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Freezer or non-freezer: Clinical assessment of freezing of gait

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ABSTRACT

Introduction: Freezing of gait (FOG) is both common and debilitating in patients with Parkinson's disease (PD). Future pathophysiology studies will depend critically upon adequate classification of patients as being either 'freezers' or 'non-freezers'. This classification should be based ideally upon objective confirmation by an experienced observer during clinical assessment. Given the known difficulties to elicit FOG when examining patients, we aimed to investigate which simple clinical test would be the most sensitive to provoke FOG objectively.

Methods: We examined 50 patients with PD, including 32 off-state freezers (defined as experiencing subjective 'gluing of the feet to the floor'). Assessment including a FOG trajectory (three trials: normal speed, fast speed, and with dual tasking) and several turning variants (180° vs. 360° turns; leftward vs. rightward turns; wide vs. narrow turning; and slow vs. fast turns).

Results: Sensitivity of the entire assessment to provoke FOG in subjective freezers was 0.74, specificity was 0.94. The most effective test to provoke FOG was rapid 360° turns in both directions and, if negative, combined with a gait trajectory with dual tasking. Repeated testing improved the diagnostic yield. The least informative tests included wide turns, 180° turns or normal speed full turns. Sensitivity to provoke objective FOG in subjective freezers was 0.65 for the rapid full turns in both directions and 0.63 for the FOG trajectory.

Discussion: The most efficient way to objectively ascertain FOG is asking patients to repeatedly make rapid 360° narrow turns from standstill, on the spot and in both directions.

1. Introduction

Freezing of gait (FOG) is an episodic gait disorder characterized by an inability to generate effective forward stepping movements [1]. FOG is common in Parkinson's disease (PD) and in many forms of atypical parkinsonism [2]. It is a distressing symptom [3,4] which, due to the unexpected nature of FOG events, commonly leads to falls [5,6].

Both clinical decision-making and future research depend critically upon adequate classification of patients as being either 'freezers' or 'non-freezers'. Currently, there is no gold standard for this classification. Most earlier studies used the subjective experience of the patient ('feet being glued to the floor'), as part of the freezing of gait questionnaire (FOGQ) [7,8]. However, some patients who deny subjective gluing may nevertheless demonstrate FOG when being examined in a profound off state (at least 12 h after the last intake of medication) [9,10]. In such cases, FOG will simply remain unnoticed in daily life where dopaminergic treatment suppresses the phenomenon [11]. Conversely, some patients may misunderstand the question and interpret 'being glued' as representing their overall akinesia which they can experience during a profound off-state (but which lacks the typical episodic nature of freezing of gait). Demonstrating the phenomenon to patients or showing a video with typical examples of FOG may be helpful in such cases [8].

Fig. 1 shows an algorithm which combines the subjective experience of patients with the objective judgment by an examiner, allowing for a classification of subjects as being either a 'non-freezer', a 'probable freezer' or a 'definite freezer' [12]. The need to adequately identify and classify freezers as such depends on the setting. In clinical practice, no freezers should be missed and, consequently, be withheld from effective treatment (e.g. optimizing medication, or offering cueing strategies). In other words, a high sensitivity of a test to identify freezers is most important in the clinical setting, even if this goes at the expense of specificity. Hence, in the clinic, it is satisfactory to define a patient as being a 'probable freezer', and for this purpose, use of the FOGQ or a question about 'feeling glued' suffices.

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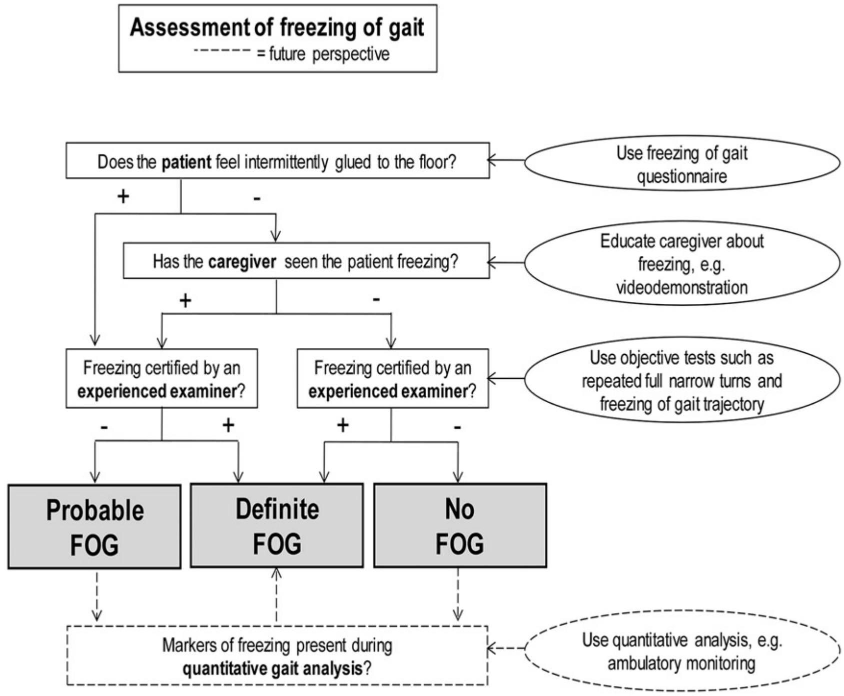

