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Normal and pathological gait: what we learn from Parkinson's disease

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Abstract

Gait and balance disorders, characterized by freezing of gait and postural instability, represent a major therapeutic challenge in Parkinson's disease (PD). These symptoms respond poorly to dopaminergic treatments, except in the early phase of the disease. Currently, no other pharmacological treatment is particularly efficient. Furthermore, high frequency stimulation of the subthalamic nucleus or internal globus pallidus is not a therapeutic option and rehabilitation appears to be the most effective approach. Since these gait and balance deficits are resistant to dopaminergic drugs, their occurrence could be related to the development of extra-dopaminergic lesions in PD patients. We provide a comprehensive description of the clinical features of gait and balance disorders in PD. We also highlight the brain networks involved in gait and balance control in animals and humans with a particular focus on the relevant structures in the context of PD, such as the mesencephalic locomotor region. We also review other neuronal systems that may be involved in the physiopathology of gait and balance disorders in PD (noradrenergic and serotoninergic systems, cerebellum and cortex). In addition, we review recent evidence regarding functional neurosurgery for gait disorders in PD and propose new directions for future therapeutic research.

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INTRODUCTION

Gait and balance disorders are a major problem with unmet therapeutic objectives during the course of Parkinson's disease (PD). While dopamine (DA) responsive symptoms can be treated, initially with dopaminergic drugs and then with stimulation of the subthalamic nucleus when severe fluctuations or dyskinesia occur, gait and balance disorders currently remain untreatable. These symptoms are not severe early in the course of PD but progress with time in the majority of cases and represent a heavier burden later in the course of the disease. The increasing impact of gait and balance disorders is mainly explained by lack of efficacy of dopamine treatments on these symptoms.[1] Likewise, high frequency stimulation of the subthalamic nucleus fails to improve gait and balance disorders resistant to levodopa and even worsen these symptoms in some cases. With disease progression, the global burden of axial symptoms increases in direct relationship with the increase in fall frequency and freezing of gait (FOG). Although the pathophysiology of gait and balance disorders in PD remains insufficiently understood, several recent studies have shown that the mesencephalic locomotor region (MLR) of the brainstem is implicated in the control of gait and balance in mammals[2] and locomotion in humans.[3, 4] More specifically, the dysfunction of cholinergic neurons of the pedunculopontine nucleus (PPN), located in the MLR, likely play a crucial role in the appearance of axial symptoms in PD. Other neuronal systems, including the locus coeruleus, the raphe nucleus, the cerebellum and the cerebral cortices, may also be involved. However, the efficacy of drugs targeting these non-dopaminergic systems (including cholinergic and monoaminergic agents) is still disappointing. Low frequency stimulation of the PPN was recently introduced in PD patients with drug-resistant gait and balance disorders. Despite initially promising individual case reports (for a review, see[5]), the overall results of controlled studies have been disappointing. In the first part of this review we describe and discuss the existing literature on the clinical features of gait and balance disorders in advanced forms of PD. We then focus on the physiology and pathophysiology of gait control and review the neuronal circuits involved, supported by evidence from experimental manipulations in various animal species, in order to propose new directions for future therapeutic research.

HYPOKINETIC GAIT AND FESTINATIONS IN PD

Dopa responsive gait and balance alterations are frequent in PD and encompass distinct patterns. Hypokinetic rigid gait is mainly characterized by a reduction of gait speed,[6] with a reduction of the step amplitude but an unchanged or slightly increased cadence. In early studies of gait at imposed speed, PD patients were able to increase their cadence but the step length remained systematically lower whatever the speed.[7] This observation suggests that gait akinesia was mainly related to a deficit in internal generation of adapted step length rather than an inability to increase the cadence. Conversely, cadence increase may be viewed as a compensatory mechanism. In line with this concept, external visual cues help to increase the step length, suggesting that only internal programming of amplitude is impaired, a finding that is consistent with general descriptions of akinesia. Postural disturbances related with hypertonia were also described in PD gait. They could be explained by a flexed and stiffened posture of the trunk throughout the gait cycle. The range motion of the hip was also reduced. All these changes are well improved by levodopa.[6] Another typical and unique gait pattern observed in PD is festination. Festinating gait is described as rapid small steps done in an attempt to keep the centre of gravity in between the

feet while the trunk is leaning forward involuntarily. The mechanisms of festination and its relationship with FOG are still debated. Although festination was found to be associated with FOG,[8] it is difficult to find an unified view to include the issue of gait initiation in this particular symptom.[9] Thus festination may also be considered as separate episodic gait impairment encountered in PD. Early in the course of PD tandem gait performance is generally normal although it is impaired in most atypical parkinsonism.[10] However the most impairing gait disruptions are related with balance deficit and FOG episodes that tend to become resistant to levodopa, thus suggesting the involvement of extra-nigral lesions.[1]

FALLS ARE A MAJOR MILESTONE IN THE EVOLUTION OF PD

In PD patients, falls induce an increased risk of mortality and morbidity mainly related to hip fractures and head injuries. Falls are a source of major disability leading to dependency, institutionalization, poor quality of life, and a residual fear of falling. The incidence of falls in PD is variable among the different available studies, with a 51–68% risk of having a fall in the year in PD patients.[11] The frequency of recurrent falls is about 50% in one year.[12] Once the first fall has occurred, the survival duration is similar in PD and in atypical parkinsonian syndromes which usually have a more severe course.[13] Clinical predictive factors of falls are a previous fall, fear of falling, disease duration and severity, abnormal axial posture and tone, cognitive impairment, decrease in arm swing (uni- or bilateral), presence of dyskinesia and antiparkinsonian treatment.[14] Most falls are unrelated to extrinsic factors, such as sliding or a collision, but are dependent upon intrinsic deficits of balance control. Falls occur mainly during posture changes, in particular during a half-turn, or while performing activities that require a double task demand (cognitive or motor).[11] The more the second task is difficult, the more the balance control is altered and fall risk increased.[11] Lastly, some authors reported proprioceptive and vestibular deficits in PD, which can participate in the occurrence of balance disturbances.[15]

