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When motor control gets out of hand: Speeding up triggers freezing in the upper limb in Parkinson's disease

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ABSTRACT

Introduction: Patients with Parkinson's disease (PD) can suffer from sudden movement arrests during upper limb tasks. The current study investigated a test to assess freezing of the upper limbs (FOUL) at two speed conditions to improve the sensitivity of FOUL detection.

Methods: Forty-nine patients with PD and 10 age-matched controls (HC) performed a freezing-provoking writing task, requiring up- and down-stroke writing at varying sizes in-between visual target zones indicating funnel-shapes on a touch-sensitive tablet. They performed five trials at their preferred speed, referred to as the Normal Funnel Task (NFT) and five trials at maximum speed, referred to as the Fast Funnel Task (FFT), in a random order.

Results: Based on a combination of kinematic criteria and video analysis, 183 FOUL episodes were detected in 24 participants (23 PD, 1 HC). The number of patients with FOUL, number of FOUL episodes and percentage time frozen were significantly higher during FFT than NFT. Most FOUL episodes occurred during writing at small (51.6%) and decreasing size (36.3%). Additionally, FOUL outcomes significantly correlated with the Montreal Cognitive Assessment and New Freezing of Gait Questionnaire.

Conclusion: As FOUL is more prevalent under higher task demands, these data offer support for the "threshold model", previously proposed to provide insight in freezing of gait (FOG) and underscoring the presupposed link between FOG and FOUL. As well, this study may provide a novel paradigm to assess FOUL in both laboratory and clinical settings.

1. Introduction

Sudden motor blocks, referred to as freezing episodes, occur not only during gait, but also during repetitive upper and lower limb movements and speech in people with Parkinson's disease (PD) [1]. This symptom can have a tremendous impact on individuals' daily living, most strikingly during gait, as freezing of gait (FOG) hampers mobility and provokes falls [2]. Freezing of the upper limbs (FOUL) also interferes with common functional activities, especially those relying on intact motor control of sequential movements that are largely governed by the basal ganglia, such as typing, driving or writing [3].

In contrast to FOG, research on FOUL is sparse and the factors that provoke it are poorly understood. Most previous studies investigated patients' kinematic properties during finger tapping and bilateral tasks (for a review see Ref. [1]), with ambivalent findings possibly as a result of large differences in task design. Also, patient characteristics, particularly disease duration and severity, have an impact on the likelihood to develop freezing [4]. So far, there is no standardized tool to assess FOUL. In clinical practice, it is generally scored as part of the finger tapping and hand movement items [5,6], components of the Movement Disorders Society – Unified Parkinson's Disease Rating Scale (MDS-UPDRS) part III. However, in a study cohort consisting solely of patients with advanced PD and clinically confirmed freezing, FOUL was only detected in 5% of the trials and in only 3 out of 15 participants while being 'on' medication [6]. A possible explanation lies in the increased attentional level related to an examination in a lab environment, which may temporarily suppress patients' freezing [7]. Remarkably, adding an auditory cue to the finger tapping task, multiplied the occurrence of FOUL from 5 to 21% of the trials. This indicates that FOUL can be provoked by manipulating task constraints [8], similar to gait [9–11]. A disadvantage of finger tapping paradigms [8] is that these strictly controlled bilateral finger movements are difficult to

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translate to uni- or bimanual tasks used in daily life. In addition, in many studies testing occurred while participants were 'off' medication, circumstances that do not match patients' average daily medication state during which most functional activities occur. Previously, we investigated FOUL during unilateral 'writing', within the spatial constraints of a funnel shape. We found that manipulating movement size during this 'Funnel task' successfully triggered FOUL in almost 30% of the tested sample when performed 'on' medication [12]. In line with several but not all other studies on FOUL [1], FOUL occurred more often in people with than without FOG.

To improve the sensitivity of the Funnel task, we relied on the ideas that drove the "threshold hypothesis" [13] to explain FOG. This hypothesis assumes that freezing is provoked as a result of the simultaneous deterioration of multiple movement features such that the motor performance is pushed below an imaginary threshold of movement breakdown. If this theory would also explain FOUL, we expect more freezing episodes during the Funnel task, when manipulating other factors in addition to movement size such as speed. Therefore, the primary objective of the current study was to determine whether imposing a higher speed, while making up and down strokes through a funnel shape, would increase the likelihood of FOUL. Specifically, we expected both the number and duration of FOUL to increase when moving at fast speed. Secondly, we aimed to identify the clinical and demographic characteristics of people with PD that display FOUL. We predicted FOUL to be correlated to disease severity, FOG severity and cognitive capacity [14]. Finally, we aimed to explore the link between task demands, clinical characteristics, FOUL episodes and kinematic abnormalities outside the freezing episodes, acting as precursors of actual motor breakdown or, at best, a more subtle form of motor failure.

