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Study on Deep brain Stimulation and Parkinson's Disease: A review

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***Abstract*— Parkinson's disease (PD) has evolved from an era of limited understanding and desperate measures in the 1930s and 1940s to the present, where it affects over 10 million individuals globally as a progressive neurodegenerative movement disorder. In the early stages, little was known about the causes or treatments for PD, leading to extreme measures such as ablating different regions of the neuraxis in hopes of improving patients' lives. While this approach resulted in common morbidity and mortality, some patients experienced improved motor signs with lesions affecting the basal ganglia or thalamus. The discovery of L-dopa marked the onset of medical therapy, overshadowing surgical interventions. However, issues like drug-induced dyskinesia and motor fluctuations associated with medical treatment prompted a resurgence of interest in surgical therapies. Concurrently, studies in monkeys, coupled with the development of a monkey model of PD using the neurotoxin MPTP, contributed significantly to understanding the functional organization of the basal ganglia. This knowledge paved the way for characterizing physiological changes in the basal ganglia in PD and proposing models of basal ganglia function and dysfunction. These foundational studies provided the scientific basis for reviving procedures like pallidotomy and the subsequent emergence of deep brain stimulation (DBS). This paper outlines the evolution of monkey studies, their role in unraveling the pathophysiology of PD, their contribution to the rationale for surgical procedures, and their instrumental role in advancing surgical therapies for treating PD.**

***Index Terms*— Parkinson's disease, deep brain stimulation, motor symptoms, basal ganglia and monkey model.**

I. INTRODUCTION

Parkinson's disease (PD) affects a significant number of individuals globally, with over 1 million people in the United States and more than 10 million worldwide grappling with its impact.

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The cardinal motor manifestations of PD include tremors, bradykinesia, rigidity, and gait and balance disturbances, varying in combinations and progressing in severity over time. Beyond these motor signs, patients may also experience nonmotor symptoms such as impaired sense of smell, constipation, orthostatic hypotension, freezing of gait, and sleep dysfunction. The origins of PD trace back to James Parkinson's 1817 description in "An Essay on the Shaking Palsy," a time when therapeutic options were limited. As symptoms worsened, desperation led to early surgical interventions, with different regions of the neuraxis being targeted for destruction in an attempt to alleviate motor signs. Despite the associated morbidity and mortality, some patients showed improvement, particularly with lesions in the thalamus or basal ganglia.

However, the lack of rationale for target selection and an understanding of the pathophysiological basis of PD posed significant challenges. The introduction of the stereotactic frame by Spiegel and Wycis aimed to address these issues, providing a methodological approach for precise lesion placement. Early versions of the stereotactic frame, though initially less successful, set the stage for advancements in surgical interventions. In the 1950s, neurosurgeon Lars Leksell's pallidotomies marked a notable improvement in PD patients' cardinal motor signs, particularly when lesions targeted the posteroventral portion of the pallidum. However, with the discovery of L-dopa in the 1960s, medical therapy gained prominence, offering significant relief from motor signs. Yet, the chronic use of L-dopa brought about its own set of challenges, prompting a re-evaluation of treatment approaches. This intricate history reflects the continuous evolution of PD management, balancing surgical and medical interventions to enhance the quality of life for those affected.

II. The understanding of the functional anatomy of the Basal Ganglia-Thalamocortical (BGTC) circuit and its relevance to Parkinson's disease (PD)

It has undergone significant evolution over the decades. In the 1930s, early surgical therapies lacked insights into the anatomical organization and functional connectivity of the BGTC circuitry. However, by the 1990s, extensive research, particularly in monkeys, had contributed to models describing the functional anatomy of the basal ganglia. Seminal studies by Mahlon DeLong in 1971 laid the groundwork for comprehending the role of the pallidum in movement. Alexander et al. (1986) further delineated BGTC circuits, categorizing them into motor, oculomotor, associative, and limbic circuits, each originating from distinct cortical regions. These circuits are projected to different parts of the striatum, pallidum, and thalamus, forming intricate feedback loops. Models of the basal ganglia's intrinsic circuitry emerged, outlining direct and indirect pathways with excitatory and inhibitory connections. Subsequent tracer studies in monkeys refined motor subcircuits and identified the hyper-direct pathway, a direct cortical projection to the subthalamic nucleus (STN). Despite these advancements, a faithful animal model replicating the Parkinsonian phenotype was lacking until the serendipitous discovery of patients who developed PD symptoms after taking MPTP, a neurotoxin found as an impurity in a synthetic opioid. The subsequent development of a monkey model of PD demonstrated cardinal motor signs, mirroring those observed in human PD. This breakthrough allowed researchers to investigate the Parkinsonian state, understand circuit changes, and explore ways to modulate abnormal activity to improve motor signs associated with PD. The combination of anatomical, physiological, and pharmacological studies in monkeys provided a valuable model to unravel the complexities of PD and explore potential therapeutic interventions.

