Rehabilitation in Parkinson's disease:

strategies for cueing

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Cover design Ivar Iding, www.kijkenluister.nl
Layout Renate Siebes, Proefschrift.nu
Printed by GVO drukkers & vormgevers B.V. | Ponsen & Looijen, Ede
ISBN 978 90 8659 295 1

The Rescue trial presented in this thesis was supported by the European Committee (grant number QRLT-2001-00120). This thesis was published with financial support of Boehringer Ingelheim bv.

VRIJE UNIVERSITEIT

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ACADEMISCH PROEFSCHRIFT

ter verkrijging van de graad Doctor aan
de Vrije Universiteit Amsterdam,
op gezag van de rector magnificus
prof.dr. L.M. Bouter,
in het openbaar te verdedigen
ten overstaan van de promotiecommissie
van de faculteit der Geneeskunde
op dinsdag 19 mei 2009 om 15.45 uur
in de aula van de universiteit,
De Boelelaan 1105

door

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geboren te Leiden

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copromotor: dr. E.E.H. van Wegen

Contents

1

General introduction

Introduction

Parkinson's disease (PD) is a severe progressive neurological disorder. A walking problem is one of the main problems for patients suffering from this disease. Physical therapy (PT), and especially training with the help of external rhythms, also named cues, can help to optimize gait and gait-related activities. The present thesis is about the effects of cueing training on gait and gait-related activities in PD.

This introduction outlines the focus of this thesis. First, background information on PD 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 will be given about the role of rehabilitation medicine in the management of patients with PD and in particular about the use of external rhythms to improve gait and gait-related activities.

History and diagnosing Parkinson's disease

In 1817, James Parkinson wrote his essay on the 'shaking palsy'.[1] Shaking palsy was defined as:

> *'involuntary tremulous motion, with lessened muscular power, in parts not in action and even when supported; with a propensity to bend the trunk forwards, and to pass from walking to a running pace: the senses and intellects being uninjured'.*

It was Jean-Martin Charcot who named shaking palsy 'Parkinson's disease' (PD), and who gave lectures about PD in the famous Parisian Salpêtrière in the late nineteenth century.[2] It took until 1912 for Fritz Heinrich Lewy to discover the abnormal proteins accumulations in neurons leading to PD, later named the 'Lewy bodies'. Finding Lewy bodies in the substantia nigra or locus ceruleus still provides the only evidence for having PD.[3] This assessment can only be done by autopsy.[3] The surest diagnosis of PD, while the patient is alive, can be obtained using neuroimaging techniques, magnetic resonance imaging (MRI) or positron emission tomography (PET). These techniques are very expensive and not widely available. Therefore patients are mostly diagnosed on three out of the four cardinal signs of PD: tremor, rigidity, bradykinesia and unilateral onset, together with a substantial and sustained response to Levodopa or dopamine agonists (criteria for probable diagnosis of PD).[3] Ninety-two percent of the clinical diagnoses of PD are confirmed at autopsy, largely because cardinal symptoms also occur in other extra-pyramidal diseases than PD, such as multiple system atrophy or progressive supranuclear palsy.[4]

Apart from the cardinal motor signs, also non-motor clinical features of PD are known; these can include psychiatric problems, cognitive disorders, autonomic dysfunction, oculomotor abnormalities and characteristic abnormalities of olfactory and visual perception.[3] However, the most prominent symptoms in patients with PD are impairments of automatic motor control. As a consequence, patients suffer from difficulties in four key areas within the field of activities: gait, balance, posture and transfers (e.g. moving in and around the bed, getting in and out of a chair).[5]

Epidemiology

PD is one of the most common neurological disorders.[6] In a prospective study an incidence of 19 PD patients on 100.000 people per year was shown.[7] The prevalence is estimated at 160 patients per 100.000 people.[8] The population of the European Union counted approximately 485 million people in 2002,[9] meaning that approximately 776.000 European inhabitants suffered from PD. PD shows a strong and consistent increase with age, with a peak incidence between 70 and 79 years.[10] With the expected rise in life expectancy in Europe, approximately 5.5 years in 2050, the number of PD patients will rise.[9] The greying European population will lead to a shortage of working people in the future, including health professionals.

The increase of PD patients will lead to great economic burden, acknowledging that health care costs for PD patients are relatively high. A PD patient in the Western and Northern European countries costs between 4700 and 8160 euros per year, increasing with the stage of the disease.[11] In particular, the costs of 'fallers' are estimated to be twice as much than of 'non-fallers'.[12]

Need for the development of a home-based rehabilitation programme

With the increasing pressure to overcome the economic burden of medical management in the next future, the European Commission (EC) is aware that patients need to stay independent for a longer time, preferably in their own home situation.[13] This aim phrased in the fifth framework of the EC is important, acknowledging that 40 to 60% of the patients show difficulties with walking, and increased risk for falling.[14-15] As a consequence, patients experience increasing problems in their activities of daily living (ADL) and lose their autonomy.

Optimal medication is not always able to reduce all motor problems.[16] Moreover, medication intake needs to be raised over the course of the disease because of wearing-off effects. As a result, the increasing dose of medication intake can lead to severe side effects, varying from motor complication to psychological problems.[17] Neurosurgery can be a worthwhile addition to medication, but is not available for every PD patient, due to its high costs and because it is not appropriate for all patients (e.g., PD patients with dementia are excluded from this technique). Because of the non-optimal availability and effects of medication and neurosurgery, additional rehabilitation care is necessary.

Rehabilitation programmes should be aimed at maintaining or increasing patients' mobility. Unfortunately, high qualitative rehabilitation programmes to fulfil this need have not been developed prior to 2002. Finding innovative techniques to maintain patients' autonomy is in line with the fifth framework, key action 6 of the EC:[13] 'the ageing population and disabilities' of the Quality of Life and Management of Living Resources Work programme, and specifically 6.4. 'Coping with the functional limitation of old age'. The priorities described in this action, line 6.4, are: (1) the development of technological products and systems contributing to greater mobility and less dependency, both inside and outside the home, including the work place; (2) the development of caring and nursing products designed to support older people in their own homes; (3) improving postural stability and preventing falls; (4) technical aids to rehabilitation; and (5) optimum forms of physical and/or cognitive exercises.

Rehabilitation management in PD patients should preferably be a multidisciplinary effort, due to the multidimensional character of symptoms that accompany PD. Examples of the different professionals involved in the care for PD patients are medical specialists (neurologists/rehabilitation physicians) to assess and make an inventory of the PD-related symptoms, instalment of medical treatment and referral to other disciplines, physical therapists to work on movement related problems, speech therapists in case of speech problems or problems with drooling or swallowing, occupational therapists to help improve limitations in participation and activities, and dieticians in case of excessive weight loss.

Professionals should work together as a team targeted on patients' needs in order to remain independent in activities of daily living (ADL) preferably in patients' own home situation. Since walking problems are amongst the main problems in PD, physical therapists are considered to be key members of the multidisciplinary team. The main aim of PT is to maximize functional ability, and to minimize secondary complications through movement rehabilitation within a context of education and support for the whole person.[18] PT is relatively cheap and can reduce the economic burden by keeping patients in their own home situation, especially when PT prevents PD patients from falling and hospitalization.[12,19]

PT —both individual and group treatment— often focuses on functional limitations (e.g., transfers, walking, stair climbing, reaching, grasping) and disabilities (e.g., hobbies, sports, social activities) and comprises mobility exercises, gait training (with or without the use of external rhythmic cues), training of daily activities, relaxation therapy and breathing exercises. Another aspect is that of educating patients (as well as their partners and families) about the disease process and the benefits of exercise therapy.

Results of a systematic review by de Goede et al.[20] supported the hypothesis that patients with PD may benefit from exercise therapy in terms of ADLs and walking ability (walking speed, stride length), but not in terms of neurological signs. The meta-analysis shows small improvements in ADLs (approximately 5%), walking speed (approximately .08 m/s or .29 km/h) and stride length (approximately 6 cm).[20] However, it is unclear whether these effect sizes are clinically relevant. The conclusions of two Cochrane reviews suggested that there was insufficient evidence to support or refute the efficacy of PT in PD, or to favour the use of one form of PT over another.[18,21]

One form of PT is therapy with the help of visual or auditory rhythms (i.e., rhythmic cues). A number of uncontrolled studies suggest that using cues is a promising tool to improve parkinsonian gait, but the methodological quality of most studies is low.

Studies on cueing: state of the art

Using a rhythm to improve gait in PD is mentioned in the literature since 1924,[22] but was not scientifically studied until 1967.[23] It was Von Meyer-Königsberg, in 1924, who described several cases of patients with parkinsonism who responded well to rhythmic dancing.[22] He noticed that dancing on march music, guided by a nurse, improved gait and posture in patients with parkinsonism. In his book 'Methods of treatment in post encephalitic parkinsonism' Witzleben wrote about visual rhythmical patterns that could be used to improve gait.[24] Examples of these visual rhythmical patterns were stepping

over pieces of wood, and over balls. An inverted cane was used as visual cue as well.

In 1967, Martin executed the first experiment on cueing.[23] He presented different patterns on the floor and instructed patients with PD to walk over these patterns. After analyzing the gait pattern of his subjects, he concluded that parallel lines, perpendicular to the walking direction, resulted in a maximum improvement of gait. In 1994, the first study on the effect of auditory cues on gait in PD was published,[25] whereas the first and only randomized controlled trial (RCT) was published in 1996.[26] This RCT was of low methodological quality and was underpowered. In one other RCT, PD patients received cueing training as part of a training programme.[27] In a narrative review, Rubinstein and colleagues found 18 studies about rhythmic cueing published until 2002.[28] Unfortunately, all studies included in this narrative review were non-controlled and of low methodological quality, heavily underpowered and mostly executed in a laboratory, except for the RCT of Thaut et al.[26] In addition, a wide variety of measurement instruments were used, which made it difficult to cluster these studies and draw a general conclusion about the effect of cueing.[28] A systematic review of published cueing studies until 2005 is presented in Chapter 2 of this thesis.

The lack of studies with high quality on the effect of cueing in PD and the call from the EC for development and evaluation of technologies and systems designed to reduce the impact of disabilities on older people, to restore their functions and to mitigate the challenge of their social and physical environments,[13] stimulated the initiation of the Rescue project. 'Rescue' is an acronym for 'Rehabilitation in Parkinson's Disease: Strategies for Cueing'.[29] This project is a collaboration of the VU University Medical Center in Amsterdam (The Netherlands), the Northumbria University in Newcastle upon Tyne (UK) and the Katholieke Universiteit Leuven (Belgium) and was financed by the EC.[13] The Rescue project's aims were:

(1) obtaining new knowledge on the mechanisms behind the effect of different cue types on gait parameters during stable condition and after contextual manipulation, and exploring the optimal conditions for effective cueing;
(2) composing a clinical battery of valid and reliable clinical tests measuring the symptoms of the disease, motor performance, functional disability, cognitive profiles, fatigue, mood disorders, quality of life and care giver strain, and find a way to monitor walking activity in daily life;
(3) developing a cueing device to facilitate gait and gait-related activities for use in the daily context;
(4) developing guidelines for the optimal use of cues, delivered by a cueing device or patterns on the floor, in the daily context;
(5) investigating the effects of an optimal therapeutic cueing programme in a single blind crossover, multicentre RCT;
(6) determining the transferability of identified and tested optimal cue types to symptoms of the disease, motor performance, amount of walking activity, functional disability, fatigue, mood disorders, quality of life and care giver strain; and
(7) determining the predicting factors for falls.

The Rescue project contained three phases: a preparation phase, a generalization phase, and a dissemination phase. The first phase was aimed to develop a cueing device, to establish guidelines and a test battery for evaluation. In addition, therapists and assessors in the Rescue project were trained to conduct the trial. In the generalization phase, the RCT was conducted, whereas in the dissemination phase found effects of the RCT were published and presented on an international European Conference in Amsterdam. In the final year of the Rescue project, the cueing guidelines were converted into an instruction CD for physical therapists and leaflets were developed to provide patients and caregivers with information about how to use cues in their own environment.

Development of a cueing device and therapeutic guidelines

For optimal use of cueing in patients' own home setting, there was a need for the development of a simple cueing device to provide different types of cueing in a manageable and comprehensive way. The development of innovative devices to improve parkinsonian gait was in line with the wishes of the EC.[13] Especially for PD patients, the device should be (1a) able to provide different types of cues; (2a) easy to handle; (3a) light weight; (4a) easy to attach to clothes to keep the arms free; and (5a) shock proof.

The cueing device was developed within the Rescue project for use in the cueing training of the RCT and met the above described criteria. The cueing device had the following characteristics: (1b) is able to provide an auditory cue (a rhythmic beep), a visual cue (a flashing light on the side of the spectacles), and a somatosensory cue (a rhythmic vibrating mini cylinder on the wrist); (2b) has two switches, one on-off switch and a switch to change modality, and two buttons, one to increase and to reduce the rhythm by one beat per minute ; (3b) is small and light weight (170 grams, 64.77 mm $\times$ 111.75 mm $\times$ 23.37 mm); (4b) has a clip to attach it to a belt or pocket and (5) is shock proof (see Figure 1a–d).

Cueing training was received from trained therapists, one in each participating country. To optimize and standardize the cueing training, guidelines were needed, knowing that there were no guidelines or treatment protocols available for optimal application of cueing in patients with PD. Therefore, a number of experiments were conducted in the gait laboratories of the VU University Medical Centre, the Katholieke Universiteit Leuven as well as in patients own homes in the environment of the University of Northumbria in order to develop guidelines and treatment protocols. The effect of different frequencies of auditory cueing (using a beep) and visual cueing (using a flashing light on the spectacles) on spatiotemporal and kinematic parameters of gait were determined. The stability of cues was tested as well, by making a walking adjustment while using auditory cues or visual cues. The experiments on auditory cueing and on visual cueing were executed in Leuven and Amsterdam, respectively. In addition to the temporal cues, experiments were conducted on spatial visual cues in the form of parallel lines on the floor to step over. These lines were projected on a screen in front of a patient, who was walking on a treadmill. This experiment on temporal and spatial visual cueing is presented in Chapter 4 of this thesis. The British members of the Rescue team conducted studies to determine cognitive profiles that facilitate cueing. Studies were conducted to determine the cognitive and behavioural

Figure 1a.
Cueing device

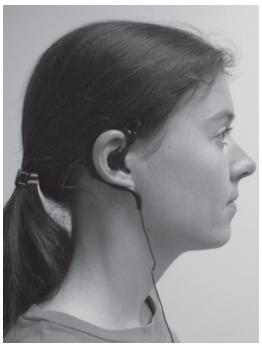

Figure 1b.
Auditory modality

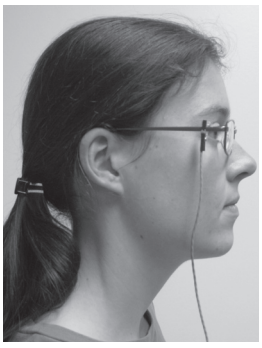

Figure 1c.
Visual modality

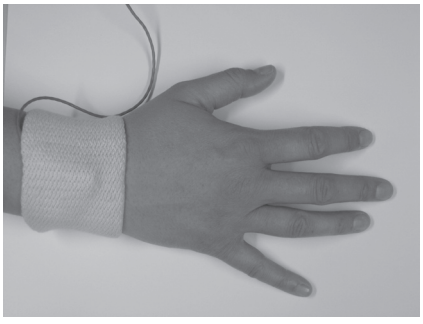

Figure 1d.
Somatosensory modality

strategies, facilitating an optimal effect of cues as well as the contextual factors impeding effective cueing.

All developed guidelines were linked to 15 therapy aims, distributed over five categories:

(1) **Gait**: improving walking speed, normalizing step/stride length, normalizing step frequency, management of freezing/festinating, training initiation of walking, improving turning;
(2) **Balance**: improving balance;
(3) Posture: training in sitting position, training in standing position, training when walking;
(4) **Transfer**: training in standing up from a chair/bed, training in sitting down on a chair/bed;
(5) **Other aims**: performing complex functional/double tasks, improving fitness, general exercises (e.g. mobility, coordination, strength).

The three physical therapists in the Rescue trial used these 15 cueing aims to tailor an optimal training programme for each participant in the study. Before the start of the Rescue trial, the three physical therapists in each country were trained in an identical application of the cueing guidelines. A diary was developed to record the used aims and cueing types during the therapy sessions.

Composing a test battery to evaluate effects of a home-based cueing programme

There is a large variety of measurement instruments to evaluate gait and gait-related activities as well as the effects of cueing in PD. Knowing that PD is a complex disease, affecting bodily functions, cognitive, psychological and social functions, a composed test battery should preferably reflect the different levels of the International Classification of Functioning (ICF).[30] The ICF is the WHO's framework for measuring health and disability at both individual and population levels.[30] The ICF framework describes how people live with their health condition, from body, individual and societal perspectives. With that, the ICF is helpful to structure a test battery and to ensure that all levels, related to PD, are included. In addition, the composed test battery should be easy to apply, and obey the main clinimetric properties such as reliability, validity and responsiveness for change, to evaluate the impact of a cueing programme on the different levels of the ICF. For the Rescue project, a choice was made in available tests that proved to be reliable and valid in laboratory settings. To confirm the reliability of the selected tests in the patients' own home situation, a reliability study was conducted to determine the inter- and intrareliability of all tests. Twenty-six patients were assessed by three assessors, reflecting the three European countries collaborating in the Rescue project. Responsiveness and feasibility of all tests in the home situation were determined as well. A part of this study is presented in Chapter 3 of this thesis. The three assessors in the Rescue trial were trained prior to the start of the trial to calibrate the assessment techniques.

It should be acknowledged that assessment instruments are random indications of patients' performance and not a continuous reflection of patients' 'real world' performance during a day. Especially in PD, clinical measurements can be very time specific, due to medication induced fluctuations and fatigue. Since the last decade, light weighted, portable equipment is available to monitor gait and gait-related activities.[31] Activity Monitoring (AM) enables collection of continuous data about patients' real performance in their own home environment, for example by using four or five accelerometers attached to the patient's body. In Chapter 5 results are presented of the effects of cueing in the home situation on the amount of walking activity, when measured with AM.

In addition to clinical assessments and AM, falling needs to be assessed. One concern of giving cueing training is that cueing may lead to an increase in fall events. Walking with cues can be experienced as a double task (paying attention to the rhythm and walking at the same time), leading to falls while walking due to loss of stability[32] or increase of gait variability.[33] Patients may walk more when learning how to facilitate walking with the help of cues. This may be another reason for a raise of falls: an increased walking activity means a higher risk to fall.

Recording falls (e.g. using post cards, calendars, phone calls, etc.) is frequently discussed in literature,[34] but there are several problems with existing methods. First, there is a recall problem: because most patients and health care providers tend to focus on consequences of falls, there is a possibility that non-injurious falls are disregarded.[35]

Cognitive impairments can worsen recall problems. The second problem for optimal recording of falls, is the variety of definitions for falling: seniors often have another perception of a fall than health care providers.[35] Frequently asking for falls and near falls, as clearly defined before the study, should be the optimal way to obtain information about the frequency of falling. In the Rescue project 'falls' were defined as 'an event that results in a person coming to rest unintentionally on the ground or lower level, not as a result of a major intrinsic event or overwhelming hazard'[36] and 'near falls' were defined as 'loss of balance where an actual fall could be prevented'. For the Rescue trial, a fall diary was developed, asking about falls and near falls, their circumstances and consequences. In Chapter 7 a model to predict falling is presented.

Aims and outline of the present thesis

The aim of the present thesis is to determine the effectiveness of identified and tested optimal therapeutic treatment and self management strategies for improving functional performance, improving the amount of physical activity and reduce the risk of falls. The transferability of identified and tested optimal cue types to a functional social setting was studied as well.

Initially, effects of external cueing will be investigated in Chapter 2, by a systematic review of all published studies on cueing training in PD until 2005. The objective of Chapter 3 was to identify reliable instruments to evaluate the effects of cueing on gait and gait-related activities. In this chapter a part of the study on clinimetric properties of the tests included in the clinical test battery of Rescue is presented. The study in Chapter 4 presents experiments conducted in the gait laboratory of the VU University Medical Centre. The pre-experiment is aimed to develop guidelines on gait training by investigating the impact of visual flow and using different visual rhythms to optimize parkinsonian gait. In Chapter 5 effects of the randomized clinical trial are presented by using the clinical test battery of Rescue, whereas effects measured with Activity Monitoring are presented in Chapter 6. Subsequently, a model aimed at identifying factors that are associated with falls in patients with PD is presented in Chapter 7. Finally, Chapter 8 presents the general discussion. In this chapter the main findings of the previous chapters are summarized, and implications are given for optimizing rehabilitation services in patients with PD. In particular, future directions are given for research and implementation of cueing guidelines to improve gait in PD.

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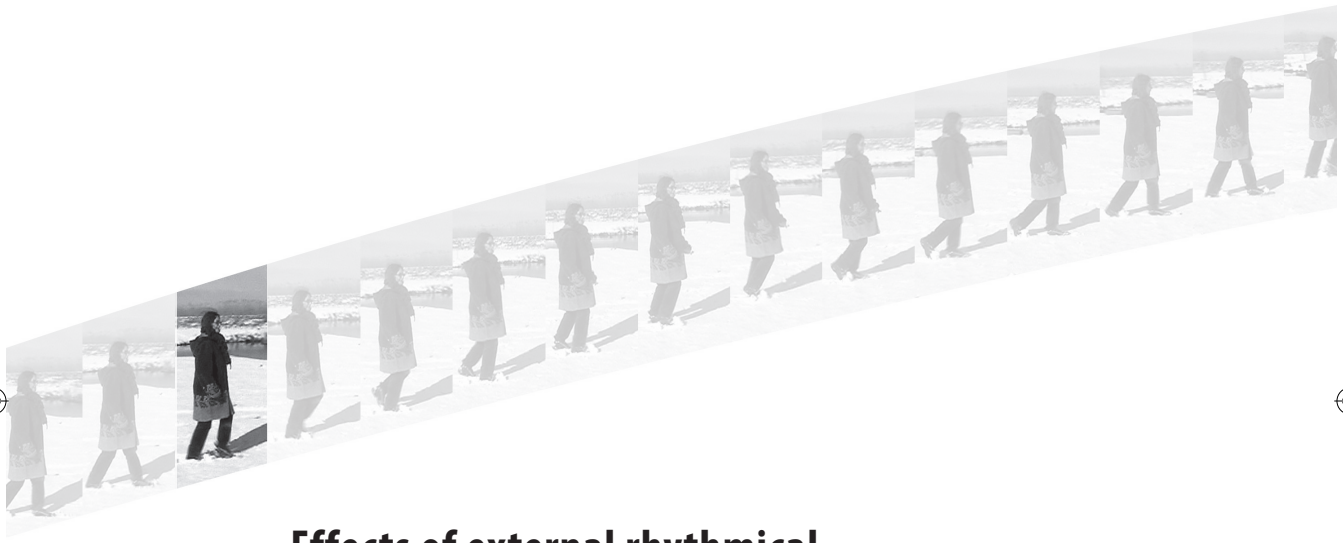

Effects of external rhythmical cueing on gait in patients with Parkinson's disease: A systematic review

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M. Deutekom, A. Nieuwboer, A. Willems,
D. Jones, I. Rochester, G. Kwakkel

Clinical Rehabilitation
2005; 19: 695-713

Abstract

Objective: To critically review studies evaluating the effects of external rhythmical cueing on gait in patients with Parkinson's disease (PD).

Methods: Articles published from 1966 to January 2005 were searched by two physiotherapists in MEDLINE, PiCarta, PEDRo, Cochrane, DocOnline, CINAHL and SUMSEARCH. 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. Based on the type of design and methodological quality a meta-analysis or best-evidence synthesis was applied.

Results: Twenty-four studies (total number of patients = 626) out of the 159 screened studies were evaluated in this systematic review. Two out of 24 were randomized controlled trails (RCT), both of high methodological quality. One 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. Best-evidence synthesis showed strong evidence for improving walking speed with the help of auditory cues. Insufficient evidence was found for the effectiveness of visual and somatosensory cueing.

Conclusion: Only one high-quality study specifically focused on the effects of auditory rhythmical cueing, suggesting that the walking speed of patients with PD can be positively influenced. However, it is unclear whether positive effects identified in the laboratory can be generalized to improved activities of daily living (ADLs) and reduced frequency of falls in the community. In addition, the sustainability of a cueing training programme remains uncertain.

Introduction

Parkinson's disease (PD) is a progressive neurological disorder, with a prevalence increasing with advancing age. In Europe, 1.8 per 100 inhabitants under the age of 65 are diagnosed with PD, whereas in the age category of 65–69 years 2.4 per 100 inhabitants are affected. For the age of 85–89 years, the prevalence increases up to 2.6 per 100 inhabitants.[1]

The idiopathic form of PD results from a degeneration of dopamine-producing cells in the substantia nigra which leads to clinical symptoms such as hypokinesia, bradykinesia, postural instability, rigidity and tremor.[2–4] These symptoms are accompanied by difficulties in motor performance such as gait problems and falls.[4–7]

Despite optimal medication therapy, gait problems associated with PD are often characterized by a decreased stride length[8] and walking speed, an increased step frequency and double limb support,[2,6] shuffling gait, gait festination and freezing.[9–11] Physical therapy is reported to be a low-cost[12–14] treatment and an useful addition to standard medication.[15–19] De Goede et al.[16] demonstrated small but significant improvements in activities of daily living (ADLs), walking speed and stride length in a meta-analysis on the effects of physical therapy on PD using a fixed effects model. Deane et al. conducted a Cochrane review[15] on the effects of physical therapy on PD. They were not able to draw firm conclusions regarding the efficacy of physical therapy, because of methodological weaknesses and due to the small number of trials at the time of their review. Recently, Gage et al.[18] reported positive effects of physical therapy on motor performance, gait, ADLs and cardiovascular fitness in their narrative review

of the effects of multidisciplinary rehabilitation on PD. All reviews included studies in which intervention was offered with the help of external rhythmic stimulation or external rhythmic cueing.

Facilitation of gait of patients with PD with the help of cueing has been reported since 1942.[20] The first detailed analysis of external cueing on gait was performed by Martin in 1967.[21] Two non-systematic reviews by Rubinstein et al.[17] and Darmon et al.[22] evaluated the effects of external cueing on gait in PD. They concluded that external cueing can significantly improve gait and gait-related activities in patients with PD.

The precise definition of a cue is problematic and intervention based on external rhythmical cueing has not been clearly defined. According to Cools,[23] cues are 'contextual or spatial stimuli which are associated with behaviour to be executed, through past experience'. Horstink et al.[24] distinguish between cues and stimuli, stating that 'cues give information on how an action should be carried out and are hence more specific than simple stimuli'. Based on the observations of Cools[23] and Horstink et al,[24] and given the fact that parkinsonian symptoms particularly affect complex and sequential movements, for the purposes of this review external rhythmical cueing is operationally defined as 'applying temporal (rhythmical) or spatial stimuli associated with the initiation and ongoing facilitation of motor activity (gait)'.[25]

The aim of the present systematic review is to add to the literature a systematic review based on (1) a qualitative synthesis method and (2) the above-mentioned, prestated definition of cueing.

Methods and materials

Literature search

Articles were compiled for this study from a number of sources. Two physical therapists (SB/OD) independently performed a search in the databases of MEDLINE (1966–2004), PiCarta, PEDro, Cochrane, DocOnline, CINAHL and SUMSEARCH using the following keywords and their combinations: Parkinson, Parkinson's disease, Parkinson disease, cue, cueing, physical therapy, physiotherapy, exercise, locomotion, gait, optical flow field, visual, auditory, sensory, tactile, behavioural, external, rhythmic, stimulus, stimuli and walking.

Studies were accepted when: (1) they investigated the effects of external rhythmical cueing on gait in patients with idiopathic PD; (2) the intervention was applied to improve gait performance; (3) they were published in a peer-reviewed journal and (4) they were written in English, German, French or Dutch. Single-case studies were excluded.

Intervention types

For the present review, the external rhythmical intervention was classified into four types of cueing: (1) auditory cueing; (2) visual cueing; (3) tactile cueing; and (4) a combination of above-mentioned types of cueing.

Data analysis

If appropriate, quantitative analysis of the results was performed separately for each intervention and restricted to RCTs. When these RCTs were comparable in terms of intervention, patient characteristics and outcome measures, statistical pooling was considered. In case of heterogeneity, with respect to intervention and measurements of outcome, or lack of RCTs, a best-evidence synthesis was applied. The method for applying a best-evidence synthesis was based on the list proposed by Van Tulder et al.[26] and modified by Steultjens et al.[27] (See Appendix 1). The design of the studies and the methodological quality was taken into account when rating the levels of evidence. The methodological quality of all studies was evaluated by two independent reviewers (IL, MD). Disagreements were resolved by discussion. If no consensus was met a third reviewer (GK) made the final decision. A kappa statistic for inter-rater agreement was calculated.

A list of methodological criteria recommended by Van Tulder et al.[26] was used to rate the methodological quality of randomised controlled trials (RCTs). This list, containing all the criteria proposed by Jadad et al.[28] and Verhagen et al.,[29] consists of 11 criteria for internal validity, six for descriptive criteria and two for statistical criteria (See Appendix 2). One modification was made regarding the specification of the eligibility criterion: this involved the addition of the Hoehn and Yahr stage.[30] Studies were considered to be of high quality if at least six criteria for internal validity, three descriptive criteria, and one statistical criterion were met.[26]

To rate the methodological quality of the studies with another design than controlled trials (i.e. pre-experimental studies[31]) the same methodological scorings list was used, with an adaptation made by Steultjens et al.[27] This adapted scorings list includes seven criteria for internal validity, five descriptive and two statistical criteria. A study with a non-controlled design was considered to be of sufficient quality if at least four internal validity criteria, two descriptive criteria and one statistical criterion were rated positively (See Appendix 2). RCTs and non-controlled studies who did not meet the above-stated criteria were considered to be of low quality.

Results

Overview of literature and rating of the studies

Based on abstracts and titles, a total of 159 articles was identified and 40 of these candidate studies investigated the effects of external rhythmical cueing. Twenty-four studies, with a total number of 626 patients included, matched all inclusion criteria and were selected for qualitative analysis.[3,32–53]

General characteristics of the different studies concerning design of the study, type of cueing, number of subjects, characteristics of the subjects, type and dose of intervention, outcome measurements and ratings of results are presented in Appendix 3.

