

We are IntechOpen, the world's leading publisher of Open Access books Built by scientists, for scientists

4,900

Open access books available

124,000

International authors and editors

140M

Downloads

Our authors are among the

154

Countries delivered to

TOP 1%

most cited scientists

12.2%

Contributors from top 500 universities



WEB OF SCIENCE™

Selection of our books indexed in the Book Citation Index
in Web of Science™ Core Collection (BKCI)

Interested in publishing with us?
Contact book.department@intechopen.com

Numbers displayed above are based on latest data collected.
For more information visit www.intechopen.com



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

(Korczyński, 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).

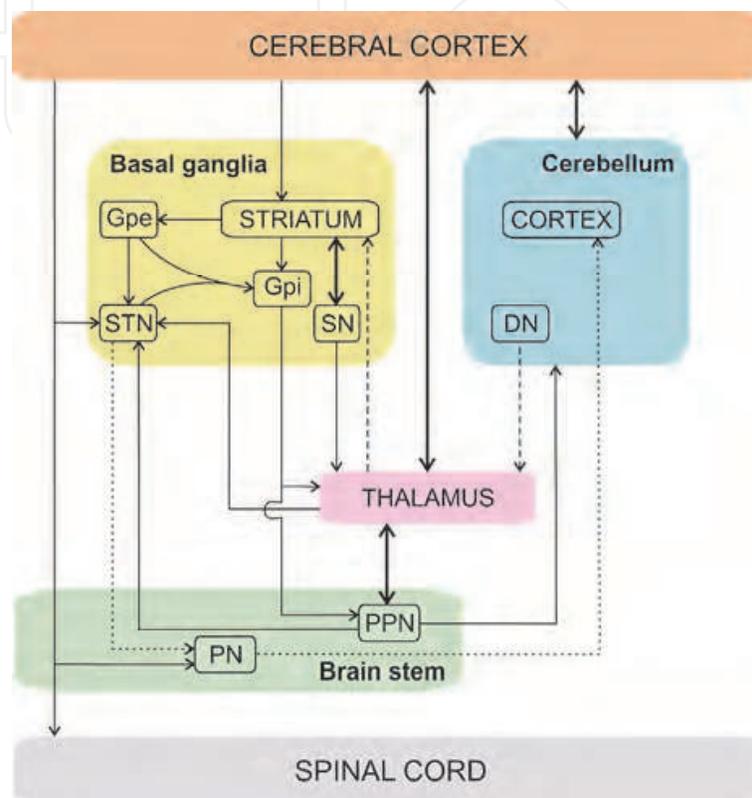


Fig. 1. Major connections of basal ganglia with brain structures. Abbreviations: DN (dentate nucleus), Gpe (external segment of the globus pallidus), Gpi (internal segment of the globus pallidus), PPN (pedunculopontine nucleus), PN (pontine nucleus), SN (substantia nigra), STN (subthalamic nucleus). 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 (Morris 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.

7. References

- Albert, MS. Cognitive and neurobiologic markers of early Alzheimer disease. (1996). *Proceedings of the National Academy of Sciences of the United States of America*, Vol.93, pp. 13547-13551, ISSN 0027-8424

- Almeida, QJ.; Frank, JS.; Roy, EA.; Jenkins, ME.; Spaulding, S.; Patla, AE.; & Jog, MS. (2005). An evaluation of sensorimotor integration during locomotion toward a target in Parkinson's disease. *Neuroscience*, Vol.134, No.1, pp. 283-293, ISSN 0306-4522
- Almeida, QJ.; Frank, JS.; Roy, EA.; Patla, AE. & Jog, MS. (2007). Dopaminergic modulation of timing control and variability in the gait of Parkinson's disease. *Movement Disorders*, Vol.22, pp. 1735-1742, ISSN 0885-3185
- Almeida, QJ. & Lebold, CA. (2010). Freezing of gait in Parkinson's disease: a perceptual cause for a motor impairment? *Journal of Neurology, Neurosurgery, and Psychiatry*, Vol.81, No.5, pp. 513-518, ISSN 0022-3050
- Alvarez, JA. & Emory, E. (2006). Executive function and the frontal lobes: a meta-analytic review. *Neuropsychology Review*, Vol.16, pp. 17-42, ISSN 1040-7308
- Androulidakis, AG.; Khan, S.; Litvak, V.; Pleydell-Pearce, CW.; Brown, P. & Gill, SS. (2008). Local field potential recordings from the pedunculopontine nucleus in a Parkinsonian patient. *Neuroreport*, Vol.19, pp. 59-62, ISSN 0959-4965
- Baatile, J.; Langbein, WE.; Weaver, F.; Maloney, C. & Jost, MB. (2000). Effect of exercise on perceived quality of life of individuals with Parkinson's disease. *Journal of Rehabilitation Research and Development*, Vol.37, pp. 529-534, ISSN 0748-7711
- Baddeley, AD.; Baddeley, HA.; Bucks, RS. & Wilcock, GK. (2001). Attentional control in Alzheimer's disease. *Brain: a Journal of Neurology*, Vol.124, pp. 1492-1508, ISSN 0006-8950
- Baker, K.; Rochester, L. & Nieuwboer, A. (2007). The immediate effect of attentional, auditory, and a combined cue strategy on gait during single and dual tasks in Parkinson's disease. *Archives of Physical Medicine and Rehabilitation*, Vol.88, pp. 1593-1600, ISSN 0003-9993
- Baltadjieva, R.; Giladi, N.; Gruendlinger, L.; Peretz, C. & Hausdorff, JM. (2006). Marked alterations in the gait timing and rhythmicity of patients with de novo Parkinson's disease. *The European Journal of Neuroscience*, Vol.24, pp. 1815-1820, ISSN 0953-816X
- Bartolić, A.; Pirtosek, Z.; Rozman, J. & Ribaric, S. (2005). Postural stability of Parkinson's disease patients is improved by decreasing rigidity. *European Journal of Neurology*, Vol.12, No.2, pp. 156-159, ISSN 1351-5101
- Bartolić, A.; Pirtosek, Z.; Rozman, J. & Ribaric, S. (2010). Tremor amplitude and tremor frequency variability in Parkinson's disease is dependent on activity and synchronisation of central oscillators in basal ganglia. *Medical Hypotheses*, Vol.74, No.2, pp. 362-365, ISSN 0306-9877
- Bedard, MA.; el Massioui, F.; Malapani, C.; Dubois, B.; Pillon, B.; Renault, B. & Agid, Y. (1998). Attentional deficits in Parkinson's disease: partial reversibility with naphthoxazine (SDZ NVI-085), a selective noradrenergic alpha 1 agonist. *Clinical Neuropharmacology*, Vol.21, pp. 108-117, ISSN 0362-5664
- Behrman, AL.; Cauraugh, JH. & Light, KE. (2000). Practice as an intervention to improve speeded motor performance and motor learning in Parkinson's disease. *Journal of the Neurological Sciences*, Vol.174, pp.127-136, ISSN 0022-510X
- Ben-Itzhak, R.; Giladi, N.; Gruendlinger, L. & Hausdorff JM. (2008). Can methylphenidate reduce fall risk in community-living older adults? A double-blind, single-dose

