

# ON THE BRAIN

THE HARVARD MAHONEY NEUROSCIENCE INSTITUTE LETTER

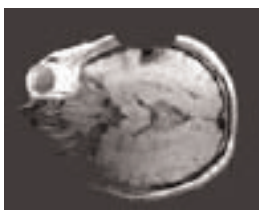
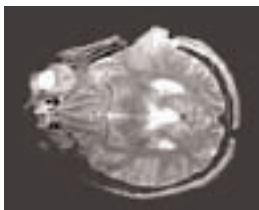
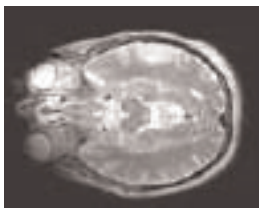


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## Intraoperative MRI May Improve Outcomes for Patients with Low-grade Gliomas

**W**HILE MOST clinicians would agree that surgery is the best approach to treating low-grade gliomas, no clinical trials have yet proven this to be true. A recent study by neurosurgeons at Brigham and Women's Hospital, however, suggests that aggressive surgical resection under intraoperative magnetic resonance imaging may improve survival rates of patients with this type of brain tumor.

"This type of surgery lowers the risk of recurrence and death," says Elizabeth B. Claus, M.D., Ph.D., a neurosurgeon at BWH and an instructor in surgery at Harvard Medical School, who led the study. "Our study showed that aggressive, total resection of the tumor is best for patient outcomes."



**Rooting out cancer.** Real-time imaging during brain surgery shows changes that occur during the operation. This sequence, taken by intraoperative MRI, shows (from top to bottom) a low-grade glioma before surgery, the compressed tumor bulging out after the craniotomy, and the resection before the bone is replaced and the incision closed. (Images courtesy of Peter Black)

Claus and her colleagues found that of the 156 patients they followed for three years after surgery, patients whose low-grade gliomas were only partially removed were 1.4 times more likely to suffer recurrence and nearly five times as likely to die than those whose tumors were completely resected.

Low-grade gliomas account for nearly 25 percent of all primary brain tumors. They are typically well-differentiated, slower growing and biologically less aggressive than other types of brain tumors; however, over time most low-grade gliomas grow into more malignant tumors to which a majority of patients succumb despite treatment.

On an MRI scan, low-grade gliomas often have no discernible margin. During surgery, says Claus, "it is extremely difficult to know what is tumor and what is normal brain tissue." Using Magnetic Resonance Therapy, an image-guided surgical method developed at the Brigham in conjunction with General Electric, neurosurgeons are better able to remove what appears to be tumor and spare healthy brain tissue.

The intraoperative procedure involves using a standard operating table inside an MRI machine. The patient lies on the bed with his head in a fixed frame. Continuous image updates and navigational support help surgeons determine how much of the tumor has been removed and how much remains in the brain, as well as confers hemostasis and other vital information, on a real-time basis.

MRI is typically used outside of the operating room prior to surgery for preliminary diagnoses and to locate tumors for surgical planning, as well as postoperatively to determine how tumors respond

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## Gene Yields Clues to Brain's Functional Asymmetry

UNLIKE THE brain in most animals, human brain function has a left/right specialization. That is, the two hemispheres of the human cerebral cortex are specialized for motor tasks, including handedness, and distinct cognitive and behavioral functions such as language, math, spatial tasks and abstract reasoning.

Christopher A. Walsh, M.D., Ph.D., the Bullard Professor of Neurology at Harvard Medical School, Tao Sun, Ph.D., an HMS neurology research fellow, and their colleagues at Beth Israel Deaconess Medical Center have isolated a gene called LMO<sub>4</sub> that is expressed differently in the left hemisphere of the cerebral cortex than in the right, which may lend clues as to why one side of the brain is dominant over the other. Their findings were reported in the May 12 online edition of *Science*.

"This right/left asymmetry," says Walsh, "is an essential part of our humanness, and learning how it comes about is important for understanding where our human abilities come from. It's part of the system that makes our brains so different from the brains of other animals."

The findings suggest a molecular regulation of early brain asymmetry and may lead to future studies on how genes cause anatomical and functional asymmetry in the human brain.

