Discovery of High-Frequency Deep Brain Stimulation for Treatment of Parkinson Disease 2014 Lasker Award

The 2014 Lasker-DeBakey Clinical Medical Research Award has been presented to Mahlon Delong, MD, and Alim-Louis Benabid, MD, PhD, to recognize and honor them for their outstanding work in the development of high-frequency deep brain stimulation of the subthalamic nucleus for the treatment of patients with advanced Parkinson disease. This Viewpoint provides a summary of their discoveries in understanding the role of the basal ganglia in movement, in determining the neurophysiology of Parkinson disease, and in the development of deep brain stimulation.

Early research by Delong was focused on the basal ganglia, a grouping of interconnected nuclei deep in the cerebral hemispheres. Although the functions of the basal ganglia were obscure, severe disturbances of voluntary and involuntary movements observed in patients with diseases affecting the basal ganglia (such as Parkinson, Huntington, and Wilson diseases) clearly suggested a prominent role of the basal ganglia in movement. Accordingly, Delong’s early studies of single cell recording in primates were focused on the role of the basal ganglia in movement. Attention was directed to the major output nucleus of the basal ganglia, the internal segment of the globus pallidus (GPI), because it was thought that neuronal activity, studied during different movement tasks, would most clearly reflect the overall contributions of the basal ganglia to movement. The output from the GPI was known to be inhibitory and thought to both facilitate and inhibit movement by appropriate increases and decreases of discharge in ensembles of individual neurons. Movement-related neurons were found throughout the basal ganglia in a specific network that Delong and colleagues designated as the “motor circuit,” which they found functioned in parallel with other basal ganglia circuits implicated in cognitive, emotional, and reward functions.

Although the loss of dopamine and its replacement with its precursor, levodopa, in the mid-1960s was found to be highly successful in treating the cardinal features of parkinsonism (slowness of movement, tremor, and muscular rigidity), the subsequent emergence of troublesome drug-induced adverse effects, in particular involuntary movements (dyskinesias) and motor fluctuations, limited its use in a significant number of patients. Better treatments were needed. It was important to explore the role of the basal ganglia circuitry responsible for Parkinson disease and chorea, in hope of learning more about their physiological basis and providing new insights into possible therapeutic interventions.

Together with colleagues, Delong examined the activity of neurons in the striatum and subthalamic nucleus, basal ganglia nuclei that both received cortical input and provided inhibitory and excitatory influences, respectively, on the output nucleus. It was well known that lesions of the subthalamic nucleus in both humans and experimental animals resulted in pronounced involuntary movements (ballismus or chorea) of the contralateral limbs, whereas depletion of dopamine in the striatum was known to cause Parkinsonism.

The introduction of a new primate model of Parkinson disease in the early 1980s using the neurotoxin 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) was a major breakthrough in Parkinson research because MPTP specifically damaged dopamine neurons in the substantia nigra and mimicked the motor features as well as the biochemistry and pathology of Parkinson disease. In initial studies in the MPTP-treated primate model, neuronal activity was found to be clearly increased and abnormally patterned in both the GPI and subthalamic nucleus, which supported the emerging circuit model, based on anatomical, neurophysiological, and metabolic imaging studies, whereby Parkinson disease resulted from increased output from the basal ganglia, which would inhibit movement and produce bradykinesia by its inhibitory effect on targeted thalamic and brainstem nuclei. The increased output from the basal ganglia in Parkinson disease was proposed to result from increased excitatory drive from the subthalamic nucleus. By contrast, a lesion in the subthalamic nucleus in primates that caused chorea was found to result in a decrease of basal ganglia output. These contrasting findings in the animal models of chorea and Parkinson disease indicated that a lesion of the subthalamic nucleus in the MPTP model of Parkinson disease would provide a direct test of the hypothesis that Parkinsonism was due to an increased excitatory drive on GPI from the subthalamic nucleus.

To test the hypothesis, Delong and his team lesioned the subthalamic nucleus in the MPTP primate model of Parkinson disease by injecting a neurotoxin directly into the subthalamic nucleus that destroyed cells while sparing fibers of passage. Within minutes there was a clear and dramatic improvement in motility and a reduction of rigidity and tremor in the contralateral limbs. As predicted by the model, transient chorea was observed in the contralateral limbs but with no disruption of voluntary movement. The publication of these findings in 1990 highlighted the key role of the subthalamic nucleus in Parkinson disease, further supporting the circuit model. Most important, however, it provided a clear rationale and potential novel target for the surgical treatment of Parkinson disease, which provided similar benefits as levodopa.

