



Deep-Brain Stimulation — Entering the Era of Human Neural-Network Modulation

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Scribonius Largus, the court physician for the Roman emperor Claudius, used an electrical torpedo fish in 50 A.D. to treat headaches and gout. More than 1000 years elapsed before the idea of thera-

peutic brain stimulation was rekindled. In 1786, Luigi Galvani demonstrated that he could conduct electricity through the nerves in a frog's leg. Later, Alessandro Volta conducted electrical current through wires and built crude but effective battery sources. Yet none of these experimenters could have predicted the usefulness of their technology in treating human disease by applying an electrical current within the human brain.

This year's Lasker-DeBakey Clinical Medical Research Award, announced September 8, recognizes the contributions of two pioneers in deep-brain stimulation (DBS): Alim-Louis Benabid, a neurosurgeon, and Mahlon DeLong, a neurologist. Their research and

its translation into clinical practice have improved the lives of more than 100,000 people with Parkinson's disease or other neurologic or neuropsychiatric disorders.

Typically, people with Parkinson's disease receive the diagnosis in the sixth or seventh decade of life. Age is the most important risk factor for the disease, and it has been estimated that 1 to 2% of people older than 60 years of age are affected. The disability associated with Parkinson's disease arises from a broad spectrum of motor symptoms (masked face, soft voice, tremor, small handwriting, rigidity, bradykinesia, dystonia, balance issues, and shuffling steps) and nonmotor symptoms (depression, anxiety, apathy, dis-

ordered sleep, and cognitive difficulties), as well as problems of the autonomic nervous system (sexual dysfunction, constipation, gastrointestinal problems, and orthostatic hypotension). Of every three patients diagnosed with Parkinson's disease, one will become unemployed within 1 year, and most will be unemployed after 5 years. On average, patients with Parkinson's disease will spend \$1,000 to \$6,000 per year on medications, and their annual risk of hospitalization exceeds 30%.

Before the late 1960s, pioneers sectioned the human brain's motor pathways, and later investigators intentionally ablated many basal ganglia regions with alcohol or the application of heat; this approach met with limited success, however, partly because of inaccurate, imprecise, and inconsistent targeting. Moreover, intentionally created bilateral brain lesions frequently led to irrevers-

ible deficits in speech, swallowing, and cognition. This surgical approach faded in popularity with the discovery of levodopa (dopamine replacement).

Before levodopa's introduction, life for patients with Parkinson's disease was dreadful. Many were institutionalized. After levodopa, it became routine for patients with Parkinson's disease to "awaken" from frozen states, and nearly all were able to live at home. Tremors faded, stiffness waned, and many patients regained their ability to walk. Yet important and unexpected challenges emerged. The most worrisome were dopamine-related, medication-induced complications. Patients began to report fluctuations (doses wearing off), freezing (especially when walking), and dancelike movements (chorea), later termed levodopa-induced dyskinesia. Many reported tremors that did not respond to pharmacotherapy. In addition, there was a growing realization that levodopa was not a cure and that the disease progressed despite miraculous "awakenings."

In the early 1970s, shortly after levodopa's introduction, Mahlon DeLong began studying a complex and neglected area of the brain. By the time DeLong joined Edward Evarts' laboratory at the National Institutes of Health, all the "good stuff" (such as the motor cortex and cerebellum) had been assigned to other researchers. He was stuck with the basal ganglia. The paucity of knowledge of even the normal anatomy and physiology of this part of the brain did not deter DeLong, who published a seminal description of electrical activity patterns in primate basal ganglia neurons and a complete description of these neurons' responses to movement.

