The effects of dopaminergic medication and task load on trembling and akinetic freezing of gait in Parkinson's disease

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Abstract

Background: In people with Parkinson's disease (PD), freezing of gait (FOG) can manifest as an absence of leg movement (akinetic) or a presence of high-frequency leg trembling. FOG is triggered most often during turning or dual-tasking when OFF-medication, but it is unclear whether the same holds true for akinetic and trembling FOG.

Objectives: To investigate the effects of dopaminergic medication and cognitive and motor tasks on trembling and akinetic FOG.

Method: Sixty-three PD patients with daily FOG performed a home-based FOG-provoking protocol OFF and ON-dopaminergic medication. FOG was video-annotated based on pre-specified definitions. We compared the % time in trembling and in akinetic FOG between OFF and ON. We also analyzed these outcomes during various motor tasks and with- and without a cognitive dual task. To identify subgroups, an exploratory k-means cluster analysis was performed.

Results: Trembling and akinetic FOG co-occurred in most patients (82.5%), although trembling was observed most frequently. Both manifestations were ameliorated by medication, but we identified 4 different patterns: a responsive mild group (n=32), an unresponsive akinetic-dominant group (n=8), and 2 trembling-dominant groups with (n=12) and without (n=11) a response to medication. Task load also affected the manifestations differentially, as dual-tasking and gait initiation induced more akinetic FOG compared to other conditions.

Conclusions: Trembling and akinetic FOG respond similarly to dopaminergic medication (except for a specific trembling subgroup), yet they are differentially influenced by FOG triggers. Altogether, we suggest that "trembling" may represent a milder form of FOG, although "trembling" as a distinct FOG-variant cannot be rule out.

1 Introduction

Freezing of gait (FOG) in Parkinson's disease (PD) is a complex, episodic and heterogeneous symptom which is incompletely understood [1] and challenging to measure [2, 3]. The term "freezing of gait" seems highly appropriate when FOG manifests itself as an absence of leg movement, known as "akinetic FOG". However, FOG can also be accompanied by characteristic high-frequency oscillations of the legs, known as "trembling FOG", during which forward progression of the feet may still occur [4–6]. Both manifestations may present within the same patient and even in the same episode, and can go together with festination. Festination is defined as a period of increasing cadence and shortening steps, sometimes accompanied by an additional forward lean of the trunk [7]. The distinction between akinetic and trembling FOG is well-recognized and may be relevant for FOG assessment and treatment [4, 6, 8]. With respect to assessment, most sensor-based outcomes of FOG rely on detecting the 3-8 Hz trembling components [9, 10] and therefore are less sensitive to akinetic FOG [11, 12]. As for treatment, evidence is emerging that trembling and akinetic FOG may have a differential response to cueing [12].

Although several studies have described the varying effects of medication on the freezing phenomenon [13–15], it is currently unclear how trembling and akinetic FOG are affected by medication. Only one study, in a small sample with limited akinetic FOG, showed that both akinetic and trembling FOG improved after administration of dopaminergic medication [4]. Moreover, it is currently unknown whether trembling and akinetic FOG are triggered differently by various motor tasks and cognitive load or whether these manifestations involve distinct pathological mechanisms. As both manifestations usually co-occur, it is also possible that they are part of the same spectrum whereby akinetic FOG represents a higher degree of freezing severity. Similarly, festination may be considered a milder form of freezing, as reflected in some scoring criteria [16, 17].

Previous work suggested that trembling FOG represents ineffective attempts of stepping due to misfiring of the locomotor oscillators as a result of receiving faulty basal ganglia output [18–20]. Trembling has also been associated with abnormal coupling between postural preparation and step generation resulting in multiple anticipatory postural adjustments (APAs) [8, 21]. Nonnekes et al. proposed that akinetic FOG is due to impairments in all three basal ganglia loops: motor, cognitive and limbic. In contrast, trembling FOG may reflect relatively preserved cognitive and limbic loops, allowing for some movement to be generated [22–24]. What these three notions have in common is that trembling appears

to indicate unsuccessful attempts to prepare or perform stepping, while akinetic FOG implies a complete inability to do so.

As only a few studies investigated the clinical correlates of FOG-manifestations [4, 11], this study aimed to address some of these open questions. Therefore, we evaluated trembling and akinetic FOG in the practical OFF and ON-medication state in a large group of daily freezers during a home-based FOG-provoking protocol. This allowed us to examine the percentage time frozen (%TF) of these manifestations in response to: 1) dopaminergic medication, 2) cognitive load and 3) various sensorimotor task conditions. We also determined the dominant manifestation per individual in OFF and ON and we explored if we could identify subgroups with distinct manifestation patterns and whether they were clinically different.

2 Methods

2.1 Design

This study was a secondary analysis of the DeFOG trial, a randomized controlled trial aimed to evaluate the effects of on-demand cueing on FOG-severity, pre-registered at clinicaltrials.gov (NCT03978507). The protocol and main findings have been published elsewhere [12, 25]. Here, we evaluated FOG-manifestations during a home-based FOG-provoking protocol at baseline, prior to randomization.

2.2 Participants

Sixty-three patients with PD and FOG were recruited from two sites: Tel Aviv Sourasky Medical Center (TASMC), Israel (n=32) and KU Leuven (KUL), Belgium (n=31). Patients were included if they had a clinical diagnosis of PD, a modified Hoehn and Yahr stage of I-IV in ON, an age of 40-90 years, the ability to walk for 5 minutes unsupported by another person, a score of >16 on the short Mini-Mental State Examination, a stable medication schedule in the past month, and daily self-reported FOG. They were excluded if they fell more than once a day, were unable to perform OFF-assessments or did not show FOG at baseline during or outside the protocol (for detailed eligibility criteria, see [25]). The protocol was approved by local ethics committees at both sites and all patients provided written informed consent before participation.

