

NEW YORK-PRESBYTERIAN Neuroscience

Affiliated with COLUMBIA UNIVERSITY COLLEGE OF PHYSICIANS and SURGEONS and WEILL MEDICAL COLLEGE OF CORNELL UNIVERSITY

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Staying on Target: Imaging In Neurosurgery

The neurosurgeon's job is a difficult one, particularly when it comes to the surgical procedures used in the treatment of movement disorders such as essential tremor, dystonia, and Parkinson's disease (PD).

"If the surgeons are off by as little as 1 mm, they won't get the benefits they're seeking," noted Michael G. Kaplitt, MD, PhD. "In fact, they could cause the patient serious side effects."

The key to success in neurostimulation procedures such as deep brain stimulation (DBS), which was approved by the Food and Drug Administration for the treatment of PD in 2002, involves hitting surgical "targets." Weill Cornell and Columbia surgeons at NewYork-Presbyterian Hospital are researching preoperative procedures to make this process more a science than an art.

"The targets have been better defined in terms of what has to be altered or modulated," said Guy M. McKhann II, MD. "For the surgeons, it's simply a matter of locating them."

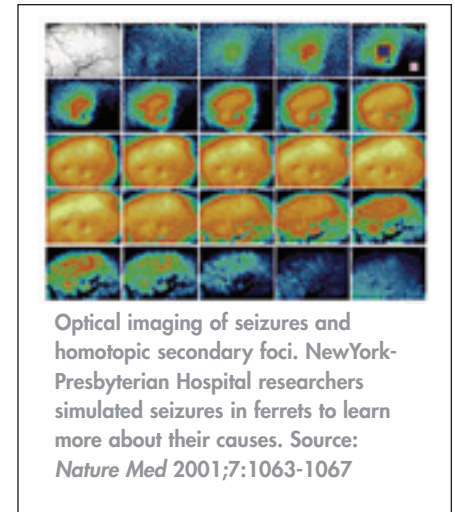
According to Robert R. Goodman, MD, PhD, all neurostimulation procedures involve the implanting of electrodes stereotactically into a specific part of the brain in order to regulate its activity. For PD, for instance, the target is the subthalamic nucleus; for dystonia it is the internal segment of the globus pallidus. Hitting these targets requires incredible precision, especially since many of them are surrounded by the

see Target, page 7

Researchers Isolate the Role Of Astrocytes in Epilepsy

Progress in treating epilepsy, the perplexing disorder that afflicts some 15 million Americans, demands ingenious experiments and novel applications of technology. Columbia and Weill Cornell researchers at NewYork-Presbyterian Hospital are involved in 2 separate and ambitious programs aimed at creating clinical advances based on recent and fundamental insights into the neurochemistry and cellular physiology of the brain.

Astrocytes have received relatively little attention in research of seizure disorders. However, they are legion in brain tissue, outnumbering neurons by about 10 to 1. They also possess voltage-dependent, high-affinity ion- and neurotransmitter uptake systems. Guy M. McKhann II MD, believes neglect of astrocytes might be unwarranted because they play a significant role in regulating neuronal behavior and consequently may have a causative role in epilepsy. Dr. McKhann's current investigations at the Epilepsy Research Laboratory arise from a series of papers, the first paper published in 1998 (*J Neurosci* 18:4425-4438), in which he and colleagues demonstrated



Optical imaging of seizures and homotopic secondary foci. NewYork-Presbyterian Hospital researchers simulated seizures in ferrets to learn more about their causes. Source: *Nature Med* 2001;7:1063-1067

a functional-based taxonomy of astrocytes in the hippocampus. Astrocytes have long been implicated in the complex regulation of the microenvironment in the brain, and a particular subtype proved to be particularly adept at uptake of potassium, a key product of neuronal activity.

Indeed, neurons at work constantly extrude potassium, of which normal extracellular levels must be maintained or see Epilepsy, page 7

TABLE of CONTENTS

Neuropathic Pain

2 New treatments for patients with neuropathy and neuropathic pain

CME Conferences

3 Information on future CME programs available through NewYork-Presbyterian Hospital and its affiliated medical schools

Treating Epilepsy

4 Researchers at NewYork-Presbyterian Hospital are leading the way in the exploration of neurostimulation techniques

Movement Disorders

5 Effective surgical approaches for the treatment of movement disorders

Investigating and Treating Troubling Neuropathies

Weill Cornell and Columbia researchers at NewYork-Presbyterian Hospital are discovering and using an ever-widening array of treatments for patients with various forms of neuropathy and neuropathic pain.

