Aus dem Zentrum für Neurologie
Neurologische Universitätsklinik Tübingen /
Hertie Institut für klinische Hirnforschung
Abteilung Neurologie mit Schwerpunkt
Neurodegenerative Erkrankungen
Ärztlicher Direktor: Prof. Dr. T. Gasser

The Effect of Dopaminergic Medication on Straight Walking and Turning in Parkinson's Disease Patients during Single and Dual Tasking

Inaugural-Dissertation
zur Erlangung des Doktorgrades
der Humanwissenschaften

der Medizinischen Fakultät
der Eberhard Karls Universität
zu Tübingen

vorgelegt von
Elshehabi, Morad

2019

Dekan: Prof. Dr. I. B. Autenrieth

1. Berichterstatter: Prof. Dr. Walter Maetzler
2. Berichterstatter: PD Dr. Axel Lindner

Tag der Disputation: 25.06.2020

To my mother and two brothers…

Table of Contents

List of Abbreviations

APA	Anticipatory Postural Adjustment
BDI-II	Beck Depression Inventory, second version
CB	Checking boxes
DBS	Deep Brain Stimulation
DLST	Double Limb Support Time
DLTV	Double Limb Support Time Variability
DT	Dual Tasking
ft	Feet
HrQoL	Health-related Quality of Life
IMU	Inertial Measurement Unit
iSAW	Instrumented Stand and Walk
iSWAY	Instrumented Sway
iTUG	Instrumented Time Up and Go
iWALK	Instrumented Long Walk
m	Meter(s)
min	Minute(s)
MAOBIs	Monoamine Oxidase Type B Inhibitors
MCI	Minimum Clinical Improvement
MMSE	Mini Mental State Examination

MWW	Mann–Whitney–Wilcoxon test
PD	Parkinson's Disease
PIGD	Postural Instability Gait Disability
RBD	Rapid Eye Movement Sleep Behaviour Disorder
s	Second(s)
SD	Standard Deviation
SN	Substantia Nigra
SNpc	Substantia Nigra pars compacta
ST	Single Tasking
STN	Subthalamic Nucleus
SS	Serial subtraction
TMT	Trail Making Test
UKPDS	UK Parkinson's Disease Society Brain Bank Clinical Diagnostic Criteria
UPDRS	Unified Parkinson's Disease Rating Scale
VTA	Ventral Tegmental Area

1. Introduction

1.1. Epidemiology and Pathoanatomy of Parkinson's Disease

The idea of neuronal loss with the progress of age was first proposed by Hodge in 1894 (Hodge 1894). Several studies have further investigated and confirmed a specific form of this phenomenon specifically in the Substania Nigra (SN) (Mann and Yates 1983; McGeer et al. 1988; Fearnley and Lees 1991). The death of the dopamine releasing neurons in the SN is then manifested in the form of Parkinson's Disease (PD) (Michel, Hirsch, and Hunot 2016; Dauer and Przedborski 2003). James Parkinson was first to describe the disease in his classic "An Essay on the Shaking Palsy" (Parkinson et al. 2002) and since then, we have come a long way in understanding the nature and course of the disease. The disease is characterized by its cardinal symptoms: bradykinesia, tremor, rigidity and impaired postural reflexes (note that this is according to the UK Parkinson's Disease Society Brain Bank (UKPDSB) Clinical Diagnostic Criteria (Hughes et al. 1992) that may be substituted by new criteria (Postuma et al. 2015) that no longer include postural reflex deficits in the cardinal criteria). This work is based on the UKPDSB criteria. These motor symptoms are central to the diagnosis of PD. In addition, increased attention is given to the non-motor symptoms of the disease particularly in the prodromal and early stages (Postuma et al. 2015).

Epidemiology

PD is the second most common neurodegenerative disease after Alzheimer's disease (Lau and Breteler 2006). Studies focusing on the epidemiology of PD have shown a prevalence rate between 5 and 346 per 100.000 persons in Europe (Von Campenhausen et al. 2005; Van Den Eeden 2003; Dauer and Przedborski 2003). New calculations (Heinzel et al. 2018) suggest that the wide range of reported incident rates might be due to different methodologies of these studies

and the incident rate may be even higher than previously reported due to the obscure nature of the disease and its symptoms. The risk of developing PD has been shown to be associated with several factors such as age, gender, ethnicity and (other) environmental factors (Tysnes and Storstein 2017; Van Den Eeden 2003). The risk of PD increases as age progresses, particularly after the age of 60 years (Von Campenhausen et al. 2005; de Rijk et al. 2000; Van Den Eeden 2003). Studies investigating the prevalence of PD found that males are more susceptible to the disease compared to females (Li et al. 1985; Mayeux et al. 1995; Fall et al. 1996). Oestrogen has been suggested as neuroprotective and hence can lower the risk of developing PD but its role is controversial (Saunders-Pullman 2003).

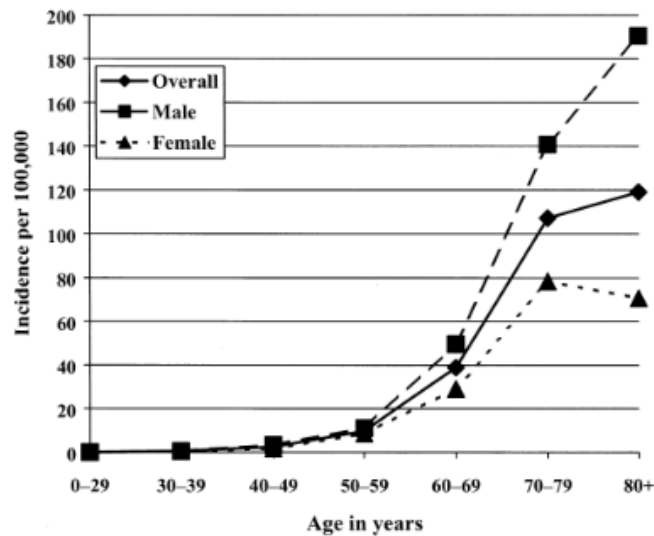**Figure1:** PD incidence by both age and gender (Van Den Eden, 2002)

Pathoanatomy

The disease affects many different neurotransmitter systems; however, the dopaminergic system, especially the neurons located in the SN, show early degeneration during the disease course of PD. Their pathological and microscopic changes precede the clinical presentation up to decades (Lang 2011; Stern, Lang, and Poewe 2012).

A sequence of changes develops in affected neurons. These neurons eventually form Lewy bodies in the perikarya and Lewy neurites in the neuronal processes. Lewy bodies contain abnormally phosphorylated neurofilaments as well as other components such as ubiquitin and alpha-synuclein (Baba et al. 1998; Gai, Blumbergs, and Blessing 1995). These protein components lose their functions long before the affected neurons degenerate (Braak and Braak 2000).

The cell bodies of the nigrostriatal neurons (located in the SN pars compacta (SNpc)) project mainly to the putamen and the loss of these neurons leads to the classical SNpc depigmentation (Dauer and Przedborski 2003). In contrast, the mesolimbic dopaminergic neurons, with their cell bodies neighbouring the SNpc in the ventral tegmental

Figure 2: A. A normally pigmented Substantia Nigra (SN) projecting neurons from the Substantia Nigra pars compacta (SNpc) and ventral tegmental area (VTA) to the putamen and caudate nuclei respectively. B. In PD, neuronal loss in the SNpc leads to depigmentation in the SNpc while the VTA remains considerably intact. Therefore, the strength of the projection to the putamen is diminished, while the projection to the caudate is affected less. C) The pathohistology of the degenerated neurons containing Lewy Bodies; to the left those with alpha-synuclein and to the right those including ubiquitin (Dauer and Przedborski 2003).

area (VTA), project their neurons to the caudate and are not as affected in PD. Hence, the dopamine transporter loss is most prominent in the putamen but less so in the caudate nucleus (Niznik et al. 1991; Dauer and Przedborski 2003).

The disease starts to present itself clinically when about 80% of the putaminal dopamine transporter and 60% of the neurons are already lost. This degeneration in the neurons projected from the SN affects the functions of various brain areas such as the motor cortex, the limbic system and the amygdala, leading to the
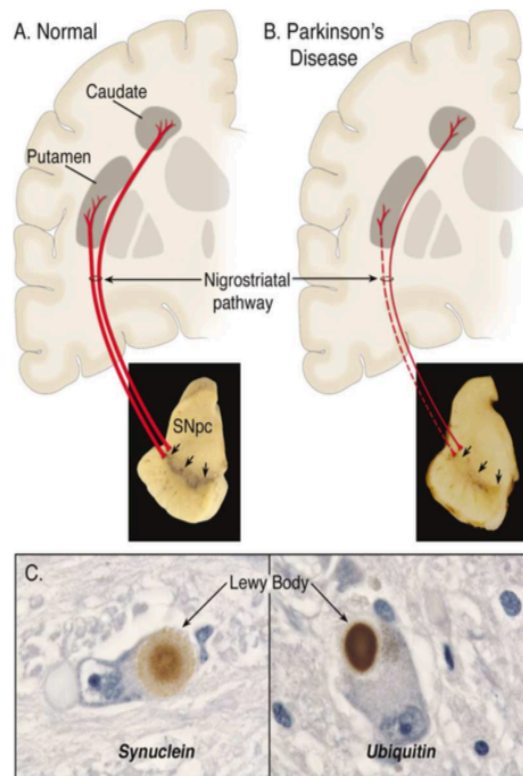
classical observed symptoms of PD (Braak and Braak 2000). Figure 2 provides histological information about these processes.

1.2.   Clinical Features

For a long time, PD has been known mostly for its motor symptoms. Recently, more emphasis has been put on the non-motor aspects of the disease even if the cardinal motor symptoms maintain their importance (Postuma et al. 2015; Postuma et al. 2016).

1.2.1. Motor Symptoms

The understanding of the disease and its motor symptoms is still evolving and changing (Postuma et al. 2016; Postuma et al. 2015). There is a plethora of motor signs and symptoms associated with PD (Mazzoni, Shabbott, and Cortés 2012). The cardinal signs of PD are bradykinesia, rigidity, tremor and loss of postural flexibility (Gelb, Oliver, and Gilman 1999; Goetz et al. 2008; Lees, Hardy, and Revesz 2009; Fahn et al. 2004). Here, I do not describe these cardinal symptoms in detail but focus on the main motor signs and symptoms related to the work at hand i.e.: gait-related symptoms.

Gait & Posture

The disease has a characteristic pattern of movement particularly in the gait and posture domain. Posture abnormalities such as flexed posture (stooped posture), camptocormia (abnormal thoracolumbar flexion), antecollis (abnormal neck flexion of minimum 45°), Pisa syndrome (lateral flexion of more than 10° in the spine) and scoliosis are commonly observed in PD (Jankovic 2008; Doherty et al. 2011; Mazzoni, Shabbott, and Cortés 2012). During walking, the clinician can observe shortened and variable steps, a decrease in pace and diminished arm swing among other characteristics (Schaafsma et al. 2003; Morris et al. 1998). A more elaborate assessment of gait in PD, using advanced technology, reveals flat foot strikes (in extreme situations, the toe can even hit the ground before the heel), prolonged double limb support time, and increased step-to-step and stride-

to-stride variability (Hughes et al. 1990; Schaafsma et al. 2003; Morris et al. 1998; Brauer and Morris 2010; Boonstra et al. 2008).
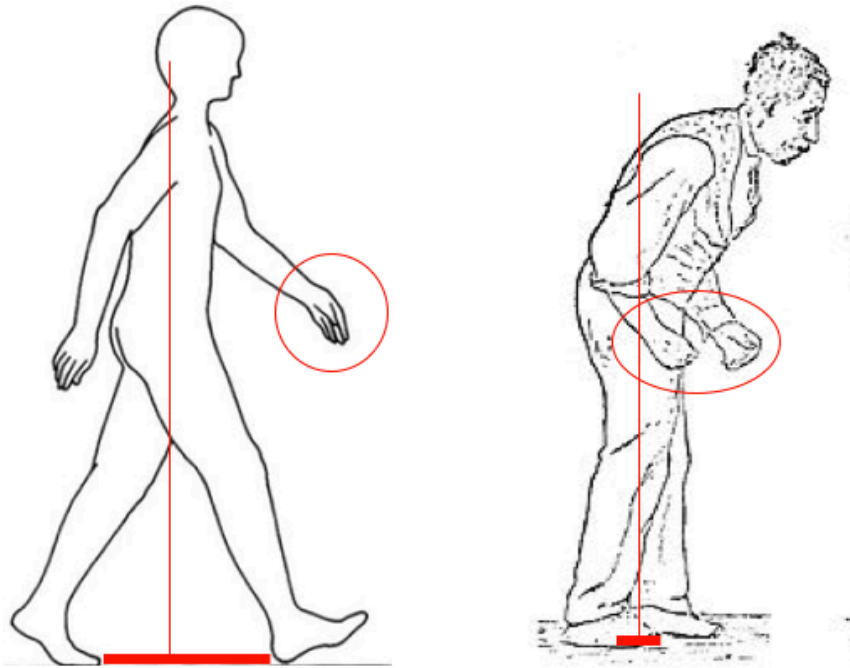
Figure 3: A normal posture and gait (left) and a classical demonstration of a PD patient (right, adapted from the original work of James Parkinson).

Furthermore, a combination of motor and cognitive (discussed below) impairments increases the risk of falling, often during turning (Haertner et al. 2018). Rigidity and bradykinesia have been reported to cause impairments in interlimb coordination in PD patients (Winogrodzka et al. 2005). Moreover, freezing of gait (interruption of walking sequences) have been documented as a common feature of PD (Jankovic 2008).

Other Motor Symptoms

PD patients often show many additional motor symptoms that vary in severity depending on the disease stage and medication. These symptoms include akinesia (delayed initiation of movement and poverty of movement), hypokinesia (reduced amplitude of movement), dexterity and difficulties standing up and

performing motor dual tasking (DT) (Mazzoni, Shabbott, and Cortés 2012). Moreover, difficulties with speech, writing and swallowing are common, especially in advanced stages of the disease (Mazzoni, Shabbott, and Cortés 2012).

1.2.2. Non-Motor Symptoms

There is a persistent perception of PD as a dominantly motor syndrome, and that motor symptoms have a central role in the disease and patient's life. Yet, more attention has been given recently to non-motor symptoms of PD (Postuma et al. 2016). These symptoms are common, relevant to daily life activities and the quality of life (van Uem et al. 2016). Therefore, a better understanding of them and the effect of the treatment of choice is important. Furthermore, several non-motor symptoms such as rapid eye movement sleep behaviour disorder (RBD) and hyposmia, have been shown to clinical present themselves often before any motor symptom is clinically observed (Poewe 2008; Postuma et al. 2012; Muslimovic et al. 2005).

The non-motor symptoms of PD can be grouped into the following (Park and Stacy 2009; Chaudhuri, Healy, and Schapira 2006):

Cognitive Symptoms

These symptoms are presented in more detail as they are specifically relevant for the topic of this work. How to observe cognitive symptoms in PD depends on the nature of the symptom itself, disease severity and the method used to asses them. A study reported that up to 80% of PD patients develop dementia (Chaudhuri and Schapira 2009). Other studies show deficits in the frontal executive functions in about 30% of PD patients (Lees and Smith 1983; Park and Stacy 2009). Further cognitive symptoms in PD include: visuospatial and visuoperceptual deficits, apathy, impaired set shifting, poor problem solving abilities, and attention inflexibility (Chaudhuri and Schapira 2009; Chaudhuri, Healy, and Schapira 2006; Park and Stacy 2009; Hobert et al. 2011). Comparable to motor symptoms, these symptoms may or may not fluctuate. Furthermore, a relevant body of literature shows impairment in DT abilities and prioritization

strategies in PD patients (Brauer and Morris 2010; Hackney and Earhart 2010; Yogev-Seligmann et al. 2010; Yogev-Seligmann, Hausdorff, and Giladi 2012).

Cognitive functions are relevantly associated with quality of gait (Yogev-Seligmann, Hausdorff, and Giladi 2008; van Iersel et al. 2008; Hobert et al. 2017) and especially with falls (Verghese et al. 2008; Holtzer, Wang, and Verghese 2012). Not surprisingly, gait quality can predict some forms of cognitive deficits (Morris et al. 2017).

More specifically, Lord and colleagues (Lord et al. 2010) have shown that executive functions, motor functions and attention, all contribute to gait velocity and gait interference in PD patients. Other studies have shown that DT is a challenging cognitive setting that negatively affects gait, particularly gait variability (Hausdorff, Balash, and Giladi 2003). Executive dysfunction exacerbates this negative effect of DT on gait variability, making it even more challenging and riskier (Yogev et al. 2005). Taken together, cognitive impairments in PD are heavily involved in gait dysfunctions and worsen the challenging effect of DT on gait parameters. As PD medication influences both, motor and cognitive deficits in PD. Hence, the understanding of the interplay between cognition and gait in PD under Off- and On- medication conditions is paramount.

Neuropsychiatric Symptoms

Depression (occurs in approximately 40% of patients), psychosis, apathy, fatigue and anxiety (occur in up to 45% of patients, respectively) are neuropsychiatric symptoms that are more common in PD than in the age-matched general population (Siciliano et al. 2018). Many patients also report visual and auditory hallucinations (Park and Stacy 2009). Some of these symptoms are induced or at least triggered by dopaminergic medication ((Swainson et al. 2000; Chaudhuri and Schapira 2009), see also below). There might be a possible overlap between some of the cognitive and neuropsychiatric deficits in PD (Chaudhuri and Schapira 2009).

Sleeping

In PD, disturbances in sleep are reported in 60-90% of patients (Park and Stacy 2009). That includes problems falling asleep (earliest and most frequent), maintaining quality sleeping and sleepiness during the day, as well as RBD (Sveinbjornsdottir 2016).

Autonomic Symptoms

Autonomic disturbances reported in PD include constipation, nausea, urogenital difficulties, sexual dysfunction, orthostatic hypotension and excessive sweating (Sveinbjornsdottir 2016).

Other Non-motor Symptoms

Various other symptoms present themselves in PD with varying prevalence. For example, sensory symptoms such as pain, hyposmia and paraesthesia are often observed clinically or reported by patients (Park and Stacy 2009; Chaudhuri and Schapira 2009). Other symptoms include blurred vision, seborrhoea, diplopia and weight loss (Chaudhuri and Schapira 2009).

1.3. Straight Walking and Turning in Parkinson's Disease

Several gait phases show changes throughout the course of the disease. Straight walking, the most studied type of walking, can provide important information about pace, variability and rhythmicity of gait in PD patients (Galna, Lord, and Rochester 2013; Lord et al. 2013).

Turning, another phase of walking, is also deteriorated in PD and associated with increased risk of freezing and falling among others (Bloem et al. 2001; Cheng et al. 2014). The complexity of turning as an activity requires complex coupling of posture and gait, continuous movement of one's centre of gravity as well as inter-limb coordination (Cheng et al. 2014; Mellone et al. 2016; Haertner et al. 2018). Turning is challenging particularly for PD patients, who often suffer from postural instability, because it requires changing direction in an ongoing movement. This movement includes a disequilibrium state during a single limb stance, something

that is difficult for patients with postural instability (Song et al. 2012; Stack and Ashburn 2008).

It is important to distinguish between straight walking and turning as they are –at least partly- planned and executed differently in the brain, in particular in older adults and PD patients (Stack, Ashburn, and Jupp 2006; Stack and Ashburn 2008; Crenna et al. 2007). Seeking safety and maintaining balance while turning, PD patients develop specific strategies to turn (Stack, Ashburn, and Jupp 2006).

There are several ways of assessing gait. Home assessment offers real-life information, that accurately reflects gait characteristics (Lipsitz et al. 1991; Lord et al. 2011; Stack, Ashburn, and Jupp 2006). However, assessing gait in artificial settings is easier to perform, and thus, much more widely used as it provides more standardized information, parameters and a chance for more variety of assessments such as walking backwards and using cues (Baker, Rochester, and Nieuwboer 2008; Hackney and Earhart 2010). An important, relatively new method of investigating gait in PD patients is through unobtrusive IMUs (Maetzler et al. 2013). Such a method provides objective and accurate information about gait characteristics, which might not be observed by the clinician because they are too subtle or they take place even before a diagnosis is reached (Mirelman, Gurevich, et al. 2011).

