Deep Brain Stimulation

A Successor to L-DOPA?

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First characterized comprehensively by Dr. James Parkinson in 1817, the disease that bears his name has become one of the most prevalent neurological afflictions in the U.S. It is second only to Alzheimer's, affecting more than a million Americans (Backer 2006). Current treatments are largely pharmacological, but a surgical procedure involving a neural implant called Deep Brain Stimulation (DBS) has shown promise to be an effective therapy against Parkinson's. This paper will discuss the characteristics of DBS therapy and compare it with the standard drug treatment, L-DOPA.

The manifestation of Parkinson's Disease (PD) in each patient is varied, ranging from mild tics to total incapacitation and motor rigidity. However, PD is progressive in nature, and its symptoms in most patients worsen over the years, eventually resulting in total dependence on nursing care. In the worst cases of PD, sufferers seem catatonic, withdrawn physically from the world, totally unmoving and unresponsive. Yet, PD does not affect the higher cognitive centers of the brain, so these patients are stuck in the prison of their frozen bodies, fully aware and conscious of their state.

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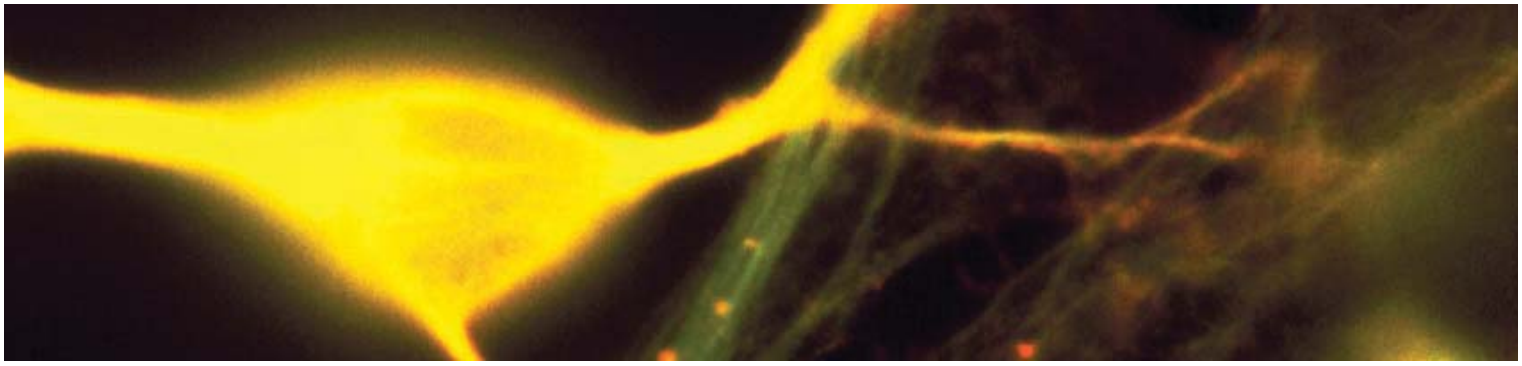
Although the cardinal symptoms of poverty of movement, muscle rigidity, and tremor have been described as far back as Galen in the 3rd century, the etiology of the disease is still unknown to this day. However, there have been a number of treatments directed at reducing the symptoms of PD. By 1960, physicians had discovered that the key feature shared among Parkinsonian patients was deficits in a mass of neuronal cell bodies located in midbrain called the substantia nigra. Meaning "black substance", the substantia nigra synthesizes and secretes a modified amino acid neurotransmitter called dopamine, affecting in particular a pathway in the brain known as the basal ganglia, which among other things, is responsible for motor initiation. Thus, without dopamine, PD patients have trouble activating this motor circuit. In 1967, a huge step in fighting the disease was made when a metabolic precursor to dopamine, 3,4-dihydroxy-L-phenylalanine (L-DOPA), was found to be effective in treating PD (Cotzias et al 1967).

