universität wien

MASTERARBEIT / MASTER'S THESIS

Titel der Masterarbeit / Title of the Master's Thesis

Cycling interventions in the treatment and research of Parkinson's disease

verfasst von / submitted by

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angestrebter akademischer Grad / in partial fulfilment of the requirements for the degree of

Master of Science (MSc)

Wien, 2020 / Vienna 2020

Studienkennzahl lt. Studienblatt / degree programme code as it appears on the student record sheet:	A 066013
Studienrichtung lt. Studienblatt / degree programme as it appears on the student record sheet:	Joint Degree Programme MEi: CogSci Cognitive Science
Betreut von / Supervisor:	Prof. Dr. Sarang Dalal

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Acknowledgements

I would like to thank Sarang for his interest to engage into the meta-analysis project on cycling and Parkinson´s disease, and for his openness of transforming the project into this master's thesis. Also, I am grateful as I think that this project has since its establishment enabled me to combine my passion for bicycling with research.

Abstract

Parkinson's disease (PD) is a progressive neurodegenerative disorder leading to compromised motor performance with impairments in gait and posture, tremor, stiffness, and slowness of movement. In addition, cognitive and affective deficits are common. To alleviate their symptoms, PD patients are encouraged to engage in physical exercise. Cycling has been reported to be a particularly suitable form of physical activity for PD patients, yet further information on the exact exercise parameters, and beneficial outcomes is needed. Furthermore, based on the observation that many PD patients are able to ride a bicycle with notable ease when contrasted with walking, cycling has proven to be an intriguing object of inquiry for neuroscientists to investigate the impacted motor network in PD by applying electrophysiological methods to compare cortical and sub-cortical motor control in PD while walking and cycling.

The goal of this thesis is to outline the benefits of cycling for PD patients from the perspective of clinicians, researchers, and the patients themselves. To this end, a meta-analysis and a review was conducted to find out how much and how consistently PD patients benefit from cycling and which PD related symptoms cycling improved. Studies investigating the preserved cycling ability are presented and discussed in reference to the complexity of the PD symptoms and defect motor control. Furthermore, the preserved ability to ride a bicycle while being possibly severely impaired physically, is briefly discussed from the perspective of embodiment and the sociology of cycling. It is pointed out that environmental design which considers individuals with varying motor and cognitive capacities can either worsen the consequences of the PD -related symptoms, or alleviate them by promoting the feeling of inclusion and belongingness to the society.

The meta-analytical review on 22 studies with 395 PD patients demonstrated that motor outcomes benefitted from cycling significantly more than cognitive measures. In particular, it was shown that balance, walking pace and capacity, and the overall life-quality of the patients improved as a result of cycling. The exercise interventions varied in their durations, intensities, and target cadences. Further research and systematic reporting is needed on the exercise parameters of intensity and cadence in particular. Also, the most disabling symp-

toms of freezing and falling, or the fear of falling should be measured in response to cycling exercise.

It is concluded that cycling is particularly beneficial for the functional performance of PD patients, improving crucial features of gait. Moreover, the findings suggest that cycling improves the overall quality of life of PD patients.

Introduction

Despite the facts that PD is known to be caused by the loss of dopaminergic neurons in the midbrain (Galvan and Wichmann, 2008), in practice a clinical diagnosis of PD is based on the presence of cardinal motor symptoms (Pedersen, 2008). The most recent MDS (Movement Disorder Society) Clinical Diagnostics Criteria for PD considers the three motor symptoms bradykinesia, tremor, and rigidity as the cardinal markers of the disease (Tysnes & Storstein, 2017). Typically, the motor symptoms manifest as slowness of movement; decreased walking velocity and paucity in the associated movements; shortened stride length; and stooped posture (Purves, Augustine, George, Fitzpartrick, et al., 2012). PD has long and complex preclinical and prodromal phases with several motor- and non-motor markers (Mahlknecht, Seppi, & Poewe, 2015; Pellicano et al., 2007).

Next to applying pharmacological and surgical treatments to treat PD patients, physical training and activity have been shown to have disease modifying effects leading to slowing down the disease progression, to an enhanced quality of everyday life, and to symptom alleviation (Abbruzzese, Marchese, Avanzino, & Pelosin, 2016; Delgado-alvarado, Marano, & Santurtún, 2020). Among the available forms of physical training, cycling is a form of aerobic exercise, and can still be an option for patients who find it difficult to walk over ground or on a treadmill (Ellis, 2020). In 2010 it was reported that some individuals diagnosed with PD, while exhibiting severe freezing of gait (FOG), were nevertheless able to ride a bicycle (Snijders & Bloem, 2010). Since then, the preserved skill to ride a bicycle, while otherwise being limited by the symptoms of PD, has been shown to positively influence cardiovascular fitness, motor skills, and overall coping, feeling of independency, social inclusion, and cognitive skills (Alberts, Linder, Penko, Lowe, & Phillips, 2011; Ridgel, Abdar, Alberts, Discenzo, & Loparo, 2013; Ridgel, Phillips, Walter, Discenzo, & Loparo, 2015; Snijders, van Kesteren, & Bloem, 2012).

Next to possibly being useful for PD patients, cycling is a particularly intriguing phenomenon also from the perspective of research when investigating the motor network of the diseased

brain. The difference in the fluency of movement during riding a bicycle compared to walking can be striking among the patients (Snijders, Toni, Ružička, & Bloem, 2011). This observation has led to studies investigating whether the preserved ability to bicycle underlies a particular mechanism, or whether this ability can be used as a marker to differentiate among various subtypes of symptoms, and contribute to the understanding of the dysfunctional motor circuit in PD (Arens et al., 2019; Gratkowski et al., 2017; Storzer et al., 2016, 2017).

Based on the above enlisted relevance of cycling in clinical practice and in research, and on the growing number of studies implementing cycling interventions in PD, a meta-analysis with a literature review on cycling exercise in PD was conducted. The goal was to find out how much and how consistently PD patients benefit from cycling and which PD related symptoms could improve from cycling. Also, it was investigated which intervention characteristics correlate with PD symptom improvement. The database for medical literature was searched to identify studies with randomized control trials (RCT), and non-randomized trials (NRCT) investigating the effects of cycling on PD patients. Out of 202 references, 22 eligible studies with 395 patients were analysed. An inverse variance-based analysis on the primary and secondary measures with sub-levels was conducted. A quality analysis addressing reporting and study design of the studies was also undertaken. From the primary measures, motor outcomes benefitted from cycling significantly more than cognitive measures. Also, across primary and secondary measures, functional outcomes demonstrated a significant benefit. Additionally, it was shown that balance, walking pace and capacity, and the Parkinson's disease questionnaire-39 (PDQ39) ratings improved as a result of cycling, while the cycling interventions varied in their durations, intensities, and target cadencies. Conclusively, the results showed that cycling is particularly beneficial for the functional and physical performance of PD patients, improving crucial features of gait. Moreover, the findings suggest that cycling improves the overall quality of life of PD patients. Based on the meta-analytical review, future perspectives are laid out; intervention-related features and rarely investigated outcome measures are pointed at.

Despite the fact that this thesis tackles a problem defined by clinical medicine – Parkinson's disease – both the phenomenon itself and the forms of treatment are complex and require interdisciplinary expertise. In the scope of this thesis, it becomes evident that if the ultimate

goal of developing a treatment paradigm is the support of independent and enhanced quality of life of PD patients, an understanding of the human mind & body beyond clinical medicine is required. Thus, despite the focus of this thesis being the clinical features of PD and the meta-analytical review of cycling exercise, PD is discussed from the perspective of the individual's relationship to the environment with the help of a bicycle. This will be done by considering cycling as a complex activity involving environmental design, sensory multimodality and the subjective experience. Literature on embodied cognition as well as cycling-related urban and environmental design will form the basis of this brief discussion.

The thesis concludes with the notion that in order to develop an optimized and personalized cycling exercise regimen for PD patients, more knowledge is needed on some of the most disabling features of PD such as fear of falling, and freezing of Gait. In addition to target an exercise regimen more efficiently, additional systematic investigations on the exercise specific parameters are required. Furthermore, it is emphasized that emotions, self-agency, and the feeling of belongingness into the immediate environment of the individual could be valuable aspects to consider in developing an enhanced quality of life of PD patients.

1. Parkinson's disease

1.1 Prevalence

Idiopathic Parkinson's disease (PD) is a hypokinetic neurodegenerative disorder, which belongs to the group of Parkinsonian disorders (Dickson, 2012)[1]. PD and its characteristic symptoms were first described by James Parkinson 1817 (Parkinson, 1817). 100 years later it was discovered that individuals suffering from PD also had a loss of dopaminergic cells in the substantia nigra pars compacta (Dauer & Przedborski, 2003). Finally, in 1957 it was found out that the neurotransmitter dopamine (DA) was relevant to PD, and soon afterwards, in 1960, it could be concluded that PD patients had notably decreased levels of dopamine in the striatum (Jankovic, 2008).

Out of all individuals diagnosed with PD, 95% of the cases are sporadic, meaning that the disease is not inherited, yet it has been established that some genes are more susceptible to the deterioration of the DA neurons, than others, making some individuals more susceptible of developing PD during the course of their lives (Dauer & Przedborski, 2003). Currently, it is estimated that in 5 to 10% of the diagnosed cases have a genetic factors involved (Tysnes & Storstein, 2017). Thus, possible biomarker-based diagnosis aids, such as genetic mutations or variants, or abnormalities in the brain, still require further investigation (Jankovic, 2008). Often times PD patients give a clumsy impression, yet the clumsiness might be underlined by pathologically different types of motoric disorders, thus it is crucial that the symptoms are evaluated in the context of each patient (Berardelli, Rothwell, Thompson, & Hallett, 2001; Jankovic, 2008). Also, the disease progression seems to be non-linear, so that deterioration might take place more quickly in the early years of the disease, slowing down later (Jankovic, 2008). Indeed, many of the PD symptoms are difficult to separate from other similar aging related deficits, and the symptoms might manifest differently between the individuals due to different profiles and lifestyles (Jankovic, 2008).

[1] Parkinsonism is a clinical term for a group of movement disorders with heterogeneous pathologies, with similar cardinal manifestations as in PD, such as bradykinesia, rigidity, and tremor. Parkinsonian disorder is a term used to describe disorders in which Parkinsonism is a crucial feature. All degenerative Parkinsonian disorders are characterized by the loss of dopaminergic neurons in the substantia nigra. Idiopathic Parkinson´s disease is a parkinsonian disorder, and belongs to Parkinsonism (Dickson, 2012).

Methodological differences between studies make prevalence estimates seem inaccurate and difficult to compare: Incidence per 100 000 persons vary between from 100 to and 200, with an annual occurrence rate of 15 per 100 000 (Tysnes & Storstein, 2017), making it, the second most common degenerative disease of the nervous system after Alzheimer's disease (Dauer & Przedborski, 2003; Purves, Augustine, George, Fitzpatrick, et al., 2012). A typical onset age of PD is 65 to 70 years, individuals younger than 40 diagnosed with PD are rare with a prevalence of less than 5% of the population cohort (Tysnes & Storstein, 2017). Overall, 0.3% of the population is affected by PD, whereas men seem to have a higher risk of the disease than women (de Lau et al., 2004).

1.2 Diagnosis

Since there is no test to diagnose the disease, the diagnosis is based on observing several clinical criteria with bradykinesia, tremor, loss of postural reflexes, and rigidity being the most common ones. Furthermore, over time the responsivity to dopamine agents is being considered when establishing the diagnosis (Rizek, Niraj, & Jog, 2016). The disease progression, in particular the aspects related to motor impairment and the related disabilities, are followed with different scales. One of the most common scales to estimate the progression of the disease is *Hoehn and Yahr-scale*, first established in 1967 (Hoehn & Yahr, 1967). The *Hoehn and Yahr-scale* is designed to compare groups of patients ranging from no signs of disease to wheelchair or bedridden stages on a scale of five stages, the first stage being the mildest form of the disease. In the following each stage is described based on the characteristic symptoms and features that separates the stages form one another ("Diagnosis Rating Scales," 2020): The stages one and two are both considered as early stages of the disease, and the stage two can take from months to years to develop from the stage one. The stage one is characterized with unilateral symptoms with minimal to no functional impairment. In the second stage the symptoms are bilateral, and the stage is characterized by several types of symptoms ranging from abnormal function in the facial muscles, speech, and posture to general slowness in daily activities. The deficits of stages one and two can easily be misattributed as normal aging, in particular if stage one is skipped, and no tremor arises in stage two. In stage two, balance is severely compromised, and the most common symptoms of PD are present such that a correct diagnosis is fairly straightforward. The third stage is

considered an intermediate stage and a crucial difference to the following stage four is that the patient can still lead a fully independent life. In stage four, the disease is severely disabling, and the patient might need assistance in walking and standing. In the last stage five, the patient is bound to a bed or wheelchair, might suffer from hallucinations and delusions, and require constant assistance ("Diagnosis Rating Scales," 2020).

For disability and impairment assessment, the most widely used clinical rating scale is the *Unified Parkinson's Disease Rating Scale* (UPDRS) originally developed in the 1980s (Fahn, 1987). The UPDRS is the most commonly used tool to assess the efficacy of treatment benefits of PD (Goetz, 2010). The original version consists of 42 items categorized in 4 sub-scales addressing different features of the disease: Part I assesses behaviour and mood related aspects such as intellectual decline, hallucinations, and depression; part II focuses on patients' subjective ratings of their ability to carry out activities of daily living, such as getting dressed, walking, and eating; part III assesses the degree of motor symptoms, including ratings for tremor, slowness (bradykinesia), stiffness (rigidity), and balance; lastly, part IV deals with treatment complications such as ratings of involuntary movements (dyskinesias), painful cramps (dystonia), and irregular medication responses (motor fluctuations) (Goetz, 2010; Martinez–Martin, Rodriguez-Blazquez, & Forjaz, 2017). Since then, the scale has been updated by commission of the Movement Disorder Society (Goetz et al., 2008), and it has been renamed the MDS-UPDRS score. The original 4 sub-scale structure was maintained. The modifications mainly concerned the scale specificity, also some overlapping items were removed, and some added. Furthermore, some linguistic and culture-specific modifications were made (Fish, 2011).

1.3 Symptoms of Parkinson's disease

It seems that the classification criteria, and the degree to which the symptoms of the different motoric and cognitive deficits are considered to represent pathologically different forms of PD varies in the literature (see Berardelli et al., 2001; Jankovic, 2008). Also, it seems the disease diagnostic criteria and the categorisation of the cardinal symptoms seem to vary with the time and accumulating knowledge of the disease. For example, tremor, rigidity, and akinesia, also known as bradykinesia and postural instability, summarized as TRAP, have been considered as the four main symptoms for diagnosing PD (Jankovic, 2008). Currently,

the most recent MDS (Movement Disorder Society) Clinical Diagnostics Criteria for PD has left the postural changes and postural instability out of the cardinal symptoms, and considers the three motor symptoms bradykinesia, tremor, and rigidity as the cardinal markers of the disease (Tysnes & Storstein, 2017). Furthermore, supportive criteria, absolute exclusion criteria and red flags (criteria which must be counterbalanced by additional supportive criteria to allow diagnosis of PD) are defined in the new diagnostic criteria (Postuma, Berg, Stern, Poewe, Olanow, et al., 2015). In practice this means that the cardinal symptom of bradykinesia must be accompanied by tremor, rigidity, or both. The supportive criteria include both motor and non-motor aspects of the disease, such as responsivity to dopaminergic therapy, asymmetric rest tremor, and the loss of olfactory sense. Absolute exclusion criteria are among other features, cerebellar abnormalities, supranuclear gaze palsy, frontotemporal cognitive changes, and cortical findings like apraxia. Early gait impairment, lack of progression in the symptoms, absence of the most common non-motor symptoms such as sleep dysfunction, and early antecollis (excessive forward flexion of the neck) have been implicated as red flags. Like previous criteria, also the updated MDS criteria are based on a two-step process of diagnosing PD. First, parkinsonism is diagnosed – in practice bradykinesia with either rest tremor, rigidity, or both – and then the criteria is applied to decide whether existing symptoms are attributable to PD (Postuma, Berg, Stern, Poewe, Olanow, et al., 2015). The new diagnostic criteria is designed so that it would lead to an improved accuracy of the diagnosis of PD such that the clinical markers are more aligned with the neuropathologically confirmed cases (Postuma, Berg, Stern, Poewe, Marek, et al., 2015; Tysnes & Storstein, 2017). Thus, a clinical diagnosis is fulfilled when at least two supportive criteria can be detected, and the absence of absolute exclusion criteria and red flags can be confirmed.

Not all PD patients exhibit all the symptoms; they might occur in different stages of the disease progression, be indicators of later being diagnosed of having PD, or they may correlate positively, or negatively with each other (Jankovic, 2008). For example, it is known that patients who are at risk of developing freezing often also have rigidity, bradykinesia, postural instability and longer duration of the disease, whereas tremor during the onset of PD, predicts a decreased risk of freezing (Jankovic, 2008). Below the most common symptoms of PD are described and discussed in more detail.

1.3.1 Bradykinesia

Bradykinesia is a disorder in the basal ganglia and a very characteristic, and one of the most early clinical features of Parkinson's disease (Jankovic, 2008). In the literature *bradykinesia*, *akinesia*, and *hypokinesia* are often used interchangeably, nevertheless despite all being symptoms of basal ganglia hypofunction, they are clinically different phenomena (Simões & Litvan, 2010). *Akinesia* is difficulty or inability in movement initiation, *hypokinesia* is decreased amplitude of movement, and *bradykinesia* is general slowness in overall movement (Simões & Litvan, 2010). Akinesia will be discussed in further detail in the chapters to follow. Behaviourally typical for bradykinesia is slowness of all kinds of movements from performing daily activities to reaction times, involving difficulties in planning, initiating and executing movements (Jankovic, 2008). Bradykinesia can be categorized as primary and secondary bradykinesia depending on the factors contributing to it (Berardelli et al., 2001). The secondary type of bradykinesia is considered to be entangled with other typical Parkinsonian symptoms of muscle weakness, rigidity, tremor and movement variability such that it is difficult to separate the symptoms and their contributing factors from one another (Berardelli et al., 2001). Strictly speaking, the primary bradykinesia is the core disorder of central movement control, which cannot be explained by the above listed secondary factors (Berardelli et al., 2001). Most likely the deficit underlying the primary bradykinesia is related to insufficient recruitment of muscle force during the movement initiation (Berardelli et al., 2001). Due to the decreased electromyographic activity, PD patients suffering from bradykinesia have problems to activate the correct muscles and they lack the required force to actually initiate and maintain large movements (Jankovic, 2008). Furthermore, typical for Parkinsonian bradykinesia is its paradoxical occurrence, kinesia paradoxica, since PD patients with bradykinesia might be able to make quick movements such as catching a ball when excited, or even running in the case of an emergency, meaning that the bradykinesia might depend on the current emotional state of the individual (Jankovic, 2008). In practice, this often means that the movement responsible motor programmes, that otherwise are compromised in PD, are somehow made possible by external triggers, such as loud sounds, music, or visual cues, thus enabling the movement.

