Influence of Multiple Ratio Split-belt Treadmill on Gait Asymmetry and Motor Learning in PD patients with Freezing of Gait

I. General information

Version and date of protocol: version 5, 14/11/2017

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Sponsor/Research Unit: Research Group for Neuromotor Rehabilitation, Faculty of Kinesiology and Rehabilitation Sciences, KU Leuven

Principal investigator: Prof. Alice Nieuwboer
Tervuursevest 101, 3000 Leuven
Tel: 016/329119
E-mail: alice.nieuwboer@kuleuven.be

Sub-investigator: Nicholas D'Cruz
Tervuursevest 101, 3000 Leuven
Tel: 016/376003
E-mail: nicholas.dcruz@kuleuven.be

Study period: 01/11/2017 – 31/10/2018

Signatures

The undersigned confirm that the following protocol has been agreed and accepted and that the Principal Investigator agrees to conduct the trial in compliance with the approved protocol and will adhere to the principles outlined in the requirements for the conduct of clinical trials in the EU as provided for in "Directive 2001/20/EC", and any subsequent amendments, GCP guidelines, the Belgian law of May 7th 2004 regarding experiments on the human person, the Sponsor's SOPs, and other regulatory requirements as amended.

I agree to ensure that the confidential information contained in this document will not be used for any other purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of the Sponsor.

I also confirm that I will make the findings of the trial publically available through publication or other dissemination tools without any unnecessary delay and that an honest accurate and transparent account of the trial will be given; and that any discrepancies from the trial as planned in this protocol will be explained.

Principal Investigator (KU Leuven)

Prof. Alice Nieuwboer		11th October 2017
……	……	……
Name & Title	*Signature*	*Date*

Principal Investigator (participating site University Kiel)

Dr. Christian Schlenstedt		12th October 2017
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Name & Title	*Signature*	*Date*

II. Dutch summary of the protocol

Titel onderzoeksproject:
Invloed van multiple ratio split-belt loopbandtraining op stapasymmetrie bij personen met de ziekte van Parkinson en gangblokkades
Deelnemers:
32 patiënten met de ziekte van Parkinson, met 'Freezing of Gait'
32 leeftijdsgematchte gezonde proefpersonen

Type studie:
Multi-centrische studie (Mono-centrisch in België) aan de Faculteit Bewegings- en Revalidatiewetenschappen
Trainingsstudie
Academische studie

Metingen:
Screeningstesten ter evaluatie van motorische en cognitieve functie bij ziekte van Parkinson
Vragenlijsten naar 'Freezing of Gait', vermoedheid en cognitie
Klinische meetschalen ter evaluatie van evenwicht en van de ernst van de 'Freezing of Gait'
5 m stappen buiten de loopband met en zonder een dubbeltaak

Training protocol:
Loopbandtraining van 6 x 5 min. Met telkens 1 min. zittende pauze

Duur experiment:
Patiënten met Parkinson en Freezing of gait: 2 sessies van 2 uur op 2 aparte testdagen
Gezonde controles: 2 sessies van 2 uur op 2 aparte testdagen

Plaats van de experimentele sessies:
Faculteit Bewegings-en Revalidatiewetenschappen, KULeuven

III. Background and rationale

Parkinson's disease (PD) is the **second most common** neurodegenerative disease [1, 2]. It has a substantial impact on patients' quality of life as well as on the socio-economic cost for society [3]. Gait problems are very prevalent in PD and markedly reduce patients' functional independence [4]. Freezing of gait (FOG) is without doubt the most disabling gait impairment and it constitutes **an independent risk factor for falls** [5]. This complex symptom is defined as an episode of substantial reduction or complete cessation of movement despite having the intention to move [6]. Current medical and surgical treatments only partly relieve FOG [7], strongly suggesting that non-dopaminergic mechanisms mediate its occurrence [8]. Therapeutic alternatives are, therefore, **urgently needed**. A growing body of literature

suggests that exercise and **motor learning can significantly improve gait** and mobility in PD [9, 10] with long term effects ranging from 4 to 48 weeks [11].

