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GROEP BIOMEDISCHE WETENSCHAPPEN

FACULTEIT BEWEGINGS- EN REVALIDATIEWETENSCHAPPEN

Locomotor asymmetry and motor switching in Parkinson's disease during tied- and split-belt treadmill walking

door Jasper Van der Donck

Masterproef aangeboden tot het behalen van de graad van Master of Science in de revalidatiewetenschappen en kinesitherapie

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Prof. Dr. A. Nieuwboer, promotor
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Woord vooraf

Graag wil ik mijn dank betuigen voor de fantastische begeleiding die ik kreeg van zowel mijn promotor, prof. Alice Nieuwboer, als mijn copromotor, Drs. Farshid Mohammadi. Zij hebben mij op een bijzonder betrokken, vriendelijke en opbouwende wijze gesteund gedurende de volledige twee academiejaren waarin ik aan deze masterproef heb gewerkt. Ik kon bij hen steeds terecht met allerhande vragen, wat ik zeer heb geapprecieerd. Het literatuuronderzoek, het testen van de proefpersonen, het bespreken van de resultaten en het schrijven van deze masterproef zouden voor mij nooit zo boeiend geworden zijn zonder de toegewijde steun van hen beiden. Verder ben ik de proefpersonen dankbaar voor hun deelname en prof. Wim Vandenberghe voor het recruteren van deze mensen. Door het uitwerken van de masterproef heb ik op een wetenschappelijke wijze kunnen nadenken en bijleren over onderwerpen die me boeien: de ziekte van Parkinson, het gangpatroon en de werking van de menselijke hersenen. Ook wat betreft de mogelijkheden van wetenschappelijk onderzoek en de gang van zaken hierin ben ik iets wijzer geworden. Over deze onderwerpen zal ik zeker blijven nadenken na mijn studie. Ten slotte ben ik mijn ouders en mijn vriendin enorm dankbaar voor de moed en de steun die ze me gegeven hebben tijdens mijn volledige opleiding.

Pulderbos, 21 mei 2013 J.V.D.D.

Situering

Dit onderzoek kadert in de zoektocht naar de specifieke gangproblemen bij de ziekte van Parkinson (Parkinson's disease, PD). De ziekte is gekenmerkt door een progressieve aantasting van meerdere hersenregio's, waarbij vooral de basale ganglia sterk degenereren. Het terugdraaien van deze aantasting is tot nu toe nog niet mogelijk, waardoor het stellen van de diagnose van PD een aangrijpende boodschap blijft voor patiënten en hun omgeving. Problemen om zich zelfstandig voort te bewegen hebben ongetwijfeld een grote impact op de levenskwaliteit van patiënten. Een veelvoorkomend symptoom dat bijzondere aandacht vereist is freezing of gait (FOG). Heel wat vragen omtrent de pathofysiologie van gangproblemen en FOG blijven tot op heden onbeantwoord. De betrachtingen van onderzoek naar gangproblematiek bij PD zijn dan ook tweevoudig. Enerzijds wordt de functionaliteit van patiënten vergroot door toepassingen in het ondersteunen en revalideren van verloren functies (directe therapeutische relevantie) en anderzijds dragen onderzoeksresultaten bij tot een beter begrip van de ziekte, met als doelstelling onder andere het uitbreiden van therapeutische opties. De Onderzoeksgroep Neuromotorische Revalidatie van het departement Revalidatiewetenschappen verricht uitgebreid onderzoek naar de revalidatie van personen met PD, onder andere op het gebied van de locomotorische problematiek. Zo richt de onderzoeksgroep zich onder meer op het ontwikkelen en doorgronden van cueing strategieën, de effectiviteit van nieuwe revalidatie-interventies, en de relatie tussen defecten in de automaticiteit van alledaagse handelingen en cognitieve compensatiemechanismen bij de ziekte van Parkinson. Naast PD worden ook andere chronische neurologische aandoeningen onderzocht, waaronder cerebrovasculaire aandoeningen en Cerebral Palsy.

Deze studie is bedoeld om inzicht te verwerven in de relatie tussen asymmetrie van het gangpatroon, triggers voor FOG, en de moeilijkheden met het behouden van een stabiel en efficiënt gangpatroon tijdens asymmetrische locomotie. De state-of-the-art ganganalyse-apparatuur van het Movements & posture Analysis Laboratory Leuven (MALL) maakt dergelijk onderzoek mogelijk. De studie kadert in een doctoraatsstudie die wordt gefinancierd door het EU Mundus programma Move-Age (http://www.move-age.eu/).

Abstract

Background: The role of asymmetry in the gait pattern of people with Parkinson's disease (PD), and especially in those with freezing of gait (FOG), needs clarification. We aimed to examine the ability of PD patients with or without FOG to adapt to an asymmetrical gait challenge and compare gait alterations with healthy controls (HC).

Methods: Spatiotemporal gait characteristics of 12 patients with PD (6 freezers) and 10 age-matched healthy controls were collected during a split-belt treadmill paradigm including different speed conditions imposed unilaterally (split-belt) and bilaterally (tied-belt) with a 3D Vicon system.

Results: During both tied- and split-belt walking, PD patients showed more asymmetry when compared to HC ($p < 0.001$). When the speed of both belts together was increased, a significant interaction effect was found indicating that unlike HC, PD patients were unable to sufficiently enlarge their stride length ($p < 0.001$). During asymmetrical speed changes, freezers showed more immediate difficulties in maintaining symmetry and balance compared to non-freezers. Patients (compared to HC, $p < 0.001$) and particularly those with FOG (compared to non-freezers, $p < 0.05$) displayed greater asymmetry when adapting to the split-belt walking, which could not be ascribed to the speed change per se. Nevertheless, patients could reverse their step length asymmetry.

Conclusions: Adapting locomotion to a split-belt treadmill was most particularly impaired in freezers because of the asymmetrical demands of the task, rather than increased speed as such. This may explain the characteristic turning difficulties in PD and its triggering effect on FOG.

Introduction

Gait problems are an important cause of a high disease burden in most people living with Parkinson's disease (PD)[1,2] and are associated with an increased fall risk.[3–5] A better understanding of the impairments that challenge gait in PD patients is needed, since therapeutic options available today often remain inadequate.[6]

Parkinson gait

Patients with PD express a more cautious gait pattern during overground walking compared with their healthy peers. They walk at a slower preferred speed[7–9] with shorter stride and step lengths[9–12], altered cadence[13], increased step width[13], decreased swing time proportion[8,10,14,15], and increased double support phase.[8] PD gait also seems to be less efficiently executed, with a higher left-right asymmetry[7,8], a greater stride-to-stride variability[7–9,16], and a poorer bilateral coordination.[7] Furthermore, gait impairments are exaggerated when taking a turn. Turning is performed more slowly, needs more steps and is scaled down in terms of stride length, step width, turning angles, and excursion of the center of mass.[17–22] Most of the changes described here are especially apparent in the 'off' state of anti-Parkinson medication. PD is also characterized by its general motor asymmetry[23,24] and postural instability.[25]

Another incapacitating feature of the disease is freezing of gait (FOG). Although very frequent in PD, many questions about the pathophysiology of this interesting phenomenon still exist.[26] At first sight, FOG seems to be a motor problem. An episode of FOG is characterized by a temporary inability to generate efficient steps.[27] Often times, the body propels forward while the feet make increasingly smaller and faster steps. From a clinical perspective, triggering conditions for FOG can be described. The most important trigger for FOG is turning[28] and other triggers also often include circumstances in which there is a need to produce locomotor asymmetry, for example initiating gait[29], and avoiding an obstacle.[30,31] In 2011 an experiment was reported that unilaterally modulated the deep brain stimulation of the subthalamic nucleus of freezers while walking on a treadmill.[32] By doing so, the gait pattern of these patients became more symmetrical and coordinated and freezing episodes were less frequent. This points to a link between FOG and left-right gait asymmetry.

However, FOG can also occur in an open runway.[33] A somewhat more theoretical point of view on the development of freezing episodes was proposed by Plotnik and colleagues.[34] They suggested that deterioration of different aspects of gait is able to accumulate and pass a threshold above which FOG can occur. We could indeed think of FOG as an ultimate disturbance of normal locomotion because in

between freezing episodes, the gait pattern of freezers is worse than that of non-freezers. This is evidenced by studies that show a greater variability in the timing of consecutive strides[14,35], a greater left-right asymmetry[35,36], and a lower bilateral coordination[35,37,38] in freezers compared to non-freezers. In addition, freezers adopt a different strategy when taking turns. Their cadence increases while non-freezers and healthy controls decrease their cadence.[28] They display a decreased control of step timing[39] and their turning arc is larger than that of non-freezers.[40] However, some of these studies are confounded by disease severity and disease duration differences between freezers and non-freezers.

Cognitive compensation

While human gait requires attentional resources[41], some automaticity is indispensable for functional locomotion. In PD, automaticity is impaired[15,42] due to the degeneration of the basal ganglia.[43] These structures also have an impact on motor functions through their connection with the cerebral cortex and the brainstem. Normally functioning basal ganglia bias the motor system towards successful movements using dopamine bursts to steer towards reward. Problems with automaticity in PD may arise from lower tonic dopamine levels, increasing the effort needed for automatic movements.[43] Therefore, PD patients probably need to rely more on compensatory cognitive resources for locomotion.

The literature also reports on various cognitive aspects of the disease. The incidence of dementia for patients with PD is reported to be four to six times that in healthy subjects[44] and, even more frequently, patients show mild cognitive impairments. They have, for example, decreased learning capacities, bradyphrenia, and difficulties with executive functions such as visuospatial perception, conflict resolution, and response inhibition.[45–49] Moreover, freezers have lower scores on tests of executive functioning than non-freezers.[50–55]

In line with this, dual tasking has been shown to interfere with walking in patients with PD with or without FOG. All gait characteristics were negatively influenced by dual tasking[56–64], including bilateral coordination[57,62] and symmetry of gait.[57,63] Additionally, during the performance of turning in freezers, dual tasking affects gait speed, cadence and the number of freezing episodes.[28] Also other attention-demanding conditions (e.g. a stressful situation[65]) can cause FOG. It was recently proposed that FOG results from the interplay between the loss of automaticity (due to basal ganglia degeneration) and inefficient cognitive control.[66]

Together, these findings support the idea that patients with PD need to rely more on cognitive resources for a functional gait, while these resources are affected by themselves, especially in freezers.[66]

Split-belt walking and PD

One way of studying the ability of subjects to deal with challenging gait tasks is by using a split-belt treadmill. By moving the belts at different speeds, external asymmetry is imposed. Adapting to this asymmetrical condition requires supraspinal control[67,68], which is also necessary in daily life to flexibly steer through different environments under different conditions. To date, a number of experiments with split-belt treadmills have been reported in other populations than PD, particularly in healthy subjects and patients with cerebellar disorders. From these experiments it was projected that the assumed central pattern generators of the spinal cord, which are thought to provide basic locomotor patterns, are able to control intralimb timing using proprioceptive feedback while the cerebellum and possibly also the cerebrum are needed for feedforward adaptation of interlimb parameters.[68–70] Step length is such a parameter which shows gradual adaptation and de-adaptation in response to split-belt manipulations in healthy adults[71] and hemispherectomy patients[69] but displays reduced and sometimes absent adaptation in cerebellar patients.[72] Given the above-described difficulties in PD and the relationships with asymmetry it is important to also investigate the performance of PD patients on a split-belt treadmill.

To our knowledge, only two split-belt studies with PD patients have been published so far. The first one is an electromyographic (EMG) study of Dietz et al. that was conducted in 1995.[73] By comparing healthy subjects to PD patients in different conditions of normal and split-belt treadmill walking, these authors found that the patient group was able to adapt their leg muscle activity to split-belt walking but showed a reduced range of possible stride frequencies and an increase in relative support duration. There was also more co-activation between antagonist muscles and a reduced activation of the gastrocnemius muscle compared to controls in the spilt-belt conditions. It was suggested that the cause for these changes was impaired proprioceptive feedback from extensor load receptors.