2.3 Assessment

The protocol was performed in the patient's home environment. After overnight withdrawal of antiparkinsonian medications of at least 12 hours, the measurement started in the practical OFF-state. This consisted of the physical evaluation of motor symptoms using the Movement Disorders Society-Unified Parkinson's Disease Rating Scale (MDS-UPDRS) part III [26] and performance of a FOG-provoking protocol. Approximately 1 hour after intake of the regular morning dose of medication, these tests were repeated in the practical ON-state. In-between test sessions, several questionnaires and clinical scales were administered to characterize the cohort, including the New Freezing of Gait-Questionnaire (NFOG-Q) [27] and Montreal Cognitive Assessment (MoCA) [28] (for details, see [25]). For patients with a deep brain stimulator (DBS), the DBS was kept on and settings were not changed during the study.

The FOG-provoking protocol consisted of different tasks in a fixed order, and was recorded using a video camera [25]. First, patients performed a Four Meter Walk (4MW) back and forth with a 180° turn. Second, the Timed-Up and Go (TUG) was performed 2x in single task (ST) and 2x with a dual task (DT). Next, four 360° turns in alternating directions were performed within a 40x40 cm square in ST and DT. A Hotspot door condition included walking through a narrow passage/doorway and turning 180° in place in a small room (e.g., a bathroom). Finally, patients selected and walked in their Personalized hotspot, which was the place at home where they reported to experience the most FOG. The DT was the serial-3 subtraction task in which patients were asked to count down in steps of three, starting each trial with a different starting number.

2.4 Outcome measure

The primary outcome of this study was percentage time frozen (%TF), expressed as the total duration of FOG relative to the total task duration. %TF was determined for each manifestation by annotating the duration of each task and each FOG-episode based on video recordings of the FOG-provoking protocol using the software Elan [29, 30]. FOG-episodes were labeled as "akinetic", "trembling" or "festination" based on published definitions [12, 25], also in **supplementary material S1**. We dealt with possible intermediate manifestations of FOG (e.g. FOG with non-tremulous leg motion) by deciding whether the characteristics of the episode best resembled trembling FOG, akinetic FOG or festination. Furthermore, episodes were divided into several manifestations if the FOG-characteristics changed, such as when leg trembling began midway through the episode.

To examine the effect of task load, the conditions were compared in two ways. First, to examine the effect of cognitive load, we compared %TF in ST and DT. We pooled the motor tasks in which cognitive load was manipulated in both medication conditions (TUG and 360° turns). Second, to examine the effects of motor load, we annotated each moment the patient was (1) initiating gait, (2) walking, (3) performing a narrow turn, or (4) performing a wide turn. Turns were considered as narrow when they were performed in place, such as the 360° turns executed within a 40x40cm square or at personalized hotspots. All turns that were not performed in place (walking with a curve), were considered as wide. Notably, the number of times each motor condition was performed varied due to the personalization of the protocol. For more details on the annotation and performance of motor conditions, see **supplementary material S1 and S2**.

Inter-rater reliability between centers was published previously based on a sub-sample of 10 patients (for details, see [12, 25]). In brief, the intraclass correlation coefficient (ICC) (2,1) with 95% confidence interval (CI) was 0.81 (0.38; 0.95) for %TF trembling, 0.90 (0.65; 0.98) for %TF akinetic FOG, 0.53 (-0.16; 0.86) for %TF festination, and 0.94 (0.78; 0.99) for %TF total FOG [12]. Due to the small %TF in festination (4.24% of total %TF), festination was pooled with trembling FOG, resulting in an ICC (95% CI) of 0.93 (0.76; 0.98) [12].

2.5 Statistical analysis

Statistical analyses were performed using the Statistical Package for the Social Sciences, version 28 (IBM SPSS Statistics, Chicago, IL, USA) and SAS software, version 9.4 for Windows (SAS Institute Inc., Cary, NC, USA). Alpha was set at 0.05. Linear Mixed Models (LMMs) with an unstructured covariance matrix were used to evaluate our main research questions. For each LMM, an inverse hyperbolic sine (IHS) transformation was applied to %TF, which improved the distribution of the residuals. The benefit of this transformation is that it can be applied directly when the dataset contains zeros [31], unlike logarithmic transformations which require an arbitrary manipulation. Tukey-Kramer adjustments were applied to the post-hoc results to correct for multiple comparisons, and absolute Cohen's d effect sizes were determined based on Satterthwaite degrees of freedom and t-statistics from the model output [32].

First, we evaluated %TF in trembling and akinetic FOG in response to dopaminergic medication, cognitive load and motor load. We investigated this at the group level using 3 LMMs, each with a different condition: (1) medication (OFF, ON), (2) cognitive load (ST, DT), (3) motor load (gait initiation, walking,

narrow turn, wide turn). The LMMs included the following independent variables: center (TASMC, KUL), condition, manifestation (trembling, akinetic) and condition*manifestation.