1.4. Treatment

1.4.1. Dopaminergic Treatment

Dopamine medication has been established as the most suitable and common medication for PD symptoms (Connolly and Lang 2014). While it is shown to improve mostly the more distal motor symptoms (Lees, Hardy, and Revesz 2009), it has a limited effect on other symptoms, in particular on gait domains such as gait variability (Lord et al. 2011; Bloem et al. 1996). It also has a limited effect on turning. Previous studies have shown that dopaminergic medication can improve peak velocity during turning as well as step duration but no other parameters such

as axial velocity (Hong and Earhart 2010; McNeely and Earhart 2011; Curtze et al. 2015).

Dopaminergic medication has a mixed effect on cognitive functions improving some of them and negatively affecting some others (Cools et al. 2001; Cools et al. 2003; Cools et al. 2007). For instance, dopaminergic medication has been shown to improve cognitive flexibility and verbal fluency (Gotham, Brown, and Marsden 1988; Cools et al. 2003), and to deteriorate some forms of learning (Cools et al. 2007).

1.4.2. Side Effects of Dopaminergic Treatment

Albeit generally well tolerated, possible short term complications of dopaminergic medication include hallucinations, nausea, vomiting and impulse control disorders (Connolly and Lang 2014). Prolonged administration of dopaminergic medication is often associated with the occurrence of dyskinesias and motor fluctuations. The prevalence of such complications is about 50% in patients who receive dopaminergic medication for more than five years (Fahn 2000). They are mainly managed by (more) continuous treatment strategies (see below). These side effects in addition to the inefficacy of dopaminergic medications in several aspects of PD lead to a need for alternative therapies and interventions for PD such are those discussed in the following section.

1.4.3. Other Lines of Treatment

Deep Brain Stimulation (DBS) and Other Continuous Treatments

In DBS, high frequency stimulation mainly of the subthalamic nucleus (STN; other areas are currently investigated) "normalizes" functionality typically disturbed in PD (Benabid et al. 2009). Since its first application in PD in 1993, it has shown to significantly improve tremor, rigidity, dyskinesia and motor fluctuation, among other symptoms. This treatment generally enables clinicians to substantially reduce dopaminergic medication and to increase health-related quality of life (HrQoL) (Benabid et al. 2009; Deuschl et al. 2006). DBS has a beneficial effect also in the postural instability gait disability (PIGD) PD subtype, especially in the first year after surgery (Fasano, Daniele, and Albanese 2012). This suggests that

this treatment has beneficial effects on gait and balance. Nonetheless, George et al. have found that DBS alone has no relevant effect on postural instability and gait disability in PD (George et al. 2010). They found a beneficial effect in the combination of DBS with Levodopa in the globus pallidus internus.

Other continuous treatment options are pumps (subcutaneous, apomorphine; via duodenal application, levodopa infusion (Timpka, Mundt-Petersen, and Odin 2016). Patients with cognitive dysfunction and those who want to omit surgical treatment are potential candidates.

Physiotherapy

Physiotherapy has been shown to improve gait, particularly gait velocity (Tomlinson et al. 2013). There are many strategies and methods for physiotherapy training such as cueing, strength and balance training, relaxation and massage, stretching, aerobic straining and trunk strength exercises (Nieuwboer et al. 2007; Keus et al. 2007; Goodwin et al. 2008). Some studies have shown positive results from alternative treatment options such as Tai Chi training, which has been shown to improve postural stability, emotional well-being, Tinetti's Falls Efficacy scale and some parts of the PD Questionnaire-39, related to daily life and communication (Li et al. 2012; Nocera et al. 2013). Furthermore, several studies have recommended exergaming for PD rehabilitation by showing significant benefit of the intervention on cognitive and motor levels (Barry, Galna, and Rochester 2014; Herz et al. 2013).

Recently Developed Treatments

Recently, stem cell therapy has made way as an option for treating motor and non-motor PD symptoms (Pantcheva et al. 2015). Another new treatment option is focused ultrasound subthalamotomy, particularly for patients with asymmetric PD (Martínez-Fernández et al. 2018) as the method is currently applied only at one side of the brain.

1.5. Dual Tasking

1.5.1. Anatomical and Functional Aspects of Dual Tasking

DT is the state of performing two tasks simultaneously and its paradigms have been used to investigate executive function (Adcock et al. 2000). There have been efforts to locate DT in the brain. However, it is more likely that executive functions are mediated by diverse systems, anatomically and functionally that vary depending on the processes involved (Adcock et al. 2000). Although the frontal lobe, parietal lobe and premotor cortex have been reported to be activated during DT, activity is probably specific for the task performed in that particular study (Wu and Hallett 2008). Moreover, the same study has shown that DT cost (DTC, deterioration in the performance of one or both tasks compared to the performance of the task under ST condition) is not dependent on the overlap between the brain areas involved in executing the two tasks (Wu and Hallett 2008).

1.5.2. Dual Tasking in Parkinson's Disease

Many studies had shown that DT has a negative effect on both primary (in this case, gait) and secondary tasks (O'Shea, Morris, and Iansek 2002; Yogev-Seligmann et al. 2010; Yogev-Seligmann, Hausdorff, and Giladi 2012). Such a negative effect is even more prominent in PD patients because of their deteriorated cognitive and mental state (Hausdorff, Balash, and Giladi 2003; Yogev-Seligmann, Hausdorff, and Giladi 2008; Hobert et al. 2011). Moreover, DT is very common in daily life. One can even argue that we are constantly in DT mode when awake. There are conflicting theories about whether the nature of the secondary task plays a role in the DTC or not (O'Shea, Morris, and Iansek 2002; Galletly and Brauer 2005). Hence, it is of great interest to investigate how DT affects straight walking and turning with secondary tasks of different nature. Most of the studies investigating the effect of medication on walking and turning are performed in single tasking (ST) conditions. To my knowledge, this is the first study to investigate turning during DT in PD patients both in Off- and On-medication conditions.

1.6. Unified Parkinson's Disease Rating Scale (UPDRS)

For the past few decades, the UPDRS (Unified PD Rating Scale) has been the method of choice for evaluating PD. The scale is in principle a clinician's assessment of specific clinical aspects of a patient. In 2007 the UPDRS underwent a revision with the Movement disorders society (MDS) (Goetz et al. 2008). A task force modified the scale to the current MDS-UPDRS version that includes the following parts:

(I)   Non-motor aspects of daily life (13 items)

(II)   Motor aspects of daily life (13 items)

(III)   Motor examination (18 items)

(IV)   Motor complications (six items)

A score between zero and four is typically given to each item of the scale as follows: 0= Normal, 1= Slight, 2= Mild, 3= Moderate and 4= Severe impairment. The shortcomings of the UPDRS, even in its modified version, includes its large subjectivity depending on the clinician's experience and opinion. Therefore, interrater variability is a common reliability issue (Richards et al. 1994).

1.7. Assessment of Movement in Parkinson's Disease using Inertial Measurement Units

Recently, technology has provided several alternatives for assessing movement disorders in general and PD in particular (Sánchez-Ferro et al. 2016). Using a camera system, force plate or Inertial Measurement Units (IMUs) is becoming preferable, or at least complementary, to using the traditional UPDRS. These methods offer objectivity and better accuracy than the naked eye. IMUs, especially, are unobtrusive, economical and usable in different environments (Maetzler et al. 2013; Sánchez-Ferro et al. 2016; Maetzler and Rochester 2015). There are many studies that show the advances as well as the challenges in the field of movement assessment in PD using IMUs (Maetzler et al. 2013; Horak, King, and Mancini 2015).

There are several brands and types of IMUs (Figure 4) (Sánchez-Ferro et al. 2016; Laurie King 2013; Donath et al. 2016). All of them include a 3D

accelerometer, measuring the acceleration of the sensor when fixed on a moving body in the three orthogonal axes (x, y, z). IMUs also include a 3D gyroscope; a device used to measure the rotation around the three axes. From the data of the gyroscope and the accelerometer combined, one could calculate the orientation of the IMU. A magnetometer is also often included in the IMU devices, but their use is limited because of the disturbances from magnetic fields in the surroundings.

Figure 4: Photograph of a typical Inertial Measurement Unit (IMU), the OPAL device (Mobility Lab®, APDM, Oregon, USA). The OPAL contains a 3D accelerometer, a 3D gyroscope and a magnetometer (Source: Mobility Lab user guide, https://bit.ly/2TPXWLy).

1.8. Study hypotheses

This study investigates the effect of dopaminergic medication on gait and turning in PD under cognitively challenging conditions using IMUs.

My main hypothesis is that dopaminergic medication improves particular aspects (e.g. velocity) of gait and turning in PD but has no significant effect on other domains of these movements (e.g. gait variability).

Furthermore, I hypothesize that the cognitively challenging conditions (in this case DT) diminish the influence the medication has on gait during the ST conditions.

Testing these hypotheses is important for a more objective assessment of the effect of dopaminergic medication on gait in PD.

This study is partially explorative, given the novelty of investigating turning parameters in ST and DT during Off- and On-medication conditions.

This work should add to the discussion on the relationship between gait and cognition, especially in PD patients.

The questions that will be explored are as follows:

- How effective is dopaminergic medication at improving straight walking and turning in mild-moderate PD patients?
- Is the same effect observed under challenging conditions i.e., DT conditions?
- What gait parameters (and domains) are responsive to the dopaminergic medication?
- How does dopaminergic medication affect two cognitive tasks of different nature and with different demands?

2. **Materials and Methods**

2.1. Original Study

The participants included in this study were part of a study investigating an inflammatory subtype of PD (Yilmaz et al. 2018). Patients were recruited from the ward and outpatients' clinic of the neurology department, University Hospital Tübingen. Moreover, some patients were recruited from a private neurology practice in Stuttgart. The inclusion criteria were age above 40 years and fulfilling the UKBBS criteria for idiopathic PD (Gibb and Lees 1988). For the substudy relevant for this document (discussed below), additional inclusion criteria were being younger than 80 years and being physically independent (no walking aid necessary).

All of the included PD patients were at stage 2 or 3 on the Hoehn & Yahr (H&Y) scale (Hoehn and Yahr 1967). Exclusion criteria were the use of central nervous system medication (except dopaminergic drugs and antidepressants) or suffering from depression (more than 19 points on the Beck's Depression Inventory (BDI-II)) or other neurodegenerative diseases.

The overall study (Yilmaz et al. 2018) included 145 PD patients from Tübingen (another cohort of 90 PD patients was included from Toronto, Canada). The patients recruited in Tübingen were asked to take part in this substudy, which made an assessment in both, Off- and On-medication necessary.

The study design included several motor and cognitive tests, patients' biomaterials investigations as well as collecting the history of chronic diseases and falls during the previous two years. The ethical committee of the medical faculty of the University of Tübingen approved the study (No. 715/2011BO2). All participants provided written informed consent prior to the assessments.

2.2. Study Design and Population

From the entire study (Yilmaz et al. 2018) which included 145 PD patients, 120 patients agreed to take part in this substudy. The Movement Disorders Society (MDS) revised UPDRS, part III (MDS-UPDRS III) was used to assess the severity of symptoms and effect of medication (Goetz et al. 2008) (see also below).

Of the 124 patients, 66 patients performed the assessment in both Off- and On-medication conditions by the time of this analysis and were hence included in the analysis.

Off-medication condition was defined and achieved when the patient skipped their medication overnight until they performed the assessment the following day (no medication for about 9-12 hours). On-medication conditions were defined according to each participant feeling "a good On-phase", typically achieved 45-90 minutes after taking the usual dopaminergic medication. Figure 5 demonstrates the course of measurement.
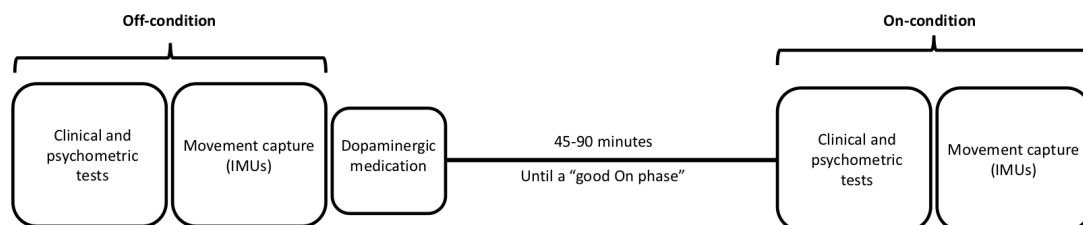
Figure 5: Flow chart of the assessments. Patients performed the same protocol during Off- and On-medication conditions with 45-90 minutes' interval for the medication to reach a "good On phase". IMUs, inertial Measurement Units.

Seven patients could not perform all the iWALK assessments (used in this work) as they felt tired or opted to not complete the protocol. I excluded patients who needed walking aid during the assessment (N=4) and Patients who performed the assessment incorrectly according to the movement capture system algorithms (N=8) were also excluded. Three patients were excluded because they performed the DT serial subtraction (SS) in steps of three (e.g.: 391, 388, 385) instead of seven. I then included only patients with at least two points improvement in the MDS-UPDRS III in the On-medication compared to the Off-

medication condition for the analysis, as this is widely considered the minimum clinically relevant improvement (MCRI). The MCRI indicates that the PD patient has indeed benefited from taking the medication (Schrag et al. 2006; Shulman et al. 2010). This led to exclusion of five more patients from the final analysis. Thus, 39 patients were included in the final dataset.

2.3. Clinical, Cognitive and Psychometric Assessments

Several tests were performed to evaluate the neurological, cognitive and psychological state of the patients. These tests are as follows:

MDS-UPDRS III

In this study, a Movement Disorder Society approved specialist performed the third part of the MDS-UPDRS on patients once during each the Off- and the On-medication conditions.

The MDS-UPDRS III consists of 18 items investigating several motor aspects, including gait and posture. The items of the MDS-UPDRS III are as follows:

Speech, facial expression, rigidity of neck and extremities, finger tapping, hand movements, pronation/supination, toe tapping, leg agility, arising from chair, gait, freezing of gait, postural stability, posture, global spontaneity of movement, postural tremor of the hands, kinetic tremor of hands, rest tremor amplitude, constancy of rest tremor.

The highest (and worst) possible score is 132 points. An exact validated classification of PD symptoms severity based on the MDS-UPDRS III score is still lacking. However, clinical experience suggests that moderate PD patients would usually have a score of 20-30 points, and severe PD patients would have a score of about 50 points.

Mini-Mental State Examination (MMSE)

The MMSE (Folstein, Folstein, and McHugh 1975) is used to screen for cognitive deficits and track the course of Alzheimer's and other diseases with an element

of dementia. The test evaluates the cognitive state of the participant in terms of: orientation, attention, computational abilities, memory, language comprehension and related skills.

The highest possible (best) score of the MMSE test is 30 points. A score below 27 indicates a cognitive restriction, a score below 24 points indicates mild dementia and a score below 10 points indicates severe dementia (Folstein, Folstein, and McHugh 1975).

Trail Making Test (TMT)

The TMT (Reitan 1958) is a neuropsychological test commonly used for assessment of divided attention, visuomotor coordination, and executive functions such as working memory and cognitive flexibility. The test consists of two parts, A and B. Part A assesses mainly motor speed. The participant is asked to connect dots numbered from 1 to 25 in an ascending order. The examiner records the time needed using a stopwatch. Part B assesses mainly cognitive flexibility and alternating attention (Drane et al. 2002). The participant is asked to connect the dots numbered 1-13 and A-L alternatively (1-A-2-B-3-C). The examiner draws the participant's attention if they make an error, which then must be corrected at the expense of the time. The overall TMT performance can be influenced by age, educational level and motivation among other factors (Lezak 1995).

Delta TMT test (B-A) is considered to best reflect "pure cognitive efficiency" (Drane et al. 2002).

BDI-II

The BDI-II (Beck et al. 1996) is a standardized psychometric test used to detect and evaluate the severity of depressive symptoms. The test includes 21 questions about sadness, un-satisfaction, anxiety about the future, guilt, self-loathing, suicidal thoughts, irritability, social insulation, decisiveness, fatigue, body perception, appetite, weight, libido, and hypochondria. Each question can be answered on a scale from 0 (no limitation) to 3 (most severe limitation) totalling 63 possible points. The scores are interpreted as follows:

0-9: minimal depression; 10-18: mild depression; 19-29: moderate depression; 30-63: severe depression (Beck, Steer, and Carbin 1988).

2.4. Tasks

2.4.1. Gait Assessments

For gait assessment, participants performed the following tests:

- **Instrumented timed up & go (iTUG) test**: In this test the participants started from a sitting position, stood up, walked for seven meters, made a turn to the left (or right), and walked back and sat down again. In this study protocol, the test was performed once starting with the left foot, walking 7 meters, making a left turn and once with the right foot, again walking 7 meters and making a right turn. A third iTUG was performed at self-selected pace over 3 meters. The patients could choose their starting foot and direction of turning during the third iTUG.

- **Instrumented sway (iSWAY) test:** Participants stood in a semi-tandem stance (left foot forward) on a foam pad for 30 seconds once with closed eyes and once with open eyes. Another variation of the test was also performed; the participant stood on the floor for 30 seconds with a wooden leg separator and arms crossed on the chest, once with closed eyes and once with the eyes open.

- **Functional reach test:** Participants stood with their right side to the wall, without leaning on it, right arm stretched forward as far as possible, body leaned forward as far as possible. They were asked to hold that position for 15 seconds before slowly going back to their starting position. The arm reach is marked on a sheet on the wall before and after leaning forward. The difference between the two markers is called the functional reach. This test gives insight into a participant's balance abilities and postural stability (Hasmann et al. 2014).

- **Five-chair-rise test:** Starting from a sitting position, participants stood up and sat down five times without depending on their hands (Whitney et al. 2005). Participants were also instructed to fully stretch their knees during standing and to lean back during sitting. This test was performed once in a convenient pace and once in a fast pace. It provides data on postural transitions, muscle power of the lower extremities and coordination.

- **Instrumented stand and walk (iSAW) test**: In this test the participant stood still for 30 seconds with the hands relaxed next to the trunk. Participant then walked for seven meters, made a turn before walking back to the start line where they stood again facing the opposite direction of their starting position. This test was performed once by starting the walk with the left foot, turning left at the seven-meter mark, and once with the right foot, turning right. This test provides data on balance, step initiation and anticipatory postural adjustments (APAs).

- **Instrumented long walk (iWALK) test** (Mancini 2011): Participants walked for one full minute up and down a well-lit 2m-wide 20m-long hallway. This assessment thus includes straight walking and turning episodes (Figure 6). Participants did not receive instructions on the foot they should use to start the walk or in which direction they should turn.
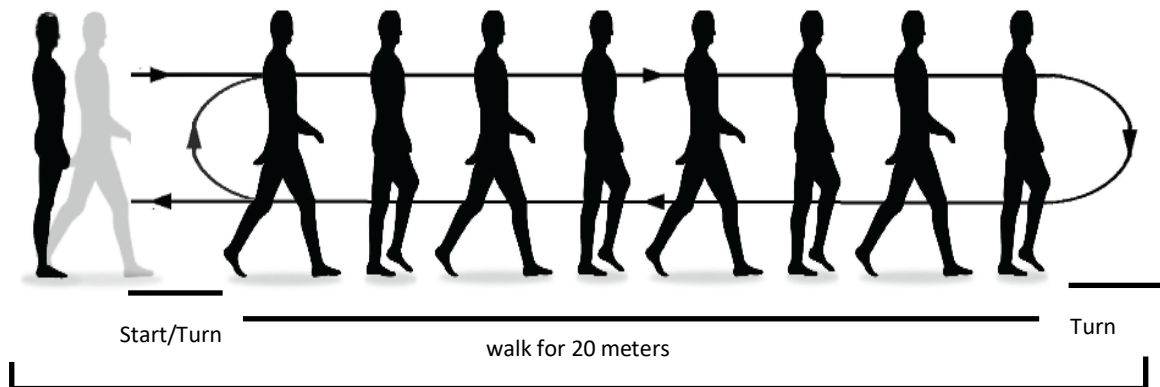
Figure 6: The iWalk assessment. Source: Mobility Lab user guide (version 22nd March 2016, https://bit.ly/2TPXWLy, Mobility Lab® APDM).