The methodological quality was assessed for two RCTs and 22 pre-experimental studies. None of these studies were controlled clinical trials (CCTs). One publication[3] presented three independent studies. These studies are separately rated on methodological

quality. In two publications[48,53] more than one study was presented. As the effects of cueing were investigated in only one study per publication, only those studies were taken into account for analysis.

The two RCTs[32,33] were of high methodological quality, five pre-experimental studies were of sufficient methodological quality,[36,41,42,47,52] and all other studies were of low methodological quality (Appendix 2). A kappa statistic of 0.84 was calculated for inter-rater agreement on scoring the list for methodological quality.[27]

Applying a quantitative analysis was not possible due to the lack of RCTs, therefore a best-evidence synthesis has been applied on all intervention types.

Auditory cueing

Fourteen studies, two RCTs[32,33] and 13 studies with a pre-experimental design[37,39-42,45-48,50,51,53] investigated the effects of auditory cueing (music, metronome) on gait (Appendix 3). Both RCTs were of high methodological quality and three studies with a pre-experimental design were of sufficient methodological quality,[41,42,47] all other studies were of low methodological quality.[37,39,40,45,46,48,50,51,53]

Measurement outcomes

Walking speed was measured in two RCTs[32,33] and in 10 studies with a pre-experimental design.[39,41,42,45-47,50,51,53] Both RCTs found significant improvement on walking speed as an outcome measurement and therefore strong evidence was shown in a best-evidence synthesis. Stride length and step frequency were measured in one RCT[32] and 11 pre-experimental studies.[39,41,42,45-48,50,51,53] As significant improvements were found for stride length and step frequency as outcome measurements in one RCT, limited evidence was available for these parameters. Step length, step-extremity ratio, double support, cycle time and base of support[41] were assessed in one pre-experimental study of sufficient quality. Step to step variability was assessed in one pre-experimental study of sufficient quality[47] and in one pre-experimental study of low quality.[54] Time[37,40] and number of steps[40] needed to complete a complex track with freezing-inducing elements (e.g. turns and doorways) were assessed in studies of low quality. Therefore, insufficient evidence was found for these gait parameters after applying a best-evidence synthesis.

Visual cueing

Fourteen studies[3,34-36,38,43,44,48,49,51-53] measured the effect of visual cueing on gait in PD (Appendix 3), however no RCTs were found investigating the effects of visual cueing on gait. Two studies showed sufficient methodological quality,[36,52] whereas 12 studies [3,34,35,38,43,44,48,49,51,53] were of low methodological quality.

Measurement outcomes

Ten studies[3,34,35,44,48,49,51,53] investigated the effect of floor markers on walking, by using stripes on the floor, perpendicular to the walking direction. All but one[36] of these studies were of low methodological quality. Therefore, insufficient evidence was found, when applying a best-evidence synthesis. Stride length was measured in two studies of sufficient methodological quality[36,52] and 10 studies of low quality.[3,34,35,44,48,49,51,53] One of

the two studies with sufficient quality[52] reported positive effects of floor markers on stride length. In the other studies,[36] no changes were found and therefore insufficient evidence was shown. Insufficient evidence was found for the effect of floor markers on step frequency,[3,34,35,44,48,49,51,53] step length, stride time, single support[36] and double support,[3,36,38] due to the low quality of the studies measuring these parameters.

Several studies investigated the effect of other visual cues than floor markers, e.g. (modified) walking sticks,[38,43] a rhythmic flashing light, mounted to the spectacles of the subjects[52] or a subject mounted light device.[44] Insufficient evidence was found for all of these visual cues, applying best-evidence synthesis.

Tactile cueing

One pre-experimental study of low quality[40] studied the effects of tactile cueing (shoulder taps) (Appendix 3). Best-evidence synthesis showed insufficient evidence for rhythmical shoulder taps on the time and number of steps needed to complete a complex track.

Combination of auditory and visual cueing

One pre-experimental study of low quality[51] investigated the effects of a combination of auditory cueing and floor markers (Appendix 3). Insufficient evidence was found for this on walking speed, stride length and step frequency, applying a best-evidence synthesis.

Discussion

This is the first systematic review of the literature using an explicit analysis method that explored the effects of external cueing on the gait of patients with PD. Two RCTs and 24 studies with a non-controlled design were identified investigating four different types of cueing and 13 different measurements of outcome. Unfortunately, only one study investigated the effects of tactile cueing on parkinsonian gait. Strong evidence was found for effects with the use of auditory cueing on walking speed in PD. Limited evidence was available for improving stride length and step frequency with the use of auditory cueing, applying best-evidence synthesis. Insufficient evidence was found for improving gait of patients with PD with the help of visual cueing (i.e. floor markers, walking sticks, subject-mounted laser beams or a flashing light mounted on the spectacles of the subject), tactile cueing (shoulder taps) or a combination of auditory and visual cueing (an auditory rhythm and floor markers).

Although external rhythmical cueing is often used in rehabilitation of patients with PD, only two RCTs investigated the effects of auditory cueing on gait. However, in the RCT of Ellis et al.[33] auditory cueing was only a third part of an exercise programme given to patients with PD (Appendix 3). It is therefore not clear whether the improved walking speed was a result of external rhythmical cueing or due to other elements in this group exercise programme. Leaving this study out, the evidence for improving gait in PD with the help of auditory cueing was reduced to limited evidence for walking speed, stride length and step frequency.

Many studies have found significant improvements of gait, but evidence for this can not be established, due to the low methodological quality of these studies, therefore pooling of the studies for quantitative meta-analysis was not possible. Steultjens et al.[27] compared effect-sizes with the levels of evidence found for the different interventions in their study and concluded that the levels of evidence confirmed the findings found with a meta-analysis, underpinning the reliability of the method used in the current study.

Although strong evidence was found in favour of auditory cueing, the interpretation of reported effects on walking speed needs further consideration. Firstly, most studies were executed in a laboratory setting and focused on instantaneous effects only, whereas four intervention studies were reported in which patients were taught to take advantage of auditory rhythms by systematic training.[32,33,37,54] In three studies an exercise programme was applied[32,33] and in two studies the subjects were able to practise using the cues in their own home situation.[32,37] Although these studies showed positive results for auditory cueing,[32,33] the impact of reported effects measured in a laboratory setting is difficult to generalize to the home. It is known that patients with PD have severe problems apply the learned skills in a clinical setting to their home situation.[55] For this reason it is preferable for intervention and assessments to be carried out in the patient's own home environment.

Secondly, the impact of walking speed on ADLs and extended ADLs remains unclear. In particular the carry-over effects of external cues on symptoms such as freezing and falling needs further investigation.

Thirdly, it is not clear how the external cues need to be presented to the patient with PD to obtain maximum effect. Both instantaneous effects and training effects were found in the current review. Future studies should focus on the best way to use the cues in the clinical setting.

A possible explanation for the uncertainty about the best way to present cues and to assess the effects on gait is the lack of a uniform definition for external cueing. For this review, a definition was formulated based on the descriptions of cues by Cools[23] and Horstink.[24] In addition, the mechanism behind external cueing remains unclear.

The present study has some limitations. The review based itself on a restricted number of languages within a limited number of electronic databases. Some relevant studies may therefore have been missed. In addition, the precise way of cueing as well as appended instruction to the cued patient was not always clear in found studies. This might have resulted in misclassification of the intervention type. Further studies should evaluate the effects of different types of cueing on gait-related activities in patients' own home situation and community, in a well-conducted RCT, including measurements related to ADLs, falling, freezing and perceived quality of life in general.

Acknowledgements

This research project was supported by a grant from the European Commission (QLK6-CT-2001-00120; Rehabilitation in Parkinson's Disease: Strategies for Cueing). We would like to thank O. Drummel and S. Bleek for doing the literature searches.

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Appendix 1 Best-evidence synthesis

Strong evidence	Provided by consistent, statistically significant findings in *outcome* measures in at least two high-quality RCTs[a]
Moderate evidence	Provided by consistent, statistically significant findings in *outcome* measures in at least one high-quality RCT and at least one low-quality RCT or high-quality CCT[a]
Limited evidence	Provided by consistent, statistically significant findings in *outcome* measures in at least one high-quality RCT
or	Provided by consistent, statistically significant findings in *outcome* measures in at least two high-quality RCTs (in absence of high-quality RCTs)
Indicative findings	Provided by consistent, statistically significant findings in outcome and/or process measures in at least one high-quality CCT or low-quality RCT[a] (in the absence of high-quality RCTs)
or	Provided by consistent, statistically significant findings in outcome and/or process measures in at least two non-controlled studies with sufficient quality (in absence of RCTs and CCTs)
No or insufficient evidence	In the case that results of eligible studies do not meet the criteria for the above stated levels of evidence
or	In the case of conflicting results (statistically significant positive and statistically significant negative) results among RCTs and CCTs
or	In the case of no eligible studies

RCT, randomized controlled trial; CCT, controlled clinical trial.

[a]If the number of studies that show evidence is <50% of the total number of studies found within the same category of methodological quality and study design (RCTs, CCTs, or non-controlled studies), no evidence will be stated.

Appendix 2 Fulfilled items of methodological quality plus quality criteria for randomized controlled trials (RCT) and non-controlled studies

First Author	Design	Items positively scored on criteria for internal validity	Items positively scored on descriptive criteria	Items positively scored on statistical criteria	MQ
Ellis[33]	RCT	b_1, b_2, f, g, i, j, l, n	a, c, d, c m_2	o, q	HQ
Thaut[32]	RCT	b_1, g, j, l, n, p	c, d, m_1	o, q	HQ
Azulay[34]	Pre-exp	f, j, l, n, p	d	o, q	LQ
Azulay[35]	Pre-exp	f, j, l, n, p	d	o, q	LQ
Bagley[36]	Pre-exp	f, j, n, p	d, m_1	q	SQ
Cubo[37]	Pre-exp	i, j, n	m_1	o, q	LQ
Del Olmo[54]	Pre-exp	j	a, d, m_1	q	LQ
Dietz[38]	Pre-exp	j, l, p	d, m_1	o, q	LQ
Ebersbach[39]	Pre-exp	j, n	a	o, q	LQ
Enzensberger[40]	Pre-exp	j, l, n	a	o	LQ
Freedland[41]	Pre-exp	j, l, n, p	d, m_1	o, q	SQ
Howe[42]	Pre-exp	f, j, l, n, p	a, d	o, q	SQ
Kompoliti[43]	Pre-exp	f, j, l, n, p	d	o	LQ
Lewis[44]	Pre-exp	f, j, l, n, p	d	o, q	LQ
McCoy[45]	Pre-exp	f, j, n	d	q	LQ
McIntosh[46]	Pre-exp	f, j, n, p	m_1	–	LQ
McIntosh[47]	Pre-exp	f, j, l, n, p	d, m_1	o	SQ
Morris[49]	Pre-exp	f, j, n	d	–	LQ
Morris[49]	Pre-exp	f, j, n	d	q	LQ
Morris, study 1[3]	Pre-exp	f, j, n	d, m_1	q	LQ
Morris, study 2[3]	Pre-exp	f, j, n	d, m_1	q	LQ
Morris, study 3[3]	Pre-exp	f, j, n	d, m_1	q	LQ
Nieuwboer[50]	Pre-exp	f, j, n	–	q	LQ
Suteerawattananon[51]	Pre-exp	f, j, n	a, d	–	LQ
Van Wegen[52]	Pre-exp	f, j, l, n, p	a, d	o	SQ
Zijlstra[53]	Pre-exp	j, l, n	–	o	LQ

RCT, randomized controlled trial; pre-exp, pre-experimental design; MQ, methodological quality; HQ, high methodological quality; SQ, sufficient methodological quality; LQ, low methodological quality.

All studies were scored on items concerning internal validity, descriptive criteria and statistical criteria.

a, a positive score on a description of the eligibility criteria; b_1, a randomization procedure has been applied; b_2, the treatment allocation was concealed; c, groups were similar at baseline; d, index and control interventions were adequately described; e, the care provider was blinded for allocation of the patients; f, co-interventions were avoid; g, compliance was acceptable; h, the patient was blinded for allocation; i, the assessor of the outcome measurements was blinded for allocation; j, the outcome measures were relevant; k, adverse effects were described; l, withdrawal/dropout rate was described; m_1, a short-term follow-up measurement was applied (at the end of the intervention); m_2, a long-term follow-up measurement was applied (after three months or later); n, the timing of outcome assessments was comparable for all groups; o, the sample size for each group was presented at randomization and for most important outcomes assessments; p, an intention-to-treat analysis was applied; q, all point estimates and measures of variability were presented; –, there are no items that can be scored positively. Criteria b_1, b_2, c, e and h were not scored for non-controlled studies.

Appendix 3 Overview of literature and rating of the studies

Reference	Study design	Cue type	Characteristics of subjects				Intervention	Results		
			Subjects (*n*)	Age (years) mean ± SD (range)	H-Y (score) mean ± SD (range)	Disease duration (score) mean ± SD (range)	Protocol	Measurement outcomes	Results	
Ellis[33]	RCT (cross-over design)	A	E=68, divided into: Early intervention=35 Late intervention=33	 64±8.4 63±8.8	 2.5±0.5 2.4±0.5	 nr nr	Therapy sessions for 6 weeks, twice a week 1.5 h, consisting of strength-, stretch-, balance-and relaxation exercises and walking exercises with auditory cueing for 15 min	Walking speed (therapy vs. no therapy)	+	
Thaut[32]	RCT	A	E=15 C1=11 C2=11	69±8 74±3 71±8	2.4 2.5 2.6	7.2±4 5.4±3 8.5±4	E=30 min walk training with music, with a rhythm embedded of 1-2 Hz, every day for 3 weeks C1=same programme as the E-group without an auditory cue C2=no intervention	Walking speed Stride length Step frequency	+ + +	
Azulay[34]	Pre-experi-mental	VRS	E=13 hC=7	68.5 (45–78) 70.3 (57–82)	2.3±0.7	6.9 (1–10)	Walking without cues, in on- and off-phase vs. walking with floor markers	 Walking speed Stride length Phase oscillation Angles hip/knee/ankle	on-phase 0 0 – –/–/–	off-phase 0 0 0 0/0/0
Azulay[35]	Pre-experi-mental	VRS	E=16 hC=16	68.8±4 65.7±5	2.3±0.5	6.3	Walking without cues vs. • walking with floor markers (fm) and normal light • with floor markers and stroboscopic light (fm + sl) to suppress the dynamic visual cues while walking	 Walking speed Stride length Step frequency	fm + + 0	fm + sl – – 0

Bagley[36]	Pre-experimental	VRS	10	77.8 (69–88)	nr	nr	Walking without cues vs. walking with floor markers	Walking speed (relative)	–	
								Stride length	+	
								Step frequency	–	
								Stride time	+	
								Single support time	+	
								Double support time	+	
								Step length	+	
Cubo[37]	Pre-experimental	A	12	65.8±11.2	Median 2 (2–4)	12.4±7.3	Subjects walked a complex track with a metronome (M) and without metronome (nc) at the start of the trial. After practicing at home for a week, subjects walked the track again. The track was a 60-ft track, in which the subject arose from a chair, walked through 2 doorways, made 4 turns and sat down.		Pretest Nc vs. M	Pretest vs. posttest (with metronome)
								Time needed to complete track	0	0
								Walking time	–	+
								Freeze time	0	0
								Number of freezing episodes	0	0
								Average duration of a freezing episode	0	0
Del Olmo[54]	Pre-experimental	A	E=15 hC=15	61.7±22 63.1±4.3	2±0.5	7.3±4.3	Pretest: subjects walked (1) at preferred speed without cues, (2) at preferred speed with a manual task, (3) at fast speed, (4) after listening to different auditory rhythms and (5) with an auditory cue A rehabilitation programme was offered to the PD patients, 5 times a week, for 4 weeks, with sessions of one hour. This programme consisted of walking exercises with cueing		Pretest vs. posttest		
									preferred gait	with manual task	fast gait
								Walking speed	0	0	0
								Step length	0	0	0
								Step frequency	0	0	0
								Step to step variability	+	0	0

Appendix 3 *(Continued)*

Reference	Study design	Cue type	Characteristics of subjects				Intervention	Results					
			Subjects (*n*)	Age (years) mean ± SD (range)	H-Y (score) mean ± SD (range)	Disease duration (score) mean ± SD (range)	Protocol	Measurement outcomes	Results				
							with sessions of one hour. This programme consisted of walking exercises with cueing After the rehabilitation programme the subjects with PD were tested again following the same protocol as the pretest						
Dietz[38]	Pre-experimental	VRS	8	70.5±8.2 (56–83)	3.5±0.8 (2–4)	8.2±5.4 (2.4–18)	Pretest: subjects walked a 60-ft track, consisting of 15 ft hallway, with a chair on one end and a doorway on the other end: unassisted and without cues vs. • with a straight walking stick (sws) • with a visual cue-stick (vcs) • floor markers (fm) Subjects practiced at home with vcs until they felt that they obtained maximum profit of it, after that they were tested again unassisted vs. vcs (posttest)		Pretest			Post-test	
									sws	vcs	fm	vcs	
								Time needed to complete track	–	–	+	0	
								Number of freezing episodes	0	0	0	0	

Ebersbach[39]	Pre-experimental	A	E1=22 hC=22	61.8±8.7 61.9±9.0	<2	<2	Walking without cues vs. walking with a metronome, set at 80% of baseline frequency	Stride length Step to step variability	+ +					
Enzens-berger[40]	Pre-experimental	A, T	E=23	nr	3–4	nr	Walking without cues vs. different cuetypes: • music: Hohenen-friedberger march (Mhf) • music: march from Prokofiev (Mp) • a metronome set at 95 bpm (M) • tactile cueing (T) applied by shoulder taps Subjects walked on a track existing of 4 x 10 meters, with 3 curves, inside and outside		Mhf	Mp	M	T		
								Time needed to complete track:						
								inside	0	0	+	–		
								outside	0	0	+	–		
								Steps needed to complete track						
								inside	+	0	+	–		
								outside	+	0	+	+		
Freedland[41]	Pre-experimental	A	E=16	74±7.2 (60–84)	nr	nr	Walking without cues (nc) as a pretest (pr) vs. 1. walking with a metronome set at baseline frequency (M) 2. 10% above baseline frequency (110) 3. without a cue as posttest (po)		M-nc	pr-M	M-110	M-po	110-po	pr-po
								Walking speed	0	0	0	0	0	+
								Step frequency	+	+	0	0	–	+
								Cycle time	+	0	0	+	–	+
								Double support	0	0	0	–	–	+
								Step length	0	0	0	+	–	+
								Step extremity-ratio (step length/ leg length)	0	0	+	0	0	+
								Base of support	0	0	0	0	0	0

Appendix 3 *(Continued)*

Reference	Study design	Cue type	Characteristics of subjects				Intervention	Results				
			Subjects (*n*)	Age (years) mean ± SD (range)	H-Y (score) mean ± SD (range)	Disease duration (score) mean ± SD (range)	Protocol	Measurement outcomes	Results			
Howe[42]	Pre-experimental	A	E=11	54 (30–67)	1–2	nr	Walking with a metronome set at baseline frequency vs. walking with a metronome set at • 15% under baseline frequency (85) • 7.5% under baseline freq. (92.5) • 7.5% above baseline freq. (107.5) • 15% above baseline freq. (115)		85	92.5	107.5	115
								Walking speed	+	0	+	+
								Stride length	0	0	0	0
								Step frequency	+	0	+	+
Kompoliti[43]	Pre-experimental	VRS	E=28	67.8±7.5	nr	13.0±7.5	Walking unassisted and without cues vs. • walking with a modified inverted walking stick (mis) • walking with a laser beam stick (lbs) Subjects walked a track consisting of a 30 ft hallway with a chair at one end and a doorway at the other end		mis		lbs	
								Time to complete track	0		0	
								Freezing episodes	0		0	

Lewis[44]	Pre-experimental	VRS	E=14 hC=14	71.3±7.6 (58–84) 70.5±6.5 (57–80)	2.8±0.8	9.1±5.7	Walking without cues vs. walking with floor markers (fm) walking with a subject mounted light device (smld) projecting 2 laser beams on the floor continuously		fm		smld	
								Walking speed	+		+	
								Stride length	+		+	
								Step frequency	+		+	
McCoy[45]	Pre-experimental	A	E=7	72.2±8.0	1–3	nr	Walking without cues vs. walking with a metronome set at: • baseline frequency (M) • 15% above baseline freq. (115%) in on-phase (on) and in off-phase (off)		M-on	M-off	115-on	115-off
								Walking speed, right side	+	+	+	+
								Walking speed, left side	+	+	+	+
								Stride length, right side	0	0	0	0
								Stride length, left side	+	+	+	+
								Step frequency	+	+	+	+
McIntosh[46]	Pre-experimental	A	E=6	71	3.2±1.0 (2–4)	7.5	Walking without cues vs. walking with a metronome set at • baseline frequency (M) • 10% above baseline frequency (110)		M		110	
								Walking speed	?		+	
								Stride length	?		+	
								Step frequency	?		+	
McIntosh[47]	Pre-experimental	A	E on = 21 E off = 10 hC=10	71±4 73±4 72±5	2.8±0.7 (2–4) 2.6±0.5 (2–3)	7.5 7.8	Walking without cueing (nc) vs. walking with music with a click tone embedded, set at: 1. baseline frequency 2. with a click tone 15% above baseline 3. without cueing to check immediate carry-over effect. In on- and off- phase.		cue vs. nc		cue vs. posttest	
								Walking speed on	+		0	
								Walking speed off	+		0	
								Step frequency on	+		0	
								Step frequency off	+		0	
								Stride length on	+		0	
								Stride length off	+		0	

Appendix 3 *(Continued)*

Reference	Study design	Cue type	Characteristics of subjects				Intervention	Results				
			Subjects (*n*)	Age (years) mean ± SD (range)	H-Y (score) mean ± SD (range)	Disease duration (score) mean ± SD (range)	Protocol	Measurement outcomes	Results			
Morris[48] *Study 3*	Pre-experimental	A VRS	E=32 hC=12	75±7.5 (65–87) nr	2.6±0.5	nr	Walking without cues vs. • walking with a metronome (M) at comfortable walking speed (c) • walking with a metronome and instructed to walk fast (f) • walking with floor markers (fm) at comfortable walking speed • walking with floor markers and instructed to walk fast		M-c	M-f	fm-c	fm-f
								Walking speed	0	+	0	0
								Stride length	0	0	+	+
								Step frequency	0	+	+	+
Morris[49]	Pre-experimental	VRS	E=15 hC=15	72.2±6.2 72.5±6.5	2.7±0.7	nr	Walking without cues (nc) vs. walking with floor markers (fm) at • comfortable walking speed (c) • fast speed (f) Outcomes parameters are compared with healthy matched subjects and rated positive if they are comparable or better.		nc-c	nc-f	fm-c	fm-f
								Walking speed	0	0	0	+
								Stride length	0	0	+	+
								Step frequency	+	+	0	+

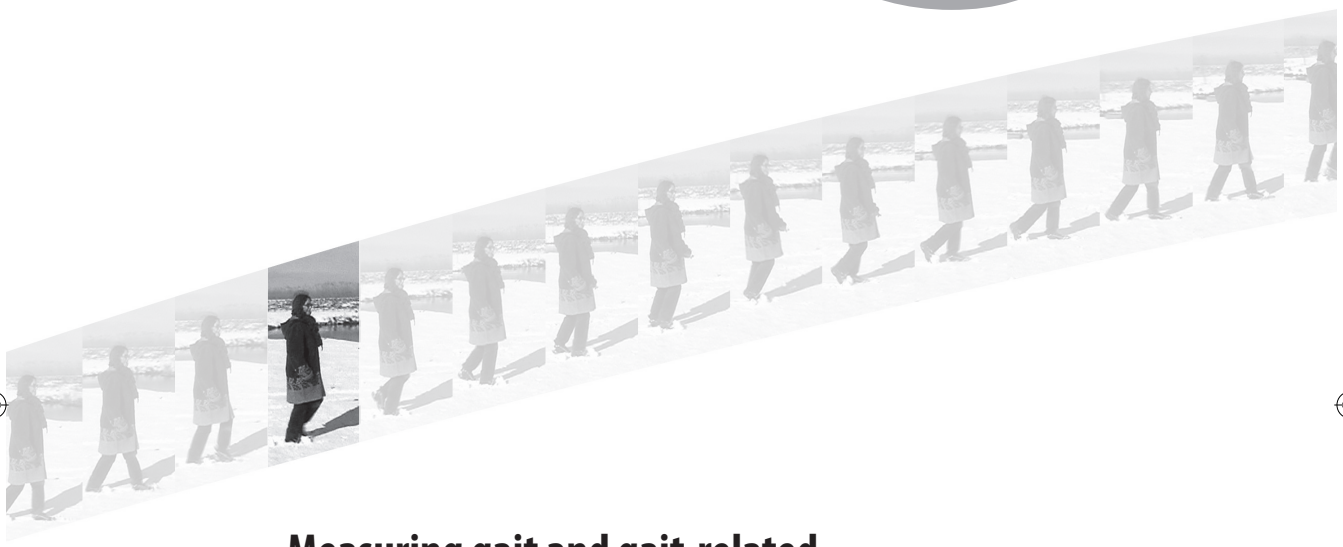
Morris[3] *Study 1*	Pre-experimental	VRS	E=16 hC=16	65.8±4.2 (67–81) 72.7 (63–68)	nr	nr	Walking without cues vs. 1. walking with floor markers (fm) 2. without cues to measure the retain effects (ret)	Walking speed Stride length Step frequency Double support	fm vs. baseline + + + +	ret vs. fm 0 0 0 0	
Study 2	Pre-experimental	VRS	E=16 hC=16	74.1±5.6 (64–82) 73.1 (63–81)	nr	nr	Walking without cues vs. • walking with floor markers (fm) • walking with fm and cognitive task (T) Cognitive tasks were graded from T1 (easy) to T5 (difficult). Outcomes parameters are compared with healthy matched subjects and rated positive if they are comparable or better.	Walking speed Stride length Step frequency Double support	baseline vs. fm + + + +	fm vs. fm + T – (>T2) – (>T2) – (T4) nr	
Study 3	Pre-experimental	VRS	E=8 hC=8	71.0±4.1 (64–75) 70.1 (59–77)	nr	nr	Walking without cues vs. 1. walking with floor markers (fm) 2. walking without cues after the cued condition to measure retention effects (ret). Subjects were aware of recording data half of the trials (o) and unaware the other half (c). The effects of the open trials (fm-o, ret-o) are compared with data of control subjects, data of the covered trials (fm-c, ret-c) with data of the open trials.	Walking speed Stride length Step frequency Double support	fmo + + + +	fmc – – – –	ret-o + + + +	ret-c – – 0 0

Appendix 3 *(Continued)*

Reference	Study design	Cue type	Characteristics of subjects				Intervention	Results					
			Subjects (*n*)	Age (years) mean ± SD (range)	H-Y (score) mean ± SD (range)	Disease duration (score) mean ± SD (range)	Protocol	Measurement outcomes	Results				
Nieuwboer[50]	Pre-experimental	A	E freezers = 10 E non-freezers = 10	68.4 (58.5–80) 60.6 (48–67)	1.5–4	68.4 (58.5–80) 60.6 (48–67)	Walking without cues (nc) vs. walking with a metronome set at baseline frequency (M). • 20% above baseline (120) • 10% above baseline (110) • 10% below baseline frequency (90) • 20% below baseline frequency (80) Cueing conditions are compared with the condition that was one step lower in frequency		M vs.nc	90 vs. 80	M vs. 90	110 vs. M	120 vs. 110
								Walking speed, freezers	?	+	+	0	+
								Walking speed, non-freezers	?	+	+	+	+
								Stride length, freezers	?	+	–	–	0
								Stride length, non-freezers	?	+	–	0	0
								Step frequency, freezers	0	+	+	+	+
								Step frequency, non-freezers	+	+	+	+	+
Suteerawattannan[51]	Pre-experimental	A VRS A+ VRS	E=24	68.9±10.4	2.8	6.9±4.5	Walking without cues (nc) vs. walking with a metronome set at 25% (M) above baseline frequency, walking on stripes with floor markers (fm) or a combination of visual and auditory cueing (M + fm)		M	fm	M + fm		
								Walking speed	+	0	+		
								Stride length	0	+	0		
								Step frequency	+	0	0		

Van Wegen[52]	Pre-experimental	VRS + VRT	E medicated = 16 E non- medicated = 8 hC=7	62.3±9.8 56.1±9.9 59.2±10.2	2.3±0.5 2.2±0.6	4.9±3.5 2.3±2.3	Walking on a treadmill without cue and with a screen in front without projection vs. a screen: • on which a hallway is projected (sc) • on which a hall way with stripes on the floor is projected (fm) • without projection, but with a flashing LED mounted on the spectacles of the subject(vrt) • on which a hall way is projected and a flashing LED mounted on the spectacles of the subject (vrt + sc)	Stride length Step frequency	sc 0 0	fm + +	vrt + +	vrt + sc + +
Zijlstra[53] *Study 1*	Pre-experimental	A, VRS	E=10 hC young = 5 hC old = 5	44–74 25–30 55–60	1.5–4	nr	Walking without cue vs. • walking with a metronome set at a self selected frequency (M), increasing to 100 • walking with floor markers (fm)	walking speed step frequency stride length	M 0 1 0		fm 0 0 0	

3



Measuring gait and gait-related activities in Parkinson's patients' own home environment: A reliability, responsiveness and feasibility study

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Parkinsonism and Related Disorders
2005; 11: 19-24

Abstract

The aim of this study was to assess reliability, responsiveness and feasibility of gait and gait-related tests in the home of patients with Parkinson's disease. The Unified Parkinson's Disease Rating Scale, a timed walking test, the Timed Get Up and Go test, the Berg Balance Scale and the Functional reach test were applied by three independent observers on 26 PD patients. Moderate to high Intraclass Correlation Coefficients were found, ranging from 0.74 to 0.88 and 0.64 to 0.87 for the intra- and inter-observer reliability, respectively. All tests showed Reliable Change Indexes under 11% and the whole test battery was applicable within 30 minutes.

