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Depressive symptoms may increase the risk of the future development of freezing of gait in patients with Parkinson's disease: Findings from a 5-year prospective study

Talia Herman[a,*], Shirley Shema-Shiratzky[a], Liraz Arie[d], Nir Giladi[a,b,c], Jeffrey M. Hausdorff[a,b,d,e]

[a] The Center for the Study of Movement, Cognition and Mobility, Neurological Institute, Tel Aviv Sourasky Medical Center, Tel Aviv, Israel
[b] Sagol School of Neuroscience, Tel Aviv University, Israel
[c] Department of Neurology, Sackler Faculty of Medicine, Tel Aviv University, Israel
[d] Department of Physical Therapy, Sackler Faculty of Medicine, Tel Aviv, Israel
[e] Rush Alzheimer's Disease Center and Department of Orthopaedic Surgery, Rush University Medical Center, Chicago, USA

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ABSTRACT

Introduction: Prospective studies identifying predictors of freezing of gait (FOG) in Parkinson's disease (PD) are limited. We aim to explore which symptoms are associated with future development of FOG in non-freezers.
Methods: Fifty-seven PD patients without FOG at baseline were re-evaluated after a mean of five years. At baseline, disease severity [Unified Parkinson's Disease Rating Scale (MDS-UPDRS)], gait under single and dual-tasking, balance, cognition and other non-motor symptoms were assessed. The new-FOG-questionnaire (NFOG-Q) determined FOG. Multivariate binary logistic regression determined independent predictors of FOG.
Results: At follow-up, 26 subjects (46%) had FOG while 31 remained non-freezers. At baseline, non-freezers (FOG-) and future freezers (FOG+) were similar ($p > 0.10$) with respect to age, gender, disease duration, dopaminergic medications, and cognitive function. However, FOG + had significantly worse scores on the Geriatric Depression Scale (GDS) (FOG+:5.2 ± 3.7; FOG-:2.4 ± 2.0, $p = 0.005$), PDQ-39, the NMS-questionnaire, UPDRS-part I, UPDRS-part III (off), and the Berg Balance Scale. In binary logistic regression, GDS, gait speed and UPDRS-III (on vs. off) were the only significant independent predictors of future FOG (GDS: OR = 10.93, $p = 0.003$, ΔUPDRS-III: OR = 1.34, $p = 0.006$). Moreover, 80% of the subjects who had marked depressive symptoms at baseline (GDS ≥ 5) developed FOG at follow-up. In contrast, only 27% of those with few depressive symptoms at baseline became freezers ($p < 0.001$).
Conclusions: Depressive symptoms apparently precede the development of FOG. While elucidation of the relationship between depression and FOG needs further study, our findings offer another perspective regarding the pathophysiology of FOG and may help clinicians to estimate the risk of developing this debilitating phenomenon.

1. Introduction

Freezing of gait (FOG) is a disabling episodic gait disturbance that is common among patients with Parkinson's disease (PD). In the early stage of the disease, about 20% of patients report experiencing FOG and this percentage reaches up to 80% in the later stages [1,2]. Although this mysterious phenomenon has been extensively investigated, its pathophysiology is still largely unknown and it is not yet clear who are the subjects that will eventually develop FOG as the disease progresses.

Traditionally, FOG has been viewed as a motor symptom related to disease severity. Nonetheless, accumulating evidence supports the hypothesis made by Giladi and Hausdorff in 2006 which suggests that emotional well-being and cognitive function play an important role in the occurrence and possibly the development of FOG [3]. Indeed, stress, anxiety, depression and poor gait performance during cognitively challenging situations have all been related to FOG [4–6]. Recent theories propose that a transient overload of the basal ganglia in response to competing, yet concurrent inputs such as cognitive, sensorimotor and emotional inputs may be associated with FOG [4–6]. Furthermore, the triad of motor disability, cognitive processes and affective symptoms were all independently associated with the severity of freezing, suggesting that one should consider the interplay between motor, cognitive

* Corresponding author. Center for the study of Movement, Cognition and Mobility, Department of Neurology, Tel Aviv Sourasky Medical Center, 6 Weizman Street, Tel Aviv, 64239, Israel.
E-mail address: talih@tlvmc.gov.il (T. Herman).

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and affective domains in the etiology of FOG [5].

