Sensorimotor transformations for balance in Parkinson's disease are temporally precise but spatially diffuse

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Abstract

Motivation

Parkinson's disease (PD) causes balance problems and falls,[1] but we know very little about how it affects balance pathways.

Muscles activate in proportion to CoM motion when balance is disturbed in animals[2] and healthy young people.[3,4] Muscle activity begins ≈100 ms after perturbation onset to stabilize the CoM independent of perturbations to individual joints.[5-7] This reactive balance activity depends on brainstem and spinal networks, with important roles for subcortical structures including thalamus and subthalamic nucleus (STN).[8,9]

We quantify the transformation from CoM perturbation to muscle activity using our sensorimotor response model (SRM). Muscle activity is characterized by feedback gains on CoM acceleration, velocity and displacement (k_a, k_v, and k_d); and sensory-neuroconduction delay (λ).

Objectives

Here, we tested whether:

1) The sensorimotor transformation governing reactive balance is disrupted in PD patients compared to matched neurotypical individuals.

2) Abnormalities in the balance sensorimotor transformation are associated with previous and future falls in PD patients.

Discussion

To our knowledge, this represents the first evidence that PD disrupts balance sensorimotor control. Although earlier studies used EMG and posturography to describe decreased *direction* speficity of muscle activity in PD,[10,11] here we show that abnormalities in the *temporal* activity suggest that sensorimotor pathways governing reactive balance are intact but disinhibited or facilitated.

How PD disease processes cause abnormal antagonist activity remains unknown. Because CoM feedback is likely encoded at the level of muscle spindles,[12] abnormal activity could result from 1) loss of somatotopy in STN, GPi, or other basal ganglia centers,[13] or 2) loss of inhibition in motor cortex.[14] Extra delays identified for the $k_a{}'$ pathway (≈18 ms) are consistent with traversal of higher centers. SRM analysis may allow us to better understand how PD affects sensorimotor transformations for balance, and identify new therapeutic approaches.

Limitations. We did not identify abnormal antagonist activity in MG, potentially because we used only one standardized perturbation size. Participants were OFF (>12h) medications, which limits external validity to real world falls in the ON state. We have also observed abnormal activation of MG in the ON medications state.[15] Finally, a controlled time-to-event analysis in a larger sample is necessary to confirm the relationship between $k_a{}'$ and time to fall.

Conclusion. These data provide compelling evidence that in PD, sensorimotor balance transformations identified before in healthy young individuals and animals are intact but dysregulated such that muscle activity is tightly linked to sensory inputs from balance perturbations, but more broadly distributed across muscles. Impaired sensorimotor control may be an important link in the causal pathway between PD and falls in the community.

Results

Sensorimotor control of the CoM: 1) is abnormal in mild-moderate PD, and, 2) is associated with falls

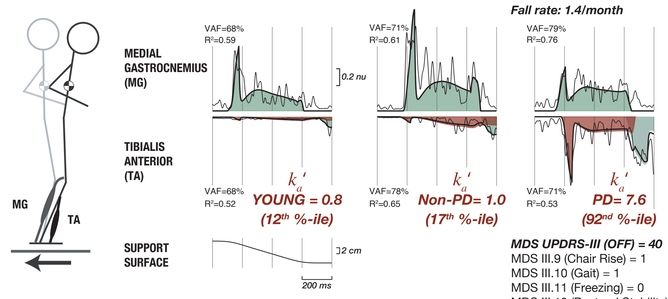
EXAMPLE CASES

A. SUPPORT SURFACE TRANSLATION PERTURBATION

B. HEALTHY YOUNG (22F)
Neurotypical

C. NEUROTYPICAL AGING (64M)
Neurotypical
No fall history

D. PARKINSON'S DISEASE (62F)
PD duration 4.9 years
1 fall in previous 6 months
Time to fall: 0.5 months
Fall rate: 1.4/month



