

GUEST EDITORIAL

Deep brain stimulation: Challenges to integrating stimulation technology with human neurobiology, neuroplasticity, and neural repair
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By the year 2040, neurodegenerative diseases, such as Alzheimer's disease, Parkinson's disease, ALS (Amyotrophic Lateral Sclerosis), and similar disorders, will overtake cancer as the second most common cause of death (1). What this means, from a practical standpoint, is that one in three of us will get a neurodegenerative disease. And if that's not bad enough, the other two of you will be paying for that individual's treatment. So it's important to pay some attention to this area. Of course, the incidences of these sorts of diseases also increase as the population ages. We are going to be facing an epidemic of neurodegenerative disease in the near future. The good news is that we have 30 or 40 years of warning. So it's time to start seriously thinking about this topic.

Let us now turn specifically to Parkinson's disease. Neurosurgeons have been interested in treating Parkinson's disease for some time (2). In fact, before the advent of drugs, neurosurgery was the mainstay of therapy. If you had Parkinson's disease in the 1940s and '50s, you were treated by a neurosurgeon, not by a neurologist. And if one looks at the number of papers published on surgery for Parkinson's disease across time and specifically for pallidal surgery, one sees that in the 1950s, there were quite a number of papers. Then in 1960s, levodopa was introduced and we entered the "ice age" of functional neurosurgery. With the introduction of levodopa and the realization of its striking clinical benefits, neurosurgical interventions all but disappeared for 30 years. Only now are we seeing a renaissance of neurosurgical procedures for the treatment of Parkinson's disease that began in the late 1990s (3,4).

The first of several reasons for this is that for many patients, the drugs are simply not doing the job. Existing pharmacological interventions have shortcomings that have taken some time to become apparent. Although patients initially respond to the drugs such as levodopa, with time and chronic use, they are less effective and

complications of their use arise. This means that patients continue to be disabled despite the best available pharmacological therapies. Second, there have been very important advances in technology. We can now operate better, and we have more effective operative procedures to offer our patients. But the third and perhaps the most important reason is that we now have a very strong scientific rationale for tackling different parts of the brain in Parkinson's disease.

Patients who were treated operatively back in the 1940s were generally awake, and written reports suggest that neurosurgeons used to just cut into different parts of the brain in what would now be considered a somewhat nonspecific manner until something interesting happened (5,6). Either the patient's symptoms improved or an adverse effect was produced to signal the stopping point of the procedure. This was the approach to neurosurgery not so long ago.

Today we have a stronger rationale for approaching neurosurgery. One of the primary reasons for the quantum advances in our understanding and approach to the problem is the series of 400 patients in the San Francisco Bay area that took the neurotoxin, MPTP (7). This is a neurotoxin that was a contaminant of designer drugs of the '70s that caused these individuals to develop a Parkinson's-like syndrome. As it turns out, the neurotoxin MPTP is relatively selective for dopaminergic neurons. It preferentially kills dopaminergic neurons, which leads to the development of the signs and symptoms of Parkinsonism, which are rigidity, tremor, akinesia (the inability to initiate movements), and other disturbances to gait and posture. Human beings are not the only ones to develop these symptoms in response to MPTP; laboratory animals develop them as well. This gave neurophysiologists the unprecedented opportunity to study what goes wrong with the brain when the dopaminergic system degenerates by giving MPTP to nonhuman primates (8). As a result, we now understand several very striking abnormalities in

neurologic function that occur as a consequence of dopamine deficiency.

The most striking abnormalities of the Parkinsonian state induced by lack of dopamine is the hyperactivity of the GPi, the internal segment of the globus pallidus (9), because of removal of inhibition coming through the striatum and increased excitatory drive from the subthalamic nucleus. The consequence of this hyperactivity in the GPi and in its sister structure, the substantia nigra pars reticulata (SNR), is an excessive inhibitory outflow to the thalamus, cortex, and brainstem locomotive areas, the pedunculoptine nucleus (PPN), which essentially shuts down the motor system (10). The situation is analogous to driving your car with the brakes on constantly. So, the goal of neurosurgery is to remove the pressure on the brakes and try to release the motor system.

