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

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Acknowledgments and disclosures

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None

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

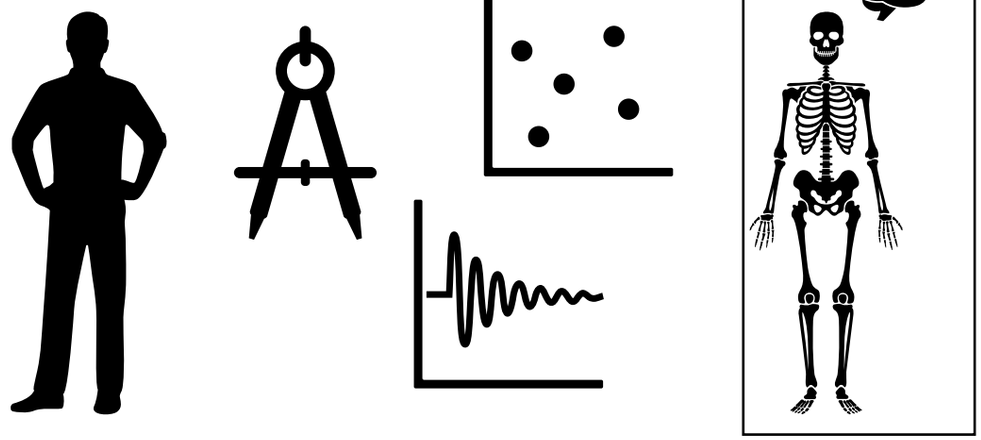
Epidemiology at the group level

Large N for natural variability

Real patients and statistics for clinical impact

Engineering at the patient level

Simulations to show how pathology affects behavior

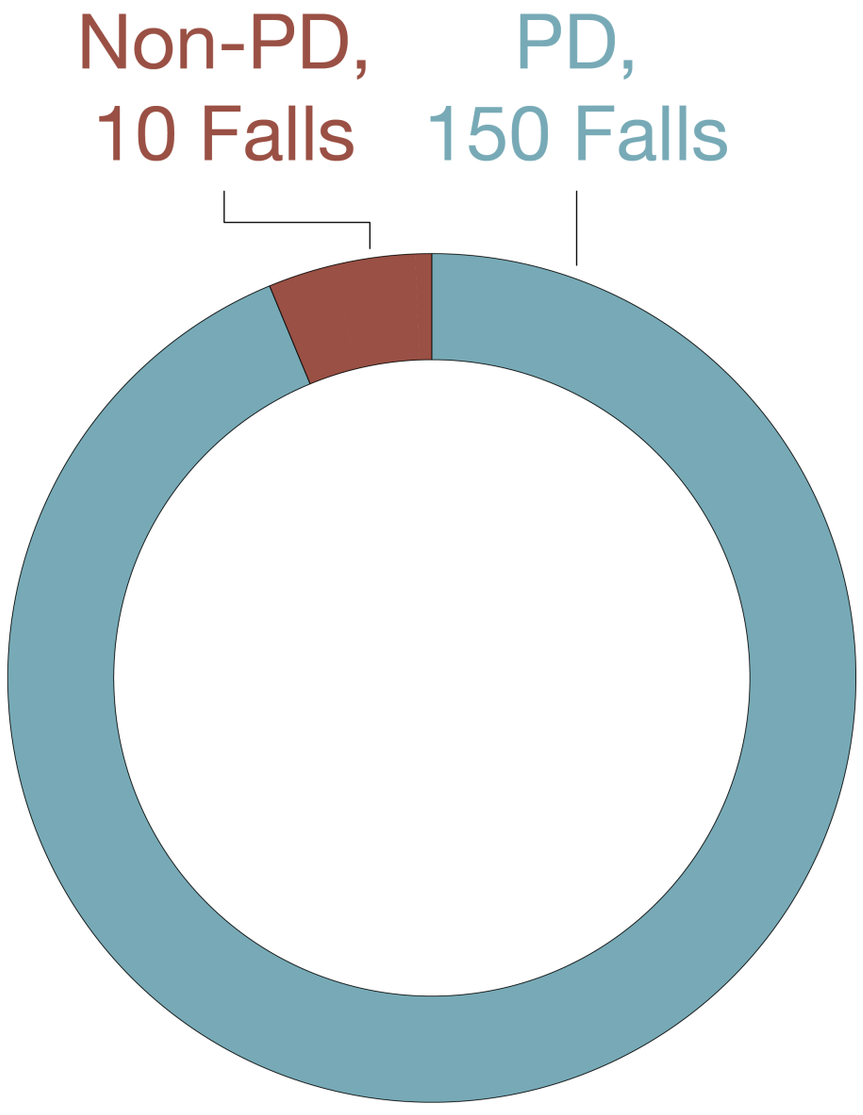


Falls are a major public health problem, especially in PD

- 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
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Agenda

