Current Study on Deep Brain Stimulation for Parkinson's Disease

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Abstract. This paper emphasizes the evolution and application of neural electrical stimulation in the context of Parkinson's disease. During the last several decades, Deep Brain Stimulation (DBS) has become a highly successful viable treatment choice for patients with advanced stages of PD and other motor disorders. DBS utilizes a device similar to a pacemaker to administer constant electrical signals to targeted regions within the brain to help patient relieve the symptoms. The DBS has been involved in the rehabilitation process of more than 80000 people, and most of them are patients with PD. Based on the specific symptoms show by patients, several targets have been approved as effective DBS targets for patients with PD. These include subthalamic nucleus (STN), globus pallidus internus (GPi), ventral intermediate nucleus (Vim), and pedunculopontine nucleus (PPN). Hence, understanding the applications and evolution of DBS techniques have significant importance for future studies of PD and brain functions.

Keywords: Deep brain stimulation, STN-DBS, Gpi-DBS, Vim-DBS, PPN-DBS.

1. Introduction

Parkinson's Disease (PD) is a gradual chronic neurodegenerative movement disorder that is distinguished by resting tremor, muscular rigidity, slowed movements, and postural instability [1]. It was first identified and mentioned by James Parkinson in 1817. People with PD may also suffer from mental and behavioral changes like insomnia, depression, and fatigue. As the second most neurodegenerative disease, PD is prevalent among old people, and approximately 1% of those who aged over 65 [2].

From a pathological perspective, PD occurs when the neuron degenerates in the substantia nigra, where the neuron mainly produces dopamine. The Substantia nigra is an area of the midbrain above the spinal cord. It belongs to part of the basal ganglia circuitry, a structure responsible for motor control and other advanced behaviors like conditional learning and cognition [3]. Substantia nigra plays a vital role in regulating motor movements and reward mechanisms. The structure can be into two segments: Pars compacta and Pars reticulata. Pars compacta and the ventral tegmental area nearby contain most dopamine neurons, which are responsible for synthesizing and releasing dopamine, a critical neurotransmitter for movement and always associated with pleasure and rewards. The neurons that release dopamine, project from the Substantia nigra to the striatum are crucial for movement control [4]. The reduction of dopamine levels in the striatum, resulting from neuronal degeneration, leads to increased activity in the Pars reticulata circuit and, hence dysfunction of gamma-aminobutyric acid (GABA) which ultimately inhibits the thalamus. Reduced activity in the thalamus hinders the activation of the frontal cortex, thus impairing motor activity, which is the primary symptom of PD [1].

The most conventionally used drugs to treat PD are Levodopa and Dopamine Agonists. they are the two principal pharmaceutical treatments; Levodopa directly converts into dopamine, and the other acts as a substitute for dopamine [5]. But when medication is no longer effective or side effects are generated due to individual differences, DBS will be introduced.

DBS involves a cardiac pacemaker-like device with wire electrodes that are implanted in some regions of the brain. These electrodes generate high-frequency electrical impulses to modulate abnormal patterns of brain activity. DBS has shown greater efficacy than medical treatment in increasing the motor capability and life quality of patients who exhibited poorly to medication, and it

is widely used to address motor-related symptoms of PD [6]. This review will summarize how DBS gradually became involved in the treatment of PD and applications regarding its four main target areas inside the brain.

2. Evolution of DBS

The historical development of DBS can be traced back to early 19th century. Giovanni Aldini applied electrical stimulation to the exposed cerebral cortex of prisoners who were executed. In 1804, he found electrical stimulation of the cortical surface evoked facial reactions, confirming the effectiveness and feasibility of cortical stimulation as a therapeutic application in treating neuropsychiatric disorders. In 1870, David Ferrier found that muscle contraction can be evoked via cortical stimulations. From 1874 to 1887, multiple pioneering researchers took major steps in the field of electrical brain stimulation in the human brains. Such experiment was first done by American physician Robert Bartholow, who experimented with electrical stimulation on the awake human brain. He was followed by Italian neuropsychiatrist Ezio Sciamanna in 1882, who conducted a series of tests on a patient with brain trauma. A year later, Alberto Alberti, an Italo-Argentine surgeon, carried out a prolonged study over eight months on a female patient whose skull tumor made the brain easily accessible for stimulation [7]. However, although these studies are preliminary, they still manage to confirm that the cerebral cortex is electrically responsive and reveal that motor functions are controlled by the opposite hemisphere of the brain.