Norman Latov, MD, PhD, is focusing on the mechanisms and treatment of inflammatory neuropathies. His laboratory is credited with discovering that certain antibodies can cause peripheral neuropathy and for developing diagnostic tests that are currently used to evaluate and manage patients with neuropathy. He and his colleagues are “trying to find markers for inflammatory neuropathies and targets for therapeutics,” said Dr. Latov. “We’re doing DNA microarray analysis on nerve biopsies, trying to identify molecules that are important for the disease process,” he added. He pointed to a paper submitted recently to the American Academy of Neurology that discussed the finding that certain molecules are upregulated in demyelinating disease (chronic inflammatory demyelinating polyneuropathy), while others are upregulated nonspecifically in inflammatory diseases. “Hopefully those will be important molecules to focus on in future research,” noted Dr. Latov.

Meanwhile, Ronald Brisman, MD, has developed a specialty in trigeminal neuralgia (TN), a disorder of the trigeminal nerve marked by agonizing bursts of facial pain that can be triggered by the slightest touch around the face and mouth or by talking, eating, or brushing the teeth. Approximately 100,000 people in the United States have the condition, and about 10,000 new cases occur each year. Dr. Brisman is one of the few neurosurgeons in the country with extensive

experience in TN. He has treated more than 2,000 patients in all. “Patients come from all parts of the world because of our recognized expertise,” he noted.

For TN patients with pain that does not respond to pharmacotherapy, or who cannot tolerate the side effects of medications, a number of options are available. These include gamma knife radiosurgery (GKRS), radiofrequency electrocoagulation, glycerol injection, balloon microcompression, and microvascular decompression.

“We’re doing DNA microarray analysis on nerve biopsies, trying to identify molecules that are important for the disease process.”

— Norman Latov, MD, PhD

Table. Pain Relief in Patients With TN Following GKRS

Months Post-GKRS	MS	Patients Reporting Pain Relief	
		Group A	Group B
6	No	89.8%	71.4%
12	No	85.2%	78.6%
6	Yes	75%	44.4%
12	Yes	57.1%	37.5%

GKRS, gamma knife radiosurgery; **MS**, multiple sclerosis
TN, trigeminal neuralgia.

Source: Brisman R. Gamma knife radiosurgery for primary management for trigeminal neuralgia. *J Neurosurg.* 2000;93(suppl 3):159-161

All procedures involve some degree of risk, according to Dr. Brisman, but GKRS, the most recent and least invasive neurosurgical treatment for TN, is the least likely to cause complications, and discomforting facial sensations called *dysesthesias* are uncommon. Between May 1998 and February 2004, Dr. Brisman performed 563 GKRS procedures on patients with TN. There were no major complications, he said, and most patients have had relief of pain (see Table for results of a published study by Dr. Brisman regarding the impact of GKRS on patients with TN-related pain).

Michael G. Kaplitt, MD, PhD, performs surgeries for movement disorders as well as for complex pain, and one of his main interests is the use of neurostimulation to block neuropathic pain. “The concept of spinal cord stimulation is based on a decades-old idea,” he said. “Back in the 1960s, it was called the gate theory of pain, which means a sensation or stimulus to a neuron can gate, or block, another stimulus.”

In the spinal cord stimulation procedure, he said, “a small electrode is implanted on the surface of the spinal cord at the point where all the sensory fibers run up to the brain. The electrode creates what is essentially a buzzing or a tingling sensation in the area of the pain” and interrupts pain signals to the brain. Not every patient with neuropathic pain is a candidate for spinal cord stimulation, but two thirds of those who are candidates benefit from the procedure.

“It is particularly effective for patients with neuropathic pain,” Dr. Kaplitt said. “Patients can turn the electrostimulation on and off and also control its intensity. We probably do about 35 or 40 of these a year. It’s extraordinarily underutilized because a lot of patients don’t know about it and they’re not referred to us. They just go on and on in pain.”

Chris Winfree, MD, will be involved in 2 research specialties. In the first, he will be collaborating with John Martin, MD, in seeking to improve spinal cord function by reinnervating injured cords with peripheral nerves. The work will involve basic scientific research in animal models as well as possible clinical trials.

