

NEW YORK-PRESBYTERIAN NEUROSCIENCE

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The Cutting Edge: Approaches for Spine Disorders

Columbia surgeons at NewYork-Presbyterian Hospital are using state-of-the-art surgical approaches and computer models to optimize outcomes in pediatric, adult, and elderly patients undergoing treatment for neuromuscular, degenerative, congenital, or idiopathic spinal deformities.

“The goal is to improve function and decrease pain in these patients with the most minimally invasive techniques available,” said Peter Angevine, MD. “We are now able to operate safely and effectively on patient populations that,

previously, we really couldn't treat, including patients with neuromuscular disorders who may have limited pulmonary function and older adult patients as well.”

Paul McCormick, MD, is best known for his techniques and outcomes associated with the microsurgical removal of spinal cord tumors, including hemangioblastomas, and different types of nerve sheath tumors, such as ependymomas and astrocytomas. His primary clinical interest is in the measurement of patient outcomes and their quality of life following different types of spinal surgery. In fact, Dr. McCormick has found that in certain subsets of populations—individuals with hemangioblastomas or patients with cysts associated with the tumors—actually note an improvement in function following

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Hospital Advances Gene Therapy Research in Parkinson's Disease

Weill Cornell researchers at NewYork-Presbyterian Hospital—led by Michael Kaplitt, MD—have presented the initial results of the first human clinical trial investigating the safety and efficacy of gene therapy in the treatment of Parkinson's disease (PD). Preliminary results from the Phase I trials have demonstrated favorable outcomes for a combined surgical/medical therapeutic approach in which surgeons insert viral vectors into cells of the subthalamic nucleus to aggressively treat patients with PD. According to Dr. Kaplitt, the results are promising enough to indicate that the approach may have possible applications for other neurologic and brain-related disorders. An article summarizing the results of the study appeared in the June issue of *The Lancet* (2007;369:2097-2105).

Dr. Kaplitt's work centers around the commonly held belief—based on current literature—that the disabling motor symptoms of PD are caused by excessive neuronal firing resulting from a loss of dopaminergic neurons in the brain. According to Dr. Kaplitt, dopaminergic neuronal loss in PD leads to changes in the circuitry of the basal ganglia, such as decreased inhibitory gamma-aminobutyric (GABA) input to the subthalamic nucleus. By instilling GABA to specific areas of the basal ganglia via a stereotactic procedure developed by Dr. Kaplitt and his team, surgeons and neurologists could, in principle, reduce the motor symptoms of PD.

Dr. Kaplitt modeled his surgical gene delivery technique specifically after proce-

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UPDATES

Motor Performance Measures: Predicting Recovery From Stroke

Individual patients' ability to recover movement lost after stroke varies, for mainly unknown reasons. Physicians predict poststroke recovery based on brain lesion size, lesion location, patient age, and degree of impairment. These are poor predictors, only accounting for approximately 50% of recovery-variance. At the Motor Performance Laboratory at NewYork-Presbyterian Hospital/Columbia University Medical Center, researchers are looking into other factors that may influence individual differences in motor recovery after stroke.

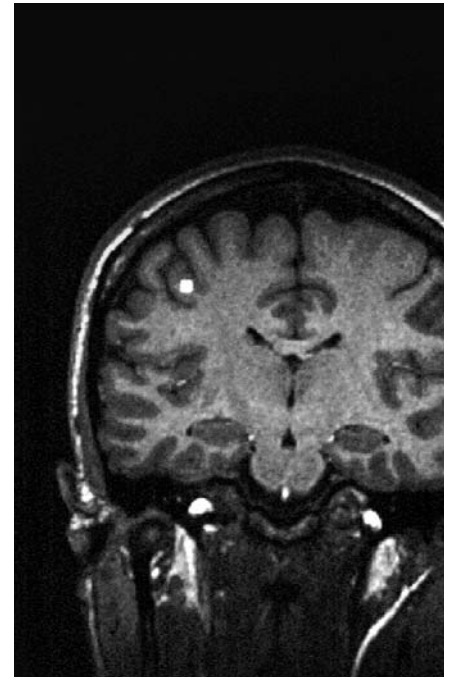
Led by John Krakauer, MD, Hospital researchers are working on studies relating to normal motor learning and motor recovery following stroke. Current work is focused on the development of experimental and computational models of normal motor learning, brain imaging of normal motor learning, and experimental and imaging studies of recovery after stroke. According to Dr. Krakauer, these investigations "mutually inform each other" because "some of the changes that occur in the brains of healthy people as they learn motor skills might have some parallels with how people actually have to relearn to move after stroke."