Using samples of human fetal brain tissue obtained from a National Institutes of Health brain bank, Walsh and his colleagues tested the hypothesis that left/right cortical asymmetry in humans results from differential gene expression at early embryonic stages, well before the onset of organized cerebral cortical function. They compared the future language area of the left brain with the corresponding region of the right brain and discovered that 27 genes behaved differently in this area of the brain. They focused on one of them called LMO<sub>4</sub>.

"In some areas, the amounts of LMO<sub>4</sub> expression are equal on both sides," Walsh says. "But the level of LMO<sub>4</sub> activity in the brain's future language area – on the left – is much lower than in the right cerebral cortex."

The researchers examined gene expression in both the left and right perisylvian cortex (a deep fissure in each cerebral hemisphere, more pronounced in the left, that separates the frontal and

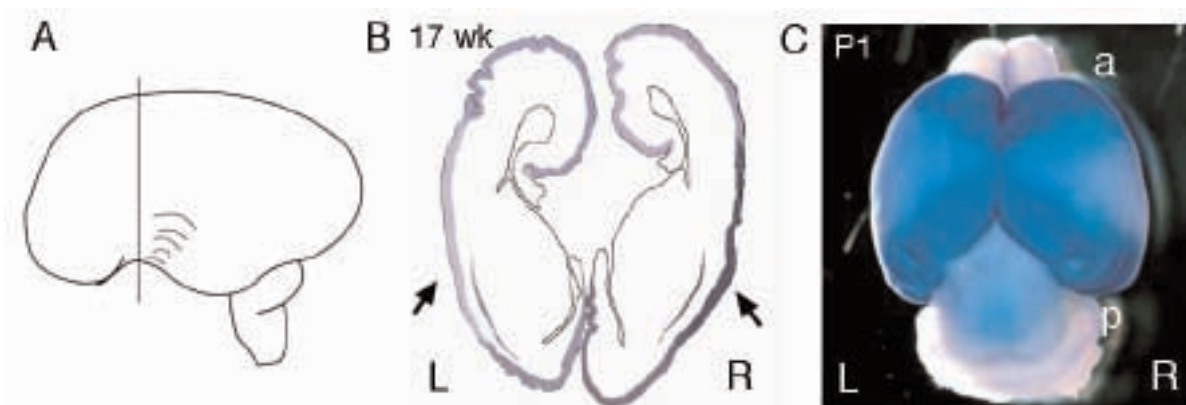
temporal lobes and is implicated in language function) during embryonic development. Sun used a technique called SAGE (serial analysis of gene expression) to compare gene expression patterns in samples of brain matter between 12 and 19 weeks of development. He identified the 27 genes that showed a left-right variation as exhibiting consistent differences at weeks 12 and 14, critical stages of embryonic development, and focused on LMO<sub>4</sub>. Sun then mapped LMO<sub>4</sub> expression outside of the perisylvian cortex and found that it was expressed equally on both the right and the left sides of the brain. Only in the perisylvian cortices did LMO<sub>4</sub> show a left-right difference.

To bolster their findings, the researchers also studied LMO<sub>4</sub> expression in the brains of mice and found that they also express the gene, but more randomly than humans. Some mice expressed higher LMO<sub>4</sub> levels on the right side of the brain, while others did so on the left.

"LMO<sub>4</sub> expression patterns have an interesting parallel with handedness in humans and paw preference in mice," says Sun. "More than 90 percent of humans are more skillful with their right hands [which are controlled by the left hemisphere of the brain] than the left. However, while there is a paw preference in individual mice, it becomes random at a population level."

In the mid-1800s, French neurosurgeon Pierre Paul Broca developed the concept of left hemisphere dominance for speech and language after observing patients with brain damage. His research was among the first discoveries of a separation of function between the left and right hemispheres of the brain. The region of the brain that bears his name – Broca's area – is located in the frontal lobe of an individual's dominant hemisphere and is primarily responsible for speech production and language articulation. Damage to this region often causes speech impairment.