III. The use of the MPTP Monkey Model

It has significantly contributed to our understanding of the pathophysiology of Parkinson's disease (PD). In studies employing this model, researchers conducted electrophysiological recordings in key regions such as the subthalamic nucleus (STN), globus pallidus internus (GPi), and globus pallidus externus (GPe) (29, 32–34). Comparative analysis with the naive state revealed notable alterations in mean discharge rates, with increased rates observed in the STN and GPi, and decreased rates in GPe. Additionally, changes in cell responsiveness to passive manipulation were noted. These findings served as the basis for proposing a "rate model" of PD, suggesting that the direct pathway (projections from the putamen to GPi) was underactive, while the indirect pathway (projections from putamen to GPe) was overactive (21, 22). According to this model, increased mean discharge rates in the STN would lead to excessive activation of the GPi, resulting in the suppression of thalamocortical activity and, subsequently, the manifestation of motor signs characteristic of Parkinson's disease (Fig. 1 A and B). A pivotal test of this hypothesis was published in Science in 1990 (35), marking a significant step forward in our understanding of the neural mechanisms underlying PD. The MPTP monkey model continues to play a crucial role in unraveling the intricacies of Parkinson's disease pathophysiology, providing valuable insights for future therapeutic interventions.

By the 1990s, advancements in surgical techniques were facilitated by improved imaging with MRI and enhanced technology in newer stereotactic frames. This led to the resurgence of pallidotomy, as first reported by Laitinen et al. in 1992 and subsequently by multiple other researchers over the following years (41–44). Despite several reports highlighting success, there were also documented cases of failures (45). While some patients experienced marked improvement, others only had transient benefits. In certain instances, the benefits diminished over a few days, while in others, the effects wore off after several years. There were debates over the mechanism underlying pallidal lesions, with conflicting opinions on whether lesions needed to include the globus pallidus externus (GPe). Muscimol studies in the MPTP monkey model had indicated that motor sign improvement was reliant on inactivating the motor region of the pallidum, adding complexity to the debate. Some argued that lesions should include GPe, while studies in monkeys showed that GPe lesions could exacerbate PD motor signs. This contention gained support when a case report detailed a PD patient who underwent pallidotomy, experienced deterioration, and lost responsiveness to levodopa. A post-mortem examination confirmed significant involvement of GPe in the lesion. As the number of pallidotomies increased, the necessity for bilateral procedures became apparent, especially for patients with bilateral disease manifestations. However, complications from bilateral pallidotomy were frequent, with reports of cognitive changes, gait disorders, worsening PD symptoms, and/or hypophonia. Seeking an alternative approach, deep brain stimulation (DBS) for PD, developed by Alim Louis Benabid, emerged as a promising solution and was introduced to the operating room (58).

