Evidence for Subtypes of Freezing of Gait in Parkinson's Disease

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ABSTRACT

Background: The purpose of this study is to identify and characterize subtypes of freezing of gait by using a novel questionnaire designed to delineate freezing patterns based on self-reported and behavioral gait assessment.

Methods: A total of 41 Parkinson's patients with freezing completed the Characterizing Freezing of Gait questionnaire that identifies situations that exacerbate freezing. This instrument underwent examination for construct validity and internal consistency, after which a data-driven clustering approach was employed to identify distinct patterns amongst individual responses. Behavioral freezing assessments in both dopaminergic states were compared across 3 identified subgroups.

Results: This novel questionnaire demonstrated construct validity (severity scores correlated with percentage of time frozen; $r = 0.54$) and internal consistency (Cronbach's $\alpha = .937$), and thus demonstrated promising utility for identifying patterns of freezing that are independently related to motor, anxiety, and attentional impairments.

Conclusions: Patients with freezing may be dissociable based on underlying neurobiological underpinnings that would have significant implications for targeting future treatments. © 2018 International Parkinson and Movement Disorder Society

Key Words: Freezing of gait; Parkinson's disease; motor; cognitive; affective; limbic; heterogeneity

Freezing of gait (FOG) remains one of the most poorly treated symptoms of Parkinson's disease (PD) with a devastating impact on quality of life.[1] Clinical observations have noted that different situations provoke FOG in different patients,[2] which has led clinicians and researchers to question whether multiple subtypes of freezing may exist.[3] Here, we examined whether specific environmental triggers, in conjunction with dopaminergic responsiveness, might distinguish subtypes of freezers who underwent detailed neurological phenotyping. The ability to accurately distinguish and appropriately identify an individual's freezing subtype provides the first step toward a much-needed, evidence-based opportunity to tailor management and allow more targeted and individualized intervention.

Methods

Participants

A total of 41 PD patients with confirmed FOG participated in this study and completed the Characterizing Freezing of Gait (C-FOG) questionnaire (see Supplementary Materials for a detailed description), along with the FOG Questionnaire (FOG-Q),[4] the Parkinson's Anxiety Scale,[5] the Mini-Mental State Exam,[6] and the Trail Making Test Parts A and B (Table 1). MDS-UPDRS part III[7] was assessed in both the ON and OFF dopaminergic state. In addition, motor asymmetry was also calculated from items 3.4 to 3.8 by subtracting the sum of the right items from the sum of the left (OFF state). This study was approved by ethics board at the University of Sydney, and all participants provided written informed consent.

Procedures

Gait was assessed using 8 walking trials[8] (see Fig. 1A) during both the OFF (after a minimum of 12 hours withdrawal) and ON dopaminergic state. The order of testing was counterbalanced across patients. All walking trials were video recorded and randomly

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TABLE 1. Demographic information for the whole sample and each subgroup of freezers

	All freezers, n = 41	Asymmetric-Motor, n = 13	Anxious, n = 15	Sensory-Attention, n = 13
Age, m (SD)	68.4 (8.3)	68.2 (9.3)	66.8 (8)	70.5 (7.8)
Gender	29 M	8 M	11 M	10 M
Disease duration, m (SD)	9.9 (4.5)	8.6 (4.8)	12.3 (3.6)	8.7 (4.1)
Hoehn & Yahr, m (SD)	2.6 (0.68)	2.5 (0.9)	2.8 (0.7)	2.7 (0.4)
UPDRS-III ON, m (SD)	35.6 (13.4)	30.9 (16.6)	38.7 (10.1)	37.7 (12.0)
UPDRS-III OFF, m (SD)	40.7 (11)	**34.6 (11.9)**[a]	**44.9 (9.6)**[a]	43.1 (8.7)
Motor asymmetry, asymmetric: bilateral	22:19	**11:2**[a]	6:9	5:8
FOG total, m (SD)	11.5 (3.9)	10.7 (3.3)	11.7 (3.0)	11.8 (5.3)
MMSE, m (SD)	28 (1.8)	28.5 (1.7)	27.4 (1.9)	28 (1.9)
TMT A, m (SD)	−0.45 (1.6)	−0.02 (1.3)	−0.79 (2.1)	−0.57 (1.2)
TMT B, m (SD)	−0.81 (1.77)	−0.32 (1.7)	−1.24 (2.1)	−0.87 (1.34)
PAS, m (SD)	12.9 (7.3)	9.9	15.5 (6.8)	13.2 (9.6)

SD, standard deviation; MDS UPDRS-III, Movement Disorders Society Unified Parkinson's Disease Rating Scale Motor Subsection; PAS, Parkinson Anxiety Scale; TMT, Trail Making Test; MMSE, Mini-Mental State Exam; FOG-Q, Freezing of Gait Questionnaire; M, male.
[a]Bolded values denote significant group differences at the $P \leq .05$ level.

distributed among 6 independent scorers (M.J.G., J.M.H., A.J.M., M.G., J.Y.Y.S., and K.E.M.). FOG was defined as any point when a participant made a paroxysmal cessation of normal progress.[9] The percentage of time spent frozen (%FOG) was calculated for each trial. Interrater variability strong across all conditions (Cronbach's $\alpha = .980$).

