to guide further surgical decision making in the event of recurrence or of residual tumor. Second, resection of tumor provides the additional benefits of removing any mass effect resulting from the tumor’s growth and also achieving a critical cytoreduction of neoplastic cells as the first step in treatment of these lesions. Finally, in patients with resectable lesions, total excision of the tumor may result in long-term oncologic control. In all cases, the goal is to achieve the surgical goals without causing new neurological deficits. Thus, the ideal surgery will achieve a tissue diagnosis along with total excision of the lesion and cause no additional neurologic morbidity. However, certain tumors, particularly those located in functionally eloquent regions, may not permit all of these goals to be achieved, and it is here that surgical judgment of the value of further resection at the risk of neurologic morbidity is most critical. In many cases, taking the resection to the extreme margins of functional tissue with the aid of intraoperative cortical/subcortical mapping will allow for a maximal resection but may induce transient partial neurologic deficits. Depending on the goals of the procedure, specific surgical endpoints may include adequate biopsy; sufficient debulking to remove mass effect from tumor; resection of tumor to eloquent tissue as determined by either anatomic topography, functional imaging, intraoperative monitoring, cortical/subcortical mapping, or neurologic deficit during awake craniotomy; or gross total resection of tumor.

Postoperative Management

After surgery, the patient is awoken from anesthesia and admitted to the intensive care unit overnight for neurological monitoring. The patient’s neurologic status is monitored, normotension is maintained, and medication for seizure prophylaxis is continued. If the patient had no seizure activity prior to surgery, the surgeon may choose to place the patient on a short course of seizure prophylaxis. Although perioperative antiepileptic medication is commonly administered for tumors, a recent prospective study has demonstrated a perioperative clinical seizure rate of only 3%, which calls into question the need for prophylactic medications for this population. The following day, the patient is transitioned out to a general floor or even home depending on the patient’s functional status. MRI with and without contrast is done prior to 72 hours after surgery to detect residual tumor. The patient will return to the clinic 10 to 14 days later for inspection of the wound and removal of staples or sutures. The initiation of chemotherapy or radiation is often delayed for 2 weeks or more from surgery, if possible, to limit the effects on wound healing.

Conclusion

A growing body of evidence shows that aggressive surgical resection of low-grade gliomas may improve symptoms, extend PFS, and even cure a select few patients. With the application of preoperative functional imaging, intraoperative navigation, and cortical stimulation, neurosurgeons are able to perform more complete resections while limiting the risk to patients. Although the treatment paradigm has moved away from biopsy and observation, that approach still has a role when the patient has a poor status or when the tumor is unresectable.

Figure 5. Low-grade glioma. A, Preoperative magnetic resonance imaging (MRI) shows a left insular glioma that extends to the frontal and temporal operculum. B, On gross inspection, the tumor can initially be identified as a gray discoloration of the cortex. Resection is then started with ultrasonic aspiration and bipolar cautery. C, The postoperative MRI shows the resection cavity with decreased mass effect on surrounding structures.
References


Introduction

Psychosis in Parkinson’s disease clinically ranges from illusions to hallucinations and delusions, with visual hallucinations being the most frequent form. Visual hallucinations develop in more than 50% of Parkinson’s disease patients and, once present, are progressive, chronic, and associated with increased nursing home placement, morbidity, and mortality. Risk factors for hallucinations in Parkinson’s disease patients include older age, advanced disease, cognitive impairment, depression, and sleep disturbances. Although dopaminergic medications play a role in the pathophysiology of Parkinson’s disease hallucinations, the development of the hallucinations extends beyond mesolimbic dopaminergic receptor hypersensitivity or stimulation. At present, however, their exact mechanisms and neurobiological substrates are not fully known. Current evidence favors multiple levels of cerebral dysfunction including aberrant “bottom-up” and “top-down” visual processing, with faulty input from the visual system and brainstem to higher cortical visual areas (eg, occipital-temporal and occipital-parietal lobes) and altered cortical integration from orbitofrontal and dorsolateral prefrontal cortex to cortical visual regions. Furthermore, these visual processing aberrations invoke the ventral “what” and dorsal “where” streams, which are responsible for object recognition and spatial location, respectively. Visual hallucinations experienced by Parkinson’s disease patients may reflect disturbances in the brain’s ability to attend to and process these visual stimuli, integrate sensory information and prior expectations, and generate correct interpretations of visual input, thereby integrating elements of attentional, cognitive, emotional, and visuoperceptive processes.

Neuroimaging studies using structural, metabolic, and functional techniques permit in vivo investigations of underlying brain abnormalities in Parkinson’s disease patients with hallucinations. Metabolic and functional neuroimaging studies in Parkinson’s disease visual hallucinators, compared to nonhallucinators, frequently reveal dysfunction in brain regions involved in visuoperception, namely the occipital, temporal, and parietal lobes, and thus suggest that the culprit may be primarily aberrant visual processing. This decreased activation in the visual “what” and “where” regions of the brain in hallucinators has been coupled in some studies with increased activation of frontal or subcortical regions in response to functional MRI visual stimulation paradigms or hyperperfusion of temporal, precentral, or frontal regions on metabolic imaging studies. Other functional MRI studies, however, reveal decreased activation in frontal regions in hallucinators just prior to image recognition or decreased activation in fronto-parietal networks. Although these somewhat differing results of metabolic and functional neuroimaging studies do not resolve the debate of “bottom-up” or “top-down” processing, they are united by the shared theme of disrupted posterior and anterior brain regions. Collectively, they suggest a role of attentional, cognitive, emotional, and visuoperceptive processes, individually or in combination, in the clinical manifestation of visual hallucinations.

Despite the predominant decreased activation in the posterior visuoperceptive brain regions found in many of the metabolic and functional neuroimaging studies, it is surprising that, to date, only one structural brain MRI study using an automated, unbiased analytic technique of whole-brain voxel-based morphometry (VBM) to compare Parkinson’s disease visual hallucinators to nonhallucinators has revealed gray matter atrophy in these areas (ie, lingual visuoperceptive region atrophy independent of cognitive status in Parkinson’s disease hallucinators).
gyrus, superior parietal lobule). Most other structural MRI studies using VBM analyses demonstrate predominantly decreased gray matter volumes in hippocampal, limbic, paralimbic, and neocortical regions in Parkinson’s disease hallucinators, compared to nonhallucinators.21-23 These brain regions, particularly the mesial temporal lobe, however, are also implicated in memory and cognitive functions26 and exhibit atrophy on structural MRI scans in Parkinson’s disease dementia patients.27 Thus, the co-occurrence of cognitive impairment or dementia in Parkinson’s disease hallucinators potentially confounds our interpretation of these MRI findings as representing neuroanatomical substrates specifically associated with hallucinations in Parkinson’s disease. Moreover, in several MRI studies, even those hallucinating Parkinson’s disease patients classified as without dementia frequently exhibited significantly worse performance on global cognitive function, memory, and executive function tests, compared to nonhallucinating Parkinson’s disease patients without dementia,24,25 thereby indicating that the examined groups were not truly of comparable cognitive abilities.

Although the pathophysiology of hallucinations may be linked to impaired attentional and visuoperceptive processing, and although their presence has been considered an important predictor of dementia,28 we hypothesize that these two behavioral abnormalities, namely hallucinations and dementia, may have distinct and independent neurobiological substrates. The identification of structural MRI differences in Parkinson’s disease hallucinators, independent of cognitive deficits, would be clinically important not only for more accurate establishment of underlying neurobiological mechanisms, but also for the development of novel therapies targeting Parkinson’s disease hallucinations and visuoperceptive functions. Thus, it is important to examine Parkinson’s disease hallucinators and nonhallucinators of comparable cognitive function to identify neuroanatomical contributions that are specific to Parkinson’s disease hallucinations. Accordingly, the aim of our study was to use structural MRI whole-brain VBM analyses to identify changes in gray matter in Parkinson’s disease participants with current and chronic visual hallucinations where dementia was controlled for, that is, where participants were matched for cognitive status (with/without dementia) to Parkinson’s disease patients without visual hallucinations.

Materials and Methods

Participants

Parkinson’s disease participants were recruited from the Rush University Medical Center movement disorders clinic as part of an ongoing study of clinical and neuroimaging markers of Parkinson’s disease-related cognitive and behavioral problems.29 From a cohort of 100 Parkinson’s disease participants, we
identified 25 with current and chronic visual hallucinations. From the remaining 75 nonhallucinators, we selected 25 who were matched to the hallucinator group on cognitive status and age. All Parkinson’s disease participants were examined by a movement disorders neurologist (J.G.G.) and met United Kingdom Parkinson’s Disease Society Brain Bank criteria. Parkinson’s disease participants had disease durations of ≥ 4 years and were on stable medication regimens. Exclusionary criteria were (1) atypical or secondary forms of parkinsonism (eg, dementia with Lewy bodies, multiple system atrophy, progressive supranuclear palsy, corticobasal degeneration, or parkinsonism due to neuroleptic exposure, cerebrovascular disease, or known structural causes); (2) severe or unstable depression; (3) anticholinergic medications (eg, trihexyphenidyl, benztropine, tricyclic antidepressants); (4) other medical or neurological reasons for cognitive impairment (eg, seizures, strokes, head trauma, significant vision or hearing deficits); or (5) contraindications to MRI (eg, cardiac pacemaker/defibrillator, surgical clips, foreign metallic implants). In Parkinson’s disease participants with dementia, all had motor symptoms for at least 1 year prior to dementia onset. The study was approved by the Institutional Review Board of Rush University Medical Center in Chicago, Illinois; participants gave written informed consent to participate in the study.

Parkinson’s disease participants were classified as current and chronic hallucinators if they met the following criteria: (1) current hallucinations: a score ≥ 1 on the Movement Disorder Society Unified Parkinson’s Disease Rating Scale (MDS-UPDRS) Part I question 1.2, “Hallucinations and Psychosis,” which determines whether the patient has seen, heard, smelled, or felt things that were not really there over the past week (the question is scored as follows: 0: normal, no hallucinations or psychotic behavior; 1: slight illusions or nonformed hallucinations, but patient recognizes them without loss of insight; 2: mild, formed hallucinations independent of environmental stimuli, no loss of insight; 3: moderate, formed hallucinations with loss of insight; 4: severe, patient has delusions or paranoia); and (2) chronic hallucinations: the presence of psychotic symptoms, occurring for at least 1 month, and fulfilling diagnostic criteria for Parkinson’s disease-associated psychosis proposed by the National Institutes of Health/National Institute of

Table 1. Clinical Features of the Parkinson’s Disease Cohorta

<table>
<thead>
<tr>
<th></th>
<th>Parkinson’s Disease Nonhallucinators (n = 25)</th>
<th>Parkinson’s Disease Hallucinators (n = 25)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Demographics</strong></td>
<td></td>
<td></td>
<td>---------</td>
</tr>
<tr>
<td>Age, y</td>
<td>75.4 (6.1)</td>
<td>74.8 (6.0)</td>
<td>0.73</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>18 (51.4)</td>
<td>17 (48.6)</td>
<td>0.76</td>
</tr>
<tr>
<td>Education, y</td>
<td>15.7 (2.9)</td>
<td>15.4 (3.3)</td>
<td>0.75</td>
</tr>
<tr>
<td>Disease duration, y</td>
<td>10.8 (4.4)</td>
<td>13.1 (4.6)</td>
<td>0.08</td>
</tr>
<tr>
<td><strong>Cognition</strong></td>
<td></td>
<td></td>
<td>---------</td>
</tr>
<tr>
<td>MMSE</td>
<td>25.1 (4.4)</td>
<td>23.9 (5.4)</td>
<td>0.38</td>
</tr>
<tr>
<td>CDR Global Score, median (range)</td>
<td>0.5 (0-2)</td>
<td>0.5 (0-2)</td>
<td>0.46</td>
</tr>
<tr>
<td>CDR Sum of Boxes</td>
<td>3.2 (3.2)</td>
<td>3.5 (3.1)</td>
<td>0.72</td>
</tr>
<tr>
<td><strong>Motor</strong></td>
<td></td>
<td></td>
<td>---------</td>
</tr>
<tr>
<td>MDS-UPDRS total motor score</td>
<td>43.5 (13.2)</td>
<td>39.0 (13.8)</td>
<td>0.24</td>
</tr>
<tr>
<td>MDS-UPDRS Hoehn and Yahr, median (range)</td>
<td>3 (2-5)</td>
<td>3 (2-5)</td>
<td>0.85</td>
</tr>
<tr>
<td><strong>Medications</strong></td>
<td></td>
<td></td>
<td>---------</td>
</tr>
<tr>
<td>LEDD, mg/d</td>
<td>787.8 (356.9)</td>
<td>808.3 (329.5)</td>
<td>0.83</td>
</tr>
<tr>
<td>Dopamine agonist use, n (%)</td>
<td>7 (14%)</td>
<td>8 (16%)</td>
<td>0.76</td>
</tr>
<tr>
<td>Antipsychotic use, n (%)</td>
<td>3 (12.0%)</td>
<td>6 (24.0%)</td>
<td>0.27</td>
</tr>
<tr>
<td>CPZ equivalent dose, mg/d</td>
<td>12.0 (37.1)</td>
<td>13.3 (27.6)</td>
<td>0.33</td>
</tr>
<tr>
<td>Cognitive medication, n (%)</td>
<td>7 (28.0%)</td>
<td>7 (28.0%)</td>
<td>1.0</td>
</tr>
</tbody>
</table>

Abbreviations: CDR, Clinical Dementia Rating; CPZ, chlorpromazine; LEDD, levodopa equivalent daily dose; MDS-UPDRS, Movement Disorder Society Unified Parkinson’s Disease Rating Scale; MMSE, Mini-Mental State Examination.

aData presented as mean (SD) unless otherwise noted.
Mental Health (NIH/NIMH) Work Group. All Parkinson’s disease hallucinators had visual hallucinations, though participants with hallucinations in other sensory modalities (e.g., auditory, olfactory, tactile) were included in this group if these hallucinations occurred in addition to visual hallucinations. Parkinson’s disease participants without hallucinations had a score of 0 (“normal”) on the MDS-UPDRS “Hallucinations and Psychosis” question and did not meet the NIH/NIMH Work Group criteria for Parkinson’s disease-associated psychosis.

