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Freezing of Upper Limbs in Parkinson's Disease: A Systematic Review

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ABSTRACT

Aim: To identify how FOUL is investigated in patients with PD.
Methods: The Preferred Reporting Items for Systematic Reviews guideline was used, and the search was carried out in four databases, with no limit on publication date.
Results: 21 original articles were included. They used a variety of terms for upper-limb freezing. Some tasks evaluated only the movement of the limbs; others used associated objects. The tasks most often used to assess FOUL were flexion and extension of the index finger, finger tapping (index finger on thumb), and Funnel Task. In these tasks, movements of small amplitude/high frequency and the presence of a dual-task elicited more FOUL episodes.
Conclusions: This review highlights the need for development and validation of FOUL detection and assessment in clinical practice. The use of an appropriate assessment will prevent false-negative results and allow the phenomenon to be identified and treated.

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Freezing of upper limb; Parkinson's disease; motor blocks

Introduction

According to the Global Burden of Disease study,[1] among 14 categories of neurological disorders, Parkinson's disease (PD) was the fastest-growing in prevalence, disability, and age-standardized death rates between 1990 and 2015. PD is characterized by progressive deterioration of the substantia nigra, the structure that produces the neurotransmitter dopamine. This loss of dopamine, mainly in the frontostriatal circuit, causes motor symptoms (rest tremor, rigidity, bradykinesia, and postural instability) and non-motor symptoms (cognitive, sensory, psychological, and autonomic dysfunction).[2] In addition to these classic motor signs, one characteristic

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that may be present in PD patients is "freezing" (motor block).[2] Freezing of gait (FOG) has been widely discussed in the literature and is described as an absence of or brief/episodic reduction in an individual's ability to perform the first step or continue the gait, despite the intention to walk.[3] This freezing also occurs in other body segments, such as the upper limbs.[4]

The pathophysiology of FOG does not appear to be limited to motor dysfunction, and its manifestation could be the result of a series of deficiencies in several neural circuits.[5,6] From the pathophysiological point of view, freezing of upper limbs (FOUL) is much less understood than FOG. There are similarities in the affected regions in FOG and FOUL, such as the *globus pallidus*, putamen, and prefrontal areas.[7] Some evidence suggests that the brainstem is affected in FOG cases but this is not yet confirmed for FOUL.[3,4] Studies have indicated that the risk of developing FOG is significantly higher in patients with a more advanced stage of the disease, with predominant deficits in gait, balance, speech, cognition, mood, and sleep.[8–10] No longitudinal studies assessing FOUL predictors have been published. Conditions that trigger FOG, such as dual-task and the use of obstacles, can also trigger FOUL in individuals with PD.[11,12] However, in general, the factors that induce FOUL and its features are still poorly understood and the criteria for clinical assessments are not standardized.[13,14] Analysis of the methods used to evaluate FOUL will help to assure the use of effective methods to detect and treat the phenomenon. The objective of this study was to summarize how FOUL is investigated in patients with PD.

Materials and methods

This study is registered in the International prospective register of systematic reviews (PROSPERO) under the protocol PROSPERO 2020 CRD42020165775. The systematic review, based on the PRISMA model, was carried out in the Scielo, Scopus, Lilacs, and PubMed databases in March 2020.

The systematic review aimed to determine the means by which FOUL is investigated in PD. The PICO method[15] was adopted: P (patients): people with PD; I (intervention): FOUL evaluation; C (comparison): PD with FOUL and PD without FOUL groups; O (outcome): upper-limb function. Two search keys were used, with the following keywords and Boolean operators in English: [("upper extremity" OR "upper limbs" OR "effectors") AND "freezing"] and [(hand or manual) AND "motor blocks" AND "Parkinson's disease"] and their Spanish and Portuguese equivalents. Original articles published in English, Spanish, and Portuguese about upper-limb freezing in Parkinson's disease were

included; while review articles, case studies, and animal studies were excluded. There was no limit on the publication date for article inclusion.

Database searches were performed independently by two reviewers (NIMM and MMA), and at the end of each phase, differences between them were resolved. When necessary, a third researcher (CLC) was called to resolve outstanding issues before proceeding to the next phase (article selection). Five selection phases were carried out: First selection: use of descriptor groups to find articles in databases; Second selection: exclusion of repeated references; Third selection: reading the titles and selecting articles for subsequent analysis of abstracts. Fourth selection: reading the abstracts of all articles obtained in the previous phase, selecting the relevant articles to read in full; Fifth selection: reading the full texts of the articles obtained in the previous selection and selecting the articles for the review.

To evaluate the quality of the studies included, the NewCastle-Ottawa scale (NCO) was used for longitudinal observational studies (cohort), with a maximum of 9 points. The article was considered of high quality when it scored ≥7 points, and of moderate quality when it scored 5 or 6 points.[16,17] The NCO scale adapted for cross-sectional observational studies, with a maximum of 10 points, classifies an article as low quality when it scores between 0 and 4 points, moderate quality with 5 or 6 points, and high quality with 7 or more points.[18,19] The PEDro scale, with a maximum of 11 points, was used to evaluate the quality of clinical trials, and a study was considered high quality if it scored at least 6 points.[20,21]

Results

The process for selecting articles from the Scielo, Scopus, Lilacs, and PubMed databases is summarized in Figure 1. No results were found with the search keys in Spanish and Portuguese. The final sample consisted of 21 articles, all in the English language, selected according to the established criteria.

The study designs were: cross-sectional observational (17), prospective longitudinal observational (1), and clinical trials (3). The study locations were Belgium (7), Canada (5), Germany (3), France (2), United States of America (1), Israel (1), Netherlands (1), and Serbia (1).

