Dealing with the Heterogeneous Presentations of Freezing of Gait: How Reliable are the Freezing Index and Heart Rate for Freezing Detection?

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Abstract

Background: Freezing of gait (FOG) is an unpredictable gait arrest that hampers the lives of 40% of people with Parkinson's disease. Because the symptom is heterogeneous in phenotypical presentation (it can present as trembling, shuffling, or akinesia) and manifests during various circumstances (it can be triggered by e.g. turning, passing doors, and dual-tasking), it is particularly difficult to detect with motion sensors. The freezing index (FI) is one of the most frequently used accelerometer-based methods for FOG detection. However, it might not adequately distinguish FOG from voluntary stops, certainly for the akinetic type of FOG. Interestingly, a previous study showed that heart rate signals could distinguish FOG from stopping and turning movements. This study aimed to investigate for which phenotypes and evoking circumstances the FI and heart rate might provide reliable signals for FOG detection.

Methods: Sixteen people with Parkinson's disease and daily freezing completed a gait trajectory designed to provoke FOG including turns, narrow passages, starting, and stopping, with and without a cognitive or motor dual-task. We compared the FI and heart rate of 406 FOG events to baseline levels, and to stopping and normal gait events (i.e. turns and narrow passages without FOG) using mixed-effects models. We specifically evaluated the influence of different types of FOG (trembling vs akinesia) and triggering situations (turning vs narrow passages; no dual-task vs cognitive dual-task vs motor dual-task) on both outcome measures.

Results: The FI increased significantly for trembling FOG, but not for akinetic FOG. Furthermore, the index increased similarly during stopping and was therefore not significantly different from FOG. In contrast, heart rate change during FOG was for all types and during all triggering situations statistically different from stopping, but not from normal gait events.

Conclusion: The FI has issues to distinguish FOG from voluntary stopping, especially of the akinetic type. In contrast, the clear distinction in heart rate change between FOG and voluntary stops, which was independent of the heterogeneous presentation of FOG, might provide a solution for this issue. Therefore, we suggest that combining a heart rate monitor with a motion sensor may be promising for future FOG detection.

1. Introduction

Parkinson's disease (PD) is the fastest growing neurological disorder in the world, affecting over 6 million people worldwide. One particularly disturbing symptom of Parkinson's disease and other parkinsonian disorders is freezing of gait (FOG): a sudden, relatively brief episode of immobility, described by patients as "if the feet are glued to the floor" (1). This sudden gait arrest affects the lives of at least 2 in 5 people with Parkinson's disease (2, 3) and it has consequences that reach beyond its effect on locomotion. Research shows an association of FOG severity not only with motor-related dimensions of quality of life like mobility, bodily discomfort, and reduction in activity of daily living, but also with non-motor-related dimensions including emotion, communication, and cognition (4). Furthermore, clear correlations with

disease severity, falls, and hospital admissions result in a high impact on caregivers and the healthcare system (5–7).

There is a great need for methods to reliably measure FOG in the home situation. Given that FOG typically manifests less during hospital visits than at home, it is challenging for clinicians and researchers to track symptom progression (8). The current golden standard for FOG detection is based on video annotations of two independent trained raters. However, this process is time-consuming, work-intensive, and raises privacy issues when applied in the home setting – potentially holding back the evaluation and development of new treatments for FOG. Several researchers have attempted to detect or predict FOG with the help of motion sensors attached to the body (9–11). If FOG can be reliably detected by motion sensors alone, this would remove the necessary human labeling element. However, the highly person-specific manifestations of FOG and the risk of overfitting because of small sample sizes are common concerns in these studies.

One of the most frequently applied detection methods is the *freezing index* (FI) developed by Moore et al. (12, 13). This index is based on the characteristic tremor in the legs during trembling and the absence of frequency components of a normal walking pattern. Based on an accelerometer on the lower limb or trunk, a ratio is calculated of the square of the power in the freezing band (3–8 Hz) over the square of the power in the locomotion band (0.5–3 Hz). When a determined threshold is exceeded, the time window is flagged as a freezing episode.

Despite its simplicity, the performances of the FI varies considerably with a reported sensitivity ranging from 73 to 91% and specificity ranging from 76 to 96% (10). The heterogeneity of FOG might be at play here (8, 11). Firstly, FOG presents differently in each person, and in general, three major phenotypes of freezing have been described: (1) *trembling*, characterized by a tremor of the legs at a frequency of 3–8 Hz; (2) *shuffling*, characterized by small steps; and (3) *akinesia*, characterized by a total absence of limb movement (1). Because the FI is specifically designed to detect the trembling type of FOG, it might come up short for the other two types. Secondly, FOG can occur during various circumstances; it can happen during turning, approaching a doorway, initiation of gait, dual-task walking, being under time pressure, etc. (1), but it has never been elucidated whether the FI works equally well under these different circumstances. Therefore, the first aim of this study was to evaluate whether the FI increases significantly under all the different types and triggering situations of FOG.

Another concern of the FI is its vulnerability to falsely classify voluntary stops or ‘normal’ gait events (such as turns without FOG) as FOG (11). On the one hand, when going from walking to standing, the power in the locomotion band decreases, hence increasing the ratio of the FI. On the other hand, normal gait events might increase the power in the freezing band, hence increasing the ratio of the FI. As a second research aim, we therefore evaluated whether the FI during stopping and during normal gait events (i.e. turns and narrow passages that did not provoke FOG) were statistically different from FOG.