Statistics and Results

To assess the concurrent validity of the C-FOG, we correlated the C-FOG items 1.1 (ie, "How often do you experience freezing of gait?") and 2.0 (ie, "How long do your freezing of gait episodes typically last?") with the total score from the FOG-Q.[4] To determine construct validity, C-FOG items 1.1 and 2.0 were correlated with %FOG. Significant associations were found between C-FOG item 1.1 and question 3 of the FOG-Q ($r = 0.47$, $P = .011$), the FOG-Q total ($r = 0.4$, $P = .041$), and the %FOG in the OFF state ($r = 0.41$, $P = .019$), indicating concurrent and construct validity. Furthermore, responses on C-FOG item 2.0 were also significantly correlated with %FOG in the OFF state ($r = 0.54$, $P = .002$). Finally, for the 12 items examining the common situations that provoke FOG, Cronbach's α was .937, indicating internal consistency.

Clustering Analysis

We used a data-driven approach to identify clusters that putatively represent previously unrecognized freezing subtypes. To demonstrate the utility of this approach, we next determined whether patients within separable freezing subtypes were characterized by distinct phenotypic measures across motor, affective, and cognitive domains. To this end, demeaned responses on section II were correlated with one another using Spearman's ρ (Fig. 1C). From this matrix, a weighted and signed version of the Louvain algorithm ($\gamma = 1$) was used to cluster these 12 items.[10] A 3-cluster solution was associated with a modularity statistic (Q) of 0.805, indicating marked community structure within the data (see Fig. 1C and Supplementary Table e1). To further characterize these clusters, we calculated an average demeaned subscore for each of the 3 clusters in each participant. Spearman's correlations were completed to examine the relationship between each cluster subscore and participants' clinical phenotypes, including %FOG and FOG-Q totals. A *k*-means analysis ($k = 3$; 100 iterations) was performed to classify each participant into 1 of the 3 freezer subgroups based on their 3-cluster subscores (the value of k was chosen to match the dimensionality found by the Louvain algorithm). Demographic group differences were examined between the 3 freezer subgroups. Finally, group differences between the clustered subscores were compared using independent *t*-tests that were planned a priori, and clustered subscores were compared within groups using paired-samples *t*-test. Because of the exploratory nature of this study, multiple-comparison corrections were not employed.

Results

Distinct associations between each of the clusters and the demographic outcomes were identified (Fig. 1D). Although cluster 1 had a significant negative association with motor symptom severity in both the dopaminergic ON ($r = -0.41$) and OFF ($r = -0.37$) states, cluster 1 also showed a significant positive association with motor asymmetry ($r = 0.34$), which revealed that greater left motor symptomology was associated with freezing in doorways while turning and initiating gait. In contrast, cluster 2 demonstrated a significant positive correlation with anxiety scores ($r = 0.41$), whereas cluster 3 had a significant

