



Summary

Parkinson's disease (PD) is a severe progressive neurological disorder. Many patients suffer from problems with mobility, especially gait and gait-related activities. Physical therapy and especially training by the help of external rhythms ('cueing') can help to optimize gait and gait-related activities.

The main focus of this thesis is on the effects of cueing training on gait and gait-related activities in patients with PD. The aims were to determine the effectiveness of optimal therapeutic treatment and self management strategies on (1) functional performance and health-related quality of life (HrQoL), (2) the amount of physical activity, and (3) the risk of falls. The transferability of therapeutic cueing to health-related quality of life and patients' own social setting was studied as well.

In **Chapter 1** the aims and outlines of the present thesis are introduced. Background information is presented from the perspective of history, epidemiology and medical management, including pharmaceutical and neurosurgical treatment options for patients with PD. Subsequently, the state of the art regarding the role of rehabilitation medicine in the management of patients with PD is presented and discussed, and in particular the use of external rhythms to improve gait and gait-related activities is addressed.

In the introduction the Rescue project is presented. 'Rescue' is an acronym for 'Rehabilitation in Parkinson's Disease: Strategies for Cueing'. This project was an international collaboration and was financed by the European Commission. The lack of high quality studies on the effect of cueing in PD and the call from the European Commission for development and evaluation of technologies and systems designed to reduce the impact of disabilities on older people, stimulated the initiation of this project.

Within the Rescue project, a large randomized clinical trial (RCT) was conducted to determine the efficacy of cueing training in the home situation of PD patients. The preparations for this RCT were described in the introduction of this thesis, including the development of a prototype cueing device, the development of guidelines for home-based cueing training and the composition of a comprehensive and valid test battery for evaluating the effects of cueing in terms of functions, activities and participation in patients with idiopathic PD.

In **Chapter 2** a systematic review is presented, evaluating the literature regarding the effects of external rhythmical cueing on gait in patients with PD. Articles published from 1966 to January 2005 were identified by two physical therapists. To be included, articles had to investigate the effects of external rhythmical cueing (i.e. auditory, visual or tactile cueing) on gait parameters in patients with idiopathic PD. Both controlled and non-controlled studies were included. The methodological quality of 24 studies (total number of patients = 626) out of the 159 screened studies was evaluated by two independent reviewers. Two of the 24 studies were RCTs, both of high methodological quality. One of these RCTs focused specifically on the effects of auditory rhythmical cueing in patients with PD and found positive effects on walking speed. The other RCT did not focus specifically on external rhythmical cueing of individual patients with PD, but on group exercises in general, including walking with cues. All other studies were pre-experimental studies. A best-evidence synthesis was applied on

included studies, showing strong evidence for improving walking speed with the help of auditory cues. Insufficient evidence was found for the effectiveness of visual and somatosensory cueing.

It is unclear whether positive effects identified in the laboratory can be generalized to improved activities of daily living (ADLs), HrQoL and reduced frequency of falls in the community. In addition the sustainability of a cueing training programme remained uncertain.

In **Chapter 3** a study is presented in which the reliability, responsiveness and feasibility of a part of the Rescue test battery was determined in patients' own home situation. The test battery contained the Unified Parkinson's Disease Rating Scale (UPDRS), a six meter timed walking test, the Timed Get Up and Go test (TGUG), the Berg Balance Scale and the Functional Reach test. All tests were applied in random order by three independent observers on 26 PD patients to determine the inter-rater reliability. One of these three observers applied the test battery two times on all patients, with 7 days between the test moments, to determine the intra-rater reliability. The test battery was shown to have moderate to excellent Intraclass Correlation Coefficients for reliability, despite the non-standardized home environment and limited clinical experience of the observers in assessing PD patients.

Responsiveness was determined by calculating the smallest detectable differences and the Reliable Change Indexes (RCI) for each assessment. All tests showed RCIs under 11%. Due to a lack of consensus on how to quantify responsiveness, strict comparison with the literature proved difficult. However, results from this study can be used as indicators for an approximate threshold in the utility of the tests as outcome measurements in a larger clinical trial.

Feasibility was determined by measuring the time needed to apply the whole test battery, including the time needed to adapt the home environment for assessments (e.g. moving furniture). The whole test battery was applicable within 30 minutes, showing sufficient feasibility.

The study in **Chapter 4** was aimed at determining the effects of rhythmic visual cueing under changing visual conditions on stride frequency and step length in patients with PD ($n=21$) and healthy age matched controls ($n=7$). All subjects performed five conditions on a motorized treadmill: walking (1) without visual cue or optic flow to determine baseline stride frequency; (2) with optic flow, using a rear-projection screen in front of the treadmill, providing the illusion of walking through a corridor; (3) with visual rhythmic spatial cueing (VRS), i.e. optic flow with transverse lines on the floor; (4) with visual temporal rhythmic cueing (VRT), i.e. a rhythmically flashing light attached to a pair of glasses, without optic flow; (5) with VRT and optic flow. After a baseline measurement, conditions 2 to 5 were randomly offered. During each condition, the speed of the treadmill was systematically increased and decreased after reaching a maximum speed. In the 4th and 5th condition subjects were asked to synchronize their stride to the VRT, with the frequency set at 10% below baseline stride frequency. Stride frequency and step length were determined using an activity monitor (AM).