At bedside, postural instability is routinely evaluated with the pull-retropulsion test (item 30 of the UPDRS part III). However, variability exists in its execution and the reproducibility is low as well as its sensitivity to the early detection of fallers.[15] In the recently validated MDS-UPDRS,[16] detailed instructions for the examiner may reduce the variability of this test. However, the outcome of clinical testing for postural instability is not related to the risk of falls.[12] Other clinical tests such as the push and release test have recently been proposed with higher sensitivity for identifying fallers. Nonspecific scales have also been proposed to evaluate balance and risk of falls in parkinsonian patients, such as the Berg Balance Scale, the Timed Up and Go (TUG) test, and the Tinetti score, with a good sensitivity to detect fallers among PD patients.[14] Recently, the Functional Gait Assessment (FGA), the Balance Evaluation System Test (BES Test), and the rapid assessment of postural instability in PD (RAPID) have been proposed for PD patients with good test-retest and inter-rater reliability, good sensitivity to detect fallers vs. non fallers and good predictive value.[17]

POSTUROGRAPHY FOR BALANCE DEFICITS IN PD

Quantitative posturographic methods measure oscillations of the center of pressure of the foot (CP) with force plates, in static or dynamic position using mobile platforms. Measures include the limit of stability and the posture sway using the sensory organization test.[18] The perturbation can be a rotation, a translation, or both combined; the changes in CP position and the pattern and latencies of lower limb muscle activations can then also be measured. In the literature, many studies report posturographic data in PD patients, but with contradictory results (online supplementary material). Even if significant differences exist between PD patients and healthy subjects at the group level, posturographic parameters are not well related to clinical postural instability or risk of falls. Their usefulness for the management of

individual patients has yet to be clearly established, in particular for assessing the effects of therapeutic interventions on balance deficit in PD patients. Posturography studies may however provide insights in the mechanisms of falls. For example, Carpenter and collaborators[19] stressed the abnormalities of upper limbs movements that could give no protections against falls in PD patients. Recently, changes in the vertical velocity of the center of mass has been shown to be sensitive to postural instability and to the effects of a treatment at the individual level.[20] However, its utility in clinical practice as well as its predictive value needs to be further evaluated.

FREEZING OF GAIT

Freezing of gait (FOG) is an episodic transient disruption of gait that typically lasts a few seconds and is associated with a unique sensation: patients feels that their feet are glued to the ground, causing them to remain in place despite making a concerted effort to overcome the motor block and move forward. FOG is not specific of PD. It may also be encountered in other degenerative disorders such as progressive supranuclear palsy, multisystem atrophy or dementia with Lewy bodies and in focal lesions of various brain structures (brainstem, basal ganglia, supplementary motor area and frontal lobes subcortical regions).[9]

When FOG occurs during gait initiation, it is characterized by repeated ineffective anticipatory postural adjustments and leads to a failure of gait initiation and sometimes to a fall. FOG may also occur while patients are walking. There is an abrupt decrease of step length and increase of step frequency and step-to-step variability that precede a complete blockade of gait and falls. Another important characteristic is the occurrence of an irregular rapid trembling in both knees.[21] FOG is often triggered by characteristic circumstances such as a half or 360°-turn,[22] obstacle (doorway) clearance, spaces with a narrow passage or unexpected visual or auditory stimuli. Fatigue, stressful situations, cognitive load[23] anxiety and depression may also elicit FOG.[24] Usually, FOG is improved by visual (e.g. marks on the ground) or auditory cueing (rhythmic sounds). Paradoxically, running, cycling or climbing stairs are performed more easily than usual gait. Generally, freezing is defined as an abrupt difficulty in starting or continuing rhythmic and repetitive movements. Freezing is also observed in other motor plans such as in repetitive bimanual motor tasks (e.g. writing) or during speech. In line with this concept, freezing (and FOG) may be viewed as an extreme form of akinesia. New tools for FOG assessment have recently been developed. For the purposes of objective evaluation, standardized tasks have been designed to elicit FOG during gait with imposed stressors, such as a fast cadence, a slow cadence or obstacle occurrence. An obstacle avoidance task during treadmill walking was also used to provoke FOG.[25] Freezing episodes can be automatically detected by means of ambulatory devices.[26] Given the difficulty in evaluating FOG, more sensitive and specific clinical and neurophysiological approaches need to be developed.

Because of its high variability, depending on environmental triggers, emotional state, cognitive inputs and medication, the frequency of FOG is difficult to measure in PD populations. In the DATATOP study, FOG was infrequent (7.1%) and rarely led to fall in early PD. Its frequency rose to 23.6% after 18 months of observation. The risk of developing FOG was increased in patients that started the disease with gait disorders and had higher scores in postural instability, rigidity, bradykinesia and speech at baseline. In contrast, tremor at onset considerably decreased the risk of subsequent FOG. At the end of follow-up, FOG was no longer associated with akinesia and hypertonia but correlated with other midline signs (speech deficit and balance disorder) suggesting that these symptoms are, at least, partially, independent of akinesia.[27] After 6–10 years of evolution, FOG was retrospectively reported by 48% to 70% of PD patients.[28] Cognitive deficits and, more specifically, low frontal test scores are also associated with FOG. FOG has a high impact on

the quality of life of PD patients far beyond its motor components since quality of life measured on the PDQ scale is affected in all its dimensions except stigma and social support.[29]