Although FOG has been extensively studied, prospective work describing the predictors of the development of FOG in PD are limited. To date, only a few studies have longitudinally followed patients with PD without FOG to explore which risk factors are associated with the development of future FOG. In the prospective 'DATATOP' study, the risk of developing FOG was higher in PD patients with predominant gait, balance and bradykinesia, consistent with the idea that FOG is, primarily, a motor problem. Additionally, a higher degree of depression at baseline (measured with the Hamilton Depression Rating Scale, HAMD), was associated with earlier development of FOG and a risk factor for the development of FOG over the course of a 18 months study [7]. A relative long 12-year follow-up study found, similarly, that motor fluctuations and higher levodopa doses at baseline were independent risk factors for the development of FOG in PD [8]. Multiple factors such as lower education, akinetic-rigid type and sleep disorders were strongly associated with FOG in a sample of 248 patients with PD [9]. Another group has just recently reported on 225 participants. They found that individuals with PD with longer disease duration, lower limb onset and presence of festination, falls, and hallucinations may be prone to develop FOG [10]. Ehgoetz Martens et al. [11] described the prediction of FOG among a large cohort of non-freezers and transitional freezers. Over 15 months of follow-up, the FOG questionnaire (older version) and the anxiety section of the HADS were the strongest predictors of the development of FOG, with an accuracy of 82%.

Taken together, these studies support the idea that changes in motor function and emotional well-being (anxiety and depression) may precede the development of FOG.

These prospective studies exhibit inconsistent results. Heterogeneity in the follow-up period, sample size, motor phenotype, domains that were examined and different assessment tools, along with variations in the definition of FOG, all may contribute to the fact that the clinical predictors of FOG in patients with PD are still uncertain and to discrepancies across studies. Thus, the heterogeneous findings of prior work warrant more and replicable evidence to identify the most robust predictors for FOG and highlight the need for the current study. Furthermore, it is important to keep in mind that relatively short follow-up periods (e.g., 1 or 2 years) for assessing predictors of FOG conversion were described in most of the previous longitudinal studies.

To better evaluate the potential predictors of the development of FOG, we leveraged an existing cohort of 110 patients with PD whose affect, motor and non-motor symptoms were evaluated [12]. Based on the examination of non-freezers at baseline and again 5 years later, we sought to investigate: 1) what percent of patients developed FOG within the 5 years of follow-up? and 2) which baseline subject characteristics and other symptoms contribute to the future development of FOG in patients with PD who do not experience FOG yet?

2. Methods

2.1. Study participants and design

The current analysis was based on a subset of PD patients derived from an earlier study that was originally designed to explore the differences in brain structures between the PD motor subtypes [12]. At baseline, the presence or absence of FOG was assessed via clinical observation and self-report structured questionnaire; the new FOG questionnaire (N-FOGQ) [13]. As part of this process, subjects watched video segments of different types of FOG (with spouse or caregiver when possible) to maximize their understanding of this phenomenon. FOG clinical evaluation was conducted during both OFF and ON medication cycle (Item 3.11 of the MDS-UPDRS). Subjects without freezing of gait at initial testing (N-FOGQ = 0; #3.11 = 0) participated in this longitudinal prospective study. The N-FOGQ and clinical observation was also administrated to determine FOG at follow-up [14].

Subjects in the original cohort were included if they were diagnosed by a movement disorders specialist as having idiopathic PD (as defined by the UK Brain Bank criteria), were between 40 and 85 years of age, and were not demented. Subjects were excluded if they had brain surgery including implanted Deep Brain Stimulation (DBS) or had significant co-morbidities likely to affect gait, e.g., acute illness, orthopedic disease, or history of stroke. In addition, subjects who declared that they cannot walk in the off medication cycle (walking aid was permitted) and patients who could not undergo MRI testing were excluded [12].

Based on the N-FOGQ scores at follow-up, two groups were generated: patients with PD who did not suffer from FOG at both time-points (non-freezers) and subjects who “converted” and became freezers during the 5 years follow-up (transitional freezers). The study was approved by the local institutional ethics committee and all participants provided informed written consent.