The cortex and the brain stem are thus apparently only innocent bystanders. It is only this disturbance in the perpetrators, GPi and SNR, that wreaks havoc by shutting down the motor system. If the disturbance in the basal ganglia output itself can be neutralized, then more normal function can be restored. One of the interesting conundrums is that no output from the GPi is actually preferable than bad output. In fact, even reducing it to zero by making a lesion and destroying the structure greatly improves the situation as the motor system works better in the absence of all output from them than in the presence of even a small amount of abnormal patterned output that disrupts the function of cortex and brain stem circuits involved in locomotion.

One example of such disturbed function can be seen in the thalamus. If you record from a single thalamic neuron in the VIM nucleus of a patient with tremor using a microelectrode, you will find that it fires in bursts of action potentials up to 10 or 15 at a time synchronously with the tremor at 4 to 6 Hz. This is very abnormal behavior. Normally the thalamic neurons will fire randomly, but when the pattern changes from a random fashion to this clustered synchronous fashion, then tremor appears. The treatment strategy is to go into the thalamus and prevent this neuron from behaving this way. One of several ways of

accomplishing this is to simply destroy the offending neurons. In fact, destroying about 10,000 of the neurons in thalamus firing in synchrony with the tremor in an operation called a thalamotomy actually causes the tremor to disappear. Another way to do this is by applying electric stimulation to these same cells. A deep brain stimulation (DBS) electrode can be inserted into the thalamus to deliver electrical current in the vicinity of these cells via an implanted stimulator. When this is done, the tremor also stops. You can therefore achieve the same result by either destroying the neurons or by passing an electrical current near them (11). The latter option is obviously more flexible. DBS electrodes with multiple contacts can be used that allow us to select the most effective stimulus location and adjust the pulse parameters for the optimal response. These procedures are very effective for dealing with tremor (12).

Another target is the globus pallidus (13,14). We estimate that you need to lesion approximately 25,000 neurons in the globus pallidus to get the beneficial effects that we see with pallidotomy. The same clinical effects can be achieved with electrical stimulation. Typically, we find our way through the brain using a microelectrode to record the electrical activity from single units as the electrode is inserted (15). The pattern of electrical activity changes as different structures are crossed, and the signature of the GPi is unique and is a positive identification for the location of the electrode. This is like traveling by car through Europe and noting the change in language as you cross the border from one country to another. The nuclear structures of the brain are populated by neurons that speak individual languages. If you understand the language, you know what nuclear structure you're in within the brain. These signatures, in proper context, are characteristic enough that one can identify the nuclear structure at the level of one cell's resolution. So these are very powerful techniques to find your way around the brain. When one is operating in the globus pallidus, it's critical to make lesions or put DBS electrodes in GPi and avoid nearby structures such as the cortical spinal tract, or optic tract axons that touch

the globus pallidus. So it's important not just to find the structure of interest, but also to avoid injury or spread of electrical current to adjacent structures.

Another target gaining popularity is the subthalamic nucleus (16,17). And here again, one can either lesion this structure or deliver electrical stimulation. Here too, stimulation and lesioning appear to accomplish similar effects with respect to the benefits of the surgery. Patients are now being implanted with stimulating electrodes bilaterally within the subthalamic nuclei. This is significant because bilateral lesions are not usually performed because lesioning both sides of the brain is considered to be of some risk in clinical practice.

It takes a lot of fine-tuning to find the right amount of current needed to eliminate the tremors and improve rigidity and akinesia. Patients make many visits to the clinic before their motor symptoms are controlled. Electrical stimulation can sometimes relieve the major symptoms of Parkinson's disease and reduce the requirements for medication. The effects on tremor are immediate and can be seen as soon as the stimulation is turned on, which is not the case for rigidity or other motor problems, since the neural circuits involved are different. Even though the tremor can be removed immediately and completely, it's important to realize that the patients still have Parkinson's disease. The stimulation is not a cure. In fact, when stimulation is removed, the symptoms reappear and patients return to their baseline states as they appeared prior to treatment. I had one patient with a left globus pallidus stimulator who actually used this to his advantage. Stimulation completely relieved his tremor on his right side, although he still showed some akinesia. Upon shutting off the stimulation, he immediately returned to his baseline Parkinsonism with rigidity and with marked tremor. This patient is an avid golfer. He sent me a letter this past year to tell me that he got a hole in one at his golf course for the first time in his life. He not only likes to golf, but he also likes to bet on the outcome of the game. So what he does is show up to the golf course with his stimulator turned off and proceeds to collect bets. I don't think I

have to tell the rest of the story. He's made a lot of money.

