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Cognition and Gait Disturbances in Parkinson's Disease

Samo Ribarič

*University of Ljubljana, Faculty of Medicine, Institute of Pathophysiology & University Clinical Centre Ljubljana, Department of Neurology, Laboratory for Movement Disorders
Slovenia*

1. Introduction

Gait is a learned, complex and almost automatic task with limited involvement of cognitive control in healthy individuals until the onset of old age (Holtzer et al., 2006). These automatic and rhythmic motor activity patterns are generated by spinal networks of motor neurons and interneurons, also called the "central pattern generators" (Dietz, 2003). The activity of these spinal networks is modulated and initiated by the basal ganglia and the brainstem nuclei (Pahapill & Lozano, 2000). The basal ganglia and their two-way connections with cortical regions and cerebellum (Fig. 1) play a central role in both movement initiation and cognitive aspects, such as executive functioning (Yogev-Seligman et al., 2008). Pathological oscillatory activity in these networks, for example in Parkinson's disease (PD), is associated with gait disorders (Bartolić et al., 2010; Timmermann & Fink 2009).

Recent studies have established the importance of cognitive control on gait in older adults; gait slowing is more prevalent in people with cognitive impairment and slow gait in healthy older adults is associated with a higher risk of cognitive impairment, including dementia (Holtzer et al., 2006). Also a slow gait velocity has been associated with an increased risk of falls, hospitalization and mortality (Verghese et al., 2010). Therefore, with the progression of age related changes or neurodegenerative changes in the brain (e.g. in PD), previously automatic actions like gait become a "controlled" processes placing additional demands on the available shrinking cognitive resources. Under these circumstances, the performance of the cognitive task may only be preserved by diverting cognitive resources from the motor task.

In adults, the contribution of cognitive control to gait is evaluated by measuring the effect that a cognitive load (e.g. simultaneous talking or counting while walking) has on gait – i.e. the dual task (DT) paradigm (Srygley et al., 2009). The effect of DT on gait velocity (DT decrement) is related to impairments in executive function and attention. The extent of DT decrement varies from non-existent to detectable in healthy older adults, but can be significant in patients with PD (PPD). Therefore, the presence and extent of DT decrement in PPD depends on the patient's cognitive reserve and the complexity of gait pattern. Postural instability and gait disorders in PD are associated with a faster rate of cognitive decline and should be considered as risk factors for developing Parkinson's disease with dementia

(Korczyn, 2001). The assessment of DT decrement is important for detecting the early stages of cognitive impairment in PPD, when isolation of specific cognitive factors which impact mobility is still possible, since progression of the disease leads to global cognitive impairment (Holtzer et al., 2006). The interference of the attention-demanding task (*e.g.* simultaneous talking or counting while walking) with gait suggests that both tasks rely on the same functional subsystem (*i.e.* executive function and attention).