- Project 1: Can Freezing of Gait persist in the “ON” state? Results using a levodopa test

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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]

Lancet TV – https://www.youtube.com/watch?v=3-wrNhyVTNE

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

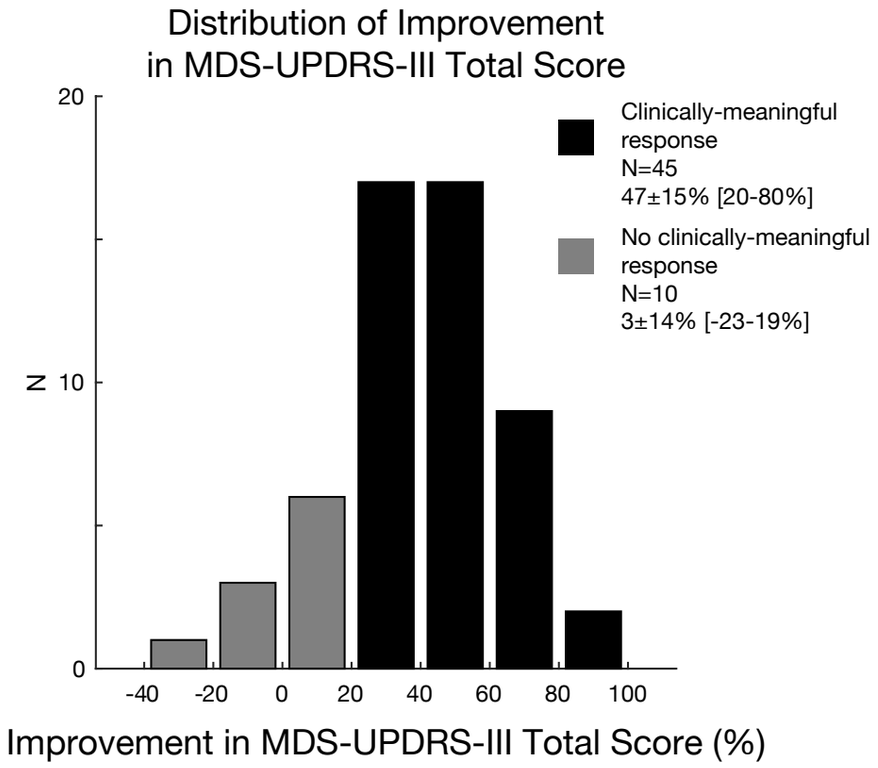
Study 1 objectives

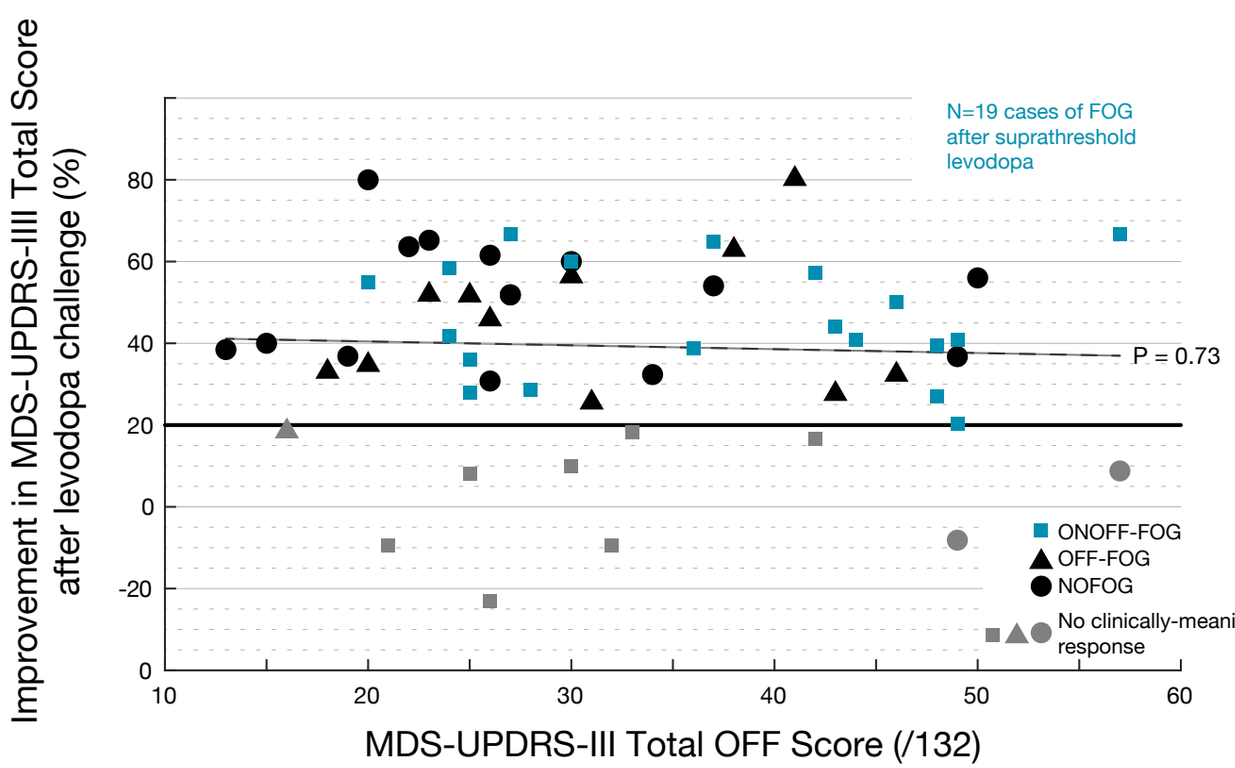