2. Methods

2.1. Participants

Forty-nine patients with PD and 10 age-matched healthy controls (HC) participated in the study. We previously investigated the potential of the Funnel task to provoke FOUL in a subset of patients and controls also included in the current study (PD: N = 34; HC: N = 10) [12]. Inclusion criteria for patients consisted of: (i) idiopathic PD, as diagnosed by the UK PD Society Brain Bank criteria [15]; (ii) Hoehn and Yahr stage (H&Y) I-III in the on-phase of the medication cycle; and (iii) presence of writing impairment as defined by MDS-UPDRS part II item 2.7 (score > 1) [16]. Exclusion criteria for both groups were: (i) Mini-Mental State Examination (MMSE) < 24 [17]; (ii) visual impairments hindering the task; (iii) medical problems which would impede handwriting; (iv) a history of depression or neurological diseases other than PD; and (v) deep brain stimulation. The study design and protocol were approved by the local Ethics Committee of the University Hospitals Leuven (S59494) and were in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki, 2013). After explanation of the study protocol, written informed consent was obtained from all participants.

2.2. Experimental procedure and tasks

All participants were evaluated by means of the Montreal Cognitive Assessment (MoCA) [18], Edinburgh Handedness Inventory [19], Hospital Anxiety and Depression Scale (HADS) [20] and Manual Ability Measure (MAM-16) [21]. Patient characteristics were assessed using the H&Y scale, MDS-UPDRS-III and New freezing of gait questionnaire (NFOG-Q) [22]. All tests were carried out while patients were in the stable 'on'-phase, approximately 1 h after medication intake. The experimental Funnel task was similar to the one described by Heremans et al. [12]. It consisted of a 13 cm long trajectory, in which two blue target lines of 2 mm width delineated the areas where participants had to make alternating up- and down-stroke writing movements with a stylus, roughly from the middle of the lower to the middle of the upper blue target line (Suppl. Fig. 1). In addition, patients were shown a practice trial on paper showing the desired density of the strokes. If this differed too much by the end of the trial, participants were shown the example again (Suppl. Fig. 1). Overall, fluent and consistent production of the strokes was encouraged to tap into automatic performance rather than emphasizing accuracy of target hits. The writing areas included large parts of 2 cm width, small parts of 0.6 cm, gradually increasing size parts (from 0.6 to 2 cm) and gradually decreasing size parts (from 2 to 0.6 cm). The Funnel task was performed at two different speeds, i.e. at comfortable pace (normal funnel task (NFT)) and at maximum speed (fast funnel task (FFT)). The task was performed on a touch-sensitive tablet (sampling frequency 200 Hz, spatial resolution 32.5 μm). Every participant completed a block of five trials at normal speed (NFT) and a block of five at fast speed (FFT), presented in random order. They were instructed to perform the task until the end of the 13 cm writing trajectory or, if they did not reach the end of the trajectory in time, until the end of the 1-min (NFT) or 40 seconds (FFT) time span. All trials were separated by 6 seconds breaks. During the task, participants could see their writing trace on the tablet, providing real-time feedback of the writing movements. Tests were carried out in a quiet room while patients were sitting in front of a table on a height-adjustable chair.

2.3. Data processing

Data were processed in Matlab R2011b (Mathworks). FOUL was analyzed in line with Heremans et al. and defined as an involuntary stop or clear absence of effective writing movements during at least 1 s [12]. Pre-defined criteria were used in identifying the FOUL episodes, similar to the procedures used to identify FOG episodes: (i) a reduction of > 50% of the target amplitude, (ii) an irregular change in cycle frequency and (iii) an increase in the freezing index [12]. Video replays of the data were used to distinguish freezing episodes from voluntary stops. Amplitude and frequency for each movement cycle were determined by the difference between the maximum and minimum spatial position per stroke and by dividing the distance of each movement cycle per time needed to complete it (cm/s). The freezing index was quantified as the power in the freeze band (3–8 Hz) divided by the power in the normal motion band (0.5–3Hz) [12]. The primary outcome was the difference in performance of the FFT versus NFT. The main outcome measures were: (i) a binary FOUL measure (1 = occurrence of at least one freezing episode; 0 = absence of freezing); (ii) the total number of FOUL episodes; (iii) the percentage of time frozen during the trajectory; and (iv) the part of the funnel where FOUL occurred. As a secondary measure, we also investigated the kinematics of the parts without freezing. Therefore, the mean movement amplitude and speed of the inter-ictal writing parts were calculated for each part of the writing trajectory separately.

