Understanding Parkinson's disease and deep brain stimulation: Role of monkey models

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Parkinson's disease (PD) is a progressive neurodegenerative movement disorder affecting over 10 million people worldwide. In the 1930s and 1940s, there was little understanding regarding what caused PD or how to treat it. In a desperate attempt to improve patients' lives different regions of the neuraxis were ablated. Morbidity and mortality were common, but some patients' motor signs improved with lesions involving the basal ganglia or thalamus. With the discovery of L-dopa, the advent of medical therapy began and surgical approaches became less frequent. It soon became apparent, however, that medical therapy was associated with side effects in the form of drug-induced dyskinesia and motor fluctuations and surgical therapies reemerged. Fortunately, during this time studies in monkeys had begun to lay the groundwork to understand the functional organization of the basal ganglia, and with the discovery of the neurotoxin MPTP, a monkey model of PD had been developed. Using this model, scientists were characterizing the physiological changes that occurred in the basal ganglia in PD and models of basal ganglia function and dysfunction were proposed. This work provided the rationale for the return of pallidotomy, and subsequently deep brain stimulation procedures. In this paper we describe the evolution of these monkey studies, how they provided a greater understanding of the pathophysiology underlying the development of PD and provided the rationale for surgical procedures, the search to understand mechanisms of DBS, and how these studies have been instrumental in understanding PD and advancing the development of surgical therapies for its treatment.

Parkinson's disease | deep brain stimulation | MPTP | nonhuman primate | basal ganglia

Parkinson's disease (PD) affects over 1 million people in the United States and over 10 million worldwide. Its cardinal motor signs are tremor, bradykinesia, rigidity, and gait and balance disorders. These exist in various combinations across patients and progress in severity over time. Other features of the disease may present at diagnosis or occur at later stages of the disease and include various combinations of nonmotor signs such as impaired sense of smell, constipation, orofacial dyskinesia, freezing of gait, and sleep dysfunction. PD was first described by James Parkinson in 1817 in *An Essay on the Shaking Palsy* (1). At that time patients had little recourse for therapy. As symptoms progressed, patients and physicians searched for a treatment, and many became desperate for some form of therapy to give them relief from their symptoms. This sense of despair led to early surgical interventions where different portions of the neuraxis were destroyed in an attempt to improve motor signs. Bucy and Case (2) and Klemme (3) lesioned the cortex and Brodwe (4) the internal capsule, while others such as Meyers (5), Spiegel et al. (6) and Spiegel and Wycis (7), Fenelon (8), Guiot and Brion (9), and Cooper (10) made lesions in regions of the thalamus and basal ganglia. Still others destroyed portions of the peduncle (11) or spinal cord (12) or ablated the posterior nerve roots (13). Many patients died while others suffered serious morbidity; however, a few improved. Those who improved were those where lesions were placed in the thalamus or basal ganglia.

The problems of the day were severalfold: There was no rationale for target selection and no understanding of the pathophysiological basis for PD motor signs, and even if one could identify a precise location in the basal ganglia or thalamus that mediated these motor signs there was no methodological approach that could consistently get the surgeons to that location. This led to the development of the stereotactic frame by Speigel and Wycis (14). Early versions of the stereotactic frame, used for patients with pain, movement disorders, and psychiatric conditions, however, were not as successful as hoped and patients continued to suffer from inconsistent benefits and significant morbidity. In the 1950s Swedish neurosurgeon Lars Leksell began a series of pallidotomies in PD patients, gradually moving his lesion location from the anterior to the anterodorsal part of the pallidum, the traditional target area at the time, to the posteroventral portion. Svensson et al. (15), in a systematic review of Leksell's 81 pallidotomy cases, reported marked improvement in the cardinal motor signs of PD in his last 19 of 20 patients who received lesions targeted to the posteroventral portion of the pallidum. This region of the pallidum would later be determined through anatomical and physiological studies in monkeys to form the sensorimotor region of the pallidum (16).