Interestingly, a previous study showed that measuring *heart rate* could also provide signals indicative of FOG that are different from voluntary stopping and turns. Namely, they observed an increase in heart rate

before and during FOG, while the heart rate decreased during sudden stops and normal turns (14). The authors postulated that the increased heart rate might be related to an activation of the autonomic nervous system and increased stress levels. However, only freezing episodes during turning were taken into consideration and the number of FOG episodes was small: about 100 episodes in a total of ten patients. If heart rate indeed increases before and during FOG independently of the type of FOG or its triggering situation, this observation might be promising for future FOG detection or even prediction. Consequently, we evaluated heart rate trends under the same conditions as we evaluated the FI.

Taken together, this study aimed to investigate under which conditions the FI and heart rate might provide reliable signals for FOG detection. In a first analysis, we determined whether the FI and heart rate increased significantly before and during FOG compared to baseline levels. A second analysis tested whether the FI and heart rate during FOG was statistically different from stopping and normal gait events (i.e. turns and narrow passages that did not provoke FOG). For both analyses we specifically evaluated the influence of different types of freezing (i.e., trembling, and akinesia) and evoking situations (i.e. turning, narrow passages; and dual-tasking).

2. Methods

Participants

We recruited 16 participants (11 male, 5 female) with idiopathic Parkinson's disease with self-reported daily freezing. Exclusion criteria were: comorbidities causing severe gait impairments, severe cognitive impairments, or the inability to walk 150 meters unaided, possessing a pacemaker, or having a deep brain stimulator.

The severity of motor symptoms was assessed by the Movement Disorder Society's Unified Parkinson's Disease Rating Scale section III (UPDRS III)(15). Furthermore, all participants completed the following questionnaire and cognitive tests: the New Freezing of Gait Questionnaire (NFOGQ) (16), the mini mental state examination (MMSE) (17), and the frontal assessment battery (FAB) (18).

All procedures were conducted according to the principles of the 1964 Declaration of Helsinki and in accordance with the Medical Research Involving Human Subjects Act (WMO). Ethical approval was given by the medical ethics committee Arnhem-Nijmegen (NL60942.091.17). All participants provided written informed consent prior to study inclusion.

Procedure

To increase the likelihood of FOG occurrence and therefore increasing the power of the study, participants were tested in the OFF medication state following an overnight withdrawal (> 12 hours after intake) of anti-Parkinson medication.

A series of gait tasks were designed to maximally trigger FOG during the study visit and to resemble real-life situations. These consisted of 360 degree turns in alternating directions and completion of the gait

trajectory shown in Fig. 1, including maneuvering between chairs (i.e. a narrow passage), 180 and 360 degree turns in both directions, stopping, and starting.

The gait tasks were conducted under three different conditions in a pseudo-randomized order: with a cognitive dual-task (cDT), with a motor dual-task (mDT), and without a dual-task (noDT). The cDT consisted of the Adjusted Auditory Stroop Task, which is specifically designed to increase cognitive workload in people with PD (19). In short, participants are asked to start or continue walking when hearing a congruent command (i.e., a male voice saying 'man' or a female voice saying 'woman'), and to stand still when hearing an incongruent command (i.e., a male voice saying 'woman' or a female voice saying 'man'). During the mDT, participants carried a tray with an object on it, increasing the demand on the motor system and simultaneously removing vision from the lower limbs (20).

In total, the participants completed four to six rounds of the gait tasks (approximately 6 minutes each) with each round including the three different DT conditions in a pseudorandomized order. Each round started with 10 seconds of standing and between each round, the participants could rest as long as needed. During all gait tasks, the participants were accompanied by a researcher to prevent them from falling.

Materials

A 32-channel portable system (Porti, Twente Medical Systems International B.V., sample frequency of 256 Hz) was used to collect 3-lead electrocardiogram (ECG) signals for heart rate monitoring and 3D accelerometer signals on the ankle and knees for motion activity.

All gait tasks were recorded by three video cameras positioned at different corners of the lab (see Fig. 1) thereby providing an overview of all the participant's body movements. The videos were annotated for the occurrence of FOG by two independent trained raters in ELAN software (the Language Archive, Nijmegen, the Netherlands) following recent guidelines (21). A FOG event was considered definite if the annotation of both raters overlapped. Otherwise, the event was in- or excluded after discussion with a third rater. In all cases, we chose the earliest and latest begin and end time from the two raters, respectively, to define the FOG event. This was to prevent the possibility that changes happening before the FOG event can be attributed to annotation differences between the two raters. Furthermore, each time the participants turned, encountered a narrow passage, started, or stopped walking, was annotated accordingly.

Data analysis

Raw data were analyzed with MATLAB (R2019a) (Mathworks, Natick, MA) and the open-source Fieldtrip toolbox developed at the Donders Institute for Brain, Cognition and Behaviour (22). All anonymized data is available on the Donders repository (<https://doi.org/10.34973/h1d5-5j25>) and analysis scripts are shared on https://github.com/helenacockx/FI-HR_duringFOG.

Freezing index (FI)

Because measuring the vertical acceleration of the shin is considered as the most effective for FI calculation and provides the highest signal-to-noise, we only included vertical acceleration of the right shin for calculation of the FI (13, 23–25). Analysis of the sensor data of the left shin showed similar results. First, the power spectrum for each sample was calculated by using 3-second time windows with Hanning tapers (window centered at the sampling point). The FI was then defined as the squared area under the curve (AUC) of the power in the freezing band (3.5-8 Hz) over the squared AUC of the power in the locomotion band (0.5-3 Hz) as indicated by the following formula (12).

$$FI = \frac{AUC(\text{power freezing band } (3.5 - 8 \text{ Hz}))^2}{AUC(\text{power locomotion band } (0.5 - 3 \text{ Hz}))^2}$$

These values were normalized by multiplying by 100 and taking the natural logarithm as proposed by Moore et al. (12).