1.3.2 Tremor

In general, tremor is rhythmic and involuntary muscle contraction manifesting as trembling movements in one or more parts of the body ("Tremor fact sheet," 2020). Overall, tremor is classified in two classes, *resting tremor*, and *action tremor*, with action tremor having several sub-classes ("Tremor fact sheet," 2020). Furthermore, as different types of tremors are characteristic to different movement disorders, the specific phenotypes often are categorized in accordance with the specific mechanism, or disorder underlying the tremor.

In PD the most common type of tremor is rest tremor (Hallett & Deuschl, 2010) which manifests during rest and relaxation, for example while lying still in bed, but not during sleep or during movement execution (Jankovic, 2008; "Tremor," 2020). In PD, resting tremor is unilateral and occurs in the frequency of 4 to 6 Hz. Resting tremor in PD is common in the hands, in particular in the distal part of the extremities (Jankovic, 2008). Due to several overlapping clinical features, rest tremor is easily confused with essential tremor, which is, similar, yet constitutes another movement disorder (Shahed & Jankovic, 2007; "Tremor," 2020). When differentiating essential tremor from parkinsonian rest tremor, care should be taken in observing the differences in tremor frequency, direction (increase / decrease) of the tremor in response to modifying factors such as rest, action or walking, and responsivity to pharmaceuticals (Jankovic, 2008)

Postural tremor, which belongs to the class of action tremor, is also fairly common among PD patients. Postural tremor is shortly defined as tremor that occurs when a person is maintaining a steady position against the gravity, like having arms stretched out to the front ("Tremor fact sheet," 2020). The distinction between the types of tremors is not always clear, yet according to a rough distinction between tremor at rest and postural tremor, can be the increased tremor frequency of postural tremor. Furthermore, rest tremor is assumed not to be related to dopamine deficit (Hallett & Deuschl, 2010). Among the types of postural tremors, it has been suggested that at least two phenotypes - *pure postural tremor* and *re-emergent tremor* - should be considered separately, as they have been shown to have different pathophysiological basis and thus require different types of treatment (Dirkx, Zach, Bloem, Hallett, & Helmich, 2018). *Re-emergent tremor* is a continuation of resting tremor reoccurring after transition from rest to posture, and it is related to dopamine deficit (Dirkx et al., 2018; Hallett & Deuschl, 2010). Pure postural tremor has a non-dopaminergic basis, and also occurs less frequently (Dirkx et al., 2018).

It seems that a clear understanding of the phenotypes of tremors is yet to be achieved, due their various forms of origin and appearance. While there are clinical situations in which a definite diagnosis of the exact type of tremor does not add value to the diagnosis or to the patient, a further understanding is important as not all types of tremors respond equally to medication (Dirkx et al., 2018; Jankovic, 2008), and as some types of tremors can be an early marker of a later occurring movement disorder (Shahed & Jankovic, 2007).

1.3.3 Rigidity

Rigidity, or stiffness, manifests as increased resistance or as a sensation of tightness in the limbs, distally and proximally, in particular during passive movements such as flexion, extension or joint rotation (Jankovic, 2008). Despite the development of objective and quantitative methods, such as portable sensors or electromyography, rigidity is most commonly assessed with clinical scales (Ferreira-sánchez, Moreno-verdú, & Cano-de-la-cuerda, 2020). A large prospective study with participants with no dementia or parkinsonism showed that personal complaints of rigidity alike stiffness, with tremor and imbalance, correlated with an increased risk of developing PD (de Lau, Koudstaal, Hofman, & Breteler, 2006). This means that, prior to a standard clinical testing, a sensation of rigidity might be an early marker of decreased levels of dopamine and a subsequent PD diagnosis. Unlike the other cardinal symptoms described above, rigidity can be associated with pain, e.g., painful shoulder being a typical problem. During later stages of the disease, rigidity can also co-occur with postural deformities which lead to flexed neck, elbows, knees and trunk postures (Jankovic, 2008).

1.3.4 Akinesia and freezing of gait

One of the most disabling symptoms in PD akinesia. Akinesia is a term used to refer to a reduced spontaneous movement such as that of facial expressions or arm swing while walking, furthermore it consists of freezing and prolonged movement initiation (Berardelli et al., 2001). While not occurring in all patients diagnosed with PD, freezing of gait (FOG) is one of the most characteristic clinical markers of PD and atypical parkinsonism, usually occurring at an advanced stage of the disease (Giladi et al., 2001; Jankovic, 2008; Müller et al., 2002). Usually, freezing affects the legs, yet it can also influence arms and the eyelids (Jankovic, 2008). FOG can be categorized into five subtypes of freezing: start hesitation, turn hesitation, hesitation in tight quarters, destination hesitation and open space hesitation (Schaafsma et al., 2003). Typically, a person who suffers from freezing might hesitate before

starting to walk, or in specific situations such as busy crossings, narrow passages, stressful events, or when approaching the desired destination (Jankovic, 2008; Okuma, 2006). Alternatively freezing simply manifests as sudden and transient moments of movement inability (Jankovic, 2008). Thus, FOG can become particularly disabling due to the social and clinical consequences (Bloem, Hausdorff, Visser, & Giladi, 2004). Furthermore, FOG is a common cause for falling and subsequent injuries as the feet seem as if they were glued to the ground while the torso and the balance are still directed to go forward (Bloem et al., 2004). Empirical studies on freezing are challenging as freezing does not necessarily occur on demand during a doctor's visit or data collection (Schaafsma et al., 2003). Freezing has ON and OFF phases, which respond to medication differently. During the ON-period patients suffering from freezing do not receive alleviation from dopaminergic therapy. Freezing episodes are usually more severe in the OFF stage of the disease, during which the duration and frequency of FOG episodes can be successfully be treated with levodopa (Schaafsma et al., 2003).

1.4 Parkinson's disease and co-morbidities with other diseases and disorders

PD does have several co-morbidities with cognitive, affective and behavioural dysfunctions, yet PD-related co-morbidities are far less understood than the most common motor dysfunctions (Santiago, Bottero, & Potashkin, 2017). A further investigation of co-morbidities in PD is crucial as they often tend to have life-quality detrimentally impacting consequences. Common non-motoric symptoms that occur in the earliest stages of the disease are cognitive impairment (attention, working memory executive functions, language, visuospatial skills, and episodic memory), dementia, constipation, fatigue, hyposomia, restless legs syndrome (RLS), sleep behaviour disorder, urinary problems, drooling and hallucinations (Jankovic, 2008; Papagno & Trojano, 2017; Santiago et al., 2017; Schapira, Chaudhuri, & Jenner, 2017). Furthermore, cancer, anemia, depression and diabetes seem to be diagnosed increasingly in PD patients (Gustafsson, Nordström, & Nordström, 2015; Santiago et al., 2017). Non-motor comorbidities are a crucial part of the PD phenotype as it is the non-motor deficits, which do not respond to the common medication, that have been shown to be most disabling in the long term (Hely, Morris, Reid, & Trafficante, 2005).

1.4.1 Dementia and cognitive decline

Dementia is a major co-morbidity of non-motor origin in PD, in particular in the advanced stage of the disease (Emre et al., 2007; Szeto et al., 2020). Dementia and an overall decline in cognitive abilities are often discussed together as dementia is better understood as a syndrome having a co-morbidity with several neurologic, neuropsychiatric, and medical conditions, rather than as a specific disease (Gale, Acar, & Daffner, 2018). A crucial clinical feature of dementia related cognitive decline is that the consequences are severely influencing the daily life and independence of the patient. Broadly categorized dementia can be caused by neuro-degenerative and non-neurodegenerative disease, the former form of dementia being more common among the elderly population (Gale et al., 2018). In order to not to be confused with other types of dementia, strictly speaking, PD dementia (PD-D) is a form of dementia developing in the course of PD, occurring a minimum of one year after the diagnosis PD. Pathologically PD-D differs from other forms of neurodegenerative dementias by demonstrating an accumulation of alpha-synuclein aggregates in neurons and other cells in the nervous system of the affected brain (Gale et al., 2018; McCann, Stevens, Cartwright, & Halliday, 2014). Furthermore, similarly to dementia with Lewy bodies, also PDD pathology has Lewy body-type degeneration in the cerebral cortex and limbic structure (Emre et al., 2007). Fluctuating cognition with impaired attention, memory, visuo-spatial and executive functions, alertness variations, recurrent visual hallucinations, and apathy are common symptoms of PDD (Emre et al., 2007; Gale et al., 2018). In clinical practice, PDD often goes unrecognised and, as a result, is not appropriately treated. As with other PD comorbidities, also with PDD the need for a alertness for the clinical diagnosis and early recognition of PDD are highlighted due to side-effect, tolerance or responsivity differences depending on the pathology of the dementia (Gale et al., 2018; Poewe et al., 2008). Furthermore, a recent line of investigation has been proposed investigating whether a correlation between the level of education and the PDD pathology, or the risk of developing a PDD has been established (Szeto et al., 2020). These observations have led to the hypothesis that higher education, by enhancing cognitive capacity, could have a compensatory effect on the cognitive decline prior to the diagnosis of dementia (Hindle, Martyr, & Clare, 2014; Szeto et al., 2020).

1.4.2 Diabetes

Diabetes Mellitus (DM) is a group of diseases involving defective glucose metabolism, resulting in elevated levels of blood sugar (hyperglycemia) (Association, 2010). Since first reported, more than 60 years ago, there is an increasing number of studies reporting an association between PD and DM (Santiago et al., 2017; Sergi, Renaud, Simola, & Martinoli, 2019). As a matter of fact, a co-morbidity with diabetes and PD, and some other neurodegenerative diseases, such as Alzheimer´s disease and amyotrophic lateral sclerosis (ALS), has been reported so frequently that diabetes is being investigated as a possible cause for neurodegeneration (Santiago et al., 2017). Currently, it is not known which pathophysiological mechanism underlies the link between diabetes and PD. Yet, based on a recent retrospective cohort study, it was suggested that the link of PD and type II diabetes underlie a genetic predisposition such that individuals with diabetes are also more likely to develop PD (De Pablo-Fernandez, Goldacre, Pakpoor, Noyce, & Warner, 2018). Alternatively, or in addition to the genetic predisposition, a shared disrupted pathogenic mechanism was postulated, such that the cell mitochondria damage caused by the type II diabetes eventually contribute to the death or dysfunction of the dopaminergic cells leading to PD (De Pablo-Fernandez et al., 2018). The latter assumption is supported by the fact that dopaminergic neurons in the substantia nigra are particularly sensitive to (hyperglycaemia induced) oxidative stress, and to mitochondrial dysfunction (Sergi et al., 2019). Understanding the mechanism underlying the role of diabetes in the etiopathogenesis of PD could potentially reduce the risk of PD by improving the glycemic control and reducing the neuronal glucotoxicity of patients with diabetes (Sergi et al., 2019).

1.4.3 Depression

Depression with its variants are a common mood disorder with a high impact of disability socially, medically, and financially (Ménard, Hodes, & Russo, 2016). Among PD patients, just as in the general population, the most common forms of depression are major or minor depression, or persistent depressive disorder (PDD). The main difference between the major and non-major forms of depression being a longer duration, and larger diversity in the symptoms of the major forms (Marsh, 2013). Most common forms of care are psycho- cognitive-behavioural therapy and psychopharmacological drug treatment. Among PD patients, depression has a co-morbid prevalence of 35% to 50% (Hely et al., 2005), making it the most

common non-motoric symptom in the PD population (Aarsland, Pahlhage, Ballard, Ehrt, & Svenningsson, 2012). In comparison with other disease with a similar degree of disabling symptoms PD patients report depression more often (Nilsson, Kessing, Soerenssen, Andersen, & Bolwig, 2002). Like in the case of diabetes, it has been postulated that depression might have a causative role in developing PD since several epidemiological studies have shown that depression proceeds PD prior to the clinical onset of the disease (Gustafsson et al., 2015; Santiago et al., 2017).

Also, the mechanisms linking PD and depression are not fully understood. Currently the explanatory mechanism is searched in the biological domains of genetics and neurobiology, as it does not seem plausible the depression would be a mere psychological response to PD (Marsh, 2013; Santiago et al., 2017). To find direct predictors or causal relationships between the vulnerability of PD patients developing depression is hard, as most of the current studies are correlational studies finding neurobiological similarities between PD and depression (Marsh, 2013). For example, according to the long-standing serotogenic hypothesis, the serotonin activity, known to be reduced in PD, could be a physiological adaptation to the, likewise reduced dopaminergic activity, and could thus function as a risk predictor of depression while explaining the development of depression in PD (Mayeux, 1990). Nevertheless, a later experimental study could not detect such a direct relationship between depression and PD despite serotonin activity being lower in depressed PD patients than in healthy controls. It was concluded that serotonin perhaps has an indirect role in PD patients developing depression as regulator of other neurotransmitters, such as dopamine and noradrenalin (Leentjens, Scholtissen, Vreeling, & Verhey, 2006). Indeed, next to the serotonergenic hypothesis the role of dopamine has gained more attention. Explanatory links have been searched in brain structural changes caused by the degeneration of dopaminergic neurons and the Lewy bodies in the substantia nigra pars compacta (Aarsland et al., 2012; Marsh, 2013). These approaches are based on the take that the dopamine related lesions – which underlie the motor deficits of PD – extend their influence beyond the mid brain involving a loss of serotonergic, and noradrenergic neurons, and thus together influence the mood regulation and reward systems of the brain (Marsh, 2013).

Next to diagnosing PD, also detecting the co-morbidity with depression needs special attention as depression can easily go unnoticed in particular in the early stages of PD (Ravina et al., 2007). Indeed, neither PD nor depression have sufficiently validated biomarkers, and the

diagnosis is left largely to self-reports which might be challenging due to lack of overall understanding of depression in the context of PD; symptom overlap; individual differences, as well as patient-doctor differences in recording and reporting the symptoms (Looi, Matias, & Ruzich, 2005; Santiago et al., 2017). A good example of the difficulty of achieving a correct diagnosis is the persistence of depressive moods: It is normal for PD patients to have depressive affective states when adapting to live with the disease, but these states should be taken seriously if they seem to persist, and the patients will not adapt emotionally to cope with the disease (Marsh, 2013). Receiving an accurate diagnosis and the corresponding treatment is also complicated by the fact that some of the symptoms in major depression and PD overlap, meaning the depression might remain unrecognized (Marsh, 2013).

An untreated depression can have particularly severe consequences among PD patients, such as a need for early initiation of dopaminergic therapy, a more rapid cognitive and physical decline, increased mortality and care-giver stress (Hughes, Ross, Mindham, & Spokes, 2004; Ravina et al., 2007; Starkstein, Mayberg, Leiguarda, Preziosi, & Robinson, 1992)

1.4.4 Sleep disorder

Sleep disorders (SD) can have nocturnal and diurnal manifestations, and the come in diverse forms including rapid eye movement (REM) sleep behaviour disorder, insomnia and severe day time sleepiness (Loddo et al., 2017). Sleep disorders among PD patients range from 41% up to 78% with patients in advanced stages of PD reporting SD more often (Barone et al., 2009). For a long time SD was believed to be a mere side effect of pharmacological therapy given to the PD patients (Jankovic, 2008). Now it seems that depending on the type of the SD, it can have a different origin, including PD pathology and the discomfort caused by the motor symptoms (Arnulf et al., 2002; Loddo et al., 2017). For example, diurnal forms of SD could be caused by the dopaminergic treatment or, by dysregulated circadian sleep-wake rhythms caused by the actual loss of dopaminergic neurons (Breen, Vuono, Nawarathna, & Fisher, 2014; Loddo et al., 2017). Alternatively, the motor symptoms themselves, such as rigidity and bradykinesia, prevent the patients from changing their position in the bed and thus cause night-time SD (Peeraully, Yong, Chokroverty, & Tan, 2012). Sleep disorders are diagnosed and rated with PD-specific scales, such as the Parkinson's Disease Sleep Scale (PDSS), and the Scales for Outcomes in PD-Sleep (SCOPA-S) (Loddo et al., 2017). Also, polysomnography can be applied, as it is based on objective physiological parameters of sleep

measurement, though it has been applied rather rarely for research purposes (Peeraully et al., 2012).

2. Pathophysiology and neurophysiology of Parkinson's disease

2.1 Pathophysiology – Defect motor control

In terms of pathophysiology, a progressive, possibly decade-long degeneration of dopaminergic neurons in the substantia nigra pars compacta (SNc) is the reason for the characteristic motor deficits in PD (Galvan and Wichmann, 2008). Once the motor symptoms occur, it can be assumed that there is already a cell loss of 30-70% in the substantia nigra (Rizek et al., 2016). Next to the loss of the DA neurons, another pathologically characteristic process of PD is the accumulation of the Lewy bodies in several locations of the afflicted brain (Rizek et al., 2016). The Lewy bodies are a protein aggregation with α-synuclein (αSyn) as their main component. The emergence and the exact contribution of Lewy bodies to neurodegenerative disorders is not fully understood (Shahmoradian et al., 2019). Nevertheless, it is known that the Lewy body aggregates accumulate into anatomically different locations, enabling the observation of the disease progression in stages characterized with different symptoms (Braak & Del Tredici, 2017; Braak et al., 2003).

In the most simple terms, the symptom origin in PD is the failed neuronal disinhibition in the basal ganglia (Purves, Augustine, George, Fitzpatrick, et al., 2012). The basal ganglia consist of the neostriatum (caudate nucleus and putamen), the external and internal pallidal segments, the subthalamic nucleus (STN), and the substantia nigra. These regions form circuits involving thalamic and cortical areas, and can further be delineated into the motor, associative, and limbic loops depending on the function of the cortical area involved. It is the motor loop of the basal ganglia that is most impacted by PD (Galvan and Wichmann, 2008). The functioning of the motor loop can further be inspected as *direct*, and *indirect pathways* where the balance of inhibitory signals is altered leading to the hypokinetic symptoms of PD (Purves, Augustine, George, Fitzpatrick, et al., 2012) (Figure 1). This alteration has the consequence that the basal ganglia control over the thalamic output to the cortex is diminished.