The other study of PD patients on a split-belt treadmill was recently published by Nanhoe-Mahabier et al. in 2013.[74] When challenged by split-belt treadmill walking, a group of seven freezers showed an increased stride time asymmetry while non-freezers and healthy subjects decreased this gait characteristic. In addition, the stride time variability increased significantly more in the freezer group. Differences in spatial measures (stride length asymmetry and stride length variability) were not found. Comparison between healthy controls and PD patients in split-belt conditions yielded no significant differences, except for the coordination between contralateral upper and lower limbs, which was less stable in PD patients.

There were a few limitations of this study. First, it was not reported how stride length was defined on the treadmill. Therefore it is not clear if the modified version of this characteristic, proposed by Reisman et al.[71] for treadmill gait analysis and commonly used in the work of Bastian and colleagues[69,71,75] was used

or not. Second, the authors mentioned to have used at least ten strides of each condition for the analysis. For gait variability, Galna et al. recently recommended to use at least 50 consecutive steps.[76] A third limitation was the choice to only look at mean values of a number of strides in the split-belt condition instead of investigating the distinct intervals within the adaptation period to study the process in more detail. For this, subjects were assumed to be fully adapted after the first 30 seconds of split-belt asymmetry. A fourth point was that the formulas to calculate asymmetry were based on strides instead of steps, the latter of which were recommended for measuring gait variability in older adults.[76]

Aim of the experiment

In the current split-belt treadmill study we aimed to investigate gait pattern adaptations to asymmetrical gait speed conditions in PD and how this relates to FOG. We will compare spatiotemporal gait variables in different circumstances of symmetrical and asymmetrical treadmill walking in PD patients with and without FOG and healthy control subjects. As such, we hope to understand the pathophysiology of FOG in the light of the possible contradiction between theories of accumulating gait decrements and theories of asymmetry.

Methods

Participants

For this cross-sectional experimental study, we recruited a sample of convenience of 22 participants of which 12 were patients with idiopathic PD and 10 were healthy age-matched control subjects (healthy controls, HC). For the patient group we included 6 freezers and 6 non-freezers, who were all recruited from the Movement Disorders Clinic of the University Hospital of Leuven (UZ Leuven) in Belgium. Healthy subjects were recruited through an existing database of volunteers. All subjects provided written informed consent. The study was approved by the local medical ethics committee of the K.U. Leuven.

The inclusion criteria for patients were (1) a diagnosis of PD based on the UK PD brain bank criteria[77] [appendix 2], (2) no other neurological disorder, (3) no other known disease or disorder that might interfere with the proposed experiments, (4) being able to participate in an experimental situation when OFF-medication for at least 12 hours, and (5) Hoehn and Yahr (H&Y) stage II or III (during OFF-medication) [appendix 3]. Patients with a subthalamic nucleus stimulator were included in the study if surgery had occurred more than one year ago. Both patients and HC were excluded if they had a score below 24/30 on the Mini Mental State Examination (MMSE) [appendix 4] or a severe medical condition affecting gait apart from PD. All patients previously participated in other studies at the K.U. Leuven between 2010 and 2012. Each subject of the freezer group showed FOG during these previous experiments, while non-freezers did not. In addition, we collected scores on the New Freezing of Gait Questionnaire (NFOG-Q) [appendix 5] using a FOG-verification video, which confirmed the present freezing status of all patients since freezers had a score of one or more and non-freezers scored zero. Freezers and non-freezers were matched for disease severity as measured with the motor section of the Unified Parkinson's Disease Rating Scale (UPDRS-III) [appendix 6].

Design and procedure

Testing of the participants took place in the Movements & posture Analysis Laboratory Leuven (MALL). We tested all participants in the morning. For PD patients this was after an overnight withdrawal of anti-Parkinson medication for at least 12 hours (OFF-medication state). The paradigm consisted of 12 minutes of walking on a split-belt treadmill (Forcelink B.V., Culemborg, The Netherlands) (see Fig. 1). Patients were kept unaware of the details of the experimental setup. Before the start of data capturing (i.e. before these 12 minutes), subject were already walking on tied belts at a speed of 3 km/h for one minute to become familiar with the treadmill. We defined 6 conditions of 2 minutes as follows. (see Fig. 2) The first 2 minutes were defined as the slow baseline tied-belt condition, in which both belts were running at

3 km/h. Then the speed of the belt under one leg was suddenly increased to 4 km/h (motor switching) and kept at this speed for the next 2 minutes while the other belt still moved at 3 km/h to induce asymmetrical walking. Figure 2 shows that we termed this phase the adaptation phase. The 3-4 km/h speed contrast proved sufficiently challenging to destabilize gait during pilot work prior to the final study. After this, belts were tied again at 3 km/h for 2 minutes. We termed this condition the de-adaptation phase in which gait was normalized to baseline values (see Fig. 2). After the first adaptation-de-adaptation sequence a second adaptation and de-adaptation phase was imposed for the other leg. For the last 2 minutes of the paradigm, the speed was increased to 4 km/h for both legs (fast baseline) to be able to differentiate between the effect of treadmill speed and the effect of asymmetry. The order of the adaptation conditions was randomized for left and right legs. Perturbations were provided suddenly since there was no time in between conditions, i.e. the end of each condition marked the beginning of the next one. To provide motor switching and to standardize the first stride, we increased the speed of one belt during the swing phase of the corresponding leg. Subjects knew in advance that the belts at some point could move at different speeds, but they were not informed about the exact onset of switching or which belt would go faster. Subjects were instructed not to look at the belts, so they had no visual feedback about the belt speed.

Fig. 1. Subject with reflective markers on the split-belt treadmill in the Movements & posture Analysis Laboratory Leuven (MALL)

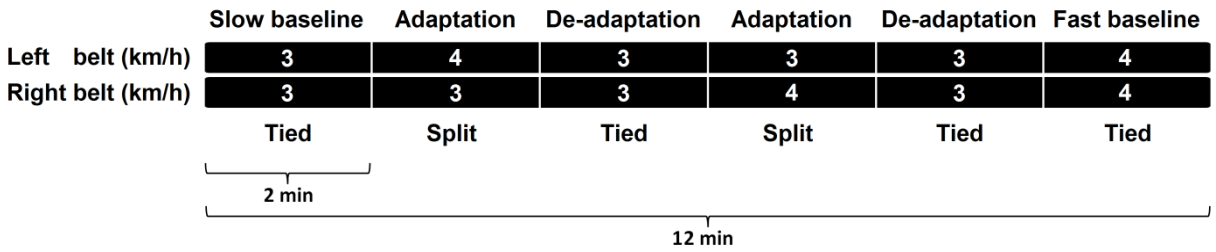

Fig. 2. Experimental conditions. The adaptation conditions were randomized for left and right legs. No time was left between conditions, i.e. the belts were never stopped during the 12-minute paradigm.

For safety reasons, patients wore a harness that was suspended from the ceiling. This consisted of girdles around the upper chest and did not support body weight or interfere with the walking pattern. We instructed the subjects not to use the handrails of the treadmill. One tester always remained in the vicinity of the patient to further ensure safety.

All participants walked barefoot on the treadmill and had 16 reflective markers on their lower limbs and pelvis. A 10-camera Vicon® motion analysis system (Vicon Nexus, Oxford Metrics, Oxford, UK) captured the position of these markers at a rate of 100 Hz. The markers were put bilaterally on the following body landmarks, based on the Plug-In Gait model for the lower limb: second metatarsal head, posterior heel (calcaneus), lateral malleolus, lateral lower leg (between ankle and knee), lateral femoral epicondyle, lateral thigh (between knee and hip), anterior superior iliac spine and posterior superior iliac spine.

After the gait test, patients were scored on the UPDRS-III and the H&Y scale while still OFF medication. In addition, patients and controls were tested with the MMSE and the Montreal Cognitive Assessment scale (MoCA scale, appendix 7), tests of general cognitive profile.

Outcome variables

For both the between group comparison (between PD patients and HC), and the subgroup comparison (between freezers and non-freezers), we calculated spatiotemporal gait characteristics as previously described in other split-belt studies.[69,71]

Baseline tied-belt conditions

We compared the slow and fast baseline conditions using six outcome variables: stride length, variability of stride length, gait asymmetry (GA), cadence, step width and swing time percentage. The modified measure of stride length proposed by Reisman et al. for treadmill gait analysis was used.[71] Hence, stride length was defined as the anterior-posterior distance traveled by the ankle marker from foot contact to foot off of one leg.

To evaluate gait variability, the within-person coefficient of variation (CV) of stride length was calculated, by the method of Lord et al.[78] that was also used in other treadmill studies[76,79]:

$$CV = \frac{\text{standard deviation of stride length}}{\text{mean stride length}} \text{ x } 100\%$$

To assess asymmetry during baseline tied-belt conditions, we used the same formula as Yogev et al.[63]:

$$GA = |\ln (SSWT/LSWT)| \text{ x } 100\ \%$$

where GA refers to gait asymmetry, and SSWT and LSWT refer to short and long swing times, i.e. the averaged durations of the swing phases of the leg with the shortest and longest swing phases, respectively.

Cadence was defined as the number of steps per minute and step width as the mediolateral distance between the ankle markers on the lateral malleoli as measured at each foot contact. The percentage of the gait cycle each leg spent in swing was calculated as the swing time divided by the stride time and multiplied by 100 %.

Motor switching, adaptation and de-adaptation

To look at the immediate effect of motor switching, we calculated the first stride length and step width of the leg following the increase in belt speed. Since the increase in belt speed was delivered during the swing phase, the first stride started at the first foot contact of the fast leg after this increase.

We also explored the possible differences in adaptation and de-adaptation periods between patients and controls and between freezers and non-freezers. We defined early, mid and late adaptation and de-adaptation periods as the first, second and third block of 40 strides, respectively, of both adaptation and de-adaptation periods. The first stride of the early adaptation block was the second stride after the change in belt speed. To assess if the groups were able to adapt their gait pattern to the asymmetrical conditions, we measured step length symmetry as the main outcome measure, according to a different method than

outlined above for tied-belt conditions. This outcome measure has been suggested to be the most sensitive measure of adaptation in split-belt treadmill walking.[69,72] This symmetry index was defined by:

$$\text{Gait symmetry} = \frac{\text{fast step length} - \text{slow step length}}{\text{fast step length} + \text{slow step length}}$$

For adaptation periods, 'fast step length' and 'slow step length' refer to the step lengths of the legs on the fast and slow belts, respectively. Although the belts moved at the same speed during de-adaptation, the same formula was used where 'fast' and 'slow' refer to the belts with the higher and lower speed during the preceding adaptation period. Positive values indicate that the leg on the fast belt had a greater step length than the leg on the slow belt, and negative values indicate the opposite.

Statistical analysis

Outcome variables were calculated with custom made Matlab scripts (Matlab 2011b). Statistical analysis was then performed using Statistical Package for the Social Sciences (SPSS) version 19.0. By performing the Kolmogorov Smirnov's (KS) test for distribution analysis, we found all data to have normal distribution ($p > 0.05$). To compare demographic and clinical characteristics between PD patients and HC we used independent t-tests while for the subgroup comparisons (freezers versus non-freezers), Mann-Whitney non-parametric tests were applied.

Baseline tied-belt conditions

For the slow and fast tied-belt conditions, two-way repeated measures ANOVA was used to evaluate the interaction of group*speed (PD versus HC and 3 versus 4 km/h) and Tukey's Post hoc analysis to determine the differences between groups and between speeds. To compare freezers and non-freezers, Mann-Whitney non-parametric tests were applied and to compare speed conditions within these subgroups, Wilcoxon non-parametric tests were used.

Motor switching, adaptation and de-adaptation

The possible differences between legs were investigated with paired t-tests with Bonferroni corrections within PD and within HC and with Wilcoxon nonparametric tests within freezers and within non-freezers. The Bonferroni corrections were performed by dividing the significance level by the number of comparisons in order to avoid type I error as a result of multiple comparisons.

To compare the differences in motor switching (the first step after split-belt speed change), and also adaptation and de-adaptation pattern between PD patients and HC, independent t-tests with Bonferroni

corrections were used. To determine these differences between freezers and non-freezers, Mann-Whitney non-parametric tests were used.

To investigate the possible relationships between motor switching, disease severity and cognitive capacities, we calculated Spearman correlation coefficients between the first stride length and width following unilaterally increased speed on the one hand and UPDRS-III, the stability item of the UPDRS-III (retropulsion response to a sudden pull on the shoulders), and MoCA scores on the other.

