Closed-loop Stimulation:

An Investigational Treatment for Refractory Epilepsy

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Epilepsy is characterized by recurrent seizures and is the third most common neurological disorder in the world, with 0.5 - 1% of the population suffering from the disease. (1) In 20 - 40% of these patients, medications alone are unable to adequately control seizures and are therefore diagnosed with drug-resistant epilepsy. (1) For 60% of patients with drug-resistant epilepsy, surgery can significantly reduce or eliminate seizures. (2, 3) Despite such treatments, 15 - 40% of all patients with epilepsy unfortunately continue to have seizures that impair their daily living. (4) In an effort to improve the quality of life for these remaining patients, both epileptologists and neurosurgeons have been turning to the use of neuromodulation – the application of electric currents to the nervous system.

Existing Types of Neuromodulation Used for Epilepsy

Over the past few decades, neuromodulation for epilepsy has grown dramatically. The FDA has approved vagus nerve stimulation (VNS) for the treatment of drug-resistant epilepsy. Other types of neuromodulation that have been explored include trigeminal nerve stimulation (TNS), deep brain stimulation (DBS), and more recently, closed-loop stimulation. Both DBS and closed-loop systems were under FDA review in 2012 as investigational therapies for epilepsy in the United States.[5]

A Brief History of Closed-Loop Neurostimulation

Unlike VNS and DBS, which administer continuous stimulation, a closed-loop neuromodulation system only delivers stimulation when it detects the beginnings of seizure activity. In that way, it functions much like a pacemaker does to stop abnormal heart rhythms. Such stimulation works to either reduce the risk of having a seizure altogether or stops seizures from spreading to other parts of the brain.

> A closed-loop system only delivers stimulation when it detects the beginnings of a seizure

Patients who are evaluated for traditional epilepsy surgery often need to undergo an initial surgical procedure to determine exactly where the seizures start. To do this, patients are monitored for seizures during a hospital stay. Brainwaves are monitored using an electroencephalogram (EEG), which involves placing electrodes on the brain surface, with wires exiting out through the skull and scalp. Once a seizure occurs, doctors can use the EEG to pinpoint the area of the brain that is causing seizures and define the target for surgery.

After promising results were observed in animal testing, closed-loop stimulation was studied in patient volunteers who were undergoing this type of invasive monitoring.[6] At first, a doctor who saw the beginnings of seizure activity on the EEG would initiate a pulse of stimulations. It was seen that in response to that method, abnormal EEG activity could be effectively stopped.[7–9]

In order for a device to function independently, however, reliable seizure detection methods had to be created. In closed-loop stimulation, the first half of the loop is seizure detection, and the second half of the loop is the resulting stimulation. Over the past few decades, seizure detection has matured significantly. Scientists and engineers have developed sophisticated signal processing to more reliably detect the onset of seizures.[10–19]

Studies in the early 2000s showed that closed-loop stimulation provided patients therapeutic benefit with no major side effects. Direct stimulation of the region of the brain suspected to start the seizures (the seizure onset zone) was found to be at least as effective in stopping seizures as indirect stimulation with DBS.[20] Patients not only had fewer seizures, but their remaining seizures were also less severe.[1,20,21]

Expected Outcomes with Closed-Loop Stimulation

These early studies laid the foundation for a large clinical trial carried out between 2005 - 2007 across multiple hospitals in the United States. The RNS® System Pivotal Clinical Investigation included 191 adult patients with medically refractory epilepsy who were implanted with a closed-loop system at 31 institutions.[22,23] Patients in the study group had their system turned on for the first 12 weeks, while those in the sham group, to which the study subjects were compared, received no stimulation. During this initial 12-week period, it was noted that patients with an active system averaged 41.5% fewer seizures. At the same time, the sham group only had a 9.4% reduction in the frequency of their seizures.[23] All patients had their system turned on after the initial 12 weeks to see the long-term effects of closed-loop stimulation. After two years, almost half of the participants had at least a 50% reduction in seizure frequency.[22,24]

Longer-term follow-up shows an increase in the percentage of patients responding to RNS® stimulation over time.[22] A 2011 update on these 191 implanted patients gave strong evidence that closed-loop stimulation significantly reduced the frequency of disabling seizures in patients who had previously tried not only anti-seizure medications, but also VNS or traditional epilepsy surgery.[23] More important than reductions in seizure frequencies are the significant improvements in quality of life reported by these patients.[23]

Benefits of a Closed-Loop Stimulation System

Since a closed-loop system provides stimulation only when triggered by early seizure activity, the brain receives less stimulation than it would with earlier types of neuromodulation, which deliver constant stimulation. This reduction in stimulation dose not only helps the battery last longer, but also decreases the potential risk of side effects from long-term continuous stimulation.[25–27] In fact, it has been shown that twice as much stimulation can be safely given with intermittent systems when compared to constant stimulation systems.[26]

Another benefit of closed-loop systems is that stimulation is targeted only at the seizure focus. In all other forms of neuromodulation (VNS, TNS, and DBS), stimulation is applied to seizure-generating circuitry and affects many parts of the brain as well. By isolating the seizure focus, normal parts of the brain are left alone and the chance of side effects is further reduced.[26]