The cerebral mechanisms underlying FOG have not been elucidated but alterations observed during physiological analysis of gait may provide important clues. Alterations of gait rhythm, gait symmetry and bilateral coordination in stepping are observed in PD patients with FOG outside episodes of freezing.[30] However, the question of whether these alterations are causative is still debated. Electromyographic studies also point to disruption of the central gait cycle timing: a consistent pattern of premature timing of lower limb muscle activity before freezing was observed that may contribute to deceleration and interruption of the movement.[31] The role of perceptual stimuli (such as doorways) as a FOG trigger also suggests that a perceptual defect may contribute to the motor impairment. Conversely, the improvement of FOG by visual clues may reveal a double deficit: increased visual dependence to compensate impaired kinesthetic feed-back and increased attentional processing in order to bypass the deficit of internal generation of appropriate lower limb movement during the automated gait cycle.[32,33]

GENERAL ORGANIZATION OF THE NETWORK INVOLVED IN BALANCE AND LOCOMOTION (Fig. 1A)

The neuronal networks involved in locomotion have been extensively studied in animals. They are hierarchically organized and include: (i) the lower effector levels, including the musculoskeletal system and the peripheral nervous system; (ii) the central locomotion pattern generators (CPGs) composed of organized groups of interneurons automatically generating rhythmic and alternating limb activity[34] (iii) several locomotor areas located at various levels in the brainstem, which control CPGs and are characterized by their ability to produce locomotor action when electrically or pharmacologically stimulated. These are the subthalamic locomotor region, the MLR and the dorsal and ventral tegmental field of the caudal pons. The MLR, composed of the PPN and cuneiform nucleus (CN), is the locomotor area known to be the most relevant in PD, and we will focus on the MLR and will not review data on the structures located in the posterior midbrain; (iv) finally, these locomotor areas are modulated by higher level control systems, including the dopaminergic and other modulatory systems, the basal ganglia and the prefrontal cortex. These locomotor circuits are modulated by sensory feedback via sensory afferent systems (somesthetic, vestibular and visual systems).

MESENCEPHALIC LOCOMOTOR REGION (MLR) IN GAIT CONTROL

Anatomical definition and connections of the MLR

Among the different locomotor areas with a direct input to the spinal cord, the MLR is of particular importance in the physiology and pathophysiology of gait. The MLR is located in the reticular formation and corresponds to the PPN and CN.[35] Both these structures were identified as groups of neurons located in the reticular formation. The presence of cholinergic neurons serves to define boundaries of the PPN in primates. The cholinergic neurons are distributed within a dense dorsolaterally located area called the PPN pars compacta and a sparse more medially located area called the PPN pars dissipata.[36] There are also non-cholinergic neurons in the PPN that are GABAergic and glutamatergic. About 40% of cholinergic neurons also express glutamate in monkeys.[37] The CN is located dorsal to the PPN and thus ventral to the superior and inferior colliculi and comprises glutamatergic and GABAergic neurons.

Both the PPN and the CN have reciprocal connections with the basal ganglia and have major outputs to the descending reticulo-spinal pathway and the ascending thalamo-cortical pathway (Fig 3) (see[38] for review). Inputs to the PPN are similar in primates and in rodents, except that projections from the deep cerebellar nuclei have only been demonstrated in monkeys[39] and that projections from the spinal cord have only been reported in rats and cats (for review, see[38]). Afferents from the basal ganglia in monkeys originate from the sensorimotor, associative and limbic anatomo-functional territories[40] suggesting that the PPN is in a position to integrate motor and non motor inputs. Ascending outputs from the PPN mainly project to dopaminergic neurons of the substantia nigra pars compacta, subthalamic nucleus, pallidum and thalamus. Descending outputs project to the pontobulbar reticular formation,[41] where the reticulo-spinal pathway originates. Interestingly, a recent study performed in rodents using optogenetics demonstrated that the activation of glutamatergic neurons of caudal hindbrain was able to elicit locomotor-like activity.[34] The connections of the CN are less well known. However, a descending projection has been reported in primates.[41] A recent study also provides evidence that the substantia nigra pars reticulata projects to both the PPN and CN, whereas the internal pallidum projects mainly to the PPN.[41]

Behavioral consequences of MLR experimental manipulations

Experiments in decerebrate animals and in alert cats demonstrated that continuous electrical stimulation (20–60 Hz) of the PPN region elicits stepping on a treadmill (see for review, see[5]). The frequency of the step cycle changes from a rapid walk to a gallop as the strength of current is increased.[42] The PPN and CN could play separate roles, since repetitive stimulation of the CN in decerebrate cats evokes locomotor movements, whereas stimulation of the PPN suppresses postural muscle tone.[2] In normal monkeys, large excitotoxic lesions of the PPN, radiofrequency lesions, local injection of GABAergic agonists, or high frequency stimulation induce akinesia (for review, see[38]). This was interpreted as the consequence of a decreased activity of the excitatory projection from the PPN to the dopaminergic nigro-striatal system. A recent study demonstrated that a small lesion of PPN cholinergic neurons is instrumental in the development of gait and balance disorders in monkeys.[4] No akinesia was found in these monkeys but gait disabilities resistant to dopaminergic drugs were observed, indicating that PPN cholinergic neurons play a central role in controlling gait and posture in primates.