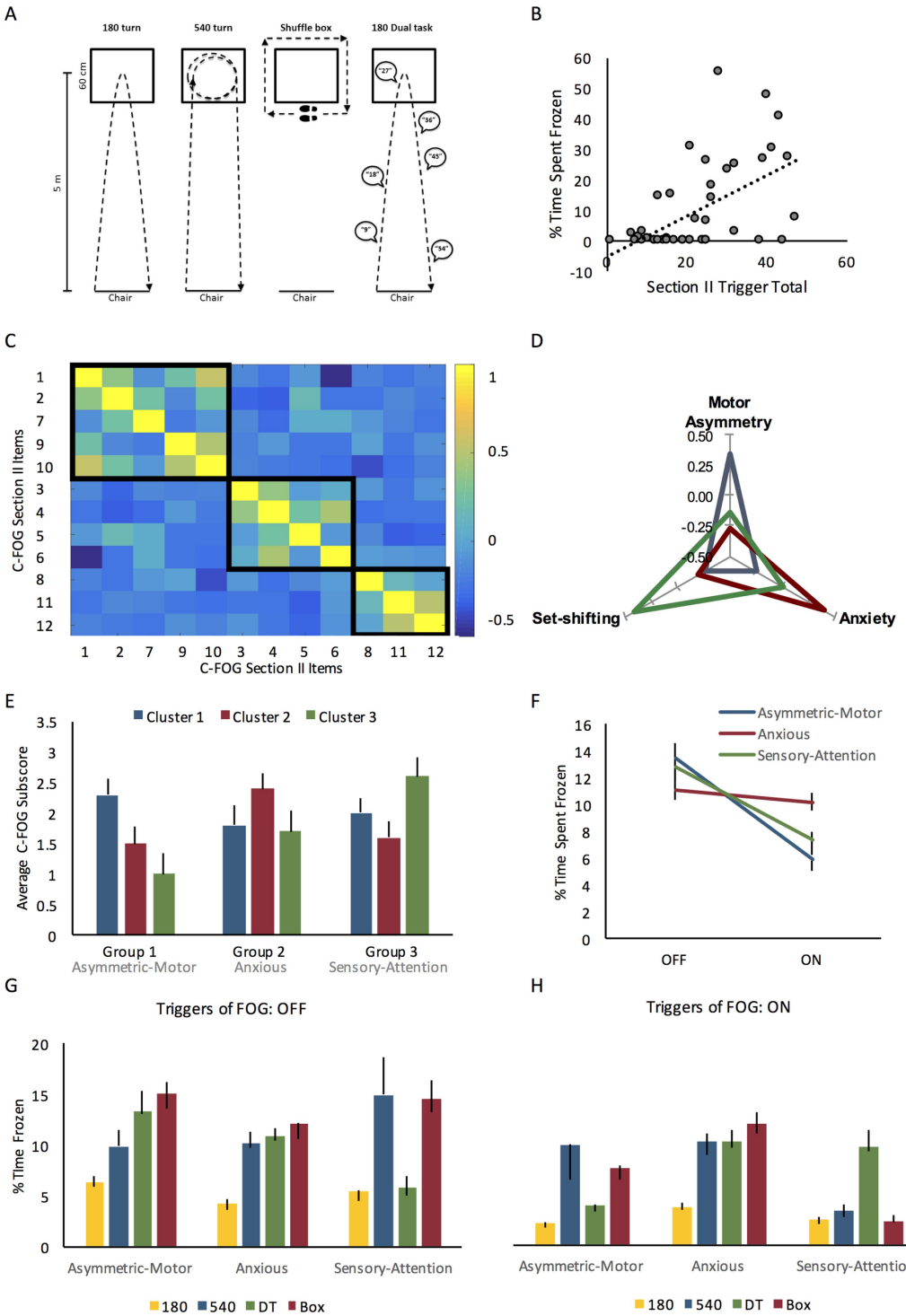

FIG. 1. (A) The modified timed gait assessment protocol. (B) The relationship between the Characterizing Freezing of Gait (C-FOG) section II total and the average percentage of time spent frozen during the timed gait assessments. (C) The similarity matrix of the C-FOG section II items ordered based on the Louvain clustering solution (which is also reported in Supplementary Material). (D) The correlation coefficient for each cluster and its relationship to motor asymmetry (bradykinesia), the score on the Parkinson's Anxiety Scale, and the performance on the Trail Making Task Part B. (E) The average subscore for each group on the section II of the C-FOG. (F) The effect of dopaminergic medication on the percent of time spent frozen during the timed gait assessment across each group. (G) The effect of condition during the timed gait assessment on the percentage of time spent frozen in the OFF dopaminergic state across each group of freezers. (H) The effect of each condition on the percentage of time spent frozen in the ON dopaminergic state across groups. DT, dual task. [Color figure can be viewed at wileyonlinelibrary.com]

relationship with attentional set shifting ($r = -0.42$). All clusters were also positively related to freezing severity measured by the percentage of time spent frozen (cluster 1, $r = 0.60$; cluster 2, $r = 0.43$; cluster 3, $r = 0.42$). Given the dissociable relationships between each cluster and the common characteristics

across the items within each cluster, we hereafter refer to the 3 freezer subgroups according to the related phenotype (ie, group 1, asymmetric-motor; group 2, anxious; group 3, sensory-attention).

Group 1 demonstrated less severe motor symptoms in the OFF state when compared with group 2 ($F_{2,35} = 3.64$, $P = .035$) and had a greater proportion of PD patients with asymmetric rather than bilateral motor impairment when compared with group 2 ($\chi^2 = 5.8$, $P = .016$) and group 3 ($\chi^2 = 5.85$, $P = .016$). There were no other statistical differences between the subgroups (Table 1).

Group 2 had the greatest score on the anxious-related items when compared with group 1 ($t_{26} = -2.19$, $P = .038$) and group 3 ($t_{26} = -1.81$, $P = .082$; Fig. 1E). In addition, group 3 had the greatest score on the set shifting–related items when compared with group 1 ($t_{24} = 4.12$, $P < .001$) and group 2 ($t_{26} = 2.23$, $P = .035$). There were no statistical differences between any of the subgroups on the motor-related items.