Introduction

Parkinson's disease (PD) is a chronic, progressive disorder characterized by movement-related symptoms such as bradykinesia, tremor, rigidity, freezing and festination. Consequently patients experience problems in gait and in gait-related activities such as balance control and transfers.[1] The consensus view is that if one wants to build an overall picture of the gait-related problems that patients with PD experience on a daily basis, a range of measurements should be used[2–5] and therefore, a comprehensive battery of tests is needed. Such a test battery should include measures that reflect the 'domain of activities' according to the International Classification of Functioning, Disability and Health (ICF).[6] The selection of tests should be based on methodological considerations regarding reliability and validity.

Performance tests to assess gait-related functioning in PD recommended in the literature include: the Unified Parkinson's Disease Rating Scale–motor examination section (UPDRS III),[7,8] the Timed Get Up and Go test (TGUG),[9] the Berg Balance Scale (BBS),[10] the Functional reach test (Fr)[10] and timed walking tests.[11,12] The full UPDRS is recommended to assess disease severity.[2,3,13–15] It has been suggested that patients with PD should preferably be treated and tested in their own home situation.[16,17] However, the reliability of these tests aimed at assessing gait and balance control has never been established in the patients' own home situation, where the circumstances are less optimal for standardization compared to a clinical setting. Therefore, the aim of the present study was to assess the reproducibility, responsiveness and feasibility of performance tests used to measure gait and gait-related problems in the patients' own home environment. A gait-related test battery was compiled for patients with PD in collaboration with three different countries within Europe. This test battery will be used in a large randomised multicenter trial (RCT) aimed at investigating the effects of cueing strategies on gait and gait-related activities in the patients' own home situation.[18]

Methods

Patient selection

Twenty-six subjects (15 male, 11 female) with a diagnosis of idiopathic PD were included in the study. The average age was 62.5 years (range 44–80 years) and average duration of symptoms was 6.5 years (range 1–20 year). Inclusion criteria were: (1) a Hoehn and Yahr[19] stage ranging from 1 to 3; (2) a stable medication regime; (3) ability

to walk independently without a walking device; (4) absence of co-morbidity that may influence mobility; (5) an age under 80 years; (5) sufficient orientation in time and place (Mini Mental State Examination, MMSE, ≥24[20]) and (6) completion of an informed consent for participation.

All PD patients were recruited from the VU University Medical Center (VUmc) and lived in a geographically defined district around Amsterdam. The study was approved by the ethics committee of the VUmc.

Measurements

The test battery was compiled to assess severity of PD and gait-related functioning. The test battery consisted of the UPDRS, including the motor examination section (UPDRS III),[2] the TGUG test,[21] the timed 10 m walk test, the BBS[22] and the Fr test.[23] In order to obtain uniformity of assessment practical guidelines were developed which included instructions on how to deal with specific difficulties inherent to testing in patients' homes, such as lack of space and obstacles that could impede proper gait and balance assessment.

Observers

Three physical therapists were employed to perform the assessments. Prior to testing, the observers were trained to apply the test battery in a uniform way in three healthy subjects and one patient with PD. In addition, they were instructed on how to use the practical guidelines. The training of the three observers was conducted by two coaches (i.e., a physical therapist (CG) and a human movement scientist (EW)) who were experienced in clinical research in PD.

Design

Patients were assessed by the three independent observers during two consecutive visits to the patient's home. All subjects were visited at approximately the same time of the day (maximum difference in time was about 1 h) to minimize existing circadian fluctuations. All patients were measured in the 'on-phase' about 1 hour after medication intake. Before assessment, randomisation was applied for the sequence of the tests as well as for the sequence in which the three observers assessed the patient.

Data analysis and statistics

The inter-observer reliability for the three observers was calculated using Intraclass Correlation Coefficients (ICC) using a two-way random effects model with an absolute agreement definition.[24] Similarly, the intra-observer reliability for one of the three assessors was determined by applying a two-way mixed effects model for absolute agreement[24] and by using the Bland and Altman method.[25] ICCs were preferred because this statistic is able to deal with dichotomous outcomes, corrects for systematic errors and can be used for more than two observers.[24] The use of ICCs and the Bland and Altman method gives complementary information as shown by Rankin and Stokes.[26] For the Bland and Altman method the 'limits of agreement' were computed, defined as $\pm 1.96 \times$ standard deviation of the difference score. Assuming a normal distribution

Table 1 Patient characteristics

Variable	Mean (SD)	Range
Age (years)[a]	62.5 (8.2)	44–80
Disease duration (years)[a]	6.5 (4.2)	1–20
Gender (M/F)[b]	15/11	
Medication[b]		
None	4	
Levodopa (in combination with benzeraside or carbidopa)	14	
Dopamine agonists	18	
Selegiline	4	
Parasympathicoliticum	1	
Other	2 (amantadine)	
Partner (Y/N)	21/5	
Modified H-Y stage[b]		
Stage 1	9	
Stage 1.5	4	
Stage 2	8	
Stage 2.5	3	
Stage 3	1	
Stage 4	0	
Stage 5	0	
Fallers[b,c]	7	
Freezers[b,d]	16	
UPDRS score[a]	41.19 (44.15)	15–71
UPDRS III[a]	23.27 (9.64)	8–39
Retropulsion test score[a,e]		
0=normal	22	
1=retropulsion, but recovers unaided	2	
2=absence of postural response; would fall if not caught by examiner	2	
3=very unstable, tends to lose balance spontaneously	0	
4=unable to stand without assistance	0	
BBS score[a]	53.77 (1.99)	46–56
Functional reach[a] (cm)	33.54 (7.36)	22–50
PG[a]	2.15 (2.15)	0–9

[a] Mean, SD standard deviation (between brackets). [b] Number of patients. [c] Posture and Gait, item 1: score ≥1. [d] Freezing of Gait Questionnaire, item 3: score ≥2. [e] Unified Parkinson's Disease Rating Scale, item 30. M, male; F, female; Y, yes; N, no; H-Y, Hoehn and Yahr Scale.

of the found differences, only 95% of the differences between two measurements per individual in a stable population will be between the limits of agreement.[25]

The responsiveness of the tests was determined using the Smallest Detectable Difference (SDD), the SDD was calculated on the basis of the standard error of measurement[27] (see Eq. (1)), assuming that the measurement errors were constant across the range of possible scores.[28]

Table 2 Intraclass Correlation Coefficients for inter-observer reliability and intra-observer reliability, smallest detectable difference and reliable change index (*N*=26)

Test	Inter-observer reliability	Intra-observer reliability	SDD	RCI (%)
UPDRS	0.78*	0.84*	15	10
UPDRS III	0.68*	0.74*	13	11
TGUG (s)	0.91*	0.93*	1.57	
10 m walk test [1]				
walking speed (m/s)	0.87*	0.81*	0.19	
step frequency (steps/min)	0.80*	0.88*	10	
BBS	0.74*	0.87*	2.84	5
Fr (cm)	0.64*	0.74*	11.5	

SDD, Smallest detectable difference; RCI, Reliable change index; UPDRS, Unified Parkinson's Disease Ratio Scale; III, motor examination section; TGUG, Timed Get Up and Go test; PG, Posture and Gait score; BBS, Berg Balance Scale; Fr, Functional reach test. * $p<0.01$.

[a] The 10 m walk test was performed at comfortable walking speed.

$$SDD = SEM \times 1.96 \times \sqrt{2} \quad \text{(Eq. 1)}$$

where SDD is smallest detectable difference, and SEM, standard error of measurement.

In order to allow comparison of responsiveness between the tests, the Reliable Change Index (RCI) was determined for each measurement by calculating the SDD as the percentage of the maximal feasible score. Each hypothesis was tested with a two-tailed analysis with 0.05 as the level of significance.

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).

Results

The patients in this study had a H-Y score ranging from 1 to 3. Patient characteristics are shown in Table 1. The duration of the first visit was approximately 45 minutes, whereas the duration of the second visit ranged from 30 to 35 minutes. The median number of days between two test sessions of the same observer was 7 (inter quartile range 3 days).

Inter- and intra-observer reliability

Table 2 shows the reliability between and within observers. ICCs for inter-observer reliability ranged from 0.64 for the Fr test to 0.91 for the TGUG. ICCs for intra-observer reliability ranged from 0.74 for the UPDRS III and the Fr test to 0.93 for the TGUG (Table 2). Bland Altman plots are displayed in Figure 1, with the dashed and

bold line representing the mean difference score between the two assessments and the two dashed lines are representing the limits of agreement. The analysis showed homogenous distribution of differences for all tests. No systematic differences (p<0.5) are found between the test and retest, except for the step frequency in the 10 m walk test. A mean systematic difference of 2.32 steps/minute was observed (p=0.06).

Responsiveness

Table 2 illustrates the SDDs for the five performance tests. Responsiveness ranged from three points on the BBS to 13 points on the UPDRS III, reflecting a RCI of 5% for the BBS up to 11% for the UPDRS III (Table 2).

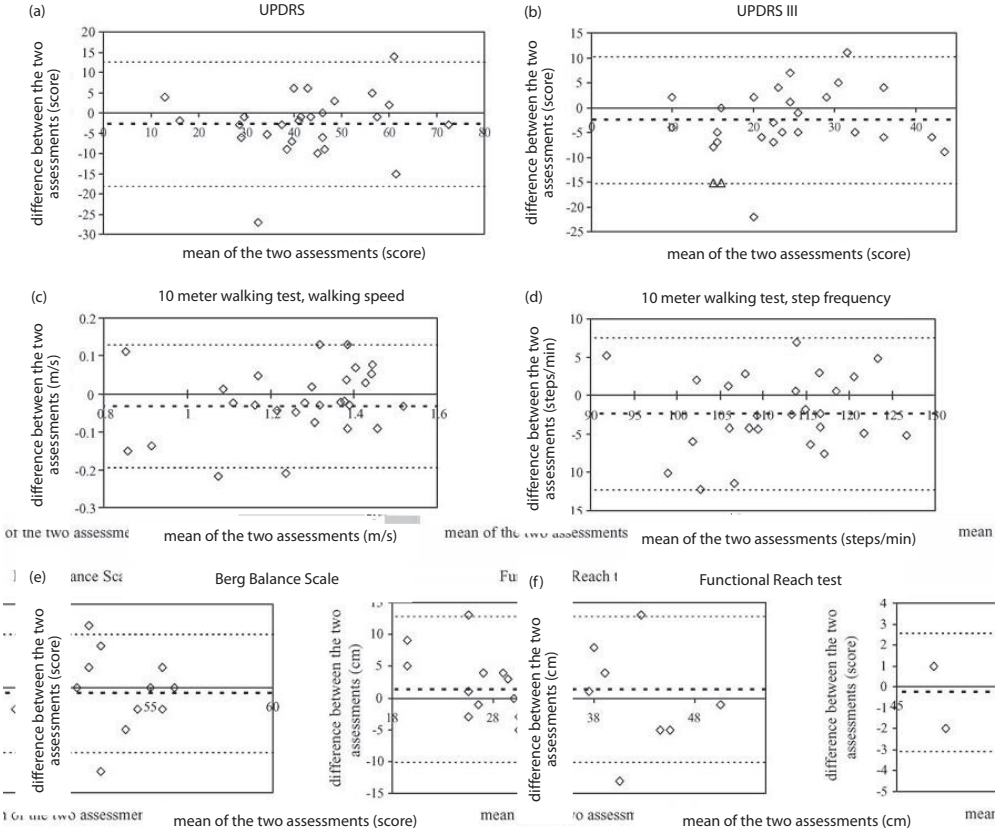

Figure 1 Agreement of the 5 tests: graphic representation according to the Bland and Altman technique. UPDRS, Unified Parkinson's Disease Ratio Scale; III, motor examination section. Dashed bold lines represent the mean difference score, dashed lines represent the limits of agreement, defined as the mean ±1.96×the standard deviation of the difference score.

Feasibility

The duration of applying the test battery ranged from 20 to 30 minutes at the first assessment, whereas the duration of the second assessment ranged from 20 to 25 minutes.

Discussion

In the present study, tests were evaluated in terms of reliability and responsiveness by three independent observers in the home environment of PD patients. In general the test battery shows moderate to excellent inter-observer reliability (ICC=0.64-0.87), and moderate to excellent intra-observer reliability (ICC=0.74-0.88) according to the classification of ICCs of Fleiss.[29] Good reliability was obtained regardless of the fact that the tests could not be completely standardised, due to the different interiors of the subjects' homes. Interestingly, despite the lack of observer experience with using the test battery in PD patients, inter- and intra-observer reliability was moderate to excellent. These findings underpin the robustness of the tests included in this battery. In addition, the average time needed to apply the whole test battery was about 25 minutes, ensuring its feasibility.

Our findings on reliability are comparable with the literature with respect to tests such as the UPDRS,[7,13,15] TGUG,[9] and 10 m walk test.[11,12] For the Fr test a higher ICC for intra-observer reliability was observed (ICC=0.64) compared to the ICC (0.42) found by Smithson et al.[10] for PD patients without a history of falls. The ICC found by Smithson et al.[10] for PD patients with a history of falls was higher (ICC=0.93) compared to the ICC found for non-fallers.[10] Although no explanation is given by Smithson and colleagues, differences in ICCs may be due to the larger between-subject variability in executing the Fr test in the population of fallers when compared to non-fallers. The PD patients in the current study were non-fallers (n=19) and fallers (n=7) which might have influenced the intra-observer reliability.

Due the lack of consensus regarding methods of measuring responsiveness in the literature,[30–32] SDDs in this study can not directly be compared with earlier reported SDDs for the tests used in the current study. In most studies responsiveness was defined as the average changes in scores relative to baseline in self-rated clinically stable and improved patients.[2,33] Two studies were found that applied the same method for determining responsiveness on some of the tests used in the present study.[34,35] In these studies where the BBS and the timed 10 m walk test were applied, the SDDs for both tests were 6 points[34] and 0.16 m/s,[35] respectively. However, these tests were investigated in patients with stroke and therefore difficult to generalize to the PD patients in the present study. Unfortunately, general accepted criteria to judge the responsiveness of these tests do not exist. Therefore, in order to interpret the calculated scores, we compared the RCIs with each other. All RCIs were 11% or less, which is in our opinion acceptable for clinical use. In particular, realizing that assessments in patients' own home environment is accompanied with a decreased ability to standardize the execution of measurements and with that higher error rates.

A limitation of the present study was that only subjects with mild to moderate disease severity were included (H-Y score ranging from 1 to 3). The battery was composed

for those who were independent in ADL and were able to perform the tests without the use of a balance or walking aid. This limits the generalisation of present findings to the population of PD patients in general. In addition, all patients were tested in the on-phase and each patient was assessed at approximately the same time of the day, however, differences in time of assessment relative to moment of medication intake could have influenced the present findings.

Conclusion

The test battery was shown to have moderate to excellent reliability, despite limited clinical experience of the observers in assessing PD patients. Agreement on practical guidelines is necessary to standardize assessments as much as possible under less optimal circumstances, such as the home situation.

Since there appears to be a lack of consensus on how to quantify responsiveness,[32] strict comparison with the literature is difficult. However, the results from the current study can be applied as indicators for an approximate threshold in the utility of the tests as outcome measures in a larger clinical trial.

Acknowledgements

This research project was supported by a grant from the European Commission (QLK6-CT-2001-00120; Rehabilitation in Parkinson's Disease: Strategies for Cueing).

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4

The effects of visual rhythms and optic flow on stride patterns of patients with Parkinson's disease

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Parkinsonism and Related Disorders
2006; 12: 21-27

Abstract

This study was aimed at determining the effects of rhythmic visual cueing under changing visual conditions on stride frequency in patients with Parkinson's disease (PD; *n*=21) and healthy age matched controls (*n*=7) while walking at different speeds on a treadmill. Stride frequency and stride length in patients with PD as well as controls were not rigidly coupled to walking speed and could be manipulated with walking speed as well as by using spatial and temporal rhythmic visual cues.

Introduction

It has been well established that patients with Parkinson's disease (PD) exhibit specific changes in gait patterns during walking. Patients with PD walk at a reduced overall speed with a shorter stride length in comparison with healthy age matched control subjects.[1] Step frequency (i.e. number of steps made in 1 minute) may be normal, but is often elevated when speed of walking is taken into account. This increased step frequency appears to be a compensation for the reduced stride length.[2] Several studies suggest that step frequency control is still intact and can be modulated for a variety of conditions.[1,3,4] On the other hand patients with PD seem to have particular difficulty with the internal regulation of stride length.[2,3,5–7]

In addition to changes in stride parameters, changes in foot fall patterns, trunk position as well as reduced trunk rotation and absence of arm swing have been observed.[8–11] Even with an 'optimal' medication regimen gait-related movement problems persist and could be related to the occurrence of falling.[12–14] Taken together, the mobility problems can have a large impact on activities of daily living in PD patients.[15–17]

In many observational studies, gait changes are investigated during tests at the preferred walking speed during over ground walking. However, since variables such as stride length and stride frequency tend to change as a function of walking speed, same-speed comparisons need to be undertaken in order to eliminate the effects of speed on stride parameters.[11,18] At a fixed speed, the shorter stride length in PD may be compensated for by an elevated step frequency.[2] Thus, when controlling for speed, adaptation of step frequency by an external rhythm might offer a possible strategy to indirectly influence stride length regulation.

Several studies have shown that auditory rhythms can positively influence stride characteristics of gait in PD, presumably by compensating for basal ganglia disease causing an inability to internally generate rhythmic movements.[9,19–22] Such external cues can be defined as providing temporal or spatial stimuli associated with the initiation and ongoing facilitation of motor activity such as gait.[23]

An alternative way to apply external rhythmic cueing in patients with hearing problems could be the provision of a visual cueing rhythm by means of a rhythmically flashing light attached to a pair of spectacles. However, to our knowledge this has not been investigated to date.

While some visual environmental stimuli such as parallel lines on the floor or lines on the pavement can elicit a more normal walking pattern in PD,[1,2,8,24,25] other visually perceived features of the environment such as thresholds, confined spaces, furniture,

narrow doorways or moving surfaces such as elevators and escalators tend to predispose patients with PD to slowing gait and/or motor blocks.[26] In the case of visual rhythmic cueing this could pose an additional problem, since multiple visual inputs (i.e. optic flow from the environment generated through walking as well as the visual rhythm) need to be accommodated.

The main purpose of the current investigation was to study the effects of rhythmic visual cueing under changing visual conditions on the stride pattern of patients with PD. Cueing consisted of a flashing light or transverse lines. The possible suppressive influences of a moving environment containing objects (doorways and thresholds in a projection of a moving virtual corridor) during cued and uncued gait was studied. In a controlled laboratory environment, kinematic gait patterns of patients with PD and healthy controls were studied during treadmill walking under baseline conditions (absence of virtual environment, no virtual corridor projection) and under optic flow conditions (projection of virtual corridor with doorways and thresholds). In addition, the effects of virtual optic flow on the use of visual rhythmic cueing were examined. So-called 'walking velocity manipulations' were performed to study the differential effects of walking speed on the influence of virtual objects during walking. It was hypothesized that using visual rhythmic cueing (i.e. a flashing light or transverse lines) it would be possible to regulate the stride frequency. Specifically, a cueing frequency lower than baseline as well as transverse lines would result in lower stride frequencies and thus larger stride lengths at the same speed. Stride parameters were expected to systematically change with walking speed. Lastly, it was expected that virtual optic flow would negatively influence this effect due to a suppressive interference effect.

Methods

Subjects

Three groups of subjects participated in the study, one group consisting of age and sex matched healthy adults (n=7), one group of non-medicated (i.e. drug-naïve) patients with PD (n=8) and a group of medicated patients with PD (n=13). Patients with idiopathic PD[27] were screened for inclusion into the study and admitted when they are on a stable medication regime (for the medicated group), without acute co-morbidity influencing mobility, under 75 years of age, free of signs of dementia (Mini Mental State Examination score > 24) and willing and able to sign a consent form for participation. Patients with mild to moderate disease severity (Hoehn-Yahr 1.5–3) were recruited. Additionally, patients who were included in the study had to (1) be able to walk independently at a walking speed of at least 3.8 km/h, (2) have a minimal score of 2 for at least at one of the items: tremor, rigidity, bradykinesia and hypokinesia on the Unified Parkinson's Disease Rating Scale (UPDRS), (3) be non-institutionalised and (4) be without severe visual deficits based on self report. Patients were recruited by phone, based on an existing database as well as referrals from several neurologists. Control subjects were recruited from the community; in addition spouses from the patient groups participated. Prior to their arrival at the hospital, subjects were informed about the study by way of an information packet. All participants signed an approved informed consent form. The Human Subjects Review Committee of the VU University

Medical Center approved the project.

Protocol

Subjects were asked to come to the Outpatient Department for an experimental session that would take between 2.5 and 3.5 hours. The session was divided into two separate sections: (1) clinical tests, and (2) a treadmill protocol. All patients were tested in the on-phase, approximately 1 hour after taking their regular medication.

Clinical tests

Prior to testing on the treadmill, subjects performed a 10 m walk test, a Timed Get Up and Go test (TGUG),[28] and a Berg Balance Scale (BBS)[29] to evaluate walking and balance performance.

Treadmill protocol

Before the protocol, subjects were fitted out with butterfly-shaped Light Emitting Diodes (LEDs, see Materials section). A harness attached to the ceiling via a rope was used for safety. Subjects subsequently were asked to walk on the treadmill. Before the actual treadmill protocol began, the comfortable as well as maximal walking speed was determined after extensive habituation. During the treadmill protocol the following variables were manipulated: visual flow, rhythmic visual cueing and walking speed.

Manipulation of visual conditions

Visual flow was manipulated by means of a 2×2 m rear projection screen positioned 75 cm in front of the treadmill: in conditions where visual flow was offered a 'virtual' corridor was projected that 'moved' at the speed of the treadmill, providing the illusion that the subject walks through the corridor. The virtual corridor contained several thresholds and doorways to mimic narrowing of the passageway, known causes of gait disturbance in PD. Visual cueing was manipulated by means of a light flash from a LED attached to a pair of glasses (rhythmic temporal cueing) as well as through transverse lines projected 60 cm apart on the floor of a virtual corridor (rhythmic spatial cueing). Consequently, subjects walked on the treadmill under the following five conditions, offered in random order:

(1) Blank screen, no projection of virtual corridor
(2) Projection of virtual corridor
(3) Projection of virtual corridor with rhythmic spatial cueing (the transverse lines)
(4) Blank screen with rhythmic temporal cueing (the flashing light)
(5) Projection of virtual corridor with rhythmic temporal cueing (the flashing light)

To promote larger stride lengths at fixed speeds, the flash-frequency of the LED on the glasses for the conditions 4 and 5, was set after subtracting ten percent from the baseline stride frequency determined previously (cf. Howe et al.[22] and Van Wegen et al.[30]). For rhythmic temporal cueing the subjects were given the instruction to 'step with your right foot in front when the light on the side of your glasses flashes'. For

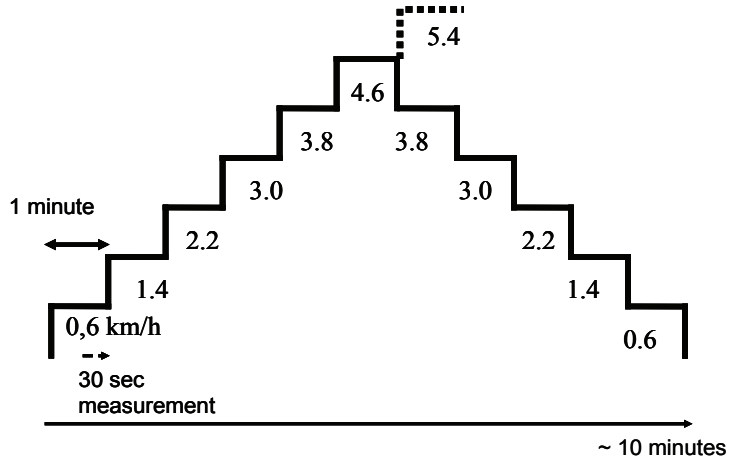

Figure 1 Systematic speed manipulation.

rhythmic spatial cueing the subjects were given the instruction to 'step on or over the approaching lines'.

Manipulation of speed

Within each condition, the speed of the treadmill was systematically increased from 0.6 to 3.8 km/h in steps of 0.8 km/h and subsequently reduced with the same steps (see Figure 1). Thus, subjects completed nine speed levels. Treadmill and flow speed were synchronized in conditions 2, 3 and 4. Each speed level lasted about 1 minute, of which the last 30 seconds were used to collect kinematic data.

Material

The experiment was performed on a treadmill (Biometrics Europe BV, Almere, The Netherlands) with a 1.2 m × 2.0 m belt. A 3D kinematic motion analysis system (Optotrak (OT), Northern Digital Inc., Canada) was used to collect position data of the extremities. Two camera units placed diagonally behind the treadmill at a distance of about 3 m were used at a sample frequency of 60 Hz. Motion was tracked from 24 infrared-light emitting diodes, attached in triads of three on eight butterfly shaped marker sets, which were placed bilaterally and on the backside of the body on the upper arm, lower arm, upper leg and the lower leg.

The virtual corridor was generated on a Silicon Graphics Workstation (Octane) and projected on a custom-made rear-projection screen by a RGB color projector (Kindermann Omega Sx 1280c).

Data analysis

Segmental angles for the extremities were calculated for the frontal, transverse and sagittal planes, using custom software. From the sagittal plane segmental angles, the stride frequency was determined using a count of the number of peaks in the thigh angle

trajectories during a 30 seconds data collection. The obtained frequency was compared with an estimation of the dominant peak power frequency using a standard Fast Fourier Transform and results proved to be identical, with average variation <0.9%.

Statistical analysis

A one-way ANOVA was applied to test for group differences on the clinical tests and subject characteristics. A general linear model for repeated measures was applied with group (3 levels, medicated PD patients, non-medicated PD patients and healthy controls), condition (5 levels, see under treadmill protocol) and velocity (9 levels, 0.6, 1.4, 2.2, 3.0, 3.8, 3.0, 2.2, 1.4 and 0.6 km/h) as factors. When significant effects were found, planned comparisons were performed to determine the location of the effect. Each hypothesis was tested with a two-tailed analysis and 0.05 as the level of significance.

Results

Since stride frequency was manipulated and correlated in a fixed manner to stride length at a constant speed only the effects on stride frequency will be discussed.

Subject characteristics

Table 1 shows subject group data. The groups did not differ with regard to age, height and weight. Although the non-medicated PD patients had lower average Hoehn and Yahr scores and lower average scores on the Mini Mental State Examination (MMSE), these were not statistically significant ($p>0.05$). The UPDRS score for the non-medicated patients was lower than the medicated patients ($p<0.05$). Since all non-medicated subjects were recently diagnosed within the last 3 years, except 1 patient who was diagnosed 5 years prior, the disease duration as well as the duration of medication usage were lower in the non-medicated group ($p<0.05$). On the clinical tests, the PD groups did not differ significantly from each other, but the medicated group performed

Table 1 Subject characteristics

Group	Age	Weight (kg)	Height (m)	Years PD	HY	UPDRS	MMSE	10m (km/h)	TUG (s)	BBS	*N*
PD med	62.3 (9.8)	82.4 (15.3)	1.79 (0.08)	5.5 (3.5)	2.3 (0.5)	52.9 (11.1)	27.8 (1.5)	3.8 (0.5)	10.3 (3.5)	52.6 (2.7)	13
PD nonmed	56.7 (9.4)	77.4 (12.0)	1.78 (0.10)	2.1 (2.2)*	2.1 (0.7)	38.4 (18.2)*	29.1 (1.4)	4.0 (0.7)	10.1 (2.8)	54.2 (2.5)	8
Controls	59.2 (10.2)	80.2 (9.4)	1.77 (0.07)			< 5	29.3 (1.3)	4.8 (0.3)*	8.1 (0.4)*	55.8 (0.4)*	7

Med, medicated; nonmed, non-medicated; PD, Parkinson's disease; HY, Hoehn Yahr; UPDRS, Unified PD Rating Scale; MMSE, Mini Mental Status Exam; m, meters; kg, kilogram; 10m, 10 meter walk test comfortable speed; TUG, Timed Up and Go test; s, seconds; BBS, Berg Balance Scale. Mean values are reported followed by bracketed standard deviation. *Significantly different from group 1; $p<0.05$.

worse on all tests as compared to the control group (p values < 0.05).

With regard to the treadmill protocol, a significant ('Group' × 'Speed') interaction effect was found for stride frequency (p<0.01), indicating a speed dependent difference between the groups. Specifically, the control group walked at significantly lower stride frequencies at 2.2, 3.0 and 3.8 km/h as compared to both PD groups (p values < 0.05, Figure 2).

Effects of walking speed

Stride frequency increased significantly with increasing speed (p<0.01). The absence of a significant ('condition' × 'speed') interaction effect (p=0.96) indicates that this applies to all conditions. Post hoc analysis showed that at all speeds except at 0.6 km/h the stride frequency in the decreasing speed range was significantly lower compared to the stride frequency for corresponding speeds in the increasing speed range (p values < 0.05).

Effects of visual conditions

Stride frequency was significantly lowered (and thus stride length enlarged) in the rhythmic cueing conditions compared to corresponding speeds in the baseline condition (conditions 3, 4, and 5 < condition 1; p<0.05; Figure 3). No significant ('group' × 'condition') interaction effect was found (p=0.99) and the reduction occurred in all groups. No difference was found between conditions 3 (virtual corridor projected with stripes), 4 (flashing light, virtual corridor not projected on screen) and 5 (flashing light, virtual corridor projected) (p>0.05). In addition, stride frequency between conditions 1 and 2 did not differ (p>0.05).

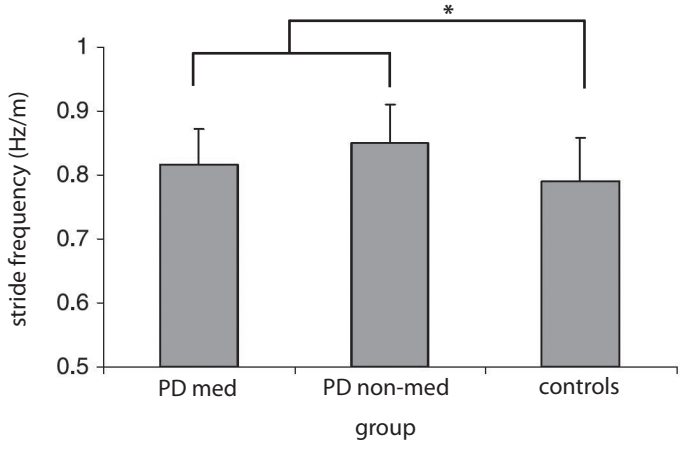

Figure 2 Stride frequency, averaged across speeds 2.2, 3.0 and 3.8 km/h (i.e. pooled). Med, medicated PD patients (n=13); nonmed, non-medicated PD patients (n=8); controls, healthy older adults (n=7). * significantly different at p<0.05.

