Assessment and exercise for Freezing of Gait in Parkinson's Disease

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“As much as Parkinson’s is about movement, the end stage is being frozen. So the more I let that happen, the more I’m gonna be stuck within that and unable to reverse that.”

(Michael J. Fox)

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Abbreviations

APA	Anticipatory Postural Adjustment
CLR	Cerebellar Locomotor Region
COM	Center Of Body Mass
COP	Center Of Pressure
DBS	Deep Brain Stimulation
DT	Dual Task
fMRI	Functional Magnetic Resonance Imaging
FOG	Freezing Of Gait
GI	Gait Initiation
IMU	Inertial Measurement Unit
MDS-UPDRS	Movement Disorder Society-Unified Parkinson's Disease Rating Scale
MLR	Mesencephalic Locomotor Region
NFOG-Q	New Freezing Of Gait-Questionnaire
PCI	Phase Coordination Index
PD	Parkinson's Disease
PPN	Pedunculopontine Nucleus
SBT	Split-Belt Treadmill
SMA	Supplementary Motor Area
ST	Single Task
STN	Subthalamic Nucleus
TBT	Regular Treadmill Training (Tied-Belt Training)

1. Introduction

Parkinson's disease (PD) is a progressive neurodegenerative disorder, characterized by multiple motor and non-motor features. It can be diagnosed by the cardinal signs which are bradykinesia, tremor and rigidity [1-3]. It is further accompanied by balance deficits and various non-motor symptoms such as dysarthria, apathy, depression, and sleep disturbances [1]. The etiology of PD has been explored extensively in the past decades, but there is still no conclusive answer to the question of what causes PD. However, researchers are sure that environmental factors as well as genetic predispositions play an important role in the development of the disease [4]. The prevalence of PD has been increasing immensely over the past decades [5]. With an increasingly ageing society this neurodegenerative disease will become even more prevalent in the years to come, with experts estimating the number of people with PD to double within the next 20 years [5]. To date there is no therapy which can stop the neurodegenerative process of the disease [6, 7], which is why standard therapy concentrates only on symptom alleviation.

Quality of life is a domain that is highly affected in people with PD. Several PD symptoms play into that. However, gait impairment is one motor symptom that most strongly affects health-related quality of life in PD [8]. In people with PD gait can be negatively affected in various ways due to the altered neural pathways and deterioration of the brain [9]. Freezing of Gait (FOG) is one type of gait impairment which about 38% of people with PD experience, incidence increases with higher disease stage, and which is also significantly correlated to quality of life [10]. The symptom is described by patients as the feeling of the feet being glued to the ground [11]. Gait impairments in PD not only limit mobility but are also associated with future falls [12], and especially FOG is an important contributor to falls [13]. Furthermore, gait impairment in PD is linked to increased comorbidity [14], which ultimately increases disability in this population.

The lack of treatment options to stop disease progression, the increasing prevalence of the disease, and the negative impact on quality of life and mobility, stress the need to explore and investigate therapeutic options for this population. Pharmacological treatment cannot alleviate all symptoms and alternative therapy options like physical therapy have become increasingly relevant in the research field. Exercise or physical therapy have the potential to complement pharmacological therapy and thereby alleviate symptoms in the PD population.

A lot of studies focus especially on improvement of gait and balance function in people with PD by using physical therapy [15]. Various types of exercise interventions have been proven effective for gait rehabilitation in individuals with PD, e.g. balance and gait training, treadmill training, cycling and resistance training [16]. This is why exercise and physical therapy are a promising pathway for PD treatment. However, except for standard physical therapy provided by a physiotherapist, exercise as a treatment option is not well implemented yet [17], as 56% of people with PD report low or no engagement at all in exercise [18]. Furthermore, it was shown that PD individuals are less physically active than their healthy peers [19, 20]. Among various reasons including motivators and barriers, this is also a structural problem caused by the scarcity of well-investigated evidence-based treatment options. Many intervention studies lack basic requirements to generate meaningful results and clear recommendations for the application of exercise therapy. This includes small sample sizes, short duration of trials, the lack of follow-up or the insufficient information about the specific exercise protocol [16, 21]. This makes it difficult to interpret the effects of the interventions and also complicated for therapists to apply research findings in practice. Furthermore, several gait-related mechanisms in PD are not yet fully understood, especially in the subgroup with FOG, which makes it challenging for selecting interventions at specific gait impairments [22].

To determine which intervention is most promising for FOG in PD and to evaluate treatment effect, reliable and valid assessment options for the symptom are needed. Developing more objective assessment options has been in the focus of research in the field of FOG. However, it is essential to further explore assessment methods to gain meaningful information about FOG in people with PD and the effect of the symptom on specific domains of gait. What we need are interventions to investigate alternative treatment options that can successfully prove the positive effects of exercise on gait impairments in PD, especially in the subgroup with FOG and to strengthen the utilization of those methods in clinical routine.

The aim of this work is to provide reliable assessment options for symptom severity and gait features in people with PD suffering from FOG (PD+FOG). On top of that, the goal is to explore the potential of a specific exercise intervention with a focus on motor learning for the rehabilitation of people with PD+FOG. This will be done in four different projects, which each contributes individual findings to the objective of this thesis. The first project aims to test the validity of the German version of the New Freezing of Gait Questionnaire to assess FOG. This

is essential for providing a suitable method to assess FOG severity for the characterization of participants characteristics in future studies in the German-speaking population. This will be followed by the evaluation of reliability of FOG related features, such as anticipatory postural adjustments and first step characteristics, during voluntary gait initiation using an accelerometer-based approach. Especially in the PD subgroup with FOG, where gait initiation can be disrupted it is important to generate reliable outcome measures for the use in clinical trials or intervention studies. With regards to therapeutic options a tool, which has been promising in rehabilitative research in neurological disorders is the split-belt treadmill (SBT). It features two belts which can run at individual speeds. By conducting a systematic literature review, the current findings on SBT walking in people with PD will be summarized and evaluated to generate an overview on the feasibility and on how the potential of SBT can be used. To build on those findings the short-term effects of different SBT protocols on FOG will be investigated, to gain more insight into how SBT can improve gait function in people with PD+FOG and to determine the most suitable and effective training modality for this therapeutic option.

2. Gait impairments in Parkinson's Disease

Motor performance and gait in individuals with PD are affected by symptoms, such as bradykinesia, rigidity and postural instability [23]. People with PD present reduced gait speed and step length [24] and also difficulties with rhythmicity [25]. Those gait deficits usually worsen when the disease progresses [26, 27], which consequently affects physical autonomy and quality of life. The following chapters will go into more depths on gait impairments of people with PD. Furthermore, FOG as one type of gait impairment in PD will be defined and its pathophysiological mechanisms will be explained. The specific gait difficulties in the subgroup of people with PD+FOG and their ability for motor learning will be addressed. Finally, the treatment options for FOG in PD will be summarized and evaluated, and the potential of exercise therapy for rehabilitation will be reviewed.

2.1 Classification of gait impairments

Gait disturbances in PD can be classified as continuous and episodic gait impairments [28-30]. The episodic gait disturbances are characterized through their random manner as they are present occasionally and intermittently and include FOG [31]. Conversely, the continuous gait disturbances are apparent consistently during walking and include gait alterations such as slowness of gait, reduced stride length, increased gait variability and gait asymmetry and impaired bilateral coordination of gait [28, 32-39]. Some continuous gait alterations have been shown to be inter-related to episodic gait disturbances, for example FOG and increased gait variability [40, 41] or gait asymmetry [42].

It has been shown that people with PD show reduced gait speed compared to age-matched healthy elderly [24, 43, 44]. This difference can be explained by reduced ankle moment, smaller range of motion during push-off and reduced hip power absorption and generation during stance time [24]. Furthermore, PD patients show reduced stride length [43-45], whereas cadence is comparable to healthy controls (HC) [43]. It has also been shown that people with PD present with increased stride variability [32, 33, 35, 36], which is especially aggravated in the subgroup with past falls [35]. On top of that, people with PD show impaired interlimb coordination [34], which is defined as the coordination between upper and lower limbs. There are not only deficits between upper and lower limbs during gait, but also between body sides, which show through asymmetries. Researchers found increased step length

asymmetry [37, 39] and step time asymmetry [37, 38] in PD patients compared to HCs. Not only the lower extremity is affected by asymmetry, also arm swing is asymmetric in people with PD, even in the early stage of the disease [46]. Peterson et al. [9] state, that the asymmetric onset of the disease, especially of the symptoms rigidity and bradykinesia, plays into this. Despite the various gait impairments there is some evidence that a normal stride pattern in terms of stride length can be achieved by people with PD by using attentional strategies [45, 47], which leads to the assumption that they have difficulties activating the respective motor control system properly. Furthermore, the abnormal step pattern in PD was also found to be independent of gait speed, as HC still had longer steps, when they walked at the speed of PD individuals [48]. This further supports the assumption that some gait impairments in PD are most likely caused by a lack of automaticity [49], especially in the subgroup with FOG [50, 51]. Therefore, PD individuals have to utilize more attentional control than HC during gait to compensate for the lack of automaticity [49].

The aforementioned gait impairments, if more severely pronounced, can be risk factors for falls in this population. Especially slower walking speed, lower cadence and shorter strides put people with PD at risk for a future fall [52]. In many cases, PD falls result in injuries [53] which can cause immobilization and thus a vicious cycle of reduced mobility. Additionally, they also increase the fear of walking which can consequently result in a decrease of physical activities [54]. Therefore, identifying those gait deficits in PD individuals is essential for providing suitable therapy options or interventions and thus prevent falls.

2.2 Pathophysiology of continuous gait disturbance

There is limited evidence about the underlying neural mechanisms of the continuous gait impairments in people with PD. Peterson et al. [9] have summarized these findings, by explaining them separately for every gait impairment. According to their work, the slowness of gait is most likely caused by pathologies of the basal ganglia. The neurodegeneration causes an overactive inhibitory output from the basal ganglia, which affects important motor areas of the brain such as the supplementary motor area (SMA). This theory is further supported by previous imaging studies, which found a reduced activity in the SMA in people with PD [55]. In line with that, researchers found a positive correlation between SMA activation and gait speed [56, 57], which further strengthens this hypothesis. Additionally, cholinergic dysfunction in combination with dopamine dysfunction may also contribute to slowed gait [9].

When trying to explain gait variability in PD through neural mechanisms, attention is a central aspect. As mentioned earlier, gait variability increases if gait becomes more a conscious stepping instead of an automatic movement [58]. An increased stride length variability compared to age-matched healthy elderly was found to be associated with dopaminergic denervation in the sensorimotor region of the striatum [59], which is relevant for gait automaticity. Additionally, increased activity of certain cortical areas plays a role, as cortical activation is linked to more voluntary control of movement [9]. According to Roemmich et al. [34] the basal ganglia and pedunculopontine nucleus dysfunction present in PD most likely contribute to the reduced interlimb coordination, as well as axial rigidity making coordination between limbs more difficult. Gait asymmetry could be directly linked to asymmetric dysfunction of the basal ganglia [9], but there is also emerging evidence that reduced transcallosal structural connectivity may be one of the mechanisms underlying gait asymmetry in PD [37].

Gait impairments in PD become even more prominent when attention needs to be divided, e.g. when an additional task has to be performed (i.e. dual task (DT)). DT gait in PD is slowed down, independent of the individual gait speed and also irrespective of the presented task [60]. Also other typical PD gait impairments worsen, such as stride length reduction, asymmetry and bilateral dyscoordination of gait as well as stride to stride variability increase [43, 61]. This phenomenon can be explained by various conceptual theories. One is the capacity theory, which states that there is a limited processing capacity of the brain, that has to be divided between tasks in a DT situation and therefore performance is reduced in one or both tasks [62]. Kelly et al. [61] are proposing various overlapping PD-specific mechanisms, like basal ganglia dysfunction and nondopaminergic pathology to explain the deficits of DT gait in PD. The aforementioned lack of gait automaticity plays into this as well. Daily life situations often require performing a simultaneous DT while walking, like talking to a friend or carrying a cup of coffee. As a high proportion of falls in PD occur during walking [63] and DT cost during walking might even be used as a fall predictor [64], this is a particularly relevant topic to address. There is some emerging evidence that PD participants with adequate baseline walking speed are able to prioritize walking over the DT which might be a mechanism protecting them from falls [60].

2.3 Freezing of Gait: definition and pathophysiology of an episodic gait disturbance

Freezing of Gait is defined as the "brief, episodic absence or marked reduction of forward progression of the feet despite the intention to walk" [11]. It is a highly disabling symptom which negatively affects mobility, can lead to falls [65] and also results in reduced quality of life [66]. It is present in about 38% of people with PD and the prevalence is positively correlated with disease stage [10]. It occurs most often during gait initiation, turning, when passing through a narrow space or approaching a destination as well as in stressful situations [67].

Regarding the actual mechanisms causing the freezing episodes there are various theoretical models, which have been summarized by Nieuwboer et al. [68]. The first hypothesis is that the accumulation of numerous motor deficits leads to a motor failure when it reaches a certain threshold, making it impossible for patients to make a step [69]. The second model, the interference model, attributes the motor breakdown to concurring cognitive, limbic and motor input [70]. According to the cognitive model, people with PD+FOG present with the inability to resolute conflict especially in situations requiring a response decision [51]. Lastly the decoupling model suspects that FOG is caused by a lack of connectivity between the programming of a motor task and the actual motor response [71]. Nieuwboer et al. [68] state that most likely a combination of the proposed models underlie the symptom and some models might be more prominent in certain FOG types. These FOG types were divided into three main phenotypes: the attention type (triggered by e.g. DT), the anxious type (triggered by e.g. walking in the dark) and the asymmetric-motor type (triggered by e.g. turning) [72]. Despite this emerging evidence there is a lack of sufficient data to fully support this clear distinction between FOG types.

It has also been theorized that FOG is linked to impaired postural control, as people with PD+FOG show a more posterior shifted center of pressure (COP) during quiet stance [73]. The association between those postural control deficits and FOG have been further investigated with regard to start hesitation, which is when FOG occurs during gait initiation. Being able to successfully initiate gait is essential in daily life and something we hardly ever think about consciously. In people with PD+FOG, where this ability is often highly disrupted, this poses an extreme burden and a huge challenge for their daily activities. Gait initiation (GI) is usually enabled by a shift of the COP laterally and posterior towards the stepping leg, which facilitates

the forward acceleration of the center of body mass (COM) towards the stance leg [74, 75]. This subtle movement is called anticipatory adjustment (APA). Individuals with PD+FOG were found to produce hypometric APAs [76, 77] with increased latency and decreased step velocity. Some findings suggest a compensatory strategy behind the small APAs as Schlenstedt et al. [76] found small medio-lateral (ML) APAs when no FOG occurred and larger ML APAs when the GI was accompanied by a FOG episode. Also they found a higher co-contraction of muscles during gait initiation [77]. The underlying mechanism of the observed alterations in APAs are still poorly understood.

The threshold model, which was proposed by Plotnik et al. [69] as one approach to explain the occurrence of FOG, states that the accumulation of various gait alterations up to a certain point ultimately results in FOG. This theory ties in with the fact that multiple continuous gait impairments are thought to be linked to FOG. Plotnik et al. [42] found that asymmetry of swing time was significantly greater in PD+FOG than PD without FOG during overground walking (ON- and OFF-medication). Similarly, Fasano et al. [78] found a significantly higher step length asymmetry in PD+FOG when walking on a treadmill. It is hypothesized that asymmetric gait is characteristic to FOG and it could also be a factor that leads to freezing episodes [42], through what was earlier explained as the threshold model. Furthermore, gait variability is a continuous gait impairment which is somehow related to FOG [79]. Stride time variability is significantly greater in PD+FOG compared to PD without FOG (ON- and OFF-medication) [40]. It is possible that one pathophysiological mechanism is accountable for both gait disturbances, especially as researchers found that FOG severity (measured by the number of FOG episodes) was correlated to stride variability [40], which leads to the theory that there might actually be a cause and effect relationship (the threshold model). However, authors conclude that increased gait variability cannot cause FOG on its own and support the assumption that numerous gait alterations are involved in this pathological phenomenon. Another continuous gait impairment which is more prominent in the subgroup with FOG is impaired bilateral coordination [80]. This was measured by means of the phase coordination index (PCI), which is a coefficient of the relative timing during one gait cycle [38]. During OFF-medication PCI was significantly higher in PD+FOG than PD without FOG, which may predispose FOG in the studied population [80]. Additionally, progressive reduction of stride length accompanied by an increase in cadence, creating hastening steps, have been observed before a FOG episode in people with PD+FOG [41]. Authors speculate that this observed loss of gait control is what

ultimately leads to the complete breakdown of locomotion (FOG episode). These findings of continuous gait alterations in people with PD+FOG were key to understanding the symptom in a different way. Before, researchers assumed that FOG was a solely transient, paroxysmal phenomenon and in between FOG episodes gait performance showed just the usual PD-specific gait alterations [40]. This advanced understanding of gait impairments in PD+FOG has provided important information for new insights into the pathophysiology of the symptom and the investigation of alternative treatment options.

FOG pathology has also been investigated with imaging methods such as functional Magnetic Resonance Imaging (fMRI). During an imaginary walking task PD+FOG showed increased activation of the mesencephalic locomotor region (MLR) [81]. In another study researchers also found altered functional connectivity between the SMA and MLR as well as SMA and cerebellar locomotor region (CLR), which is suspected to be a compensatory mechanism for reduced connectivity between SMA and subthalamic nucleus (STN) [82]. Other authors found similar results and besides the altered functional connectivity also differences in structural connectivity were detected. Wang et al. [83] showed that PD+FOG present with altered pedunculopontine nucleus (PPN) functional connectivity as well as white matter abnormalities, compared to PD without FOG. Recently, de Lima-Pardini et al. [84] investigated functional connectivity during a leg lifting task which was modeling the APA in the scanner. They found that PD+FOG showed more activation in the SMA compared to PD without FOG and therefore the SMA likely has a more central role instead of being integrated in a broader network [84]. Through fMRI-studies it is possible to investigate pathological alterations in PD+FOG, however those findings cannot determine if there is a causal relationship between the mentioned alterations and FOG.

2.3.1 How to assess Freezing of Gait

Due to the episodic nature of FOG it can be challenging to assess the symptom during clinical practice or for research purposes. When people with PD+FOG concentrate on their walking it is often not present, which is most likely the case in an unnatural environment where gait is examined by a clinician or researcher. Therefore, we need to rely on various subjective and objective methods to quantify FOG and also proxies need to be taken into account [85]. Subjective methods include questions that are part of the Movement Disorder Society-Unified Parkinson's Disease Rating Scale (MDS-UPDRS), writing a symptom diary [86] or the specifically

designed New Freezing of Gait-Questionnaire (NFOG-Q) [87]. They all rely on the patient remembering the FOG episodes, their duration and quantity. Recall bias, especially in the older PD population who often presents with cognitive deficits, is a problematic issue. Furthermore, not every person with PD has a clear understanding of what FOG entails and it can be hard to differentiate other gait deficits or bradykinesia from FOG.

Therefore, different objective methods for the assessment of FOG have gained attention in research over the past years. One option to test for the presence of FOG are FOG-provoking tasks or trajectories. They mostly include turning in place in alternating direction, walking through narrow passages, or performing additional dual tasks. A standardized test for this is the Ziegler Score [88], which uses an ordinal Likert-scale to test severity of FOG for individual tasks with increasing complexity. For the application in research this tool has the advantage that the clinically relevant change has been investigated for this method [89]. Therefore, it can provide information about if a treatment or an intervention was meaningful for the individual. Nantel et al. [90] developed a stepping-in-place task performed on a force platform which was used to quantify FOG severity. This is similar to the repetitive rapid 360 degree turning task, which Snijders et al. [91] used to elicit FOG and to definitely distinct between "Freezers" and "Non-freezers". Video ratings of gait tasks such as the well-established Timed Up-and-Go test have also been used previously [92], however experience and training necessary in this case and rating can be lengthy. Although this method might be more practical for clinical use, it does lack sufficient reliability. Therefore, the use of even more objective tools has been emerging in this field.

Using inertial measurement units (IMUs) to quantify movement has become increasingly popular in movement science overall and thus is also one of the most promising methods for assessment of FOG in PD. IMU's provide the possibility to measure outside the laboratory setting in daily life [93, 94]. This is particularly relevant due to the explained phenomenon that FOG episode cannot always be elicited in a laboratory. Moore et al. [95] were among the first to use frequency of the characteristic trembling of the legs for an algorithm to quantify FOG [96]. With this algorithm, the start and end of FOG episodes can be determined und thus the duration of FOG can be quantified when tested in a laboratory. But this method also has its downsides, as it determines FOG only when a certain movement frequency is exceeded. Some types of freezing like akinetic FOG cannot be detected with this method [85]. Using a similar

approach, authors also developed a FOG ratio to quantify the severity of freezing using frequency information from an accelerometer measuring the anterior-posterior shin acceleration [96]. This score was significantly correlated with the clinical rating of the freezing and NFOG-Q scores. The mentioned algorithms have all been tested in the laboratory and have also involved movements which are not usually performed during daily life. Therefore, it is important to explore options to detect and measure FOG in the unsupervised home environment. Some researchers already found promising results, however they stress that their findings are not validated yet [97]. With increasing research, it might be possible to switch out IMU's for smartphones that have accelerometers and gyroscopes in the future. This option has led to promising results in the laboratory setting [98], and would make this assessment even more applicable and convenient. Due to the explained difficulties in the assessment of FOG itself, it is important to consider investigating alternative parameters which can stand as a proxy for FOG. In this context wearable sensors can be used to quantify FOG-related continuous gait features or characteristics of gait initiation [76, 79]. If those parameters can be reliably detected, they could be used to reveal intervention effects.

It would be beneficial for researchers, clinicians and therapists to combine the aforementioned methods to assess FOG in PD. Despite their downsides, subjective methods using questionnaire tools provide valuable information. However, only by pairing them with more objective methods it is possible to gain conclusive information about FOG severity. The use of wearable sensors provides various possibilities to measure FOG in the laboratory and is also one of the most promising options for home assessment in the future.

2.3.2 Freezing of gait and motor learning

People with PD show difficulties with motor learning [39, 99, 100]. Understanding the mechanism underlying their motor learning deficits is necessary to provide effective therapy for this population [101]. Research suggests that people with PD can learn novel tasks through motor learning however, they might take more time to learn, have reduced outcomes and cannot generalize the learned task to other conditions as easily as healthy individuals [101]. When adding FOG into the equation, the motor learning ability is further compromised, as this subgroup shows worse learning, deficits in savings and less ability to generalize a learned motor task [102-104]. Furthermore, Mohammadi et al. [105] found that people with PD+FOG also have difficulty with switching from one motor program to another and adapting it, which

is also considered to be part of motor learning. Despite those findings, literature on motor learning in PD+FOG is scarce. There are several factors which can affect motor learning in PD in general. Some of them are related to pathological mechanism in the frontostriatal system [106, 107], the impaired interplay between cortical and sub-cortical areas [108] or deficits in executive function [109, 110]. Due to the mentioned deficits, it is essential to provide adequate circumstances for people with PD to learn new motor tasks in an exercise therapy setting. It is important to repeat training sufficiently to support feedforward learning mechanisms in PD [101], which will help with learning and savings. Furthermore, individual feedback or physical support can be beneficial to start with and should be reduced slowly in the process [101]. Using cueing, a form of external spatial or temporal stimuli to facilitate movement [111], can be particularly helpful for the subgroup of PD+FOG in this context [101]. Some researchers found that especially predictable continuous cueing can have positive effects as it targets feedforward-mechanisms [112]. This ties in with previous work which showed that PD+FOG have more difficulty with implicit motor learning [104], and therefore they might benefit from more explicit cues [99, 112, 113]. Other options to facilitate motor learning in PD+FOG could be adopting technology like virtual reality or artificial perturbations (treadmill or platform) to help to simulate everyday challenges and train those situations in a safe environment in the laboratory.

2.3.3 Therapeutic options to treat Freezing of Gait

Dopaminergic medication is the standard therapy used in a vast majority of PD individuals to treat multiple symptom domains. It has been shown previously, that dopaminergic medication can improve gait pattern, including FOG [114, 115]. Optimizing levodopa intake can reduce the OFF-time and also the FOG severity [116, 117], by reducing frequency and number of episodes. This is highly relevant as FOG occurs more often during the OFF-phases [10, 116]. Despite the positive effects, there are some downsides to the use of this medication, as patients need to comply with the prescribed medication intake schedule to have the best possible effect. However, adherence to medication schedule was found to be at least under 70% in PD and even lower with increasing number of tablets per day [118]. The medication effect usually starts to wear off after a couple of hours which can create large fluctuations in motor function during the course of a day. One option to reduce those motor-fluctuations and reduce OFF-phases is levodopa-carbidopa intestinal gel. However, it is not suitable for all PD

individuals as it needs to be administered through an intestinal probe [119]. Despite the mentioned studies which showed positive effects, there exists, to our knowledge, no meta-analysis on the effect of medication on FOG [119]. Various other non-dopaminergic drugs have been investigated to treat FOG, however results were inconclusive and beneficial effects limited [120].

One alternative option to the standard medication is the implantation of a brain-stimulating electrode. The main advantage of this option is the continuous stimulation of the brain, which can reduce motor fluctuation and reduce OFF-phases. However, deep brain stimulation (DBS) is only reserved for younger PD individuals due to the risk factors of brain surgery in the older population and also dopaminergic medication cannot be replaced completely. People with PD and DBS can also have side effects from the stimulation. Researchers have found that high frequency subthalamic nucleus stimulation (STN-DBS) effectively improved FOG in the majority of PD individuals [121], even for longer periods (up to 4 years), however only when OFF medication. The authors attribute the lack of effect when patients were ON medication to the levodopa responsiveness of FOG in the investigated study participants. Gao et al. [119] state that also low frequency STN-DBS has some positive effect on FOG, although it has not been confirmed in a meta-analysis. There are several other forms of temporary (non-invasive) stimulation including spinal cord, vagus nerve and transcranial stimulation, however their effect on FOG is not as well investigated and they sometimes show contradictory results [119].

