

Advances in Therapeutic Options for Gait and Balance in Parkinson's Disease

Nicolaas I Bohnen, MD, PhD,¹ Roger L Albin, MD,² Martijn LTM Müller, PhD³ and Kelvin L Chou, MD⁴

1. Professor, Functional Neuroimaging, Cognitive and Mobility Laboratory, Departments of Radiology and Neurology, University of Michigan, and Veterans Administration, Ann Arbor; 2. Professor, Department of Neurology, University of Michigan, and Veterans Administration, Ann Arbor; 3. Research Investigator, Department of Radiology, University of Michigan; 4. Clinical Associate Professor, Departments of Neurology and Neurosurgery, University of Michigan

Abstract

There is a need to explore non-dopaminergic approaches to treating balance and gait problems in Parkinson's disease (PD). There is emerging evidence on the role of cholinergic denervation of the pedunculo-pontine nucleus (PPN) thalamus system and falls in PD. Preliminary clinical trial data suggest that the subgroup of PD patients with frequent falls may be suitable candidates for future cholinergic augmentation clinical trials. Recent controlled clinical trials using methylphenidate have been unable to confirm earlier reports of improved gait in PD. Although progressive deterioration of axial motor symptoms occur with deep brain stimulation of the subthalamic nucleus or globus pallidus interna, new preliminary research suggests that other surgical stimulation sites, such as the PPN, may have a potential benefit on gait and balance impairments in PD. Continuing vigorous exercise and physical fitness should be highly encouraged to patients with PD who are at risk of physical deconditioning and fear of falling, but effective antifall physical therapy interventions remain an unmet clinical need.

Keywords

Acetylcholine, dopamine, noradrenergic, deep brain stimulation, exercise, falls, mobility, Parkinson's disease, pedunculo-pontine nucleus, striatum, substantia nigra

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Correspondence: Nicolaas I Bohnen, MD, PhD, Functional Neuroimaging, Cognitive and Mobility Laboratory, Departments of Radiology and Neurology, University of Michigan, 24 Frank Lloyd Wright Drive, Box 362, Ann Arbor, MI 48105-9755. E: nbohen@umich.edu

Parkinson's disease (PD) is a clinical syndrome consisting of a variable combination of the four cardinal features of resting tremor, rigidity, bradykinesia, and postural instability.¹ Akinesia, defined as inability to initiate movement (e.g. gait ignition failure) or sustain movement (e.g. sudden freezes), is considered by some to be the fifth cardinal feature of PD.² Most motor features of PD are believed to result mainly from loss of striatal dopamine secondary to the degeneration of dopaminergic neurons of the substantia nigra pars compacta (SNpc).³ The greater the neuronal loss in the SNpc, the lower the striatal dopamine concentration and the more severe the parkinsonian symptoms, particularly bradykinesia.⁴ The rate of disease progression is highly variable among PD patients. Patients with tremor-predominant disease at onset, for example, tend to progress more slowly than patients with early prominent postural instability and gait disturbances (PIGD).⁵

Clinical characteristics of parkinsonian locomotor patterns include slow gait and reduced angular excursion of joints such as shoulder, knee, and trunk joints.^{6,7} With disease progression, stooped posture, short steps, and shuffling (the latter associated with reduced ground clearance and festination) become more prominent features.⁷⁻⁹ Falls are common in PD. Unlike falls in the general population, which result generally from slipping

or tripping incidents, the majority of falls in PD occur during routine walking, stopping, turning, and standing up or bending down maneuvers.^{10,11} One prospective survey of relatively mildly affected PD patients found that 60 % fell during a six-month period and 33 % had multiple falls in this period.¹² Fall risk in PD is a bell-shaped function of disease severity,¹³ reaching a maximum during Hoehn and Yahr stage 3 and decreasing in later stages as patients become less mobile.^{14,15} The emergence of postural instability marks the onset of increased risk for severe disability in PD patients as up to 40 % of patients with postural instability have multiple falls which may result in injury, including potentially crippling hip and wrist fractures.¹⁶

Because of the primary basal ganglia involvement in PD, it is often asserted that postural control impairments are mainly attributable to the dopaminergic deficits. The majority of postural control and gait impairments associated with falls are resistant to dopaminergic treatment.¹⁷ While some gait parameters, including stride length, gait velocity, and movement amplitudes, improve with dopaminergic treatment,^{6,18-21} other features, including temporal parameters (e.g. cadence, swing and stance duration), kinetic abnormalities, and gait variability, are treatment resistant.^{20,22,23} There is an increasing research effort in exploring non-dopaminergic correlates of gait impairment in PD.

Locomotor and Postural Control Centers

Bipedal locomotion in humans is a complex sensorimotor task requiring dynamic interaction between spinal locomotor pattern generators and hierarchically organized supraspinal locomotion centers in the brainstem, cerebellum, and forebrain. The cerebral networks are believed to modulate locomotion (e.g. gait initiation, termination, velocity, direction, and spatial orientation) and to control balance and gait by integration of multisensory information.²⁴ Our knowledge of the hierarchical network of supraspinal locomotion centers is derived largely from basic science studies in cats, an animal with quadrupedal locomotion.^{25,26} While it is likely that the anatomic systems for gait and balance are conserved in mammals, the important details of interconnectivity and physiologic regulation are likely to differ significantly. The most important regions are the cerebellar locomotor region, the mesencephalic locomotor region, and the subthalamic locomotor region. The basal ganglia, including the striatum, pallidum, subthalamic nucleus (STN), and substantia nigra, are involved in a number of parallel, functionally segregated cortical–subcortical circuits.²⁷ These circuits support a wide range of sensorimotor, cognitive, and emotional–motivational brain functions. A main role of the basal ganglia is learning and selection of the most appropriate motor or behavioral programs.²⁸ Dopaminergic signaling within the basal ganglia is clearly involved in reward-based learning and action selection.²⁹ Normal dopaminergic function is probably particularly important for establishment, selection, and sequencing of habitual patterns of action.³⁰