The Device

The first closed-loop stimulation system to be implanted is the responsive neurostimulator system (RNS®) by NeuroPace, Inc. (Mountain View, CA).[31] It consists of a main component, about the size of a pocket watch (measuring 4 x 6 x 0.7cm) connected to two electrodes.[21] The main component contains a battery and a computer that can analyze EEG readings and administer stimulation once it detects a seizure onset. Two types of electrodes can be used in any combination with this system. One type (a subdural electrode) consists of a strip of four disc-shaped contacts that is placed on the surface of the brain. The other type (a depth electrode) is made up of a strip of cylindrical contacts that is placed into the brain tissue itself. Both types of electrodes are made of a combination of platinum and iridium, which is able to safely administer therapeutic stimulation without generating a harmful reaction from the surrounding tissue.[3,21]

Components of the system that are not implanted include a physician programmer, a patient data transmitter used for storing EEG data, and a telemetry wand for wireless transmission of data.[25] These tools allow doctors to transfer the recorded information to a computer for detailed analysis. By doing this, the clinician can see how the device is working, and fine-tune the stimulation programs if necessary.[28]

Being Evaluated for a Closed-Loop Stimulation System

Closed-loop stimulation may be offered to patients 18 years or older who have medically refractory epilepsy and are not candidates for traditional surgery.[23] It also may be offered to patients who have previously undergone traditional epilepsy surgery and continue to suffer from intractable epilepsy.[21,29] Similarly, patients who had a VNS implanted may also be offered this treatment.[21,30] For patients to be eligible, the exact location of their particular seizure focus must be known in order to direct stimulation there.[23] A closed-loop system is generally not recommended for epilepsy patients who have more than two distinct seizure foci, since a maximum of only two electrodes can be implanted.[3]

Implantation of a Closed-Loop Stimulation System

Electrodes are only placed in brain areas shown to generate seizures, with the exact placement tailored to each patient. The main component, containing the battery and computer, is designed to be implanted within the skull itself (see image). There are lower rates of infection and hardware failure from this placement compared to traditional systems (like VNS and DBS), in which the battery is implanted under the skin, but over the ribs in the chest.[32]
Implantation of the RNS® closed-loop system involves shaving the hair off one side of the head prior to making a fairly large incision in the scalp. Once the skull is exposed, two small holes (about 14mm in diameter) are made for the two electrodes. After the electrodes are in the proper position, covers are placed over the holes to help hold the electrodes in place. The location for implantation of the main component is then determined based on these two holes. A cavity for the main component is drilled out so that the device sits flush with the surface of the skull. The electrodes are connected to the main component and the incision is closed.[3]

Risks Involved

During the RNS® System Pivotal Clinical Investigation, the rate of serious complications within the first month of implantation was reported to be 12%, which is comparable to the 15% risk of similar events in patients undergoing invasive monitoring with intracranial electrodes.[23] Common side effects include implant site pain and headache. Less commonly, patients will experience infection, bleeding, or death.[23] Although the complication rate increases to 18.3% over the course of the first 3 months after implantation, this complication rate is favorable in comparison to the overall rate of 36% associated with DBS for Parkinson's disease or essential tremor.[33–37]

At this time, long-term experience beyond five years is currently very limited and the side effects of intermittent, long-term (also termed "chronic") stimulation remain unclear.

Future Directions

A great deal of research remains to be done in closed-loop stimulation for the treatment of epilepsy. Both parts of the closed-loop – seizure detection and stimulation for halting seizures – must not only be individually optimized, but also work in unison with each other.

Seizure Detection versus Seizure Prediction

The earlier stimulation is applied, the more effective it is at stopping abnormal EEG activity.[38] Therefore, both scientists and engineers are working to improve seizure detection, and possibly even predict them. The International Workshop On Seizure Prediction has been held since 2002 to gather and develop new methods.[11,39]

Current algorithms analyze the EEG signal itself to detect changes that may represent seizure activity. While these systems are very sensitive to abnormalities in the EEG, they will often flag events that are not truly seizures. Therefore, extensive research is being done on signal processing that will help detect reliable changes in EEG signals that may not be otherwise be visible to the naked eye.

The promise of predicting seizures has been supported evidence of changes in EEG activity that occur 7-10 seconds before clinical symptoms.[11] Some researchers have even reported noticing changes in neuronal activity as early as 7 hours prior to the seizure itself.[15]

Optimization of Stimulation Parameters

Stimulation parameters to halt seizure activity must also be improved. Currently, these parameters are based mainly on experience with DBS and with stimulation performed as part of an evaluation for surgical removal of a seizure focus.

Technological Advances

The rise of new technologies will only improve our ability to create a more effective closed-loop neurostimulator. Improved wireless transmission of high quality data would significantly reduce the amount of hardware that needs to be implanted. This innovation would allow future versions of such neurostimulators to keep the larger elements of the device in a module to wear on a belt or a vest.[40]

Future applications of closed-loop systems may also be able to track the levels of certain chemicals in the brain. This information could be used independently or along with EEG data in predicting brain states consistent with activity prior to or during a seizure.[40]

The examples above are only a sample of the possibilities that exist for closed-loop neurostimulator systems. In all aspects of neuromodulation, continued collaboration between engineers and doctors will help to advance the field – and ultimately provide higher levels of care for patients.

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