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Freezing of Gait in Parkinson's Disease: Invasive and Noninvasive Neuromodulation

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Abstract

Introduction: Freezing of gait (FoG) is one of the most disabling yet poorly understood symptoms of Parkinson's disease (PD). FoG is an episodic gait pattern characterized by the inability to step that occurs on initiation or turning while walking, particularly with perception of tight surroundings. This phenomenon impairs balance, increases falls, and reduces the quality of life.

Materials and Methods: Clinical–anatomical correlations, electrophysiology, and functional imaging have generated several mechanistic hypotheses, ranging from the most distal (abnormal central pattern generators of the spinal cord) to the most proximal (frontal executive dysfunction). Here, we review the neuroanatomy and pathophysiology of gait initiation in the context of FoG, and we discuss targets of central nervous system neuromodulation and their outcomes so far. The

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Authorship Statements

Shervin Rahimpour, Wendy Gaztanaga, Stephano J. Chang, Iahn Cajigas, and Doris Wang conceived of the manuscript, all authors helped in the preparation of the manuscript draft. All authors approved the final manuscript.

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PubMed database was searched using these key words: neuromodulation, freezing of gait, Parkinson's disease, and gait disorders.

Conclusion: Despite these investigations, the pathogenesis of this process remains poorly understood. The evidence presented in this review suggests FoG to be a heterogenous phenomenon without a single unifying pathologic target. Future studies rigorously assessing targets as well as multimodal approaches will be essential to define the next generation of therapeutic treatments.

Keywords

Deep Brain Stimulation; freezing; gait; Parkinsons disease

INTRODUCTION

Freezing of gait (FoG) is a disabling yet poorly understood phenomenon common in advanced Parkinsonian syndromes (1,2). FoG is defined as a "brief, episodic absence or marked reduction of forward progression of the feet despite the intention to walk" (3). Up to 63% of patients with idiopathic Parkinson's disease (PD) and 88% of patients with microvascular ischemia experience FoG, with increasing incidence in later stages of both diseases. It is also a common feature of Parkinson's plus syndromes (including progressive supra nuclear palsy, multiple system atrophy, and corticobasal degeneration) (4–6). Risk factors for FoG include male sex, left-sided disease onset, early gait abnormalities, more axial symptoms, higher daily dose of levodopa, and other nonmotor symptoms such as hallucinations, depression, and anxiety. Episodes can be brief or exceed 30 sec (7). Specifically, three patterns of FoG have been distinguished including: 1) trembling in place, 2) shuffling forward, and 3) complete akinesia. These episodes are more likely to occur when initiating walking, turning, and passing through narrow passages or certain circumstances such as approaching a destination (8). Other provocative circumstances include approaching doorways, dual-tasking, distractions, crowded places, and being under time pressure. Interestingly, ameliorating factors such as emotional valence and visual and auditory cueing can shift the focus of a patient's attention and reduce FoG (9–11). This notion is consistent with the cued shift in patient's attention leading to conscious activation of compensatory cortical pathways for impaired subcortical control of gait (12).

FoG causes falls, reduces quality of life, and likelihood of independent living (13). Furthermore, the functional impact of FoG is independently linked to reduced health-related quality of life (HRQoL), irrespective of other general disease severity measures (1). Standard medical treatment for PD, dopamine replacement therapy, have shown limited benefit (14). While research into this debilitating symptom is of growing interest, effective therapies remain elusive. This is because normal gait is a complex process that involves concomitant balance and locomotion processes. A hierarchy of supraspinal regions send signals to the central pattern generators (CPG) of the spinal cord to modify stereotyped locomotion in certain situations such as initiating gait, turning, stopping, and avoiding obstacles. The locomotor network involves spinal CPGs, mesencephalic and cerebellar locomotor areas (MLR, CLR), subthalamic locomotor region (SLR) and various cortical areas including frontal–parietal, supplementary motor, and motor areas (Fig. 1).

Given the multiple neural networks involved with gait, there is a growing interest in using neuromodulation of these areas to ameliorate FoG. Targets for treatment have included deep brain stimulation (DBS) of the subthalamic nucleus (STN), globus pallidus internus (GPi), pedunculopontine nucleus (PPN), combined stimulation of these regions, and spinal cord stimulation (SCS) as well as noninvasive transcranial magnetic stimulation (rTMS), transcranial direct current stimulation (tDCS), and noninvasive vagus nerve stimulation (nVNS). Our aim here is to review the physiology of this relatively common and debilitating clinical phenomenon and discuss current paradigms for therapeutic invasive and noninvasive neuromodulation with a particular focus on interventions of the central nervous system. The PubMed database was searched using the following key words: neuromodulation, freezing of gait, Parkinson's disease, and gait disorders.

NEUROANATOMY AND PHYSIOLOGY OF GAIT

Walking demands a complex and balanced recruitment of neuronal systems requiring attention, afferent information processing and intentional adjustments (15,16). The motor cortex, midbrain, hindbrain, and basal ganglia are all involved in the decision making and planning of locomotion. Most of what is known about the hierarchical network of supraspinal locomotion centers and normal gait comes from animal studies. These studies have revealed three locomotor regions: the MLR in the mesopontine tegmentum, the SLR in the lateral hypothalamic region and CLR in the mid-part of the cerebellum (Table 1).

Human imaging studies corroborate these findings suggesting that the organization of these supraspinal locomotor centers is largely conserved. The first step in locomotion is behavior selection. The principal selection system is the basal ganglia, which allows for selection of a particular motor pattern in a behavioral and reward context (24). The striatum receives input from the cortex and in turn projects to the globus pallidus externa, substantia nigra pars compacta and the output nuclei of the basal ganglia (GPi and substantia nigra pars reticulata [SNr]). The basal ganglia output nuclei in turn project to the MLR for subconscious aspects of tone, postural balance and gait control. Specifically, GABA-ergic nigrotegmental efferents from the SNr terminate in non-cholinergic neurons (preferentially) and cholinergic neurons of the MLR (SNr-MLR system). These efferents have tonic neural activity, which must be suppressed to release the MLR from tonic inhibition when locomotion is initiated. Stimulation of the SNr in decerebrate cats with removed striatum, thalamus and cerebral cortex, but preserved SNr, blocks muscle tone suppression (lateral SNr) and reduces the number of step cycles (medial SNr) (25). Stimulation at higher strengths eventually stops MLR-activated locomotion. Thus, these nigrotegmental projections control both the steady state (e.g., postural control and rhythmic limb movements) and dynamic state (e.g., initiation and termination) of locomotion (26). Stimulation of the MLR in decerebrate cats increases postural tone and speed of walking or even galloping and therefore serves as a control unit (17,18). Since its first description in cats, this conserved locomotor network node has been demonstrated in multiple vertebrate species (27–29) with later electrophysiological and functional imaging studies supporting its existence in humans (30,31). Anatomically, the MLR consists of the pedunculopontine tegmental nucleus (PPN), cuneiform nucleus (CN) and subcuneiform nucleus. The PPN is further divided into PPN pars compacta and PPN pars dissipata. Neurons in this region contain glutamatergic (pars dissipata) and cholinergic

(primarily pars compacta) projections to the reticular formation in the lower brainstem which then send an important glutamatergic facilitatory pathway to the spinal CPGs (32). It should be noted that the premotor cortex and supplementary motor area (SMA) also have dense projections directly to the brainstem reticular formation (33).