Another treatment option which may overcome the above-mentioned drawbacks is exercise, which ranges from behavioral interventions to physiotherapy or gait training. The differential effects of physiotherapy interventions on FOG have been reviewed in a meta-analysis by Cosentino et al. [122]. In their analysis, which included a total of 913 people with PD+FOG, they found short-term improvements in FOG with moderate effect sizes when compared to a control treatment or no treatment. The reviewed studies included various types of interventions such as treadmill training [123, 124], action observation training [125-128], cueing [111, 129-131], exercise programs [132-134], home-based exercise [135-137] and aquatic training [138-140]. It was also found that longer interventions showed larger effect sizes as well as interventions that were specifically tailored to PD. This included two types of FOG-specific treadmill training. A curved treadmill training [123], which was specifically designed to target turning difficulties in PD+FOG, or combining regular treadmill training with

cues was shown to be effective to reduce FOG severity [124]. Another type of intervention that has been investigated in the rehabilitation of FOG is Nordic walking. It had a positive effect on PD+FOG as the participants experienced less FOG during gait initiation and turning after the training intervention [141]. These are promising results, which need to be confirmed by larger interventions to increase credibility of this therapy.

Cueing is one of the most popular options which can help people with FOG to overcome the FOG episodes using specific tricks [142]. Sometimes cueing devices like smart glasses [120] or laser shoes [143] are used, but even simple cues like lines on the floor or a metronome can help [144]. The effect of cueing on FOG in the meta-analysis of Cosentino et al. [122] was not significant in contrast to results from a previous narrative review [144]. Those contradictory results could be attributed to the small number of controlled trials that are available to date as well as inadequate outcome measures. Cueing can also be used in combination with wearable sensor technology, as researchers are also working on predictive systems to prevent FOG at the earliest signs [120]. In this context, real-time biofeedback is a promising method. The aforementioned algorithms (see chapter 2.3) are not able to detect FOG in real-time so far [85], but some researchers have been working on developing such real-time algorithms [145-147]. This method has the advantage to detect gait deterioration before the occurrence of FOG and therefore potentially allows FOG-prevention through feedback, e.g. through auditory cues [145-147]. One option of closed-loop feedback using tactile cueing during gait initiation was investigated by Schlenstedt et al. [77]; it did not improve first step initiation but impacted first step preparation. This does not diminish the general potential of cueing for gait initiation as other researchers have found positive effects of auditory gait cueing on gait initiation in PD+FOG [148].

Designing training programs with a focus on motor learning principles might be especially beneficial for PD+FOG. Plotnik et al. [149] showed that such an intervention could potentially decrease FOG burden, by training FOG-provoking situations. Another study showed positive effects of a motor-cognitive training on FOG episodes under DT [150]. However, in both of these investigations improvement of FOG was only measured by the observed number of FOG episodes during the laboratory assessments. This limits the findings as the improvements might not translate to the home situation.

Another innovative approach in the field of treadmill training, which is not included in the meta-analysis as studies were not controlled, is the use of a SBT. A SBT has two belts which can run at individual speed. Thus, it creates an artificial gait asymmetry and requires adaptation to the switch that occurs once one of the belts slows down or speeds up. It has been successfully used to reduce gait asymmetry in individuals post-stroke and might be promising for PD+FOG. Fasano et al. [78] found that walking on a SBT had a positive aftereffect on step length asymmetry, bilateral coordination, and the sequence effect. These defective gait domains are linked to FOG and therefore improving them might be beneficial for PD+FOG [78]. However, a lot of questions regarding the application of SBT in PD+FOG remain unanswered. It is not clear how the SBT training should be designed to achieve the best results, how many times per week it should be applied and how long the effects last. To successfully establish SBT in rehabilitation of PD+FOG these research gaps need to be addressed.

There are various reasons why there is still a lack of the most effective treatment for FOG despite decades of research in this field. Often clinical trials lack suitable outcome measures to claim the effects of different types of interventions. This was highlighted earlier (chapter 2.3), when explaining the assessment options of FOG in PD. Cosentino et al. [122] state that a majority of the studies use subjective questionnaire tools (like the NFOG-Q) to detect FOG severity. However, there have been some reservations about the suitability of the NFOG-Q as an outcome measure in clinical trials [151], which needs to be considered in the interpretation of those results. As to date there is no ideal method to assess FOG using only one tool, most studies have to combine questionnaire tools with objective measurement options (e.g. IMUs). Research in the field has yet to provide the minimal detectable change or the clinically relevant change for most of the assessment options to derive conclusions about the effectiveness of interventions. On top of that, the different phenotypes of FOG could need individual approaches for therapeutic interventions that are customized to the specific needs.

Despite the shortcomings in the research of exercise or physiotherapy in the rehabilitation of FOG, it is still one of the most promising options due to its numerous possibilities to target FOG-related gait deficits and possible pathological mechanisms.

3. Research aims

In consequence of the mentioned challenges regarding the assessment and treatment of FOG and FOG-related gait deficits there emerge several starting points for this thesis. First, one of the most established assessment tools for FOG, the NFOG-Q, has no validated German translation available. This is striking as the questionnaire has been established for several years and has been used in numerous publications in German-speaking individuals. Research into the validation of assessment tools might not be ground-breaking but it is fundamental. Therefore, study 1 of this thesis addresses this research gap. Second, investigating gait initiation and especially APAs in people with PD+FOG using IMUs has become increasingly common. However, previous literature into reliability has not examined the within-session reliability. It remains unclear how many trials should be conducted within a single assessment to generate reliable results in the various outcome parameters. Furthermore, there are no insights into potential systematic errors between trials. It is important to gather this information in people with PD+FOG as their gait shows more variability. Especially under DT conditions their gait pattern is altered and the impact on reliability is unknown. Study 2 is dedicated to enquiring this matter. Third, the use of SBT in the rehabilitation of neurological disorders is promising. In people with PD SBT paradigms have been investigated, however those results have not been systematically reviewed. To design future studies in this field based on the state of research it is essential to gain insight into the feasibility, the application options and the effects of SBT in people with PD. This topic is addressed in study 3 by a systematic review. Lastly, despite being a promising approach, SBT for rehabilitation in people with PD+FOG is not yet established in clinical routine. This is mainly because the effects have only been studied scarcely so far. There is a lack of data about the most effective SBT setting, the differential effects compared to TBT as well as aftereffects and savings. To further explore the effects of SBT in a long-term intervention, these open questions need to be addressed first, which will be done within study 4 of this thesis.

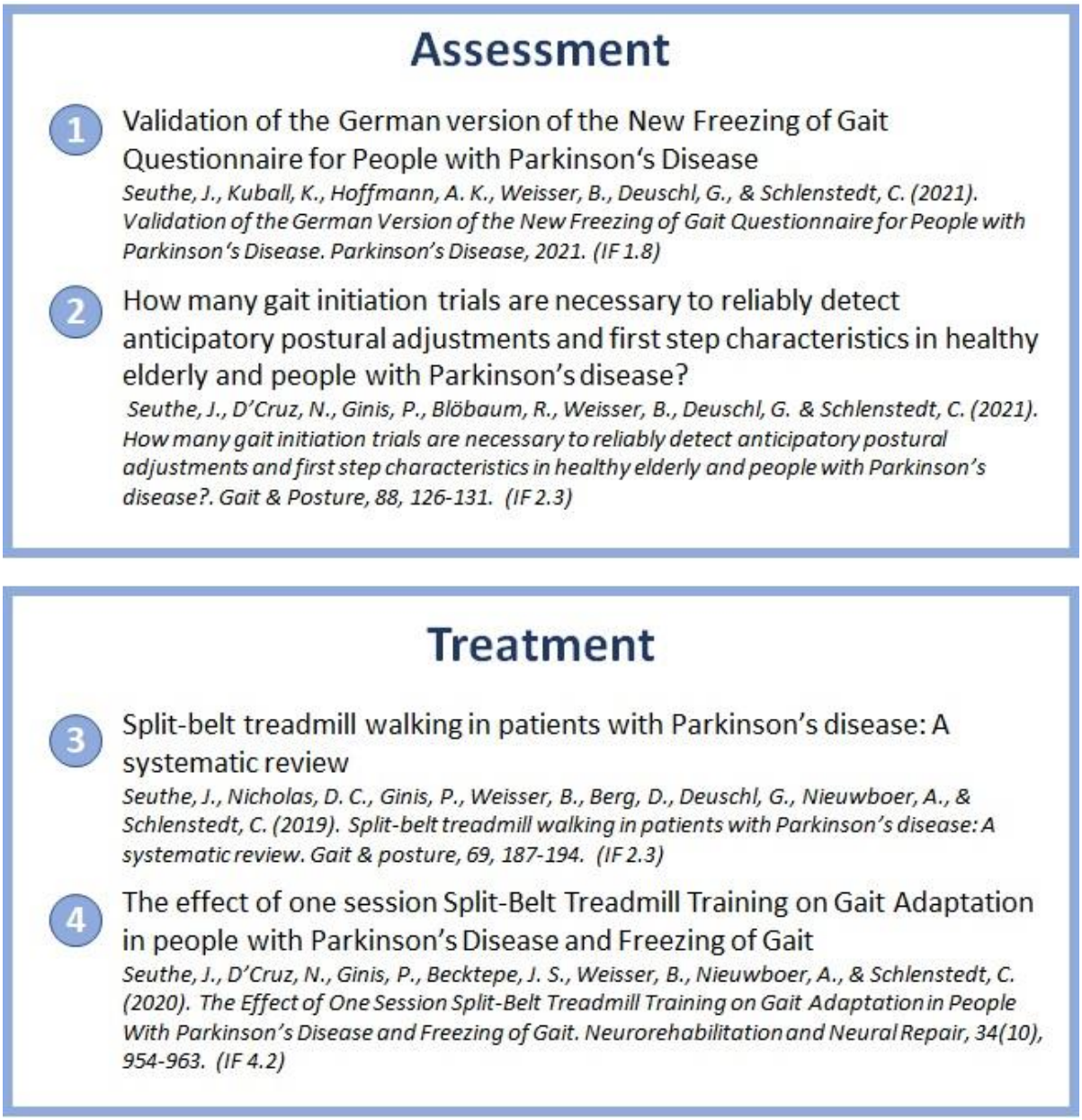

Figure 3.1 Studies included in this thesis. Displayed are the titles and the authors of each publication and the scientific journals. IF=Impact factor.

In the following a short background and the objectives of the studies will be presented.

Study 1: The NFOG-Q is the most commonly used tool to evaluate FOG frequency and severity as well as some dimensions of how FOG affects individuals. This study is set out to provide an appropriate German translation of the NFOG-Q for use in future studies using this instrument in German-speaking participants. Furthermore, it aims to test the internal consistency of this newly developed version in a population of people with PD+FOG. This leads to the following objective:

To investigate the validity of the German translation of the NFOG-Q.

Study 2: Anticipatory adjustments, which are important to enable gait initiation can be assessed using wearable sensors. Using sensors is an affordable method, which is quick and portable. However, it is not known how many trials of gait initiation need to be performed to reliably measure APA characteristics and first step parameters. Therefore, this work aims to answer this question by investigating 5 trials of gait initiation in HC and PD+FOG. This leads to the following objective:

> *To investigate the within-session reliability of APAs and first step characteristics in people with PD+FOG and HC.*

Study 3: In light of the lack of well-investigated exercise interventions targeting gait impairments in PD, Split-Belt treadmill is a promising tool. As people with PD, and particularly the subgroup with FOG, experience increased gait asymmetry, the Split-Belt treadmill has great potential for therapeutic use. Therefore, this work aimed to systematically evaluate previous findings on SBT walking in people with PD. The focus was set on the different methodological approaches, using various SBT paradigms, the ability of people with PD to safely walk on the SBT, the differences in short-term adaptation between PD and HC and the characteristic features observed in the subgroup with FOG. This leads to the following objective:

> *To systematically evaluate findings regarding the feasibility and efficacy of split-belt treadmill walking in people with PD and HC.*

Study 4: In order to effectively use SBT for long-term training interventions in PD+FOG, we need information about the effects on gait. With the aim to investigate the effects of SBT on gait adaptation, we designed a SBT training protocol, deriving from the knowledge of the systematic review. Different SBT conditions, using different ratios between belt speeds and a different number of switches in belt speeds were applied. This leads to the following objective:

> *To evaluate various SBT protocols and their differential effects on gait adaptation in people with PD+FOG and HC.*

Each study was published or is in the process of publication at a peer-reviewed scientific journal of the field. The title, authors, journal and impact factor (IF) of each publication can be found in Figure 1. To enhance readability and generate a single overall reference list the citation numbers, were continued throughout the articles.

4. Study 1: Validation of the of the German version of the New Freezing of Gait Questionnaire for people with Parkinson's Disease

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4.1 Abstract

Freezing of Gait (FOG) in Parkinson's Disease (PD) is a highly disabling symptom which impacts quality of life. The New FOG Questionnaire (NFOG-Q) is the most commonly used tool worldwide to characterize FOG severity in PD. This study aims to provide a German translation of the NFOG-Q and to assess its' validity in people with PD. The questionnaire was translated using forward-backward translation. Validity was tested in 57 PD with FOG via Cronbach's alpha for internal consistency and Spearman correlations with several clinical measures to quantify disease severity, mobility, fall risk and cognitive state for convergent and divergent validity. The German version of the NFOG-Q shows good internal consistency (Cα=0.84). Furthermore NFOG-Q score was significantly correlated with the MDS-UPDRS III, H&Y stage, Timed up and Go test and the subjective fear of falling (FES-I). The lack of correlation with cognition (MoCA) points towards good divergent validity. This study provides a German

version of the NFOG-Q which proofed to be valid for the assessment of FOG severity in individuals with PD.

4.2 Introduction

Freezing of Gait (FOG) is a debilitating symptom in people with Parkinson's Disease (PD) and is defined as a „brief, episodic absence or marked reduction of forward progression of the feet despite the intention to walk" [67]. It is often associated with falls due to the abrupt disruption of gait and also negatively impacts quality of life [66]. Due to its unpredictable and paroxysmal nature it is often difficult to assess [41]. FOG commonly occurs during movements such as gait initiation, turning, when navigating through a narrow space (e.g. doorway, cluttered area), when reaching a destination or when presented with an additional cognitive or stress component during gait [11]. So far, no gold standard exists to diagnose FOG and to measure FOG severity. Different approaches have been used such as self-reported measures using questionnaires [11, 152], FOG provoking gait trajectories [88] or instrumented analysis with the use of wearable sensors [96]. In clinical routine there can be a high false negative rate of patients subjectively reporting FOG which is not visible during the visit and thus not measured objectively. Hence standardized assessment tools are needed to detect FOG and quantify its frequency and severity in order to adjust therapy and develop therapeutic approaches. Despite the shortcomings of questionnaire tools, they can be helpful as they are easy and quick to conduct and they may provide useful information of experiences in daily life activity of the patient. Therefore, the New Freezing of Gait-Questionnaire (NFOG-Q), an updated version the Freezing of Gait Questionnaire [153] had been developed [87]. The NFOGQ consists of 9 items and can be administered in approx. 10 minutes. It covers multiple dimensions of the symptom. Not only does it quantify the frequency and the duration of FOG in various situations, but it also investigates the psychological strain and the consequences for daily activities for the patient, which can be especially helpful for clinical decisions regarding treatment. So far, the NFOG-Q has been widely used as one of the most relevant measures to quantify the occurrence and the severity of FOG [151, 154-156]. To the best of our knowledge, no validated German translation of the NFOGQ exist.

The aim of this study is to develop a German translation of the NFOG-Q, which can be used consistently in German speaking countries and to examine its' validity for people with PD with FOG. Given the association of FOG to disease severity, balance, fall risk and cognition, we

suspect the German translation of the NFOG-Q to be related to several clinical measures representing these domains.

4.3 Methods

Subjects

Fifty-seven people with idiopathic PD and FOG were examined for this study. Subjects were recruited from the outpatient clinic, the neurological and neurogeriatric ward at the University Hospital Schleswig-Holstein, Kiel, Germany (n=39) and from Segeberger Klinikien, Bad Segeberg, Germany (n=18). Inclusion criteria were the diagnosis of idiopathic PD (according to UK PD Brain Bank criteria), preserved walking ability and patient-reported occurrence of FOG in the past 4 weeks, by asking "Did you experience 'freezing episodes' over the past month?". Exclusion criteria were any other neurological disease or orthopedic conditions restricting gait. The study was conducted according to the ethical principles of the Declaration of Helsinki and was approved by the local ethical committee of the University Hospital Schleswig-Holstein. All participants provided written informed consent prior participation.

Development of the German version of the NFOG-Q

The NFOG-Q is a subjective patient-reported measure [87] with 9 items using 2- to 5-point ordinal scales. It consists of three parts. The first part (item 1) aims to differentiate between Freezers and Non-Freezers by asking about the occurrence of FOG within the past month. Furthermore, it offers a video with different examples of different types and severities of FOG to visualize the symptom for patients that might not know what FOG is or are unsure if what they are experiencing is FOG. The second part (item 2-6) characterizes the severity of FOG by asking how often the freezing occurs in specific situations and how long episodes last. The third part (item 7-9) investigates how FOG affects people with PD in their everyday life. According to the 8 items of part II and III the total score can range between 0 and 28 points, with higher scores representing more severe FOG.

The cross-cultural validation was carried out in two stages. First a bilingual native German speaker, who was aware of the concepts being examined in the questionnaire, translated the original NFOG-Q from English into German (JS). After that translation a retranslation was conducted by another bilingual native German speaker (CS), who was familiar with the field and with the original English NFOG-Q. Finally, the original version and the retranslated version

were reviewed by the two translators for incongruencies and differences were discussed with another movement disorders specialist. Necessary changes were made to ensure comprehensibility and clarity. The German version of the NFOG-Q can be downloaded as supplemental material online.

Testing procedure and assessment tools

For this study we applied a cross-sectional design. Tests were carried out during the ON state of medication, to ensure patients were in a good physical state regarding their motor and non-motor symptoms. Participants were not assisted by caregivers during the assessment of the NFOG-Q. To assess validity of the German version of the NFOG-Q, the translated NFOG-Q was related to the following clinical measures: to assess overall disease severity, the Movement-Disorders-Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS) part III and the Hoehn & Yahr (H&Y) scale was conducted. Balance and mobility was measured using the Timed up and Go Test (TUG). To assess the impact of cognition, the TUG was performed under single (ST) and dual task (DT) condition (serial threes backward subtraction) and DT cost (difference between ST and DT) was calculated. Furthermore, the Montreal Cognitive Assessment (MoCA) was conducted. Fall risk was assessed using the Falls Efficacy Scale-International (FES-I) and number of falls over the past 6 months.

Statistical analysis

For the analysis descriptive statistics (mean, standard deviation, minimum and maximum) were calculated to characterize the distribution or possible floor or ceiling effects of outcome measures. Internal consistency reliability was assessed using Cronbach's α (Ca). Recent literature highlights the problem with the arbitrary but often used value of 0.7 for good internal consistency [157], which might not always be sufficient to claim good internal consistency. That is why we will not provide an interpretation of Ca by different cut-offs previously mentioned in the literature, but rather interpret the results in the context of the investigated instrument. Generally a high Ca reflects high internal consistency [158]. Additionally, to investigate convergent and divergent validity, Spearman's rho correlations were calculated between the different clinical measures. Furthermore, a sub-analysis was performed for participants with cognitive impairments (MoCA< 21) [159]. It is noteworthy that inconsistency exist with regard to cut-off values for cognitive impairments in PD [159].

Statistical analysis was performed using R Studio [160].

4.4 Results

No major differences were found between the retranslated English version of the NFOG-Q to the original version. Minor differences (slight variation in the phrasing of the questions) were discussed between the two translators and the third movement disorders specialist to get a final German version of the NFOG-Q to which all investigators agreed to.

Table 4.1 Participant characteristics (n=57)

Outcome measure	**Mean ± SD (range)**
Age (y)	69.91 ± 9.882 (48-86)
Sex (m/f)	39/18
Disease duration (y; n= 55)	12,42 ± 6,863 (1-30)
H&Y (1/2/3/4) (n= 55)	1/6/36/13
MDS-UPDRS III	30.61 ± 16.12 (3-69)
TUG in sec (ST)	19.14 ± 16.45 (8-107)
TUG in sec (DT)	23.73 ± 19.89 (9-128)
FES-I	33.81 ± 11.53 (16-62)
Number of falls[a]	3.79 ± 6.57 (0-40)
MoCA	23.65 ± 3.633 (15-29)

[a] in the past 6 months, SD= standard deviation, y= years, m= male, f= female, H&Y=Hoehn and Yahr stage , MDS-UPDRS-III= Movement Disorder Society-Unified Parkinson's Disease Rating Scale part III, TUG=Timed up and Go, ST=single task, DT=dual task, FES-I=Falls Efficacy Scale-International, MoCA= Montreal Cognitive Assessment

Participant characteristics can be found in Table 4.1. Total scores of the German version of the NFOG-Q ranged between 7 and 28 with a mean of 17.82 (±6.29). Cronbach's α was 0.84 for the scale, suggesting a high internal consistency. The standardized Ca for each item can be found in Table 4.2.

The total NFOG-Q Score of the German version was significantly correlated with the MDS-UPDRS III ($r=0.280$, $p=0.038$) and with H&Y scale ($r=0.390$, $p=0.003$) (Table 4.3). Furthermore, it was correlated with the TUG (ST: $r=0.440$, $p<0.001$; DT: $r=0.535$, $p<0.001$, DT cost: : $r=0.384$, $p=0.005$) and the fear of falling assessed by the FES-I ($r=0.600$, $p<0.001$). We found no

significant correlation of the total NFOG-Q score with the disease duration (r=-0.064, p=0.643), the retrospective number of falls (r=0.179 p=0.183) and the MoCA (r=-0.148, p=0.272).

Table 4.2 Standardized Cronbach's α for each ordinal-scale item

NFOG-Q item	Cronbach's α
2	0.84
3	0.83
4	0.81
5	0.82
6	0.81
7	0.82
8	0.83
9	0.82

Table 4.3 Correlations of NFOG-Q with other outcome measures (n=57)

Outcome measure	Spearmann's rho	p-value
MDS-UPDRS-III	0.280	0.035*
H&Y	0.390	0.003*
Disease duration	-0.074	0.594
TUG (ST)	0.425	<0.001**
TUG (DT)	0.525	<0.001**
DT cost	0.384	0.005*
FES-I	0.583	<0.001**
Number of falls[a]	0.175	0.192
MoCA	-0.155	0.250

[a] *in the past 6 months, MDS-UPDRS-III= Movement Disorder Society-Unified Parkinson's Disease Rating Scale part III, H&Y=Hoehn and Yahr stage, TUG= Timed up and Go, ST=single task, DT=dual task, FES-I=Falls Efficacy Scale-International, MoCA= Montreal Cognitive Assessment, *significant, **highly significant*

Table 4.4 Correlations of NFOG-Q with other outcome measures only for subjects without major cognitive impairment (n=45)

Outcome measure	Spearmann's rho	p-value
MDS-UPDRS-III	0.266	0.085
H&Y	0.425	0.005*
Disease duration	0.024	0.881
TUG (ST)	0.493	<0.001**
TUG (DT)	0.567	<0.001**
DT cost	0.433	0.006*
FES-I	0.595	<0.001**
Number of falls[a]	0.120	0.445
MoCA	-0.074	0.638

[a] *in the past 6 months, MDS-UPDRS-III= Movement Disorder Society-Unified Parkinson's Disease Rating Scale part III, H&Y=Hoehn and Yahr stage, TUG= Timed up and Go, ST=single task, DT=dual task, FES-I=Falls Efficacy Scale-International, MoCA= Montreal Cognitive Assessment, *significant, **highly significant*

Excluding cognitively impaired participants revealed that Cronbacha's α only changed marginally to 0.83 (n=45). However, correlation of the NFOG-Q score with the MDS-UPDRS-III in the subgroup without major cognitive impairment was not significant. For details of all correlations in this subanalysis see Table 4.4. Internal consistency for individuals with major cognitive impairment (n=12, MoCA <21,) was also high (Cα=0.89).

4.5 Discussion

A German translation of the NFOG-Q was developed, and its' validity investigated for people with PD and FOG. We found high internal consistency for our German version of the NFOG-Q, as the items are interrelated but not redundant. Our results are in line with previous studies: Internal consistency of the original old version of the FOG-Q has been reported to range between 0.89 and 0.9 (Cronbach's α) for the original English version [152] and 0.83 for the German version [161]. Similarly, the NFOG-Q in the original English version showed a Cronbach's α of 0.84 [87], similar to what we found.

In contrast to the German validation of the FOG-Q [161] we found the total score to be significantly correlated to the MDS-UPDRS III, as well as to the TUG. This is proof of good construct validity as general motor symptoms and gait function are thought to be related with FOG [119]. Furthermore H&Y stage also showed a significant correlation to the NFOG-Q total score of our German version. It has been shown previously that the general occurrence of FOG [162] and also severity of FOG [163, 164] is linked to overall disease severity, which is in line with our findings.

As expected, individuals with higher NFOG-Q scores also presented with a higher fear of falling (FES-I), which was also found in previous cross-cultural validation studies of the FOG-Q [163, 165]. As FOG can disrupt gait abruptly this FOG-related fear of falling and a generally large impact of FOG on their daily activities translates to a higher overall fear of falling.

Our German version of the NFOG-Q was associated with the performance of the TUG as previously also reported for the FOG-Q [164, 165]. It was also correlated with the TUG while performing an additional cognitive task but not with the MoCA. This rather inconsistent results reflect current findings about the association between FOG and cognition as some studies support this association [166-168] whereas others do not [169]. The fact that the NFOG-Q was not correlated with the MoCA but with the dual-tasking TUG might reflect that FOG is less related to global cognition [169] than to specific cognitive impairments such as dual tasking. The impaired simultaneous conduction of a cognitive and motor task might represent increased cognitive control (due to reduced automaticity) in PD+FOG when performing a motor tasks, reducing cognitive resources for the cognitive task.

Assessment of FOG through questionnaire tools relies on the subjective perception of each patient and how well they recall the incidences of the symptom. Previous research has shown, that PD+FOG commonly underestimate the severity of their symptom [87]. Furthermore, already the classification of Freezer and Non-Freezer can sometimes be problematic. It could be the case that OFF akinesia is mistaken for FOG by people with PD, but this has not been investigated yet. Moreover, it is noteworthy that the NFOG-Q should ideally only be administered with non-demented individuals [161]. This was not the case in this study, as some subjects scored below proposed cut-off values in the MoCA. As participants need to recall incidents of FOG retrospectively for a period of 4 weeks and need to have good self-perception, this adds some bias to the current work. However, results revealed similar Ca

when excluding cognitively impaired participants and when analyzing the subgroup of cognitively impaired subjects separately.