During his fellowship, Dr. Krakauer worked in the motor control laboratory of Claude Ghez, MD, in the Center of Neurobiology and Behavior at NewYork-Presbyterian/Columbia, of a functional magnetic resonance imaging (fMRI) study of poststroke recovery. The researchers examined subjects' brains 1 week after

stroke and 3 to 6 months later. The study included fMRI images of 8 subjects with their first corticospinal tract infarction compared with images of 6 control subjects. fMRI activity was measured during a simple finger-touch task. The type and location of measurable brain activity differed between the stroke patients and the control subjects, suggesting that the brains of the stroke patients were reorganizing. However, the interpretation of such studies can be confounded by what is known as the "performance confound." Dr. Krakauer's study was a follow-up to work done by his colleague Randolph Marshall, MD.

"Dr. Marshall led what was really the first study to perform functional imaging on patients early after stroke and then followed them out longitudinally with repeat scanning," noted Dr. Krakauer. "So you could actually look at changes in functional brain imaging over time and see how that related to their recovery."

When fMRI repeat scanning is done following a stroke, brain activity differs at various time points. The differences in brain activity represent either underlying motor recovery or patient performance change. Distinguishing between the 2 types of activity is difficult, however. Drs. Krakauer and Marshall bypassed this problem by imaging brains of individuals who had experienced transient ischemic attacks. These people experienced no permanent changes in motor function because they were identified based on reversible symptoms. Because



Measurements taken during fMRI have shown distinct brain activity in stroke patients as compared to healthy patients. These findings indicate that the brains of stroke patients may "reorganize."

there was no change in their movement, brain activity changes over time had to be the result of brain reorganization and recovery, not performance.

Subjects performed a simple motor task while in the scanner. The investigators saw increased brain activation in the hemisphere on the same side as the hand performing the task; the opposite hemisphere normally controls movement. This provided evidence that the brain had reorganized, despite no observable motor deficit.

Since his fellowship, Dr. Krakauer's more recent work has focused on finding ways to identify brain activity specifically related to motor learning and motor recovery, while controlling for the changes in performance inevitably accompanying these processes.

"The means that we have employed to control for performance confounds have varied depending on whether we are studying motor learning or motor recovery," he said. "But the logic is the same."

In an ongoing study of motor recovery, Drs. Krakauer and Marshall and colleagues—Eric Zarahn, MD, and Ronald Lazar, MD—performed fMRI on subjects within 48 hours after stroke. Subjects squeezed their fist, or attempted to, while in the scanner. The researchers first identified brain activation associated

"Maybe people are walking around with different underlying capacities to recover from stroke before they ever have one."

—John Krakauer, MD

with fist-squeezing, then evaluated patients using the Fugel-Meyer scale. Any activation in the scanner that correlated with the way the subjects performed on Fugel-Meyer was considered to be performance-related and was factored out of the analysis. All remaining activity was considered to be related to brain reorganization. The researchers then calculated—using this remaining activity—the activation that correlated not with the subjects' performance at the time of scanning, but with their ability to do the same task 3 months later.

Using this method, the researchers identified an activation pattern 24 to 48 hours following a stroke that accounts for approximately 90% of people's variance in recovery 3 months after stroke. This method predicted recovery far better than standard clinical measures. Interestingly, the primary components of this pattern lay outside of primary motor cortex and premotor cortex, areas that project directly to muscles via the spinal cord.

According to Dr. Krakauer, different people may express the recovery pattern to varying degrees. "Maybe people are walking around with different underlying capacities to recover from stroke before they ever have one," he said. Ultimately, he believes that it might be possible to stimulate the brain to increase expression of the recovery pattern to promote post-stroke motor recovery, but admitted this could be far in the future. He emphasized that translational research should include physiological studies that begin in patients and not just secondary patient studies after initial work in animal models.

"Drs. Marshall and Lazar helped me appreciate this," he noted. "Their cerebral localization lab and I hope our Motor Performance lab, is a model for this kind of research. Measurement in patients is what physician-scientists based in academic medical centers are uniquely suited to do."

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Consciousness Trial Offers Promise For Recovery From Brain Trauma

Investigators at New York-Presbyterian Hospital/Weill Cornell Medical Center, led by Nicholas D. Schiff, MD, are using the latest neuroimaging technologies and therapeutic approaches in an effort to improve understanding of and treatment options for “consciousness disorders” caused by brain trauma.

injuries to improve their quality of life, and assist them and their families with their care.”