Table 1 shows the article scores on the quality scales, the descriptions of the terms used for the phenomenon, and the definitions of criteria for FOUL in the studies. 14 observational studies were assigned a score of moderate quality and 4 were scored as high quality. The lack of representative samples and information on sample-size calculation were common issues affecting the classification of the studies. The 3 clinical trials were rated highly. The terms used for freezing of the upper limbs varied; the

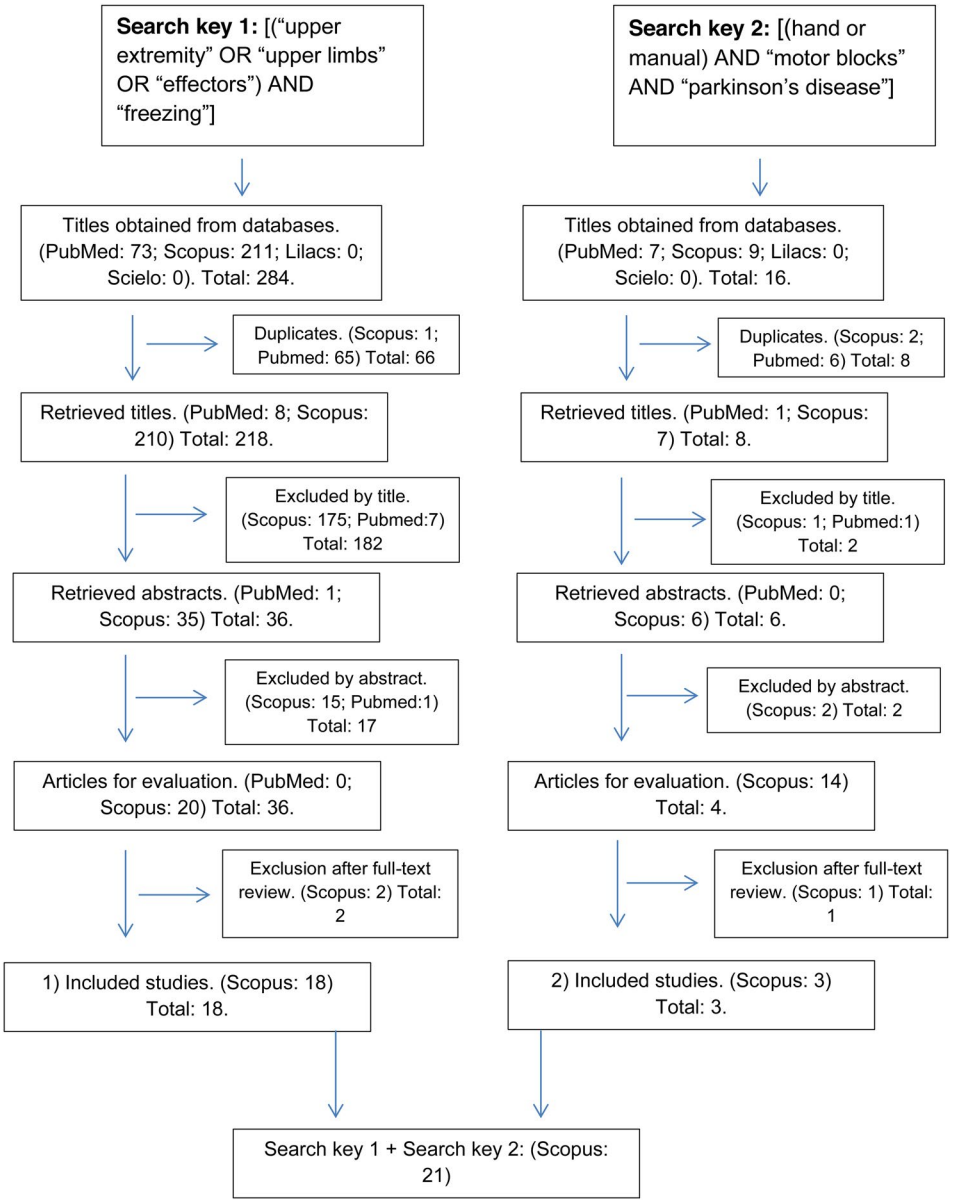

Figure 1. Articles selection flowchart.

most frequent acronym was FOUL. The term "manual motor blocks" was used in mainly older studies and in only one more recent study.[22–24] Of the 21 articles, 14 different criteria were identified to characterize the FOUL phenomenon. Despite these differences, certain concepts were used in most of the studies: "inability to perform movements", "sudden stop", "absence of movements", and "reduction in movement amplitude and frequency".

Table 1. Classification of articles by methodological quality, description of terms used for the phenomenon, and definitions of criteria for FOUL.

Authors (Year)/ Country	Methodological quality (Score achieved/ maximum score)	Term for FOUL	Definition of FOUL criteria
Ziv et al.[22] / Israel	NCO adapted – 6/10	*"Manual motor blocks (MMBs)"*	Situation in which the interval between two sequential touches on a key exceeds the normal average interval (previously defined) between touches + 2 standard deviations.
Almeida et al.[26] / Canada	NCO adapted – 6/10	*"Freezing"*	Interruption of repetitive voluntary movements commonly characterized by sudden and short-duration episodes of movement arrest. Period of 1 s in a test, in which no change in range of motion was observed.
Almeida et al.[27] / Canada	NCO adapted – 5/10	*"Freezing"*	Temporary inability to perform voluntary movements. Period of at least 1 s in which one or both members do not show movement, or the presence of a delayed response (longer than 2 s) to an auditory stimulus.
Popovic et al.[23] / Serbia	NCO adapted – 5/10	*"Motor block – (MB)"*	Sudden unintentional stop of hand movement.
Nieuwboer et al.[42]/ Belgium	NCO adapted – 6/10	*"Freezing of upper limb (FO-UL)"*	Period of more than 1 s, in which one or both limbs did not show movement, preceded by amplitude reduction and /or increased or irregular cycling frequency.
Vercruysse et al.[14]/ Belgium	NCO adapted – 6/10	*"Upper-limb freezing episodes* – (FO-UL)"	Period of involuntary movement absence or markedly reduced cyclic movements, visually determined as: start of abnormally small movement cycles (<50% of the initial amplitude) accompanied by irregular cycle frequency.
Vercruysse et al.[12]/ Belgium	NCO adapted – 6/10	*"Freezing during upper limb motion* – (FO-UL)"	
Janssen et al.[43]/ Netherlands	Pedro – 8/11	*"Freezing of upper limbs* – (FOUL)"	
Williams et al.[44]/ United States of America	NCO adapted – 7/10	*"Freezing of the upper extremity* – (FO-UE)"	Sudden stop or decrease in motion range, which deviated from the calculated average antiphase cycle range in one of two ways: (1) motion stopped by ≥75% of the mean range of the antiphase duration or (2) the range of motion ≤50% of the average amplitude of the antiphase cycle, accompanied by an irregular cycle frequency and which continued for at least twice the average duration of the antiphase cycle.
Barbe et al.[40] / Germany	NCO adapted – 6/10	*"Freezing of the upper limb"* – (FOUL)"	Reduced amplitude of at least 50% in relation to the average amplitude of the test, with 0.5 s minimum duration.
Delval et al.[28] / France	NCO – 6/9	*"Freezing episodes of the hands"*	
Delval et al.[13]/ France	NCO adapted – 6/10	*"Freezing episodes of the hands"*	