2.2. Clinical evaluation

Details with regards to demographics, co-morbidities (e.g., stroke, hypertension, diabetes) and medication usage were obtained. Disease severity was evaluated using the Unified Parkinson's Disease Rating Scale, the MDS-UPDRS [15]; the motor part of the UPDRS was administered both off and on medication. Item 3.11 was utilized to confirm FOG objectively. The levodopa equivalent daily dose (LEDD) was calculated for each subject according to established methods [16]. Several performance-based tests assessed fall risk, gait and functional mobility including the Berg Balance Scale, the Dynamic Gait Index and the Timed up and go test. Participants walked back and forth in a 30 m corridor while wearing a small, lightweight body-fixed sensor (McRoberts, DynaPort Hybrid system, the Netherlands) attached with a belt to their lower back. Gait was evaluated during both single and dual tasking (serial subtraction of threes), first at off and again 45–60 min after medication intake (i.e., “on state”). Gait speed was determined by measuring the average time the subjects walked the middle 10 m of the long corridor. The sensor-based gait measures are described in the Supplementary Material.

Together with the motor examination, we evaluated a range of non-motor symptoms. The short version (15-item) of the Geriatric Depression Scale (GDS) [17] was administrated to assess emotional well-being and depressive symptoms. Subsequently, the GDS score was used as an index to differentiate between subjects with marked depressive symptoms (GDS $\geq$ 5) from non-depressed participants (GDS $<$ 5 points or below). The cutoff point of 5 was chosen based on previous reports [18,19]. In addition to the subjective report of the Geriatric Depression Scale, medications that were prescribed for depression or anxiety were recorded to better understand the influence of mood and mental well-being on the development of FOG. In addition, we examined specific features of the UPDRS part I to evaluate the role of anxiety and hallucinations because of previous reports which identified these as potential predictors of FOG.

We administrated the Activities-specific Balance Confidence scale (ABC) [20] to assess the level of fear of falling. The 30-item Non-Motor Symptoms Questionnaire (NMSQuest) [21] was computed. Additionally, the SCOPA-AUT [22] characterized a variety of non-motor symptoms, e.g., cardiovascular, sleep/fatigue, urinary/gastrointestinal and sexual function. To assess sleep disturbances, the Pittsburgh Sleep Quality Index was administrated [23]. The perceived health-related quality of life was determined using the PDQ-39 [24]. Finally, cognitive capabilities were assessed via the Mini Mental State Exam (MMSE), the Montreal Cognitive Assessment (MoCA) and the Trail Making Tests (TMT) A and B (color version), a classic test of executive function and cognitive flexibility.

2.3. Statistical analyses

Analyses were performed using Statistical Package for the Social

Sciences (SPSS) version 22. Means and standard deviations (SD) were calculated for all dependent variables. We used a two step process to identify independent predictors of the development of FOG. First, baseline differences between future non-freezers and future freezers were determined using Student's t-test or the Mann-Whitney *U* test for continous measures, as appropriate. Dichotomous measures (i.e., gender and the prevalence of depressive symptoms) were compared between groups using the Chi-square procedure. Measures that were significantly different between the two groups based on this initial screening process (i.e., p-value < 0.05) were considered as potential independent predictors for the future development of FOG. Second, these variables were included in backward logistic regression models. To rule out collinearity of the data, the correlation coefficients between independent variables were inspected among the same family of measures. When high correlations (i.e., $r > 0.7$) were found, one of the two correlated variables was removed from the model. The Box-Tidwell procedure was applied to test the linearity of the continuous variables with respect to the logit of the dependent variable. In addition we ensured that the dependent outcome (i.e., presence or absence of FOG) had mutually exclusive and exhaustive categories. A secondary analysis was conducted to explore how anxiety and hallucinations, (i.e., items from the UPDRS-I and NMS) measures that have been previously shown to be associated with the future development of FOG, affect the model. The logistic regression model results are reported using odds ratio (OR) and 95% confidence intervals (CIs).

3. Results

3.1. Participant characteristics

Fifty seven PD patients without FOG at baseline were re-evaluated at a mean of five years later (see Fig. 1). The mean age of the cohort was 65.2 ± 9.5 years, 32% were female, and the mean disease duration was 4.4 ± 2.6 years at baseline. The Hoehn and Yahr (H&Y) staging off medication ranged from 2 to 3.5. At baseline, 49.1% of the subjects were rated as H&Y stage 2, 47.3% as H&Y stage 3 and 3.5% were rated as H&Y stage 3.5.