Humans need both sides of their brains for optimal performance. Damage to the left hemisphere generally leads to right-sided paralysis, loss of speech, an inability to read or understand words, and reduced logical information processing. Right hemisphere damage causes left-sided paralysis, an inability to understand subtlety and the emotional meaning of language, and a decreased ability to



**LMO<sub>4</sub> expression in embryonic 17 week (17 wk) human and postnatal day 1 (P1) mouse cortices. Human LMO<sub>4</sub> expression level in the cortical plate is higher in the right perisylvian region than the left (arrows). LMO<sub>4</sub> has high expression in anterior (a) and posterior (p) and non-expression in between in the P1 mouse cortex. (Image courtesy of Christopher A. Walsh, M.D., Ph.D., and Tao Sun, Ph.D.)**

decipher language patterns. People with right hemisphere brain damage experience language problems that are more subtle than those with damage on the left, in part because, in most people, the language centers are located in the left hemisphere. Walsh's research builds on studies showing that certain genes act differently in various areas of the brain. For example, specific patterns of gene expression are responsible for laying out the body's basic architecture, ensuring that vital organs grow where they are supposed to. This knowledge led Walsh and other researchers to pursue the question of genetic influence on functional asymmetry in the human brain.

In his laboratory, Walsh also studies genes that regulate the development and function of the human cerebral cortex. Mutations in these genes alter the normal asymmetry of the brain in a number of diseases, including dyslexia, schizophrenia and autism.

The researchers' next step is to identify asymmetrically expressed genes at earlier stages of brain development and compare asymmetrical gene expression in humans and other primate brains.

"It will be extremely interesting to study how distinct human brain functions are evolved and specified," says Sun.

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to treatment or progress. In 1990, General Electric Medical Systems approached Ferenc Jolesz, M.D., the B. Leonard Holman Professor of Radiology at BWH, and Peter Black, Ph.D., M.D., C.M., the Franc D. Ingraham Professor of Neurosurgery at Children's Hospital, about developing an MRI device that could be used for real-time intraoperative guidance. The Magnetic Resonance Therapy machine was first introduced for clinical practice at the Brigham in 1993, and the first craniotomy for brain tumor resection using the machine was conducted at the hospital in 1996. Since then, neurosurgeons at the Brigham have done more than 750 cran-

iotomies using the unit, making it one of the leading centers in the country for such therapy.

In their March 15 *Cancer* paper, the researchers wrote: "A benefit of this therapy is that tumor resections that are judged complete by either surgical field of view or preoperative imaging may be confirmed with reimaging while the patient is still in the operating room."

Claus says the goal of the surgery is the removal of the entire tumor "unless it's dangerous to the brain," especially its speech and motor areas. Tumors in these areas, she says, are not totally removed to prevent possible functional deficits as a result of the surgery. In cases where tumors are near these centers of the brain, the surgical team

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## Restoring Breathing After Spinal Cord Injury

WHILE MANY people equate limb paralysis with spinal cord injury (SCI), breathing abnormalities are actually the leading cause of morbidity and mortality in patients suffering from these devastating injuries. Respiratory impairments resulting from injuries to the cervical spinal cord, where most human spinal injuries occur, often render patients ventilator dependent, drastically compromising their quality of life.

Using a widely available anti-anxiety drug called buspirone, researchers at Harvard Medical School have been able to temporarily restore breathing in rats with injuries at the mid-cervical (C-5) level of the spinal cord. If the same results can be reproduced in humans, buspirone therapy may reduce the need for mechanical ventilation following SCI.

“We found that, even with dramatic trauma [to the spinal cord], breathing function was restored to pre-injury levels,” says HMS assistant professor Yang Teng, M.D., Ph.D., director of spinal cord injury research at the Veterans Administration Boston Healthcare system. The work of Teng and his colleagues, including Howard Choi, M.D., a postdoctoral fellow in physical medicine and rehabilitation, was published in the May 4 issue of the *Journal of Neuroscience*.

Victims of spinal cord injuries often suffer a form of respiratory failure caused when breathing is not strong enough to deliver sufficient oxygen to the body or rid it of toxic carbon dioxide. This results when the cervical cord fails to transform breathing drives originated in the brainstem center into respiratory muscle movement. Teng and his team studied injuries to the cervical region of the spine (the upper region of the spinal cord in the neck area) in rats, whose respiratory system is similar to that of humans. Damage to this area of the spinal cord produces the most serious breathing abnormalities. In most cases of SCI, the motoneurons in the phrenic nerve are damaged. This nerve carries impulses to and from the diaphragm, the primary muscle involved in respiration.