Because of the loss of the dopaminergic neurons in the substantia nigra pars compacta, the input from those neurons to the caudate and putamen is diminished, further complicating the transient inhibitory tasks of caudate and putamen. Finally, this leads to a tonic inhibition from the globus pallidus to the thalamus, leading to a diminished excitation of the motor cortex (Purves, Augustine, George, Fitzpatrick, et al., 2012).

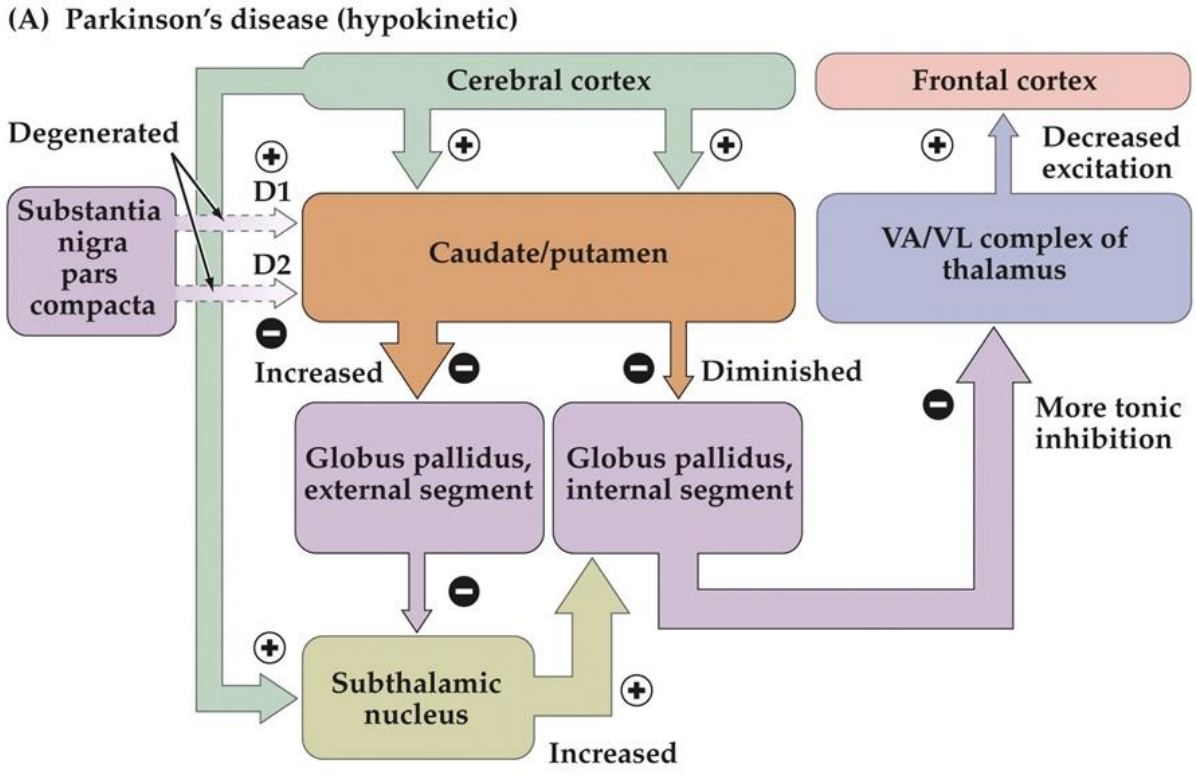

Figure 1. Movement control pathway in Parkinson's disease

Schematic representation of the neuronal mechanism underlying a hypokinetic movement disorder such as PD. The dopaminergic input from the substantia nigra pars compacta are reduced, as represented by the dashed arrows. This leads to a lack of inhibition from the caudate and putamen to the globus pallidus, leading to a sustained tonic inhibition from the internal segment of the globus pallidus to the thalamus. Finally, this has the consequence that the thalamic excitation of the motor cortex is reduced, as represented by the thinner arrows from the thalamus to the frontal cortex. (Image from Purves et al., 2012)

Despite that the loss of the dopaminergic neurons is known to be the cause of the disease, it is not known why these specific neurons begin to deteriorate in the first place, eventually

leading to the diagnosis of PD (Jankovic, 2008). Furthermore, the pathophysiology of PD is not fully understood, for example the specific involvement and changes in striatum, brainstem, thalamus and cortex are not as well understood as the changes in globus pallidus external (GPe), STN, globus pallidus internal (GBi), and substantia nigra pars reticulata (SNPr). Nevertheless, it can be concluded that with the abnormalities in the basal ganglia, thalamus and cortex, parkinsonism can best be understood as a disease of a distributed brain network (Galvan and Wichmann, 2008).

2.2 Neurophysiology – Abnormal oscillatory activity

The abnormal neurophysiological activity in the basal ganglia caused by the degeneration of the dopaminergic cells can methodologically be inspected as changes in the neural firing rates and abnormal burst patterns, in the oscillatory activity, and in the neuronal synchrony (Galvan and Wichmann, 2008). The abnormal firing rate activity in the basal ganglia became the basis for the so-called *rate model*. The rate model allowed the inspection of the above explained dysfunction of the primary and secondary motor pathways in terms of neuronal firing rates in the basal ganglia circuitry. The model postulates that the corticostriatal activity of the indirect pathway becomes hyperactive due to the loss of dopaminergic inhibition, and thus results in an increased inhibition of the GPe activity. This, in turn, was considered to disinhibit the STN–GPi communication, leading to an increased inhibition in the direct pathway of the GPi (DeLong & Wichmann, 2009; Galvan and Wichmann, 2008) , as explained in Figure 1 above. Nevertheless, with the increased research on the pathophysiological functioning of the basal ganglia, the rate model has been criticized being too rigid not explaining some essential pathophysiological observations of movement disorders, and PD symptoms in particular (Brown, 2006; DeLong & Wichmann, 2009). For example, based on the rate model, lesions resulting from the dopamine depletion in the GPi should lead to parkinsonian dyskinesias, but this is not the case (Brown, 2003; DeLong & Wichmann, 2009). Since then, the attention has been directed to observing oscillatory activity instead of solely focusing on the bursting pattern in the pathophysiologically defined functional units of motor circuitry (Brown, 2003; DeLong & Wichmann, 2009).

Neuronal oscillatory synchronisation is part of normally functioning brain activity, nevertheless in PD, as in other movement disorders, the oscillatory activity in motor networks is disturbed leading to hypo- or hyper-synchrony in certain frequency bands (Brown, 2003). By now, several studies have shown that the loss of dopamine in the mid-brain of PD patients leads to abnormally sustained beta band activity (~ 15 – 30 Hz): Experiments with animals, and with PD patients, both on the levels of single cells as well as larger neural ensembles have shown that overt activity in the beta range is toned down during motor movement, or in response to deep brain stimulation and pharmacological therapy (Brown, 2003; Cassidy et al., 2002; Georgiades et al., 2019; Kühn et al., 2008; Levy et al., 2002). Studies applying local field potential (LFP) technique, and cortical electroencephalography (EEG) have shown that the increased beta-band activity is located to the deep structures of the motor circuit such as basal ganglia, STN, and GP reaching to the cortical networks as well (Kühn et al., 2005; Mallet et al., 2008; Silberstein et al., 2005; Weinberger et al., 2006).

When contrasting PD symptoms in their on- and off-stages, or in response to stages of movement and non-movement, thinking in terms of oscillatory patterns is more informative due to the functional complexity of the motor network: Next to focusing on abnormal beta-band oscillations, including also frequencies < 10Hz and those > 60Hz, the symptoms can be better understood as each frequency range can be temporarily coupled to cerebral motor areas, without merely focusing on the motor circuit in the mid-brain (Brown, 2003). It seems that the STN and GPi demonstrate synchronized oscillatory activity in the two lower ranges (< 10Hz and those of 11 – 30Hz), such that the connectivity from the basal ganglia is towards cortical areas in lower frequencies of < 10 Hz, while the 11 -30Hz connectivity is from the cortical motor area towards the basal ganglia in a PD brain (Figure 2) (Brown, 2003). Both of these connections are assumed to be antiketic, meaning that they contribute to the reduction of motor movement. In contrast, an increased prokinetic STN GPi oscillatory synchrony in the range > 60 Hz, seems to take place from the subthalamic regions to the cortical motor areas when a PD patient is treated with a dopaminergic medication (Brown, 2003).

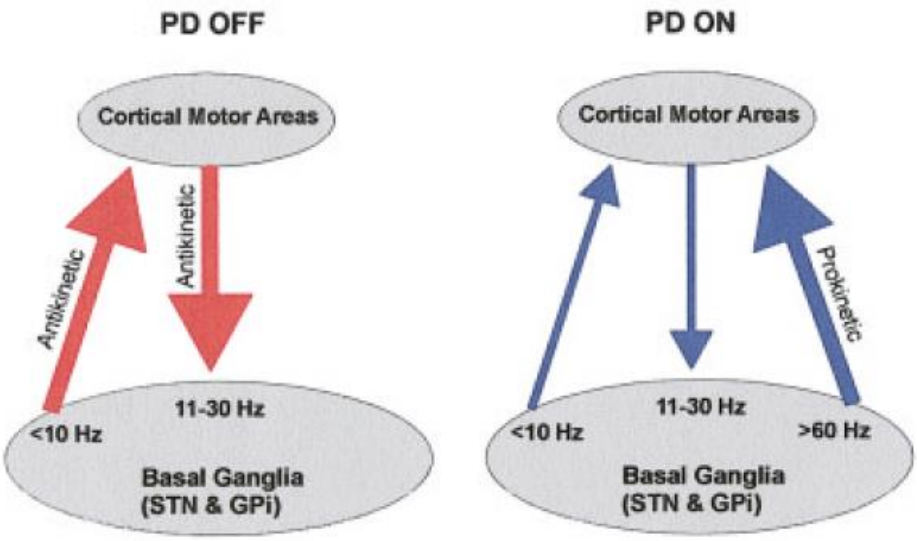

Figure 2.
Schematic illustration of three oscillatory ranges of < 10Hz, 11 – 30Hz, and > 60Hz, and the functional role of their synchronisation in the Basal ganglia in PD during the time without medication (PD OFF), and with medication (PD ON). The arrows indicate the direction of the connectivity, and their functional role of either akinetic or prokinetic contribution to the motor movement.
(Image is from Brown, 2003).

As the abnormal oscillatory activity occurs temporarily synchronously to motor tasks, or prior to motor task preparation, experimenting with the oscillatory patterns has shown to be a revealing parameter of PD brain functioning. While the abnormal oscillatory activity in all frequency bands in PD is not fully understood, there seems to be agreement that the sustained beta-band activity is a reliable biomarker of persisting parkinsonian symptoms (Holt et al., 2019).

3. Treatment of Parkinson's disease

3.1 Pharmacological treatment

Parkinson's disease is usually treated with medication, yet the currently available medication does not prevent the dopaminergic neurons from degenerating, they merely treat the symptoms (Dauer & Przedborski, 2003). The fact that there are no fully validated biomarkers that help detecting the disease in the very early stage makes testing and developing of drug therapies challenging (Santiago et al., 2017). The most widely used medication is levodopa, which has notably lowered the mortality rate which was three times higher in the age-matched group of healthy individuals prior to the introduction of the medication (Dauer & Przedborski, 2003). Despite Levodopa being the most widely used medication, there is no single recommendation for treatment, thus the choice depends on several factors such severity and subjective judgment of the patient. In the case of very mild symptoms it is possible that no therapy is initiated (Rizek et al., 2016). One side effect of levodopa is levodopa-induced abnormal movements, which is why in the case of early onset symptoms dopamine agonists are recommended instead; the side effects of levodopa furthermore accumulate and increase as a results of long usage (Rizek et al., 2016). However, the advantages gained from postponing levodopa are lost within 10 years into the disease progression. If the disease onset is later in life, levodopa is usually preferred instead of dopamine agonists or monoamine oxidase B inhibitors because levodopa is more effective in preventing the motor symptoms (Rizek et al., 2016). The variability in genetic risk factors, clinical symptoms, disease progression and treatment response encourage researchers to find personalized solution to treat PD patients. Yet, this would require a more advanced understanding of the clinical subtypes of the PD. In the literature, there seem to be disagreements about the categories of the sub-types, and currently no formal subtype classification exist, yet two postulated sub-types are based on the onset age of PD and tremor dominance (Berg, Postuma, Bloem, & Chan, 2014). It seems that patients with a young onset age have a more robust response to levodopa treatment and fewer cognition related abnormalities, whereas patients with tremor as a dominant symptoms have been shown to have a better prognosis and fewer cognitive challenges (Berg et al., 2014). Yet further advancement in the personal-

ized medicine would indeed require more molecular and clinical data to better understand the sub-types of the disease.

3.2 Adjuvant therapies in the treatment of Parkinson's disease

PD provides interesting opportunities for developing alternative therapy forms due to the spatially restricted loss of the dopaminergic neurons in the substantia nigra pars compacta. Also, it is an advantage that the phenotype of the degenerating dopaminergic neurons is homogeneous and defined (Purves, Augustine, George, Fitzpatrick, et al., 2012). One such method, though still in its infancy, would be *gene therapy* in which the disease phenotype could be corrected by introducing a new genetic information to the affected organism. Another novel approach would be *stem cell therapy*, in which the self-renewing and multipotent stem cells are identified and promoted to develop into a desired cell type, such as into dopaminergic neurons in the case of PD (Purves, Augustine, George, Fitzpatrick, et al., 2012).

It is possible that the efficacy of levodopa fluctuates throughout the day such that the motor- and non-motor symptoms vary accordingly. To provide these patients with continuous dopaminergic stimulation, a surgical option of deep brain stimulation exists as an alternative treatment since more than two decades (Benabid, 2003). The targeted regions are the GBi and STN (Rizek et al., 2016). Here the choice of the correct locations depends on the nature of the symptoms. For example, in some cases where the patients have received treatment to the STN, the depression symptoms have worsened, whereas as a result of the stimulation in the globus pallidus, the depression symptoms improved (Rizek et al., 2016). In cases where a steady stimulation is required, yet where deep brain stimulation does not come to question, an alternative is levodopa-cardiopa intestinal gel can be an option. The gel is injected into the jejunum of the patients. The gel therapy is not restricted by age, or neurocognitive reasons, yet patients suffering from severe dementia might be excluded due to the unsuitability of the jejunum administration (Pickut, van de Linden, Dethy, Van de Maele, & Zegers de Beyl, 2014; Rizek et al., 2016). Overall, the levodopa-carbidopa gel treatment has been rather successful, demonstrating 90% of respondents to report an enhanced quality of life after the treatment in a 7-year follow-up study (Zibetti et al., 2014).

Conclusively, there is no single correct approach that would apply to all individuals with PD when it comes to prescribing the correct therapy. The type of therapy depends on the onset age of the disease, severity of symptoms, and whether they are more motoric or cognitive in nature. Also, the dose, type and need for medication might be assessed several times during the life time of a PD patient (Pickut et al., 2014; Rizek et al., 2016).

3.3 Exercise in Parkinson's disease

In addition to pharmaceutical and the above mentioned surgical treatments, adjuvant forms of therapy such as physical exercise, and physical activity in general have been shown to alleviate both motor and cognitive symptoms in PD (Abbruzzese et al., 2016; Delgado-alvarado et al., 2020). Despite often being used interchangeably, physical activity refers to a wide range of bodily movements produced by skeletal muscles resulting in energy expenditure, while physical exercise is a subset of physical activity characterized by being planned, structured, and repetitive, usually aiming at a certain goal of improvement or maintenance of physical fitness (Caspersen, Powell, & Christenson, 1985). While there is no indication that exercise would terminate disease progression, it can be considered as disease modifying when underlying pathological or pathophysiological disease processes are delayed while being accompanied by improvement in clinical signs and symptoms (Ellis & Rochester, 2018). Physiological-, functional-, clinical-, and central neuroplastic changes, as well as surrogate markers of neurodegeneration have been suggested as different targets of disease modification by physical exercise (Ellis 2018). Exercise-based functional training in particular can be targeted to enhance functional mobility by utilizing enhanced strength, endurance, balance and flexibility to support efficient performance of specific tasks (Ellis & Rochester, 2018).

3.4 Cycling as physical exercise treatment

3.4.1 The preserved ability to ride a bicycle despite Parkinson's disease

In 2010 a written case-report accompanied with video material describing a 58-year old man being able to ride bicycle despite being diagnosed with PD was released (Snijders & Bloem, 2010). The man had a diagnosis of idiopathic PD for 10 years, and he suffered from severe FOG. In particular he had difficulties in initiating gait, and he was only able to take small shuffling steps when receiving a visual cue placed in front of his leg on the floor. He was

unable to make an axial turn. Attempts to walk often resulted in a forward festination and a subsequent fall on the ground unless he was being caught by an assistant. Also, it was reported that immediately after dismounting the bicycle, the symptoms of gait freezing reoccurred.

This case-study was followed by a semi-structured interview report with 45 patients diagnosed with PD (Snijders et al., 2012). 25 of the patients were so called freezers (based on subjective report of the feeling of being occasionally glued to the ground), and the remaining 20 patients were non-freezers. None of the 20 non-freezers reported any freezing, sensations of being blocked, nor asserting irregular pressure on the pedals while cycling. Only one female patient among the freezers reported occasional freezing while cycling such that her legs felt occasionally blocked, unable to actively push the pedals. Nevertheless, these sensations of freezing on the bike were much less frequent and less severe than when occurring during walking. Eight further patients of the freezers reported occasional irregular pressure on the pedals without inability to push the pedals. The remaining 14 freezers reported no difficulties while starting to cycle, nor during cycling.

While both of the above described reports do not represent standardized clinical testing, but are case reports, and more qualitative in nature, they nevertheless made the preserved ability to ride a bicycle a known phenomenon among researchers, clinicians and health professionals. Also, despite calling for further investigations, the latter study was a preliminary indication for the preserved cycling ability being fairly common among PD patients. Since then, the reported observation has led to research projects aiming to understand the underlying neuronal motor-control and pathophysiological mechanisms enabling bicycle riding despite PD.