Since then, L-DOPA has been used as the gold standard treatment in reducing the various symptoms of PD, being able to awaken even the most severely immobilized Parkinsonian patients from their dysfunctions. The therapeutic mechanism of L-DOPA is simple: once it has entered into the brain, it is enzymatically converted to dopamine, thus mitigating PD induced deficits in the nigral dopaminergic system. At the same time, L-DOPA's seemingly miraculous successes in reducing motor rigidity have been tempered by its potentially intolerable side effects. With effects described as a "yo-yo", medication can be a mixed blessing, swinging the patient from a deeply immobile Parkinsonian state to a pathological state of excess. These excesses of movement include involuntary muscular twitching, uncontrolled movements, and pathological euphorias—a once "happy state" induced by L-DOPA that "starts to crack, slip, break down, and crumble…to perversion and decay" (Sacks 1973).

Because of the problematic side effects of L-DOPA treatment, many alternative approaches to Parkinson's have been explored in recent years, ranging from dopamine mimicking molecules called agonists (Schapira 2007) to stem cell therapies (Astradsson et al 2008). Deep brain stimulation is another one of these alternative treatments for PD which has grown in popularity in recent years. Developed by Benabid et al. in 1987, DBS is not a dopaminergic or even a pharmacological treatment. Instead of introducing a chemical substrate, DBS involves the implantation of a neural pacemaker deep within the brain, one that modulates the brain circuitry affected by Parkinson's disease much in the way a coronary implant affects the beating of the heart. This is accomplished by the surgical placement of an electrode within the affected areas of the brain, with wires running out from the skull, down



to a control device implanted within the chest (fig. 1). The patient has full control of the pacemaker and can switch it on whenever an episode of immobility occurs by passing a magnet over the control device, sending an electrical waveform down the lead. This pulse of electricity sent by the pacemaker can artificially modulate the neuronal activity of its target, ultimately compensating for the lack of dopamine (Benabid et al 1993).

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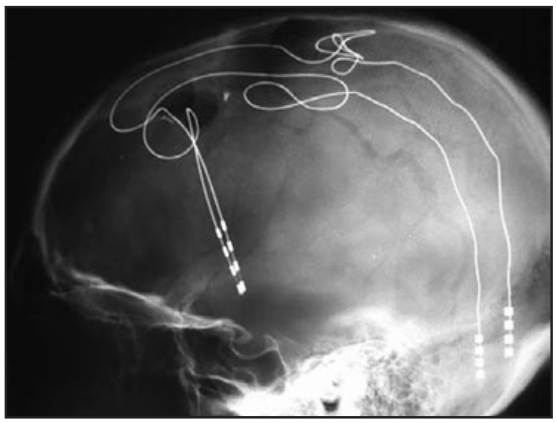
Currently, the most popular site of electrode implantation is the subthalamic nucleus (STN) (Ahlskog 2007). The STN, like the substantia nigra, is a part of the basal ganglial circuit. In simple terms, this "circuit" is a pathway composed of discrete clusters of neurons, each modulating the activity of its successors in the circuit. The net sum of this circuit affects a part of the brain called the motor cortex, which is responsible in planning and executing voluntary movements. Despite the growing popularity of DBS, researchers have yet to come to a consensus on its exact mechanism. However, a variety of explanations have been given as to exactly why electrical pulses affect this pathway from reducing the STN's inhibition of an excitatory pathway, to increasing the "regularity" of neuronal firing (Hashimoto et al 2001), to cutting down on signal noise of the basal ganglia's output (Montgomery et al 2008).

Despite the many unanswered questions about the mechanism of DBS, its ability to hinder the crippling symptoms of PD has been well established. Furthermore, as a therapy, DBS has several advantages over traditional surgical treatments for PD. Firstly, DBS is modifiable, with the patient fully in control of activating and deactivating the device, depending on the severity of their symptoms at any given time. For most commercially available neurostimulators, this on-off switching of the power unit is accomplished by passing a magnet over the imbedded device in the chest (Medtronic 2008). Thus the patient can activate the pacemaker whenever experiencing a period of severe symptom onset. In comparison, traditional surgical procedures used to treat PD require the permanently killing the neurons of the STN with a heated probe, and once completed is irreversible (Song 2006). Secondly, the parameters of the electrical waveform can be tweaked, with adjustable voltage, frequency, and pulse width (Sydow 2008). This "fine-tuning" of the pacemaker allows for greater specificity to suit the idiosyncrasies of each patient.

