Frequency of Stimulation: The Most Important DBS Parameter in Improvement of Freezing of Gait in Parkinson's Disease

Parkinson's disease (PD) is the second most common neurodegenerative disorder after Alzheimer's disease that affects about 1% of adults over the age of 60 years. The typical features include bradykinesia, resting tremor, rigidity, and loss of postural reflexes. Dysarthria, dysphagia, gait, and postural disorders are axial symptoms and are often one of the main causes of long-term impairment and disability in PD patients.

Gait difficulties appear due to the progressive loss of postural reflexes and are a common and debilitating feature in PD patients that can manifest in the prodromal and early disease stages. The typical gait disorders include stooped posture, festination gait, short shuffling steps, freezing of gait (FOG), and falls. FOG is, defined as an episodic inability to generate effective steps in the absence of any known cause other than parkinsonism or higher-level gait disorders. It is commonly observed during step initiation, turning, or when faced with obstacles, doorways, stress, dual tasking, and distraction. FOG is considered an independent risk factor for falls and fractures. It usually occurs in the off-state, but occasionally on-state FOG is also seen.

These gait disorders adversely impact independence and quality of life. Dopaminergic medications improve some gait disorders in the early stage. However, in the later part of the disease, these gait disorders tend to worsen in spite of optimal dopaminergic medications.[1] This highly variable response to dopaminergic medications is due to the multifaceted etiology of gait disorders in PD. These gait disorders in PD are a complex interaction between the pathology, age-related changes, compensatory mechanisms, and later reduced mobility.

This necessitates additional therapeutic interventions to mitigate these symptoms, reduce falls, and increase physical activity.[2]

Deep brain stimulation (DBS) is known to improve most of the motor symptoms of PD. Subthalamic nucleus DBS (STN-DBS) is a long-term effective treatment in advanced PD patients. In the long-term, STN-DBS provides stable improvement of motor complications, bradykinesia, tremor, and rigidity but has little impact on axial symptoms and cognitive decline. However, the effect on FOG, other axial symptoms, and gait disorders are not clear. Some types of FOG improve with levodopa or subthalamic nucleus (STN) deep brain stimulation (levodopa-responsive FOG), whereas others do not (levodopa-resistant FOG) or even get worse with long-lasting levodopa therapy.[3] Hence, this heterogeneous symptom has been divided into three categories: dopaminergic-resistant, dopaminergic-sensitive, and dopaminergic drug-provoked FOG.

In a recent study, FOG and other axial symptoms of PD improve within the first 2 years of DBS. It was also superior to the best medical treatment group.[4] Previous studies have shown improvement of FOG after bilateral STN-DBS up to one year after surgery, which is like the improvement that was seen with pre-operative drug therapy. In addition, several studies have documented improvement of FOG, only when it was present in the medication-off condition. Stimulation frequency has been observed as one of the determinants of outcomes in patients with FOG.

Low-frequency (60 Hz) stimulation of STN improves severe FOG in advanced PD.[5] This beneficial effect on gait could be due to the therapeutic spread of current to the pedunculopontine nucleus (PPN), as the STN and PPN are situated very close to each other. Several other studies using low-frequency (60 Hz) stimulation have produced a positive effect on gait and speech.[6] Low-frequency stimulation of PPN also improves FOG in PD patients.

Xie T *et al*.[7] reported 2 cases of PD who developed FOG immediately after activation of the STN DBS using a frequency of 130 Hz, which disappeared immediately after switching the frequency to 60Hz. This effect of low frequency on FOG persisted till the 10-month follow-up and was present in both medications off and on states. Studies have shown that the combined stimulation of STN and PPN is more effective than bilateral STN stimulation in improving the FOG.[8]

Adaptive DBS, which is a newer approach to stimulating the brain, can identify the neural biomarkers associated with FOG and can deliver the stimulus in response to the fluctuating biomarkers. Studies have identified an increased beta-gamma phase-amplitude coupling (PAC) in the motor cortex during FOG episodes in PD patients compared to normal walking. STN-DBS reduces this phase coupling and thereby improves FOG. It has been suggested that the beta band waveform asymmetries likely contribute to the increased PAC.[9]

Although most of the studies have confirmed the benefits of low-frequency stimulation on FOG, it is unclear whether this benefit lasts longer. In the study by Huang C,[10] they assessed the changes in frequency parameters of STN-DBS stimulation over a period of 6 months that is required to optimize gait in PD patients.

These patients were assessed using freezing of gait (FOG) and stand-walk-sit (SWS) scores in the medication 'ON' state that was done at baseline and after 6 months. The frequencies tested were 60 Hz, 90 Hz, 130 Hz, and 180 Hz with a constant voltage and pulse width. They showed that the optimal frequency for FOG varies in patients and both low and high frequency may be useful. They also demonstrated the optimal frequency for improving FOG changes over the period.

Studies have demonstrated a loss of connectivity between the STN and supplementary motor area (SMA) and a functional reorganization within the locomotor network in patients with FOG. There is greater communication between the SMA and the mesencephalic and cerebellar locomotor region (MLR and CLR).[11] Abnormal functional connectivity of the PPN is also observed in PD patients with FOG. STN-DBS by modifying these different targets and networks and by improving cognitive functions is thought to improve FOG in these patients.

In this study, as the voltage and pulse width were kept constant, the effect of DBS was most likely due to the frequency and could not be due to the spread of stimulation to adjacent areas.[10]

This study lends evidence to the changes in frequency alone that can be made to improve FOG without changing the stimulation voltage and hence may help in improving the battery life. Further studies involving a larger cohort of PD patients with DBS are needed to understand this interesting phenomenon and the effect of DBS parameters in improving this condition.

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