Bilateral Leg Stepping Coherence as a Predictor of Freezing of Gait in Patients With Parkinson's Disease Walking With Wearable Sensors

Tal Krasovsky, Benedetta Heimler, Or Koren, Noam Galor, Sharon Hassin-Baer, Gabi Zeilig, and Meir Plotnik

***Abstract*— Freezing of Gait (FOG) is among the most debilitating symptoms of Parkinson's Disease (PD), characterized by a sudden inability to generate effective stepping. In preparation for the development of a real-time FOG prediction and intervention device, this work presents a novel FOG prediction algorithm based on detection of altered interlimb coordination of the legs, as measured using two inertial movement sensors and analyzed using a wavelet coherence algorithm. *Methods*: Fourteen participants with PD (in OFF state) were asked to walk in challenging conditions (e.g. with turning, dual-task walking, etc.) while wearing inertial motion sensors (waist, 2 shanks) and being videotaped. Occasionally, participants were asked to voluntarily stop (VOL). FOG and VOL events were identified by trained researchers based on videos. Wavelet analysis was performed on shank sagittal velocity signals and a synchronization loss threshold (SLT) was defined and compared between FOG and VOL. A proof-of-concept analysis was performed for a subset of the data to obtain preliminary classification characteristics of the novel measure. *Results*: 128 FOG and 42 VOL episodes were analyzed. SLT occurred earlier for FOG (MED = 1.81 sec prior to stop, IQR = 1.57) than for VOL events (MED = 0.22 sec, IQR = 0.76) ($Z = -4.3$, $p < 0.001$, ES = 1.15). These time differences were not related with measures of disease severity. Preliminary results demonstrate sensitivity of 98%, specificity of 42% (mostly due to 'turns' detection) and balanced accuracy of 70% for SLT-based prediction, with good differentiation between FOG and VOL. *Conclusions*: Wavelet analysis provides a relatively simple, promising approach for prediction of FOG in people with PD.**

***Index Terms*— Gait, prediction, movement disorders, wavelet analysis, interlimb coordination.**

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This work involved human subjects or animals in its research. Approval of all ethical and experimental procedures and protocols was granted by the Helsinki Committee at Sheba Medical Center.

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I. Introduction

THE study of the clinical benefit of the use of wearable mobility sensors by persons with Parkinson's disease (PD) has rapidly grown in recent years [1]. The motivation behind this line of research is to improve diagnostic power, while capturing the behavioral performance during everyday life rather than through subjective assessments by clinicians, i.e., the current 'gold standard' procedure [2].

A. The Use of Wearable Mobility Sensors in the Context of Freezing of Gait

One of the main PD-related symptoms that is proposed to benefit from the use of wearable mobility sensors in free living settings, is freezing of gait (FOG) [3]. FOG is among the most debilitating symptoms of PD and is characterized by a sudden inability to generate effective stepping, despite the intention of the patient to keep walking [4]. Although typically lasting only a few seconds [5], freezes can lead to falls [6], thus making FOG-related fall risk an ever-present concern, ultimately contributing to a reduced quality of life for these patients [7]. Crucially, FOG events only partially benefit from available medical PD-related treatments, therefore strengthening the need for effective rehabilitation-oriented coping strategies [8], [9].

Considerable effort has been devoted to utilize wearable mobility sensors to automatically detect, and even predict FOG events [7], to improve the ability to accurately diagnose the existence, severity (e.g., frequency of occurrence) and the impact of FOG on the sufferer [1], [7]. In addition, automatic FOG detection (identification of a FOG while it is occurring)

or prediction (identification of a FOG based on pre-FOG data) can also be used within rehabilitative treatments aiming at alleviating FOG symptomatology. Specifically, accumulating evidence suggests that certain behavior modifying strategies, such as external sensory cueing, can be effective in shortening the duration of FOG events or even reducing their propensity [3], [10]. Therefore, in recent years it has been suggested that the ultimate solution for FOG effective treatment/coping strategy should be a device pairing automatic FOG prediction with behavioral strategies such as external sensory cueing, aimed at reducing the likelihood of a freezing event [3]. However, such a device has not been developed yet, mainly due to the difficulty in identifying an efficient approach to FOG prediction, with the main issue being the high inter-individuals and even intra-individuals variability among FOG episodes that therefore requires high degrees of flexibility in the proposed prediction algorithm [7]. This may suggest that complex approaches based on machine-learning techniques for instance, may solve this problem [11], [12], [13], [14], [15]. However, if the predictive algorithm requires too many stages of calculations (e.g., when selecting many complex features), it could induce unacceptable delays when computing power is limited as it is the case for many wearable devices, thus hampering real-time applications. To address this issue, we present here a novel FOG predictive algorithm based on the monitoring of the between-legs coordination during gait, which we propose may allow to take the documented variability in FOG occurrences into account, while also limiting necessary computing power, and ultimately therefore establishing itself as a viable solution for real-time FOG prediction.