“If these motoneurons cannot operate,” says Teng, “the breathing system is jeopardized. Breathing becomes very shallow and rapid, leading to a lack of oxygen in the body.”

Two years ago, Teng and his colleagues discovered that they could temporarily restore breathing in rats with injuries to the thoracic spine, a level lower than the cervical spine, by using the serotonin receptor agonists 8-OH DPAT and buspirone. Teng’s recently published study found that buspirone could restore breathing in animals with even more



Yang D. Teng, Ph.D., M.D.

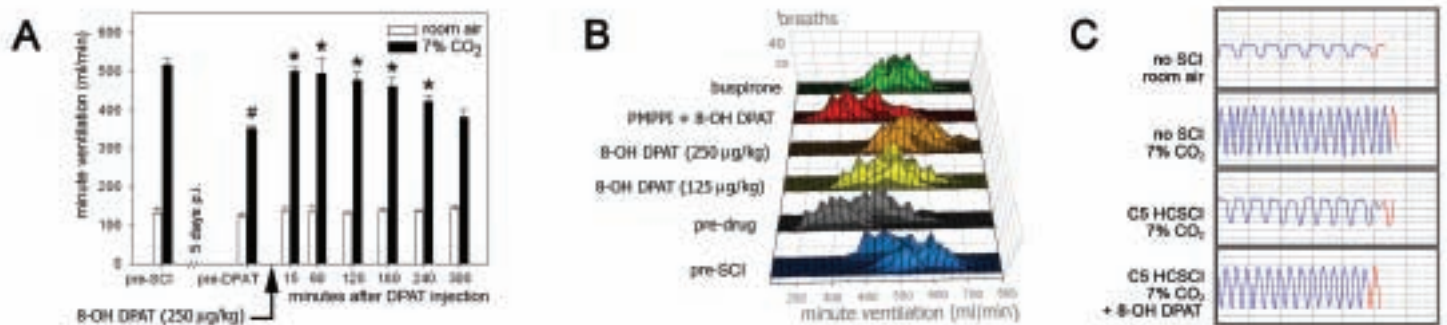


Figure 1. Beneficial effects of 5-HT<sub>1A</sub> activating drugs (8-OH DPAT & buspirone) on respiration after SCI. (A) 8-OH DPAT significantly stimulated respiration in chronic SCI rats challenged with 7% CO<sub>2</sub>. \* – significantly different than pre-treatment levels. # – significantly different than pre-injury baseline. (B) Minute ventilation response to 7% CO<sub>2</sub> stimulus in rats (n = 12 per group) at pre-SCI, two weeks post severe cervical SCI (p.i.) without drug treatment, two weeks under 8-OH DPAT (125 µg/kg or 250 µg/kg), p-MPPI (an 8-OH DPAT blocker) + 8-OH DPAT or buspirone treatment; each colored block of lines represents the ventilation responses for rats during 7% CO<sub>2</sub> challenge. Left shift of the curve blocks means better respiration, and right shift worse ventilation. (C) Plethysmograph recordings of an uninjured rat breathing room air or under 7% CO<sub>2</sub> stimulation (top two panels) and a rat two weeks after severe cervical SCI (breathing 7% CO<sub>2</sub> before and after administration of 8-OH DPAT). Higher amplitude and frequency represent better ventilation (bottom two panels). (Image courtesy of Yang Teng)

severe spinal cord injuries (injuries to the higher regions of the spinal cord are generally more severe).

Buspirone, called a 5HT<sub>1A</sub> agonist, has been shown to stimulate respiration in patients with sleep apnea, which is characterized by repeated, involuntary breathing pauses during sleep that are often associated with choking sensations that awaken the patient. Other studies have shown that serotonin 1A agonists can improve respiratory function after a morphine or Phenobarbital overdose.

In their study, Teng, Choi and their colleagues surgically injured the cervical spinal cords of rats to simulate the human breathing deficits that occur following SCI. They then injected buspirone into the animals' abdomens and measured their post-injury breathing levels against their pre-injury breathing levels. They found that introduction of the 5HT<sub>1A</sub> agonist effectively restored respiratory function to pre-injury levels up to four hours after a single administration of the drug.