According to Dr. Schiff, who has been studying consciousness and other issues related to brain injury for more than 10 years, patients suffering severe traumatic brain injury often experience widespread

loss of cerebral connectivity. It is assumed that this loss of connectivity is what leads to the failure of the brain mechanisms that support communication and other important functions. Until recently, no treatment had been shown to promote recovery by restoring function in cases of MCS; historically, consciousness disorders that persist for more than 12 months have been considered irreversible.

Using neuroimaging technologies, however, Dr. Schiff and his team have recently been able to identify functioning “large-scale” cerebral networks in MCS patients. According to Dr. Schiff, these findings indicate that in some cases MCS may be perpetuated by the

“Our observations, years after the injury occurred, challenge the existing practice of early treatment discontinuation for patients with only inconsistent interactive behaviors, and motivate further research to develop therapeutic interventions.”

—Nicholas D. Schiff, MD

Dr. Schiff and his team have published a number of papers describing the role of positron emission tomography, functional magnetic resonance imaging, and quantitative electroencephalography and in the diagnosis and assessment of patients in vegetative state (VS) and minimally conscious state (MCS) (*J Head Trauma Rehabil.* 2006;21:388-397).

The team has also worked with deep brain stimulation (DBS)—a technology Columbia and Weill Cornell researchers at New York-Presbyterian Hospital have been using for several years in the treatment of Parkinson’s disease and epilepsy—to improve the function of surviving residual brain networks in patients in MCS following brain trauma (*Nature.* 2007;448:600-603). This is the first time DBS has been used on MCS patients.

“These findings are a first step toward developing a systematic approach to the evaluation and treatment of patients with severe brain injuries,” Dr. Schiff noted. “We hope that, with further research, it will build a foundation for better understanding of what may be possible to offer patients who have suffered serious brain



Nicholas D. Schiff, MD, and his team are working with deep brain stimulation to improve the function of surviving residual brain networks in patients in MCS following brain trauma.

“underactivation” of these networks, and that residual functional capacity could be supported by therapeutic interventions.

Dr. Schiff and his team worked with colleagues at JFK Johnson Rehabilitation Institute-Center for Head Injuries in Edison, NJ and the Cleveland Clinic Center for Neurological Restoration to perform DBS on a 38-year-old male patient who had been in an MCS for 6 years (following an assault) at the time of intervention. Using image-guided navigation, DBS targets the central thalamus and other deep-brain structures through the use of tiny electrodes that are implanted in the patient’s brain and connected to programmable pacemaker batteries in the chest. In the study patient, the procedure took 10 hours to perform (due, in part, to complications from the original injury).

Following an initial titration period—during which the team calibrated the dose and timing of treatments—the patient began receiving DBS treatments intermittently over the course of the 6-month, double-blinded on/off crossover

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Video EEG Presents New Implications For Diagnosis, Treatment of Epilepsy

Columbia and Weill Cornell neurologists and neurosurgeons working in the Epilepsy Monitoring Unit (EMU) at NewYork-Presbyterian Hospital are developing new diagnostic and treatment approaches, in an effort to reduce symptoms and improve quality of life in patients suffering from the neurologic disorder. At the center of these efforts has been the use of continuous video electroencephalographic brain monitoring (cEEG), a state-of-the-art technology now being used in the management of patients at the Hospital with a number of acute neurologic conditions.

According to Cynthia Harden, MD, physicians in the EMU are using cEEG to record patient behavior and brain activity during episodes, to classify these seizures so that the proper treatment can be applied, and to gather information on multiple seizures to pinpoint their origin and determine if patients are candidates for resective epilepsy surgery. cEEG monitoring can also assist neurologists in distinguishing nonepileptic seizures, which mimic epileptic seizures but are characterized by normal brain waves from actual seizures. Because nonepileptic seizures are often found to be psychogenic in nature, psychologic and/or psychiatric treatment approaches have successfully resolved them in more than 50% of reported cases.

“Approximately 30% of our admissions to the unit come from these types of seizures,” said Frank Gilliam, MD, citing the importance of identifying these seizures with video cEEG monitoring “so we can educate the families that they don’t have to go back to the ER with every spell.”

