Gait Disturbances in Movement Disorders: A Motor-Cognitive Problem

9

Frederico Pieruccini-Faria, Carolina R.A. Silveira, and Quincy J. Almeida

Abstract

Individuals with movement disorders (MD) have gait deficits including impaired automaticity and instability. Despite specific impairments in motor control networks, recent evidence suggests that cognitive deficits are common in individuals with MD and can magnify their gait problems. In this chapter, we present studies showing that locomotor difficulties among individuals with MD are mainly observed in those with cognitive deficits and during complex walking situations in which demands in cognitive and sensorimotor processing increase. Overall, studies demonstrate that gait disturbances and cognitive impairment coexist in MD and together accelerate the loss of mobility in these individuals.

Keywords

Movement disorders • Elderly • Gait • Cognition • Motor control • Falls • Mobility • Motor planning

F. Pieruccini-Faria (✉)
Schulich School of Medicine & Dentistry, University of Western Ontario, London, ON, Canada

Lawson Health Research Institute, London, ON, Canada
e-mail: fpierucc@uwo.ca

C.R.A. Silveira
Lawson Health Research Institute, London, ON, Canada
e-mail: Carolina.Silveira@sjhc.london.on.ca

Q.J. Almeida
Movement Disorders Research & Rehabilitation Centre, Wilfrid Laurier University, Waterloo, ON, Canada
e-mail: qalmeida@wlu.ca

F.A. Barbieri, R. Vitório (eds.), *Locomotion and Posture in Older Adults*,
DOI 10.1007/978-3-319-48980-3_9

9.1 The Relationship Between Gait and Cognition in Movement Disorders

Movement disorders (MD) result from dysfunction of subcortical areas, such as the basal ganglia (BG), as well as cortical areas within the brain. Neurodegenerative processes can compromise the automaticity of well-learned movements such as gait, where increased conscious control (and hence cognitive systems) may be relied upon to perform movements. The relationship between cognitive control and movement performance is often observed when individuals with MD have their attention divided by secondary tasks while walking. As a result of divided attention, walking performance in those with MD can be profoundly impaired compared to healthy individuals. In addition, individuals with MD who have cognitive decline appear to be more susceptible to gait impairments due to their inability to use cognitive resources required to plan and control movements. During complex walking situations (e.g., cluttered environment), the increased cognitive and sensory processing required to plan gait modifications may have a strong impact on the walking performance of individuals with MD. Thus, abnormal gait control while walking in complex situations may result from an overloaded or inefficient cognitive system in MD. In this chapter we review different aspects of gait control associated with cognition in different MD, and in different walking contexts.

9.2 Parkinson's Disease

Parkinson's disease (PD) is the most prevalent MD. The incidence of PD is nearly 1 % in the population and 2 % in people over 60 years of age [1–3]. PD is characterized by an accelerated degenerative process of dopaminergic neurons in the *substantia nigra pars compacta* of the BG. Decreased striatal dopamine affects the functioning of all structures which comprise the BG and consequently impairs the control of well-learned movements, such as gait [4]. In PD, gait impairments are characterized by reductions in step length and velocity, and also increased step-to-step variations in time and distance (i.e., gait variability) [5–7]. These gait impairments may be even greater when individuals with PD have their attention divided by secondary tasks during walking [8–14].

Specifically, velocity and gait variability are the most sensitive gait parameters to dual-task interference in PD. Although the diversity of dual tasks found in the literature makes comparison between studies difficult, gait of individuals with PD is more influenced during the performance of more complex secondary tasks. For example, gait impairments are worse when individuals with PD walk while subtracting by 7's compared to subtracting by 3's [9], or when they are asked to carry a tray with glasses compared to a tray without glasses [12], or when those glasses are full compared to empty glasses [13]. Among gait parameters affected by dual-task interference, gait variability has been shown to be a sensitive measure when dual-task complexity has been increased and may represent the processing

overload created by these tasks. It is important to note, however, that the relationship between gait and cognition may vary depending on the cognitive status and specific motor symptoms (e.g., freezing of gait) of individuals with PD. These aspects will be further discussed in the sections below.

9.3 The Influence of Cognitive Decline on Gait of Individuals with Parkinson's Disease

Previous research has shown that approximately 26 % of non-demented individuals with PD may exhibit a form of mild cognitive impairment, with main deficits being found in the executive/attentional, memory, and visuospatial domains [15]. In addition, a longitudinal study demonstrated that by the 10-year mark from diagnosis, approximately 46 % of individuals with PD had been clinically diagnosed with dementia [16]. These findings support the notion that motor and cognitive dysfunction may coexist in PD even in the early stages of disease and increase in severity in the later stages of disease progression. Interestingly, it has been shown that individuals with predominant postural instability and gait dysfunction (PIGD) have faster rate of decline in both cognitive and motor function than those with predominant tremor symptoms [17]. This selective association between cognitive impairment and PIGD symptoms suggests that the progression of cognitive and mobility deficits may share similar underlying mechanisms in PD.