“My focus will be to look at patients who have chronic neurological pain that is amenable to surgery,” said Dr. Winfree.

“We don’t know what the potential is.” He added that while it was not likely that the patients in the trials would walk again as a result of the work, their muscle tone might improve as well as their bladder and bowel function, and there might be a reduction in spasticity.

Dr. Winfree’s other research interest is facial pain. “One treatment in particular, motor cortex stimulation, is something that hasn’t been done here,” he said. “I hope to do a clinical trial looking at its effectiveness in facial pain patients.”

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CME Conferences

The following CME conferences feature faculty from Columbia and Weill Cornell:

Brain Tumors: Advances in Diagnosis & Treatment—A Comprehensive Review

DATE: Friday, October 8, 2004

LOCATION: Grand Hyatt New York in New York City

Full Day, maximum of 8 category 1 credits.

Brain Attack and Cerebrovascular Disease, Update 2004—Consensus and Controversy

DATE: Friday, November 19, 2004

LOCATION: Grand Hyatt New York in New York City.

Full Day, maximum of 8 category 1 credits.

To register for both seminars, or for more information, CALL toll-free 1 (866) 697-7755 or ONLINE at www.nypneuro.org

NewYork-Presbyterian Neuroscience

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The Role of Neurostimulation in Epilepsy

Noting the success of neurostimulation in treating patients with Parkinson's disease, Columbia and Weill Cornell researchers at NewYork-Presbyterian Hospital are leading the way in exploration of stimulation techniques in treating epilepsy.

"We know that 30% to 40% of patients with epilepsy are not completely controlled with medication," noted Carl W. Bazil, MD, PhD. "That's a huge number."

And not all of them are candidates for traditional surgical therapy. According to Douglas R. Labar, MD, PhD, the most commonly used surgical approach to epilepsy has historically involved resection of an epileptic focus in the brain, the theory being "if you remove the epileptogenic source successfully, you'll be 100% seizure-free." But in some patients, the seizure focus cannot be found or isolated or the source of the seizure is in an "eloquent" area, one in which there will be a very debilitating effect if it is removed.

Unlike more traditional procedures, neurostimulation is reversible. Its flexibility also allows surgeons to "modify the settings" to enhance the effectiveness or minimize side effects. Use of neurostimulation therapy for epilepsy is becoming more and more prevalent. Researchers believe antiseizure effects can be achieved through the appropriate targeting of applied electrical activation at selected nervous system sites, without the common sedative side effects of antiepileptic medications. The neurostimulation options being studied include:

Vagus Nerve Stimulation (VNS)

Surgeons are working with VNS, the most common form of neurostimulation. The stimulator is placed on the patient's vagus nerve—located on the left side of the neck—and is operated with a battery placed on the patient's chest. Because it

is inserted into a peripheral nerve, not the brain, surgical risks are theoretically lower. According to Theodore M. Schwartz, MD, VNS decreases the severity and frequency of seizures in about 40% of the patients in whom it is used, but patients rarely become seizure-free. There is some indication, however, that VNS leads to changes in the brain chemistry over time.



In DBS, electrodes are surgically inserted into the patient's anterior thalamus, which receives projections from various other brain structures thought to be involved in generating seizures, including the temporal lobe, and projects to the cingulate cortex.

Transcranial Magnetic Stimulation (TMS)

Andy C. Dean, MD, PhD, is using TMS to measure both chronic and acute changes in patients using VNS. In TMS, a coil is placed on the surface of the patient's scalp. A current is run through the coil, generating a magnetic field that, in turn, noninvasively generates an electric current in the brain. "We've found that patients with epilepsy have a greater excitability in the brain," noted Dr. Dean. "We're looking to see if we can modify that excitability."

Deep Brain Stimulation (DBS)

Both DBS and responsive neurostimulation (RNS), which is discussed below, involve implanting an electrical device in the brain and then fine-tuning both the device's output and the patient's medications in subsequent visits. Weill Cornell

and Columbia researchers are currently studying DBS for epilepsy as part of the SANTE (Stimulation of the Anterior Nucleus Thalamus in Epilepsy) trials. DBS has already been approved for treating Parkinson's disease and other movement disorders.