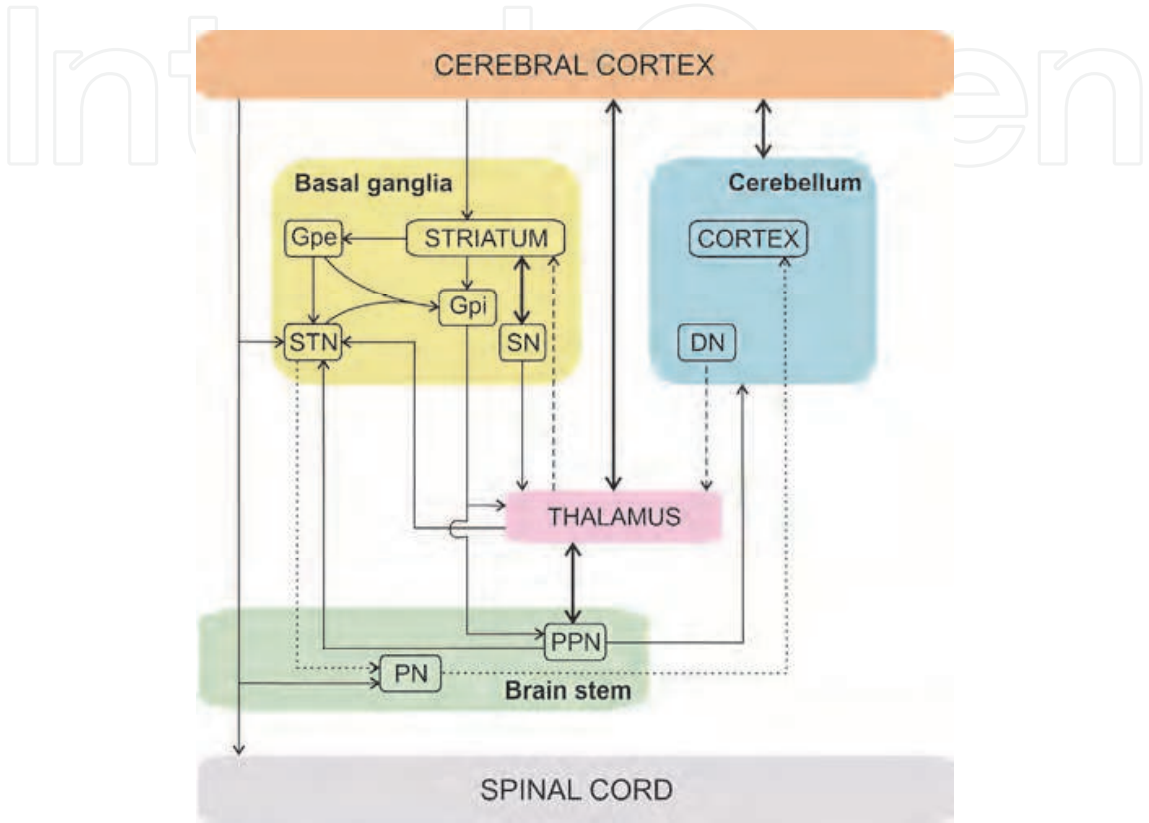


Fig. 1. Major connections of basal ganglia with brain structures. Abbreviations: DN (dentate nucleus), Gpe (external segment of the globus pallidus), Gpi (internal segment of the globus pallidus), PPN (pedunculo-pontine nucleus), PN (pontine nucleus), SN (substantia nigra), STN (subthalamic nucleus). Dotted lines mark the connections between cerebellum and basal ganglia. SN is anatomically part of the brainstem and functionally part of the basal ganglia. The STN is anatomically part of the subthalamus but functionally part of the basal ganglia. The basal ganglia and the cerebellum form multisynaptic loops with the cerebral cortex. Recently, a disynaptic projection between the output nuclei of the cerebellum (the DN) and the input stage of basal ganglia processing (the striatum) was identified (Hoshi et al., 2005) and a return pathway from the STN projecting to the cerebellar cortex (via the PN) was also described (Bostan et al., 2010). These disynaptic connections between the basal ganglia and the cerebellum could have functional importance for human movement and cognition.

Cognitive motor interference in PPD is clinically important since assessment and monitoring of a person's DT performance contributes to assessment of the patient's everyday motor ability, to informed goal setting and to treatment planning (Morris et al., 2010). The level of DT interference, and the precise conditions and task combinations under which it occurs, may vary between patients and over time. Motor tasks performed under DT conditions provide a better index of the patient's functional everyday ability than a motor task

performed under a single task condition since everyday activities often involve concurrent cognitive and motor components (Yogev-Seligman et al., 2008). To summarize, understanding the nature, prevalence, and prognosis of DT decrements is important for assessment and rehabilitation of the PPD.

2. Dual tasking and gait

Gait is a complex form of motor behavior that is influenced by mental processes under normal and pathological conditions. The contribution of cognition to gait is particularly evident in PPD with gait disorders who have a reduced ability to perform multiple tasks simultaneously, either because the central processing abilities have become too limited, or because patients fail to properly prioritize their balance control over other less important tasks (Bloem et al., 2006; Yogev-Seligman et al., 2008).

The higher cognitive processes, that use and modify information from different brain regions to modulate and produce behavior, are collectively known as executive function (Yogev-Seligman et al., 2008). The executive function (EF) integrates cognitive and behavioral components necessary for effective, goal-directed actions and for the control of intentional resources thus enabling the human being to manage independent daily activities (Stuss & Alexander, 2000; Stuss & Levine, 2002). The major components of EF are intentional behavior, self-awareness, planning, action monitoring, attention with DT and response inhibition (Stuss et al., 2000). The anterior parts of the frontal lobes deal with aspects of self-regulation (e.g. inhibition and self-awareness) and the dorsal parts deal with reasoning processes. Impairment of one or more of EF components reduces the ability to walk efficiently and safely (Yogev-Seligman et al., 2008). For example, poor self-awareness of limitations, an aspect of impaired volition, increases the risk of falling in elderly patients with dementia (van Iersel et al., 2006) or a reduced capacity to perform DT predisposes the PPD and gait disorders to freezing of gait and falls (see Section 3 for details). The concept that a specific component of the EF can be linked to a discrete brain region is a simplification since neuroimaging studies attempting to localize the activity of EF report inconsistent findings (Alvarez & Emory, 2006; Stuss & Alexander, 2000). This would suggest that connections among the frontal lobes and other cortical and subcortical brain regions are as important to the EF as discrete regions of the frontal lobes and that information sharing between brain regions depends on the specific task that is dealt with by the EF. For example, different EF tasks activate different frontal and parietal areas and also other areas of the brain (Collette et al., 2006). A practical implication of these facts is that patients without frontal lesions could, in theory, display clinical signs of impaired EF (Yogev-Seligman et al., 2008).

Age related changes to the frontal lobes (Craik & Grady, 2002) include lesions of diffused white matter, which might affect fronto-striatal circuits and impair EF (Buckner, 2004). White matter hyper-intensities on magnetic resonance imaging were associated with a decline of EF, but not with the level of general intelligence (Gunning-Dixon & Raz, 2003). Loss of dendritic branching in the prefrontal cortex is also associated with a decline in performance on EF tests (Burke & Barnes, 2006). Age-associated decline in dopaminergic activity in the frontal areas is also related to poorer performance on executive tasks (Burke & Barnes, 2006; Gunning-Dixon & Raz, 2003). EF is generally persevered in healthy and normal aging, with the exception of, for example attention, that shows a subtle decline (Yogev-Seligman et al., 2008). However, there is a great variability in frontal brain changes

among aging individuals in terms of the magnitude, age when changes occur, and the influence of education and lifestyle (Buckner, 2004). Therefore cognitive evaluation should include the individual's ability to carry out independent daily activities that tax the EF.

The relationship between EF and gait performance, in 926 older adults with a normal cognitive function, was reported by Ble and coworkers (Ble et al., 2005). They evaluated the effect of DT, simultaneous walking over an obstacle course and solving a Trail Making Test (TMT) (*i.e.* testing cognitive flexibility), in non-demented older adults. Poor and moderate performance on the TMT was associated with decreased gait speed on the obstacle course, although the mean speeds in all three groups were within normal limits. The conclusion of the study was that EF is independently associated with tasks of lower extremity function that require high intentional demand (*i.e.* DT). Similar results were reported in a study that evaluated the association between gait velocity and cognitive function in 186 cognitively normal elders (Holtzer et al., 2006). Holtzer and coworkers reported on the associations between speed of processing, attention, memory, language and EF on the one hand and gait velocity on the other. EF and memory were correlated with gait speed under DT conditions but verbal IQ was not (Holtzer et al., 2006).