Although pallidotomy had demonstrated some success in the 1950s, with the discovery of L-dopa patients were significantly improved without the associated risk of lesion surgery, motor signs were greatly attenuated, and in the 1960s the advent of medical therapy began (17, 18). Although the thinking at the time was that a problem had been solved, it soon became apparent that chronic use of L-dopa leads to its own set of problems in the form of dyskinesia, motor fluctuations, wearing off, and cognitive side effects. Drugs “holidays” were implemented in some, which gave modest improvement but were risky and painful for the patient and benefits were short-lived.

The development of motor complications associated with L-dopa led to the rekindling of surgical therapy in the 1980s, and a report of the benefit of pallidotomy by Laflaîne et al. (19) was published in 1992. There was a difference now, however, between what was known about the anatomy and physiology of this region...
the state of understanding at the time of early surgical interventions. A monkey model of PD had been developed and an immense amount of knowledge regarding the anatomy and physiology of the basal ganglia and related pathways had provided a greater understanding of the pathophysiology of PD. In addition, new technology in the form of imaging and more accurate stereotactic frames and atlases had been developed. An advent of surgical therapy for PD had now begun once again, driven in large part by the many years of foundational work dedicated to understanding the functional organization of basal ganglia–thalamocortical (BGTC) circuitry in monkeys.

**Functional Anatomy of the BGTC Circuit and the MPTP Monkey Model of PD**

From the time of early surgical therapies reported in the 1930s, where little was understood regarding anatomical organization and functional connectivity of BGTC circuitry, by the 1990s a mass of research on the BGTC network led to models describing the functional anatomy of the basal ganglia. Drawing upon years of anatomy and electrophysiology studies in monkeys beginning with a seminal study by Mahlon DeLong in 1971 (20) regarding the role of the pallidum in movement, in 1986 Alexander et al. (16) described the basal ganglia in terms of several functionally segregated BGTC circuits. These consisted of motor, oculomotor, associative, and limbic circuits each originating from separate cortical regions projecting to different regions of the striatum, pallidum, and thalamus while returning to the cortical areas from which they took origin. From these models of the intrinsic circuitry of the basal ganglia were developed and the concept of direct and indirect pathways with excitatory and inhibitory connections was established (21, 22).

Subsequent tracer studies further defined motor subcircuits (23) and the hyperdirect pathway, a direct projection from the cortex to the subthalamic nucleus (STN) (24, 25). Although this model of the intrinsic circuitry of the basal ganglia developed from studies in monkeys permitted the development of hypotheses regarding the changes that would be predicted in a dopamine-depleted state such as PD, there was little confirmation of these predictions given the lack of an animal model that faithfully reproduced the parkinsonian phenotype. Furthermore, electrophysiological recordings in humans had no control to compare them to. Through a serendipitous series of events that occurred in the early 1980s a series of patients were described who had suddenly developed a phenotypic picture of PD. It was later discovered that they had taken a medication, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), that contained 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), an impurity created during the synthesis of MPPP, and which is a prodrug to the potent neurotoxin 1-methyl-4-phenylpyridinium (MPP+). A batch of the synthetic opioid was obtained from "friendly" drug dealers and was noted to contain almost pure MPTP. The discovery of MPTP and the development of parkinsonism by those who had taken the drug was published in *Science* in 1983 (26), and it was immediately recognized that this compound had enormous potential to revolutionize the Parkinson's research field. From there multiple investigators worked with the drug and the development of a monkey model of PD was reported in PNAS (27) The monkey model demonstrated most of all the cardinal motor signs of PD except for tremor, including bradykinesia/akinesia, rigidity, gait and postural imbalance, freezing, and dyskinesia when given L-dopa. This was a major breakthrough as now a model of the disease was available. Whether it was a true reflection of the human disease was yet to be determined; however, subsequent recordings from the basal ganglia in humans mirrored those obtained in the MPTP monkey model (28–31). Now when combined with previous anatomical and physiological studies in monkeys a model of PD was available to begin to understand what happens in the parkinsonian state, what changes in the circuit, and whether there could be a way to modulate the abnormal activity to improve the motor signs associated with PD.

