

Neurotechnology: A New Approach for Treating Brain Disorders

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ABSTRACT

Advances in neuroscience, engineering and computer technologies are creating opportunities to connect the brain directly to devices to treat a variety of disorders, both neurological and psychiatric. They are opening a new field of neuroscience called “neurotechnology.” This article reviews efforts in this area that are ongoing at Brown University and the hospitals affiliated with Brown’s Alpert Medical School. Two general approaches are being used. One uses advanced electrodes to “sense” the activity of many individual neurons in the cerebral cortex and then use that activity for therapeutic purposes. The other uses various types of devices to stimulate specific networks in the brain in order to restore normal function and alleviate symptoms.

KEYWORDS: Neurotechnology, neuroscience advances, BrainGate

INTRODUCTION

Diseases and disorders of the nervous system have proven to be especially difficult to treat in part because of the complexity of the brain. Most efforts have focused on the development of behavioral or pharmacological therapies. However, with advances in engineering and computer technologies, alternative “device-based” approaches are being explored as potential tools for treating a number of conditions ranging from paralysis to movement disorders to mental illness.

Researchers at Brown University and its affiliated hospitals are international leaders in this approach, known as “neurotechnology.” This collaborative, interdisciplinary effort has followed two approaches. One takes advantage of devices to detect brain activity and then uses that information for therapeutic purposes. The second uses devices to change brain activity in ways that can restore normal function. The work has benefited from the collaboration between the Norman Prince Neurosciences Institute (NPNI) and the Brown Institute for Brain Science (BIBS).

SENSING THE BRAIN

BrainGate research

The BrainGate research project is a multi-institutional effort based at Brown that is focused on improving the ability of



In a significant advance for brain-machine interfaces, engineers in the Brown Institute for Brain Science have developed a novel wireless, broadband, rechargeable, fully implantable brain sensor that has performed well in animal models. Here engineers Arto Nurmikko and Ming Yin examine their prototype device.

paralyzed people to interact with the world. It uses a technologically advanced array of 96 electrodes implanted in the motor cortex of patients paralyzed as the result of stroke, injury or disease. These electrodes are able to measure the activity of individual neurons while people imagine moving their own arm. Computer algorithms translate that input to output that can be used to move a cursor on a computer screen¹ or, more recently, to move a robotic arm in a coordinated and purposeful manner.² In a dramatic demonstration in 2012, a paralyzed woman used BrainGate to control a robotic arm to give herself a drink of coffee² – the first time she has been able to do that in 15 years! In 2013, the BrainGate team received the inaugural Israel Brain Prize for this advance.

A remarkable finding of this project is that a very small number of neurons – fewer than 100 – can provide sufficient information to encode such complex movements. The current system does not replicate the speed and dexterity of natural arm and hand movements. However, innovations in signal decoding are improving control and “sensing” technology is making it possible to incorporate the activity of

more neurons into the system. As this trend progresses, the ability of paralyzed patients to control robotic devices should improve dramatically.

Engineers at Brown are also making rapid progress in developing a next-generation BrainGate device that transmits neural signals wirelessly.³ That technology will enable patients to use the BrainGate approach in more ambulatory, real-life situations, untethered from a computer. It will also advance the possibility of amputees using this approach to better control prosthetic limbs. Other studies, using non-human primates, suggest that it will eventually be possible to use this approach to control movements of a patient's paralyzed limb by stimulating muscles directly.⁴

Multi-electrode arrays

Multi-electrode arrays are also providing new insights into brain activity during epileptic seizures. To plan for epilepsy surgery, doctors often record activity from the brains of patients using electrocorticography (ECoG). In this procedure a large array of 50 or more electrodes is placed directly on the surface of the cortex in the region suspected to be the source of the seizures. Recordings can be made over a week or more while the patients are alert and off anti-seizure medications in an effort to record seizure activity and localize its source. These standard ECoG arrays do not, however, reveal the activity of single neurons.

As part of this procedure it is now possible to insert the same 96-electrode array used in the BrainGate system into the region suspected to be the source of seizure activity. This is being done by a team of clinicians, scientists and engineers at Brown and Rhode Island Hospital, in collaboration with colleagues at Massachusetts General Hospital. Thus, for the first time, the activity of individual neurons is being recorded and analyzed before, during, and after seizures. An initial report of the results from four research participants illustrates the potential power of this approach.⁵ This study showed that seizures are not comprised of hyper-synchronized neuronal firing as previously suspected. Instead the patterns of activity are quite heterogeneous during the seizure. In comparison, at the end of the seizure almost all neural activity is suppressed for several seconds.

Perhaps the most surprising and significant finding in this study was the discovery that many neurons, even ones well outside the area of seizure origin, showed significant changes in activity minutes prior to the onset of the seizure. Thus, chronically implanted electrodes that record individual neurons could become reliable tools for identifying seizures prior to their onset. If this proves to be the case, it could lead to closed-loop devices able to treat epilepsy by stopping seizures before they start, by injecting a drug or an electrical current into the region of the seizure's onset. The



VIDEO: Paralyzed woman uses thoughts to sip coffee

FDA recently approved such a device based on ECoG recording technology and implanted stimulating electrodes (NeuroPace RNS System®).

ALTERING ACTIVITY

Deep brain stimulation (DBS) use in various disorders

Physicians have been altering brain activity to treat psychiatric disorders since the 1930s in those patients with

the most severe and intractable symptoms.⁶ However, in recent years, these techniques have become progressively more refined.