We also explored the heterogeneity of manifestations in OFF and ON across subjects. The dominant manifestation was determined per individual based on the highest %TF. Furthermore, subgroups were identified using a k-means cluster analysis using 1000 iterations, which optimizes the position for a pre-specified number (k) of centroids. As input, we used %TF trembling and akinetic FOG in OFF and ON. Since this was an exploratory analysis, we selected a k=4 model after a visualization of the output. This resulted in similar groups as a k=3 model, but with an additional distinction between a dopamine-responsive and unresponsive group with otherwise similar characteristics. The silhouette index for the k=4 model was 0.57, representing an adequate similarity within-clusters and a dissimilarity between-clusters (range -1 to 1, higher=better) [33]. These four groups were compared on two outcomes: 1) medication effects and 2) %TF of the manifestations, using a LMM including: center, cluster (k=4), medication, manifestation, cluster*medication, cluster*manifestation, medication*manifestation, and cluster*medication*manifestation. In addition, clinical outcomes were compared between the 4 groups non-parametrically or parametrically, depending on the type and distribution of the outcome (see legend **table 1**).

3 Results

3.1 Participants and protocol

As shown in **table 1**, participants had overall a long disease duration (median (IQR): 11.0 (9.00)) years, a high LEDD (median (IQR): 705 (625)) mg/day, high self-reported FOG-severity (NFOG-Q, mean (SD): 20.7 (3.94)) and presented with mild cognitive impairment (MoCA, median (IQR): 25.0 (4.00)). Confirming the eligibility criteria, all 63 patients showed FOG during the home protocol. During the protocol, walking periods were annotated most often (mean number (SD)=36.5 (12.2) times), followed by narrow turns (36.0 (6.34) times), gait initiation (16.1 (7.56) times), and wide turns (10.2 (6.73) times) (see **supplementary material S2**).

Table 1: Descriptive data and FOG-characteristics of total sample and the subgroups from the cluster analysis.

Descriptives	Total (N=63)	Mild (n=32)	Trembling-responsive (n=12)	Trembling-nonresponsive (n=11)	Akinetic-dominant (n=8)	p-value
Age (years)	68.2 (7.61)	66.3 (6.72)	69.9 (7.48)	72.7 (8.70)	66.9 (7.90)	p=0.080
Disease duration (years)*	11.0 (9.00)	12.5 (9.00)	11.0 (6.00)	9.00 (11.0)	12.0 (15.0)	p=0.997
Gender (Male / Female)^	44 / 19	22 / 10	9 / 3	8 / 3	5 / 3	p=0.937
Presence DBS (Yes / No)^	12 / 51	4 / 28	3 / 9	3 / 8	2 / 6	p=0.608
MDS-UPDRS total, ON	76.2 (20.1)	69.2 (19.1)	78.4 (24.6)	82.4 (13.5)	92.5 (12.3)	p=0.013[a]
MDS-UPDRS III, OFF	44.4 (12.0)	41.4 (12.4)	48.5 (12.5)	43.6 (9.91)	51.4 (8.99)	p=0.103
MDS-UPDRS III, ON	35.6 (11.1)	32.6 (11.8)	35.8 (11.5)	38.8 (6.85)	43.3 (9.13)	p=0.066
MDS-UPDRS III, OFF-ON*	7.00 (7.00)	7.00 (9.00)	11.0 (13.0)	5.00 (7.00)	5.50 (11.0)	p=0.235
UPDRS IV*	4.00 (7.00)	4.00 (6.00)	8.00 (6.00)	3.00 (8.00)	4.50 (8.00)	p=0.430
LEDD (mg/day)*	705 (625)	683 (495)	783 (819)	650 (764)	523 (815)	p=0.361
NFOG-Q	20.7 (3.94)	19.5 (3.63)	20.3 (4.39)	22.2 (3.76)	24.1 (2.30)	p=0.011[a]
MoCA*	25.0 (4.00)	26.0 (4.00)	24.0 (1.00)	24.0 (5.00)	26.0 (3.00)	p=0.109
%N with OFF-FOG^	7.94%	12.5%	8.33%	0.00%	0.00%	p=0.466
%N with dominant trembling FOG, OFF+ON^	63.5%	56.3%	100%	90.9%	0.00%	p<0.001[b]
%N with trembling FOG, OFF+ON^	98.4%	96.9%	100%	100%	100%	p=0.805
%N with akinetic FOG, OFF+ON^	84.1%	84.4%	83.3%	72.7%	100%	p=0.460
%N with trembling & akinetic FOG, OFF+ON^	82.5%	81.3%	83.3%	72.7%	100%	p=0.481

DBS: deep brain stimulation. MDS-UPDRS: Movement Disorder Society-Unified Parkinson's Disease Rating Scale (0-260, part III in ON) [26]. OFF: >12h withdrawal of dopaminergic medication. ON: 1 hour after intake of dopaminergic medication. MDS-UPDRS III: motor assessment (0-132). MDS-UPDRS IV: motor complications (0-24). LEDD: Levodopa equivalent daily dose [34]. NFOG-Q: New freezing of gait questionnaire (0-28) [27]. MoCA: Montreal Cognitive Assessment (0-30) [28]. OFF-FOG: when FOG is present in OFF but not in ON. %N: percentage of people relative to the total sample. %N with trembling and/or akinetic FOG: %N with presence of trembling and/or akinetic FOG. %N with dominant trembling FOG: %N with a higher %TF for trembling than akinetic FOG. IQR: interquartile range. SD: standard deviation. Values are presented as mean (SD) and tested between the 4 subgroups using one-way analysis of variance and Tukey HSD post-hoc tests. When marked by *, values are reported as median (IQR) and tested using Kruskal Wallis Test. When marked by ^, values are reported as percentages or frequencies, and tested using Pearson's Chi-Square with pairwise Z-tests (Bonferroni corrected). [a] Tukey HSD post-hoc analysis revealed a significant difference between the mild and the akinetic-dominant group (MDS-UPDRS total, ON: p=0.014; NFOG-Q: p=0.013). [b] Pairwise Z-tests revealed a significant difference between the mild and trembling-responsive group, and between the akinetic-dominant and all other groups