At follow-up, 31 participants (54%) remained non-freezers (NFOG-Q; item#1 = 0) while 26 subjects reported that they had experienced freezing episodes over the past month of testing (NFOG-Q; item#1 = 1); in other words, 46% of the subjects who were non-freezers at baseline transitioned into being freezers. The average NFOG-Q score describing FOG severity among the transitional freezers was 16.31 ± 7.65. None of the participants at baseline had a score > 1 on the UPDRS-part III, #3.11- FOG item, both off and on. Table 1 summarizes the baseline characteristics of the non-freezers and the transitional freezers. As shown, the two groups were similar with respect to the demographic features and most measures of disease severity. At follow-up, 10 subjects (41.6%) had a score > 1 on the UPDRS- III, (#3.11, FOG item). The Supplementary Material Table 1 summarizes the characteristics of the non-freezers and the transitional freezers at follow-up.

3.2. Motor aspects between non-freezers and the transitional freezers

Gait, balance and other motor measures were similar between the groups at baseline, and only a few variables were significantly different between the non-freezers and the transitional freezers. At baseline, the transitional freezers walked slower and had slightly worse balance, compared to the non-freezers. Interestingly, all other gait features were not different between the non-freezers and future freezers (see Supplementary Material Table 2). The Dynamic Gait Index and the Timed up and Go scores were also similar between the groups. While the total score of the UPDRS did not differ between the two groups, the UPDRS part III in the off medication state (only) was significantly higher (worse) at baseline in the subjects who later developed FOG (see Table 1).

3.3. Depressive symptoms

Patients who developed FOG at follow-up reported a significantly higher burden of depressive symptoms at baseline, compared to subjects who remained non-freezers. The average GDS score among the transitional freezers was significantly higher, 5.15 ± 3.68, as compared to only 2.45 ± 2.03 in the non-freezers at baseline ($p = 0.005$). From another perspective, when we stratified the cohort into subjects with or without marked depressive symptoms, 80% of the subjects who had marked depressive symptoms at baseline (i.e., a GDS score of 5 points or higher) developed FOG during the 5 years follow-up. In contrast, among those with few depressive symptoms at baseline (GDS < 5), only 27% were transitional freezers ($p < 0.001$, see Fig. 2).

To explore the effect of anti-depressant pharmacological treatment, additional analysis revealed that 8 out of the 57 participants (14%) were prescribed with medications such as Citalopram, Clomipramine, Sertraline, Duloxetine or Venlafaxine at baseline. Nonetheless, the prevalence of anti-depressant usage at baseline was comparable between non-freezers and the transitional freezers (Pearson's chi-square; $p = 0.301$).

3.4. Other non-motor aspects in non-freezers and the transitional freezers

Table 1 compares other non-motor symptoms between the two groups at baseline. In general, the transitional freezers reported significantly worse health-related quality of life, represented by scores on the PDQ-39 ($p = 0.012$). Additionally, at baseline, the burden of non-motor aspects of daily living (UPDRS-I total score) was significantly greater in transitional freezers (11.50 ± 6.50), compared to non-freezers (8.03 ± 4.33; $p = 0.020$). Only the transitional freezers reported on hallucinations and psychosis (#1.2) compared to the non-freezers (0.27 ± 0.67 vs. 0 ± 0, $p = 0.025$; respectively). In line with the results of the GDS, depressed mood (#1.3) differed significantly between groups (non-freezers 0.42 ± 0.72 vs. transitional freezers 0.85 ± 0.83; $p = 0.018$). Nonetheless, anxious mood (#1.4) was similar between groups (non-freezers 0.58 ± 0.56 vs. transitional freezers 0.92 ± 0.94; $p = 0.214$).

Subjects who later developed FOG tended to have worse scores in the NMS-questionnaire ($p = 0.058$) and the SCOPA-AUT ($p = 0.083$) compared to the non-freezers. In contrast, the level of fear of falling and all cognitive domains were similar between the groups at baseline ($p > 0.129$).

3.5. Independent predictors of transition to FOG

Table 2 exhibits the results of the prediction model. The GDS index (i.e., the dichotomous score for depression), gait speed and the change in UPDRS-III between on and off medication, were the only significant independent predictors of the future development of FOG. Subjects with marked depressive symptoms (i.e., GDS score ≥ 5) were 10.93 times more likely to develop FOG over the 5 year of follow-up than the non-depressed subjects ($p = 0.003$). Higher change in UPDRS-III scores (on vs. off) was associated with mildly increased odds of developing FOG during follow-up (OR: 1.34; $p = 0.006$). Gait speed had a minor contribution in predicting FOG (OR:0.01; $p = 0.032$). The addition of single items of anxiety and hallucinations scores (based on the UPDRS-I and NMS) to the model did not have a significant effect on these findings, and therefore were not included in Table 2. The regression model which included the GDS index together with the gait speed and ΔUPDRS-III, correctly classified 75.0% of the cases, with a sensitivity of 69.2% and specificity of 80.0%.