Vercruysse et al.[4] / Belgium	NCO adapted – 6/10	*"Upper limb freezing – (FOUL)"*	A period of involuntary movement arrest or a clear absence of effective cyclical movements. Visually, movements were characterized with at least two of the following three conditions: (1) abnormally reduced amplitude <50% of the reference cycle; (2) irregular frequency; and (3) freezing index >1.
Brown et al.[29] / Canada	NCO adapted – 6/10	*"Upper limb motor blocks – (ULMB)"*	75% amplitude reduction for at least 1 s.
Heremans et al.[25] / Belgium	NCO adapted – 6/10	*"Freezing of the upper limbs – (FOUL)"*	Involuntary interruption or clear absence of effective writing movements for at least 1 s. They were visually determined as ineffective movement cycles preceded or characterized by a decreased writing range (<50% of the target range), frequency of irregular cycles, and/or an increase in the freezing index.
Heremans et al.[41] / Belgium	NCO adapted – 5/10	*"Freezing of the upper limbs – (FOUL)"*	
Broeder et al.[38] / Belgium	PEDro – 8/11	*"Freezing of the upper limbs – (FOUL)"*	
Scholten et al.[45] / Germany	NCO adapted – 7/10	*"Upper limb freezing"*	According to the three criteria: deflection of amplitude touch decreased below 1 N (below 50% of the requested 2 N force modulation), (ii) the duration exceeded 1 s, and (iii) the frequency increased above 3 Hz based on the biomechanical record.
Scholten et al.[46]/ Germany	NCO adapted – 7/10	*"Upper-limb freezing – (ULF)"*	
Jehu et al.[30] / Canada	NCO adapted – 7/10	*"Freezing of the upper limbs"*	Temporary inability to generate effective movements.
Khoshnam et al.[24]/ Canada	PEDro – 6/11	*"Manual motor blocks (MMBs)"*	Interruption in rhythm greater than the average interval sum between finger touch and greater than twice the standard deviation between the finger touch.

FOUL: freezing of upper limb; NCO adapted: NewCastle Ottawa scale, version adapted by Herzog et al. 2013[18] and Wang et al. 2017[19]; PEDro: Physiotherapy Evidence Database; N: newton; Hz: hertz.

The sample size ranged from 15 to 60 individuals (Table 2). No study evaluated patients with disease stage 4 or 5 according to the Hoehn & Yahr disease scale. Regarding medication use, some studies evaluated patients only during the ON state (after dopamine medication replacement),[13,24–26,33–35] others in the OFF state (after withdrawal from dopamine replacement),[4,12,14,27–29,31,36,37] and a few in both the ON and OFF states.[30,32,38] Only one study investigated the ON state in newly diagnosed patients[22] who had never undergone treatment. One study[23] did not indicate the status of the medication. Most articles divided the sample into PD patients with and without FOG. Different activities/tasks were used to evaluate FOUL (Table 2). In tasks that required only movements of the body segments, the segment and the movement of the upper limb to be analyzed differed. The following were evaluated: flexion and extension of the index finger;[12,14,28] tapping the index finger on the thumb, simulating a pinching movement;[13,30] flexion, wrist extension[32] without physical limits in the environment, and flexion, wrist extension[31] physically limited by a table,

tapping the table; and pronation and supination[30] movements of the forearm. The Funnel task, also used, consists of a trajectory of 13 cm in which two blue lines, each 2 mm wide, delimit the areas where individuals must alternate movements of writing in wider and narrower spaces, with a pen. The writing areas are 2 cm wide, alternating with 0.6 cm sections, gradually increasing from 0.6 to 2 cm wide and gradually decreasing from 2 to 0.6 cm wide.[33]

In general, the FOUL triggers were the quick[4,12,29,41–44] and small-amplitude[4,12,25,38,41–44] movements described in Table 2. In the studies that used the Funnel Task, the smallest amplitude used was 2 cm and the larger amplitude was 4 cm.[27,33–35] In other studies a comfortable self-selected range was chosen for each patient, and based on that, the smallest amplitude needed to be 66% of the comfortable range.[4,12,14] The same idea was used in "speed," where a comfortable self-selected speed was determined for each patient and then the patient was instructed to increase that speed by 33%,[4,12,14,28] 50%,[29] or up to his/her maximum.[27] Other researchers gradually increased the frequency cycle from 0.75 to 2 Hz at set intervals, using a metronome.[32] Also used as triggers were coordination antiphase[12,25,26,31,32] (coordination of alternating movements; for example, simultaneous flexion of the right wrist and extension of the left one) and dual-task.

Regarding the upper limb, although the frequency/number of cases and mean duration of the episodes (0.8–5.98 s) varied widely among the studies, the groups with FOG showed more episodes of FOUL, which was more often present on the most-affected side of the disease (Table 2). Only one study did not find episodes of FOUL in its patients with and without FOG.[38] The values used to express the number of episodes of FOUL were: number of episodes (separated by each condition investigated;[24,29,30,34–36] per patient[22,34,37]) number of patients who presented FOUL (total;[28,34,37] separated by each condition investigated;[13,45] separated only by PD + FOG and PD – FOG;[4,12,14,25,42] or separated by PD + FOG and PD – FOG and in conditions OFF and ON[30]); percentage of trials in which FOUL occurred (total in the study;[23,25,27] separated by each condition investigated[13,26–29,31,52]) and percentage of occurrence of FOUL (according to the more- and less-affected side of the body;[28,32] unilaterally and bilaterally;[4,14] for each condition investigated[14,32,34])

Discussion

The present study performed a systematic review of freezing of the upper limbs in PD in order to determine the methods used to investigate FOUL in PD. A comprehensive analysis of articles that investigated episodes of FOUL is useful, since this phenomenon can cause difficulty in performing

Table 2. Sample, evaluation, triggers, and quantitative description of freezing of the upper limbs.