Many significant differences were identified when the effects of different situations within each subgroup were compared. Freezers in group 1 reported most commonly experiencing freezing on motor-related items (eg, initiating gait, turning and walking through doorways), and their average score on the motor-related items was significantly greater than both the anxious-related items ($t_{12} = 4.12$, $P = .001$) and the set shifting–related items ($t_{12} = 7.2$, $P < .001$). Group 1 also reported higher scores on average for the anxious-related items (eg, when rushed, anxious, and distracted) compared to the set shifting–related items (eg, walking in the dark, clutter or on a slope; $t_{12} = 2.9$, $P = .034$). Freezers in group 2 reported most commonly experiencing freezing on anxiety-related items compared to both the motor-related items ($t_{14} = -3.91$, $P = .002$) and the set shifting–related items ($t_{14} = 4.34$, $P = .001$). Finally, freezers in group 3 reported most commonly experiencing freezing on set shifting–related items compared to the motor- and anxious-related items ($t_{12} = -3.67$, $P = 003$; $t_{12} = -5.5$, $P < .001$). Group 2 also reported higher scores on average for the motor-related items compared to the anxious-related items ($t_{12} = 2.5$, $P = .028$).

As a result of the smaller cohort with walking assessments, bootstrapping with replacement (100 samples) was used to estimate confidence intervals within each walking condition (reported in Supplementary Tables e2 and e3). When collapsed across walking conditions, groups 1 and 3 displayed worse FOG in their OFF state (ie, increased average percent time spent frozen), which was substantially reduced when tested in their ON state (Fig. 1F), whereas this pattern was not present in freezers from group 2.

In the ON state (Fig. 1H), group 1 demonstrated the majority of their freezing during the walking trials with a 540° turn, and substantially less freezing while performing the walking trials with dual task or 180° turn. Group 2 demonstrated a similar amount of freezing across all 3 walking conditions (540° turns, dual task, and Box Shuffle) compared to 180°. Finally, group 3 demonstrated most of their FOG while performing the dual task with substantially less freezing across the other 3 conditions.

In the OFF state, the pattern of freezing among the different subtypes of freezers changed (Fig. 1G). Overall, walking around a tight square (ie, Box Shuffle) became one of the most provocative conditions across all the subgroups of freezers. Group 1 experienced substantially more freezing when performing the dual-task walking trial, whereas group 3 experienced substantially more freezing when performing the walking trial with a 540° turn. Notably, freezers in group 3 experienced much less freezing in the OFF state during the dual task; however, 4 participants from this subgroup could not complete their walking assessments in the OFF state because of the severity of their freezing.

Discussion

In this study, we introduce the C-FOG questionnaire as a promising instrument for detecting and classifying subtypes of freezers. Unlike other freezing questionnaires, the C-FOG provides novel insights into the heterogeneity inherent to freezing and the situations that trigger this enigmatic phenomenon. Together, these results provide preliminary evidence for distinct asymmetric-motor, anxious, and sensory-attention phenotypes within FOG. This heretofore unrecognized heterogeneity may underlie known inconsistencies in prior empirical literature.[3]

The freezing phenotypes identified in this study putatively represent cohorts with distinct upstream dysfunctions in which idiosyncratic pathophysiological mechanisms overwhelm specialized neural circuitry unique to each phenotypic subtype, which then ultimately manifests via a common inhibitory brain stem pathway that arrests ongoing gait processes.[11,12] This interpretation predicts that different subtypes of patients with FOG should each demonstrate unique susceptibility to situations that provoke freezing, which should in turn be directly linked to the particular domains that relate to their phenotypic expression. For example, if one is highly anxious, the incoming input from the limbic system to the striatum could overload the processing capacity of the gait system, leading to FOG. In contrast, an individual with impaired motor automaticity (and hence, an overreliance on the cognitive control of gait), may fall victim to instances that perturb or divide cognitive resources. However, in each case, the final common pathway

may indeed be shared. Future studies are now required to disambiguate these alternatives.

To provide true clinical utility, our study should be replicated in an expanded cohort, with the identified clusters used as statistical priors. Further multicenter research is also needed to determine whether these findings are reproducible and reliable. Future studies should also carefully consider the type of dopaminergic treatments to determine whether therapeutic patterns contribute to the FOG phenotypes observed in this preliminary study. Nonetheless, the proposition of different subtypes of freezing has important clinical implications for individualized and targeted treatment strategies. ■

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Supporting Data

Additional Supporting Information may be found in the online version of this article at the publisher's website.

Evidence for the Role of *FMR1* Gray Zone Alleles as a Risk Factor for Parkinsonism in Females

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ABSTRACT

Background and Objective There is convincing evidence that small CGG expansion (41-54 repeats): *FMR1* "gray zone" alleles (GZ) contribute to the risk of parkinsonism in males, but there is insufficient corresponding data in females. This study intends to fill this gap.

Methods We screened whole-blood–derived DNA from a cohort of 601 females diagnosed with idiopathic PD, and

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