Variation in anxiety and depression with Freezing of Gait subtype in Parkinson's disease

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Introduction

Affective symptoms including depression and anxiety are reported to be associated with freezing of gait (FOG).

- Freezing of gait is a disabling symptom common in Parkinson's disease (PD) with unclear underlying pathophysiology.[1,2]
- Depressive symptoms increase the risk of developing FOG,[3,4] and FOG episodes can also be directly elicited by increasing anxiety – for example, via virtual environments.[5]
- Therefore, it has been suggested that affective symptoms may contribute to the pathogenesis of FOG.[6]

FOG may have distinct subtypes, including levodopa responsive (RFOG) and unresponsive (URFOG) variants.

- In PD, FOG generally occurs late in the disease course and during "off" or "on" states with the latter being unresponsive to dopaminergic therapy or cueing.[1,2]
- However, FOG can also occur in the absence of other parkinsonian symptoms,[7] and may therefore reflect nondopaminergic pathophysiology.

We tested whether associations between affective symptoms and FOG varied across FOG subtypes.

- We used a multinomial logistic regression approach to determine whether anxiety or depression are associated with specific FOG subtypes (no freezing, "NOFOG" vs. levodopa-responsive freezing, "RFOG," vs. levodopa-unresponsive freezing, "URFOG").
- We hypothesized that the prevalence of FOG would be elevated in PD patients with mood or anxiety disorders after adjusting for clinical and demographic covariates.

Data sources

Study population

- N=135 consecutive PD patients from Emory Movement Disorders Clinic.
- Exclusion criteria: late-stage dementia, history of primary psychotic disorder, cerebrovascular disease, or multiple head injuries, past neuroleptic use, findings suggestive of atypical parkinsonism.

Table 1. Demographic and clinical characteristics of patients with levodopa responsive (RFOG levodopa unresponsive FOG (URFOG) or no FOG (NOFOG).

Characteristic	RFOG N=20	URFOG N=16	NOFOG N=99	P Value
Mean±SD [Range]				
Age (y)	65±9 [50—81]	70±7 [59—81]	64±9 [38—80]	0.05
PD duration (y)	11±5 [3–22]†	8±5 [3—21]	7±4 [1–22]†	0.002
Age at onset (y)	54±10 [33–69]†	62±10 [40–76]†	58±9 [32–80]	0.03
UPDRS-III (points)[a]	20±9 [8–41]	21±5 [12–33]†	16±8 [2–43]†	0.003
FOG-Q (points)[a]	9±4 [2–19]†	10±4 [2–19]‡	2±1 [0–5]†,‡	<0.001
Education (y)	15±2 [12–20]	15±3 [12–20]	16±2 [11–20]	0.07
MoCA (points)	24±4 [16–30]	21±5 [11–29]†	25±3 [16–30]†	0.001
N (%)				
Sex				0.96
Male	14 (70)	11 (69)	65 (66)	
On PD meds[b]	19 (95)	11 (69)	77 (79)	0.11
Levodopa	16 (80)	9 (56)	44 (44)	0.01
Dopamine agonists	14 (70)†	4 (25)†	44 (44)	0.02
COMT inhibitors	4 (20)	1 (6)	7 (7)	0.17
Amantadine	3 (15)	3 (19)	14 (14)	0.86
MAO inhibitors	3 (15)	2 (12)	20 (20)	0.82
On other meds	5 (25)	6 (38)	31 (31)	0.72
SSRIs	2 (10)	3 (19)	11 (1)	0.62
SNRIs	1 (5)	1 (6)	8 (8)	0.87
NDRIs	0 (0)	0 (0)	3 (3)	0.57
SARIs	0 (0)	0 (0)	1 (1)	0.83
Selegiline	1 (5)	0 (0)	1 (1)	0.47
Quetiapine	1 (5)	3 (19)	3 (3)	0.03
Benzodiazepines	2 (10)	1 (6)	12 (12)	0.91

Abbreviations: UPDRS-III, Unified Parkinson's Disease Rating Scale, Part III, Motor Exam;[9] MoCA, Montreal Cognitive Assessment;[10] FOG-Q, Freezing of Gait Questionnaire;[11] PD, Parkinson's disease; meds, medications; COMT, catechol-O-methyl transferase; MAO, monoamine oxidase; SSRI, selective serotonin reuptake inhibitor; SNRI, serotonin–norepinephrine reuptake inhibitor; NDRI, norepinephrine-dopamine reuptake inhibitor; SARI, serotonin antagonist and reuptake inhibitor. [a]N=129. [b]Medication information was available for 134 patients. †,‡Common superscripts indicate significant differences between the marked groups.