"Activation of 5HT<sub>1A</sub> agonists can counteract respiratory abnormalities in cervical SCI," says Teng. "They represent a novel therapeutic strategy, potentially applicable to a much wider population of patients at all stages of post-SCI. Specifically, we believe that buspirone, a well-tolerated pharmaceutical agent, merits consideration for human trials in post-SCI respiratory dysfunction."

Buspirone has no known major clinical drawbacks and has been typically used for treating patients with anxiety disorders, says Teng, unlike another class of anti-anxiety drugs – such as benzodiazepines – that have been shown to suppress breathing.

Teng cautions that buspirone therapy may not be effective in restoring breathing in all SCI patients, saying those who are "on the threshold of needing ventilator support" are the most likely candidates.

"This compound may help patients in that border area who further deteriorate and have to be linked to a ventilator," he says. "Over time, buspirone may slow down or completely prevent further deterioration of breathing problems that require a ventilator."

The goal of Teng's future research with human patients is to develop effective therapeutics that will give patients a better prognosis in terms of breathing restoration, with the hope of keeping



**From left to right: Prof. Ian Robertson, Dean of Research, Trinity College Dublin; Sir Anthony O'Reilly, Pro Chancellor, Trinity College Dublin; Hildegard Mahoney, Chairman, The Harvard Mahoney Neuroscience Institute; Dr. John Hegarty, Provost, Trinity College Dublin; and Mr. Bill Walsh, Member of the Scientific and Advisory Board, Trinity College Institute of Neuroscience, speakers at the celebration of the new Dr. Thomas Mitchell Chair in Neuroscience at Trinity College Dublin, on June 21, 2005.**

them ventilator free. Important to scientists, he adds, is their finding that adult cord gray matter (a tissue sector where neurons are predominantly located) possesses a dynamic plasticity (i.e., neural network reorganization) potential that can be targeted to develop therapeutics. One way to investigate this is by conducting a more detailed study of serotonin receptor changes in patients with spinal cord lesions at different levels of severity.

Armed with a better understanding of the molecular and cellular mechanisms of the respiratory system, Teng is now studying the use of stem cells to reconstitute the breathing center in the brainstem. He has preliminary results but says more research needs to be conducted.

"For patients with neurons already lost to injury," he says, "the future may be stem cell therapies to reconstitute the breathing circuitry. For those whose neurons are spared but whose function is jeopardized, we want to use another serotonin agonist to further augment respiratory function. At some point, we may be able to use these approaches in conjunction with one another to treat a wider array of SCI patients."

## Magnetic Stimulation of Brain May Aid Stroke Recovery

**F**OR THE pianist, the concept of interhemispheric inhibition can be a nightmare. Interhemispheric inhibition is the mechanism by which activity is inhibited in one focal area of the brain by the contralateral brain area. This mechanism, transmitted by callosal fibers, prevents mirror movements. When the left motor cortex area is activated to generate movements in the right hand, inhibitory input is sent to the right motor cortex to inhibit left hand movement. That way, the brain sends signals to only one hand when only one hand is required to perform a task – thus, the nightmare for the pianist, who relies on using both hands simultaneously to play.

“This is a normal mechanism to enhance movement,” says Felipe Fregni, M.D., of Beth Israel Deaconess Medical Center. “Following a stroke, however, this mechanism becomes maladaptive. As one side of the brain is damaged [by the stroke], the healthy side becomes disinhibited, possibly due to the reduction in transcallosal inhibition from the stroke-damaged hemisphere.”



This image displays a picture of TMS being applied by an experimenter. Both the coil and the subject have affixed to them a tracking device so that the head/coil position can be monitored in real time. Therefore, the motor cortex can be accurately targeted and stimulated in patients with stroke to improve motor function. (Image courtesy of Dr. Felipe Fregni)

Using a technique called repetitive transcranial magnetic stimulation (rTMS), Fregni and his colleagues at the Harvard Center for Non-Invasive Brain Stimulation at BIDMC recently studied the use of magnetic pulses to modulate brain activity and improve motor function in stroke patients. According to a paper in the May 24 issue of *Neurology*, patients improved by as much as 50 percent on reaction-time tests when stimulation was applied to the healthy side of the brain. This reduced brain activity in the unaffected hemisphere and promoted increased activity in the damaged hemisphere.