3.4.2 The postulated mechanisms of ease of cycling in PD

It has been reported that the ability to continue cycling might be such a crucial feature prior to having a PD diagnosis, that it could be used as a so called “red marker” to delineate PD patients from those of diagnosed with atypical parkinsonism (Aerts, Abdo, & Bloem, 2011). It was shown with 111 patients who had parkinsonism without a PD diagnosis, that only 2 out of 45 of the ones who later on received the PD diagnosis, reported quitting cycling,

while 34 out of 64 participants who remained diagnosed with atypical parkinsonism lost the ability to cycle, or quit. A statistical analysis of the results confirmed that cycling ability, or the lack of it could be used as a predictive marker to separate parkinsonism from PD. The authors speculated that the more extensive extranigral pathology of parkinsonism might be the cause for the motorically highly intricate process of cycling being more disturbed in parkinsonism than in PD (Aerts et al., 2011).

In addition to the reports on the prevalence of preserved cycling ability, few studies have approached possible differences in the neuronal motor control by comparing the oscillatory dynamics while cycling and walking. A study applying EEG on healthy participants, was able to demonstrate that cycling and walking underlie different cortical oscillatory activity, and that cycling has less motor control during pedalling movement when coupled with muscle tone (EMG) (Storzer et al., 2016). In particular, it was shown that the high beta-band frequencies (23 – 35Hz) were more strongly suppressed during cycling, than during walking. Furthermore, the observed increase bounced back stronger immediately after terminating pedalling. Walking showed a persistent decrease in the Alpha frequency range (8 – 12Hz). Likewise, a study with healthy participants contrasting active pedalling to passive pedalling on a recumbent bicycle, showed that distributed beta desynchronisation was larger during passive pedalling (no muscle contraction). Despite the first study having been done with healthy participants, the results provide an indication to a possible mechanism why cycling might remain possible for PD patients, as it seems to tone down the increased beta-band activity, which can be considered as a biomarker of a PD pathology, and of a high probability of PD symptoms being present (Holt et al., 2019). Furthermore, the latter study indicates that the cortical areas are involved in movement control during cycling.

A study measuring LFPs from the STN with DBS electrodes patients replicated the above results finding stronger beta-band suppression during cycling than walking (Storzer et al., 2017). Nevertheless, here the source of the suppression was observed in the sub-thalamic nuclei, instead of the cortex, and similar activity was observed across freezers and non-freezers. In addition, it was found that the freezers showed a deviating pattern of activity during movement, as they had an elevated narrow-band beta (~ 18 Hz) activity even during the absence of freezing. These results show that movement control is distinct already in the

sub-cortical level resulting in different beta-band activity depending on the type of the performed movement (cycling vs walking).

Regarding further postulations about the differences of cycling and walking, and the features of cycling that enable fluency of movement despite PD, it has been postulated that the rotating pedals could act as an external pacing cue keeping the legs in fixed amplitude and phase (Snijders & Bloem, 2010; Snijders et al., 2012; Storzer et al., 2016). Furthermore, it was speculated that the power transmission system of the bicycle – the gears, the chain and the pedals – keep the legs in movement even if the muscular system might momentarily be compromised. Also, the momentum of the circular movement of the pedals might assist the more affected side of the patient by maintaining the movement (Snijders et al., 2012). Another postulated mechanism is based on the differences between walking and cycling, as it has been suggested that the loss of the dopaminergic cells might influence different parts of the motor-control circuit in the brain, being more detrimental to the motor circuit controlling gait than cycling (Snijders & Bloem, 2010). Nevertheless, the later hypothesis remains speculative, as a distinction of possibly separate motor networks of cycling and walking has not been established. Furthermore, walking has been suggested to be more demanding in motor terms than cycling, as pedalling requires less lateral postural adjustments, compared to leg-swinging while walking (Storzer et al., 2017).

While at the moment the ability of preserved cycling remains unsolved, it is unlikely that it is a mere phenomenon of so called *kinesia paradoxica,* as cycling ability remains preserved at all times (Snijders et al., 2012). Next to cycling, it has been reported that PD patients can move to music, or to auditory cueing (Bella et al., 2017; Ghai, Ghai, Schmitz, & Effenberg, 2018). Thus, aligned with the here presented topic of cycling, music has been established as a similar line of research, of having a therapeutic relevance while being of interest of researchers. Nevertheless, the term *kinesia paradoxica* is usually used to refer to movements which, most of the time are compromised and only occasionally can be performed normally, with ease (Banou, 2015). As the currently available pharmaceutical medication for PD only treats the symptoms, at best improving the daily coping of the patients, while not terminating the disease progression (Dauer & Przedborski, 2003), developing and further understanding of well-targeted adjuvant forms of physical exercise would be of crucial im-

portance. This need is highlighted also as there is an increasing number of treatments being developed with modern technologies including virtual reality applications, and the implementation of wearable technologies enabling more personalized treatment of PD (Mazzetta et al., 2019; Mirelman et al., 2016; Ribas, Alves da Silva, Corrêa, Teive, & Valderramas, 2017).

4. Cycling as embodied and situated activity

In the following paragraphs embodied and situated human cognition will be investigated by inspecting the relationship of *rider-machine-space* (Cox, 2019). It is discussed which implications an embodied approach to human cognition could have to the here presents topic of PD. First, the embodied approach to human cognition is summarized against the background of cognitive science, after which similar approaches from the sociology of cycling are briefly presented. Finally, it is discussed why this philosophical excursion might be useful, and which practical implications an embodied understanding of the rider-machine-space could possibly have for individuals with compromised motor and physical capacities, such as PD patients.

4.1 Embodiment in cognitive science

Starting from Descartes's dualistic view on mind and body, human cognition had been, and perhaps partially still is, considered as rule-governed problem solving (Anderson, 2003). In short, *cognitivism* represents the line of thought according to which thinking - the central functioning of the mind - is rule-based manipulation of mental representations (Anderson, 2003). Cognitivism, or cognitive realism, has three core elements: representation, formalism and rule-based transformation which function in isolation from the given situation, environment or from the body of the individual (or agent) (Varela, Thompson, & Rosch, 1991). Based on this view on human cognitive activity such as problem solving can be inspected on the levels of task domains which have a set of pre-defined states (Varela et al., 1991). In this type of mechanistic understanding on cognition there is no room for the influence of situatedness, or the human body, as everything is performed based on pre-existing rules.

An opposing view on human cognition comes from enactivism according to which perception, and representation are contextual depending on the embodied interaction with the surrounding world, such that cognition depends on the physical characteristics, abilities, practical activity, and the environment of the individual (Anderson, 2003). From this line of thought it follows that representations about the world, rather than being formally operated by certain rules, are bodily sublimations of current state of affairs. Thus, the structure of

the conceptual schemes of humans is based on the current practical criteria, rather than on abstract and logical ones.

When cognition is considered embodied, it can be inspected on the levels of *physiology*, *evolutional history*, *practical activity*, and *socio-cultural situatedness* (Lakoff & Johnson, 1999). On the physiological level all the processes related to thinking must have a neural foundation because the understanding of experience, perception and movement can, to a certain degree, be explained by inspecting the human perceptual and motor systems (Anderson, 2003; Lakoff & Johnson, 1999). The evolutional aspect is explained by not thinking of human radically distinct to animals, but rather by considering humans on an evolutional continuum, such that humans' advanced cognition depends on the skills and abilities to continue life in the evolutionally inherited environment. In line with the practical activity, cognition develops using the environment to create structures, which help and simplify survival in adherence to individual-specific needs and goals, rather than using the already existing environment as best available model of the current situation. Based on the socio-cultural situatedness, the individual interacts with, not only with artefacts and objects, but with cultural and social structures, which can be abstract, or concrete. From this it follows that the actions of an agent can go beyond direct environmental impacts, by being cultural or social in their nature.

4.2 Embodiment in Vélomobility

Human relationship to bicycles and to cycling as an activity is being investigated across academic disciplines of mobility & transport studies, engineering, design, anthropology, sociology and sport sciences. Furthermore, stake holders with political or societal agendas on social and cultural inclusion, sustainability, and urban design are involved in cycling related activities and advocacy. A recently published work allows the inspection of cycling through sociological methods drawing from the scholar contributions of the above-mentioned academic disciplines (Cox, 2019). The author uses the term *vélomobility* to describe cycling, not only as a mere activity of cycling, but as a system involving social structures, environments, and the physical act of riding a bicycle. Furthermore, the author refers to scholars of philosophy and history (cf. for example Augé, 2008; Fournel, 2001; Gell, 1988; Hachleitner, Marschik, Müllner, & Zappe, 2013 in Cox, 2019) who write about cycling from a non-representational perspective where cycling is a form of transcendence, where the environ-

ment, the perceptual processes, and cycling is a form of transformation where the body and the legs become the motor, and the bicycle is not a tool of forward directed movement but rather a transformative technology. Common to these writings is the personal insight, passion, experientiality of cycling, and attribution of political and historical meaning onto bicycles. Against this background, a shift from *ontological realism* to *constructivism* in the sociology of cycling can be identified (Cox, 2019). According to the realist ontology, reality with its objective attributes exists independent of an individual, whereas a social constructivist approach emphasizes individual's experience and interpretation of the socially produced understanding of the reality, up to the point that a practice, such as cycling, *produces* reality (Bonham & Johnson, 2015). In this practice the human body is seen as a corporeal resource with its skills and deficits. Following the acknowledgement where environment, individual and the technology ought to be considered together, the individual, with his or her experience needs to be in the foreground when aiming to understand mobility.

Ethnographic participation is a method in social science where the researcher is mobily co-present in the act of movement, aiming to capture experiential features of affect, kinaesthesia, multisensoriality and transience of the activity, investigating the *emplacement* of embodied practices (Larsen, 2014). Autoethnography is a method, usually conducted by writing or by filming, where the researcher explores the ephemeral and corporeal experiences that make cycling meaningful, rather than useful. Both of the ethnographic methods can highlight changes in affective capacities, routines and skills to which one could otherwise remain oblivious as they would be considered as normal functions of mundane activity (Larsen, 2014). (Auto)ethnographic methods are considered to capture something that cannot be captured otherwise, for example even if the process of cycling was considered as a multi-sensory process using methods from perception psychology, this approach alone would not be sufficient in translating into experientiality.

Inspected from an academic perspective the above described approaches to sociology of cycling seem like literary achievements with rich language and descriptions rendering the question, how could this intimate and solipsist first person approach be applied on societal level. Yet, the acknowledgement of cycling being embodied and the aim of putting an experiencing individual into the foreground helps to detect several otherwise invisible mobility-related aspects, while offering interesting starting points to understand vélomobility in the

society. Furthermore, it is against this background of seamless co-existence of the environment, technology, and the individual which allows the inspection of what it could mean for PD patient to, not only maintain the ability to ride a bicycle, but to be able to realise cycling.

4.3 Acknowledging "the triad" of individual, environment and technology

When the triad of individual, environment and technology, and their interaction is recognized, it appears that modern mobility studies consider mobility mainly through a utilitarian lens where the environment is viewed from the perspective of enabled individuals with intact bodily functions (Cox, 2019). If individuals with different capabilities are inspected, it becomes visible that different environments create different orders of control (Cox, 2019). When the environment is primarily designed for automobile vehicles, it follows that everything else, such as cycling lanes, is built to response to their particularities, creating an environment where the perceptually and functionally most able bodied individuals perform the best, as they (or their bodies) know how to respond to the environment. Simultaneously, making the controllability for the less-able-bodied individuals unachievable. Following the line of thought of the environment as levels of controllability, it becomes evident how e.g. junctions, road conditions, exposure to the elements, visibility, etc. not only create different challenges for individuals with varying skills, or capabilities, but they create a different experience. Considering an urban cycling commute or leisure ride from the perspective of an individual with compromised motor or cognitive capacity, such as PD, actually leads to reinforcing the features of the disease which are reflected back from the environment, if the individual is continuously faced with the sensation of fear and failure of coping.

Building rigid environment only to certain groups of individuals for certain purposes (such as a commute to the city center), without remaining alert to the different needs of other groups, is *environmental determinism* (Kidder, 2009) which at its worst leads to social exclusion keeping certain groups undetected, and not considered. Whereas smart and inclusive design can, at its best be self-esteem promoting. With restricting design certain groups of people are taken away the possibility of reinforcing or re-discovering their identities and the sensations of belongingness, attributes which seem common in ethnographic descriptions of cycling (Cox, 2019; Kidder, 2009; Larsen, 2017). Furthermore, considering bicycle as a medium of transformation, applying and acquiring riding skills have been postulated as a crucial

feature of experiencing the transformation (Cox, 2019). Thus, for individuals such as PD patients, this dimension would be of a particular importance, as the control of voluntary movement is, at least partially, beyond the control of most of the PD patients when off the bike. Even more so, as the ability to ride, and to manoeuvre a bicycle has been indicated as a crucial part of social inclusion in bicycle riding, also knowing that the required competence reinforces the confidence (Cox, 2019). An enabling environment, possibility of skill learning or re-learning, social inclusion and autonomy are features that should be promoted among PD patients.

As the environment, in particular in most of the urban spaces is, if not unsuitable, at least risky for individuals with slower reaction times, lowered perceptual capacity, or otherwise limited executive functioning, modern technology offers options of indoor cycling. Nevertheless, it can be assumed that the potential of indoor training remains limited if the experience of riding is only considered from a functional perspective. *Sensescapes* (exposure to sounds, smells, and the impact of elemental conditions of sun, wind and rain) are an integral part of outdoor mobility of a non-enclosed form of transport, such bicycle (Cox, 2019). Currently, indoor cycling features a very limited number of elements of realistic cycling, mostly those of visual perception, and route profile. Some software of indoor training have included the social dimensions, mainly to promote competitive riding, thus rather enhancing the functional perspective of an increased training effect. Hence, the identity of belongingness with the environment and the experience of social inclusion, *participatory relationality* (Cox, 2019), is still not part of indoor riding. An interesting future question is whether a technology capable to cater to all needs as described above, would suffice to create the feeling of belongingness.

4.4 Concluding remarks

Above, the difference of considering human cognition embodied and situated versus rule-governed problems solver in the context of cognitive science was briefly discussed. Furthermore, a similar paradigm shift of incorporating the situated body into understanding human behaviour was inspected from the multidisciplinary perspective of sociology of bicycle riding. While, perhaps remaining superficial considering the depth of the topic, neverthe-

less the aim was to inspect the several ways in which cycling should be seen as well-being promoting, beyond physical and functional measures, for individuals with compromised motor and cognitive capacity, such as PD patients. It was demonstrated how the self-image of individuals can be dependent on considerate (or inconsiderate) environmental design, and in which ways it can influence the feeling of belongingness. Furthermore, despite the challenging features of a disease such as PD, the self-agency, the possibility of learning and re-learning, and the right to be *emplaced* in the environment with the able-bodied can be a crucial factor in either emphasizing the disease specific deficits, or in alleviating them.

5. Meta-analysis and review study

5.1 Problem formulation

Among the diversity of physical exercise forms, the need to develop a goal-based rehabilitation has been highlighted (Abbruzzese et al., 2016), as thus far there has not been knowhow to target or customize adjuvant forms of exercise to patient´s individual needs (Ellis & Rochester, 2018). To enable a more detailed understanding of correct targeting of adjuvant physical therapies more studies and metal-analyses are needed as it seems that the success of physical exercise depends on a multitude of factors such as duration, intensity and format of the exercise; targeted symptoms; personal motivation and disease related barriers; as well as the current diseases stage (Cosentino et al., 2020; Ellis et al., 2013; Kelly et al., 2017; Schenkman et al., 2018; Schootemeijer et al., 2020). A more thorough understanding about the efficacy is particularly important, as new forms and technologies around exercise therapies are being increasingly established (Georgiades et al., 2019; Mirelman et al., 2016; Ribas et al., 2017).

To answer to the above-raised issues regarding the specificity of an exercise regimen a meta-analysis with a review on the current status of cycling as an adjuvant form of exercise is conducted. This review is motivated by the need to create more refined understanding of customizing physical exercise to cater to individual needs of PD patients. A meta-analysis is conducted on the efficacy of the motor and cognitive outcome measures as well as overall life satisfaction of PD patients. Also, the efficacy of cycling exercise on functional outcome measures is analysed. In addition, the types of cycling interventions, their duration and other exercise related parameters are summarized. It is hypothesized that cycling will result in improvements in versatile outcome measures, indicating that the benefits of a bicycle intervention not only include but even go beyond an improvement of the physical condition of the patients. The goal of the review is to provide a characterisation of the current status of cycling exercise regimen for PD patients, and to point at features which need further research.

5.2 Methods

5.2.1 Eligibility criteria

Only original English- and German language peer-reviewed research articles were included in the present review. The criteria for the eligible studies were as follows: At least the treatment group had to have a diagnosis of PD. Regarding the definition of bicycle treatment of the included studies, recumbent, tandem, motorized, non-motorized, and stationary bicycle ergometers were considered. Furthermore, studies were included if the pedalling was done with hands, instead of with feet. Nevertheless, studies were not eligible if the intervention was only imagined, or only in virtual reality without an actual bicycle. To the control treatment no limitations were set, as long as the treatment did not involve cycling. While randomized control trials (RCT) have been the golden standard of empirical testing (), and the preferred study design to be included in a meta-analysis, here also non-randomized trials (NRCT) were included. The main inclusion criteria was that the study was an original report applying quantitative measures to investigate the effects of an intervention, while providing quantitative pre and post outcome measures with the appropriate measures of averages and variability on the efficacy of the treatment. The inclusion of NRCT-studies was considered justified as they can be the main source of evidence for several intended effects of interventions (Higgins et al., 2013). Indeed, including NRCT-studies is increasingly common in particular among non-pharmacological studies, investigating the effectiveness of therapeutic interventions (NRSI) (Faber, Ravaud, Riveros, Perrodeau, & Dechartres, 2016). Furthermore, the importance of incorporating NRCT studies, as well as standardizing their analysis and quality assessment has been emphasized in recent literature (Higgins et al., 2013; Norris et al., 2013; Reeves et al., 2013). Reviews and meta-analysis were excluded. Also, studies were excluded if their main outcome measures were largely deviant from the rest of the outcome measures, such as neurophysiological, or metabolic activity.