The effect of DT on gait is substantially larger in patients with stroke, Parkinson's disease or Alzheimer's disease than in healthy, age-matched groups (Yogev-Seligman et al., 2008). These pathological conditions of the brain are well known to degrade EF and to reduce the ability to divide attention (Albert, 1996; Baddeley et al., 2001; Bedard et al., 1998; Buckner, 2004; Dubois & Pillon, 1997). In addition, these patients have an altered, less automatic walking pattern suggesting a larger involvement of EF in the execution of gait during normal daily activities (Baltadjieva et al., 2006; Giladi & Nieuwboer, 2008; Nakamura et al., 1996; Rochester et al., 2004; Schaafsma et al., 2003). Therefore, when the ability of the EF to perform dual tasking is overcome in PPD, this can be initially observed as a slower gait speed, shorter strides, increased double support time, increased stride-to-stride variability (Yogev et al., 2005; Plotnik et al., 2008, 2009, 2011a,b) and ultimately as freezing of gait and falls.

DT elicited falls are not unique to PD. Lundin-Olsson and coworkers reported that older adults who could not "walk and talk" had a high incidence of falls, while those subjects who could walk and talk were much less prone to future falls (Lundin-Olsson et al., 1997). The participants in this study were able to walk with or without aids and able to follow simple instructions. The most common diagnoses in this group of older adults were dementia, depression and previous stroke (Lundin-Olsson et al., 1997).

The human brain has a default, posture first prioritization, presumably an evolutionary trait to reduce the risk of falls, which can be demonstrated in experimental conditions (Yogev-Seligman et al., 2008). Healthy young adults and healthy elderly tend to give priority to the stability of gait when walking and performing a cognitive task (Bloem et al., 2001a,b). Brain areas associated with prioritization between motor and cognitive demands are the prefrontal cortex and the anterior cingulate cortex (Dreher & Grafman, 2003; MacDonald et al., 2000). In healthy adults dual tasking while walking reduces the quality of the concurrent non-walking task, but the gait pattern and stability remain normal (Gerin-Lajoie et al., 2005; Lindenberger et al., 2000; Schrodt et al., 2004). In contrast to healthy adults, PPD disease have a weakened "posture first" strategy which makes them prone to perform all tasks simultaneously thus increasing their risk of falling in dual tasking situations (Bloem et al., 2001 a,b). An independent contributing factor that also increases the risk of falling in PPD is

impaired motor learning (Bloem et al., 2001a,b; Harrington et al., 1990; Heindel et al., 1989; Soliveri et al., 1997).

Recently, it has been demonstrated that the DT effect is stronger in PPD who have a high risk of gait instability and fall, compared to patients with PPD with a lower risk (Plotnik et al., 2011a,b). The conclusion of this study was that specific cognitive capacities (executive function and attention) are impaired among PPD who tend to fall. In addition, the DT effects on gait were observed even when the patients responded to therapy – were in the "on" phase.

The relationship between DT, cognitive function and specific properties of gait (*i.e.* general mobility, gait variability and bilateral gait function) was investigated among PPD suffering from motor response fluctuations during the "on" state (Plotnik et al., 2011b). The authors concluded that the degree to which these gait parameters deteriorated during DT (compared to usual walking) was correlated with the baseline levels of impaired motor and cognitive capacities and that this relationship was conserved even during optimal medication.

3. Gait disorders in Parkinson's disease

Parkinson disease is a common disorder among older adults with an incidence rate of 16 to 19 per 100,000 per year. Worldwide, about 6 million people are currently living with this progressive neurological condition (Twelves et al., 2003). Gait disorders are a distinctive characteristic of PD; a slow, short stepped shuffling and forward-stooped gait with asymmetrical arm swing (Morris et al., 2010). Gait disorder includes difficulties with the execution of well-learned movement sequences (*e.g.* walking, turning, writing, and transfers) and some people with PD report freezing, falls, cognitive impairment, and autonomic disturbances (Simuni & Sethi, 2008) which affect quality of life and participation in societal roles (Visser et al., 2009).

The clinically observed differences between tremor-dominant and postural instability subtypes of PD are reflected in cerebral blood flow changes during single photon emission computed tomography. Patients with postural instability and gait difficulty had hypoperfusion in the anterior cingulate cortex and primary visual cortex that was not observed in the tremor-dominant group of PPD. The observed frontal reduction in perfusion in patients with gait disorders is consistent with the expected frontal executive function deficits in these patients (Yogev-Seligman et al., 2008).

A recent meta-analysis of falling in PD (pooled sample size 473 patients) reported that the average 3-month fall rate was 46% (Pickering et al., 2007). Even among patients without prior falls, the fall rate was considerable (21%). The conclusion of the study is that all of the patients with PD have a substantial risk of falling, even when they have not fallen previously. Maximal treatment with levodopa does not prevent the occurrence of falls, consistent with the hypothesis that axial disability in late stage Parkinson's disease is largely doparesistant - due to extranigral and nondopaminergic brain lesions (Boonstra et al., 2008; Hely et al., 2008). Two explanations were given for the perseverance of falls and an increased risk of fractures in levodopa treated patients with PD. Levodopa could cause adverse effects that predispose patients to falls (*e.g.* violent dyskinesias, drug-induced orthostatic hypotension) or patients on levodopa become more mobile and therefore more prone to falls (Boonstra et al., 2008). That patient mobility can predispose to falls is consistent with the fact that fall rates decrease with disease progression, probably because patients become increasingly immobilized (Pickering et al., 2007).

3.1 Freezing of gait

Gait disorders, especially episodic gait disorders are particularly incapacitating because patients cannot easily adjust their behavior to these paroxysmal walking problems (Snijders et al., 2007). An important and extremely debilitating gait disorder is freezing of gait (FOG). FOG occurs when patients with PD experience episodes during which they are either unable to start walking or while walking, suddenly fail to continue moving forward. Because FOG is sudden and unpredictable, it is an important cause of falls and injuries and is also independently associated with a decreased quality of life (Moore et al., 2007a). FOG is not unique to PD and is a more common and an earlier feature in other parkinsonian syndromes (e.g. primary progressive freezing of gait, multisystem atrophy, pure akinesia, vascular parkinsonism, progressive supranuclear palsy, or dementia of Lewy body type); for a review see Thanvi and coworkers (Thanvi & Treadwell, 2010). A comprehensive definition of FOG that includes its paroxysmal nature, association with gait disorders, and the influence of various external and internal stimuli is that FOG is "an episodic inability to generate effective stepping in the absence of any known cause other than Parkinsonism or high level gait disorders. It is most commonly experienced during turning and step initiation but also when faced with spatial constraint, stress, and distraction. Focused attention and external stimuli can overcome the episode" (Giladi & Nieuwboer, 2008).

