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.
- Depressive symptoms increase the risk of developing FOG, and FOG episodes can also be directly elicited by increasing anxiety – for example, via virtual environments.
- Therefore, it has been suggested that affective symptoms may contribute to the pathogenesis of FOG.

FOG may have distinct subtypes, including levodopa responsive (RF OG) 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.
- However, FOG can also occur in the absence of other parkinsonian symptoms, and may therefore reflect non dopaminergic 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, “RF OG,” 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>
<thead>
<tr>
<th>Variable</th>
<th>N=20</th>
<th>N=16</th>
<th>N=99</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>65±9 [50—81]</td>
<td>70±9 [69—85]</td>
<td>68±9 [68—88]</td>
</tr>
<tr>
<td>Age at onset (y)</td>
<td>54±12 [33—83]</td>
<td>62±16 [46—87]</td>
<td>59±12 [40—76]</td>
</tr>
<tr>
<td>UPDRS-III (points)</td>
<td>56±23 [22—102]</td>
<td>50±23 [22—100]</td>
<td>55±22 [20—100]</td>
</tr>
<tr>
<td>Gender</td>
<td>0.96</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>14 (70)</td>
<td>11 (69)</td>
<td>65 (66)</td>
</tr>
<tr>
<td>On PD meds</td>
<td>18 (90)</td>
<td>11 (69)</td>
<td>77 (78)</td>
</tr>
<tr>
<td>Levodopa</td>
<td>16 (80)</td>
<td>9 (56)</td>
<td>44 (44)</td>
</tr>
<tr>
<td>Cognitively apoprtic</td>
<td>1 (6)</td>
<td>0 (0)</td>
<td>0 (0)</td>
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<tr>
<td>MCI criteria</td>
<td>4 (20)</td>
<td>1 (6)</td>
<td>7 (7)</td>
</tr>
<tr>
<td>Amnestic</td>
<td>3 (15)</td>
<td>3 (19)</td>
<td>14 (14)</td>
</tr>
<tr>
<td>AAT criteria</td>
<td>5 (25)</td>
<td>2 (12)</td>
<td>20 (20)</td>
</tr>
<tr>
<td>GAIT measures</td>
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<td>1 (6)</td>
<td>1 (1)</td>
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<td>SSRS</td>
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<td>1 (6)</td>
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<td>DSQ</td>
<td>2 (10)</td>
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Significant differences were observed in questionnaire scores between FOG and NOFOG (BDI-II, P=0.04; BAI, P=0.05) and between RFOG and NOFOG (BDI-II, P=0.02; BAI, P=0.01).

Results

Depression and Anxiety were associated with RFOG but not URFOG

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

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

- Increased symptom severity (BDI-II) 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=0.05) but not between URFOG and RFOG (BDI-II, P=0.01; 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 risk factors for FOG12 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.