5.2.2 Search strategy

The PubMed database for biomedical literature was searched. Studies published from --- to --- were included. This was set as the time frame, as the observation of preserve cycling ability in PD wasn´t reported until 2010 (). After conducting several preliminary search with dif-

ferent keyword combinations, the keywords ‘bicycl*’; ‘cycling; bik*’, and ‘Parkinson’ MeSH were used for the final search.

5.2.3 Study selection and data extraction

The study selection was done independently by two reviewers, M.T. and B.W. using the Covidence Systematic review software (Covidence). First, the imported articles where screened based on title and abstract, then based on the full text. Any occurring conflicts on inclusion were solved by the third reviewer S.D. Upon inclusion, the following qualitative and quantitative information about each study was extracted into a table.

Publication: Authors, publishing year, journal

Study: Study design, number of individuals in treatment and control group

Effect size measures: Quantitative measures on pre and post treatment

Participant demographics: Age, gender, disease duration,

Intervention characteristics: Bicycle type, cadence, treatment session duration, overall treatment duration, exercise intensity in heart rate & perceived exertion

5.3 Meta-analysis

5.3.1 Quality analysis

Commonly in meta-analyses the Cochrane Collaboration´s risk of bias tool is deployed to assess the possible bias in the trial conduct of the included studies (J. P. T. Higgins et al., 2011). Here, this tool was not used, as it is targeted to RCT studies assuming that each study used randomisation to allocate the participants into control or treatment groups. Instead, a more versatile checklist, Standard Quality Assessment Criteria Checklist (QualSyst), developed for evaluating primary research papers was used (Kmet, Lee, & Cook, 2004). This was deemed appropriate as it is developed in particular for meta-analyses including both RCT and NRCT studies, addressing the risk of bias with a 14-item checklist concerning the internal validity of the studies, as well as the quality of the reporting (Table 1.). Two reviewers assessed the included studies independently, answering each question with “Yes”, “Partial”, “No”, or “Not applicable”. Finally, based on the weights each answer is given to by the developers of the QualSyst tool, each study received a score assessing the overall quality. The quality assessment was not used to set cuts-offs for study inclusion, rather it was used as an

additional information about the overall quality of the included studies. The score is based on the average of the score from the independent reviewers. Also, a two-sample F-test for the variance of the scores was conducted, followed by a two-sample T-test to test for a difference in the ratings given by the reviewers.

Table 1.A Standard Quality Assessment Criteria Checklist

Quality Assessment Criteria		Yes	Partial	No	N/A
1.	Question / objective sufficiently described?				
2.	Study design evident and appropriate?				
3.	Method of subject/comparison group selection or source of information/input variables described and appropriate?				
4.	Subject (and comparison group, if applicable) characteristics sufficiently described?				
5.	If interventional and random allocation was possible, was it described?				
6.	If interventional and blinding of investigators was possible, was it reported?				
7.	If interventional and blinding of subjects was possible, was it reported?				
8.	Outcome and (if applicable) exposure measure(s) well defined and robust to measurement / misclassification bias? means of assessment reported?				
9.	Sample size appropriate?				
10.	Analytic methods described/justified and appropriate?				
11.	Some estimate of variance is reported for the main results?				
12.	Controlled for confounding?				
13.	Results reported in sufficient detail?				
14.	Conclusions supported by the results types?				

The table summarizes the questions of the Quality Assessments Criteria used for the quality analysis of the included studies. The criteria could be rated with the answers “Yes”, “Partial”, “No”, or “Not applicable (N/A)” depending on the accuracy of the statement in the left column.

5.3.2 Publication bias

To address whether the included literature might have been subject to publication bias, the small sample bias method was applied for the primary outcome measures to test for the presence of a possible bias. The method is based on the assumption that studies with a small sample size are prone to not to provide high effect sizes (Schwarzer, 2007), nor high statistical significances, and thus may not be get published at all in the case of non-significant results (Rothstein, Hanah, Sutton, Alexander, & Borenstein, 2006). This would mean that the whole sample of the included studies could show a lack of small studies featuring very small or negative effect sizes, while still including small studies with higher effect sizes and higher significances.

5.3.3. Effect size of the treatment

The analysis of the treatment efficacy was based on the generic inverse-variance method which uses the effect size, and a weighted measure of variance for each study to calculate the pooled effect size describing the overall effect. The given weight for each study is the inverse of the variance. Here, the effect sizes were based on continuous outcome data, and they were pooled using a Random-Effects Model (Borenstein, Hedges, Higgins, Julian, & Rothstein, Hanah, 2011), assuming that not all studies come from the same population. This approach was chosen instead of the Fixed-Effects Model as it is realistic to assume that there is variance among the clinical population that should be considered in the analysis. Here, the Hedges' bias-corrected standardised mean difference (g) was used to calculate the effect size. To calculate the between-study variance, tau^2, the Sidik-Jonkman-method (SJ) was chosen. The SJ was chosen in favour of over the DerSimonian-Laird-method (DL) commonly applied in meta-analysis studies, as the DL-method has been reported to have a tendency for producing false positives, in particular among meta-analyses with a small sample size of studies, and a large heterogeneity (Harrer, Cuijpers, & Ebert., 2019; Inthout, Ioannidis, & Borm, 2014).

The analysis was conducted with the R (R Core Team, 2019) and RStudio software (Team, 2020), by using the meta (Schwarzer, 2007) and metaphor (Viechtbauer, 2010) packages which were developed for meta-analyses and is based on the inverse variance method. For the RCT studies, the individual effect size and the variance were calculated for the post measures of the treatment and the control group. The NRCT studies consisted of two types of studies; some compared Parkinson's disease patients with healthy participants, and some applied a repeated design, comparing PD patients before and after treatment. Ideally, the individual effect sizes and given weights for the studies comparing healthy participants and PD patients would be based on difference measures, comparing the difference in the pre and post treatment outcome measure of the PD patients with that of the healthy controls. Nevertheless, this approach would have required access to the individual data of each participant, as a reliable calculation of the variance would not have been possible otherwise. This approach was not deemed feasible as it would have only worked if the individual data

was provided for each study, and for all outcome measures of interest. Thus, as the included studies already would include repeated measure designs with only PD patients, in which the individual effect size would be calculated for the pre- and post-treatment measures, the outcomes of all NRCT studies were grouped together and analysed in the same manner. This means, that the outcomes of the healthy participants were excluded, and only the individual effect sizes of the PDs pre and post treatment measures were compared. In the case of studies with multiple measuring time points, the earliest and the latest time points were chosen. Also, in the case of studies which had more than two treatment options, cycling was contrasted, if available, with no-treatment, or with standard care. In cases where the required information was not reported explicitly enough, the authors were contacted.

In the initial analysis all the included studies were grouped together, and the effect size of the primary measures was tested. A primary measure was defined as it was stated in the corresponding original paper. If there were multiple primary measures, or if a primary measure was not named explicitly, a measure was chosen for the analysis that was best aligned with the research question and the rest of the outcome measures of the meta-analysis. Moreover, the above described inverse variance-based analysis was applied on the secondary outcomes. First, outcome measures that could be defined to be functional were tested for their effect size. An outcome was defined as functional if it could be considered to enable general movement and mobility of the body. Functional parameters have been suggested to be one of the several target sectors of disease modifying exercise (Ellis & Rochester, 2018). Thereafter the secondary outcomes were investigated in more detail, as it was investigated whether cycling influenced four outcomes of gait (Cadence, Step length, Velocity) and walking capacity (6MWT (6 minute walking test)), as well as Bradykinesia, Tremor, Balance, PDQ39-Questionnaire (Parkinson's Disease Questionnaire 39) (Jenkinson, Fitzpatrick, Peto, Greenhall, & Hyman, 1997), UPDRS Questionnaire (Unified Parkinson's disease rating, motor sub-scale) (Fish, 2011), and Quality of life. The outcome measures in the category Quality of life consist of different measures which can be considered to contribute to the overall quality of one's life, such as depression, activities of daily living, or overall wellbeing.

Finally, four sub-level analyses were conducted. It was investigated whether the results from the primary measures demonstrated differences as levels of design (RCT and NRCT), and secondly as levels of outcome type (motor and cognitive). Furthermore, it was investi-

gated whether the results depended on cadence (high and low), and treatment duration (immediate vs long-term effect). The design level was applied to investigate whether RCT and NRCT studies differ in their effect sizes. The distinction between motor and cognitive outcome measures was applied to test whether either of the outcome types would gain a larger benefit from a cycling intervention. For the sake of clarity, here the term motor is being used, even though the term includes several types of parameters measuring physical, and mobility-related measures. Cadence and treatment duration were applied as sub-levels to test whether certain treatment-specific features would indicate better outcomes. Cadence was categorized as low when it was 60 RPM or less, and high if it was 61 RPM or more. An effect was considered immediate if it was performed only once, and long-term if treatment sessions were more than 1. All sub-level tests were performed on the primary outcomes.

5.3.4 Measures of heterogeneity

Here, due to the different designs and patient groups, as well as due to the various types of combined primary measures, it could be expected that there is clinical and statistical heterogeneity present in the pooled effect size (Fletcher, 2007). The random-effects-model outputs three different measures: 1) between study heterogeneity, 2) the above-mentioned between study variance (Tau^2), and 3) Cochran´s Q and Higgin´s & Thompson´s I^2. All three report slightly different aspects of heterogeneity, and thus have a suitability of being an appropriate indicator of heterogeneity depending on the individual sample sizes of the studies, as well as the overall number of studies included in the meta-analysis (Harrer et al., 2019). Thus, when estimating the present heterogeneity all measures should be considered, including 95 % confidence intervals (CI). In particular, the I^2 is inspected as it gives a percentage estimate of the variability not caused by the sampling error and has an approximate rule of interpreting the results as small (25%), medium (50%), or large (75%) effects (Julian Higgins & Thompson, 2002). In addition, to investigate between study heterogeneity, measures were taken to inspect the effect size contribution of individual studies. First, confidence interval (CI) based outliers were detected using the meta package in R (Schwarzer, 2007). Second, to find out whether the results would change by not including some studies, an influence analysis based on the “Leave-One-Out-method” was chosen. This method reports several measures of between study heterogeneity to test how much the results would change,

if each study was left out at a time. Finally, studies that were outside the average confidence interval or contributed a particularly high influence were removed from the final pooling.

5.4 Results

5.4.1 Study characteristics

The literature search resulted in 202 references, including one duplicate. Based on screening the titles and abstracts, 141 references were removed leaving 60 references for a full text screening. The full text screening resulted in removing 38 papers due to wrong outcomes measures, wrong study designs, wrong interventions, or due to insufficient reporting of outcome data. The literature search is reported below in the (Figure 3.) using The Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) flow diagram. For the complete references of the included studies, please refer to the Appendix A.

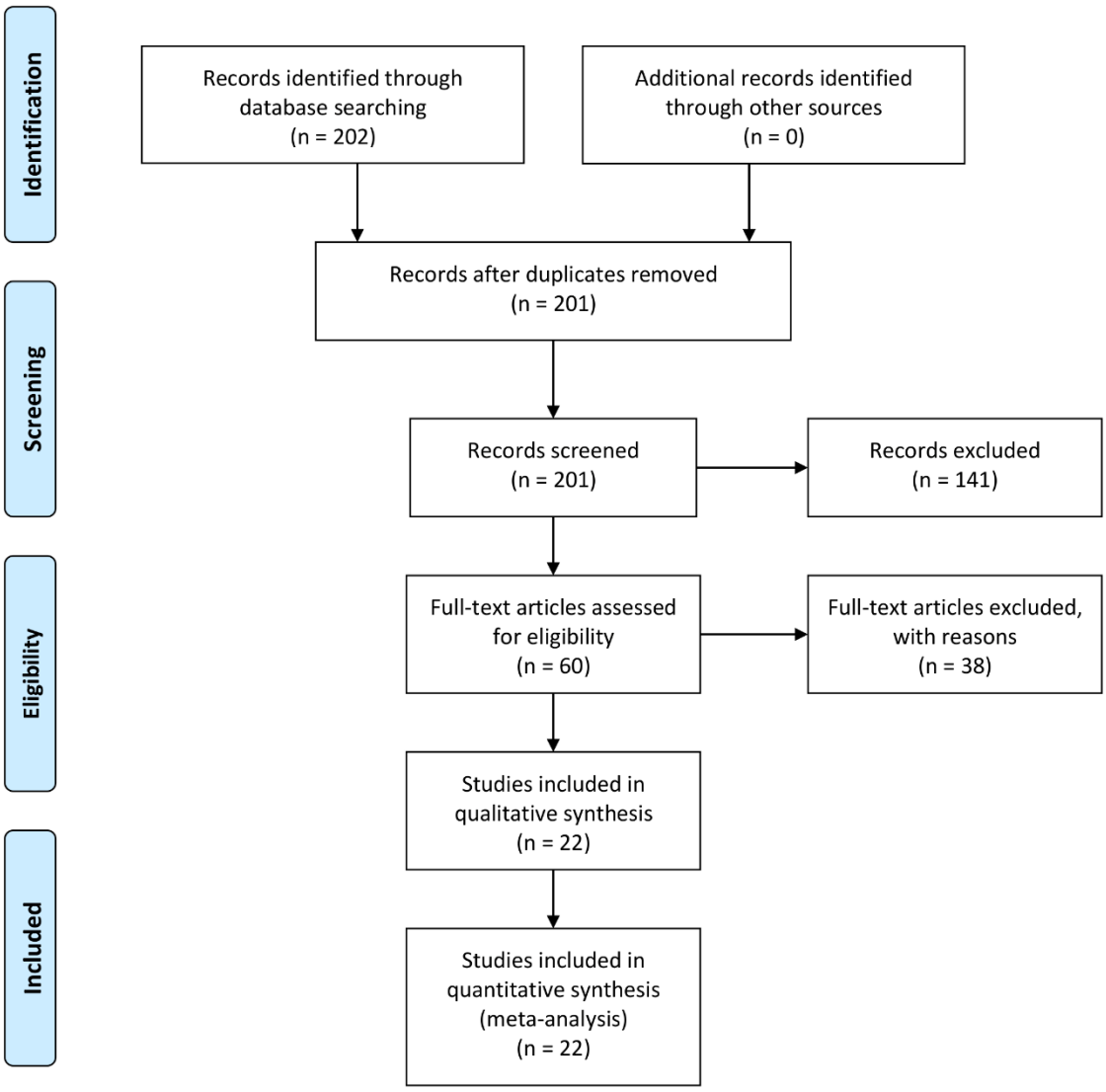

Figure 3.
Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) flow diagram of the literature search.

5.4.2 Participant demographics

Of the 22 included studies seven were RCT studies meaning that the participant population consisting of PD patients were randomized either to treatment, or to control group. Out of the remaining 15 NRCT studies ten were repeated design studies where at least two time-point measures (pre and post treatment) were reported based one group of PD patients. The remaining five studies were studies where the same treatment was given to healthy controls, and the PD population. As pointed out in the analysis section, these studies were grouped together with the studies with no control group to compare their pre and post treatment measures

Table 2. Study demographics, primary outcomes, and intervention characteristics

Study	Primary Outcome	Out-come Type	Control Group	Female Treatm.	Male Treatm.	Female Control	Male Con-trol	Age Treatm.	Age Control	Disease Duration Treatm.	Disease Duration Control	Heart rate	RPE	H&Y Treat	H&Y Control	H&Y Target
Arcolin et al., 2016	6 MinWT	Physical	PD	7	9	7	6	67.8	68.7	4.7	6.5	NA	11 to 14	2.3	2.3	1.5 - 3
Demonceau et al., 2016	Peak work load	Physical	PD	4	12	5	10	65	63.3	5	5	Moni-tored	12.3	1.5	1.5	1 to 3
Ferraz et al., 2018	6 MinWT	Physical	PD	9	11	6	16	67	71	6	4	50-75%	15	2.5	2.5	2 to 3
Harper et al., 2019	Executive function	Cogni-tion	PD	NA	NA	NA	NA	65.05	64.87	NA	NA	88.4 bpm	11.2	NA	NA	NA
Qutubuddin et al., 2013	UPDRS-III	Physical	PD	NA	NA	NA	NA	68.2	68.2	7.2	7.2	NA	NA	NA	NA	NA
Ridgel et al., 2011a	Tremor	Physical	PD	7	13	3	9	62.8	64.6	5.2	6.5	73	6 to 8	2	1.6	1 to 3
Tollár et al., 2019	UPDRS II	Physical	PD	14	11	11	13	70.6	67.7	7.5	7.3	119.5	13.6	2.4	2.4	2 to 3
Means of the RCT-studies				**41**	**56**	**32**	**54**	**66.6**	**66.9**	**5.9**	**6.1**			**2.14**	**2.06**	
Chang et al., 2018	UPDRS III	Physical	Repeat-ed	4	9	4	9	59.7	59.7	6.44	6.44	50-55%	Moni-tored	1.96	1.96	1 to 2.5
Corbett et al., 2013	ROM Hip exten-sion	Physical	Repeat-ed	4	13	4	13	64	64	8.7	8.7	60 - 70%	NA	1.8	1.8	1 to 3
Duchesne et al., 2015	TMT-A&B	Cogni-tion	Repeat-ed	6	13	6	13	59	59	8.1	8.1	60-80%	Moni-tored	2	2	1 to 2
Fiorelli et al., 2019	TMT-B	Cogni-tion	Repeat-ed	6	6	6	6	66.5	66.5	5.7	5.7	NA	15-17	NA	NA	1 to 3

Hazamy et al., 2017	Visual Memory	Cogni-tion	Repeat-ed	NA	NA	NA	NA	66.23	66.23	NA	NA	Moni-tored	NA	NA	NA	1 to 3
McGough 2016	FTSTS	Physical	Repeat-ed	16	25	16	25	62.7	62.7	5.4	5.4	Moni-tored	Moni-tored	NA	NA	0 to 4
Nadeau et al., 2017	Walking speed	Physical	Repeat-ed	6	13	6	13	59	59	8.1	8.1	up to 80%	Moni-tored	2.1	2.1	1 to 2
Nadeau et al., 2019	RT visual	Physical	Repeat-ed	6	13	6	13	59	59	8.1	8.1	NA	Moni-tored	2.1	2.1	1 to 2
Peacock et al., 2014	Muscle strength leg press	Physical	Repeat-ed	NA	NA	NA	NA	67.6	67.6	NA	NA	110-160 bpm	11 to 16	NA	NA	1 to 3
Ridgel et al., 2011b	TMT-B	Cogni-tion	Repeat-ed	7	12	7	12	63	63	5.1	5.1	73 bpm	6 to 8	1.9	1.9	1 to 3
Ridgel et al., 2012	Bradykine-sia	Physical	Repeat-ed	6	4	6	4	64.5	64.5	6.5	6.5	98 bpm	13.3	1.8	1.8	1 to 3
Steib et al., 2018	Time in balance	Physical	Repeat-ed	4	13	4	13	64.4	64.4	NA	NA	60 - 70%	6 to 20	2.1	2.1	1 - 2.5
Tabak et al., 2013	PDCRS	Cogni-tion	Repeat-ed	1	1	1	1	66.5	66.5	10.5	10.5	97 bpm	Moni-tored	NA	NA	NA
Uygur et al., 2015	4SST	Physical	Repeat-ed	1	9	1	9	64.6	64.6	4.1	4.1	Moni-tored	NA	1.95	1.95	<3.0
Uygur et al., 2017	H&Y Scale	Physical	Repeat-ed	4	10	4	10	62.4	62.4	3.3	3.3	Moni-tored	13.7	2.54	2.54	<3.0
Means of the NRCT-studies				**71**	**141**	**71**	**141**	**63.3**		**6.7**				**2.03**		
Overall means				112	197	103	195	64.3	64.4	6.4	6.5			2.06	2.04	

In the treatment groups of the RCT studies there were 97 participants (41 females and 56 males), in the corresponding control groups there were 86 participants (32 females and 54 males) (Table 2). In the NRCT studies the number of the participants was 212 (71 females and 141 males). The average age in the RCT studies was 66.6 years in the treatment group, and 66.9 years in the control group. In the NRCTS studies the average age was 63.3. The disease duration in the treatment group of the RCT studies was 5,9 years, and in the corresponding control group it was 6.1 years. In the NRCT group the average disease duration was 6.7 years.