Authors	Sample	Motor task evaluated/described	FOUL triggers investigated	Quantitative description of the phenomenon (Amount)	Quantitative description of the phenomenon (Duration)
Ziv et al.[22]	**PD** (39): DN (13); NF (14); FL (12) PD + FOG (16); PD – FOG (23) **CTRLs** (17)	Tapping index finger on a key sequentially for 15 s.	NI	**PD:** *No. of episodes:* 2.6 per patient. PD (DN): 2.6 episodes per patient PD (NF): 2.6 episodes per patient PD (FL): 2.5 episodes per patient **CTRLs:** *No. of episodes:* 2.0 per patient.	**PD** *Total duration of motor blocks as % of exercise time:* 7% PD (DN): 6.0% PD (NF): 7.4% PD (FL): 7.4% **CTRLs:** *Total duration of motor blocks as % of exercise time:* 4.6%
Almeida et al.[26]	**PD** (13) **CTRLs** (13)	Slide two 9 × 13 cm metal blocks with an 8 cm plastic handle, one in each hand, along a marked 16 cm path. The participants performed movements in phase and in antiphase in one of three speeds of the metronome (0.75, 1.25 and 1.75 Hz, in ascending order) and in two different conditions of auditory signaling (with and without suggestion) for 20 s.	Antiphase coordination: FOUL episodes occurred only during antiphase coordination.	**PD:** *% of the trials in which FOUL occurred:* 8.1% (in only anti-phase tasks). **CTRLs:** episodes were not observed.	Not shown
Almeida et al.[27]	**PD** (13) **CTRLs** (13)	Slide two 9 × 13 cm metal blocks with an 8 cm plastic handle, one in each hand, along a marked 16 cm path. The participants performed movements in phase and in antiphase in one of three speeds of the metronome (0.75, 1.25 and 1.75 Hz) for 20 s. Participants were instructed to make the phase change as soon as they heard an auditory stimulus at 10 s of the activity.	Change of phase coordination to antiphase: worsening of FOUL (significance not reported).	**PD:** *% of the trials with FOUL in which participants were asked to switch from the in-phase to the anti-phase pattern:* 53.9% *% of the trials with FOUL in which participants were asked to switch from the anti-phase to the in-phase pattern:* 15.5% **CTRLs:** FOUL episodes were not observed.	Not shown

Popovic et al.[23]	**PD** (8)	Move a mouse 50 times from point X to point Y, without lifting it from a drawing tablet	NI	**PD:** *% of the trials in which FOUL occurred:* 12%	Not shown
Nieuwboer et al.[42]	**PD** (20): PD + FOG (10) PD − FOG (10) **CTRLs** (5)	Alternating movements of writing in small (2 cm) and large (4 cm) amplitudes and in normal and maximum self-determined speeds for 30 s. One pen in the right hand and another in the left performing antiphase movements (simultaneous flexion of one wrist with extension of the other). With and without a visual clue (lines demarcating the amplitude to be reached).	Faster speed: speed increased FOUL frequency, but not significantly ($p = 0.81$). Smaller amplitude: no difference.	**PD:** *% of the trials in which FOUL occurred:* 10.4% *% of the trials in which FOUL occurred during normal speed:* 3.8% *% of the trials in which FOUL occurred during maximum speed:* 5.4% *% of the trials in which FOUL occurred with visual feedback:* 1.3% *% of the trials in which FOUL occurred without visual feedback:* 3.8% *No. of patients who presented FOUL:* PD + FOG: 7 PD − FOG: 1 No differences were found in the FOUL frequency between the conditions of small and large amplitude. **CTRLs:** No episodes were observed.	Not shown
Vercruysse et al.[14]	**PD** (23): PD + FOG (11) PD − FOG (12) **CTRLs** (11)	Flexion and extension of left and right index fingers, with external auditory cue in the first 6 movement cycles and then without auditory cue. The required range was comfortable or smaller (66% of the comfortable range). The frequency of movement was normal (comfortable = 100%) or fast (133% of comfortable) requiring phase or antiphase coordination.	Faster speed and smaller amplitude were not investigated as FOUL triggers.	**PD:** *FOUL frequency in the condition requiring alternating fast and small-amplitude movements:* 17% *FOUL frequency in the condition requiring simultaneous slow and large-amplitude movements:* 7% *FOUL frequency occurring bilaterally:* 31% *FOUL frequency occurring unilaterally:* 69% *FOUL frequency occurring unilaterally on the more-affected side:* 75% *FOUL frequency occurring unilaterally on the less-affected side:* 25% *No. of patients who presented FOUL* PD + FOG: 9 PD − FOG: 2 No difference in FOUL frequency between in-phase and anti-phase and between normal and high-frequency conditions. Small-amplitude conditions tended to provoke more freezing episodes compared to large-amplitude conditions. **CTRLs:** not shown	**PD:** *Duration of FOUL episodes (mean):* 5.98 s, 82% lasting more than 1 s.

Vercruysse et al.[12]	**PD** (23): PD + FOG (11) PD − FOG (12) **CTRLs** (11)	Flexion and extension of the left and right index fingers. The required range was comfortable or smaller (66% of the comfortable range). The movement frequency was normal (comfortable = 100%) or fast (133%). Requiring phase or antiphase coordination. Auditory stimulation guided the first 6 cycles of movement to allow correct frequency manipulations, then the rhythm was maintained for 25 s.	Speed: no difference ($p = 0.47$). Smaller amplitude: worsened but not significantly ($p = 0.081$). Antiphase coordination: no difference ($p = 0.23$).	**PD:** *No. of trials with FOUL:* 64 *No. of patients who presented FOUL* PD + FOG: 8 PD − FOG: 2 **CTRLs:** not shown.	Not shown
Williams et al.[44]	**PD** (27): PD + FOG (16) PD − FOG (11) **CTRLs** (18)	Alternating and bilateral pointing movements under four conditions for 15 s: Initial condition (e.g., 1 movement/s, 10 cm between targets), Fast (50% faster than Initial condition, 10 cm between targets), Small (e.g.: 1 movement/s, 5 cm between targets) and Small Fast (50% faster than Initial condition, 5 cm between targets).	Smaller amplitude and increased speed: difference in no. of episodes was not significant ($p = 0.61$).	**PD:** PD + FOG: *No. of episodes in Baseline:* 10 *No. of episodes in Fast condition:* 12 *No. of episodes in Small condition:* 8 *No. of episodes in Small Fast condition:* 6 *% of total trials with at least one episode in Baseline condition:* 11.0% *% of total trials with at least one episode in Fast condition:* 21.8% *% of total trials with at least one episode in Small condition:* 14.5% *% of total trials with at least one episode in Small Fast condition:* 9.5% PD − FOG: *No. of episodes in Baseline:* 4 *No. of episodes in Fast condition:* 5 *No. of episodes in Small condition:* 4 *No. of episodes in Small Fast condition:* 12 *% of total trials with at least one episode in Baseline condition:* 3.7% *% of total trials with at least one episode in Fast condition:* 6.2% *% of total trials with at least one episode in Small condition:* 3.7% *% of total trials with at least one episode in Small Fast condition:* 11.2% **CTRLs:** *No. of episodes in Small Fast condition:* 1 *% of total trials with at least one episode in Small Fast condition:* 0.01%	Not shown