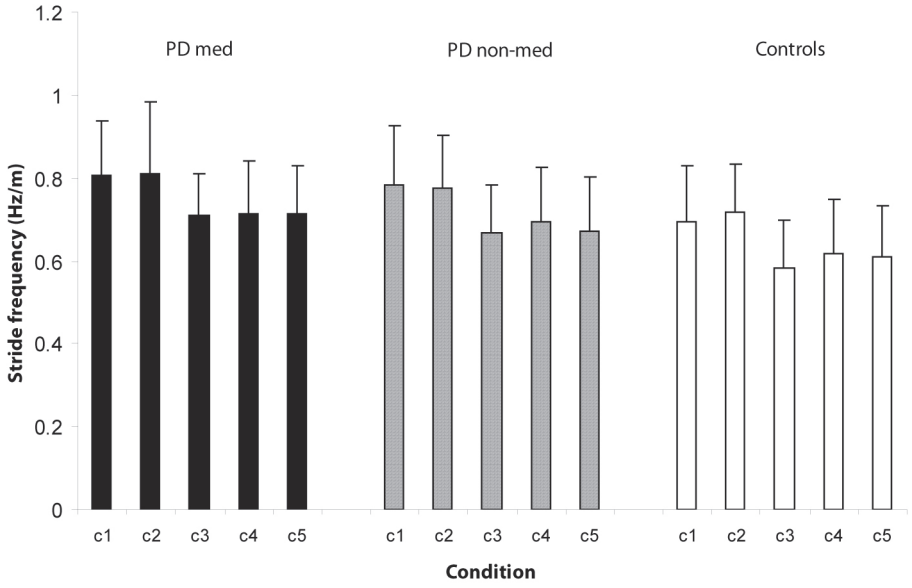

Figure 3 Stride frequency (normalized for leg length) as a function of condition in the three groups. Means and between subjects standard deviations are shown. Med, medicated PD patients (*n*=13); nonmed, non-medicated PD patients (*n*=8); controls, healthy older adults (*n*=7). c1, blank screen, no projection of virtual corridor; c2, projection of virtual corridor; c3, projection of virtual corridor with transverse lines on the floor; c4, blank screen with rhythmic visual cueing; c5, projection of virtual corridor with rhythmic visual cueing.

Discussion

The aim of this study was to examine the effects of temporal and spatial visual rhythms as external cues on the stride pattern of patients with Parkinson's disease. The main finding was that both transverse stripes projected in a virtual corridor as well as a flashing light attached to a pair of spectacles can be used to lower the stride frequency while maintaining walking speed. This effect occurred in both PD patients and controls. The results also suggest that optic flow information during walking does not impair nor facilitate the use of a rhythmic flashing light to manipulate stride frequency. In addition, it was shown that the stride frequency obtained at higher speeds is maintained during subsequent lowering of walking speed.

The results confirm that PD patients walk with smaller steps when controlling for walking speed, which is consistent with the literature.[1–3,6,7,31] However, in the current experiment this effect is speed dependent, since there was no difference at 0.6 and 1.4 km/h. Although the same subjects were not compared on and off medication, the fact that the stride frequency in the medicated patients tended to be less elevated compared to the non-medicated patients does suggest that dopamine (replacement) therapy can improve stride frequency to a certain extent.

The current study also confirms results from earlier studies that have found positive effects of transverse stripes on parkinsonian gait.[1,2,8,24–26,32,33] To our knowledge this is the first study that has used projected transverse stripes in a virtual corridor while walking on a treadmill, where walking speed was kept constant at each speed level. Azulay et al. have suggested that the effect is caused by the fact that the approaching stripes have certain dynamic properties that encourage stepping over or on the stripes, perhaps through alternative visuo-motor circuits.[24] Alternatively, the stripes could simply attract attention to the walking pattern itself, relieving emphasis on automatic motor function.[1,26]

Several studies have shown positive effects of external (auditory) rhythms on stride characteristics of gait in PD (a form of temporal cueing). It is suggested that the external cues compensate for the inability to internally generate cued rhythmic movements caused by basal ganglia disease resulting in disturbed relay of information to the supplementary motor area (SMA).[9,19–22] In the current study an alternative method of external temporal cueing was investigated, namely by means of a flashing light. The results show that this is a viable and relatively simple alternative: at comparable speeds the stride frequency was systematically lower when subjects were cued at 10% below their baseline stride frequency. Since walking speed was constant within each speed level, the slower rhythm resulted in larger strides. This result confirms that PD patients (as well as healthy controls) are able to adjust their walking patterns flexibly using an external visual rhythm without changing walking speed. Howe et al. have used auditory cueing at 85% of baseline frequency and found a slowing of walking speed and the stepping rhythm.[22] A slower walking speed could however be an undesirable effect of cueing since the characteristic pattern of small steps does not change.

The mechanism for bypassing the defective pallidocortical projections with a visual rhythm could be similar to that for auditory cueing (cf. McIntosh et al.[20]). Connections from the visual system project via the lateral geniculate nucleus of the thalamus to the visual cortex and lateral pre-motorcortex, where sensory information is received for externally guided movements.[34,35] Additionally, alternative sensory visuo-motor circuits passing to the cerebellum and in particular the dentate nucleus, may also be involved in the generation and/or guidance of movement based on visual cues.[36,37]

The phenomenon that stride frequency was lower at the decreasing speeds compared to the same speed levels in the increasing speed range is known as 'hysteresis' in (bio) physics. As with the frequency manipulations, this hysteresis effect was not group-specific, indicating that it may be a more general phenomenon. Hysteresis-effects under systematic walking speed manipulations have been observed in previous studies in stride parameters and trunk rotation in healthy subjects,*38* patients with PD*39* and stroke.[40] Apparently an initial increase in walking speed has in itself a positive effect on the gait pattern during subsequent lowering of speed, confirming that the stride frequency is not coupled to walking speed in a fixed manner. The hysteresis-effect could be viewed as emerging from an after-effect, where the kinematic changes accompanying higher speeds are maintained during subsequent lower speed levels. Simply performing such a walking speed manipulation could be an effective and easy method to influence and perhaps normalize the pathologic gait pattern of patients with PD.

Small spaces, moving surfaces such as escalators and elevators as well as discontinuities in the floor surface such as thresholds, furniture or narrow doorways can lead to unwanted stagnation or even freezing of the gait of patients with PD. The current results confirm that simultaneous presentation of transverse stripes on the floor of a virtual corridor containing thresholds and doorways can enhance the stride pattern of PD patients.[24,41] In combination with the explicit control of walking speed on a treadmill, the current approach to facilitate locomotor function could prove to be a useful treatment option for PD.

Interestingly, the presentation of the virtual corridor containing thresholds and doorways did not have a noticeable effect on the average stride frequency since there was no difference between condition 1 (baseline) and condition 2 (virtual corridor, no cueing). While it is possible that the projected environment was not convincing enough, almost all subjects felt that they were really walking through the corridor. It is possible that the average stride frequency did not change due to the fact that the doorways and thresholds were relatively far apart. There could have been a more instantaneous effect, influencing the consistency (i.e. the variability) of the stride pattern. Prokop et al. found an elevated stride length variability and slower walking speed in healthy subjects during presentation of an optic flow field during treadmill walking.[41] Studies suggest that increased stride variability is related to susceptibility to falls in patients with PD, and that stride variability may be responsive to dopamine therapy.[42,43] Although subtle effects on stride variability cannot be ruled out, our PD groups were relatively young and had moderately low disease severity. Therefore stride variability may not have been very much affected; however, this requires further investigation.

The third research question concerned the possibility that presentation of the virtual corridor would suppress the effect of visual rhythmic cueing using the flashing light, as Parkinson patients may be more dependent on visual information for locomotion.*24* The results showed no effect of projected optic flow on the stride parameters: the stride frequency in condition 4 was significantly lowered compared to condition 1 (baseline) and 2 (virtual corridor, no cueing) and there was no difference between conditions 4 (cueing with flash, with virtual corridor) and 5 (cueing with flash, without virtual corridor). This suggests that a moving visual surround, which also occurs during normal walking through the environment, does not impede the use of the flashing cue-light, which is consistent with observations in our clinic. A possible explanation for the absence of a suppressive effect during cued conditions, which was supported by subjective comments from the patients, is that focal attention is drawn away from the possibly destabilizing visual stimuli in the environment, allowing gait to proceed undisturbed under the guidance of the visual rhythm.

Conclusion

The current experiment shows that the stride pattern of patients with PD is not rigidly coupled to walking speed and can be manipulated with visual cueing techniques as well as with a systematic manipulation of walking speed. It was shown that a rhythmically flashing light as well as projection of virtual stripes can be used to enhance the stride length of patients with Parkinson's disease. This indicates that pathological gait can be influenced by visual rhythmic entrainment strategies using alternate sensory motor

pathways in the presence of basal ganglia dysfunction. This cueing-method could therefore be a useful alternative for patients who cannot or will not use auditory cues. Additionally, the used protocol provides an excellent way to control walking speed at the same time.

Obviously, the transfer to and implementation in every day activities of this cueing method needs to be further investigated. In addition, the effects of cueing-therapy have not been systematically investigated in the home environment of patients with PD. The European project Rescue is directed at investigating these issues in a randomized controlled trial.

Acknowledgements

This study was supported by a grant from the European Committee (The Rescue project, grant number QLK6-CT-2001-00120). We would like to thank all participants for their contribution and A. Nanne and I. Wijbrands for their assistance in data collection.

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5

Cueing training in the home improves gait-related mobility in Parkinson's disease: The Rescue trial

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Journal of Neurology, Neurosurgery, and Psychiatry
2007; 78: 134-140

Abstract

Objectives: Gait and mobility problems remain difficult to treat in people with Parkinson's disease (PD). The Rescue trial investigated the effects of a home physical therapy programme based on rhythmical cueing on gait and gait-related activity.

Methods: A single-blind randomized crossover trial was set up, including 153 patients with PD aged between 41 and 80 years and in Hoehn & Yahr stage II to IV. Subjects allocated to early intervention (n=76) received a three-week home cueing programme using a prototype cueing device followed by three weeks without training. Patients allocated to late intervention (n=77) underwent the same intervention and control period in reverse order. After the initial 6 weeks, both groups had a 6 week follow-up without training. Posture and Gait scores (PG scores) measured at 3, 67, and 12 weeks by blind testers were the primary outcome measure. Secondary outcomes included specific measures on gait, freezing and balance, functional activities, quality of life and carer strain.

Results: Small but significant improvements were found after intervention of 4.2% on the PG scores (p=0.005). Severity of freezing was reduced by 5.5% as measured in freezers only (p=0.007). Gait speed (p=0.005), step length (p<.0001) and timed balance tests (p=0.003) improved in the full cohort. Other than a greater confidence to carry out functional activities (Falls Efficacy Scale, p=0.04), no carry-over effects were observed in functional and quality of life domains. Effects of intervention reduced significantly at 6 week follow-up.

Conclusions: Cueing training in the home has specific effects on gait, freezing and balance. The wearing-off of intervention effects underscores the need for permanent cueing devices and follow-up treatment. Cueing training may be a useful therapeutic adjunct to the overall management of gait disturbance in PD.

Introduction

In neurological patients, Parkinson's disease (PD) is the most common disorder leading to gait disturbance and falls.[1] Despite advances in pharmacological therapies and surgical techniques, gait and balance deficits still persist and are associated with loss of independence, immobility and high cost for health care systems.[2] Therefore, the development of rehabilitation approaches that work in conjunction with current treatment is important to manage these problems.

Recent systematic reviews concluded that there was insufficient evidence to support or refute the efficacy of physical therapy in PD, or to support the use of one form of physical therapy over another.[3,4] Studies suffered from methodological problems. However, reviewers did comment that the efficacy of physical therapy had improved through the addition of cueing techniques. Cueing is defined as using external temporal or spatial stimuli to facilitate movement (gait) initiation and continuation. Recent reviews into cueing suggest that it can have an immediate and powerful effect on gait performance in people with PD, indicating improvements in walking speed, step length and step frequency.[5,6] The influence of cueing has mainly been studied in single session experiments in laboratory settings.[7-11] Results demonstrate a short-term correction of gait and gait initiation and suggest that carry-over to uncued performance and its generalization to activities of daily living (ADL) is limited. Using cues in a therapeutic setting is more complex as the 'modality' of cue delivery (visual, auditory or somatosensory) and the cue 'parameter' selected for movement correction (frequency or size of step) have to be adapted to the needs of the patient. Apart from two limited

studies into the retention effects of cues, to date no work has evaluated the clinical application and prolonged training effects of cues in the home to improve walking in a functional context.[12,13] Furthermore, improved mobility with cues may have an adverse effect and distract attention, increasing the risk of falling.[14,15]

The primary objective of this study was to investigate the efficacy of a home-based cueing programme on parameters of gait, gait-related activity and health-related quality of life in people with PD. We hypothesized that a three-week period of home-based cueing training would result in measurable improvements of selected gait parameters immediately after treatment, but that these effects might decrease after 6 weeks without cueing.

Methods

Study population

We recruited 153 patients with idiopathic PD from three European centres, Northumbria University, Newcastle upon Tyne (UK), Katholieke Universiteit of Leuven (B) and the Vrije Universiteit Medical Centre of Amsterdam (NL). The study was approved by the ethics committee of each participating centre. All patients gave informed written consent to the study. Eligibility criteria were (1) showing mild to severe gait disturbance with score >1 on the Unified Parkinson's Disease Rating Scale (UPDRS; item 29);[16] (2) diagnosis of idiopathic PD, defined by the UK Brain Bank Criteria);[17] (3) stable medication usage; (4) Hoehn & Yahr stage II–IV; and (5) age 18–80 years. Patients were excluded if they had (1) undergone deep brain stimulation or other stereotactic neurosurgery; (2) a cognitive impairment (Mini Mental State Examination scores <24);[18] (3) disorders interfering with participation in cueing training, including neurological (stroke, MS, tumour), cardiopulmonary (chronic obstructive disorders, angina pectoris) and orthopaedic (osteoarthritis, rheumatoid arthritis and back pain) conditions; (4) unpredictable and long lasting off-periods (score=1 item 37 and score >2 on item 39 of the UPDRS);[16] and (5) participated in a physical therapy programme two months prior to commencing the trial.

Design and procedures

The present study was a single blind, randomized, clinical trial with a crossover design with no wash-out period. The choice of design was based upon previous evidence of the short-lasting effects of cueing,[5,6] the advantage of providing treatment for all participants, and increasing the statistical power within the constraints of research funding. In each centre patients were randomly allocated in permuted blocks of six to an early or late intervention group by an independent investigator not involved in data analysis. Allocation was concealed by the use of opaque sealed envelopes. The early group received a cueing programme delivered in nine treatment sessions for 30 minutes over 3 weeks, immediately followed by 3 weeks in which no training was received. Subjects in the late group were put on a three-week waiting list, immediately followed by 3 weeks of cueing training. Both treatment arms underwent a follow-up period of 6 weeks without training. Medical treatment continued unchanged throughout the study. Prior to the trial, Rescue therapists and testers underwent separate training

sessions lasting a full week to standardize procedures in all centres.

Intervention

Cueing training was delivered in the home by one therapist in each country. A prototype cueing device, specifically developed for the study, provided three rhythmical cueing modalities: (1) auditory (a beep delivered through an earpiece); (2) visual (light flashes delivered through a Light Emitting Diode attached to a pair of glasses); and (3) somatosensory (pulsed vibrations delivered by a miniature cylinder worn under a wristband). Patients tried all cueing modalities in the first week but trained with their preferred modality. Through addressing the temporal aspects of gait, cueing training aimed to improve step length and walking speed, prevent freezing episodes and improve balance.

Cued practice was applied during a variety of tasks and environmental situations and consisted of the following components: gait initiation and termination,[10,11] heel strike and push-off, sideways and backwards stepping, walking while dual tasking[19] and walking over various surfaces and long distances.[8] For freezers, cues were applied to facilitate continuation of gait during turns and manoeuvres in tight places and doorways. Based on previous experiments undertaken by the Rescue consortium[19-22] and the literature,[5,6] evidence-based cueing guidelines were drawn up, specifying the cueing parameters and instructions for different profiles of patients (available on CD-Rom http://www.rescueproject.org/). Cues were generally delivered at patients' preferred frequency (determined for an indoor and outdoor environment) and adjusted to increase step length and walking speed, depending on aims of therapy. In case patients had freezing, cueing frequency was started at preferred rhythm and adjusted to lower rhythms to avoid hastened stepping if needed.[22] Chiefly, patients were instructed to match their heel strike with the cueing rhythm and keep on stepping through turns or during other manoeuvres. Specific instructions to maintain or enlarge step length or heel strike with every cue were added if and when required. Therapists recorded the content and amount of therapy in a diary in 15 minute units.

Outcome measures

As this study wanted to measure the training effects, and not the immediate effects of cueing, outcome measures were tested without the cueing device. Most outcomes described below were tested for reliability and validity in the home prior to the trial by three testers and during two consecutive visits. Part of this study, including the full methodology, was published elsewhere.[23] As the Rescue trial included repeated measures carried out by the same tester, the intraclass correlation coefficients (ICC) for within raters of each outcome are described in the following sections:

(1) The primary outcome measure was the PG score, a composite score of gait and balance UPDRS items (13–15 and 29–30), reflecting the main aims of cueing training (ICC=0.79).

(2) To explore the specific effects of cueing training secondary outcome measures consisted of:

(a) **Gait and balance measures:** 10m walk test at the person's preferred walking speed using a stopwatch to calculate gait speed (m/s) (ICC=0.81), step length (m) and step frequency (steps/min); Functional reach[24] (Fr; ICC=0.74); timed single leg and tandem stance until subjects reached a maximum of 30 s; Freezing of Gait Questionnaire[25] (FOGQ; ICC=0.84); and Timed Get Up and Go Test[26] (TGUG; ICC=0.88). Timed walking and Get Up and Go tests were standardized for each patient's home.

(b) **Activity measures:** Nottingham Extended Activities of Daily Living Index[27] (NEADL; ICC=0.93) and Falls Efficacy Scale[28] (FES; ICC=0.88).

(c) **Participation measures:** Parkinson's Disease Questionnaire-39[29] (PDQ-39; ICC=0.79) and Carer Strain Index[30] (CSI; ICC=0.85).

A falls diary was left in the patient's home during the trial period to indicate the number of falls as a measure of possible adverse cueing effects. A dichotomized score was derived (falls=1 or no falls=0) at crossover and at the end of therapy from the recorded number of falls during the previous three-week periods and at follow-up for the previous 6 weeks. At $test_1$, the dichotomized score was calculated from the number of falls during the previous 3 months.

Descriptive measures included the Mini Mental State Exam (MMSE),[13] the Brixton Test[31] for executive function and the Hospital Anxiety and Depression Scale (HADS).[32]

Assessment Protocol

All outcome measures were assessed immediately prior to randomization ($test_1$) and at 3 ($test_2$), 6 ($test_3$), and 12 weeks ($test_4$). One trained tester in each centre, not involved in training and blind to group allocation, performed all assessments in the patient's home. Each patient was assessed at the same time of day in the on-phase, approximately 1 hour after medication intake, in order to control for variations due to the medication cycle. The order of tests was randomized for each patient. Testers verified that patients had taken their medication and the efficacy of medication was checked at each assessment.

Statistical analysis

Power analysis prior to the trial indicated that 150 patients were required for a 10% change relative to baseline values on the PG score (0.6 points) with a power of 80% and a critical value of 5% for statistical significance, allowing a drop-out of 10%.

The success of blinding and randomization procedures was explored by comparing early and late groups using Wilcoxon-Mann-Whitney U tests, Chi-square tests and unpaired *t* tests.

Exploratory analysis revealed carry-over effects of treatment in the control period ($test_3$-$test_2$) in the early group. Hence, intervention effects were estimated using the first three assessments ($test_{1,2,3}$) with multiple linear regression models accounting for repeated measures. Where appropriate a linear, logistic or Cox regression model was

fitted for each outcome with PROC MIXED and PROC GENMOD in SAS (version 8.2). In each model the same predictors were adopted, including indicators to represent time, intervention and carry-over. A logistic regression model with generalized estimating equations (GEE) evaluated the effect of intervention on the risk of falling. A Cox regression model with frailty term verified the impact of intervention on the hazard of failing the timed balance tests (inability to remain standing for a maximum 30 s), using the coxph function in Splus 2000. To explore whether cueing had an effect on movements which were not targeted by training, upper limb repetitive movement scores (UPDRS items 23–25) were analyzed.

Change at follow-up was assessed by comparing the change between $test_3$ and $test_4$ using a model with two factors (time and group) fitted onto outcomes of $test_{1,2,3,4}$ for early and late groups taken together. For continuous outcomes a trivariate normal distribution for error components was assumed. Data were transformed where necessary to meet normality assumptions and baseline values were reported as medians and interquartile ranges.

Two-tailed analysis was performed on all tests with a significance level of 5%. Given the exploratory nature of the secondary outcomes analysis, no Bonferroni correction was applied. Intervention effects are reported as β estimates and standard errors (SE) for the linear regression models. Odds and hazard ratios (=exp(β)) with 95% confidence intervals are presented for the logistic and Cox regression models.

The statistical models adopted in this study assumed that missing values occur randomly, using the remaining information even if occasional missing values are present. Missing values occurred in 1.7% of all outcomes over the four time points and 1.3% over the three time points. As all patients received treatment

Results

Trial profile

The trial flow chart (Figure 1) shows that out of 289 potential candidates, 153 patients (53%) were eligible for inclusion into the study. Patients were mostly excluded because of gait being insufficiently impaired (*n*=44), co-morbidity (*n*=25), deep brain stimulation (*n*=15) and an inability to commit time (*n*=15). Suitable patients were randomly allocated to the early (*n*=76) or late intervention group (*n*=77). One patient dropped out 3 weeks after randomization due to a necessary alteration of medication. In total 605 (99%) of the planned 612 measurements were performed. Medication intake remained stable throughout the trial. Comparison between the observers' guess of allocation (early or late) and the actual patient assignment indicated that the blinding procedure was successful as 56.1% (*n*=87) was allocated correctly and 43.1% (*n*=66) incorrectly (Chi-square=2.94, *p*=0.09).

Comparison of early and late intervention

Patients received equal amounts of therapy in the early (271.8 minutes) and late groups (270.4 minutes) (*t*=0.27; *p*=0.79).

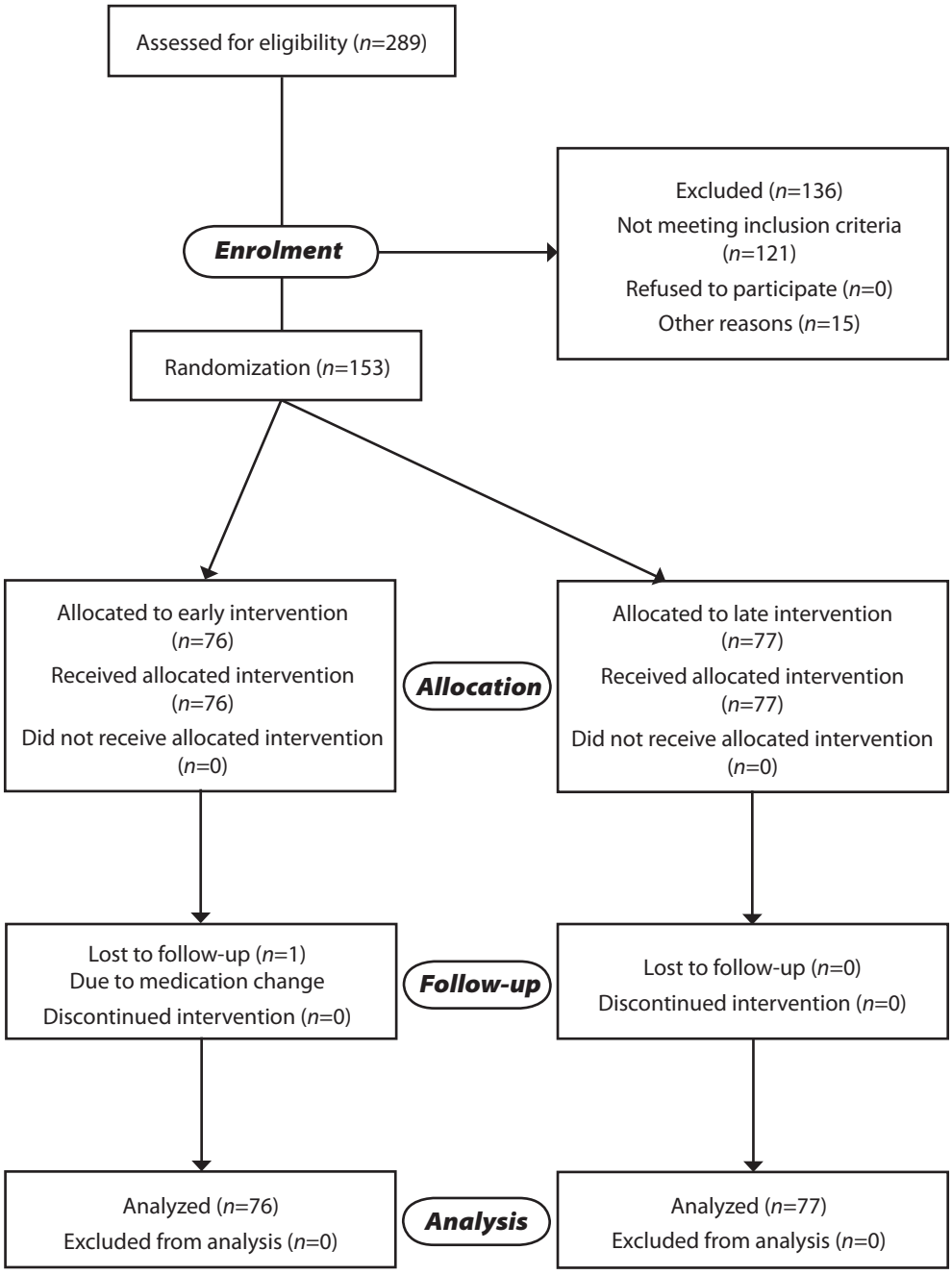

Figure 1 Trial flow chart.

There were no important differences between the clinical profiles of the two intervention groups (see Table 1). Most patients had mild to moderate disease severity as 46.4% of patients (*n*=71) were in Hoehn & Yahr stage II, 41.8% (*n*=64) in stage III and 11.8% (*n*=18) in stage IV. Both early and late groups included similar numbers of freezers defined as having at least weekly freezing episodes (*n*=31 [20.3%] in early and *n*=32 [20.9%] in late), as defined by a score >1 on item 3 of the Freezing of Gait Questionnaire. Table 2 shows the median and interquartile ranges of all outcomes at tests 1–4. No significant group differences were found for primary and secondary outcomes at test$_1$, confirming the success of the randomization procedure. Table 2 shows that 41% in the early and 39% in late group reported at least one episode of falling in the 3 months prior to trial onset.

Treatment effects

Table 3 shows the estimated intervention effects corrected for time and carry-over. The primary outcome, the PG score, improved by 4.2% after intervention (*p*=0.005). As for the secondary outcomes, gait speed (*p*=0.005) and step length (*p*<0.0001) improved by

Table 1 Comparison between early and late allocation groups

	Early *n*=76 Median (Q1–Q3)	Late *n*=77 Median (Q1–Q3)	*p* value
Demography			
M/F[a]	48/28	40/37	0.16
Age	67.5 (61.5–72)	69 (62.5–73)	0.7
PD characteristics			
Disease duration	7 (4–11)	8 (4–12)	0.59
H&Y (on)	2.5 (2.5–3)	3 (2.5–3)	0.56
H&Y II/III/IV[a]	39/29/8	32/35/10	0.48
Freezers/Non-freezers[a]	31/45	32/45	0.92
Clinical data			
UPDRS total (on)	54 (46–65.5)	56 (49–63)	0.62
UPDRS I (on)	4 (2–5)	3 (2–4)	0.1
UPDRS II (on)	16 (12–19.5)	16 (12–20)	0.67
UPDRS III (on)	31 (25–37)	34 (28–41)	0.32
UPDRS IV (on)	3 (1–5)	2 (1–5)	0.43
Levodopa (mg)	500 (300–700)	350 (200–550)	0.07
MMSE	28.5 (27–30)	29 (27–30)	0.99
Brixton	4 (2–6)	4.0 (2–6)	0.45
HADS anxiety	6.5 (4–10)	6 (4–10)	0.97
HADS depression	7.5 (5–10)	6 (4.5–9)	0.45

M/F, male and female; H&Y (on), Hoehn &Yahr stages during on; H&Y II/III/IV, Hoehn &Yahr stages II, II, IV during on; UPDRS, Unified Parkinson's Disease Rating Scale part I, II, III, IV and total score; MMSE, Mini Mental State Examination; HADS, Hospital Anxiety and Depression Scale; Q1–Q3, Interquartile Range. [a] Expressed as number of patients and *p* value based on Chi-square test.