The test was performed in four conditions:

- ST, fast pace walking.
- ST, normal pace walking.
- DT, fast pace walking + checking boxes (CB).
- DT, fast pace walking + SS.

The iWALK test is the movement assessment used in this analysis. It provides data on gait and turning parameters, which I analysed here.

2.4.2. Secondary Cognitive Tasks

The Checking Boxes (CB) task is a cognitive task with a substantial motor component. Based on the study protocol of Hobert an colleagues (Hobert et al. 2011), participants checked 32 empty boxes on a sheet, while standing, in ST condition. Participants were instructed to always check the boxes in the same direction (top down, left to right).

The Serial Subtraction (SS) task is a series of 7-steps subtractions. During ST, participants performed the task as a series of ten subtractions, starting from the number 406, while standing, by saying the numbers out loud, and as fast as they could. When the test had to be repeated for any reason, participants were given another three-digit number (396). This task is complex and considered cognitively

demanding (O'Shea, Morris, and Iansek 2002; Shumway-Cook, Brauer, and Woollacott 2000). For some participants, the SS was too complex with the 7-steps calculation. They were then given an easier task of subtracting 3-steps from a 3-digit number. These participants were, as mentioned in the methods, excluded from the analysis for incompatibility with the rest of the cohort.

During DT, participants were asked to perform the secondary task as fast as possible, with the explicit instruction "walk as fast as possible without running and check the boxes / calculate SS also as fast as possible" to avoid creating a biased prioritisation of one task over the other.

2.5. Movement Capture

Participants wore eight inertial measurement units (IMUs) named OPAL from the Mobility Lab system (Mobility Lab®, APDM, Oregon, USA) (Mancini 2011) (Figure 6). The Mobility Lab system also includes an access point, a docking station and the software for data acquisition, analysis and export of results. Components of the Mobility Lab system are shown in Figure 7.
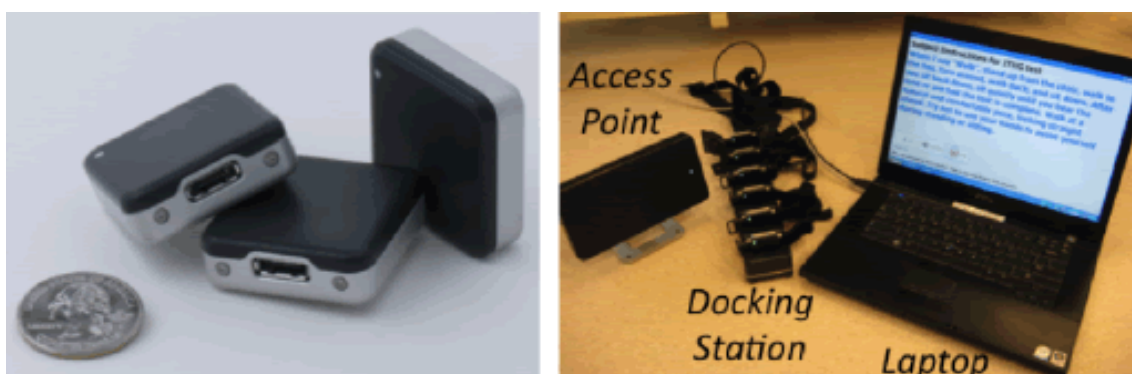

Figure 7: The Mobility Lab system includes an access point, a docking station, IMUs and a software with validated algorithms (Mancini 2011).

The access point streams the data from the IMUs directly to the laptop during the assessment as long as the IMUs are within a range of 20m from the access point.

When the IMUs are out of range, data are stored on the internal storage and then streamed to the access point as soon as they are in range again.

The docking station is used to calibrate the IMUs before each measurement session, to charge the IMUs batteries and to turn them off at the end of the session.

When starting a measurement, all used IMUs synchronize together through the software and the data are streamed online to the access point using WiFi channels.

These IMUs were distributed on the body as follows (see also Figure 8): one on the trunk (chest), one on the lumbar area, one on each wrist, one on each shin and one on each foot. They were all fixed on the body parts using adjustable elastic washable belts. The iWALK test uses data from the arms, waist and feet IMUs.

The Mobility Lab system includes algorithms for the analysis of different movements and activities. Merging data from the accelerometer, gyroscope and magnetometer, the algorithm uses the so called "quaternion", a mathematical system applied to the mechanics in three-dimensions (Mancini 2011).

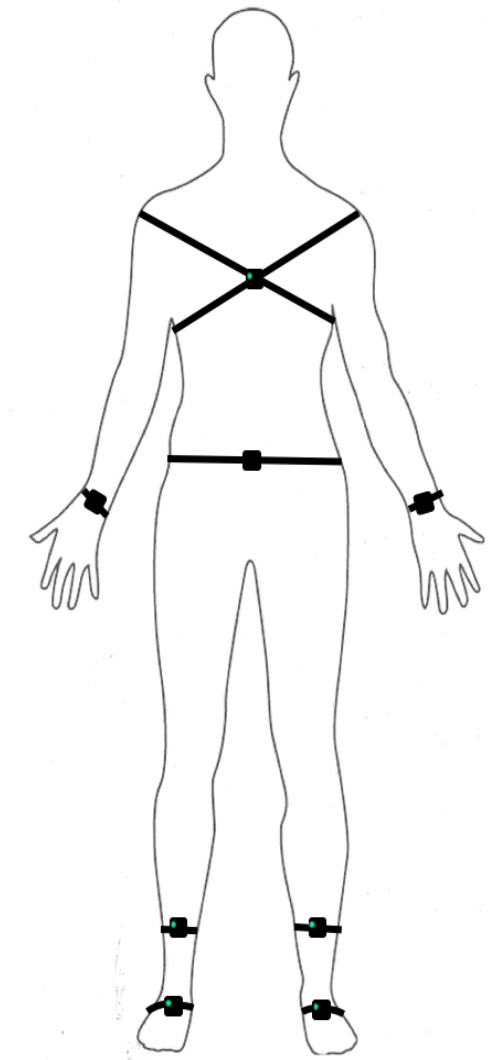**Figure 8:** Self-made visualisation of the positioning of eight IMUs on the patient's body. All IMUs had the same orientation and were synchronized together.

2.6. Data Extraction and Analysis

Based on previous work on gait domains, I focused my analysis on gait parameters that belong to relevant and independent gait domains (Lord et al. 2013). These parameters were: gait velocity, stride duration, double limb support

time, stride duration variability, double limb support variability and stride length asymmetry. Stride duration variability and double limb support variability were calculated from the standard deviation [SD] of the first 30 steps of straight walking. Previous work has shown the reliability of this approach (Galna, Lord, and Rochester 2013).

The above-mentioned parameters are defined as follows:

- Gait velocity: the distance in meters covered per second [m/s].
- Step frequency: the average number of steps performed per minute [steps/min].
- Double limb support time: the percentage of time spent with both feet on the floor from the total gait cycle time [%].
- Stride length asymmetry: the average difference in the length of strides performed with the left and those performed with the right leg [SD].
- Stride duration variability: the stride to stride fluctuation in duration [SD].
- Double limb support time variability: the fluctuation in double limb support duration from one gait cycle to the other [SD].

For the turning phase, turning is defined by the system's developers as any rotation of 45° or more around the Y axis with a duration of 0.5s-10s (Pearson et al. 2013). I selected turning parameters that have been established by previous studies as independent and clinically relevant parameters (Stack and Ashburn 2008; Hong and Earhart 2010). Turning parameters were defined as follows:

- Total duration: the time in seconds required in average to perform a turn of 180° [s].
- Step duration: the average time in seconds required to perform one step during turning [s].
- Number of steps: the average number of steps a participant performs during the turn [steps/turn].
- Peak velocity: the maximum velocity of turning around the Y axis [°/s].

- Last step duration: the average duration of the last step of walking before turning starts [s].

Data extraction and calculation of variability parameters and preparation for statistical analysis were performed using a script written by the author using Matlab 8.4 (MathWorks, Natick, Massachusetts). The Matlab functions used in this step are provided as Supplementary Material 1 and 2 at the end of this work.

2.7. Data Analysis and Statistics

Since ST CB was calculated as the time needed to check 32 boxes as fast possible, while DT was performed as checking as many boxes as possible in one minute. I normalized the performance using the following equation:

$$No. of\ boxes\ in\ 60s\ in\ ST = \frac{60s}{time\ for\ 32\ boxes} * 32$$

Similarly, for SS, ST was performed by recording the time needed to perform ten consecutive subtractions as fast as possible. In DT SS, participants performed as many subtractions as they could in one minute. I normalized the performance using the following equation:

$$No. of\ subtractions\ in\ 60s\ ST = \frac{60s}{time\ for\ 10\ subtractions} * 10$$

Paired t-test was used to compare between the Off- and On-medication conditions. Mann-Whitney-Wilcoxon (MWW) test was performed as an alternative when the data were not normally distributed. I tested for the normal distribution of the data using the Shapiro-Wilk test (Field 2013). I set the significance level at

p<0.05. I did not correct for multiple testing due to the partially exploratory nature of this study. Data analysis was performed using JMP software 11.1.1 (SAS institute, 2014).

3. **Results**

Results of the cognitive testing (MMSE) show that the participants did not suffer from significant cognitive impairment. Participants scored on average 29 points. BDI-II score of my participants was 7 points on average.

3.1. Effect of Medication on MDS-UPDRS III Score

As defined in the exclusion criteria, the dopaminergic medication improved the MDS-UPDRS III score of all participants included in the analysis by minimum two points. The average MDS-UPDRS III score of all participants decreased significantly (nine points on average) during the On-medications compared to the Off-medication condition ($p<0.0001$) (Table 1).

Table 1: Demographic data of participants in Off- and On-medication conditions.
Data are presented in mean and standard deviation (SD). Data comparison was performed using paired t-test. Significance level was set at $p<0.05$.
BDI-II, Beck Depression Inventory; F, Female; H&Y, Hoehn and Yahr, MDS-UPDRS III, motor part of the Movement Disorders Society Revised-Unified Parkinson's Disease Rating Scale; M, male; MMSE, Mini-Mental State Examination.

	Off-medication	On-medication	*p*-value
Age [years]	65.2 (6.9)		
Gender	M:31; F:8		
MMSE (0-30)	-	29 (2)	
BDI-II (0-63)	-	7 (6)	
MDS-UPDRS III (0-132)	30 (9)	21 (7)	**< 0.0001**
H&Y (0-5)	35 patients in stage 2 4 patients in stage 3		

3.2. Effect of Medication on Straight Walking during ST and DT

For straight walking during ST, gait velocity was significantly higher during the On-medication condition than during Off-mediation condition (p=0.03). No significant differences were observed in other measured gait parameters during ST. Step frequency was comparable between Off- and On-medication (129 vs 128 steps/m; p=0.25). Double limb support time was 16.3% and 16.2% of gait cycle time (p=0.78) under Off- and On-medication conditions, respectively. Stride length asymmetry was recorded at 1.60m/s and 1.50m/s during Off- and On-medication conditions (p_{MWW}=0.26). Stride duration variability was 0.03s (p=0.78) during both Off- and On-medication conditions. Double limb support variability was 2.2% and 2.4% (p=0.76), during Off- and On-medication respectively. A visual overview of the parameter measured is provided in Figure 9.

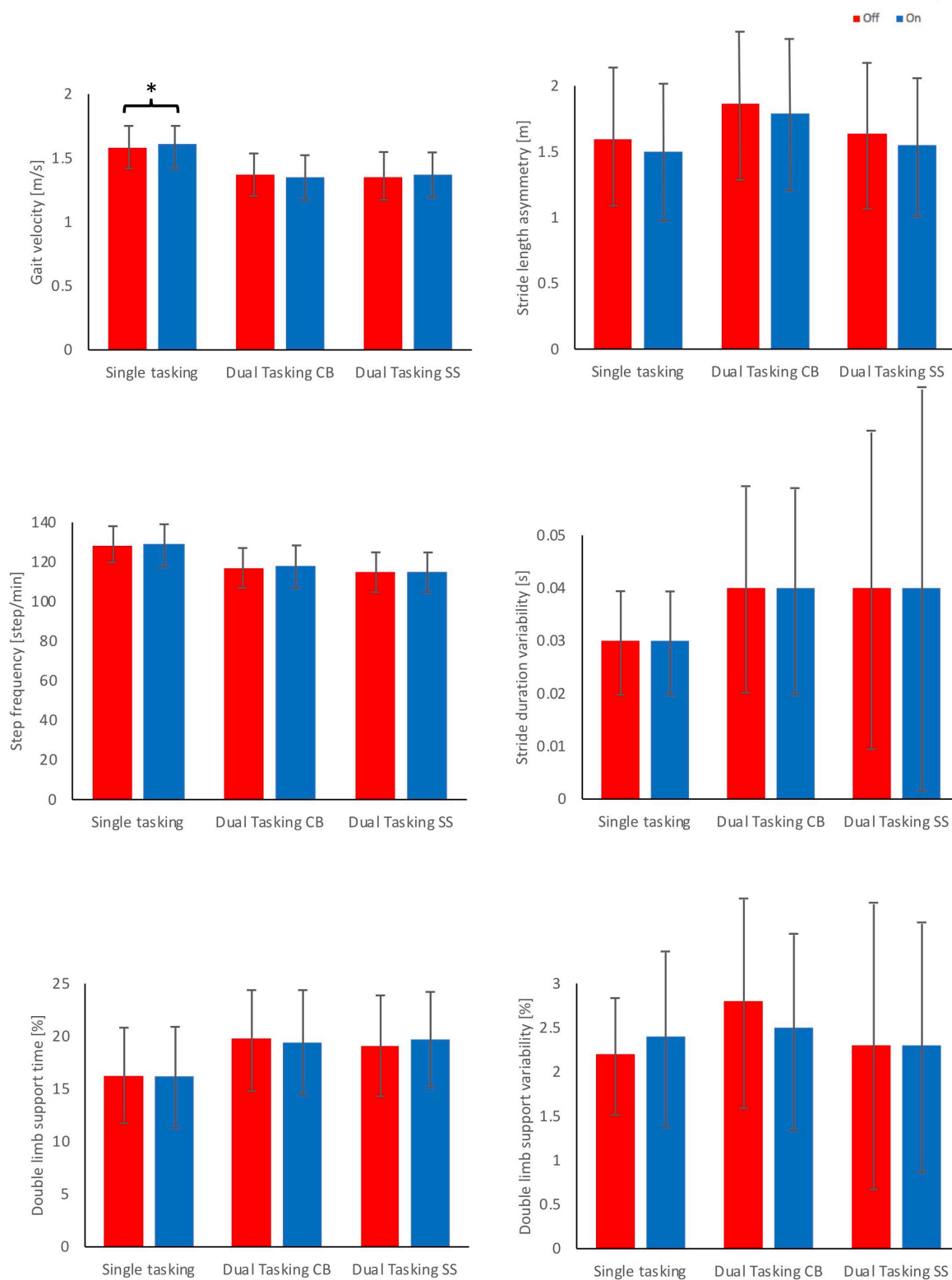**Figure 9:** Straight walking parameters in Off (red)- and On-medication (blue) conditions during ST and DT. Comparisons performed using paired t-test when the data were normally distributed and Mann Whitney U test when the data were non-normally distributed.

%: percentage of gait cycle time; *: significant difference (*p*<0.05); CB: checking boxes; m: meter; s: seconds; SS: serial subtraction.

For straight walking during DT (CB), no significant effect of medication on any of the assessed gait parameters could be seen (Table 2). Gait velocity was recorded at average 1.35 m/s in On-medication compared to 1.37 m/s during Off-medication (p=0.18). Step frequency was observed at 139 steps/min in On-medication compared to 138 steps/min during Off-medication conditions (p=0.49). Double limb support time was 19.4% of gait cycle time during On-medication compared to 19.7% during Off-medication (p=0.78). Stride length symmetry was 1.50 [SD] during On-medication compared to 1.60 [SD] during Off-medication (p=0.78). Stride time variability was 0.04 [SD] in Off- and On-medication conditions during DT conditions with both secondary tasks (p=0.76). Double limb support variability was 2.4 [SD] during On-medication compared to 2.2 [SD] during the Off-medication (p_{MWW}=0.27).

Straight walking parameters during DT of SS did not show any significant change under the influence of dopaminergic medication. Gait velocity during On-medication conditions was 1.37 m/s compared to 1.35 m/s during Off-medication (p=0.27). Step frequency was averaged at 155 step/min during both Off- and On-medication conditions (p_{MWW}=0.96). Double limb support time was recorded at 19.7% of gait cycle time in On-medication conditions compared to 19.1% during Off-medication conditions. Stride length asymmetry during On-medication conditions was recorded at 1.55 [SD] compared to 1.66 [SD] during the Off-medication conditions (p_{MWW}=0.34). Stride duration variability was 0.04 [SD] during both conditions (p_{MWW}=0.90). Double limb support time variability (2.4 [SD], p_{MWW}=0.69) was comparable between Off- and On-medication conditions.

Table 2: Performance of straight walking during Off- and On-medication conditions in ST and DT.
Data presented in mean and (Standard deviation, SD). Paired t-test was used for normally distributed data. Mann-Whitney U test (*italic*) was used for non-normally distributed data. Significance level was $p<0.05$. DT, dual tasking; ST, single tasking.

Parameter	Off-medication	On-medication	*p*-value
Straight walking (ST)			
Gait velocity [m/s]	1.58 (0.16)	1.61 (0.16)	**0.03**
Step frequency [steps/min]	128 (9)	129 (13)	0.25
Double limb support time [%]	16.3 (4.3)	16.2 (4.6)	0.78
Stride length asymmetry [SD]	1.60 (0.54)	1.50 (0.53)	*0.26*
Stride duration variability [SD]	0.03 (0.01)	0.03 (0.01)	0.78
Double limb support variability [SD]	2.2 (0.7)	2.4 (1.0)	*0.27*
Straight walking during CB (DT)			
Gait velocity [m/s]	1.37 (0.17)	1.35 (0.19)	0.18
Step frequency [steps/min]	117 (11)	118 (13)	0.49
Double limb support time [%]	19.7 (4.5)	19.4 (4.9)	0.56
Stride length asymmetry [SD]	1.87 (0.60)	1.79 (0.66)	*0.35*
Stride duration variability [SD]	0.04 (0.02)	0.04 (0.02)	*0.76*
Double limb support variability [SD]	2.8 (1.2)	2.5 (1.1)	*0.22*
Straight walking during SS (DT)			
Gait velocity [m/s]	1.35 (0.21)	1.37 (0.18)	0.27
Step frequency [steps/min]	115 (11)	115 (11)	*0.96*
Double limb support time [%]	19.1 (4.6)	19.7 (4.2)	0.77
Stride length asymmetry [SD]	1.64 (0.59)	1.55 (0.56)	*0.34*
Stride duration variability [SD]	0.04 (0.03)	0.04 (0.04)	*0.90*
Double limb support variability [SD]	2.3 (1.6)	2.3 (1.4)	*0.69*

3.3. Effect of Medication on Turning Parameters during ST and DT

For turning parameters during ST, step duration (p_{MWW}=0.048) was shorter (0.53s and 0.51s in Off- and On-medication conditions), and peak velocity (p=0.04) was higher during On-medication (173°/s) condition compared to Off-medication condition (164°/s).

In the remaining parameters, no significant change was recorded between the different medication conditions. The following parameters are still mentioned: The total duration of turns on average decreased by 0.2s during On-medication conditions (p_{MWW}=0.18). The number of steps performed per turn was 6 steps in Off-medication and 5 steps in On-medication (p_{MWW}=0.23). The duration of the last step before turning remained virtually unchanged at 0.48s in both Off- and On-medication conditions (p=0.18).