In a study published by Dr. Gilliam and colleagues, researchers reviewed sample cEEG readings from 9 patients and found that that local hypersynchrony might be a marker for epileptogenic cortex (*Epilepsia*. 2006;47:1402-1406). By using this information to interpret cEEG readings, they postulated that neurologists and other clinicians could better

distinguish between varying types of seizure activity and reach more definitive diagnoses of epilepsy. The researchers estimated that this could ultimately reduce healthcare treatment costs for epilepsy by up to 90%.

“Many of these patients who were thought to have pharmaco-resistant epilepsy, ultimately, with EEG monitoring, were found to never have had epilepsy to begin with,” he said.

cEEG is also used to evaluate patients for surgery. According to Dr. Gilliam, there has been a bias against epilepsy surgery historically, because of perceived safety issues. However, surgeons at NewYork-Presbyterian Hospital have optimized outcomes with traditional procedures such as resective surgery and corpus callosotomy using cEEG. The time of refractory epilepsy before evaluation in the EEG monitoring unit has been about the same for the past 5 years as it was when the surgery became available at NewYork-Presbyterian Hospital some 20 years ago.

because they’re processing all these new concepts and ideas about treatment, and thinking about their potential for life without seizures.”

As a result of the perceived safety concerns, Dr. Gilliam added, surgery is an often underused factor in the epilepsy treatment armamentarium. Researchers at NewYork-Presbyterian/Columbia are currently involved in a study designed to measure patient preferences with regard to outcomes following surgery. The goal of the study is to create a tool to aid patients in the decision-making process as they evaluate treatment options. Researchers are also investigating the efficacy of a responsive neurotransmitter that is surgically implanted into the brain of epilepsy patients. The implant can detect the onset of seizures and hopefully prevent them, by directing electric stimulus to the appropriate part of the brain.

“There are an estimated 100,000 to 200,000 candidates for epilepsy surgery in the US, and probably some 2,000 pro-

“We still haven’t found the magic bullet for epilepsy. Sometimes we hit a home run with these new compounds, helping people achieve significant improvement a lot faster than if they had to wait for the compounds to come to market. We have been fortunate here to have studied essentially all of the newer anti-seizure medicines in clinical trials before they were available by prescription.”

—Cynthia Harden, MD

“Patients who have suffered with recurrent seizures for many years that are pharmaco-resistant can come in and receive an evaluation in the EMU in 4 to 6 days that defines their future treatment,” said Dr. Gilliam. “It’s a very intense and emotional time for them

cedures are done each year,” said Dr. Gilliam. “Traditional surgery has been available since the 1950s, but we can now perform video and digital brainwave analysis that dramatically facilitates our

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trial. After 6 months of treatment, many functional improvements were noted including recovery of spoken communication in the form of 1- to 3-word responses, consistent oral feeding (the patient had remained on tube feedings for more than 6 years), and recovery of controlled arm movements.

“The frequency of specific cognitively mediated behaviors and functional limb control and oral feeding increased during periods in which DBS was on, as compared with periods in which it was off,” said Dr. Schiff. “We believe the DBS compensates for a loss of arousal regulation that is normally controlled by the frontal lobe in the intact brain. These findings provide evidence that

DBS can promote significant late functional recovery from severe traumatic brain injury. Our observations, years after the injury occurred, challenge the existing practice of early treatment discontinuation for patients with only inconsistent interactive behaviors, and motivate further research to develop therapeutic interventions.”

Late recovery of this magnitude is rare in patients with chronic MCS, however, according to Dr. Schiff. The key to success in this case may have been the neuroimaging findings of Hospital researchers. According to Dr. Schiff, structural remodeling of the brain to distinguish the pathophysiologic basis of VS and MCS following severe injury may play a role in late functional recoveries. Introduction of neuroimaging into the

clinical evaluation process, he said, will require developing frameworks for longitudinal assessments of cerebral function. He and his team are now focusing on the development of markers for identifying patients who may harbor potential for meaningful recovery. Modeling, in combination with treatment approaches such as DBS, may ultimately revolutionize the standard of care for chronically under-responsive patients.

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Epilepsy

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ability to identify the epileptogenic region and its relationship to eloquent cortex. The vast majority of people have seizures coming from somewhere other than eloquent cortex, so we can safely do surgery.” He added that with epilepsy surgery, approximately 70% of patients are immediately seizure-free and more than 80% have a significant reduction in seizures.