Another area that when stimulated evokes locomotion is in the lateral hypothalamic area, a region that also projects to the reticular formation. Decerebration studies of cats reveal this area to be between the precollicular post-and pre-mammillary levels and is known as the SLR (34–36). When decerebration is made below this region, the cat is able to initiate locomotion but only with electrical or chemical stimulation of the MLR. However, with transection above this region cats can spontaneously initiate locomotion with well-coordinated and appropriate equilibrium control (34,36). This region has direct connections with the brainstem.

Stimulation of the SLR or MLR in decerebrate cats has been shown to evoke locomotor movements; however, coordination of the fore- and hindlimbs is greatly affected and there is development of extensor rigidity (37). These findings suggest that the cerebellum plays a critical role in generating and monitoring (through proprioceptive afferents) appropriate patterns of limb movements, regulation of balance and adaptation of posture and locomotion through practice (15). Mori et al. later demonstrated in cats that stimulation of the midline CLR (i.e., fastigial nucleus) can independently induce locomotion (23,38). Neuroimaging studies suggest a similar region exists in humans. In studies with mental imagery of gait or foot pedals monitoring active stepping during fMRI, focal increases in the interfastigial cerebellum and cerebellar vermis are observed and postulated to represent the human CLR (30,39).

Once animals start locomotion, muscle tone is regulated by spinal interneuronal networks known as CPGs that generate rhythmic activity in the absence of supraspinal rhythmic inputs (40). Rhythmic activity is sent to interneurons of the intermediate region (lamina IV–VII of Rexed), which are then transmitted to ipsilateral limb motor neurons. Lamina VIII interneurons project to the contralateral limb contributing to left–right gait cycle alterations (41). Activity of this network is modulated by sensory afferents (40,43). For example, proprioceptors in extensor muscles regulate transition from stance to swing phase. This rhythm and pattern is monitored by supraspinal structures via the spinothalamic, spinoretricular, and spinocerebellar tracts (44).

It is important to note that while the basic principles regarding locomotion and neuronal control have been largely preserved during evolution, the mechanism of gait in bipedal humans is fundamentally different from quadrupedal animals. Animal studies have revealed that the evolution of quadrupedal to bipedal locomotion did not affect principal anatomic structures; however, connectivity between principle nuclei may differ between species. For example, with respect to the PPN, the topography and morphological structure are similar in most mammals, but the distribution of cholinergic, glutamatergic and GABA-ergic neurons and degree of afferent and efferent fibers vary. These differences, including the normal vs. parkinsonian state, may account for species- and disease-dependent outcomes in experimental settings (45).

PATHOPHYSIOLOGY OF FREEZING OF GAIT

While poorly understood, there are hypotheses on the pathogenesis of FoG based on clinical–anatomical correlations, functional imaging, and neurophysiology studies (46). Hypotheses for the origin of FoG have ranged from failure of distal sources (central pattern generators of the spinal cord) to more proximal dysfunction (the frontal lobe) along the locomotion axis.

In PD, GABA-ergic output levels are abnormally increased. Takakusaki et al. proposed that gait disturbances are produced by abnormal increases in SNr-induced inhibition of the MLR (26). Furthermore, features of PD-induced gait deficiencies resemble SNr-stimulated movement (25). Non-human primate studies also confirm the importance of cholinergic neurons in the PPN in the control of gait (47,48). Damage to these neurons is associated with frequent falling in PD (49–51). However, there is no consensus regarding a common anatomical location that accounts for FoG. It is likely the case that FoG is a manifestation of an imbalance or dysregulation of one or several key nodes along the locomotor network manifesting in the same clinical phenotype (Fig. 1). Advances in imaging and neurophysiology have supported this interpretation: many neurological conditions are disorders of network perturbations, the so-called circuitopathies (52). Extending this concept to FoG, in a lesion-network mapping investigation Fasano et al. reviewed 14 cases of lesion-induced FoG (53). While lesion locations were heterogenous (parasagittal frontal areas, left postcentral gyrus, cerebellum, midbrain tegmentum, brainstem, and basal ganglia), >90% of lesions were functionally connected to a focal area in the dorsal medial cerebellum. Diffusion tensor imaging in patients with PD and FoG has also demonstrated decreased connectivity between the PPN and the cerebellum (54). While the lesion-network mapping findings may not share the same neuroanatomical substrate with PD associated FoG, they highlight the involvement of the cerebellum as an important node and possible target for future therapies (55).

Studies have also examined FoG neural circuitry using resting-state fMRI (rs-fMRI) with a virtual reality (VR) gait paradigm. Gilat et al. used a VR turning condition to trigger freezing in 17 patients with FoG. Findings in this study demonstrated increased activation in inferior frontal regions, which have been implicated in the recruitment of a putative stopping network (56). The hypothesis generated from these studies suggest frontal activation of an aberrant stopping signal via hyperdirect connections to the STN resulting in the arrest of locomotion. FoG has been associated with reduced functional connectivity within visual, sensorimotor, attentional fronto-parietal areas, and default mode networks (57). Reduced functional connectivity of the MLR and CLR with the SMA has also been observed and thought to reflect a decreased automatic control of movement, as well as reduced functional connectivity between the STN and SMA proposed to reflect reduced capacity to inhibit competing motor programs (58). Interestingly, a recent rs-fMRI study by Potvin-Desrochers et al. demonstrated increased thalamic/GPi connectivity with visual areas as well as between the left putamen and cerebellum in patients with FoG compared to those without. In contrast to prior studies, this increased connectivity in cortical and subcortical regions involved in sensory and visuospatial processing may serve as a compensatory pathway for sensorimotor deficits in FoG (59). A limitation of functional imaging studies is that they do not capture

the brain network activities during gait freezing episodes. Therefore, while they inform us about the overall network activity patterns in patients with FoG tendencies, they do not represent actual brain dynamics during FoG.

Outside of neuroimaging studies, electrophysiological data obtained from DBS have also revealed important information on the pathophysiology of FoG. The *decoupling model*, as proposed by Jacobs et al., describes FoG events as a decoupling between preplanned motor programs and the motor output response (60). In a recent study, Pozzi et al. investigated the communication between the cortex and subthalamic nucleus in patients who underwent STN-DBS (61). During effective walking, the cortex and STN were synchronized in the low-frequency band (4–13 Hz). In contrast, freezing episodes were characterized by cortical–subcortical decoupling. These findings were specific to locomotor cortical areas (i.e., SMA, primary motor and parietal cortex). A recent fMRI study evaluated door-way provoked FoG using virtual reality and found selective hypoactivation in the preSMA bilaterally (62). These studies suggest that FoG reflects a degree of impaired and disrupted signaling between certain locomotor cortical areas and the STN (63).

While the pathophysiology of FoG gleaned from these studies is variable, invasive, and noninvasive neuromodulation interventions of different targets have had some promising results in modulating the network outlined to prevent the expression of FoG (Table 2 and Fig. 2).