Tied- versus split-belt conditions

Comparison between the stride length of motor switching and the mean stride length during the baseline 4 km/h tied-belt condition was made with paired t-tests with Bonferroni corrections in HC and in PD, and with Wilcoxon non-parametric tests in freezers and in non-freezers. These tests were carried out to examine whether or not the gait characteristics of motor switching were merely a result of the imposed higher speed.

Results

No patient or control subject fell during the testing and no subject grabbed the handrail although we observed more difficulties in maintaining balance among PD subjects during the experiment. During the testing, no FOG was elicited. One freezer and one non-freezer could not execute the walking task with treadmill speeds of 3 and 4 km/h, but were able to walk with a 2 and 3 km/h contrast. The same two subjects failed to prevent themselves from looking downwards, despite repeated instructions to keep looking ahead. To see if data were biased by these two subjects, analysis for all outcome measures was carried out with and without inclusion of these patients. This revealed that inclusion had no influence on the differences between PD and HC groups nor on the differences between freezer and non-freezer groups and elicited no outlier values (> 2*SD). Therefore, results of these two subjects were included in the analysis.

Demographic and clinical characteristics

A description of the demographic and clinical characteristics of the participants is provided in Table 1. Both the freezer and the non-freezer group consisted of 4 males and 2 females. The control group included 5 males and 5 females. There was no significant difference between PD patients and controls for all demographic and clinical measures: age, height, weight, and cognitive status (measured with MMSE and MoCA) ($p > 0.05$). Moreover, there was no significant difference in height, weight, disease duration, disease severity (measured with UPDRS-III in off-medication state), and cognitive status (measured with MMSE and MoCA) between freezers and non-freezers ($p > 0.05$). Although UPDRS-III scores indicated equal disease severity, H&Y scores differed (3.0 for freezers versus 2.3 for non-freezers, $p = 0.02$). Mean age of freezers on the other hand was lower than that of non-freezers (61.0 ± 4.6 years versus 68.5 ± 3.4 years, $p = 0.02$).

Comparison between the legs

Comparing the outcomes of the most and the least affected legs of PD patients (determined by comparing UPDRS-III scores for left and right legs), we found only a significant difference for the stride length of the first stride of motor switching: the most affected leg of patients took a shorter stride ($p < 0.05$). For all other comparisons, there was no significant difference in any outcome measure between both legs of patients. In the control group the dominant and non-dominant legs (expressing hemisphere dominance) were not significantly different in any of the conditions. Therefore, we only reported the measures of the most affected leg in PD and the non-dominant leg of controls, except for the results of the motor switching stride.

Baseline tied-belt conditions

A comparison between groups for the slow and fast baseline conditions is presented in Table 2. For the comparison between PD and HC, two-way repeated measures ANOVA revealed significant interaction effects of group by speed for stride length, CV of stride length, GA and cadence ($p < 0.001$, see Fig. 3), but not for step width and swing time percentage ($p > 0.05$). While healthy subjects only increased their stride length when confronted with the faster treadmill speed (increase from 59.3 ± 1.1 cm to 74.4 ± 1.9 cm, $p = 0.005$) and non-significantly decreased their cadence (from 62.2 ± 2.2 to 60.5 ± 1.2 steps per minute, $p = 0.740$), the PD group responded by increasing their stride length to a lesser extent than HC (from 48.1 ± 4.5 cm to 57.0 ± 5.6 cm, $p = 0.02$) and by clearly increasing their cadence (from 75.0 ± 6.2 to 87.7 ± 9.9 steps per minute, $p = 0.002$). Additionally, Figure 3B and 3C reveal that PD patients significantly increased their stride length variability (i.e. CV of stride length) and GA when confronted with the higher speed condition while these spatiotemporal variables remained unchanged in HC. In the PD group, both freezers and non-freezers displayed this same locomotor strategy of increase in all variables apart from swing time percentage.

Post hoc analysis showed that all six outcome variables were significantly different between PD patients and HC in both speed conditions (Table 2 and Fig. 3): PD patients had significantly shorter stride length, higher CV of stride length, higher GA, higher cadence, larger step width and lower swing time percentage (all p values < 0.001). These differences were less apparent between freezers and non-freezers. Still, in both baseline conditions, freezers had higher GA ($p = 0.004$ for 3 km/h and $p = 0.006$ for 4 km/h), wider steps ($p = 0.002$ for both 3 km/h and 4 km/h) and lower swing time percentage compared to non-freezers. In the fast baseline condition, the freezer group had shorter strides than the non-freezer group almost reaching significance ($p = 0.07$).

Motor switching

Data of the first stride following motor switching are provided in Table 3.1 and 3.2. Table 3.1 shows differences between the two limbs of patients and controls, when walking on the fast belt. For both freezers and non-freezers, the stride length of the most disease-affected leg was significantly shorter when confronted with the fast belt compared with the stride length of the least affected leg while that leg was on the fast belt ($p = 0.020$ for freezers and $p = 0.030$ for non-freezers). Step width did not differ between the legs ($p = 0.110$ for freezers and $p = 0.290$ for non-freezers). In controls, we found no difference between the dominant and the non-dominant leg ($p > 0.05$). For all comparisons between groups and subgroups however, results were not influenced by differences between legs. In Table 3.2 it can be seen that stride length and step width were significantly different for both the comparisons between patients' most affected and controls' non-dominant legs, and between patients' least affected and controls' dominant legs ($p < 0.05$). PD patients took significantly shorter and wider first strides

compared with HC during motor switching. Subgroup analysis showed that this pattern was exaggerated in freezers, i.e. they took shorter and wider strides than non-freezers ($p < 0.05$). Comparing the stride length of motor switching with the mean stride length during the baseline 4 km/h tied-belt condition revealed a significant difference for all groups ($p = 0.000$ for PD patients and HC, $p = 0.012$ for most affected leg of freezers, $p = 0.019$ for least affected leg of freezers, $p = 0.028$ for most affected leg of non-freezers, $p = 0.029$ for least affected leg of non-freezers).

For PD patients, a moderately strong correlation was found between the stability item of the UPDRS-III and the stride length and step width of the first stride following motor switching (Spearman's ρ: -0.627 for stride length and 0.628 for step width, both p values = 0.029). Thus, patients scoring worse on the stability item of the UPDRS-III took smaller first strides with a greater step width. Total UPDRS-III and MoCA scores showed no significant correlation with these first stride characteristics ($p > 0.05$).

Adaptation and de-adaptation periods

A step-by-step graphical representation of step length symmetry data during the adaptation and de-adaptation periods is provided in Figure 4. Statistical comparison of the mean data for early, mid and late periods of adaptation and de-adaptation are presented in Table 4. The data reveal that PD patients were able to adapt and de-adapt to split-belt treadmill walking although they showed a greater asymmetry in step length than their healthy counterparts throughout the whole adaptation and de-adaptation periods ($p < 0.001$). Moreover, freezers showed worse results compared to non-freezers: their gait was more asymmetrical ($p = 0.02$ for early and late adaptation periods and $p = 0.01$ for mid adaptation and all de-adaptation periods). During adaptation, the level of asymmetry, that was substantially increased by the split-belt perturbation, gradually decreased towards a more symmetrical pattern at the end of the two minutes of split-belt condition for both patients and controls. At the start of de-adaptation, symmetry was lost and during de-adaptation it also showed gradual recovery. Thus, both patients and controls showed after-effects during de-adaptation periods, indicative of motor learning. Figure 4 shows that patients with PD seem to adapt more slowly than HC subjects during the first 10 strides of the early adaptation period, i.e. the first 10 strides after motor switching. The analysis was repeated after correction for baseline asymmetry between the groups and the same results were found.

Table 1. Demographic and clinical characteristics of participants

Group	#	Male/Female	Age (yrs)[a]	Height (cm)[a]	Weight (kg)[a]	Disease duration (yrs)[a]	UPDRS-III [a,b]	H&Y [a,b]	MMSE [a,b]	MoCA [a,b]
PD	12	8/4	64.8 ± 5.5	169.4 ± 7.2	73.3 ± 13.5	13.3 ± 5.6	37.8 ± 9.9	2.7 ± 0.5	28.1 ± 1.3	27.3 ± 1.2
HC	10	5/5	64.0 ± 5.3	170.5 ± 8.9	67.9 ± 8.7	–	–	–	28.8 ± 0.9	27.4 ± 1.2
p value [c]	–	–	0.75	0.29	0.76	–	–	–	0.16	0.77
FR	6	4/2	61.0 ± 4.6	170.2 ± 6.1	74.7 ± 16.9	15.3 ± 6.3	38.5 ± 9.7	3.0 ± 0.0	28.5 ± 0.8	27.7 ± 1.0
nFR	6	4/2	68.5 ± 3.4	168.7 ± 8.7	72.0 ± 10.5	11.3 ± 4.3	37.0 ± 11.0	2.3 ± 0.5	27.7 ± 1.6	26.8 ± 1.3
p value [c]	–	–	0.02	0.82	0.59	0.34	0.94	0.02	0.39	0.31

[a] Data reported as mean values ± SD.

[b] Scores on UPDRS-III, H&Y, MMSE (maximum score is 30), and MoCA (maximum score is 30) were determined in the OFF medication state.

[c] Independent t-tests for comparison between PD and HC and Mann-Whitney non-parametric tests for comparison between FR and nFR groups.

#, number of participants; yrs, years; UPDRS-III, Unified Parkinson's Disease Rating Scale part III; H&Y, Hoehn and Yahr stage; MMSE, Mini Mental State Examination; MoCA, Montreal Cognitive Assessment; HC, healthy controls; FR, freezers; nFR, non-freezers.

Table 2. Slow (3 km/h) and fast (4 km/h) baseline conditions

Condition	Outcome variable		**PD**	**HC**	p value [a]	**FR**	**nFR**	p value [b]
3 km/h	**Stride length (cm)**		47.3 ± 3.7	59.3 ± 1.0	0.000**	46.0 ± 4.8	48.6 ± 1.9	0.59
4 km/h	**Stride length (cm)**		57.0 ± 5.6	74.4 ± 1.4	0.000**	56.4 ± 8.3	57.5 ± 0.7	0.07
		p value [c]	0.02*	0.005**		0.03*	0.03*	
3 km/h	**CV Stride length (%)**		6.9 ± 1.1	3.5 ± 0.6	0.000**	7.2 ± 1.5	6.5 ± 0.5	0.18
4 km/h	**CV Stride length (%)**		7.8 ± 1.5	3.5 ± 0.6	0.000**	8.0 ± 2.1	7.5 ± 0.5	0.18
		p value [c]	0.001**	0.92		0.04*	0.01*	
3 km/h	**Gait asymmetry (%)**		2.8 ± 0.6	1.2 ± 0.1	0.000**	3.4 ± 0.2	2.2 ± 0.4	0.004**
4 km/h	**Gait asymmetry (%)**		3.1 ± 0.6	1.2 ± 0.1	0.000**	3.7 ± 0.3	2.6 ± 0.4	0.006**
		p value [c]	0.03*	0.99		0.04*	0.03*	
3 km/h	**Cadence (steps.min^{-1})**		75.2 ± 2.2	62.0 ± 0.5	0.000**	76.1 ± 2.3	74.3 ± 1.8	0.20
4 km/h	**Cadence (steps.min^{-1})**		87.4 ± 2.6	60.6 ± 0.5	0.000**	88.8 ± 1.6	86.1 ± 2.8	0.078
		p value [c]	0.002**	0.74		0.03*	0.03*	
3 km/h	**Step width (cm)**		32.1 ± 1.0	29.7 ± 0.5	0.000**	32.8 ± 0.6	31.4 ±0.9	0.002**
4 km/h	**Step width (cm)**		32.6 ± 0.9	29.9 ± 0.5	0.000**	33.3 ± 0.5	31.8 ± 0.1	0.002**
		p value [c]	0.002**	0.55		0.03*	0.03*	
3 km/h	**Swing percentage (%)**		32.3 ± 1.2	35.1 ± 0.5	0.000**	31.8 ± 1.2	32.8 ± 1.1	0.041*
4 km/h	**Swing percentage (%)**		32.6 ± 1.3	35.3 ± 0.4	0.000**	32.0 ± 1.1	33.3 ± 1.2	0.041*
		p value [c]	0.44	0.56		0.47	0.31	

Data are reported as mean values ± SD for the most affected leg of PD patients and the non-dominant leg of HC.