DeLong, along with Garrett

Alexander and Peter Strick, broke open research on basal ganglia and Parkinson's disease in 1986 when they introduced the segregated circuit hypothesis — the idea that the basal ganglia and associated areas of cortex and thalamus could be divided into separate territories, with little functional or anatomical crosstalk.¹ This observation seeded a new understanding of human neural networks, paving the way for electrical modulation. It also clarified that many of the symptoms of neurologic and neuropsychiatric diseases could be associated with dysfunction in specific cortical–basal ganglia brain circuits. DeLong, Hagai Bergman, and Thomas Wichmann tested this hypothesis by destroying the subthalamic nucleus in a primate model of Parkinson's disease, and they demonstrated improvement in disease symptoms.² Soon thereafter, electricity was introduced as a modulation-based approach to the brain circuits in Parkinson's disease (see Fig. 1). A French neurosurgeon, Alim-Louis Benabid, would take the courageous step of leaving a wire that could provide continuous electrical current inside a human brain.

In 1987, Benabid operated on an elderly man who had tremor. He had previously created a brain lesion to treat this tremor, but he was concerned about the potential adverse effects associated with doing the same in the other hemisphere. And so, in a second procedure, he addressed the contralateral tremor. He passed a large test probe several centimeters below the brain's surface. He knew from previous surgeries that low-frequency stimulation worsened tremor and that faster pulses suppressed it. Benabid left a neurostimulator in the man's

brain. He implanted a wire with four metal contacts at its tip. This wire, the DBS lead, was then connected to an external battery source. Benabid and colleagues programmed the device using a small box with buttons and archaic-looking switches. As simple as the system was, it turned out to be very powerful, allowing Benabid and Pierre Pollack to individualize the settings; the results are described in several seminal articles.^{3,4}

Although the biology and mechanisms underpinning DBS therapy remain unclear, we now know that normal human brain function is largely mediated through rhythmic oscillations that continuously repeat. These oscillations can change and modulate, ultimately affecting cognitive, behavioral, and motor function. If an oscillation goes bad, it can cause a disabling tremor or other symptom of Parkinson's disease. Rogue brain circuits stuck in states of abnormal oscillation in many diseases have become candidates for DBS therapy. Changes in neurophysiology, neurochemistry, neurovascular structures, and neurogenesis may also underpin the benefits of DBS therapy.⁵

Before therapeutic DBS was developed, neurologists, neurosurgeons, psychiatrists, and rehabilitation therapists labored largely in isolation from one another when treating patients with Parkinson's disease. DBS therapy's success spurred the formation of multidisciplinary teams, whose members evaluate candidates for DBS and together personalize the therapy. This personalization includes selecting, on the basis of symptoms, the brain regions to target and planning preoperative and postoperative care. Although DBS teams typically have many members, I believe the most impor-