The following limitations have to be noticed: First, there may be some bias in the translation process, as the re-translator was also familiar with the original English NFOG-Q. Second, no a-priori sample size calculation has been performed. However, post-hoc power analysis revealed power of 0.7 for the correlation of the NFOG-Q with the MDS-UPDRS and above 0.9 for the other significant correlations.

Recent work has shown poor test-retest-reliability resulting in a high rate of minimal detectable change of the NFOG-Q [151]. This suggests that the NFOG-Q might be less useful to detect treatment effects. The use of instrumented based measures therefore might be a good addition when investigating FOG based treatment interventions.

4.6 Conclusion

This study provides a German version of the NFOG-Q which proofed to be valid for the assessment of FOG severity in people with PD. However, for the use in longitudinal studies, the additional use of more objective methods should be considered. Clinicians, therapists and researchers can use the questionnaire to characterize the severity of the symptoms as well as consequences on daily life in their patients or study participants. Especially for clinical routine it is a useful tool and quick to administer. The German version of the NFOG-Q can be used consistently in German speaking countries and can be downloaded at:

https://www.neurologie.uni-kiel.de/de/neuromechanik-neurorehabilitation/downloads/nfogq-german.pdf

5. Study 2: How many gait initiation trials are necessary to reliably detect anticipatory postural adjustments and first step characteristics in healthy elderly and people with Parkinson's disease?

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5.1 Abstract

Background: The gait initiation (GI) process can be characterized by anticipatory postural adjustments (APAs) and first step characteristics. However, even within a constrained environment, it is unclear how many trials are necessary to obtain a reliable measurement of the GI process within one assessment.

Research question: How many gait initiation trials are necessary to reliably detect APAs and first step characteristics in healthy elderly (HC) and people with Parkinson's disease with Freezing of Gait (PD+FOG) under single (ST) and dual task (DT) conditions and are there any potential systematic errors?

Study 2: How many gait initiation trials are necessary to reliably detect anticipatory postural adjustments and first step characteristics in healthy elderly and people with Parkinson's disease?

Methods: Thirty-eight PD+FOG (ON-medication) and 30 HC performed 5 trials of GI under ST and DT (auditory stroop test). APAs and first-step-outcomes were captured with IMUs placed on the lower back and on each foot. Intraclass correlation coefficients (ICCs) and the standard error of measurement (SEM) were computed to investigate reliability and mixed model analysis to find potential systematic errors. Additionally, we computed an estimation for the number of necessary trials to reach acceptable reliability (ICC=0.75) for each outcome.

Results: ICCs varied from low reliability to excellent reliability across outcomes in PD+FOG and HC. ICCs were comparable under ST and DT for most outcomes. SEM results confirmed the ICC results. A systematic error was found for the first trial in first step ROM. Number of necessary trials varied largely across outcomes.

Significance: Within-session reliability varied across outcomes but was similar for PD+FOG and HC, and ST and DT. ML size of APA and first step ROM were most reliable, whereas APA duration and latency were least reliable. Depending on the outcome of interest, future studies should conduct multiple trials of GI to increase reliability.

Keywords: Anticipatory postural adjustment; gait initiation; reliability; Parkinson's Disease

5.2 Introduction

Anticipatory postural adjustments (APAs) are used by individuals to facilitate gait initiation (GI). They enable the acceleration of the center of mass forward and laterally towards the stance leg by moving the center of pressure posteriorly and laterally towards the stepping leg [74, 75]. Usually when initiating gait voluntarily a single APAs is performed. However, multiple APAs or the absence of an APA have been reported in people with Parkinson's Disease (PD)[170].

APAs can be detected using force plates or by the use of inertial measurement units (IMUs), the latter have recently become a widely used method in the field [171]. IMUs are especially useful as they can offer a flexible non-stationary solution to measure APAs in the clinic or in free-living situations. Widely used characteristics to describe APAs and first step characteristics via IMUs are: anterior-posterior (AP) APA size, medio-lateral (ML) APA size, APA duration and APA latency as well as first step range of motion (ROM) and first step velocity. APA metrics have been used to investigate neurophysiological mechanisms as well as to study

intervention effects [77, 172]. In healthy adults, The AP size of APAs is linked to the gait velocity as initiating gait with higher velocity requires greater forward propulsion of the COM and thus a larger AP APA size [173]. Individuals with PD present hypometric APAs of a longer duration than healthy age-matched controls (HC). They also show a higher step latency and reduced step velocity of the first step [73, 74, 174-176] and a higher amount of hip-abductors-cocontraction [77]. Levodopa medication has been shown to improve APAs in PD, by increasing the size and reducing the duration of the APA [174, 177].

APA production in people with PD and Freezing of Gait (PD+FOG) is proposed to be related to FOG, especially start hesitation [178], despite conflicting literature. Findings of smaller ML APA size in PD+FOG when no FOG occurs and when performing an additional cognitive tasks and larger ML APA size when FOG does occur have led to the hypothesis that hypometric APAs may also signify a compensatory adjustment [76]. Attention load was also found to modulate APAs in PD+FOG, making them more inappropriate and larger [179]. An additional dual task (DT) affects step characteristics more in PD+FOG than PD without FOG by increasing the duration of the first step [180]. Generally, PD+FOG present more often with multiple APAs during compensatory stepping [181], however not during voluntary stepping [76]. One study showed that trembling of the knees was actually accompanied by multiple short APAs which resulted in failed gait initiation [170]. In contrast, auditory stimuli or verbal instruction where shown to improve step preparation by helping PD+FOG to perform APAs more quickly and reducing the clinically observed start hesitation [148, 182].

IMU-measured APAs in people with PD were previously found to produce valid results [171]. Test-retest reliability within one day of the mean of three trials was found to be moderate to excellent in various outcomes of the GI process [171]. Despite the previously published research in the field, it remains unclear how many gait initiation trials need to be assessed in one session to produce reliable results for the assessment of APAs and first step characteristics. This aspect is especially of importance during clinical trials or clinical routine where time for assessment is often limited. Additionally, it is unclear whether potential systematic errors exist between trials. In PD+FOG this question is even more important as gait is more variable and gait initiation more inconsistent for this subgroup due to the start hesitation phenomenon. Furthermore, since an additional DT leads to higher variability during

gait in both PD and healthy elderly [36, 183], it may impact the reliability of APAs as well, which is yet to be investigated. Therefore, this study aims to investigate the within-session reliability and potential systematic errors of various measures of the preparation and execution of the first step of multiple trials of gait initiation, as measured by IMUs, and to compare results between PD+FOG and HC under single task (ST) and DT conditions. Furthermore, the impact of an additional cognitive task on the reliability of GI measures will be investigated. Finally, the minimal number of gait initiation trials that is needed to produce reliable results will be determined.

5.3 Methods

Subjects

This is a sub-analysis of data of a larger trial, which was conducted at two centers (CAU Kiel, Germany and KU Leuven, Belgium) (Clinical Trail No: NCT03725215). In total, 68 participants took part. The local ethics committees at the respective sites approved the study protocol and all participants gave their written informed consent prior participation. Only subjects that presented evaluable data for 5 gait initiation trials within the respective condition (ST and DT) were analyzed, resulting in different numbers of participants in each group and condition (PD-total: n=38, PD-ST: n=32, PD-DT: n=24, HC-total: n=30, HC-ST: n=28, HC-DT: n=23). This also included trials where participants did not perform any APA prior to gait initiation (32.5% in PD and 10.98% in HC). All assessments were performed in the clinical ON state of medication (PD only).

Testing

The gait initiation trials were conducted as follows: Participants were standing still with a standardized stance position (provided by a template, 10 cm distance between heels and 30-degree outward rotation) for about 5 seconds. A visual signal was shown to the participants to indicate when the 5 seconds are over and participants were asked to then initiate gait whenever they felt comfortable. They performed a total of 5 gait initiations at comfortable speed, each followed by a period of straight-line walking (about 10 meters). Participants first performed gait initiation under ST conditions. Afterwards the DT condition was introduced. The DT was an auditory Stroop task with the words "high" and "low" which were in a high

pitch or a low pitch (randomly congruent or incongruent with varying interval). Participants were asked to name the pitch of the stimuli as quickly as possible. Participants completed one bout of the auditory Stroop task while sitting, before pairing it with the gait initiation and walking. The auditory Stroop was started when participants where in the standardized stance position, hence at least 5 seconds before initiating gait. No instructions were given about prioritization of one of the tasks.

Data was collected using three IMUs (APDM, Mobility Lab, 128 Hz), located on the lower back and on the dorsum of both feet. We used the same algorithm as described previously [76]. In brief, the data of the IMUs was filtered (Butterworth filter, cut-off 3 Hz), APAs were defined from when the acceleration of the trunk exceeded 3 standard deviations of the postural sway during quiet stance. Start and end of an APA were determined when trunk acceleration exceeded 1 standard deviation of the postural sway during quiet stance. The data was analyzed using a partly automated Matlab [184] script, which was run by a trained movement scientist and computed the following outcome parameters: ML and AP APA size, APA duration, latency, first step ROM and first step velocity. ML APA size is the peak medio-lateral acceleration of the trunk. AP APA size hence is the peak anterior-posterior acceleration of the trunk. Both are calculated from the lower back sensor. APA duration and APA latency describe the temporal aspect of the APA being the time from start to end of the APA and the time from start of the APA to toe off respectively. First step ROM was measured by the ROM traveled by the foot sensor from toe-off to heel-strike. First step velocity was derived from the time participants needed for the first step.

Statistical analysis

Evaluation of trial and condition effects was conducted using linear mixed model with a trial*condition*group interaction, with a random intercept for each participant. Models were run for using the "lmer-package" in RStudio [160].

To investigate inter-trial reliability, intraclass correlation coefficients (ICCs) and the respective 95 % confidence intervals (CI) were computed using the "ICC"-function from the "psych-package" in RStudio [160]. This function automatically excludes missing values. We chose the two-way random effects models to assess reliability [185]. Furthermore, both single

measurement (ICC(2,1)) and average measurement (ICC(2,k)), based on absolute agreement, were calculated. ICC (2,1) shows reliability for future assessment based on a single measurement whereas ICC (2,k) shows reliability over the mean of k (k=5) measurements. Koo et al. [186] stated that ICCs below 0.5 indicate poor reliability, values between 0.5 and 0.75 indicate moderate reliability, values between 0.75 and 0.9 indicate good reliability and values above 0.9 indicate excellent reliability. CI's were carefully reviewed to derive information about whether ICC's were comparable or different (e.g. between conditions or groups).

To further explore measurement precision [187], we calculated the standard error of measurement (SEM) which is presented as an absolute value (with the same units as the measurement of interest) and as a percentage ratio of the mean values for each parameter. Additionally, we estimated the number of trials needed to reach ICC of 0.75 according to the Spearman-Brown formula (estimated n=(0.75*(1-ICC))/(ICC*(1-0.75))) [188-190].

5.4 Results

Participants characteristics are presented in Table 5.1. People with PD and HC did not differ with respect to age (p=0.674 and gender (p=0.145). People with PD+FOG did not experience any FOG episodes in the gait initiation trials.

Table 5.1 Participants characteristics

	PD+FOG	**HC**	**p.value**
Age (yrs)	68.21 (±10.36)	70.33 (±6.38)	0.674
Sex (f/m)	9/29	13/17	0.145
Mini-BESTest (0-24)	20.61 (±5.19)	25.07 (±2.45)	p<0.001
MoCA (0-30)	24.43 (±3.29)	27.07 (±2.64)	p<0.001
H&Y (1/2/3/4/5)	1/15/18/4/0	-	
DD (yrs)	12.90 (±7.47)	-	
MDS-UPDRS-III (0-132)	35.89 (±15.08)	-	
NFOG-Q Score (0-28)	16.33 (±5.77)	-	

Note. Values show Mean±SD. HC=healthy control, PD+FOG=persons with Parkinson's Disease and Freezing of Gait, Mini-BESTest= Mini-Balance Evaluation System Test, MoCA= Montreal Cognitive Assessment, H&Y= Hoehn&Yahr Stage, DD=disease duration, MDS-UPDRS= Movement Disorder Society-Unified Parkinson's Disease Rating Scale, NFOG-Q=New Freezing of Gait Questionnaire

Reliability of gait initiation assessment varies among outcome measures

Results showed that within-session reliability varied across the different outcomes of the GI process and in some cases across conditions. ICC (2,1) and ICC (2,k) are presented separately for PD+FOG (Table 5.2) and HC (Table 5.3) and for each condition (ST and DT), and ICC (2,k) is further visualized in Figure 1.

Single measure ICC's (ICC (2,1)) were generally low-moderate in both PD+FOG and HC. PD+FOG showed moderate reliability) for ML APA size, first step ROM under DT and first step velocity under ST. ICC's were below 0.5 (low reliability) for AP APA size, APA duration, APA latency under ST and DT, first step ROM under ST and first step velocity under DT. Results were similar for HC, only first step ROM under DT conditions reached good reliability. Other than that HC presented moderate reliability in many variables (ML APA size under ST and DT conditions and first step ROM and first step velocity under ST conditions) and poor reliability (AP APA size, APA duration and APA latency under ST and DT conditions and first step velocity under DT conditions). Reliability was similar for PD+FOG and HC (Figure 5.1).

For the mean of 5 trials of gait initiation (ICC (2,k)), in PD+FOG the ML and AP APA size, the first step velocity and the first step ROM showed good reliability under ST and DT conditions (except AP APA size under DT). APA duration and latency (ST and DT) were moderately reliable for the mean of 5 trials of gait initiation. In HC ML APA size and first step ROM show highest reliability with excellent scores. They reached good reliability for first step velocity (only ST). Furthermore, they showed moderate reliability of AP APA size, APA duration and APA latency under ST and DT conditions and first step velocity under DT conditions.

The SEM and SEM (%) for all measured APA and first step outcomes are presented for PD+FOG (Table 5.2) and HC (Table 5.3) separately subdivided for each condition (ST and DT). The SEM aligned with the ICC for most APA and first step parameters. However, AP APA size showed a large SEM in PD+FOG despite a high ICC.

Differences in reliability between ST and DT conditions

Comparison of confidence intervals suggests that there were no differences in reliability between the ST and DT conditions for all parameters, except first step velocity (see Figure 5.1). In HC this was the parameter showing a significant difference between conditions. In PD+FOG

we found as well that parameters show similar reliability between ST and DT conditions. Only ICC(2,k) of AP APA size was much lower under DT compared to ST, however as CI's overlap slightly we can't certainly say that they differ significantly.

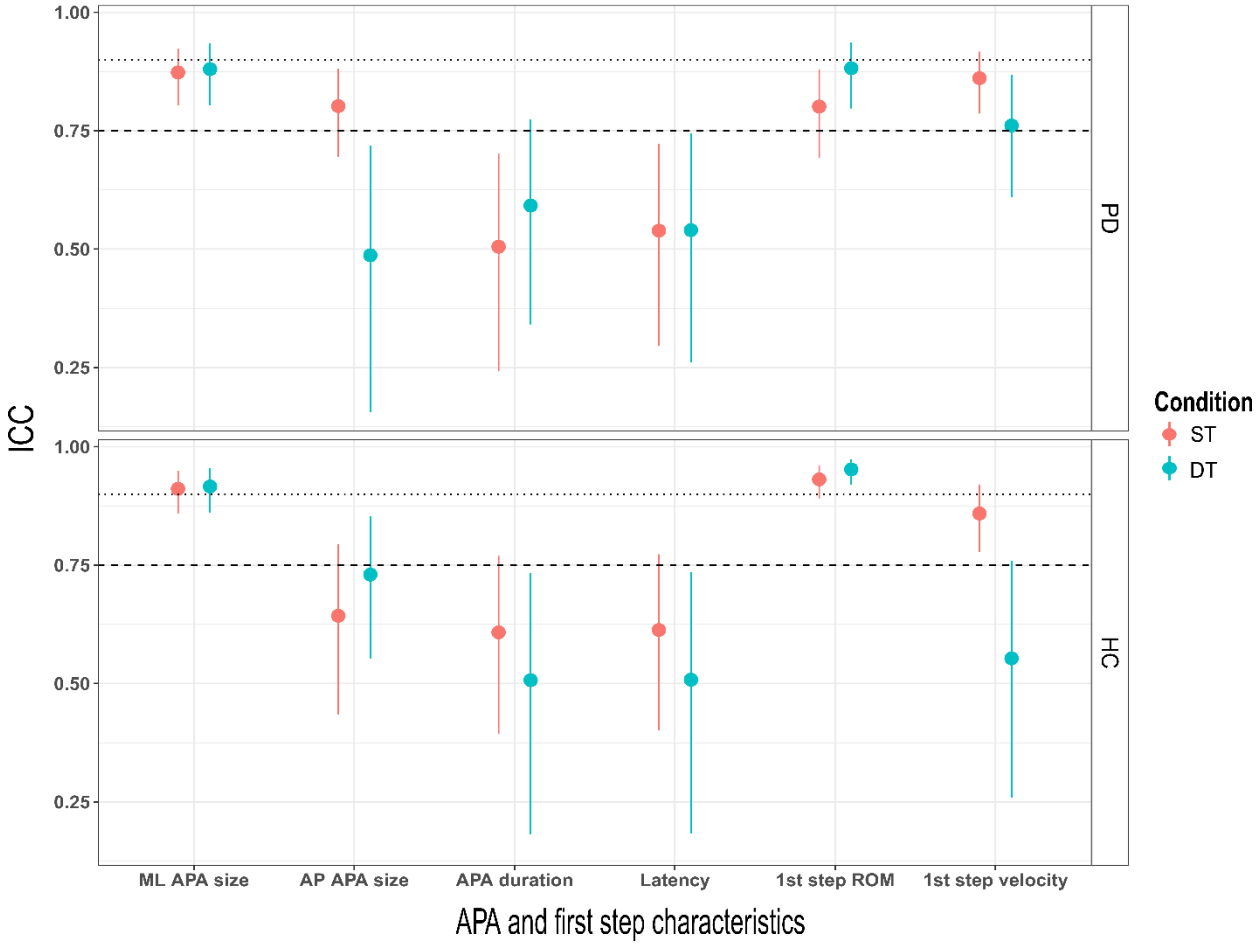

Figure 5.1 ICC (2,k) for PD+FOG and HC. Values above the dashed line indicate good reliability. Values above the dotted line indicate excellent reliability. The figure shows ICCs with lower and upper 95% confidence intervals.

Table 5.2 ICC of APA and first step characteristics in PD+FOG

variable	cond	mean	SD	type	ICC	lower bound	upper bound	n	SEM	SEM (%)	Needed trials for ICC=0.75
APA_ML	ST	0.042	0.021	ICC (2,1)	0.578	0.450	0.707	32	0.014	32.421	2
APA_ML	ST			ICC (2,k)	0.873	0.804	0.924	32	0.007	17.814	
APA_ML	DT	0.044	0.020	ICC (2,1)	0.596	0.450	0.741	24	0.013	29.285	2
APA_ML	DT			ICC (2,k)	0.880	0.804	0.935	24	0.007	15.924	
APA_AP	ST	0.041	0.027	ICC (2,1)	0.447	0.313	0.596	32	0.020	48.200	4
APA_AP	ST			ICC (2,k)	0.802	0.695	0.881	32	0.012	28.867	
APA_AP	DT	0.035	0.018	ICC (2,1)	0.159	0.036	0.339	24	0.017	47.461	16
APA_AP	DT			ICC (2,k)	0.487	0.156	0.719	24	0.013	37.086	
APA_Dur	ST	0.574	0.408	ICC (2,1)	0.170	0.060	0.320	32	0.372	64.758	15
APA_Dur	ST			ICC (2,k)	0.505	0.243	0.702	32	0.287	49.977	
APA_Dur	DT	0.599	0.401	ICC (2,1)	0.225	0.094	0.406	24	0.353	59.033	10
APA_Dur	DT			ICC (2,k)	0.592	0.341	0.774	24	0.256	42.831	
Latency	ST	0.719	0.400	ICC (2,1)	0.190	0.078	0.342	32	0.360	50.119	13
Latency	ST			ICC (2,k)	0.539	0.296	0.722	32	0.272	37.787	
Latency	DT	0.749	0.417	ICC (2,1)	0.190	0.066	0.368	24	0.376	50.153	13
Latency	DT			ICC (2,k)	0.540	0.261	0.744	24	0.283	37.793	
1st_StepROM	ST	27.810	9.252	ICC (2,1)	0.446	0.311	0.596	32	6.889	24.771	4
1st_StepROM	ST			ICC (2,k)	0.801	0.693	0.880	32	4.130	14.851	

Study 2: How many gait initiation trials are necessary to reliably detect anticipatory postural adjustments and first step characteristics in healthy elderly and people with Parkinson's disease?

1st_StepROM	DT	26.657	9.501	ICC (2,1)	0.598	0.441	0.746	24	6.021	22.586	2
1st_StepROM	DT			ICC (2,k)	0.882	0.797	0.936	24	3.268	12.260	
1st_StepVelo	ST	0.381	0.112	ICC (2,1)	0.553	0.423	0.687	32	0.075	19.712	2
1st_StepVelo	ST			ICC (2,k)	0.861	0.786	0.917	32	0.042	10.997	
1st_StepVelo	DT	0.393	0.170	ICC (2,1)	0.389	0.239	0.569	24	0.133	33.792	5
1st_StepVelo	DT			ICC (2,k)	0.761	0.610	0.868	24	0.083	21.136	

Table 5.3 ICC of APA and first step characteristics in HC

variable	cond	mean	SD	type	ICC	lower bound	upper bound	n	SEM	SEM (%)	Needed trials for ICC=0.75
APA_ML	ST	0.049	0.021	ICC (2,1)	0.672	0.549	0.787	28	0.012	25.185	1
APA_ML	ST			ICC (2,k)	0.911	0.859	0.949	28	0.006	13.115	
APA_ML	DT	0.047	0.020	ICC (2,1)	0.687	0.554	0.809	23	0.011	24.048	1
APA_ML	DT			ICC (2,k)	0.916	0.861	0.955	23	0.006	12.425	
APA_AP	ST	0.042	0.020	ICC (2,1)	0.265	0.133	0.435	28	0.017	41.404	8
APA_AP	ST			ICC (2,k)	0.643	0.435	0.794	28	0.012	28.857	
APA_AP	DT	0.039	0.021	ICC (2,1)	0.351	0.198	0.540	23	0.017	42.817	6
APA_AP	DT			ICC (2,k)	0.730	0.552	0.854	23	0.011	27.616	
APA_Dur	ST	0.538	0.262	ICC (2,1)	0.237	0.115	0.401	28	0.229	42.544	10
APA_Dur	ST			ICC (2,k)	0.608	0.393	0.770	28	0.164	30.482	
APA_Dur	DT	0.530	0.316	ICC (2,1)	0.171	0.043	0.356	23	0.288	54.392	15
APA_Dur	DT			ICC (2,k)	0.507	0.182	0.734	23	0.222	41.925	
Latency	ST	0.669	0.264	ICC (2,1)	0.241	0.118	0.405	28	0.230	34.315	9
Latency	ST			ICC (2,k)	0.613	0.401	0.773	28	0.164	24.487	
Latency	DT	0.724	0.400	ICC (2,1)	0.171	0.043	0.357	23	0.364	50.358	15
Latency	DT			ICC (2,k)	0.508	0.183	0.735	23	0.281	38.795	
1st_StepROM	ST	31.110	6.983	ICC (2,1)	0.731	0.617	0.830	28	3.625	11.651	1

Study 2: How many gait initiation trials are necessary to reliably detect anticipatory postural adjustments and first step characteristics in healthy elderly and people with Parkinson's disease?

1st_StepROM	ST			ICC (2,k)	0.931	0.890	0.961	28	1.830	5.883	
1st_StepROM	DT	29.163	7.803	ICC (2,1)	0.798	0.698	0.882	23	3.504	12.016	1
1st_StepROM	DT			ICC (2,k)	0.952	0.920	0.974	23	1.711	5.868	
1st_StepVelo	ST	0.380	0.088	ICC (2,1)	0.550	0.411	0.694	28	0.059	15.512	2
1st_StepVelo	ST			ICC (2,k)	0.859	0.777	0.919	28	0.033	8.671	
1st_StepVelo	DT	0.453	0.330	ICC (2,1)	0.199	0.065	0.387	23	0.296	65.189	12
1st_StepVelo	DT			ICC (2,k)	0.553	0.259	0.759	23	0.221	48.663	

Systematic errors

A significant effect of trial was found for first step ROM ($p<0.001$). Post-hoc comparisons show that the first trial has significantly reduced first step ROM compared to the following trials under ST and DT conditions (1-2 $p=0.004$; 1-3 $p<0.001$; 1-4 $p=0.002$; 1-5 $p<0.001$). Exclusion of the first trial did not have a large effect on reliability. There was a slight increasement in reliability of the parameters that showed good reliability anyways (MP APA size, first step ROM) and a decrease of reliability in parameters that showed low reliability (APA duration, latency). Furthermore, we found a significant trial-by-condition interaction for APA duration ($p=0.037$). According to post-hoc tests, the first trial under ST conditions differed significantly from the other trails, showing a larger APA duration (1-2 $p<0.001$; 1-3 $p=0.042$; 1-4 $p<0.001$; 1-5 $p=0.005$), while for DT conditions that was not the case. All other outcome measures did not show any significant trial, condition, or interaction effects.

Estimated number of needed trials for reliability

The estimated number of trials needed to reach an ICC of 0.75 varies across the different GI variables. ML APA size and first Step ROM were the only outcomes that showed good reliability already after few trials: HC need to perform only 1 trial under ST and DT conditions for reliable results in ML APA size and first step ROM. PD needed 2 trials for ML APA size (ST & DT) and DT first step ROM and 4 trials for ST first step ROM. For first step velocity, HC needed 2 trials (only ST) and PD+FOG required 2 and 5 trials (ST & DT respectively). In contrast, there were several APA and first step outcomes where PD+FOG and HC were estimated to need more than 5 trials to reach good reliability, with some metrics (APA duration and latency) even requiring 10 or more trials for good reliability (for details see Table 5.2 and Table 5.3).

5.5 Discussion

This study investigated within-session reliability of IMU based assessments of APAs and first step characteristics in PD+FOG and HC.