The Parkinson’s disease participants were matched by their cognitive status, defined as either with or without dementia, so that the hallucinator and nonhallucinator groups had equal numbers of participants with dementia. Dementia was defined by MDS Parkinson’s disease dementia (PDD) criteria and determined in a consensus conference involving a neurologist specializing in movement disorders and neuropsychiatry (J.G.G.) and 2 senior neuropsychologists (G.T.S., B.B.), using the clinical and neuropsychological data described below and previously published methods. The Parkinson’s disease participant groups were also matched by age (± 3 years).

Evaluations

Clinical evaluations included assessments of demographics, medications, and disease-related features including the MDS-UPDRS and Hoehn and Yahr stage. Dopaminergic medications for Parkinson’s disease were converted to chlorpromazine equivalents. Parkinson’s disease participants underwent comprehensive cognitive evaluations including assessments of demographics, age (± 3 years).

Cognitive domain scores were calculated by averaging z scores for neuropsychological tests within specific domains.

Magnetic Resonance Imaging Acquisition and Processing

Magnetic resonance images were acquired on a 1.5-T Signa scanner (GE Healthcare). Participants underwent a 3-dimensional MRI with a T1-weighted magnetization-prepared rapid acquisition with gradient echo scan (MPRAGE) sequence with the following parameters: 166 contiguous sagittal images, 1.2 mm thick, matrix = 192×192, field of view = 24 cm, echo time = minimum full, repetition time = 1000 ms, flip angle = 8°, NEX 1, phase field of view 1, and band width 15.63 Hz.

Structural imaging data were preprocessed and analyzed using statistical parametric mapping 8 (SPM8) (http://www.fil.ion.ucl.ac.uk/spm) implemented in Matlab 7.4a (MathWorks). The VBM8 toolbox was used to perform the following steps on the raw images: segmentation into gray matter, white matter, and cerebrospinal fluid based on tissue probability maps; and using DARTEL processing techniques, which provide an algorithm for accurate diffeomorphic image registration; normalization of gray matter segments to a gray matter template in Montreal Neurological Institute (MNI) space; modulation of the normalized gray matter images with the Jacobian determinants; and smoothing of images with a 3-dimensional Gaussian filter of 8 mm full width at half maximum (FWHM). An estimation of total intracranial volume was calculated from the addition of global gray, white, and cerebrospinal fluid volume carried out by SPM8 as part of the standard processing stream and was included as a covariate in the analysis of covariance when comparing gray matter volumes between the Parkinson’s disease hallucinator and nonhallucinator groups. Voxels that demonstrated significant group differences between Parkinson’s disease hallucinators and nonhallucinators were used to create regions of interest and extract volume measurements using the statistical parametric mapping sample volume function. Multiple linear regression models were used to examine the relationship between the gray matter volumes for these regions (i.e., independent variable) and severity of hallucinations as measured by the MDS-UPDRS Part I question 1.2. Neuroanatomical regions of significance were identified with the statistical parametric mapping glassbrain2 program, which names the MNI coordinates used in statistical parametric mapping and adds corresponding Talairach coordinates based on the Wake Forest University PickAtlas database (fmri.wfubmc.edu/software/PickAtlas). Corresponding Brodmann areas for neuroanatomical regions of significance were identified using Talairach Daemon (www.talairach.org). All MRI processing and analyses were performed blinded to participant identity and clinical diagnosis.
Statistical Analyses

Statistical analyses for demographic and disease-related variables were performed with SPSS 18.0 for Mac (PASW 19; SPSS Inc) using 2-tailed t tests or chi-squared tests as appropriate. Statistical significance for these analyses was set at $P < .05$. For image analyses, between-group voxel-wise comparisons were conducted with the general linear model within SPM8. Group differences were tested using a whole-brain approach. The significance threshold for differences on image analyses was set at $P < .01$, uncorrected, with a cluster extent threshold, $k = 10$. Relationships between gray matter volumes extracted from the regions that significantly differed between groups and the hallucination severity, as measured by the MDS-UPDRS “Hallucinations and Psychosis” item, were examined in the Parkinson’s disease hallucinators using the SPM8 multiple regression (correlation) module with the same statistical and cluster thresholds as the whole-brain analysis.

Results

Clinical Characteristics

Twenty-five Parkinson’s disease participants with current and chronic hallucinations were compared to 25 Parkinson’s disease participants without hallucinations. All hallucinators had visual hallucinations as their primary modality; additional auditory hallucinations were present in 6 of 25 hallucinators. Of the hallucinations, the median score for the MDS-UPDRS question on hallucinations and psychosis was 2 (range, 1-4), with 10 participants (40%) with illusions or nonformed hallucinations (score 1); 11 participants (44%) with mild, formed hallucinations with insight (score 2); 2 participants (8%) with moderate, formed hallucinations without insight (score 3); and 2 participants (8%) with delusions (score 4). There were no significant differences between the hallucinator and nonhallucinator participants in age, gender, education, or duration of Parkinson’s disease (Table 1). The two Parkinson’s disease groups were matched

<table>
<thead>
<tr>
<th>Domain</th>
<th>Parkinson’s Disease Nonhallucinators (n = 25)</th>
<th>Parkinson’s Disease Hallucinators (n = 25)</th>
<th>$P$ Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Attention/working memory</td>
<td>$-2.13 (1.6)$</td>
<td>$-2.01 (1.5)$</td>
<td>0.78</td>
</tr>
<tr>
<td>Executive function</td>
<td>$-2.2 (1.2)$</td>
<td>$-2.0 (1.3)$</td>
<td>0.55</td>
</tr>
<tr>
<td>Language</td>
<td>$-1.2 (1.4)$</td>
<td>$-1.1 (1.3)$</td>
<td>0.80</td>
</tr>
<tr>
<td>Memory</td>
<td>$-2.2 (1.4)$</td>
<td>$-1.8 (1.5)$</td>
<td>0.37</td>
</tr>
<tr>
<td>Visuospatial function</td>
<td>$-2.1 (2.0)$</td>
<td>$-2.8 (1.9)$</td>
<td>0.19</td>
</tr>
</tbody>
</table>

*Data presented as mean (SD).
in terms of their cognitive status with 12 participants with dementia and 13 participants without dementia per group. There were no significant differences between the hallucinator and nonhallucinator groups in global cognitive measures, namely mean MMSE scores, CDR global scores, or CDR sum of boxes scores. Also, the groups did not significantly differ in their performance across the 5 cognitive domains, depicted as mean $z$ scores of neuropsychological tests in the domains of attention/working memory, executive function, language, memory, and visuospatial functions (Table 2). Finally, the Parkinson’s disease groups did not differ significantly in motor severity scores, measured by the MDS-UPDRS part III motor score and Hoehn and Yahr stage, or dopaminergic medications for Parkinson’s disease, including levodopa equivalent doses and use of dopamine agonists. Cognitive medications (ie, cholinesterase inhibitors or memantine) were used by 7 participants in each Parkinson’s disease group. Antipsychotic medications (ie, quetiapine) were used by 6 hallucinators and 3 nonhallucinators; the nonhallucinators, however, were taking low-dose quetiapine for problems with sleep and impulsivity rather than hallucinations.

<table>
<thead>
<tr>
<th>Region (BA)</th>
<th>Cluster Size (mm$^3$)</th>
<th>Cluster Significance</th>
<th>T value</th>
<th>Z value</th>
<th>Talairach Coordinates (x, y, z)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Right cuneus (BA 18)</td>
<td>482</td>
<td>0.001</td>
<td>3.16</td>
<td>2.99</td>
<td>1, −72, 19</td>
</tr>
<tr>
<td>Right fusiform gyrus (BA 20)</td>
<td>335</td>
<td>0.001</td>
<td>3.43</td>
<td>3.23</td>
<td>43, −5, −22</td>
</tr>
<tr>
<td>Left inferior parietal lobule (BA 40)</td>
<td>187</td>
<td>0.001</td>
<td>3.37</td>
<td>3.17</td>
<td>−39, −51, 38</td>
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<tr>
<td>Left precentral gyrus (BA 6)</td>
<td>169</td>
<td>0.001</td>
<td>3.21</td>
<td>3.04</td>
<td>−61, −11, 39</td>
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<tr>
<td>Right middle occipital gyrus (BA 18)</td>
<td>140</td>
<td>0.005</td>
<td>2.68</td>
<td>2.58</td>
<td>9, −97, 15</td>
</tr>
<tr>
<td>Right middle occipital gyrus (BA 19)</td>
<td>140</td>
<td>0.001</td>
<td>3.46</td>
<td>3.25</td>
<td>36, −75, 7</td>
</tr>
<tr>
<td>Left cuneus (BA 17)</td>
<td>139</td>
<td>0.002</td>
<td>3.07</td>
<td>2.92</td>
<td>−18, −78, 5</td>
</tr>
<tr>
<td>Right lingual gyrus (BA 19)</td>
<td>113</td>
<td>0.003</td>
<td>2.94</td>
<td>2.8</td>
<td>19, −64, 3</td>
</tr>
<tr>
<td>Right inferior parietal lobule (BA 40)</td>
<td>105</td>
<td>0.001</td>
<td>3.15</td>
<td>2.98</td>
<td>40, −53, 43</td>
</tr>
<tr>
<td>Right cingulate gyrus (BA 24)</td>
<td>89</td>
<td>0.001</td>
<td>3.54</td>
<td>3.32</td>
<td>9, 0, 29</td>
</tr>
<tr>
<td>Left/right cingulate gyrus (BA 24)</td>
<td>53</td>
<td>0.002</td>
<td>3.07</td>
<td>2.92</td>
<td>0, 5, 40</td>
</tr>
<tr>
<td>Left fusiform/subgyral gyrus (BA 20)</td>
<td>39</td>
<td>0.003</td>
<td>2.87</td>
<td>2.74</td>
<td>−43, −13, −20</td>
</tr>
<tr>
<td>Left paracentral lobule (BA 5)</td>
<td>38</td>
<td>0.006</td>
<td>2.64</td>
<td>2.53</td>
<td>−16, −42, 55</td>
</tr>
<tr>
<td>Left middle occipital gyrus (BA 18)</td>
<td>37</td>
<td>0.001</td>
<td>3.03</td>
<td>3.03</td>
<td>−30, −80, 1</td>
</tr>
<tr>
<td>Left cingulate gyrus (BA 31)</td>
<td>23</td>
<td>0.003</td>
<td>2.92</td>
<td>2.78</td>
<td>−15, −36, 36</td>
</tr>
<tr>
<td>Left middle occipital gyrus (BA 19)</td>
<td>21</td>
<td>0.006</td>
<td>2.64</td>
<td>2.54</td>
<td>−52, −78, 5</td>
</tr>
<tr>
<td>Right precentral gyrus (BA 6)</td>
<td>18</td>
<td>0.004</td>
<td>2.73</td>
<td>2.62</td>
<td>65, 6, 19</td>
</tr>
<tr>
<td>Right lingual gyrus (BA 18)</td>
<td>17</td>
<td>0.007</td>
<td>2.55</td>
<td>2.46</td>
<td>6, −83, −5</td>
</tr>
</tbody>
</table>

Table 3. Anatomical Location of Areas Showing Significant Differences in Gray Matter Volume Between Parkinson’s Disease Participants With Hallucinations and Without Hallucinations

Abbreviation: BA, Brodmann area.

**Image Analyses**

On whole-brain VBM analyses, the Parkinson’s disease hallucinators exhibited significant clusters of reduced gray matter volume compared to the nonhallucinators. The regions where the hallucinators exhibited reduced gray matter volumes included the bilateral cunei, fusiform, middle occipital, precentral, and cingulate gyri and inferior parietal lobules; right lingual gyrus; and left paracentral gyrus (Figure 1, Table 3). We did not detect any gray matter volume differences between the two groups in the mesial temporal lobe, insula, or brainstem, which were regions specifically examined given findings in previous studies. There were no cerebral areas where the nonhallucinators had significantly greater gray matter volume loss than hallucinators.