Differences in clinical and demographic covariates between FOG groups

- All patients with Depression on SCID (N=15) were diagnosed with some form of recurrent major depressive disorder. Patients indicated with Anxiety on SCID were diagnosed with Generalized Anxiety Disorder, N=8; Specific Phobia, N=3; Panic Disorder, N=1; PTSD, N=2.
- No significant differences in psychiatric medications with the exception of increased prevalence of the atypical antipsychotic quetiapine (Seroquel) in URFOG.
- No significant differences in MAO-B inhibitors, COMT inhibitors, or selegiline, previously suggested to be protective against FOG.[8]

Analysis

Study variables

Primary outcome: Freezing Status

- FOG based on Freezing of Gait questionnaire (FOG-Q)[11] item 3 >0.[12]
- Responsive (RFOG) or unresponsive (URFOG) grouping based on self-report.[12]

Primary exposures: Depression and Anxiety (SCID)

- Assessed via Structured Clinical Interview for DSM-IV-TR.[13]

Primary exposures: Depression and Anxiety (questionnaires)

- Beck Depression Inventory–II (BDI-II)[14]
- Beck Anxiety Inventory (BAI)[15]

Multinomial logistic regression

Associations between Depression or Anxiety and FOG subtype were calculated as Odds Ratios (OR) ±95% CI for RFOG vs. NOFOG and URFOG vs. NOFOG. Predictors were:

1. **Presence vs. absence of depression and anxiety (SCID)**
2. **Severity of depression and anxiety (BDI-II and BAI)**

- Covariates: age, sex, years of education, MoCA score, severity of motor symptoms (UPDRS-III), disease duration.

$$\ln\left(\frac{p(RFOG)}{p(NOFOG)}\right) = \beta_{R0} + \beta_{RDEP}\cdot(\mathrm{DEP}{=}1) + \textstyle\sum_j \beta_{Rj}\cdot \mathrm{cov}_j$$

$$\ln\left(\frac{p(URFOG)}{p(NOFOG)}\right) = \beta_{U0} + \beta_{UDEP}\cdot(\mathrm{DEP}{=}1) + \textstyle\sum_j \beta_{Uj}\cdot \mathrm{cov}_j$$

- BDI-II and BAI scores wer entered both as continuous covariates and after dichotomizing (BDI-II>13; BAI>14).[16]

Results

Depression and Anxiety were associated with RFOG but not URFOG

- Current depression (SCID) was associated with increased odds of RFOG (P=0.02), but not URFOG (P=0.93).
- Similar associations were observed for current anxiety.

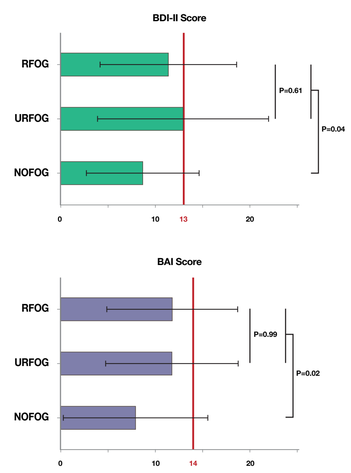
Table 2. Associations between depression and anxiety and FOG subtype.

Variable	RFOG vs. NOFOG OR [95% CI]	P Value	URFOG vs. NOFOG OR [95% CI]	P Value
Current depression (SCID)[a]	4.84 [1.24-19.00]	0.02*	0.91 [0.10-8.50]	0.93
Current anxiety (SCID)[a]	3.89 [0.92-16.50]	0.07	1.05 [0.10-10.96]	0.97
BDI-II score[b]	1.04 [0.96-1.13]	0.32	1.08 [0.99-1.17]	0.08
BAI score[c]	1.03 [0.96-1.12]	0.41	1.03 [0.95-1.12]	0.43
BDI-II > 13[b]	1.43 [0.39-5.17]	0.59	2.78 [0.74-10.49]	0.13
BAI > 14[c]	2.50 [0.67-9.26]	0.17	5.92 [1.22-28.68]	0.03*

Minimum P Value after correction for multiple comparisons ≈ 0.16.

Depression and anxiety symptom severity were elevated in both RFOG and URFOG

- Increased symptom severity (BAI) was associated with increased odds of URFOG.
- Significant differences were observed in questionnaire scores between FOG and NOFOG (BDI-II, P=0.04; BAI, P=0.02) but not between URFOG and RFOG (BDI-II, P=0.61; BAI, 12.9±9.0 vs. 11.4±7.2; P=0.99).



Discussion

Depression and Anxiety may be differentially associated with levodopa-responsive FOG.

- Results are consistent with previous work that anxiety and depression are significant risk factors for FOG[3,4] and suggest that these associations may be strongest for levodopa-responsive FOG. The generally stronger effects shown here for depression may reflect increased homogeneity among depression diagnoses.
- One model proposes that 'cross-talk' between motor and limbic cortico-subcortical pathways results in FOG,[17] speculated to result from competition between circuits for a finite amount of neurotransmitter. These results suggest that if this model is valid, it is probably only true for levodopa-responsive FOG. The underlying mechanisms for levodopa-unresponsive FOG remain unknown.

Limitations

- FOG state was determined via self-report. We are validating these results in an independent sample with motor testing under levodopa challenge.

Conclusions

- Anxiety and depression may be differentially associated with levodopa-responsive FOG. Levodopa-unresponsive FOG may reflect distinct underlying pathophysiology.

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