Reliability differs between APA outcomes

Reliability was shown to be moderate to good in most of the selected outcomes of the GI process for the mean of 5 trials in both PD+FOG and HC. Similarly to Mancini et al. [171] who

investigated inter-session reliability we found reliability to be lower in AP APA size and APA duration. However, the low ICC values for single measures compared to average measure reflected a high within-subject variance in relation to overall variance. Thus, we conclude that some of the outcomes (AP APA size, APA duration, APA latency, first step ROM ST, first step velocity DT) should only be used if the mean of multiple trials can be computed. Our results thereby strengthen previous studies [171], where this was already addressed by including multiple trials of gait initiation in the analysis. However, a lot of studies do not report the number of trials that was conducted to obtain the presented results [172, 180, 191]. In the light of the current findings, this is problematic as reliability might be constrained. In our study, ML size of APA and first step ROM were relatively robust and the conduction of only one or two trials was sufficient to receive reliable results. Especially the good reliability of first step ROM strengthens its potential as an important outcome measure for clinical gait assessment as previous work has shown, that it is sensitive to differentiate between PD and HC even at an early disease stage and also could be used as a disease progression marker [191]. However, other outcomes (AP APA size, APA duration, latency) were less reliable and the estimation of trials needed to reach good reliability (ICC=0.75) for those variables where up to ten and more trials.

Furthermore, the calculation of the SEM, as a measure of precision and within subject variance, added to our results, showing that AP APA size in PD+FOG had a high SEM despite an acceptable ICC value. This indicates that AP APA size, which is a characteristic feature of gait initiation in PD who have difficulty in generating the posterior shift of COP [148], needs to be interpreted with caution. In this case, the high reliability contradicted to some extent the low precision of the parameter and therefore the responsiveness of the outcome. The latter is important for interpreting the effects sizes in the context of test-retest error in future clinical trials.

Reliability is comparable between groups and conditions

Reliability of the outcomes of the GI process is comparable between the PD+FOG and HC group. This is striking as the participants with PD were quite severely affected by their disease and showed a serious motor impairment. However it can be explained by the medication status of the participants, as dopaminergic medication has a great effect on gait initiation

[192]. Due to the comparable reliability between groups, the recommendations made to improve the reliability should generalize well to multiple clinical populations and tasks. Furthermore, the difference between reliability under ST and DT conditions in PD and HC was not as pronounced as expected. The largest differences were in AP APA size in PD+FOG and first step velocity in HC showing less reliable results during the dual task condition. We suspect this to be due to increased variability caused by the cognitive load of the DT. It may be that participants prioritized the cognitive task over the motor task, although no instruction on task prioritization was given.

Systematic error for first gait initiation trial

Mixed model analysis has shown that there is a systematic error for first step ROM. It seems that the first trial is not representative of overall first step ROM in PD+FOG and HC. The first step ROM was significantly smaller in the following trials. We speculate that this could be due to the unnatural situation of the test condition (e.g. foot template) and that participants needed to accustom to the test situation. However, as excluding the first trial did not substantially improve reliability of this outcome and no trial effect was found in the other outcomes, we do not recommend to discard the first trial.

The following limitations have to be mentioned. First, for several trials, APAs and first step kinematics could not be analyzed due to the fact that for some trials, the stance phase was too short to be analyzed as some participants started walking before seeing the visual signal or due to noise within the stance period caused by dyskinesia (PD only). This leaded to a relatively high amount of missing data. Second, although participants were not instructed to initiate gait immediately after having seen the visual signal but whenever they felt comfortable, we cannot rule out that the visual signal cued the gait initiation process and therefore may have impacted results.

5.6 Conclusion

Within-session reliability of IMU-based assessment of APAs and first step kinematics varied across outcomes but was similar for HC and PD+FOG. Performing a DT did not affect reliability of the GI metrics, with the exception of APA AP size and first step velocity, which worsened. Results showed that 5 trials were sufficient to obtain acceptable reliability for most outcome

measures, however for ML size of APA and first step ROM 2 trials were already sufficient to produce reliable results (except DT for PD). AP size of APA, APA duration, first step latency and first step velocity are less reliable and more trials are needed to receive representative results. Dependent on the outcome of interest, future studies should average GI variables over multiple trials and the number of trials should be reported.

6. Study 3: Split-belt treadmill walking in patients with Parkinson's disease: A systematic review

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6.1 Abstract

Background: Walking on a split-belt treadmill (SBT) can help to modulate an asymmetric gait, particularly for people with neurological conditions, such as Parkinson's disease (PD), where asymmetry plays a role due to the laterality of the disease.

Research question: This systematic review critically evaluates the literature on SBT in PD. First, different SBT paradigms and methodological approaches were evaluated. Second, the review explored how people with PD adapt their gait to different SBT conditions compared to healthy controls (HC).

Methods: We conducted a systematic search of the PubMED, PsychINFO, and Web of Knowledge databases. Original research articles, published in English and investigating SBT walking in people with PD, were included.

Results: From the 925 studies originally identified, seven met the inclusion criteria and were selected for evaluation (n = 118 individuals with PD of whom 44 had freezing of gait (FOG)).

The SBT paradigms varied across studies regarding the SBT settings, definitions of gait variables, and criteria for determining dominance of body side. Gait variability and bilateral coordination were found to adapt to the SBT condition similarly in people with PD and healthy controls (HC). Inconsistent results were found with respect to the adaptation of gait asymmetry, for the differences between PD and HC participants. The subgroup of people with PD and FOG showed reduced accuracy in detecting belt speed differences and slower adaptation to SBT conditions.

Conclusion: Individuals with mild to moderately severe PD adapted similarly to HCs to SBT walking for gait variability and bilateral gait coordination. However, those with FOG had impaired perception of belt speed differences and did not adapt their gait so readily. Although SBT can be useful for modulating gait asymmetry in some people with PD, it was not beneficial for all. We recommend standardization of SBT protocols for clinical practice in future studies.

Keywords: Parkinson's disease, split-belt treadmill, gait adaptation

6.2 Introduction

Parkinson's disease (PD) is one of the most prevalent neurodegenerative disorders, especially in elderly people [193], with an increased risk of mortality [194]. Pharmacological treatment does not always bring relief for all symptoms, and alternative methods, such as physical therapy, are arguably necessary [195, 196]. Most rehabilitation research has focused on improving gait and balance in people with PD. Different exercise interventions (e.g., balance and gait training, treadmill training, cycling, resistance training) appear to improve gait in individuals with PD [197]. Recent work on complex motor training requiring high postural and cognitive demands has shown positive effects on balance and a reduction in the fear of falling in people with PD [198] along with an increase in postural stability and a better gait [199]. Furthermore, treadmill training was associated with increased stride length, lower cadence, and better foot clearance [200]. Beside the immediate effects, long-term treadmill training also induced clinically relevant improvements of over-ground gait speed and stride length [21].

A split-belt-treadmill (SBT) has two belts, which can either run at the same speed (tied) or at different speeds (split). A SBT can be used to modulate gait and to investigate the ability of an individual to adapt to novel gait patterns, as the system imposes asymmetric walking. When a split belt condition is imposed, an individual's walking pattern adapts by modifying spatial

and/or temporal gait parameters [201]. Healthy individuals adapt their walking to SBT conditions by immediately increasing the stance time of the leg on the slow belt, inducing step length asymmetry [202]. Over time, this initial asymmetry of step length, double support time, and inter-limb phasing diminishes [202]. When returning belts to the same speed, short-term aftereffects are present because asymmetry parameters are elevated compared to baseline [202].

The impact of the SBT has been studied in unimpaired people and those with neurological conditions, such as stroke [203-209] and cerebral palsy [210]. The SBT was shown to be effective in restoring a more symmetrical walking pattern in individuals who had suffered a stroke with gait adaptations being retained for up to 3 months [209]. In individuals with PD, the cardinal motor symptoms generally present asymmetrically with one side initially being more affected than the other due to the lateral progression of the disease [211]. Hence, a SBT is arguably useful for investigating gait asymmetry and motor skill learning in patients with PD [39, 78, 105, 212-215].

Freezing of gait (FOG) is defined as the inability to perform effective sequential steps despite having the intention to walk [11]. Depending on the disease stage, between 20-80% of people living with PD are affected by FOG [68]. FOG frequently occurs during asymmetric motor tasks, such as gait initiation and turning [116]. People with PD who have FOG (PD+FOG) show increased gait asymmetry compared to those without FOG (PD-FOG) [42]. Those persons with FOG also have greater deficits in switching from one motor pattern to another [216]. Both gait asymmetry and motor switching can be investigated using SBT training. This suggests that the investigation of SBT walking in PD+FOG is particularly interesting as it may offer further insight into FOG pathology. In addition, manipulating gait asymmetry using deep brain stimulation has been shown to diminish FOG [217].

This systematic review and critical evaluation of the literature summarizes the existing evidence on SBT walking in individuals with PD. First, we discuss different SBT paradigms and methodological approaches. Second, we summarize how people with PD adapt their gait to different SBT conditions in comparison to HC.

6.3 Methods

Search strategy

A systematic literature search was conducted of the *PubMED, PsychINFO,* and *Web of Science* databases until April 2018. The following search strategy was used: *([split-belt* OR split belt OR splitbelt OR walking adaptation OR gait adaptation OR locomotor adaptation OR motor adaptation OR motor learning] AND parkinson*)*. The key terms were selected based on keywords in articles focusing on SBT walking. Only original research articles, published in English, investigating SBT in people with PD were included.

Study selection

The search employed "All Fields" (*PubMED, PsychINFO*) or "Topics" (*Web of Knowledge*). Figure 6.1 shows the flow diagram of the literature search. A total of 925 results were identified from the following databases: 218 results for *PubMED* (from 1950); 162 results for *PsychINFO* (from 1806) and 545 results for *Web of Knowledge* (from 1900). After removing duplicates and screening titles, 399 publications were retained for further screening. After screening abstracts or keywords, seven studies were selected for full-text evaluation. The excluded studies either investigated cohorts other than PD or did not include an SBT paradigm. The seven full texts were checked for eligibility according to the predefined criteria and were all included in the evaluation. Due to the small number of included studies and the variable used methodologies, the conduction of a meta-analysis was not feasible. Although a preliminary study of SBT usage with individuals with PD was performed in 1995, the literature on this topic remains scarce. A rating for the level of evidence was conducted according to Gross & Johnston [218]. The main criteria for quality evaluation were randomization, a control group, and the blinding of subjects and investigators.

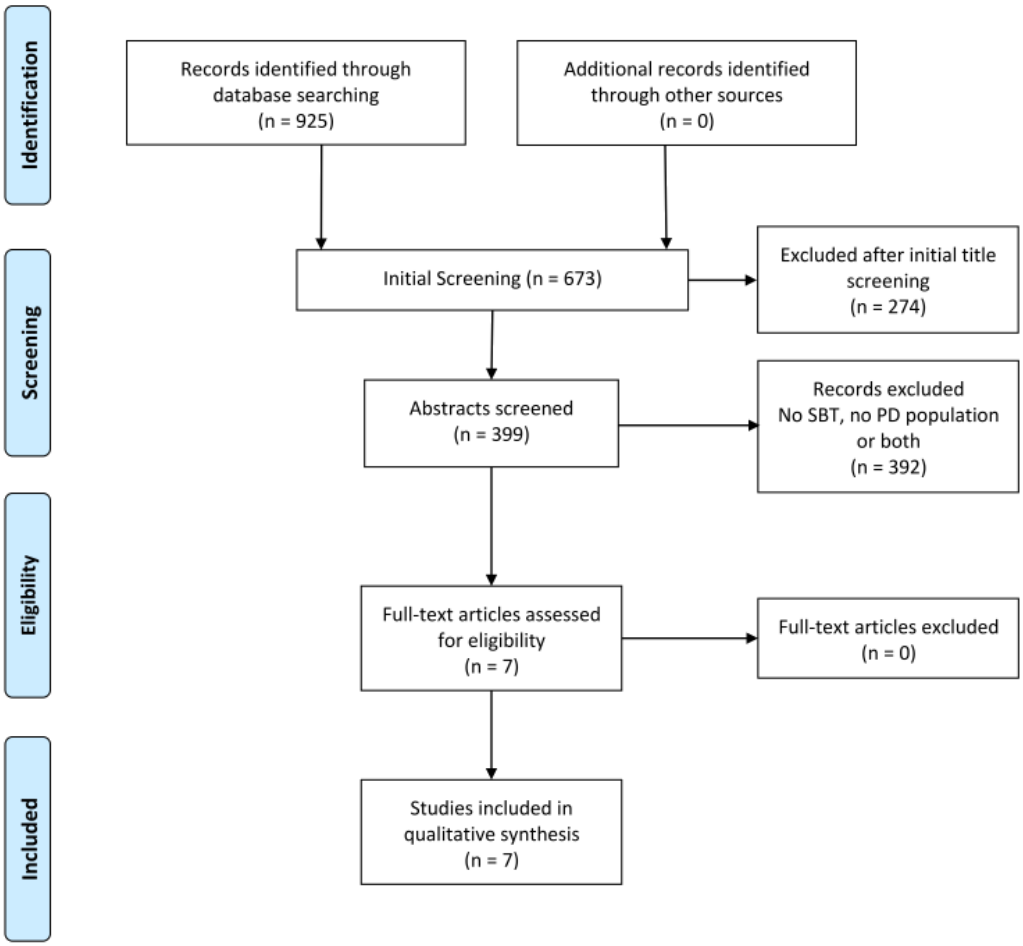

Figure 6.1 PRISMA flow diagram of systematic literature search and study selection; n=number of publications; SBT=Split-Belt Treadmill; PD=Parkinson's Disease.

6.4 Results

The level of evidence was found to be III for all included articles. Studies either had a control group of healthy individuals or participants served as their own controls when different SBT conditions were compared [218].

Participants

The studies varied with regard to the number of participants with PD and ranged from n = 10 [213] up to n = 25 [214] (Table 6.1). The age of the participants ranged between 58.3 and 66.8 years, with the disease severity varying between Hoehn & Yahr (H&Y) scale 2.1 and 2.6 [39, 105, 212-214]. The percentage of female participants was on average 25% for people with PD (three studies did not report gender distribution). In five studies, healthy controls (HC) served as a control group receiving the same intervention/walking protocol [105, 212-215]. Within the HC group, age ranged between 60.6 and 65.3 years with an average of 35.3% female

participants [105, 212, 214]. One study also included young healthy adults with a mean age of 22.3 years (n = 15) [39]. Four studies investigated the differences between PD+FOG and PD-FOG [78, 105, 212, 214]. The PD+FOG and PD-FOG groups showed similar disease severity in two studies, [212, 214] whereas disease duration was different in one study [214] and similar in others [78, 105, 212]. In most of the studies, participants had not previously walked on a SBT [39, 78, 105, 212-214]. Participants with PD were tested in the medication OFF state [78, 105, 212], ON state [39, 214, 215] or both ON and OFF states [213].

Table 6.1 Characteristics of the studies.

	Subjects		Main Outcome Measures	Main Results
	PD	**HC**		
Dietz et al. (1995)	n=14 Age: 61.0 (±11.4) **Med-ON** Disease severity: mild (n=10) moderate (n=4)	n=10 Age: 60.6 (±6.0)	• EMG activity and modulation (M. tibialis anterior & M. gastrocnemius medialis)	• PD do not tolerate higher differences in belt speeds • PD patients show smaller range of stride frequencies in different SBT and TB velocities • Greater co-activation in antagonistic leg muscle in PD during SBT and TB
Nanhoe-Mahabier et al. (2013)	PD-FOG: n=7 Age: 62.1 (±2.7) **Med-OFF** H&Y: 2.1 (±0.1) DD: 6.3 (±0.9) UPDRS III: 26.0 (±2.6) PD+FOG: n=7 Age: 64.1 (±2.3) **Med-OFF** H&Y: 2.4 (±0.1) DD: 8.4 (±1.4) UPDRS III: 29.0 (±0.6)	n=10 Age: 62.4 (±1.7)	• Stride length and stride time • Stride length and stride time asymmetry • Stride length and stride time variability • Interlimb coordination • Phase coordination index (PCI)	• Stride time asymmetry and variability was significantly increased in PD+FOG compared to PD-FOG during SBT, stride length asymmetry does not seem to differ in between PD+FOG and PD-FOG
Roemmich et al. (2014a)	n=13 Age: 64.1 (±8.8) **Med-ON** UPDRS III: 24.6 (±9.4)	HYA: n=15 Age: 22.3 (±3.3) HOA: n=15 Age: 65.2 (±8.1)	• Step length • Limb excursion* • Stance time • Asymmetry of the mentioned parameters	• Step length of worst side (HC: non-dominant leg; PD: MAS) exceeded step length of best side after split-belt walking with best side walking on the slow belt • Step length and limb excursion* asymmetry showed different patterns during different split-belt conditions • PD had worse step length asymmetry at baseline, but adapted similarly to HC
Roemmich et al. (2014b)	n=10 Age: 66.8 (±7.3) **Med-ON and -OFF** H&Y ON: 2.5 (±0.4) H&Y OFF: 2.6 (±0.3) DD: 5.4 (±2.7) UPDRS ON: 36.7	N/A	• Step length • Step length asymmetry • Anterior-Posterior Ground Reaction Forces (AP-GRFs) • Limb propulsive impulse	• Locomotor adaptation and savings (re-adaptation to SBT) were unaffected by medication state • Aftereffects (tied-adaptation) for step length asymmetry were diminished in the Med-OFF

	UPDRS OFF: 39.6			
Mohammadi et al. (2015)	PD-FOG: n=12 Age: 62.4 (±7.4) **Med-OFF** H&Y OFF: 2 (n=8) 3 (n=4) DD: 11.9 (±4.8) UPDRS III OFF: 34.6 (±10.5) PD+FOG: n=10 Age: 60.4 (±5.4) **Med-OFF** H&Y OFF: 2 (n=4) 3 (n=6) DD: 14.6 (±5.7) UPDRS III OFF: 38.1 (±7.8)	n=12 Age: 61.9 (±6.2)	• Step length • Step length asymmetry • Limb excursion	• PD+FOG adapt step length asymmetry slower compared to PD-FOG and HC in during SBT and after SBT • During split-adaptation PD+FOG increased limb excursion of the faster leg to a lower extent compared to Non-Freezers and HC • PD+FOG reduced limb excursion of slower leg to a larger extent compared to PD-FOG and HC • The freezing severity (N-FOGQ) is associated with changes in step length asymmetry and larger asymmetry values
Fasano et al. (2016)	PD-FOG: n=6 Age: 58.3 (±10.9) **Med-OFF** H&Y: 2-3 DD: 12.7 (±6.0) UPDRS III OFF: 31.7 (±5.2) UPDRS III ON: 14.7 (±1.4) PD+FOG: n=14 Age: 61.4 (±7.7) **Med-OFF** H&Y: 2-3 DD: 12.0 (±5.6) UPDRS III OFF: 31.4 (±8.5) UPDRS III ON: 15.3 (±9.7)	N/A	• Step length • Symmetry of gait (symmetry ratio) • Phase coordination index (PCI) • Stride time • Stride time variability	• In contrast to reducing the speed of the side with the shorter step length, reducing the side with the longer step length leads to an improvement in spatial symmetry (step length) and bilateral limb coordination (PCI) and reduced sequence effect in PD patients (in tied-adaptation). • Step length of worst side was significantly higher in post-tied compared to tied-baseline • Gait features associated with FOG are interrelated
Beckers et al. (2017)	PD-FOG: n=12 Age: 63.0 (±8.6) **Med-ON** H&Y: 2.2 (±0.4) DD: 5.7 (±3.5) MDS-UPDRS III: 29.5 (±11.2)	n=12 Age: 65.3 (±8.1)	• Perception accuracy • Perception threshold • Step length asymmetry • Stance time asymmetry • Limb excursion	• PD+FOG show worse accuracy to correctly detect speed differences between both legs • No difference in perception threshold between groups and sides • For all participants the correct identification of belt speed differences correlated with gait asymmetry and step length

	PD+FOG:n=13 Age: 67.0 (±7.2) **Med-ON** H&Y: 2.6±0.5 DD: 13.7±5.2 MDS-UPDRS III: 38.1±14.4			• Within PD+FOG response accuracy correlated with step length and gait variability

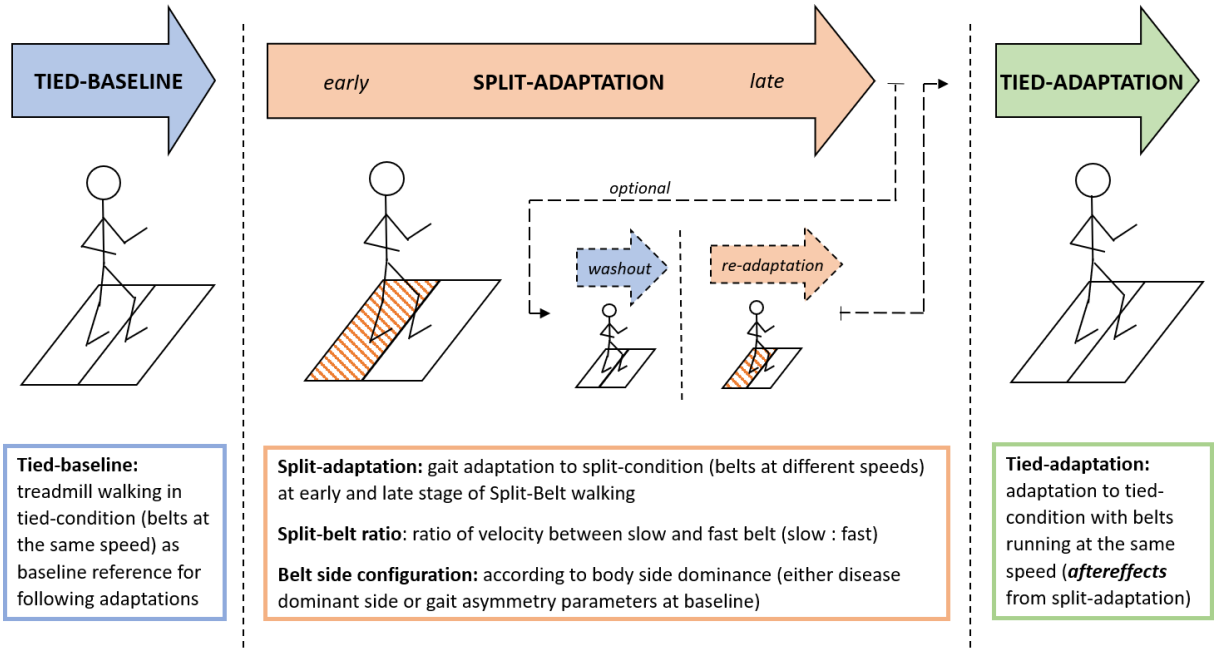

Figure 6.2 Overview of phases and terms in Split-Belt Treadmill walking.

Intervention

Figure 6.2 provides an overview of the different phases of a SBT paradigm. Tied-baseline refers to the period when both belts run at the same speed (normal treadmill walking) before a SBT condition is applied. Split-adaptation is the adaptation phase when both belts run at different velocities. This is followed by tied-adaptation in which both belts run at the same speed again and aftereffects can be studied. The SBT paradigms varied across the reviewed studies (Table 6.2). The duration of the applied SBT conditions ranged from 2 to 20 minutes. Five studies used fixed SBT velocities [105, 212-215], whereas SBT velocity was adjusted according to over-ground walking speed in the other two studies [39, 78]. The split-belt ratio, which describes the ratio of the two belts' velocities, varied between 3:4 and 1:2 [39, 78, 105, 212, 213, 215]. In one study, a steadily increasing ratio of up to 1:1.6 [214] was applied (Table 6.2). Two studies used a SBT configuration referring to only one body side (e.g., reducing the velocity of the least affected side) [39, 213]. The other studies tested the effects of SBT on both limbs [78, 105, 212, 214, 215]. The use of handrails was allowed in one study [39] whereas in other studies, it was not allowed [105, 214] or not further specified [78, 212, 213, 215]. One study used special glasses to block the lower visual field of the participants to evaluate their perception of belt speed without visual input from the belts [214].

Table 6.2 SBT paradigm characteristics of the included studies.

Study	SBT Duration	Belts' speed	Split-Belt Ratio	Belt Side Configuration	Definition of body side dominance
Dietz et al. (1995)	2x 1 min	1.8 km/h 3.6 km/h	1:2	both	not assessed
Nanhoe-Mahabier et al. (2013)	2x 2 min	2 km/h 3 km/h	2:3	both	not reported
Roemmich et al. (2014a)	10 min washout 3 min	fast comfortable walking speed for fast belt	1:2	BS on slower belt	WS/BS: more/less PD affected body side as self-reported and confirmed by highest/lowest lateral UPDRS III subscores
Roemmich et al. (2014b)	10 min washout 5 min	1.8 km/h 3.6 km/h	1:2	BS on slower belt	WS/BS: more/less PD affected body leg as self-reported and confirmed by highest/lowest lateral UPDRS III subscores
Mohammadi et al. (2015)	2x 2 min	3 km/h 4 km/h	3:4	both	WS/BS: more/less PD affected body side as defined by highest/lowest lateral UPDRS III subscores
Fasano et al. (2016)	2x 10 min	Individual walking speed	3:4	both	WS/BS: body side with shorter/longer step length during baseline
Bekkers et al. (2017)	Until perception of belt speed difference (max. 3 min) x2 per side	3 km/h at baseline	max. 1:1.6 (steadily increasing)	both (x2)	WS/BS: more/less PD affected body side as defined by highest/lowest lateral MDS-UPDRS III subscores

Various methodological approaches in SBT studies

Dominance of body side

Five studies investigated SBT walking and accounted for a specific body side [39, 78, 105, 213, 214]. Table 6.2 shows that four of the included studies defined the best side as the body side with lower UPDRS motor subscores [39, 105, 213, 214]. One of the studies defined the

best/worst side according to the body side with the leg with a longer/shorter step length during baseline testing [78]. Two studies did not account for any specific body side [212, 215].

The study conducted by Fasano et al. [78] was the only one that interpreted adaptations to SBT walking with respect to body side, with shorter versus longer step length reported separately. The authors found that reducing the belt's velocity of the side with the longer step length (best side reduction (BSR)) led to improvements in symmetry and bilateral coordination of gait in tied walking after SBT. Step length asymmetry improved through an increase in step length of the side with the shorter step length following SBT-BSR. In contrast, when reducing the belt of the side with the shorter step length (worst side reduction (WSR)) different aftereffects were found. This condition resulted in significantly increased asymmetry and an elevated phase coordination index (PCI, a measure of bilateral coordination between the legs) in comparison to the tied-baseline condition.