Involvement of the MLR in normal and pathologic gait in humans

Imaging studies in humans also support a role of the MLR in normal and pathological gait. In healthy volunteers, a PET scan study showed that fronto-parietal areas and basal ganglia were activated by walking with obstacles,[43] while fMRI studies during the imagination of gait showed activation of a circuit including the frontal and parietal cortices, basal ganglia, cerebellum, midbrain tegmentum and pons.[44] Interestingly, an activation in the mesencephalon was also shown during imagined running[3] and more particularly in the MLR during imagined fast gait,[4] suggesting that this region is involved in the control of gait cadence in humans, as previously suggested by single cell recording during lower limb rhythmic movements.[45] During imagery of gait, PD patients with FOG showed more activity in the MLR than patients without FOG.[46] Moreover, atrophy of gray matter in a small portion of the MLR mesencephalon atrophy has been reported in parkinsonian patients with FOG.[46]

A dysfunctioning of MLR cholinergic neurons responsible for gait and balance disorders has recently been highlighted. Indeed, post-mortem studies showed that the degree of cholinergic neuronal loss within the PPN in PD patients is correlated with the level of DA cell loss[47] and, importantly, with the occurrence of falls.[4] In this study, no statistically

significant difference of cell loss was found in the CN between faller and non-faller PD patients. In line with a possible causal relationship between cholinergic loss in the PPN and falls, cholinergic terminations within the thalamus were decreased in faller PD patients compared to non-faller PD patients.[48]

Involvement of other structures relevant for gait dysfunction in PD

Brainstem—Evidence for relationships between gait disorders and noradrenalin and serotonin systems is anecdotal and has yet to be fully elucidated. The hypothesis that noradrenergic neurons of the locus coeruleus, known to degenerate in PD,[49] may contribute to gait and balance disorders in PD and in other neurodegenerative disorders has recently been proposed.[50] Neurons utilizing noradrenalin, an excitatory neurotransmitter, are mainly located in the locus coeruleus, and innervate widespread areas in the central nervous system including cortex, cerebellum and spinal cord. Because the coeruleo-cerebellar and coeruleo-spinal pathways are involved in autonomic regulation and postural reflexes,[51] their degeneration may also explain the postural instability observed in PD. Serotonin, mainly located in the raphe nuclei in the brainstem, is also known to modulate the rhythm and pattern of locomotion, in particular the accuracy of alternation between antagonistic discharges.[52] Serotonin levels in cerebrospinal fluid are reduced in PD patients and in particular in PD patients with severe gait and balance disorders.[53]

Cortex and cerebellum—The motor cerebral cortices and the cerebellum are known to be involved in locomotor control. Even if there is currently no direct evidence of their role in the pathophysiology of gait and balance disorders in PD, functional imaging studies suggest interesting correlations. Freezing of gait has been studied in patients with PD using radiotracer studies. Gait disorders were related to decreased perfusion in various brain areas including bilateral orbitofrontal cortex,[54] and parieto-frontal areas including the SMA (see[9] for review). SPECT has been used to investigate the mechanisms underlying the improvement of hypokinetic gait in PD patients when exposed to visual stimuli (the “paradoxical gait”). PD patients showed enhanced activation in the lateral premotor cortex to a significantly greater degree than control subjects,[55] suggesting that the premotor cortex compensates for the impaired supplementary motor area function in PD patients. Hypometabolism assessed using positron emission tomography with (18)[F]-fluorodesoxyglucose was more severe in PD patients with than without FOG in several cortical areas, including parietal regions.[56]

A hyperactivation has also been found in PD patients in the cerebellum, a structure known to be crucial for motor coordination and balance control.[57] This hyperactivation was interpreted as a strategy of the central nervous system to compensate for the defective function of the basal ganglia and brainstem but could also be causative. Thus, unraveling the role of cerebellar dysfunction in gait and balance deficits in PD may represent a major challenge for the future.

MEDICATION OPTIONS AND REHABILITATION

The response of gait and balance disorders to levodopa is inconstant and decreases over time. Only a few trials have tested drugs targeting extra-dopaminergic systems for FOG or balance deficits in PD. A recent study demonstrated that a central cholinesterase inhibitor reduced the number of falls by 0.12 falls/day in comparison with placebo (0.25 falls/day, p_0.049).[58] Thus, the number of patients to treat to avoid one fall was 8.3 in this study. Another trial suggested that methylphenidate could improve OFF-dopa FOG whereas a beneficial effect on FOG persisting ON-dopa was less obvious.[59] However, these results remain controversial since a recent study reported that methylphenidate was not effective and could even worsen the severity of PD symptoms.[60] Finally, rehabilitation programs

targeting gait and balance are widely used in clinical practice although scientific evidence for choosing the optimal method is still lacking. Interestingly, an experimental study in mice intoxicated with MPTP suggested that treadmill exercise could improve balance/locomotion and increase the DA level in the dorsal striatum.[61] In PD patients, various rehabilitation approaches were evaluated in controlled trials (see online supplementary material). Nearly all types of rehabilitation methods are beneficial in comparison with no intervention. Interestingly, home based exercise programs could also be efficient to reduce the risk of injurious falls and recurrent near falling.[62]

Given the seminal importance of the cholinergic lesion of the PPN in the pathophysiology of gait disorders, drugs targeting this system should be further explored. Despite the relative lack of response to inhibitors of cholinesterase, this strategy should not be discarded, since the pro-cholinergic effect could be hampered by the degeneration of terminations within the targets of PPN cholinergic neurons. From a pathophysiological standpoint, there is evidence to support the use of direct cholinergic agonists. Nicotine would be convenient to use and its effects on gait and balance parameters could be tested. However, as nicotine is not specific to the PPN cholinergic system, its potential effects could be masked by the action on other targets such as cerebral cortex and striatal interneurons. Thus, further research aimed at identifying the subtypes of cholinergic receptors involved in gait and balance may help with the process of screening new drugs. Interestingly, a recent study performed in the lamprey[63] suggested that muscarinic cholinergic receptors could be critical for driving activation of the reticulo-spinal pathway from the MLR. Thus, further study focused on the role of muscarinic receptors in mammals could provide new therapeutic options for gait disorders in PD. Similar approaches could be applied to the noradrenergic system, which could also be involved in gait and balance disorders in PD patients. Even though an improvement of gait has been reported in PD patients after administration of the 5-HT2 receptor antagonist ritanserin (an anxiolytic substance),[64] the specific effect of serotoninergic drugs on gait has never been studied.