Effective integration of sensory information about the visuospatial environment, body, and limb position is essential for postural control. Standing posture, for example, is affected by perturbations of visual, vestibular, and proprioceptive sensory systems.^{31–33} The specific role of the basal ganglia in postural control is complex and only beginning to be unraveled, but it is believed to be involved in several functions, including:

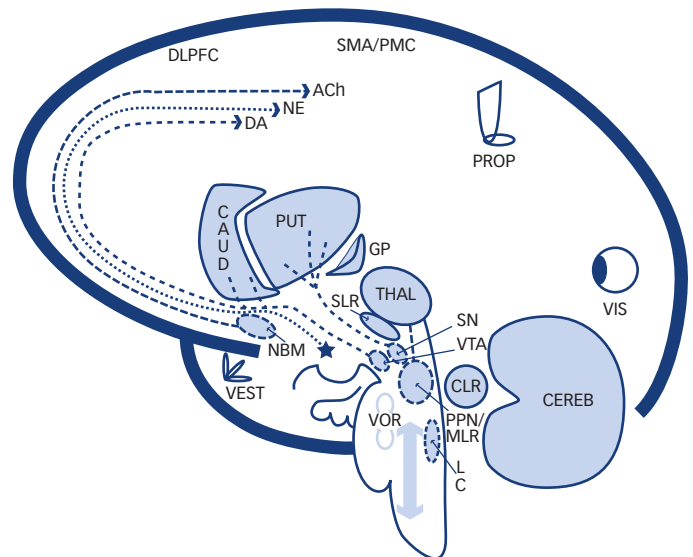
- sensory channel integration;
- selection of automatic postural reactions generated in response to motor and sensory perturbations, such as moving visual environments;
- motor control flexibility and adaptability: for example, appropriate corrective postural reactions generated in an attempt to prevent a fall are dependent upon the characteristics of the perturbation and environmental changes;
- regulation of muscle tone; and
- modulation of the impact of cognitive factors on balance and gait, such as attention, multitasking, and knowledge or expectation of a potential perturbation, or fear of falling.³⁴

Figure 1 provides a schematic overview of the main locomotor and postural control centers in the brain.

Parkinsonian Gait and Deficits in Central Motor Control

PD affects complex gait activities such as gait initiation, braking, and turning. These are gait elements that require the execution of coordinated sequential and/or simultaneous motor programs essential to maintain equilibrium and to generate new movements. Healthy controls are able to harmoniously perform such complex motor tasks, but PD patients exhibit impairment of these functions, resulting in freezing, postural instability, and falls.^{8,9,35,36} PD patients have difficulty stopping and

Figure 1: Schematic of the Sensory Systems, Locomotor Regions, Cortical and Subcortical Regions, and Neurochemical Projections Involved in the Regulation of Balance and Gait



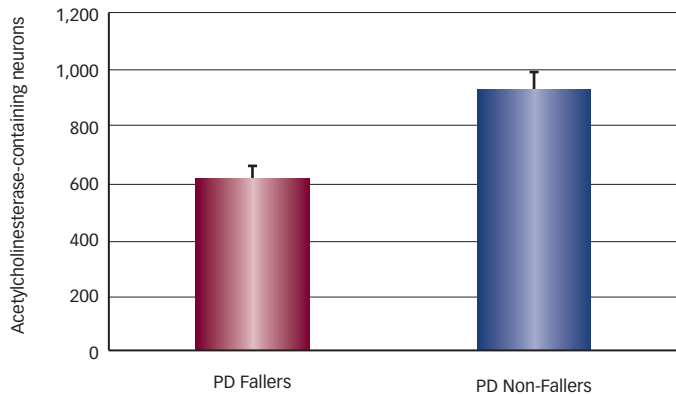
* Originates from the locus ceruleus (LC). ACh = acetylcholine; CAUD = caudate nucleus; CEREB = cerebellum; CLR = cerebellar locomotor region; DA = dopamine; DLPFC = dorsolateral prefrontal cortex; GP = globus pallidus; MLR = mesencephalic locomotor region; NBM = nucleus basalis of Meynert; NE = norepinephrine; PMC = primary motor cortex; PPN = pedunculopontine nucleus; PROP = proprioception; PUT = putamen; SLR = subthalamic locomotor region; SMA = supplementary motor area; SN = substantia nigra; THAL = thalamus; VEST = vestibular; VIS = vision; VOR = vestibulo-ocular reflex; VTA = ventral tegmental area.

turning, especially when in confined spaces.⁷ Freezing of gait, usually manifested as abrupt cessation of leg movement during walking, is a common cause of falls. Sudden freezes may be related to altered cortical regulation of movement execution together with progressive impairment of mesencephalic locomotor center function (see below).³⁷