Testing procedure and gait variables

Some studies divided the protocol into early, mid, and late split-adaptation conditions [39, 78, 213]. Other studies averaged the findings over the split-adaptation phase [212, 215]. The aftereffects for the tied-adaptation condition were analyzed in most cases [39, 78, 105, 213]. With one exception [215] all studies used motion-capture systems to analyze gait with sampling frequencies between 100 and 240 Hz. The studies used different methods to calculate spatial gait parameters making it difficult to compare the results: Three of the studies calculated step length as suggested by Hoogkamer et al. [219] using the distance of ankle markers at heel strike [39, 105, 213] whereas one study defined step length as the product of step time and belt velocity [78]. Others did not report how step length was calculated, stating merely that ground reaction forces were used to determine gait events [214].

The following temporal parameters were investigated: cadence [78, 213], stride time [78, 212], duration of stance- [39, 78, 213, 214], swing- [78] and double limb support phase [78, 215]. Furthermore, gait variability [78, 105, 212, 214] and PCI [78, 212] were evaluated. Table 6.3 summarizes the different formulas used to calculate asymmetry. All of the studies that evaluated gait asymmetry used spatial asymmetry parameters [39, 78, 105, 212-214] and only two studies additionally calculated temporal asymmetry parameters [39, 212].

Table 6.3 Calculation of asymmetry parameters

	Calculation of asymmetry parameters		Reference
A	$\frac{(\text{fast leg parameter} - \text{slow leg parameter})}{(\text{fast leg parameter} + \text{slow leg parameter})}$	a value of '0' indicates perfect symmetry, e.g. positive values indicate a longer step length of the fast leg and negative values a longer step length of the slow leg	[21, 22]
B	$\frac{\lvert(\text{right step length} - \text{left step length})\rvert}{(\text{right step length} - \text{left step length})}$	a value of '0' indicates perfect symmetry, only measures the degree of asymmetry without indicating the side which performs the longer step	[23, 24]
C	$\frac{(\text{max stride length} - \text{min stride length})}{\text{max stride length}} \text{x} 100\%$	describes the degree of asymmetry as a percentage with higher values indicating higher asymmetry	[25]
D	$\frac{\text{fast step length}}{\text{slow step length}}$	a value of '1' indicates perfect symmetry, whereas values below '1' indicate a longer step length of the slow side (leg walking on the slower belt) and values above '1' longer step length of the fast side.	[26]

Adaptation of gait in people with Parkinson's disease compared to healthy controls

The following results focus only on the interaction-effects between individuals with PD and HC when comparing the adaptation to different SBT conditions. Inconsistent results were found with respect to the adaptation of gait asymmetry. Roemmich et al. found that PD and HC adapted similarly in step length asymmetry during SBT walking, despite a higher baseline asymmetry in individuals with PD [39]. They showed that for the late split-adaptation condition, step length asymmetry reached values close to the tied-baseline condition. The aftereffect was characterized by a change in step length asymmetry (side with initially shorter step length took longer steps). Furthermore, people with PD adapted comparably to HC for stride length and stride time asymmetry [212]. In contrast, Mohammadi et al. observed a significantly increased step length asymmetry and limb excursion asymmetry during the switch to split-adaptation in PD-FOG compared to HC and in PD+FOG compared to PD-FOG [105]. Roemmich et al. detected a significant group by time interaction in stride length asymmetry, showing that PD did not increase stride length from early to late split-adaptation like it did in HC [39]. For stance time asymmetry, the group by time interaction was also significant, indicating that people with PD did not increase stance time asymmetry as much as healthy younger adults (HYA) during split-adaptation conditions or as younger and older adults during tied-adaptation conditions [39].

For gait variability, no differences in adaptation were found between individuals with PD and HC. Furthermore, the bilateral coordination of gait (measured by the PCI) was modulated in various SBT conditions to the same degree in the PD group as in HC group [212]. Additionally, no significant differences in the changes of upper and lower limb coordination were found between the PD and HC groups [212].

Muscular activity was investigated by Dietz and colleagues during SBT walking in the PD group. They found significantly greater co-activation in antagonistic leg muscles in people with PD during tied-baseline and split-adaptation conditions [215] as compared to HC.

Altered adaptation of people with PD with freezing of gait

With respect to individuals with PD with FOG, Mohammadi et al. showed that PD+FOG adapted their step length asymmetry more slowly compared to PD-FOG [105]. This was the case in both the split-adaptation and the tied-adaptation conditions and was explained by the differences in gait parameter adaptation. Fasano and colleagues found that the detrimental effect of reducing the speed of the side with the larger step length (best side reduction, BSR) during split-adaptation was significantly correlated with FOG severity, indicating that more severe FOG led to a larger reduction in step length [78]. Furthermore, FOG severity, as measured by the Freezing of Gait Questionnaire (FOGQ), seemed to be linked to step length asymmetry after switching to SBT [105]. This study also reported difficulties with SBT walking for one PD+FOG patient who experienced FOG and another one who had a festination episode during the switch from tied-baseline to split-adaptation [105].

Bekkers et al. found that PD+FOG had reduced accuracy to detect gait speed differences of the two belts, although the perception threshold of SBT condition did not differ between groups [214]. Furthermore, increased gait variability, along with smaller step length and limb excursion, were associated with perception deficits. Therefore, the authors concluded that this perception deficit in PD+FOG may partly explain the SBT differences found between the PD+FOG and PD-FOG groups. Interestingly, no elevated proprioceptive deficit was found in the PD+FOG group through joint position sense testing. Regarding the side dominance, there were some patients who were unable to identify any speed difference with increased belt velocity on the most affected side. This could point toward a perception deficit that is side dependent [214].

Effect of levodopa

The effect of dopaminergic medication was investigated in only one study [213]. The authors did not find an effect of dopaminergic medication on the split-adaptation and re-adaptation (repeated SBT walking after over-ground washout) of the newly learned gait pattern during SBT walking. However, withholding levodopa led to decreased aftereffects in tied-adaptation [213]. The authors concluded that interventions using SBT in PD patients should test participants in the optimally medicated state.

Safety and adverse events

In the reviewed studies, safety precautions were not always reported. Most often, it was noted that to prevent falls, a safety harness was used during treadmill walking [105, 212-214]. The participants were also allowed to use the handrails, if necessary [213]. Furthermore, familiarization periods to normal treadmill walking [39, 105, 213-215] and SBT walking [215] were provided. To avoid injuries, some studies did not include participants with orthopedic contraindications [39, 78, 213]. However, the influence of anxiety when walking on a SBT was generally not assessed. None of the included studies reported on the occurrence of falls, even though walking on a treadmill that had spilt belts was novel for most of the participants. Mohammadi at el. [105] reported that FOG and gait festination occurring during SBT walking for two participants. They speculated that this was associated with a switching deficit in PD+FOG. In the other trials, none of the participants experienced FOG [78, 212]. Overall, studies had poor reporting of adverse events.

6.5 Discussion

This review provided preliminary evidence that gait training using a treadmill with a spilt belt can help to improve walking in some individuals with PD, particularly where asymmetry was evident. Various methodological approaches were used in the studies reviewed, such as different SBT conditions regarding belt velocity, belt speed differences, and a variety of gait parameters, as outcomes. The literature varied according to the definition of gait parameters in PD. Hoogkamer et al. [219] previously proposed a consistent definition for limb excursion as the distance traveled from heel strike until toe-off, for one foot, instead of using the term stride length. Furthermore, step lengt*h* was defined as the distance between the feet for each gait event (either distance between toe markers before lift-off of the foot or the distance

between ankle markers at heel strike of the leading foot) [219]. In contrast, some of the included studies used step time and belt speed to calculate step length [78] or did not provide the calculation method [214]. Different calculations were used for asymmetry variables. Gait asymmetry (defined as (fast leg parameter - slow leg parameter)/(fast leg parameter + slow leg parameter)) has been previously used in studies with HC [220-222] or neurological conditions [205, 221, 223]. The advantage of this definition is that no absolute values are used. Therefore, not only the degree of asymmetry is described, but also the laterality of the asymmetry (which side is longer/shorter). This aspect is important, as it has been shown that SBT walking can lead to a larger step length of the leg with the shorter initial step length in tied-adaptation conditions [39, 213].

Another inconsistency in the evaluated studies related to the treadmill velocity used. There were a few studies using fixed belt speeds not accounting for the individual over-ground gait speed. This could bias the results, as gait speed can vary across participants.

Another important methodological issue was the belt side configuration according to the dominance of the leg or body side. The studies included in this review used different methods to define dominance of body side. The MDS-UPDRS III lateral subscore was mostly used to determine the most affected body side [39, 105, 213, 214]. However, it has been suggested that gait asymmetry is not necessarily related to asymmetry as defined by the MDS-UPDRS III [42]. Using step length to determine the best and less able side is another approach closer related to gait asymmetry. Further research is necessary to investigate the relationship of step length asymmetry and disease laterality.

For the safe conduction of SBT interventions, several precautions need to be taken into account. Participants with contraindications (such as comorbidities, very advanced age, severe movement disorders, and advanced stages of disease) should be excluded, and a safety harness should be used. Additional use of handrails and extended familiarization to the SBT condition should be provided, if necessary. None of the included studies addressed the possible impact of anxiety on safety or motor performance, and none of the studies reported adverse events, which should be implemented in future studies.

This review showed that many people with PD were able to adapt to SBT walking in a similar way to HC. Although slowed down by a larger initial asymmetry, adaptations of step length asymmetry followed a similar pattern to HC. However, not all gait parameters showed preserved adaptation in response to this form of treadmill training [39]. Stride length and

stance time asymmetry did not always adapt to the same extent in persons with PD as for HC. Moreover, the transfer of the newly learned gait patterns to over-ground walking was not investigated for the PD group. The aftereffects for over-ground walking were studied in HC and found to be lower compared to the retention of training for the treadmill, with greater retention for temporal gait parameters [224].

Fasano et. al found that reducing the belt velocity for the side with the longer step length led to more symmetrical gait in the PD group [78]. This has also been investigated in stroke, where gait was modulated during SBT using error augmentation mechanisms [207]. When the paretic leg walked on the slower belt, step length of the paretic leg increased for the early split-adaptation condition, creating larger step length asymmetry [225]. During the adaptation process, asymmetry reached values close to baseline, and asymmetry improved in the tied-adaptation condition. In chronic stroke patients, the exaggeration of initial step length asymmetry was found to be effective in improving step length asymmetry, relative to the tied-baseline condition. This error augmentation strategy was thought to be successful because attention was implicitly drawn to the error with the aim to correct it [225].

In the current review, the subgroup with freezing of gait had an adaptation deficit that might have been caused by higher baseline asymmetry [105, 212]. It has been shown that SBT can lead to reduced gait coordination and increased sequence effect (progressive slowing of movement/stepping) [78]. This supports the link between asymmetry and FOG episodes [78]. A reduction of step length of the least affected side could lead to FOG episodes when a certain threshold is reached [69]. The theory of a specific threshold after which FOG occurs is supported by previous literature [226]. The authors proposed that several gait alterations could be causal for a FOG episode when they exceed a certain level. Others suggest that the asymmetry itself is not the main problem, rather the impaired switching ability is at fault [105]. Perception deficits might also play a role [214]. It is most likely that not just one gait characteristic is at the core of the difficulties with SBT walking in PD+FOG, but rather there is an interplay of various deficits.

Nanhoe-Mahabier et al. [212] proposed that the cerebellum might be involved in the adaptation deficit in people with FOG. This is supported by findings regarding altered structural [82, 227-229] and functional [82] connectivity between the pedunculopontine nucleus (PPN) and the cerebellar locomotor region (CLR), suggesting a greater cerebellar deficit in PD+FOG [229]. Furthermore, there has been some work on resting state brain activity

in PD+FOG that suggests that the cerebellum could play a role in the pathology [230]. Inter-limb coordination and temporal aspects of gait control are challenged in SBT walking, and the cerebellum plays an essential role in the coordination of these gait features [201]. Conversely, the implicit nature of split-adaptation conditions might enhance the activation of the cerebellum when it is used as a training tool [105].

SBT walking in PD has only been investigated in single sessions, and prolonged training interventions have not been conducted to date. From the work done with stroke patients, there is some evidence for the effectiveness of repeated SBT walking to lower gait asymmetry using the error augmentation strategy with improvements being sustained for one to three months [203, 209]. Future studies should investigate the transfer to over-ground walking of repeated SBT training in people with PD.

There were several limitations of this systematic review. The number of existing studies about SBT in people with PD was small, and the level of evidence appeared to be comparatively low. Therefore, results have to be interpreted with caution. Safety precautions and contraindications were not adequately addressed. Furthermore, only a brief level of evidence analysis using the American Academy of Neurology classification scheme requirements for therapeutic questions was included. A further, more detailed, higher quality analysis, such as PEDro, was not used, as most of the items of the PEDro scale were not appropriate for the nature of the included studies (no randomized controlled intervention studies).

6.6 Conclusion

This systematic review showed that many people with mild to moderately severe PD adapted similarly to HC for gait variability and asymmetry when walking on a SBT. For these people, SBT enabled them to modulate gait asymmetry. People with FOG showed adaptation deficits and impaired perception of belt speed differences. Further research focusing on the detection of the most effective SBT conditions and transfer of training to over-ground walking is necessary. Additionally, future studies should address safety precautions and the impact of anxiety. The effectiveness of long-term SBT training interventions also awaits investigation as a rehabilitative strategy for people with PD.

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7. Study 4: The effect of one session Split-Belt Treadmill Training on Gait Adaptation in people with Parkinson's Disease and Freezing of Gait

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7.1 Abstract

Background: Freezing of Gait (FOG) in Parkinson's disease (PD) is associated with gait asymmetry and switching difficulty. A Split-Belt-treadmill may potentially address those deficits.

Objective: To investigate the immediate and retention effects of one session split-belt-treadmill training (SBT) in contrast to regular treadmill-training (TBT) on gait asymmetry and adaptation in people with PD and FOG (PD+FOG) and healthy controls (HC). Additionally, to investigate differential effects of three SBT protocols and compare different gait adaptation outcomes.

Methods: PD+FOG (n=45) and HC (n=36) were randomized to one of three SBT groups (belt speeds' ratio 0.75:1; 0.5:1 or changing ratios) or TBT group. Participants were tested at Pre,

Post and 24-hour Retention after one treadmill training session. Gait asymmetry was measured during a standardized adaptation test on the split-belt-treadmill.

Results: SBT proved beneficial for gait adaptation in PD+FOG and HC ($p<0.0001$), however HC improved more. SBT with changing ratios demonstrated significant effects on gait adaptation from Pre to Post in PD+FOG, supported by strong effect sizes ($d=1.14$) and improvements being retained for 24 hours. Mean step length asymmetry during initial exposure was lower in HC compared to PD+FOG ($p=0.035$) and differentiated best between the groups.

Conclusions: PD+FOG improved gait adaptation after a single SBT session although effects were smaller than in HC. SBT with changing ratios was the most effective to ameliorate gait adaptation in PD+FOG. These promising results warrant future study on whether long-term SBT strengthens adaptation in PD+FOG and has potential to induce a better resilience to FOG.

Clinical Trial ID: NCT03725215

Keywords: Parkinson's disease, Freezing of Gait, Split-belt treadmill, Gait adaptation

7.2 Introduction

People with Parkinson's Disease (PD) show various gait disturbances including reduced step length and gait speed [45, 48]. Additionally, individuals with PD may suffer from Freezing of Gait (FOG), a highly disabling symptom prevalent in about 38% of early PD , and increasingly present in those with greater disease severity [10]. FOG is characterized by a "brief, episodic absence or marked reduction of forward progression of the feet despite having the intention to walk" [11, 67]. FOG is thought to occur when multiple gait deficits deteriorate simultaneously and thus surpass the FOG-threshold [69]. Among these gait deficits are a higher gait variability, gait asymmetry and worse bilateral coordination of gait [40, 226, 231]. Furthermore, FOG often occurs when gait needs to be adapted to external requirements, such as during turns, walking through narrow passages or when initiating gait [116]. Additionally, cognitive load when performing a dual task may elicit FOG [232]. As well as motor switching deficits, people with FOG (PD+FOG) show more difficulty with cognitive set shifting [166, 233] compared to those without FOG (PD-FOG) [216]. The association between FOG and motor adaptation deficits is further supported as walking on a split-belt treadmill under changing

belts' speed conditions elicited FOG-episodes [105], even if not many. Besides adaptation, split-belt walking challenges bilateral coordination of gait and asymmetrical walking [234].

Split-belt walking has been investigated in healthy individuals [39, 235, 236] as well as in various neurological conditions [203, 205, 209, 210], including PD (for review see [237]). Most studies have focused on the immediate split-belt walking effects on gait adaptation, tied-adaptation (when the belts return back to tied speed) and re-adaptation (when split-belt walking is repeated) in one session using steady contrasts between belt speeds of 0.75:1 or 0.5:1. In PD, these studies revealed that adaptation was not significantly different during early (first five strides) split-belt walking in people with PD compared to healthy controls (HC) [39]. Additionally, adaptation ability was reduced in PD+FOG compared to PD-FOG [105, 212] and aftereffects were greater with levodopa intake [213]. Finally, PD+FOG had impaired speed difference perception compared to PD-FOG [214] during split-belt walking. Split-belt-conditions can incur gait perturbations subconsciously, demanding largely implicit adaptation to asymmetrical conditions, but whether this can also lead to substantial changes in the capacity to adapt in daily life is still unclear. Interestingly, a recent study showed that implicit surface perturbation training in older adults was retained and led to reduced injurious falls over a period of 3 months [238]. This led to the hypothesis that split-belt training (SBT) may lead to maintaining of adaptive behavior in PD. If consolidated gait adaptation could be achieved after prolonged and progressive exposure (not investigated here), it is possible that individuals with FOG could develop a more resilient gait pattern for handling FOG-provoking circumstances. However, even the short-term training responses to split-belt perturbations in one session are still unknown in PD. Also, it is unclear which split-belt contrasts would lead to the best practice results. Besides the split-belt contrasts, it is also still not known if SBT is superior to regular treadmill walking to improve FOG related gait deficits. Although regular treadmill training is successful in improving several gait measures such as gait speed and stride length [21, 197], its effects to improve adaptation ability is not known yet in PD.

For all these reasons, we conducted a proof-of-principle study into the effects of SBT on gait adaptation in PD+FOG. First (aim 1), we aimed to investigate if SBT versus tied-belt training (TBT) led to similar immediate gains and retention in healthy individuals as in PD+FOG. Second (aim 2), we wanted to determine which of the following 3 SBT-contrasts was most effective to

improve gait adaptation and asymmetry in PD+FOG: 1) SBT75 with a belt speed ratio of 0.75:1 [105] and 2) SBT50 with a belt speed ratio of 0.5:1 [203] have been used previously in PD to target adaptation, 3) SBTCR changing ratios which was newly introduced to bring in a switching component, not addressed by the steady contrasts. Previous studies, quantified gait changes during SBT-walking using gait asymmetry outcomes. Hence, as a third aim, we explored which outcome best captured gait adaptation differences when comparing PD with HC in a standardized test protocol, which we developed for the purpose of this study.

7.3 Methods

This study was conducted at CAU Kiel, Germany and KU Leuven, Belgium. Regular meetings were held either at one of the sides or online to design the trial and to get a detailed view of the conditions at each side. Furthermore, during a pilot period, one of the testers from Kiel visited the Leuven laboratory to follow assessment and training in order to ensure high comparability of the procedures, instruments and environment between the centers. The trial was registered at ClinicalTrial.gov (ID: NCT03725215). Participants were included in this study between 01/2018 and 05/2019. Recruitment was continuously ongoing during this period.

Participants

A total number of 45 individuals with PD+FOG and 36 healthy age-matched controls (HC) were included in the study. People with PD were included if they were diagnosed with idiopathic PD with confirmed FOG according to the New Freezing of Gait Questionnaire (NFOG-Q, item 1) [87], had no other neurological diseases and a stable medication for at least 4 weeks. Age-matched HC were included if they had no history of neurological disease. Exclusion criteria for both PD and HC were: 1) unable to walk without assistive devices (e.g. walking aid) for a minimum of 5 minutes; 2) cognitive impairment (Mini Mental State Examination (MMSE) ≤ 24)[239]; and 3) orthopedic or other health conditions that could influence walking. None of the participants had previous SBT experience. The study was approved by ethical committees of CAU Kiel (Approval number: D 454/13) and KU Leuven (Approval number: B322201734218) and participants gave written informed consent prior to participation.

Study design

We employed a non-blinded randomized controlled design. Participants were randomly allocated to one of four training groups (SBT75; SBT50; SBT-CR and TBT) stratified by H&Y stage (PD+FOG) and age (HC). Random blocks were generated for each H&Y stage and each age group to ensure balanced distribution among training groups. Randomization was performed by an external person in each center who was not involved in the conduct of the study. The study protocol consisted of three assessments which were conducted before (Pre), after (Post) and 24 hours after (Retention) the training session to investigate short-term consolidation (Fig. 7.1).

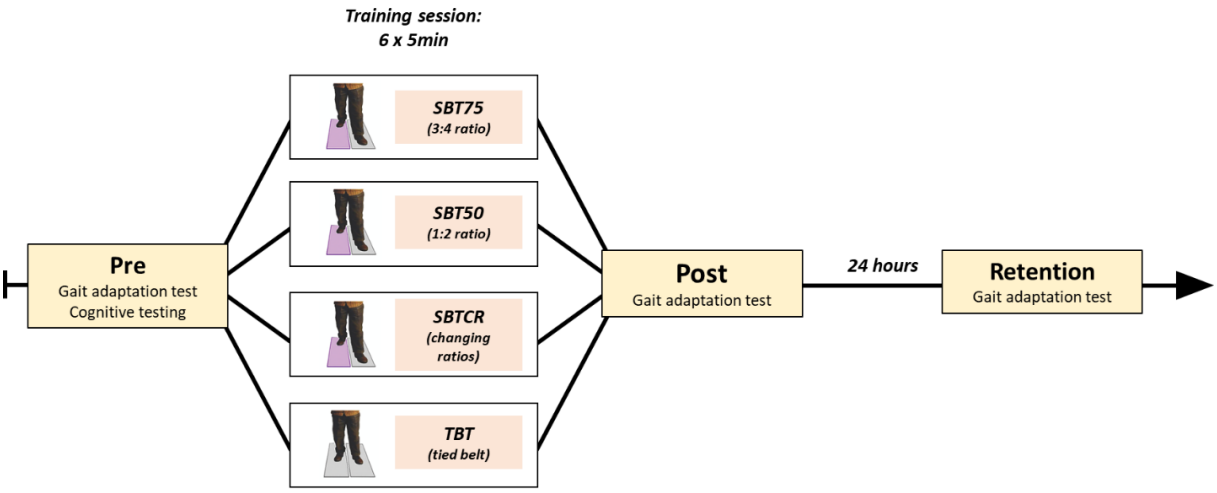

Figure 7.1 Study protocol with Pre, Post, and Retention assessment and training groups.

Testing and training were conducted in the ON state of medication. Medication intake was recorded and rigorously standardized between tests. Subjective self-reported medication status was checked at the beginning of the tests. Subjects were asked to walk without holding onto the handrails of the treadmill if possible. Participants who could not walk without holding the handrails, always kept their hands onto the handrails. During testing and training, all participants wore a safety harness (climbing harness with shoulder straps, a middle strap around the hips and leg loops) secured to the ceiling without providing body weight support.

Standardized gait adaptation test

To test the ability of people with PD+FOG to adapt to changing gait conditions, we designed an adaptation test in which participants had to walk on the split-belt treadmill for 90 seconds (see Fig. 7.2). The first 30 seconds belts ran at the participants' comfortable over-ground speed

(Tied-Baseline), which was assessed through prior overground gait analysis with reflective markers using initial and terminal contact for the calculation [240]. Then, speed was reduced by 50% on one side for 30 seconds (Split-Adaptation). Next, both belts were brought back to the same speed for 30 seconds (Tied-Adaptation) (Fig. 7.2) Thus, two switches of belt speeds were administered per test. The belt speed switches were administered by a computerized protocol. The gait adaptation test was performed twice so that both legs were exposed to the reduced belt speed and this at the three time points (Pre, Post and Retention). The order of the leg that was reduced first was counterbalanced across participants, but kept consistent within each participant.

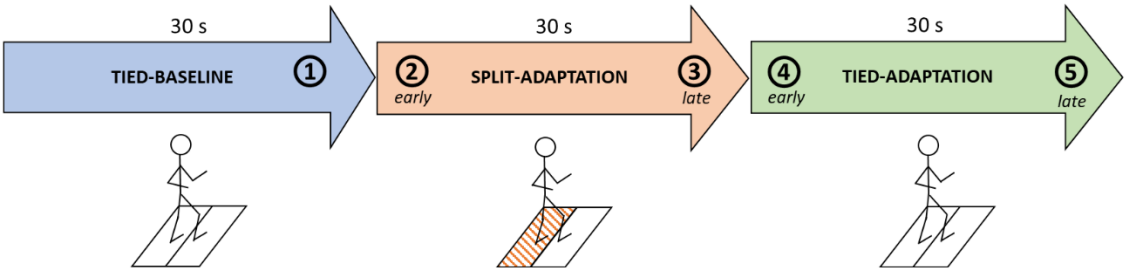

Figure 7.2 Split-belt treadmill (SBT) adaptation test (shaded area indicates a reduction of belt speed by 50% on one side; phases: 1 = baseline, 2 = early-split, 3 = late-split, 4 = early-tied, 5 = late-tied).

Descriptors and Outcome Measures

At Pre-assessment, the Movement Disorders Society Unified Parkinson's Disease Rating Scale Part III (MDS-UPDRS-III) was assessed (PD only). Cognitive and balance functions were tested using the Montreal Cognitive Assessment (MoCA) and the Mini-Balance Evaluation System Test (Mini-BESTest), respectively.