TARGETS OF NEUROMODULATION

Noninvasive

Transcranial Magnetic Stimulation—TMS induces electrical current through a rapidly changing magnetic field that activates cortical neurons located up to 2–3 cm beneath the scalp (103). To date, there have been six studies (sample size varying from 7 to 32 patients) investigating the effects of repetitive TMS (rTMS) on FoG in PD (9, 64–68). Six of the studies compared the effects between real and sham rTMS, while one study performed dual stimulation comparing the effects of rTMS + tDCS and rTMS + sham tDCS. In a meta-analysis of these six studies (91 PD patients), rTMS showed a beneficial effect on FoG questionnaire scores and Unified Parkinson's Disease Rating Scale (UPDRS)–III in PD patients (104). However, there were no significant differences in turning steps, turning time, or Timed Up and Go. Subgroup analysis according to stimulation site showed neither motor cortex stimulation nor frontal cortex stimulation had beneficial effect on FoG. These results should be cautiously interpreted as a small number of studies were included with heterogeneous stimulation protocols (stimulation intensity, coil design, number of sessions). Another recent randomized controlled trial including 30 PD patients with FoG showed that ten sessions of high-frequency (10 Hz) rTMS over the SMA had beneficial effects on FoG including improvement in the FoG questionnaire score, MDS-UPDRS-III and other gait variables (total duration, cadence, turn duration, and turn to sit duration). This study also found that the beneficial effects could last up to four weeks following stimulation (69). In a pseudorandomized, double-blinded parallel study comparing SMA and motor cortex stimulation Kim and colleagues also found reduction in freezing episodes after two sessions of high-frequency SMA stimulation in 12 PD patients (70). These results suggest that SMA

stimulation may be a better target in PD patients with FoG. However, future large cohort randomized studies are needed to confirm these findings as well as duration of therapy, particularly since short-term treatments have limited span of effect.

Transcranial Direct-Current Stimulation—tDCS is a portable, wearable brain stimulation device that delivers a low electric current to the scalp and facilitates cortical excitability. It works by applying a positive (anodal) or negative (cathodal) current via electrodes to an area. Several studies have investigated the efficacy of tDCS for FoG in PD patients. A specific crossover, double-blinded, randomized, sham-controlled study that included ten PD patients with medication resistant FoG and five sessions of 2 mA anodal tDCS on primary motor cortex showed benefits on FoG as measured by the Stand-Walk-Sit test with reduction in number and duration of FoG episodes, along with a significant reduction in the UPDRS score (71). Another crossover double-blind, randomized, sham-controlled study applied one session multibipolar tDCS electrodes stimulating only primary motor cortex in PD patients with FoG, which did not improve FoG. However, after stimulating both the primary motor cortex and left dorsolateral prefrontal cortex, the performance in FoG-provoking, Stroop and Timed Up and Go tests were improved (72). Notably, the left dorsolateral prefrontal cortex was not stimulated alone. This low-cost, noninvasive option could conceivably be used as an adjunct home therapy to help alleviate FoG. These findings should be interpreted cautiously as it is unclear if there is long-term retention with repeated tDCS sessions. Given the role of cognitive executive function in FoG, multitargeted stimulation involving this cognitive domain may have value though additional research is needed.

Noninvasive Vagal Nerve Stimulation—The mechanism of action of nVNS on FoG is unknown. Farrand et al. found that nVNS for ten days increased locomotion in a rodent model of PD. Their hypothesis regarding the mechanism of action for this treatment consists of nVNS activating locus coeruleus neurons, which are thought to degenerate even prior to substantia nigra dopaminergic neurons in PD (105). Since then, an open-label, pilot study explored the effect of single dose, nVNS on gait pattern in 12 patients with FoG. A total of two treatments were applied to the left vagus nerve in the left side of the neck below the mandibular angle, medial to the sternocleidomastoid muscle, with an interval of 15 min between two treatments. The treatments included 120 sec of continuous stimulation. Assessments were performed just before and 15 min following the application of nVNS. The study demonstrated improvements in time and steps taken for turning and steps taken for start hesitation but not necessarily freezing episodes (73). Outside of the tolerability of nVNS, conclusions from this small open-label study are highly preliminary in the absence of a randomized, placebo/sham-controlled multidose trial. A follow-up randomized controlled study is currently underway to corroborate these initial findings (106).

Invasive

DBS: Subthalamic Nucleus—DBS involves the surgical implantation of electrodes into specific targets of the brain and the delivery of constant or intermittent electricity from an implanted battery source. While most studies agree that STN-DBS is advantageous for tremors and dopaminergic medication control, fewer studies agree on the benefit or harm of

using STN stimulation for posture and FoG. Some report improvements in posture, gait, and balance following STN-DBS, but with greater improvement if these symptoms were initially responsive to levodopa treatment prior to surgery (74,107,108). In a secondary analysis of the EarlyStim randomized trial at three years after STN DBS 52% of patients in the control group experienced freezing whereas this was reduced to 34% in the active DBS group (75). Long-term follow up studies, however, have found that these effects on balance and gait tend to diminish with time after surgery (76,77). A study that focused on examining PD patients and videotaping them at baseline, one, five, and ten years after surgery found that stimulation and medications, used alone or together, did not ameliorate the axial signs at the five- and ten-years end points. Importantly, they proposed that the initial overall benefit to motor symptoms induced by STN stimulation mostly diminished with time due to worsening of these axial signs (76). Some authors even suggest that DBS may induce or aggravate FoG and postural instability with falls (78). A long-term follow-up study followed 20 patients with eight years of continuous stimulation and found that postural stability actually worsened over this time period with no difference in the ON- or OFF-medication state (77). Similarly, one of the longer-term follow-up studies found that after 20 or more years of STN stimulation, 64% of the patients gradually started reporting falls, and there was an overall higher prevalence of axial and non-levodopa-responsive symptoms with longer follow-up (79). Additionally, simply increasing the stimulation amplitude can worsen gait and increase freezing episodes (80). However, there is no study that has compared degree of FoG due to natural disease progression to those receiving long-term DBS. While the previously mentioned studies used standard high-frequency DBS (130–180 Hz), there is growing evidence that low-frequency STN stimulation (60–80 Hz) is more helpful in improving FoG (109). Possible theories on the mechanism of benefit for low-frequency stimulation include: 1) better current spread to the PPN (only 5–8 mm away from the STN) and 2) ability to override abnormal neuronal oscillations to boost prokinetic gamma band activity (110). One study of seven patients who experienced FoG found that compared to routine 130 Hz, 60 Hz stimulation significantly reduced FoG and more importantly, benefits persisted over an average six-weeks assessment (109). Moreover, several studies have found that bilateral STN stimulation produces greater improvement in gait than unilateral stimulation (81,82). This is expected as unilateral stimulation would only work on the contralateral side of the body, while bilateral stimulation would improve both sides. This phenomenon could possibly be due to basal ganglia structures in both hemispheres participating in the control of walking through brainstem projections by means of the pedunculopontine area (111).