Table 2 Medians and interquartile ranges of the outcomes in early and late intervention groups at $test_1$–$test_4$

	$test_1$ Median (Q1–Q3)	$test_2$ Median (Q1–Q3)	$test_3$ Median (Q1–Q3)	$test_4$ Median (Q1–Q3)
Primary Outcome				
PG score (0–20)				
Early	6.0 (4.0–8.0)	4.0 (3.0–7.0)	4.0 (3.0–6.0)	4.0 (3.0–7.0)
Late	7.0 (5.0–8.5)	6.0 (4.0–8.0)	4.0 (3.0–6.0)	5.0 (3.0–7.0)
Secondary Outcomes				
Walking speed (m/s)				
Early	0.86 (0.73–0.98)	0.94 (0.80–1.1)	0.94 (0.80–1.1)	0.92 (0.81–1.1)
Late	0.83 (0.68–0.98)	0.83 (0.72–1)	0.93 (0.77–1.1)	0.94 (0.76–1.1)
Step length (m)				
Early	0.51 (0.44–0.58)	0.55 (0.48–0.63)	0.56 (0.47–0.62)	0.54 (0.46–0.60)
Late	0.50 (0.43–0.56)	0.51 (0.43–0.58)	0.55 (0.47–0.62)	0.55 (0.48–0.60)
Step Freq (steps/min)				
Early	101.6 (92.5–110)	102 (89.4–108.1)	102.2 (92.5–109.2)	102.2 (95.2–111)
Late	99 (91.6–109.6)	102.5 (94.3–112.6)	101 (94–108.6)	104.2 (97.2–112)
Functional reach (cm)				
Early	25.9 (20.9–31)	26.3 (23–30.5)	27.5 (20.3–33)	26.9 (23–31.4)
Late	25.2 (20.2–30.5)	25.5 (19.8–30.7)	28.6 (21.6–34.3)	26.5 (19–31)
Single stance (s)				
Early	9 (3.8–20.9)	11.2 (5.3–24.4)	12 (5.5–23.2)	11 (5.2–22.1)
Late	9.1 (3.9–21)	9.5 (3.6–19.3)	14.2 (6.3–24)	12.6 (4.2–21.8)
Tandem stance (s)				
Early	22 (9.3–30)	26.7 (14.3–30)	22.0 (11.1–30)	23.1 (10.4–30)
Late	23.1 (8.0–30)	20.7 (8.6–30)	24.6 (11.1–30)	22.1 (10.2–30)
TGUG (s)				
Early	13.2 (10.9–17.7)	12.3 (10.8–15)	11.8 (10.7–15.7)	12.2 (11.0–15.6)
Late	13.9 (12.0–17.9)	12.7 (11.1–15.7)	12.1 (10.6–15.1)	12.2 (10.7–15.5)
FOGQ (0–24)				
Early	8 (4–14)	8 (3–12)	7 (3–11.5)	7 (3–12.5)
Late	8 (4.5–12)	9 (4–12)	8 (3–11)	8 (4–12)
NEADL (0–66)				
Early	41 (32–53.8)	42 (33–51)	42.5 (36.3–53.5)	46 (35.8–53.3)
Late	40 (35–51)	42.5 (23.3–54)	46 (34–51)	43.5 (35–51)
FES (0–130)				
Early	85 (65.3–107.8)	91 (71–111)	94 (66–110)	90 (65.5–111.5)
Late	78 (57–99.5)	82 (54–104)	85 (70–108.3)	81 (57.5–105.5)
PDQ-39 (total %)				
Early	35.4 (22.7–42.6)	31.3 (22.2–40.9)	30.9 (20–42.3)	34.2 (21.8–40.8)
Late	37.8 (27.6–45.9)	37.2 (25.9–42.7)	32.3 (20.7–41.4)	35.6 (22.8–43.5)
CSI (0–13)				
Early	4 (1–5.8)	3 (1–4)	3.0 (1–6)	1 (0–3)
Late	2 (1–5)	4 (1–5.5)	3.0 (0–5)	1.5 (0–3.3)
Falling (yes/no, % yes)[a]				
Early	31/44 (41%)	18/58 (24%)	8/67 (11%)	16/59 (21%)
Late	30/47 (39%)	14/63 (18%)	10/67 (13%)	13/64 (17%)

PG score, Posture and Gait score; FOGQ, Freezing of Gait Questionnaire; FES, Falls Efficacy Scale; TGUG, Timed Get Up and Go test; NEADL, Nottingham Extended ADL Index; PDQ-39, Parkinson's Disease Questionnaire; CSI, Carer Strain Index.

[a] Falling, time periods of falls diary at each test period differ ($test_1$=3 months, $test_2$=3 weeks, $test_3$=3 weeks, $test_4$=6 weeks). Figures represent numbers of patients who fell. One missing value was obtained at $test_1$ in the early group and at $test_3$ and $test_4$ due to drop-out.

5 cm/s and 4 cm, respectively. No significant change in step frequency was observed (p=0.08). The Fr test did not show an intervention effect (p=0.18). However, the clustered tandem and one leg standing tests showed that the chance of failing these tests was decreased by 36% following intervention (hazard ratio=0.64; 95 CI%: 0.48–0.87; p=0.003). The TGUG did not show improvement after intervention. As for the severity of freezing, the FOGQ scores were not significantly affected by cueing therapy (p=0.25) after transformation. Data revealed a bimodal distribution indicating a group with low scores (non-freezers) and one with high scores (freezers). When the FOGQ scores were re-analysed on freezers only (n=63), defined as having at least a weekly freezing frequency, a significant reduction of 5.5% of freezing severity was found (ß estimate =−1.33±0.48, p=0.007).

Intervention effects presented in Table 3 are smaller compared with the change in median values before and after intervention for the early and late groups in Table 2 as a result of the statistical control for time and carry-over effects. For example, the PG score improved from a median of 6 to 4 after treatment, suggesting a 10% rather than

Table 3 Intervention effects and change at follow-up (difference $test_4$–$test_3$)

	Intervention ß estimate (SE)	Change in units[a] % range[b]	*p* value	Follow-up ß estimate (SE) $test_4$–$test_3$	*p* value
Primary outcomes					
PG score (0–20)	−0.85 (0.3)	4.2 %	0.005	0.582 (0.14)	<0.0001
Secondary outcomes					
Gait & balance					
Speed (m/s)	0.05 (0.02) ↑	5.0 cm/s[a]	0.005	−0.02 (0.007 ↓	0.03
Step length (m)	0.04 (0.009) ↑	4.0 cm[a]	0.0001	−0.02 (0.004)↓	<0.0001
Step frequency (steps/min)	−2.1 (1.19) ↑	−2.1 step/min[a]	0.08	1.24 (0.56) ↓	0.03
Functional reach (cm)	1.3 (0.97) ↑	1.3 cm[a]	0.18	−1.08 (0.46) ↓	0.02
Tandem stance (s)	–	–	–	–	–
Single leg stance (s)	–	–	–	–	–
TGUG (s)	−0.002 (0.73) ↑	2 ms	0.6	0.14 (0.2) ↓	0.47
FOGQ (0–24)	−0.86 (0.44) ↑	3.6%[b]	0.25[c]	0.8 (0.21) ↓	0.0002
Activity					
NEADL (0–66)	1.71 (0.94) ↑	2.6%[b]	0.07	−0.65 (0.5) ↓	0.2
FES (0–130)	4.77 (2.29) ↑	3.7%[b]	0.04	−2.92 (1.22)↓	0.02
Participation					
PDQ-39 (total %)	−1.36 (1.14) ↑	1.4%	0.23	0.99 (0.52) ↓	0.06
CSI (0–13)	−0.76 (0.32) ↑	5.8%[b]	0.14[c]	0.15 (0.18) ↓	0.42

PG score, Posture and Gait score; FOGQ, Freezing of Gait Questionnaire; TGUG, Timed Get Up and Go test; NEADL, Nottingham Extended ADL Index; FES, Falls Efficacy Scale; PDQ-39, Parkinson's Disease Questionnaire; CSI, Carer Strain Index.

[a] Change expressed in measured units, positive figures represent an improvement

[b] Change expressed in % of the scoring range, positive figures represent an improvement

[c] After transformation

↑ estimate represents change in direction of improvement

↓ estimate represents change in direction of deterioration

a 4.2% change of the scoring range. Overall, carry-over effects were only statistically significant for step length in the early group at $test_3$ (p=0.014). Time effects showed significant improvements for the PG score (p=0.03), gait speed (p=0.04) and the TGUG (p=0.004).

For the secondary outcomes in the activity domain improvements were found on the FES (p=0.03), indicating that patients felt more confident during gait-related activities. ADL function as measured by the NEADL was not significantly altered (p=0.07). The PDQ-39 scores (p=0.23) and the CSI were not significantly changed after intervention (p=0.14). The GEE model showed no significant increase or decrease for the probability of falling as a result of treatment (odds ratio=1.4; 95 CI%: 0.63–3.1; p=0.4). Separate analysis of the upper limb repetitive movement scores of the UPDRS (III) showed no significant treatment effect (ß=−1.1±0.62; p=0.08). Most patients (n=95, 67%) chose auditory cueing as their preferred cueing modality, while 57 patients (n=58, 33%) favoured somatosensory cueing.

Follow-up ($test_4$–$test_3$)

Table 3 also shows the change at follow-up. Most intervention effects in the gait and balance domains declined significantly from 6 to 12 weeks. Secondary outcomes at activity and participation levels also tended to decline at $test_4$, a pattern which was significant for the FES. The chance of failing the balance tests at $test_4$ was increased as compared with $test_3$ (HR=1.12; 95 CI%: 0.96–1.32) but this difference was not significant (p=0.15). Table 2 shows that more patients reported a fall at $test_4$ compared with $test_3$, but this may reflect the fact that at $test_4$ a period of 6 weeks was assessed as opposed to 3 weeks at $test_3$.

Discussion

This is the first large scale randomized clinical trial investigating the effects of a cueing training programme delivered at home using a multi-modality cueing device. The main findings indicate that nine sessions of cueing training demonstrated a significant improvement in gait and gait-related mobility in people with PD, but that these effects were small and specific. The cueing method was widely accepted and well-tolerated in a wide range of patients ranging from Hoehn & Yahr stages II–IV, as evidenced by only one drop-out.

The present findings showed that a period of training with cues in the homes of people with PD resulted in improvement of gait immediately after intervention. We found a significant increase in walking speed and step amplitude accompanied by a tendency to reduce step frequency. This finding is in agreement with earlier work, showing that the potential to generate a more normal gait pattern can be tapped in PD.[7] When looking at freezers separately, a significant change on the FOGQ after intervention was found, signifying a reduction of freezing severity. This is an important finding, as freezing is particularly resistant to drug treatment and often associated with falling.[33] This result contradicts earlier work, in which freezers were provided with a metronome for one week at home without clear benefits.[34] In contrast, during the Rescue trial cueing therapy was provided by therapists, who used specific guidelines to set the

cueing frequency to the needs of freezers and instructed patients on how to prevent and overcome freezing in their daily environment for a three-week period.[22]

Increased rates of falls in people with PD are well documented and have been attributed to preserved mobility in this population.[2,35] We were, therefore, concerned that any improvements in mobility due to therapeutic cueing could have resulted in an increased risk of falls. Our results, however, showed no evidence for this but rather an improved balance and increased confidence not to fall. Given the limited power to detect changes in fall rates using a fall diary methodology over a short time span, the present results need cautious interpretation.

Subjects were trained for three weeks with cues and were evaluated without wearing the device to see if the effects were maintained. The present results showed training effects in the absence of cues, indicating that some degree of motor learning is preserved in PD. Whereas most studies investigated the immediate benefits of cued performance, our findings confirm the limited evidence available of improved uncued performance after training with cues.[6,8,12]

The effects found in this study can be considered robust and not attributable to measurement error or learning effects. All but three outcome measures had established test retest reliability in the home situation[23] and the order of testing was randomized. In order to estimate the effects of intervention separately from carry-over and time effects, the statistical analysis controlled for these factors, providing a conservative estimation of treatment effects.

The fact that intervention effects were small could reflect a limitation of cueing training in the home setting. However, current effects sizes are in line with those observed in recent meta-analyses on physical therapy in PD[3,4] and in other conditions such as stroke.[36,37] The limited effects may also be explained by the relatively short training duration. Training intensity rather than content was found to be a key factor in stroke research and may be equally crucial in PD.[37] In this study training intensity was stipulated by the maximum number of physical therapy sessions at home allowed for reimbursement according to existing health care policies. This raises the question of what the optimal duration and intensity of cueing training is and how this should be delivered over time.

What actually constitutes clinically relevant results in rehabilitation of a chronic degenerative disorder is still unclear at this point. Possibly the improvements of gait and balance were too small to carry-over to ADL and perceived quality of life. Alternatively, the narrow focus of the intervention may have led to specific effects, as we showed that repetitive upper limb movements were not affected by cueing therapy. Equally, in other fields of rehabilitation lack of generalization is a common feature.[36,37]

Training effects were not sustained at 6 week follow-up as a significant reduction in most outcomes was apparent. Similarly, Nieuwboer et al.[38] showed a significant deterioration at 12 weeks after training with cues, and Thaut et al.[39] found a declining slope from 4 to 6 week follow-up. Other authors reported negligible reductions at 4 to 6 weeks after cueing training.[12,40]

The impact of placebo effects as a result of increased attention during therapy was not

controlled for, which is a limitation of this study. Although the specificity of the results argues against a general effect of increased attention, effects of gait-related attention rather than cueing cannot be ruled out. Previously, it was shown that gait training with auditory cues was more effective than training without cues and no training.[8]

Lack of Bonferroni correction and the fact that at $test_3$ and $test_4$ testers were aware of patients having received therapy, inherent to a repeated measures design, warrant careful interpretation of the results. However, testers were not unblinded to treatment allocation at any time point.

The findings of this study cannot be generalized to people with PD who have significant cognitive decline and other co-morbidities. Especially in the later disease stages, cues may overburden cognitive resources and increase fall risk.[14] Future work should focus on determining such at-risk patients. Equally, the possibility that cues may actually reduce attentional cost in patients who are not at risk requires further investigation. Recently, we found that during cued performance of dual tasks, gait parameters improved rather than deteriorated.[19] Future studies, assessing cueing effects over a longer period of time, will be able to determine whether habituation occurs to the stimulus of the cue and verify our findings on fall risk associated with cueing over longer periods. In addition, the cost-effectiveness of an extended therapeutic cueing programme possibly supplemented with a permanent cueing device needs further investigation. Although most patients preferred the auditory cueing modality (67%), a large number (33%) perceived somatosensory cueing as a well-tolerated and discrete alternative. At present, auditory cueing alone can be provided at relatively low cost using metronomes with earphones or via digital music players.

We conclude that cueing training in the home situation has a small and specific benefit for managing gait and freezing in patients with Parkinson's disease. In addition, this study has highlighted important questions on how to deliver cueing training in the most optimal way.

Acknowledgements

We gratefully acknowledge the financial support from the European Commission Framework V funding; QLK6-2001-00120. We would like to acknowledge the contribution of Professor Rowena Plant in gaining funding. Prof. Dr. E.C.H. Wolters (MD, PhD), Dr. H.W. Berendse (MD, PhD), Dr. C.M. Zijlmans (MD, PhD), Prof. Dr. R. Dom (MD, PhD), Dr. D. Burn (MD) and Dr. R. Walker (MD) are acknowledged for referral of patients. We gratefully acknowledge assistance with data analysis from S. Fieuws and K. Desloovere. We particularly want to acknowledge the patients with Parkinson's disease and their carers who participated in this study.

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6

Does cueing training improve physical activity in patients with Parkinson's disease? The Rescue trial

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Submitted for publication

Abstract

Objectives: To investigate the effects of a home cueing training programme on functional walking activity in patients with Parkinson's disease (PD).

Design and procedures: In a single-blind, randomized crossover trial, PD patients allocated to early intervention received cueing training for 3 weeks. Patients allocated to late intervention received training in the following 3 weeks. Training was applied at home, using a prototype cueing device.

Measurements: Activity monitoring (AM) was applied at baseline, 3, 6, and 12 weeks in the patient's home, to record body movements.

Data analysis: Postures and motions were classified as percentage of total time spent on (1) static activity, further specified as % sitting and % standing, and (2) dynamic activity, further specified as % walking, % walking periods exceeding 5 sec (W>5s), and % walking periods exceeding 10 sec (W>10s).

Statistics: Random coefficient analysis was used for all variables.

Results: 153 patients participated in this trial. Significant improvements were found for dynamic activity (+4%, $p<0.01$), static activity (-3%, $p<0.01$), walking (+4%, $p<0.01$), W>5s (+3%, $p<0.05$) and W>10s (+3%, $p<0.01$). All intervention effects declined significantly at 6 weeks follow-up.

Conclusion: Cueing training in PD patients' own home significantly improves the amount of walking as recorded by AM. Treatment effects significantly reduced after the intervention period, pointing to the need for permanent cueing devices and follow-up cueing training.

Introduction

Parkinson's disease (PD) is one of the most common neurological disorders in elderly people.[1] Between the age of 55 and 85 years, 4.2% of all women and 6.1% of all men develop PD.[2] The major motor symptoms in PD are tremor, rigidity, bradykinesia and postural instability, resulting in problems with gait, balance, transfers and posture.[3] These problems can lead to reduced mobility and less activity, which in turn can cause increased dependency and social isolation and thereby reduce quality of life.[4] It is therefore important to encourage patients to maintain their mobility and to stay active, for example by referring them to physical training programmes.[5-7]

In a randomized controlled trial (RCT) with the acronym Rescue (REhabilitation in Parkinson's disease Strategies for CUEing), it was shown that a cueing programme improved Posture and Gait scores (PG), gait speed, step length and timed balance tests in patients with PD.[8] In addition, secure mobility during functional activities was improved and freezers showed a reduction in the severity of freezing. These Rescue trial results are single, cross-sectional snapshots of the capacity of the PD patients and were obtained in the on-phase of medication. Results from such clinical testing are assumed to reflect patients' 'real-world' activities related to gait. However, test performance achieved in optimally medicated situations, often when patients are not fatigued, combined with patients' desire to perform optimally, may overestimate their actual performance.

Contrastingly, ambulatory activity monitoring (AM) provides an objective way to determine type and amount of gait-related activities for several hours per day.[9] Therefore AM could provide more 'real-world' information about patients' behaviour

during a day, irrespective of daily fluctuations in on- and off-phases. AM is a reliable and valid method for determining walking activity in PD patients.[10,11] In a recent reliability study, high Intra Class Correlation coefficients (ICCs) ranging from .81 to .96 were found for monitoring walking in patients with PD.[10]

The objective of the present study is to investigate the effect of cueing training on the amount of physical activity, specifically walking, in patients with PD, when monitored in their own home environment. It was hypothesized that overall dynamic activity, specifically walking activity, would increase following cueing training. A second aim of this study was to investigate the reliability of AM over a three-week interval.

Methods

For the Rescue trial 153 patients were recruited in three different countries: 48 patients were recruited at Northumbria University, Newcastle upon Tyne (UK), 51 patients were recruited at the Katholieke Universiteit Leuven (Belgium), and 54 patients were recruited at the VU University Medical Center, Amsterdam (The Netherlands). Main eligibility criteria were (1) idiopathic PD; (2) Hoehn and Yahr[12] stage II–IV; (3) showing mild to severe gait disturbances; (4) stable medication usage; (5) age 18–80 years; and (6) absence of cognitive impairment and disorders interfering with participation in cueing therapy. A more detailed description of all eligibility criteria can be found in Nieuwboer et al.[8] All patients gave a written informed consent. The study was approved by all medical ethics committees of participating centres.

Design and procedures

The Rescue trial was a single blind, randomized clinical trial with crossover design. Patients were randomly allocated using permuted blocks of six to an early or late intervention group by an independent person, otherwise not involved in the study. Allocation was concealed, using opaque sealed envelopes. The early intervention group received cueing training for a period of 3 weeks immediately after randomization. The training programme consisted of nine sessions of 30 minutes over 3 weeks and was immediately followed by a control period of 3 weeks. The late intervention group was put on a waiting list for the first 3 weeks and subsequently received the same cueing programme in the second 3 weeks. The early intervention group had a follow-up period of 9 weeks, the late training group of 6 weeks. Medication treatment stayed stable throughout the study. Prior to the trial all Rescue therapists and assessors participated in joint training sessions to standardize their treatment and assessment procedures. Each country had one therapist and one assessor.

Intervention

Each participant received cueing training in the home situation with the help of a prototype cueing device. This cueing device was specifically developed for this project and provided three rhythmical cueing modalities: (1) an auditory modality (a beep); (2) a visual modality (a flashing light at the side of the spectacles); and (3) a somatosensory modality (a miniature vibrating cylinder on the wrist).[8] Patients tried out every modality during the first week and practised with their preferred cueing

modality in the second 2 weeks. In addition to the cueing device, parallel lines on the floor or pavement were used in the training as visual cues. Cueing training was aimed at improving gait and gait-related activities (such as step length, walking speed and management of freezing).

Based on previous experiments undertaken by the Rescue consortium[13-16] and the literature,[17,18] evidence based guidelines were drawn up, specifying the cueing parameters and instructions for different profiles of patients (available on CD-ROM, http://www.rescueproject.org). Patients were instructed to use the cues and encouraged to practise without the assistance of the therapist outside the regular training time.

Outcome measures

In addition to recording time, the following outcomes were analyzed:

(1) The percentage time spent on static activity (% static activity). Static activity was defined as all activities without movements. In the present study statistic activity reflected the actual amount of standing, sitting and lying.

(1a) Percentage time spent on standing alone (% standing), and

(1b) Percentage time spent on sitting alone (% sitting);

(2) The percentage time spent on dynamic activity (% dynamic activity). Dynamic activity was defined as all activities where movements were involved. In the present study dynamic activity reflected the actual time spent on walking, transfers, turning, stair walking and cycling.

(3) Percentage time spent on walking alone (% walking), further specified as:

(3a) Average number of walking periods registered per hour exceeding 5 seconds (Walk>5s), and

(3b) Average number of walking periods registered per hour exceeding 10 seconds (Walk>10s).

Assessment Protocol

All patients were tested by an assessor in their home environment prior to randomization (t_1) and at 3 (t_2), 6 (t_3) and 12 weeks (t_4). The assessor was blind to group allocation. Each patient was visited at approximately the same time of the day in the on-phase, about 1 hour after medication intake, in order to control for variations due to the medication cycle. A test battery was used to assess gait and gait-related activities of the patient (for results, see Nieuwboer et al.).[8] In addition, an AM (Vitaport3, TEMEC instruments b.v., Kerkrade, The Netherlands) was applied by the assessor to record the body movements of the subject during the day. On average 5 hours later the assessor visited the patient again to remove the AM. In order to measure the effects of practice with cueing and not the immediate effects during cueing, the cueing device was not used during monitoring. Moreover, training was not received on testing days.

The activity monitor consisted of a montage of five accelerometers connected to a portable data recorder worn on a belt around the waist. The accelerometers were

attached to the body as follows: one on each leg positioned on the lateral aspect of the thigh midway between the greater trochanter of the femur and the midpoint of the patella, orientated in the sagittal plane; three accelerometers were placed on the lower third of the sternum, with the sensors on a specially designed block positioned so that they were orientated in the sagittal, longitudinal and transverse planes. The skin was prepared by cleaning the area with an alcohol swab and shaving when necessary. The accelerometers were mounted on a piece of thin foam and attached to the skin using Hypafix tape (HypafixR, BSN Medical). Each accelerometer was connected to a portable battery powered activity monitor (Vitaport 3, TEMEC Instruments Inc) by cables that ran under the clothes.

Data were sampled at a frequency of 256 Hz and stored at 32 Hz on a removable flash memory card for offline analysis. The accelerometers recorded gravitational force and accelerations of the moving lower limbs and trunk. The data were analyzed using a specifically designed software program (Vitagraph) (TEMEC Instruments Inc) which classified activity into static activity (i.e. sitting and standing) and dynamic activity (amount of walking and walking periods exceeding 5 seconds and 10 seconds). The patient was kept naïve about the function of the activity monitor and was instructed to maintain the usual daily activities.

Analysis

AM data was initially processed using Vitagraph (TEMEC Instruments Inc). Data were analyzed using SPSS (SPSS-Inc, Chicago, IL, USA). As data were not normally distributed, non-parametric tests were used for data comparison between the early and the late intervention group (Mann-Whitney U test). Demographic details, PD characteristics and clinical measures were compared using independent two-tailed t tests. The level of significance was set at p=0.05.

Data from t1 and t2 of the late intervention group was used to investigate the reliability of AM. ICCs, using a two-way mixed model with an absolute agreement definition, were employed to calculate reliability of % static and % dynamic activity.[19] According to the recommendations of Fleiss,[20] ICC values under .40 represent poor reliability, values between .40 and .75 moderate to good reliability and ICCs above .70 represent excellent reliability. Agreement was further analyzed using the Bland and Altman method;[21] the 'limits of agreement', defined as $\pm 1.96 \times$ standard deviation of the difference scores, were computed.

Intervention effects were estimated using the first three assessments (t_1, t_2, t_3). Random coefficient analysis was used assuming a normal distribution for evaluating the effects of intervention on % static activity, % dynamic activity, % standing, % sitting, % walking, W>5s, and W>10s (MLWinN version 2.02).[22] When the outcome variable failed to show a normal distribution on visual inspection, a logarithmic or square root transformation was applied. In this multilevel model effects of intervention were corrected for differences of the outcome variable at baseline, time effects and carry-over effects. In addition, possible interaction effects between intervention and time were investigated for significance.[22] Change at follow-up was assessed by comparing the change between t_3 and t_4 using a model with two factors (time and group) fitted

onto outcomes of t_1, t_2, t_3, t_4 for distribution, for early and late intervention groups together. Two-tailed analysis was performed on all tests with a significance level of 5%. Intervention effects are reported as β estimates.

Results

Out of 289 potential candidates, 153 patients participated in the present study. A trial flow chart is presented in Nieuwboer et al.[8] Participants were randomly allocated to the early intervention group (*n*=76) or late intervention group (*n*=77). Both groups showed comparable baseline characteristics (see Table 1) confirming the success of the randomization procedure.

As all patients received training, with only one drop-out occurring 3 weeks after randomization because of a necessary change of medication, an 'intention-to-treat' analysis was not necessary. Patients did not report any falls or other problems while wearing the activity monitors. In total 556 of all 612 AM data, representing collected

Table 1 Comparison between early and late intervention groups for demography, characteristics of Parkinson's disease, clinical data and data derived from activity monitoring at baseline

	Early intervention group (*n*=76) Median (Q1–Q3)	Late intervention group (*n*=77) Median (Q1–Q3)	*p* value
Demography			
Gender (M/F)[a]	48/28	40/37	0.16
Age (years)	67.5 (61.5–72)	69 (62.5–73)	0.70
PD Characteristics			
Disease duration (years)	7 (4–11)	8 (4–12)	0.59
H&Y (on)	2.5 (2.5–3)	3 (2.5–3)	0.56
Freezers/non-freezers[a]	31/45	32/45	0.92
Clinical data			
UPDRS total	54 (46–65.5)	56 (49–63)	0.62
UPDRS motor scale	31 (25–37)	34 (28–41)	0.32
Levodopa (mg)	500 (300–700)	350 (200–550)	0.07
Data derived from AM			
Registration time (hours)	4.9 (3.5–5.8)	4.56 (3.7–5.5)	0.17
% time spent on dynamic activity	9.4 (5.2–16.7)	10.6 (4.8–16.3)	0.74
% time spent on static activity	90.6 (81.8–94.8)	89.1 (83.7–95.2)	0.55
% time spent on sitting	50.3 (38.6–65.6)	49.2 (35.5–63.6)	0.49
% time spent on standing	25.0 (15.5–36.0)	25.8 (16.0–32.6)	0.69
% time spent on walking	7.3 (4.0–10.9)	7.9 (4.2–13.6)	0.55
N walking period > 5 sec per hour	13.7 (7.9–21.5)	13.5 (8.6–18.9)	0.65
N walking periods > 10 sec per hour	8.6 (4.4–13.0)	8.0 (5.2–12.0)	0.93

AM, activity monitoring; N, number; Q1–Q3, interquartile range; PD, Parkinson's disease; M/F, male and female; H&Y (on), Hoehn and Yahr during on; UPDRS, Unified Parkinson's Disease Rating Scale; Y/N, yes/no. [a]Expressed as number of patients and *p* values based on Mann-Whitney U tests.

data of actual intended four repeated measurements within 153 included patients, were available for random coefficient modeling.

All AM data showed a normal distribution upon visual inspection. Monitoring proved to be reliable over a three-week interval as can be seen in Table 2. Figure 1 shows the Bland and Altman plots for the different outcome measurements with the upper and lower dashed lines for 95% limits of agreement and the bold line representing the mean difference score between two assessments. The visual plots showed sufficient agreement between two consecutive measurements for the different outcomes of AM.

Table 3 shows the median and interquartile ranges of all outcomes at test 1–4. Average recording time was 4.6 hours (median 4.8 hours) and did not differ between testing days (p>0.9). The mean amount of therapy received in the early intervention group (271.8 minutes) was not significantly different from the late intervention group (270.4 minutes) (t=0.27; p=0.79). In addition, no significant differences were observed in the type of cueing modality (t=0.24; p=0.86) or the aims of the cueing intervention (t=0.29; p=0.91). Most patients (n=95, 67%) chose auditory cueing as their preferred cueing modality, while 57 patients (n=58, 33%) favoured somatosensory cueing.

Treatment effects

Table 4 shows the estimated intervention effects corrected for time and carry-over; correction for interaction effects was not necessary. The % dynamic activity improved by 4.2% (p< 0.01); an equal decrement in % static activity was shown. No significant effect was shown for % sitting and % standing. The % walking increased by 4.5% (p<0.001). W>5s was 2.6 times higher per hour (p<0.01) after cueing training and on average W>10s was 2.9 higher per hour (p<0.001) after the intervention phase.

Follow-up (t_3–t_4)

Table 4 also shows the change at follow-up. All intervention effects declined between 6 to 12 weeks. The % dynamic activity was reduced by 4.2% (p<0.001) and the % static activity by 4.7% (p<0.001). The % sitting increased by 4.2% (p=0.02); the % standing

Table 2 Intraclass correlation coefficients, two-mixed model with absolute agreement definition

Variable	ICC (95% CI)
Registration time	.68 (.53–.78)
Dynamic activity	.81 (.71–.87)
Static activity	.76 (.65–84)
Sitting	.59 (.42–.72)
Standing	.50 (.31–65)
Walking	.72 (.58–.81)
Walking periods exceeding 5 seconds	.68 (.53–.78)
Walking periods exceeding 10 seconds	.73 (.60–.82)

ICC, Intra Class Correlation coefficients; CI, Confidence Interval.