During the DT CB assessment, no significant influence of medication on gait could be observed. The following parameters are still mentioned: The mean total duration of the turns increased by 0.4s under the dopaminergic medication influence (p_{MWW}=0.68). Step duration decreased by 0.3s (p_{MWW}=0.30). The number of steps per turn was 7 during both Off- and On-medication conditions (p_{MWW}=0.90). Peak velocity of turning was recorded at 129°/s during On-medication compared to 130°/s during Off-medication conditions (p=0.84). Last step duration was 0.53s during both Off- and On-medication conditions (p=0.49). Details are presented in Figure 10.
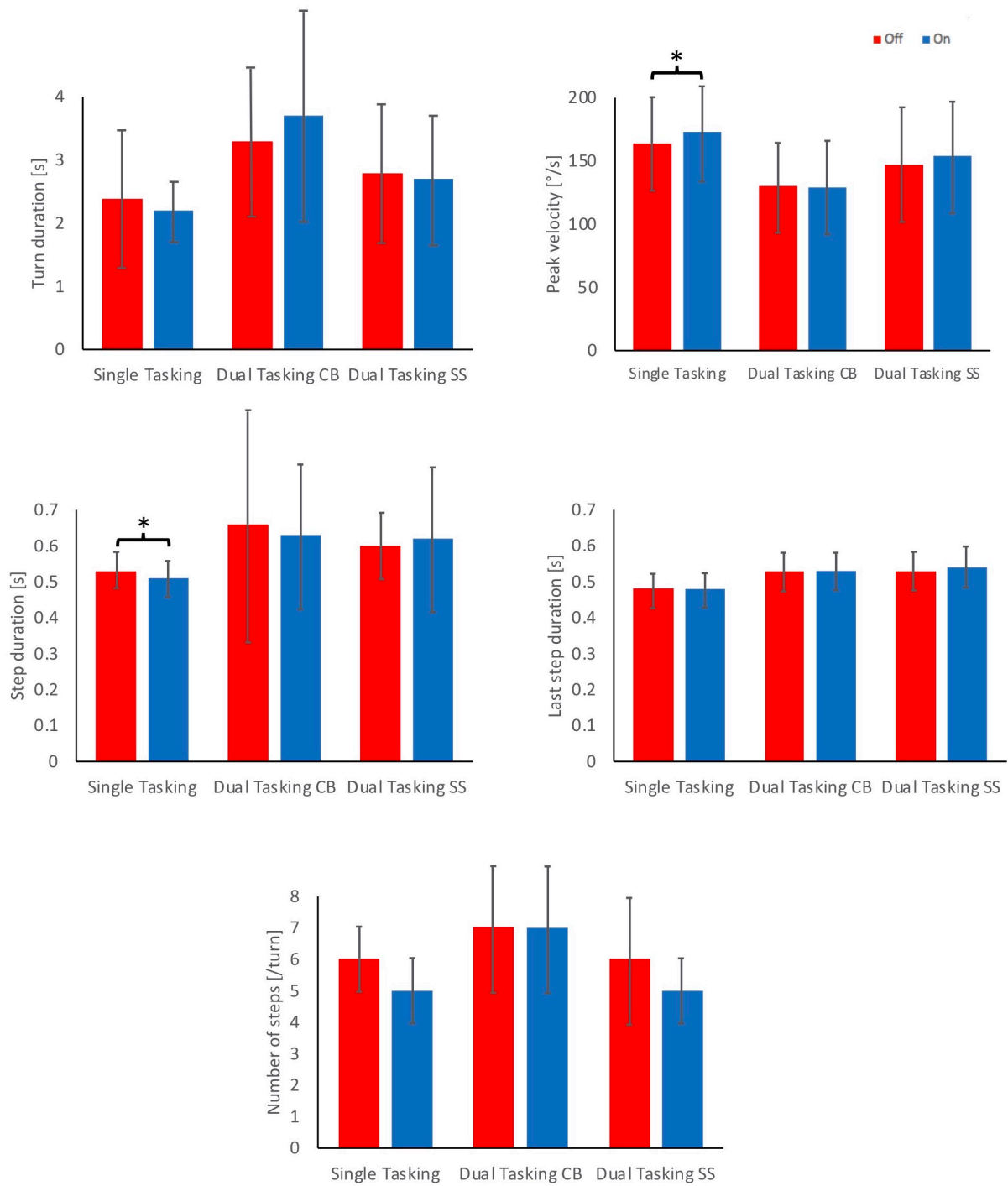
Figure 10: Turning parameters in Off (red)- and On-medication (blue) conditions during ST and DT. Comparisons were performed using paired t-test when the data were normally distributed and Mann Whitney U when the data were non-normally distributed.

*, significant difference (*p*<0.05); CB, checking boxes; SS, serial subtraction.

In the DT SS assessments, no significant changes in turning parameters could be observed. The duration of turn was 2.8s in Off-medication conditions and 2.7s in On-medication conditions (p_{MWW}=0.41). Step duration during turns was 0.60s during Off-medication conditions, compared to 0.62s during On-medication (p_{MWW}=0.41). Participants performed on average 6 steps/turn in the Off-medication conditions and 5 steps/turn in On- medication conditions (p_{MWW}=0.09). Peak velocity of turning was 147°/s during Off-medication and 154°/s in On-medication conditions (p=0.31). The duration of the last step before turning was 0.53s during Off-medication and 0.54s during On-medication (p=0.63).

Table 3: Performances of turning during Off- and On-medication conditions in ST and DT. Data presented in mean and (Standard Deviation, SD). *P*-values are of paired t-test when data is in normal distribution and Mann-Whitney U (*italic*) when they are not. Significance level was $p<0.05$. CB, checking boxes; DT, dual tasking; SS, serial subtraction; ST, single tasking.

Parameter	Off-medication	On-medication	*p*-value
Turning (ST)			
Total duration [s]	2.4 (1.1)	2.2 (0.5)	*0.18*
Step duration [s]	0.53 (0.05)	0.51 (0.05)	***0.048***
Number of steps [steps/turn]	6 (1)	5 (1)	*0.23*
Peak velocity [°/s]	164 (34)	173 (37)	**0.04**
Last step duration [s]	0.48 (0.04)	0.48 (0.04)	0.18
Turning during CB (DT)			
Total duration [s]	3.3 (1.0)	3.7 (1.5)	*0.68*
Step duration [s]	0.66 (0.32)	0.63 (0.19)	*0.30*
Number of steps [steps/turn]	7 (2)	7 (2)	*0.90*
Peak velocity [°/s]	130 (32)	129 (35)	0.84
Last step duration [s]	0.53 (0.06)	0.53 (0.05)	0.49
Turning during SS (DT)			

Total duration [s]	2.8 (1.1)	2.7 (0.9)	*0.41*
Step duration [s]	0.60 (0.09)	0.62 (0.20)	*0.41*
Number of steps [steps/turn]	6 (2)	5 (1)	*0.09*
Peak velocity [^{o}/s]	147 (42)	154 (40)	0.31
Last step duration [s]	0.53 (0.06)	0.54 (0.08)	*0.63*

3.4. Effect of Medication on Secondary Cognitive Tasks

The speed of CB was significantly higher during On-medication compared to Off-medication condition.

During ST, participants checked 89 and 98 box/min during Off- and On-medication (p=0.04), respectively. **During DT,** participants performed 60 and 65 box/min in Off- and On-medication (p=0.04). Details on CB performance are presented in Table 4 and in Figure 11.
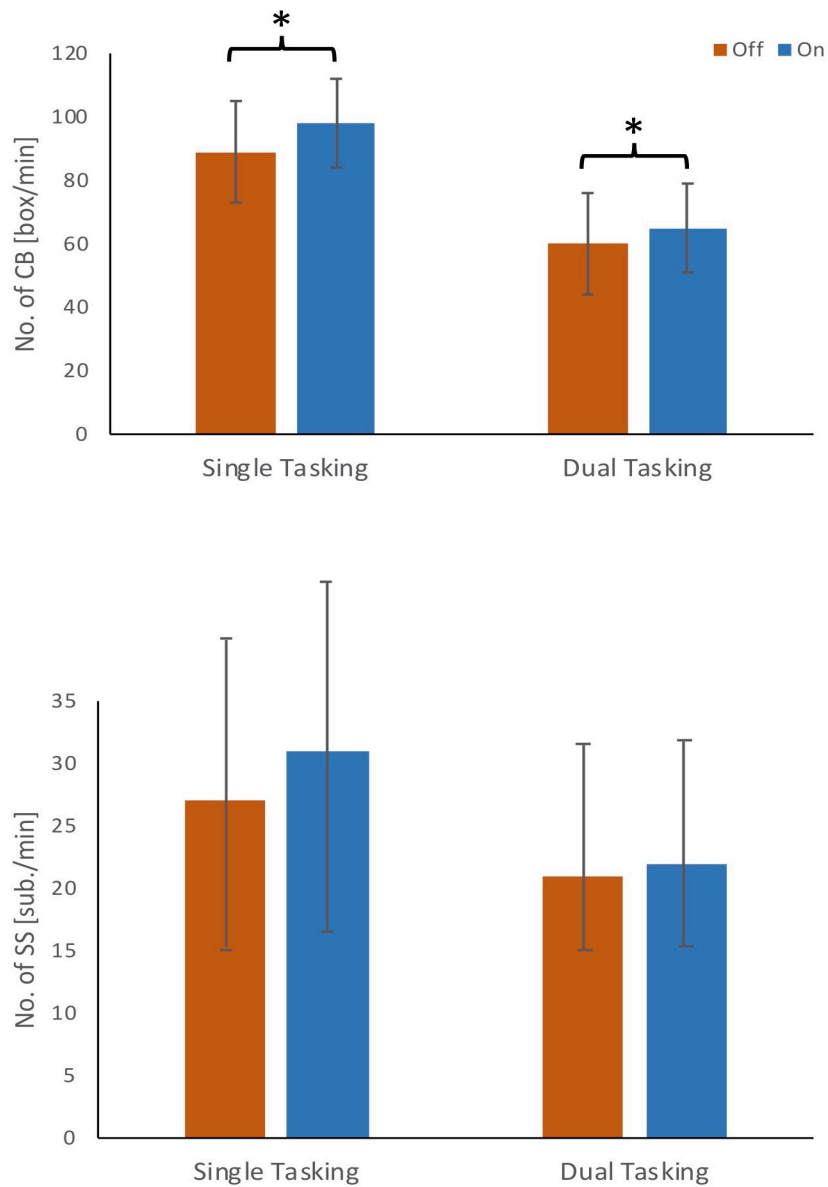
Figure 11: Secondary tasks performance in Off (orange)- and On-medication (blue) conditions during single and dual tasking. *, significant difference (*p*<0.05). Comparisons performed using paired t-test.

CB, checking boxes; min, minute; SS, serial subtraction; sub, subtraction.

The SS speed, **during ST,** participants performed 27 and 31 subtractions/min in Off- and On-medication, respectively (*p*=0.51). **During DT,** they performed 21

and 22 subtractions/min during Off- and On-medication conditions, respectively (p=0.85) (Table 4, Figure 11).

Table 4: Performances of secondary tasks during Off- and On-medication conditions in ST and DT.
Values are presented with mean and (Standard Deviation, SD). *P*-values are from paired t-test and Mann-Whitney U (*italic*). Significance level was at $p<0.05$. CB, checking boxes; DT, dual tasking; SS, serial subtraction; ST, single tasking; sub., subtraction.

Parameter	Off-medication	On-medication	*p*-value
Secondary Tasks			
Speed of CB **ST** [box/min]	89 (16)	98 (16)	**0.04**
Speed of CB **DT** [box/min]	60 (16)	65 (14)	**0.04**
Speed of SS **ST** [sub./min]	27 (16)	31 (18)	*0.51*
Speed of SS **DT** [sub./min]	21 (11)	22 (11)	*0.85*

4. Discussion

In this work, I investigated the effect of dopaminergic medication on straight walking, turning and two cognitive tasks during ST and DT conditions. Dopaminergic medication has been the treatment of choice for PD for the past few decades (Connolly and Lang 2014). Albeit the deteriorating effect on some PD symptoms, it has been shown to improve other motor symptoms as well as several cognitive functions (Fahn et al. 2004; Cools et al. 2007; Cools et al. 2003; Cools et al. 2001; Swainson et al. 2000). For example, it is well established that the following aspects respond positively to dopaminergic treatment: tremors, akinesia, rigidity (Pogarell et al. 2002; Schrag et al. 1999), and cognitive flexibility (Cools et al. 2003). However, it is less well investigated, which effect dopaminergic medication has on straight walking and turning, especially under DT conditions, as these aspects are difficult to evaluate with the "naked" clinical eye. Due to advances in technology, we now have the means to objectively assess the effect and benefits of dopaminergic medication on such features and functions.

I hypothesized that dopaminergic medication will have a positive effect on some gait parameters during straight walking, e.g. gait velocity, stride length and swing velocity (Blin et al. 1991), but no significant effect on some other parameters, e.g. stride duration and gait variability, which has been reported to be resistant to dopaminergic medication (Blin et al. 1991; Lord et al. 2011).
I also hypothesized that the medication will have positive effects on some turning parameters such as the peak velocity and total duration of turning (Curtze et al. 2015), but no significant effect on other parameters such as the number of steps needed to turn and step duration (Curtze et al. 2015; Hong and Earhart 2010; McNeely and Earhart 2011).
I tested that effect during ST and DT, for gait parameters during straight walking and turning phases, hypothesising a more limited effect of medication during DT.

I also aimed to explore the effect of medication on two different types of cognitive tasks in PD during ST and DT conditions. These two tasks were CB, a secondary cognitive task with a rather motor nature and SS, a secondary task that demands complex executive functions processes.

For these purposes, I used a recent technology to assess movement in PD, i.e. IMUs (Sánchez-Ferro et al. 2016; Horak, King, and Mancini 2015). IMUs, are economic, unobtrusive and can be used in the lab or home environments. As the use is uncomplicated, it is an assessment with high potential also for peripheral hospitals and regions with low income and limited access to health systems. They provide a plethora of data parameters in various relevant gait domains and other types of human movement.

My study showed that dopaminergic medication has a limited effect on straight walking (improved only gait velocity) and turning (improved step duration and peak velocity), and that this beneficial effect was only observed during ST. During DT, I didn't find considerable benefits. I also found that dopaminergic medication improved the motor aspects of cognition associated with motor planning and fine motor functions but didn't improve the complex task associated with cognitive flexibility.

4.1. Gait and Turning in Parkinson's Disease

Gait is an important part of daily life activities, and is more complex than originally thought (Hausdorff et al. 2005). Gait deficits in PD are common, and often presented by significantly declined velocity, small and fast steps, diminished arm swing, deviated posture and a remarkable axial rigidity. These deficits result in high-risk gait patterns, leading to e.g. falls (Schaafsma et al. 2003; M. Morris et al. 1998). Moreover, PD patients' physical independence and social life are often significantly affected by deteriorated gait velocity and increased postural instability (van Uem et al. 2016).

Turning is basically a part of walking but has recently been investigated more often independently from (straight) walking because of its importance for daily activities and relation to falls (Cheng et al. 2014; Mellone et al. 2016). It is also very probable that turning is planned and executed at least in part independently from straight walking networks in the human brain (Cheng et al. 2014; Mellone et al. 2016). Moreover, turning is often impaired in PD patients, and linked to higher risk of falling and freezing (Cheng et al. 2014; Haertner et al. 2018; El-Gohary et al. 2014). PD patients seem to develop different strategies for safe well-balanced turning (Stack, Ashburn, and Jupp 2006; McNeely and Earhart 2011).

Taken together, safe walking and turning are paramount to PD patients. Selecting the ideal treatment is hence crucial in tackling gait and turning deficits in PD. As the effects of potential treatment (also beyond the treatment presented here) on straight walking and turning may differ, the following discussion will address the findings of straight walking and turning separately.

4.2. The Effect of Dopaminergic Medication on Straight Walking during Single and Dual Tasking

A main finding of this study is the limited effect of dopaminergic medication on straight walking during ST and even more during DT. The improvement of gait velocity by medication during ST is consistent with previous work (Baltadjieva et al. 2006; Lord et al. 2011). Previous studies also showed that medication improved some gait domains only during ST but had no positive effect during the more daily-relevant DT conditions (Silsupadol et al. 2006; Hackney and Earhart 2010). Although the medication may thus have only a limited effect, it may still be relevant for single patients, e.g. when the main issue is to walk from one place to another.

My results also confirm previous studies suggesting that step frequency and double limb support variability do not improve by dopaminergic medication during ST (Almeida et al. 2007; Schaafsma et al. 2003).

Almeida et al compared the gait of 19 and 23 idiopathic PD patients in Off- and On-medication conditions, respectively. They also measured 30 participants as

control group. Data from this study were extracted from a 14-ft pressure-sensitive carpet, which is designed to detect foot pressure (e.g., during walking). Results of this study show that double limb support variability was higher in the PD Off-medication group than in the control group but was not different from the On-medication state. It must however be taken into consideration that the study included two separate groups measured in Off- and On-medication and did not include intraindividual comparisons in its design. This could limit the conclusions drawn from the findings regarding the causality of medication on gait differences.

Furthermore, as in my study, others have shown that stride duration variability is not significantly influenced by dopaminergic medication (Lord et al. 2011; Hausdorff, Balash, and Giladi 2003). This means that an improvement in time domain-related gait variability in general is not expected from dopaminergic medication during ST or DT conditions. This indicates that even though all these gait domains are affected by PD (Almeida et al. 2007; Schaafsma et al. 2003), they are probably not relevantly triggered by deficits in the dopaminergic system and consequently not responsive to dopaminergic medication. Although it is impossible to draw a definite conclusion at this point, it is possible that at least some gait parameters that deteriorate in PD are mostly affected by (deterioration of) neurotransmitter systems associated with, e.g., cognitive deficits. This assumption is supported by the increase in gait variability during DT conditions, which are cognitively challenging. It is also supported by previous work (Hausdorff, Balash, and Giladi 2003) showing that gait variability deteriorates under cognitively challenging conditions. In their study, Hausdorff and colleagues investigated 10 idiopathic PD patients during their On-medication condition. These participants walked a 20m-hallway in ST normal pace settings, and again in DT conditions while performing the SS task (similar to the SS task in this work). The main findings of their study were the much larger (154%) stride time variability and what they described as a "hesitant gait" (describe here what they mean with the term) during DT compared to ST. The authors concluded that DT conditions exacerbates gait variability and further impairs stable walking in PD. They recommended interventions for PD patients with focus on limiting

distractions and DT during walking, in hope to maintain a more stable, safe gait. In other words, they recommended a "more cognitive" approach to improve gait variability rather than using medication (or motor training).

Is gait velocity alone enough?

Gait velocity is an important parameter for the independent performance of daily life activities in both older adults and PD patients. It is often used as a predictor of survival and adverse effects such as falling (Studenski et al. 2011; Montero-Odasso et al. 2005). An improved gait velocity can help patients maintain independency and a better social life. Hence, it is possible that the lone improvement in gait velocity from the dopaminergic medication is satisfying for many patients.

On the other hand, it is possible that improving gait velocity without improving further parameters of gait that are important for dynamic stability (such as postural control and variability) (Henderson et al. 2016; Boonstra et al. 2008) may lead to dangerous situations per se as the higher velocity is not compensated by the postural system. It may also give a false sense of safety for PD patients and thus lead to a higher risk of falling. Moreover, dopaminergic medication often has side effects (motor, cognitive and emotional), and the right balance between the benefits (coming from improved mobility) and disadvantages has to be determined in every single case.

Taking together, PD patients can benefit from dopaminergic medication concerning gait velocity under ST conditions, but it should always be discussed and decided on an individual basis whether this gain of velocity is relevant for the patient given the risks and side effects discussed above.

4.3. The Effect of Medication on Turning during Single and Dual Tasking

Turning is an important phase of gait and is linked to a higher risk of freezing and falling (Cheng et al. 2014; McNeely and Earhart 2011). Turning requires complex

planning, locomotion and postural control. A relatively limited number of studies in PD focused on the turning phase of walking even though it has a significant role clinically and in patients' daily life (Hong and Earhart 2010; Curtze et al. 2015; McNeely and Earhart 2011). Even fewer studies investigated the effect of medication on turning parameters in PD. To my knowledge, this is the first study to investigate turning in PD during both ST and DT, and the first to show the effect of medication on turning during DT conditions.

