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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.

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

improvement [10]. In another study of 11 patients with PD, gait improvement was observed in all patients at 3 h after switching the stimulation frequency from 130 to 80 Hz; however, at the last follow-up at 15 months, only 5 patients (45%) reported some subjective benefit in their gait with LFS [18]. Tremor exacerbation can be experienced by some patients after lowering the stimulation frequency [9,18]. Among 45 patients with PD, 7 (15.5%) were switched back to HFS within 48 h due to worsening tremor and other parkinsonian symptoms when stimulation was provided at 80 Hz or less [10]. This observation suggests that patients with tremor-dominant PD have a lower probability to remain on LFS in the long term due to exacerbation of disabling tremor [5,18].

The effect of very low stimulation frequencies in the STN has also been explored in PD. Stimulation frequencies between 5 and 10 Hz can worsen akinesia [19–21]. In one study, the finger tapping rate statistically decreased 11.8% and 7.4% using 5 and 20 Hz stimulation frequencies, respectively, compared to no stimulation [22]. Other authors have found decreased tapping rates by 8% and slowed grip force by about 15% with stimulation at 20 Hz in 16 patients with PD [23,24]. Despite these negative results with very LFS, improved verbal fluency and peak force in self-initiated isometric elbow flexion and finger pinch was observed using stimulation at 10 Hz compared to 130 Hz or no stimulation in a group of patients with PD [25,26].

2.2. Physiopathology mechanisms of LFS in the STN

DBS can provide benefit for movement disorders through several mechanisms [27–29]. Motor symptoms in PD such as rigidity and bradykinesia have been associated with increased synchronization of low frequency rhythmic oscillations within the beta band throughout the basal ganglia and motor cortex in the medication "off" state [30,31]. Desynchronization of oscillatory beta activity with simultaneous increase in activity within the gamma band is associated with movement facilitation (Table 2) [32–42]. Subthalamic stimulation using frequencies above 70 Hz has reduced pathological synchronized beta band activity in the basal ganglia and thalamus [43]; although stimulation at 20 Hz increased synchronization within the beta band in the basal ganglia promoting akinesia in some studies [22,44]. HFS of the GPi in nonhuman primates and the entopeduncular nucleus in rats (the homolog to GPi in humans) can also shift the neuronal oscillatory activity from the beta to the gamma band throughout the motor cortex and striatum in the parkinsonian state [45,46]. Simulation models have demonstrated that disruption of intrinsic burst activity is better achieved with a stimulation frequency of 130 Hz rather than 65 Hz [47]. Furthermore, the coefficient of variation of instantaneous firing rates in neurons decreased with stimulation frequencies above 90 Hz and increased during stimulation frequencies below 50 Hz, indicating that the neuronal firing activity becomes more regular with higher stimulation frequencies [48]. It has been hypothesized that stimulation with low frequencies may result in longer interpulse intervals promoting rebound activity in the stimulated and downstream nuclei, increasing abnormal synchronized activity within the beta band [48]. This is supported by recordings of rebound spikes in the thalamus when a pause of 20 msec or longer is introduced during continuous stimulation [49–51]. However, whether STN stimulation below 20–30 Hz increases synchronization within the beta band in patients with PD is disputed by some clinical observation showing no worsening of akinesia with these frequencies [52] and the still debatable role of beta oscillatory activity in the pathogenesis of parkinsonism, which is supported by lack of clear evidence that the degree of such synchronization within the beta band is directly related to the motor deficits and degree of motor improvement with levodopa [36]. Furthermore, in monkeys with gradually induced parkinsonism, synchronous oscillatory activity in the GPi is observed following the appearance of bradykinesia [53].

