The Turning and Barrier Course: a standardized tool for identifying freezing of gait and demonstrating the efficacy of deep brain stimulation

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Abstract

Freezing of gait (FOG) is a devastating axial motor symptom in Parkinson's disease leading to falls, decreased mobility and quality of life. Reliably eliciting FOG and quantifying impaired gait has been difficult in the clinic and laboratory, and have prevented elucidation of underlying neurobiomechanical mechanisms, making this symptom one of the unsolved challenges in the treatment of Parkinson's disease. The efficacy of treating FOG with different frequencies of subthalamic deep brain stimulation (STN DBS) is unclear, and this may be due to the variety of methodologies used to assess FOG. In this study we validated an instrumented gait task, the turning and barrier course (TBC) with the international standard FOG questionnaire (FOG-Q, $r = 0.74$, $p < 0.001$). The TBC is easy to assemble and mimics real-life environments that elicit FOG. Non-freezing gait arrhythmicity, shank angular velocity and stride time from the TBC differentiated freezers from non-freezers ($p < 0.01$) and predicted FOG severity. Both 60 Hz and 140 Hz STN DBS improved percent time freezing ($p < 0.05$) and non-freezing gait arrhythmicity and shank angular velocity in freezers ($p < 0.05$), which were restored to non-freezer values. A novel logistic regression model determined that the combination of gait arrhythmicity, stride time, swing angular range and asymmetry best predicted FOG. These may serve as functionally relevant behavioral signals for kinematic closed loop neurostimulation for FOG and gait impairment in PD.

Abbreviations

FOG = freezing of gait; DBS = deep brain stimulation; STN = subthalamic nucleus; TBC = Turning and Barrier Course; FW = forward walking; Inertial Measurement Unit = IMU; FOG-Q = Freezing of Gait Questionnaire; LOOCV = leave-one-out cross validation; AUROC = Area Under Receiver Operator Curve; UPDRS = Unified Parkinson's Disease Rating Scale

Introduction

Gait impairment and freezing of gait (FOG) are common in neurodegenerative diseases such as Parkinson's disease (PD), and lead to falls (Giladi et al., 1992; Lippa et al., 2007; Morgan et al., 2007) resulting in injury, loss of independence, institutionalization and even death (Bloem et al., 2004; Brozova et al., 2009). Over 10 million people are affected by Parkinson's disease worldwide, and close to 75% of PD people have gait impairment and FOG as the disease progresses (Panisset, 2004). Understanding and treating these motor disorders are a paramount unmet need, and they were given the highest priority at the National Institute of Neurological Disorders and Stroke 2014 PD conference (Sieber et al., 2014). Gait impairment is characterized by the loss of regular rhythmic alternating foot stepping associated with normal forward locomotion. FOG is an intermittent, involuntary and often sudden inability to perform alternating stepping: the feet appear 'glued' to the ground while the upper body continues its original trajectory. FOG manifests as patients attempt to initiate walking, while turning, and while navigating obstacles. Both gait impairment and FOG have unpredictable responses to dopaminergic medication and/or continuous high frequency open loop deep brain stimulation (DBS) (Merola et al., 2011; Schlenstedt et al., 2017). Although gait impairment and FOG may improve on lower frequency (60 Hz) subthalamic DBS, PD tremor may worsen and most patients do not tolerate 60 Hz DBS for long periods of time (Moreau et al., 2008; Xie et al., 2017, 2015).

It is difficult to assess the severity of FOG because it is an episodic phenomenon and may not occur during clinical examinations due to the patient's increased attention to gait and the lack of obstacles and narrow doorways in a standard clinic. A recent review showcased several available assessment tools for FOG including history taking, questionnaires, home-based

assessments, and clinic-based measurements (Barthel et al., 2016). The authors concluded that there is no "unique methodological tool that encompasses the entire complexity of FOG" and "further development of such an assessment tool requires understanding and thorough analysis of the specific FOG characteristics" (Barthel et al., 2016).

Several studies have employed wearable inertial sensors in a variety of different tasks, such as turning 360 degrees in place for two minutes, walking around cones, or walking during dual tasking, to monitor, detect and predict FOG (Coste et al., 2014; Khemani et al., 2015; Kim et al., 2015; Kwon et al., 2014; Palmerini et al., 2017; Rezvanian and Lockhart, 2016; Silva de Lima et al., 2017; Zach et al., 2015). These tasks have improved the detection resolution of FOG but are either not representative of real-world environments or still require a clinical rater to detect freezing episodes, and cannot objectively measure gait impairment, such as arrhythmicity, that is correlated with FOG (Anidi et al., 2018; Hausdorff, 2009; Nantel et al., 2011; Plotnik and Hausdorff, 2008; Syrkin-Nikolau et al., 2017). An unmet need is a reliable, reproducible, objective measure of gait impairment and FOG using an easy to construct forward walking task, that mimics real-world environments that trigger FOG. Such an instrumented task will enable objective and quantitative assessments of patient progression, therapeutic interventions and provide relevant kinematic variables for closed loop deep brain stimulation for FOG in PD.

The main goals of this study were to (1) validate a standardized, instrumented gait task, the Turning and Barrier Course (TBC) that mimics real-life environments, to use the TBC (2) to discover relevant IMU-based gait parameters for detecting FOG in PD and (3) to demonstrate the effect of lower and high frequency subthalamic deep brain stimulation (STN DBS) on quantitative measures of non-freezing gait and FOG.

Materials and Methods

Human subjects

Twenty-three PD subjects (8 female), and 12 age-matched healthy controls (11 female), participated in the study. Subjects were recruited from the Stanford Movement Disorders Center and were not pre-selected based on a history of FOG. Subjects were excluded if they had peripheral neuropathy, hip/knee prostheses, structural brain disorders, or any visual/anatomical abnormalities that affected their walking. For all PD subjects, long-acting dopaminergic medication was withdrawn over 24h (72h for extended-release dopamine agonists), and short-acting medication was withdrawn over 12h before all study visits. A certified rater performed the Movement Disorder Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS III) motor disability scale, and the Freezing of Gait Questionnaire (FOG-Q) on all subjects. Four subjects had FOG-Q scores taken from a prior research visit within the last 4 months. Subjects were classified as a freezer or non-freezer based on the FOG-Q question 3 (FOG-Q3): *Do you feel that your feet get glued to the floor while walking, turning or when trying to initiate walking?* The scores are as follows: *0 – never, 1 – about once a month, 2 – about once a week, 3 – about once a day, 4 – whenever walking*. A freezer was defined as a subject with a FOG-Q3 ≥ 2, and/or if the subject exhibited a freezing event during the tasks. All tasks were visually inspected by the experimenter and offline by a blinded, experienced neurologist to determine the occurrence of freezing. Control subjects were excluded if they reported neurological deficits or interfering pathology that affected their gait. All subjects gave their written informed consent to participate in the study, which was FDA and Stanford IRB approved.

Experimental protocol

All experiments were performed off therapy (medication and/or DBS). Subjects performed two gait tasks: Forward Walking (FW) and the Turning and Barrier Course (TBC), in a randomized order. Both tasks started with 20s of quiet standing. For the FW task, subjects walked in a straight line for 10m, turned around and returned, and repeated this for a total of 40 m. The FW task was conducted in a makeshift hallway at least 5.5 feet wide formed by a wall and room dividers (Bretford Mobile Screens, Pivot Interiors Inc., Pleasanton, CA). The room dividers were 6.5 feet high and a maximum of 3.75 inches wide. In the TBC, subjects walked around and through a narrow opening formed by room dividers (Syrkin-Nikolau et al., 2017), Figure 1A.