Because DBS offers continuous stimulation, Guy M. McKhann II, MD, suspects that it will be useful in a subgroup of epilepsy patients if it is more effective than VNS. Dr. Labar theorizes that if DBS and RNS do not at least match the seizure reduction rate of VNS, they may not be worth using, since they are both more invasive. In DBS, electrodes are surgically inserted into the patient's anterior thalamus, which receives projections from various other brain structures thought to be involved in generating seizures, including the temporal lobe, and projects to the cingulate cortex.

"The anterior thalamus is believed to be in the middle of a circuit by which a seizure can spread," noted Michael G. Kaplitt, MD, PhD. Interrupting that circuit, goes the theory, destroys the seizure's path, stopping it from occurring. "All of our experience over the past few years indicates that stimulators are better tolerated than lesions and have longer-lasting affects."

DBS for epilepsy requires modification of the surgical approach used in movement disorder surgery. It is a stereotactic operation in which a coordinate system enables the surgeon to target a specific location in the brain with millimeter-by-millimeter accuracy. Instead of tissue ablation to create lesions that reduce motor symptoms, the surgeon inserts electrodes into the brain through burr holes in the skull. Neurologists with expertise in brain mapping procedures use this technique to ensure proper placement of the stimulators. During DBS, however, the patient remains awake and helps the surgical team guide electrode placement by answering various questions concerning symptoms and sensations. For patients with bilateral symptoms, electrode insertion is performed on both sides of the brain.

Responsive Neurostimulation (RNS)

RNS aims to meet a more complex
see [Neurostimulation](#), page 6

New Surgical Approaches in the Treatment of Movement Disorders

While there have been many significant innovations in the treatment of movement disorders, many of these newer therapeutic options are palliative measures as opposed to cures. Hence, further research is vital. Columbia and Weill Cornell researchers at NewYork-Presbyterian Hospital are leading the way in efforts to find even more effective new approaches to the treatment of movement disorders such as Parkinson's disease (PD), dystonia, and Tourette's syndrome.

"We've established a base for patient participation in a variety of investigations, such as neuroprotective drugs to retard the progression of certain diseases," noted David M. Eidelberg, MD, PhD.

Columbia surgeons at NewYork-Presbyterian Hospital have gained extensive experience investigating the efficacy of gamma knife radiation in conditions such as epilepsy, brain tumors, and trigeminal neuralgia. According to Guy M. McKhann II, MD, the procedure uses an MRI guidance system to target 201 focused beams of radiation to the specific target to create the lesion. This technique can be applied to patients with movement disorders who are at high risk for an invasive surgical procedure.

Weill Cornell researcher Michael G. Kaplitt, MD, PhD, is leading a Phase I clinical trial investigating the use of gene therapy to treat PD. Earlier this year, he began using an adeno-associated virus to "carry" surgical infusion of healthy genes into the brain of PD patients. It is hoped that the genes will stimulate the production of gamma-aminobutyric acid (GABA) into the subthalamic nucleus. Dr. Kaplitt and others believe that restoring GABA to specific areas of the basal ganglia could, in principle, reduce the motor symptoms of PD. This plausible long-term solution might be implemented by introducing modified recombinant viruses equipped with the gene that expresses the GABA-producing enzyme glutamic acid decarboxylase.

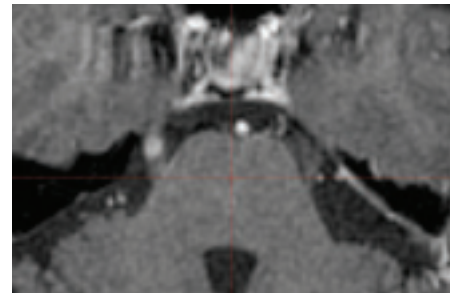
"It's what these cells need," noted Dr. Kaplitt. "The lack of it is what makes them so hyperactive in PD." The premise is similar to that of electrical stimulation by a probe except, according to Dr. Kaplitt, "we're trying to more naturally recreate the neurochemical environment of the circuit that controls movement. That way (unlike with deep brain stimulation [DBS]), we don't have to leave any electrodes or batteries in the patient."

"We've established a base for patient participation in a variety of investigations, such as neuroprotective drugs to retard the progression of certain diseases."