MDS UPDRS-III (OFF) = 40
MDS III.9 (Chair Rise) = 1
MDS III.10 (Gait) = 1
MDS III.11 (Freezing) = 0
MDS III.12 (Postural Stability) = 1

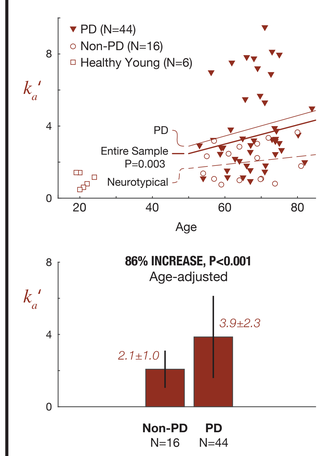
Agonist MG is explained by stabilizing CoM feedback
- Initial burst ≈100-150 ms after onset , plateau period ≈400-600 ms duration
- Well explained by feedback of CoM motion (green; VAF 68-79%)

Antagonist TA in PD is explained by a mixture of stabilizing and destabilizing CoM feedback
- Antagonist TA is highly abnormal in PD, with profoundly increased activity at ≈100-150 ms.
- Explained by feedback of CoM motion that reinforces perturbation (red; VAF 71%)

This patient went on to fall multiple times
- 7 unique falls reported since study entry
- 5/7 involved CoM control (entering a car, dismounting a bicycle, turning in a restaurant)

PD vs. NON-PD

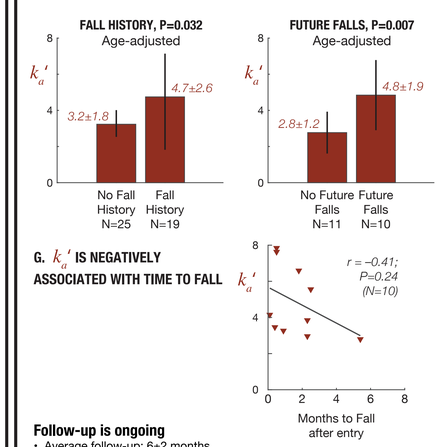
E. $k_a{}'$ IS ELEVATED BY 86% IN PD (P<0.001)



PAST AND FUTURE FALLS

F. $k_a{}'$ IS ELEVATED BY 47% (P=0.032) IN PD PATIENTS WITH FALL HISTORY AND BY 71% (P=0.007) IN PD PATIENTS WHO WILL GO ON TO FALL

G. $k_a{}'$ IS NEGATIVELY ASSOCIATED WITH TIME TO FALL



Follow-up is ongoing
- Average follow-up: 6±2 months
- Range: 2-10 months

Methods

Participants and setting

N=44 PD / N=23 NON-PD participants

- Recruited as part of two studies: a randomized rehabilitation trial and an observational study of 1-year fall risk
- ≈3 hour testing battery in 12-hour OFF medication state
- Informed consent according to procedures approved by Emory and Georgia Tech IRB

Differences between PD and Neurotypical groups

- No differences between PD and Non-PD groups on age, sex, height, weight, or overall cognition (MoCA): minimum observed P-value=0.34)
- Behavioral balance and gait outcomes poorer among PD: Mini-BESTest (P=0.001), FAB (P=0.028), DGI (P=0.043), BBS (P=0.040)
- Previous falls more prevalent among PD (45% vs. 13%; p=0.010; OR±95%CI: 5.33 [1.38, 20.54])

TABLE 1. Study participants.