Barbe et al.[40]	**PD** (22): - PD + FOG (11) - PD – FOG (11)	Finger Tapping (index finger on the thumb) and Diadochokinesia (alternating rapid movements of pronation and supination). Bilateral antiphase coordination for 10 s.	NI	**PD:** **Task 1 (Finger Tapping):** PD OFF + FOG: *No. of episodes:* 35 *No. of patients presenting FOUL*: 6 PD ON + FOG: *No. of episodes:* 24 *No. of patients presenting FOUL*: 7 PD OFF – FOG: *No. of episodes:* 8 *No. of patients presenting FOUL*: 4 PD ON – FOG: *No. of episodes:* 5 *No. of patients presenting FOUL*: 1 **Task 2 (Diadochokinesia):** PD OFF + FOG: *No. of episodes: 6* *No. of patients presenting FOUL*: 2 PD ON + FOG: *No. of episodes:* 2 *No. of patients presenting FOUL*: 2 PD OFF – FOG: *No. of episodes:* 17 *No. of patients presenting FOUL*: 5 PD ON – FOG: *No. of episodes:* 4 *No. of patients presenting FOUL*: 3	**PD:** **Task 1 (Finger Tapping):** PD OFF + FOG: *Total time of FOUL (mean)*: 29.3 s PD ON + FOG: *Total time of FOUL (mean)*: 16.3 s PD OFF – FOG: *Total time of FOUL (mean)*: 5.5 s PD ON – FOG: *Total time of FOUL (mean)*: 3.0 s **Task 2 (Diadochokinesia):** PD OFF + FOG: *Total time of FOUL (mean)*: 4.2 s PD ON + FOG: *Total time of FOUL (mean)*: 1.9 s PD OFF – FOG: *Total time of FOUL (mean)*: 13.3 s PD ON – FOG: *Total time of FOUL (mean)*: 2.3 s
Vercruysse et al.[4]	**PD** (32): PD + FOG (16) PD – FOG (16) **CTRLs** (16)	Flexion and extension of index fingers for 30 s. Coordination in phase and antiphase, range of motion (comfortable and less) and movement frequency (comfortable and fast). The movement frequency was normal (comfortable = 100%) or fast (133%).	Fast speed, small range of motion: more episodes of FOUL with a longer duration (did not mention significance).	**PD**: *FOUL frequency occurring bilaterally:* 51.9% *FOUL frequency occurring unilaterally on the left side:* 32.1% *FOUL frequency occurring unilaterally on the right side:* 15.9% *% of patients who presented FOUL* PD + FOG: 9 PD – FOG: 1 More freezing episodes were observed during elicitation conditions (high-frequency and low-amplitude conditions) compared to freezing-resistance conditions (comfortable amplitude and speed). **CTRLs**: not shown	**PD**: *Duration of FOUL episodes (mean):* 4.89 s

Brown et al.[29]	**PD** (15) PD + FOG: 5 PD − FOG: 10 **CTRLs** (15)	**Experiment 1:** Bimanual wrist flexion-extension, synchronized with a metronome for 50 s with gradual speed increase. The cycle frequency was gradually increased from 0.75 to 2 Hz at set intervals. Phase or antiphase coordination in one of three sensory conditions: no vision, normal vision or increased vision. **Experiment 2:** – Part 1: Coordination initiated in one of the phase patterns. Attempts in one of two frequencies (1 or 2 Hz) and in one of two sensory conditions were made: no vision or normal vision. – Part 2: the participants were instructed to make an intentional change between phases in the middle of the tests.	**Experiment 1:** – Increased speed: ($p < 0.001$). – Sensory conditions: no effect ($p > 0.05$). – Antiphase coordination: no effect ($p > 0.05$). **Experiment 2:** **Part 1** – Increased speed: $p < 0.001$. – Sensory conditions: no effect ($p > 0.05$). – Antiphase coordination: $p < 0.001$. **Part 2** – Increased speed: $p < 0.001$. – Change in and performance of the antiphase coordination: $p < 0.001$.	**PD:** **– Experiment 1:** *No. of patients who presented FOUL:* PD + FOG: 2 PD − FOG: 4 *% of FOUL in PD OFF on the more-affected side*: 40.9% *% of FOUL in PD OFF on the less-affected side*: 2.3% *% of FOUL in PD ON on the more-affected side*: 31.8% *% of FOUL in PD ON on the less-affected side*: 6.8% **– Experiment 2:** Before the auditory suggestion to change phase pattern**:** *No. of patients who presented FOUL:* PD + FOG: 1 PD − FOG: 4 *% of FOUL in PD OFF on the more-affected side*: 45.3% *% FOUL in PD ON on the more-affected side*: 50.9% After the suggestion to change phase pattern: *No. of patients who presented FOUL:* 8 PD + FOG: 3 PD − FOG: 5 *% of FOUL in PD OFF on the more-affected side*: 40.2% *% of FOUL in PD ON on the more-affected side*: 48.0% **CTRLs:** FOUL was not found	**PD:** **– Experiment 1:** *Duration of FOUL episodes (mean):* 2.75 s **– Experiment 2:** Before the auditory suggestion to switch phase pattern: *Duration of FOUL episodes (mean):* 2.6 s After the suggestion to change phase pattern: *Duration of FOUL episodes (mean):* 3.0 s
Heremans et al.[25]	**PD** (34): PD + FOG (17) PD − FOG (17) **CTRLs** (10)	Funnel task using the right hand for 1 min, 5 attempts with a 6-s pause between them without auditory cues.	Small amplitude: $p < 0.01$	**PD:** *No. of patients who presented FOUL:* PD + FOG: 8 PD − FOG: 2 *% of FOUL during the minor parts of the writing trajectory:* 53.9% *% of FOUL in the parts where patients had to gradually decrease the writing size:* 34.6%. **CTRLs:** 1 patient demonstrated 1 FOUL episode	**PD:** *Duration of FOUL episodes (mean):* 3.6 s, 29.4% lasting more than 1 s