At Pre, Post and Retention, gait was measured using six reflective passive markers placed at the lateral malleolus and heel and tip of the shoes of both right and left foot, allowing precise measurements with limited skin movements. Gait parameters were calculated with custom Matlab scripts [184] using 3D-data from a motion capture system (Kiel: Qualisys Motion Capture Systems, Gothenburg, Sweden; Leuven: Vicon Motion Systems Ltd , Oxford, United Kingdom). Both systems were calibrated according to the respective manufacturers instructions before each test session and provide highly comparable results [241]. Sampling

frequency was 100 Hz. Test-retest and inter-rater reliability has been reported to be good for this method [242].

Step length asymmetry and limb excursion asymmetry were calculated following according to previous SBT research [237]:

$$\frac{(\text{fast leg parameter} - \text{slow leg parameter})}{(\text{fast leg parameter} + \text{slow leg parameter})}$$

For this formula a value of '0' indicates perfect symmetry, positive values indicate a longer step length of the fast leg and negative values a longer step length of the slow leg. Limb excursion was calculated as the distance travelled during the stance phase while walking on the treadmill [219]. To get one overall measure of gait adaptation, gait variables were averaged over the whole adaptation test (90 seconds). This was done to simplify the model allowing to investigate the various interactions between group, training-group and time points (Pre, Post, Retention). In order to investigate the changes in gait adaptation in more detail for the different training groups, parameters were evaluated at the different parts of the adaptation test (averaged over the initial 5 seconds in the part) including: 1) baseline, 2) early-split, 3) late-split, 4) early-tied and 5) late-tied (Fig. 7.1).

Physical and mental fatigue were measured using visual analogue scales in the style of VAS-F [243] prior to and immediately after the training.

Treadmill training

Participants were trained for 30 minutes in blocks of 5 minutes with a one-minute rest between blocks. They completed one of four different training protocols: The three SBT training groups trained with a reduction in speed of one belt of 25% (SBT75) or 50% while the other belt run at 100% of their individual overground gait speed. The first group trained with one belt running at 75% (SBT75) of the individual over-ground walking speed, the second group with one side at 50% (SBT50) and the third group trained with one belt changing between 50 and 75% (SBTCR, for details see S2) while the other belt ran at 100% of the individual overground gait speed. For SBTCR the belt speed switches were administered by a computerized protocol. The last group trained under tied-belt (TBT) condition with both belts running at the same speed. For SBT purposes, the leg with the initial longer step length during over-ground walking was reduced (best side reduction=BSR), as previously Fasano et al. found

this paradigm to have positive aftereffects in multiple gait domains (symmetry, bilateral coordination, sequence effect) [78].

Statistical analysis

Descriptive statistics for PD+FOG and HC contrast were compared using Mann-Whitney-U Tests. Furthermore, the Kruskal-Wallis Test was used to test for baseline differences in age, disease severity, motor score and cognitive state between PD+FOG in the four different training groups. With respect to study aim 1, multilevel regression models were applied to investigate the group*time*training-group interaction on mean gait adaptation variables with the factor group (2 levels: PD+FOG vs. HC), the factor time (3 levels: Pre, Post, Retention) and the factor training-group (2 levels: pooled SBT vs. TBT). To address study aim 2, the model was adapted and ran only for the PD+FOG group to investigate the training-group*time interaction for mean gait adaptation variables with the factor training-group (4 levels: SBT75, SBT50, SBTCR and TBT) and the factor time (Pre, Post, Retention). Furthermore, to investigate the differences between the training groups and time points with respect to the different parts of the gait adaptation test the model was ran for each part (baseline, early-split, late-split, early-tied and late-tied) separately. Models were run on the dependent variables step length asymmetry and limb excursion asymmetry for non-normalized data as different baseline asymmetry was accounted for in the statistical models. Additionally, center (2 levels, Kiel & Leuven) and treadmill velocity were added as covariates to investigate potential influence on the results. The used models deal with missing data using maximum likelihood estimation. Normality of residuals was assessed with histograms and Q-Q plots. Post-hoc-tests were performed to interpret the effects using Tukey-adjustment (95% confidence interval) for multiple comparisons. Furthermore, effect sizes (Cohen's d) were calculated for the PD+FOG to compare effects of the different training modes for the reduction of step length asymmetry (Pre-Post) and interpreted as follows: large: $d \geq 0.8$, medium: d 0.8 - 0.5, small: d 0.5 - 0.2 [244]. Finally, in line with the exploratory aim, to verify which outcomes are most suitable to capture for gait adaptation ability (study aim 3), differences in mean gait asymmetry in PD+FOG and HC (at Pre) were tested using student's t-test. To account for different baseline asymmetry, for this analysis mean gait asymmetry was normalized by subtracting baseline asymmetry during preceding tied-belt phase. Furthermore, outcome measures were Pearson correlated with measures of fatigue (visual analogue scale for physical and mental fatigue)

and clinically assessed motor performance (MDS-UPDRS III). A-priori sample size calculation was not conducted due to the proof of principle character of this study and the novelty of outcome measures. Statistical analysis was performed in RStudio software [160].

7.4 Results

PD+FOG and HC did not differ in baseline characteristics regarding age and sex. People with PD had compromised balance and cognitive function compared to HC (see Table 7.1). Furthermore, individuals with PD were evenly distributed amongst the four different training groups regarding age, cognition, disease duration, disease severity, FOG severity and daily levodopa dosage. Eleven participants used handrail support during SBT walking (3 HCs and 8 PD+FOG) and there were no adverse events. The flowchart (S. 7.1) in supplementary materials presents the flow of subjects through the study. Table 7.2 illustrates that there was no difference in age, disease severity, cognitive or motor function measures in PD+FOG between the four training groups (p-values range: 0.6 - 0.84) with similar FOG-severity (p=0.83).

Table 7.1 Participant characteristics (n=81).

	HC (n=36)	PD+FOG (n=45)	p-value
Age (yrs)	69.5 (66-74)	71 (60-77)	0.588
Sex (f/m)	16/20	12/33	0.151
Mini-BESTest (0-24)	26(24-27)	21(17-25)	<0.001*
MoCA (0-30)	28 (26-29)	25 (22-27)	<0.001*
H&Y (1/2/3/4/5)	-	1/18/20/6/0	-
MDS-UPDRS III (0-132)	-	32.5 (25.7-46)	-
NFOG-Q (0-28)	-	16 (12-20)	-
DD (yrs)		13 (7-15)	

Note. Values show median (Q1-Q3). HC=healthy control, PD+FOG=persons with Parkinson's Disease and Freezing of Gait, Mini-BESTest= Mini-Balance Evaluation System Test, MoCA= Montreal Cognitive Assessment, H&Y= Hoehn&Yahr Stage, MDS-UPDRS= Movement Disorder Society-Unified Parkinson's Disease Rating Scale, NFOG-Q=New Freezing of Gait Questionnaire, DD=disease duration.

Table 7.2 Characteristics of individuals with PD+FOG

	SBT50 (n=11)	SBT75 (n=12)	SBTCR (n=12)	TBT (n=10)	p-value*
Age (yrs)	71 (66-76.5)	66.5 (59.3-75)	71.5 (63.8-77.5)	67 (55-76.8)	0.679
MoCA (0-30)	24 (20.5-25.5)	25 (22.5-28)	25.5 (23.8-28)	26.5 (21.5-27)	0.611
H&Y (1/2/3/4/5)	0/3/6/2/0	0/5/5/2/0	0/6/5/1/0	1/4/4/1/0	0.604
MDS-UPDRS III (0-132)	35 (25.5-41)	43 (24.5-52)	33.5 (26-41.3)	32.5 (23-50.3)	0.837
NFOG-Q (0-28)	15 (10.5-19)	15 (14.5-20.5)	17.5 (13.8-18.3)	16 (9.5-20.8)	0.833
LEDD	810 (715.3-932.9)	814 (681-915)	805 (631.3-930.1)	773 (600-1061.1)	0.995

Note. Values show median (Q1-Q3). MoCA= Montreal Cognitive Assessment, H&Y= Hoehn&Yahr Stage, MDS-UPDRS= Movement Disorder Society-Unified Parkinson's Disease Rating Scale, NFOG-Q=New Freezing of Gait Questionnaire, LEDD=Levodopa equivalent daily dose.*Kruskal-Wallis-Test

The following results will only focus on the gait adaptation test during which the belt side with the longer step length was reduced, as this was most aligned with the training purpose.

Effect of SBT in PD+FOG compared to healthy controls

When investigating study aim 1, there was a significant group*time interaction (p=0.005) for mean step length asymmetry, showing that HCs improved to a higher extent compared to PD+FOG, regardless of the training protocol they finished. Despite this finding PD+FOG did benefit from the training session as they could reduce their gait asymmetry significantly from Pre to Retention (p<0.001). For the comparison of the training modes we found a significant training-group*time interaction (p<0.0001) for the pooled SBT groups versus TBT for all participants. Post-hoc tests revealed that mean step length asymmetry changed significantly in SBT groups (pooled data) from Pre to Post (p<0.001) and Pre to Retention (p<0.001), whereas no significant differences were found for the TBT group. Interaction of group*time*training-group for the pooled data (SBT vs. TBT) was not significant (p=0.249).

With respect to mean limb excursion asymmetry, no significant group*time*training-group, group*time or training-group*time interactions were found.

PD+FOG showed significantly higher levels of physical fatigue ($p<0.0001$) after the training compared to HC, but no correlation was found between fatigue and the reduction in step length asymmetry. However, motor performance as measured with the MDS-UPDRS III was associated with physical fatigue in people with PD, showing that those individuals with poor motor ability showed higher levels of physical fatigue after the training session ($p=0.02$, $r=0.38$).

Different SBT training protocols in people with PD with FOG

For the comparison of the different training groups within PD there was a significant training-group*time interaction for mean step length asymmetry ($p=0.015$). Post-hoc tests revealed that only the group that trained under changing ratios condition significantly reduced their mean step length asymmetry during the gait adaptation task from Pre to Post ($p=0.046$, Fig. 7.3). The effect sizes of the changes from Pre to Post for the SBT groups versus TBT group were as follows: SBT75% vs. TBT: $d = 0.81$; SBT50 vs. TBT: $d = 0.63$ and SBTCR vs. TBT: $d = 1.14$.

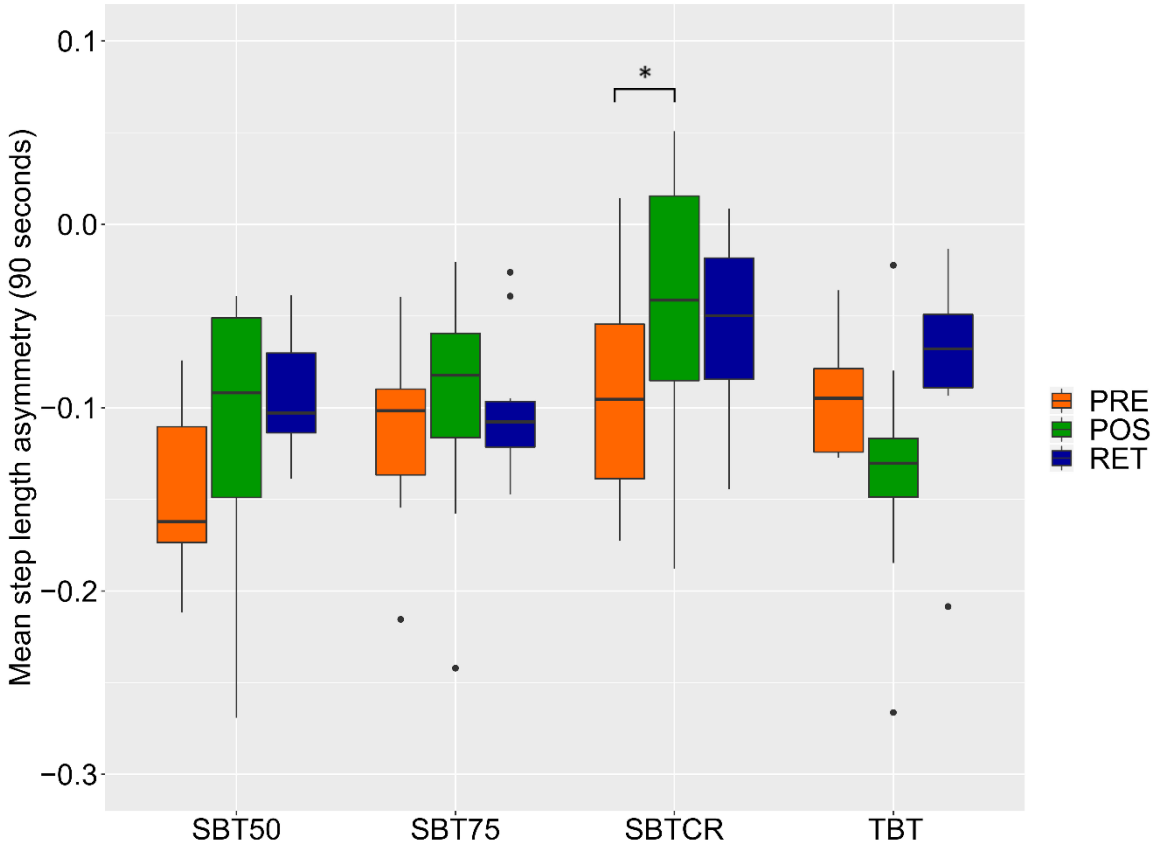

Figure 7.3 Mean step length asymmetry in people with Parkinson's disease and freezing of gait (PD + FOG) before, after, and 24 hours after an split-belt treadmill (SBT) training session. A value of zero

indicates a perfect gait adaptation. Displayed is the median with the lower and upper hinges representing the first and third quartile. Data points outside the mentioned quartiles are displayed as outliers. *Significance level of P < .05.

When investigating the different parts of the gait adaptation test in more detail, there was a significant time*training-group interaction (p<0.022) in the early-split (first 5 seconds). During that part of adaptation, SBT50 significantly reduced the step length asymmetry from Pre to Post (p<0.05) as well as from Pre to Retention (p<0.005). The SBTCR group also showed improvements during early-split, but this did not reach statistical significance. There were no significant effects for the other phases of the gait adaptation test.

For mean limb excursion asymmetry there was no significant training-group*time interaction. Adding the individual treadmill velocity or the center as a covariate to the respective models did not change the results. The various training groups did not differ in physical or mental fatigue between after completing the training session in PD+FOG.

Clinical associations of SBT adaptation

To explore which outcome captures gait adaptation most appropriately (study aim 3), differences in mean step length and mean limb excursion asymmetry between PD and HC were investigated at Pre. Mean step length asymmetry and mean limb excursion asymmetry were significantly lower in HC compared to PD+FOG (p=0.035 and p=0.015, respectively) during the adaptation test. Regarding the different parts of the adaptation test, step length asymmetry was significantly different between the groups at late-split (p=0.03) and early-tied (p=0.003) and for limb excursion asymmetry during early-split (p=0.0009) and late-split (p=0.03). Mean step length asymmetry of PD+FOG at Pre was negatively correlated with disease duration (r=-0.305, p=0.049) and MDS-UPDRS-III (r=-0.384, p =0.012). However, mean step length asymmetry was not correlated with freezing severity as captured by the NFOGQ-Score or age.

7.5 Discussion

People with PD with FOG improve gait adaptation with SBT

This study explored the potential of using SBT as a rehabilitation method for people with FOG by practicing their ability to adapt their gait pattern to asymmetrical circumstances in one session. For this aim, the immediate and retention effects of a single SBT session were

compared to TBT in PD+FOG and HC. Results showed that SBT but not TBT improved gait adaptation immediately after the training and, even more importantly, improvements were retained up till 24 hours. Although the effects were larger in HC, PD+FOG still significantly benefitted from SBT. Another study comparing split-belt adaptation in people with PD and HC found that despite different baseline asymmetry, PD showed the ability to adapt their step length asymmetry similarly to HC particularly in the early phase of adaptation [39]. This is in contrast with our findings, but may be explained by the fact that our PD participants were highly affected by the disease in terms of motor ability (MDS-UPDRS III) and had a long disease duration. Additionally, our participants experienced FOG, a gait deficit which was shown to be correlated to greater step length and limb excursion asymmetry during split-belt walking compared to people without FOG or HC [105].

Given the association between FOG and motor adaptation deficits as well as the link between FOG and gait asymmetry that have been shown in previous research, our findings are promising since gait deficits related to FOG were improved and retained after a single session of SBT. The finding that effects were retained after 24 hours highlights the potential to use SBT within longer rehabilitation programs.

The advantage of SBT is that it modulates gait more implicitly without attention being consciously drawn to the adaptation task. Furthermore, repeated adaptations of the gait pattern may improve the flexible adaptation of the movement to new tasks and may train motor switching, which could potentially improve motor performance in a more sustained manner [245]. Especially, prolonged training could positively impact the connectivity in specific brain circuits like the cerebellar locomotor region [246], as this area is known to have an important role in the adjustment of gait to asymmetrical speeds [247]. Darter et al. [248] found an association between symmetry and dynamic stability during split-belt walking in healthy young adults, suggesting that improving symmetry might also be an approach to improve an individuals' walking stability through the use of SBT. Additionally, Reisman et al. [202] stated that locomotor adaptation helps with automatization of gait, which is affected in PD and even more in PD+FOG. This is particularly important in situations where attentional focus is required for simultaneous tasks (e.g. talking while walking). The fact that people with FOG were able to automatically modulate their gait is a surprising result, knowing that indirect locomotor pathway, involving the basal ganglia, is more affected in this subgroup [249]. This

could point to the fact that the cerebellar circuits became more involved in the processing of gait adaptation with repeated exposure to SBT [202].

Usually improvement of step length asymmetry would be expected to be largest immediately after the training and then diminish 24 hours later, like observed in HCs. However, in PD+FOG the improvement was the largest from Pre to Retention. The smaller improvement at Post within PD+FOG compared to HC might be due to fatigue as PD+FOG reported higher rate of physical fatigue than HC after the training session.

Training with changing SBT conditions is most effective

As our second aim, we investigated which of the SBT conditions was most effective to improve gait adaptation in PD+FOG. The condition with changing belt speed ratios (SBTCR) showed strongest effects to improve gait adaptation and effect sizes were the largest compared to tied-belt training. We speculate that the changing ratio condition led to the greatest gains because it specifically trained the ability to rapidly and flexibly switch between motor patterns, which is usually difficult for people with PD [101]. Through the changing ratio condition participants were exposed to recurring switches which required constant adjustments of the motor pattern. Task variability is known to be necessary to retain newly learned motor skills in neurorehabilitation [250], which could have facilitated adaptation in the SBTCR group.

SBT50 seemed to be especially effective to modulate step length asymmetry during the early phase of the SBT adaptation test. This could have been derived from the long exposure to the split-belt condition with the high ratio during the training.

The identification of the most effective SBT contrast is important to design long-term SBT protocols. The evidence suggests, that SBTCR is most effective and by implementing a greater amount of high contrast that effect could be enhanced even more. However, step length asymmetry during Retention was quite similar in SBTCR and TBT. There were no differences in mental or physical fatigue in PD+FOG between training groups, which could have explained the differences between the training protocols.

Gait asymmetry to quantify adaptation ability

Study aim 3 focused on the assessment of gait adaptation using a SBT adaptation test, possibly relevant as a future treatment outcome. We averaged different measures of gait asymmetry

over the 90s SBT adaptation test. HC showed lower average values of step length asymmetry during the SBT adaptation test compared to PD+FOG, indicating better gait adaptation. In PD+FOG this was also correlated with disease duration and MDS-UPDRS III, showing that PD+FOG with longer disease duration and more severe motor symptoms present with greater asymmetry (lower values below zero). Similarly, limb excursion asymmetry showed differences between groups with lower values in HC. Therefore, we concluded that lower values of averaged gait asymmetry (step length asymmetry or limb excursion asymmetry) during the adaptation test represented better gait adaptation and therefore could serve as a future outcome. This conclusion is supported further by lower values of gait adaptability after SBT, showing that it was responsive to training.

Limitations

Firstly, due to combining Pre- and Post-assessments and the 30-min training session, the first day of testing was potentially fatiguing. Although we had three drop-outs due to fatigue, we found no correlation between fatigue and the observed improvement in gait adaptability. However, fatigue could have influenced assessment at the Post-test. Secondly, we allowed participants to hold handrails if necessary, shown to impact motor adaptation [251]. More PD+FOG than HC held the handrails, which may explain the different results between groups. However, even with handrails positive results were found, testifying the feasibility of the SBT-approach for rehabilitation. Especially for the subgroup with FOG, who often have more sever balance deficits and higher fall risk [155], it is common practice and unavoidable to use handrails. Therefore, it appears that the current findings generalize to clinical practice. Another limitation is the unblinding of the assessors. Although for most of the testing movement analysis systems were used limiting an influence of the assessor, a bias by the unblinding cannot be ruled out. Additionally, although the overall sample size was solid, this study is not safe of underestimating the observed effects due to the smaller sample sizes in the four training groups. Lastly, medication state can limit the interpretability of results in clinical trials with people with PD, as On and Off states can change individually and are difficult to assess. Additionally, responsiveness of FOG to medication (e.g. Off-FOG; On-Off-FOG) was not evaluated.

7.6 Conclusion

This proof-of-principle study evaluated the value of a single SBT versus a TBT session in HCs and PD+FOG, a group with notoriously serious gait disorders, on their ability to adapt and re-adapt gait to asymmetrical and symmetrical belt speeds. We found SBT to be superior to TBT to improve gait adaptation in people with PD+FOG, although effects were smaller compared to HCs. Improvements were retained after 24 hours, illustrating the potential of this training approach for future intervention studies. We also found that the changing ratios mode led to the greatest effect sizes, when compared with TBT in PD. Training proved feasible as fatigue was not associated with adaptation ability. Finally, we also found that measuring gait asymmetry during the gait adaptation test could be used to quantify adaptation ability in PD. Future studies should investigate whether long-term SBT using the changing ratios conditions leads to improved gait adaptability on over-ground tasks and whether training effects can be retained over a longer period. Additionally, further investigation needs to be done on whether improved gait adaptation can lead to a reduction in the occurrence of FOG.

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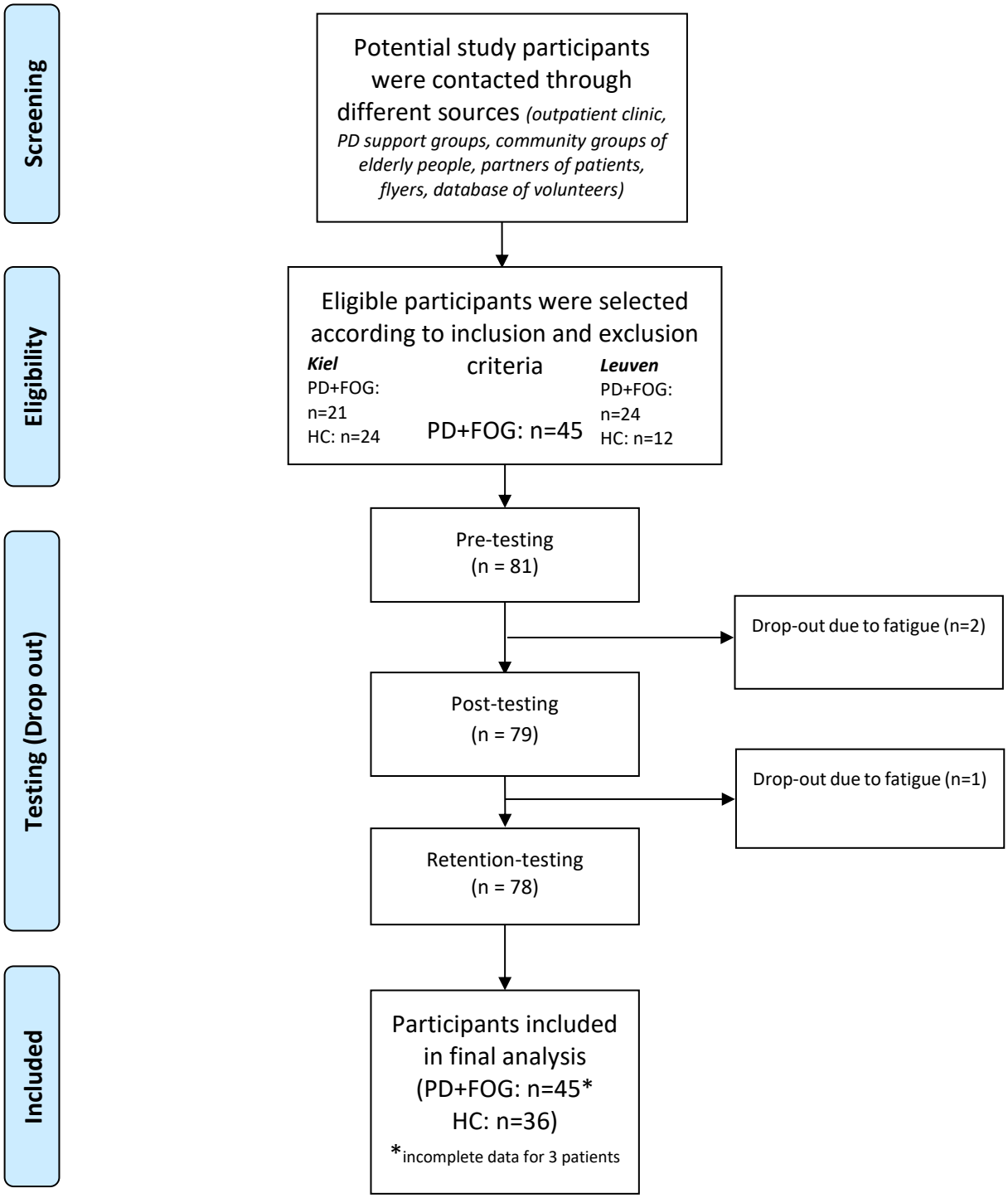
Conflict of interest

The Authors declare that there is no conflict of interest.



Supplementary 7.1 Flow diagram of recruitment process and and study conduction; n=number of participants; PD+FOG= Parkinson's Disease with Freezing of Gait, HC=healthy controls

Supplementary 7.2 SBTCR training protocol at the two study sites

SBTCR		Block 1	Block 2	Block 3	Block 4	Block 5	Block 6	Block 7	Block 8	Block 9	Total time of 3:4 (in s)	Total time of 1:2 (in s)
Kiel	Ratio	3:4	1:2	3:4	1:2	3:4	1:2	3:4	1:2	3:4	150	150
	Time (in s)	25	45	30	35	30	40	35	30	30		
Leuven	Ratio	3:4	1:2	3:4	1:2	3:4	1:2	3:4	1:2		150	150
	Time (in s)	37.5	37.5	37.5	37.5	37.5	37.5	37.5	37.5			

Notes. Switches between blocks were standardized at the same acceleration by a computerized protocol. The protocol was kept consistent within participant at each center.