[a] Tukey's Post hoc analysis between group comparison. [b] Mann-Whitney non-parametric tests.

[c] Tukey's Post hoc analysis within PD and HC groups, Wilcoxon non-parametric tests within FR and nFR groups.

** significant at 0.010 level, * significant at 0.050 level.

Gait asymmetry = |ln (SSWT/LSWT)| x 100 %.

PD, Parkinson's disease; HC, healthy controls; FR, freezers; nFR, non-freezers; CV, coefficient of variation.

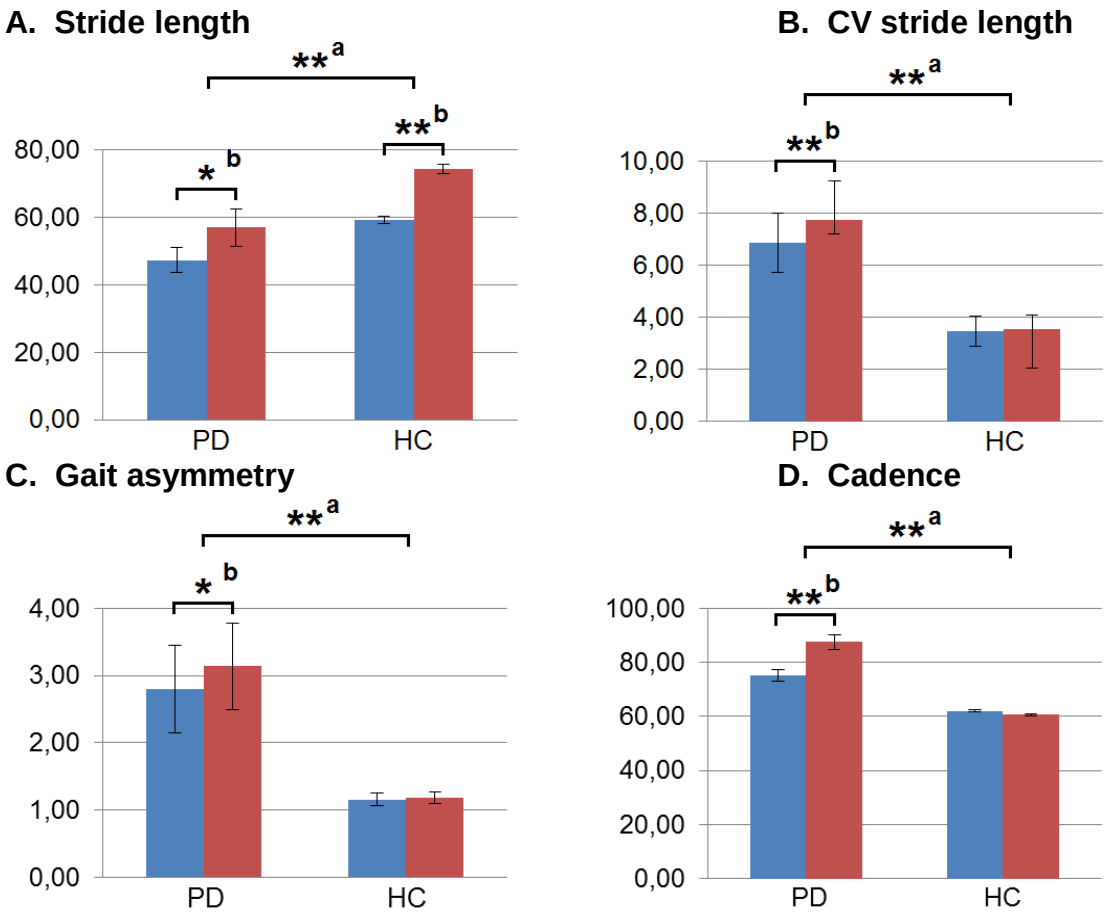

Fig. 3. Comparison of mean values between the most affected leg of PD patients and the non-dominant leg of HC in the slow (3 km/h) and fast (4 km/h) baseline conditions.
Error bars represent standard error of the mean.
[a] Two-way repeated measures ANOVA interaction effect, all p values < 0.001.
[b] Tukey's Post hoc analysis within PD and HC groups.
** significant at 0.010 level, * significant at 0.050 level.
CV, coefficient of variation; PD, Parkinson's disease; HC, healthy controls.

Table 3.1 Differences between legs during first stride of motor switching

Outcome variable	PD Most affected	PD Least affected	p value [a]	FR Most affected	FR Least affected	p value [b]
Stride length (cm)	43.0 ± 3.6	45.8 ± 3.1	0.002**	40.2 ± 3.0	43.9 ± 3.3	0.02*
Step width (cm)	33.1 ± 1.0	32.6 ± 1.0	0.06	33.4 ± 0.8	33.6 ± 0.5	0.11
	HC Non-dominant	HC dominant	p value [a]	nFR Most affected	nFR Least affected	p value [b]
Stride length (cm)	59.2 ± 1.0	58.4 ± 3.1	0.07	45.8 ± 0.9	47.8 ± 0.6	0.03*
Step width (cm)	28.8 ± 0.5	29.7 ± 0.5	0.15	32.2 ± 0.2	31.9 ± 0.1	0.29

Data reported as mean values ± SD.
[a] Paired t-tests with Bonferroni corrections, significance level is 0.050/4 = 0.01. [b] Wilcoxon non-parametric tests.
** significant at 0.010 level, * significant at 0.050 level.
PD, Parkinson's disease; HC, healthy controls; FR, freezers; nFR, non-freezers.

Table 3.2 First stride of motor switching

Outcome variable	PD Least affected	HC dominant	p value [a]	FR Least affected	nFR Least affected	p value [b]
Stride length (cm)	45.8 ± 3.1	58.4 ± 3.1	< 0.001**	43.9 ± 3.3	47.8 ± 0.6	0.004**
Step width (cm)	32.6 ± 1.0	29.7 ± 0.5	< 0.001**	33.4 ± 0.8	31.9 ± 0.1	0.005**
	PD Most affected	HC Non-dominant	p value [a]	FR Most affected	nFR Most affected	p value [b]
Stride length (cm)	43.0 ± 3.6	59.2 ± 1.0	< 0.001**	40.2 ± 3.0	45.8 ± 0.9	0.004**
Step width (cm)	33.1 ± 1.0	28.8 ± 0.5	< 0.001**	34.0 ± 0.5	32.2 ± 0.2	0.004**

Data reported as mean values ± SD.
[a] Independent t-tests with Bonferroni corrections, significance level is 0.05/4 = 0.01. [b] Mann-Whitney non-parametric tests.
** significant at 0.010 level
PD, Parkinson's disease; HC, healthy controls; FR, freezers; nFR, non-freezers.

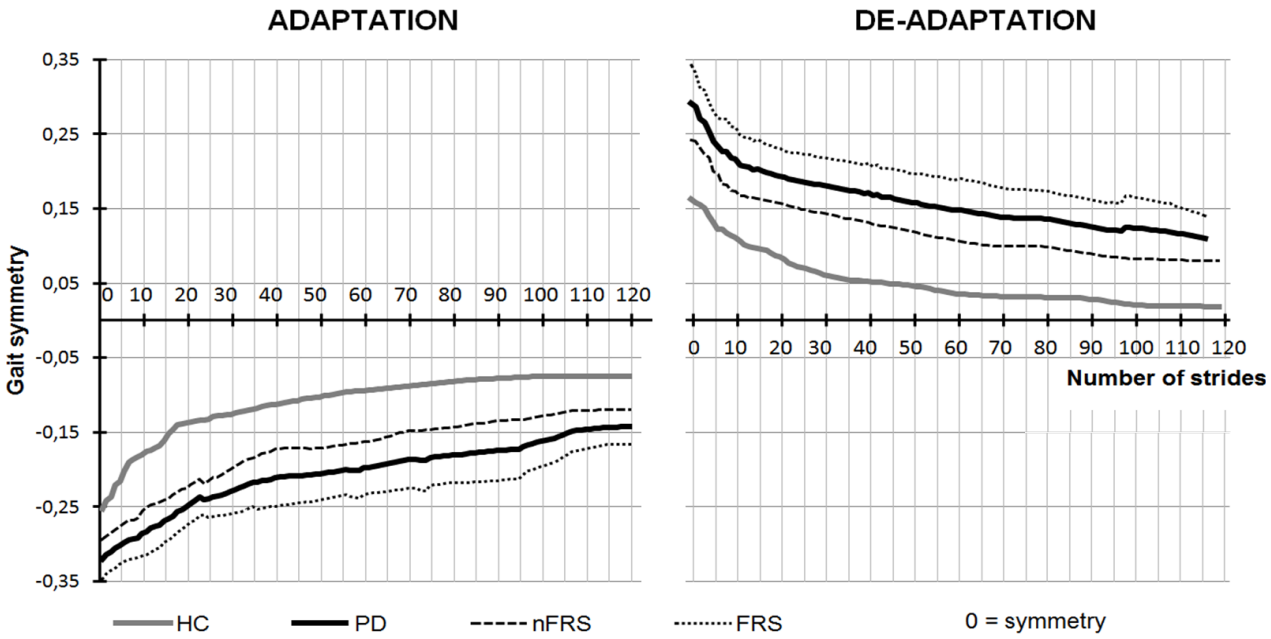

Fig. 4. Adaptation and de-adaptation of gait symmetry.

Data represent the adaptation conditions in which the most affected leg of PD patients and the non-dominant leg of HC was on the fast belt and the de-adaptation conditions following these adaptation conditions. On the X-axis the number of strides are indicated, the Y-axis represents gait symmetry (ratio, no unit).

$$\text{Gait symmetry} = \frac{\text{fast step length} - \text{slow step length}}{\text{fast step length} + \text{slow step length}}$$

Positive values indicate that the leg on the fast belt had the greatest step length, negative values indicate the opposite.

Table 4. Adaptation (split-belt) and de-adaptation (tied-belt) periods

Gait symmetry	PD	HC	p value [a]	FR	nFR	p value [b]
Early adaptation	-0.26	-0.15	< 0.001	-0.28	-0.23	0.02*
Mid adaptation	-0.20	-0.9	< 0.001	-0.23	-0.16	0.01**
Late adaptation	-0.16	-0.8	< 0.001	-0.19	-0.13	0.02*
Early de-adaptation	0.20	0.9	< 0.001	0.24	0.17	0.01**
Mid de-adaptation	0.15	0.4	< 0.001	0.19	0.11	0.01**
Late de-adaptation	0.12	0.2	< 0.001	0.16	0.9	0.01**

Mean data of the most affected leg of PD patients and the non-dominant leg of HC are reported.
Positive values indicate that the leg on the fast belt had the greatest step length, negative values indicate the opposite.
Early adaptation was defined as the first block of 40 strides after the onset of the perturbation, mid and late adaptation as the second and third block of 40 strides, respectively. For de-adaptation analogous definitions were used.
[a] Independent t-tests with Bonferroni corrections, significance level is 0.050/6 = 0.008.
[b] Mann-Whitney Non-parametric tests.
** significant at 0.010 level
PD, Parkinson's disease; HC, healthy controls; FR, freezers; nFR, non-freezers.

Discussion

In this study we investigated the effects of imposing asymmetry on the gait pattern of patients with PD using a split-belt paradigm. We were also interested in how gait asymmetry and gait adaptation differed in patients with and without FOG. Generally our findings indicate particular difficulties in treadmill walking at high speeds and in asymmetrical conditions (with split belts) for patients with PD. These difficulties were exaggerated in the subgroup of freezers.