On the other hand, evidence links clinical improvement of parkinsonism with stimulation within prokinetic frequencies. In one study, the investigators measured the local field potentials in the STN from externalized DBS leads in 13 patients with PD, and customized the stimulation frequency to the peak gamma (30–100 Hz) frequency observed with medication and wrist movements [52]. High variability in peak activities within the theta, beta, and gamma bands were observed between subjects. Interestingly, stimulation at individual gamma frequencies significantly improved the motor UPDRS score with no difference compared to HFS (usually 130 Hz), suggesting that DBS at customized gamma frequencies (prokinetic) might be enough to improve parkinsonian symptoms [52]. However, this study does not explain why some patients with PD may have a selective improvement in gait and other axial symptoms with LFS. A simple decrease in TEED by lowering the stimulation frequency would not explain such selective improvement in gait but may decrease overstimulation of corticobulbar/corticospinal fibers potentially improving speech. One possible explanation of gait improvement is that the current may spread to mesencephalic locomotor centers, including the PPN which is located 5 mm below the STN. These structures respond better to LFS (see discussion below). However, this is unlikely as the caudal PPN is the one that responds better to DBS and one study did not show benefit in gait and balance performance when stimulation of the dorsal and ventral STN was compared [54]. Another possibility is that reciprocal connections between the STN and the PPN may be stimulated leading to an effect of the latter structure with clinical benefit at low frequencies. A recent study showed that STN stimulation in patients performing imagined gait increased regional cerebral blood flow (rCBF) in the PPN/mesencephalic locomotor centers [55]. However, whether these changes in rCBF represented a primary phenomenon or a compensatory response is unknown.

Table 2
Summary of oscillatory band activities recorded in the basal ganglia in patients with Parkinson's disease.

Activity range in Hz	Clinical and physiopathology implications
4–7 Hz (theta)	Frequency associated with levodopa induced dyskinesias [32,33]. A 4–6 Hz frequency is associated to tremor in patients with PD.
7–12 Hz (alpha)	Increased coherence has been observed between the STN and temporal cortex; movements induce coherence reduction which is more prominent in the medication "on" state [41].
13–30 Hz (beta)	Peak activity in the beta band is characteristic of the parkinsonism in the medication "off" state. Increased coherence between the STN and ipsilateral sensorimotor and premotor cortex is observed in patients with PD [40]. Activity attenuation in this band is observed in the medication "on" state.
30–100 Hz (gamma)	Observed in the medication "on" state of PD, associated with a prokinetic effect. STN activity at 60–90 Hz shows coherence activity with the ipsilateral M1 [42]. Individualized STN DBS at this frequency has been observed as effective as HFS to improve motor symptoms in PD [52].
>100 Hz (high frequencies)	Levodopa increases 300 Hz activity in the STN in the medication "on" state, particularly when movement-related [34]. Absence of 300 Hz STN activity may be a pathophysiological clue in PD.

M1: primary motor cortex; PD: Parkinson's disease; STN: subthalamic nucleus.

3. Low-frequency stimulation of the pedunculopontine nucleus in parkinsonian disorders

3.1. Clinical experience

The PPN is a reticular structure located in the caudal ponto-mesencephalic tegmentum, with the rostral end beginning below the red nucleus continuing caudally up to the locus coeruleus [56]. The PPN has been used as a target for DBS in patients with PD since 2005 [57,58]. PPN stimulation has been shown to improve FOG and falls in PD, with bilateral stimulation yielding better results than unilateral stimulation [59,60]. A positive effect in working memory, delayed recall, executive functions, improved sleep architecture with reduced number of awakenings, and daytime sleepiness has also been observed with PPN DBS [61,62]. PPN DBS has also been employed to treat medication-refractory primary progressive freezing of gait [63,64], and the gait disorder of progressive supranuclear palsy [56,65,66] with limited success.

Improvement in FOG and falls in patients with PD treated with PPN DBS has been obtained mainly with stimulation frequencies between 20 and 45 Hz [67,68], with gait deterioration observed in some instances with frequencies above 60 Hz [65]. Little or no effect has been observed in most patients with stimulation frequencies above 45 Hz [58]; except for a short case series that showed benefit with frequencies between 50 and 70 Hz [69]. Although tolerance to LFS has been reported, requiring progressively higher stimulation frequencies, this observation needs confirmation [65,67]. Despite some encouraging results, PPN DBS is considered experimental and far from becoming a routine clinical practice.