B. Bilateral Coordination of Gait and Freezing

Several gait impairments are associated with FOG including dysrhythmia [16], [17], [18], gait symmetry [19], [20], dynamic postural control [21], [22], step scaling [23], [24], and bilateral coordination of gait [25], [26], [27], [28]. We posit, for example, that during turns, which are the most prevalent walking circumstance triggering freezing [e.g., [29]], the left- right stepping-phase pattern is challenged due to the asymmetrical stepping requirements (one leg needs to cover longer distance), thus leading to a failure in the bilateral coordination of gait which results in higher propensity for FOG episodes [25], [30].

Building on these assumptions, in this work, we investigate whether FOG episodes can be predicted based on changes in interlimb coordination which are captured by mobility sensors attached bilaterally to the shanks. Initial previous attempts to use this approach, yielded conflicting results [31], [32], [33]. We propose here a novel solution based on a continuous measure of coherence between the signals simultaneously recorded from the two legs. We hypothesize that a FOG episode will be preceded by a drop in the coherence between the two signals [32]. More specifically, we first extract the signal of the shank sensors (i.e, gyroscope operating around the medio-lateral axis) to obtain their spectral properties over time. Then, we calculate the degree of coherence between these signals, obtained from both legs, which is a representation of the coordination between them in both time and frequency domains.

In the present study we aim to evaluate the efficiency of this FOG prediction approach by comparing it to the visual detection of a FOG episode's onset based on post-hoc video inspection. Note that the latter approach relies solely on an observer's subjective evaluation and by definition can detect freezing events only once they start (i.e., FOG detection rather than prediction) and it is currently still considered as the 'gold standard' procedure for FOG detection. We hypothesize as a first step that our proposed approach based on the detection of a drop in the coherence between the legs during gait as a biomarker for un upcoming FOG event, will identify freezes prior to the identification of the same episode via visual inspection. Furthermore, we also aim to evaluate the extent to which our proposed approach can differentiate a FOG episode from a voluntary stop (VOL), namely, two events the output of which is similar (i.e., a sudden interruption of gait) but that completely differ in their significance, therefore representing a crucial discriminative feature for efficient real-life FOG prediction. Following these two steps, which characterize the change in bilateral coordination of gait prior to FOG and VOL events, we analyze as a proof of concept the algorithm's ability to predict FOG episodes without anchoring the analyses to the video-based FOG annotations, thus obtaining the algorithm's confusion matrix characteristics.

II. Materials and Methods

A. Participants

Experiments were conducted in the Research Center of Advanced Technologies in Rehabilitation at Sheba Medical Center. Participants (N = 14; mean age: 65.1 years, SD = ±9.9; 3 females) were recruited from the Movement Disorders Institute, and from the rehabilitation hospital according to the following criteria: people over the age of 50, diagnosed with idiopathic PD, routinely treated with levodopa (L-dopa) and able to walk unassisted for >100m with no pain. The presence of FOG episodes was ascertained using the presence of 2 conditions: (1) an answer of "more than once a day" to the 2nd item of the New Freezing Of Gait Questionnaire (NFOGQ [34]) – "How frequently do you experience freezing episodes", and (2) the treating neurologist's report. Participants were excluded if they presented significant psychiatric, neurologic or orthopedic comorbidities (e.g., psychotic disorders; depression; cognitive impairments; severe osteoarthritis). The experimental protocol was approved by the institutional review board (IRB) of the Sheba Medical center. All participants signed an informed consent prior to entering the study. Data gathered in these experiments were published in part [35], [36], [37].