In patients with early PD, loss of dopamine is predominantly in the posterior putamen, whereas the anteroventral striatum is relatively spared.³⁸ However, the caudate nucleus, which has a more prominent role in striatocortical cognitive functions,²⁷ becomes more involved with advancing PD. Striatofrontal pathways have been implicated as playing a compensatory role in gait control in patients with PD. For example, a brain positron emission tomography study found that gait activity in normal elderly people was associated with a significant decrease in dopamine activity in the putamen, with patients with PD demonstrating a more prominent decrease in the caudate nucleus and frontal cortex.³⁹ Abnormal caudate nucleus function has been implicated in patients with PD and freezing of gait, suggesting failure of the compensatory striatofrontal pathway functions as a possible mechanism.⁴⁰

Gait in PD during a freezing episode can be improved by simple sensory cues, such as visual (guiding stripes on the floor) or auditory cues.^{41–45} One interpretation of the beneficial impact of appropriate sensory cueing is that dopamine-depleted basal ganglia are unable to integrate internal/external cues critical to gait and balance. Simple sensory cueing enhances cue saliency. An alternative explanation is that accurate external cues facilitate focusing of attentional resources on balance/gait during complex or simultaneous tasks and enable accurate visuospatial orientation.

Figure 2: Post Mortem Findings of Reduced Pedunculopontine Nucleus Acetylcholinesterase Containing Neurons Showing Lower Activity in Parkinson's Disease Fallers Compared with Non-fallers⁷³



PD = Parkinson's disease.

Cognitive Deficits, Gait Variability, and Falls in Parkinson's Disease

Alterations in cognitive function (and presumably general cortical function) are linked to gait disturbances.⁴⁶ In a simple, elegant study, Lundin-Olsson et al. showed that older adults who could not walk and talk ('stopped walking while talking') were at higher risk for falling, while those subjects who could walk and talk at the same time were much less prone to falls.⁴⁷ This observation suggests that simultaneous performance of two attention-demanding tasks (walking and talking) may cause competition for cognitive resources or a challenge for the brain to appropriately prioritize the two tasks, a so-called 'posture-first' strategy.

Selective cognitive impairments, especially executive function and attentional deficits, are commonly present in patients with mild, early PD.^{48,49} Dual tasking represents an executive cognitive function heavily dependent on basic operations of working memory and attention.⁵⁰ Gait and balance are challenged when concurrent tasks have to be performed, which may lead to increased gait variability.⁵¹⁻⁵³

Cognitive or complex sensorimotor (such as carrying a tray) dual interference tasks produce significant differences in gait parameters between PD and control subjects.⁵⁴⁻⁵⁶ Camicioli et al., for example, examined the effects of a simultaneous verbal fluency task on walking in PD subjects with freezing of gait and found that these subjects exhibited a greater increase in the number of steps needed to complete the walk when performing the verbal fluency task.⁵⁴

Modulation of gait variability, considered a reflection of ability to regulate gait, deteriorates in PD.^{22,57,58} Competing demands of gait and other tasks may lead to increased gait variability.⁵¹⁻⁵³ Yogev et al. have reported on the increased swing phase duration variability in PD patients compared with control persons.⁵² Springer et al. and Yogev et al. reported correlations between executive dysfunction and gait variability under usual walking conditions. These correlations became stronger under dual task conditions among elderly non-demented fallers and among patients with PD.^{52,59} These data support the concept that executive cognitive impairment, especially the limited ability to

perform dual tasking, has a negative impact on gait functions, increases gait variability, and results in increased risk of falling.^{59,60} These data emphasize the importance of cortical dysfunction in gait control in PD patients. A significant component of this cortical dysfunction may be attributable to loss of cholinergic innervation (see below).

Multisystem Degeneration in Parkinson's Disease—Recent Emphasis on Mobility Impairments and Non-dopaminergic Systems

Although nigrostriatal dopaminergic denervation is a key pathobiologic mechanism in PD, there is also converging evidence of degeneration of other monoaminergic (serotonin and norepinephrine) and cholinergic neurotransmitter systems.^{61,62} The cholinergic system has been implicated in mobility functions in PD not only because of its cortical role in directing attention but also secondary to degeneration of cholinergic cells in the pedunculopontine nucleus in the brainstem.⁶³

The Pedunculopontine Nucleus

The pedunculopontine nucleus–laterodorsal tegmental complex (PPN-LDTC; hereafter referred to as the PPN) is a brainstem locomotor center⁶⁴ which degenerates in PD.⁶⁵ The PPN is located in the dorsolateral part of the ponto-mesencephalic tegmentum.^{66,67} An important point is that the PPN should not be regarded as synonymous with the mesencephalic locomotor region. The latter is a physiologic construct defined by stimulation experiments. The PPN is probably a component of the mesencephalic locomotor region, which appears to be larger than the anatomically defined PPN. Definitions of the PPN vary and there is still debate about its borders, constituents, and internal organization. The PPN is composed of cholinergic and non-cholinergic neurons with a wide array of neurotransmitters and neuropeptides, and neuromodulators expressed by PPN neurons.^{68,69} PPN neurons exhibit a wide variety of connections across much of the neuraxis, including important connections to several subcortical regions, other brainstem structures, and the spinal cord.⁶⁹ The PPN is connected reciprocally with the limbic system, several basal ganglia nuclei (globus pallidus, substantia nigra, STN), and the brainstem reticular formation (for careful reviews see Alam et al.⁶⁷ and Winn⁶⁹). The robust interconnections between the PPN and the basal ganglia have led some to regard the PPN as an integral component of the basal ganglia system.⁷⁰ Some PPN neurons may receive inputs from the deep cerebellar nucleus, a potential link between the basal ganglia and cerebellar motor systems. The caudally directed corticolimbic–ventral striatal–ventral pallidal–PPN–pontomedullary reticular nuclei–spinal cord pathway seems to be involved in the initiation, acceleration, deceleration, and termination of locomotion.⁶⁶ This pathway is under the control of the deep cerebellar and basal ganglia nuclei at the level of the PPN, particularly via potent inputs from the medial globus pallidus, substantia nigra pars reticulata, and STN.