However, the study also raised concerns regarding the potential return to functional surgery, with its draw-
backs of hemorrhage and permanent deficits. DeLong's group, like others, chose to return to the radiofrequency-lesioning approach, targeting GPi (pallidotomy), which had gained favor in the early part of the previous era of functional stereotactic surgery, but had been later largely abandoned except by a few neurosurgeons. Pallidotomy improved parkinsonism and had added value as well, in that it was effective in reducing levodopa-induced dyskinasias and motor fluctuations. Moreover, with an increased understanding of the critical target within the GPi, it was possible to obtain more predictable and effective benefits with pallidotomy, but at the ever-present risk of permanent irreversible complications of radiofrequency lesioning.

Neurosurgeons were striving for less invasive methods because they knew that ablative procedures were irreversible, their size was difficult to control, and they were too often associated with adverse effects or even deficits, sometimes persistent, and particularly when they were performed bilaterally. In particular, ablative procedures of the subthalamic nucleus were not undertaken largely because of the risk of persistent chorea.

The key development was the application of the discovery of a far less invasive and reversible means of surgically targeting and modulating brain structures by Benabid. In 1987, Benabid and his team observed, serendipitously, the paradoxical inhibitory effect of electrical high-frequency (>100 Hz) stimulation (HFS) during a routine radiofrequency lesion (thalatomy) in the thalamic target ventrallis intermedius to treat a patient with essential tremor. While testing for adverse effects (dysesthesias or muscular contractions) in the thalamus prior to making a lesion, Benabid and colleagues unexpectedly observed that the patient’s tremor, although unaltered when electrically stimulated between 30 and 50 Hz, could be abruptly and reversibly stopped when stimulated at 100 Hz. This was successfully reproduced in a number of patients.

Benabid and his team felt that they might have found a way to achieve the same effects as lesioning, but more safely and reversibly, if they implanted an electrode for long-term HFS in the thalamic target. Part of the equipment needed to test long-term HFS in patients was commercially available. When patients with intractable tremor, both essential tremor and parkinsonian tremor, were then offered the new treatment in place of conventional thalatomy, the results were most encouraging and well received by movement disorder neurologists and neurosurgeons. Although HFS of the thalamus produced similar results as thalatomy, it proved to be a more efficient and stable approach, with low morbidity even when performed bilaterally. The benefit, however, for patients with Parkinson disease was largely for tremor and had little or no benefit for akinesia or rigidity. Logically, the procedure was also subsequently extended to other targets previously used with ablative lesions, such as pallidotomy in the GPi. Similarly, HFS of the ventralis intermedius was subsequently successfully applied to other indications for thalamotomy, such as dystonia, and tardive dyskinesias.

The mechanism of action of HFS was not easily understood. Because of the similar clinical effects of lesioning and HFS, it was at first thought of as simply reversibly inhibiting the nucleus. The Benabid’s team initially suggested that HFS could be a form of “jamming.” Introducing continuous HFS would cancel or override the abnormal activity in the stimulated target, the involved network could no longer lock on it, and the periodic behavior (tremor) would stop.

Nevertheless, the low morbidity and reversibility of HFS made it the method of choice to safely investigate new hypotheses and targets. In 1990, after the report by DeLong and colleagues that lesioning of the subthalamic nucleus in the MPTP primate model of Parkinson disease alleviated parkinsonian symptoms, Benabid and his team, based on their 6-year experience of thalamic HFS in various indications, decided to undertake the first clinical trial of HFS in 1993 for patients with advanced Parkinson disease. They successfully demonstrated the same beneficial results as in the animal model without inducing hemiballism or other complications. Importantly, it was found that HFS of the subthalamic nucleus not only relieved the symptoms of tremor, rigidity, and akinesia, but also largely eliminated the disruptive drug-induced effects of involuntary movements and motor fluctuations, which are the most important indications for deep brain stimulation of the subthalamic nucleus.

The benefits of deep brain stimulation have subsequently been shown in clinical trials to persist for years and to improve motor function and quality of life and provide better results than best medical therapy. High-frequency stimulation is a purely symptomatic therapy, and so far no curative or disease modifying effects have been observed, although this is an area of active investigation. This “new area of therapy” is considered as the second major breakthrough for Parkinson disease following the discovery of levodopa.

The current broad panel of targets available for HFS (thalamus, GPi, internal capsule, subthalamic nucleus, nucleus accumbens, pedunculopontine nucleus, anterior and posterior nuclei of the hypothalamus, and others under investigation) provide potential new treatments for numerous neurological disorders (tardive dyskinesias, cluster headaches, Tourette syndrome, epilepsy, and obesity) and has helped to revive psychosurgery (obsessive-compulsive disorders, depression, anorexia, Alzheimer disease, and addictions). Clearly, the introduction of deep brain HFS delivered in the subthalamic nucleus is a unique example of the richness of combining methodological development and progress in basic neurosciences.