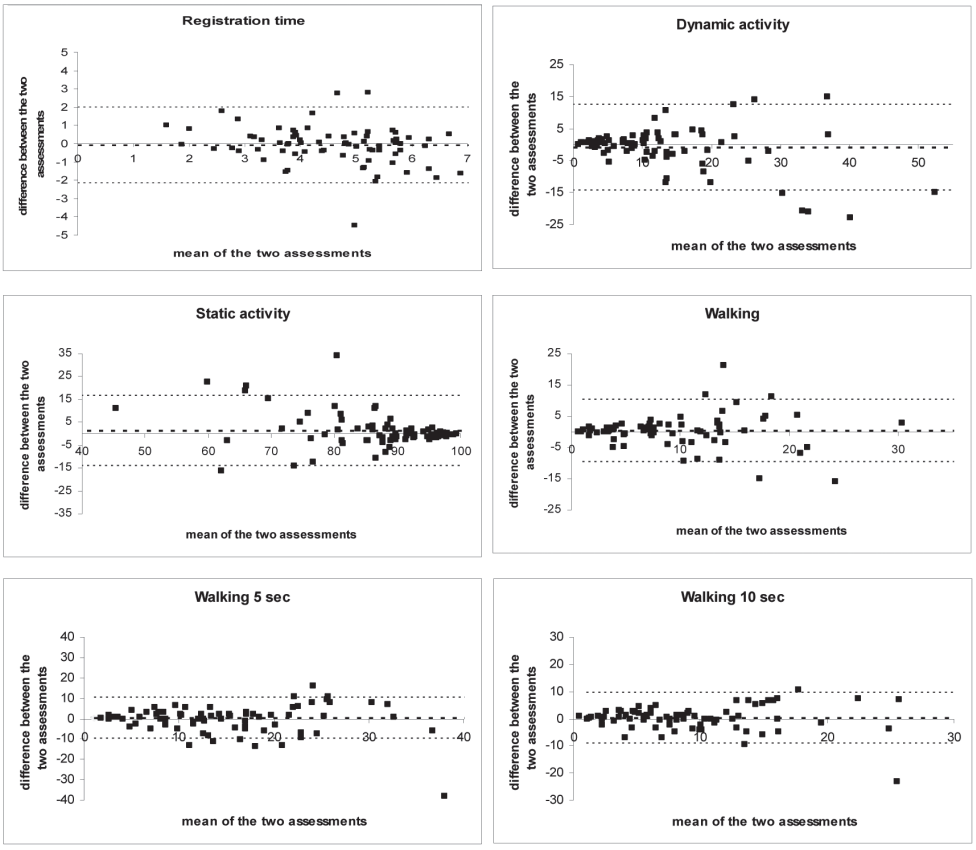

Figure 1 Agreement of eight outcome measurements following Bland Altman plots.

did not change significantly. The % walking decreased by 3.6% (p<0.001), while W>5s decreased by 3.3% (p<0.001) and W>10s by 2.7% (p<0.001).

Discussion

The present study was aimed at investigating the effects of cueing training on the amount of physical activity in patients with PD, when monitored in their own home environment. In line with a previous study,[10] AM proved to be a reliable method for monitoring gait performance with fair to good reliability (ICC=.50–.72) for registration time, static activities, sitting, standing, and excellent reliability (ICC=.76–.81) for dynamic activities, W>5s and W>10s. In addition, Bland Altman plots[20] showed good to excellent agreement between two consecutive AM measurements with respect to the different static and dynamic activities of AM.

The present study showed that cueing therapy has a significant positive effect on dynamic activity, especially on % walking. The amount of walking in the training group

Table 3 Medians and interquartile ranges of the outcomes in the early and late intervention groups at t_1–t_4

	t_1 Median (Q1–Q3)	t_2 Median (Q1–Q3)	t_3 Median (Q1–Q3)	t_4 Median (Q1–Q3)
Registration time (hours)				
Early	4.9 (3.5–5.8)	4.6 (3.6–5.6)	4.8 (3.6–5.5)	4.5 (3.4–5.7)
Late	4.6 (3.7–5.5)	4.7 (3.7–5.8)	4.8 (3.6–5.5)	4.9 (3.5–5.5)
% time spent on dynamic activity[a]				
Early	9.4 (5.2–16.7)	13.7 (7.3–22.7)	11.7 (6.4–21.3)	9.6 (5.5–15.4)
Late	10.6 (4.8–16.3)	9.6 (5.8–18.9)	15.1 (7.4–22.8)	11.3 (6.6–20.5)
% time spent on static activity[a]				
Early	90.6 (81.8–94.8)	86.3 (76.9–92.7)	88.3 (77.9–93.6)	90.3 (83.5–94.5)
Late	89.1 (83.7–95.2)	89.8 (80.6–94.2)	84.0 (73.9–92.4)	88.7 (79.4–93.4)
% time spent on sitting[a]				
Early	50.3 (38.6–65.6)	40.8 (32.2–59.3)	46.8 (33.7–60.7)	49.6 (34.2–59.5)
Late	49.2(35.5–63.6)	48.7 (34.5–59.4)	45.9 (35.5–57.4)	48.8 (34.2–65.3)
% time spent on standing[a]				
Early	25.0 (15.5–36.0)	25.8 (19.1–37.8)	24.3 (17.6–35.7)	25.3 (16.0–38.7)
Late	25.8 (16.0–32.6)	28.7 (17.4–39.2)	23.5 (16.2–32.1)	25.6 (19.0–38.0)
% time spent on walking[a]				
Early	7.3 (4.0–10.9)	10.4 (6.0–18.7)	8.5 (4.8–13.0)	6.6 (4.1–11.7)
Late	7.9 (4.2–13.6)	7.6 (3.4–12.9)	11.8 (5.9–18.5)	7.9 (4.5–15.0)
N walking periods > 5 s per h				
Early	13.7 (7.9–21.5)	15.1 (11.1–24.2)	15.3 (9.4–23.7)	14.1 (10.0–20.3)
Late	13.5 (8.6–18.9)	14.9 (8.3–20.3)	15.7 (9.6–26.1)	14.8 (10.1–22.6)
N walking periods > 10 s per h				
Early	8.6 (4.3–13.0)	9.6 (5.9–14.5)	8.8 (5.5–14.7)	7.8 (5.4–12.0)
Late	8.0 (5.2–12.0)	8. 5 (4.2–12.2)	9.8 (6.2–17.1)	8.1 (5.6–14.9)

Q1–Q3, interquartile range; N, number; s, seconds; h, hour. [a]of total registration time.

Table 4 Intervention effects (t_1–t_2) and change at follow-up (difference t_3–t_4)

	Intervention β estimate (SE)	Change in minutes	Follow-up β estimate (SE)
% time spent on dynamic activity[a]	4.23[b]	11.9	−4.17[b]
% time spent on static activity[a]	−3.34[b]	9.4	4.69[b]
% time spent on sitting[a]	−3.48	9.8	4.20[c]
% time spent on standing[a]	−1.41	4.0	−0.98
% time spent on walking[a]	4.46[b]	12.6	−3.57[b]
N walking periods > 5 s per hour	2.63[c]	2.6 numbers	−3.32[b]
N walking periods > 10 s per hour	2.90[b]	2.9 numbers	−2.68[b]

SE, standard error; s, seconds; N, number. [a]of total registration time. [b]$p<0.01$. [c]$p<0.05$.

improved by 4.5% when compared to patients allocated to the control group. When extrapolating the increased walking performance to a whole day of 12 waking hours, the present finding suggests an increased amount of walking activity of 32 minutes per day. This amount meets the criteria of 30 minutes of recommended physical activity per day by the Center of Disease Control and Prevention/American College of Sports Medicine.[23]

The present findings are in line with the results from clinical assessments in the Rescue trial.[8] Briefly, clinical assessments showed a 4.2% increase on the posture and gait score, a 5.0 cm/s increase in walking speed, a 4.0 cm increase in step length, and a 5.5 % reduction in severity of freezing symptoms according to the Freezing of Gait Questionnaire when analyzed in freezers only.[8] The agreement in effects between AM and clinical gait assessments suggests that improvements in clinically used outcomes such as posture and gait score, step length and gait speed reflect a general enhancement in patients' actual walking performance. A major advantage of AM is that patients do not have to undergo a fatiguing test battery and more detailed information about the actual activity profile is achieved.[24]

The improvement in dynamic activity was diminished at follow-up, assessed at 9 weeks after the end of cueing training for the early intervention group and 6 weeks for the late intervention group. This suggests that the effect of cueing training wears off and that continuous training with use of a permanent cueing device may be indicated for people with PD. The optimal dose-response relationship needs to be investigated in future studies. The impact of placebo effects as a result of increased attention during therapy was not controlled for, which is a limitation of this study.

AM may cause so-called 'reactivity effects': subjects may, consciously or subconsciously, limit their movements due to the presence of the recorder, its weight and the wiring, or because they are afraid to break or damage the monitoring equipment. On the other hand, subjects may be more active in order to 'make the measurement better' and meet the expectations of the research goal. Therefore it is important to prevent AM-induced behavioural adaptations by keeping the participants naïve about the purpose of the AM device, and giving appropriate instructions about maintaining usual daily routines.

A limitation of the AM device used in the present study is that the accelerometers do not produce valid information about spatial parameters of gait such as step length, walking distance and with that speed. In particular, it is difficult to quantify parameters such as step length in patients with PD where the variability in step-to-step length is large.[25,26] Lack of insight into patients' on-off status is another limitation in this study. It is, for example, not known whether patients walked more during their off periods after receiving cueing training. This may be addressed by asking patients to record their on-off status in a diary whilst undertaking AM to provide complementary data. Future studies should focus on gait parameters including walking speed, step length and interlimb coordination of parkinsonian gait during 'on' and 'off' periods. In addition, efforts should be made to develop smaller and cheaper AM devices that are wireless-enabled and better able to monitor continuously for more than 48 hours.

The application of AM in patients with neurological disorders such as PD to evaluate

the effects of a rehabilitation programme is new in the field of neurology. However, it should be noted that AM can also be used for evaluating other interventions such as medication[27] and deep brain stimulation on motor performance. Moreover, AM proved to be a harmless, non-invasive way of collecting 'real world' information about postures and activity undertaken in patients' own environment for extended periods of time.

Data from the current study further support the positive effects of cueing in PD as found in earlier studies,[8,18] however, the neurological mechanisms underpinning these effects are still unclear. Studies suggest that cueing may stimulate alternative cortical pathways (e.g. visual motor pathways)[28] to bypass the basal ganglia, whereas other studies suggest that cueing synchronizes the simultaneous timing of interlimb coordination in the cerebellum needed for normal gait.[29,30] Further studies are needed to investigate the neurophysiological mechanisms underpinning the effectiveness of rhythmic cueing in patients with PD.

Acknowledgements

This research project was supported by a grant from the European Commission (QLK6-CT-2001-00120; Rehabilitation in Parkinson's Disease: Strategies for Cueing).

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7

Identifying fallers with Parkinson's disease using home-based tests: Who is at risk?

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Movement Disorders
2008; 23: 2411-2415

Abstract

Objectives: To determine risk factors for falling in patients with Parkinson's disease (PD) using home-based assessments and to develop a prediction model.

Methods: Data on falls, balance, gait-related activities and non-motor symptoms were obtained from 153 PD patients (Hoehn-Yahr 2–4) in their home. Fifty-one candidate determinants for falling were independently tested using bivariate logistic regression analysis. A multivariate logistic regression model was developed to identify patients susceptible to falls.

Results: Sixty-six subjects (43%) were classified as fallers. Eighteen determinants for falling were selected. The final multivariate model showed an accuracy of 74% and included: (1) Freezing of Gait Questionnaire, (2) Timed Get Up and Go (TGUG) score, (3) disease duration, and (4) item 15 of the Unified Parkinson's Disease Rating Scale.

Conclusion: Based on disease duration, freezing symptoms, walking problems and a prolonged TGUG duration, assessed in the home situation, it was possible to accurately identify 74% of PD patients as fallers.

Introduction

According to the USA Centre of Disease Control and Prevention (CDC),[1] more than one third of community-dwelling older adults experienced one or more falls every year, and approximately 460.000 of these patients were hospitalized. The incidence of falls in patients with Parkinson's disease (PD) is disproportionably high, with several prospective cohort studies reporting an incidence between 50 and 70%.[2-4]

In addition to the fact that falls in PD can lead to injury and even death,[5] most patients may suffer from lack of activity and psychosocial consequences such as fear of falling, and indirectly from social isolation and depression.[6] Falls also have economic implications for health services; a recent study showed that the direct medical costs of fallers with PD are on average about twice as much as for non-fallers with PD.[7]

In contrast with the burden of falling in PD, risk factors related to falls are largely unknown and the underlying mechanisms responsible for falling are not well understood. Although many studies have been aimed at identifying factors related to falls, only a few studies investigated the underlying prognostic factors for falling. To date prediction models have identified age,[8] gender,[9] disease duration,[3,9] disease severity,[2,10] dementia,[3] autonomic dysfunction,[8] incontinence for urine,[9] symmetrical onset of the disease,[3] variability of stride time,[10] loss of arm swing,[3] a slow score on the Timed Get and Go test (TGUG),[9] a high score on the Romberg test,[4] prior falls,[2-4] impaired ambulation,[11] impaired lower limb motor planning[11] and orthostatis as prognostic factors.[2,3]

Factors found to be related with the incidence of falling should be easy to assess, preferably in the patient's own home,[12-14] by health care professionals who can play an important role in fall prevention for PD patients.

The first aim of the present study was to establish factors related with the risk of falling in PD patients from measurement instruments that can be used in patients' homes. Subsequently, a multivariate logistic regression model was derived to identify those patients who are fallers.

Subjects and methods

Design

The data presented in the current study were obtained from baseline measurements of a multi-centre, single-blinded randomized clinical trial (RCT) with crossover design.[13] In this RCT, known as "Rescue", PD patients received cueing training in their home situation. All assessments to evaluate the predictive validity of this study were performed in the patient's own home (for complete description of variables see reference 13). During testing patients were in the 'on-phase', when medication is optimal.

Study population

Data from 153 patients with idiopathic PD were used. Patients were recruited in three international centres and the study was approved by the medical ethics committee of each participating centre. All patients gave informed written consent to the study. Eligibility criteria included age 18–80 years, mild to moderate PD symptoms, Hoehn and Yahr (H-Y)[15] stage II–IV, mild to severe gait disturbances, sufficient cognitive functioning, and absence of co-morbidity that may influence mobility. A complete description of the eligibility criteria can be found in Nieuwboer et al.[13]

Table 1 Scores on candidate determinants and bivariate analysis on subject characteristics (*n*=153)

Candidate determinant	Median (Q1–Q3)	Bivariate analysis			
		B (β coefficient)	SE	Odds ratio (95% CI)	*p* value
Age (years)	67 (7.5)[a]	.42	.36	1.52 (.75–3.08)	.25
Gender (male/female)		–.11	.33	.90 (.47–1.72)	.75
Weight (kg)	70.9 (13.2)[a]	.14	.33	1.16 (.61–2.19)	.44
Height (m)	1.7 (0.1)[a]	.25	.33	1.29 (.68–2.44)	.44
Leg length difference (cm)	0.4 (0.9)[a]	.14	.37	1.15 (.56–2.35)	.70
Disease duration (years)	8.3 (5.1)[a]	.732	.33	2.08(1.08–3.99)	.03
Hoehn and Yahr stage	3 (2.5–3)	1.22	.49	3.39 (1.29–8.92)	.01
Dominant side of the disease (L/R)		.32	.33	1.37 (.72–2.6)	.34
Use of levodopa (yes/no)		–.05	.51	.95(.35–2.57)	.34
Use of other medication		–.38	.36	.68 (.34–1.39)	.29
No medication use		.44	1.24	1.55 (.14–17.44)	.72

N, number of patients; Q, interquartile range; SE, standard error of estimate; CI, confidence interval; kg, kilograms; m, meter; cm, centimetre; L, left; R, right. [a]mean (standard deviation).

Table 2 Scores on candidate determinants and bivariate analysis on bodily functions (*n*=153)

Candidate determinant	Median (Q1–Q3)	Bivariate analysis			
		B (β coefficient)	SE	Odds ratio (95% CI)	*p* value
Mini Mental State Examination	29 (27–30)	–.84	1.17	.43 (.04–4.24)	.47
Hospital Anxiety and Depression Scale–depression	7 (5–9.5)	–.06	.38	.95 (.45–1.99)	.88
UPDRS 3 depression	1 (0–1)	.32	.33	1.37 (.72–2.62)	.34
MFI					
general	14 (11–17)	–.038	.33	.96 (.508–1.827)	.91
physical fatigue	14 (11–18)	.12	.33	1.12 (.59–2.13)	.73
reduced activity	14 (10–17)	–.19	.33	.82 (.43–1.57)	.56
reduced motivation	11 (8–14)	.00	.33	1.01 (.53–1.91)	.99
mental fatigue	11 (6–14)	.60	.34	1.83 (.10–3.53)	.07
Falls Efficacy Scale	82 (61–104.5)	–1.04	.34	.36(.18–.69)	.00
Brixton test (scaled score)	4 (2–6)	.44	.38	1.55 (.80–3.01)	.19
Modified Dyskinesia Scale	0 (0–0)	.43	.41	1.53 (.68–3.45)	.30
UPDRS					
42 hypotension	0 (0–0)	–.37	.54	.69 (.24–1.98)	.49
32 dyskinesia duration	0 (0–1)	.38	.34	1.46 (.75–2.84)	.27
33 dyskinesia severity	0 (0–0)	.35	.40	1.42 (.65–3.10)	.38
34 dyskinesia pain	0 (0–0)	.82	.60	2.26 (.70–7.27)	.17
35 dyskinesia dystonia	0 (0–0)	.40	.34	1.49 (.77–2.87)	.24
14 freezing	1 (0–2)	1.20	.37	3.31 (1.60–6.84)	.00
22 rigidity	6 (4–8)	.35	.33	1.41 (.74–2.71)	.30
31 bradykinesia	3 (2–4)	.56	.33	1.76(.91–3.38)	.09
29 gait	2 (1–2)	1.02	.35	2.78 (1.41–5.51)	.00
FOGQ, items 3, 4, 5, 6	5 (0–8.5)	1.42	.35	4.16 (2.10–8.23)	.00
6 meter walk test					
speed (m/s)	0.8 (0.3–1.3) [a]	.44	.34	1.55 (.80–3.0)	.20
cadence (steps/min)	100.3 (11.8) [a]	.72	.34	2.05(1.06–3.95)	.03
step length (m)	0.5 (0.1) [a]	.16	.33	1.18 (.61–2.25)	.62

N, number of patients; Q, interquartile range; SE, standard error of estimate; CI, confidence interval; UPDRS, Unified Parkinson's Disease Rating Scale; MFI, Multi Dimensional Fatigue Inventory; FOGQ, Freezing of Gait Questionnaire; m, meter; min, minute. [a]mean (standard deviation).

Dependent variable

A fall was defined as 'an event that results in a person coming to rest unintentionally on the ground or lower level, not as a result of a major intrinsic event or overwhelming hazard.[16] Subjects were classified as fallers or non-fallers, based on item 13 of the Unified Parkinson's Disease Rating Scale (UPDRS).[17] Fallers were defined as patients scoring one point (rare falls) or higher. Non-fallers were defined as patients who scored a zero on this item.

Independent variables

Existing literature was reviewed for known determinants which are associated with falls in PD. Based on the literature and expert opinion 51 candidate determinants were identified (see Tables 1–4).

Data analysis

The 51 selected variables for prediction were dichotomized on the basis of clinically meaningful cut offs. If this information was absent or data showed a skewed distribution, either a split-median approach or an optimal cut off in sensitivity and specificity analysis in a Receiver Operating Characteristic (ROC) curve was adopted. The association between these variables and falls among PD patients was investigated performing a bivariate logistic regression analysis for each candidate determinant separately. Only candidate determinants with a liberal significance level of $p<0.2$ were selected for multivariate regression analysis. To avoid collinearity between included determinants, candidate determinants were removed if Spearman rank order correlation coefficients were above 0.7. In the multivariate analysis, stepwise backward and forward approaches (both conditional) were applied to verify robustness of the model. Each hypothesis was tested two-tailed ($p<0.05$).

Results

Table 5 presents the main patient characteristics. Sixty-six patients (43%) were classified as fallers and 87 (57%) as non-fallers. No severe injuries due to falls were reported.

Bivariate associations between falls and independent variables

Table 6 shows the test results, odds ratios (OR) and their 95% confidence interval (95% CI) for the 18 determinants who were related to falls with a liberal significance level of $p<0.2$, as determined with bivariate logistic regression. Thirteen of these determinants were statistically significant related to falls ($p<0.05$) Significant collinearity ($r>.7$) was found for the sum score of items 3, 4, 5 and 6 of the Freezing of Gait Questionnaire (FOGQ)[18] and UPDRS item 14, of which the latter was consequently removed.

Multivariate modelling

A model for the probability of falling was derived, containing four determinants (Table 6).

Accuracy of the model with FOGQ alone was 65.3%, adding the TGUG increased the

Table 3 Scores on candidate determinants and bivariate analysis at activity level (*n*=153)

Candidate determinant	Median (Q1–Q3)	Bivariate analysis			
		B (β coefficients)	SE	Odds ratio (95% CI)	*p* value
UPDRS 15 walking	2 (1–2)	1.49	.39	4.46 (2.06–9.64)	.00
UPDRS 30 pull test	1 (1–2)	.46	.46	1.32 (.54–3.22)	.55
Timed Single Leg Stance					
left (s)	12.2 (29.7)[a,b]	.42	.42	1.21 (.53–2.75)	.66
right (s)	12.9 (10.6)[a,b]	–.49	.43	.61 (.26–1.42)	.25
Timed Tandem Stance					
left (s)	19.3 (10.9)[a,b]	–.39	.34	.68 (.35–1.31)	.25
right (s)	20.3 (10.6)[a,b]	–.15	.34	.86 (.45–1.67)	.66
Functional reach (cm)	25.5 (7.9)[a]	–.65	.34	.52 (.27–1.01)	.05
UPDRS 28 posture	1 (1–2)	.76	.55	2.14 (.72–6.33)	.17
Timed Get Up and Go test (s)	13.5 (11.5– 7.8)[a]	1.10	.35	2.99(1.51–5.93)	.00
NEAI					
mobility	19 (15–21)	.96	.34	2.61(1.35–5.04)	.02
kitchen	17 (14–20)	.33	.33	1.39 (.73–2.65)	.32
domestic	14 (9–16)	.78	.33	2.10(1.14–4.19)	.02
leisure	16 (13–20)	–1.21	.34	.30(.15–.59)	.00

N, number of patients; SE, standard error of estimate; Q, interquartile range; CI, confidence interval; UPDRS, Unified Parkinson's Disease Rating Scale; s, seconds; cm, centimetre; NEAI, Nottingham Extended ADL Index. [a] mean (standard deviation). [b] maximum duration 30 seconds.

Table 4 Scores on candidate determinants and bivariate analysis at participation level (*n*=153)

Candidate determinant	Median (Q1–Q3)	Bivariate analysis			
		B (β coefficient)	SE	Odds ratio (95% CI)	*p* value
PDQ, mobility	50 (32.5–67.5)	–.15	.65	.86 (.46–1.64)	.33
PDQ, Activities of Daily Life	50 (33.3–68.8)	1.21	.35	3.34(1.69–6.61)	.00
PDQ, emotions	33.3 (16.7–50)	.31	.34	1.37 (.72–2.60)	.33

N, number of patients; Q, interquartile range; SE, standard error of estimate; CI, confidence interval; PDQ, Parkinson's Disease Questionnaire.

Table 5 Patient characteristics and scores (*n*=153)

	Number	Mean (SD)	Range	Median (Q1–Q3)
Age (years)		67 (7.5)	41–82	68 (62–72.5)
Disease Duration (years)		8.3 (5.1)	1–25	8 (4–12)
Gender (male/female)	88/65			
Weight (kg)		70.9 (13.2)	44–115	70 (62–76.7)
Height (m)		1.7 (0.1)	1.5–2.0	1.7 (1.6–1.8)
Leg length difference (cm)		0.4 (0.9)	0–1.0	0 (0–1)
Dominant side of the disease (L/R)	72/81			
Medication (number of patients)				
users of levodopa	134			
users of other anti-Parkinsonia medication (e.g. agonists, selegiline)	16			
no medication users	3			
Presence of hypotension, UPDRS item 42 (yes/no)	17/136			
Hoehn and Yahr stage		2.8 (0.6)	1–3	2.5
Falls (fallers/non-fallers)				
UPDRS item 13	66/87			

N, number of patients; SD, standard deviation; Q, interquartile range; kg, kilogram; m, meter; cm, centimeter; L, left; R, right; UPDRS, Unified Parkinson's Disease Rating Scale.

accuracy to 70.7%, adding item 15 of the UPDRS (i.e., walking) improved accuracy to 71.4%, and completing the model with disease duration correctly classified 74% of the patients as fallers or non-fallers.

Using a forward approach, the model showed 71% sensitivity for identifying fallers and a 76% specificity for identifying non-fallers, a positive predictive value (PPV) of 70% and a negative predictive value (NPV) of 77%. Using a backward approach, 72% sensitivity and 77% specificity and a PPV of 70% and a NPV of 79% were found.

Discussion

The present study shows that 43% of the 153 PD patients could be identified as fallers according to the UPDRS item 13. This finding confirms that falling is a common event in PD patients and is comparable to previous results.[2,4,9,10] Our multivariate regression model suggests that patients who are fallers are more likely to suffer from freezing (FOGQ sum score of items 3, 4, 5 and 6), have longer disease duration, experience problems with walking (UPDRS item 15) and need more time for standing up, walking, turning and sitting down (TGUG). The accuracy of this prediction model was 74%, also suggesting that in 26% of the cases the model was inaccurate. 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 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.

Table 6 Scores, bivariate analysis, forward and backward multivariate analysis (*n*=53)

Determinant	Median (Q1–Q3)	Bivariate analysis				Multivariate analysis	
						Forward	Backward
		B (β coefficient)	SE	Odds ratio (95% CI)	*p* value	odds ratio (95% CI)	odds ratio (95% CI)
Disease duration (years)	8.3 (5.1)[a]	.73	.33	2.08 (1.08–3.99)	.03	2.16 (1.01–4.62)	2.24 (1.05–4.78)
Hoehn and Yahr stage	3 (2.5–3)	1.22	.49	3.39 (1.29–8.92)	.01		
MFI mental fatigue	11 (6–14)	.60	.34	1.83 (.10–3.53)	.07		
Falls Efficacy Scale	82 (61–104.5)	–1.04	.34	.36 (.18–.69)	.00		
Brixton test (scaled score)	4 (2–6)	.44	.38	1.55 (.80–3.01)	.19		
UPDRS							
14 freezing	1 (0–2)	1.20	.37	3.31 (1.60–6.84)	.00		
15 walking	2 (1–2)	1.49	.39	4.46 (2.06–9.64)	.00	2.97 (1.26–7.00)	2.97 (1.26–7.00)
29 gait	2 (1–2)	1.02	.35	2.78 (1.41–5.51)	.00		
30 posture	1 (1–2)	.27	.46	1.32 (.54–3.32)	.55		
31 bradykinesia	3 (2–4)	.56	.33	1.76 (.91–3.38)	.09		
34 pain	0 (0–0)	.82	.60	2.26 (.70–7.27)	.17		
FOGQ, items 3, 4, 5, 6	5 (0–8.5)	1.42	.35	4.16 (2.10–8.23)	.00	3.56 (1.65–7.68)	3.30 (1.49–7.33)
6 meter walk test, cadence (steps/min)	100.3 (11.8)[a]	.72	.34	2.05 (1.06–3.95)	.03		
Functional reach (cm)	25.5 (7.9)[a]	–.65	.34	.52 (.27–1.01)	.05		
Timed Get Up and Go test (s)	15.6 (7.04)[a]	1.10	.35	3.00(1.51–5.93)	.00	3.29 (1.48–7.30)	3.30 (1.49–7.33)
Nottingham Extended ADL Index							
Mobility	19 (15–21)	.96	.34	2.61 (1.35–5.04)	.02		
Domestic	14 (9–16)	.78	.33	2.10 (1.14–4.19)	.02		
Leisure	16 (13–20)	–1.21	.34	.30 (.15–59)	.00		

N, number of patients; Q, interquartile range; SE, standard error of estimate; CI, confidence interval; MFI, multidimensional fatigue inventory; UPDRS, Unified Parkinson's Disease Rating Scale; FOGQ, Freezing of Gait Questionnaire; cm, centimetres; s, seconds; min, minute. [a]mean (standard deviation).

In earlier studies, disease duration[3,9] and the TGUG,[9] but not freezing and gait problems according to the UPDRS, have been identified as independent factors predicting falls. Disease duration,[2,10] freezing[10] and UPDRS item 15 (walking)[10] were investigated for their predictive validity for falling in the literature. They failed, however, to be included in existing prediction models due to their high association with other related factors and differences in the patient population.

Clinical symptoms related to falling, for example freezing, tend to show variations with respect to medication intake as well as day to day fluctuations. Traditional prediction models do not account for the impact of these time-dependent fluctuations on the changing relationship between determinants and outcome (i.e. falls). Future prognostic studies should therefore investigate the longitudinal relationship between candidate determinants and observed outcomes by monitoring patients on a continuous basis in the home environment, using, for example, ambulatory accelerometry.[19,20]

A limitation is the retrospective design of this study. It has been suggested that more fallers can be classified correctly by using a prospective design.[2,6] Moreover, previous falls seem to be a key predictor for falls.[2,4] Due to the retrospective design previous falls could not be assessed validly in this study.

In the present study, patients with mild to moderate PD symptoms participated. To obtain a better view on falls, more mildly affected patients and severely affected patients should also be studied. In addition, future studies should also include patients with symptoms such as dementia, knowing that cognitive disorders seem to be an independent factor that contributes to a high incidence of falling.[3,21]

In conclusion, the present study provides clinically important insight into factors related to falls in mild to moderately affected PD patients obtained using home-based tests. These patients typically show a reduced walking ability and are referred for physical therapy to improve gait and prevent falls.

Acknowledgements

This study was supported by the European Committee (The RESCUE project, grant number QRLT-2001-00120.) We would like to thank all participants for their contribution and Robert Giedrojc, Ingrid Beelen and Anouk Holthuis for their assistance in data collection.

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8

General discussion

Introduction

The major aim of this thesis was to determine the effectiveness of external rhythmic cues to improve gait and gait-related activities, and with that, increasing the amount of physical activity in patients with Parkinson's disease (PD). This was also the major aim of the Rescue project, a collaborative project of the VU University Medical Center in Amsterdam, the Katholieke Universiteit Leuven (Belgium) and the Northumbria University in NewCastle (UK). Other objectives of the Rescue project were to: (1) generate new knowledge on external rhythmic cues, as well as behavioral and environmental factors affecting their use; (2) develop an optimized set of cueing strategies, including a prototype cueing device, and test this in a randomized controlled trial (RCT); and (3) communicate the results of the RCT widely to patient organizations and health care professionals.