2.4. Statistical analysis

Data were analyzed using STATISTICA (Statistical Analysis Software, version 10) with $\alpha \leq 0.05$. Normality and equality of variance were checked for all variables using Kolmogorov Smirnov and Levene's tests. Clinical characteristics were compared between groups using independent t-tests for normally distributed data, Mann-Whitney U tests for non-normally distributed data and Fisher's exact tests for categorical data. For the main outcome measures, Wilcoxon signed rank tests were used for comparisons between continuous outcomes. The binary FOUL scores were analyzed using McNemar Chi square tests and Fisher's exact tests. Spearman's rank correlations were carried out to test the relationship between the upper limb freezing outcomes, the score on the NFOG-Q and clinical outcomes (age, MMSE, MoCA, HADS-A, HADS-D, MAM-16, disease duration, H&Y stage, MDS-UPDRS-III, Levodopa Equivalent Dose (LED)) in the total group and in the subgroup of individuals with FOUL only (PD + FOUL). PD + FOUL were

Table 1
Demographic and clinical characteristics of study participants.

	PD (N = 49)	HC (N = 10)	P-value PD vs HC	PD + FOUL (N = 29)	PD-FOUL (N = 20)	P-value PD + FOUL vs PD-FOUL
Age (years)	63.4 ± 9.3	65.8 ± 8.4	0.46	63.7 ± 10.1	63.1 ± 8.3	0.83
Gender (M/F)	34/15	4/6	0.08	21/8	13/7	0.40
EHI (%)	100 (88.9–100)	100 (90–100)	0.75	90 (80–100)	100 (90–100)	0.19
MMSE (0–30)	29 (28–30)	29 (29–30)	0.10	29 (28–29)	29 (28–30)	0.21
MoCA (0–30)	26 (25–27)	28.5 (26–29)	0.01	26 (23–27)	27 (26.5–28)	< 0.01
MAM-16 (0–64)	58 (54–60)	64 (64–64)	< 0.01	58 (55–60)	58 (50.5–60.5)	0.71
HADS-A (0–21)	5.5 ± 4.1	3.2 ± 2.0	0.09	5.5 ± 4.0	5.5 ± 4.2	0.99
HADS-D (0–21)	4.5 ± 3.1	2.3 ± 2.2	0.03	4.2 ± 2.9	5.0 ± 3.4	0.41
Disease duration (years)	6.7 ± 4.6	–	–	7.0 ± 5.0	6.2 ± 4.0	0.55
H&Y (0–5)	2 (2–2)	–	–	2 (2–2)	2 (2–2)	0.79
MDS-UPDRS-III (0–132)	30.3 ± 14.8	–	–	30.1 ± 14.4	30.6 ± 15.7	0.89
LED (mg/24h)	492.1 ± 302.4	–	–	506.6 ± 291.1	471.1 ± 324.6	0.69
NFOG-Q (0–28)	0 (0–1)	–	–	0 (0–4)	0 (0–13)	0.21

Abbreviations: PD = patients with Parkinson's disease; HC = healthy control subjects; PD + FOUL = PD patients with upper limb freezing; PD-FOUL = PD patients without upper limb freezing; EHI = Edinburgh Handedness Inventory; MMSE = Mini Mental State Examination; MoCA = Montreal Cognitive Assessment; MAM = Manual Ability Measure; HADS = Hopsital Anxiety and Depression Scale - Anxiety or Depression subscale; H&Y = Hoehn and Yahr stage; MDS-UPDRS-III = Movement Disorders Society - Unified Parkinson's Disease Rating Scale part 3; LED = L-dopa-equivalent daily dose; NFOG-Q = New freezing of gait questionnaire. Results are presented as the mean (± standard deviation) for normally distributed data and as median (1st quartile, 3rd quartile) for non-normally distributed data.

defined as patients who experienced at least one freezing episode during testing, PD-FOUL as those without freezing episodes. The amplitude and speed of the kinematic trajectories outside the freezing episodes were compared between groups by means of a 2 × 2 x 4 repeated measures ANOVA with group (PD + FOUL vs PD-FOUL) as a between-subjects factor and speed (FFT, NFT) and size (small, large, decreasing size, increasing) as within-subjects factors. Tukey HSD post hoc tests were performed where appropriate.