The results obtained in Parkinson's disease are certainly encouraging, and the DBS techniques described are being applied to other disorders such as dystonia, which is characterized by involuntary twisting movements of the body (18). A mutation in a gene called torsion A on chromosome nine causes a particularly serious form of the disorder. I was involved in the case of a child with this problem who was perfectly normal until the age of six when he started developing twisting movements in his legs, trunk, and arms that progressively worsened. He remained cognitively normal despite this, and images of his brain revealed nothing out of the ordinary. This child did not respond to drugs, could not sit, and could not walk for one year when he came to see us. The only way this child could get around independently was by dragging himself across the floor. Five of his siblings also have the disorder, which has been devastating to the family. This is a very disabling and crippling disease with a progressive course that is nonresponsive to medication and very refractory to medical therapy. Three months after bilateral pallidal procedures, he was well on the way to achieving near normal function (19). Initially, there was no response at all to the surgery. But improvement started at one week postsurgery and continued progressively. Neuroplasticity and relearning are definitely important contributing factors. It's now been 6 years since this child was operated on with very satisfactory results. He went back to school and went back to riding a bicycle and playing soccer. The case shows how a disturbance in the globus pallidus can influence the function of the entire motor system and how removing this disturbance by lesioning or by using electrical stimulation can release the motor system to function in a more normal fashion.

These examples illustrate that DBS can exert quite dramatic effects on the brain. But how does this work? The results from DBS look like those from ablation surgery, but is it really creating a lesion in the brain? To explore this, we studied patients with essential tremor, which is five to ten times more common than Parkinson's

disease. This is a disorder where patients have an inherited tremor that can respond to alcohol or beta blocking drugs. When tremor is disabling, surgery, thalamotomy, or thalamic stimulation can be effective. The results over time are mixed but very interesting. In approximately 40 percent of patients, just the mere implantation of the electrode reduces the tremor score significantly post-surgery even with the stimulator off. When the stimulator is turned on, further improvement is observed and the tremor goes away to a large extent. So for about 40 percent of the patients, even at 5 years follow-up, stimulation results in the abolition of the tremor, which returns when the stimulation is removed. This is the classic response we would have expected from the Parkinson's disease experience.

Then there's another group of about 30 percent of central tremor patients who didn't read the textbooks. This group behaves differently as they lose the benefit of stimulation after a year or so, although they responded well initially. For example at 3 months postimplant, the tremor goes away with stimulation, but over time, the response diminishes as tolerance develops. In other words, their tremor initially went away but reappeared over time, and no matter how the stimulus parameters were manipulated, it was impossible to recapture the benefit. Some of these patients actually request that their stimulating devices be removed.

The last group is perhaps the most interesting. These are patients who initially get a very good benefit but eventually don't need the stimulation any more. After stimulating for 24 hours a day for 1 to 2 years, the tremor is gone even without the stimulation. At 5 years without stimulation, the effect is preserved. These patients are effectively "cured" of their tremor. Now what's happening? Is this like the flow of water slowly carving out the Grand Canyon, where small amounts of continuous stimulation over a long period of time eventually make a change in brain? Another possibility may be that stimulation might be creating a lesion in the brain, because we know if we destroy these cells that things would also improve. But this is unlikely because there's no evidence of tissue damage in

the brains of patients who have died after long-term stimulation (20). So, long-term stimulation actually appears to change the brain itself. The neural networks involved in generating the pathological motor activity appear to be permanently modified by the stimulation. This neural plasticity to DBS has the consequence that there's no longer a need for on-going stimulation and is certainly an area that we need to more completely understand so we can exploit it for therapeutic gain.