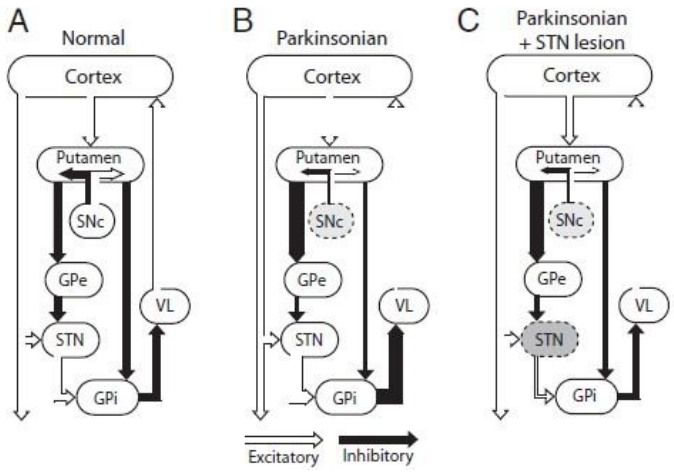

Figure 1

Fig. 1 illustrates the state of understanding regarding the anatomical connectivity within the basal ganglia–thalamocortical circuit at a specific point in time. (A) Represents the normal state, with open and closed arrows denoting excitatory and inhibitory connections, respectively. Key components include the substantia nigra, pars compacta (SNc), ventrolateral nucleus of the thalamus (VL), globus pallidus internus (GPe), globus pallidus externus (GPi), and subthalamic nucleus (STN). (B) Depicts MPTP-induced parkinsonism, where the administration of the neurotoxin MPTP damages dopaminergic cells in the SNc, resulting in changes in overall activity in individual projections. The loss of nigrostriatal projections leads to an increase in GPi activity due to heightened excitatory drive from the STN and decreased direct inhibitory input from the striatum. This scenario hypothesizes that excessive inhibition of the thalamocortical circuitry may underlie Parkinsonian motor signs. (C) Represents the effect of STN lesions in parkinsonism, demonstrating that lesions in the STN reduce the excitatory drive for the STN to GPi, resulting in reduced mean discharge rates in GPi and an improvement in motor signs (35). These insights, derived from studies in monkeys with MPTP-induced parkinsonism, have significantly contributed to the understanding of Parkinson's disease (PD) pathophysiology and provided a rationale for surgical interventions in PD treatment. Adapted with permission from AAAS (American Association for the Advancement of Science).

IV. DBS AND THE ROLE OF MONKEY RESEARCH

Before surgically lesioning a subcortical structure, surgeons traditionally applied a small electrical current to assess its impact on the targeted symptoms, a procedure common in thalamotomy for patients with tremors. Dr.

Alim-Louis Benabid proposed a chronic method for delivering stimulation to the target brain region, leading to the development of deep brain stimulation (DBS) as a prominent surgical therapy for tremors. Following initial testing in the MPTP monkey model, DBS extended its applications to the treatment of Parkinson's disease (PD) and later expanded to various neurological and psychiatric disorders. While DBS effectively alleviated motor signs associated with PD, understanding its mechanism of action became imperative. As its impact varied significantly across centers and patients, investigating the underlying mechanisms gained significance for improved clinical outcomes. Early studies, conducted in both animal models and humans with PD, focused on recording activity near the stimulation site.

Drawing parallels between the behavioral effects of pallidotomy and DBS, which both involved tissue destruction and decreased output, researchers hypothesized that DBS operated similarly. Human studies during microelectrode mapping before lead implantation demonstrated suppression of neuronal activity near the stimulation site. However, the impact on distant brain areas remained unknown and unassessable in humans. To address this, a DBS approach was developed in the MPTP monkey model, closely mimicking the human procedure. This involved implanting a scaled-down DBS lead and using the same pulse generator as in patients. Crucially, correlations between changes in physiological activity and improvements in motor signs during stimulation were established, providing valuable insights into the mechanisms underlying DBS efficacy. This innovative approach in the MPTP monkey model has played a pivotal role in advancing our understanding of DBS and its applications in treating neurological disorders.

V. Conclusion

In conclusion, studies involving monkeys have played a pivotal role in enhancing our comprehension of the pathophysiological changes occurring in the brain during Parkinson's disease (PD). The amalgamation of anatomical, neurophysiological, and imaging investigations in monkeys has been instrumental in elucidating the intricate functional organization of basal ganglia circuitry. These studies have particularly emphasized the significance of the motor circuit and its pivotal role in both hypo- and hyperkinetic disorders associated with PD. Through the invaluable insights gained from monkey research, our understanding of the neural mechanisms underlying PD has been enriched, laying a foundation for advancements in therapeutic strategies and contributing significantly to the progress in the field of neurology facilitated by techniques not feasible in humans, has allowed for the implementation of novel therapies for individuals with Parkinson's disease (PD) and other neurological and psychiatric disorders.