Repetitive transcranial magnetic stimulation is a procedure in which electrical activity in the brain is influenced by a pulsed magnetic field. During the procedure, an insulated wire coil is placed on the scalp. An electrical current is then passed through the wire coil, generating a magnetic field that can be focused onto specific areas of the cortex. The stimulus can be modulated to increase or decrease brain activity depending on the parameters that are used (e.g., frequency of stimulation, number of sessions).

Introduced in the mid-1980s as a neurodiagnostic tool, rTMS has been used to treat depression, which is correlated with decreased levels of activity in the prefrontal cortex, particularly on the left side. The specific area stimulated to treat depression is the dorsolateral prefrontal cortex, which is connected to the limbic system that plays a role in mood modulation and major depression. This region of the brain is located close to the scalp a few inches above the temple, making it easily accessible to the magnetic field.

rTMS has also been used to study nerve fibers, create a functional map of the brain, and investigate the sensory and cognitive aspects of cortical processing. Studies show that it may have therapeutic potential for patients with Parkinson's disease, schizophrenia and bipolar disorder.

Fregni and his colleagues studied 10 patients who had suffered a stroke within the last 12 months, comparing them to six healthy individuals. Using different parameters, including sham stimulation (which does not induce a magnetic field), the stroke patients received three sessions of rTMS to the unaffected hemisphere of the brain. All of the

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**This illustration depicts the sites that were stimulated by TMS in patients with chronic stroke. Note that the healthy, ipsilateral (relative to the hand motor deficit) primary motor and premotor cortex were stimulated. (Image courtesy of Dr. Felipe Fregni)**

study participants were given the same battery of tests, including simple reaction time, finger tapping and a pegboard test, to evaluate the motor function of the hand that was affected by the stroke. The motor function of stroke patients receiving real rTMS improved, while the healthy controls and those receiving sham stimulation showed no motor improvement.

Other studies have shown that invasive forms of cortical stimulation, including electrical treatments and psychosurgery, are useful in promoting stroke recovery. “These results are exciting,” says Fregni, “because magnetic stimulation is a non-invasive, painless therapy that can be done while patients are awake.”

Fregni says that for rTMS to be used in clinical practice at least 10 to 20 consecutive sessions would be required to have any therapeutic benefit. He says that studies of rTMS to treat depression have shown that five consecutive days of treatment showed small improvements and that 20 consecutive days of treatment have shown much longer-lasting effects, often up to two to three months. Because the benefit from this new treatment depends on the presence of intact areas of the motor cortex in the damaged hemisphere,

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uses imaging and real-time changes in the behavior of awake patients to direct them away from certain regions of the brain.

Patients typically do well following the intraoperative MRI procedure, with many returning home only days after surgery. Claus says one reason total resection is important is because of the age of many patients affected by low-grade gliomas (the mean age in the study was 42). “These patients,” she adds, “are fairly young, in the prime of their lives, and otherwise generally healthy.”

While the current primary treatment options for low-grade glioma include both surgical resection and/or radiotherapy, it remains unclear what the optimal treatment is. Certain types of low-grade gliomas, such as oligodendrogliomas, appear to respond well to chemotherapy. One study showed a positive relation between glioma resection and survival, but most of the patients had high-grade or mixed gliomas. To date, four clinical trials have enrolled adult patients with low-grade gliomas; however, none were randomized according to total tumor resection.

“To our knowledge,” says Claus, “no population-based effort exists that has focused exclusively on patients with low-grade gliomas. The current data suggest a benefit associated with surgery, but this finding should be considered preliminary and will require formal confirmation either within the context of a randomized clinical trial or a large, population-based project.”

Claus says the next step is to seek funding for a clinical trial or to use statistical methods that mimic randomizing patients in an attempt to determine if total surgical resection of low-grade gliomas is indeed the optimal treatment for such tumors.

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patients with small brain lesions or mild to moderate motor deficits are the optimum candidates for this procedure.

In his lab, Fregni and his colleagues are now studying the effects of rTMS in a larger population of patients, including those with more severe deficits, as well the effects of consecutive sessions on stroke patients. They are also examining the use of rTMS to stimulate the right hemisphere to improve language deficits in stroke patients with left-sided lesions.

"This is a very new treatment," says Fregni. "Many neurologists haven't even heard of rTMS as a treatment for stroke. It will take a while before it can be used clinically."

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