Early studies investigated the influence of specific cognitive functions on gait in PD. Deficits in attention and executive functions were associated with impaired gait in individuals with PD, especially during dual-task walking [9, 18]. In contrast to research in older adults with mild cognitive impairment [19], performance on memory tests were not associated with changes in gait in PD. These findings support the notion that specific cognitive functions (i.e., attention and executive functions) are associated with gait disturbances in PD.

Executive functions compose a cognitive domain required for our ability to inhibit irrelevant information, to update or maintain relevant information in memory, to plan complex actions, and to general attentional control [20]. These functions allow the adaptation of responses to novel situations and play an important role when managing situations in which automatic responses are not sufficient for optimal performance. Thus, deficits in executive functions may interfere with the ability of individuals with PD to adapt gait when dealing with complex environments (e.g., cluttered spaces) or performing multiple tasks.

With respect to gait, poor performance on tests assessing executive functions has been associated specifically with reduction in speed and increased step-to-step variability when individuals with PD perform dual-task walking [9]. According to Yogev and colleagues [9], individuals with PD may use cognitive resources to alleviate difficulties to maintain the consistency of walking rhythm. Hence, if individuals with PD present impaired cognitive function (e.g., executive functions), it is reasonable to predict that they may be less able to maintain a stable walking

rhythm. Since unstable walking rhythm has been associated with increased risk of falls in older adults [21], this may imply greater risk of falls among individuals with PD with cognitive decline compared to those with normal cognitive status.

In addition to the findings described above, a relationship between cognition and a very debilitating symptom known as freezing of gait has also been identified in individuals with PD. The role of cognitive deficits in the freezing phenomenon is described in greater detail in the following section.

9.4 The Relationship Between Cognition and Freezing of Gait in Parkinson's Disease

Freezing of gait (FOG) is a phenomenon that affects nearly 50 % of all individuals with PD, being more prevalent during later stages of the disease [22, 23]. FOG can be defined as a sudden interruption of walking progression which makes individuals feel as if their feet are "glued" to the ground, irrespective of their intention to move forward [24]. Several perspectives have attempted to explain this phenomenon in PD including reduced cognitive processing capacity [25, 26], impaired bilateral coordination [27], impaired sensory-perceptual processing [28–30], motor planning deficits [31–33], asymmetric degeneration of subcortical areas (e.g., BG and pedunculopontine nucleus) [34, 35], and altered emotional processing [36, 37]. Individuals with PD who experience FOG present typical gait disturbances such as increased step-to-step variability [38], shortened step length [31], and asymmetrical steps [27]. Importantly, when individuals with PD who experience FOG have to adapt their walking pattern to change direction (turning), deal with obstacles (doorways) or situations that impose greater cognitive demand (dual-task), these gait abnormalities are exacerbated and freezing episodes are more likely to occur [28, 39–41]. Although the underlying mechanisms of FOG are unknown, research has consistently demonstrated an association between FOG and deficits in executive functions. More specifically, FOG has been associated with difficulties in attentional set-shifting [42] and conflict resolution [26]. In addition, the notion that deficits in cognitive networks could contribute to FOG has been supported by neuroimaging research.

Brain imaging studies in virtual reality environments have exposed patients to conditions which elicit FOG episodes, for example, locomotion through narrow spaces in addition to attention demanding dual-tasks [25]. It was found that an overload in attentional networks during these FOG provoking situations increased the inhibitory output from BG to motor centers in the brainstem in individuals with PD, such as the mesencephalic locomotor area and the pedunculopontine nucleus, which are areas responsible for the initiation and cessation of locomotion in humans [43]. However, this abnormal inhibitory output from BG to locomotor centers in the brainstem was stronger among freezers compared to non-freezers. Results from imaging studies may help to explain why complex walking situations which demand increased cognitive control and sensorimotor integration for stepping adaptations elicit FOG episodes. Thus, understanding how complex walking

situations influence gait in PD help us better understand the underlying mechanisms of severe gait impairments such as FOG, as well as clarifying the relationship between cognition and gait in PD.