The PPN sends profuse ascending cholinergic efferent fibers to almost all the thalamic nuclei,⁶⁴ and thalamic cholinergic terminal density is a measure of PPN integrity. The PPN degenerates in akinetic disorders such as PD and progressive supranuclear palsy.⁶¹ There are reports that about 50 % of the large cholinergic neurons of the lateral PPN degenerate in PD.^{61,63,71-73} A recent study reported *post mortem* findings of greater loss of cholinergic PPN neurons (34 %) in PD fallers compared with PD non-fallers (see Figure 2).⁷³

PPN dysfunction–degeneration is associated with dopamine-resistant akinesia, one of the most disabling features of PD.^{65,74} Similarly, experimental PPN destruction in non-human primates is associated with bradykinesia, akinesia, and prominent postural control deficits.⁷³ Stimulation of the PPN increases movement in animals, while inhibition decreases it.^{74,75} These findings have significant implications for the treatment of PD and related disorders.

The Basal Forebrain Cholinergic System

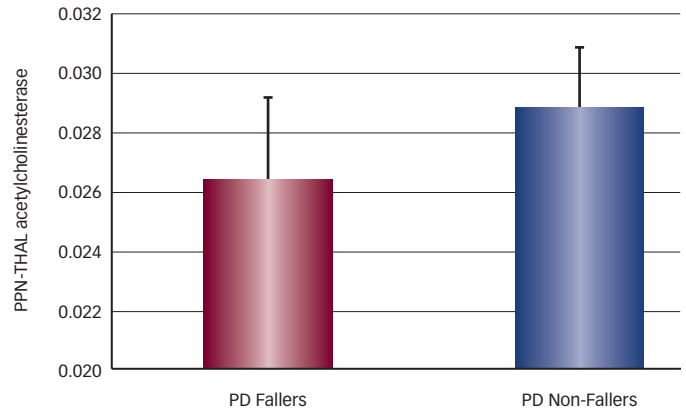
Cholinergic afferents to the cortex play an important role in a variety of cognitive functions, including attention, memory encoding, and executive function.⁷⁶ Degeneration of basal forebrain cholinergic corticopetal projections is a prominent feature of PD, and cortical cholinergic deficits of PD exceed those of Alzheimer's disease.⁷⁷ In the Braak model of ascending pathology, basal forebrain degeneration occurs approximately concurrently with substantia nigra pars compacta degeneration. The degree of basal forebrain cholinergic system neurodegeneration, however, varies among PD patients, with some patients exhibiting relative preservation of cortical cholinergic innervation.⁷⁸ Loss of cortical cholinergic innervation is associated with cognitive deficits in PD and is likely to degrade the attentional and executive functions required for normal gait and postural functions.⁷⁹ This inference is consistent with recent rodent experiments in which animals with dual nigrostriatal dopaminergic and basal forebrain cholinergic lesions exhibit prominent motor performance deficits in tasks requiring sustained attention.⁸⁰

Consequences of Multifocal Neurodegeneration in Parkinson's Disease—Falls and Cholinergic Systems as an Example

Given that PD is a multisystem neurodegeneration, differences in the degree of or rate of degeneration of different central nervous systems may account for differences in phenotypic features. In early-stage PD there is evidence of uniform and severe dopaminergic denervation, but subcortical and cortical cholinergic denervation is more heterogeneous, with some PD subjects exhibiting diminished regional cholinergic innervation and others showing relatively normal regional cholinergic innervation. We showed previously that PD fallers (defined as falls not due to freezing) did not differ in the degree of nigrostriatal dopaminergic denervation but had significantly decreased PPN-thalamic and cortical cholinergic innervation compared with non-fallers (see *Figure 3*).⁸¹ Cholinergic system degeneration is probably both a partial cause of and a marker for cognitive dysfunction in PD. Cholinergic system degeneration or dysfunction may also provide a conceptual framework to explain why patients with higher postural instability and gait disturbances in Lewy body parkinsonism are at increased risk of developing dementia.^{82,83}

These data indicate the presence of heterogeneity of cholinergic denervation with PD. We also found evidence of heterogeneity of mobility impairments in our study. A 2 x 2 table shows that distinct subgroups with PD subjects have falls (not attributable to freezing) versus subjects having freezing of gait or a combination of the two (see *Table 1*). PD subjects with freezing of gait had lower dopamine activity in the caudate nucleus (–12.2 %, analysis of variance F=5.4, p<0.05) but not in the anterior (F=0.6, p=NS) or posterior putamen (F=0.30, p=NS) as shown by [C-11]dihydrotetraabenazine positron emission tomography. Freezing of gait may represent a failure of a dopaminergic compensatory striatofrontal mechanism in PD.