**Contributions of Research Using the MPTP Monkey Model to Understanding the Pathophysiology of PD**

Using the MPTP monkey model of PD electrophysiological recordings in the STN, globus pallidus internus (GPi) and globus pallidus externus (GPe) were performed by several groups (29, 32–34). Compared to the naive state these studies reported changes in mean discharge rate with increased rates in the STN and GPe and decreased rates in GPe as well as a loss of specificity and increased number of cells responsive to passive manipulation (29, 33). Based on these findings a “rate model” of PD was proposed in which the direct pathway, projections from the putamen to GPi, was underactive and the indirect pathway, projections from putamen to GPe, was overactive (21, 22). This model hypothesized that mean discharge rates in the STN would therefore be increased in PD, leading to excessive activation of the GPe and suppression of thalamocortical activity leading in turn to the manifestation of Parkinson’s motor signs (Fig. 1 A and B). A seminal test of this hypothesis was published in *Science* in 1990 (35).

Bergman et al. (35) performed ibotenic acid lesions in the STN in the MPTP monkey model of PD and observed marked improvement in bradykinesia/akinesia and rigidity (Fig. 1 C). The development of the MPTP monkey model of PD had led to testable hypotheses that renewed interest in and supported the role of surgical therapy for the treatment of PD. Although these findings were extremely important and replicated by other groups (36–38), surgeons were hesitant to perform subthalamotomies for PD patients given the history of patients developing hemiballismus following ischemic strokes involving this region (39, 40). History, however, had been replete with trials of pallidotomy and although inconsistent in its effect on PD motor signs there was now an understanding of the underlying pathophysiology and a rationale for GPi lesions (pallidotomy) based on these monkey studies. In
addition, results from previous studies in monkeys delineating the presence of functionally segregated circuits with motor functions localized to the posterolateral “sensorimotor” region of the GPi provided an explanation for the findings by Svennson that posterior pallidotomy for tremors were more effective than the classical anteromedial target. Moreover, by the 1990s surgeons had better means by which to get to the target given the development of more advanced imaging with MRI and improved technology with newer stereotactic frames. Thus, the revival of pallidotomy emerged, first reported by Laitinen et al. (19) in 1992 and by multiple others over the ensuing years (41–44). Despite numerous reports of success, however, there were also reported failures (45). While some reported marked improvement, others reported transient benefit. In some cases benefit was lost over days (46), while in others it wore off after several years (47, 48). Still others argued it improved some motor signs but not others (49, 50). Although muscimol studies in the MPTP monkey model had demonstrated that improvement in motor signs was dependent on inactivation of the motor region of the pallidum (51) there was debate over the mechanism underlying pallidal lesions, with some arguing that they needed to include GPi (19). This was troublesome given studies in monkeys had demonstrated that lesions in GPi could worsen PD motor signs (52). This was substantiated when a case report was published of a PD patient who had undergone GPi毁损。This worsened and lost their response to levodopa (53). Following the patient’s death, it was confirmed that the lesion had significantly involved the GPi.

During this time the number of pallidotomies grew and given PD is a progressive disorder bilateral pallidotomies were required for patients with disease affecting both sides of the body. Complications with bilateral pallidotomy, however, were too frequent, with some reporting cognitive changes, gait disorders, worsening PD, and/or hypophonia (54–57). An alternative approach was needed, and deep brain stimulation (DBS) for PD, developed by Alim Louis Benabid, was brought to the operating room (58).

**DBS and the Role of Monkey Research**

Prior to lesioning a subcortical structure, a surgeon would pass a small amount of electrical current to assess whether or not there was an effect on the symptoms to be treated. This was true for patients with tremor undergoing thalamotomy. One such surgeon, Dr. Alim-Louis Benabid, proposed developing a chronic method to apply stimulation to the target brain region and in conjunction with industry brought DBS to the forefront of surgery for PD. This evolved into the development of DBS after initial testing in the MPTP monkey model (59) and has since been considered for a variety of neurological as well as psychiatric disorders. Although DBS was demonstrated effective in alleviating the motor signs associated with PD (60), little was understood concerning its mechanism of action. With the advent of DBS and its demonstrated benefit to patients with PD, together with the fact it could be performed on both sides of the brain with few side effects compared to lesioning, a search for how it worked, for mechanisms, began. This took on greater importance as the effect of DBS on PD motor signs varied significantly across centers and within centers across patients (61–63). To improve clinical outcomes and provide greater consistently in its effect it became critically important to understand how it worked.

