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Review article

Low-frequency deep brain stimulation for movement disorders

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ABSTRACT

Introduction: Traditionally, deep brain stimulation (DBS) for movement disorders (MDs) is provided using stimulation frequencies equal to or above 100 Hz. However, recent evidence suggests that relatively low-frequency stimulation (LFS) below 100 Hz is an option to treat some patients with MDs.
Objectives: We aimed to review the clinical and pathophysiological evidence supporting the use of stimulation frequencies below 100 Hz in different MDs.
Results: Stimulation of the subthalamic nucleus at 60 Hz has provided benefit in gait and other axial symptoms such as swallowing and speech. Stimulation of the pedunculopontine nucleus between 20 and 45 Hz can provide benefit in freezing of gait, cognition, and sleep quality in select patients with Parkinson's disease. Stimulation of the globus pallidus internus below 100 Hz in patients with dystonia has provided benefit at the beginning of the therapy, although progressively higher stimulation frequencies seem to be necessary to maintain the clinical benefit. Relative LFS can lower energy requirements and reduce battery usage—a useful feature, particularly in patients treated with high current energy.
Conclusions: DBS at frequencies below 100 Hz is a therapeutic option in select cases of Parkinson's disease with freezing of gait and other axial symptoms, and in select patients with dystonia and other hyperkinetic movements, particularly those requiring an energy-saving strategy.
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1. Introduction

Deep brain stimulation (DBS) provides robust benefit in hypo- and hyperkinetic movement disorders (MDs). The thalamus was the first target stimulated with high frequencies leading to proven improvement of parkinsonian and other forms of tremor. High frequency stimulation (HFS) usually above 100 Hz was then successfully used to stimulate the subthalamic nucleus (STN) and the globus pallidus internus (GPi) in patients with Parkinson's disease (PD). The use of HFS has been translated to other movement disorders such as dystonia. However, more recent clinical evidence has shown that some axial motor symptoms in PD may improve with low-frequency stimulation (LFS) below 100 Hz in the STN and pedunculopontine nucleus (PPN). Moreover, patients with dystonia and other hyperkinetic movements may obtain clinical benefit with relative LFS in the GPi. In this study, we aim to review the evidence for treating patients with PD and hyperkinetic MDs with stimulation frequencies below 100 Hz. We use the term LFS relative to the custom stimulation commonly used in clinical practice above 100 Hz, but the reader should be aware that there is not a universal definition for LFS.

2. Low-frequency stimulation of the subthalamic nucleus in Parkinson's disease

2.1. Clinical experience

DBS of the STN at frequencies between 130 and 185 Hz can provide robust benefit in levodopa-responsive appendicular symptoms such as rigidity, bradykinesia, and tremor [1]. However, gait and other axial symptoms may be levodopa- and stimulation-resistant and the positive effect of subthalamic HFS usually declines over time [2,3]. In a prospective study, freezing of gait (FOG) at baseline was still present in 45% of PD patients treated with HFS of the STN at 6 and 12 months [4]. These observations have led some researchers to evaluate the effect of LFS in gait and axial symptoms in patients with PD (Table 1).

In one of the first attempts to assess the effect of subthalamic LFS on severe gait disorder, 13 PD patients were studied with low

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Table 1
Summary of published case-series of gait disorder related to Parkinson's disease treated with low frequency STN stimulation.

Author/year	Number of studied patients	Study design	HFS (Hz)	LFS (Hz)	Clinical outcome/follow-up
Moreau et al. (2008)	13	Randomized by frequency Blinded assessments	130	60[a]	LFS improved FOG and other gait features, but not UPDRS-III scores. Clinical benefit sustained up to 8 months.
Brozova et al. (2009)	12	Non-randomized Non-blinded assessments	N.A.	60[a]	Three patients did not tolerate LFS acutely due to symptom exacerbation. The remaining 9 patients had significant improvement in gait, balance and speech at 8–12 weeks.
Xie et al. (2011)	2	Non-randomized Non-blinded assessments	130	60	Both patients had deterioration of UPDRS-III scores with HFS, with improvement after switching to LFS. LFS remained effective for 10 months in both cases.
Ricchi et al. (2012)	11	Non-randomized Blinded and non-blinded assessments	130	80[a]	Gait improvement was observed in all patients at 3 h after switching to LFS. However global improvement was observed in only 5 patients at 15 months.
Sidiropoulos et al. (2013)	45	Non-randomized Non-blinded assessments	130 –185	80 (39)[a] 60 (6)	No significant improvement in speech, gait and balance was observed with LFS. Patients were followed up to 4 years and only 12 out of 45 patients remained on LFS.
Khoo et al. (2014)	14	Randomized by frequency Double-blinded	130	60	LFS provided statistical significant improvement in total UPDRS-III scores, axial motor signs and akinesia. No long term follow-up is reported.
Phibbs et al. (2014)	20	Randomized by frequency Double-blinded	130	60	No significant differences in stride length between low and high frequencies. Two patients had significant subjective improvement with LFS. Gait evaluation was carried out 60 min after switching frequencies.
Xie et al. (2015)	7	Randomized by frequency Double-blinded	130	60	LFS reduced FOG and axial parkinsonian symptoms, aspiration frequency and swallowing difficulty with patients in the medication "on" state. Benefits persisted at the 6-week assessment.
Vallabhajosula et al. (2015)	19	Randomized by frequency Blinded and non-blinded assessments	>100	60[b]	No significant differences in postural control and gait were observed between HFS and LFS.
Randhani et al. (2015)	5	Non-randomized Non-blinded assessments	130 –185	60	Improvement in gait disorder, segmental symptoms and LID. Benefit was sustained at 2–6 months follow-up.