Fig. 1. Freezer classification algorithm.

However, in research studies aiming to study the underlying pathophysiology, it is vital to have a high specificity, in order not to include false-positive freezers, especially when performing between-group comparisons. Ideally, in a research setting patients are classified more strictly as being either 'definite freezers' or 'non-freezers'. For this purpose, objective measures (observer-based) are also required. However, objective confirmation is challenging, because it is generally difficult to elicit FOG during a clinical assessment, and even more so in an experimental environment [13]. This would hinder research, because patient inclusion would be more difficult. An objective test with a high sensitivity to elicit FOG will make it easier to match patients with and without FOG for disease severity, because patients who do not show FOG during clinical assessment are usually less severely affected [14]. More complex tasks and combinations of tests appear to offer a greater diagnostic yield [15]. In a recent study, full turns in combination with a dual task elicited most FOG episodes, and this provoked FOG in 50% of subjective freezers [10]. Preferably, more sensitive methods to elicit FOG will become available.

Here, we examined which objective clinical tests are most sensitive to elicit FOG. Our aim was to determine which clinical tests are most sensitive to classify 'definite' freezers. Based on our own clinical experience and on previous research [15,16], we hypothesized that several specific factors might influence our ability to classify freezers. This included the following specific hypotheses and predictions: turning range (narrow versus wide turn, narrow turns expected to be most provocative), turning speed (slow versus fast, fast turns expected to be most provocative), turning direction (most affected versus less affected side, turning towards the most affected expected to be most provocative) and turn extent (180 versus 360° turns, full turns expected to be most provocative). To minimize strain on patients and researchers in future practice, we aimed to arrive at the minimum amount of tests needed to get a maximum diagnostic yield. Hence, we also hypothesized that rapid axial turns would be as sensitive in classifying freezers as a more elaborate and more time-consuming FOG trajectory.

2. Methods

2.1. Patients

We included 50 patients (Table 1) that were recruited by telephone from the total database of our large outpatients clinic of the Parkinson Centre Nijmegen. Inclusion criteria were idiopathic PD, defined according to the UK PD Brain bank criteria [17], Hoehn and Yahr stage 2–3, the ability to come to the department for research studies, and to perform the experiment in an OFF state (because these subjects represent the patients that are typically used for research studies). To assess patient-rated (subjective) FOG, we used the new Freezing of Gait Questionnaire (NFOG-Q) [8]. We included thirty-two subjects with a subjective history of FOG (i.e. they answered 'yes' to the question: 'Do you sometimes feel as if your feet are being glued to the floor?'). We only included patients whose FOG was most prominent during an OFF state. In addition, we included 18 patients without a history of subjective FOG. Exclusion criteria included other causes for gait impairment (such as severe arthrosis or neuropathy) and Mini Mental State Examination <25. The study was conducted in accordance with the declaration of Helsinki. All subjects gave informed consent, as approved by the local medical ethics committee.

We examined 46 patients during a practically defined OFF condition (in the morning, >12 h after intake of the last dose of dopaminergic medication). The four remaining patients could not withhold their medication for 12 h and were tested in the morning during a subjective OFF state ('end of dose' effect of the first morning dose), just prior to intake of the second medication dose.

Table 1
Clinical characteristics.