FOG occurs when spatiotemporal motor control breaks down and is associated with gait cycle variability, **reduced stride amplitude** and hastening of gait timing. Furthermore, FOG is also related to between-limb coordination deficits and **gait asymmetry** [12-14]. The strong link between FOG and gait asymmetry [14, 15] is underscored by the fact that turning – which is a highly asymmetric task, is the most important trigger of FOG [16, 17].

Split-belt treadmill walking, whereby the walking speed of each leg can be manipulated independently, is a useful tool to study both motor switching and modulating gait asymmetry. In a recent study at our lab, motor switching ability during different asymmetric split-belt conditions was studied in patients with and without FOG. It was shown that non-freezers were **able to adapt spatial gait symmetry** to different switching split-belt conditions similarly as healthy controls. However, **adaptive capacity was reduced in freezers** (figure 1A) [18]. The powerfulness of the split-belt paradigm was also confirmed by the fact that immediately after the switch, FOG was evoked in two cases. In another study from the group at Christian-Albrechts University Kiel (CAUK), Germany, the **short-term effects of 10 minutes split-belt walking** were studied through reducing the belt velocity of either the body side with the longer or shorter step length in PD. **Gait asymmetry, bilateral coordination and the consecutive reduction in step lengths were improved** in the tied-belt condition after subjects walked with reduced velocity at the side with the longer step length ("better side reduction") (figure 1B) [19]. These exciting pilot results provide **proof-of-principle evidence** for the current project. To consolidate these findings, our research group in collaboration with the group at Kiel will undertake two studies, probing short term motor adaptation (present study) and prolonged motor learning (future study) to alleviate freezing-related gait deficits.

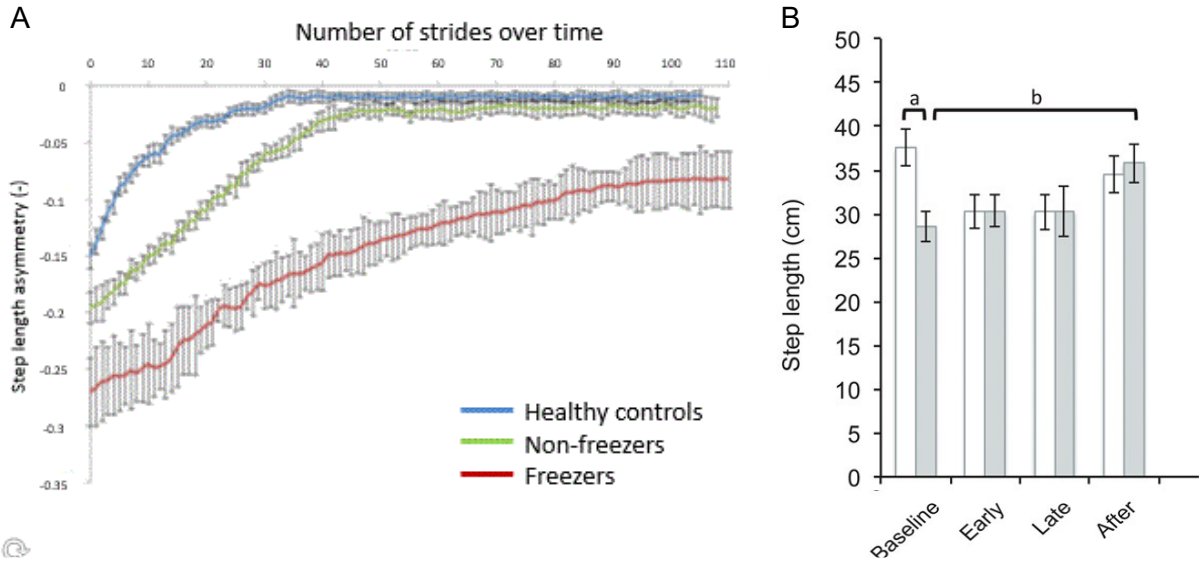

Figure 1. A) Impaired adaptive capacity of patients with PD with FOG during split-belt gait (data from KUL: mod. according to Mohammadi et al. 2015); B) Step length during baseline, early and late split-belt adaptation (25% reduced belt's speed of the leg with the longer step length (best-side reduction)) and after effect (data from CAUK: mod. according to Fasano et al. 2016).