At another level of analysis, we need to acknowledge that we still don't really have a very good understanding of what's going on when we apply stimulation to the brain. When we say we're applying electrical stimulation in the subthalamic nucleus (STN), what we really mean is that there's a stimulating electrode in the STN, which affects an unknown number and unknown kinds of neural elements at an unknown distance in the vicinity of the electrodes. We really don't have a very good understanding of what the electrical currents are actually doing to the brain. But it works, right? So how could it work? Well I could only think of about 11 possible mechanisms such as depolarization, jamming, blocking potassium channels, blocking calcium channels, and so on. Electrical stimulation has effects in both antegrade and retrograde directions, but we don't know if it's predominantly the axons, the dendrites, or the cell bodies that we're affecting. We don't know how much of the stimulation could be causing neural plasticity, driving neural networks, or acting neuroprotectively. Could we effectively be producing a temporary blockade by enhancing inhibitory activity? We also don't know anything about the effects of chronic stimulation of nonneuronal cells. What happens to the glia? Do they make neurotrophins in response to this for example? And, of course, any combination of these mechanisms, or in fact none of these mechanisms, could be important.

To try to address the mechanism of action of stimulation, we've put two electrodes in the internal segment of the globus pallidus—one for stimulation and one for recording. This way, we can measure the consequences of stimulation on a neuron that is some distance removed from the electrode. As you recall the GPi has a very

high tonic activity in Parkinsonism, firing at about a hundred times a second. With these two microelectrodes, we can see what happens to a neuron that is firing abnormally when we stimulate only a couple of millimeters away. What we found is that we can actually inhibit the firing of these overactive neurons by stimulating neighboring areas. Every time there's a stimulus, the neuron stops firing and the duration of this arrest is in the order of 20 to 25 ms. The phenomenon is repeatable at various stimulus rates, and at a rate above 50 Hz, the neuron shuts down completely (because the inhibition lasts for about 20 ms). The outcomes of these experiments were recently published (21).

It appears as if stimulation is activating the axons that are impinging upon this postsynaptic neuron. We know that the axons in the internal segment of the globus pallidus come from two sources, the striatum and the external segment of the globus pallidus (Gpe). We know those are inhibitory GABA-ergic axons. This suggests that stimulation may, in fact, excite axon terminals and that these axon terminals are releasing their GABA, which is going across the synaptic cleft, interacting with GABA A receptors in the post synaptic cell and shutting down activity in the postsynaptic neuron. So it may be that what DBS is actually doing is activating intrinsic inhibitory pathways in the brain and really what we're doing is using DBS to harness intrinsic GABA-ergic mechanisms to shutdown local neurons.

Now if this is true, then you should be able to mimic the effects of DBS by injecting GABA directly into the brain. To confirm this hypothesis of how DBS may work, we tried to duplicate its effects with GABA microinjections in six patients with essential tremor. We know that when the VIM nucleus is stimulated, tremor disappears, which we reconfirmed in these patients with peripheral electromyographic (EMG) recordings. At the same target sites populated with tremor cells arrested by stimulation, we injected approximately 2 to 5 ml of muscimol, a GABA-A specific agonist. After 5 ml of GABA agonist, there was approximately a 90 percent reduction in tremor (22), which was very similar to the action of DBS. Although muscimol affects pri-

marily the cell bodies and DBS probably preferentially affects axons based on the relative chronaxies of the axonal and cell body elements (23), the therapeutic effects are essentially identical. This provides indirect evidence that DBS may be working by activating inhibitory mechanisms by enlisting GABA-ergic nerve transmission.

We have gone on to try this in other targets such as the subthalamic nucleus in patients with Parkinson's disease with similar results. Five ml of muscimol reduced the baseline tremor to zero, and the addition of another 5 ml arrested rigidity. Increases in the magnitude of voluntary wrist movement 7 minutes after injection were maintained at 14 minutes postinjection (24).