3.2. Physiopathology mechanisms of LFS in the PPN

The PPN has a complex organization with the rostral region having reciprocal connection with the basal ganglia and containing inhibitory neurons expressing gamma aminobutyric acid (GABA) [70]. The caudal region of the PPN is rich in glutamatergic and cholinergic neurons and projects widely to the cortex and locomotor centers in the spinal cord [71]. Oscillations in the alpha range represent the main frequency observed in the caudal PPN in patients with PD, whereas oscillations in the beta range are observed mainly in the rostral PPN; this latter frequency is probably transmitted from the basal ganglia [72–74]. Alpha oscillations are implicated in attention and allocation of processing recourses with suppression of task-irrelevant distractions [74,75]. Theta oscillations are implicated in sensory feedback between the PPN and the sensorimotor cortex [76]. A correlation between increased alpha oscillations in the PPN and improved gait performance has been observed, with alpha attenuation associated with FOG [74]. Levodopa strongly promotes oscillatory alpha synchronization in the PPN coupling with cortical activity [77] with simultaneous decrease in the oscillatory activity within the beta and gamma bands [71,78]. Although some studies have shown increased activity in the beta band with dopaminergic medication, the significance of this finding is unclear [74,78].

It has been hypothesized that DBS induces a driving effect in the PPN, rather than a blocking or inhibiting one [58,70]. This is supported by experimental studies showing that after delivering increasingly higher intracellular currents in single patch-clamped PPN neurons, virtually all of them increased their firing frequency but plateaued at 40–60 Hz [79,80]. It has been proposed that this frequency plateau in PPN cells explains the requirement to stimulate at low frequencies in order to induce locomotion [80]. Furthermore, the PPN seems to be overinhibited in PD by increased GABA-ergic input from the GPi [81,82]. This inhibition would be overcome by DBS.

It has been hypothesized that increased alpha activity induced by relative LFS promotes attention and suppresses task-irrelevant distractions; the concomitant decrease in beta activity would lead to less akinesia reducing episodes of FOG [70]. This is supported by the observation that the best therapeutic efficacy is obtained when the electrode is placed in the site of maximal alpha activity [74]; and PPN stimulation has been demonstrated to reduce activity within the beta band in the STN of 6-hydroxydopamine (6-OHDA) rat model of PD [83]. Moreover, PPN DBS can induce a significant increase in rCBF in several brain areas including the ipsilateral ventral midbrain region (comprising the PPN), and the supplementary motor area [84–86]. The latter is implicated in internally generated motor actions. It should be considered that PPN neurons are under a process of degeneration and increased compensatory activity of PPN neurons has been registered in experimental models during the initial phases of the disease; these changes may partially explain the heterogeneous clinical effects of PPN DBS with no benefit obtained in some cases [87,88].

4. Low-frequency stimulation of the thalamus

The ventral intermediate nucleus (VIM) of the thalamus has been the main target for DBS to suppress tremor in patients with PD or essential tremor (ET). Tremor suppression has a strong dependency to stimulation frequency in patients with ET, with maximal benefit reported with frequencies between 90 and 100 Hz [89,90]. Stimulation below 50 Hz usually does not suppress tremor and can induce myoclonic jerks or worsen tremor [91,92]. Intentional tremor is exacerbated usually more than postural tremor [93]. Computational modeling has shown that HFS reduces the output firing of thalamocortical neurons by masking its intrinsic burst activity, whereas LFS seems to supplement the amplitude of such activity leading to tremor exacerbation [94]. Relatively long pauses during thalamic stimulation may also increase tremor [95]. A decreased activation of the motor cortex has been observed in an animal model using thalamic HFS, whereas the opposite effect is observed with LFS [96].