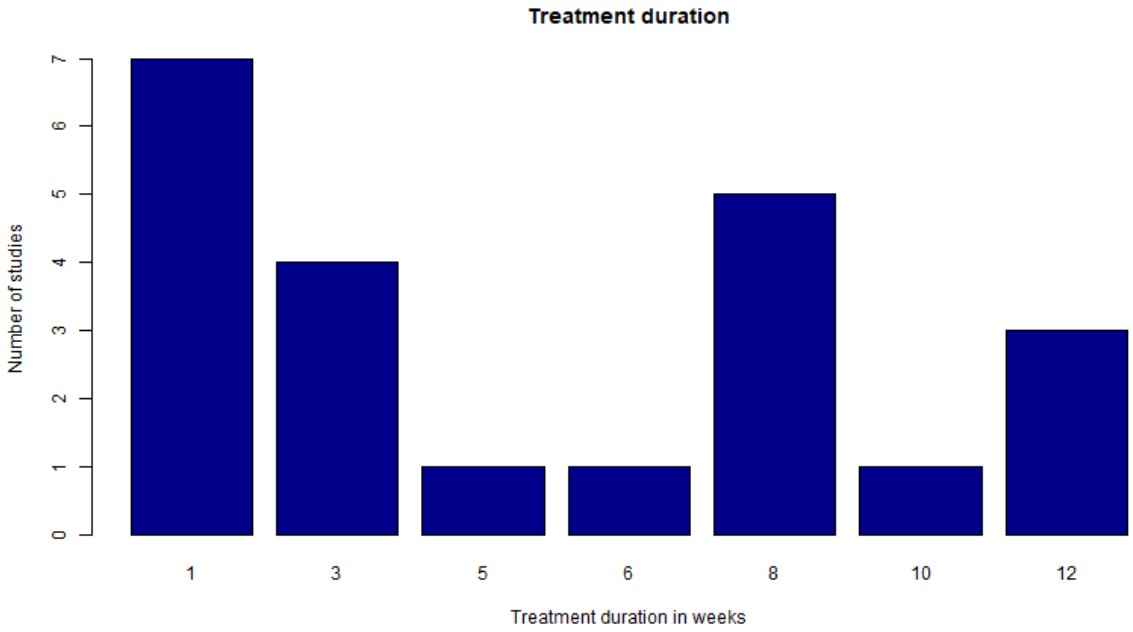

Figure 4.
Treatment duration of the cycling intervention in weeks.

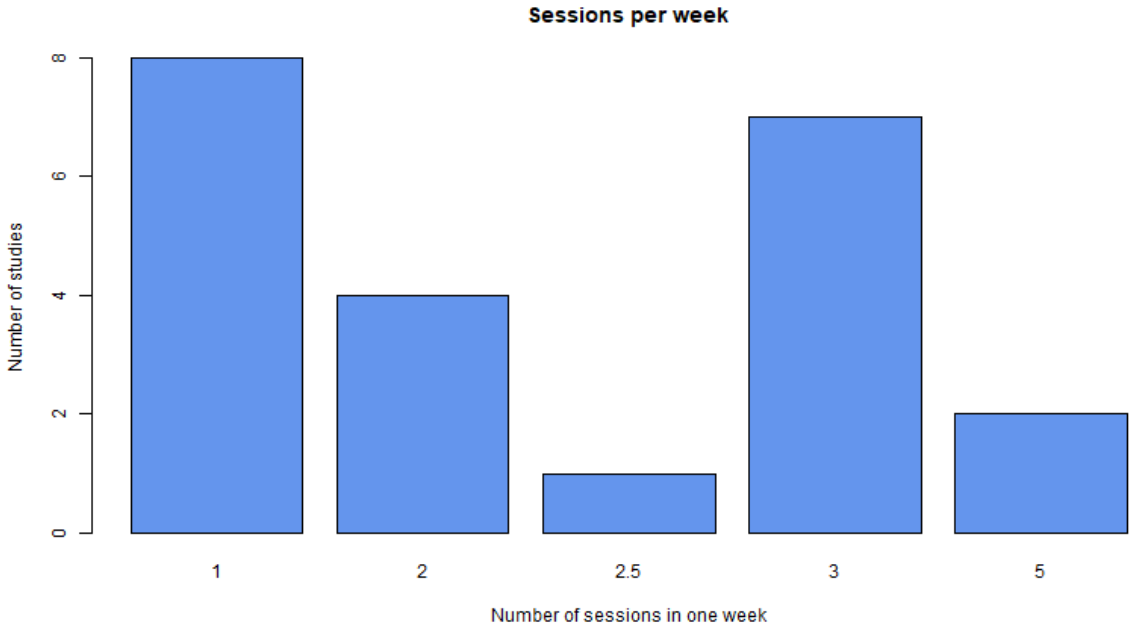

Figure 5.
Number cycling intervention sessions per week.

5.4.3 Cycling intervention characteristics

The reporting of the exercise intensities varied widely across the studies: Independent of the study design five reported to have monitored the heart rate during the treatment without any further details, while four studies did not report any statement on the heart rate. Six studies reported an average ranging between 73 and 160 beats per minute (bpm). The remaining seven studies reported the heart rate as a percentage either from the estimated capacity, or from an actual measured capacity. In the latter seven studies the percentage varied between 60 to 80% of the maximum heart rate. The treatment duration varied between one and twelve weeks with an average of 2.3 weeks (Figure 4.). Sessions per week varied between one to five sessions in a week. Out of the 22 included studies, three did not report the cycling cadence (rpm), one reported it to be on a “comfortable” level, while the remaining 18 reported the cadence. In the Figure 4. the cadence is reported in groups of ten rpm, starting at 40 to 50rpm and going up to 80 to 90rpm. The Figure 4 shows that nine out of the 18 reporting studies aimed at a cadence of 70 to 80rpm, or 80 to 90rpm. An assisted cycling intervention was reported by 41% of the studies, while 59% reported the intervention to have been non-assisted. For further details on the intervention characteristics, see the Table 2, and the Figures 4 to 7.

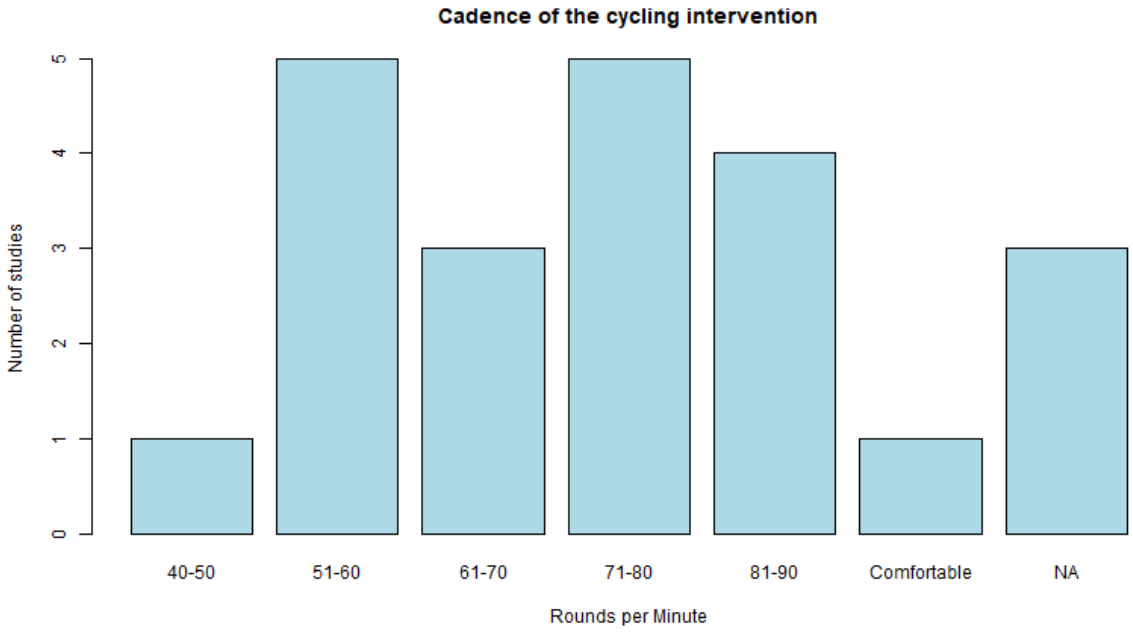

Figure 6.
The measured cadence of the intervention binned into groups starting at 40 rpm and ending at 90 rpm.

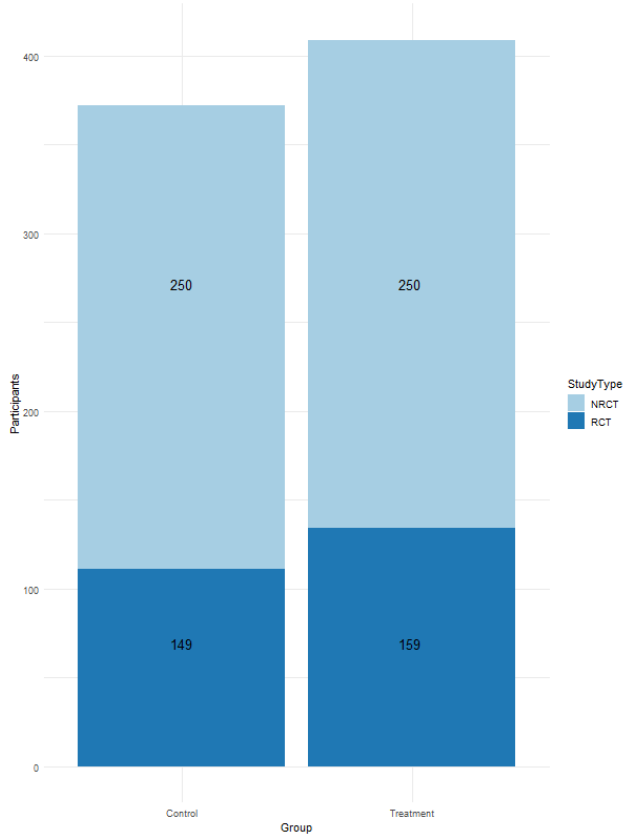

Figure 7.
Number of participants in the treatment and control groups of randomized and non-randomized trials

5.4.4 Quality analysis

The F-test for the equality of the variances of the quality scores of both reviewers showed that there was no significant variance $F(1, 21) = 1.2$, $p = 0.34$. Also, the following t-test confirmed that the quality scores did not vary significantly $t(42) = 1.0$, $p = 0.33$. Thus, the mean score averaged across the scores given by each reviewer can be inspected (Table 3). The given scores ranged from 0.65 to 0.96, the best possible score being 1.0. An average score across all studies was 0.81 with a standard deviation of 0.08, and a median of 0.8.

Table 3. The outcomes of the quality assessment.

Overall score			
Author	**Reviewer I**	**Reviewer II**	**Mean**
Arcolin et al., 2016	0.93	0.96	0.95
Demonceau et al., 2016	0.73	0.85	0.79
Ferraz et al., 2018	0.92	0.88	0.9
Tollàr et al., 2019	0.96	0.96	0.96
Qutubuddin et al., 2013	0.88	0.81	0.85
Ridgel et al., 2011a	0.73	0.73	0.73
Harper et al., 2019	0.69	0.86	0.76
Duchesne et al., 2015	0.88	0.95	0.92
Hazamy et al., 2017	0.79	0.69	0.74
Nadeau et al., 2017	0.71	0.91	0.81
Peacock et al., 2014	0.79	0.83	0.81
Nadeau et al., 2019	0.75	0.95	0.85
Chang et al.,2018	0.86	0.86	0.86
McGough et al., 2016	0.77	0.77	0.77
Tabak et al., 2013	0.7	0.72	0.71
Uygur et al., 2017	0.65	0.64	0.65
Ridgel et al., 2012	0.71	0.73	0.72
Ridgel et al., 2011b	0.79	0.83	0.81
Corbett et al., 2013	0.86	0.69	0.78
Steib et al., 2018	0.71	0.82	0.77
Fiorelli et al., 2019	0.81	0.83	0.82
Uygur et al., 2015	0.79	0.75	0.77

Below are the averaged *quality* assessments of two independent reviewers, and the averages of the scores across both means.

5.4.5 Publication bias

The funnel plot (Figure 7) shows that the included studies are equally distributed around the line of pooled effect size (the dashed vertical line in the middle of the funnel), thus not indicating a risk of bias. This is which is confirmed by Egger´s statistical test of the intercept on the funnel plot asymmetry (*Intercept* = 1.88; [*CI* = -0.27 - 4.04, *t* = 1.71], *p* = 0.10) (Figure 7).

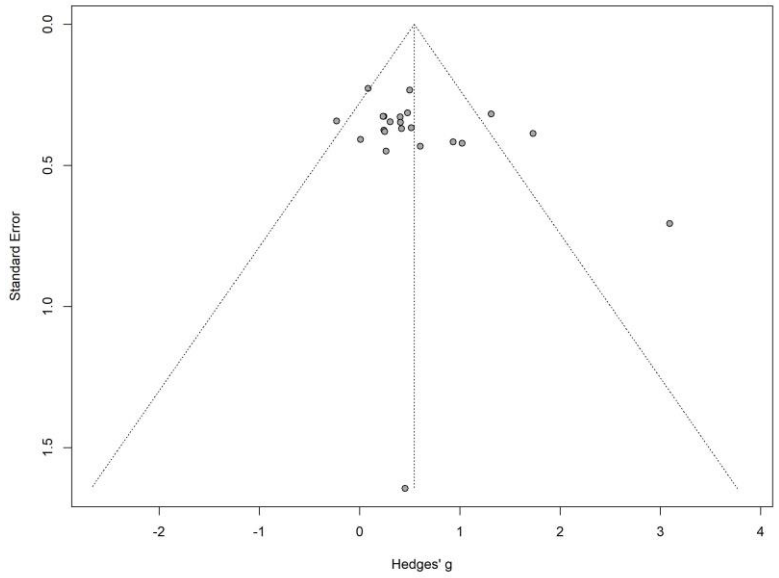

Figure 7. A funnel plot of the publication bias assessment.
As the smaller studies are expected to have higher SE, they are expected to be located at the lower end of the y-axis, while the studies with more participants are expected to show a lower SE, and thus be at the upper end of the y-axis.

5.4.6 Primary Measures

To test the overall efficacy of a cycling intervention, the primary measures from all 22 studies were pooled together, and the pooled SMD showed a significant effect (k 22; SMD 0.55; [0.27, - 0.82], t = 4.16, p < 0.001), yet also a substantial between studies heterogeneity (I^2 = 53.5%). Based on the outlier detection analysis, two studies (Nadeau et al., 2017 and Ridgel et al., 2012) were detected to be outside the CI. Furthermore, based on the influence analysis, next to detecting the two above mentioned studies as outliers due to high effect size influence and high heterogeneity, an additional study (Tollár et al., 2019) was marked as contributing to high heterogeneity and effect size (Figure 5.). The latter was also marked by the leave one out method as a contributor to a high I^2 (Figure 6.). Thus, three studies were removed from the final effect size pooling of the primary measures. Now, the overall effect size is smaller, but also there is no substantial heterogeneity in the results (k 19; SMD 0.35;

[0.21, - 0.48], t = 5.47, p < 0.001, I^2 = 0,0%) (Figure 7.). The sub-level by the outcome type test (motor vs. cognitive) revealed a significant difference between the groups (p 0.02) (Motor 13; SMD 0.42; [0.27, - 0.58]), and (Cognition 6; SMD 0.15; [-0.11, - 0.4]). The sub-level by design analysis revealed no significant difference between the groups (p 0.5) (RCT 7; SMD 0.29; [0.00, - 0.57]), and (NRCT 12; SMD 0.38; [0.21, - 0.55]).