Here then is an example of how injecting a neuroactive substance in a small and well-defined area of the brain can have a profound effect similar to DBS. We estimate that we only need to involve about 10,000 to 20,000 neurons to produce these results. We can calculate how fast the muscimol spreads by seeing how far the wave of inhibition of neuronal activity takes place. This is interesting because it brings forth the possibility that we not only can use DBS to help our patients, but we may also be able to use chronic delivery of minute amounts of neuroactive substances. It's possible to envision, for example, putting a catheter into these brain targets and delivering muscimol or something else in small, microliter amounts and getting the same therapeutic effects. You could even get quite sophisticated and couple a pump to deliver the neuroactive substance in response to tremor in a closed loop involving a sensor that could perhaps resemble a wristwatch. When the sensor detects a tremor, the pump injects muscimol until the tremor goes away. One could envision a closed loop system either using DBS or a neuroactive substance like muscimol to block this pathological neural activity in the brain. Perhaps a similar approach could be applied not only to treat movement disorders, but epilepsy or other disorders. What if you injected lidocaine to anesthetize neurons, or muscimol inhibited GABA-ergic neurons into an epileptic focus? Or into areas that were hyperactive during chronic pain? Would you be able to block those areas as

well and obtain a therapeutic effect? In addition to neuroactive substances, perhaps we could inject substances to influence the level and activity of enzymes involved in the metabolism of neurotransmitters. One could also administer lesioning agents designed to affect specific neuronal populations, thus creating very specific lesions by infusing a chemical agent. One could also envision infusing trophic factors, neuroprotective agents, and so on. The issues are of course, which agents to use in what concentrations in which locations for what desired effect.

For example, another series of patients of ours received intraventricular GDNF (glial cell-derived neurotrophic factor) so that further degeneration and progress of their Parkinson's disease could be prevented. As I've mentioned, DBS and ablation surgery treat only the symptoms of Parkinsonism and not the cause. By injecting a neurotrophic agent into the ventricles, we hoped that we could produce some protective effect and arrest the progress of the disease. However, this trial was unsuccessful because patients became ill, developing nausea, and sensory disturbances with the injections. In retrospect, the problem was one of delivery. Delivering the agent into the ventricles and the CSF essentially washed all one hundred billion neurons of the entire brain with GDNF, when we needed to target only the hundred thousand or so nigral neurons. If we are more selective in delivery, we may be able to overcome these difficulties.

There's potential in gene therapy as well. One can envisage introducing genes, either through vectors that are viral-based or nonviral-based, that prevent the metabolism of dopamine and enhance the utilization of what little is produced by the degenerating dopaminergic terminals characteristic of Parkinson's disease. Another strategy may be to apply neuroprotective agents—genes that may be able to prevent the neuronal death that occurs in Parkinson's. This is not so far-fetched because this experiment is being done in the lab now and this experiment by Jeff Kordower and his group who have shown that one can protect dopaminergic neurons by viral delivery of GDNF in primate models of Parkinson's disease (25). So using gene therapy in Parkinson's disease in humans may be closer

than you think. This is the direction the field is going, and it's moving very rapidly.

Attempts to regenerate the neurons that die as a result of spinal cord injury can be applied to various other neurologic disorders such as Parkinson's. Neurons can be transplanted to the human brain and can survive for long periods of time, but more and more attention is being given to the possibility of harnessing intrinsic stem cells in the brain rather than transplants from other sources. These neuronal stem cells are in the periventricular zone of the brain. It may be possible to mobilize them to differentiate along the direction that is necessary to repopulate the missing neurons of the subthalamus. And in fact it may not even be necessary to use neuronal stem cells, since researchers are now doing interesting tricks like turning blood cells into neurons (26). This is a modern version of alchemy. Precursor cells from the peripheral blood can be harvested and, with the appropriate set of trophic factors, converted into neurons. Even a patient's skin cells can, with the appropriate cues, be made to differentiate into neuronal phenotypes (27) which could then be used to repopulate the missing neuron populations.

Despite all of this progress, we still have no way of stopping the illness. Neurons that are supposed to last for 120 or 130 years are still dying and producing the signs and symptoms of Parkinson's disease. So the fundamental question is, What's killing them? There are certain clues from genetics, and we know there are three mutations in three genes that cause Parkinson's disease. We also know that environmental toxins may be playing a role. Viruses have also been implicated. Autoimmune processes and other mechanisms are all possibilities.