DBS: Globus Pallidus Internus—While some studies have reported worsening of gait following GPi stimulation, others have reported temporary benefit (83,112). Of the most positive studies, Krack et al. reported a 5.5 point reduction of the gait score of the UPDRS-II (includes “walking,” “freezing,” and “falling” items) and UPDRS-III (“gait” and “postural instability”) when comparing pre-operative OFF state and six-month post-operative follow-up (OFF-levodopa/on-stimulation). However, this effect has been shown to diminish over time (84,85,113,114). When OFF-medication, stimulation-induced improvement of FoG was present after two years and persisted up to four years post-surgery (84,114). However, while there is improvement one-year post-surgery with combined treatment (ON-medication, ON-stimulation), no difference is seen from the ON-medication pre-stimulation baseline at three

to four years (85). Chronic DBS of the posteroventral GPi for dystonia may also induce a hypokinetic gait disorder with FoG with same phenomenology as in advanced PD. In a retrospective study by Schrader et al., of the 71 patients studied six patients (8.5%) developed a new stimulation induced gait disorder that worsened with increasing voltage (115). Similarly, a prospective study of ten dystonia patients found hypokinetic gait disorders and decreased step length following chronic GPi DBS (116). Given these mixed and failed long-term results, studies have focused on augmenting GPi or STN stimulation with PPN DBS (91).

DBS: Pedunculopontine Nucleus—The PPN in the mesencephalic tegmentum is an uncommon site for DBS in PD patients. However, this area has become a more intriguing target following the findings that apart from loss of dopaminergic nigrostriatal neurons, PD patients with a tendency to fall have been found to also have a loss of cholinergic neurons in the PPN and a decrease in thalamic cholinesterase activity (47,49). These findings were also tested using normal and parkinsonian monkeys where lesioning the cholinergic neurons in the PPN induced gait and postural deficits resistant to levodopa treatment (47). A meta-analysis published in 2017 provided evidence that PPN-DBS may improve FoG and falling in PD depending on the duration of follow-up and types of outcome measures used by the authors (117). Specifically, FoG was only found to be significantly improved by PPN DBS at three months after surgery in the drug-OFF state as measured by the UPDRS item 14 (117). Other studies also suggest that the efficacy of PPN DBS may dissipate over time (86). A long-term study of PD patients with PPN DBS for two years demonstrated that patient-reported freezing was significantly better when compared with baseline both in the ON and OFF-medication states. However, after four years of follow-up, this difference was no longer detectable for the cohort as a whole. Interestingly, a third of the patients did have a significant and sustained benefit for falls and freezing from baseline even at four years follow-up, suggesting that some unknown factor(s) may distinguish between responders and nonresponders (86).

Also controversial are the optimal parameters of stimulation in this region, such as whether unilateral or bilateral PPN stimulation is superior. Multiple randomized, double-blinded studies have demonstrated that unilateral PPN DBS improves FoG symptoms and markedly decreases number of falls experienced within at least one to two years of follow-up (86,87). Similarly, other randomized, double-blinded, cross-over studies have found that bilateral PPN-DBS, together with levodopa treatment, produced a significant decrease of the freezing episodes and the frequency of falls (88). No study has directly compared unilateral and bilateral PPN stimulation, and so it remains unclear if the benefits of bilateral stimulation outweigh the risks of implanting a second electrode. With regards to frequency of stimulation, it is generally believed that constant, low-frequency PPN stimulation has a better effect (118) with most studies using frequencies ranging from 15 to 70 Hz. However, a study using up to 130 Hz also found a significant decrease of the freezing episodes and the frequency of falls (88). To date, there is still a lack of a comparative study between high- and low-frequency PPN stimulation (118). While PPN-DBS does appear to be a promising intervention for FoG for early-onset gait disturbances as well as therapy resistant gait freezing despite STN/GPi, it is important to highlight that much of these data have been

collected from fewer than 100 total cases, including a heterogenous patient population with medication refractory freezing (119). In addition, there is great variability in methodology between surgical centers. Therefore, for PPN-DBS to become an established target for FoG in PD, it would require a collaborative effort between experienced centers with standardized clinical methodology (120).

DBS: Cuneiform Nucleus—The CN is an adjacent structure to the PPN related to modulation of both sensory and motor systems and was the original site identified as the MLR in cats by Shik and colleagues (18,121). However, despite their proximity, electrical mapping studies in animals demonstrate distinct effects on locomotion, with several studies favoring CN stimulation for the initiation and control of locomotion (19,20). This is supported mechanistically by optogenetic studies in rodents, which identify glutamatergic neurons in the CN as being the principal locus for initiating and increasing the speed of locomotion, while the activation of cholinergic neurons in the PPN failed to initiate locomotion (123–124). Although a computational modeling study of DBS in this region suggested that electrode shifts of as little as 1 mm could significantly decrease target activation selectivity, there have not yet been any clinical studies specifically looking at the effects of CN stimulation on FoG. However, at least two clinical studies in patients with PD have shown that the best effects on gait occur with active contacts located slightly posterior to the PPN, in other words closer to the cuneiform and subcuneiform nuclei (89,125). A prospective pilot trial of directional CN DBS is also currently underway (clinicaltrials.gov NCT04218526). These studies support the idea that optimizing electrode position in this region could improve results and that this may be an important factor underlying the variability of responsiveness to therapy reported to date (126).

DBS: Combined Stimulation—Given that DBS stimulation of only a single nucleus, such as STN, PPN, or GPi, cannot improve all symptoms of PD patients, some researchers have proposed combined stimulation of these nuclei to improve other PD symptoms, including FoG. Unfortunately, very few studies are concerned with combined stimulation and its effects on FoG. A randomized, double-blinded study revealed that bilateral PPN-DBS (25 Hz), in conjunction with standard STN-DBS (130–185 Hz), improved gait and postural instability (127). Importantly, in this study, the authors may have targeted the peripeduncular nucleus instead of the PPN, a distinct mid-brain structure, warranting some caution in interpretation of their results (128,129). Another study followed one PD patient and found that isolated bilateral PPN or GPi stimulation had a small impact on FoG, yet combined stimulation had a marked effect on reducing FoG (90). A recent review concludes that the combined stimulation of PPN and STN or GPi, or STN and SNr, may be useful for the treatment of FoG in PD patients (118). A prospective trial of combined PPN + GPi stimulation (bilaterally) in five patients with predominant freezing showed no benefit with rapid worsening of the freezing, over 5–12 months, though did reveal some aspects of synchronized circuitry between the two structures (91). Regarding combined STN + SNr stimulation, this is an attractive approach to modulating the SNr-MLR system using co-stimulation of the SNr on a caudal electrode contact of a lead with rostral contacts in the STN (130). Advanced programming of conventional DBS electrodes (Medtronic Neuromodulation, Minneapolis, MN, USA) with “interleaved pulses” or multiple-source

current steering with directional leads (Abbott Neuromodulation, Plano, TX, USA and Boston Scientific, Valencia, CA, USA) allows independent stimulation of the different contacts and therefore targets. Using this paradigm, a randomized control trial by Weiss et al. investigated SNr stimulation in the treatment of axial motor impairment in PD (92). In the 12 patients studied, combined stimulation resulted in improved FoG assessment course (p = 0.006) and decreased FoG episodes and improved FoG questionnaire scores, although not significant. Importantly, SNr stimulation was well tolerated without clinically relevant neuropsychiatric adverse effects. A subsequent study by Scholten et al. analyzed biomechanical parameters during unconstrained walking in 12 PD patients comparing STN-alone and SNr-alone stimulation (93). SNr stimulation improved temporal parameters of gait (swing time symmetry). Subsequent correlation analysis suggested that more medial localization of the SNr contact resulted in stronger regularization of gait. More recently, a study evaluating high-frequency STN stimulation combined with low-frequency SNr stimulation found sustained improvements in PD-associated gait disorders including freezing episodes (94). Efficacy of STN + SNr stimulation is under further investigation in a multicenter randomized controlled trial (clinicaltrials.gov. NCT02588144).