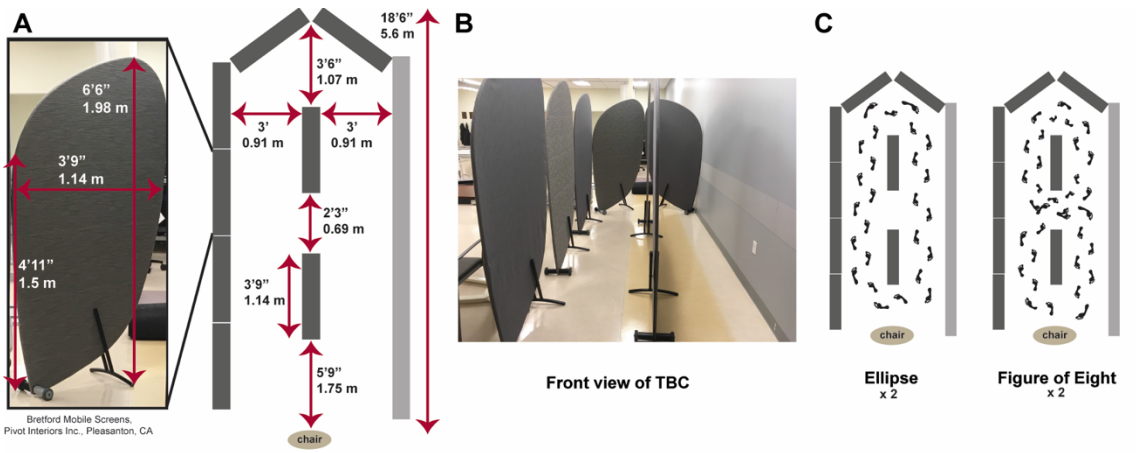


Figure 1. TBC dimensions and specifications. (A) TBC individual barrier dimensions and course specifications. Tall barriers limited visual field around turns and narrow passageway simulates real-world environment. (B) Front view and (C) aerial view of TBC. Subjects walked in two ellipses then two figures of eight around barriers and repeat starting on both the left and right side.

The TBC was enclosed by a row of dividers on one side and a wall on the other, Fig. 1B, which limited the extent of the subjects' visual field; the aisles of the TBC were the same width as a standard minimum hallway (3 feet) in the U.S., and the narrow opening between dividers (2.25

feet) was the same width as a standard doorway, Fig. 1A. After the initial standing rest period, the subject was instructed to sit on the chair. At the 'Go' command, the subject was instructed to stand up, walk around the dividers twice in an ellipse, and then walk in a 'figure eight', around and through the opening between the dividers, twice, before sitting down again, Fig. 1C. The subject was then instructed to repeat the task in the opposite direction, for a total of four ellipses and four figures of eight. The direction order was randomized per subject.

Data acquisition and analysis

Shank angular velocity was measured during the gait tasks using wearable inertial measurement units (IMUs, APDM, Inc., Portland, OR), which were positioned in a standardized manner for all subjects laterally on both shanks. Signals from the IMU tri-axial gyroscope, accelerometer and magnetometer were sampled at 128 Hz. Care was taken to align the sensor on the shank so that the positive Z-axis was lateral and picked up the gait angular velocity in the sagittal plane. The data were filtered using a zero phase 8th order low pass Butterworth filter with a 9 Hz cut-off frequency and principal component analysis was used to align the angular velocity with the sagittal plane. We used signals from the gyroscope and accelerometer for this study. Using the aligned Z-angular velocity, the beginning of the swing phase (positive slope zero crossing), end of swing phase (subsequent negative slope zero crossing), and peak shank angular velocities (first positive peak following the beginning of swing phase) were identified, Figure 2.

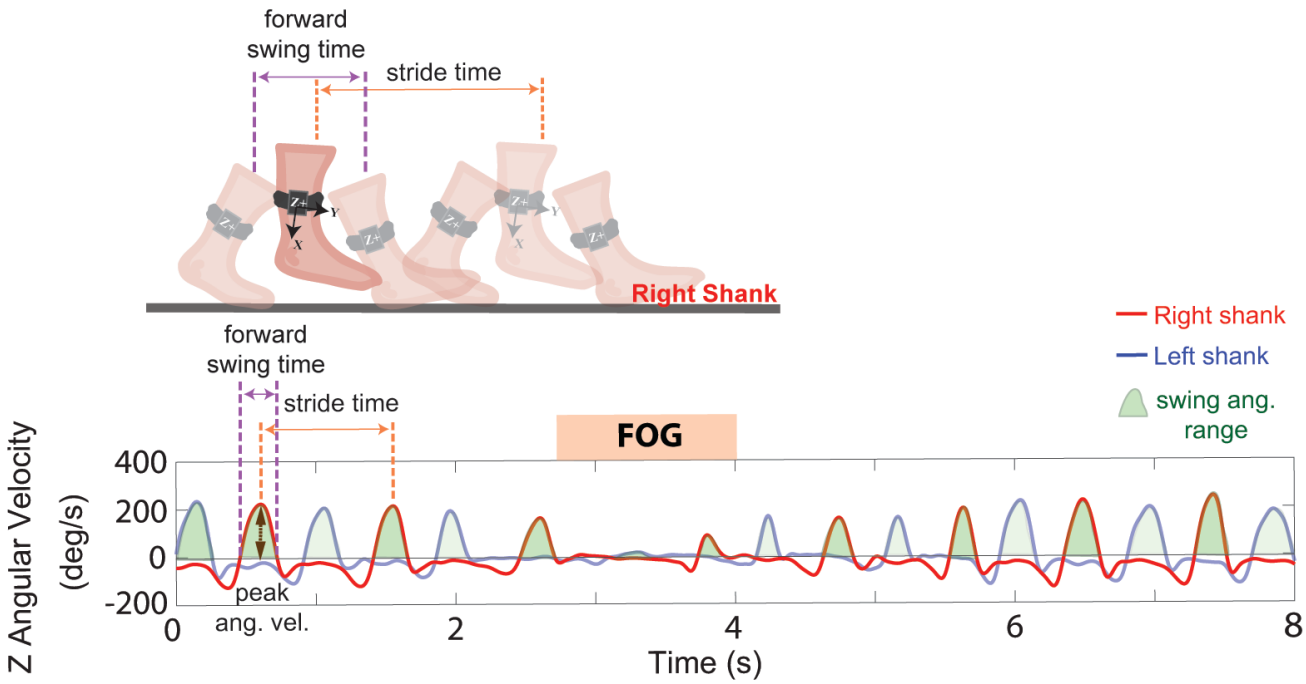


Figure 2. Schematic of two gait cycles and definition of gait parameters including stride time, forward swing time, swing angular range and peak angular velocities. Gait parameters extracted from shank sagittal (about the Z-axis) angular velocity data for the left (blue) and right (red) legs during periods of non-freezing walking, and freezing of gait (FOG) marked by a neurologist (shaded apricot).

Forward swing times (time between subsequent zero crossings of the same leg) and stride times (time between consecutive peak angular velocities) were calculated from these data points. Swing angular range was calculated as the area under the Z angular velocity curve during the swing time. Swing times and stride times were then used to calculate asymmetry and arrhythmicity respectively, during periods where the subject was not freezing. Asymmetry was defined as: asymmetry = 100 × |ln(SSWT/LSWT)|, where SSWT and LSWT correspond to the leg with the shortest and longest mean swing time over the trials, respectively and arrhythmicity was defined as: arrhythmicity = the mean stride time coefficient of variation (CV) of both legs (Nantel et al., 2011; Plotnik et al., 2005; Plotnik and Hausdorff, 2008). A large stride time CV is indicative of a less rhythmic gait.

External videos of all tasks were acquired on an encrypted clinical iPad (Apple Inc., Sunnyvale, CA) and synchronized with the APDM data capture system through the Videography application (Appologics Inc., Germany).