The Rescue project fits within the aims of the Fifth Framework of the European Commission (EC), to keep patients longer in their own home situation, independently and safe, with preservation of their quality of life,[1] acknowledging that approximately 800.000 people in Europe suffer from PD in 2008,[2,3] and that about 60% of these patients have walking problems. The present thesis further supports the hypothesis that rhythmic cueing is a simple, effective and safe adjunct therapy to normalize gait.

The Rescue project consisted of three phases:

Preparation phase: Prior to the Rescue project, there was limited knowledge about the optimal use of rhythmic cues in PD, as shown in the systematic review on cueing studies presented in Chapter 2 of this thesis.[4] In the preparation phase experiments in the laboratories at Amsterdam and Leuven were involved to investigate the effects and stability of visual, auditory and somatosensory cues.[5-7] These experiments made use of a cueing device, which was developed within the preparation phase and provided three cueing modalities: (1) a visual cue (with a flashing light attached to the patient's spectacles); (2) an auditory cue (beep); and (3) a somatosensory cue (a vibrating mini-cylinder, which could be worn under a wrist band). The study on visual cueing, which is presented in Chapter 4 of this thesis, found positive effects of visual cueing on step length and step frequency.[6] Cognitive and behavioral profiles facilitating cueing and contextual factors impeding effective cueing were studied in Newcastle.[8,9]

The results of these experiments were used to develop practical guidelines for optimal use of the cueing device (available on CD-ROM, http://www.rescueproject.org). Three physical therapists, one in each participating centre, were trained in the use of these cueing guidelines and providing standardized cueing training to the patients who were included in the RCT. Furthermore, three assessors, one in each centre, were trained in applying the activity monitor and executing the generic test battery to ensure reliability of assessments across all centers involved. The clinical assessments with the test battery were all tested for inter- and intra-rater reliability, feasibility and responsiveness when applied in the home situation.[10] The results which are presented in Chapter 3 of the present thesis, showed moderate to high intra-class correlation coefficients for inter- and intra-rater reliability.[10]

Generalisation phase: The effects of guideline-based cueing training were investigated in a crossover randomized controlled clinical trial across all centers involved. Patients were randomly allocated to an early intervention phase or in a late intervention phase, using sealed opaque envelopes. The intervention for patients in the early intervention phase ended after 3 weeks, while patients allocated to the late intervention phase received their training in the second 3-week period. After this period, there was a 6-week sustainability period. During the intervention phase, patients received cueing training in their own home environment. The cueing intervention consisted of 30-minute sessions of cueing training, three times a week, for 3 weeks. The training was provided by one trained physical therapist in each country (i.e. stratum of the RCT). Assessments were executed at the start of the trial, after the first 3 weeks, after the second 3 weeks and after the sustainability phase. Results obtained with the clinical test battery are presented in Chapter 5 of this thesis,[11] and show positive effects of cueing on gait and gait-related activities. Results obtained with activity monitoring (AM) are presented in Chapter 6 of this thesis,[12] and show an increase in walking activity after cueing training.

Dissemination phase: In the final phase of the Rescue project, results of the Rescue study were communicated at conferences, including a special 'Rescue conference'. In addition materials presenting cueing strategies for PD patients, caregivers and professionals have been developed and physical therapists and movement therapists are being trained by members of the Rescue team.

This final chapter of the thesis discusses the specific and non-specific effects of cueing followed by a critical appraisal of some methodological issues, the cueing training offered and the international collaboration in the Rescue project. This thesis ends with some recommendations for future research.

Effects of cueing in PD

Impact of specific effects of cueing in PD

The RESCUE trial[11] is the largest trial on gait training in PD to date.[13] It involved 153 patients, who followed a 3-week cueing programme in their own home environment. After the intervention period, significant effects were found on the Posture and Gait score (PG), a composite score of gait and balance items from the Unified Parkinson's Disease Rating Scale[14,15] (4.2%), as well as on gait speed (5 cm/s) and step length (4 cm). These findings suggest that instantaneous effects of cueing reported in the systematic review[4] and the laboratory studies of the preparation phase of the Rescue project[5-7] can be transferred to the home setting of PD patients. Since effects washed out when patients did no longer receive cueing training at home any more, cueing training should ideally be continued in order to sustain its effects. Future studies should focus on investigating the dose-response relationship of cueing in order to determine the optimal dosage of cueing training. It is important to note that patients were assessed without using a cueing device or rhythms, suggesting that cueing-induced improvements are not entirely instantaneous.[11] This finding may support suggestions from recent studies on intensive training in animal models of PD that cueing training could involve anatomical and metabolic plasticity.[13] These studies[16-20]

suggested that higher training intensities (without cueing) may be neuroprotective by reducing striatal dopaminergic loss and promoting improved behavioral outcomes.[13] This neuroprotective mechanism and the dose-response relationship for cueing training in PD need to be studied further. If cueing training has neuroprotective effects, it can offer a breakthrough method in the treatment of PD. The study by Fisher[21] showed small changes in brain excitability following transcranial magnetic stimulation (TMS) after an intensive exercise programme in early PD, underpinning the hypothesis of learning-dependent plasticity.

Future studies should focus on mechanisms of cueing in the brain, involving the various kinds of cues and dose-response relations. Participants of the Rescue trial varied in the experiences they reported when using cues. Some patients reported that the rhythm made them focus on when or where (in the case of lines on the floor) to put their foot on the ground, whereas others had the feeling that they were being 'pushed' to walk, when using a rhythmic cue. These two different kinds of experiences among the PD patients may suggest that different brain systems are involved. Using cues consciously, thus forcing patients to pay attention to the cyclic rhythm of gait, suggests that there is an emphasis on cortical pathways, avoiding the automatic motor control of the basal ganglia. The feeling of being pushed into the right rhythm by enforcing time constraints in cyclic motor control such as gait, may support the theory of avoiding the basal ganglia by rerouting motor control via the sensorimotor cortex and anchoring the optimal timing of cyclic movements by the cerebellum. This suggestion was supported by Rochester and colleagues,[22] who concluded in a recent publication that external rhythmic cues can reduce attentional load as it informs the motor system about the temporal sequencing of a task thus avoiding the need to internally plan and prepare.

Currently, Van Wegen and colleagues are investigating the involvement of different parts of the brains during cueing in a study called 'Unravelling the effect of rhythmic external cueing on mobility: synchronization and use of alternative brain circuitry in the parkinsonian brain' at the VU University Medical Center in Amsterdam.[23]

Although the reported effects of cueing training on gait and gait-related activities reported in the Rescue trial are relatively small, they are comparable to calculated overall effect sizes or standardized mean differences reflecting the impact of exercise therapy in rehabilitation medicine.[24] The small but significant improvement in parkinsonian gait is an important finding that reflects an improvement in gait performance. For example, improvement in gait speed is accompanied by improvement in kinematic parameters[6] and is a genuine reflection of ambulatory performance.[25]

Chapter 6 of this thesis[12] also shows that these small improvements in gait and gait-related activities translate into increased daily activity as measured by activity monitoring (AM). This latter finding suggests that improvements in gait measured by using standard assessments, such as gait speed and PG, reflect increased ambulatory 'real world' activity performed in the patients' own home setting.[12] Interestingly, not only gait performance but also standing balance improved significantly in our patient sample as was shown by the tandem and one leg standing tests. The probability of failing to pass the one leg standing tests was decreased by 36% in those who had received the cueing training.[11] This finding may be related to the aim of the therapy

in which patients were trained to prolong their single leg support, by increasing their step length and normalizing their step frequency. In other words, this prolonged single leg support phase may have positively influenced standing balance.

Although the effects we found did not result in a significantly reduced number of falls or near falls, they did not result in an increase in fall incidences either. However, the time interval between two consecutive assessments may have been too short to identify significant differences in fall frequencies.

The results of the 6 meter walking test allow the conclusion that step length did increase with increased walking speed. However, the Rescue trial provided no information about, e.g., inter-limb coordination, pelvic thoracic rotations, postural inflexibility or arm swing, neither from the 6 meter walking test, nor from AM. These parameters are disturbed in most patients[26-29] and are closely related to falls.[30-32] Using additional accelerometers for the upper limbs and gyroscopes with AM in future studies may yield more detailed information on arm and trunk movements.

Non-specific effects of cueing in PD

The improvements in walking speed and amount of walking activity indicate a significant improvement in mobility. The literature suggest that these improvements generalize to other parameters in PD. Unpublished results of the Rescue study show a significant decrease in fatigue for the domains of 'activity' and 'general fatigue', assessed with the Multi Dimensional Fatigue Inventory (MFI-20). This is in line with other studies, where an increase in activity leads to a conception of reduced fatigue.[33] Confidence not to fall during gait-related tasks (assessed with the Falls Efficacy Scale) improved as well.

A significant improvement was also found for depression, assessed with the 'depression' subscale of the Hospital Anxiety and Depression Scale.[34] The attention component as well as the training sessions may have led to a reduction in depressive feelings, as supported by studies on physical exercises and depressive feelings.[35]

No significant improvements were found in terms of other non-specific measurements An explanation could be that the training period was too short to allow the amount of ADL and caregiver load to be adjusted to the newly acquired strategies.

Learning from the Rescue study and how to proceed

Methods

Design

The research reported on in the present thesis, used a crossover design. A requirement for the use of a crossover design is that the effects of an intervention are instantaneous preferably showing a return to baseline state at the point of crossover after the end of the intervention. Preliminary experiments with cueing did show that the effects of rhythmic cueing are instantaneous and disappear after ending rhythmic cueing. The study of Morris[36] supports the wash-out of effects after the removal of a cue as reviewed in Chapter 2 of this thesis.[4] Using a crossover design gives all patients the opportunity

to profit from the intervention, avoiding ethical issues about receiving or not receiving therapy. A crossover design also offers a more efficient comparison of treatment modalities than a parallel design.[37] As a result, fewer patients are required to achieve the same statistical power and precision, because all patients are their own control.[37] A disadvantage of a crossover design can be the risk of carry-over effects, interfering with the intervention effects, when the effects of the intervention do not completely return to the baseline state after the intervention ends, making comparisons between the two after the moment of crossover impossible. The Rescue trial therefore used an analysis that took carry-over effects into account in the calculation of intervention effects. A significant positive carry-over effect was found only for step length.

Because of the fluctuations in performance over the day due to medication, PD patients should preferably undergo a number of assessments over time to reduce the large within-subject variances in outcomes. A randomized clinical trial with repeated measures in time may give more precise estimates of outcome measures and should be considered in future research on PD.[38]

The impact of placebo effects resulting from increased attention during training was not controlled for, which is a limitation of the Rescue trial. However, the specificity of treatment effects in terms of gait performance suggests that findings are difficult to explain on the basis of attention alone. To control for placebo effects in future studies, cueing training given by a therapist would preferably need to be compared with a non-cueing therapy given by a therapist, controlling for the amount of attention. However, the study may be threatened by contamination which should be prevented.

More high quality RCTs should be initiated to study the effect of cueing programmes in order to underpin existing guidelines with high quality research. Studies should work on the basis of the CONSORT agreement[1] to ensure high methodological quality and sufficient statistical power by using an appropriate number of subjects.

Optimizing the clinical test battery

A key issue in PD research is that the primary outcome measure should be in line with the focus of the therapy.[38] An example of a frequently used test is the Timed Get Up and Go test (TGUG)[39] where standing up, walking, turning and sitting down are combined in one test, with the total time needed for these actions as an outcome measurement. This time does not reflect a patient's ability to make a safe turn, since pivoting is less safe but much faster than a 'stepping through strategy'. In other words, the therapeutic aim of getting patients to perform normal safe gait is incompatible with the aim of increasing the speed in the TGUG.[38] Ideally, the primary outcome measure should reflect the change that is likely to be introduced by the therapy applied.

In addition, clinical tests should fit in with the domains of the International Classification of Functioning, Disability and Health (ICF).[40] Unfortunately, this can not be said of most tests. For example, the Unified Parkinson's Disease Rating Scale (UPDRS)[14,15] is multidimensional and reflects a mixture of different constructs at different levels of the ICF, making findings from trials difficult to interpret.[38] Obviously, there is a need for a valid and feasible test battery in which each test reflects one specific symptom or one underlying construct.[38] This requires a better understanding of the underlying

mechanisms of symptoms such as rigidity or freezing in order to develop valid tests.

There is a general need for a comprehensive core set of valid measurements recommended for trials and clinical practice. This core set should be recommended in the rehabilitation guidelines for PD allowing comparison of effects that are claimed.[38]

Improving ambulant monitoring

The benefits of cueing training for walking performance in patients' own environment can only be understood if additional information is available about the association between improvement in gait speed and performance and walking ability in the community.[41] The literature offers no studies about this relationship. In addition, the impact of cueing-induced gait improvements on ADL independency needs further investigation in combination with the tendency to increase on ADL, according to the Nottingham Extended ADL Index (NEAI) after receiving cueing training.

Our study used activity monitoring (AM) to examine the amount of activity over a regular week day, AM was used. AM is a reliable[12,42] and valid[43] method to record movements in PD. Some disadvantages of the used monitor in the Rescue project are the size and weight of the monitor, the wires connecting accelerometers and recorder, and the limitation of battery and storage capacity.

The development of a light-weight, wireless device with the capacity to store data for a couple of days would help to investigate activity patterns for several days and nights. Small wireless ambulatory monitors, using Bluetooth to send their information directly to a researcher's computer, already exist.[44] These systems are small and do not interfere with movements. Unfortunately these systems only work within a limited radius of the receiver. To avoid this problem, data can be sent to the assessor with the help of SMS, but activity monitors with this option are still heavy and large, and lack sufficient battery capacity.[45,46] Newly developed systems could also be used to monitor the amount of activity on optimal medication installation, as well as in studies on new medications or neurosurgery in PD and other neurological disorders. Newly developed algorithms to detect and classify freezing and falling symptoms will offer the opportunity to develop new intervention programmes aimed to prevent these problems.

Small, light weight and wireless AM may reduce reactivity effects, that is the effects that some people may have avoided activities, because of wires connecting the data logger and sensors or because of the size and weight of the data logger. Finally, the use of AM that monitors daily activities may introduce a Hawthorne effect, i.e. a temporary chance to behavior in response to a change in the environmental conditions. In our study, however, AM was applied in patients in the early and late phases.

Improving the identification of falls

In the Rescue project, 43% of the patients could be classified as fallers on the basis of item 13 of the UPDRS. Other prospective studies have reported incidence rates for falling in PD patients of between 50 and 70%.[30,47] Still, a major problem with recording falls is the lack of a uniform definition of falls in the literature, and hence a valid way to record falls and near falls.[48] In the present study 'a fall' was defined as 'an event that results in a person coming to rest unintentionally on the ground or another lower level,

not as the result of a major intrinsic event or overwhelming hazard'.[49] The incidence of falling was measured by means of a falls diary. The problem of a falls diaries is that of recalling a fall. Asking specific questions about falls encourages a full account, including details on embarrassing or insignificant falls that fallers might have omitted otherwise.[50] In the Rescue trial a diary was used asking about falls and details, with questions such as (1) where did you fall? (2) What were you doing or trying to do at the moment you fell? (3) What caused the fall? (4) How did you land on the floor? (5) How did you get up from the floor?

In a recent study on fall diaries,[50] 8% of the diaries were excluded from analysis, because they were unintelligible, due to micrographia, or unusable due to incomplete data. In the Rescue trial, assessors asked the patients about fall events at every assessment (four times in 12 weeks), while therapists asked the patients about falls at every session (for 3 weeks) and helped them to fill out the diaries if necessary, to reduce recall problems and unusable falls diaries.

An alternative way to detect 'fall movements' might be the use of accelerometers on the chest[44] or pelvis.[51] However, this detection of fall movements probably does not offer sufficient sensitivity to identify falls: most patients lack the right strategies to lie themselves down in their beds and therefore let themselves fall on their beds. Other patients let themselves fall on the floor to pull themselves onto their beds thereafter. This example illustrates that it can be difficult to use accelerometers to discriminate between an intentional fall and an accident. Therefore, future studies will need to discriminate between intentionally and unintentionally coming to rest at a lower level. The construction of algorithms to detect and classify freezing and falling symptoms will offer opportunities to develop new intervention programmes to prevent these problems.

The multivariate regression model presented in Chapter 7 of this thesis[52] suggests that patients who are fallers are more likely to suffer from freezing, have longer disease duration, experience problems with walking and need more time to complete the TGUG. The accuracy of this prediction model was 74%, implying that model was inaccurate in 26% 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 to identify patients at risk of falling using home-based tests, especially when the fall history is unknown. The present model may therefore serve to indicate directions for further research in order to refine and develop tests reflecting the underlying mechanisms of falling.[52]

A more accurate model for falling requires a better understanding of the underlying constructs. Laboratory research on falls, e.g. by using a catwalk with unexpected trips as was done in the studies by Pijnappels,[53] can provide more insight into the biomechanics of falls and fall avoidance. Knowledge of mechanisms underlying problems of freezing and turning, both of which are risk factors, may provide the opportunities to develop tests and algorithms based on the underlying constructs of falling.

In addition to this, longitudinal models are required in which the quasi-causal relation between time-dependent determinants, such as severity of freezing, are associated with observed changes in postural control and the incidence of falling.

Improving guidelines and improving implementation strategies for cueing training

In the first week of the intervention period in our study, patients tried all cueing modalities: auditory, visual, and somatosensory cueing. In the remaining 2 weeks, patients used a cue type of their choice, to practice with: 67% of these patients chose the auditory cue, 33% chose the somatosensory cue (33%). In a survey that was held after the intervention period, patients were asked to explain their choice. Most patients reported that they had opted for the 'clearest cue', being the auditory cue. Other patients reported that they preferred a concealable cue, the somatosensory cue. The somatosensory cue was worn under a wrist band, which could be hidden in a sleeve. Patients who frequently walked outside and used their cue to facilitate gait while shopping for example, preferred this less visible cue. In addition to the cueing device, visual spatial cues, like stripes on the floor, or lines in the pavement were used for 11.22±11.4% of the total time spent on therapy.[54]

Patients with severe dyskinesia showed problems with (1) inserting the cylinder of the somatosensory cue under their wrist band, and (2) pulling out cables, connecting the earpiece or cylinder with the cueing device, due to uncontrolled large movements of their arm or neck.

Visual rhythmic cues, provided by a flashing light on the spectacles, were less popular than other cue types. Findings from the study by Rochester and colleagues, suggest that visual rhythmic cueing demands for double tasking and consequently worsens gait.[22]

There is thus a need for a cheap cueing device providing an auditory and a somatosensory cue, to give patients the opportunity to use cues in daily life. This cueing device should preferably be smaller than the prototype cueing device, and the vibrating cylinder should be replaced by something that is easier to use by patients with severe dyskinesia. One option could be a kind of watch with an integrated vibration device (like that in a cell phone). A wireless system using Bluetooth to connect the earpiece to the rhythmic signals from the watch would help patients with dyskinesia. This would also be perceived as a more elegant solution than one using wires, probably stimulating patients to use the device for ADLs outside their house.

A multiple regression analysis was utilized for all used guidelines and cue types, to explain the variance of outcomes for the positive outcome measurements of the Rescue trial. This analysis indicated that the positive effects of cueing were irrespective of the cue type, confirming our hypothesis that each modality, provided by the cueing device, has the same effects. This implies that therapists and patients can use any available cue, mostly a metronome in the absence of somatosensory cues.[56]

The same analysis showed that using gait-specific guidelines for therapy led to an improvement in gait and gait-related activities. These findings further support the theory by Kwakkel and colleagues[38] that the effects of physical therapy are specific to task and context in patients with PD, and are similar to other neurological diseases such as stroke[38,55] and MS.[57] Therapists therefore need to be specifically trained to use guidelines and give cueing training.

It is important to emphasize that the cueing training did not lead to an increase in fall

events. It was expected that patients would walk much when using cues and a possible side effect of increased activity can be an increase in fall events. Walking and paying attention to a cue could be experienced as double tasking, which is also known to be a risk factor for falling.[58] The effect of the three different cueing modalities (auditory, visual and somatosensory) on gait performance has been investigated using a single and a double task.[22] Patients were asked to walk with a tray with two glasses filled with water. Gait parameters were recorded, using AM. Results showed an improvement in walking speed for the auditory and somatosensory cue, indicating that these types of cues might facilitate double tasking. By contrast visual cues worsened gait velocity, implying that paying attention to a flashing light interfered with gait performance.

This experiment suggests that auditory and somatosensory cues do not act as distracters while walking and therefore probably do not increase the number of fall events. The results on the interferences between the different cue types and gait supported the finding on preference for auditory and somatosensory cue types found among the patient population in the Rescue trial.

Improving international collaboration and dissemination of knowledge

The Rescue trial was the first RCT in rehabilitation medicine that was financed by the European Commission (EC). This project taught us much about the cultural similarities and differences between the British, Belgium and Dutch situations.

Differences in the content of cueing training were minimized by training the three therapists prior to the trial to ensure that they used the guidelines and the cueing device in a similar way and used the same diary to record their therapy goals as well as the same strategies to work on these goals. During the period of the trial, they stayed in contact using e-mail, phone and MSN Messenger, to make sure that they were still working in the same way. Difficult cases were analyzed by the therapists together to make sure that they kept using the same strategies. Despite this training, the client-therapists interactions differed between the countries. For example, the role of the therapists as a helping assistant was less prominent in The Netherlands and more pronounced in Belgium and the UK, whereas in The Netherlands more of the responsibility for the success of implementing therapy guidelines was put on the client. These cultural differences were probably the reason why the content of the cueing programmes was slightly different, in that the Dutch therapist put more emphasis on gait, the Belgian therapist concentrated more on postural control, and the British therapist emphasized posture in therapy.[54]

Other differences relate to governmental issues and reimbursement policies of insurance companies. These differences may have led to differences in e.g. visits to the doctor, the amount of physical therapy provided and the use of medication. Because we had expected these differences patients were stratified on the basis of country and subsequently randomized to the early or late intervention regime.

The Rescue team met a few times a year to stay updated on the state of affairs and work on further developments within the project. E-mail and internet were used frequently to keep each other informed. A website facilitated the exchange of data and information on therapy and assessments. The collaboration between the three

countries was successful.

As the core of Rescue was concerned with the transfer of evidence-based rehabilitation methods to the environment of patients' everyday lives, it was of major importance that the results of the project were disseminated internationally. A special 'Rescue conference' was held in Amsterdam, in March 2005, where results of the study were presented. Additionally, results of the study have been presented world wide at various conferences on Parkinson's disease, neurology, rehabilitation medicine and physical therapy. Work sheets on strategies in cueing have been developed for PD patients, caregivers and professionals, and are available through the internet (www.rescueproject.org). A DVD is available with demonstrations of cueing, with clear (printable) instructions for patients (Dutch version via www.parkinson-vereniging.nl and English version available via www.Parkinsondvd.com). Physical therapists and movement therapists in The Netherlands have the opportunity to join networks specializing in PD.[59] Within these networks, physical therapists are trained to use guidelines for physical therapy in PD, including the use of rhythmic cues, by members of the Rescue team.

Recommendations for future research on cueing

Involvement of a wider variety of patients with parkinsonisms

In the Rescue trial one patient was classified as Hoehn and Yahr (H-Y)[60] stage 1, 134 patients were classified as H-Y stages 2 and 3, whereas 18 patients were classified as H-Y stage 4. By definition these stage 4 patients experienced walking and balance problems and were at risk for falls. The effects of cueing training in H-Y stage 4 need further investigation. It would also be interesting to study the effects of rhythmic cueing in PD patients in early stages, H-Y 1. Patients in early stages often do not complain about walking problems, but already show deviations in their gait pattern.[61] Recently, Fisher and colleagues showed improvements in gait speed, step length and range of motion of different joints after intensive treadmill training in early stages of PD.[21] When training patients at different stages of their disease it is important to work on therapy aims that are compatible with these stages.[62]

Future studies on cueing in PD should also include patients suffering from cognitive disorders, since PD is often associated with cognitive impairment. Prospective studies show incidence rates for dementia in PD ranging from 19 to 78.2%.[63] Disturbed executive functioning is also a major problem in PD. Since patients may not rely on higher functioning planning and sequencing,[64] cueing might be suitable for patients with cognitive impairments, because of its instantaneous character and because it has been suggested that external rhythmic cues can reduce attentional load as they inform the motor system about the temporal sequencing of a task.[22]

Patients with parkinsonisms such as Progressive Supranuclear Palsy (PSP) and Multi System Atrophy (MSA) might also benefit from cueing training. Yet, more research is needed to study the effects of cueing on gait in these specific patients groups. In addition, recent studies also suggest that other patient groups with neurological disorders, such as stroke, benefit from rhythmic cueing.[65,66]

Efficiency of cueing training

Cueing training is a relatively cheap intervention, because it requires only a cueing device (or metronome). A physical therapist can provide appropriate instructions that allow patients to cue themselves. Moreover, in view of to the benefits of cueing therapy, there might be less need for medication and inpatient health care, thanks to fewer falls and increased mobility. Future studies should focus on the cost-effectiveness of cueing programmes in terms of reduced medication intake and the opportunity for patients to continue to live at their own home with improved health-related quality of life.

Conclusion

The research presented in this thesis allows the conclusion that cueing training is an important addition to the multidisciplinary treatment of PD patients with mild to moderate disease characteristics. The cueing training did not lead to additional falls and the effects of the training were irrespective of the cue type. More research is required to develop outcome measures to match the goals of the therapy. Such a core set of assessments used by different disciplines should preferably be unidimensional at a specific ICF level. More research needs to be done to examine the neuronal mechanisms behind cueing, to investigate possible neuroprotectiveness of cueing training and to determine the optimal dose-response relationship for a long-lasting effect of cueing training. Therapists worldwide need to be trained to provide cueing training and financial resources should be provided, through insurance companies and ministries of health, to make cueing training at home available for every patient with PD.

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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 appraized 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.

Revalidatie bij de ziekte van Parkinson:

strategieën voor cueing

Samenvatting

De ziekte van Parkinson is een ernstige progressieve neurologische stoornis. Veel patiënten met deze ziekte ervaren problemen met mobiliteit. Vooral lopen en activiteiten die gerelateerd zijn aan lopen leiden tot een afname in Activiteiten van het Dagelijks Leven (ADL). Het belangrijkste doel in dit proefschrift was om vast te stellen of het aanbieden van externe ritmes (cueing) tijdens het lopen onder begeleiding van een fysiotherapeut een veilige methode is om de loopvaardigheden bij Parkinsonpatiënten in hun thuissituatie te verbeteren. In dit proefschrift werd onderzocht wat de effecten zijn van optimale cueingtherapie, inclusief strategieën waarbij patiënten zelf cueing leren gebruiken, op het gebied van (1) functionele prestaties en gezondheidgerelateerde kwaliteit van leven, (2) de hoeveelheid fysieke activiteit, en (3) het risico op vallen. Daarnaast werd gekeken in hoeverre door cueingtherapie geïntroduceerde verbeteringen in loopvaardigheid ook aanleiding gaven tot een betere ervaren kwaliteit van het leven.

In **Hoofdstuk 1** werden de doelen en de structuur van dit proefschrift uiteengezet. Achtergrondinformatie werd gegeven vanuit historisch, epidemiologisch en medisch perspectief. Vervolgens werd de 'state of the art' van revalidatiegeneeskunde bij Parkinsonpatiënten beschreven en bediscussieerd. In het bijzonder werd daarbij het gebruik van externe ritmes, om het lopen en daaraan gerelateerde activiteiten te verbeteren, belicht. In de inleiding werd het Rescue-project gepresenteerd. Rescue is een acroniem voor 'Rehabilitation in Parkinson's Disease: Strategies for Cueing' (revalidatie bij de ziekte van Parkinson: strategieën voor cueing). Dit project betrof een internationale samenwerking en werd gefinancierd door de Europese Commissie. De initiatie van het Europese project werd enerzijds gelegitimeerd door een gebrek aan kennis over de eventuele meerwaarde van ritmische cueing tijdens het lopen bij patiënten met de ziekte Parkinson, en anderzijds door de vraag van de Europese Commissie om nieuwe technologieën te ontwikkelen die in staat zouden zijn om, onder andere, Parkinsonpatiënten langer in hun eigen woonomgeving te laten functioneren.

Binnen het Rescue-project werd een multicenter gerandomiseerd klinisch onderzoek (RCT) uitgevoerd, verdeeld over drie Europese landen. De Rescue-trial had tot doel om de effecten van cueing bij Parkinson patiënten in de thuissituatie te onderzoeken. De voorbereidingen voor de uitvoering van deze multicenter trial zijn beschreven in de inleiding. Deze voorbereidingen bestonden, onder andere, uit (1) de ontwikkeling van een draagbaar cueingapparaat waarmee verschillende soorten ritmes kunnen worden gegenereerd; (2) de ontwikkeling van behandelrichtlijnen voor het gebruik van het prototype cueingapparaat en toepassen van cueingstrategieën in de thuissituatie, en (3) de samenstelling van een alomvattende testbatterij om de effecten van cueing te kunnen meten op het niveau van functies, activiteiten en participatie.

In **Hoofdstuk 2** is een systematische review gepresenteerd, bedoeld om alle literatuur over het effect van cueing op het lopen van Parkinsonpatiënten te evalueren voor wat betreft methodologische kwaliteit en effectiviteit. Twee fysiotherapeuten zochten systematisch via verschillende elektronische databestanden naar alle effectstudies die gepubliceerd waren tussen 1966 en januari 2005. In deze artikelen moest een studie beschreven zijn over het effect van cueing (auditief, visueel of tactiel) op gangparameters van patiënten met idiopatische Parkinson. Uiteindelijk werden 24

van de 159 gescreende studies voor methodologische beoordeling geïncludeerd. Twee onafhankelijk beoordelaars evalueerden de methodologische kwaliteit van de geïncludeerde studies. Twee van de 24 studies waren RCT's. Beide studies hadden een hoge methodologische kwaliteit. Eén van deze RCT's was specifiek gericht op effecten van auditieve ritmes op het lopen van Parkinsonpatiënten. In deze studie werd een positief effect op loopsnelheid gevonden. In de andere RCT werd onderzoek gedaan naar oefentherapie in groepsverband; cueingtraining was in deze studie slechts een onderdeel van de oefentherapie. Alle andere studies waren pre-experimentele studies. Een 'best evidence synthese' werd toegepast op alle geïncludeerde studies en liet sterke bewijskracht zien voor het verhogen van loopsnelheid met behulp van auditieve cues. Er werd onvoldoende bewijs gevonden voor het effect van visuele en tactiele cues. Het is onduidelijk of de positieve effecten die gevonden zijn in het laboratorium ook gegeneraliseerd kunnen worden naar verbeteringen van ADL's, gezondheidgerelateerde kwaliteit van leven en een vermindering van valincidenten. Daarnaast is het ook nog onduidelijk of cueingtraining beklijft na het stoppen van de therapie.