Spinal Cord Stimulation—Numerous clinical case reports and studies have reported that SCS is beneficial in improving FoG in PD patients. These studies were inspired by preclinical experiments which showed that epidural stimulation of the spinal cord improved symptoms of akinesia, abnormal gait, posture, and bradykinesia in rodent and primate models of PD (131–133). Although the clinical effect of SCS in the ameliorating the cardinal PD motor symptoms such as bradykinesia, tremor, and akinesia was limited, its effect on postural instability and gait disorders (PIGD) was quite remarkable. It is, however, worth noting that most of the initial SCS case studies were conducted as open label investigations in PD patients with chronic pain comorbidity (for a detailed review of pre-2017 studies, see (134)). Nevertheless, more recently, SCS has shown efficacy in improving FoG symptoms in patients who were earlier either previously treated with DBS or who did not have pain as a comorbidity (95,96). Quantitative measurement tools such as Inertial Measurement Unit sensors and movement analysis software have helped to understand how SCS improves gait, balance, and postural symptoms. A recent study in four PD patients who experienced postural instability and gait disturbances despite seven to eight years of subthalamic DBS showed that high-frequency upper thoracic (T2–T4) SCS at 300 Hz improved FoG questionnaire scores measured six months post-surgery as compared to baseline scores (95). Patients demonstrated 50–65% improvement in several gait measurements, including 56% improvement in FoG. Subsequently, a follow-up study explored the role of anticipatory postural adjustment (APA) and reactive postural responses on FoG and found that 300 Hz SCS reduced FoG duration along with reduction in the duration of APA during step initiation (98). Another study in five advanced PD patients with gait disturbances and FoG reported that mid-thoracic SCS (T8–T10) improved FoG questionnaire scores by 26.8% at six months follow-up (96). Mean number of FoG episodes and mean duration of FoG episodes measured quantitatively using a gait-mat showed remarkable reduction of 93.2% and 85.5%, respectively, between pre-surgery baseline and one to four months post-surgery periods. Thereafter, the same group reported that improvement in FoG-Q scores, FoG episodes, and duration of FoG episodes was sustained

in those patients three-years post-SCS surgery (97). Additional studies have explored prospective thoracic SCS with moderate benefits (135–137).

More recently, researchers have explored high cervical implantation, instead of thoracic, and burst stimulation pattern instead of tonic stimulation. These researchers reported satisfactory improvements in axial symptoms of gait and posture as well as changes in emotional symptoms (99, 138,139). SCS at 60 Hz was also tested in two patients with corticobasal syndrome, and one of the two subjects displayed dramatic recovery of gait and FoG symptoms at three and six months post-SCS intervention (140). Another report showed that 60 Hz SCS improved FoG in a patient with multiple system atrophy with predominant parkinsonism (141). The aforementioned reports in multiple patient populations with parkinsonian symptoms suggest that SCS has a fundamental effect on the pathophysiology of gait, which are affected by Parkinson-like neurological disorders. While the mechanism by which SCS improves FoG is not known, it is hypothesized that SCS desynchronizes corticostriatal low-frequency oscillations by activating the large diameter dorsal column fibers in the spinal cord (134). The hypothesis that SCS modulates supraspinal neuronal activity was successfully demonstrated in animal models but has yet to be tested in clinical populations (142,143). Although the exact SCS parameters with maximal therapeutic effect on FoG have yet to be ascertained, recent studies have hint at the efficacy of burst patterns and others have proposed that the incorporation of closed-loop stimulation paradigms may further improve efficacy (139,144). Additional clinical research on the role of SCS in modulating neuronal circuits responsible for FoG needs to be conducted with special emphasis on determining optimal stimulation parameters.

CONCLUSIONS AND FUTURE PERSPECTIVES

While many unknowns remain regarding the mechanism and treatment of FoG, much can be gleaned from the therapeutic targets discussed in this review. Mounting evidence suggests that FoG is not the result of a focal process but likely the product of multiple abnormally modulated regions along the locomotor network. Animal studies, while effective in describing the basics of normal gait physiology and gait control, have limitations when applying to humans. fMRI and lesion network mapping in humans have also been helpful in unraveling the neural substrate of FoG but provide an incomplete picture. Studies to date utilizing DBS, SCS, TMS, and tDCS have helped identify potential access points for neuromodulation of the locomotor network. This includes previously mentioned cortical, subcortical, and cerebellar targets. Because of the equipoise of anecdotal reports, these targets and interventions need rigorous clinical trial evaluation. Unique to FoG, compared to other more persistent symptoms of PD, is its episodic nature. Thus, an optimized therapy might include a bio-signature of an oncoming event prior to the freeze or fall that would intervene and reset the locomotion network. With newly emerging technologies such as directional stimulation and the ability to chronically record local field potentials, the prospect for the development of a closed-loop adaptive system is high. The evidence presented in this review suggest FoG to be a heterogenous phenomenon (akinetic, trembling, responsiveness to environment) without a single unifying pathologic target. Future studies rigorously assessing targets as well as multimodal approaches are essential to define the next generation of therapeutic treatments for this debilitating symptom.

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COMMENTS

This paper is a comprehensive review of the current status of neuromodulation for treatment of freezing of gait.

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The authors hit a difficult topic about putative pathophysiological mechanisms and neuromodulation approaches to treat FoG. The complexity of the topic is grounded on many levels: the fine-tuned interplay of cortical, subcortical and spinal neuronal network components in locomotion control on a physiological basis; the clinical variability of the symptom in PD patients as well as the overall difficulty to objectively assess the magnitude of FoG and therapeutic outcome measures. Regarding anatomical and physiological aspects of FoG, classical concepts of circumscribed locomotor regions in the mid-brain, cerebellum and brain stem should be revised given their diverse role in multiple behavioral functions. Modern views point out the network aspects of a distributed locomotor system with multiple cortical and subcortical nodes. The diverse neuromodulation approaches have targeted various components of this network and are summarized in this review. Despite their promising results, all of them share the same difficulties and methodological concerns: the low number of included patients, variable and partly inadequate outcome measures and a lack of adequate controls and blinding.

For future investigations, there is a need for conducting multicenter trials to yield adequate sample sizes and to apply clear-defined and adequate outcome measures if relevant improvements of treatments shall be achieved.

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The manuscript reports important insights regarding neurophysiological aspects of the freezing of gait phenomenon, which can be a highly debilitating motor symptom in Parkinson’s disease and other neurological conditions. The detailed discussion offers insights to the underlying pathophysiological mechanisms, current invasive and non-invasive therapeutical strategies, pitfalls and future opportunities.