A logistic regression model of freezing of gait

We developed a logistic regression model to calculate the probability that a given stride was part of a freezing episode. It was trained using 8 gait parameters (peak shank angular velocity, stride time, swing angular range, arrhythmicity, asymmetry, freeze index, peak shank angular velocity of the previous step, stride time of the previous step) and ground truth binary labels (FOG = 1, no FOG = 0), from an experienced neurologist's (HBS) video-determined ratings of freezing behavior. VCode software (Hagedorn, Hailpern, & Karahalios, 2008), was used to mark the strides that exemplified freezing behavior in each video with an accuracy of 10ms. Individual strides were identified using the shank angular velocity trace as described above, and gait parameters were extracted for each stride. The following gait parameters were calculated for each leg independently: peak shank angular velocity, stride time, swing time and swing angular range. The stride time and peak shank angular velocity were normalized to averages from the subject's forward walking so that subjects could be combined and compared to one another in the model. The peak shank angular velocity for the previous stride was also included as an input parameter in the model to capture the assumption that if the step before had characteristics of a freeze, then this step might be more likely to be a freeze. The swing and stride times for both legs were then concatenated so that arrhythmicity and asymmetry over the past 6 strides could be calculated. The "Forward Freeze Index" was inspired by the "Freeze Index" (Moore et al., 2008), and used antero-posterior accelerations instead of vertical

accelerations, making it similar to the "Frequency Ratio" (Mancini et al., 2012). We used a window of 2s rather than 4s because 2s was closer to the mean stride time, and therefore consistent with our other stride-by-stride metrics. The power spectrum was calculated for the antero-posterior shank accelerations over a 500ms window with 80% overlap. The Forward Freeze Index was calculated as the square of the total power in the freeze band (3-8 Hz) over a 2s window, divided by the square of the total power in the locomotor band (0.5-3 Hz) over the same 2s window.

Analysis of gait parameters was performed in MATLAB (version 9.2, The MathWorks Inc. Natick, MA, USA), and the logistic regression model was constructed using R (R Core Team (2017)). We used logistic regression with L1 regularization (LASSO) to predict whether a step was freezing or not. To evaluate model performance, we used leave-one-out cross validation (LOOCV), which we refer to as external LOOCV. In each step, we selected the best regularization parameter using internal LOOCV. We found that the variables selected by the internal LOOCV were consistent across all runs, giving the combination of variables that best identified FOG.

Investigating effects of DBS frequency in a subset of the PD cohort

A subset of the cohort, twelve PD subjects (7 freezers and 5 non-freezers), had been treated with at least 21 months of optimized, continuous high frequency subthalamic deep brain stimulation (STN DBS) using an implanted, investigative, concurrent sensing and stimulating, neurostimulator (Activa® PC + S, FDA-IDE approved; model 3389 leads, Medtronic, Inc.). Kinematic recordings were obtained, off medication, during randomized presentations of no, 60 Hz, and 140 Hz STN DBS while subjects performed the TBC. The voltage was the same at both

frequencies for each subject's STN. At least five minutes was allotted between experiments to allow the subjects to rest.

Statistics

A Holm-Sidak two-way repeated measures analyses of variance (ANOVA) was used to calculate the effect of Group (Control, Non-Freezer and Freezer) or Task (Forward Walking, TBC Ellipse, TBC Figure Eight), on average peak shank angular velocity, stride time, asymmetry and arrhythmicity for the three groups during non-freezing walking. Student's t-tests were used for the comparison of demographics between the freezer, non-freezer and control groups. Paired t-tests were used to compare UPDRS III scores between visits for subjects with repeated visits. Paired t-tests were used to compare the effects of different stimulation frequencies on average peak shank angular velocity, stride time, asymmetry and arrhythmicity within each group for each task. Post hoc analyses were conducted to compare between stimulation conditions. The relationship between percent time freezing and FOG-Q3 response was investigated using a Spearman correlation analysis. The relationship between percent time freezing and average peak shank angular velocity, stride time, asymmetry and arrhythmicity during non-freezing walking was investigated using a Pearson correlation analysis to compare freezers' non-freezing walking with the severity of their freezing behavior. All statistical testing was performed in either R Studio (R Core Team (2017)), or SigmaPlot (Systat Software, San Jose, CA) using two-tailed tests with significance levels of $p < .05$.

Results

Human subjects

Among the 23 PD subjects, there were 8 freezers, 13 non-freezers, and 2 subjects who converted from the definition of a non-freezer to that of a freezer between two visits. Non-freezers and controls were of similar ages, while freezers were younger (65.92 ± 7.58, 66.86 ± 8.78 years, 57.95 ± 6.14, respectively, $p < 0.05$). Disease duration was similar between the freezer and non-freezer groups (9.3 ± 2.8, 8.9 ± 4.2 years respectively). Freezers had a higher off medication UPDRS III motor score than non-freezers (39.8 ± 9.2, 24.1 ± 13.6 respectively, $p < 0.01$), and all PD patients had higher UPDRS III motor scores than controls ($p < 0.001$). All subjects completed all walking tasks, except two freezers who could not complete the TBC, and one non-freezer whose sensor data was unusable, and these three subjects were excluded. Three healthy control subjects were excluded due to arthritis (N=2) or Essential Tremor (N=1), which affected their walking. The average total durations of FW and the TBC were 33.1 ± 8.7 and 157.4 ± 88.9 seconds, respectively.

Eleven subjects had repeat visits, and two of these subjects converted from the non-freezer classification to the freezer classification between testing dates. The length between repeated visits was 433 ± 71 days (mean ± SD), and patients' UPDRS III score was similar between visits (32.4 ± 12.0, 35.7 ± 14.8, respectively, $p = 0.054$). The average change in UPDRS III motor score (3.2 ± 4.3) was above the minimal clinically important deterioration of 2.3-2.7 on the UPDRS III (Shulman et al., 2010). Because of this, repeated patient visits were treated independently. Data from 40 visits (9 from controls, 13 from freezers, and 18 from non-freezers) were used to examine how the three different cohorts completed the gait tasks while OFF stimulation. A leave-one-out cross validation was used to develop and test the logistic regression model, where all data from a single patient was either left out in the test set, or included in the

training set, so as not to bias the model. In assessing the effects of lower and high frequency STN DBS on subjects in the TBC, there were no repeat visits.

Non-freezing gait parameters differentiated freezers from non-freezers during the TBC

Freezers exhibited more arrhythmic non-freezing gait than non-freezers and controls during both the ellipses and figure eights of the TBC ($p < 0.01$), Figure 3A, whereas all three groups exhibited rhythmic gait during FW.