In the 1930s, clinicians made great progress in exploring therapeutic applications and the potential of brain stimulation. In 1938, Ugo Cerletti introduced electroshock therapy to severe psychosis, marking the first modern therapeutic application of brain stimulation. By applying an electric current to the skull induced epileptic seizures. Such a method briefly restructured the link between neurons and led to clinical improvements in patients [7]. In 1936, 'Montreal Procedure', developed by neurosurgeon Wilder Penfield as a treatment for epilepsy. During the surgery, patients were kept conscious and the surgeon stimulated different areas of their cerebral cortex. By observing their responses to corresponding stimulation in different brain areas, the surgeon tried to locate the diseased area and thus remove it. In 1947, stereotactic apparatus was introduced, a device allowing medical professionals to dive deeper into the brain. Later, the development of stereotactic apparatus led to stereotactic neurosurgery, a new branch in neurosurgery. This subject became a platform where crucial skills, equipment, and talents accumulate, eventually contributing to the development of DBS as a therapeutic approach [8].

With the invention of the stereotactic apparatus in the 1950s, movement disorders such as PD were managed by removing or lesioning specific brain areas that associate with motor control. In the case of PD, the thalamus and globus pallidus were the selected as the target brain regions. Although the surgery performed unexpected relief of tremor and rigidity, it always accompanies a high mortality rate, around 10 % [9]. In the 1960s, multiple studies observed that high-frequency stimulation of target areas shown similar effects as surgical lesions, whereas low-frequency stimulation generally worsens motor symptoms [10]. However, due to the invention of levodopa in 1968, there was a sharp decline in stereotactic neurosurgery. The neurologist became less inclined to refer PD patients for surgical treatments, considering the high surgical risk of ablative surgery. Levodopa, which is affordable, non-invasive, and highly effective in helping patients relieve the PD symptoms, soon became a more appealing option [11]. From 1987 to 1991, the situation took a turn, when levodopa was not effective for multiple patients suffering from PD and additional movement disorders. French neurosurgeon Alim-Louis Benabid noticed during the surgery that applying stimulation with high frequency to ventral intermediate nucleus (VIM) can reduce tremors in patients with PD [12]. At the same time, American NIH scientist Mahlon DeLong and other researchers testified the technique in animals. They discovered that inactivating the STN via surgical removal or high-frequency stimulation resulted a reduction in the motor symptoms of PD in monkeys with MPTP [13]. From

1994 to 1998, Benabid and his team used DBS to deactivate the STN in PD patients, and they observed that tremors, rigidity, and bradykinesia were improved [14].

In 1996, VIM-DBS was sanctioned as the therapeutic approach for PD by the U.S. Food and Drug Administration (FDA). In 2001, the FDA expanded the authorized uses for DBS, permitting its application in either STN or GPi for patients with advanced PD. From then on, DBS has been widely used in PD patients. In 2009, a clinical research initiated by the National Institute of Neurological Disorders and Stroke (NINDS) and NIH showed that DBS was more effective than treatment with Levodopa for PD. In recognition of their role in the advancement of DBS for PD, DeLong and Benabid were honored with the Lasker-DeBakey Clinical Medical Research Award in 2014.

3. DBS Applications

3.1. Subthalamic Nucleus Deep Brain Stimulation (STN-DBS)

The subthalamic nucleus (STN) is one of the most selected areas for DBS in PD. It is in the diencephalon, playing a crucial role in the basal ganglia circuitry and movement regulation. This nucleus receives signals from the structures in including external globus pallidus (GPe), the cerebral cortex, thalamus, and brain stem and sends signals to the globus pallidus and substantia nigra pars reticulata [4]. STN primarily contains excitatory glutaminergic neurons that help inhibit unintended movements by enhancing its excitatory signals to the GPi. When the neurons that release GABA in the GPi are activated, it will deactivate the thalamus, thus resulting in decreased movement [15]. STN-DBS decreases the neuronal activity of STN, suppressing the overactive states of SNpr and GPi. As a result, this reduces the excessive inhibition exerted on the cerebral cortex and improves bradykinesia and rigidity [16].