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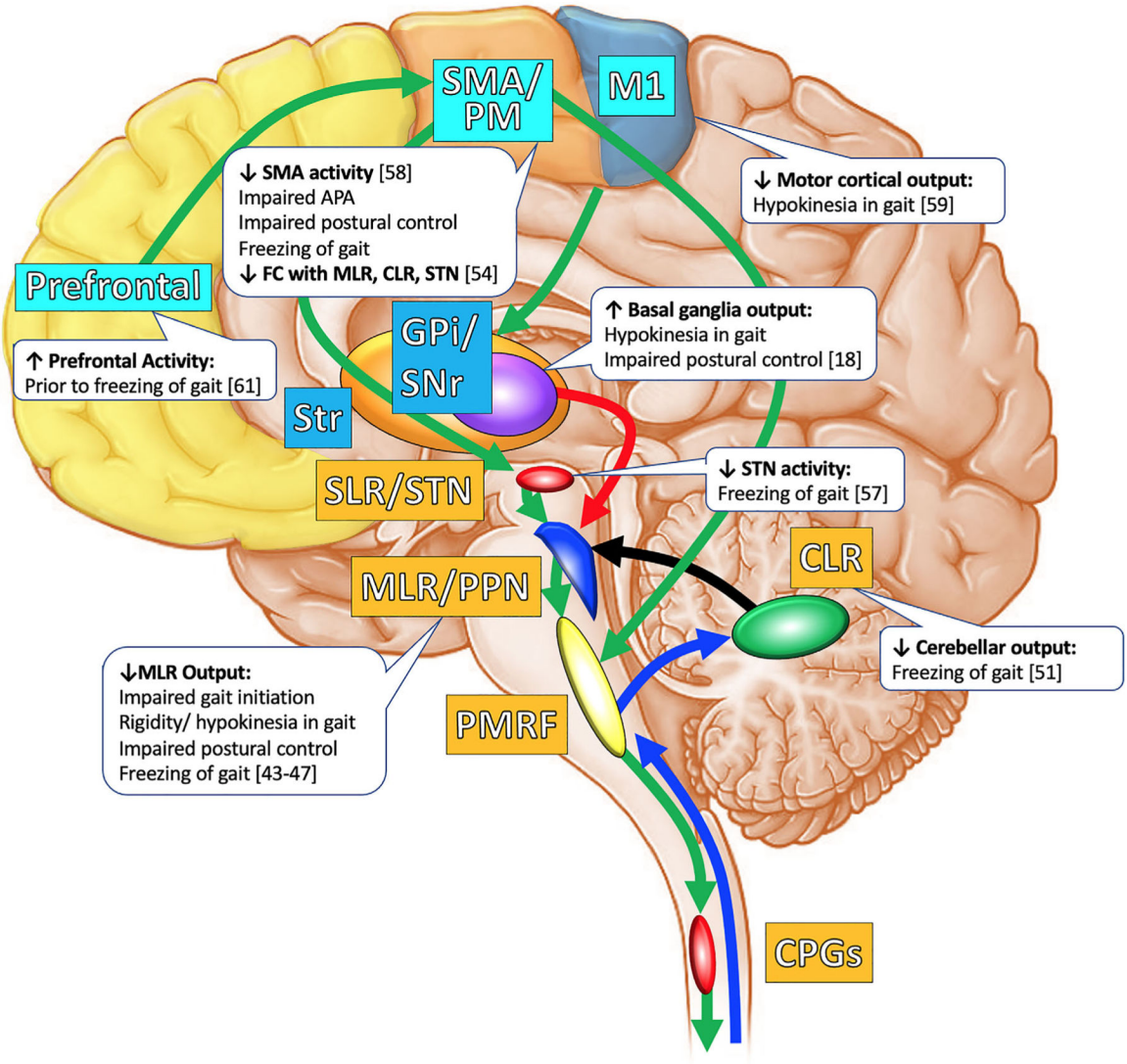

Figure 1.

Supraspinal locomotion centers and areas implicated in freezing of gait. Schematic drawing of the supraspinal motor network of locomotor control. Cortical signals convey motor commands (via the direct/indirect and hyperdirect pathways) to the basal ganglia which then conveys information to the mesencephalic locomotor region (MLR). The MLR represents a crossroad of information coming from the basal ganglia and the cerebellum, which receives sensory feedback from ascending spinal pathways (blue arrows). Several of these regions are implicated in Parkinson's disease (PD) postural instability and gait disorders including freezing of gait. Feedforward motor commands are displayed in green (activating) and red (inhibiting). CLR, cerebellar locomotion region; CPGs, central pattern generators; GPi, globus pallidus internus; M1, primary motor cortex; MLR/PPN, mesencephalic locomotor region/pedunculopontine nucleus; PMRF, pontomedullary reticular formation; SLR/STN, subthalamic locomotor region/subthalamic nucleus; SMA/PM, supplementary motor area/ premotor cortex.

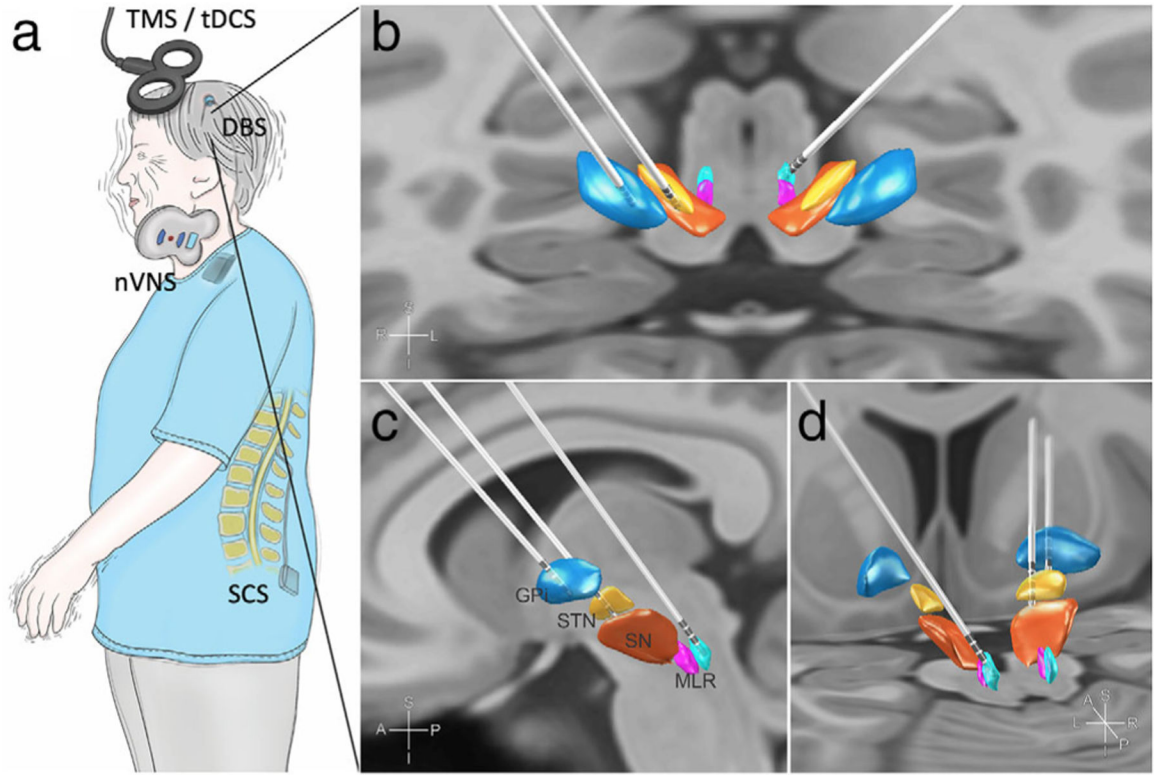

Figure 2.