3.2 Manifestations in response to medication and task load

First, we evaluated the occurrence of trembling and akinetic FOG at the group level in response to dopaminergic medication, as well as cognitive and motor tasks. As shown in **figure 1a**, %TF was higher in OFF than ON (d=0.65, p<0.001) and was higher for trembling than for akinetic FOG (d=0.54, p<0.001). However, medication did not affect %TF differently for trembling or akinetic FOG (medication*manifestation: d=0.08, p=0.515).

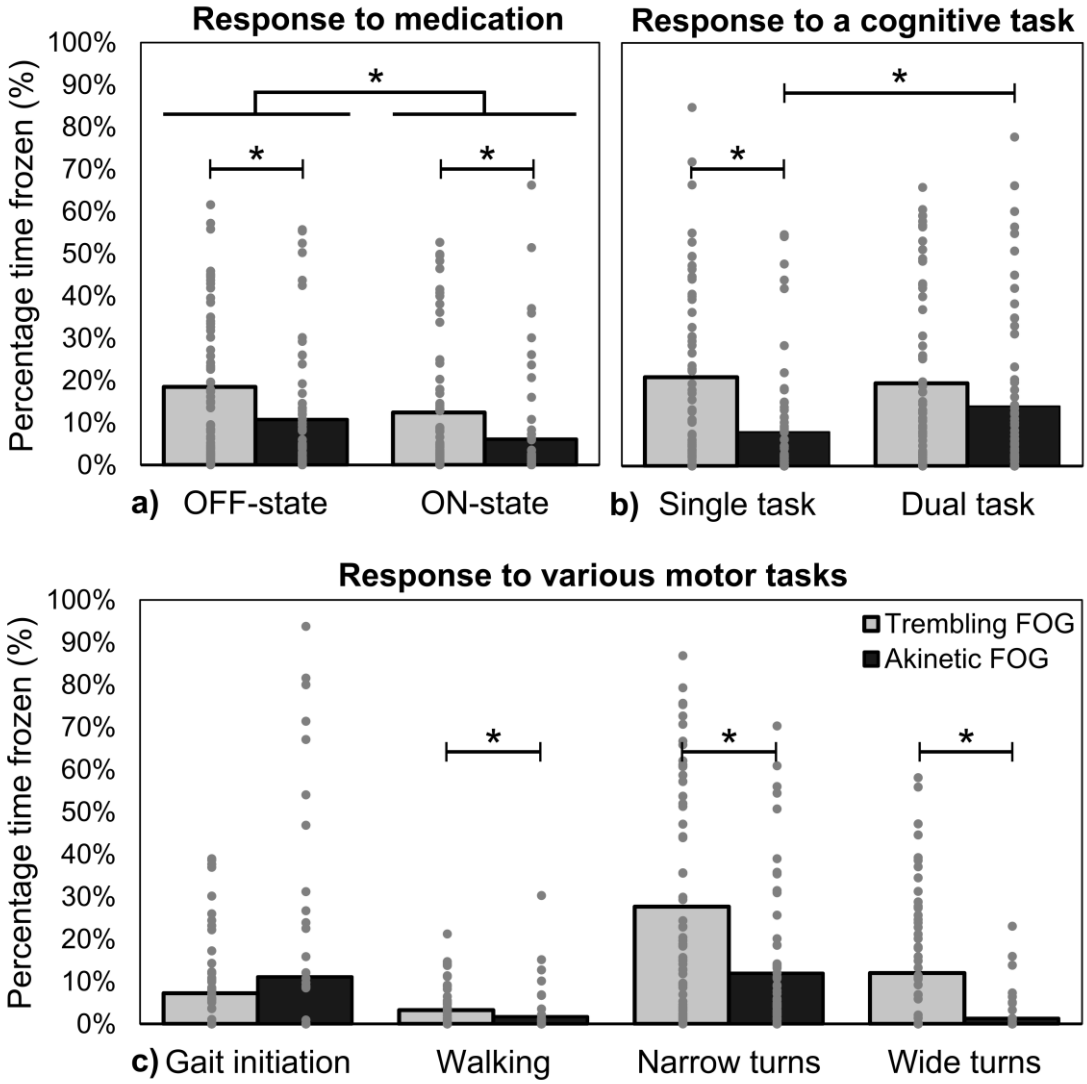

Fig. 1: Manifestations of FOG in response to a: dopaminergic medication, b: a cognitive task and c: various motor tasks. Percentage time frozen is presented as mean with individual data points, for trembling FOG (grey) and akinetic FOG (black). * indicates significant differences between trembling FOG and akinetic FOG and between medication and task conditions (p<0.05). In c, significant differences between motor tasks for trembling and akinetic FOG are not indicated

In contrast, %TF trembling and akinetic FOG were differently affected by the cognitive task (d=0.47, p<0.001) and by various motor tasks (d=0.34; p<0.001). **Figure 1b** displays that akinetic FOG was worse during dual tasking (d=0.55, p<0.001), whereas %TF trembling was similar in both ST and DT (d=0.18, p=0.509). As a result, the dominance of trembling in ST (d=0.64, p<0.001) was no longer significant in the DT condition (d=0.24, p=0.221). When evaluating motor conditions (**figure 1c**), gait initiation appeared to evoke more akinetic than trembling FOG on average. Although this was unsupported by a statistical difference (%TF akinetic=11.1%, trembling=7.26%, p=0.919), it was different from the other motor tasks which elicited a higher %TF in trembling than akinetic FOG (walking: %TF akinetic=1.68%, trembling=3.25%; narrow turns: %TF akinetic=11.9%, trembling=27.7%; wide turns: %TF akinetic=1.33%, trembling=12.0%; ds≥0.54; ps≤0.002). Narrow turns was the most provocative condition for trembling and akinetic %TF compared to the other conditions (ps≤0.009). Gait initiation triggered more akinetic FOG (ps≤0.024) than walking and wide turns.