9.5 Cognition and Complex Gait Navigation in Parkinson's Disease

Walking in real-world situations often requires step adaptations to change directions and to avoid contact with obstacles. These gait modifications impose increased demand on cognitive and sensory processing. Reduced striatal dopaminergic activity may limit processing resources magnifying motor disturbances when individuals with PD face complex locomotor situations including obstacle avoidance [44, 45]. Consequently, during these demanding locomotor situations, gait impairments can be exacerbated (slowness, FOG, trips, and the loss of balance) in individuals with PD. Recent studies have shown that approaching obstacles, a situation that demands planning, can overload cognitive processing and exacerbates gait impairments (e.g., increased step-to-step variability) in individuals with PD [28, 29, 32, 33]. Additionally, executive function decline is associated with erroneous stepping planning during obstacle crossing [32]. Planning refers to the preparation/conceptualization of movements. Importantly, gait disturbances associated with increased motor planning complexity were found to be exacerbated in freezers especially when they performed a secondary cognitive task during obstacle approaching and crossing. Another recent study also showed that decreased visual feedback of self-motion overloaded processing resources of individuals with PD increasing the effects of dual-task on gait control [46]. This study showed that individuals with PD tripped more on a visible obstacle when they needed to rely on their impaired proprioceptive system (walking in the dark) and perform a cognitive dual-task compared to healthy individuals. Gait instability (step-to-step variability) during obstacle approach in individuals with PD was higher than in healthy controls only during the condition of reduced visual feedback of self-motion (dark). This result suggests that processing resources to plan gait adaptations may become overloaded because individuals with PD would be using cognition (e.g., attention) to supervise faulty sensorimotor integration to prevent motor and planning errors. Difficulties to automatically process sensory information could force patients to control movements using a more conscious control [47] which can be observed in increased gait variability and dual-task cost while approaching the obstacle. In support of this interpretation, previous research has shown that when individuals with PD are trained to focus attention on sensorimotor information (moving with eyes closed), a significant improvement in gait was found during a complex walking task involving postural threat [48]. Hence, attention might be used by individuals with PD to compensate for sensory-perceptual impairments. Thus, it is important to consider the relationship between impaired sensorimotor integration and the reliance on high-order cognitive processing (e.g., executive functions) in individuals with PD.

Another complex locomotor situation which results in gait difficulties among individuals with PD is turning. Difficulties to turn around the body axis are one of the most common complaints among people with PD, and it may cause extreme gait slowness, loss of balance, and FOG. It has been demonstrated that individuals with FOG had greater gait variability than non-freezers when performing sharper turns (180°) compared wider turns (90°) [40]. In this study, the gait abnormalities found in freezers were suggested to be associated with increased cognitive demand to control steps during sharper turns. Another study demonstrated that freezers had increased brain activity in prefrontal areas compared to healthy age-matched controls only prior to a planned turn compared to an unplanned turn. This study suggested that turning deficits in individuals with FOG may be related to an overload in cognitive processing during movement planning [49]. Therefore, in individuals with PD and especially those with FOG, processing capacity may be overloaded when planning complex gait adjustments. This overload in processing capacity may be attributed to both reduced striatal dopaminergic activity (i.e., reduced BG processing capacity) and impaired cognitive function (executive functions) which may magnify sensorimotor deficits (e.g., slowness, instability) while performing drastic gait and postural adjustments during locomotion.

9.6 Falls and Cognition in Parkinson's Disease

Falls are one of the main causes of hospitalization, decreased mobility, and poor quality of life among individuals with PD [50, 51]. Although the underlying mechanism of falls in PD may be multifactorial, a relationship between cognition and increased risk of falls has been previously demonstrated [52, 53]. Interestingly, a study showed that individuals with PD and elderly fallers have common deficits in executive functions that distinguish them from elderly non-fallers [54]. As previously described, impairments in executive functions may contribute to an inability to adapt gait especially during complex walking situations and may expose individuals with PD to greater risk of falls. In addition to cognitive decline, individuals with PD who have a high incidence of falls also present greater step-to-step variability compared to those with low incidence of falls [55]. Therefore, deficits in executive functions and gait stability (e.g., increased step-to-step variability) are hallmarks of PD fallers [56].

Although the degeneration of the dopaminergic system plays a critical role on gait impairments in PD, recent research has shown that individuals with PD who frequently fall had reduced thalamic cholinergic activity compared to PD non-fallers [57]. Thalamic cholinergic activity is modulated by a brainstem structure called pedunculopontine nucleus, which plays an important role on gait and balance control [43]. Therefore, it might be that impaired cholinergic activity in the pedunculopontine nucleus may also contribute to gait impairments and increased risk of falls among those with PD. This is in line with previous research showing that gait parameters important to gait stability, such as stride time and double support variabilities, are not responsive to dopaminergic medication [58, 59].

In support of the assumption that cholinergic and dopaminergic systems have different but not independent roles in gait control, a recent review [60] identified that falls' incidence in PD may increase if cognitive networks modulated by the cholinergic system are not able to supervise errors in sensorimotor integration, which is primarily modulated by the dopaminergic system. In other words, falls may reflect an inability of individuals with PD to use attentional resources to supervise sensorimotor feedback.