PD patients on average walked with a higher stride frequency and shorter step length compared to controls. In addition, a hysteresis effect was observed during the walking speed manipulations, in which stride frequency was lower at the decreasing speeds compared to the same speed levels in the increasing speed range. Both VRS and VRT resulted in lower stride frequencies (and thus larger strides) compared to the non-cued conditions.

The study showed that stride frequency and stride length in PD patients, as well as in controls, is not rigidly coupled to walking speed and can be manipulated by manipulation of walking speed as well as by using spatial and temporal rhythmic visual cues. This indicates that for patients with PD, the regulation of stride parameters may be susceptible to relatively straightforward therapeutic intervention strategies by using systematic manipulation of walking speed as well as rhythmic visual cueing.

In **Chapters 5** and **6** results of the Rescue trial are presented. The Rescue trial investigated the effects of cueing training in the home using cueing techniques during gait and gait-related activities in three countries (i.e., New Castle, UK, Leuven, Belgium and Amsterdam, The Netherlands). Hundred-and-fifty-three PD patients with mild to moderate disease severity were included in a single-blind randomized cross-over trial. Subjects allocated to early intervention ($n=76$) received a three-week home cueing programme using a prototype cueing device followed by 3 weeks without training. Patients allocated to late intervention ($n=77$) underwent the same intervention and control period in reverse order. After the first 6 weeks post randomization, both groups had a 6 week follow-up without training. The Posture and Gait score (PG score) assessed at baseline, 3, 6, and 12 weeks was the primary outcome measure. Secondary outcomes included specific measures on gait, freezing and balance, functional activities, quality of life and carer strain, covering all levels of the International Classification of Functioning (ICF). In addition, all subjects wore an AM on testing days to record body movements and postures. Within each district, all clinical assessments as well as AM measurements were applied by trained assessors who were blinded for treatment allocation.

In **Chapter 5** results of the clinical tests are presented, showing small but significant improvements after intervention on the PG scores, severity of freezing, gait speed, step length, timed balance tests and a greater confidence to carry out functional activities (Falls Efficacy Scale). No carry-over effects were observed in ADLs and quality of life domains. In **Chapter 6** results of the AM are presented, showing significant improvements for dynamic activity, walking, and walking periods exceeding 5 seconds and 10 seconds and a reduction of static activity. Cueing training may thus be considered a useful therapeutic adjunct to the overall management of gait disturbance in PD. Effects of intervention, measured with clinical tests and with AM, reduced significantly at 6 weeks follow-up. The wearing off of intervention effects underscores the need for permanent cueing devices and follow-up treatment.

In **Chapter 7** a prediction model for the risk of falling in PD was developed based on determinants extracted from home-based assessments. Data on gait, gait-related activities, balance and on non-motor symptoms were obtained from 153 patients in their own home. Sixty-six patients were classified as fallers. Based on the existing

literature and expert opinions, 50 candidate determinants for falling were selected. Eighteen out of these 50 candidate determinants for falling showed a significant association with falling in a bivariate logistic regression analysis. Multivariate logistic regression modelling showed that: (1) Freezing of gait, (2) TGUG score, (3) disease duration, and (4) problems with walking, assessed with UPDRS item 15, significantly identified patients at risk for falling. The multivariate model identified fallers accurately in 74% of the cases. This accuracy is in line with the existing literature and we believe that the model could be used as an indication for identifying patients who are at risk of falling using home-based tests, especially when the fall history is unknown. Therefore, the present model may serve as a direction for further research in order to refine and develop tests that reflect the underlying mechanisms of falling, such as freezing, more validly, and that can be reliably implemented in the home situation. In line with this aim, future studies should further investigate the underlying mechanisms that cause falling in PD, in order to optimize the identification of patients at risk.

In **Chapter 8** the impact of specific and non-specific effects of cueing is discussed in the light of the aims of the Rescue project. Methodological issues, the content of the applied cueing training and international collaboration of the Rescue project are critically appraised in this general discussion, and recommendations for future research are presented. Based on this thesis, it is concluded that cueing training is an important evidence based component of the multidisciplinary treatment of patients with mild to moderate idiopathic PD. In addition, cueing training does not lead to falls and effects of training were irrespective of the cue type. Recommendations on future research are focused on the development of measurement outcomes in line with the aims of therapy or training. These measurement outcomes should preferably be constructed unidimensionally in line with the domains of the ICF. Apart from a test battery consisting of a comprehensive core set of measurement instruments, more research is needed to develop a light weight, small AM with sufficient storage and battery capacity to record physical activity for several days. With such an AM, a reliable way to detect and classify freezing and falls should be developed and with that new interventions aimed at preventing these problems. Other recommendations for future research are to investigate the neurophysiological mechanisms behind cueing, to investigate a possible neuroprotective role of cueing training and to determine the optimal dose-response relationship for more permanent effects of cueing training on mobility. Future studies on cueing should also involve patients with early and late stages of idiopathic PD including cognitive impairments. In addition, effects of cueing in patient groups with other parkinsonisms, such as multisystem atrophy or progressive supranuclear palsy, should be studied. Furthermore, a cheap permanent 'cueing device' providing auditory or somatosensory cues needs to be developed, giving patients the opportunity to use cues during performance of ADL. Finally, attention should be paid to the implementation of evidence based guidelines for health care professionals in which cueing is used as a safe way of training in the home environment of their patients.

| Summary