- cross-over study. *Journal of the American Geriatrics Society*, Vol.56, pp. 695–700, ISSN 0002-8614
- Bergen, JL.; Toole, T.; Elliott, RG.; Wallace, B.; Robinson, K. & Maitland, CG. (2002). Aerobic exercise intervention improves aerobic capacity and movement initiation in Parkinson's disease patients. *NeuroRehabilitation*, Vol.17, pp. 1621–1628, ISSN 1053-8135
- Ble, A.; Volpato, S.; Zuliani, G.; Guralnik, JM.; Bandinelli, S.; Lauretani, F.; Bartali, B.; Maraldi, C.; Fellin, R. & Ferrucci, L. (2005). Executive function correlates with walking speed in older persons: the InCHIANTI study. *Journal of the American Geriatrics Society*, Vol.53, No.3, (March), pp. 410-415, ISSN 0002-8614
- Bloem, BR.; Valkenburg, VV.; Slabbekoorn, M. & van Dijk, JG. (2001a). The multiple tasks test. Strategies in Parkinson's disease. *Experimental Brain Research*, Vol.137, No.3-4, pp. 478-486, ISSN 0014-4819
- Bloem, BR.; Valkenburg, VV.; Slabbekoorn, M. & Willemsen, MD. (2001b). The multiple tasks test: development and normal strategies. *Gait & Posture*, Vol.14, No.3, pp.191-202, ISSN 0966-6362
- Bloem, BR. & Bhatia, KP. (2004a). Gait and balance in basal ganglia disorders. In: *Clinical disorders of balance, posture and gait*, AM. Bronstein, T. Brandt, JG. Nutt, MH. Woollacott, (Eds.), 173-206, London: Arnold; ISBN 0-340-80657-5
- Bloem, BR.; Hausdorff, JM.; Visser, JE. & Giladi, N. (2004b). Falls and freezing of gait in Parkinson's disease: a review of two interconnected, episodic phenomena. *Movement Disorders*, Vol.19, pp. 871-884, ISSN 0885-3185
- Bloem, BR.; Grimbergen, YA.; van Dijk, JG. & Munneke, M. (2006). The "posture second" strategy: a review of wrong priorities in Parkinson's disease. *Journal of the Neurological Sciences*, Vol.248, No.1-2, pp. 196–204, ISSN 0022-510X
- Boonstra, TA.; van der Kooij, H.; Munneke, M. & Bloem, BR. (2008). Gait disorders and balance disturbances in Parkinson's disease: clinical update and pathophysiology. *Current Opinion in Neurology*, Vol.21, No.4, pp. 461-471, ISSN 1350-7540
- Bostan, AC.; Dum, RP. & Strick, PL. (2010). The basal ganglia communicate with the cerebellum. *Proceedings of the National Academy of Sciences of the United States of America*, Vol.107, No.18, (May 4), pp. 8452-8456, ISSN 0027-8424
- Brauer, SG. & Morris, ME. (2010). Can people with Parkinson's disease improve dual tasking when walking? *Gait Posture*, Vol.31, No.2, pp. 229-233, ISSN 0966-6362
- Brown, LA.; Cooper, SA.; Doan, JB.; Dickin, DC.; Whishaw, IQ.; Pellis, SM. & Suchowersky, O. (2006). Parkinsonian deficits in sensory integration for postural control: temporal response to changes in visual input. *Parkinsonism & Related Disorders*, Vol.12, pp. 376–381, ISSN 1353-8020
- Buckner, RL. (2004). Memory and executive function in aging and AD: multiple factors that cause decline and reserve factors that compensate. *Neuron*, Vol.44, pp.195-208, ISSN 0896-6273
- Burini, D.; Farabollini, B. & Iacucci, S. (2006). A randomized controlled cross-over trial of aerobic training versus qigong in advanced Parkinson's disease. *Europa Medicophysics*, Vol.4, pp. 231–238, ISSN 0014-2573