Baseline tied-belt performance of PD patients

All comparisons of kinematic variables of PD patients versus HC revealed significant differences, meaning that the PD gait pattern could be distinguished from that of controls despite the fact that they walked on a treadmill which could have had a normalizing effect on gait. These findings may be ascribed to the fact that the experiment was conducted off-medication. In line with previous work, PD patients displayed several decrements in their gait performance during the slow (3 km/h) baseline condition. Compared to controls, they had a more asymmetrical gait, a shorter stride length that was less consistent (higher CV), a higher cadence, a greater step width, and a lower swing time percentage (all p values < 0.001). In the fast baseline condition, with tied belts moving at 4 km/h, the gait pattern of the patient group compared to that of their healthy counterparts was even worse regarding these parameters (two-way repeated measures ANOVA, $p < 0.001$) except for step width and swing time percentage. Note that stride length of the PD group was higher in the 4 km/h condition compared to the 3 km/h condition, as in the HC, but that the difference in stride length between PD and HC groups became greater as revealed by the significant interaction effect. Thus, while HC simply reacted to the higher speed by mainly increasing their stride length, PD patients showed less increase of stride length and an overall deterioration of their gait. Two patients were not able to walk with treadmill speeds of 3 and 4 km/h, that were chosen after pilot testing. For these patients, the experimental conditions were adapted to 2 and 3 km/h. This may indicate that PD patients with moderate disease severity have a lower upper limit of possible (split-belt) treadmill speeds than healthy subjects do, at least in the off state of anti-Parkinson medication.

The recent split-belt treadmill study of Nanhoe-Mahabier et al.[74] found for tied-belt walking a difference between PD patients and healthy subjects only for stride length asymmetry but not for stride length or stride length variability. Several differences between this study and the present work should be taken into account when comparing results. Our measure of asymmetry was based on swing times instead of stride lengths. Moreover, we used the modified definition of step and stride length for treadmill gait analysis[71] instead of the common definition for overground walking, which may have been used by Nanhoe-Mahabier et al., although this is not clarified in the paper. As a result, all measures that were used in the

present study are different from the measures used by Nanhoe-Mahabier et al. Besides the differences in outcome measures, the speed conditions were also higher in our study (3 and 4 km/h versus 2 and 3 km/h). Finally, our sample of PD patients had a more severe disease profile as evidenced by a UPDRS-III score of about 10 points higher and a disease duration of about 6 years longer.

Deficits in maintaining symmetry in tied- and split-belt walking

Our results provide strong support for the link between PD and locomotor asymmetry. During both baseline conditions (symmetrical conditions), the patient group walked with significantly higher swing time asymmetry values compared to the control group ($p = 0.000$). Furthermore, the asymmetrical locomotor task proved to be more challenging for PD patients than for HC. They had a significantly decreased stride length and increased step width of the first stride of motor switching ($p < 0.001$), and a greater step length asymmetry at the start of the adaptation period ($p < 0.001$ for the early adaptation period). When comparing the first stride length of motor switching with the first stride length of the baseline 4 km/h tied-belt condition, a significant difference was also found ($p = 0.000$), indicating that the shorter stride length was not simply a result of the higher speed per se, but instead seemed to be a result of the asymmetry itself. The fact that patients shortened their stride length and increased their step width would suggest that asymmetrical gait imposed a balance challenge as well as a gait pattern disturbance. During the two minutes of the adaptation phase after the switch to spilt belts, patients never reached the same symmetry level of the HC ($p < 0.001$). When the belts became tied again (i.e. at the beginning of the de-adaptation period), the size of the after-effect was also greater for the PD group compared to the HC ($p < 0.001$ for the early de-adaptation period), but in the opposite direction as during adaptation. These findings on split-belt walking revealed that besides their marked gait asymmetry, PD patients also showed impaired abilities to minimize the perturbing effects of sudden imposed asymmetry or the sudden return to symmetry. Our results highlighted gait differences between PD patients and HC that were not observed in the study of Nanhoe-Mahabier et al.[74], which showed no difference in stride length asymmetry between PD patients and healthy subjects. The same methodological differences as mentioned for tied-belt walking could explain these contrasting findings, as well as the fact that we compared longer periods of split-belt walking and did not exclude the first 30 seconds from the analysis.

As in a previous split-belt study in young and older adults, walking on a treadmill with split belts was possible for healthy people even without completely adapting step lengths accordingly.[80] In this study, 3 possible reasons for incomplete adaptation were discussed, some of which can probably be applied to PD as well. First, PD patients could have had an incorrect proprioception of the error caused by the asymmetrical belts (as well as the error caused by a return of symmetry after being more or less adapted). This could explain the greater asymmetry at which they start both the adaptation and de-adaptation periods and the greater asymmetry throughout the rest of the adaptation and de-adaptation phases.

Second, their ability to restore symmetry of step lengths (i.e. changing parameters of locomotion) might be impaired. This may be related to an impaired scaling of amplitude which has been found to be characteristic of PD[81] and which is supported by the fact that the most affected side also showed more difficulties with adaptation. Nevertheless, during adaptation and de-adaptation periods, the patients clearly showed that they were able to reverse the left-right asymmetry of step lengths. Therefore, this hypothesis is not likely for PD patients. Third, strategic considerations could play a role since the disadvantages of adapting might be greater than the advantages. Such disadvantages could be that adaptation would require extra postural control, supraspinal involvement, or muscular effort to maintain gait.

Importantly, our results of adaptation and de-adaptation show that PD patients were still able to completely reverse the asymmetrical nature of their gait pattern (see Fig. 4). This indicates that the spatial asymmetry of PD patients' gait is not caused by an inability to create equal step lengths per se. Dietz et al. reported that PD patients could adapt their muscle activity to split-belt walking but that they also showed more co-activation and a reduced gastrocnemius muscle activity.[73] The authors suggested that these changes could be caused by an impaired proprioceptive feedback from the muscles. In the current study we did not test patients' proprioceptive ability. Some studies[82,83] suggest that in PD there are greater proprioceptive integration difficulties, particularly in freezers. Future research should be aimed to unravel whether a greater lack of sensory awareness may have contributed to the differences between PD and HC.

As mentioned above, side-differences of motor symptoms (as measured with UPDRS-III) were only apparent in the stride length of motor switching. On average, the most affected leg took a significantly shorter motor switching stride than the least affected one ($p = 0.002$), while all other spatiotemporal variables did not differ as a function of disease dominance. If a link between asymmetry of gait and asymmetry of motor symptoms exists, it seemed to have only a minor impact from the results of this study. This is in agreement with Spildooren et al.[84] (during turning), Nanhoe-Mahabier et al.[74] (during tied- and split-belt walking) and Plotnik et al.[36] (during overground walking), all of whom found no relation between disease dominance and gait asymmetry.

Freezing as an ultimate gait disturbance?

We analyzed gait characteristics between the subgroups of freezers and non-freezers. For baseline conditions, some gait impairments that were found in PD in general proved to be more pronounced in those with FOG. These were a greater temporal gait asymmetry ($p = 0.004$ for 3 km/h and $p = 0.006$ for 4 km/h), a decreased swing time percentage ($p = 0.041$ for 3 and 4 km/h), and an increased step width ($p = 0.002$ for 3 and 4 km/h). Most of these results are in agreement with previous findings. A recent study of

treadmill walking found an association between gait asymmetry and the FOG questionnaire in freezers.[85] The higher swing time asymmetry found in the present study is in agreement with the results of Plotnik et al.[36], using the same measure during overground walking. A study of Hackney et al.[10] also found lower swing time percentages for freezers compared to non-freezers but similar heel-to-heel base of support during overground walking. The fact that we found a difference in step width between subgroups could be due to the additional challenge of walking on a treadmill. In our study, stride length tended to be shorter for freezers compared to non-freezers during the 4 km/h baseline condition, although not significantly ($p = 0.07$). In a larger sample, this difference might be more apparent. However, from our results it seemed that freezers and non-freezers had the same strategy of changing gait parameters when confronted with a higher treadmill speed. As such, we did not find that freezers were driven towards an episode of FOG by increasing the treadmill speed from 3 to 4 km/h. The threshold hypothesis, put forward by Plotnik et al.[34], would have predicted this.

During split-belt conditions, freezers also performed worse than their non-freezing counterparts. Their shorter stride length and greater step width at the point of motor switching and the observation of greater asymmetry during adaptation and de-adaptation may indicate that deficits in dealing with asymmetrical locomotor tasks accumulated in those with FOG. This finding is particularly striking in the light of a small sample of patients of similar disease severity, pointing to a FOG-specific deficit. Courtine and Schieppati argued that split-belt locomotion resembles turning because it induces asymmetry of stride length and asymmetry of the relative duration of stance and swing.[86] Although treadmill walking is not completely comparable to overground walking, the problems with split-belt locomotion for freezers observed in this study point to similar mechanisms at play during asymmetry-related difficulties in turning for PD patients and especially for freezers.

The study of Nanhoe-Mahabier et al.[74] in contrast found no significant difference between freezers and non-freezers during tied-belt walking and no difference between these groups in split-belt walking for spatial outcome measures. This study did find however that freezers had a higher stride time asymmetry and variability during split-belt treadmill walking.

The same differences between the study of Nanhoe-Mahabier and the present study that are described above for the comparisons between PD patients and HC can possibly explain the discrepancy in findings in comparing freezers with non-freezers (differences in the definition of stride and step length, the formula of asymmetry, belt speeds, disease severity, disease duration, and analysis of longer adaptation and de-adaptation periods).

FOG itself was not elicited but we think this could be possible by further challenging the ability of patients to switch their locomotor pattern, for example by adding an attention-demanding dual task as was done during turning in an earlier study.[28] It was previously found that dual tasking impairs split-belt

walking in healthy adults.[87] Our findings of progressive gait decrements from healthy to Parkinson-affected and from non-freezers to freezers could, theoretically, be consistent with the hypothesis of a threshold for FOG as proposed by Plotnik et al.[34] However, because no FOG-episodes were apparent we do not have direct evidence to support this. If the hypothesis is true, we expect in future studies that FOG-episodes will come to the fore after a number of steps in the adaptation phase, particularly when patients show impaired locomotor adaptation.

Capability for split-belt adaptation is altered

This is the first study to demonstrate that PD patients show adaptation of step length symmetry during asymmetrical walking on a split-belt treadmill. Nevertheless, they never reached the symmetry level of the HC. The observation that PD patients performed worse than HC could indicate that brain structures that are damaged in PD are involved in adaptation to an asymmetrical environment in the healthy brain. When visually analyzing the curve of adaptation, it seemed that during approximately the first 10 strides patients adapted more slowly than their healthy counterparts. Future studies need to undertake curve analysis of the slopes to statistically confirm this finding. We also found that split-belt adaptation and de-adaptation were worse in freezers. Quite apart from the occurrence of FOG-episodes, this is an important finding. It may signify that freezers have more difficulty with adapting locomotion to daily circumstances making them more vulnerable to falling. This coincides with recent findings that FOG is a predictor of falling.[4] The impairments that we found in adaptation and de-adaptation could, to some extent, be due to the cognitive requirements of asymmetrical split-belt perturbations[87] since PD affects both automaticity and executive functioning. This line of reasoning must be further investigated, for example in a dual-task paradigm.

The ability of PD patients to adapt their step length asymmetry was, however, not totally lost. Cerebellar patients showed more marked difficulties in adapting to split-belt walking.[72] Although in PD some changes of cerebellar function were observed[88], our results suggest that basal ganglia damage in PD patients with moderate disease severity does not totally preclude locomotor adaptation to a split-belt treadmill.

Postural control

Although we did not directly measure postural control during treadmill walking, a few findings together could point to PD-related problems in keeping dynamic stability during functional walking and more so in freezers compared to non-freezers. Results show an increased step width, decreased swing time percentage and increased stride length variability compared to healthy subjects during baseline tied-belt walking (all p values = 0.000). Motor switching caused a decreased stride length and a wider step width not only when compared with HC ($p < 0.001$), but also in comparison to the 4 km/h tied-belt condition (p

= 0.000). Adaptation and de-adaptation conditions resulted in higher step length asymmetry for PD patients compared to HC. In freezers, most of these decrements were more profound. Furthermore, a correlation was found between the stability item of the UPDRS-III (response to a sudden pull) and characteristics of the first motor switching stride (ρ = -0.627 for stride length and ρ = 0.628 for step width, both p values = 0.029). In older adults, step width and step length asymmetry have been found to determine the postural control domain of gait[89] and both swing time percentage and variability of stride length are related to falls.[90,91] In PD, stride time variability was also related to falls.[5]

Limitations and future studies

A few limitations of the present study can be considered. First, our subgroups of freezers and non-freezers had a low number of subjects. Therefore, some differences between patients with and without FOG may have been masked. A second limitation was that we could have analyzed the adaptation and de-adaptation periods more extensively. We did analyse an important measure of adaptation, step length asymmetry, but chose not to evaluate intralimb parameters such as swing time proportion and stride length during adaptation and de-adaptation periods. These variables are known to reflect feedback mechanisms of gait and probably do not require supraspinal control.[69] We therefore reasoned that they are not likely to be impaired in PD but it is, however, theoretically possible that they are altered since central nervous system degenerations are widespread in PD. In future research, intralimb parameters could be included as well as a statistical analysis of the slopes of the adaptation and de-adaptation graphs. A third limitation concerns the underlying cause of differences in the level of asymmetry between groups and subgroups during split-belt walking. As mentioned, there are at least three hypothetical causes including impaired proprioception, inability to change locomotor parameters, and strategic considerations. Proprioceptive differences between groups could for example be tested in future experiments by asking patients which belt goes faster and by comparing the response times.