8. Discussion and conclusions

In the following the results of the studies will be summarized and put into perspective regarding previous research in the field. Furthermore, the limitations will be evaluated to facilitate the interpretation of the findings. Lastly, the consequent implications and recommendations will be presented to facilitate the design and conduction of future research.

The first study of this work concentrated on the validity of FOG assessment via a questionnaire. The quantification of FOG frequency and severity can be done with the New Freezing of Gait-Questionnaire for which we provided a valid German version. Clinicians, therapists, and researchers can use the NFOG-Q to characterize the severity of the symptoms as well as consequences on daily life in their patients or study participants. It is especially useful for clinical routine as it is quickly administered. However, for the use in research it should be combined with more objective assessment tools to gain a more conclusive picture of the symptom. The German version of the NFOG-Q can be used in all German speaking countries.

The second study focused on the reliability of gait initiation measurement using IMU's in people with PD+FOG and HC. We could show that different outcome measures of APAs and first step characteristics present with varying reliability in PD+FOG and HC. The most reliable measures were ML APA size, first step ROM and first step velocity. We found that at least two trials of gait initiation were needed for reliable results of ML size of APA and first step ROM (except ST for PD) but more trials were needed for the other GI outcomes. Especially, APA duration, APA latency and AP APA size proved lower reliability, which makes them less suitable as outcome measures when using this method. Previous literature using the same method should be interpreted carefully considering the current findings and future studies should use multiple trials to generate reliable results, depending on the outcome of interest.

The third study of this work concentrated on the potential of SBT walking as a therapeutic option for people with PD. In a systematic review the past literature on SBT walking in PD was summarized and evaluated extensively. It was shown that SBT walking was safe and feasible for people with PD, as long as strong contraindications are ruled out. Furthermore, the people with PD in the reviewed studies were able to adapt their gait to SBT conditions in a similar pattern as healthy individuals, however their adaptation process was slower. The subgroup with PD+FOG showed increased difficulty during adaptation as well as impaired perception of

belt speed differences. The transfer of the newly learned gait pattern to overground walking was not investigated in the evaluated studies, which limits the interpretability of the effects. Also, it stresses the need for clinical trials to address this research gap and gain more insight into the actual benefit that people with PD could have during daily life walking. Furthermore, the review showed that selection of outcome parameters, the choice of belt speed ratios and the side of the imposed asymmetry have a great effect on the adaptation process. Therefore, those parameters need to be selected carefully with the goal of the intervention in mind.

Deriving from the knowledge gathered in the systematic review we designed a study protocol which aimed to investigate the effect of one session SBT walking on gait adaptation in PD+FOG and HC. We let participants train under one of three SBT settings or a tied belt setting (regular TT). It was shown that one training session of SBT walking could significantly improve gait adaptation in PD+FOG and HC, compared to regular TBT. Furthermore, the training setting with changing belt speed ratios was found to be most effective in PD+FOG. There is a lack of studies investigating the long-term effects of SBT training in PD, however in other neurological populations like stroke, SBT has been successfully used to reduce gait asymmetry. It is unclear if similar improvements can be achieved in PD, but the presented findings show that there is the potential for this tool to have a positive effect on gait in PD as well. We are moving forward on finding answers to this question by currently conducting a randomized controlled training intervention investigating the short-term and retention effects of SBT training versus regular TT. The findings of this work have helped in designing a training protocol with changing conditions, adequate training frequency (3x per week), and a prolonged training period (4 weeks) which has the potential to improve gait in individuals with PD+FOG.

Taken together, gait impairments in PD are very prominent and disabling. Especially FOG has a major effect on mobility and daily activities and at the same times increases the risk for future falls. Assessment of FOG and FOG-related gait deficits needs to be conducted using valid and reliable tools. Furthermore, there is the need for alternative treatment options, which need to be designed to address the specific demands and challenges people with PD+FOG face. This thesis has shown results regarding the validity and reliability of different assessment methods to evaluate FOG in people with PD. It provides a valid German version of the NFOGQ as one of the most frequently used assessment tools. Additionally, the thesis gives clear methodological recommendations to increase reliability when assessing gait initiation as a proxy of FOG. Furthermore, it has revealed the potential of SBT to treat gait impairments in

PD. Finally, the findings give important implications for the design of future SBT intervention studies in the population of PD+FOG.

9. Zusammenfassung (Summary in German)

Einleitung

Morbus Parkinson (MP) ist eine neurodegenerative Erkrankung, die mit verschiedenen motorischen und nicht-motorischen Symptomen einhergeht. Sie ist charakterisiert durch die Kardinalsymptome Tremor, Bradykinese und Rigidität [1-3]. Es gibt bisher keine Therapie, welche den neurodegenerativen Prozess der Erkrankung stoppen kann [6, 7], weshalb die Standardtherapie vor allem auf die Linderung der Symptome abzielt. Trotz intensiver Forschung auf dem Gebiet ist die genaue Ursache der Erkrankung noch ungeklärt und eine Heilung derzeit nicht möglich. [4]. Auf Grund der alternden Bevölkerung steigt zudem die Prävalenz der Parkinson-Erkrankung [5].

Die Lebensqualität von Menschen mit MP wir maßgeblich durch verschiedene motorische und nicht-motorische Symptome beeinträchtigt [8]. Das motorische Symptom, welches sich am stärksten auf die gesundheitsbezogene Lebensqualität auswirkt ist die Gangstörung [8]. Bei Personen mit MP kann das Gangbild in verschiedenster Weise beeinträchtigt sein, unter anderem durch Gangfreezing *(Freezing of Gait – FOG),* kurze, episodische Gangblockaden, welche mit einer reduzierten Lebensqualität einhergehen [10]. Die Gangschwierigkeiten wirken sich negativ auf die Mobilität aus und sind mit Stürzen assoziiert [12], besonders bei Personen mit MP und Gangfreezing (MP+FOG) [13], wodurch ein unabhängiger Lebensstil eingeschränkt wird.

Die steigende Prävalenz der Parkinson-Erkrankung und ihre Auswirkungen auf die Lebensqualität und Mobilität der Betroffenen zeigen, wie wichtig es ist, die Behandlungsoptionen für MP weiter zu untersuchen und zu verbessern. Trotz der guten Wirksamkeit medikamentöser oder invasiver Therapien können damit nicht alle Symptome ausreichend behandelt werden, wodurch die Bewegungstherapie zunehmend an Bedeutung gewinnt. Verschiedene Trainingsinterventionen haben bereits positive Effekte auf den Gang bei Personen mit MP gezeigt, dazu zählen zum Beispiel Gleichgewichts- und Gangtraining, Laufbandtraining, Ergometertraining und Krafttraining [16]. Jedoch sind, abgesehen von der Physiotherapie, viele dieser Optionen nicht etabliert, was unter anderem an der Qualität der durchgeführten Studien liegt. Oftmals fehlen geeignete Outcome Parameter, die Stichproben sind klein, das Studienprotokoll enthält keinen Follow-up oder es fehlen Informationen und

Empfehlungen für die praktische Umsetzung der Interventionen [16, 21]. Hinzu kommt, dass noch nicht alle neuronalen Mechanismen von Gangdefiziten bei MP, insbesondere bei Gangfreezing, vollständig geklärt sind und es somit schwieriger ist, Interventionen speziell darauf abzustimmen [22].

Ein Ziel dieser Arbeit ist es Untersuchungsmethoden zur Erfassung von Gangfreezing und Freezing-assoziierten Gangdefiziten zu untersuchen. Eine etablierte Untersuchungsmethode ist der *New Freezing of Gait-Questionnaire,* ein Fragebogen zur Erfassung der Häufigkeit und des Schweregrads von Gangfreezing. Eine deutsche Version dieses Fragebogens wird auf ihre Validität zur Erfassung von Gangfreezing überprüft. Des Weiteren wird die Erfassung der posturalen Vorbereitungsphase der Ganginitiierung bei Personen mit MP und Gangfreezing in den Fokus genommen. Die Messung dieser Charakteristika mithilfe von Bewegungssensoren soll bei Personen mit MP+FOG und gesunden Älteren auf ihre Reliabilität untersucht werden. In einem zweiten Teil dieser Arbeit soll das Potenzial einer speziellen Form der Bewegungstherapie untersucht werden. In einer systematischen Übersichtsarbeit werden die Umsetzbarkeit und die Effekte von Split-Belt-Laufband Therapie bei Personen mit MP evaluiert. Abschließend werden die Kurzzeiteffekte einer Trainingseinheit auf dem Split-Belt-Laufband auf die Ganganpassungsfähigkeit von Personen mit MP+FOG und gesunden Älteren untersucht. Zur Bearbeitung dieser Zielsetzungen wurden vier Publikationen angefertigt.

Gangstörungen bei Personen mit Morbus Parkinson

Motorik und Gang werden bei Personen mit MP hauptsächlich durch die Kardinalsymptome beeinträchtigt [23]. Im Folgenden werden die Gangdefizite bei Personen mit MP zusammengefasst. Vor allem das Gangfreezing als eine Form der Gangstörung wird genauer in den Fokus genommen und zugrunde liegenden neuronalen Mechanismen erörtert. Abschließend werden die Therapieoptionen zur Verbesserung von Gangfreezing und dabei die besondere Rolle der Bewegungstherapie näher beleuchtet.

Klassifikation von Gangstörungen

Die Gangdefizite von Personen mit MP können in kontinuierliche und episodische Gangstörungen strukturiert werden [28, 29].. Die kontinuierlichen Gangstörungen sind persistierend, treten somit durchgehend beim Gehen auf, und beinhalten zum Beispiel reduzierte Schrittlänge und reduzierte Ganggeschwindigkeit, erhöhte Gangvariabilität und

Gangasymmetrie und schlechtere bilaterale Koordination [28, 32-39]. Im Gegensatz dazu charakterisieren sich die episodischen Gangstörungen durch ihr zufälliges und phasenweises Auftreten, unter welchen sich das Gangfreezing einordnen lässt [31]. Trotz dieser Unterscheidung stehen beide Formen der Gangstörungen im Zusammenhang, da zum Beispiel Gangfreezing als episodische Störung auch mit verstärkten kontinuierlichen Gangdefiziten, wie zum Beispiel erhöhter Gangvariabilität [40] und Gangasymmetrie [42], assoziiert werden konnte.

Pathophysiologie kontinuierlicher Gangstörungen

Das Gangbild von Personen mit MP unterscheidet sich in zeitlichen sowie räumlichen Gangparametern von dem gesunder Älterer. Zum einen weisen Personen mit MP eine reduzierte Ganggeschwindigkeit auf [24, 43, 44]. Hinzu kommt eine geringere Schrittlänge [43-45] und erhöhte Gangvariabilität [32, 35, 36, 94]. Personen mit MP haben außerdem Defizite bei der Abstimmung der Koordination von oberer und unterer Extremität [34] und weisen eine erhöhte Gangasymmetrie, in Bezug auf Schrittlänge [37, 39] und Schrittzeit [37, 38] auf. Die Asymmetrie hängt höchstwahrscheinlich vor allem mit dem asymmetrischen Beginn und Fortschreiten der Erkrankung zusammen [9]. Es konnte gezeigt werden, dass Personen mit Morbus Parkinson durch Aufmerksamkeitsstrategien vergleichbare Schrittlängen wie Gesunde erreichen können. Das legt nahe, dass für die Durchführung automatisierter Bewegungen bei Personen mit Parkinson zusätzlich andere (z.B. frontale) Hirnregionen involviert sind. Die zugrunde liegenden neuronalen Mechanismen finden sich zumeist in den Basalganglien, welche verstärkt inhibitorische Signale senden und damit Hirnregionen wie den Supplementären Motorkortex hemmen [9], wodurch der Gang verlangsamt wird. Man geht davon aus, dass die Probleme mit der Automatisierung des Gangs (z.B. Gangvariabilität) mit dem Dopaminmangel in den senso-motorischen Arealen des Striatums zusammenhängen [59]. Gangstörungen bei Personen mit MP werden noch verstärkt, wenn die Aufmerksamkeit während des Gehens zusätzlich auf eine andere Aufgabe gelenkt wird. Dies verlangsamt den Gang zusätzlich [60] und führt zu einer Verschlechterung der Gangsymmetrie, der bilateralen Koordination und höherer Gangvariabilität [43, 61]. Dieses Defizit kann vor allem durch die Kapazitätstheorie erklärt werden, nach der verfügbare Ressourcen zwischen zwei konkurrierenden Aufgaben aufgeteilt werden müssen, wobei sich die Ausführung von einer

oder beiden Aufgaben verschlechtert [62]. Die fehlende Automatisierung des Ganges spielt hier ebenfalls hinein [62].

Einige der beschriebenen Gangstörungen stehen in Zusammenhang mit in einem erhöhten Sturzrisiko bei Personen mit MP. Vor allem reduzierte Ganggeschwindigkeit, niedrige Kadenz und kürzere Schritte gehen bei MP mit einem erhöhten Sturzrisiko einher [52]. Ein solcher Sturz resultiert dann zudem oft in reduzierter Mobilität und erhöhter Sturzangst [54]. Deshalb ist die Identifizierung solcher Gangdefizite für die Entwicklung geeigneter Therapieoptionen essenziell. Außerdem sollten bei der Gestaltung von therapeutischen Interventionen die neuronalen Mechanismen des Symptoms besonders beachtet werden.

Gangfreezing bei Morbus Parkinson: Definition und Pathophysiologie

Gangfreezing wird als ein „kurzes, episodisches Ausbleiben oder eine deutliche Reduktion der Vorwärtsbewegung der Füße, trotz der Intention (weiter) zu gehen“ [11], definiert. Es ist ein höchst einschränkendes Symptom, welches die Mobilität der Person erheblich beeinträchtigt, das Sturzrisiko erhöht [65] und ebenso mit einer verringerten gesundheitsbezogenen Lebensqualität einhergeht [66].

Es wird angenommen, dass FOG zudem mit Defiziten der posturalen Kontrolle zusammenhängt [73]. Dies wurde speziell in Hinblick auf die Starthemmung, eine Form des FOG die bei der Ganginitiierung auftritt, untersucht. Die Ganginitiierung ist bei Personen mit Gangfreezing gestört und stellt eine Belastung und Herausforderung im Alltag dar. Die Ganginitiierung wird durch eine subtile Bewegung eingeleitet, welche man *anticipatory postural adjustment* (APA) nennt. Dabei verschiebt sich der Druckmittelpunkt zuerst nach lateral posterior zum Bein, welches den Schritt macht, um eine Vorwärtsbeschleunigung des Masseschwerpunktes in Richtung des Standbeins zu ermöglichen [74, 75]. Bei Personen mit MP+FOG sind diese APAs hypometrisch und weisen eine erhöhte Latenz und verringerte Schrittgeschwindigkeit auf [76, 77]. Außerdem unterliegen sie vermutlich einem kompensatorischen Mechanismus, denn man fand kleine APAs, wenn kein FOG auftrat und große APAs, wenn die Ganginitiierung von FOG begleitet war [76].

Es gibt verschiedene kontinuierliche Gangdefizite, die mit dem Gangfreezing assoziiert sind. Dazu gehören die Gangasymmetrie, welche bei Personen MP+FOG stärker ausgeprägt ist als bei denen ohne FOG [42, 78], die Gangvariabilität, welche signifikant erhöht ist und mit dem

Schweregrad des Gangfreezings korreliert [40], sowie eine schlechtere bilaterale Koordination [80]. Diese Gangdefizite könnten bei einer Anhäufung ein Auslöser für das FOG sein, wie es in dem Schwellenmodell vermutet wird [68]. Die Erkenntnisse zu den kontinuierlichen Gangstörungen bei Personen mit MP+FOG haben das Verständnis des Symptoms grundlegend verändert. Zuvor ging man davon aus, dass die Personen mit Gangfreezing zwischen ihren Freezing-Episoden nur die ohnehin MP-spezifischen Gangveränderungen aufweisen [40]. Dieses vertiefte Verständnis von Gangstörungen bei Personen mit FOG lieferte wichtige Einblicke in die Pathophysiologie und war wegweisend für die Untersuchung von alternativen Behandlungsoptionen für das Symptom.

Die zugrunde liegende Pathophysiologie des Symptoms wurde unter anderem in Bildgebungsstudien untersucht. Dabei fand man vor allem eine veränderte funktionelle sowie zum Teil auch strukturelle Konnektivität in bestimmten Hirnregionen, welche für die Motorik zuständig sind [82, 83]. Jedoch sind die kausalen Zusammenhänge zwischen den beobachteten Veränderungen im Gehirn und dem Auftreten von FOG noch größtenteils unklar. Jedoch wurden bezüglich der neuronalen Mechanismen des Symptoms bereits verschiedene theoretische Modelle aufgestellt, welche das Auftreten von FOG zu erklären versuchen. Zum einen wird das Schwellenmodell (*threshold model*) definiert, welches die Anhäufung verschiedener motorischer Defizite als Auslöser für Gangfreezing sieht [69]. Zum anderen gibt es das Interferenzmodell (*interference model*), welches davon ausgeht, dass die gleichzeitige Verarbeitung von sensorischem, motorischem und limbischem Input, das FOG hervorruft [70]. Des Weiteren wird das Abkopplungsmodell (*decoupling model*) definiert, welches fehlende Konnektivität zwischen der Programmierung und der tatsächlichen Ausführung einer motorischen Aufgabe als Auslöser für FOG betrachtet [71]. Es ist wahrscheinlich, dass ein Zusammenspiel aus den verschiedenen Modellen das Auftreten von FOG erklären kann und je nach Phänotyp verschiedene Komponenten im Vordergrund stehen [68].

Erhebung von Gangfreezing

Die Diagnose, sowie die Beurteilung des Schweregrads von Gangfreezing findet in der klinischen Routine oft nur durch Beobachtung des Gangbilds und Befragung des Betroffenen statt. Doch nicht immer ist das Gangfreezing während einer klinischen Untersuchung zu sehen, obgleich die Person vom Auftreten berichtet. Um das Symptom genauer zu untersuchen

benötigt es standardisierte Tools [85]. Eine Möglichkeit ist die Verwendung von Fragebögen, wie dem *New Freezing of Gait-Questionnaire* (NFOG-Q) [87]. Dieser international etablierte Test erfragt die Häufigkeit und den Schweregrad von *Freezing of Gait* innerhalb der letzten 4 Wochen, sowie dessen Auswirkungen auf alltägliche Aktivitäten. Jedoch stütz dieser sich nur auf das subjektive Empfinden der Befragten und erfordert ausreichende kognitive Kapazitäten um die Freezingepisoden retrospektiv korrekt angeben zu können [151].

Da Freezing oft in speziellen Situationen vorkommt (Ganginitiierung, Drehungen, enge Umgebung), wurden verschiedene Tests entwickelt, um Freezingepisoden zu provozieren und diese anschließend zu quantifizieren. Ein Beispiel für einen solchen Test ist der Ziegler Score [88]. Er verbindet verschiedene, für Personen mit MP+FOG herausfordernde Aufgaben, wie Drehbewegungen, das Gehen durch Engpässe oder das Gehen bei zusätzlicher kognitiver Aufgabe, welche dann mithilfe einer Ordinalskala bewertet werden. Vor allen Dingen im Bereich der Forschung bietet der Ziegler Score den Vorteil, dass über den *clinically relevant change* Informationen über die klinische Wirksamkeit einer Behandlung abgebildet werden können [89]. Seit einiger Zeit haben jedoch Methoden, welche das *Freezing of Gait* mithilfe von Bewegungssensoren quantifizieren, an Aufmerksamkeit gewonnen. Diese Sensoren können hochfrequente Bewegungen, wie zum Beispiel das häufig auftretende Zittern und Beben der Unterschenkel bei einer Starthemmung aufzeichnen [95, 96]. Diese Methode bietet neue Möglichkeiten der Untersuchung von Gangfreezing, da sie die Anwendung außerhalb von Laborsituationen z.B. im häuslichen Umfeld ermöglichen kann [85, 93, 94]. Die Algorithmen, welche die Daten der Bewegungssensoren analysieren, nutzen dafür hauptsächlich Informationen über die Frequenz der Bewegungen und können damit Start und Ende einer Freezingepisode, sowie ihre Dauer bestimmen. Jedoch ist es damit nicht möglich akinetisches Gangfreezing zu erkennen [85]. Mancini et al. [96] entwickelten einen Algorithmus, welcher einen *Freezing Ratio* errechnet, um den Schweregrad des Gangfreezings zu beschreiben. Dieser korrelierte signifikant mit dem klinischen Rating und dem NFOG-Q Score. Diese Algorithmen sind bisher nur für die Anwendung im Labor geeignet, weshalb die Anwendung im häuslichen Umfeld weiter untersucht werden muss. Einige Forscher erzielten bereits aussichtsreiche Ergebnisse, jedoch sind diese noch nicht ausreichend validiert [97]. Aufgrund der bereits erläuterten Schwierigkeiten bei der Untersuchung von FOG ist es wichtig die Erhebung alternative Parameter, welche mit Gangfreezing assoziiert sind, in Betracht zu ziehen. Tragbare Sensoren können deshalb nicht nur zur Erkennung der eigentlichen

Freezingepisoden genutzt werden, sondern auch Aufschluss über Aspekte des Gangbilds oder der Ganginitiierung geben, welche mit FOG in Verbindung stehen [76, 79]. Es wichtig die Erhebung entsprechender Parameter auf ihre Reliabilität zu untersuchen, um sie zukünftig für die Abbildung von Interventionseffekten nutzen zu können.

Für eine ganzheitliche Beurteilung von FOG ist es vorteilhaft verschiedene der genannten Untersuchungsmethoden zu kombinieren. Trotz der Nachteile der subjektiven Erhebungsmethoden mittels Fragebögen, können diese valide Informationen über das Symptom liefern. Idealerweise sollten Ärzte, Wissenschaftler und Therapeuten sie mit objektiveren Methoden kombinieren, um ein vollständiges Bild über das Symptom zu erlangen.

Gangfreezing und Motorisches Lernen

Personen mit MP+FOG haben Schwierigkeiten mit motorischem Lernen [39, 99, 100]. Um geeignete und effektive Therapieoptionen für Personen mit Gangfreezing zu entwickeln ist es entscheidend, die Mechanismen ihrer Defizite beim motorischen Lernen zu verstehen [101]. Personen mit MP sind in der Lage neue motorische Aufgaben zu lernen, jedoch brauchen sie dazu mehr Zeit, ihre Erfolge sind geringer und sie können die Aufgaben schlechter auf andere Situationen übertragen [101]. Bei Personen mit FOG ist die Fähigkeit zum motorischen Lernen noch stärker beeinträchtigt; sie zeigen geringere Lernerfolge, Defizite bei der Speicherung des Gelernten und schlechtere Generalisierung [51, 102, 103]. Es gibt verschiedene Faktoren, welche sich auf das motorische Lernen bei Personen mit MP auswirken. Unter anderem vermutet man, dass pathologische Mechanismen des frontostriatalen Systems [106, 107], ein beeinträchtigtes Zusammenspiel zwischen kortikalen und subkortikalen Arealen [108] sowie Defizite der Exekutivfunktion [109, 110] eine Rolle spielen. Aufgrund der beschriebenen Defizite ist es wichtig geeignete Rahmenbedingungen zu schaffen, um es Personen mit MP zu erleichtern neue motorische Aufgaben zu lernen. Ausreichend Wiederholung, individuelles Feedback oder Cueing können sich positiv auf das motorische Lernen auswirken, vor allem bei Personen mit Gangfreezing [101].

Therapie bei Gangfreezing

Das Gangfreezing bei Personen mit MP kann mit entsprechender Medikation [115-117] oder invasiven Verfahren wie der Tiefen Hirnstimulation [119, 121] behandelt werden. Da FOG

jedoch auch unter Medikation auftreten kann beziehungsweise häufig dann auftritt, wenn die Wirkung der Medikamente nachlässt, sind alternative Behandlungsmethoden wie aktivierende Therapien insbesondere bei diesem Sympton von großer Bedeutung. Bei den aktivierenden Therapien nimmt der Bereich *Cueing* (*Cue* (Engl.): Reiz; Signal) einen wichtigen Teil ein. *Cueing* bezeichnet die Verwendung von auditiven (z.B. Metronom), visuellen (z.B. Linien auf dem Boden) oder taktilen (z.B. Vibrationsfeedback) Signalen, welche es dem Patienten erleichtern sollen eine Blockade zu überwinden/vermeiden und (wieder) loszugehen [144]. *Cueing*-Ansätze werden aber auch in Verbindung mit tragbaren Sensoren verwendet, um geschlossene Feedbacksysteme zu entwickeln, bei denen die Sensoren den Beginn einer Freezing Episode frühzeitig erkennen und diese dann durch *Cueing* verhindert werden könnten [145-147]. Ebenso wurde untersucht ob diese Methode durch sensorisches Feedback auch die Ganginitiierung verbessern kann, was jedoch nicht gezeigt werden konnte [77].

Ein weiterer Teil der aktivierenden Therapien wird durch längerfristige bewegungstherapeutische Interventionen gebildet [122]. Dazu zählten unter anderem Laufbandtraining [123, 124], *Action Observation Training* [125-128], *Cueing* [111, 129-131], Kraft- und Gleichgewichtstraining [132-134], Training im häuslichen Umfeld [135-137] und Wassergymnastik [138-140]. Auch *Nordic Walking* zeigte positive Effekte zur Vermeidung von Freezing [141], jedoch müssen diese Ergebnisse noch in größeren Untersuchungen bestätigt werden. Ein anderer Ansatz, welcher jedoch noch nicht in einem kontrollierten Studiendesign untersucht wurde, ist das Gehen auf einem Split-Belt Laufband (SBT). Dies wurde bereits erfolgreich in der Schlaganfall-Rehabilitation eingesetzt [206, 207, 209] und könnte auch für die Rehabilitation bei MP+FOG genutzt werden. So wurde zum Beispiel bereits ein positiver Kurzzeiteffekt von SBT auf die Schrittlängenasymmetrie, bilaterale Koordination und auf die progressive Reduzierung der Schrittlänge festgestellt [78], welche jeweils mit Gangfreezing zusammenhängen.