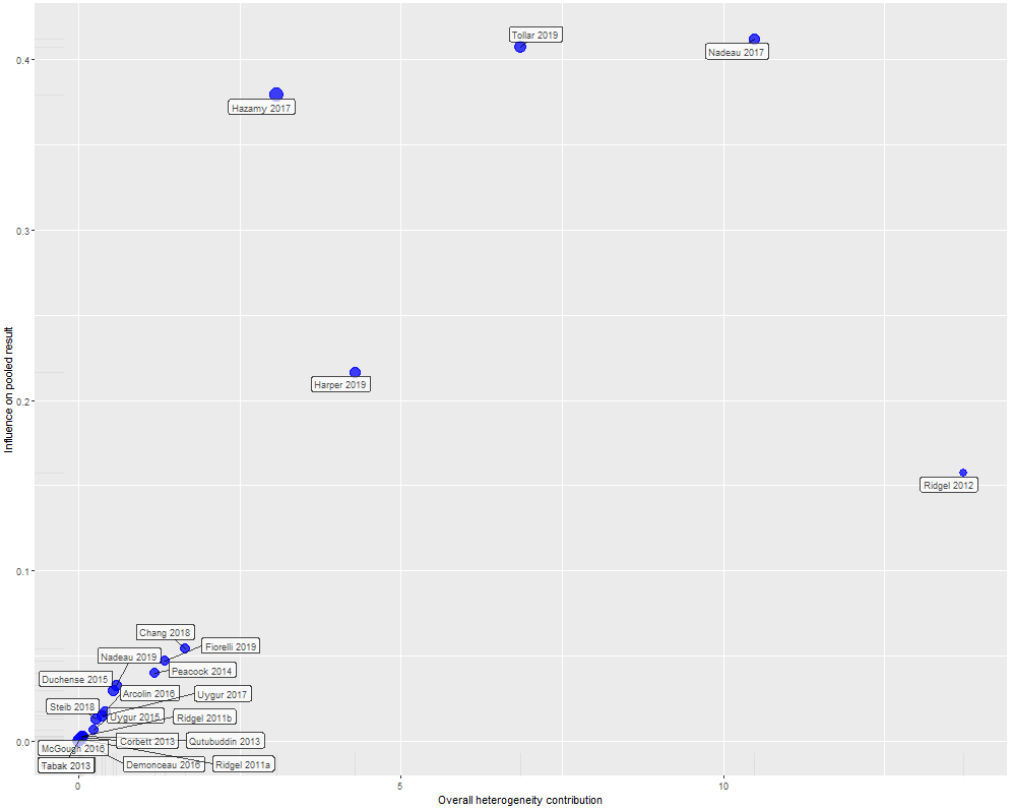

Figure 9. Influence analysis.
The Baujatplot on the primary measures shows on the x-axis the overall heterogeneity contribution of the studies, and the y-axis shows the pooled effect size of each study. Based on the plot it can be seen that some studies contributed to the final effect size of the primary measures with a high heterogeneity and high effect size.

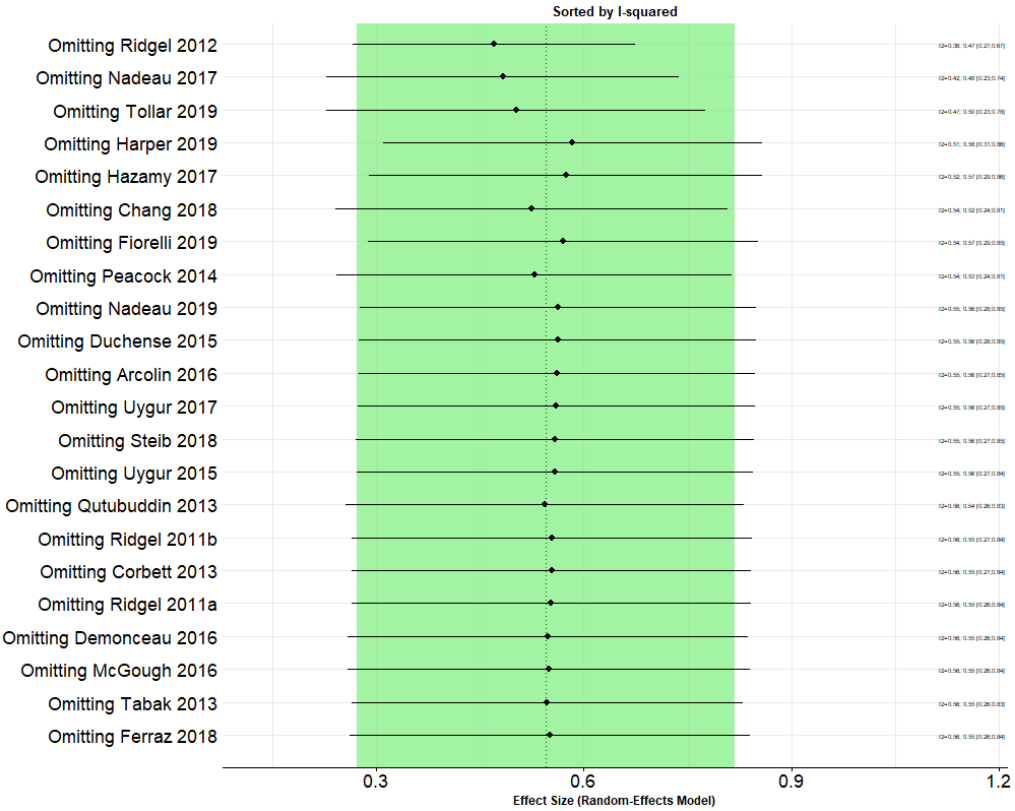

Figure 10. Leave-one-out based on I^2.
The plot above demonstrates how the overall pooled effect size (in the x-axis) of the primary measures would change if each study at the time was left out. The studies are organized based on the increasing order of the I^2-value of heterogeneity. I^2 is the percentage of the variability in the effect size not caused by sampling error.

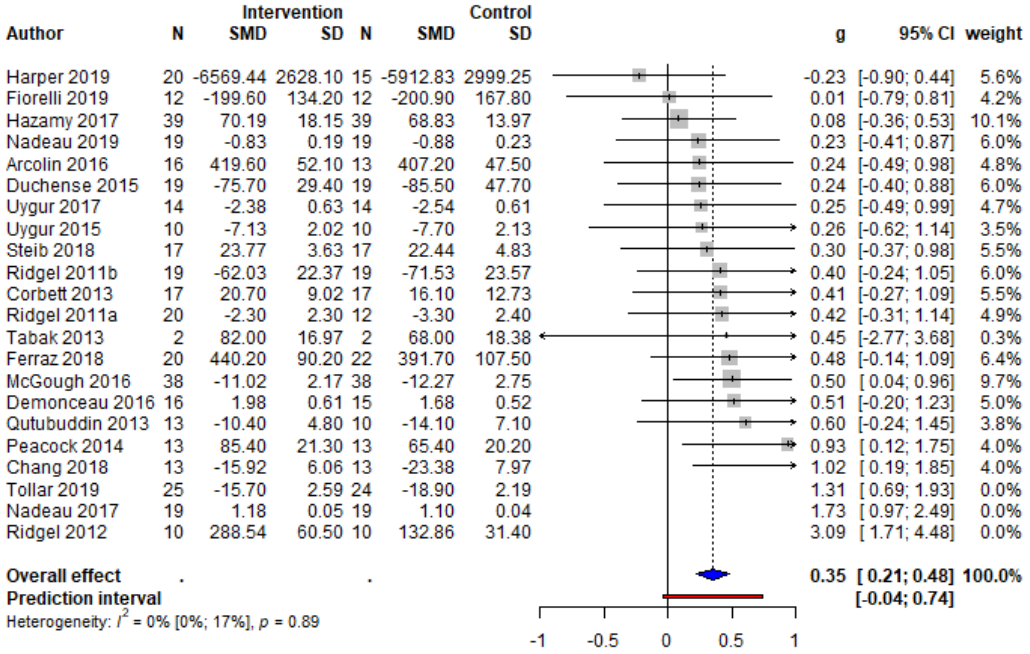

Figure 11.

Forest plot on the primary measures after excluding three studies. The x-axis shows the overall effect size prediction interval ranging from -1 to 1, a higher value representing higher improvement. I^2 = Higgin´s & Thompson´s I^2 represent the percentage estimate of the variability not caused by the sampling error in the overall effect size. The p-value indicated the probability of the specific amount of heterogeneity available in the data.

Starting from the left upper corner of the image: Author = First author and the publication year of the included study, N = number participants in the intervention group, SMD = standardized mean difference of the measured outcome per study in the intervention group, SD = standard deviation of the SMD, followed by the same values for the control group. g = Hedge´s bias-correct standardized mean difference size based on the inverse of the variance, 95 % CI = 95% confidence interval, weight = The weight each study is given based on the inverse of the variance. If the value is 0%, it means that the study has been excluded from the forest plot.

5.5 Secondary measures

5.5.1 Gait – 6-MWT

After removing one study (Tollár et al., 2019) based on the influence analysis, the 6-MWT is the at the limit demonstrating significant benefit from the intervention with a p-value of 0.05 (*k* 3; SMD 0.55; [0.00, - 0.90], *t* = 4.32, *p* = 0.05) (Figure 12.).

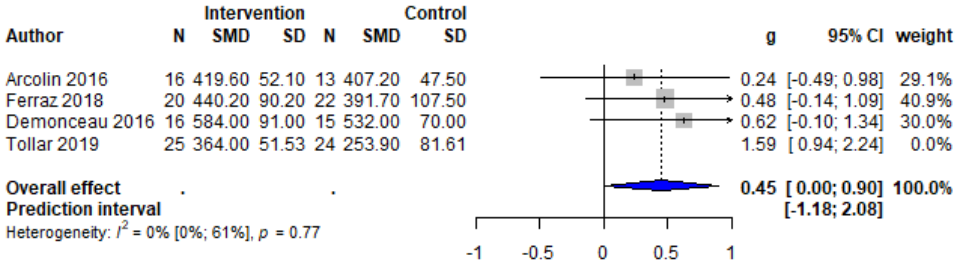

Figure 12.
Effect of cycling intervention on the 6MWT. N (number of studies), SMD (Standardized mean difference), SD (Standard deviation), CI (Confidence interval), I² (Percentage of variability)

5.5.2 Gait – Cadence

The initial pooled effect size is also at the limit of significance demonstrating an effect of the intervention on cadence while walking (*k* 6; SMD 0.60; [0.00, - 1.21], *t* = 2.59, *p* = 0.05). As the heterogeneity is large (I^2 = 60%), based on the influence analysis a study contributing to high heterogeneity and high effect size is omitted (Nadeau et al., 2017) leading to reduction of heterogeneity (I^2 = 24.3%), and the simultaneous reduction of the model significance (*k* 5; SMD 0.42; [-0.09, - 0.94], *t* = 2.29, *p* = 0.08)

5.5.3 Gait – Step length

Based on the five included studies, the intervention has no effect on the step length (*k* 5; SMD 0.15; [-0.08, - 0.29], *t* = 1.85, *p* = 0.14, I^2 = 0.0%).

5.5.4 Gait – Velocity

After the removal of two studies (Tollár et al., 2019; Nadeau et al., 2017) based on the influence analysis, the heterogeneity of the initially significant, but high heterogeneity model (k 10; SMD 0.57; [-0.12, - 1.02], t = 2.88, p = 0.02, I² = 66.5%) is reduced while still demonstrating a significant effect of the intervention on the gait velocity (k 8; SMD 0.26; [-0.09, - 0.43], t = 3.63, p = 0.01, I² = 0.0%) (Figure 13.).

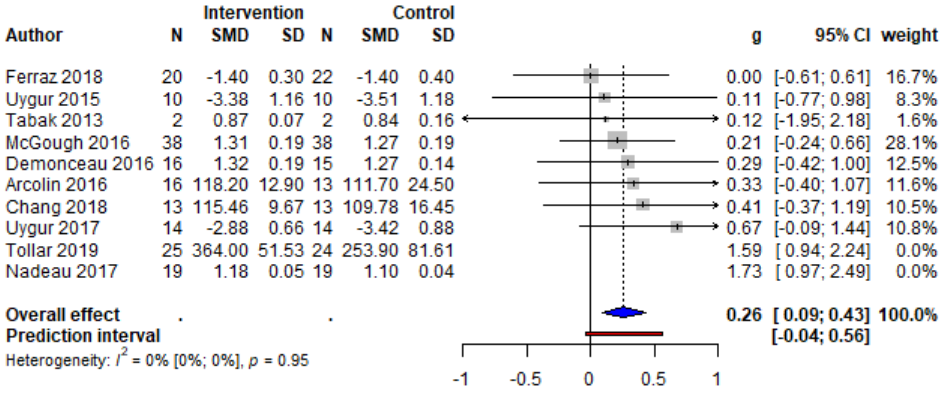

Figure 13.
Effect of cycling intervention on the gait velocity. N (number of studies), SMD (Standardized mean difference), SD (Standard deviation), CI (Confidence interval), I^2 (Percentage of variability)

5.5.5 Bradykinesia

There is no significant effect of cycling on bradykinesia outcome measures based on the four included studies (*k* 4; SMD 1.3; [-0.45, - 3.04], *t* = 2.37, *p* = 0.1, I^2 = 73.0%).

5.5.6 Tremor

Also, the tremor symptoms do not seem to benefit from the intervention with four included studies (*k* 4; SMD 0.18; [-0.14, - 0.51], *t* = 1.77, *p* = 0.17, I^2 = 0.0%).

5.5.7 Balance

The outcome measure balance with 9 included studies does not demonstrate a significant benefit from the intervention (*k* 9; SMD 0.51; [-0.13, - 1.14], *t* = 1.84, *p* = 0.1, I^2 = 71.4%). Yet, the CI-base outlier detection suggests the removal of one study (Nadeau, 2017) which leads to an improved model and a small significant effect of the intervention (*k* 8; SMD 0.25; [-0.05, - 0.45], *t* = 3.01, *p* = 0.02, I^2 = 0.0%) (Figure 14.)

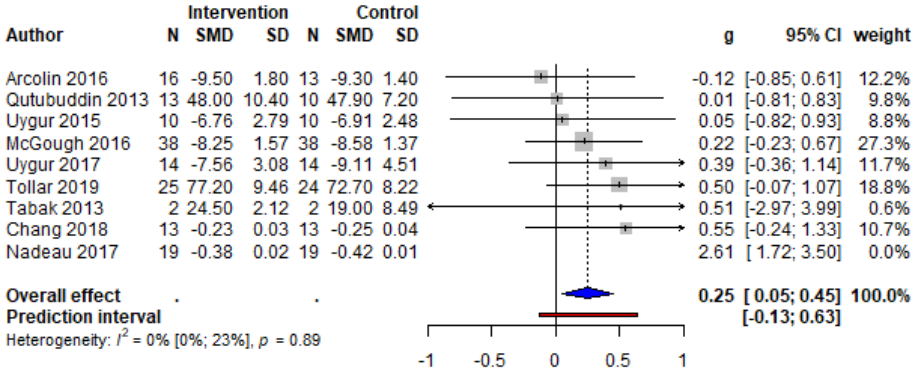

Figure 14.
Effect of cycling intervention on balance. N (number of studies), SMD (Standardized mean difference), SD (Standard deviation), CI (Confidence interval), I² (Percentage of variability)

5.5.8 PDQ39-Questionnaire

Based on the initial pooling of the effect size with nine included studies the results of the PDQ39-questionnaire there is a non-significant and slightly heterogenous effect (*k* 6; SMD 0.35; [-0.17, - 0.88], *t* = 1.74, *p* = 0.14, I^2 = 35.2%). Based on the influence analysis, one study is removed as it contributes with high heterogeneity and high effect size resulting in a high and significant effect size (*k* 5; SMD 0.55; [0.25, - 0.86], *t* = 4.98, *p* = 0.01, I^2 = 0.0%) (Figure 15.).

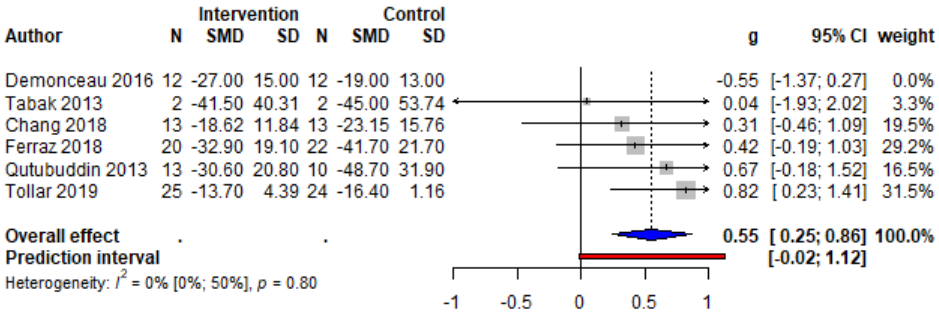

Figure 15.
Effect of cycling intervention on the PDQ-39 score. N (number of studies), SMD (Standardized mean difference), SD (Standard deviation), CI (Confidence interval), I² (Percentage of variability).

5.5.9 UPDRS-Motor questionnaire

The motor sub section of the UPDRS questionnaire does not demonstrate a significant effect of benefitting from the cycling intervention (*k* 6; SMD 0.55; [-0.06, - 1.17], *t* = 2.31, *p* = 0.07, I^2 = 63.3%), also removal of a study contributing to high heterogeneity and effect size does not change the result (*k* 5; SMD 0.37; [-0.23, - 0.98], *t* = 1.7, *p* = 0.16, I^2 = 37.3%).

5.5.9.1 Quality of Life

When grouping together different measures of quality of life, it seems that there is no significant improvement (*k* 8; SMD 0.23; [-0.14, - 0.6], *t* = 1.46, *p* = 0.18, I^2 = 25.7%).

5.6 Discussion

The present findings demonstrated a significant effect of improvement in the primary outcome measures. When cognition and motor measures were applied as sub-levels, it is revealed that the effect size of the outcomes measuring motor and other types of physical parameters improved significantly more from the intervention when compared to the outcomes measuring cognitive performance. Also, when the outcomes were grouped based on physical functionality across primary and secondary measures, a medium-sized improvement was demonstrated.

Also, it was shown that interventions that were implemented more than once lead to better outcomes, thus demonstrating that longer-term exercise should be preferred over one-time sessions aiming at immediate effects when designing cycling interventions. Nevertheless, based on this review it is not possible to draw conclusions whether cycling is best applied as goal-orientated form of exercise, or whether it is beneficial also in the form of general physical activity.

The pace of walking as measured with the different tests of velocity show a moderate effect of benefitting from the intervention. In addition, the 6MWT measuring walking capacity in general, consisting of aerobic capacity and endurance showed a significant improvement. Also, Balance showed a small effect of improvement, and the PDQ-39, measuring coping abilities in the daily living of the patients, showed a large improvement. Instead, no substantial improvement was shown in the measures of bradykinesia, tremor, cadence, nor step

length, nor in the overall life quality. Also, the Motor Subscale of the UPDRS showed no improvement.

