Understanding falls at the patient and group level in Parkinson’s disease

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I use a translational approach to study balance and falls in Parkinson’s disease

Epidemiology at the group level
- Large N for natural variability
- Real patients and statistics for clinical impact

Engineering at the patient level
- Simulations to show how pathology affects behavior
Falls are a major public health problem, especially in PD

- Falls are the main cause of accidental death in individuals ≥ 65 years old.\(^1\)

- PD increases fall risk (6 month risk ratio vs. matched healthy adults = 6.1 [2.5–15.1]),\(^2\) but causes remain poorly understood.\(^3,4\)

- A diverse group of PD patients, caregivers, and health professionals recently ranked balance problems and falls as their #1 research priority for PD.\(^5\)

\(^1\)Deandrea et al., Epidemiol 2010 (primarily USA/Europe); \(^2\)Bloem et al., J Neurol 2001
\(^3\)Grimbergen et al., Curr Opin Neurol 2004; \(^4\)Paul et al., Mov Disord 2013; \(^5\)Lord et al., Mov Disord 2016
Agenda

- Project 1: Can Freezing of Gait persist in the “ON” state? Results using a levodopa test
- Project 2: Leg (but not arm or neck) rigidity is associated with fall history in Parkinson’s disease
Freezing of Gait is poorly understood but a major contributor to falls

• “A brief arrest of stepping when initiating gait, turning, and walking straight ahead”¹

• ~2nd largest predictor of fall risk.²

• “ON” state FoG reported by patients (≈38%)³ has been called “pseudo-ON” or “levodopa-induced”⁴

¹McKay, Goldstein, Sommerfeld, Bernhard, Perez-Parra, Factor, BioRxiv 667071 [Preprint], 2019; ²Paul et al., Mov Disord 2013 ³Perez-Lloret et al., JAMA Neurol 2014; ⁴Fasano and Lang, Lancet Neurol 2015
Study 1 objectives

- Test whether presumed levodopa-unresponsive freezing of gait actually persists with adequate levodopa treatment.

- Test whether other parkinsonian features and responsiveness to levodopa varies across patients without FOG (NOFOG), with levodopa-responsive FOG (OFF-FOG) and with levodopa-unresponsive FOG (ONOFF-FOG).
We studied N=55 people with PD with a “levodopa challenge” paradigm

- Test 1: MDS-UPDRS-III “OFF” first thing in the morning, 12+ hours since last medication

- Break to take medications (≈400 mg levodopa equivalent, ≈150% of typical morning dose)

- Wait until patients reported effects (30 minutes-3 hours)

- Test 2: MDS-UPDRS-III “ON”
FOG can persist even in the presence of therapeutic acute levodopa challenge

**Graph:**
- **X-axis:** Improvement in MDS-UPDRS-III Total Score (%)
- **Y-axis:** Distribution of Improvement in MDS-UPDRS-III Total Score
- **Legend:**
  - Clinically-meaningful response
    - N=45
    - 47±15% [20-80%]
  - No clinically-meaningful response
    - N=10
    - 3±14% [-23-19%]

**Improvement in MDS-UPDRS-III Total Score after levodopa challenge (%)**
- **X-axis:** MDS-UPDRS-III Total OFF Score (/132)
- **Y-axis:** Improvement in MDS-UPDRS-III Total Score after levodopa challenge (%)
- **Legend:**
  - ONOFF-FOG
  - OFF-FOG
  - NOFOG
  - No clinically-meaningful response
  - N=19 cases of FOG after suprathreshold levodopa

**Statistical Details:**
- P = 0.73
People with ONOFF-FOG had otherwise typical parkinsonian features

**FOG group effect, P<0.05, RM-ANOVA

**FOG group effect, P<0.01

Significant medication state effect in all domains, except:
- Item III.12, Postural stability (absence of symptom)
- Item III.1, Speech (absence of effect)
- Item III.8, Leg agility (absence of effect)
- Item III.16, Kinetic tremor

Significant FoG group effect:
- Item III.11, FoG
- Item III.10, Gait
- Item III.12, Postural stability
- Item III.1, Speech
- Item III.8, Leg agility
- Item III.6, Hand pronation/supination

Significant FoG group × medication state interaction:
- Item III.11, FoG

Study 1 results and conclusions

- Levodopa challenge brought about a full “ON” state in 45/55 patients (19 ONOFF-FOG, 11 OFF-FOG, 15 NOFOG) – **most people responded**

- Highly significant association between serum levodopa level and total MDS-UPDRS-III score that was similar across groups – **everyone had PD**

- MDS-UPDRS-III scores and response to levodopa were similar across groups, consistent with PD (some significant effects of group were identified for other axial parkinsonian features) – **everyone had PD**

- **Conclusion**: FOG can persist in the full “ON” state brought about by ample dopaminergic dosing in PD. These data provide evidence that ONOFF-FOG is distinct from responsive freezing.
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MDS-UPDRS-III estimation with neural networks

MDS UPDRS-III Motor Exam Item 3.4: “Finger Tapping”