The greatest benefit of DBS therapy is the ability of the patient to control the onset and duration of the treatment. This flexibility did not exist in previous therapies of PD, particularly L-DOPA. In many cases,



Savvapanman

The image above shows electrodes implanted into the brain of a Parkinson's patient.

patients on L-DOPA felt trapped by the program of medication in a vicious cycle, one that oscillated between increasingly severe side effects of the drug and the simultaneous loss of therapeutic efficacy. This feeling of helplessness, of being deprived

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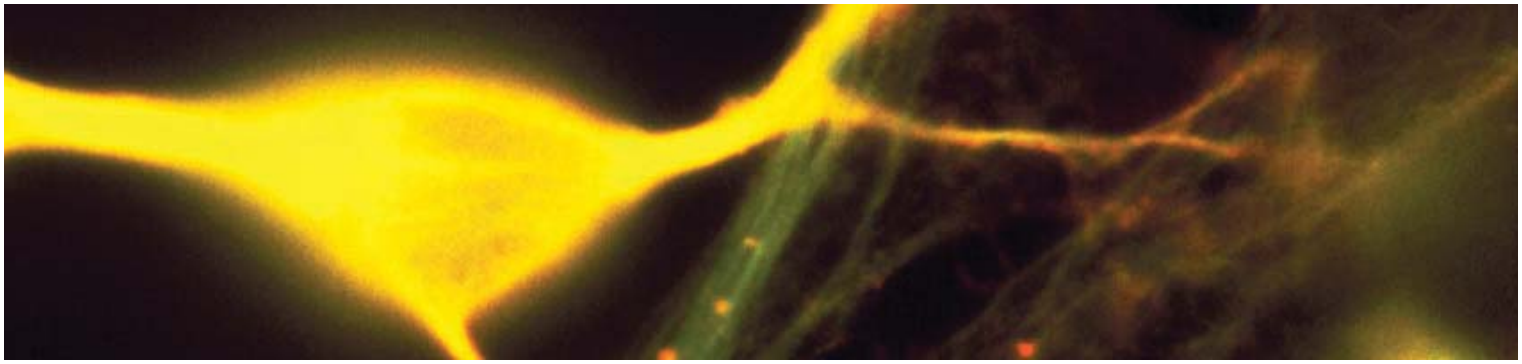
agency, is an issue DBS resolves by placing control of the pacemaker in the hands of the patient. In contrast, the L-DOPA regimen is administered regularly and independent of the onset of muscle rigidity.

Although DBS has shown much promise as a therapy for PD, it is not without its drawbacks. DBS itself has relatively few side effects, but the procedure for implantation is nonetheless an invasive brain surgery, with risk of complication that correlates with the experience of the surgical team. Furthermore, limitations presented by the hardware include the battery life of the imbedded stimulator, the migration of the electrode in the brain, and the susceptibility of the implant to electronic interference. Perhaps the greatest drawback to DBS is that it is a symptomatic treatment at best, for it cannot stop the progression of the disease and is not a cure. Because of these issues, DBS at present is relegated for only the most severe Parkinsonian patients who have become unresponsive to L-DOPA.

Despite its problems, DBS has proven to be an increasingly prevalent therapy. Not only does it free the patient from the prison of PD, but DBS also skirts the loss of efficacy and intolerable side effects of L-DOPA. With over 35,000 implant procedures preformed (Song 2006), neurostimulator implantation has the potential to supplant dopamine replacement as the treatment par excellence for PD. By offering a more flexible and adaptable response which returns agency back to the patient, DBS is a powerful new tool used in the fight against Parkinson's disease.



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