

## Neuron

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### Experimental electrode implant treatment shows promise for helping severely depressed

### Study experiments with surgically implanted electrodes in patients who were not responding to all other available treatments

**Toronto, CANADA** - A team of Toronto researchers says it has obtained promising early results from a landmark surgical study of the use of deep brain stimulation (DBS) in severely depressed patients who were otherwise resistant to standard types of treatment.

Significant clinical response was seen in four of the six study patients with chronic stimulation of the subgenual cingulate region, with sustained improvement through six months to the study endpoint. While DBS in other brain areas has been used to treat disorders such as epilepsy and Parkinson's disease, this is the first report of DBS in the subgenual region for major depression. The technique involves high frequency electrical stimulation to a targeted area of the brain for the purposes of modulating that region's activity. The subgenual cingulate area was specifically targeted based on growing evidence of its critical role in depression.

The study, a collaboration of scientists from The Rotman Research Institute at Baycrest Centre for Geriatric Care, the Division of Neurosurgery at Toronto Western Hospital (University Health Network), and the departments of Psychiatry (UHN and the Centre for Addiction and Mental Health), all affiliated with University of Toronto, is published in the **March 3 issue of Neuron**.

"This is a hypothesis-driven, brain-based strategy for the treatment of the most severely ill depressed patients," says lead investigator **Dr. Helen Mayberg**, now at Emory University School of Medicine in Atlanta.

Dr. Mayberg, a neurologist who is internationally renowned for her studies of depression pathophysiology and treatment, teamed up with Toronto Western Hospital surgeon **Dr. Andres Lozano**, one of the world's authorities on deep brain stimulation. Dr. Sidney Kennedy of UHN and an authority on the diagnosis and treatment of mood disorders, was the lead psychiatric collaborator.

#### The strategy

The subgenual cingulate region (Cg25) -- located in a band that runs deep within the frontal lobes, down the midline -- is an area previously identified as playing a critical role in modulating sadness and negative mood states in both healthy and depressed individuals.

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“Guided by Dr. Mayberg’s previous research findings on the critical role of Cg25 in mood regulation and antidepressant drug response, we hypothesized that if we could re-tune this abnormally functioning circuit by way of a surgical intervention that uses electrical stimulation, we could produce clinical benefit in patients with refractory depression,” says Dr. Lozano.

### **The patients**

Six patients diagnosed with refractory depression, with a median age of 46, were recruited from across Ontario for the study. These were patients who failed to respond to a minimum of four different anti-depressant treatments, including medications, evidence-based psychotherapy or electroconvulsive therapy. While there were no serious adverse effects from the experimental DBS treatment, two patients were removed from the study at the six-month point after failing to show a sustained clinical benefit.

### **The surgery**

The procedure involved Dr. Lozano drilling two holes about the diameter of a 5-cent piece into the skull with the patient awake and under local anesthetic. Guided by magnetic resonance imaging to confirm the precise anatomic location of the grey and white matter of area 25, he inserted two thin wires with electrode contacts down to the white matter tracts adjacent to the Cg25 area. The other ends of the wires were tunneled through to the lower neck area and hooked up to a pulse generator implant that directs an electrical current. The entire system, likened to a “brain pacemaker”, is under the skin. Researchers determined the most efficacious voltage, pulse width and frequency for each patient and tracked their clinical response using positron emission tomography (brain imaging of cerebral blood flow activity) along with a comprehensive battery of neuropsychological tests. This tracking was done at baseline “pre-surgery” and at monthly intervals for 6 months.

Drs. Mayberg and Lozano noted a “striking and sustained remission of depression” in four of six patients who completed the study. In addition, as documented by the PET scan studies, not only was over-activity of Cg25 reversed but there were widespread changes in the frontal cortex, hypothalamus and brainstem, consistent with findings seen with successful response to medication or psychotherapy in less severely ill patients.

All four patients are still receiving chronic stimulation and continue to meet criteria for clinical remission.

### **Implications for future**

Dr. Mayberg cautions that the Cg25 DBS study is only a “proof of principle”. It is the culmination of 15 years of research using brain imaging technology that has worked to characterize functional brain abnormalities in major depression and mechanisms of various antidepressant treatments.

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“We tested the effects of targeted brain stimulation based on our past research findings. We see depression as a complex disturbance of specific circuits in the brain responsible for regulating mood and emotions,” says Dr. Mayberg. “This approach is similar to that taken in Parkinson’s disease, where by careful research of the relevant motor circuits, DBS was developed to modulate these dysfunctional circuits and is now used to treat the most severely ill patients. We hypothesized that if DBS could locally modulate a critical node within this mood circuit, such modulation would result in clinical improvement – and it appears it did.”

“Our study shows that areas of the brain that are on *overdrive* in patients with severe depression can be pinpointed, turned down and brought to a more normal level of activity using electrical stimulation,” adds Dr. Lozano. “This in turn can lead to a lifting of depression in certain patients.”

The study’s findings lay the foundation for a larger study to hopefully replicate, refine and extend these first results. “If the safety and benefits we have observed are maintained across other future studies, we could see this approach applied in the years to come as a clinical therapy for patients who fail current treatments and continue to suffer with severe depression,” says Dr. Lozano.

The study was supported by a distinguished Investigator Award to Dr. Helen Mayberg from the National Alliance for Research in Schizophrenia and Depression.

**Media can obtain a copy of the study from Heidi Hardman, press officer at Neuron, office (617) 397-2879, cell (857) 928-5630, or [hhardman@cell.com](mailto:hhardman@cell.com)**

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