3.3 Heterogeneity of manifestations in OFF and ON

When exploring individual patterns of manifestations, it was notable that 82.5% of patients had a mixture of trembling and akinetic FOG (**figure 2** and **table 1**). Ten patients only exhibited trembling FOG and 1 person had only akinetic FOG. Despite the similar medication effects on group level, the pattern of improvement of trembling and akinetic FOG was variable between patients. **Figure 2a** shows that the dominant manifestation in OFF was trembling FOG in 40 patients and akinetic FOG in 23 patients. After medication intake, ten patients had a different dominant manifestation compared to OFF. More specifically, six were akinetic-dominant in OFF and became trembling-dominant in ON and 4 showed the reverse pattern. Overall, in ON, 39 and 19 patients had predominantly trembling and akinetic FOG, respectively (**figure 2b**). Five patients did not have FOG in ON (OFF-FOG), of which 1 had missing data for the 360° turns ST and DT.

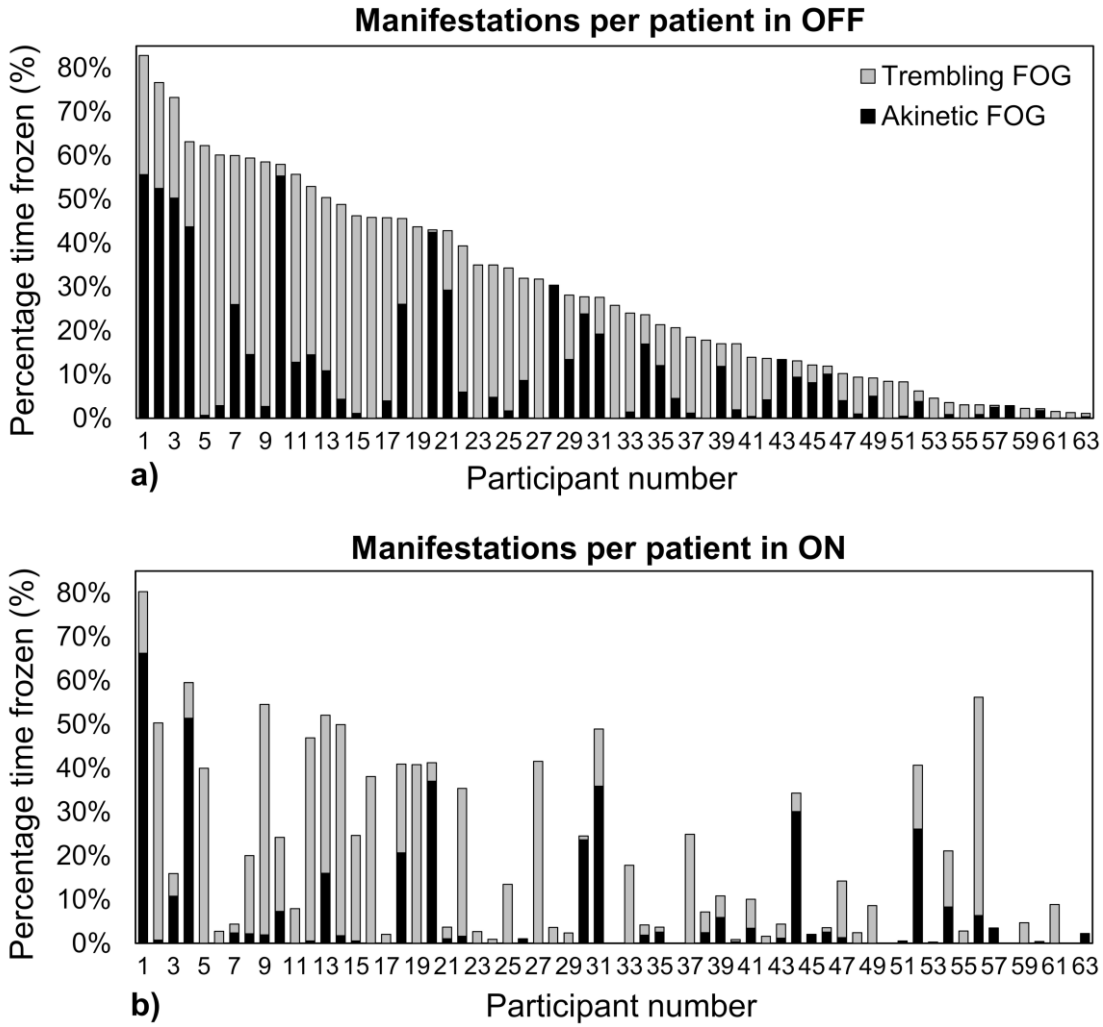

Fig. 2: The manifestation of FOG per participant, a) in OFF and b) in ON. Percentage time frozen is presented as the mean per participant in trembling FOG (grey) and akinetic FOG (black). Participants were ordered from 1 to 63 based on %TF in OFF (numbering matched in OFF and ON)