The answers will come from animal experimentation. Work done by Suneil Kalia and Li Liu in my laboratory examined the survival of dopaminergic neurons in response to MPTP, the toxin that the drug addicts took. Two weeks to four weeks after administering MPTP, you see a tremendous death of the dopaminergic neurons. So this is one model of dopaminergic cell death. Other experiments with these neurons clearly show nuclear condensation, which is consistent

with apoptotic cell death. So could apoptosis also be playing a role in Parkinson's disease? The answer is probably yes. There's some experimental evidence now in animals that if you inhibit apoptosis, you can slow down the neurodegeneration seen in these diseases (28). Although we have very good symptomatic treatments, the Holy Grail remains: to slow down the illness.

In our laboratory we have also looked at what may be the changes in gene expression that accompany cell death in Parkinson's models. There is specific increased expression of some genes and down regulation of other genes in response to injury. We're also now looking at the changes in gene expression that occur as a consequence of electrical stimulation. If we're going to explain the long-term effects of electrical stimulation, we're going to have to see what genes are turned on by electrical stimulation and what genes are turned off. It may be that these genes that are turned on and off are important not just for the symptomatic effects, but also for the explanation of some of the neuroprotective effects or of why the benefits can outlast the stimulation in certain individuals. In fact, if one is able to block some of the genes that are turned on, and if indeed they are the deleterious genes contributing to disease in the first place, then we may even be able to reverse the pathology. This type of reversal of pathology by genetic manipulation has been demonstrated in animals. When the mutant Huntingtin molecule is turned off in animal models of Huntington's disease, the animals recover, they regain their motor function, and the aggregates that are seen in the Huntington's disappear and their neurons recover (29). This type of "molecular neurosurgery" is something that is only going to increase in importance in the future. If turning off or influencing the expression of molecules in the brain will have beneficial effects, then there's no reason to think electrical stimulation could not be used as a conduit for similar beneficial gene expression in neurons as well.

So where do we go from here? Well, I'm a surgeon, and so I'm always interested in making surgery better, safer, and more accessible. I think we need to continue to develop, evaluate, and

compare the current surgical techniques that we have and also to see how do they stack up compared to emerging therapies. Ultimately though, whether we're talking about Alzheimer's or Parkinson's or Huntington's disease, we still don't have any way of slowing down or stopping these illnesses. And I think this is where we have to go. We are now in a position to say, "Okay, we've learned something about movement disorders. Let's now see if we can apply these same kinds of techniques to other problems that affect the nervous system. Let's leverage this knowledge into tackling other problems that affect our patients." Some of the things we might consider are epilepsy, pain, psychiatric disease, eating disorders, sleeping disturbances, and even memory disturbances and cognitive function. Some examples are in order.

On the basis of experimental data, where the anterior nucleus has been involved in the initiation and propagation of generalized seizures (30), we've implanted electrodes in the anterior nucleus of the thalamus and in the dorsal media nucleus of the five patients. The top two contacts of a four contact DBS electrode were located in the anterior nucleus, and because they have a span of 10.45 mm, the bottom two contacts were in the dorsal medial nucleus of the thalamus. Now, you can record the EEG from these implanted electrodes and pick up seizure-like electrical activity in the thalamus. This is interesting because it can serve as a warning. You may have several seconds of advance warning in which to intervene before the seizure occurs. Wouldn't it be interesting if, based on this trigger, we could intervene and stop those neurons from going into a full-blown clinical seizure by applying electrical stimulation or even a drug to anesthetize them? I think that this is an area of promise. In this small series of five patients, the results were mixed but encouraging. Two showed no effect, one patient showed a 50 percent reduction in seizures, and two others showed about an 80–90 percent reduction in their seizures. These are very disabled patients with generalized convulsions of about 100 seizures a month who had failed all other medical therapy. Again, these are patients for whom there is not much

else to offer and who desperately need novel treatment strategies.