3. Results

PD and HC were matched for age, gender, handedness, HADS Anxiety scale and MMSE scores. PD patients had a worse manual ability (MAM-16: $U = 5.0$, $p < 0.01$), worse cognitive profile (MoCA: $U = 120.5$, $p = 0.02$) and showed more signs of depression (HADS-D: $t(57) = -2.17$, $p = 0.03$) than healthy controls. Additionally, PD + FOUL had a significantly worse cognitive profile than PD-FOUL (MoCA: $U = 146.5$, $p < 0.01$). Clinical characteristics are provided in Table 1.

3.1. Upper limb freezing episodes

Looking at the binary FOUL score, we found at least one freezing episode in 24 out of 59 participants (23/49 PD, 1/10 HC) during FFT, while only in 13 participants (all PD) during NFT, a pattern which was statistically significant ($\chi^2(1) = 12.2$, $p < 0.01$) (Table 2). Regarding the number of freezing episodes, 123 FOUL episodes were detected during FFT and 60 during NFT. This amount was also significantly higher during the fast compared to the normal speed condition ($Z = 1.93$, $p = 0.05$) (Table 2). Similarly, the percentage time frozen was significantly higher during the FFT compared to the NFT ($Z = 2.13$, $p = 0.03$) (Table 2). The part in which FOUL episodes occurred did not differ between FFT and NFT. For both conditions, the majority of FOUL occurred while patients had to write at continuously small or gradually decreasing size (Table 2). FOUL episodes were rare when writing at large or gradually increasing size. Overall, imposing a higher speed increased the sensitivity to detect FOUL.

3.2. Correlations between FOUL, FOG and clinical outcomes

In all participants, all investigated FOUL outcomes correlated significantly with patients' cognitive ability as measured by the MoCA scale during both speed conditions (FFT: binary FOUL score: $\rho = -0.34$, number of FOUL episodes: $\rho = -0.31$; % time frozen: $\rho = -0.34$; NFT: binary FOUL score: $\rho = -0.31$, number of FOUL episodes: $\rho = -0.28$; % time frozen: $\rho = -0.30$) (all $p < 0.05$).

In PD + FOUL, the number of FOUL episodes during both speed conditions correlated with the NFOG-Q scores and this pattern was stronger during NFT ($\rho = 0.65$) compared to FFT ($\rho = 0.43$) (both $p < 0.05$) (Fig. 1). No significant correlations were found between NFOG-Q scores and percentage time frozen. As well, no significant correlations were demonstrated in the PD + FOUL group between FOUL outcomes and any of the other clinical characteristics.

3.3. Upper limb performance outside the freezing episodes

3.3.1. Writing amplitude

A 2 × 2 x 4 ANOVA showed a significant interaction between group

Table 2
Characteristics of the upper limb freezing episodes.

	FFT		NFT	
	PD	HC	PD	HC
Binary FOUL score	0.47 ± 0.50	0.10 ± 0.32	0.27 ± 0.45	0.0 ± 0.0
Number of freezing episodes (per person)	2.5 ± 4.2	0.1 ± 0.3	1.2 ± 2.8	0.0 ± 0.0
% time frozen (per person)	3.8 ± 7.4	0.1 ± 0.2	1.7 ± 4.6	0.0 ± 0.0
Occurrence of FOUL (%): small part	39.5	100	63.7	–
Occurrence of FOUL (%): large part	5.0	–	7.3	–
Occurrence of FOUL (%): increasing part	8.4	–	3.6	–
Occurrence of FOUL (%): decreasing part	47.1	–	25.4	–

For the binary FOUL score, number of freezing episodes and % time frozen, the mean ± standard deviation are presented.
Abbreviations: FFT = fast funnel task; NFT = normal speed funnel task; PD = patients with Parkinson's disease; HC = healthy control subjects; FOUL = freezing of the upper limbs.