About half of patients with PD experience FOG and risk factors include male gender and an akinetic-rigid subtype of PD (Macht et al., 2007; Lamberti et al., 1997). FOG tends to appear only under certain situations for example at gait initiation, approaching a destination, passing through a narrow passage or on turning (Thanvi & Treadwell, 2010). Distraction or dual tasking during such situations (e.g. talking while walking, counting backwards or carrying a glass of water while walking) increase the incidence of FOG. Paradoxically, an intense external stimulus such as an alarm bell may briefly ameliorate freezing and patients develop visual or audio cues (Bloem et al., 2004a) to overcome FOG attacks (e.g. stepping over objects or walking to a music or a beat). The severity of FOG varies from forward shuffling with small step, to trembling in place, to total akinesia in "off" period.

Patients tend to under report FOG episodes in the outpatient consultation unless they are specifically asked about it (Thanvi & Treadwell, 2010). Therefore a FOG specific questionnaire, comparing patients' ratings with those of the carers', may be a useful aid to for a more realistic assessment of FOG occurrence (Nieuwboer et al., 2009). Patients usually experience FOG as brief episodes lasting for a few seconds when their walking suddenly comes to a halt, and they feel as though their feet are "glued" to the floor. With increasing severity of FOG the patient moves forward shuffling with small steps, trembles in place or in most severe cases patients cannot move forward at all. The two unique features of FOG in PD are that FOG is often worse during the "off" state and rarely occurs in "on" state. FOG is common in the akinetic rigid variety of PD but can also occur in the tremor predominant type of PD (Lamberti et al., 1997).

Hausdorff and coworkers demonstrated that the ability to regulate stride-to-stride timing during gait is severely impaired in FOG patients compared with other individuals with Parkinson's disease (Hausdorff et al., 2003). Therefore, analysis of stride-to-stride variability could be a useful method for identifying characteristics of gait that are closely linked to FOG and could predict its occurrence. However, patients with PD that experience FOG also display premature muscle activation and termination patterns before a freezing episode, leading to an abnormally long stance phase (Nieuwboer et al., 2001, 2004). This altered timing suggests

that a central timing deficit could predispose PPD to FOG (Almeida et al., 2007). Perceptual judgement deficits have been identified as a contributing factor to motor impairment in PD (Johnson et al., 2004). For example, PPD are unable to accurately evaluate self-motion in relation to upcoming obstacles (Almeida et al., 2005). Therefore, a central timing deficit could be the consequence of an altered perceptual processing capabilities (Almeida et al., 2010) in PPD that experience FOG. This mechanism could explain the occurrence of FOG when PPD move through confined spaces.

PPD report feeling too large to pass through small spaces, even though they are aware that doorways are designed for human size (Lee & Harris, 1999). A recent study indirectly evaluated the influence of space perception on gait in individuals with Parkinson's disease who experience FOG, other Parkinson's disease patients (absent of FOG) and healthy age-matched participants (Almeida et al., 2010). Individuals with Parkinson's disease were tested while on dopaminergic medication. The objective was to evaluate the effect of doorway size on gait before reaching the doorway in these three groups of subjects. Almeida and coworkers reported (Almeida et al., 2010) that patients with FOG, while approaching a narrow doorway, already exhibit alterations to gait (shortened step length, increased gait variability, increased base of support) indicative of an upcoming freezing episode. These changes were not evident in non-FOG individuals with Parkinson's disease, or healthy participants. The conclusion of the study was that indicators of freezing occur when patients approach what they perceive to be a confined space, suggesting that online perceptual processes must be interrupting the initial movement plan to pass through the doorway. Therefore, impaired perceptual ability could be an important factor contributing to FOG in PPD. Since PPD, that experience FOG, were most affected (in terms of step length and velocity) upon their first encounter with the doorway, practice (*i.e.* repeated passing through a doorway) could help PPD improve their spatial perception. Finally, FOG is difficult to elicit in a laboratory setting. Therefore it is important to consider whether patients categorized as non-freezers in a laboratory setting may experience of FOG within their home environment (Almeida et al., 2010).

3.2 Falls

At present, it is not possible to accurately predict the occurrence of falls in PPD. This is particularly true for prior nonfallers (Boonstra et al., 2008). The best available predictor of falling is two or more falls in the previous year. Fear of falling had a moderate sensitivity in predicting falls among prior nonfallers, suggesting that patients may sense their own instability before it can be detected on physical examination (Pickering et al., 2007). Fear of falling can be evaluated with the Activities-specific Balance Confidence (ABC) scale, which has been validated for use in Parkinson's disease (Peretz et al., 2006). Although fear of falling was also associated with prior falls in other studies, alternative determinants of falls were also reported ranging from impaired ambulation, impaired lower-limb motor planning to orthostasis (Bloem et al., 2004b; Dennison et al., 2007; Williams et al., 2006). Several methods were developed for the clinical and quantitative assessment of gait, FOG, postural instability and balance confidence (Dibble et al., 2006, 2008; Jacobs et al., 2006a, 2006b; Kegelmeyer et al., 2007; Moore et al., 2007b, 2008; Peppe et al., 2007; Peretz et al., 2006; Plotnik et al., 2007) but only a few studies are focused on predicting falls in PPD (Dibble et al., 2006; Jacobs et al., 2006a). The three key pathophysiological factors that seem to be relevant for the development of falls in PPD are turning, axial asymmetry and sensorimotor integration (Boonstra et al., 2008).

