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Deep Brain Stimulation Frequency Modulation in Parkinson's Disease - One Size May Not Fit All

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Deep Brain Stimulation (DBS) is an effective therapeutic modality for patients with Parkinson's Disease who have developed complications from longstanding levodopa such as dyskinesias and motor fluctuations. It produces robust responses to segmental symptoms (ie, bradykinesia, tremor, rigidity) while attenuating involuntary dyskinetic movements and smoothing out 'on' and 'off' period cycling. The subthalamic nucleus and the globus pallidus interna are widely accepted surgical targets for stimulation therapy, with STN more commonly used, though superiority has not been established [1-4].

Long-term outcome studies reveal sustained stable responses to rigidity, tremor, motor fluctuations, and dyskinesias among patients with bilateral DBS, mostly STN based [3,5-7]. Bradykinesia improvement also persisted but trended upwards as time went on, though remaining below preoperative baseline. Axial symptoms such as gait, postural stability, freezing of gait, and speech oftentimes transiently responded to stimulation and continued to deteriorate over time. Despite many of the DBS outcome studies having been conducted in patients with short disease duration, Merola and colleagues [8] described the development of progressive axial symptoms in patients treated with STN-DBS with more than 20 years disease duration. These symptoms globally lose any levodopa responsiveness and the synergism of stimulation ON/medication ON condition wanes as well, underscoring the likely contribution of non-dopaminergic systems in their phenotype.

High Frequency Stimulation (HFS) and Temporal Pattern Effects

The hypodopaminergic state changes the integrity of the intrinsic, tonic neuronal activity in the basal ganglia producing excessive synchronous neuronal activity in the beta frequency (13-30Hz) [9], hence the reduction in beta oscillations observed with dopamine replacement therapy [10]. This excessive beta synchrony is associated with increased cortical phase-amplitude coupling between the STN and cortex [11]. HFS-DBS mediates neuronal activity through excitatory or inhibitory changes but also influences the pattern and rates of neuronal firing– regularizing increased burst activity and simultaneously suppressing synchronized oscillations [12-15]. In addition, DBS reversibly reduces the strength of the cortical phase-amplitude coupling [11].

Suppression of beta oscillations has been related to improved motor performance, specifically bradykinesia and rigidity, and reaction time [16,17] in Parkinson's patients. Interestingly, rest tremor response does not seem to be linked to attenuation of beta oscillations suggesting a differential role of the cerebellar network its pathophysiology. Mounting evidence suggests that the frequency of deep brain stimulation governs much of the therapeutic gain through attenuation of the pathological activity and regularization of neuronal activity. Suppression of beta oscillatory activity in the STN is achieved at 130Hz or 185Hz and in the GPi at >70Hz [12,13,18,19]. In addition to the frequency, the therapeutic effect may also depend on the pattern of stimulation with worsening of tremor and UPDRS motor scores observed when the pattern is irregular [20]. Birdno et al. 2012 [21] showed that pauses in the stimulation pattern rather than temporally non-regular DBS produces deleterious motor effects. Bradykinesia and tremor improved above 50Hz with a ceiling effect reached between 130-185Hz, highlighting the parallel clinical correlation produced with continuous HFS [22]. Worsening of these symptoms occurred when cycling settings [23] were used, supporting the notion that disrupted, non-regular stimulation at a neuronal level, whether generated from an externalized system or internalized neurostimulator, parallels similar clinical outcomes.

The Paradox of Low FrequencyStimulation (LFS)

Low Frequency Stimulation, on the other hand, tends not to only worsen motor symptoms such as akinesia and tremor [24,25], but fails to override pathological oscillations [14]. It has been posited that this is attributed to the long interpulse intervals failing to mask intrinsic activity and/or facilitate rebound burst activity in the target nuclei [14]. However, a recent study testing hand opening and closing in PD patients, using an instrumented glove at multiple frequencies (low and high) did not find worsening of bradykinesia at low frequencies in a drug naïve state with Total Electrical Energy Delivered (TEED) kept constant, thus challenging the prevailing view that LFS is inefficacious [26].