Figure 3: In Vivo Positron Emission Tomography Findings of Pedunclopontine Nucleus-thalamus Cholinergic Activity in Parkinson's Disease Non-fallers and Fallers



Parkinson's disease (PD) fallers had lower pedunclopontine nucleus (PPN)-thalamic cholinergic activity than PD non-fallers. THAL = thalamus.

Table 1: Subgroups of Parkinson's Disease Patients with Freezing of Gait, Falls, a Combination, or None

		FoG		
		No	Yes	
Falls (Not due to FoG)	No	22 (51.2 %)	5 (11.6 %)	27
	Yes	8 (18.6 %)	8 (18.6 %)	16
		30	13	43

$\chi^2 = 4.7$ (p<0.05)

There are distinct subgroups of Parkinson's disease patients showing either specific mobility impairments of freezing of gait (FoG) and falls (not related to FoG) alone, a combination of these impairments, or absence of these impairments.

Taken together, our findings suggest that specific mobility impairments may be related to neurodegeneration in specific brain regions.

The Locus Ceruleus

Other transmitter systems, such as central noradrenergic pathways, are affected in PD and may be involved in gait and balance deficits. Noradrenergic pathways have been implicated in alertness and other cortical attention functions important for gait control in PD.⁸⁴ The locus ceruleus is a small nucleus located in the pontine tegmentum and is the main source of norepinephrine for the brain and spinal cord.⁸⁵ There is significant degeneration of the locus ceruleus in PD.⁸⁶

Non-specific White Matter Degeneration and Impaired Balance and Posture in Parkinson's Disease

Areas with altered signal intensity in white matter are encountered frequently on brain imaging studies in the elderly.⁸⁷ These white matter abnormalities or leukoaraiosis are commonly associated with small-vessel

cerebrovascular disease.⁸⁸ In otherwise normal older adults, white matter abnormalities have been associated with subtle abnormalities of balance and gait.⁸⁹⁻⁹¹ As white matter changes are associated with motor dysfunction in otherwise normal elderly adults, comorbid leukoaraiosis could be predicted to contribute also to clinical features in PD. We recently reported that comorbid white matter disease is a greater determinant of axial motor impairment and stooped posture than nigrostriatal dopaminergic denervation in PD.⁹² This conclusion is consistent with an emerging theme in neurodegeneration research: the importance of interactions among vascular, neuro-inflammatory, and neurodegenerative pathologies.⁹³ It is possible that aggressive management of vascular or inflammatory risk factors in PD patients, especially when initiated early in the disease course, could reduce the severity of axial motor dysfunction in PD.

Cholinergic Pharmacotherapy and Motor Functions

These relationships between cholinergic deficits and gait/posture abnormalities raise the question as to whether cholinergic therapy may have a place in the management of mobility problems in PD. Results of a recent placebo-controlled clinical trial showed that treatment with the acetylcholinesterase inhibitor donepezil for six weeks reduced the frequency of falls by about 50 % in frequently falling PD subjects (defined as falling or nearly falling more than two times per week).⁹⁴ Subjects with the highest baseline rate of falls demonstrated the most improvement. However, donepezil did not improve performance on the Berg balance scale, balance confidence scores, or parkinsonian motor scores. One subject withdrew from the study owing to worsening of tremor. While this result needs to be replicated in a larger study, the outcome is encouraging. Interestingly, two subjects with freezing of gait did not appear to benefit from donepezil. Donepezil effects could be mediated by effects in multiple cholinergic pathways. There could be cortical cognitive benefits of improved attention or executive functions⁹⁵⁻⁹⁷ or improved subcortical PPN-thalamus projection function.⁷⁰

The variable outcomes in this small study, with worsening of tremor in one subject and reduced falls in frequently falling subjects, suggests that caution is in order and that careful selection of patients for cholinergic drug therapy of motor functions will be needed. Cholinergic denervation in PD, especially in non-demented PD subjects, is variable, with some subjects exhibiting relatively preserved cholinergic pathways. Further studies are needed to determine the relationship between specific motor phenotypes in PD and the degree and regional distribution of cholinergic denervation so that an appropriate subset of patients can be selected for potentially beneficial cholinergic augmentation therapy to treat imbalance and falls in PD. Preliminary data, however, indicate that the subgroup of PD patients with frequent falls (two or more per week) may be suitable candidates for future cholinergic augmentation studies.

Cholinesterase inhibitors will augment cholinergic neurotransmission in all cholinergic pathways, potentially decreasing the therapeutic index of this drug class. An emerging potential alternative is selective targeting of nicotinic cholinergic receptors. These ligand-gated ion channels are composed of a variety of subunits with differential distribution of receptor subtypes throughout the brain. Receptor-subtype-specific compounds exist and are under development. Some of these compounds may allow

modulation of specific cholinergic pathways. Sarter et al. predict that one family of selective nicotinic agonists will specifically enhance cortical attentional mechanisms.⁹⁸ In PD patients with cortical cholinergic deficits, compounds of this type may ameliorate the executive-attentional deficits that contribute to gait and postural control problems.

