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REVIEW/MISE AU POINT

Characterization and quantification of freezing of gait in Parkinson's disease: Can detection algorithms replace clinical expert opinion?

Caractérisation et quantification du freezing *de la marche dans la maladie de Parkinson : les algorithmes de détection automatique remplacent-ils l'expérience du clinicien ?*

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Summary Freezing of gait is a paroxysmal phenomenon that is frequently reported by the parkinsonian patients or their entourage. The phenomenon significantly alters quality of life but is often difficult to characterize in the physician's office. In the present review, we focus on the clinical characterization and quantification of freezing of gait. Various biomechanical methods (based mainly on time-frequency analysis) can be used to determine time-domain characteristics of freezing of gait. Methods already used to study non-gait freezing of other effectors (the lower limbs, upper limbs and orofacial area) are also being developed for the analysis of freezing in functional magnetic resonance imaging protocols. Here, we review the reliability of these methods and compare them with reliability of information obtained from physical examination and detailed analysis of the patient's medical history.

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MOTS CLÉS
Freezing de la marche ;
Maladie de Parkinson ;
Quantification

Résumé Le *freezing* de la marche est un trouble paroxystique souvent difficile à mettre en évidence dans un environnement médical malgré le fait qu'il soit souvent rapporté par le patient ou son entourage et qu'il ait un retentissement important sur la qualité de vie des patients parkinsoniens. Dans cette revue, nous nous sommes focalisés sur la caractérisation et la quantification du *freezing* de la marche. Diverses méthodes étudiant sa structure temporelle, basées principalement sur les analyses temps-fréquence, sont présentées. Des méthodes utilisées pour caractériser des équivalents de *freezing* sur d'autres effecteurs (membres inférieurs et supérieurs, sphère orofaciale) sont aussi développées dans le but d'étudier le *freezing* en imagerie fonctionnelle. La fiabilité de ces méthodes est évaluée et comparée à l'évaluation clinique (incluant une anamnèse précise).

Parkinson's disease (PD) is characterized by axial signs; these notably include gait impairments that worsen over the course of the disease. Patients walk more slowly, with a shorter step length, higher cadence [40] and greater step time variability [26]. These gait impairments (which are present in most patients with PD) may be associated with paroxysmal events, such as freezing of gait (FoG) and/or festination [6]. During FoG, the feet appear to be more or less ''glued'' to the ground, with a dramatic change of cadence. Signs of shaking and asynchronous movement (described as ''trembling in place'') may occur as the result of ineffective efforts to move forward, particularly during step initiation [32]. Another FoG pattern (characterized by a frozen, akinetic state) has also been described [6]. Nutt et al. [49] defined FoG as the ''absence or marked reduction of the forward progression of the feet, despite the intention to walk''. One of the strengths of this definition (based on clinical evaluation) is that it encompasses the different subtypes of FoG. Freezing is most commonly experienced during turning, step initiation and when faced with spatial constraints, stress, and/or distraction: this often corresponds to passing through a narrow doorway or reaching a destination, although FoG may also occasionally occur during walking in a straight line in open space [59,66]. Focused attention and external stimuli (cues) can overcome a FoG episode or, on the contrary, trigger it [37].

Gait festination is defined as a tendency to move forward with faster but smaller, ''tottering'' steps. It is associated with a forward displacement of the center of gravity (in front of the feet) [21]. FoG and festination often occur in the same patient, and display very similar spatiotemporal anomalies in the steps preceding the FoG phenomenon [10,45].

FoG is frequently reported in PD: in 81% of patients after 20 years of disease (in an Australian cohort) [29], and in 87% after 11 years (in a Chinese cohort) [4]. In the DATATOP cohort [22], FoG was present in early-stage disease (in 26% of L-dopa-naive patients). Furthermore, FoG is reportedly an independent risk factor for falls [52] and impairs quality of life [54]. FoG and festination are debilitating problems because of their relative resistance to treatment by levodopa [16,54] (as is the case for most axial signs). Moreover, the effects of subthalamic nucleus deep brain stimulation on FoG are subject to debate [19]. Hence, FoG is a frequent, serious problem in PD and must be closely monitored.

A detailed analysis of the patient's clinical history is necessary and will provide information on self-reported FoG and the latter's relationship with dopaminergic medication [3]. Given this context, what advantages might automated quantification methods provide in the detection of FoG and the characterization of its pathophysiological mechanism?

In the present review, we shall successively focus on:

- the clinical characterization and quantification of FoG;
- biomechanical methods for characterizing FoG;
- useful applications of these methods (e.g. for the objective detection of FoG and assessment of its pathophysiological basis).

The clinical assessment of FoG

In most publications, the classification of patients as ''freezers'' has been based on the patient's retrospective self-assessment of FoG over a period of time (often the previous week) using various questionnaires. The most frequently used tools are the Unified Parkinson's Disease Rating Scale (UPDRS) part 2, item 14 (''freezing'') [18] and item 2.13 of the more recent Movement Disorders Society (MDS)-UPDRS questionnaire [24]. Patients rate their propensity to freeze over the previous week on a scale from 0 (no FoG) to 4 (frequent falls due to freezing for the UPDRS, and the need to use a walking aid or someone's help for the MDS-UPDRS). The Freezing of Gait Questionnaire (FOG-Q) and the new FOG-Q (NFOG-Q, which includes a video showing several subtypes of FoG) [20,23,47] can be used to identify freezing behavior. Indeed, FOG-Q question 3 (''Do you feel that your feet get glued to the floor while walking, making a turn or when trying to initiate walking [freezing]?'') was at least as good as item 14 of UPDRS part 2 for distinguishing between freezers and non-freezers. Snijders et al. [64] developed a decision tree for refining the classification of freezers into three categories: (i) a ''self-reported freezer,'' (ii) a ''probable freezer'' (i.e. when FoG is confirmed by a third person, such as caregiver) and (iii) a ''definite freezer'' (when freezing is actually observed during formal, objective testing). Other less specific gait and balance scales could be useful to assess FoG and have recently proved to be able to differentiate freezers and non-freezers [15]: the Mini-BESTest and Berg Balance Scale. Both tests take

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approximately 15 min to administer and are reliable in predicting falls in people with PD [14].