- Burke, SN. & Barnes, CA. (2006). Neural plasticity in the ageing brain. *Nature Reviews Neuroscience*, Vol.7, pp.30-40, ISSN 1471-003X
- Canning, CG.; Ada, L. & Woodhouse, E. (2008). Multiple-task walking training in people with mild to moderate Parkinson's disease: a pilot study. *Clinical Rehabilitation*, Vol.22, pp. 226-233, ISSN 0269-2155
- Chandler, J.; Duncan, PW.; Kochersberger, G. & Studenski, S. (1998). Is lower extremity strength gain associated with improvement in physical performance and disability in frail, community-dwelling elders? *Archives of Physical Medicine and Rehabilitation*, Vol.79, pp.24 -30, ISSN 0003-9993
- Christiansen, CL.; Schenkman, ML.; Kohrt WM, et al. (2009). Energy expenditure in people with Parkinson's disease during treadmill walking, Presented at: *Combined Sections Meeting of the American Physical Therapy Association*; pp. 9-12, February Las Vegas, Nevada.
- Clissold, BG.; McColl, CD.; Reardon, KR.; Shiff, M. & Kempster, PA. (2006). Longitudinal study of the motor response to levodopa in Parkinson's disease. *Movement Disorders*, Vol.21, pp. 2116-2121, ISSN 0885-3185
- Collette, F.; Hogge, M.; Salmon, E. & Van der Linden, M. (2006). Exploration of the neural substrates of executive functioning by functional neuroimaging. *Neuroscience*, Vol.139, No.1, pp. 209-221, ISSN 0306-4522
- Craik, FIM. & Grady, CL. (2002). Aging, memory, and frontal lobe functioning. In: *Principles of frontal lobe function*, D.T. Stuss, R.T. Knight (Eds.), Oxford University Press, p 528-540, New York
- Cubo, E.; Moore, CG.; Leurgans, S. & Goetz, CG. (2003). Wheeled and standard walkers in Parkinson's disease patients with gait freezing. *Parkinsonism & Related Disorders*, Vol.10, No.1, pp. 9-14, ISSN 1353-8020
- Dennison, AC.; Noorigian, JV.; Robinson, KM.; Fisman, DN.; Cianci, HJ.; Moberg, P.; Bunting-Perry, L.; Martine, R.; Duda, J. & Stern, MB. (2007). Falling in Parkinson disease: identifying and prioritizing risk factors in recurrent fallers. *American Journal of Physical Medicine & Rehabilitation*, Vol.86, pp. 621-632, ISSN 0894-9115
- Devos, D.; Krystkowiak, P.; Clement, F.; Dujardin, K.; Cottencin, O.; Waucquier, N.; Ajebbar, K.; Thielemans, B.; Kroumova, M.; Duhamel, A.; Destée, A.; Bordet, R. & Defebvre, L. (2007). Improvement of gait by chronic, high doses of methylphenidate in patients with advanced Parkinson's disease. *Journal of Neurology, Neurosurgery, and Psychiatry*, Vol.78, pp. 470-475, ISSN 0022-3050
- Dibble, LE.; Nicholson, DE.; Shultz, B.; MacWilliams, BA.; Marcus, RL. & Moncur, C. (2004). Sensory cueing effects on maximal speed gait initiation in persons with Parkinson's disease and healthy elders. *Gait & Posture*, Vol.19, pp. 215-225, ISSN 0966-6362
- Dibble, LE. & Lange, M. (2006). Predicting falls in individuals with Parkinson disease: a reconsideration of clinical balance measures. *Journal of Neurologic Physical Therapy*, Vol.30, pp. 60-67, ISSN 1557-0576
- Dibble, LE.; Christensen, J.; Ballard, DJ. & Foreman, KB. (2008). Diagnosis of fall risk in Parkinson disease: an analysis of individual and collective clinical balance test interpretation. *Physical Therapy*, Vol.88, pp. 323-332, ISSN 0031-9023

- Dietz, MA.; Goetz, CG. & Stebbins, GT. (1990). Evaluation of a modified inverted walking stick as a treatment for parkinsonian freezing episodes. *Movement Disorders*, Vol.5, pp. 243-247, ISSN 0885-3185
- Dietz, V. (2003). Spinal cord pattern generators for locomotion. *Clinical Neurophysiology*, Vol.114, No.8, pp. 1379-1389, ISSN 1388-2457
- Dobrossy, MD. & Dunnett, SB. (2003). Motor training effects on recovery of function after striatal lesions and striatal grafts. *Experimental Neurology*, Vol.184, pp. 274-284, ISSN 0014-4886
- Dreher, JC. & Grafman, J. (2003). Dissociating the roles of the rostral anterior cingulate and the lateral prefrontal cortices in performing two tasks simultaneously or successively. *Cerebral Cortex*, Vol.13, pp. 329-339, ISSN 1047-3211
- Dubois, B. & Pillon, B. (1997). Cognitive deficits in Parkinson's disease. *Journal of Neurology*, Vol.244, pp. 2-8, ISSN 0340-5354
- Ellis, T.; Goede, CJ.; Feldman, R.; Wolters, EC.; Kwakkel, G. & Wagenaar, RC. (2005). Efficacy of a physical therapy program in patients with Parkinson's disease: a randomised control trial. *Archives of Physical Medicine and Rehabilitation*, Vol.4, pp. 626-632, ISSN 0003-9993
- Falvo, MJ.; Schilling, BK. & Earhart, GM. (2008). Parkinson's disease and resistive exercise: rationale, review, and recommendations. *Movement Disorders*, Vol.23, pp. 1-11, ISSN 0885-3185
- Fisher, BE.; Wu, AD.; Salem, GJ.; Song, J.; Lin, CH.; Yip, J.; Cen, S.; Gordon, J.; Jakowec, M. & Petzinger, G. (2008). The effect of exercise training in improving motor performance and corticomotor excitability in people with early Parkinson's disease. *Archives of Physical Medicine and Rehabilitation*, Vol.89, No.7, pp. 1221-1229, ISSN 0003-9993
- Frazzitta, G; Maestri, R; Uccellini, D; Bertotti, G. & Abelli, P. (2009). Rehabilitation treatment of gait in patients with Parkinson's disease with freezing: a comparison between two physical therapy protocols using visual and auditory cues with or without treadmill training. *Movement Disorders*, Vol.24, pp.1139-1143, ISSN 0885-3185
- Gan, J.; Xie-Brustolin, J.; Mertens, P.; Polo, G.; Klinger, H.; Mollion, H.; Benatru, I.; Henry, E.; Broussolle, E. & Thobois, S. (2007). Bilateral subthalamic nucleus stimulation in advanced Parkinson's disease: three years follow-up. *Journal of Neurology*, Vol.254, pp. 99-106, ISSN 0340-5354
- Genever, RW.; Downes, TW. & Medcalf, P. (2005). Fracture rates in Parkinson's disease compared with age- and gender-matched controls: a retrospective cohort study. *Age and Ageing*, Vol.34, pp. 21-24, ISSN 0002-0729
- Gerin-Lajoie, M.; Richards, CL. & McFadyen, BJ. (2005). The negotiation of stationary and moving obstructions during walking: anticipatory locomotor adaptations and preservation of personal space. *Motor Control*, Vol.9, pp. 242-269, ISSN 1087-1640
- Giladi, N.; Gurevich, T.; Shabtai, H.; Paleacu, D. & Simon, ES. (2001). The effect of botulinum toxin injections to the calf muscles on freezing of gait in parkinsonism: a pilot study. *Journal of Neurology*, Vol.248, No.7, pp. 572-576, ISSN 0340-5354
- Giladi, N. & Nieuwboer A. (2008). Understanding and treating freezing of gait in parkinsonism, proposed working definition, and setting the stage. *Movement Disorders*, Vol.23, (Suppl 2), pp. S423-5, ISSN 0885-3185