—David M. Eidelberg, MD, PhD

Choosing patients for these (and other new therapies) and monitoring their outcomes is a team approach using surgeons, neurologists, nurse practitioners, and other neurologic experts throughout NewYork-Presbyterian Hospital. "If a surgeon doesn't have good knowledge of the patients and the disease process," said Robert R. Goodman, MD, PhD, "it's impossible to really decide which patient would be viable for one therapy over another."

A team of neurologists led by Blair Ford, MD, works with the 2 movement disorder neurosurgeons at Columbia as patients move toward surgery. Dr. Ford's team is heavily involved in the evaluation of the patients to ensure that they are good candidates for surgery, and to isolate the procedure that would be most effective in their specific case. "The neurologist screens the patient to make sure



An MRI of a gamma knife patient, several months after treatment.

they're a good surgical candidate," noted Dr. Ford. "After all, a positive outcome depends on choosing patients who'll truly benefit from the procedure."

Dr. Eidelberg's major research efforts now involve PET scans for assessing movement disorders. "Imaging was a very important component in the development of surgeries in the mid- to late 1990s," he said. "These techniques allow us to assess the natural history of these diseases and to analyze the therapeutic outcomes in various disorders."

Currently, he is working closely with Dr. Kaplitt's team to develop new methods for assessing their outcomes. Imaging also allows neurosurgeons and neurologists to evaluate both chemical changes and differences in brain circuitry, including differences between the PD patient's brain and that of someone not affected.

Claire Henchcliffe, MD, DPhil, focuses primarily on pre- and post-op therapies for PD patients. She points out that with DBS, patients must always continue to come back for follow-up, even after the initial fairly frequent follow-ups are over. "They need long-term follow-up," she explained. "As long as the disease progresses, we need to make continuous adjustments to their stimulators."

Could gene therapy (or any of the other new approaches) eliminate the need for such fine-tuning, perhaps even stop the progress of the disease? That is the question these experts seek to answer.

"No one has ever put a gene directly into an adult human being's own brain cell for anything, let alone PD," noted Dr. Kaplitt. "If it proves safe and effective, it has implications not only for PD, but holds out hope for a variety of disorders. You could put genes in to change the way neurons function or to

see [Movement Disorders](#), page 6

Movement Disorders

continued from page 5

protect cells from dying; all these things become possible.”

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Neurostimulation

continued from page 4

goal. “It’s the first device that is actually trying to respond to something happening in the brain,” said Robert R. Goodman, MD, PhD. RNS is only delivered on an as-needed basis, compared with the continuous stimulation of DBS or VNS. The patient’s brain wave (electroencephalogram [EEG]) characteristics are programmed into the device, and when the device sees that seizure pattern, it delivers the stimulation to stop the seizure.

According to Dr. Schwartz, implanting the RNS is tricky because the epilepsy must be confined to a limited focal area. RNS candidates are “patients with partial onset seizures with 1 or 2 foci, but for some reason they aren’t candidates for having that focus surgically removed.” RNS benefits patients who have refractory seizures in a portion of the brain that is still functioning between seizures.

The goal of the research efforts involving all of these neurostimulation alternatives is not to simply replace resection with neurostimulation but to determine the different situations for which these options are ideally suited.

“A lot of patients who could be

referred for curative treatment aren’t,” said Dr. Schwartz. “Many times the doctors just don’t know their patient would be a candidate for a curative surgical procedure. Any patient who continues to have seizures should be considered.”

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Target

continued from page 1

brain's other important structures. "The subthalamic nucleus is about 6 mm," said Dr. McKhann.

Computerized brain mapping affords surgeons an accurate "picture" of the target—and, more importantly, its location. Prior to surgery, patients undergo an MRI, which surgeons such as Dr. Kaplitt use to map out the initial operation plan on their desk. Dr. Kaplitt can store those MRI results on a disk, which he can bring with him to the OR. While in the OR, patients undergo a CT scan. By performing the 2 imaging procedures separately, surgeons can optimize targeting.

"To precisely fine-tune the target in the operating room, patients must be awake and off their medications. The longer that the surgery takes, the more chance there is for patients to become uncomfortable or have complications," said Dr. Kaplitt. "The MRI gives me a nice, detailed view, but it's subject to distortion and takes a long time. CT scans don't give you the detail, but they're not prone to distortion and can be performed in less than 5 minutes on the day of surgery." By overlapping the 2 images using



A Parkinson's patient. Treating PD with a surgical procedure such as DBS requires precision.

the most advanced image analysis tools, surgeons are armed with the information that they need to more quickly and accurately hit their target.