Patients in these studies were typically stimulated with a pulse width of 60 us and variable voltage. FOG: freezing of gait; HFS: High frequency stimulation; LID levodopa-induced dyskinesias; LFS: low frequency stimulation; UPDRS-III: Unified Parkinson's Disease Rating Scale motor score; N.A. not applicable or described.
[a] Adapting voltage to maintain the same total delivered energy.
[b] Used both non-adaptive voltage and adaptive voltage to LFS to maintain total delivered energy.

(60 Hz) and high (130 Hz) stimulation frequencies [5]. Freezing episodes were significantly lowered using 60 Hz compared with 130 Hz; clinical benefit was still present at 8 months in 85% of cases [5]. Although FOG is usually observed months to years after starting DBS therapy [1], this symptom may develop or worsen immediately in a small proportion of patients with PD upon activation of newly placed electrodes using HFS, followed by rapid improvement after lowering the stimulation frequency to 60 Hz in the medication "on" and "off" state [6,7]. These observations were replicated in a double-blinded study including 14 patients with PD [8]. After optimizing the active contacts, stimulation at 60 Hz improved an additional 4.6 points on the motor score of the Unified Parkinson's Disease Rating Scale (UPDRS) compared with stimulation at 130 Hz [8]. Stimulation at 60 Hz of the most distal contacts presumably in the ventral STN seems to provide the largest benefit in motor and gait performance [5,7,8], contrasting with observations indicating that the dorsolateral part of the STN is the ideal target for DBS in PD.

LFS has been reported to improve other axial parkinsonian symptoms besides gait. In a study of seven patients with PD, the swallowing function was assessed by means of three modified barium swallow studies with stimulation at 60 Hz, 130 Hz, and the DBS turned off in a random order [9]. In that study, stimulation at 60 Hz reduced the aspiration frequency by 57% and improved subjective swallowing difficulty perception by 80% compared with stimulation at 130 Hz [9]. Subjective speech improvement has also been reported with LFS [10]. In a double-blinded randomized study of 11 patients with PD, a statistically significant improvement in maximum phonation time, median fundamental voice frequency, and item 18 (speech) of the UPDRS were detected using 60 Hz STN stimulation compared with 130 Hz [11]. Increased respiratory driving pressure, velopharyngeal, and vocal fold closure were also observed as the stimulation frequency was progressively lowered in two other reports [12,13]. The effect of different stimulation frequencies in hand bradykinesia has also been investigated using an instrumented glove [14]. No gradient effect for lower frequencies was found in that study; instead, diverse frequencies (low and high) resulted in specific peaks of increased movement amplitudes (less bradykinesia) that varied among individuals [14]. In another study, stimulation at 80 Hz was more effective than 130 Hz to control dyskinesia and dystonia in 10 patients with PD; however, 4 of these patients were returned to HFS due to worsening parkinsonism [15].

Despite these encouraging results, some studies have reported no benefit with subthalamic LFS in PD (Table 1). In a nonblinded study that included 45 patients with PD and loss or no axial benefit with HFS; participants were switched to 80 Hz ($n = 39$) and 60 Hz ($n = 6$) stimulation, followed by voltage adjustment to keep the total electrical energy delivered (TEED) at levels comparable to HFS [10]. No significant improvements in gait and axial scores of the UPDRS were observed with LFS [10]. Other studies have not reported significant differences in step length and velocity during gait initiation and the UPDRS motor score between 60 Hz and >100 Hz stimulation [16,17]. Another question is whether the benefit of LFS can be sustained in the long term. In the study by Sidiropoulos and colleagues, only 12 out of 45 patients (26.6%) remained on LFS at a mean follow-up of 111 days, but mainly due to subjective

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