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Editorial

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Moran Gilat

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Towards closed-loop deep brain stimulation for freezing of gait in Parkinson's disease

Moran Gilat

Research Group for Neuromotor Rehabilitation, Department of Rehabilitation,
KU Leuven, Leuven, Belgium.

Corresponding Author:

Dr Moran Gilat (PhD)

KU Leuven

Department of Rehabilitation

Tervuursevest 101, 3001, Leuven

Belgium

E: moran.gilat@kuleuven.be

Freezing of gait (FOG) is a highly debilitating symptom of advanced Parkinson's disease (PD) during which patients experience a sudden inability to take a step while walking, turning or when attempting to initiate gait, often resulting in falls (Nutt et al. 2011). FOG has a complex and heterogeneous pathophysiology whereby the impaired habitual control of gait in PD becomes vulnerable to interference from consecutive processing across motor, cognitive and limbic cortico-striatal circuits in the absence of striatal dopamine, whilst the ability to apply executive control over gait diminishes as a result of progressing extra-nigral neuropathology (Bohnen and Jahn 2013; Lewis and Shine 2016). Models of FOG suggest it could be due to transient over-activity in the subthalamic nucleus (STN), which leads to a surge of inhibitory projections from the globus pallidus internus and substantia nigra pars reticulata to the 'final common pathway' of the brainstem locomotor regions that control gait (Figure 1A) (Lewis and Shine 2016). The STN is indeed the main output structure of the indirect cortico-striatal pathways that are overly active in PD during the dopaminergic *off* state resulting in motor inhibition. The cortico-STN hyper-direct pathway further blocks motor output during instances of response conflict that likely arise more frequently in advanced PD due to worsening sensorimotor deficits (Shine et al. 2013; Nambu et al. 2015). However, the exact role of the STN in FOG still needs further elucidation. Manipulating STN deep brain stimulation (STN-DBS) frequencies therefore provides an interesting window in clarifying the modulatory role of the STN in the etiology of FOG in PD.

High-frequency (120-140 Hz) STN-DBS is the treatment of choice for many patients with PD, as it provides sustained improvements of motor signs that are dopamine responsive but cannot be optimally relieved with medications due to dosage limiting side-effects (Rodríguez-Oroz et al. 2012). The effectiveness of high-frequency STN-DBS has been linked to the attenuation of tremor related (4-7 Hz) oscillations as well as pathological beta (15-30 Hz) oscillations that are prominent across the cortico-basal ganglia circuits in PD during the *off* state (Kühn et al. 2008; Blumenfeld et al. 2017). Unfortunately, however, high-frequency STN-DBS does not satisfactorily alleviate axial motor signs that are partly dopamine resistant, such as FOG, and may even aggravate these symptoms for some patients (Moreau et al. 2008; Xie et al. 2012). Many specialized centers therefore consider dopamine resistant FOG as an exclusion criterion for receiving high-frequency STN-DBS. Moreover, DBS in PD is currently applied using pre-set stimulation settings that remain static over time (i.e., *open-loop*), often requiring multiple post-operative parameter iterations to achieve the desired clinical benefits and probably limiting the effectiveness of DBS for paroxysmal symptoms, such as FOG (Udupa and Chen 2015; Gilat et al. 2018).

In this issue of *Clinical Neurophysiology*, Varriale and colleagues (Varriale et al. 2018) provide important evidence of how different STN-DBS settings impact on gait initiation performance in PD. In a double blind and randomized controlled manner, conditions before and after STN-DBS surgery, both ON and OFF medication and with low (80 Hz) and high (130 Hz) DBS frequency settings were compared. Most interestingly, stimulation effects were assessed during both a simple task condition

(n=19), when patients initiated gait in response to a single auditory tone, as well as in a complex task condition (n=9) when presented with congruent and incongruent visual cues depicting go or no-go trials. The complex task condition was used to investigate patient's ability to simultaneously process cognitive and motor information (Varriale et al. 2018), requiring consecutive processing across parallel cortico-basal ganglia circuits that converge in the STN and often leads to FOG (Lewis and Shine 2016).