Based on our findings, it seems worthwhile to investigate the use of asymmetrical treadmill training as a rehabilitation strategy for PD patients with marked locomotor asymmetry. A recent study reported a beneficial effect of treadmill training with auditory and visual cues on temporal gait asymmetry in a sample of 60 PD patients.[85] By using a split-belt treadmill, this learning process might be accelerated. We found that it is possible for PD patients to completely reverse their step length asymmetry from one side to the other and previous research in stroke survivors has indicated transfer of adaptation effects from split-belt treadmill walking to overground walking.[92,93]

Future studies with larger samples may confirm our results and could further challenge walking abilities for example by adding an attention-demanding dual task. By loading cognitive resources, gait deficits could become more pronounced because of interference between executive networks and because of the

decreased possibility to use compensatory mechanisms. FOG could also be further investigated by correlating between freezing severity and asymmetry or adaptation parameters in a larger sample. Also, our results add to the existing evidence on gait impairments in freezers outside of FOG episodes, indicating the importance of subgroup analysis when investigating gait deficits of PD patients.

In conclusion, our results show that patients with PD have difficulties in producing a symmetrical and efficient gait pattern, especially when they are challenged by an asymmetrical demand on locomotion and when FOG is a part of their disease. Both an increase in speed and a difference in speed of the belts proved difficult for PD patients. Importantly, we found that PD patients were not able to adapt their gait pattern to a split-belt treadmill as well as healthy subjects, probably because of deficits in proprioception or impaired supraspinal control. However, patients with PD can change their step lengths and even reverse their step length asymmetry on a split-belt treadmill. From a rehabilitation perspective, it is therefore interesting that split-belt treadmill training can possibly enhance normalization of asymmetry. Our results in freezers specifically point to the accumulation of impairments when trying to achieve symmetry, rather than overall accumulating gait decrements. It is likely that turning during overground walking results in impaired gait and episodes of freezing due to similar demands of asymmetry as imposed by a split-belt treadmill. Finally, a possible link between gait asymmetry and general motor asymmetry seems weak. Future studies need to further clarify the relative contributions of proprioception, postural control and cognitive resources to difficulties that PD patients, and freezers in particular, experience in maintaining symmetry under asymmetrical conditions.

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Appendices

Appendix 1. UK PD Brain Bank Criteria

Step 1. Diagnosis of Parkinsonian Syndrome

- Bradykinesia
- At least one of the following
    - Muscular rigidity
    - 4-6 Hz rest tremor
    - postural instability not caused by primary visual, vestibular, cerebellar, or proprioceptive dysfunction

Step 2 Exclusion criteria for Parkinson's disease

- history of repeated strokes with stepwise progression of parkinsonian features
- history of repeated head injury
- history of definite encephalitis
- oculogyric crises
- neuroleptic treatment at onset of symptoms
- more than one affected relative
- sustained remission
- strictly unilateral features after 3 years
- supranuclear gaze palsy
- cerebellar signs
- early severe autonomic involvement
- early severe dementia with disturbances of memory, language, and praxis
- Babinski sign
- presence of cerebral tumor or communication hydrocephalus on imaging study
- negative response to large doses of levodopa in absence of malabsorption
- MPTP exposure

Step 3 supportive prospective positive criteria for Parkinson's disease

Three or more required for diagnosis of definite Parkinson's disease in combination with step one

- Unilateral onset
- Rest tremor present
- Progressive disorder
- Persistent asymmetry affecting side of onset most
- Excellent response (70-100%) to levodopa
- Severe levodopa-induced chorea
- Levodopa response for 5 years or more
- Clinical course of ten years or more

Appendix 2. Hoehn & Yahr (H&Y) scale

Stage 0	Asymptomatic
Stage 1	Unilateral involvement only usually with minimal or no functional disability
Stage 2	Bilateral or midline involvement without impairment of balance
Stage 3	Bilateral disease: mild to moderate disability with impaired postural reflexes; physically independent
Stage 4	Severely disabling disease; still able to walk or stand unassisted
Stage 5	Confinement to bed or wheelchair unless aided

Appendix 3. Mini Mental State Examination (MMSE), Dutch version

Patiënt:	Datum:
Onderzoeker:	Score: /30

1. Oriëntatie in tijd en ruimte

- **Wat is de volledige datum van vandaag?**

1.1. Tijd: Ken 1 punt per correct antwoord toe (score: 0-5)

- **In welk jaartal zijn we?** Jaartal ☐
- **In welk seizoen zijn we?** Seizoen ☐
- **In welke maand zijn we?** Maand ☐
- **Welke dag is het vandaag?** Dag ☐
- **De hoeveelste is het vandaag?** Datum ☐

1.2. Ruimte: (score 0-5)

- **In welk land leven wij?** Land ☐
- **In welke provincie zijn we?** Provincie ☐
- **In welk(e) stad/dorp zijn we?** Stad ☐
- **In welk hospitaal/centrum bent u?** *of* **Hoe is mijn naam?** Centrum ☐
- **Op welke verdieping bent u?** Verdieping ☐

2. Inprentingsvermogen

- **Ik noem drie woorden. Als ik ze gezegd heb, moet u ze alle drie herhalen.**
  Lees de woorden voor aan 1 woord per seconde. Laat ze daarna herhalen en noteer elk correct woord. (1 punt voor elk correct antwoord – score 0-3)
- **Sigaar** Sigaar ☐
- **Bloem** Bloem ☐
- **Deur** Deur ☐

Als de patiënt ze niet correct herhaalt, zeg ze dan opnieuw voor en herhaal tot 6 maal.
Tel hier echter géén punten voor. Aantal pogingen: ☐
Onthoud deze woorden goed, want ik ga ze u straks nog eens vragen.

3. Aandacht

A. Wilt u van het getal 100, 7 aftrekken?
Van de uitkomst trekt u dan telkens weer 7 af en zo verder tot ik "stop" zeg.
Elke juiste aftrekking levert 1 punt op (vb. 93, 87, 80, 72, 65 geeft een score van 3).
Wanneer de eerste berekening foutief is, wordt dit als foutief aangerekend maar wel gecorrigeerd.
Daarna vraagt u: "Hoeveel is 93 min 7?" Vanaf dan vraagt u: "En verder?"

	(93)	O
	(86) of -7	O
	(79) of -7	O
	(72) of -7	O
	(65) of -7	O

B. Wilt u het woord "dorst" van achteren naar voren spellen?

(1 punt voor elke correcte letter op de juiste plaats)	T	O
	S	O
	R	O
	O	O
	D	O

Zowel test 3A als 3B worden afgenomen.
Vergelijk de scores van test A en test B en weerhoud enkel de hoogste score.
Schrap de andere en tel die niet mee in de eindscore.

Hoogste score: ☐

4. Geheugen

- **Welk waren de drie woorden die u moest onthouden?**
  (score 0-3)

	Sigaar ☐
	Bloem ☐
	Deur ☐

5. Taal

5.1. Benoemen

• **Wat is dit?** Wijs een horloge aan.	Horloge ☐
• **Wat is dit?** Wijs een potlood aan.	Potlood ☐

5.2. Herhalen

• **Wilt u de volgende zin herhalen: "Geen als, en of maar".**	Correct ☐

5.3. Begrip

- **Neem dit papier met uw rechterhand, vouw het in twee en leg het op de grond.**

(1 punt voor elke goede handeling)	Neemt papier ☐
	Vouwt papier ☐
	Legt op grond ☐

5.4. Lezen

- **Lees wat op dit papier staat en doe wat gevraagd wordt.**

Hou het papier omhoog, waarop staat 'SLUIT UW OGEN'	Sluit ogen ☐

5.5. Schrijven

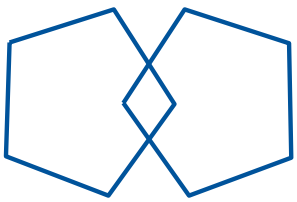
- **Kan u voor mij een zin opschrijven?**

De zin moet een onderwerp en werkwoord bevatten en betekenis hebben. Fouten in de spelling en grammatica worden niet beoordeeld.	Zin ☐

6. Constructieve vaardigheid

- **Kan u deze figuur natekenen?**
  Toon de twee vijfhoeken.
  Voor een correct antwoord moeten er tien hoeken zijn, waarvan er twee mekaar kruisen.

Figuur ☐



Totaalscore

Tel alle goede antwoorden op (let op bij test 3A en 3B) en noteer het totaal in de rechterbovenhoek (maximumscore = 30)

Appendix 4. New Freezing of Gait Questionnaire (NFOG-Q), Dutch version

Deel 1 – Onderscheid freezer – niet-freezer

Score on off

1. Heeft u de afgelopen maand freezing-episodes ervaren?
   Freezing is het gevoel dat uw voeten tijdelijk aan de grond vast plakken. Dit komt vooral voor bij het starten, een bocht maken of door smalle of drukke ruimtes lopen. Soms kan het gepaard gaan met trillen van de benen of kleine schuifelpassen. We zullen samen een korte video bekijken van de verschillende manieren waarop freezing kan optreden. Let op, hoe lang deze episodes duren, omdat u er straks vragen over kunt verwachten (tester toont de klok op de video!).

   0. Ik heb geen freezing-episodes meegemaakt in de voorbije maand
   1. Ik heb wel freezing-episodes meegemaakt in de voorbije maand

Deel 2 – Ernst van freezing; frequentie en duur

2. Hoe vaak ervaart u freezing-episodes?

   0. Minder dan 1 keer per week
   1. Weinig, ongeveer 1 keer per week
   2. Dikwijls, ongeveer 1 keer per dag
   3. Heel dikwijls, meer dan 1 keer per dag

3. Hoe vaak ervaart u freezing-episodes terwijl u draait?

   0. Nooit
   1. Heel zelden, ongeveer 1 keer per maand
   2. Weinig, ongeveer 1 keer per week
   3. Dikwijls, ongeveer 1 keer per dag
   4. Heel dikwijls, meer dan 1 keer per dag

Bij een antwoord van 1 of meer, ga naar vraag 4. Als het antwoord 0 is, ga direct naar 5.

4. Hoe lang duurt uw langste freezing-episode bij het draaien?

   1. Heel kort, 1 seconde
   2. Kort, 2 – 5 seconden
   3. Lang, tussen 5 en 30 seconden
   4. Zeer lang, niet in staat om binnen de 30 seconden weer te gaan (lopen).

5. Hoe vaak ervaart u freezing-episodes als u de eerste stap zet om te gaan (lopen)?

   0. Nooit
   1. Heel zelden, ongeveer 1 keer per maand
   2. Weinig, ongeveer 1 keer per week
   3. Dikwijls, ongeveer 1 keer per dag
   4. Heel dikwijls, meer dan 1 keer per dag

Bij een antwoord van 1 of meer, ga naar vraag 6. Als het antwoord 0 is, ga direct naar 7.