9.7 Huntington's Disease

Huntington's disease (HD) is an MD caused by progressive degeneration of the striatum (i.e., caudate nucleus and putamen). The putamen and the caudate nucleus are important neural structures for sensorimotor [61] and cognitive [62] processing, respectively. Impairments in these subcortical structures affect the ability of human beings to suppress motor outputs and behaviors. In addition to subcortical deficits, cortical areas are also affected by HD. The combination of subcortical and cortical impairments can cause significant cognitive and behavioral deficits, in addition to severe movement disturbances. Individuals with HD exhibit hyperkinetic and involuntary movements (chorea) in later stages of the disease. The pathological mechanism underlying movement impairments in HD also have an important influence on gait.

Gait characteristics in HD include wide base of support, lateral swaying, spontaneous knee flexion, variable cadence, and parkinsonian features [63]. Although individuals with HD present some parkinsonian gait characteristics (e.g., variability and slowness), the abnormal gait pattern observed in HD is not associated with deficits to regulate the amplitude of steps, such as in PD. Individuals with HD exhibit difficulties to maintain a consistent timing or pace between steps. This increased gait variability of step timing in individuals with HD may be indicative of poor stability and reduced gait automaticity.

Due to extensive subcortical and cortical damage, it is challenging to establish causality between striatum damage and cognitive deficits in individuals with HD. Previous research has shown that cognitive deficits found in individuals with HD differ from those observed in Alzheimer's disease, which is a neurological disease known to affect primarily cortical areas [64]. For example, Brandt and colleagues [64] showed that while individuals with Alzheimer's disease showed deficits in memory (word recall) and orientation (date) sections of the Mini-Mental State Exam, those with HD were more impaired in executive functions (serial subtractions). More specifically, Lawrence et al. [65] found that individuals with HD present a specific pattern of deficits in executive functions such as planning and set-shifting. The pattern of deficits in executive functions observed in individuals with HD differed from that found in individuals with PD (subcortical), but it was similar to individuals with frontal lobe lesions (cortical). Thus, even though cognitive deficits in HD may be primarily caused by striatal dysfunction, cortical dysfunction as a result of widespread lesions in the brain may also contribute to

these cognitive deficits. If this is the case, it might be that the ability of individuals with HD to compensate for gait deficits through the cognitive system may be limited especially when cognitive resources are challenged while walking.

A study revealed that a cognitive dual-task (counting backwards in steps of 2 or 3) affected gait in individuals with HD more than a motor task (carrying a tray with glasses) [66]. The cognitive dual-task provoked slower gait speed, decreased cadence, and shorter stride length (all compared to free gait condition), whereas the same dual-task interference was not observed in healthy control individuals. This study showed that individuals with HD depend on attentional resources to control their steps while walking. Given that attentional control over steps should improve gait impairments in HD, directing attention to a metronome while walking should improve the timing control of steps. However, a study demonstrated that individuals with HD did not improve gait under these conditions [67]. According to this study, the lack of gait improvement while external cues were provided to individuals with HD was due to attentional deficits. Thus, attentional deficits may affect the ability of these individuals to synchronize their steps with external cues (e.g., auditory signals produced by a metronome).

Taken together, the severity of cognitive deficits in HD may influence gait and prevent these individuals from utilizing cognitive resources to compensate for gait deficits.

9.8 Progressive Supranuclear Palsy

Progressive supranuclear palsy (PSP) is a MD caused by abnormal accumulation of tau protein-positive filamentous known as neurofibrillary tangles in the glia and neurons [68–70]. This abnormal neuronal formation is found to be more concentrated in areas of the brainstem responsible for gaze and gait control. Since motor symptoms in PSP and PD are very similar, the absence of downgaze is the most important criterion to differentiate PSP from PD. Movement impairments observed in individuals with PSP consist of the absence of downgaze movements, staring look due to eyelid retraction, trunk rigidity, bradykinesia, hypometric movements, and FOG. Deficits in gait and postural control are thought to be related to an increased number of falls among those with PSP [71]. In addition, when compared to PD, individuals with PSP may exhibit shorter step length and increased cadence when asked to walk fast [72]. These walking patterns suggest that gait deficits in PSP may result from difficulties setting an appropriate step length to modulate gait speed at the cortical level. Additionally, cortical areas in the brain that underlie executive functions are also affected by PSP, posing a complex scenario which involves the deterioration of both gait and cognitive functions.

Cognitive deficits in individuals with PSP are mainly characterized by slowness of thinking and impaired executive functions, although memory and visuospatial processing (e.g., difficulty to identify shapes and objects accurately) may also be impaired [73, 74]. Individuals with PSP also have impaired performance on cognitive tests sensitive to frontal lobe dysfunction. More specifically, Robbins and

colleagues [75] showed that individuals with PSP performed worse than age-matched controls on short-term memory, spatial working memory, planning, and set-shifting tests. Although the pattern of deficits found in individuals with PSP resemble those observed in individuals with PD, deficits were found to be more severe in individuals with PSP when compared to those with PD [75]. Since PSP is a rare MD, a small number of studies investigating the relationship between gait and cognition exist in the literature.