IV. Study objectives

Motor adaptation refers to behavioural changes induced by new environmental dynamics, commonly studied by inducing an unfamiliar perturbation into an otherwise familiar task. Here, split-belt speed manipulations will be used **to study implicit motor adaptation**, i.e. without raising conscious attention to the adaptive behaviour nor demanding an explicit strategy [18]. Motor adaptation plays an important role in **the acquisition (early) phase of motor learning**, the hallmark of which is reaching a stable level of performance. In contrast, the late consolidation phase of motor learning is characterized by: 1) **automatization**, or the ability to withstand dual task interference; 2) **transfer**, or the ability to generalize to untrained circumstances and 3) **retention**, or the ability to sustain improvements after a period without practice. [20]. Our previous work has shown that despite disease-related damage, **patients with PD can still reconfigure neural networks** to optimize motor control and achieve partially consolidated motor learning gains [21]. Interestingly, from recent study on manual tasks, it appears that **variable practice** (random versus blocked) and practice requiring greater adaptation (with versus without contextual interference) led to **worse immediate performance but better learning retention** in PD and older adults. This strongly suggests that in order to enhance better storage in motor memory and automatic retrieval of practice gains, **practice conditions are critical**. In this project, we want to study these phenomena for the first time during gait. More specifically, we want to know how PD impacts upon maintenance of stride amplitude when adapting to varying split-belt conditions in order to achieve robust learning.

<u>Research Questions and Hypothesis</u>

We aim to investigate two research questions:

We intend to better understand the impact of PD on the **adaptive response to different split-belt conditions** relative to healthy age-matched controls.

We will investigate the short-term effects of different split-belt conditions in order to determine the **optimal conditions for long-term training** in patients with FOG and test which condition leads to the best 24-hour retention.

We hypothesize that being exposed to larger contrasts between split-belt speeds (ratio) will result in improved gait symmetry and better savings in motor memory, thus leading to better retention effects and this more so in controls than in PD. We also hypothesize that variable split-belt conditions (changing ratios) will lead to better adaptive capacity to transitions than steady split-belt walking with a consistent ratio.

V. Methodology of the research

Number of participants: This pilot study investigating the short-term effects of split-belt walking on gait asymmetry and motor learning is conducted in collaboration with CAUK and will include a total number of 128 participants i.e 64 at each centre comprising 32 patients with PD and 32 healthy controls.

Recruitment: Older adults will be recruited from an existing database of healthy volunteers. Recruitment of PD patients will be conducted via a database of patients that has been built up over the years in our laboratory in collaboration with the neurologist at the Movement Disorders clinic at UZ Leuven (Prof. Dr. Wim Vandenberghe). Flyers containing study information will be handed to people expressing interest to participate.

Inclusion and Exclusion Criteria: PD patients with FOG who can walk at least 5 minutes at a stretch will be included in this study. Exclusion criteria are: participation in treadmill training in the 3 months prior to the study, other neurological impairments, orthopedic injuries that could influence gait or balance, cardiovascular exercise risk factors, dementia or self-reported DBS-related postural or gait disturbances.

Design: Patients will be tested in the ON phase of medication on consecutive days in a session of about 2 hours. Figure 2 shows that the included subjects will be randomized into 4 treatment groups to compare the impact of different (3:4 and 1:2) and changing ratios of split-belt walking relative to traditional treadmill training (Tied-Belt). Effects will be analysed pre-post (I-II) and after 24 hours (III) retention. The second training session (III-IV) will explore the possible benefits of repeated training and serves as a pilot for a larger training study.