Variable	PD N=45	Non-PD N=23	Total N=68
Age, y	68 ± 7	66 ± 8	67 ± 7
Sex			
Male, n (%)	24 (53)	8 (35)	32 (47)
Female, n (%)	21 (47)	15 (65)	36 (53)
Height, cm	170 ± 10	169 ± 11	169 ± 10
Weight, kg	77 ± 14	78 ± 15	77 ± 14
MoCA, /30	27.8 ± 1.4	27.5 ± 1.6	27.7 ± 1.5
PD duration, y	7.4 ± 4.8		
MDS UPDRS-III, /132	36.3 ± 13.0		
LED, mg[a]	724 ± 353		
Freezing of Gait			
Nonfreezer, n (%)	29 (64)		
Freezer, n (%)	16 (36)		
PD Phenotype			
PIGD, n (%)	28 (62)		
TD, n (%)	13 (29)		
Indet, n (%)	4 (9)		
Fall History[a]			
Nonfaller, n (%)	25 (55)	20 (87)	45 (66)
Faller, n (%)	20 (45)	3 (13)	23 (44)
Balance outcomes			
Mini-BESTest, /28[b,a]	22.1 ± 4.0	25.6 ± 1.7	23.4 ± 3.7
FAB, /40[c,d]	29.8 ± 5.5	33.2 ± 2.7	30.9 ± 5.0
DGI, /24[c,d]	20.4 ± 3.5	22.3 ± 1.3	21.0 ± 3.1
BBS, /56[c,d]	52.9 ± 5.5	55.0 ± 1.3	53.6 ± 3.4

[1]P<0.010 between PD and Non-PD, χ^2 test. [b]P<0.05 between PD and Non-PD, *t*-test. [a]N=42. Two patients had not yet begun pharmacotherapy and detailed dosage information was unavailable

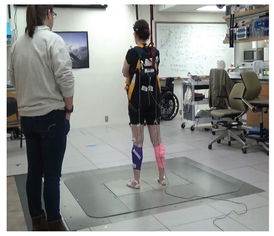
N=44 PD and N=16 neurotypical participants included in SRM analyses

- Additional outcomes in overall project (not shown)
- N=8 participants excluded from SRM analyses due to kinematic data limitations (N=8) and potentially altered diagnosis (N=1); no effects on group contrasts

N=21 PD enrolled in prospective falls tracking for 1 year (ongoing)

Reactive balance testing

Bilateral EMG, kinematics, kinetics as previously in PD patients and young healthy individuals



Motion capture

Safety harness

Surface EMG

Force Plates

Perturbation platform

Ramp-and-hold support surface translation perturbations

- 36–60, delivered in unpredictable order randomly among 12 directions evenly distributed in the horizontal plane
- Peak acceleration: 0.1 g; peak velocity: 25 cm/s; peak displacement: 7.5 cm
- Perturbations within ±30° of anterior-posterior were entered into analyses using anterior-posterior components of CoM motion

Sensorimotor Response Modeling

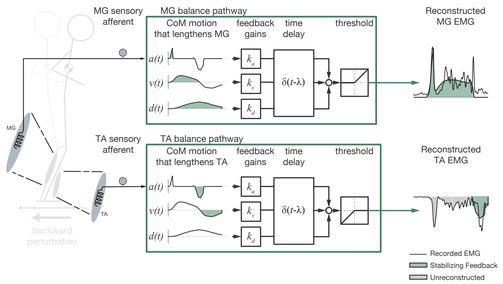
- SRM parameters (κ, λ) that best reproduced the entire time course of muscle activity were found by minimizing an error term calculated between recorded EMG and reconstructed signals

$$\min_{k,\lambda}\left\{\mu_s\int_0^{t_{end}} e^2 dt + \mu_m \max(|e|) + \mu_k k^T k\right\}$$

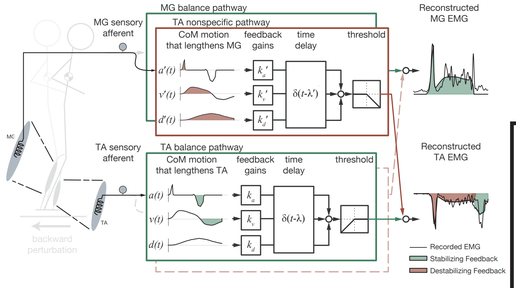
- Muscle spindle "stiction" was modeled by allowing acceleration encoding for a fixed time period τ after the onset of platform acceleration and deceleration. Values of τ were fixed at 75 ms
- Numerical solutions identified using the interior point algorithm implemented in *fmincon.m*