The cluster analysis resulted in four subgroups with differences in their dopaminergic response (cluster*medication: d=0.66, p<0.001) and different patterns of dominant FOG-manifestations (cluster*manifestation: d=1.27; p<0.001). **Figure 3** shows that group 1 was the largest (n=32), which we termed the “mild” group. Patients presented mostly with mild FOG and similar levels of trembling and akinetic FOG (no manifestation difference: d=0.27, p=0.426). %TF improved significantly in ON (d=0.47, p=0.011) in this group. Patients in the second and third group had severe trembling FOG, but the “trembling-responsive” group (n=12) showed a significant effect of medication on %TF (d=0.82; p<0.001), whereas the “trembling-nonresponsive” group (n=11) did not (d=0.08, p=0.998). Patients in the fourth group (n=8) had predominantly akinetic FOG (see **table 1**), although all patients experienced trembling FOG as well (manifestation difference: d=0.41, p=0.046). In this “akinetic-dominant” group,

%TF in akinetic FOG was higher compared to all other groups (p<0.001) and %TF did not improve by medication (d=0.08, p=0.999). No group differences were found for the relative number of patients (%N) with trembling FOG, akinetic FOG or both. Out of the 5 people with OFF-FOG, 4 were in the mild group and 1 was in the trembling-responsive group (**table 1**). Differences between the groups could not be explained by pooling festination with trembling. For an overview of post-hoc comparisons, see **supplementary material S3**.

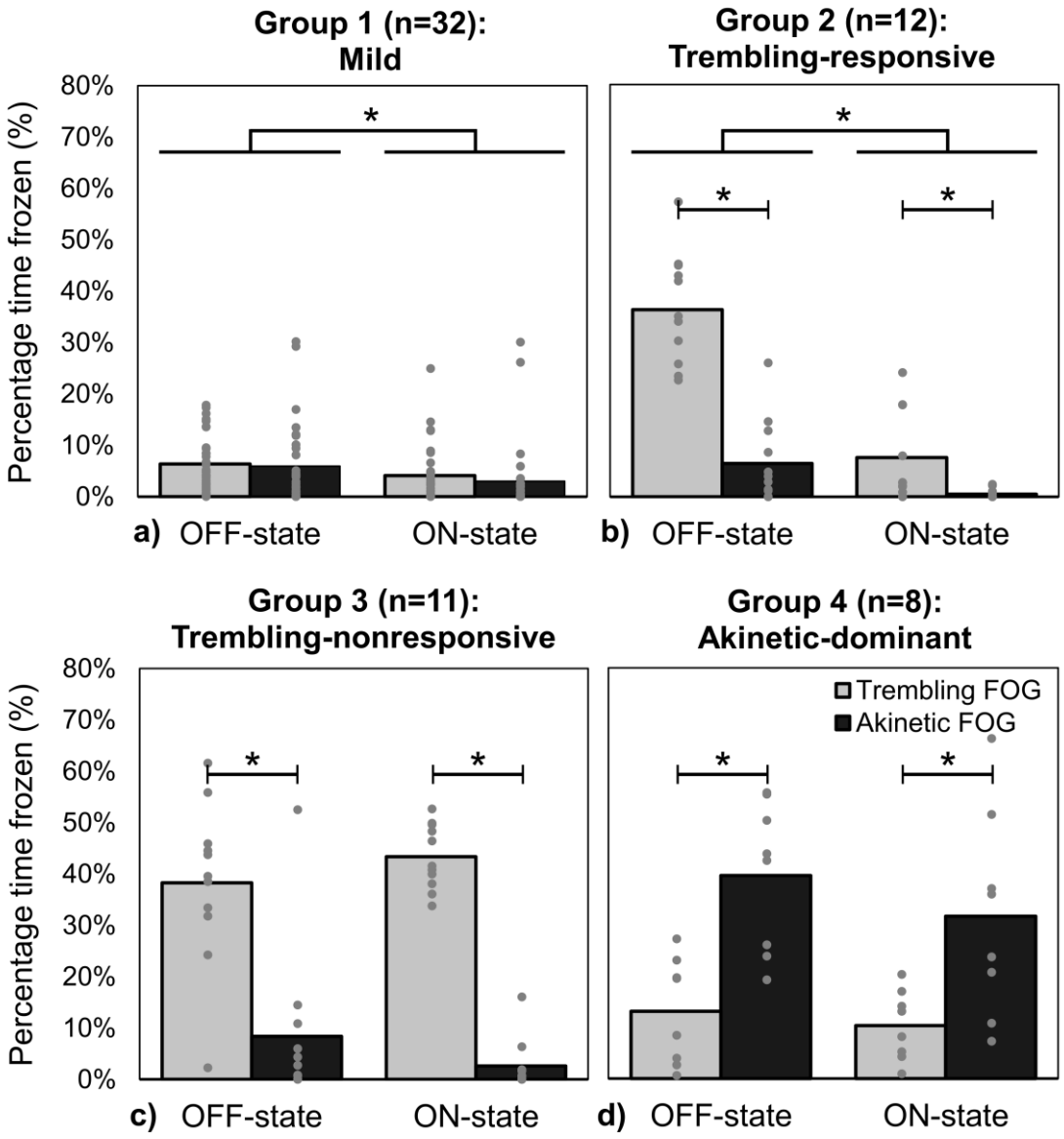

Fig. 3: Clusters of response to dopaminergic medication and FOG-manifestations. Percentage time frozen is presented as mean with individual data points, for trembling FOG (grey) and akinetic FOG (black). * indicates significant differences between the OFF-state and ON-state (post-hoc group*medication) and between trembling FOG and akinetic FOG (post-hoc group*manifestation) (p<0.05)