B. Instruments

Participants wore three Mobility Lab Opal^{TM} motion sensors (APDM Inc., Portland, OR), each weighing 22 grams, 48.5 × 36.5 × 13.5 mm. Sensors included 3 degrees-of-freedom accelerometers, gyroscopes and magnetometer data. Two sensors were placed on the shanks and one was located on the waist of participants. Sampling rate was set at 128 Hz.

In addition, walking trials were videotaped using a camera with a 60Hz sampling rate. For post-hoc annotation, the onset of the motion capture system was included in the video in order to enable synchronization. Video-motion sensors' synchronization was accomplished by performing three taps on one of the sensors by the experimenter, taps which were recorded on camera and identified from the sensor data in post-processing. Video annotations were extracted using Windows Movie Maker software on a desktop computer.

C. Experimental Protocol

All sessions were conducted in the morning and while participants were in the OFF state (>12 hours from last L-dopa medication intake). Participants were asked to fill a demographics questionnaire, followed by an assessment of PD motor severity (using part 3 of the Unified Parkinson's Disease Scale (MDS-UPDRS [38]) and an assessment of FOG severity using the NFOGQ [34]. The amount of anti-parkinsonian medications was evaluated by calculating the L-dopa equivalent daily dose (LEDD) [39].

Participants were asked to perform a series of gait trials: (1) walking with turns (WWT): continuously walking for ∼5 minutes between two cones set ∼ 12 meters apart. Additionally, another cone would be occasionally positioned 20 cm from a wall (and between the two aforementioned cones), creating a narrow passage. (2) WWT with dual-task (DT): participants repeated the latter trial, but this time they were required to perform a summing task of digits while walking. Specifically, patients heard 10 digits presented sequentially 3 seconds apart, and were required to sum up the numbers silently (i.e., without speaking), and provide the final answer at the end of each list. 3) Figure Eight (FE): continuously walking for ∼5 minutes in a figure eight pattern between two cones set 2.5 meters apart. 4) FE with DT: participants repeated the latter trial, this time walking while summing digits, i.e., using the same protocol described above. During some of the trials, participants were occasionally asked to voluntarily stop for ∼8 seconds and then resume walking. Please note that while all participants performed the WWT, not all participants completed the whole gait protocol. This work is part of a larger study, where 24 people with PD and FOG were included. However, for the current analysis we included only those participants who actually froze during the experiment (N = 14). Furthermore, only gait trials during which FOG episodes or voluntary stops (VOL) occurred were included in the analysis.

D. Data Analysis

Data analysis was divided into 2 sections. First, the synchronization loss threshold (SLT) was calculated for each FOG/VOL event separately (i.e., identified from the videos' annotations), and a comparison between SLT and FOG/VOL timing is presented. We did this as a first step, to evaluate when SLT occurs in FOG/VOL and whether SLT properties differ between the two events. Then, as a proof of concept for the feasibility of this approach, we evaluated SLT sensitivity/specificity as predictor of FOG on a subset of the data.

1) Identification of the SLT: Timing of FOG and VOL events was determined and annotated off-line based on the videos of the gait trials by three expert researchers (BH, OK, MP), who have relevant experience either as clinicians, or as researchers trained for annotating videos by expert clinicians. Each trial was manually annotated by 2 evaluators, and discrepancies in identification of events were resolved by a third independent evaluator. Data of timing of events was parsed and synchronized with motion sensor data using custom-written Matlab routines (The Mathworks inc., Natick, MA). Sensor gyroscopic data were filtered using a second order low-pass Butterworth filter (dual-pass, 70Hz cutoff). Timing of gait events was identified according to changes in sagittal plane angular velocity from the motion sensors at the shanks [40] and step and stride lengths were determined using the law of cosines and anthropometric information for each participant [41]. Spatiotemporal gait parameters for periods without FOG were extracted from walking periods prior to FOG and VOL episodes (as described below).

To evaluate temporal changes in bilateral coordination of the legs prior to FOG or VOL, sagittal plane angular velocity signals from shank sensors were used. This signal is less noisy than acceleration signals and is routinely used to identify changes in leg movement (i.e. transitions between swing and stance, etc.) [40]. For each FOG/VOL event identified through the video, sagittal plane angular velocity signal was extracted and examined. For this analysis, a period of 5 gait cycles prior to the video identification of FOG/VOL onset was required, which must have been free of prior FOG events. The sagittal velocity signal was analyzed using wavelet analysis [42] which enables the analysis of nonstationary time series signals in which the spectral properties of the signal vary over time. A signal is convolved with a wavelet function of a specific shape scaled to different dimensions. By performing this procedure N times (N being the length of the original signal), time- and frequency-dependent power spectra can be obtained. Using wavelet analysis, two time series can be inspected for coherence (cross-wavelet spectrum) simultaneously in time and frequency domains. The level of coherence between the signals can be computed for every point in time and every frequency within the signals' power spectra.