Monkey models have proven invaluable in this regard, providing a platform to develop and rigorously test hypotheses in a manner not achievable in human studies but readily translatable to humans. The study of PD and deep brain stimulation (DBS) serves as just one illustration of the immense value that monkey studies contribute to our endeavors in comprehending and treating human diseases. The ability to investigate neural mechanisms in a controlled and translatable context has significantly advanced our understanding and treatment strategies for a spectrum of disorders affecting the nervous system.

References

[1] J. Parkinson, An Essay on the Shaking Palsy (Sherwood, Neely, and Jones, London, 1817).

[2] P. C. Bucy, T. J. Case, Tremor: Physiologic mechanism and abolition by surgical means. Arch. Neurol. Psychiatry 41, 721–746 (1939).

[3] R. Klemme, Surgical treatment of dystonia, paralysis agitans, and athetosis. Arch. Neurol. Psychiatry 44, 926 (1940).

[4] J. Browder, Section of the fibers of the anterior limb of the internal capsule in parkinsonism. Am. J. Surg. 75, 264–268 (1948).

[5] R. Meyers, The modification of alternating tremors, rigidity, and festination of surgery of the basal ganglia. Res. Publ. Assoc. Res. Nerv. Ment. Dis. 21, 602–665 (1942).

[6] E. A. Spiegel, H. T. Wycis, H. W. Baird, 3rd, Long-range effects of electropallidoansotomy in extrapyramidal and convulsive disorders. Neurology 8, 734–740 (1958).

[7] E. A. Spiegel, H. T. Wycis, Pallidothalamotomy in chorea. Arch. Neurol. Psychiatry 64, 295–296 (1950).

[8] F. Fenelon, Neurosurgery of parkinsonian syndrome by direct intervention on the extrapyramidal tracts immediately below the lenticular nucleus. Communicationfollowed by film showing patient before and after intervention. Rev. Neurol. (Paris) 83, 437–440 (1950).

[9] G. Guiot, S. Brion, Neurosurgery of choreoathetosic and Parkinsonian syndromes. Sem Hop. 28, 2095–2099 (1952).

[10] I. S. Cooper, Chemopallidectomy: An investigative technique in geriatric parkinsonians. Science 121, 217–218 (1955).

[11] A. E. Walker, Cerebral pedunculotomy for the relief of involuntary movements. II. Parkinsonian tremor. J. Nerv. Ment. Dis. 116, 766–775 (1952).

[12] T. J. Putnam, E. Herz, Results of spinal pyramidotomy in the treatment of the parkinsonian syndrome. Arch. Neurol. Psychiatry 63, 357–366 (1950).
[13] R. Leriche, Ueber chirurgischen Eingriff bei Parkinson'scher Krankheit. Neurol Zeitblaetter 13, 1093–1096 (1912).
[14] E. A. Spiegel, H. T. Wycis, M. Marks, A. J. Lee, Stereotaxic apparatus for operations on the human brain. Science 106, 349–350 (1947).
[15] E. Svennilson, A. Torvik, R. Lowe, L. Leksell, Treatment of parkinsonism by stereotatic thermolesions in the pallidal region. A clinical evaluation of 81 cases. Acta Psychiatr. Scand. 35, 358–377 (1960).
[16] G. E. Alexander, M. R. DeLong, P. L. Strick, Parallel organization of functionally segregated circuits linking basal ganglia and cortex. Annu. Rev. Neurosci. 9, 357–381 (1986).
[17] W. Birkmayer, O. Hornykiewicz, The L-3,4-dioxyphenylalanine (DOPA)-effect in Parkinson-akinesia. Wien. Klin. Wochenschr. 73, 787–788 (1961).
[18] G. C. Cotzias, P. S. Papavasiliou, R. Gellene, L-dopa in Parkinson's syndrome. N. Engl. J. Med. 281, 272 (1969).
[19] L. V. Laitinen, A. T. Bergenheim, M. I. Hariz, Leksell's posteroventral pallidotomy in the treatment of Parkinson's disease. J. Neurosurg. 76, 53–61 (1992).