Heart rate

Prior to analysis, the ECG was examined for heart arrhythmias and the best quality lead was selected. R peaks were detected by the Pan Tompkins algorithm (26, 27). Singular ectopic beats were automatically identified and replaced by a beat falling exactly between its neighboring beats. Remaining artifacts were selected visually and replaced with *nan* values.

Statistics

The FI, and heart rate were averaged over 3-second time windows during FOG (0 to + 3 seconds after FOG onset), during a preFOG period (-3 to 0 seconds before FOG onset), and during baseline (-6 to -3 seconds before FOG onset). Similarly, the same time windows ([-6 to -3]; [-3 to 0]; and [0 to 3] seconds) were considered for normal gait events and stop events. A normal gait event was defined as a turn or narrow passage without a FOG event within a 6-second margin. Stop events were labeled with the trigger ‘turn’ or ‘narrow passage’, based on its closest gait event. FOG events, stops, or normal gait events preceded by another FOG episode within 6 seconds were excluded from the analysis.

Mean FI and heart rate values were exported to RStudio (RStudio 1.2.1335; RStudio, Inc., Boston, MA), and analyzed with linear mixed-effects models using the package lme4 (28). A first model was fitted to compare the FI and the heart rate before and during FOG with baseline levels. The model contained fixed effects for *time* (factors baseline, preFOG and FOG; treatment contrast coded), FOG *type* (factors trembling or akinesia; sum contrast coded), FOG *trigger* (factors turning or narrow passage; sum contrast coded), *DT* condition (factors cDT, mDT, or noDT; sum contrast coded), and interaction effects of the last four with time. To correct for individual differences in FI thresholds and average heart rate, a random intercept was included for *participant*. Additionally, a random intercept for *trial* was included to baseline correct heart rate levels. It makes no sense to baseline correct the FI because this parameter is usually evaluated based on absolute values rather than relative values, so no random intercept for trial was included for this model.. This resulted in the following formulas:

$$FI \sim type * time + trigger * time + DT * time + (1|participant) \quad (model\ 1.a)$$

$$heart\ rate \sim type * time + trigger * time + DT * time + (1|participant) + (1|trial) \quad (model\ 1.b)$$

A second model was fitted to compare FI and heart rate change during FOG to the control conditions ‘normal gait event’ and ‘stopping’. Heart rate change was calculated as the difference in heart rate between the [0 to 3] and [-3 to 0] seconds time windows. No difference was taken for the FI because this parameter is usually evaluated based on absolute values and not on relative values. The model included fixed effects for *condition* (factors FOG, normal gait event, and stopping; treatment contrast coded), FOG *type*, FOG *trigger*, *DT* condition, and the interaction effects of the last four with condition. A random intercept was included for *participant*. The formulas were as follows:

$$FI \sim type * condition + trigger * condition + DT * condition + (1|participant) \quad (model\ 2.a)$$

$$heart\ rate\ change \sim type * condition + trigger * condition + DT * condition + (1|participant) \quad (model\ 2.b)$$

Assumptions of the models were checked. Fixed effects of all models were tested for statistical significance using Type III F tests with Kenward-Roger adjustment to the degrees of freedom via the car package (29). Significance level was set at 0.05. Post-hoc analysis for significant main and interaction effects were computed via the emmeans package (30) with Kenward-Roger adjustments to the degrees of freedom and Dunnett’s correction for p-values (in case of significant interaction effects).

3. Results

Participant characteristics

Table 1 summarizes the participant characteristics. Median age was 68.5 (interquartile range 63-74.25) and median disease duration was 11 years (interquartile range 7.75–13.25). One of the sixteen participants was excluded from analysis because of data loss due to a detached ECG sensor. Median heart rate during the resting periods was 83.9 bpm (interquartile range 79.6–88.1 bpm); median heart rate variability during rest, defined as the coefficient of variation, was 1.6% (interquartile range 1.0-2.2%).

Table 1
participant characteristics

	Median	Interquartile range
Age	68.5	63-74.25
Gender (% male)	69	
Disease duration	11	7.75–13.25
Daily levodopa dosage (mg)	1120	500–1300
MDS-UPDRS part III	23.5	19-26.75
H&Y	2	2–3
MMSE	27	26–29
FAB	16	14.75–17.25
NFOGQ	19.5	16.5-23.25
HR rest (bpm)	83.5	78.4–87.2
HRV rest (%)	1.5	1.0-2.1

MDS-UPDRS part III: Movement Disorders Society Unified Parkinson Disease Rating scale part III, *H&Y*: Hoehn and Yahr Staging Scale, *MMSE*: mini-mental state examination (range 0–30), *FAB*: Frontal Assessment Battery (range 0–18), *NFOGQ*: New Freezing of Gait Questionnaire (range 0–28), *HR rest*: heart rate during the first 10 seconds of standing preceding each round, *HRV rest*: heart rate variability defined as the coefficient of variation during the first 10 seconds of standing preceding each round.

FOG annotations

In total, 4683 gait events and 685 freezing episodes were observed with a high interrater agreement (kappa correlation coefficient 0.90; Spearman correlation for number and total duration of FOG of 0.84 and 0.89 respectively). The median duration of the FOG events was 5.8 seconds (interquartile range 3.4–11.5 sec.).