3.2. Globus Pallidus Internus Deep Brain Stimulation (Gpi-DBS)

Globus Pallidus Internus (GPi) is another most common DBS target in PD. It is one of the major components of globus pallidus (GP). GP is a triangular structure situated on the inner side of the putamen. It has two separate nuclei, the external segments and the internal segments, each with different functions. And the internal segment is GPi [17]. GPi is the output nucleus, which primarily sends information to the thalamus. The whole circuit is that the SNpc stimulates the striatum by releasing dopamine to activate D1 receptors. The activated striatum then sends inhibitory signals to the GPi and some to the SNpr, which inhibits their inhibitory effect. Without the inhibition, the thalamic nuclei can activate the motor cortex through corticospinal pathways, thereby facilitating the required movement [18]. Gpi-DBS also has a direct impact on bradykinesia, rigidity, and tremor. There is a continuing debate on whether GPi or STN is a more suitable target for DBS. According to a three-year follow-up of advanced PD patients in 2016, clinicians conclude that in the period without medication, motor symptoms and overall wellbeing show greater improvement following STN-DBS compared to GPi-DBS [19].

3.3. Ventral Intermediate Nucleus Deep Brain Stimulation (Vim-DBS)

The ventral intermediate nucleus (Vim) is a highly efficient target for treating tremors. It is at the bottom edge of the ventral lateral thalamus [20]. The neurons in the ventral lateral thalamic nuclei fire in synchronized bursts, and the timing of these bursts closely correlates with the occurrence of peripheral tremors. Under certain circumstances, a single electrode implantation in the ventral lateral thalamic nuclei can halt tremors in the opposite side of the body for several weeks. However, the Vim-DBS does not generate significant effects on improving rigidity and bradykinesia among PD patients [21]. Those major symptoms of PD still rely on the STN-DBS and GPi-DBS.

3.4. Pedunculopontine Nucleus Deep Brain Stimulation (PPN-DBS)

The Pedunculopontine Nucleus (PPN) is a newly suggested target for DBS. It is found in the dorsolateral region of the ponto-mesencephalic tegmentum. PPN consists of two subdivisions: pars compacta and the pars dissipatus, which has mixed cholinergic and non-cholinergic neurons with both incoming and outgoing connections to various areas including the cerebral cortex, thalamus, basal ganglia, cerebellum, and spinal cord [22]. The PPN-DBS has a significant effect on balance problem in PD. And using PPN-DBS with traditional STN-DBS at the same time could be effective for improving walking and enhancing dopamine level, especially in individuals who have experienced little effect of STN-DBS [23].

4. Conclusion

DBS development is a milestone for treating PD and various movement disorders. From its preliminary experiment in the early 19th century to an FDA-approved treatment for advanced PD, DBS has become a reliable and well-established treatment for various motor disorders. After a series of explorations and efforts, we have developed multiple target brain regions for DBS. Clinicians could align the specific symptoms of each patient with appropriate DBS targets to help patients relieve those symptoms effectively, with minimal side effects. At the same time, DBS is also broadening its field to major psychiatric diseases, including but not limited to epilepsy, obesity, major depression, and obsessive-compulsive disorder. DBS is a technique with great potential and a promising future, yet its mechanics and corresponding ethical issues still remain unanswered. With ongoing technological improvement, interdisciplinary collaboration, and the enthusiasm of researchers in the neuroscience field, making it possible to figure out these questions in the near future.

This review presented the significant events during the development of DBS therapy, the current applications, and how it eventually became a primary treatment for advanced PD. Combining with some latest information, this review provides general ideas of historical development and current utilization of DBS methods in PD.

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