

Protocol Targets Frontal Cortex to Quell Depression

BY ERIK L. GOLDMAN
Contributing Writer

NEW YORK — Researchers at Columbia University and the New York State Psychiatric Institute are using the tools of neuroimaging to modernize electroconvulsive therapy for severe depression and other psychiatric disorders.

By applying principles similar to those used in rational drug design, they are endeavoring to design highly targeted ECT protocols that focus electrical current to those brain regions involved in generating the debilitating symptoms of depression, while minimizing the distribution of charge through uninvolved areas of the brain.

"We're trying to develop new forms of focal brain stimulation. We're learning a lot about the anatomy and the circuitry of mood regulation and dysregulation in the brain," Dr. Robert Berman said at a symposium sponsored by NARSAD, the Mental Health Research Association.

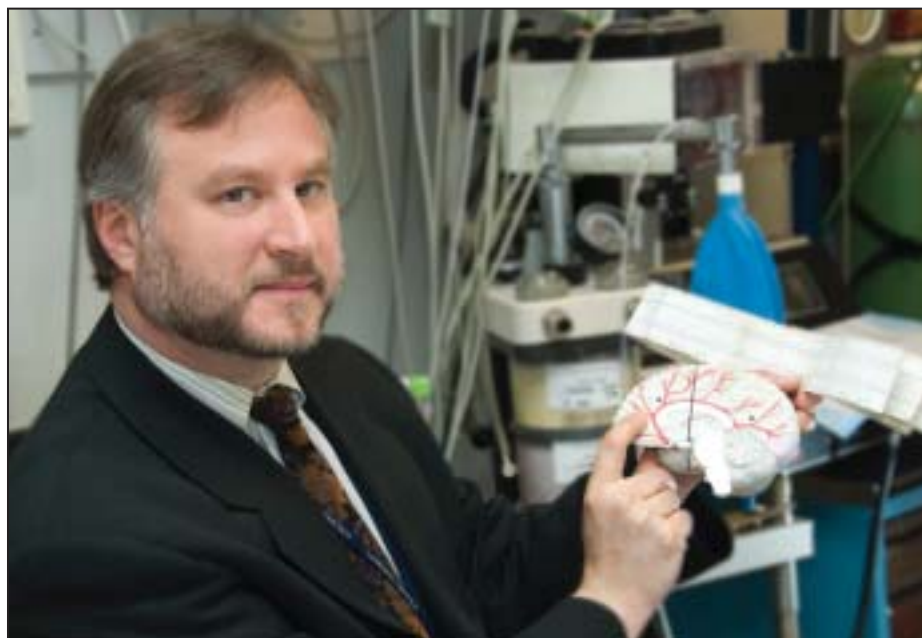
Dr. Berman, a recipient of NARSAD's 2006 young investigator award, has been working with Harold Sackeim, Ph.D., on a new protocol called focal electrically applied seizure therapy (FEAST), a still experimental approach that directs the electrical charges to discrete areas of the frontal lobes.

For many patients with severe, crippling depression, ECT is still a reasonable treatment option. In many studies, only one-third of patients with the most severe forms of depression obtain meaningful relief with antidepressant medications, and among those who do, side effects can be a long-term problem. For some, ECT is the only treatment that can provide symptom control.

Right unilateral ECT has largely replaced bilateral ECT, with a corresponding decrease in cognitive side effects, but Dr. Berman and Dr. Sackeim believe that ECT can be made even more focal.

Electricity applied to the cranium generally spreads through all areas of the brain, including regions thought to contribute to the cognitive side effects of ECT, thus compromising the risk-benefit ratio. Dr. Berman's work is focused on minimizing this problem.

He believes that the evolution of drug design can provide a meaningful framework for the future development of ECT and other forms of brain stimulation, such



Dr. Robert Berman says that the FEAST system directs electrical charges to brain regions that generate debilitating depression and other psychiatric disorders.

as transcranial magnetic stimulation (TMS). "Medications go all over the brain and all over the body. Many of the side effects of medications are systemic," Dr. Berman said. Targeted modulation of specific neurocircuitry may be a much more focused and favorable way to treat."

"Rational drug design" is based on the idea that if the particular anatomical and neurochemical pathways that are involved in producing a set of symptoms are known, then molecular structures to fit those pathways can be designed. "Our idea is to develop 'rational brain-stimulation design,'" he said.

The first step in this direction is the identification of specific brain regions involved in mood regulation. Dr. Berman and his colleagues have reviewed neuroimaging studies comparing responders versus non-responders to a host of antidepressant therapies, including medication, conventional ECT, and transcranial magnetic stimulation. "The scans show that some of the parts of the brain that light up in responders are common to all these different therapies, so this is helping us to define the relevant targets," he said.