Noradrenergic Pharmacotherapy and Mobility in Parkinson's Disease

The amphetamine derivative methylphenidate inhibits catecholamine re-uptake, increasing brain dopamine and norepinephrine levels. Methylphenidate is used to treat patients with attention-deficit and hyperactivity disorder. Early observations of methylphenidate effects in PD suggest that this compound is not useful for ameliorating cognitive and affective symptoms, but in certain cases it improves attention.⁹⁹ The effects of methylphenidate on motor deficits are somewhat controversial. Some small, open-label pilot studies have suggested that low-dose methylphenidate may improve gait, and especially freezing, in patients with severe PD, without the need for exogenous levodopa.⁹⁹⁻¹⁰¹ This result was not confirmed by other trials.^{102,103} A recent randomized, placebo-controlled, double-blind six-month trial showed that methylphenidate in doses up to 80 mg per day did not improve gait and tended to worsen measures of motor function, sleepiness, and quality of life.¹⁰⁴ Atomoxetine is a selective inhibitor of norepinephrine uptake; a small study failed to find significant benefits in gait and balance scores with atomoxetine in PD.¹⁰⁵

Effects of Subthalamic Nucleus or Pallidal Deep Brain Stimulation on Gait and Balance in Parkinson's Disease

Deep Brain Stimulation for Parkinson's Disease—Indications and Targets

Deep brain stimulation (DBS) is a surgical procedure in which a stimulating electrode is implanted within an identified target in the brain and is connected by wires to a pulse generator implanted under the skin overlying the chest. When the generator is turned on, electrical signals are delivered to the brain and improve the symptoms of PD. DBS is considered for PD patients with significant motor fluctuations, characterized by wearing-off or dyskinesias, despite optimal medical management. PD patients with medication-refractory tremor may also be candidates for DBS.^{106,107} There are three surgical targets for PD: the ventralis intermedius nucleus of the thalamus, the STN, and the globus pallidus interna (GPI). Stimulation of the STN and GPI can improve three of the cardinal symptoms of PD (rest tremor, bradykinesia, and rigidity). It is well accepted that stimulation of the ventralis intermedius nucleus of the thalamus helps parkinsonian tremor only and does not improve bradykinesia or rigidity.¹⁰⁸ Therefore, there is no literature on the effects of thalamic stimulation on gait and balance in PD. The effects of STN or GPI stimulation on gait and balance have been documented but remain somewhat controversial.

Deep Brain Stimulation for Parkinson's Disease—Short-term Effects on Gait and Balance

Bakker et al. performed a systematic review of early studies examining the effect of STN and GPI DBS on PIGD symptoms in PD.¹⁰⁹ Nine studies reported the effects of bilateral GPI stimulation and 10 studies reported the effects of bilateral STN stimulation. Most of the studies included in

this review reported results six months after surgery, but there were some studies with follow-up of up to 12 months. Overall, PIGD symptoms significantly improved with both STN and GPi stimulation in both the medication 'off' state and 'on' state, but more so in the medication 'off' state. Both STN and GPi stimulation improved timed tests of PIGD as well as gait and balance performance on quantitative gait analysis and posturography.

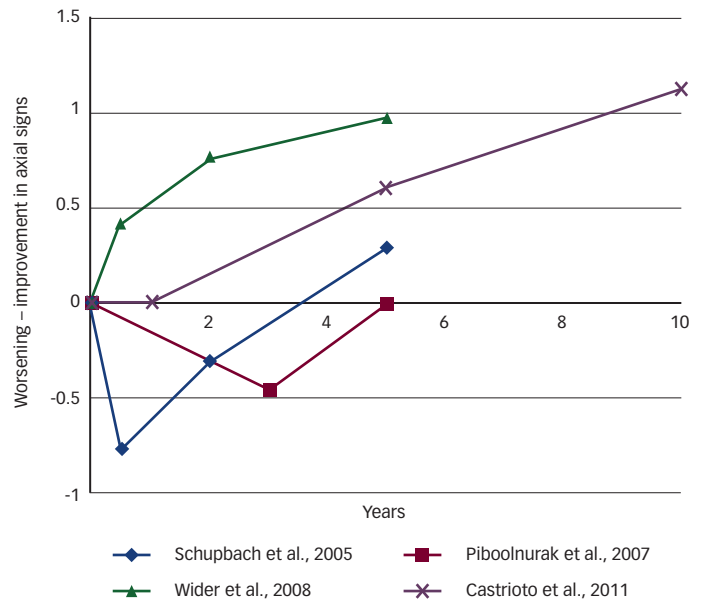
These results seem to contradict the results of a recent blinded controlled trial of DBS in PD,¹¹⁰ which reported six-month outcomes of 255 patients randomized to DBS or best medical therapy. While PIGD symptoms were not specifically examined and reported, the motor portion of the Unified Parkinson's Disease Rating Scale (UPDRS) improved significantly and patients had more 'on' time with DBS. Despite this, subjects in the DBS arm of this trial had more falls and gait disturbances in the first three months after receiving surgery than subjects in the best medical therapy group. At six months, there were no differences in the percentage of subjects experiencing gait disturbance between the two groups, but falls remained more prominent in the DBS group. In a separate article reporting 24-month outcomes of these subjects after randomization to STN or GPi stimulation,¹¹¹ the number of patients with falls or gait disturbance at 24 months did not differ significantly between the two different targets.

It is unclear why PIGD scores improve with DBS yet patients undergoing DBS seem to have more falls, at least initially after DBS surgery. The improvement in PIGD scores could simply result from improvement in bradykinesia and rigidity which previously affected gait and balance. Such improved motor function could cause patients to engage in activities that they previously avoided, resulting in more falls. It is also well known that increasing stimulation can transiently worsen dyskinesia, especially with STN stimulation.¹¹² Transient increased dyskinesias may also impact gait and contribute to falls in the short term. There are many other contributors to gait and posture other than bradykinesia, rigidity, and dyskinesia. Such systems, such as the complex network responsible for postural control described earlier, could be directly affected by DBS as well.