The ''gold standard'' of FoG assessment is thus a clinical evaluation of video recordings of ambulating patients by one, two or three raters (ideally, experts in FoG assessment) [30]. One of the main problems highlighted by Snijders et al. [64] is that physical examination in a lab environment or in the physician's office can temporarily suppress a patient's FoG. This failure to elicit the FoG phenomenon is inconvenient for physicians who need to base their evaluation on observations in the consulting room. Nevertheless, various triggers can be used to elicit FoG in medical or laboratory environments: FoG typically occurs during a shift of attention or a circumstantial directional change, such as turns, while starting to walk, moving in tight quarters, and when dual tasking (e.g. walking and talking at the same time) [59]. Turning around appears to be the strongest triggering factor for FoG [66]. The stress associated with the need to move under time pressure may also trigger FoG. Snijders et al. [64] have suggested the use of a dedicated ''gait trajectory'' that features specific FoG triggers (gait initiation, followed by a narrow passage, dual tasking and rapid 360° axial turns in both directions). This gait trajectory was subsequently used in studies of drug treatments [13,38,39].

The number of FoG episodes observed during the execution of a FoG trajectory is widely used in clinical research and requires the evaluation of this phenomenon by different raters. An episode of FoG is often very short (less than 2 s) but can sometimes last longer (up to several minutes), making the number of this indicator FoG episodes a very imprecise quantitative marker for FoG. With a view to avoiding this obstacle, a composite score (based on number of episodes of FoG and their duration) has also been developed; short episodes of FoG (lasting less than 10 s) are given a score of 1, medium-length episodes (lasting between 10 and 30 s) are given a score of 2 and episodes lasting for more than 30 s are given a score of 3 [13,38,39]. A recent study evaluated the quantification of FoG in terms of both the number of FoG episodes and the percent time frozen (cumulative duration of freezing episodes/total duration of the walking task); percent time frozen proved to be a more reliable metric [41]. The reliability of clinical video assessment for the number of freezing events was moderate (intraclass correlation coefficient [ICC]: 0.63), whereas the inter-rater agreement was higher for percent time frozen (ICC: 0.73). When percent time frozen is calculated, it is less critical whether the patient has several sequential FoG episodes or one long episode. The marked variability from one clinician to another suggests that caution should be used when comparing subjective ratings across centers.

The biomechanical assessment of FoG

Two different approaches for studying gait in freezers have been described in the literature: (i) focusing on continuous coordination of the lower limbs during gait but outside actual FoG episodes, and (ii) describing the FoG episodes themselves. Firstly, freezers and non-freezers show time-domain differences in stride regulation outside actual FoG episodes. In fact, freezers show abnormally high stride-to-stride variability [27] and higher asymmetry of gait (defined as the differences between left and right swing times) [57]. Quadrupedal locomotion (i.e. the synchronization between ipsilateral arm swings and contralateral leg swings) is also altered in freezers [43]. Chee et al. [7] suggested that failure to generate adequate movement amplitudes (reflected by a progressive decrease in step length) and disturbed step timing (a phenomenon known as the ''sequence effect'') were major factors in the pathophysiology of FoG. Continuous gait abnormalities of freezers have been recently investigated for a long time period (3 days). Weiss et al. [72] used a tri-axis accelerometer worn on a belt on the lower back. They evaluated different characteristics of gait during 1-min windows excluding FoG episodes: quantity measures such as total time walking, number of steps and cadence but also quality measures were computed. These latter included different variables in the frequency domain: the width of the dominant peak in the power spectrum (this reflects the variability of the gait, in that the larger the width, the more variable the gait pattern). Stride regularity was the amplitude of the second peak in the autocorrelation signal and reflected the consistency of the stride. The harmonic ratio was derived as the ratio between the even and odd harmonics of the gait signal. A higher vertical and anterior-posterior, and a lower medio-lateral harmonic ratio indicate a smoother gait pattern. Not surprisingly, freezer patients exhibited higher stride variability (larger width of the dominant peak in the power spectral density) and regularity, and higher vertical and antero-posterior and lower lateral harmonic ratio but no differences in quantitative measures.

Secondly, the physiological events immediately preceding a FoG episode and during the episode are characterized by various differences. In a small study (involving only five PD patients), the cadence was found to rise just before a FoG episode; this was accompanied by incomplete shifting of the centre of pressure from one foot to the other [68]. Another study found that FoG episodes were preceded by increased cadence and decreased stride length [45,46]. No significant differences between festinating and pre-freezing strides were found, suggesting that these two phenomena have common features [45].

Start hesitation associated with FoG is also a common manifestation in PD, and represents a particular FoG subtype (for a review, see [11]) with leg trembling or even complete akinesia during gait initiation. Other markers of gait initiation FoG have been described and are related to step execution. Okada et al. [50] investigated abnormalities in the first three steps after gait initiation in patients with PD patients with and without FoG; they found that the medial deviation of the centre of pressure from the first heel contact position was a sensitive marker of the severity of FoG. The same researchers [51] compared the characteristics of the swing and support legs during gait initiation in small groups of freezers and non-freezers. It was found that abnormal variability of the initial swing side and prolonged first double-limb support were specifically related to FoG. Our research group has studied anticipatory postural adjustments before gait initiation in 30 PD patients with or without FoG: the presence of multiple anticipatory postural adjustments (as described by Jacobs et al. [32]) and the absence of adequate postural perturbation (i.e. the absence of a center of pressure shift towards the swing leg) corresponding to complete akinesia were much