This identification—coupled with general improvements in ECT technology over the last 20 years—has made rational, targeted delivery of current a reality. Dr. Sackeim and his colleagues have developed a system that can focus the electrical puls-

es only to specific areas in the frontal cortex, while sparing parts of the brain that may not be involved in the antidepressant response but may give rise to side effects. The FEAST approach works, at least in principle.

They recently tested the system in monkeys, after implanting each animal with three recording electrodes containing 10 leads each. These were placed, under MRI guidance, at 30 specific sites all over the brain, providing 30 recording sites spaces throughout the brain. This allowed the researchers to track exactly where the FEAST current traveled, as well as the local neuronal response—including intracerebral EEG, compared with conventional ECT and magnetic stimulation.

The experiment suggested that FEAST is capable of inducing seizures, including EEG-only seizures, without convulsions originating primarily in the frontal portion of the brain, with decreased spread of the electrical impulse to the temporal lobes. "The FEAST protocol single-pulse electrical voltage is high in front and low in the back, which is exactly what we want to see. The topography of the induced voltage is controllable; FEAST induces seizures safely and reliably, and these seizures are more focal than those induced by conventional ECT," Dr. Berman said. The next step is a pilot clinical trial, to test the efficacy and safety of

this approach in human subjects with severe depression who do not respond to drug therapies.

Commenting on the presentation, Dr. J. John Mann, chief of the department of neuroscience at the New York State Psychiatric Institute, said this approach holds tremendous potential for improving the treatment of severe depression because it can potentially spare patients from the adverse effects—especially memory loss—that infrequently accompany conventional ECT.

"Over the past 10-15 years, we've been able to map in detail the parts of the brain affected by depression, and identify the [anatomical sites] responsible for the specific components of what we call depression," Dr. Mann said. "The parts of the brain adversely affected by ECT and responsible for memory loss are not essentially involved in the depression syndrome, and therefore, they should be spared."

If focally induced seizures that do not result in generalized motor convulsions are shown to be clinically effective, there would be other benefits as well. In routine ECT, muscle blocking agents are used to dampen the motor convulsion, protecting patients from injury. The greatest risk to ECT patients actually comes from the anesthetic agents used than from the ECT treatment itself, and any reduction in anesthetic would make ECT considerably safer. According to Dr. Berman, there's also a possibility that a protocol like FEAST might be used to induce focal neurogenesis, an objective that's been something of a Holy Grail for generations of research neurologists.

"We don't really know how neurons are induced to divide. But we know that ECT stimulates robust neurogenesis in the hippocampus and there is now some evidence for neurogenesis in other parts of the cortex as well," he said.

Dr. Berman acknowledged, however, that routine clinical applications of FEAST—or any of the other new, experimental forms of brain stimulation—are still several years in the offing.

"Before patients will be able to have access to this, it will have to be presented to and approved by the [Food and Drug Administration]. We need to demonstrate that it really is an improvement over standard ECT." ■

Depression Diagnosis Rose 2.4-Fold in 12 Years

SAN DIEGO — Between 1990 and 2001, the number of children and adolescents diagnosed with depression increased 2.4-fold, and the use of serotonin reuptake inhibitors increased from 21% to 40%, Linda M. Robison reported during a poster session at the annual meeting of the American Academy of Child and Adolescent Psychiatry.

In a study led by her associate, David A. Sclar, B.Pharm, of the Washington State University

College of Pharmacy in Pullman, Wash., U.S. National Ambulatory Medical Care Survey data were used to determine the population-adjusted rates of office-based physician visits that resulted in a diagnosis of depression in patients aged 5-18 years between 1990 and 2001.

Over the 12-year time period, the population-adjusted rate of depression increased 2.4-fold, from 12.9 per 1,000 patients to 31.1 per 1,000 patients.

At the same time, the number of patients who were prescribed an antidepressant increased from 44% in 1990-1993 to 59% in 1998-2001. The use of SSRIs increased from 21% in 1990-1993 to 40% in 1998-2001, while the use of tricyclic antidepressants fell from 21% to 3%.

The study was supported by the National Alliance for Research on Schizophrenia and Depression.

—Doug Brunk

DATA WATCH

Suicide Rate Is Rising in 15- to 19-Year-Olds

	2003	2004	Trend
Suicide rate	7.3	8.2	▲
Death rate (all causes)	66.4	66.1	▼

Note: Rate per 100,000 population, based on 2003 and 2004 data from the Centers for Disease Control and Prevention.
Source: Pediatrics 2007;119:345-60