5. Low-frequency stimulation of the globus pallidus for dystonia and other hyperkinetic movements

5.1. Clinical experience

DBS of the GPi has proved effective for dystonia and other hyperkinetic movements [97–99]. In these patients, the current frequency and amplitude have been demonstrated to be the most important parameters associated with benefit, with a stimulation frequency above 60 Hz providing symptomatic relief [100]. However, the stimulation parameters used to treat dystonia were not developed specifically for this group of disorders and instead they were adopted from previous experience in PD and ET [101]. Although several studies have proved that stimulation frequencies between 130 and 185 Hz are effective to improve several types of dystonia [97,102], within the last decade the use of HFS for dystonia has been challenged by some authors reporting benefit with stimulation frequencies below 100 Hz (Table 3). In a study assessing the effect of 60 Hz stimulation since the beginning of the therapy, the authors studied 15 patients with dystonia, 12 of them with positive *DYT1* gene mutation [101]. Improvement in motor and disability scores of 81% and 34%, respectively, were reported in that study [101]. In other cases, maximal dystonia relief was achieved with GPi stimulation at 50 Hz but using high pulse widths between 500 and 1,000 μsec [103,104]. It has also been suggested that lower pallidal stimulation frequencies may help to decrease the side effects of stimulating undesired structures. For example, one

Table 3
Summary of published case-series of dystonia and other hyperkinetic movements treated with low frequency stimulation of the GPi and STN.

Author/ year	Movement disorder	Number of studied patients	Study design	Target Nucleus	DBS parameters: Frequency (Hz) Pulse width (msec) Amplitude (V)	Clinical outcome/follow-up
Goto et al., 2002	CD	3	Non-randomized Non-blinded assessments	GPi	50–60 Hz 500 μs 4.5–8.0 V	Robust benefit in the TWSTRS total severity, total pain and total disability scores was observed in all patients at one year.
Alterman et al., 2007	Primary torsion dystonia	15	Non-randomized Non-blinded assessments	GPi	60 Hz 120–270 μs 2.5–3.5 V	BFMDRS motor scores improved from 38% at 1 month to 89% at 1 year. Disability scores also improved.
Limotai et al., 2011	Cranial-cervical dystonia	6	Randomized video evaluations Blinded assessments	GPi	10 and 60 Hz 60 and 180 μs 1.5 and 3.2 V	Six patients were studied but only 2 with LFS, because one did not tolerate HFS and another had better response to LFS at 1 year.
Li et al., 2012	Chorea-acanthocytosis	2	Non-randomized Non-blinded assessments	GPi	40 Hz 60 μs 3.5 V	Marked improvement in chorea and limited in dystonia in both patients at 4 weeks.
Kim et al., 2012	CD	14	Non-randomized Non-blinded assessments	GPi	70–160 Hz 60–210 μs 2.2–3.6 V	Mean improvement of 78.4% in severity, 68.4% in disability and 66.8% in pain subscores of TWSTRS at 2 years.
Velez-Lago et al., 2012	CD	13	Non-randomized Non-blinded retrospective assessments	GPi	60 Hz 150–210 μs 2.0–3.5 V	At the last follow-up, 5 (38.5%) of patients remained with LFS. Average follow-up was 24 months.
Ostrem et al., 2014	CD and upper limb dystonia	7	Randomized order of videotaped evaluations Blinded assessments	STN	60 vs. 130 Hz 60 μs 1.5–4.1V	Evaluations were carried out at 3 months with LFS, at 6 and 12 months with HFS. Improvement in BFMDRS-M: LFS vs. HFS: 16.6 vs. 52.3% and in TWSTRS: 9.5% vs. 45.2%.