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more frequent in freezers than in non-freezers [12]. Another approach is based on analyzing the frequency of leg movements and the associated muscle contractions prior to and during a FoG episode. One early report noted an intermittent, pathologic co-contraction (flexors and extensors of the foot) at a frequency of about 4 Hz in a single case with FoG [17]. High-frequency oscillations of stepping during FoG have also been observed in another study (of 5 patients) [68]. A new approach was initiated by a series of studies that used spectral analysis of insole forces prior to and during FoG episodes [51]. As expected, a narrow peak at a frequency of around 1 Hz (which corresponds to the frequency of stepping) characterized normal gait, whereas an abnormal peak in the 3—6 Hz band was associated with FoG episodes. The latter peak clearly differed from tremor or increases in cadence prior to or during the FoG episode. These findings were confirmed in a study that used a different approach, namely frequency analyses of vertical leg motion as measured by accelerometers attached to the shank [35]. The results showed that FoG episodes were characterized by an increase in the 3—8 Hz band and a decrease in the 0.5—3 Hz band. Moore et al. [35] defined a freeze index that was defined as a ratio of mean power in the 3—8 Hz band/0.5—3 Hz band: the higher the ratio, the more frequently FoG episodes occurred. This approach also appeared to be of value in a treadmill-based paradigm of obstacle-crossing that evokes subtle FoG episodes [10]. Time-frequency analysis (with combinations of a sliding fast Fourier transform and a wavelet transform) identified FoG episodes within goniometer signals. The frequency analysis yielded a well-characterized, typical, qualitative pattern: an increase in dominant frequency in the 0 to 3 Hz band (festination) before the FoG episode, followed by a decrease in power in the 0 to 3 Hz band and an increase in power in the 3 to 8 Hz band during the FoG episode. This pattern was associated with an elevated freezing index. These approaches detected even very brief FoG episodes with acceptable sensitivity (75—83%) and specificity (> 95%). More recently, this accelerometry-derived method has been validated [41] by the demonstration of strong agreement with clinician ratings of the number of episodes (ICC: 0.78) and the percent time frozen (ICC: 0.93). A representative time-frequency analysis in a PD patient performing three turns (with several FoG episodes) is shown in Fig. 1 (personal data). We used the freezing index (described by Moore et al. [35]) and a wavelet transform method [9] to characterize FoG.

Furthermore, a power spectrum analysis of vertical acceleration of the leg showed that leg trembling during gait initiation was associated with high-frequency components in the 3—8 Hz band; this feature was not apparent when the patient was standing [35]. In our experience, these algorithms (visual inspection of changes in frequency power or use of the freeze index) cannot detect akinesia with a lack of anticipatory postural adjustments.

Lastly, other methods have also been used to quantify FoG episodes. Hausdorf et al. [28] reported a time-series analysis for determining whether the force variations during a FoG episode were uncorrelated and random or whether they were structured in the time-domain. A fractal analysis was combined with a detrended fluctuation analysis. An exponent value close to 0.5 would have indicated that the force fluctuations during FoG are random. In fact, the value was 1.7 ± 0.1 (close to the value expected for Brownian noise), which indicates a roughly structured signal with complex organization in the time-domain.

Popovic et al. [58] have also used correlation analysis to detect FoG. Briefly, the dependence between two periodic time-series was quantified with Pearson's correlation coefficient. The coefficient was close to 1 when patients walked without FoG but decreased during a FoG episode (due to the lack of periodicity). The times at which FoG was detected by visual inspection or in an automated correlation analysis were roughly similar [58]. Taken as a whole, these results demonstrate the validity of methods for the objective measurement of freezing.

Useful applications: non-gait equivalents of FoG

Another important point relates to the need to gain a better understanding of the pathophysiology of FoG. Recently, mental imagery of gait [8,34,55,56,65] and virtual-reality tasks [60,62,65] have provided researchers with new ways of studying FoG. Given that patients remain in the supine position in fMRI/PET machines, tasks intended to trigger equivalents of FoG (which can be well characterized) have been developed over recent years. Further explanations on brain imaging techniques and protocols used in mental imagery of freezing can be found in extensive reviews on the topic [31,33]. We can add that imaging of real gait has been performed in parkinsonian patients using Tc-99 m hexamethylpropyleneamine oxime perfusion in non-freezers [25], or more recently ^{18}fluoro-deoxyglucose PET in freezers [67].

Freezing of other effectors

Equivalents of FoG can also be observed in the upper limbs during bimanual tasks involving motor coordination, such as tapping [73] or the performance of anti-phase movements [2]. Indeed, episodes of freezing of the upper limbs are found to be correlated with FoG scores, independently of the severity of disease or cognitive impairment [48,69,73]. However, the link between FoG and freezing of the upper limbs is not fully established. The two phenomena do have common features: episodes of freezing of the upper limbs are preceded by much the same spatiotemporal abnormalities as those seen before FoG [48] with an acceleration in cadence and a marked decrease in amplitude [69]. Low-amplitude imposed hand movements appear to cause freezing of the upper limbs more readily [69], as does an imposed reduction in step length [7]. As seen with FoG, the spectral analysis of a freezing of the upper limbs highlights an increase in high-frequency bands (above 3 Hz) [69]. However, not all studies of the upper limbs in patients with FoG have observed spatial and temporal coordination outside episodes of FoG [48]. Moreover, freezing of the upper limbs may occur more frequently than FoG does [48,73]. It is also unclear whether freezing of the upper limbs appears earlier than FoG.

Freezing in the orofacial area has also been described by using diadocokinetic tasks (the repetition of syllables); these can lead to a sudden speech arrest in which the subject is unable to produce the entire sound. This

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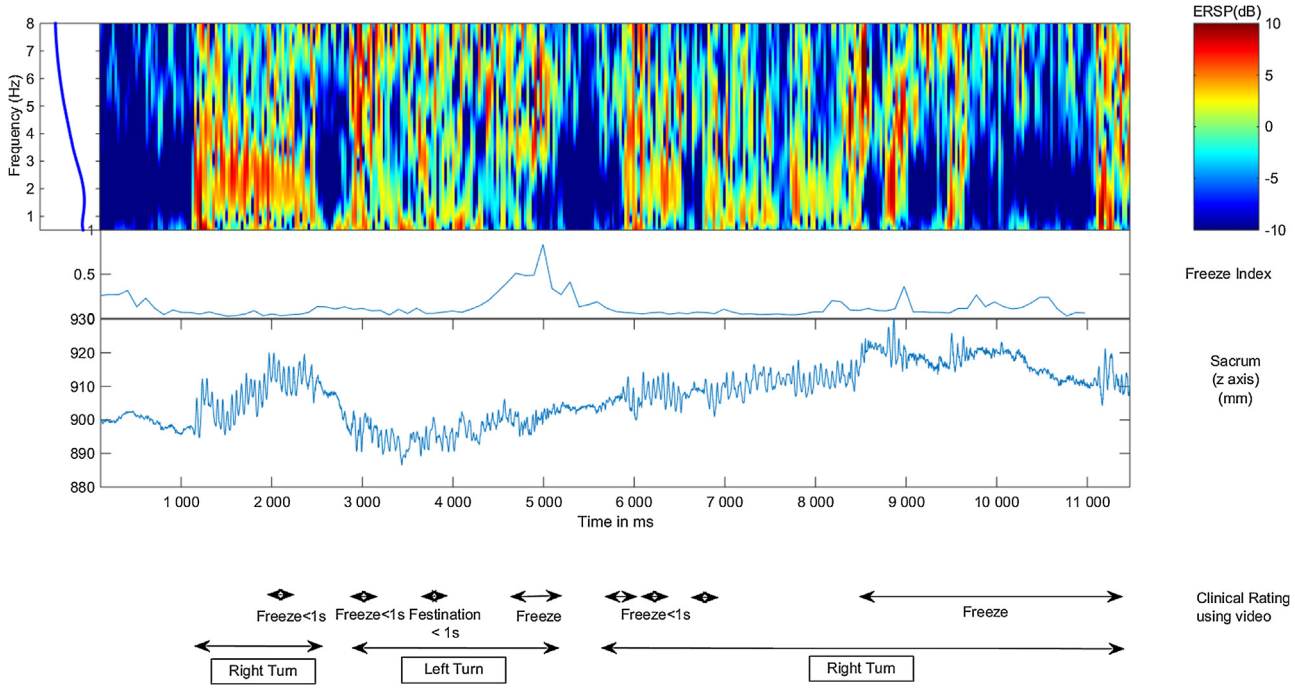