FUNCTIONAL SURGERY

Usual targets for deep brain stimulation (DBS) (Fig 1B)

The effect of each DBS target used to treat PD patients was evaluated on gait and balance disorders (for review, see [65]). Both short- and long-term follow-up studies indicate that high frequency stimulation of the ventral intermediate thalamic nucleus (VIM) has no effect on parkinsonian gait and balance disorders.[66] Pallidal high frequency stimulation can mildly improve only dopa-responsive postural deficit and FOG, but this effect disappears in 3 to 4 years.[67] Bilateral high frequency stimulation of the subthalamic nucleus is also effective on dopa-responsive gait disorders in PD patients. Quantitative posturographic methods showed an improvement of the amplitude of anticipatory postural adjustments and of the ability to actively brake the falling phase in the center of gravity.[20] The improvement was also significant in reducing anticipatory phase duration and postural oscillations, with a reduction of falls. For the majority of patients in long-term follow-up, gait and balance disorders became resistant to levodopa and to subthalamic DBS and could even be worsened by DBS.[68] Manipulating stimulation parameters can sometimes specifically reduce gait and balance disorders. Low frequency (60 Hertz) stimulation of the subthalamic nucleus has been shown to reduce significantly FOG,[68] but this setting was less effective at alleviating the cardinal symptoms and cannot be proposed as a chronic treatment for severe PD patients.

Surgical treatments: state of the art and future perspectives (Fig 1B)

Acute high frequency stimulation of the substantia nigra pars reticulata (SNr) has been shown to improve axial symptoms and postural control during gait but had no effect on

cardinal symptoms.[69] The mechanism of action to explain this specific effect on postural control could be a modulation of the descending non-dopaminergic network linking the SNr to the MLR. However, SNr projections to MLR in human are not as prominent as those from internal pallidum in non-human primates and rodents.[5] If SNr-DBS cannot be proposed alone as a treatment for advanced PD patients, this specific gait improvement may represent a new surgical approach in association with other therapies in PD patients.

Within the MLR, it has recently been proposed that the PPN specifically controls axial symptoms resistant to levodopa, and may be a promising target for DBS. The aim was to activate the remaining PPN cholinergic neurons to improve axial symptoms including FOG and balance deficits in PD patients. The first studies in humans involved advanced PD patients with DBS electrodes already implanted in the STN, and concluded that the addition of bilateral PPN low frequency stimulation could be effective to control gait and balance disorders (for review see [5]). The clinical results obtained and the locations of the electrodes have been discussed elsewhere.[70] Three years later, two double-blind controlled studies in six PD patients each concluded that: 1. FOG can be improved by PPN stimulation but the overall results remain disappointing;[71] 2. unilateral PPN stimulation in patients without STN stimulation may be sufficient to reduce falls significantly.[72] These heterogeneous outcomes emphasize the need to determine optimal inclusion criteria as well as the optimal surgical target within the MLR. In fact, the CN may also provide an interesting target to treat gait and balance disorders. These nuclei of the brainstem are not easy to target using conventional MRI methods, although specific MRI protocols allowing accurate targeting have recently been validated in human cadavers.[73]

Given the ascending and descending projections of the PPN to the thalamic centromedian nucleus and to the reticulo-spinal pathway, it may be worthwhile to investigate stimulation of these two structures for treating gait and balance disorders in PD. The centromedian nucleus is also easier to target and less risky than nuclei within the brainstem. This target should be evaluated, first experimentally in animal models and subsequently in patients for this specific indication. Spinal cord electrical stimulation using epidural electrodes is another potential surgical target, which would also be less invasive. In parkinsonian rodents, epidural thoracic electrical stimulation of the dorsal columns in the spinal cord was able to restore locomotion.[74] However, a subsequent human study reported no therapeutic effect of spinal cord stimulation in two PD patients.[75] It is possible that the development of new electrodes to stimulate the spinal cord may improve the outcome of spinal cord stimulation for gait disorders. The development of new stimulation technology and surgical approaches is an important avenue for future research, and it will be important to test and validate these developments in parkinsonian monkeys with gait disorders[4] to evaluate their therapeutic potential in humans.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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References