- Gunning-Dixon, FM. & Raz, N. (2003). Neuroanatomical correlates of selected executive functions in middle-aged and older adults: a prospective MRI study. *Neuropsychologia*, Vol.41, pp. 1929-1941, ISSN 0028-3932
- Harrington, DL.; Haaland, KY.; Yeo, RA. & Marder, E. (1990). Procedural memory in Parkinson's disease: impaired motor but not visuoperceptual learning. *Journal of Clinical and Experimental Neuropsychology*, Vol.12, pp. 323-339, ISSN 1380-3395
- Hausdorff, JM.; Schaafsma, JD.; Balash, Y.; Bartels, AL.; Gurevich, T. & Giladi, N. (2003). Impaired regulation of stride variability in Parkinson's disease subjects with freezing of gait. *Experimental Brain Research*, Vol.149, pp. 187-194, ISSN 0014-4819
- Heindel, WC.; Salmon, DP.; Shults, CW.; Walicke, PA. & Butters, N. (1989). Neuropsychological evidence for multiple implicit memory systems: a comparison of Alzheimer's, Huntington's, and Parkinson's disease patients. *The Journal of Neuroscience*, Vol.9, No.2, pp.582-587, ISSN 0270-6474
- Hely, MA.; Reid, WG.; Adena, MA.; Halliday, GM. & Morris, JG. (2008). The Sydney multicenter study of Parkinson's disease: the inevitability of dementia at 20 years. *Movement Disorders*, Vol.23, pp.837-844, ISSN 0885-3185
- Holtzer, R.; Verghese, J.; Xue, X. & Lipton, RB. (2006). Cognitive processes related to gait velocity: results from the Einstein Aging Study. *Neuropsychology*, Vol.20, No.2, pp. 215-223, ISSN 0894-4105
- Hoshi, E., Tremblay, L., Féger, J., Carras, PL. & Strick, PL. (2005) The cerebellum communicates with the basal ganglia. *Nature Neuroscience*, Vol.8, No.11, pp1491-1493, ISSN 1097-6256
- Huxham, F.; Gong, J.; Baker, R.; Morris, M. & Iansek, R. (2006). Defining spatial parameters for nonlinear walking. *Gait & Posture*, Vol.23, pp. 159-163, ISSN: 0966-6362
- Jacobs, JV. & Horak, FB. (2006a). Abnormal proprioceptive-motor integration contributes to hypometric postural responses of subjects with Parkinson's disease. *Neuroscience*, Vol.141, pp. 999-1009, ISSN 0306-4522
- Jacobs, JV.; Horak, FB.; Tran, VK. & Nutt, JG. (2006b). Multiple balance tests improve the assessment of postural stability in subjects with Parkinson's disease. *Journal of Neurology, Neurosurgery, and Psychiatry*, Vol.77, No.3, pp. 322-326, ISSN 0022-3050
- Jacobs, JV.; Horak, FB.; Van, TK. & Nutt, JG. (2006c). An alternative clinical postural stability test for patients with Parkinson's disease. *Journal of Neurology*, Vol.253, pp. 1404-1413, ISSN 0340-5354
- Jankovic, J. (2009). Atomoxetine for freezing of gait in Parkinson disease. *Journal of the Neurological sciences*, Vol.284, No.1-2, (September), pp. 177-178, ISSN 0022-510X
- Johnson, AM.; Almeida, QJ.; Stough, C.; Thompson, JC.; Singarayer, R. & Jog, MS. (2004). Visual inspection time in Parkinson's disease: deficits in early stages of cognitive processing. *Neuropsychologia*, Vol.42, pp. 577-583, ISSN 0028-3932
- Kamata, N.; Matsuo, Y.; Yoneda, T.; Shinohara, H.; Inoue, S. & Abe, K. (2007). Overestimation of stability limits leads to a high frequency of falls in patients with Parkinson's disease. *Clinical Rehabilitation*, Vol.21, pp. 357-361, ISSN 0269-2155
- Kegelmeyer, DA.; Kloos, AD.; Thomas, KM. & Kostyk, SK. (2007). Reliability and validity of the tinetti mobility test for individuals with Parkinson disease. *Physical Therapy*, Vol.87, pp. 1369-1378, ISSN 0031-9023