- Test whether presumed levodopa-unresponsive freezing of gait actually persists with adequate levodopa treatment
- Test whether other parkinsonian features and responsiveness to levodopa varies across patients without FOG (NOFOG), with levodopa-responsive FOG (OFF-FOG) and with levodopa-unresponsive 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”

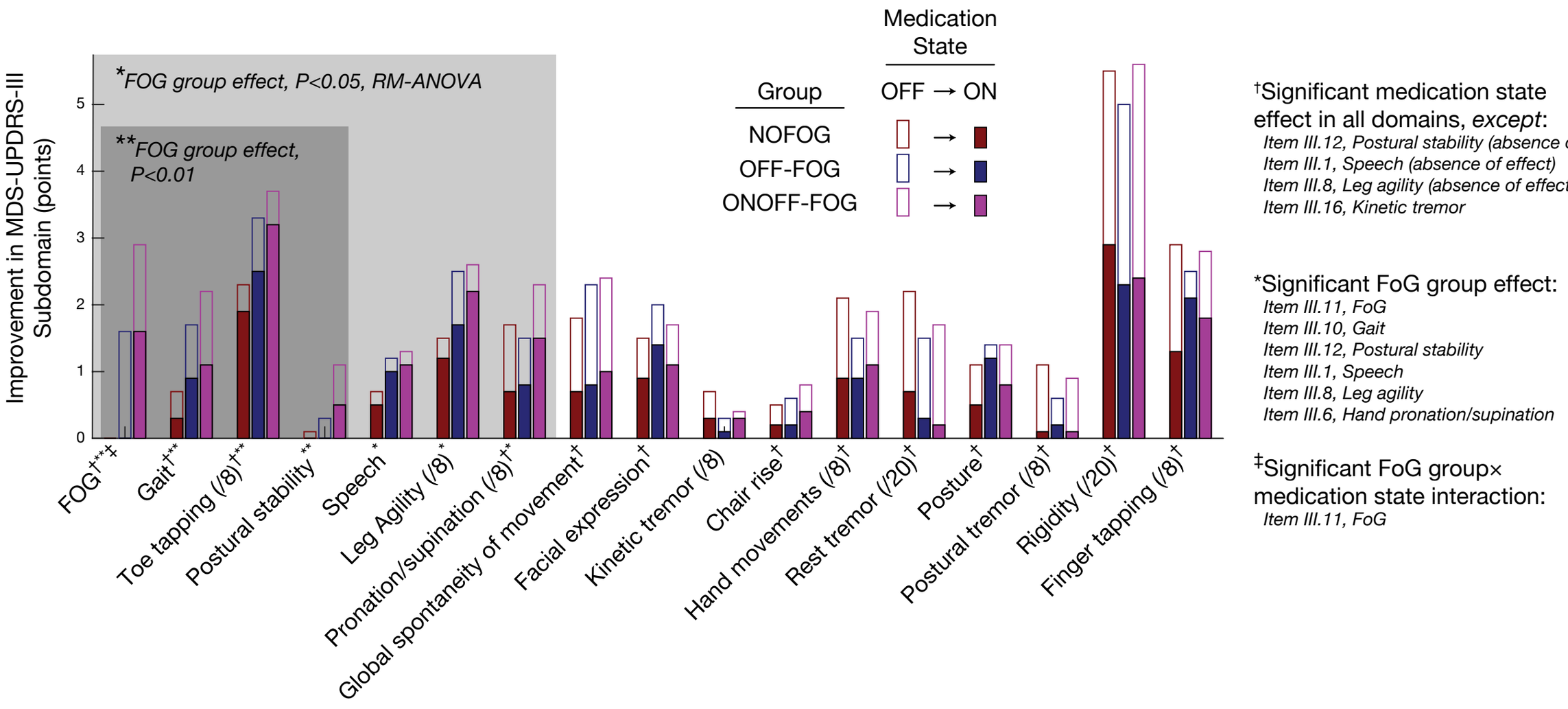
FOG can persist even in the presence of therapeutic acute levodopa challenge