Sensorimotor Feedback Scenarios

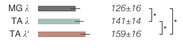
Stabilizing CoM Feedback



Stabilizing + Destabilizing CoM Feedback

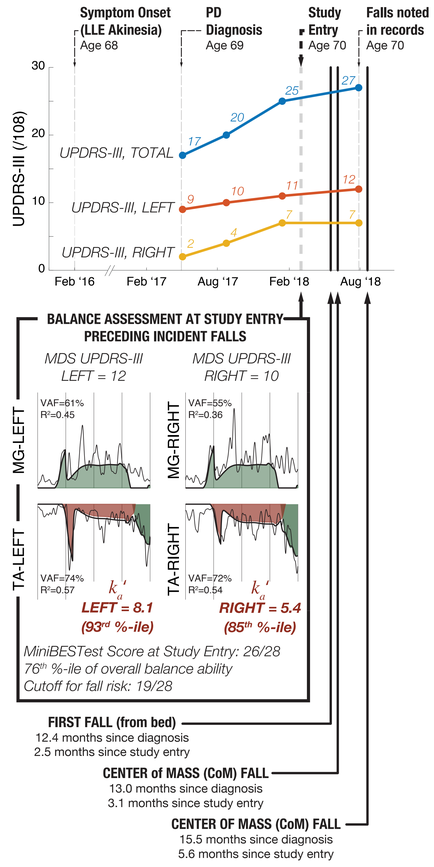


Identified delay times



Case Study

3) Abnormal sensorimotor control can precede first falls in *de novo* PD.



At study entry, this de novo PD patient (70y, m):

- Had not begun pharmacotherapy
- Had no fall history
- Had nigrostriatal dopamine degeneration on DaTSCAN

Sensorimotor control abnormalities despite high performance on behavioral balance measures

- High values of $k_a{}'$
- Near-perfect score on Mini-BESTest (26/28)

Repeated falls associated with impaired CoM control after entry

- Initial fall from bed 2.5 months after study entry
- Two falls shortly thereafter (3.1 months and 5.6 months), involving turning or reaching above his head while gardening
- Reports to the study team that his left leg "gave out."

Discussion – Case Study

This case provides compelling evidence that SRM analysis can identify those at risk for "first falls" in time to direct them to appropriate interventions. It also provides evidence that postural abnormalities associated with falls identified with SRM analysis precede – rather than result from, as in a compensatory strategy – balance impairments. Clinical tests derived from SRM analysis could therefore potentially identify fall-prone PD patients for interventions.[16-22]

Abbreviations

APR: Automatic Postural Response;2,5,23 BBS: Berg Balance Scale;24 CoM: Center of body Mass;2,5,23 DGI: Dynamic Gait Index;25 FAB: Fullerton Advanced Balance Scale;26 FOG: Freezing of Gait;27 LED: Levodopa Equivalent Dose;28 MDS UPDRS-III: Unified Parkinson's Disease Rating Scale, Part III, Motor Exam, Movement Disorders Society revision;29 MG: Medial Gastrocnemius (ankle plantarflexor/knee flexor) Mini-BESTest: Balance Evaluation Systems Test, "Mini" revision;26 MoCA: Montreal Cognitive Assessment;30 PD: Parkinson's Disease PIGD: Postural Instability/Gait Difficulty;31 SRM: Sensorimotor Response Model;2,5,23 TA: Tibialis Anterior (ankle dorsiflexor) TD: Tremor Dominant;31 VAF: Variance Accounted For 3

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Support

NIH K25 HD086276
R01 HD046922

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