- Kelly, VE.; Samii, A.; Slimp, JC.; Price, R.; Goodkin, R. & Shumway-Cook, A. (2006). Gait changes in response to subthalamic nucleus stimulation in people with Parkinson disease: a case series report. *Journal of Neurologic Physical Therapy*, Vol.30, pp. 184-194, ISSN 1557-0576
- Keus, SH.; Bloem, BR.; Hendriks, EJ.; Bredero-Cohen, AB. & Munneke, M. (2007). Evidence-based analysis of physical therapy in Parkinson's disease with recommendations for practice and research. *Movement Disorders*, Vol.22, pp. 451-460, ISSN 0885-3185
- King, LA. & Horak, FB. (2008). Lateral stepping for postural correction in Parkinson's disease. *Archives of Physical Medicine and Rehabilitation*, Vol.89, pp. 492-499, ISSN 0003-9993
- Korczyn, AD. (2001). Dementia in Parkinson's disease. *Journal of Neurology*, Vol.248 (Suppl 3), pp. III1-4, ISSN 0340-5354
- Lamberti, P.; Armenise, S.; Castaldo, V.; de Mari, M.; Iliceto, G.; Tronci, P. & Serlenga, L. (1997). Freezing gait in Parkinson's disease. *European Neurology*, Vol.38, pp. 297-301, ISSN 0014-3022
- Laurin, D.; Verreault, R.; Lindsay, J.; MacPherson, K. & Rockwood, K. (2001). Physical activity and risk of cognitive impairment and dementia in elderly persons. *Archives of Neurology*, Vol.58, pp. 498-504, ISSN 0003-9942
- Lee, AC. & Harris, JP. (1999). Problems with perception of space in Parkinson's disease. *Neuro-Ophthalmology*, Vol.22, pp. 1-15, ISSN 0165-8107
- Lee, MS.; Kim, HS. & Lyoo, CH. (2005). "Off" gait freezing and temporal discrimination threshold in patients with Parkinson disease. *Neurology*, Vol.64, pp. 670-674, ISSN 0028-3878
- Leu-Semenescu, S.; Roze, E.; Vidailhet, M.; Legrand, AP.; Trocello, JM.; Cochen, V.; Sangla, S. & Apartis E. (2007). Myoclonus or tremor in orthostatism: an under-recognized cause of unsteadiness in Parkinson's disease. *Movement Disorders*, Vol.22, No.14, (October), pp. 2063-2069, ISSN 0885-3185
- Li, KZ.; Roudaia, E.; Lussier, M.; Bherer, L.; Leroux, A. & McKinley, PA. (2010). Benefits of cognitive dual-task training on balance performance in healthy older adults. *The Journals of Gerontology. Series A, Biological Sciences and Medical Sciences*, Vol.65, No.12, pp. 1344-1352, ISSN 1079-5006
- Lindenberger, U.; Marsiske, M. & Baltes, PB. (2000). Memorizing while walking: increase in dual-task costs from young adulthood to old age. *Psychology and Aging*, Vol.15, pp. 417-436, ISSN 0882-7974
- Lundin-Olsson, L.; Nyberg, L. & Gustafson, Y. (1997). "Stops walking when talking" as a predictor of falls in elderly people. *Lancet*, Vol.349, No.9052, (March), pp. 617, ISSN 0140-6736
- MacDonald, AW. 3rd.; Cohen, JD.; Stenger, VA. & Carter, CS. (2000). Dissociating the role of the dorsolateral prefrontal and anterior cingulate cortex in cognitive control. *Science*, Vol.288, pp. 1835-1838, ISSN 0036-8075
- Macht, M.; Kaussner, Y.; Möller, JC.; Stiasny-Kolster, K.; Eggert, KM.; Krüger, HP. & Ellgring, H. (2007). Predictors of freezing in Parkinson's disease: a survey of 6,620 patients. *Movement Disorders*, Vol.22, No.7, 953-956, ISSN 0885-3185
- Martin JP. (1967). *The basal ganglia and posture*. Pitman Medical, ASIN B0000CNL13, London

- Melton, L.J. 3rd, Leibson, CL.; Achenbach, SJ.; Bower, JH.; Maraganore, DM.; Oberg, AL. & Rocca, WA. (2006). Fracture risk after the diagnosis of Parkinson's disease: influence of concomitant dementia. *Movement Disorders*, Vol.21, No.9, pp. 1361-1367, ISSN 0885-3185
- Mille, ML.; Johnson, HM.; Martinez, KM.; Simuni, T. & Rogers, MW. (2007). Acute effects of a lateral postural assist on voluntary step initiation in patients with Parkinson's disease. *Movement Disorders*, Vol.22, No.1, pp. 20-27, ISSN 0885-3185
- Mirelman, A.; Maidan, I.; Herman, T.; Deutsch, JE.; Giladi, N. & Hausdorff, JM. (2011). Virtual reality for gait training: can it induce motor learning to enhance complex walking and reduce fall risk in patients with Parkinson's disease? *The Journals of Gerontology. Series A, Biological Sciences and Medical Sciences*, Vol.66, No.4, (February), pp. 234-240, ISSN 1079-5006
- Moore, O.; Peretz, C. & Giladi, N. (2007a). Freezing of gait affects quality of life of peoples with Parkinson's disease beyond its relationships with mobility and gait. *Movement Disorders*, Vol.22, pp. 2192-2195, ISSN 0885-3185
- Moore, ST.; Macdougall, HG.; Gracies, JM.; Cohen, HS. & Ondo, WG. (2007b). Long-term monitoring of gait in Parkinson's disease. *Gait & Posture*, Vol.26, No.2, pp. 200-207, ISSN 0966-6362
- Moore, ST.; MacDougall, HG. & Ondo, WG. (2008). Ambulatory monitoring of freezing of gait in Parkinson's disease. *Journal of Neuroscience Methods*, Vol.167, No.2, pp. 340-348, ISSN 0165-0270
- Moreau, C.; Defebvre, L.; Destée, A.; Bleuse, S.; Clement, F.; Blatt, JL.; Krystkowiak, P. & Devos, D. (2008). STN-DBS frequency effects on freezing of gait in advanced Parkinson disease. *Neurology*, Vol.71, No.2, pp. 80-84, ISSN 0028-3878
- Morris ME. (2000). Movement disorders in people with Parkinson disease: a model for physical therapy. *Physical Therapy*, Vol.80, pp. 578-597, ISSN 0031-9023
- Morris, ME. (2006). Locomotor training in people with Parkinson disease. *Physical Therapy*, Vol.86, pp. 1426-1435, ISSN 0031-9023
- Morris, ME.; Iansek, R. & Kirkwood, B. (2009). A randomized controlled trial of movement strategies compared with exercise for people with Parkinson's disease. *Movement Disorders*, Vol.24, pp. 64 -71, ISSN 0885-3185
- Morris, ME.; Martin, CL. & Schenkman, ML. (2010). Striding out with Parkinson disease: evidence-based physical therapy for gait disorders. *Physical Therapy*, Vol.90, No.(2), pp. 280-288, ISSN 0031-9023
- Nakamura, T.; Meguro, K. & Sasaki, H. (1996). Relationship between falls and stride length variability in senile dementia of the Alzheimer type. *Gerontology*, Vol.42, pp. 108-113, ISSN 0304-324X
- Narabayashi, H.; Kondo, T.; Yokochi, F. & Nagatsu, T. (1987). Clinical effects of L-threo-3,4-dihydroxyphenylserine in cases of parkinsonism and pure akinesia. *Advances in Neurology*, Vol.45, pp. 593-602, ISSN: 0091-3952
- Nieuwboer, A.; Dom, R.; De Weerd, W.; Desloovere, K.; Fieuws, S. & Broens-Kaucsik, E. (2001). Abnormalities of the spatiotemporal characteristics of gait at the onset of freezing in Parkinson's disease. *Movement Disorders*, Vol.16, No.6, pp. 1066-1075, ISSN 0885-3185