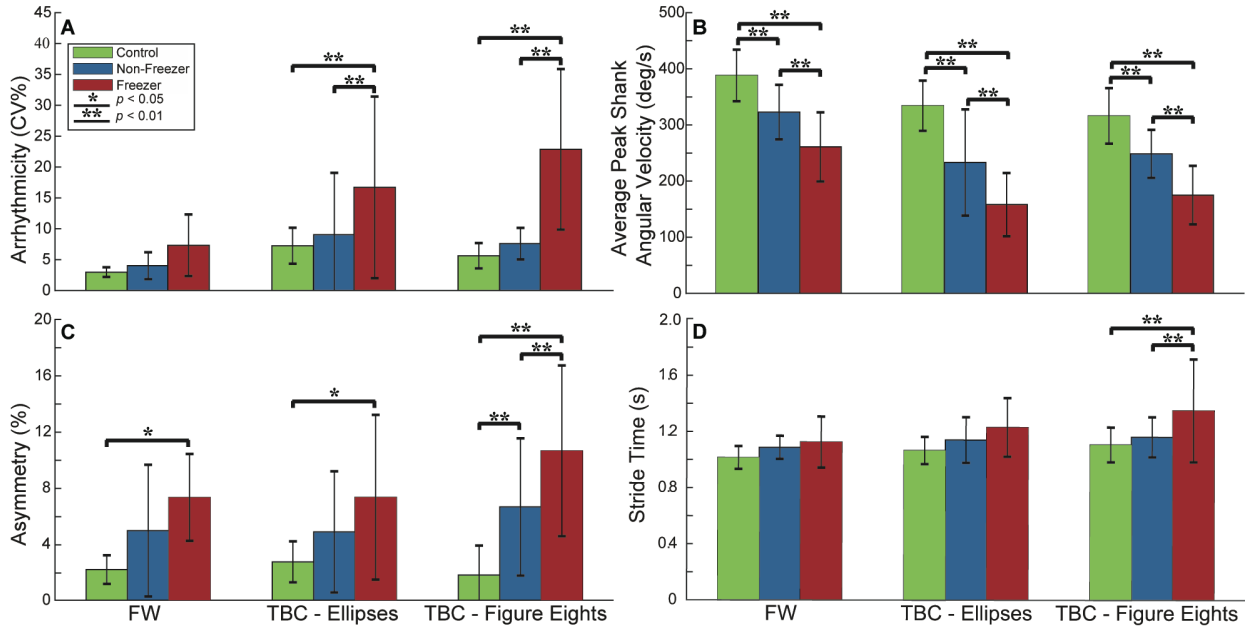


Figure 3. Gait parameters during non-freezing walking differentiated groups, especially during the TBC. (A) Arrhythmicity (B) Average peak shank angular velocity (C) Asymmetry (D) Stride time. Error bars represent standard deviation. * denotes $p < 0.05$ and ** denotes $p < 0.01$.

Freezers' average peak shank angular velocity, or "shank angular velocity" for convenience, was lower than that of non-freezers and controls during non-freezing gait of the FW and the TBC tasks ($p < 0.01$, Fig 3B). Freezers' non-freezing gait was more asymmetric than controls in every gait task ($p < 0.05$, Fig 3C), but asymmetry only differentiated freezers from non-freezers

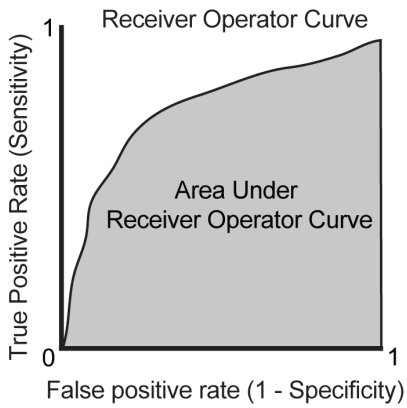
during the figure eights of the TBC ($p < 0.01$). Non-freezing gait stride time differentiated freezers from non-freezers and healthy controls only during figure eights of the TBC ($p < 0.01$, Fig.3D).

The TBC elicited more gait impairment than FW among freezers

Freezers' non-freezing gait during both the ellipses and figures of eight of the TBC demonstrated greater arrhythmicity compared to their non-freezing gait during FW, Fig. 3A, ($p = 0.002$, $p < 0.001$, respectively), and their arrhythmicity was greater in the figures of eight than in the ellipses of the TBC ($p < 0.05$). Freezers' non-freezing shank angular velocity was lower during the TBC compared to FW, Fig. 3B, ($p < 0.001$) but was not different between ellipses and figures of eight. Freezers' stride times were slower during the TBC compared to FW, Fig. 3D, ($p < 0.05$), and were slower in the figures of eight than in the ellipses of the TBC ($p = 0.01$). The only difference among tasks for both the non-freezer and control groups was lower shank angular velocity in both the TBC ellipses and figures of eight compared to FW, Fig 3B ($p < 0.01$). During the TBC, all freezers and none of the non-freezers experienced a freezing event. Freezers spent an average of 33.0 ± 24.2 % of the time freezing in the TBC, compared to 0.19 % of the time freezing during forward walking (as determined by the blinded neurologist). There was a strong correlation between the time spent freezing in the TBC and a subjects' report of freezing severity from the FOG-Q3 ($r = 0.74$, $p < 0.001$). There was no correlation between the time spent freezing during FW and a subjects' report of freezing severity from the FOG-Q3 ($r = 0.28$, $p = 0.075$).

Gait features in logistic regression model detect freezing on a step-by-step basis

We trained and tested a logistic regression model to determine whether an individual gait cycle was part of a freezing episode or not, Figure 4. The model was trained using individual freezer's gait cycles and "gold standard" ground truth labels from the neurologist.



	Swing Ang. Range (t)	Stride Time (t)	Arrhythmicity (t-5:t)	Asymmetry (t-5:t)	Swing Time (t)	Peak Shank AV (t)	Peak Shank AV (t-1)	Forward Freeze Index (t-3:t)
AUROC	0.595	0.511	0.630	0.603	0.595	0.665	0.659	0.575
	0.750							
	0.753							
	0.754							

Figure 4. Area Under the Receiver Operator Curve (AUROC) values for different model iterations using leave-one-out cross validation on the freezer group. First row: AUROC values using individual gait parameters, second-fourth rows: AUROC values for different combinations of gait parameters. (Peak Shank AV = Peak Shank Angular Velocity)

The model was tested and evaluated using external LOOCV. We evaluated the model with a single gait parameter (swing angular range, stride time, arrhythmicity, asymmetry, swing time, or peak shank angular velocity) of the current and previous step and with the Forward Freeze Index (first row Fig. 4). It was then evaluated with all gait parameters (second row Fig. 4), and with the combination of the five gait parameters that significantly contributed to the model when tested individually (stride time, swing time, swing angular range, gait arrhythmicity and gait asymmetry of the past six steps; third row Fig. 4). We then used logistic regression with L1 regularization (LASSO), choosing the regularization parameters using internal LOOCV, and then evaluated performance using external LOOCV. This revealed that the model with the highest AUROC for detecting that a step was part of a freezing episode combined four gait parameters:

stride time, swing angular range, arrhythmicity and asymmetry of the past six steps; this yielded an AUROC of 0.754, (fourth row Fig. 4). The coefficients for this logistic regression model were 2.034 (arrhythmicity over the last six steps), 0.0931 (stride time), -0.0615 (swing angular range), and 0.0003 (asymmetry over the last six steps), with an intercept of 0.941.

The time spent freezing in the TBC for all subjects, identified by the logistic regression model, showed a robust correlation with the subject's score on FOG-Q3 (r = 0.69, $p < 0.001$). The percent time freezing predicted by the model for the healthy control subjects and non-freezers was less than 1% for each subject, except for one subject who had one step erroneously classified as freezing resulting in 2.5% time spent freezing in the TBC.

Percent time spent freezing correlated with freezers' gait parameters during non-freezing gait in the TBC

Freezers' gait arrhythmicity, during non-freezing gait in both ellipses and figures of eight but not during FW, correlated with their percent time freezing in the TBC, as determined by the model (r = 0.95, r = 0.93 respectively, $p < 0.001$ for both), Figure 5.

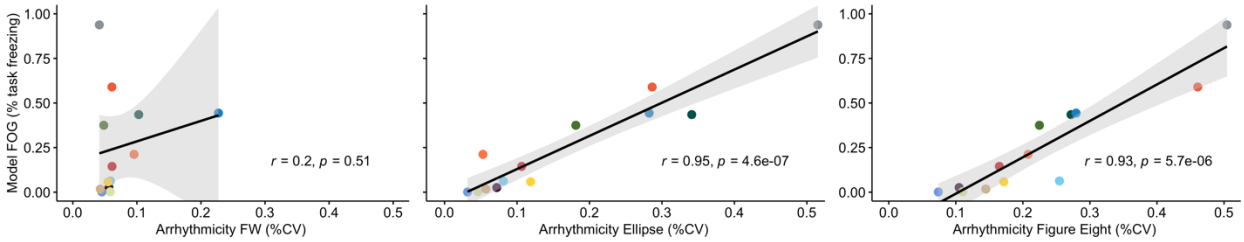


Figure 5. Freezers' arrhythmicity during non-freezing walking in the TBC, but not FW, correlates with percent time spent freezing in the TBC. Each color corresponds to a patient.