There was a significant relationship between the gray matter volumes, calculated for those regions in which the hallucinating participants demonstrated reduced gray matter, and the severity of hallucinations, measured by the MDS-UPDRS “Hallucination and Psychosis” item. Four of the 18 regions that had reduced gray matter volumes on VBM analysis in
the hallucinating patients significantly contributed to the regression model \((P = .027)\): left inferior parietal lobule, left cuneus, right lingual gyrus, and right precentral gyrus (Table 4).

To further explore the potential dissociation of neuroanatomical regions involved in hallucinations and dementia, we compared Parkinson's disease participants with and without dementia, controlling for hallucination status, on whole-brain VBM analyses using a 2 (with versus without dementia) by 2 (hallucinator versus nonhallucinator) factorial design (Figure 2, Table 5). In this analysis, participants with dementia had significantly reduced gray matter volumes in predominantly frontal and temporal regions, including bilateral parahippocampal gyri; inferior frontal, medial frontal, and middle frontal gyri; superior temporal gyri; and insula; right uncus, amygdala; and left claustrum and hippocampus, compared to participants without dementia \((P < .01\) uncorrected, \(k = 10\)). However, we did not detect gray matter atrophy in the occipital-temporal-parietal regions that are typically associated with visuoperceptual functions and were found in our hallucinator versus nonhallucinator comparison.

**Discussion**

Our study has several key findings. Compared to Parkinson's disease participants without hallucinations, Parkinson's disease participants with current and chronic visual hallucinations exhibit reduced gray matter volume on structural brain MRI in regions specifically associated with visuoperceptual function, independent of cognitive status. These regions of gray matter atrophy in the hallucinators correspond selectively and neuroanatomically to brain areas associated with visuoperceptual processing and include the ventral “what” and dorsal “where” visual streams. These regions, frequently implicated in theories of visual hallucinations in Parkinson's disease (discussed below), have been shown to exhibit decreased perfusion or activation in metabolic or functional neuroimaging studies of Parkinson's disease patients with hallucinations, but have not previously demonstrated atrophy in most structural MRI studies, possibly because of confounds of comorbid cognitive impairment. In contrast to several structural MRI studies, we did not detect gray matter volume loss in the hallucinators in brain regions that are frequently associated with cognitive impairment and dementia in Parkinson's disease such as mesial temporal, insular, limbic, or frontal lobe regions. Conversely, when controlling for hallucinations, we demonstrated atrophy in these frontal, insular, limbic, and temporal regions in Parkinson's disease participants with dementia but not in the posterior occipital-temporal-parietal regions. Thus, our structural MRI findings of highly localized structural brain abnormalities in the visuoperceptive system and the fact that the hallucinations experienced by Parkinson's disease participants are predominantly visual ones suggest that specific brain and behavior relationships underlie hallucinations in Parkinson's disease. Our findings also suggest that the neuroanatomical substrates involved in visual hallucinations in Parkinson's disease are distinct from those typically found on structural MRI analyses in cognitive impairment or dementia in Parkinson's disease, a dissociation that has not previously been shown.

The gray matter atrophy in the Parkinson's disease hallucinator participants found in our study is of particular interest in terms of clinico-anatomical correlations, because the affected regions play essential roles in primary and secondary visual processing and visuoperceptual functions. Specifically, the brain regions exhibiting atrophy selectively involve (1) areas responsible for determining patterns, light intensity, colors, shapes, words, visual memory, and primary visual processing (ie, the middle occipital gyrus, lingual gyrus, and cuneus); (2) areas responsible for recognizing faces and body regions (ie, the fusiform gyrus, which forms part of the visuoperceptive ventral “what” stream); and (3) areas responsible for multimodal processing and network connections among areas involved in motor, sensory, emotional, language, cognitive, attentional, and visuospatial functions (ie, inferior parietal lobule and cingulate gyrus). These clinico-anatomical correlations may even help explain why the majority of hallucinations in Parkinson's disease are visual ones, manifesting as misperceptions of still or moving objects, or as hallucinations of altered faces or figures, and frequently invoking heightened

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**Table 4. Anatomical Location of Areas Showing a Significant Relationship to Hallucination Severity**

<table>
<thead>
<tr>
<th>Region (BA)</th>
<th>Cluster Size (mm³)</th>
<th>Cluster Significance</th>
<th>T value</th>
<th>Z value</th>
<th>Talairach Coordinates (x, y, z)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Left inferior parietal lobule (BA 40)</td>
<td>62</td>
<td>0.001</td>
<td>4.11</td>
<td>3.52</td>
<td>(-37, -53, 44)</td>
</tr>
<tr>
<td>Left cuneus (BA 18)</td>
<td>22</td>
<td>0.001</td>
<td>3.56</td>
<td>3.15</td>
<td>(-4, -82, 17)</td>
</tr>
<tr>
<td>Right lingual gyrus (BA 19)</td>
<td>22</td>
<td>0.003</td>
<td>3.08</td>
<td>2.79</td>
<td>(18, -68, 5)</td>
</tr>
<tr>
<td>Right precentral gyrus (BA 6)</td>
<td>15</td>
<td>0.001</td>
<td>3.41</td>
<td>3.04</td>
<td>(64, 4, 22)</td>
</tr>
</tbody>
</table>

Abbreviation: BA, Brodmann area.
emotions. Furthermore, it is interesting to note that similar clinico-anatomical correlates have been detected in VBM studies of schizophrenia. For example, participants with schizophrenia experiencing auditory verbal hallucinations demonstrate reduced gray matter volume in the bilateral superior temporal gyrus including the Heschl gyri, an area involved in auditory processing. These findings of brain-behavior correlates in schizophrenic participants, as well as in our study of Parkinson's disease hallucinators, support a model of aberrant neural system processing at different levels of sensory processing.

Our findings of gray matter atrophy in predominantly visuoperceptive regions in the hallucinating Parkinson's disease participants differ from findings of several other structural MRI studies in which the Parkinson's disease hallucinators exhibited primarily hippocampal or temporal, insular, frontal, or thalamic or pedunculopontine atrophy, compared to Parkinson's disease nonhallucinators. Several differences in clinical and imaging methodologies between those studies and ours could account for these differences. One key difference is our careful control of cognitive abilities when comparing Parkinson's disease hallucinators and nonhallucinators. The two groups in our study had comparable numbers of participants with and without dementia in each group and did not differ significantly on scores of the 5 cognitive domains tested. In several other studies, in contrast, the Parkinson's disease hallucinators had greater cognitive impairment than the nonhallucinators. In addition, studies have varied with regard to the definitions of Parkinson's disease dementia (eg, MMSE scores < 24; Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision [DSM-IV-TR] criteria; or MDS PDD criteria) that were used as criteria either to include participants or to exclude participants if the study focused on Parkinson's disease without dementia. The tendency toward worse cognitive function in Parkinson's disease participants with hallucinations could lead to greater detection of atrophy on structural MRI in mesial temporal lobe, limbic, and neocortical regions. Gray matter atrophy in these areas has been detected in Parkinson's disease patients with cognitive impairment and dementia in several structural MRI studies. Furthermore, greater amnestic deficits in those hallucinating Parkinson's disease participants classified as having dementia by DSM-IV-TR criteria, which require memory impairment by definition, could also contribute to gray matter atrophy in the mesial temporal lobe on MRI, an area implicated in declarative memory function. Even when Parkinson's disease hallucinators were considered to be without dementia in many of these studies, they performed worse on tests of global cognitive function and on multiple cognitive domains compared to Parkinson's disease nonhallucinators. The hallucinators had worse scores on (1) the MMSE; (2) memory on verbal list learning and recall tests; (3) visual memory; (4) attention and executive function on tests of fluency, set shifting, and interference; and (5) visuospatial function with facial recognition tasks. Other important differences among structural MRI studies include various definitions of visual hallucinations (eg, frequency, severity, and/or rating scales used), sample sizes (eg, ranging from 8 to 46 Parkinson's disease hallucinators in studies), and imaging methods (eg, MRI scanners, SPM versions, whole-brain VBM or selective region of interest approaches, choices in smoothing kernels, cluster threshold significance, and corrections for multiple comparisons used). An additional consideration is that in other studies, the Parkinson's disease hallucinators compared to the nonhallucinators had worse motor impairment, longer disease duration, and greater depressed mood on standard rating scales. Our matching for cognitive status and age, along with the lack of significant between-group differences in Parkinson's disease duration, motor severity, or depression, in the hallucinators and nonhallucinators represents a major strength of our study and thus allows for the first time a clinico-anatomical analysis that separates the regions associated with hallucinations from those associated with dementia as two distinct, but sometimes overlapping, clinical problems.

To the best of our knowledge, only one other structural MRI study has detected greater gray matter atrophy in regions associated with visual processing in Parkinson's disease hallucinators compared to nonhallucinators. Our findings further extend this work, which demonstrated gray matter atrophy in three regions, the left lingual gyrus and bilateral superior parietal lobes, in Parkinson's disease hallucinator participants. The structural MRI findings of gray matter atrophy in visuoperceptive regions in Parkinson's disease hallucinators complement previous metabolic and functional neuroimaging studies, which reveal that similar regions are affected. These studies show decreased cerebral perfusion or glucose metabolism in posterior (ie, occipital, parietal, and temporal) regions, and decreased activation of similar regions in functional MRI visual stimulation paradigms. Together, these neuroimaging studies suggest that structural abnormalities in the brain’s visual processing areas may not only form the basis for these abnormally decreased metabolic or cortical activation patterns, but also might even explain the clinical presentation of visual rather than nonvisual hallucinations. The exact mechanisms by which these structural, metabolic, or functional aberrations relate to the severity of visual hallucinations in Parkinson's disease are not fully elucidated. In our study, 4 of the 18 identified regions of gray matter atrophy in the Parkinson's disease hallucinators (ie, left inferior parietal lobule, left cuneus, right lingual gyrus, and right precentral gyrus) showed the greatest relationship to hallucination severity scores. The majority of these areas perform different roles in the visuoperceptive system, ranging from processing of visual stimuli (eg, cuneus and lingual gyrus) to integrating multimodal information.
The inferior parietal lobule, in particular, may play a pivotal role in the presence and severity of visual hallucinations in Parkinson’s disease due to its connectivity to multiple other brain regions involved in a wide array of motor, sensory, language, and visual functions. It is not known, however, whether gray matter atrophy in visuoperceptive regions could be the consequence (rather than the cause) of long-standing visual hallucinations in Parkinson’s disease patients. Multimodal neuroimaging studies performed at the same time point in hallucinators may help answer questions regarding the temporal relationship of structural changes to metabolic and functional abnormalities (ie, do the decreased perfusion or activation patterns result from structural atrophy or might they occur at an early disease stage, prior to structural changes?).

Several theoretical explanations for visual hallucinations have been proposed. These include impairment in the visual system from the retina to higher-order visual processing; cortical release phenomena due to sensory deafferentation such as in the Charles Bonnet syndrome; cortical irritation or excitability; abnormalities in various perceptual, attentional, arousal, or cognitive processes; or dysregulation of external perception and internal image production across the visual system, brainstem, and subcortical and cortical regions. Deficits in the primary visual system due to dopamine cell loss in the retina or structural changes in retinal thickness in Parkinson’s disease may contribute to hallucinations, and hallucinators exhibit reduced contrast sensitivity, color discrimination, and visual acuity compared to nonhallucinators. Hallucinations may result from either increased misperceptions of visual stimuli in a visually deprived environment or by the chronic deafferentation of higher-order visual regions. This chronic denervation could be hypothesized to lead to subsequent brain atrophy selectively in visuoperceptive regions. Other theories of hallucinations emphasize impairment in cognitive, attentional, and visuoperceptive processes, spanning the neuroanatomical levels of the brainstem and the subcortical and cortical regions. Each theory focuses on the relationship of hallucinations to distinct elements such as impaired arousal or vigilance, sleep-wake disturbances or dream intrusions, altered attention and/or specific cognitive processes (eg, set-shifting, executive functions, or visuospatial abilities), abnormal inference and modulation of internal and external perceptions, or altered higher-order visuoperceptive processing. Our structural MRI findings, with abnormalities in primarily “what” and “where” visuoperceptive regions, best fit with the “bottom-up” model of altered visuoperceptive processing but also share features of impaired attentional models of Parkinson’s disease hallucinations. Regional atrophy also occurred in the inferior parietal lobule and cingulate gyrus, which are two areas implicated in visuoperceptive processing, visuospatial orientation, and visual memory but also multisensory integration, attentional, and emotional processes. Structural abnormalities in the visuoperceptive pathways and “hub” regions suggest that there may be a “disconnection” between posterior and anterior parts of the brain in hallucinators, as seen in several metabolic and functional neuroimaging studies. Future integrated studies using multimodal structural, functional, and metabolic neuroimaging techniques; physiological measures of vision and sleep/arousal; and experimental attentional, cognitive, and visuoperceptive tasks may provide insights into how these various theories contribute to the development of hallucinations in Parkinson’s disease.