1. Blin O, Ferrandez AM, Pailhous J, et al. Dopa-sensitive and dopa-resistant gait parameters in Parkinson's disease. J Neurol Sci. 1991; 103(1):51–4. [PubMed: 1865232]
2. Takakusaki K, Habaguchi T, Ohtinata-Sugimoto J, et al. Basal ganglia efferents to the brainstem centers controlling postural muscle tone and locomotion: a new concept for understanding motor disorders in basal ganglia dysfunction. Neuroscience. 2003; 119:293–308. [PubMed: 12763089]
3. Jahn K, Deutschlander A, Stephan T, et al. Imaging human supraspinal locomotor centers in brainstem and cerebellum. Neuro Image. 2008; 39:786–92. [PubMed: 18029199]
4. Karachi C, Grabli D, Bernard FA, et al. Cholinergic mesencephalic neurons are involved in gait and postural disorders in Parkinson disease. J Clin Invest. 2010; 120:2745–54. [PubMed: 20628197]
5. Alam M, Schwabe K, Krauss JK. The pedunculopontine nucleus area: critical evaluation of interspecies differences relevant for its use as a target for deep brain stimulation. Brain. 2011; 134:11–23. [PubMed: 21147837]
6. Stolze H, Kuhtz-Buschbeck JP, Drücke H, et al. Comparative analysis of the gait disorder of normal pressure hydrocephalus and Parkinson's disease. J Neurol Neurosurg Psychiatry. 2001; 70(3):289–97. [PubMed: 11181848]
7. Morris ME, Iansek R, Matyas TA, et al. The pathogenesis of gait hypokinesia in Parkinson's disease. Brain. 1994; 117:1169–81. [PubMed: 7953597]
8. Giladi N, Shabtai H, Rozenberg E, et al. Gait festination in Parkinson's disease. Parkinsonism Relat Disord. 2001; 7(2):135–138. [PubMed: 11248595]
9. Nutt JG, Bloem BR, Giladi N, et al. Freezing of gait: moving forward on a mysterious clinical phenomenon. Lancet Neurol. 2011; 10(8):734–44. [PubMed: 21777828]
10. Abdo WF, Borm GF, Munneke M, et al. Ten steps to identify atypical parkinsonism. J Neurol Neurosurg Psychiatry. 2006; 77(12):1367–9. [PubMed: 16847047]
11. Bloem BR, Grimbergen YA, Cramer M, et al. Prospective assessment of falls in Parkinson's disease. J Neurol. 2001; 248:950–8. [PubMed: 11757958]
12. Wood BH, Bilclough JA, Bowron A, et al. Incidence and prediction of falls in Parkinson's disease: a prospective multidisciplinary study. J Neurol Neurosurg Psychiatry. 2002; 72:721–5. [PubMed: 12023412]
13. Wenning GK, Ebersbach G, Verny M, et al. Progression of falls in postmortem-confirmed parkinsonian disorders. Mov Disord. 1999; 14:947–50. [PubMed: 10584668]
14. Kerr GK, Worringham CJ, Cole MH, et al. Predictors of future falls in Parkinson disease. Neurology. 2010; 75:116–24. [PubMed: 20574039]
15. Jacobs JV, Horak FB, Van Tran K, et al. An alternative clinical postural stability test for patients with Parkinson's disease. J Neurol. 2006; 253:1404–13. [PubMed: 16788773]
16. Goetz CG, Tilley BC, Shaftman SR, et al. Movement Disorder Society-sponsored revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS): scale presentation and clinimetric testing results. Mov Disord. 2008; 23(15):2129–70. [PubMed: 19025984]
17. Chong RK, Morgan J, Mehta SH, et al. Rapid assessment of postural instability in Parkinson's disease (RAPID): a pilot study. Eur J Neurol. 2011; 18:260–5. [PubMed: 20586791]
18. Frenklach A, Louie S, Koop MM, et al. Excessive postural sway and the risk of falls at different stages of Parkinson's disease. Mov Disord. 2009; 24:377–85. [PubMed: 18972546]
19. Carpenter MG, Allum JH, Honegger F, et al. Postural abnormalities to multidirectional stance perturbations in Parkinson's disease. J Neurol Neurosurg Psychiatry. 2004; 75(9):1245–54. [PubMed: 15314109]
20. Chastan N, Do MC, Bonneville F, et al. Gait and balance disorders in Parkinson's disease: impaired active braking of the fall of centre of gravity. Mov Disord. 2009; 24:188–95. [PubMed: 18973252]
21. Moore ST, MacDougall HG, Ondo WG. Ambulatory monitoring of freezing of gait in Parkinson's disease. J Neurosci Methods. 2008; 167(2):340–8. [PubMed: 17928063]
22. Snijders AH, Haaxma CA, Hagen YJ, et al. Freezer or non-freezer: clinical assessment of freezing of gait. Parkinsonism Relat Disord. 2012; 18(2):149–54. [PubMed: 21968033]

23. Spildooren J, Vercruysse S, Desloovere K, et al. Freezing of gait in Parkinson's disease: the impact of dual-tasking and turning. Mov Disord. 2010; 25:2563–70. [PubMed: 20632376]
24. Giladi N, Hausdorff JM. The role of mental function in the pathogenesis of freezing of gait in Parkinson's disease. J Neurol Sci. 2006; 248:173–6. [PubMed: 16780886]
25. Snijders AH, Nijkrake MJ, Bakker M, et al. Clinimetrics of freezing of gait. Mov Disord. 2008; 23:S468–74. [PubMed: 18668628]
26. Mitoma H, Yoneyama M, Orimo S. 24-hour recording of parkinsonian gait using a portable gait rhythmogram. Intern Med. 2010; 49:2401–8. [PubMed: 21088340]
27. Giladi N, McDermott MP, Fahn S, et al. Freezing of gait in PD: prospective assessment in the DATATOP cohort. Neurology. 2001; 56:1712–21. [PubMed: 11425939]
28. Lopez IC, Ruiz PJ, Del Pozo SV, et al. Motor complications in Parkinson's disease: ten year follow-up study. Mov Disord. 2010; 25:2735–39. [PubMed: 20931632]
29. Moore O, Peretz C, Giladi N. Freezing of gait affects quality of life of peoples with Parkinson's disease beyond its relationships with mobility and gait. Mov Disord. 2007; 22:2192–95. [PubMed: 17712856]
30. Plotnik M, Hausdorff JM. The role of gait rhythmicity and bilateral coordination of stepping in the pathophysiology of freezing of gait in Parkinson's disease. Mov Disord. 2008; 23:S444–50. [PubMed: 18668626]
31. Nieuwboer A, Dom R, De Weerdt W, et al. Electromyographic profiles of gait prior to onset of freezing episodes in patients with Parkinson's disease. Brain. 2004; 127:1650–60. [PubMed: 15128621]
32. Azulay JP, Mesure S, Blin O. Influence of visual cues on gait in Parkinson's disease: contribution to attention or sensory dependence? J Neurol Sci. 2006; 248:192–5. [PubMed: 16765379]
33. Hanakawa T, Fukuyama H, Katsumi Y, et al. Enhanced lateral premotor activity during paradoxical gait in Parkinson's disease. Ann Neurol. 1999; 45:329–336. [PubMed: 10072047]
34. Hägglund M, Borgius L, Dougherty KJ, et al. Activation of groups of excitatory neurons in the mammalian spinal cord or hindbrain evokes locomotion. Nat Neurosci. 2010; 13:246–52. [PubMed: 20081850]
35. Garcia-Rill E. The pedunculopontine nucleus. Progress in Neurobiology. 1991; 36:363–89. [PubMed: 1887068]
36. Mesulam MM, Mufson EJ, Levey AI, et al. Atlas of cholinergic neurons in the forebrain and upper brainstem of the macaque based on monoclonal choline acetyltransferase immunohistochemistry and acetylcholinesterase histochemistry. Neuroscience. 1984; 12:669–86. [PubMed: 6382047]
37. Lavoie B, Parent A. Pedunculopontine nucleus in the squirrel monkey: distribution of cholinergic and monoaminergic neurons in the mesopontine tegmentum with evidence for the presence of glutamate in cholinergic neurons. J Comp Neurol. 1994; 344:190–209. [PubMed: 7915726]
38. Pahapill PA, Lozano AM. The pedunculopontine nucleus and Parkinson's disease. Brain. 2000; 123:1767–83. [PubMed: 10960043]
39. Hazrati LN, Parent A. Projection from the deep cerebellar nuclei to the pedunculopontine nucleus in the squirrel monkey. Brain Res. 1992; 585(1–2):267–71. [PubMed: 1380869]
40. Shink E, Sidibe M, Smith Y. Efferent connections of the internal globus pallidus in the squirrel monkey: II. Topography and synaptic organization of pallidal efferents to the pedunculopontine nucleus. J Comp Neurol. 1997; 382:348–63. [PubMed: 9183698]
41. Rolland AS, Karachi C, Muriel MP, et al. Internal pallidum and substantia nigra control different parts of the mesopontine reticular formation in primate. Mov Disord. 2011; 26:1648–56. [PubMed: 21469212]
42. Grillner, S. Control of locomotion in bipeds, tetrapods and fish. In: Brooks, VB., editor. Handbook of Physiology - the nervous system II. Baltimore: 1981. p. 1199-1236.
43. Malouin F, Richards CL, Jackson PL, et al. Brain activations during motor imagery of locomotor-related tasks: a PET study. Hum Brain Mapp. 2003; 19:47–62. [PubMed: 12731103]
44. Jahn K, Deutschlander A, Stephan T, et al. Brain activation patterns during imagined stance and locomotion in functional magnetic resonance imaging. Neuro Image. 2004; 22:1722–31. [PubMed: 15275928]

