Profile of Mahlon DeLong and Alim Benabid, 2014 Lasker-DeBakey Medical Research Awardees

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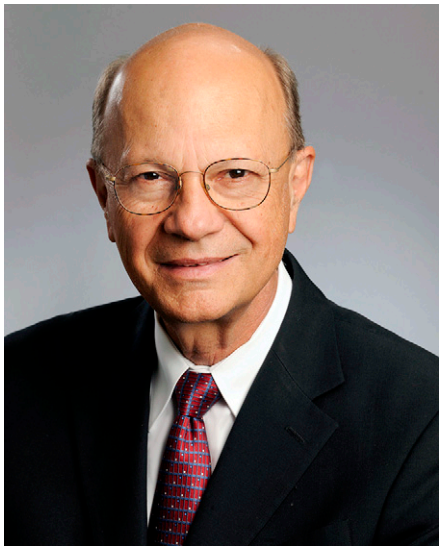
Mahlon DeLong and Alim Benabid are the recipients of the 2014 Lasker Award for their work leading to the development of deep brain stimulation as a treatment for Parkinson's disease (PD). Their work is a tribute to how experimental laboratory research can lead to the development of new therapies for neurological diseases.

PD affects ~1 million persons in North America and 5 million persons worldwide. It is clinically characterized by slowness of movement, rest tremor, rigidity, gait impairment, and postural disturbance, and pathologically characterized by degeneration of neurons in the substantia nigra pars compacta (SNc) with a reduction in the neurotransmitter dopamine. Treatment is primarily based on a dopamine replacement strategy using the dopamine precursor levodopa (for which Georges Cotzias received the 1969 Lasker award). Over the last 50 years, levodopa has benefited millions of patients with PD and it remains the gold standard. However, chronic treatment is complicated by the development of motor complications (fluctuations in motor response and involuntary movements known as dyskinesias) in the majority of cases. These limit the benefit of the drug and can represent a source of severe disability. The search for a satisfactory treatment for levodopa-induced motor complications that does not compromise motor control has been a major goal of PD research.



Mahlon DeLong. Image courtesy of The Albert and Mary Lasker Foundation.

Mahlon DeLong is a neurologist and neurophysiologist working at Emory University and formerly at Johns Hopkins University. His research focused on understanding the organization of the basal ganglia and determining how it is altered in PD. The basal ganglia is comprised of a group of subcortical nuclei that includes the striatum, the globus pallidus pars externa (GPe), the globus pallidus pars interna (GPi), the subthalamic nucleus (STN), the substantia nigra pars reticulate (SNr), and the SNc. Collectively, they form a complex network that facilitates the selection and execution of normal movement while inhibiting unwanted ones. Using neurophysiologic techniques (i.e., recording of neurons' electrical activity), Dr. DeLong demonstrated that motor regions in the basal ganglia form reciprocal connections with motor regions in the cerebral cortex with the striatum representing the major input region of the basal ganglia and the GPi/SNr the major output region (1). He then explored the connections within the basal ganglia and demonstrated the somatotopic organization of the striatum, GPi, and STN and their functional connections (1). Based on these observations and work performed by other investigators using anatomic, molecular, and autoradiographic techniques (2, 3), he developed the concept that the striatum and pallidum are connected by two pathways: the direct and indirect striato-pallidal pathways (Fig. 1*A*), which have opposite effects on pallidal output neurons (2). The GABAergic neurons in the direct pathway have an inhibitory effect, whereas the indirect pathway provides excitatory effects by way of glutamatergic neurons in the STN. Dopamine modulates this basal ganglia network by having an excitatory effect on D1 bearing neurons in the inhibitory direct pathway and by having an inhibitory effect via its actions on D2 bearing neurons in the excitatory indirect pathway. Based on the model, DeLong hypothesized that dopamine depletion would result in reduced excitation of direct pathway neurons and increased excitation of neurons in the indirect pathway, leading to increased firing of pallidal GABAergic output neurons. This in turn would cause excessive inhibition of the thalamus, reduced activation of motor regions in the cerebral cortex, and the development of parkinsonian features (Fig. 1*B*). Critically important in this regard, he was

Alim-Louis Benabid. Image courtesy of Pierre Jayet.