Deep Brain Stimulation for Parkinson's Disease— Long-term Studies on Gait and Balance

A common theme in long-term studies of DBS in PD is the sustained control of cardinal symptoms such as bradykinesia, tremor, and rigidity.¹¹²⁻¹¹⁶ An equally common finding in these long-term studies, however, is worsening gait function. One recent study, for example, reported 10-year outcomes of bilateral STN DBS in PD.¹¹⁷ Although improvements in tremor and bradykinesia were sustained, axial motor scores showed progressive deterioration over time (-53.6 % at five years and -101.8 % at 10 years). Posture also significantly deteriorated over time (-80 % both at five and 10 years). This phenomenon seems to occur with both STN and GPi stimulation, and in long-term studies has been attributed to the progression of dopamine-resistant symptoms. A relevant question, however, is whether DBS site placement has differential long-term effects on gait function. Direct comparisons are difficult because most centers typically implant primarily in one site, with more centers choosing the STN. A recently published meta-regression analysis of long-term studies of bilateral DBS addresses

Figure 4: Change in Axial Signs Over Time in Long-term Studies of Subthalamic Nucleus Deep Brain Stimulation



Studies reporting axial motor scores with at least five years of follow-up were included in this figure. The graph shows the standardized difference between axial motor scores recorded at various time-points after surgery in the medication 'on' and stimulation 'on' state. The standardized change score was the difference between the axial motor score at the assessment time after surgery and the baseline score, divided by the average standard deviation of each score. A change score <0 indicates improvement, while a change score >0 indicates worsening.

potential differences in progression of PIGD features in patients receiving STN versus GPi DBS.¹¹⁸ There were sustained improvements in tremor, bradykinesia, and rigidity in both STN and GPi DBS with minimal deterioration over time. Progression of balance and gait deficits, however, apparently varied with DBS site selection. In the 'on' medication state, balance and gait initially improved with DBS but by two years were worse than the pre-operative 'on' medication state in the STN group, whereas there was no deterioration in postural stability and gait in the GPi group.

These results suggest that the long-term progression of PIGD features may be different with GPi stimulation than with STN stimulation and that GPi is a better target for patients with significant balance and gait problems. The reasons for this discrepancy are not clear, but medications are typically reduced more with STN DBS compared with GPi DBS.¹¹¹ It is possible that sustained higher levels of dopaminergic medications over time in GPi patients lead to less progression of PIGD symptoms. It may be that there is adaptation to commonly used stimulation settings over time, and that patients receiving STN DBS experience such adaptation over time. A recent study on the 10-year outcome of bilateral STN DBS in PD reported that, although improvements in tremor and bradykinesia were sustained, axial motor scores showed the most progressive deterioration over time (-53.6 % at five years and -101.8 % at 10 years).¹¹⁷ Posture also deteriorated significantly over time. These findings suggest a lack of neuroprotective effects of DBS on PD progression (see Figure 4).

Another group examined whether modifying DBS frequency in patients with STN DBS could improve gait and freezing episodes developing several years after surgery.¹¹⁹ The rationale for this intervention was the

finding that low-frequency stimulation of the PPN may improve gait disorders in PD. Freezing seemed to improve with high-voltage 60 Hz stimulation compared with standard or high-voltage 130 Hz stimulation. Brozova et al. found that, of the 12 patients who were switched to 60 Hz stimulation, three could not tolerate the change because of worsened parkinsonian symptoms.¹²⁰ This suggests that lower-frequency stimulation may not be the answer for everyone who has gait problems after STN DBS. More studies are clearly needed to determine the appropriate patients for low-frequency STN DBS.

Pedunculopontine Nucleus Deep Brain Stimulation for Gait and Balance Dysfunction in Parkinson's Disease

Because of progressive decline in gait and balance functions in PD patients who have undergone DBS, there has been recent interest in other brain targets to address features not helped by STN or GPI DBS. The most promising target is the PPN. Evidence that PPN degeneration/dysfunction occurs in PD and the important role of the PPN in gait and postural stability, coupled with the fact that stimulation of the PPN in animal models increases locomotor activity,^{74,121,122} led to interest in PPN stimulation for gait dysfunction in PD.

The first two case series of low-frequency PPN stimulation in patients with PD reported both significant improvement in gait and posture and improved UPDRS total motor scores.^{123,124} Subsequent reports, unfortunately, are not as impressive.¹²⁵⁻¹²⁷ Moro et al. reported six patients with PD who underwent low-frequency unilateral PPN stimulation and demonstrated improvements in falls and freezing of gait at three months compared with the baseline 'off medication' state.¹²⁶ There were, however, no improvements in the UPDRS total motor or in gait/posture scores. Ferraye et al. reported an open-label study of bilateral PPN stimulation in six PD patients who had previously undergone STN DBS but with gait and postural problems unresponsive to STN DBS.¹²⁵ There was significant improvement in freezing of gait and falls at one year compared with baseline, but blinded 'on' and 'off' stimulation comparisons at one year failed to demonstrate any difference in gait or posture.