Their findings showed that compared to being OFF, both dopamine and either DBS setting improved simple gait initiation with only a slight enhancement seen during low- versus high-frequency DBS (Varriale et al. 2018). During the complex task condition, however, a significant effect of stimulation was found, whereby high-frequency DBS worsened gait initiation significantly more than low-frequency DBS. This study thus provides important behavioral evidence that isolated motor programs can be passed through when applying either stimulation setting, whereas high-frequency STN-DBS impairs PD patient's ability to simultaneously process motor and cognitive information during complex gait tasks. In contrast, low-frequency DBS helped to prevent cognitive-motor interference and likely allowed for compensatory gait control. Although the authors did not measure FOG directly, gait initiation commonly provokes FOG and serves as a good proxy for this gait complication.

One possibility for the differential effect of STN-DBS on FOG, described by Varriale et al. (2018), could be overflow of stimulation to the nearby pedunculopontine nucleus where high frequencies can cause gait cessation and low frequencies facilitate gait (Plaha and Gill 2005; Moreau et al. 2008). However, the story is likely more complicated, as low-frequency stimulation applied to the PPN does not convincingly alleviate FOG (Nonnekes et al. 2015). Instead, the effects could be related to oscillatory changes in the STN itself, as summarized in Figure 1B. High-beta frequencies have been related to activity in the hyper-direct pathway, whereas low-beta frequencies have been related to oscillations across cortico-basal ganglia circuits that could be patient specific (i.e. non-pathological) (Oswal et al. 2016; Blumenfeld et al. 2017). Coherence in the alpha range was also found between the STN and the temporoparietal cortex implicated with compensatory top-down control of movements in PD (Litvak et al. 2011; Wu et al. 2015). Interestingly, recent evidence from concurrent STN and kinematic recordings of hand movements in PD revealed that both high- and low-frequency DBS improved limb bradykinesia by attenuating the sub-band of high-beta oscillations in the STN (Oswal et al. 2016; Blumenfeld et al. 2017). However, high-frequency DBS also attenuated oscillations across the tremor and alpha/low beta (11-15 Hz) bands, whereas low-frequency DBS amplified the functional coupling and synchrony across these lower frequencies (Blumenfeld et al. 2017). Together, this indicates that (1) the effectiveness of STN-DBS for limb bradykinesia may be primarily due to the attenuation of high-beta oscillations related to the hyper-direct pathway; and (2) that low frequency DBS may benefit FOG by

enhancing neural coupling in cortico-basal ganglia and compensatory motor circuits whilst consequently also letting tremor related oscillations through.

It is therefore generally agreed that the future of DBS in PD lies in the development of *adaptive* and *closed-loop* DBS systems that can automatically adjust the output stimulation based on feedback about changes in neural activity or behaviour (Kuo et al. 2018). Encouragingly, researchers have already been able to develop such an adaptive DBS system that could automatically switch stimulation on/off depending on changes in STN local field potential beta power activity. The findings of the first trials in PD were encouraging by showing an overall improvement in motor signs, whilst requiring substantially less stimulation in total (Little et al. 2016). However, turning off high-frequency STN-DBS is unlikely to resolve FOG, which is still most severe in the *off* dopaminergic state for the majority of patients (Nutt et al. 2011). Instead, growing evidence now suggests that closed-loop STN-DBS can be made more effective by lowering the stimulation to 60-80 Hz during periods of imminent FOG (Moreau et al. 2008; Xie et al. 2012; Varriale et al. 2018), while switching to high-frequency stimulation during rest to prevent tremor and other symptoms (Figure 1C) (Blumenfeld et al. 2017). It is important to note, however, that neither DBS setting alleviated step initiation deficits more than a supra-dose of dopaminergic medication, indicating that a combination of low-frequency DBS and levodopa will likely be needed to adequately manage FOG in PD (Varriale et al. 2018).

Taken together, the work by Varriale et al. (2018) and other expert groups studying the role of STN frequencies on motor behaviors in PD provides new insights into the neurophysiology underlying FOG. The differential responses and the various possible mechanisms of high- and low STN-DBS frequencies provide a stronger rationale for developing closed-looped DBS systems with potential to prevent the manifestation of FOG. I, for one, am excited to see how this field develops over the coming years.

Conflict of interest

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Figure Legend

Figure 1. Theoretical model of FOG (A) and how effects of different STN-DBS frequencies (B) provide merit for developing closed-loop STN-DBS systems for FOG (C) (see Lewis and Shine 2016; Blumenfeld et al. 2017; Varriale et al. 2018).

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