Standardization: Testing and training methods and protocol as well as patient instructions will be standardised across the two centres by documentation of procedures as well as through regular communication. Researchers from both groups will attend initial measurements and in addition, during the first 3 months of the project, a monthly skype call between researchers will be held to check the fidelity of procedures and ensure adherence.

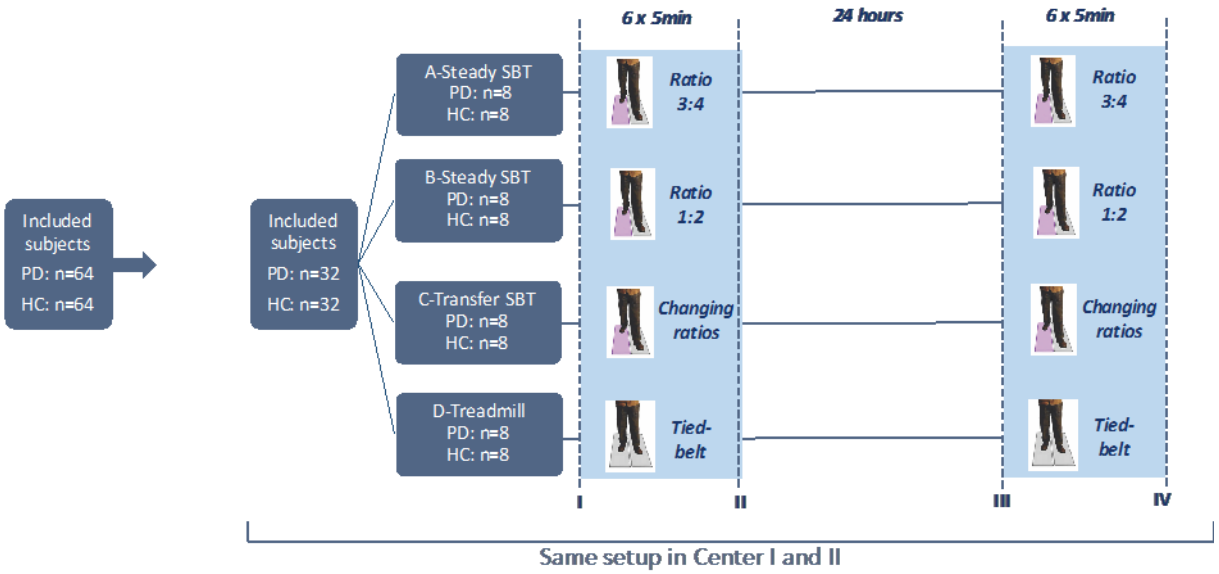

Figure 2. Study design. 128 participants will be recruited across the two centres and data will be pooled for analysis. SBT, Split-belt Treadmill; PD, Parkinson's disease; HC, healthy control.

Intervention

Participants will first walk normally (5 x 5m) at a comfortable pace to assess **overground walking speed** and to assess which leg has the longer/shorter step length. **Best/worst side** will be further confirmed with a toe-tapping test and by asking the PD patients about their more/less affected PD side. Next, participants will walk on the treadmill for a maximum of 3 minutes to get familiar with treadmill walking, reaching their overground gait speed. Intervention will consist of one training session of 6 x 5 min. treadmill gait with 1 min. rest in between [12]. Participants are not allowed to walk overground during the rest but a chair will be provided if necessary. Subjects are wearing a harness to prevent falling. Belt speed will be adjusted according to the individual's comfortable overground gait velocity. Previous studies have shown **improved gait symmetry after split-belt conditions with slower belt speed of the side with the longer step length ('best side reduction')** in PD and stroke [19, 23]. As it has been shown that belt speed ratio but not absolute speed impacts on gait asymmetry (unpublished data), we chose to decrease the belt speed of the side with the longer step length rather than increasing the belt speed of the side with the shorter step length. Also, to avoid hastening, the 'best side reduction' principle will be adopted using a 3:4 or 1:2 ratios (table 1).