Furthermore, several studies probed the therapeutic effects of low

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frequency (60 - 80Hz) for gait disorders [27-30] among advanced PD patients with severe axial and gait disturbance, which are often refractory to HFS-DBS and L-Dopa. The results have been conflicting and likely related to differences in methodology. For example, two blinded studies examined changes in gait and axial symptoms on a cohort of advanced PD patients and showed contrary results. In the first study, the authors reported sustained clinical gait benefit in 13 patients over 8 months on 60Hz frequency with TEED controlled and ventral contacts utilized in 10 of the 13 patients [27]. In the second study, Sidiropolous et al.[28], while not controlling fully for TEED, reported no benefits of frequency <80Hz in 45 patients. In addition, a partially blinded study by Ricchi and colleagues [29], showed transient benefits in axial symptoms at 80Hz frequency while controlled for TEED, with majority of stimulation flowing through dorsal contacts used in 10 of 11 patients. Khoo et al [31]. revealed that the optimal contacts for 60Hz DBS were located ventrally and that the randomized, double blinded, prospective crossover comparison between 60-Hz and 130Hz yielded a better response of axial symptoms to 60Hz frequency. Interestingly, the analyses were done in the ON dopaminergic medication state, but were not controlled for TEED.

Though the efficacy of low frequency stimulation of the STN remains undetermined, the suggestion that ventral lead contacts as well as the ON-medication state are important for efficacy for this type of stimulation require further investigation. In parallel, Moro and colleagues [32] showed that stimulating the pedunculopontine nucleus (PPN), which lies caudal to the STN, at 25Hz in advanced PD patients with axial dysfunction and freezing improves their gait. Steffani et al [33] demonstrated further synergism between STN(HFS)-PPN(LFS) in the ON-medication state with improvement of axial symptoms produced beyond that of stimulating either target individually. In addition, Weiss and colleagues [34] reported reduced freezing with simultaneous stimulation of STN and SNr at 125Hz from the same DBS lead. These studies underscore the concept of different targets having their own unique intrinsic pathologic activity being modulated by different frequencies to produce similar clinical outcomes. This potentially implicates the mechanistic theory of resonance interactions among various nested, oscillating circuits subserving motor functions [35]. Biochemical studies reveal that such resonance can impact the inhibitory or excitatory status of the target nucleus based on the type of frequency modulation being delivered [36].

Frequency-dependent modulation has also been reported to ameliorate involuntary movements such as dyskinesias [37] and improve intelligibility of PD patients with dysarthropneumophonia [38] through low frequency STN stimulation. But, frequency modulation is not restricted to the STN, as there is extensive experience described with pallidal (GPi) stimulation in treating primary dystonia with high frequency (130-185Hz) [39-43] and low frequency (60Hz) [44,45] stimulation. Interestingly, bradykinetic movements (ie, micrographia, hypomimia) and hypokinetic gait with freezing have been reported as adverse effects of HFS in a number of case series [46-49]. Schrader and colleagues [49] reported an incidence of 8.5% of a new gait disorder among 71 patients with dystonia who underwent DBS. Ventral contacts seemed to be related to the development of this hypokinetic state. Reduction in frequency improved bradykinetic movements among a cohort of cranial-segmental dystonia patients that developed gait disorder on HFS, but the majority experienced a worsening of dystonia symptoms [46]. There have been no reports to date of hypokinesia in dystonia patients treated with LFS from the outset.

Conclusion

Despite the wide spread use of HFS in treating Parkinson's motor symptoms, evidence of low frequency stimulation efficacy, whether in the STN, PPN, or GPi, cannot be overlooked. It speaks to the likelihood that pathological neuronal synchrony and oscillatory patterns are not the only unique entities in the disease state, but are features of altered large networks [50,51] that may have differential responses at various nodes based on the frequency of stimulation delivered. Further studies will need to investigate the role clinical (i.e., age, disease duration, phenotype), surgical targeting, and genetics have in frequency modulation efficacy and how that relates to the network changes being derived from a growing body of large scale electrophysiological and neuroimaging evidence.

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