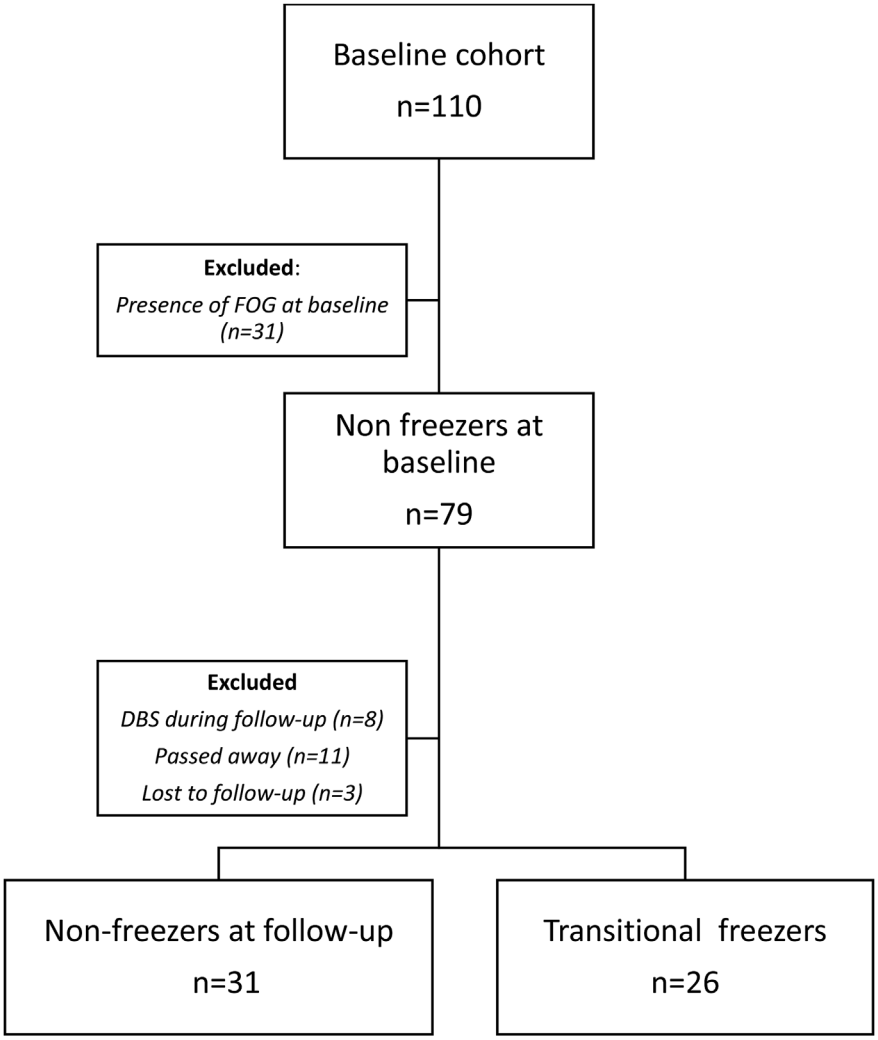

Fig. 1. Flowchart of recruitment and follow-up for FOG.

4. Discussion

The main finding that arises from this investigation is that depressive symptoms apparently precede the development of FOG in a sample of PD patients who did not yet suffer from this phenomenon at baseline. Additionally, more than three-quarters of the subjects who had marked depressive symptoms at baseline developed FOG during the 5 years of follow-up, while less than a third developed FOG among those with few depressive symptoms (recall Fig. 2). Although the transitional freezers had slightly worse performance in gait and balance than the non-freezers at baseline, these motor alterations apparently had only a minor effect on the risk of developing future FOG in our cohort. The burden of health-related quality of life was higher in the transitional freezers as compared to the non-freezers at baseline, which point to the need for early intervention. From another perspective, our finding is in line with the work by Walton et al. [25]. They found that FOG severity was a strong independent contributor to health-related quality of life, likely to stem from the impact of FOG on mobility and independence. These observations highlight the importance of non-motor symptoms, and especially decreased mood, in marking the potential conversion of patients with PD into being freezers.