Freezers' peak shank angular velocity and stride time during non-freezing gait in figures of eight (not in ellipses or FW) also correlated with their percent time spent freezing in the TBC (r = -0.75, $p < 0.01$ (shank angular velocity); r = 0.59, $p = 0.03$ (stride time)). There was no correlation

between gait asymmetry during non-freezing walking in TBC, or between any gait parameter during FW, with percent time freezing in the TBC. These results demonstrate that increased gait arrhythmicity of non-freezing gait during both ellipses and figures of eight of the TBC was a marker of FOG severity in PD freezers. Decreased peak shank angular velocity and increased stride time of non-freezing gait in the figures of eight were also markers of FOG severity.

Sixty Hz and 140 Hz STN DBS improved non-freezing gait and FOG in freezers during the TBC

Both lower (60 Hz) and high (140 Hz) frequency STN DBS decreased the percent time spent freezing in the TBC for freezers (5 ± 7%, 9 ± 10%, respectively, $p < 0.05$) compared to OFF DBS (35 ± 23%), such that it was not different from that of non-freezers (whose percent time spent freezing was zero). S1 Video highlights the decrease in percent time freezing seen during 60 Hz or 140 Hz DBS versus OFF DBS in a representative patient walking in one ellipse and passing through the narrow passageway in the TBC. This patient went from 53% task freezing while OFF DBS, to 6% task freezing on both 60 Hz and 140 Hz DBS. Freezers' gait arrhythmicity and shank angular velocity of non-freezing gait during the TBC improved to values no different from those of non-freezers during both 60 Hz and 140 Hz DBS ($p< 0.01$, Figure 6); their shank angular velocity was greater during 140 Hz compared to 60 Hz DBS ($p = 0.02$). Freezers also decreased their stride time during 140 Hz DBS ($p = 0.01$).

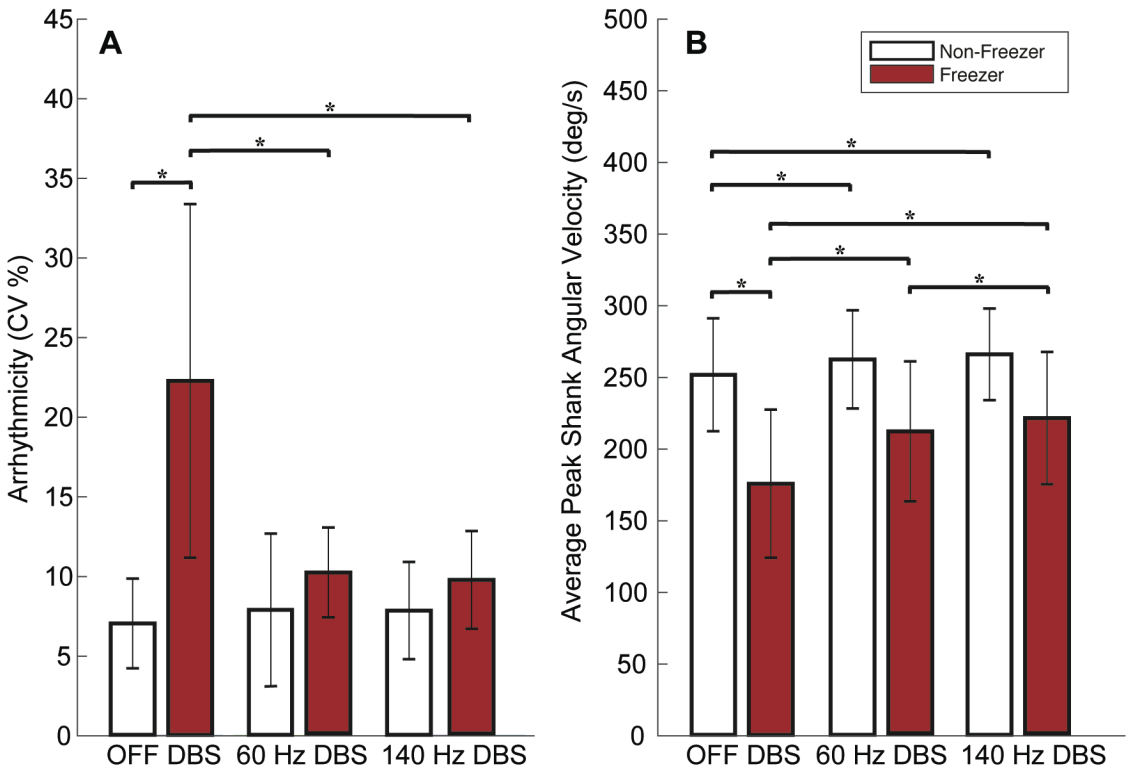


Figure 6. Changes in (A) arrhythmicity and (B) average peak shank angular velocity in freezers (red) and non-freezers (white) during walking in the TBC while OFF and on 60 Hz and 140 Hz DBS. During DBS, freezers' arrhythmicity and average peak shank angular velocity improve to values characteristic of non-freezers. Error bars represent standard deviation.

Non-freezers increased their shank angular velocity ($p < 0.05$) during both 60 Hz and 140 Hz DBS, and decreased their stride time ($p < 0.05$) during 140 Hz DBS, but their arrhythmicity was not altered (Figure 6). Freezers' and non-freezers' asymmetry during the TBC were unchanged by DBS.

Discussion

This study has validated the Turning and Barrier Course (TBC) as a useful task to elicit FOG, the degree of which correlated with the international standard FOG questionnaire (FOG-Q, r = 0.74, $p < 0.001$). The TBC distinguished PD freezers from PD non-freezers and healthy controls based on objective measures even during non-freezing gait. Non-freezing walking in

figures of eight of the TBC differentiated freezers from non-freezers in all four gait parameters (arrhythmicity, asymmetry, shank angular velocity and stride time), whereas differentiation during non-freezing walking in ellipses was seen in two (arrhythmicity and shank angular velocity) and in FW only in one (shank angular velocity). The TBC was superior at eliciting freezing episodes compared to 40 meters of forward walking, which is the standard clinical test of PD gait.

A logistic regression model, using individual and combinations of gait parameters during the TBC, was trained to determine whether an individual gait cycle was part of a freezing episode that was then validated against gold standard neurologist-identified freezing events. The area under the receiver operating curve (AUROC) was greatest (0.754) when the model used a combination of stride time, swing angular range, arrhythmicity and asymmetry of the past six steps. The TBC and this objective algorithm were combined to demonstrate that freezers' gait arrhythmicity during non-freezing gait in both the ellipses and figures of eight of the TBC strongly correlated with their percent time freezing, which could also be predicted by their shank angular velocity and stride time during non-freezing gait in the figures of eight. The TBC was then used to explore the effect of 60 Hz and 140 Hz STN DBS on PD gait in situations that mimic real-life scenarios known to elicit FOG. Both frequencies of STN DBS restored freezers' non-freezing gait metrics and percent time freezing to being no different from that of non-freezers, demonstrating that 60 Hz and 140 Hz STN DBS improve FOG in PD.