PPD often experience difficulty turning around (clinically described as en-bloc-turning), either while lying recumbent in bed or when standing upright. These turning problems are clinically relevant for PPD because falls are associated with hip fractures. Measuring the time during a 180° axial turn or counting the number of steps are simple and adequate methods for the assessment of turning (Huxham et al., 2006; Willems et al., 2007;) since PPD require more steps and also turn slower than controls. Alternative ambulatory monitors, that evaluate for example peak yaw and peak roll angular velocity of the trunk (Visser et al., 2007) — both are reduced in PD — are also available (Moore et al., 2008; Plotnik et al., 2007). Turning problems could be the consequence of poor interlimb coordination (Baltadjieva et al., 2006; Hausdorff et al., 2003) when the two legs have to move more "in phase" rather than "out of phase" as is usual during over ground straight walking. Another important factor that could contribute to difficulties in turning is axial stiffness and loss of intersegmental axial coordination. PPD have an increased resistance to passive axial rotations that was resistant to levodopa treatment in contrast to the limb movements, which appear to be controlled by separate dopaminergic neural systems (Baltadjieva et al., 2006; Wright et al., 2007).

Some PPD exhibited unsteadiness associated with orthostatic tremor of varying frequency (from 4 to 18 Hz) or orthostatic myoclonus; patients with fast tremor improved on clonazepam and patients with slow tremor or myoclonus improved on levodopa, and sometimes benefited further when clonazepam was added (Leu-Semenescu et al., 2007).

Idiopathic Parkinson's disease is by definition an asymmetrical disease. A study on 35 patients with Parkinson's disease who were not yet treated with any antiparkinsonian medication showed that asymmetries in gait (detected with simple pressure-sensitive insoles) are also present in the early stage of PD and are not merely a side effect of medication or a late disease complication (Baltadjieva et al., 2006). Gait asymmetry could be detected even though stride-to-stride variability (previously thought to be one of the most sensitive measures of gait changes in Parkinson's disease) was normal in these early PPD. In addition, subtle asymmetries in balance control can be detected in Parkinson's disease by carefully analyzing the independent contribution of both legs to stance control, even before these changes are visually detected on clinical examination (van der Kooij et al., 2007).

Disturbed motor programming of postural corrections within the basal ganglia is not the only cause for postural instability in PD, since some motor deficits are at least partially due to central proprioceptive disturbances (Boonstra et al., 2008). When PPD were standing on a supporting platform and perturbed under conditions where they were dependent on proprioceptive feedback to maintain balance, they swayed abnormally, but were still able to partially correct this with visual feedback (Vaugoyeau et al., 2007). Compared to controls, the switch from proprioceptive-dependent to vision-dependent balance control is slower in PPD, suggesting an inappropriate changing between different sensory modalities (Brown et al., 2006). Further evidence that proprioceptive disturbances could contribute to gait disorders was provided by two studies that evaluated the response of PPD to tendon vibration and to a functional reach task. The response to tendon vibration was exaggerated and does not habituate well in patients with advanced PD (Valkovic et al., 2006). When PPD were asked to extend the arm forward as far as possible, with both feet fixed at the floor they tended to overestimate their limits of stability (Kamata et al., 2007). Therefore proprioceptive disturbances could produce a distorted body scheme and thus explain some changes in gait, for example the stooped posture of patients with Parkinson's disease, of which they are often subjectively unaware (Boonstra et al., 2008).

In human, the normal response to an imminent fall is stretching out the arms and taking compensatory steps. PPD have difficulties initiating a compensatory step (Jacobs et al., 2006a,b,c; King et al., 2008). The failure to initiate a compensatory step could be due to impairment of anticipatory postural adjustments; normally a lateral weight shift precedes a contralateral limb swing (King et al., 2008). Visual cues facilitate the initiation of compensatory stepping in PPD and initiation is inhibited when patients are unable to see their legs (Jacobs et al., 2006a,b,c; Mille et al., 2007). The importance of cuing in PPD is discussed under Section 4.4 Physical Therapy.

4. Treatment of gait disorders in Parkinsons disease

One of the most serious complications of FOG is falls. Although FOG and falls usually occur in the later stages of PD they are typically an early feature of atypical parkinsonian syndromes (Thanvi & Treadwell, 2010). The unpredictable and episodic nature of occurrence of FOG and falls poses a serious challenge to the patients, carers and the physicians. Frequent falls lead to injuries (*e.g.* fractures), fear of falling, restriction of mobility, and social isolation (Thanvi & Treadwell, 2010). FOG is often associated with cognitive and speech impairment, incontinence and falls. Therefore, it is best managed with a multidisciplinary team approach (Thanvi & Treadwell, 2010).

There is no universally effective therapy available to treat FOG (Thanvi & Treadwell, 2010). In PD, "off" period FOG responds initially well to interventions aimed at improving "on" time, though with increasing disease severity it becomes treatment refractory (like other L-dopa resistant features such as axial symptoms and postural disturbances). DT and very stressful conditions (*e.g.* crossing a busy road at a point not marked with a zebra crossing) increase the probability of FOG, whereas focused attention strategies (*e.g.* visual, auditory or sensory cueing), and a moderate amount of emotional stress can improve FOG (Thanvi & Treadwell, 2010). Patients often use a type of focused attention strategy to improve their freezing, and physiotherapists exploit them for gait training.