To date, there have been few neuropathological studies of Parkinson’s disease participants with hallucinations. In those clinico-pathological studies that were carried out, Lewy

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**Figure 2.** Location of significant clusters of gray matter volume loss in Parkinson’s disease participants with dementia compared to Parkinson’s disease participants without dementia. Results overlapped on a T1-weighted image of healthy, control brain. Yellow color indicates significantly different areas involving inferior frontal, medial frontal, and middle frontal and superior temporal gyri; parahippocampal gyrus; hippocampus; amygdala; insula; uncus; and claustrum (A, sagittal; B, coronal; C, axial slices). P < .01, uncorrected.
bodies were reported in the amygdala, parahippocampus, frontal and parietal lobes, and inferior temporal cortex in Parkinson’s disease hallucinators.\textsuperscript{52,53} Interestingly, the inferior temporal cortex comprises part of the ventral stream visuoperceptive pathway responsible for representation of complex object features and facial perception. However, Lewy bodies were negligible in the occipital lobe in one study\textsuperscript{52} and not examined in the other.\textsuperscript{53} Small sample sizes, presence of cognitive deficits or dementia in the hallucinators, and overall more advanced disease at death, however, pose challenges for parsing out neuropathological changes specific to hallucinations. These findings also suggest that other neuropathologies, neurochemical alterations (ie, abnormal serotonergic\textsuperscript{54,55} or cholinergic receptor binding\textsuperscript{56}), or

<table>
<thead>
<tr>
<th>Region (BA)</th>
<th>Cluster Size (mm\textsuperscript{3})</th>
<th>Cluster Significance</th>
<th>T value</th>
<th>Z value</th>
<th>Talairach Coordinates (x, y, z)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Left parahippocampal gyrus, hippocampus (BA 35, 28)</td>
<td>1222</td>
<td>0.001</td>
<td>3.41</td>
<td>3.2</td>
<td>–19, –21, –15</td>
</tr>
<tr>
<td>Right inferior frontal gyrus, parahippocampal gyrus, amygdala (BA 47)</td>
<td>1038</td>
<td>0.001</td>
<td>3.46</td>
<td>3.24</td>
<td>25, 15, –23</td>
</tr>
<tr>
<td>Right middle frontal gyrus (BA 8, 9)</td>
<td>503</td>
<td>0.001</td>
<td>3.33</td>
<td>3.13</td>
<td>28, 31, 34</td>
</tr>
<tr>
<td>Left medial frontal gyrus (BA 11)</td>
<td>469</td>
<td>0.001</td>
<td>3.6</td>
<td>3.35</td>
<td>–7, 27, –13</td>
</tr>
<tr>
<td>Right middle frontal gyrus (BA 6, 10)</td>
<td>376</td>
<td>0.001</td>
<td>3.51</td>
<td>3.28</td>
<td>36, 40, 12</td>
</tr>
<tr>
<td>Right middle frontal gyrus (BA 6)</td>
<td>341</td>
<td>0.001</td>
<td>3.75</td>
<td>3.47</td>
<td>31, 1, 44</td>
</tr>
<tr>
<td>Left claustrum</td>
<td>260</td>
<td>0.005</td>
<td>2.72</td>
<td>2.6</td>
<td>–31, 3, 1</td>
</tr>
<tr>
<td>Left middle frontal gyrus (BA 10, 46)</td>
<td>255</td>
<td>0.001</td>
<td>3.38</td>
<td>3.17</td>
<td>–34, 40, 9</td>
</tr>
<tr>
<td>Right medial frontal gyrus (BA 11)</td>
<td>234</td>
<td>0.001</td>
<td>3.16</td>
<td>2.98</td>
<td>1, 57, –18</td>
</tr>
<tr>
<td>Right superior temporal lobe (BA 21)</td>
<td>178</td>
<td>0.003</td>
<td>2.95</td>
<td>2.81</td>
<td>56, 2, –10</td>
</tr>
<tr>
<td>Left insula (BA 13)</td>
<td>166</td>
<td>0.001</td>
<td>3.23</td>
<td>3.04</td>
<td>–37, –21, 22</td>
</tr>
<tr>
<td>Right inferior frontal gyrus (BA 9)</td>
<td>130</td>
<td>0.001</td>
<td>3.2</td>
<td>3.02</td>
<td>34, 11, 23</td>
</tr>
<tr>
<td>Right inferior frontal gyrus (BA 6)</td>
<td>111</td>
<td>0.001</td>
<td>3.44</td>
<td>3.22</td>
<td>19, –2, 54</td>
</tr>
<tr>
<td>Right temporal gyrus (BA 21)</td>
<td>109</td>
<td>0.003</td>
<td>2.9</td>
<td>2.76</td>
<td>46, –11, –8</td>
</tr>
<tr>
<td>Left medial frontal gyrus (BA 9)</td>
<td>105</td>
<td>0.001</td>
<td>3.69</td>
<td>3.42</td>
<td>–21, 26, 30</td>
</tr>
<tr>
<td>Right inferior frontal gyrus (BA 11)</td>
<td>103</td>
<td>0.005</td>
<td>2.72</td>
<td>2.6</td>
<td>24, 36, –18</td>
</tr>
<tr>
<td>Left superior temporal gyrus (BA 22)</td>
<td>76</td>
<td>0.002</td>
<td>3.04</td>
<td>2.88</td>
<td>–67, –37, 14</td>
</tr>
<tr>
<td>Left insula (BA 13)</td>
<td>70</td>
<td>0.005</td>
<td>2.71</td>
<td>2.59</td>
<td>–40, –32, 21</td>
</tr>
<tr>
<td>Left inferior frontal gyrus (BA 47)</td>
<td>66</td>
<td>0.004</td>
<td>2.75</td>
<td>2.63</td>
<td>–21, 31, –22</td>
</tr>
<tr>
<td>Right insula (BA 13)</td>
<td>60</td>
<td>0.005</td>
<td>2.7</td>
<td>2.58</td>
<td>39, –28, 19</td>
</tr>
<tr>
<td>Left superior temporal gyrus (BA 13)</td>
<td>54</td>
<td>0.001</td>
<td>3.12</td>
<td>2.95</td>
<td>–50, –46, 20</td>
</tr>
<tr>
<td>Left parahippocampal gyrus (BA 19)</td>
<td>53</td>
<td>0.004</td>
<td>2.78</td>
<td>2.65</td>
<td>–19, –44, –2</td>
</tr>
<tr>
<td>Left inferior frontal gyrus (BA 9)</td>
<td>48</td>
<td>0.003</td>
<td>2.9</td>
<td>2.75</td>
<td>–36, 10, 23</td>
</tr>
<tr>
<td>Left superior temporal gyrus (BA 22)</td>
<td>41</td>
<td>0.006</td>
<td>2.64</td>
<td>2.53</td>
<td>–59, –26, 3</td>
</tr>
<tr>
<td>Right uncus (BA 28)</td>
<td>35</td>
<td>0.005</td>
<td>2.66</td>
<td>2.55</td>
<td>22, –15, –35</td>
</tr>
<tr>
<td>Left superior temporal gyrus (BA 22)</td>
<td>29</td>
<td>0.006</td>
<td>2.64</td>
<td>2.53</td>
<td>–48, –26, 3</td>
</tr>
<tr>
<td>Right superior temporal gyrus (BA 38)</td>
<td>21</td>
<td>0.006</td>
<td>2.61</td>
<td>2.5</td>
<td>42, –1, –18</td>
</tr>
<tr>
<td>Left inferior frontal gyrus (BA 47)</td>
<td>20</td>
<td>0.008</td>
<td>2.49</td>
<td>2.4</td>
<td>–31, 18, –21</td>
</tr>
</tbody>
</table>

Abbreviation: BA, Brodmann area.
disrupted white matter pathways (ie, inferior longitudinal fasciculus)\(^5\) may play a role in the atrophy in occipital and related visuoperceptive regions found on structural MRI of Parkinson’s disease hallucinators.

In our study, in addition to gray matter volume loss predominantly in visuoperceptive areas in the hallucinators compared to the nonhallucinators, we also detected reduced gray matter volume in the precentral gyrus (premotor cortex). Although the two Parkinson’s disease groups did not differ significantly in motor scores (as measured by the MDS-UPDRS part III and by Hoehn and Yahr stage) or in disease duration, the hallucinators had slightly longer disease durations (mean 13.1 ± 4.6 years versus 10.8 ± 4.4 years). Considering clinico-anatomical correlates, we hypothesize that the greater precentral gyrus atrophy in the hallucinator group might possibly relate to their slightly longer disease course or to a greater degree of motor dysfunction that was not captured by the demographic or disease-related variables of interest in our study.

We acknowledge that this study has some limitations, including a relatively small sample size, which although smaller than in one study\(^2\) is larger than in several previously published structural MRI studies.\(^22-24,44\) Even so, larger sample sizes of cognitively well-matched hallucinators and nonhallucinators are needed to validate these gray matter atrophy results with more stringent statistical corrections, which minimize potential false positives. Our findings of distinct structural MRI brain-behavior correlates for hallucinations and dementia, however, may generate hypotheses and new models regarding these two frequent and disabling complications in Parkinson’s disease. At present, we cannot establish the underlying neuropathology associated with the gray matter atrophy detected on MRI, but future postmortem studies will be informative. Although the Parkinson’s disease groups were matched on cognitive deficits and age, they were not matched for use of antipsychotic medications. It is notable that even when some of the hallucinators were treated for the condition, the underlying structural abnormalities were evident. Whether antipsychotic treatment per se can produce structural changes on brain MRI remains a question for future studies of Parkinson’s disease hallucinators. Lastly, we cannot confirm that the Parkinson’s disease nonhallucinators will never become hallucinators. Planned longitudinal follow-up studies with careful monitoring will permit assessment of “conversion” and clinical and neuroimaging risk factors.

In conclusion, the structural abnormalities detected in participants with Parkinson’s disease with current and chronic visual hallucinations suggest that there are distinct regional patterns of gray matter atrophy associated with visual hallucinations in Parkinson’s disease, independent of cognitive impairment or dementia. Reduced gray matter in these brain regions that subserve visuoperceptive functions may contribute to aberrant processing of visual input, especially in the ventral “what” and dorsal “where” visual streams, and thus lead to the clinical manifestations of visual hallucinatory phenomena in Parkinson’s disease. These neuroanatomical findings provide the basis for future studies investigating the role of neural network dysfunction in visual hallucinations in Parkinson’s disease and ultimately providing patients with novel therapies that target hallucinations and visuoperceptive dysfunction.

Funding

K23NS060949 (J.G.G.). The Rush University Section of Parkinson Disease and Movement Disorders is supported by a center grant from the Parkinson’s Disease Foundation.
References


Clinical and Radiographic Analysis of an Artificial Cervical Disc: 7-Year Follow-Up From the Prestige Prospective Randomized Controlled Clinical Trial

J. Kenneth Burkus, MD; Vincent C. Traynelis, MD; Regis W. Haid Jr, MD; Praveen V. Mummaneni, MD

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Introduction

Clinical and radiographic outcomes have been reported from several prospective studies of patients undergoing cervical disc replacement with a metal-on-metal implant.1-4 An early clinical prospective observational cohort study of 15 patients reported successful clinical and radiographic outcomes in the treatment of symptomatic cervical radiculopathy.5 An optimized ball-and-trough-designed implant (Prestige Cervical Disc, Medtronic) was then developed and used in a prospective randomized trial.3 Fifty-five patients were enrolled in this pilot study at 4 investigational sites. At 24-month follow-up, Neck Disability Index (NDI) scores showed improvement that favored the disc replacement group over the control group, and motion was maintained at the treated level. In 2002, a large-scale, prospective, randomized, multicenter study was initiated in which this metal-on-metal disc prosthesis was compared with anterior cervical discectomy and fusion in patients who had symptomatic single-level cervical degenerative disc disease.6 Investigators reported the interim data from this randomized controlled trial (RCT) in previous publications.6,7 These early clinical reports have shown that the prosthesis maintained segmental spinal motion and was associated with improved neurological success, clinical outcomes, and reduced secondary surgical procedures when compared with anterior cervical discectomy and fusion. These improvements in outcomes were similar to other early clinical and radiographic findings for the Bryan Cervical Disc (Medtronic),8 the ProDisc-C (Synthes, Inc),9 Kineflex|C (SpinalMotion),1 and the Mobi-C (LDR)10,11 devices. At 24 months in these cervical disc replacement RCTs, the postoperative data showed improvement in all clinical outcome measures, and patients treated with the artificial disc had a statistically greater overall success rate.12,13

The safety and efficacy of cervical disc prostheses beyond the initial 24-month follow-up has not been as widely reported. Reports from RCTs with 4 years of follow-up have been published for the Bryan Disc14 and with 5 years of follow-up for the ProDisc-C.15 The final 2-year and interim 5-year data from the Prestige disc RCT have been published.6,7 The purpose of this article is to report the final 7-year clinical and radiographic outcomes from the Prestige disc RCT.