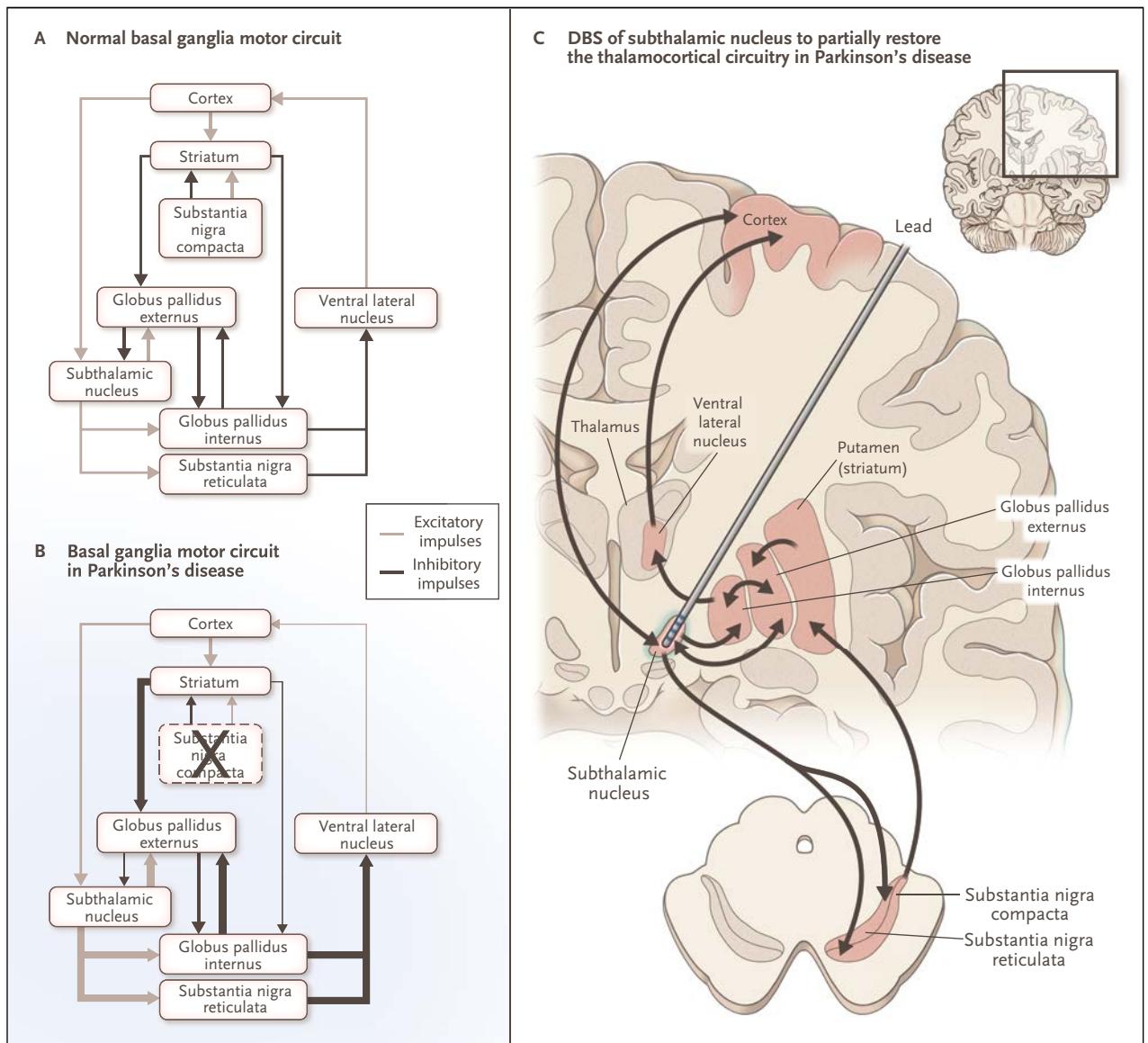


Figure 1. The DeLong “Box” Models of Basal Ganglia Circuitry and Their Use in Guiding Deep-Brain Stimulation (DBS).

Panel A shows the group of brain circuits called the basal ganglia as they behave in the normal condition. Dark arrows indicate inhibitory activity, and lighter arrows excitatory activity. Panel B shows how the circuits change as a result of Parkinson's disease. When the substantia nigra degenerates, the physiological output is changed across the entire circuit. There are particular changes in the rate and pattern of cellular activity in the globus pallidus internus and substantia nigra reticulata that lead to inhibition of the thalamus and the cortex. Thicker lines indicate increases in activity, and thinner lines decreases. Mahlon DeLong devised this box model by recording electrical activity from various brain regions and showed that he could improve Parkinson's disease symptoms by making lesions in particular areas of circuitry. Panel C shows how basal ganglia circuitry can be altered by the insertion of a DBS lead into the subthalamic nucleus. Areas referred to in Panels A and B are shaded in red. Electrical stimuli convert the physiology in the box model to restore the output from the thalamus to the cortex, approximating that of normal basal ganglia.

tant element for success has been the partnership between neurologist and neurosurgeon. It is therefore fitting that the Lasker Award for DBS therapy has been given to a neurologist and a neurosurgeon.