Figure 2.B-D shows the distribution of FOG episodes over the participants for each FOG type, triggering event, and DT condition. 81% of all freezing was annotated as trembling, but was often seen in combination with shuffling (6%), as reflected by a low interrater agreement for both types (in 86% of the shuffling events, the raters disagreed on the FOG type). Because both likely share a similar pathophysiological substrate that is different from akinesia (31, 32), we decided to compare the combination of trembling-shuffling with akinesia. Notably, akinesia -accounting for 13% of the events- was mainly present in two of the participants (see Fig. 2.B, orange). Turning, as expected from the literature (33–35), was most provocative for FOG (73% of the events), followed by narrow passages (19%) and starting hesitation (6%). The first two, turning and narrow passages, were considered for

further analysis. The number of FOG events was comparable over the three DT conditions: 36% of the episodes occurred during noDT, 35% during cDT, and 29% during mDT. After exclusion of trials that were close (< 6 seconds) to other FOG episodes, 406 FOG events, 377 stops, and 1446 normal gait events were included in the analysis.

Freezing index (FI)

Figure 3.A shows the overall time course of the FI during FOG, normal gait events and stopping. Overall, the FI increased over time during FOG (orange), while it remained at the same level during normal gait events (green). However, the FI also increased during stopping (blue).

The first model (model 1.a), evaluating the increase of the FI during preFOG and FOG compared to baseline levels, showed that the FI increased significantly over time (main effect of time: $FI_{(time)}$: $p < 0.001$), but that its performance was dependent on the type of FOG (significant interaction effect between time and type: $FI_{(time*type)}$: $p < 0.001$) (Table 2). Figure 4.A-C shows the results of the post-hoc analyses of this model. The FI increased significantly for trembling during preFOG (post-hoc $FI_{(preFOG-baseline)}$: $B = 0.39$, $p = 0.018$) and during FOG compared to baseline (post-hoc $FI_{(FOG-baseline)}$: $B = 1.87$, $p < 0.001$), but not for akinesia (post-hoc $FI_{(FOG-baseline)}$: $B = 0.48$, $p = 0.270$) (Fig. 4.A). No significant interaction effects were found for trigger or for DT. The significant main effects for type ($p = 0.024$), for trigger ($p = 0.033$), and for DT ($p < 0.001$) indicate that the FI was different at baseline for these conditions. Overall, these results show that the FI performed as expected (i.e., significant increase compared to baseline) to detect the trembling type of FOG in all tested circumstances, but not for the akinetic type.

Figure 5.A-C shows the results the second model (model 2.a) that compared the FI during FOG, normal gait events, and stops under all conditions. For the ideal FOG detector, the green (FOG – normal gait event), and blue (FOG - stopping) point ranges would appear above the zero threshold line. Significant interaction effects were found between condition (i.e., FOG-normal gait event, or FOG-stop) and all three factors (type, trigger and DT) ($FI_{(condition*type)}$: $p < 0.001$; $FI_{(condition*trigger)}$: $p < 0.001$; $FI_{(condition*DT)}$: $p = 0.012$), indicating that the performance of the FI differed significantly between the conditions (Table 2).

Firstly, the distinctiveness of the FI was dependent on the type of FOG (Fig. 5.A). More specifically, for trembling FOG, the difference between FOG and a normal gait event was significant (post-hoc $FI_{(FOG-normal\ gait\ event)}$: $B = 1.92$, $p < 0.001$), but not between FOG and stopping (post-hoc $FI_{(FOG-stop)}$: $B = 0.37$, $p = 0.559$). In contrast, for akinetic FOG, the difference between FOG and a normal gait event was smaller (post-hoc $FI_{(FOG-normal\ gait\ event)}$: $B = 0.58$, $p = 0.019$), and between FOG and stopping even reversed, i.e. the FI during akinetic FOG was lower than during stopping (post-hoc $FI_{(FOG-stop)}$: $B = -1.21$, $p < 0.001$). Even though this reversed relationship was significant, this has no clinical advantage because the FI should rise *above* a certain threshold to identify a FOG episode. A significant main effect of type of the second model indicated again that FI during akinesia was lower than during trembling ($p < 0.001$) (Table 2).

Secondly, the relation of the FI between FOG and a normal gait event depended on the trigger (Fig. 5.B). In a narrow passage, the FI was higher during an event with FOG than without FOG (post-hoc $FI_{(FOG-normal\ gait\ event)}$: $B = 2.08$, $p < 0.001$); but for turning, the relationship became smaller (post-hoc $FI_{(FOG-normal\ gait\ event)}$: $B = 0.42$, $p = 0.002$).

Thirdly, the difference in FI between FOG and a normal gait event varied between DT conditions, with slightly smaller differences between FOG and a normal gait event during cDT and mDT than during noDT (Fig. 5.C).

Taken together, these results show that the FI performs well to differentiate FOG from normal gait events (although only marginally significant for akinetic FOG, or when comparing FOG turns with normal turns), but not to differentiate FOG from stopping.

Heart rate

Figure 3.B shows that overall, heart rate increased during FOG compared to baseline levels, while a clear drop in heart rate was seen during stopping, which is in line with previous studies (14, 36, 37). However, in contrast to previous findings (14), in our results heart rate increased during normal gait events.

Indeed, the first model (model 1.b) showed a significant main effect of time ($HR_{(time)}$: $p = 0.006$), with post-hoc analysis revealing a significant increase in heart rate during FOG compared to baseline ($HR_{(FOG-baseline)}$: $B = 0.29$, $p = 0.001$), but not during preFOG ($HR_{(preFOG-baseline)}$: $B = 0.69$, $p = 0.253$) (Table 2). The increase in heart rate was dependent on type ($HR_{(time*type)}$: $p < 0.001$), and on DT condition ($HR_{(time*DT)}$: $p = 0.011$), but not on the triggering event ($HR_{(time*trigger)}$: $p = 0.312$).