BRMDRS (M): Burke-Fahn-Marsden Dystonia Rating Scale (motor); CD: cervical dystonia; TWSTRS: Toronto Western Spasmodic Torticollis Rating Scale; UDRS: Unified Dystonia Rating Scale; HFS: High frequency stimulation; LFS: Low frequency stimulation. DBS parameters reported in means or ranges.

reported patient was able to achieve marked benefit in his dystonia using ventral contacts within the GPi, but only when using an 80-Hz stimulation frequency to avoid side effects [105]. LFS has also been used in two out of six patients with cranial-cervical dystonia, due to lack of response or worsening blepharospasm with HFS [106,107]. Marked improvement in chorea and moderate in dystonia has been described in three patients with chorea-acanthocytosis treated with bilateral GPi DBS at 40 Hz [108,109]. Although some of these patients have been reported to suffer an exacerbation of their abnormal movements with HFS [109], one patient with chorea-acanthocytosis had worsening truncal spasm with stimulation frequencies between 40 and 50 Hz [110]. GPi stimulation at 65 Hz has provided benefit in selected patients with Tourette syndrome [111].

If stimulation frequencies below 100 Hz in the GPi can provide benefit for dystonia, an important question is whether such improvement is sustained as observed in patients treated with HFS [112]. Among 14 patients with cervical dystonia treated with bilateral GPi stimulation started at 70 Hz, a gradual increase to a mean of 100 Hz after a 2-year follow-up was necessary in order to keep an overall improvement in the Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS) above 70% [113]. In another study, only 6 out of 13 patients (46%) with cervical dystonia treated with GPi DBS remained with a stimulation frequency of 60 Hz at 6 months [114]. Duration of dystonic symptoms and age at the time of surgery were the only factors that predicted a sustained benefit from pallidal DBS at 60 Hz in dystonia [101,114]; whereas gender, age at disease onset, dystonia severity at baseline, and *DYT1* status were not predictors of patients remaining on LFS in the long term [101,114].

The reported experience indicating benefit with LFS in dystonia contrasts with other studies reporting no benefit or worsening of dystonic symptoms using frequencies below 100 Hz [115,116]. In a study of five patients with primary dystonia, an improvement in dystonic symptoms was observed with stimulation frequencies above 130 Hz, with a significant deterioration when stimulation was provided at 5 and 50 Hz [116]. However, in that study the symptoms were evaluated 4 h after switching to a specific frequency, a time considered too short to fully assess the effects of DBS in dystonia [105,116]. Subthalamic stimulation at 60 Hz has also been used in seven patients with dystonia within the first 3 months after starting the therapy and then switched to HFS (130 Hz) [117]. A lower improvement in dystonia scales was observed with LFS compared to HFS. However, this difference could be attributed at least partially to a difference in the total duration of the stimulation (less with 60 Hz) [117].

A motor syndrome characterized by gait difficulties with FOG and hypokinesia in body parts not affected by dystonia has been described mainly in patients with focal dystonia undergoing GPi DBS [118–122], leading to a difficult tradeoff between the beneficial effects of the stimulation on dystonia and the motor syndrome when adjusting the stimulation settings [118–124]. Some authors have suggested that stimulation between 100 and 110 Hz may be helpful to improve this syndrome, but additional evidence is needed to confirm this observation [120,122].

Patients with dystonia treated with GPi DBS frequently require high TEED due to the use of high voltage and pulse widths, usually above 120 μs, which leads to rapid battery depletion and frequent replacement of pulse generators, in some cases every 18–36 months [101]. In this case, LFS may provide a robust battery saving

method. In one study, battery life was significantly longer using stimulation at 60 Hz compared with HFS (≥100 Hz): 79.9 vs. 32.2 months, respectively [114].