Smaller, sleeker, more energy-

efficient units are on the horizon. Better lead designs will permit more precise current delivery. Real-time monitoring of the neural-circuit physiology is driving the field toward smarter technologies. Remote monitoring and ad-

justment of devices may become possible. In its current form, however, the technology has several limitations. Current can spread into unintended brain regions, causing side effects, and DBS usually doesn't effectively

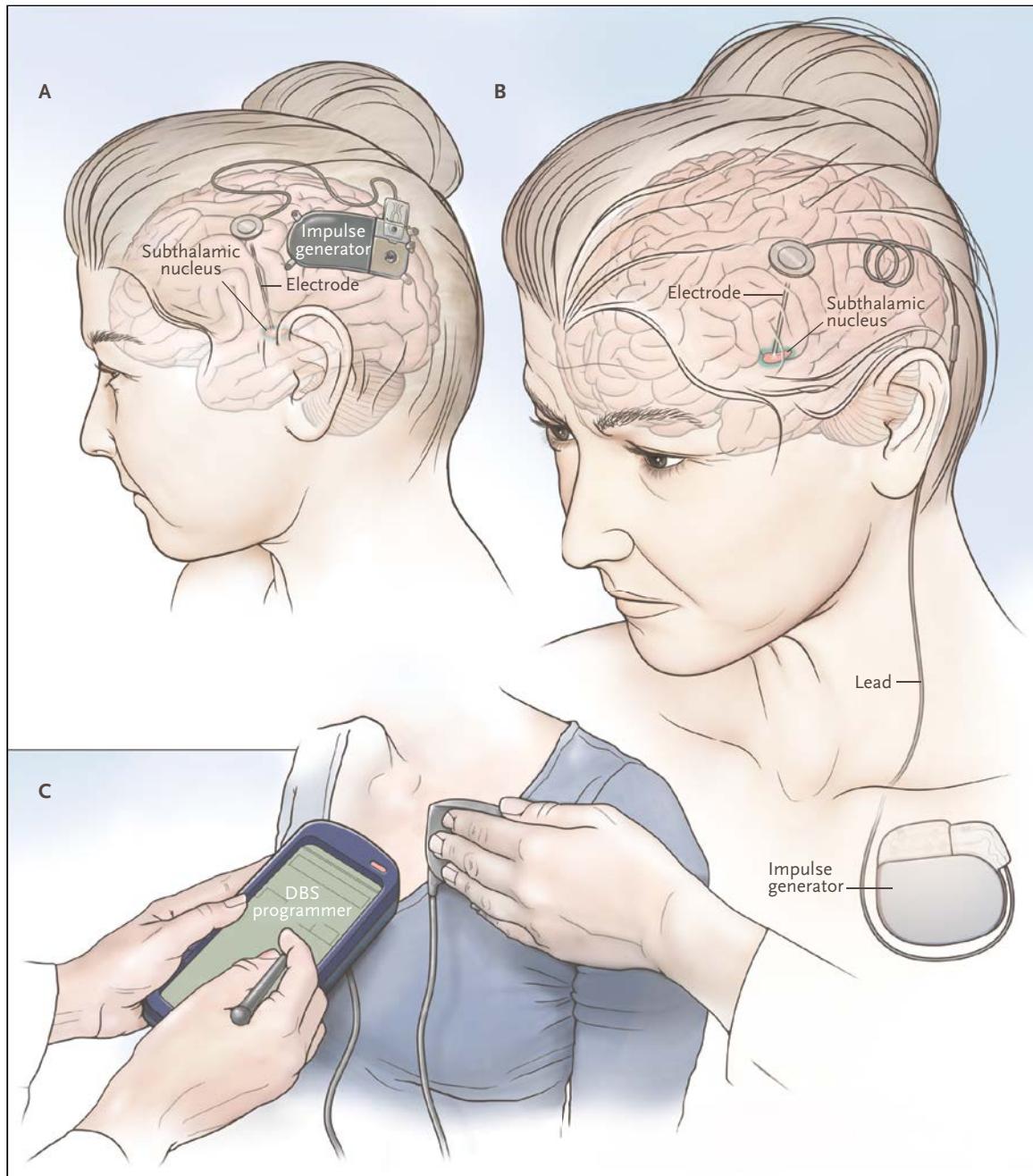


Figure 2. Devices for DBS.