Let V_R and V_L be the sagittal plane angular velocity signals of the right and left leg, respectively. The cross-wavelet spectrum is defined as the complex conjugate

$$W^{V_R V_L} = W^{V_R} W^{V_L *} \tag{1}$$

where W^{V_R} and W^{V_L} are the wavelet transforms of V_R and V_L, respectively.

For this dataset, a complex gaussian wavelet was selected due to its similarity with the velocity signal [43]. Since the cross-wavelet transform is complex, the cross-wavelet power was defined as $|W^{V_R V_L}|$, summed across all scaling factors and divided by the maximum power to obtain a coherence index (ranging from 0 to 1). The coherence was calculated for the 5 gait cycles preceding a FOG/VOL event, since this time period was assumed to include the deterioration of inter-limb coordination associated with FOG [30]. The coherence index was smoothed using a dual-pass, 2nd order Butterworth

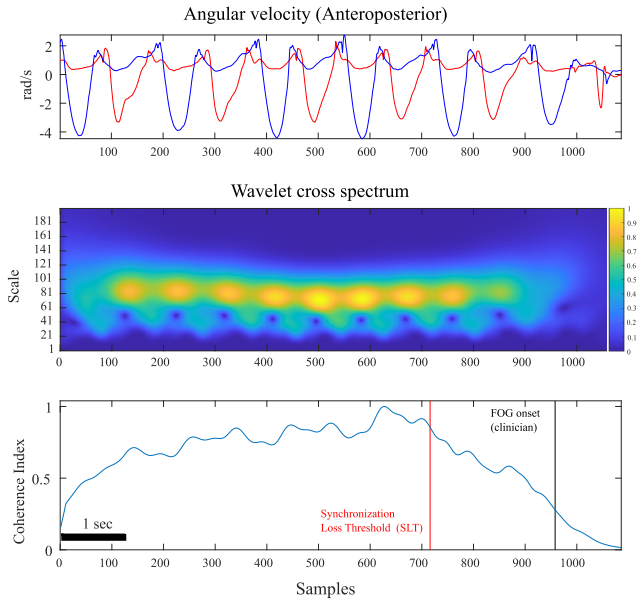

Fig. 1. Example of coherence calculation. The top panel describes anteroposterior (sagittal plane) angular velocity profiles for the right (red) and left (blue) shanks. Center panel describes the wavelet cross spectrum values per sample and scale (a wavelet property, inversely related to frequency). Hot colors denote better synchronization between shank velocity signals. The bottom panel describes the coherence index, identified as the normalized value of maximum coherence for each sample. The drop in coherence is identified using a red vertical line. The black line identifies the clinician's identification of a FOG.

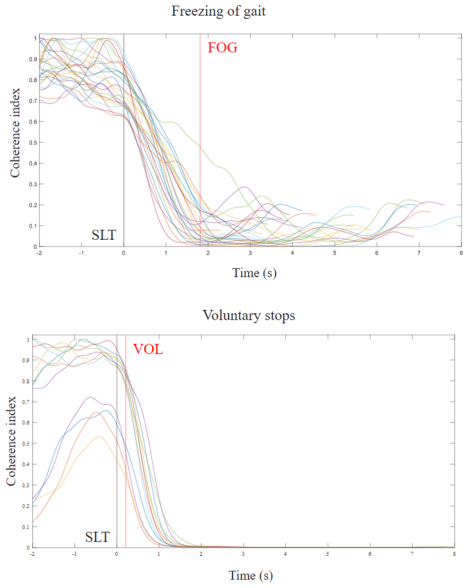

Fig. 2. Coherence index computed for one patient prior to and following FOG events (top panel) and Voluntary stops (bottom panel). Each trace represents the coherence index calculated circa an event (FOG/VOL). The black vertical line marks the point of SLT, the red vertical line marks the point of initiation of FOG/VOL according to the researcher annotation of the video. All traces are aligned according to the timing of the SLT.

low-pass filter (5 Hz cutoff) and a sudden drop in coherence index was identified as the point when the derivative of the coherence index dropped below negative 0.1 for a period of >0.5s. This point was identified as the SLT. SLT was computed automatically for each FOG or VOL event. Figure 1 depicts the process of coherence calculation and determining SLT timing. The time difference between SLT and clinician-defined onset of FOG/VOL was calculated and compared between FOG and VOL events.