Table 1: Belt speed of the 4 treatment groups

Group	Belt speed ratio	Belt speed of the leg with the longer step length (% of overground gait speed)	Belt speed of the leg with the shorter step length (% of overground gait speed)
A-Steady Split-belt Treadmill	3:4	75%	100%
B-Steady Split-belt Treadmill	1:2	50%	100%
C-Transfer Split-belt Treadmill	changing	50-75%	100%
D-Treadmill (tied-belt)	1:1	100%	100%

Outcome Measures

Laboratory FOG assessment: A FOG ratio score will be calculated [24]. FOG will be analysed with accelerometer sensors (APDM) during FOG provoking tasks (360° turning in place (right/left side alternating) for 1 minute with and without a cognitive dual task.

Overground gait analysis: the following gait variables will be analysed during 5 trials of 5m gait with comfortable pace (assessed via accelerometer sensors (APDM) and Vicon/Qualisys motion capture analysis): step length, gait asymmetry, gait variability, bilateral coordination [25] and gait velocity.

Treadmill gait analysis: adaptive capacity during transitions will be assessed by analysing the above mentioned variables during changing split-belt conditions. Retroreflective markers will be placed bilaterally on the limbs to allow gait analysis at 100Hz with infrared cameras.

Descriptors: MDS-Unified Parkinson's Disease Rating Scale (MDS-UPDRS) [26], New Freezing of Gait Questionnaire [27], Mini Mental State Exam (MMSE) [28], Montreal Cognitive Assessment (MoCA) [29], Frontal Assessment Battery, Falls Efficacy Scale International (FES-I), Mini-BESTest [30], Borg Rating of Perceived Exertion, Visual Analogue Scale for fatigue and number of falls during the last 6 months.

VI. Planned Statistical analysis & Data Management

Data storage: Part of the data obtained on paper (e.g. questionnaires, informed consent forms) will be stored in an excel file. The data obtained by computerized measures will all be stored in the original digital files, and the main variables will be stored in excel datafiles. All data will regularly be backed up to a secure KU Leuven server.

Statistics: Data from both centres will be pooled for the statistical analysis. The immediate effects and short term (24 hour) retention of split-belt treadmill training on overground gait symmetry and the freezing ratio during the turning task are the **main outcomes of interest**. Repeated measures ANOVA with group and training condition as between subjects factors will be employed in order to test this. Effect sizes will be determined and a post-hoc power calculation will be performed to ascertain sample sizes for a planned larger training study.

VII. Safety

Our laboratory has vast experience with testing patients with PD. Testing will be carried out in a standard movement laboratory setting when using their normal medication. Subjects will be asked to wear well-fitting, flat-heeled and comfortable shoes for walking during the session and a safety harness will be provided while on the treadmill to avoid falls at all times In between trials, sufficient seated rest periods will be inserted to avoid fatigue. Two experienced testers will be present at all times to ensure safety of the participants. If patients require their normal medication, this will be accommodated. No interference with normal intake is foreseen.

VIII. Costs

Full reimbursement of travel expenses for the people with Parkinson's disease and age-matched controls (i.e. the healthy elderly) will be covered by the project. There will be no additional reimbursements.

IX. Ethics

The protocol is submitted for review to the **local Ethics Committee** of the KU Leuven (Commissie Medische Ethiek UZ Leuven, Herestraat 49, 3000 Leuven). The study will be performed in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki, 1967) and the principles of GCP. Any subsequent protocol amendments will be submitted to the Ethics Committee and Regulatory Authorities for approval.

After complete explanation of the study protocol, **written informed consent** will be obtained from all participants prior to participation in the experiment.