	N	Age	Gender	UPDRS	H&Y	Disease duration	N-FOGQ
Objective freezers[a]	25	64	88% male	36.8	2.5	10.7	16.6
Only subjective freezers[b]	8	61	63% male	29.9	2.3	6.5	8.1
Non-freezers	17	62	65% male	26.9	2.1	7	0
All patients	50	62	76% male	32.3	2.3	8.7	9.6

H&Y = Hoehn and Yahr Rating Scale; UPDRS = Unified Parkinson's Disease Rating Scale part 3; N-FOGQ = New Freezing of Gait Questionnaire. H&Y and UPDRS values are measured during 'OFF' state.

[a] Objective freezers: Patients that showed freezing upon examination (definite freezers).

[b] Only subjective freezers: Patients that told they were freezing on history, but did not show freezing upon extensive examination.

2.2. Clinical test battery

To assess the effect of turning range (narrow versus wide turn), turning speed, turning direction and turn extent (180 versus 360° turns), patients performed the following tests:

- Narrow half turns. Patients arose from a chair, walked 2.5 m, and then made a 180° turn in a narrow quarter. The turning direction was self-selected. This was repeated twice, once at preferred speed, and once as rapidly as possible.
- Wide half turns. Same as above, but now using a wide turn around a chair. This test was performed by only 33 patients (20 subjective freezers).
- Normal speed full turns. Patients performed 360° turns from standstill in narrow quarters, at self-selected speed, with two leftward turns to and two rightward turns, in random order.
- Rapid full turns. Same as above, but now as rapidly as possible.

In addition, to be able to compare the turning with the FOG trajectory, patients performed the following trajectories:

- Normal speed gait trajectory. Patients performed a 15-m walking trajectory [15] at self-selected speed. The trajectory consisted of rising from a chair, walking through a narrow passage (created by two chairs placed 50 cm apart), stopping and starting again, a full narrow turn (360°) in one self-selected direction, followed by one and a half turn (540°) in the opposite direction, and walking straight back to the chair.
- Dual task gait trajectory. Same as above, with a cognitive dual task (subtracting serial sevens from 100).
- Rapid speed gait trajectory. Same as above, but now as rapidly as possible.

The tasks were administered in semi counter balanced fashion. We always started with the 180° turns. Half of the patients then first performed the 360° turns and subsequently the gait trajectory, the other half performed these tests the other way round. During the 360° turns the normal speed turns were always performed first, but the direction of turns was counter balanced (randomly). The gait trajectory always started at normal speed, was repeated as rapidly as possible, and then with dual task.

2.3. Outcome

The entire experiment was videotaped for offline visual analysis. Two independent and experienced raters (AS & CH) scored the videos for presence of FOG. The definition used to score FOG was an obvious episode with ineffective stepping [1]. If the two raters disagreed, consensus was reached in discussion with a third rater (BRB). Inter-rater reliability was assessed using Cohen's kappa, both for all trials separately as for the classification as a freezer.

2.4. Best way to provoke FOG

To assess our hypothesis that rapid axial turns would be as effective in classifying freezers as a more elaborate FOG trajectory, we assessed specificity and sensitivity of the rapid turns (4 turns) and the FOG trajectory (normal speed, rapid speed and dual tasks combined). For this analysis, as a gold standard we set the answer 'yes' to the question: 'Do you sometimes feel as if your feet are being glued to the floor?' of the NFOG-Q. In addition, we evaluated which components of the FOG trajectory provoked FOG, to see whether other components then turning were of added value.

Next, we assessed the ability of the separate tests to classify freezers as 'definite freezers', and investigated which combination of tests would have found all 'definite freezers' in our sample.

2.5. Provoking factors during turning

We made several specific comparisons to explore the effect of the different provoking factors during turning (using Wilcoxon's signed rank test for related samples). Each time, the outcome was a binary classification: the test elicited FOG in a patient (1) or not (0). Hence, we did not intend to provide a severity score to assess FOG, as described recently [18]. We specifically examined the following predefined contrasts:

- Space: wide vs. narrow 180° turns (one turn for each condition).
- Range: 180° vs. 360° turns (one slow and one rapid 180° turn were compared to one slow and one rapid 360° turn).
- Speed: rapid versus self-selected speed (two turns each).
- Laterality: turn to the most affected side vs. turn to the least affected side (four turns each).
- Uni- or bilateral: turns into one direction only versus turns into both directions (four compared to eight turns).
- Repetition: four vs. eight turns to both sides (four turns were compared to eight turns).

SPSS 16.0 was used for statistic testing, with α-value set at 0.0083 to correct for six multiple comparisons (Bonferroni).