McKay, Goldstein, Sommerfeld, Bernhard, Perez-Parra, Factor, *BioRxiv* 667071 [Preprint], 2019. doi:10.1101/667071.

People with ONOFF-FOG had otherwise typical parkinsonian features



†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*

McKay, Goldstein, Sommerfeld, Bernhard, Perez-Parra, Factor, *BioRxiv* 667071 [Preprint], 2019. doi:10.1101/667071.

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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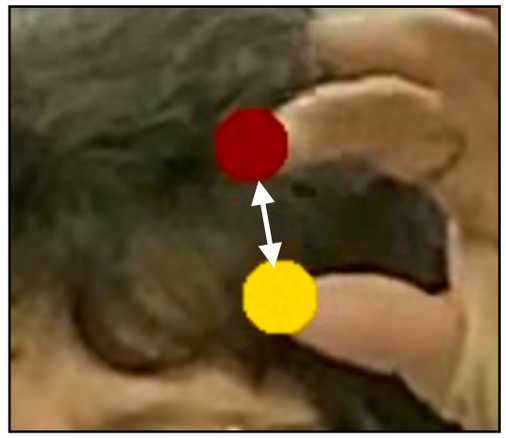
MDS-UPDRS-III estimation with neural networks

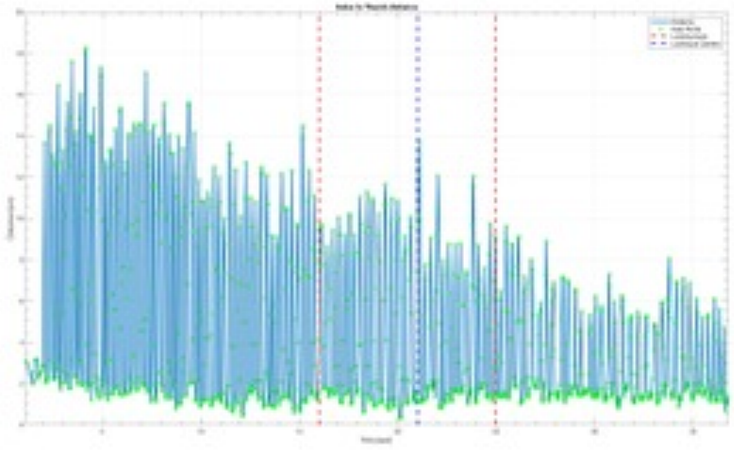
MDS UPDRS-III Motor Exam Item 3.4: “Finger Tapping”