Red and yellow dots are tracked using a neural network

Distance between dots vs. time

DeepLabCut analysis courtesy Benjamin Fuhrer

DeepLabCut: Mathis et al., Nat Neurosci, 2018
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Falls are a major public health problem, especially in PD

- Falls are the main cause of accidental death in individuals ≥ 65 years old.¹

- PD increases fall risk (6 month risk ratio vs. matched healthy adults = 6.1 [2.5–15.1]),² but causes remain poorly understood.³,⁴

- A diverse group of PD patients, caregivers, and health professionals recently ranked balance problems and falls as their #1 research priority for PD.⁵

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³Grimbergen et al., Curr Opin Neurol 2004; ⁴Paul et al., Mov Disord 2013; ⁵Lord et al., Mov Disord 2016
Leg rigidity is an understudied risk factor for falls in PD

- One study\(^1\) found no association between whole body rigidity and falls.
- But, simulations suggest\(^2\) that leg rigidity may contribute to falls.

\(^1\)Latt et al., *Mov Disord* 2009; \(^2\)Bingham, Choi, Ting, *J Neurophysiol* 2011
We compared rigidity scores in N=216 people with PD with and without frequent falls.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>All Participants, N = 216</th>
<th>Nonfallers, n = 181</th>
<th>Fallers, n = 35</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yr</td>
<td>65.7 ± 9.7</td>
<td>65.5 ± 9.6</td>
<td>67.1 ± 10.3</td>
<td>0.35</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>78 (36)</td>
<td>60 (33)</td>
<td>18 (52)</td>
<td>0.04</td>
</tr>
<tr>
<td>Male</td>
<td>138 (64)</td>
<td>121 (67)</td>
<td>17 (48)</td>
<td></td>
</tr>
<tr>
<td>MoCA (/30)</td>
<td>24.7 ± 3.6^I</td>
<td>24.8 ± 3.6^2</td>
<td>24.2 ± 4.0^3</td>
<td>0.37</td>
</tr>
<tr>
<td>Education, y</td>
<td>16.1 ± 2.2^f</td>
<td>16.1 ± 2.3^g</td>
<td>16.2 ± 1.7</td>
<td>0.92</td>
</tr>
<tr>
<td>Disease duration, yr</td>
<td>7.4 ± 4.5</td>
<td>6.9 ± 4.1</td>
<td>9.9 ± 5.7</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Age at onset, yr</td>
<td>58.3 ± 10.6</td>
<td>58.6 ± 10.1</td>
<td>57.3 ± 12.9</td>
<td>0.58</td>
</tr>
<tr>
<td>UPDRS-III score (/108)</td>
<td>22.0 ± 10.0</td>
<td>20.6 ± 9.2</td>
<td>29.5 ± 10.5</td>
<td>&lt;&lt;0.01</td>
</tr>
<tr>
<td>FOG-Q total (/24)</td>
<td>4.5 ± 4.6</td>
<td>3.5 ± 3.9</td>
<td>9.6 ± 4.9</td>
<td>&lt;&lt;0.01</td>
</tr>
<tr>
<td>FOG-GF total (/64)</td>
<td>8.6 ± 9.0</td>
<td>6.1 ± 6.2</td>
<td>21.1 ± 10.9</td>
<td>&lt;&lt;0.01</td>
</tr>
<tr>
<td>Freezing of gait</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Freezer</td>
<td>59 (27)</td>
<td>35 (19)</td>
<td>24 (69)</td>
<td>&lt;&lt;0.01</td>
</tr>
<tr>
<td>Nonfreezer</td>
<td>157 (73)</td>
<td>146 (81)</td>
<td>11 (31)</td>
<td></td>
</tr>
</tbody>
</table>

Values are shown as either mean ± standard deviation or N (%). P values reflect univariate tests of central tendency (t tests or \( \chi^2 \) tests) between fallers and nonfallers.
We found that leg rigidity (but not arm or neck) is associated with falls in PD.

Odds Ratio for frequent falls, adjusted for age, sex, UPDRS-III, PD duration, FoG (N=216)

- **Lower Limb Rigidity Score, P=0.01**
  - 1.61 (1.10–2.37)

- **Total Rigidity Score, P=0.29**
  - 1.09 (0.93–1.27)

- **Neck Rigidity Score, P=0.99**
  - 1.00 (0.54–1.87)

- **Upper Limb Rigidity Score, P=0.14**
  - 0.71 (0.45–1.11)

*McKay, Hackney, Factor, Ting, Mov Disord Clin Prac 2019*
Study 2 results and conclusions

• To our knowledge, this is the first study to demonstrate an association between leg rigidity and falls in PD.

• In addition to common features on exam that raise concerns to neurologists that falls may be impending, leg rigidity may be a clinically observable and modifiable parkinsonian feature associated with falls.

• Rigid patients have increased muscle responses to passive movements\(^1,2\) and background muscle activity\(^3\) which may increase joint stiffness. This may be modifiable.

• Conclusion: Prospective studies of the relationships between rigidity and fall risk in PD could provide new information.

\(^1\)Berardelli et al., *J Neurol Neurosurg Psychiatry* 1983; \(^2\)Tatton and Lee, *Brain Res* 1975; \(^3\)Marusiak et al., *Clin Biomech* 2012
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