Scholten et al.[45]	**PD + FOG** (14) **CTLRs** (13)	Touch right index finger on a key for 20 s Touch right index finger on a key simultaneously with a phonemic verbal fluency task (10 consonants, 1 consonant per block of 20 s)	Dual-task ($p = 0.007$)	**PD + FOG:** *No. of episodes during the single motor task:* 9 *No. of episodes during the dual-task:* 72 *No. of patients who presented FOUL during the single motor task:* 3 *No. of patients who presented FOUL during the dual-task:* 9 **CTLRs:** not shown	**PD + FOG:** *Duration of FOUL episodes during the single motor task (mean):* 1.9 s *Duration of FOUL episodes during the dual-motor task (mean):* 2.3 s
Scholten et al.[46]	**PD + FOG** (14) **CTLRs** (13)	Touch right index finger on a key for 20 s Touch right index finger on a key simultaneously with a phonemic verbal fluency task (10 consonants, 1 consonant per block of 20 s)	Dual-task (did not mention significance).	**PD + FOG:** *No. of patients who presented FOUL:* 9 *No. of episodes:* 7 per patient **CTLRs:** not shown	**PD + FOG:** *Duration of FOUL episodes (mean):* 2.3 s
Delval et al.[28]	**PD** (30) **CTLRs** (30)	Bimanual task of hitting hands on the table at least 30 times. Antiphase coordination at a frequency imposed by a metronome in random order at 1, 2, 3, 4, 5, 6 or 7 Hz.	Antiphase coordination (did not mention significance).	**PD:** *% of the trials with FOUL at Baseline*: 12 to 14% *% of the trials with FOUL after 2 years*: 10 to 12% **CTLRs:** *% of the trials with FOUL at Baseline*: 2 to 4%	Not shown.
Delval et al.[13]	**PD + FOG (15)**	Tapping of fingers (index on thumb) 30 times one-sided, with and without following the rhythm of a metronome set to 4 Hz.	Metronome use: $p < 0.001$.	**PD + FOG:** *No. of patients who presented FOUL in the absence of the metronome:* 3 *No. of patients who presented FOUL in the presence of the metronome:* 7 *% of the trials with FOUL in the absence of the metronome:* 5% *% of the trials with FOUL in the presence of the metronome:* 21%	**PD + FOG:** *Duration of FOUL episodes without the metronome (mean):* 0.84 s *Duration of FOUL episodes with the metronome (mean):* 1.1 s

Janssen et al.[43]	**PD + FOG** (17)	Rhythmic flexion and antiphase extension movements using the two index fingers. In four different conditions, three times each: normal amplitude, 45° and normal speed, 100% (NANS); normal amplitude and fast speed, 133% (NAFS); small amplitude, 30° and normal speed, 100% (SANS); and small amplitude, 30° and fast speed, 133% (SAFS). Both hands were covered and could not be seen.	Small amplitude: ($p = 0.000$) Higher speed ($p = 0.000$)	**PD + FOG** *No. of patients who presented FOUL:*17 *% of the trials in which FOUL occurred bilaterally:* 54% *% of the trials in which FOUL occurred unilaterally on the more-affected side:* 31% *% of the trials in which FOUL occurred unilaterally on the less-affected side:* 15%	**PD + FOG** *Duration of FOUL episodes (mean):* 3.1 s; in 42% the duration was less than 1 s and in 66% less than 2 s.
Jehu et al.[30]	**PD** (17) PD + FOG (5) PD − FOG (12) **CTRLS** (9)	Standing repetitive pointing task: Pointing at a target located at a distance of 50% of the patient's arm length. One trial of 30 s and one of 120 s.	NI	No episodes found.	Not shown.

Khoshnam et al.[24]	**PD** (11)	Touch the tip of the index finger on a key for 20 s, first with the right finger and after 3 min with the left finger	NI	**More-affected side:** *No. of episodes in the GVS OFF trials:* 1.4 *No. of episodes in the GVS ON trials:* 1.5 **Less-affected side:** *No. of episodes in the GVS OFF trials:* 1.8 *No. of episodes in the GVS ON trials:* 1.3 **Both sides:** *No. of episodes in the GVS OFF trials:* 1.6 *No. of episodes in the GVS ON trials:* 1.4	**More-affected side:** *Duration of episodes in the GVS OFF trials:* 3.2 s *Duration of episodes in the GVS ON trials:* 3.0 s **Less-affected side:** *Duration of episodes in the GVS OFF trials:* 3.1 s *Duration of episodes in the GVS ON trials:* 2.3 s **Both sides:** *Duration of episodes in the GVS OFF trials:* 3.1 s *Duration of episodes in the GVS ON trials:* 2.7 s
Broeder et al.[38]	**PD** (10) **CTRLs** (10)	Funnel Task using the right hand for 1 min. 5 attempts each.	Small amplitude ($p < 0.0005$)	**PD**: *% of the trials with FOUL during tDCS:* 18% *% of the trials with FOUL during placebo (sham):* 38% Task (Small part): *No. of FOUL episodes during tDCS:* 4 *No. of FOUL episodes during placebo (sham):* 20 Task (Large part): *No. of FOUL episodes during tDCS:* 2 *No. of FOUL episodes during placebo (sham):* 0 Task (Decreasing part): *No. of FOUL episodes during tDCS:* 1 *No. of FOUL episodes during placebo (sham):* 11 Task (Increasing part): *No. of FOUL episodes during tDCS:* 5 *No. of FOUL episodes during placebo (sham):* 7 **CTRLs:** 2 controls presented 3 episodes of FOUL, 2 of them during placebo (sham) condition and 1 during tDCS.	Not shown.