My findings show that dopaminergic medication has a limited positive effect on turning during ST. It only improved step duration and peak velocity of turning. These findings are in line with previous studies showing improvement in these parameters during ST conditions (Hong and Earhart 2010; Curtze et al. 2015). A previous study (Curtze et al. 2015) presents a ranking of responsiveness of turning parameters to Levodopa (under ST conditions). In this study, the authors investigated gait, balance, posture and turning in 104 patients with a protocol of three iSAW assessments (30s standing still followed by 7m straight walking and a 180° turn). The difference in that study protocol, compared to this study, may make straight walking results incomparable. The turning results in the above-mentioned study and this are, however, comparable and support one another. Similar to their work, I found peak velocity of turning to be most responsive to the dopaminergic medication. However, I found step duration during turning to be the only additional sensitive parameter to dopaminergic medication. Mean step duration was ranked least responsive in Curzte's work. It's possible that this difference in results is due to the differences in the two protocols. My study included multiple turns per assessment, each performed after 20m of walking, while they included one turn per assessment after a 7m walk only.

I included PD patients in a mild-moderate disease stage, and the other study (Curtze et al. 2015) also partly included patients that were more severely affected. It is thus also possible that this difference has an effect on the respective results, and, consequently, patients in different PD stages may respond to dopaminergic medication differently in terms of turning parameters. If that is the case, it might be useful to explore if responsiveness of turning parameters, e.g. step duration, to dopaminergic medication can serve as a progression marker in PD.

Previous studies showed that older individuals, in particular PD patients, develop their own strategies to ensure a safer turning (Stack, Ashburn, and Jupp 2006). Examples of strategies adopted by PD patients for safe turning are spinning in place, making more steps over a longer curvature to turn and splitting a turn into smaller parts of movements with pauses in between (Stack, Ashburn, and Jupp 2006). It would be interesting to compare the medication effect on these strategies, which is beyond the scope of the work presented here and should be investigated in future studies.

Regarding how turning parameters respond to dopaminergic medication during DT conditions, none of the parameters investigated here responded to the medication. I could not find, to the date of composing this work, any studies that can confirm, support or contradict these findings. As discussed above, it's possible that the complexity of a concurrent cognitive task may limit the benefits of the dopaminergic medication. We have also established that turning is a complex movement that requires planning and complicated dynamics. These two factors combined might be the reason turning during DT don't benefit at all from the dopaminergic medication.

4.4. The Effect of Dopaminergic Medication on the MDS-UPDRS III Score

An improvement in the MDS-UPDRS III score (Goetz et al. 2008) between Off- and On-medication was given –per definition- in all 39 patients selected for my analysis. Previous studies suggest that a minimum of two points improvement must be observed in order to consider it clinically significant, a difference termed "minimum clinically relevant improvement" (MCRI) (Schrag et al. 2006; Shulman et al. 2010). I recognize that the medication had a positive effect on the motor functions of the participants, but this was obviously not seen in (and thus, not due to) straight walking and turning parameters assessed here during ST and during DT. It is thus probable that the improvement seen in the MDS-UPDRS III is mostly

due to improvements of the fine motor functions in the upper limbs. This argument is supported by the observed improvement in the CB speed as it has a fine motor component.

4.5. How Does Dopaminergic Medication Affect Cognition?

Cognitive impairment is a common symptom of PD. It can be in the form of deficits in components such as memory, attention, and motor planning. The challenging DT conditions magnify these deficits, and hence, increase the risk of e.g. falling. In this study, dopaminergic medication improved the cognitive functions with mainly a motor component (CB) but not the more complex task related to executive functions (SS). This effect was observed during both ST and DT.

The disparity of effectiveness on different cognitive tasks may be due to different reasons. First, SS might be too complex and cognitively challenging to improve with dopaminergic medication, in contrast to CB, the cognitively easier task to perform. Secondly, it is possible that an improvement in the movement, not cognition itself, is what led to the improved secondary task of CB. Thirdly, it can be argued that most patients perceive SS as more difficult than CB, hence, riskier and more dangerous. Thus, they focus on safe walking when performing such a "dangerous" task. However, the medication did not improve SS even during ST, when no risks were imposed, which speaks against this possibility. Fourthly, it is well possible that the more complex secondary task depends more on non-dopaminergic pathways and networks, such as the cholinergic system. In fact, recent literature shows that cholinesterase inhibitors have a beneficial effect on mobility that is associated with cognitive load. For example, (Chung et al. 2010) showed that postural stability improved in 23 fallers with PD, who were given cholinesterase inhibitors. That led to a 40% decrease in their falling frequency compared to placebo treatment. The authors concluded that cholinergic medication may have improved attention in these patients which led to less falls. This assumption also argues for the central role of cognitive functions in PD patients' movement. Moreover, the association between cholinergic pathways and postural stability has also been shown in older adults in recent work (Arnold

et al. 2018). Whether the influence is directly motor or rather through improving cognition (as Chung et al suggest) is a question that should be further investigated.

Another recent work (Henderson et al. 2016) found that rivastigmine (an acetylcholinesterase inhibitor) improved gait variability during normal walking and simple DT in PD patients compared to those who were given placebo. However, gait variability did not improve during "difficult" DT. Based on that, one can argue that firstly, the difficulty of the secondary task (cognitive challenge) does affect the motor benefits gained from the medication and may block them. Secondly, PD patients can be advised to avoid DT conditions only when the secondary task is "too difficult" for the medication to be effective.

Taken together, these observations indicate that cognitive tasks with simple aspects are to a certain degree responsive to dopaminergic medication and can be targeted with such treatments options and the complexity of some other cognitive tasks may block -or may not be responsive to- (the effect of) dopaminergic medication as shown by (Henderson et al. 2016).

I mentioned above the possibility that the dopaminergic medication had no positive effect on the cognitive abilities and the improvement in CB speed was caused purely by the improvement in the fine motor functions as shown in the MDS-UPDRS-III score. This interpretation is in line with the work showing that motor impairments e.g.: rigidity and bradykinesia in the upper limbs are indeed responsive to dopaminergic medication, independent of whether they are performed alone or simultaneously with another task (Schrag et al. 1999). Furthermore, this finding is consistent with the high direct correlation of the Purdue pegboard test scores and the nigrostriatal dopaminergic deficit as measured with Fluorodopa positron emission tomography (Vingerhoets et al. 1997).

As a consequence, the effect of dopaminergic medication on cognition as observed in this study investigating straight and curved walking as well as the body of literature investigating this aspect, motivates to use treatment strategies for PD that do not only focus on one mechanism and a specific drug. Combining

medication with cognitive therapy and most probably also physio- and occupational therapy seems most promising also for PD patients with deficits in gait and turning. In the following, I will elaborate on some treatment options, which I consider potentially useful for these patients. However, it should be noted that direct evidence supporting these treatment options is currently not fully sufficient.

- Treadmill Training

In their review, (Mehrholz et al. 2015) analysed 18 treatment studies in PD using treadmill training. Results of these studies indicate that treadmill training improves gait velocity and step length. While that is directly beneficial to PD patients by improving their quality of life, an improved gait velocity is also a predictor of a better life expectancy (Montero-Odasso et al. 2005). The mechanics of treadmill walking could also increase gait regularity. It is thus probable that the same PD patients tested in this study would benefit from treadmill training, at least concerning deficits during straight walking under ST conditions.

In regard to DT, Mirelman et al. (Mirelman, Maidan, et al. 2011) showed that four weeks of treadmill combined with virtual reality training improved DT gait velocity and decreased gait variability in 20 PD patients. In a more recent and larger work (Mirelman et al. 2016), the authors showed that treadmill training in addition to virtual reality training (i.e.: in DT training) benefited postural control and led to less falls and risk of falling compared to treadmill training alone.

These findings together strongly suggest that treadmill training benefits ST and DT walking in PD patients and that DT treadmill training is even more beneficial than ST training. Moreover, the improvements in gait variability, which is resistant to dopaminergic medication, argue for combining this type of training with the medication to target more dopaminergic-resistant gait parameters.

Regarding treadmill training to improve turning in PD, it's difficult to target and train turning, because the treadmill is made for straight walking by design. Nonetheless, Hong and Earhart (Hong and Earhart 2008) did show that treadmill training can improve freezing of gait symptoms during turning in PD patients.

Based on this finding, it is reasonable to hypothesize that turning per se might also benefit from treadmill training.

- Exergaming Training

Recent studies have shown benefits of exergaming on movement in PD patients (Barry, Galna, and Rochester 2014; Mirelman et al. 2016). Stride length improved in PD patients who received exergaming training. Moreover, this improvement was observed during DT conditions. This implies an improvement also in the cognitive aspects of the disease.

The convenience of exergaming, being available to patients at home and for unlimited time is an advantage to consider in the application of such methods discussed here.

- Tai Chi Training

It has been shown that Tai Chi has positive effects on postural stability, ST gait velocity and step length in PD patients (Li et al. 2012). This effect was also better than some other investigated methods such as stretching and strength training. Another study investigating 31 participants (Wayne et al. 2015) found that six months of Tai Chi training improved DT gait velocity and gait variability. The study also showed that Tai Chi experts had a lower (better) DT gait variability than novel Tai Chi participants. It is interesting to note that the benefits of Tai Chi training are more prominent during DT than ST. The reason for this may be that Tai Chi includes both motor and cognitive aspects. This assumption is indirectly supported by another study which found an effect of Tai Chi on emotional well-being score, digits backwords test and fear of falling (as part of the Tinetti Falls Efficacy Scale) (Nocera et al. 2013). This advantage (improving gait during DT) may nominate Tai Chi practice as a fitting training method particularly for PD patients who typically show difficulties with DT.

- Cueing

Another method of improving gait, e.g. by preventing freezing, in PD is the use of cues. Cues can be auditory, visual or tactile.

A recent work by Ghai et al. (Ghai et al. 2018) reviewed 50 studies investigating the effect of rhythmic auditory cues on gait in PD. Taken together, these studies show that auditory cueing training improves gait velocity, cadence, step length and gait variability in PD patients during straight walking. Sessions of 20-45 minutes of training are recommended for patients, three to five times a week (Lohnes and Earhart 2011).

Other studies, such as (Fietzek et al. 2014), show the positive effect of different forms of cueing (visual and tactile) on straight walking in PD, improving velocity and step length, and decreasing freezing episodes.

Regarding turning, one study (Nieuwboer et al. 2009) investigated the short-term effect of different cueing modalities on the duration of turns. The intervention performed in 153 PD patients increased the mean speed of turning. They, however, suggest that the effect on functionality needs to be further studied. Another study (Spildooren et al. 2012) found that cueing training decreased freezing of gait episodes during turning. These benefits disappeared in a very short time after the cueing stopped, which however should not lead us to conclude that the treatment is not effective (medication has also effects over limited periods of time if not continuously given).

- Cognitive Training

As shown in my results and in the literature discussed above, cognition has an important influence on gait. More specifically, one study (Holtzer, Wang, and Verghese 2012) showed that executive attention is related with gait velocity and step length during both ST and DT. The cognitive state and abilities of PD patients affect the quality of their gait. For example, deteriorated executive functions are associated with wrong prioritisation strategies in PD, resulting in a higher risk of e.g. falling (van Iersel et al. 2008). It has also been proven that cognitively challenging conditions (e.g. DT) lead to slower gait and higher risk of falling and freezing (Beauchet et al. 2009).

Hence, cognitive training could be very beneficial for some PD patients. Improving attention, attention flexibility and executive functions will most likely

improve postural stability and safety, particularly during turning (Petzinger et al. 2013; Geritz, Maetzler, and Schlenstedt 2018).

In their work, Walton and colleagues (Walton et al. 2014) showed that targeted cognitive training can improve executive processes and thus decrease the risk and occurrence of freezing of gait in PD. One study (Yogev-Seligmann et al. 2012) proposed a training program for PD patients to improve their DT walking. They performed four walking assessments: one ST and three DT with the following secondary tasks (SS, information processes and open-ended complex questions). They then received four weeks of cognitive training that was specifically designed to improve the SS and information processes. After the training, participants performed the walking assessments again. Gait velocity improved in all patients in all DT conditions, including the condition that did not receive specific training (open-ended complex questions). Gait (stride time) variability also improved with training. The improvements in gait in these patients were still observable four weeks after the training. The study however included only seven PD patients. Another study (Milman et al. 2014) included a larger cohort (18 PD patients) and a longer training period (12 weeks). Patients were asked to play certain computer games designed to improve executive function and attention, for 30 minutes, three times a week for three months. The TUG performance in these patients was recorded before and after the training program. In this study, as in the one mentioned above, gait velocity and variability improved. In addition, turning speed and turning duration also improved during the TUG assessments.

What we learn from these studies is that cognitive training in different forms improves several aspects of gait and turning in PD patients during ST and DT. I could not find studies specifically examining the effects of cognitive training on DT turning. Therefore, future work should tackle this point. However, given the established benefits on cognitive and motor symptoms as well as freezing in PD, it is likely that DT turning also benefits from cognitive training.

Taken together, gait velocity has been shown to improve by medication and several other methods of intervention such as treadmill training, cueing and Tai

Chi. In addition, the methods discussed above have the capacity to improve various aspects of PD. It is thus most likely that a multifaceted treatment plan is the most promising and effective approach to treatment of straight walking and turning deficits in PD. However, especially the effects of the above-discussed methods on DT performance, which is most relevant for daily life, has to be investigated in much more detail.

An additional point to consider while creating a treatment plan, is the long-term benefits of a method. Cueing for example, as shown in some studies above, failed to create a benefit for PD patients on the long term, which may be a disadvantage especially for patients with low motivation and retention. On the other hand, cognitive training benefits were still observable weeks after the end of treatment.

For many years, almost all PD patients were treated solely by neurologists or by general practitioners. In recent years, interdisciplinary frameworks for treating PD (and similar diseases) have been adopted in many health care systems (Van Der Eijk et al. 2013; Giladi et al. 2014). In these frameworks, teams of specialized healthcare professionals communicate and organize the treatment plans, training and daily activities of the patients. For instance, the neurologist handles the medications and the general orchestration of the treatment plan. The physiotherapist and occupational therapists build and execute a plan for physical and occupational training while nurses specialized in PD can address medical issues seen in PD patients when they visit them in the home environment. The neuropsychologists contribute by providing cognitive assessment and training to PD patients.

This interdisciplinary approach includes several strategies that have been mentioned above and provide PD patients with a better chance to cope with the disease. The practical application of this interdisciplinary framework is already being implemented in several places in Germany's leading hospitals and spreading to be a norm in Europe (Van Der Eijk et al. 2013; Bloem and Munneke 2014).

4.6. The Use of Inertial Measurement Units to Assess Parkinson's Disease

Using IMUs, we could quantify and compare detailed aspects of walking and turning. Relevant parameters such as stride duration variability, double limb support time variability, peak velocity of turning, are practically impossible to quantify by the naked eye. This study adds to the increasing evidence of the importance of using advanced technology such as IMUs to assess movement in PD and other diseases (Sánchez-Ferro et al. 2016).

There have been efforts to further exploit the objectivity and accuracy of IMUs to even create a gait quality scale replacing the motor part of UPDRS (Klucken et al. 2013). Although these efforts might be premature, it is likely that the future of assessing PD will eventually include such technology as a standard assessment tool (Hansen, Sanchez-Ferro, and Maetzler 2018).

There are several types of technologies to quantify movement. Motion capture camera systems, pressure mats, and IMUs have all been extensively investigated and used mainly in research settings. The advantages IMUs hold over other options are their economic and unobtrusive nature and foremost, their applicability in almost any environment, including at home. It is expected that patients will soon be able to export their own data and have insights into their motor functions or the treatment efficacy on their own (Hansen, Sanchez-Ferro, and Maetzler 2018).

4.7. Limitations and Future Work

A limitation of this study is the relatively narrow window of patients' selection in terms of disease stage (mild to moderate PD). This work should thus be interpreted with caution, especially before generalising its findings to other disease stages. Another limitation is the assessment of cognitive tasks using a stopwatch, which is not as objective and granular as more sophisticated evaluation systems (such as integrated smartphone applications). It would also be interesting to explore more parameters of the cognitive tasks such as the accuracy of SS, not only speed. My work, however, provides an important insight into the effect of dopaminergic medication on different walking phases during DT.

Moreover, this work fittingly combines several motor, cognitive and clinical aspects of the disease. This encourages future studies to explore these aspects and deficits of PD and highlights how they affect each other.

Future work can include further analysis of parameters from the postural stability domain. Whether used independently or combined with gait (i.e. PIGD complex), it should provide useful insights into the effect of the dopaminergic medication on the gait domain as well. It would also be interesting to know if certain types of treatment are more beneficial for patients in different environments (e.g., at home), which can influence the execution of certain movements.

Further analysis can also compare in more depth the effect of different types of cognitive tasks (here CB and SS) on straight walking and turning during Off- and On-medication conditions especially from a cognitive perspective.

5. Conclusion

Dopaminergic medication, the most common treatment choice in PD, has a limited effect on straight walking and turning during ST. Namely, it improves gait velocity during straight walking, and improves step duration and peak velocity parameters of turning. Furthermore, it has no significant influence on these activities during the more daily-relevant DT conditions. The medication seems to have a mixed effect on cognition, improving the speed of cognitive tasks with substantial motor component but not more complex cognitive tasks using executive functions.

From these observations, I suggest that a more multifaceted and multidisciplinary treatment strategy for PD could be more effective than drug treatment alone. This strategy can include, e.g., medication (also beyond dopaminergic treatment, e.g., choline esterase inhibitors), cognitive therapy, physio- and occupational therapy. Until this multifaceted and trans-disciplinary treatment is becoming a reality country-wide, patients should be reminded to prioritize safe walking, particularly during DT, where the medication is not significantly beneficial.

Lastly, as shown here, wearable technology enables a more granular and an objective assessment of PD treatment compared to other methods such as the clinical eye. In the future, many other questions regarding PD can be investigated using this method.

6. **Summary**

Parkinson's disease (PD) is a neurodegenerative disease that leads to a continuous deterioration in the motor, cognitive and behavioural functions of the brain. The degeneration of the dopamine-releasing neurons in the basal ganglia throughout the course of the disease can be compensated, at least to some extent, by dopaminergic medication.

Dopaminergic medication has various effects on different aspects of PD. On one hand, it improves several motor and cognitive functions such as distal movement, cognitive flexibility and attention switching. On the other hand, it has no positive effect on others, such as some aspects of gait and turning. It might even have a negative effect on some of the cognitive processes. In regard to straight walking and turning, two common phases of our daily walking routine that are particularly interesting in PD patients, dopaminergic medication has been shown to improve some gait domains e.g. velocity; but does not seem to have a relevant impact on other gait domains such as variability and rhythmicity. Moreover, most of the studies investigating gait in PD are performed during single tasking (ST) conditions. It is thus important and daily-life relevant to study gait during dual tasking (DT) because we are constantly performing at least two tasks if not more during our normal lives.

In this study, I investigated the effect of dopaminergic medication on straight walking and turning in PD patients during ST and DT. During DT I used two secondary tasks: the CB task, which is a cognitive task with a substantial motor component, and a more complex cognitive task of serial subtractions. My data show that during DT dopaminergic medication had no significant effect on straight walking or on turning parameters assessed with IMUs. During single tasking, only gait velocity was improved by the medication for straight walking. Step duration and peak velocity parameters improved during the turning phase. An additional finding was the positive effect of dopaminergic medication on CB during ST and DT, but not SS.

My findings suggest that dopaminergic medication has no significant effect on straight walking and turning during the more daily relevant DT conditions. These

findings call for alternative treatment strategies and different methods of management. They also shed light on the positive effect of the dopaminergic medication on cognitive tasks with (relatively simple) motor components, rather than on complex tasks. This is important when targeting certain disabilities in PD patients to know what functions can be improved using dopaminergic medication.

7. Deutsche Zusammenfassung

Das idiopathische Parkinson-Syndrom (IPS) ist eine neurodegenerative Erkrankung, die mit der Beeinträchtigung von Motorik, Kognition und Verhalten einhergeht. Die Krankheit führt zu einer zunehmenden Degeneration von Dopamin-ausschüttenden Neuronen in den Basalganglien, welche in der Regel durch dopaminerge Medikamente behandelt wird.

Dopaminerge Medikation hat verschiedene Effekte auf die unterschiedlichen Symptome des IPS. Sie verbessert verschiedene motorische und kognitive Funktionen, wie zum Beispiel Bewegungsabläufe, kognitive Flexibilität und Aufmerksamkeit. Jedoch hat die Medikation auf andere Bereiche, wie Gang und Drehbewegungen, keine positiven Effekte und kann auf bestimmte kognitive Prozesse sogar negativ einwirken.