Materials and Methods

Study Design

This prospective, randomized, nonblinded study was conducted under an approved investigational device exemption (IDE). Patients in the IDE trial were followed in this Food and Drug Administration (FDA)-regulated postapproval study for an additional 5 years, resulting in a total of 7 years of follow-up. Institutional review board approval was obtained from all participating centers, and informed consent was obtained for all patients enrolled in the follow-up studies. The clinical trial registration number for this study is NCT00642876 (http://www.ClinicalTrials.gov).

Between October 2002 and August 2004, 541 patients were enrolled at 31 investigational sites and underwent surgery. The patients were randomly assigned to 1 of 2 treatment groups: the investigational group received the Prestige disc, and the control group underwent an interbody fusion using allograft with plate fixation. Data were
collected preoperatively, intraoperatively, and at 1.5, 3, 6, 12, 24, 36, 60, and 84 months postoperatively. Adverse events and secondary surgeries were recorded at each follow-up visit.

**Patient Demographics**

The 2 treatment groups were similar demographically, and there were no statistically significant differences \((P < .05)\) for the variables of age, sex, smoking, or work status (Table 1). All patients were between the ages of 22 and 73 years and had symptomatic degenerative cervical disc disease at the C3-C4 or C6-C7 levels. For at least 6 weeks before their surgery, all patients had neck and arm pain that was recalcitrant to nonoperative treatment modalities, such as physical therapy, reduced activities, and anti-inflammatory medications.

All patients were considered candidates for a single-level anterior cervical decompression and interbody fusion and had plain radiographic findings that documented single-level cervical disc disease and at least one additional confirmatory neuroradiographic study, such as magnetic resonance imaging or computed tomography-enhanced myelography that was consistent with clinical findings and complaints.

Patients were excluded from the study if they had cervical spinal conditions other than single-level symptomatic degenerative disc disease or evidence of instability. Other exclusion criteria were symptomatic disc disease at level C2-C3 or C7-T1, a history of discitis, or a medical condition that required medication, such as steroids or nonsteroidal anti-inflammatory medications that could interfere with fusion.

**Patient Follow-Up**

A total of 541 patients were treated in the RCT; 276 patients were assigned to the investigational group, and 265 patients were assigned to the control treatment group (Figure 1). One center declined to participate in the long-term follow-up study after the initial 24-month evaluation period was completed. As a result of the nonparticipating site, 8 patients (4 each in the investigational group and control group) were excluded from this study, leaving 533 patients who were eligible for the FDA postapproval follow-up.

**Clinical Outcome Measures**

Overall success was the primary clinical outcome measure for this clinical trial. A patient’s outcome was considered an overall success if all of the following conditions were met: (1) postoperative NDI score improvement of at least a 15-point increase from preoperative score; (2) maintenance or improvement in neurological status; (3) disc height success (the functional spinal unit [FSU] was measured to assess for any loss of disc height due to subsidence); (4) no serious adverse event classified as implant associated or implant/surgical procedure associated; and (5) no additional surgical procedure classified as a “failure.”

When overall success was assessed, it was apparent that in some instances the radiographic images did not allow clear visualization of the FSU, and, therefore, adequate disc height measurements were unobtainable. For this reason, overall success rates were computed with and without inclusion of disc height success as a component of overall success. When disc height success was included as a component of overall success,

<table>
<thead>
<tr>
<th>Table 1. Patient Demographic Data</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Variable</strong></td>
</tr>
<tr>
<td>No. of patients</td>
</tr>
<tr>
<td>Age, y</td>
</tr>
<tr>
<td>mean</td>
</tr>
<tr>
<td>range</td>
</tr>
<tr>
<td>Mean weight, lb</td>
</tr>
<tr>
<td>Male, %</td>
</tr>
<tr>
<td>Workers’ compensation, %</td>
</tr>
<tr>
<td>Litigation, %</td>
</tr>
<tr>
<td>Alcohol use, %</td>
</tr>
<tr>
<td>Tobacco use, %</td>
</tr>
<tr>
<td>Work status, %</td>
</tr>
</tbody>
</table>

*For continuous variables, \(P\) values are from analysis of variance, and for categorical variables, they are from the Fisher's exact test.*
patients in whom the radiographic images did not permit disc height measurement were excluded from the analysis.

Secondary and additional clinical outcome measures included the Physical Component Summary (PCS) of the 36-Item Short Form Health Survey (SF-36), neck and arm pain scores (100-point scale, which was the product of duration [1- to 10-point scale] multiplied by intensity [1- to 10-point scale]), and return-to-work status.

**Radiographic Assessments**

Plain radiographic studies were obtained preoperatively, intraoperatively, and at 1.5, 3, 6, 12, 24, 36, 60, and 84 months postoperatively. Neutral anteroposterior and lateral radiographs and dynamic flexion-extension lateral radiographs were obtained at each study point. Sagittal plane angulation motion was measured on dynamic lateral radiographs using the Cobb technique. Subsidence was measured by comparing the FSU height from 1.5 months after surgery. This calculation required that the entire vertebral body above and below the index surgical level could be visualized. For centralization of assessments and measurements, radiographs taken at each investigational site were evaluated at the same core-imaging laboratory (SYNARC) through all study periods. Two independent radiographic reviewers and an adjudicator determined radiographic findings in both treatment groups. Some radiographs could not be interpreted by radiologists because the prominent shoulders obscured critical portions of the radiographic images. For these reasons, the numbers of complete radiographic assessments varied from the numbers of clinical assessments at each of the study’s follow-up intervals.

**Adverse Events**

An adverse event was defined as any clinically adverse sign, symptom, syndrome, or illness that occurred or worsened during either the operative or postoperative observation periods, regardless of causality, that was not being measured otherwise in the study. The adverse event information recorded was based on the following: (1) signs or symptoms detected during the physical examination, (2) the clinical evaluation of the participant, (3) the participant interview, and (4) the medical charts monitored during the study. Adverse events were collected for the duration of the entire study.

**Secondary Surgical Procedures**

Secondary surgical procedures at the level of the index procedure were classified according to the IDE trial protocol as revisions, removals, supplemental fixations, or reoperations. In this investigation, a revision surgery was defined as any procedure that adjusts or modifies the original implant configuration (implant repositioning). A removal surgery was defined as a procedure in which 1 or more components of the original implant was removed and replaced with a different type of implant. For example, removal of the Prestige implant and replacement with an interbody cage and anterior plate would be classified as a removal surgery. A supplemental
fixation procedure, such as posterior wiring or plating, provided additional stabilization to the index surgical site. This definition included the application of an external bone growth stimulator as a supplemental fixation procedure; however, data are summarized separately in this article. A secondary surgical procedure was classified as a reoperation if the procedure was carried out at the index level and was not classified as a revision, removal, or supplemental fixation. An example of a reoperation would be a posterior foraminotomy to relieve persistent nerve root pressure at the index surgical level.

Statistical Analysis

Statistical comparisons were based primarily on the observed and recorded follow-up data. Missing values for patients who were lost to follow-up were not imputed. For outcomes of the patients requiring an additional surgical procedure that was classified as a failure (removal, revision, or supplemental fixation), the observations immediately before the second surgery were carried over for all future evaluation periods.

For statistical comparisons of demographic differences between the groups, analysis of variance was used for continuous variables, and Fisher’s exact test was used for categorical data. Assessment of the statistical significance of postoperative improvement from preoperative values within each treatment group was performed using a paired t test.

For the binary outcome variables, such as overall success, the success rate of the investigational group and the control group were compared using a z test with the standard

<table>
<thead>
<tr>
<th>Variable</th>
<th>Investigational Group</th>
<th>Control Group</th>
<th>P Valuea</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of Patients</td>
<td>Mean ± SD</td>
<td>No. of Patients</td>
</tr>
<tr>
<td>NDI</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Preoperative</td>
<td>276</td>
<td>55.7 ± 14.8</td>
<td>264</td>
</tr>
<tr>
<td>24 mo</td>
<td>253</td>
<td>20.0 ± 21.4</td>
<td>220</td>
</tr>
<tr>
<td>36 mo</td>
<td>197</td>
<td>18.9 ± 21.5</td>
<td>160</td>
</tr>
<tr>
<td>60 mo</td>
<td>219</td>
<td>17.5 ± 20.4</td>
<td>188</td>
</tr>
<tr>
<td>84 mo</td>
<td>211</td>
<td>18.1 ± 20.0</td>
<td>181</td>
</tr>
<tr>
<td>Arm pain</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Preoperative</td>
<td>276</td>
<td>59.1 ± 29.4</td>
<td>264</td>
</tr>
<tr>
<td>24 mo</td>
<td>253</td>
<td>13.9 ± 24.6</td>
<td>220</td>
</tr>
<tr>
<td>36 mo</td>
<td>197</td>
<td>12.9 ± 24.4</td>
<td>161</td>
</tr>
<tr>
<td>60 mo</td>
<td>218</td>
<td>10.6 ± 21.5</td>
<td>189</td>
</tr>
<tr>
<td>84 mo</td>
<td>210</td>
<td>12.7 ± 24.1</td>
<td>181</td>
</tr>
<tr>
<td>Neck pain</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Preoperative</td>
<td>276</td>
<td>68.2 ± 22.7</td>
<td>264</td>
</tr>
<tr>
<td>24 mo</td>
<td>253</td>
<td>15.6 ± 24.4</td>
<td>220</td>
</tr>
<tr>
<td>36 mo</td>
<td>197</td>
<td>14.2 ± 23.0</td>
<td>161</td>
</tr>
<tr>
<td>60 mo</td>
<td>217</td>
<td>12.7 ± 22.4</td>
<td>189</td>
</tr>
<tr>
<td>84 mo</td>
<td>210</td>
<td>13.1 ± 23.3</td>
<td>181</td>
</tr>
<tr>
<td>SF-36 PCS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Preoperative</td>
<td>275</td>
<td>31.9 ± 7.0</td>
<td>263</td>
</tr>
<tr>
<td>24 mo</td>
<td>248</td>
<td>44.6 ± 12.2</td>
<td>218</td>
</tr>
<tr>
<td>36 mo</td>
<td>197</td>
<td>45.6 ± 11.9</td>
<td>160</td>
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<tr>
<td>60 mo</td>
<td>217</td>
<td>45.8 ± 11.7</td>
<td>187</td>
</tr>
<tr>
<td>84 mo</td>
<td>209</td>
<td>45.1 ± 12.0</td>
<td>179</td>
</tr>
</tbody>
</table>

Abbreviations: NDI, Neck Disability Index; SF-36 PCS, 36-Item Short Form Health Survey Physical Component Summary.

*The P values are for comparisons between the treatment groups from the analysis of covariance with preoperative score as the covariate.
deviation derived using the Farrington-Manning method.

Analysis of covariance was used with the preoperative score as the covariate for comparing postoperative continuous measurements and improvements such as NDI. One-sided P values were reported for most clinical outcomes, except for additional surgical procedures and adverse events. Time-to-event analysis was performed for comparing adverse events between the treatment groups, and the log-rank test was used to determine statistical significance. A P value < .05 was used to evaluate statistical significance without adjusting for multiple comparisons. The primary study objective for the postapproval study was to assess noninferiority (with a 10% margin) in overall success at 7 years comparing the investigational group to the control group. If noninferiority was established, superiority was also assessed. Noninferiority P values are not presented in this article.

Results

Follow-up rates at 60 and 84 months were 79.7% and 76.8%, respectively, for the investigational group and 71.7% and 69.1%, respectively, for the control group (Figure 1). The overall follow-up rate at 84 months was 73% (395 of 541 patients). There were 212 patients in the investigational group and 183 in the control group. Follow-up rates were based on the number of patients who had at least 1 complete outcome measure at that interval. Note that more patients reached the 60-month follow-up time point by 2012 than reported in our previous publication.

Overall Success

At 60 and 84 months, noninferiority in overall success comparing the investigational and control groups was confirmed. At 60 months, the overall success rates with the FSU measure were 71.3% for the investigational group and 65.2% for the control group, a 6.1% difference that was not statistically significant (P = .129) (Figure 2). When the FSU measure was excluded, the overall success rates at 60 months were 78.2% and 71.8% for the investigational and control groups, respectively, a 6.4% difference that was also not statistically significant (P = .069). However, at 84 months the overall success rates with and without the FSU measure were both significantly higher in the investigational group. Overall success rates with the FSU measure were 72.6% and 60.0% for the investigational and control groups, respectively (P = .010), and were 75.0% and 63.7% without the FSU measure for the investigational and control groups, respectively (P = .008).

NDI Scores

The NDI questionnaire measures the level of pain and disability associated with various activities. The NDI scores improved significantly in both groups from the preoperative scores by 1.5 months, and these improvements were maintained through 7 years (P < .001). For the investigational group, average NDI scores improved 37.6 points at 84 months from a mean preoperative score of 55.7. For the control group, average NDI scores improved 32.6 points at 84 months from a mean preoperative score of 56.4. These improvements were similar to those at 60 months, which were 38.2 points and 34.7 points for the investigational and control groups, respectively. At both the 60-month and 84-month periods, there were significant between-group differences in favor of arthroplasty (P = .014 and .002, respectively) (Table 2).