Figure 1 Example of a PD patient performing three 360° turns (see also the video in the Supplementary data). Several methods were used to identify FoG episodes: (1): clinical rating of a videotape (provided in the Supplementary data) by two movement disorders neurologists (AD and CT). Episodes of FoG and festination are indicated below the time axis; (2): a time-frequency method using wavelet transformation [9] of the sacrum's vertical position; by using 1 cycles at the lowest frequency (0.5 Hz) and 8 at the highest frequency (8 Hz), we generated 400 time points (1115.1 to 114684.9 ms). The window is 223 samples wide (2230 ms) and enabled the estimation of 615 linearly spaced frequencies from 0.5 Hz to 8.0 Hz. For computing time/frequency parameters, we calculated the decomposition event-related spectral power (ERSP) using the EEGlab interactive MATLAB toolbox, [9]. Increases in power are shown in red and decreases are shown in blue (the whole trial was considered as the baseline because we made no assumptions as to whether or not the patient presented FoG); (3): frequency spectra of the sacrum's vertical position (z axis). A ''locomotor'' band encompassed the frequency components from 0.5 to 3 Hz, and a ''freeze'' band encompassed the range from 3 to 8 Hz (at the top of the figure). Just below, the freeze index (FI) at time t was defined as the square of the area under the power spectrum in a 6 s data window (centered on time t) in the 'freeze' band, divided by the square of the area under the spectrum in the ''locomotor'' band (from 0 to 1). Analyses were performed using a custom MATLAB script developed in-house; (4): methods based on either on a reduction in signal amplitude (visual inspection or computed algorithms, see [69]) or an increase in latency between footsteps [62] have also been described (not performed here). A motor arrests were defined as a time interval between two alternating ''footsteps'' of more than twice the patient's modal footstep latency [63]. If clinical rating was considered to be the gold standard, the FI only identified long-lasting FoG episodes (i.e. an increase in the FI in the event of FoG). This is probably due to the window width used (6 s, the same as in the original article [35], but probably too long for this short trial). Time-frequency analysis provided important information on FoG: the decrease in power in the locomotor band (for this subject, the mean frequency during gait was about 2 Hz) is replaced by an increase in higher frequencies (3—8 Hz). This method detects short FoG episodes with good sensitivity but lacks specificity. However, voluntary stops were well identified by the method (with a decrease in power in the 0.5—3 Hz band but also in 3—8 Hz band, as seen before and between turns). Visual inspection of the sacrum's vertical position also identified FoG episodes and can be combined with the use of algorithms based on variations in signal amplitude, peak-to-peak latency [63] or correlation functions [58].

phenomenon occurs for imposed frequencies ranging from 4 to 6 Hz and is accompanied by a reduction in the amplitude of lip movements [1]. Speech impairment was present in 1.9% of the patients in the DATATOP cohort (early-stage PD) and was associated with the development of FoG over time, with various problems: palilalia, tachyphemia and speech pauses or vocal arrests (speech freezing) [22,71]. Gait and speech disturbance are both considered to be axial signs of PD, suggesting common physiopathological mechanisms and features for speech and gait disorders in PD: gait velocity, cadence and stride length alterations observed during gait were found to be correlated with the time delay of speech initiation, speech rate and the number of repetitions per sentence during reading in PD patients with and without FoG [53]. Orofacial festination also appears to be a common feature in patients with FoG, since episodes of hastening and motor blocks during a diadocokinetic task (repetition of syllables) were more frequent in PD patients who also experienced festination and FoG [36]. The methods used to characterize these FoG equivalents are based variously on visual inspection [48], time-frequency transforms (with an increase in the 3—8 Hz band) [70], a decrease in signal amplitude [5] and increase in the time interval between two rhythmic productions [63] (see Fig. 2).