45. Piallat B, Chabardes S, Torres N, et al. Gait is associated with an increase in tonic firing of the sub-cuneiform nucleus neurons. Neuroscience. 2009; 158:1201–5. [PubMed: 19063948]
46. Snijders AH, Leunissen I, Bakker M, et al. Gait-related cerebral alterations in patients with Parkinson's disease with freezing of gait. Brain. 2011; 134:59–72. [PubMed: 21126990]
47. Zweig RM, Jankel WR, Hedreen JC, et al. The pedunculopontine nucleus in Parkinson's disease. Ann Neurol. 1989; 26:41–6. [PubMed: 2549845]
48. Bohnen NI, Muller ML, Koeppe RA, et al. History of falls in Parkinson disease is associated with reduced cholinergic activity. Neurology. 2009; 73:1670–76. [PubMed: 19917989]
49. Tohgi H, Abe T, Saheki M, et al. Concentration of catecholamines and indoleamines in the cerebrospinal fluid of patients with vascular parkinsonism compared to Parkinson's disease patients. J Neural Transm. 1997; 104:441–9. [PubMed: 9295176]
50. Grimbergen YA, Langston JW, Roos RA, et al. Postural instability in Parkinson's disease: the adrenergic hypothesis and the locus coeruleus. Expert Rev Neurother. 2009; 9:279–90. [PubMed: 19210201]
51. Timmann D, Horak FB. Prediction and set-dependent scaling of early postural responses in cerebellar patients. Brain. 1997; 120:327–37. [PubMed: 9117379]
52. Dunbar MJ, Tran MA, Whelan PJ. Endogenous extracellular serotonin modulates the spinal locomotor network of the neonatal mouse. J Physiol. 2010; 588:139–56. [PubMed: 19884315]
53. Iacono RP, Kuniyoshi SM, Ahlman JR, et al. Concentrations of indoleamine metabolic intermediates in the ventricular cerebrospinal fluid of advanced Parkinson's patients with severe postural instability and gait disorders. J Neural Transm. 1997; 104:451–9. [PubMed: 9295177]
54. Matsui H, Udaka F, Miyoshi T, et al. Three-demensional stereotactic surface projection study of freezing of gait and brain perfusion image in Parkinson's disease. Mov Disord. 2005; 20:1272–127. [PubMed: 16007622]
55. Hanakawa T, Fukuyama H, Katsumi Y, et al. Enhanced lateral premotor activity during paradoxical gait in Parkinson's disease. Ann Neurol. 1999; 5:329–336. [PubMed: 10072047]
56. Bartels AL, de Jong BM, Giladi N, et al. Striatal dopa and glucose metabolism in PD patients with freezing of gait. Mov Disord. 2006; 21(9):1326–32. [PubMed: 16721756]
57. Wu T, Hallett M. A functional MRI study of automatic movements in patients with Parkinson's disease. Brain. 2005; 128:2250–9. [PubMed: 15958505]
58. Chung KA, Lobb BM, Nutt JG, et al. Effects of a central cholinesterase inhibitor on reducing falls in Parkinson disease. Neurology. 2010; 75:1263–9. [PubMed: 20810998]
59. Devos D, Krystkowiak P, Clement F, et al. Improvement of gait by chronic, high doses of methylphenidate in patients with advanced Parkinson's disease. J Neurol Neurosurg Psychiatry. 2007; 78:470–5. [PubMed: 17098845]
60. Espay AJ, Dwivedi AK, Payne M, et al. Methylphenidate for gait impairment in Parkinson disease: a randomized clinical trial. Neurology. 2011; 76:1256–62. [PubMed: 21464430]
61. Petzinger GM, Walsh JP, Akopian G, et al. Effects of treadmill exercise on dopaminergic transmission in the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine-lesioned mouse model of basal ganglia injury. J Neurosci. 2007; 27:5291–300. [PubMed: 17507552]
62. Hyndman D, Ashburn A. Stops walking when talking as a predictor of falls in people with stroke living in the community. J Neurol Neurosurg Psychiatry. 2004; 75(7):994–7. [PubMed: 15201358]
63. Smetana R, Juvin L, Dubuc R, et al. A parallel cholinergic brainstem pathway for enhancing locomotor drive. Nat Neurosci. 2010; 13:731–8. [PubMed: 20473293]
64. Henderson J, Yiannikas C, Graham JS. Effect of ritanserin, a highly selective 5-HT2 antagonist, on Parkinson's disease. Clin Exp Neurol. 1992; 29:277–82. [PubMed: 1343870]
65. Ferraye MU, Debu B, Fraix V, et al. Effects of subthalamic nucleus stimulation and levodopa on freezing of gait in Parkinson disease. Neurology. 2008; 70:1431–7. [PubMed: 18413568]
66. Hariz MI, Rehncrona S, Quinn NP, et al. Multicenter study on deep brain stimulation in Parkinson's disease: an independent assessment of reported adverse events at 4 years. Mov Disord. 2008; 23:416–21. [PubMed: 18067188]
67. Houeto JL, Damier P, Bejjani PB, et al. Subthalamic stimulation in Parkinson disease: a multidisciplinary approach. Arch Neurol. 2000; 57:461–5. [PubMed: 10768618]