The current prospective results are consistent with speculation raised back in 2006 [3] and previous reports which suggested that mental aspects play an important role in the occurrence and possibly the development of FOG. Two previous studies reported higher scores on the Hamilton Depression/Anxiety Rating Scale at baseline in freezers [9,10]. In addition, anxiety and depression were also described as potential risk-factors for future FOG [7,9–11]. These two affective disorders frequently accompany PD in various stages of the disease [26]. Thus, it is not surprising that both anxiety and depression may have been associated with the development of FOG.

Previous research demonstrated a link between depression and basal ganglia impairment, particularly involving the left hemisphere, and extends this finding to include anxiety [27]. Anxiety or depression are not only prodromal 'risk factors' for the development of PD, some patients experience anxiety and depression as part of a 'wearing off' phenomenon. This implies that disparate mechanisms such as loss of serotonergic/noradrenergic cells in the brainstem can cause similar clinical features as the hypo-dopaminergic state [28]. A seven-fold loss of nigral neurons has been found in post-mortem brains from depressed PD patients compared to non-depressed [29]. A strong association between depressive and anxiety symptoms and the decreased binding to dopamine transporters in the striatum was observed [28]. Frontal lobe dysfunction, common in PD and manifested by dys-executive syndrome, may also be associated with depression [30]. Thus, frontal pathology may serve as a mediator in the interrelation between depression and FOG [3]. Still, the pathophysiology of depression and anxiety in PD remain complex and are not adequately understood. Further work is needed to understand the time course and the relationship between emotional changes, patho-physiology and the development of FOG.

Although the present results cannot demonstrate cause-and-effect, they may shed light on shared processes of FOG development. Several

Table 1
Subject characteristics of non-freezers and transitional freezers at baseline.

	Non-freezers n = 31	Transitional freezers n = 26	P-value
Demographics and disease related			
Age [Yrs]	65.6 ± 9.3	64.8 ± 10.0	0.759
Gender [M/F]	19/12	20/6	0.206
Education [Yrs]	16.0 ± 3.3	14.8 ± 3.1	0.155
Disease duration [Yrs]	4.5 ± 2.9	4.2 ± 2.3	0.879
Motor subtype [TD/PIGD]	14/17	15/10	0.297
Levodopa equivalent daily dose [mg]	450.4 ± 264.0	435.9 ± 278.8	0.866
UPDRS Total (on)	49.1 ± 15.9	56.9 ± 19.3	0.161
UPDRS Part III (off)	32.52 ± 11.67	39.50 ± 11.70	**0.029**
UPDRS Part III (on)	28.9 ± 11.0	32.3 ± 11.5	0.263
Δ UPDRS III (difference off vs. on)	3.6 ± 4.1	7.2 ± 5.1	**0.005**
UPDRS item#3.11	0	0	1.000
Gait and balance (on)			
Berg balance scale	54.70 ± 2.33	53.10 ± 2.87	**0.003**
Timed up and go [sec]	9.04 ± 2.52	9.69 ± 2.17	0.179
Dynamic gait index	22.26 ± 2.32	22.31 ± 1.46	0.346
Gait speed [m/sec]	1.24 ± 0.21	1.13 ± 0.19	**0.045**
Non-motor symptoms and cognitive function			
Geriatric depression scale	2.45 ± 2.03	5.15 ± 3.68	**0.005**
Non-motor symptoms questionnaire	6.32 ± 3.30	8.80 ± 4.88	0.058
SCOPA-AUT	11.52 ± 7.46	15.58 ± 9.90	0.083
Parkinson's disease questionnaire (PDQ-39)	15.19 ± 9.63	22.81 ± 12.38	**0.012**
Pittsburgh sleep quality index	6.13 ± 4.15	5.81 ± 3.05	0.640
Activities-specific balance confidence scale [%]	92.70 ± 11.57	90.66 ± 10.20	0.155
Mini Mental State Examination	29.13 ± 1.18	28.58 ± 1.79	0.129
Montreal cognitive assessment	25.00 ± 2.72	25.58 ± 3.47	0.238
Trail making test part A [sec]	70.10 ± 40.03	83.85 ± 51.78	0.151
Trail making test part B [sec]	133.45 ± 66.53	139.68 ± 63.32	0.711
Trail making test B-A [sec]	63.35 ± 37.41	64.28 ± 45.50	0.934

Significant values ($p < 0.05$) are bolded.