- Nieuwboer, A.; Dom, R.; De Weerd, W.; Desloovere, K.; Janssens, L. & Stijn, V. (2004). Electromyographic profiles of gait prior to onset of freezing episodes in patients with Parkinson's disease. *Brain: a Journal of Neurology*, Vol.127, No. 7, pp.1650-1660, ISSN 0006-8950
- Nieuwboer, A.; Kwakkel, G.; Rochester, I.; Jones, D.; van Wegen, E.; Willems, AM.; Chavret, F.; Hetherington, V.; Baker, K. & Lim, I. (2007). Cueing training in the home improves gait-related mobility in Parkinson's disease: the RESCUE trial. *Journal of Neurology, Neurosurgery, and Psychiatry*, Vol.78, pp. 134-140, ISSN 0022-3050
- Nieuwboer, A.; Rochester, L.; Herman, T.; Vandenberghe, W.; Emil, GE.; Thomaes, T. & Giladi, N. (2009). Reliability of the new freezing of gait questionnaire: agreement between patients with Parkinson's disease and their carers. *Gait & Posture*, Vol.30, pp. 459-463, ISSN 0966-6362
- Pahapill, PA. & Lozano, AM. (2000). The pedunculopontine nucleus and Parkinson's disease. *Brain*, Vol.123, pp. 767-783, ISSN 0006-8950
- Parkinson Study Group. (2001). Dopamine transporter brain imaging to assess the effects of pramipexole vs levodopa on Parkinson disease progression. *JAMA*, Vol.287, No.13, pp. 1653-1661, ISSN 0098-7484
- Parkinson Study Group. (2003). Does levodopa slow or hasten the rate of progression of Parkinson's disease? The results of the ELLDOPA trial. *Neurology*, Vol.60, No.5, (Suppl 1), pp. A80-A81, ISSN 0028-3878
- Peppe, A.; Ranaldi, A.; Chiavalon, C.; Gasbarra, A.; Colleparado, A.; Romeo, R.; Pasqualetti, P. & Caltagirone, C. (2007). Global Mobility Task: index for evaluating motor impairment and motor rehabilitation programs in Parkinson's disease patients. *Acta Neurologica Scandinavica*, Vol.116, No.3, pp. 182-189, ISSN 0001-6314
- Peretz, C.; Herman, T.; Hausdorff, JM. & Giladi, N. (2006). Assessing fear of falling: can a short version of the activities-specific balance confidence scale be useful? *Movement Disorders*, Vol. 21, pp. 2101-2105, ISSN 0885-3185
- Pickering, RM.; Grimbergen, YA.; Rigney, U.; Ashburn, A.; Mazibrada, G.; Wood, B.; Gray, P.; Kerr, G. & Bloem, BR. (2007). A meta-analysis of six prospective studies of falling in Parkinson's disease. *Movement Disorders*, Vol.22, pp. 1892-1900, ISSN 0885-3185
- Plotnik, M.; Giladi, N. & Hausdorff, JM. (2007). A new measure for quantifying the bilateral coordination of human gait: effects of aging and Parkinson's disease. *Experimental Brain Research*, Vol.181, pp. 561-570, ISSN 0014-4819
- Plotnik, M. & Hausdorff, JM. (2008). The role of gait rhythmicity and bilateral coordination of stepping in the pathophysiology of freezing of gait in Parkinson's disease. *Movement Disorders* Vol.23 (Suppl 2), pp. S444-S450, ISSN 0885-3185
- Plotnik, M.; Giladi, N. & Hausdorff, JM. (2009). Bilateral coordination of gait and Parkinson's disease: the effects of dual tasking. *Journal of Neurology, Neurosurgery, and Psychiatry*, Vol.80, No. 3, (March), pp. 347-350, ISSN 0022-3050
- Plotnik, M.; Giladi, N.; Dagan, Y. & Hausdorff, JM. (2011a). Postural instability and fall risk in Parkinson's disease: impaired dual tasking, pacing, and bilateral coordination of gait during the "ON" medication state. *Experimental Brain Research*, Jan 30. [Epub ahead of print]