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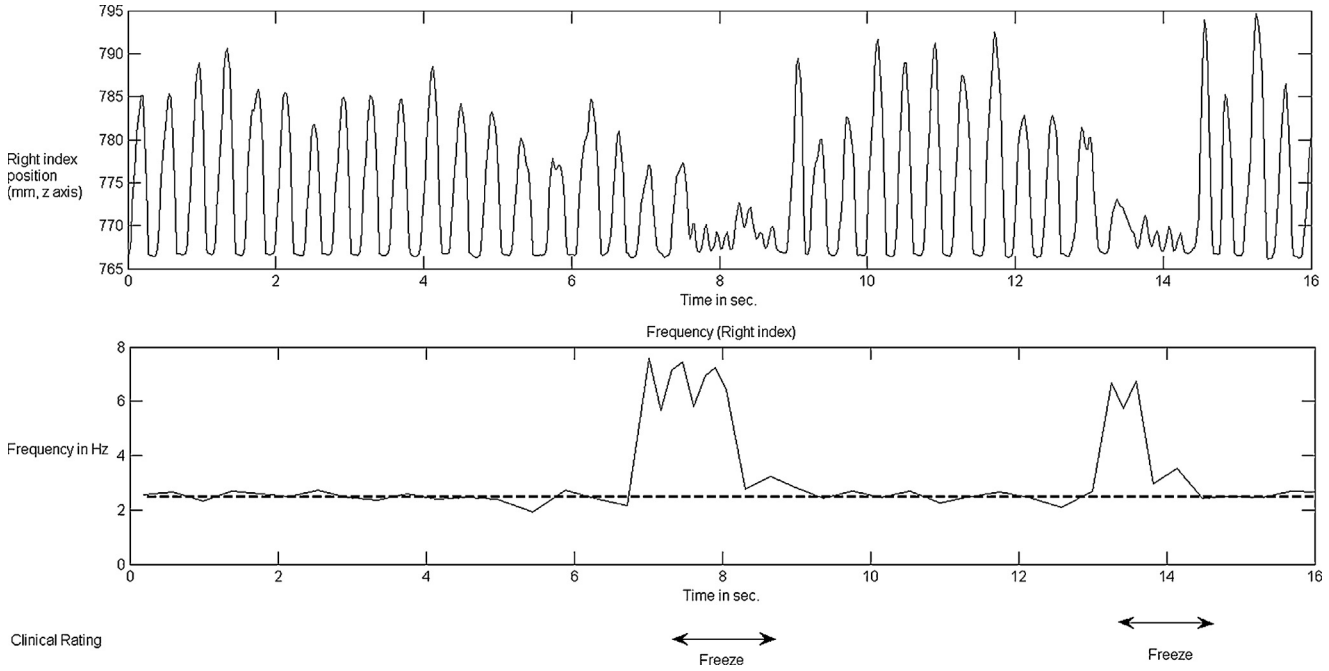

Figure 2 A patient with PD performing alternate index fingers tapping on a table in time with a metronome (5 Hz). The frequency of the right index finger at baseline was 2.5 Hz but increased in the ''freeze'' band in the event of an episode of freezing. Other algorithms described in the literature are based on detection of increased latency between movements [15] or a reduction in signal amplitude (via visual inspection or computer algorithms, see [73]). The amplitude threshold varies from one study to another: two standard deviations in [42] and 50% of the amplitude outside the FoG episode in [5].

Models of triggers for FoG-like episodes

Nantel et al. [44] evaluated the ability of a repetitive ''stepping in place'' task on a force platform to identify FoG. The researchers detected FoG during the task using the FOG-Q and an automatic, computerized algorithm based on the detection of peaks and troughs in the force signal (values below 15% and above 85%). A freezing episode was defined as an abnormally long time interval between peaks. The algorithm's identification of ''freezers'' correlated with the FOG-Q. The specificity and sensitivity of detection were respectively 93% and 87%. The number and duration of FoG episodes detected by the algorithm correlated with visual inspection. Hence, this method could be used for gait analyses under ecological conditions.

Naismith and Lewis [42] developed a virtual-reality paradigm based on the hypothesis that FoG could be elicited by cognitive overload during concomitant cognitive and motor tasks. Patients had to navigate through a virtual corridor (by making alternating movements in the supine position) while performing a modified Stroop color word task that would dictate their stopping pattern. For example, patients were told that if the word was displayed in its congruent color (e.g. ''BLUE'' written in blue) they should continue walking. However, if the word appeared in an incongruent color (e.g. ''BLUE'' written in green), they should treat it as a STOP cue and wait until the ''WALK'' prompt appeared before resuming their movements. The task's ability to trigger equivalents of freezing was defined by a tapping reaction time that fell outside 2 standard deviations of the mean measurement. This objective detection was significantly correlated with self-reported FoG-Q scores. In an fMRI study, this task was adapted for the lower limbs (stepping in place while in the supine position) in order to study the neural substrates of FoG [60,61,63]. Other algorithms have been used to identify equivalents of FoG — the detection of an increased gap between consecutive ''footsteps'', for example [63].

Lastly, other virtual-reality tasks have been used to manipulate environmental and cognitive factors influencing FoG (the fear of falling, for example) [62].

Conclusion

Clinical expert opinion remains the gold standard for characterizing FoG. Quantification now tends to be based on percent time frozen rather than the number of episodes, although a combination of the two metrics can be used. Automatic detection (based on time-frequency methods) is highly sensitive and specific, although determination of a pathological threshold is sometimes difficult. Models of FoG (such as stepping in place) could facilitate threshold determination, and might easily and rapidly provide a freezing index for a given patient.

Furthermore, these methods can be applied in an ambulatory environment (to test a supposed therapeutic effect under ecological conditions, for instance). Various sensors (accelerometers, goniometers, force-measuring insoles, etc.) have been used to determine kinematic variations. These wearable sensors can be useful to detect FoG phenomenona but also abnormalities of continuous gait excluding FoG. Other approaches are based on variability

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in time and/or amplitude signals. FoG has similarities with perturbations of rhythmic movements of the upper limbs, lower limbs and orofacial area. However, these equivalents of FoG are mainly used to study the pathophysiological basis of the phenomenon, rather than to clinically characterize FoG.

Disclosure of interest

The authors declare that they have no competing interest.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.neucli.2015.09.009.

References

[1] Ackermann H, Gröne BF, Hoch G, Schönle PW. Speech freezing in Parkinson's disease: a kinematic analysis of orofacial movements by means of electromagnetic articulography. Folia Phoniatr (Basel) 1993;45:84—9.

[2] Almeida QJ, Wishart LR, Lee TD. Bimanual coordination deficits with Parkinson's disease: the influence of movement speed and external cueing. Mov Disord 2002;17:30—7.

[3] Amboni M, Stocchi F, Abbruzzese G, Morgante L, Onofrj M, Ruggieri S, et al. Prevalence and associated features of self-reported freezing of gait in Parkinson disease: The DEEP FOG study. Parkinsonism Relat Disord 2015, http://dx.doi.org/10.1016/j.parkreldis.2015.03.028.

[4] Auyeung M, Tsoi TH, Mok V, Cheung CM, Lee CN, Li R, et al. Ten year survival and outcomes in a prospective cohort of new onset Chinese Parkinson's disease patients. J Neurol Neurosurg Psychiatry 2012;83:607—11, http://dx.doi.org/10.1136/jnnp-2011-301590.

[5] Barbe MT, Amarell M, Snijders AH, Florin E, Quatuor E-L, Schönau E, et al. Gait and upper limb variability in Parkinson's disease patients with and without freezing of gait. J Neurol 2014;261:330—42, http://dx.doi.org/10.1007/s00415-013-7199-1.

