Deep-Brain Stimulation: An Electrode for All Occasions?

25 May, 2010. Deep-brain stimulation (DBS) is not just for shakes and trembles any more. With the advent of improved brain imaging, researchers are linking certain parts of brain anatomy to conditions ranging from addiction to Alzheimer disease. And for every MRI or CT scan showing a hot spot, it seems, there increasingly is a surgeon waiting to stick an electrode in it. "I do not think there is any disease that is 'safe' right now," quipped Jerrold Vitek, a dementia with Lewy bodies (DLB) pioneer who is set to take over the Department of Neurology at the University of Minnesota in Minneapolis-St. Paul this July. "If you have a hammer, everything looks like a nail."

DBS is creeping into the realm of psychiatric disorders such as obsessive-compulsive disorder (OCD), Tourette syndrome, and depression. Small studies show that the treatment is often effective and causes minimal side effects (reviewed in Kuhn et al., 2010). In part, the use of DBS in psychiatric conditions was inspired by unexpected results when doctors attempted stimulation to treat Parkinson's. A couple of people with both PD and OCD, who received DBS for the Parkinson's symptoms, also experienced a reduction in obsessive and compulsive behaviors (Mallet et al., 2002). In another case, a woman who received DBS to relieve Parkinson's experienced profound sadness when certain parts of her brain were stimulated. The effect quickly disappeared when the electrodes were turned off (Bejjani et al., 1999). These side effects led researchers to suspect that thoughts and feelings, as well as movement, could be subject to alteration by DBS. Conditions such as Tourette's (reviewed in Temel and Visser-Vandewalle, 2004) and OCD (Jung et al., 2006) have also responded to deep brain lesions, a precursor to DBS used in the past.

Diminishing Depression

Given the small but real risks inherent in brain surgery, DBS tends to become an option when a disease is serious and other therapies have failed. There are many conditions that, at least in some people, resist the best medicine currently on offer. For example, Helen Mayberg of Emory University in Atlanta, Georgia, works on treatment-resistant depression (TRD). The patients she works with have had major depression for years, and tried medication, psychological therapy, and electroconvulsive therapy, to no avail. Many are unable to work. "They are dangerously and intractably ill," she said.

Mayberg was able to turn the images she saw on brain scans of sad or depressed people into a novel therapy for the condition. This is the first time, Mayberg said, that a targeted treatment came directly from images, with no other basis for potential efficacy. She and others observed that the subgenual cingulate cortex is overactive in people with TRD. Activity in the region also turns up with negative mood in healthy people (Mayberg et al., 1999). "We are interested in turning the activity down," Mayberg said.

Mayberg, then at the University of Toronto in Ontario, initially tried DBS of the subgenual cingulate in six people (Mayberg et al., 2005). Later, she and others expanded the trial to include 14 more patients (Lozano et al., 2008). They saw effects even in the operating room, when surgeons stimulated the target area to make sure electrodes were properly placed. Spontaneously, some subjects reported that the room suddenly looked brighter, or that they experienced a "disappearance of the void" (Mayberg et al., 2005). By six months after the surgery, 60 percent of recipients had

some response, and 35 percent were considered in remission (Lozano et al., 2008). DBS for depression is currently under trial in a study run by St. Jude Medical, Inc., of St. Paul, Minnesota, a maker of DBS devices, Mayberg said.

Mayberg cautioned that DBS marks only the beginning of a person's recovery from TRD. "This does not make you happy," she said. "This turns negative off." The recipient must take the next step to regain a positive outlook. And just as a person who has, say, hip replacement surgery needs rehab, people who have DBS for depression need "psychological rehab," Mayberg said, to help them adjust.

If I Had a Hammer….

Currently, DBS is FDA-approved for essential tremor, Parkinson disease, and dystonia. The FDA also allows some people with OCD to receive the device. Efficacy for this condition is under study but remains unproven. Beyond that, researchers are trying DBS for a whole laundry list of conditions (reviewed in Awan et al., 2009). Clinical trials are underway for Huntington disease, cluster headache, pain, epilepsy, and Tourette syndrome.

Some scientists hope that even conditions that cause their primary pathology outside of the brain may respond to DBS. For example, amyotrophic lateral sclerosis manifests primarily in the spinal cord—but researchers using single-photon emission computed tomography discovered lesions in the cortex of four people with ALS. They attempted DBS with these four in a preliminary study. Two years later, two of the people had only mild progression of the illness, which is normally fatal within three to five years, and their lesions had disappeared. The third recipient's disease continued to progress after the first few months; the fourth, however, committed suicide (Sidoti and Agrillo, 2006).

Most DBS targets are based on what researchers know about how the brain works, but at least one, for Alzheimer disease, was discovered by more roundabout means. In 2008, researchers from Toronto Western Hospital in Ontario reported on a surprising finding (Hamani et al., 2008). They were hoping to help an obese man stem his desire for food. The 50-year-old, 420-pound man had tried dieting, psychological therapy, and medication without success. He feared that even if he received bariatric surgery, he would continue to overeat.

The researchers targeted the hypothalamus, an area known to influence feeding in animals (Takaki et al., 1992). In the past, doctors had targeted this region with lesions to treat obesity (Quaade, 1974).

During the surgery, the doctors turned on the signal to the electrodes to ensure they were hitting the target area. They asked the man, who was awake during the procedure, if he felt any change in hunger. He did not—but he did notice a strange sense of déjà vu. Suddenly, he flashed back 30 years to a scene in a park, surrounded by friends. He recognized his girlfriend from that time. When the doctors turned off the stimulation, the memory vanished; they turned it back on and the memory resurfaced.

"We were caught completely by surprise," said study author Andres Lozano. "We knew immediately that this was something very significant."

The hypothalamus is involved in memory as well as appetite (Soriano-Mas et al., 2005). In tests following the surgery, the researchers also found the obese man was more likely to remember word pairings when the stimulator was on; using electromagnetic tomography, they saw that the stimulation activated the brain's memory circuit. (They used this method because the man was too large for a standard PET or MRI scan.) As to the effect on obesity, the man reported reduced cravings and did lose more than 25 pounds, but gained them back when he started turning off the neurostimulator to snack at night.

Based on this serendipitous, if anecdotal, finding, the researchers launched a small trial with six subjects to see if DBS can improve memory in six people with mild Alzheimer disease. Although DBS cannot repair the degenerated tissue lost in Alzheimer's, Lozano hopes that it can improve input to "innocent bystander" parts of the brain that, while healthy themselves, are missing input from damaged neurons. Lozano expects to publish the results within the next few months. Researchers in the French city of Nice in 2009 listed a similar trial, though it is not recruiting yet.

In a related study, researchers in Germany this year began testing DBS for Alzheimer's. Unlike the Toronto and the Nice groups, who are targeting the fornix region, this group is tickling the nucleus basalis of Meynert, an area known to degenerate in AD (see ARF related news story on Freund et al., 2009).

"These are exciting times," Mayberg said of the rapidly expanding DBS field. "As we learn more about the brain, we are going to be able to help people in ways we had not thought about before."—Amber Dance.