3. Results

3.1. Classification of freezers

Clinical assessment revealed objective FOG in 24 of the 32 patients with a subjective history of FOG. The patients with definite FOG had a higher NFOG-Q score then the patients with only subjective FOG (Table 1). In addition, FOG was elicited during clinical assessment in one of the 18 patients without history of freezing. Hence, 25 subjects with objective 'definite' FOG were available to evaluate the diagnostic yield of the various tests. The combination of all objective tests thus showed a sensitivity for FOG of 0.74 (95% confidence interval (CI) 0.55–0.88) and a specificity of 0.94 (CI 0.73–1.0).

Inter-rater reliability was excellent for the classification as a freezer (agreement 97%, Cohen's kappa 0.93), and very high for all trials rated separately (agreement 96%, Cohen's kappa 0.89).

3.2. Best way to provoke FOG

Taking as a gold standard the NFOG-Q, rapid full turns (four turns) had a sensitivity of 0.65 (CI 0.45–0.81) and a specificity of 1.00 (CI 0.81–1.0). The gait trajectory (three times) had a sensitivity of 0.63 (CI 0.44–0.80) and a specificity of 0.94 (CI 0.73–1.0) (1 patient without feeling glued on history was rated to experience FOG during the gait trajectory upon gait initiation).

The elements of the gait trajectory differed in their ability to provoke FOG (Fig. 2). The element that provoked most FOG was turning, where FOG occurred in all but two of the 21 patients that froze during the gait trajectory (90%). These two remaining patients only showed FOG upon gait initiation.

A combination of 'Rapid full turns', 'Dual task gait trajectory' and 'Normal speed gait trajectory' provoked FOG in all definite freezers

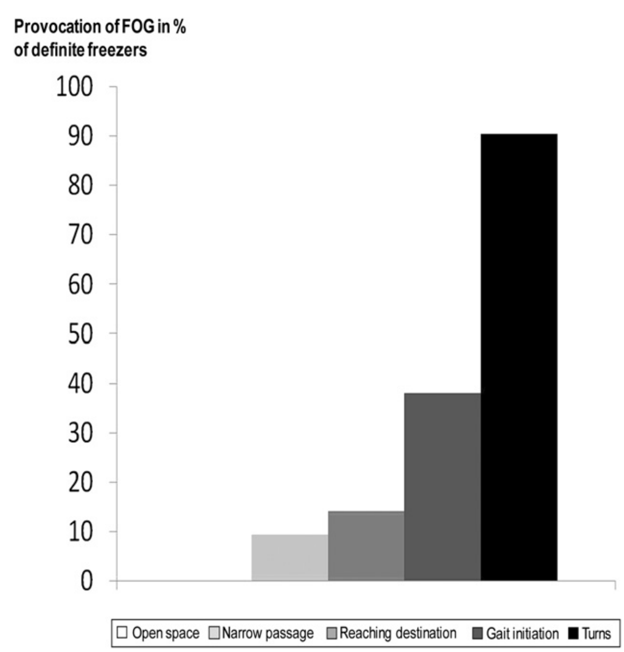

Fig. 2. Provocation of FOG by the different elements of the gait trajectory. Percentage of definite (objective) freezers that show FOG upon each different element of the gait trajectory.

(Table 2 shows FOG provocation of separate and combined tests). This remained true when the rapid turns were performed only into the least affected direction. Performing rapid turns is easier and less time-consuming than performing the gait trajectory. Indeed, including only the full narrow turns (four at normal speed, and four rapidly) already elicited FOG in 88% of the definite freezers.

3.3. *Provoking factors during turning*

Comparisons between the different conditions are shown in Fig. 3 and Table 2. Turning space (wide vs. narrow turn), turning range (full versus half) and turning speed all influenced the percentage of freezers that showed objective FOG (Fig. 3A–C) with an α-value of <0.05, but these effect was not significant anymore when corrected for multiple comparisons. Whether patients turned to their most or least affected side did not affect the diagnostic yield (65% of definite freezers showed FOG when turning to the most affected side, and 74% to least affected side, Wilcoxon's $Z = -0.6$, $p = 0.53$). However, nine patients (43% of definite freezers) exclusively froze when turning to one specific side, and not when they turned to the other side. Turning to both sides tended to yield more freezers than turning to one side ($p = 0.026$, Fig. 3D). However, this could reflect a repetition effect, because comparing four turns to eight turns gave a significant difference (Fig. 3D).