[6] Bloem BR, Hausdorff JM, Visser JE, Giladi N. Falls and freezing of gait in Parkinson's disease: a review of two interconnected, episodic phenomena. Mov Disord 2004;19:871—84, http://dx.doi.org/10.1002/mds.20115.

[7] Chee R, Murphy A, Danoudis M, Georgiou-Karistianis N, Iansek R. Gait freezing in Parkinson's disease and the stride length sequence effect interaction. Brain 2009;132:2151—60, http://dx.doi.org/10.1093/brain/awp053.

[8] Crémers J, Dessoullières A, Garraux G. Hemispheric specialization during mental imagery of brisk walking. Hum Brain Mapp 2012;33:873—82, http://dx.doi.org/10.1002/hbm.2125.5.

[9] Delorme A, Makeig S. EEGLAB: an open source toolbox for analysis of single-trial EEG dynamics including independent component analysis. J Neurosci Methods 2004;134:9—21, http://dx.doi.org/10.1016/j.jneumeth.2003.10.009.

[10] Delval A, Snijders AH, Weerdesteyn V, Duysens JE, Defebvre L, Giladi N, et al. Objective detection of subtle freezing of gait episodes in Parkinson's disease. Mov Disord 2010;25:1684—93, http://dx.doi.org/10.1002/mds.23159.

[11] Delval A, Tard C, Defebvre L. Why we should study gait initiation in Parkinson's disease. Neurophysiol Clin Clin Neurophysiol 2014;44:69—76, http://dx.doi.org/10.1016/j.neucli.2013.10.127.

[12] Delval A, Moreau C, Bleuse S, Tard C, Ryckewaert G, Devos D, et al. Auditory cueing of gait initiation in Parkinson's disease patients with freezing of gait. Clin Neurophysiol 2014;125:1675—81, http://dx.doi.org/10.1016/j.clinph.2013.12.101.

[13] Delval A, Moreau C, Bleuse S, Guehl D, Bestaven E, Guillaud E, et al. Gait and attentional performance in freezers under methylphenidate. Gait Posture 2015;41:384—8, http://dx.doi.org/10.1016/j.gaitpost.2014.10.022.

[14] Duncan RP, Leddy AL, Cavanaugh JT, Dibble LE, Ellis TD, Ford MP, et al. Accuracy of fall prediction in Parkinson disease: six-month and 12-month prospective analyses. Park Dis 2012;2012:237673, http://dx.doi.org/10.1155/2012/237673.

[15] Duncan RP, Cavanaugh JT, Earhart GM, Ellis TD, Ford MP, Foreman KB, et al. External validation of a simple clinical tool used to predict falls in people with Parkinson disease. Parkinsonism Relat Disord 2015, http://dx.doi.org/10.1016/j.parkreldis.2015.05.008.

[16] Espay AJ, Fasano A, van Nuenen BFL, Payne MM, Snijders AH, Bloem BR. On'' state freezing of gait in Parkinson disease. Neurology 2012;78:454—7, http://dx.doi.org/10.1212/WNL.0b013e3182477ec0.

[17] Fahn S. The freezing phenomenon in parkinsonism. Adv Neurol 1995;67:53—63.

[18] Fahn S, Elton RL, members of the UPDRS, development committee. Recent development in Parkinson's disease. In: Fahn S, Marsden CD, Calne DB, Goldstein M, editors. Unified Parkinson's disease rating scale, Vol2. NJ: Florham Park; 1987.

[19] Ferraye MU, Debû B, Fraix V, Xie-Brustolin J, Chabardès S, Krack P, et al. Effects of subthalamic nucleus stimulation and levodopa on freezing of gait in Parkinson disease. Neurology 2008;70:1431—7, http://dx.doi.org/10.1212/01.wnl.0000310416.90757.85.

[20] Giladi, Shabtai, Simon, Biran, Tal, Korczyn. Construction of freezing of gait questionnaire for patients with Parkinsonism. Parkinsonism Relat Disord 2000;6:165—70.

[21] Giladi N, Shabtai H, Rozenberg E, Shabtai E. Gait festination in Parkinson's disease. Parkinsonism Relat Disord 2001;7:135—8.

[22] Giladi N, McDermott MP, Fahn S, Przedborski S, Jankovic J, Stern M, et al. Freezing of gait in PD: prospective assessment in the DATATOP cohort. Neurology 2001;56:1712—21.

[23] Giladi N, Tal J, Azulay T, Rascol O, Brooks DJ, Melamed E, et al. Validation of the freezing of gait questionnaire in patients with Parkinson's disease. Mov Disord 2009;24:655—61, http://dx.doi.org/10.1002/mds.2174.5.

[24] Goetz CG, Tilley BC, Shaftman SR, Stebbins GT, Fahn S, Martinez-Martin P, et al. Movement Disorder Society-sponsored revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS): scale presentation and clinimetric testing results. Mov Disord 2008;23:2129—70, http://dx.doi.org/10.1002/mds.22340.

[25] Hanakawa T, Fukuyama H, Katsumi Y, Honda M, Shibasaki H. Enhanced lateral premotor activity during paradoxical gait in Parkinson's disease. Ann Neurol 1999;45:329—36.

[26] Hausdorff JM, Cudkowicz ME, Firtion R, Wei JY, Goldberger AL. Gait variability and basal ganglia disorders: stride-to-stride variations of gait cycle timing in Parkinson's disease and Huntington's disease. Mov Disord 1998;13:428—37, http://dx.doi.org/10.1002/mds.870130310.

[27] Hausdorff JM, Schaafsma JD, Balash Y, Bartels AL, Gurevich T, Giladi N. Impaired regulation of stride variability in Parkinson's disease subjects with freezing of gait. Exp Brain Res 2003;149:187—94, http://dx.doi.org/10.1007/s00221-002-1354-8.

[28] Hausdorff JM, Balash Y, Giladi N. Time series analysis of leg movements during freezing of gait in Parkinson's disease: akinesia, rhyme or reason? Phys Stat Mech

Its Appl 2003;321:565—70, http://dx.doi.org/10.1016/S0378-4371(02)01744-2.

[29] Hely MA, Reid WGJ, Adena MA, Halliday GM, Morris JGL. The Sydney multicenter study of Parkinson's disease: the inevitability of dementia at 20 years. Mov Disord 2008;23:837—44, http://dx.doi.org/10.1002/mds.21956.