DeepLabCut analysis courtesy Benjamin Fuhrer

Red and yellow dots are tracked using a neural network



Distance between dots vs. time



DeepLabCut: Mathis et al., *Nat Neurosci*, 2018

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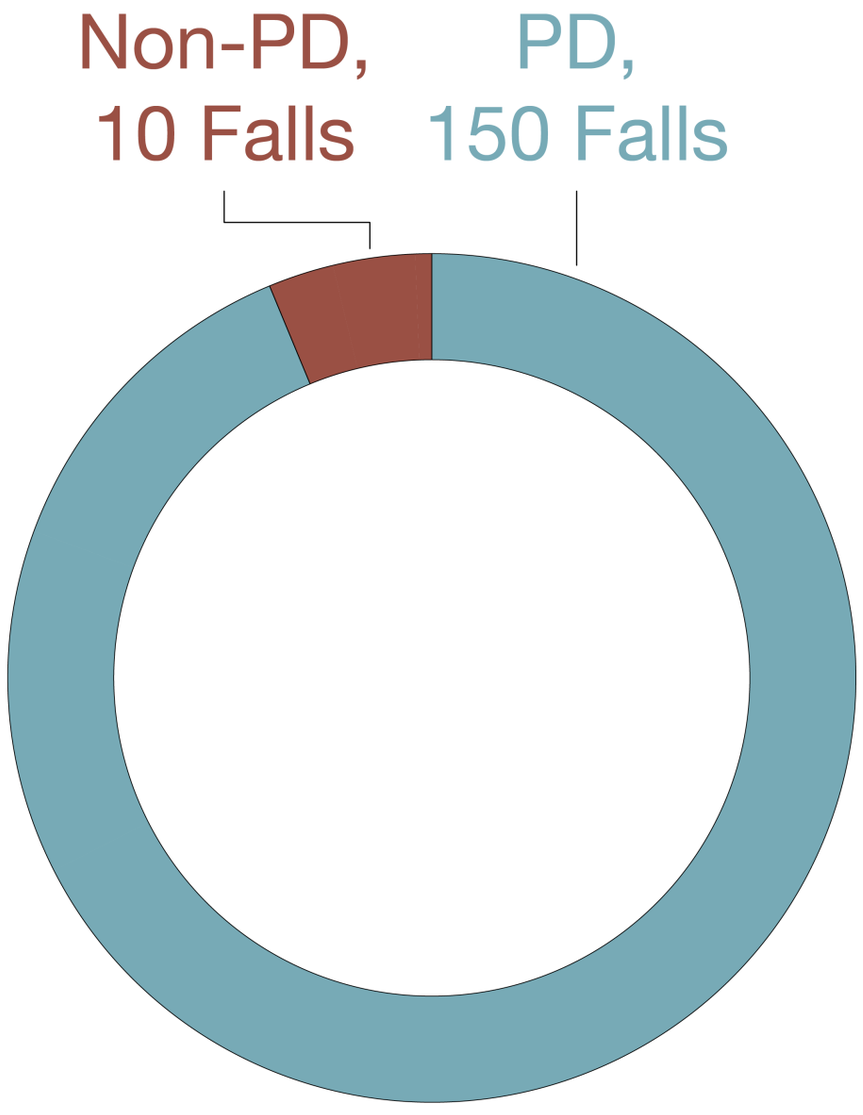