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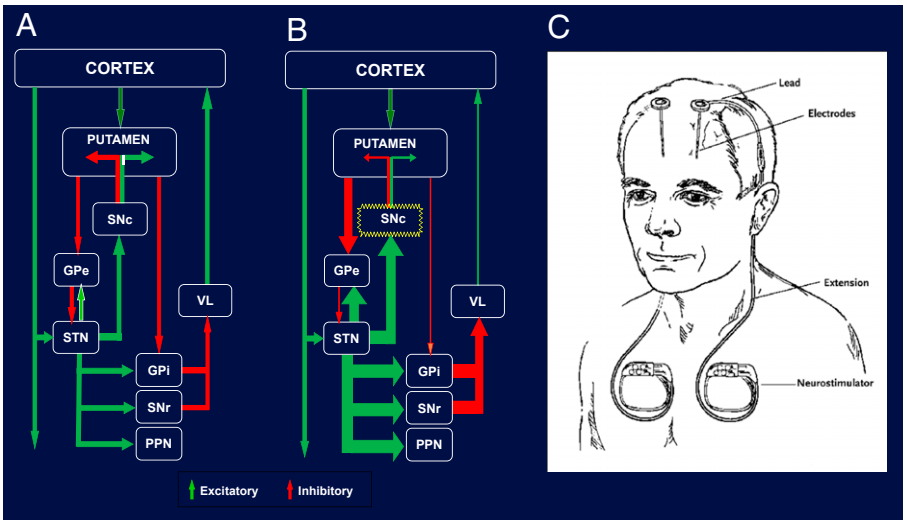

Fig. 1. (*A*) Schematic illustration of the basal ganglia-thalamic-cortica-basal ganglia connections in the normal condition according to the model proposed by DeLong. The model illustrates the inhibitory striato-pallidal direct pathway and the excitatory indirect pathway with synaptic connections in the GPe and STN. GABAergic inhibitory connections are represented in red and gluatamatergic excitatory fibers in green. Modified from ref. 19. (*B*) Schematic representation of the basal ganglia-thalamic-cortica-basal ganglia connections in the parkinsonian state. Note that a dopamine lesion results in reduced excitation of the direct pathway and reduced inhibition of neurons in the indirect pathway, resulting in disinhibition of the STN s and increased firing of neurons in the GPi/SNr. This in turn leads to excessive inhibition of the thalamus and decreased activation of cortical motor regions, resulting in parkinsonian motor features. This concept led to the suggestion that lesions in the STN or GPi might provide anti-parkinsonian benefits. Modified from ref. 19. (*C*) Schematic representation of the DBS system used by Benabid in the treatment of PD. An electrode is inserted into the target region and a lead is connected s.c. to a battery-driven pacemaker inserted over the chest wall. Stimulation settings including electrode configuration, voltage, and pulse width can be adjusted to optimize benefit and minimize side effects. Figure courtesy of Medtronics, Inc.

able to demonstrate that parkinsonian features were associated with increased neuronal firing in the STN (4) and that lesions in the sensory-motor regions of the STN (5) led to a reduction in excessive GPi neuronal activity in parkinsonian animals and marked motor improvement (6).

This experimental work suggested that the motor regions of the GPi or STN might be good targets for treating patients with PD. Lesions of the GPi (pallidotomy) had been historically used as a treatment for PD, but largely disappeared following the introduction of levodopa. Based on his experimental work, DeLong and others developed a renewed interest in pallidotomy. They specifically targeted the sensory-motor region of the GPi and reported improvement in contralateral parkinsonian features following unilateral pallidotomy (7, 8), with restored activation of cortical motor areas (9). Interestingly, dramatic improvement was also seen in contralateral dyskinesia, although this was not predicted by the proposed model (the model predicts that a lesion of the GPi would reduce pallidal output, disinhibit the thalamus, increase cortical excitation, and cause rather than ameliorate dyskinesia). It is now thought that the antidyskinesia effect of pallidotomy likely result from disruption of an abnormal firing pattern in pallidal neurons that is not entirely frequency dependent (10).

Although unilateral pallidotomy provides contralateral benefits, PD is a bilateral disease, and bilateral lesions are associated with potentially serious side effects including dysphagia, dysarthria, and cognitive impairment. Most physicians are therefore reluctant to perform bilateral lesion procedures. Further, although the STN is the preferred target based on anatomo-physiological considerations, lesioning the STN is potentially associated with a severe form of dyskinesia known as hemiballismus and, therefore, subthalamotomy is not commonly undertaken.