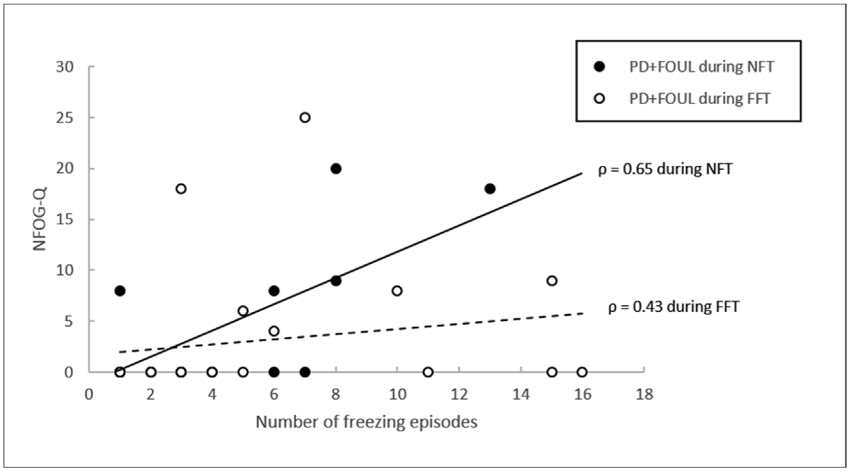

Fig. 1. Number of freezing episodes and patients' scores on the New freezing of gait questionnaire for all PD patients with upper limb freezing during the Normal (NFT) and Fast Funnel Task (FFT). Trendlines represent the significant correlations between both parameters during both speed conditions.

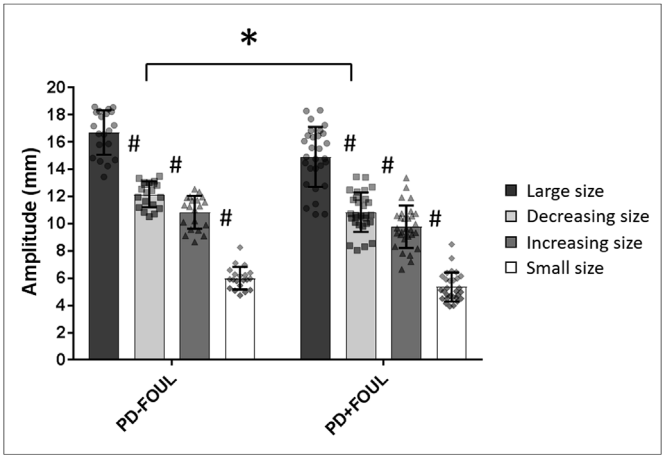

Fig. 2. Writing amplitude (mm) in the interictal parts for patients with and without freezing of the upper limbs. Individual data points are provided in grey. The main effect for groups (indicated with *) shows a significant difference between PD-FOUL and PD + FOUL. The main effect for Size (indicated with #) showed significant differences between all four sizes. Data are displayed as group means and standard deviations. Significance levels are indicated at alpha ≤ 0.05.

and size ($F(3,14) = 5.5$; $p = 0.02$) and between speed and size ($F(3,141) = 65.9$; $p < 0.01$). PD + FOUL moved with significantly smaller amplitude than PD-FOUL during all parts of the trajectory (small: $p = 0.03$; large: $p < 0.01$; increasing: $p < 0.01$; decreasing: $p < 0.01$) (Fig. 2). In both groups, amplitude was higher during the NFT compared to the FFT for the large ($p < 0.01$) and decreasing size parts ($p < 0.01$), but the opposite was found for the increasing size parts ($p < 0.01$). No difference between NFT and FFT was found when writing at small size.

3.3.2. Writing speed

For speed, a 2 × 2 x 4 ANOVA also indicated a significant interaction between speed and size when comparing PD + FOUL and PD-FOUL ($F(3,141) = 15.6$; $p < 0.01$). All patients moved at higher speed during the FFT than NFT ($p < 0.01$ for all comparisons).

4. Discussion

The current study aimed to investigate the robustness of studying the funnel paradigm for freezing of the upper limb (FOUL) by manipulating movement speed on top of movement size. Results revealed that increasing speed more than doubled the number and duration (% time frozen) of freezing episodes and provoked FOUL in about half of the participants with PD. Moreover, significant correlations were found between FOUL outcomes and individuals' cognitive performance and NFOG-Q scores, the latter in the FOUL sub-group only. Finally, exploratory analysis of the kinematics outside the freezing episodes demonstrated that patients with FOUL were more prone to experience motor deterioration in general, irrespective of freezing. Interestingly, PD patients were able to compensate for the loss of movement amplitude in up- and downstrokes requiring an increasing, but not a decreasing size in the fast speed condition.