Invasive and non-invasive therapies for freezing of gait. a. Noninvasive interventions include TMS, tDCS, and nVNS. Invasive interventions include DBS and SCS. b–d. Three-dimensional views of FoG DBS targets. Reconstructions were created in Lead-DBS using available MNI-space subcortical atlases (98–100). b. Frontal top view, (c) sagittal view, and (d) posterior oblique view of DBS electrodes targeting the GPi, STN, and the MLR (CnF in cyan and PPN in fuchsia). CnF, cuneiform nucleus; PPN, pedunculopontine nucleus; SN, substantia nigra; STN, subthalamic nucleus.

Table 1.

Supraspinal Locomotion Centers in Mammals.

Locomotor region	Putative anatomical target	Studied animal	References
Mesencephalic locomotor region	PPN	Cat, rat	(17)
	CnF	Cat, rat, macaque	(18–20)
	Medioventral to PPN	Rat	(21)
Subthalamic locomotor region	Lateral hypothalamus	Cat	(22)
Cerebellar locomotor region	Fasciculus uncinatus (hook bundle of Russell)	Cat	(23)

CnF, cuneiform nucleus; PPN, pedunculopontine nucleus.

Table 2.

Summary of Studies.

Study	Target	Population	Protocol	Results
Noninvasive neuromodulation (TMS, tDCS, nVNS)				
Chang et al. (64)	TMS to primary motor cortex and tDCS over left dorsolateral prefrontal cortex	*N* = 32 PD with FoG	TMS over primary motor cortex of the lower leg and tDCS over the dorsolateral prefrontal cortex vs. TMS alone	• Improvement in FoG, motor function, and ambulatory function (no significant difference between groups) • Improvement in executive function only in dual-mode group
Dagan et al. (9)	TMS over medial PFC	*N = 9* advanced PD	Real vs. sham	• Improvement in FoG-provoking test scores, motor part of UPDRS, and gait variability after real TMS compared to sham • Self-report of FoG severity and cognitive scores did not improve
El-Tamawy et al. (65)	TMS to leg area of motor cortex	*N* = 16 advanced PD	Real vs. sham	• Improvement of FoG-Q short form, significant decrease in number of falls and widened stride length No improvement in UPDRS score and other gait variables
Kim et al. (66)	TMS over the lower leg primary motor cortex	*N* = 17 PD	RCT: real vs. sham	• Improvement in steps required to complete standing start 180 turn test and FoG-Q • Improvement in timed up and go test and UPDRS
Lee et al (67)	TMS over primary motor cortex of lower leg, SMA, and DLPFC	*N* = 20 PD with FoG	Real vs. sham	• Improvement in timed up and go test, number of turn steps and turn time, and UPDRS-III scores after TMS over the primary motor cortex and DLPFC
Oh et al. (68)	TMS over both motor cortices and DLPFC	*N* = 12 PD	RCT: real vs. sham	• Improvement in FoG-Q and UPDRS-III maintained until six weeks from baseline
Mi et al. (69)	TMS to SMA	*N* = 30 PD with FoG	RCT: real vs. sham	• Improvement in the FoG-Q, UPDRS-III, and several gait variables including total duration, cadence, turn duration, and turn to sit duration in the TMS group
Kim et al. (70)	TMS to SMA and motor cortex	*N* = 12 PD with FoG	TMS of SMA vs. TMS of motor cortex	• Greater reduction in freezing episodes with SMA than motor cortex stimulation
Valentino et al. (71)	tDCS to motor cortex	*N* = 10 PD with FoG	Cross-over, double blind: TMS vs. sham	• Improvement of gait as assessed by stand walk sit test, reduced number and duration of FoG episodes, reduction in UPDRS score in the tDCS group
Dagan et al. (72)	tDCS to the primary motor cortex and DLPFC	*N* = 20 PD with FoG	tDCS of primary motor cortex and DLPFC vs. primary	• Improvement on FoG-provoking test, timed up and go, and stroop test with simultaneous stimulation of primary motor cortex and DLPFC

Study	Target	Population	Protocol	Results
			motor cortex only vs. sham	• No improvement after primary motor cortex only or sham stimulation
Mondal et al. (73)	nVNS	*N* = 12 PD with FoG	Pre vs. post nVNS	• Reduction in UPDRS-III and number of steps taken while turning • No significant differences in gait parameters including velocity, step length, and stride velocity variability
DBS (STN, GPi, PPN, CN, combined)				
Vercruysse et al. (74)	STN	*N* = 41 PD with FoG	STN-DBS vs. best medical treatment	• STN-DBS increased the likelihood to convert from being a freezer to a nonfreezer at 6- and 12-months follow-up • Forty-five percent of freezers still experiencing FoG at 6- and 12-months follow-up • Three baseline nonfreezers developed FoG during follow-up.
Barbe et al. (75)	STN	*N* = 151 PD (79 with FoG)	STN-DBS vs. best medical therapy	• Proportion of patients with FoG in the STN-DBS group decreased from 52% to 34% at 24-months follow-up, no such reduction was found in the best medical therapy group • Improvements in number of steps to complete gait test and axial signs in the STN-DBS group but not in the best medical treatment group
Castrioto et al. (76)	STN	*N* = 18 advanced PD	Pre vs. post STN-DBS (ten years follow-up)	• STN-DBS significantly improved UPDRS total motor score, resting, action tremor, and bradykinesia, as well as levodopa equivalent daily dose; however, axial signs showed the most progressive decline in stimulation and levodopa response over follow up (−53.6% at five years and −101.8% at ten years) as measured by UPDRS sub-scores
Fasano et al (77)	STN	*N* = 20 PD	Pre vs. Post STN-DBS (eight years follow-up)	• Improvement in overall motor function as assessed by the UPDRS five years from baseline, but these results were only partly retained by eight-years follow-up. Specifically, gait and postural stability as measured by UPDRS items 29 and 30, respectively, significantly worsened ($p < 0.05$).
Follett et al. (78)	STN and GPi	*N* = 299 PD	STN vs. GPi- DBS	• At 24-months follow-up, 42.9% of the STN-DBS group and 38.2% of the GPi-STN group developed falls, while 30.6% of STN-DBS and 32.2% of GPi-DBS developed moderate-severe gait disturbances. Neither of these differences reached significance
Merola et al. (79)	STN	*N* = 19 early onset PD	Pre vs. Post STN-DBS (>20 year follow-up)	• Clinical and neuropsychological performance progressively worsened during the course of follow-up. While only 16% of patients suffered from falls at baseline, 64% developed falls after over seven years of follow-up. While 0% of patients had FoG at baseline, 64% had developed levodopa unresponsive FoG
Moreau et al. (80)	STN	*N* = 13 PD with severe gait disorders	STN-DBS usual vs. high voltages and 130 Hz vs. 60 Hz frequency	• Number of freezing episodes were significant lower at the 60 Hz—high voltage mode and higher at the 130 Hz—high voltage mode