Previous research has shown that individuals with PSP who fall more frequently were more affected by a cognitive-motor task (counting backwards) than those with a low incidence of falls [76]. This study concluded that gait impairments and falls may result from a combination of deficits in functioning of the brainstem and prefrontal cortical regions in individuals with PSP. Furthermore, a recent study showed that individuals with PSP with high incidence of falls demonstrated greater impairment in executive and visuospatial functions compared to those with a lower incidence of falls [71]. These findings suggest that impairments in gait and balance in individuals with PSP may be strongly influenced by cognition and may affect the ability of individuals with PSP to navigate safely.

Although the relationship between cognition, gait impairments, and falls in PSP seems obvious, the contribution of downgaze impairments to falls incidence remains unclear and might have been a confounder in previous investigations. Downgaze deficits could have a negative effect on planning of foot elevation when individuals with PSP walk on uneven terrains. Furthermore, difficulties to shift gaze to the lower visual field while walking could cause erroneous step adjustments consequently contributing to trips, loss of balance, and falls. Therefore, studies should investigate not only falls occurrence among individuals with PSP but also how these falls happened. For example, if the majority of falls happened after trips on uneven terrain, it is possible that downgaze impairments have important contribution to falls compared to situations where patients were distracted while walking on even terrains. However, this hypothesis still needs to be confirmed in future studies.

9.9 Final Considerations

In conclusion, individuals with PD, HD, or PSP may present similar gait deficits that could be caused by decreased movement automaticity. Consequently, individuals with these MD may rely on the cognitive system to compensate for gait deficits. The coexistence of both motor and cognitive deficits in most MD is important to note. Furthermore, the severity of cognitive deficits, such as attention, may limit the ability of those with MD to adapt gait in complex situations and utilize sensory information to improve gait. Therefore, rehabilitation programs should combine motor and cognitive therapies to improve gait in MD.

Acknowledgment This work was supported in part by the National Council for Scientific and Technological Development, Brazil (CNPq), as scholarship to FPF and CRAS.

References

1. Alves G, Forsaa EB, Pedersen KF, Dreetz Gjerstad M, Larsen JP. Epidemiology of Parkinson's disease. J Neurol. 2008;255 Suppl 5:18–32.
2. Rajput AH, Birdi S. Epidemiology of Parkinson's disease. Parkinsonism Relat Disord. 1997;3 (4):175–86.
3. de Lau LM, Breteler MM. Epidemiology of Parkinson's disease. Lancet Neurol. 2006;5 (6):525–35.
4. Poldrack RA, Sabb FW, Foerde K, Tom SM, Asarnow RF, Bookheimer SY, et al. The neural correlates of motor skill automaticity. J Neurosci. 2005;25(22):5356–64.
5. Morris ME, Iansek R, Matyas TA, Summers JJ. The pathogenesis of gait hypokinesia in Parkinson's disease. Brain. 1994;117(Pt 5):1169–81.
6. Morris ME, Iansek R, Matyas TA, Summers JJ. Stride length regulation in Parkinson's disease. Normalization strategies and underlying mechanisms. Brain. 1996;119(Pt 2):551–68.
7. Rochester L, Baker K, Nieuwboer A, Burn D. Targeting dopa-sensitive and dopa-resistant gait dysfunction in Parkinson's disease: selective responses to internal and external cues. Mov Disord. 2011;26(3):430–5.
8. Hausdorff JM, Balash J, Giladi N. Effects of cognitive challenge on gait variability in patients with Parkinson's disease. J Geriatr Psychiatry Neurol. 2003;16(1):53–8.
9. Yogev G, Giladi N, Peretz C, Springer S, Simon ES, Hausdorff JM. Dual tasking, gait rhythmicity, and Parkinson's disease: which aspects of gait are attention demanding? Eur J Neurosci. 2005;22(5):1248–56.
10. Baker K, Rochester L, Nieuwboer A. The immediate effect of attentional, auditory, and a combined cue strategy on gait during single and dual tasks in Parkinson's disease. Arch Phys Med Rehabil. 2007;88(12):1593–600.
11. Rochester L, Hetherington V, Jones D, Nieuwboer A, Willems AM, Kwakkel G, et al. Attending to the task: interference effects of functional tasks on walking in Parkinson's disease and the roles of cognition, depression, fatigue, and balance. Arch Phys Med Rehabil. 2004;85 (10):1578–85.
12. Rochester L, Hetherington V, Jones D, Nieuwboer A, Willems AM, Kwakkel G, et al. The effect of external rhythmic cues (auditory and visual) on walking during a functional task in homes of people with Parkinson's disease. Arch Phys Med Rehabil. 2005;86(5):999–1006.
13. Bond JM, Morris M. Goal-directed secondary motor tasks: their effects on gait in subjects with Parkinson disease. Arch Phys Med Rehabil. 2000;81(1):110–6.
14. O'Shea S, Morris ME, Iansek R. Dual task interference during gait in people with Parkinson disease: effects of motor versus cognitive secondary tasks. Phys Ther. 2002;82(9):888–97.
15. Aarsland D, Bronnick K, Williams-Gray C, Weintraub D, Marder K, Kulisevsky J, et al. Mild cognitive impairment in Parkinson disease: a multicenter pooled analysis. Neurology. 2010;75 (12):1062–9.
16. Williams-Gray CH, Mason SL, Evans JR, Foltynie T, Brayne C, Robbins TW, et al. The CamPaIGN study of Parkinson's disease: 10-year outlook in an incident population-based cohort. J Neurol Neurosurg Psychiatry. 2013;84(11):1258–64.
17. Burn DJ, Rowan EN, Allan LM, Molloy S, O'Brien JT, McKeith IG. Motor subtype and cognitive decline in Parkinson's disease, Parkinson's disease with dementia, and dementia with Lewy bodies. J Neurol Neurosurg Psychiatry. 2006;77(5):585–9.
18. Lord S, Rochester L, Hetherington V, Allcock LM, Burn D. Executive dysfunction and attention contribute to gait interference in 'off' state Parkinson's Disease. Gait Posture. 2010;31(2):169–74.
19. Montero-Odasso M, Oteng-Amoako A, Speechley M, Gopaul K, Beauchet O, Annweiler C, et al. The motor signature of mild cognitive impairment: results from the gait and brain study. J Gerontol A Biol Sci Med Sci. 2014;69(11):1415–21.