Alim Benabid is a French neurosurgeon who works at the Joseph Fourier University in Grenoble, France. His research focused on stereotactic neurosurgery to treat diseases such as PD. Two decades ago, brief pulses of electrical stimulation were routinely delivered to a proposed target to determine whether the electrode was correctly placed before performing a lesion. Benabid observed that high-frequency stimulation of the ventro-intermediate (Vim) nucleus of the thalamus was associated with a dramatic improvement in tremor, which reversed when the stimulation was discontinued. He reasoned that if short bursts of high-frequency stimulation could simulate the benefits associated with a lesion, then long-lasting benefits might be achieved by providing continuous high frequency stimulation without the need to make a lesion at all. To accomplish this, he used deep brain stimulation (DBS), a procedure where microelectrode recordings are used to identify the desired target, a lead with multiple electrodes is placed into the target, and the lead is connected to a permanent pacemaker implanted s.c. over the chest wall (Fig. 1*C*). The advantages of DBS include the opportunity to (*i*) obtain a desired effect without making a lesion, (*ii*) optimize clinical benefit and reduce side effects by adjusting the stimulator settings (electrode configuration, voltage, pulse duration) at any time, (*iii*) turn off the stimulator completely in the case of stimulation-related serious adverse events, (*iv*) perform surgery bilaterally with relative safety, and (*v*) target the STN without fear of hemiballismus.

In his first set of clinical experiments, he performed the DBS procedure targeting the Vim nucleus of the thalamus in a patient with a severe bilateral tremor. The patient had previously undergone a unilateral thalamotomy and required a procedure on the other side, which entailed the risks associated with bilateral lesions. Dramatic improvement was obtained following stimulation, with no adverse effects (11). He subsequently performed DBS of the Vim as the initial procedure for patients with a severe tremor, thereby avoiding the need to make a lesion at all, and obtained long-term antitremor benefits with no serious adverse events (12).

The next challenge was to tackle PD, where tremor is a feature, but disability is more related to rigidity and bradykinesia. Based on the work of DeLong and a series of experiments by other groups in the MPTP monkey model, Benabid knew that neurons in the STN were overactive in the dopamine-depleted PD state and that blocking this excessive activity with structural or chemical lesions improved all parkinsonian features in the monkey model. Importantly, studies of DBS in the MPTP monkey targeting the STN were also associated with marked and persistent motor improvement (13). Based on these observations, Benabid and colleagues studied DBS-STN in PD patients. He used microelectrode recording techniques to define the sensory-motor region of the STN and demonstrated that this treatment provided dramatic benefits for the major motor features of PD (14). Importantly, dramatic benefits were also observed for both motor fluctuations and dyskinesias (14). Similar results were subsequently observed with

DBS of the GPi. These benefits have now been confirmed in large-scale double-blind controlled studies (15, 16) and in a randomized trial comparing DBS to best medical therapy (17).

DBS of the STN or GPi is now routinely used for the treatment of levodopa-induced motor complications or severe tremor in patients with PD that cannot be controlled with medical therapy. The precise mechanism of action of DBS has not been fully elucidated; possible explanations include depolarization blockade, activation of inhibitory circuits, retrograde cortical activation, and jamming of abnormal signals. DBS is not without side effects; these can be associated with the surgical procedure, the hardware, or the stimulation itself. Importantly, however, the side effects associated with bilateral lesions are largely avoided, and it is estimated that more than 100,000 persons with PD have benefited from this procedure. Indeed, there is now some evidence suggesting the potential value of performing DBS an earlier stage of the disease when motor complications first begin (18). DBS of the GPi has also been established to be an effective treatment for dystonia, and other DBS targets are currently being investigated as a possible treatment for many other disorders including gait disorders, depression, Tourette syndrome, and obsessive compulsive disorder.

Obviously many individuals have contributed to the success of this story that has benefited so many patients. However, much of the credit must go to the work of Mahlon DeLong who helped to define the STN and GPi as rational targets for a PD surgical therapy and to Alim Benabid who developed the DBS procedure for PD, allowing the STN to be targeted and bilateral procedures to be performed with relative safely. The late David Marsden once commented that he had seen two miracles in his professional career: levodopa and DBS. It is only fitting that the authors of each of these great achievements have been awarded with the Lasker Award.

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