The NDI success criterion is based on the preoperative NDI score. A 15-point or greater NDI score improvement after
surgery was required to be considered a successful outcome. The 2 groups demonstrated similar rates of NDI success at 60 and 84 months, which were 85.4% and 83.4%, respectively, for the investigational group and 84.8% and 80.1%, respectively, for the control group. There were no significant between-group differences in NDI success rates at 60 months ($P = .293$) or at 84 months ($P = .109$).

**Arm Pain**

Arm pain scores improved significantly in all groups from the preoperative scores by 1.5 months, and these improvements were maintained through 7 years ($P < .001$). For the investigational group, average arm pain scores improved 46.4 points at 84 months, from a mean preoperative score of 59.1. The control group showed comparable improvement in arm pain scores, improving an average of 47.4 points from a preoperative score of 62.4. There were no significant between-group differences in arm pain scores at 60 months ($P = .092$) or at 84 months ($P = .174$) (Table 2).

**Neck Pain**

Neck pain scores improved significantly in both groups from the preoperative scores by 1.5 months, and these improvements were maintained through 7 years ($P < .001$). For the investigational group, average neck pain scores improved 55.1 points at 84 months, from a mean preoperative score of 68.2. For the control group, average neck pain scores improved 49.9 points at 84 months, from a preoperative score of 69.3. Neck pain was significantly lower ($P = .033$) at 60 months in the investigational group (12.7) than in the control group (16.9), and was also significantly lower ($P = .004$) at 84 months in the investigational group (13.1) than in the control group (19.4) (Table 2).

**SF-36 PCS**

The SF-36 measures specific health concepts related to physical functioning, social functioning, and health perceptions. SF-36 PCS scores improved significantly in both groups from preoperative scores by 6 months ($P < .001$), which was the first postoperative period for SF-36 evaluation, and these improvements were maintained through 7 years. There were no significant between-group differences in SF-36 PCS at 60 months (45.8 points and 44.7 points for the investigational and control groups, respectively) ($P = .098$). At 84 months, the SF-36 PCS score for the investigational group was 45.1 points compared with 43.2 points in the control group ($P = .017$) (Table 2).

**Neurological Success**

Neurological status of the patients was determined by measuring 3 objective clinical findings: motor function, sensory function, and deep tendon reflexes. Neurological success for each of these 3 objective findings was based on postoperative maintenance or improvement in condition compared with preoperative status. Overall neurological status success was determined by maintenance or improvement in all 3 clinical findings.

![Figure 3](image-url)  

*Figure 3.* Neurological success rates in the investigational group and control group. The $P$ values are 1-sided from normal approximation with standard error derived from the Farrington-Manning method.
In the investigational group, overall neurological success (maintenance or improvement) rates were high, exceeding 88% at all follow-up intervals (Figure 3). The overall success rates of neurological status in the investigational group were 92.2% and 88.2%, respectively, at 60 and 84 months, compared with 85.7% and 79.7% in the control group ($P = .017$ and .011, respectively). The neurological success rate may have been influenced by the difference in surgical technique between the study groups. The arthroplasty surgical technique required an extensive posterior and posterolateral decompression across the disc space. In the arthroplasty group, the entire posterior annulus and posterior longitudinal ligament was resected. Uncovertebral joints were partially removed, enlarging the neuroforamina. This extensive dissection and decompression was not required in the fusion control group. Indirect enlargement of the neuroforamina through intradiscal distraction was permitted in the control group. Assuming missing-equals-failure for patients lost to follow-up, the differences between the treatment groups in neurological success remain in favor of the investigational arthroplasty group (Table 3).

**Work Status**

Before surgery, 65.9% of the investigational group was working compared with 62.6% of the control group. At 84 months, the percentage of working patients was 73.9% in the investigational group and 73.1% in the control group, reflecting no difference between the groups. Statistical tests were not done at each follow-up interval to determine if differences in working rates were statistically significant; instead, time to return to work was compared between the 2 treatment groups using the Kaplan-Meier approach. The difference in days after surgery for return to work between the two groups ($P = .022$; Wilcoxon test) favored an earlier return to work in the investigational group. A Cox proportional hazard model, adjusting for preoperative work status, was also used to evaluate differences in days for return to work and again demonstrated an earlier return to work in the disc arthroplasty group ($P = .033$).

**Radiographic Outcomes**

The radiographic outcomes were based on measurements recorded by 2 independent radiologists. In the control group, sagittal angular motion was restricted after surgery. The fusion success rate was 97.8% (131 of 133) at 60 months and 96.9% (127 of 131) at 84 months.

In the investigational group, the Prestige implant effectively maintained sagittal angular motion averaging 6.67° at 60 months and 6.75° at 84 months after surgery (Figures 4 and 5). Preoperatively, sagittal angulation at the target disc space averaged 7.55°. Sagittal angular motion greater than 4° and less than or equal to 20° was seen in 70.5% (146 of 207) of patients at 60 months and in 68.8% (141 of 205) of patients at 84 months (Figures 6 and 7). In the investigational patients, bridging bone was observed in 13 of 209 patients (6.2%) with complete radiographic follow-up at 60 months and in 20 of 201 patients (10.0%) at 84 months, as compared to 2 of 250 patients (0.8%) at 24 months.

FSU failure, a surrogate measure of subsidence, was defined as a decrease of more than 2 mm in FSU height from 1.5 months after surgery. This calculation required that the entire vertebral body above and below the index surgical level be able to be visualized, which was not possible in all of the patients with complete sets of radiographs. In those patients with adequate visualization of the vertebral bodies, FSU failure was observed in 12 of 165 patients (7.3%) at 60 months and 7 of 166 patients (4.2%) at 84 months. As a comparison, the corresponding FSU failure rates in the control group were 6 of 134 patients (4.5%) at 60 months and 4 of 127 patients (3.1%) at 84 months. There was no statistically significant difference in those rates between the 2 treatment groups at 60 months ($P = .844$) or 84 months ($P = .683$).

At the 84-month follow-up examination, 1 of 204 patients (0.5%) showed radiographic evidence of disc implant

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### Table 3. Comparison of Observed Neurological Success Rates

<table>
<thead>
<tr>
<th>Period</th>
<th>Neurological Success Determination</th>
<th>Neurological Success, %</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Investigational</td>
</tr>
<tr>
<td>24 mo</td>
<td>Observed</td>
<td>91.6</td>
</tr>
<tr>
<td></td>
<td>Imputing LTFU as failures</td>
<td>83.3</td>
</tr>
<tr>
<td>60 mo</td>
<td>Observed</td>
<td>92.2</td>
</tr>
<tr>
<td></td>
<td>Imputing LTFU as failures</td>
<td>73.2</td>
</tr>
<tr>
<td>84 mo</td>
<td>Observed</td>
<td>88.2</td>
</tr>
<tr>
<td></td>
<td>Imputing LTFU as failures</td>
<td>67.4</td>
</tr>
</tbody>
</table>

Abbreviation: LTFU, lost to follow-up.

*Rates were calculated by imputing patients who were lost to follow-up as failures.*
Adjacent-Segment Angular Motion

Adjacent-level disc degeneration and ossification were not specific data points captured in this study; however, the independent radiologists reviewed adjacent-segment angular motion patterns. At 6 weeks postoperatively, motion at the superior adjacent segment was 10.6° and 9.7° for the investigational and control groups respectively ($P = .041$). There were no other significant between-group differences in motion at adjacent levels at any other time point ($P > .097$).

In the investigational group, at the adjacent disc spaces, sagittal angular motion was effectively maintained above the implant, averaging 10.7° at 60 months (208 patients) and 11.4° at 84 months after surgery (206 patients). In the control group, similar motion patterns were seen at the superior disc space averaging 10.7° at 60 months (179 patients) and remained unchanged at 10.7° at 84 months after surgery (170 patients). At the disc space level below the index surgery, in the investigational group, sagittal angular motion averaged 8.0° at 60 months (126 patients) and 7.7° at 84 months after surgery (134 patients). In the control group, sagittal angular motion averaged 8.4° at 60 months (111 patients) and 8.5° at 84 months (113 patients) after surgery.

Adverse Events

Adverse events reported by both groups are included in Table 4. There were 259 of 276 (97.7%) investigational group patients and 232 of 265 (94.5%) control group patients who reported at least 1 adverse event ($P = .958$) through completion of the study. Excluding nonunion, there were only 2 categories of adverse event in which the occurrence
Dysphagia and Dysphonia

Complaints of dysphagia and dysphonia were identified and recorded as adverse events in both treatment groups. At 84-month follow-up, the cumulative rate for the control group was 10.5% compared with a cumulative rate of 11.5% for the investigational group. There was no statistically significant difference between the groups.

Table 4. Summary and Comparison of All Adverse Events Based on Life-Table Method

<table>
<thead>
<tr>
<th>Adverse Event Category</th>
<th>24-Mo Follow-Up Window (911 days)</th>
<th>Cumulative Through Study Completion</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(Investigational (n = 276))</td>
<td>(Control (n = 265))</td>
</tr>
<tr>
<td>No. of Patients (Cumulative Rate %)</td>
<td>No. of Patients (Cumulative Rate %)</td>
<td>No. of Patients (Cumulative Rate %)</td>
</tr>
<tr>
<td>Patients with any adverse events</td>
<td>235 (86.4)</td>
<td>219 (87.5)</td>
</tr>
<tr>
<td>Anatomic technical difficulty</td>
<td>1 (0.4)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Cancer</td>
<td>5 (1.9)</td>
<td>2 (0.8)</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>18 (6.8)</td>
<td>13 (5.5)</td>
</tr>
<tr>
<td>Carpal tunnel syndrome</td>
<td>18 (6.8)</td>
<td>7 (2.9)</td>
</tr>
<tr>
<td>Death</td>
<td>0 (0.0)</td>
<td>3 (1.3)</td>
</tr>
<tr>
<td>Dysphagia/dysphonia</td>
<td>24 (8.7)</td>
<td>22 (8.4)</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>30 (11.2)</td>
<td>30 (12.5)</td>
</tr>
<tr>
<td>Implant displacement/loosening</td>
<td>2 (0.8)</td>
<td>5 (2.1)</td>
</tr>
<tr>
<td>Infection</td>
<td>32 (11.9)</td>
<td>24 (10.0)</td>
</tr>
<tr>
<td>Neck or arm pain</td>
<td>145 (53.8)</td>
<td>121 (48.8)</td>
</tr>
<tr>
<td>Neurological</td>
<td>68 (25.2)</td>
<td>60 (24.6)</td>
</tr>
<tr>
<td>Nonunion</td>
<td>0 (0.0)</td>
<td>9 (3.6)</td>
</tr>
<tr>
<td>Nonunion (outcome pending)</td>
<td>0 (0.0)</td>
<td>21 (8.9)</td>
</tr>
<tr>
<td>Other</td>
<td>81 (30.2)</td>
<td>85 (35.0)</td>
</tr>
<tr>
<td>Other pain</td>
<td>82 (31.1)</td>
<td>64 (26.3)</td>
</tr>
<tr>
<td>Respiratory</td>
<td>10 (3.8)</td>
<td>8 (3.4)</td>
</tr>
<tr>
<td>Spinal event</td>
<td>23 (8.6)</td>
<td>50 (20.6)</td>
</tr>
<tr>
<td>Subsidence</td>
<td>1 (0.4)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Trauma</td>
<td>72 (27.2)</td>
<td>50 (20.8)</td>
</tr>
<tr>
<td>Urogenital</td>
<td>20 (7.7)</td>
<td>8 (3.3)</td>
</tr>
<tr>
<td>Intraoperative vascular injury</td>
<td>5 (1.8)</td>
<td>2 (0.8)</td>
</tr>
</tbody>
</table>

* Cumulative rates include adverse events from patients who withdrew from the study.
* The *P* values are from log-rank test for time-to-event analysis.

Secondary Surgical Procedures

Secondary surgical procedures performed after the index operation occurred in both the investigational and the control treatment groups (Table 5). At 84 months of follow-up, 11 patients in the investigational disc arthroplasty group had secondary surgeries (cumulative rate 13.7%) performed at the initial treatment level; 29 patients in the fusion control group had second surgeries (cumulative rate 13.7%) performed at the index level (*P* < .001).

Revision Surgery

There were no (0%) revision surgeries, defined as any procedure that adjusted or modified the original implant.
configuration, in the investigational group compared with 5 revision surgeries in 5 control patients (2.1%), which resulted in a significant between-group difference (P = .019).

Supplemental Fixation

Procedures that provided additional stabilization at the index surgical site were considered supplemental fixation procedures. In the IDE trial protocol, use of an external bone growth stimulator was also considered as supplemental fixation. In the control group, 5 patients (2.3%) underwent supplemental posterior spinal fixation surgeries, compared with no investigational patients (P = .017), and 7 patients (3.0%) had application of an external bone graft stimulator to treat suspected symptomatic nonunion arising from the index fusion procedures, whereas no investigational patients underwent application of a bone growth stimulator (P = .005). The use of bone growth stimulators is not included in the comparison of surgical procedures in this article because bone growth stimulators were used only in the control group.