The TBC is a powerful, standardized task for assessing impaired gait in PD

It has been difficult to develop an objective measure of FOG since it is challenging to elicit FOG in the clinic or laboratory, where there are few obstacles, tight corners, or narrow

door openings (Nieuwboer and Giladi, 2008). Tasks that have been shown to provoke FOG include rapid clockwise and counterclockwise 360 degree turns in place, and walking with dual tasking (Snijders et al., 2012). We have previously shown that freezing episodes can be elicited and objectively measured during a stepping in place task on dual force plates and performance was highly correlated with the FOG-Q3 (Nantel et al., 2011). In designing the TBC, we desired a forward walking task that did not involve cognitive loading but rather situational triggers for FOG that were representative of real-world scenarios (Syrkin-Nikolau et al., 2017), and which was instrumented to provide objective metrics that would be ideal for testing FOG detection algorithms or for understanding the interaction of FOG with therapy. In this study, we demonstrate the TBC, a task that mimics real-world environments, is simple to assemble and can provide objective measures of FOG and gait impairment that correlate with the patient's self-reported FOG-Q score. Freezers' arrhythmicity during non-freezing walking in the TBC was correlated with the percent time spent freezing in the TBC, and therefore could predict the magnitude of freezing behavior freezers may experience in the real world. The TBC elicited more severe freezing behavior than FW, the standard clinical test of PD gait, and we validated freezing behavior in the TBC to the FOG-Q. The TBC differentiated freezers from non-freezers and controls during non-freezing gait and it accentuated gait impairment among freezers compared to FW, marked by increased gait arrhythmicity, asymmetry, stride time and decreased shank angular velocity. These results demonstrate that the TBC is a simple, useful and standardized tool to elicit and explore the impaired gait during both non-freezing walking and FOG.

Objective detection of freezing behavior using the TBC

Many automated FOG detection algorithms have been reported (Coste et al., 2014; Kim et al., 2015; Moore et al., 2013, 2008; Rezvanian and Lockhart, 2016; Zach et al., 2015), but are consistently limited by small datasets (Silva de Lima et al., 2017). Standardized datasets are needed, so that more comprehensive algorithms that cater to the extensive variance seen in Parkinson's impaired gait and FOG can be tested. The IMU data collected during the TBC in this study was useful for developing an automatic classifier of freezing: using the gait parameters from freezers, we were able to train a logistic regression model to detect freezing behavior on a step-by-step basis. The model classified each individual stride as freezing behavior or not, based on the gait parameters from that stride or a combination of strides before it. This model, even with a relatively small sample size (9 individual freezers), had an area under the receiver operator curve of 0.754, using a combination of gait arrhythmicity, shank angular range, stride time and gait asymmetry, which falls within the range of other shank-IMU-based FOG detection algorithms that reach sensitivities and specificities ranging from 73-99% (Silva de Lima et al., 2017). Many of these algorithms detect FOG based on high frequency components of leg linear acceleration corresponding to leg trembling-FOG , but (Moore et al., 2008) often have lower sensitivity to non-trembling FOG, despite high specificity. Upon inspection, our algorithm was successful at identifying both non-trembling and trembling-FOG as our final model did not rely on the presence of these spectral components. We also validated this model to the gold standard FOG assessment, the FOG-Q.

Increased gait arrhythmicity during non-freezing gait was the strongest predictor of FOG severity, followed by decreased shank angular velocity and increased stride time. These provide relevant and validated control variables for closed loop DBS driven by behavioral signals during

non-freezing gait, that may act to prevent actual freezing episodes and may improve the efficacy of DBS for FOG in PD.

FOG and gait impairment in freezers improve during STN DBS in the TBC

Studies examining the effect of STN DBS on gait and FOG have used clinical assessments such as the UPDRS III (Brozova et al., 2009; Khoo et al., 2014; Moreau et al., 2008; Morris et al., 2017; Ramdhani et al., 2015; Ricchi et al., 2012; Stegemoller et al., 2013; Xie et al., 2015), or forward walking tasks like stand-walk-sit tests (Anidi et al., 2018; Moreau et al., 2008; Ricchi et al., 2012; Stegemoller et al., 2013; Vallabhajosula et al., 2015; Xie et al., 2015) and patient self-reports (Sidiropoulos et al., 2013; Xie et al., 2015) for assessment. Some showed that lower frequency (60 Hz) DBS was better at reducing FOG even in early DBS implants (Ramdhani et al., 2015), and that high frequency (130 Hz) DBS was not. However, these findings were not always reproducible (Xie et al., 2017, 2015). This could be due to the inability of tests to elicit FOG, or the lack of objective, high resolution data. With access to PD freezers, resolute data capture methods, and a task that reliably elicits FOG, we demonstrated that STN DBS improved both FOG and predictors of FOG during non-freezing gait in a gait task that mimicked real-life environments that elicit FOG. During the TBC, freezers spent less time freezing during either frequency of DBS compared to no DBS, which is similar to our reports of the effect of DBS on the stepping in place and forward walking tasks (Anidi et al., 2018). Freezers' gait parameters also improved with both 60 Hz and 140 Hz DBS, to levels that were not different from that of non-freezers', whose gait parameters were largely unchanged by DBS. These results demonstrate that if kinematic features associated with freezing behavior are absent, then there is no change in gait dynamics with either frequency of DBS. This 'if it isn't broken, it

doesn't need fixing' effect of DBS has been observed in gait (Anidi et al., 2018; Vallabhajosula et al., 2015) and in aspects of postural instability (Bronte-Stewart, 2002; Shivitz et al., 2006; Vallabhajosula et al., 2015).

Our previous investigations of the effect of 60 Hz and 140 Hz DBS on repetitive stepping in place and on progressive bradykinesia demonstrated that 60 Hz DBS promoted more regularity in ongoing movement (Anidi et al., 2018; Blumenfeld et al., 2017). In this study, non-freezing gait arrhythmicity improved during both frequencies of DBS. Sixty Hz DBS has been shown to be consistently effective in improving axial symptoms in patients with FOG (Xie et al., 2015), though it is not obvious whether 60 Hz versus 140 Hz is better for FOG in real-world walking tasks. This aligns with conclusions drawn in Vallabhajosula et al., 2015, who found that gait and postural performances with low and high frequency stimulations were largely similar (Vallabhajosula et al., 2015). The results of this study suggest that FOG and the arrhythmicity of non-freezing gait improved during both 60 Hz and 140 Hz DBS, whereas aspects related to increased speed, such as increased shank angular velocity and decreased stride time, showed more improvement during 140 Hz in the freezer cohort.

Altogether this is valuable assurance for patients and clinicians that STN DBS can improve gait and FOG, and that both 60 Hz and 140 Hz improve FOG in real-world walking tasks.

Limitations

Only freezers were used to train and test the logistic regression model, so that the incidence of freezing events was sufficient. Future models might include bootstrapping methods or collect more data to increase the sizes of the training and test sets. In the leave-one-out cross

validation, we also kept subjects, who had multiple visits' worth of data together. For example, if Subject X had two different visits then data from both visits were either in the training set *or* in the test set. We felt that it was most appropriate not to separate subject data from the same person because it was inherently correlated. In the logistic regression model, the stride times and shank angular velocities in the TBC were normalized to the individual's averages from FW. This normalization procedure allowed comparison among individuals whose natural FW speeds varied. In future model versions absolute measures could also be tested.

Conclusions

This study has validated the Turning and Barrier Course (TBC) as a gait task that reliably elicited FOG, was highly correlated with the FOG-Q, and was superior to 40 m of forward walking in differentiating freezers from non-freezers during non-freezing gait and eliciting FOG. The TBC is a standardized walking and turning task that mimics real-life environments that are known to elicit FOG; we provide the source and dimensions of the components and the course, that will allow standardization if useful to other groups. Gait parameters, such as arrhythmicity, asymmetry, peak shank angular velocity, and stride time during non-freezing gait, in the figures of eight of the TBC distinguished PD freezers from non-freezers and from healthy controls. A logistic regression model was developed that was able to detect freezing behavior on a step-by-step basis; the best performance used a combination of increased stride time, decreased swing angular range, increased arrhythmicity and increased asymmetry of the past six steps. Increased gait arrhythmicity, decreased average shank angular velocity and increased mean stride time during non-freezing gait in all or elements of the TBC were highly correlated with the percent time freezing in the task. The TBC and the algorithm were used to investigate the efficacy of 60

Hz and 140 Hz STN DBS for gait impairment and FOG. Freezers' gait arrhythmicity, peak shank angular velocity of non-freezing gait and percent time spent freezing improved to values no different from those of non-freezers during both 60 Hz and 140 Hz DBS. High frequency (140 Hz) DBS was superior to 60 Hz DBS for elements of gait speed (shank angular velocity and stride time) in freezers and both frequencies of DBS improved elements of gait speed in non-freezers.