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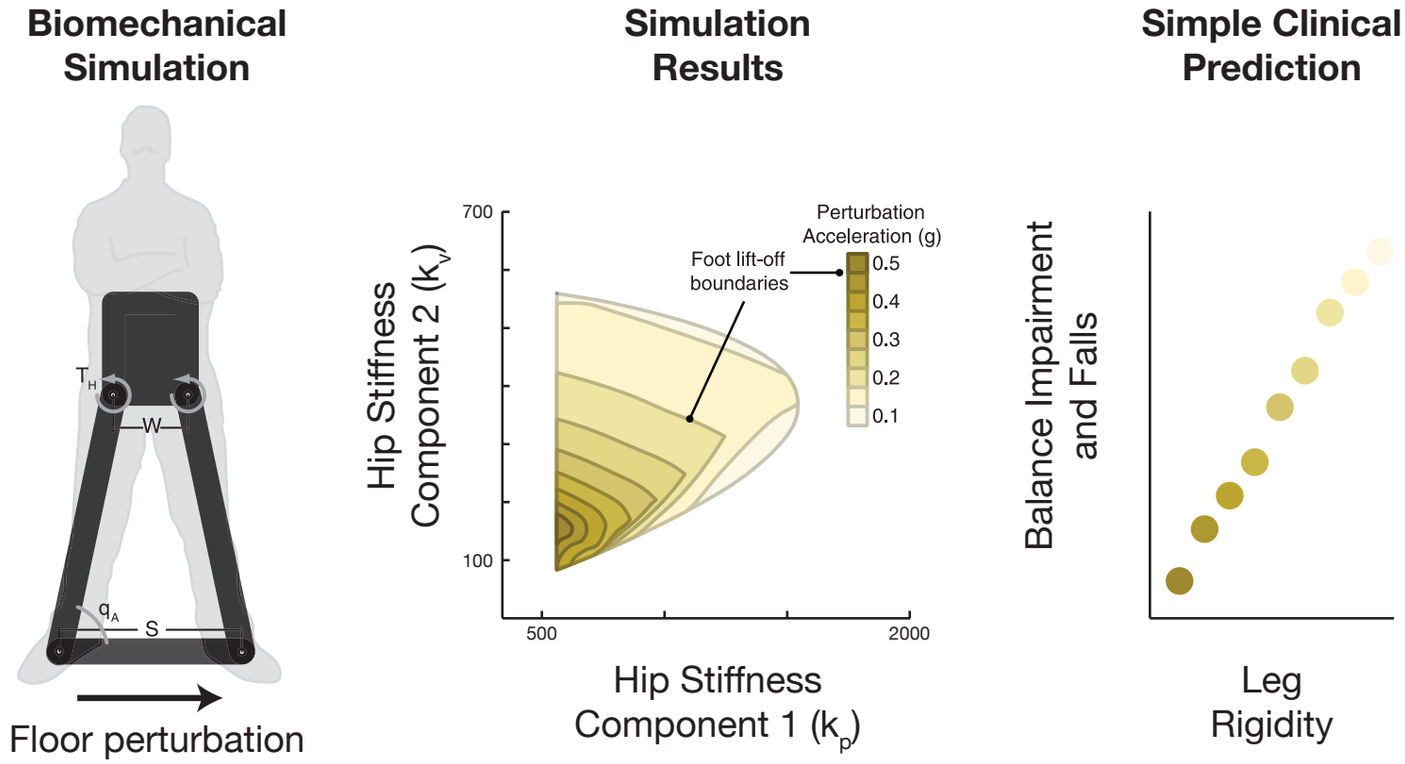
Leg rigidity is an understudied risk factor for falls in PD