4.1 Dopaminergic drugs

FOG in patients with PD is considered dopamine resistant. Although the proportion of PD patients with motor disability increases with time, these deficits do not become unresponsive to levodopa (Clissold et al., 2006). The "off" phase FOG does respond to treatment with dopaminergic drugs. The "off" FOG is more common and often more severe than "on" freezing (Thanvi & Treadwell, 2010). L-dopa was shown to reduce "off" freezing (Lee et al., 2005) or reduce the frequency of the "off" period FOG (Schaafsma et al., 2003). Patients treated with L-dopa are less likely to have FOG compared with those who received placebo (Parkinson Study Group 2003). Dopaminergic receptor agonists also improve motor symptoms and increase "on" time in fluctuating PD patients. Apomorphine improves postural stability of PPD by decreasing rigidity (Bartolić et al. 2005). When compared to patients treated with ropinirole (Rascol et al., 2000) or pramipexole (Parkinson Study Group, 2001), L-dopa treated patients had less frequent episodes of FOG. L-dopa may adversely affect gait or balance control. One study (Almeida et al., 2007) showed that timing of gait to an external stimulus was worse in medicated patients compared with patients who had withdrawn from medication, presumably due to drug-induced dyskinesias.

4.2 Monoamine oxidase B inhibitors

Compared to placebo, Selegiline reduces the frequency of FOG in PPD (Giladi et al., 2001). This effect was also shown in the late stages of PD (Zuñiga et al., 2006). Similar observations were reported for Rasagiline when used as an adjunct to L-dopa (Giladi et al., 2004, as cited in Thanvi & Treadwell, 2010).

4.3 Miscellaneous drugs

L-Threo-DOPS, a norepinephrine precursor, has been shown to improve FOG in one study, (Narabayashi et al., 1987) but not in the other (Quinn et al., 1984). Improved gait and balance in advanced PD was achieved with Atomoxetine (Jankovic, 2009) but these results have to be evaluated in controlled trials.

Methylphenidate, a central nervous system stimulator traditionally used for treating attention-deficit hyperactivity disorder, can decrease fall risks in community dwelling older adults, presumably by increasing availability of striatal dopamine or by improving attention (Ben-Itzhak et al., 2008). Trials have also shown that methylphenidate improves gait and FOG in PPD (Devos et al., 2007; Pollak et al., 2007).

4.4 Physical therapy

Adherence to a regular exercise regimen may be the most difficult challenge for the physical therapist and the patient (Morris et al., 2010). The development and progression of non-motor signs of PD (depression, apathy, and lack of initiative) also has a significant negative effect on patient compliance to the exercise regimen (Morris et al., 2010). The efficacy of physical therapy is evaluated by gait-related outcomes including assessment of kinematics of gait (*e.g.* stride length), assessment of functional factors (*e.g.* walk distance over a defined time interval, ability to climb stairs or raise from chair), and assessment of factors associated with postural control that are closely related to gait (*e.g.* incidence of FOG or falls). Physical therapy of PPD has three objectives: strategy training, management of secondary sequelae and promotion of physical activities (Morris et al., 2010).

4.4.1 Strategy training

The first objective is to teach the patient how to move more easily and to maintain postural stability by using cognitive strategies that target the primary motor control deficit in the basal ganglia, brain stem, and motor cortex. The two forms of strategy training are compensatory strategies to bypass the defective basal ganglia and learning strategies to improve performance through practice (Morris et al., 2010). The theoretical rationale for using cognitive strategies is that the use of executive function of the frontal cortex, to regulate movement size or timing by consciously thinking about the desired movement, enables people with PD to compensate for the neurotransmitter imbalance in the basal ganglia.

Some of the first evidence that movement strategies can compensate for hypokinesia and thus assist people with PD to balance, move and walk more easily was provided by Morris and colleagues (Morris et al., 2000, 2006, 2009). For example, external cues, such as white lines on the floor or a rhythmical beat provided by a metronome or music, enable elderly people with moderate to severe PD to walk with longer steps and at a more normal stepping rate. Cueing is an established therapy for gait training of patients with PD. Theoretically, external cues could reduce attentional loads by reducing the need to prepare and plan a

movement, but this hypothesis requires further testing (Boonstra et al., 2008). The effect of visual cues on FOG was first reported in 1967 (Martin, 1967) and several following studies reported transient beneficial effects of cueing in single or limited sessions (Cubo et al., 2003; Dibble et al., 2004; Dietz et al., 1990). For example, a three week home physiotherapy programme based on rhythmical cueing on gait and gait related activity in PPD reported significant improvements in gait and FOG questionnaire scores in the treatment group. Unfortunately, the effects were short-lived and disappeared by the 12 week follow-up (Nieuwboer et al., 2007). A recent study reported greater benefits with treadmill training plus auditory and visual cues than rehabilitation with cues but no treadmill training (Frazzitta et al., 2009). Apart from the transient beneficial effect of cueing an additional concern is that cueing strategies, even when effective in the lab under carefully controlled "single task" conditions, may not benefit patients in daily life complex situations, that typically requiring patients to deal with multiple tasks simultaneously (Boonstra et al., 2008). Two studies have shown that some, but not all, cueing strategies benefit patients in daily life complex situations. Auditory cues improved walking speed during a DT situation, whereas somatosensory cues had no effect, and visual cues had a negative effect. Rhythmic auditory cues had no effect in a single task situation (*i.e.* normal walking) (Baker et al., 2007; Rochester et al., 2007). The explanation for the latter result was that the participants were challenged more during the DT, or that patients relied more on external information during the complex tasks (Rochester et al., 2007).

Virtual reality represents a new and promising cueing strategy. A recent paper reported on the effects of 6 weeks of treadmill training (TT) with virtual reality (VR) on the mobility of PPD (Mirelman et al., 2011). The results of this study indicate that intensive and progressive TT with VR is viable for PPD and may significantly improve physical performance and gait beyond the previously reported improvements of TT alone (Mirelman et al., 2011). By promoting the development of new motor and cognitive strategies for obstacle navigation, training with TT + VR positively affected complex gait conditions such as walking with DT, obstacle negotiation, and even certain aspects of cognitive function (attention and memory) (Mirelman et al., 2011). In addition, the negative effects of drug therapy on gait became smaller after training with TT + VR and were significantly better than those observed after intensive TT alone (Mirelman et al., 2011). In summary, this study contributes to the growing body of evidence that suggests that motor and cognitive improvement may be achievable among older adults with PD (Li et al., 2010; Verghese et al., 2010). However, larger scale, randomized controlled studies are needed to firmly establish efficacy and the long-term retention effects of TT with VR on cognitive, motor function, and fall risk in patients with PD (Mirelman et al., 2011).