This study has provided a useful standardized gait task that we hope will be easy to assemble and which reliably elicited FOG in PD. Tools and tasks such as the instrumented TBC, which provide objective measures of pathological behavior, are necessary for designing and assessing personalized interventions and therapies; we have demonstrated the usefulness of this tool for FOG, one of the most debilitating symptoms of PD. Widespread use of this tool can lead to standardized large datasets, with which freezing prediction algorithms can be optimized to improve therapies and interventions for gait impairment in PD and a wider range of movement disorders.

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Declaration of Interest

Dr. Bronte-Stewart is a member of the clinical advisory board for Medtronic Inc.

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References

Anidi, C., O'Day, J.J., Anderson, R.W., Afzal, M.F., Syrkin-Nikolau, J., Velisar, A., Bronte-Stewart, H.M., 2018. Neuromodulation targets pathological not physiological beta bursts during gait in Parkinson's disease. Neurobiol. Dis. 120. https://doi.org/10.1016/j.nbd.2018.09.004

Barthel, C., Mallia, E., Debû, B., Bloem, B.R., Ferraye, M.U., 2016. The Practicalities of Assessing Freezing of Gait. J. Parkinsons. Dis. 6, 667–674. https://doi.org/10.3233/JPD-160927

Bloem, B.R., Hausdorff, J.M., Visser, J.E., Giladi, N., 2004. Falls and freezing of gait in Parkinson's disease: A review of two interconnected, episodic phenomena. Mov. Disord. 19, 871–884. https://doi.org/10.1002/mds.20115

Blumenfeld, Z., Koop, M.M., Prieto, T.E., Shreve, L.A., Velisar, A., Quinn, E.J., Trager, M.H., Brontë-Stewart, H., 2017. Sixty-hertz stimulation improves bradykinesia and amplifies subthalamic low-frequency oscillations. Mov. Disord. 32, 80–88. https://doi.org/10.1002/mds.26837

Bronte-Stewart, H.M., 2002. Postural instability in idiopathic Parkinson's disease: the role of

medication and unilateral pallidotomy. Brain 125, 2100–2114. https://doi.org/10.1093/brain/awf207

Brozova, H., Stochl, J., Roth, J., Ruzicka, E., 2009. Fear of falling has greater influence than other aspects of gait disorders on quality of life in patients with Parkinson's disease. Neuro Endocrinol. Lett. 30, 453–7.

Coste, C., Sijobert, B., Pissard-Gibollet, R., Pasquier, M., Espiau, B., Geny, C., 2014. Detection of Freezing of Gait in Parkinson Disease: Preliminary Results. Sensors 14, 6819–6827. https://doi.org/10.3390/s140406819

Giladi, N., McMahon, D., Przedborski, S., Flaster, E., Guillory, S., Kostic, V., Fahn, S., 1992. Motor blocks in Parkinson's disease. Neurology 42, 333–339. https://doi.org/10.1212/wnl.42.2.333

Hagedorn, J., Hailpern, J., and Karahalios, K., 2008. VCode and VData: Illustrating a new Framework for Supporting the Video Annotation Workflow. Extended Abstracts of AVI 2008.

Hausdorff, J.M., 2009. Gait dynamics in Parkinson's disease: common and distinct behavior among stride length, gait variability, and fractal-like scaling. Chaos 19, 26113. https://doi.org/10.1063/1.3147408

Khemani, P., Dewey, R.B., BH, Q., MP, B., A, B., RG, C., H, O., YJ, J., HJ, K., HJ, K., O, S., E, D., 2015. Deep Brain Stimulation of the Subthalamic Nucleus. JAMA Neurol. 72, 499. https://doi.org/10.1001/jamaneurol.2015.36

Khoo, H.M., Kishima, H., Hosomi, K., Maruo, T., Tani, N., Oshino, S., Shimokawa, T., Yokoe, M., Mochizuki, H., Saitoh, Y., Yoshimine, T., 2014. Low-frequency subthalamic nucleus stimulation in Parkinson's disease: a randomized clinical trial. Mov. Disord. 29, 270–274.

https://doi.org/10.1002/mds.25810

Kim, H., Lee, H.J., Lee, W., Kwon, S., Kim, S.K., Jeon, H.S., Park, H., Shin, C.W., Yi, W.J., Jeon, B.S., Park, K.S., 2015. Unconstrained detection of freezing of Gait in Parkinson's disease patients using smartphone, in: 2015 37th Annual International Conference of the IEEE Engineering in Medicine and Biology Society (EMBC). pp. 3751–3754. https://doi.org/10.1109/EMBC.2015.7319209

Kwon, Y., Park, S.H., Kim, J.-W., Ho, Y., Jeon, H.-M., Bang, M.-J., Jung, G.-I., Lee, S.-M., Eom, G.-M., Koh, S.-B., Lee, J.-W., Jeon, H.S., 2014. A practical method for the detection of freezing of gait in patients with Parkinson's disease. Clin. Interv. Aging 9, 1709–19. https://doi.org/10.2147/CIA.S69773

Lippa, C.F., Duda, J.E., Grossman, M., Hurtig, H.I., Aarsland, D., Boeve, B.F., Brooks, D.J., Dickson, D.W., Dubois, B., Emre, M., Fahn, S., Farmer, J.M., Galasko, D., Galvin, J.E., Goetz, C.G., Growdon, J.H., Gwinn-Hardy, K.A., Hardy, J., Heutink, P., Iwatsubo, T., Kosaka, K., Lee, V.M.Y., Leverenz, J.B., Masliah, E., McKeith, I.G., Nussbaum, R.L., Olanow, C.W., Ravina, B.M., Singleton, A.B., Tanner, C.M., Trojanowski, J.Q., Wszolek, Z.K., 2007. DLB and PDD boundary issues: Diagnosis, treatment, molecular pathology, and biomarkers. Neurology. https://doi.org/10.1212/01.wnl.0000256715.13907.d3

Mancini, M., Priest, K.C., Nutt, J.G., Horak, F.B., 2012. Quantifying freezing of gait in Parkinson's disease during the instrumented timed up and go test. 2012 Annu. Int. Conf. IEEE Eng. Med. Biol. Soc. 1198–1201. https://doi.org/10.1109/EMBC.2012.6346151

Merola, A., Zibetti, M., Angrisano, S., Rizzi, L., Ricchi, V., Artusi, C.A., Lanotte, M., Rizzone, M.G., Lopiano, L., 2011. Parkinson's disease progression at 30 years: a study of subthalamic deep brain-stimulated patients. Brain 134, 2074–2084.

https://doi.org/10.1093/brain/awr121

Moore, S.T., MacDougall, H.G., Ondo, W.G., 2008. Ambulatory monitoring of freezing of gait in Parkinson's disease. J. Neurosci. Methods 167, 340–348. https://doi.org/10.1016/j.jneumeth.2007.08.023

Moore, S.T., Yungher, D.A., Morris, T.R., Dilda, V., MacDougall, H.G., Shine, J.M., Naismith, S.L., Lewis, S.J., 2013. Autonomous identification of freezing of gait in Parkinson's disease from lower-body segmental accelerometry. J. Neuroeng. Rehabil. 10, 19. https://doi.org/10.1186/1743-0003-10-19

Moreau, C., Defebvre, L., Destee, A., Bleuse, S., Clement, F., Blatt, J.L., Krystkowiak, P., Devos, D., 2008. STN-DBS frequency effects on freezing of gait in advanced Parkinson disease. Neurology 71, 80–84. https://doi.org/10.1212/01.wnl.0000303972.16279.46

Morgan, D., Funk, M., Crossley, M., Basran, J., Kirk, A., Dal Bello-Haas, V., 2007. The potential of gait analysis to contribute to differential diagnosis of early stage dementia: current research and future directions. Can. J. Aging.