Heremans et al.[41]	**PD** (49) **CTLRs** (10)	Funnel Task at two speeds: fast in 40 s (FFT) and normal in 1 min. (NFT). 5 attempts each.	Small amplitude (did not mention significance) Fast speed ($p < 0.01$).	**PD:** *No. of patients with FOUL:* 29 Task (FFT): *Total no. of episodes:*123 *No. of episodes per person:* 2.5 *% time frozen*: 3.8% *% of FOUL in smaller parts:* 39.5% *% of FOUL in larger parts:* 5% *% of FOUL in increasing parts:* 8.4% *% of FOUL in decreasing parts:* 47.1% Task (NFT): *Total No. of episodes:* 60 *No. of episodes per person:* 1.2 *% time frozen*: 1.7% *% of FOUL in smaller parts:* 63.7% *% of FOUL in larger parts: 7.3*% *% of FOUL in increasing parts: 3.*6% *% of FOUL in decreasing parts:* 25.4% **CTRLs:** 1 control presented FOUL episodes	Not shown.

CTRLs: controls; DN: patients who have never undergone drug treatment; FFT: fast funnel task; FL: Patients on chronic levodopa therapy, with a fluctuating daily response to the medication; FOG: freezing of gait; FOUL: freezing of upper limb; GVS: galvanic vestibular stimulation; NF: Patients treated with levodopa for at least 6 months, without experiencing fluctuating responses to the medication; NFT: normal funnel task; NI: not investigated; PD: Parkinson's disease; PD OFF: group of patients after withdrawal from dopamine replacement; PD ON: group of patients after dopamine medication replacement; tDCS: transcranial Direction Current Stimulation.

daily activities. The hands are positioned by the upper limbs and allow primitive movements such as carrying, lifting, pushing, pulling, handling, reaching, stabilizing, and manipulating objects.[39,40] The combination of these movements allows execution of functional movements such as manipulating a zipper, cutting food, and opening a jar.[40] Deficits in primitive movements and consequently in functional movements can cause difficulty in carrying out activities of daily living such as eating, dressing, and writing.[39,41–43] Along with changes in gait, dysfunctions in upper-limb movements are common in PD but are often neglected despite their importance in daily life.[44]

Most of the studies (67%) included in this review were classified as moderate quality and the others as high quality. Most studies (81%) did not describe the sample calculation and/or did not provide a representative sample. New studies that address these methodological issues are needed, although the lack of standardized protocols to evaluate FOUL may also have affected the quality of the articles.

Compared to the number of published studies on FOG, to date few studies have investigated FOUL, and the term used for the phenomenon differs among studies. The lack of a uniform terminology impeded the search for the articles described here. Because this is the same motor phenomenon, standardization of the nomenclature is essential to facilitate communication and understanding of the topic for this research area and also for the clinic, to enable correct interpretation and application.[45]

There was no consensus on the clinical characteristics necessary to confirm the presence of FOUL. Analysis of the selected studies found 14 different criteria used to confirm the presence of FOUL. In general, most studies (52%) mentioned 2 characteristics: reduced range of motion and irregularity in the frequency of movement. The Freezing Index (FI) was also used as part of the criteria for defining FOUL.[4,33,35] The FI is obtained through kinematic evaluation and spectral analysis of the frequencies of movements. The FI is the ratio between two powers, motion with freezing (3 to 8 Hz) and normal (0 to 3 Hz).[46] It was developed for studies evaluating FOG, but the value of FI > 1 has previously been validated as a critical threshold to detect freezing episodes during movements of the upper limbs.[14] Evaluation using the FI is difficult to implement in clinical practice because of its high cost. Standardization of clinical criteria for determining FOUL is essential to prevent misunderstandings and inconsistencies in the interpretation of data on FOUL, which could affect the selection of patients for treatment or clinical trials.

The studies also differed in the use of dopaminergic medication during the evaluation, and one study[23] did not indicate the medication status of the patients. Perhaps this variable should be addressed, since FOG can be classified into the phenotypes “OFF” FOG state and “ON” FOG state.[47] The

OFF FOG state is the freezing episode that occurs when an individual is in the OFF state of the medication, and the ON FOG state manifests even after an individual is in the ON state, under the effect of medication. This is particularly important because physical and occupational therapists can observe if FOUL is present only in the OFF state and if it persists during the ON state. Based on studies that evaluated patients in the ON and OFF states, Barbe et al.[30] found that although FOUL tends to be more frequent in the OFF condition, this was not a significant difference. Brown et al.[32] did not observe this trend and Jehu et al.[38] did not find episodes of FOUL.

The articles described here used different activities/tasks to detect FOUL, most often a) flexion and extension of the index finger, b) finger tapping (index finger on thumb), and c) Funnel task. These mobility/coordination tasks, although they did not need instruments or objects to perform, required special techniques and apparatus to analyze and detect FOUL, such as electromyography and software for kinematic analysis.[4,8,11,12,30,37] These resources are not present in the majority of rehabilitation clinics and therefore cannot be applied in clinical practice.

The Funnel Task has been studied to facilitate identification of this phenomenon.[33–35] This is a writing task; patients with PD have severe writing problems, which are more pronounced in patients with FOG.[44] The Funnel Task requires certain materials (electronic writing tablet, data-processing software) that may not be accessible to most professionals in clinical practice. Heremans et al.[34] reported that this task can be easily reproduced using paper and pencil, but to date, no study has validated the test with this procedure.

In sum, we lack a gold-standard validated, reliable, and accessible instrument/questionnaire to assess the presence of FOUL in different situations/contexts of activities of the upper limbs. This poses a clinical challenge since the lack of a rapid, accurate, and systematic means to detect this phenomenon also implies the lack of a targeted intervention to manage this symptom.[48] In addition, different types of assessment must be carried out to confirm the occurrence of freezing. Researchers[6] suggest that clinical observation with quantitative objectives should be combined with self-reported assessments to identify FOUL.