PPD with moderate postural instability, and a preserved cognitive function, walk with long, fast steps simply by focusing their attention on walking with long steps, even when floor markers are absent (Morris et al., 2009). Learning strategies to improve gait through practice (*e.g.* mentally rehearsing the desired movement pattern before the action is performed) are based on the theory that the ability to move normally is not lost in PD. Instead, there is an activation problem that can be overcome through targeted physical therapy together with optimal pharmacotherapy (Morris et al., 2010). The ability to learn a new motor skill is present in the early stages of PD. For example, the capacity to learn new upper-limb movement sequences was retained in people in the early to middle stages of PD (Behrman et al., 2000) and an increased multiple-task walking speed in people with mild PD could be

achieved with a multiple-task gait training program that combined walking with cognitive and manual activity practice (Canning et al., 2008). A recent study by Brauer and co-workers (Brauer et al., 2010) confirmed the assumption that PPD can be trained to walk with long steps under dual task conditions.

To summarize, physical therapy should be adjusted to the progression of PD. For patients with a mild to moderate gait disorder and conserved cognitive capacity, the aim of physical therapy is to maximize motor skill learning by high intensity, variable, distributed practice regimens with regular booster sessions over the longer term. For patients with advanced gait disorders or cognitive impairment the recommended physical therapy would be repetition of a given movement or action sequence, avoidance of multitasking, use of external cues and reminders, and segmentation of actions into simple components (Dubois & Pillon, 1997; Morris et al., 2010).

4.4.2 Management of secondary sequelae

The second objective of physical therapy, management of secondary sequelae, is concerned with the management of secondary pathological conditions affecting the musculoskeletal and cardiorespiratory systems that occur as a result of deconditioning, reduced physical activity, advanced age, and comorbid conditions (Morris et al., 2010). Some of the changes in the musculoskeletal and cardiorespiratory systems of patients in the advanced stages of PD are also due to concurrent age related changes. Therefore studies that aim to develop physical training strategies specific for PPD should include age matched controls. Management of secondary pathological conditions (*e.g.* weakness, loss of range, loss of range of motion of axial structures, or reduced aerobic capacity) alone can improve balance, gait, and function in PPD without influencing the primary central nervous system disorder affecting the basal ganglia (Schenkman & Butler, 1989; Schenkman et al., 2000). For example, loss of lower-extremity strength contributes to gait disorders, falls, and functional decline in older people (Chandler et al., 1998; Falvo et al., 2008). Such loss of lower-extremity strength can be compensated by an appropriate physical training programme as demonstrated by Dibble and coworkers (Dibble & Lange, 2006) who showed that a high-intensity eccentric quadriceps muscle strengthening program increased quadriceps muscle volume, improved 6-minute walk distance, and improved stair descent time. PPD have a less efficient muscle work and thus less efficient movement than age matched controls. Adults with PD used as much as 20% more oxygen to perform bicycling tasks than did the people without PD (Protas et al., 1996) and people with PD consume more oxygen than people without PD at every walking speed from 1 to 4 mph (Christiansen et al., 2009). Aerobic conditioning programs can improve the efficiency of maximum oxygen consumption, movement and kinematics of gait (Bergen et al., 2002; Burini et al., 2006; Schenkman et al., 2008). To sustain the benefits of physical therapy, individuals should continue exercising at least a few times per week as part of their daily routine. Patients in the early stages of PD should be reassessed by a physical therapist at least annually and more often in later stages of the disease to progress their exercise program (Morris et al., 2010).

A combination of physical impairments (*e.g.* FOG), cognitive dysfunction (*e.g.* depression and dementia), and fatigue predispose PPD toward a sedentary lifestyle (van Eijkeren et al., 2008). Regular physical activity of PPD is vital, since physical activity has positive effects in preventing the well known complications of immobility (*e.g.* an increased risk of cardiovascular disease, type-2 diabetes mellitus, osteoporosis and obesity). Osteoporosis

prevention is particularly important for PPD because they have an increased risk of falling (Pickering et al., 2007) and for fall-related fractures (Genever et al., 2005; Melton et al., 2006). Exercise may also slow down the progression of cognitive decline (Yaffe et al., 2001; van Gelder et al., 2004) or dementia (Laurin et al., 2001). Also, animal studies suggest that physical activity could slow down disease progression in PD (Tillerson et al., 2003). Therefore, it is vital to develop a reliable strategy to stimulate an active lifestyle in PD.

PPD can participate in exercise classes and improve their physical fitness but have difficulty in sustaining their active lifestyle (Keus et al., 2007). **Nordic walking** (*i.e.* Polestriding) is rapidly gaining popularity as a way to improve physical fitness in PD (van Eijkeren et al., 2008). Nordic walking combines simplicity and accessibility of walking with a full body walking workout that can burn significantly more calories without having to walk faster, due to the incorporation of many large body muscles. A practical advantage is that Nordic walking can be done year round in any climate (van Eijkeren et al., 2008). Two recent studies in PPD demonstrated short-term beneficial effects of Nordic walking on walking speed and stride length, as well as on UPDRS motor scores and quality of life (Baatile et al., 2000; Reuter et al., 2006). The long term effects of Nordic walking were evaluated in a study by Eijkeren et al. (van Eijkeren et al., 2008). The results of this study show that a 6-week Nordic walking program is associated with an improved walking speed, a faster TUG test, and increased timed walking distance and an improved quality of life in PPD even 5 months after training (van Eijkeren et al., 2008). Although all three studies are preliminary their encouraging results justify a large scale, randomized clinical trial.