Implant Removal

Eight nonelective implant removals occurred in both treatment groups (P = .808). All patients underwent removal of the disc implant and interbody fusion because of persistent radicular pain. No disc arthroplasty implants were electively removed; in the control group, 13 patients (7.0%) underwent elective removal.

Reoperation

Reoperations occurred in both treatment groups at similar rates. The investigational group had a reoperation rate of 1.5% (4 patients) compared with 3.0% (4 patients) in the control group.

Secondary Surgery at Adjacent Levels

Secondary surgeries at adjacent cervical levels occurred as stand-alone procedures and also involved revision surgery at the initial index surgical level. Secondary surgery that involved only an adjacent level occurred in 8 patients (3.9%) in the investigational group and 10 patients (5.4%) in the control group (P = .451). The cumulative rates are calculated from the log-rank test.

Through 84 months, 11 investigational patients (4.6%) and 24 control patients (11.9%) underwent secondary surgeries that involved adjacent levels (P = .008) (Figure 8).

Discussion

A large-scale, prospective, randomized, multicenter study in which the Prestige disc was compared with anterior cervical discectomy and fusion was initiated in 2002. Investigators reported the interim data from this study as patients enrolled in the study began their 24-, 36-, and 60-month evaluations. In this article, we report the final 60- and 84-month outcomes from this study.
With the use of the Prestige disc implant in patients with single-level cervical degenerative disc disease, sustained clinical and radiographic improvements in validated clinical outcome measurements were maintained at 84 months following surgery. A slightly earlier return to work was seen in the disc replacement group. The Prestige disc maintained physiologic segmental motion after implantation at the index surgical level; motion was also maintained at both adjacent-level disc spaces. Preservation of segmental motion may be related to a reduction in degenerative radiographic findings in adjacent segments in patients treated with arthroplasty. In addition, there was only 1 implant migration through 84 months and low rates of bridging bone at the implant site.

Similar outcomes were reported with the Bryan disc in an RCT at 12- and 24-month follow-up. The postoperative data from that study showed improvement in all clinical outcome measures by 12 months; at 24 months after surgery, the disc replacement group had a statistically greater improvement in the primary outcome variables, including NDI score and overall success, than the fusion group. These clinical and radiographic improvements were maintained out to 4 years. Outcomes at 2 and 5 years have been reported for the ProDisc-C cervical disc replacement. In an RCT evaluating the surgical treatment of single-level cervical disc disease, investigators reported that in the ProDisc-C treatment group there was a statistically and clinically significant improvement at 2 and 5 years compared to baseline. At 5 years, ProDisc-C patients had statistically significantly less neck pain intensity and frequency compared with the fusion control group.

In a different RCT of a metal-on-metal cervical disc replacement (Kineflex | C) in patients with 24 months of

![Figure 6](image1)

**Figure 6.** A, Preoperative lateral radiograph showing disc space narrowing and radial osteophyte formation at the C5-C6 level. B, Lateral extension radiograph shows 8° of lordosis across the C5-C6 interspace. C, Lateral flexion radiograph shows that the C5-C6 interspace only flexes to 0°.

![Figure 7](image2)

**Figure 7.** A, Postoperative lateral radiograph obtained at 84 months, showing the disc prosthesis in place at the C5-C6 level. B, Lateral extension radiograph showing 4° of lordosis at the C5-C6 interspace. C, Lateral flexion radiograph showing an increase to 5° of kyphosis at the interspace.
follow-up, investigators reported similar outcomes to the Prestige disc. Mean NDI and visual analog pain scores improved significantly by 6 weeks after surgery and remained significantly improved throughout the 24-month follow-up period. The overall success rate was significantly greater in the disc replacement group when compared with the fusion group.

Dysphagia is a common occurrence after anterior cervical spinal procedures. Surgical level, number of levels, instrumentation, and operative time have been associated with its occurrence. In addition, a correlation between intraoperative pharynx/esophagus retraction and postoperative swallowing disturbances has been established. There were no differences in the incidence of dysphagia or dysphonia between the two groups at any of the time frames studied. The incidence of postoperative dysphagia and the long-term resolution of the dysphagia were similar in a previously reported RCT.

The Prestige disc is able to maintain sagittal angular motion throughout 7 years postoperatively at the index surgical site. In addition, the superior and inferior adjacent levels to the index surgery showed similar motion preservation for preoperative measurements. Motion preservation after cervical disc replacement is affected by spontaneous fusion and the development of heterotopic ossification. Differences in occurrence rate of heterotopic ossification are, in part, related to the prosthesis type. The Prestige disc has the lowest rate of heterotopic ossification formation reported among contemporary RCTs for cervical disc replacements.

Conclusions

Cervical disc arthroplasty has the potential for preserving motion at the operated level while providing biomechanical stability and global neck mobility and may result in a reduction in adjacent-segment degeneration. The Prestige disc maintains improved clinical outcomes and segmental motion after implantation at 7 years of follow-up.

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Disclosures

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Since the commencement of the clinical study, author 1 has not had an equity interest (such as ownership, stock, or stock options) in Medtronic, Inc. Since the commencement of the clinical study, author 1 has not received compensation in which the value of compensation could be affected by study outcome, such as a royalty interest.

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Author 4 is not a consultant for nor has he received payments from Medtronic, the manufacturer of the PRESTIGE implant. Author 4 has received honoraria from Globus and DePuy Spine and has received a royalty from DePuy Spine related to thoracolumbar instrumentation but not related to any cervical implant.
References


“In neurology, it’s not just coming to a diagnosis; it’s also instructing and helping the patient cope with their illness. Our philosophy is that we have to treat the whole patient and not just the diagnosis.”

– Jordan Topel, MD, general neurologist
Select Publications (2014)*

Departments of Neurological Sciences and Neurological Surgery


*Biology from the neurosciences at Rush University Medical Center are indicated in bold.


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Department of Neurological Sciences

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• Dose Study in Patients with Mild-Moderate Alzheimer's Disease
• Anti-Amyloid Treatment in Asymptomatic Alzheimer's Disease
• Community-Based End-of-Life Intervention for African-American Dementia Caregivers

Zoe Arvanatakis, MD, MS
• Vascular Cognitive and Motor Decline: Impact of aPL

Roumen Balabanov, MD
• Dosage Study in Subjects with Relapsing Remitting Multiple Sclerosis

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• National Alzheimer's Coordinating Center (NACC)
• Role of the Innate Immune System in Aging and Development of Alzheimer's Disease
• Development of Lewy Bodies Biofluid Signatures by Targeted Proteomics
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• Risk Factors, Pathology, and Clinical Expressions of Alzheimer's Disease

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• Epidemiologic Study of Impaired Decision-Making in Preclinical Alzheimer's Disease
• Characterizing the Behavior Profile of Healthy Cognitive Aging

Aron Buchman, MD
• Identifying Genetic Determinants of Human Sleep and Circadian Rhythms
• Brain and Spinal Cord Microvascular Pathology in Late-Life Motor Impairment
• The Clinical Profile of Parkinson's Disease Pathology

Laurel Cherian, MD
• Study to Prevent Major Vascular Events in Patients with Acute Ischemic Stroke

Cynthia Comella, MD
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• Assess Safety of Dysport in Adults with Cervical Dystonia

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• Adult Neurological Phenotypes of Fragile X Gray Zone Expansion
• Exploratory Study of Different Doses of Endurance Exercise in People with Parkinson's Disease

S. Duke Han, PhD
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Aikaterini Kompoliti, MD
• Oral Treatment for Subjects with Moderate to Severe Parkinson’s Disease
• Assess Sustained Effects of Droxidopa Therapy in Patients with Neurogenic Hypotension

George Lopez, MD, PhD
• Minimally Invasive Surgery Plus rtPA in the Treatment of Intracerebral Hemorrhage

Elliott Mufson, PhD
• Chronic Effects of Neurotrauma Consortium Award
• Cellular and Molecular Medial Temporal Lobe Pathology in Elderly Pre-Mild Cognitive Impairment Subjects
• Neurobiology of Mild Cognitive Impairment in the Elderly

Dan Nicholson, PhD
• Proteomic Reconstructive Microscopy of Healthy and Diseased Dendrites

Kalipada Pahan, PhD
• Experimental Autoimmune Encephalomyelitis Study in Animal Cellular/Biochemical Assays
• Cinnamon, Ciliary Neurotrophic Factor (CNTF), and Experimental Autoimmune Encephalomyelitis (EAE)
• RANTES and Eotaxin: New Players in Parkinson's Disease Progression

Nina Paleologos, MD
• Trial for Seizure Prophylaxis in Patients with Malignant Gliomas

Julie Schneider, MD
• Epidemiologic Study of TDP-43 Pathology in Aging and Dementia

Raj Shah, MD
• Long-Term Safety Extension of Studies with Mild to Moderate Alzheimer’s Disease
• Study for Detection of Cerebral β-Amyloid Compared to Postmortem Histopathology
• β-Amyloid Imaging with Positron Emission Tomography in Prediction Progression in Alzheimer’s Disease
• Biomarker Algorithm for Prognosis of Risk of Developing Mild Cognitive Impairment in Alzheimer’s Disease
• Study in Subjects with Amnestic Mild Cognitive Impairment Due to Alzheimer’s Disease
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• CAPriCORN
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Sepehr Sani, MD
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Vincent Traynelis, MD
- Intubation Mechanics of the Stable and Unstable Cervical Spine
- Critical Analysis of Extubation Parameters for Patients Undergoing Combined Anterior Posterior Cervical Fusion
- Efficacy of Riluzole in Patients with Cervical Spondylotic Myelopathy Undergoing Surgical Treatment
Volume and Quality Data

Volumes, neurology and neurological surgery

Neurology volumes*, fiscal years 2010-2014

Neurology outpatient visits, fiscal years 2010-2014

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

Neurological surgery outpatient visits, fiscal years 2010-2014

Volume of patients monitored for epilepsy, calendar years 2010-2014

Rush had the highest volume of neurosurgical discharges in the Chicago region for fiscal years 2011-2014.

Neurological surgery volume of major cases by area, fiscal year 2014

Rush had the highest volume of neurosurgical discharges in the Chicago region for fiscal years 2011-2014.
Mortality, neurology and neurological surgery

**Neurological surgery mortality o/e, fiscal years 2010-2014**

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<th>Year</th>
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<th>2011</th>
<th>2012</th>
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<td>0.71</td>
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<td>0.79</td>
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</table>

Source: University HealthSystem Consortium clinical database

**Neurology mortality o/e, fiscal years 2010-2014**

<table>
<thead>
<tr>
<th>Year</th>
<th>2010</th>
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<th>2014</th>
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<tr>
<td>Mortality index</td>
<td>0.72</td>
<td>0.87</td>
<td>0.75</td>
<td>0.77</td>
<td>0.95</td>
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</table>

Source: University HealthSystem Consortium clinical database

Quality indicators, stroke

**Median times to endovascular recanalization treatment at Rush**

- Door to groin time: 42 min.
- Groin to recanalization time: 32 min.

Source: Data from SWIFT-PRIME trial

**Stroke IV tPA rate %, fiscal year 2014**

- Ischemic stroke: 22.47%
- Intracerebral hemorrhage: 19.16%
- Subarachnoid hemorrhage: 5.96%
- Total: 26.95%

Source: Get With the Guidelines stroke registry

**Stroke inpatient mortality %, fiscal year 2014**

- Ischemic stroke: 4.38%
- Intracerebral hemorrhage: 22.25%
- Subarachnoid hemorrhage: 16.84%

Source: Get With the Guidelines stroke registry

Rush had the fastest door to groin and groin to recanalization times of any participating SWIFT-PRIME trial sites. See page 2 for more information about the trial.

**Stroke case volumes, fiscal year 2014**

- Total: 965 Cases
  - Subarachnoid hemorrhage: 139 (14.40%)
  - Intracerebral hemorrhage: 261 (27.05%)
  - Ischemic stroke: 503 (52.12%)
  - Transient ischemic attack (<24 hours): 62 (6.43%)
From a beloved Disney mascot to professional athletes to patients of all ages with scoliosis, neurological spine surgeons at Rush have treated patients with the full gamut of spine conditions. Together, these physicians have more than 75 years of experience. During that time, they have pioneered several minimally invasive techniques, including minimally invasive decompression of cervical and lumbar stenosis and unilateral transforaminal lumbar interbody fusion.

Here, Vincent Traynelis, MD, director of spine neurosurgery at Rush, sits down with colleagues Richard Fessler, MD, PhD, John O’Toole, MD, MS, Ricardo Fontes, MD, PhD, and Harel Deutsch, MD, to discuss the future of spine surgery and the importance of finding the right treatment for each patient—and what goes into that decision-making process.

On recent advances in spine surgery

**Traynelis:** Let’s start with discussing advances that have changed spine surgery.

**Fontes:** We understand spinal deformity a lot better than we did ten years ago. It’s opened up a number of new treatments for patients who would otherwise be relegated to palliative treatment like morphine pumps and spinal cord stimulators. The big national and international registries that we participate in have shown that surgery can effectively treat quality of life in these patients with adult spinal deformity, such as from scoliosis, and that nonoperative treatments actually are not as effective.