4. Discussion

Our goal was to define the most sensitive, simple clinical test to classify 'definite' freezers. Using various scenarios combined, we found 0.74 sensitivity to elicit definite FOG in PD patients with a subjective history of freezing ('probable' FOG). Moreover, unambiguous FOG was observed during this assessment in 5% of patients who firmly denied the characteristic gluing experience of FOG in daily life. The most effective test to provoke FOG was rapid 360° turns in both directions and, if negative, combined with a gait trajectory with dual tasking. Repeated testing improved the diagnostic yield. The least informative tests included wide turns, 180° turns or normal speed full turns. Rapid full turns (four turns) were as sensitive to objectively provoke FOG in subjective freezers as FOG trajectories (three trajectories, including six turns).

This study confirms the challenge of provoking FOG in patients who complain of 'feeling glued to the floor'. It is especially difficult to elicit FOG in patients with less severe subjective FOG, as measured by the NFOG-Q. In addition, similar to another study [10], we found that one of the 18 subjective 'non-freezers' did actually show clear FOG during our extensive clinical assessment. Two factors may explain this. First, the assessment took place during a practically defined off-period, and this may unveil FOG that remains unnoticed in daily life where dopaminergic treatment suppresses the phenomenon [19]. This is why research studies into FOG should preferably examine patients during the off-period. Second, our extensive test battery exposed patients to situations which they have 'learned' – either consciously or subconsciously – to avoid in daily life. For example, the spontaneous behavior of many patients is to take wide and careful turns, while our present results suggest that rapid turns in tight quarters are the best way to provoke FOG. We therefore recommend using such rapid, narrow turns as part of the test battery to classify patients as either freezers or non-freezers.

Our findings confirm that turning is the best way to provoke FOG in PD [10,15,18]. We also showed that repeated full turns in

Table 2
Ability of the different task to classify patients as 'definite freezers' (freezing of gait episode(s) seen on examination).

ONE task provoking at least one FOG episode		**(% of definite freezers)**
Task 1	Rapid full turns	84%
Task 2	Dual task gait trajectory	68%
Task 3	Normal speed gait trajectory	60%
Task 4	Normal speed full turns	48%
Task 5	Rapid speed gait trajectory	48%
Task 6	Narrow half turns	40%
Task 7	Wide half turns	0%
TWO tasks provoking at least one FOG episode		
Task 1 and 2	Rapid full turns, dual task gait trajectory	96%
Task 1 and 4	Rapid full turns, normal gait trajectory	92%
Task 1 and 3	Rapid full turns, normal speed full turns	88%
Task 2 and 3	Normal gait trajectory, dual task gait trajectory	84%
THREE tasks provoking at least one FOG episode		
Task 1, 2, 3	Rapid full turns, dual task gait trajectory, normal gait trajectory	100%