Beim hier untersuchten Geradeausgehen und Drehen, zwei gewöhnlichen Komponenten beim Gehen im Alltag, die von besonderem Interesse bei Parkinsonpatienten sind, hat die Medikation einen positiven Einfluss auf einige Gangparameter wie zum Beispiel Ganggeschwindigkeit. Sie hat jedoch keinen Effekt in anderen Bereichen wie Variabilität und Rhythmus. Anders als in den meisten Studien wird das Gangbild hier nicht nur unter Single Task (ST) Bedingungen, sondern auch unter Dual Task (DT) Bedingungen untersucht. Dies bildet den Alltag der Parkinsonpatienten deutlich besser ab, da sie während ihrer alltäglichen Aktivitäten oft mindestens zwei Aufgaben gleichzeitig durchführen. Daher werden in dieser Studie die Effekte dopaminerger Medikation bei Personen mit Parkinson auf das Geradeausgehen und Drehen unter ST und DT Bedingungen untersucht.

Als DT wurden zwei sekundäre Aufgaben verwendet, eine Ankreuzaufgabe, welche eine motorische Komponente beinhaltet und eine komplexere kognitive Aufgabe, bei der die Probanden fortlaufend subtrahieren. Die Daten zeigen, dass die dopaminerge Medikation bei der DT Bedingung keinerlei Einfluss auf die untersuchten Parameter beim Gehen und Drehen hatte. Während der ST Bedingung konnte nur die Ganggeschwindigkeit durch die Medikation erhöht werden. Beim Drehen wurden die Schrittzeit und die maximale Geschwindigkeit verbessert. Zusätzlich hatte die Medikation einen positiven Einfluss auf die

Schnelligkeit der Ankreuzaufgabe, jedoch nicht auf die Schnelligkeit der Subtraktionsaufgabe. Unsere Ergebnisse weisen darauf hin, dass dopaminerge Medikation keinen signifikanten Effekt auf das Geradeausgehen und Drehen bei alltagsrelevanten DT Aufgaben hat. Dieses Ergebnis betont die Bedeutung von alternativen Behandlungsstrategien und eines alternativen Behandlungsmanagements. Zudem ist der positive Effekt der Medikation auf kognitive Aufgaben mit motorischer Komponente hervorzuheben, der im Gegensatz zum fehlenden Effekt der Medikation auf komplexere, forderndere kognitive Aufgaben steht. Diese Erkenntnisse sind wichtig um Funktionseinschränkungen der Parkinsonpatienten gezielt zu behandeln, mit dem Wissen welche Bereiche durch die dopaminerge Medikation positiv beeinflusst werden können.

8. **References**

Adcock, R A, R T Constable, J C Gore, and P S Goldman-Rakic. 2000. "Functional Neuroanatomy of Executive Processes Involved in Dual-Task Performance." *Proceedengs of the National Academy of Sciences U S A* 97 (7): 3567–72. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=10725387.

Almeida, Quincy J., James S. Frank, Eric A. Roy, Aftab E. Patla, and Mandar S. Jog. 2007. "Dopaminergic Modulation of Timing Control and Variability in the Gait of Parkinson's Disease." *Movement Disorders* 22 (12): 1735–42. https://doi.org/10.1002/mds.21603.

Arnold, Carina, Claudia Schulte, Mariana Moscovich, Ulrike Sünkel, Laura Zaunbrecher, Florian Metzger, Thomas Gasser, et al. 2018. "Cholinergic Pathway SNPs and Postural Control in 477 Older Adults." *Frontiers in Aging Neuroscience*. https://doi.org/10.3389/fnagi.2018.00260.

Baba, M, S Nakajo, P H Tu, T Tomita, K Nakaya, V M Lee, J Q Trojanowski, and T Iwatsubo. 1998. "Aggregation of Alpha-Synuclein in Lewy Bodies of Sporadic Parkinson's Disease and Dementia with Lewy Bodies." *The American Journal of Pathology* 152 (4): 879–84. https://doi.org/10.1086/281267.

Baker, Katherine, Lynn Rochester, and Alice Nieuwboer. 2008. "The Effect of Cues on Gait Variability-Reducing the Attentional Cost of Walking in People with Parkinson's Disease." *Parkinsonism and Related Disorders* 14 (4): 314–20. https://doi.org/10.1016/j.parkreldis.2007.09.008.

Baltadjieva, Rossitza, Nir Giladi, Leor Gruendlinger, Chava Peretz, and Jeffrey M. Hausdorff. 2006. "Marked Alterations in the Gait Timing and Rhythmicity of Patients with de Novo Parkinson's Disease." *European Journal of Neuroscience* 24 (6): 1815–20. https://doi.org/10.1111/j.1460-9568.2006.05033.x.

Barry, Gillian, Brook Galna, and Lynn Rochester. 2014. "The Role of Exergaming in Parkinson's Disease Rehabilitation: A Systematic Review of the Evidence." *Journal of NeuroEngineering and Rehabilitation*. https://doi.org/10.1186/1743-0003-11-33.

Beauchet, O., C. Annweiler, V. Dubost, G. Allali, R. W. Kressig, S. Bridenbaugh, G. Berrut, F. Assal, and F. R. Herrmann. 2009. "Stops Walking When Talking: A Predictor of Falls in Older Adults?" *European Journal of Neurology*. https://doi.org/10.1111/j.1468-1331.2009.02612.x.

Beck, A T, R A Steer, R Ball, and W Ranieri. 1996. "Comparison of Beck Depression Inventories -IA and -II in Psychiatric Outpatients." *Journal of Personality Assessment* 67 (3): 588–97. https://doi.org/10.1207/s15327752jpa6703_13.

Beck, Aaron T., Robert A. Steer, and Margery G. Carbin. 1988. "Psychometric Properties of the Beck Depression Inventory: Twenty-Five Years of Evaluation." *Clinical Psychology Review*. https://doi.org/10.1016/0272-7358(88)90050-5.

Benabid, Alim Louis, Stephan Chabardes, John Mitrofanis, and Pierre Pollak. 2009. "Deep Brain Stimulation of the Subthalamic Nucleus for the Treatment of Parkinson's Disease." *The Lancet Neurology*. https://doi.org/10.1016/S1474-4422(08)70291-6.

Blin, O, A M Ferrandez, J Pailhous, and G Serratrice. 1991. "Dopa-Sensitive and Dopa-Resistant Gait Parameters in Parkinson's Disease." *Journal of the Neurological Sciences* 103 (1): 51–54. https://doi.org/10.1016/0022-510X(91)90283-D.

Bloem, B R, D J Beckley, J G van Dijk, A H Zwinderman, M P Remler, and R A Roos. 1996. "Influence of Dopaminergic Medication on Automatic Postural Responses and Balance Impairment in Parkinson's Disease." *Movement Disorders : Official Journal of the Movement Disorder Society* 11 (5): 509–21. https://doi.org/10.1002/mds.870110506.

Bloem, Bastiaan R., Yvette A M Grimbergen, Monique Cramer, Mirjam Willemsen, and Aeilko H. Zwinderman. 2001. "Prospective Assessment of Falls in Parkinson's Disease." *Journal of Neurology* 248 (11): 950–58. https://doi.org/10.1007/s004150170047.

Bloem, Bastiaan R., and Marten Munneke. 2014. "Revolutionising Management of Chronic Disease: The ParkinsonNet Approach." *BMJ (Online)*. https://doi.org/10.1136/bmj.g1838.

Boonstra, Tjitske A, Herman van der Kooij, Marten Munneke, and Bastiaan R Bloem. 2008. "Gait Disorders and Balance Disturbances in Parkinson's Disease: Clinical Update and Pathophysiology." *Current Opinion in Neurology* 21 (4): 461–71. https://doi.org/10.1097/WCO.0b013e328305bdaf.

Braak, H., and E. Braak. 2000. "Pathoanatomy of Parkinson's Disease." *Journal of Neurology* 247 (S2): II3–10. https://doi.org/10.1007/PL00007758.

Brauer, Sandra G., and Meg E. Morris. 2010. "Can People with Parkinson's Disease Improve Dual Tasking When Walking?" *Gait and Posture* 31 (2): 229–33. https://doi.org/10.1016/j.gaitpost.2009.10.011.

Campenhausen, Sonja Von, Bernhard Bornschein, Regina Wick, Kai Bötzel, Cristina Sampaio, Werner Poewe, Wolfgang Oertel, Uwe Siebert, Karin Berger, and Richard Dodel. 2005. "Prevalence and Incidence of Parkinson's Disease in Europe." *European Neuropsychopharmacology* 15 (4): 473–90. https://doi.org/10.1016/j.euroneuro.2005.04.007.

Chaudhuri, K. Ray, and Anthony HV Schapira. 2009. "Non-Motor Symptoms of Parkinson's Disease: Dopaminergic Pathophysiology and Treatment." *The Lancet Neurology*. https://doi.org/10.1016/S1474-4422(09)70068-7.

Chaudhuri, K Ray, Daniel G Healy, and Anthony HV Schapira. 2006. "Non-Motor Symptoms of Parkinson's Disease: Diagnosis and Management."

The Lancet Neurology 5 (3): 235–45. https://doi.org/10.1016/S1474-4422(06)70373-8.

Cheng, Fang Yu, Yea Ru Yang, Chung Jen Wang, Yih Ru Wu, Shih Jung Cheng, Han Cheng Wang, and Ray Yau Wang. 2014. "Factors Influencing Turning and Its Relationship with Falls in Individuals with Parkinson's Disease." *PLoS ONE* 9 (4). https://doi.org/10.1371/journal.pone.0093572.

Chung, Kathryn A., Brenna M. Lobb, John G. Nutt, and Fay B. Horak. 2010. "Effects of a Central Cholinesterase Inhibitor on Reducing Falls in Parkinson Disease." *Neurology*. https://doi.org/10.1212/WNL.0b013e3181f6128c.

Connolly, Barbara S, and Anthony E Lang. 2014. "Pharmacological Treatment of Parkinson Disease: A Review." *JAMA : The Journal of the American Medical Association* 311 (16): 1670–83. https://doi.org/10.1001/jama.2014.3654.

Cools, R, R A Barker, B J Sahakian, and T W Robbins. 2001. "Enhanced or Impaired Cognitive Function in Parkinson's Disease as a Function of Dopaminergic Medication and Task Demands." *Cerebral Cortex (New York, N.Y. : 1991)*. Vol. 11. https://doi.org/10.1093/cercor/11.12.1136.

Cools, Roshan, Roger A. Barker, Barbara J. Sahakian, and Trevor W. Robbins. 2003. "L-Dopa Medication Remediates Cognitive Inflexibility, but Increases Impulsivity in Patients with Parkinson's Disease." *Neuropsychologia* 41 (11): 1431–41. https://doi.org/10.1016/S0028-3932(03)00117-9.

Cools, Roshan, Simon J G Lewis, Luke Clark, Roger A Barker, and Trevor W Robbins. 2007. "L-DOPA Disrupts Activity in the Nucleus Accumbens during Reversal Learning in Parkinson's Disease." *Neuropsychopharmacology : Official Publication of the American College of Neuropsychopharmacology*. Vol. 32. https://doi.org/10.1038/sj.npp.1301153.

Crenna, P., I. Carpinella, M. Rabuffetti, E. Calabrese, P. Mazzoleni, R. Nemni, and M. Ferrarin. 2007. "The Association between Impaired Turning and Normal Straight Walking in Parkinson's Disease." *Gait and Posture* 26 (2): 172–78. https://doi.org/10.1016/j.gaitpost.2007.04.010.

Curtze, Carolin, John G Nutt, Patricia Carlson-Kuhta, Martina Mancini, and Fay B Horak. 2015. "Levodopa Is a Double-Edged Sword for Balance and Gait in People With Parkinson's Disease." *Movement Disorders : Official Journal of the Movement Disorder Society*, June. https://doi.org/10.1002/mds.26269.

Dauer, William, and Serge Przedborski. 2003. "Parkinson's Disease: Mechanisms and Models." *Neuron*. https://doi.org/10.1016/S0896-6273(03)00568-3.

Deuschl, Günther, Carmen Schade-Brittinger, Paul Krack, Jens Volkmann, Helmut Schäfer, Kai Bötzel, Christine Daniels, et al. 2006. "A Randomized Trial of Deep-Brain Stimulation for Parkinson's Disease." *New England Journal of Medicine* 355 (9): 896–908. https://doi.org/10.1056/NEJMoa060281.

Doherty, Karen M., Bart P. van de Warrenburg, Maria Cecilia Peralta, Laura Silveira-Moriyama, Jean Philippe Azulay, Oscar S. Gershanik, and Bastiaan R. Bloem. 2011. "Postural Deformities in Parkinson's Disease." *The Lancet Neurology*. https://doi.org/10.1016/S1474-4422(11)70067-9.

Donath, Lars, Oliver Faude, Eric Lichtenstein, Corina Nuesch, and Annegret Mündermann. 2016. "Validity and Reliability of a Portable Gait Analysis System for Measuring Spatiotemporal Gait Characteristics: Comparison to an Instrumented Treadmill." *Journal of NeuroEngineering and Rehabilitation* 13 (1). https://doi.org/10.1186/s12984-016-0115-z.

Drane, Daniel L, Robert L Yuspeh, Justin S Huthwaite, and Lacey K Klingler. 2002. "Demographic Characteristics and Normative Observations for Derived-Trail Making Test Indices." *Neuropsychiatry, Neuropsychology, and Behavioral Neurology*. https://doi.org/10.1093/arclin/15.8.687a.

Eeden, S. K. Van Den. 2003. "Incidence of Parkinson's Disease: Variation by Age, Gender, and Race/Ethnicity." *American Journal of Epidemiology* 157 (>11): 1015–22. https://doi.org/10.1093/aje/kwg068.

Eijk, Martijn Van Der, Frouke A.P. Nijhuis, Marjan J. Faber, and Bastiaan R. Bloem. 2013. "Moving from Physician-Centered Care towards Patient-Centered Care for Parkinson's Disease Patients." *Parkinsonism and Related Disorders*. https://doi.org/10.1016/j.parkreldis.2013.04.022.

El-Gohary, Mahmoud, Sean Pearson, James McNames, Martina Mancini, Fay Horak, Sabato Mellone, and Lorenzo Chiari. 2014. "Continuous Monitoring of Turning in Patients with Movement Disability." *Sensors (Switzerland)* 14 (1): 356–69. https://doi.org/10.3390/s140100356.

Fahn, S. 2000. "The Spectrum of Levodopa-Induced Dyskinesias." *Annals of Neurology*.

Fahn, Stanley, David Oakes, Ira Shoulson, Karl Kieburtz, Alice Rudolph, Anthony Lang, C Warren Olanow, Caroline Tanner, and Kenneth Marek. 2004. "Levodopa and the Progression of Parkinson's Disease." *The New England Journal of Medicine*. Vol. 351. https://doi.org/10.1007/s11910-005-0069-1.

Fall, Per Arne, Olav Axelson, Mats Fredriksson, Gunilla Hansson, Björn Lindvall, Jan Edvin Olsson, and Ann Kathrine Granérus. 1996. "Age-Standardized Incidence and Prevalence of Parkinson's Disease in a Swedish Community." *Journal of Clinical Epidemiology* 49 (6): 637–41. https://doi.org/10.1016/0895-4356(96)00003-0.

Fasano, Alfonso, Antonio Daniele, and Alberto Albanese. 2012. "Review Treatment of Motor and Non-Motor Features of Parkinson ' s Disease with Deep Brain Stimulation." *Lancet Neurology* 11: 429–42. //203.4.147.238.

Fearnley, Julian M., and Andrew J. Lees. 1991. "Ageing and Parkinson's Disease: Substantia Nigra Regional Selectivity." *Brain* 114 (5): 2283–2301. https://doi.org/10.1093/brain/114.5.2283.

Field, Andy. 2013. "Andy Field - Discovering Statistics Using SPSS." *Lavoisier.Fr*. https://doi.org/10.1111/j.1365-2648.2007.04270_1.x.

Fietzek, Urban M., Frauke E. Schroeteler, Kerstin Ziegler, Jens Zwosta, and Andres O. Ceballos-Baumann. 2014. "Randomized Cross-over Trial to Investigate the Efficacy of a Two-Week Physiotherapy Programme with Repetitive Exercises of Cueing to Reduce the Severity of Freezing of Gait in Patients with Parkinson's Disease." *Clinical Rehabilitation*. https://doi.org/10.1177/0269215514527299.

Folstein, Marshal F., Susan E. Folstein, and Paul R. McHugh. 1975. "'Mini-Mental State.'" *Journal of Psychiatric Research*. https://doi.org/10.1016/0022-3956(75)90026-6.

Gai, W. P., P. C. Blumbergs, and W. W. Blessing. 1995. "Microtubule-Associated Protein 5 Is a Component of Lewy Bodies and Lewy Neurites in the Brainstem and Forebrain Regions Affected in Parkinson's Disease." *Acta Neuropathologica* 91 (1): 78–81. https://doi.org/10.1007/s004010050395.

Galletly, Robyn, and Sandra G Brauer. 2005. "Does the Type of Concurrent Task Affect Preferred and Cued Gait in People with Parkinson's Disease?" *The Australian Journal of Physiotherapy*. Vol. 51. https://doi.org/10.1016/S0004-9514(05)70024-6.

Galna, B, S Lord, and L Rochester. 2013. "Is Gait Variability Reliable in Older Adults and Parkinson's Disease? Towards an Optimal Testing Protocol." *Gait Posture* 37 (4): 580–85. https://doi.org/10.1016/j.gaitpost.2012.09.025.

Gelb, D J, E Oliver, and S Gilman. 1999. "Diagnostic Criteria for Parkinson Disease." *Archives of Neurology* 56 (1): 33–39. https://doi.org/10.1001/archneur.56.1.33.

George, RJS, JG Nutt, KJ Burchiel, and FB Horak. 2010. "A Meta-Regression of the Long-Term Effects of Deep Brain Stimulation on Balance and Gait in PD." *Neurology* 75 (14): 1292–99. http://www.neurology.org/content/75/14/1292.short.

Geritz, Johanna, Walter Maetzler, and Christian Schlenstedt. 2018. "[Influence of Computer-Based Cognitive Training on Mobility in Healthy Older Adults : A Systematic Review]." *Zeitschrift Fur Gerontologie Und Geriatrie* 51 (2): 184–92. https://doi.org/10.1007/s00391-018-1369-9.

Ghai, Shashank, Ishan Ghai, Gerd Schmitz, and Alfred O. Effenberg. 2018. "Effect of Rhythmic Auditory Cueing on Parkinsonian Gait: A Systematic Review and Meta-Analysis." *Scientific Reports*. https://doi.org/10.1038/s41598-017-16232-5.

Gibb, W R, and A J Lees. 1988. "A Comparison of Clinical and Pathological Features of Young- and Old-Onset Parkinson's Disease." *Neurology* 38 (9): 1402–6. https://doi.org/10.1212/WNL.38.9.1402.

Giladi, Nir, Yael Manor, Ariela Hilel, and Tanya Gurevich. 2014. "Interdisciplinary Teamwork for the Treatment of People with Parkinson's Disease and Their Families." *Current Neurology and Neuroscience Reports*. https://doi.org/10.1007/s11910-014-0493-1.

Goetz, Christopher G., Barbara C. Tilley, Stephanie R. Shaftman, Glenn T.

Stebbins, Stanley Fahn, Pablo Martinez-Martin, Werner Poewe, et al. 2008. "Movement Disorder Society-Sponsored Revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS): Scale Presentation and Clinimetric Testing Results." *Movement Disorders* 23 (15): 2129–70. https://doi.org/10.1002/mds.22340.

Goodwin, Victoria A., Suzanne H. Richards, Rod S. Taylor, Adrian H. Taylor, and John L. Campbell. 2008. "The Effectiveness of Exercise Interventions for People with Parkinson's Disease: A Systematic Review and Meta-Analysis." *Movement Disorders*. https://doi.org/10.1002/mds.21922.