The investigators will treat all information and data relating to the study **confidentially** and will not distribute this information to third parties or use it for any other purpose than the current study. Data will be coded and will be protected from disclosure outside the research environment.

The collection, processing and disclosure of personal data, such as patient health and medical information is subject to compliance with applicable personal data protection and the processing of personal data (Directive 95/46/EC and Belgian law of December 8, 1992 on the Protection of the Privacy in relation to the Processing of Personal Data).

X. Insurance

In accordance with the Belgian Law relating to experiments on human persons dated May 7, 2004, **Sponsor shall assume, even without fault, the responsibility of any damages** incurred by a Study Patient and linked directly or indirectly to the participation to the Study, and shall provide compensation therefore through its insurance. **Sponsor delegates** his insurance duty (pursuant to art 29 of the Belgian Law relating to experiments on human persons dated May 7, 2004,) **for participants in other countries than Belgium** to the respective participating site(s) of that country, who hereby accept(s).

References

[1] Pringsheim T, Jette N, Frolkis A, Steeves TD. The prevalence of Parkinson's disease: a systematic review and meta-analysis. Mov Disord. 2014;29:1583-90.

[2] Muangpaisan W, Mathews A, Hori H, Seidel D. A systematic review of the worldwide prevalence and incidence of Parkinson's disease. J Med Assoc Thai. 2011;94:749-55.

[3] Boland DF, Stacy M. The economic and quality of life burden associated with Parkinson's disease: a focus on symptoms. Am J Manag Care. 2012;18:S168-75.
[4] Walton CC, Shine JM, Hall JM, O'Callaghan C, Mowszowski L, Gilat M, et al. The major impact of freezing of gait on quality of life in Parkinson's disease. J Neurol. 2015;262:108-15.
[5] Latt MD, Lord SR, Morris JG, Fung VS. Clinical and physiological assessments for elucidating falls risk in Parkinson's disease. Mov Disord. 2009;24:1280-9.
[6] Giladi N, Treves TA, Simon ES, Shabtai H, Orlov Y, Kandinov B, et al. Freezing of gait in patients with advanced Parkinson's disease. J Neural Transm. 2001;108:53-61.
[7] Schlenstedt C, Shalash A, Muthuraman M, Falk D, Witt K, Deuschl G. Effect of high-frequency subthalamic neurostimulation on gait and freezing of gait in Parkinson's disease: a systematic review and meta-analysis. Eur J Neurol. 2016.
[8] Nutt JG, Bloem BR, Giladi N, Hallett M, Horak FB, Nieuwboer A. Freezing of gait: moving forward on a mysterious clinical phenomenon. Lancet Neurol. 2011;10:734-44.
[9] Tomlinson CL, Herd CP, Clarke CE, Meek C, Patel S, Stowe R, et al. Physiotherapy for Parkinson's disease: a comparison of techniques. Cochrane Database Syst Rev. 2014;6:CD002815.
[10] Petzinger GM, Holschneider DP, Fisher BE, McEwen S, Kintz N, Halliday M, et al. The Effects of Exercise on Dopamine Neurotransmission in Parkinson's Disease: Targeting Neuroplasticity to Modulate Basal Ganglia Circuitry. Brain Plast. 2015;1:29-39.
[11] Shen X, Wong-Yu IS, Mak MK. Effects of Exercise on Falls, Balance, and Gait Ability in Parkinson's Disease: A Meta-analysis. Neurorehabil Neural Repair. 2016;30:512-27.
[12] Peterson DS, Plotnik M, Hausdorff JM, Earhart GM. Evidence for a relationship between bilateral coordination during complex gait tasks and freezing of gait in Parkinson's disease. Parkinsonism Relat Disord. 2012:1022-6.
[13] Plotnik M, Giladi N, Hausdorff JM. Bilateral coordination of walking and freezing of gait in Parkinson's disease. Eur J Neurosci. 2008;27:1999-2006.
[14] Plotnik M, Giladi N, Hausdorff JM. Is freezing of gait in Parkinson's disease a result of multiple gait impairments? Implications for treatment. Parkinson's disease. 2012;2012:459321.
[15] Plotnik M, Giladi N, Balash Y, Peretz C, Hausdorff JM. Is freezing of gait in Parkinson's disease related to asymmetric motor function? Ann Neurol. 2005;57:656-63.
[16] Moore ST, MacDougall HG, Ondo WG. Ambulatory monitoring of freezing of gait in Parkinson's disease. J Neurosci Methods. 2008;167:340-8.
[17] Schaafsma JD, Balash Y, Gurevich T, Bartels AL, Hausdorff JM, Giladi N. Characterization of freezing of gait subtypes and the response of each to levodopa in Parkinson's disease. Eur J Neurol. 2003;10:391-8.
[18] Mohammadi F, Bruijn SM, Vervoort G, van Wegen EE, Kwakkel G, Verschueren S, et al. Motor switching and motor adaptation deficits contribute to freezing of gait in Parkinson's disease. Neurorehabil Neural Repair. 2015;29:132-42.