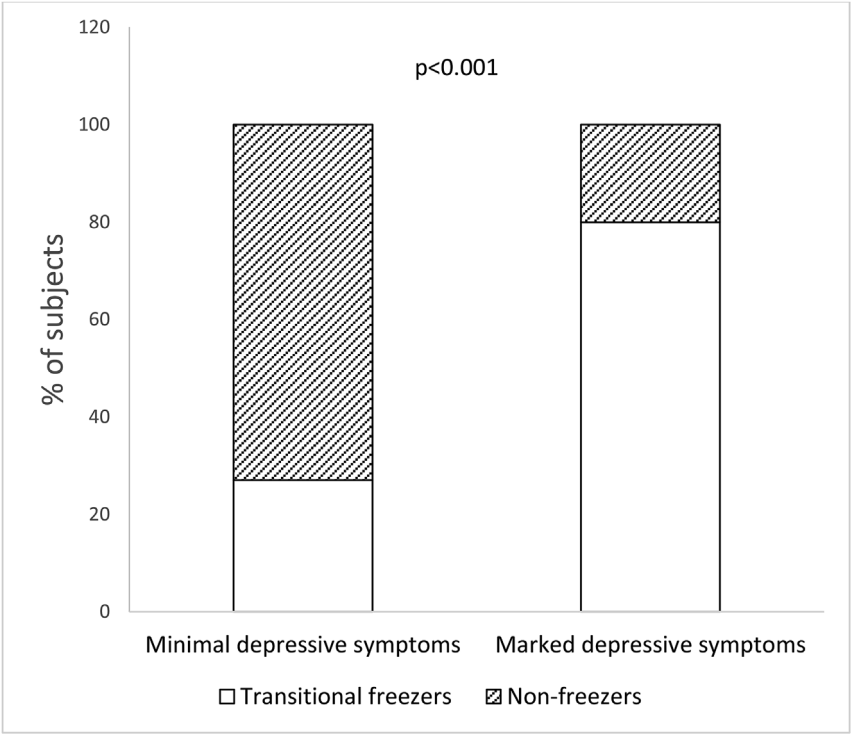

Fig. 2. The percentage of subjects with and without FOG in relation to depressive symptoms, based on scores above or below 5 on the Geriatric Depression Scale. The frequency of future FOG was 3 times higher in subjects with marked vs. minimal depressive symptoms.

hypotheses for the underlying mechanisms have been suggested to explain why and when FOG occurs including abnormal gait pattern generation, failure of central drive and automaticity of movement, problems with coupling of posture with gait, perceptual malfunction and frontal executive dysfunction [2,31,32]. All of these possibilities emphasize the motor, cognitive and visuo-spatial contribution to FOG. Still, the pathophysiologic mechanisms that contribute to FOG remain unclear. Depression and mood changes are not yet typically considered to be a part of the underlying mechanisms in FOG. Nevertheless, the present results are in line with growing evidence suggesting that limbic

Table 2
Motor and non-motor predictors of freezing of gait.

	B (SE)	Odds ratio	95% CI	P-value
Geriatric depression scale index[a]	2.392 (0.813)	**10.93**	2.22–53.81	**0.003**
Berg balance scale	−0.073 (0.174)	0.93	0.66–1.31	0.674
UPDRS-III (off)	0.044 (0.035)	1.045	0.98–1.12	0.216
UPDRS-I	−0.025 (0.081)	0.98	0.83–1.14	0.756
Δ UPDRS III (difference off vs. on)	0.291 (0.105)	**1.34**	1.09–1.64	**0.006**
Usual gait speed (on)	−4.575 (2.131)	**0.01**	0.00–0.672	**0.032**

Significant independent predictors are bolded.
[a] Dichotomous index stratified by the cutoff point 5 to screen for depression.

involvement and mood disturbances might be considered in the mechanisms of FOG [3,33,34].

FOG and depression are similar in nature as they encompass multiple brain regions, and tend to be more prevalent in patients with PD at the more advanced stages [2]. Accumulating evidence from neuroimaging studies suggest that multiple cortical, subcortical and limbic brain regions are involved in depression along with some connectivity abnormalities in cortico-limbic networks [35]. The majority of PD patients will eventually develop FOG as the disease progresses [1,2], and the current findings suggests the interesting probability that absence of depression at relatively early stages of PD either plays a role or marking another mechanism that might protect against the development of FOG. At the same time, one can cautiously speculate whether medical intervention targeting depression and/or anxiety might delay FOG onset. Antidepressant medication usage in our cohort did not differ between the groups thus we cannot answer this question at the moment nor can we rule out the pharmaco-therapeutic potential effect on FOG. Furthermore, one should bear in mind that non-motor symptoms such as depression and anxiety are often misdiagnosed, under-estimated and not adequately treated in many patients with PD [36]. This notion should be further investigated in research and in clinical fields.