Clinical characteristics for the four groups are presented in **table 1**. The patients with a DBS were divided well over the clusters (p=0.608). The akinetic-dominant group demonstrated worse severity compared to the mild group on self-reported FOG (NFOG-Q: p=0.013) and disease symptoms (MDS-UPDRS total: p=0.014). Other clinical differences were not significant but visual analysis of the results showed that the akinetic-dominant group had on average preserved cognitive scores and a low LEDD. The trembling-responsive group had the highest average LEDD. Patients in the trembling-nonresponsive group had on average the highest age, the lowest cognitive scores, and lower overall levodopa responsiveness (MDS-UPDRS part III OFF-ON), especially when compared with the trembling-responsive group.

4 Discussion

In this study, we investigated for the first time the prevalence of trembling and akinetic FOG across a wide array of triggering conditions in 63 daily freezers. These tests were conducted in the home setting during FOG-provoking tasks, both in the practical OFF and ON medication states. Corroborating previous work [4, 11], we found that trembling occurred more than akinetic FOG. Nonetheless, most participants presented with a mixture of manifestations (82.5%) and akinetic FOG was dominant in 23 participants (in OFF). In general, dopaminergic medication ameliorated both trembling and akinetic FOG [4]. However, we also identified distinct subgroups with different responses to medication in particular between the two trembling-dominant groups. Furthermore, while trembling was the most pronounced feature, we found that the manifestation of trembling and akinetic FOG depended on the triggering conditions. Specifically, akinetic FOG emerged more during gait initiation than other motor triggers and was worsened by a cognitive DT, unlike trembling FOG.

We did not find a different effect of dopaminergic medication on the global occurrence of trembling and akinetic FOG. However, the pattern of improvement was not consistent at the individual level nor at the subgroup level. Not all akinetic dominant subjects in OFF became more trembling in ON, as in four subjects the reverse was observed, suggesting that dopaminergic mechanisms are involved in both manifestations, but affect patients differently. Previously, different phenotypes of levodopa responsiveness were proposed for FOG in general [13, 14, 35]. In this cohort, we included predominantly people with so-called pseudo-ON-FOG [35] (FOG present in both ON and OFF and not fully resolved by levodopa) and identified only five people with probable OFF-FOG (FOG in OFF only) and no people with ON-FOG. The large heterogeneity of manifestations and their response to medication was also

demonstrated by the four subgroups ascertained by a cluster analysis. We found a significant medication effect in the mild group and the trembling-responsive group, but not in the trembling-nonresponsive and akinetic-dominant groups. Particularly the distinction between responsive and nonresponsive trembling subgroups raises further questions. The clinical characteristics and the number of people with pseudo-ON-FOG in these subgroups were similar, unlikely explaining the differences in medication response. The responsiveness to levodopa in general could have played a role, given that the unresponsive trembling group also showed a lower medication response on the MDS-UPDRS III scores. Finally, it is possible that the freezers in the two non-responsive groups were receiving a sub-optimal dose of medication to effectively alleviate their FOG. Especially in the akinetic-dominant group, it was notable that the average LEDD was very low in relation to the high disease duration and FOG-severity. In addition, we speculate that the cholinergic system may also be differentially involved in the pattern of FOG manifestations, as was found for responsive and non-responsive tremor and fallers and non-fallers [36, 37].

We also demonstrated that exposure to different motor and cognitive task conditions changed the pattern of manifestations. Irrespective of manifestation, FOG is determined by the faulty selection or execution of a motor plan within the automatic gait circuitry [1, 38–40]. Akinetic FOG was more associated with gait initiation and dual tasking than other tasks. During gait initiation, akinetic FOG may occur due to a failure to flexibly overcome sustained inhibition of the selected motor plan after a period of stable stance [1]. Similarly, during the cognitive DT, which induced a continuous load, sustained inhibition may contribute to akinetic FOG. Previous FOG models suggested that neural overload could produce a bottleneck, preventing the generation of stepping [41]. Rather than overload itself, we propose that akinetic FOG may reflect an inability to recruit specific compensatory processes to overcome sustained inhibition, exacerbated by distraction. This aligns with previous work suggesting that freezers exhibit a pronounced disconnection between the frontal lobe and the basal ganglia [42, 43], which may impair compensatory processing. A study on upper limb freezing demonstrated that movement re-initiation after freezing, but not after voluntary stopping, required specific activation of cortical areas involved in attention [44]. Interestingly, behaviorally we found that patients in the akinetic-dominant group tended to have preserved cognition relative to their disease severity (not different from the other groups). Still, intact global cognitive capacity does not rule out the possibility that cognitive distraction

from a dual task could prevent goal-directed motor control from overcoming or bypassing the inhibition of these automatically selected motor programs [44].