Es gibt mehrere Gründe, warum man noch nicht die *eine* effektive Therapie für Gangfreezing gefunden hat. Dazu gehört auch, dass viele Methoden zur Quantifizierung des Symptoms nicht geeignet sind, um Therapieeffekte abzubilden. Ein Großteil der beschriebenen Studien nutzt subjektive Fragebögen wie zum Beispiel den NFOG-Q um die Effektivität der jeweiligen Therapieform zu evaluieren [122]. Dass der NFOG-Q jedoch nicht als Hauptparameter für die

Erfassung von Therapieeffekten bei klinische Studien geeignet ist, wurde erst kürzlich festgestellt [151] und auch bei vielen anderen Untersuchungsmethoden existieren keine Informationen ab wann eine Veränderung des Parameters als klinisch relevant betrachtet werden kann.

Trotz dieser Unzulänglichkeiten ist die Bewegungstherapie eine sehr vielversprechende Behandlungsoption für Personen mit MP+FOG, da sie auf vielfältige Weise auf die FOG-typischen Gangdefizite abzielen kann.

Ziele dieser Dissertation

Aus den bereits erläuterten Herausforderungen bei der Untersuchung und Therapie von FOG und FOG-assoziierten Gangdefiziten ergeben sich die Anknüpfungspunkte für diese Arbeit. Zunächst existiert für den NFOG-Q, ein sehr etabliertes Erhebungsinstrument von FOG, bisher keine validierte deutsche Übersetzung. Die Untersuchung von Validität ist nicht bahnbrechend, jedoch fundamental vor allem bei einem so schwer quantifizierbaren Symptom und wird deshalb im Rahmen von Studie 1 umgesetzt. Des Weiteren ist der Einsatz von tragbaren Sensoren bei der Untersuchung der Ganginitiierung und insbesondere APAs bei Personen mit MP+FOG im Fokus. Er wurde bereits auf seine Test-Retest-Reliabilität untersucht. Jedoch ist bisher unklar wie viele Trials innerhalb einer Untersuchung durchgeführt werden müssen, um reliable Ergebnisse für die verschiedenen Schritt- und APA-Parameter zu generieren, ob potenzielle systematische Fehler zwischen den Trials bestehen und welchen Einfluss eine kognitiven Zusatzaufgabe auf die Reliabilität hat. Studie 2 untersucht diese Aspekte. Im Bereich der Therapie ist die Nutzung von SBT bei Personen mit neurologischen Erkrankungen vielversprechend. Verschiedene SBT Paradigmen wurden bereits bei Personen mit MP untersucht, die Ergebnisse allerdings nicht systematisch aufgearbeitet. Um erfolgreiche Trainingsinterventionen basierend auf den bisherigen Erkenntnissen zu entwerfen, ist es wichtig die Anwendbarkeit, Anwendungsoptionen und Effekte von SBT bei Personen mit MP zu kennen. Dies wird durch ein systematisches Review im Rahmen von Studie 3 adressiert. Darüber hinaus ist SBT bisher nicht in der Rehabilitation von Personen mit MP+FOG etabliert, da die Effekte bislang unzureichend untersucht wurden. Konkrete Daten bezüglich der effektivsten Einstellung des SBT, der Vorteile gegenüber traditionellem Laufbandtraining und der Nachwirkung und Speicherung der Effekte sind nicht

vorhanden. Um die Langzeiteffekte von SBT bei Personen mit MP+FOG zukünftig untersuchen zu können, müssen diese Modalitäten zuerst klargestellt werden.

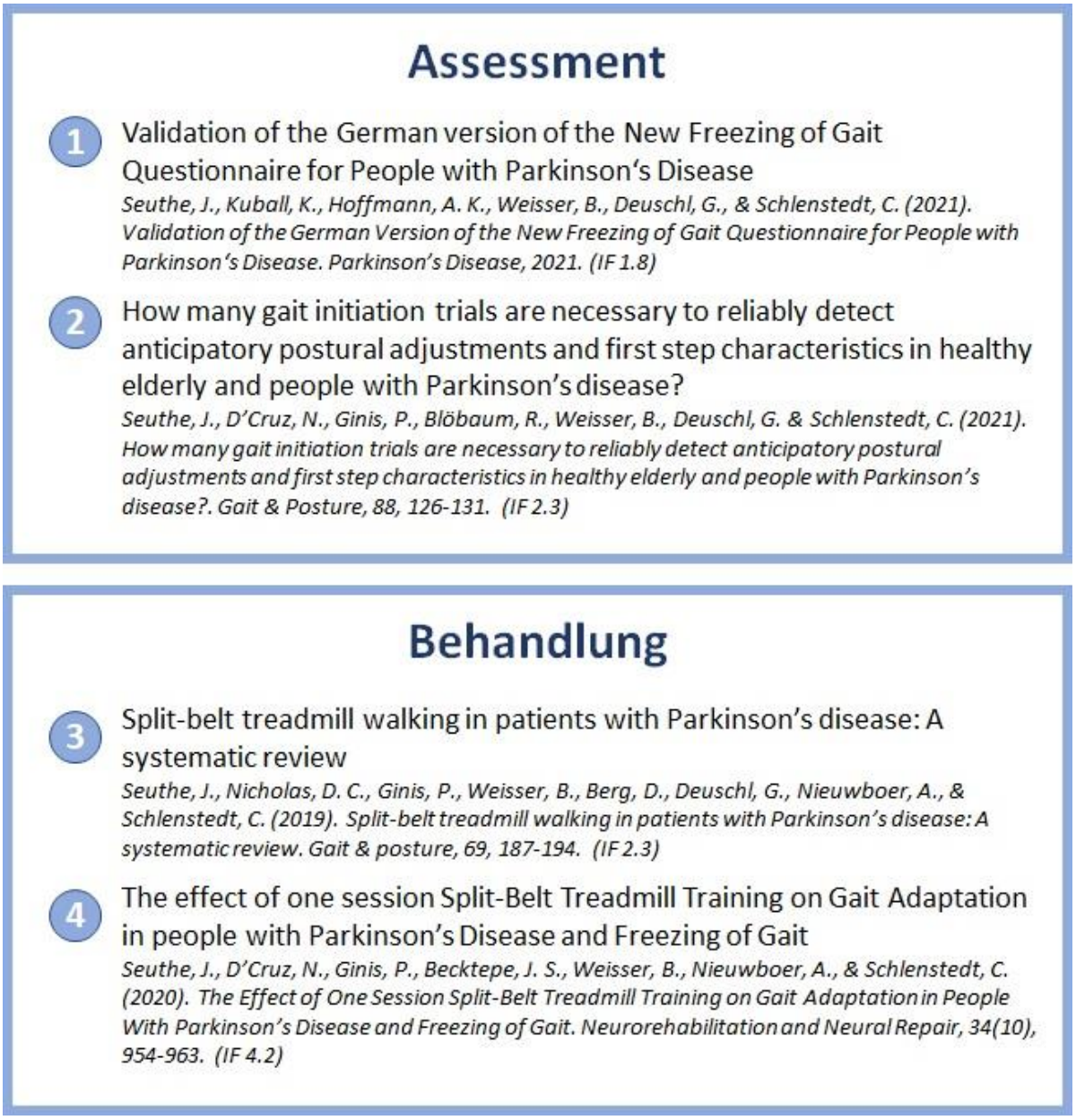


Abbildung 1. Studien dieser Dissertation (Titel, Autoren und wissenschaftliche Zeitschrift). IF=Impact Faktor

Daraus folgend adressiert diese Dissertation folgende vier Ziele:

Studie 1: *Die Validierung der deutschen Version des New Freezing of Gait Questionnaires für Personen mit M. Parkinson.*

Studie 2: *Die Untersuchung der Reliabilität der Vorbereitung und Ausführung der Ganginitiierung bei Personen mit M. Parkinson und Freezing sowie gesunden Älteren.*

Studie 3: *Die Erstellung einer systematischen Übersicht der Literatur über Split-Belt-Laufband bei Personen mit M. Parkinson.*

Studie 4: *Die Untersuchung der Effekte einer Einheit Split-Belt-Laufbandtherapie auf die Ganganpassung bei Personen mit M. Parkinson mit Freezing.*

Studien

Im Folgenden werden die Studien dieser Dissertation zusammengefasst. Dabei wird jeweils eine kurze Einleitung gegeben, gefolgt von dem Ziel der Studie und der verwendeten Methode. Anschließend werden die wichtigsten Ergebnisse zusammengetragen und diskutiert, sowie ein Fazit gezogen.

Zusammenfassung Studie 1

Einleitung: Eine etablierte Methode zur Quantifizierung des Schweregrad des Symptoms Gangfreezing ist der weltweit genutzte *New Freezing of Gait-Questionnaire* (NFOG-Q).

Ziel der Studie: Die Bereitstellung einer deutschen Übersetzung des NFOG-Q und die Untersuchung der Validität dieses Instruments bei Personen mit MP+FOG.

Methode: Zur Übersetzung wurde die Methode der Vorwärts-Rückwärts-Übersetzung verwendet. Die übersetzte Version des NFOG-Q wurde bei insgesamt 58 Proband*innen mit MP und Gangfreezing erhoben. Zudem wurden verschiedene klinische Variablen wie Schweregrad der Erkrankung (Hoehn und Yahr – H&Y) und der motorischen Symptome (*Movement Disorder Society-Unified Parkinson's Disease Rating Scale Part III* - MDS-UPDRS III), Mobilität (*Timed up and Go* -TUG, *single task* und *dual task*), Sturzangst (*Falls Efficacy Scale-International* – FES-I) und kognitiver Status (*Montreal Cognitive Assessment* - MoCA) aufgenommen. Die Validität wurde mithilfe des Cronbach's Alpha (Cα) auf Interne Konsistenz,

sowie über die Korrelationen (Spearman's rho) mit den genannten klinischen Variablen auf die Validität überprüft.

Ergebnisse: Die deutsche Version des NFOG-Q zeigte eine hohe interne Konsistenz (Cα=0.84). Außerdem war der NFOG-Q Score signifikant mit dem MDS-UPDRS III, der H&Y Stufe, dem TUG, sowie dem FES-I korreliert. Die fehlende Korrelation mit Aspekten der Kognition deutet auf gut divergente Validität hin. Eine hohe interne Konsistenz konnte auch bei der Subgruppe der Personen mit kognitiven Defiziten festgestellt werden (Cα=0.89).

Diskussion: Unsere Analyse zeigte eine hohe interne Konsistenz, somit hängen die einzelnen Items zusammen, sind aber nicht redundant. Die Ergebnisse stimmen mit denen vorheriger Untersuchung überein, welche ebenfalls eine hohe interne Konsistenz der originalen englischen Version des NFOG-Q und des Vorgängers *Freezing of Gait-Questionnaire* (FOG-Q) sowie der deutschen Version des FOG-Q zeigten [87, 152, 161]. Im Gegensatz zu der deutsche Validierung des FOG-Q [161] fanden wir jedoch eine signifikante Korrelation zwischen dem Gesamtscore und dem MDS-UPDRS III sowie dem TUG. Dies deutet auf eine gute Konstruktvalidität hin, da die motorischen Symptome und das Gangbild [119] und auch der Schweregrad der Erkrankung [162-164] mit Gangfreezing zusammenhängen. Die Korrelation mit der subjektiven Sturzangst ist ebenfalls eine Bestätigung der Ergebnisse anderer Validierungsstudien [163, 165]. Die signifikante Korrelation mit dem TUG mit DT bei gleichzeitig fehlender Korrelation mit dem MoCA deute darauf hin, dass Gangfreezing weniger mit globaler Kognition zusammenhängt [169], als vielmehr mit aufgabenspezifischer Dual Task Fähigkeit. Obwohl wir für die Subgruppe mit kognitiver Einschränkung vergleichbare Ergebnisse bezüglich der Validität generieren konnten, wird empfohlen den Fragebogen nur mit nicht-dementen Patienten durchzuführen [161], was eine Limitation dieser Studie darstellt. Außerdem zeigte der NFOG-Q in einer aktuellen Studie eine unzureichende Test-Retest Reliabilität [151], weshalb er nicht als alleiniges Outcome zur Erfassung von Therapieeffekten genutzt werden sollte.

Fazit: Diese Studie belegt die Validität einer deutschen Version des NFOG-Q zur Erfassung des Schweregrads von Gangfreezing und veröffentlicht diese Übersetzung für zukünftige Nutzung in Forschung und Klinik. In der Forschung ist die Anwendung des NFOG-Q vor allem in Kombination mit ergänzenden objektiven Assessment-Verfahren zu empfehlen.

Zusammenfassung Studie 2

Einleitung: Die posturale Vorbereitung (*Anticipatory Postural Adjustment* (APA)) bei der Ganginitiierung ist eine fast unmerkliche Bewegung bei der der Masseschwerpunkt des Körpers Richtung Standbein verlagert wird um das Schwungbein zu entlasten [74, 75]. APAs reliabel zu messen ist besonders in Hinblick auf die Untersuchung von Interventionseffekten wichtig, um die Mechanismen der Ganginitiierung zu erforschen und ebenso den Einfluss von Aufmerksamkeit auf das Gangbild zu quantifizieren. APAs und die Parameter des ersten Schrittes können mit inertialen Messeinheiten (*inertial measurement units*-IMUs) detektiert werden [171]. Bisher ist unklar wie viele Versuche ausgeführt werden müssen, um reliable Daten zum Prozess der Ganginitiierung zu erhalten. Deshalb wurde in dieser Studie die Reliabilität von mehreren Versuchen innerhalb einer Testung untersucht und des Weiteren der Einfluss von Pathologie (Morbus Parkinson mit Gangfreezing – MP+FOG) und Ablenkung (mit und ohne kognitive Zusatzaufgabe, *single task* (ST) und *dual task* (DT)) auf die Reliabilität näher beleuchtet.

Ziel der Studie: Die Reliabilität der APAs-Messung mit IMUs innerhalb einer Testung bei gesunden Älteren (*healthy controls*-HC) und Personen mit MP+FOG soll untersucht werden. Außerdem soll getestet werden, ob sich die Reliabilität unter ST und DT Bedingungen unterscheidet, sowie ob es systematische Fehler zwischen den untersuchten Tests gibt.

Methode: Achtunddreißig Personen mit MD+FOG (unter Medikation) und 30 gleichalte HC wurden untersucht und absolvierten hierzu jeweils 5 Ganginitiierungen mit und ohne kognitiver Zusatzaufgabe. Die APAs und Parameter des ersten Schrittes wurden mit Hilfe von IMUs am unteren Rücken und auf den Füßen aufgezeichnet. Intraklassen Korrelationen (ICCs: basierend auf Einzelwert (2,1) oder Mittelwert (2,k)) sowie Standardfehler der Messung wurden berechnet, um die Reliabilität zu untersuchen, während gemischte Modelle zur Untersuchung potenzieller systematischer Fehler herangezogen wurden. Zusätzlich wurde noch eine mathematische Schätzung der Anzahl an Versuchen für die Erreichung einer akzeptablen Reliabilität (ICC>0.75) für jeden Parameter durchgeführt.

Ergebnisse: ICCs(2,k) waren über 0.75 bei der medio-lateralen (ML) Größe der APAs, bei der *Range of motion* (ROM) des ersten Schrittes und bei der Schrittgeschwindigkeit (nur ST) und zwischen 0.5 und 0.75 bei der anterior-posterioren (AP) Größe des APAs (nur ST), APA Dauer und bei der Latenzzeit des erste Schrittes bei PD+FOG und HC. ICCs unter DT Bedingungen

waren vergleichbar zu den ST ICCs, mit Ausnahme von AP APA Größe bei MP+FOG und Schrittgeschwindigkeit bei HC, wo die Reliabilität unter DT Bedingungen geringer war (ICC<0.75). Die Anzahl der benötigten Trials zum Erreichen von akzeptabler Reliabilität variierten je nach Parameter zwischen 1 und 16. Für die ML APA Größe und ROM des ersten Schrittes (außer ST bei MP+FOG) war die geschätzte Mindestanzahl der benötigten Trials bei 2 für MP+FOG und bei lediglich 1 für HC. Es gab einen systematischen Fehler für das erste *Trial* der ROM des ersten Schrittes, welche im Vergleich zu den darauffolgenden 4 *Trials* signifikant niedriger war; dieser Effekt war stärker bei MP+FOG.

Diskussion: Die Reliabilität variierte zwischen den APA- und Schritt-Parametern, was auch mit vorherigen Ergebnissen übereinstimmt [171], zwischen HC und MP+FOG ist sie jedoch vergleichbar. Das Durchführen einer zusätzlichen kognitiven Aufgabe führte zu reduzierter Reliabilität bei der AP Größe der APAs bei MP+FOG und der Schrittgeschwindigkeit bei HC, während sich bei den anderen Parametern im Vergleich zu ST Bedingungen eine ähnliche Reliabilität zeigte. Die Durchführung von 2 Trials reichte für die reliable Messung von ML Größe des APAs und ROM des ersten Schritts (außer ST bei MP+FOG) aus, jedoch werden für die anderen Parameter mehr Trials benötigt. Die sehr gute Reliabilität der ROM des ersten Schritts, stärkt das Potenzial dieses Parameters als ein wichtiges Outcome bei der Ganganalyse und die Möglichkeit ihn als Parkinson Progressionsmarker zu verwenden [191].

Fazit: In Abhängigkeit des Outcomes welches untersucht wird, sollten in zukünftigen Studien mindestens zwei jedoch idealerweise mehrere Trials der Ganginitiierung durchgeführt werden um reliable Daten über die Ganginitiierung bei gesunden Älteren und Personen mit MP+FOG zu erhalten.

Zusammenfassung Studie 3

Theoretischer Hintergrund: Mithilfe eines Split-Belt-Laufbands (SBT) ist es möglich das Gangbild zu modellieren, insbesondere Gangasymmetrie. Vor allem Patienten mit neurologischen Erkrankungen wie MP, bei denen Asymmetrie durch die Lateralisierung der Erkrankung eine Rolle spielt, können davon profitieren [78, 105].

Ziel der Studie: Diese systematische Übersicht evaluiert die Literatur zu SBT bei Personen mit MP. Zuerst wurden verschiedene methodische Herangehensweisen und Einstellungsoptionen

des SBT zusammengefasst. Anschließend wurde analysiert, wie sich Personen mit MP an verschiedene Bedingungen auf dem SBT anpassen können.

Methode: Es wurde eine systematische Literaturrecherche auf den Datenbanken PubMED, PsychINFO und Web of Knowledge durchgeführt. Folgende Suchbegriffe wurden verwendet: *(split-belt* OR split belt OR splitbelt OR walking adaptation OR gait adaptation OR locomotor adaptation OR motor adaptation OR motor learning) AND parkinson**. Es wurden ausschließlich Originalartikel in englischer Sprache, welche die Anwendung von SBT bei Personen mit MP untersucht haben, eingeschlossen.

Ergebnisse: Von 925 bei der Literatursuche identifizierten Artikeln, entsprachen sieben den Einschlusskriterien und wurden somit für die Evaluation ausgewählt [39, 78, 105, 212-215]. Insgesamt wurden in den ausgewählten Studien 118 Personen mit Parkinson, davon 44 mit Gangfreezing, untersucht. Die SBT Einstellungen, die untersuchten Gangvariablen und ihre Berechnung, sowie die Kriterien zur Bestimmung der dominanten Körperseiten waren in den verschiedenen Studien sehr unterschiedlich. Personen mit MP konnten ihre Gangvariabilität und bilaterale Koordination auf dem SBT ähnlich wie gesunde Kontrollprobanden anpassen. Die Untersuchungen zu Unterschieden bei der Anpassung der Gangasymmetrie von Personen mit MP und gesunden Kontrollprobanden zeigten gemischte Ergebnisse. Hatten die Personen zusätzlich das Symptom Gangfreezing, konnten sie sich langsamer an die Bedingungen auf dem SBT anpassen und hatten zudem Schwierigkeiten die unterschiedliche Geschwindigkeit der Laufbandseiten wahrzunehmen.

Diskussion: Diese systematische Übersicht zeigt, dass keine Bedenken bezüglich der sicheren Anwendung von Split-Belt-Laufband bei Personen mit MP bestehen. Außerdem liefert sie erste Hinweise, dass das Gehen auf dem Split-Belt-Laufband das Gangbild von Personen mit MP positiv beeinflussen kann, denn die Personen mit MP zeigen ähnliche Anpassungsmuster wie Gesunde im gleichen Alter [39]. Da die untersuchten Gangparameter und verwendeten Einstellungen auf dem SBT sich stark unterschieden, ist es wichtig diese zukünftig entsprechend der Zielsetzung des Studienprotokolls zu wählen. Des Weiteren müssen für die Durchführung eines solchen Protokolls mit Personen mit MP bestimmte Sicherheitsvorkehrungen getroffen werden, wie das Tragen eines Sicherheitsgurts, die Durchführung einer Eingewöhnungsphase, die Verfügbarkeit eines Handlaufs und der Ausschluss von Kontraindikationen.

Fazit: Probanden mit milder bis moderat schwerer Parkinsonerkrankung konnten sich ähnlich wie gesunde Kontrollprobanden bezüglich ihrer Gangvariabilität und bilateralen Koordination an das SBT anpassen. Jedoch hatten die Personen mit MP+FOG Probleme bei der Wahrnehmung der unterschiedlichen Geschwindigkeiten der Laufbandseiten und konnten ihr Gangbild nicht so schnell anpassen [214]. Trotz des Potenzials des SBT für die Modulation von Gangasymmetrie, konnten nicht alle Studienteilnehmer*innen mit MP davon profitieren. Wir empfehlen die Standardisierung von SBT Protokollen für zukünftige Studien in diesem Forschungsfeld.

Zusammenfassung Studie 4

Einleitung: Gangfreezing bei Personen mit MP ist mit Gangasymmetrie und einer reduzierten motorischen und kognitiven Anpassungsfähigkeit assoziiert [42, 105]. Das SBT ist ein Tool was beide Defizite adressieren kann und somit als potenzielle Therapiemöglichkeit sehr interessant ist.

Ziel der Studie: Die direkten Effekte sowie Kurzzeiteffekte einer Trainingseinheit auf dem SBT im Vergleich zu konventionellem Laufbandtraining auf die Gangasymmetrie bei Personen mit MP und Gangfreezing und gesunden Älteren zu untersuchen. Zudem soll die Effektivität drei unterschiedlicher SBT Trainingsprotokolle verglichen werden, sowie ein geeigneter Parameter zur Untersuchung von Gangadaptation auf dem SBT festgelegt werden.

Methode: Personen mit MP+FOG (n=45) und gesunde Ältere (n=36) wurden in eine von drei SBT-Gruppen (Laufband *Ratio* 0.75:1, 0.5:1 oder wechselnde *Ratios*) oder eine konventionelle Laufbandgruppe (*tied-belt training* - TBT) randomisiert. Die Studienteilnehmer*innen wurden vor (*Pre*), direkt nach (*Post*) und 24 Stunden nach (*Retention*) der Trainingseinheit untersucht. Während eines standardisierten Adaptationstest auf dem SBT wurde Gangasymmetrie gemessen.

Ergebnisse: Das Training auf dem SBT zeigte positive Effekte auf die Ganganpassungsfähigkeit sowohl bei Personen mit MP+FOG als auch bei gesunden Älteren ($p<0.0001$), wobei sich die Gesunden stärker verbesserten. Die Gruppe, welche unter wechselnden SBT Bedingungen trainierte zeigte eine signifikante Verbesserung der Ganganpassungsfähigkeit von *Pre* zu *Post* bei den Personen mit MP. Dies wurde ebenfalls durch große Effektstärken bestätigt wir ($d=1.14$) und die Effekte hielten bis zu 24 Stunden an. Die mittlere Schrittlängenasymmetrie

beim erstmaligen Gehen auf dem SBT war bei den gesunden Älteren niedriger als bei den mit MP erkrankten Proband*innen (p=0.035) und ist somit geeignet, um zwischen den Gruppen zu differenzieren.

Diskussion: Personen mit MP+FOG konnten ihre Ganganpassungsfähigkeit nach einer einzelnen Trainingseinheit auf dem SBT verbessern, jedoch sind die Effekte kleiner als bei Gesunden. Die Verbesserung der mit dem Gangfreezing zusammenhängenden Gangasymmetrie durch nur eine einzige Trainingseinheit ist vielversprechend. Wiederholtes Training auf dem SBT könnte sich sogar positiv auf die Konnektivität bestimmter Hirnregionen auswirken [247]. Außerdem könnte das Trainieren der Anpassungsfähigkeit auf dem SBT mit der Automatisierung des Gangbilds helfen [202], welche besonders bei Personen mit Gangfreezing Defizite aufweist. Das Trainieren unter wechselnden SBT Bedingungen war bei der Verbesserung der Ganganpassungsfähigkeit am effektivsten, vermutlich da besonders schnelle und flexible Anpassungsfähigkeit des Gangbilds trainiert wurde, wobei Personen mit MP+FOG oft Schwierigkeiten haben [101].

Fazit: Diese Erkenntnisse bilden die Grundlage für zukünftige Studien bezüglich der Langzeiteffekte von Split-Belt-Laufbandtherapie und potenzieller positiver Effekte auf das Symptom Gangfreezing.

Fazit

Diese Arbeit konnte durch die Validierung einer deutschen Version des NFOG-Q einen Beitrag zur einheitlichen Erhebung des Schweregrads von Gangfreezing im deutschsprachigen Raum beisteuern. Es wurde außerdem die Reliabilität der Erhebung von Parametern bei der Ganginitiierung von gesunden Älteren und Personen mit MP+FOG überprüft und Empfehlungen für zukünftige Untersuchungen ausgesprochen. Split-Belt-Laufbandtherapie wurde als neue Trainingsform der aktivierenden Therapien zu Behandlung von Gangstörungen untersucht. Eine systematische Übersicht der Literatur bestätigt die Anwendbarkeit und zeigt erste Kurzzeiteffekte bei M. Parkinson. Abschließend wurden auf Basis dieser Erkenntnisse verschiedene Trainingsbedingungen auf dem Split-Belt-Laufband verglichen. Die Arbeit zeigt positive Effekte von einer Einheit Split-Belt-Laufbandtherapie auf die Ganganpassungsfähigkeit als wichtiger mit *Freezing* in Zusammenhang stehenden Gangdefizit. Außerdem konnten bedeutende Informationen für das Design zukünftiger, langfristiger Trainingsinterventionen gewonnen werden.

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