Here's another interesting example. In a patient with phantom pain secondary to a leg amputation, we were able to stimulate the thalamus, in which there was a tremendous amount of abnormal activity indicative of sensation. In this particular patient, thalamic stimulation resulted in projections of parasthesias in the missing limb. But the really interesting thing is that with brain imaging techniques, we were able to visualize corresponding activation in the leg somatosensory cortex. The point is that we can assess the results of DBS not only by how the patient does with the functional outcome but also by noting which parts of the brain are responsible for these effects. Perhaps this technique can help distinguish and choose between those patients that can expect a good result (31). Maybe this type of pattern of activity on a functional MRI (fMRI) or on a positron emission tomography (PET) scan will help us titrate our stimulation to know when we've hit the right parameters. Are these parameters going to be the same in everyone or will they vary from patient to patient? These are some of the challenging questions that brain imaging might help us answer.

Can stimulation be used to make you smarter? Maybe. It turns out that vagal nerve stimulation in rats allows them to do better on cognitive tests (32). If this is true in a rat, how about people? Some evidence here too (31)!

And how about psychiatric disease? My colleague Helen Mayberg is interested in depression and uses PET imaging in her patients with depression. And it turns out that neurosurgeons are not foreign to psychiatric surgery. Dr. Mayberg has found that there are striking changes in the physiology of the brain in patients with depression who are treated with and who respond to pharmacological interventions (33). Well, I think we may be able to modulate these areas using neurosurgical techniques. If the patients are refractory to the drugs, then we may be able to go into these areas and turn them down either with electrical stimulation or direct application of a drug as I previously described. So modulating the activities of these

areas in the brain, as guided by neural imaging techniques, is revolutionizing the field.

So let's go into some topics bordering more on science fiction, such as the use of DBS for other problems such as eating disorders. The control of appetite is tightly regulated by the hypothalamus as clearly established in animal experiments. For example, if you are a cat and if someone lesions your ventral medial hypothalamus, you eat voraciously and continuously regardless of your nutritional status. On the other hand, if you're a cat and someone lesions your ventral lateral hypothalamus, you stop eating and become emaciated. So neuronal activity, or lack thereof, can have very strong effects on appetite. It turns out that neurosurgeons have already made this leap by lesioning the hypothalamus in humans to treat obesity. Seven patients in Denmark were treated in this fashion and all lost weight in response to coagulation of the lateral hypothalamus (34,35). However, over a year after intervention they all regained the weight and the initial effect was lost. Now what are the prospects of DBS in such cases? The main advantage of DBS is that you can regulate it, you can titrate it, you can turn it on, and you can turn it off and adjust the stimulus parameters to counter the accommodation phenomenon. So there may be a possibility of using deep brain stimulation in these same targets to have longer lasting effects.

I'd like to finish with the following thought. It is estimated that at this rate of explosion of knowledge and of computer power, in approximately 30 or 35 years there will be a merging of mind and machine. That is to say that the brain will be able to communicate directly with computers and vice versa. This is work by Ray Kurzweil (36). The brain has approximately a hundred billion neurons, each with about 104 synapses. So it's a neural network with only about 1,015 connections and 1 ms access time required for a synaptic event. These numbers are not too far out of the reach of the most powerful machines available today and can conceivable start to become manageable with another generation of increasing computing power. So if we can deal with say 1,018 computations per second, then you've got yourself a

computational model of the human brain. In this case it's possible that the biological brain could talk seamlessly to the electronic brain. You might be able to plug a chip into your brain and instantly download knowledge. Say you want to learn math. Well then you go to the store, buy the appropriate chip and pop it in. And if your grandchildren want to be neurosurgeons, they just buy those chips and in 5 minutes, they're installing these devices. The potential is really unimaginable. I don't know how much of this is science fiction and how much of this will actually become reality, but what is clear is that, in neurosurgery at least, the future is not what it used to be.

The field of integrating stimulation technology with human neurobiology is exciting. There's a great need for our continued work. Our patients with spinal cord injury, with neurodegenerative diseases, with epilepsy, and with pain all have unfilled needs. There are a tremendous number of patients that continue to suffer and need our help. I think the talent is here. I think the tools are here. We should work together to move this entire field forward. There's tremendous potential. We will go as far as our imagination and our will, will take us.

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EDITOR'S NOTE

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