Namely, Fig. 4.D shows a clear and significant increase in heart rate for trembling during preFOG (post-hoc $HR_{(preFOG-baseline)}$: $B = 0.36$, $p = 0.029$) and FOG periods (post-hoc $HR_{(FOG-baseline)}$: $B = 1.26$, $p < 0.001$), while the increase during akinesia was not significant in these periods (post-hoc $HR_{(preFOG-baseline)}$: $B = 0.27$, $p = 0.729$ and post-hoc $HR_{(FOG-baseline)}$: $B = 0.12$, $p = 0.896$ respectively). Considering the DT conditions, heart rate increased significantly during FOG for the noDT and the cDT condition (post-hoc $HR_{(FOG-baseline)}$: $B = 0.69$, $p = 0.009$ and $HR_{(FOG-baseline)}$: $B = 1.13$, $p < 0.001$), but not for the mDT condition ($HR_{(FOG-baseline)}$: $B = 0.26$, $p = 0.525$) (Fig. 4.I).

Of less interest, a significant main effect of the first model was found for trigger ($HR_{(trigger)}$: $p = 0.006$) and DT ($HR_{(DT)}$: $p < 0.001$), meaning that the heart rate levels for these conditions differed at baseline (Table 2). Namely, heart rate was higher during baseline levels of narrow passages than during turning (post-hoc $HR_{(narrow\ passage - turn)}$: $B = 1.47$, $p = 0.007$), and heart rate during baseline levels of mDT was higher than during noDT (post-hoc $HR_{(mDT-noDT)}$: $B = 1.35$, $p = 0.020$) or cDT ($HR_{(mDT-cDT)}$: $B = 2.20$, $p < 0.001$).

Overall, these results confirm that heart rate increases before and during trembling FOG, but stays at a similar level during akinetic FOG. Furthermore, the heart rate during the mDT condition had significantly

higher baseline levels and did not increase significantly during FOG.

The second model (model 2.b) investigated the differences in heart rate changes during FOG with stopping and normal gait events (Fig. 5.D-F). Of major interest, a significant interaction effect was found between condition and type ($HR_{(\text{condition} \times \text{type})}$; $p = 0.005$) (Table 2, Fig. 5.D). For both trembling and akinesia, heart rate change was significantly different from stopping (post-hoc $HR_{(\text{FOG-stop})}$: $B = 2.41$, $p < 0.001$ and $HR_{(\text{FOG-stop})}$: $B = 1.14$, $p = 0.004$ respectively). However, heart rate change during a normal gait event was not different from trembling (post-hoc $HR_{(\text{FOG-normal gait event})}$: $B = 0.18$, $p = 0.473$), or from akinesia (post-hoc $HR_{(\text{FOG-normal gait event})}$: $B = -0.86$, $p = 0.058$).

Moreover, a significant interaction effect was observed between condition and DT with a slightly smaller difference in heart rate change between FOG and normal gait event for the noDT condition than the other two conditions (Fig. 5.F). In addition, a significant main effect of the second model was seen for type and DT ($HR_{(\text{type})}$: $p = 0.005$; $HR_{(\text{DT})}$: $p = 0.0003$) indicating differences in heart rate change for these factors during the FOG condition (Table 2). More specifically, heart rate change was greater during trembling compared to akinesia (post-hoc $HR_{(\text{trembling-akinesia})}$: $B = 0.16$, $p = 0.0014$); and greater during cDT than noDT (post-hoc $HR_{(\text{cDT-noDT})}$: $B = 0.46$, $p < 0.0001$).

In conclusion, heart rate change was significantly different between FOG and stopping of any type and triggering situation, but not between FOG and a normal gait event.

Table 2
results of the type III F test (with Kenward-Roger adjustment for degrees of freedom) for the fixed effects
of the mixed models

	Model 1.a:				Model 1.b:			
	FI ~ type*time + trigger*time + DT*time + (1 participant)				heart rate ~ type*time + trigger*time + DT*time + (1 participant) + (1 trial)			
	F	Df	Df.res	p value	F	Df	Df.res	p value
(Intercept)	170.70	1	24	< 0.001*	1355.21	1	14.907	< 0.001*
time	15.00	2	1189	< 0.001*	5.13	2	802	0.006*
trigger	4.55	1	1195	0.033*	7.64	1	468	0.006*
type	5.13	1	1180	0.024*	2.48	1	426	0.116
DT	9.27	2	1191	< 0.001*	10.76	2	475	< 0.001*
time*time	10.35	2	1189	< 0.001*	7.27	2	802	0.001*
time*trigger	0.52	2	1189	0.595	1.17	2	802	0.312
time*DT	2.33	4	1189	0.054	3.28	4	802	0.011*
	Model 2.a:				Model 2.b:			
	FI ~ type*condition + trigger*condition + DT*condition + (1 participant)				heart rate change ~ type*condition + trigger*condition + DT*condition + (1 participant)			
	F	Df	Df.res	p value	F	Df	Df.res	p value
(Intercept)	325.54	1	24	< 0.001*	2.91	1	292	0.089
condition	71.69	2	2204	< 0.001*	60.15	2	2167	< 0.001*
trigger	0.91	1	2205	0.340	2.75	1	2199	0.097
DT	1.99	2	2202	0.137	5.92	2	2212	0.003*
type	32.67	1	2212	< 0.001*	7.82	1	1687	0.005*
condition*trigger	43.10	2	2202	< 0.001*	2.43	2	2209	0.088
condition*DT	3.24	4	2201	0.012*	2.86	4	2210	0.022*
condition*type	17.19	2	2207	< 0.001*	5.26	2	1985	0.005*
*p < 0.05 ; F = F values; Df = degrees of freedom; Df.res = residual degrees of freedom; FI = freezing index, DT = dual-task								