- 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

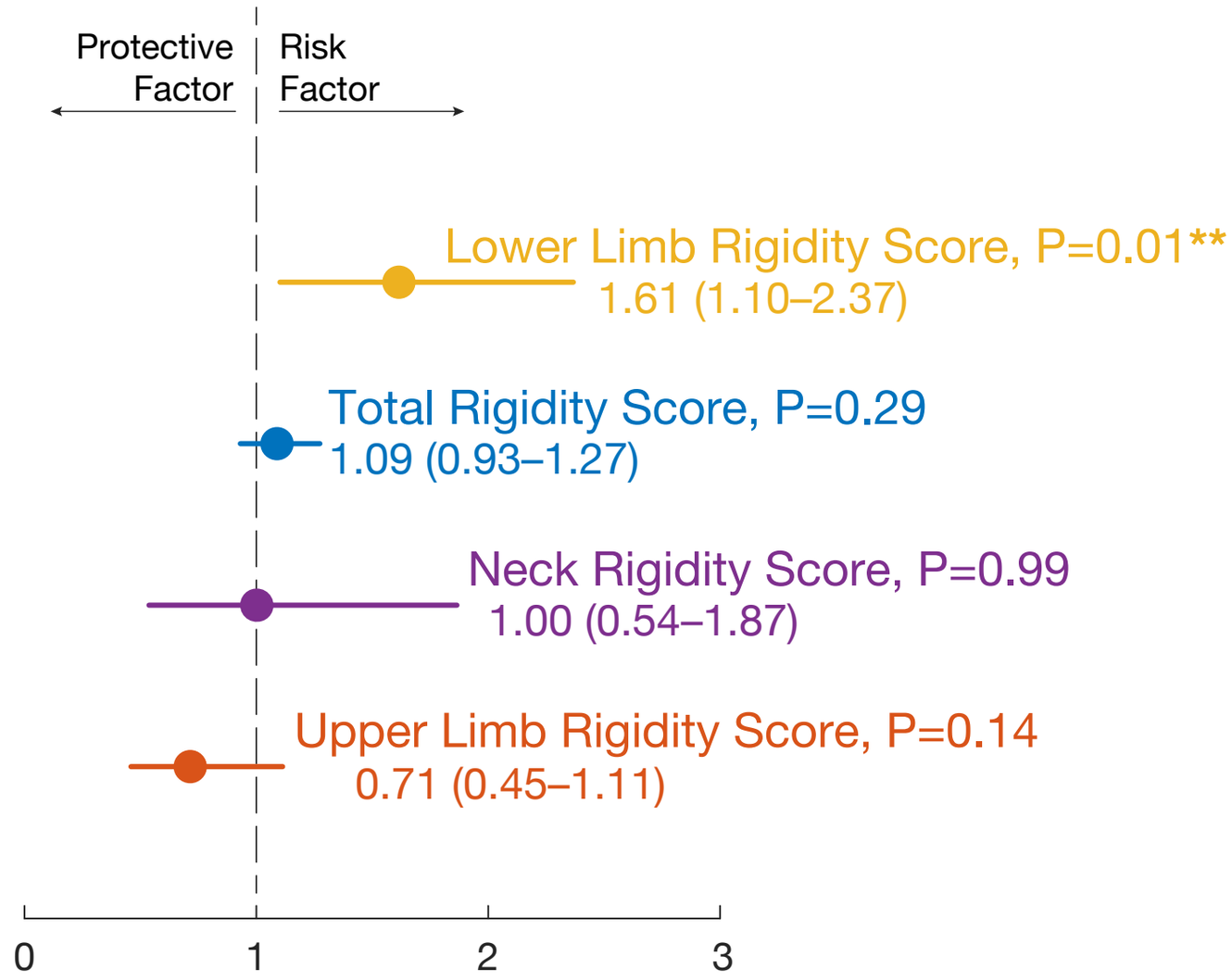
We compared rigidity scores in N=216 people with PD with and without frequent falls

TABLE 1 *Demographic and clinical features of the study population overall and stratified on presence of previous monthly falls*

Characteristic	All Participants, N = 216	Nonfallers, n = 181	Fallers, n = 35	*P* Value
Age, yr	65.7 ± 9.7	65.5 ± 9.6	67.1 ± 10.3	0.35
Sex				
Female	78 (36)	60 (33)	18 (52)	0.04
Male	138 (64)	121 (67)	17 (48)	
MoCA (/30)	24.7 ± 3.6[1]	24.8 ± 3.6[2]	24.2 ± 4.0[3]	0.37
Education, y	16.1 ± 2.2[4]	16.1 ± 2.3[5]	16.2 ± 1.7	0.92
Disease duration, yr	7.4 ± 4.5	6.9 ± 4.1	9.9 ± 5.7	<0.01
Age at onset, yr	58.3 ± 10.6	58.6 ± 10.1	57.3 ± 12.9	0.58
UPDRS-III score (/108)	22.0 ± 10.0	20.6 ± 9.2	29.5 ± 10.5	<<0.01
FOG-Q total (/24)	4.5 ± 4.6	3.5 ± 3.9	9.6 ± 4.9	<<0.01
FOG-GF total (/64)	8.6 ± 9.0	6.1 ± 6.2	21.1 ± 10.9	<<0.01
Freezing of gait				
Freezer	59 (27)	35 (19)	24 (69)	<<0.01
Nonfreezer	157 (73)	146 (81)	11 (31)	

Values are shown as either mean ± standard deviation or N (%). *P* values reflect univariate tests of central tendency (*t* tests or χ^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)

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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