Study	Target	Population	Protocol	Results
Chenji et al. (81)	STN	*N* = 17 advanced PD	STN-DBS bilateral vs. unilateral left vs. unilateral right	• Gait performance declined under cognitive dual-task conditions, independent of stimulation state • Bilateral stimulation produced greater improvement in step length and double limb support time than unilateral stimulation
Lizarraga et al. (82)	STN	*N* = 22 PD with dopamine-resistant gait dysfunction	Bilateral vs. right vs. left vs. off stimulation	• Motor and gait scores significantly improved with bilateral vs. unilateral STN-DBS • Stride length and velocity significantly improved with, right- and left-sided stimulation • Stride length significantly improved with right-sided vs. left-sided and bilateral vs. left-sided stimulation • Turning time tended to improve with bilateral and right-sided more than with left STN-DBS • Bilateral STN-DBS yielded greater improvement in motor and gait scores in PD patients. Yet, unilateral stimulation has similar effects on gait kinematics
Krack et al. (83)	STN and GPi	*N* = 13 PD	STN vs. GPi	• Slight worsening of on-drug period freezing was found in three out of five GPi-stimulated patients
Ghika et al. (84)	GPi	*N* = 6 PD	Pre vs. post GPi stimulation	• A slight worsening after one year was observed and three patients developed levodopa- and stimulation-resistant gait ignition failure and minimal fluctuations at one year
Volkmann et al. (85)	GPi and STN	*N* = 11 advanced PD	Pre vs. post GPi stimulation (five years follow-up) followed by STN-DBS	• While posture and gait UPDRS-subscores showed significant improvement during the first three years of follow-up, this effect was lost by five years follow-up
Mestre et al. (86)	PPN	*N* = 9 PD	Pre vs. post PPN-DBS (four years follow-up)	• Improvement in patient-reported freezing when compared with baseline at two years. • No significant change in outcomes, at four years; however, four of six patients were responders for off-time patient-reported freezing and falling
Moro et al. (87)	PPN	*N* = 6 advanced PD with significant gait abnormalities	Pre vs. post PPN-DBS	• Patients reported a significant reduction in falls in on and off medication states both at 3 and 12 months after PPN-DBS
Welter et al. (88)	PPN	*N* = 6 PD	Real PPN-DBS vs. sham and on vs. off levodopa treatment	• Combination of PPN-DBS and levodopa treatment produced a significant decrease of freezing episodes • Frequency of falls also decreased in three out of four patients • PPN-DBS significantly improved the anticipatory postural adjustments and double-stance duration but not the length and speed of the first step • Step length and speed improved after surgery without PPN-DBS (lesioning effect of PPN-DBS)

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Study	Target	Population	Protocol	Results
				• Quality of life was also significantly improved with PPN-DBS
Ferraye et al. (89)	PPN	*N* = 6 PD with FoG after STN-DBS	Double blind, cross-over	• Improvement in duration of freezing episodes as well as falls related to freezing • Composite gait score, Giladi questionnaire score, and walking protocol did not significantly change, nor did the results during the double-blind evaluation • Individual results showed major improvement of all gait measures in one patient, moderate improvement of some tests in four patients and global worsening in one patient
Schrader et al. (90)	PPN and GPi	*N* = 1 advanced PD	Case report	• Isolated GPi and PPN DBS had moderate effects on gait ignition and FoG, best results were observed with combined stimulation
Molina et al. (91)	PPN and GPi	*N* = 5 PD	Prospective trial	• No benefit with rapid worsening of freezing over 5–12 months
Weiss et al. (92)	STN + SN pars reticulata	*N* = 12 PD	Cross-over, double-blind	• Combined stimulation of STN and SNr improved freezing of gait, whereas balance impairment remained unchanged
Scholten et al. (93)	STN and SNr	*N* = 12 PD with STN-DBS and FoG	STN vs. SNr	• Improvement in both the spatial features (stride length, stride length variability) and the temporal parameters of gait in STN stimulation only • SNr stimulation improved temporal parameters of gait (swing time asymmetry). Correlation analysis suggested that patients with more medial localization of the SNr contact associated with a stronger regularization of gait
Valldeoriola et al. (94)	STN and SNr	*N* = 6 PD	Low-frequency SNr vs. high-frequency STN vs. combined	• Combined stimulation of STN and SNr improved outcomes in four patients including FoG-Q, Tinetti balance and walking assessing tool and UPDR • SNr stimulation alone did not produce better results than combination or STN alone in any patient
Spinal cord stimulation (SCS)				
Pinto et al. (95)	SCS and STN	*N* = 4 PD with gait disturbances after STN-DBS	Pre vs. post SCS	• SCS had approximately 5065% improvement in gait measurements and 35–45% in UPDRS III and quality-of-life scores • During blinded evaluations, significant improvement in the timed up and go and 20-m-walk tests (only at 300 Hz)
Samotus et al. (96)	SCS	*N* = 5 PD with significant	FoGPre vs post SCS (six months follow-up)	• SCS setting combinations of 300–400 μsec/30–130 Hz provided gait improvements • Mean number of FoG episodes reduced significantly
Samotus et al. (97)	SCS	*N* = 4 PD with significant	FoGUpdate study: Pre vs. post SCS (three years follow-up)	• Mean UPDRS-III score was reduced by 6.2% at three-years. UPDRS-III sub-scores for rigidity and axial symptoms were improved by 23.1% and 20.4%, respectively; however bradykinesia sub-scores increased by 9.4%. • Mean FoG-Q and PDQ-8 scores were reduced by 18.3% and by 21.9%, respectively

Study	Target	Population	Protocol	Results
				• Participants continued to demonstrate a reduction in the number of FoG episodes during straight walking at three-years compared to pre-SCS • Mean duration per FoG episode increased in two participants by 36.5% • Mean stride velocity remained increased in participant #2 by 202.4%, remained unchanged in participant #3 and was reduced in two participants by 26.3% at three-years. Mean step length, swing phase and single support phase was increased by a mean 14.5% at 3-years. Step time variability was reduced by 34.9% in three participants. Mean step length, stride velocity and swing phase variability increased by a mean 29.9% in two participants and was unchanged in two participants.
de Lima et al. (98)	SCS	*N* = 4 PD with FoG	Pre vs. Post SCS	• SCS improved FoG and anticipatory postural responses • SCS failed to improve reactive postural responses • SCS seems to influence cortical motor circuits, involving the supplementary motor area
Mazzone et al. (99)	SCS	*N* = 18 PD or atypical parkinsonism	Tonic high cervical SCS (T-HCSCS) vs. burst high cervical SCS (B-HCSCS)	• B-HCSCS was more effective and had more consistent effects than T-HCSCS in reducing pain • B-HCSCS improved UPDRS scores, including motor sub-items and tremor and H&Y score • Motor benefits appeared quickly after the beginning of B-HCSCS, in contrast to long latency improvements induced by T-HCSCS • B-HCSCS also improved gait and ability of patients to correctly perform a cognitive-motor task requiring inhibition of a prepared movement • B-HCSCS ameliorated autonomic control in the investigated patient