Morris, R., Lord, S., Lawson, R.A., Coleman, S., Galna, B., Duncan, G.W., Khoo, T.K., Yarnall, A.J., Burn, D.J., Rochester, L., 2017. Gait Rather Than Cognition Predicts Decline in Specific Cognitive Domains in Early Parkinson's Disease. Journals Gerontol. Ser. A 00, 1–7. https://doi.org/10.1093/gerona/glx071

Nantel, J., de Solages, C., Bronte-Stewart, H., 2011. Repetitive stepping in place identifies and measures freezing episodes in subjects with Parkinson's disease. Gait Posture 34, 329–333. https://doi.org/10.1016/j.gaitpost.2011.05.020

Nieuwboer, A., Giladi, N., 2008. The challenge of evaluating freezing of gait in patients with Parkinson's disease. Br. J. Neurosurg. 22, S16–S18.

https://doi.org/10.1080/02688690802448376

Palmerini, L., Rocchi, L., Mazilu, S., Gazit, E., Hausdorff, J.M., Chiari, L., 2017. Identification of characteristic motor patterns preceding freezing of gait in Parkinson's disease using wearable sensors. Front. Neurol. 8, 1–12. https://doi.org/10.3389/fneur.2017.00394

Panisset, M., 2004. Freezing of gait in Parkinson's disease. Neurol. Clin. 22, S53-62. https://doi.org/10.1016/j.ncl.2004.05.004

Plotnik, M., Giladi, N., Balash, Y., Peretz, C., Hausdorff, J.M., 2005. Is freezing of gait in Parkinson's disease related to asymmetric motor function? Ann. Neurol. 57, 656–663. https://doi.org/10.1002/ana.20452

Plotnik, M., Hausdorff, J.M., 2008. The role of gait rhythmicity and bilateral coordination of stepping in the pathophysiology of freezing of gait in Parkinson's disease. Mov. Disord. 23, 444–450. https://doi.org/10.1002/mds.21984

Ramdhani, R.A., Patel, A., Swope, D., Kopell, B.H., 2015. Early Use of 60 Hz Frequency Subthalamic Stimulation in Parkinson's Disease: A Case Series and Review. Neuromodulation 18, 664–669. https://doi.org/10.1111/ner.12288

R Core Team (2017). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL https://www.R-project.org/.

Rezvanian, S., Lockhart, T., 2016. Towards Real-Time Detection of Freezing of Gait Using Wavelet Transform on Wireless Accelerometer Data. Sensors 16, 475. https://doi.org/10.3390/s16040475

Ricchi, V., Zibetti, M., Angrisano, S., Merola, A., Arduino, N., Artusi, C.A., Rizzone, M., Lopiano, L., Lanotte, M., 2012. Transient effects of 80 Hz stimulation on gait in STN DBS treated PD patients: a 15 months follow-up study. Brain Stimul. 5, 388–392.

https://doi.org/10.1016/j.brs.2011.07.001

Schlenstedt, C., Shalash, A., Muthuraman, M., Falk, D., Witt, K., Deuschl, G., 2017. 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. 24, 18–26. https://doi.org/10.1111/ene.13167

Shivitz, N., Koop, M.M., Fahimi, J., Heit, G., Bronte-Stewart, H.M., 2006. Bilateral subthalamic nucleus deep brain stimulation improves certain aspects of postural control in Parkinson's disease, whereas medication does not. Mov. Disord. 21, 1088–1097. https://doi.org/10.1002/mds.20905

Shulman, L.M., Gruber-Baldini, A.L., Anderson, K.E., Fishman, P.S., Reich, S.G., Weiner, W.J., 2010. The clinically important difference on the unified Parkinson's disease rating scale. Arch. Neurol. 67, 64–70. https://doi.org/10.1001/archneurol.2009.295

Sidiropoulos, C., Walsh, R., Meaney, C., Poon, Y.Y., Fallis, M., Moro, E., 2013. Low-frequency subthalamic nucleus deep brain stimulation for axial symptoms in advanced Parkinson's disease. J. Neurol. 260, 2306–2311. https://doi.org/10.1007/s00415-013-6983-2

Sieber, B.-A.A., Landis, S., Koroshetz, W., Bateman, R., Siderowf, A., Galpern, W.R., Dunlop, J., Finkbeiner, S., Sutherland, M., Wang, H., Lee, V.M.Y., Orr, H.T., Gwinn, K., Ludwig, K., Taylor, A., Torborg, C., Montine, T.J., 2014. Prioritized research recommendations from the National Institute of Neurological Disorders and Stroke Parkinson's Disease 2014 Conference. Ann. Neurol. 76, 469–472. https://doi.org/10.1002/ana.24261

Silva de Lima, A.L., Evers, L.J.W., Hahn, T., Bataille, L., Hamilton, J.L., Little, M.A., Okuma, Y., Bloem, B.R., Faber, M.J., 2017. Freezing of gait and fall detection in Parkinson's disease using wearable sensors: a systematic review. J. Neurol. 264, 1642–1654.

https://doi.org/10.1007/s00415-017-8424-0

Snijders, A.H., Haaxma, C.A., Hagen, Y.J., Munneke, M., Bloem, B.R., 2012. Freezer or non-freezer: clinical assessment of freezing of gait. Parkinsonism Relat. Disord. 18, 149–154. https://doi.org/10.1016/j.parkreldis.2011.09.006

Stegemoller, E.L., Vallabhajosula, S., Haq, I., Hwynn, N., Hass, C.J., Okun, M.S., 2013. Selective use of low frequency stimulation in Parkinson's disease based on absence of tremor. NeuroRehabilitation 33, 305–312. https://doi.org/10.3233/NRE-130960

Syrkin-Nikolau, J., Koop, M.M., Prieto, T., Anidi, C., Afzal, M.F., Velisar, A., Blumenfeld, Z., Martin, T., Trager, M., Bronte-Stewart, H., 2017. Subthalamic neural entropy is a feature of freezing of gait in freely moving people with Parkinson's disease. Neurobiol. Dis. 108, 288–297. https://doi.org/10.1016/j.nbd.2017.09.002

Vallabhajosula, S., Haq, I.U., Hwynn, N., Oyama, G., Okun, M., Tillman, M.D., Hass, C.J., 2015. Low-frequency versus high-frequency subthalamic nucleus deep brain stimulation on postural control and gait in Parkinson's disease: a quantitative study. Brain Stimul. 8, 64–75. https://doi.org/10.1016/j.brs.2014.10.011

Xie, T., Padmanaban, M., Bloom, L., MacCracken, E., Bertacchi, B., Dachman, A., Warnke, P., 2017. Effect of low versus high frequency stimulation on freezing of gait and other axial symptoms in Parkinson patients with bilateral STN DBS: a mini-review. Transl. Neurodegener. 6, 13. https://doi.org/10.1186/s40035-017-0083-7

Xie, T., Vigil, J., MacCracken, E., Gasparaitis, A., Young, J., Kang, W., Bernard, J., Warnke, P., Kang, U.J., 2015. Low-frequency stimulation of STN-DBS reduces aspiration and freezing of gait in patients with PD. Neurology 84, 415–420. https://doi.org/10.1212/WNL.0000000000001184

Zach, H., Janssen, A.M., Snijders, A.H., Delval, A., Ferraye, M.U., Auff, E., Weerdesteyn, V., Bloem, B.R., Nonnekes, J., 2015. Identifying freezing of gait in Parkinson's disease during freezing provoking tasks using waist-mounted accelerometry. Parkinsonism Relat. Disord. 21, 1362–1366. https://doi.org/10.1016/j.parkreldis.2015.09.051