[19] Fasano A, Schlenstedt C, Herzog J, Plotnik M, Rose FE, Volkmann J, et al. Split-belt locomotion in Parkinson's disease links asymmetry, dyscoordination and sequence effect. Gait Posture. 2016;48:6-12.
[20] Dayan E, Cohen LG. Neuroplasticity subserving motor skill learning. Neuron. 2011;72:443-54.
[21] Nieuwboer A, Rochester L, Muncks L, Swinnen SP. Motor learning in Parkinson's disease: limitations and potential for rehabilitation. Parkinsonism Relat Disord. 2009;15 Suppl 3:S53-8.
[22] Klamroth, S., Steib, S., Gaßner, H., Goßler, J., Winkler, J., Eskofier, B., … Pfeifer, K. (2016). Immediate effects of perturbation treadmill training on gait and postural control in patients with Parkinson's disease. Gait and Posture, 50, 102–108.
[23] Reisman DS, McLean H, Keller J, Danks KA, Bastian AJ. Repeated Split-Belt Treadmill Training Improves Poststroke Step Length Asymmetry. Neurorehabil Neural Repair. 2013.
[24] Mancini, M., Smulders, K., Cohen, R. G., Horak, F. B., Giladi, N., & Nutt, J. G. (2017). The clinical significance of freezing while turning in Parkinson's disease. Neuroscience, 343, 222-228.
[25] Plotnik M, Giladi N, Hausdorff JM. A new measure for quantifying the bilateral coordination of human gait: effects of aging and Parkinson's disease. Exp Brain Res. 2007;181:561-70.
[26] Goetz CG, Tilley BC, Shaftman SR, Stebbins GT, Fahn S, Martinez-Martin P, et al. Movement Disorder Society-sponsored revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS): scale presentation and clinimetric testing results. Mov Disord. 2008;23:2129-70.
[27] Nieuwboer A, Rochester L, Herman T, Vandenberghe W, Emil GE, Thomaes T, et al. Reliability of the new freezing of gait questionnaire: agreement between patients with Parkinson's disease and their carers. Gait Posture. 2009;30:459-63.
[28] Folstein MF, Folstein SE, McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res. 1975;12:189-98.
[29] Nasreddine ZS, Phillips NA, Bedirian V, Charbonneau S, Whitehead V, Collin I, et al. The Montreal Cognitive Assessment, MoCA: a brief screening tool for mild cognitive impairment. J Am Geriatr Soc. 2005;53:695-9.
[30] Löfgren, N., Lenholm, E., Conradsson, D., Ståhle, A., & Franzén, E. (2014). The Mini-BESTest - a clinically reproducible tool for balance evaluations in mild to moderate Parkinson's disease? BMC Neurology, 14, 235. http://doi.org/10.1186/s12883-014-0235-7