6. Hoe lang duurt uw langste freezing-episode als u de eerste stap zet om te gaan (lopen)?

    1. Heel kort, 1 seconde
    2. Kort, 2 – 5 seconden
    3. Lang, tussen 5 en 30 seconden
    4. Zeer lang, niet in staat om binnen de 30 seconden te stappen

Deel 3 – Impact van freezing op dagelijks leven

7. Hoe storend zijn de freezing-episodes voor uw dagelijkse mobiliteit?

    0. Helemaal niet
    1. Weinig
    2. Matig
    3. Erg

8. Veroorzaken de freezing-episodes gevoelens van onzekerheid of angst om te vallen?

    0. Helemaal niet
    1. Weinig
    2. Matig
    3. Erg

9. Hebben uw freezing-episodes een invloed op uw dagelijkse activiteiten?

    0. Helemaal niet, ik voer taken zoals normaal uit
    1. Weinig, ik vermijd slechts sommige taken
    2. Matig, ik vermijd een substantieel deel (ongeveer de helft) van mijn dagelijkse activiteiten
    3. Belangrijk, ik ben heel beperkt in het uitvoeren van de meeste dagelijkse activiteiten

Totale score:
Deel 1:
Deel 2:
Deel 3:

Appendix 5. Motor section of the Unified Parkinson's Disease Rating Scale (UPDRS-III)

Part III: Motor Examination

Overview: This portion of the scale assesses the motor signs of PD. In administering Part III of the MDS-UPDRS the examiner should comply with the following guidelines:

At the top of the form, mark whether the patient is on medication for treating the symptoms of Parkinson's disease and, if on levodopa, the time since the last dose.

Also, if the patient is receiving medication for treating the symptoms of Parkinson's Disease, mark the patient's clinical state using the following definitions:

ON is the typical functional state when patients are receiving medication and have a good response.
OFF is the typical functional state when patients have a poor response in spite of taking medications.

The investigator should "rate what you see". Admittedly, concurrent medical problems such as stroke, paralysis, arthritis, contracture, and orthopedic problems such as hip or knee replacement and scoliosis may interfere with individual items in the motor examination. In situations where it is absolutely impossible to test (e.g., amputations, plegia, limb in a cast), use the notation "**UR**" for Unable to Rate. Otherwise, rate the performance of each task as the patient performs in the context of co-morbidities.

All items must have an integer rating (no half points, no missing ratings).

Specific instructions are provided for the testing of each item. These should be followed in all instances. The investigator demonstrates while describing tasks the patient is to perform and rates function immediately thereafter. For Global Spontaneous Movement and Rest Tremor items (3.14 and 3.17), these items have been placed purposefully at the end of the scale because clinical information pertinent to the score will be obtained throughout the entire examination.

At the end of the rating, indicate if dyskinesia (chorea or dystonia) was present at the time of the examination, and if so, whether these movements interfered with the motor examination.

3a Is the patient on medication for treating the symptoms of Parkinson's Disease? ☐ No ☐ Yes

3b If the patient is receiving medication for treating the symptoms of Parkinson's Disease, mark the patient's clinical state using the following definitions:

☐ ON: On is the typical functional state when patients are receiving medication and have a good response.

☐ OFF: Off is the typical functional state when patients have a poor response in spite of taking medications.

3c Is the patient on Levodopa ? ☐ No ☐ Yes

3.C1 If yes, minutes since last levodopa dose: _____

	SCORE
3.1 SPEECH Instructions to examiner: Listen to the patient's free-flowing speech and engage in conversation if necessary. Suggested topics: ask about the patient's work, hobbies, exercise, or how he got to the doctor's office. Evaluate volume, modulation (prosody) and clarity, including slurring, palilalia (repetition of syllables) and tachyphemia (rapid speech, running syllables together). 0: Normal: No speech problems. 1: Slight: Loss of modulation, diction or volume, but still all words easy to understand. 2: Mild: Loss of modulation, diction, or volume, with a few words unclear, but the overall sentences easy to follow. 3: Moderate: Speech is difficult to understand to the point that some, but not most, sentences are poorly understood. 4: Severe: Most speech is difficult to understand or unintelligible.	☐
3.2 FACIAL EXPRESSION Instructions to examiner: Observe the patient sitting at rest for 10 seconds, without talking and also while talking. Observe eye-blink frequency, masked facies or loss of facial expression, spontaneous smiling and parting of lips. 0: Normal: Normal facial expression. 1: Slight: Minimal masked facies manifested only by decreased frequency of blinking. 2: Mild: In addition to decreased eye-blink frequency, Masked facies present in the lower face as well, namely fewer movements around the mouth, such as less spontaneous smiling, but lips not parted. 3: Moderate: Masked facies with lips parted some of the time when the mouth is at rest. 4: Severe: Masked facies with lips parted most of the time when the mouth is at rest.	☐

	SCORE
3.3 RIGIDITY Instructions to examiner: Rigidity is judged on slow passive movement of major joints with the patient in a relaxed position and the examiner manipulating the limbs and neck. First, test without an activation maneuver. Test and rate neck and each limb separately. For arms, test the wrist and elbow joints simultaneously. For legs, test the hip and knee joints simultaneously. If no rigidity is detected, use an activation maneuver such as tapping fingers, fist opening/closing, or heel tapping in a limb not being tested. Explain to the patient to go as limp as possible as you test for rigidity. 0: Normal: No rigidity. 1: Slight: Rigidity only detected with activation maneuver. 2: Mild: Rigidity detected without the activation maneuver, but full range of motion is easily achieved. 3: Moderate: Rigidity detected without the activation maneuver; full range of motion is achieved with effort. 4: Severe: Rigidity detected without the activation maneuver and full range of motion not achieved.	☐ Neck ☐ RUE ☐ LUE ☐ RLE ☐ LLE
3.4 FINGER TAPPING Instructions to examiner: Each hand is tested separately. Demonstrate the task, but do not continue to perform the task while the patient is being tested. Instruct the patient to tap the index finger on the thumb 10 times as quickly AND as big as possible. Rate each side separately, evaluating speed, amplitude, hesitations, halts and decrementing amplitude. 0: Normal: No problems. 1: Slight: Any of the following: a) the regular rhythm is broken with one or two interruptions or hesitations of the tapping movement; b) slight slowing; c) the amplitude decrements near the end of the 10 taps. 2: Mild: Any of the following: a) 3 to 5 interruptions during tapping; b) mild slowing; c) the amplitude decrements midway in the 10-tap sequence. 3: Moderate: Any of the following: a) more than 5 interruptions during tapping or at least one longer arrest (freeze) in ongoing movement; b) moderate slowing; c) the amplitude decrements starting after the 1st tap. 4: Severe: Cannot or can only barely perform the task because of slowing, interruptions or decrements.	☐ R ☐ L

	SCORE
3.5 HAND MOVEMENTS Instructions to examiner: Test each hand separately. Demonstrate the task, but do not continue to perform the task while the patient is being tested. Instruct the patient to make a tight fist with the arm bent at the elbow so that the palm faces the examiner. Have the patient open the hand 10 times as fully AND as quickly as possible. If the patient fails to make a tight fist or to open the hand fully, remind him/ her to do so. Rate each side separately, evaluating speed, amplitude, hesitations, halts and decrementing amplitude. 0: Normal: No problem. 1: Slight: Any of the following: a) the regular rhythm is broken with one or two interruptions or hesitations of the movement; b) slight slowing; c) the amplitude decrements near the end of the task. 2: Mild: Any of the following: a) 3 to 5 interruptions during the movements; b) mild slowing; c) the amplitude decrements midway in the task. 3: Moderate: Any of the following: a) more than 5 interruptions during the movement or at least one longer arrest (freeze) in ongoing movement; b) moderate slowing; c) the amplitude decrements starting after the 1st open-and-close sequence. 4: Severe: Cannot or can only barely perform the task because of slowing, interruptions or decrements.	☐ R ☐ L
3.6 PRONATION-SUPINATION MOVEMENTS OF HANDS Instructions to examiner: Test each hand separately. Demonstrate the task, but do not continue to perform the task while the patient is being tested. Instruct the patient to extend the arm out in front of his/her body with the palms down; then to turn the palm up and down alternately 10 times as fast and as fully as possible. Rate each side separately, evaluating speed, amplitude, hesitations, halts and decrementing amplitude. 0: Normal: No problems. 1: Slight: Any of the following: a) the regular rhythm is broken with one or two interruptions or hesitations of the movement; b) slight slowing; c) the amplitude decrements near the end of the sequence. 2: Mild: Any of the following: a) 3 to 5 interruptions during the movements; b) mild slowing; c) the amplitude decrements midway in the sequence. 3: Moderate: Any of the following: a) more than 5 interruptions during the movement or at least one longer arrest (freeze) in ongoing movement; b) moderate slowing c) the amplitude decrements starting after the 1st supination-pronation sequence. 4: Severe: Cannot or can only barely perform the task because of slowing, interruptions or decrements.	☐ R ☐ L

	SCORE
3.7 TOE TAPPING Instructions to examiner: Have the patient sit in a straight-backed chair with arms, both feet on the floor. Test each foot separately. Demonstrate the task, but do not continue to perform the task while the patient is being tested. Instruct the patient to place the heel on the ground in a comfortable position and then tap the toes 10 times as big and as fast as possible. Rate each side separately, evaluating speed, amplitude, hesitations, halts and decrementing amplitude. 0: Normal: No problem. 1: Slight: Any of the following: a) the regular rhythm is broken with one or two interruptions or hesitations of the tapping movement; b) slight slowing; c) amplitude decrements near the end of the ten taps. 2: Mild: Any of the following: a) 3 to 5 interruptions during the tapping movements; b) mild slowing; c) amplitude decrements midway in the task. 3: Moderate: Any of the following: a) more than 5 interruptions during the tapping movements or at least one longer arrest (freeze) in ongoing movement; b) moderate slowing; c) amplitude decrements after the first tap. 4: Severe: Cannot or can only barely perform the task because of slowing, interruptions or decrements.	☐ R ☐ L
3.8 LEG AGILITY Instructions to examiner: Have the patient sit in a straight-backed chair with arms. The patient should have both feet comfortably on the floor. Test each leg separately. Demonstrate the task, but do not continue to perform the task while the patient is being tested. Instruct the patient to place the foot on the ground in a comfortable position and then raise and stomp the foot on the ground 10 times as high and as fast as possible. Rate each side separately, evaluating speed, amplitude, hesitations, halts and decrementing amplitude. 0: Normal: No problems. 1: Slight: Any of the following: a) the regular rhythm is broken with one or two interruptions or hesitations of the movement; b) slight slowing; c) amplitude decrements near the end of the task. 2: Mild: Any of the following: a) 3 to 5 interruptions during the movements; b) mild slowness; c) amplitude decrements midway in the task. 3: Moderate: Any of the following: a) more than 5 interruptions during the movement or at least one longer arrest (freeze) in ongoing movement; b) moderate slowing in speed; c) amplitude decrements after the first tap. 4: Severe: Cannot or can only barely perform the task because of slowing, interruptions or decrements.	☐ R ☐ L

	SCORE
3.9 ARISING FROM CHAIR Instructions to examiner: Have the patient sit in a straight-backed chair with arms, with both feet on the floor and sitting back in the chair (if the patient is not too short). Ask the patient to cross his/her arms across the chest and then to stand up. If the patient is not successful, repeat this attempt a maximum up to two more times. If still unsuccessful, allow the patient to move forward in the chair to arise with arms folded across the chest. Allow only one attempt in this situation. If unsuccessful, allow the patient to push off using his/her hands on the arms of the chair. Allow a maximum of three trials of pushing off. If still not successful, assist the patient to arise. After the patient stands up, observe the posture for item 3.13 0: Normal: No problems. Able to arise quickly without hesitation. 1: Slight: Arising is slower than normal; or may need more than one attempt; or may need to move forward in the chair to arise. No need to use the arms of the chair. 2: Mild: Pushes self up from arms of chair without difficulty. 3: Moderate: Needs to push off, but tends to fall back; or may have to try more than one time using arms of chair, but can get up without help. 4: Severe: Unable to arise without help.	☐
3.10 GAIT Instructions to examiner: Testing gait is best performed by having the patient walking away from and towards the examiner so that both right and left sides of the body can be easily observed simultaneously. The patient should walk at least 10 meters (30 feet), then turn around and return to the examiner. This item measures multiple behaviors: stride amplitude, stride speed, height of foot lift, heel strike during walking, turning, and arm swing, but not freezing. Assess also for "freezing of gait" (next item 3.11) while patient is walking. Observe posture for item 3.13 0: Normal: No problems. 1: Slight: Independent walking with minor gait impairment. 2: Mild: Independent walking but with substantial gait impairment. 3: Moderate: Requires an assistance device for safe walking (walking stick, walker) but not a person. 4: Severe: Cannot walk at all or only with another person's assistance.	☐