In **Hoofdstuk 3** werd de betrouwbaarheid, responsiviteit en gebruiksvriendelijkheid van een deel van de RESCUE-testbatterij onderzocht. Dit onderzoek vond plaats bij 26 Parkinsonpatiënten in de thuissituatie. De testbatterij bestond uit de Unified Parkinson's Disease Rating Scale (UPDRS), een geklokte 6-meter looptest, de Timed Get Up and Go test (TGUG), de Berg Balance Scale en de Functional reach test. Om de interbeoordelaarbetrouwbaarheid te bepalen werden alle tests, in gerandomiseerde volgorde, afgenomen door drie onafhankelijke beoordelaars bij 26 Parkinsonpatiënten. Om de intrabeoordelaarbetrouwbaarheid vast te stellen nam één van de beoordelaars de testbatterij twee keer af, met een periode van 7 dagen tussen beide meetmomenten. Er werden matige tot uitstekende intraclass correlatiecoëfficiënten (ICC's) gevonden. De responsiviteit werd bepaald door de 95% grenzen van de meetfout (Smallest Detectable Difference en Reliable Change Index; RCI) van ieder meetinstrument te berekenen. Alle meetinstrumenten hadden een RCI onder de 11%. Het is moeilijk om deze waarde met de literatuur te vergelijken omdat er geen consensus is over hoe responsiviteit gekwalificeerd zou moeten worden. Wel kunnen de resultaten van deze studie gebruikt worden als een richtlijn om vast te stellen hoe groot het effect minimaal moet zijn om voorbij de 95% betrouwbaarheidsgrenzen van de meetfout te kunnen komen. De gebruiksvriendelijkheid werd bepaald door het meten van de tijd die nodig was om de hele testbatterij af te nemen, inclusief de tijd die nodig was om de thuisomgeving van de patiënt aan te passen aan de tests, zoals het verschuiven van meubelstukken. De hele testbatterij kon worden afgenomen binnen 30 minuten, wat als voldoende beschouwd werd voor de praktijk.

In **Hoofdstuk 4** werd het effect van ritmische visuele cues op de staplengte en de schredefrequentie tijdens het lopen onderzocht. In dit pre-experiment werden aan patiënten en gezonde proefpersonen verschillende visuele condities aangeboden tijdens het lopen op een lopende band. Deze metingen werden gedaan bij Parkinsonpatiënten (n=21) en gezonde proefpersonen van dezelfde leeftijd (n=7). Alle proefpersonen voerden vijf condities uit op een lopende band:

(1) Lopen zonder een visuele cue of optische flow, om de uitgangswaarde van de schredefrequentie te bepalen.

(2) Lopen met een virtuele gang geprojecteerd op een scherm op 75 cm afstand voor de lopende band. Tijdens het lopen op de band had de virtuele gang dezelfde 'optische flow' als de lopende band, waardoor de proefpersonen het idee hadden dat zij door een gang liepen.
(3) Lopen op de band met visuele ritmische spatiële cues (VRS) met behulp van dwarse strepen op de vloer van de virtuele gang.
(4) Lopen op de band met visuele ritmische temporele cues (VRT), met behulp van een ritmisch knipperend lampje dat aan een bril was vastgemaakt.
(5) Lopen op de band met de combinatie VRT en optische flow.

Na de baselinemeting werden de condities 2 tot en met 5 in een gerandomiseerde volgorde aangeboden. De snelheid van de lopende band werd bij iedere conditie systematisch verhoogd. Na het behalen van de maximale loopsnelheid werd de band weer met dezelfde stappen verlaagd. Proefpersonen werden tijdens de vierde en vijfde conditie gevraagd om hun schrede af te stemmen op het ritme van de VRT, waarbij de frequentie 10% onder de uitgangswaarde werd ingesteld. De schredefrequentie en staplengte werden gemeten met behulp van een activiteitenmonitor (AM). Parkinsonpatiënten liepen gemiddeld met een hogere schredefrequentie en een kortere staplengte dan de gezonde proefpersonen uit de controlegroep. Daarnaast bleek de schredefrequentie tijdens het opvoeren van de loopsnelheid op de lopende band systematisch hoger te zijn dan bij overeenkomstige snelheid tijdens het verlagen van de snelheid van de lopende band. Zowel VRS als VRT resulteerde in lagere schredefrequenties (en dus grotere schredelengtes) vergeleken met de condities zonder cues.

Dit onderzoek liet zien dat schredefrequentie en staplengte bij een gegeven loopsnelheid kunnen worden genormaliseerd door patiënten met de ziekte van Parkinson visuele ritmes aan te bieden tijdens het lopen op een lopende band. Dit laatste suggereert dat het gebruik van visuele cues therapeutisch kunnen worden aangewend om het gangbeeld bij Parkinsonpatiënten gunstig te beïnvloeden.

In **Hoofdstuk 5** en **6** worden de resultaten van de Rescue-trial gepresenteerd. In de Rescue-trial werden de effecten van cueing training in de thuissituatie van Parkinsonpatiënten onderzocht tijdens lopen en aan lopen gerelateerde activiteiten. Dit onderzoek werd uitgevoerd in drie landen (Newcastle, Verenigd Koninkrijk, Leuven, België en Amsterdam, Nederland). Honderddrieënvijftig Parkinsonpatiënten met milde tot matige symptomen van de ziekte van Parkinson werden geïncludeerd in een enkelblind gerandomiseerd cross-over onderzoek. Proefpersonen die in de vroege interventiegroep ingeloot waren (n=76), kregen gedurende de eerste 3 weken een cueingprogramma van 9 behandelingen van 30 minuten aan huis aangeboden. Tijdens deze behandelingen werd cueing aangeboden met behulp van een prototype cueingapparaat. Vervolgens werden de patiënten in de vroege interventiegroep nog eens 3 weken zonder training vervolgd. Patiënten die in de late interventiegroep ingeloot waren (n=77) werden eerst 3 weken op de wachtlijst geplaatst en kregen pas na deze weken een cueingprogramma. Zes weken na de randomisatie werden beide groepen nog eens gedurende een follow-upperiode van 6 weken zonder training gevolgd om vast te stellen in hoeverre de behandeleffecten ook blijvend van aard waren. De primaire uitkomstmaat was de Posture and Gait score (PG score). Deze werd bepaald op de baseline, na 3, 6, en na 12 weken. Tot de secundaire uitkomstmaten

behoorden metingen die gericht waren op het lopen, freezing en balans, functionele activiteiten, kwaliteit van leven en de belasting van de partner, waarbij alle niveaus van de 'International Classification of Functioning, Disability and Health' (ICF) aan bod kwamen. Aanvullend droegen alle proefpersonen een AM op de dagen dat ze getest werden om lichaamsbewegingen en houdingen te registreren. Binnen ieder land werden zowel alle klinische metingen, als de AM-metingen afgenomen door getrainde onderzoekers, die er niet van op de hoogte waren of de geïncludeerde patiënt in de vroege of de late interventiegroep was ingeloot.

In **Hoofdstuk 5** werden de resultaten van de klinische metingen weergegeven. Deze lieten kleine, maar significante verbeteringen zien na interventie op de PG scores, mate van freezing, loopsnelheid, stapgrootte, geklokte balanstests en een groter vertrouwen bij het uitvoeren van functionele activiteiten (Falls Efficacy Scale). Er werden geen effecten gevonden in ADL's en kwaliteit van leven, die het gevolg van de klinische verbeteringen hadden kunnen zijn.

In **Hoofdstuk 6** werden de resultaten van de AM weergegeven. Resultaten lieten conform de klinische metingen, een toename zien van zogenaamde dynamische activiteit. Lopen en loopperioden met een duur van meer dan 5 en 10 seconden bleken statistisch significant toe te nemen, terwijl een afname te zien was van alle statische activiteiten zoals zitten en liggen. De resultaten met AM bevestigen dat het geven van 9 behandelingen cueingtherapie loopvaardigheid en aan lopen gerelateerde activiteiten in de thuissituatie een gunstige invloed heeft op patiënten met de ziekte van Parkinson. Echter, de RESCUE-trial laat ook zien dat de effecten over 6 weken weer verdwijnen na het stoppen van de cueingtherapie. De tijdelijke aard van het effect van cueingtherapie op het lopen benadrukt de noodzaak van permanent gebruik van cueingapparaten en het voortzetten van de behandelingen.

In **Hoofdstuk 7** werd een predictiemodel voor het risico op vallen ontwikkeld. Data aangaande lopen, aan lopen gerelateerde activiteiten, balans en non-motor symptomen werden bij 153 Parkinsonpatiënten in hun eigen thuissituatie verkregen. Zesenzestig patiënten werden op basis van item 13 van de UPDRS als 'vallers' geïdentificeerd. Met behulp van bestaande literatuur en meningen van experts werden 50 verschillende determinanten geselecteerd die een mogelijke voorspelling zouden kunnen geven voor de kans op vallen bij patiënten met de ziekte van Parkinson. Op basis van een bivariate regressieanalyse bleek dat achttien van deze 50 determinanten een significante associatie hadden met vallen. Modelleren met behulp van een multivariate logistische regressietechniek liet zien dat patiënten een significant hoger risico liepen om te vallen wanneer zij slecht scoorden op: (1) Freezing bij het lopen, (2) TGUG score, (3) ziekteduur en (4) problemen met lopen als gemeten met item 15 van de UPDRS. Op basis van deze vijf determinanten in het multivariate regressiemodel konden 'vallers' in 74% correct worden geïdentificeerd. Deze positief en negatief voorspelde waarde in het predictiemodel is vergelijkbaar met de bestaande literatuur. Het model kan gebruikt worden om patiënten die een verhoogd risico hebben op vallen te identificeren, vooral wanneer de valgeschiedenis van de patiënt nog onbekend is. Het klinische model zou ook richtinggevend kunnen zijn voor verder onderzoek naar de oorzaak van vallen, met als uiteindelijk doel nieuwe meetinstrumenten te ontwikkelen die de achterliggende mechanismen van vallen valide kunnen meten.

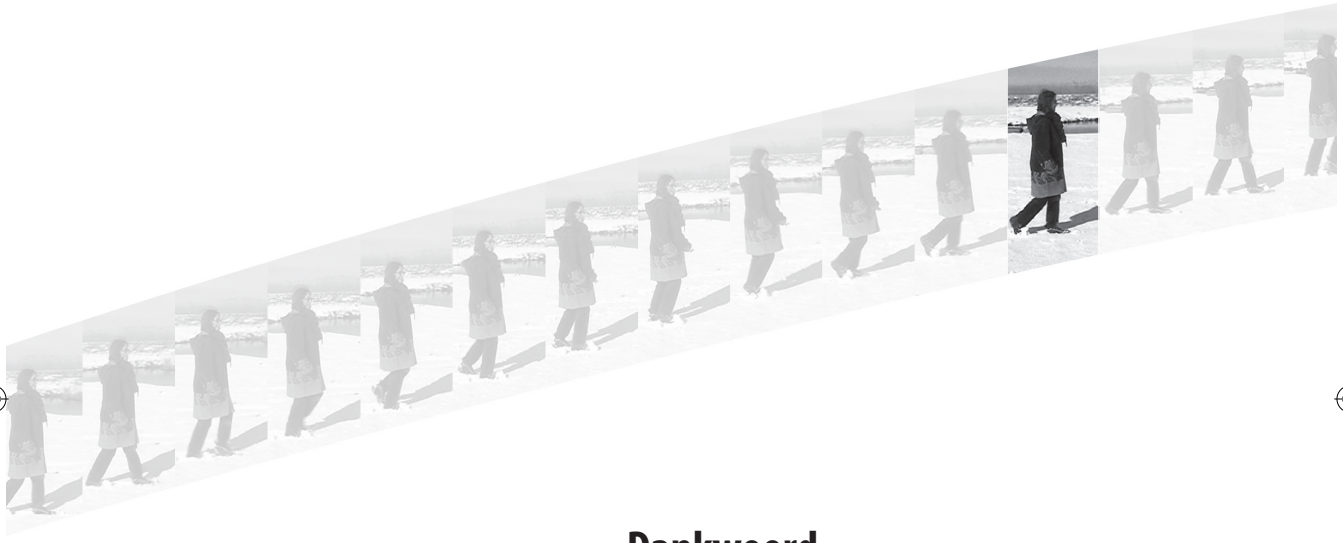
In **Hoofdstuk 8** werd de impact van de specifieke en non-specifieke effecten van cueing bediscussieerd, gezien vanuit de doelen die gesteld werden in het Rescue-project. Methodologische vraagstukken, de inhoud van de cueingtraining en de internationale samenwerking in het Rescue-project werden in dit hoofdstuk kritisch beschouwd. Daarnaast werden er aanbevelingen voor toekomstig onderzoek gedaan. Op basis van deze thesis werd geconcludeerd dat cueingtraining een belangrijke 'evidence based' behandelmethode is, die deel uit moet maken van de multidisciplinaire behandeling van patiënten met milde tot matige symptomen van de ziekte van Parkinson. Bovendien laat de RESCUE-trial zien dat cueingtraining een veilige therapie is die het risico tot meer valincidenten niet onnodig vergroot. Tenslotte lijken de effecten onafhankelijk te zijn van het type cue dat aangeboden wordt, zoals visueel, auditief of somatosensorisch. Aanbevelingen voor toekomstig onderzoek richten zich voornamelijk op het ontwikkelen van meetinstrumenten die meer in lijn zijn met de doelen van therapie. Huidige meetinstrumenten zijn veelal multicomponentindexen die niet specifiek een vaardigheid, zoals lopen, meten. Toekomstige meetinstrumenten zouden dan ook bij voorkeur unidimensioneel geconstrueerd moeten zijn en specifiek een vaardigheid binnen het domein 'activiteiten' van het ICF in kaart moeten kunnen brengen.

Naast een testbatterij, bestaand uit een alomvattende basisset van meetinstrumenten, zou er ook aandacht moeten zijn voor het ontwikkelen van een kleine, draadloze AM. Deze AM moet voldoende opslagcapaciteit hebben en genoeg accucapaciteit om bewegingen op een aantal opeenvolgende dagen te registreren. Met een dergelijke AM zou het ook mogelijk moeten zijn om een manier te ontwikkelen waarmee freezing en vallen op een valide wijze gemeten kunnen worden. Op basis van identificatie van nieuwe algoritmes voor freezingverschijnselen tijdens het lopen kunnen betere interventietechnieken ontwikkeld worden.

Qua onderzoeksdesign zou voor toekomstig revalidatieonderzoek bij patiënten met de ziekte van Parkinson meer gebruik moeten worden gemaakt van gecontroleerde effectonderzoeken met herhaalde metingen in de tijd, om effecten van fluctuaties in medicatiegebruik beter te kunnen controleren.

Verder werd in dit hoofdstuk aanbevolen om het achterliggende neurofysiologische werkingsmechanisme van cueing te onderzoeken. Kennis over het werkingsmechanisme geeft nieuw inzicht in de mogelijke neuroprotectieve rol van ritmische cueing en geeft inzicht in de optimale dosis-respons-relatie van cueing bij de ziekte van Parkinson.

In toekomstig onderzoek zullen ook patiënten uit vroege en late stadia van idiopathische Parkinson moeten worden geïncludeerd, evenals patiënten met cognitieve functiestoornissen. Daarnaast zouden effecten van cueing ook onderzocht moeten worden bij patiënten met parkinsonisme, zoals multiple systeem atrofie of progressieve supranucleaire paralyse. Tot besluit zou er in de toekomst een goedkoop cueingapparaat ontwikkeld moeten worden, dat zowel auditieve als tactiele ritmes kan genereren, om op deze manier patiënten de mogelijkheid te geven om cues te gebruiken tijdens ADL's. Daarnaast zou er dan ook aandacht gegeven moeten worden aan de implementatie van richtlijnen voor professionals, om hun patiënten op een veilige wijze in hun eigen thuisomgeving met cues te trainen.



Dankwoord

Ik houd niet zo van die uitgebreide, overenthousiaste dankwoorden. Maar een kort, zakelijk en nuchter dankwoord dat hebben jullie niet verdiend, ook jij, die ik ongetwijfeld ga vergeten, niet. Een middenweg proberen dan maar.

Ik ben nooit aan dit proefschrift begonnen, ik schreef een stukje. Dat stukje was na 21 keer bijvijlen publicabel en dat herhaalde zich met een ander stukje. 'Je bent halverwege', werd mij aanmoedigend van de zijlijn toegeschreeuwd, dus door… Maar terugblikkend lijkt altijd alles gemakkelijker dan wanneer je er midden in zit. Die eerste helft leek achteraf dus een makkie, het aantal versies van beide artikelen was ik voor het gemak vergeten. Gedurende de tweede helft heb ik me vaak afgevraagd waar ik aan begonnen was. Maar met jullie hulp, ook die van jou, is het allemaal gelukt!

Allereerst bedank ik de deelnemers van het Rescue-project. Wat een ervaring om bij 54 Noord-Hollanders drie keer per week, drie weken lang, welkom te zijn. Het 'Man-Bijt-Hond-Gevoel' bekroop me wel eens, in al die verschillende levens, met verschillende interieurs en verschillende achtergronden. Velen bedankten me na afloop met de woorden: 'dank je voor alle behandelingen, ik deed eigenlijk mee voor de wetenschap, maar ik heb er zelf ook nog wat aan gehad, ik loop écht beter'. Dankzij jullie en de deelnemers in België en Engeland konden we ook *bewijzen* dat de behandelingen 'beter lopen' tot gevolg hebben! In het bijzonder bedank ik de deelnemer die ik filmde in een dik pak sneeuw rondom haar huis. Beelden van deze opname mocht ik van haar gebruiken voor de omslag van dit proefschrift.

Dan mijn promotor en co-promotor. Gert, schreeuwen aan de zijlijn, maar ook rustig alle methodologie nog eens uitleggen op het white board in zijn kamer en eindeloos mijn stukken lezen en suggesties aandragen voor verbeteringen. Gert, je hebt me tot dit project aangezet, me er doorheen geloodst (soms gesleurd) en bent tot het einde blijven aanmoedigen: het moest af. Dat is gelukt! Dank! Erwin, co-promotor en voorbeeld. Rust en relativeringsvermogen, dat kon ik wel gebruiken in dit traject. Als het allemaal 'heel erg' leek wat ik opgeschreven had, liet jij me zien wat er al 'heel erg goed' was en hielp me de rest van afstand nog eens goed te bekijken en aan te passen. Dank!

Dank ook aan de leden van de leescommissie, prof. dr. E.Ch. Wolters, prof. dr. G.J. Lankhorst, prof. dr. B.R. Bloem en prof. dr. H.J. Stam, voor het lezen en beoordelen van mijn proefschrift.

Ook dank aan mijn collega's: de fysio's van het VUMC, die de omstandigheden creëerden waarin het Rescue-onderzoek uitgevoerd kon worden en altijd belangstellend vroegen hoe het ging met het project, maar ook met mij persoonlijk los van het project. Dank voor jullie warmte en steun. My colleagues from the Rescue project in Belgium and the UK, I have learned a lot from this international adventure, thank you for everything. De fysiotherapeuten die mij vervingen bij ziekte en vakantie, Cees en Ingrid, die mij ook zo veel hebben geleerd over de ziekte van Parkinson. En natuurlijk ook dank aan mijn kamergenoten, de eerste jaren Cees, Erwin (ik noem jullie gewoon twee keer!) en Alex, de laatste jaren, Marc, Cees (vooruit, drie keer) en Benno. Het was fijn tussen deze mannen, naast stoere praat, gezellige klets en emotionele steun, vooral discussie en hulp over en weer in de wetenschappelijke taken: samen literatuur zoeken, met elkaar

puzzelen op lastige statistiek, presentaties van elkaar bekijken en nog veel meer.

Beste Renate, fijn dat je jouw scherpe blik over dit boekje liet gaan, wat zaten er nog veel foutjes in… Je hebt het boekje prachtig vorm gegeven. Lieve Ivar, wat een mooi idee had jij voor de omslag, prachtig uitgewerkt ook. Renate en Ivar, zonder jullie was dit boekje nooit zo mooi geworden! Dank!

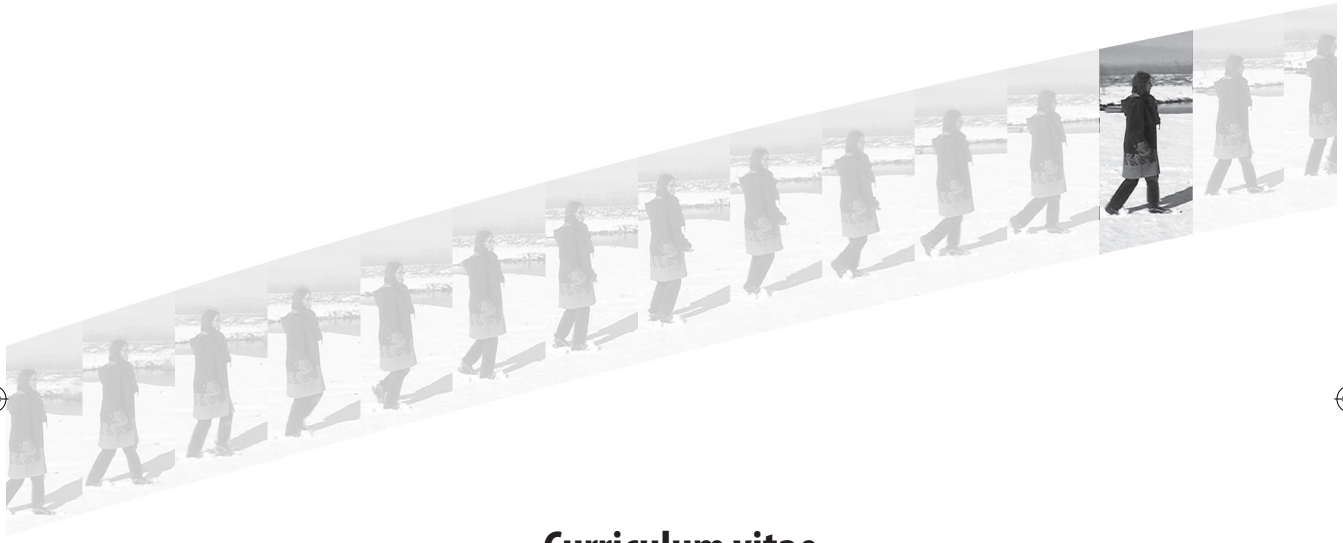
Lieve vrienden, lieve familie, dank voor jullie support. Marieke en Marije, fijn dat jullie mijn paranimfen zijn, jullie hebben me echt geholpen. Op me in gepraat als ik het niet meer zo zag zitten, maar ook flessen open getrokken als er iets te vieren was. Verder iedereen die op Maarten paste als ik echt even een stuk wilde opschieten. Vooral Mama en Hans, dank voor de weekenden waarin ik Maarten écht heel graag kwijt wilde (en daarna weer heel graag terug).

Mensen die overleden zijn kun je niet bedanken, wel kun je ze noemen, dat doe ik dan ook. Allereerst mijn vader die ik nooit gekend heb, 3 was ik toen hij stierf. Zenuwarts was hij, ik vind het een bijzonder gevoel dat ik de fascinatie voor het brein deel met hem. Ik vond nog een studieboek van hem, uit de jaren '50. De behandelwijzen zijn sindsdien gelukkig erg veranderd, ook voor wat betreft 'paralysis agitans', maar even voelde ik me erg verbonden met mijn vader, bij het lezen en begrijpen van de teksten in dat boek.

Dan natuurlijk mijn lieve Ditmer. 'Ik moest maar niet promoveren', hadden zijn collega's gezegd, 'dat kost je je huwelijk: zij alleen maar stress en achter de computer, dat wordt niets'. In het nieuwe huis richtte hij wél een werkkamer voor me in, met groot bureau. Aan iedereen die een rondleiding kreeg in ons nieuwe huis zei hij trots: 'en hier gaat Inge haar proefschrift afschrijven'. Ik heb het gedaan, maar hij was er niet meer bij. Wel in mijn gedachten, iedere dag. Ik heb de flessen champagne gemist, de etentjes bij sjieke tenten, waar we ongetwijfeld alle kleine succesjes van de afronding hadden gevierd, de geaccepteerde artikelen, het inleveren van het boekje, de goedkeuring van de leescommissie en straks de grande finale: Het is stil zonder jou…

Als laatste bedank ik mijn zonnestraaltje. Lieve kleine Maarten, je hebt geen idee wat ik aan het doen ben, maar je hield me op de grond. Voordat jij er was werkte ik regelmatig tot laat op de VU door, thuis vervolgens tot diep in de nacht en vond ik het heel belangrijk om alles zo goed en snel mogelijk te doen. Toen jij kwam, kwam je op de allereerste plaats: ik moest voor jou een goede moeder zijn, dus fit blijven, regelmatig leven en goed eten. Eén keer floot je me terug, ik zat te werken tot diep in de nacht en was de tijd vergeten. Toen stond jij ineens in je pyjamaatje naast me of je bij mij in bed mocht. Ik schrok, was helemaal de tijd vergeten. De computer ging onmiddellijk uit. Ik weet zeker dat ik tegen je vader had gezegd dat ik nog 'heel even' iets moest afmaken.

Allen dank, ja, ook jij.



Curriculum vitae

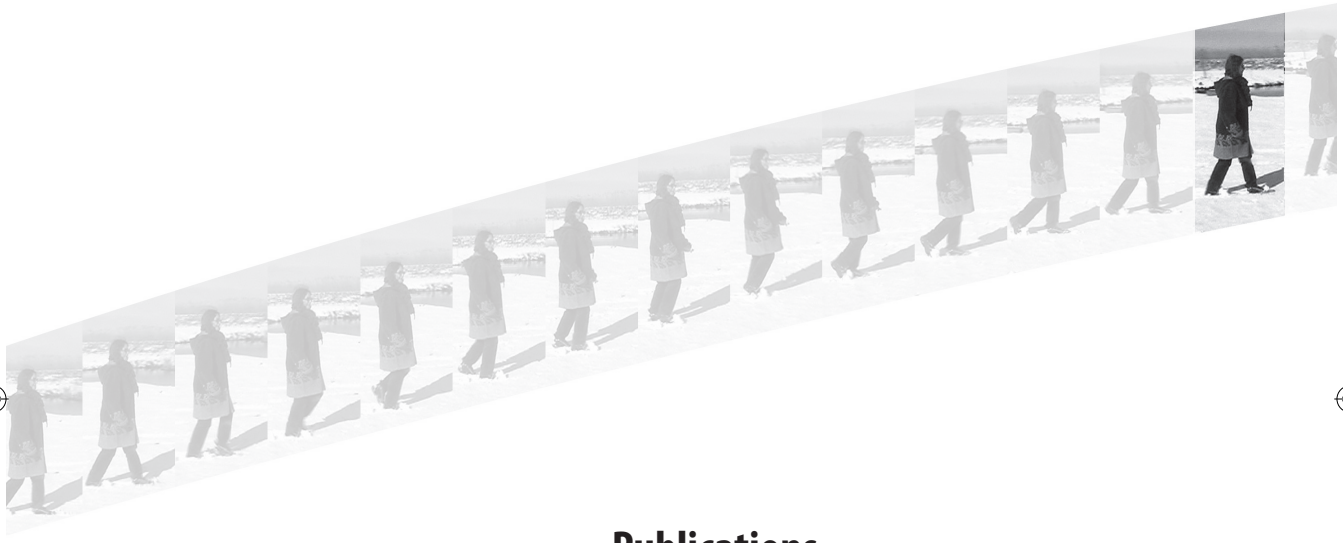
Inge Lim werd geboren op 13 oktober 1974 in Leiden. Na het behalen van het gymnasiumdiploma aan het Stedelijk Gymnasium te Haarlem studeerde zij een jaar Pedagogische en Onderwijskundige Wetenschappen aan de Universiteit van Amsterdam. Na het behalen van de propedeuse in 1995 begon zij aan de studie Bewegingswetenschappen aan de Vrije Universiteit te Amsterdam. In 1999 deed zij een deel van haar studie in Boston (VS), waar ze stage liep aan Sargent College, Boston University. In 1999 behaalde zij haar doctoraal examen. In datzelfde jaar begon zij aan de verkorte opleiding tot fysiotherapeut aan de Hogeschool van Utrecht en in 2002 haalde zij haar diploma.

In 2002 werd Inge aangesteld als fysiotherapeut en onderzoeker door (inmiddels professor) dr. Gert Kwakkel aan het VU Medisch Centrum, voor het Rescue-project. In dit door de Europese Commissie gefinancierde project gaf zij aan alle Parkinsonpatiënten, die in het kader van de studie in Nederland waren geïncludeerd, in de thuissituatie training met behulp van ritmen. Het Rescue-project heeft geleid tot dit proefschrift. Hoewel het project in 2005 eindigde, is Inge doorgegaan met het schrijven van artikelen.

Tijdens het zeventiende wereldcongres voor 'Parkinson's Disease and Related Disorders' in december 2007 won zij de eerste prijs voor 'young scientists' door een deel van het Rescue-project, over de relatie tussen de inhoud van het trainingsprogramma en de resultaten van de hoofdstudie, te presenteren.

Van 2005 tot 2008 was Inge regiocoördinator voor Noord-Holland binnen een door ZonMw gesubsidieerd doelmatigheidsonderzoek (ParkNet-onderzoek) naar de kosteneffectiviteit van het implementeren van evidence based behandelrichtlijnen voor fysiotherapie bij patiënten met de ziekte van Parkinson. Inge is nauw betrokken geweest bij de scholing van fysiotherapeuten in het ParkNet-onderzoek

Inge is gastdocent bij de Vrije Universiteit, het Nederlands Paramedisch Instituut en het ParkinsonNet. Momenteel werkt zij als fysiotherapeut op de afdeling neurologie van het VU Medisch Centrum.



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