Gotham, A M, R G Brown, and C D Marsden. 1988. "'Frontal' Cognitive Function in Patients with Parkinson's Disease 'on' and 'off' Levodopa." *Brain* 111: 299–321. https://doi.org/10.1093/brain/111.2.299.

Hackney, M. E., and G. M. Earhart. 2010. "The Effects of a Secondary Task on Forward and Backward Walking in Parkinson's Disease." *Neurorehabilitation and Neural Repair*. https://doi.org/10.1177/1545968309341061.

Haertner, Linda Maja, Morad Elshehabi, Laura Zaunbrecher, Hoang Minh Pham, Corina Maetzler, Janet Maria Theresia Van Uem, Markus A Hobert, et al. 2018. "Effect of Fear of Falling on Turning Performance in Parkinson's Disease in the Lab and at Home." *Frontiers in Aging Neuroscience* 10: 78. https://doi.org/10.3389/FNAGI.2018.00078.

Hansen, Clint, Alvaro Sanchez-Ferro, and Walter Maetzler. 2018. "How Mobile Health Technology and Electronic Health Records Will Change Care of Patients with Parkinson's Disease." Edited by Patrik Brundin, J. William Langston, and Bastiaan R. Bloem. *Journal of Parkinson's Disease* 8 (s1): S41–45. https://doi.org/10.3233/JPD-181498.

Hasmann, Sandra E., Daniela Berg, Markus A. Hobert, David Weiss, Ulrich Lindemann, Johannes Streffer, Inga Liepelt-Scarfone, and Walter Maetzler. 2014. "Instrumented Functional Reach Test Differentiates Individuals at High Risk for Parkinson's Disease from Controls." *Frontiers in Aging Neuroscience*. https://doi.org/10.3389/fnagi.2014.00286.

Hausdorff, Jeffrey M., Jackov Balash, and Nir Giladi. 2003. "Effects of Cognitive Challenge on Gait Variability in Patients with Parkinson's Disease." *Journal of Geriatric Psychiatry and Neurology*. https://doi.org/10.1177/0891988702250580.

Hausdorff, Jeffrey M., Galit Yogev, Shmuel Springer, Ely S. Simon, and Nir Giladi. 2005. "Walking Is More like Catching than Tapping: Gait in the Elderly as a Complex Cognitive Task." *Experimental Brain Research*. https://doi.org/10.1007/s00221-005-2280-3.

Heinzel, Sebastian, Daniela Berg, Sebastian Binder, Georg Ebersbach, Lennart Hickstein, Heinz Herbst, Michael Lorrain, et al. 2018. "Do We Need to Rethink the Epidemiology and Healthcare Utilization of Parkinson's Disease in Germany?" *Frontiers in Neurology*. https://doi.org/10.3389/fneur.2018.00500.

Henderson, Emily J., Stephen R. Lord, Matthew A. Brodie, Daisy M. Gaunt,

Andrew D. Lawrence, Jacqueline C.T. Close, A. L. Whone, and Y. Ben-Shlomo. 2016. "Rivastigmine for Gait Stability in Patients with Parkinson's Disease (ReSPonD): A Randomised, Double-Blind, Placebo-Controlled, Phase 2 Trial." *The Lancet Neurology*. https://doi.org/10.1016/S1474-4422(15)00389-0.

Herz, Nathan B., Shyamal H. Mehta, Kapil D. Sethi, Paula Jackson, Patricia Hall, and John C. Morgan. 2013. "Nintendo Wii Rehabilitation ('Wii-Hab') Provides Benefits InParkinson's Disease." *Parkinsonism and Related Disorders* 19 (11): 1039–42. https://doi.org/10.1016/j.parkreldis.2013.07.014.

Hobert, Markus A., Sinja I. Meyer, Sandra E. Hasmann, Florian G. Metzger, Ulrike Suenkel, Gerhard W. Eschweiler, Daniela Berg, and Walter Maetzler. 2017. "Gait Is Associated with Cognitive Flexibility: A Dual-Tasking Study in Healthy Older People." *Frontiers in Aging Neuroscience* 9 (MAY). https://doi.org/10.3389/fnagi.2017.00154.

Hobert, Markus A., Raphael Niebler, Sinja I. Meyer, Kathrin Brockmann, Clemens Becker, Heiko Huber, Alexandra Gaenslen, et al. 2011. "Poor Trail Making Test Performance Is Directly Associated with Altered Dual Task Prioritization in the Elderly – Baseline Results from the TREND Study." Edited by Jerson Laks. *PLoS ONE* 6 (11): e27831. https://doi.org/10.1371/journal.pone.0027831.

Hodge, C. F. 1894. "Changes in Ganglion Cells from Birth to Senile Death. Observations on Man and Honey-Bee." *The Journal of Physiology* 17 (1–2): 128–34. https://doi.org/10.1113/jphysiol.1894.sp000522.

Hoehn, M M, and M D Yahr. 1967. "Parkinsonism: Onset, Progression and Mortality." *Neurology* 17 (5): 427–42. https://doi.org/10.1212/WNL.17.5.427.

Holtzer, Roee, Cuiling Wang, and Joe Verghese. 2012. "The Relationship between Attention and Gait in Aging: Facts and Fallacies." *Motor Control* 16 (1): 64–80. https://doi.org/10.1123/mcj.16.1.64.

Hong, Minna, and Gammon M. Earhart. 2008. "Rotating Treadmill Training Reduces Freezing in Parkinson Disease: Preliminary Observations." *Parkinsonism and Related Disorders*. https://doi.org/10.1016/j.parkreldis.2007.07.003.

Hong, Minna, and Gammon M Earhart. 2010. "Effects of Medication on Turning Deficits in Individuals with Parkinson's Disease." *Journal of Neurologic Physical Therapy : JNPT* 34 (1): 11–16. https://doi.org/10.1097/NPT.0b013e3181d070fe.

Horak, F., L. King, and M. Mancini. 2015. "Role of Body-Worn Movement Monitor Technology for Balance and Gait Rehabilitation." *Physical Therapy* 95 (3): 461–70. https://doi.org/10.2522/ptj.20140253.

Hughes, A. J., S. E. Daniel, L. Kilford, and A. J. Lees. 1992. "Accuracy of Clinical Diagnosis of Idiopathic Parkinson's Disease: A Clinico-Pathological Study of 100 Cases." *Journal of Neurology Neurosurgery and Psychiatry*. https://doi.org/10.1136/jnnp.55.3.181.

Hughes, JR, SG Bowes, AL Leeman, CJ O'Neill, AA Deshmukh, PW Nicholson, SM Dobbs, and RJ Dobbs. 1990. "Parkinsonian Abnormality of Foot Strike: A Phenomenon of Ageing and/or One Responsive to Levodopa Therapy?" *British Journal of Clinical Pharmacology* 29 (2): 179–86. https://doi.org/10.1111/j.1365-2125.1990.tb03617.x.

Iersel, Marianne B van, Roy P C Kessels, Bastiaan R Bloem, André L M Verbeek, and Marcel G M Olde Rikkert. 2008. "Executive Functions Are Associated with Gait and Balance in Community-Living Elderly People." *The Journals of Gerontology. Series A, Biological Sciences and Medical Sciences*. https://doi.org/10.1016/S1353-8020(08)70217-7.

Jankovic, J. 2008. "Parkinson's Disease: Clinical Features and Diagnosis." *Journal of Neurology, Neurosurgery and Psychiatry*. https://doi.org/10.1136/jnnp.2007.131045.

Keus, Samyra H J, Bastiaan R. Bloem, Erik J M Hendriks, Alexandra B. Bredero-Cohen, and Marten Munneke. 2007. "Evidence-Based Analysis of Physical Therapy in Parkinson's Disease with Recommendations for Practice and Research." *Movement Disorders* 22 (4): 451–60. https://doi.org/10.1002/mds.21244.

Klucken, Jochen, Jens Barth, Patrick Kugler, Johannes Schlachetzki, Thore Henze, Franz Marxreiter, Zacharias Kohl, et al. 2013. "Unbiased and Mobile Gait Analysis Detects Motor Impairment in Parkinson's Disease." Edited by Mathias Toft. *PLoS ONE* 8 (2): e56956. https://doi.org/10.1371/journal.pone.0056956.

Lang, Anthony E. 2011. "A Critical Appraisal of the Premotor Symptoms of Parkinson's Disease: Potential Usefulness in Early Diagnosis and Design of Neuroprotective Trials." *Movement Disorders*. https://doi.org/10.1002/mds.23609.

Lau, Lonneke M L De, and Monique M B Breteler. 2006. "Epidemiology of Parkinson ' s Disease." *The Lancet. Neurology* 5 (June): 525–35. https://doi.org/18(3) : 231 – 238.

Laurie King, Martina Mancini. 2013. "Mobility Lab to Assess Balance and Gait with Synchronized Body-Worn Sensors." *Journal of Bioengineering and Biomedical Sciences*. https://doi.org/10.4172/2155-9538.S1-007.

Lees, A J, and E Smith. 1983. "Cognitive Deficits in the Early Stages of Parkinson's Disease." *Brain* 106: 257–70. https://doi.org/10.1093/brain/106.2.257.

Lees, Andrew J, John Hardy, and Tamas Revesz. 2009. "Parkinson's Disease." *Lancet* 373 (9680): 2055–66. https://doi.org/10.1016/S0140-6736(09)60492-X.

Lezak, Muriel Deutsch. 1995. *Neuropsychological Assessment, 3rd Ed. Neuropsychological Assessment, 3rd Ed.*

Li, Fuzhong, Peter Harmer, Kathleen Fitzgerald, Elizabeth Eckstrom, Ronald Stock, Johnny Galver, Gianni Maddalozzo, and Sara S Batya. 2012. "Tai Chi and Postural Stability in Patients with Parkinson's Disease." *The New*

England Journal of Medicine 366 (6): 511–19.
https://doi.org/10.1056/NEJMoa1107911.

Li, S.-c., B. S. Schoenberg, C.-c. Wang, X.-m. Cheng, D.-y. Rui, C. L. Bolis, and D. G. Schoenberg. 1985. "A Prevalence Survey of Parkinson's Disease and Other Movement Disorders in the People's Republic of China." *Archives of Neurology* 42 (7): 655–57.
https://doi.org/10.1001/archneur.1985.04060070045013.

Lipsitz, L A, P V Jonsson, M M Kelley, and J S Koestner. 1991. "Causes and Correlates of Recurrent Falls in Ambulatory Frail Elderly." *Journal of Gerontology* 46 (4): M114–22.

Lohnes, Corey A., and Gammon M. Earhart. 2011. "The Impact of Attentional, Auditory, and Combined Cues on Walking during Single and Cognitive Dual Tasks in Parkinson Disease." *Gait and Posture*.
https://doi.org/10.1016/j.gaitpost.2010.12.029.

Lord, Sue, Katherine Baker, Alice Nieuwboer, David Burn, and Lynn Rochester. 2011. "Gait Variability in Parkinson's Disease: An Indicator of Non-Dopaminergic Contributors to Gait Dysfunction?" *Journal of Neurology* 258 (4): 566–72. https://doi.org/10.1007/s00415-010-5789-8.

Lord, Sue, Brook Galna, Joe Verghese, Shirley Coleman, David Burn, and Lynn Rochester. 2013. "Independent Domains of Gait in Older Adults and Associated Motor and Nonmotor Attributes: Validation of a Factor Analysis Approach." *Journals of Gerontology - Series A Biological Sciences and Medical Sciences* 68 (7): 820–27. https://doi.org/10.1093/gerona/gls255.

Lord, Sue, Lynn Rochester, Vicki Hetherington, Liesl M. Allcock, and David Burn. 2010. "Executive Dysfunction and Attention Contribute to Gait Interference in 'off' State Parkinson's Disease." *Gait and Posture*.
https://doi.org/10.1016/j.gaitpost.2009.09.019.

Maetzler, Walter, Josefa Domingos, Karin Srulijes, Joaquim J. Ferreira, and Bastiaan R. Bloem. 2013. "Quantitative Wearable Sensors for Objective Assessment of Parkinson's Disease." *Movement Disorders*.
https://doi.org/10.1002/mds.25628.

Maetzler, Walter, and Lynn Rochester. 2015. "Body-Worn Sensors--the Brave New World of Clinical Measurement?" *Movement Disorders : Official Journal of the Movement Disorder Society*, 2015.
https://doi.org/10.1002/mds.26317.

Mancini, Martina. 2011. "Mobility Lab to Assess Balance and Gait with Synchronized Body-Worn Sensors." *Journal of Bioengineering and Biomedical Science* Suppl 1: 1–5. https://doi.org/10.4172/2155-9538.S1-007.

Mann, D M, and P O Yates. 1983. "Possible Role of Neuromelanin in the Pathogenesis of Parkinson's Disease." *Mechanisms of Ageing and Development* 21 (2): 193–203. https://doi.org/10.1016/0047-6374(83)90074-X.

Martínez-Fernández, Raul, Rafael Rodríguez-Rojas, Marta del Álamo, Frida

Hernández-Fernández, Jose A. Pineda-Pardo, Michele Dileone, Fernando Alonso-Frech, et al. 2018. "Focused Ultrasound Subthalamotomy in Patients with Asymmetric Parkinson's Disease: A Pilot Study." *The Lancet Neurology*. https://doi.org/10.1016/S1474-4422(17)30403-9.

Mayeux, R, K Marder, L J Cote, J Denaro, N Hemenegildo, H Mejia, M X Tang, R Lantigua, D Wilder, and B Gurland. 1995. "The Frequency of Idiopathic Parkinson's Disease by Age, Ethnic Group, and Sex in Northern Manhattan, 1988-1993." *American Journal of Epidemiology* 142 (8): 820–27. https://doi.org/10.2460/javma.241.4.417.

Mazzoni, Pietro, Britne Shabbott, and Juan Camilo Cortés. 2012. "Motor Control Abnormalities in Parkinson's Disease." *Cold Spring Harbor Perspectives in Medicine* 2 (6). https://doi.org/10.1101/cshperspect.a009282.

McGeer, Patrick L., Shigeru Itagaki, Haruhiko Akiyama, and Edith G. McGeer. 1988. "Rate of Cell Death in Parkinsonism Indicates Active Neuropathological Process." *Annals of Neurology* 24 (4): 574–76. https://doi.org/10.1002/ana.410240415.

McNeely, Marie E., and Gammon M. Earhart. 2011. "The Effects of Medication on Turning in People with Parkinson Disease with and without Freezing of Gait." *Journal of Parkinson's Disease* 1 (3): 259–70. https://doi.org/10.3233/JPD-2011-11030.

Mehrholz, Jan, Joachim Kugler, Alexander Storch, Marcus Pohl, Bernhard Elsner, and Kathleen Hirsch. 2015. "Treadmill Training for Patients with Parkinson's Disease." *The Cochrane Database of Systematic Reviews*. https://doi.org/10.1002/14651858.CD007830.pub3.

Mellone, Sabato, Martina Mancini, Laurie A. King, Fay B. Horak, and Lorenzo Chiari. 2016. "The Quality of Turning in Parkinson's Disease: A Compensatory Strategy to Prevent Postural Instability?" *Journal of NeuroEngineering and Rehabilitation* 13 (1). https://doi.org/10.1186/s12984-016-0147-4.

Michel, Patrick P., Etienne C. Hirsch, and Stéphane Hunot. 2016. "Understanding Dopaminergic Cell Death Pathways in Parkinson Disease." *Neuron*. https://doi.org/10.1016/j.neuron.2016.03.038.

Milman, Uzi, Hagit Atias, Aner Weiss, Anat Mirelman, and Jeffrey M. Hausdorff. 2014. "Can Cognitive Remediation Improve Mobility in Patients with Parkinson's Disease? Findings from a 12 Week Pilot Study." *Journal of Parkinson's Disease*. https://doi.org/10.3233/JPD-130321.

Mirelman, Anat, Tanya Gurevich, Nir Giladi, Anat Bar-Shira, Avi Orr-Urtreger, and Jeffrey M. Hausdorff. 2011. "Gait Alterations in Healthy Carriers of the LRRK2 G2019S Mutation." *Annals of Neurology* 69 (1): 193–97. https://doi.org/10.1002/ana.22165.

Mirelman, Anat, Inbal Maidan, Talia Herman, Judith E. Deutsch, Nir Giladi, and Jeffrey M. Hausdorff. 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?" *Journals of Gerontology - Series A Biological Sciences and Medical Sciences*.

https://doi.org/10.1093/gerona/glq201.

Mirelman, Anat, Lynn Rochester, Inbal Maidan, Silvia Del Din, Lisa Alcock, Freek Nieuwhof, Marcel Olde Rikkert, et al. 2016. "Addition of a Non-Immersive Virtual Reality Component to Treadmill Training to Reduce Fall Risk in Older Adults (V-TIME): A Randomised Controlled Trial." *The Lancet*. https://doi.org/10.1016/S0140-6736(16)31325-3.

Montero-Odasso, Manuel, Marcelo Schapira, Enrique R. Soriano, Miguel Varela, Roberta Kaplan, Luis A. Camera, and L. Marcelo Mayorga. 2005. "Gait Velocity as a Single Predictor of Adverse Events in Healthy Seniors Aged 75 Years and Older." *Journals of Gerontology - Series A Biological Sciences and Medical Sciences*. https://doi.org/10.1093/gerona/60.10.1304.

Morris, Meg, Robert Iansek, Thomas Matyas, and Jeffery Summers. 1998. "Abnormalities in the Stride Length-Cadence Relation in Parkinsonian Gait." *Movement Disorders* 13 (1): 61–69. https://doi.org/10.1002/mds.870130115.

Morris, Rosie, Sue Lord, Rachael A. Lawson, Shirley Coleman, Brook Galna, Gordon W. Duncan, Tien K. Khoo, Alison J. Yarnall, David J. Burn, and Lynn Rochester. 2017. "Gait Rather Than Cognition Predicts Decline in Specific Cognitive Domains in Early Parkinson's Disease." *The Journals of Gerontology: Series A* 71 (May): 1616–23. https://doi.org/10.1093/gerona/glx071.

Muslimovic, Dino, Bart Post, Johannes D Speelman, and Ben Schmand. 2005. "Cognitive Profile of Patients with Newly Diagnosed Parkinson Disease." *Neurology* 65 (8): 1239–45. https://doi.org/10.1212/01.wnl.0000180516.69442.95.

Nieuwboer, A., G. Kwakkel, L. Rochester, D. Jones, E. Van Wegen, A. M. Willems, F. Chavret, V. Hetherington, K. Baker, and I. Lim. 2007. "Cueing Training in the Home Improves Gait-Related Mobility in Parkinson's Disease: The RESCUE Trial." *Journal of Neurology, Neurosurgery and Psychiatry* 78 (2): 134–40. https://doi.org/10.1136/jnnp.200X.097923.

Nieuwboer, Alice, Katherine Baker, Anne Marie Willems, Diana Jones, Joke Spildooren, Inge Lim, Gert Kwakkel, Erwin Van Wegen, and Lynn Rochester. 2009. "The Short-Term Effects of Different Cueing Modalities on Turn Speed in People with Parkinson's Disease." *Neurorehabilitation and Neural Repair*. https://doi.org/10.1177/1545968309337136.

Niznik, Hyman B., Evan F. Fogel, Frank F. Fassos, and Philip Seeman. 1991. "The Dopamine Transporter Is Absent in Parkinsonian Putamen and Reduced in the Caudate Nucleus." *Journal of Neurochemistry* 56 (1): 192–98. https://doi.org/10.1111/j.1471-4159.1991.tb02580.x.

Nocera, Joe R, Shinichi Amano, Srikant Vallabhajosula, and Chris J Hass. 2013. "Tai Chi Exercise to Improve Non-Motor Symptoms of Parkinson's Disease." *Journal of Yoga & Physical Therapy* 3 (6): 997–1003. https://doi.org/10.4172/2157-7595.1000137.

O'Shea, Simone, Meg E Morris, and Robert Iansek. 2002. "Dual Task

Interference during Gait in People with Parkinson Disease: Effects of Motor versus Cognitive Secondary Tasks." *Physical Therapy* 82 (9): 888–97.