For those patients who will benefit from drug therapy for epilepsy, researchers at the EMU are also studying a number of new therapeutic options. Currently, they are evaluating the use of natural progesterone in women of child-bearing years. Throughout his career, Dr. Gilliam has served as lead investigator on multiple studies of epilepsy treatments, including carbamazepine, phenobarbital, and primidone. Today, he and his colleagues at NewYork-Presbyterian/Columbia (including 4 epileptologists) are involved in a number of pivotal trials measuring the safety and efficacy of agents such as rufinamide and pregabalin.

“There are an estimated 100,000 to 200,000 candidates for epilepsy surgery in the US, and probably some 2,000 procedures are done each year. We can now perform video and digital brainwave analysis that dramatically facilitates our ability to identify the epileptogenic region.”

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“We still haven’t found the magic bullet for epilepsy,” noted Dr. Harden. “Sometimes we hit a home run with these new compounds, helping people achieve significant improvement a lot faster than if they had to wait for the compounds to come to market. We have been fortunate here to have studied essentially all of the newer anti-seizure medicines in clinical trials before they were available by prescription.”

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Spine

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surgery, whereas in most patients the goal is just to maintain function.

Currently, Dr. McCormick and his team are in the data-collection phase of a study with approximately 135 patients with nerve sheath tumors. Dr. McCormick has developed a classification of these tumors to help other surgeons determine when it is safe to sacrifice the nerve that gives origin to the tumor and under what circumstances the nerve root needs to be preserved in order for the function to maintain a certain normalcy; he plans to publish his findings later this year.

“Essentially, this is a surgical algorithm looking at the different strategies you can use for different subtypes, making surgery more custom developed for a particular patient,” he said. “My research focuses on trying to better understand how we’re helping people, and in quantifying that. Ultimately, this will make us better doctors because we will be able to say, ‘Well, these are the circumstances under which these patients do very well in this surgery, and we know this because of these specific factors.’ It certainly helps me in terms of deciding which procedure to do and when to do it, and hopefully it will help others as well.”

Meanwhile, Dr. Angevine and his colleagues are treating patients in their 70s and 80s using aggressive surgical interventions and achieving some excellent outcomes. His research work focuses largely on measuring, assessing, and analyzing surgical outcomes in older adults with degenerative spinal deformities. His analyses include economic examination of the costs associated with treatment compared with the benefits of restored quality of life.

“We can perform more complex spinal reconstructions than ever before,” he said. “But the real questions are in whom can we do this safely and in whom can we also do it effectively?”

Dr. Angevine performs osteotomies to restore sagittal balance in older people with degenerative or iatrogenic spinal deformities. Using the technique, he and his colleagues have been able to decrease pain and increase function, allowing many

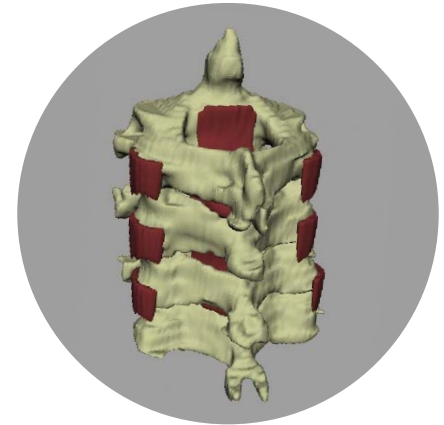
of these patients to stand upright following surgery. In terms of recent developments that have facilitated these surgeries, Dr. Angevine cites the continuous improvement in the use of transpedicular screws over the past decade, along with the more recent development of bone morphogenetic proteins to enhance the formation of a bony fusion.

Michael Kaiser, MD, has completed subspecialty training in treating complex spinal disorders and tumors of the spine and spinal cord, with a focused interest on complex cervicothoracic reconstructions. His research interests include motion preservation technology, allowing surgeons to effectively treat spinal degenerative disease while avoiding a fusion, “which is a biomechanically abnormal environment,” he noted.

“We now have relatively novel technology that allows us to maintain physiologic motion and avoid the increased stress placed on the neighboring spinal segments that occurs following the traditional spinal fusion,” he added.

Dr. Kaiser is currently the primary investigator in an ongoing FDA-approved Investigational Device Exemption trial examining the safety and efficacy of a new artificial disc for the cervical spine; the study is indicated for patients between 20 and 65 years of age with single-level cervical disc disease. The team has used the device in 3 patients so far, effectively decompressing their spinal cords. Enrollment for the study is expected to continue through 2008.