5.2. Physiopathology mechanisms of LFS in the GPi

The mechanisms of action of GPi DBS in dystonia are not fully understood. It has been suggested that GPi-DBS disrupts the abnormal activity and transmission in the basal ganglia-thalamocortical circuit [121,125]. Patients with dystonia have less beta and more theta (4–10 Hz) oscillatory activity in the GPi compared to patients with PD [126–128], with bilateral desynchronization in both bands induced by sensory tricks [129]. Dystonic spasms have been associated with increased theta, alpha, and low beta activity (3–18 Hz) in the GPi [130]. DBS seems to suppress pathologically enhanced theta activity in the GPi improving phasic dystonic movements, whereas it has been hypothesized that improvement in tonic components may depend on long-term plastic changes induced by the stimulation [131]. Recordings of neuronal spontaneous activity in patients undergoing GPi DBS have demonstrated a lower mean firing rate in dystonia (~55 Hz) compared to PD (~95 Hz) [127,132]. The mean GPi discharge rate has been inversely correlated with the severity of dystonia [127]. Although local field potential activity less than 10 Hz in the thalamus, STN, and pallidum has been observed coherence with dystonic movements and seems to drive EMG oscillations in affected muscles [115,133,134].

Stimulation of the GPi seems to entrain the spiking neurons around the electrode leading to strong stimulus-locked modulations in firing probability which normalizes or suppresses abnormal firing patterns [135]. It has been hypothesized that stimulation frequencies exceeding the mean pallidal oscillatory activity in dystonia (~50 Hz) would be enough to modulate this abnormal activity and dystonic movements [113]. This is supported by the observation that the average firing rate of the GPi decreases as the stimulation frequency increases and was silenced with a stimulation frequency above 50 Hz in one study [136]. This has led to a proposal that the minimum effective stimulation frequency may be related to the firing rate of the target [101,111]. However, it is unclear why dystonia patients effectively treated with stimulation frequencies below 100 Hz since the beginning of the therapy eventually require higher stimulation frequencies to maintain such improvement. Unlike tremor and parkinsonism, full improvement of dystonia with DBS usually takes several months, probably owing to the time required to remove maladaptative plasticity in the basal ganglia-cortical circuits [27]. Whether this change in abnormal plasticity is similar or less pronounced with stimulation frequencies below 100 Hz is unknown.

6. Conclusions

Despite encouraging results obtained in some studies using LFS for diverse MDs, higher level of evidence with randomized and blinded studies including a larger number of cases is necessary to better define which factors predict a favorable clinical outcome with stimulation below 100 Hz in order to improve the selection of patients undergoing this therapy. Whether or not to increase the stimulation amplitude and therefore the electric field and volume of tissue activated when using LFS in PD patients is still an open question, as some studies have shown benefit of LFS without applying this adjustment (Table 1). In the meantime, we suggest that a stimulation frequency between 60 and 80 Hz can be tried in PD patients manifesting gait deterioration or lack of improvement with HFS, while PPN DBS might be used on an experimental basis. Currently, some evidence suggests that individual STN stimulation at specific gamma frequencies may be helpful to improve PD symptoms; such frequencies may be useful in the future for feedback in closed-loop DBS. Relative LFS in patients with dystonia and other hyperkinetic movements implanted with nonrechargeable impulse generators can be used to optimize energy consumption and prolong battery life.

Author roles

1) Research project: A. Conception, B. Organization, C. Execution; 2) Statistical Analysis: A. Design, B. Execution, C. Review and Critique; 3) Manuscript: A. Writing of the first draft, B. Review and Critique.

José Fidel Baizabal-Carvallo: 1A, 1B, 1C, 3A,3B.

Marlene Alonso-Juarez: 1A, 1B, 1C, 3B.

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Review criteria

We performed a systematic search in PubMed, using the terms “deep brain stimulation” or “DBS” combined with the terms “low frequency”,“ low frequency stimulation”, “gait disorder”, “Parkinson's disease”, “dystonia”, “tremor” and “chorea”. Only papers in English language were selected for this review. A total of 987 manuscripts published from 1998 to 2015 were obtained following the search criteria using all keywords, with overlap among searches. The final reference list was generated after selecting the manuscripts with key information regarding the selected topic.

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