2) SLT as a Predictor of FOG: In a secondary, proof-of-concept analysis, a subset of the data containing only straight-line walking (no figure-8 trials) was examined. The coherence index was calculated across the entire walking trial similarly to the above-described method. In order to increase the possibility of differentiating between FOG and VOL, we modified our algorithm incorporating in it the insights we gained from the first analysis approach presented here: 1) we identified transitions from coherence>0.5 to coherence < 0.3. 2) we examined the derivative of the coherence, and in case it had a local minimum < −0.75 (sharp drop), we classified the event as a VOL. 3) we evaluated the decrease in coherence by identifying local maxima in the coherence derivative, i.e. to ascertain whether the coherence drop was smooth (Fig. 2, Fig. 3). If there was at least one local maximum in the signal, we classified the event as a FOG. Otherwise, it was not reported at all.

E. Statistical Analysis

The normality of outcome variables was assessed using the Shapiro-Wilk test. Since the timings of the events as well as the difference between initiation of FOG/VOL and the SLT were not normally distributed (Shapiro-Wilk test < 0.05), Wilcoxon signed rank tests were used to compare SLT and onset of FOG, and Mann-Whitney U tests were used to compare the time difference between SLT and event onset across event types (FOG/VOL). Effect sizes for Mann-Whitney U tests were calculated using the formula ES = Z/sqrt(n). Spearman's correlations were used to evaluate whether time differences between SLT and clinician-defined onset of FOG depend on clinical disease severity. For FOG prediction, sensitivity, specificity, and balanced accuracy were computed using standard formulae based on the confusion matrix. Statistical analyses were performed in SPSS (IBM inc., version 25), and using MedCalc online calculator for diagnostic tests (https://www.medcalc.org/calc/diagnostic_test.php).

III. Results

A. Identification of SLT Prior to FOG and VOL Events

In total, 128 FOG episodes and 42 voluntary stops were analyzed from N = 14 patients. Patients' characteristics are described in Table I. The timing of the initiation of FOG events (as defined by video analysis) was significantly later than the SLT for both FOG events ($Z = -7.04$, $p < 0.001$, ES=1.88) and VOL events ($Z = -2.89$, $p = 0.004$, $ES = 0.77$).

Furthermore, the time difference between SLT and initiation of FOG/VOL events was significantly larger for FOG events (MED = 1.81 sec, IQR = 1.57) than for VOL events (MED = 0.22 sec, IQR = 0.76) ($Z = -4.3$, $p < 0.001$, $ES = 1.15$). Figure 2 demonstrates these findings by presenting data taken from one example participant. In Figure 2, coherence traces of one example patient are depicted. Here, the longer time difference between the SLT and the clinician's event initiation

TABLE I
CHARACTERISTICS OF PATIENTS

	Sex	Age	MDS-UPDRS OFF	NFOGQ	LEDD	Gait speed (m/s) M±SD	No. of FOG events	No. of VOL events
1	M	61	42	25	1031	0.82±0.23	10	2
2	F	66	12	21	460	0.61±0.06	4	1
3	M	54		26	1330	0.72±0.08	5	0
4	M	47	36	17	1050	0.83±0.09	3	0
5	M	63			716	0.76±0.18	11	0
6	M	78	24	21	1425	0.58±0.20	17	4
7	M	79	27	30		0.40±0.14	5	0
8	M	67	10	22	875	0.73±0.17	26	12
9	M	52	10	22	1463	0.78±0.06	6	10
10	M	76	11	18	806	0.79±0.06	2	0
11	M	69	2	23	1460	0.75±0.16	23	10
12	F	59	7	22	1085	0.73±0.31	4	0
13	M	65	32	23	1554	0.45±0.13	7	1
14	F	75	19	21	960	0.42±0.17	5	2

TABLE II
CONFUSION MATRIX FOR SLT-BASED PREDICTION

	Actual FOG	*No actual FOG*
SLT-predicted+	TP=50	FP=38
SLT-predicted-	FN=1	TN=28

TP=True positive; FP=True negative; FN=False negative; TN=True negative

can be clearly seen in the case of FOG-related coherence traces (top) as compared to VOL-related coherences drops (bottom). Note that all FOG and VOL coherence traces are aligned to the SLT.