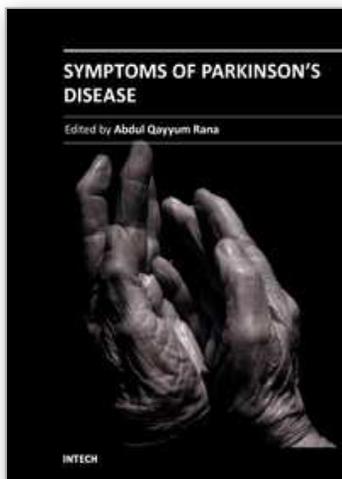
- Plotnik, M.; Dagan, Y.; Gurevich, T.; Giladi, N. & Hausdorff, JM. (2011b). Effects of cognitive function on gait and dual tasking abilities in patients with Parkinson's disease suffering from motor response fluctuations. *Experimental Brain Research*, Vol.208, No.2, pp. 169-179, ISSN 0014-4819
- Pollak, L.; Dobronevsky, Y.; Prohorov, T.; Bahunker, S. & Rabey, JM. (2007). Low dose methylphenidate improves freezing in advanced Parkinson's disease during off-state. *Journal of Neural Transmission. Supplementum*, Vol.72, pp. 145-148, ISSN 0303-6995
- Protas, EJ.; Stanley, RK.; Jankovic, J. & MacNeill, B. (1996). Cardiovascular and metabolic responses to upper- and lower-extremity exercise in men with idiopathic Parkinson's disease. *Physical Therapy*, Vol.76, pp. 34-40, ISSN 0031-9023
- Quinn, N.; Perlmutter, J. & Marsden, CD. (1984). Acute administration of L-Threo-DOPS does not affect the freezing phenomenon in parkinsonian patients. *Neurology*, Vol.34, pp. 149A, ISSN 0028-3878
- Rascol, O.; Brooks, DJ.; Korczyn, AD.; De Deyn, PP.; Clarke, CE. & Lang, AE. (2000). A five-year study of the incidence of dyskinesia in patients with early Parkinson's disease who were treated with ropinirole or levodopa. *The New England journal of medicine*, Vol.342, pp. 1484-1491, ISSN 0028-4793
- Reuter, I.; Leone, P.; Schwed, M. & Oechsner, M. (2006). Effect of Nordic walking in Parkinson's disease. *Movement Disorders*, Vol.21, pp. S567, ISSN 0885-3185
- Rochester, L.; Hetherington, V.; Jones, D.; Nieuwboer, A.; Willems, AM.; Kwakkel, G. & Van Wegen, E. (2004). Attending to the task: interference effects of functional tasks on walking in Parkinson's disease and the roles of cognition, depression, fatigue, and balance. *Archives of Physical Medicine and Rehabilitation*, Vol.85, pp. 1578-1585, ISSN 0003-9993
- Rochester, L.; Nieuwboer, A.; Baker, K.; Hetherington, V.; Willems, AM.; Chavret, F.; Kwakkel, G.; Van Wegen, E.; Lim, I. & Jones, D. (2007). The attentional cost of external rhythmical cues and their impact on gait in Parkinson's disease: effect of cue modality and task complexity. *Journal of Neural Transmission*, Vol.114, pp. 1243-1248, ISSN 0300-9564
- Schaafsma, JD.; Giladi, N.; Balash, Y., Bartels, AL., Gurevich, T. & Hausdorff, JM. (2003). Gait dynamics in Parkinson's disease: relationship to Parkinsonian features, falls and response to levodopa. *Journal of the Neurological Sciences*, Vol.212, pp. :47-53, ISSN 0022-510X
- Schenkman, ML. & Butler, RB. (1989). A model for multisystem evaluation treatment of individuals with Parkinson's disease. *Physical Therapy*, Vol.69, pp. 932-944, ISSN 0031-9023
- Schenkman, ML.; Cutson, TM.; Kuchibhatla, M.; Chandler, J.; Pieper, CF.; Ray, L. & Laub, KC. (1998). Exercise to improve spinal flexibility and function for people with Parkinson's disease: a randomized, controlled trial. *Journal of the American Geriatrics Society*, Vol.46, pp. 1207-1216, ISSN 0002-8614
- Schenkman, ML.; Morey, M. & Kuchibhatla, M. (2000). Spinal flexibility and balance control among community-dwelling adults with and without Parkinson's disease. *The*

- Journals of Gerontology. Series A, Biological Sciences and Medical Sciences*, Vol.55, pp. M441-M445, ISSN 1079-5006
- Schenkman, ML.; Hall, D., Kumar, R. & Kohrt, WM. (2008). Endurance exercise training to improve economy of movement of people with Parkinson disease: three case reports. *Physical Therapy*, Vol.88, pp. 63-76, ISSN 0031-9023
- Schrodt, LA.; Mercer, VS.; Giuliani, CA. & Hartman, M. (2004). Characteristics of stepping over an obstacle in community dwelling older adults under dual-task conditions. *Gait & Posture* Vol.19, pp. 279-287, ISSN 0966-6362
- Simuni, T. & Sethi, K. (2008). Nonmotor manifestations of Parkinson's disease. *Annals of Neurology*, Vol.64 (Suppl 2), pp. S65-S80, ISSN 0364-5134
- Snijders, AH.; van de Warrenburg, BP.; Giladi, N. & Bloem, BR. (2007). Neurological gait disorders in elderly people: clinical approach and classification. *Lancet Neurology*, Vol.6, pp. 63-74, ISSN 1474-4422
- Soliveri, P.; Brown, RG.; Jahanshahi, M.; Caraceni, T. & Marsden, CD. (1997), Learning manual pursuit tracking skills in patients with Parkinson's disease. *Brain: a Journal of Neurology*, Vol.120, pp. 1325-1337, ISSN 0006-8950
- Srygley, JM.; Mirelman, A.; Herman, T.; Giladi, N. & Hausdorff, JM. (2009). When does walking alter thinking? Age and task associated findings. *Brain Research*, Vol.1253, pp. 92-99, ISSN 0006-8993
- Stefani, A.; Lozano, AM.; Peppe, A.; Stanzione, P.; Galati, S.; Tropepi, D.; Pierantozzi, M.; Brusa, L.; Scarnati, E. & Mazzone, P. (2007). Bilateral deep brain stimulation of the pedunculopontine and subthalamic nuclei in severe Parkinson's disease. *Brain: a Journal of Neurology*, Vol.130, pp. 1596-1607, ISSN 0006-8950
- Stuss, DT. & Alexander, MP. (2000). Executive functions and the frontal lobes: a conceptual view. *Psychological Research*, Vol.63, pp. 289-298, ISSN 0340-0727
- Stuss, DT. & Levine, B. (2002). Adult clinical neuropsychology: lessons from studies of the frontal lobes. *Annual Review of Psychology*, Vol.53, pp. 401-433, ISSN 0066-4308
- Thanvi, B. & Treadwell, SD. (2010). Freezing of gait in older people: associated conditions, clinical aspects, assessment and treatment. *Postgraduate Medical Journal*, Vol.86, No.1018, pp. 472-477, ISSN 0032-5473
- Tillerson, JL.; Caudle, WM.; Reveron, ME. & Miller, GW. (2003). Exercise induces behavioral recovery and attenuates neurochemical deficits in rodent models of Parkinson's disease. *Neuroscience*, Vol.119, pp. 899-911, ISSN 0306-4522
- Timmermann, L. & Fink, GR. (2009). Modulating pathological oscillatory activity in Parkinson's disease: What's the rhythm? *Experimental Neurology*, Vol.215, No.2, pp. 209-211, ISSN 0014-4886
- Tommasi, G.; Lopiano, L.; Zibetti, M.; Cinquepalmi, A.; Fronda, C.; Bergamasco, B.; Ducati, A. & Lanotte, M. (2007). Freezing and hypokinesia of gait induced by stimulation of the subthalamic region. *Journal of the Neurological Sciences*, Vol.258, pp. 99-103, ISSN 0022-510X
- Twelves, D.; Perkins, KS. & Counsell, C. (2003). Systematic review of incidence studies of Parkinson's disease. *Movement Disorders*, Vol.18, No.1, pp.19-31, ISSN 0885-3185