Regarding the FOUL triggers, in general, small amplitude/high frequency movements increased the number of episodes.[29,32] Different parameters were used to determine the amplitude and velocity of the movements. This variation in methods emphasizes the need for standardization so that occupational therapists and physical therapists can know when a movement can be considered faster (in velocity) or smaller (in amplitude) in clinical practice. In studies that used the Funnel Task, many FOUL episodes were triggered when the size of the letters was to be gradually reduced.[33–35] Heremans et al.[33] noted that this decrease in amplitude in the writing task

is likely to require greater cognitive control and less automatic movement. Perhaps the main factor that induces FOUL is the required change in attention.[30] When individuals with PD perform a simple motor task of tapping their fingers during the ON state of medication, they over-activate cognitive areas of tertiary association in the cerebellum.[49] Individuals with PD may use more cognitive functions when performing simple movements compared to individuals without the disease.[49]

According to Scholten et al,[36] who assessed the effect of the dual-task on FOUL initiation, the phonemic verbal-fluency cognitive task increased the susceptibility to FOUL in PD. Scholten et al.[36] suggested that the dual-task overloaded cortical motor processing, increasing susceptibility to FOUL. Studies that evaluated the motor performance of upper limbs and dual-task have recently appeared,[50–52] but further investigation of the relationship between the presence of FOUL and dual-task is needed. One study that evaluated the effects of a dual cognitive task on writing performance found deficits in PD patients more specifically during small writing movements.[52] In that case, the dual cognitive task consisted of counting how many sounds were produced while writing.[52] The patients in these studies had no cognitive impairments, and three of the studies[36,50,51] used scores lower than 24 on the Mini Mental State Examination as exclusion criteria. In patients with cognitive impairment, the presence of a dual-task can be even more impactful. The use of a metronome at 4 Hz triggered FOUL in the task of tapping the fingers in time with the metronome, which was considered a stressful dual-task condition.[13] In a study with FOG patients, only a few individuals preferred a continuous beat of the metronome (even though its frequency was comfortable), indicating that it was more uncomfortable than the therapist's verbal feedback (warning to "speed up" or "slow down" the gait).[53] In contrast, Vercruysse et al.[12,14] considered that FOUL triggered without cognitive load and auditory stimuli were important for an improvement in FOUL during task performance. This variability of triggers is also found when the subject of the research is FOG. One study reported the existence of three possible FOG subtypes, classified according to the type of trigger that provokes freezing in the most intense way: 1) motor (group that froze more when turning); 2) cognitive (group that froze more during dual-task situations); and 3) limbic (group with no predominance of a specific trigger, but froze less when relaxation strategies were used).[54] Although published information on FOUL is sparse, there may be triggers (motor, cognitive, and limbic) that provoke different FOUL subtypes. For this reason, researchers must consider conducting clinical assessments that include non-motor symptoms (in this case cognitive and limbic functions) to detect FOUL.[6]

FOUL proved to be present in patients with early PD and may be a symptom that precedes the onset of FOG, predicting a worse prognosis.[22,31]

However, FOUL occurred not only in individuals with PD, but also, although much less frequently, in healthy controls.[22,29,31,33–35] This may have occurred because nigrostriatal projection neurons are more prone to degeneration due to aging.[55] Only one study[38] did not identify the occurrence of FOUL in individuals with PD, and the authors explained that the motor task used may have affected this result. The type of task can affect whether FOUL is detected or not. Therefore, many patients could have a false-negative result for FOUL if the motor task is not appropriate for clinical testing.

The outcomes of the quantitative assessments of FOUL episodes were varied and different. As presented, some studies used similar values, but even those with the same types of values used different methods, which makes comparison difficult. The number of episodes per patient ranged from 2.6 to 7.0, but the study that reported 7.0[37] selected only patients with akinetic-rigid symptom dominance. The akinetic rigid subtype is a risk factor associated with the development of freezing in PD.[10] The total percentage of trials in which FOUL occurred was similar among the three studies[23,25,27] that used this value, 8.1% to 12%. They all used anti-phase movements, and two[23,25] used similar tasks (moving objects) in the evaluation. When the parameters involved disease laterality, more FOUL episodes occurred on the most-affected side.[14,28,32] One study[14] found more unilateral episodes (69%) and on the most-affected side; in contrast, another[4] found more bilateral episodes (51.9%) and did not mention which side was more affected. As is apparent, the FOUL phenomenon can be assessed unilaterally and/or bilaterally, and the role of PD laterality must be confirmed. The values (number of patients, episodes, percentage of trials or episodes), separated by the conditions investigated, varied according to the type of the task used, but in general, the number of patients who presented FOUL was higher in the group of patients with FOG. Neuroimaging studies indicated that in patients with FOG, episodes of FOUL were associated with increased cortical brain activity in the supplementary motor area, dorsal prefrontal cortex, primary sensorimotor cortex, and anterior prefrontal cortex, whereas subcortical activity in the globus pallidus and putamen was diminished. This cortical hyperactivation can be characterized as a dysfunction or as an attempt to compensate.[4,37] To better understand the pathophysiology of FOUL and the similarities and differences between these two freezing phenomena, FOG and FOUL, patients with and without FOG should be included in the sample with FOUL to be evaluated.[34]

Conclusion

This review describes how FOUL has been investigated in patients with PD, the assessments used to evaluate and detect FOUL, and its different nomenclatures. The variation in the sample profiles and methods used in the studies made it difficult to compare articles and establish a consensus.

We also indicate aspects that need further research. The term most frequently assigned to the phenomenon was "freezing of upper limbs", but some recent studies have used other terms. Different activities/tasks were used to detect FOUL; although there is insufficient evidence to support the clinical utility of a particular activity, the tasks most often used were evaluation of the mobility of the index finger, alone or in a pinching movement with the thumb, and a writing task (the Funnel Task). The activities of upper limbs that require movements of small amplitude/high frequency as well as the presence of a dual task elicited more episodes of FOUL in individuals with PD, with or without the use of medication.

This review indicates the need for development and validation of FOUL detection assessment in clinical practice. Unlike FOG, which is freezing of a specific motor activity (gait), FOUL encompasses all motor activities performed with the upper limbs. The infinity of motor repertoires of the upper limbs, especially of the hands, requires an assessment that takes into account the different functional contexts in order to detect the spectrum of the possibility of freezing in this body part and to prevent false-negative results. Protocols for evaluating FOUL must also include non-motor symptoms such as cognitive and limbic. Once a valid, reliable, and accessible assessment protocol has been developed, physical and occupational therapists can plan interventions focused on this phenomenon. Adoption of a standard term for freezing of the upper limbs is important to avoid misconceptions related to health conditions presented by people with PD. These therapeutic interventions can be useful to improve the functioning of the upper limbs and consequently the performance of daily activities by individuals with PD.

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