4. Discussion

We set out to characterize the FI and heart rate during FOG in different situations to evaluate under which conditions these features might provide reliable signals for FOG detection. Overall, the FI worked well to distinguish trembling FOG from normal walking (significant increase compared to baseline levels) or from normal gait events, but had difficulties to distinguish FOG from stopping or to detect akinetic FOG. In contrast, the heart rate change could clearly differentiate between stopping and FOG of both types or during any triggering situation, but did not show significant differences from normal gait events.

The freezing index (FI)

As a first research question we evaluated whether the FI increased significantly during FOG independently of the type of FOG or triggering situation. As can be appreciated from Fig. 4.A-C, the FI increased significantly during FOG independently of the trigger or DT condition, but this was only true for the trembling type of FOG. This is unsurprising, as the FI is based on the characteristic tremor of the lower limb during trembling which is, by definition, not present during akinesia. Although akinesia is less common than trembling (also witnessed in our dataset), it is particularly difficult to detect (32, 38).

The second research question evaluated whether the FI was able to distinguish FOG from other gait events and stopping. Regarding the normal gait events, Fig. 3.A clearly shows that the FI can differentiate well between FOG (orange line) and normal gait events (green line). However, the results of the mixed model analysis showed that these differences are smaller when comparing akinetic FOG to normal gait events (Fig. 5.A), or when comparing turning FOG to normal turns (Fig. 5.B). The former can be explained by a lack of FI increase during akinesia; the latter can be explained by a similar increase in the FI during turns with and without FOG. Indeed, we observed a higher increase in the freezing band than in the motor band during normal turning, resulting in a net increase in the FI. For this study, we particularly asked participants to turn on the spot with small steps instead of big steps or a pirouette, thereby probably increasing the power in the 3.5-8 Hz band, hence explaining the increase in the FI. These instructions were given to increase the likelihood of triggering FOG, but represent, nevertheless, a turning behavior with high risks to provoke FOG. This observation therefore underlines the importance of not only comparing FOG events to walking or standing, but also to its triggering events without FOG (e.g., normal turning). Likewise, researchers should specifically consider FOG events of different types, and triggered by different conditions when developing FOG detection algorithms, to ensure detection performance in daily life.

Secondly, when comparing the FI during FOG (orange line) to stopping (blue line) (Fig. 3.A), no clear differences are observed. Indeed, Fig. 5.A-C shows blue point ranges that are close to zero, indicating that differences between FOG and stopping were not significant, or are even below zero, indicating that the relationship reversed, i.e. the FI during akinetic FOG and turning FOG was lower than during stopping. Even though this reversed relationship was significant, this has no clinical advantage because the FI should rise *above* a certain threshold to identify a FOG episode. The increase in the FI during stopping can be explained as follows: when no movements are performed, both the power in the freezing band and

locomotion band take such small values that the ratio of both is dominated by the remaining sensor noise (24), in this case increasing the FI.

Some researchers have proposed a solution to deal with the rising FI during normal stops, by introducing an extra threshold: only when the total power (0.5-8 Hz) exceeds a certain total power threshold, the FI is calculated (23, 24). Supplementary Fig. 1 shows the overall time course of this modified version of the FI (mFI) during FOG, normal gait events, and stopping. Indeed, the mFI increased less during stops than the FI, but was still not significantly different from FOG. Moreover, the difference in the mFI between FOG and normal gait events became smaller. We therefore argue that the extra total power threshold marginally improved the distinction between FOG and stopping, but at the cost of differentiating between FOG and normal gait events.

Heart rate

Consistent with previous studies, we found a significant increase in heart rate during trembling FOG for all triggering situations (14, 36, 37), except for the mDT condition which also displayed higher heart rate levels during baseline (Fig. 4.A-F). The imposed increase in mental work load of carrying the tray might explain the increased baseline levels (39). However, it remains unclear why heart rate did not significantly increase during FOG for the mDT condition. We speculate that saturation effects might have played a role: autonomic cardiovascular dysfunction is prevalent in Parkinson's disease, resulting in lower heart rate variability, thereby preventing a further increase of the already high baseline levels (40). Because the cDT included an episodic type of DT, namely starting or stopping based on episodic auditory stimuli, this condition had lower heart rate baseline levels and therefore a significant heart rate increase during FOG.

Furthermore, heart rate increased less during akinesia than during trembling (Fig. 4.D). Akinetic freezing mainly occurred in two participants; supplementary Fig. 2-A and 2-B show the heart rate during akinesia for these participants. Surprisingly, the trends are opposite: heart rate decreased slightly during FOG in participant 8, while it increased in participant 15. A possible explanation for this is that participant 8, although not yet known on inclusion, eventually got the alternative diagnosis of multiple system atrophy (MSA). FOG is estimated to be present in 40–75% of MSA patients (41, 42), but the pathophysiology of FOG in MSA might be distinct from PD (43). Therefore, the cardiovascular system might respond differently in MSA. Nevertheless, more research is needed to investigate the differences in neural pathways and cardiovascular responses during FOG in MSA and other parkinsonian syndromes.