To ensure optimum outcomes from DBS, NewYork-Presbyterian Hospital employs a team approach that includes neurologists, neurosurgeons, and nurse practitioners. Prior to surgery, experienced neurologists such as Blair Ford, MD, determine if the patient's problem is actually true PD; they also ensure that it is a form of the disorder that might benefit from surgery. The neurologists and their teams are responsible for the very complicated and time-consuming fine-tuning of both the neurostimulation

device and changes in medication that patients have to undergo following surgery. Noted Dr. Goodman, "The more we see of this surgery, the more some of us are starting to think patients should have it sooner rather than later."

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Epilepsy

continued from page 1

the neurons become toxic. Astrocytes help perform that function. "From very limited human data and from rodent data, we know that if we perturb astrocyte function, we can cause a seizure or cell death," noted Dr. McKhann.

As the information processing cells of the central nervous system, neurons have been the focus of most epilepsy research related to brain function. But their vulnerability to high levels of chemicals regulated by astrocytes raises the issue of whether the latter might lay at the root of epileptogenesis.

"How much are astrocytes contributing to development and maintenance of epilepsy?" asked Dr. McKhann. His specific hypothesis holds that after a first seizure due to some insult to brain tissue—traumatic, lesion-related, chemi-

"How much are astrocytes potentially contributing to development and maintenance of epilepsy?"

— Guy M. McKhann II, MD

cal, or genetic—a person only becomes epileptic with the appearance of subsequent spontaneous seizures. The initial event is known to give rise to "reactive gliosis," a proliferation of astrocytes around the site of the seizure. Dr. McKhann said that he suspects these new cells do not mature normally and are unable to regulate levels of potassium and glutamate.

He and his colleagues currently

experiment with both rodent models and human tissue removed from epileptic patients. If astrocytes do prove to actively contribute to the development of epilepsy, they will also represent a strategic target for therapeutic intervention. "If we can block the alterations in astrocytes from developing, or restore astrocyte function, then we can potentially develop a novel anti-epileptogenic or anti-seizure strategy," he explained.

Mapping seizure events using optical imaging represents another approach that may lead to a more refined grasp of epilepsy, improving outcomes in neurosurgery while at the same time fulfilling a broader aim of charting the human cortex. Theodore M. Schwartz, MD, heads this effort, and his research has now moved beyond ferret brains and rat models to neurosurgical interventions in humans.

see Epilepsy, page 8

Although techniques such as MRI and PET scans have advanced brain visualization in multiple new directions, they represent a snapshot approach. Importantly, they lack the temporal dimension that would enable epileptiform events to be visualized as they happen. Taking advantage of optical imaging techniques used in sensory physiology, Dr. Schwartz and his colleagues have created in vivo maps of epileptic events in cortical brain tissue. These maps provide critical information concerning metabolic processes, blood flow, and fluid shifts.

Dr. Schwartz' initial research, published in a landmark study several years ago, involved ferrets (*Nature Med* 2001; 7:1063-1067) and took advantage of the fact that specially patterned visual stimuli can provoke seizure-like events in the mammalian brain. After mapping

the functional architecture of the ferret's visual cortex, epileptic foci were induced using intrinsic signaling. These predictable foci could be controlled and events on the cortical surface were optically recorded. Resulting computer-driven images provided a set of pictures that show the effects of epileptiform events in brain tissue over time.

In subsequent research, Dr. Schwartz and his colleagues developed rat models of epilepsy for optical imaging in the laboratory and have begun working with human subjects. In surgical interventions, optical imaging replaces the electrode arrays ordinarily used to track epileptic foci.

"The optical signal will give you information beyond what we can get from electrode arrays," said Dr. Schwartz. "It will provide interesting and different information that will help us understand epilepsy—how it develops, where it comes from, and where it spreads."

A further advantage to optical imaging

may be that, like electrode array techniques, it can also be employed to offer unprecedented resolution of neuroactivity in the centers of language, vision, and other sensations, according to Dr. Schwartz. This helps the researchers develop new knowledge of the brain and may make neurosurgery safer and more effective. Noted Dr. Schwartz, "We have a special opportunity in neurosurgery, with the exposed brain, to explore basic human physiology."

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