Early studies on mechanisms of DBS were performed in both animal models and humans with PD and were based on recording near the site of stimulation (64–70). Based on the observation that the behavioral effect of pallidotomy and DBS were similar, with lesions destroying tissue and decreasing output from the lesioned structure, it was hypothesized that DBS must do the same. Indeed, early studies in humans conducted during the classical microelectrode mapping procedure prior to lead implantation found suppression of neuronal activity near the site of stimulation (64, 65). What happened to other brain areas outside the immediate area of the stimulated structure, however, was unknown and could not be assessed in the human. A way was needed in which one could study how DBS affected structures in the circuit not just at the DBS target but at other nodes in the BGTC network, in sites that project to, and receive projections from, the site of stimulation. To address this question, a DBS approach was developed in the MPTP monkey model of PD that closely replicated that in humans by implanting a scaled-down DBS lead and using the same pulse generator that was used in patients (72). Of critical importance was ensuring that any observations of changes in physiological activity could be correlated to improvement in motor signs during stimulation, and methods were devised to assess these motor signs. Last, a method whereby recordings of neuronal activity were able to be made during stimulation, rather than following discontinuation of stimulation (73), was needed. The results of this study were surprising to the DBS community in that STN DBS led to increased mean discharge rates in both GPi and GPi, sites projecting to and receiving projections from the STN (ref. 74 and Fig. 2 A–D). Rather than suppression of output from the STN as hypothesized by many, rates in GPi and GPi were increased during STN stimulation, leading to what could only be construed as activation of output from the site of stimulation. With prolonged periods of stimulation, the increased rate in GPi was sustained (Fig. 2D). Given the rate model was well accepted at the time, this observation of increased mean discharge rates in GPi associated with improvement in motor signs required a reassessment of the similar model. More recently, the model has resulted in stimulus-synchronized firings revealed in the poststimulus time histograms, where spike activity in the GPi rather than occurring randomly was focused at ~3.5 ms following the stimulation pulse in STN (Fig. 2B). Stimulation produced a more regular firing pattern compared to pretimulation and poststimulation periods (Fig. 2C), supporting the role of temporal firing patterns, rather than just firing rate, in the basal ganglia in the development of PD and the underlying mechanism of action of DBS (74).

The ability to record neuronal activity throughout the motor circuit in the monkey model and histologically confirm the local effects of the DBS electrode and the DBS target led to the development of ways to further study into the mechanisms underlying DBS that could not be obtained in patients. Its value is further reinforced by the vast number of studies now being conducted in the MPTP monkey model of PD that continue to refine our understanding of how DBS works and use this knowledge to advance the treatment for patients with PD. Subsequent studies have since reported the effect of STN, GPi, and GPi DBS on network activity throughout the BGTC circuit (refs. 75–82 and Fig. 2 E–H). Interestingly, it has been demonstrated that STN, GPi, and GPi stimulation, although imposing different changes in the network (74, 75, 78, 82, 83), suggestive of the idea that the therapeutic mechanisms of DBS may vary depending on the target and location of the DBS lead within that target.

Supported by monkey studies, PD is increasingly recognized as a network disorder involving changes in synchronized oscillatory activity and coupling within and between cortical and subcortical brain areas. Enhanced synchronization between pallidal segments has been demonstrated in the MPTP monkey model of PD as well as changes in synchronized oscillatory activity within and across nodal points in the BGTC circuit (84–89). Unique to these monkey studies, and unfeasible in humans, is the ability to examine neuronal changes within the same subject in normal and diseased states while varying the pattern of stimulation as well as the target site. Together with studies of local field potential (LFP) activity in humans demonstrating a relationship between beta band activity and severity of PD, alternative models of PD have been developed (90). In addition, novel approaches to DBS are being developed that focus on stimulation patterns directed at desynchronizing oscillatory activity in low-frequency bands while inducing plasticity in the network associated with long-term improvement in motor signs even with discontinuation of stimulation (91–93). Other human and monkey studies have focused on the development of devices and algorithms to sense neural oscillations in real time and use them to trigger when
Next Steps to Exploring the BGTC Network in PD and DBS Using the Monkey MPTP Model of PD