Still, our results suggest the intriguing possibility that similar to olfaction deficits (i.e., decreased smell), RBD, and constipation that are evidently prodromal signs that precede PD diagnosis, mood alterations in early stages may precede FOG onset later. It remains to be determined whether anti-depressants and other medications that improve mental aspects can help to delay FOG onset.

The present study has several limitations. Perhaps, most importantly, in the current work, unfortunately, we did not use a designated questionnaire (e.g., HADS) to assess anxiety, a mental function that has been previously found to be associated with FOG. Since anxiety and depression often co-occur in PD [37] it is possible that anxiety contributed in part to the prediction of FOG. When we used the anxiety items of the UPDRS, we did not find that it was predictive of FOG, however, this single item may not optimally capture anxiety in the way that designated tests do. The follow-up was conducted at one time point, only after a mean of 5 years. Therefore, the exact time of conversion during the course of the disease is unknown, and the interesting question of whether the early convertors differed from the later ones cannot be answered. This relatively longer period of follow-up, as compared to the literature (e.g., 1–3 years) may also explain some of our negative findings. Somewhat surprisingly, we did not observe associations between gait, balance, speech, LEDD and sleep and future FOG. Perhaps the time from testing and appearance of FOG plays a role here. It could be that testing closer to the development of FOG would reveal common associations with FOG that were not found in the current study. FOG was determined using self-report validated questionnaire and clinical observation by movement disorders specialists as well as by observation in both OFF and ON medication. Thus, it is likely to be quite reliable. However, FOG was not quantified with body-worn sensor or other equipment. Lastly, even though our sample size was sufficient to detect group differences, a larger cohort would be beneficial and might enable generalization of the findings. Still, the key findings which suggest that emotional well-being precedes the development of FOG are not likely to be affected by these limitations.

At the same time, the strengths of the present work derive from several facts. First, unlike many previous reports, our non-freezers and the transitional freezers were similar at baseline with respect to age, disease duration and LEDD. This similarity enabled us to explore associations and prediction of FOG beyond disease severity and L-dopa effect, which is important since those variables are closely associated with FOG. Second, our follow-up study was conducted after 5 years, a relatively long period, whereas some groups used only 1–3 years, much closer to the onset of FOG, impinging on the interpretation of the results. Finally, the association between depressive symptoms and future FOG were very strong and notable through several different clinical tools (i.e., GDS, mood items of the UPDRS-I and the NMS questionnaire), suggestive of its robust quality.

Regarding the longitudinal nature of this work, it is still unknown how many subjects will eventually become a freezer. A longer follow-up period is needed. Furthermore, it would be interesting to determine if an unlimited follow-up period shows that all the individuals from the present cohort eventually convert to freezers and to assess whether the transition from a non-freezer to future freezer is just a matter of time. Additionally, in the future, it will be motivating to further evaluate the possible existence of different FOG phenotypes, as suggested recently by Ehgoetz Martens et al. [33] and the relationship to emotional well-being. They investigated the neural mechanisms of FOG heterogeneity and concluded that functional connectivity during freezing is correlated to particular cognitive, motor and limbic features. Even so, early identification of patients with PD who have an increased risk of developing FOG will be valuable for the patients, caregivers and healthcare planning by improving treatment strategies in the future.

Disclosure of conflicts of interest

TH, LA, SS declare no financial or other conflicts of interest.

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Prof. Giladi serves as a member of the Editorial Board for the Journal of Parkinson's Disease. He serves as consultant to Teva-NeuroDerm, Biogen, Pharma2B, Denali, Abbvie, AccelMed, Monfort and UCB. He receives royalties from LTI and payment for lectures at Teva, UCB, Abviee, Bial and Movement Disorder Society. He received research support from the Michael J. Fox Foundation, the National Parkinson Foundation, the European Union 7th Framework Program and the Israel Science Foundation as well as from Teva NNE program, Biogen, LTI, and Pfizer.

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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.2018.09.013.

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