20. Miyake A, Friedman NP, Emerson MJ, Witzki AH, Howerter A, Wager TD. The unity and diversity of executive functions and their contributions to complex "Frontal Lobe" tasks: a latent variable analysis. Cogn Psychol. 2000;41(1):49–100.
21. Springer S, Giladi N, Peretz C, Yogev G, Simon ES, Hausdorff JM. Dual-tasking effects on gait variability: the role of aging, falls, and executive function. Mov Disord. 2006;21 (7):950–7.
22. Giladi N, Kao R, Fahn S. Freezing phenomenon in patients with parkinsonian syndromes. Mov Disord. 1997;12(3):302–5.
23. Giladi N. Freezing of gait. Clin overview Adv Neurol. 2001;87:191–7.
24. Nutt JG, Bloem BR, Giladi N, Hallett M, Horak FB, Nieuwboer A. Freezing of gait: moving forward on a mysterious clinical phenomenon. Lancet Neurol. 2011;10(8):734–44.
25. Shine JM, Matar E, Ward PB, Bolitho SJ, Gilat M, Pearson M, et al. Exploring the cortical and subcortical functional magnetic resonance imaging changes associated with freezing in Parkinson's disease. Brain. 2013;136(Pt 4):1204–15.
26. Vandenbossche J, Deroost N, Soetens E, Spildooren J, Vercruysse S, Nieuwboer A, et al. Freezing of gait in Parkinson disease is associated with impaired conflict resolution. Neurorehabil Neural Repair. 2011;25(8):765–73.
27. Plotnik M, Giladi N, Balash Y, Peretz C, Hausdorff JM. Is freezing of gait in Parkinson's disease related to asymmetric motor function? Ann Neurol. 2005;57(5):656–63.
28. Almeida QJ, Lebold CA. Freezing of gait in Parkinson's disease: a perceptual cause for a motor impairment? J Neurol Neurosurg Psychiatry. 2010;81(5):513–8.
29. Silveira CRA, Ehgoetz Martens KA, Pieruccini-Faria F, Bell-Boucher D, Roy EA, Almeida QJ. Disentangling perceptual judgment and online feedback deficits in Parkinson's freezing of gait. J Neurol. 2015;262(7):1629–36.
30. Ehgoetz Martens KA, Pieruccini-Faria F, Almeida QJ. Could sensory mechanisms be a core factor that underlies freezing of gait in Parkinson's disease? PLoS One. 2013;8(5), e62602.
31. Chee R, Murphy A, Danoudis M, Georgiou-Karistianis N, Iansek R. Gait freezing in Parkinson's disease and the stride length sequence effect interaction. Brain. 2009; 132:2151–60.
32. Pieruccini-Faria F, Jones JA, Almeida QJ. Motor planning in Parkinson's disease patients experiencing freezing of gait: the influence of cognitive load when approaching obstacles. Brain Cogn. 2014;87:76–85. Epub 2014/04/15.
33. Knobl P, Kielstra L, Almeida Q. The relationship between motor planning and freezing of gait in Parkinson's disease. J Neurol Neurosurg Psychiatry. 2012;83(1):98–101.
34. Pieruccini-Faria F, Ehgoetz Martens KA, Silveira CRA, Jones JA, Almeida QJ. Side of basal ganglia degeneration influences freezing of gait in Parkinson's disease. Behav Neurosci. 2015;29(2):214–8.
35. Fling BW, Cohen RG, Mancini M, Nutt JG, Fair DA, Horak FB. Asymmetric pedunculopontine network connectivity in parkinsonian patients with freezing of gait. Brain. 2013;136(Pt 8):2405–18.
36. Lieberman A. Are freezing of gait (FOG) and panic related? J Neurol Sci. 2006;248 (1-2):219–22.
37. Ehgoetz Martens KA, Ellard CG, Almeida QJ. Does anxiety cause freezing of gait in Parkinson's disease? PLoS One. 2014;9(9), e106561.
38. Hausdorff JM, Schaafsma JD, Balash Y, Bartels AL, Gurevich T, Giladi N. Impaired regulation of stride variability in Parkinson's disease subjects with freezing of gait. Exp Brain Res. 2003;149(2):187–94.
39. Nieuwboer A, Dom R, De Weerdt W, Desloovere K, Janssens L, Stijn V. Electromyographic profiles of gait prior to onset of freezing episodes in patients with Parkinson's disease. Brain. 2004;127(Pt 7):1650–60.
40. Bhatt H, Pieruccini-Faria F, Almeida QJ. Dynamics of turning sharpness influences freezing of gait in Parkinson's disease. Parkinsonism Relat Disord. 2013;19(2):181–5.