Time differences between SLT and onset of FOG/VOL events did not correlate with measures of severity (i.e. MDS-UPDRS, NFOGQ, LEDD) or with gait speed, stride length or time prior to the FOG events (all p-values > 0.18).

B. SLT as a Predictor of FOG

The subset of the data (including straight-line walking trials only) included 51 FOG and 20 VOL events in total. The confusion matrix for the prediction algorithm is presented in Table II. The SLT drop algorithm correctly identified 50/51 FOGs (98.04% sensitivity, CI [89.55% to 99.95%]). However, specificity was low (42.42%, CI [30.34% to 55.21%] resulting in balanced accuracy of 70.23%. Out of 38 False positives, 4 were voluntary stops and 34 were turns. In addition to these 38 FPs, in 5 instances 'false' FOG events were identified during straight line walking. These were cases where gait deteriorated but did not result in video-based identification of FOG (these were not entered to the confusion matrix since it would be impossible to add all instances where straight line walking was not identified as FOG to the true negative count). Out of 28 True negatives, 16 were voluntary stops and 12 were turns.

IV. DISCUSSION

Results of the current study found convincing evidence that about 1.8 seconds prior to FOG episodes, the level of left-right stepping coherence decreases. Importantly, this was found to be significantly earlier than the drop observed prior to voluntary stops (i.e., about 0.2 seconds prior to stopping). This result adds to previous literature [33] and is in agreement with previous evidence, that FOG is associated with impaired bilateral coordination of stepping [25]. Based on this finding, we developed an SLT-based algorithm for FOG prediction. Our proof-of-concept analysis showed that this algorithm correctly identified 98% of FOGs. The algorithm specificity however was 42%, mainly due to identifying FOG episodes falsely during turns while largely succeeding in differentiating between FOG and VOL events.

A. Benefits of Using Bilateral Coordination of Stepping for FOG Predictions

The current work is embedded within the emerging line of works aiming at predicting FOG events based on data collected from 3D inertial wearable sensors [14], [15], [33], [44]. These works demonstrated that it is possible to identify precursor signs of FOG (pre-FOG) by comparing pre-FOG and gait periods and comparing various spatiotemporal gait parameters. The common assumption is that before FOG occurs, a discernable change in the gait pattern can be detected (threshold-based model [30]). Indeed, pre-FOG is characterized by a change in stride length but not cadence [16], and different gait features, derived from accelerometer and gyroscope data obtained during gait, have shown variable degrees of sensitivity to pre-FOG [14], [15], [33], [44]. The current work is in agreement with previous studies, i.e., [33], which identified interlimb coordination (specifically left-right cross-correlation) as a gait feature which, together with other features, could potentially differentiate pre-FOG from regular gait. Importantly, these results were not compared with voluntary stops, in turn not providing information regarding the extent to which the aforementioned FOG-predictive measures could discern between these two types of events. A different approach [14] used machine learning algorithms and demonstrated that features based on time and frequency domains of accelerometer data (collected from lower back and one leg) can predict FOG 1.72 seconds prior to occurrence. However, it is difficult to compare between the results of these previous studies since they rely on sensor data from different body segments, with the latter work relying on mobility information collected from one leg only. Furthermore, the complexity of this highly sensitive and specific machine learning algorithm is high [14], ultimately increasing the required computational power. This may be problematic given that the final aim of these algorithms is to be deployed in real-time [3], and most wearable devices have currently limited computational power.