68. Moreau C, Defebvre L, Destee A, et al. STN-DBS frequency effects on freezing of gait in advanced Parkinson disease. Neurology. 2008; 71:80–4. [PubMed: 18420482]
69. Chastan N, Westby GW, Yelnik J, et al. Effects of nigral stimulation on locomotion and postural stability in patients with Parkinson's disease. Brain. 2009; 132:172–84. [PubMed: 19001482]
70. Yelnik J. PPN or PPD, what is the target for deep brain stimulation in Parkinson's disease? Brain. 2007; 130:e79. [PubMed: 17586558]
71. Ferraye MU, Debu B, Fraix V, et al. Effects of pedunculopontine nucleus area stimulation on gait disorders in Parkinson's disease. Brain. 2010; 133:205–14. [PubMed: 19773356]
72. Moro E, Hamani C, Poon YY, et al. Unilateral pedunculopontine stimulation improves falls in Parkinson's disease. Brain. 2010; 133:215–24. [PubMed: 19846583]
73. Zrinzo L, Zrinzo LV, Massey LA, et al. Targeting of the pedunculopontine nucleus by an MRI-guided approach: a cadaver study. J Neural Transm. 2011; 118(10):1487–95. [PubMed: 21484277]
74. Fuentes R, Petersson P, Siesser WB, et al. Spinal cord stimulation restores locomotion in animal models of Parkinson's disease. Science. 2009; 323:1578–82. [PubMed: 19299613]
75. Thevathasan W, Mazzone P, Jha A, et al. Spinal cord stimulation failed to relieve akinesia or restore locomotion in Parkinson disease. Neurology. 2010; 74:1325–27. [PubMed: 20404313]

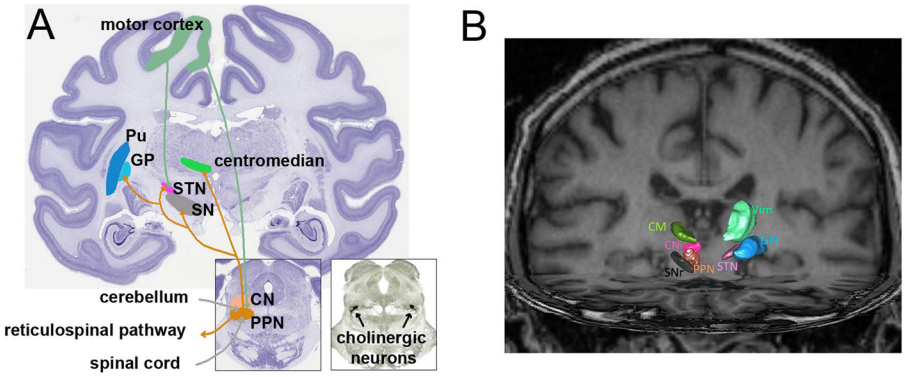

Figure 1.

A. Anatomy and connectivity of the pedunculopontine (PPN) and cuneiform nuclei (CN) in primates. Both nuclei have reciprocal connections with the basal ganglia (GP, globus pallidus; Pu, putamen; SN, substantia nigra; STN, subthalamic nucleus). They also receive inputs from the cerebellum and motor cortices. The existence of inputs from the spinal cord remains to be demonstrated in monkeys. The PPN and CN have major outputs to the descending reticulo-spinal pathway and the ascending thalamo-cortical pathway through the thalamic centromedian nucleus. Cholinergic neurons in the PPN visualized using NADPH-diaphorase histochemistry are also represented in a transverse brainstem section (lower right panel).

B. Anterior view of surgical targets for Parkinson disease. Targets are defined in a three-dimensional histological atlas, with axial and coronal sections of the corresponding post-mortem T1-weighted MRI. The usual targets are visualized on the right hemisphere: GPi, internal globus pallidus; STN, subthalamic nucleus; Vim, ventral intermediate thalamic nucleus. New targets are visualized on the left hemisphere: CM, thalamic centromedian nucleus; CN, cuneiform nucleus; PPN, pedunculopontine nucleus; SNr, substantia nigra pars reticulata.