Collaborating with an interdisciplinary team that includes Michael Downe, PhD, Dr. Kaiser is also working on a computer simulation of the cervical spine that provides both an anatomically and a biomechanically accurate 3-dimensional representation of the cervical spine. According to Dr. Kaiser, the model is intended to serve both as an educational tool for residents in training and as a diagnostic instrument to determine the long-term effects of a specific procedure prior to surgery. The team is working on the interactive aspects, which include having the model provide tactile feedback, thus enabling the user to experience the sensation of tissue manipulation, such as drilling bone. A significant advantage of this approach is that sur-



A 3-dimensional cervical spine model. The white structures are bone, and red structures are ligaments.

geons in training will learn the limitations of tissue manipulation without actually operating on a specific patient.

“We’re starting on the cervical spine, which is my area of interest,” Dr. Kaiser said, “but ultimately we’d like to create models for the entire spine, simulating the effects of a procedure 10, 15, or 20 years down the line. We have designed this model for biomechanical testing as well as for interactive capabilities, so a person will be able to perform a virtual operation by visualizing the model on the computer screen while manipulating a handheld instrument.”

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Gene Therapy

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dures used in deep brain stimulation (DBS). Unlike DBS, however, gene therapy requires only 1 treatment, no implantation of a stimulator, and no follow-up to optimize the stimulator or change batteries. The treatment may also have another positive effect: GABA may increase in other areas of the brain that subthalamic nucleus neurons send axons to, suppressing other regions of the hyperactive circuitry. The trial, conducted primarily at NewYork-Presbyterian/Weill Cornell Medical Center, was designed to measure the safety, tolerability, and potential efficacy of the unilateral subthalamic viral vector injection of the glutamic acid decarboxylase (GAD) gene with adeno-associated virus (AAV) into the subthalamic nucleus of 12 patients with PD. Patients were randomized to the following treat-

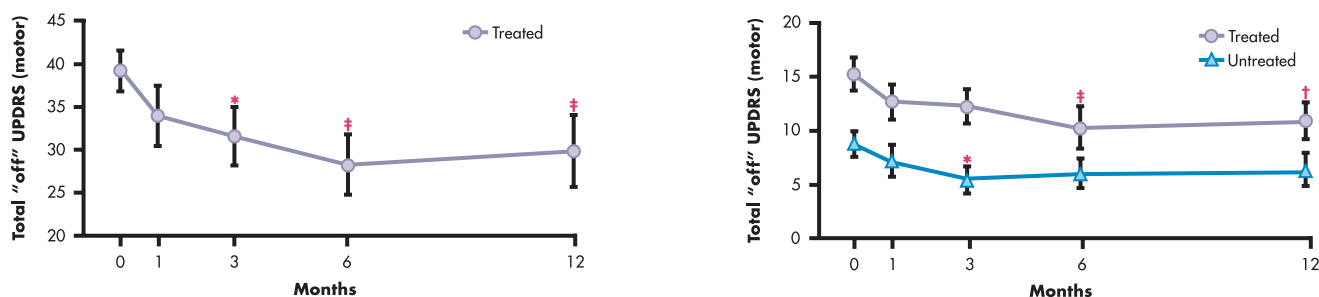
ments: 4 patients received low-dose AAV-GAD, 4 were given medium-dose, and 4 were given high-dose.

After 12 months of follow-up, based on Unified Parkinson's Disease Rating Scale (UPDRS) motor ratings, 10 patients receiving gene therapy demonstrated substantial improvement in both the "off" and "on" states (Figure), primarily on the side of the body contralateral to surgery. These improvements were measurable as early as 3 months following treatment. In all, 4 patients showed 0% to 20% improvement, 2 showed 20% to 40% improvement, and 4 showed >40% in whole body "off" period motor UPDRS. In addition, although improvement in Activities of Daily Living scores ("off" and "on" states) were not significant during the course of the study, there was a trend towards improvement in the off state ratings at 12 months. No significant adverse events related to gene therapy were reported.

Although proven medications exist, including levodopa, Dr. Kaplitt thinks that treatments for PD can still be improved. Patients, he noted, eventually stop responding to medications and also develop side effects, particularly since drugs affect the whole brain rather than only the specific area involved in the disease. "The value of gene therapy is that we can take a gene and make rational predictions and go in and manipulate that gene," said Dr. Kaplitt. "We view this first trial as a stepping-stone for using gene therapy for a whole host of neurological conditions."

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Figure. Clinical improvement in motor ratings.



Note: At each time point, the motor component of the UPDRS was measured 12 h after discontinuation of oral medications ("off" state).

Source: Kaplitt M, et al. Lancet. 2007;369:2097-2105.

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