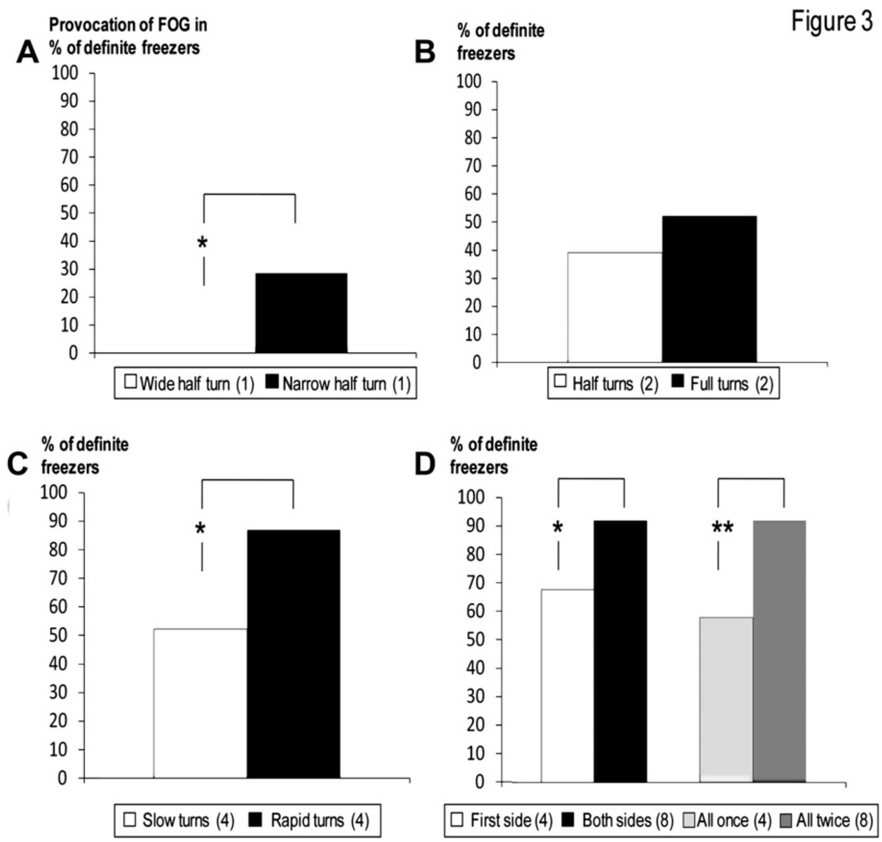

Fig. 3. Provocation of FOG by different testing tests. Percentage of definite (objective) freezers that show FOG upon the different turning tests. Between brackets: number of turns. * = p value between 0.05 and 0.0083. ** = p-value < 0.0083 (Bonferroni corrected for performing 6 comparisons). A: Turning range (Wide versus narrow half turn, $z = -2$, $p = 0.046$). B: Turning extent (Half versus full turn, $z = -0.6$, $p = 0.56$). C: Turning speed (Normal versus rapid turns, $z = -2.5$, $p = 0.011$). D: Side or repetition. Turns to first versus to both sides ($Z = -2.2$, $p = 0.025$), one turn each condition (right, left, normal, rapid) versus two turns each condition ($Z = -2.6$, $p = 0.008$).

both direction (four turns) are as effective – and more efficient – in provoking FOG as an elaborative gait trajectory (three times, including a total of six turns). Indeed, when FOG occurred during the gait trajectory, this was usually during turning.

Narrow turns identified more freezers than wide turns. This is probably because a narrow turn imposes a greater amount of temporal and spatial asymmetry of steps compared to wider turns [20]. The step length of particularly the leg on the inner side of the turn decreases during a narrow turn, and such a decreasing step length can provoke FOG [21].

The observed effect of repetition underscores that examiners should not stop when the first test is normal. It may be speculated that the effect of repetition is caused by the suppression of FOG by initial anxiety of being examined or the attention given to a task when performed for the first time [22]. However, a closer look at our data does not support this: 10 patients showed FOG in the first turns of the conditions, but not in the second, while 6 patients showed FOG in the second turn of the condition, but not in the first. Probably the effect of repetition just highlights the episodic quality of FOG: sometimes it is there and sometimes it is not.

A recent study showed that a combination of full turns with dual tasking elicited most FOG episodes [10]. In this study, 24 turns (of which 12 were full turns) elicited FOG in 50% of 14 subjective freezers. Using eight full turns, we elicited FOG in 66% of a comparable sample of 32 subjective freezers. The 'full turns' used in both studies were different: Spildooren and colleagues used turns around a small marker after walking towards this marker [10], whereas we used turns 'on the spot' from standstill. Another potentially relevant difference is that we requested subjects to turn 'as rapidly as possible' during four of the eight turns, and this may explain the slightly higher diagnostic yield in our study. Importantly, Spildooren and colleagues found that adding a dual task to the turning tasks further improved the diagnostic yield for FOG [10]. This dual tasking benefit was less prominent in our study, likely because their dual task difficulty was better selected and more challenging (specifically, Spildooren and colleagues used a color classification task, for which the load could be varied without increasing the level of difficulty). Indeed, more complex multitask conditions show great sensitivity to balance deficits in PD and correlate better to falls in daily life than simple dual task conditions [23]. A small disadvantage to using dual tasks is the risk of increasing the false-positive classification rate, because it can be difficult to differentiate the akinetic form of FOG from more purposeful stops, as in the 'stops walking when talking' phenomenon [24].

Rapid full turns (four turns) were as sensitive to objectively provoke FOG in subjective freezers as FOG trajectories (three trajectories, including six turns). We propose as an objective test for the classification of freezers in research studies to perform at least eight rapid full turns (four into each direction, 'on the spot', each time from standstill). If negative, a gait trajectory involving dual tasking may be added. Future work now needs to validate this approach. An additional question is whether adding straight walking with short steps (25% of step length) adds something to this classification of freezers [21,21]. Such careful objective testing should be part of future research, thus reducing misclassification in pathophysiology studies.

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