Pantcheva, Paolina, Stephanny Reyes, Jaclyn Hoover, Sussannah Kaelber, and Cesar V. Borlongan. 2015. "Treating Non-Motor Symptoms of Parkinsons Disease with Transplantation of Stem Cells." *Expert Review of Neurotherapeutics*. https://doi.org/10.1586/14737175.2015.1091727.

Park, Ariane, and Mark Stacy. 2009. "Non-Motor Symptoms in Parkinson's Disease." In *Journal of Neurology*. Vol. 256. https://doi.org/10.1007/s00415-009-5240-1.

Parkinson, James, Filipa L Campos, Bárbara Coimbra, José M Pêgo, Carla Rodrigues, Rui Lima, Ana J Rodrigues, et al. 2002. "An Essay on the Shaking Palsy." *The Journal of Neuropsychiatry and Clinical Neurosciences*. https://doi.org/10.1176/jnp.14.2.223.

Pearson, S, M Mancini, M El-Gohary, J McNames, and F Horak. 2013. "Turn Detection and Characterization with Inertial Sensors." *1st International Congress on Sports Science Research and Technology Support, IcSPORTS 2013* Vilamoura,: 19–22. https://doi.org/10.5220/0004647000190022.

Petzinger, Giselle M., Beth E. Fisher, Sarah McEwen, Jeff A. Beeler, John P. Walsh, and Michael W. Jakowec. 2013. "Exercise-Enhanced Neuroplasticity Targeting Motor and Cognitive Circuitry in Parkinson's Disease." *The Lancet Neurology*. https://doi.org/10.1016/S1474-4422(13)70123-6.

Poewe, W. 2008. "Non-Motor Symptoms in Parkinson's Disease." *European Journal of Neurology*. https://doi.org/10.1111/j.1468-1331.2008.02056.x.

Pogarell, Oliver, T. Gasser, J. J. Van Hilten, S. Spieker, S. Pollentier, D. Meier, and W. H. Oertel. 2002. "Pramipexole in Patients with Parkinson's Disease and Marked Drug Resistant Tremor: A Randomised, Double Blind, Placebo Controlled Multicentre Study." *Journal of Neurology Neurosurgery and Psychiatry*. https://doi.org/10.1136/jnnp.72.6.713.

Postuma, R. B., A. E. Lang, J. F. Gagnon, A. Pelletier, and J. Y. Montplaisir. 2012. "How Does Parkinsonism Start? Prodromal Parkinsonism Motor Changes in Idiopathic REM Sleep Behaviour Disorder." *Brain* 135 (6): 1860–70. https://doi.org/10.1093/brain/aws093.

Postuma, Ronald B., Daniela Berg, Charles H. Adler, Bastiaan R. Bloem, Piu Chan, Günther Deuschl, Thomas Gasser, et al. 2016. "The New Definition and Diagnostic Criteria of Parkinson's Disease." *The Lancet Neurology*. https://doi.org/10.1016/S1474-4422(16)00116-2.

Postuma, Ronald B., Daniela Berg, Matthew Stern, Werner Poewe, C. Warren Olanow, Wolfgang Oertel, José Obeso, et al. 2015. "MDS Clinical Diagnostic Criteria for Parkinson's Disease." *Movement Disorders*. https://doi.org/10.1002/mds.26424.

Reitan, RM. 1958. "Validity of the Trail Making Test as an Indicator of Organic Brain Damage." *Perceptual and Motor Skills* 8: 271–76.

https://doi.org/10.2466/PMS.8.7.271-276.

Richards, Marcus, Karen Marder, Lucien Cote, and Richard Mayeux. 1994. "Interrater Reliability of the Unified Parkinson's Disease Rating Scale Motor Examination." *Movement Disorders* 9 (1): 89–91. https://doi.org/10.1002/mds.870090114.

Rijk, M C de, L J Launer, K Berger, M M Breteler, J F Dartigues, M Baldereschi, L Fratiglioni, et al. 2000. "Prevalence of Parkinson's Disease in Europe: A Collaborative Study of Population-Based Cohorts. Neurologic Diseases in the Elderly Research Group." *Neurology* 54 (11 Suppl 5): S21-3. https://doi.org/10.1212/WNL.54.11.21A.

Sánchez-Ferro, Álvaro, Morad Elshehabi, Catarina Godinho, Dina Salkovic, Markus A. Hobert, Josefa Domingos, Janet M.T. van Uem, Joaquim J. Ferreira, and Walter Maetzler. 2016. "New Methods for the Assessment of Parkinson's Disease (2005 to 2015): A Systematic Review." *Movement Disorders* 31 (9): 1283–92. https://doi.org/10.1002/mds.26723.

Saunders-Pullman, Rachel. 2003. "Estrogens and Parkinson Disease: Neuroprotective, Symptomatic, Neither, or Both?" *Endocrine*. https://doi.org/10.1385/ENDO:21:1:81.

Schaafsma, Joanna D., Nir Giladi, Yacov Balash, Anna L. Bartels, Tanya Gurevich, and Jeffrey M. Hausdorff. 2003. "Gait Dynamics in Parkinson's Disease: Relationship to Parkinsonian Features, Falls and Response to Levodopa." *Journal of the Neurological Sciences* 212 (1–2): 47–53. https://doi.org/10.1016/S0022-510X(03)00104-7.

Schrag, Anette, Cristina Sampaio, Nicholas Counsell, and Werner Poewe. 2006. "Minimal Clinically Important Change on the Unified Parkinson's Disease Rating Scale." *Movement Disorders* 21 (8): 1200–1207. https://doi.org/10.1002/mds.20914.

Schrag, Anette, Ludwig Schelosky, Udo Scholz, and Werner Poewe. 1999. "Reduction of Parkinsonian Signs in Patients with Parkinson's Disease by Dopaminergic versus Anticholinergic Single-Dose Challenges." *Movement Disorders*. https://doi.org/10.1002/1531-8257(199903)14:2<252::AID-MDS1009>3.0.CO;2-N.

Shulman, Lisa M, Ann L Gruber-Baldini, Karen E Anderson, Paul S Fishman, Stephen G Reich, and William J Weiner. 2010. "The Clinically Important Difference on the Unified Parkinson's Disease Rating Scale." *Archives of Neurology* 67 (1): 64–70. https://doi.org/10.1001/archneurol.2009.295.

Shumway-Cook, A, Sandy Brauer, and Marjorie Woollacott. 2000. "Timed Up & Go Test (TUG)." *Missouri.Edu* 80: 9–10.

Siciliano, Mattia, Luigi Trojano, Gabriella Santangelo, Rosa De Micco, Gioacchino Tedeschi, and Alessandro Tessitore. 2018. "Fatigue in Parkinson's Disease: A Systematic Review and Meta-Analysis." *Movement Disorders*. https://doi.org/10.1002/mds.27461.

Silsupadol, Patima, Ka-Chun Siu, Anne Shumway-Cook, and Marjorie H Woollacott. 2006. "Training of Balance under Single- and Dual-Task

Conditions in Older Adults with Balance Impairment." *Physical Therapy* 86 (2): 269–81. https://doi.org/10.1016/S0966-6362(05)80442-4.

Song, Jooeun, Susan Sigward, Beth Fisher, and George J. Salem. 2012. "Altered Dynamic Postural Control during Step Turning in Persons with Early-Stage Parkinson's Disease." *Parkinson's Disease*. https://doi.org/10.1155/2012/386962.

Spildooren, J., S. Vercruysse, P. Meyns, J. Vandenbossche, E. Heremans, K. Desloovere, W. Vandenberghe, and A. Nieuwboer. 2012. "Turning and Unilateral Cueing in Parkinson's Disease Patients with and without Freezing of Gait." *Neuroscience*. https://doi.org/10.1016/j.neuroscience.2012.01.024.

Stack, E, and A Ashburn. 2008. "Dysfunctional Turning in Parkinson's Disease." *Disability and Rehabilitation* 30 (16): 1222–29. https://doi.org/10.1080/09638280701829938.

Stack, E L, A M Ashburn, and K E Jupp. 2006. "Strategies Used by People with Parkinson's Disease Who Report Difficulty Turning." *Parkinsonism & Related Disorders* 12 (2): 87–92. https://doi.org/10.1016/j.parkreldis.2005.08.008.

Stack, Emma L, Ann M Ashburn, and Kate E Jupp. 2006. "Strategies Used by People with Parkinson's Disease Who Report Difficulty Turning." *Parkinsonism & Related Disorders* 12 (2): 87–92. https://doi.org/10.1016/j.parkreldis.2005.08.008.

Stern, Matthew B., Anthony Lang, and Werner Poewe. 2012. "Toward a Redefinition of Parkinson's Disease." *Movement Disorders*. https://doi.org/10.1002/mds.24051.

Studenski, Stephanie, Subashan Perera, Kushang Patel, Caterina Rosano, Kimberly Faulkner, Marco Inzitari, Jennifer Brach, et al. 2011. "Gait Speed and Survival in Older Adults." *JAMA : The Journal of the American Medical Association* 305 (1): 50–58. https://doi.org/10.1001/jama.2010.1923.

Sveinbjornsdottir, Sigurlaug. 2016. "The Clinical Symptoms of Parkinson's Disease." *Journal of Neurochemistry*. https://doi.org/10.1111/jnc.13691.

Swainson, R., R. D. Rogers, B. J. Sahakian, B. A. Summers, C. E. Polkey, and T. W. Robbins. 2000. "Probabilistic Learning and Reversal Deficits in Patients with Parkinson's Disease or Frontal or Temporal Lobe Lesions: Possible Adverse Effects of Dopaminergic Medication." *Neuropsychologia*. https://doi.org/10.1016/S0028-3932(99)00103-7.

Timpka, Jonathan, Ulrika Mundt-Petersen, and Per Odin. 2016. "Continuous Dopaminergic Stimulation Therapy for Parkinson's Disease – Recent Advances." *Current Opinion in Neurology* 29 (4): 474–79. https://doi.org/10.1097/WCO.0000000000000354.

Tomlinson, Claire L., Smitaa Patel, Charmaine Meek, Clare P. Herd, Carl E. Clarke, Rebecca Stowe, Laila Shah, et al. 2013. "Physiotherapy versus Placebo or No Intervention in Parkinson's Disease." *Cochrane Database of Systematic Reviews*. https://doi.org/10.1002/14651858.CD002817.pub4.

Tysnes, Ole Bjørn, and Anette Storstein. 2017. "Epidemiology of Parkinson's Disease." *Journal of Neural Transmission*. https://doi.org/10.1007/s00702-017-1686-y.

Uem, Janet M.T. van, Johan Marinus, Colleen Canning, Rob van Lummel, Richard Dodel, Inga Liepelt-Scarfone, Daniela Berg, Meg E. Morris, and Walter Maetzler. 2016. "Health-Related Quality of Life in Patients with Parkinson's Disease-A Systematic Review Based on the ICF Model." *Neuroscience and Biobehavioral Reviews*. https://doi.org/10.1016/j.neubiorev.2015.11.014.

Verghese, Joe, Matthew Robbins, Roee Holtzer, Molly Zimmerman, Cuiling Wang, Xiaonan Xue, and Richard B. Lipton. 2008. "Gait Dysfunction in Mild Cognitive Impairment Syndromes." *Journal of the American Geriatrics Society* 56 (7): 1244–51. https://doi.org/10.1111/j.1532-5415.2008.01758.x.

Vingerhoets, F. J. G., Michael Schulzer, Donald B. Calne, and Barry J. Snow. 1997. "Which Clinical Sign of Parkinson's Disease Best Reflects the Nigrostriatal Lesion?" *Annals of Neurology* 41 (1): 58–64. https://doi.org/10.1002/ana.410410111.

Walton, Courtney C., James M. Shine, Loren Mowszowski, Sharon L. Naismith, and Simon J.G. Lewis. 2014. "Freezing of Gait in Parkinson's Disease: Current Treatments and the Potential Role for Cognitive Training." *Restorative Neurology and Neuroscience*. https://doi.org/10.3233/RNN-130370.

Wayne, Peter M., Jeffrey M. Hausdorff, Matthew Lough, Brian J. Gow, Lewis Lipsitz, Vera Novak, Eric A. Macklin, Chung-Kang Peng, and Brad Manor. 2015. "Tai Chi Training May Reduce Dual Task Gait Variability, a Potential Mediator of Fall Risk, in Healthy Older Adults: Cross-Sectional and Randomized Trial Studies." *Frontiers in Human Neuroscience*. https://doi.org/10.3389/fnhum.2015.00332.

Whitney, Susan L, Diane M Wrisley, Gregory F Marchetti, Michael A Gee, Mark S Redfern, and Joseph M Furman. 2005. "Clinical Measurement of Sit-to-Stand Performance in People With Balance Disorders: Validity of Data for the Five-Times-Sit-to-Stand Test." *Physical Therapy* 85 (10): 1034–45. https://doi.org/10.1093/ptj/85.10.1034.

Winogrodzka, Ania, Robert C. Wagenaar, Jan Booij, and Eric C. Wolters. 2005. "Rigidity and Bradykinesia Reduce Interlimb Coordination in Parkinsonian Gait." *Archives of Physical Medicine and Rehabilitation* 86 (2): 183–89. https://doi.org/10.1016/j.apmr.2004.09.010.

Wu, T, and M Hallett. 2008. "Neural Correlates of Dual Task Performance in Patients with Parkinson's Disease." *Journal of Neurology, Neurosurgery, and Psychiatry* 79 (7): 760–66. https://doi.org/10.1136/jnnp.2007.126599.

Yilmaz, Rezzak, Antonio P. Strafella, Alice Bernard, Claudia Schulte, Lieneke van den Heuvel, Nicole Schneiderhan-Marra, Thomas Knorpp, et al. 2018. "Serum Inflammatory Profile for the Discrimination of Clinical Subtypes in Parkinson's Disease." *Frontiers in Neurology* 9 (December): 1123. https://doi.org/10.3389/fneur.2018.01123.

Yogev-Seligmann, Galit, Nir Giladi, Marina Brozgol, and Jeffrey M. Hausdorff. 2012. "A Training Program to Improve Gait While Dual Tasking in Patients with Parkinson's Disease: A Pilot Study." *Archives of Physical Medicine and Rehabilitation*. https://doi.org/10.1016/j.apmr.2011.06.005.

Yogev-Seligmann, Galit, Jeffrey M. Hausdorff, and Nir Giladi. 2008. "The Role of Executive Function and Attention in Gait." *Movement Disorders*. https://doi.org/10.1002/mds.21720.

Togev-Seligmann, Hausdorff, Giladi. 2012. "Do We Always Prioritize Balance When Walking? Towards an Integrated Model of Task Prioritization." *Movement Disorders*. https://doi.org/10.1002/mds.24963.

Yogev-Seligmann, Galit, Yael Rotem-Galili, Anat Mirelman, Ruth Dickstein, Nir Giladi, and Jeffrey M Hausdorff. 2010. "How Does Explicit Prioritization Alter Walking during Dual-Task Performance? Effects of Age and Sex on Gait Speed and Variability." *Physical Therapy* 90 (2): 177–86. https://doi.org/10.2522/ptj.20090043.

Yogev, Galit, Nir Giladi, Chava Peretz, Shmuel Springer, Ely S. Simon, and Jeffrey M. Hausdorff. 2005. "Dual Tasking, Gait Rhythmicity, and Parkinson's Disease: Which Aspects of Gait Are Attention Demanding?" *European Journal of Neuroscience*. https://doi.org/10.1111/j.1460-9568.2005.04298.x.

9. Supplementary Materials

A:

```matlab
function trenddata (f)

% Make sure all your paths are correct.

%Please add a list of your files names. don't forget the ' '. They have to
%be coloured purple.

subjectList = {
    '3008on'
    '3008off'
    }

%The next line to automatically count the number of your subjects from the
%list you added above. NO NEED TO EDIT THIS.
nSubjects = length(subjectList)

%This line is to create a matrix. Raws are subjects, coulmns are values you
%wil get later from the csv files.

mybigmatrix = zeros(nSubjects,128);

%This loop runs through everysubject, fitch it's csv file, takes the values
%you want, organize it in only one line for each subjects and put subjects
%in one table and finally export the table in a csv file.

for i=1:nSubjects

    try

        subjectDir = subjectList{i}

        myFiles = dir(['..' filesep 'converted' filesep 'PDgait' filesep subjectDir
        filesep '13' filesep '*.csv'])
        csvPath = ['..' filesep 'converted' filesep 'PDgait' filesep subjectDir filesep
        '13' filesep myFiles(1).name]

        mydata = csvread(csvPath,13,1);

        %select the lines and columns you want from the matrix. (Lines are
        %parameters, columns contain data you will use in statistics).
        myspecific = mydata([1:end],[5:6]);

        %Convert the new matrix into a vector so it's showed as one raw in you
        %excel table. make sure the numbers fit with those in the previous
        %line.
        myraw = reshape(myspecific,1,128);

        %UPDAED: The next few lines are to make the organisation of your
        %values more consistent with the csv files. it goes
        %(mean,cov,mean,cov) instead of (mean,mean,mean,cov,cov,cov).
        %Please edit the numbers 64,128 depending on the number of
        %parameters you are extracting.
        meansraw = myraw(1:64)
        covsraw = myraw(65:end)

        organisedraw = zeros(1,128)
        organisedraw(1:2:end)= meansraw
        organisedraw(2:2:end)= covsraw


        %creat a grand matrix where all files are add in a form of one raw per
        %subject

        mybigmatrix(i,:)= organisedraw;


    end
end

%Creat a new csv file. Please edit the path according to your device.

csvwrite('/Users/donmarat/Desktop/MD/PDgait_on&off.csv',mybigmatrix)


end
```

B:

```matlab
function E = CalculateVariabilityMLAB

%load your files, CHECK PATH
F = dir ('iwalks/*.csv')

% Replace the 153 with the number of files you have in the directory.
for K = 1:153

    FileName = ['iwalks/' F(K).name];

    %The 31 here is the row number (which gait parameter).
    % The 9 is where the individual steps start.
    R = csvread(FileName,31,9);

    %The 40 because most patients have 40, many don't reach .
    RR = R(1:1,1:40);

    M(K, 1:40) = RR


    clear RR;
end

csvwrite('CalculateVariability.csv', M)

end
```

Supplementary Material 1:
 A: A short MATLAB function written to navigate the Mobility Lab export CSV file, fetch the specific data needed and generate a table with data from all study participants. Please note, this script is compatible with the Mobility Lab version used at the time of the analysis, 2016.
B: A MATLAB function written to navigate the Mobility Lab export CSV file and fetch the variability measures of a certain parameters from individual steps in a specific step count. This function can be used for any gait parameter available in the Mobility lab CSV file export as long as data of each step is available in the file.

10. Declaration of Own Work

(Erklärung zum Eigenanteil der Dissertationsschrift)

Die Arbeit wurde in der Neurologie Klinik, Universitätklinikum Tübingen durch mich, Herr Morad Elshehabi und unter Betreuung von Prof. Dr. med. Walter Maetzler durchgeführt. Die Konzeption der Studie erfolgte in Zusammenarbeit mit Prof. Maetzler und Herrn Markus Hobert. Die Datenerhebung wurde von Frau Kati Meier und Frau Susanne Nußbaum mit technischen Unterstützung des Autors (Herr Elshehabi) durchgeführt.

Dateneingabe wurde von Herrn Elshehabi, Frau Maier und Frau Carina Arnold durchgeführt.

Herr Elshehabi war für die technische Aspekte der Studie, sowie die Kommunikation mit dem Bewegungsanalysesystem (Mobility Lab) Entwickler (APDM, Oregon, USA) verantwortlich.

Die statistische Auswertung erfolgte eigenständig durch mich mit Unterstützung durch Prof. Maetzler und Herrn Hobert.

Ich versichere, das Manuskript selbständig verfasst zu haben und

keine weiteren als die von mir angegebenen Quellen verwendet zu haben.

Kiel, den

07.05.2019

Morad Elshehabi

11. **Publications**

This work has been also published as an original research article in the open access journal *Frontiers in Aging Neuroscience*.

M. Elshehabi, K.S. Maier, S.E. Hasmann, S. Nussbaum, H. Herbst, T. Heger, et al.Limited effect of dopaminergic medication on straight walking and turning in early-to-moderate Parkinson's disease during single and dual tasking
Front. Aging Neurosci., 8 (2016), p. 4

12. **Acknowledgment**