- Valkovic, P.; Krafczyk, S. & Botzel, K. (2006). Postural reactions to soleus muscle vibration in Parkinson's disease: scaling deteriorates as disease progresses. *Neuroscience Letters*, Vol.401, pp. 92-96, ISSN 0304-3940
- van der Kooij, H.; van Asseldonk, EH.; Geelen, J.; van Vugt, JP. & Bloem, BR. (2007). Detecting asymmetries in balance control with system identification: first experimental results from Parkinson patients. *Journal of Neural Transmission*, Vol.114, pp. 1333-1337, ISSN 0300-9564
- van Eijkeren, FJ.; Reijmers, RS.; Kleinveld, MJ.; Minten, A., Bruggen, JP. & Bloem, BR. (2008). Nordic walking improves mobility in Parkinson's disease. *Movement Disorders*, Vol.23, No.15, pp. 2239-2243, ISSN 0885-3185
- van Gelder, BM.; Tijhuis, MA.; Kalmijn, S., Giampaoli, S.; Nissinen, A. & Kromhout, D. (2004). Physical activity in relation to cognitive decline in elderly men: the FINE Study. *Neurology*, Vol.63, pp. 2316-2321, ISSN 0028-3878
- van Iersel, MB.; Verbeek, AL.; Bloem, BR.; Munneke, M., Esselink, RA. & Rikkert, MG. (2006). Frail elderly patients with dementia go too fast. *Journal of Neurology, Neurosurgery, and Psychiatry*, Vol.77, pp. 874-876, ISSN 0022-3050
- Vaugoyeau, M., Viel, S.; Assaiante, C.; Amblard, B. & Azulay, JP. (2007). Impaired vertical postural control and proprioceptive integration deficits in Parkinson's disease. *Neuroscience* Vol.146, pp. 852-863, ISSN 0306-4522
- Vergheze, J.; Mahoney, J.; Ambrose, AF.; Wang, C. & Holtzer, R. (2010). Effect of cognitive remediation on gait in sedentary seniors. *The Journals of Gerontology. Series A, Biological Sciences and Medical Sciences*, Vol.65, No.12, pp. 1338-1343, ISSN 1079-5006
- Visser, JE.; Voermans, NC.; Oude Nijhuis, LB.; van der Eijk, M.; Nijk, R.; Munneke, M. & Bloem, BR. (2007). Quantification of trunk rotations during turning and walking in Parkinson's disease. *Clinical Neurophysiology*, Vol.118, pp. 1602-1606, ISSN 1388-2457
- Visser, M.; Verbaan, D.; van Rooden, S.; Marinus, J.; van Hilten, J. & Stiggelbout, A. (2009). A longitudinal evaluation of health-related quality of life of patients with Parkinson's disease. *Value Health*, Vol.12, pp. 392-396, ISSN 1098-3015
- Willems, AM.; Nieuwboer, A.; Chavret, F.; Desloovere, K.; Dom, R.; Rochester, L.; Kwakkel, G.; van Wegen, E. & Jones, D. (2007). Turning in Parkinson's disease patients and controls: the effect of auditory cues. *Movement Disorders*, Vol.22, pp. 1871-1878, ISSN 0885-3185
- Williams, DR.; Watt, HC. & Lees, AJ. (2006). Predictors of falls and fractures in bradykinetic rigid syndromes: a retrospective study. *Journal of Neurology, Neurosurgery, and Psychiatry*, Vol.77, pp. 468-473, ISSN 0022-3050
- Wright, WG.; Gurfinkel, VS.; Nutt, J.; Horak, FB. & Cordo, PJ. (2007). Axial hypertonicity in Parkinson's disease: direct measurements of trunk and hip torque. *Experimental Neurology*, Vol.208, pp. 38-46, ISSN 0014-4886
- Yaffe, K.; Barnes, D.; Nevitt, M.; Lui, LY. & Covinsky, K. (2001). A prospective study of physical activity and cognitive decline in elderly women: women who walk. *Archives of Internal Medicine*, Vol.161, pp. 1703-1708, ISSN 0730-188X
- Yelnik, J. (2007). PPN or PPD, what is the target for deep brain stimulation in Parkinson's disease? *Brain: a Journal of Neurology*, Vol.130, (Pt6), pp. 1596-607, ISSN 0006-8950

- Yogev, G.; Giladi, N.; Peretz, C.; Springer, S.; Simon, ES, & Hausdorff, JM. (2005). Dual tasking, gait rhythmicity, and Parkinson's disease: which aspects of gait are attention demanding? *The European Journal of Neuroscience*, Vol.22, pp. 1248-1256, ISSN 0953-816X
- Yogev-Seligmann, G.; Hausdorff, JM. & Giladi, N. (2008). The role of executive function and attention in gait. *Movement Disorders*, Vol.23, No.3, pp. 329-342, ISSN 0885-3185
- Zúñiga, C.; Lester, J.; Cersósimo, MG.; Díaz, S. & Micheli, FE. (2006). Treatment of primary progressive freezing of gait with high doses of selegiline. *Clinical Neuropharmacology*, Vol.29, pp. 20-21, ISSN 0362-5664

IntechOpen



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>

INTECH
open science | open minds

InTech Europe

University Campus STeP Ri
Slavka Krautzeka 83/A
51000 Rijeka, Croatia
Phone: +385 (51) 770 447
Fax: +385 (51) 686 166
www.intechopen.com

InTech China

Unit 405, Office Block, Hotel Equatorial Shanghai
No.65, Yan An Road (West), Shanghai, 200040, China
中国上海市延安西路65号上海国际贵都大饭店办公楼405单元
Phone: +86-21-62489820
Fax: +86-21-62489821

© 2011 The Author(s). Licensee IntechOpen. This chapter is distributed under the terms of the [Creative Commons Attribution-NonCommercial-ShareAlike-3.0 License](#), which permits use, distribution and reproduction for non-commercial purposes, provided the original is properly cited and derivative works building on this content are distributed under the same license.

IntechOpen

IntechOpen