In the current work we attempt to reduce the complexity of the problem by using locomotor coordination as key for FOG prediction [45]. This was done based on previous work [25], [28] in an attempt to minimize the amount of computations that are required to be carried out during walking, ultimately thus aiming at maximizing the efficiency of FOG predictor systems. Coordination is considered to be a higher-order property of the locomotor system, and can be measured in several ways [45]. In the current work, the measure of stepping coherence was selected over the traditionally-used measure of cross-correlation e.g. [33]. Cross-correlation calculates the correlation in the time-domain between two vectors, and therefore it is a computationally expensive process requiring to constantly buffer an increasingly large amount of data. This may generate a less temporally-sensitive identification of immediate changes

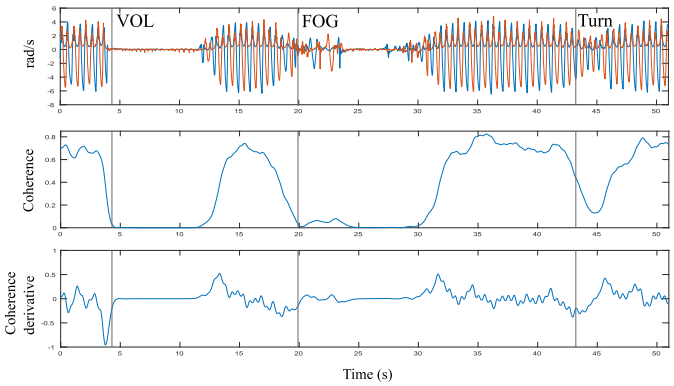

Fig. 3. An example for use of coherence in longer time scales to predict FOG. A representative trace from one subject is presented, containing a voluntary stop, followed by a FOG episode and a turn. The top panel shows the angular velocity signal. The middle and bottom panels represent the coherence and the derivative of the coherence, respectively. Vertical lines mark video-based detection of events. Different patterns of change in coherence are demonstrated for the three event types. This type of observation preceded the proof-of-concept analysis for FOG prediction.

in interlimb coordination. Thus cross-correlations are more suitable to be performed off-line once the entire signal is obtained (but see recent attempts to adapt it to real-time, though using more complex algorithms than the one we describe here [46]). In contrast, wavelet analysis (i.e., the analytical approach used here) involves both time and frequency domains, and thus we believe that it will accurately detect changes in coordination patterns in a timely manner, without requiring a long buffer of data.

Finally, accumulating evidence aiming at investigating the pathophysiology of FOG events in the human brain using functional Magnetic Resonance Imagining (fMRI) suggests that FOG is associated with paroxysmal functional decoupling between cortical and subcortical (basal ganglia) gait-related regions, namely, documenting cortical hyperactivity flanked by decreased sub-cortical activity [47], [48]. In other words, these works showed that when there is an alteration in the footstep patterns leading to FOG, this is accompanied by a drop in the coordination between large-scale brain networks. Considering this evidence, therefore, it seemed appropriate to rely on a drop in the interlimb coordination, operationalized via a drop in the stepping coherence, as a measure for FOG prediction as this might likely be the pre-FOG physiological outcomes of a larger-scale coordination failure.

Our proof-of-concept analysis demonstrated that the current approach allows FOG prediction with high sensitivity. The value of 98% sensitivity is higher than that reported for a prediction model based on machine learning and motion sensors-based data [49], motion and plantar pressure sensors [7] as well as that of an EEG-based prediction model [50]. However, we also demonstrated specificity of 42.4%. While our algorithm largely successfully differentiated between FOG and VOL events, it mistakenly classified a high rate of turns as FOG (see example of coherence in both cases in Fig. 3). First of all, the high success in differentiating between FOG and VOL events is a strength of this work given that previous FOG predictive algorithms often did not take VOL into consideration and excluded VOL events from analyses [15], [51]. Nonetheless, it is crucial for FOG prediction algorithms to take VOL into account and future studies may work towards further improving the sensitivity of this differentiation. The issue related to turns, however, is unfortunately embedded within our approach of predicting FOG relying on alterations in stepping coherence. Indeed, during turning interlimb coordination dynamics is altered in general, and specifically in PD. Turns are also frequently reported as a trigger for FOG [25], [30] with one of the most influential proposals suggesting that high FOG propensity during turns is due to the challenge in bilateral coordination intrinsically characterizing turning behavior (i.e., one leg needs to cover longer distance thus requiring asymmetrical stepping) [25], [30]. Future studies may work towards the improvement of turn/FOG differentiation. It should be noted, for instance, that turn data based on magnetometer was not incorporated in the current analysis, and this may be a future focus of examination. However, given that often FOG is triggered by turning, careful consideration should be taken for identifying turn-related vs. non turn-related FOG. It is finally also worth considering that, since the final aim of FOG prediction algorithms is to be paired with FOG coping strategies such as external sensory cueing [3], it might be an advantage to alert the users prior to turns, given that, as mentioned above, turning is often triggering FOG events.