Several possibilities may explain the variability in results of PPN stimulation in PD. First, the PPN is a difficult structure to pin down anatomically in humans and the PPN is difficult to visualize on traditional magnetic resonance sequences.^{67,128} The regions targeted in recent studies are somewhat different and differential targeting may explain discrepant results. Another factor is the difficulty of finding a suitable stimulation site within the PPN when severe degeneration, such as in PD fallers, has already occurred.⁷³ There may also be differences related to how many different targets are being stimulated. For example, Moro et al.¹²⁶ investigated unilateral PPN stimulation only, while other studies reported patients with both bilateral STN and PPN stimulation.^{124,125} A recent study reports significant improvement in axial motor scores when DBS of the PPN is combined with stimulation of the caudal zone incerta in patients with PD.¹²⁹ The studies by Ferraye et al. and Moro et al. suggest that patients with freezing of gait and falls related to freezing may benefit more from PPN stimulation than patients with postural instability only.^{125,126} It is clear that further studies are needed to better characterize PPN targeting, patient selection, and efficacy of PPN stimulation and stimulation of other targets on gait and balance dysfunction in PD.

Physical Therapy and Exercise in the Management of Gait and Balance Problems in Parkinson's Disease

Physical therapy management of gait disorders in people with PD has three key elements.¹³⁰ The first element is teaching the person how to move more easily and to maintain postural stability by using cognitive strategies. This is known as 'strategy training' and targets the primary motor control deficit in the basal ganglia, brainstem, and motor cortex. The second element of physical therapy is the management of secondary sequelae affecting the musculoskeletal and cardiorespiratory systems that occur as a result of deconditioning, reduced physical activity, advanced age, and comorbid conditions. The third element is the promotion of physical activities that assist the person in making lifelong changes in exercise and physical activity habits as well as preventing falls.

Current approaches with physical therapy interventions have significant limitations. The strategy training approach depends considerably on patient commitment and intact cognitive capacities. As described above, cognitive impairments may be an important contributor to impaired gait and balance function in PD. The PD patients most in need of rehabilitation of their gait and balance problems may be least able to participate in this therapeutic modality. This is particularly true for patients with more advanced PD, where the prevalence of cognitive impairment, including overt dementia, is high.

A critical review of the literature by Kwakkel et al. noted that the effects of physical therapy are task- and context-specific and have limited long-term carry-over effects in PD patients' home environments.¹³¹ Kwakkel et al. emphasize the need for long-term treatment programs for PD patients. In this respect, exercise programs that can be maintained in the home situation would be preferred. A large body of empiric evidence suggests that exercise programs may be an effective strategy to delay or reverse functional decline for people with PD.^{132,133} Recent reviews have concluded that exercise is beneficial with regard to physical functioning, health-related quality of life, strength, balance, and gait speed for people with PD, but caution that good-quality research is needed.^{132,133}

A recent meta-analysis of the effects of exercise and motor training on balance and falls in PD conclude a significant but small benefit on balance-related performance measures.¹³⁴ However, there was no beneficial effect on falls in PD. These findings indicate that it remains unclear whether exercise and motor training alone can effectively reduce falls in PD.

Novel physical therapy and exercise interventions may also be useful. Recent controlled clinical trials show gait improvements with treadmill exercise.^{135,136} Alternative treatment modalities, such as tai chi,¹³⁷ have shown modest improvements in gait and balance in PD. Although evidence remains anecdotal, bicycling exercise may be of particular benefit in patients with PD and freezing of gait.³⁷ Further research is needed to demonstrate the efficacy and safety of cycling in more advanced PD. It is interesting to note that changes in executive functions occur after acute bouts of passive cycling in PD, suggesting a striatocortically mediated process.¹³⁸ Combinations of novel pharmacotherapies and novel physical therapy and/or exercise interventions may be useful in delaying or ameliorating gait and balance problems in PD.

Conclusions

Gait disorders and postural instability are common in patients with PD and respond poorly to dopaminergic agents effective for other features of PD. Gait and balance impairments in PD probably result from an intricate interplay of multisystem degenerations and neurotransmitter deficiencies extending beyond loss of dopaminergic nigral neurons. We showed recently that cholinergic denervation, especially of the thalamus, rather than the degree of nigrostriatal dopaminergic denervation, is associated with falls in PD. Our results are consistent with a key role for the PPN in the maintenance of balance in humans and with PPN dysfunction/degeneration as a cause of impaired postural control and gait in PD. Other recent evidence suggests that PPN degeneration is associated with akinesia, including gait ignition failure and gait freezing, in PD. Degeneration of cholinergic corticopetal afferents from the basal forebrain complex may play a role in executive function and attentional deficits contributing to gait and balance dysfunction in PD. Although

STN DBS in PD patients produces sustained benefits for tremor and bradykinesia, axial motor function continues to decline. Low-frequency DBS of the PPN is emerging as a treatment for postural and gait disorders in PD, although the PPN is a technically challenging target. New lines of research are emerging exploring non-dopaminergic pharmacologic treatments of gait and balance problems in PD. Cholinergic therapies may benefit frequently falling PD patients. Contrary to open-label experiences, a recent placebo-controlled study did not find gait improvements with methylphenidate therapy in PD. Non-pharmacologic and non-surgical approaches to treating mobility problems in PD emphasize the increasing importance of exercise and physical fitness in PD. As comorbid white matter disease is associated with impaired axial symptoms and increased stooped posture in PD, it is possible that aggressive management of vascular or inflammatory risk factors, especially when initiated early in the disease course, could reduce the severity of axial motor dysfunction in PD. ■

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