41. Spildooren J, Vercruysse S, Desloovere K, Vandenberghe W, Kerckhofs E, Nieuwboer A. Freezing of gait in Parkinson's disease: the impact of dual-tasking and turning. Mov Disord. 2010;25(15):2563–70.
42. Naismith SL, Shine JM, Lewis SJ. The specific contributions of set-shifting to freezing of gait in Parkinson's disease. Mov Disord. 2010;25(8):1000–4.
43. Pahapill PA, Lozano AM. The pedunculopontine nucleus and Parkinson's disease. Brain. 2000;123(Pt 9):1767–83.
44. Pieruccini-Faria F, Jones JA, Almeida QJ. Insight into dopamine-dependent planning deficits in Parkinson's disease: a sharing of cognitive & sensory resources. Neuroscience. 2016;318:219–29.
45. Pieruccini-Faria F, Vitorio R, Almeida QJ, Silveira CRA, Caetano MJ, Stella F, et al. Evaluating the acute contributions of dopaminergic replacement to gait with obstacles in Parkinson's disease. J Mot Behav. 2013;45(5):369–80.
46. Pieruccini-Faria F, Ehgoetz Martens KA, Silveira CRA, Jones JA, Almeida QJ. Interactions between cognitive and sensory load while planning and controlling complex gait adaptations in Parkinson's disease. BMC Neurol. 2014;14(1):250.
47. Redgrave P, Rodriguez M, Smith Y, Rodriguez-Oroz MC, Lehericy S, Bergman H, et al. Goal-directed and habitual control in the basal ganglia: implications for Parkinson's disease. Nat Rev Neurosci. 2010;11(11):760–72.
48. Sage MD, Almeida QJ. Symptom and gait changes after sensory attention focused exercise vs aerobic training in Parkinson's disease. Mov Disord. 2009;24(8):1132–8.
49. Maidan I, Bernad-Elazari H, Gazit E, Giladi N, Hausdorff JM, Mirelman A. Changes in oxygenated hemoglobin link freezing of gait to frontal activation in patients with Parkinson disease: an fNIRS study of transient motor-cognitive failures. J Neurol. 2015.
50. Gazibara T, Pekmezovic T, Tepavcevic DK, Tomic A, Stankovic I, Kostic VS, et al. Circumstances of falls and fall-related injuries among patients with Parkinson's disease in an outpatient setting. Geriatr Nurs. 2014;35(5):364–9.
51. Grimbergen YA, Munneke M, Bloem BR. Falls in Parkinson's disease. Curr Opin Neurol. 2004;17(4):405–15.
52. Amboni M, Barone P, Hausdorff JM. Cognitive contributions to gait and falls: evidence and implications. Mov Disord. 2013;28(11):1520–33.
53. Camicioli R, Majumdar SR. Relationship between mild cognitive impairment and falls in older people with and without Parkinson's disease: 1-Year Prospective Cohort Study. Gait Posture. 2010;32(1):87–91.
54. Hausdorff JM, Doniger GM, Springer S, Yogev G, Simon ES, Giladi N. A common cognitive profile in elderly fallers and in patients with Parkinson's disease: the prominence of impaired executive function and attention. Exp Aging Res. 2006;32(4):411–29.
55. Yogev G, Plotnik M, Peretz C, Giladi N, Hausdorff JM. Gait asymmetry in patients with Parkinson's disease and elderly fallers: when does the bilateral coordination of gait require attention? Exp Brain Res. 2007;177(3):336–46.
56. Amboni M, Barone P, Iuppariello L, Lista I, Tranfaglia R, Fasano A, et al. Gait patterns in Parkinsonian patients with or without mild cognitive impairment. Mov Disord. 2012;27 (12):1536–43.
57. Bohnen NI, Muller ML, Koeppe RA, Studenski SA, Kilbourn MA, Frey KA, et al. History of falls in Parkinson disease is associated with reduced cholinergic activity. Neurology. 2009;73 (20):1670–6.
58. Blin O, Ferrandez AM, Pailhous J, Serratrice G. Dopa-sensitive and dopa-resistant gait parameters in Parkinson's disease. J Neurol Sci. 1991;103(1):51–4.
59. Lord S, Baker K, Nieuwboer A, Burn D, Rochester L. Gait variability in Parkinson's disease: an indicator of non-dopaminergic contributors to gait dysfunction? J Neurol. 2011;258 (4):566–72.
60. Sarter M, Albin RL, Kucinski A, Lustig C. Where attention falls: increased risk of falls from the converging impact of cortical cholinergic and midbrain dopamine loss on striatal function. Exp Neurol. 2014;257:120–9.