[30] Heremans E, Nieuwboer A, Vercruysse S. Freezing of gait in Parkinson's disease: where are we now? Curr Neurol Neurosci Rep 2013;13:350, http://dx.doi.org/10.1007/s11910-013-0350-7.

[31] Herman T, Giladi N, Hausdorff JM. Neuroimaging as a window into gait disturbances and freezing of gait in patients with Parkinson's disease. Curr Neurol Neurosci Rep 2013;13:411, http://dx.doi.org/10.1007/s11910-013-0411-y.

[32] Jacobs JV, Nutt JG, Carlson-Kuhta P, Stephens M, Horak FB. Knee trembling during freezing of gait represents multiple anticipatory postural adjustments. Exp Neurol 2009;215:334—41, http://dx.doi.org/10.1016/j.expneurol.2008.10.019.

[33] Maillet A, Pollak P, Debû B. Imaging gait disorders in parkinsonism: a review. J Neurol Neurosurg Psychiatry 2012;83:986—93, http://dx.doi.org/10.1136/jnnp-2012-302461.

[34] Maillet A, Thobois S, Fraix V, Redouté J, Le Bars D, Lavenne F, et al. Neural substrates of levodopa-responsive gait disorders and freezing in advanced Parkinson's disease: a kinesthetic imagery approach. Hum Brain Mapp 2015;36:959—80, http://dx.doi.org/10.1002/hbm.22679.

[35] Moore ST, MacDougall HG, Ondo WG. Ambulatory monitoring of freezing of gait in Parkinson's disease. J Neurosci Methods 2008;167:340—8, http://dx.doi.org/10.1016/j.jneumeth.2007.08.023.

[36] Moreau C, Ozsancak C, Blatt J-L, Derambure P, Destee A, Defebvre L. Oral festination in Parkinson's disease: biomechanical analysis and correlation with festination and freezing of gait. Mov Disord 2007;22:1503—6, http://dx.doi.org/10.1002/mds.21549.

[37] Moreau C, Defebvre L, Bleuse S, Blatt JL, Duhamel A, Bloem BR, et al. Externally provoked freezing of gait in open runways in advanced Parkinson's disease results from motor and mental collapse. J Neural Transm 2008;115:1431—6, http://dx.doi.org/10.1007/s00702-008-0099-3.

[38] Moreau C, Delval A, Defebvre L, Dujardin K, Duhamel A, Petyt G, et al. Methylphenidate for gait hypokinesia and freezing in patients with Parkinson's disease undergoing subthalamic stimulation: a multicentre, parallel, randomised, placebo-controlled trial. Lancet Neurol 2012;11:589—96, http://dx.doi.org/10.1016/S1474-4422(12)70106-0.

[39] Moreau C, Delval A, Tiffreau V, Defebvre L, Dujardin K, Duhamel A, et al. Memantine for axial signs in Parkinson's disease: a randomised, double-blind, placebo-controlled pilot study. J Neurol Neurosurg Psychiatry 2013;84(5):552—5, http://dx.doi.org/10.1136/jnnp-2012-203182.

[40] Morris ME, Iansek R, Matyas TA, Summers JJ. The pathogenesis of gait hypokinesia in Parkinson's disease. Brain J Neurol 1994;117(Pt 5):1169—81.

[41] Morris TR, Cho C, Dilda V, Shine JM, Naismith SL, Lewis SJG, et al. A comparison of clinical and objective measures of freezing of gait in Parkinson's disease. Parkinsonism Relat Disord 2012;18(5):572—7, http://dx.doi.org/10.1016/j.parkreldis.2012.03.001.

[42] Naismith SL, Lewis SJG. A novel paradigm for modelling freezing of gait in Parkinson's disease. J Clin Neurosci 2010;17:984—7, http://dx.doi.org/10.1016/j.jocn.2009.12.006.

[43] Nanhoe-Mahabier W, Snijders AH, Delval A, Weerdesteyn V, Duysens J, Overeem S, et al. Walking patterns in Parkinson's disease with and without freezing of gait. Neuroscience 2011;182:217—24, http://dx.doi.org/10.1016/j.neuroscience.2011.02.061.

[44] Nantel J, de Solages C, Bronte-Stewart H. Repetitive stepping in place identifies and measures freezing episodes in subjects with Parkinson's disease. Gait Posture 2011;34:329—33, http://dx.doi.org/10.1016/j.gaitpost.2011.05.020.

[45] Nieuwboer A, Dom R, De Weerdt W, Desloovere K, Fieuws S, Broens-Kaucsik E. Abnormalities of the spatiotemporal characteristics of gait at the onset of freezing in Parkinson's disease. Mov Disord 2001;16:1066—75.

[46] Nieuwboer A, Dom R, De Weerdt W, Desloovere K, Janssens L, Stijn V. Electromyographic profiles of gait prior to onset of freezing episodes in patients with Parkinson's disease. Brain J Neurol 2004;127:1650—60, http://dx.doi.org/10.1093/brain/awh189.

[47] Nieuwboer A, Rochester L, Herman T, Vandenberghe W, Emil GE, Thomaes T, et al. Reliability of the new freezing of gait questionnaire: agreement between patients with Parkinson's disease and their carers. Gait Posture 2009;30:459—63, http://dx.doi.org/10.1016/j.gaitpost.2009.07.108.

[48] Nieuwboer A, Vercruysse S, Feys P, Levin O, Spildooren J, Swinnen S. Upper limb movement interruptions are correlated to freezing of gait in Parkinson's disease. Eur J Neurosci 2009;29:1422—30, http://dx.doi.org/10.1111/j.1460-9568.2009.0668.1.x.

[49] Nutt JG, Bloem BR, Giladi N, Hallett M, Horak FB, Nieuwboer A. Freezing of gait: moving forward on a mysterious clinical phenomenon. Lancet Neurol 2011;10:734—44, http://dx.doi.org/10.1016/S1474-4422(11)70143-0.

[50] Okada Y, Fukumoto T, Takatori K, Nagino K, Hiraoka K. Abnormalities of the first three steps of gait initiation in patients with Parkinson's disease with freezing of gait. Park Dis 2011;2011:202937, http://dx.doi.org/10.4061/2011/202937.

[51] Okada Y, Fukumoto T, Takatori K, Nagino K, Hiraoka K. Variable initial swing side and prolonged double limb support represent abnormalities of the first three steps of gait initiation in patients with Parkinson's disease with freezing of gait. Front Neurol 2011;2:85, http://dx.doi.org/10.3389/fneur.2011.00085.