Panel A shows a DBS lead with its neurostimulator (battery source) located on the skull, reducing the risk of fracture and possibly of infections. Panel B shows a patient with a DBS lead implanted in the brain and connected through an extension cable to a neurostimulator located in the chest below the clavicle. Panel C shows how a clinician at the bedside changes the DBS settings using a programming device held over the neurostimulator.

treat all symptoms. Most commonly, the battery source for neurostimulators has been placed in the subclavicular region (see Fig. 2), but this configuration has

been associated with high risks of lead fracture and infection.

Nevertheless, DBS has had an enormous effect on the treatment of Parkinson's disease. It has also

been used to treat essential tremor, dystonia, and epilepsy and in experimental treatments of obsessive-compulsive disorder, depression, Alzheimer's disease, and



An interactive graphic is available at NEJM.org.

Tourette's syndrome (see interactive graphic, available with the full text of this article at NEJM.org). DBS therapy is usually considered only after all other treatments have been exhausted, but becoming "bionic" has provided many patients with a new lease on life. Thanks in large part to the contributions of two extraordinary scientists, we have entered the era of human neural-network modulation.

Disclosure forms provided by the author are available with the full text of this article at NEJM.org.

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2009 H1N1 Influenza and Pregnancy — 5 Years Later

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In April 2009, a novel influenza A virus, now referred to as influenza A(H1N1)pdm09 virus (2009 H1N1), was identified in two children in California, and shortly thereafter, the second U.S. death associated with 2009 H1N1 occurred in a previously healthy pregnant woman. The virus spread rapidly throughout the United States and the world, and on June 11, 2009, the World Health Organization raised the global pandemic alert to 6, its highest level. Five years have now passed since that pandemic, and in that time, much has been learned about influenza's effects on pregnant women and infants. Nevertheless, cases of severe influenza illness, hospitalizations, and deaths among young and middle-aged adults, including pregnant women, were reported during the 2013–2014 influenza season, when 2009 H1N1 was again the predominant circulating influenza virus in the United States.¹ These severe outcomes among pregnant women prompted us to review lessons learned

from the pandemic and ways of reducing influenza's effects during pregnancy in future influenza seasons.

Although data were available before the 2009 pandemic suggesting that pregnant women were at increased risk for influenza-associated complications, the pandemic provided solid data on this vulnerability.² Pregnant women with 2009 H1N1 influenza were at substantially higher risk for hospitalization than the general population, and they accounted for approximately 5% of deaths from 2009 H1N1 influenza that were reported to the Centers for Disease Control and Prevention (CDC), even though pregnant women make up only about 1% of the population. Moreover, the 2009 pandemic virus was also bad for babies: infants born to women who had been severely ill with influenza complications had increased risk for adverse outcomes such as preterm birth or small size for gestational age.²

The 2009 H1N1 pandemic brought a change in our approach

to treating influenza in pregnancy. Previously, pregnant women with influenza had been treated primarily if they had other high-risk medical conditions or severe disease. During the 2009 pandemic, however, the CDC recommended that empirical antiviral therapy be initiated as soon as possible during the clinical course if the patient was pregnant or had recently delivered. This represented a significant shift in antiviral treatment guidance: it was recommended that pregnant women with suspected 2009 H1N1 influenza receive prompt antiviral therapy, regardless of risk factors, severity of illness, history, or the results of diagnostic testing.²

Before the pandemic, we had little information on the benefits of treating pregnant women with an antiviral medication, since pregnant women had been excluded from clinical trials of these medications. During the pandemic, we learned that treating pregnant women with such a medication makes a difference.