Fig. 3 highlights the utility of the MPTP monkey model to explore brain networks impacted in PD to understand and improve DBS technologies. While previous studies have largely focused on single-cell recordings from a single site in the BGTC circuit, newly developed approaches in the monkey model of PD are focusing on simultaneous recordings from large populations of neurons together with LFP activity across several nodes in the network (Fig. 3A). Multiple conditions can be examined using these approaches comparing within each subject the changes that occur within the network from normal to PD at increasing levels of severity (Fig. 3C), and from PD to PD + DBS using a variety of stimulation parameters. One can record the effect of DBS on LFP and unit activity across multiple cortical and subcortical regions simultaneously before, during, and after stimulation and differentiate the effect of stimulation on behavior and network activity with DBS at different sites in the brain (Fig. 3E). Moreover, histological verification can be done to confirm dopaminergic cell loss and locations of implantation and recording sites (Fig. 3B). Such approaches allow for the exploration of novel brain targets and different DBS approaches (Fig. 3D) that can easily be translated to humans and applied to other neurological and psychiatric disorders. These approaches have led to a better understanding of how DBS affects network function and how it alters subcortical–cortical coupling in PD, provided a description of how changes in the level of vigilance can alter network activity, and brought to our attention that physiological biomarkers of PD are dynamic, not static; they vary over time, location within the network, and with the behavioral state of the animal (102). By recording from populations of neurons in motor and nonmotor regions of the cortex simultaneously we have been able to observe how these regions are changed in the PD state and how communication across cortical regions is modified both at rest and during performance of motor tasks. While we can closely monitor changes in the BGTC circuit, these MPTP monkey populations of pallidal and thalamic neurons during therapeutic STN stimulation, illustrating that stimulation evokes complex temporal patterns of firing activity in these nuclei. (G) PSTHs of STN, GPe, VA/VLo, and VPLo neurons during therapeutic GPe stimulation. (H) Average PSTHs of populations of pallidal and thalamic neurons during therapeutic STN stimulation, illustrating that stimulation evokes complex temporal patterns of firing activity in these nuclei.
models of PD also allow for recordings of neuronal activity in brainstem areas and histological confirmation of recording sites. The pedunculopontine nucleus (PPN) plays an important role in locomotion and has been explored as a DBS target to alleviate gait disturbances which are debilitating in a subset of PD patients but often poorly controlled by STN or GPi DBS. Studies examining the role of PPN DBS in the human, however, have been fraught with inconsistency due in large part to the inability to do detailed, thorough recordings in these regions without inducing severe side effects. Those who have performed DBS in this region in humans cannot be sure of the recording locations, the precise site of lead placement, or the physiological effect on other structures as they are limited to the site of the DBS target. Through wireless recordings of brain activity from parkinsonian monkeys walking on a gait mat one can begin to understand the underlying neuronal signature for freezing of gait, a critical first step to using DBS for its treatment. The importance of monkey models in addressing these questions cannot be overemphasized.

**Conclusion**

Studies in monkeys have been instrumental in understanding the pathophysiological changes that occur in the brain in PD. Anatomical, neurophysiological, and imaging studies in monkeys have contributed enormously to our understanding of the functional organization of basal ganglia circuitry, in particular the importance of the motor circuit and its role in both hypo- and hyperkinetic disorders. They have led directly to the development and refinement of surgical procedures such as pallidotomy.
and DBS in the STN and GPi that have helped hundreds of thousands of people with PD and through this understanding its relationship to behavior, employing techniques not feasible in humans, we have been able to implement new therapies for people with PD as well as other neurological and psychiatric disorders. These models provide the ability to develop and test hypotheses in a rigorous fashion not possible in the human condition but are easily translatable to humans. PD and DBS is but one example of how valuable monkey studies are in our efforts to understand and treat human disease.

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