	SCORE
3.11 FREEZING OF GAIT Instructions to examiner: While assessing gait, also assess for the presence of any gait freezing episodes. Observe for start hesitation and stuttering movements especially when turning and reaching the end of the task. To the extent that safety permits, patients may NOT use sensory tricks during the assessment. 0: Normal: No freezing. 1: Slight: Freezes on starting, turning or walking through doorway with a single halt during any of these events, but then continues smoothly without freezing during straight walking. 2: Mild: Freezes on starting, turning or walking through doorway with more than one halt during any of these activities, but continues smoothly without freezing during straight walking. 3: Moderate: Freezes once during straight walking. 4: Severe: Freezes multiple times during straight walking.	☐
3.12 POSTURAL STABILITY Instructions to examiner: The test examines the response to sudden body displacement produced by a quick, forceful pull on the shoulders while the patient is standing erect with eyes open and feet comfortably apart and parallel to each other. Test retropulsion. Stand behind the patient and instruct the patient on what is about to happen. Explain that s/he is allowed to take a step backwards to avoid falling. There should be a solid wall behind the examiner, at least 1-2 meters away to allow for the observation of the number of retropulsive steps. The first pull is an instructional demonstration and is purposely milder and not rated. The second time the shoulders are pulled briskly and forcefully towards the examiner with enough force to displace the center of gravity so that patient MUST take a step backwards. The examiner needs to be ready to catch the patient, but must stand sufficiently back so as to allow enough room for the patient to take several steps to recover independently. Do not allow the patient to flex the body abnormally forward in anticipation of the pull. Observe for the number of steps backwards or falling. Up to and including two steps for recovery is considered normal, so abnormal ratings begin with three steps. If the patient fails to understand the test, the examiner can repeat the test so that the rating is based on an assessment that the examiner feels reflects the patient's limitations rather than misunderstanding or lack of preparedness. Observe standing posture for item 3.13 0: Normal: No problems: Recovers with one or two steps. 1: Slight: 3-5 steps, but subject recovers unaided. 2: Mild: More than 5 steps, but subject recovers unaided. 3: Moderate: Stands safely, but with absence of postural response; falls if not caught by examiner. 4: Severe: Very unstable, tends to lose balance spontaneously or with just a gentle pull on the shoulders.	☐

	SCORE
3.13 POSTURE Instructions to examiner: Posture is assessed with the patient standing erect after arising from a chair, during walking , and while being tested for postural reflexes. If you notice poor posture, tell the patient to stand up straight and see if the posture improves (see option 2 below). Rate the worst posture seen in these three observation points. Observe for flexion and side-to-side leaning. 0: Normal: No problems. 1: Slight: Not quite erect, but posture could be normal for older person. 2: Mild: Definite flexion, scoliosis or leaning to one side, but patient can correct posture to normal posture when asked to do so. 3: Moderate: Stooped posture, scoliosis or leaning to one side that cannot be corrected volitionally to a normal posture by the patient. 4: Severe: Flexion, scoliosis or leaning with extreme abnormality of posture.	☐
3.14 GLOBAL SPONTANEITY OF MOVEMENT (BODY BRADYKINESIA) Instructions to examiner: This global rating combines all observations on slowness, hesitancy, and small amplitude and poverty of movement in general, including a reduction of gesturing and of crossing the legs. This assessment is based on the examiner's global impression after observing for spontaneous gestures while sitting, and the nature of arising and walking. 0: Normal: No problems. 1: Slight: Slight global slowness and poverty of spontaneous movements. 2: Mild: Mild global slowness and poverty of spontaneous movements. 3: Moderate: Moderate global slowness and poverty of spontaneous movements. 4: Severe: Severe global slowness and poverty of spontaneous movements.	☐
3.15 POSTURAL TREMOR OF THE HANDS Instructions to examiner: All tremor, including re-emergent rest tremor, that is present in this posture is to be included in this rating. Rate each hand separately. Rate the highest amplitude seen. Instruct the patient to stretch the arms out in front of the body with palms down. The wrist should be straight and the fingers comfortably separated so that they do not touch each other. Observe this posture for 10 seconds. 0: Normal: No tremor. 1: Slight: Tremor is present but less than 1 cm in amplitude. 2: Mild: Tremor is at least 1 but less than 3 cm in amplitude. 3: Moderate: Tremor is at least 3 but less than 10 cm in amplitude. 4: Severe: Tremor is at least 10 cm in amplitude.	☐ R ☐ L

	SCORE
3.16 KINETIC TREMOR OF THE HANDS Instructions to examiner: This is tested by the finger-to-nose maneuver. With the arm starting from the outstretched position, have the patient perform at least three finger-to-nose maneuvers with each hand reaching as far as possible to touch the examiner's finger. The finger-to-nose maneuver should be performed slowly enough not to hide any tremor that could occur with very fast arm movements. Repeat with the other hand, rating each hand separately. The tremor can be present throughout the movement or as the tremor reaches either target (nose or finger). Rate the highest amplitude seen. 0: Normal: No tremor. 1: Slight: Tremor is present but less than 1 cm in amplitude. 2: Mild: Tremor is at least 1 but less than 3 cm in amplitude. 3: Moderate: Tremor is at least 3 but less than 10 cm in amplitude. 4: Severe: Tremor is at least 10 cm in amplitude.	☐ R ☐ L
3.17 REST TREMOR AMPLITUDE Instructions to examiner: This and the next item have been placed purposefully at the end of the examination to allow the rater to gather observations on rest tremor that may appear at any time during the exam, including when quietly sitting, during walking and during activities when some body parts are moving but others are at rest. Score the maximum amplitude that is seen at any time as the final score. Rate only the amplitude and not the persistence or the intermittency of the tremor. As part of this rating, the patient should sit quietly in a chair with the hands placed on the arms of the chair (not in the lap) and the feet comfortably supported on the floor for 10 seconds with no other directives. Rest tremor is assessed separately for all four limbs and also for the lip/jaw. Rate only the maximum amplitude that is seen at any time as the final rating. Extremity ratings 0: Normal: No tremor. 1: Slight.: < 1 cm in maximal amplitude. 2: Mild: > 1 cm but < 3 cm in maximal amplitude. 3: Moderate: 3 - 10 cm in maximal amplitude. 4: Severe: > 10 cm in maximal amplitude. Lip/Jaw ratings 0: Normal: No tremor. 1: Slight: < 1 cm in maximal amplitude. 2: Mild: > 1 cm but < 2 cm in maximal amplitude. 3: Moderate: > 2 cm but < 3 cm in maximal amplitude. 4: Severe: > 3 cm in maximal amplitude.	☐ RUE ☐ LUE ☐ RLE ☐ LLE ☐ Lip/Jaw

	SCORE
3.18 CONSTANCY OF REST TREMOR Instructions to examiner: This item receives one rating for all rest tremor and focuses on the constancy of rest tremor during the examination period when different body parts are variously at rest. It is rated purposefully at the end of the examination so that several minutes of information can be coalesced into the rating. 0: Normal: No tremor. 1: Slight: Tremor at rest is present < 25% of the entire examination period. 2: Mild: Tremor at rest is present 26-50% of the entire examination period. 3: Moderate: Tremor at rest is present 51-75% of the entire examination period. 4: Severe: Tremor at rest is present > 75% of the entire examination period.	☐
DYSKINESIA IMPACT ON PART III RATINGS A. Were dyskinesias (chorea or dystonia) present during examination? ☐ No ☐ Yes B. If yes, did these movements interfere with your ratings? ☐ No ☐ Yes	
HOEHN AND YAHR STAGE 0: Asymptomatic. 1: Unilateral involvement only. 2: Bilateral involvement without impairment of balance. 3: Mile to moderate involvement; some postural instability but physically independent; needs assistance to recover from pull test. 4: Severe disability; still able to walk or stand unassisted. 5: Wheelchair bound or bedridden unless aided.	☐

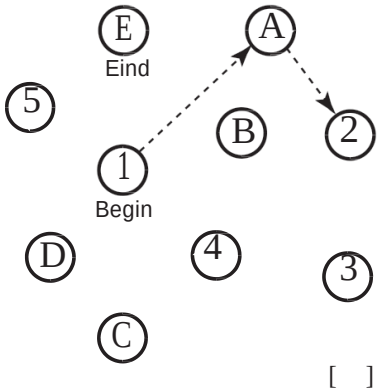
Appendix 6. Montreal Cognitive Assessment (MoCA) scale, Dutch version

Nederlandse versie

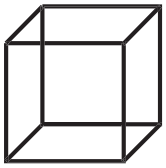
MONTREAL COGNITIVE ASSESSMENT (MOCA)

Geboortedatum:
Jaren opleiding: Naam:
Geslacht: Datum:

VISUOSPATIEEL/EXECUTIEF — PUNTEN



Kopieer de kubus



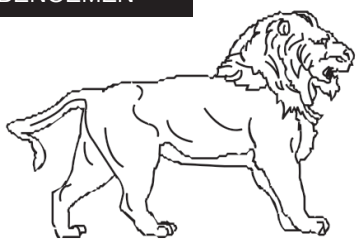
[ ] [ ]

Teken een klok (tien over elf) (3 punten)

[ ] Omtrek [ ] Cijfers [ ] Wijzers

__/5

BENOEMEN



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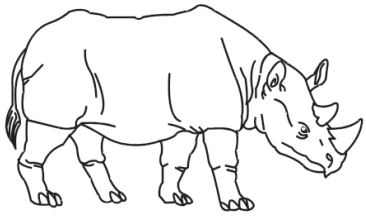

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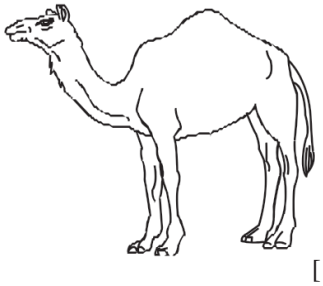

[ ]

__/3

GEHEUGEN

Lees de woorden op, proefpersoon moet ze nazeggen. Neem 2 maal af. Laat ze na 5 min. opnieuw opnoemen.

	GEZICHT	FLUWEEL	KERK	MADELIEF	ROOD
1e afname					
2e afname					

Geen punten

AANDACHT

Lees de rij cijfers op (1 cijfer/sec). Proefpersoon moet ze in dezelfde volgorde nazeggen **[ ] 2 1 8 5 4**
Proefpersoon moet ze in omgekeerde volgorde nazeggen **[ ] 7 4 2** __/2

Lees de rij letters op. De proefpersoon moet bij iedere letter A met zijn hand op de tafel tikken. Geen punten bij ≥ 2 ft
[ ] **F B A C M N A A J K L B A F A K D E A A A J A M O F A A B** __/1

Serieel 7 aftrekken, beginnend bij 100 **[ ] 93** **[ ] 86** **[ ] 79** **[ ] 72** **[ ] 65**
4 of 5 goed: **3 pt** 2 of 3 goed: **2 pt** 1 goed: **1 pt** 0 goed: **0 pt** __/3

TAAL

Zeg na: Ik weet alleen dat Jan vandaag geholpen zou worden. [ ]
De kat verstopte zich altijd onder de bank als er honden in de kamer waren. [ ] __/2

Fluency: Noem binnen één minuut zo veel mogelijk woorden die beginnen met de letter D [ ] (N ≥ 11 woorden) __/1

ABSTRACTIE

Overeenkomst tussen bijv. banaan en sinaasappel = fruit [ ] trein-fiets [ ] horloge-liniaal __/2

UITGESTELDE RECALL

	Woorden moeten herinnerd worden **zonder cue**	GEZICHT [ ]	FLUWEEL [ ]	KERK [ ]	MADELIEF [ ]	ROOD [ ]
Optioneel	Categoriecue					
	Meerkeuzecue					

Punten alleen voor recall zonder cue __/5

ORIËNTATIE

[ ] Datum [ ] Maand [ ] Jaar [ ] Dag [ ] Locatie [ ] Plaats __/6

www.mocatest.org

Normaal ≥ 26 / 30

TOTAAL __/30

Tel er 1 pt bij op indien ≤ 12 jr opleiding