B. Future Directions and Challenges

This work demonstrates the potential of using bilateral coordination as a measure to sensitively predict upcoming freezing events, i.e., anticipating of ∼2 seconds the actual FOG episode. This strengthens and advances previous evidence by providing a relatively simple solution crucially resulting in an average "horizon" (i.e., how soon we can predict that a FOG event will occur) which is larger than that identified in previous work [14]. This is very relevant within the framework of the research investigating potential solutions for FOG treatment. It is believed that the most promising approach in this field is the use of integrated systems that deploy FOG prediction algorithms in real-time to alert of an upcoming FOG event, and then enable the triggering of behavioral strategies to alleviate or avert the freezing event, e.g., by delivering external sensory cues [3]. Our novel measure to quantify bilateral coordination, namely stepping coherence, is based on the signal's time and frequency domains and, crucially, requires a minimal amount of gait cycles to be computed, therefore being suited for real-time FOG prediction applications. While there are previous works assessing the effectiveness of various real-time algorithms for FOG prediction [3], an integrated system incorporating also behavioral FOG-averting strategies is yet to be developed. One of the main reasons slowing down progresses in this direction, it is the fact that a satisfactory algorithm for real-time FOG prediction has not yet been identified. We propose that bilateral coordination quantified through stepping coherence measurements holds potential to become a crucial measure for real-time FOG prediction algorithms relying on mobility sensors. This suggestion stems from various considerations: first the fact that, as stated above, the drop in bilateral coordination between the legs has a solid neuro-physiological hypothesis supporting its crucial role in

pre-FOG periods, i.e., the fact that it could be the outcome of the functional decoupling documented before and during FOG between large-scale cortical and sub-cortical brain networks [47], [48]. This is supported also by the fact that our algorithm was able to successfully differentiate pre-FOG from voluntary stops, thus highlighting differences between these two types of drop in interlimb coherence. Second, recording the data requires a relatively simple set-up, facilitating and encouraging usability. Third, calculating stepping coherence is an easy computational task, thus allowing real-time computations with minimal delays. By combining these advantages, we believe that future work can utilize the current approach in the development of real-time algorithms for detection and prediction of FOG.

Accumulating evidence has demonstrated accurate FOG detection and, in some cases prediction, based on different signals, including EEG [50], [52], [53] as well as other physiological signals such as heart-rate [54], [55], suggesting that incorporating neural and physiological dynamics can improve FOG prediction [56], [57]. While the current work did not incorporate additional sensors, future work should evaluate if/the extent to which additional sensors (i.e. neural, physiological) further improve FOG predictivity. We believe that the simplicity of our data reduction approach where a single criterion signal is generated (i.e., stepping coherence) from two sensors positioned on the shanks, is a strength of this work as it provides a powerful means to integrate data from multiple mobility sensors. It should be noted, however, that a balance may exist between the benefits of adding sensors to improve FOG predictability, and the potential problems that the use of multimodal sensors can cause, e.g., decreasing both users' usability and computational power. Future works may therefore address this important issue and identify the most efficient multimodal sensors' combination to maximize FOG prediction.

C. Limitations

The current work did not adapt the FOG prediction algorithm to individual participants. For instance, we documented variability in the 2 seconds "horizon" for FOG prediction, which may stem from individual differences in the underlying FOG-triggering mechanisms. Given the documented variability in FOG manifestations e.g. [58] and [59] as well as the variability exhibited in the current study, future studies will need to explore the possibility that an optimal FOG prediction algorithm would need to be adapted to individual gait characteristics and/or to the specific multi-modal neurophysiological profile of each patient. This study contains a relatively small sample of people with PD and FOG, who were heterogeneous in their manifestation of FOG events. In addition, we collected and thus analyzed fewer voluntary stops than FOG episodes (see Table I). However, stop-related signals showed less variability than FOG-related ones and the difference between the two event types had a large effect size. A final limitation is associated with our proof-of-concept analysis, which was based on a subset of the dataset involving straight-line walking only. This analysis highlighted the fact that interlimb coordination varies during turns and inevitably lowers the value of coherence, which results in a high rate of false positives. To this end, a closer investigation of turn-related FOG and their differentiating characteristics from other FOG episodes is warranted.

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