Postural instability and falling are a common clinical problem, and a reason for immobilisation, and a reduced quality of life among PD patients (Bloem, Grimbergen, Cramer, Willemsen, & Zwinderman, 2001; Fasano, Canning, Hausdorff, Lord, & Rochester, 2017; Silva de Lima et al., 2020). This meta-analysis did not allow the measurement of falling rate directly due to lack of studies addressing it. Nevertheless, addressing falling rate as an outcome of cycling exercise might be of a particular future interest as it has been shown that balance training enhances the reduction of fear of falling (Canning, Paul, & Nieuwboer, 2014). Thus, as this meta-analysis showed that cycling benefits balance, the results imply indirectly that cycling might contribute to reduced risk of falling. Nevertheless, this hypothesis should be tested with an outcome measures directly addressing falling, or the fear of it. This would be of particular importance, as cycling could be an alternative for patients who either are prevented, or too uncomfortable to engage in an activity where falling is possible, e.g. for treadmill training.

Recent meta-analyses have shown that freezing of gait (FOG) can benefit from physiotherapy and of physical exercise in general (Cosentino et al., 2020; Delgado-alvarado et al., 2020). Due to lack of FOG being an outcome measure in the here included studies, this meta-analysis cannot provide any information about the influence of cycling on FOG. Nevertheless, this would be of interest, as there is evidence for freezers and non-freezers to respond differently to cycling in their basal ganglia by demonstrating an increase in the narrow band beta range (~ 18Hz) compared to patients less susceptible to freezing (Storzer et al., 2017). Against this notion, it would be crucial to further investigate the possible benefits of cycling in particular on patients suffering from freezing for an enhanced customisation of a possible cycling intervention.

The PDQ-39 is a questionnaire implemented by health and social care professionals to assess an overall self-reported quality of life of PD patients, and it is commonly used to investigate changes in response to treatment. The questionnaire consists of 8 dimensions assessing the frequency of experienced difficulties in daily living including social situations,

relationships and communication ("The Parkinson's Disease Questionnaire (PDQ39)," 2020). Due to the wide variety of the 8 dimensions (mobility, activities of daily living, emotional well-being, stigma, social support, cognitions, communication, and bodily discomfort) of the PDQ-39 (Jenkinson, 2014), it would be beneficial to address the subscales, in particular as the outcome measure *quality of life* of this meta-analysis was not significant. The outcome *quality of life* consisted of different measures of depression, wellbeing, and disability. Thus, based on the here presented results it cannot be concluded in further detail in which aspects of wellbeing & functioning the improvement takes place. Nevertheless, the large effect size (SMD 0.55) of the PDQ-39 of this meta-analysis is an encouraging indication about the benefits of cycling going beyond physical improvement, thus benefitting coping in daily life, and the self-rated overall quality of life.

There is evidence that moderate to high intensity physical exercise is well tolerated by PD patients, leading to better outcomes than low intensity training (Kelly et al., 2017; Schenkman et al., 2018). In this meta-analysis it was addressed whether the primary outcome measures showed a difference in the effect size depending on whether the cadence was high or low, but no difference in the outcomes was shown. Nevertheless, not all studies reported the cadence, and also cadence alone is not a sufficient measure of training intensity. Other measures of intensity, such as heart rate and rate of perceived exertion were reported rather variably, either not at all, in different units, or they were merely monitored, thus drawing further conclusion about the role of intensity isn´t feasible based on the current data. Cadence and pedalling resistance are easily varied parameters of cycling. Despite there already being studies, which systematically vary these parameters, more comparative studies are needed to better understand the customizability of cycling. This is an important notion, as cycling has the potential of catering to both high- and low intensity exercise while allowing the customisation of the intensity of skeletomuscular activation, and overall mobility by varying the ratio of cadence and resistance.

Patients´ own motivation, and possible barriers of exercising are a major factor in the success of physical exercise and overall activity (Schootemeijer et al., 2020). In the here included studies, no conclusions can be drawn about the subjective ratings towards the exercise itself. Thus, for a successful clinical practice there clearly is a need to assess patient´s own

judgement of the exercise program, as well as the overall suitability in terms of practical implementation into one´s own daily life. Furthermore, other affective dimensions such as the influence of the exercise on self-esteem might be of interest knowing the contrast in the ease of the movement between cycling and walking, even among the patients who tend to freeze (Snijders et al., 2012). Also, this would be of interest knowing how fear of falling can prevent PD patients from being active and lead to an increasing sedentary life-style (Bloem et al., 2001; Jonasson, Nilsson, Lexell, & Carlsson, 2018) . Indeed, the importance of considering safety and preference features have been suggested to be a decisive factor, in whether clinician promotes treadmill, or cycling to a patient (Ellis, 2020). Furthermore, for future studies it would be beneficial to assess for any differences in targeting exercise to early, middle, or later disease stages (Cosentino et al., 2020; Ellis, 2020).

Theoretically, the main concern when including NRCT studies is that the baseline measurements of the different groups are not equal due to a lack of randomisation in the treatment allocation, thus leading to biased results (Higgins & Altman, 2008). To observe and minimize any possible bias, several methodological precautions were taken. Firstly, instead of using the most common Cochrane Risk of Bias assessment, which is customized for RCT-studies in particular, a thorough and versatile assessment of quality designed to include NRCT studies was applied. Furthermore, the statistical analysis was based on the assumption that the clinical population can be so heterogeneous that an additional parameter of random confound should be considered, thus leading to choose the Random Effect Model over a Fixed Effect Model to inspect the intervention efficacy. Furthermore, conservative, multi-step statistical testing with different measures of heterogeneity was chosen to point at any studies contributing to a large heterogeneity. Lastly, the primary outcomes were inspected on the sub levels of being NRCT or RCT to test whether the study design led to differences in the found effect sizes. In the case of some of the outcome measures, the robust testing led to a decrease of the effect sizes when compared to the initial pooling, yet the robust heterogeneity measures were chosen to ensure a good overall quality of the final effect sizes.

5.7 Limitations

Theoretically, the main concern when including NRCT studies is that the baseline measurements of the different groups are not equal due to a lack of randomisation in the treatment

allocation, thus leading to biased results (Higgins & Altman, 2008). To observe and minimize any possible bias, several methodological precautions were taken. Firstly, instead of using the most common Cochrane Risk of Bias assessment, which is customized for RCT-studies in particular, a thorough and versatile assessment of quality designed to include NRCT studies was applied. Furthermore, the statistical analysis was based on the assumption that the clinical population can be so heterogeneous that an additional parameter of random confound should be considered, thus leading to choose the Random Effect Model over a Fixed Effect Model to inspect the intervention efficacy. Furthermore, conservative, multi-step statistical testing with different measures of heterogeneity was chosen to point at any studies contributing to a large heterogeneity. Lastly, the primary outcomes were inspected on the sub levels of being NRCT or RCT to test whether the study design led to differences in the found effect sizes. In the case of some of the outcome measures, the robust testing led to a decrease of the effect sizes when compared to the initial pooling, yet the robust heterogeneity measures were chosen to ensure a good overall quality of the final effect sizes.

6. Conclusion and future research

It is well known that the cause of idiopathic Parkinson's disease is the slow depletion of dopaminergic neurons in the mid brain. The consequences of the disease for the PD patients and their spouses or care givers are diverse, and not fully understood. While the main symptoms are related to motor dysfunction, the cascade of life quality reducing challenges and co-morbidities is notable and requires further research.

This master's thesis aimed to outline how complex PD can be from the clinical and individual perspective. This was done by inspecting the clinical features of the disease and their manifestations on the levels of motor performance, cognition and overall well-being. Also, the most common co-morbidities, depression, diabetes, dementia & overall cognitive decline, and sleep disorders were discussed. It was pointed out that many of the co-morbidities might remain unrecognized or untreated, either due to lack of clinical diagnostic understanding, or due to insufficient knowledge on the relationship of the disease and normal aging, or on the causality of the symptoms. Which symptoms are clinical manifestations part of PD pathogenesis, and which symptoms belong to normal aging? Does PD develop due to depression-related neurotransmitter dysfunction, or does PD lead to depression, dementia, and sleep disorders? To point at the historical and ongoing scientific development of understanding PD, the clinical criteria and the theories linking neuropathophysiological and neurophysiological models of the disease were outlined: The motor dysfunction is better understood when inspecting the neuronal functioning of the mid brain motor network, and its relationship to the cortical areas in terms of oscillatory activity, rather than focusing on anatomically more restricted bursting patterns.

Furthermore, physical exercise as a form of adjuvant therapy was discussed. Also, based on pre-existing studies, cycling was introduced as an intriguing topic of further research from the scientific perspective. Studies investigating the neuromotor differences by contrasting cycling and walking have discovered stronger beta-band suppression during cycling, and also discovered a narrow-beta band *signature* in patients more susceptible to freezing, paving the way for further research to understand how cycling might alleviate the symptoms of

freezers, in particular. With the brief excursion into the literature of sociology of cycling and enactivist approaches to human cognition, the relationship of body, environment, and the human mind, it was discussed how important and far-reaching consequences the simple act of cycling could have for PD patients in terms of the experience of social belongingness and sensorial multimodality, learning & re-learning, self-esteem and self-agency. The role of inclusive environmental design was discussed to point out that design can either emphasize the disease deficits or alleviate them by allowing the individuals to be emplaced. Indeed, thinking in terms of an increasingly inclusive environmental design, the cultural climate of the society can be assumed to have a large role in either supporting or preventing inclusion. Many European countries are involved in the development of overall cycling culture (cf. European Cycling Federation, 2020), instead of focusing only on the traffic infra, considering a wide variety of needs and aspects. Also, an excellent example of inclusive awareness is a project called *Cycling without ages* with the motto *"The right to the wind in your hair"* (Cycling without ages, 2020) where the very idea is to enable elderly people to have the bodily sensation that one gets when moving in an uncovered vehicle. The influence of the cultural climate should not be underestimated as acceptance, tolerance and support would surely be required when including individuals with different capacities and needs into the mobile environment.

The empirical part of the thesis focused on the meta-analysis and review on the state-of-the-art understanding of cycling exercise and its features in the rehabilitation and symptom alleviation of PD patients. The meta-analysis and literature review provide evidence that cycling is a versatile form of physical exercise for PD patients. Considering the clinical relevance of the findings, the results support the application of cycling, in particular to improve gait related parameters of balance, walking pace, and overall walking capacity. Furthermore, based on the strong effect of the outcome measure PDQ39, the benefits of cycling go beyond physical improvement, resulting in an increased quality of daily living. Also, the results indicate that the effects of cycling are based on longer term exercise rather than on immediate effects of single sessions. Conclusively, it seems that cycling can be tolerated by PD patients, and that it leads to versatile improvements. Yet, it also seems that the effects of cycling, and physical exercising in general are rather specific, and when it comes to a more detailed understanding, or prescribing a physical exercise regimen based on personalised

needs and preferences, the current knowledge remains scattered. Based on the review, it is concluded that more studies are needed to directly address the potential benefit of cycling on the most common, functionally and psychologically disabling symptoms such as falling, and FOG (Bloem et al., 2004; Giladi et al., 2001). Also, defining the optimal intensity, and cadence of cycling exercise, as well as recognizing the optimal stage of disease progression for cycling therapy need clarification.

Appendix A

The following papers were included into the meta-analysis and review.

1. Arcolin, I. et al. (2016) 'Intensive cycle ergometer training improves gait speed and endurance in patients with Parkinson's disease: A comparison with treadmill training', Restorative Neurology and Neuroscience, 34(1), pp. 125–138. doi: 10.3233/RNN-150506.

2. Chang, H.-C. (2018) 'An 8-Week Low-Intensity Progressive Cycling Training', 14(2), pp. 225–233.

3. Corbett, D. B., Peer, K. S. and Ridgel, A. L. (2013) 'Biomechanical muscle stimulation and active-assisted cycling improves active range of motion in individuals with Parkinson's disease', *NeuroRehabilitation*, 33(2), pp. 313–322. doi: 10.3233/NRE-130961.

4. Demonceau, M. *et al.* (2016) 'Effects of 12 weeks of aerobic or strength training in addition to standard care in Parkinson ' s disease : a controlled study . EUROPEAN JOURNAL OF PHYSICAL AND REHABILITATION Subscription : Information about subscribing to Minerva Medica journals is onl'.

5. Duchesne, C. *et al.* (2016) 'Influence of aerobic exercise training on the neural correlates of motor learning in Parkinson's disease individuals', *NeuroImage: Clinical*. Elsevier B.V., 12, pp. 559–569. doi: 10.1016/j.nicl.2016.09.011.

6. Ferraz, D. D. *et al.* (2018) 'The Effects of Functional Training, Bicycle Exercise, and Exergaming on Walking Capacity of Elderly Patients With Parkinson Disease: A Pilot Randomized Controlled Single-blinded Trial', *Archives of Physical Medicine and Rehabilitation*. Elsevier Inc, 99(5), pp. 826–833. doi: 10.1016/j.apmr.2017.12.014.

7. Fiorelli, C. M. *et al.* (2019) 'Differential acute effect of high-intensity interval or continuous moderate exercise on cognition in individuals with Parkinson's disease', *Journal of Physical Activity and Health*, 16(2), pp. 157–164. doi: 10.1123/jpah.2018-0189.

8. Harper, S. A. *et al.* (2019) 'Non-motor symptoms after one week of high cadence cycling in Parkinson's disease', *International Journal of Environmental Research and Public Health*, 16(12). doi: 10.3390/ijerph16122104.

9. Hazamy, A. A. *et al.* (2017) 'Improved cognition while cycling in Parkinson's disease patients and healthy adults', *Brain and Cognition*, 113, pp. 23–31. doi: 10.1016/j.bandc.2017.01.002.

10. McGough, E. L. *et al.* (2016) 'A tandem cycling program: Feasibility and physical performance outcomes in people with Parkinson disease', *Journal of Neurologic Physical Therapy*, 40(4), pp. 223–229. doi: 10.1097/NPT.0000000000000146.

11. Nadeau, A. *et al.* (2017) 'A 12-week cycling training regimen improves gait and executive functions concomitantly in people with parkinson's disease', *Frontiers in Human Neuroscience*, 10(January), pp. 1–10. doi: 10.3389/fnhum.2016.00690.

12. Nadeau, A. *et al.* (2018) 'A 12-Week Cycling Training Regimen Improves Upper Limb Functions in People With Parkinson's Disease', *Frontiers in Human Neuroscience*, 12(January), pp. 1–10. doi: 10.3389/fnhum.2018.00351.

13. Peacock, C. A. *et al.* (2014) 'Introducing a multifaceted exercise intervention particular to older adults diagnosed with parkinson's disease: A preliminary study', *Aging Clinical and Experimental Research*, 26(4), pp. 403–409. doi: 10.1007/s40520-013-0189-4.

14. Qutubuddin, A. *et al.* (2013) 'Parkinson's Disease and Forced Exercise: A Preliminary Study',

Rehabilitation Research and Practice, 2013, pp. 1–5. doi: 10.1155/2013/375267.

15. Ridgel, A. L., Muller, M. D., *et al.* (2011) 'Acute effects of passive leg cycling on upper extremity tremor and bradykinesia in Parkinson's disease.', *The Physician and sportsmedicine*, 39(3), pp. 83–93. doi: 10.3810/psm.2011.09.1924.

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Appendix B

[Abstract in German]

Die Parkinson-Krankheit (PK) ist eine progressive, neurodegenerative Störung, die zur Verschlechterung der motorischen Funktionen führt und dabei den Gang und die Körperhaltung beeinflusst. Tremor, Steifheit und allgemeine Verlangsamung der Bewegungsabläufe ist ebenso üblich wie kognitive und emotionale Defizite. Um ihre Symptome zu lindern, wird PK-Patienten empfohlen, körperliche Übungen zu praktizieren. Radfahren hat sich hierbei als eine besonders gut geeignete Form von körperlicher Übung für die Patienten erwiesen, da viele Patienten trotz erheblicher motorischer Beschwerden die Fähigkeit Radzufahren behalten. Es sind jedoch mehr Informationen nötigt, um genaue Übungsparameter bestimmen sowie nützliche Ergebnisse erzielen zu können

Zusätzlich hat sich Radfahren, im Vergleich zum Gehen, als ein faszinierender Ausgangspunkt in den Neurowissenschaften erwiesen, um mehr über das beeinflusste motorische Netzwerk durch die Anwendung von elektro-physiologischen Methoden durch Vergleich von kortikaler und subkortikaler motorischer Kontrolle während des Radfahrens und Gehens zu erfahren

Das Ziel dieser Masterarbeit ist es, die Vorteile des Radfahrens für PK-Patienten aus der Perspektive der klinischen Mitarbeiter/innen, Forscher/innen und Patient/innen zu diskutieren. Um dieses Ziel zu erreichen, wurden ein Meta-Analyse und ein Review durchgeführt. Es wurde gefragt, in welchem Ausmaß und wie beständig die PK-Patienten von Fahrradübungen profitieren, und welche Symptome durch diese Intervention sich im Besonderen verbesserten. Studien, die die erhaltene Fähigkeit des Radfahrens erforschen, werden im Rahme des komplexen und vielfältigen Symptombilds sowie der defekten Motorkontrolle diskutiert. Zusätzlich wird kurz die erhaltene Fähigkeit des Radfahrens trotz erheblicher motorischer Schwierigkeiten aus der Perspektive des Embodiments und der Soziologie erläutert. Es wird darauf hingewiesen, dass das Gestaltung der Umgebung, welches unterschiedliche motorische und kognitive Fähigkeiten berücksichtig, das Symptombild von PK-Patienten entweder unterstützen oder verschlimmern kann.

Der meta-analytische review beinhaltet 22 Studien mit 395 PK-Patienten. Aus den Ergebnissen geht hervor, dass es sich die motorischen Fähigkeiten signifikant verbesserten im Vergleich zu den kognitiven Fähigkeiten. Vor allem wurde gezeigt, dass das Gleichgewicht, die Gehgeschwindigkeit und die Gehkapazität sowie die allgemeine Lebensqualität sich durch Radfahren und Radfahrübungen verbesserten. Die Übungsprogramme variierten in ihrer Dauer, Intensität und in der Zielkadenz. Zusätzliche Studien sowie systematich erhobene Daten sind notwendig, um genauer Aussagen über die Rolle der Intensität und Kadenz machen zu können. Der Einfluss vom Radfahren auf die am meisten beeinträchtigenden Symptome wie Erstarren, Stürzen und die Angst vor Stürzen muss hierzu gemessen werden.

Es wird geschlossen, dass Radfahren vor allem die funktionelle Leistung unterstützt und kritische Funktionen beim Gang verbessert. Zusätzlich wird durch Radfahren die allgemeine Lebensqualität der PK-Patienten verbessert.

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