As for trembling FOG, we project two possible explanations. First, we found that the trembling groups had lower self-reported FOG-severity and disease severity than the akinetic-dominant group. Nonnekes et al. posited that akinetic FOG may involve a broader range of motor and non-motor circuit deficits preventing step generation, unlike in trembling FOG in which non-motor contributions are relatively intact [23]. We speculate that trembling may represent a “milder” impairment of inhibitory motor control that is unrelated to non-motor involvement. Rather than sustained inhibition, trembling may be governed by subthreshold inhibition, which permits partial execution of the motor plan, but which is repeatedly interrupted as inhibition intermittently reaches the motor threshold without sufficient strength to generate a step. Future longitudinal studies that document FOG manifestations over time are required to confirm whether trembling FOG, and possibly festination, signify a milder form of FOG.

Second, trembling may reflect an erroneous motor output of the locomotor circuits, more likely to occur when having to adjust the motor plan to more demanding motor conditions, such as turning. This mechanism may prompt maladaptive high-frequency oscillations of excitation and inhibition of the muscle activity involved in stepping [23]. These abnormal oscillations were earlier suggested to arise from excitatory projections from the Globus Pallidus internus (GPi) to the Subthalamic Nucleus (STN), and inhibitory back-projections from the GPi to the STN [20, 45]. A recent study in people with predominantly trembling FOG showed that activation-deactivation abnormalities in the STN, picked up with local field potential recordings, heralded rhythmic instability of the gait cycles. Consequently, rhythmic reciprocal inhibition, as assessed with lower limb electromyography, was found to be compromised in the pre-FOG phase as well as during actual FOG [46]. Tentatively, it is also possible that the cerebellar-thalamo-cortical pathways are involved in the trembling features of FOG, as the cerebellum is known to (1) modulate the brainstem’s locomotor region’s output [1], (2) process motor error prediction [47] and (3) partake in the tremor-network [36]. That said, despite the seemingly similar oscillatory motor output, trembling FOG is unlikely to reflect the “classic tremor”, due to its wider frequency power spectrum and paroxysmal nature [5]. Finally, as FOG is not always purely akinetic or trembling and has intermediate manifestations, it is likely that the malfunctioning of different neural pathways are involved in the many abnormal oscillatory phenomena frequently observed in FOG [1, 20].

Unlike what is often assumed, the present results demonstrated that akinetic FOG was substantially present in this cohort of daily freezers (in 84.1% of freezers) [22, 48]. This has important implications, as sensor-based outcomes are increasingly advocated for FOG-measurement and often utilize high frequency trembling for algorithm-based FOG detection [9, 10]. In the absence of prominent trembling, there could thus be a risk of false negative classification of akinetic episodes [11, 12], especially during gait initiation and DT-conditions. Engineers and computer scientists need to take this finding into account when developing FOG detection algorithms. Classification performance to distinguish akinetic FOG from voluntary stopping may benefit from training (deep learning) algorithms on a dataset including akinetic FOG and stops, and/or from adding physiological features of movement [11, 49].

We measured participants at home in the practically defined OFF- and ON-state, and not in supra-ON. Although this complicates the interpretation of medication responsiveness, our paradigm closely reflects the medication states experienced in daily life. Measuring in the home environment was standardized within patients, but the actual home circumstances were different across patients, which may have influenced our findings. Because this study was part of a larger clinical trial, we manipulated the medication and task conditions in a fixed order, and therefore order effects may have affected our results. Also, the cluster analysis was exploratory, and not replicated in a different cohort. Because of the small samples in some subgroups, the results could be sensitive to noise. Although the inclusion of daily freezers is representative of the clinical end-user, the findings may not generalize to less severe freezers and those with ON-freezing [35].

Lastly, classification of manifestations using video annotations is challenging [3] and we strongly recommend to develop new guidelines to improve and standardize this methodology across studies. Consistent with previous work [11, 50], we found that inter-rater reliability for annotating manifestations was lower, though still acceptable, compared to the reliability for marking total %TF. Intermediate manifestations were categorized according to the manifestation which they most closely resembled. At present, there is no consensus on whether festination reflects a separate manifestation of FOG or should be considered a distinct gait problem [5, 17, 48, 51, 52]. In the present study, festination was infrequent, distributed evenly across the subgroups, and pooled with trembling FOG. Future studies should investigate whether trembling FOG and festination have a similar response to medication and triggers as trembling and akinetic FOG.

Taken together, this study addressed some major gaps in the literature on the occurrence of trembling and akinetic FOG, demonstrating several novel findings. First, akinetic FOG is substantially present in daily freezers and although trembling is the dominant feature, both manifestations emerge in most individuals. Second, trembling and akinetic FOG respond similarly to dopaminergic medication, yet are differentially impacted by FOG-triggering conditions. Although neurophysiological tests are required to unravel the precise underlying mechanisms, trembling FOG may indicate a less severe inhibitory impairment compared to akinetic FOG. Finally, there are dopamine-responsive and dopamine-unresponsive trembling-dominant freezers, which suggests that different neural networks could be involved in these distinct subgroups.

5 Statements and declarations

5.1 Funding and competing interests

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5.2 Ethics approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration. The study was approved by the local Ethics committees in Israel (study: 0908-18-TLV) and in Belgium (EC Research UZ/KU Leuven, study: S62453).

5.3 Consent to participate

Informed consent was obtained from all individual participants included in the study.

5.4 Data availability

The data that were used in this study are available on request from the corresponding author.

5.5 Author roles

Conceptualization: AN, JMH. Methodology: DZ, PG, AN. Formal analysis: DZ. Investigation: DZ, PG, TH. Writing – Original draft: DZ. Writing – Review & Editing: DZ, PG, TH, MG, ND, LP, EG, JMH, AN. Supervision: PG, AN, JMH. Funding acquisition: JMH, AN.

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