Although the quantity of heart rate increase during FOG varied between the different evoking situations and types of FOG, the significant difference with the clear heart rate drop during stopping is outstandingly persistent (the blue point ranges in Fig. 5.D-F are always far above zero). This can also be explained biologically: autonomic adjustments of the heart rate during exercise, which are both centrally and locally regulated, are dependent on a person's perceived effort, independently of whether the attempt to move is successful or not (44, 45). For example, if stuck in deep snow, you make great efforts to escape, which increases your heart rate, but your efforts might be fruitless. Following on from this, it seems logical that heart rate decreases during voluntary stopping, while it increases during the efforts to move during FOG.

Previous studies attribute the increase in heart rate during FOG to elevated stress levels (14, 37). Our findings do not contradict this hypothesis, but we note that not only stress may play a role, but that the increased heart rate can also be a normal physiological response.

While the difference in heart rate change between FOG and stopping is strong, no clear differences in heart rate change between FOG and normal gait events are observed (orange vs green line in Fig. 3.C), for none of the conditions (green point ranges in Fig. 5.D-F are close to zero). This is in contrast with findings by Maidan and colleagues (14) where heart rate decreased during a normal turn. This disagreement may be due to a difference in effort during turning, for example, because the participants in our study turned with shorter and faster steps. However, this does not explain the increased heart rate when encountering a narrow passage. Alternatively, we can explain this by a conditioning mechanism; as chances of freezing grow when turning or approaching a narrow passage, the perceived exertion or stress levels rise, causing heart rate to increase.

Recommendations:

The main purpose of this study was to evaluate the use of motion sensors and heart rate monitors for future FOG detection algorithms. Although only looking at group effects in the data rather than trials separately, the FI seemed to perform reasonably well to distinguish FOG from walking or normal gait events. However, we also showed that its performance is highly dependent on the presence of the characteristic trembling of the leg (during trembling FOG) and it might confuse stopping with FOG. Because FOG is particularly variable in presentation, it is challenging to acquire a one-size-fits-all algorithm based on motion sensors. Of course, person-specific models can be trained, but in practice, this means that for each individual a new annotated dataset needs to be generated (10).

Instead of trying to characterize all possible FOG patterns using leg-mounted motion sensors, we can also focus on what FOG has in common. During the 2010 FOG workshop, freezing of gait was unified under the following definition: “a brief, episodic absence or marked reduction of forward progression of the feet despite the intention to walk” (46, 47). It should be relatively simple to measure a reduction in forward progression, for example with a motion sensor close to the center of gravity (e.g. a phone in the back pocket)(48), by measuring the speed of the wheels of a walker, or by measuring the cross-correlation between the left and right foot angular velocity as proposed by a recently published study (49). However, the second part of the definition ‘despite the intention to walk’ is crucial for differentiating FOG from voluntary stopping. As explained previously, the heart rate can reflect someone’s effort to move independent of its success, hence opening the possibility to distinguish voluntary from involuntary stops. The results of this study clearly demonstrated that heart rate indeed can make this distinction for any type and situation of FOG. Therefore, we suggest that the combination of a motion sensor and heart rate monitor, rather than each sensor alone, could improve FOG detection algorithms.

While heart rate is easy to measure and smartwatches that collect heart rate data are readily available, certain aspects should be taken into consideration. Firstly, heart rate monitors should be precise enough to pick up small differences. The difference in heart rate change between FOG and stopping counted only

1.78 bpm on average, so devices should be able to detect differences of approximately 1–2 bpm. Secondly, autonomic dysfunction is prevalent in PD and some patients might take beta-adrenergic blocking agents for tremor reduction, thereby blunting possible cardiovascular responses (40). As a consequence, variances in heart rate might become so small that even very precise monitors are not able to detect relevant changes. Thirdly, other changes in the physical, emotional, and cognitive state may modulate heart rate. Therefore, the effect of such states during standing should be investigated and compared to FOG events. Lastly, although this concept sounds promising for akinesia detection, more data is needed to confirm this hypothesis.

Limitations

We acknowledge a couple of limitations. Firstly, the goal of this study was to look at group-level average data in the FI and the heart rate to investigate future directions for FOG detection algorithms. Therefore, we cannot draw conclusions on the performance of the FI and heart rate on a single trial level. Nevertheless, by analyzing the data with linear mixed models, single trials were taken into consideration while being corrected for differences between participants. Secondly, the FI and heart rate were averaged over 3-second time windows potentially not capturing the very short FOG episodes. However, over 80% of the FOG episodes were longer than 3 seconds and excluding the shorter trials did not influence the data substantially. Nevertheless, future research should conclude whether measuring heart rate would still be useful for detection of short FOG episodes. Thirdly, the gait trajectory included many tasks that succeeded each other rapidly. Although we excluded trials that were preceded by a FOG within 6 seconds, carry-over effects cannot entirely be eliminated.

Conclusion

We clearly showed that the FI can differentiate well between FOG and normal gait events, but has issues to distinguish FOG from stopping and to detect akinetic FOG, and can produce false-positives during other gait events like normal turns. Subsequently, we confirmed that heart rate increases during FOG episodes that were triggered during various situations. We suggest that the significant difference in heart rate change between any type or condition of FOG and stopping, may help to improve FOG detection algorithms based on motion sensors measuring forward body progression. This concept might be particularly promising for akinesia detection.