[52] Okuma Y. Freezing of gait and falls in Parkinson's disease. J Park Dis 2014;4:255—60, http://dx.doi.org/10.3233/JPD-130282.

[53] Park HK, Yoo JY, Kwon M, Lee J-H, Lee SJ, Kim SR, et al. Gait freezing and speech disturbance in Parkinson's disease. Neurol Sci 2014;35:357—63, http://dx.doi.org/10.1007/s10072-013-1519-1.

[54] Perez-Lloret S, Negre-Pages L, Damier P, Delval A, Derkinderen P, Destée A, et al. Prevalence, determinants, and effect on quality of life of freezing of gait in Parkinson disease. JAMA Neurol 2014;71:884—90, http://dx.doi.org/10.1001/jamaneurol.2014.753.

[55] Peterson DS, Pickett KA, Duncan R, Perlmutter J, Earhart GM. Gait-related brain activity in people with Parkinson disease with freezing of gait. PloS One 2014;9:e90634, http://dx.doi.org/10.1371/journal.pone.0090634.

[56] Peterson DS, Pickett KA, Duncan RP, Perlmutter JS, Earhart GM. Brain activity during complex imagined gait tasks in Parkinson disease. Clin Neurophysiol 2014;125:995—1005, http://dx.doi.org/10.1016/j.clinph.2013.10.008.

[57] Plotnik M, Giladi N, Balash Y, Peretz C, Hausdorff JM. Is freezing of gait in Parkinson's disease related to asymmetric motor function? Ann Neurol 2005;57:656—63, http://dx.doi.org/10.1002/ana.20452.

[58] Popovic MB, Djuric-Jovicic M, Radovanovic S, Petrovic I, Kostic V. A simple method to assess freezing of gait in Parkinson's disease patients. Braz J Med Biol Res 2010;43:883—9.

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[59] Schaafsma JD, Balash Y, Gurevich T, Bartels AL, Hausdorff JM, Giladi N. Characterization of freezing of gait subtypes and the response of each to levodopa in Parkinson's disease. Eur J Neurol 2003;10:391—8.
[60] Shine JM, Ward PB, Naismith SL, Pearson M, Lewis SJG. Utilising functional MRI (fMRI) to explore the freezing phenomenon in Parkinson's disease. J Clin Neurosci 2011;18:807—10, http://dx.doi.org/10.1016/j.jocn.2011.02.003.
[61] Shine JM, Naismith SL, Palavra NC, Lewis SJG, Moore ST, Dilda V, et al. Attentional set-shifting deficits correlate with the severity of freezing of gait in Parkinson's disease. Parkinsonism Relat Disord 2013;19(3):388—90, http://dx.doi.org/10.1016/j.parkreldis.2012.7.015.
[62] Shine JM, Matar E, Ward PB, Bolitho SJ, Pearson M, Naismith SL, et al. Differential neural activation patterns in patients with Parkinson's disease and freezing of gait in response to concurrent cognitive and motor load. PloS One 2013;8:e52602, http://dx.doi.org/10.1371/journal.pone.0052602.
[63] Shine JM, Matar E, Ward PB, Frank MJ, Moustafa AA, Pearson M, et al. Freezing of gait in Parkinson's disease is associated with functional decoupling between the cognitive control network and the basal ganglia. Brain J Neurol 2013;136:3671—81, http://dx.doi.org/10.1093/brain/awt272.
[64] Snijders AH, Nijkrake MJ, Bakker M, Munneke M, Wind C, Bloem BR. Clinimetrics of freezing of gait. Mov Disord 2008;23(Suppl 2):S468—74, http://dx.doi.org/10.1002/mds.2214.4.
[65] Snijders AH, Leunissen I, Bakker M, Overeem S, Helmich RC, Bloem BR, et al. Gait-related cerebral alterations in patients with Parkinson's disease with freezing of gait. Brain J Neurol 2011;134:59—72, http://dx.doi.org/10.1093/brain/awq324.
[66] Snijders AH, Haaxma CA, Hagen YJ, Munneke M, Bloem BR. Freezer or non-freezer: clinical assessment of freezing of gait. Parkinsonism Relat Disord 2012;18:149—54, http://dx.doi.org/10.1016/j.parkreldis.2011.09.006.
[67] Tard C, Delval A, Devos D, Lopes R, Lenfant P, Dujardin K, et al. Brain metabolic abnormalities during gait with freezing in Parkinson's disease. Neuroscience 2015, http://dx.doi.org/10.1016/j.neuroscience.2015.08.063.
[68] Ueno E, Yanagisawa N, Takami M. Gait disorders in parkinsonism. A study with floor reaction forces and EMG. Adv Neurol 1993;60:414—8.
[69] Vercruysse S, Spildooren J, Heremans E, Vandenbossche J, Wenderoth N, Swinnen SP, et al. Abnormalities and cue dependence of rhythmical upper-limb movements in Parkinson patients with freezing of gait. Neurorehabil Neural Repair 2012;26:636—45, http://dx.doi.org/10.1177/1545968311431964.
[70] Vercruysse S, Spildooren J, Heremans E, Vandenbossche J, Levin O, Wenderoth N, et al. Freezing in Parkinson's disease: a spatiotemporal motor disorder beyond gait. Mov Disord 2012;27:254—63, http://dx.doi.org/10.1002/mds.24015.
[71] Vercruysse S, Gilat M, Shine JM, Heremans E, Lewis S, Nieuwboer A. Freezing beyond gait in Parkinson's disease: a review of current neurobehavioral evidence. Neurosci Biobehav Rev 2014;43:213—27, http://dx.doi.org/10.1016/j.neubiorev.2014.04.010.
[72] Weiss A, Herman T, Giladi N, Hausdorff JM. New evidence for gait abnormalities among Parkinson's disease patients who suffer from freezing of gait: insights using a body-fixed sensor worn for 3 days. J Neural Transm 2015;122:403—10, http://dx.doi.org/10.1007/s00702-014-1279-y.
[73] Ziv I, Avraham M, Dabby R, Zoldan J, Djaldetti R, Melamed E. Early-occurrence of manual motor blocks in Parkinson's disease: a quantitative assessment. Acta Neurol Scand 1999;99:106—11.

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