In the 1980s a new form of stimulation was developed primarily to treat tremors and other abnormal movements in patients with Parkinson's disease^{7,8} who had severe medication-related problems. Neurosurgeons had discovered that small lesions deep in the brain, in the sub-thalamus and the globus pallidus, could greatly reduce certain symptoms in patients whose responses to drug therapy were problematic. Subsequently, they discovered that high-frequency stimulation in these same areas had similar effects. Since lesions are not reversible and can cause complications, if not properly placed, deep brain stimulation (DBS) has become increasingly common as it causes minimal brain damage, can be adjusted with changes in stimulation and the electrodes can be removed. Today there are close to 100,000 people worldwide with DBS electrodes. The vast majority has been implanted for the treatment of Parkinson's disease and other movement disorders, including essential tremor and dystonia.

DBS is also being tested as a potential treatment for a number of other conditions. These include epilepsy,⁹ Tourette's syndrome,¹⁰ motor problems of multiple sclerosis¹¹ and several others. Within NPNI and BIBS, most research using DBS has focused on mood disorders – depression¹² and obsessive-compulsive disorder (OCD).¹³ The rationale behind this is a growing body of evidence that these disorders are related to dysfunctions of networks of neurons involving the prefrontal cortex,¹⁴⁻¹⁶ much like the symptoms of Parkinson's disease are related to networks involving the motor cortex.

Researchers do not yet agree on the best target for treating depression with DBS. A group from Butler Hospital and the Providence Veterans Affairs Medical Center has focused on an area deep in the forebrain that includes the ventral portion of the anterior limb of the internal capsule and the adjacent striatum (VC/VS). In 2009 they reported that about half of a group of 15 patients with refractive major depression benefitted from DBS in this region with no adverse effects.¹²

Of those who responded, all showed significant improvement in standard mood-rating scales and about 40% were in remission when last examined (up to 4 years postoperatively). In comparison, others have stimulated the medial

surface of the cortex in an area known as the sub-callosal cingulate gyrus (area 25) – also part of the mood disorder circuitry – and they report similar benefits.¹⁷

Efforts are also underway to evaluate the effectiveness of DBS in the VC/VS for treating severe, unresponsive OCD. In a recent multi-center study, about two-thirds of patients responded positively to treatment for 12 months.¹³ When the stimulation was interrupted, the responders quickly fell into a severely depressive state, which was reversed when the stimulation resumed.

The reason that some patients do not respond to stimulation is not understood, although it is presumed to be related to the placement of the stimulating electrode. This is currently being addressed by a large multi-institutional team, including researchers from Brown, Harvard, the University of Rochester, the University of Pittsburgh and the University of Puerto Rico, that is supported by a grant from the National Institute of Mental Health. They are studying the neural mechanisms that underlie DBS stimulation and the cortical networks that are associated with OCD with the expectation that the results will reveal more effective targets and stimulus parameters.

The use of DBS to treat Alzheimer's disease has also received attention recently. Lozano and colleagues¹⁸ stimulated the fornix and hypothalamus in a patient who was part of a study using DBS to treat obesity and observed that stimulation invoked memories. This led to a preliminary study of six patients with early-stage symptoms of Alzheimer's disease. Of the six, two showed improved function on standard memory tests for a year. The performance of a third patient was unchanged although it would normally be expected to get worse during this period. The other three patients continued to worsen as typical Alzheimer's patients do. This study lacked controls but was suggestive of positive cognitive benefits from DBS.

Based on these preliminary results, a phase 1–2 clinical trial is now underway to test safety and efficacy in 20–30 patients. Rhode Island and Butler Hospitals are collaborating as one of the sites. Surgery is being done at Rhode Island Hospital and testing is being conducted at Butler. In this one-year trial, only half of the patients will be stimulated and neither the patients nor the testers will know who was stimulated until the end of the trial. After the results are known, all patients will have the option of turning on their stimulators if they want. This study design will greatly mitigate placebo effects and investigator bias.

DBS shows great promise for a number of conditions. However, DBS is an invasive surgical technique that comes with small risks for bleeding and infection. It is also expensive. NPNI and BIBS researchers are exploring other techniques to stimulate the brain non-invasively and inexpensively. These techniques include transcranial magnetic stimulation (TMS) and transcranial direct or alternating current stimulation (tDCS or tACS). All involve the excitation or inhibition of brain activity by passing a current outside the

head. TMS uses a strong magnetic pulse, placed next to the skull, to induce an electric current in the adjacent cortical surface. TDCS and tACS apply a direct (tDCS) or alternating (tACS) current to the scalp, which causes subtle changes in the activity of the underlying region of the cerebral cortex. The equipment required for all three is relatively inexpensive and can be used on patients by trained technicians. All of these techniques have been shown capable of affecting mood¹⁹ and compulsions.²⁰

In 2008 the FDA approved TMS as a treatment for severe, intractable depression and all three stimulation techniques are being actively explored for a variety of other applications by research teams at the Center for Neurorestoration and Neurotechnology at the Providence VA Medical Center. Disorders being studied include OCD, Post Traumatic Stress Disorder and chronic pain. In addition, evidence suggests that TMS and tDCS may enhance plasticity in the cortex. Thus, this research team is also investigating the possibility that stimulation could be used to enhance the benefits of rehabilitation therapy following stroke or other forms of brain injury.

SUMMARY

Researchers in NPNI and BIBS are collaborating on all of the efforts described above. They are located at different institutions in Providence, including Brown University and hospitals affiliated with Brown's Alpert Medical School. They are members of teams that are using neurotechnology to develop novel treatments for patients suffering with a wide variety of neurological and psychiatric disorders. This area of research demands coordination and collaboration between clinicians, neuroscientists, engineers, mathematicians and computer scientists. It is also an area where Providence already stands out on the world stage and is poised to expand its prominence.

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Disclosures

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