The current study showed that the occurrence of FOUL multiplies when spatial and temporal task constraints were applied to increase motor load. Moreover, these results were found while 'on' medication and during a unimanual task. The striking speed effects, superimposed on amplitude, on freezing severity is in line with previous work on gait [11] and bilateral upper limb movements [23–25]. Contrary to other studies [6,24,26,27], task speed was not imposed by a metronome in the current paradigm. Instead, patients were simply instructed to perform the writing movement as fast as possible. Although this leads to a less standardized test setting, it has the advantage that movement pace is individualized and that all participants, irrespective of disease severity, are pushed to the limits of their capacity. This could also partially explain the high number of patients experiencing FOUL in comparison to studies using task designs with a fixed rhythm. Altogether, the Fast Funnel Task may be a particularly suitable tool to examine FOUL in clinical practice (see Supplementary materials), as we have demonstrated that it sufficiently loads the motor system even while 'on' medication.

In addition, the Funnel task provides insight in the hypokinetic behavior which is experienced in many patients with PD, and even more so in those with FOUL. A better understanding of these symptoms is fundamental for the development of effective therapeutic strategies to tackle the disabling upper limb motor problems affecting a large part of the PD population. We interpret the fact that when patients reached towards a target line indicating an increasing size, they may have experienced an energizing of movement (also called a cueing effect). Yet when the target line indicated a reduction of performance (decreasing size), undershooting or de-energizing of movement followed. Combining fast speed with declining amplitudes may also be particularly challenging for keeping the neural coding of movement cycles sufficiently desynchronized to allow sustained repetitions [26].

The increase in both FOUL and motor abnormalities outside the freezing episodes during the fast speed condition is consistent with the threshold model [13]. This theory states that manipulating several

seemingly independent factors can jointly cause people to cross an imaginary or critical threshold, resulting in FOG, once a critical load is reached. A significant correlation was observed between all FOUL outcomes and participants' MoCA scores, implying that people with less cognitive capacity are more prone to develop FOUL. This confirms the existing literature on FOG, describing a specific role of cognitive factors in its manifestation [28]. Scholten et al. recently indicated that an increase of left prefrontal beta band synchronization in PD is predictive for upper limb freezing and stated that this increment may underscore the relevance of prefrontal executive dysfunction in freezing susceptibility [29]. As such, freezing has been associated with a motor-cognitive overload in previous studies [30], although disease progression may be a confounder in this relationship.

Despite the significant correlation between FOUL and NFOG-Q in PD + FOUL, FOUL was also observed in a substantial group of non-gait freezers. Interestingly, FOUL outcomes in our study did not correlate with parameters of disease severity. Delval et al. [31] showed that freezing and festination of the upper and lower limbs are observed soon after the diagnosis of PD, and often precede the occurrence of severe gait deficits and FOG. Although this idea needs further study, we can speculate that repetitive movements of segmental effectors at high pace and small amplitude may be an early biomarker to identify patients at risk to develop FOG. However, mechanisms underlying FOUL should not be uncritically translated to FOG [5]. In contrast to some recent studies [6,29], we recommend to include both patients with and without FOG when examining FOUL in the future, as the link between both phenomena can only be examined without selection bias. What is more, freezing probably reflects a continuous motor deficit rather than a dichotomous phenomenon.

A limitation of the current study is the imbalance in number of PD patients and healthy controls. However, we included healthy controls merely to investigate if FOUL sporadically occurred in healthy people [8,31] and no further comparisons were made. Secondly, we did not apply a fixed movement pace for all participants, but instructed them to write either at comfortable pace (NFT) or as fast as possible (FFT). While this pushes all patients to their individual limits, this also leads to less standardized testing.

In conclusion, the current study showed that upper limb freezing is more prevalent under higher task demands, in people with limited cognitive reserve and in those suffering from gait freezing. The Fast Funnel Task may provide a novel paradigm to assess FOUL in a laboratory or clinical setting. We believe that a better understanding and diagnosis of FOUL and related upper limb problems will aid the development of effective therapeutic strategies to improve arm- and hand function in people with PD.

Conflicts of interest

The authors declare no competing interests.

Authors' contribution

All authors contributed to the research design. EH, SB and EN were responsible for recruitment and assessments. EH was principally responsible for data-analysis and drafting of the manuscript. All authors critically reviewed the manuscript and approved the submitted version.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.parkreldis.2019.04.005.

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