At Rush we have a whole team of surgeons who are able to address that through minimally invasive and open techniques, and a lot of other specialists—ICU, rehab physicians—are involved in the care as well.

**Traynelis:** While adolescent idiopathic scoliosis is a prominent disease, the aging population of our country has
resulted in a large number of patients with scoliosis from degenerative processes. So, now degenerative deformity has become a huge issue in spinal surgery, at least in terms of the magnitude of patient numbers.

More is understood about deformity and there are newer techniques, yet a great deal of thought must be given to each patient in terms of how much intervention is enough and how much is too much. And interventions must be planned not only with an eye to what will address the current problem, but also what will minimize the potential for further trouble in the future.

Fontes: For those of us who treat adult deformity, I think the most obvious example of progress is people who have a lot of back and leg pain because of disc degeneration and prior surgeries. And because of this, they’re considerably bent forward.

That’s a problem we understand a lot better now. We’re able to correct it much better using minimally invasive techniques and, when necessary, we can use more conventional open techniques. We can make a difference with these patients, who otherwise in the past would have been considered to have huge problems and not be candidates for surgery. Now we can offer something for them, and it’s been shown extensively that it improves their quality of life.

Traynelis: And these patients, the degenerative deformity patients who are generally in their 60s and 70s, they still have a lot of things they want to do. They’ve given up everything because their quality of life is so bad.

O’Toole: That’s right; they are baseline very active people who have essentially developed these deformities that are disabling. I had a patient who was an instructor for chefs, and he would have to stand at the teaching kitchen all day. He just progressively got more and more deformity and just couldn’t work anymore.

A few months after surgery, he was already back at work and upright and feeling good. Same thing with the patients who like to work in their gardens.

Traynelis: They’re approaching retirement and all of a sudden in their golden years…

O’Toole: Right, and their recreational activity is golf…

Traynelis: And they can’t do anything but just sit in a chair because they’re miserable.

O’Toole: And these types of operative interventions can get these people back to those activities.

Fontes: Those are really some of the happiest patients we have. It’s truly impressive.

Fessler: Yes, I can give you an extreme scoliosis example. I had a patient with adult degenerative scoliosis. His passion was playing basketball. Not only could he not play basketball, but he was having difficulty walking down the block. We corrected his scoliosis using minimally invasive technique. He is now playing basketball every week.

Traynelis: And of course along with these advances, there’s fusion, which is a critically important part of treating many patients with spine problems, and progress in terms of improvements in instrumentation and the way we place instrumentation, such as with navigation.

O’Toole: Yes, but I think more important is the research that Drs Traynelis and Deutsch have done in non-fusion technology: specifically total disc replacement and arthroplasty: Dr Traynelis has been a leader in cervical arthroplasty research, and Dr Deutsch has been a leader in lumbar arthroplasty research.

Fusion is not necessarily the answer to all problems. It’s the answer to many problems, but we’re constantly looking for new and different solutions, and we here at Rush are actively involved in research efforts to make that happen.

Traynelis: For arthroplasty there are now quality data going out seven years that show that this, for the proper patient, is a durable treatment. In fact, that’s one of the articles in this publication. And, the results are better than those with fusion. But it has to be noted that arthroplasty is not for everyone. For a certain select group of patients, it is the better choice. The key is always to select the right treatment for the clinical problem.

Deutsch: Many people know that when you have a fusion, the levels adjacent to that fusion may be affected, and the arthroplasty potentially prevents that. That’s especially important in younger patients.

For instance, I’ve had a lot of success with artificial discs in police officers. They’re highly motivated to go back to work, and the perceived restrictions they would have if they had a fusion deter them from having one. And then they end up having artificial discs, and they can return to work.

Fontes: Of course it’s also important to mention that through the use of minimally invasive techniques, typically we can achieve a fusion pretty successfully without the need for a huge operation.

Fessler: The other impact that the minimally invasive scoliosis surgery has is that we’ve reduced blood loss from liters to literally 100 to 200 cc. Most patients don’t require transfusions, and we’ve reduced complications from 70% to 10%, comparing open to minimally invasive techniques.
O’Toole: I think that gets to the deformity part of it too, as you think about big fusion operations and what people go through in terms of complications following surgery. Many of us are trying to apply more minimally invasive techniques to reduce complication rates, reduce recovery times and ultimately still produce similar excellent outcomes for what is a very challenging disease and patient population. That’s where a lot of the current research is focusing.

On finding the right procedure for the right patient

Traynelis: It is important to first correctly diagnose the factors creating the problem after which one is able to determine the possible interventions. As with artificial discs, it’s about appropriate patient selection and the thought that goes into deciding which procedure is right for each patient. A previously operated patient with extensive instrumentation may not be a candidate for minimally invasive. It’s a great option for people, but, again, the value of the Rush neurosurgery spine program is that all of these techniques are available, and the collective experience of the surgeons is very broad and deep.

O’Toole: Among surgery disciplines, clinical decision making in spine surgery is one of the most complicated there is, I think. And it’s largely due to the fact that, although there are clinical practice guidelines that exist for what we do, many of the patients we see don’t fit nicely into the categories that some of those guidelines dictate.

Moreover, when you’re talking about spine surgery, you’re talking about at least two different organ systems: the musculoskeletal system and the nervous system. A lot goes into determining which aspects of the patient’s problems are related to one thing or another, the extent of your treatment, the consequences of this treatment, as well as the patient’s wishes.

So, a lot of these elements have to factor into those decisions. That’s where having colleagues like you guys around is such a huge advantage, because we’re able to bounce off different ideas and think about all these issues that are rarely simple in many of these patients.
Traynelis: There are two things that contribute to a good patient outcome—and they’re equally important. The first is the planning: If you have a bad plan and you choose the wrong thing to do, no matter how well you do it, it won’t work. We have the ability to talk to each other and create the right plan. Almost always there are at least two of us in clinic at any time. This facilitates immediate discussion when an unusual or challenging case arises. We also have a regular spine conference where cases can be reviewed.

The planning is just as hard as executing it, which is the second phase: executing the surgery properly. Before entering the operating room, especially for these bigger cases, hours have been spent studying anatomy, measuring angles and discussing options amongst ourselves, and explaining all to the patient. Both the planning and execution are critical to having a good outcome.

On limiting radiation exposure

Fontes: In addition to surgical outcomes, another quality issue we’re examining is radiation, particularly in deformity. Radiation exposure is a big concern for patients, especially for patients with scoliosis who get repeat tests over time, such as the pediatric and adolescent population. So, we’re aware of that and are continuing to look at ways to address this issue.

O’Toole: Ricardo [Fontes] and I have been working on this issue quite a bit. We’re looking at intraoperative radiation exposures, so we extensively use image-guided navigation in the operating room. Basically it involves an intraoperative CT-type machine that acquires images and allows us to then use 3-D navigation with a computerized system to work in the spine that ordinarily would require a lot of intraoperative X-ray or fluoroscopy. We’ve demonstrated substantial reductions in radiation exposures using this kind of technology.

Traynelis: To the patient and the team?

O’Toole: Yes, to everyone involved.

Fontes: That’s huge, especially from the patient safety standpoint. And, in addition to reducing radiation exposure, with this technology the placement of implants is much more accurate and leads to fewer revisions.

Traynelis: Each year we are more cognizant of the potential deleterious effects of X-rays, and the images ordered are limited without compromising care. For instance, instead of automatically getting the standard six views of the spine, if really two will show what is of concern, only two views are ordered.

O’Toole: Yes, and along those lines, a lot of what’s changed spinal cancer care both in terms of what we do on a day-to-day basis and in improving care for patients is the role of stereotactic radiosurgery—particularly in the treatment of metastatic disease to the spine. We’re now able to perform surgeries that are somewhat less morbid or fraught with complications because we can apply this more powerful radiation technique to get better control.

So, the paradigm has shifted in terms of care of these patients and what we can do. We’re able to do more for patients with metastatic disease in terms of achieving pain relief, neurological preservation of function, and spinal stability.

Traynelis: Yes, that’s important because some of the techniques that have changed—for both radiation and surgery—result in quicker recoveries. For people whose time is more limited, that’s important. It gets them out of the hospital, functioning and doing what they want to do.

On measuring—and learning from—outcomes data

O’Toole: And with regard to function, a big quality focus for us recently has been collecting patient-reported outcome measures, which is really the standard of care now for spine surgery in general. Wouldn’t you guys agree? We utilize a number of different outcome measures that let us know how patients are doing through a digital online platform that patients use to fill out various questionnaires both before surgery and after surgery.

We’re able now to trend these kinds of changes over time, which allows us to focus specifically on how we’re doing with quality in the care of these patients. That’s been a groundbreaking thing for us in that we’re getting real-time responses from patients about how they’re doing. This has allowed us to transform the way that we’re doing our own quality assurance measures.

Traynelis: Our plan going forward is to examine these data at regular intervals, see what our results are and look at other benchmarks. Each time we look at the data, we want the numbers to be better. So, we continually ask, “What can we do to improve this outcome?”

On the importance of collaboration

O’Toole: Our collaborations with colleagues throughout Rush help in this regard as well. For instance, you see the advantages of working in an institution like Rush clearly in cancer because what has happened with spinal oncology is a turn towards interdisciplinary care. We run a comprehensive spine tumor clinic through the Rush University Cancer Center. It’s co-directed by myself and Aidnag Diaz [MD, MPH], one of the radiation oncologists here.
The idea is that for patients with metastatic cancer to the spine, in particular, that’s not their only disease problem. So we take the view that we’re trying to look at the patient in a holistic way, at their overall cancer care: What are the goals for this patient in light of the extent of their disease, and what can we do for the spinal component of the problem? In some cases, that means radiation alone, sometimes it means surgery, and sometimes it means both or neither. All of this is done under the aegis of the medical oncologist and the patient’s other care providers, so that we are all providing a comprehensive treatment plan.

**Traynelis:** Yes, an advantage of practicing at Rush is that you’re part of a team—you have a group of highly skilled partners and each of them, although they all are excellent general spine surgeons, each person has some extra area of focus. That helps us as a group, and it’s also to the advantage of the patient. If a patient comes to me with a problem that’s not something I manage regularly, then I can send that person to one of my colleagues.

**O’Toole:** In addition, we have the advantage of collaborative relationships with the excellent departments here that are associated with the spine. For example, as I noted earlier, the medical and radiation oncology departments, and the partnerships we have with them with working with patients with spinal tumors. And the movement disorders group is a big part of what affects us in spine surgery because Parkinson’s disease patients often will have a lot of spinal issues. And they’re a fantastic group, as are our other neurology colleagues. We also work with the folks in physical medicine and rehabilitation…

**Traynelis:** Yes, and our rehabilitation center.

**O’Toole:** We have a strong group here. So, it’s these other service lines that intersect with spine surgery and the high quality that’s present in those other groups as well that elevates the work we do.

**On the future of spinal surgery**

**Traynelis:** So looking forward, what’s next for spinal surgery? Dr Fontes, you’ve done key basic research investigating disc degeneration in the laboratory and how and where this occurs. These results certainly represent new knowledge and may lead to improved outcomes at some point in the future.

**Fontes:** Well, as you know, it’s all very experimental at this point. But, at some point, the future of spinal surgery will involve manipulating discs. There’s a lot of data from the laboratory, and we understand this process a lot better now. Dr Fessler, would you want to speak more about disc regeneration?

**Fessler:** Yes, it is experimental, but we are able to do it in smaller animals. It’s a question of time until we can do that in larger animals. And then the question is how we actually implement that in humans, whether it’s going to be an injection to regrow within the disc or whether we grow the disc outside and then implant an entire disc. Those answers are still in the future.

**Traynelis:** Yes, the exciting point is that even though this is down the road, we have people here participating in what the future will be. So, it is a futuristic idea. But smartphones once were futuristic.

**Fessler:** The other futuristic thing we’ve got going on is that we’re just starting to enroll in the next spinal cord stem cell transplantation study for cervical spinal cord injury.

This is actually the third trial that I’ve been involved in personally. The first was in the mid-90s of transplantation of human embryonic spinal cord. The second was in the mid-2000s for stem cell transplantation into individuals with thoracic-level spinal cord injuries.

This is the first study that will be done in subacute spinal cord injury in the cervical spinal cord. We are much more hopeful in achieving some kind of a functional effect because the length that the cells have to grow is much shorter than the mid-thoracic spinal cord. If we can grow 2 cm, we might be able to return some hand function, for example. It’s a very exciting study.

**Deutsch:** We’re also involved in a trial of a vaccine against staph, which is the most common cause of surgical infections, and the main risk for complications in spine surgery, especially open surgery. The hope is that future patients may get a vaccine a week before they have surgery, and that may reduce infection rates significantly. It’s going to be a randomized study where people get the vaccine or placebo.

**Traynelis:** If it works, then the vaccine could be offered to all patients who have surgery, which would be a great advance. 😊
For a patient consultation or referral to a neurologist at Rush, please call (312) 942-4500.

For a neurosurgeon at Rush, call (312) 942-6644.

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