Abbreviations

AUC: area under the curve

cDT: cognitive dual-task

DT: dual-task

ECG: electrocardiography

FAB: Frontal Assessment Battery

FI: freezing index

FOG: freezing of gait

HR: heart rate

HRV: heart rate variability

MDS-UPDRS: Movement Disorders Society Unified Parkinson Disease scale

mDT: motor dual-task

mFI: modified freezing index

MMSE: mini-mental state examination

MSA: Multiple System Atrophy

NFOGQ: new freezing of gait questionnaire

noDT: no dual-task

PD: Parkinson's disease

Declarations

Ethics approval and consent to participate

All procedures were conducted according to the principles of the 1964 Declaration of Helsinki and in accordance with the Medical Research Involving Human subjects Act (WMO). Ethical approval was given by the medical ethics committee Arnhem-Nijmegen (NL60942.091.17). All participants provided written informed consent prior to study inclusion.

Consent for publication

Not applicable.

Availability of data and materials

The anonymized dataset supporting the conclusions of this article is available in the Donders repository in BIDS-like format (<https://bids.neuroimaging.io/>), with project identifier 62003212_01 and hyperlink <https://doi.org/10.34973/h1d5-5j25>. All analysis code of this manuscript can be found on https://github.com/helenacockx/FI-HR_duringFOG.

Competing interests

The authors declare that they have no competing interests.

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Author's contributions

HC was involved in data analysis, interpretation of the data, writing of the manuscript, creation of the tables and figures, and editing the final version for submission. JN was involved in the conception and design of the study, the ethical approval of the protocol, and critical appraisal of the manuscript. BB was involved in conception and design of the study and interpretation of the data. IC was involved in interpretation of the data, and critical revision of the manuscript. RW and YW were involved in the conception and design of the study, the acquisition, the interpretation of the data, critical revision of the manuscript, and supervision over the study. All authors read and approved the final manuscript.

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Figures

Figure 1

Overview of the performed gait tasks Overview of the performed gait tasks. Each round started with 10 seconds of standing at the starting point followed by 360 degree turns in alternating directions with and without a cDT (30 seconds each, in pseudorandomized order). Next, the participants preceded with the gait trajectory as indicated by the orange arrows, passing between the chair and wall (47 cm wide); passing through the doorway (89 cm wide) into the narrow quarter where they completed a 180 and 360 degree turn in alternating directions; passing between the chairs (54 cm wide); walking straight, making a 180 degree turn and walking back between the chairs and the chair and the wall to the starting point where the gait trajectory was started over. The gait trajectory was performed with a cDT, a mDT or noDT for 90 seconds each, in a pseudorandomized order. In total, at least four of such rounds of approximately 6 minutes were completed and in between each round participants could rest as long as needed. All gait tasks were recorded by three video cameras positioned at strategic locations of the lab. (cDT = cognitive dual-task; mDT = motor dual-task; noDT = no dual-task)

Figure 2

Overview of the annotated FOG events. A: boxplots of the FOG duration (sec.) for each participant. The data is clipped at 75 sec. (3 events were longer than this upper limit). B-D: Subdivision of the number of annotated FOG events per type (B), trigger (C), and DT condition (D) for each participant. (FOG = Freezing of Gait; DT = dual-task)

Figure 3

Overall time course of the FI and heart rate Overall time course of the FI (A), and heart rate (B) for FOG (orange), normal gait events (green), and, stopping (blue). The lines with the shaded areas represent the mean values with confidence intervals over the 15 included participants (n=15). The heart rate was z-transformed and baseline corrected (-6 to -3 sec.) to account for individual variances in baseline heart rate and heart rate variability. No z-transformation was applied to the FI because these values are usually

evaluated based on absolute values rather than relative values. The boxes indicate the time intervals over which the variables are averaged when exporting to Rstudio: baseline (-6 to -3 seconds), preFOG (-3 to 0 seconds), and FOG (0 to 3 seconds). The figures were created with MATLAB (R2019a) and the Fieldtrip toolbox. (FI = Freezing Index; FOG = Freezing of Gait)

Figure 4

Results of the post-hoc analyses of the linear mixed model analysis of the first model Results of the post-hoc analyses of the linear mixed-model analysis of the first model comparing the FI (first row, model 1.a, and heart rate (second row, model 1.b) for the differences between preFOG and baseline (light orange), and FOG and baseline (dark orange). The point ranges indicate the estimated differences with standard errors of the post-hoc analyses for each FOG type (first column), FOG trigger (second column), and DT condition (third column), but the symbols are only filled when significant interaction effects were found for this factor by time. This means that the panels with the hollow symbols followed the main effects of table 2. Results of the post-hoc analysis that were significant after p-value correction are indicated with an asterisk. Figures were created with the ggplot2 package in Rstudio. (FI = Freezing Index; FOG = Freezing of Gait; noDT = no dual-task; cDT = cognitive dual-task; mDT = motor dual-task)

Model 2: FOG vs normal gait event vs stop

Figure 5

Results of the post-hoc analyses of the linear mixed model analysis of the second model Results of the post-hoc analyses of the linear mixed-model analysis of the second model comparing the FI (first row, model 2.a), and heart rate change (second row, model 2.b) for the differences between FOG and a normal gait event (green), and FOG and stopping (blue). The point ranges indicate the estimated differences with standard errors of the post-hoc analyses for each FOG type (first column), FOG trigger (second column), and DT condition (third column), but the symbols are only filled when a significant interaction effect of this factor was found with condition (i.e. FOG-normal gait event or FOG-stop). This means that the panel with the hollow symbols followed the main effects of table 2. Results of the post-hoc analysis that were significant after p-value correction are indicated with an asterisk. Figures were created with the ggplot2 package in Rstudio. (FI = Freezing Index; FOG = Freezing of Gait; noDT = no dual-task; cDT = cognitive dual-task; mDT = motor dual-task)

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