Abnormal sensorimotor transformations for balance in Parkinson disease are associated with falls

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Acknowledgments and disclosures

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In PD, falls are common, and may primarily result from impaired CoM control

6-month prospective falls tracking in N=59 patients and N=55 healthy spouses, Bloem et al., J Neurol 2001
We use a multidirectional perturbation balance platform to quantify CoM control in PD.
Mechanisms underlying the complex temporal patterns during “coactivation” responses are unknown.

Figure 41–15
The basal ganglia are important for adapting postural responses to a sudden change in initial conditions. (Adapted, with permission, from Horak, Nutt, and Nashner 1992.)

A. When a normal subject switches from upright stance to sitting he immediately modifies his response to backward movement of the support platform. The postural response to movement while seated does not involve the leg muscles—the gastrocnemius (GAS) and hamstrings (HAM)—but does activate the paraspinal muscles (PSP) and with shorter latency than in the response to movement while standing. (ABD, abdominals; QUAD, quadriceps; TIB, tibialis anterior.)

B. A patient with Parkinson disease does not suppress the leg-muscle response in the first trial after switching from standing to sitting. The postural response of this subject is similar for both initial positions: antagonist muscles (purple) are activated along with agonists (pink).
Study objectives

- Test whether CoM feedback control is abnormal in mild-moderate PD (N=44, age 68±7y, PD duration 7±5y) compared to age-matched controls (N=18, 66±8y) and young controls (N=6, 21±2y).

- Test whether abnormal CoM feedback control is associated with previous falls and (preliminary data) future falls.
The sensorimotor response model (SRM) describes CoM control during balance.

Sensory estimates of center of mass (CoM) motion → Sensorimotor Response Model (SRM) → Motor responses measured with electromyogram (EMG)

The sensorimotor response model (SRM) describes CoM control during balance.

Intact and lesioned cats: Lockhart, Ting, Nat Neurosci 2007
Young (22F)  
\[ VAF = 0.80 \quad R^2 = 0.60 \]  

Non-PD (64M)  
\[ VAF = 0.78 \quad R^2 = 0.56 \]  

PD (62F)  
\[ VAF = 0.90 \quad R^2 = 0.72 \]  

\[ k_a' = 0.8 \quad R^2 = 0.65 \]  
\[ k_a' = 1.0 \quad R^2 = 0.59 \]  
\[ k_a' = 7.6 \quad R^2 = 0.53 \]  

McKay et al. in prep
We quantified destabilizing CoM acceleration feedback with parameter $k_a'$.
TA $k_a'$ is abnormally high in Parkinson’s disease

TA antagonist pathway

TA balance-correcting pathway

McKay et al. in prep

N=68
N=44, PD
N=18, Non-PD
N=6, Young
TA $k_a'$ is associated with presence of and number of previous falls.

Presence of previous falls: ANOVA

- $k_a'$ histogram with bars for 0, 1, and $\geq 2$ falls, labeled N=67 and ***$P<0.0001$.

Number of previous falls: negative binomial regression

- Graph showing $\beta_{k_a'}=0.69$ with ***$P<0.0001$.

6 Month Retrospective Fall Frequency

- Stratified 6 Month Retrospective Fall Frequency with N=39.

Analyses control for age, sex, MoCA score, PD, FoG.

McKay et al. in prep
TA $k_a'$ is associated with time to fall and with fall risk (interim analysis)

**Univariate association with time to fall**

$r = -0.50$

N=12

$\text{Months until first fall after study entry}$

$\text{Proportion without Falls}$

Low $k_a'$

High $k_a'$

**Multivariate Survival analysis**

HR=2.47

N=21

$\text{Months after study entry}$

*Covariates: age, sex, MoCA score, PD, FoG.*
Case study: CoM control in de novo PD without fall history

Symptom Onset (LLE Akinesia) Age 68
Abnormal DAT Scan
Clinic PD Diagnosis Age 69
Study Entry Age 70

UPDRS-III, TOTAL
UPDRS-III, LEFT
UPDRS-III, RIGHT

Feb ’16 // Feb ’17 // Aug ’17 // Feb ’18 // Aug ’18

Study Month 3, fall from bed
Study Month 5, fall while digging a hole to plant an azalea
Study Month 6, fall while operating a pole saw to trim an overhead branch

MDS UPDRS-III
Left = 12
Right = 10

MiniBESTest Score at Study Entry: 26/28
Activities-Specific Balance Confidence: 90/100

\( k_a' = 8.1 \) (93rd %-ile)
\( k_a' = 5.4 \) (85th %-ile)
Results summary

• CoM control of balance is disrupted in PD.

• SRM parameter $k_a'$ represents abnormal destabilizing feedback. 5/7 other feedback parameters vary significantly with healthy aging.

• Abnormal destabilizing feedback is associated with previous and future falls.

• Abnormal destabilizing feedback can precede first falls and can be present when behavioral balance measures and self-assessed balance confidence is acceptable.
Discussion

- We are currently evaluating SRM approach to predict fall risk. Next generation versions of clinical scales (MDS UPDRS-III, Mini-Best) could potentially incorporate additional dynamic balance elements.

- Dopamine challenge paradigms\(^1\) could provide further insight into neuroanatomy and physiology of this deficit.

- TA antagonist activity could reflect pathology\(^2\) in brain regions implicated in balance tasks (MLR/PPN).\(^3\) The PPN receives cholinergic spinal input that could carry CoM feedback information\(^4\) originating in muscle spindles.\(^5,6\) This could be less responsive to levodopa.

- TA antagonist activity could reflect pathology in thalamic regions necessary and sufficient for this balance task\(^7\) that are degenerated in PD patients with fall history.\(^8\) The thalamus is under tonic drive from basal ganglia output nuclei.\(^9\) This could be more responsive to levodopa.

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\(^{1}\) McKay, Factor et al., bioRxiv 2019; \(^{2}\) Braak et al., Neurobiol Aging 2003; \(^{3}\) Karachi et al., J Clin Invest 2010

\(^{4}\) Pahapill and Lozano, Brain 2000; \(^{5}\) Honeycutt and Nichols, J Neurophysiol 2009; \(^{6}\) Blum et al., PLoS Comp Biol 2017

\(^{7}\) Honeycutt 2009 [Thesis]; \(^{8}\) Bohnen et al., Ann Neurol 2019; \(^{9}\) Wichmann and DeLong, Neurotherapeutics 2016
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