61. Goble DJ, Coxon JP, Van Impe A, Geurts M, Van Hecke W, Sunaert S, et al. The neural basis of central proprioceptive processing in older versus younger adults: an important sensory role for right putamen. Hum Brain Mapp. 2012;33(4):895–908.
62. Lewis SJ, Dove A, Robbins TW, Barker RA, Owen AM. Striatal contributions to working memory: a functional magnetic resonance imaging study in humans. Eur J Neurosci. 2004;19 (3):755–60. Epub 2004/02/27.
63. Koller WC, Trimble J. The gait abnormality of Huntington's disease. Neurology. 1985;35 (10):1450–4.
64. Brandt J, Folstein SE, Folstein MF. Differential cognitive impairment in Alzheimer's disease and Huntington's disease. Ann Neurol. 1988;23(6):555–61.
65. Lawrence AD, Sahakian BJ, Robbins TW. Cognitive functions and corticostriatal circuits: insights from Huntington's disease. Trends Cogn Sci. 1998;2(10):379–88.
66. Delval A, Krystkowiak P, Delliaux M, Dujardin K, Blatt JL, Destee A, et al. Role of attentional resources on gait performance in Huntington's disease. Mov Disord. 2008;23(5):684–9.
67. Thaut MH, Miltner R, Lange HW, Hurt CP, Hoemberg V. Velocity modulation and rhythmic synchronization of gait in Huntington's disease. Mov Disord. 1999;14(5):808–19.
68. Esterhammer R, Schocke M, Seppi K. Basal ganglia cellular pathology in multiple system atrophy, progressive supranuclear palsy and Parkinson disease. Can quantitative magnetic resonance spectroscopic imaging make the difference? Eur J Neurol. 2010;17(9):1111–2.
69. Piao YS, Hayashi S, Wakabayashi K, Kakita A, Aida I, Yamada M, et al. Cerebellar cortical tau pathology in progressive supranuclear palsy and corticobasal degeneration. Acta Neuropathol. 2002;103(5):469–74.
70. Ghatak NR, Nochlin D, Hadfield MG. Neurofibrillary pathology in progressive supranuclear palsy. Acta Neuropathol. 1980;52(1):73–6.
71. Kim SL, Lee MJ, Lee MS. Cognitive dysfunction associated with falls in progressive supranuclear palsy. Gait Posture. 2014;40(4):605–9.
72. Egerton T, Williams DR, Iansek R. Comparison of gait in progressive supranuclear palsy Parkinson's disease and healthy older adults. BMC Neurol. 2012;12:116.
73. Burrell JR, Hodges JR, Rowe JB. Cognition in corticobasal syndrome and progressive supranuclear palsy: a review. Mov Disord. 2014;29(5):684–93.
74. Grafman J, Litvan I, Stark M. Neuropsychological features of progressive supranuclear palsy. Brain Cogn. 1995;28(3):311–20.
75. Robbins TW, James M, Owen AM, Lange KW, Lees AJ, Leigh PN, et al. Cognitive deficits in progressive supranuclear palsy, Parkinson's disease, and multiple system atrophy in tests sensitive to frontal lobe dysfunction. J Neurol Neurosurg Psychiatry. 1994;57(1):79–88.
76. Lindemann U, Nicolai S, Beische D, Becker C, Srulijes K, Dietzel E, et al. Clinical and dual-tasking aspects in frequent and infrequent fallers with progressive supranuclear palsy. Mov Disord. 2010;25(8):1040–6.