4.4.3 Promotion of physical activities

The final, third objective of physical therapy, is the promotion of physical activities that assist the person in making lifelong changes in exercise and physical activity habits as well as preventing FOG and falls (Morris et al., 2010). Because of the chronic, progressive nature of PD, sustained exercise is vital to maintain the benefits of physical therapy by integrating physical activity into the patient's daily life. This is supported by follow-up data from human exercise interventions that have demonstrated a gradual return to baseline abilities after the supervised intervention was terminated (Mooris et al., 2009; Schenkman et al., 1998; Ellis et al., 2005). Research suggests that exercise not only enables people to maintain functional ability but could also have a neuroprotective effect. Tillerson and coworkers (Tillerson et al., 2003) reported that motorized treadmill running twice daily for 10 days enhanced motor performance and brain neurochemistry in 2 different rat models of PD. Also Dobrossy and Dunnett (Dobrossy & Dunnett, 2003) reported that rats that received motor training after striatal lesions or striatal grafts showed partial recovery in spontaneous movements and skilled motor performance. Research on human subjects suggests that high-intensity exercise can normalize corticomotor excitability in the early stages of PD (Fisher et al., 2008).

4.5 Deep brain stimulation

The internal globus pallidus (GPi) and the subthalamic nucleus (STN) are the most common targets for deep brain stimulation in the treatment of PPD (Thanvi & Treadwell, 2010). L-dopa induced dyskinesias and fluctuations are treated with stimulation of the GPi and STN stimulation is used to treat PD motor symptoms (*e.g.* tremor). Some of the effect of STN stimulation may act *via* "downward" projections onto the pedunculopontine nucleus (Gan et al., 2007).

Bilateral STN stimulation is an effective treatment for PD, for symptoms of the upper and lower limbs that responded well to levodopa preoperatively (Boonstra et al., 2008). The effects of STN stimulation on axial motor signs are less clear because of the differences in surgical techniques, candidates selected for surgery and outcome measures used (Boonstra et al., 2008). There are increasing concerns that deep brain stimulation of the STN may worsen axial mobility either as an immediate adverse effect of surgery, or as a longterm complication (Boonstra et al., 2008). After a 3-year follow-up of 36 patients with Parkinson's disease, STN stimulation had improved the United Parkinson's Disease Rating Scale (UPDRS) motor score and gait score but dopa-unresponsive axial signs had worsened in some patients (Gan et al., 2007). Another study, investigating gait changes after STN stimulation, found that gait improved in half the patients, but had worsened in the others (Kelly et al., 2006). It has been suggested that variability in electrode placement can explain the inconsistent effects of STN stimulation on axial mobility across PPD (Boonstra et al., 2008). For example, misplaced electrodes could unintentionally stimulate the pedunclopontine nucleus (Tommasi et al., 2007) which, when stimulated at high frequencies, worsens gait and balance (Androulidakis et al., 2008; Stefani et al., 2007). This hypothesis was addressed in a study of patients with Parkinson's disease with severe postoperative gait disorders whose outcome measures (including UPDRS, a timed walking task and FOG) improved when the stimulator frequency settings (130Hz) were changed to 60 Hz (Moreau et al., 2008).

An alternative target for DBS in patients with advanced PD is the pedunclopontine nucleus (Stefani et al., 2007). The effect of simultaneous bilateral implantation of electrodes in both the STN and pedunclopontine nucleus was studied in a group of six PPD (Stefani et al., 2007). During the "on" state, pedunclopontine stimulation alone had a positive effect on the UPDRS items for gait and balance, whereas STN stimulation did not. The pedunclopontine stimulation improved axial symptoms directly postoperatively and this persisted for 6 months. An alternative explanation for these results, the unintentional stimulation of nucleus peripeduncularis (Yelnik, 2007), has been suggested.

5. Conclusion

There is a need for further studies that investigate the treatment of gait disorders in patients with Parkinson's disease since there is still no universally effective therapy available. Recent research has identified novel gait parameters for evaluating freezing of gait and falls, with the potential to contribute to the prevention and treatment of gait disorders, that still have to be validated in large scale, randomized clinical trials.

6. Acknowledgement

This work was supported by the Slovenian Research Agency of the Republic of Slovenia, Grant number P3-0171.

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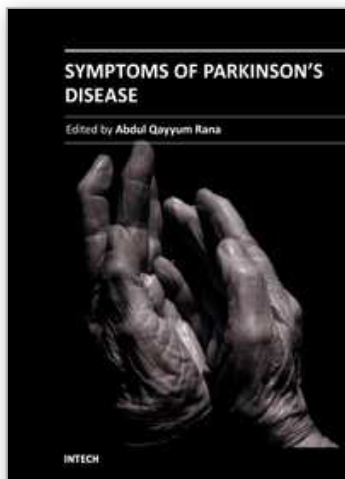
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Symptoms of Parkinson's Disease

Edited by Prof. Abdul Qayyum Rana

ISBN 978-953-307-464-1

Hard cover, 202 pages

Publisher InTech

Published online 22, September, 2011

Published in print edition September, 2011

This book about Parkinson's disease provides a detailed account of various aspects of this complicated neurological condition. Although most of the important motor and non-motor symptoms of Parkinson's disease have been discussed in this book, but in particular a detailed account has been provided about the most disabling symptoms such as dementia, depression, and other psychiatric as well as gastrointestinal symptoms. The mechanisms responsible for the development of these symptoms have also been discussed. Not only the clinicians may benefit from this book but also basic scientists can get enough information from the various chapters which have been written by well known faculty.

How to reference

In order to correctly reference this scholarly work, feel free to copy and paste the following:

Samo Ribarič (2011). Cognition and Gait Disturbances in Parkinson's Disease, Symptoms of Parkinson's Disease, Prof. Abdul Qayyum Rana (Ed.), ISBN: 978-953-307-464-1, InTech, Available from: <http://www.intechopen.com/books/symptoms-of-parkinson-s-disease/cognition-and-gait-disturbances-in-parkinson-s-disease>

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Phone: +86-21-62489820
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